

ENANTIOSELECTIVE AZA-HENRY REACTION OF *t*-BOC PROTECTED  
IMINES AND NITROALKANES WITH BIFUNCTIONAL SQUARAMIDE  
ORGANOCATALYSTS

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IMINES AND NITROALKANES WITH BIFUNCTIONAL SQUARAMIDE  
ORGANOCATALYSTS**

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## ABSTRACT

### ENANTIOSELECTIVE AZA-HENRY REACTION OF *t*-BOC PROTECTED IMINES AND NITROALKANES WITH BIFUNCTIONAL SQUARAMIDE ORGANOCATALYSTS

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The first part of this thesis comprises the application of a Cinchona alkaloid derived, bifunctional squaramide organocatalyst in the aza-Henry reaction of *t*-Boc protected imines and nitroalkanes. The target chiral  $\beta$ -nitroamines are chosen because; they are quite feasible for the corresponding  $\alpha$ -amino acids and 1,2-diamines, which are basic structural motif in many natural products and key materials of the many pharmaceuticals. In this part, 12 different chiral  $\beta$ -nitroamine derivatives were synthesized with quinine based novel bifunctional organocatalyst, which has been developed in our group, up to 91% ee under the optimized condition with 10 mol% catalyst loading.

In the second part of the thesis, preliminary studies of enantioselective Henry, aldol, decarboxylative aldol and Friedel-Crafts type substitution domino reactions were conducted with bifunctional organocatalysts. Among these studies, the best result was achieved with Friedel-Crafts type substitution domino reaction as 92% ee in 10 minutes.

**Keywords:** asymmetric synthesis, organocatalysis, enantioselectivity, aza-Henry, aldol, decarboxylative aldol, Friedel-Crafts, domino

## ÖZ

### BİFONKSİYONEL SKUARAMİT ORGANOKATALİZÖRLER İLE *t*-BOC KORUNUMLU İMİNLERİN NİTROALKANLARLA ENANTİYOSEÇİCİ AZA-HENRY TEPKİMESİ

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Bu tezin ilk kısmı, Cinchona alkaloid türevinden sentezlenen bifonksiyonel skuaramit organokatalizörünün, nitroalkanlar ile *t*-Boc korunumlu iminlerin tepkimesindeki uygulamasını içermektedir. Hedeflenen kiral  $\beta$ -nitroamin yapıları  $\alpha$ -amino asitlere, pek çok doğal ürünün yapısında ve önemli ilaç hammaddesinde kullanılan 1,2-diaminlere kolayca çevrilebilmesiyle bilinen önemli ara ürünlerdir. Bu kısımda 12 farklı kiral  $\beta$ -nitroamin türevi, grubumuzda sentezlenen kinin temelli özgün bifonksiyonel organokatalizör yardımıyla, %10 mol miktarında optimize edilmiş koşul ile %91 enantiyoseçiciliklere kadar sentezlenmiştir.

Tezin ikinci kısmında Henry, aldol, dekarboksilatif aldol ve Friedel-Crafts tipi süstitüsyon domino tepkimelerinin bifonksiyonel organokatalizör yardımıyla öncül çalışmaları yapılmıştır. İçlerindeki en iyi sonuç Friedel-Crafts tipi süstitüsyon domino tepkimesi ile %92 enantiyoseçicilikle 10 dakikada elde edilmiştir.

**Anahtar Kelimeler:** asimetrik sentez, organokataliz, enantiyoseçicilik, aza-Henry, aldol, dekarboksilatif aldol, Friedel-Crafts, domino

*To my beloved grandfathers*

*Rest in Peace...*

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## TABLE OF CONTENTS

ABSTRACT .....	v
ÖZ .....	vi
ACKNOWLEDGEMENTS.....	viii
TABLE OF CONTENTS .....	x
LIST OF TABLES.....	xiv
LIST OF FIGURES .....	xv
LIST OF SCHEMES .....	xix
LIST OF ABBREVIATIONS .....	xx
CHAPTERS.....	1
1. INTRODUCTION .....	1
1.1. Why is the Asymmetric Synthesis Important? .....	1
1.2. How Do We Synthesize the Chiral Molecules? .....	2
1.2.1. Chiral Pool.....	2
1.2.2. Kinetic Resolution.....	3
1.2.3. Asymmetric Catalysis .....	3
1.3. Organocatalysis in Asymmetric Synthesis .....	4
1.3.1. Classifications of Organocatalysts .....	4
1.3.2. Natural Products in Organocatalysts: Cinchona Alkaloids .....	5
1.3.3. Bifunctional Organocatalysis .....	6
1.3.4. Squaramides in Organocatalysis .....	7
1.4. Aza-Henry Reactions.....	8
1.5. Miscellaneous Reactions with Organocatalysts .....	12
1.5.1. Henry Reactions .....	12
1.5.2. Aldol Reactions .....	13
1.5.2.1. Decarboxylative Aldol Reactions.....	14

1.5.3. Friedel-Crafts / Substitution Domino Type Reactions.....	14
1.6. Aim of the Work.....	15
2. RESULTS AND DISCUSSION.....	17
2.1. Synthesis of <i>t</i> -Butyl Squaramide Anchored Bifunctional Organocatalysts .	17
2.2. Evaluation of the Bifunctional Organocatalysts in Aza-Henry Reaction....	18
2.2.1. Aza-Henry Reaction of <i>t</i> -Boc Protected Imines with Nitroalkanes .....	18
2.2.2. Aza-Henry Reaction of Tosyl Protected Imines with Nitroalkanes.....	28
2.3. Evaluation of the Bifunctional Organocatalysts in Henry Reaction .....	29
2.4. Evaluation of the 2-aminoDMAP Backbone in Aldol Reaction .....	31
2.5. Evaluation of the Bifunctional Organocatalysts in Decarboxylative Aldol Reaction .....	33
2.6. Evaluation of the Bifunctional Organocatalysts in Friedel- Crafts/Substitution Domino Reaction.....	35
3. EXPERIMENTAL .....	37
3.1 Materials and Methods .....	37
3.2 Synthesis of 9-amino (9-deoxy)epihydroquinine <b>58</b> .....	38
3.3 Synthesis of <i>t</i> -Butyl Mono-Squaramide <b>57</b> .....	38
3.4 Synthesis of <i>t</i> -Butyl Squaramide / Quinine Catalyst <b>51</b> .....	39
3.5 Synthesis of 2-AminoDMAP <b>56</b> .....	40
3.6 Synthesis of <i>t</i> -Butyl squaramide / 2-aminoDMAP catalyst <b>48</b> .....	40
3.7 Synthesis of <i>t</i> -Boc Protected Imines .....	41
3.8 General Procedure for Aza-Henry Reaction: Nitromethane Addition to <i>t</i> -Boc Protected Imines .....	41
3.8.1 Synthesis of <i>tert</i> -butyl ( <i>S</i> )-(2-nitro-1-phenylethyl) carbamate ( <b>24a</b> ).....	42
3.8.2 Synthesis of <i>tert</i> -butyl ( <i>S</i> )-(1-(4-methoxyphenyl)-2-nitroethyl) carbamate ( <b>24b</b> ).....	43
3.8.3 Synthesis of <i>tert</i> -butyl ( <i>S</i> )-(2-nitro-1-( <i>o</i> -tolyl)ethyl) carbamate ( <b>24c</b> ) ...	43
3.8.4 Synthesis of <i>tert</i> -butyl ( <i>S</i> )-(1-(3-chlorophenyl)-2-nitroethyl) carbamate ( <b>24d</b> ) .....	44
3.8.5 Synthesis of <i>tert</i> -butyl ( <i>S</i> )-(1-(4-bromophenyl)-2-nitroethyl) carbamate ( <b>24e</b> ) .....	45

3.8.6	Synthesis of <i>tert</i> -butyl ( <i>S</i> )-(2-nitro-1-( <i>p</i> -tolyl)ethyl) carbamate ( <b>24f</b> ) ...	45
3.8.7	Synthesis of <i>tert</i> -butyl ( <i>S</i> )-(1-(3-methoxyphenyl)-2-nitroethyl) carbamate ( <b>24g</b> ) .....	46
3.8.8	Synthesis of <i>tert</i> -butyl ( <i>S</i> )-(1-(2-bromophenyl)-2-nitroethyl) carbamate ( <b>24h</b> ) .....	46
3.8.9	Synthesis of <i>tert</i> -butyl ((1 <i>R</i> ,2 <i>S</i> )-2-nitro-1-phenylpropyl) carbamate ( <b>28a</b> ) .....	47
3.8.10	Synthesis of <i>tert</i> -butyl ((1 <i>R</i> ,2 <i>S</i> )-1-(4-methoxyphenyl)-2-nitropropyl) carbamate ( <b>28b</b> ) .....	48
3.8.11	Synthesis of <i>tert</i> -butyl ((1 <i>R</i> ,2 <i>S</i> )-2-nitro-1-( <i>o</i> -tolyl)propyl) carbamate ( <b>28c</b> ) .....	49
3.8.12	Synthesis of <i>tert</i> -butyl (2-nitro-1-phenylbutyl)carbamate ( <b>31a</b> ) .....	50
3.9	Synthesis of Tosyl Protected Imines .....	50
3.10	General Procedure for Aza-Henry Reaction: Nitromethane Addition to Tosyl Protected Imines .....	51
3.10.1	Synthesis of ( <i>S</i> )-4-methyl- <i>N</i> -(2-nitro-1-phenylethyl)benzenesulfonamide ( <b>22a</b> ) .....	52
3.11	General Procedure for Henry Reaction: Nitromethane Addition to Aldehydes .....	52
3.11.1	Synthesis of ( <i>S</i> )-2-nitro-1-(4-nitrophenyl)ethan-1-ol ( <b>35b</b> ) .....	53
3.12	General Procedure for Aldol Reaction: Acetone/Cyclohexanone Addition to Aldehydes .....	53
3.12.1	Synthesis of ( <i>S</i> )-4-hydroxy-4-(4-nitrophenyl)butan-2-one ( <b>37b</b> ) .....	54
3.12.2	Synthesis of 2-(hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one ( <b>60b</b> ) .....	54
3.13	Synthesis of $\alpha$ -Amidohemimalonates .....	55
3.14	General Procedure for Decarboxylative Aldol Reaction: Aldehyde Addition to $\alpha$ -Amidohemimalonates .....	56
3.14.1	Synthesis of ethyl 2-benzamido-3-hydroxy-3-(4-nitrophenyl)propanoate ( <b>55b</b> ) .....	57
3.15	Synthesis of ( <i>Z</i> )-(2-bromo-2-nitrovinyl)benzene ( <b>43</b> ) .....	57

3.16	General Procedure for Friedel-Crafts/Substitution Domino Reaction: ( <i>Z</i> )- (2-bromo-2-nitrovinyl)benzene ( <b>43</b> ) and $\beta$ -naphthol ( <b>42</b> ).....	58
3.16.1	Synthesis of 2-nitro-1-phenyl-1,2-dihydronaphtho[2,1- <i>b</i> ]furan ( <b>44a</b> ) .	58
4.	CONCLUSION .....	61
	REFERENCES .....	63
	APPENDICES .....	69
A.	NMR DATA .....	69
B.	HPLC DATA .....	91
C.	GC-MS DATA.....	109

## LIST OF TABLES

### TABLES

<b>Table 1.</b> Catalyst screening .....	19
<b>Table 2.</b> Solvent Screening .....	20
<b>Table 3.</b> Temperature Screening .....	20
<b>Table 4.</b> Temperature Screening with other derivatives .....	21
<b>Table 5.</b> Catalyst loading and concentration screening.....	22
<b>Table 6.</b> Derivatization study with catalyst <b>48</b> .....	22
<b>Table 7.</b> Catalyst screening with the quinine based squaramides .....	23
<b>Table 8.</b> Solvent screening with catalyst <b>51</b> .....	24
<b>Table 9.</b> Additional temperature and concentration screenings with catalyst <b>51</b> .....	25
<b>Table 10.</b> Derivatization with catalyst <b>51</b> .....	26
<b>Table 11.</b> Catalyst screening and catalyst loading of tosyl imines .....	28
<b>Table 12.</b> Additional screenings of tosyl imines.....	29
<b>Table 13.</b> Catalyst screening and catalyst loading of Henry reaction.....	30
<b>Table 14.</b> Additional solvent and temperature screenings of Henry reaction.....	31
<b>Table 15.</b> Screenings of Aldol reaction with acetone .....	32
<b>Table 16.</b> Screenings of Aldol reaction with cyclohexanone ( <b>59</b> ).....	32
<b>Table 17.</b> Screenings of Aldol reaction with binary catalyst system.....	33
<b>Table 18.</b> Screenings of Decarboxylative Aldol reaction with bifunctional organocatalysts .....	34

## LIST OF FIGURES

### FIGURES

<b>Figure 1.</b> Molecular structures of thalidomide .....	1
<b>Figure 2.</b> Drug approval charts after 2000.....	2
<b>Figure 3.</b> Covalent catalysis.....	4
<b>Figure 4.</b> Commonly used generic activation modes of organocatalysts <sup>7,13-16</sup> . ....	5
<b>Figure 5.</b> Examples of Cinchona alkaloids.....	6
<b>Figure 6.</b> Schreiner thiourea .....	7
<b>Figure 7.</b> The distance between N-attached hydrogens in <i>N,N'</i> -dimethylthiourea and <i>N,N'</i> -dimethylsquaramide.....	8
<b>Figure 8.</b> Bifunctional organocatalysts developed in our research group .....	15
<b>Figure 9.</b> 2-AminoDMAP based bifunctional organocatalysts .....	18
<b>Figure 10.</b> Quinine based bifunctional organocatalysts.....	23
<b>Figure 11.</b> Proposed transition state model .....	27
<b>Figure 12.</b> Cinchona derivative of thiourea <b>27</b> and urea <b>61</b> organocatalysts .....	34
<b>Figure A. 1.</b> <sup>1</sup> H NMR spectrum of compound <b>51</b> .....	69
<b>Figure A. 2.</b> <sup>13</sup> C NMR spectrum of compound <b>51</b> .....	69
<b>Figure A. 3.</b> <sup>1</sup> H NMR spectrum of compound <b>24a</b> .....	70
<b>Figure A. 4.</b> <sup>13</sup> C NMR spectrum of compound <b>24a</b> .....	70
<b>Figure A. 5.</b> <sup>1</sup> H NMR spectrum of compound <b>24b</b> .....	71
<b>Figure A. 6.</b> <sup>13</sup> C NMR spectrum of compound <b>24b</b> .....	71
<b>Figure A. 7.</b> <sup>1</sup> H NMR spectrum of compound <b>24c</b> .....	72
<b>Figure A. 8.</b> <sup>13</sup> C NMR spectrum of compound <b>24c</b> .....	72
<b>Figure A. 9.</b> <sup>1</sup> H NMR spectrum of compound <b>24d</b> .....	73
<b>Figure A. 10.</b> <sup>13</sup> C NMR spectrum of compound <b>24d</b> .....	73
<b>Figure A. 11.</b> <sup>1</sup> H NMR spectrum of compound <b>24e</b> .....	74
<b>Figure A. 12.</b> <sup>13</sup> C NMR spectrum of compound <b>24e</b> .....	74
<b>Figure A. 13.</b> <sup>1</sup> H NMR spectrum of compound <b>24f</b> .....	75

<b>Figure A. 14.</b> $^{13}\text{C}$ NMR spectrum of compound <b>24f</b> .....	75
<b>Figure A. 15.</b> $^1\text{H}$ NMR spectrum of compound <b>24g</b> .....	76
<b>Figure A. 16.</b> $^{13}\text{C}$ NMR spectrum of compound <b>24g</b> .....	76
<b>Figure A. 17.</b> $^1\text{H}$ NMR spectrum of compound <b>24h</b> .....	77
<b>Figure A. 18.</b> $^{13}\text{C}$ NMR spectrum of compound <b>24h</b> .....	77
<b>Figure A. 19.</b> $^1\text{H}$ NMR spectrum of diastereomeric mixture <b>28a</b> .....	78
<b>Figure A. 20.</b> $^{13}\text{C}$ NMR spectrum of diastereomeric mixture <b>28a</b> .....	78
<b>Figure A. 21.</b> $^1\text{H}$ NMR spectrum of diastereomeric mixture <b>28b</b> .....	79
<b>Figure A. 22.</b> $^{13}\text{C}$ NMR spectrum of diastereomeric mixture <b>28b</b> .....	79
<b>Figure A. 23.</b> $^1\text{H}$ NMR spectrum of diastereomeric mixture <b>28c</b> .....	80
<b>Figure A. 24.</b> $^{13}\text{C}$ NMR spectrum of diastereomeric mixture <b>28c</b> .....	80
<b>Figure A. 25.</b> $^1\text{H}$ NMR spectrum of diastereomeric mixture <b>31a</b> .....	81
<b>Figure A. 26.</b> $^{13}\text{C}$ NMR spectrum of diastereomeric mixture <b>31a</b> .....	81
<b>Figure A. 27.</b> $^1\text{H}$ NMR spectrum of compound <b>21</b> .....	82
<b>Figure A. 28.</b> $^{13}\text{C}$ NMR spectrum of compound <b>21</b> .....	82
<b>Figure A. 29.</b> $^1\text{H}$ NMR spectrum of compound <b>22a</b> .....	83
<b>Figure A. 30.</b> $^{13}\text{C}$ NMR spectrum of compound <b>22a</b> .....	83
<b>Figure A. 31.</b> $^1\text{H}$ NMR spectrum of compound <b>35b</b> .....	84
<b>Figure A. 32.</b> $^{13}\text{C}$ NMR spectrum of compound <b>35b</b> .....	84
<b>Figure A. 33.</b> $^1\text{H}$ NMR spectrum of compound <b>37b</b> .....	85
<b>Figure A. 34.</b> $^{13}\text{C}$ NMR spectrum of compound <b>37b</b> .....	85
<b>Figure A. 35.</b> $^1\text{H}$ NMR spectrum of <i>anti</i> - <b>60b</b> .....	86
<b>Figure A. 36.</b> $^{13}\text{C}$ NMR spectrum of <i>anti</i> - <b>60b</b> .....	86
<b>Figure A. 37.</b> $^1\text{H}$ NMR spectrum of compound <b>60b</b> .....	87
<b>Figure A. 38.</b> $^{13}\text{C}$ NMR spectrum of compound <b>60b</b> .....	87
<b>Figure A. 39.</b> $^1\text{H}$ NMR spectrum of compound <b>54</b> .....	88
<b>Figure A. 40.</b> $^{13}\text{C}$ NMR spectrum of compound <b>54</b> .....	88
<b>Figure A. 41.</b> $^1\text{H}$ NMR spectrum of compound <b>55b</b> .....	89
<b>Figure A. 42.</b> $^{13}\text{C}$ NMR spectrum of compound <b>55b</b> .....	89
<b>Figure A. 43.</b> $^1\text{H}$ NMR spectrum of compound <b>44a</b> .....	90
<b>Figure A. 44.</b> $^{13}\text{C}$ NMR spectrum of compound <b>44a</b> .....	90
<b>Figure B. 1.</b> HPLC chromatogram of <i>rac</i> - <b>24a</b> .....	91

<b>Figure B. 2.</b> HPLC chromatogram of enantiomerically enriched <b>24a</b> .....	91
<b>Figure B. 3.</b> HPLC chromatogram of <i>rac</i> - <b>24b</b> .....	92
<b>Figure B. 4.</b> HPLC chromatogram of enantiomerically enriched <b>24b</b> .....	92
<b>Figure B. 5.</b> HPLC chromatogram of <i>rac</i> - <b>24c</b> .....	93
<b>Figure B. 6.</b> HPLC chromatogram of enantiomerically enriched <b>24c</b> .....	93
<b>Figure B. 7.</b> HPLC chromatogram of <i>rac</i> - <b>24d</b> .....	94
<b>Figure B. 8.</b> HPLC chromatogram of enantiomerically enriched <b>24d</b> .....	94
<b>Figure B. 9.</b> HPLC chromatogram of <i>rac</i> - <b>24e</b> .....	95
<b>Figure B. 10.</b> HPLC chromatogram of enantiomerically enriched <b>24e</b> .....	95
<b>Figure B. 11.</b> HPLC chromatogram of <i>rac</i> - <b>24f</b> .....	96
<b>Figure B. 12.</b> HPLC chromatogram of enantiomerically enriched <b>24f</b> .....	96
<b>Figure B. 13.</b> HPLC chromatogram of <i>rac</i> - <b>24g</b> .....	97
<b>Figure B. 14.</b> HPLC chromatogram of enantiomerically enriched <b>24g</b> .....	97
<b>Figure B. 15.</b> HPLC chromatogram of <i>rac</i> - <b>24h</b> .....	98
<b>Figure B. 16.</b> HPLC chromatogram of enantiomerically enriched <b>24h</b> .....	98
<b>Figure B. 17.</b> HPLC chromatogram of diastereomeric mixture of <i>rac</i> - <b>28a</b> .....	99
<b>Figure B. 18.</b> HPLC chromatogram of enantiomerically enriched <b>28a</b> .....	99
<b>Figure B. 19.</b> HPLC chromatogram of diastereomeric mixture of <i>rac</i> - <b>28b</b> .....	100
<b>Figure B. 20.</b> HPLC chromatogram of enantiomerically enriched <b>28b</b> .....	100
<b>Figure B. 21.</b> HPLC chromatogram of <i>rac</i> - <b>28c</b> .....	101
<b>Figure B. 22.</b> HPLC chromatogram of enantiomerically enriched <b>28c</b> .....	101
<b>Figure B. 23.</b> HPLC chromatogram of <i>rac</i> - <b>31a</b> .....	102
<b>Figure B. 24.</b> HPLC chromatogram of enantiomerically enriched <b>31a</b> .....	102
<b>Figure B. 25.</b> HPLC chromatogram of <i>rac</i> - <b>22a</b> .....	103
<b>Figure B. 26.</b> HPLC chromatogram of enantiomerically enriched <b>22a</b> .....	103
<b>Figure B. 27.</b> HPLC chromatogram of <i>rac</i> - <b>35b</b> .....	104
<b>Figure B. 28.</b> HPLC chromatogram of enantiomerically enriched <b>35b</b> .....	104
<b>Figure B. 29.</b> HPLC chromatogram of <i>rac</i> - <b>37b</b> .....	105
<b>Figure B. 30.</b> HPLC chromatogram of enantiomerically enriched <b>37b</b> .....	105
<b>Figure B. 31.</b> HPLC chromatogram of <i>rac</i> - <b>55b</b> .....	106
<b>Figure B. 32.</b> HPLC chromatogram of enantiomerically enriched <b>55b</b> .....	106
<b>Figure B. 33.</b> HPLC chromatogram of <i>rac</i> - <b>44a</b> .....	107

<b>Figure B. 34.</b> HPLC chromatogram of enantiomerically enriched <b>44a</b> .....	107
<b>Figure C. 1.</b> GC-MS chromatogram of 1 h reaction.....	109
<b>Figure C. 2.</b> GC-MS chromatogram of 5 h reaction.....	109
<b>Figure C. 3.</b> GC-MS chromatogram of compound <b>24a</b> .....	110
<b>Figure C. 4.</b> GC-MS chromatogram of compound <b>24b</b> .....	111
<b>Figure C. 5.</b> GC-MS chromatogram of compound <b>24c</b> .....	112
<b>Figure C. 6.</b> GC-MS chromatogram of compound <b>24d</b> .....	113
<b>Figure C. 7.</b> GC-MS chromatogram of compound <b>24e</b> .....	114
<b>Figure C. 8.</b> GC-MS chromatogram of compound <b>24f</b> .....	115
<b>Figure C. 9.</b> GC-MS chromatogram of compound <b>24g</b> .....	116
<b>Figure C. 10.</b> GC-MS chromatogram of compound <b>24h</b> .....	117
<b>Figure C. 11.</b> GC-MS chromatogram of compound <b>28a</b> .....	118
<b>Figure C. 12.</b> GC-MS chromatogram of compound <b>28b</b> .....	119
<b>Figure C. 13.</b> GC-MS chromatogram of compound <b>28c</b> .....	120
<b>Figure C. 14.</b> GC-MS chromatogram of compound <b>31a</b> .....	121

## LIST OF SCHEMES

### SCHEMES

<b>Scheme 1.</b> The first remarkable study with Cinchona alkaloids.....	6
<b>Scheme 2.</b> The first bifunctional organocatalyst and its application in the Michael addition.....	7
<b>Scheme 3.</b> The first example of nitro-Mannich reaction .....	8
<b>Scheme 4.</b> Revised structure of the first example of nitro-Mannich reaction.....	9
<b>Scheme 5.</b> The first nitro-Mannich reaction with preformed imine .....	9
<b>Scheme 6.</b> The first catalytic example of aza-Henry reaction .....	10
<b>Scheme 7.</b> The first organocatalytic aza-Henry reaction .....	10
<b>Scheme 8.</b> Organocatalytic aza-Henry study with quinine derived catalyst.....	11
<b>Scheme 9.</b> Reaction of <i>t</i> -Boc imines and nitroalkanes with bis-thiourea catalyst .....	11
<b>Scheme 10.</b> Modular bifunctional thiourea with quinine organocatalyst in aza-Henry reaction .....	12
<b>Scheme 11.</b> Squaramide type quinine based organocatalyst in aza-Henry reaction ..	12
<b>Scheme 12.</b> Organocatalytic Henry reaction by Hiemstra.....	13
<b>Scheme 13.</b> Organocatalytic aldol reaction by Cheng .....	13
<b>Scheme 14.</b> Organocatalytic decarboxylative aldol reaction by Song.....	14
<b>Scheme 15.</b> Organocatalytic Friedel-Crafts / substitution domino reaction by Alemán .....	14
<b>Scheme 16.</b> Representative route of the reaction.....	15
<b>Scheme 17.</b> Organocatalytic Henry reaction.....	16
<b>Scheme 18.</b> Organocatalytic aldol reaction.....	16
<b>Scheme 19.</b> Organocatalytic decarboxylative aldol reaction .....	16
<b>Scheme 20.</b> Organocatalytic Friedel-crafts / substitution domino reaction .....	16
<b>Scheme 21.</b> Synthetic route for <i>t</i> -butyl squaramide / 2-aminoDMAP .....	17
<b>Scheme 22.</b> Synthetic route for <i>t</i> -butyl squaramide / quinine.....	18
<b>Scheme 23.</b> Mechanistic pathway of decarboxylative aldol reaction .....	34

## LIST OF ABBREVIATIONS

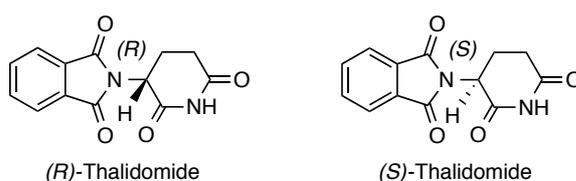
<b>BINAM</b>	: 1,1'-Binaphthalene-2,2'-diamine
<b>Cbz</b>	: Carboxybenzyl
<b>DMAP</b>	: 4-Dimethylamino pyridine
<b>MS</b>	: Molecular Sieves
<b>MTBE</b>	: Methyl <i>tert</i> -butyl ether
<b>SOMO</b>	: Singly Occupied Molecular Orbital
<b><i>t</i>-Boc</b>	: <i>tert</i> -Butoxycarbonyl

## CHAPTER 1

### INTRODUCTION

#### 1.1. Why is the Asymmetric Synthesis Important?

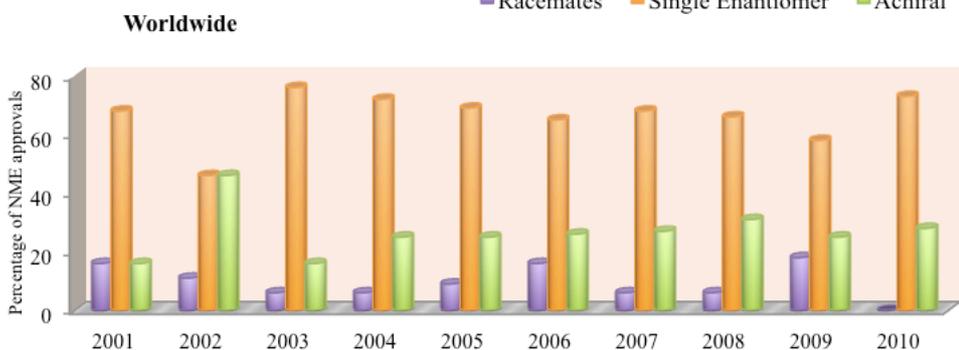
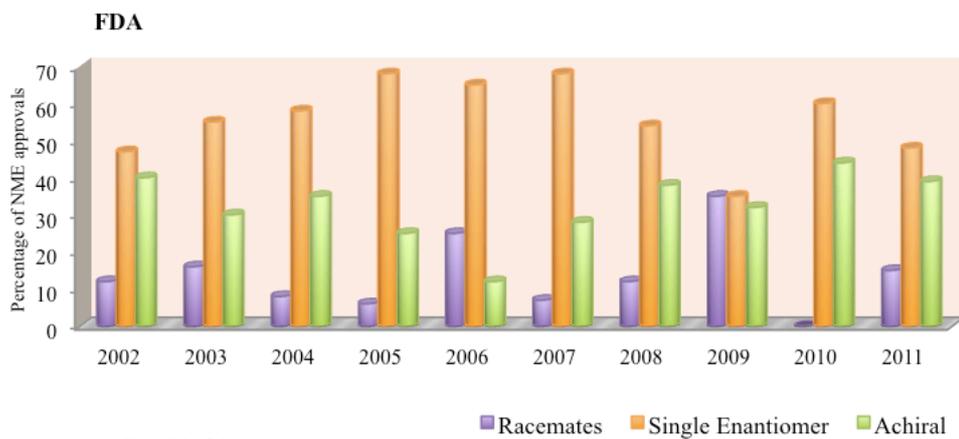
Most of the living systems, the vital components in particular, contain at least one chiral center. This uniqueness causes the enantiomers of these molecules to diverse in the expected results, as in the thalidomide drug disaster case in West Germany in the late 1950s. Thalidomide was synthesized by Chemie Grünenthal, a German company, and used as sedative to stop morning sickness of pregnant women. In the beginning, it was thought that this drug helps women; however, there had been a drastic increase in the birth defects in the worldwide rapidly. After this drug usage nearly more than 10,000 case were reported.<sup>1</sup> Subsequent studies showed that (*R*)-(+)-enantiomer provides the sedative effect; whereas, the (*S*)-(-)-enantiomer causes the birth defects (Figure 1).<sup>2</sup>



**Figure 1.** Molecular structures of thalidomide

This situation forced the drug industry to pay more attention to the chirality concept and improve their products. As the awareness increases, the approval of chiral drugs by Food and Drug Administration (FDA) has also been increased (Figure 2).<sup>3</sup>

Especially, after 2000, drug companies focus on to choose single enantiomer of the active manners.



**Figure 2.** Drug approval charts after 2000

## 1.2. How Do We Synthesize the Chiral Molecules?

There are many ways to synthesize chiral molecules. They can be divided into three main subtitles as chiral pool, kinetic resolution and asymmetric catalysis.

### 1.2.1. Chiral Pool

In this approach, the desired molecules are developed from the naturally occurring chiral products. Basically carbohydrates, amino acids, terpenes etc. are used as starting materials. Although this approach provides the highest enantiomerically pure compounds, the minority of the natural compounds made the scientist to study on another approaches.<sup>4</sup>

### **1.2.2. Kinetic Resolution**

In the kinetic resolution case, the chiral products are obtained from their racemic mixtures and in this method, enzymes or chiral chemicals are used. One enantiomer reacts much faster compared to the other, affording the products in high enantiomerically excess form.<sup>5</sup>

### **1.2.3. Asymmetric Catalysis**

Among the asymmetric synthesis methods, the largest library belongs to the asymmetric catalysis. The general idea is to use small molecules, called ‘catalysts’, in order to accelerate the reaction rate and decrease the activation energy of the reaction without changing the desired product’s structure. Diversity of these reagents can be improved or enhanced in many ways. The main idea for this approach is to synthesize the chiral molecules from prochiral ones with the help of chiral catalyst or reagents. Usually, small, man-made organic molecules are preferred to use, and this approach, also provides an economical way to get highly enantioenriched compounds.<sup>6</sup>

In the literature, many catalytic studies and many catalysts have been reported. These catalysis concepts are divided into three main subjects as; biocatalysis, transition metal catalysis and organocatalysis. We became familiar with the new concept called “organocatalysis” in the last decade.<sup>7</sup>

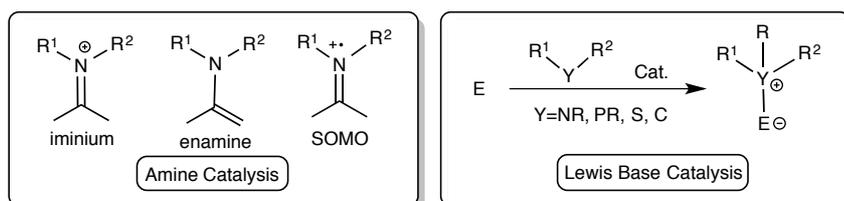
“Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom”.<sup>8</sup> These compounds mainly contain carbon, hydrogen, nitrogen, oxygen and sulfur atoms and called “organocatalysts”.

Although the catalytic use of small organic molecules is known for a century, the applications can be considered as a new research area. After the mid-1990’s there has been a sharp increase in the organocatalytic research.<sup>7</sup>

### 1.3. Organocatalysis in Asymmetric Synthesis

#### 1.3.1. Classifications of Organocatalysts

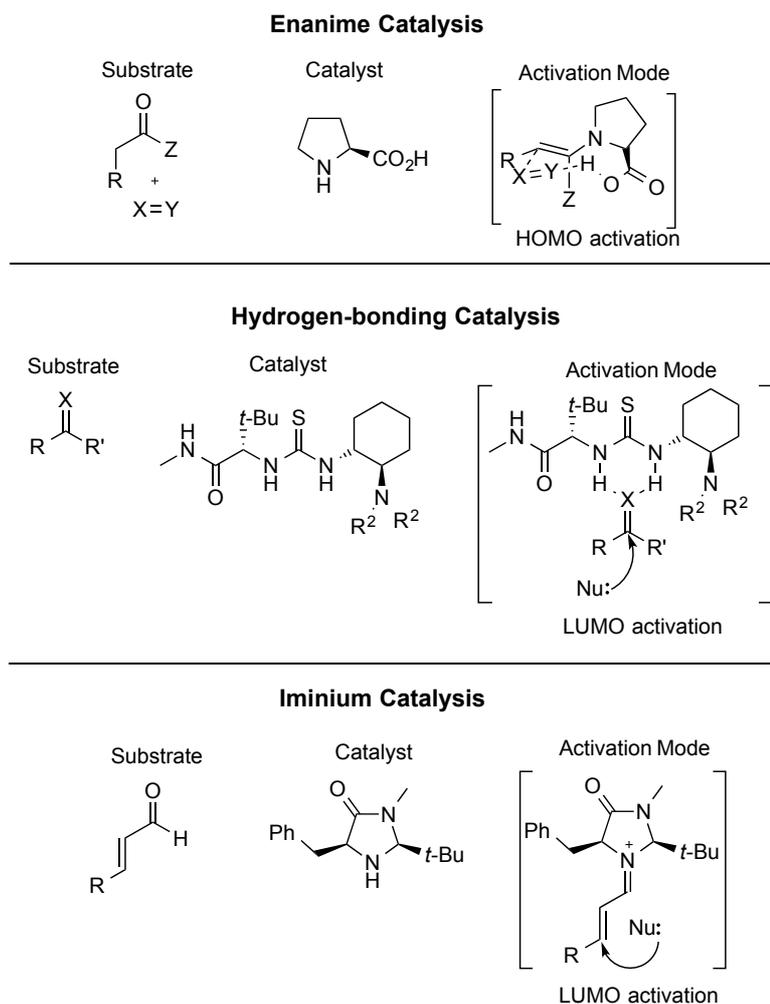
The first classification of the organocatalysts belongs to Berkessel and it can be considered by their interactions between substrates as covalent interaction or non-covalent interaction. In the covalent bond interaction, a new chemical (covalent) bond occurs between the catalyst and substrate; whereas in the non-covalent case, the weak binding takes place such as hydrogen bonding or ionic interactions.<sup>9</sup> The iminium, enamine, SOMO or Lewis base type catalysts considered as covalent catalysis (Figure 3).<sup>10</sup> On the other hand, Brønsted acid, phase transfer, hydrogen bonding, Brønsted base catalysts are grouped into the non-covalent catalysts.<sup>11</sup>



**Figure 3.** Covalent catalysis

Seayed and List announced another classification in 2005.<sup>12</sup> According to their mechanistic cycle proposal, organocatalysts act as either Lewis acid, Lewis base, Brønsted acid or Brønsted base.

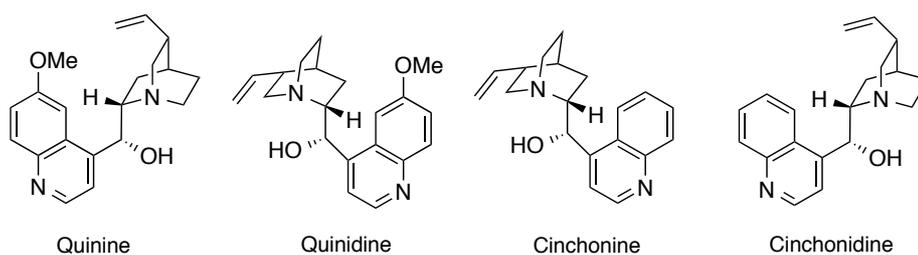
In 2008, MacMillan published an article in *Nature*<sup>7</sup>, about the development of organocatalysts. He classified the organocatalysts by their activation and induction modes. The most commonly used ones can be considered as; enamine catalyst, hydrogen-bonding catalyst and iminium catalyst. The active manner of the catalyst takes the lead role in the intermediate of the reaction to perform highly enantiomeric species in these types of catalysts. The main idea is increasing the HOMO level or decreasing the LUMO level (Figure 4).



**Figure 4.** Commonly used generic activation modes of organocatalysts<sup>7,13-16</sup>.

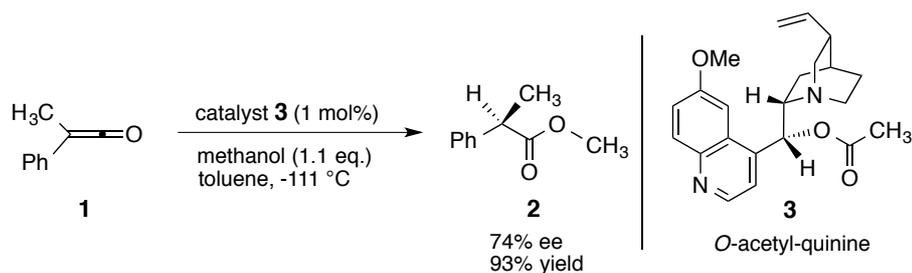
### 1.3.2. Natural Products in Organocatalysts: Cinchona Alkaloids

Cinchona alkaloids, the natural products isolated from Cinchona trees, and used as catalysts since 1800s. In 1812, Pierre-Joseph Pelletier and Joseph Bienaimé Caventou isolated the first Cinchona alkaloid: “quinine”.<sup>17</sup> However, the catalytic usage of these alkaloids was discovered after 1912.<sup>18</sup> Although the first trials were not very satisfying, in the last three decades there has been an increase in the reports of catalytic studies with different Cinchona examples (Figure 5).



**Figure 5.** Examples of Cinchona alkaloids

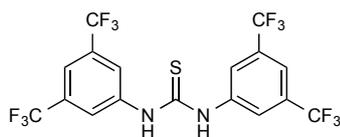
The first remarkable study with these alkaloids was reported by Pracejus, by using *O*-acetyl-quinine **3** as catalyst. He performed a reaction between phenylmethylketene (**1**) and methanol (Scheme 1). With a few amount of catalyst, the result was quite significant. Although reaction was carried out a very low temperatures, the chemical yield was also good as 93% and the enantiomeric excess was found 74%.<sup>19</sup>



**Scheme 1.** The first remarkable study with Cinchona alkaloids

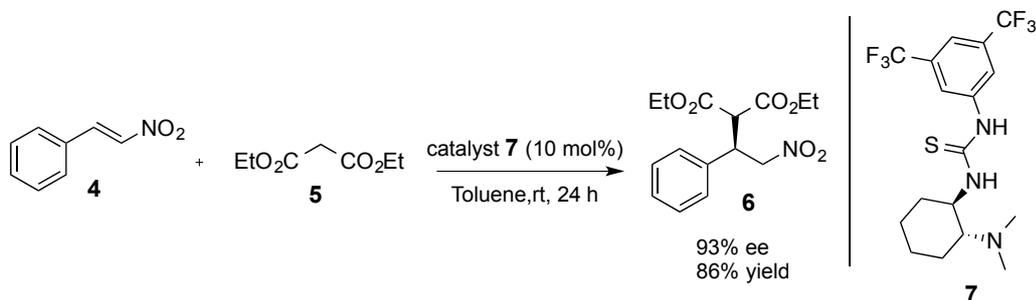
### 1.3.3. Bifunctional Organocatalysis

One of the biggest breakthroughs in the organocatalytic studies came in the 2003. Takemoto and his co-workers submitted a new type of catalyst, called “bifunctional organocatalyst”, includes both acidic and basic moieties, all in one unit.<sup>20</sup> These types of catalysts provide an easy way in the activation of both substrates simultaneously. They derived an organocatalyst from Schreiner thiourea catalyst; provide a high hydrogen-bond interaction with the substrates (Figure 6).<sup>21</sup>



**Figure 6.** Schreiner thiourea

Takemoto and his co-workers performed the Michael Addition of diethylmalonate (**5**) to *trans*- $\beta$ -nitrostyrene (**4**) using thiourea type bifunctional organocatalyst **7** (Scheme 2).

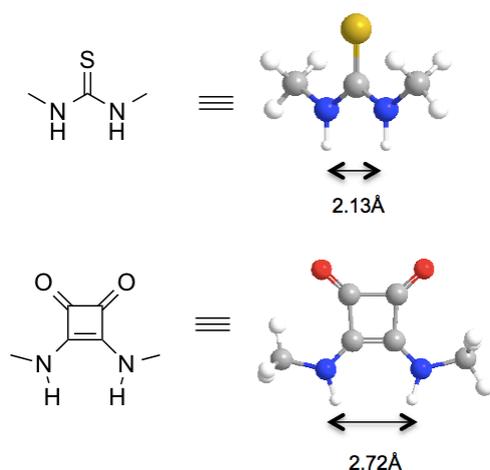


**Scheme 2.** The first bifunctional organocatalyst and its application in the Michael addition

In their catalyst, (*R,R*)-1,2-cyclohexyldiamine unit was used for the chiral scaffold, the basic part of the catalyst is used for the activation of nucleophile by raising HOMO level, and the acidic part, thiourea moiety, is used for the activation of the electrophile by decreasing the LUMO levels.<sup>20</sup>

#### 1.3.4. Squaramides in Organocatalysis

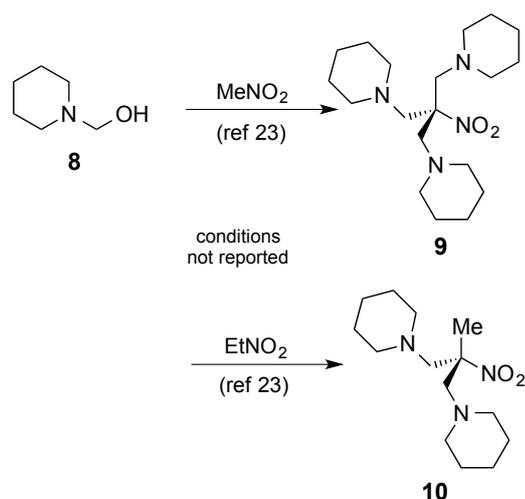
Thiourea type catalysts make it possible to interact substrates with H-bonding and there are many of them to widen the library. However, this brings us to find other H-bonding source. Rawal *et al.* brought a new acidic moiety in to the literature.<sup>22</sup> They claimed that the squaric acid moiety, depicted in Figure 7, provides a higher spacer than thiourea. The angle of the hydrogens in the squaric acid makes the H-bonding more effective in the transition states.



**Figure 7.** The distance between N-attached hydrogens in *N,N'*-dimethylthiourea and *N,N'*-dimethylsquaramide

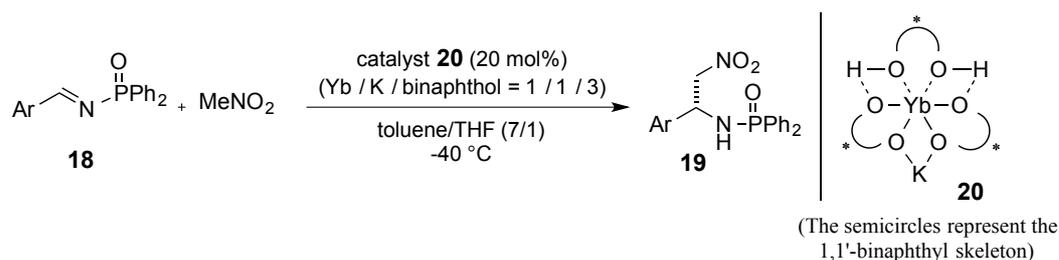
#### 1.4. Aza-Henry Reactions

Aza-Henry reaction is a modified Henry reaction that occurs between nitroalkanes and imines to form  $\beta$ -nitroamine products. It is also known as nitro-Mannich reaction, which is the nucleophilic addition of nitronates to the electrophilic imine species to produce new C-C bond. Louis Henry published the first report of this reaction in 1896.<sup>23</sup> In his study, methanolamine **8** was treated with nitromethane and nitroethane to give di- **10** and tripiperidines **9** (Scheme 3).



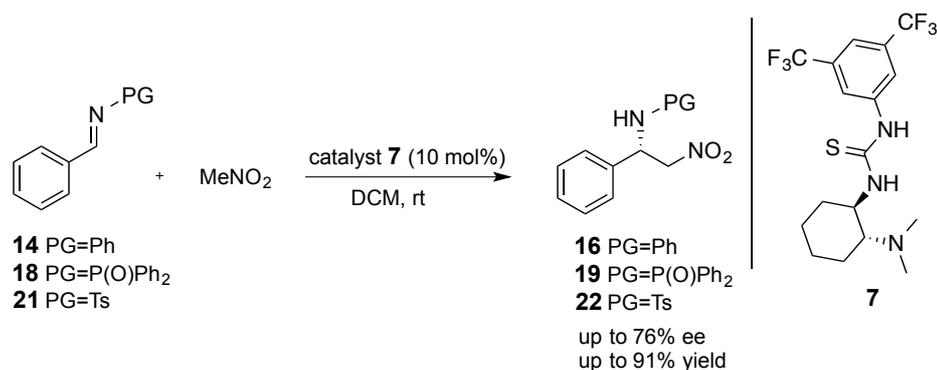
**Scheme 3.** The first example of nitro-Mannich reaction





**Scheme 6.** The first catalytic example of aza-Henry reaction

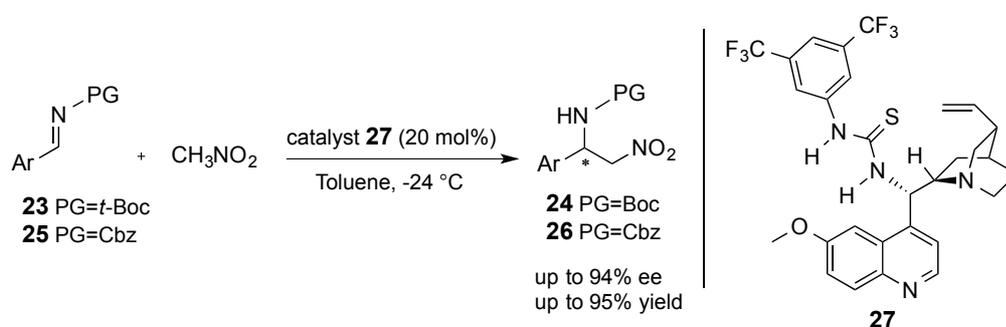
In 2004, Takemoto and his co-workers reported the first enantioselective nitro-Mannich reaction by using a bifunctional organocatalyst **7**. Various *N*-protected imines were reacted with nitromethane by catalyst **7** (Scheme 7).<sup>27</sup>



**Scheme 7.** The first organocatalytic aza-Henry reaction

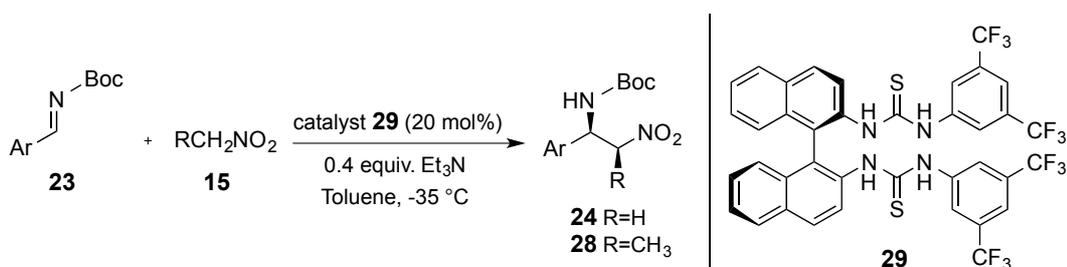
Moderating  $\beta$ -nitroaldol products with high enantioselectivities is not an easy with *t*-Boc protected imines and nitromethane by using bifunctional organocatalysts due to low conversions. Most of the literature examples show that many scientists prefer to work with nitroethane or other nitroalkane derivatives due to their high acidity. (pKa of nitromethane,<sup>28</sup> nitroethane<sup>29</sup> and 1-nitropropane<sup>30</sup> is 10.2, 8.6, 8.92, respectively, in water at 25°C.) Unfortunately, only some of the catalysts work well with nitromethane, and these reactions performed with high catalyst loading scope usually. Sgarzani *et al.* tested several protecting groups on imine with nitromethane using Cinchona alkaloids as catalyst. The most efficient result was obtained with 20 mol% quinine in mesitylene as 61% ee in 18 hours with 90% conversion.<sup>31</sup> They also screened the effect of modification on the catalyst by using *t*-Boc and Cbz protections. Among the modified catalysts, 3,5-bis(trifluoromethyl)benzene

isothiocyanate substituted one **27** gave the best result with *t*-Boc protected imine in 88% ee. The optimized form of that study is shown in Scheme 8.



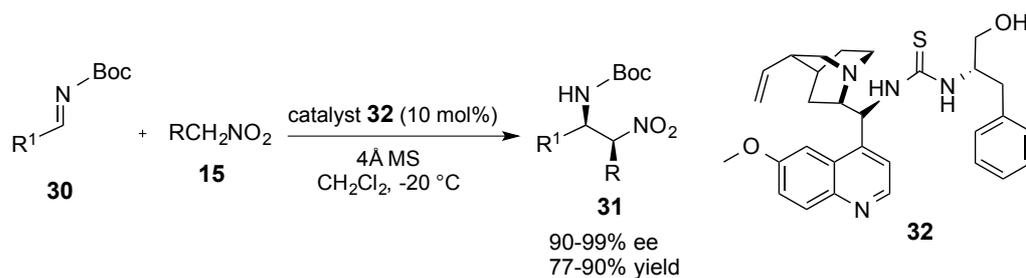
**Scheme 8.** Organocatalytic aza-Henry study with quinine derived catalyst

Rampalakos and Wulff also studied on *t*-Boc imines with nitromethane with their novel bis-thiourea organocatalyst **29** in 2008. Their organocatalyst was based on BINAM as chiral scaffold and the best condition of their reaction was shown in Scheme 9.<sup>32</sup> The maximum enantioselectivity was obtained with 3-chloro substituted imine as 91%. Although they used Et<sub>3</sub>N as additive, yields are quite low. The best chemical yield was obtained with the 1-naphthyl substituted as 65%.



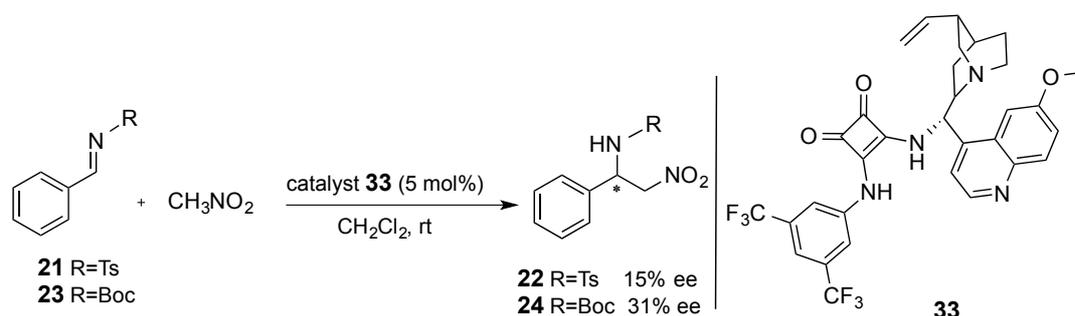
**Scheme 9.** Reaction of *t*-Boc imines and nitroalkanes with bis-thiourea catalyst

In 2012, Zhang *et al.* worked on the same study with quinine based modular bifunctional chiral thiourea **32**. After the optimization, derivatization of the imines was conducted with nitromethane and nitroethane, respectively.<sup>33</sup> Their enantiomeric excess values and yields are excellent in both cases without regarding electronic properties of the substituents (Scheme 10).



**Scheme 10.** Modular bifunctional thiourea with quinine organocatalyst in aza-Henry reaction

The first example of the squaramide type bifunctional catalyst **33** in the aza-Henry reaction was published by Du and co-workers in 2013.<sup>34</sup> Although the main subject was about benzothiazole imines, *t*-Boc and tosyl protected imines were also tested under their optimized condition. However, the enantioselectivities were very low compared with their imine bearing benzothiazole (Scheme 11).



**Scheme 11.** Squaramide type quinone based organocatalyst in aza-Henry reaction

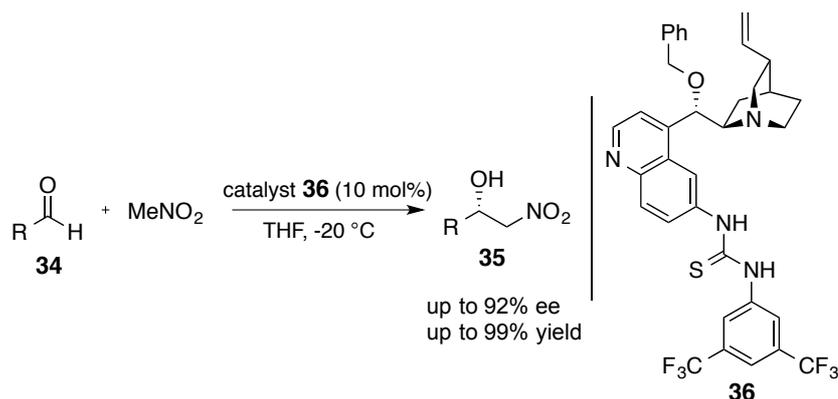
## 1.5. Miscellaneous Reactions with Organocatalysts

### 1.5.1. Henry Reactions

Henry reaction simply occurs between an aldehyde or a ketone and a nitroalkane to yield  $\beta$ -nitroalcohol products.<sup>35</sup> The resultant  $\beta$ -nitroalcohol motif would have generally possess a stereogenic center by the use of prochiral aldehyde or ketone. In the asymmetric version of Henry reaction, it is quite hard to control the

stereoselectivity in the final products due to fast background reaction. Therefore, there is a limitation in the organocatalytic study of Henry reactions.<sup>36</sup>

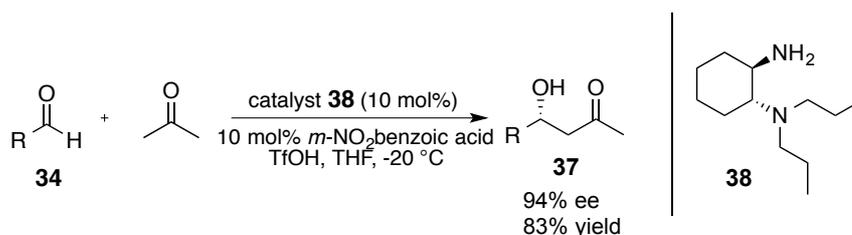
One of the successful studies was done by Hiemstra *et al.* using cinchona derived organocatalyst **36**.<sup>37</sup> The reaction were performed with 10 mol% catalyst in THF to afford  $\beta$ -nitroalcohol products **35** in very high chemical yields and enantioselectivities (Scheme 12).



**Scheme 12.** Organocatalytic Henry reaction by Hiemstra

### 1.5.2. Aldol Reactions

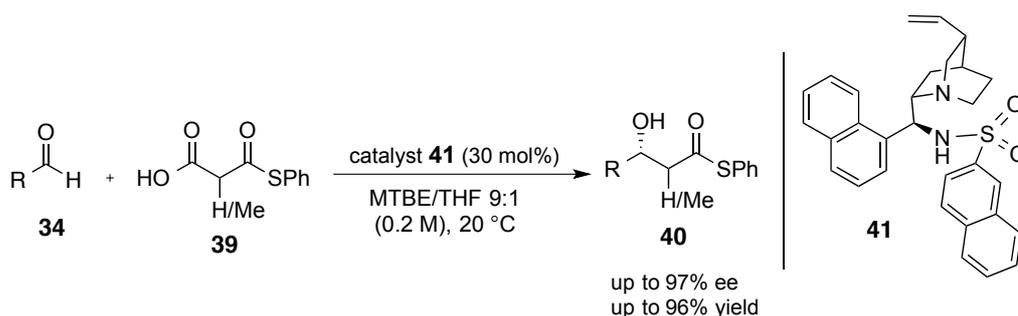
Asymmetric aldol type reactions are also one of the remarkable C-C bond formation reactions for affording highly enantioenriched  $\beta$ -hydroxy carbonyl products.<sup>38</sup> In literature, tremendous amount of organocatalytic reactions exist. Herein, the study of Cheng and co-workers<sup>39</sup> is depicted in Scheme 13, since the organocatalysts chosen resembles our own organocatalyst library backbone. They used primary and tertiary amine based organocatalytic system instead of bifunctional organocatalyst. The best result was obtained with the catalyst **38** in 94% ee and 83% chemical yield.



**Scheme 13.** Organocatalytic aldol reaction by Cheng

### 1.5.2.1. Decarboxylative Aldol Reactions

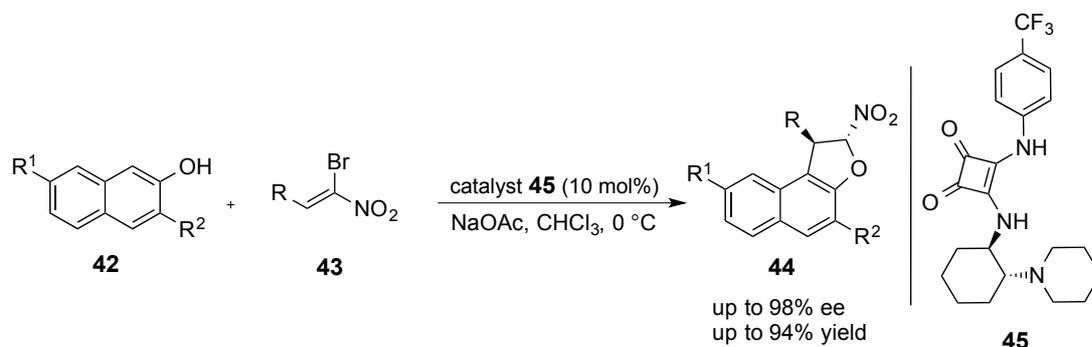
Decarboxylative aldol reactions are a useful way to synthesize  $\beta$ -hydroxy- $\alpha$ -aminoacid<sup>40</sup> and  $\beta$ -hydroxy-thioester<sup>41</sup> derivatives. There is only one example performed by Song *et al.* in literature, with malonic acid half thioesters (MAHTs) **39** and different aldehydes **34** in presence of sulfonamide sulfonamide-based organocatalyst **41** as shown in Scheme 14.



**Scheme 14.** Organocatalytic decarboxylative aldol reaction by Song

### 1.5.3. Friedel-Crafts / Substitution Domino Type Reactions

This type of reactions are used to perform dihydrobenzofuran (DHB) and dihydronaphthofuran skeletons, which are very important pharmaceutical precursors.<sup>42</sup> Nevertheless, the asymmetric study of these skeletons are not very common. In 2013, Alemán and co-workers succeeded to synthesize almost enantiomerically pure *trans*-dihydroarylfuran derivatives **44** starting with (*Z*)-bromonitroalkenes **43** and  $\beta$ -naphthols **42** by squaramide type organocatalyst **45** (Scheme 15).<sup>43</sup>

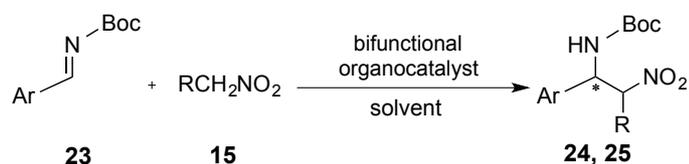


**Scheme 15.** Organocatalytic Friedel-Crafts / substitution domino reaction by Alemán

## 1.6. Aim of the Work

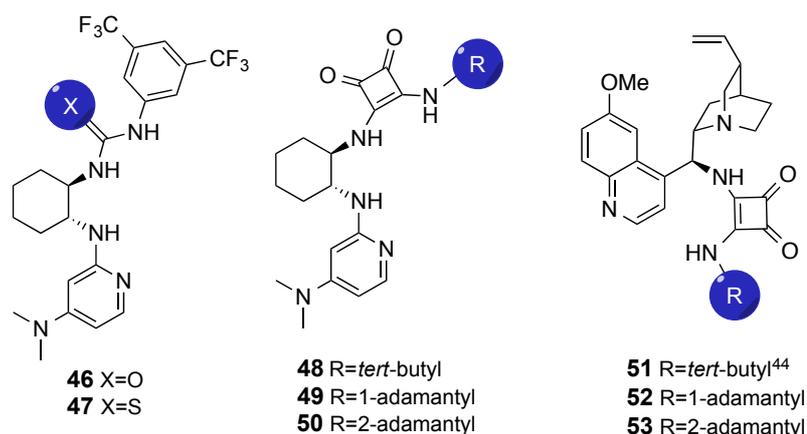
In this thesis, the main objective was to test our research group's bifunctional organocatalysts in different types of reactions

The first part we aimed to optimize aza-Henry reaction of the *t*-Boc protected imines and nitroalkanes to obtain chiral  $\beta$ -nitroamines using 2-aminoDMAP and quinine based squaramide type bifunctional organocatalysts (Scheme 16). These target  $\beta$ -nitroamines were chosen because; they are quite feasible for the corresponding 1,2-diamines,  $\alpha$ -aminoacids, etc.



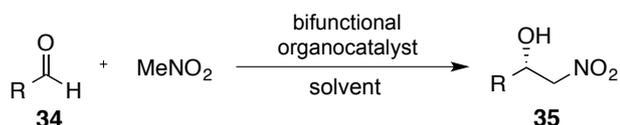
**Scheme 16.** Representative route of the reaction

In our research group, we developed a wide range of bifunctional organocatalyst library, including two main chiral scaffold as 2-aminoDMAP and quinine type Cinchona alkaloid. (Figure 8).

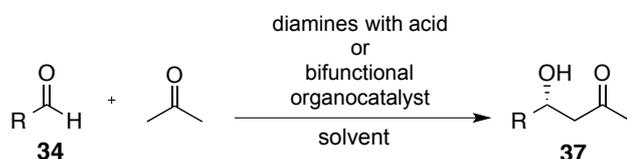


**Figure 8.** Bifunctional organocatalysts developed in our research group

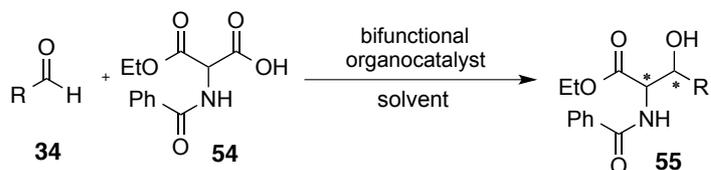
In the second part of the thesis, we planned to test the efficacy of those bifunctional organocatalysts in different types of reactions such as Henry (Scheme 17), aldol (Scheme 18), decarboxylative aldol (Scheme 19) and Friedel-Crafts / substitution type domino (Scheme 19) reactions to see their utility.



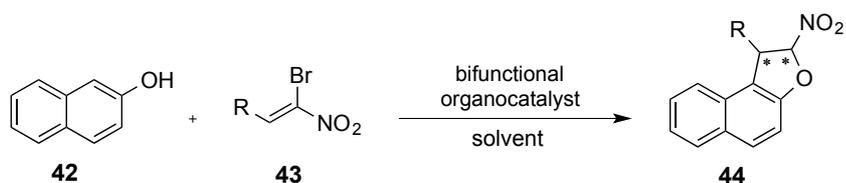
**Scheme 17.** Organocatalytic Henry reaction



**Scheme 18.** Organocatalytic aldol reaction



**Scheme 19.** Organocatalytic decarboxylative aldol reaction



**Scheme 20.** Organocatalytic Friedel-Crafts / substitution domino reaction

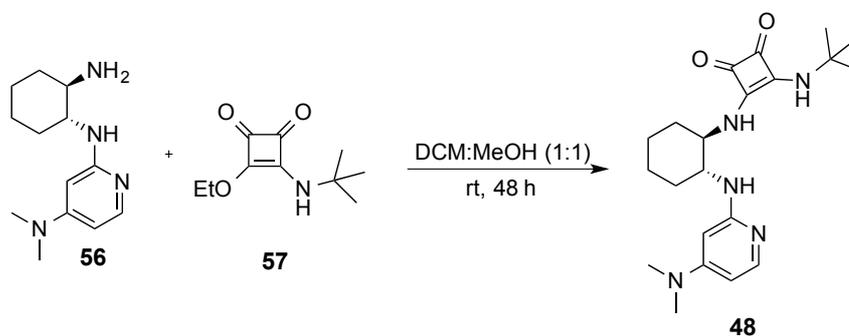
## CHAPTER 2

### RESULTS AND DISCUSSION

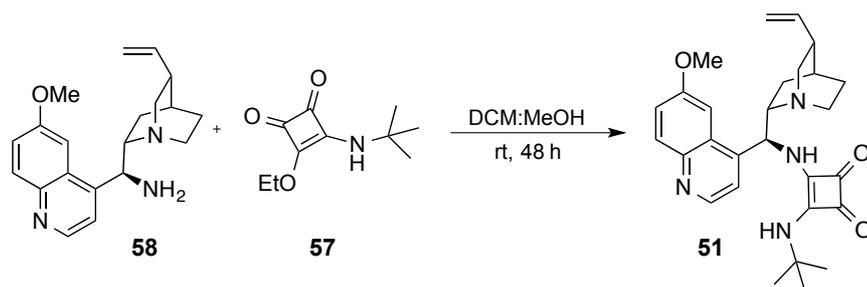
#### 2.1. Synthesis of *t*-Butyl Squaramide Anchored Bifunctional Organocatalysts

In our research group, we have developed many bifunctional organocatalysts. These catalysts can be categorized as two major sets of chiral scaffolds. The first set includes 2-aminoDMAP<sup>45</sup> basic unit derived from (*R,R*)-1,2-cyclohexyldiamine as chiral scaffold, whereas the second set involves the quinine amine<sup>46</sup> as chiral base. By anchoring different acidic moieties, such as urea, thiourea and squaramide motifs, we can synthesize different types of bifunctional organocatalysts.

General route for the synthesis of *t*-butyl squaramide type organocatalyst is used in this thesis depicted in Scheme 21 and 22. After synthesizing 2-aminoDMAP **56** and monosquarate<sup>47</sup> **57** separately, they were coupled in DCM:MeOH mixture at room temperature to obtain desired organocatalyst **48**. By using the same procedure, quinine amine **58** and monosquarate **57** result in organocatalyst **51** (Scheme 22).<sup>48</sup>



**Scheme 21.** Synthetic route for *t*-butyl squaramide / 2-aminoDMAP

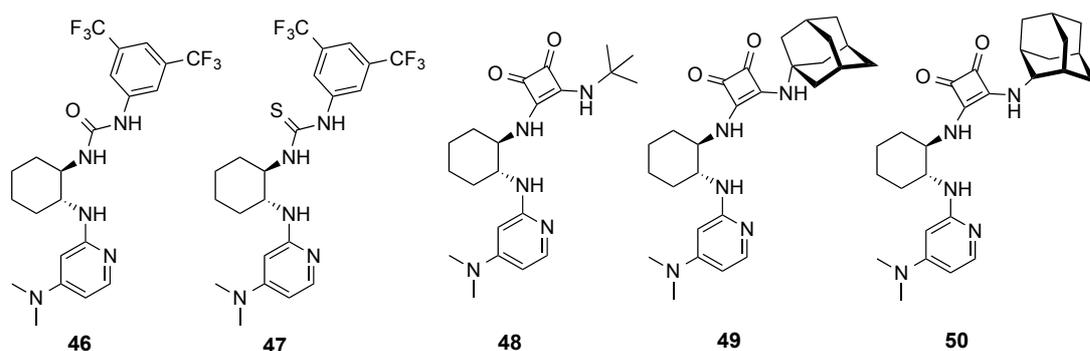


**Scheme 22.** Synthetic route for *t*-butyl squaramide / quinine

## 2.2. Evaluation of the Bifunctional Organocatalysts in Aza-Henry Reaction

### 2.2.1. Aza-Henry Reaction of *t*-Boc Protected Imines with Nitroalkanes

Aza-Henry reaction has been initiated with the organocatalysts, involving 2-aminoDMAP based urea **46**, thiourea **47** and three different squaramides **48-50** as acidic moieties, developed in Tanyeli's research group. Benzaldehyde derived *t*-Boc protected imine **23** was reacted with nitroethane to test the efficiencies of organocatalysts **46-50** in 5 mol% and 2 mol%. The results are given in Table 1. The structures of organocatalysts used in testing reactions are depicted in Figure 9.

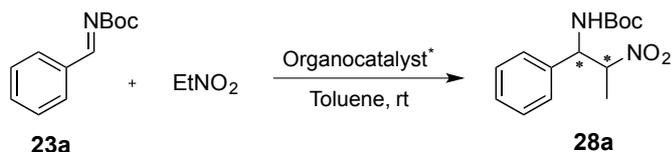


**Figure 9.** 2-AminoDMAP based bifunctional organocatalysts

Among the results, 2 mol% of organocatalyst **48** gave the best result in terms of enantioselectivity of major diastereomeric product (Table 1, entry 8); therefore, it was chosen to be tested for further trials as 1 mol% and 10 mol% catalyst loading. Although 10 mol% catalyst loading (entry 11) afforded high diastereomeric ratio as

92:8 %, we could not get acceptable level of enantioselectivities in both major and minor products. In the case of 1 mol% catalyst loading of **48** (entry 12) slight decrease was observed in terms of diastereoselectivity as 88:12 % compared to 10 mol% catalyst loading. No good ee values were observed.

**Table 1.** Catalyst screening

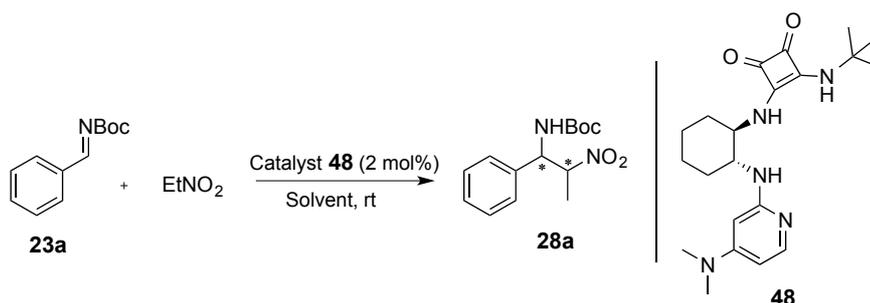


Entry	Catalyst	Cat. Loading (%)	Time (h)	Major ee%	Minor ee%	dr (%)
1	46	5	1.5	17	30	72:28
2	47	5	1.5	9	Rac	93:07
3	48	5	1.5	Rac	Rac	80:20
4	49	5	1.5	5	30	93:07
5	50	5	1.5	Rac	47	80:20
6	46	2	2.5	16	13	71:29
7	47	2	2.5	Rac	3	92:08
<b>8</b>	<b>48</b>	<b>2</b>	<b>2.5</b>	<b>19</b>	<b>30</b>	<b>78:22</b>
9	49	2	2.5	10	33	87:13
10	50	2	2.5	13	36	69:31
11	48	10	1.0	6	36	92:8
12	48	1	3.5	10	20	88:12

All of the experiments are conducted in 0.1 M with full conversion.

We continued with further optimization studies with solvent screening (Table 2). Among the screened solvents DCM proved to be the best one with 31% ee in 45 minutes (entry 3).

The next optimization step was temperature screening performed with 2 mol% *t*-butyl / 2-aminoDMAP **48** in dichloromethane (Table 3). Since the reaction rate was high and it would cause low stereoselectivity, we decided to lower the temperature. Unfortunately decreasing temperature induced fluctuations in enantiomeric excess values.

**Table 2.** Solvent Screening

Entry	Solvent	Time (h/m)	Major ee%	Minor ee%	dr (%)
1	Toluene	2 h	19	30	78:22
2	CH <sub>3</sub> CN	1 h	20	11	96:4
<b>3</b>	<b>DCM</b>	<b>45 min</b>	<b>31</b>	<b>30</b>	<b>79:21</b>
4	Chloroform	1 h	15	18	88:12
5	THF	30 min	10	7	96:4
6	1,4-Dioxane	45 min	13	24	96:4
7	Xylene	30 min	6	16	96:4
8	Hexane	45 min	17	4	89:11

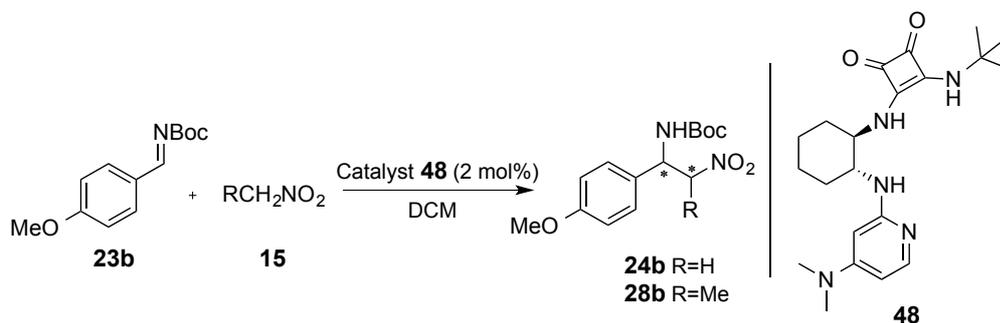
All of the experiments are conducted in 0.1 M with full conversion.

We could not observe consistent results at different temperatures as given in Table 3. Therefore we tracked the reaction with GC-MS and realized that there was a slight decrease in the product amount as well as increase in the starting material at different time intervals during the course of the reaction. (Appendix- C, Figure C. 1. & Figure C. 2., 1 h & 5 h, respectively) We concluded that fluctuated results could be attributed to retro-Mannich type reaction.

**Table 3.** Temperature Screening

Entry	Temperature (°C)	Time (h)	Major ee%	Minor ee%	dr (%)
1	0	2.5	4	11	97:3
2	-15	4	30	27	98:2
<b>3</b>	<b>-30</b>	<b>5</b>	<b>40</b>	<b>26</b>	<b>93:7</b>
4	-40	7	23	7	71:29
<b>5</b>	<b>-50</b>	<b>8</b>	<b>40</b>	<b>4</b>	<b>96:4</b>
6	-60	16	23	17	88:12
7	-75	9	20	10	86:14

All of the experiments are conducted in 0.1 M with full conversion in DCM.

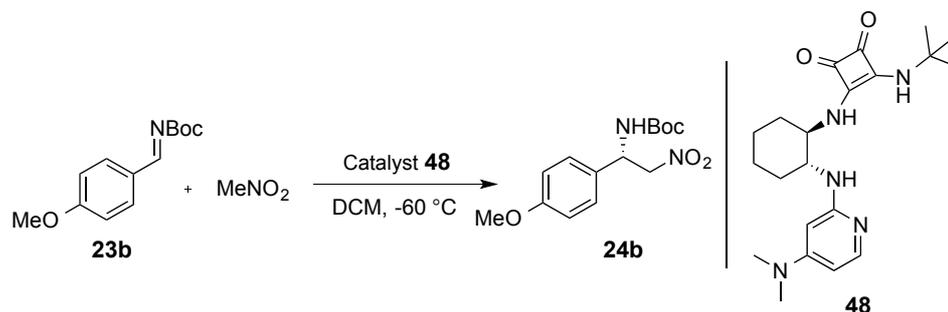
**Table 4.** Temperature Screening with other derivatives

Entry	R	Temperature (°C)	Time (h)	Conversion*	ee (%)	dr (%)
1	Me	-30	24	100	59 <sup>a</sup> /11 <sup>b</sup>	97:3
2	Me	-40	24	100	63 <sup>a</sup> /73 <sup>b</sup>	97:3
3	H	-40	24	70	55	-
4	H	-50	69	45	64	-
5	H	-60	75	28*	66	-

All of the experiments are conducted in 0.2 M. <sup>a</sup>Major diastereomer, <sup>b</sup>minor diastereomer \*Calculated with GC-MS.

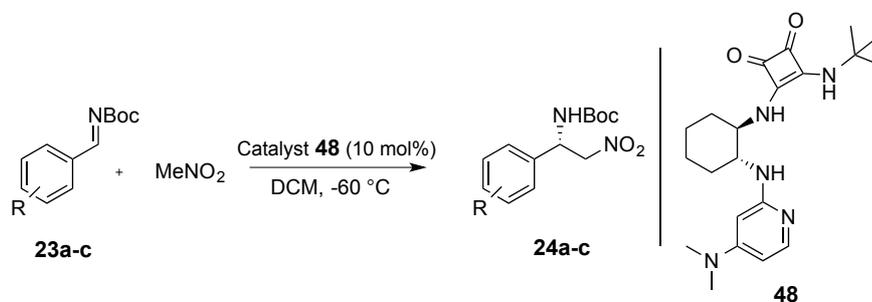
We continued to temperature screening with *p*-anisaldehyde derived imine and nitroalkanes (Table 4). A drastic increase in enantioselectivity was observed with nitroethane at -30 °C and -40 °C as 59 and 63%, respectively, for the major isomer (entries 1 and 2). With nitromethane, a consistent increase was observed in terms of enantioselectivity, as 55, 64 and 66% at -40, -50 and -60 °C, respectively (entries 3, 4 and 5). In contrast to benzaldehyde derived imine case, the reaction durations increased, presumably due to the electron-donating group on the para position and also the low acidity of nitromethane. Since the best result was obtained at -60 °C, we decided to proceed further optimization studies with that temperature and with nitromethane. In order to increase the reaction rate, catalyst loading was increased (Table 5).

Although the best result was obtained with 15 mol% of catalyst as 76% ee, further optimizations were performed with 10 mol% catalyst loading by using 3 different imine derivatives (Table 6). Among the derivatives, the unsubstituted imine gave the best result in 48 hours as 73% ee in 92% conversion (Table 6, entry 1).

**Table 5.** Catalyst loading and concentration screening

Entry	Cat. Loading (%)	Concentration (M)	Time (h)	Conversion (%)	ee (%)
1	2	0.2	75	28	66
2	2	0.1	168	21	31
3	2	0.3	192	75	60
4	5	0.2	50	50	66
5	10	0.2	75	55	70
<b>6</b>	<b>15</b>	<b>0.2</b>	<b>71</b>	<b>75</b>	<b>76</b>

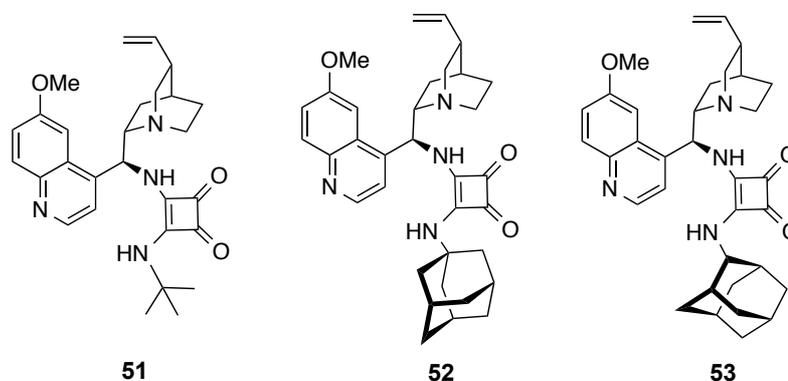
Conversions are calculated with GC-MS.

**Table 6.** Derivatization study with catalyst **48**

Entry	R	Time (h)	Conversion (%)	ee (%)
1		48	92	73
2		75	55	70
3		120	75	57

All of the experiments are conducted with 0.2M. Conversions are calculated with GC-MS.

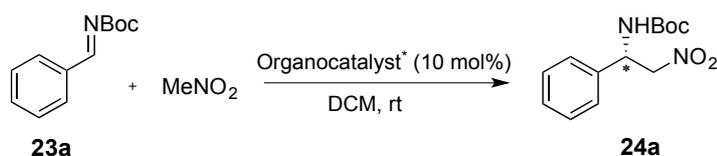
The model aza-Henry reaction was also performed with the quinine based bifunctional organocatalysts **51-53** (Figure 10).



**Figure 10.** Quinine based bifunctional organocatalysts

With these organocatalysts **51-53**, reaction durations were too long by comparing with 2-aminoDMAP organocatalysts **46-50** (Table 7). However, drastic increase was observed in enantioselectivities, in particular with the *t*-butyl / quinine organocatalyst **51** (Table 7, entry 1). Moreover, no retro-Mannich reaction was observed.

**Table 7.** Catalyst screening with the quinine based squaramides



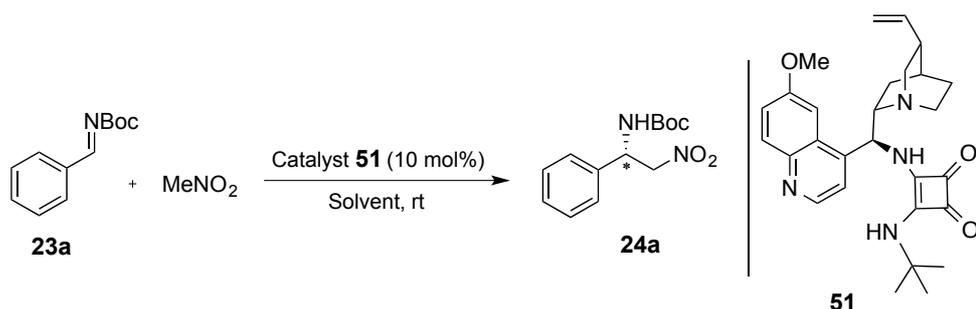
Entry	Catalyst	Time (h)	Conversion (%)	ee (%)
<b>1</b>	<b>51</b>	<b>21 h</b>	<b>95</b>	<b>83</b>
2	52	27 h	98	75
3	53	48 h	95	70

All of the experiments are conducted with 0.2 M. Conversions are calculated with GC-MS.

After choosing the organocatalyst **51** as the best one, further solvent screening studies were done (Table 8). Of the screened solvents, DCM was found to be the

best, once again both in terms of reaction duration and enantioselectivity (Table 8, entry 1). Enantioselectivities in other solvents were quite similar to that of DCM, yet they were not suitable for this reaction since reaction duration was longer. In hexane, the reaction did not occur due to low solubility of both the catalyst and nitromethane (Table 8, entry 3).

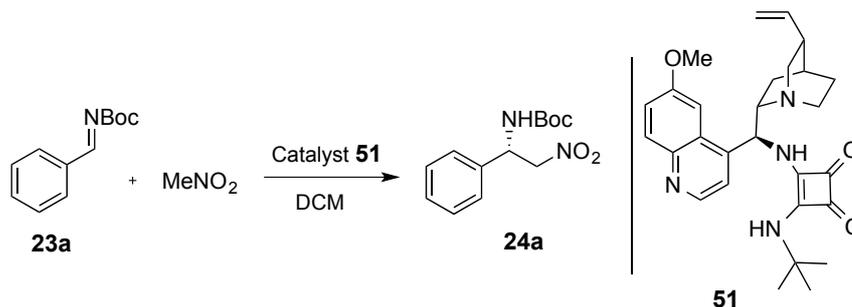
**Table 8.** Solvent screening with catalyst **51**



Entry	Solvent	Time (h)	Conversion (%)	ee (%)
1	DCM	21	95	83
2	Toluene	71	59	80
3	Hexane	No Reaction		
4	Chloroform	71	71	80
5	THF	71	40	77

All of the experiments are conducted with 0.2 M. Conversions are calculated with GC-MS.

As the next step, temperature and concentration parameters were tested (Table 9). The reaction rates were slower than those at room temperature as expected. However, no significant change was observed in enantioselectivities at 0 °C or -40 °C (entries 2 and 3). In addition, at -60 °C, the reaction did not occur. So far, all the reactions were performed with 0.2 M concentration. We also tested 0.1 M and 0.3 M concentrations (entries 5 and 6). Dilution caused a slight increase in enantioselectivity; therefore, we decided to continue with 0.1 M concentration (Table 9, entry 5).

**Table 9.** Additional temperature and concentration screenings with catalyst **51**

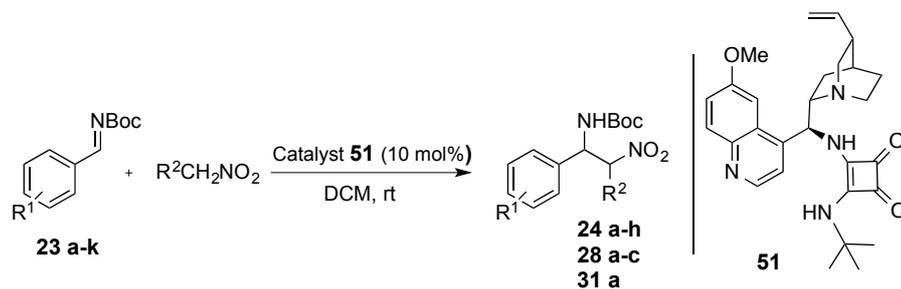
Entry	Cat. Loading (%)	Temperature (°C)	Concentration (M)	Time (h)	Conversion (%)	ee (%)
1	10	r.t.	0.2	21	95	83
2	10	0	0.2	71	92	80
3	10	-40	0.2	120	97	80
4	10	-60	0.2		No Reaction	
<b>5</b>	<b>10</b>	<b>r.t.</b>	<b>0.1</b>	<b>24</b>	<b>96</b>	<b>85</b>
6	10	r.t.	0.3	71	40	77
7	5	r.t.	0.1	36	92	80

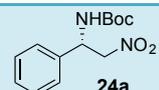
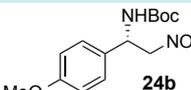
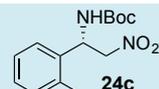
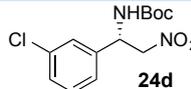
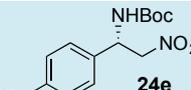
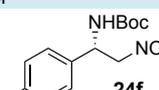
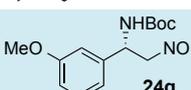
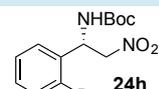
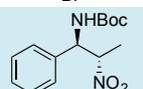
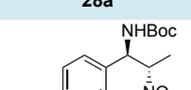
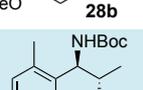
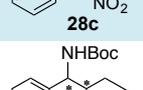
Conversions are calculated with GC-MS.

Consequently, the parameters, 10 mol% of organocatalyst **51**, 0.1 M concentration in DCM at room temperature were determined to be the best condition for aza-Henry reaction.

In the last part of this study, the optimized parameters were applied to different *t*-Boc protected imine derivatives with both nitromethane and nitroethane. The results are summarized in Table 10. It was clearly observed that the electron donating groups on the phenyl ring cause elongation of reaction durations, whereas the electron withdrawing groups cause a decrease in reaction duration. However, the direct effect of these groups on the enantioselectivity could not be observed. All the results were quite similar in terms of enantioselectivity, except for 3-chloro substituted imine, which was found to be 64% ee.

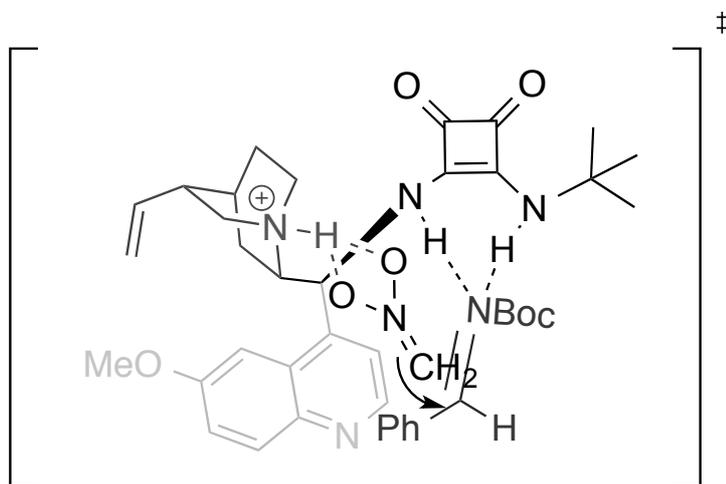
**Table 10.** Derivatization with catalyst **51**



Entry	Products	$R^2$	Time (h)	Conversion (%)	ee (%)	dr <sup>c</sup> (%)
1	 <b>24a</b>	H	24	96	85	-
2	 <b>24b</b>	H	71	91	75	-
3	 <b>24c</b>	H	44	100	91	-
4	 <b>24d</b>	H	21	91	64	-
5	 <b>24e</b>	H	16	100	91	-
6	 <b>24f</b>	H	28	100	91	-
7	 <b>24g</b>	H	25	98	85	-
8	 <b>24h</b>	H	22	93	82	-
9	 <b>28a</b>	Me	22	85	90 <sup>a</sup> /80 <sup>b</sup>	72/28
10	 <b>28b</b>	Me	70	76	44 <sup>a</sup> /36 <sup>b</sup>	75/25
11	 <b>28c</b>	Me	26	100	55 <sup>a</sup> /66 <sup>b</sup>	62/38
12	 <b>31a</b>	Et	20	96	89 <sup>a</sup> /86 <sup>b</sup>	78/22

All of the experiments are conducted with 0.1 M. Conversions are calculated with GC-MS. <sup>a</sup>Anti, <sup>b</sup>syn product. <sup>c</sup>Determined with both GC-MS and HPLC (*anti/syn*).

In order to understand the selectivity of the aza-Henry reaction of nitromethane to *t*-Boc protected imines **23** catalyzed by bifunctional quinine derived squaramide organocatalyst **51** we proposed a transition-state model. Based on the proposed activation modes of nucleophile and electrophile, a plausible transition state model was designed to show the origin of the enantioselectivity. In the transition state, the deprotonation of nitroalkane is achieved by interaction *via* H bond while, the squaramide moiety activated the *t*-Boc imine through double hydrogen bonding. Nitromethane anion attacked the activated imine from the *Si*-face.

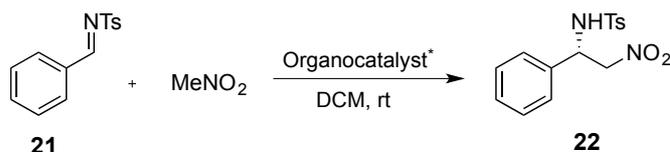


**Figure 11.** Proposed transition state model

## 2.2.2. Aza-Henry Reaction of Tosyl Protected Imines with Nitroalkanes

We have also tested the efficiencies of organocatalysts developed in our group by using tosyl-protected imines with nitroalkanes in aza-Henry reaction (Table 11). The 2-aminoDMAP based ones were tested with 5 mol% catalyst loading. *t*-Butyl squaramide **48** and 1-adamantyl squaramide **49** showed promising results (Table 11, entry 2 and 3, respectively). We decreased the catalyst amount to 2 mol%, and *t*-butyl squaramide **48** gave best result as 52% ee (Table 11, entry 5). Quinine type organocatalysts **50-53** were also screened with 2 mol% catalyst loading; however, none of them gave better result than organocatalyst **48**.

**Table 11.** Catalyst screening and catalyst loading of tosyl imines



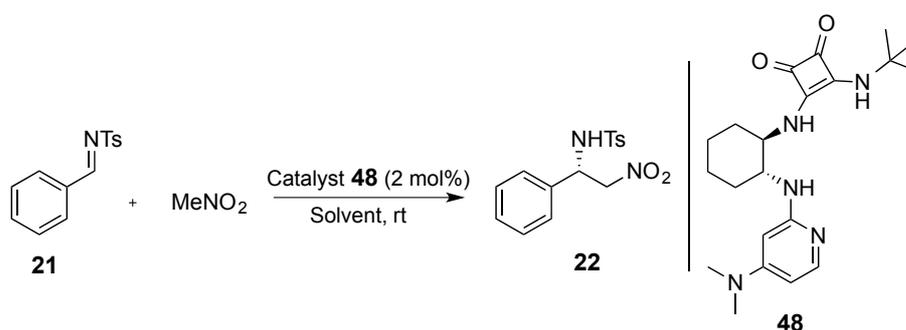
Entry	Catalyst	Cat. Loading (%)	Time (h)	Isolated Yield (%)	ee (%)
1	46	5	21	56	11
2	48	5	21	96	47
3	49	5	21	95	49
4	50	5	21	90	19
<b>5</b>	<b>48</b>	<b>2</b>	<b>24</b>	<b>93</b>	<b>52</b>
6	49	2	7	65	25
7	51	2	31	78	25
8	52	2	75	63	31
9	53	2	72	83	17
10	48	1	24	92	30

All of the experiments are conducted with 0.2 M.

Using 2 mol% organocatalyst **48**, solvent screening was performed (Table 12). In addition to DCM, 6 other solvents were tested in this reaction. Among these solvents acetonitrile was found to be the best as 58% ee in 27 hours with 87% isolated yield (Table 12, entry 3).

The concentration parameter of the reaction was also tested by using acetonitrile. Nevertheless, the result did not change; 0.2 M was better than the others. We also lowered the temperature to 0 °C, the enantioselectivity also decreased. Among these trials of tosyl imine reaction with nitromethane, the best condition was found as 2 mol% of organocatalyst **48**, 0.2 M concentration in acetonitrile at room temperature (Table 12, entry 3).

**Table 12.** Additional screenings of tosyl imines



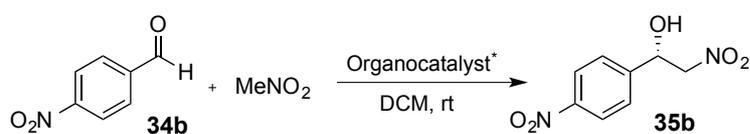
Entry	Solvent	Temperature (°C)	Concentration (M)	Time (h)	Isolated Yield (%)	ee (%)
1	DCM	r.t.	0.2	24	93	52
2	Toluene	r.t.	0.2	7	90	19
3	<b>CH<sub>3</sub>CN</b>	<b>r.t.</b>	<b>0.2</b>	<b>27</b>	<b>87</b>	<b>58</b>
4	Chloroform	r.t.	0.2	31	67	35
5	Xylene	r.t.	0.2	64	81	35
6	1,4-Dioxane	r.t.	0.2	9	90	19
7	Hexane	r.t.	0.2	24	85	43
8	CH <sub>3</sub> CN	r.t.	0.1	72	88	35
9	CH <sub>3</sub> CN	r.t.	0.3	62	95	42
10	CH <sub>3</sub> CN	0	0.2	45	90	50

### 2.3. Evaluation of the Bifunctional Organocatalysts in Henry Reaction

Conducting of Henry reaction with an organocatalyst is very hard, because the background reaction occurs very fast and could cause uncontrollable stereoselectivity. However, we still wanted to see our organocatalysts' utility in the

reaction of aldehydes with nitromethane. For this purpose, *p*-nitrobenzaldehyde (**34b**) and nitromethane underwent the reaction in the presence of 2-aminoDMAP organocatalysts **46-50** (Table 13). Starting with 5 mol% catalyst loading afforded quite fast reaction and resulted in racemic product. Even lowering the catalyst loading to 2 mol%, the results did not change. The best one still belonged to urea / 2-aminoDMAP catalyst **46** with 6% ee.

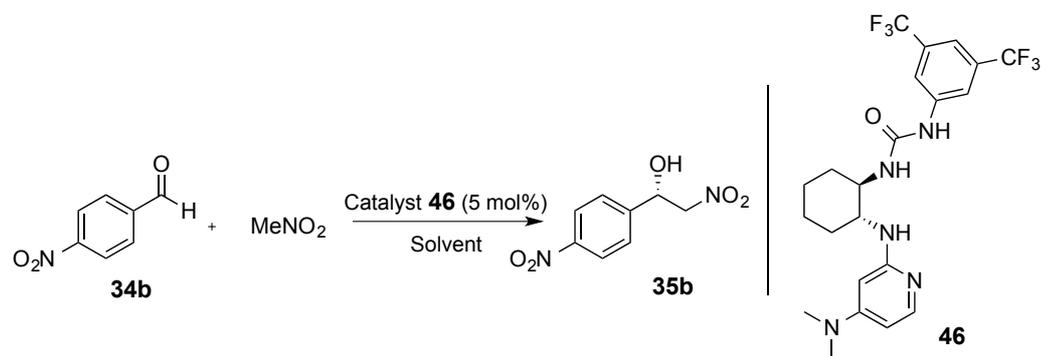
**Table 13.** Catalyst screening and catalyst loading of Henry reaction



Entry	Catalyst	Cat. Loading (%)	Time (h)	Isolated Yield (%)	ee (%)
<b>1</b>	<b>46</b>	<b>5</b>	<b>3</b>	<b>75</b>	<b>6</b>
2	47	5	3	80	Rac
3	48	5	3	90	3
4	49	5	3	80	Rac
5	50	5	3	85	Rac
6	46	2	2	40	Rac
7	47	2	2	40	Rac
8	48	2	2	84	Rac
9	49	2	2	78	Rac
10	50	2	2	80	Rac

All of the experiments are conducted with 0.2 M.

We did trials further with urea catalyst **46** in different solvents and at low temperatures. However, none of the trials led to a good result, we got maximum 7% ee in hexane and 9% ee in toluene at the room temperature (Table 14, entry 2 and 6, respectively).

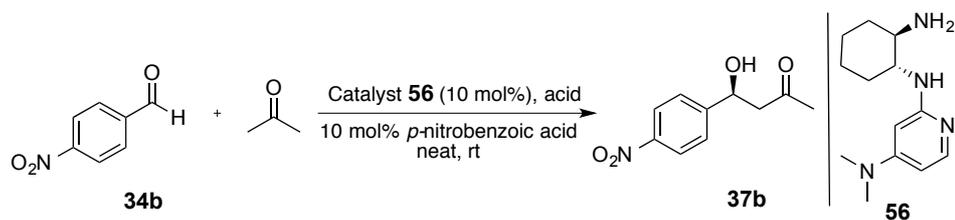
**Table 14.** Additional solvent and temperature screenings of Henry reaction

Entry	Solvent	Temperature (°C)	Time (h)	Isolated Yield (%)	ee (%)
1	DCM	rt	3	75	6
2	Toluene	rt	2	50	9
3	CH <sub>3</sub> CN	rt	3	65	Rac
4	Chloroform	rt	4	73	Rac
5	Xylene	rt	3	20	Rac
6	Hexane	rt	1	95	7
7	DCM	-40	3	50	Rac
8	Toluene	-40	4	53	Rac
9	Hexane	-40	3	75	Rac

All of the experiments are conducted with 0.2M.

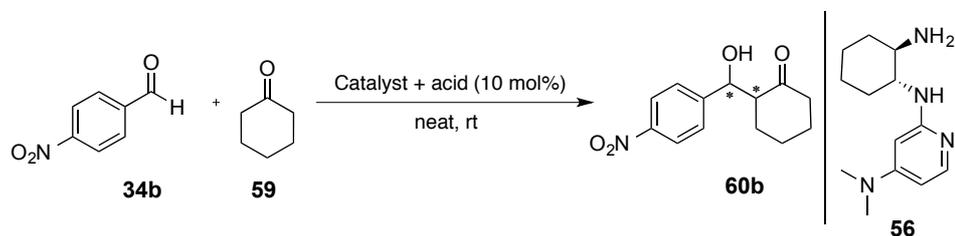
#### 2.4. Evaluation of the 2-aminoDMAP Backbone in Aldol Reaction

In this part of the study, we focused on testing efficacy of primary amine motif of 2-aminoDMAP **56** with Brønsted acid in the aldol reactions. *p*-Nitrobenzaldehyde (**34b**) and acetone were chosen as substrates and the reactions were performed on the basis of literature example.<sup>39</sup> Wide range of Brønsted acids with different molar ratios were screened in the presence or absence of *p*-nitrobenzoic acid at room temperature. The results are summarized in Table 15. The best result was obtained as 43% ee with TFA and AcOH with low isolated yields (entries 5 and 8, respectively).

**Table 15.** Screenings of Aldol reaction with acetone

Entry	Acid	Molar Ratio <sup>a</sup> (organocat:acid)	2 <sup>nd</sup> Acid	Time (h/d)	Isolated yield (%)	ee (%)
1	TfOH	1:1	+	5 days	23	25
2	TfOH	1:2	-	46 h	nd	Rac
3	TfOH	1:3	-	46 h	nd	Rac
4	PTSA	1:1	-	15 days	12	Rac
<b>5</b>	<b>TFA</b>	<b>1:1</b>	-	<b>71 h</b>	<b>38</b>	<b>43</b>
6	TFA	1:1	+	70 h	12	38
7	TFA	1:2	+	94 h	6	21
<b>8</b>	<b>AcOH</b>	<b>1:1</b>	<b>+</b>	<b>94 h</b>	<b>30</b>	<b>43</b>
9	PhCOOH	1:1	+	94 h	nd	35
10	4-NO <sub>2</sub> PhCOOH	1:1	+	94 h	11	29
11	Picric	1:1	+	94 h	28	23
12	TFA	1:1.5	-	48 h	8	25
13 <sup>b</sup>	TFA	1:1.5	-	48 h	4	26
14	-	-	-	67 h	12 <sup>c</sup>	11

<sup>a</sup>With respect to 10 mol% organocatalyst. <sup>b</sup>Isolated salt of TFA and 2-aminoDMAP. <sup>c</sup>Calculated with crude NMR.

**Table 16.** Screenings of Aldol reaction with cyclohexanone (**59**)

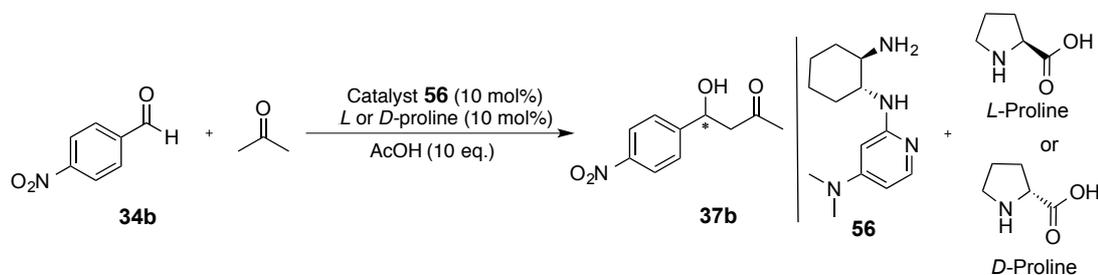
Entry	Catalyst	Acid	Molar Ratio <sup>a</sup> (organocat:acid).	Time (h/d)	Syn ee (%)	Anti ee (%)	dr (%)
1	56	-	-	73 h	6	6	57:43
2	56	TFA	1:1	46 h	7	25	64:36
<b>3<sup>b</sup></b>	<b>56</b>	<b>TFA</b>	<b>1:1.5</b>	<b>46 h</b>	<b>26</b>	<b>24</b>	<b>60:40</b>

<sup>a</sup>With respect to 10 mol% organocatalyst. <sup>b</sup>Isolated salt of TFA and 2-aminoDMAP.

In the further trials, cyclohexanone **59** was replaced with acetone. Unfortunately, no good results could be obtained (Table 16).

The final trial of aldol reaction was performed with binary organocatalyst system (2-aminoDMAP **56** and *L* or *D*-proline) in the reaction of *p*-nitrobenzaldehyde **34b** and acetone (Table 17). Under these circumstances, the reaction rates drastically increased. The resultant aldol products gave the same enantioselectivity as 41% ee in different enantiomeric forms, it could be concluded that the source of enantioselectivity was presumably depending upon proline.

**Table 17.** Screenings of Aldol reaction with binary catalyst system

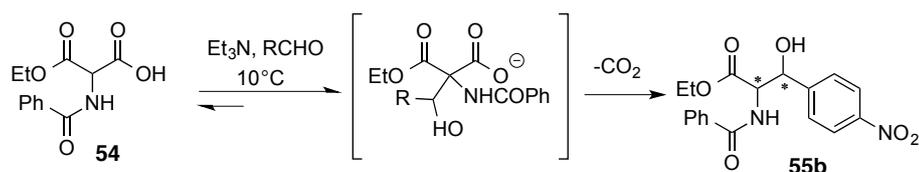


Entry	Catalyst	Acid	Molar Ratio <sup>a</sup> (organocat:acid).	Time (h/d)	Isolated Yield (%)	ee (%)
1	<b>56</b> + <i>L</i> -proline	AcOH	1:10	35 h	52	-41
2	<b>56</b> + <i>D</i> -proline	AcOH	1:10	33 h	50	41

<sup>a</sup>With respect to 10 mol% organocatalyst.

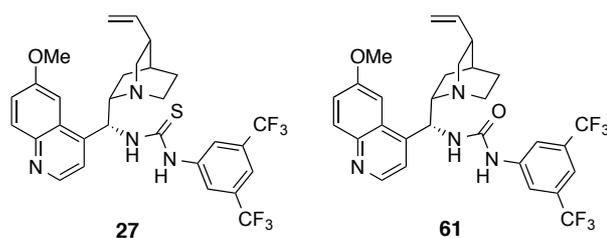
## 2.5. Evaluation of the Bifunctional Organocatalysts in Decarboxylative Aldol Reaction

Decarboxylative studies are quite new in the asymmetric synthesis and there are only a few examples with bifunctional organocatalyst.<sup>40,41</sup> In 2013, Rouden and co-workers showed the excellent diastereoselective (only *anti* product) synthesis of *anti*- $\beta$ -hydroxy- $\alpha$ -amino acids from  $\alpha$ -amido hemimalonates with various aldehydes by using different organic bases (Scheme 23).



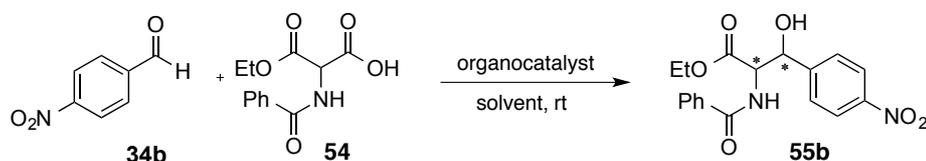
**Scheme 23.** Mechanistic pathway of decarboxylative aldol reaction

Herein, we performed the same reaction with our organocatalysts to get both enantioselectively and diastereoselectively enriched products. The catalyst screening was done with 10 mol% organocatalyst **47**, **48** and cinchona derivatives thiourea **27** urea **61** ones, known in literature, the structures of **27** and **61** are depicted in Figure 11. The most promising result was obtained with organocatalyst **48** as 55% ee (entry 1). Other enantiomer's ee% has not yet been determined, because we have not found an applicable HPLC condition.



**Figure 12.** Cinchona derivative of thiourea **27** and urea **61** organocatalysts

**Table 18.** Screenings of Decarboxylative Aldol reaction with bifunctional organocatalysts



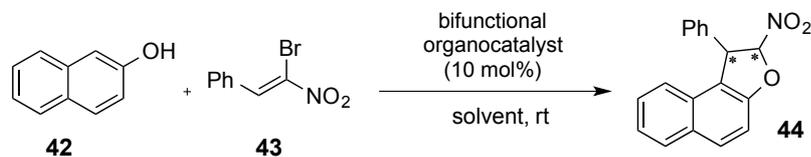
Entry	Catalyst	Solvent	Cat. Loading (%)	Time (d)	ee <sup>a</sup> (%)
1	48	DCM	10	7	55
2	47	DCM	10	7	35
3	48	CH <sub>3</sub> CN	10	5	36
4	61	DCM	10	6	31
5	62	DCM	10	8	40

All the experiments were conducted with 0.13 M. <sup>a</sup>Anti product.

## 2.6. Evaluation of the Bifunctional Organocatalysts in Friedel-Crafts/Substitution Domino Reaction

Domino reactions are another trending topic in organocatalytic studies in the recent years.<sup>49,50</sup> Friedel-Crafts/substitution is the most common and widely used C-C bond forming reaction in synthetic organic chemistry. In this part of the thesis, it was chosen as the key step in domino reaction to afford disubstituted dihydronaphthofuran derivatives possessing two chiral centers in enantiomerically enriched form. For this purpose, (*Z*)-(2-bromo-2-nitrovinyl)benzene (**43**) and  $\beta$ -naphthol (**42**) were used to perform model organocatalytic Friedel-Crafts/substitution domino type reaction. Initial studies involved the screening studies of 2-aminoDMAP based organocatalyst **48**, **49**, **50** and quinine based organocatalyst **51**, **52**, **53**. The results are summarized in Table 19. First experiment was carried out with 10 mol% organocatalyst **51** in chloroform at room temperature and monitored by TLC and directly afforded with one diastereomer due to the stereospecific S<sub>N</sub>2 type reaction. Although HPLC measurement of this product showed promising result as 70% ee, the reaction rate was too slow and the chemical yield was almost 50% after 48 hours (entry 1). This is presumably due to the HBr evolved during the course of the reaction that would block the active site of the catalyst, thus leads a decrease in the reaction rate.<sup>44</sup> In order to prevent the inhibition factor, inorganic bases were used. Fortunately, we observed the positive effect in terms of reaction duration as full conversion for 24 h (entry 5). Of the screened organocatalysts, *t*-butyl / quinine **51** proved to be the best one. Further base screening was done with Cs<sub>2</sub>CO<sub>3</sub> and drastic decrease was observed in terms of reaction duration for 1 hour in 69% ee (entry 8). When the reaction was performed in DCM with Cs<sub>2</sub>CO<sub>3</sub>, the reaction completed with full conversion in 10 minutes with quite enantioselectivity as 92% ee (entry 9).

**Table 19.** Screenings of Friedel-Crafts / Substitution Domino Reaction with bifunctional organocatalysts



Entry <sup>a</sup>	Catalyst	Solvent	Base	Time (h/m)	ee%
1 <sup>b</sup>	51	CHCl <sub>3</sub>	-	48 h	70
2	48	CHCl <sub>3</sub>	NaOAc	26 h	5
3	49	CHCl <sub>3</sub>	NaOAc	26.5 h	7
4	50	CHCl <sub>3</sub>	NaOAc	26 h	Rac
5	51	CHCl <sub>3</sub>	NaOAc	24 h	65
6	52	CHCl <sub>3</sub>	NaOAc	24 h	50
7	53	CHCl <sub>3</sub>	NaOAc	22 h	49
8	51	CHCl <sub>3</sub>	Cs <sub>2</sub> CO <sub>3</sub>	1 h	69
<b>9</b>	<b>51</b>	<b>DCM</b>	<b>Cs<sub>2</sub>CO<sub>3</sub></b>	<b>10 mins</b>	<b>92</b>

<sup>a</sup>All the experiments were conducted with 0.5 M with full conversion. Bases were used 1 equivalent (except entry 1). <sup>b</sup>50% conversion was obtained.

## CHAPTER 3

### EXPERIMENTAL

#### 3.1 Materials and Methods

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  on Bruker Spectrospin Avance DPX-400 spectrometer. The chemical shifts were reported in ppm relative to  $\text{CDCl}_3$  ( $\delta$  7.26 and 77.0 for  $^1\text{H}$  and  $^{13}\text{C}$  NMR, respectively) as the internal standard, and the data are specified as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), bd (broad doublet), t (triplet), td (triplet of doublet), tt (triplet of triplet), m (multiplet) and coupling constants ( $J$ ) in Hertz (Hz).

HPLC chromatograms were recorded on Dionex & Thermo-Finnigan HPLC system. Daicel ADH, IA, ODH, ASH, OJH chiral columns were used with different solvent systems. The mass spectra were recorded on Thermo Scientific DSQ II Single Quadrupole GC/MS. HRMS data were detected on a Agilent 6224 TOF LC/ MS at UNAM, Bilkent University.

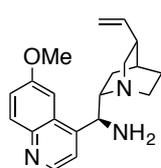
Infrared measurements were done on Thermo Nicolet IS10 ATR / FT-IR spectrophotometer. Optical rotations were measured with Rudolph Scientific Autopol III polarimeter and reported as follows  $[\alpha]_D^T$  (c is in gram per 100 mL solvent). Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Using Merck Silica Gel 60, flash column chromatographies were performed. Reactions were monitored by thin layer chromatography using precoated silica gel plates (Merck Silica Gel PF-254), visualized by UV-light and polymolybden phosphoric acid in ethanol and potassium permanganate stain as appropriate. All extracts were dried over anhydrous magnesium sulphate and solutions were concentrated under vacuum by using rotary evaporator.

Only characterization data of novel compounds are given in experimental section and related literature is cited.

Compounds names were written with ChemBioDraw 14.0.

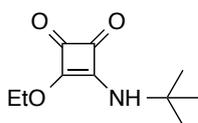
### 3.2 Synthesis of 9-amino (9-deoxy)epihydroquinine 58



The following literature procedure is performed<sup>46</sup>: Quinine (3.24 g, 10.0 mmol) and triphenylphosphine (3.15 g, 12.0 mmol) were dissolved in 50 mL of dry THF and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (2.43 g, 12.0 mmol) was added all at once. Then solution of diphenyl phosphoryl azide (3.30 g, 12.0 mmol) in 20 mL of dry THF was added dropwise at 0 °C. The mixture was allowed to warm to room temperature. After being stirred for 12h, the solution was heated to 50 °C for 2 h. Then triphenylphosphine (3.41 g, 13.0 mmol) was added and heating was maintained until the gas evolution has ceased (2 h). The solution was cooled to room temperature, and 1 mL of water was added and the solution was stirred for 3 h. Solvents were removed in vacuo and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and 10% hydrochloric acid (1:1, 100 mL). The aqueous phase was washed with CH<sub>2</sub>Cl<sub>2</sub> (4 × 50 mL). Then the aqueous phase was made alkaline with excess aqueous ammonia and was washed with CH<sub>2</sub>Cl<sub>2</sub> (4 × 50 mL). The combined organic phases was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/MeOH/aq. NH<sub>4</sub>OH = 50/50/1 as eluent) affording the title compound as yellowish viscous oil in 75% isolated yield.

Spectroscopic data are in accordance with the literature.<sup>46</sup>

### 3.3 Synthesis of *t*-Butyl Mono-Squaramide 57

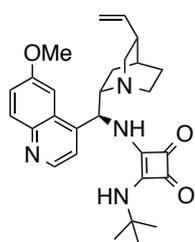


Squaric acid (4.3 mmol, 500 mg) was refluxed under argon atmosphere during 3h by using absolute ethanol (7 mL). Then the solvent was evaporated under vacuum, and this procedure is

repeated for three times for 30 minutes reflux. The last evaporation affords diethyl squarate as very light yellow oil. In order to make the mono-squaramide, the diethyl squarate is added to *tert*-butylamine (1 eq) solution in 4 mL DCM and stirred for 24 hours at room temperature. The product was purified with silica gel and EtOAc:Hexane (1:3) as eluent, obtained with 90% yield as white solid.

Spectroscopic data are in accordance with the literature.<sup>47</sup>

### 3.4 Synthesis of *t*-Butyl Squaramide / Quinine Catalyst **51**



Mono-squaramide ester (0.2 mmol) was added to a solution of quinine **58** (0.2 mmol) in DCM:MeOH (1:1) mixture. The reaction was stirred 48 hours at room temperature and directly loaded on to silica gel column, which is eluted with gradient EtOAc:MeOH. Product was obtained with 92% yield as slightly white solid.

Mp= 260 °C (decomposed).

Optical rotation was determined as  $[\alpha]_D^{20} = -180.2^\circ$  (c=0.1, CH<sub>2</sub>Cl<sub>2</sub>).

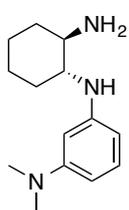
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 8.69 (d, *J*=4.5 Hz, 1H), 8.03 (d, *J*=9.2 Hz, 1H), 7.79 (bs, 1H), 7.54 (d, *J*=4.6 Hz, 1H), 7.41 (dd, *J*=9.1, 2.6 Hz, 1H), 6.08 (bs, 1H), 5.74 (ddd, *J*= 17.4, 10.1, 7.3 Hz, 1H), 4.95 (dd, *J*=16.3, 9.7 Hz, 1H), 3.96 (s, 3H), 3.44 (bs, 2H), 3.21-3.10 (m, 1H), 2.72 (bd, *J*=11.4 Hz, 2H), 2.26 (bs, 1H), 1.71-1.51 (m, 3H), 1.48-1.42 (m, 1H), 1.19 (s, 9H), 0.8 (bs, 1H). 2 protons are not located.

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 182.3, 181.5, 168.3, 168.1, 158.8, 147.8, 144.9, 144.0, 140.6, 131.8, 128.0, 122.5, 119.7, 115.3, 101.6, 60.4, 56.2, 55.9, 53.3, 41.0, 39.1, 30.6, 29.8, 27.5, 27.4, 25.8.

**IR(neat)**: 3362, 3226, 2979, 1793, 1653, 1624, 1585, 1526, 1474, 1367, 1223 cm<sup>-1</sup>.

**HRMS**: Exact mass calculated for [C<sub>28</sub>H<sub>34</sub>N<sub>4</sub>O<sub>3</sub>+H]<sup>+</sup>: 475.2709; found as 475.2712.

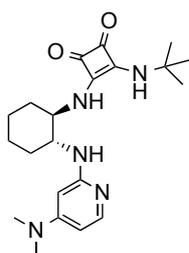
### 3.5 Synthesis of 2-AminoDMAP 56



CuBr (0.2 mmol, 200.8 mg) and K<sub>3</sub>PO<sub>4</sub> (2.0 mmol, 2.9 g) were added to an oven-dried Schlenk tube and this tube was evacuated and backfilled with argon thrice. (*R,R*)-cyclohexanediamine (1.2 mmol, 960 mg) and 2-bromoDMAP (1 mmol, 1.4 g) were added and same procedure was applied. Dry 1,4-dioxane (7.8 mL) was added under argon atmosphere and the reaction mixture was stirred at 110 °C for 24 hours. The resulting green-blue suspension mixture was left at room temperature for cooling. Then 2 mL of water and 2 mL of concentrated ammonia solution was added. The resulting dark blue solution was extracted with dichloromethane (3 x 25 mL). Then organic phase was washed with brine and dried over MgSO<sub>4</sub>. The product was purified by flash column chromatography on silica gel using gradient saturated DCM (using with ammonia solution) and MeOH. Desired product **66** was obtained as light brown solid with 40% yield.

Spectroscopic data are in accordance with the literature.<sup>45</sup>

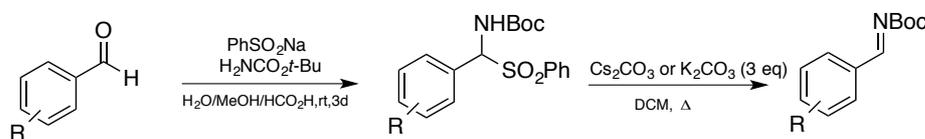
### 3.6 Synthesis of *t*-Butyl squaramide / 2-aminoDMAP catalyst 48



Mono-squaramide ester **57** (0.2 mmol) was added to a solution of 2-aminoDMAP **56** (0.2 mmol) in DCM:MeOH (1:1) mixture. The reaction was stirred 48 hours at room temperature and directly loaded on to silica gel column, which is eluted with gradient saturated DCM:MeOH. Product was afforded with 90% yield as slightly light brown solid.

Spectroscopic data are in accordance with the literature.<sup>48</sup>

### 3.7 Synthesis of *t*-Boc Protected Imines



The following slightly modified literature procedure is performed<sup>51-53</sup>:

The aldehyde (15 mmol) was suspended in 2:1:0.7 H<sub>2</sub>O/MeOH/HCO<sub>2</sub>H (40 mL) and stirred until the mixture became homogeneous. (Gentle heating was necessary to achieve complete dissolution in most cases). Sodium benzenesulfonic acid (20 mmol) and *tert*-butyl carbamate (10 mmol) were added sequentially. The reaction mixture was stirred for 3 days, the solids collected by filtration and triturated with H<sub>2</sub>O and then diethylether to leave the sulfonylcarbamate.

A suspension of flame dried Cs<sub>2</sub>CO<sub>3</sub> or K<sub>2</sub>CO<sub>3</sub> (6.0 mmol) in a solution of the sulfonylcarbamate (2.0 mmol) in dry, alcohol-free CH<sub>2</sub>Cl<sub>2</sub> (40 mL) was heated at reflux. Small aliquots were removed periodically, filtered, and analyzed by <sup>1</sup>H NMR spectroscopy (using CDCl<sub>3</sub> treated with K<sub>2</sub>CO<sub>3</sub> to remove trace HCl which hydrolyzes the *N*-Boc imine) to confirm completion of the reaction (1-4 h). The reaction mixture was cooled to room temperature, diluted with hexane (40 mL), stirred for 10 min, and filtered. The filtrate was concentrated in vacuo at < 20 °C to leave the *N*-Boc imine.

### 3.8 General Procedure for Aza-Henry Reaction: Nitromethane Addition to *t*-Boc Protected Imines

*Racemic synthesis;*

Imine (0.1 mmol), nitromethane (0.35 mmol) and Et<sub>3</sub>N (0.01 mmol) were dissolved in DCM (1 mL) and stirred at room temperature. The reaction was monitored with GC-MS upon the consumption of limiting reactant, directly loaded into column chromatography. EtOAc:Hexane mixtures was used as eluent to purify the products.

*Asymmetric synthesis;*

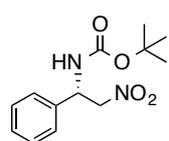
Imine (0.1 mmol), *t*-butyl/quinine **51** (0.01 mmol) was dissolved in DCM (0.8 mL) for half an hour. Then nitromethane (0.35 mmol) was added to solution and stirred at room temperature. The reaction was monitored with GC-MS upon the consumption of limiting reactant, directly loaded into column chromatography. EtOAc:Hexane mixtures was used as eluent to purify the products.

The following GC-MS method was performed on Thermo TR-5MS 30m x 0.25 mm ID x 0.25  $\mu$ m film, 5% Phenyl Polysilphenylene-siloxane column (260F142P) to track the reactions: Flow = 1.0 mL/min, oven = 0.1 min at 50 °C, to 200 °C at 20 °C/min, 0.1 min at 200 °C; to 260 °C at 10 °C/min, 3.0 min at 260 °C, inlet=220 °C, MS-Transfer Line=250 °C.

### 3.8.1 Synthesis of *tert*-butyl (*S*)-(2-nitro-1-phenylethyl) carbamate (**24a**)

General procedure starting from nitromethane and *tert*-butyl (phenylmethylene) carbamate afforded to desired chiral product with 96% conversion and 85% ee in 24 h as a white solid.

Optical rotation was determined as  $[\alpha]_D^{25} = +18.48^\circ$  ( $c=0.25$ ,  $\text{CH}_2\text{Cl}_2$ ).



$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38-7.35 (m, 2H), 7.32-7.27 (m, 3H), 5.37 (bs, 2H), 4.83 (bs, 1H), 4.73-4.65 (m, 1H), 1.43 (s, 9H).

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  154.9, 136.9, 129.3, 128.8, 126.5, 80.8, 79.0, 52.9, 28.4.

**HPLC**: Chiralpak ADH column, 95:5 (n-hexane/*i*-PrOH), flow rate 1.0 mL/min, 210 nm, temp=25 °C,  $t_{\text{major}} = 29.3$  min,  $t_{\text{minor}} = 31.6$  min.

**GC-MS**: Retention time: 10.57 min.

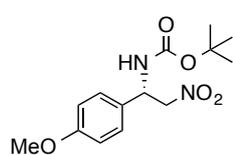
$[\text{M}/\text{Z}]^+ = 57.08, 91.04, 117.05, 119.05, 132.06, 164.03, 177.03, 224.01$ .

**IR(neat)**: 3376, 2977, 1685, 1545, 1517, 1255, 1165, 1025, 796, 699  $\text{cm}^{-1}$

### 3.8.2 Synthesis of *tert*-butyl (*S*)-(1-(4-methoxyphenyl)-2-nitroethyl) carbamate (24b)

General procedure starting from nitromethane and *N*-Boc-4-methoxybenzylideneamine afforded to desired chiral product with 91% conversion and 75% ee in 71 h as a white solid.

Optical rotation was determined as  $[\alpha]_D^{25} = +19.36^\circ$  (c=0.25, CH<sub>2</sub>Cl<sub>2</sub>).



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.24 (d, 2H), 6.91 (d, 2H), 5.36-5.30 (m, 1H), 5.24 (d, *J*=7.3 Hz, 1H), 4.85 (bs, 1H), 4.68 (dd, *J*=12.5, 5.8 Hz, 1H), 3.82 (s, 3H), 1.45 (s, 9H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 159.7, 154.7, 128.9, 127.6, 114.5, 136.9, 129.2, 128.7, 126.3, 80.5, 55.3, 52.5, 28.3.

**HPLC:** Chiralpak OJH, 92:8 (n-hexane/*i*-PrOH), flow rate 1.0 mL/min, 210 nm, temp=25 °C, *t*<sub>major</sub>= 43.7 min, *t*<sub>minor</sub>= 48.9 min.

**GC-MS:** Retention time: 10.99 min.

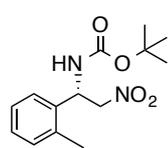
$[M/Z]^+ = 57.09, 77.03, 104.03, 106.05, 120.05, 149.99, 162.92, 164.05$ .

**IR(neat):** 3362, 2983, 1689, 1551, 1513, 1247, 1164, 1020, 830, 541 cm<sup>-1</sup>

### 3.8.3 Synthesis of *tert*-butyl (*S*)-(2-nitro-1-(*o*-tolyl)ethyl) carbamate (24c)

General procedure starting from nitromethane and *tert*-Butyl *N*-[(2-methylphenyl)methylene] carbamate afforded to desired chiral product with full conversion and 91% ee in 44 h as a white solid.

Optical rotation was determined as  $[\alpha]_D^{25} = +28.08^\circ$  (c=0.25, CH<sub>2</sub>Cl<sub>2</sub>).



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.22 (bs, 4H), 5.65 (d, *J*=5.49 Hz, 1H), 5.22 (bs, 1H), 4.79 (bs, 1H), 4.75 (bs, 1H), 4.66 (bs, 1H), 2.44 (s, 3H), 1.42 (s, 9H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  154.8, 135.9, 135.4, 131.3, 128.6, 126.9, 125.1, 78.1, 49.5, 29.3, 19.2.

**HPLC:** Chiralpak ODH, 90:10 (n-hexane/i-PrOH), flow rate 1.0 mL/min, 210 nm, temp=25 °C,  $t_{\text{minor}}$ = 17.0 min,  $t_{\text{major}}$ = 31.1 min.

**GC-MS:** Retention time: 11.02 min.

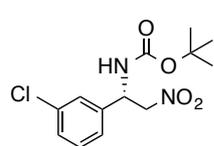
$[\text{M}/\text{Z}]^+ = 57.09, 59.07, 91.05, 117.06, 119.07, 132.07, 164.04, 177.05, 224.03.$

**IR(neat):** 3363, 2980, 1688, 1541, 1526, 1251  $\text{cm}^{-1}$

### 3.8.4 Synthesis of *tert*-butyl (*S*)-(1-(3-chlorophenyl)-2-nitroethyl) carbamate (24d)

General procedure starting from nitromethane and *tert*-Butyl N-[(3-chlorophenyl)methylene] carbamate afforded to desired chiral product with 91% conversion and 64% ee in 21h as a white solid.

Optical rotation was determined as  $[\alpha]_D^{25} = +16.16^\circ$  ( $c=0.25$ ,  $\text{CH}_2\text{Cl}_2$ ).



$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.33-7.27 (m, 4H), 5.48 (bs, 1H), 5.36 (bs, 1H), 4.81 (bs, 1H), 4.73-4.62 (m, 1H), 1.43 (s, 9H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  154.9, 139.1, 135.1, 130.4, 128.9, 126.6, 124.5, 80.9, 78.6, 52.3, 28.2.

**HPLC:** Chiralpak ADH, 90:10 (n-hexane/i-PrOH), flow rate 1.0 mL/min, 210 nm, temp=25 °C,  $t_{\text{major}}$ = 10.5 min,  $t_{\text{minor}}$ = 13.9 min.

**GC-MS:** Retention time: 11.95 min.

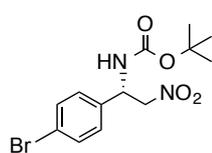
$[\text{M}/\text{Z}]^+ = 57.09, 59.06, 77.03, 103.04, 138.00, 196.95.$

**IR(neat):** 3362, 2978, 2929, 1687, 1556, 1367, 1248, 1158, 696  $\text{cm}^{-1}$

### 3.8.5 Synthesis of *tert*-butyl (*S*)-(1-(4-bromophenyl)-2-nitroethyl) carbamate (24e)

General procedure starting from nitromethane and *tert*-Butyl *N*-[(4-bromo)methylene] carbamate afforded to desired chiral product with full conversion and 91% ee in 16 h as a white solid.

Optical rotation was determined as  $[\alpha]_D^{25} = +18.23^\circ$  ( $c=0.25$ ,  $\text{CH}_2\text{Cl}_2$ ).



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.51 (d,  $J=8.5$ , 2H), 7.19 (d,  $J=8.5$ , 2H), 5.33 (bs, 2H), 4.82 (bs, 1H), 4.74-4.65 (m, 1H), 1.43 (s, 9H).

**$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  154.8, 137.5, 132.4, 131.6, 128.2, 127.8, 122.8, 81.2, 78.7, 52.3, 28.4.

**HPLC**: Chiralpak ADH, 95:5 (n-hexane/*i*-PrOH), flow rate 1.0 mL/min, 210 nm, temp=25 °C,  $t_{\text{major}} = 30.4$  min,  $t_{\text{minor}} = 41.3$  min.

**GC-MS**: Retention time: 13.00 min.

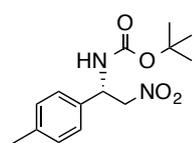
$[\text{M}/\text{Z}]^+ = 57.08, 59.06, 77.05, 102.40, 183.93, 197.96, 240.90, 243.93$ .

**IR(neat)**: 3337, 2977, 2928, 2855, 1697, 1556, 1487, 1367, 1157, 1010  $\text{cm}^{-1}$

### 3.8.6 Synthesis of *tert*-butyl (*S*)-(2-nitro-1-(*p*-tolyl)ethyl) carbamate (24f)

General procedure starting from nitromethane and *N*-[(4-methylphenyl)methylene] carbamate afforded to desired chiral product with full conversion and 91% ee in 28h as a white solid.

Optical rotation was determined as  $[\alpha]_D^{25} = +21.92^\circ$  ( $c=0.25$ ,  $\text{CH}_2\text{Cl}_2$ ).



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.18 (s, 4H), 5.33 (bs, 2H), 4.82 (bs, 1H), 4.72-4.62 (m, 1H), 2.33 (s, 3H), 1.43 (s, 9H).

**$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  154.9, 138.7, 134.0, 129.9, 126.4, 80.7, 79.1, 52.8, 28.4, 21.2.

**HPLC:** Chiralpak ADH, 75:25 (n-hexane/i-PrOH), flow rate 1.0 mL/min, 210 nm, temp=5 °C,  $t_{\text{major}}=15.5$  min,  $t_{\text{minor}}=18.1$  min.

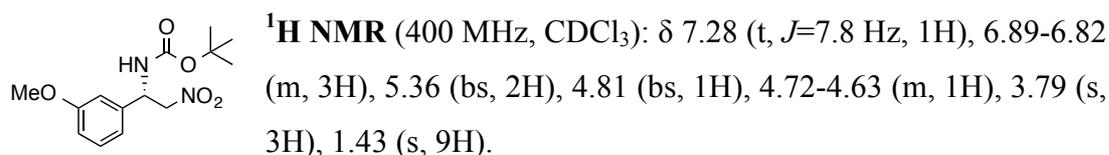
**GC-MS:** Retention time: 11.35 min.

$[M/Z]^+=57.09, 59.06, 91.04, 118.05, 120.06, 164.00, 177.04, 178.05$ .

**IR(neat):** 3365, 2979, 2929, 1685, 1554, 1515, 1367, 1251, 1164, 817  $\text{cm}^{-1}$

### 3.8.7 Synthesis of *tert*-butyl (*S*)-(1-(3-methoxyphenyl)-2-nitroethyl) carbamate (24g)

General procedure starting from nitromethane and *N*-[(3-methoxyphenyl)methylene] carbamate afforded to desired chiral product with 98% conversion and 85% ee in 25 h as a white solid.



**$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  160.2, 154.9, 138.7, 130.4, 118.5, 113.9, 112.5, 80.8, 78.9, 55.4, 52.9, 28.4.

**HPLC:** Chiralpak IA, 90:10 (n-hexane/i-PrOH), flow rate 1.0 mL/min, 210 nm, temp=25 °C,  $t_{\text{major}}=17.6$  min,  $t_{\text{minor}}=25.2$  min.

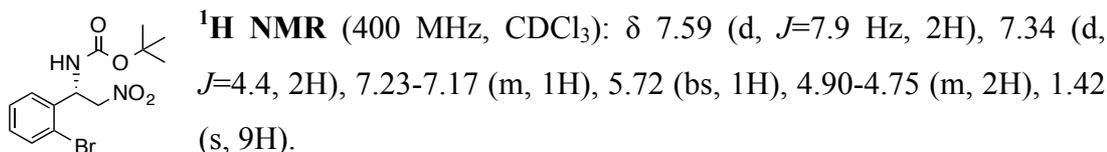
**GC-MS:** Retention time: 12.26 min.

$[M/Z]^+=57.08, 59.05, 77.04, 105.05, 119.05, 134.04, 150.07, 193.01, 194.04$ .

**IR(neat):** 3318, 2972, 2850, 2372, 1749, 1716, 1489, 1474, 1396, 1068, 1073  $\text{cm}^{-1}$

### 3.8.8 Synthesis of *tert*-butyl (*S*)-(1-(2-bromophenyl)-2-nitroethyl) carbamate (24h)

General procedure starting from nitromethane and *N*-[(2-bromophenyl)methylene] carbamate afforded to desired chiral product with 93% conversion and 82% ee in 22 h as a white solid.



**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ154.6, 135.5, 133.8, 130.3, 128.3, 128.1, 122.9, 80.9, 77.6, 52.7, 28.4.

**HPLC:** Chiralpak ADH, 85:15 (n-hexane/*i*-PrOH), flow rate 1.0 mL/min, 210 nm, temp=25 °C, *t*<sub>major</sub>= 9.1 min, *t*<sub>minor</sub>= 13.0 min.

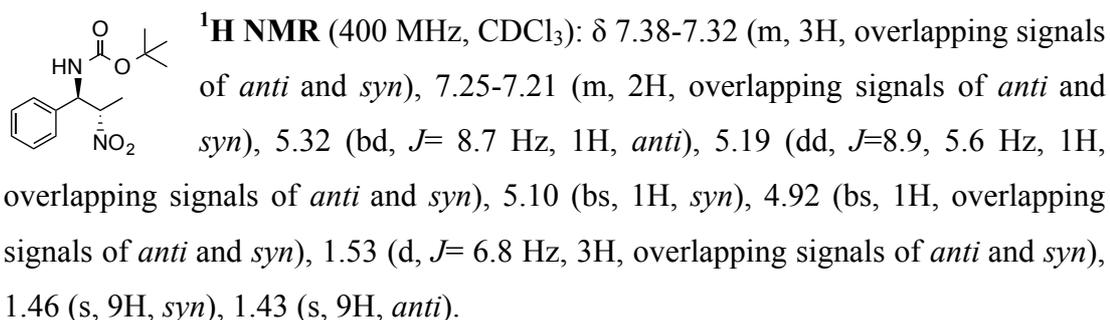
**GC-MS:** Retention time: 12.18 min.

[*M/Z*]<sup>+</sup>= 57.08, 59.05, 77.05, 103.06, 118.05, 147.99, 181.94, 183.94, 185.94, 208.99, 277.90.

**IR(neat):** 3353, 2981, 2933, 1700, 1558, 1488, 1369, 1325, 1162, 1126, 1068 cm<sup>-1</sup>

### 3.8.9 Synthesis of *tert*-butyl ((1*R*,2*S*)-2-nitro-1-phenylpropyl) carbamate (28a)

General procedure starting from nitroethane and *tert*-butyl (phenylmethylene) carbamate afforded to desired chiral product mixture of *syn/anti*-isomers with ratio 72:28 (*anti/syn*) with 85% conversion in 22 h as a white solid.



**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): (*anti* product) δ155.1, 136.6, 129.1, 128.7, 127.0, 85.9, 80.6, 57.6, 23.8, 15.3. (*syn* product) δ155.1, 136.6, 129.1, 128.5, 126.6, 86.8, 80.6, 57.5, 25.4, 17.1.

**HPLC:** Chiralpak ADH, 95:5 (n-hexane/i-PrOH), flow rate 1.0 mL/min, 210 nm, temp=25 °C,  $t_{\text{major},\text{syn}}=19.3$  min,  $t_{\text{minor},\text{syn}}=22.2$  min,  $t_{\text{minor},\text{anti}}=25.5$  min,  $t_{\text{major},\text{anti}}=32.4$  min.

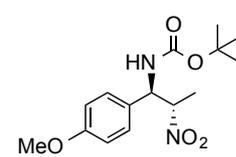
**GC-MS:** Retention time: 10.46 min (major diastereomer) / 10.64 min (minor diastereomer)

$[M/Z]^+=57.08, 59.06, 78.04, 104.03, 106.04, 117.06, 150.02, 177.00, 206.05$ .

**IR(neat):** 3370, 3009, 2977, 2914, 2360, 1681, 1548, 1520, 1170, 701  $\text{cm}^{-1}$

### 3.8.10 Synthesis of *tert*-butyl ((1*R*,2*S*)-1-(4-methoxyphenyl)-2-nitropropyl) carbamate (28b)

General procedure starting from nitroethane and *N*-Boc-4-methoxybenzylideneamine afforded to desired chiral product mixture of *syn/anti*-isomers with ratio 75:25 (*anti/syn*) with 76% conversion in 70 h as a white solid.

 **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.16 (d,  $J=8.7$  Hz, 2H, *syn*), 7.15 (overlapping signals, 2H, *anti*), 6.87 (d,  $J=8.7$  Hz, 2H, *syn*), 7.86 (overlapping signals, 2H, *anti*), 5.58 (d,  $J=9.3$  Hz, 1H, *syn*), 5.35 (bs, 1H, *anti*), 5.10 (dd,  $J=8.7, 6.1$  Hz, 1H, *anti*), 5.01 (bs, 1H, *syn*), 4.90 (bs, 1H, overlapping signals of *anti* and *syn*), 3.78 (s, 3H, *syn*), 3.77 (s, 3H, *anti*), 1.51 (d,  $J=6.7$  Hz, 3H, *anti*), 1.49 (bs, 3H, *syn*), 1.42 (s, 9H, *anti*), 1.40 (s, 9H, *syn*).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): (*anti* product)  $\delta$ 159.8, 155.2, 128.2, 127.8, 114.4, 86.1, 80.5, 57.1, 55.7, 29.8, 15.6. (*syn* product)  $\delta$ 159.7, 155.0, 129.6, 127.1, 114.5, 86.9, 80.5, 56.9, 55.4, 28.4, 17.0.

**HPLC:** Chiralpak IA, 85:15 (n-hexane/i-PrOH), flow rate 0.5 mL/min, 210 nm, temp=25 °C,  $t_{\text{minor},\text{anti}}=18.2$  min,  $t_{\text{major},\text{anti}}=19.6$  min,  $t_{\text{minor},\text{syn}}=20.8$  min,  $t_{\text{major},\text{syn}}=24.9$  min.

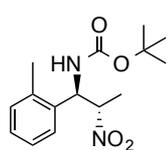
**GC-MS:** Retention time: 12.53 min (major diastereomer) / 12.66 min (minor diastereomer)

$[M/Z]^+$  = 57.10, 59.07, 77.07, 109.07, 136.10, 148.11, 180.06, 207.13.

**IR(neat):** 3340, 2979, 2933, 2237, 1683, 1550, 1516, 1252, 1174, 1028, 837  $\text{cm}^{-1}$

### 3.8.11 Synthesis of *tert*-butyl ((1*R*,2*S*)-2-nitro-1-(*o*-tolyl)propyl) carbamate (28c)

General procedure starting from nitroethane and *N*-[(2-methylphenyl)methylene] carbamate afforded to desired chiral product mixture of *syn/anti*-isomers with ratio 62:38 (*anti/syn*) with full conversion in 26 h as a colorless solid.



**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.22-7.17 (bs, overlapping signals of *anti* and *syn*, 4H) 5.59-5.3 (m, 1H, *syn*), 5.35 (bs, 1H, *anti*), 5.38 (bs, 1H, *syn*), 4.90-4.80 (bs, overlapping signals of *anti* and *syn*), 2.46 (s, 3H, *anti*), 2.45 (s, 3H, *syn*), 1.61 (d,  $J = 6.7$  Hz, 3H, overlapping signals of *anti* and *syn*), 1.42 (s, 9H, *anti*), 1.99 (s, 9H, *syn*).

**$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ ): (*anti* product)  $\delta$  155.1, 136.3, 135.7, 131.2, 128.4, 126.8, 125.4, 85.2, 80.5, 53.6, 28.3, 19.7, 16.9. (*syn* product)  $\delta$  155.1, 136.3, 135.8, 131.4, 128.5, 127.0, 125.1, 86.8, 80.5, 53.5, 29.8, 19.5, 15.5.

**HPLC:** Chiralpak ADH, 80:20 (n-hexane/*i*-PrOH), flow rate 0.5 mL/min, 210 nm, temp=25  $^\circ\text{C}$ ,  $t_{\text{minor},\text{syn}} = 13.5$  min,  $t_{\text{major},\text{syn}} = 14.5$  min,  $t_{\text{minor},\text{anti}} = 15.6$  min,  $t_{\text{major},\text{anti}} = 23.7$  min.

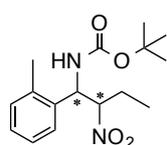
**GC-MS:** Retention time: 10.95 min (major diastereomer) / 11.13 min (minor diastereomer)

$[M/Z]^+$  = 57.11, 59.09, 91.05, 120.11, 164.08.

**IR(neat):** 3335, 2977, 2929, 2362, 1700, 1554, 1365, 1165  $\text{cm}^{-1}$

### 3.8.12 Synthesis of *tert*-butyl (2-nitro-1-phenylbutyl)carbamate (31a)

General procedure starting from 1-nitropropane and *tert*-butyl (phenylmethylene) carbamate afforded to desired chiral product mixture of *syn/anti*-isomers with ratio 72:28 (*anti/syn*) with 96% conversion in 20 h as a white solid.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ 7.38-7.30 (m, 3H, overlapping signals of *anti* and *syn*), 7.25-7.22 (m, 2H, overlapping signals of *anti* and *syn*), 5.71 (bd, *J*=7.2 Hz, 1H, *syn*) 5.15 (bs, 1H, overlapping signals of *anti* and *syn*), 4.74 (bs, 1H, *anti*), 2.09-2.01 (m, 1H, overlapping signals of *anti* and *syn*) 1.91-1.86 (m, 1H, *anti*), 1.84-1.73 (m, 1H, *syn*), 1.46 (s, 9H, *syn*), 1.42 (s, 9H, *anti*), 0.98 (t, *J*= 7.0 Hz, 3H, *anti*), 0.97 (t, *J*= 7.3 Hz, 3H, *syn*)

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): (*anti* product) δ154.9, 137.7, 128.9, 128.7, 126.9, 93.0, 80.4, 56.8, 29.7, 24.9, 10.5. (*syn* product) δ155.1, 137.7, 129.0, 128.4, 126.3, 93.8, 80.4, 55.9, 28.3, 24.9, 10.3.

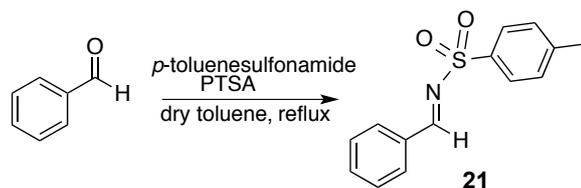
**HPLC**: Chiralpak ASH, 95:5 (n-hexane/*i*-PrOH), flow rate 0.5 mL/min, 214 nm, temp=25 °C, *t*<sub>major,*syn*</sub> = 19.0 min, *t*<sub>major,*anti*</sub> = 23.7 min, *t*<sub>minor,*anti*</sub> = 26.5 min, *t*<sub>minor,*syn*</sub> = 28.7 min.

**GC-MS**: Retention time: 10.89 min (major diastereomer) / 11.02 min (minor diastereomer)

[*M/Z*]<sup>+</sup> = 57.10, 59.08, 104.07, 106.08, 150.05, 192.11.

**IR(neat)**: 3370, 2977, 2925, 2361, 1682, 1549, 1520, 1359, 1169, 701 cm<sup>-1</sup>

### 3.9 Synthesis of Tosyl Protected Imines



*p*-toluenesulfonamide (29.2 mmol, 5.0 g) and benzaldehyde (35.04 mmol, 3.72 g) were dissolved in dry toluene (20.0 mL) under argon atmosphere. 1-2 crystals of PTSA was added and refluxed for 3 hours. After 3 hours, <sup>1</sup>H NMR analysis of aliquot taken from reaction mixture indicated the complete conversion to product. Solvent was removed under vacuum and product was washed with diethyl ether to remove impurities. Pure product was obtained with 95% yield as a white solid.<sup>54</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ9.03 (s, 1H), 7.94-7.85 (m, 4H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.68 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 2.43 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ170.3, 144.7, 135.2, 135.1, 132.8, 131.4, 129.9, 129.2, 128.2, 21.7.

### **3.10 General Procedure for Aza-Henry Reaction: Nitromethane Addition to Tosyl Protected Imines**

#### *Racemic synthesis;*

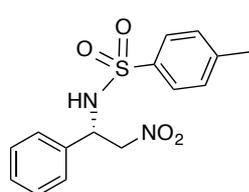
Tosyl imine (0.1 mmol), nitromethane (0.35 mmol) and Et<sub>3</sub>N (0.01 mmol) were dissolved in DCM (1 mL) and stirred at room temperature. The reaction was monitored with TLC upon the consumption of limiting reactant, directly loaded into column chromatography. EtOAc:Hexane mixtures was used as eluent to purify the products.

#### *Asymmetric synthesis;*

Tosyl imine (0.1 mmol) and *t*-butyl/2-aminoDMAP **48** (0.002 mmol) was dissolved in acetonitrile (0.3 mL) for half an hour. Then nitromethane (0.35 mmol) was added to solution and stirred at the room temperature. The reaction was monitored with TLC upon the consumption of limiting reactant, directly loaded into column chromatography. EtOAc:Hexane mixtures was used as eluent to purify the products.

### 3.10.1 Synthesis of (*S*)-4-methyl-*N*-(2-nitro-1-phenylethyl)benzenesulfonamide (**22a**)

General procedure starting from nitromethane and (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide afforded to desired chiral product with 87% conversion and 58% ee in 27 h as a white solid.



$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.63 (d,  $J$ = 8.3 Hz, 2H), 7.26-7.20 (m, 5H), 7.10-7.06 (m, 2H) 5.67 (d,  $J$ = 8.0 Hz, 1H), 5.00 (dd,  $J$ =14.2, 6.8 Hz, 1H) 4.84-4.78 (m, 1H), 4.68-4.62 (m, 1H), 2.39 (s, 3H).

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ 144.1, 136.6, 135.4, 129.9, 129.3, 127.3, 126.6, 79.1, 55.6, 21.5.

**HPLC**: Chiralpak ODH column, 80:20 (n-hexane/*i*-PrOH), flow rate 1.0 mL/min, 220 nm, temp=25 °C,  $t_{\text{minor}}$ = 19.2 min,  $t_{\text{major}}$ = 22.1 min.

### 3.11 General Procedure for Henry Reaction: Nitromethane Addition to Aldehydes

*Racemic synthesis*;

*p*-Nitrobenzaldehyde (**34b**) (0.1 mmol), nitromethane (0.35 mmol) and  $\text{Et}_3\text{N}$  (0.01 mmol) were dissolved in DCM (1 mL) and stirred at room temperature. The reaction was monitored with TLC upon the consumption of limiting reactant, directly loaded into column chromatography. EtOAc:Hexane mixtures was used as eluent to purify the products.

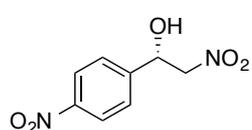
*Asymmetric synthesis*;

*p*-Nitrobenzaldehyde (**34b**) (0.1 mmol) and *urea*/2-aminoDMAP **46** (0.005 mmol) was dissolved in toluene (0.3 mL) for half an hour. Then nitromethane (0.35 mmol) was added to solution and stirred at room temperature. The reaction was monitored

with TLC upon the consumption of limiting reactant, directly loaded into column chromatography. EtOAc:Hexane mixtures was used as eluent to purify the products.

### 3.11.1 Synthesis of (*S*)-2-nitro-1-(4-nitrophenyl)ethan-1-ol (**35b**)

General procedure starting from nitromethane and *p*-nitrobenzaldehyde (**34b**) afforded to desired chiral product with full conversion and 7% ee in 1 h as a yellow solid.



<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.19 (d, *J*=8.8, 2H), 7.56 (d, *J*=8.6, 2H), 5.57-5.52 (m, 1H), 4.58-4.48 (m, 2H), 3.20 (bs, 1H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 148.2, 145.1, 127.1, 124.3, 80.7, 70.1.

**HPLC:** Chiralpak IA column, 80:20 (n-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, temp=25 °C, *t*<sub>major</sub>= 13.5 min, *t*<sub>minor</sub>= 17.5 min.

## 3.12 General Procedure for Aldol Reaction: Acetone/Cyclohexanone Addition to Aldehydes

*Racemic synthesis;*

*p*-Nitrobenzaldehyde (**34b**) (0.2 mmol), acetone/cyclohexanone (4 mmol) and pyrrolidine (0.06 mmol) were dissolved in water (0.3 mL) and stirred at room temperature for 10 minutes. The reaction was monitored with TLC upon the consumption of limiting reactant, directly loaded into column chromatography. EtOAc:Hexane mixtures was used as eluent to purify the products.<sup>55</sup>

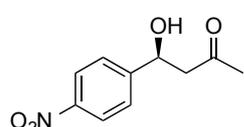
*Asymmetric synthesis;*

2-AminoDMAP **55** (0.01 mol) was dissolved in trace amount of DCM then Brønsted acid was added and stirred at room temperature for half an hour. *p*-Nitrobenzaldehyde (**34b**) (0.1 mmol) and acetone/cyclohexanone (**60**) (0.35 mmol)

was added to the solution. The reaction was monitored with TLC upon the consumption of limiting reactant, directly loaded into column chromatography. EtOAc:Hexane mixtures was used as eluent to purify the products.

### 3.12.1 Synthesis of (*S*)-4-hydroxy-4-(4-nitrophenyl)butan-2-one (**37b**)

General procedure starting from acetone and *p*-nitrobenzaldehyde (**34b**) by using TFA as Brønsted acid afforded to desired chiral product with 38% isolated yield and 43% ee in 71 h as a yellow solid.



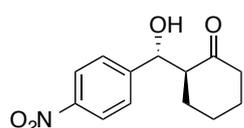
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.20 (d,  $J=8.8$  Hz, 2H), 7.53 (d,  $J=8.6$  Hz, 2H), 5.26 (dd,  $J=7.7$ , 4.4 Hz, 1H), 3.63 (bs, 1H), 2.87-2.82 (m, 2H), 2.22 (s, 3H).

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ): 208.6, 150.1, 147.4, 126.5, 123.9, 69.0, 51.6, 30.8.

**HPLC**: Chiralpak ASH column, 75:25 (n-hexane/*i*-PrOH), flow rate 0.5 mL/min, 210 nm, temp=25 °C,  $t_{\text{minor}}$ = 23.2 min,  $t_{\text{major}}$ = 29.8 min.

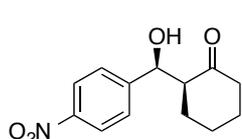
### 3.12.2 Synthesis of 2-(hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (**60b**)

General procedure starting from cyclohexanone (**59**) and *p*-nitrobenzaldehyde (**34b**) afforded to desired chiral product with chiral product mixture of *syn/anti*-isomers with ratio 60:40 (*syn/anti*) in 46 h as a yellow solid.



$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.21 (d,  $J=8.8$  Hz, 2H), 7.51 (d,  $J=8.7$  Hz, 2H), 4.90 (dd,  $J=8.4$ , 1.5 Hz, 1H), 4.07 (d,  $J=2.8$  Hz, 1H), 2.62-2.55 (m, 1H), 2.53-2.47 (m, 1H), 2.36 (td,  $J=13.4$ , 6.2 Hz, 1H), 2.15-2.08 (m, 1H), 1.88-1.80 (m, 1H), 1.72-1.36 (m, 1H).

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ): 214.7, 148.4, 147.6, 127.8, 123.6, 74.0, 57.1, 42.7, 30.8, 27.6, 24.7.

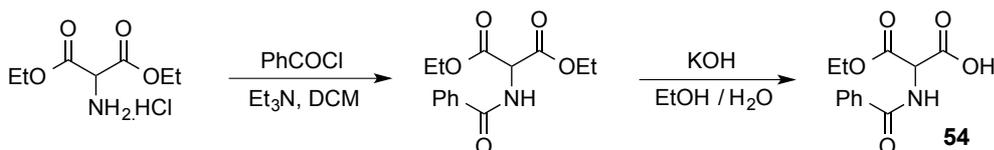


$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.24 (d,  $J= 8.8$  Hz, 2H), 7.49 (d,  $J= 8.7$  Hz, 2H), 5.48 (bs, 1H), 3.15 (bs, 1H) 2.67-2.60 (m, 1H), 2.52-2.46 (m, 1H), 2.40 (td,  $J= 13.4, 6.1$  Hz, 1H), 2.15-2.08 (m, 1H), 1.89-1.83 (m, 1H), 1.75-1.50 (m, 4H).

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ): 214.8, 149.3, 147.6, 126.7, 123.6, 70.2, 56.9, 42.7, 27.9, 26.0, 24.9.

**HPLC:** Chiralpak ADH column, 90:10 (n-hexane/i-PrOH), flow rate 1.0 mL/min, 210 nm, temp=25 °C,  $t_{\text{syn,minor}}= 17.4$  min,  $t_{\text{syn,major}}= 20.5$  min,  $t_{\text{anti,minor}}= 22.7$  min,  $t_{\text{anti,major}}= 30.2$  min.

### 3.13 Synthesis of $\alpha$ -Amidohemimalonates



The following slightly modified literature procedures are combined:<sup>40, 56</sup>

500 mg diethylmalonate hydrochloride (2.36 mmol, 1 eq.) and 1 mL  $\text{Et}_3\text{N}$  (7.087 mmol, 3 eq.) was added to 35 mL DCM and stirred for 15 minutes. 0.275 mL benzoyl chloride (2.36 mmol, 1 eq.) was added at 0 °C dropwise and the reaction was stirred for 15 h at room temperature. After 15 h, the reaction mixture was diluted with DCM, washed with HCl (1 N) and extracted with DCM. The combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure. Purification of the crude product was performed by recrystallization from EtOAc/Heptane (1:10) afforded as white needles in 90% yield.

Benzoyl protected aminomalonate (1eq) was dissolved in 1:10  $\text{H}_2\text{O}$ :EtOH mixture. A solution of KOH (1.2 eq) in 1:10  $\text{H}_2\text{O}$ :EtOH again and added dropwise to the reaction at 0 °C. The reaction is stirred at room temperature for 24 hours. HCl (1 N) was added dropwise until pH=1, then the mixture was saturated with NaCl and extracted twice with EtOAc. The combined organic layers were dried with  $\text{MgSO}_4$

and concentrated under reduced pressure. Crude product was washed saturated NaHCO<sub>3</sub> and extracted with ether. After acidifying the water phase with 1 N HCl until pH=1, extraction was performed with ether to obtain the resultant product as yellowish solid in 45% yield.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>): δ9.94 (bs, 1H), 7.84-7.80 (m, 2H), 7.52 (tt, *J*= 7.4 Hz, 1.9 Hz, 1H), 7.45-7.40 (m, 2H), 5.37 (d, *J*= 6.7 Hz, 1H), 4.30-4.25 (m, 2H), 1.29 (t, *J*= 7.14 Hz, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ168.5, 168.1, 166.5, 132.6, 132.5, 128.8, 127.5, 63.2, 57.0, 14.0.

### **3.14 General Procedure for Decarboxylative Aldol Reaction: Aldehyde Addition to $\alpha$ -Amidohemimalonates**

#### *Racemic synthesis;*

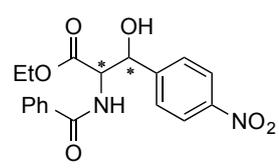
Et<sub>3</sub>N (1 eq) was added to a solution of malonic acid half ester **54** (1 eq) in dry THF (0.3 mL for 0.2 mmol). aldehyde (1.2 eq) was added to the solution and the reaction mixture was stirred at room temperature for 15 h. Reaction was directly loaded into column chromatography. 30:70 EtOAc:Cyclohexane mixture was used as eluent to purify the products.

#### *Asymmetric synthesis;*

0.16 mmol of aldehyde, 0.13 mmol of malonic acid half ester **54** and 0.01 mmol of *t*-butyl /2-aminoDMAP **48** was dissolved in DCM (1.0 mL) and stirred at the room temperature. The reaction was monitored with TLC upon the consumption of limiting reactant, directly loaded into column chromatography. 30:70 EtOAc:Cyclohexane mixture was used as eluent to purify the products.

### 3.14.1 Synthesis of ethyl 2-benzamido-3-hydroxy-3-(4-nitrophenyl)propanoate (**55b**)

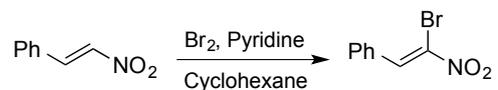
General procedure starting from 0.13 mmol of malonic acid half ester **54** and *p*-nitrobenzaldehyde (**34b**) afforded to desired chiral product with 40% isolated yield and 55% ee in 7 days as a white solid.

  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.19 (d,  $J=8.8$  Hz, 2H), 7.70-7.66 (m, 2H), 7.61 (d,  $J=8.5$  Hz, 2H), 7.52 (tt,  $J=7.4, 1.22$  Hz, 1H), 7.44-7.40 (m, 3H), 6.87 (d,  $J=8.8$  Hz, 1H), 5.50 (d,  $J=3.0$  Hz, 1H), 5.15 (dd,  $J=8.7, 3.1$  Hz, 1H), 4.32-4.21 (m, 2H), 1.29 (t,  $J=7.2$  Hz, 3H).

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.1, 169.0, 147.8, 147.0, 132.7, 132.0, 129.0, 127.3, 127.1, 123.6, 75.0, 62.8, 60.1, 14.2.

**HPLC**: Chiralpak ASH column, 80:20 (n-hexane/*i*-PrOH), flow rate 1.0 mL/min, 210 nm, temp=25 °C,  $t_{\text{minor}}$ = 11.6 min,  $t_{\text{major}}$ = 18.1 min.

### 3.15 Synthesis of (*Z*)-(2-bromo-2-nitrovinyl)benzene (**43**)



The following literature procedure is performed:<sup>57</sup>

To a rt stirred solution of  $\beta$ -nitrostyrene **21** (5.0 mmol) in pyridine (6.5 mmol) and cyclohexane (20 mL) was added neat  $\text{Br}_2$  (6.0 mmol) dropwise over 5 min. The cloudy yellow reaction was then heated to reflux and stirred for 4-12 h (monitored by TLC). The reaction mixture was then transferred to a single-neck round-bottom flask with the aid of ethyl acetate. The solvent was removed, and the resulting residue was taken up in ethyl acetate (50 mL). The organic layer was washed with aqueous

Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (1.0 M, 2 × 20 mL), H<sub>2</sub>O (20 mL), and brine (20 mL) and then dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed in vacuo to give a crude solid that was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/petroleum ether gradient).

Spectroscopic data are in accordance with the literature.<sup>57</sup>

### **3.16 General Procedure for Friedel-Crafts/Substitution Domino Reaction: (Z)-(2-bromo-2-nitrovinyl)benzene (43) and β-naphthol (42)**

*Racemic synthesis;*

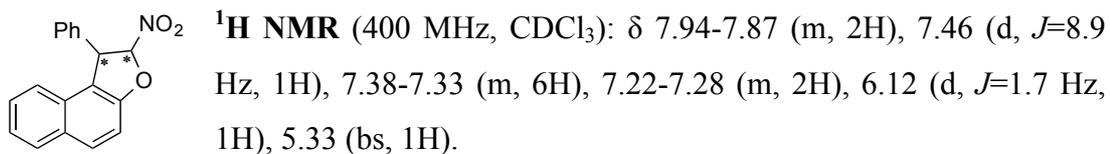
0.18 mmol β-naphthol (**42**), 0.1 mmol (Z)-(2-bromo-2-nitrovinyl)benzene (**43**), and 0.01 mmol of Et<sub>3</sub>N were dissolved and stirred at the room temperature. The reaction was monitored with TLC upon the consumption of limiting reactant, directly loaded into column chromatography. EtOAc:Hexane mixtures was used as eluent to purify the products.

*Asymmetric synthesis;*

0.1 mmol (Z)-(2-bromo-2-nitrovinyl)benzene (**43**), 0.18 mmol β-naphthol (**42**) and 0.01 mmol of t-butyl/quinine **51** were dissolved in 0.2 mL DCM and stirred at the room temperature. The reaction was monitored with TLC upon the consumption of limiting reactant, directly loaded into column chromatography. EtOAc:Hexane mixtures was used as eluent to purify the products.

#### **3.16.1 Synthesis of 2-nitro-1-phenyl-1,2-dihydronaphtho[2,1-b]furan (44a)**

General procedure starting from (Z)-(2-bromo-2-nitrovinyl)benzene (**43**) and β-naphthol (**42**) afforded to desired chiral product with full conversion and 92% ee in 10 minutes as a white solid.



**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>): δ 156.4, 138.1, 131.6, 129.5, 129.2, 128.6, 127.8, 127.7, 123.1, 118.4, 112.7, 112.0, 55.5.

**HPLC:** Chiralpak ODH column, 90:10 (n-hexane/*i*-PrOH), flow rate 1.0 mL/min, 220 nm, temp=25 °C, *t*<sub>minor</sub>= 8.2 min, *t*<sub>major</sub>= 9.4 min.



## CHAPTER 4

### CONCLUSION

In this study, novel bifunctional organocatalysts, developed in Tanyeli's research group were tested in five different types of reactions. In the first part, aza-Henry reaction of *t*-Boc protected imines were tested both with 2-aminoDMAP and quinine based bifunctional organocatalysts with nitroalkanes. The best result was obtained with 10 mol% of organocatalyst **51**, 0.1M concentration in DCM at room temperature. Under this condition, derivatization studies were done with different imines and nitroalkanes. The enantioselectivities were found up to 91% ee with full conversions for *o*-methyl **24c**, *p*-bromo **24e** and *p*-methyl **24f** substituted imine derivatives with nitromethane. In the same reaction, tosyl protected imine **21** was also tested; however, ee value did not exceed 52% with *t*-butyl / 2-aminoDMAP organocatalyst **48**.

In the second part of the thesis, pioneering studies have done in Henry, aldol, decarboxylative aldol and Friedel-Crafts/Substitution Domino reactions. Unfortunately, in Henry reaction none of the trials showed enantioenriched result. In the aldol reaction study, maximum of 41% ee was achieved with 2-aminoDMAP **56** and proline binary organocatalyst system. Although there are not a lot of studies where decarboxylative aldol study is experimented, the first results indicates that it can be improved with additional screenings. Among the aforementioned reactions, Friedel-Crafts/Substitution Domino reaction gave the most promising result, in terms of enantioselectivity and reaction rate as 92% ee in 10 minutes with full conversion, respectively. Optimization study will continue and the derivatization of the starting materials will be accomplished in the optimized condition in the near future.



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## APPENDIX A

### NMR DATA

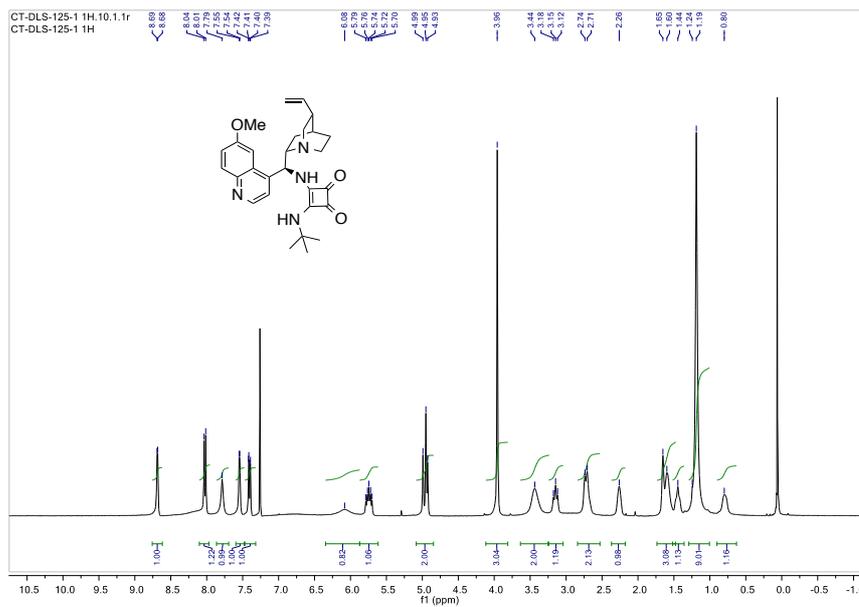


Figure A. 1.  $^1\text{H}$  NMR spectrum of compound 51

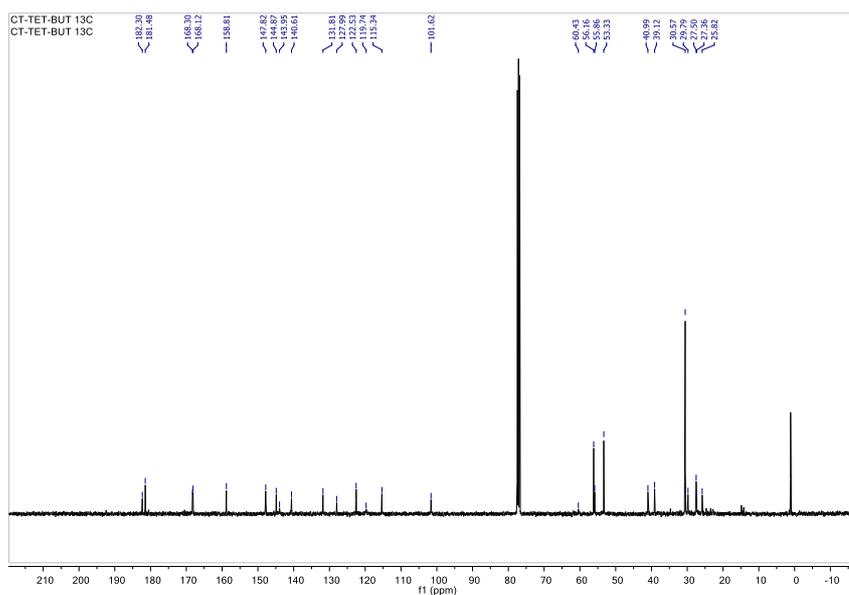


Figure A. 2.  $^{13}\text{C}$  NMR spectrum of compound 51

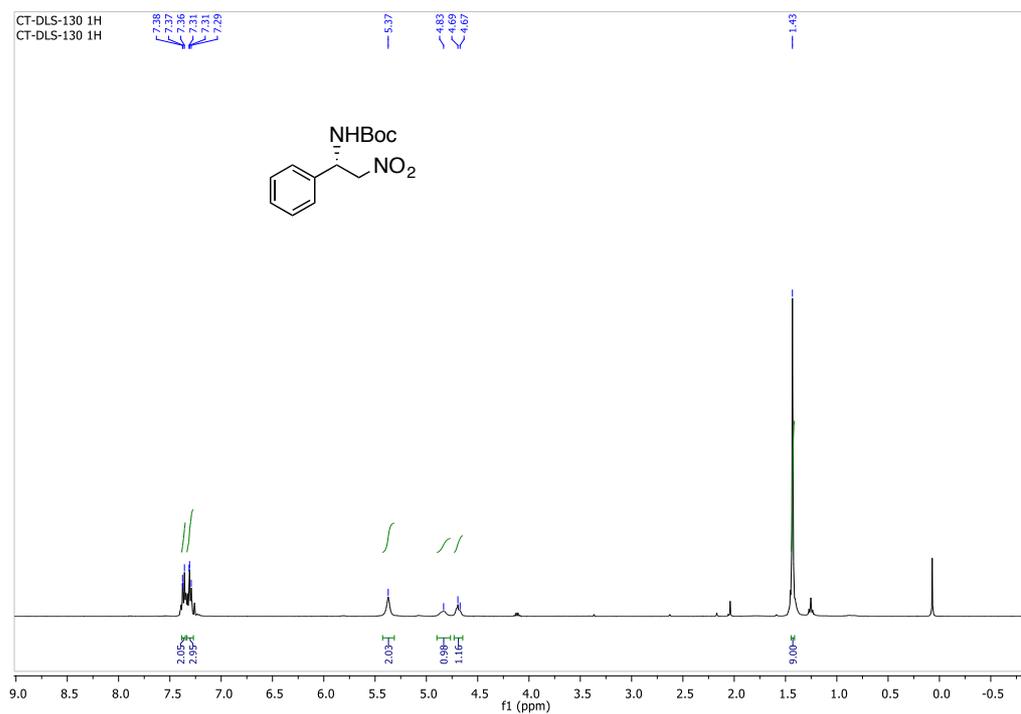


Figure A. 3.  $^1\text{H}$  NMR spectrum of compound 24a

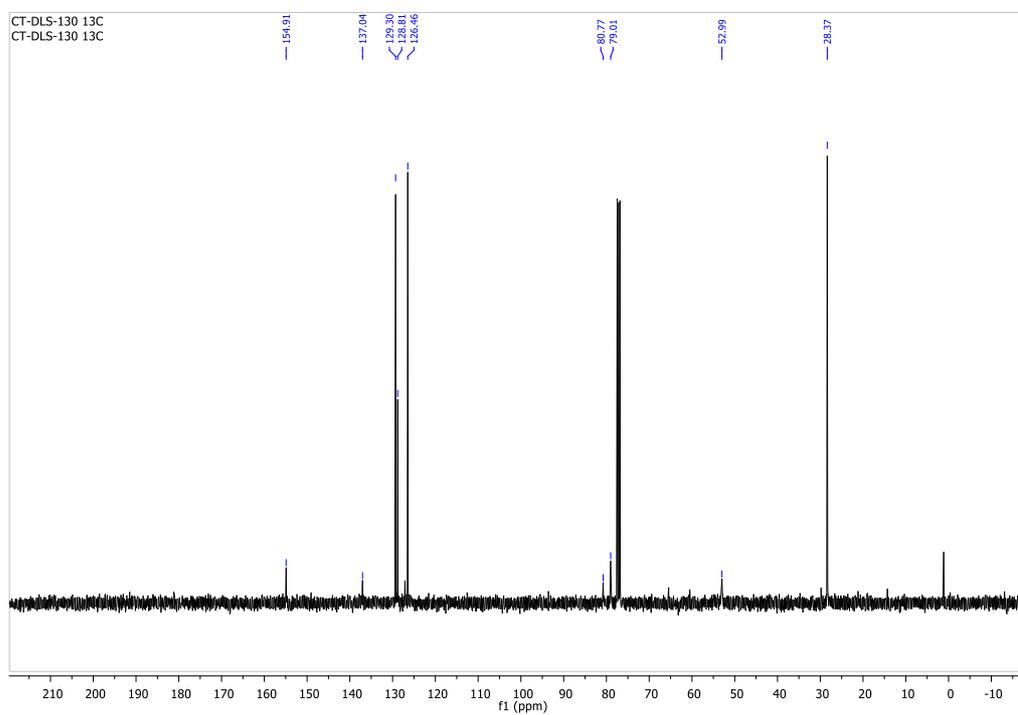


Figure A. 4.  $^{13}\text{C}$  NMR spectrum of compound 24a

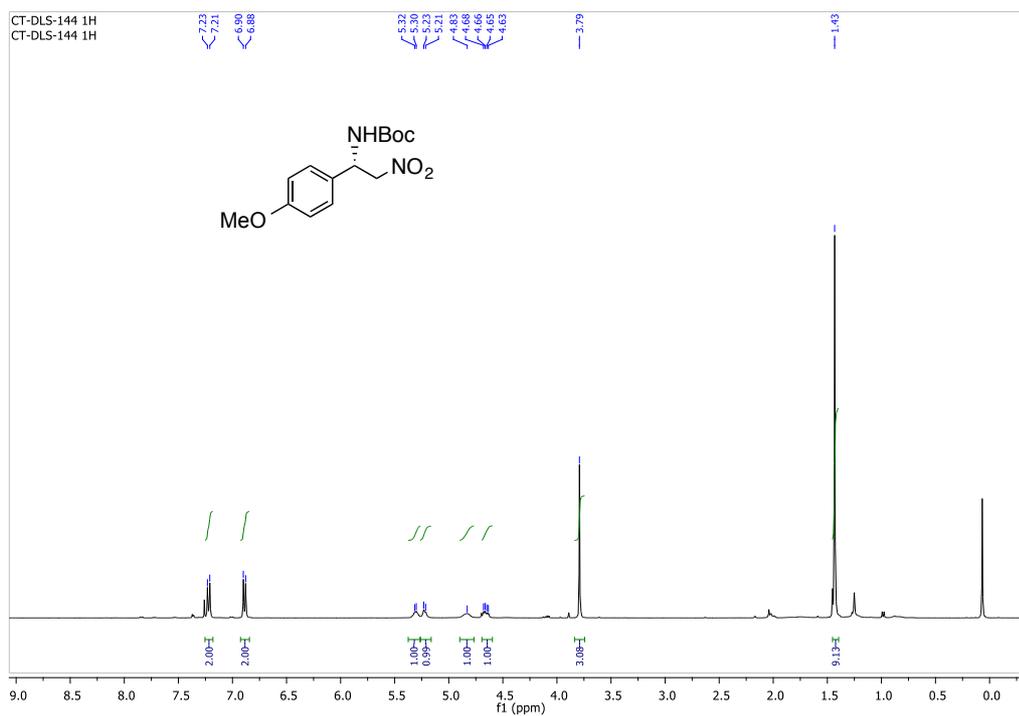


Figure A. 5.  $^1\text{H}$  NMR spectrum of compound 24b

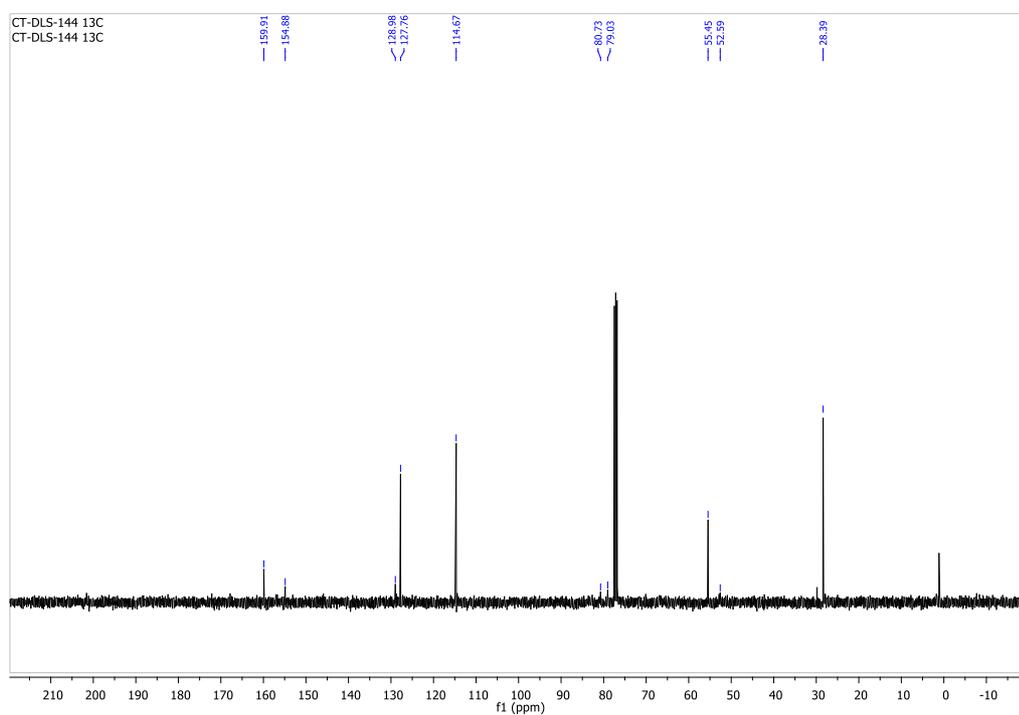
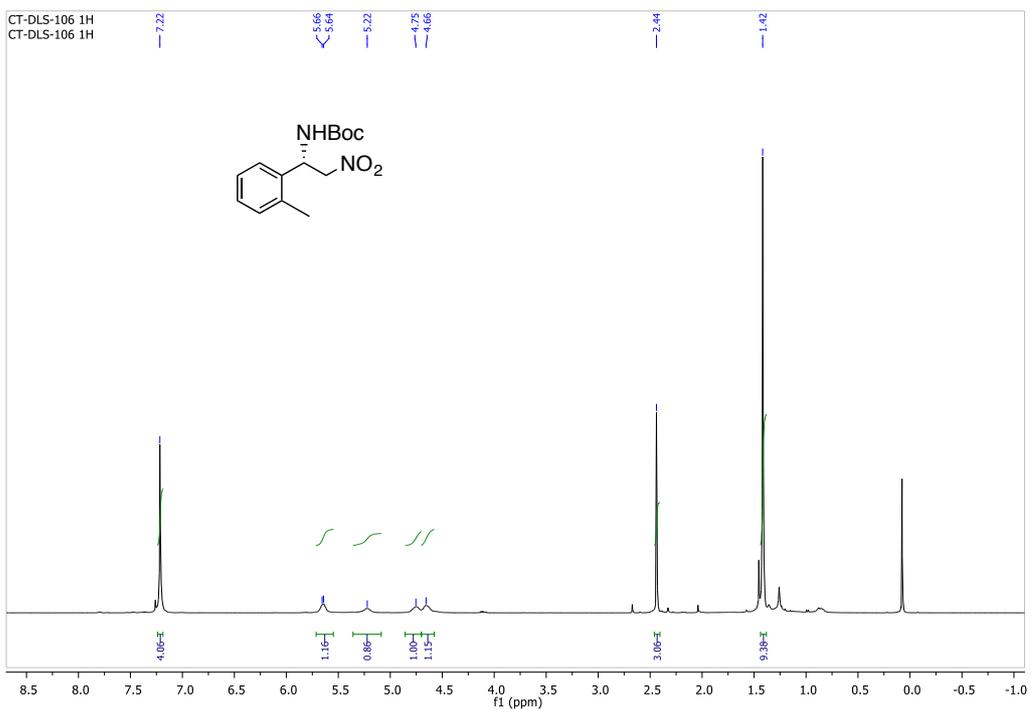
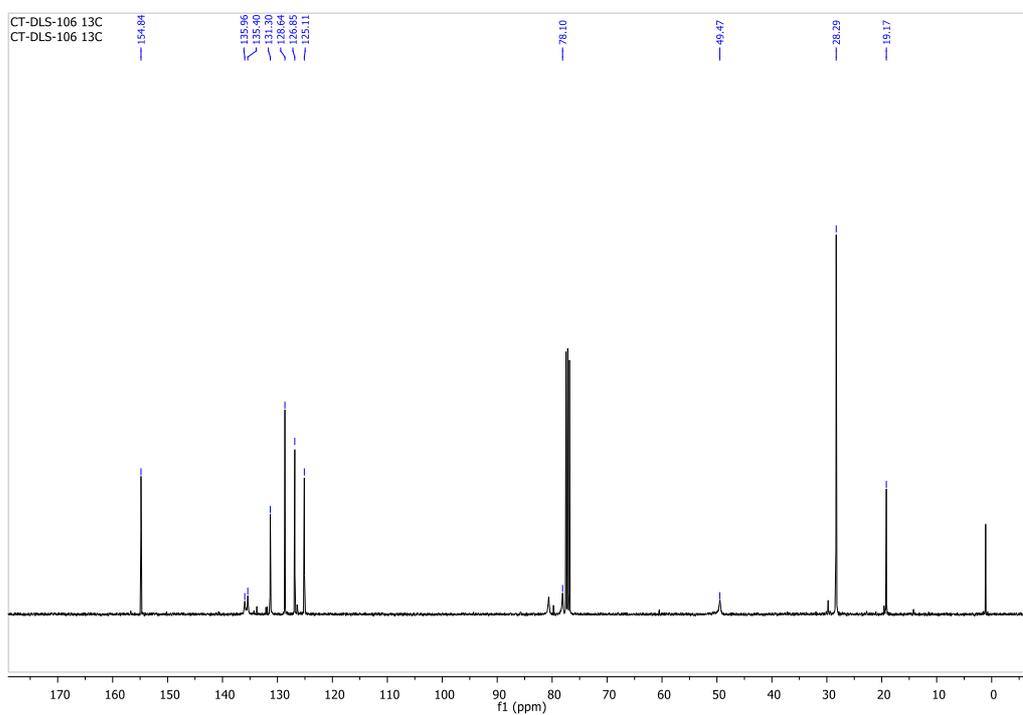


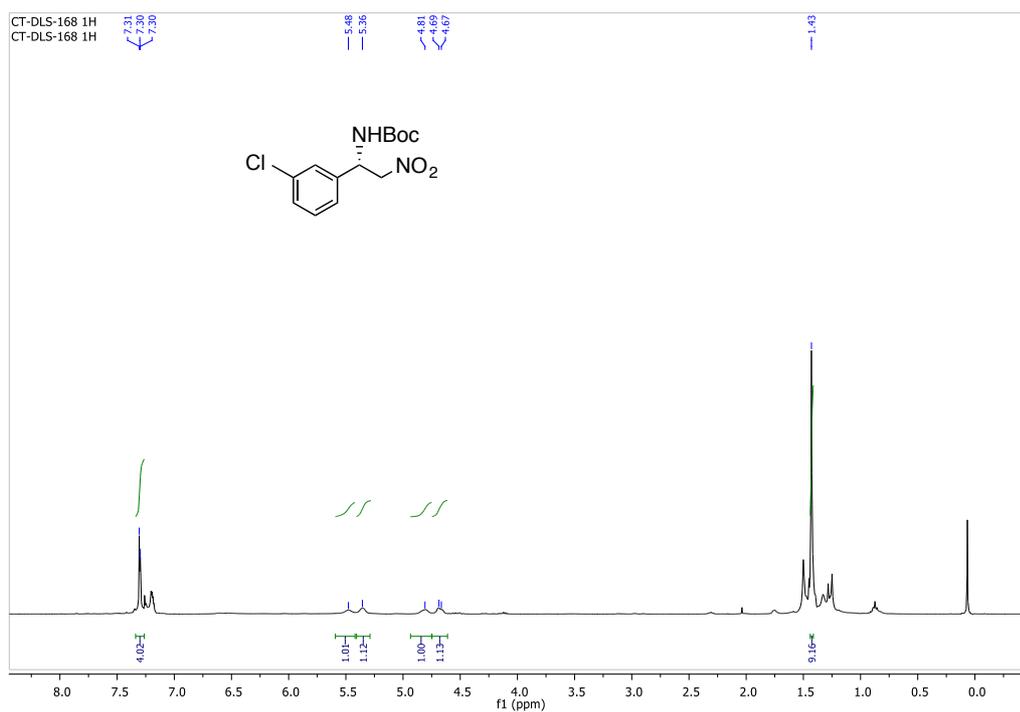
Figure A. 6.  $^{13}\text{C}$  NMR spectrum of compound 24b



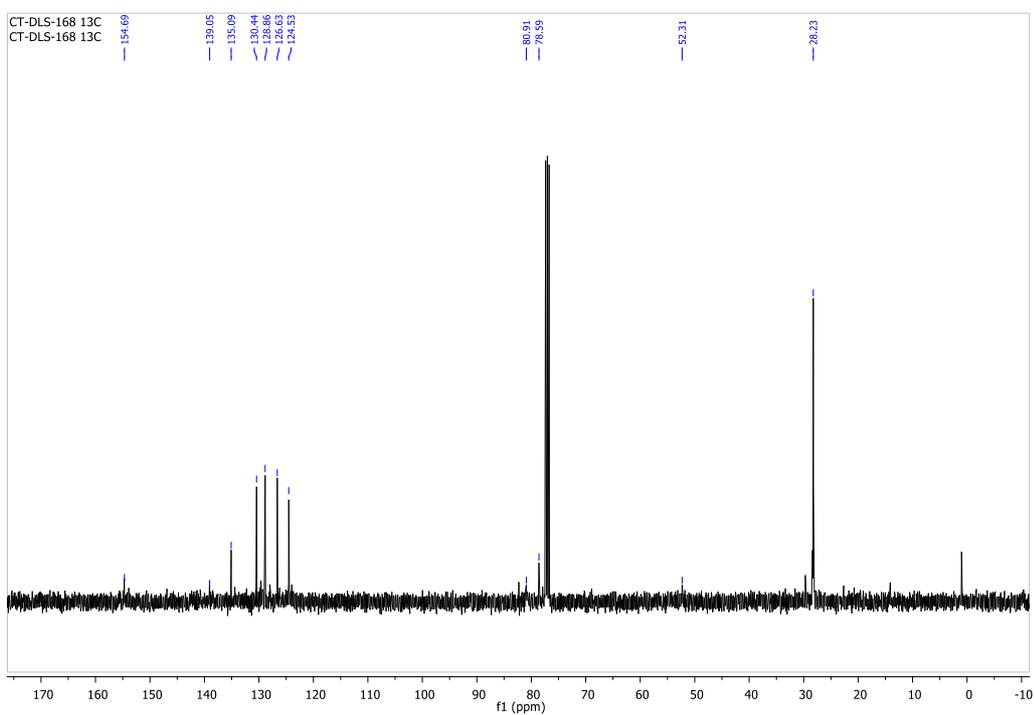
**Figure A. 7.** <sup>1</sup>H NMR spectrum of compound **24c**



**Figure A. 8.** <sup>13</sup>C NMR spectrum of compound **24c**



**Figure A. 9.** <sup>1</sup>H NMR spectrum of compound **24d**



**Figure A. 10.** <sup>13</sup>C NMR spectrum of compound **24d**

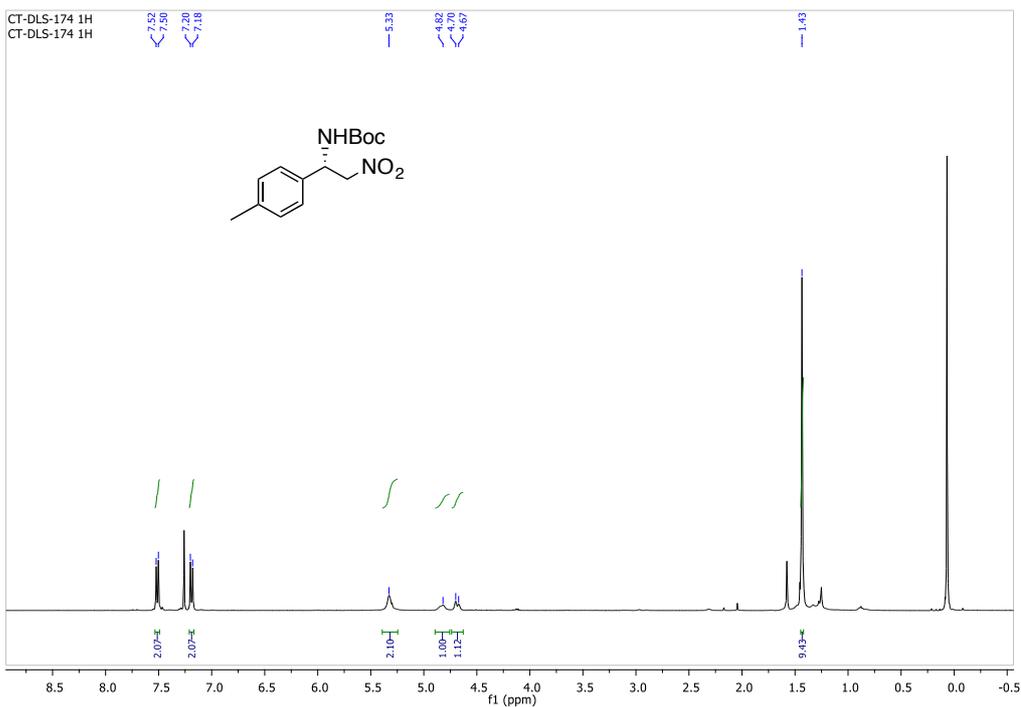


Figure A. 11.  $^1\text{H}$  NMR spectrum of compound 24e

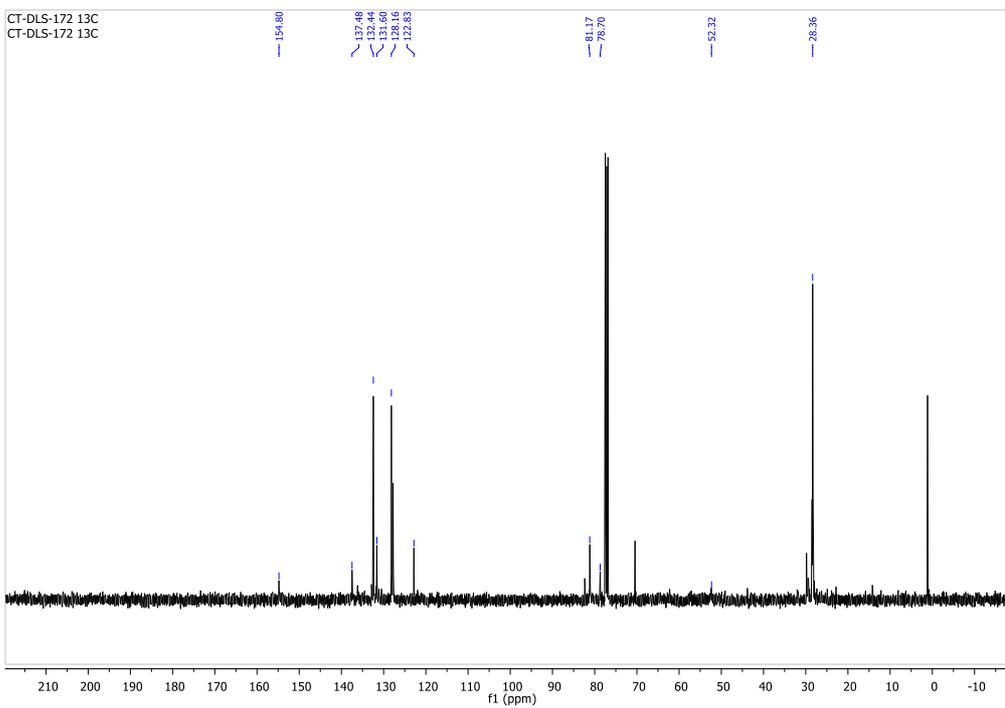
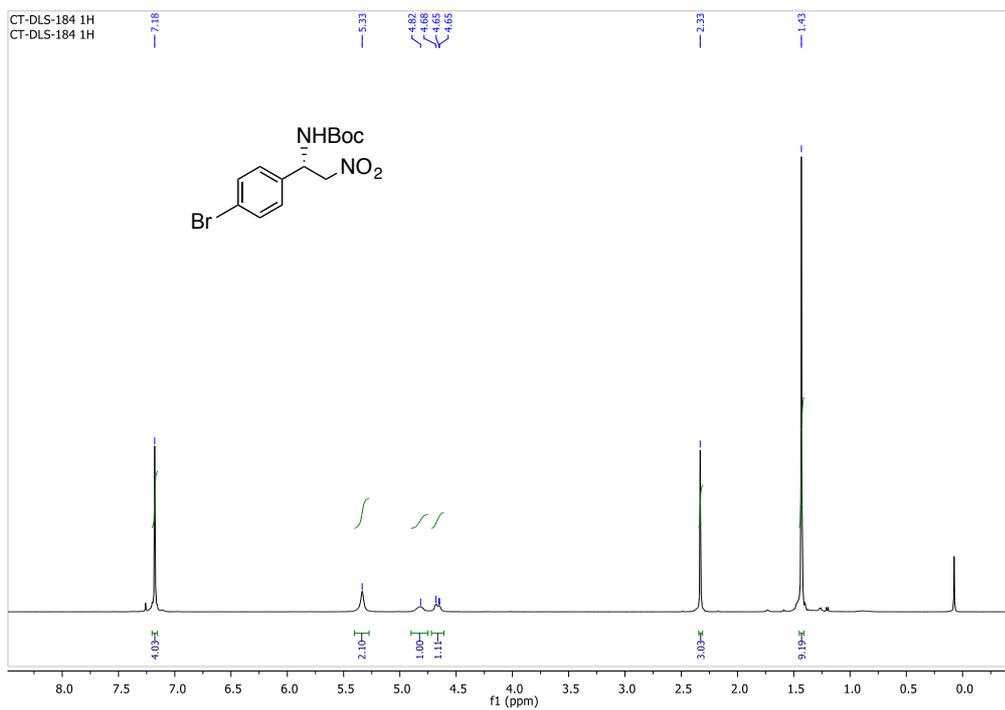
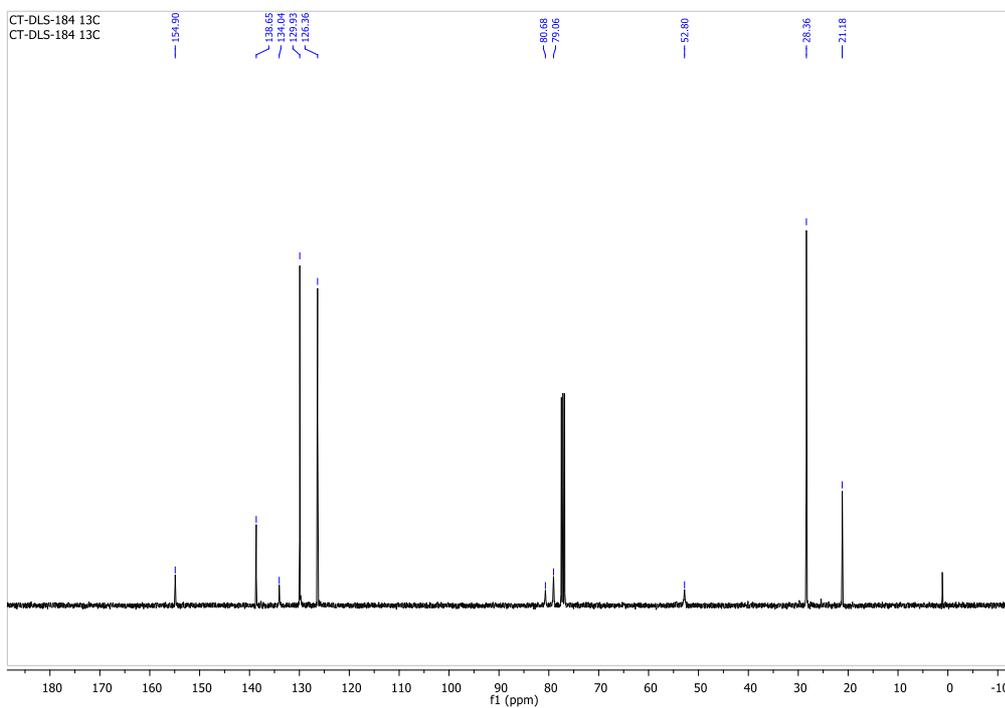


Figure A. 12.  $^{13}\text{C}$  NMR spectrum of compound 24e



**Figure A. 13.**  $^1\text{H}$  NMR spectrum of compound **24f**



**Figure A. 14.**  $^{13}\text{C}$  NMR spectrum of compound **24f**

**Z**

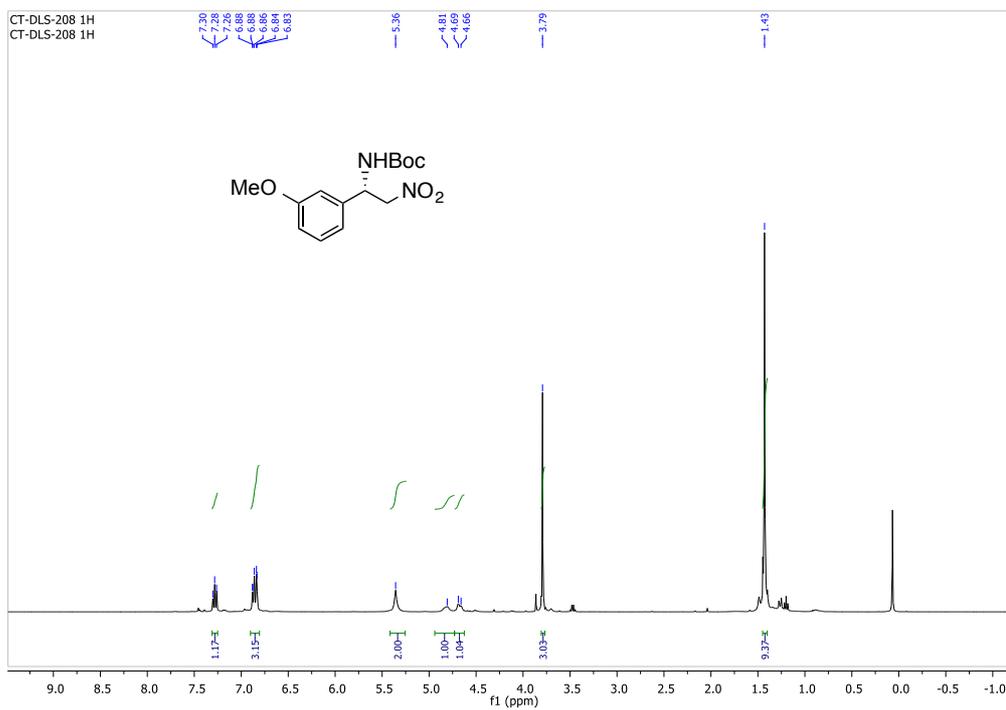


Figure A. 15. <sup>1</sup>H NMR spectrum of compound 24g

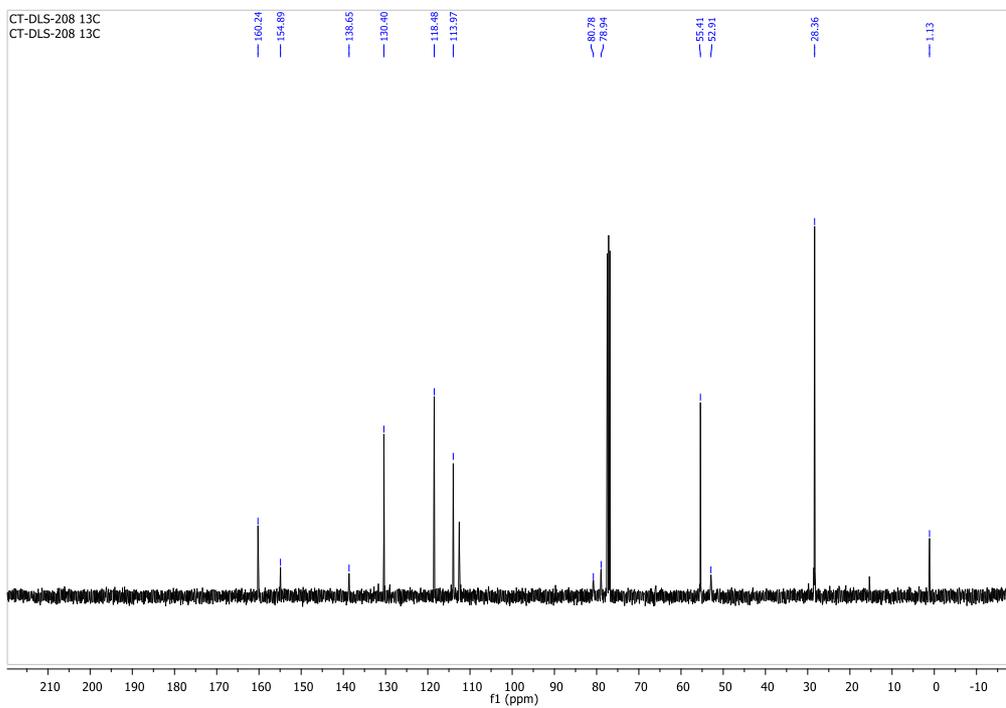


Figure A. 16. <sup>13</sup>C NMR spectrum of compound 24g

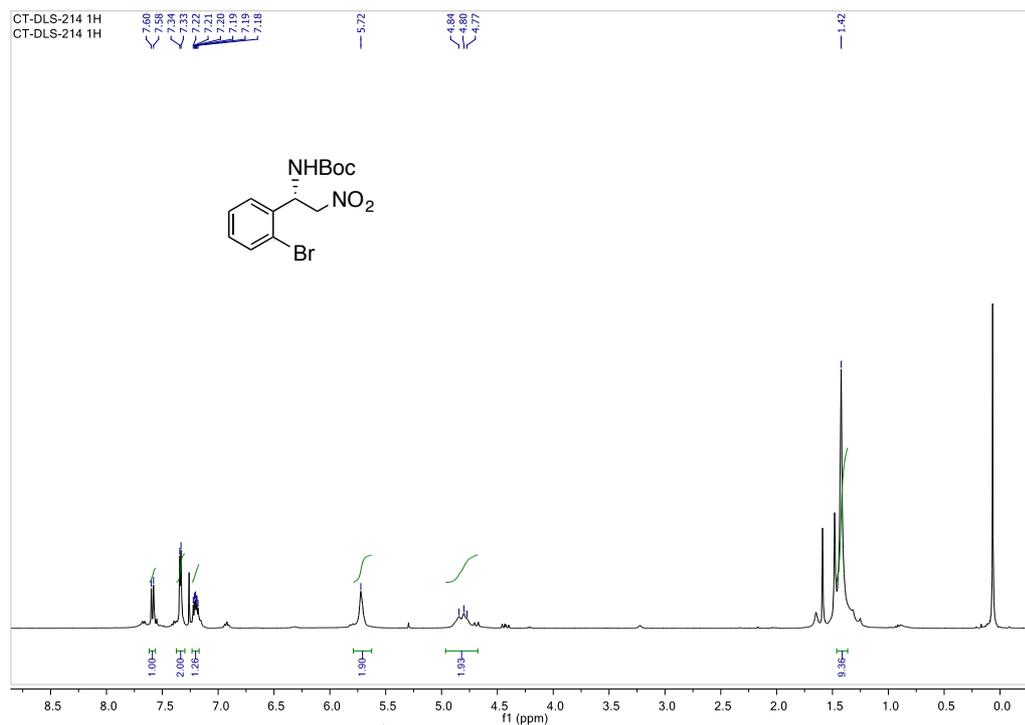


Figure A. 17.  $^1\text{H}$  NMR spectrum of compound 24h

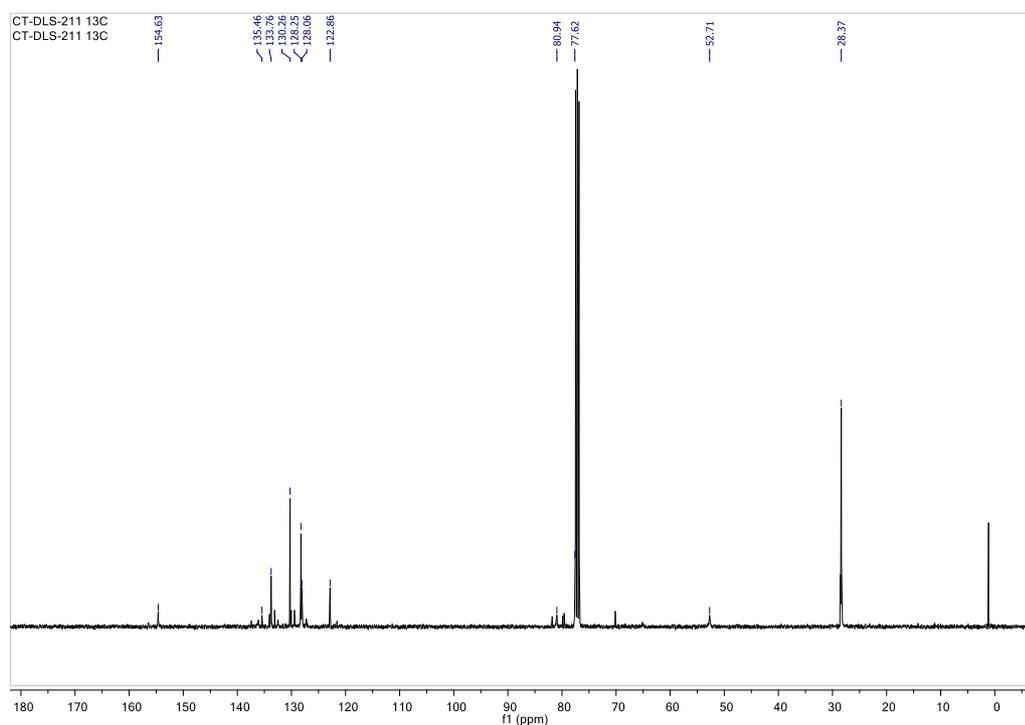


Figure A. 18.  $^{13}\text{C}$  NMR spectrum of compound 24h

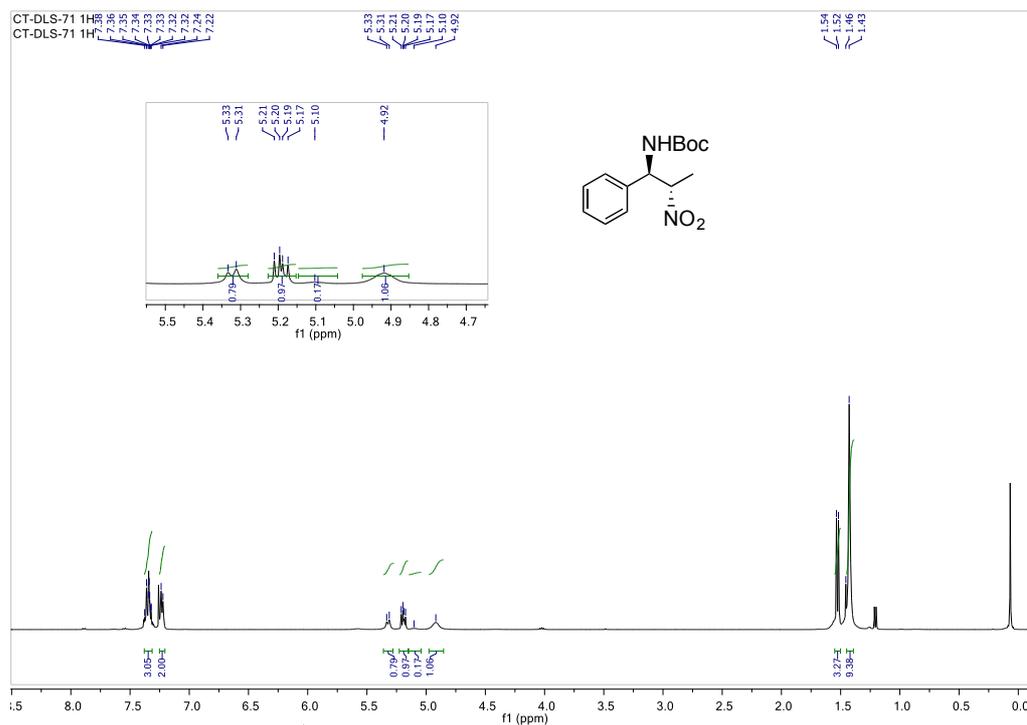


Figure A. 19. <sup>1</sup>H NMR spectrum of diastereomeric mixture **28a**

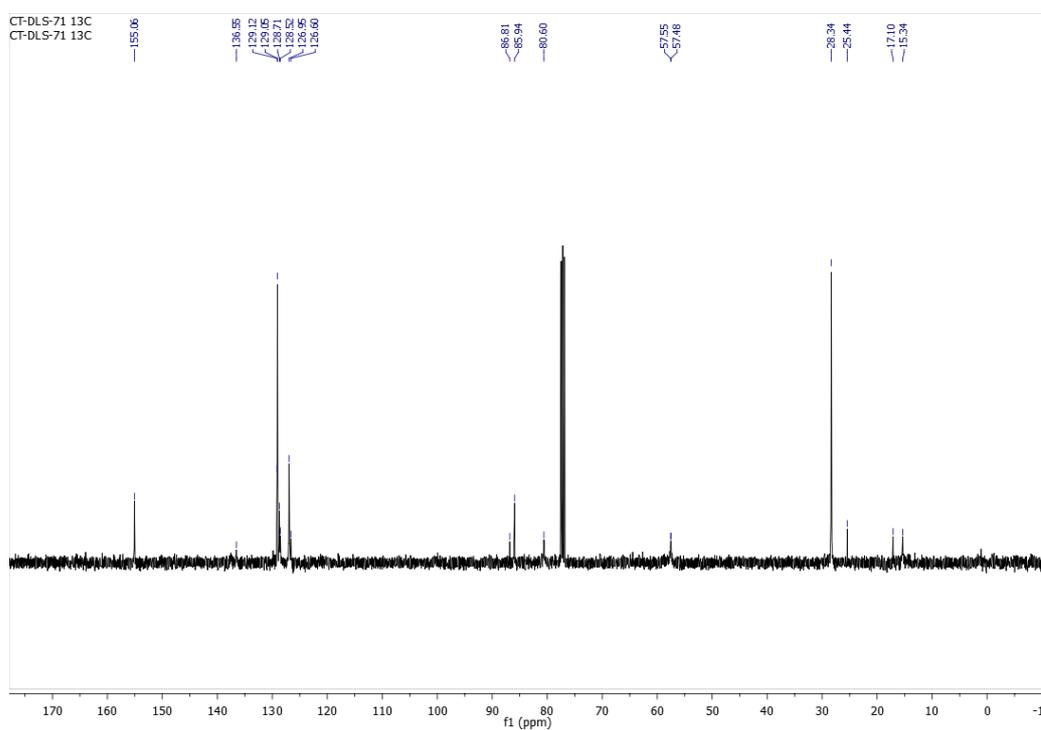


Figure A. 20. <sup>13</sup>C NMR spectrum of diastereomeric mixture **28a**

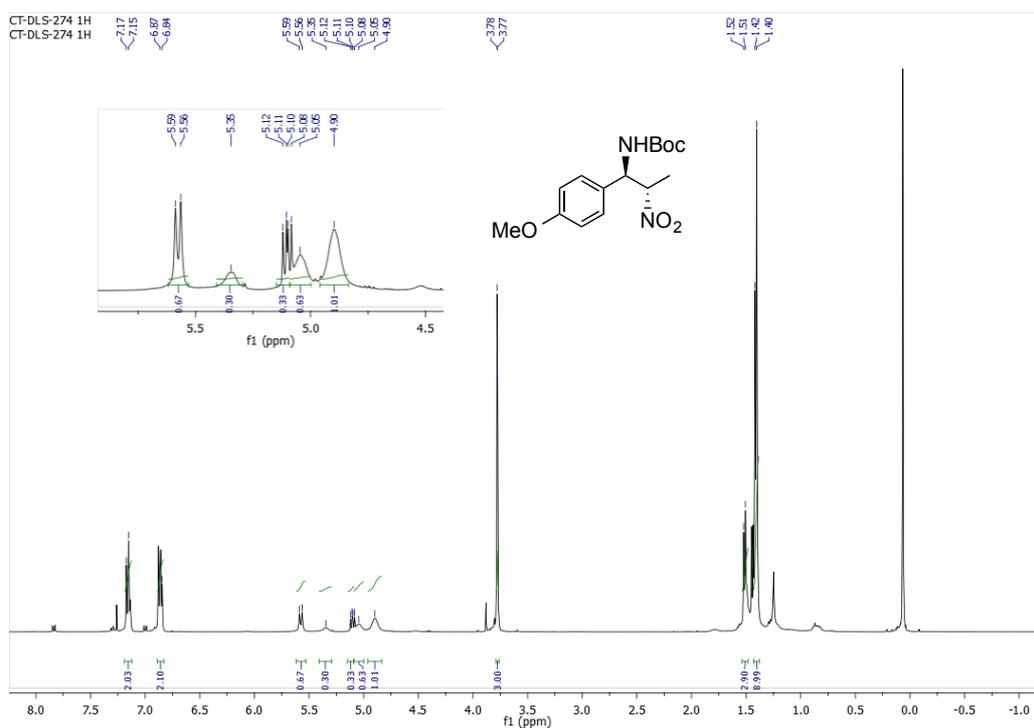


Figure A. 21. <sup>1</sup>H NMR spectrum of diastereomeric mixture **28b**

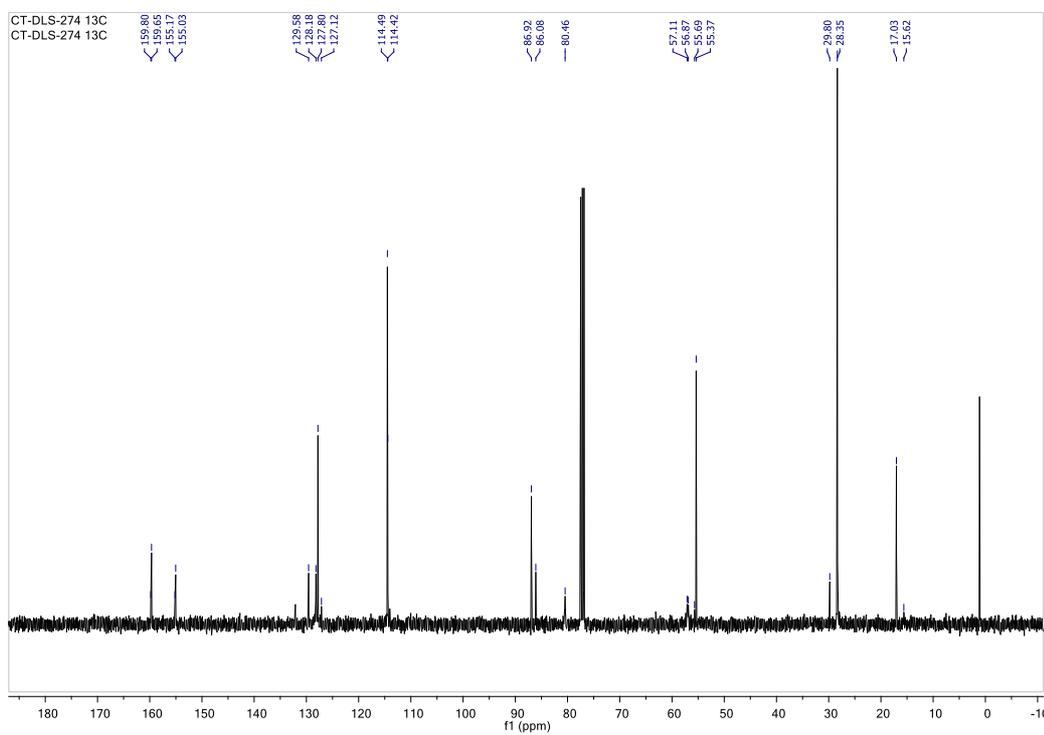


Figure A. 22. <sup>13</sup>C NMR spectrum of diastereomeric mixture **28b**

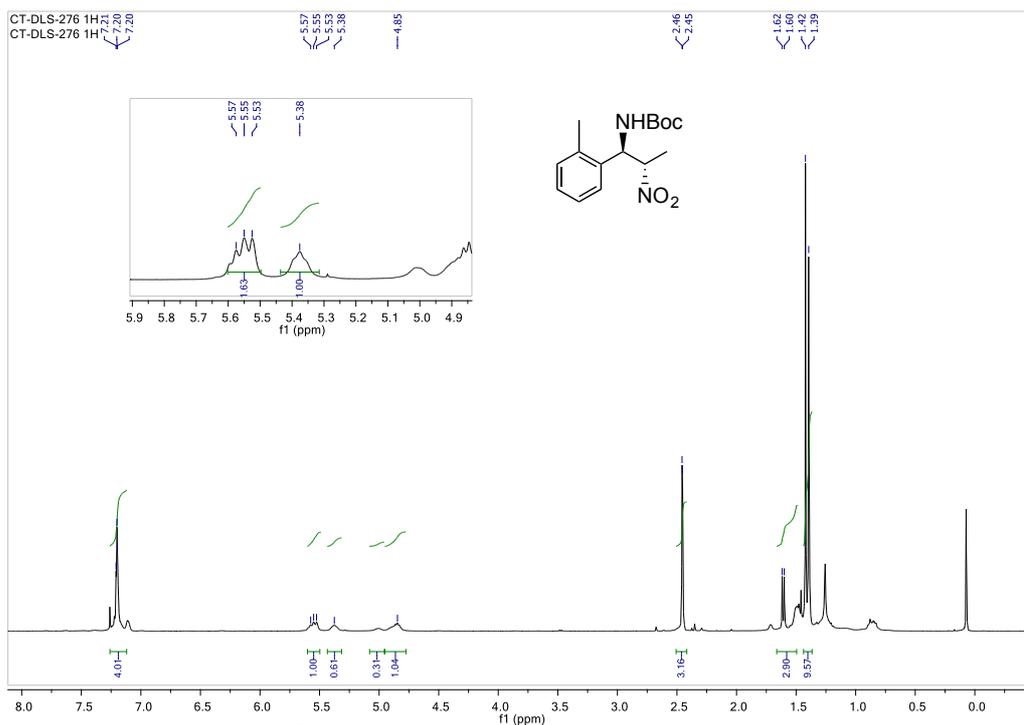


Figure A. 23.  $^1\text{H}$  NMR spectrum of diastereomeric mixture **28c**

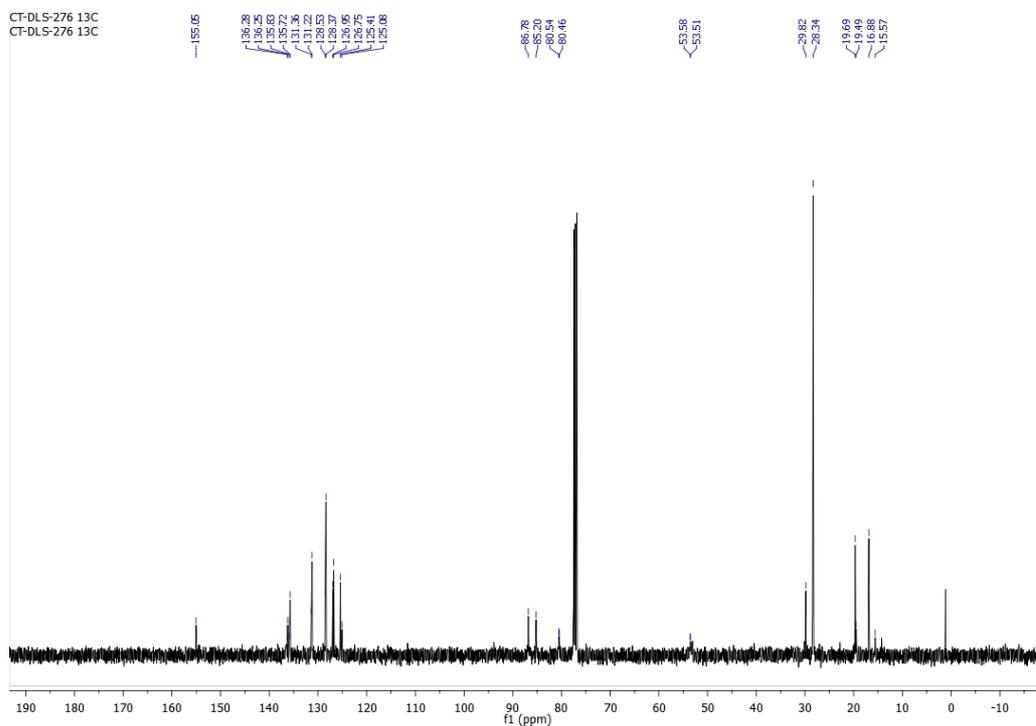


Figure A. 24.  $^{13}\text{C}$  NMR spectrum of diastereomeric mixture **28c**

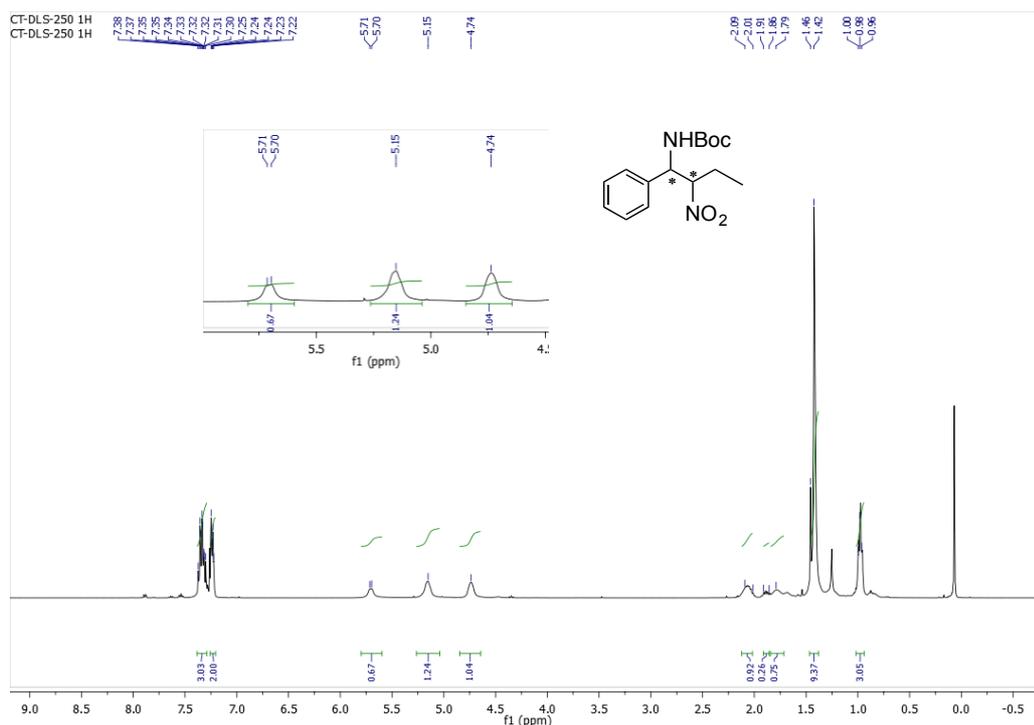


Figure A. 25.  $^1\text{H}$  NMR spectrum of diastereomeric mixture **31a**

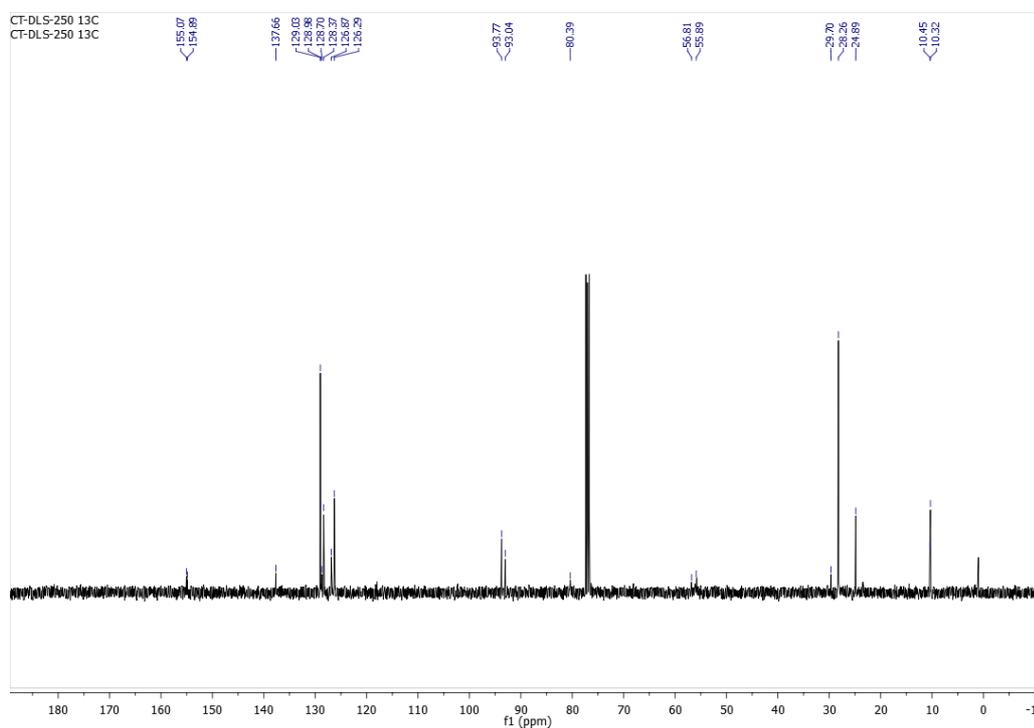


Figure A. 26.  $^{13}\text{C}$  NMR spectrum of diastereomeric mixture **31a**

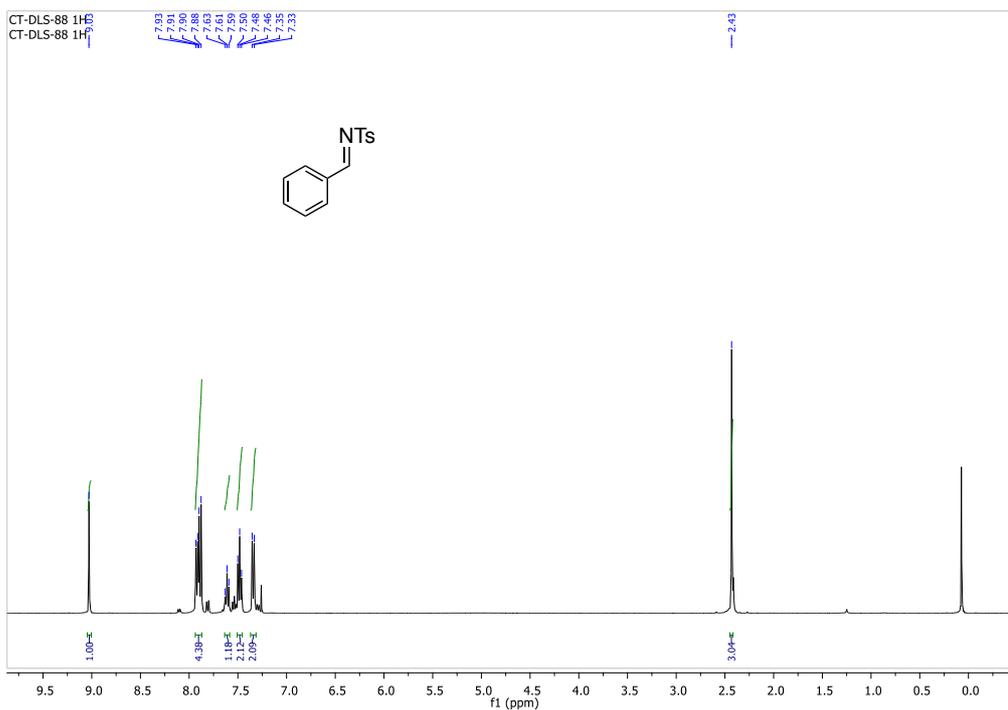


Figure A. 27.  $^1\text{H}$  NMR spectrum of compound 21

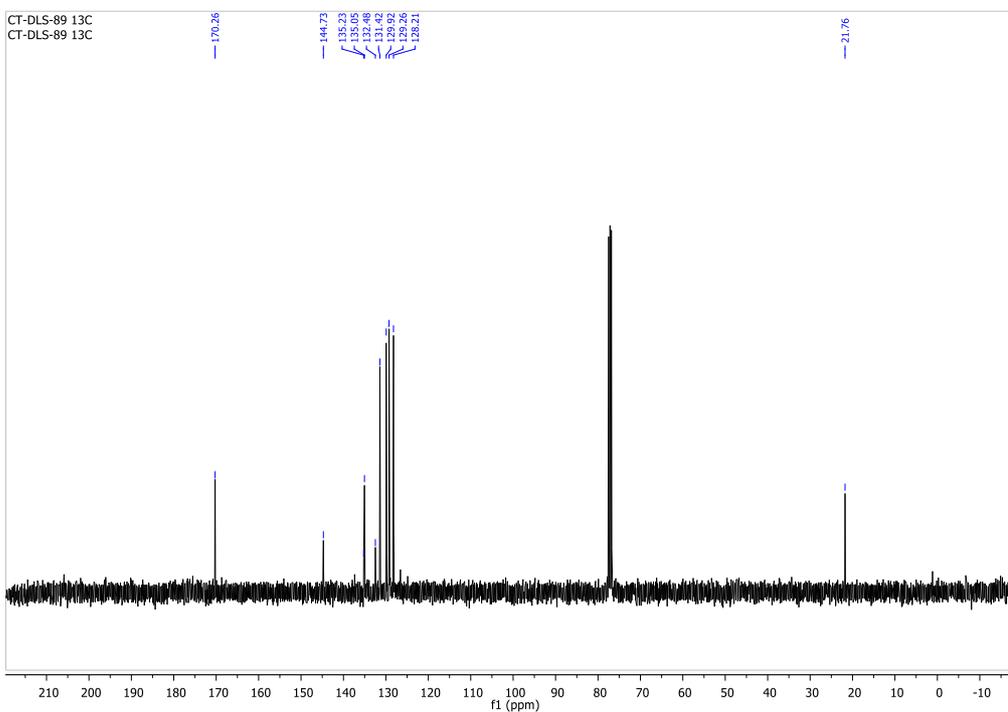


Figure A. 28.  $^{13}\text{C}$  NMR spectrum of compound 21

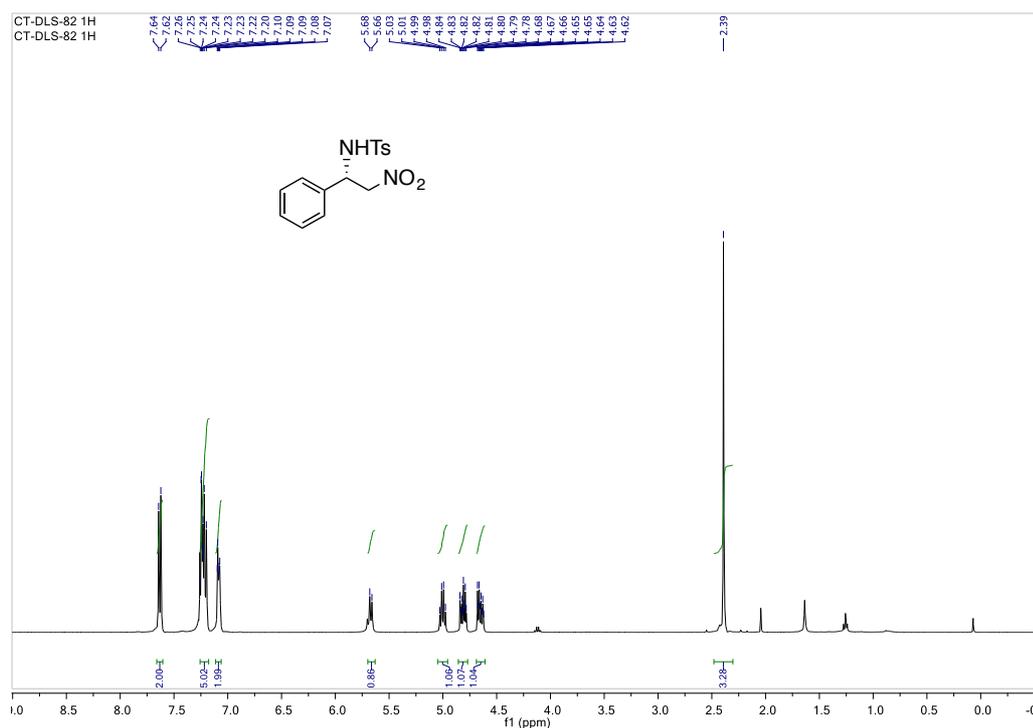


Figure A. 29. <sup>1</sup>H NMR spectrum of compound 22a

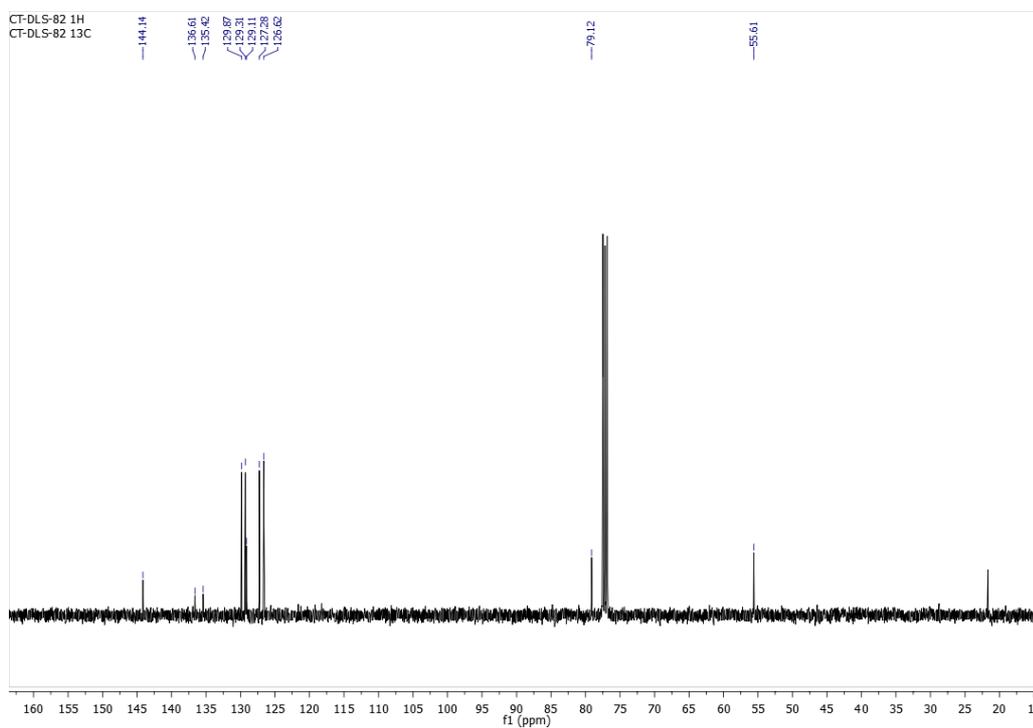


Figure A. 30. <sup>13</sup>C NMR spectrum of compound 22a

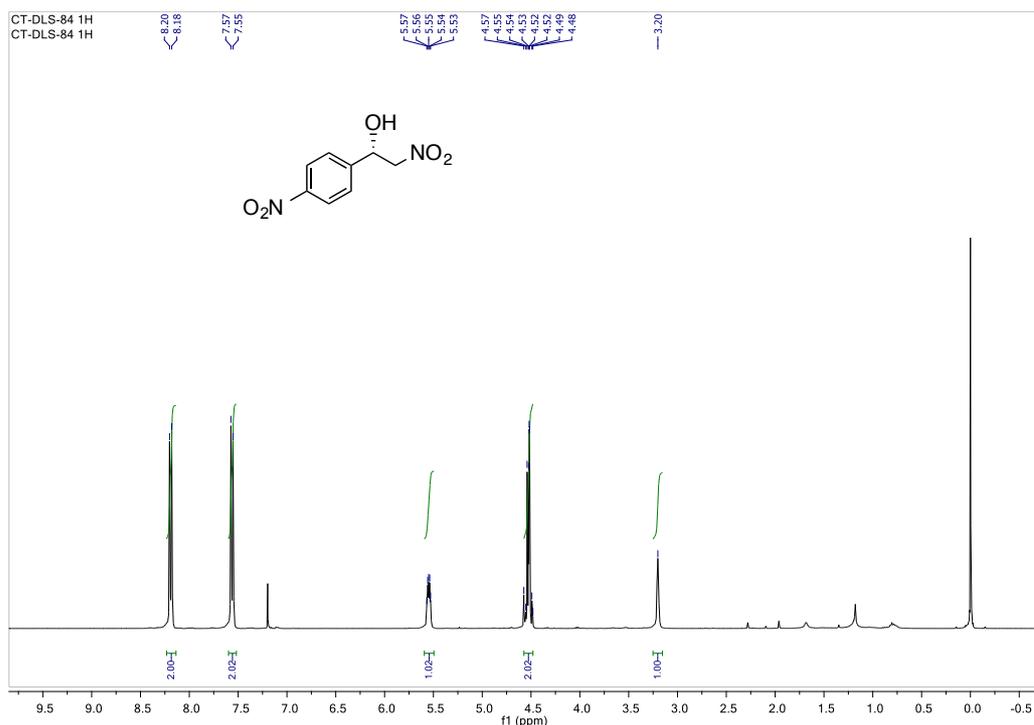


Figure A. 31.  $^1\text{H}$  NMR spectrum of compound 35b

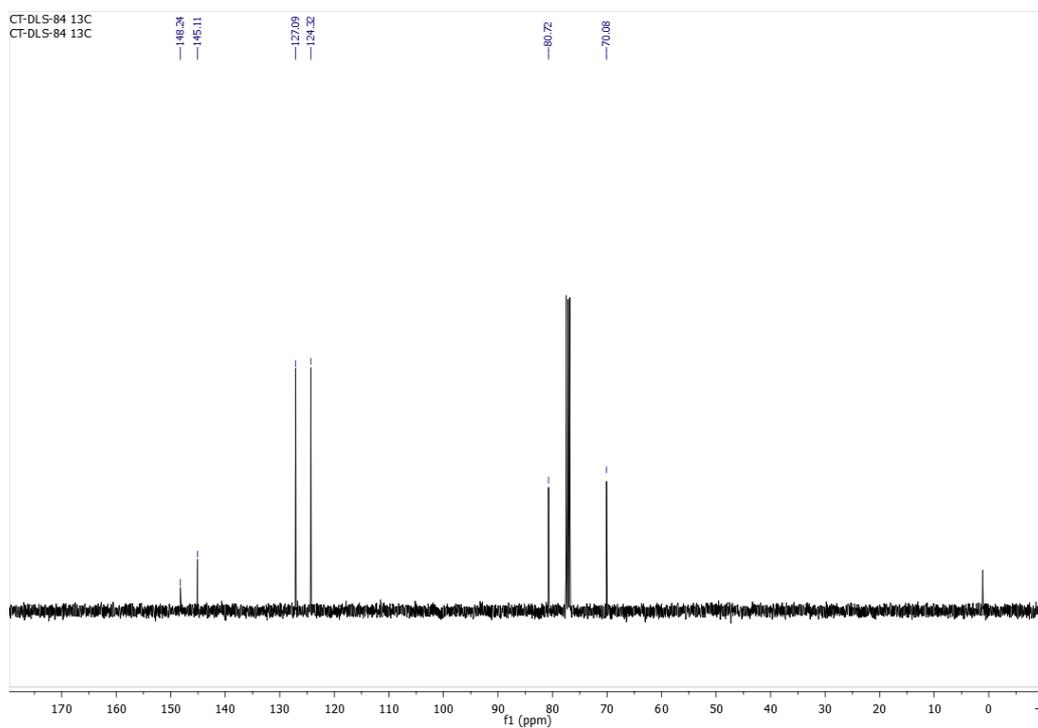


Figure A. 32.  $^{13}\text{C}$  NMR spectrum of compound 35b

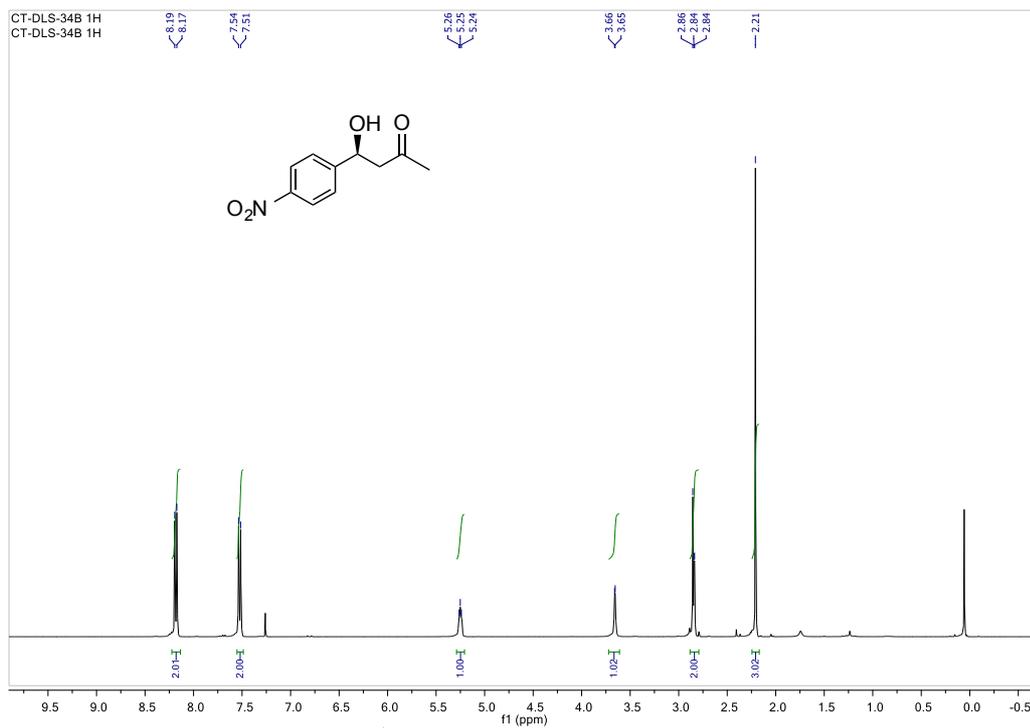


Figure A. 33.  $^1\text{H}$  NMR spectrum of compound 37b

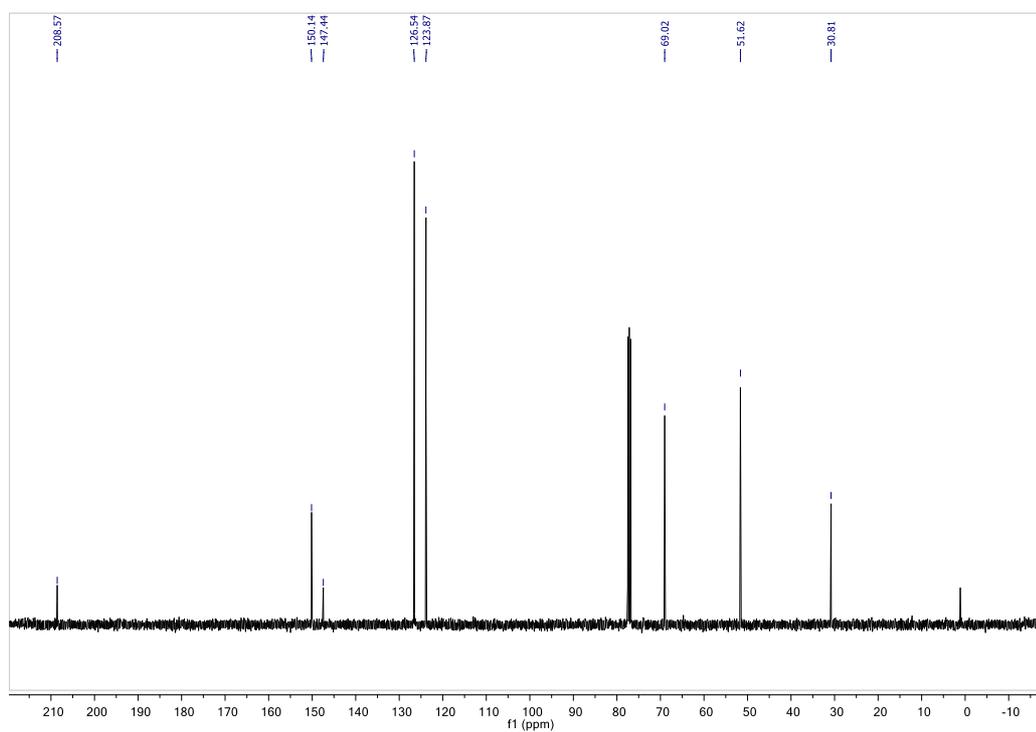


Figure A. 34.  $^{13}\text{C}$  NMR spectrum of compound 37b

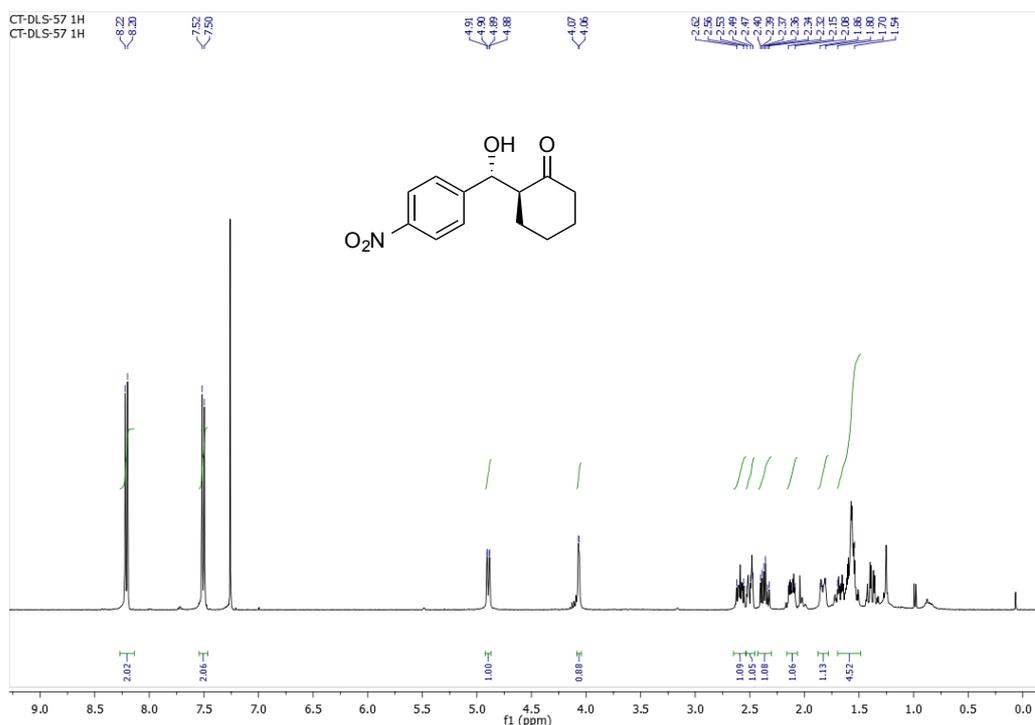


Figure A. 35. <sup>1</sup>H NMR spectrum of *anti*-60b

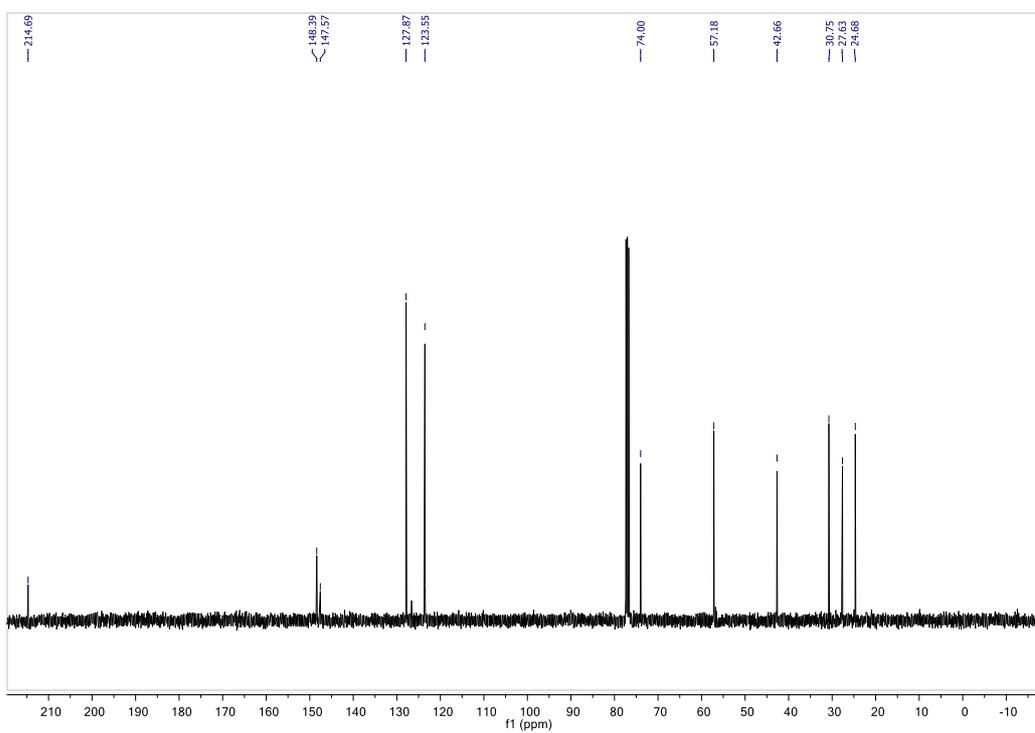


Figure A. 36. <sup>13</sup>C NMR spectrum of *anti*-60b

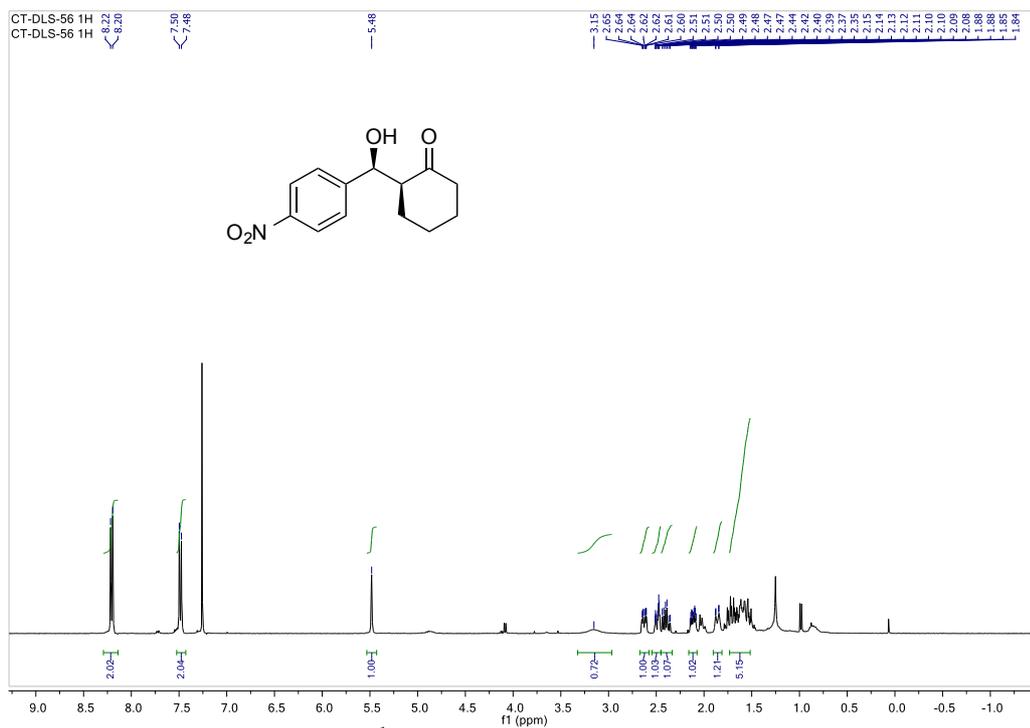


Figure A. 37. <sup>1</sup>H NMR spectrum of compound 60b

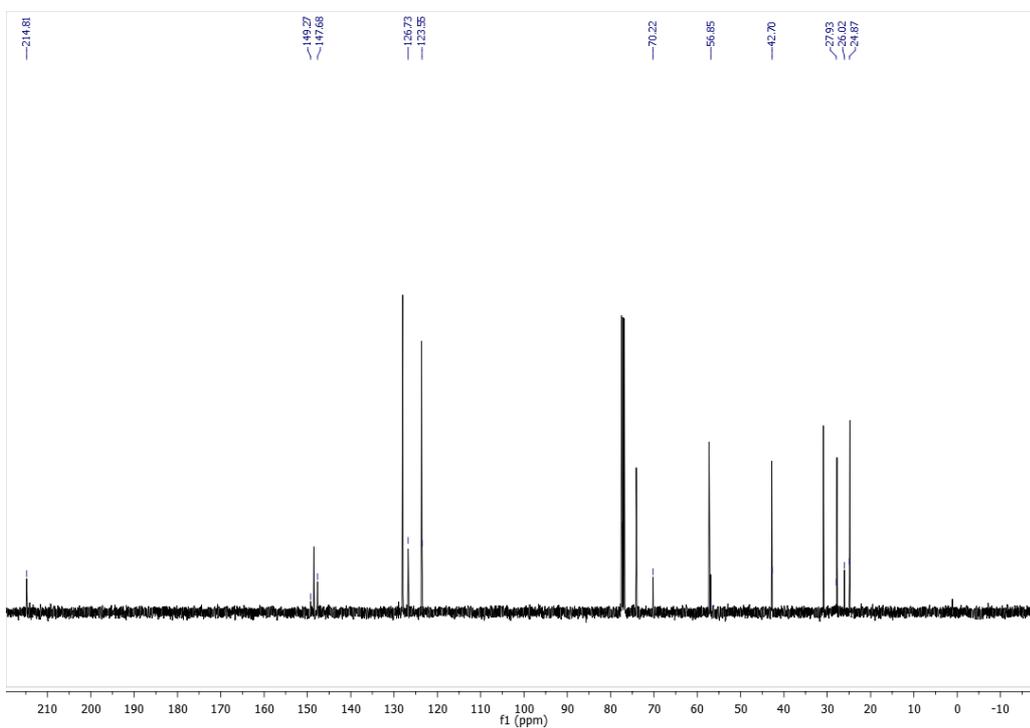


Figure A. 38. <sup>13</sup>C NMR spectrum of compound 60b

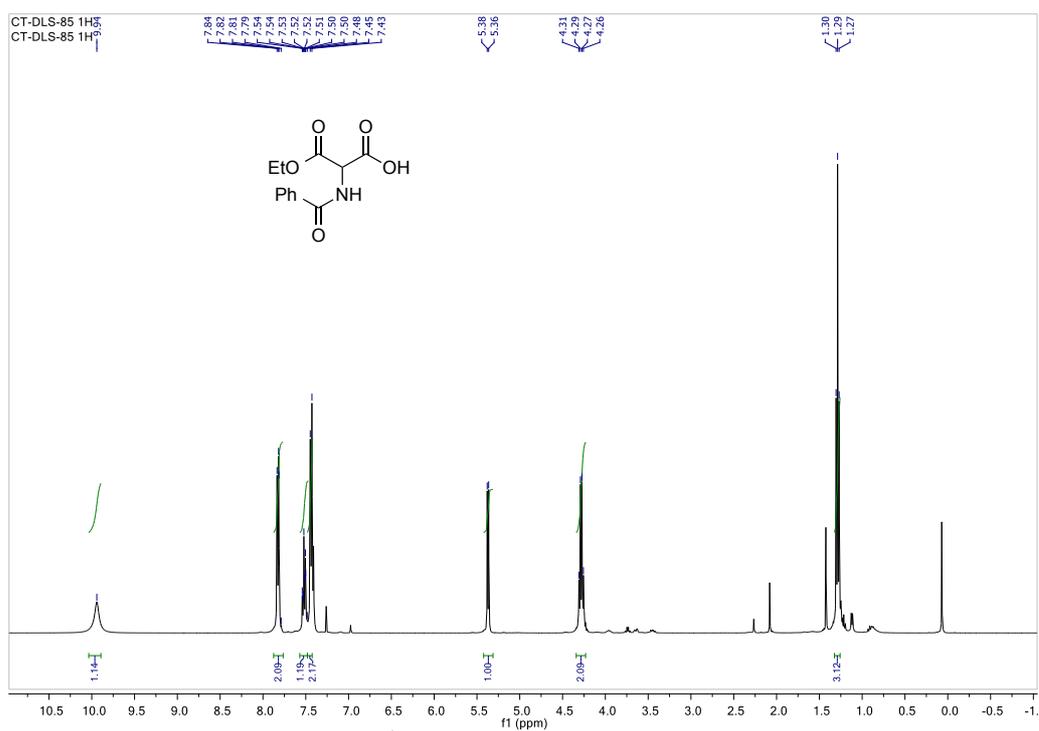


Figure A. 39.  $^1\text{H}$  NMR spectrum of compound 54

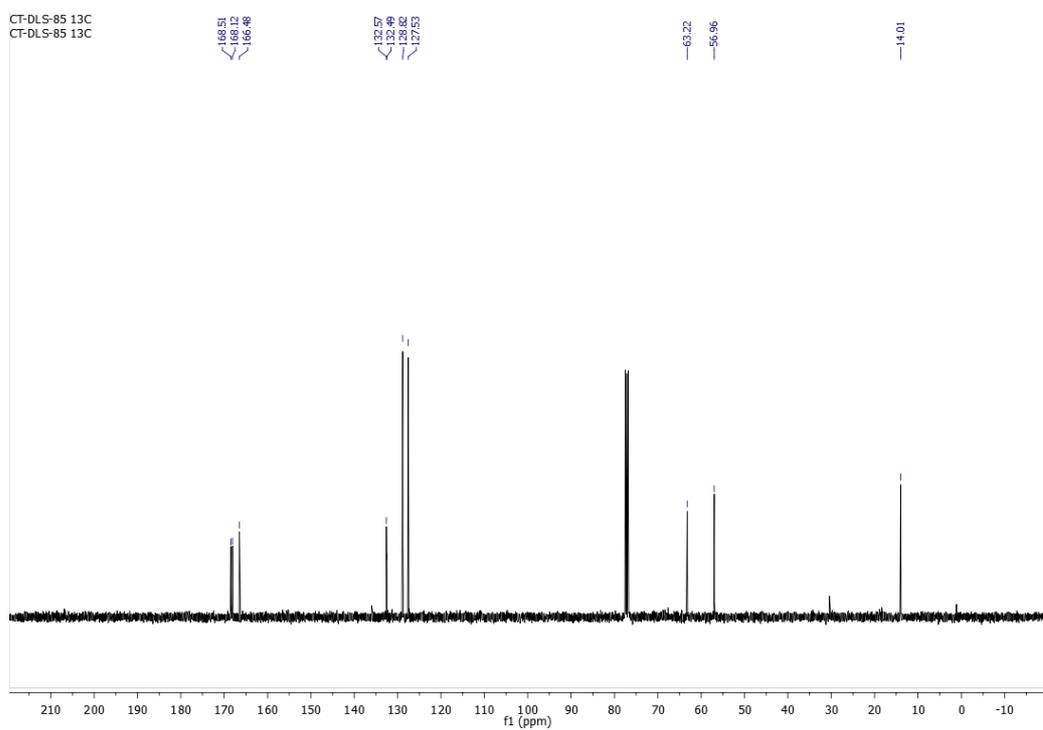
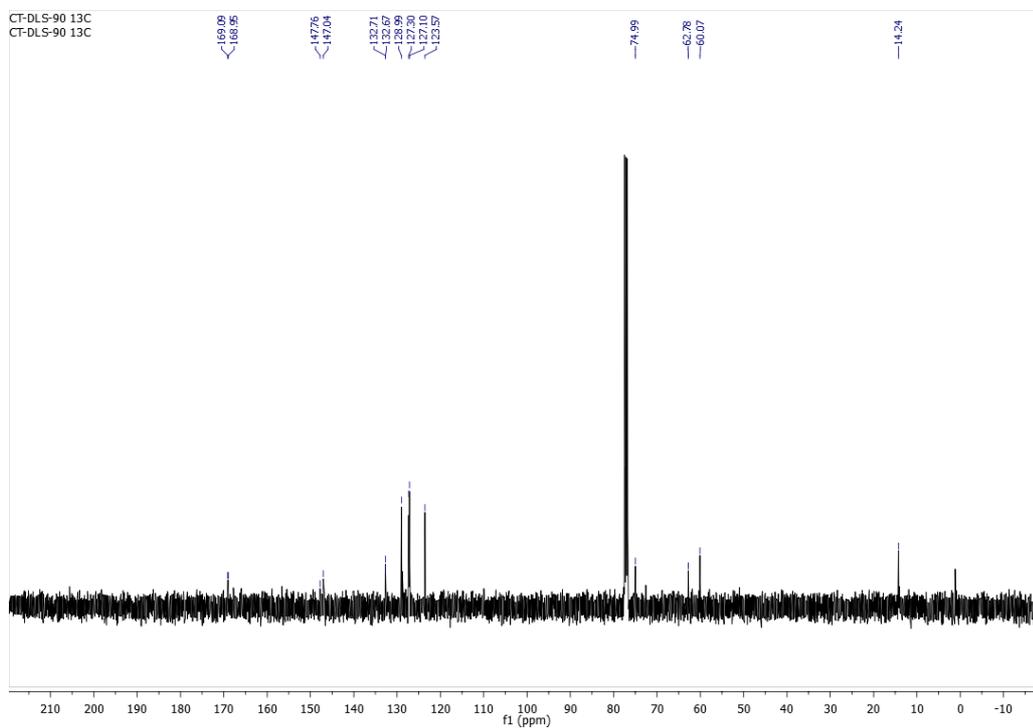
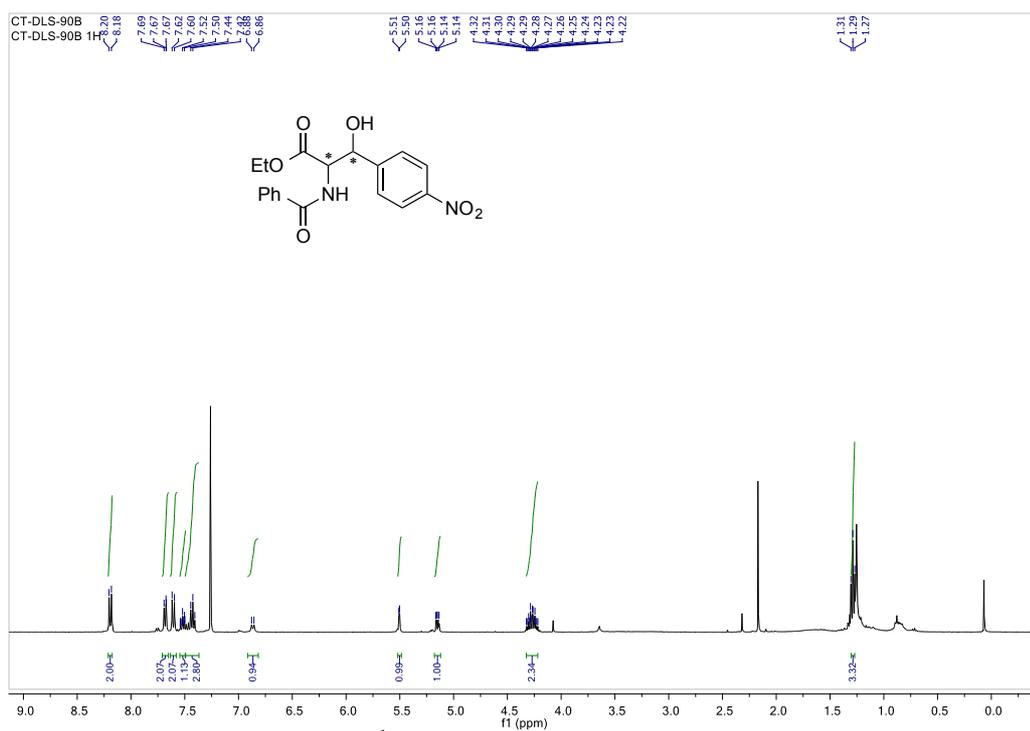


Figure A. 40.  $^{13}\text{C}$  NMR spectrum of compound 54



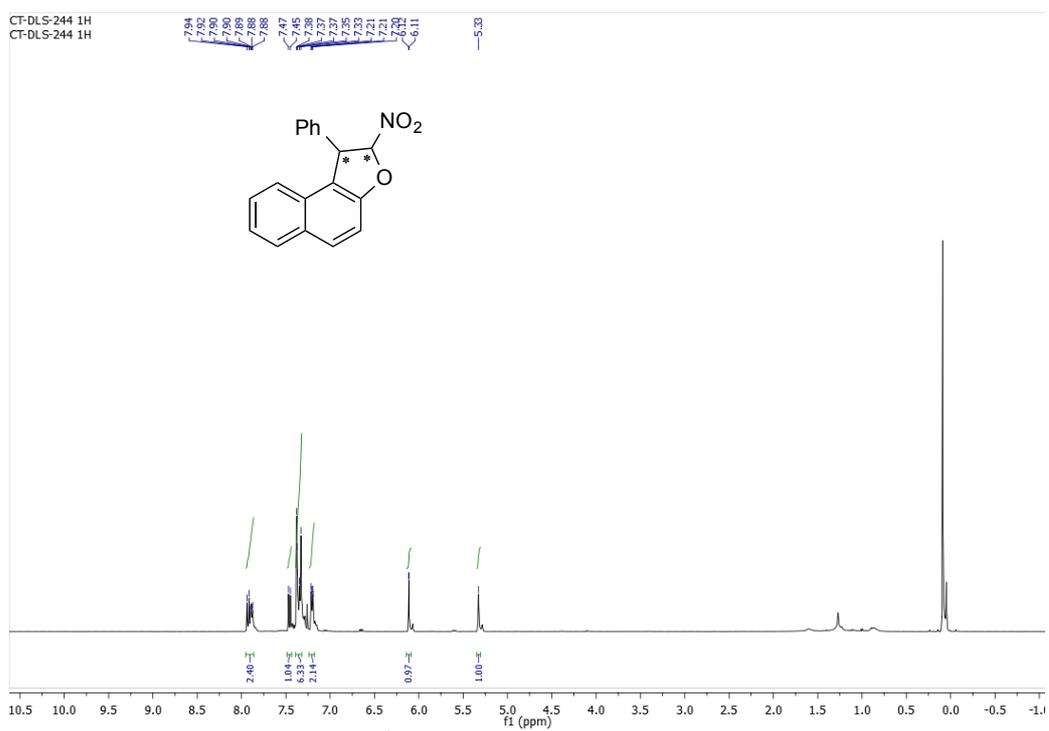


Figure A. 43.  $^1\text{H}$  NMR spectrum of compound 44a

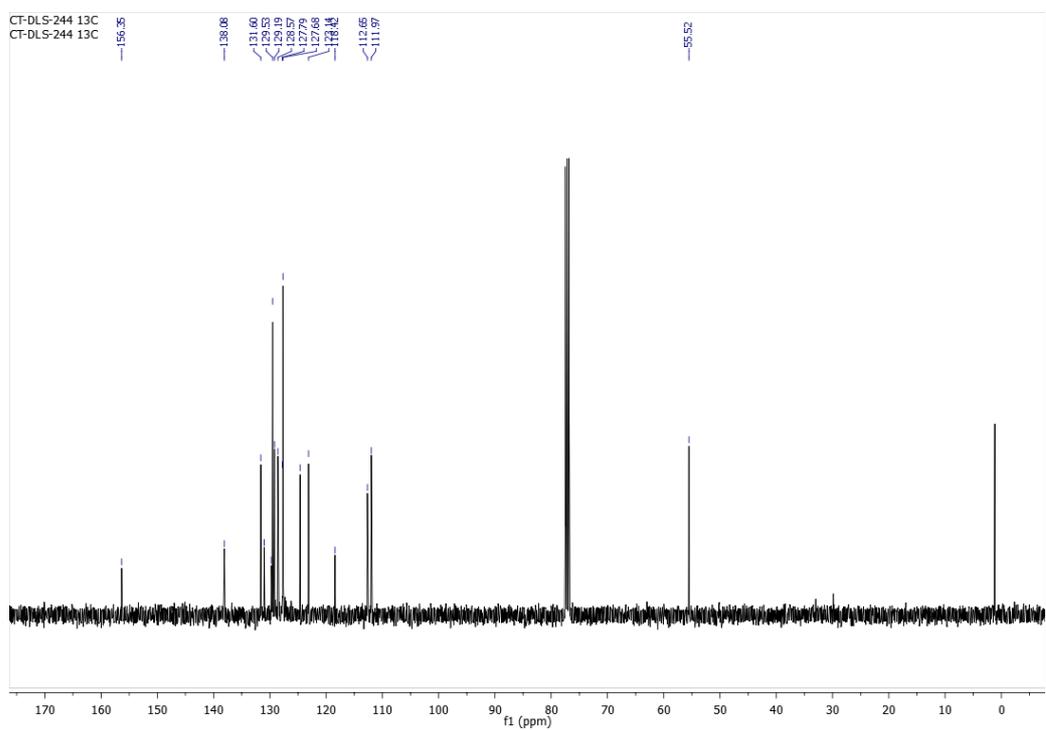


Figure A. 44.  $^{13}\text{C}$  NMR spectrum of compound 44a

## APPENDIX B

### HPLC DATA

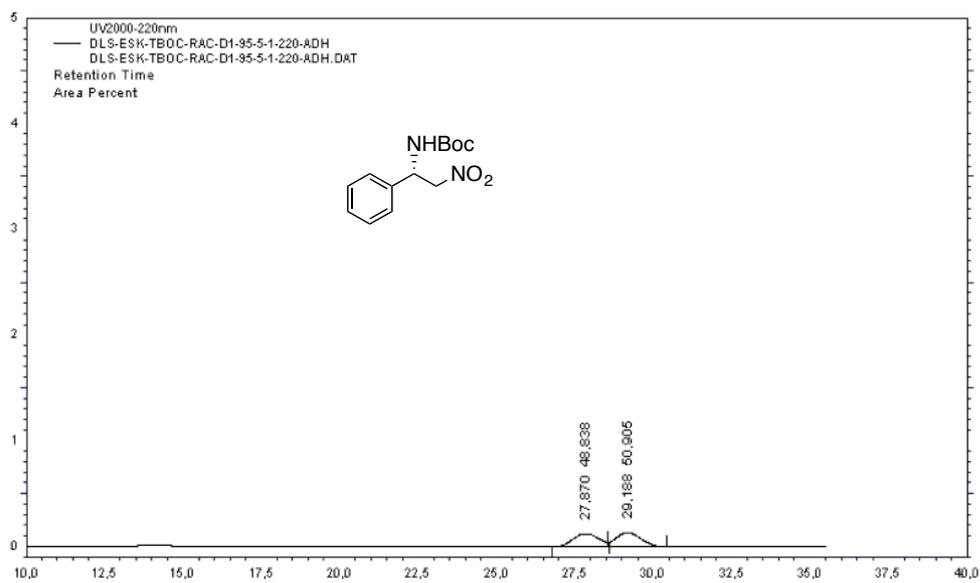


Figure B. 1. HPLC chromatogram of *rac*-24a

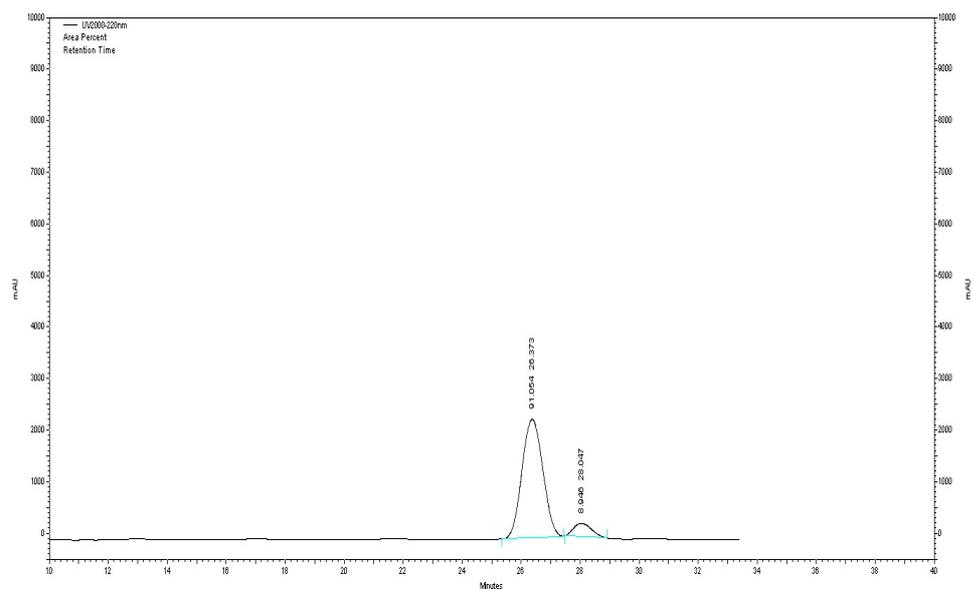
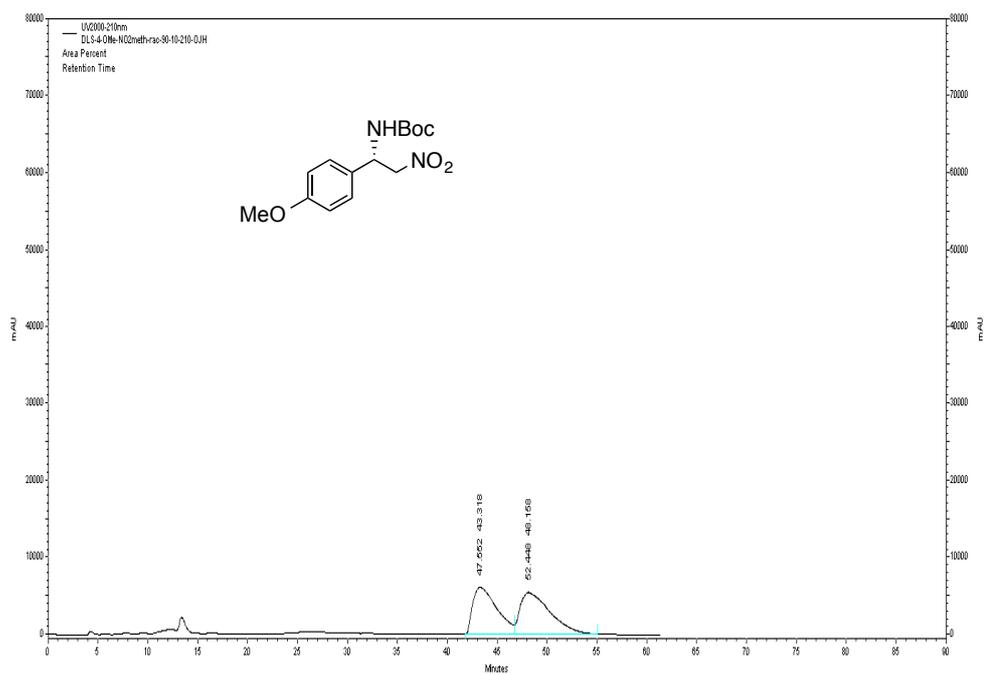
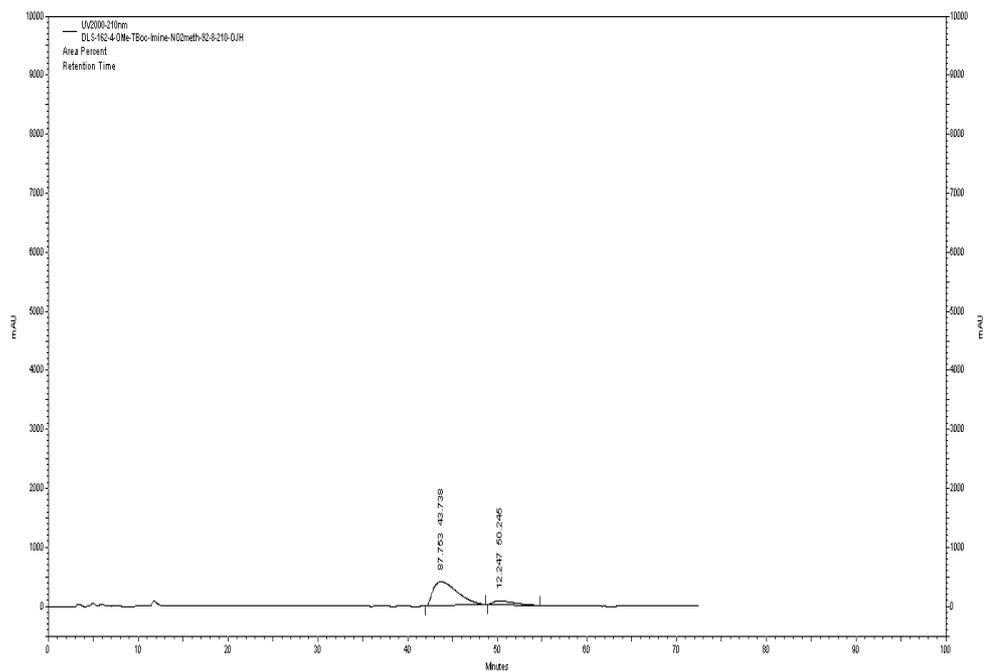


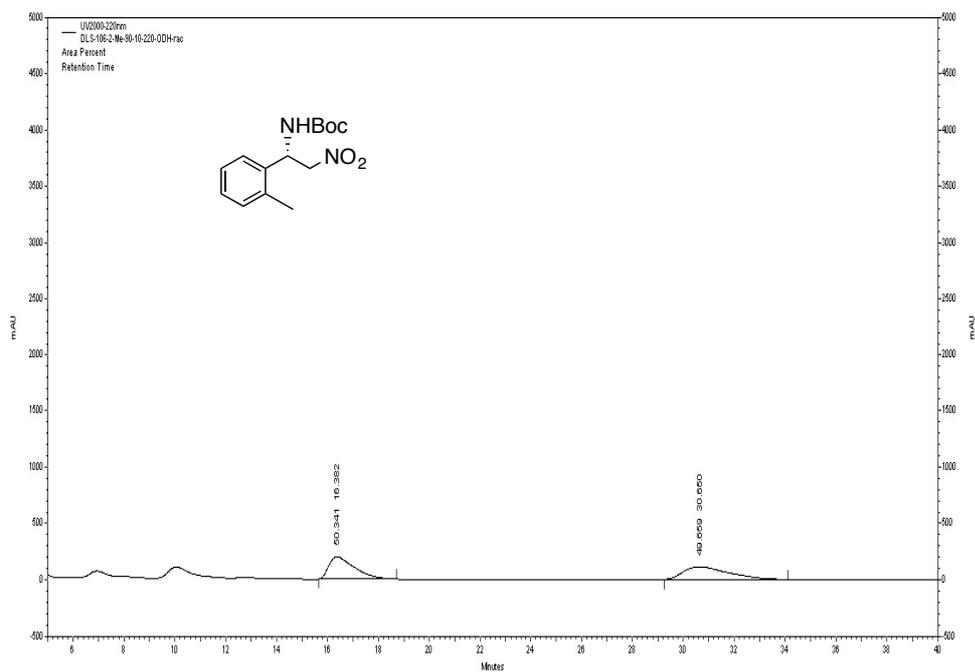
Figure B. 2. HPLC chromatogram of enantiomerically enriched 24a



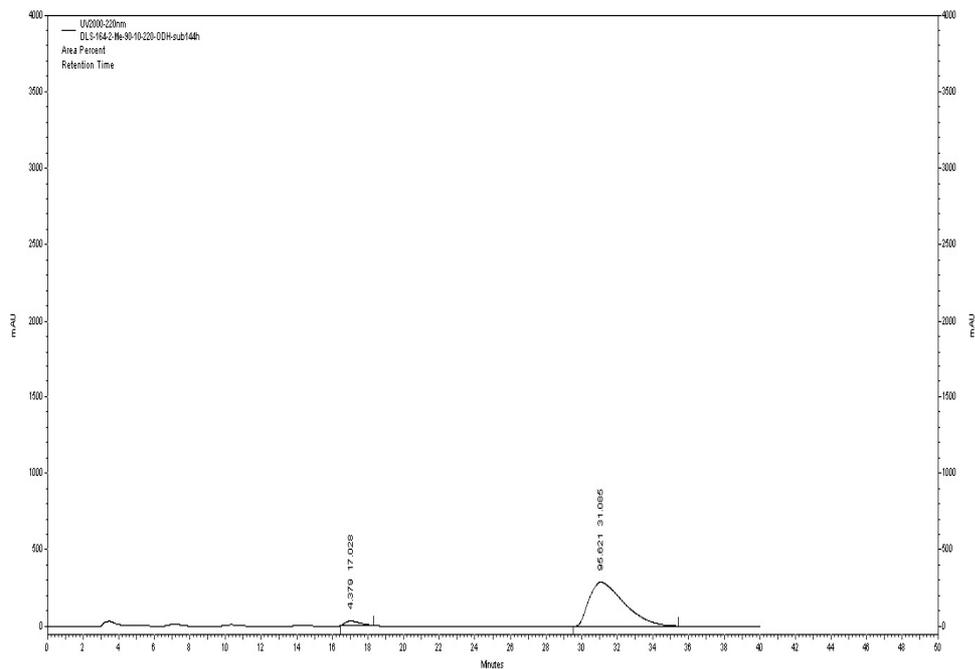
**Figure B. 3.** HPLC chromatogram of *rac*-24b



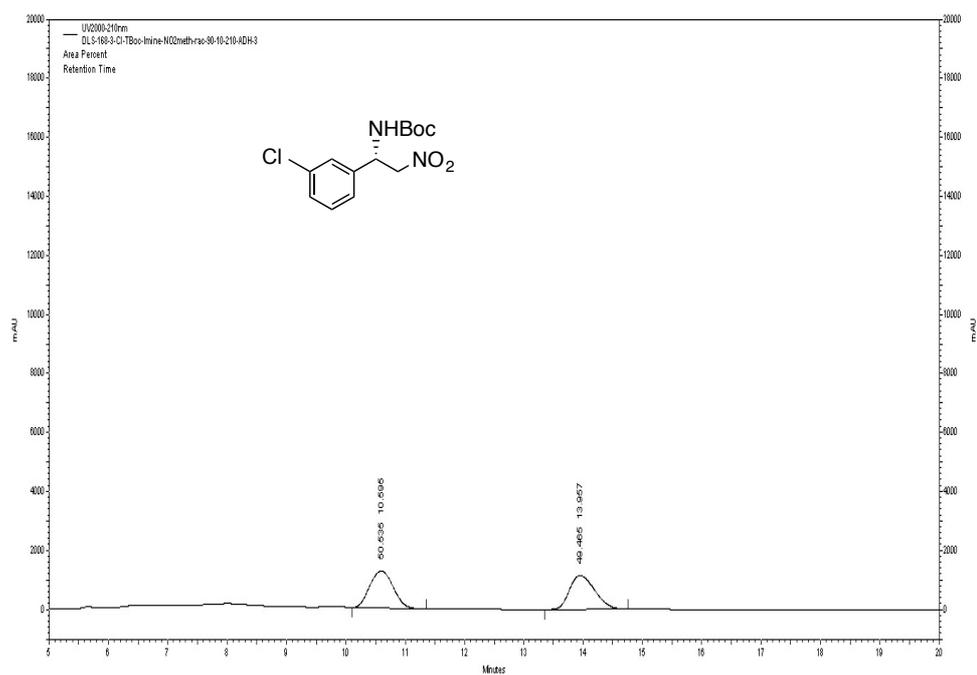
**Figure B. 4.** HPLC chromatogram of enantiomerically enriched 24b



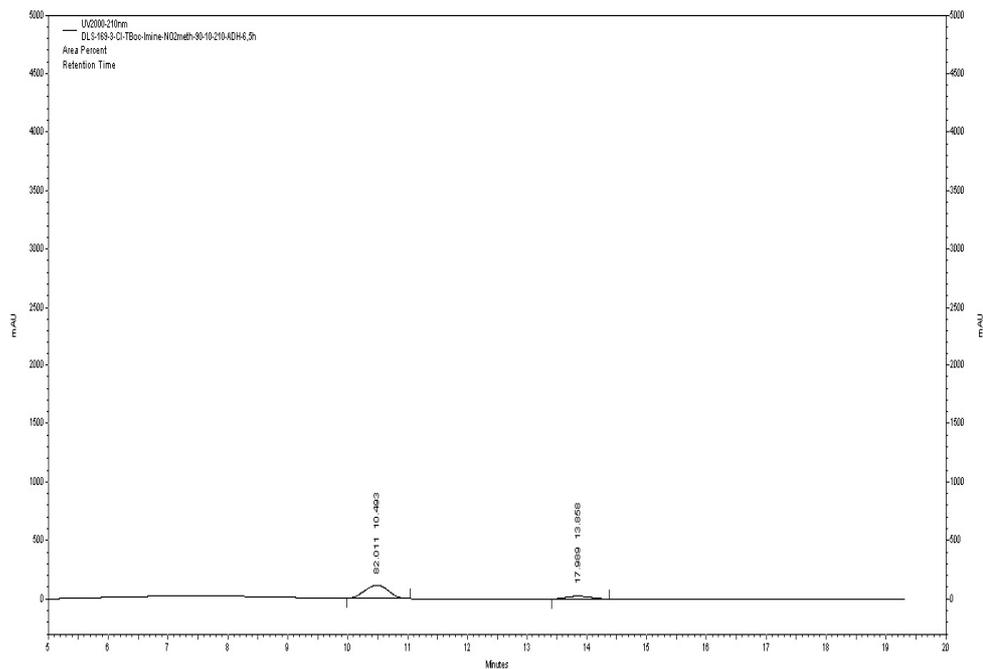
**Figure B. 5.** HPLC chromatogram of *rac*-24c



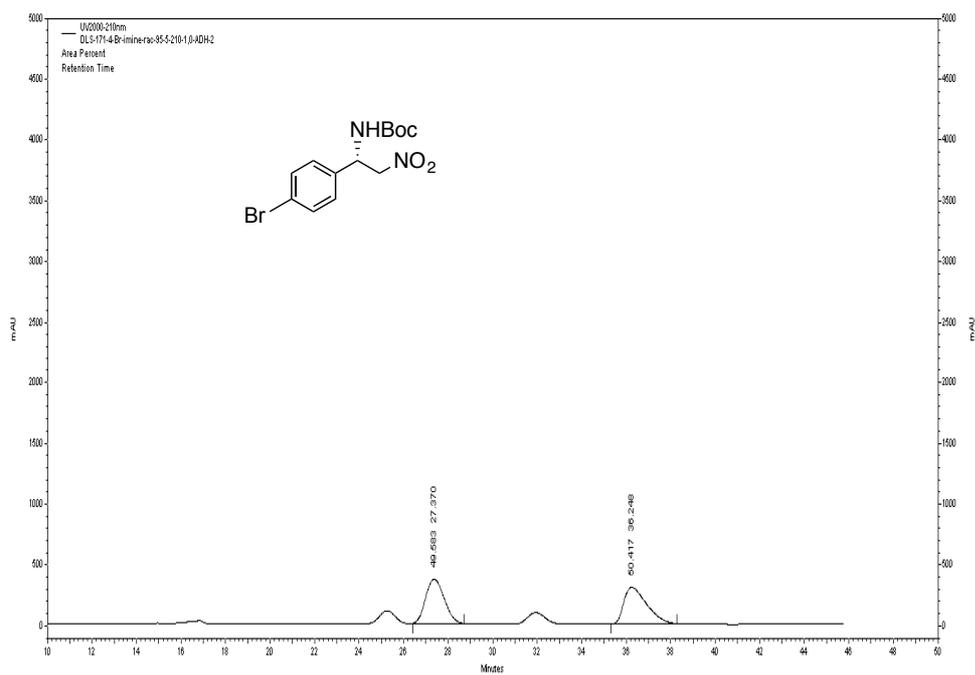
**Figure B. 6.** HPLC chromatogram of enantiomerically enriched 24c



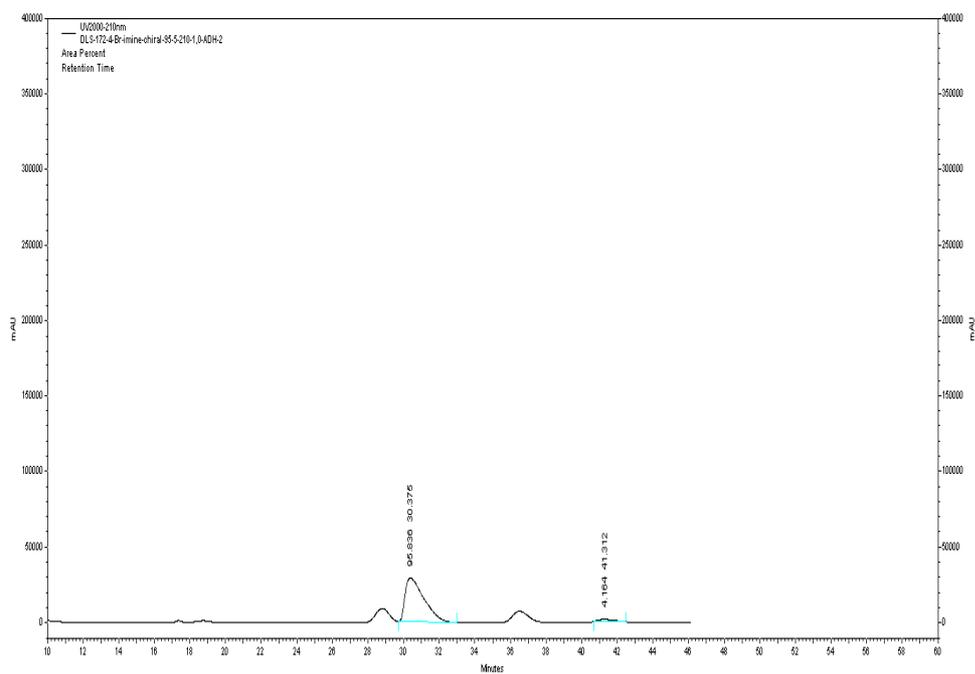
**Figure B. 7.** HPLC chromatogram of *rac*-24d



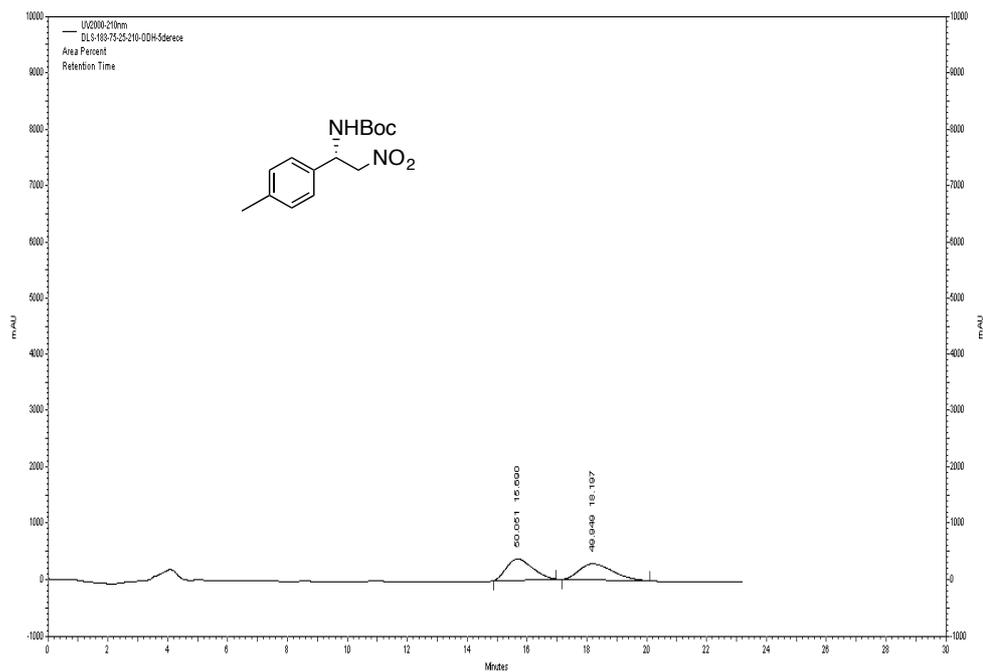
**Figure B. 8.** HPLC chromatogram of enantiomerically enriched 24d



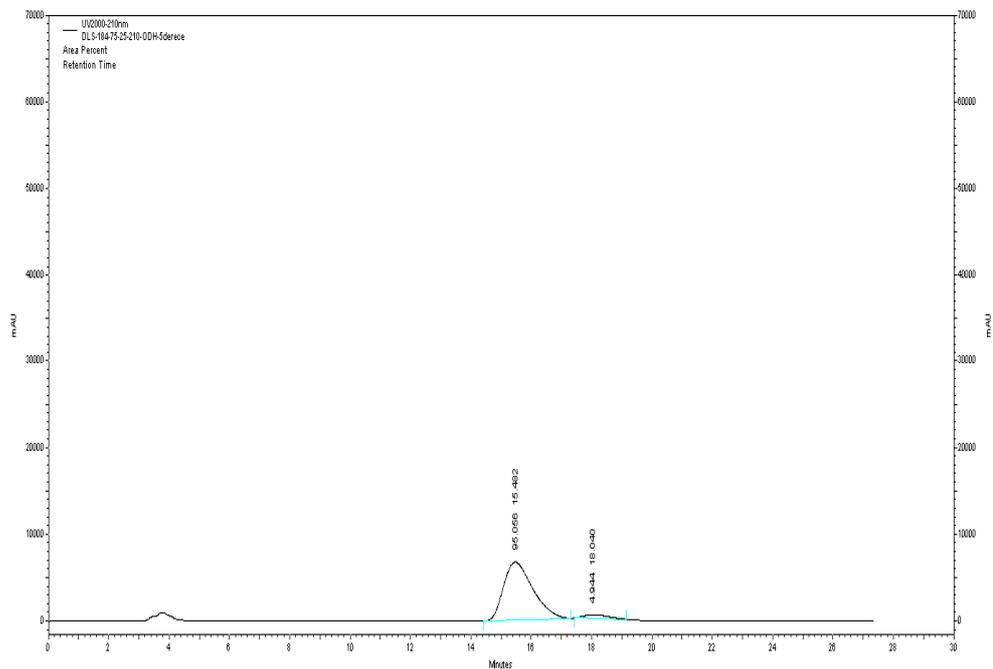
**Figure B. 9.** HPLC chromatogram of *rac*-24e



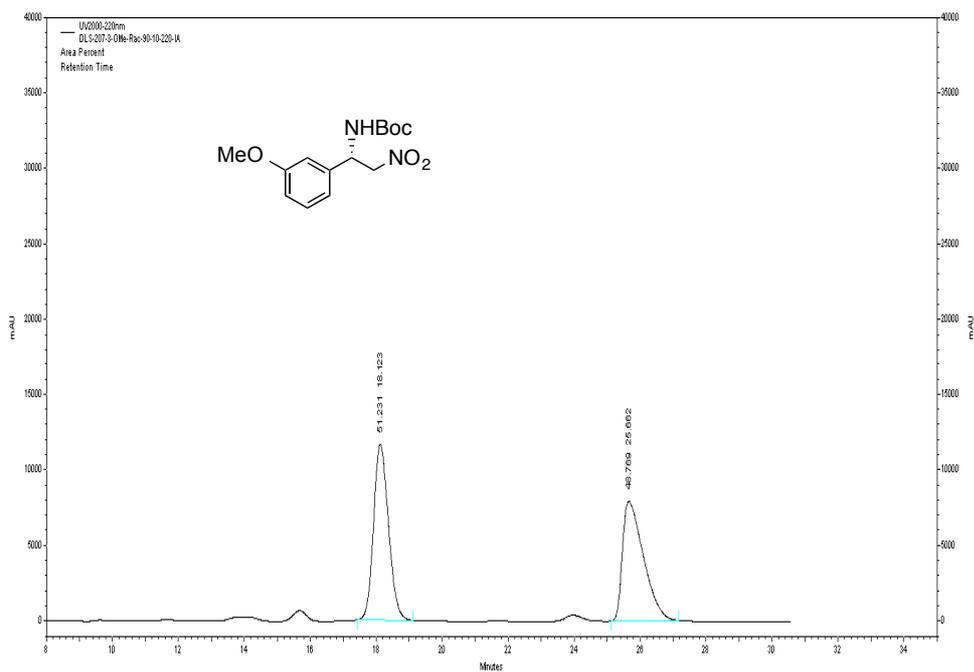
**Figure B. 10.** HPLC chromatogram of enantiomerically enriched 24e



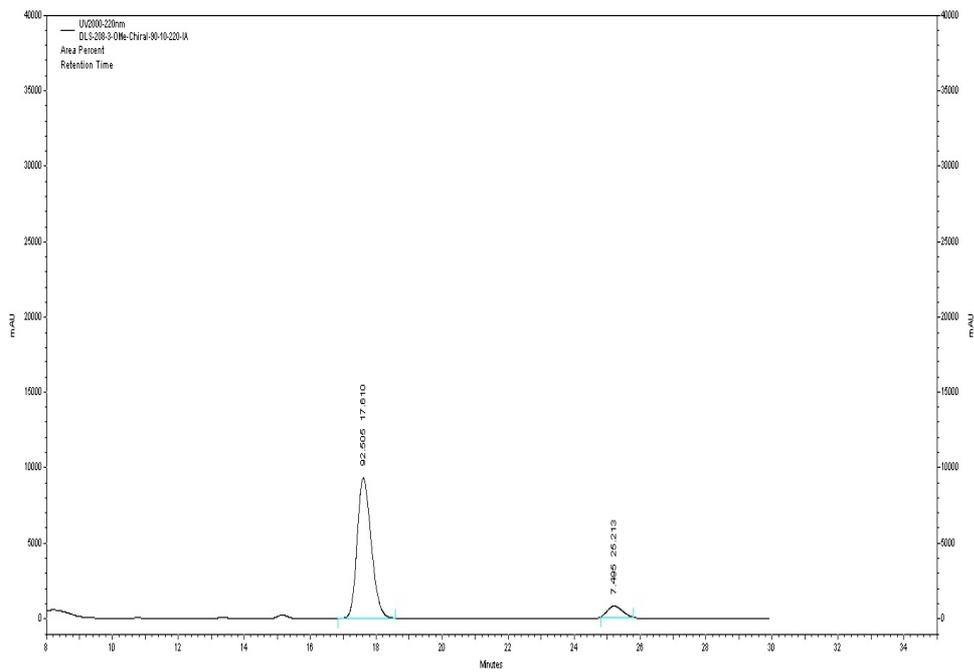
**Figure B. 11.** HPLC chromatogram of *rac*-24f



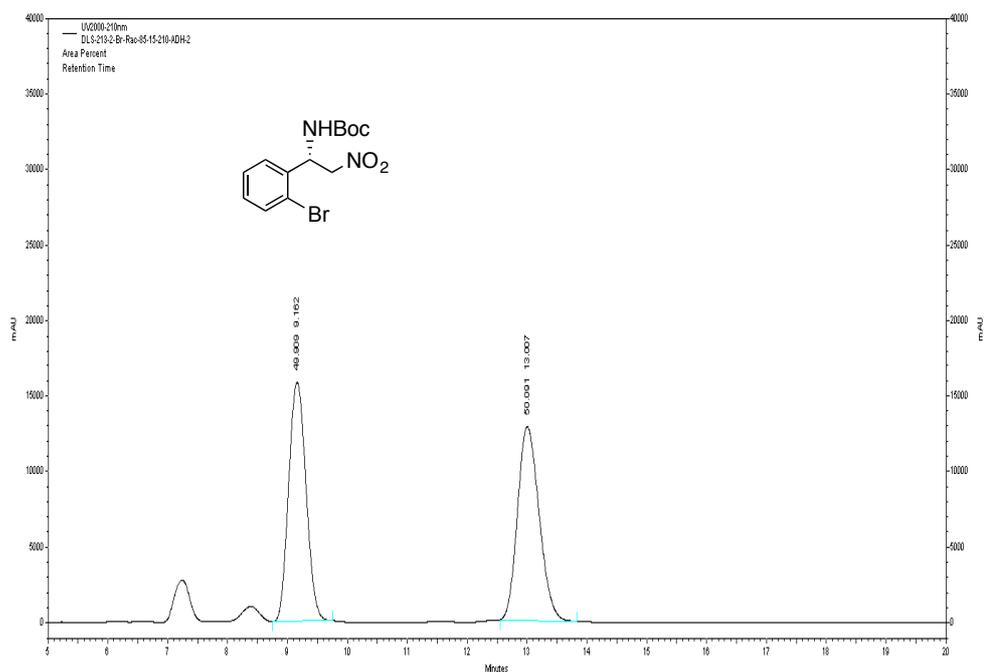
**Figure B. 12.** HPLC chromatogram of enantiomerically enriched 24f



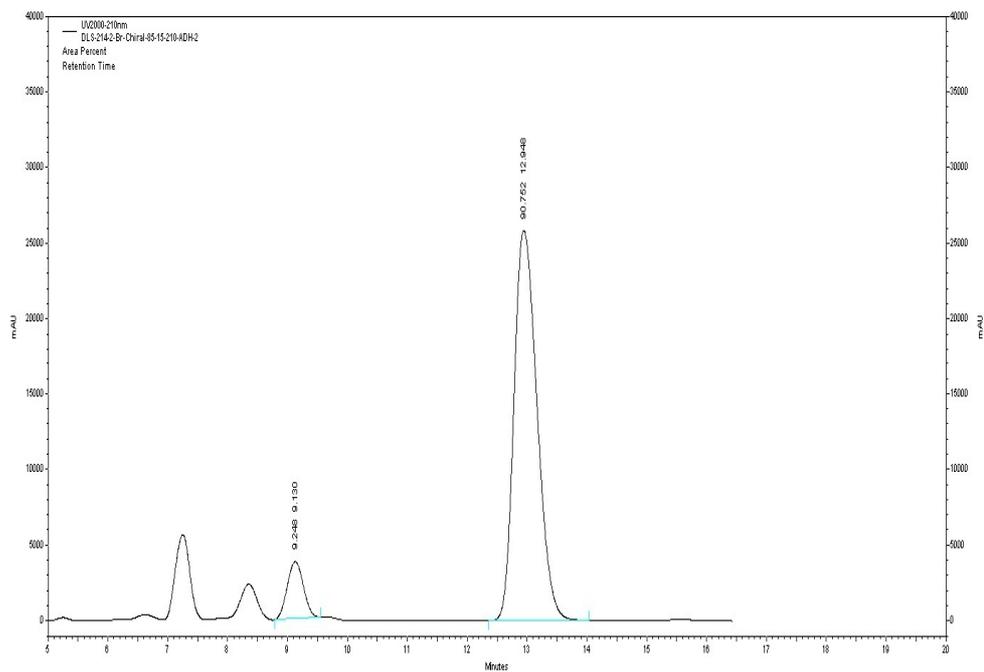
**Figure B. 13.** HPLC chromatogram of *rac*-24g



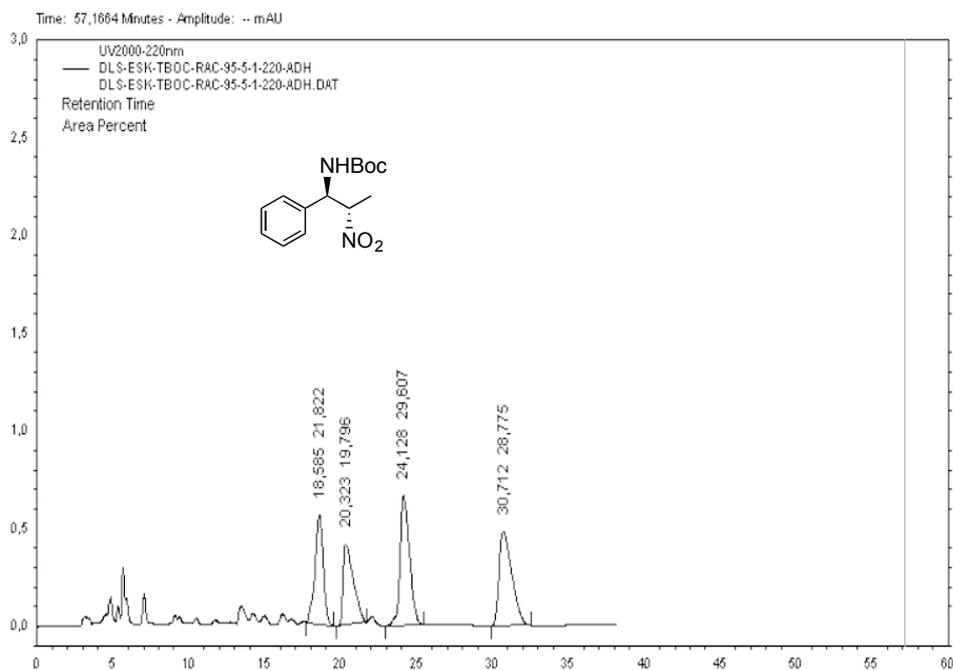
**Figure B. 14.** HPLC chromatogram of enantiomerically enriched 24g



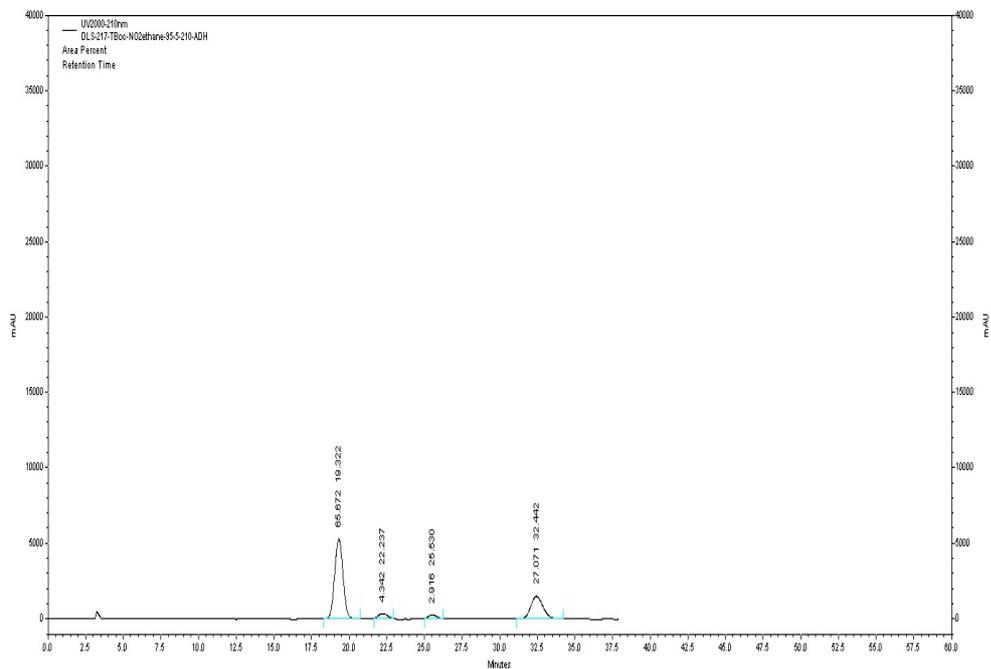
**Figure B. 15.** HPLC chromatogram of *rac*-24h



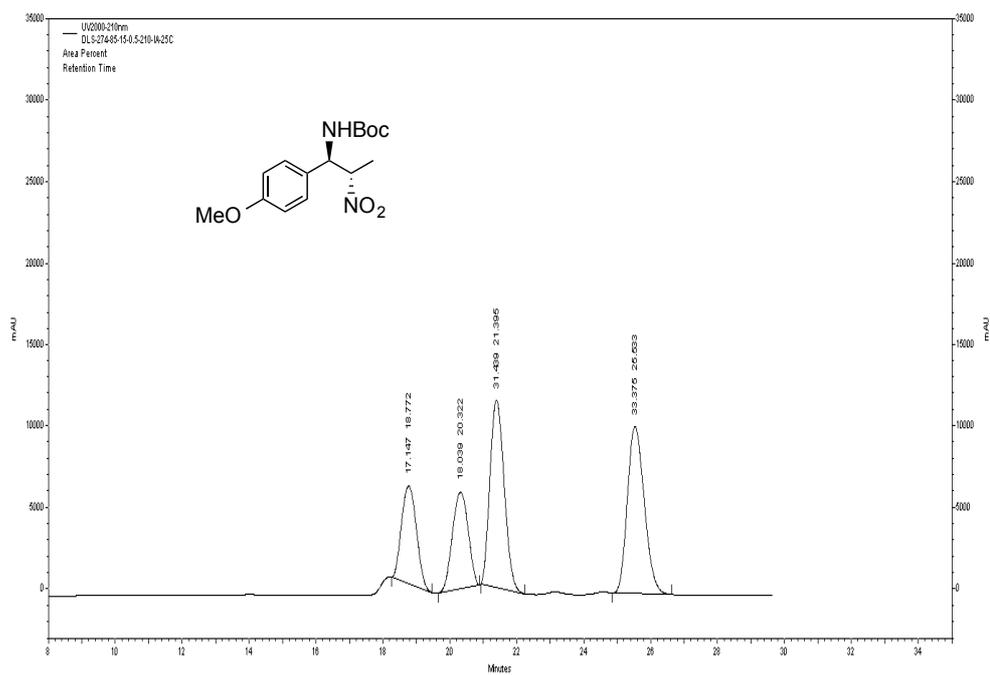
**Figure B. 16.** HPLC chromatogram of enantiomerically enriched 24h



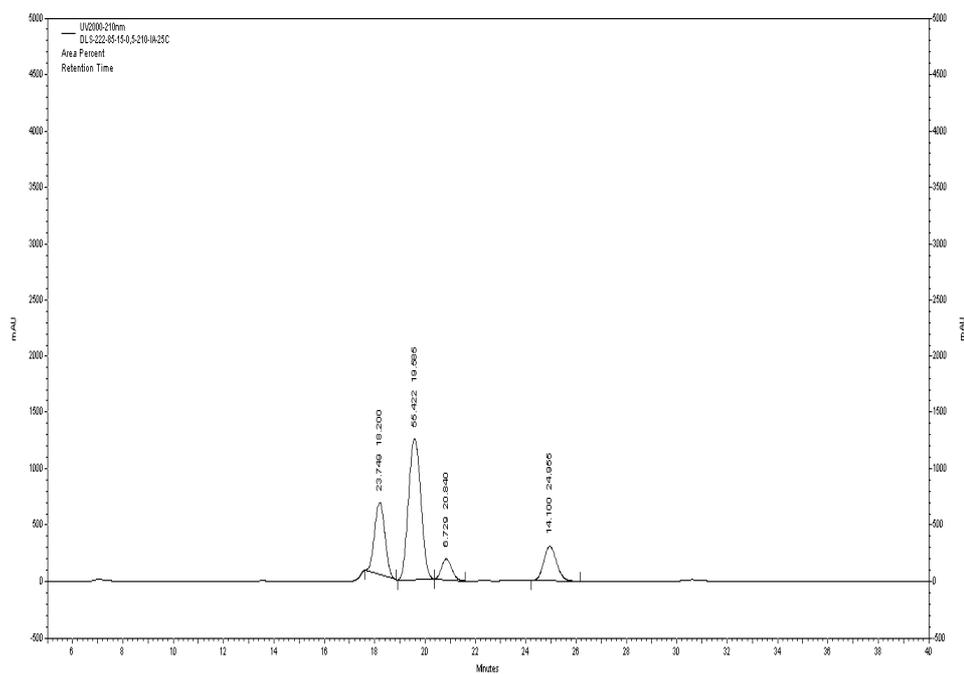
**Figure B. 17.** HPLC chromatogram of diastereomeric mixture of *rac*-**28a**



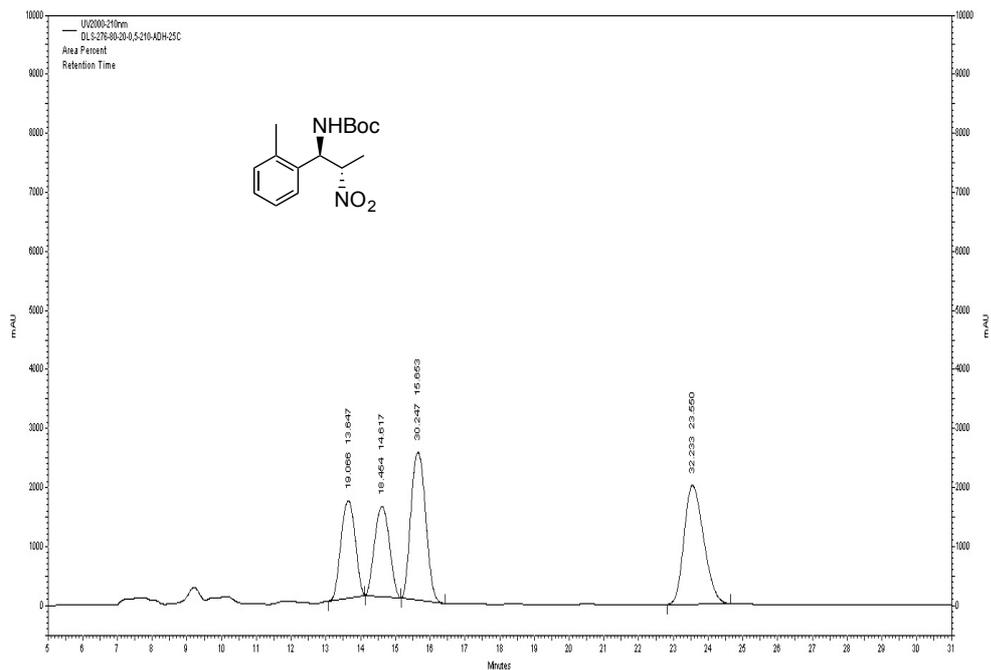
**Figure B. 18.** HPLC chromatogram of enantiomerically enriched **28a**



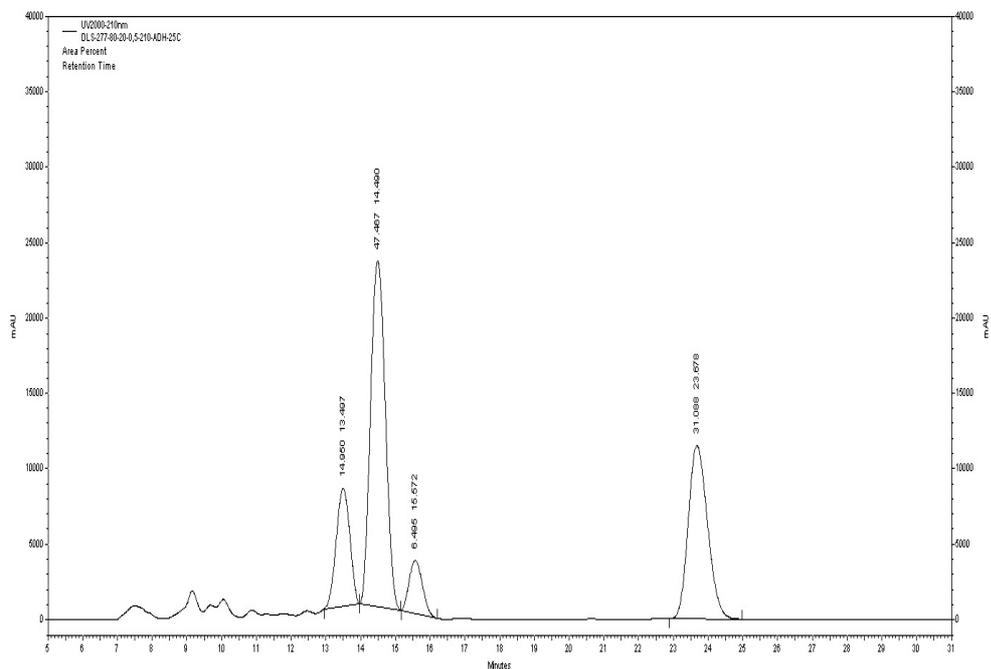
**Figure B. 19.** HPLC chromatogram of diastereomeric mixture of *rac*-**28b**



**Figure B. 20.** HPLC chromatogram of enantiomerically enriched **28b**



**Figure B. 21.** HPLC chromatogram of *rac*-28c



**Figure B. 22.** HPLC chromatogram of enantiomerically enriched 28c

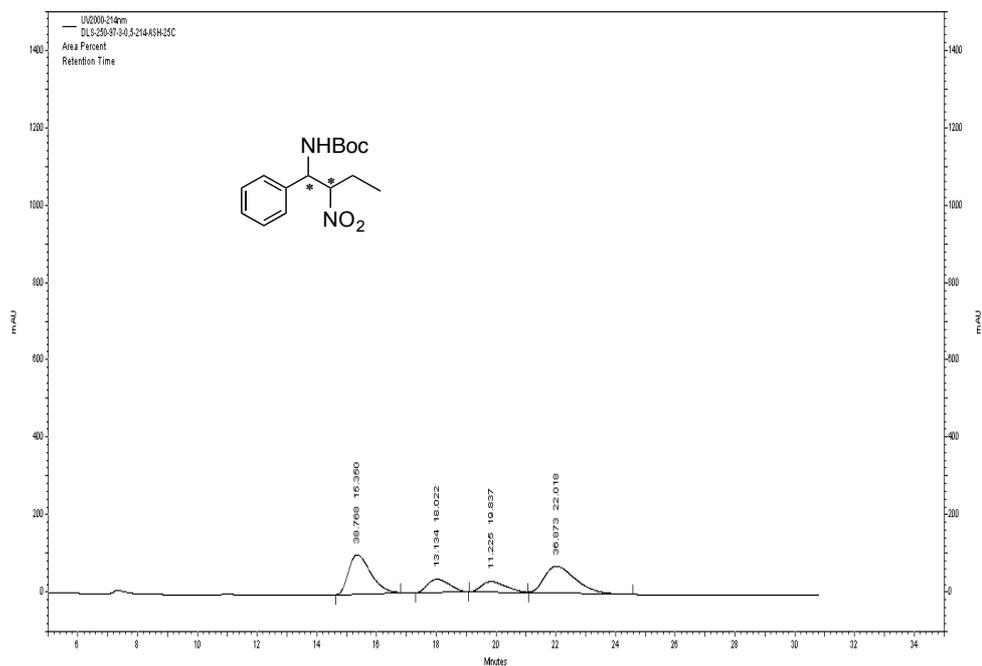


Figure B. 23. HPLC chromatogram of *rac*-31a

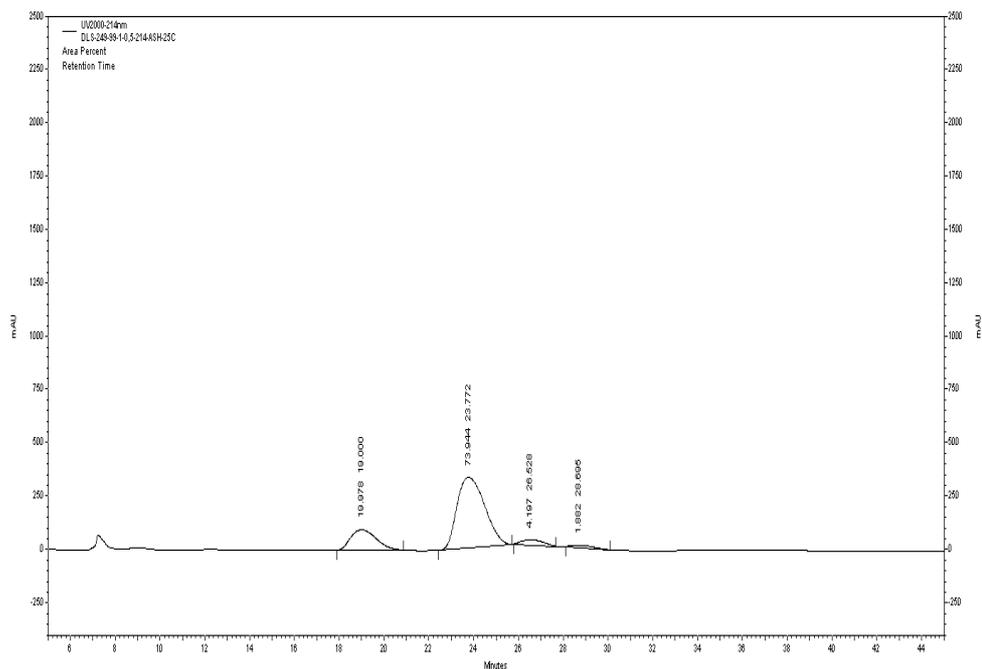
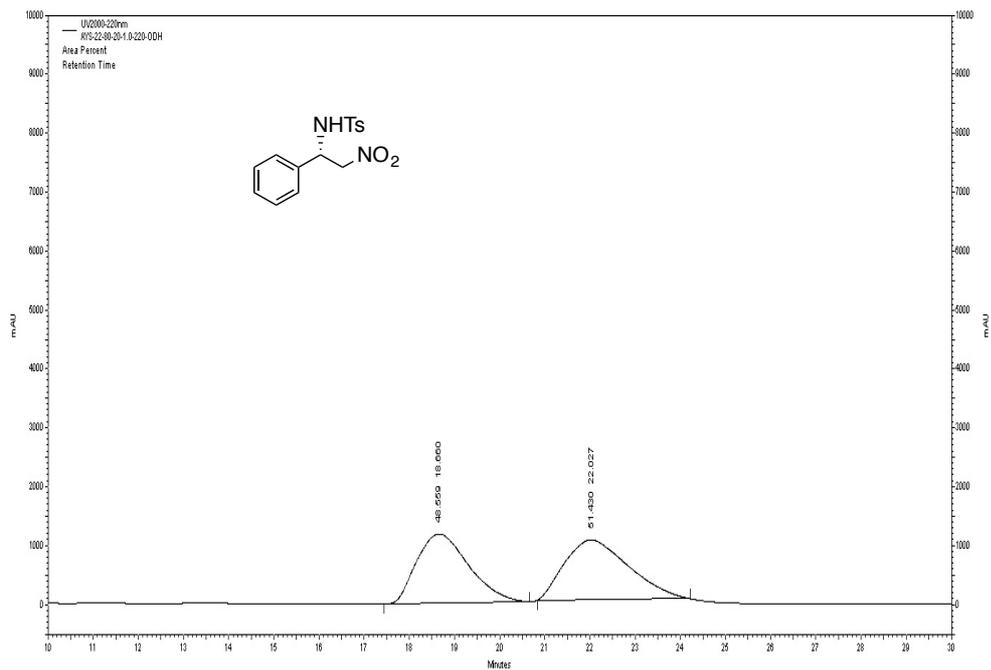
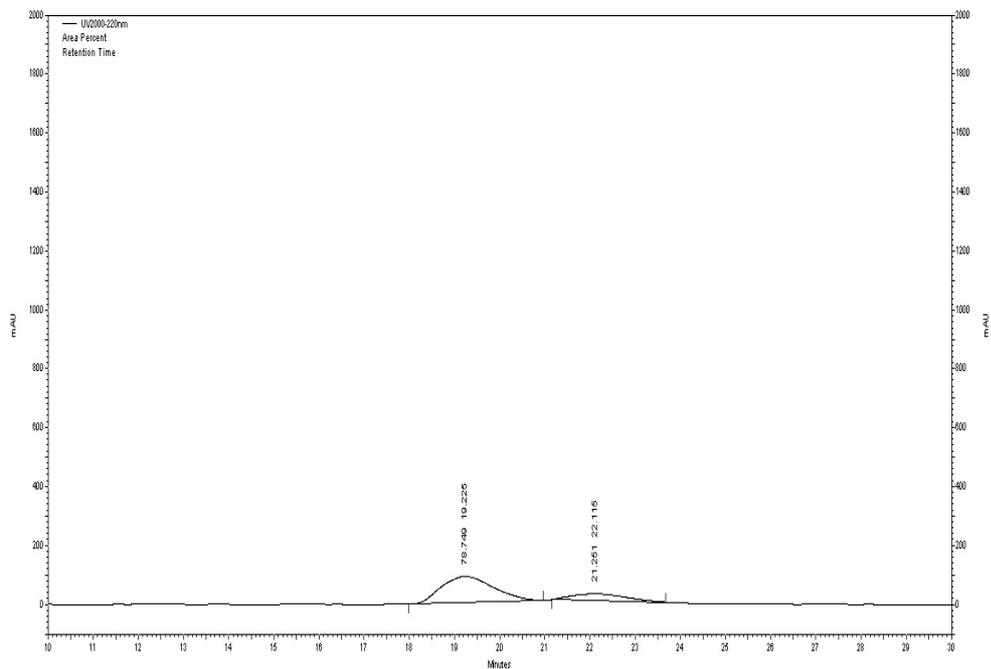


Figure B. 24. HPLC chromatogram of enantiomerically enriched 31a



**Figure B. 25.** HPLC chromatogram of *rac-22a*



**Figure B. 26.** HPLC chromatogram of enantiomerically enriched **22a**

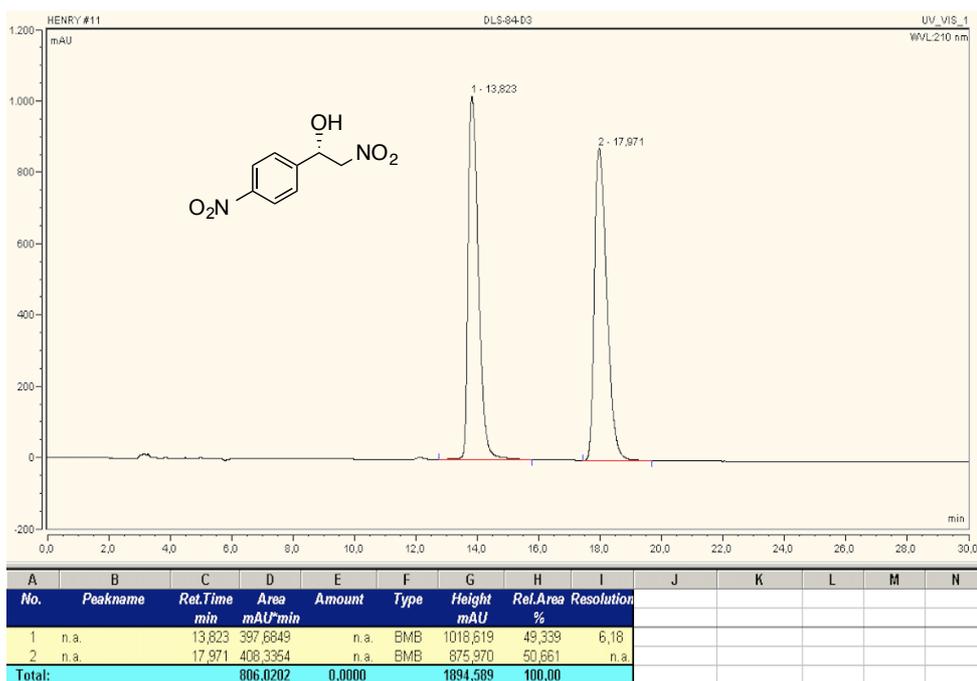


Figure B. 27. HPLC chromatogram of *rac*-35b

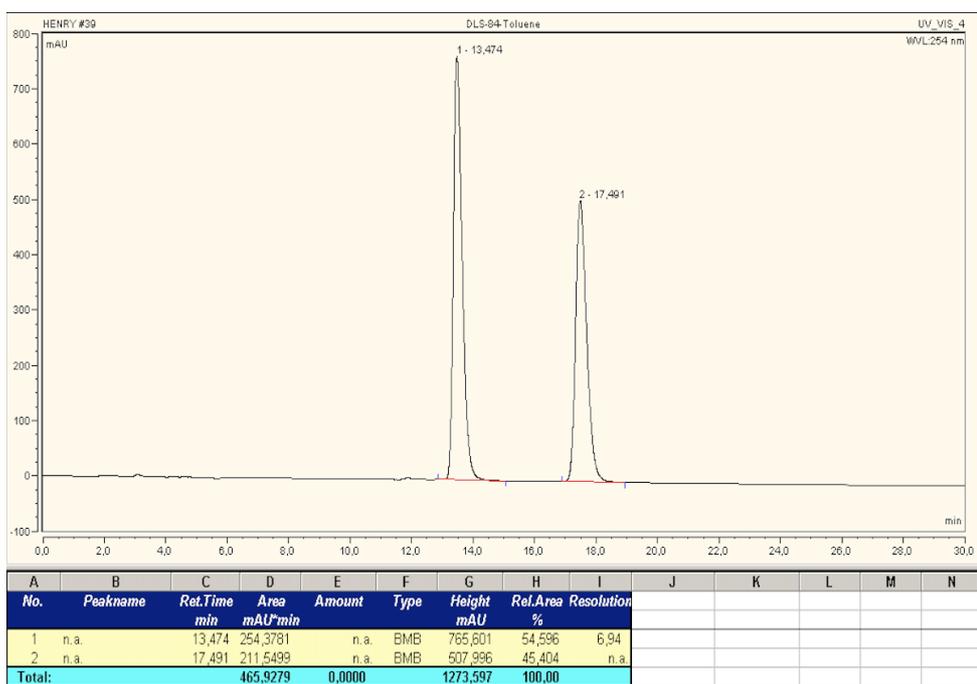


Figure B. 28. HPLC chromatogram of enantiomerically enriched 35b

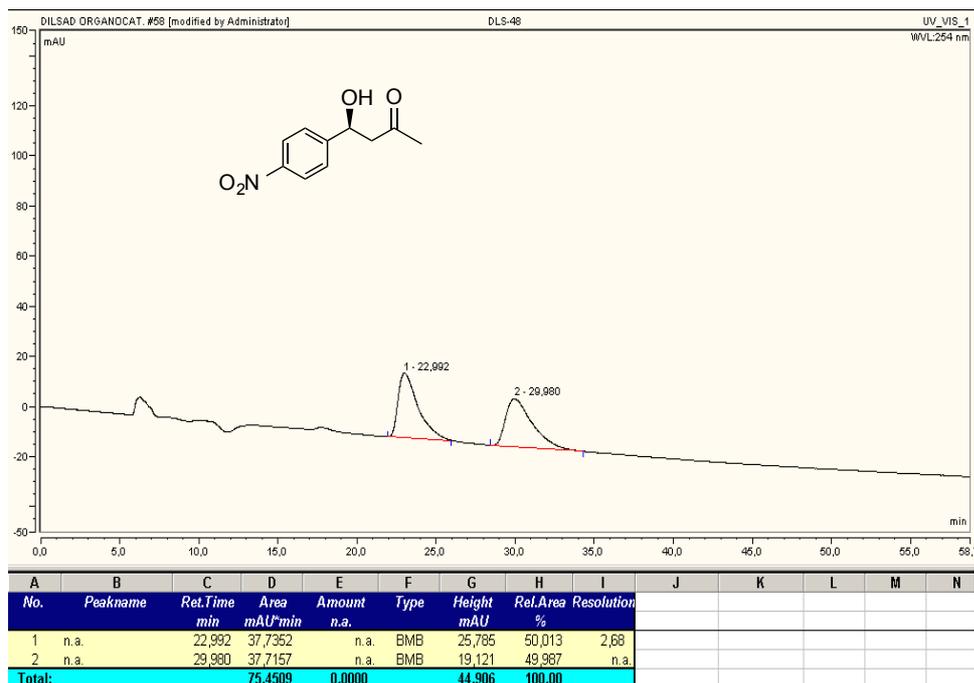


Figure B. 29. HPLC chromatogram of *rac*-37b

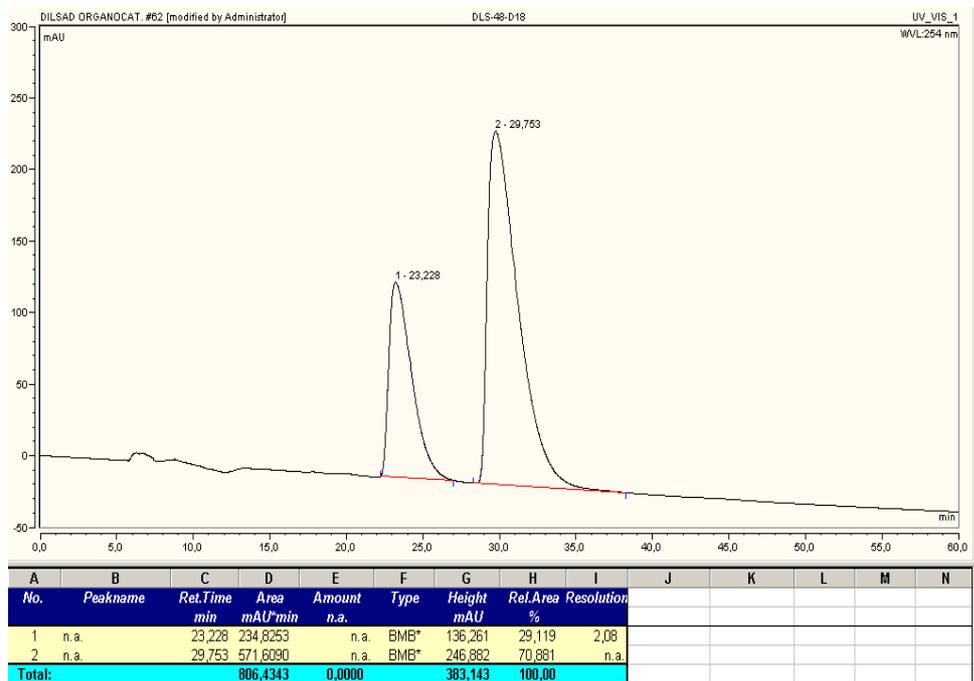


Figure B. 30. HPLC chromatogram of enantiomerically enriched 37b

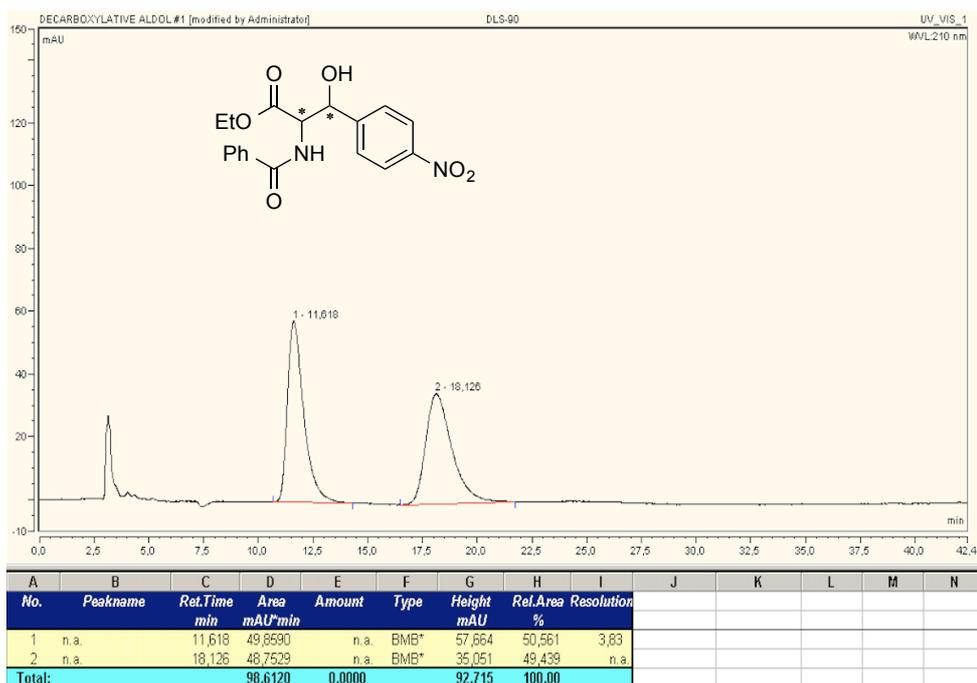


Figure B. 31. HPLC chromatogram of *rac*-55b

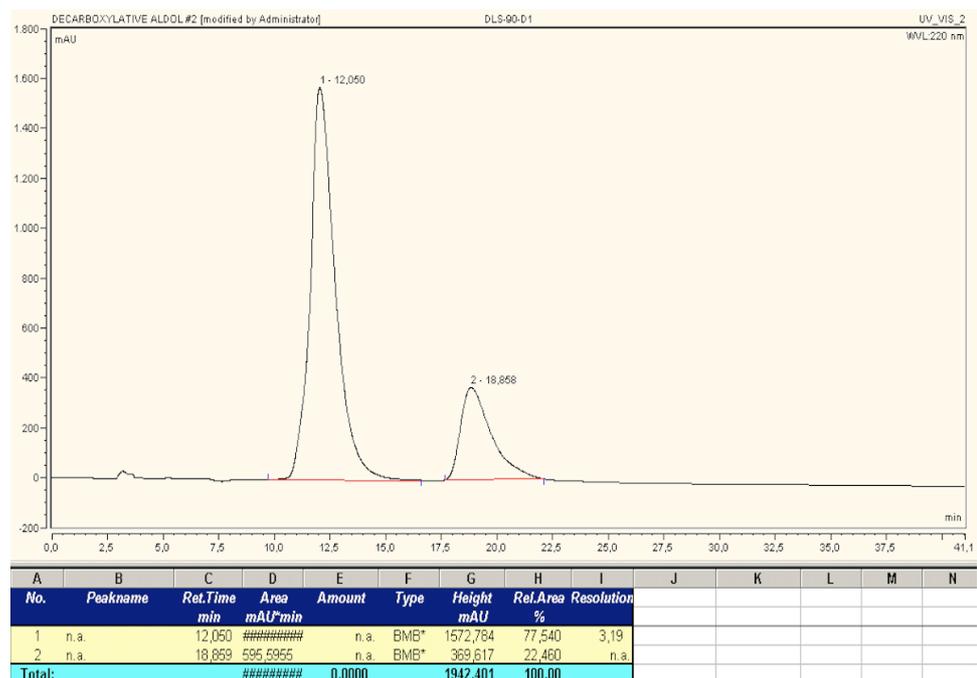
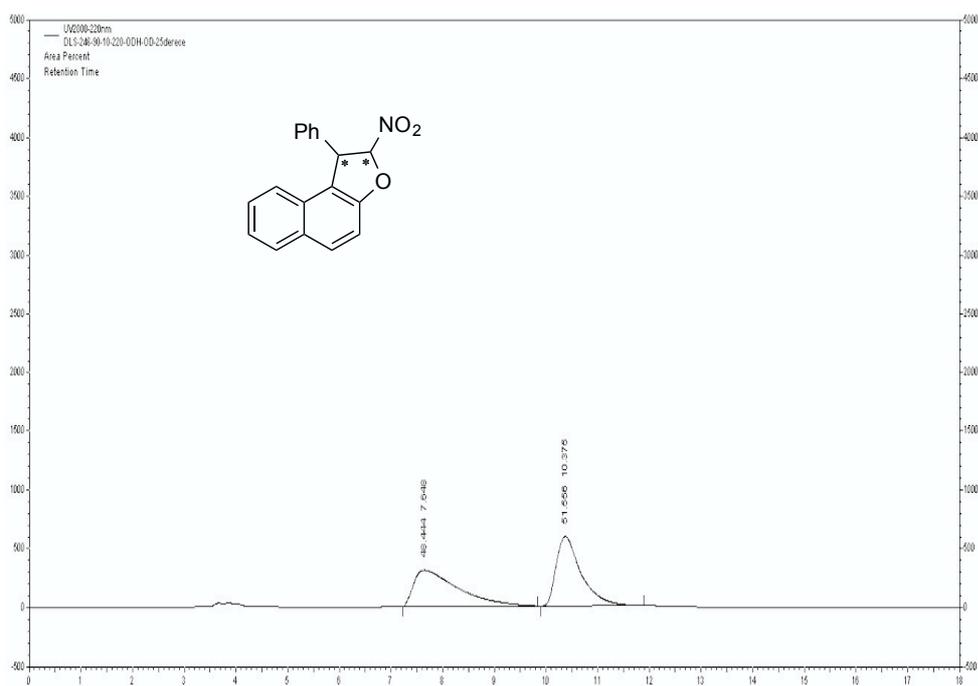
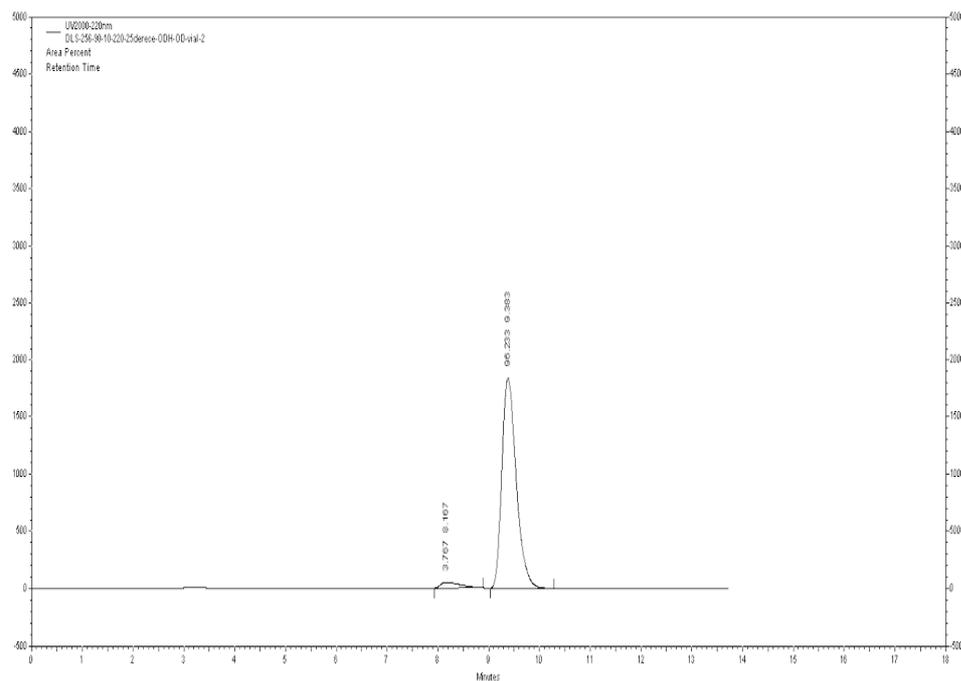


Figure B. 32. HPLC chromatogram of enantiomerically enriched 55b



**Figure B. 33.** HPLC chromatogram of *rac*-44a

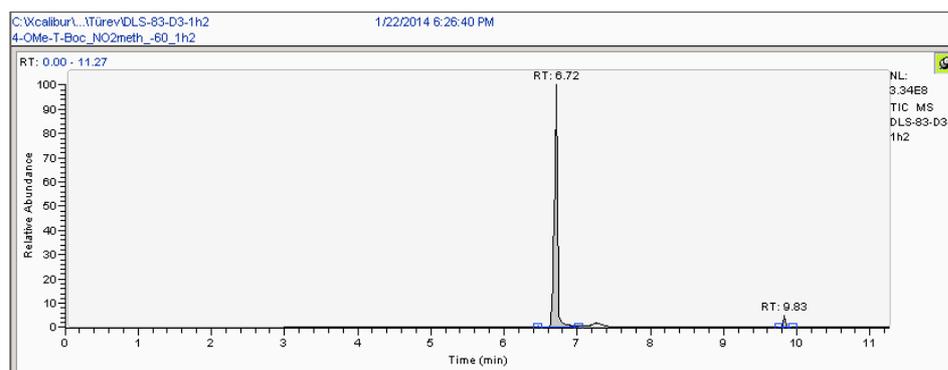


**Figure B. 34.** HPLC chromatogram of enantiomerically enriched 44a



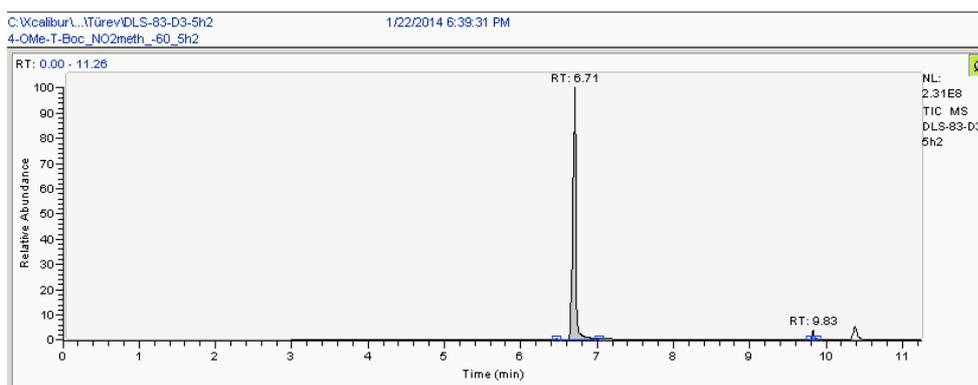
## APPENDIX C

### GC-MS DATA



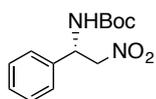
PEAK LIST						
DLS-83-D3-1h2.RAW						
RT: 0.00 - 11.27						
Number of detected peaks: 2						
Apex RT	Start RT	End RT	Area	%Area	Height	%Height
6.72	6.45	7.01	1.04E+09	96.43	3.34E+08	95.45
9.83	9.76	9.94	38492904	3.57	15905215	4.55

**Figure C. 1.** GC-MS chromatogram of 1 h reaction

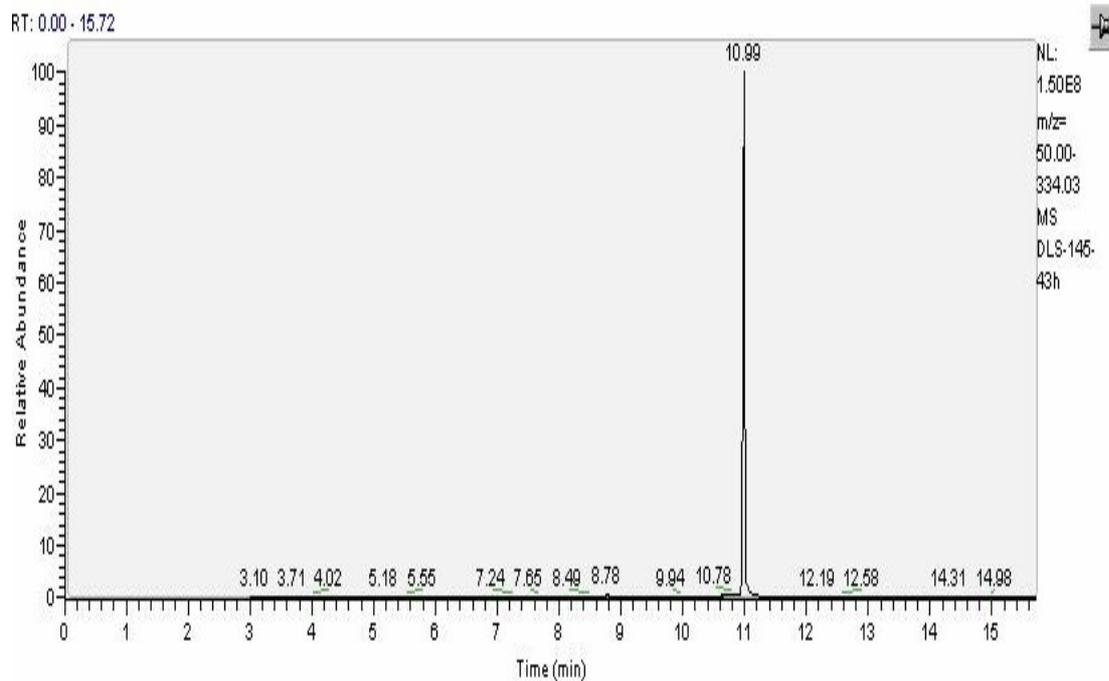


PEAK LIST						
DLS-83-D3-5h2.RAW						
RT: 0.00 - 11.26						
Number of detected peaks: 2						
Apex RT	Start RT	End RT	Area	%Area	Height	%Height
6.71	6.46	7.01	6.86E+08	97.46	2.31E+08	96.49
9.83	9.79	9.87	17860700	2.54	8408721	3.51

**Figure C. 2.** GC-MS chromatogram of 5 h reaction



:\\calibur\...Türev\DLS-145-43h 10/22/2014 10:03:02 AM  
 -Me-TBoc\_imine\_NO2meth\_rt\_10mol%\_tbutylquinine\_DCM-43h



DLS-145-43h #665 RT: 10.99 AV: 1 NL: 2.81E7

T: + e Full ms [50.00-400.00]

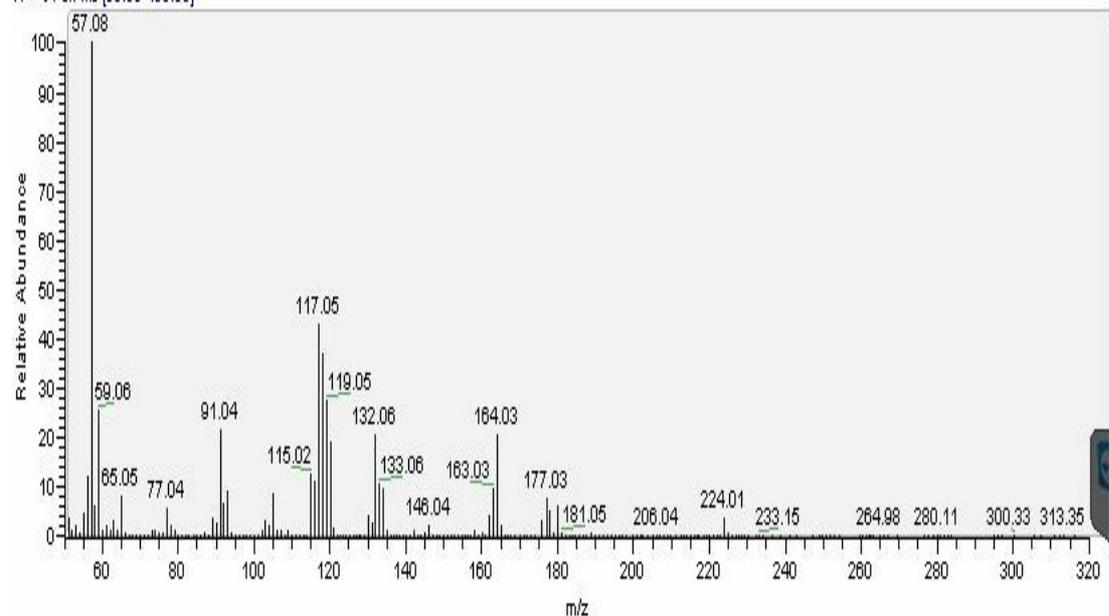
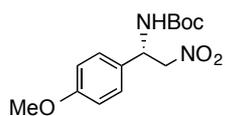
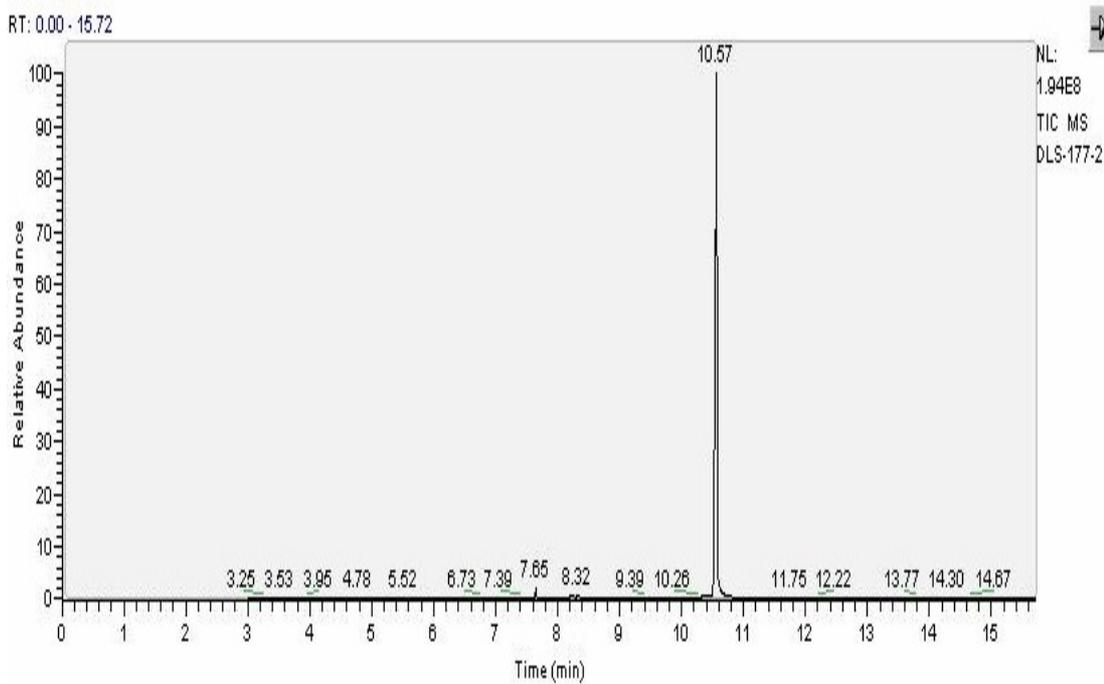


Figure C. 3. GC-MS chromatogram of compound 24a



:\\calibur\...Unsubstituent\DLS-177-2  
Boc\_imine\_NO2meth\_10mol%butylquinine\_0.2M\_22h

11/25/2014 11:42:12 AM



DLS-177-2 #630 RT: 10.57 AV: 1 NL: 4.15E7

T: + e Full ms [50.00-400.00]

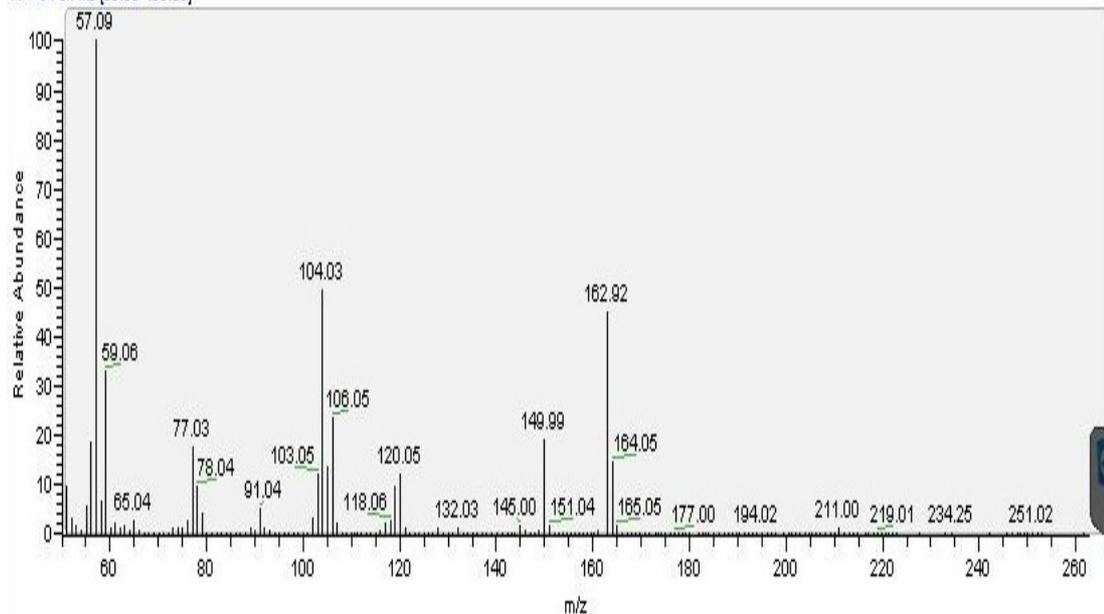


Figure C. 4. GC-MS chromatogram of compound 24b

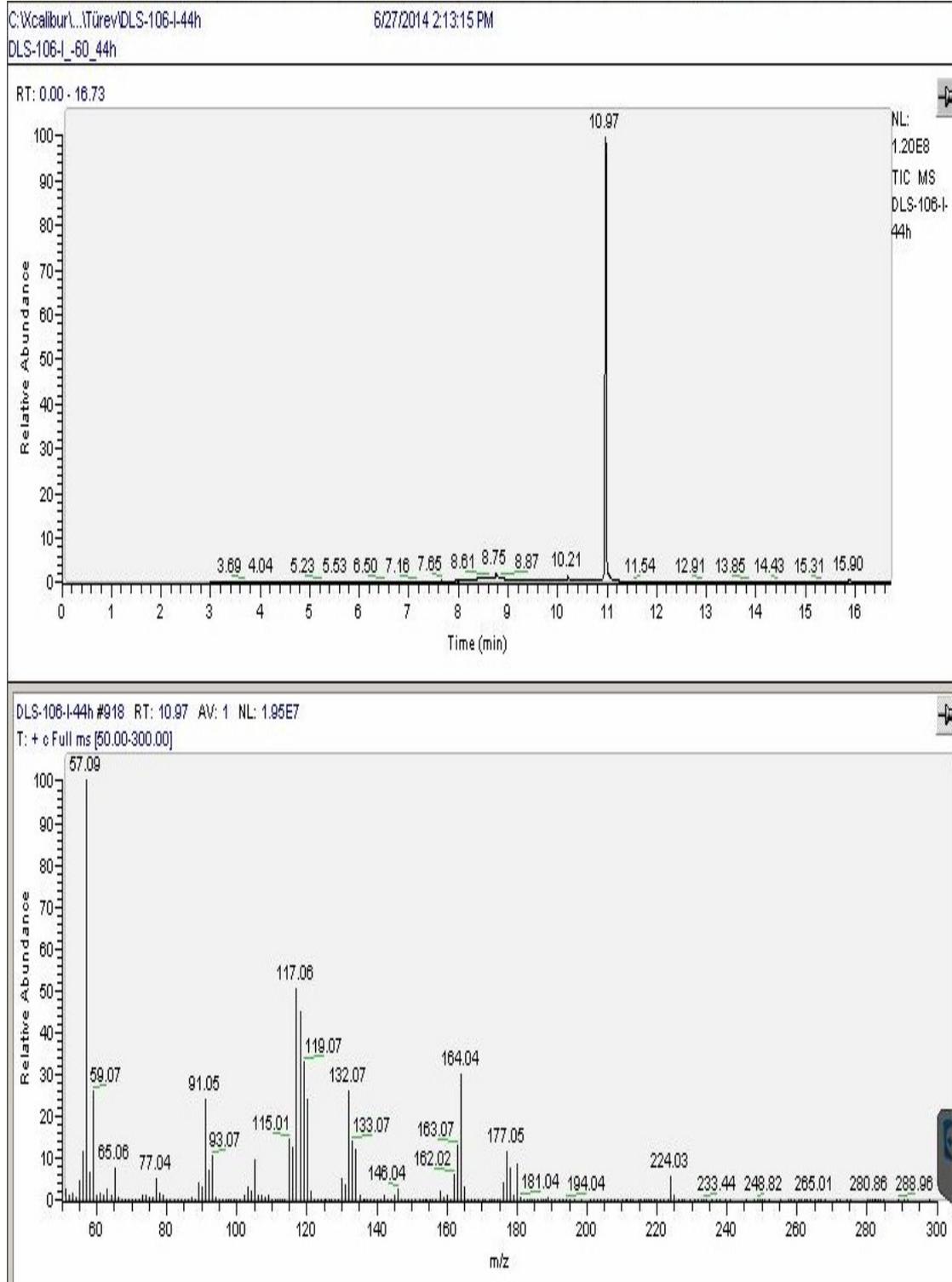
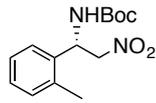
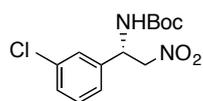
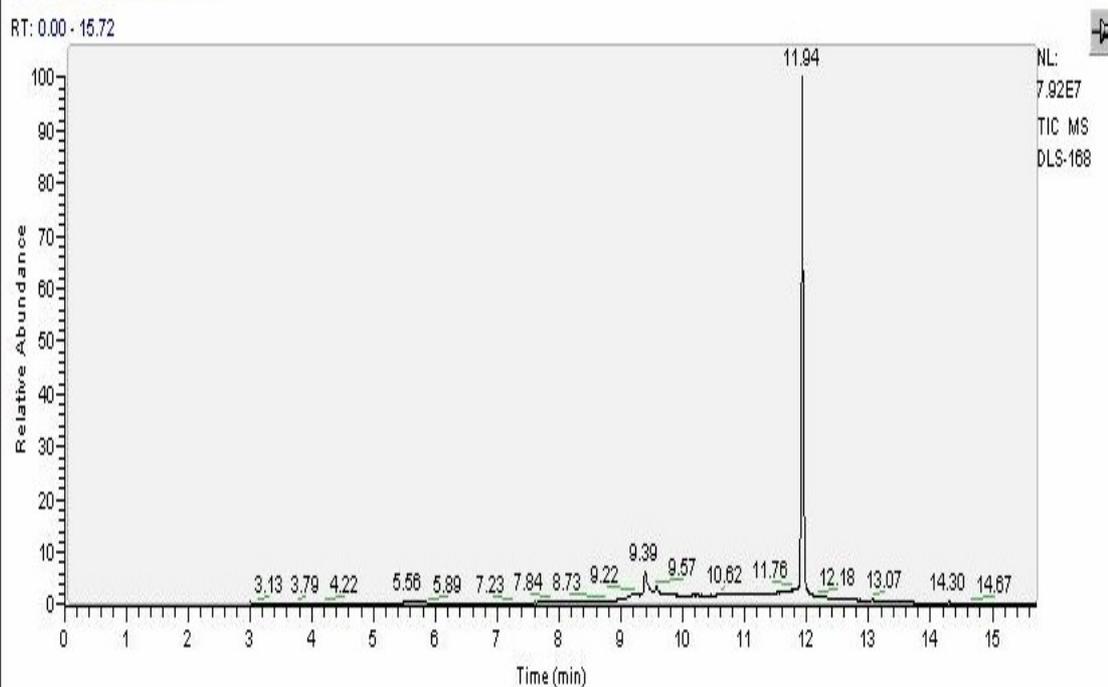


Figure C. 5. GC-MS chromatogram of compound 24c



C:\xcalibur\...Türev\DLS-168  
3-Cl-TBoc\_imine\_NO2meth\_rt\_rac

11/12/2014 5:19:31 PM



DLS-168 #744 RT: 11.94 AV: 1 NL: 1.87E7  
T: + c Full ms [50.00-400.00]

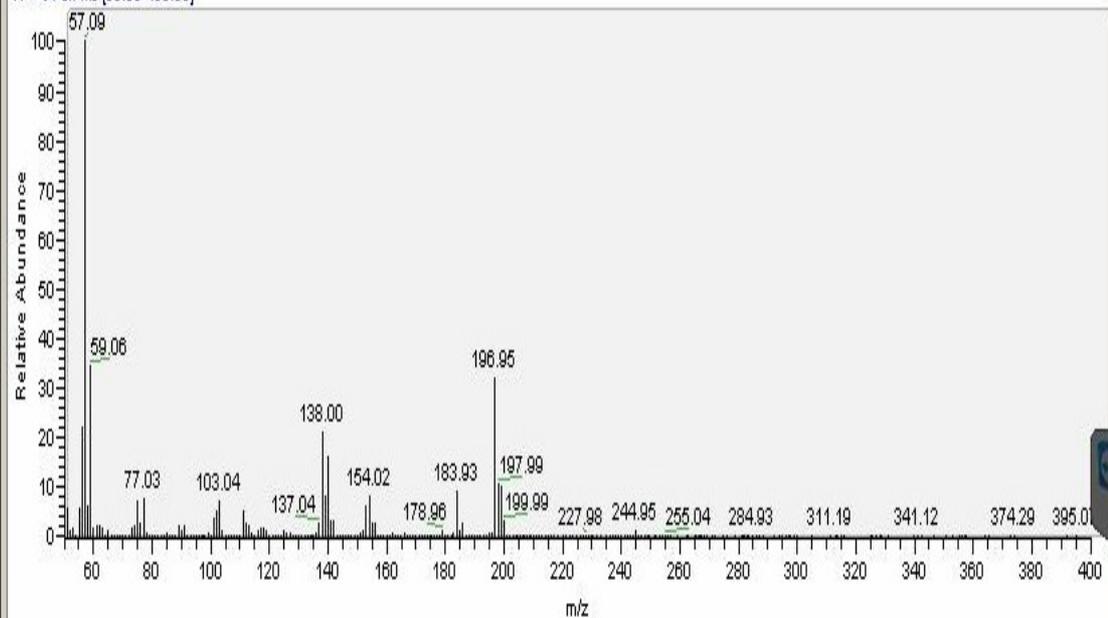
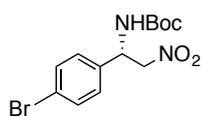


Figure C. 6. GC-MS chromatogram of compound 24d



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11/19/2014 4:55:12 PM

4-Br-TBoc\_imine\_NO2meth\_10mol%tbutylquinine

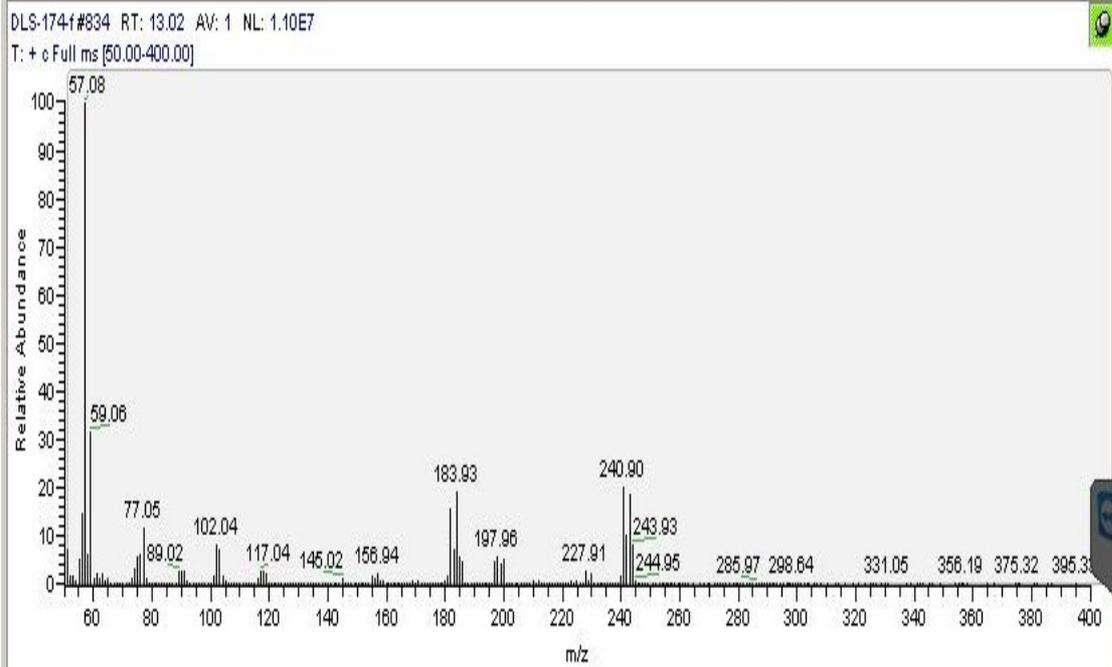
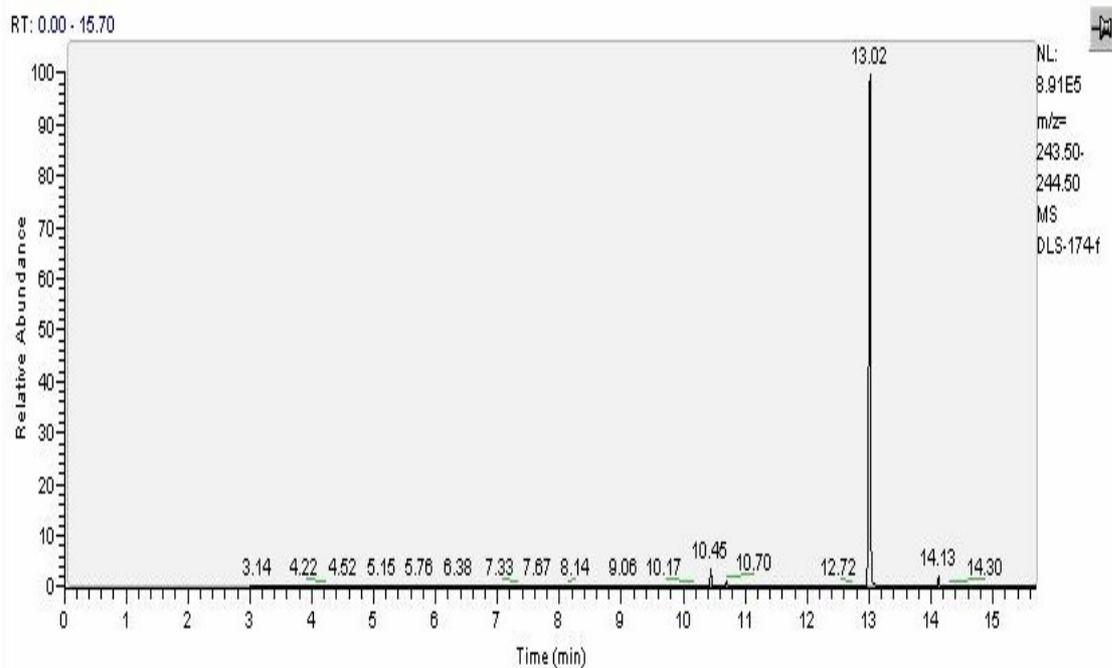
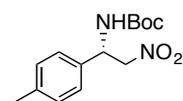


Figure C. 7. GC-MS chromatogram of compound **24e**



C:\xcalibur\...Türev\DLS-184-50h  
4-Me-TBoc\_imine\_NO2meth\_10mol%butylquinine\_0,1M

12/5/2014 12:00:57 PM

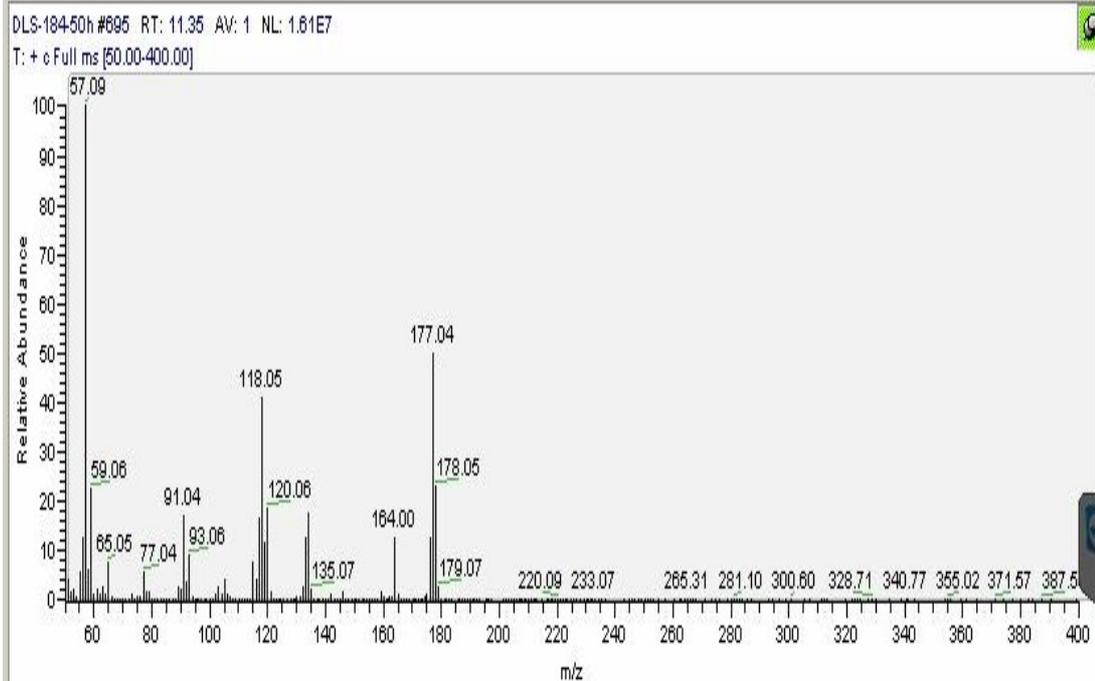
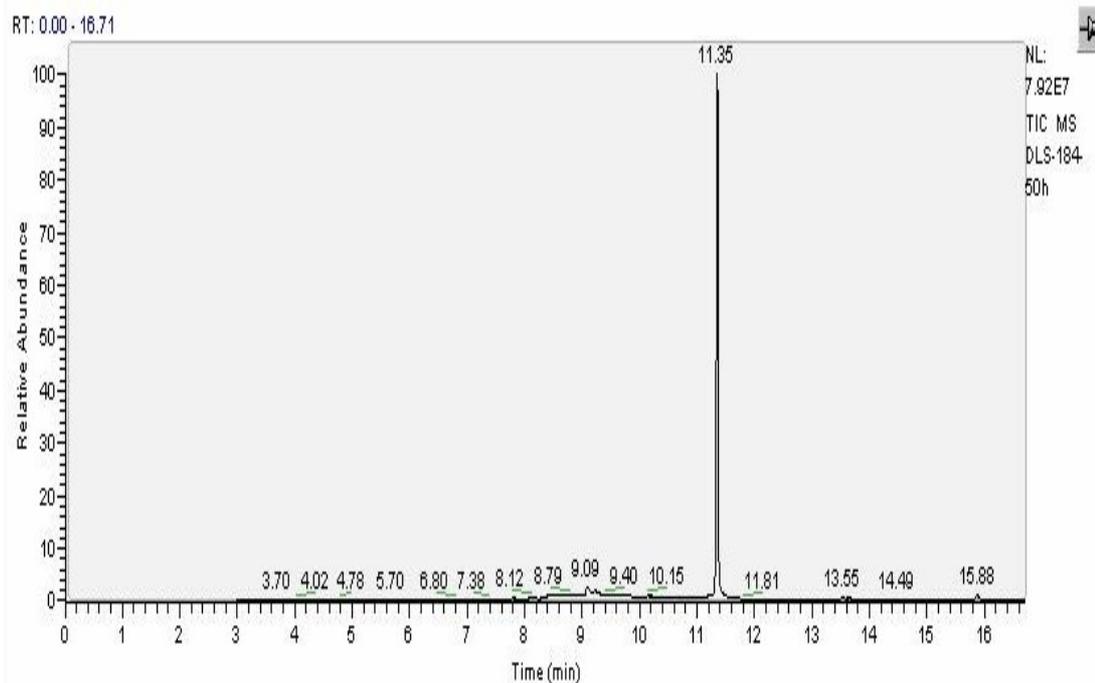
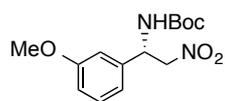


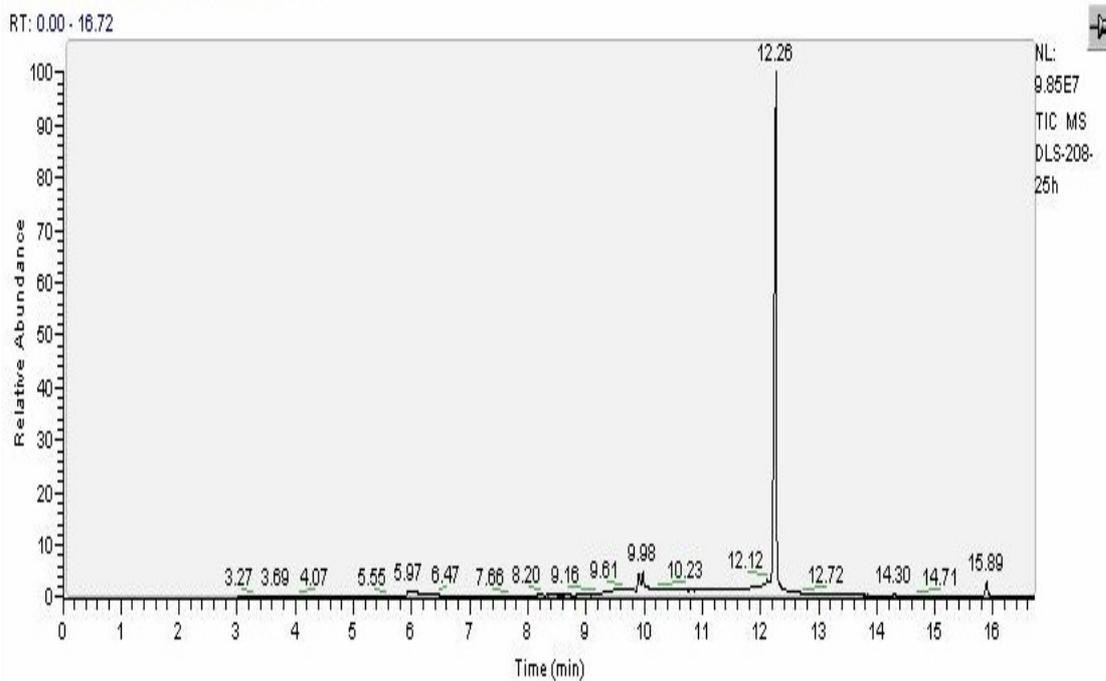
Figure C. 8. GC-MS chromatogram of compound 24f



C:\Xcalibur\...Türev\DLS-208-25h

12/20/2014 1:02:43 PM

2-NO2\_imine\_NO2meth\_10mol%butylquinine\_25h



DLS-208-25h #771 RT: 12.26 AV: 1 NL: 2.20E7

T: + e Full ms [50.00-400.00]

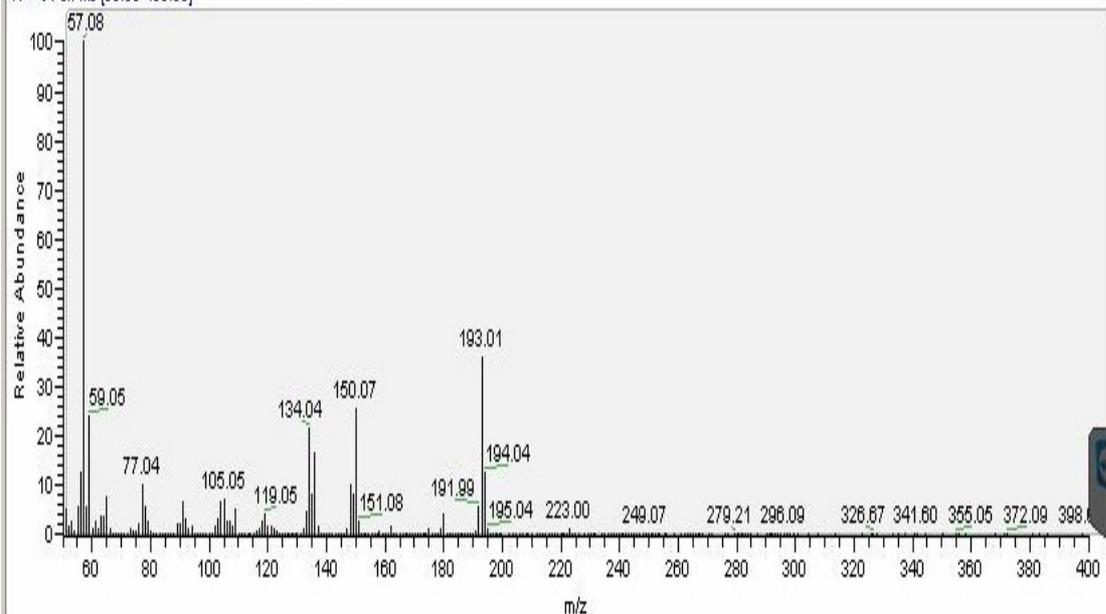
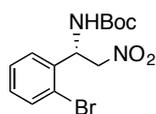
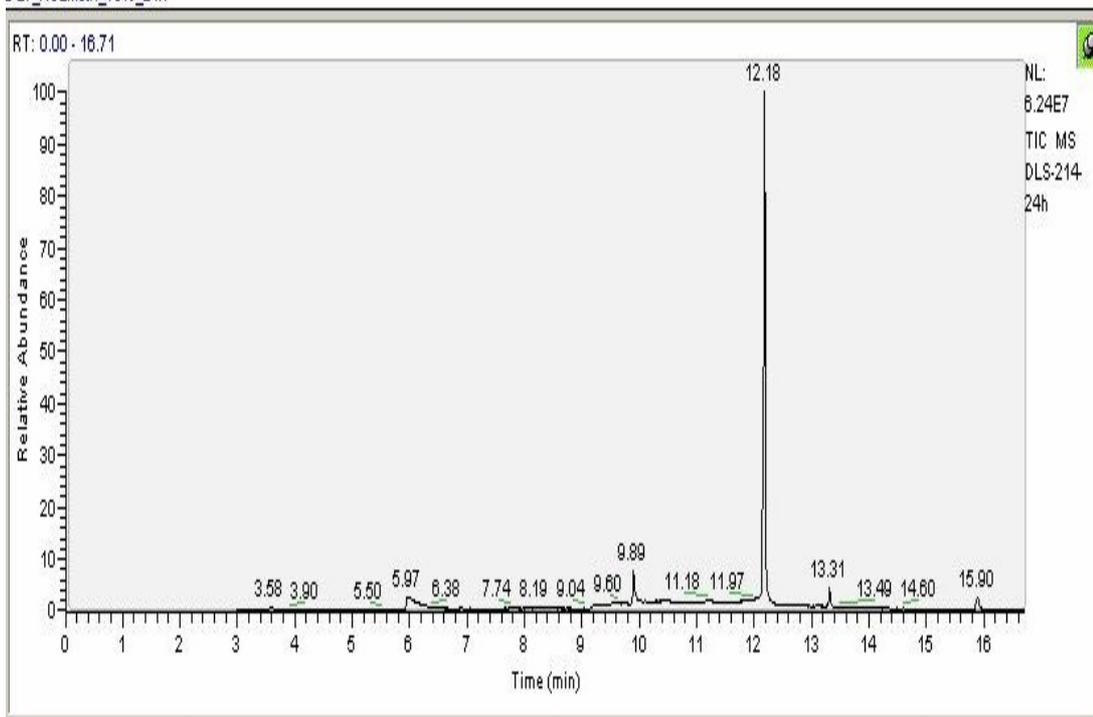


Figure C. 9. GC-MS chromatogram of compound 24g



C:\Vcalburk\1Türev\DLS-214-24h  
2-Br\_NO2meth\_10%\_24h

1/14/2015 2:03:03 PM



DLS-214-24h #764 RT: 12.18 AV: 1 NL: 1.40E7

T: + c Full ms [50.00-400.00]

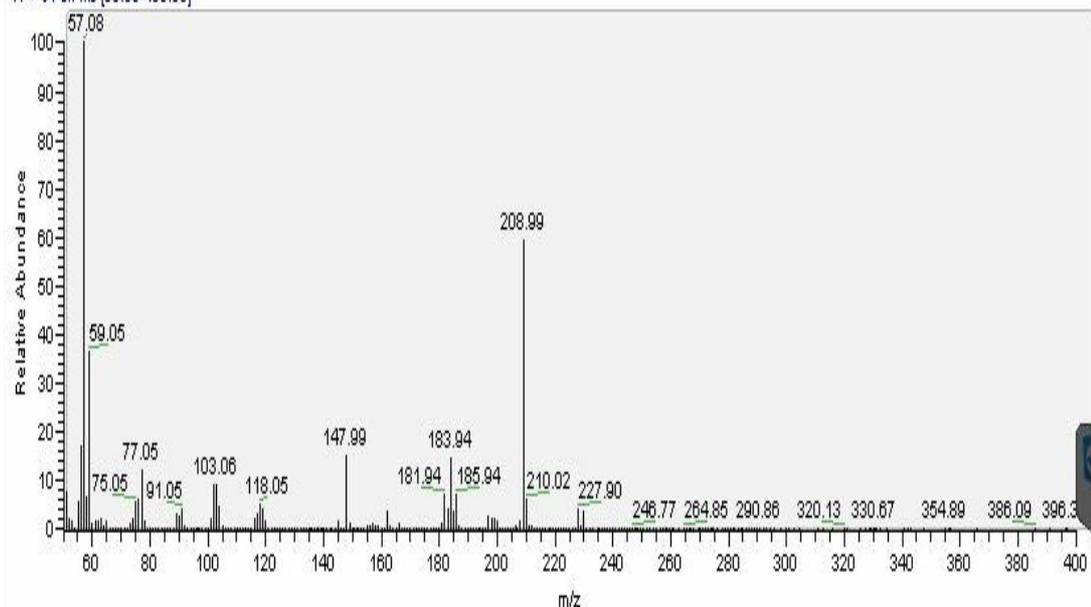
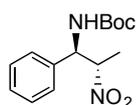


Figure C. 10. GC-MS chromatogram of compound 24h



C:\Xcalibur\...Türev\DLS-217-22h  
TBoc\_NO2ethane\_10%\_22h

1/15/2015 2:11:40 PM

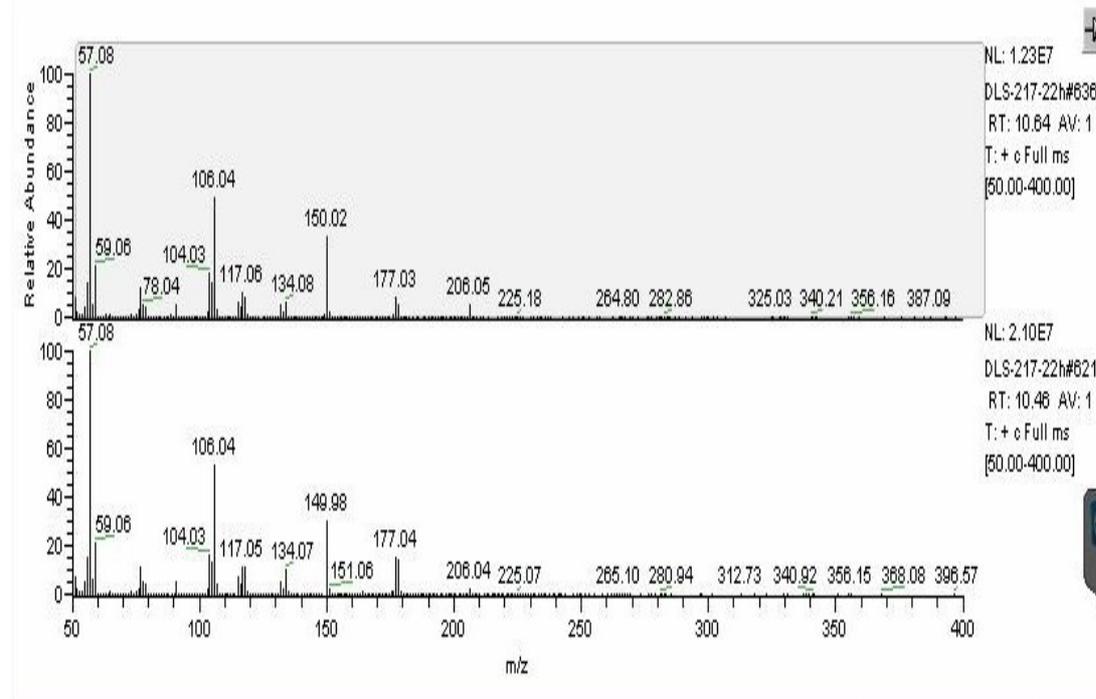
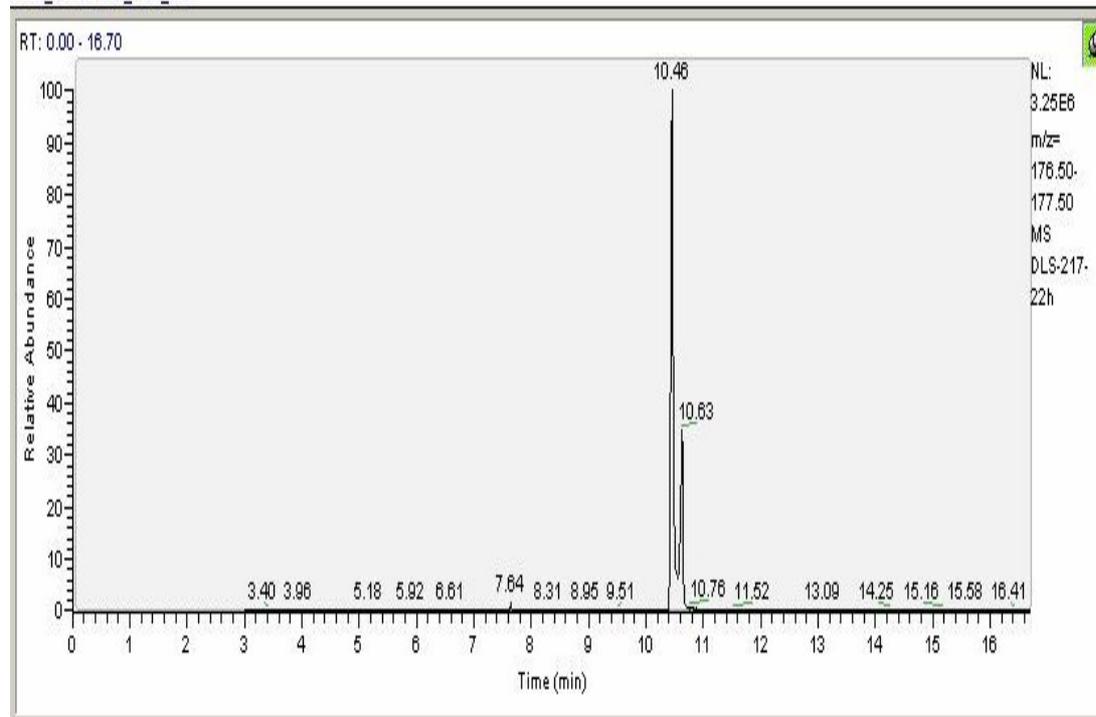
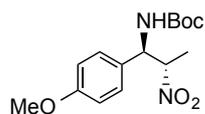


Figure C. 11. GC-MS chromatogram of compound 28a



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6/22/2015 4:26:02 PM

4-Ome\_NE\_rac

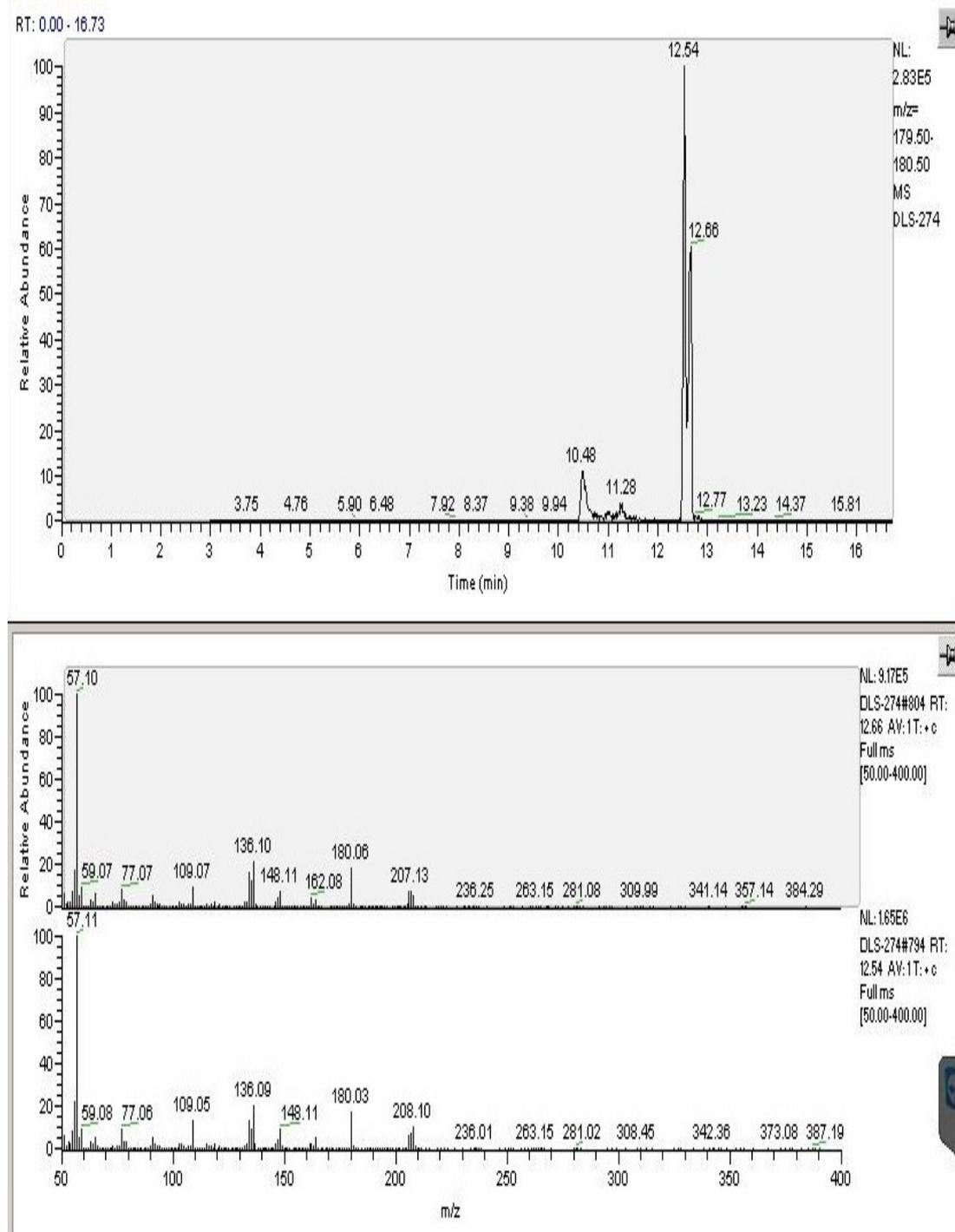
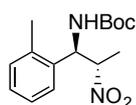
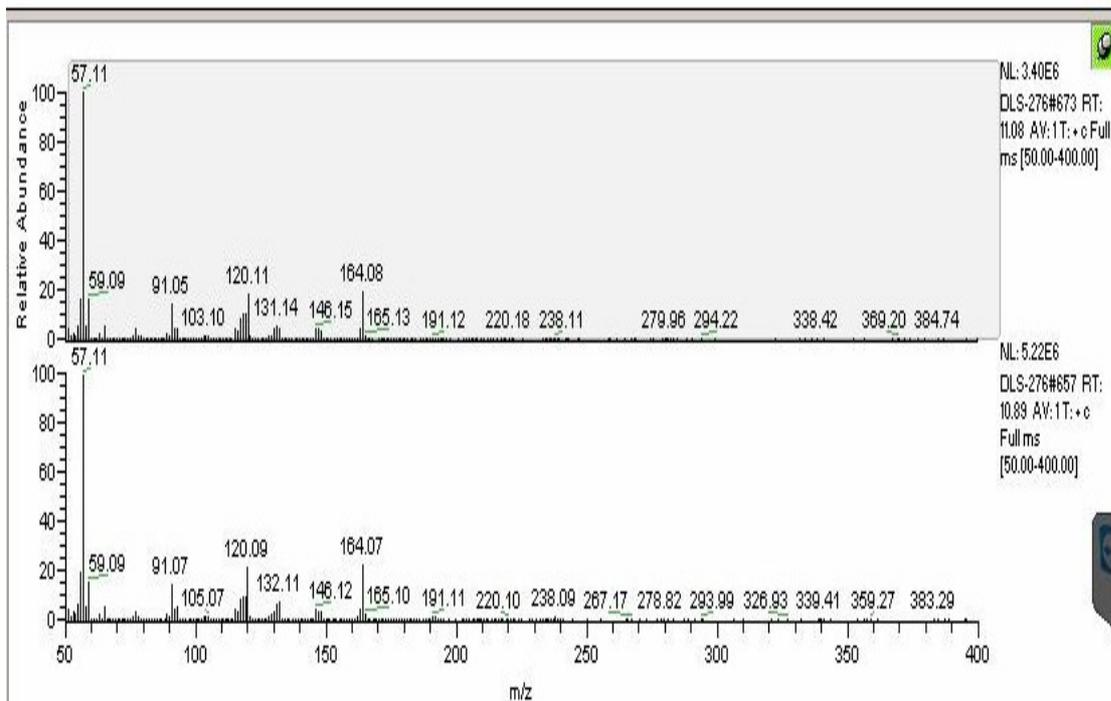
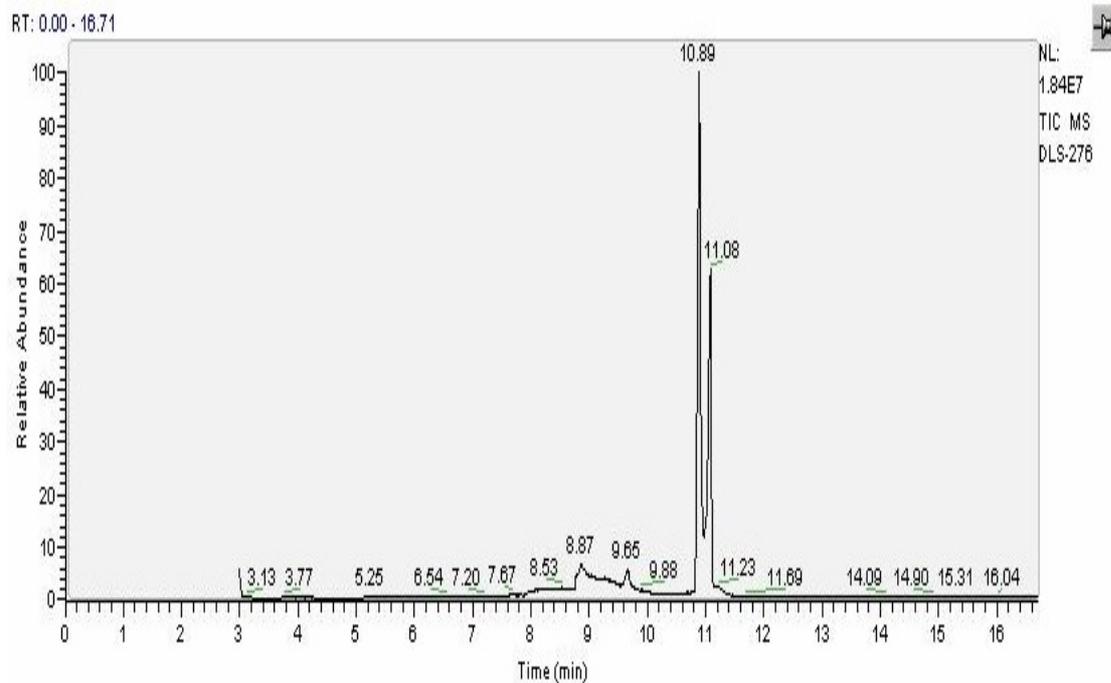


Figure C. 12. GC-MS chromatogram of compound 28b

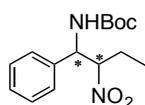


D:\Kcalibur\...türev\DLS-276  
2-Me\_NE\_rac

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**Figure C. 13.** GC-MS chromatogram of compound **28c**



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6/22/2015 4:07:39 PM

Unsub\_NP\_rac

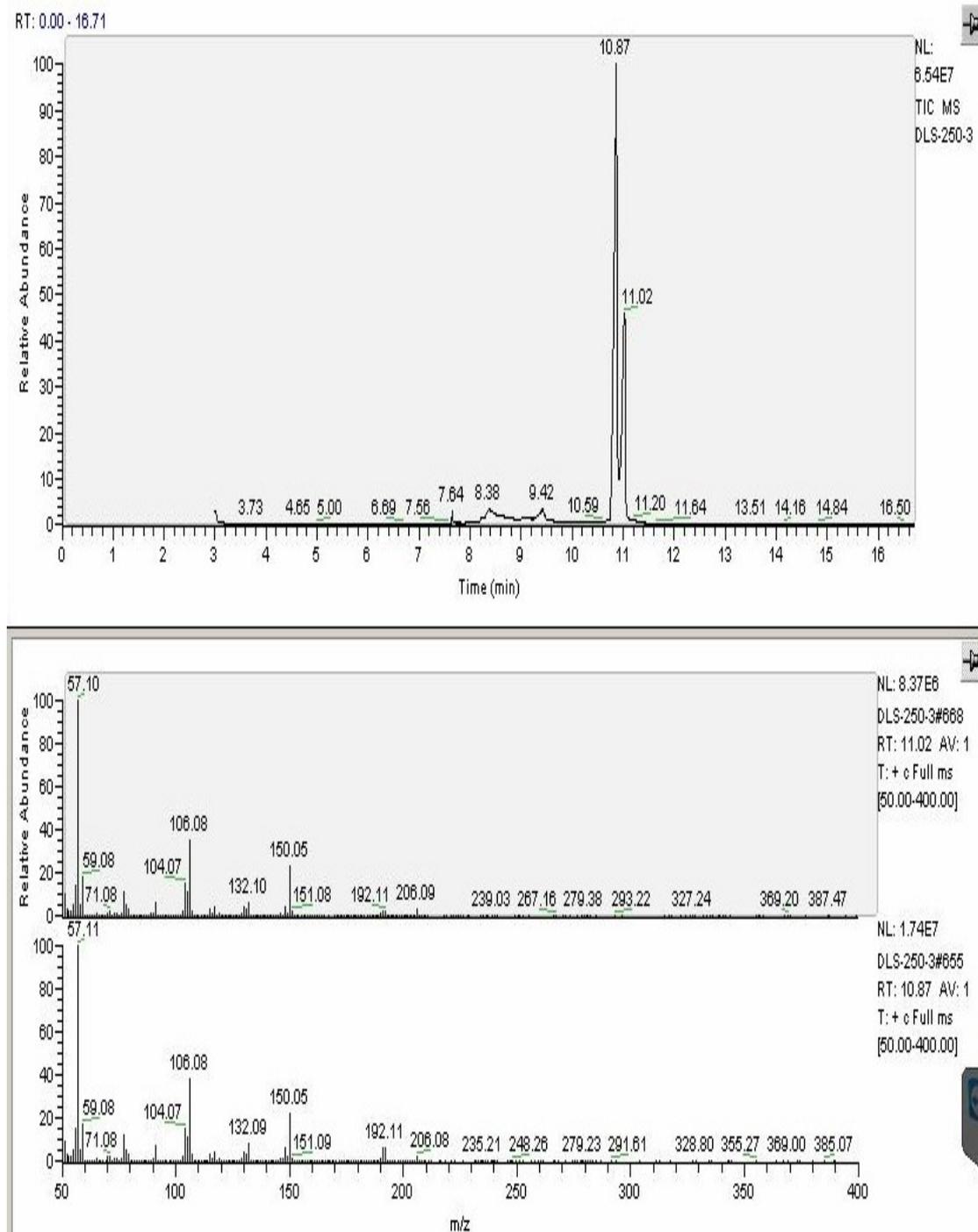


Figure C. 14. GC-MS chromatogram of compound 31a