



HAL
open science

Michael addition-initiated organocatalytic enantioselective multicomponent reactions with 1,3-dicarbonyls

Haiying Du

► **To cite this version:**

Haiying Du. Michael addition-initiated organocatalytic enantioselective multicomponent reactions with 1,3-dicarbonyls. Organic chemistry. Ecole Centrale Marseille, 2014. English. NNT : 2014ECDM0002 . tel-01198378

HAL Id: tel-01198378

<https://theses.hal.science/tel-01198378>

Submitted on 12 Sep 2015

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

École Doctorale des Sciences Chimiques – ED 250

Institut des Sciences Moléculaires de Marseille (*iSm2*)-UMR 7313

THÈSE DE DOCTORAT

pour obtenir le grade de

DOCTEUR de l'ÉCOLE CENTRALE de MARSEILLE

Discipline : chimie organique

MICHAEL ADDITION-INITIATED ORGANOCATALYTIC ENANTIOSELECTIVE MULTICOMPONENT REACTIONS WITH 1,3-DICARBONYLS

Par

Haiying DU

Soutenue publiquement le 11 septembre 2014 devant le jury composé de :

Mme Christine GRECK	Professeur des Universités Université de Versailles Saint-Quentin-en-Yvelines	Rapporteur
Mme Laurence GRIMAUD	Chargée de Recherches CNRS Ecole Nationale Supérieure Paris	Rapporteur
Mme Florence POPOWYCZ	Professeur des Universités Institut National des Sciences Appliquées Lyon	Examineur
M. Thierry CONSTANTIEUX	Professeur des Universités Aix-Marseille Université	Directeur de Thèse
M. Xavier BUGAUT	Maître de Conférences Aix-Marseille Université	Co-encadrant de Thèse

ACKNOWLEDGMENTS

My thesis has been realized with the partnership of the Ecole Centrale de Marseille and a financial grant provided by the China Scholarship Council (CSC). Many thanks to all of the people who have helped me and shared unforgettable times with me in the STeRéO team of the Institut des Sciences Moléculaires de Marseille (iSm2, UMR 7313).

During the 3 years of my Ph.D, I experienced the most wonderful and useful period of my life, where I gained a lot of knowledge about organic chemistry, and knowing lots of friends from different cultures. Moreover, I have had the opportunity to study in a different and challenging environment as well as learning about other cultures. Most importantly it helped me discover my real interests.

Firstly, I would like to thank my advisor Prof. Thierry Constantieux for giving me the opportunity to work on this project, who supported me along my Ph.D studies and research and for the careful corrections on this manuscript. I would like to thank my other advisor Dr. Xavier Bugaut for letting me know more about organic chemistry and educating me lots of skills such as how to analyze the 2D NMR, and introducing me into the world of organocatalysis and for giving me lots of good ideas and advice for the experiments. Secondly, I also would like to thank Prof. Jean Rodriguez for his scientific advice and kind help.

I would like to thank Prof. Christine Greck, Professor at the Université de Versailles Saint-Quentin-en-Yvelines and Dr. Laurence Grimaud, CNRS researcher at Ecole Normale Supérieure Paris who accepted to be the “rapporteurs” of this manuscript. I also thank Prof. Florence Popowycz, Professor at the Institut National des Sciences Appliquées Lyon, to be member of jury.

I also would like to thank all the members of STeRéO group for their kind help during these three years in France. Special thanks to Sylvie Bernard, who kindly helped me for lots of things.

I would like to warmly thank Dr. Michel Giorgi for X-ray crystallography, Nicolas Vanthuyne and Marion Jean for HPLC analyses and the whole team of the Spectropole.

Last but not the least, I would like to thank my family for giving me support for studies and life: my parents, my younger sister, my husband. I also would like to thank all of my Chinese teachers and friends for their kind help in the past. Ce mémoire de thèse se concentre sur le développement de réactions multicomposants énantiosélectives de dérivés 1,3-dicarbonylés en présence d'un organocatalyseur, en vue de préparer des motifs polyhétérocycliques fusionnés.

RESUME

Ce mémoire de thèse se concentre sur le développement de réactions multicomposants énantiosélectives de dérivés 1,3-dicarbonylés en présence d'un organocatalyseur, en vue de préparer des motifs polyhétérocycliques fusionnés.

Dans un premier temps, nous décrivons nos résultats initiaux sur une réaction multicomposants énantiosélective avec des énals et des amines primaires simples. Au vu des faibles énantiosélectivités obtenues, des amines fonctionnalisées ont ensuite été introduites dans ces réactions, permettant ainsi de synthétiser des pyrrolo-piperazines et d'autres molécules hétérocycliques polyfonctionnalisées énantioenrichies, toutes obtenues avec des rendements intéressants et des énantiosélectivités élevées.

Ayant utilisé avec succès des β -cétoamides α -méthyléniques dans ces réactions multicomposantes, nous avons réalisé par ailleurs que leur simple addition de Michael sur des oléfines pauvres en électrons n'avait jamais été décrite en version organocatalysée. Nous avons donc étudié leur réaction avec des nitrooléfines en présence d'organocatalyseurs chiraux, et les produits attendus ont alors été obtenus avec de bons rendements et d'excellentes diastéro- et énantiosélectivités.

Mots-clés : Addition de Michael, 1,3-Dicarbonyles, Énantiosélectivité, Organocatalyse, Réactions Multicomposants.

ABSTRACT

This thesis focuses on the development of enantioselective multicomponent reactions with 1,3-dicarbonyls in the presence of an organocatalyst, to synthesize fused polyheterocyclic motives.

At first, we describe our initial results on an enantioselective multicomponent reaction with enals and simple primary amines. In view of the low enantioselectivities achieved, functionalized amines were then introduced in these reactions, thereby synthesizing enantioenriched pyrrolpiperazines and other polyfunctionalized heterocyclic molecules, all obtained with attractive yields and high enantioselectivities.

Having successfully used methylene β -ketoamides in these enantioselective MCRs, we realized also that their simple Michael addition to electron-poor olefins had never been described in organocatalytic conditions. We therefore studied their reaction with nitroolefins in the presence of various chiral organocatalysts, and the expected products were pleasingly obtained with high yields, excellent diastereo- and enantioselectivities.

Keywords: 1,3-Dicarbonyls, Enantioselectivity, Michael addition, Multicomponent reactions, Organocatalysis.

**TABLE OF CONTENTS
AND ABBREVIATIONS**

TABLE OF CONTENTS

ACKNOWLEDGMENTS	I
RESUME.....	III
ABSTRACT	V
TABLE OF CONTENTS	IX
LIST OF ABBREVIATIONS	XIII
FRENCH SUMMARY	1
GENERAL INTRODUCTION	13
I. BIBLIOGRAPHIC PART	17
I.1 THE MICHAEL ADDITION	17
I.1.1 HISTORY OF THE MICHAEL ADDITION.....	17
I.1.2 MECHANISM OF THE MICHAEL ADDITION	18
I.1.3 ENANTIOSELECTIVE MICHAEL ADDITION	18
I.2 ORGANOCATALYTIC ENANTIOSELECTIVE MICHAEL ADDITION OF	
1,3-DICARBONYL SUBSTRATES	19
I.2.1 ORGANOCATALYSIS: DEFINITION AND HISTORICAL BACKGROUND	19
I.2.1.1 SIGNIFICANCE OF ORGANOCATALYSIS	19
I.2.1.2 DEFINITION OF ORGANOCATALYSIS.....	19
I.2.1.3 HISTORY OF ORGANOCATALYSIS.....	20
I.2.1.4 DIFFERENT TYPES OF ORGANOCATALYSIS.....	22
I.2.2 THE MICHAEL ADDITION OF 1,3-DICARBONYLS: A VERY CONVENIENT	
PLATFORM FOR ENANTIOSELECTIVE ORGANOCATALYSIS	24
I.2.2.1 COVALENT ACTIVATION.....	24
I.2.2.2 NON-COVALENT ACTIVATION	30
I.2.2.3 BIFUNCTIONAL ORGANOCATALYSTS	32
I.2.2.4 TRIFUNCTIONAL ORGANOCATALYSTS.....	41
I.2.2.5 PHASE-TRANSFER CATALYSIS.....	42
I.3 DOMINO AND MULTICOMPONENT REACTIONS BASED ON THE MICHAEL	
ADDITION OF 1,3-DICARBONYL SUBSTRATES.....	46
I.3.1 ENANTIOSELECTIVE DOMINO REACTIONS BASED-ON THE MICHAEL ADDITION	
OF 1,3-DICARBONYL SUBSTRATES	47
I.3.1.1 IMINIUM-ENAMINE ACTIVATION MODE.....	47
I.3.1.2 IMINIUM ACTIVATION COMBINED WITH OTHER TRANSFORMATIONS	52
I.3.1.3 NON-COVALENT ACTIVATION MODES.....	58
I.3.2 NON-ENANTIOSELECTIVE MULTICOMPONENT REACTIONS BASED ON THE	
MICHAEL ADDITION OF 1,3-DICARBONYL SUBSTRATES.....	62
I.3.3 ORGANOCATALYTIC ENANTIOSELECTIVE MULTICOMPONENT REACTIONS	
BASED ON THE MICHAEL ADDITION OF 1,3-DICARBONYL SUBSTRATES	67

I.4	SUMMARY	69
II.	ORGANOCATALYST-CONTROLLED CHEMOSELECTIVE THREE-COMPONENT REACTIONS	75
II.1	SELECTION OF SUBSTRATES AND SYNTHESIS OF RACEMIC PRODUCT	76
II.2	ORGANOCATALYST-CONTROLLED CHEMODIVERGENT THREE-COMPONENT REACTION: PRELIMINARY RESULTS.....	77
II.2.1	CATALYST SCREENING	77
II.2.1.1	IMINIUM/ENAMINE-TYPE ACTIVATION	77
II.2.1.2	NON-COVALENT ORGANOCATALYSTS.....	79
II.2.2	STUDY OF THE RELATIVE CONFIGURATION.....	81
II.2.2.1	BRIDGED BICYCLE	81
II.2.2.2	FUSED BICYCLE	82
II.3	CONCLUSIONS	83
III.	ORGANOCATALYTIC ENANTIOSELECTIVE MULTICOMPONENT SYNTHESIS OF PYRROLOPIPERAZINES	87
III.1	CATALYST SCREENING.....	89
III.1.1	IMINIUM/ENAMINE-TYPE ACTIVATION.....	89
III.1.2	BIFUNCTIONAL ORGANOCATALYST	90
III.2	OPTIMIZATION OF THE REACTION CONDITIONS	91
III.2.1	OPTIMIZATION OF THE TEMPERATURE	91
III.2.2	OPTIMIZATION OF THE SOLVENT	92
III.2.3	ADDITIVES AND COMPARISON WITH THE SEQUENTIAL REACTION.....	92
III.3	SCOPE OF THE REACTION.....	93
III.3.1	SCOPE OF β -KETOESTERS.....	94
III.3.1.1	VARIATION OF THE ESTER SUBSTITUENT	94
III.3.1.2	VARIATION OF THE KETONE SUBSTITUENT.....	94
III.3.1.3	USE OF CYCLIC β -KETOESTERS	95
III.3.2	SCOPE OF α,β -UNSATURATED ALDEHYDES	96
III.3.2.1	β -AROMATIC ENALS	96
III.3.2.2	β -HETEROAROMATIC ENALS	97
III.3.2.3	β -ALKYL ENALS.....	98
III.3.2.1	(<i>E</i>)-ETHYL 4-OXOBUT-2-ENOATE	98
III.3.3	SCOPE OF <i>N</i> -(2-AMINOETHYL)PYRROLES	99
III.3.3.1	PREPARATION OF THE STARTING MATERIALS	99
III.3.3.2	REACTIONS WITH THE SUBSTITUTED <i>N</i> -(2-AMINOETHYL)PYRROLES.....	101
III.3.3.3	ATTEMPTS TO USE <i>N</i> -(2-AMINOETHYL)INDOLE DERIVATIVES.....	102
III.4	SCOPE OF VARIOUS NUCLEOPHILES	103
III.4.1	ACYCLIC 1,3-DIKETONES	103
III.4.2	CYCLIC 1,3-DIKETONES	105
III.4.3	β -KETOAMIDES.....	106
III.4.4	β -KETHIOESTERS	107
III.4.5	β -KETOSULFONES.....	108
III.4.6	β -KETOPHOSPHONATES	110

III.4.7	1-ACETYLDOLIN-3-ONES.....	111
III.5	STUDY OF THE ABSOLUTE AND RELATIVE CONFIGURATIONS.....	114
III.6	CROSSOVER STUDIES.....	115
III.7	POST-FUNCTIONALIZATION.....	116
III.7.1	DIELS-ALDER REACTIONS.....	117
III.7.2	REDUCTION OF THE DOUBLE BOND.....	117
III.7.3	EPIMERIZATION OF THE STEREOGENIC CENTER BEARING THE ESTER SUBSTITUENT.....	119
III.7.4	REDUCTION OF THE ESTER PART.....	119
III.8	CONCLUSIONS.....	120
IV.	SYNTHESIS OF ENANTIOENRICHED POLYFUNCTIONALIZED HETEROCYCLES BY 3-CR OR 4-CR.....	123
IV.1	ORIGINS OF THE REACTION DESIGN.....	123
IV.2	CHOICE OF THE BEST FUNCTIONALIZED AMINE.....	123
IV.3	3-CR WITH B-KETOAMIDES.....	126
IV.3.1	pKa OF DIFFERENT 1,3-DICARBONYL COMPOUNDS.....	126
IV.3.2	OPTIMIZATION OF THE REACTION CONDITIONS.....	127
IV.3.2.1	<i>OPTIMIZATION OF THE SOLVENT AND THE RATIO BETWEEN THE STARTING MATERIALS.....</i>	<i>127</i>
IV.3.3	EVALUATION OF ORGANOCATALYSTS, ADDITIVES, TEMPERATURES AND REACTION TIME.....	127
IV.4	SEQUENTIAL TRIMOLECULAR TRANSFORMATION.....	129
IV.5	THE SCOPE.....	130
IV.6	POST-FUNCTIONALIZATION.....	130
IV.7	FOUR-COMPONENT REACTION.....	131
IV.8	CONCLUSIONS.....	134
V.	ORGANOCATALYTIC ENANTIO- AND DIASTEREOSELECTIVE CONJUGATE ADDITION OF B-KETOAMIDES TO NITROOLEFINS.....	137
V.1	PREPARATION OF B-KETOAMIDES.....	137
V.2	THE MICHAEL ADDITION OF B-KETOAMIDES TO α,β -UNSATURATED ALDEHYDES.....	138
V.3	THE MICHAEL ADDITION OF B-KETOAMIDES TO NITROOLEFINS.....	139
V.3.1	WORKING HYPOTHESIS.....	139
V.3.2	ORGANOCATALYTIC ADDITION OF ACYCLIC β -KETOAMIDES TO NITROOLEFINS.....	140
V.3.2.1	<i>OPTIMIZATION OF THE REACTION CONDITIONS WITH WEINREB β-KETOAMIDE.....</i>	<i>140</i>
V.3.2.2	<i>SCOPE OF NITROOLEFINS.....</i>	<i>142</i>
V.3.2.3	<i>SCOPE AND LIMITATIONS OF WEINREB β-KETOAMIDES.....</i>	<i>143</i>
V.3.2.4	<i>SCOPE OF ACYCLIC TERTIARY β-KETOAMIDES.....</i>	<i>143</i>
V.3.2.5	<i>ATTEMPTES TO EXTEND THE REACTION TO ACYCLIC SECONDARY β-KETOAMIDES....</i>	<i>144</i>
V.3.2.6	<i>RELATIVE AND ABSOLUTE CONFIGURATIONS OF THE MICHAEL ADDUCTS.....</i>	<i>145</i>
V.3.3	RATIONALIZATION OF THE REACTIVITY AND THE SELECTIVITY.....	146
V.3.3.1	<i>KINETIC STUDIES.....</i>	<i>146</i>

V.3.3.2	<i>ORIGIN OF DIASTEREOSELECTIVITY</i>	147
V.3.3.3	<i>PROPOSED TRANSITION STATE TO ACCOUNT FOR THE STEREOSELECTIVITIES</i>	150
V.3.4	ATTEMPTS TO OBTAIN THE OTHER DIASTEREOMER	151
V.3.5	SYNTHETIC USEFULNESS OF THE TRANSFORMATION	153
V.3.5.1	<i>SCALE-UP OF THE REACTION</i>	153
V.3.5.2	<i>POST-FUNCTIONALIZATION OF THE ADDUCTS</i>	154
V.3.6	CONCLUSIONS	158
	GENERAL CONCLUSION AND PERSPECTIVES	161
I.	EXPERIMENTAL TECHNOLOGIES	165
I.1	GENERAL PROCEDURES	165
I.2	STARTING MATERIALS	165
I.3	INSTRUMENTATION	165
II.	EXPERIMENTAL PART OF ORGANOCATALYST-CONTROLLED CHEMOSELECTIVE THREE-COMPONENT REACTIONS	167
II.1	CATALYTIC REACTION	167
III.	EXPERIMENTAL PART OF ORGANOCATALYTIC ENANTIOSELECTIVE MULTICOMPONENT SYNTHESIS OF PYRROLOPIPERAZINES	171
III.1	PREPARATION OF STARTING MATERIALS	171
III.1.1	PREPARATION OF SUBSTITUTED PYRROLES	171
III.1.2	PREPARATION OF N-(2-AMINOETHYL)PYRROLES	172
III.1.3	PREPARATION OF α,β-UNSATURATED ALDEHYDES	174
III.2	METHODOLOGY FOR THE OPTIMIZATION OF REACTION CONDITIONS	175
III.3	GENERAL PROCEDURE, SYNTHESIS AND CHARACTERIZATION OF PRODUCTS	177
	EXPERIMENTAL PART OF SYNTHESIS OF ENANTIOENRICHED POLYFUNCTIONALIZED HETEROCYCLES BY 3-CR OR 4-CR	231
IV.	EXPERIMENTAL PART OF ORGANOCATALYTIC ENANTIO- AND DIASTEREOSELECTIVE CONJUGATE ADDITION OF B-KETOAMIDES TO NITROOLEFINS	240
IV.1	PREPARATION OF B-KETOAMIDES	240
IV.2	GENERAL PROCEDURE, SYNTHESIS AND CHARACTERIZATION OF PRODUCTS	248
IV.3	PREPARATIVE-SCALE REACTIONS AND POST-FUNCTIONALIZATIONS:	270
IV.3.1	Preparative-scale reactions:	270
IV.3.1.1	<i>Preparative-scale reaction (1.00-mmol):</i>	270
IV.3.1.2	<i>Neat preparative-scale reaction (2.00-mmol):</i>	270
IV.3.2	Diastereoselective ketone reduction	271
IV.3.3	Other post-functionalizations	275
	REFERENCES	281

LIST OF ABBREVIATIONS

Boc	<i>tert</i> -Butyloxycarbonyl
CAN	Cerium (IV) Ammonium Nitrate
COSY	¹ H, ¹ H-Chemical-shift COrrrelation SpectroscopY
DIBAL	Diisobutylaluminum hydride
DDQ	2,3-Dichloro-5,6-dicyano- <i>p</i> -benzoquinone
DABCO	1,4-Diazabicyclo[2.2.2]octane
DFT	Density Functional Theory
DBU	1,8-Diazabicyclo[5.4.0]unec-7-ene
equiv.	Equivalents
<i>ee</i>	Enantiomeric excess
HFIP	Hexafluoroisopropan-2-ol
HOMO	Highest Occupied Molecular Orbital
HMQC	Heteronuclear Multiple Quantum Coherence
HMBC	Heteronuclear Multiple-Bond Correlation
HRMS	High Resolution Mass Spectrometry
IBX	2-Iodoxybenzoic acid
LUMO	Lowest Unoccupied Molecular Orbital
LDA	Lithium Diisopropylamide
Mp	Melting point
m/z	Mass to charge ratio
MVK	Methyl vinyl ketone
MBFTs	Multiple Bond-Forming Transformations
MCRs	Multicomponent reactions
NHC	N-Heterocyclic carbenes
PTC	Phase-Transfer Catalysis
PE	Petroleum Ether
quant	Quantitative
r.t.	room temperature
SOMO	Singly-Occupied Molecular Orbitals
TEA	Triethylamine
TBAF	TetraButylAmmonium Fluoride trihydrate
TBS	<i>tert</i> -butyldimethylsilyl
TMS	trimethylsilyl
MW	MicroWave
XRD	X-Ray Diffraction

FRENCH SUMMARY

FRENCH SUMMARY

INTRODUCTION :

Dans un contexte sociétal et environnemental de plus en plus complexe, la chimie doit continuer à apporter des réponses aux divers problèmes synthétiques qui lui sont posés, tout en considérant comme primordiales les questions écologiques et économiques. Dans ce contexte, un certain nombre de stratégies ont été définies et regroupées sous le vocable de « chimie verte » afin d'inciter la communauté des chimistes à développer des méthodes de synthèse plus respectueuses de l'environnement. Les réactions multicomposants,^[1] qui répondent à l'impératif d'économie d'étapes, et l'organocatalyse,^[2] qui vise à réduire l'utilisation de métaux polluants et onéreux, apparaissent comme deux outils intéressants pour atteindre les objectifs d'une chimie plus verte.

Les réactions multicomposants consistent en la combinaison d'au moins trois réactifs dont la majorité des atomes sont intégrés dans le produit final, sans modifications des conditions au cours de la réaction. Elles représentent un puissant outil au service des chimistes de synthèse car elles permettent de générer rapidement de la complexité moléculaires à partir de substrats simples. L'organocatalyse, quant-à elle, regroupent l'ensemble des réactions qui peuvent être accélérées par l'ajout d'une quantité sub-stœchiométrique d'un composé purement organique, nommé organocatalyseur. Très souvent, cet organocatalyseur est une molécule chirale, ce qui va permettre de contrôler les centres stéréogènes créés lors de la réaction. Au cours de ces trois années de thèse, nous nous sommes proposés d'étudier comment l'organocatalyse et les réactions multicomposants peuvent se combiner.^[3,4] Les dérivés 1,3-dicarbonylés ont été utilisés comme substrats communs dans les différentes réactions étudiées, en se basant sur des réactions précédemment développées en série racémique et en conditions thermiques au laboratoire.^[5,6]

¹ (a) J. Zhu, H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**; (b) B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439-4486; (c) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2011**, *50*, 6234-6246; (d) A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083-3135.

² P. I. Dalko, *Comprehensive Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2013**.

³ (a) C. de Graaff, E. Ruijter, R. V. A. Orru, *Chem. Soc. Rev.* **2012**, *41*, 3969-4009; (b) C. M. Marson, *Chem. Soc. Rev.* **2012**, *41*, 7712-7722.

⁴ Au cours de ma thèse, une post-doctorante a travaillé sur un sujet similaire. Voir: M. M. Sanchez Duque, O. Baslé, Y. Génisson, J.-C. Plaquevent, X. Bugaut, T. Constantieux, J. Rodriguez, *Angew. Chem. Int. Ed.* **2013**, *52*, 14143-14146.

⁵ (a) C. Simon, J.-F. Peyronel, J. Rodriguez, *Org. Lett.* **2001**, *3*, 2145-2148; (b) C. Simon, F. Liéby-Muller, J.-F. Peyronel, T. Constantieux, J. Rodriguez, *Synlett* **2003**, 2301-2304; (c) F. Liéby-Muller, T. Constantieux, J. Rodriguez, *J. Am. Chem. Soc.* **2005**, *127*, 17176-17177; (d) F. Liéby-Muller, T. Constantieux, J. Rodriguez, *Synlett* **2007**, 1323-1324.

⁶ Revues : (a) C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 4957-4980; (b) D. Bonne, Y. Coquerel, T. Constantieux, J. Rodriguez, *Tetrahedron: Asymmetry* **2010**, *21*, 1085-1109; (c) D. Bonne, T. Constantieux, Y. Coquerel, J. Rodriguez, *Chem. Eur. J.* **2013**, *19*, 2218-2231; (d) X. Bugaut, D. Bonne, Y. Coquerel, J. Rodriguez, T. Constantieux, *Curr. Org. Chem.* **2013**, *17*, 1920-1928.

I) REACTIONS TROIS-COMPOSANTS CHIMIOSELECTIVES CONTROLEES PAR UN ORGANOCATALYSEUR :

Nos investigations ont commencé par la combinaison d'un β -cétocyclohexane, d'un énal et d'une amine primaire non fonctionnalisée. Les travaux du laboratoire sur cette combinaison en conditions thermiques avait démontré que l'encombrement stérique de l'amine guidait l'obtention chimiosélective de bicycles fusionnés **1** ou pontés **2** (Schéma 1).^[5b]

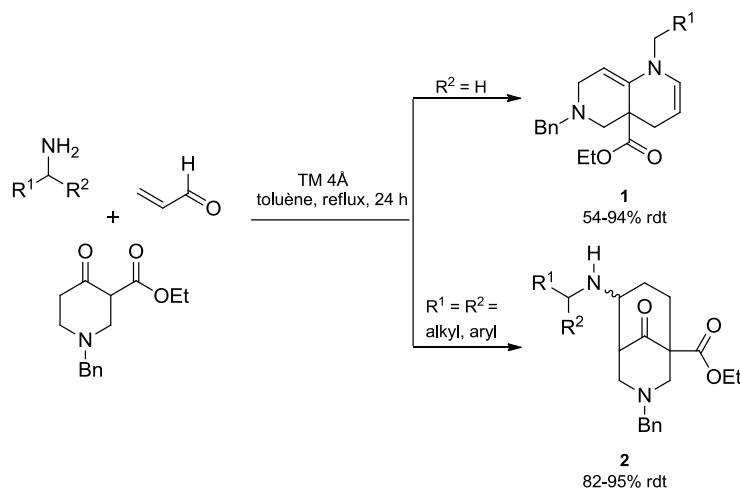


Schéma 1. Réactions multicomposants chimiosélectives entre l'éthoxycarbonyl pipéridone, l'acroléine et des amines primaires

Afin d'évaluer la possibilité de développer une version énantiosélective de cette réaction, l'éthyl 2-oxocyclopentanecarboxylate, la méthacroléine et l'allylamine ont été placées en présence de divers organocatalyseurs dans la toluène à température ambiante (Schéma 2).

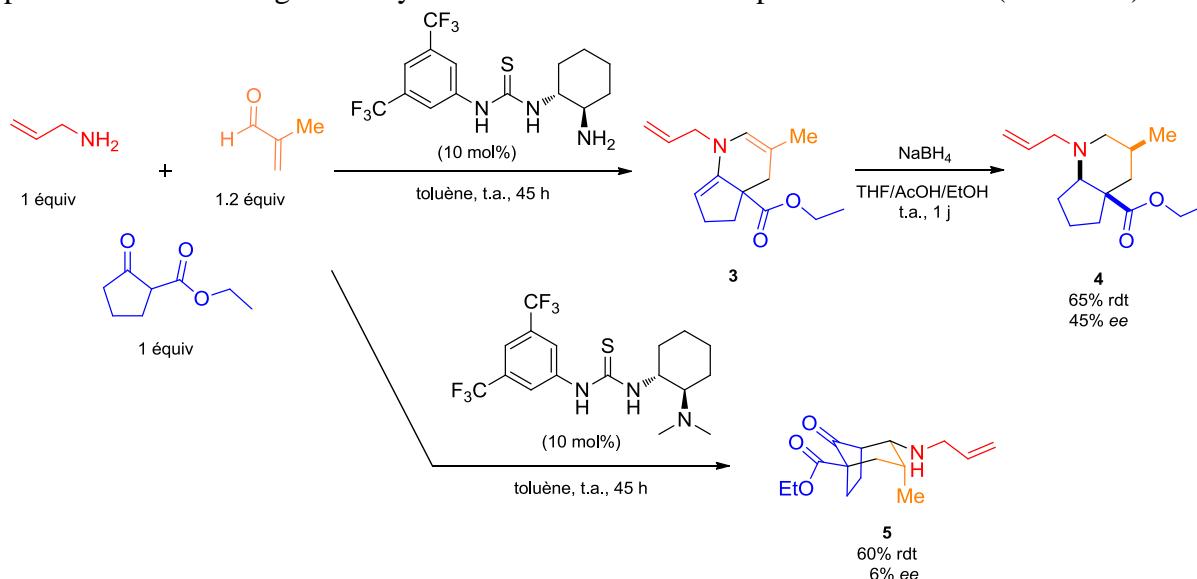


Schéma 2. Résultats initiaux sur la réaction multicomposants énantiosélective entre l'éthyl 2-oxocyclopentanecarboxylate, la méthacroléine et l'allylamine : chimiosélectivité guidée par le mode d'action des organocatalyseurs

Il est rapidement apparu que le mode d'activation de l'organocatalyseur permettait de contrôler l'obtention chimiosélective de l'une ou l'autre des familles de produits : une activation covalente de type iminium conduisait à la formation exclusive de la diènamine **3**, immédiatement réduite en cyclopentapipéridine **4** en raison de sa faible stabilité, tandis qu'une activation non-covalente par liaison hydrogène résultait dans la formation du bicyclic ponté **5**. Toutefois, malgré nos efforts d'optimisation par la modification de la structure des catalyseurs et l'ajout d'additifs, les énantiosélectivités sont restées faibles: 45% d'excès énantiomérique pour la première famille de produits et 6% pour la seconde. Au vu de ces limitations, nous avons redirigé nos efforts vers l'utilisation d'amines fonctionnalisées, ce qui fera l'objet du prochain chapitre de cette thèse.

II) REACTION MULTICOMPOSANTS ORGANOCATALYSEE ENANTIOSELECTIVE POUR LA SYNTHESE DE PYRROLOPIPERAZINES :

En 2007, notre équipe a montré qu'il était possible de réaliser une séquence addition de Michael-formation d'un ion iminium-cyclisation de Pictet-Spengler en utilisant une amine fonctionnalisée par un groupement pyrrole dans des réactions trois-composants. En fonction de l'utilisation de β -dicarbonyls linéaires ou cycliques, des pyrrolopipérazines tri- ou tétracycliques **6** ou **7** ont été obtenues avec de bons rendements (Schéma 3).^[5d]

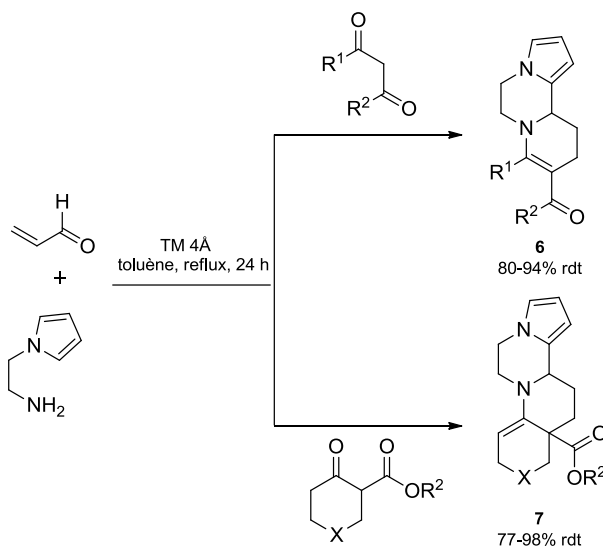


Schéma 3. Réaction multicomposants pour la synthèse de pyrrolopipérazines racémiques

Au vu des activités biologiques variées des pyrrolopipérazines,^[7] développer des voies

⁷ (a) I. L. Jirkovsky, *Vol. 4,188,389*, United States, **1980**; (b) A. J. Ratcliffe, R. J. A. Walsh, T. N. Majid, S. Thuraiatnam, S. Amendola, D. J. Aldous, J. E. Souness, C. Nemecek, S. Wentzler, C. Venot, *Vol. WO 03/024967 A2*, **2003**; (c) J. P. Cain, A. V. Mayorov, M. Cai, H. Wang, B. Tan, K. Chandler, Y. Lee, R. R. Petrov, D. Trivedi, V. J. Hruby, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5462-5467; (d) B. Merla, T. Christoph, S. Oberbörtsch, K. Schiene, G. Bahrenberg, R. Frank, S. Kühnert, W. Schröder, in *WO 2008/046582 A1*,

d'accès énantiosélectives pour ces composés représente un enjeu synthétique important.^[8] Au début de nos travaux, il existait déjà des précédents de séquences domino Michael-Pictet-Spengler organocatalysées. En effet, en 2009, le groupe de Franzén avait mis au point une réaction bimoléculaire entre des amidoesters portant un aromatique riche en électrons et des énales,^[9] tandis que, l'année suivante, le groupe de Zhao avait démontré que ce schéma de réactivité était applicable en version trimoléculaire séquentielle en utilisant la tryptamine comme troisième partenaire.^[10] Dans ces deux réactions, l'ajout d'un acide est nécessaire dans un second temps pour effectuer la cyclisation de Pictet-Spengler,^[11] et les pyrroles ne sont pas compatibles avec ces conditions réactionnelles.^[9b] Toutes ces transformations utilisent comme catalyseurs des amines secondaires dérivées de la proline, qui activent l'énal sous forme d'un ion iminium α,β -insaturé qui peut subir l'addition de Michael énantiosélective du dérivé β -dicarbonylé.^[12] En partant de ces conditions réactionnelles, nous avons développé une réaction multicomposants organocatalysée énantiosélective pour la synthèse de pyrrolopipérazines tricycliques **9** (Schéma 4). L'optimisation des conditions réactionnelles a fait apparaître quatre observations principales :

1. Seul le catalyseur **8** est efficace dans cette réaction, les autres amines secondaires testées délivrant le produit avec des rendements et excès énantiomériques faibles.
2. L'ajout d'acide comme co-catalyseur tend à diminuer le rendement de la réaction.
3. La réaction en version multicomposants est plus sélective que l'alternative séquentielle, illustrant l'intérêt des réactions multicomposants pour la piégeage d'intermédiaires réactionnels sensibles, évitant ainsi leur racémisation.
4. Les solvants apolaires aromatiques, notamment le trifluorotoluène, sont optimaux pour cette transformation.

Cette nouvelle réaction multicomposants énantiosélective a été appliquée à 21 exemples différents, avec des variations substantielles de chacun des substrats (β -cétioester linéaire, β -alkyl ou -arylénal et 2-(aminoéthyl)pyrrole différemment substitués). Les énantiosélectivités ont en général été très bonnes, même si la température de la réaction a dû être légèrement abaissée pour certains substrats plus réactifs afin de la préserver. En revanche, la cyclisation de Pictet-Spengler n'est pas diastéréosélective et les deux diastéréomères ont généralement été formés en proportions similaires. Toutefois, ils pouvaient la plupart du temps être séparés par chromatographie sur colonne, offrant ainsi la possibilité de générer rapidement une grande

2008.

⁸ Un nombre limité de synthèses énantiosélectives de pyrrolopipérazines a pour l'instant été rapporté : (a) B. M. Trost, M. Osipov, G. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 15800-15807; (b) M. Bandini, A. Bottoni, A. Eichholzer, G. P. Miscione, M. Stenta, *Chem. Eur. J.* **2010**, *16*, 12462-12473; (c) Y. He, M. Lin, Z. Li, X. Liang, G. Li, J. C. Antilla, *Org. Lett.* **2011**, *13*, 4490-4493.

⁹ (a) J. Franzén, A. Fisher, *Angew. Chem. Int. Ed.* **2009**, *48*, 787-791; (b) W. Zhang, J. Franzén, *Adv. Synth. Catal.* **2010**, *352*, 499-518; (c) W. Zhang, J. Bah, A. Wohlfarth, J. Franzén, *Chem. Eur. J.* **2011**, *17*, 13814-13824.

¹⁰ X. Wu, X. Dai, L. Nie, H. Fang, J. Chen, Z. Ren, W. Cao, G. Zhao, *Chem. Commun.* **2010**, *46*, 2733-2735.

¹¹ J. Stöckigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 8538-8564.

¹² (a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 794-797; (b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215; (c) L.-W. Xu, L. Li, Z.-H. Shi, *Adv. Synth. Catal.* **2010**, *352*, 243-279; (d) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248-264.

diversité moléculaire.

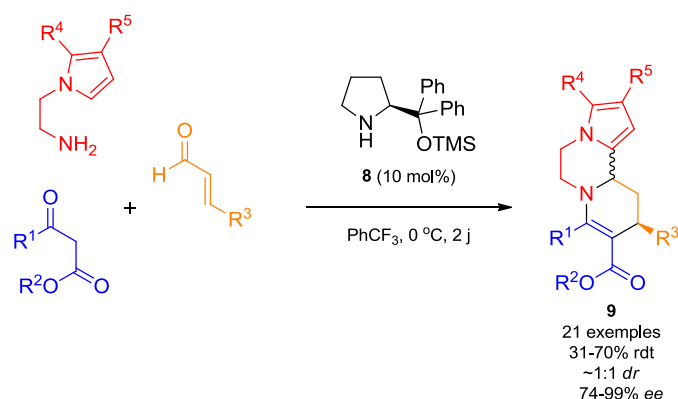


Schéma 4. Synthèse de pyrrolopipérazines énantiométriques par réaction multicomposants organocatalysée

Un certain nombre de tentatives de remplacement du β -cétoester linéaire par d'autres pronucléophiles a été réalisé, en utilisant notamment des β -cétoesters cycliques, β -dicétones linéaires et cycliques, β -cétoamides, β -cétothioesters, β -cétosulfones, β -cétophosphonates et 1-acétylindolin-3-ones. Tous ses substrats à l'exception des β -cétophosphonates ont également permis d'obtenir les pyrrolopipérazines correspondantes, mais en général avec une efficacité moindre, malgré une ré-optimisation des conditions réactionnelles pour chaque pronucléophile. Nous avons également montré que ces conditions réactionnelles sont spécifiques de la grande nucléophilie du pyrrole, puisque les substrats de type 2-(aminoéthyl)indole ne cyclisent pas dans les conditions de la réaction.^[13]

Par ailleurs, la double liaison du motif énaminoester du diastéréomère *cis* du produit a été hydrogénée avec une diastéréosélectivité totale (Schéma 5). L'hydrogénation de son épimère, ainsi que d'autres tentatives de post-fonctionnalisation (épimérisation, réaction de Diels-Alder) ont quant à elles donné des résultats mitigés.

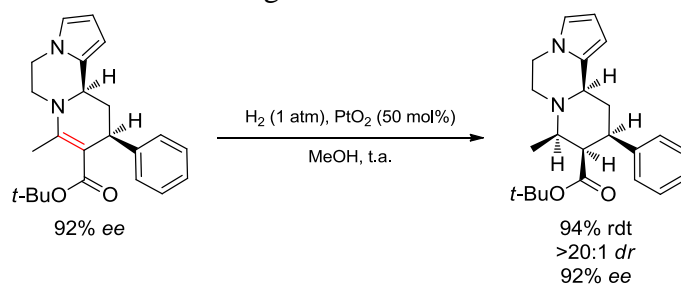


Schéma 5. Post-fonctionnalisation des pyrrolopipérazines énantiométriques par hydrogénation

III) SYNTHÈSE D'HÉTÉROCYCLES POLYFONCTIONNALISÉS ENANTIOENRICHIS PAR 3-CR ET 4-CR :

Ayant réussi à développer une réaction multicomposants organocatalysée énantiosélective pour le synthèse de pyrrolopipérazines, nous avons voulu évaluer la possibilité d'utiliser d'autres amines fonctionnalisées dans cette réaction. Une évaluation de différents

¹³ T. A. Nigst, M. Westermaier, A. R. Ofial, H. Mayr, *Eur. J. Org. Chem.* **2008**, 2369-2374.

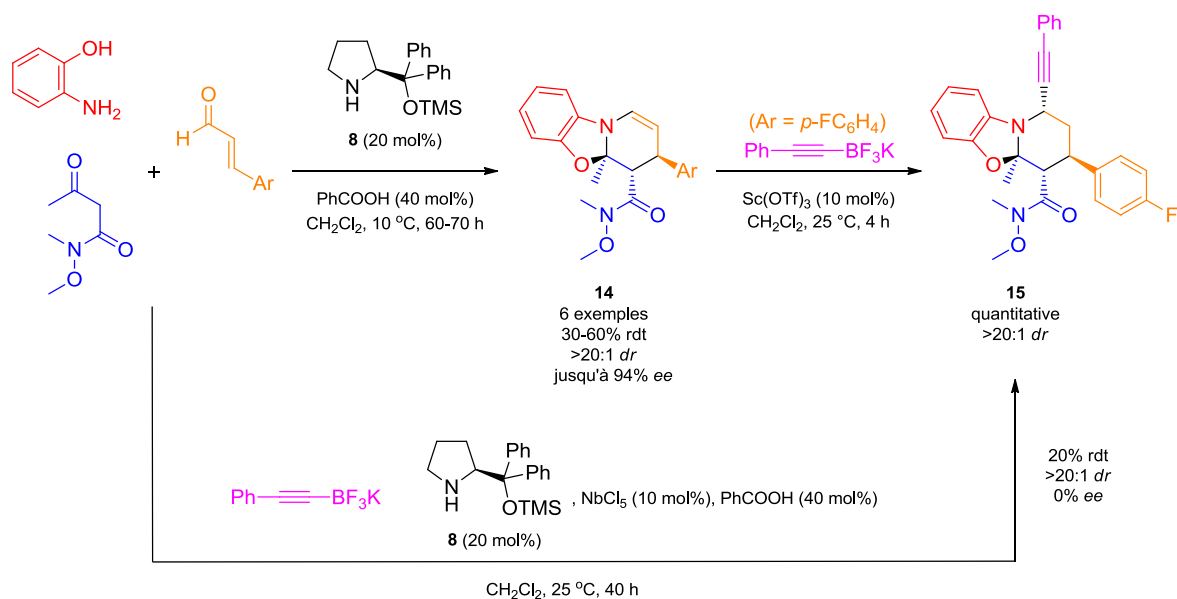


Schéma 7 Réactions trois- et quatre-composants avec le 2-aminophénol : résultats après optimisation

IV) ADDITION CONJUGUEE ORGANOCATALYSEE ENANTIOSELECTIVE ET DIASTEREOSELECTIVE DE β -CETOAMIDES SUR LES NITROOLEFINES :

Ayant mis en lumière une différence de réactivité et de sélectivité entre les β -cétosters et les β -cétamides dans le chapitre précédent, nous avons souhaité l'exploiter dans d'autres transformations. L'addition de Michael des dérivés β -dicarbonylés sur les nitrooléfines est une des réactions les plus étudiées en organocatalyse.^[15] Les travaux de Takemoto et de Rawal ont notamment permis de montrer que les organocatalyseurs bifonctionnels basés sur des motifs thiourées ou squaramides étaient particulièrement efficaces dans cette transformation, permettant l'obtention de rendements et d'excès énantiomériques élevés.^[16] Toutefois, pour les α -méthylène β -cétosters, aucune diastéréosélectivité n'est possible à cause de l'épimérisation du centre stéréogène en α .^[17] En nous basant sur la moindre acidité des β -cétamides par rapport aux β -cétosters, nous avons émis l'hypothèse qu'il serait possible de contrôler les deux centres stéréogènes lors de l'addition de Michael de ceux-ci sur les nitrooléfines (Schéma 8).

¹⁵ C. Roux, C. Bressy, in *Comprehensive Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH Verlag GmbH & Co. KGaA, **2013**, pp. 1013-1042.

¹⁶ (a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673; (b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119-125; (c) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416-14417.

¹⁷ R. Manzano, J. M. Andrés, R. Pedrosa, *Synlett* **2011**, 2205-2207.

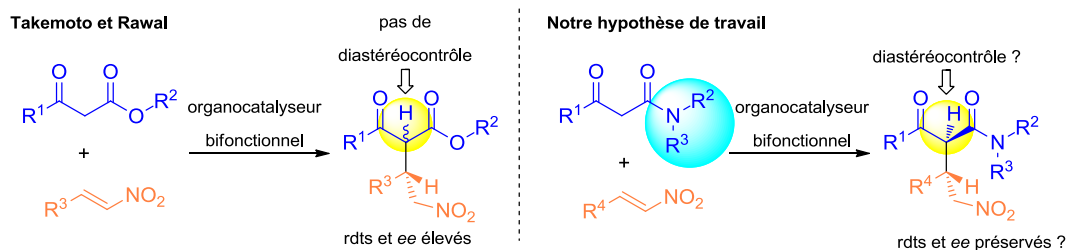


Schéma 8 Addition de Michael de dérivés 1,3-dicarbonylés sur les nitrooléfines : notre hypothèse de travail

Au cours de l'optimisation des conditions réactionnelles, nous avons observé que plusieurs conditions étaient nécessaires pour répondre au cahier des charges que nous nous étions fixé (Schéma 9) :

1. Le β -cétamide de Weinreb **16** a permis d'obtenir le produit **17** avec une bonne diastéréosélectivité, quand les amides secondaires résultaient en un mélange semblable à celui obtenu avec les esters.
2. Parmi les catalyseurs que nous avons évalués, les squaramides, et tout particulièrement ceux portant un groupement non-aromatique sur l'atome d'azote tel que **18**, étaient la seule famille de catalyseurs rendant possible le contrôle de la diastéréosélectivité de la réaction.

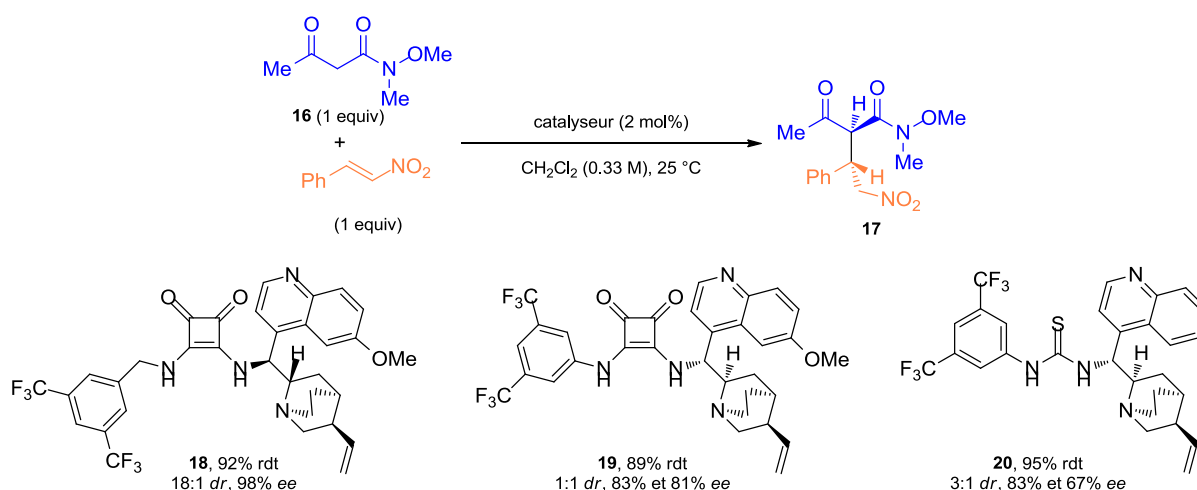


Schéma 9 Addition de Michael de β -cétamides sur les nitrooléfines : conditions optimisées

Avec ces conditions réactionnelles optimisées, nous avons pu démontrer que cette réaction est transposable sur une grande variété de substrats (Schéma 10), que ce soit des β -cétamides de Weinreb ou tertiaires portant un groupement alkyle ou aryle sur la cétone ou des nitrooléfines substituées en position β par des aromatiques, hétéroaromatiques ou des chaînes alkyles. Les produits **21** ont en général été obtenus avec des rendements, énantio- et diastéréosélectivités élevés. L'utilité synthétique de cette méthode tient également à la possibilité de réaliser cette réaction à une échelle synthétique (2 mmol), avec une faible charge catalytique (0,5 mol%) et en absence de solvant, sans modifier significativement le résultat. Par ailleurs, un certain nombre de post-fonctionnalisations sont possibles, telle que la réduction diastéréosélective de la fonction cétone en alcool secondaire, où la transformation de l'amide de Weinreb en aldéhyde par traitement au LiAlH_4 .

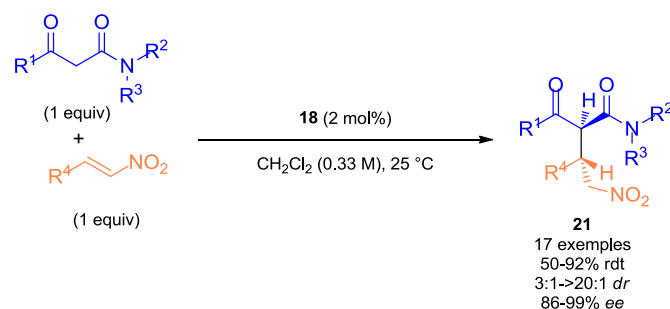


Schéma 10 Addition de Michael de β-cétoamides sur les nitrooléfines : généralité de la réaction

Au vu de ces résultats, nous avons souhaité déterminer quelle était l'origine de la forte diastéréosélectivité observé dans cette réaction. Pour cela, nous avons conduit un certain nombre d'études mécanistiques:

1. Tout d'abord, quand le produit de la réaction est de nouveau placé dans les conditions réactionnelles en présence d'une nouvelle nitrooléfine, on n'observe pas de réactivité, ce qui signifie que la réaction n'est pas réversible.
2. Si le produit **17** avec un excellent *dr* est placé en présence d'un catalyseur non-sélectif, alors aucune épimérisation n'est observée. Dans le même temps, si ce produit sous forme d'un mélange 1:1 des deux diastéréomères est mis en présence du catalyseur sélectif **18**, aucune amélioration du rapport diastéréomérique n'est obtenu. Nous pouvons alors conclure que le produit ne s'épimérise pas dans les conditions réactionnelles, indiquant ainsi que nous sommes dans un scénario de diastéréosélection cinétique contrôlée par le catalyseur lors de la formation de la liaison carbone-carbone.
3. Un tracé du logarithme du rapport diastéréomérique en fonction des paramètres stériques de Charton des différents substituants R^1 de la cétone a permis de mettre en évidence une relation linéaire avec l'énergie libre, quand ce substituant est un groupement alkyle (Schéma 11).^[18] Cette relation linéaire permet d'affirmer que la diastéréosélectivité de la réaction est sous contrôle stérique.

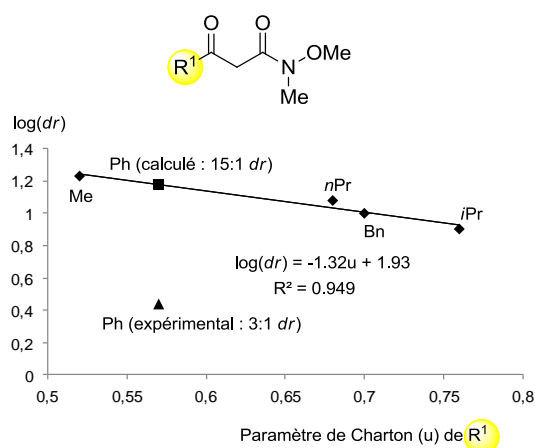


Schéma 11 Relation linéaire entre $\log(dr)$ et les paramètres stériques de Charton du groupement R^1

¹⁸ (a) R. W. Taft, *J. Am. Chem. Soc.* **1953**, *75*, 4538-4539; (b) M. Charton, *J. Am. Chem. Soc.* **1975**, *97*, 1552-1556; (c) M. Charton, *J. Org. Chem.* **1976**, *41*, 2217-2220; (d) M. S. Sigman, J. J. Miller, *J. Org. Chem.* **2009**, *74*, 7633-7643.

CONCLUSION ET PERSPECTIVES :

En conclusion, lors de ces trois années de thèse, nous avons abordé la possibilité de conduire des réactions multicomposants énantiosélectives par l'utilisation d'organocatalyseurs. Nous avons notamment pu appliquer cette stratégie à des réactions entre des dérivés β -dicarboxylés, des énals et des amines fonctionnalisées soit par un cycle pyrrole,^[19] soit par une fonction phénol. Au cours de ces travaux, nous avons également remarqué que les β -cétamides peuvent avoir des comportements différents par rapport aux β -cétosters et nous avons tiré profit de ces différences pour les appliquer dans une réaction d'addition énantio- et diastéréosélective sur des nitrooléfines.^[20]

Nos futurs programmes de recherche vont se concentrer sur le développement d'autres réactions multicomposants initiées par une addition de Michael organocatalysée énantiosélective de dérivés β -dicarboxylés et également sur la mise en réaction de β -cétamides avec diverses entités électrophiles.

¹⁹ H. Du, J. Rodriguez, X. Bugaut, T. Constantieux, *Adv. Synth. Catal.* **2014**, 356, 851-856.

²⁰ H. Du, J. Rodriguez, X. Bugaut, T. Constantieux, *Chem. Eur. J.* **2014**, 20, 8458-8466.

GENERAL INTRODUCTION

GENERAL INTRODUCTION

In the modern chemistry world, with the rapid development of the pharmaceutical and agrochemical industries, diastereoselective and enantioselective synthetic routes to construct new complex targets are needed, which encourage chemists to develop innovative and efficient methods. In addition, the development of more sustainable chemistry is one of the current concerns of our society. To this propose, the concept of green chemistry has been proposed, which include 12 principles for better eco-friendliness and cost-efficiency. These new concepts are guiding the development of new synthetic schemes.

How can organic chemists provide solutions that fulfil both these challenges? Multicomponent reactions play an important role since they offer an access in a single synthetic operation to variously functionalized molecules with high molecular complexity. The development of enantioselective catalytic methods can also help to attain greener chemistry. Not only they reduce the amount of waste by introducing a sub-stoichiometric amount of catalyst, but they also allow a selective access to enantioenriched chiral molecules. This aspect is very important in the pharmaceutical field where generally the molecule responsible for this activity is a chiral molecule as a single enantiomer. Among the methods of asymmetric catalysis, organocatalysis is gaining more and more attention. Indeed, it has many advantages, including ease of access to the catalysts, stability and high functional compatibility, low cost and low toxicity. Therefore the combination of multicomponent reactions and organocatalysis could achieve a high degree of efficiency and selectivity while being in agreement with the principles of green chemistry.

Recently, our research group has initiated a research theme focusing on the development of enantioselective multicomponent reactions involving 1,3-dicarbonyl derivatives, initiated by a Michael addition. These sequences generally involve a 1,3-dicarbonyl derivative, a Michael acceptor and an amine to afford polyfunctionalized heterocycles with a high level of complexity.

In this context, the work developed during the three years of my PhD thesis has focused on three main objectives:

- 1) Firstly, we have undertaken a study of an enantioselective multicomponent reaction with simple amines.
- 2) In view of the low enantioselectivities, Secondly, we turned our attention towards functionalized amines to synthesize enantioenriched pyrrolpiperazines and other polyfunctionalized heterocyclic molecules, which were obtained with high enantioselectivities.
- 3) Finally, having realized the potential of simple linear β -ketoamides in enantioselective multicomponent reactions, we also used them for the first time in the Michael addition to nitroolefins by using bifunctional organocatalysis.

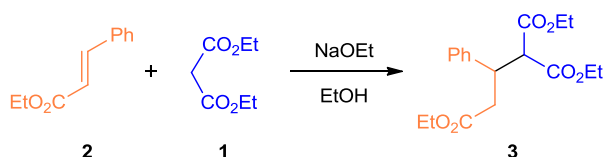
I. BIBLIOGRAPHIC PART

I. BIBLIOGRAPHIC PART

I.1 THE MICHAEL ADDITION

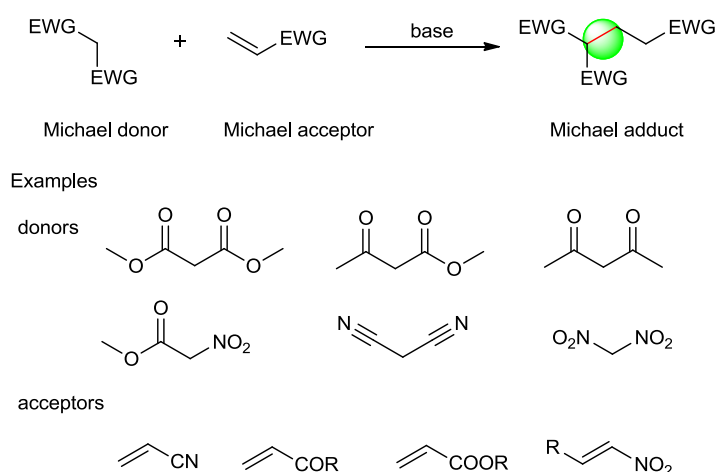
I.1.1 HISTORY OF THE MICHAEL ADDITION

In 1883, Komnenos discovered the first example of a carbon nucleophile adding to an electron-deficient carbon-carbon double bond by observing the facile addition of the anion of diethyl malonate to ethylidene malonate.^[1] Four years after, Arthur Michael systematically investigated the reactions of various stabilized anions with α,β -unsaturated systems, as for example the conjugate addition of diethyl malonate **1** to the double bond of ethyl cinnamate **2** in the presence of sodium ethoxide to provide a substituted pentanedioic acid diester **3** (Scheme I- 1).^[2] Since this discovery, the Michael addition reaction^[3] proved capable of wide applicability, becoming a very important tool in organic synthesis.^[4, 5]



Scheme I- 1 A seminal example of Michael addition reaction (Michael, 1887).

It has been applied in numerous carbon-carbon bond-forming reactions of stabilized anions called Michael donors with activated alkenes or electron-poor alkenes called Michael acceptors, with the use of a base (Scheme I- 2).^[6]



Scheme I- 2 The model of the Michael addition reaction and examples of Michael donors and Michael acceptors.

I.1.2 MECHANISM OF THE MICHAEL ADDITION

Knowing the mechanism of a reaction is very important to elaborate new variations of this transformation. The mechanism of the Michael addition can be divided in three elemental steps. The first step is the formation of the enolate by deprotonation of the pronucleophile by the base; the second step is the key carbon-carbon bond formation where the enolate tends to react with the Michael acceptor via conjugate addition; the last step consists in the reprotonation of the newly formed enolate with regeneration of the base catalyst (Figure I-1).^[7]

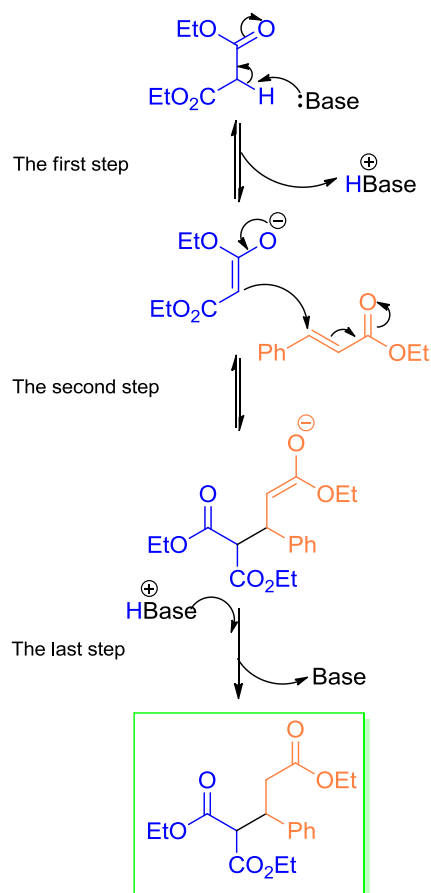


Figure I- 1 The mechanism of the Michael addition.

I.1.3 ENANTIOSELECTIVE MICHAEL ADDITION

During the process of a Michael addition, one or several stereogenic center(s) can be installed. For this reason, a large number of research groups in the world have engaged in the development of enantioselective Michael additions, and this reaction can now be considered as one of the most powerful and reliable tools for the stereocontrolled formation of carbon-carbon and carbon-heteroatom bonds.^[8, 9] Historically, the catalytic methodologies typically employed for the enantioselective Michael addition have been transition metal

catalysis and enzymatic methods.^[10] Since 2000, organocatalysis has emerged as a new, powerful and environmentally friendly methodology for the catalytic synthesis of enantiomerically enriched organic compounds.^[11]

I.2 ORGANOCATALYTIC ENANTIOSELECTIVE MICHAEL ADDITION OF 1,3-DICARBONYL SUBSTRATES

I.2.1 ORGANOCATALYSIS: DEFINITION AND HISTORICAL BACKGROUND

I.2.1.1 SIGNIFICANCE OF ORGANOCATALYSIS

In the field of modern synthetic organic chemistry, enantioselective reactions are of immense importance, because two enantiomers can have very different biological activities. For this reason, there is an increasing demand for enantiomerically pure compounds in pharmaceuticals, fragrances, cosmetics, agrochemicals, fine chemicals, or as synthetic intermediates. In order to obtain enantiomerically pure compounds, many researchers have dedicated long-term efforts at optimizing transition metal or enzyme-catalyzed reactions. The development of transition metal complexes with chiral ligands has enabled the synthesis of enantiomerically pure compounds.^[10, 12] But the toxicity and hazard of the chemicals should be considered and there is a clear need for alternatives that are less costly, less damaging to the environment, and that employ less toxic reagents so as to meet with the requirements of sustainable and green chemistry.^[13] In this context, a new approach to the catalytic production of enantiomerically pure organic compounds has emerged since 2000: organocatalysis.^[8, 9, 14]

I.2.1.2 DEFINITION OF ORGANOCATALYSIS

What is an organocatalyst? This word encompasses all “organic” molecules that have the ability to accelerate one or several elemental steps of a chemical reaction. Organocatalysts consist of small, low-to-medium-molecular-weight organic compounds, containing mainly carbon, hydrogen, nitrogen, sulfur and phosphorus atoms.^[10] In their strict definition, they should not contain any metallic element. However, in a broader descriptive definition, catalysts that include metals that are not part of the active center of the molecule, such as metallophosphites^[15] or Fu's catalyst^[16, 17] are generally also considered to be organocatalysts (Figure I- 2).

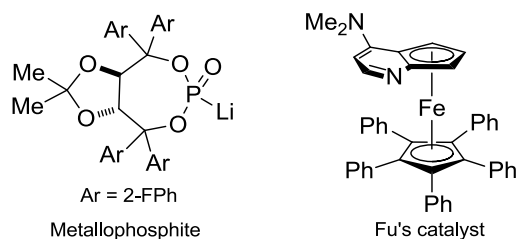


Figure I- 2 The examples of metallophosphites and Fu's catalyst.

Organocatalysts, which are mimicking the way enzymes catalyze reactions, have several advantages over other types of catalysts:

(i) Firstly, their lack of sensitivity to moisture and oxygen, and therefore, special reaction conditions, e.g. inert atmosphere, low temperatures, absolute solvents, etc., are generally not required, with the notable exception of N-heterocyclic carbenes.^[14, 18-21]

(ii) Secondly, their ready availability, robustness, low cost, and low toxicity can confer a huge direct benefit in the production of pharmaceutical intermediates when compared with some transition metal catalysts or enzymes.^[6]

(iii) Thirdly, they are usually easily separated from the product at the end of the reaction, rendering the processes more environmentally friendly.^[8]

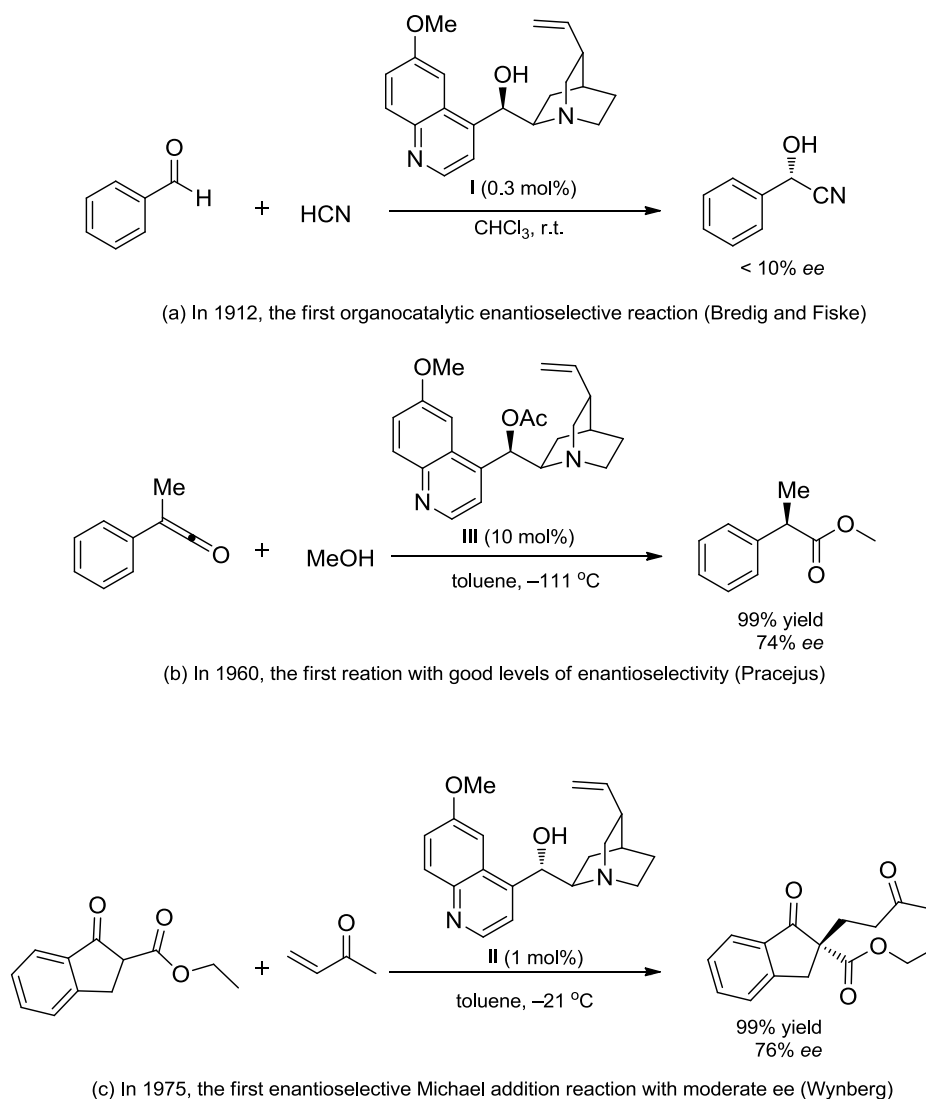
Hence, organocatalytic reactions are becoming more and more popular as powerful tools for the construction of complex molecular skeletons, and they have been already applied in total synthesis of natural products and biologically active molecules.^[22-24]

I.2.1.3 HISTORY OF ORGANOCATALYSIS

The historic roots of organocatalysis go back to the understanding of the catalytic activity and selectivity of enzymes and attempts to mimic them by using low-molecular-weight compounds.^[25, 26] In 1928, the German chemist Wolfgang Langenbeck first used the term organic catalysis ("organische Katalyse" in German).^[27] In fact, as early as 1912, Bredig and Fiske had already reported the first example of an asymmetric organocatalytic reaction by reacting benzaldehyde with hydrogen cyanide in the presence of the alkaloids quinine (**I**) or quinidine (**II**) to obtain the optically active enantiomeric cyanohydrin products with a low enantioselectivity ($ee < 10\%$) (Scheme I- 3a).^[28] However, this observation represented a breakthrough from a conceptual level.

The next seminal step in the early history of organocatalysis arrived in 1960, when Pracejus reported that the reaction of methyl phenyl ketene with methanol could be catalyzed by cinchona alkaloid derivative *O*-acetyl quinine (**III**) to deliver quantitatively the desired product with 74% ee .^[29] This constitutes the first report of good levels of enantioselectivity in an organocatalytic reaction (Scheme I- 3b). Based on Pracejus' previous report about cinchona alkaloids, in 1973, Langström and Bergson firstly described the enantioselective Michael addition of β -ketoester to acrolein catalyzed by optically active 2-(hydroxymethyl)-quinuclidine in benzene at room temperature. Although the enantioselectivity was not determined, the authors disclosed that the final Michael adduct had optical activity.^[30] Soon after, Wynberg developed a series of enantioselective Michael

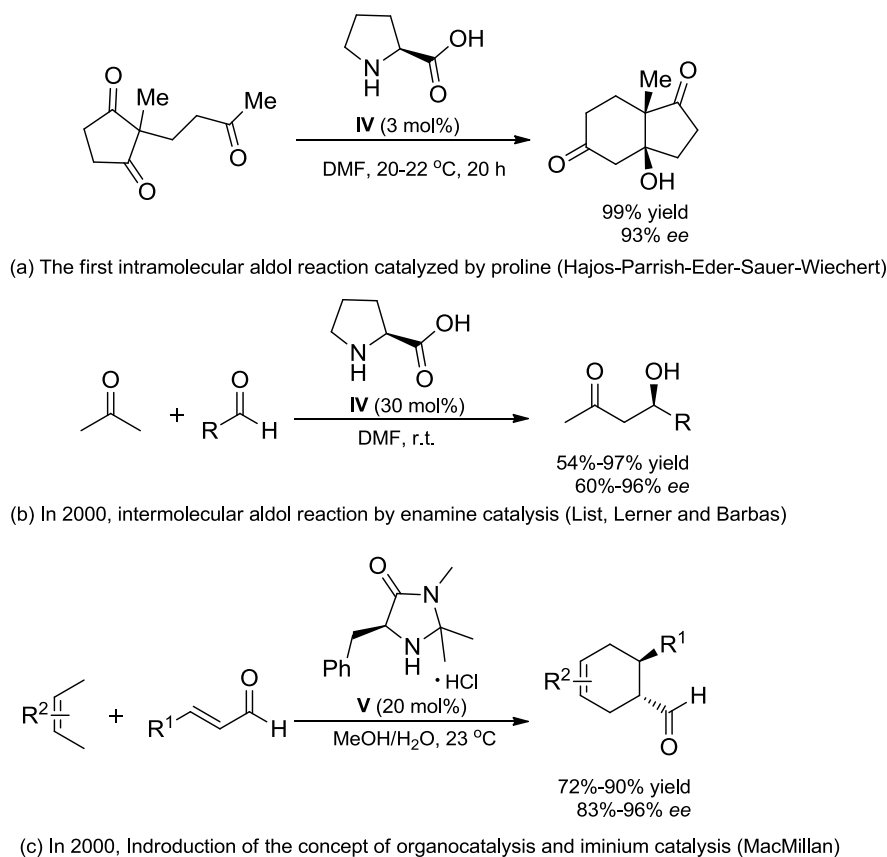
additions catalyzed by cinchona alkaloid, obtaining excellent yields and high enantiomeric excesses (Scheme I- 3c).^[31-34] Moreover, they observed that natural cinchona alkaloids were excellent catalysts, all the more as these molecules possess a C9 OH group which can be modified. Cinchona alkaloids have since then developed as one of the most widely used family of organocatalysts.^[35]



Scheme I- 3 The first examples of organocatalytic enantioselective reactions.

Another important highlight in the development of organocatalysis is the asymmetric, amine-catalyzed aldolization, with proline (**IV**) as the catalyst developed independently by Eder, Sauer, and Wiechert (1971) and Hajos and Parrish (1974) (Scheme I- 4a).^[36, 37] Although they postulated the reaction was carried on by an enamine mechanism, they did not describe proline-catalyzed direct intermolecular asymmetric aldol reaction. At the same time, Wiechert group first reported the enantioselective Michael addition of cyclic 1,3-diketones to vinyl ketones under quinine catalysis, with good yields and moderate enantiomeric excesses.^[36] Only little progress was then made in enamine catalysis until 2000 and the work of List, Lerner and Barbas applying amino acid proline to other aldol reactions in an intermolecular fashion (Scheme I- 4b).^[38] Almost simultaneously, D. W. C. MacMillan

presented results on the enantioselective amine Diels-Alder reaction catalyzed by imidazolidinone (**V**) through iminium activation, in a paper that helped popularizing the word "organocatalysis" (Scheme I- 4c).^[39] These two concomitant reports and the conceptualization in terms of activation modes that they brought about, triggered the boom of the field of organocatalysis that has continuously expanded since then.

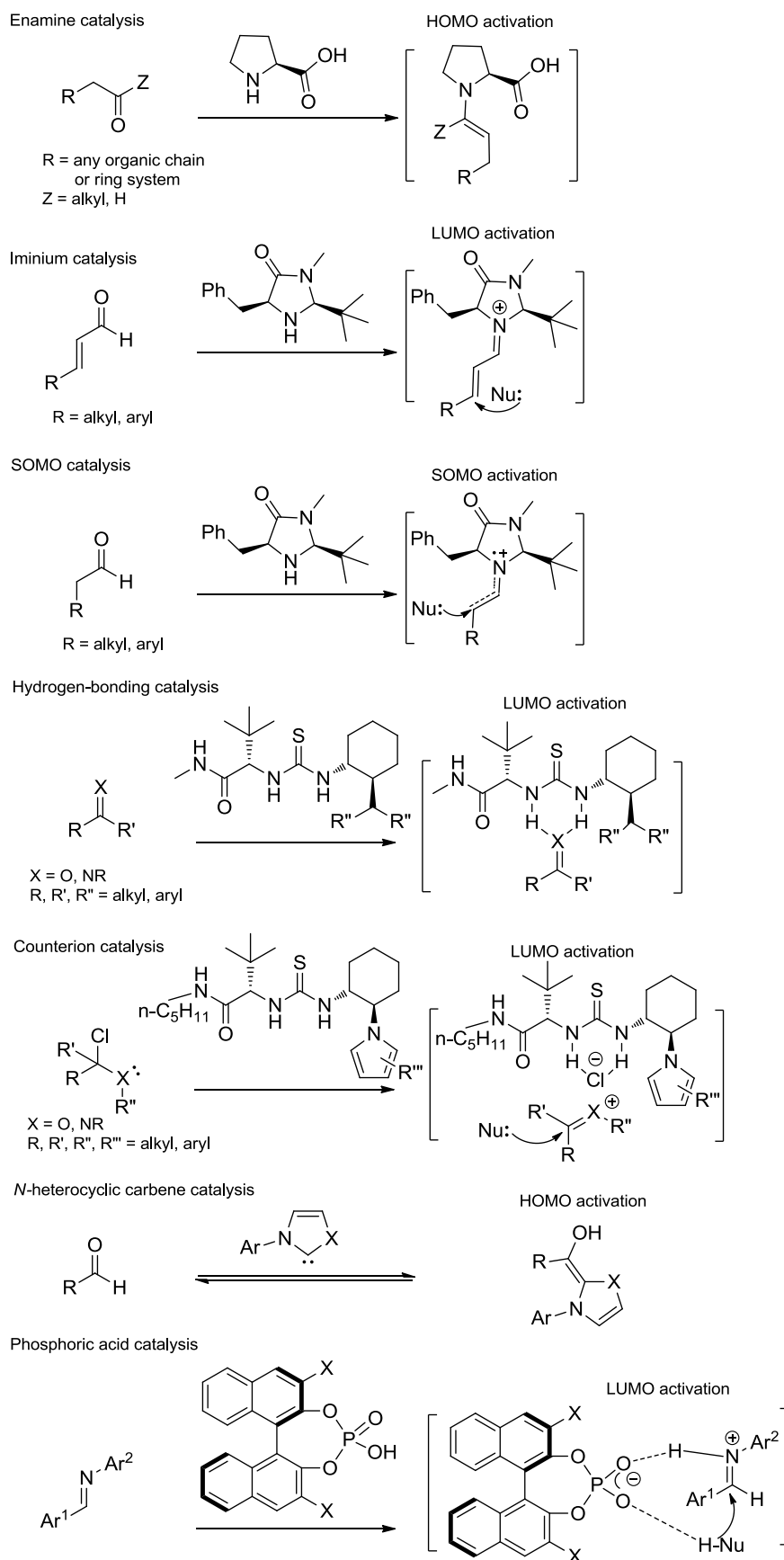


Scheme I- 4 Examples of the reaction in the presence of organocatalysts.

1.2.1.4 DIFFERENT TYPES OF ORGANOCATALYSIS

It's only in the last fifteen years that organocatalysis has become a field of central importance for the enantioselective synthesis of chiral molecules. Enantioselective organocatalytic reactions, according to the nature of the interactions between the substrate and the catalyst are usually classified into "covalent catalysis" and "non-covalent catalysis". The former family includes aminocatalysts^[14] (enamine, iminium and radical-iminium cation, SOMO catalysis), N-heterocyclic carbenes^[19, 21], ylides, N-acylammonium salts and so on. The latter category covers hydrogen-bonding complexes (ureas, thioureas, squaramides, phosphoric acids^[40]), phase-transfer catalysts, tertiary amines and so on (Table I-1).

Table I- 1 Generic modes of activation usually used in organocatalysis.



I.2.2 THE MICHAEL ADDITION OF 1,3-DICARBONYLS: A VERY CONVENIENT PLATFORM FOR ENANTIOSELECTIVE ORGANOCATALYSIS

For decades, many research programs have focused on the development of 1,3-dicarbonyl substrates as Michael donors. These polyfunctional scaffolds possess four nucleophilic and two electrophilic potential reactive sites, even up to five different nucleophilic sites when β -ketoamides are considered (Figure I- 3).^[41, 42]

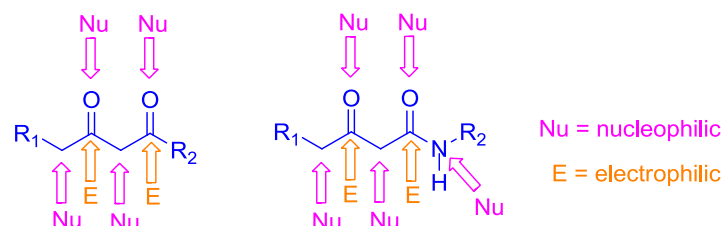
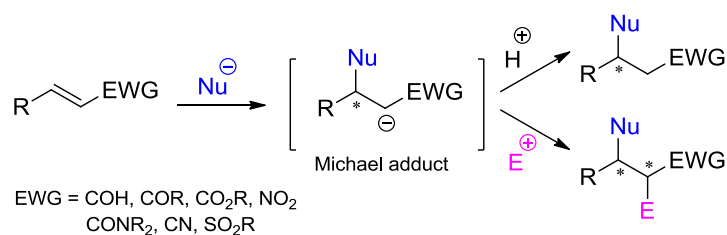


Figure I- 3 Potential reaction sites in 1,3-dicarbonyl substrates.

In this context, 1,3-dicarbonyl substrates readily participate as pronucleophiles (also referred to as donors) in Michael additions, properties that have led to new powerful synthetic strategies allowing the efficient diastereoselective and enantioselective construction of complex targets by using various chiral organocatalysts (Scheme I- 5).^[43]



Scheme I- 5 General strategies for the enantioselective Michael addition.

In this section, we will focus on the latest improvements made in enantioselective organocatalytic Michael additions of 1,3-dicarbonyl derivatives, classified according to the type of organocatalyst.

I.2.2.1 COVALENT ACTIVATION

I.2.2.1.1 IMINIUM-TYPE ACTIVATION OR ENAMINE-TYPE ACTIVATION

Primary or secondary amines can be employed as catalysts in Michael additions by forming covalent bond with aldehydes or ketones.^[43] There are two main modes of activation: iminium-type activation and enamine-type activation.^[44, 45]

Some examples of catalysts following this type of activation are presented in Figure I- 4. It is possible to tell from these examples that proline and its derivatives are the most common structural units in this family of catalysts. In addition to their mainly covalent activation mode, these catalysts **IV**, **V**, **VI**, **VII** can also bear additional functionalities that enable secondary interactions with the substrates. For example, catalysts **VIII**, **IX**, **X** possess a hydrogen-bonding donor unit, whereas catalyst exhibits a tertiary amino group that can activate the pronucleophile by deprotonation.

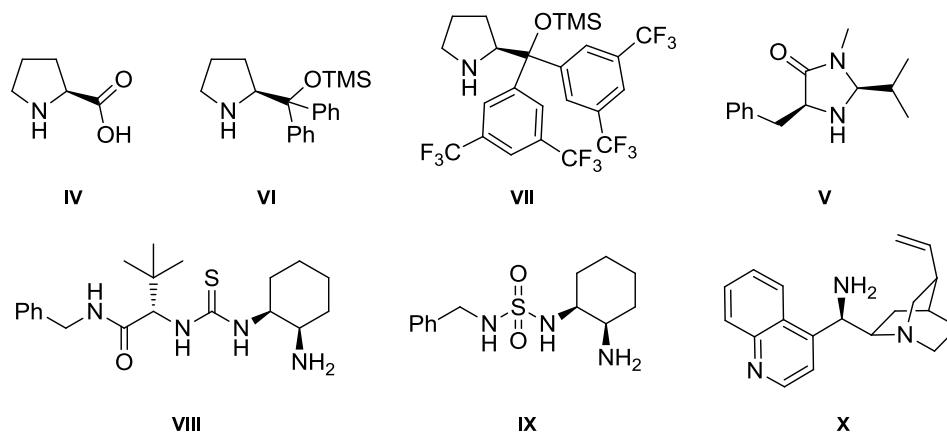
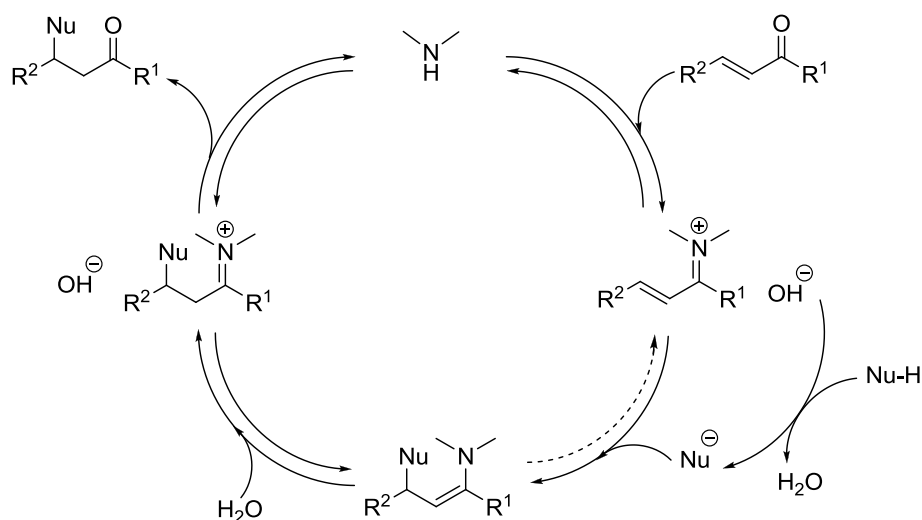


Figure I- 4 Examples of secondary amine catalysts.

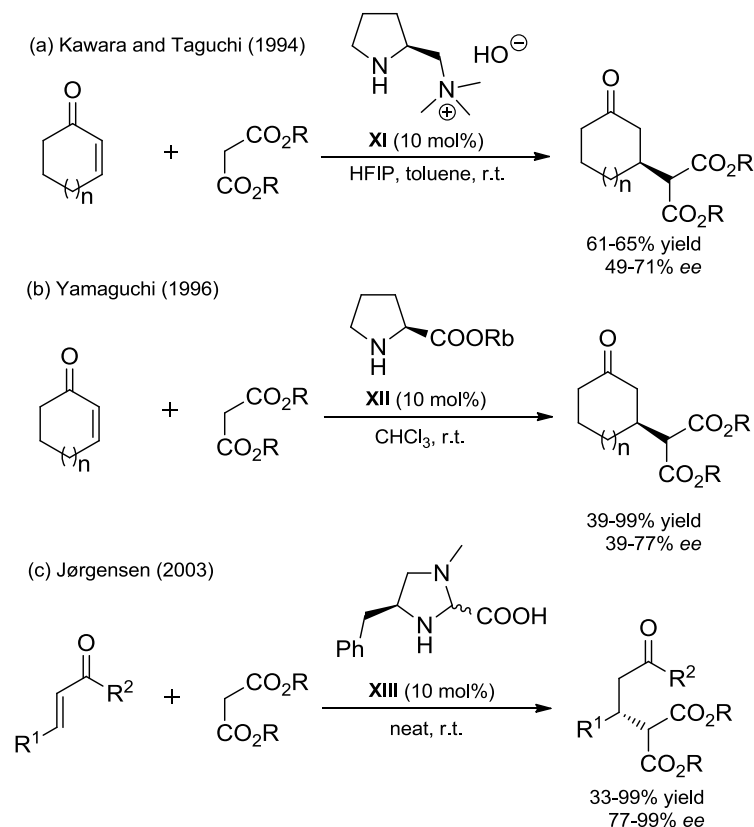


Scheme I- 6 Proposed catalytic cycle for amine-catalyzed Michael additions via iminium-type activation.

These chiral primary and secondary amine catalysts have already been shown to catalyze the enantioselective Michael addition of enolizable carbonyl compounds to electron-poor alkenes via the formation of an iminium or an enamine. In the iminium-type activation mode, firstly, the catalyst reacts with the electrophile counterpart to form an intermediate iminium ion (Scheme I- 6).^[45] Secondly, the nucleophile adds to the intermediate iminium ion and thus delivers an enamine intermediate. At last, the Michael adduct and the amine catalyst are released via an hydrolysis step. Meanwhile, a subsequent catalytic cycle restart. A key parameter of this mode of activation to achieve excellent enantioinduction is the control of the

geometry of the iminium ion intermediate. Moreover it was found that a Brønsted acid as co-catalyst can often assist the formation and the hydrolysis of the iminium intermediate in these reactions.

In 1994, Kawara and Taguchi first reported the enantioselective Michael addition of malonates to cyclic and acyclic enones catalyzed by chiral (2-pyrrolidinylmethyl)ammonium hydroxide (**XI**) and hexafluoroisopropanol (HFIP) as the Brønsted acid co-catalyst to obtain the Michael adducts in moderate yields and enantioselectivities (Scheme I- 7a).^[46] The enones with the enantiopure amine catalyst forms an activated iminium ion with lowered LUMO energy, which reacts with the malonate anions.



Scheme I- 7 Early examples of enantioselective Michael additions.

Soon after, Yamaguchi and co-workers also reported the same reactivity via iminium-type activation, but catalyzed by L-proline rubidium salt **XII** (Scheme I- 7b).^[47] Several years after, Jørgensen and co-workers reported the Michael addition of malonates to acyclic enones with excellent yields and enantiomeric excess with the use of a novel imidazolidine catalyst **XIII** (Scheme I- 7c).^[48] Moreover, the outstanding performance of this methodology has been applied in the one step synthesis of the anticoagulant warfarin catalyzed by the chiral imidazolidine derivatives **XIV**.^[49] In 2006, Ley and co-worker also extended the use of their new proline tetrazole catalyst, called 5-pyrrolidin-2-yl tetrazole **XV**, in the same reaction with good yields and good to high enantioselectivities.^[50] A large variety of primary and secondary amine catalysts have since then been developed to catalyze the Michael addition of various nucleophiles to enones. For example, in 2009, Feng and co-workers utilized the C2-symmetric diamide catalysts (**XVI**) for iminium-type activation in

the enantioselective Michael addition of 4-hydroxycoumarin to α,β -unsaturated ketones with high yields (up to 99%) and enantioselectivities (up to 89% *ee*) under mild conditions.^[51]

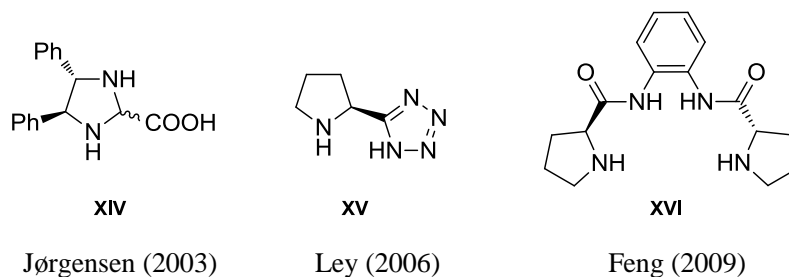
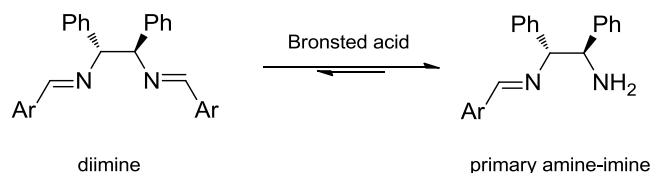


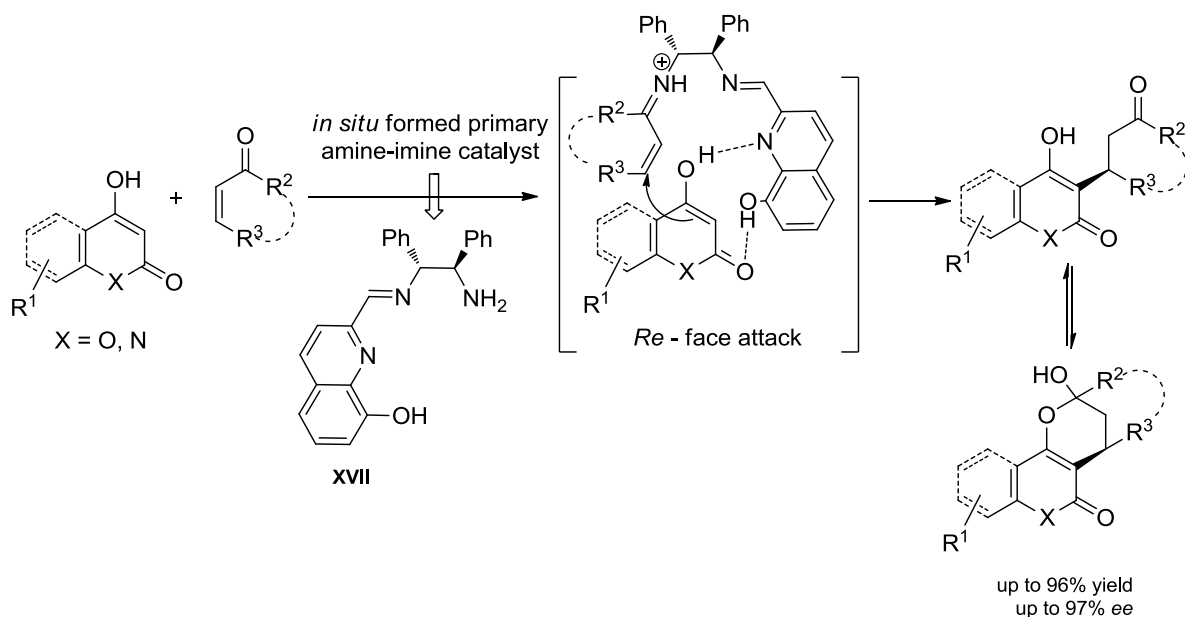
Figure I- 5 Structures of the various catalysts for iminium activation.

In 2011, Cheng and co-workers first reported that the same reactivity can be observed with *in situ* formed primary amine-imine organocatalyst **XVII**, with excellent results. The primary amine-imine catalyst has been synthesized *in situ* under acidic conditions through hydrolysis of a chiral diimine precursor (Scheme I- 8).^[52]



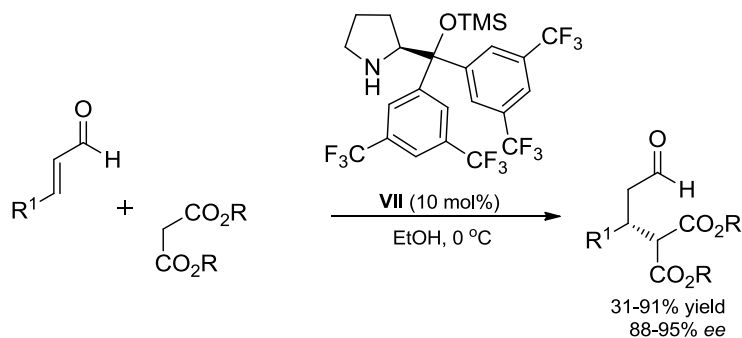
Scheme I- 8 A chiral diimine precursor.

The interaction between the enone and the amine produces the active iminium ion, and then, the 4-hydroxycoumarin, positioned by hydrogen bonding, adds to the active iminium from the *Re* face, affording the major stereoisomer (Scheme I- 9).^[52]



Scheme I- 9 Enantioselective synthesis of coumarin derivatives catalyzed by an *in situ* formed primary amine-imine catalyst (Cheng, 2011).

In 2006, Jørgensen and co-workers first reported that α,β -unsaturated aldehydes can also react with malonates as pronucleophiles in the Michael addition via iminium-type activation. The results indicated that α,β -unsaturated aldehydes can also be excellent substrates in this reaction by using *O*-trimethylsilyl-protected diarylprolinol (**VII**) as a very efficient catalyst (Scheme I- 10).^[53] In 2012, Lu and co-workers used the outstanding performance of this methodology as a key step to synthesize ramelteon (Figure I- 6).^[54]



Scheme I- 10 The first example of α,β -unsaturated aldehydes as Michael acceptors via iminium-type activation (Jørgensen, 2006).

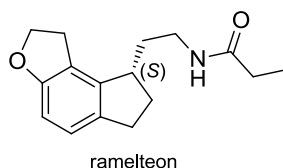


Figure I- 6 The structure of ramelteon.

The same reactivity is also observed with heterogeneous catalysts such as morphosynthesized L-proline mesoporous silica **XVIII** (Figure I- 7) designed by Park in 2008.^[55] In the same line, in 2009, Zlotin and co-workers developed a recoverable organocatalyst, which is *O*-TMS- α,α -diphenyl-(*S*)-prolinol (**XIX**), for the enantioselective Michael reaction between α,β -enals and dialkyl malonates under mild conditions to afford the respective adducts in high yields (up to 98%) and high enantioselectivities (*ee* up to 99%).^[56]

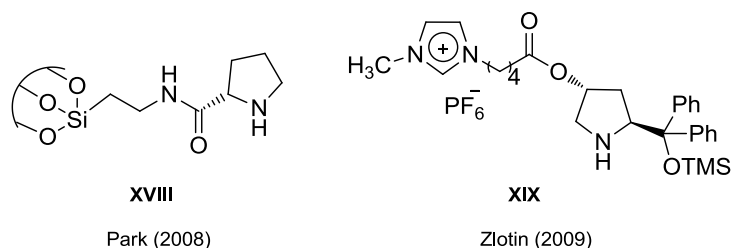
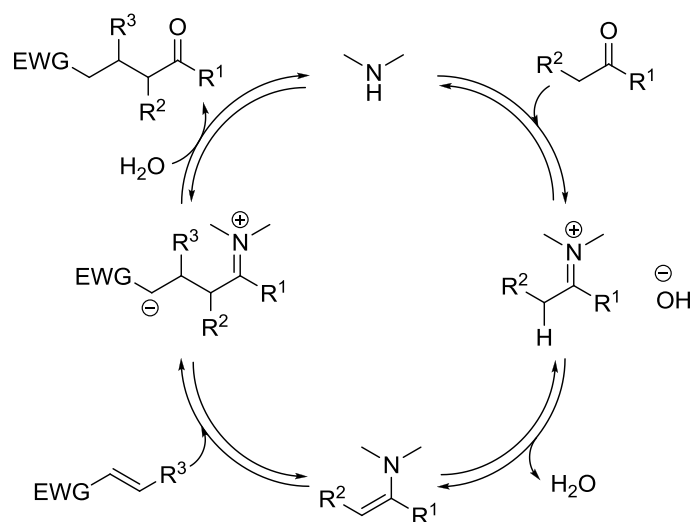


Figure I- 7 The structure of the catalysts.

All these reports have shown that this strategy via iminium-type activation is typically applied to malonates or related 1,3-dicarbonyl compounds, which are rather acidic carbon

nucleophiles. On the opposite, in the enamine-type activation mode (Scheme I- 11), firstly, the catalyst activates the Michael donor reagent and allows for the reaction to be carried out under neutral conditions. This strategy is limited to the use of Michael donors capable of forming enamines, that is to say enolizable aldehydes or ketones. Up to now, there are no report of the Michael addition of 1,3-dicarbonyl substrates via enamine-type activation. To explain this observation, we can surmise that enamines formed from 1,3-dicarbonyl compounds are not reactive enough because of their stabilization by conjugation with the second carbonyl group.

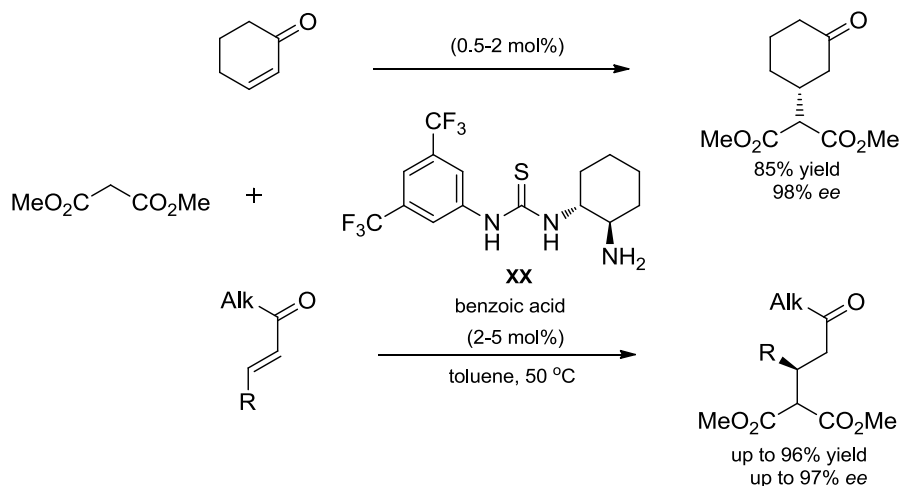


Scheme I- 11 Proposed catalytic cycle for amine-catalyzed Michael additions via enamine-type activation.

Since they use similar catalysts, both iminium-type activation and enamine-type activation can be combined in the same reaction. These domino reactions will be discussed in the second part of this bibliographic introduction.

1.2.2.1.2 BIFUNCTIONAL IMINIUM ACTIVATION

The iminium-type activation can combine with hydrogen bonding in the process of reaction. In 2012, Kwiatkowski and co-workers observed that readily available primary amine-thiourea **XX** derived from 1,2-diaminocyclohexane was an efficient catalyst for the Michael addition of malonates to various enones. Moreover, they found that the addition of weak acids (benzoic acid) as co-catalysts and increasing the temperature to 50 °C can improve the efficiency of the reaction (Scheme I- 12).^[57]

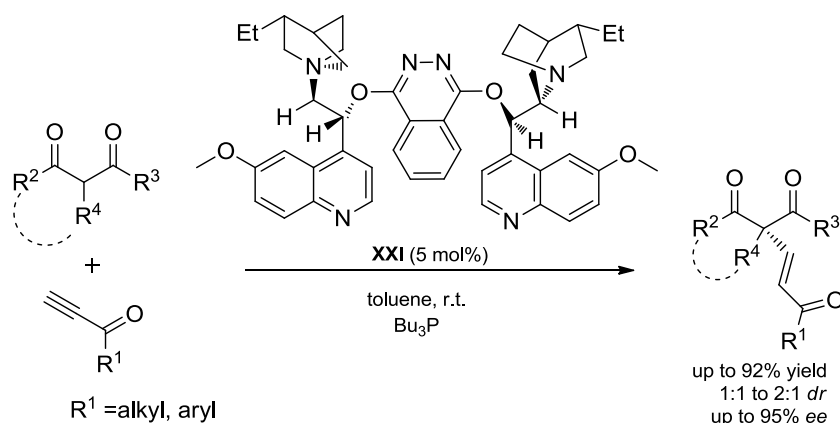


Scheme I- 12 Addition of malonates to various enones catalyzed by primary amine-thioureas (Kwiatkowski, 2012)

I.2.2.2 NON-COVALENT ACTIVATION

I.2.2.2.1 BRØNSTED BASE ACTIVATION

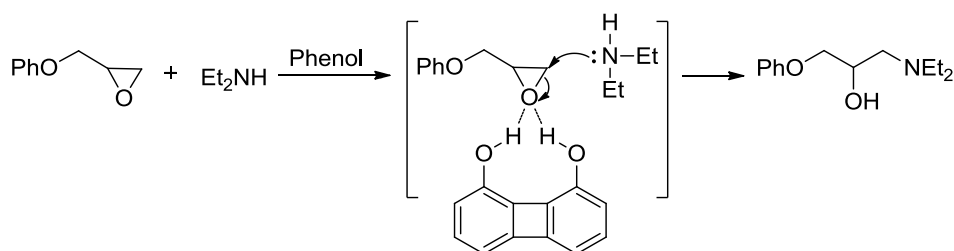
In 2004, Jørgensen and co-workers have presented the first Michael addition of β -dicarbonyl compounds to alkynones using chiral cinchona alkaloid-derived (DHQ)₂PHAL (**XXI**) as a very efficient catalyst. Alkynones bearing both aromatic or aliphatic substituents were suitable substrates and the addition of the β -diketones proceeded in high yields and good to high enantiomeric excesses, but afforded the products as a 1:1 to 2:1 mixture of *E*- and *Z*-isomers (Scheme I- 13).^[58]



Scheme I- 13 The first Michael addition of β -dicarbonyl compounds to alkynones catalyzed by chiral cinchona alkaloid-derived catalyst (Jørgensen, 2004).

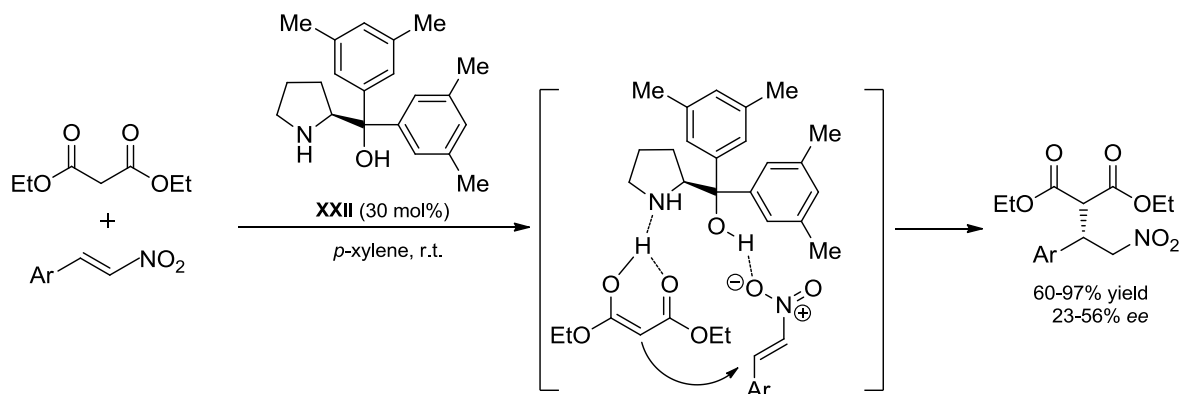
1.2.2.2.2 HYDROGEN BONDING ACTIVATION

As early as 1985, Hine and co-workers have disclosed the opening of an epoxide by a nucleophile via hydrogen bonding with different phenols (Scheme I- 14).^[59] They investigated the reaction speed constants and realized that phenols able of multiple hydrogen bonding can dramatically increase the efficiency of the reaction. Multiple hydrogen bonding has since been recognized as a very efficient way to activate substrates.



Scheme I- 14 The reaction of phenyl glycidyl ether with diethylamine catalyzed by various phenols.

Because the commercially available α,α -L-diaryl prolinol (**XXII**) includes a secondary amine and a hydroxyl group, which can recognize several functional groups through hydrogen-bonding interaction, this molecule has been employed as catalyst in several examples of Michael additions. In 2006, Lattanzi applied this catalyst (**XXII**) in the enantioselective Michael addition of malonate esters to nitroalkenes, obtaining good yields of product but with only moderate enantioselectivities (Scheme I- 15).^[60] The authors also proposed a mechanism where the secondary amine activates the malonate and the hydroxyl group activates the nitroalkene by hydrogen-bonding interactions, meaning that the catalyst was involved in simultaneous hydrogen-bonding activation of both the nucleophile and the electrophile.



Scheme I- 15 The enantioselective Michael addition of malonate esters to nitroalkene catalyzed by α,α -L-diaryl prolinol (Lattanzi, 2006).

In 2009, the same authors then extended their methodology to cyclic β -ketoesters, using hexafluorobenzene instead of *p*-xylene as solvent, allowing a dramatic improvement of the results in terms of enantioselectivity. At the same time, the origin of stereoselectivity and the role of hexafluorobenzene have been clarified by DFT calculations.^[61]

1.2.2.3 BIFUNCTIONAL ORGANOCATALYSTS

Bifunctional organocatalysts activate both reaction partners: usually, one active site can increase the nucleophilicity of the donor while the electron-withdrawing group of the Michael acceptor creates hydrogen bonding with the other active site in the transition state. Since the first reported example of bifunctional organocatalytic enantioselective Michael addition by Wynberg in 1975,^[31] there has been lots of publications in this area and the reaction has become one of the important methods for the enantioselective carbon-carbon bond formation. Especially, several chiral motives have been used for promoting the reaction including chiral thioureas, cinchona alkaloids, chiral diamines complexes etc (Figure I- 8).

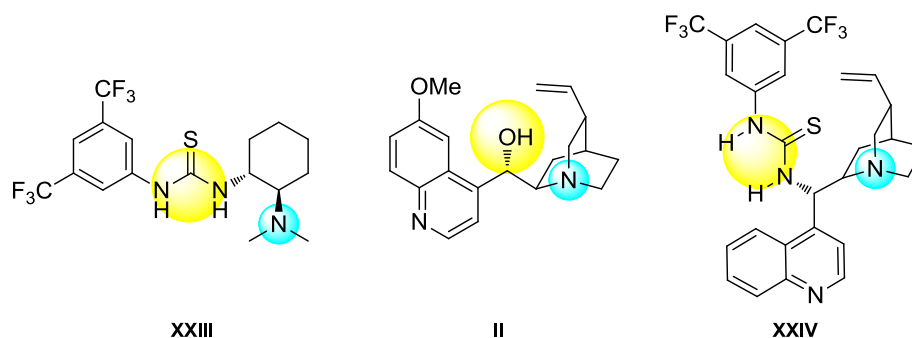
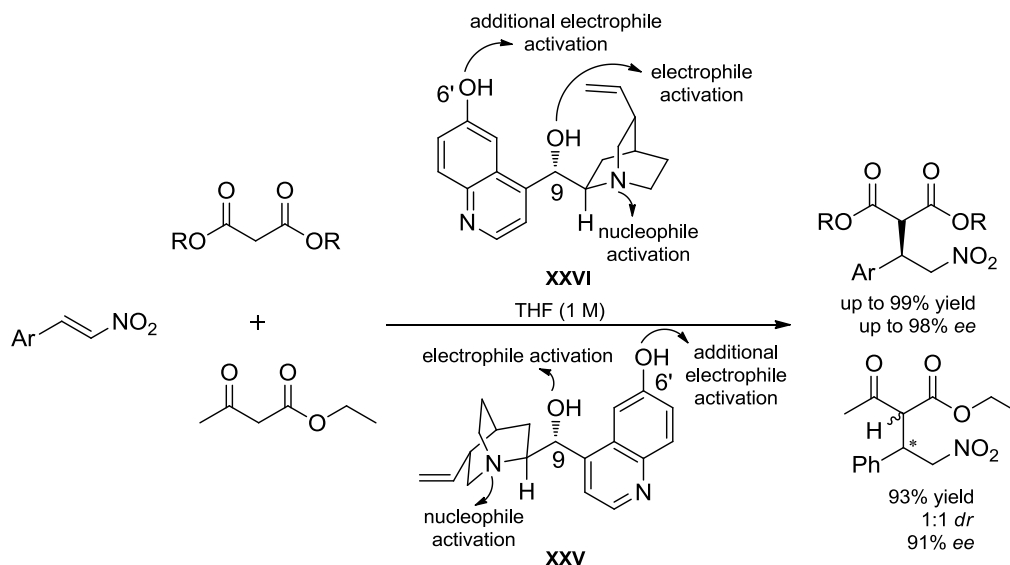


Figure I- 8 Examples of bifunctional catalysts.

1.2.2.3.1 Reactions Catalyzed by Chiral Cinchona Alkaloid Derivatives

In 1981, Wynberg and Hiemstra reported that natural quinuclidine-type cinchona alkaloids can act as efficient bifunctional organocatalysts for the Michael addition. Unfortunately, the final product was obtained with moderate enantiomeric excesses.^[33] Since that time, because cinchona alkaloids possess a tunable functional group at the C9 position (OH, NH₂ or NHTs), and the C6' position, which can add further stabilizing interactions or may activate and coordinate suitable substrates, they have been largely used as starting materials to prepare diversified organocatalysts.^[62-66] Several approaches have been directed toward extending their synthetic utility.

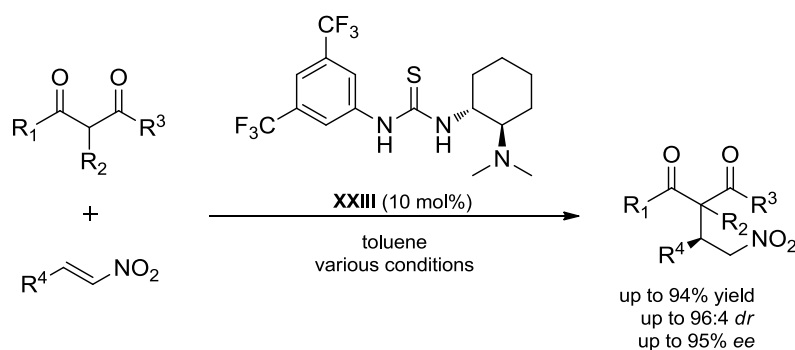
In 2004, Deng and co-workers first reported that bifunctional organic catalysts based on cinchona alkaloids can be applied in the conjugate addition of malonates and β -ketoesters to nitroalkenes. In spite of the long reaction time (up to 108 h), whatever aromatic or aliphatic nitroalkenes were put into reaction, the adducts were obtained with excellent enantiomeric excesses and yields (Scheme I- 16). It was demonstrated that the readily available 6'-demethylated quinine **XXV** and quinidine **XXVI** alkaloids are considerably more active and selective catalysts than their natural 6'-methylated analogues. Moreover, a model for the activation of the nucleophile and the electrophile by cinchona alkaloids was provided.^[67] The same authors then reported that this bifunctional chiral organic catalyst acts as an efficiency catalyst for the Michael addition of α -substituted β -dicarbonyl donors to α,β -unsaturated aldehydes.^[68]



Scheme I- 16 Reaction of malonates and β -ketoesters with nitroalkenes catalyzed by derivatives of cinchona alkaloid (Deng, 2004).

1.2.2.3.2 Reactions Catalyzed by Chiral (Thio)ureas

As shown by the early work of Hine,^[59] multiple hydrogen bonding is far more efficient than single hydrogen bonding to activate substrates. For this reason, many research groups have devoted efforts at developing new bifunctional organocatalysts that integrate a motif, such as thiourea, which is able to make several hydrogen bonds. In 1998, Jacobsen and co-workers first reported a chiral bifunctional organocatalyst including the thiourea moiety and applied it in the enantioselective Strecker reaction.^[69] It is only five years later that Takemoto and co-workers reported for the first time that the enantioselective Michael addition of α -substituted β -ketoesters to nitroolefins can be catalyzed by the novel bifunctional thiourea catalyst **XXIII**. It possesses a thiourea moiety and a tertiary amino group on a chiral scaffold and afforded the Michael adducts in excellent yields (up to 94%), enantioselectivities (up to 95%) and diastereoselectivities (up to 96:4) (Scheme I- 17).^[70, 71]



Scheme I- 17 Addition of α -substituted β -ketoesters to nitroolefins catalyzed by the bifunctional thiourea catalyst (Takemoto, 2003).

Moreover, from a mechanistic point of view, the authors have provided evidence that the thiourea moiety interacts with the nitro group via hydrogen-bonding activation and the neighboring tertiary amino group activates the α -substituted β -ketoesters by deprotonation.^[71] An alternative mechanism based on DFT calculations has been proposed by Soós and Pápai, in which the nucleophile is coordinated to the thiourea and the nitro group to the ammonium moiety.^[72] Both models predict the same stereochemical outcome and are regularly used to rationalize the results obtained in related transformations (Figure I- 9).

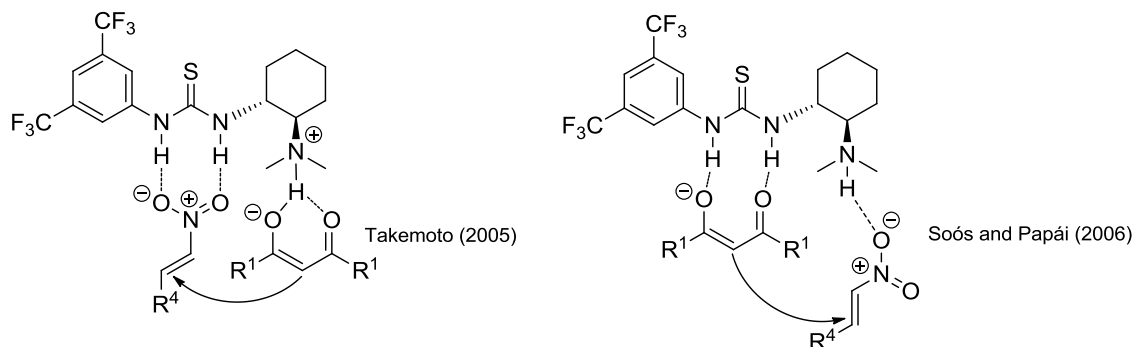
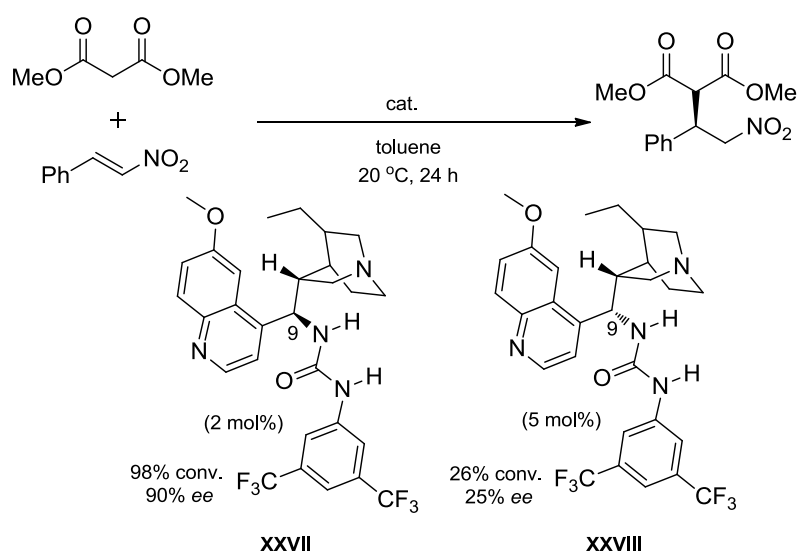


Figure I- 9 Proposed modes of activation of bifunctional thioureas.

The introduction of bifunctional organocatalysts based on the thiourea moiety has marked a breakthrough in organocatalysis. Because chiral (thio)ureas can get involved in molecular recognition processes via selective formation of hydrogen bonding,^[73, 74] many research groups have engaged in the design of new thiourea bifunctional catalyst which can be applied in enantioselective Michael additions of 1,3-dicarbonyl substrates.^[75-78] Only selected key developments are presented below.

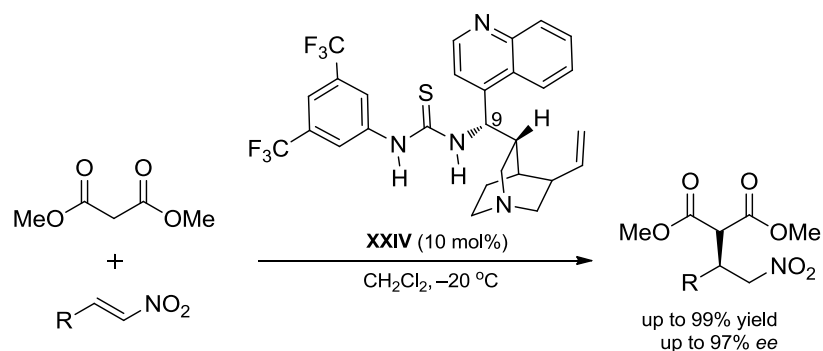
In 2005, Soós^[79], Connon^[80] and Dixon^[81] independently reported that the cinchona alkaloid structural backbone could be modified by substituting the hydroxyl group at C9 with an aryl(thio)urea moiety.



Scheme I- 18 Addition of dimethyl malonate to nitroalkenes catalyzed by cinchona alkaloid-based ureas (Connon, 2005).

Soós and co-workers applied the new bifunctional compounds for enantioselective conjugate addition of nitromethane to chalcones^[79]. In the same time, Connon and co-workers applied catalysts **XXVII** or **XXVIII** to the Michael addition of dimethyl malonate to nitro alkenes. Interestingly, the inversion of the absolute configuration at C9 in these thio(urea)-substituted systems dramatically improved catalyst activity and selectivity (Scheme I- 18).^[80]

Dixon and co-workers developed a similar thiourea derivative (**XXIV**) from 9-amino (9-deoxy)epicinchonine, which is an effective bifunctional organocatalyst to induce high enantioselectivities in the addition of malonates to a range of nitroolefins. Moreover, they found that aliphatic nitroolefins reacted more slowly than their aromatic counterparts and slight deterioration in enantioselectivity was witnessed (Scheme I- 19).^[81]



Scheme I- 19 Addition of malonates to a range of nitroolefins catalyzed by cinchona alkaloid–based thioureas (Dixon, 2005).

Moreover, in 2008, Dixon applied these thiourea-type organocatalysts to target-oriented syntheses of (*R*)-rolipram and (3*S*,4*R*)-paroxetine (Figure I- 10).^[82] The key step in the synthesis was the enantioselective Michael addition of dimethyl malonate to the functionalized aromatic nitroalkene.

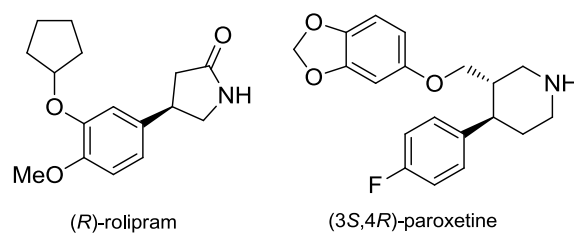
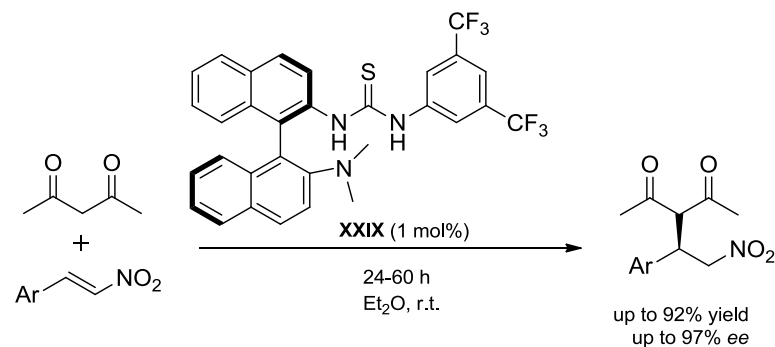


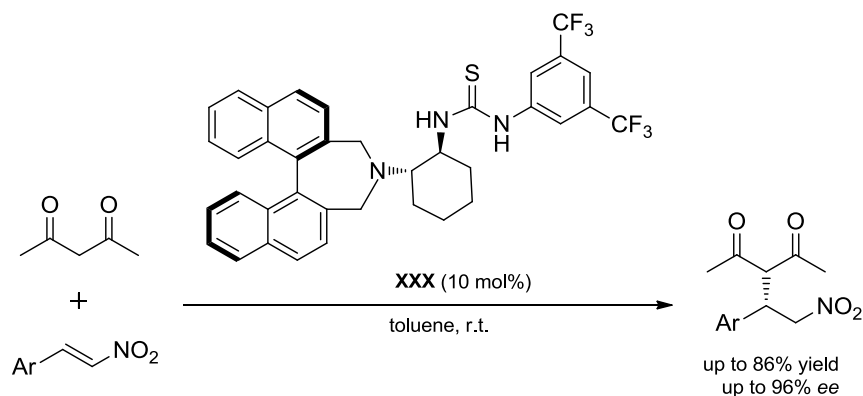
Figure I- 10 the structure of (*R*)-rolipram and (3*S*,4*R*)-paroxetine.

Also in 2005, Wang and co-workers have designed a bifunctional binaphthyl-derived amino thiourea catalyst **XXIX**, which integrates an axially chiral binaphthyl unit instead of the cyclohexane ring. This catalyst can act as an efficient organocatalyst (as low as 1 mol%) for Michael additions of 1,3-diketones to nitroolefins with remarkably high enantioselectivities (Scheme I- 20). Moreover, the Michael addition products can be easily converted into valuable α -substituted- β -amino acid building blocks.^[83]



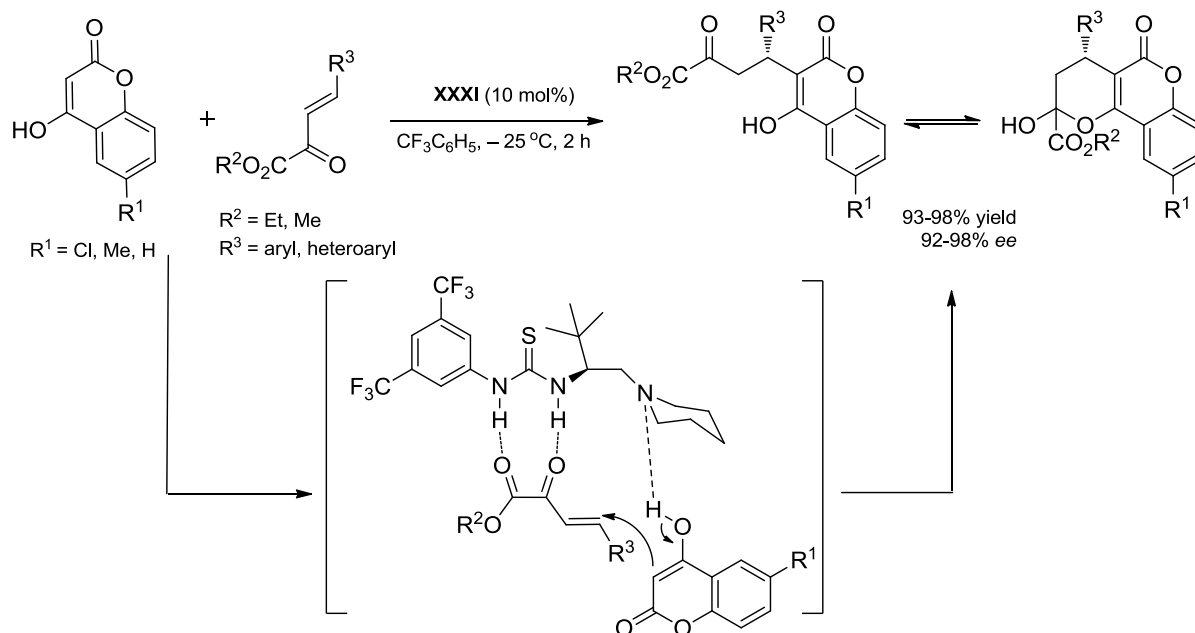
Scheme I- 20 Addition of diketones to nitroolefins catalyzed by an axially chiral bifunctional thiourea (Wang, 2005).

Soon after, Shao and co-workers have extended this concept to a bifunctional binaphthyl-derived amino thiourea catalyst **XXX**, which bears both central and axial chiral elements. This catalyst also ensured an excellent reactivity between 1,3-dicarbonyl compounds and nitroolefins (Scheme I- 21).^[84] However, further work was required to apply related catalysts in Michael additions to other Michael acceptors than nitroolefins.



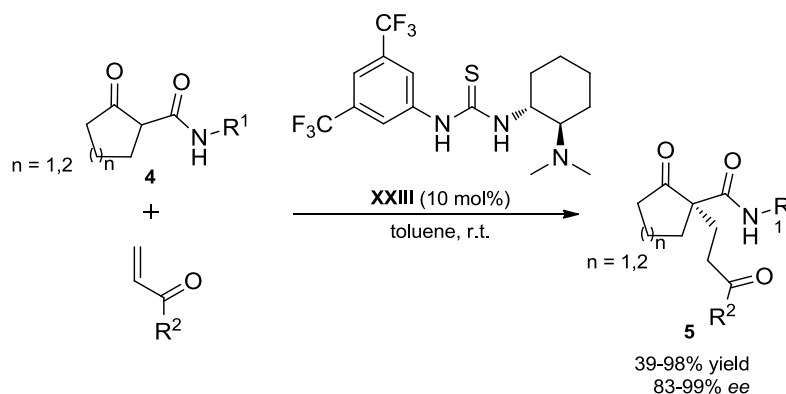
Scheme I- 21 Addition of diketones to nitroolefins catalyzed by bifunctional binaphthyl-derived amino thiourea catalyst (Shao, 2008).

It is only in 2010 that Wang and co-workers applied a new chiral amine thiourea catalyst **XXXI** for the preparation of chiral coumarins through hydrogen-bonding-mediated enantioselective Michael addition between 4-hydroxy-2*H*-chromen-2-one and β,γ -unsaturated ketoesters. The coumarin products were obtained with high yields and excellent enantioselectivities (up to 98% *ee*) (Scheme I- 22).^[85]



Scheme I- 22 Addition of 4-hydroxy-2H-chromen-2-one to β,γ -unsaturated ketoesters catalyzed by a new chiral amine thiourea (Wang, 2010).

In 2011, our research group first found that bifunctional thiourea catalyst **XXIII** can be employed for the enantioselective Michael addition of α -substituted β -ketoamides **4** to unsaturated carbonyls to obtain the corresponding adducts **5** that are containing a highly functionalized all-carbon quaternary stereocenter in good yields and high to excellent enantiomeric excesses (Scheme I- 23).^[86]



Scheme I- 23 Addition of α -substituted β -ketoamides to unsaturated carbonyls by using Takemoto catalyst (our research group, 2011).

In this context, lots of research groups extend the advantage to synthesize the bifunctional primary amine-ureas catalyst, and apply these catalysts for different Michael addition reactions of 1,3-dicarbonyl substrates. For example, In 2011, Dixon and co-workers reported the stereoselective synthesis of (–)-nakadomarin A (Figure I- 11), in which the key step was bifunctional primary amine-urea catalyzed Michael addition of 1,3-dicarbonyl pronucleophile to nitroolefins.^[87]

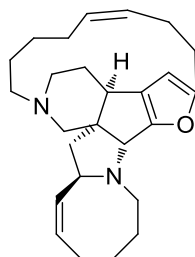
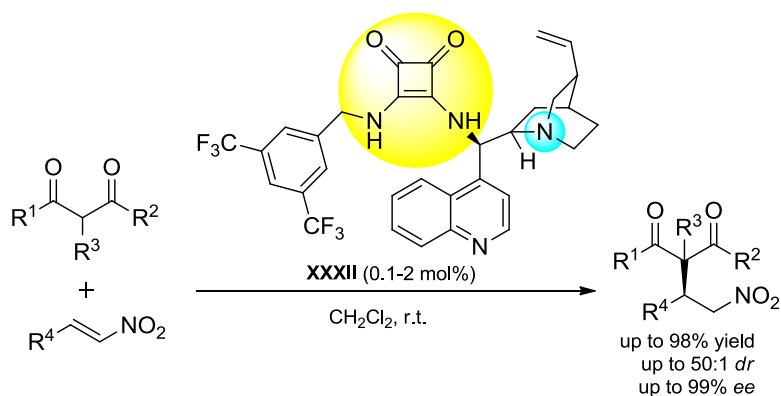


Figure I- 11 The structure of (-)-nakadomarin A.

In addition to these applications of chiral bifunctional organocatalysts to the development of new reactions, Cheng and co-workers in 2010 reported a physical organic study on their structure-activity-enantioselectivity relationships, which showed the pK_a values of chiral thiourea catalysts are essential for evaluating the catalysts' hydrogen-bonding abilities.^[88] Further progress in this field has led to the development of synthetically modified bifunctional cinchona-based catalysts and their application with various substrates. Many other research groups reported enantioselective Michael additions of different 1,3-dicarbonyl substrates (such as fluorinated nucleophiles^[89], C-succinimidyl esters^[90], 2-oxindole-3-carboxylate esters^[91], 2,2-disubstituted oxindoles^[92]) to nitroalkenes, α,β -unsaturated aldehyde or enones such as 2-enoylpyridines^[93] under functionalized cinchona alkaloid catalysis.

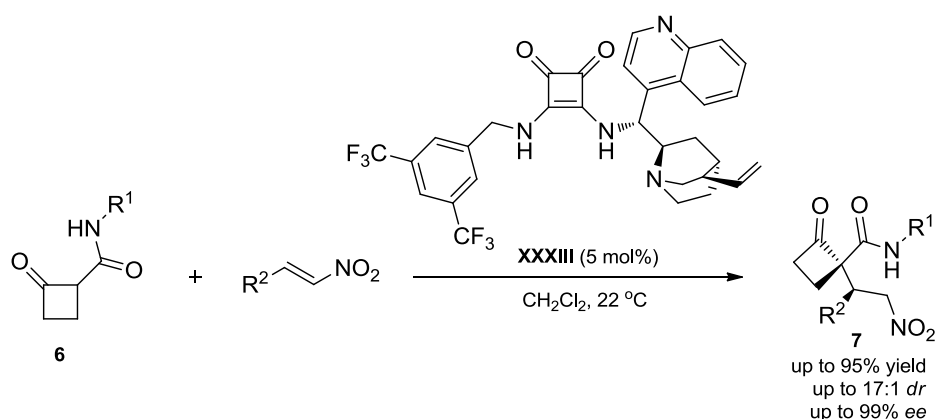
I.2.2.3.3 Reactions Catalyzed by Chiral Squaramides

In 2005, Xie and co-workers reported the first example of the squaramide motif applied in enantioselective catalysis, but the squaric amino alcohols was used as a ligand and not as a bifunctional catalyst.^[94] However, in 2008, Rawal and co-workers developed a new family of cinchona alkaloid-based squaramide catalysts **XXXII**, which were applied in the Michael addition of active methylene compounds to nitroalkenes, providing the desired Michael adducts with excellent yields and enantiomeric excesses (Scheme I- 24).^[95] Moreover, it was discovered that the squaramide catalyst exhibit a superior activity compared to its thiourea counterpart as only very low catalyst loadings (less than 1 mol%) were required to achieve complete conversion of starting materials in 8-24 h. According to the authors, the faster catalyst turnover is a result of the greater spacing (2.72 Å) between the N-H groups in the bisamides, which results in a better fit to the nitroalkene. Soon after, Xu and co-workers described that the bifunctional squaramides also promote the enantioselective Michael addition of 4-hydroxycoumarins and 4-hydroxypyronone to β,γ -unsaturated α -ketoesters.^[96] No matter whether the Michael acceptor was substituted with an aromatic or an alkyl group, the catalytic enantioselective reaction performed efficiently with only 2.5 mol% of the catalyst in 3-12 h to afford the chiral enantioenriched desired derivatives in good yields with excellent enantioselectivities (up to >99% *ee*).



Scheme I- 24 Addition of active methylene compounds to nitroalkenes catalyzed by cinchona alkaloid–based squaramide (Rawal, 2008).

Thus, lots of research groups extended the advantage to synthesize bifunctional cinchona alkaloid–based squaramide catalysts^[97, 98], and apply these catalysts in different Michael additions of 1,3-dicarbonyl substrates. In this context, for example, in 2012, our research group disclosed the enantioselective organocatalytic Michael addition of 2-substituted cyclobutanone derivatives **6** to nitroolefins in the presence of **XXXIII**, providing functionalized cyclobutanones **7** with excellent results (Scheme I- 25).^[99] Moreover, it was found that the specific activation or stabilization of the cyclobutanones with a secondary amide was crucial to the success of the approach.



Scheme I- 25 Michael addition of 2-substituted cyclobutanone derivatives to nitroolefins.

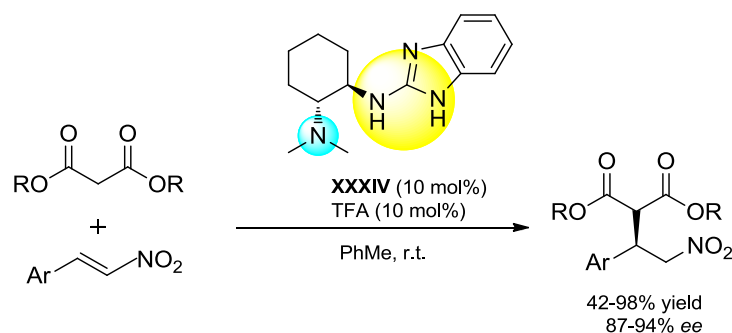
It is interesting to note that the enantioselective Michael addition of 1,3-dicarbonyl to nitroalkenes using new bifunctional cinchona-based squaramide organocatalysts can also proceed in brine, with dramatic acceleration compared to that in organic solvents due to the hydrophobic effect, as described by Song and co-workers in 2011.^[100]

From these examples, it is shown that bifunctional organocatalysts based-on squaramides may differ from the analogous urea/thiourea-based catalysts, especially, in respect of their reactivity and selectivity. Moreover, compared with analogous urea/thiourea-based catalysts, because of their duality, rigidity, increased H-bond length and canted H-bond angle, the squaramides often provide faster reactions and higher catalyst turnovers.^[101] However, recent theoretical studies by Soós and Pápai suggest that their mode of activation is closely related to

the one of bifunctional thioureas.^[102]

1.2.2.3.4 Reactions Catalyzed by Chiral Benzimidazoles

In 2009, Nájera and co-workers introduced an alternative hydrogen-bonding motif: they utilized chiral 2-aminobenzimidazoles **XXXIV** as recoverable catalyst in the addition of 1,3-dicarbonyl compounds to nitroalkenes, with TFA as co-catalyst in toluene at r.t. or 0 °C. The Michael adducts were obtained in high yields and enantioselectivities (Scheme I- 26).^[103] This reaction pathway is consistent with the model described by Soós and Pápai for thioureas.^[72]



Scheme I- 26 Addition of 1,3-dicarbonyl compounds to nitroalkenes catalyzed by chiral 2-aminobenzimidazoles (Nájera, 2009).

The same authors then extended this family of catalysts to synthesize a new chiral C_2 -symmetric bis(2-aminobenzimidazole) (**XXXV**) (Figure I- 12), which efficiently promoted the Michael addition of β -diketones, β -ketoesters, and malonates to maleimide and *N*-substituted maleimides, affording the corresponding Michael adducts in excellent yields and enantiomeric excesses.^[104]

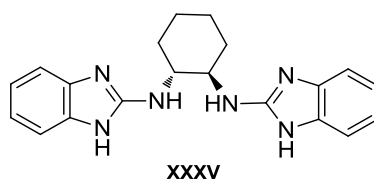
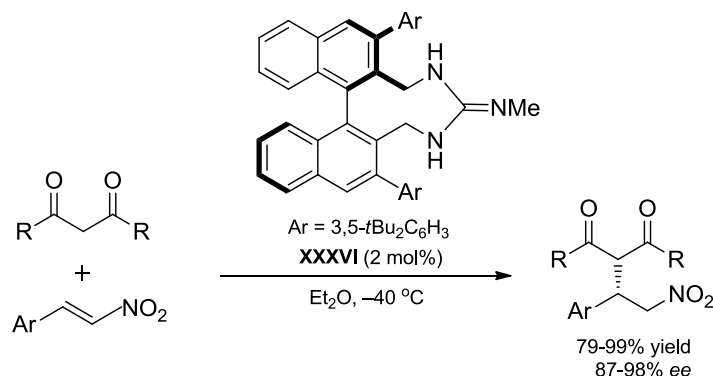


Figure I- 12 The structure of the chiral C_2 -symmetric bis(2-aminobenzimidazole).

1.2.2.3.5 Reactions Catalyzed by Chiral Guanidines

Chiral guanidines have also been employed as catalysts in Michael addition of 1,3-dicarbonyl substrates: they first behave as strong Brønsted base and their conjugated acid is then able to make hydrogen bonding with the two substrates. In 2006, Terada and co-workers developed the axially chiral guanidine **XXXVI** and applied it in the Michael addition of 1,3-dicarbonyl compounds to nitroolefins. The desired products have been

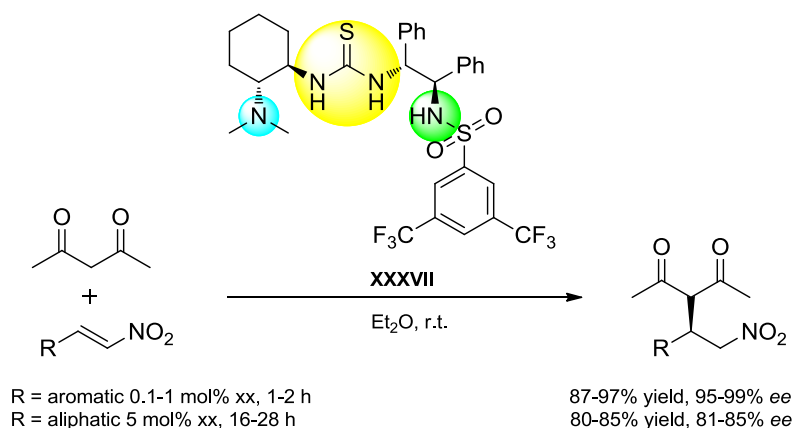
obtained with excellent yields and enantiomeric excesses using just 2 mol%, or even 0.4 mol% of catalyst in Et₂O (Scheme I- 27).^[105]



Scheme I- 27 Addition of 1,3-dicarbonyl compounds to nitroolefins catalyzed by chiral guanidines (Terada, 2006).

1.2.2.4 TRIFUNCTIONAL ORGANOCATALYSTS

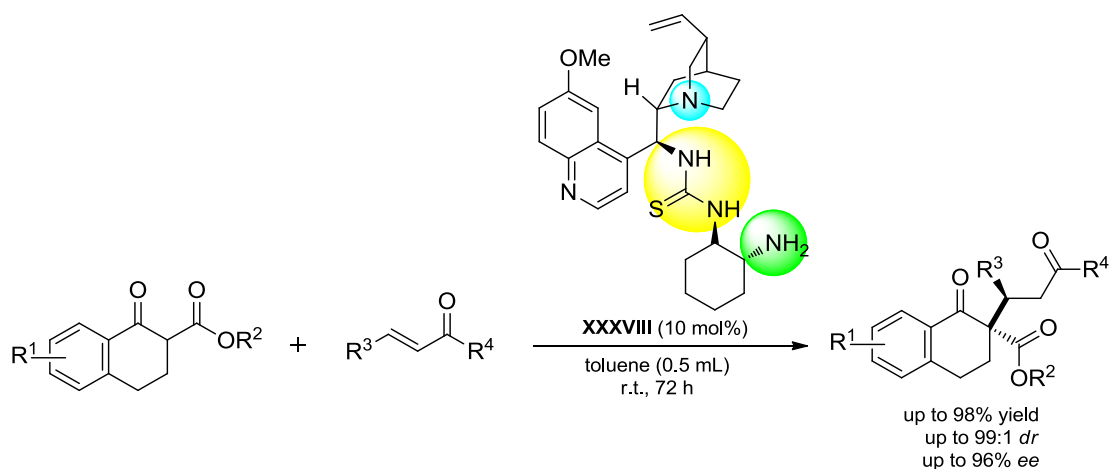
Recently, some research groups focused on the development of multifunctional catalysts, which exhibit three functional active sites. In 2008, Wang and co-workers developed a chiral amine-thioureas catalyst **XXXVII** bearing multiple hydrogen bonding donor sites for the Michael addition of acetylacetone to nitroolefins. With both aromatic and aliphatic substitutes on the nitroolefins, the yields and enantiomeric excesses were satisfactory. They also proposed that multiple hydrogen bonding donors play an important role in accelerating reactions, improving yields and enantioselectivities (Scheme I- 28).^[106]



Scheme I- 28 Addition of acetylacetone to nitroolefins catalyzed by multifunctional catalysts (Wang, 2008).

In 2009, Ye and co-workers developed a new type of cinchona alkaloid-based primary amine thiourea organocatalysts **XXXVIII** derived from 1,2-diaminocyclohexane and 9-amino (9-deoxy) cinchona alkaloid for the enantioselective Michael addition of malonates^[107] or α -alkyl- β -ketoesters^[108] to enones under mild conditions with excellent yields (up to 98%)

and enantioselectivities (up to 99%) (Scheme I- 29). They also proposed a possible transition state for the enantioselective Michael addition based on single-crystal X-ray analysis and their previous work (Figure I- 13).^[108]



Scheme I- 29 Addition of malonates or α -alkyl- β -ketoesters to enones catalyzed by cinchona alkaloid-based primary amine thiourea (Ye, 2009).

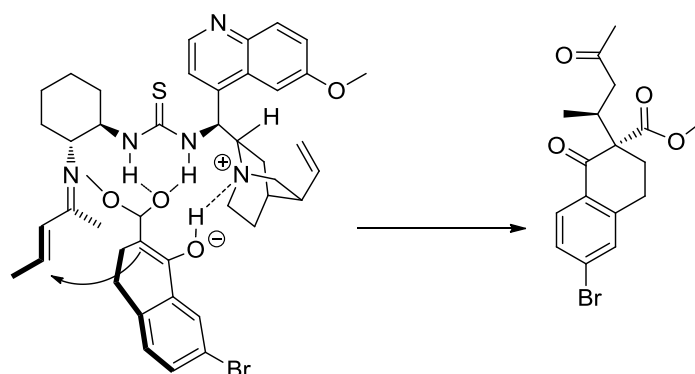


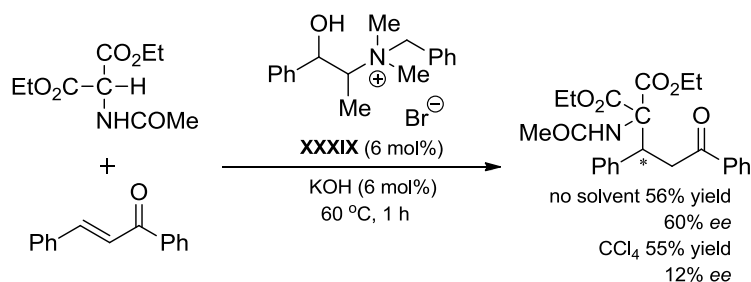
Figure I- 13 Proposed possible transition state.

I.2.2.5 PHASE-TRANSFER CATALYSIS

In 1971, Starks provided a definition of phase-transfer catalysis (PTC): *Catalysis is believed to be due to the ability of the organic-soluble cations to repeatedly bring anions into the organic phase in a form suitable for reaction, and the effect is termed phase-transfer catalysis.*^[109]

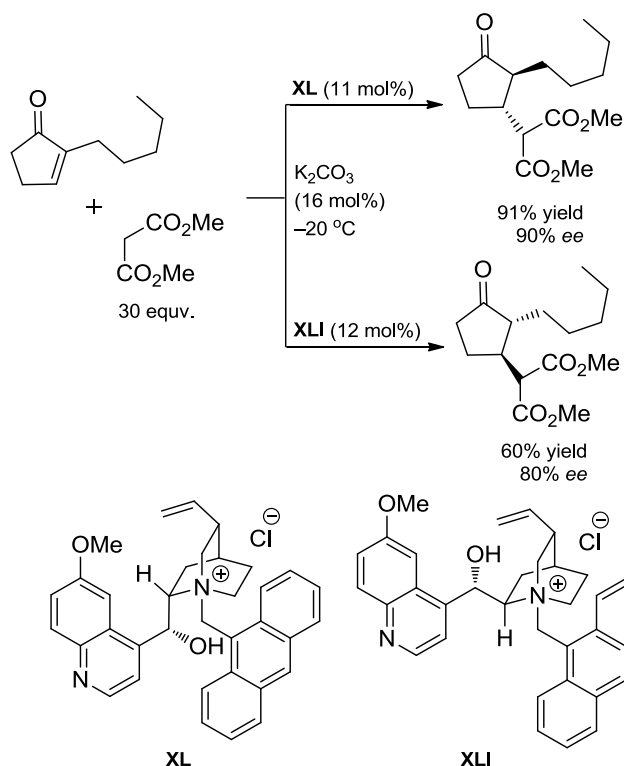
The idea of using PTC in enantioselective Michael additions of 1,3-dicarbonyl substrates goes back to 1989 with the work of Loupy and co-workers, who developed an enantioselective Michael addition of acetylamino malonate to chalcone in the presence of quaternary salts **XXXIX** derived from (+) or (-) *N*-methylephedrine (Scheme I- 30).^[63, 110, 111] Moreover, they discovered that the enantiomeric excesses were significantly increased by omitting the organic solvent during the reaction. In 1993, the same group extended the scope of this PTC transformation and found π - π attractive interactions between aryl groups of the

catalyst and the chalcone are responsible for the enantioselectivity of the reaction. These π - π interactions can be enhanced when reactions are performed without solvent.^[112]



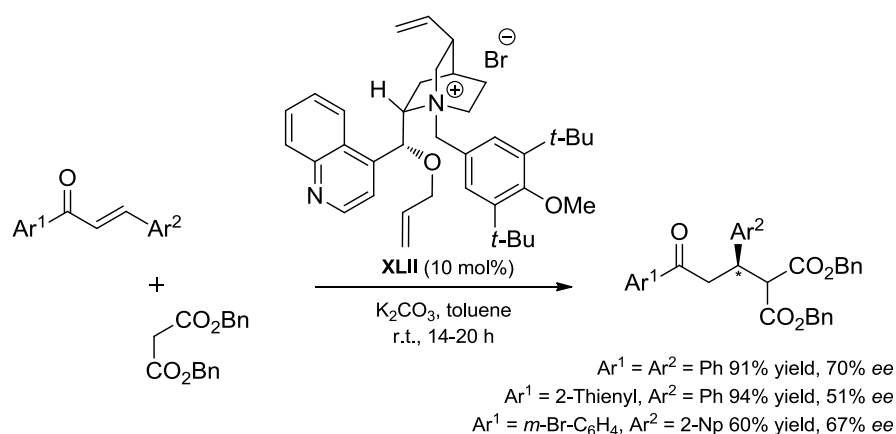
Scheme I- 30 Addition of acetylaminomalonnate to chalcone catalyzed by *N*-methylephedrine (Loupy, 1989).

Several years after, Plaquevent and co-workers carried out the enantioselective Michael addition of simple dimethyl malonate to 2-pentyl-2-cyclopentenone in the presence of PTC using quinine- or quinidine derivatives **XL** or **XLI** as catalyst and potassium carbonate as a base. High enantiomeric excesses were obtained (Scheme I- 31).^[113]



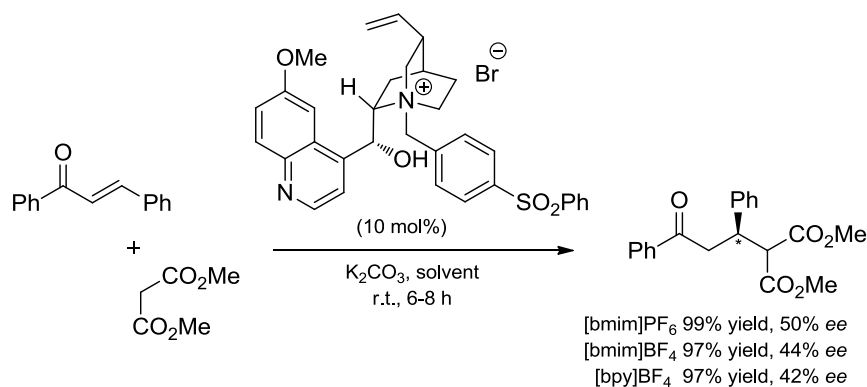
Scheme I- 31 Addition of simple dimethyl malonnate to 2-pentyl-2-cyclopentenone catalyzed by quinine- or quinidine-derived PTCs (Plaquevent, 2000).

In 2001, Kim and co-workers performed phase-transfer catalysis using chiral quaternary ammonium salt **XLII**, which catalyzed the Michael addition of malonates to chalcone derivatives at room temperature by using 10 mol% of catalyst and an excess amount of potassium carbonate, to afford the corresponding Michael adducts in good yields with good to moderate enantiomeric excesses (Scheme I- 32).^[114]



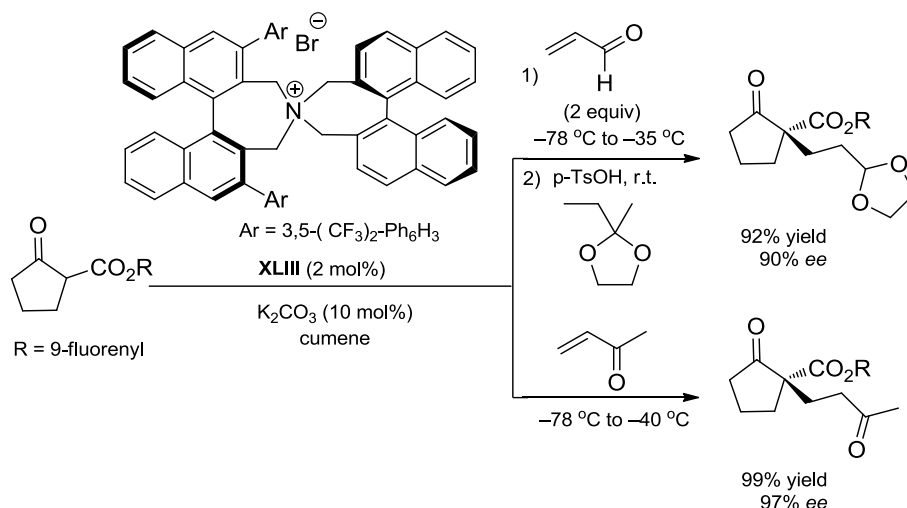
Scheme I- 32 Addition of malonates to chalcone derivatives catalyzed by chiral quaternary ammonium salt (Kim, 2001).

In 2003, Salunkhe and co-workers replaced the organic solvent by an ionic liquid in the phase-transfer catalyzed enantioselective Michael reaction of dimethyl malonate with chalcone. The reaction afforded the desired products in excellent yields in relatively short reaction time, albeit with moderate enantioselectivities (Scheme I- 33).^[115]



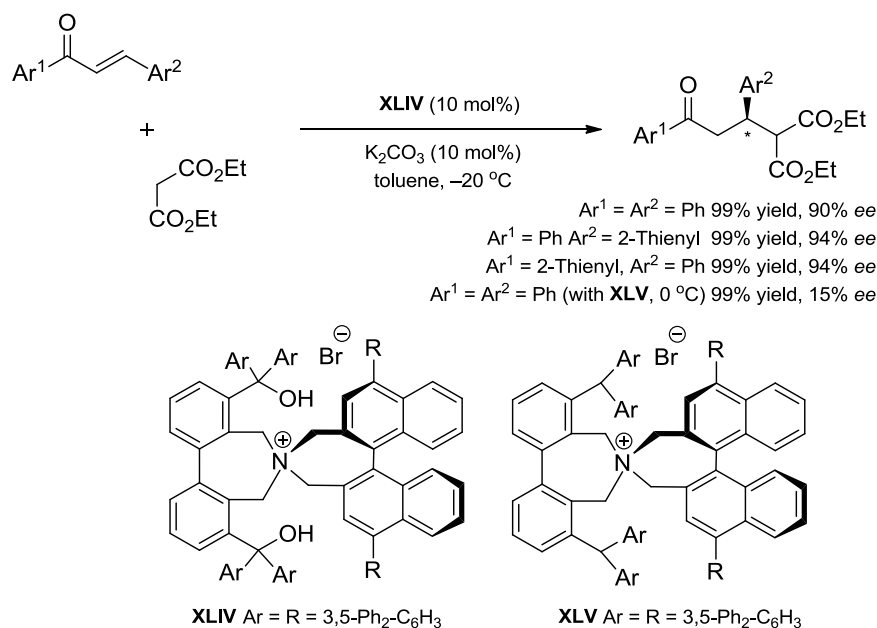
Scheme I- 33 Reaction of dimethyl malonate with chalcone catalyzed by a PTC in an ionic liquid (Salunkhe, 2003).

In the same year, Maruoka and co-workers presented a highly enantioselective Michael reaction of β -ketoesters to α,β -unsaturated aldehydes or α,β -unsaturated ketones (methyl vinyl ketone) catalyzed by the new chiral PTC **XLIII** (2 mol% loading) and potassium carbonate (10 mol%). The desired products that include a new quaternary stereocenter were obtained quantitatively with excellent enantioselectivities (Scheme I- 34).^[116]



Scheme I- 34 Reaction of β -ketoesters with α,β -unsaturated aldehydes or α,β -unsaturated ketones catalyzed by a new chiral PTC (Maruoka, 2003).

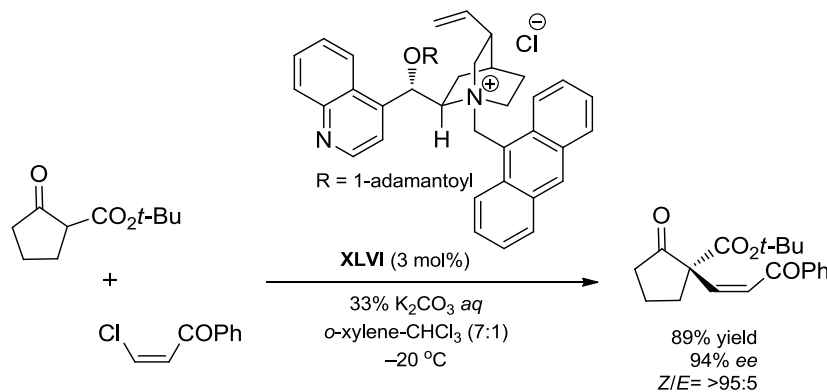
Later on, the same group improved the structure of their chiral PTC **XLIV** with additional functions to obtain excellent yields and enantioselectivities in the Michael addition of malonates to chalcone derivatives (Scheme I- 35).^[117] It was found that when the catalyst **XLV** lacks the hydroxyl functionalities, the enantioselectivity was markedly decreased.



Scheme I- 35 Addition of malonates to chalcone derivatives catalyzed by chiral PTC with additional functions (Maruoka, 2005).

In 2006, Jørgensen and co-workers reported a new dihydrocinchonine-derived PTC **XLVI** including a bulky 1-adamantoyl group. It was applied in the reaction of β -chloroenones with cyclic β -ketoesters to form products with a *Z*-configured double bond with high yields and excellent enantioselectivities (Scheme I- 36).^[118] Based on this successful example, Jørgensen and co-workers extended this research to other substrates using the same catalyst.

In 2007, they have applied β -halo-alkynes as acceptors and other cyclic β -ketoesters as donors in related transformations.^[119] They also described the first enantioselective 1,6-addition of cyclic β -ketoesters to electro-poor δ -unsubstituted dienes. They investigated variations of the structures of both the dienes and the β -ketoesters, obtaining excellent yields (up to 99%) and enantioselectivities (up to 95%).^[120] In 2008, Jørgensen and co-workers performed the Michael addition of cyclic β -ketoesters to different allenes once again using the same catalyst in the same conditions.^[121]



Scheme I- 36 Reaction of β -chloroenones with cyclic β -ketoesters catalyzed by dihydrocinchonine-derived PTC (Jørgensen, 2006).

Finally, it must be mentioned that the group of Najera has also reported the enantioselective Michael addition of cyclic β -ketoesters to different acceptors in the presence of chiral PTC using cinchona-derived ammonium salts.^[122]

I.3 DOMINO AND MULTICOMPONENT REACTIONS BASED ON THE MICHAEL ADDITION OF 1,3-DICARBONYL SUBSTRATES

Many research programs in modern organic chemistry focus on the development of green chemistry.^[123] Green chemistry is based on several important principles.^[124] For example, synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product. Chemical products should be designed to produce their desired function while minimizing their toxicity. Moreover, in order to save steps in a synthetic plans, multiple bond-forming transformations (MBFTs) have been developed.^[125] Domino and multicomponent reactions can allow the creation of several covalent bonds in the same reaction conditions, helping to meet the principles of green chemistry.^[126, 127]

Because 1,3-dicarbonyl substrates display several nucleophilic and electrophilic potential reaction sites, they represent very interesting substrates for domino and multicomponent reactions.^[41, 42] In this section, we will focus on the key seminal reports and the latest improvements of domino and multicomponent reactions based on the Michael addition of 1,3-dicarbonyl substrates. Since there is a very abundant literature on domino reactions^[128] and our research interests were focused on the control of enantioselectivity, we will restrict

our presentation of domino reactions to enantioselective organocatalytic transformations. On the contrary, multicomponent reactions are rarer and a general overview of these transformations, either enantioselective or not, will be provided in this section.

I.3.1 ENANTIOSELECTIVE DOMINO REACTIONS BASED-ON THE MICHAEL ADDITION OF 1,3-DICARBONYL SUBSTRATES

In 1999, Tietze provided a generally accepted definition of domino reactions: “*a domino reaction is a process involving two or more bond-forming transformations (usually carbon-carbon bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step*” (Figure I- 14).^[126]

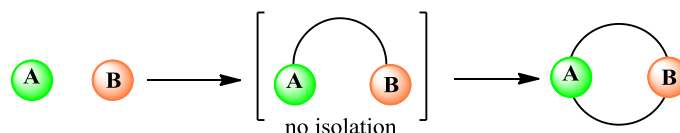
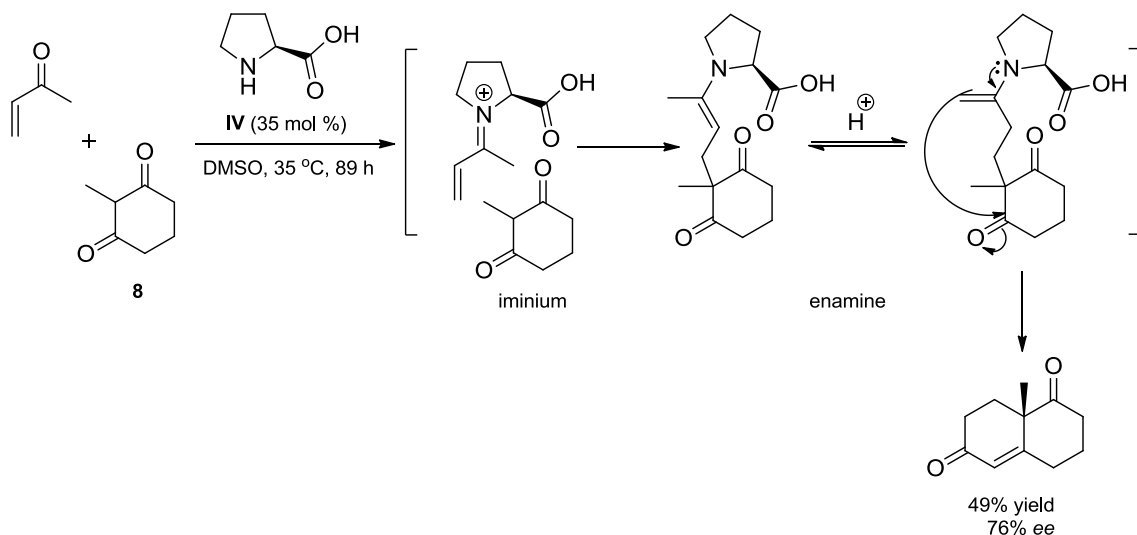


Figure I- 14 The model of the domino reactions.

Domino reactions are by nature step economic processes as several bonds are formed in one sequence.^[126] In particular, domino reactions mediated by organocatalysts are in a way biomimetic, as the same reactivity principle are involved in the biosynthesis of complex natural products. Thus, chemists have recently devoted efforts to the development of enantioselective domino reactions based on the Michael addition of 1,3-dicarbonyl substrates. Because organocatalysis involves several activation modes,^[14] the reactions will be presented by their type of activation.^[129]

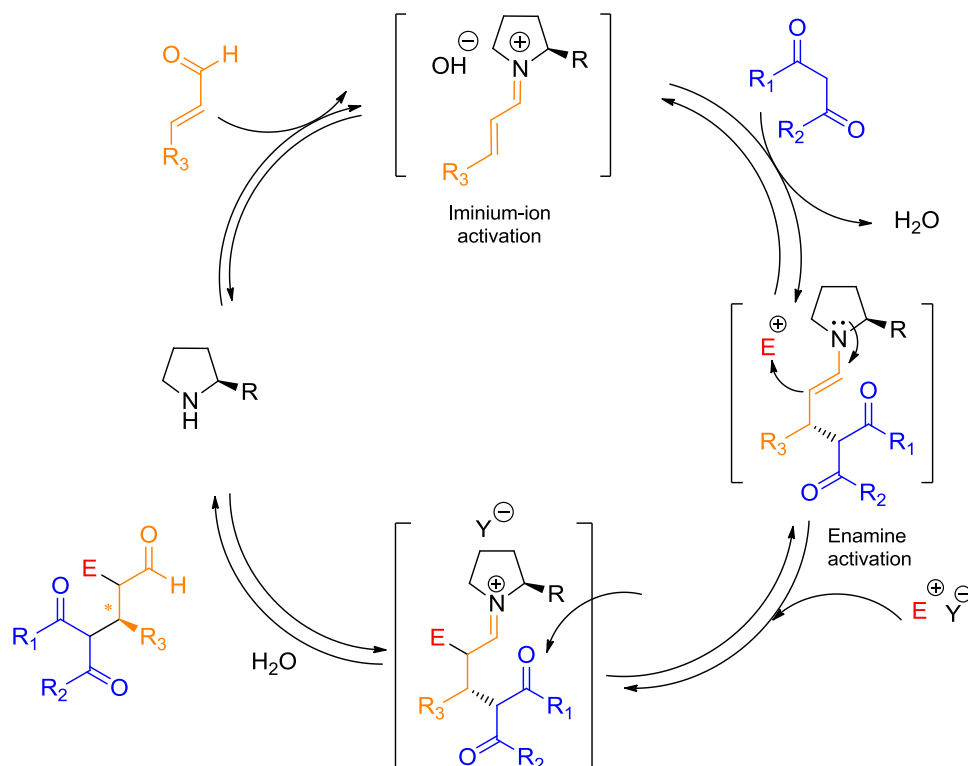
I.3.1.1 IMINIUM-ENAMINE ACTIVATION MODE

The iminium-enamine activation is probably one of the most important activation mode in organocatalysis. In 2000, Bui and Barbas reported for the first time an organocatalytic domino reaction based on an iminium-enamine sequence with methyl vinyl ketones. This domino reaction includes two different processes: a Michael addition and an aldol condensation. Wieland-Miescher ketone was obtained from the reaction of 2-methylcyclohexane-1,3-dione **8** with methyl vinyl ketone by using L-proline (**IV**) (35 mol%), affording the final product in 49% yield with 76% *ee* (Scheme I- 37).^[130]



Scheme I- 37 The domino synthesis of Wieland-Miescher ketone and methyl vinyl ketones catalyzed by L-proline (Barbas III, 2000).

Since this report, there has been a rapid increase of organocatalytic domino reactions relying on iminium-enamine activation. All these reactions are catalyzed by a chiral secondary amine and make use of an α,β -unsaturated aldehyde or an α,β -unsaturated ketone as the Michael acceptor. The following mechanism has been proposed to explain the results obtained in iminium-enamine organocatalytic domino reactions (Scheme I- 38).^[131, 132]

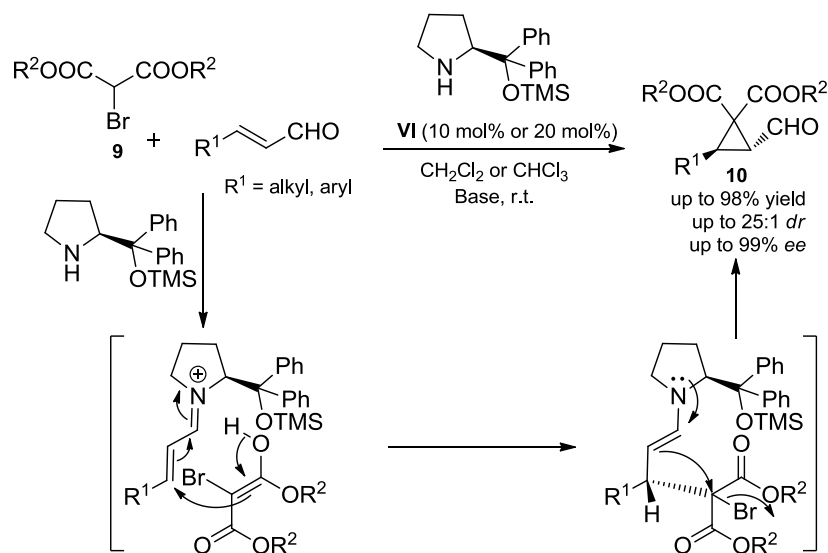


Scheme I- 38 The model of an iminium-enamine activation in domino reactions.

As previously reported for the use of TMS-protected prolinols as organocatalysts, the R group of the secondary amine catalyst is usually a bulky residue. In the Michael addition

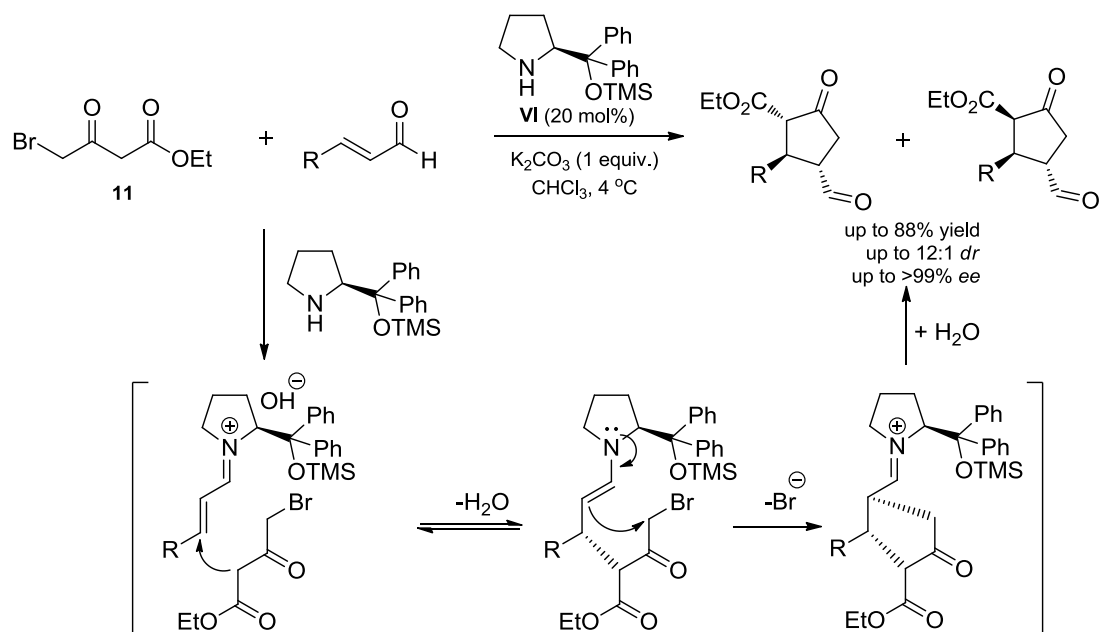
process, the stereogenic center formed in the catalytic cycle is controlled by a *Re*-face attack (opposite to the bulky group) of the nucleophile on the planar iminium ion intermediate.^[132]

In 2007, almost simultaneously, both the groups of Wang^[133] and Córdova^[134] have independently developed highly enantioselective organocatalytic cyclopropanation reactions of α,β -unsaturated aldehydes and 2-bromomalonate or 2-bromoacetoacetate esters **9**, catalyzed by the chiral secondary amine **VI**, and obtained 2-formylcyclopropanes **10** with high yields, high diastereoselectivities and up to 99% *ee* (Scheme I- 39).^[133] This reaction proceeds through a Michael addition followed by the α -alkylation of the enamine intermediate to obtain the cyclopropane motif. It is worth noting the ambivalent character of the malonic carbon, which successively plays the role of nucleophile and electrophile. Soon after, Rios and co-workers have once again extended this reactivity to 2-bromoketoesters as the nucleophile to obtain chiral cyclopropanes including a quaternary carbon with high diastereocontrol in the same reaction conditions.^[135]



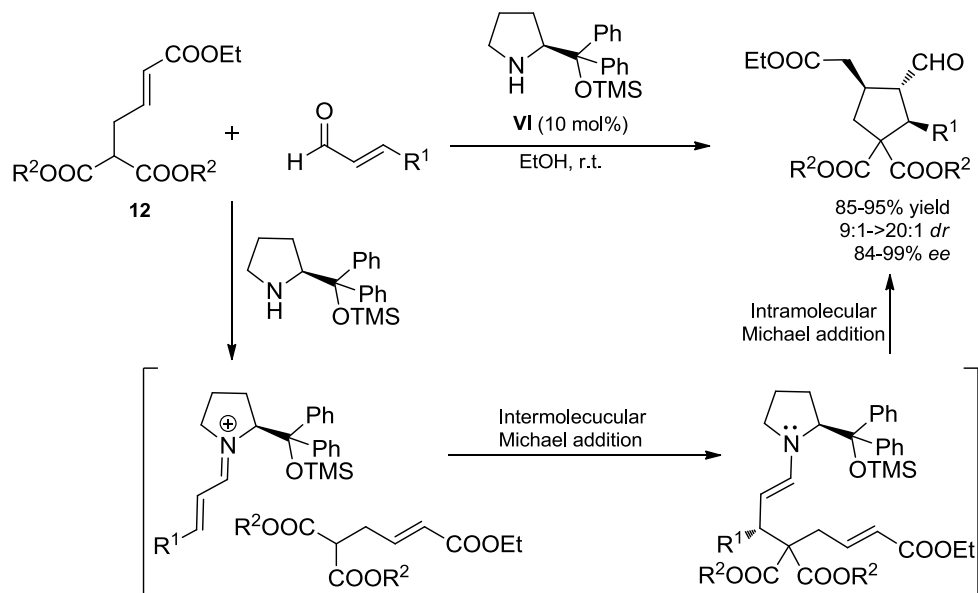
Scheme I- 39 Cyclopropanation reaction of α,β -unsaturated aldehydes and 2-bromomalonate catalyzed by a chiral secondary amine (Wang, 2007).

In 2007, the group of Córdova has utilized 4-bromoacetoacetate **11** instead of 2-bromomalonate in presence of the same chiral secondary amine **VI** (20 mol%) and 1.0 equivalent of potassium carbonate in $CHCl_3$ at 4 °C. The cyclopentanone ring was obtained with three new stereocenters in good yields and enantiomeric excesses (Scheme I- 40).^[136]



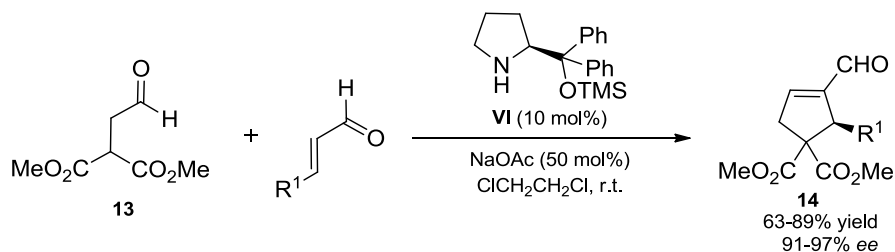
Scheme I- 40 Cyclopropanation reaction of α,β -unsaturated aldehydes and 4-bromoacetoacetate catalyzed by chiral secondary amines (Córdova, 2007).

In 2007, the group of Wang has also contributed to the synthesis of functionalized chiral five-membered carbocycles. These reactions are initiated by the Michael addition of malonate derivatives. Firstly, they developed an enantioselective double Michael addition sequence between α,β -unsaturated aldehydes and γ -malonyl- α,β -unsaturated esters **12** in the presence of the chiral secondary amine **VI** in ethanol (Scheme I- 41).^[137] Cyclopentanes with three stereogenic centers are formed in high yields, diastereocontrol and enantioselectivities.



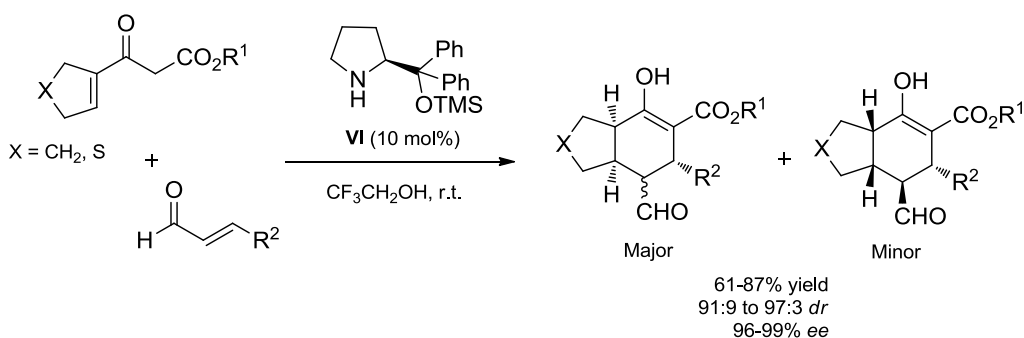
Scheme I- 41 Double Michael additions between α,β -unsaturated aldehydes and γ -malonate- α,β -unsaturated esters (Wang, 2007).

Secondly, they developed an enantioselective Michael addition/aldol sequence between α,β -unsaturated aldehydes and dimethyl 2-oxoethylmalonate **13** by using the same secondary amine catalyst **VI**. This sequence delivered functionalized chiral cyclopentenones **14** with high yields and excellent enantioselectivities (Scheme I- 42).^[138]



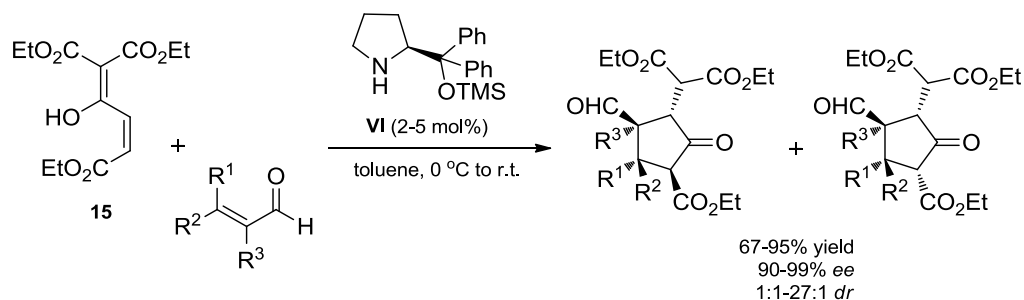
Scheme I- 42 Michael addition/aldol sequence between α,β -unsaturated aldehydes and dimethyl 2-oxoethylmalonate (Wang, 2007).

Shortly after, Brenner employed the same catalyst (**VI**) to promote an efficient domino Michael-Michael cascade of Nazarov reagents to α,β -unsaturated aldehydes in trifluoroethanol at room temperature through the iminium-enamine activation mode to form highly substituted fused carbocycles as 91:9 to 97:3 mixtures of diastereomers (Scheme I- 43).^[139]



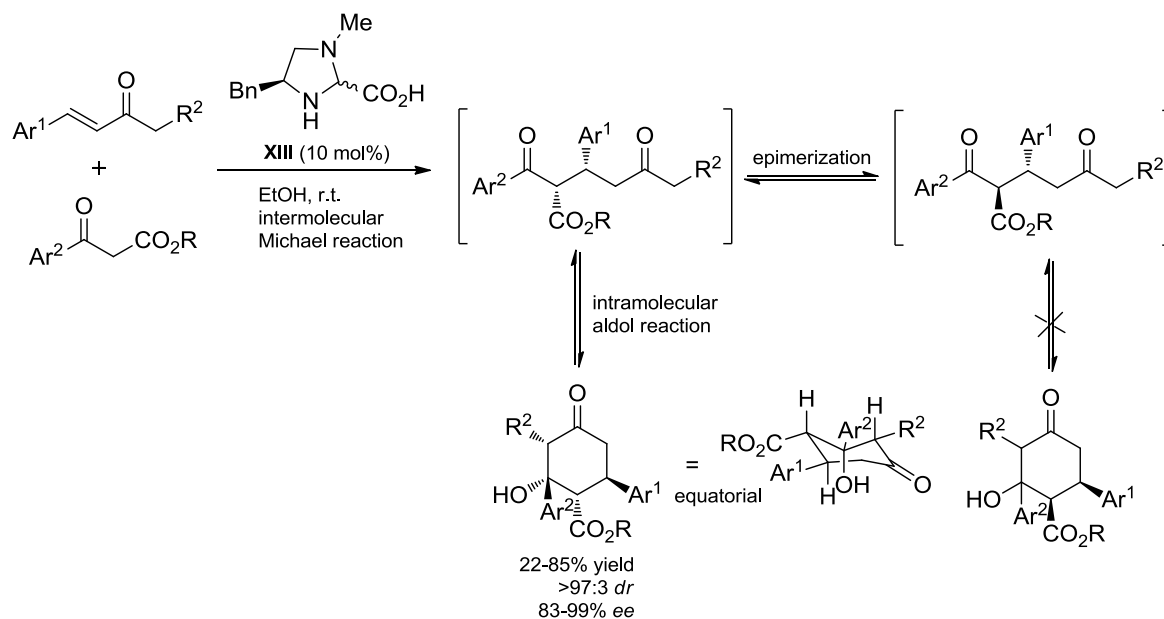
Scheme I- 43 Michael-Michael cascade reaction of functionalized β -ketoesters with α,β -unsaturated aldehydes (Brenner, 2009).

As an extension of the iminium-enamine activation mode, in 2010, Ma discussed the domino double Michael addition of α,β -unsaturated aldehydes and ketoesters **15** bearing a highly electron-deficient olefin unit, still with the same aminocatalyst **VI** (2-5 mol%). The final polysubstituted cyclopentanones possessing four contiguous stereocenters were obtained with excellent enantioselectivities (Scheme I- 44).^[140] Moreover, this transformation represents the first example of the utilization of less-reactive α,β - or β,β -disubstituted α,β -unsaturated aldehydes as Michael acceptors in organocatalytic reactions, allowing the creation of two quaternary stereogenic centers.

Scheme I- 44 Double Michael addition of α,β -unsaturated aldehydes and ketoesters (Ma, 2010).

I.3.1.2 IMINIUM ACTIVATION COMBINED WITH OTHER TRANSFORMATIONS

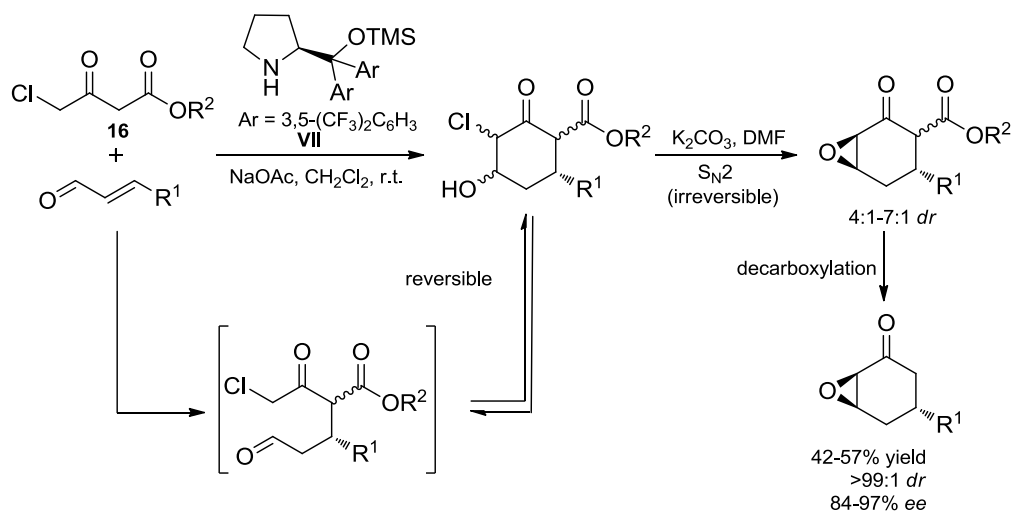
Domino reactions initiated by a Michael addition through iminium activation can also further proceed via other steps, in which the organocatalyst might not play an active role. In 2004, the group of Jørgensen developed the first enantioselective domino Michael-aldol reaction of α,β -unsaturated ketones and acyclic β -ketoesters using chiral imidazolidine catalyst **XIII** to give cyclohexanones with three or four stereogenic centers, with excellent enantioselectivities and as single diastereomers (Scheme I- 45).^[141]

Scheme I- 45 Domino Michael-aldol reaction of α,β -unsaturated ketones and acyclic β -ketoesters (Jørgensen, 2004).

The authors also proposed an explanation for the diastereoselectivity. In this domino sequence, the intermolecular Michael addition was followed by an intramolecular aldol reaction step. The initial formation of the Michael adduct forges two stereogenic centers, of which only the Ar^1 -substituted stereogenic carbon center is configurationally stable. Indeed, the position between the ester and ketone substituents is highly acidic, thus this stereogenic

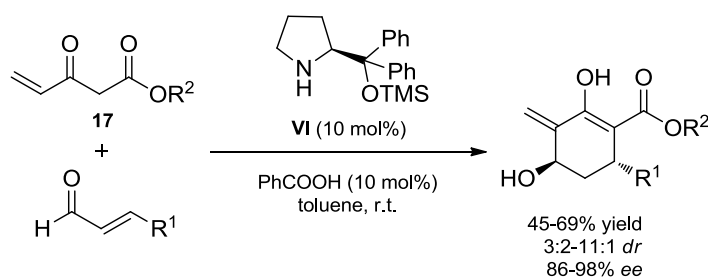
center can epimerize. Interestingly, the intramolecular aldol reaction proceeds only from the *syn* Michael adduct and with high diastereocontrol to form the highly functionalized six-membered ring. Although the last step is likely to be base-catalyzed, the possibility that it proceed through enamine activation could not be ruled out.

Soon after, the same group developed an organocatalytic domino Michael-aldol sequence followed by an intramolecular S_N2 reaction. α,β -Unsaturated aldehydes and γ -chloro- β -ketoesters **16** were coupled by using chiral secondary amine catalyst **VII** and sodium acetate and potassium carbonate as the bases (Scheme I- 46).^[142] The final epoxy-cyclohexanones or 2-chlorocyclohex-2-ene derivatives were obtained with up to four stereocenters.



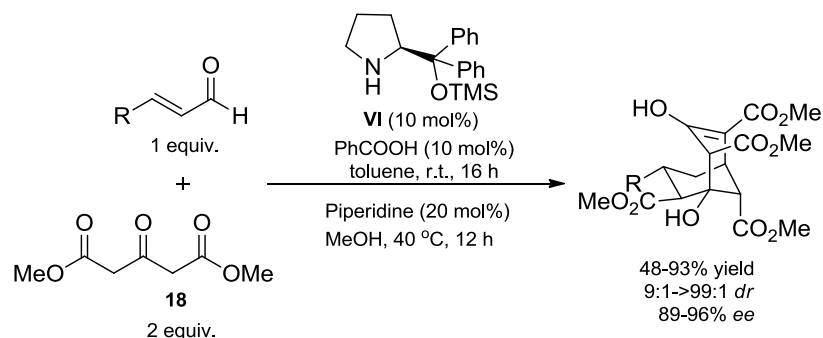
Scheme I- 46 Domino Michael-aldol and intramolecular S_N2 reaction of α,β -unsaturated aldehydes and γ -chloro- β -ketoesters (Jørgensen, 2006).

The same group extended this reactivity pattern to the Michael addition-initiated reaction of *tert*-butyl-3-oxo-butyric ester **17** with α,β -unsaturated aldehydes to obtain optically active cyclohex-2-enone derivatives in aqueous solutions or under solvent-free conditions.^[143] In 2008, they also reported the diastereo- and enantioselective Michael/Morita-Baylis-Hillman tandem reaction of α,β -unsaturated aldehydes with Nazarov reagents. The two steps are catalyzed by the chiral secondary amine (**VI**), which acts as a Lewis base in the Morita-Baylis-Hillman reaction, to afford cyclohexenones with excellent enantioselectivities (Scheme I- 47).^[144]



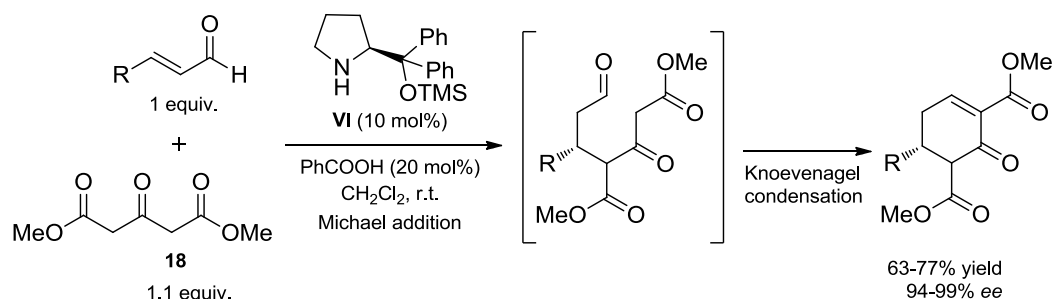
Scheme I- 47 Michael/Morita-Baylis-Hillman tandem reaction of α,β -unsaturated aldehydes with Nazarov reagents (Jørgensen, 2008).

Later on, the group of Jørgensen once again extended this reactivity to the reaction of an α,β -unsaturated aldehyde and dimethyl 3-oxopentanedioate **18** in a 1:2 ratio, in the presence of **VI** (10 mol%) and piperidine (20 mol%). In this pseudo three-component reaction, the catalyst allows to selectively form four new carbon-carbon bonds and six new stereocenters, and thereby 1 out of 64 possible stereoisomers is obtained with excellent diastereo- and enantioselectivities (Scheme I- 48).^[145]



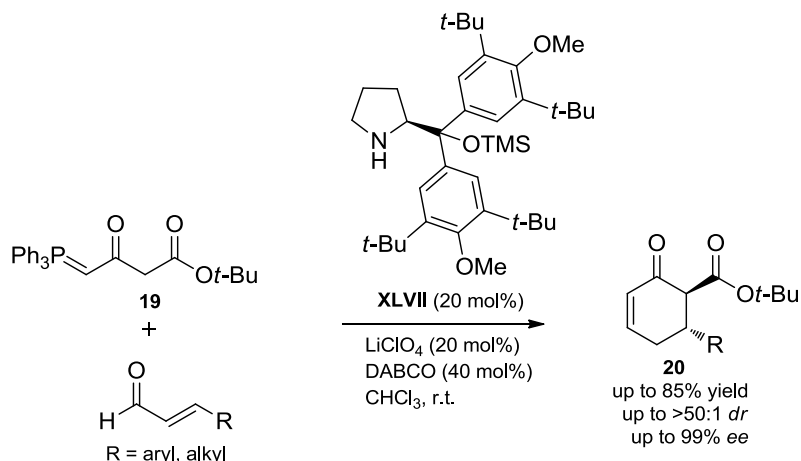
Scheme I- 48 Domino reaction of α,β -unsaturated aldehyde and dimethyl 3-oxopentanedioate (Jørgensen, 2008).

In parallel, Hayashi and co-workers selected the same substrates but changed their ratio to 1:1.1. With **VI** (10 mol%) and benzoic acid (20 mol%) as the catalysts, a Michael addition/Knoevenagel condensation occurred: this formal carbo [3+3] cycloaddition delivered substituted cyclohexenone derivatives with excellent enantioselectivities (up to 99% *ee*) (Scheme I- 49).^[146]



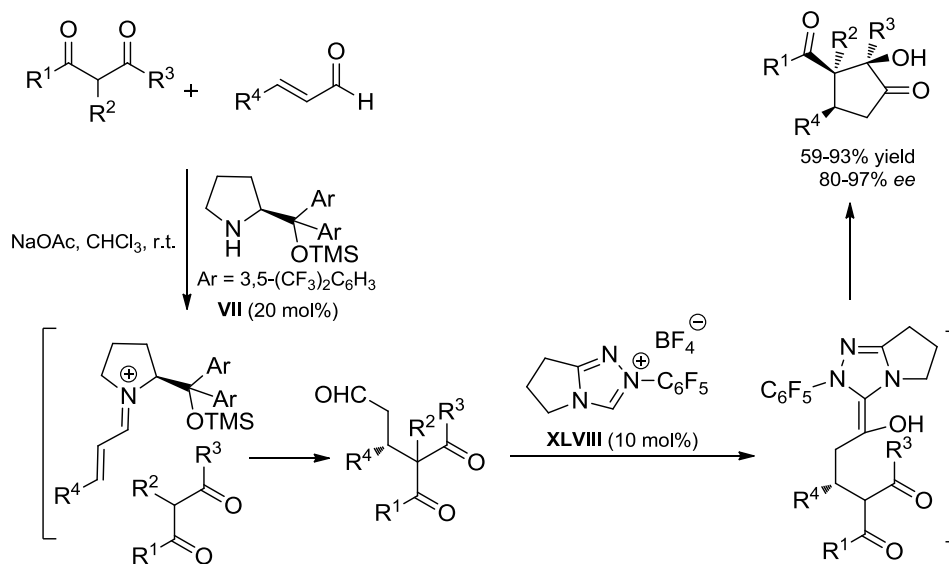
Scheme I- 49 The Michael addition/Knoevenagel condensation between cinnamaldehyde and dimethyl 3-oxopentanedioate (Hayashi, 2009).

In 2009, Chen and co-workers have developed a newly designed bulky chiral secondary amine **XLVII** derived from proline, which, together with LiClO_4 and DABCO as co-catalysts, was applied to an enantioselective Michael addition-Wittig olefination domino reaction of (3-carboxy-2-oxopropylidene)triphenylphosphorane **19** and α,β -unsaturated aldehydes to afford the corresponding formal [3+3] cycloadducts **20** in excellent diastereo- and enantioselectivities (up to >50:1 *dr*, 86-99% *ee*) (Scheme I- 50).^[147]



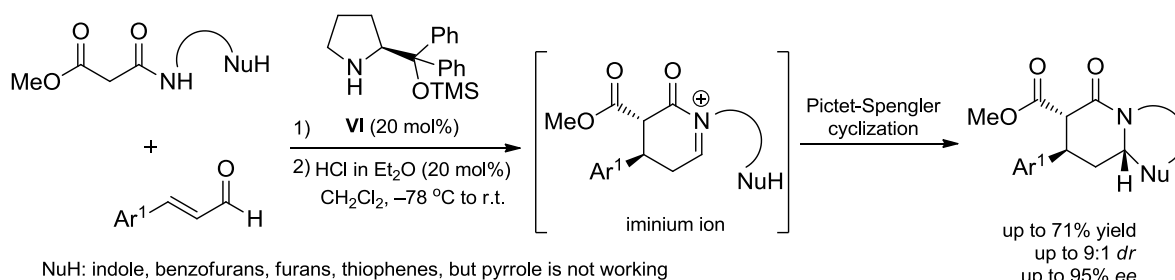
Scheme I- 50 Michael addition-Wittig olefination domino reaction (Chen, 2009).

In 2009, Rovis developed a multicatalytic (secondary amine/*N*-heterocyclic carbene) enantioselective domino reaction of 1,3-diketones with α,β -unsaturated aldehydes to prepare chiral α -hydroxycyclopentanones including three contiguous stereocenters (Scheme I- 51).^[148] Firstly, the secondary amine catalyst **VII** reacts with the α,β -unsaturated aldehyde to form an iminium ion intermediate, and then the 1,3-diketone adds from *Re* face to forge two of the stereocenters. Secondly, the intermediate Michael adduct underwent an intramolecular cross acyloin reaction in the presence of the carbene precursor **XLVIII** to afford the final cyclopentanones via a formal [3+2] cycloaddition process. The only drawback of this method was that the diastereomeric ratio was only 2:1 to 6:1. However, this example highlights the power of domino reactions and cooperative catalysis, as the products were obtained with lower enantioselectivities if the two steps were run in a sequential fashion.

Scheme I- 51 Domino reaction of 1,3-diketones to α,β -unsaturated aldehyde catalyzed by secondary amine/*N*-heterocyclic carbenes (Rovis, 2009).

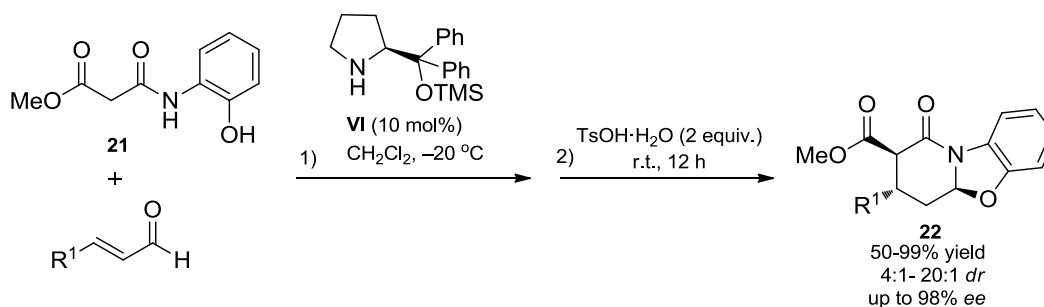
β -Carbamoylestere are also suitable substrates for organocatalytic domino reactions, since the additional reactive center (the nitrogen atom of the amide) can participate in the

reaction sequence. In 2009, Franzén and co-workers reported the first organocatalytic enantioselective transformation involving an enantioselective Michael addition followed by an iminium formation/diastereoselective Pictet-Spengler cyclization between β -carbamoylestes and aromatic α,β -unsaturated aldehydes. The same Hayashi-Jørgensen catalyst **VI** (20 mol%) was used in the first step whereas the addition of HCl in diethyl ether (20 mol%) was required for the cyclization on the acyliminium ion to provide both indolo[2,3a]quinolizidines and benzo[*a*]quinolizidines products (Scheme I- 52).^[149] The same reaction conditions were extended to a larger variety of electron-rich aromatic rings including benzofurans, furans and thiophenes. Unfortunately, for pyrroles, due to competing pathways, only traces of product were obtained.^[150]



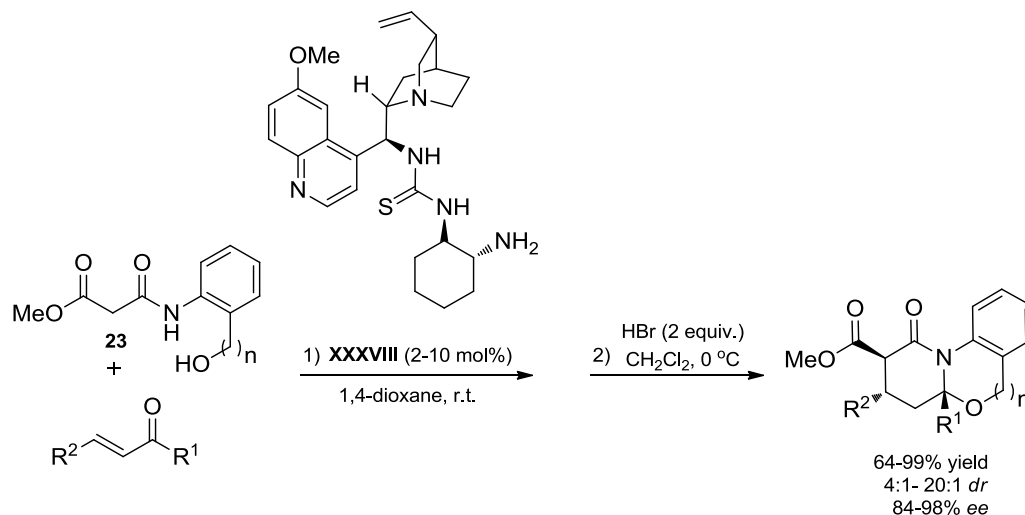
Scheme I- 52 Michael addition/iminium formation/Pictet-Spengler cyclization between β -carbamoylestes and aromatic α,β -unsaturated aldehydes (Franzén, 2009).

In the same year, Rios and co-workers developed the Michael addition of amidomalonates **21** to different α,β -unsaturated aldehyde also catalyzed by secondary amine **VI** (20 mol%), with potassium acetate as additive in 2,2,2-trifluoroethanol, to form the corresponding hemiaminals **22** with high yields and excellent enantioselectivities (up to 99%).^[151] In 2011, Ye and co-workers described a related one-pot domino reaction involving a Michael addition followed by an intramolecular cyclization via an intermediate *N*-acyliminium ion for the synthesis of oxazolidines (Scheme I- 53).^[152] Especially, the annulation step requires activation by a strong acid. After optimization, *p*-toluenesulfonic acid ensures an excellent diastereoselectivity compared with any other acid that had been examined. The reaction may be carried out with aliphatic and aromatic aldehydes with very good enantiomeric excesses but low diastereoselectivities are obtained with aliphatic aldehydes.



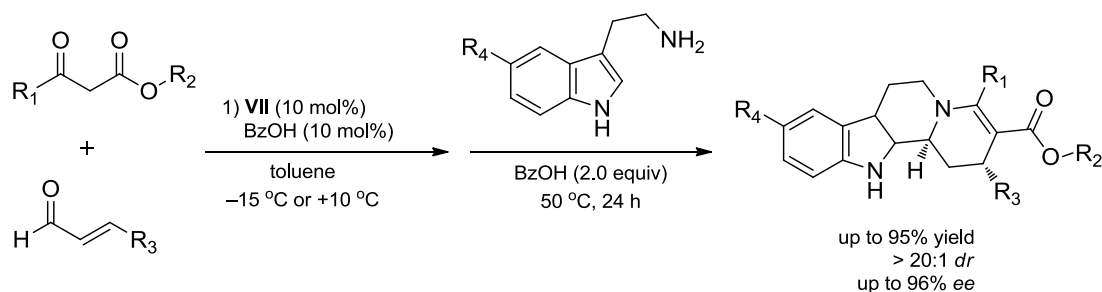
Scheme I- 53 Michael addition/intramolecular cyclization via an intermediate *N*-acyliminium for the synthesis of oxazolidines (Ye, 2011).

In the same line, the group of Ye showed that α,β -unsaturated ketones **23** can be used in a related transformation. This time, they used a multifunctional catalyst derived from cinchona alkaloid **XXXVIII**. The primary amine function of the catalyst allows to activate α,β -unsaturated ketones as iminium ions for their Michael addition with β -carbamoylestere. In the final annulation step, a chiral tetrasubstituted carbon center with satisfactory selectivities has been constructed by using HBr (Scheme I- 54).^[153] The authors showed that both the primary amine and the thiourea part were important to improve the enantioselectivity.



Scheme I- 54 Reactions between functionalized secondary β -carbamoylestere and α,β -unsaturated ketones (Ye, 2011).

In this context, Zhao and co-workers in 2010 employed the same strategy as Franzén (Scheme I- 51) to synthesize fused indole derivatives.^[154] Three different readily available starting materials (an acyclic β -ketoester, an α,β -unsaturated aldehyde and a tryptamine derivative) were involved. The last one was added after the completion of the Michael addition and heating in the presence of an excess of benzoic acid was necessary to ensure the cyclization. (Scheme I- 55).^[154] Soon after, Rueping and co-workers extended this reactivity to cyclic diketones, besides tryptamine, other nucleophiles including *o*-aminobenzylamine and anthranilamide also participated in this transformation, giving rise to pyridoquinolines and quinazolinones.^[155, 156]



Scheme I- 55 Domino reactions between acyclic β -ketoester, an α,β -unsaturated aldehyde and a tryptamine derivative (Zhao, 2010).

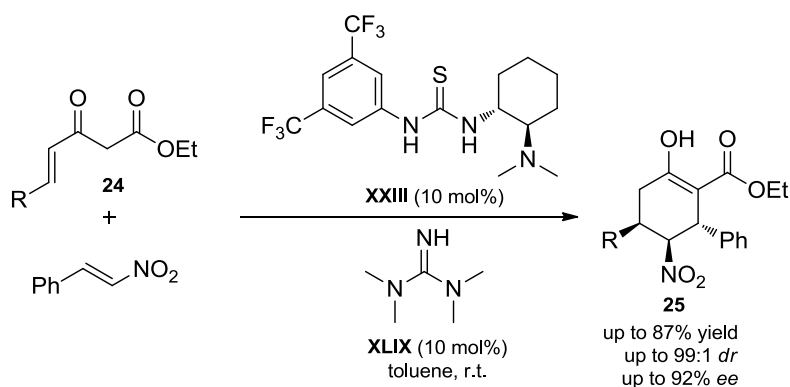
Shortly after, Bonjoch and co-workers first developed an effective catalytic method to

synthesize morphanes by a Robinson/aza-Michael intramolecular reaction by using chiral secondary amine **VI** and LiOH in *i*PrOH and H₂O.^[157]

I.3.1.3 NON-COVALENT ACTIVATION MODES

All the above-mentioned examples rely on an activation mode involving the covalent bonding of the catalyst with at least one of the substrates. However, hydrogen-bonding interactions and other non-covalent activation modes have already been used by many research groups in domino reactions.

In 2004, the group of Takemoto reported the first example of enantioselective double Michael additions of γ,δ -unsaturated β -ketoesters **24** to nitroolefins using bifunctional thiourea **XXIII** and 1,1,3,3-tetramethylguanidine **XLIX** as catalysts to synthesize 4-nitrocyclohexanone derivatives **25** that have three contiguous stereogenic centers with good to high diastereoselectivities and up to 92% *ee* (Scheme I- 56).^[158, 159]



Scheme I- 56 Double Michael additions of γ,δ -unsaturated β -ketoesters to nitroolefins (Takemoto, 2004).

As previously known, the bifunctional thiourea **XXIII** first activated these substrates through deprotonation and hydrogen bonding for the first Michael addition to obtain the Michael adduct.^[71] Then, an intramolecular Michael addition catalyzed by 1,1,3,3-tetramethylguanidine **XLIX** afforded the cyclohexanones. In the same time, the author applied this strategy to the synthesis of (–)-epibatidine (Figure I- 15) that is a biologically active natural product.^[158]

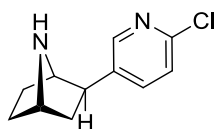
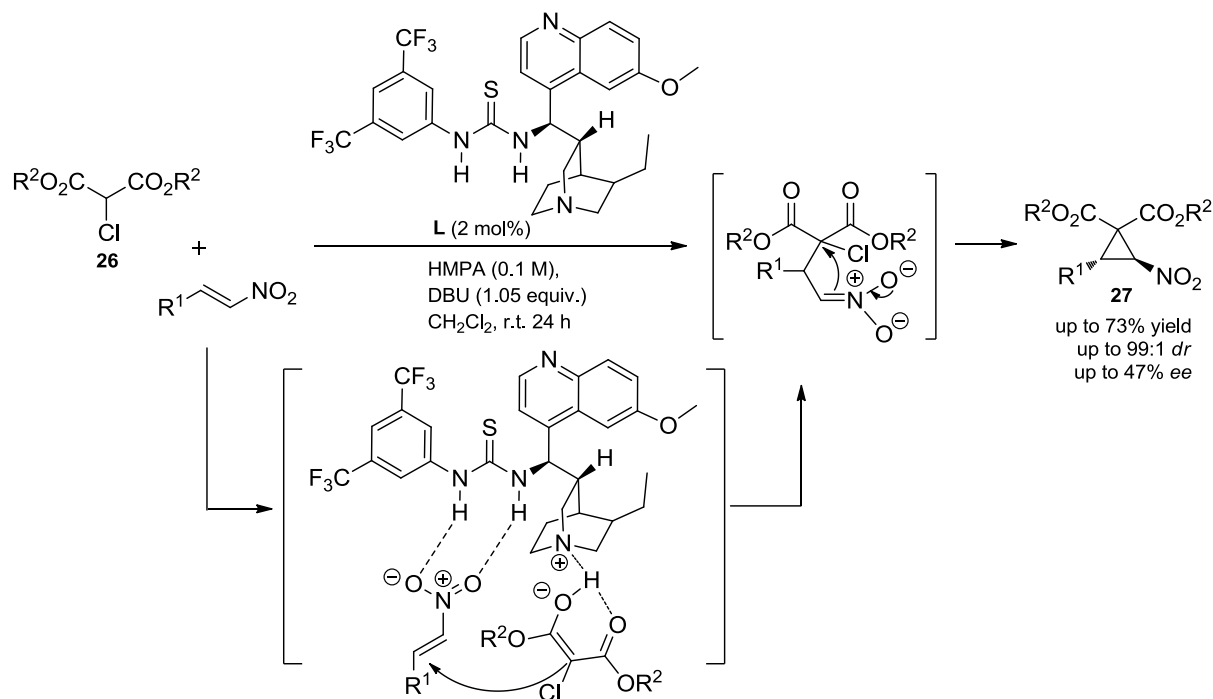


Figure I- 15 The structure of (–)-epibatidine.

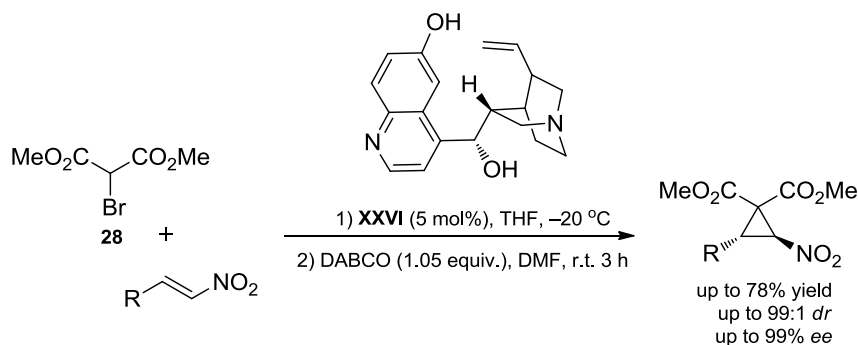
Shortly after, the group of Connon reported that highly functionalized nitrocyclopropanes can be synthesized by the Michael addition of dimethyl chloromalonates **26** to a variety of nitroolefins catalyzed by a chiral bifunctional cinchona alkaloid-based organocatalyst **L** (at low catalyst loadings), to lead to a Michael adduct, which cyclizes to

form the cyclopropane **27** in the presence of DBU with outstanding diastereoselectivity (Scheme I- 57).^[160] However, the enantioselectivity was only moderate in all the examples. Although related Michael addition-alkylation domino reactions had been previously reported (see scheme I-36), the activation mode is different: in the present case, since the organocatalyst **L** activates the substrates by hydrogen-bonding interactions.



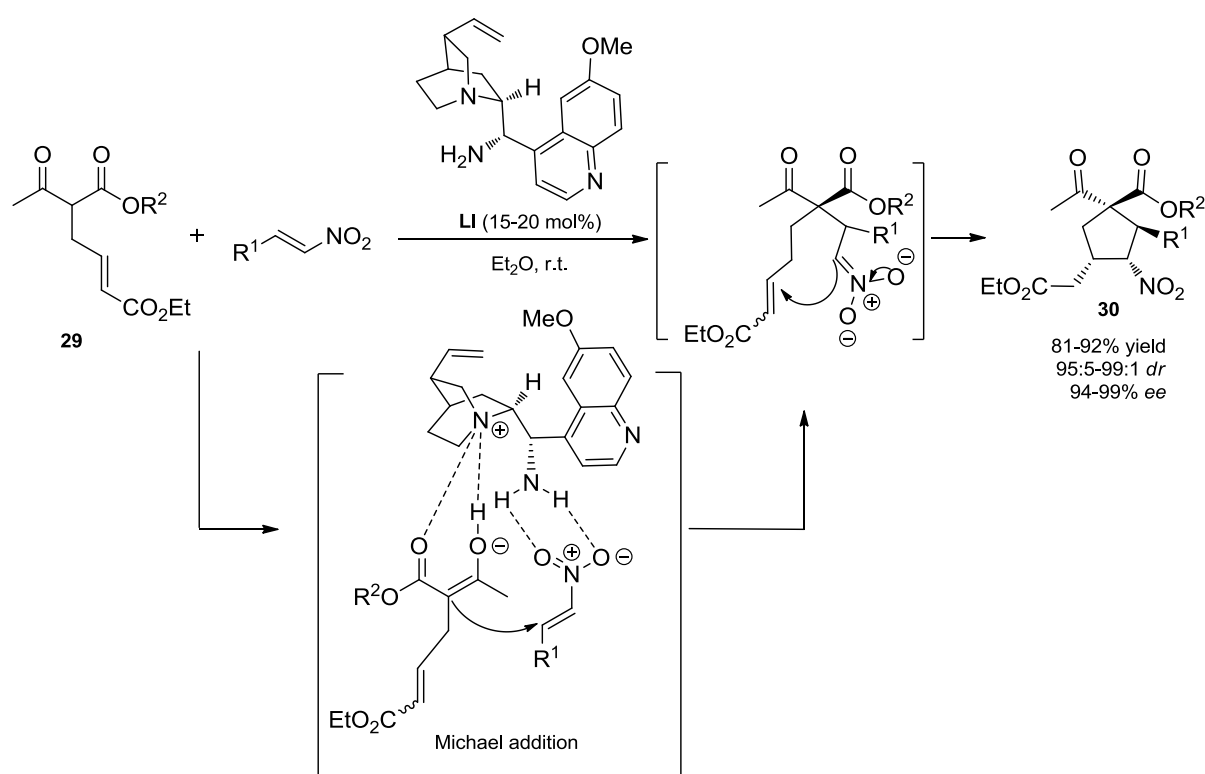
Scheme I- 57 Addition of dimethyl chloromalonate to a variety of nitroolefins catalyzed by a bifunctional cinchona alkaloid-based thiourea (Connon, 2006).

Three years later, Yan and co-workers have made an improvement of this strategy for the synthesis of nitrocyclopropanes via Michael addition of dimethyl bromomalonate **28** to α,β -unsaturated nitroalkenes and the consequent intramolecular alkylation catalyzed by cinchona alkaloid **XXVI** (5 mol%), which activates the substrates by hydrogen-bonding interactions, and DABCO to enable the cyclization. This reaction proceeds with good yields, excellent diastereo- and enantioselectivities (Scheme I- 58).^[161]



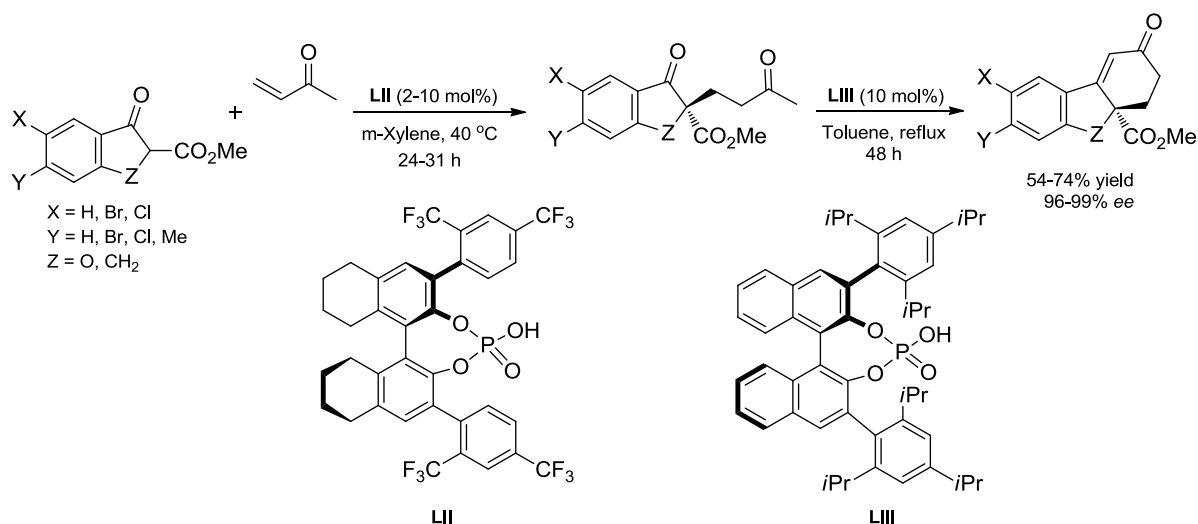
Scheme I- 58 Addition of dimethyl bromomalonate to α,β -unsaturated nitroalkenes catalyzed by a cinchona alkaloid (Yan, 2009).

In 2008, the group of Zhong used 9-amino-9-deoxyepiquinine **LI** to catalyze a double Michael addition sequence between nitroolefins and 1,3-dicarbonyl derivatives functionalized with an α,β -unsaturated ester **29**, which provides an expedient access to multifunctionalized five-membered rings **30** (Scheme I- 59).^[162] There are two Michael acceptors in the sequence, with the nitroolefins being slightly more reactive than the α,β -unsaturated ester, ensuring the chemoselectivity of the transformation. As other cinchona alkaloid-derived catalysts, this one activates both the Michael donor and acceptor by hydrogen-bonding interactions. Firstly, the reaction started from the addition of the 1,3-dicarbonyl derivative to nitrostyrene. Secondly, the nitronate generated *in situ* cyclizes via an intramolecular Michael addition to the α,β -unsaturated ester. The same group also reported the parallel domino reaction by a Michael-Henry sequence to synthesize chiral enantioenriched cyclopentanes. The only difference is the use of a ketone moiety instead of the α,β -unsaturated ester.^[163]



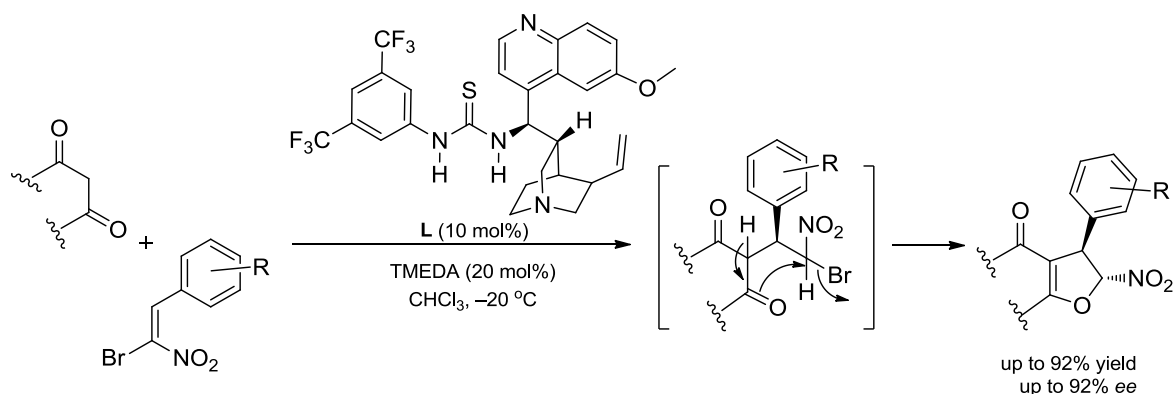
Scheme I- 59 Double Michael reaction between nitroolefins and 1,3-dicarbonyl derivatives catalyzed by 9-amino-9-deoxyepiquinine (Zhong, 2008).

In 2009, the group of Akiyama described a Robinson-type annulation based on an enantioselective Michael addition and a subsequent aldol reaction catalyzed by two structurally different chiral phosphoric acids. The first phosphoric acid **LII** catalyzed the enantioselective Michael addition of β -ketoesters to methyl vinyl ketone (MVK) and the second one **LIII** catalyzed the intramolecular aldol reaction with kinetic resolution followed by dehydration (Scheme I- 60).^[164]



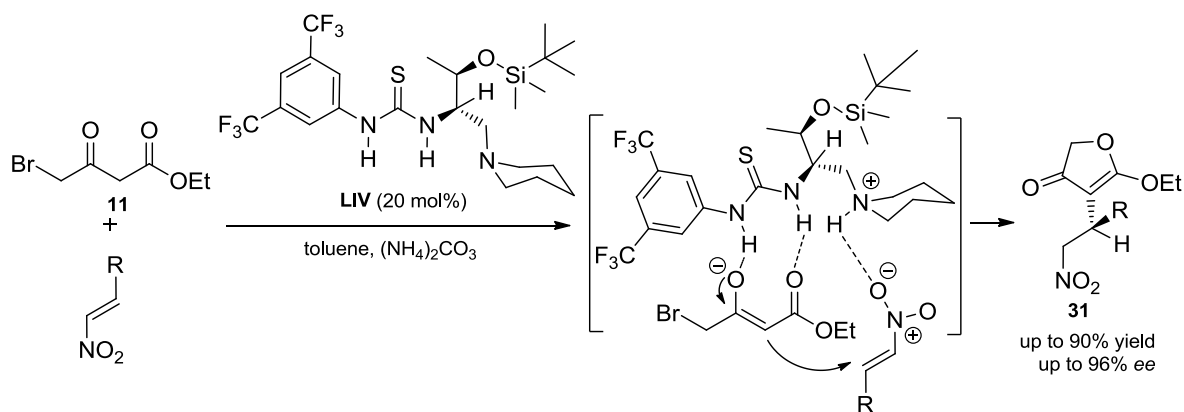
Scheme I- 60 Robinson-type annulation between β -ketoesters and methyl vinyl ketone catalyzed by two structurally different chiral phosphoric acids (Akiyama, 2009).

In 2010, Rueping and co-workers have extended the domino Michael addition-alkylation strategy to the synthesis of enantioenriched dihydrofurans between diketones and (*E*)- β -bromo- β -nitrostyrenes catalyzed by chiral bifunctional thiourea **L** (Scheme I- 61).^[165] The mechanism was the same as in the previously presented transformations (Scheme I- 57). The reactions proceeded in good yields, with good enantioselectivities and with high functional group tolerance.



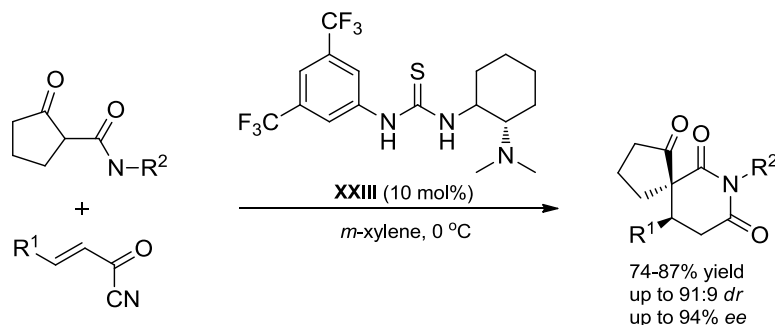
Scheme I- 61 Between diketones and (*E*)- β -bromo- β -nitrostyrenes catalyzed by chiral bifunctional thiourea (Rueping, 2010).

Moreover, the group of Lu for the first time synthesized L-threonine-derived tertiary amine/thiourea catalyst **LIV** and used it to promote the domino Michael addition-alkylation reaction of 4-bromoacetoacetate **11** to nitroolefins for the synthesis of 3(*2H*)-furanones **31** in high yields and with excellent enantioselectivities (Scheme I- 62).^[166] When 4-bromo-1,3-diketone was used instead of 4-bromoacetoacetate in this transformation under the standard condition, the expected furanone was obtained with only 53% yield and 50% *ee*. Meanwhile, the by-product resulting from the self-cyclization of 4-bromodiketone was obtained in 30% yield.



Scheme I- 62 The domino Michael addition-alkylation reaction for synthesis 3(2*H*)-furanones (Lu, 2012).

In this context, Lu and co-workers recently reported a Michael addition followed by intramolecular cyclization between methyl or ethyl acetoacetates and trifluoromethylated acrylamides to give trifluoromethylated lactones in good yields and moderate enantioselectivities.^[167] Earlier this year, our research group also reported an enantioselective organocatalytic Michael addition-intramolecular acylation sequence between cyclic β -ketoamides and α,β -unsaturated acyl cyanides as new bis-electrophiles (Scheme I- 63).^[168] The spiroimide products were obtained by a formal [3+3]cyclization. Moreover, the first chiral functionalized glutarimides were obtained by this method with excellent enantioselectivities.



Scheme I- 63 The domino Michael-intramolecular acylation sequence between cyclic β -ketoamides and α,β -unsaturated acyl cyanides (our research group, 2014).

I.3.2 NON-ENANTIOSELECTIVE MULTICOMPONENT REACTIONS BASED ON THE MICHAEL ADDITION OF 1,3-DICARBONYL SUBSTRATES

Multicomponent reactions (MCRs) are organic transformations, in which three or more starting materials react with each other to generate a single product. In this processes, several new bonds are created in a single operation (Figure I- 16).^[169-171] In the general context of sustainable chemistry, this strategy has several advantages.^[172]

- 1) It is by nature step-economical when compared with traditional stepwise synthesis.
- 2) It is experimentally simple as all the starting materials are added at the same time.
- 3) It is often atom-economy^[173] as most of the starting material atoms are generally integrated in the final product.
- 4) It is environmentally friendly: only the isolation of the final product is required, reducing the production of waste.

Therefore, multicomponent reactions are considered to approach the realization of the ideal synthesis.^[174] Multicomponent reactions rely on the use of polyfunctional substrates that are able to react at different position in a chemoselective manner with the other reaction partners. For example, isocyanide are among the most popular reactants involved in many MCRs such as the Ugi or the Passerini reactions.^[175-179]

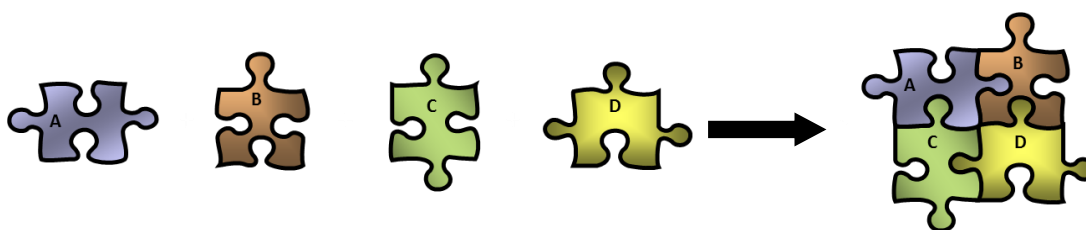
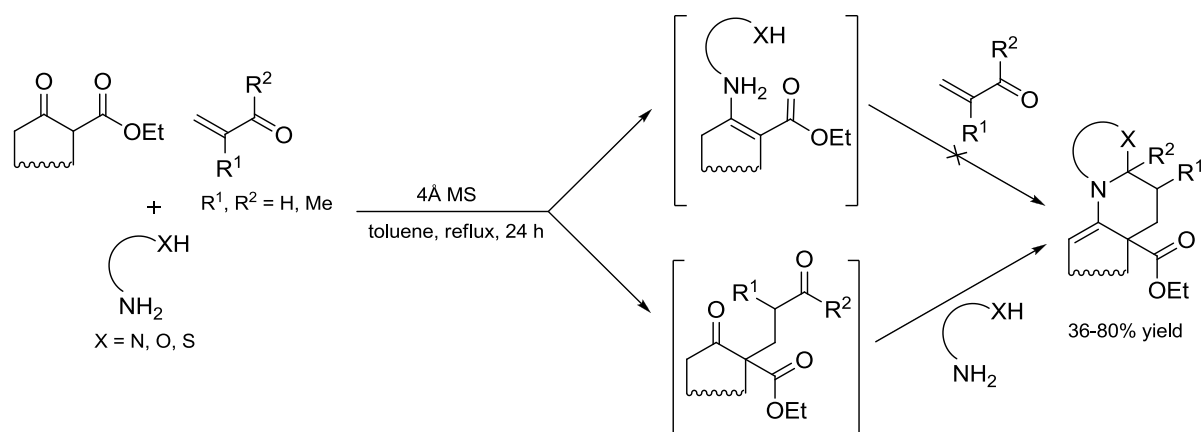


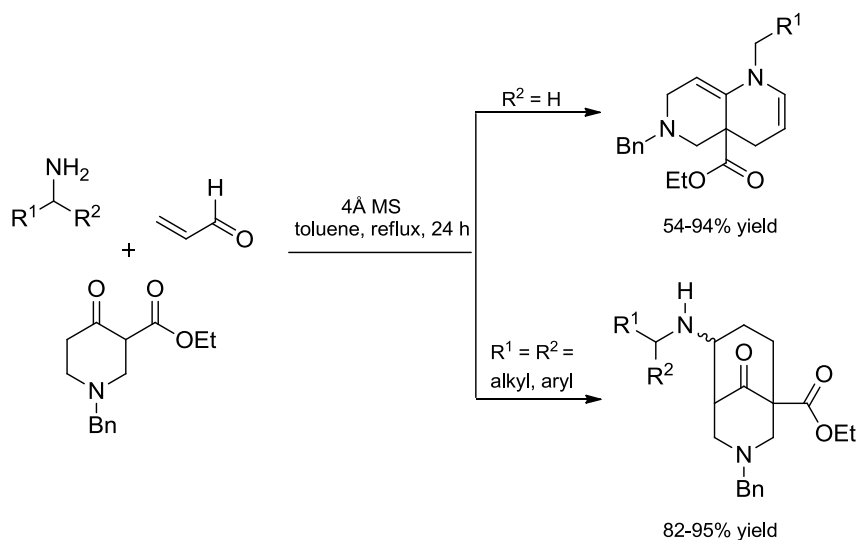
Figure I- 16 The model of multicomponent reactions.

β -Dicarbonyls being multifunctional substrates combining both nucleophilic and electrophilic reactive sites, they are by nature well-disposed to engage into multicomponent reactions. This potentiality was recognized already in the 19th century with the development of both the Hantzsch dihydropyridine synthesis^[180] and the Biginelli dihydropyrimidine synthesis.^[181] However, it is only in 1979 that Eschenmoser and co-workers have reported the first multicomponent reactions based on the Michael addition of 1,3-dicarbonyl for the synthesis of macrolides. The starting materials involved three components (acrolein, 2-methyl-1,3-cyclohexanedione and methylmalonate).^[182] Other similar MCRs were not explored until 2001, when our research group developed the first Michael addition-initiated multicomponent domino reaction between 1,3-dicarbonyls, α,β -unsaturated aldehydes or ketones and functionalized primary amines in refluxing toluene in the presence of 4Å molecular sieves, resulting in the formation of polyheterocyclic structures (Scheme I- 64).^[183] It is believed that the initial step is the Michael addition as the stepwise control experiment did not proceed from the preformed enaminoester.



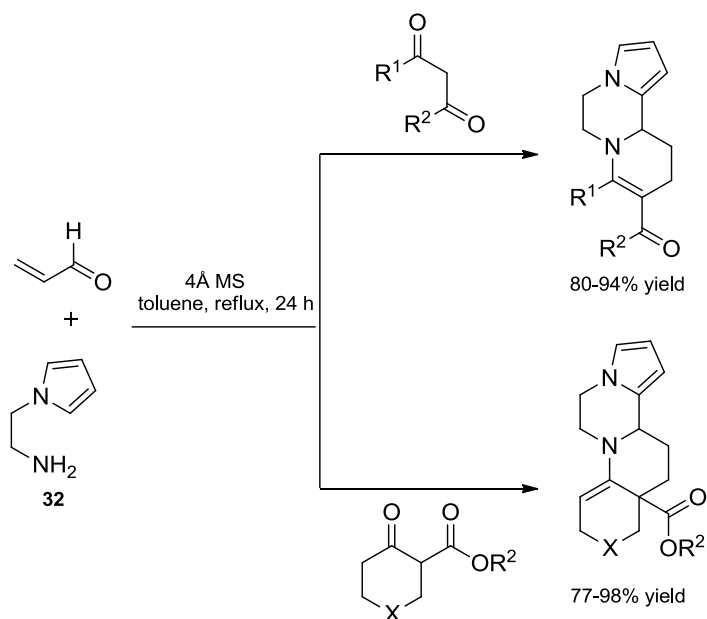
Scheme I- 64 The first Michael addition-initiated multicomponent domino reaction between 1,3-dicarbonyls, α,β -unsaturated aldehydes or ketones and functionalized primary amines (our research group, 2001).

With this novel reactivity pattern in hand, it was applied to different functionalized amines to obtain diversified polyheterocyclic compounds. For example, the reaction proceeded between ethoxycarbonyl piperidone, acrolein and primary amines (Scheme I-65).^[184] According to the substitution of the amine, two distinct families of final products were obtained either 1,6-hydronaphthyridines or aminoazabicyclo[3.3.1]nonanes.



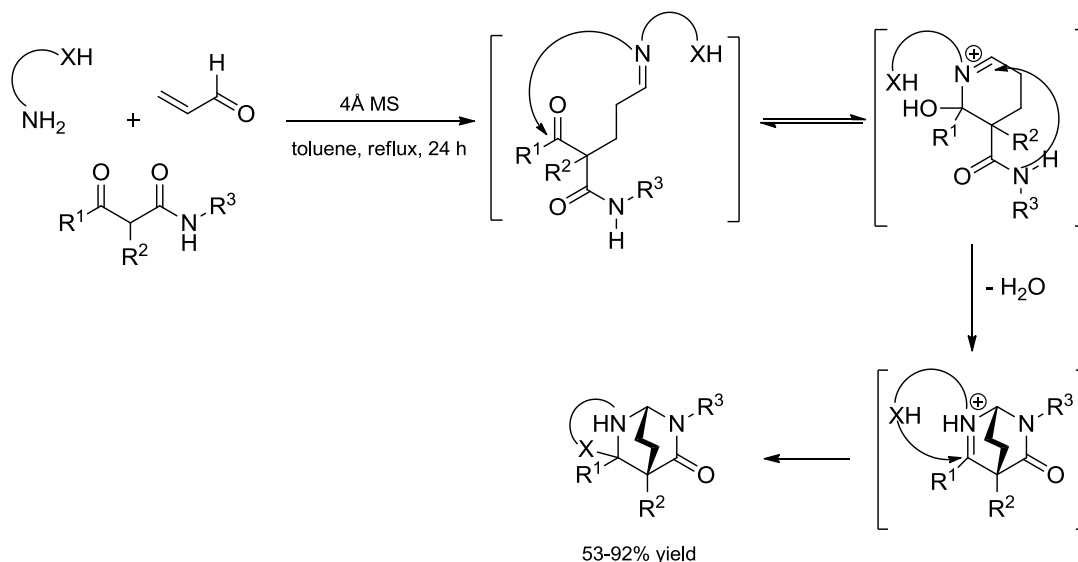
Scheme I- 65 MCRs between ethoxycarbonyl piperidone, acrolein and primary amines (our research group, 2003).

Shortly after, *N*-(2-aminoethyl) pyrrole **32** was for the first time used in a multicomponent reaction in combination with β -ketoesters and acrolein to provide pyrrolpiperazines (Scheme I- 66).^[185] This reaction consists of a Michael addition followed by the formation of an iminium ion intermediate, trapped in situ via a Pictet–Spengler–type cyclization. With the use of α -substituted cyclic ketoester, the final product was a tetracyclic compound with an azasteroid skeleton, obtained in high yield and as only one diastereomer.



Scheme I- 66 MCRs between β -ketoesters, acrolein and *N*-(2-aminoethyl) pyrrole (our research group, 2007).

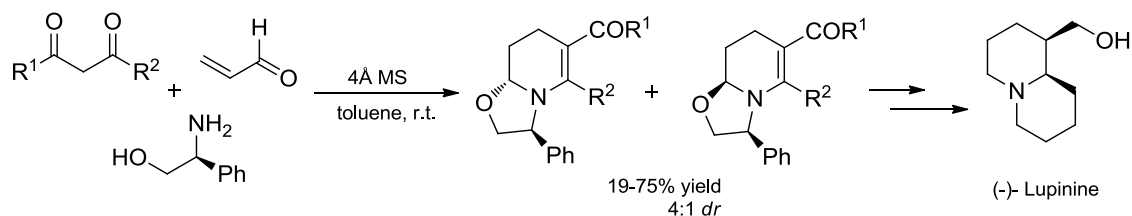
Finally, when β -ketoamides are used instead of β -ketoesters as the pronucleophile in the three-component reaction, the original 2,6-diazabicyclo[2.2.2]octane skeleton (2,6-DABCO) was formed (Scheme I- 67).^[186] Because β -ketoamides possess one additional nucleophilic position on the amide nitrogen atom, in this transformation, two different iminium intermediates were generated and trapped by two nucleophilic atoms: the nitrogen atom of the amide and an heteroatom or an electron-rich aromatic ring of the amine partner.



Scheme I- 67 Three-component reaction of β -ketoamides, acrolein and an amine functionalized with a pendant nucleophile (our research group, 2005).

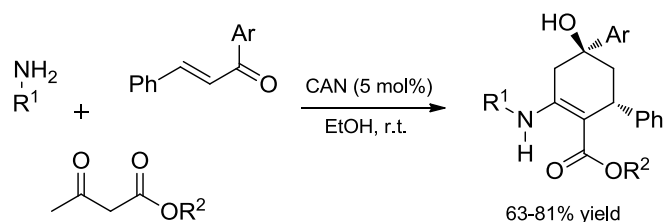
Related transformations have also been reported by other research groups. In 2008, Lhommet and co-workers proposed the three-component reaction between acrolein, (*S*)-2-phenylglycinol and various β -dicarbonyl compounds by using 4Å molecular sieves at

room temperature to synthesize bicyclic functionalized tetrahydropyridines with moderate diastereoselectivities (Scheme I- 68).^[187] The author also illustrated their method by the total synthesis of the quinolizidine alkaloid (-)-lupinine using bicyclic functionalized tetrahydropyridines as precursors in five steps and in 29% overall yield.



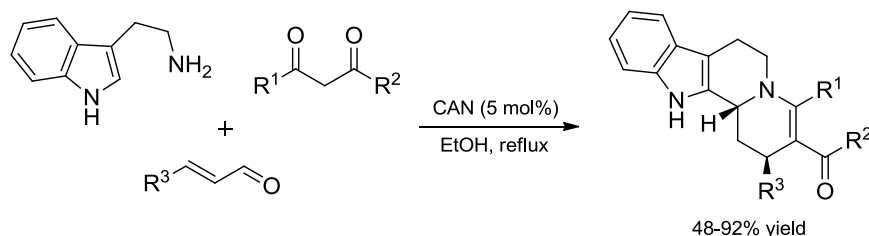
Scheme I- 68 Three-component reaction between acrolein, (*S*)-2-phenylglycinol and various β -dicarbonyl compounds (Lhommet, 2008).

In the same year, the group of Menéndez reported that cerium (IV) ammonium nitrate (CAN) instead of 4Å molecular sieves can catalyze the three-component reaction between alkylamines, β -ketoesters, and chalcones in EtOH affording *cis*-4,6-disubstituted 2-alkylaminocyclohexene-1-carboxylic esters with complete diastereoselectivity (Scheme I- 69).^[188] This reaction is initiated by a CAN-catalyzed reaction between alkylamines and β -ketoesters followed by a Michael addition, imine-enamine tautomerism and a final cyclization step.



Scheme I- 69 Three-component reaction between alkylamines, β -ketoesters, and chalcones catalyzed by CAN (Menéndez, 2008).

More recently, an extrapolation of this work was proposed for the three-component reaction of tryptamines, α,β -unsaturated aldehydes and various β -dicarbonyl compounds in the presence of CAN for the preparation of indoloquinolizines (Scheme I- 70).^[189]



Scheme I- 70 Three-component reaction of tryptamines, α,β -unsaturated aldehydes and various β -dicarbonyl compounds catalyzed by CAN (Menéndez, 2013).

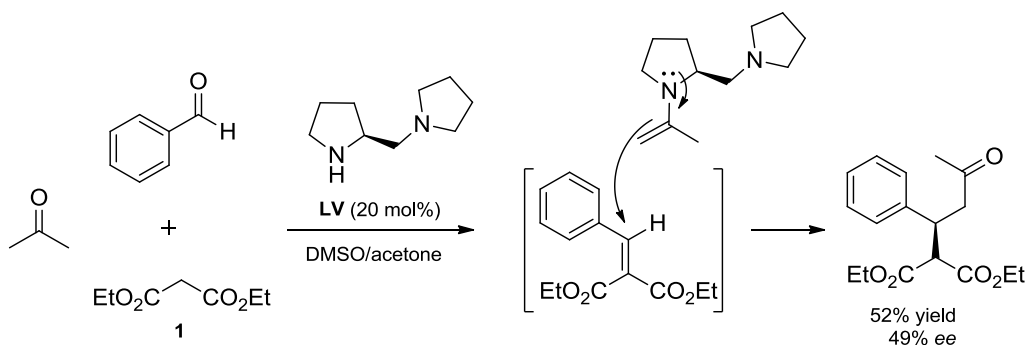
Two rings of the final product are generated through the creation of two C-C and two C-N bonds. The reaction is initiated by β -enaminone formation, followed by a Michael

addition, a 6-*exo*-trig cyclization, an iminium formation, and a Pictet–Spengler cyclization.

I.3.3 ORGANOCATALYTIC ENANTIOSELECTIVE MULTICOMPONENT REACTIONS BASED ON THE MICHAEL ADDITION OF 1,3-DICARBONYL SUBSTRATES

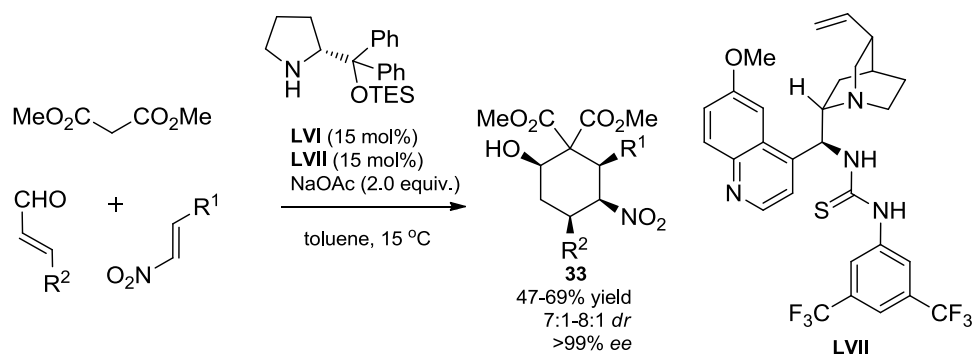
An organocatalytic enantioselective multicomponent reaction can be defined as a reaction between three or more reagents introduced at the same time by using a substoichiometric amount of a chiral organocatalyst. During this reaction, the formation of two or more bonds occurs as well as control over at least one newly formed stereogenic center.^[41, 170, 174, 190] As organocatalysts generally exhibit a high functional group tolerance, they are especially suited for multicomponent reactions. Indeed, one of the biggest challenges to develop these transformations is to prevent the non-productive interaction of the chiral catalyst with the additional reaction partners that are not involved in the enantioselective step.

The first example of organocatalytic enantioselective Michael-type multicomponent reaction was reported by the group of Barbas in 2001 (Scheme I- 71).^[191] The alkylidene malonates was synthesized in situ between benzaldehyde and diethylmalonate by a Knoevenagel reaction catalyzed by (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine (**LV**), and then followed by the enantioselective Michael addition of the alkylidene malonates and acetone. Although the results of the sequence were not completely satisfactory in terms of yields and enantioselectivities, it opened the field of Michael addition-initiated multicomponent reactions.



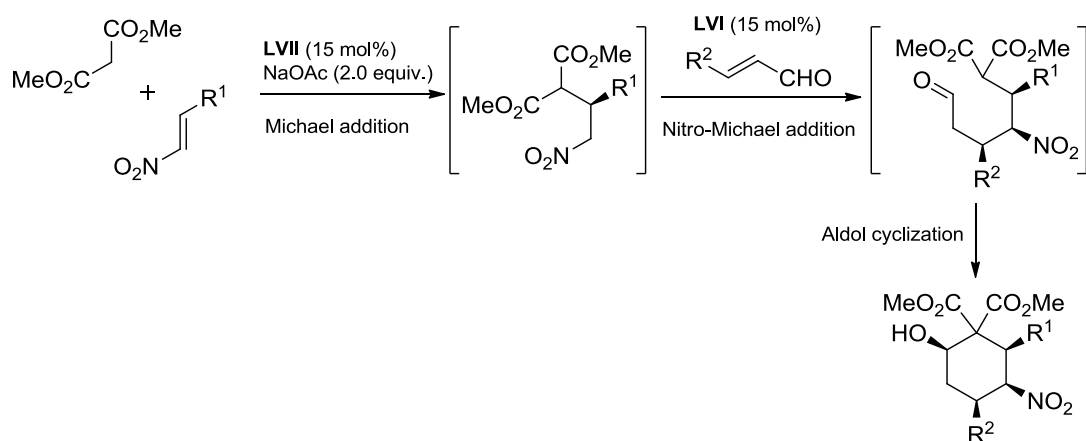
Scheme I- 71 The first example of organocatalytic enantioselective Michael addition-initiated multicomponent reaction (Barbas III, 2001).

In 2009, Dixon and co-workers reported a three-component tandem reaction comprising malonate esters, nitroolefins and α,β -unsaturated aldehydes to form polysubstituted cyclohexanes **33**, using a combination of bifunctional thiourea catalyst **LVI** and secondary amine catalyst **LVII** (Scheme I- 72).^[192]



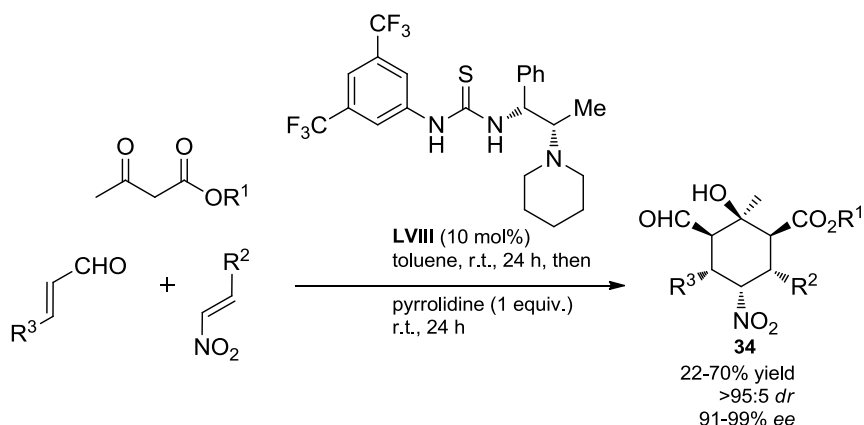
Scheme I- 72 Three-component domino reaction comprising malonate esters, nitroolefins and α,β -unsaturated aldehydes (Dixon, 2009).

The reaction has been suggested to proceed via bifunctional thiourea catalyst activation of malonate esters and nitroalkene leading to an enantioselective Michael addition. The Michael adduct subsequently undergoes a regioselective nitro-Michael reaction to the enal under iminium activation by the aminocatalyst producing another intermediate, which undergoes a base-promoted aldol cyclization to generate the desired product (Scheme I-73).^[192]



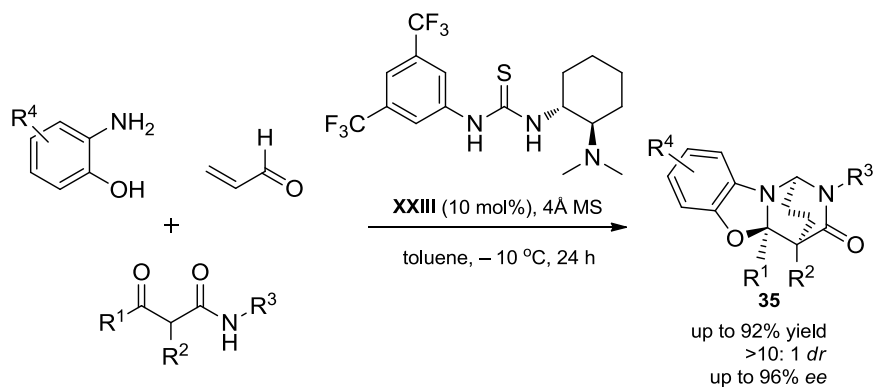
Scheme I- 73 Proposed mechanism for the three-component reaction (Dixon, 2009).

More recently, Enders and co-workers reported a three-component enantioselective methodology to synthesize polyfunctionalized cyclohexanes **34** from 1,3-ketoesters, nitroalkanes, and α,β -unsaturated aldehydes, catalyzed by bifunctional thiourea catalyst **LVIII** and pyrrolidine (Scheme I-74).^[193] The reaction is initiated by an enantioselective Michael addition controlled by the bifunctional catalyst, and pyrrolidine provides the diastereoselective Michael/aldol sequence through covalent iminium/enamine activation. The final products that bear six contiguous stereogenic centers are obtained in moderate to good yields and excellent stereoselectivities.



Scheme I- 74 Three-component reaction of 1,3-ketoesters, nitroalkanes, and α,β -unsaturated aldehydes (Enders, 2012).

At the beginning of my thesis, our research group had just started devoting efforts to introduce enantioselective organocatalysis in our previously developed Michael addition-initiated multicomponent reactions. In this context, Maria del Mar Sanchez Duque has developed during her thesis an enantioselective version of our synthesis of 2,6-DABCOs **35**^[186] from β -ketoamides, acrolein and aminophenols in the presence of bifunctional catalyst **XXIII** and crushed 4Å molecular sieves in dry toluene at -10°C (Scheme I- 75). The products were obtained in high yields and diastereoselectivities, with moderate to good enantioselectivities.^[194]



Scheme I- 75 The first example of enantioselective organocatalytic synthesis of 2,6-DABCOs by MCR (our research group, 2013).

I.4 SUMMARY

The importance of organocatalysis as a tool to obtain enantiomerically pure or enantioenriched compounds is recognized in the whole community of chemists. Moreover, 1,3-dicarbonyl derivatives are very important for the synthesis of polyheterocycles. The advantage of domino and multicomponent reactions has been known according to the previous example. However, up to now, organocatalytic multicomponent reactions based on

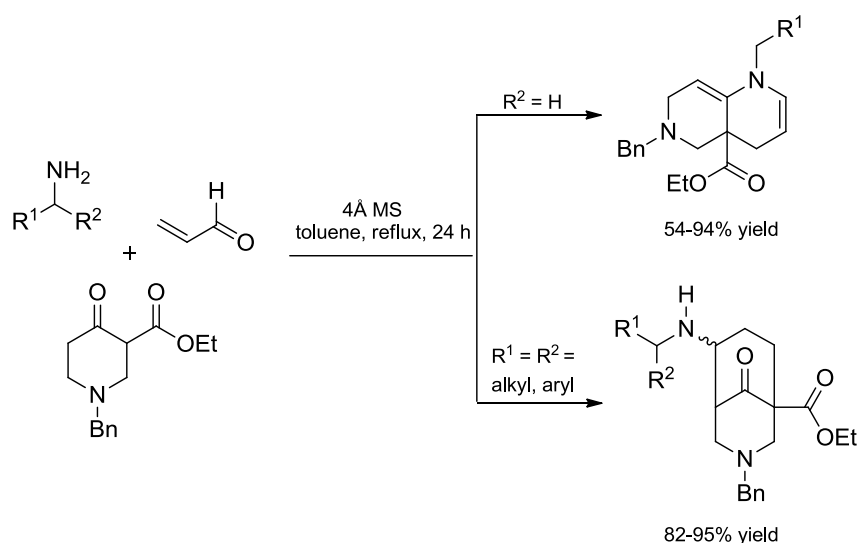
the 1,3-dicarbonyl derivatives still remains scarce in the literature. Therefore, we have decided to focus our work on the challenging development of new multicomponent enantioselective reactions.

Original contributions

**II. ORGANOCATALYST-CONTROLLED
CHEMOSELECTIVE THREE-COMPONENT
REACTIONS**

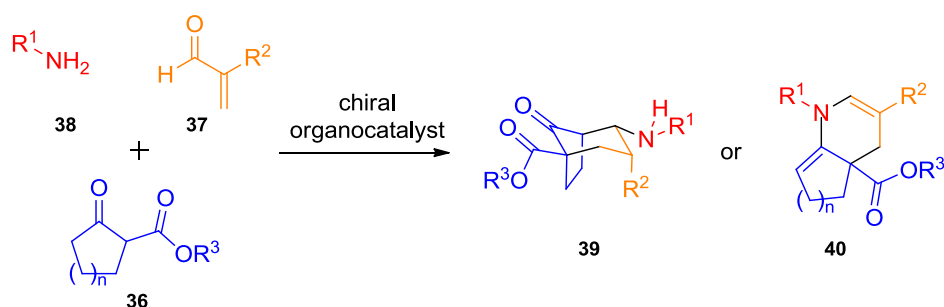
II. ORGANOCATALYST-CONTROLLED CHEMOSELECTIVE THREE-COMPONENT REACTIONS

For more than ten years, our group has been involved in the development of new multicomponent reactions that make use of the Michael addition of 1,3-dicarbonyl compounds to trigger the formation of valuable products, including a large variety of heterocycles.^[41, 42, 195] Especially, in 2003, our group reported a MCR that proceeds between ethoxycarbonyl piperidone, acrolein and simple primary amines (Scheme II- 1).^[184] During the study of this transformation, it was shown that either bridged or fused polycyclic could be formed depending on the substitution of the amine.



Scheme II- 1 MCRs between ethoxycarbonyl piperidone, acrolein and primary amines (our research group, 2003).

However, no enantioselective version of this reaction has been reported to date. We reasoned that using more general carbocyclic β -ketoesters **36**, still in combination with an enal **37** and a primary amine **38**, and adding an organocatalyst could open synthetic routes towards enantioenriched aminooxobicyclo[3.2.1]octan-8-ones **39** or cycloalka[*b*]piperidines **40** (Scheme II- 2).



Scheme II- 2 General strategy for our initial multicomponent enantioselective reactions.

Both these bridged and fused polycycles are ubiquitous motives that are present in

natural products and bioactive compounds, such as NMDA receptor antagonist,^[196] products with psychotrope activity,^[197-199] or 14-dehydrogenicunin B^[200] (Figure II- 1).

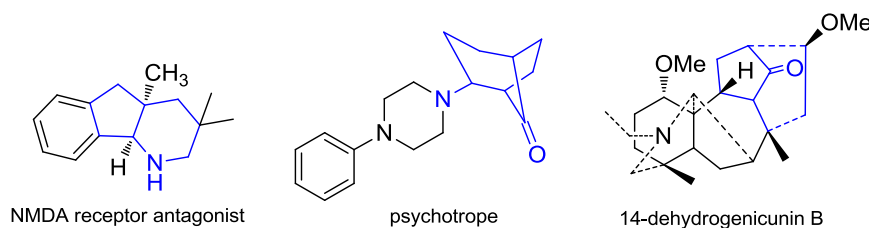
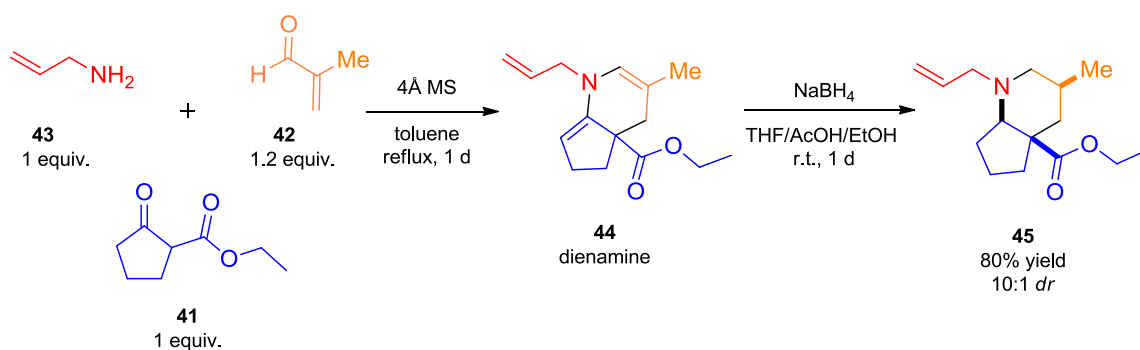


Figure II- 1 The structure of natural products and bioactive compounds including bridged or fused polycycles.

New methods to access these polycyclic motives in an enantioselective fashion need to be invented. Therefore, we focused our initial efforts on the development of an organocatalytic three-component reactions between a cyclic β -ketoester, methacrolein and a primary amine.

II.1 SELECTION OF SUBSTRATES AND SYNTHESIS OF RACEMIC PRODUCT

In order to enable the determination of enantiomeric excesses, every new enantioselective reaction must be accompanied by the synthesis of the product as a racemate. As a model reaction, we first selected ethyl cyclopentanecarboxylate **41**, methacrolein **42** and allylamine **43** as substrates, which were reacted in the presence of 4Å MS in refluxing toluene during one day. Because the dienamine **44** was not stable on silica gel, its direct reduction was performed by adding sodium borohydride in a mixture of THF, ethanol and glacial acetic acid. Product **45** was finally obtained with 80% isolated yield and 10:1 *dr* (Scheme II- 3).



Scheme II- 3 The racemic three-component reaction of ethyl cyclopentanecarboxylate, methacrolein and allylamine.

II.2 ORGANOCATALYST-CONTROLLED CHEMODIVERGENT THREE-COMPONENT REACTION: PRELIMINARY RESULTS

This model reaction was systematically investigated in the presence of different organocatalysts in order to find the most suitable activation mode.

II.2.1 CATALYST SCREENING

II.2.1.1 IMINIUM/ENAMINE-TYPE ACTIVATION

II.2.1.1.1 PROLINE-DERIVED SECONDARY AMINES

To start, secondary amine catalysts that are providing iminium or enamine-type activation were tested. From the bibliographic part, we know that these catalysts are very effective in activating the Michael addition of acyclic 1,3-dicarbonyl derivatives with α,β -unsaturated aldehydes.^[53, 132, 149, 201] In contrast, the catalyst **VI** proved inefficient in this model reaction (Figure II- 2): after 45 h, only trace amount of the desired product were obtained. Even with the addition of benzoic acid (20 mol%) as co-catalyst, which is known to accelerate the formation and the hydrolysis of the iminium ion intermediates, the reactivity did not increase. Up to now, this type of catalysts have not been reported to activate methacrolein, probably because of the added steric hindrance of the methyl group compared to other enals.

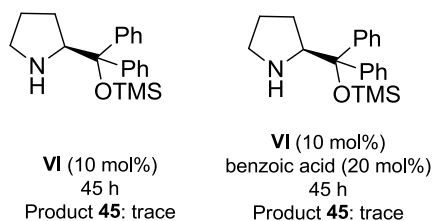


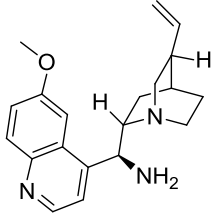
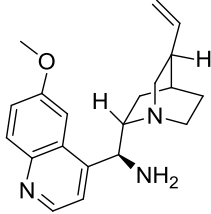
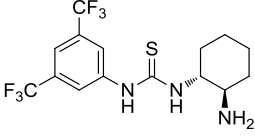
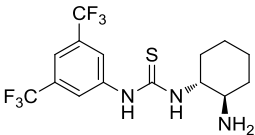
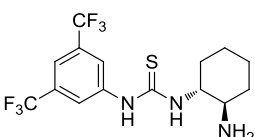
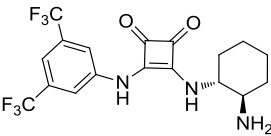
Figure II- 2 Evaluation of secondary amine catalysts.

II.2.1.1.2 PRIMARY AMINES

We decided to move to the use of less hindered primary amines that can also lead to iminium or enamine-type activation, even with more hindered substrates. To begin, we performed the reaction with a natural cinchona alkaloid-derived primary amine (**LI**), which is known to provide good result in the Michael addition of 1,3-dicarbonyl to enones.^[67, 162, 202] When we applied it to the model reaction, no product was formed after 45 h at room

temperature (Table II- 1, entry 1). This time, the addition of benzoic acid as co-catalyst, to improve the reactivity, proved useful and product **45** was obtained with 45% yield but with very low enantioselectivity (Table II- 1, entry 2).

Table II- 1 Evaluation of primary amine catalysts.

entry	catalyst	additive	temperature	yield	ee
1	 LI	no	r.t.	no product	n.d.
2	 LI	benzoic acid (20 mol%)	r.t.	45%	7%
3	 XX	no	r.t.	65%	45%
4	 XX	no	0 °C	52%	37%
5	 XX	4Å MS (200 mg)	r.t.	77%	0%
6	 LXI	4Å MS (200 mg)	r.t.	18%	12%

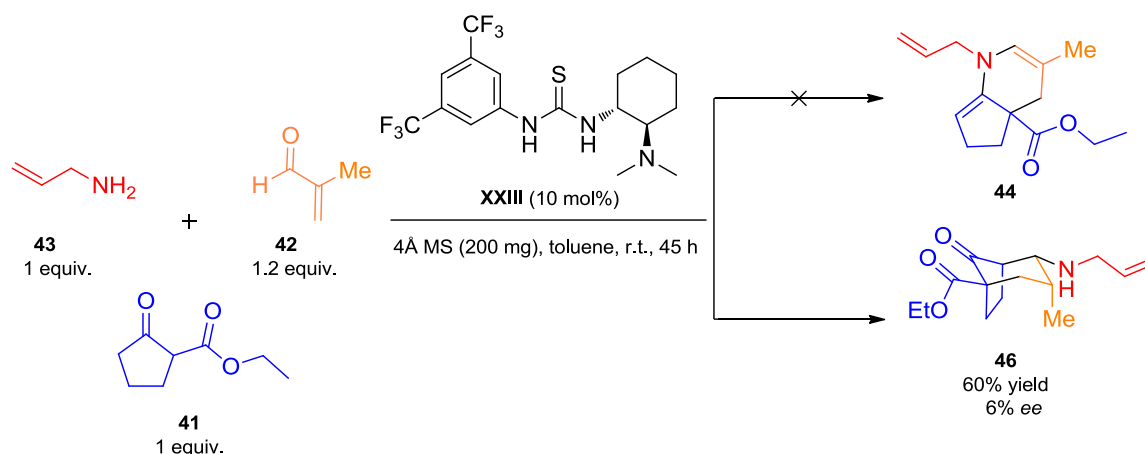
Primary amine-thiourea **XX** is also a good catalyst for the reaction between 1,3-dicarbonyl derivatives and various enones.^[57] This bifunctional catalyst possesses a primary amine to effect covalent activation of the electrophile, while the hydrogen-bonding

moiety ensures a selective approach of the other reaction partner. Therefore, this catalyst **XX** (10 mol%) was tested in the model reaction at room temperature. Finally, after 45 h, the desired product **45** has been obtained with 65% yield and an encouraging 45% *ee* (Table II- 1, entry 3). In an attempt to increase the enantioselectivity, the temperature was decreased to 0 °C. Unfortunately, both the yield and the enantiomeric excess were diminished in these conditions (Table II- 1, entry 4). It should be noted that the addition of 4Å MS improved the yield of the reaction but the product was then obtained as a racemic mixture probably due to the participation of 4Å MS as a catalyst in this reaction instead of the chiral primary amine (Table II- 1, entry 5).

In 2008, Rawal and co-workers reported that the greater spacing between the N-H groups in squaramides (2.72 Å) when compared with thioureas (2.12 Å) can be of interesting features in different organocatalytic transformations.^[95, 203] Therefore catalyst **LXI** was also evaluated in the studied reaction, but both the yield and the enantioselectivity remained low (Table II- 1, entry 6). The primary amine starting material (allylamine **43**) can react directly with methacrolein, competing with the chiral primary amine catalyst. This competition could explain why the desired product was obtained with low or no enantioselectivities.

II.2.1.2 NON-COVALENT ORGANOCATALYSTS

As shown in the bibliographic part, chiral thioureas are very good hydrogen bond donors that can be combined with a tertiary amine to design efficient bifunctional non-covalent organocatalysts^[57, 71] Therefore, bifunctional thiourea catalysts were investigated in this model reaction. Surprisingly, the commercially available Takemoto catalyst **XXIII** did not provide the expected product **45**, but the bridged bicyclic compound **46** with 60% yield (Scheme II- 4).

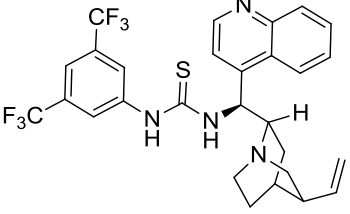
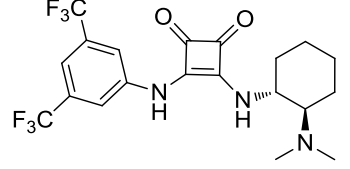
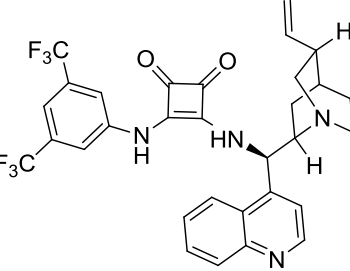
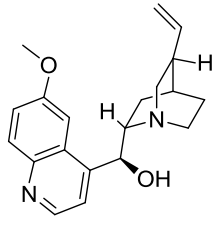
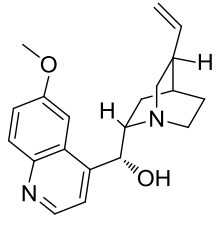


Scheme II- 4 Evaluation of Takemoto catalyst.

The racemic product **46** was prepared by using racemic Takemoto catalyst. When trying to evaluate the enantiomeric excess of this compound, we realized that its stability in the chiral column was low, making it difficult to obtain a precise value. In the end, we managed only to measure a very modest enantiomeric excess of 6%. As an alternative method to

determine the enantiomeric excess, europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] was combined with the bridged bicyclic compound **46** in order to transform the two enantiomers into two diastereomeric complexes. Unfortunately, compound **46** was not stable in the presence of the europium complex.

Table II- 2 Evaluation of various bifunctional non-covalent organocatalysts.

entry	Cat.	additives	temperature	yields (%)	<i>ee</i> (%)
1	 XXIV	4Å MS (200 mg)	r.t.	42%	n.d.
2	 LXII	4Å MS (200 mg)	r.t.	34%	n.d.
3	 LXIII	4Å MS (200 mg)	r.t.	23%	n.d.
4	 I	no	r.t.	trace	n.d.
5	 II	4Å MS (200 mg)	r.t.	trace	n.d.

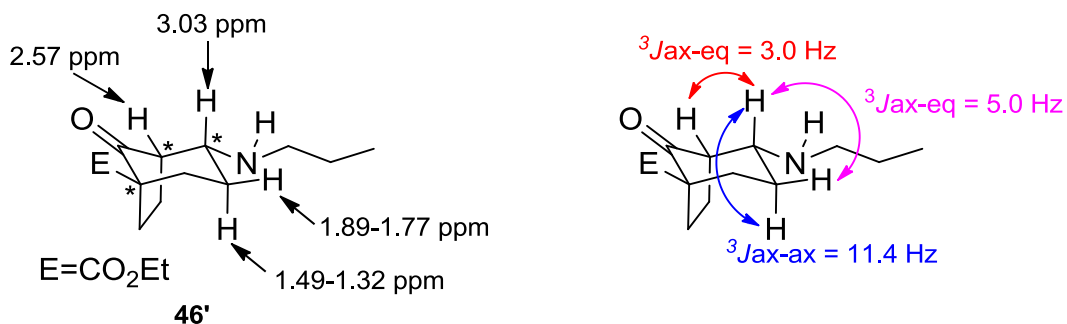
We decided to screen other bifunctional tertiary amine-hydrogen-bond donor catalysts to try to optimize the formation of product **46**. In the presence of 4Å MS (200 mg), catalyst **XXIV** provided product **46** in 42% yield (Table II- 2, entry 1). We also tried chiral squaramide catalysts bearing a tertiary amine in this model reaction. Whatever the catalyst was **LXII** or **LXIII**, the yield did not increase compared with the Takemoto's catalyst (Table II- 2, entries 2 and 3). The direct use of a cinchona alkaloid did not allow to obtain product **46** (Table II- 2, entries 4 and 5). In all these reactions, only traces of product **45** were obtained, highlighting the high chemoselectivity of the reaction in the presence of these non-covalent organocatalysts. Moreover, given the difficulties encountered to measure the enantiomeric excess of the product, this part of the project was skipped as we decided to direct our efforts towards other Michael-addition initiated multicomponent reactions (see next section).

II.2.2 STUDY OF THE RELATIVE CONFIGURATION

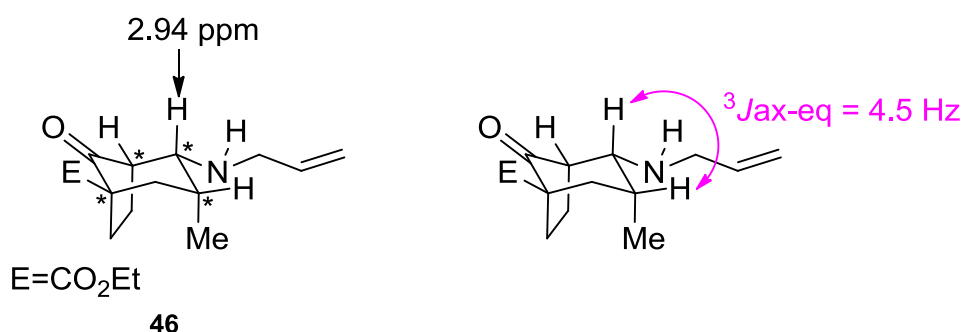
As early as 1995, our group has reported the structural assignment of similar derivatives, which could be achieved by the observation of the characteristic coupling constant patterns in the ^1H NMR spectra.^[204] Indeed, as a consequence of the Karplus equation, the $^3J_{\text{HH}}$ coupling constants will depend on the dihedral angle between the two C-H bonds. More specifically, protons that are in a *trans* diaxial relationship will present the highest coupling constants (around 12 to 14 Hz).

II.2.2.1 BRIDGED BICYCLE

In this context, the relative configuration of the bicyclic products obtained with acrolein in the racemic series had already been determined by studying the ^1H NMR spectrum of compound **46'**, after attribution of all the signals thanks to COSY, HMQC and HMBC analyses. The relative configuration of the two bridgehead carbon atoms is interdependent, which means we only need to determine the relative configuration of one of these carbon atoms with the last stereogenic center. The proton on the carbon atom α to the nitrogen atom has its signal at 3.03 ppm. It exhibits three $^3J_{\text{HH}}$ coupling constants of 11.4, 5.0 and 3.0 Hz, respectively. This observation means that this proton is in axial position and couples with only one other axial proton. For this reason, the proton on the bridgehead carbon atom is in equatorial position.



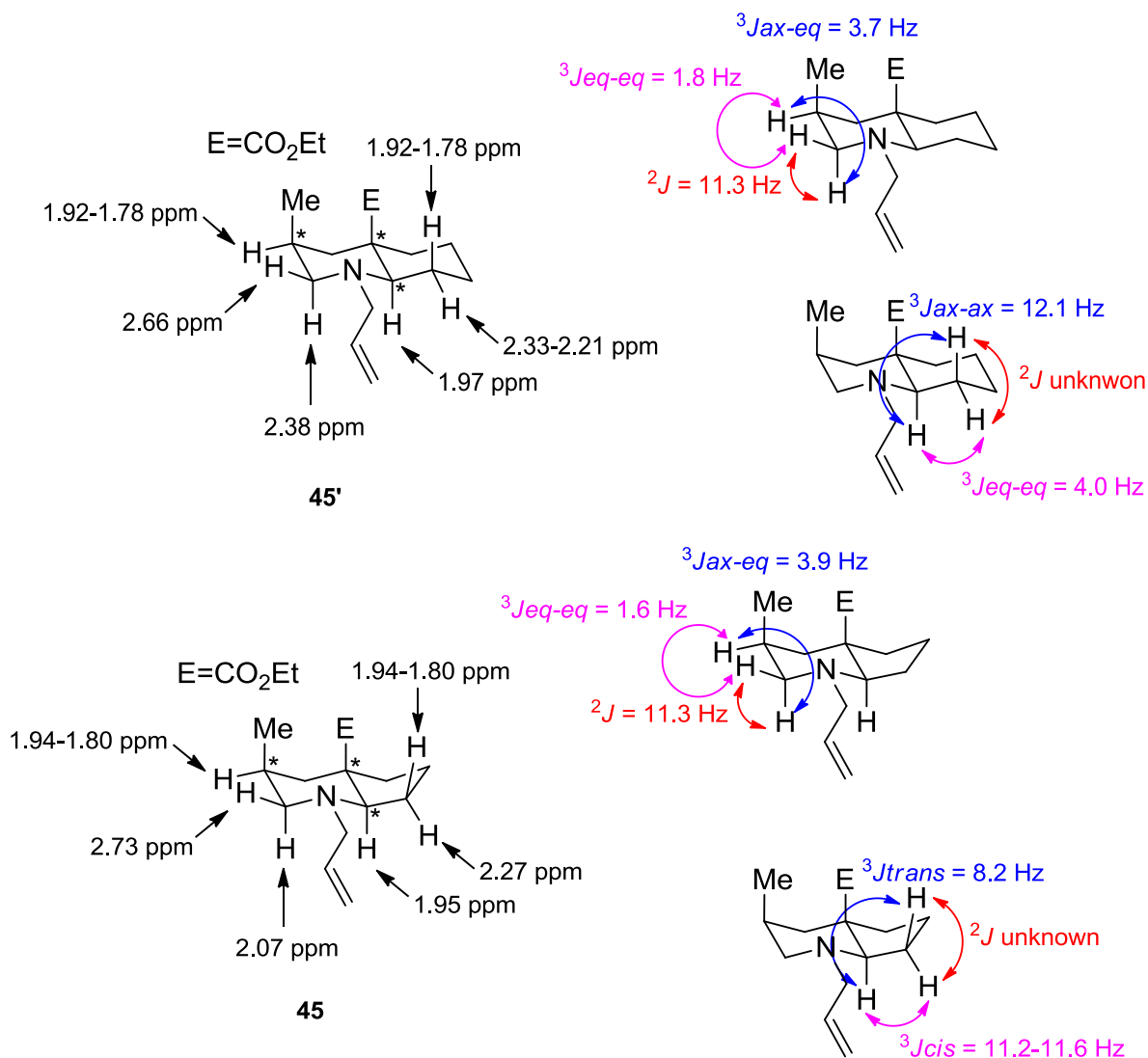
In the case of product **46**, the relative configuration of the fourth stereogenic center had to be attributed. The disappearance of the $^3J_{ax-ax}$ coupling constants for the proton at 2.94 ppm indicated that the methyl group is located in axial position.



II.2.2.2 FUSED BICYCLE

Prior to this study, racemic 6,6- and 6,5-fused bicycles had been prepared. At first, we studied the 6,6-bicyclic system, in which the identification of $^3J_{ax-ax}$ coupling constants provides solid support to the proposed relative configurations. All protons and carbons of product **45'** were attributed thanks to 2D NMR studies. On the nitrogen-containing ring, the absence of a high $^3J_{ax-ax}$ coupling constant between proton H₁₁ and protons H_{13a} and H_{13b} shows that H₁₁ is in equatorial position and the methyl group in axial position. Proton H₁ at the ring junction exhibits a $^3J_{ax-ax}$ coupling constant of 12.1 Hz with proton H_{2b} and is therefore located in axial position. We can then propose a *trans* ring junction, which is expected for this kind of systems.

We then conducted a similar analysis on compound **45** in the 6,5 series. Once again, the methyl group in the heterocycle is in axial position and the two rings are fused with a *trans* junction.



II.3 CONCLUSIONS

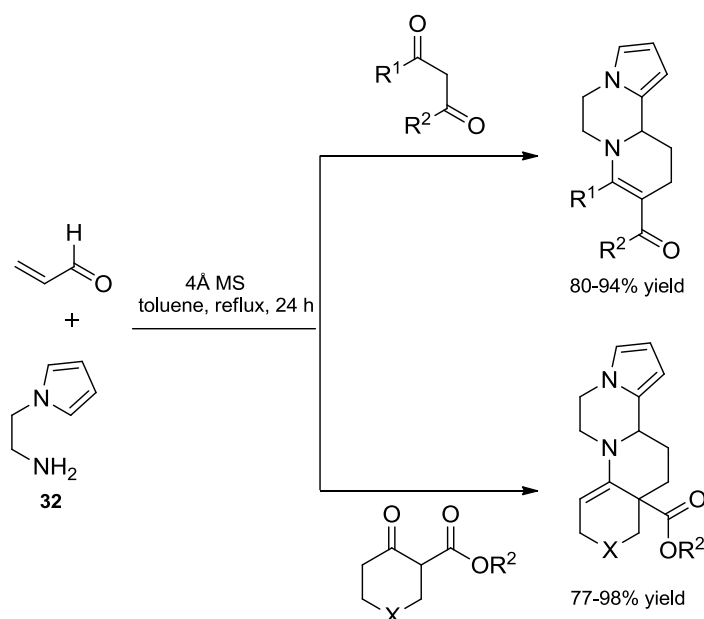
In this section, we presented our attempts to synthesize enantioenriched bridged and fused polycycles on a model multicomponent reaction in the presence of different organocatalysts. Although low enantioselectivities were obtained, an organocatalyst-controlled chemoselective three-component reaction was observed.^[205] Based on these initial results, different substrates have been investigated in other organocatalytic three-component reactions. These results will be discussed in the two following chapters.

**III. ORGANOCATALYTIC ENANTIOSELECTIVE
MULTICOMPONENT SYNTHESIS OF
PYRROLOPIPERAZINES**

III. ORGANOCATALYTIC MULTICOMPONENT PYRROLOPIPERAZINES

ENANTIOSELECTIVE SYNTHESIS OF

In view of our difficulties to apply organocatalysis to the reactions between cyclic β -ketoesters, enals and simple amines, we turned our attention towards another transformation, of which a racemic variant had already been developed in our group a few years ago. As we have seen it in the bibliographic part, in 2007, our group reported a new MCR that proceeded between various β -ketoesters, acrolein and *N*-(2-aminoethyl)pyrrole **32** to provide previously unknown tricyclic pyrroloperazines (Scheme III- 1).^[185] This reaction involves at first a Michael addition, followed by the formation of an iminium ion and its trapping via a Pictet-Spengler-type reaction.



Scheme III- 1 MCRs proceeded between β -ketoester, acrolein and *N*-(2-aminoethyl) pyrrole (our research group, 2007).

Although nothing is known about the bioactivity of such tricyclic pyrroloperazines, the diverse biological activities of other pyrroloperazine derivatives have been evaluated (Figure III- 1). As early as 1980, Jirkovsky reported the biological activities of pyrroloperazines derivatives **47** (where R¹ is a lower alkyl, cycloalkyl, phenyl or phenyl mono-, di- or trisubstituted with lower alkyl or lower alkoxy chains; R² is a hydrogen, lower alkyl, cycloalkyl, 2-(indole-3-yl)ethyl or phenylalkylene), which were central nervous system agents exhibiting antidepressant activity similar to amitriptyline, nortriptyline and imipramine.^[206] In 2003, Ratcliffe and co-workers discovered other pyrroloperazines derivatives **48** (where R¹, R² and R³ are various alkyl chains, aryl and heteroaryl rings, hydrogens, cyano groups and halogen atoms), which applied as focal adhesion kinase (FAK) inhibitors. Such FAK inhibitors may be used especially for the treatment or prevention of diseases, such as breast, colon, lung and prostate cancer.^[207] Shortly after, Hruby and co-workers synthesized small molecule peptide mimetics **49**, which could be used as

antagonists of melanocortin receptors, a family of 7-transmembrane G protein-coupled receptors that are involved in eating disorders.^[208] At last, in 2008, Merla and co-workers invented a family of pyrroloperazine derivatives **50**, which could behave as pain management agents.^[209] These results have already shown that the pyrroloperazines derivatives had various potential biological applications. Given the importance of the stereochemistry of the molecules on their interactions with biological receptors, the development of enantioselective routes towards pyrroloperazines is of great interest.

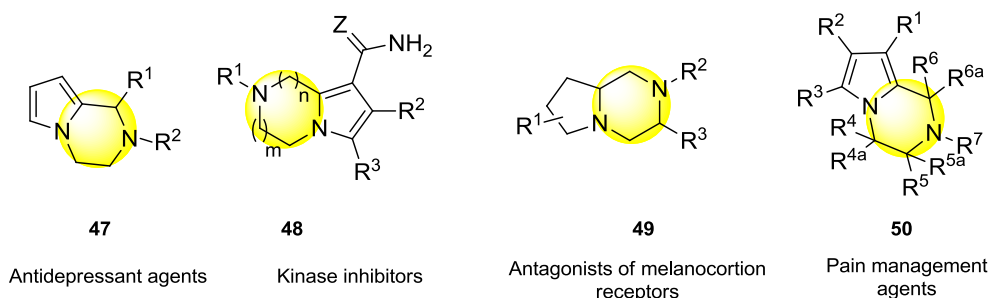
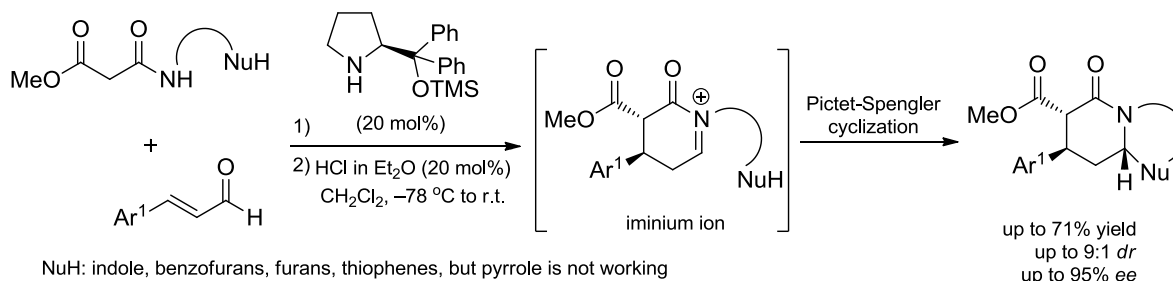


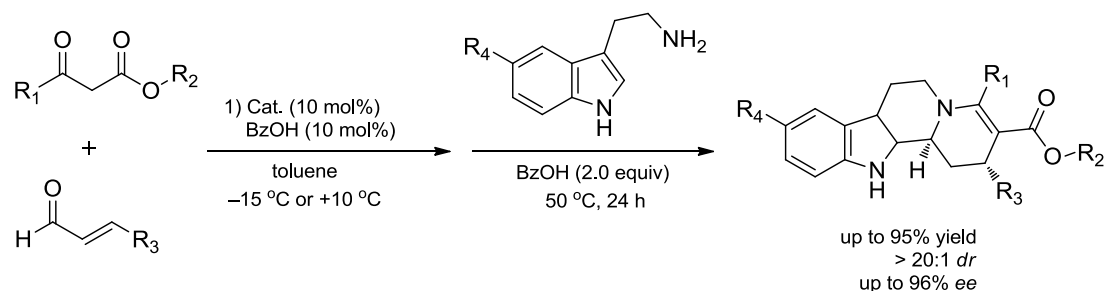
Figure III- 1 The structure of diverse biological activities of pyrroloperazines derivatives.

In 2009, Franzén and co-workers reported the first organocatalytic enantioselective transformation involving an enantioselective Michael addition followed by an iminium formation/diastereoselective Pictet-Spengler cyclization between β -carbamoylestere and aromatic α,β -unsaturated aldehydes (Scheme III- 2).^[149] And then, related reactions sequences had already been reported.^[150, 210]



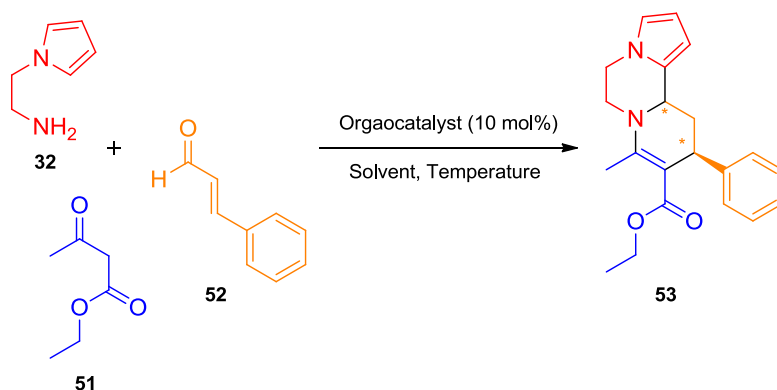
Scheme III- 2 Michael addition/iminium formation/Pictet-Spengler cyclization between β -carbamoylestere and aromatic α,β -unsaturated aldehydes (Franzén, 2009).

In 2010, Zhao and co-workers employed the same strategy that was sequential trimolecular transformations to synthesize fused indole derivatives.^[154] Three different readily available starting materials (an acyclic β -ketoester, an α,β -unsaturated aldehyde and a tryptamine derivative) were involved. The last one was added after the completion of the Michael addition and heating in the presence of an excess of benzoic acid was necessary to ensure the cyclization (Scheme III- 3).^[154] Soon after, Rueping and co-workers extended this reactivity to cyclic diketones, and besides tryptamine, other nucleophiles including *o*-aminobenzylamine and anthranilamide also participated in this transformation, giving rise to pyridoquinolines and quinazolinones.^[155, 156]



Scheme III- 3 Domino reactions between acyclic β -ketoester, an α,β -unsaturated aldehyde and a tryptamine derivative (Zhao, 2010).

However, all these precedents do not involve the use of a pyrrole as the electron-rich aromatic ring that acts as the nucleophile in the last step, letting us think that there was an interesting opportunity for the development of an enantioselective version of our multicomponent reaction. Based on the literature precedents, we selected acyclic methylene β -ketoesters **51** and β -substituted enals **52** as substrates of choice to begin the study of this reaction (Scheme III- 4).



Scheme III- 4 Model reaction of the organocatalytic enantioselective MCR based on β -ketoester.

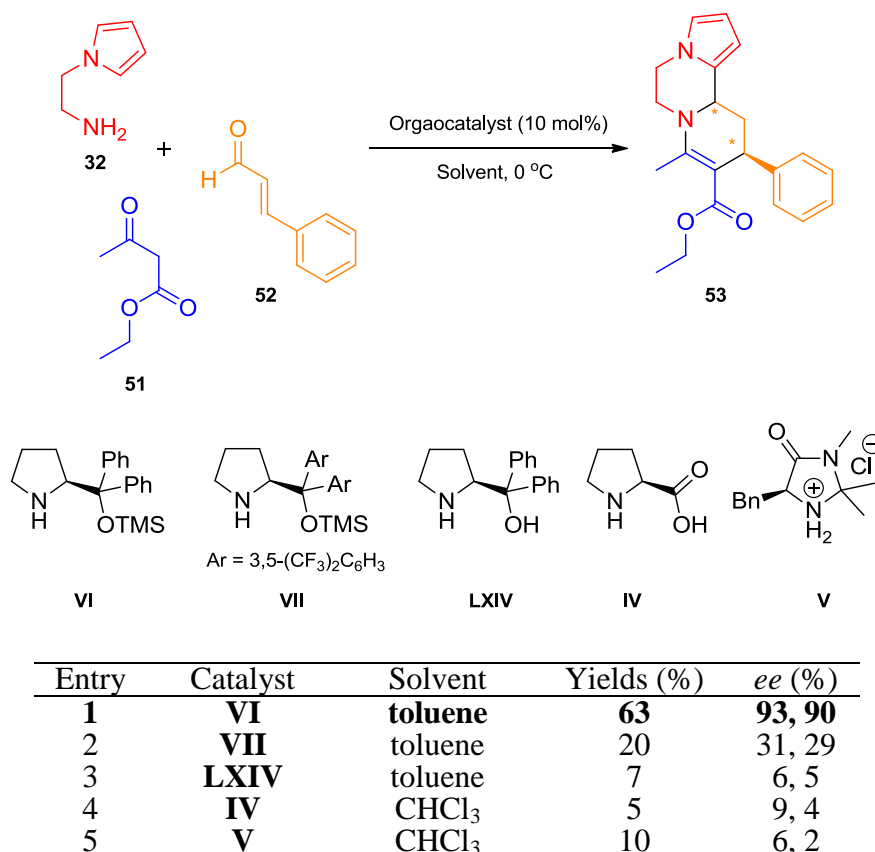
III.1 CATALYST SCREENING

III.1.1 IMINIUM/ENAMINE-TYPE ACTIVATION

To start our investigations, chiral secondary amine catalysts were screened, because it is well known that they are active and selective in reactions with α,β -unsaturated aldehydes via iminium-type activation.^[149, 154] They were put into reaction with ethyl acetoacetate **51** (0.2 mmol, 1 equiv.), cinnamaldehyde **52** (0.3 mmol, 1.5 equiv.) and *N*-(2-aminoethyl)pyrrole **32** (0.2 mmol, 1 equiv.) at 0 °C during two days. With catalyst **VI**, the expected fused tricyclic pyrroloperazine **53** was obtained in 63% yield, as a ~1:1 mixture of two diastereomers (Table III- 1, Entry 1). These initial results were very encouraging given that this reaction requires the formation of four new bonds and two new stereogenic centers. Pleasingly,

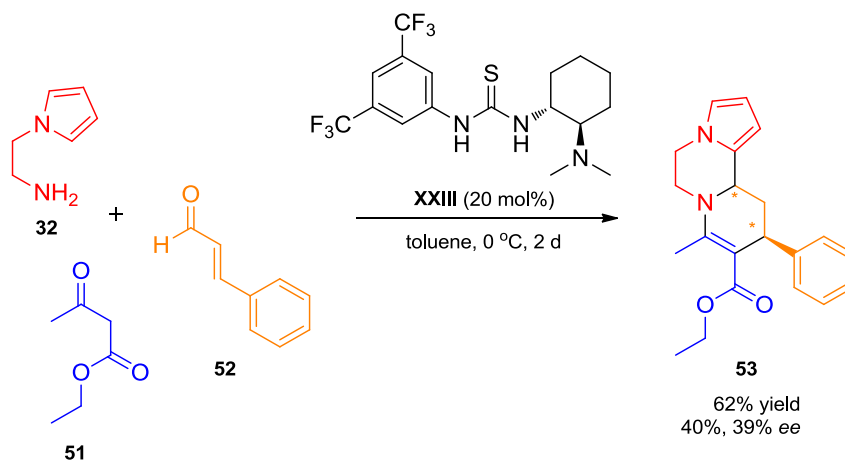
enantiomeric excesses higher than 90% were observed for both diastereomers. We continued to investigate other secondary amine catalysts **VII**, **LXIV**, **IV**, **V**. Unfortunately all of them, including proline **IV** and MacMillan catalyst **V**, delivered the expected product in very low yields and enantioselectivities, highlighting the unique behavior of catalyst **VI** in this transformation (Table III- 1, Entries 2-5).

Table III- 1 Evaluation of various chiral secondary amine catalysts.



III.1.2 BIFUNCTIONAL ORGANOCATALYST

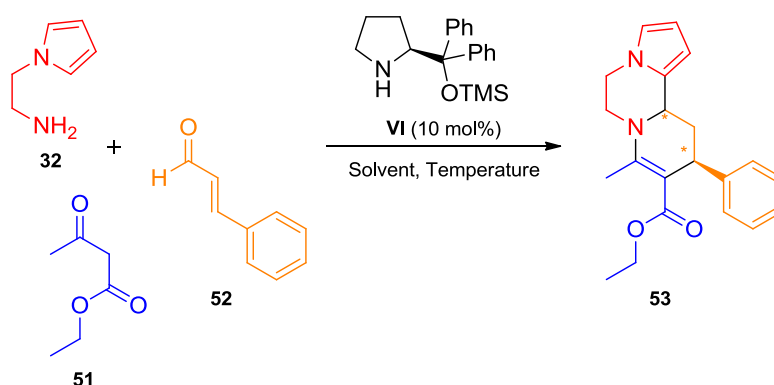
As a control reaction to verify that iminium activation was indeed the best mode of activation for this reaction, and since we knew from other studies that bifunctional thioureas could interact with α,β -unsaturated aldehyde via hydrogen bonding,^[194] we have investigated this Takemoto's catalyst **XXIII** in the model reaction (Scheme III- 5). The desired product has been obtained with a similar yield (62%), but the enantiomeric excesses were only 40% and 39% for the two diastereomers, respectively, showing that this type of catalyst is less potent in our system.



Scheme III- 5 Evaluation of Takemoto's catalyst.

III.2 OPTIMIZATION OF THE REACTION CONDITIONS

With catalyst **VI** as the best one for the title transformation, we then investigated the reaction conditions by varying the solvent, the temperature, adding additives and comparing the multicomponent reaction with the sequential one (Scheme III- 6).



Scheme III- 6 Investigation of the reaction conditions.

III.2.1 OPTIMIZATION OF THE TEMPERATURE

Variations of temperature affected both the yield and the enantiomeric excess of the product, but not the diastereoselectivity of the reaction. Variations of the reaction temperature around 0 °C (Table III- 2, Entry 3) did not lead to an improvement of the results. Not surprisingly, increasing the temperature to 10 °C or even room temperature allowed obtaining higher yields, but this positive effect was at the cost of slightly reduced enantioselectivities (Table III- 2, Entries 1 and 2). Quite unexpectedly, decreasing the reaction temperature to -10 °C severely impeded the enantioselectivity. Thus, running the reaction at 0 °C is the

optimal temperature for our system.

Table III- 2 Evaluation of various temperatures.

Entry	Temperature	Yields (%)	<i>ee</i> (%)
1	r.t.	66	89, 85
2	10 °C	81	92, 72
3	0 °C	63	93, 90
4	-10 °C	45	65, 55

III.2.2 OPTIMIZATION OF THE SOLVENT

The solvent also had a marked influence on the yield and enantiomeric excesses (Table III- 3). Compared to toluene (Table III- 3, Entry 1), CHCl₃ as the solvent improved the yield but at the cost of reduced enantioselectivity (Table III- 3, Entry 2). Both THF (Table III- 3, Entry 3) and CH₃CN (Table III- 3, Entry 4), which are more polar reaction media, reduced the enantioselectivity, whatever the yields were good or not. Fluorinated aromatic solvent such as hexafluorobenzene (Table III- 3, Entry 5)^[61] and trifluorotoluene (Table III- 3, Entry 6) were also very efficient, the latter one affording the desired product with higher yield (68%) and enantiomeric excesses (96%, 94%). Although the final Pictet-Spengler cyclization proceeds with no diastereoselectivity (~1:1), the two isomers can be separated by traditional flash chromatography, allowing for the fast generation of molecular diversity, as shown in the results of Entry 6. Both the absolute and the relative configurations of the products were determined during the study of the reaction scope. Details can be found in section III.5. In the scope study presented below, the yield of *cis*-diastereomer will always be given first, followed by the yield of *trans*-diastereomer.

Table III- 3 Evaluation of various solvents.

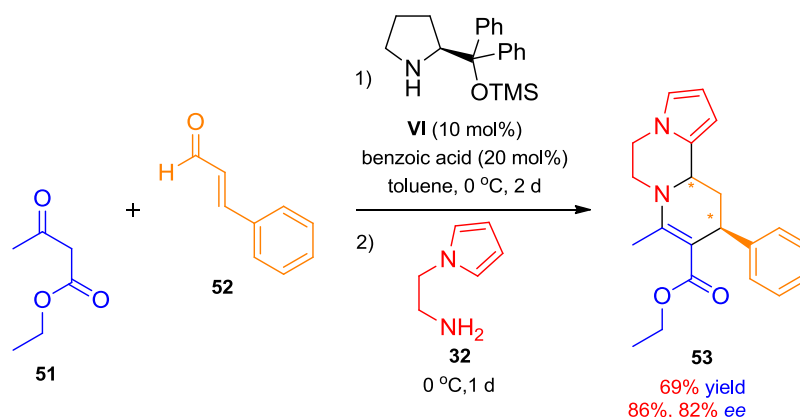
Entry	Solvent	Yields (%)	<i>ee</i> (%)
1	toluene	63	93, 90
2	CHCl ₃	77	82, 75
3	THF	impure product	87, 56
4	CH ₃ CN	impure product	83, 81
5	C ₆ F ₆	70	90, 89
6	CF₃C₆H₅	68 (35, 33)	96, 94

III.2.3 ADDITIVES AND COMPARISON WITH THE SEQUENTIAL REACTION

Quite often, various additives are used in iminium ion activation since they can accelerate the reaction, decrease the catalyst loading or increase the yield and the stereoselectivities.

Although diversified (hetero)arenes can be used in several sequences consisting of a Michael addition followed by an iminium ion trapping via Pictet-Spengler cyclization in the presence of acidic additives,^[149, 154, 155, 211-215] it is not the case for pyrroles because of their sensitivity to acids. Accordingly, in order to test and verify this explanation, we tried to use benzoic acid as co-catalyst (20 mol%) in the model reaction, which resulted in a lower yield of product (46% yield), with no improvement of the stereoselectivities.

At the same time, as the group of Zhao reported the sequential reaction with indoles (Scheme III- 3),^[154] we tried to run a sequential reaction in the presence of the acidic additive (Scheme III- 7). Firstly, acetoacetate reacted with cinnamaldehyde by using catalyst **VI** (10 mol%) and benzoic acid (20 mol%) in toluene at 0 °C for two days. Secondly, after two days, the sensitive pyrrole reactant **32** was added and the reaction mixture kept at 0 °C for an additional day. At last, the desired product was obtained with good yield (69%), but a significant erosion of the enantiomeric excess of both diastereomers was observed (down to 86% and 82%, respectively). The groups of Jørgensen^[132] and Rovis^[148] have already observed the same phenomenon in related transformations. It could be explained by a reversibility-induced racemization of the intermediate Michael adduct. *For this reason, running the reaction in a multicomponent fashion clearly appears as an efficient strategy, which can prevent the loss of optical purity of racemization-sensitive reactive intermediates.*



Scheme III- 7 Comparison with the sequential reaction.

All in all, the optimized reaction conditions were to run the MCR in the presence of the catalyst **VI** (10 mol%) in trifluorotoluene at 0 °C during 2 days.

III.3 SCOPE OF THE REACTION

Having found suitably optimized conditions, we studied the possibility of varying all three starting materials.

III.3.1 SCOPE OF β -KETOESTERS

There are two parts that can be modified in the β -ketoester: the substituent of the ester and the one of the ketone.

III.3.1.1 VARIATION OF THE ESTER SUBSTITUENT

To start, we investigated the influence of the bulkiness of the ester group. Different β -ketoesters were exposed to the standard reaction conditions in the presence of cinnamaldehyde **52** and *N*-(2-aminoethyl)pyrrole **32**. No matter whether an ethyl, methyl, isopropyl or *tert*-butyl substituent was placed on the ester, all provided the expected products **53-56** with good yields and enantiomeric excesses higher than 90% (Figure III- 2). Moreover, the two diastereomers can be conveniently separated. As it is often the case, the enantioselectivity was a little bit lower for the less bulky methyl ester, whereas it culminated at 98% for its isopropyl counterpart. Moreover, the reaction with the *tert*-butyl ketoester could also be run on a 2-mmol scale while preserving both the yield (56%: 27% + 29%) and the enantioselectivity (92%, 94%) of product **56**.

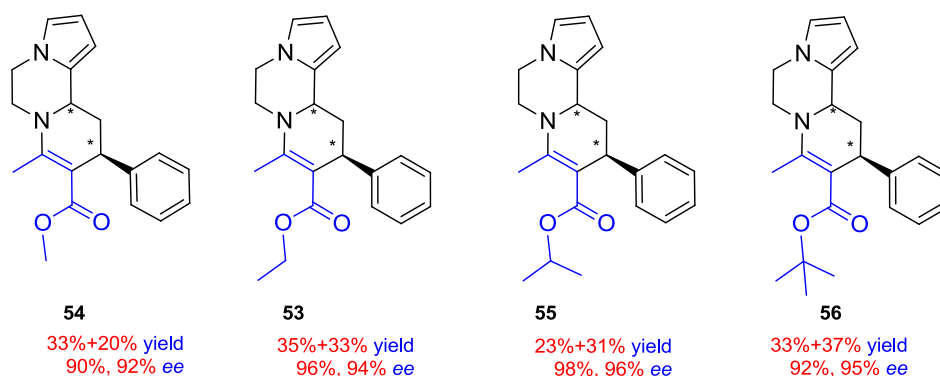


Figure III- 2 Variation of the ester substituent.

III.3.1.2 VARIATION OF THE KETONE SUBSTITUENT

The ketone substituent could also be varied, by using alkyl or aryl groups (Figure III- 3). Firstly, an ethyl chain instead of the methyl group tended to increase the yield of product **57** and the enantioselectivity remained unchanged. Secondly, with the replacement of the methyl group by an aromatic ring, the reaction proceeded in the standard reaction conditions, but with unsatisfying results. The reaction temperature had to be lowered to -10 °C to ensure a good enantioselectivity (94%, 93%), but at the cost of a lower yield (40%). Moreover, the two diastereomers of product **58**, obtained as a \sim 1.4:1 ratio, could not be separated.

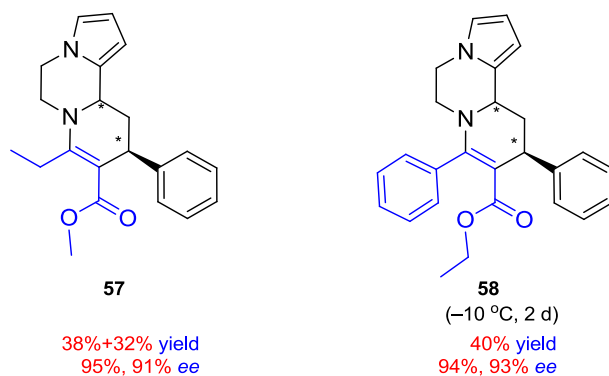
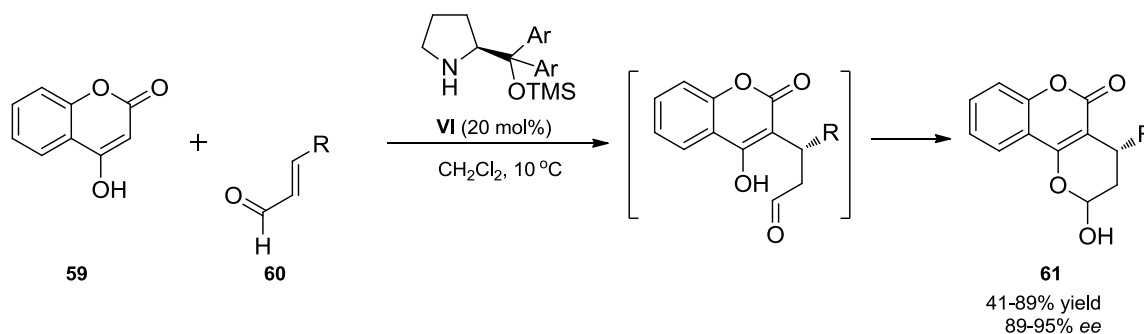


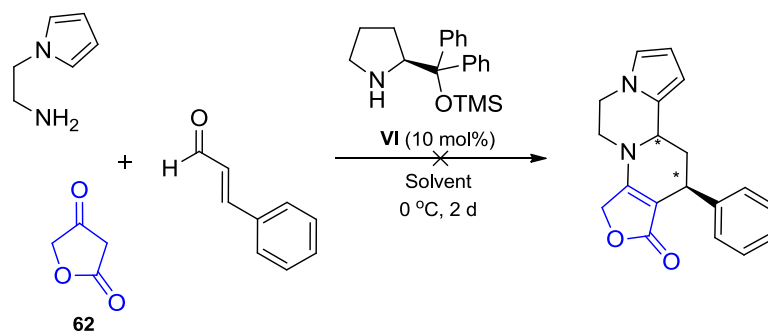
Figure III- 3 Variation of the ketone substituent.

III.3.1.3 USE OF CYCLIC β -KETOESTERS

In 2008, the group of Rueping reported the highly enantioselective Michael addition of 4-hydroxycoumarin **59** to aliphatic and aromatic α,β -unsaturated aldehydes **60**. After a subsequent cyclization the pyranocoumarins **61** were obtained with moderate to good isolated yields and high enantioselectivities (Scheme III- 8).^[216]

Scheme III- 8 The enantioselective Michael addition of 4-hydroxycoumarin to aliphatic and aromatic α,β -unsaturated aldehydes (Rueping, 2008).

Based-on these results, 4-hydroxycoumarin might be a good substrate for our three-component reaction. Unfortunately, the desired product was not obtained. Similarly, tetronic acid was also placed in the reaction conditions. Whatever trifluorotoluene, CH_2Cl_2 , CH_3CN , ethanol or THF was used as the solvent, tetronic acid could not dissolve and the reaction did not proceed. Therefore it appears that cyclic β -ketoesters **62** cannot be used directly as substrates for the 3CR in the standard reaction conditions.



Scheme III- 9 Attempts to introduce tetronic acid in the three-component synthesis of pyrrollopiperazines.

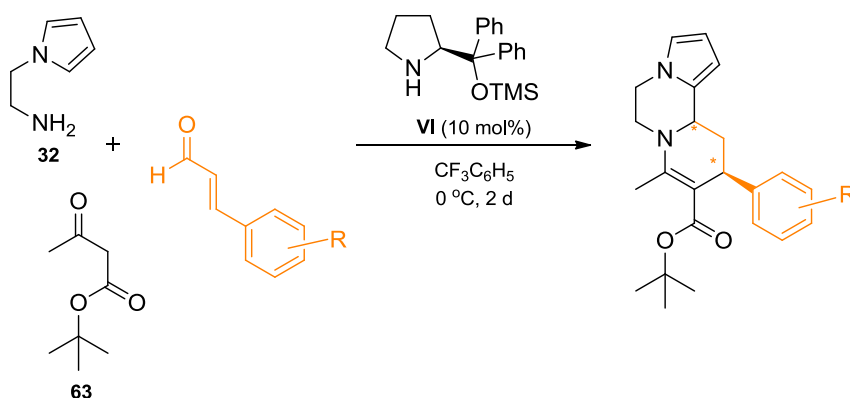
III.3.2 SCOPE OF α,β -UNSATURATED ALDEHYDES

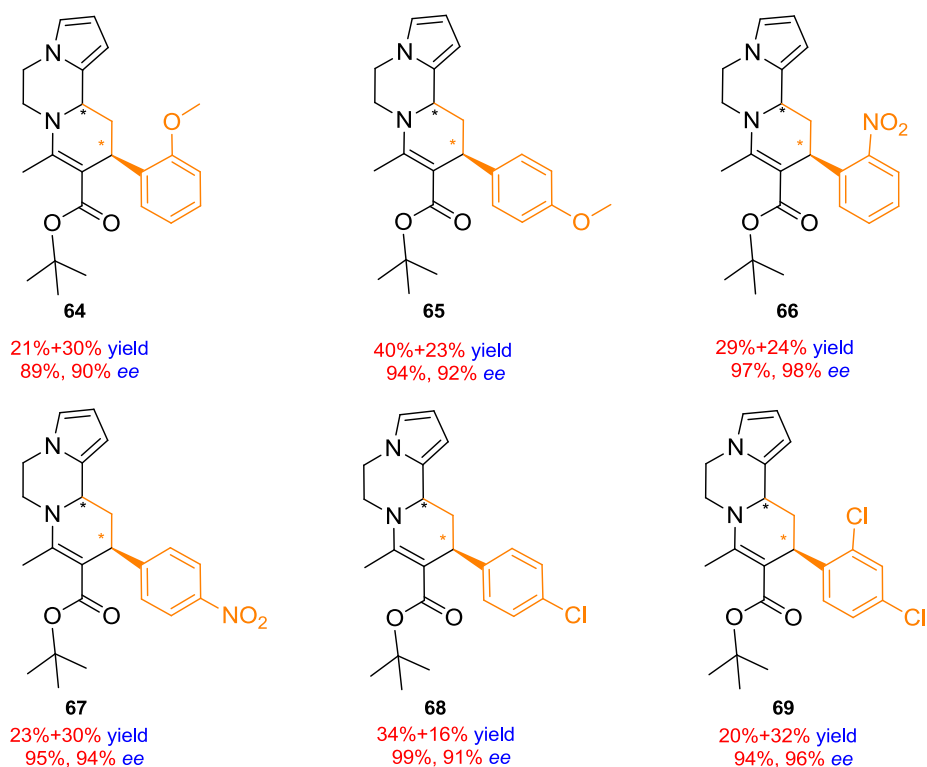
In the standard reaction conditions, *tert*-butyl acetoacetate **63**, which was selected because it afforded products that were easier to purify, and *N*-(2-aminoethyl)pyrrole **32** reacted with different α,β -unsaturated aldehydes.

III.3.2.1 β -AROMATIC ENALS

We investigated different aromatic-substituted aldehydes that provided the corresponding desired products **64-69** with reasonable yields and high enantioselectivities (Table III- 4), no matter whether they were substituted with electron-donating or electron-withdrawing groups. Especially, in the case of 4-chlorocinnamaldehyde an enantiomeric excess of 99% could be attained. On the opposite, in the case of 2-methoxycinnamaldehyde a small decrease in the enantioselectivities was observed.

Table III- 4 Scope of different aromatic-substituted enals.





III.3.2.2 β -HETEROAROMATIC ENALS

β -Heterocyclic aldehydes also participated in the transformation (Figure III- 4). In the standard reaction conditions, 3-(3-thienyl)acrolein provided product **70** with reasonable yield and excellent enantiomeric excesses. In contrast, in the case of 3-(2-furyl)acrolein, so as to obtain good results, the temperature had to be decreased to $-20\text{ }^{\circ}\text{C}$ to ensure good enantioselectivities but at the same time this modification of the reaction conditions also resulted in a lower yield of product **71**.

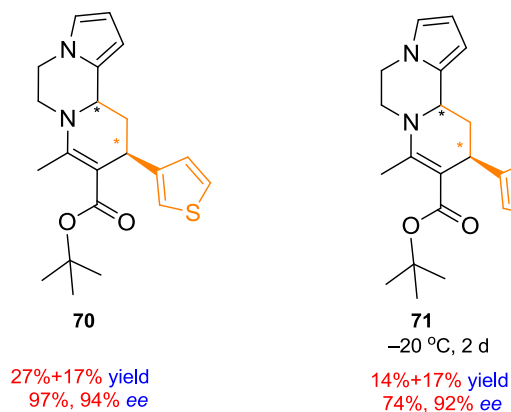


Figure III- 4 Scope of β -heteroaromatic enals.

III.3.2.3 β -ALKYL ENALS

When acrolein was involved in this transformation in toluene at room temperature for two days, the product **72** was obtained with 65% yield. However, since the organocatalyst could not control the Pictet-Spengler cyclization step, this product was racemic. With β -alkyl aldehydes, only the *cis*-diastereomer of products **73-74** could be isolated after chromatography with reduced enantioselectivities, even though both diastereomers were present in the crude reaction mixtures (Figure III- 5).

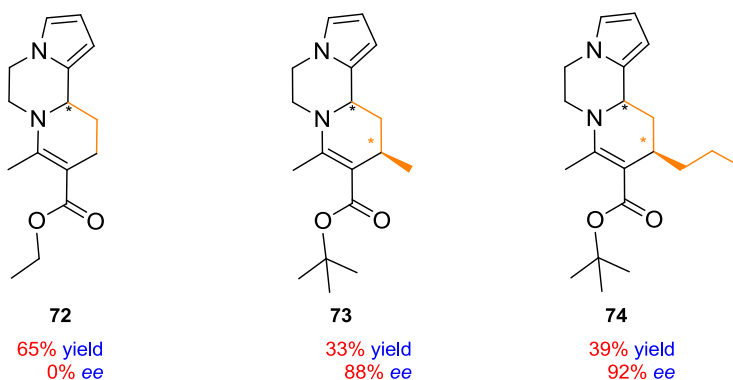
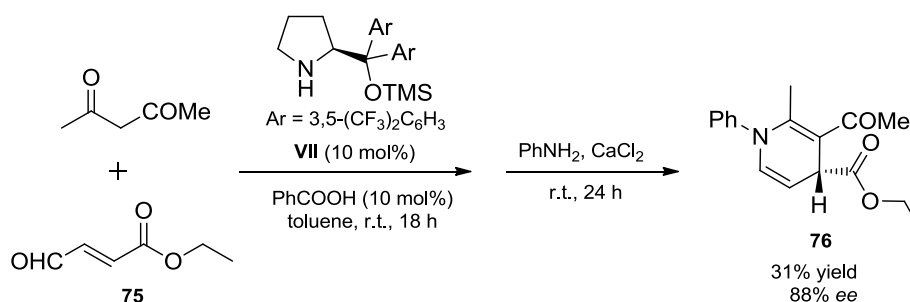


Figure III- 5 Scope of β -alkyl enals.

III.3.2.1 (*E*)-ETHYL 4-OXOBUT-2-ENOATE

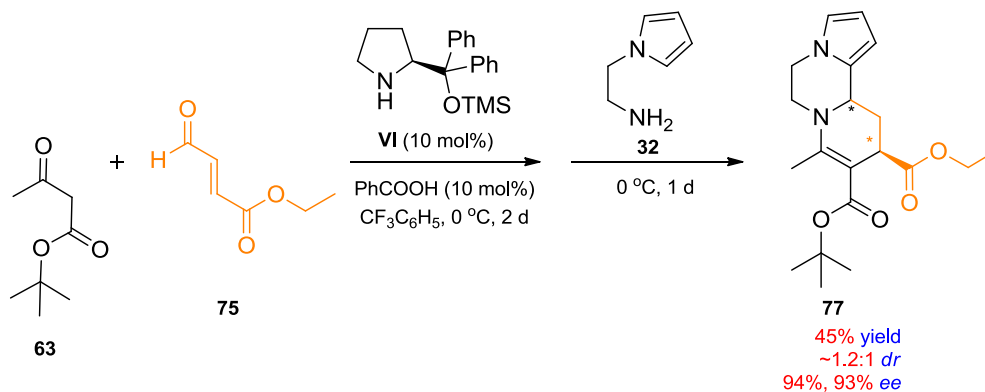
In 2008, the group of Jørgensen discovered that the one-pot reaction of (*E*)-ethyl 4-oxobut-2-enoate **75** with β -diketones and phenylamine in the presence of secondary amine catalyst **VII** at room temperature could deliver optically active polysubstituted 1,4-dihydropyridines **76** in 31% yield and with an enantiomeric excess of 88% (Scheme III-10).^[132]



Scheme III- 10 The one-pot reaction of (*E*)-ethyl 4-oxobut-2-enoate with β -ketoesters and phenylamine.

However, up to now, this enal has never been used in organocatalytic enantioselective MCRs. Thus, we attempted to combine it^[217] with the standard substrates in the presence of **VI** (10 mol%), with or without benzoic acid as co-catalyst in various solvents (CF₃C₆H₅, CH₂Cl₂, CH₃CN) at different temperatures (r.t. or 0 °C). Unfortunately, the expected product

77 was not found, probably because the high reactivity of this enal led to numerous side reactions. Then, following Jørgensen's stepwise method, the desired tricyclic pyrrolo-piperazine **77** has been obtained with 45% yield, with 94%, 93% *ee* for the two diastereomers, respectively (Scheme III- 11).



Scheme III- 11 The one-pot reaction of (*E*)-ethyl 4-oxobut-2-enoate, *tert*-butyl acetoacetate and *N*-(2-aminoethyl)pyrrole.

III.3.3 SCOPE OF *N*-(2-AMINOETHYL)PYRROLES

Finally, the third reaction partner, id est the *N*-(2-aminoethyl)pyrrole **32**, was modified, after preparation of diversely substituted starting materials. In fact, in 2008, Mayr and co-workers reported the nucleophilic reactivities of pyrrole and its derivatives. They found that alkyl groups had an enormous activating effect on the nucleophilicities of pyrroles (Figure III- 6).^[218] Thus, according to the nucleophilicities of pyrroles, various substituted pyrroles were prepared.

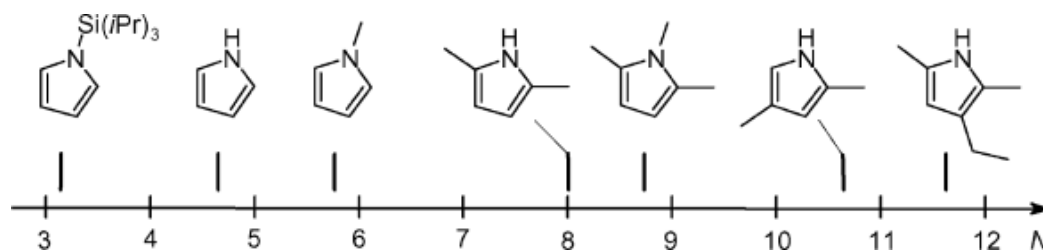
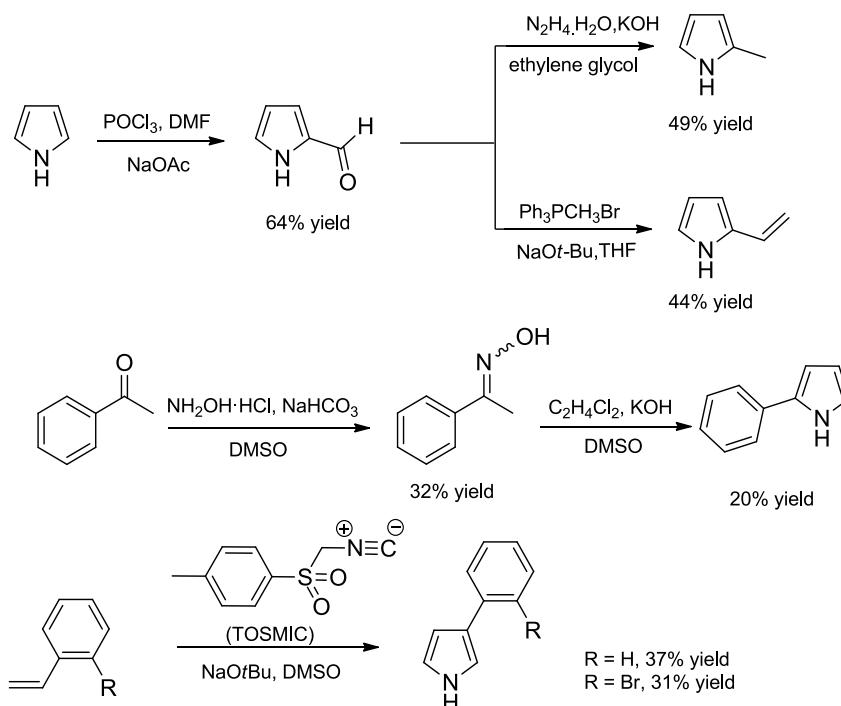


Figure III- 6 The nucleophilicity of pyrrole derivatives.

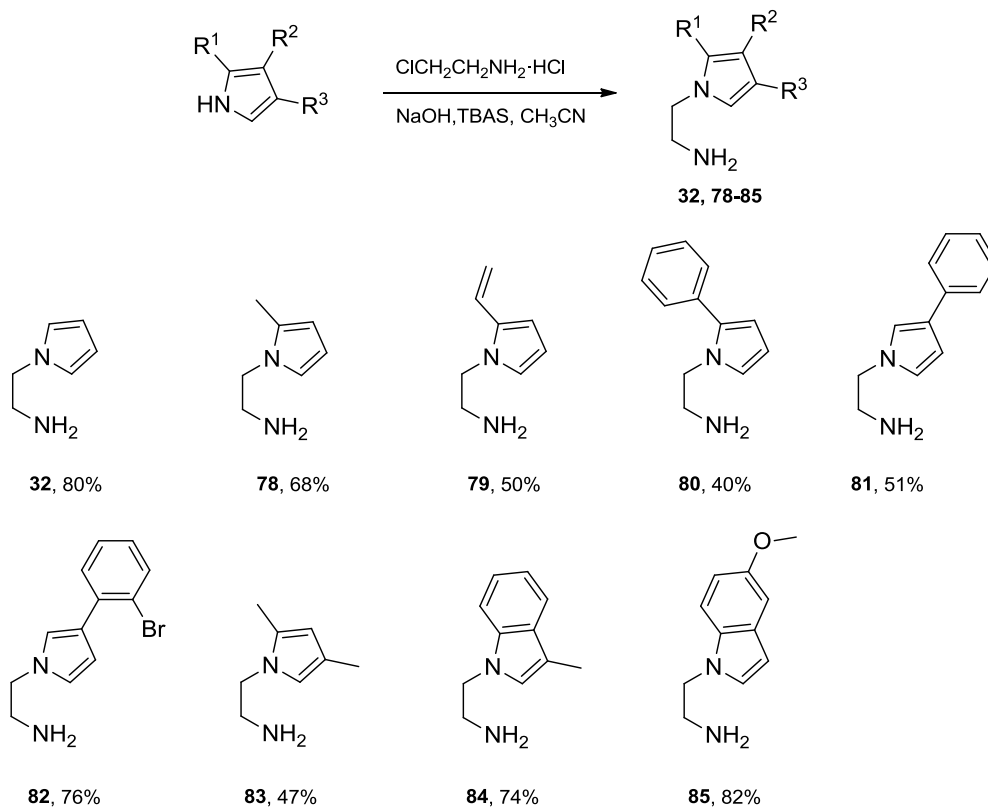
III.3.3.1 PREPARATION OF THE STARTING MATERIALS

Most of the substituted pyrroles required for this study were not commercially available. Therefore, we first needed to synthesize them by the known literature methods (Scheme III- 12).^[219-224] The yields of these syntheses have not been optimized.



Scheme III- 12 The synthesis of the substituted pyrroles.

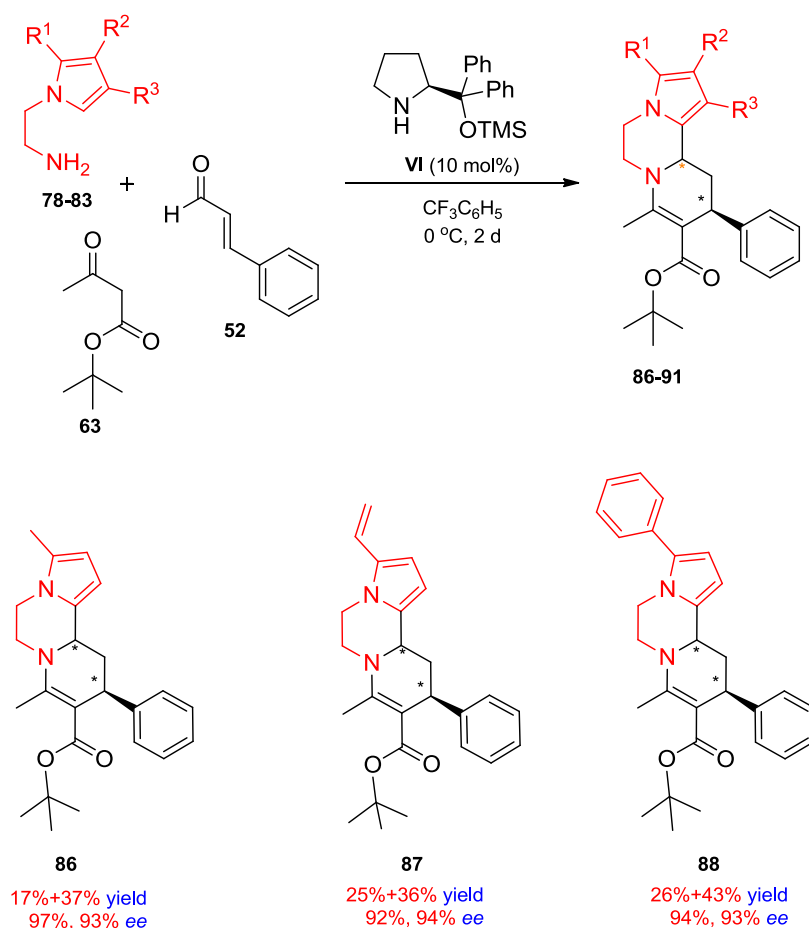
Once we had diversely substituted pyrroles in hand, they could very conveniently be alkylated with the chlorohydrate of 2-chloroethylamine in phase-transfer conditions to deliver the desired *N*-(2-aminoethyl)pyrroles **32**, **78-83** in 40-82% yields (Table III- 5).^[221, 225] *N*-substituted indoles **84-85** could be prepared by the same method.

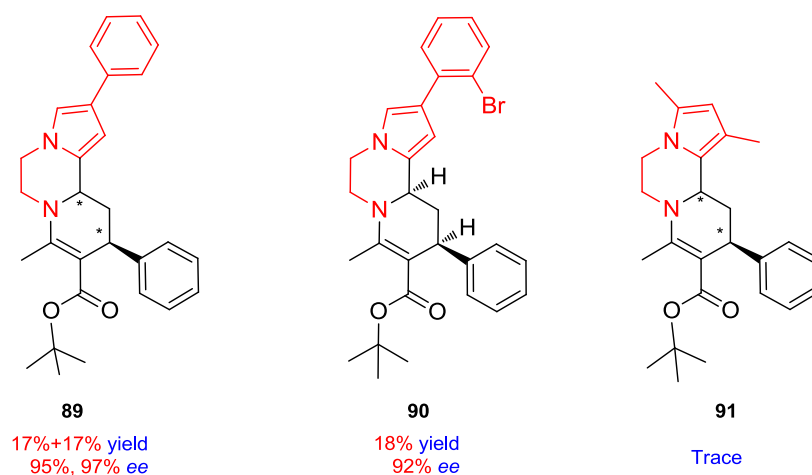
Table III- 5 Preparation of various *N*-(2-aminoethyl)pyrroles or indoles.

III.3.3.2 REACTIONS WITH THE SUBSTITUTED N-(2-AMINOETHYL)PYRROLES

No matter whether the pyrrole ring was substituted in position 2 with a methyl, a vinyl or a phenyl group, the corresponding desired compounds **86-88** were produced in the standard reaction conditions (Table III- 6). Moreover, the 3-phenyl-substituted pyrrole derivative was also accommodated and regioselectively provided the desired product **89** with excellent enantioselectivities but a lower yield. However, with the slightly electron-poor and more hindered 3-(2-bromophenyl)-substituted pyrrole derivative, only the *cis*-diastereomer of the expected product **90** was isolated with low yield. With a more electron-rich 2,4-dimethylpyrrole ring, only traces of pyrroloperazines **91** were obtained. At the same time, a large amount of the product of direct Pictet-Spengler annulation of *N*-(2-aminoethyl)pyrrole **32** with cinnamaldehyde **52** and other by-products were also obtained.^[221, 226] From this result, we can deduce that the multicomponent reaction cannot be carried out on pyrrole derivatives with nucleophilicities higher than 10 in Mayr's scale.^[218]

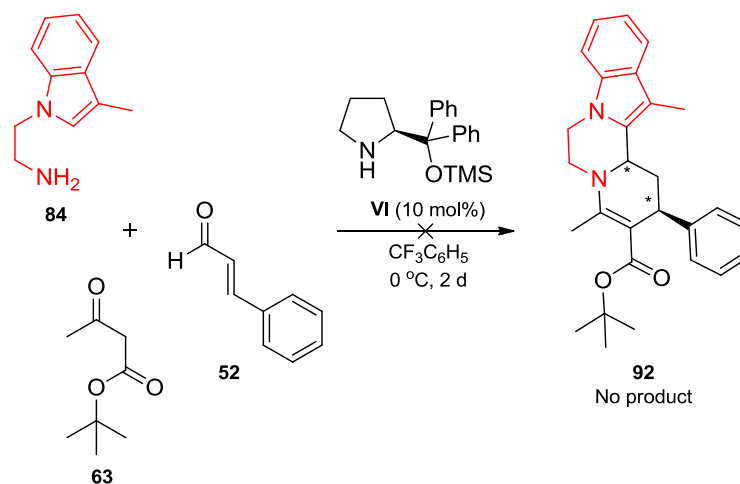
Table III- 6 Scope of pyrrole derivatives.





III.3.3.3 ATTEMPTS TO USE *N*-(2-AMINOETHYL)INDOLE DERIVATIVES

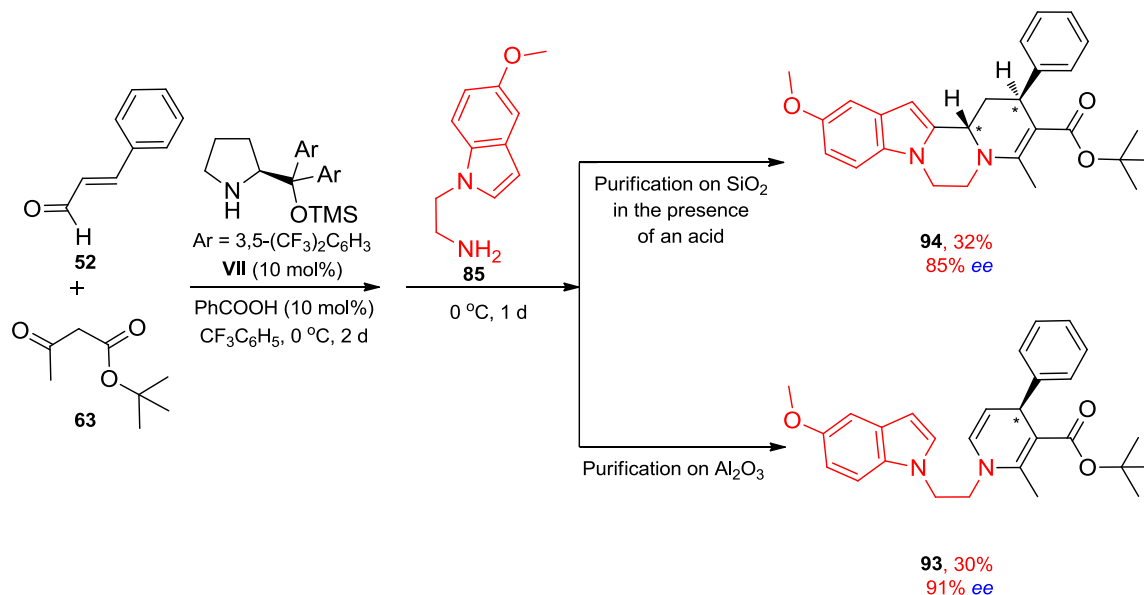
We continued by investigating *N*-(2-aminoethyl)-indole derivatives **84-85** in the present MCR, to see whether it could be extended to other heterocycles. However, *N*-(2-aminoethyl)-3-methylindole **84**, for example, did not provide any desired product **92** (Scheme III- 13).



Scheme III- 13 Attempt of MCR with *N*-(2-aminoethyl)-2-methyl-indole.

When we once again checked the table of the nucleophilicities of indoles,^[218] we realized that pyrrole and 5-methoxy-1*H*-indole have similar nucleophilicities. Therefore, *N*-(2-aminoethyl)-5-methoxyindole **85** was applied in the multicomponent reaction. It was disappointing to note that the expected fused cyclic indole derivative did not form. An attempt was therefore made in sequential one-pot conditions. Depending on the conditions of purification, the 1,4-dihydropyridine **93** or the indolopiperazine **94** have been obtained (Scheme III- 14). A purification by flash chromatography on silica gel (eluent: PE/EtOAc 4:1 and then PE/EtOAc/AcOH 4:1:0.025), provided the pure cyclized product **94** with 32% yield and 85% *ee*. On the opposite, a purification by flash column chromatography on neutral

aluminium oxide (eluent: PE/EtOAc 6:1), afforded the non-cyclized product **93** with 30% yield and 91% *ee*. Crude ^1H NMR spectra showed the presence of only **93**, indicating that the cyclization had in fact occurred during the purification in acidic conditions. This is in accordance with the literature precedents, in which the indole derivatives require the presence of an acid to promote the Pictet-Spengler cyclization.^[154]



Scheme III- 14 Three-component reaction with an electron-rich indole derivative: importance of the purification conditions.

III.4 SCOPE OF VARIOUS NUCLEOPHILES

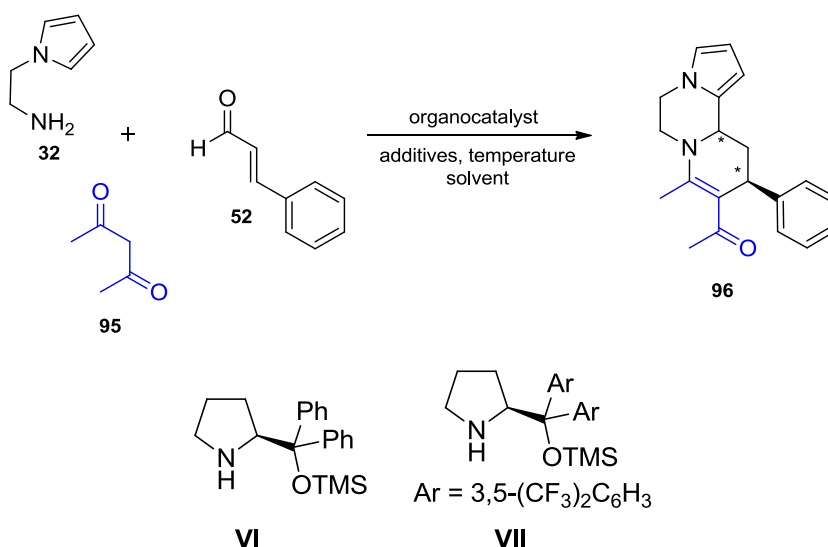
To further extend the usefulness of this new organocatalytic multicomponent reaction, various other nucleophiles were also evaluated in this transformation.

III.4.1 ACYCLIC 1,3-DIKETONES

Our initial investigations were carried out with acetylacetone **95** as the pronucleophile that was mixed with cinnamaldehyde **52** and *N*-(2-aminoethyl)pyrrole **32** (Table III- 7) by using catalyst **VI** in trifluorotoluene at $0\text{ }^\circ\text{C}$. Pleasingly, the targeted pyrroloperazine **96** was formed (Table III- 7, Entry 1), showing that the reaction can be extended to acyclic 1,3-diketones in the standard reaction conditions. However, the yield of the isolated product was lower than 30 % and it was not separated from some impurities, calling for further reoptimization. The enantiomeric excess of one diastereomer could be measured and amounted to 72%. Alternative secondary amine catalyst **VII** was used in this transformation, but the desired product was not formed (Table III- 7, Entry 2). The use of acetic acid (10 mol%) as co-catalyst improved the yields of the product, but the enantioselectivity remained low (Table III- 7, Entry 3). To continue the optimization of the reaction condition, the use of

benzoic acid (10 mol%) as co-catalyst somewhat increased the enantioselectivity (Table III- 7, Entry 4). A further improvement was achieved with benzoic acid (10 mol%) lowering the temperature from 0 °C to -10 °C (Table III- 7, Entry 5). Moreover, when increasing the quantity of benzoic acid to 20 mol%, the enantioselectivity was once again improved (Table III- 7, Entry 6), but a stoichiometric amount of additive was deleterious to the enantioselectivity (Table III- 7, Entry 7). Pleasingly, we eventually found that with the use of benzoic acid (20 mol%) in CH₂Cl₂ at -10 °C (Table III- 7, Entry 8), the desired product was obtained with good yield and excellent enantioselectivities for both isomers.

Table III- 7 The organocatalytic enantioselective MCR of acetylacetone, cinnamaldehyde and *N*-(2-aminoethyl)pyrrole.



Entry	Cat. (10mol%)	Additive (mol%)	Temperature	Solvent	Time	Yields (%)	ee (%)
1	VI	None	0 °C	CF ₃ C ₆ H ₅	48 h	< 30	72, -
2	VII	None	0 °C	CF ₃ C ₆ H ₅	48 h	None	None
3	VI	CH ₃ COOH (10 mol%)	0 °C	CF ₃ C ₆ H ₅	48 h	~ 60	64, -
4	VI	PhCOOH (10 mol%)	0 °C	CF ₃ C ₆ H ₅	48 h	~ 60	82, -
5	VI	PhCOOH (10 mol%)	-10 °C	CF ₃ C ₆ H ₅	66 h	-	86,90
6	VI	PhCOOH (20 mol%)	-10 °C	CF ₃ C ₆ H ₅	66 h	-	90,90
7	VI	PhCOOH (1 equiv.)	-10 °C	CF ₃ C ₆ H ₅	66 h	59(25,34)	89,80
8	VI	PhCOOH (20 mol%)	-10 °C	CH₂Cl₂	48 h	68(45,23)	94,91

Using these reoptimized reaction conditions (Table III- 7, Entry 8), 4-chlorocinnamaldehyde afforded product **97** in moderate yield and high enantioselectivities for both isomers (Figure III- 7). Further work will be carried out in the future to assess the generality of this reaction with linear 1,3-diketones.

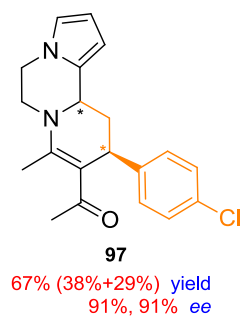
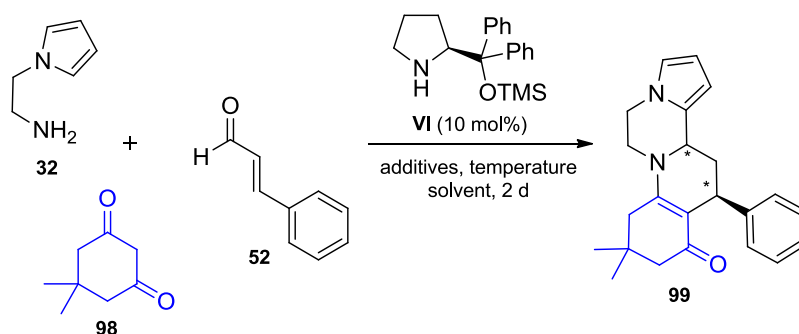


Figure III- 7 4-Chlorocinnamaldehyde as a Michael acceptor in the MCR with acetylacetone.

III.4.2 CYCLIC 1,3-DIKETONES

Having shown that acyclic 1,3-diketones **98** are effective pronucleophiles in the title MCR, we wanted to explore whether cyclic 1,3-diketones,^[155, 227] unlike cyclic 1,3-ketoesters, can also be used in this transformation (Table III- 8).

Table III- 8 The organocatalytic enantioselective MCR of dimedone, cinnamaldehyde and *N*-(2-aminoethyl)pyrrole.



Entry	Additive (mol%)	Temperature	Solvent	Yields(%)	ee(%)
1	None	0 °C	CF ₃ C ₆ H ₅	~ 51	64
2	PhCOOH (10 mol%)	0 °C	CF ₃ C ₆ H ₅	~ 32	47
3	PhCOOH (20 mol%)	0 °C	CF ₃ C ₆ H ₅	~39	36
4	PhCOOH (10 mol%)	0 °C	CH ₂ Cl ₂	~ 58	52
5	None	10 °C	CH ₂ Cl ₂	~ 58	57
6	PhCOOH (20 mol%)	10 °C	CF ₃ C ₆ H ₅	~ 46	35
7	CH ₃ COOH (20 mol%)	10 °C	CF ₃ C ₆ H ₅	~ 52	41
8	PhCOOH (10 mol%)	r.t.	CF ₃ C ₆ H ₅	~ 56	50

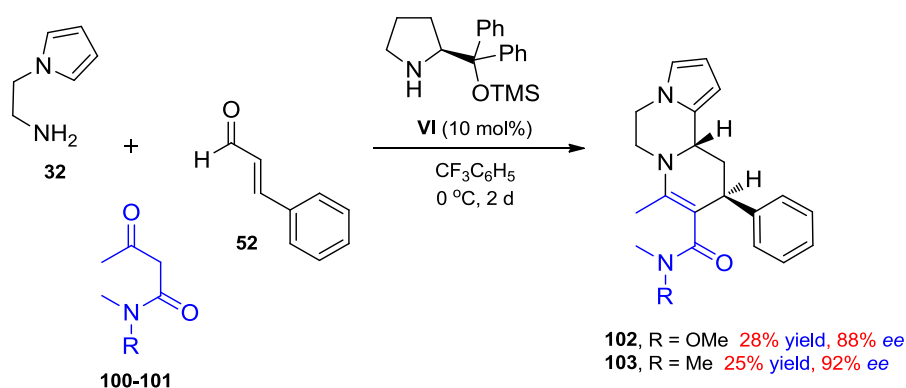
To that purpose, we attempted to examine various additives, temperatures and solvents in

the reaction with dimedone (Table III- 8). At last, the desired product **99** could be found in the crude ^1H NMR and ^{13}C NMR spectra. Unfortunately, pure products could not be obtained due to the presence of some impurities eluting together with them in the process of purification. Moreover, the enantioselectivities were not satisfactory (around 50% *ee*), even when changing the reaction conditions. At the current stage of our research, cyclic 1,3-diketones are therefore not suitable pronucleophiles for this transformation.

III.4.3 β -KETOAMIDES

In the bibliographic part, we have seen that β -ketoamides as new pronucleophiles have been used in enantioselective Michael additions in the presence of various Michael acceptors (Scheme I- 23).^[168, 228] Up to now, there is only one example reporting the use of β -ketoamides in an organocatalytic MCR, namely the enantioselective synthesis of 2,6-DABCOs (Scheme I- 75).^[194]

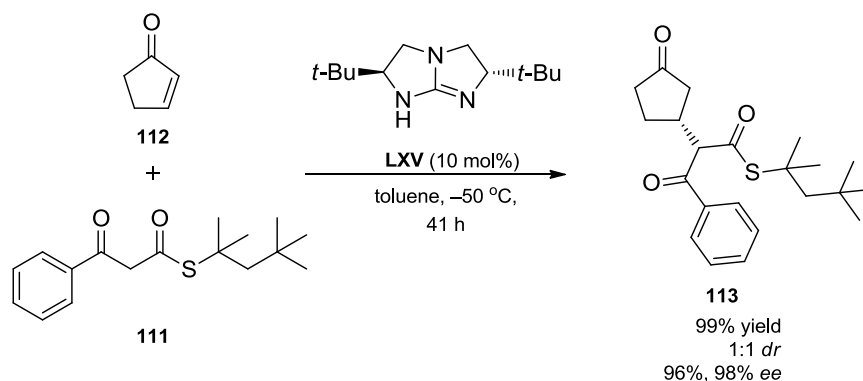
Weinreb amides have been shown to act as robust synthetic equivalents for aldehydes and an excellent acylating agent for organolithium or organomagnesium reagents.^[229, 230] Hence, we envisaged that β -ketoamide **100** including a Weinreb moiety could be an interesting candidate for the multicomponent synthesis of pyrrollopiperazines. Therefore, it was placed in the standard reaction conditions, together with cinnamaldehyde **52** and *N*-(2-aminoethyl)pyrrole **32**, secondary amine catalyst **VI** in trifluorotoluene at 0 °C (Scheme III- 15). The expected product **102** could be identified in the crude ^1H NMR and ^{13}C NMR spectra. However, the same problem arose as with cyclic 1,3-diketones: the purification was not possible by traditional flash chromatography. Only *trans* diastereomer of the product **102** could be obtained pure, with 28% yield and 88% *ee*, while the other one always stayed with some impurities. Next, the corresponding tertiary β -ketoamide **101** has also been employed in this transformation, but the same problems of purification were encountered. Only *trans* diastereomer of **103** was obtained pure with 25% isolated yield and 92% *ee*.



Scheme III- 15 The organocatalytic enantioselective MCR of β -ketoamides, cinnamaldehyde and *N*-(2-aminoethyl)pyrrole.

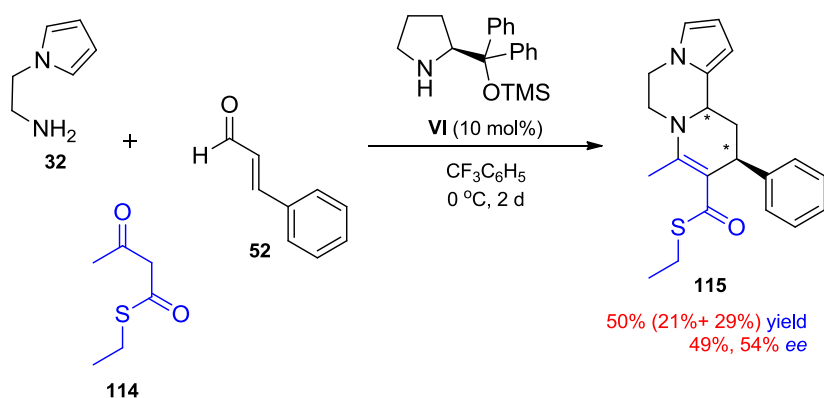
III.4.4 β -KETOTHIOESTERS

In 2007, Tan and co-workers reported that the enantioselective Michael addition of β -ketothioesters **111** with cyclic enones **112** can be performed using chiral bicyclic guanidine **LXV** (Scheme III- 16).^[231] The desired products **113** were obtained with high yields (99%) and enantiomeric excesses (96%, 98%), but as a 1:1 mixture of diastereomers. Shortly after, the group of Rovis also investigated β -ketothioesters in their domino reaction under the multicatalytic secondary amine/*N*-heterocyclic carbene combination (Scheme I- 51). However, the diastereoselectivity was also not very satisfactory (around 3.5:1 *dr*).



Scheme III- 16 The enantioselective Michael addition of β -ketothioesters with cyclic enones (Tan, 2007).

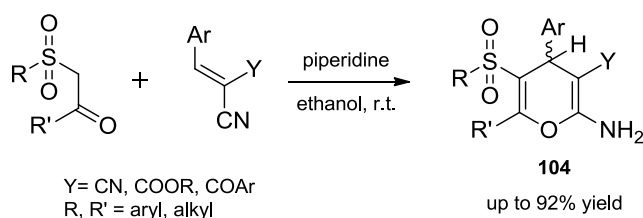
In line of these results, we wanted to try the MCR combining *S*-ethyl acetothioacetate **114** with cinnamaldehyde **52** and *N*-(2-aminoethyl)pyrrole **32** in the presence of catalyst **VI** in trifluorotoluene at 0 °C (Scheme III- 17). Unfortunately, even though the expected product **115** has been obtained with a reasonable yield as two diastereomers, the enantioselectivity of this reaction was low. With *S*-phenyl acetothioacetate as the nucleophile, the desired product did not form.



Scheme III- 17 The organocatalytic enantioselective MCR of *S*-ethyl acetothioacetate, cinnamaldehyde and *N*-(2-aminoethyl)pyrrole.

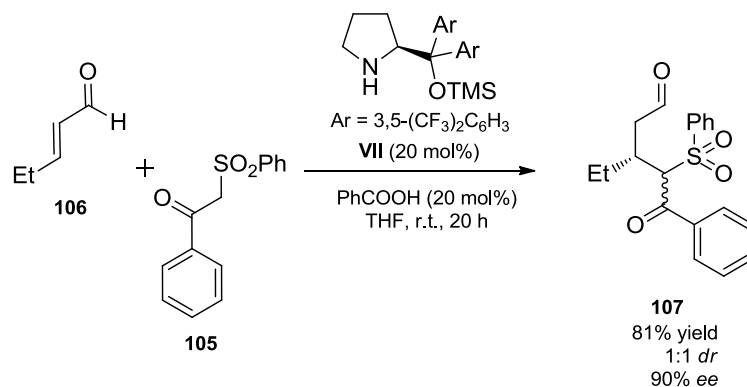
III.4.5 β -KETOSULFONES

In 1997, Marco reported for the first time the Michael addition of β -ketosulfones to highly activated Michael acceptors by using piperidine in ethanol at room temperature, providing the desired product **104** with moderate to good yields (Scheme III- 18).^[232] Because β -ketosulfones present two versatile functions (ketone and sulfone) in the same structure, they have recently been used in some interesting nucleophilic addition reactions.^[233-239]

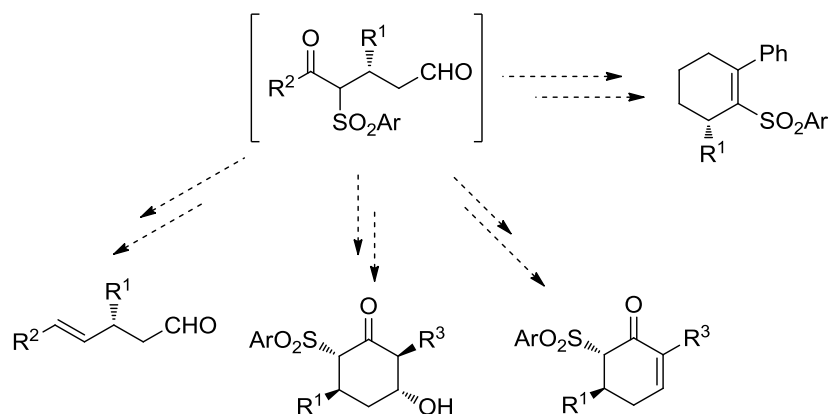


Scheme III- 18 The Michael addition of β -ketosulfones to highly activated Michael acceptors (Marco, 1997).

Especially, in 2010, Alemán and co-workers investigated the organocatalytic Michael addition of β -ketosulfones to α,β -unsaturated aldehydes by using phenylsulfonylacetophenone **105** and 2-pentenal **106** as the starting materials in different reaction conditions.^[237] At last, they found that the reaction proceeded in the presence of aminocatalyst **VII** (20 mol%) and benzoic acid (20 mol%) as co-catalyst in THF at room temperature (Scheme III- 19). After 20 h, the desired product **107** has been obtained with 81% isolated yield and 90% *ee*, but without diastereoselectivity. Moreover, the author disclosed multiple transformations of **107** into different valuable products by one-pot or tandem reactions (Scheme III- 20).



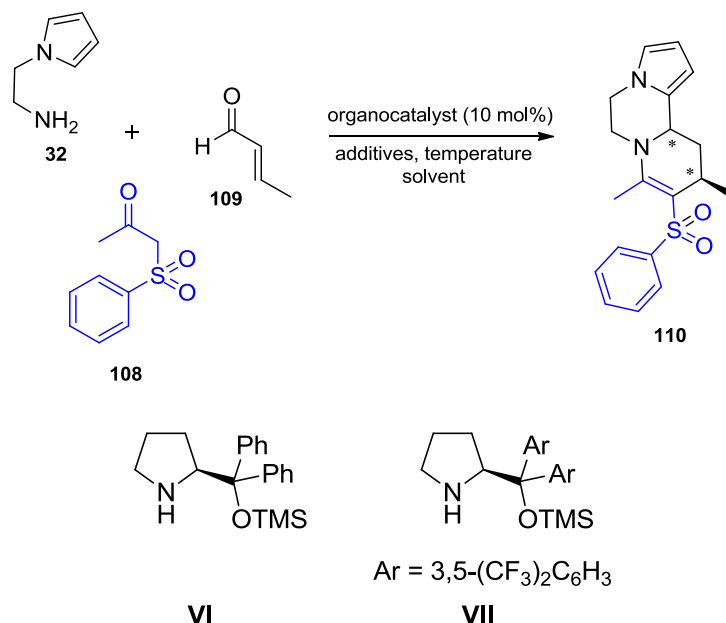
Scheme III- 19 The Michael addition of β -ketosulfones to α,β -unsaturated aldehydes (Alemán, 2010).



Scheme III- 20 Transformations of the primary adducts into different products by one-pot or tandem reactions.

Shortly after, Enders and co-workers reported the synthesis of polyfunctionalized cyclopentanones starting from β -ketosulfones and enals through a Michael/cross-acyloin cascade reaction by using dual secondary amine/*N*-heterocyclic carbene catalysis.^[238] Based on these precedents, we wanted to study the possibility of having a β -ketosulfone **108** participating in our MCR, in combination with crotonaldehyde **109** and *N*-(2-aminoethyl)pyrrole **32** (Table III- 9).

Inspired by Aléman reaction conditions,^[237] we tried to investigate this reaction in the presence of catalyst **VI** in trifluorotoluene, but at r.t. (Table III- 9, Entry 1). After 48 h, we were glad that the expected product **110** was formed with a reasonable isolated yield (~45%) and encouraging enantiomeric excesses (77% and 76%). Because the product was not easily separated by traditional flash chromatography, impurities accounting for less than 10% in ¹H NMR remained with the product. We hypothesized that changing the reaction conditions might reduce the formation of these impurities and help to provide the pure desired product. Consequently, we continued the optimization of the reaction conditions. Another secondary amine catalyst **VII** was used in replacement of catalyst **VI**. Unfortunately, both the yield and enantioselectivities were decreased (Table III- 9, Entry 2). In an attempt to improve the activation, other solvents (THF and CHCl₃) were evaluated in the model reaction (Table III- 9, Entries 3 and 5), providing slightly improved results. On the contrary, the use of benzoic acid as co-catalyst did not improve the results (Table III- 9, Entry 4 and Entry 7). However, decreasing the temperature to 0 °C and prolonged reaction time in CHCl₃ or trifluorotoluene provided better results (Table III- 9, Entry 6 and Entry 8). Unfortunately, it was regrettable that pure expected product **110** could not be obtained. In addition to this, when we tried cinnamaldehyde in this transformation, no expected product was formed.

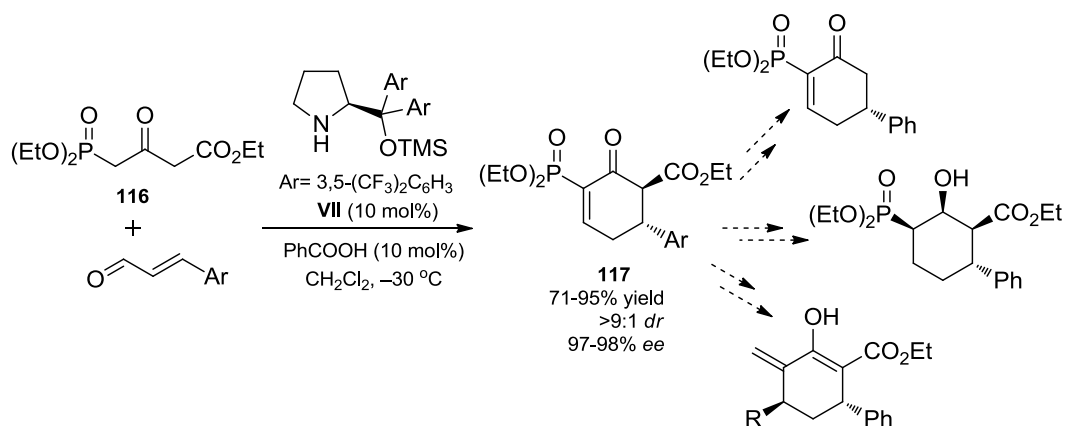
Table III- 9 The organocatalytic enantioselective MCR of a β -ketosulfones, crotonaldehyde and *N*-(2-aminoethyl)pyrrole.

Entry	Cat.	Additives (mol%)	Temperature	Solvent	Times	Yields (%)	<i>ee</i> (%)
1	VI	None	r.t.	CF ₃ C ₆ H ₅	48 h	~ 45	77, 76
2	VII	None	r.t.	CF ₃ C ₆ H ₅	48 h	~ 30	38, 33
3	VI	None	r.t.	THF	48 h	~ 51	60, 60
4	VI	PhCOOH (20 mol%)	r.t.	THF	48 h	~ 55	60, 61
5	VI	None	r.t.	CHCl ₃	48 h	~ 61	74, 71
6	VI	None	0 °C	CHCl ₃	96 h	~ 60	77, 75
7	VI	PhCOOH (20 mol%)	0 °C	CHCl ₃	96 h	~ 63 (36, 27)	68, 69
8	VI	None	0 °C	CF ₃ C ₆ H ₅	96 h	~ 53 (31, 22)	89, 85

III.4.6 β -KETOPHOSPHONATES

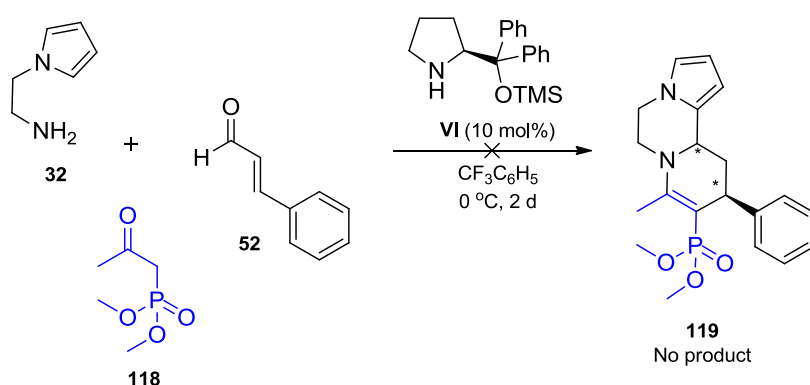
Until now, organocatalytic conjugate additions using β -ketophosphonates as Michael donors have rarely been studied. In 2007, the group of Delarue-Cochin first realized that the enantioselective Michael reaction between chiral β -enamino phosphonates and various electrophilic alkenes, by using (*S*)-1-phenylethylamine as the catalyst, could provide α,α -disubstituted β -ketophosphonates in good yields and with moderate enantioselectivities.^[240] In 2009, Jørgensen and co-workers envisioned the first organocatalytic domino Michael-Knoevenagel condensation reaction for the synthesis of 3-diethoxyphosphoryl-2-oxocyclohex-3-enecarboxylates **117** (Scheme III- 21).^[241] The reaction involved the Michael addition of ethyl 4-diethoxyphosphoryl-3-oxobutanoate **116** to α,β -unsaturated aldehydes by using iminium activation, followed by a Knoevenagel

condensation to deliver the target compounds **117**. The author argued that this class of phosphonates was especially interesting due to their potential synthetic utility to reach higher molecular complexity. Moreover, other groups disclosed that β -ketophosphonates were molecules of biological importance. Based on this concept, the group of Zhou reported the first organocatalytic Michael addition of simple β -ketophosphonates to nitroolefins in the presence of a bifunctional chiral thiourea catalyst, which provided valuable α -substituted β -ketophosphonates in good yields and enantioselectivities.^[242]



Scheme III- 21 The first organocatalytic domino reaction including ethyl β -ketophosphonates (Jørgensen, 2009).

Therefore, a β -ketophosphonate **118** has been used in our MCR together with cinnamaldehyde **52** and *N*-(2-aminoethyl)pyrrole **32** in the standard reaction conditions. Disappointingly, the expected product **119** could not be identified in the crude reaction mixture (Scheme III- 22).

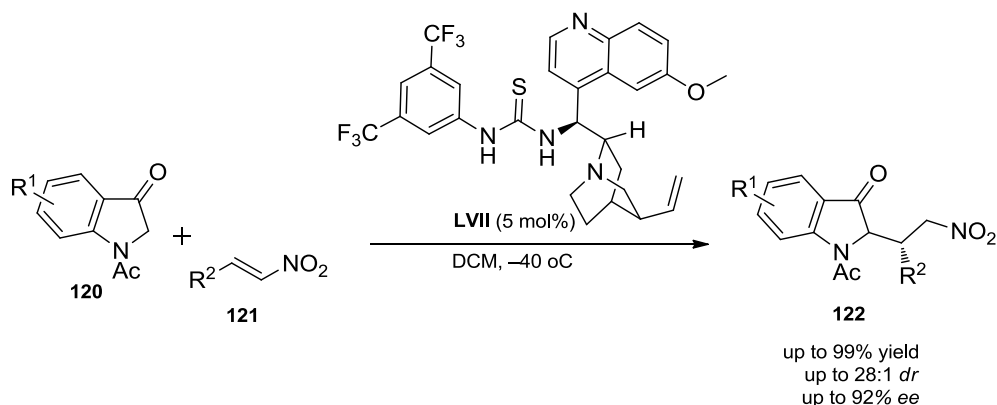


Scheme III- 22 The organocatalytic enantioselective MCR of a β -ketophosphonates, cinnamaldehyde and *N*-(2-aminoethyl)pyrrole.

III.4.7 1-ACETYLINDOLIN-3-ONES

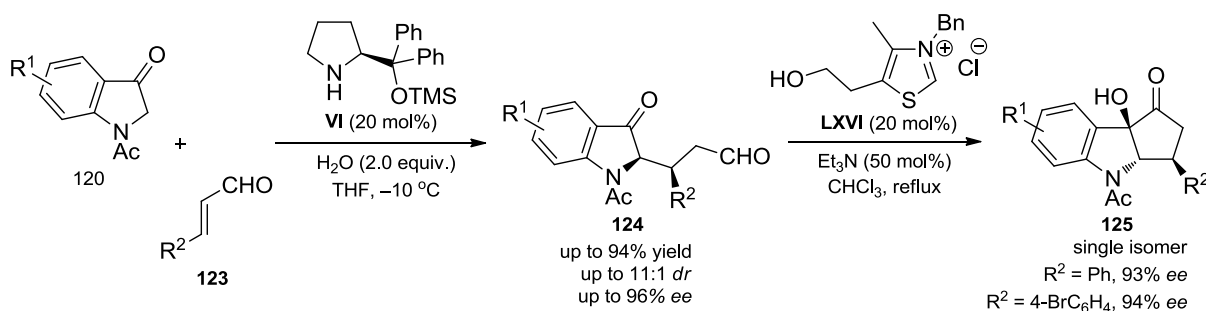
Substituted indolin-3-ones have frequently been used in the synthesis of pharmaceutical compounds and biologically active natural products in recent years.^[243-248] Therefore,

substituted indolin-3-ones represent a class of important building blocks for indole-related compounds. However, up to now, only three examples of the enantioselective synthesis of indolin-3-ones derivatives have been reported. In 2011, the group of Xu first disclosed the enantioselective Michael addition of 1-acetylindolin-3-ones **120** to β -nitrostyrenes **121** by using a bifunctional thioureas catalyst **LVII** (Scheme III- 23).^[249] The Michael adducts **122** were obtained with excellent yields (up to 99%) and good stereoselectivities (up to 28:1 *dr* and 92% *ee*).



Scheme III- 23 The enantioselective Michael addition of 1-acetylindolin-3-ones to β -nitrostyrenes (Xu, 2011).

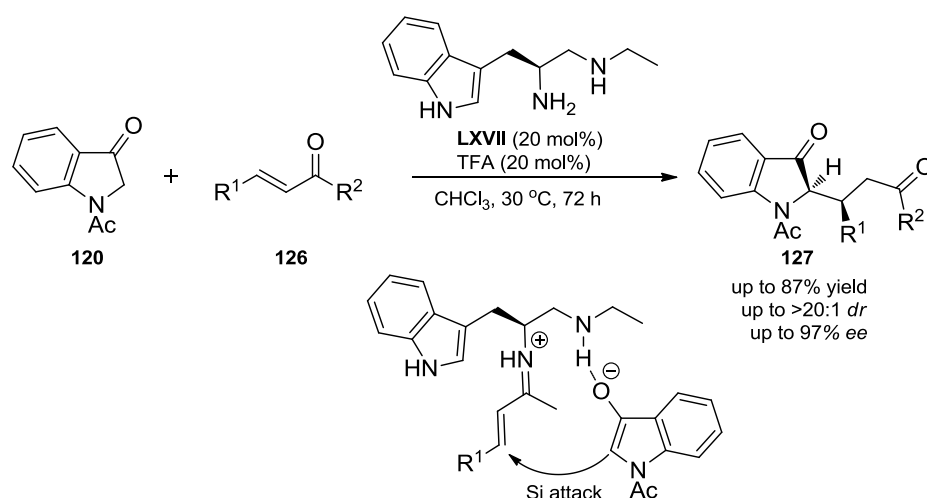
In the same time, the same group demonstrated that the secondary amine catalyst **VI** is efficient for the enantioselective Michael addition of 1-acetylindolin-3-ones **120** to α,β -unsaturated aldehydes **123** (Scheme III- 24), providing the 2-substituted indolin-3-one derivatives **124** in high yields (up to 94%) with good stereoselectivities (up to 11:1 *dr* and 96% *ee*).^[250] Moreover, these 2-substituted indolin-3-one derivatives could be easily transformed in the presence of a *N*-heterocyclic carbene catalyst **LXVI** into substituted cyclopentyl[*b*]indolines **125** containing a bicyclic tertiary alcohol, which might become building blocks for the total synthesis of indole-related natural products.



Scheme III- 24 The enantioselective Michael addition of 1-acetylindolin-3-ones to α,β -unsaturated aldehydes (Xu, 2011).

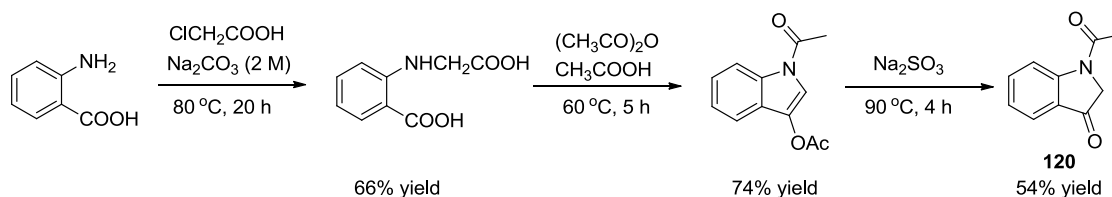
In the same year, the group of Wang designed a new primary-secondary diamine catalyst **LXVII** for the enantioselective preparation of 2-substituted indolin-3-one derivatives **127** starting from 1-acetylindolin-3-ones **120** and various enones **126**, which gave the corresponding Michael adducts in good yields, moderate to high diastereoselectivities, and

excellent enantioselectivities (Scheme III- 25).^[251] Moreover, the authors also proposed a transition state where the catalyst **LXVII** could interact with the substrate to form both the iminium ion and an anion stabilized by hydrogen bonding.



Scheme III- 25 The enantioselective Michael addition of 1-acetylimidol-3-ones and various enones, with the proposed transition state (Wang, 2011).

New synthetic approaches towards enantiopure products including functionalized indole moieties being of high interest, we tried to investigate the behavior of 1-acetylimidol-3-ones **120** that can be conveniently prepared in three steps from anthranilic acid (Scheme III- 26)^[246, 252] in our MCR in combination with cinnamaldehyde **52** and *N*-(2-aminoethyl)pyrrole **32** in the presence of the secondary amine catalyst **VI** (Table III- 10). It should be pointed out that the formation of an enamine on the ketone of 1-acetylimidol-3-one might be a favored process as it would result in the aromatization of the five-membered ring to deliver an indole motif.

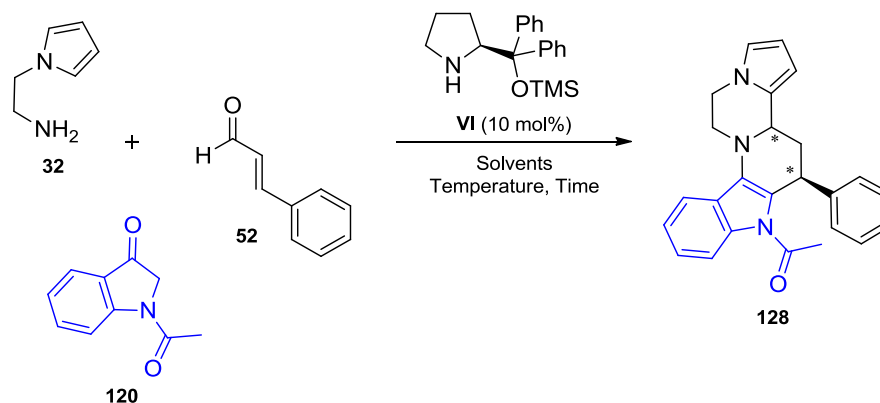


Scheme III- 26 The synthesis of 1-acetylimidol-3-ones according to the literature.

We initially examined this MCR by using **VI** (10 mol%) in trifluorotoluene at 0 °C during two days (Table III- 10, Entry 1). Pleasingly, the desired product was obtained with about 69% yield and 80% *ee* for both diastereomers (~1.6:1 *dr*) which could unfortunately not be separated by traditional flash chromatography. We tried to change the solvent from trifluorotoluene to CH₂Cl₂, THF, THF/H₂O (20:1) and CF₃CH₂OH respectively. An improvement was achieved in CH₂Cl₂ (68% yield, ~1.5:1 *dr* and 88%, 87% *ee*) (Table III- 10, Entry 2), whereas other solvents resulted in lower yields and enantioselectivities (Table III- 10, Entries 3-5). Decreasing the temperature to -10 °C and extending the reaction time to 3 days led to **128** in 32% yield but only a minor increase of enantioselectivities (Table III- 10, Entry 6). Under these reoptimized reaction conditions, 2-oxindoles^[253] and *Boc*-protected

2-oxindole^[254] have been used in this transformation. Unfortunately, the expected products were not obtained.

Table III- 10 The organocatalytic enantioselective MCR of 1-acetylindolin-3-one, cinnamaldehyde and *N*-(2-aminoethyl)pyrrole.



Entry	Temperature	Solvent	Times	Yields(%)	<i>ee</i> (%)
1	0 °C	CF ₃ C ₆ H ₅	2 d	~ 69	80,80
2	0 °C	CH ₂ Cl ₂	2 d	68	88,87
3	0 °C	THF	2 d	~38	74,84
4	0 °C	THF/H ₂ O (20:1)	2 d	~30	59,67
5	0 °C	CF ₃ CH ₂ OH	2 d	~21	8, 11
6	-10 °C	CH ₂ Cl ₂	3 d	~32	89,92

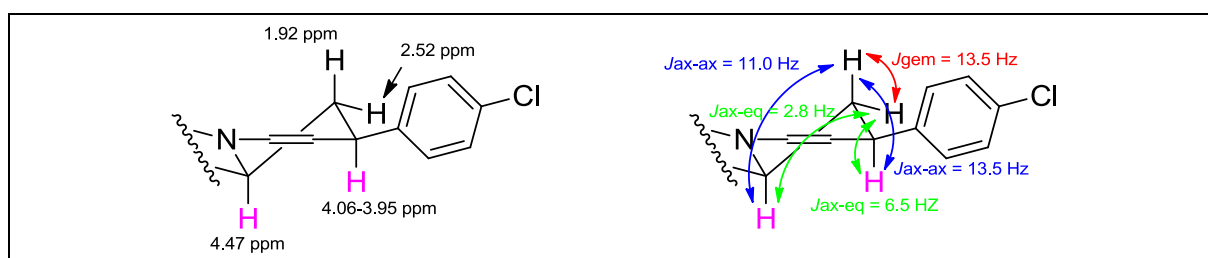
III.5 STUDY OF THE ABSOLUTE AND RELATIVE CONFIGURATIONS

The absolute configurations of the products were attributed by analogy with related organocatalytic Michael additions:^[132] with the use of catalyst VI, the Michael addition delivers the product with a (*S*)-configuration.

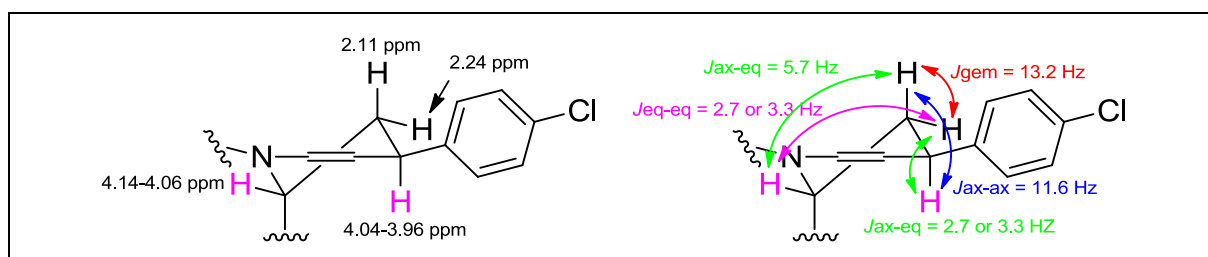
The relative configurations of the products were assigned by the analysis of the coupling constants in ¹H NMR (the study below is given on compound 56). At first, all the signals of the protons and carbon atoms of both diastereomers of product 56 were attributed thanks to 2D NMR studies (COSY, HMQC and HMBC). On the schemes below that represent the coupling constants between the protons of the tetrahydropyridine ring, the methyl- and ester substituents on the alkene are omitted for clarity. The tetrahydropyridine ring is likely to adopt a half-chair conformation with the bulky aromatic substituent in pseudo-equatorial position. By the application of Karplus equation:

- the ²*J*_{gem} between two geminal protons will have values between 11 and 14 Hz.
- the ³*J*_{ax-ax} between two axial protons on adjacent carbons will have values between 11 and 14 Hz.
- the ³*J*_{ax-eq} and ³*J*_{eq-eq} between two protons on adjacent carbons that are not both in axial positions will have values between 2 and 7 Hz.

cis-diastereomer: for the *cis*-diastereomer, the axial proton of the methylene group (at 1.92 ppm) shows characteristic couplings with three coupling constants between 11 and 13.5 Hz: one with the geminal proton and two with protons on the adjacent carbons, with which it is positioned in a *trans*-1,2-diaxial relationship. As a consequence, the two protons of the methine groups (at 4.06-3.95 ppm and 4.47 ppm) are positioned in a *cis*-1,3-diaxial relationship.



trans-diastereomer: for the *trans*-diastereomer, the axial proton of the methylene group (at 2.11 ppm) has only one proton on the adjacent carbons, with which it is positioned in a *trans*-1,2-diaxial relationship. As a consequence, the two protons of the methine groups (at 4.04-3.96 ppm and 4.14-4.06 ppm) are positioned in a *trans*-1,3-axial-equatorial relationship.

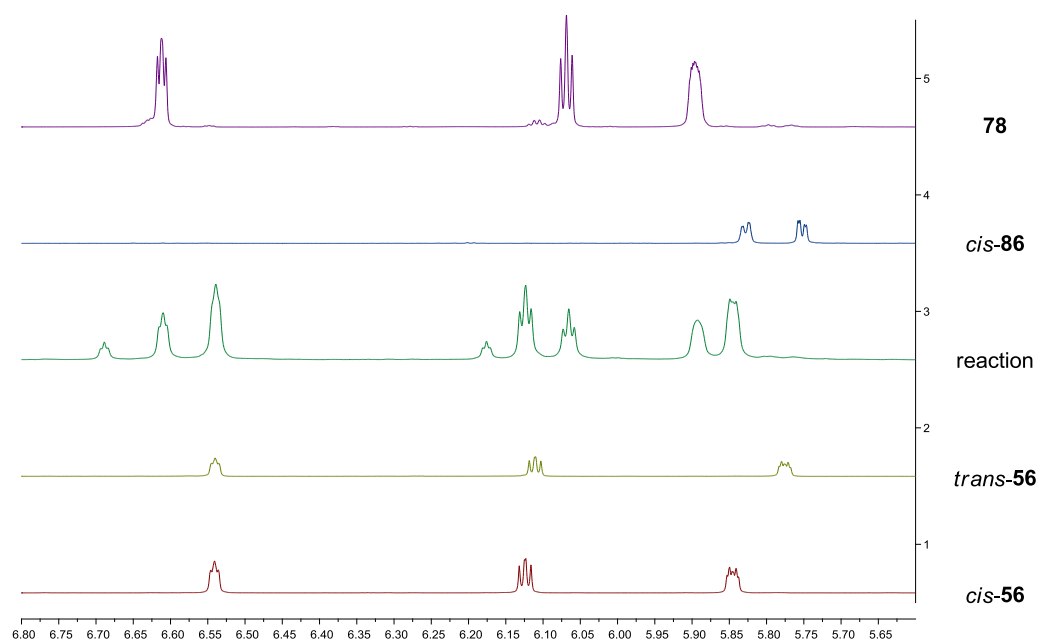
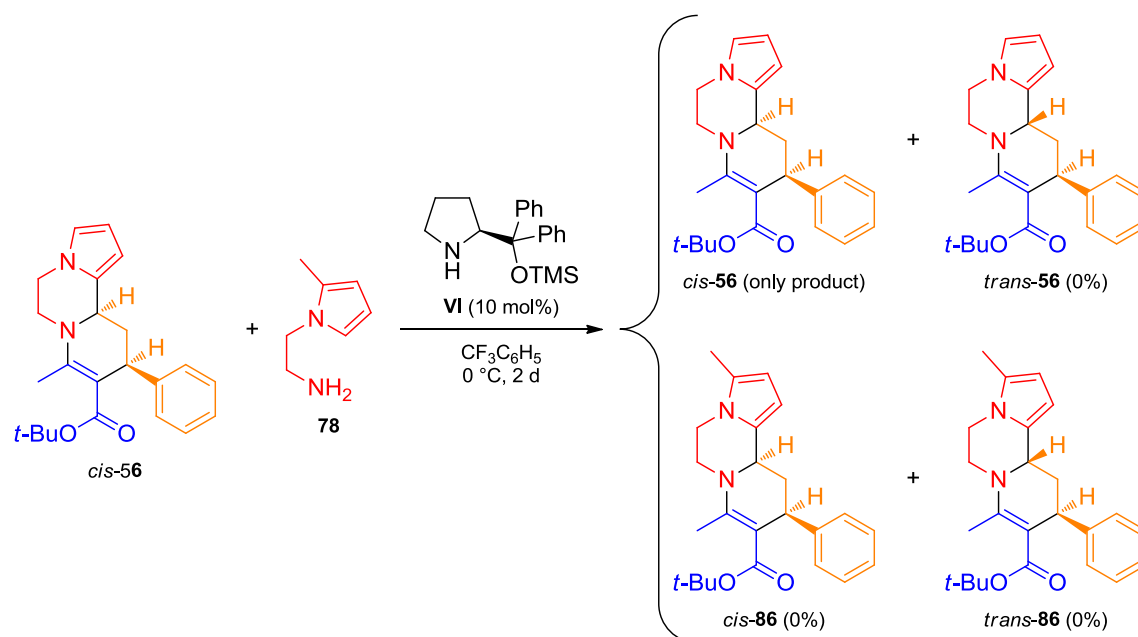


III.6 CROSSOVER STUDIES

A crossover reaction was conducted to check the reversibility of the reaction, especially the final Pictet-Spengler cyclization. Product *cis*-**56** and substituted *N*-(2-aminoethyl)pyrrole **78** were placed in the standard reaction conditions (Table III- 11). After two days, the only pyrroloperazine present in the reaction mixture was *cis*-**56**. This result demonstrates that:

- The reaction is not reversible.
- No significant epimerization occurs in the reaction conditions and the mixture of diastereomers is not the result of an equilibration.

Table III- 11 Crossover reaction to evaluate the reversibility of the reaction and the potential epimerization of the product.

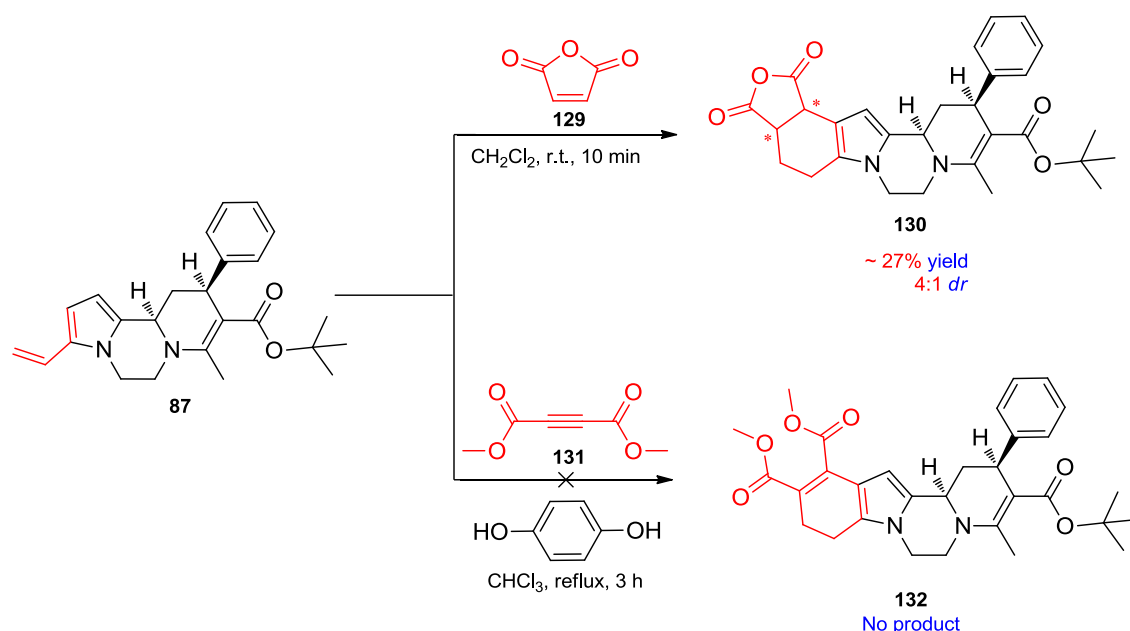


III.7 POST-FUNCTIONALIZATION

In order to extend the usefulness of the pyrroloperazine derivatives that we have prepared, some post-functionalizations have been investigated.

III.7.1 DIELS-ALDER REACTIONS

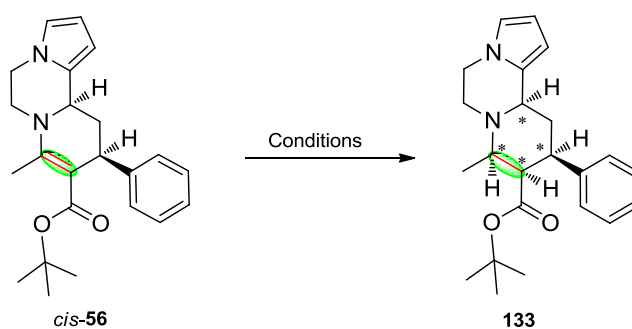
As early as 1980, Jones and co-workers disclosed for the first time the synthesis of tetrahydroindoles starting from vinylpyrroles and maleic anhydride **129** by Diels-Alder cycloaddition followed by the reinstating of aromaticity by isomerization.^[255] The authors said vinylpyrroles were not stable in the air, therefore they prepared them in situ just prior to the cycloaddition. With the pyrroloperazine **87** including a vinyl moiety, we attempted to synthesize the fused cyclic tetrahydroindole **130** by reaction with maleic anhydride in CH₂Cl₂ at room temperature during 10 min. From the crude ¹H NMR, **130** could be identified as two diastereomers in a 4:1 ratio. However, after purification, **130** was obtained with low yield and contaminated with some impurities (Scheme III- 27). Dimethyl 2-butynedioate **131** was also introduced as dienophile in the Diels-Alder cycloaddition with vinylpyrrole **87**. Unfortunately, even though the starting material was consumed, neither the desired product **132** nor the corresponding aromatized indole derivative was found at the end of the reaction.



Scheme III- 27 Diels-Alder reactions of the 3CR product with the 2-vinylpyrrole moiety.

III.7.2 REDUCTION OF THE DOUBLE BOND

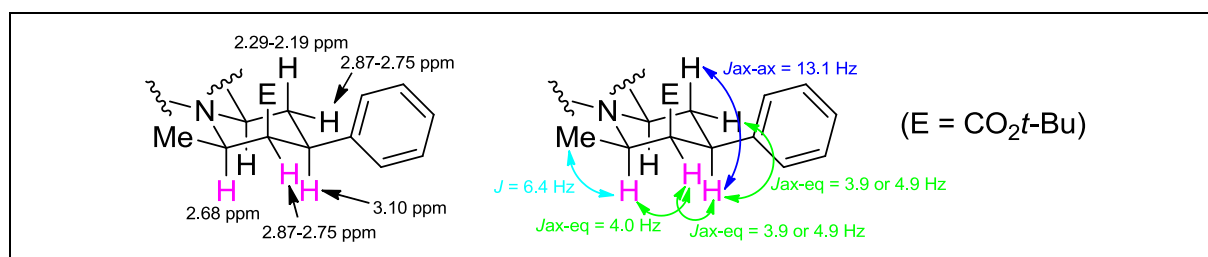
The highly enantiomerically enriched pyrroloperazines obtained by the organocatalytic MCR are multifunctional synthetic platforms that can be converted into other optically active heterocycles by conventional reactions. The tricyclic *cis*-**56** was chosen firstly for further manipulation (Table III- 12). We intended to carry out the reduction of the double bond of the enaminoester moiety, with the creation of two new stereogenic centers.

Table III- 12 Reduction of the enaminoester for the *cis* diastereomer.

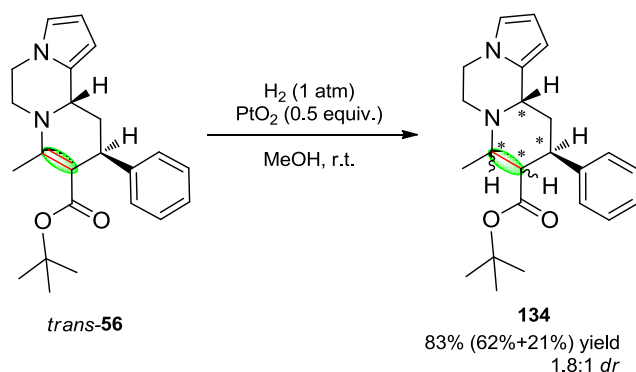
Entry	Conditions	Yields (%)	<i>dr</i>	<i>ee</i> (%)
1	NaBH ₄ , AcOH, THF, 0 °C	68	1.6:1	n.d.
2	NaBH(OAc) ₃ , CH ₂ Cl ₂ , r.t. to 50 °C	58	>20:1	n.d.
3	H ₂ (1 atm), PtO ₂ (0.5 equiv), MeOH, r.t.	94	>20:1	92

Firstly, the reduction was carried out by using sodium borohydride as reductant at 0 °C in THF in the presence of acetic acid (Table III- 12, Entry 1).^[256, 257] The expected product has been obtained, but with a disappointing 1.6:1 *dr* and the two diastereomers could not be separated by flash chromatography. Secondly, a solution of NaBH(OAc)₃ was prepared in situ by adding sodium borohydride to acetic acid.^[258, 259] Under this condition, pleasingly, the reaction was diastereoselective but only a moderate yield of product **133** was obtained (Table III- 12, Entry 2). Thirdly, *cis*-**56** was exposed to hydrogen gas in the presence of a catalytic amount of PtO₂ in MeOH at r.t. (Table III- 12, Entry 3).^[260] Interestingly, the only isomer of expected product **133** was obtained with excellent yield and without erosion of the enantiomeric ratio.

¹H, ¹³C and 2D NMR analyses of the hydrogenated product **133**: allowed the attribution of its relative configuration. The coupling constants values on the hydrogenated product **133** confirmed that the all-*cis* diastereomer has been obtained: the two hydrogen atoms were incorporated on the same face of the alkene and the hydrogenation occurred on the face of the enaminoester opposite to the bulky aromatic group.



We tried to apply these optimized reaction conditions for the reduction of the enaminoester of the other diastereomer *trans*-**56** (Scheme III- 28). The hydrogenated product **134** was obtained with 83% yield but as a mixture of diastereomers in a 1.8:1 ratio. This lack of selectivity may arise from a non-selective facial approach during the hydrogenation or from an epimerization of the stereogenic center in α position of the ester group. Numerous overlapping between the signals in ¹H NMR prevented us from determining the relative configurations of the two new stereogenic centers.

Scheme III- 28 Reduction of the enaminoester for the *trans* diastereomer.

III.7.3 EPIMERIZATION OF THE STEREOGENIC CENTER BEARING THE ESTER SUBSTITUENT

Because the ester substituent in all-*cis* product **133** is placed in the thermodynamically less favorable axial position, we hypothesized that this product could be epimerized into **135**. We evaluated different basic reactions conditions by treating **133** with lithium diisopropylamide (LDA) in THF^[261] or sodium methoxide in methanol,^[262] but the conversion into the epimer **135** never reached more than 30% (Table III- 13, Entries 1-2).

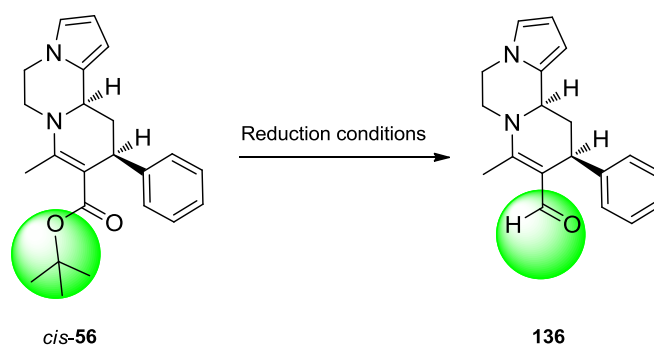
Table III- 13 Attempts of epimerization.

Entry	Conditions	Conversion (%)
1	LDA, THF -78 °C to r.t., 16 h	29
2	MeONa/MeOH, reflux, 24 h	26

III.7.4 REDUCTION OF THE ESTER PART

To obtain the aldehyde **136**, we attempted to reduce *cis*-**56** with DIBAL in different solvents at -78 °C.^[263] It was disappointing to see that the expected aldehyde **136** was not obtained (Table III- 14).

Table III- 14 Reduction of the ester part.



Entry	Conditions	Yields (%)
1	DIBAL (2.0 equiv), Et₂O , -78 °C	Not dissolved
2	DIBAL (2.0 equiv), CH₂Cl₂ , -78 °C, 2 h	none
3	DIBAL (2.0 equiv), THF , -78 °C, 15 min	degraded
4	DIBAL (2.0 equiv), toluene-THF , -78 °C, 15 min	degraded

III.8 CONCLUSIONS

In conclusion, we have developed a new enantioselective three-component reaction between β -ketoesters, enals and *N*-(2-aminoethyl)pyrroles.^[264] Highly enantioenriched fused tricyclic piperazines, with hypothetical biological activities, have been obtained in moderate yields and as two diastereomers that were generally separated by flash chromatography. We have also investigated diversified pronucleophiles in this reaction and several of them could participate upon reoptimization of the reaction conditions. At last, we show that post-functionalization of the product was possible to lead to new structures possessing additional stereogenic centers.

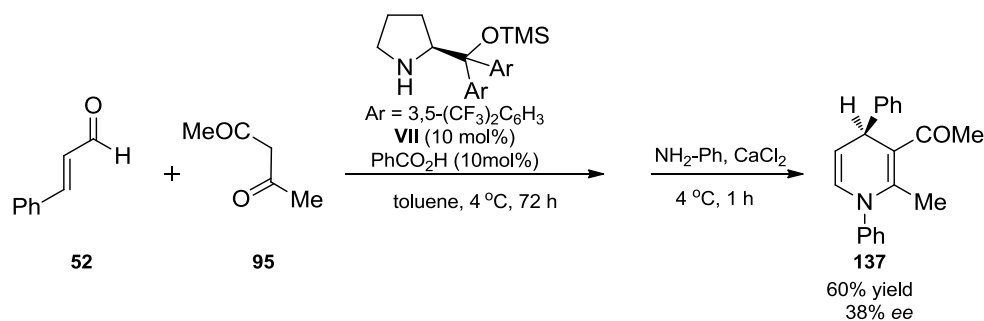
**IV. SYNTHESIS OF ENANTIOENRICHED
POLYFUNCTIONALIZED HETEROCYCLES BY
3-CR OR 4-CR**

IV. SYNTHESIS OF ENANTIOENRICHED POLYFUNCTIONALIZED HETEROCYCLES BY 3-CR OR 4-CR

As disclosed in the previous section, we could develop a new enantioselective MCR involving various 1,3-dicarbonyls or related Michael donors, α,β -unsaturated aldehydes and functionalized amines to allow the formation of enantioenriched pyrroloperazines. This process creates three new bonds and two new stereogenic centers in a highly step- and atom-economical fashion. Therefore, we wanted to further explore this reactivity by replacing the *N*-(2-aminoethyl)pyrrole moiety by heteroatom-functionalized amines to obtain other interesting polycyclic heterocycles.

IV.1 ORIGINS OF THE REACTION DESIGN

Our initial inspiration came from a report by the group of Jørgensen in 2008 who studied the combination of acetoacetate **95** and cinnamaldehyde **52** with a subsequent addition of amines to afford 1,4-dihydropyridines **137** (Scheme IV- 1).^[132] However, this reaction was limited to the use of β -alkyl substituted enals as the ones bearing aromatic groups delivered the products with low enantioselectivities. The authors ascribed these disappointing results to a racemization by retro-Michael followed by an unselective Michael addition when the amine is added. We hypothesized that a suitably functionalized amine might help to shift the equilibrium and therefore help to prevent this reversibility-induced racemization.

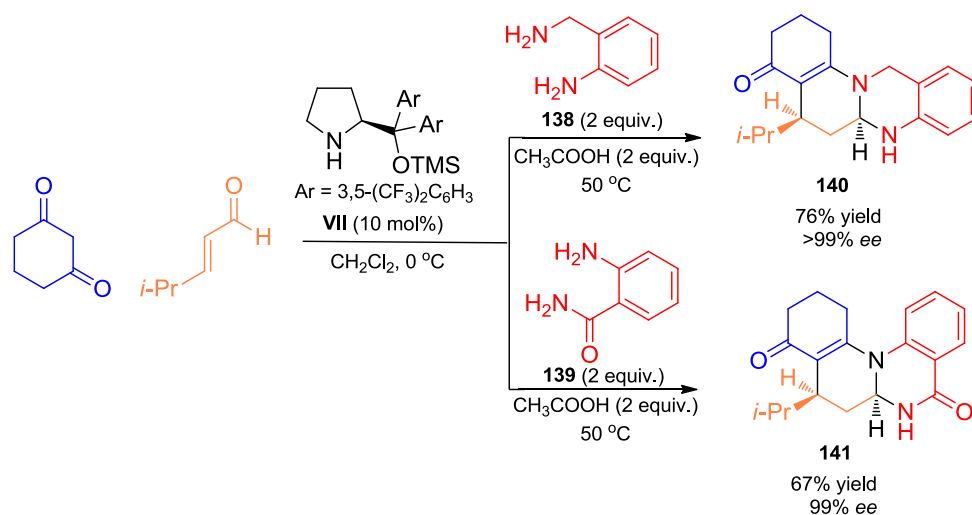


Scheme IV- 1 Synthesis of 1,4-dihydropyridines catalyzed by **VII** (Jørgensen, 2008).

IV.2 CHOICE OF THE BEST FUNCTIONALIZED AMINE

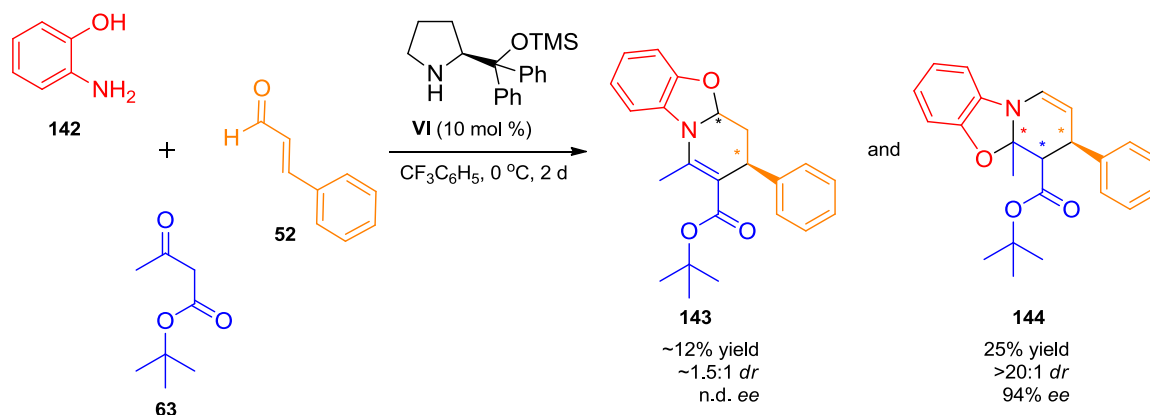
In the bibliographic part, we have already seen that the corresponding trimolecular sequential couplings, involving nitrogen-centered bisnucleophiles such as 2-aminobenzylamine **138** or anthranilamide **139**, had been developed by the group of Rueping (Scheme IV- 2).^[155] The corresponding pyridoquinazoline **140** and pyridoquinazolinone **141** respectively, have been obtained with high enantioselectivities. However, this reaction was

limited to cyclic diketones as the Michael donors and the temperature of the reaction had to be increased to 50 °C after the addition of the amine to ensure the cyclization. Such an elevated temperature might preclude the development of an enantioselective reaction as the organocatalytic Michael addition is likely to proceed with reduced enantioselectivity when increasing the temperature.



Scheme IV- 2 Trimolecular sequential couplings involving 2-aminobenzylamine or anthranilamide (Rueping, 2011).

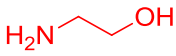
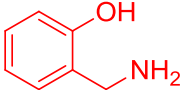
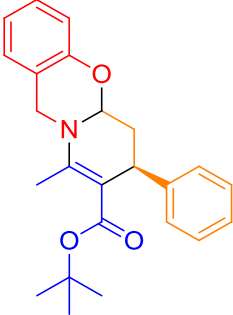
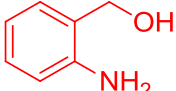
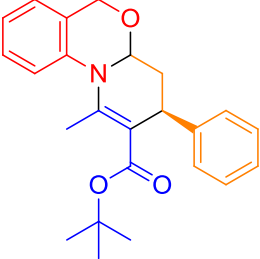
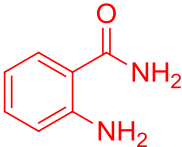
Based on the recent successful results of our research group in the use of 2-aminophenols in another enantioselective organocatalytic MCR (Scheme I- 75),^[194] we started our investigations by mixing *tert*-butyl acetoacetate **63**, cinnamaldehyde **52** and 2-aminophenol **142** in the presence of organocatalyst **VI** in trifluorotoluene at 0 °C (Scheme IV- 3). Pleasingly, early analyses by TCL and crude ^1H NMR revealed that 2-aminophenol was actually participating in the MCR. After two days, a mixture of two regioisomeric products **143** and **144** was obtained. The former product **143** was formed as two diastereomers ($\sim 12\%$ yield, $\sim 1.5:1$ *dr*) but, in contrast, the latter product **144** was isolated as only one diastereomer in 25% yield and with 94% *ee*.



Scheme IV- 3 First attempt of an organocatalytic enantioselective MCR of ethyl acetoacetate, cinnamaldehyde and 2-aminophenol.

Facing these mixed results, we continued to inspect other functionalized amines in this transformation under the standard reaction conditions to try to identify a more regio- and /or stereoselective combination. When introducing 2-aminoethanol **145** into this transformation (Table IV- 1, Entry 1), the expected product did not form. In contrast, 2-(aminoethyl)phenol **146** allowed the cyclization to deliver the enaminoester-containing regioisomer **147** in 76% yield, with 1.8:1 *dr* and 94% *ee* for the major diastereomer (Table IV- 1, Entry 2). On the opposite, 2-aminobenzyl alcohol **148** and anthranilamide **139** gave disappointing results (Table IV- 1, Entry 3-4), highlighting the unique behavior of the phenol function to participate in this multicomponent reaction.

Table IV- 1 Evaluation of various functionalized amines.

Entry	Amines	Products	Yields (%)	<i>dr</i>	<i>ee</i> (%)
1	 145	no product	n.d.	n.d.	n.d.
2	 146	 147	76	1.8:1	94, n.d.
3	 148	 149	27	1.3:1	88, n.d.
4	 139	Complex mixture	n.d.	n.d.	n.d.

IV.3 3-CR WITH β -KETOAMIDES

IV.3.1 pKa OF DIFFERENT 1,3-DICARBONYL COMPOUNDS

α -Positions of 1,3-dicarbonyl compounds have different acidities in DMSO and these values can be accessed in the Bordwell pKa table (Figure IV- 1).

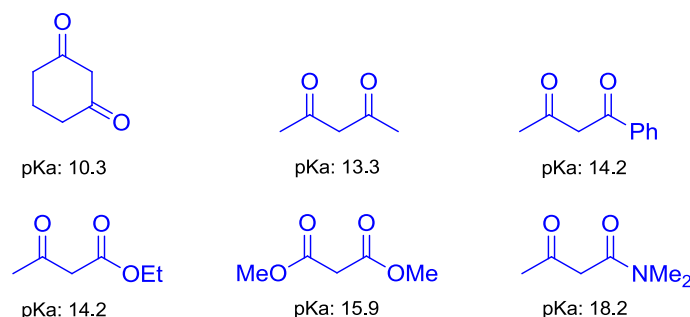
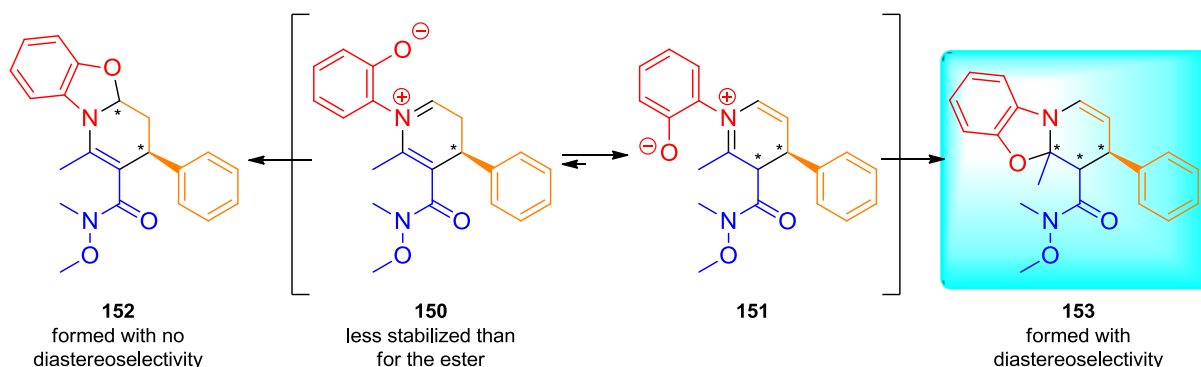


Figure IV- 1 The pKa values of various 1,3-dicarbonyl compounds in DMSO.

Comparing acyclic β -ketoesters with acyclic β -ketoamides, deprotonation in α -position of β -ketoesters is 10^4 more facile than for β -ketoamides, resulting in a far easier activation by organocatalysts and probably explaining why they have been used a lot more often. In the previous section, we have shown that β -ketoamides, and especially Weinreb β -ketoamide, can participate in the multicomponent synthesis of pyrrollopiperazines (Scheme III- 15). We hypothesized that the reduced acidity of the α -position when using β -ketoamides will also influence the equilibrium between the two iminium ions **150** and **151** that are the direct precursors of the two regioisomeric products **152** and **153** (Scheme IV- 4). More specifically, the reduced stabilization of **152** for the amide-containing substrate might shift the equilibrium in the other direction favoring the formation of product **153**, which is all the more interesting as its formation is highly diastereoselective.



Scheme IV- 4 Our working hypothesis for the use of Weinreb β -ketoamide in the MCR with cinnamaldehyde and 2-aminophenol.

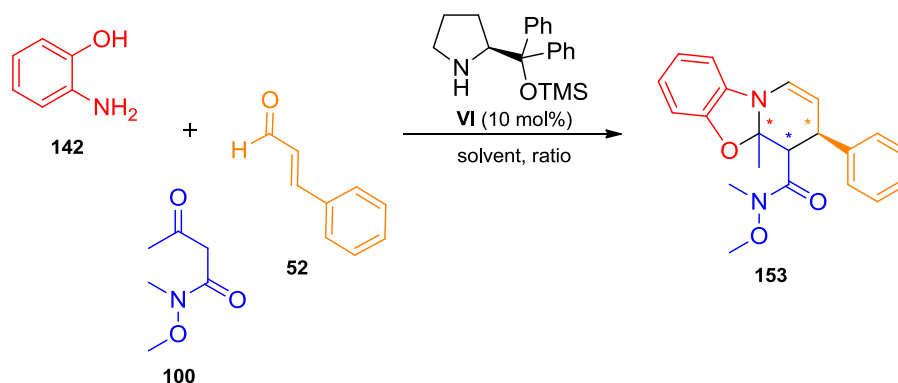
Based on this context, the three-component reaction of Weinreb β -ketoamide, α,β -unsaturated aldehyde and substituted aminophenol will be investigated in this section.

IV.3.2 OPTIMIZATION OF THE REACTION CONDITIONS

IV.3.2.1 OPTIMIZATION OF THE SOLVENT AND THE RATIO BETWEEN THE STARTING MATERIALS

We started to investigate the reaction of Weinreb β -ketoamide **100** (1 equiv.) in the reaction conditions that had been used for the corresponding ketoester: cinnamaldehyde **52** (1.5 equiv.) and 2-aminophenol **142** (1 equiv.) in the presence of catalyst **VI** (10 mol%) in trifluorotoluene at 0 °C during 24 h (Table IV- 2). Excitingly, the targeted product **153** was formed as the only regioisomer, showing the viability of our hypothesis. However, the yield of the isolated product remained low (19% yield, Table IV- 2, Entry 1). CH_2Cl_2 , another solvent that is frequently used for this iminium activation, provided 28% yield with also only one isomer and 93% *ee* (Table IV- 2, Entry 2). From the crude ^1H NMR, we found that the Weinreb β -ketoamide did not completely convert. Thus, we wanted to change the ratio of starting materials, which unfortunately resulted in only marginal improvement of the yield (Table IV- 2, Entries 3-4).

Table IV- 2 Evaluation of the solvent and the ratio between starting materials.



Entry	Solvents	Ratio (100:52:142)	NMR Yields (%)	Yields (%)	<i>dr</i>	<i>ee</i> (%)
1	$\text{CF}_3\text{C}_6\text{H}_5$	1:1.5:1	27	19	>20:1	n.d.
2	CH_2Cl_2	1:1.5:1	38	28	>20:1	93
3	CH_2Cl_2	1:1.5:1.5	28	n.d.	>20:1	n.d.
4	CH_2Cl_2	1:3:3	43	30	>20:1	n.d.

IV.3.3 EVALUATION OF ORGANOCATALYSTS, ADDITIVES, TEMPERATURES AND REACTION TIME

From this initial encouraging result, we initiated an optimization of all reaction parameters to try to improve the yield of product **153**. On many occasions, additives have

played an important role in reactions under iminium activation. Hence, benzoic acid **154** (20 mol%) as co-catalyst was introduced into this MCR (Table IV- 3, Entry 1). Pleasingly, the yield was somewhat increased and both the diastereo- and the enantioselectivity were preserved. Then, increasing the quantities of catalyst **VI** and benzoic acid **154** (Table IV- 3, Entries 2-3) was slightly beneficial. When prolonging the reaction time to 96 h, the yield climbed up to 52% (Table IV- 3, Entry 4). A further increase of the quantity of benzoic acid **154** to 1.0 equiv. did not improve the results (Table IV- 3, Entry 5). However, by increasing the reaction temperature to 10 °C or 25 °C, further improvement was achieved (Table IV- 3, Entries 6-8). Especially, the yield was significantly increased at 10 °C for 70 h (60%, Table IV- 3, Entry 7), with no impact on the stereoselectivities. Using other secondary amine catalysts or other carboxylic acid as additives disappointingly provided worse results (Table IV- 3, Entries 9-13). This project has since then been taken over by a first-year PhD student in our group. He tried to evaluate other solvents for this reaction. If alcohols as the solvent could speed up the reaction and allow to attain higher yields, this was at the cost of a complete loss of the diastereoselectivity. Moreover, the student who took over this project carried out NMR studies, including NOESY experiments, to attribute the relative configurations of the products.

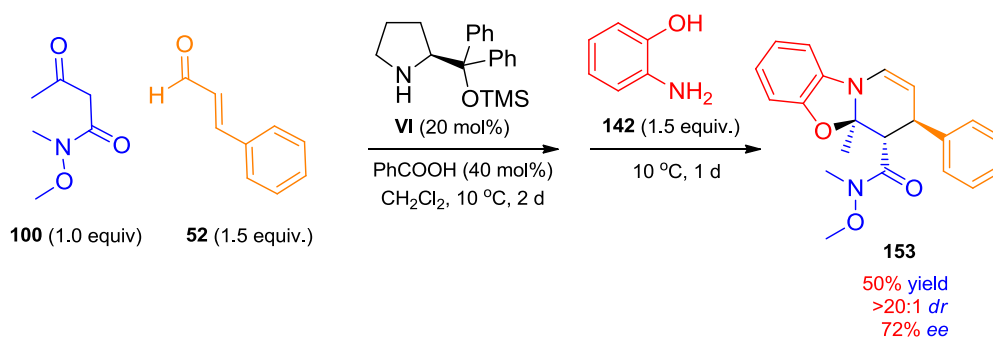
Table IV- 3 Evaluation of organocatalysts, additives, temperatures and reaction time.

Ar = 3,5-(CF₃)₂C₆H₃

Entry	Temperatures	Additives				Time (h)	NMR Yields (%)	Yields (%)	ee (%)
		154 (20 mol%)	155 (20 mol%)	156 (20 mol%)	157 (20 mol%)				
1	0 °C	VI (10 mol%)				24	38	32	95
2	0 °C	VI				24	41	n.d.	n.d.
3	0 °C	VI				24	43	36	n.d.
4	0 °C	VI				96	57	52	95
5	0 °C	VI				96	57	n.d.	n.d.
6	10 °C	VI				24	42	36	94
7	10 °C	VI				70	70	60	94
8	25 °C	VI				47	56	51	91
9	10 °C	VII				24	23	n.d.	n.d.
10	10 °C	LVIX				24	6	n.d.	n.d.
11	10 °C	VI				24	28	n.d.	n.d.
12	10 °C	VI				60	37	n.d.	n.d.
13	10 °C	VI				60	12	n.d.	n.d.

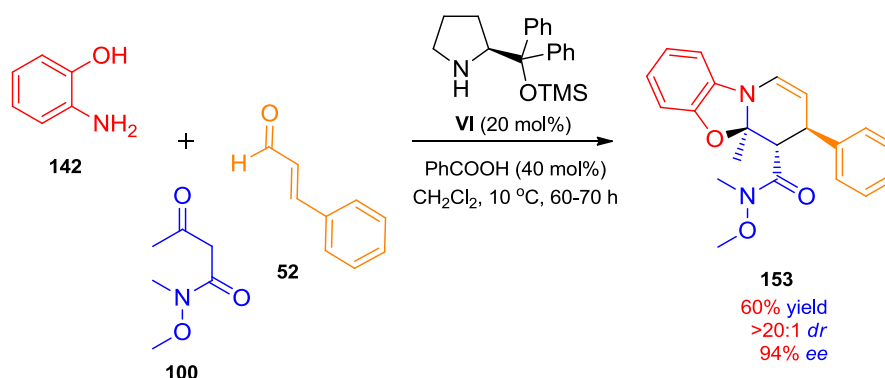
IV.4 SEQUENTIAL TRIMOLECULAR TRANSFORMATION

In order to assess the effect of the 2-aminophenol on the enantioselective step, we tried to run a sequential trimolecular reaction in the presence of catalyst **VI** (20 mol%) with or without benzoic acid **154** (40 mol%) in CH_2Cl_2 at 10°C (Scheme IV- 5). Firstly, the reaction started with Weinreb β -ketoamide **100** (1.0 equiv.) and cinnamaldehyde **52** (1.5 equiv.). Secondly, after two days, 2-aminophenol **142** (1.5 equiv.) was added and the reaction mixture stirred on for another day. At last, control of the crude reaction mixture by ^1H NMR showed that the expected product **153** had formed in 23% ^1H NMR yield without benzoic acid, and in 57% ^1H NMR yield with benzoic acid. For the latter reaction, the isolated yield was 50%, with $>20:1$ *dr* and 72% *ee*. This transformation is once again highlighting the power of the multicomponent reaction as the direct trapping of sensitive intermediates can help to prevent their racemization.



Scheme IV- 5 Evaluation of the sequential trimolecular reaction.

Up to present, the best reaction conditions consist in mixing Weinreb β -ketoamide **100** (1 equiv.), cinnamaldehyde **52** (1.5 equiv.) and 2-aminophenol **142** (1 equiv.) by using **VI** (20 mol%) and benzoic acid (40 mol%) as co-catalyst in CH_2Cl_2 at 10°C during 60-70 h (Scheme IV- 6).



Scheme IV- 6 The organocatalytic enantioselective MCR of Weinreb β -ketoamide, cinnamaldehyde and 2-aminophenol.

IV.5 THE SCOPE

Using the optimized reaction conditions (see Scheme IV- 6), we began to study the scope of the MCR involving Weinreb β -ketoamide **100** (Figure IV- 2). As expected, diversely substituted enals, no matter whether they bear an aromatic ring with electron-donating groups, electron-withdrawing groups, an heteroaromatic or an alkyl group provided the desired products **158-162** with reasonable yields, high diastereo- and enantioselectivities. A small decrease of yield could be noted only in the case of 4-methoxycinnamaldehyde, (*E*)-3-(furan-2-yl)acrylaldehyde and crotonaldehyde. This observation means that the aromatic substituted aldehydes with electron-withdrawing groups might be more suitable for this transformation.

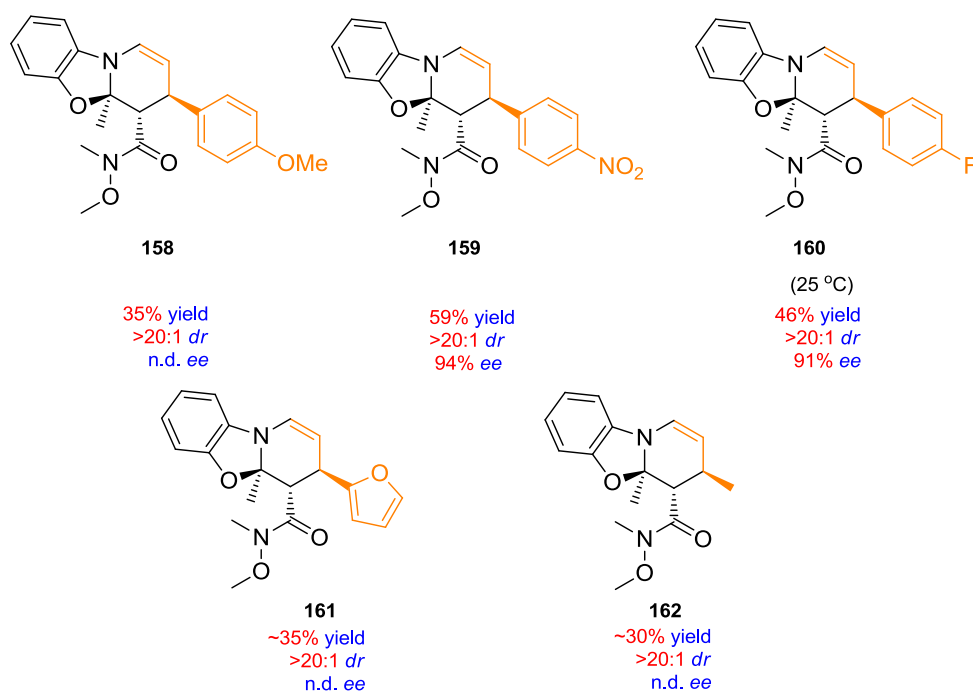
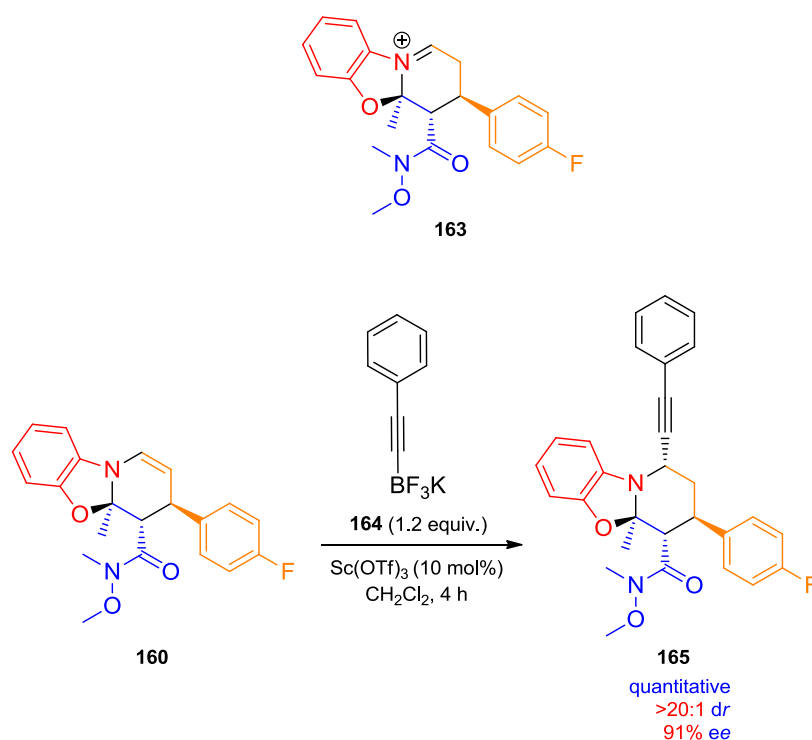


Figure IV- 2 Scope of Michael acceptors.

IV.6 POST-FUNCTIONALIZATION

To document the potential of the new tricyclic products **160** as building blocks in synthesis, we further investigated follow-up chemistry (Scheme IV- 7). When this product is treated with $\text{Sc}(\text{OTf})_3$ as a Lewis acid, we can expect to observe the equilibrium of the enamine with the iminium ion **163**. The iminium ion **163** could then be trapped with potassium alkynyltrifluoroborate **164** through a Petasis reaction.^[265, 266] When we attempted this reaction, the starting materials **160** were completely converted and the product **165** was formed in quantitative yield. Pleasingly, no erosion of the enantiomeric excess was observed and the newly created center was fully controlled as the product was isolated as a single diastereomer.

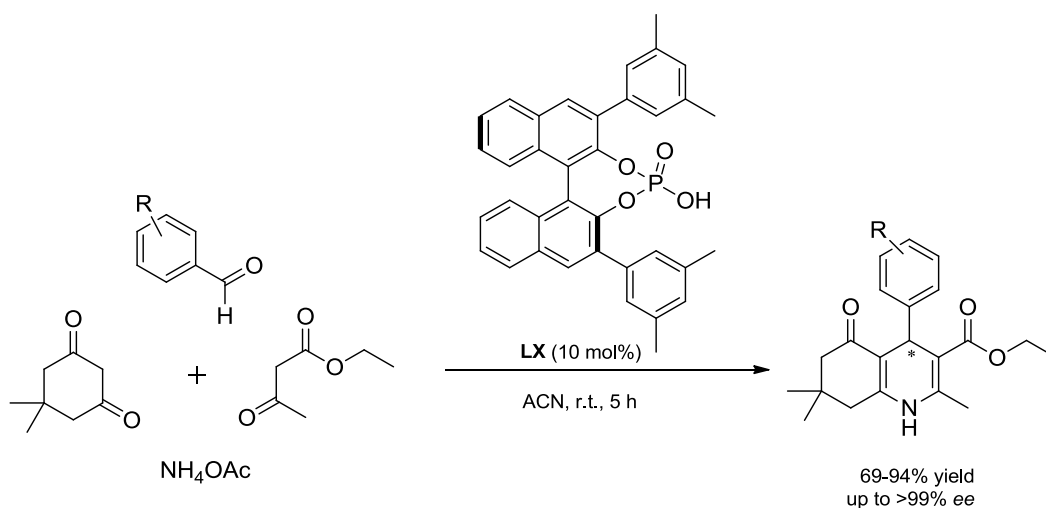


Scheme IV- 7 Post-functionalization of the 3CR adducts with a potassium alkynyltrifluoroborate.

When observing the high efficiency of this post-functionalization, we wondered whether it would be possible to directly form product **165** by a four-component reaction under cooperative catalysis conditions, in the presence of both the organocatalyst and the metal catalyst,^[267, 268] a field that has received more and more attention since the initial results of Córdoba in 2006.^[269]

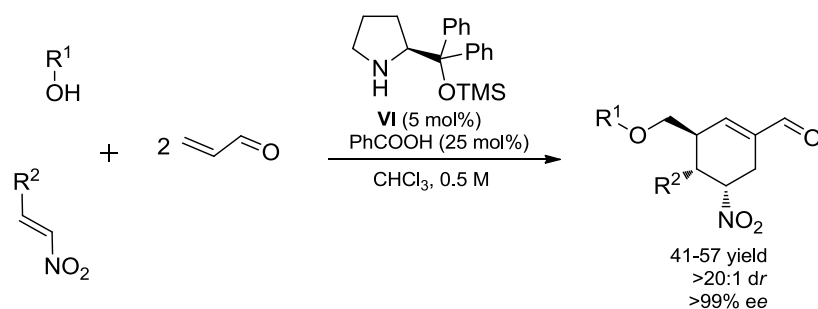
IV.7 FOUR-COMPONENT REACTION

Even though the historical pseudo 4-CR Hantzsch reaction is one of the most studied and widely used MCR, because of the high degree of diversity it allows to attain and the usefulness of the 1,4-dihydropyridines it generates, enantioselective four-component reactions are very rare. In 2009, the group of Gestwicki reported the first example of enantioselective four-component Hantzsch reaction catalyzed by a chiral phosphoric acid (Scheme IV- 8).^[226]

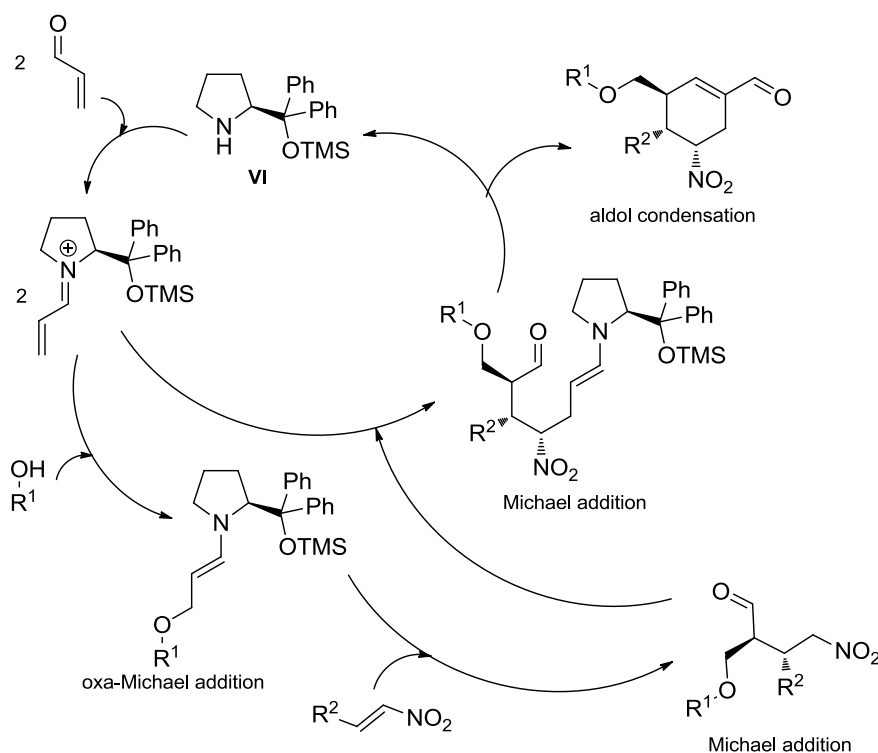


Scheme IV- 8 Enantioselective four-component Hantzsch reaction (Gestwicki, 2009).

In the same year, Gong and co-workers have envisioned a pseudo-four-component quadruple domino reaction (Scheme IV- 9) through iminium-enamine-iminium-enamine sequential activation initiated by an oxa-Michael addition of an alcohol to acrolein (Scheme IV- 10).^[270]

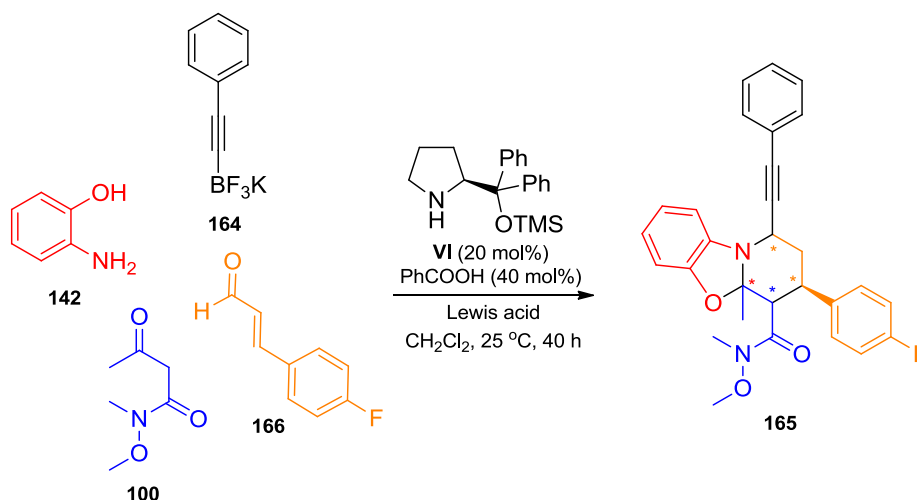


Scheme IV- 9 Organocatalytic pseudo-four-component domino oxa-Michael/Michael/Michael/aldol condensation reaction (Gong, 2009).



Scheme IV- 10 The proposed mechanism for Gong's pseudo-4CR.

However, up to present, no enantioselective four-component reaction of 1,3-dicarbonyl substrates initiated by an enantioselective Michael addition has been reported. Based on these concepts, we attempted to develop an enantioselective four-component reaction of Weinreb β -ketoamide **100**, *trans*-4-fluorocinnamaldehyde **166**, 2-aminophenol **142** and potassium alkynyltrifluoroborate **164** by using a combination of an organocatalyst with a Lewis acid in CH_2Cl_2 at 25 °C (Table IV- 4). Thus, *trans*-4-fluorocinnamaldehyde **166** was firstly chosen as the Michael acceptor in this transformation to allow checking potentially complex crude reaction mixtures by ^{19}F NMR. We initially started to investigate the reaction without Lewis acid (Table IV- 5, Entry 1): as expected, only the 3-CR product **153** was found in ^{19}F NMR, proving that the potassium organotrifluoroborate does not seem to interact with the initial steps of the reaction. Lewis acids and transition metal catalysts, such as $\text{Sc}(\text{OTf})_3$, CuI , $[\text{Rh}(\text{cod})\text{Cl}]_2$, NbCl_5 , ZrCl_4 , FeCl_3 and AlCl_3 , which are frequently combined with organocatalysts and/or used to catalyze additions of potassium organotrifluoroborates to electrophiles, were evaluated (Entries 2-9). Only strong chloride-containing Lewis acids (NbCl_5 , ZrCl_4 , FeCl_3 and AlCl_3) used in at least 10 mol% provided 4-CR product **165** in 10 to 20% ^{19}F NMR yields. Unfortunately, low yields were obtained after purification and product **165** was racemic. From this result, it clearly appears that the secondary amine catalyst cannot act efficiently and selectively in the presence of catalysts that are able to effect the final Petasis reaction. For this reason, we decided to skip this part of the project.

Table IV- 6 Attempts of organocatalytic enantioselective four-component reaction of Weinreb β -ketoamide, cinnamaldehyde, 2-aminophenol and potassium alkynyltrifluoroborate.

Entry	Lewis acid (mol%)	153 (3-CR) ¹⁹ F NMR Yields (%)	165 (4-CR) ¹⁹ F NMR Yields (%)	165 (4-CR) <i>ee</i> (%)
1	None	82	None	n.d.
2	Sc(OTf) ₃ (10)	54	None	n.d.
3	CuI(10)	57	None	n.d.
4	[Rh(cod)Cl] ₂ (5)	47	None	n.d.
5	NbCl ₅ (10)	None	20	0
6	NbCl ₅ (5)	None	1	n.d.
7	ZrCl ₄ (10)	4	21	0
8	FeCl ₃ (10)	4	11	0
9	AlCl ₃ (10)	4	11	n.d.

IV.8 CONCLUSIONS

In summary, we brought about a proof of concept for the possibility to carry out an enantioselective organocatalytic three-component reaction between Weinreb β -ketoamide **100**, α,β -unsaturated aldehyde **123** and 2-aminophenol **142** in the presence of aminocatalyst **VI** and benzoic acid **154** as co-catalyst, providing the functionalized tricyclic product **153**, **158-162** with interesting yield, >20:1 *dr* and excellent enantioselectivities. Comparing β -ketoester with Weinreb β -ketoamide in the MCR, we have shown that Weinreb β -ketoamide had a unique ability at controlling the regio- and diastereoselectivity of the reaction. Although the synthesis of enantioenriched product **165** by a four-component reaction in the presence of both an organocatalyst and a Lewis acid failed, the two-step sequential access to this product opens up interesting perspective for the valorization of the 3-CR products.

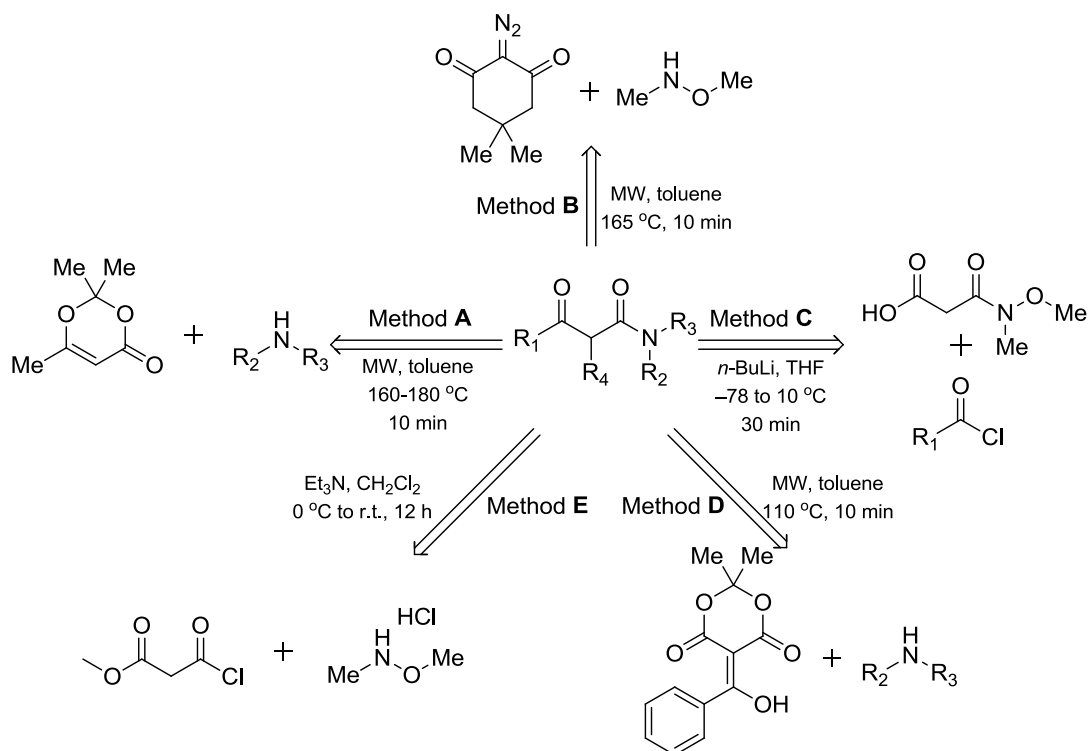
**V. ORGANOCATALYTIC ENANTIO- AND
DIASTEREOSELECTIVE CONJUGATE ADDITION
OF β -KETOAMIDES TO NITROOLEFINS**

V. ORGANOCATALYTIC ENANTIO- AND DIASTEREOSELECTIVE CONJUGATE ADDITION OF β -KETOAMIDES TO NITROOLEFINS

In the previous section, we have noticed that applying a Weinreb β -ketoamide in an organocatalytic MCR helped to control the regioselectivity of the reaction, whereas β -ketoesters were affording mixtures of regioisomers. Intrigued by this selectivity, and realizing that simple organocatalytic enantioselective conjugate addition of β -ketoamide to a Michael acceptor has not been reported, we engaged on the study of this transformation.

V.1 PREPARATION OF β -KETOAMIDES

Only few β -ketoamides are commercially available, therefore it was necessary to find an efficient and general methodology to synthesize them. A few years ago, our laboratory developed a synthesis of β -ketoamides based on a Wolff rearrangement of diazodiketones and trapping of the resulting ketoketene by an amine, under microwave irradiation.^[271, 272] This method could be applied to the synthesis of the cyclic β -ketoamides we required (Scheme V-1, method B). Complementary synthetic routes proceeding through ketoketenes (methods A and D) were also used.^[273]



Scheme V- 1 Different synthetic routes to synthesize the β -ketoamides.

Some other substrates were prepared following a literature described condensation of an aliphatic acyl chloride with a β -carbamoylcarboxylic acid (method C).^[274, 275] To finish with, the Weinreb amide substituted with a β -ester functionality was formed by combining methyl 3-chloro-3-oxopropanoate with *N,O*-dimethylhydroxylamine hydrochloride (method E).^[276] According to all these diverse methodologies, all the following substrates were obtained in moderate to high yields (Figure V- 1).

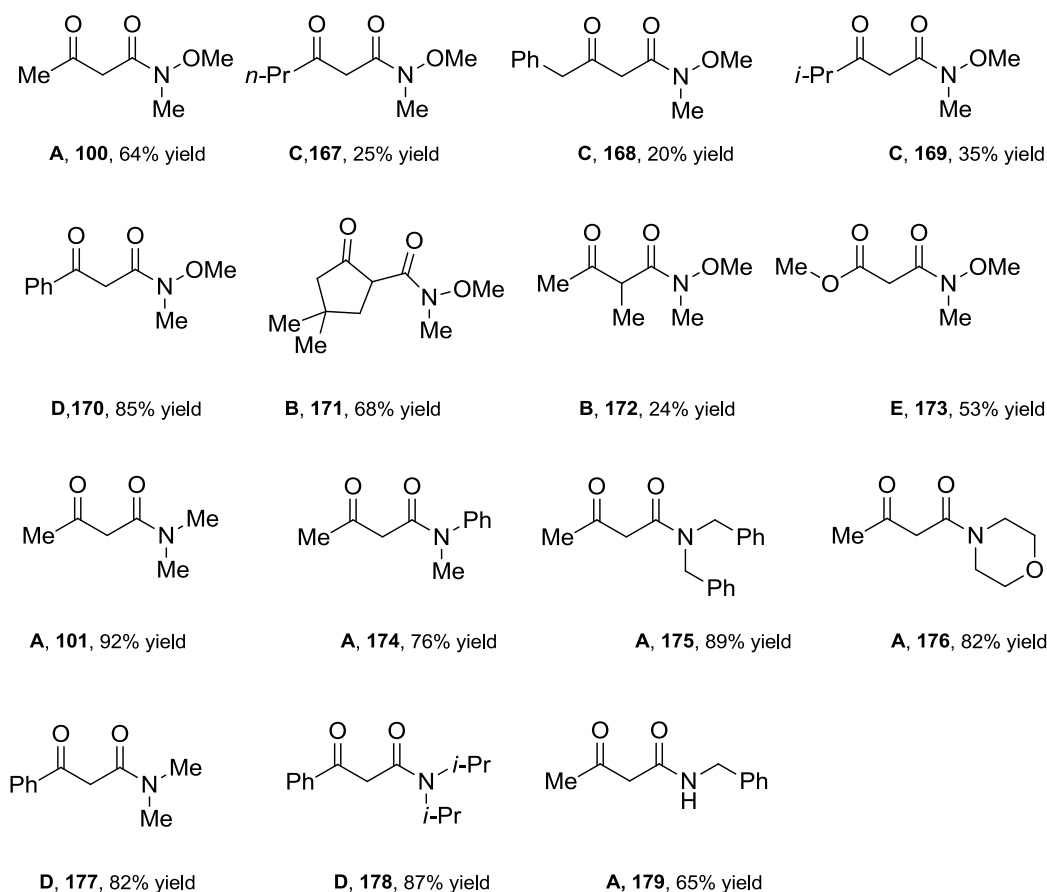
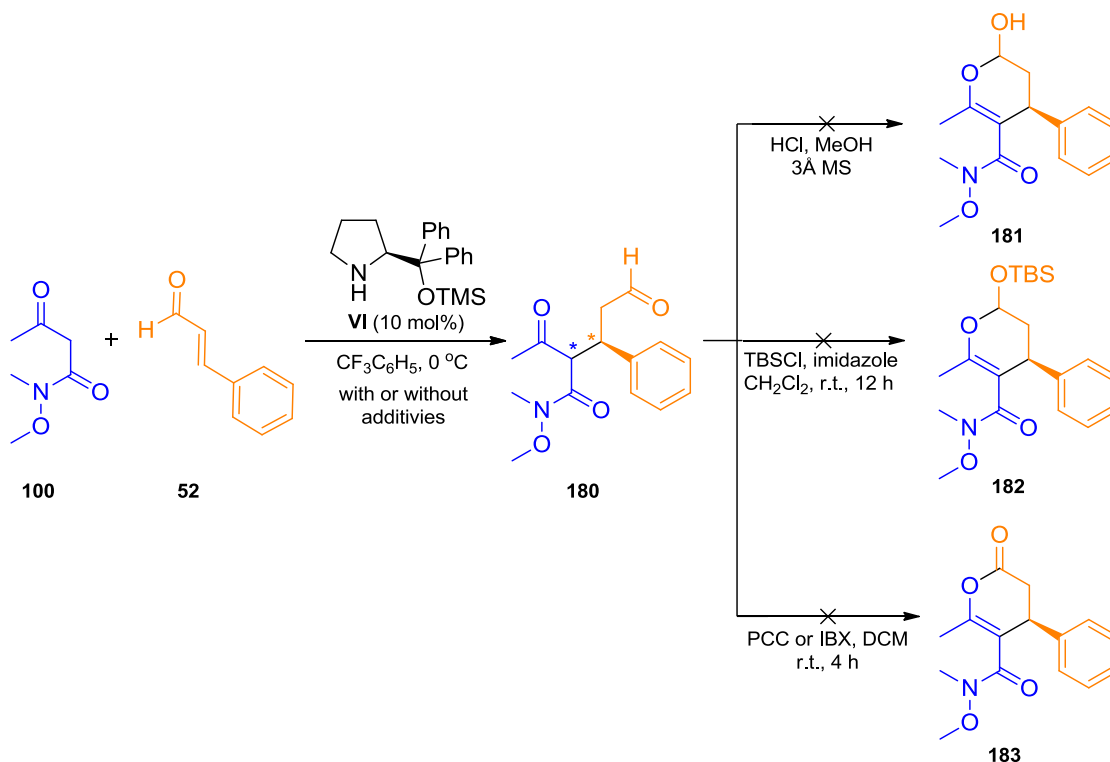


Figure V- 1 Synthesis of the β -ketoamides: 20-92% yields.

V.2 THE MICHAEL ADDITION OF β -KETOAMIDES TO α,β -UNSATURATED ALDEHYDES

In the two previous chapters, we could show that Weinreb β -ketoamide **100** was able to participate in organocatalytic Michael addition-initiated MCRs. In the literature, the direct organocatalytic conjugate addition of Weinreb β -ketoamide to electron-poor alkenes was not described.^[277] Thus, we investigated first the enantioselective organocatalytic Michael addition of Weinreb β -ketoamide **100** to cinnamaldehyde **52** in the presence **VI** (10 mol%) in trifluorotoluene at 0 °C (Scheme V- 2). After 36 h, only 40% of starting materials were converted. To speed up the reaction, 4-nitrobenzoic acid (10 mol%) was added as co-catalyst: after 72 h, the product **180** was obtained as a mixture of two diastereomers (\sim 1:1 *dr*) with about 35-38% yield, but it could not be separated from some impurities. We also attempted to

use 4-nitrocinnamaldehyde instead of cinnamaldehyde as the Michael acceptor in this transformation, and then measure the enantiomeric excess of the product, which was unfortunately also not stable on the chiral column. Several post-functionalization to force the cyclization between the ketone and the aldehyde and obtain more stable derivatives **181**, **182**^[278] or **183**^[279, 280] were attempted, but without success. In view of these difficulties, we decided to switch to nitroolefins as Michael acceptors.



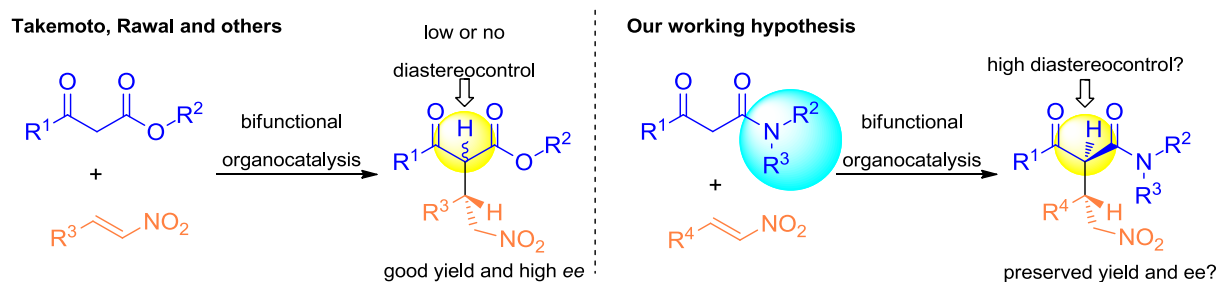
Scheme V- 2 Attempt of organocatalytic enantioselective Michael addition of Weinreb β -ketoamide to cinnamaldehyde.

V.3 THE MICHAEL ADDITION OF β -KETOAMIDES TO NITROOLEFINS

V.3.1 WORKING HYPOTHESIS

In the bibliographic part, we have already described that a large variety of β -dicarbonyls can add to nitroolefins under bifunctional H-bonding organocatalysis (Scheme I- 17) (Scheme I- 24).^[70, 71, 95] Especially, the bifunctional squaramide catalyst developed by the group of Rawal is very efficient in this reaction. One limitation of this transformation is that no diastereoselectivity is obtained when linear methylene β -ketoesters are used as pronucleophiles, because of the epimerization of the stereogenic center between the two carbonyl groups (Scheme V- 3). We hypothesized that the reduced acidity of β -ketoamides compared with β -ketoesters could help solving this issue. Herein, we studied the Michael

addition of β -ketoamides to nitroolefins in the presence of bifunctional squaramide catalysts.

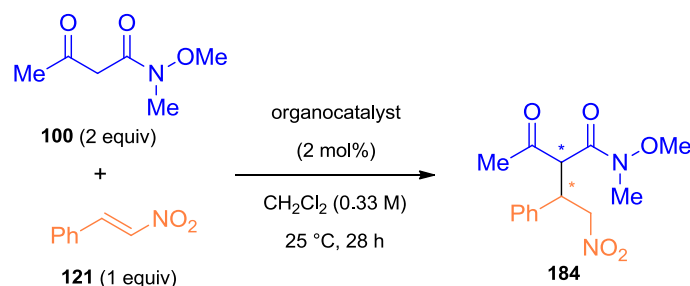


Scheme V- 3 A remaining challenge for the conjugate addition of β -dicarbonyls to nitroolefins: diastereoselectivity with linear substrates.

V.3.2 ORGANOCATALYTIC ADDITION OF ACYCLIC β -KETOAMIDES TO NITROOLEFINS

V.3.2.1 OPTIMIZATION OF THE REACTION CONDITIONS WITH WEINREB β -KETOAMIDE

The optimization of the reaction conditions was carried out in the presence of catalyst (**2** mol%) in CH_2Cl_2 (0.33 M) at 25 °C. We started with a 2:1 ratio between **100** and **121**, which is usually the case in related transformations (Scheme V- 4).

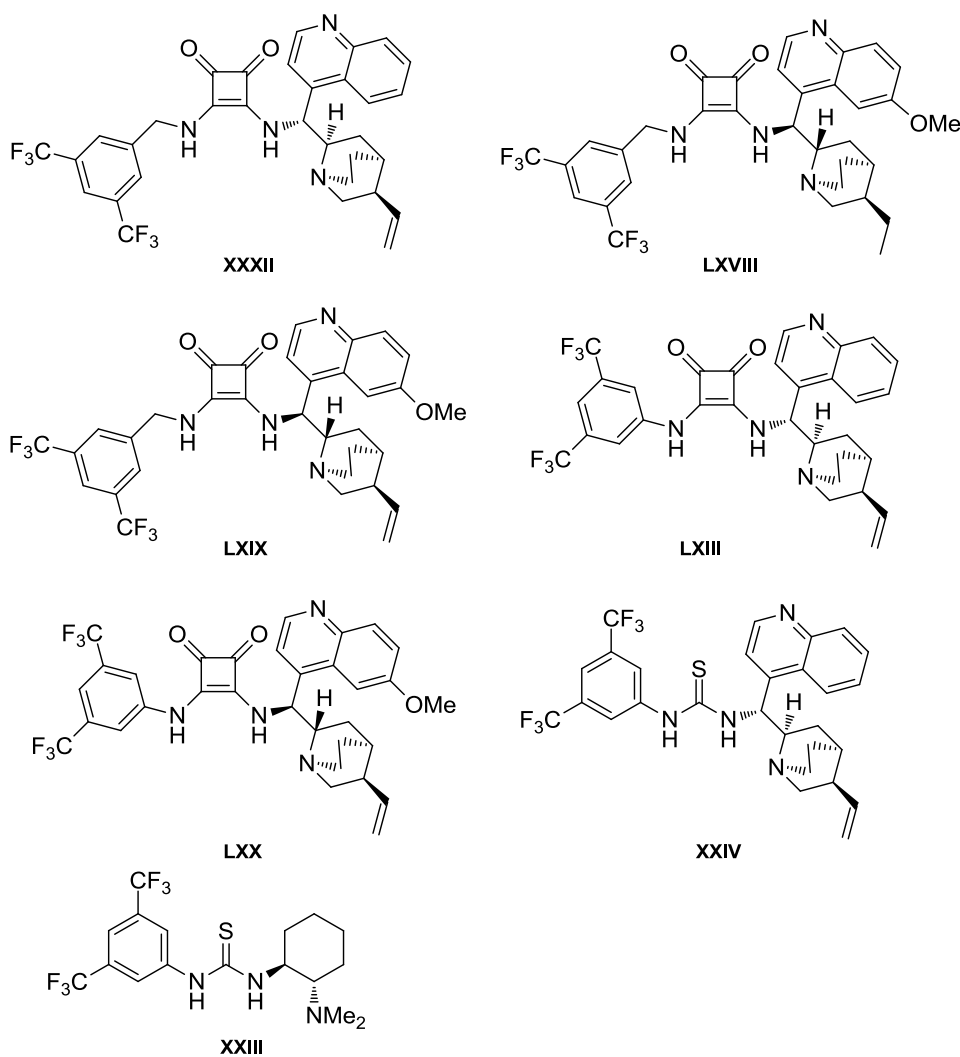


Scheme V- 4 The organocatalytic enantioselective Michael addition of Weinreb β -ketoamide to nitroolefins.

Firstly, different bifunctional squaramides or thioureas were investigated in this model transformation (Table V- 1). After 28 h of reaction, pleasingly, the catalysts **XXXII**, **LXVIII** and **LXIX** provided the expected product **184** with high yield, diastereoselectivity and enantioselectivity (Table V- 1, Entries 1-3), with catalyst **LXIX** giving the best results (Table V- 1, Entry 3). In contrast, the use of squaramides bearing an aromatic moiety on the nitrogen atom (the catalysts **LXIII** and **LXX**) instead of the 3,5-bis(trifluoromethyl)benzylamine unit (Table V- 1, Entries 4-5) severely impeded the enantioselectivity and completely annihilated the diastereoselectivity of the model reaction. In a similar way, the bifunctional thiourea catalysts **XXIV** and **XXIII** afforded the target product **184** with high yield, but were unable to control the diastereoselectivity of the process: product was obtained with low

diastereoselectivity and moderate enantioselectivity (Table V- 1, Entries 6-7). Fortunately, we found that a ratio of 1:1 between both substrates could be used in this transformation: the selected catalyst **LXIX** (2 mol%) provided the product **184** with unchanged efficiency (92% yield, 18:1 *dr*, 98% *ee*, Table V- 1, Entry 8). Pleasingly, the reaction was even faster than we had initially assumed since the starting materials were fully converted after 14 h at 25 °C.

Table V- 1 Evolution of various bifunctional organocatalysts.



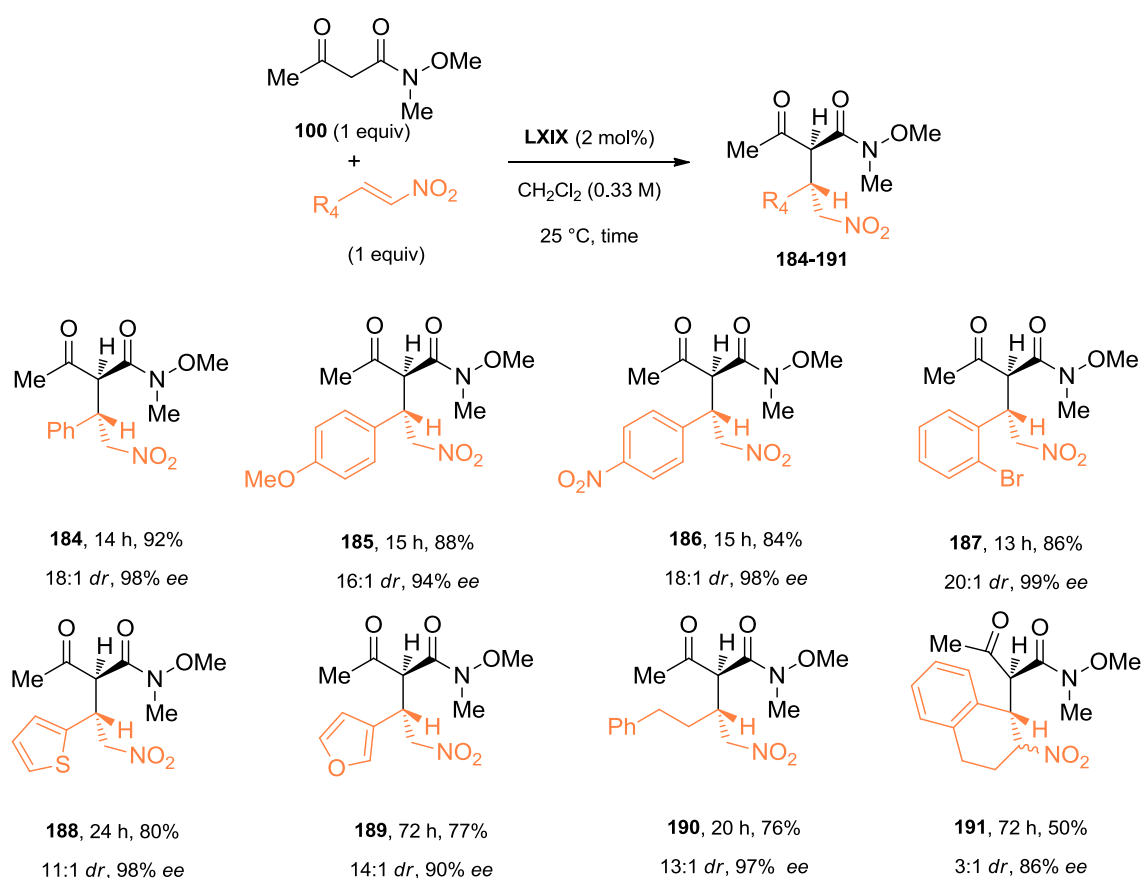
Entry	Catalyst	Yields(%)	<i>dr</i>	<i>ee</i> (%)
1	XXXII	97	15:1	-95
2	LXVIII	94	17:1	98
3	LXIX	99	16:1	98
4	LXIII	91	1:1	-73, 76
5	LXX	89	1:1	83, -81
6	XXIV	95	3:1	-83, 67
7	XXIII	97	1:1	60, -66
8	LXIX	92	18:1	98

V.3.2.2 SCOPE OF NITROOLEFINS

Using the optimized reaction conditions, the scope and limitations of the reaction with acyclic Weinreb β -ketoamides were studied (Table V- 2). Various nitroolefins were tested in the standard reaction conditions with **100** as the reaction partner. Aryl-substituted nitroolefins were studied firstly. As expected, both electron-rich (e.g. *p*-methoxy-substituted) or electron-poor (e.g. *p*-nitro-,*ortho*-bromide-substituted) aryl groups gave the corresponding desired products **184-187** with high yields and excellent diastereo- and enantioselectivities. When β -heteroaromatic nitroolefins participated in this transformation, the expected products **188-189** were also formed in high yields, but a small decrease of the diastereo- and enantioselectivities was noticed.

We next explored the generality of the reaction by switching to non-aromatic nitroolefins. The product **190** was obtained with 76% yield, 13:1 *dr* and 97% *ee*. As recently highlighted by Duschmalé and Wennemers, more-substituted nitroolefins are more challenging substrates in this kind of transformation.^[99, 281] 3-Nitro-2*H*-chromene participated in this transformation under the optimized conditions, furnishing the adduct **191** in lower yield and acceptable enantioselectivity. In fact, the stereogenic center between the two carbonyl groups was still efficiently controlled, but due to the presence of an additional stereogenic center α to the nitro group a mixture of diastereomers was observed.

Table V- 2 Evaluation of various nitroolefins.



V.3.2.3 SCOPE AND LIMITATIONS OF WEINREB β -KETOAMIDES

Different Weinreb β -ketoamides were then exposed to the optimized reaction conditions in the presence of β -nitroolefins **121** (Figure V- 2). All the tested Weinreb β -ketoamides with a linear alkyl chain provided the expected products **192-194** with reasonable yields and excellent enantioselectivities. However, substrates bearing a bulkier ramified alkyl chain or an aromatic group along with cyclic Weinreb β -ketoamide somewhat impeded the diastereoselectivity. To obtain product **196**, 10 mol% of catalyst **LXIX** were required, and, even after 72 h, the conversion was not complete. All in all, the major diastereomers of products **192-196** were still formed with high enantioselectivities. On the opposite, the products **197-198** did not form even with increased catalyst loading (10 mol%) and prolonged reaction time. Because the α position of substrate **198** is less acidic than those of Weinreb β -ketoamides, its activation is more difficult, explaining why there is no reaction with the nitroolefin.

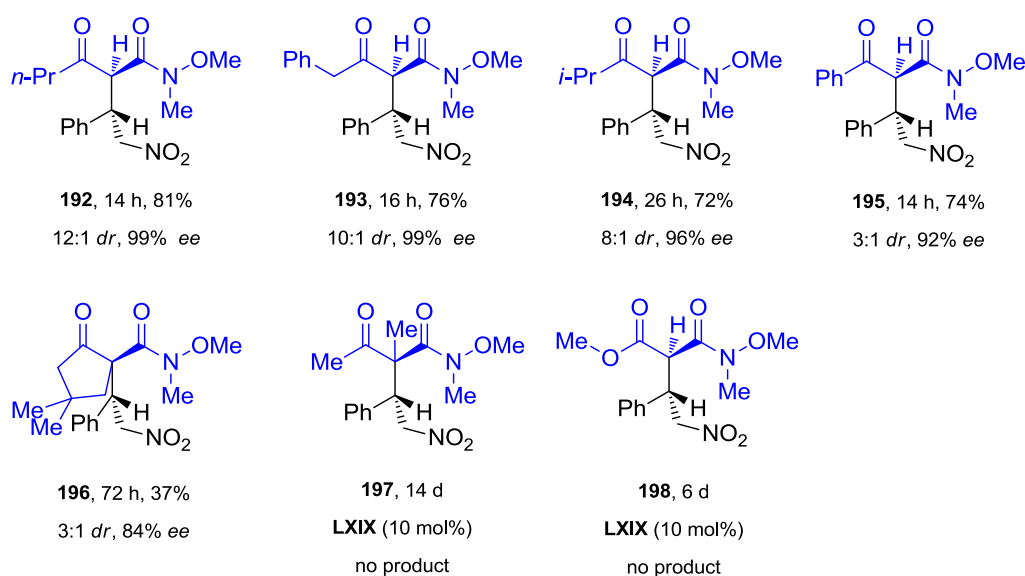
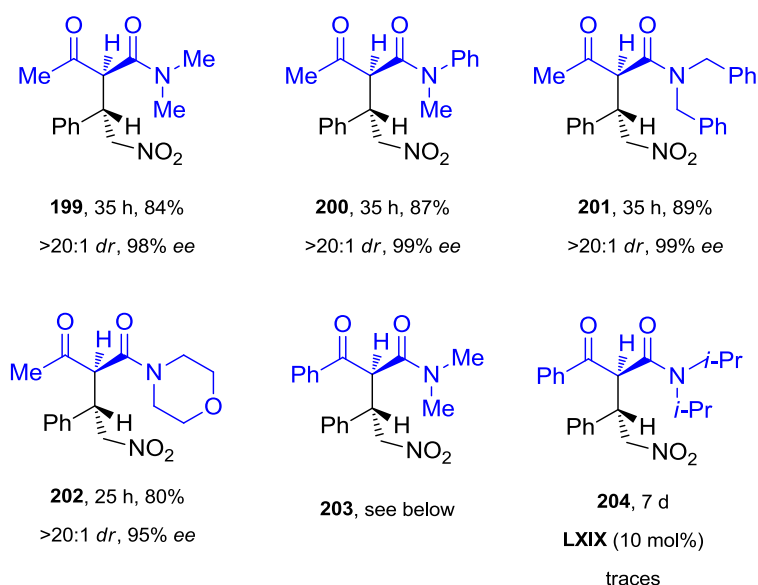


Figure V- 2 Evolution of various Weinreb β -ketoamides.

V.3.2.4 SCOPE OF ACYCLIC TERTIARY β -KETOAMIDES

We next continued to investigate the less-activated acyclic tertiary β -ketoamides (Table V- 3). Pleasingly, when using tertiary β -ketoamide **101** in place of Weinreb β -ketoamide **100** under the standard reaction conditions, even though the reaction had to be run for 35 h, the product **199** was formed with yield and enantioselectivity similar to the Weinreb amide counterpart. Interestingly, the diastereoselectivity of the process was completely controlled, since the second diastereomer of the product was not even observed in the crude ^1H NMR spectrum. As expected, the products **199-202** were formed with similar results as **199**. Note that once again the substrate with a phenyl substituent at the ketone moiety proved more challenging. Under the optimized reaction conditions, even after 6 days, the starting materials had not been completely converted. The product **203** was isolated in only 38% yield, but the

diastereo- and enantioselectivity still remained high (Table V- 3, Entry 1). When increasing the amount of catalyst **LXIX** to 10 mol% and of nitroolefin **121** to 1.2 equiv., the yield was increased, but unfortunately, the diastereoselectivity was strongly reduced (Table V- 3, Entry 2). In contrast, keeping the catalyst loading at 2 mol% and once again increasing the quantity of nitroolefin **121** to a three-fold excess, the expected product **203** was obtained with 75% yield, 6:1 *dr* and 95% *ee* for the major diastereomer (Table V- 3, Entry 3). When using a more sterically hindered amide substrate, only traces of product **204** were obtained even with 10 mol% catalyst and a reaction time extended to 7 days.

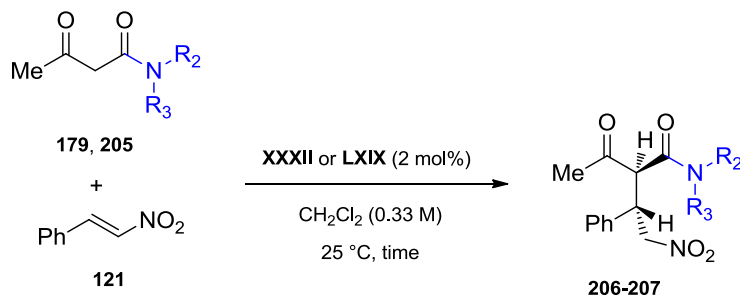
Table V- 3 Evaluation of various tertiary β -ketoamides.

Entry	Catalyst	Ratio (177:121)	Time (d)	Yields (%)	<i>dr</i>	<i>ee</i> (%)
1	LXIX (2 mol%)	1:1	6	38	8:1	95, 68
2	LXIX (10 mol%)	1:1.2	6	68	2:1	92, 89
3	LXIX (2 mol%)	1:3	5	75	6:1	95, 69

V.3.2.5 ATTEMPTES TO EXTEND THE REACTION TO ACYCLIC SECONDARY β -KETOAMIDES

In the past years, our research group had already reported the organocatalytic Michael addition of cyclic α -substituted β -ketoamides to α,β -unsaturated carbonyl compounds^[86, 168, 194, 282] or nitroolefins.^[99] It has been highlighted that the presence of a proton on the nitrogen atom was very important for both reactivity and enantioselectivity. If the proton was replaced by an alkyl or aryl group, the reaction could not proceed. Moreover, the acidity of the secondary amide could be correlated with the observed enantioselectivities. In this context, we wanted to evaluate acyclic secondary β -ketoamides in the present transformation (both in the initial reaction conditions and in the optimized ones). Firstly, *N*-phenyl secondary

β -ketoamide **205** was engaged in the reaction: the adduct **206** was formed with acceptable yield and enantioselectivity, but unfortunately, with a disappointing diastereoselectivity (Table V- 4, Entries 1 and 2). Using the corresponding *N*-benzyl secondary β -ketoamide **179**, the results were not really improved: the diastereoselectivity was slightly better but the enantioselectivity was not satisfactory (Table V- 4, Entries 3 and 4).

Table V- 4 Evaluation of various acyclic secondary β -ketoamides.

Entry	Ratio (179/205:121)	Catalyst	R ²	R ³	Yields (%)	<i>dr</i>	<i>ee</i> (%)
1	1:1	LXIX	Ph	H	81	2:1	94, 95
2	2:1	XXXII	Ph	H	73	2:1	95, 69
3	1:1	LXIX	CH ₂ Ph	H	70	5:1	74, 38
4	2:1	XXXII	CH ₂ Ph	H	78	2:1	69, 58

V.3.2.6 RELATIVE AND ABSOLUTE CONFIGURATIONS OF THE MICHAEL ADDUCTS

To understand the activation mode of the catalyst, it is of great interest to know the absolute and relative configurations of the stereogenic centers formed during the Michael addition. This determination could be achieved using X-ray diffraction and the crystal structure of **187** allowed to attribute it as being the (2*S*,3*S*) stereoisomer (Figure V- 3).

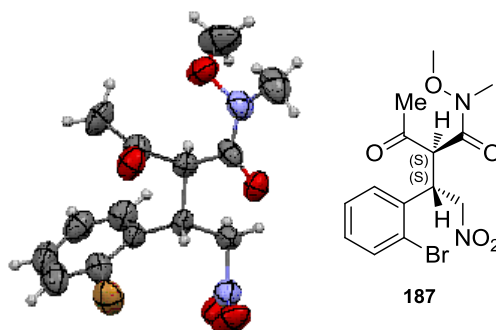
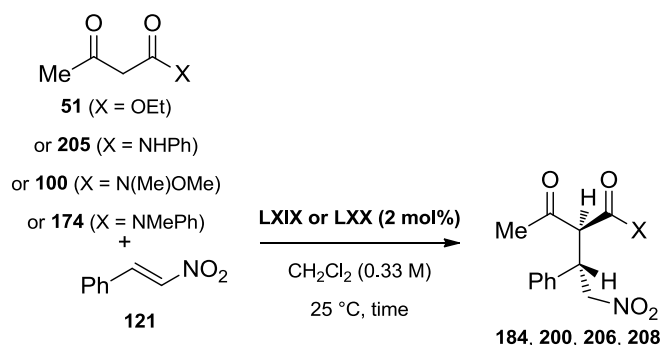


Figure V- 3 Determination of the absolute and relative configurations by X-ray diffraction.

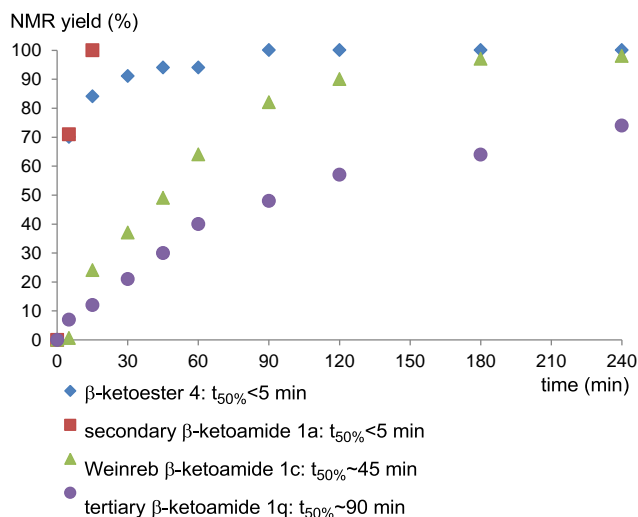
V.3.3 RATIONALIZATION OF THE REACTIVITY AND THE SELECTIVITY

V.3.3.1 KINETIC STUDIES

Rationalization and mechanistic studies are very important to make reactions more predictable and favor their further integrations in synthetic plans towards more complex products. Therefore, we aimed to understand which factors, both on substrates and catalysts, could account for the diastereoselectivity of the reaction. We firstly investigated the kinetic profiles with four different pronucleophiles in the standard reaction conditions: the progress of the reactions with β -ketoester **51**, secondary β -ketoamide **205**, Weinreb β -ketoamide **100** and tertiary β -ketoamide **174**, were monitored by ^1H NMR spectroscopy. From the reaction profiles (Figure V- 4 A), we could see that reactions with both ethyl acetoacetate **51** and the secondary β -ketoamide **205** have reached 50% conversion in less than 5 min, highlighting the exceptional reactivity of squaramide catalyst **LXIX**. Moreover, the secondary amide **205** seemed to be even more reactive than the standard ketoester **51**, since full conversion was attained within 15 min. In contrast, the substrate **100** and **174** resulted in slightly slower reactions as 45 min or 90 min were respectively required to attain 50% conversion. However, full conversion could still be observed after a few hours of reaction.



A) Reaction profile with different pronucleophiles (catalyst III)



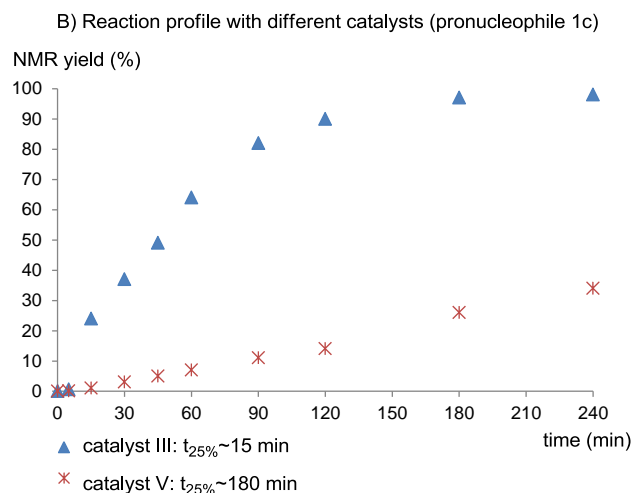


Figure V- 4 Kinetic study for comparison of the different 1,3-dicarbonyl substrates.

In the optimization reaction process, we had found differences in the behaviors of catalysts with an electron-poor benzylic or aromatic unit. Herein, the advancement of the reaction was monitored in the presence of catalysts **LXIX** and **LXX** with Weinreb β -ketoamide as the substrate (Figure V- 4 B). The catalyst **LXIX** was not only far more selective, but also 12 times more active. As the group of Cheng reported, the catalyst **LXIX** is less acidic than **LXX**.^[283] It is common belief that stronger acidities result in both better activity and selectivity of hydrogen-bonding organocatalysts,^[88, 283, 284] in clear contrast with our results, which are however in line with the rare reports on *N*-alkyl catalysts' performance.^[283, 285]

V.3.3.2 ORIGIN OF DIASTEREOSELECTIVITY

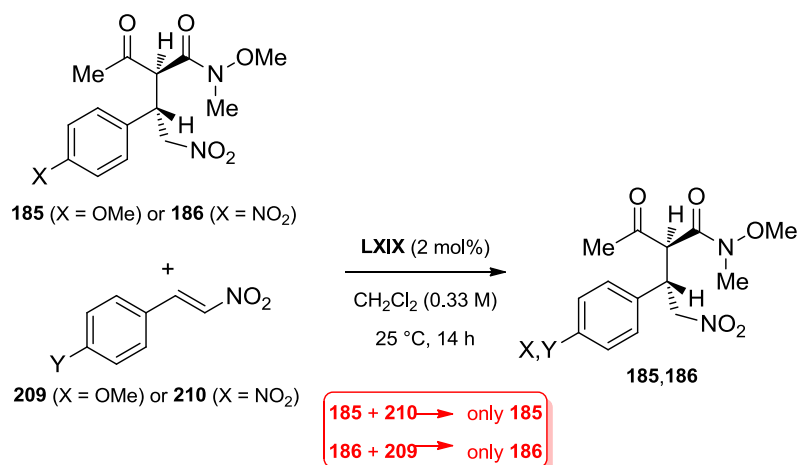
To explain the high diastereoselectivity of the reaction, two different proposals have been investigated:

1. The kinetic scenario, in which the C-C bond formation is intrinsically highly diastereoselective and the remaining proton in the α -position cannot be abstracted by the catalyst **LXIX**.
2. The thermodynamic scenario, in which the catalyst epimerizes the final product into its more stable diastereomer.

V.3.3.2.1 REVERSIBILITY TEST

To know whether the reaction is reversible or not, we have designed two crossover experiments between adducts **185/186** and nitroolefins **209/210** under the standard reaction conditions (Scheme V- 5). After 14 h, no cross-over product could be observed by ^1H NMR.

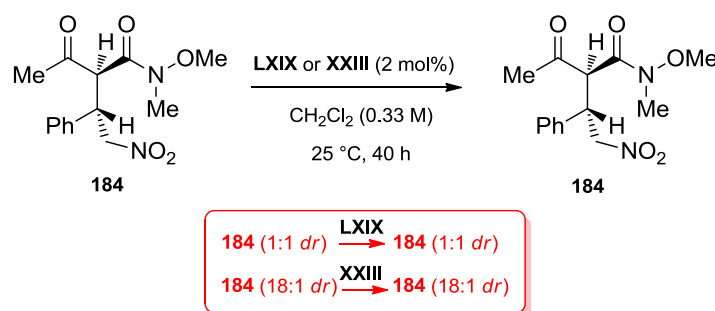
From this result, we determined that the reaction was irreversible.



Scheme V- 5 Reversibility test.

V.3.3.2.2 EPIMERIZATION STUDIES OF β -KETOAMIDES

Having secured the irreversibility of the reaction, epimerization studies were performed. Product **184** with high 18:1 *dr* was placed in the presence of the unselective catalyst **XXIII** and, at the same time, the same compound with 1:1 *dr* was exposed to the best catalyst **LXIX** (Scheme V- 6). In both reactions, we could observe that the *dr* of the final product had not changed, meaning that no epimerization happens in the reaction conditions. As a consequence, this observation indicates that the catalyst could control the highly diastereoselective carbon-carbon bond-forming step in the kinetic scenario.

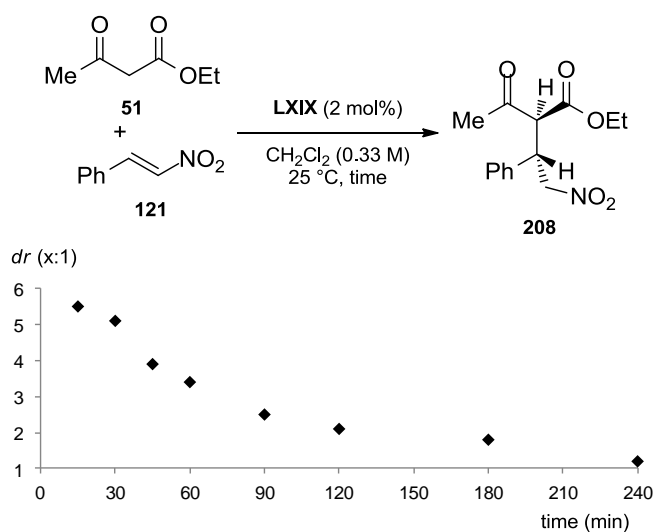


Scheme V- 6 Epimerisation studies of the adducts with β -ketoamides.

V.3.3.2.3 EPIMERIZATION STUDIES OF β -KETOESTERS

The potential epimerization of adducts obtained from β -ketoester was investigated. In the process of the reaction of ethyl acetoacetate and nitroolefins, the *dr* of the final product **208** was monitored over time (Scheme V- 7). From the results, we could observe that the diastereomeric ratio of final product was moderate at the beginning of the reaction (~5.5:1 *dr*)

and that the product then unselectively epimerizes ($\sim 1:1$ *dr*). These results were in accordance with a report by Pedrosa and co-workers, who had carried out a similar study in the presence of the corresponding bifunctional thiourea catalyst.^[286]



Scheme V- 7 Epimerisation studies for β -ketoamides.

V.3.3.2.4 RELATIONSHIP BETWEEN THE CHARTON STERIC PARAMETER OF THE KETONE SUBSTITUENT AND THE DIASTEREOSELECTIVITY

To try to understand which structural elements on the β -ketoamide influence the diastereoselectivity, we have plotted $\log(dr)$ in function of the Charton steric parameters of the ketone substituents,^[287-289] in order to identify a linear free-energy relationship.^[290-296] We found that the diastereoselectivity tended to decrease with more bulky substrates (products **184** and **192-195**), and a linear relationship was indeed observed for aliphatic ketones **100** and **167-170** with an acceptable correlation factor (Figure V- 5). Not surprisingly, replacing Weinreb β -ketoamides by bulkier tertiary amides could increase the steric difference between the ketone and the amide moieties, resulting in an improvement of the diastereoselectivity.

For the aromatic ketone, **195** was obtained with 3:1 *dr* instead of the predicted 15:1 *dr* with a coplanar aromatic group. The other possible orientation of the aromatic group (perpendicular) gives a Charton value of 1.66. However, because this value would predict the other diastereomer to be the major one, with only modest selectivity, it was not considered. In fact, the aromatic group influences not only the steric properties of the substrate, but also its electronic properties. Accordingly, this reduced diastereoselectivity can be ascribed to an epimerization of the more acidic α position. The sensibility of the *dr* of product **203** to the amount of catalyst **LXIX** goes in the same direction.

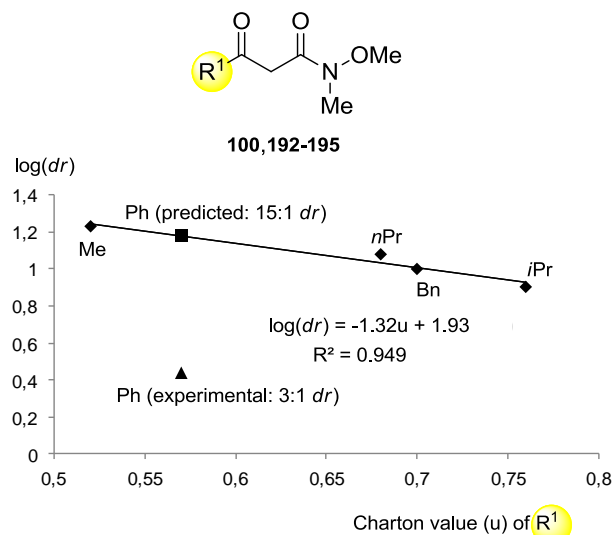
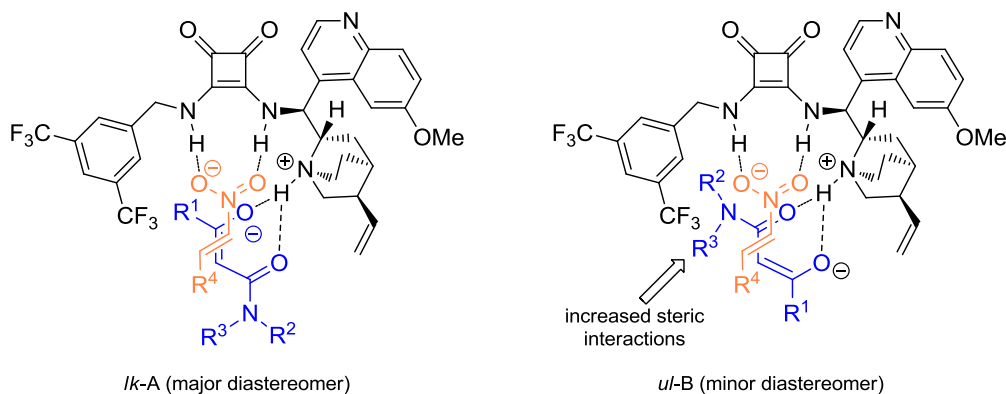


Figure V- 5 Linear free-energy relationship between dr and charton steric parameters of the ketone substituents.

V.3.3.3 PROPOSED TRANSITION STATE TO ACCOUNT FOR THE STEREOSELECTIVITIES

In the bibliographic part, we have already talked about the two main models that are used to explain the reactions with bifunctional thiourea catalyst (Figure I- 9).^[71, 72, 297] Although there are differing in their organization, they predict the same absolute configuration for the stereogenic center created during the reaction. Similarly, several transition states could be proposed to explain how the bifunctional squaramide organocatalyst activate the substrates. A Takemoto-type model had first been put forward for a primary amine-containing squaramide,^[95, 99, 298] but very recent studies are more supportive of the Papaí-Sóos model.^[102] In this context, in order to explain the absolute and relative configuration of products **184-195**, we had proposed the transition states **A** and **B** (Figure V- 6), with the squaramide moiety and the tertiary amine group on the chiral scaffold, which would be able to activate both substrates simultaneously and control the approach of the nucleophile to the nitroolefin.^[44, 71, 72, 95]



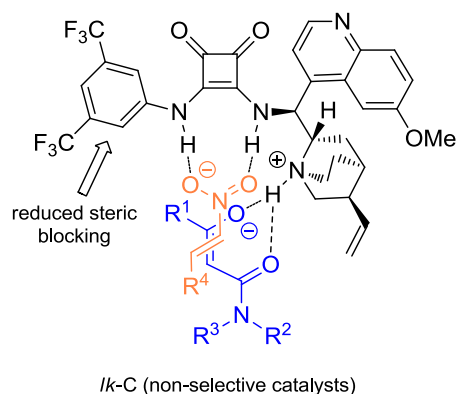


Figure V- 6 Proposed transition states to explain the stereoselectivity of the reaction.

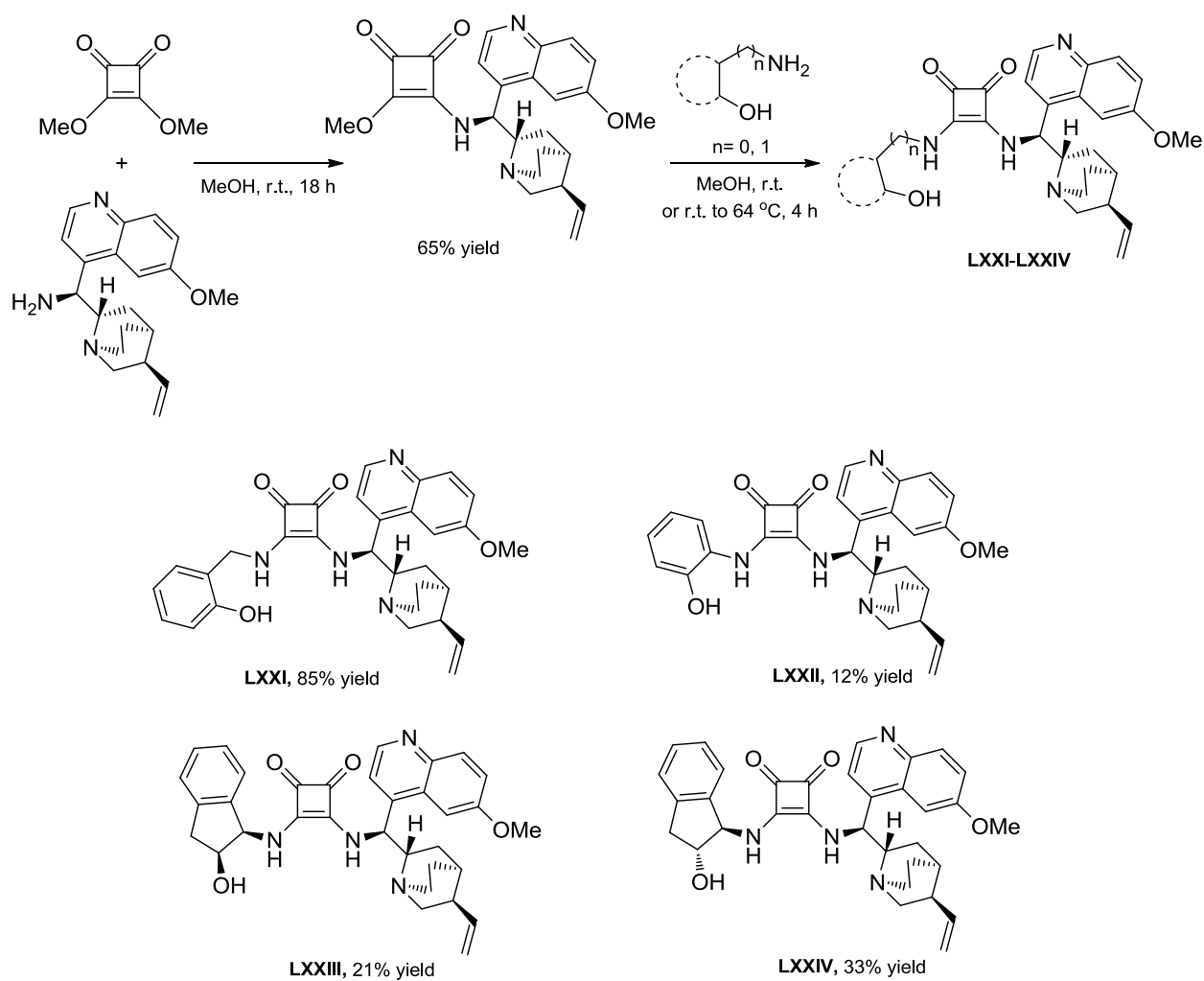
For our reaction, the squaramide moiety easily interacts with nitroolefins via multiple hydrogen-bonding activation, enhancing the electrophilic character of the reacting carbon center. On the other hand, the neighboring tertiary amino group activates the Weinreb β -ketoamide, forming a highly nucleophilic enolate species. Moreover, according to the previous example,^[99] we have observed that the diastereoselectivity originated from the addition of the *Si* face of the enolized Weinreb β -ketoamide to the *Si* face of the nitroolefin. This positioning could be achieved if the substituent of the ketone is put on the side of the catalyst, forming the transition state **A**. On the contrary, if the substituent of the Weinreb amide is placed on this side, offering the transition state **B**, then the bulkier tertiary amide points towards the catalytic pocket, what increases steric interactions. In addition to this, additional hydrogen bonding between the ammonium nitrogen atom and the Lewis basic oxygen atom of the amide might also help to rigidify the transition state and improve the stereoselectivities. The observed linear free energy/Charton steric parameter relationship (Figure V- 5) indicates that, with bulkier R^1 groups, the difference between the size of the two substituents is lower, bringing the transition states *lk-A* and *ul-B* closer in energy, thereby reducing the diastereoselectivity. Consequently, switching from Weinreb amide to bulkier other tertiary amides could improve the facial selectivity, accounting for the higher diastereoselectivities. The non-selectivity of the *N*-aryl catalysts **LXIII**, **LXX**, **XXIV**, **XXIII** could tentatively be explained by the lower flexibility of the aryl group compared to its benzyl counterpart in transition state *lk-C*, resulting in a loss of discrimination between both topocities (Figure V- 6).

V.3.4 ATTEMPTS TO OBTAIN THE OTHER DIASTEREOMER

Having developed an efficient method to obtain the *like* adduct of β -ketoamides to nitroolefins, we wondered whether it would be feasible to reverse the diastereoselectivity of the reaction. In accordance with our proposed model, we needed to favor transition state **B**. To achieve this goal, we surmised that we could make the amide part approach the catalyst by creating an additional hydrogen bonding interaction between the catalyst and the highly Lewis basic oxygen atom of the Weinreb amide. At first, we have designed and synthesized a series of new organocatalysts (Table V- 5, **LXXI-LXXIV**) involving an alcohol or a phenol in the

bifunctional squaramide catalyst and then we attempted to investigate the combination of equimolar quantities of both starting materials in the presence of catalyst **LXXI** (Table V- 5, Entry 1). Unfortunately, the additional phenol group had very limited effect on the reaction outcome as the product **184** was formed with 88% yield, 15:1 *dr* in favor of the *like* diastereomer and 99% *ee*. Catalysts **LXXII**, **LXXIII** and **LXXIV** all afforded disappointing results (Table V- 5, Entries 2-4). Further work, with functionalities that have better hydrogen bonding abilities would be required to better assess the feasibility of this diastereoselectivity reversal.

Table V- 5 Synthesis and evaluation of various new organocatalysts to try to obtain the *unlike* diastereomer.



Entry	Catalyst	Yields (%)	<i>dr</i>	<i>ee</i> (%)
1	LXXI	88	15:1	99
2	LXXII	19	1.5:1	82, -80
3	LXXIII	68	2:1	72, -74
4	LXXIV	53	1:1	55, -77

V.3.5 SYNTHETIC USEFULNESS OF THE TRANSFORMATION

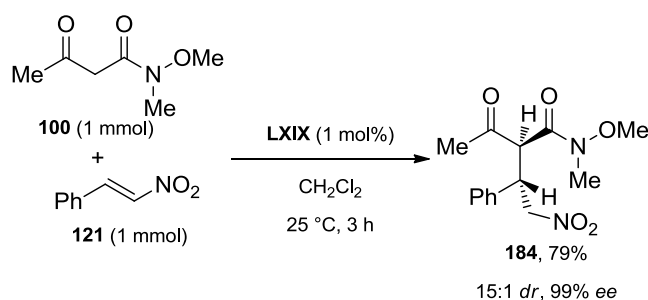
In order to certify the potential of the Michael adducts obtained from Weinreb β -ketoamides as building blocks in synthesis, we further investigated follow-up chemistry.

V.3.5.1 SCALE-UP OF THE REACTION

At first, it was very important to verify whether the reaction performs well on synthetically useful scale.

V.3.5.1.1 PREPARATIVE-SCALE REACTION (1-mmol)

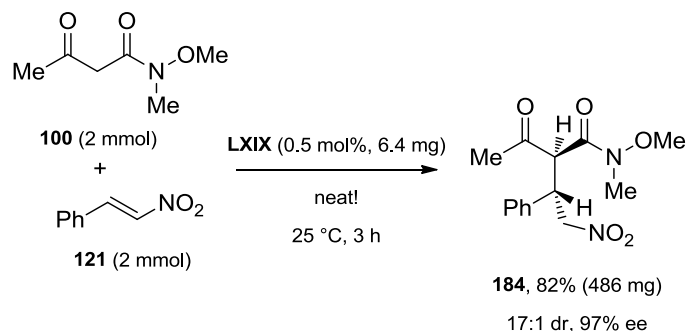
The reaction could be run on 1 mmol under the standard reaction conditions, with only 1 mol% of catalyst **LXIX** (Scheme V- 8). After 3h, the expected product **184** was formed with a slightly lower yield (79%), excellent *dr* and enantioselectivity.



Scheme V- 8 Preparative scale reaction.

V.3.5.1.2 NEAT PREPARATIVE-SCALE REACTION (2-mmol)

If our reaction fulfils several of the principles of green chemistry, a drawback is the use of toxic and polluting CH_2Cl_2 as solvent. It is with great pleasure that we discovered that the reaction could also be run on 2-mmol scale under the optimization reaction conditions without any solvent and only 0.5 mol% of catalyst **LXIX** (Scheme V- 9). After 3 h, the product **184** was obtained with 82% yield (more than 480 mg of compound) and virtually unchanged stereoselectivities (17:1 *dr* and 97% *ee*).



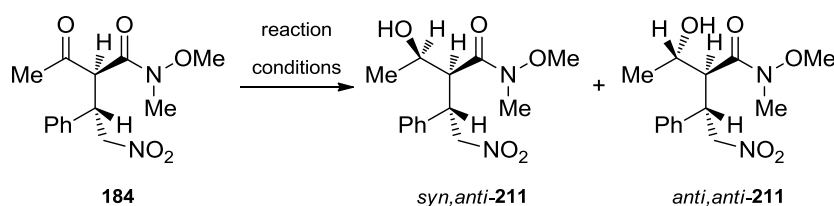
Scheme V- 9 Preparative scale reaction in neat conditions.

V.3.5.2 POST-FUNCTIONALIZATION OF THE ADDUCTS

Michael adducts **184-196** possess several functional groups: a ketone, a Weinreb amide and a nitro group. It was interesting to show that various chiral enantioenriched motifs of synthetic interest could be accessed by the chemoselective modification of these functionalities.

V.3.5.2.1 DIASTEREOSELECTIVE KETONE REDUCTION

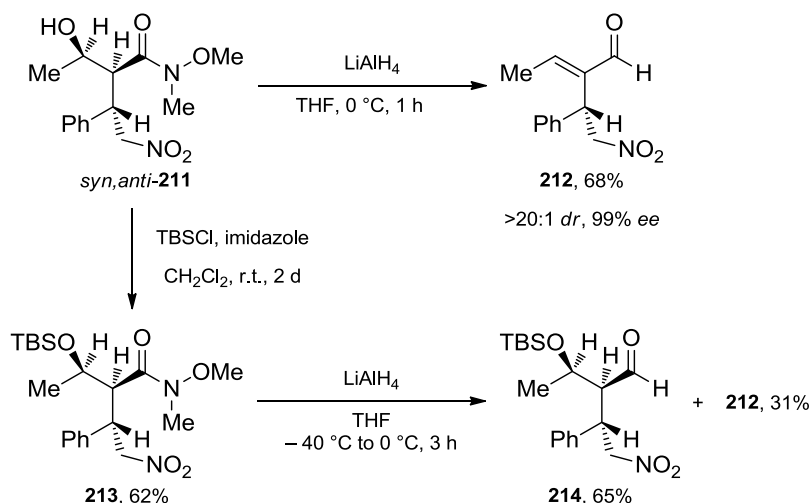
The main feature of using acyclic methylene Weinreb β -ketoamides is the control of the relative configuration of the stereogenic center between the two carbonyl groups. Hence, firstly, the diastereoselective reduction of the ketone group of **184** was investigated to enable efficient access to densely functionalized stereo triads (Table V- 6). As early as 1991, the group of Utimoto have reported that α -chiral β -dicarbonyl compounds could be reduced by using NaBH_4 in the presence of a Lewis acid.^[299] Herein, when **184** was put together with NaBH_4 and MnBr_2 in MeOH at 0 °C, after 10 min the product *syn,anti-211* was obtained with 75% isolated yield and with 13:1 *dr* (Table V- 6, Entry 1). Preparing its epimer *anti,anti-211*, required extensive optimization of the reaction conditions, as various known methods gave disappointing results (Table V- 6, Entries 2-8). Finally, when **184** was treated with Me_4NBH_4 ^[300] in MeOH at -40 °C, after 4 h the product *anti,anti-211* was formed with 78% isolated yield and 7:1 *dr* (Table V- 6, Entry 9).

Table V- 6 Diastereoselective reduction of the ketone group of **184**.

Entry	Reaction conditions	Yield ^a	<i>dr</i> ^b (<i>syn,anti/anti,anti</i>)
1	NaBH ₄ , MnBr ₂ , MeOH, 0 °C, 10 min	75% (<i>syn,anti</i>)	13:1
2	KBHET ₃ , Et ₂ O, -78 °C, 20 min	degradation	-
3	NaBH(OAc) ₃ , AcOH, r.t., 2.5 h	no reaction	-
4	NaBH ₄ , AcOH, r.t., 2.5 h	no reaction	-
5	NaBH ₄ , MeOH, 0 °C, 10 min	45% (<i>anti,anti</i>)	1:2.5
6	NaBH ₄ , CF ₃ CH ₂ OH, 0 °C, 10 min	not purified	3:1
7	NaBH ₄ , MeOH, -40 °C, 4 h	not purified	1:3
8	Me ₄ NBH ₄ , MeOH, 0 °C, 30 min	54% (<i>anti,anti</i>)	1:3
9	Me ₄ NBH ₄ , MeOH, -40 °C, 4 h	78% (<i>anti,anti</i>)	1:7

V.3.5.2.2 REDUCTION OF THE WEINREB AMIDE

Weinreb amides can be selectively reduced to aldehydes. Therefore, we tried to use the hydroxyl derivatives **211** as potential precursors for the challenging synthesis of α -chiral β -hydroxyaldehydes (Scheme V- 10). Firstly, *syn,anti*-**211** was exposed to LiAlH₄ in THF at 0 °C. After 1 h, not only had the Weinreb amide been reduced to the aldehyde, but also the alcohol was eliminated, affording product **212** with 68% isolated yield as a single diastereomer, and without affecting the enantiomeric excess. Although two stereogenic centers disappeared in the process, the product obtained in this transformation is still interesting and could not be prepared enantioselectively before. Indeed, in their attempt to synthesize enantioenriched **212** via an (*S*)-proline-catalyzed Rauhut-Currier reaction between crotonaldehyde and β -nitrostyrene, the group of Córdova did not obtain any enantioselectivity.^[301]



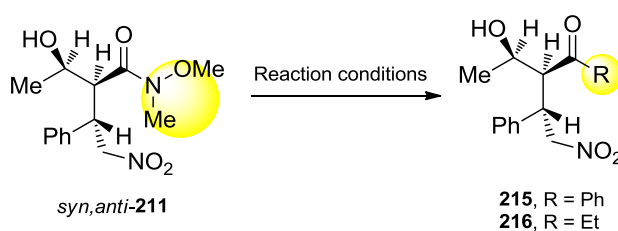
Scheme V- 10 Post-functionalization of the Weinreb amide.

To avoid the dehydration of the fragile β -hydroxyaldehyde, we firstly needed to protect the alcohol as the *tert*-butyldimethylsilyl ether **213** (Scheme V- 10). Pleasingly, the product **213** was reduced by LiAlH_4 to get the versatile protected β -hydroxyaldehyde **214** with 65% isolated yield, even though the formation of **212** could not be completely avoided.

V.3.5.2.3 OTHER ATTEMPTS OF POST-FUNCTIONALIZATION

Next, attempts of conversion of the Weinreb amide into ketones were carried out. Unfortunately, upon reaction with Grignard reagents in Et_2O at $0\text{ }^\circ\text{C}$, the expected ketones **215** or **216** were not obtained (Table V- 7, Entries 1-2).

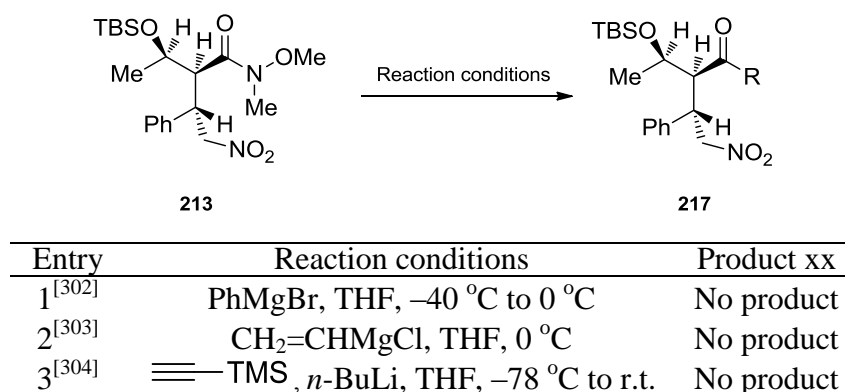
Table V- 7 Attempts of transformation of the Weinreb amide into ketones.



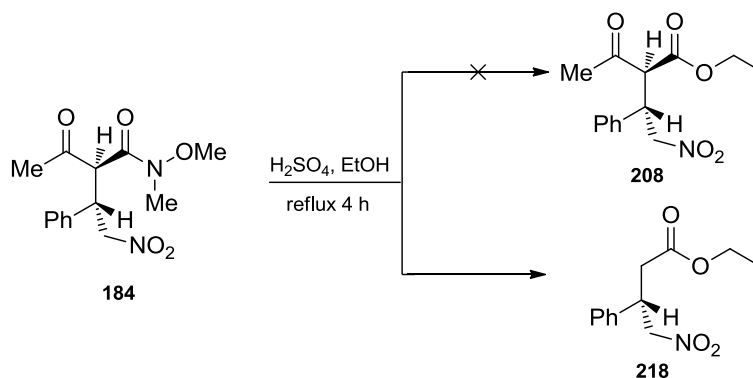
Entry	Reaction conditions	Product xx
1 ^[302]	$\text{PhMgBr, Et}_2\text{O, 0 } ^\circ\text{C}$	No product
2 ^[302]	$\text{EtMgBr, Et}_2\text{O, 0 } ^\circ\text{C}$	No product

Herein, we thought that once again protecting the alcohol of *syn,anti*-**211** could be useful. When the Weinreb amide with TBS-protected alcohol was reacted with different nucleophilic organometallic reagents in various reaction conditions (Table V- 8, Entries 1-3), once again the expected ketones did not form. Although the reasons for these failures are not clear at the moment, we can suspect that the nitro function is playing a role.

Table V- 8 Attempts of Weinreb ketone synthesis on the substrate with TBS-protected alcohol.



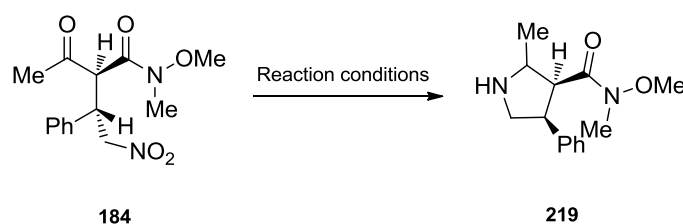
To continue exploring the post-functionalization of the Weinreb amide, the product **3c** was refluxed in EtOH for 4 h in the presence of H₂SO₄ (Scheme V- 11). While we were aiming to prepare β -ketoester **208**, product of transesterification and deacylation **218** was formed. Suspecting that traces of water in EtOH were maybe responsible for this reactivity, we used dry EtOH, but the reaction still provided the same product **218**.



Scheme V- 11 Post-functionalization of the Weinreb amide.

A traditional post-functionalization of the products of Michael additions to nitroolefins is their conversion into chiral lactams by reduction of the nitro group into the amine followed by reductive amination with the ketone moiety. Various classic reaction conditions were evaluated (Table V- 9, Entries 1-5), and although the product **219** could sometimes be found in the crude reaction mixture, its purification was not possible because many impurities were present.

Table V- 9 Attempts to synthesize the chiral lactam.



Entry	Reaction conditions	Product xx
1 ^[89]	Fe/CH ₃ COOH, NaBH ₃ CN	No product
2 ^[305]	Activated zinc powder, CH ₃ COOH, THF	Yes but not isolable
3 ^[306]	Pd/C, H ₂ (1 atm), MeOH, r.t., 14 h	No product
4	Pd/C, H ₂ (1 atm), CH ₃ COOH, r.t., 14 h	No product
5 ^[307]	NaBH(OAc) ₃ , MeOH, <i>p</i> -TsOH, 3 Å MS	Yes but not isolable

V.3.6 CONCLUSIONS

In summary, the first addition of acyclic β -ketoamides to nitroolefins in the presence of a bifunctional squaramide organocatalyst has been developed.^[308] Similar to the reactions with other 1,3-dicarbonyl substrates, the expected products were obtained with high yields and enantioselectivities. In addition, some unprecedented features were uncovered in this study. Firstly, for the acyclic tertiary methylene β -ketoamides, the second stereogenic center between the two carbonyl groups could be controlled with high diastereoselectivities. Secondly, the reaction proceeded with equimolar quantities of both reactants, did not requiring an excess of pronucleophile to obtain high efficiency. Thirdly, quantitative evaluation of the structural elements influencing the selectivity will help improving the predictability of the results in related transformations. Fourthly, the dramatic differences in terms of reactivity and selectivity between *N*-benzyl- and *N*-aryl-squaramides in the studied reaction could be quantified, which could be helpful in the selection of the ideal catalyst when developing new transformations. Finally, interesting β -hydroxyaldehyde could be obtained by post-functionalization of the Michael adducts.

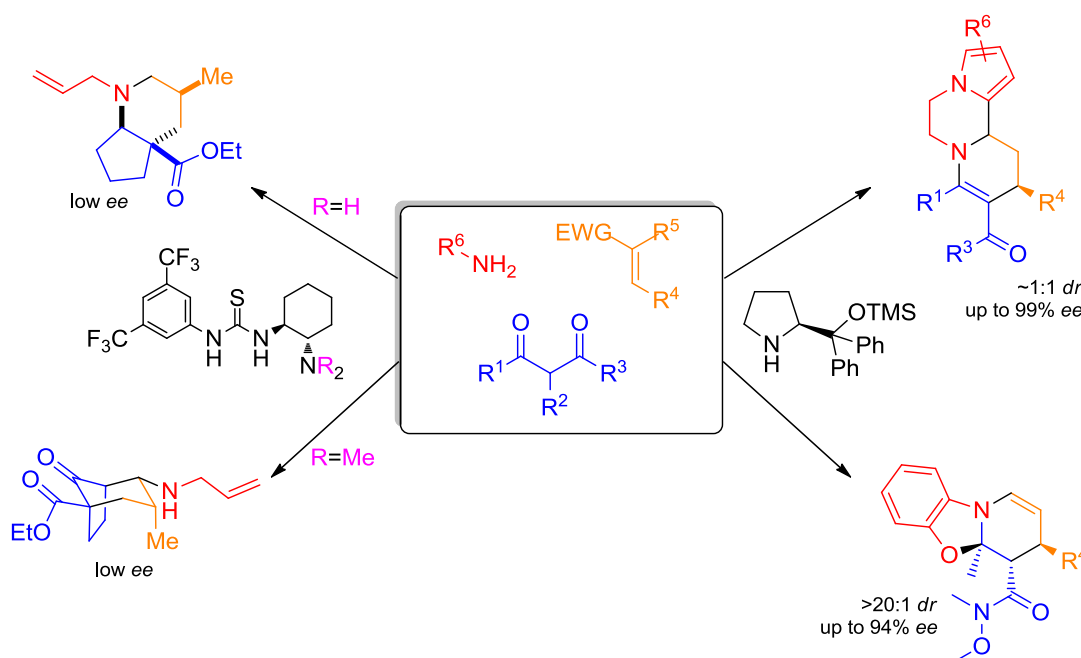
GENERAL CONCLUSION AND PERSPECTIVES

GENERAL CONCLUSION AND PERSPECTIVES

The aim of my thesis was to develop organocatalytic enantioselective variants of Michael-addition initiated multicomponent reactions of β -dicarbonyls, starting from the racemic versions of these reactions developed in the laboratory a few years ago.

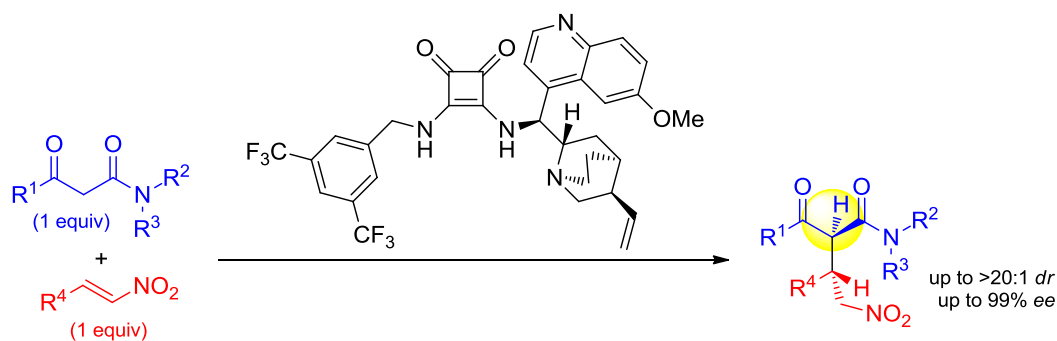
At first, we have studied the combination of cyclic β -ketoesters, methacrolein and simple primary amines in the presence of various organocatalysts. We realized that the mode of activation of the organocatalyst was governing the chemoselectivity of the reaction, allowing the production of two different families of compounds from the same starting materials, albeit with modest enantioselectivities.

In the second part, we have developed a new enantioselective three-component reaction of various 1,3-dicarbonyl substrates, α,β -unsaturated aldehydes and *N*-(2-aminoethyl)pyrroles catalyzed by secondary amine catalyst in order to prepare enantioenriched tricyclic pyrrollopiperazines. Good yields and excellent enantiomeric excess were obtained. Based on this reactivity, in the third part, methylene β -ketoamides, α,β -unsaturated aldehydes and amines functionalized with a pendant nucleophiles, such as 2-aminophenols, were introduced in the three-component reaction initiated by an enantioselective Michael addition. The expected products were obtained with reasonable yield and excellent diastereo- and enantioselectivities.



In the last part, attracted by the synthetic potential of methylene β -ketoamides, we developed for the first time the enantioselective Michael addition of these donors to nitroolefins, catalyzed by a bifunctional squaramide catalyst. Compared with the reactions of

their extensively studied β -ketoester counterparts, the expected products were still obtained not only with good yields and enantioselectivities, but also with high diastereoselectivities. Moreover, competition and kinetic studies were conducted in order to rationalize the observed reactivity and selectivities. The high level of diastereocontrol dramatically increases the synthetic usefulness of the transformation.



Further work will aim at completing the study of the multicomponent reaction between Weinreb β -ketoamides, α,β -unsaturated aldehydes and 2-aminophenols, with a focus on their post-functionalization to obtain original chiral enantioenriched scaffolds. The combination of the Michael addition with other transformations (for example Diels-Alder cycloadditions) could also help further increasing the molecular complexity.

In addition to this, we believe that the potential of β -ketoamides in organocatalysis has still not been completely fulfilled and we will further try to assess their unique behavior in the presence of other electrophilic species.

EXPERIMENTAL PART

I. EXPERIMENTAL TECHNOLOGIES

I.1 GENERAL PROCEDURES

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 aluminum plates (Macherey-Nagel) containing a 254 nm fluorescent indicator. TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and to vanillin (2 g of vanillin and 4 mL of concentrated H₂SO₄ in 100 mL of EtOH) followed by heating. Flash column chromatography was performed using silica gel (35–70 μm, 60 Å, Acros).

I.2 STARTING MATERIALS

Unless specified, commercial reagents and solvents were used as received.

- All reagents were purchased and used without further purification.
- CH₂Cl₂, toluene, Et₂O, THF were dried using a M-Braun SPS-800 system.
- α,β-unsaturated aldehyde was distilled before use.
- AcOH is glacial acetic acid.
- crotonaldehyde, *trans*-2-hexen-1-al and *trans*- cinnamaldehyde were distilled just prior to use.
- secondary amine catalyst **VII**, **VIII** was purchased from Sigma-Aldrich. Catalysts **XXIII**, **I**, **II** are commercially available and other catalysts were prepared according to known literature procedure.
- Crushed 4Å molecular sieves was stored in an oven at 110 °C.
- MeOH was dried on 3Å molecular sieves.

I.3 INSTRUMENTATION

- Proton nuclear magnetic resonance (¹H NMR) spectra were recorded with a Bruker AV 400 spectrometer. Proton chemical shifts are reported in parts per million (δ scale), and are referenced using residual protium in the NMR solvent (CDCl₃: δ 7.26 (CHCl₃) or DMSO-D₆: δ 2.50 ((CD₂H)(CD₃)SO). Data are reported as follows: chemical shift (multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quadruplet, hept = heptuplet, m = multiplet), coupling constant(s) (Hz), integration).

- Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded with a Bruker AV 400 spectrometer. Carbon chemical shifts are reported in parts per million (δ scale), and are referenced using the carbon resonances of the solvent (δ

77.16 (CHCl₃). Data are reported as follows: chemical shift (CH_n where n is the number of hydrogen atoms linked to the carbon atom).

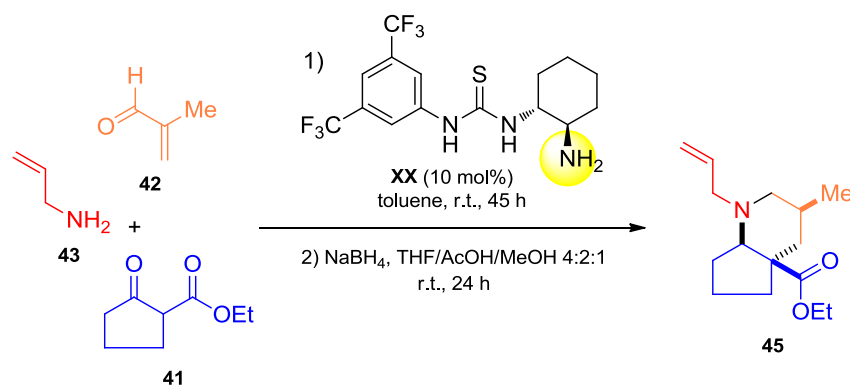
- Optical Rotations were recorded on a Perkin Elmer 241 Polarimeter at 589 nm and 20 °C and specific rotations are reported as follows: specific rotation (concentration in grams/100 mL of solution, solvent).

- High resolution mass spectra (HRMS) were recorded on a Waters Synapt G2 HDMS apparatus using a positive electrospray (ESI) ionization source.

- HPLC analyses for the determination of enantiomeric excesses were performed on a Merck-Hitachi system equipped with the following chiral columns: Chiralpak AS-H, Chiralpak AZ-H, Chiralpak AD-H, Chiralpak IA, Chiralpak IE, (*S,S*)-Whelk-O1, Chiralpak ID, Chiralcel OD-3, Lux-Amylose-2, Lux-Cellulose-4, Lux-Amylose-2, Chiralcel OJ-H, Lux-Cellulose-2.

II. EXPERIMENTAL PART OF ORGANOCATALYST-CONTROLLED CHEMOSELECTIVE THREE-COMPONENT REACTIONS

II.1 CATALYTIC REACTION



A 25-mL flask filled with argon was equipped with a magnetic stirrer bar. Toluene (5 mL) was then added followed by organocatalyst **XX** (12.3 mg, 0.032 mmol, 10 mol%). Then, ethyl 2-oxocyclopentanecarboxylate **41** (50 mg, 46.3 μ L, 0.32 mmol, 1.0 equiv) was added followed by methacrolein **42** (31.2 μ L, 0.38 mmol, 1.2 equiv), and allylamine **43** (24.0 μ L, 0.32 mmol, 1.0 equiv). After complete conversion of the β -ketoester, checked by TLC, the solution was filtered through a short pad of Celite, which was thoroughly washed with toluene. The solvent was evaporated under reduced pressure to obtain the crude dienamine.

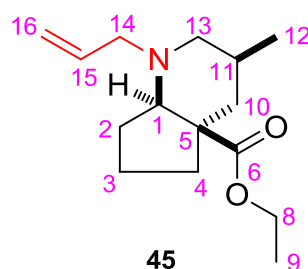
In a 50-mL flask equipped with a magnetic stirring bar, were added the crude dienamine dissolved in THF (2 mL), and NaBH₄ (72.6 mg, 1.92 mmol, 6 equiv) under argon. Secondly, AcOH (1 mL) was slowly added (caution: gas evolution), followed by EtOH (0.5 mL). The resultant suspension was stirred at r.t. for 24 h. After completion of the reaction, most of the solvent was removed under reduced pressure. Water (5 mL), 10% NaOH solution (5 mL) and Et₂O (5 mL) were added. The organic layer was separated and the aqueous phase was further extracted with Et₂O (3 \times 10 mL). The organic layer was then washed with water (2 \times 10 mL), brine (15 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated giving the crude product, which was analyzed by ¹³C NMR to measure the diastereomeric ratio. Crude product obtained with 10:1 *dr*. Purification was performed on a silica gel column affording the pure product **45** (65% yield, 45% *ee*). Analyses were in accordance with those obtained when the reaction was performed with 4 Å MS.

Racemates was prepared following the general procedure using 4 Å MS.

TLC (PE/EtOAc 1:3) R_f 0.05 (KMnO₄).

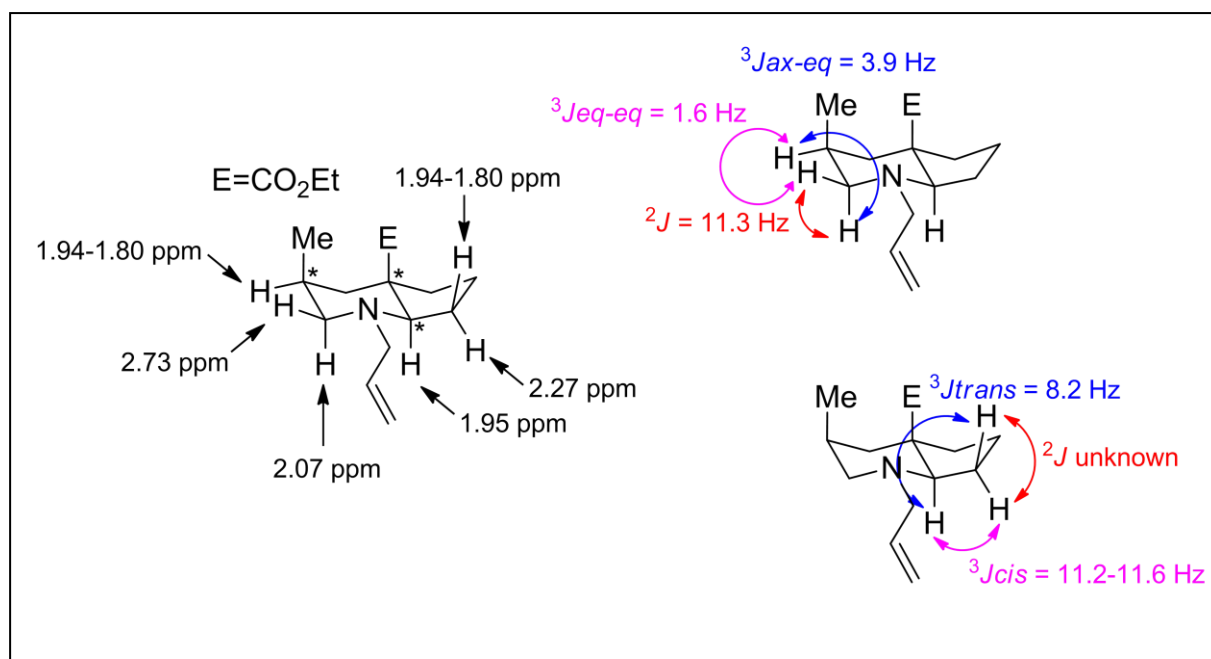
HRMS (ESI) calc'd for [C₁₅H₂₅NO₂+H]⁺: 252.1958, found: 252.1959.

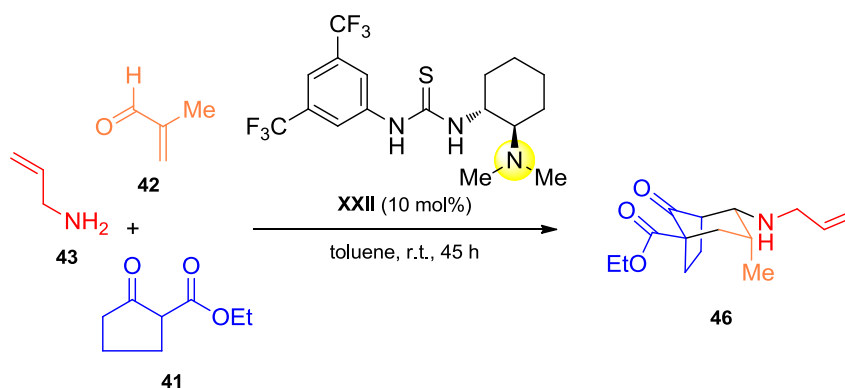
HPLC (S,S)-Whelk-O1, Hexane/Isopropanol+TEA 98/2, 25 °C, 0.5 ml/min, λ = 230 nm,
 τ_{major} = 8.28 min, τ_{minor} = 9.23 min.



$^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 5.94 (dddd, $J = 17.4, 10.2, 7.7, 5.3$ Hz, 1H, H_{15}), 5.16 (ddd, $J = 17.2, 3.1, 1.9$ Hz, 1H, H_{16a}), 5.09 (ddd, $J = 10.2, 2.8, 1.4$ Hz, 1H, H_{16b}), 4.10 (q, $J = 7.1$ Hz, 2H, H_{8a} and H_{8b}), 3.40 (ddt, $J = 13.9, 5.3, 1.6$ Hz, 1H, H_{14a}), 2.87 (dd, $J = 13.9, 7.7$ Hz, 1H, H_{14b}), 2.73 (dt, $J = 11.3, 1.6$ Hz, 1H, H_{13a}), 2.44 (dt, $J = 13.1, 1.6$ Hz, 1H, H_{10a}), 2.27 (tdd, $J = 11.2, 9.1, 7.9$ Hz, 1H, H_{2a}), 2.07 (dd, $J = 11.3, 3.9$ Hz, 1H, H_{13b}), 1.95 (dd, $J = 11.6, 8.2$ Hz, 1H, H_1), 1.94 – 1.80 (m, 3H, H_{2b} , H_{4a} and H_{11}), 1.68 – 1.59 (m, 2H, H_{3a} and H_{3b}), 1.49 – 1.39 (m, 1H, H_{4b}), 1.32 (dd, $J = 13.1, 5.5$ Hz, 1H, H_{10b}), 1.23 (t, $J = 7.1$ Hz, 3H, H_9), 0.96 (d, $J = 7.4$ Hz, 3H, H_{12}).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ (ppm) 175.8 (C_6), 135.7 (C_{15}), 117.1 (C_{16}), 72.9 (C_1), 60.6 (C_{13}), 59.6 (C_8), 59.0 (C_{14}), 50.8 (C_5), 40.2 (C_{10}), 37.1 (C_4), 29.5 (C_{11}), 26.0 (C_2), 19.54 (C_{12}), 19.50 (C_3), 14.2 (C_9).



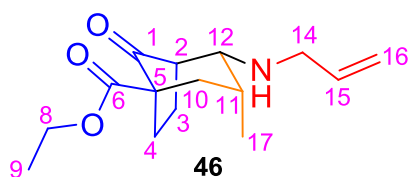


A 25-mL two-necked flask filled with argon was equipped a magnetic stirrer bar. Toluene (5 mL) was then added followed by organocatalyst **XXII** (13.2 mg, 0.032 mmol, 10 mol%). Then, ethyl 2-oxocyclopentanecarboxylate **41** (50 mg, 46.3 μ L, 0.32 mmol, 1.0 equiv) was added followed by methacrolein **42** (31.2 μ L, 0.38 mmol, 1.2 equiv), and allylamine **43** (24.0 μ L, 0.32 mmol, 1.0 equiv). After complete conversion of ethyl 2-oxocyclopentanecarboxylate, checked by TLC, the solution was filtered through a short pad of Celite, which was thoroughly washed with toluene. The solvent was evaporated under reduced pressure to obtain crude compound, which was analyzed by ^{13}C NMR to measure the diastereomeric ratio. Crude product obtained with 6:1 *dr*. Purification was performed on a silica gel column affording the pure product **46** (60% yield, 6% *ee*). Racemate was prepared following the same procedure using racemic organocatalyst **XXII**.

TLC (PE/EtOAc/Et₃N 3:1:0.025) *R_f* 0.65 (KMnO₄).

HRMS (ESI) calc'd for [C₁₅H₂₃NO₃+H]⁺: 266.1751, found: 266.1751.

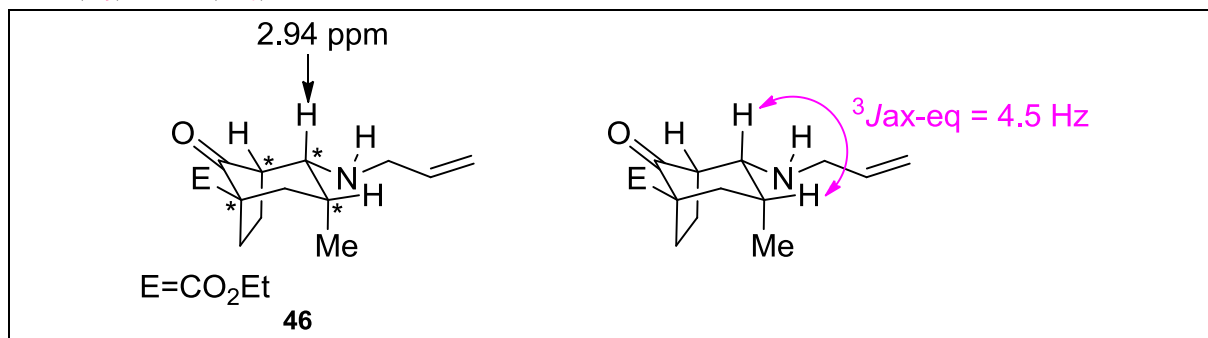
HPLC Chiralpak AD-H, Hexane/Ethanol 95/5, 25 °C, 1 ml/min, λ = 220 nm, τ_{major} = 6.80 min, τ_{minor} = 8.31 min.



^1H NMR (400 MHz, CDCl₃) δ (ppm) 5.79 (dddd, J = 16.9, 10.2, 6.5, 5.6 Hz, 1H, **H₁₅**), 5.11 (ddd, J = 17.2, 3.2, 1.6 Hz, 1H, **H_{16a}**), 5.01 (ddd, J = 10.2, 2.9, 1.5 Hz, 1H, **H_{16b}**), 4.23 – 4.05 (m, 2H, **H_{8a}** and **H_{8b}**), 3.39 (ddt, J = 14.1, 5.5, 1.5 Hz, 1H, **H_{14a}**), 3.15 – 3.05 (m, 1H, **H_{14b}**), 2.94 (td, J = 4.5, 2.0 Hz, 1H, **H₁₂**), 2.59 – 2.45 (m, 2H, **H₂** and **H₁₁**), 2.36 – 2.22 (m, 1H, **H_{4a}**), 2.16 (td, J = 13.1, 1.3 Hz, 1H, **H_{10a}**), 2.00 (dddd, J = 15.1, 13.1, 9.0, 4.5 Hz, 2H, **H_{10b}** and **H_{4b}**), 1.85 (ddd, J = 13.1, 4.9, 2.0 Hz, 1H, **H_{3a}**), 1.74 – 1.62 (m, 1H, **H_{3b}**), 1.22 (t, J = 7.1 Hz, 3H, **H₉**), 0.96 (d, J = 6.6 Hz, 3H, **H₁₇**).

^{13}C NMR (101 MHz, CDCl₃) δ (ppm) 212.5 (**C₁**), 171.3 (**C₆**), 137.1 (**C₁₅**), 116.0 (**C₁₆**), 67.1 (**C₁₂**), 61.1 (**C₈**), 57.0 (**C₅**), 50.0 (**C₂**), 48.6 (**C₁₄**), 42.0 (**C₁₀**), 28.5 (**C₁₁**), 27.0 (**C₄**), 20.2 (**C₃**),

16.3 (C₉), 14.2 (C₁₇).

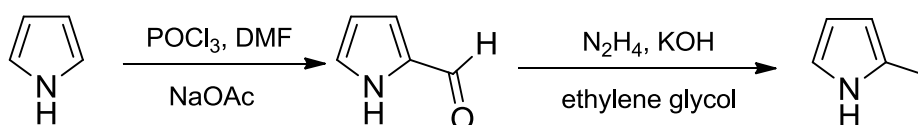


III. EXPERIMENTAL PART OF ORGANOCATALYTIC ENANTIOSELECTIVE MULTICOMPONENT SYNTHESIS OF PYRROLOPIPERAZINES

III.1 PREPARATION OF STARTING MATERIALS

III.1.1 PREPARATION OF SUBSTITUTED PYRROLES

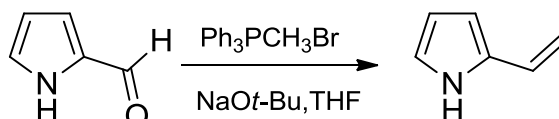
2-Methylpyrrole



2-Formylpyrrole in two steps according to known literature procedures:^[219, 220] yield 49% as a colorless liquid.

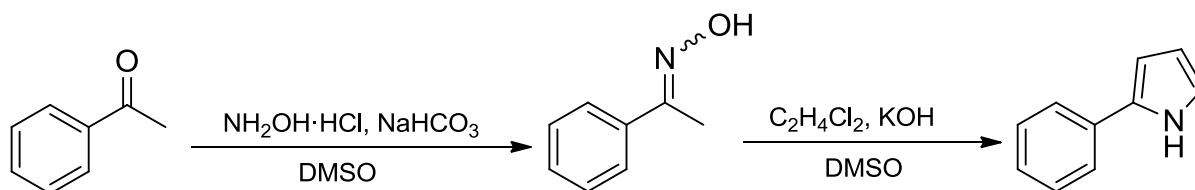
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.91 (br s, 1H), 6.72 (dd, *J* = 4.1, 2.8 Hz, 1H), 6.22 (dd, *J* = 5.7, 2.8 Hz, 1H), 6.00 (br s, 1H), 2.35 (s, 3H).

2-Vinylpyrrole



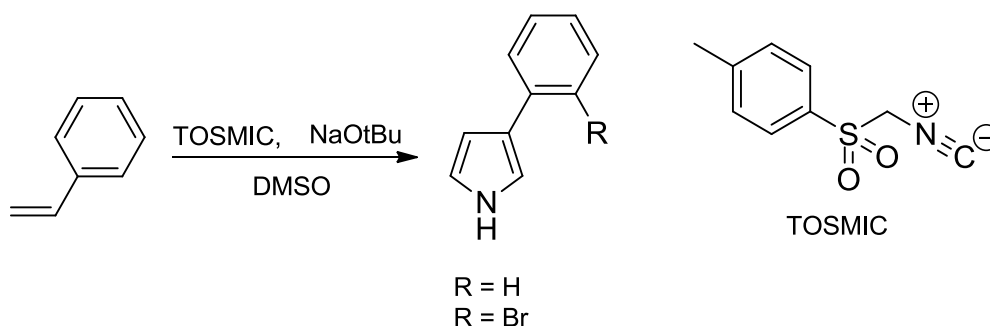
2-Vinylpyrrole was prepared in two steps according to known literature procedures:^[222] yield 44% as a colorless liquid.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.23 (br s, 1H), 6.77 (dd, *J* = 4.1, 2.8 Hz, 1H), 6.60 (dd, *J* = 17.8, 11.2 Hz, 1H), 6.30-6.26 (m, 1H), 6.24 (dd, *J* = 5.8, 2.8 Hz, 1H), 5.29 (d, *J* = 17.8 Hz, 1H), 5.03 (d, *J* = 11.2 Hz, 1H).

2-Phenylpyrrole

2-Phenylpyrrole was prepared in two step from acetophenone according to known literature procedures:^[223] yield 20% as a brown solid.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.18 (br s, 1H), 7.34 – 7.27 (m, 2H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.12 – 7.04 (m, 1H), 6.66 (dd, *J* = 4.1, 2.6 Hz, 1H), 6.46 – 6.39 (m, 1H), 6.23 – 6.15 (m, 1H).

3-Phenylpyrrole

3-Phenylpyrrole was prepared according to known literature procedures:^[224] yield 37% as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.15 (br s, 1H), 7.79 – 7.75 (m, 2H), 7.60 – 7.55 (m, 2H), 7.44 – 7.39 (m, 1H), 7.15 – 7.11 (m, 1H), 6.87 (dd, *J* = 4.7, 2.7 Hz, 1H), 6.76 (td, *J* = 2.7, 1.7 Hz, 1H).

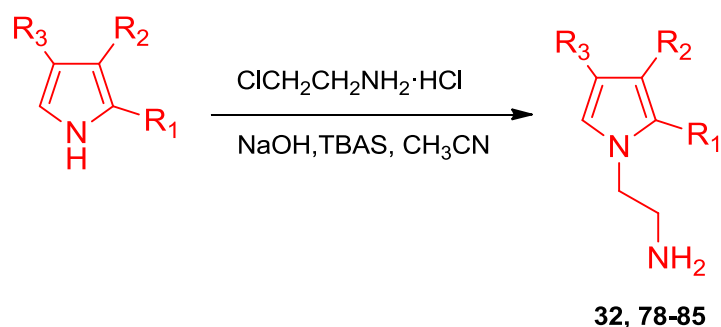
3-(2-bromophenyl)pyrrole was prepared according to known literature procedures: yield 31% as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.33 (s, 1H), 7.63 (dt, *J* = 4.4, 2.2 Hz, 1H), 7.45 (dt, *J* = 4.8, 2.4 Hz, 1H), 7.30 (td, *J* = 7.6, 1.1 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.07 (ddd, *J* = 7.8, 6.4, 2.4 Hz, 1H), 6.90 – 6.82 (m, 1H), 6.54 (t, *J* = 4.0 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) 137.0 (C), 133.8 (CH), 131.0 (CH), 127.4 (CH), 127.3 (CH), 123.6 (C), 122.4 (C), 117.8 (CH), 109.8 (CH).

III.1.2 PREPARATION OF N-(2-AMINOETHYL)PYRROLES

N-(2-aminoethyl)pyrroles were prepared according to known literature procedures.^[225]



***N*-(2-Aminoethyl)pyrrole 32:** yield 80% as a pale yellow liquid.

¹H NMR (300 MHz, CDCl₃) δ (ppm) 6.63 (t, *J* = 2.1 Hz, 2H), 6.14 (t, *J* = 2.1 Hz, 2H), 3.83 (t, *J* = 6.0 Hz, 2H), 2.92 (t, *J* = 6.0 Hz, 2H), 0.97 (br s, 2H).

***N*-(2-Aminoethyl)-2-methylpyrrole 78:** yield 68% as a pale yellow liquid.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 6.67 – 6.57 (m, 1H), 6.07 (t, *J* = 3.1 Hz, 1H), 5.93 – 5.82 (m, 1H), 3.87 (t, *J* = 6.2 Hz, 2H), 2.99 (t, *J* = 6.2 Hz, 2H), 2.25 (s, 3H), 1.23 (br s, 2H).

***N*-(2-Aminoethyl)-2-vinylpyrrole 79:** yield 50% as a pale yellow liquid.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 6.70 – 6.63 (m, 1H), 6.58 (dd, *J* = 17.3, 11.2 Hz, 1H), 6.40 (dd, *J* = 3.6, 1.5 Hz, 1H), 6.15 – 6.09 (m, 1H), 5.50 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.04 (dd, *J* = 11.2, 1.3 Hz, 1H), 3.95 (t, *J* = 6.1 Hz, 2H), 2.97 (t, *J* = 6.1 Hz, 2H), 1.30 (br s, 2H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 131.7 (C), 125.5 (CH), 122.6 (CH), 111.5 (CH₂), 108.3 (CH), 106.7 (CH), 50.1 (CH₂), 43.3 (CH₂).

***N*-(2-Aminoethyl)-2-phenylpyrrole 80:** yield 40% as a yellow liquid.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.41 (d, *J* = 4.4 Hz, 4H), 7.33 (dd, *J* = 8.5, 4.2 Hz, 1H), 6.82 (dd, *J* = 2.5, 2.0 Hz, 1H), 6.26 (dd, *J* = 3.5, 2.5 Hz, 1H), 6.23 (dd, *J* = 3.5, 2.0 Hz, 1H), 4.02 (t, *J* = 6.3 Hz, 2H), 2.88 (t, *J* = 6.3 Hz, 2H), 1.15 (br s, 2H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 134.5 (C), 133.5 (C), 129.0 (2 CH), 128.4 (2 CH), 127.0 (CH), 122.2 (CH), 109.2 (CH), 108.1 (CH), 50.2 (CH₂), 43.1 (CH₂).

***N*-(2-Aminoethyl)-3-phenylpyrrole 81:** yield 51% as a yellow liquid.

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.53 – 7.49 (m, 2H), 7.36 – 7.30 (m, 2H), 7.19 – 7.13 (m, 1H), 6.99 (t, *J* = 2.0 Hz, 1H), 6.71 (t, *J* = 2.5 Hz, 1H), 6.48 (dd, *J* = 2.7, 1.8 Hz, 1H), 3.98 – 3.92 (m, 2H), 3.10 – 3.03 (m, 2H), 1.25 (br s, 2H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 135.9 (C), 128.7 (2 CH), 125.5 (CH), 125.2 (C), 125.1 (2 CH), 121.92 (CH), 117.60 (CH), 106.64 (CH), 53.16 (CH₂), 43.33 (CH₂).

2-(3-(2-bromophenyl)-1H-pyrrol-1-yl)ethanamine 82: yield 76% as a yellow liquid.

¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.62 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.44 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.28 (td, *J* = 7.6, 1.3 Hz, 1H), 7.11 (t, *J* = 2.0 Hz, 1H), 7.04 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H), 6.71 (t, *J* = 2.4 Hz, 1H), 6.48 (dd, *J* = 2.6, 1.8 Hz, 1H), 3.95 (t, *J* = 5.8 Hz, 2H), 3.06 (t, *J* = 5.8 Hz, 2H), 1.19 (s, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 136.8 (C), 133.6 (CH), 130.7 (CH), 127.4 (CH), 127.0 (CH), 123.3 (C), 122.0 (C), 120.7 (CH), 120.6 (CH), 109.6 (CH), 53.1 (CH_2), 43.3 (CH_2).

HRMS (ESI) calc'd for $[\text{C}_{12}\text{H}_{13}\text{N}_2\text{Br} + \text{H}]^+$: 265.0335, found: 265.0333.

***N*-(2-Aminoethyl)-2,4-dimethylpyrrole 83**: yield 47% as a yellow liquid.

^1H NMR (400 MHz, CDCl_3) δ (ppm) 6.38 (br s, 1H), 5.74 (br s, 1H), 3.82 (d, $J = 6.2$ Hz, 2H), 2.97 (d, $J = 6.2$ Hz, 2H), 2.21 (s, 3H), 2.07 (s, 3H), 1.36 (br s, 2H).

2-(3-Methyl-1*H*-indol-1-yl)ethanamine 84: yield 74% as a yellow liquid.

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.68 (d, $J = 7.9$ Hz, 1H), 7.38 (dt, $J = 8.2, 1.0$ Hz, 1H), 7.29 (dd, $J = 8.2, 6.8$ Hz, 1H), 7.25 – 7.16 (m, 1H), 6.94 (d, $J = 1.3$ Hz, 1H), 4.11 (t, $J = 6.0$ Hz, 2H), 3.09 (t, $J = 6.0$ Hz, 2H), 2.43 (t, $J = 1.2$ Hz, 3H), 1.09 (br s, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 136.4 (C), 128.8 (C), 125.7 (CH), 121.4 (CH), 119.0 (CH), 118.6 (CH), 110.3 (C), 109.1 (CH), 49.2 (CH_2), 42.2 (CH_2), 9.5 (CH_3).

2-(5-methoxy-1*H*-indol-1-yl)ethanamine 85: yield 82% as a yellow liquid.

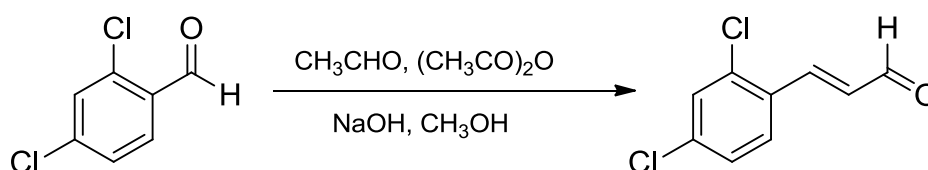
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.18 (d, $J = 8.6$ Hz, 1H), 7.06 – 7.00 (m, 2H), 6.81 (d, $J = 8.8$ Hz, 1H), 6.35 (d, $J = 8.8$ Hz, 1H), 4.08 (d, $J = 5.4$ Hz, 2H), 3.78 (s, 3H), 3.02 (d, $J = 5.4$ Hz, 2H), 1.13 (s, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 154.2 (C), 131.5 (C), 129.2 (C), 128.7 (CH), 112.0 (CH), 110.2 (CH), 102.7 (CH), 101.0 (CH), 56.0 (CH_3), 49.8 (CH_2), 42.2 (CH_2).

HRMS (ESI) calc'd for $[\text{C}_{11}\text{H}_{14}\text{N}_2\text{O} + \text{H}]^+$: 191.1179, found: 191.1177.

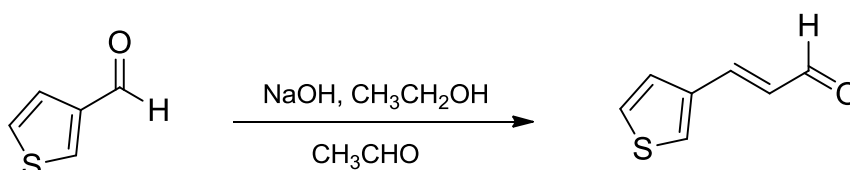
III.1.3 PREPARATION OF α,β -UNSATURATED ALDEHYDES

(*E*)-2,4-Dichlorocinnamaldehyde



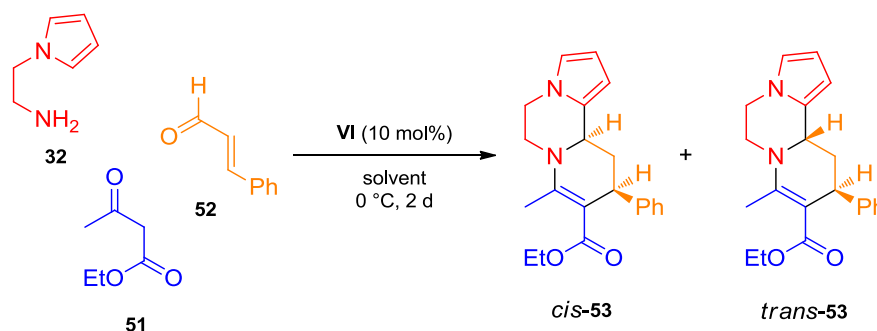
(*E*)-2,4-dichlorocinnamaldehyde was prepared according to known literature procedures:^[309, 310]

(*E*)-3-(3-Thienyl)acrolein



(*E*)-3-(3-thienyl)acrolein was prepared according to known literature procedures:^[311]

III.2 METHODOLOGY FOR THE OPTIMIZATION OF REACTION CONDITIONS



A reaction tube was charged with the catalyst **VI** (0.020 mmol, 0.1 equiv), the solvent (2.5 mL), flushed with argon and placed at the desired temperature. Ethyl acetoacetate **51** (26.0 mg, 25.3 μ L, 0.200 mmol, 1 equiv) was then added followed by freshly distilled cinnamaldehyde **52** (39.7 mg, 37.8 μ L, 0.300 mmol, 1.5 equiv) and *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). After 2 days, the solution was directly purified by flash column chromatography on silica gel to provide the pyrrollopiperazines **53** as two diastereomers

Enantiomeric excesses were determined by HPLC performed on Merck-Hitachi system using the following parameters:

- 1st diastereomer:

Chiral column: Lux-Amylose-2

Temperature: 25 °C

Eluent: Hexane/EtOH 95:5

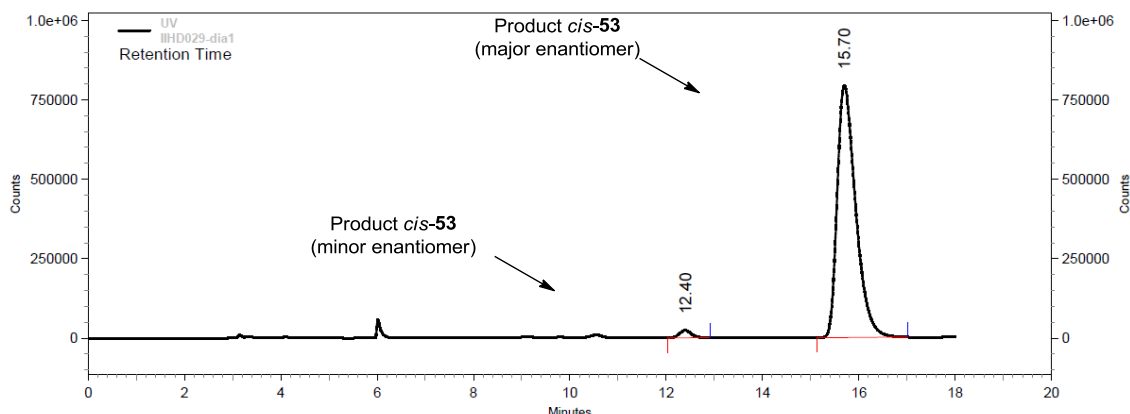
Flow rate: 1.0 mL/min

Wavelength of UV detector: $\lambda = 254$ nm.

The major enantiomer has a retention time of 15.70 min and the minor one a retention time of 12.40 min.

Sample : IIHD029-dia1

Method description : Lux-Amylose-2, Hexane/ethanol 95/5, 1 ml/min, UV 254 nm et polarimetre



UV Results						
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)	
12.40	404823	1.88	3.13	0.00	0.00	
15.70	21154602	98.12	4.23	0.00	5.66	
Totals		21559425	100.00			

• 2nd diastereomer:

Chiral column: Chiralpak AD-H

Temperature: 25 °C

Eluent: Hexane/EtOH 80:20

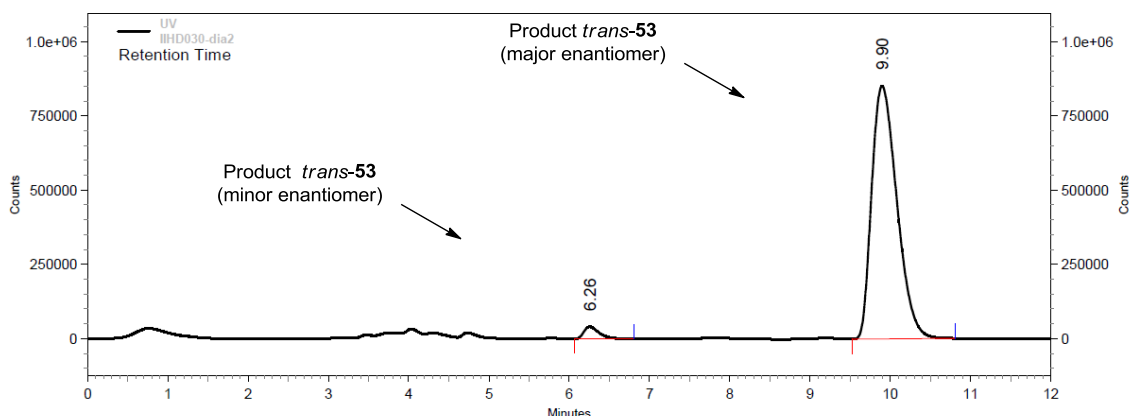
Flow rate: 1.0 mL/min

Wavelength of UV detector: $\lambda = 254$ nm.

The major enantiomer has a retention time of 9.90 min and the minor one a retention time of 6.26 min.

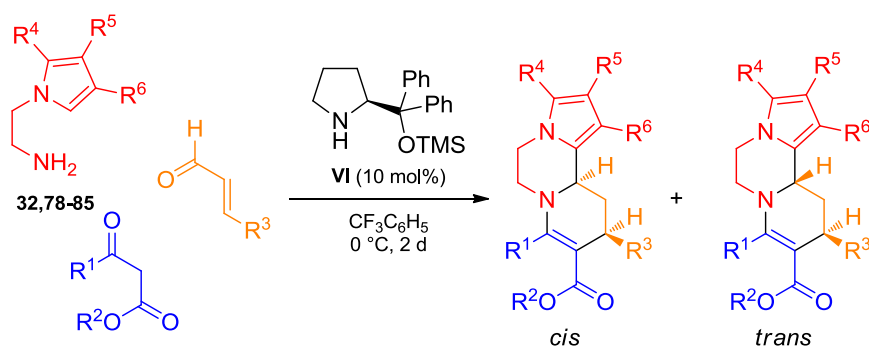
Sample : IIHD030-dia2

Method description : Chiralpak AD-H, Hexane/ethanol 80/20, 1 ml/min, UV 254 nm et CD254nm



UV Results						
Retention Time	Area	Area %	Capacity factor	Relative RT	Resolution (USP)	
6.26	539137	2.81	1.09	1.00	0.00	
9.90	18619821	97.19	2.30	2.12	7.82	
Totals		19158958	100.00			

III.3 GENERAL PROCEDURE, SYNTHESIS AND CHARACTERIZATION OF PRODUCTS



General procedure (reactions were carried out on a 0.200-mmol scale):

A reaction tube was charged with (*S*)-(-)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **VI** (6.6 mg, 0.020 mmol, 0.1 equiv), dry α,α,α-trifluorotoluene (2.5 mL), flushed with argon and placed at 0 °C. β-ketoester (0.200 mmol, 1 equiv) was then added followed by freshly distilled α,β-unsaturated aldehyde (0.300 mmol, 1.5 equiv) and *N*-(2-aminoethyl)pyrrole **32**, **78-85** (0.200 mmol, 1 equiv). After 2 days, the solution was directly purified by flash column chromatography on silica gel to provide the pyrrolidopiperazines as two diastereomers.

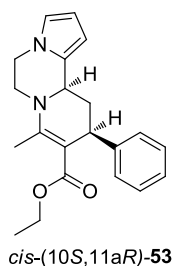
Racemates **53-58**, **64-74**, **86**, **92** were prepared by refluxing in toluene in the presence of 4Å MS.^[185]

Racemates **87-91** and **77** were prepared following the general procedure using racemic catalyst.

Ethyl 8-methyl-10-phenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 53

Prepared according to the general procedure using ethyl acetoacetate **51** (26.0 mg, 25.3 μL , 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μL , 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL , 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 4:1 then PE/Et₂O/AcOH 4:1: 0.025) afforded *cis*-(10*S*,11*aR*)-**53** as a yellow oil (23.5mg, 0.070 mmol, 35% yield, 96% *ee*) and *trans*-(10*S*,11*aS*)-**53** as a pale yellow oil (22.2 mg, 0.066 mmol, 33% yield, 94% *ee*).

***cis*-(10*S*,11*aR*)-diastereomer 53:**



TLC (PE/Et₂O 4:1) *R_f* 0.50 (UV, vanillin).

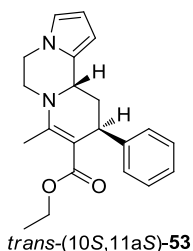
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.24 – 7.09 (m, 5H), 6.56 – 6.51 (m, 1H), 6.11 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.85 – 5.80 (m, 1H), 4.49 (dd, *J* = 10.9, 2.5 Hz, 1H), 4.08 – 3.99 (m, 4H), 3.73 (qd, *J* = 7.1, 1.8 Hz, 2H), 3.39 – 3.29 (m, 1H), 2.62 – 2.54 (m, 1H), 2.46 (d, *J* = 1.4 Hz, 3H), 2.06 – 1.94 (m, 1H), 0.75 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 169.2 (C), 151.7 (C), 147.3 (C), 129.3 (C), 128.2 (2 CH), 126.9 (2 CH), 125.7 (CH), 118.5 (CH), 108.6 (CH), 104.2 (C), 103.3 (CH), 59.1 (CH₂), 53.8 (CH), 45.3 (CH₂), 43.9 (CH₂), 41.6 (CH), 40.5 (CH₂), 16.8 (CH₃), 13.8 (CH₃).

HRMS (ESI) calc'd for [C₂₁H₂₄N₂O₂+H]⁺: 337.1911, found: 337.1911.

HPLC Lux-Amylose-2, Hexane/EtOH 95:5, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 15.70 min, τ_{minor} = 12.40 min.

$[\alpha]_{\text{D}}^{20}$ = – 114.7 (c 0.08, CHCl₃).

trans-(10S,11aS)-diastereomer 53:

TLC (PE/Et₂O 4:1) R_f 0.34 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.22 – 7.07 (m, 5H), 6.52 – 6.43 (m, 1H), 6.04 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.71 (dt, *J* = 3.4, 1.3 Hz, 1H), 4.16 (d, *J* = 3.6 Hz, 1H), 4.11 – 4.00 (m, 2H), 4.02 – 3.91 (m, 2H), 3.93 – 3.82 (m, 2H), 3.32 (ddd, *J* = 13.8, 10.0, 4.2 Hz, 1H), 2.50 (s, 3H), 2.27 (ddd, *J* = 13.1, 3.5, 2.6 Hz, 1H), 2.05 (ddd, *J* = 13.1, 11.8, 5.4 Hz, 1H), 0.91 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 169.1 (C), 153.6 (C), 147.2 (C), 129.9 (C), 128.2 (2 CH), 127.9 (2 CH), 125.9 (CH), 118.8 (CH), 108.5 (CH), 102.8 (CH), 99.3 (C), 59.2 (CH₂), 49.6 (CH), 45.2 (CH₂), 44.5 (CH₂), 38.2 (CH), 35.9 (CH₂), 17.5 (CH₃), 14.3 (CH₃).

HRMS (ESI) calc'd for [C₂₁H₂₄N₂O₂+H]⁺: 337.1911, found: 337.1913.

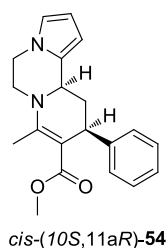
HPLC Chiralpak AD-H, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 9.90 min, τ_{minor} = 6.26 min.

[α]_D²⁰ = – 240.3 (c 0.23, CHCl₃).

Methyl 8-methyl-10-phenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 54

Prepared according to the general procedure using methyl acetoacetate (23.3 mg, 21.6 μL , 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μL , 0.300 mmol, 1.5 equiv) and *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL , 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 4:1 then PE/Et₂O/AcOH 4:1:0.025) afforded as two diastereomers: *cis*-(10*S*,11*aR*)-**54** as a yellow oil (21.3mg, 0.066 mmol, 33% yield, 90% *ee*) and *trans*-(10*S*,11*aS*)-**54** as a pale yellow oil (12.9 mg, 0.040 mmol, 20% yield, 92% *ee*).

***cis*-(10*S*,11*aR*)-diastereomer 54:**



TLC (PE/Et₂O 4:1) *R_f* 0.37 (UV, vanillin).

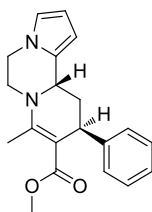
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.27 – 7.19 (m, 2H), 7.17 – 7.08 (m, 3H), 6.55 – 6.52 (m, 1H), 6.10 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.91 (dt, *J* = 3.4, 1.3 Hz, 1H), 4.51 (dd, *J* = 10.5, 2.7 Hz, 1H), 4.10 – 3.99 (m, 4H), 3.37 (td, *J* = 9.9, 5.9 Hz, 1H), 3.27 (s, 3H), 2.59 (ddd, *J* = 13.6, 6.5, 3.0 Hz, 1H), 2.48 (d, *J* = 1.3 Hz, 3H), 2.09 – 1.99 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 169.7 (C), 151.9 (C), 147.1 (C), 129.3 (C), 128.2 (2 CH), 126.8 (2 CH), 125.7 (CH), 118.5 (CH), 108.7 (CH), 104.0 (C), 103.3 (CH), 53.8 (CH), 50.3 (CH₃), 45.2 (CH₂), 44.0 (CH₂), 41.4 (CH), 40.2 (CH₂), 16.9 (CH₃).

HRMS (ESI) calc'd for [C₂₀H₂₂N₂O₂+H]⁺: 323.1754, found: 323.1752.

HPLC Lux-Amylose-2, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 8.20 min, τ_{minor} = 6.96 min.

$[\alpha]_{\text{D}}^{20}$ = -112 (c 0.05, CHCl₃).

trans-(10S,11aR)-diastereomer 54:*trans*-(10S,11aR)-**54**

TLC (PE/Et₂O 4:1) R_f 0.11 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.31 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 6.47 – 6.46 (m, 1H), 6.11 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.79 (dt, *J* = 3.4, 1.3 Hz, 1H), 4.16 (d, *J* = 2.9 Hz, 1H), 4.12 – 3.96 (m, 2H), 4.00 – 3.87 (m, 2H), 3.42 (s, 3H), 3.39 (ddd, *J* = 13.8, 10.1, 4.2 Hz, 1H), 2.52 (s, 3H), 2.29 (ddd, *J* = 13.1, 3.6, 2.6 Hz, 1H), 2.11 – 1.98 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 169.6 (C), 153.9 (C), 146.8 (C), 129.9 (C), 128.3 (2 CH), 127.9 (2 CH), 126.0 (CH), 118.8 (CH), 108.5 (CH), 102.8 (CH), 98.5 (C), 50.9 (CH₃), 49.6 (CH), 45.1 (CH₂), 44.5 (CH₂), 38.0 (CH), 35.9 (CH₂), 17.5 (CH₃).

HRMS (ESI) calc'd for [C₂₀H₂₂N₂O₂+H]⁺: 323.1754, found: 323.1748.

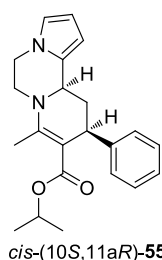
HPLC Chiralpak AD-H, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 11.00 min, τ_{minor} = 7.24 min.

[α]_D²⁰ = -160 (c 0.08, CHCl₃).

Isopropyl 8-methyl-10-phenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 55

Prepared according to the general procedure using isopropyl acetoacetate (28.8 mg, 29.2 μL , 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μL , 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL , 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc 6:1 then PE/EtOAc/ 6:1:0.025) afforded *cis*-(10*S*,11*aR*)-**55** as a pale yellow powder (15.8 mg, 0.045 mmol, 23% yield, 98% *ee*) and *trans*-(10*S*,11*aS*)-**55** as a yellow oil (21.7 mg, 0.062 mmol, 31% yield, 96% *ee*).

***cis*-(10*S*,11*aR*)-diastereomer 55:**



TLC (PE/Et₂O 4:1) *R_f* 0.34 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.19 – 6.99 (m, 5H), 6.49 – 6.42 (m, 1H), 6.03 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.78 – 5.74 (m, 1H), 4.58 (sept, *J* = 6.2 Hz, 1H), 4.41 (dd, *J* = 11.0, 2.3 Hz, 1H), 4.02 – 3.86 (m, 4H), 3.29 – 3.19 (m, 1H), 2.48 (ddd, *J* = 13.5, 6.5, 2.8 Hz, 1H), 2.38 (d, *J* = 1.4 Hz, 3H), 1.89 (dt, *J* = 13.5, 11.4 Hz, 1H), 0.97 (d, *J* = 6.2 Hz, 3H), 0.38 (d, *J* = 6.2 Hz, 3H).

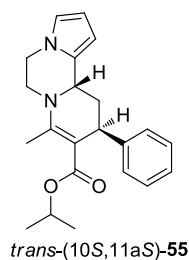
¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.7 (C), 151.4 (C), 147.5 (C), 129.4 (C), 128.3 (2 CH), 127.0 (2 CH), 125.8 (CH), 118.5 (CH), 108.7 (CH), 104.5 (C), 103.2 (CH), 66.3 (CH), 53.9 (CH), 45.3 (CH₂), 43.9 (CH₂), 41.7 (CH), 40.7 (CH₂), 22.1 (CH₃), 20.7 (CH₃), 16.8 (CH₃).

HRMS (ESI) calc'd for [C₂₂H₂₆N₂O₂+H]⁺: 351.2067, found: 351.2067.

HPLC (*S,S*)-Whelk-O1, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 8.14 min, τ_{minor} = 6.87 min.

$[\alpha]_{\text{D}}^{20}$ = -37.3 (c 0.08, CHCl₃).

m.p. = 163-164 °C.

trans-(10S,11aS)-diastereomer 55:

TLC (PE/Et₂O 4:1) R_f 0.23 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.37 – 7.32 (m, 2H), 7.30 – 7.21 (m, 3H), 6.58 – 6.49 (m, 1H), 6.12 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.82 – 5.77 (m, 1H), 4.82 (sept, *J* = 6.2 Hz, 1H), 4.23 – 4.09 (m, 3H), 4.06 – 3.98 (m, 2H), 3.40 (ddd, *J* = 13.7, 9.8, 4.3 Hz, 1H), 2.57 (d, *J* = 0.6 Hz, 3H), 2.33 (ddd, *J* = 13.2, 3.4, 2.5 Hz, 1H), 2.13 (ddd, *J* = 13.2, 11.7, 5.6 Hz, 1H), 1.12 (d, *J* = 6.2 Hz, 3H), 0.75 (d, *J* = 6.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.6 (C), 153.4 (C), 147.5 (C), 129.9 (C), 128.1 (2 CH), 128.0 (2 CH), 125.9 (CH), 118.8 (CH), 108.5 (CH), 102.9 (CH), 100.1 (C), 66.1 (CH), 49.6 (CH), 45.2 (CH₂), 44.4 (CH₂), 38.4 (CH), 36.0 (CH₂), 22.3 (CH₃), 21.5 (CH₃), 17.5 (CH₃).

HRMS (ESI) calc'd for [C₂₂H₂₆N₂O₂+H]⁺: 351.2067, found: 351.2065.

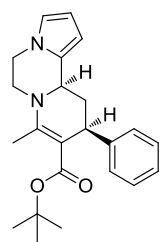
HPLC Chiralpak AD-H, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 6.81 min, τ_{minor} = 5.22 min.

[α]_D²⁰ = -98.2 (c 0.17, CHCl₃).

tert-Butyl 8-methyl-10-phenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 56

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μL , 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μL , 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL , 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc 8:1) afforded *cis*-(10*S*,11*aR*)-**56** as a white powder (24.0 mg, 0.066 mmol, 33% yield, 92% *ee*) and *trans*-(10*S*,11*aS*)-**56** as a pale yellow oil (26.9 mg, 0.075 mmol, 37% yield, 95% *ee*).

***cis*-(10*S*,11*aR*) diastereomer 56:**



cis-(10*S*,11*aR*)-**56**

TLC (PE/EtOAc 4:1) R_f 0.4 (UV, vanillin).

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.20 (m, 5H), 6.57 – 6.51 (m, 1H), 6.12 (dd, $J = 3.5$, 2.8 Hz, 1H), 5.87 – 5.81 (m, 1H), 4.48 (dd, $J = 11.5$, 2.7 Hz, 1H), 4.10 – 3.94 (m, 4H), 3.30 (ddd, $J = 13.2$, 9.8, 4.0 Hz, 1H), 2.56 (ddd, $J = 13.5$, 6.4, 2.7 Hz, 1H), 2.41 (d, $J = 1.5$ Hz, 3H), 1.96 (dt, $J = 13.5$, 11.5 Hz, 1H), 1.03 (s, 9H).

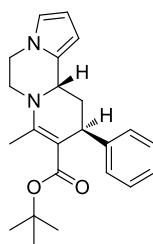
^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 168.7 (C), 150.1 (C), 147.4 (C), 129.6 (C), 128.3 (2 CH), 127.3 (2 CH), 125.9 (CH), 118.6 (CH), 108.7 (CH), 106.1 (C), 103.2 (CH), 79.1 (C), 53.9 (CH), 45.4 (CH_2), 43.8 (CH_2), 42.1 (CH), 40.6 (CH_2), 27.8 (3 CH_3), 16.6 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_2+\text{H}]^+$: 365.2224, found: 365.2219.

HPLC Chiralcel OJ-H, Hexane/EtOH 80:20, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 5.85$ min, $\tau_{\text{minor}} = 7.66$ min.

$[\alpha]_{\text{D}}^{20} = -118.9$ (c 0.09, CHCl_3).

m.p. = 161-162 $^\circ\text{C}$.

trans-(10S,11aS) diastereomer 56:*trans*-(10S,11aS)-56

TLC (PE/EtOAc 4:1) R_f 0.30 (UV, vanillin).

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.30 – 7.24 (m, 2H), 7.24 – 7.13 (m, 3H), 6.56 – 6.51 (m, 1H), 6.11 (dd, $J = 3.4, 2.8$ Hz, 1H), 5.78 (dt, $J = 3.4, 1.3$ Hz, 1H), 4.19 – 4.07 (m, 3H), 4.05 – 3.96 (m, 2H), 3.42 – 3.33 (m, 1H), 2.52 (d, $J = 0.6$ Hz, 3H), 2.29 (ddd, $J = 13.2, 3.2, 2.7$ Hz, 1H), 2.13 (ddd, $J = 13.2, 11.5, 5.8$ Hz, 1H), 1.18 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 168.7 (C), 152.8 (C), 147.8 (C), 130.0 (C), 128.14 (2 CH), 128.09 (2 CH), 125.9 (CH), 118.8 (CH), 108.5 (CH), 102.8 (CH), 101.7 (C), 78.6 (C), 49.6 (CH), 45.3 (CH_2), 44.4 (CH_2), 39.0 (CH), 36.1 (CH_2), 28.2 (3 CH_3), 17.5 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_2 + \text{H}]^+$: 365.2224, found: 365.2218.

HPLC Chiralcel OD-3, Hexane/EtOH 95:5, 25 °C, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 6.72$ min, $\tau_{\text{minor}} = 6.04$ min.

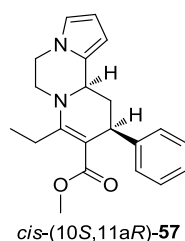
$[\alpha]_{\text{D}}^{20} = -117.6$ (c 0.08, CHCl_3).

m.p. = 160-161 °C.

Methyl 8-ethyl-10-phenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 57

Prepared according to the general procedure using methyl 3-oxovalerate (36.0 mg, 25.1 μL , 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μL , 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL , 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 4:1 then PE/Et₂O/AcOH 4:1:0.025) afforded *cis*-(10*S*,11*aR*)-**57** as a yellow oil (25.6 mg, 0.076 mmol, 38% yield, 95% *ee*) and *trans*-(10*S*,11*aS*)-**57** as a yellow oil (21.5 mg, 0.064 mmol, 32% yield, 91% *ee*).

***cis*-(10*S*,11*aR*) diastereomer 57:**



TLC (PE/Et₂O 4:1) *R_f* 0.38 (UV, vanillin).

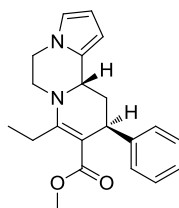
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.25 – 7.17 (m, 2H), 7.16 – 7.06 (m, 3H), 6.56 – 6.50 (m, 1H), 6.10 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.83 – 5.79 (m, 1H), 4.48 (dd, *J* = 10.6, 2.7 Hz, 1H), 4.08 – 4.00 (m, 3H), 3.95 (dt, *J* = 13.2, 3.7 Hz, 1H), 3.39 (ddd, *J* = 8.6, 6.8, 3.3 Hz, 1H), 3.25 (s, 3H), 3.00 (dq, *J* = 14.9, 7.5 Hz, 1H), 2.86 (dq, *J* = 14.9, 7.5 Hz, 1H), 2.55 (ddd, *J* = 13.5, 6.8, 3.0 Hz, 1H), 1.98 (dt, *J* = 13.5, 10.9 Hz, 1H), 1.23 (t, *J* = 7.5 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 169.3 (C), 157.6 (C), 147.2 (C), 129.4 (C), 128.3 (2 CH), 126.8 (2 CH), 125.7 (CH), 118.6 (CH), 108.7 (CH), 103.4 (CH), 103.1 (C), 53.9 (CH), 50.3 (CH₃), 45.6 (CH₂), 43.8 (CH₂), 41.4 (CH), 40.5 (CH₂), 22.7 (CH₂), 13.8 (CH₃).

HRMS (ESI) calc'd for [C₂₁H₂₄N₂O₂+H]⁺: 337.1911, found: 337.1916.

HPLC Chiralpak AD-H, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 7.92 min, τ_{minor} = 5.62 min.

$[\alpha]_{\text{D}}^{20}$ = +51.4 (c 0.18, CHCl₃).

trans-(10S,11aS) diastereomer 57:*trans*-(10S,11aS)-57

TLC (PE/Et₂O 4:1) R_f 0.27 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.32 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 6.56 – 6.50 (m, 1H), 6.11 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.81 – 5.73 (m, 1H), 4.22 (dd, *J* = 4.9, 2.3 Hz, 1H), 4.20 – 4.07 (m, 2H), 4.07 – 3.97 (m, 2H), 3.49 (s, 3H), 3.44 – 3.34 (m, 2H), 2.78 (dq, *J* = 14.3, 7.4 Hz, 1H), 2.35 (ddd, *J* = 13.1, 3.7, 2.6 Hz, 1H), 2.10 (ddd, *J* = 13.1, 12.0, 5.1 Hz, 1H), 1.31 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.9 (C), 159.4 (C), 147.0 (C), 129.9 (C), 128.3 (2 CH), 127.8 (2 CH), 126.0 (CH), 118.7 (CH), 108.6 (CH), 102.9 (CH), 97.0 (C), 50.8 (CH₃), 49.7 (CH), 45.4 (CH₂), 44.1 (CH₂), 37.7 (CH), 36.1 (CH₂), 22.9 (CH₂), 13.6 (CH₃).

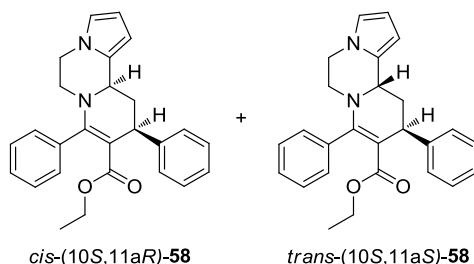
HRMS (ESI) calc'd for [C₂₁H₂₄N₂O₂+H]⁺: 337.1911, found: 337.1910.

HPLC Chiralpak AD-H, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 7.43 min, τ_{minor} = 5.72 min.

[α]_D²⁰ = -52.5 (c 0.08, CHCl₃).

Ethyl 8,10-diphenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-Carboxylate 58

Prepared according to the general procedure using ethyl benzoylacetate (38.4 mg, 34.6 μL , 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μL , 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL , 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 4:1) afforded **58** as a yellow oil, as a ~1.4:1 mixture of two diastereoisomers (31.9 mg, 0.08 mmol, 40% yield, 94% *ee* and 93% *ee*).



TLC (PE/Et₂O 4:1) *R_f* 0.34 (UV, vanillin).

HRMS (ESI) calc'd for [C₂₆H₂₆N₂O₂+H]⁺: 399.2067, found: 399.2073.

***cis*-(10*S*,11*aR*) diastereomer (major) 58:**

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.49-7.18 (m, 9H), 7.17-7.10 (m, 1H), 6.53-6.49 (m, 1H), 6.13 (dd, *J*=3.4, 2.8 Hz, 1H), 5.90 (dt, *J* = 13.5, 11.5 Hz, 1H), 4.64 (dd, *J* = 11.0, 2.5 Hz, 1H), 4.15 (dd, *J* = 11.3, 6.5 Hz, 1H), 3.92–3.78 (m, 2H), 3.53 (q, *J* = 7.1, 2H), 3.31 (dt, *J* = 13.3, 4.1 Hz, 1H), 3.19–3.04 (m, 1H), 2.69 (ddd, *J* = 13.6, 6.5, 2.9 Hz, 1H), 2.15 (dt, *J* = 13.6, 11.2 Hz, 1H), 0.56 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.1 (C), 155.0 (C), 146.5 (C), 137.8 (C), 129.1 (C), 128.7-128.3 (7 CH), 127.0 (2 CH), 125.9 (2 CH), 118.8 (CH), 108.6 (C), 106.4 (C), 103.3 (CH), 59.0 (CH₂), 54.3 (CH), 45.6 (CH₂), 45.4 (CH₂), 41.6 (CH), 40.3 (CH₂), 13.5 (CH₃).

HPLC Chiralcel OD-3, Hexane/EtOH 95/5, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 10.50 min, τ_{minor} = 9.08 min.

***trans*-(10*S*,11*aS*) diastereomer (minor) 58:**

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.49-7.18 (m, 10H), 6.53-6.49 (m, 1H), 6.13 (dd, *J*=3.4, 2.8 Hz, 1H), 5.82 (dt, *J* = 3.4, 1.4 Hz, 1H), 4.34 (dd, *J* = 11.6, 3.6 Hz, 1H), 4.29 (dd, *J* = 5.3, 2.3 Hz, 1H), 3.92–3.78 (m, 2H), 3.69 (qd, *J* = 7.1, 0.6 Hz, 2H), 3.37 (dt, *J* = 13.4, 3.9 Hz, 1H), 3.19–3.04 (m, 1H), 2.41 (ddd, *J* = 13.2, 3.6, 2.5 Hz, 1H), 2.27 (ddd, *J* = 13.2, 11.8, 5.3 Hz, 1H), 0.70 (t, *J* = 7.1 Hz, 3H).

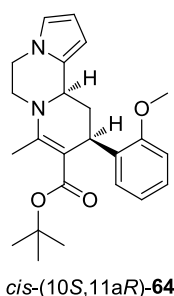
¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.3 (C), 155.7 (C), 146.6 (C), 138.1 (C), 129.4 (C), 128.7-128.3 (7 CH), 127.9 (2 CH), 126.1 (2 CH), 118.9 (CH), 108.5 (C), 102.9 (CH), 101.5 (C), 59.0 (CH₂), 49.8 (CH), 45.5 (CH₂), 45.4 (CH₂), 38.3 (CH), 36.0 (CH₂), 13.7 (CH₃).

HPLC Chiralcel OD-3, Hexane/EtOH 95/5, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 13.84 min, τ_{minor} = 11.45 min.

tert-Butyl 10-(2-methoxyphenyl)-8-methyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 64

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-2-methoxycinnamaldehyde (48.7 mg, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 4:1 then PE/Et₂O/AcOH 4:1:0.025) afforded *cis*-(10*S*,11*aR*)-**64** as a pale yellow solid (16.6 mg, 0.042 mmol, 21% yield, 89% *ee*) and *trans*-(10*S*,11*aS*)-**64** as a pale yellow oil (23.4 mg, 0.059 mmol, 30% yield, 90% *ee*).

***cis*-(10*S*,11*aR*) diastereomer 64:**



TLC (PE/Et₂O 4:1) *R_f* 0.27 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.14 – 7.05 (m, 2H), 6.84 – 6.78 (m, 2H), 6.55 – 6.50 (m, 1H), 6.10 (dd, *J* = 3.3, 2.9 Hz, 1H), 5.86 – 5.82 (m, 1H), 4.54 – 4.43 (m, 2H), 4.05 – 3.94 (m, 3H), 3.86 (s, 3H), 3.30 (ddd, *J* = 13.2, 9.8, 4.0 Hz, 1H), 2.55 (ddd, *J* = 13.3, 6.4, 2.8 Hz, 1H), 2.41 (d, *J* = 1.5 Hz, 3H), 1.86 (dt, *J* = 13.2, 11.1 Hz, 1H), 1.02 (s, 9H).

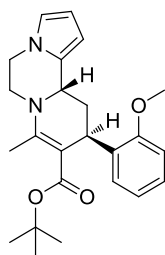
¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.8 (C), 156.8 (C), 150.6 (C), 135.7 (C), 129.9 (C), 127.0 (CH), 126.6 (CH), 120.9 (CH), 118.4 (CH), 110.0 (CH), 108.6 (CH), 106.4 (C), 103.2 (CH), 78.8 (C), 55.3 (CH₃), 54.1 (CH), 45.4 (CH₂), 43.9 (CH₂), 38.0 (CH₂), 33.5 (CH), 27.8 (3 CH₃), 16.7 (CH₃).

HRMS (ESI) calc'd for [C₂₄H₃₀N₂O₃+H]⁺: 395.2329, found: 395.2329.

HPLC Lux-Cellulose-2, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 5.14 min, τ_{minor} = 5.99 min.

$[\alpha]_{\text{D}}^{20}$ = -21.3 (c 0.23, CHCl₃).

m.p. = 159-160 °C.

trans-(10S,11aS) diastereomer 64:*trans*-(10*S*,11*aS*)-**64**

TLC (PE/Et₂O 4:1) *R_f* 0.17 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.15 (td, *J* = 8.0, 1.7 Hz, 1H), 7.05 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.90 – 6.81 (m, 2H), 6.54 – 6.51 (m, 1H), 6.10 (dd, *J* = 3.4, 2.9 Hz, 1H), 5.80 – 5.75 (m, 1H), 4.51 (d, *J* = 5.6 Hz, 1H), 4.15 – 3.96 (m, 4H), 3.89 (s, 3H), 3.36 (ddd, *J* = 13.6, 10.0, 4.6 Hz, 1H), 2.52 (d, *J* = 0.6 Hz, 3H), 2.29 (ddd, *J* = 13.3, 3.2, 2.1 Hz, 1H), 2.03 (ddd, *J* = 13.3, 11.8, 6.0 Hz, 1H), 1.15 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.7 (C), 156.9 (C), 153.2 (C), 135.8 (C), 130.3 (C), 129.3 (CH), 126.8 (CH), 119.9 (CH), 118.6 (CH), 110.1 (CH), 108.4 (CH), 102.9 (CH), 101.9 (C), 78.3 (C), 55.4 (CH₃), 50.0 (CH), 45.3 (CH₂), 44.3 (CH₂), 33.7 (CH₂), 32.5 (CH), 28.2 (3 CH₃), 17.6 (CH₃).

HRMS (ESI) calc'd for [C₂₄H₃₀N₂O₃+H]⁺: 395.2329, found: 395.2327.

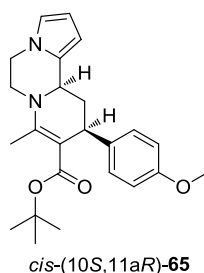
HPLC Chiralcel OJ-H, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 8.45 min, τ_{minor} = 7.38 min.

[α]_D²⁰ = -12.8 (c 0.13, CHCl₃).

tert-Butyl 10-(4-methoxyphenyl)-8-methyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2a]pyrrolo [2,1-c] pyrazine-9-carboxylate 65

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-4-methoxycinnamaldehyde (48.7 mg, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc 4:1 then PE/EtOAc/AcOH 4:1:0.025) afforded *cis*-(10*S*,11*aR*)-**65** as a pale yellow oil (31.2 mg, 0.079 mmol, 40% yield, 94% *ee*) and *trans*-(10*S*,11*aS*)-**65** as a pale yellow oil (18.3 mg, 0.046 mmol, 23% yield, 92% *ee*).

cis-(10*S*,11*aR*) diastereomer 65:



TLC (PE/EtOAc 4:1) R_f 0.33 (UV, vanillin).

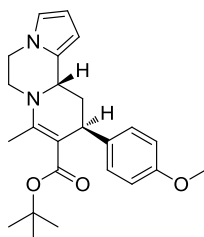
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.10 (m, 2H), 6.79 (m, 2H), 6.58 – 6.52 (m, 1H), 6.12 (dd, $J = 3.5, 2.8$ Hz, 1H), 5.86 – 5.81 (m, 1H), 4.45 (dd, $J = 11.2, 2.2$ Hz, 1H), 4.04 – 3.91 (m, 4H), 3.76 (s, 3H), 3.27 (ddd, $J = 13.5, 9.9, 4.1$ Hz, 1H), 2.51 (ddd, $J = 13.5, 6.8, 3.0$ Hz, 1H), 2.37 (d, $J = 1.5$ Hz, 3H), 1.94 (dt, $J = 13.5, 11.5$ Hz, 1H), 1.06 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 168.9 (C), 158.0 (C), 149.6 (C), 139.4 (C), 129.7 (C), 128.3 (2 CH), 118.6 (CH), 113.8 (2 CH), 108.7 (CH), 106.7 (C), 103.1 (CH), 79.1 (C), 55.5 (CH₃), 54.0 (CH), 45.4 (CH₂), 43.9 (CH₂), 41.3 (CH), 40.6 (CH₂), 27.9 (3 CH₃), 16.6 (CH₃).

HRMS (ESI) calc'd for $[\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_3+\text{H}]^+$: 395.2329, found: 395.2330.

HPLC Lux-Cellulose-2, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 5.68$ min, $\tau_{\text{minor}} = 6.35$ min.

$[\alpha]_{\text{D}}^{20} = -43$ (c 0.10, CHCl_3).

trans-(10*S*,11*aS*) diastereomer 65:*trans*-(10*S*,11*aS*)-**65**

TLC (PE/EtOAc 4:1) *R*_f 0.27 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.15 – 7.09 (m, 2H), 6.84 – 6.79 (m, 2H), 6.57 – 6.51 (m, 1H), 6.11 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.80 – 5.75 (m, 1H), 4.15 – 4.05 (m, 3H), 4.05 – 3.96 (m, 2H), 3.79 (s, 3H), 3.36 (ddd, *J* = 13.7, 9.8, 4.6 Hz, 1H), 2.50 (d, *J* = 0.6 Hz, 3H), 2.25 (ddd, *J* = 13.1, 3.2, 2.6 Hz, 1H), 2.08 (ddd, *J* = 13.1, 11.6, 5.7 Hz, 1H), 1.20 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.8 (C), 157.9 (C), 152.5 (C), 140.0 (C), 130.1 (C), 129.0 (2 CH), 118.7 (CH), 113.5 (2 CH), 108.5 (CH), 102.8 (CH), 102.1 (C), 78.6 (C), 55.4 (CH₃), 49.5 (CH), 45.3 (CH₂), 44.4 (CH₂), 38.1 (CH), 36.3 (CH₂), 28.3 (3 CH₃), 17.6 (CH₃).

HRMS (ESI) calc'd for [C₂₄H₃₀N₂O₃+H]⁺: 395.2329, found: 395.2330.

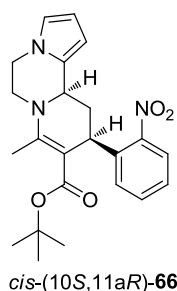
HPLC (*S,S*)-Whelk-O1, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 9.41 min, τ_{minor} = 7.30 min.

[α]_D²⁰ = –80 (c 0.23, CHCl₃).

tert-Butyl 8-methyl-10-(2-nitrophenyl)-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 66

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-2-nitrocinnamaldehyde (53.2 mg, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 2:1 then PE/Et₂O/AcOH 2:1:0.025) afforded *cis*-(10*S*,11*aR*)-**66** as a pale yellow oil (23.7 mg, 0.058 mmol, 29% yield, 97% *ee*) and *trans*-(10*S*,11*aS*)-**66** as a pale yellow oil (19.6 mg, 0.048 mmol, 24% yield, 98% *ee*).

***cis*-(10*S*,11*aR*) diastereomer 66:**



TLC (PE/Et₂O 2:1) *R_f* 0.27 (UV, vanillin).

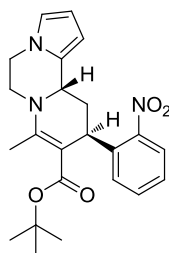
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.80 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.31 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.27 – 7.24 (m, 1H), 6.58 – 6.51 (m, 1H), 6.09 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.90 – 5.83 (m, 1H), 4.55 – 4.48 (m, 2H), 4.09 – 3.99 (m, 3H), 3.37 (ddd, *J* = 15.8, 10.2, 5.6 Hz, 1H), 2.93 (ddd, *J* = 13.4, 6.5, 3.0 Hz, 1H), 2.48 (d, *J* = 1.3 Hz, 3H), 1.96 (dt, *J* = 13.4, 10.5 Hz, 1H), 1.00 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.0 (C), 152.8 (C), 149.9 (C), 143.0 (C), 132.9 (CH), 129.2 (C), 128.7 (CH), 126.4 (CH), 124.1 (CH), 118.6 (CH), 108.8 (CH), 104.2 (C), 103.6 (CH), 79.2 (C), 53.6 (CH), 45.2 (CH₂), 44.0 (CH₂), 38.2 (CH₂), 36.6 (CH), 27.9 (3 CH₃), 16.8 (CH₃).

HRMS (ESI) calc'd for [C₂₃H₂₇N₃O₄+H]⁺: 410.2074, found: 410.2077.

HPLC Chiralpak AD-H, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 6.01 min, τ_{minor} = 4.83 min.

$[\alpha]_{\text{D}}^{20}$ = -29 (c 0.10, CHCl₃).

trans-(10S,11aS) diastereomer 66:*trans*-(10S,11aS)-66

TLC (PE/Et₂O 2:1) R_f 0.17 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.88 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.42 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.36 – 7.31 (m, 1H), 6.61 – 6.54 (m, 1H), 6.14 (dd, *J* = 3.4, 2.9 Hz, 1H), 5.89 – 5.84 (m, 1H), 4.56 (d, *J* = 5.3 Hz, 1H), 4.31 (dd, *J* = 11.2, 3.4 Hz, 1H), 4.15 (dt, *J* = 13.3, 3.6 Hz, 1H), 4.10 – 3.99 (m, 2H), 3.46 (ddd, *J* = 13.7, 9.6, 4.4 Hz, 1H), 2.55 (s, 3H), 2.49 (dt, *J* = 13.8, 3.2 Hz, 1H), 2.28 (ddd, *J* = 13.8, 11.3, 6.4 Hz, 1H), 1.09 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 167.9 (C), 154.2 (C), 149.7 (C), 142.6 (C), 132.4 (CH), 130.7 (CH), 129.3 (C), 126.9 (CH), 124.6 (CH), 119.0 (CH), 108.7 (CH), 103.3 (CH), 101.0 (C), 78.9 (C), 49.7 (CH), 45.1 (CH₂), 44.5 (CH₂), 35.0 (CH), 34.4 (CH₂), 28.1 (3 CH₃), 17.3 (CH₃).

HRMS (ESI) calc'd for [C₂₃H₂₇N₃O₄+H]⁺: 410.2074, found: 410.2075.

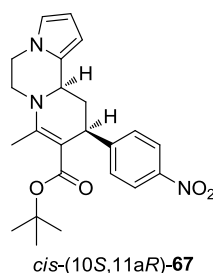
HPLC Chiralcel OD-3, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 11.53 min, τ_{minor} = 6.53 min.

[α]_D²⁰ = +21.3 (c 0.08, CHCl₃).

tert-Butyl 8-methyl-10-(4-nitrophenyl)-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 67

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μL , 0.200 mmol, 1 equiv), *trans*-4-nitrocinnamaldehyde (53.2 mg, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL , 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 2:1 then PE/Et₂O/AcOH 2:1:0.025) afforded *cis*-(10*S*,11*aR*)-**67** as a pale yellow oil (17.5 mg, 0.046 mmol, 23% yield, 95% *ee*) and *trans*-(10*S*,11*aS*)-**67** as a pale yellow oil (22.9 mg, 0.060 mmol, 30% yield, 94% *ee*).

***cis*-(10*S*,11*aR*) diastereomer 67:**



TLC (PE/Et₂O 2:1) *R_f* 0.27 (UV, vanillin).

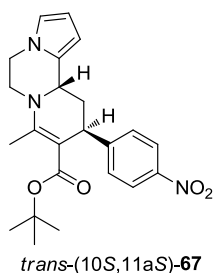
¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.08 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.54 – 6.48 (m, 1H), 6.05 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.74 – 5.67 (m, 1H), 4.52 (dd, *J* = 9.9, 2.8 Hz, 1H), 4.15 (dd, *J* = 10.0, 7.3 Hz, 1H), 4.07 – 3.94 (m, 3H), 3.42 – 3.31 (m, 1H), 2.54 (ddd, *J* = 13.5, 6.6, 3.1 Hz, 1H), 2.48 (d, *J* = 1.2 Hz, 3H), 1.96 (dt, *J* = 13.5, 10.2 Hz, 1H), 1.06 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.0 (C), 156.0 (C), 152.6 (C), 146.2 (C), 128.8 (C), 127.8 (2 CH), 123.6 (2 CH), 118.7 (CH), 108.7 (CH), 103.54 (CH), 103.47 (C), 79.4 (C), 53.4 (CH), 45.2 (CH₂), 44.1 (CH₂), 41.6 (CH), 39.5 (CH₂), 28.1 (3 CH₃), 16.9 (CH₃).

HRMS (ESI) calc'd for [C₂₃H₂₇N₃O₄+H]⁺: 410.2074, found: 410.2075.

HPLC Lux-Amylose-2, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 11.82 min, τ_{minor} = 7.76 min.

$[\alpha]_{\text{D}}^{20}$ = -39.3 (c 0.15, CHCl₃).

trans-(10S,11aS) diastereomer 67:

TLC (PE/Et₂O 2:1) R_f 0.17 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.16 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 6.61 – 6.53 (m, 1H), 6.12 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.81 – 5.74 (m, 1H), 4.23 (d, *J* = 4.3 Hz, 1H), 4.15 – 3.97 (m, 4H), 3.41 (ddd, *J* = 13.6, 9.2, 4.8 Hz, 1H), 2.56 (s, 3H), 2.29 (ddd, *J* = 13.5, 4.1, 2.6 Hz, 1H), 2.25 – 2.18 (m, 1H), 1.19 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.1 (C), 155.9 (C), 153.8 (C), 146.5 (C), 129.1 (C), 128.8 (2 CH), 123.6 (2 CH), 119.0 (CH), 108.6 (CH), 103.0 (CH), 99.8 (C), 79.0 (C), 49.4 (CH), 45.1 (CH₂), 44.4 (CH₂), 39.2 (CH), 35.8 (CH₂), 28.3 (3 CH₃), 17.4 (CH₃).

HRMS (ESI) calc'd for [C₂₃H₂₇N₃O₄+H]⁺: 410.2074, found: 410.2073.

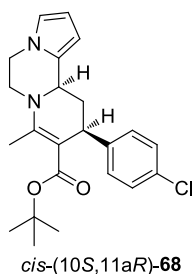
HPLC Lux-Amylose-2, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 10.26 min, τ_{minor} = 8.32 min.

[α]_D²⁰ = -22 (c 0.10, CHCl₃).

tert-Butyl 10-(4-chlorophenyl)-8-methyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo [2,1-c] pyrazine-9-carboxylate 68

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-4-chlorocinnamaldehyde (50.0 mg, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 4:1 then PE/Et₂O/AcOH 4:1:0.025) afforded *cis*-(10*S*,11*aR*)-**68** as a pale yellow solid (27.1 mg, 0.068 mmol, 34% yield, 99% *ee*) and *trans*-(10*S*,11*aS*)-**68** as a pale yellow oil (12.8 mg, 0.032 mmol, 16% yield, 91% *ee*).

***cis*-(10*S*,11*aR*) diastereomer 68:**



TLC (PE/Et₂O 4:1) *R_f* 0.22 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.20 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.57 – 6.51 (m, 1H), 6.11 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.84 – 5.78 (m, 1H), 4.47 (dd, *J* = 11.0, 2.8 Hz, 1H), 4.06 – 3.95 (m, 4H), 3.36 – 3.26 (m, 1H), 2.52 (ddd, *J* = 13.5, 6.5, 2.8 Hz, 1H), 2.41 (d, *J* = 1.4 Hz, 3H), 1.92 (dt, *J* = 13.5, 11.0 Hz, 1H), 1.07 (s, 9H).

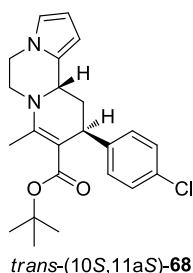
¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.5 (C), 150.8 (C), 146.1 (C), 131.3 (C), 129.3 (C), 128.6 (2 CH), 128.3 (2 CH), 118.6 (CH), 108.7 (CH), 105.3 (C), 103.2 (CH), 79.2 (C), 53.7 (CH), 45.3 (CH₂), 43.9 (CH₂), 41.4 (CH), 40.3 (CH₂), 27.9 (3 CH₃), 16.7 (CH₃).

HRMS (ESI) calc'd for [C₂₃H₂₇N₂O₂Cl+H]⁺: 399.1834, found: 399.1835.

HPLC Chiralpak AD-H, Hexane/Isopropanol 95/5, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 9.87 min, τ_{minor} = 8.49 min.

$[\alpha]_{\text{D}}^{20}$ = –23 (c 0.20, CHCl₃).

m.p. = 156–157 °C.

trans-(10S,11aS) diastereomer 68:

TLC (PE/Et₂O 4:1) *R_f* 0.18 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.27 – 7.23 (m, 2H), 7.20 – 7.14 (m, 2H), 6.57 – 6.52 (m, 1H), 6.12 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.81 – 5.74 (m, 1H), 4.14 – 4.06 (m, 3H), 4.04 – 3.96 (m, 2H), 3.37 (ddd, *J* = 13.7, 9.4, 4.7 Hz, 1H), 2.52 (s, 3H), 2.24 (ddd, *J* = 13.2, 3.3, 2.7 Hz, 1H), 2.11 (ddd, *J* = 13.2, 11.6, 5.7 Hz, 1H), 1.20 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.5 (C), 153.1 (C), 146.4 (C), 131.6 (C), 129.7 (C), 129.4 (2 CH), 128.3 (2 CH), 118.9 (CH), 108.5 (CH), 102.9 (CH), 101.1 (C), 78.7 (C), 49.4 (CH), 45.2 (CH₂), 44.4 (CH₂), 38.5 (CH), 36.1 (CH₂), 28.3 (3 CH₃), 17.5 (CH₃).

HRMS (ESI) calc'd for [C₂₃H₂₇N₂O₂Cl+H]⁺: 399.1834, found: 399.1833.

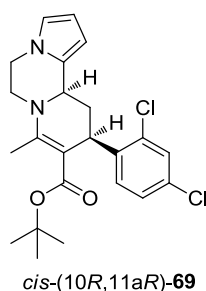
HPLC Chiralcel OD-3, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 6.13 min, τ_{minor} = 5.15 min.

[α]_D²⁰ = -17.5 (c 0.08, CHCl₃).

tert-Butyl 10-(2,4-dichlorophenyl)-8-methyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 69

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-2,4-dichlorocinnamaldehyde (50.0 mg, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 8:1 then PE/Et₂O/AcOH 8:1:0.025) afforded *cis*-(10*R*,11*aR*)-**69** as a pale yellow solid (17.3 mg, 0.040 mmol, 20% yield, 94% *ee*) and *trans*-(10*R*,11*aS*)-**69** as a pale yellow oil (27.7 mg, 0.064 mmol, 32% yield, 96% *ee*).

cis-(10*R*,11*aR*) diastereomer 69:



TLC (PE/Et₂O 8:1) *R_f* 0.21 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.33 (d, *J* = 2.0 Hz, 1H), 7.02 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.54 – 6.48 (m, 1H), 6.06 (dd, *J* = 3.4, 2.9 Hz, 1H), 5.77 – 5.70 (m, 1H), 4.53 – 4.44 (m, 2H), 4.07 – 3.96 (m, 3H), 3.35 (ddd, *J* = 13.0, 8.5, 5.5 Hz, 1H), 2.56 (ddd, *J* = 13.9, 6.6, 3.2 Hz, 1H), 2.47 (d, *J* = 1.3 Hz, 3H), 1.86 (dt, *J* = 13.5, 9.9 Hz, 1H), 1.10 (s, 9H).

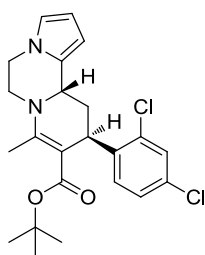
¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.1 (C), 152.5 (C), 143.6 (C), 133.8 (C), 131.6 (C), 129.1 (C), 128.8 (CH), 128.4 (CH), 127.2 (CH), 118.6 (CH), 108.7 (CH), 104.0 (C), 103.4 (CH), 79.2 (C), 53.5 (CH), 45.2 (CH₂), 44.1 (CH₂), 37.0 (CH), 36.6 (CH₂), 28.0 (3 CH₃), 16.8 (CH₃).

HRMS (ESI) calc'd for [C₂₃H₂₆N₂O₂Cl₂+H]⁺: 433.1444, found: 433.1427.

HPLC Chiralcel OD-3, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 11.51 min, τ_{minor} = 5.94 min.

$[\alpha]_{\text{D}}^{20}$ = -100 (c 0.05, CHCl₃).

m.p. = 163-164 °C.

trans-(10R,11aS) diastereomer 69:*trans*-(10R,11aS)-**69**

TLC (PE/Et₂O 8:1) R_f 0.15 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.42 – 7.39 (m, 1H), 7.15 – 7.12 (m, 2H), 6.58 – 6.53 (m, 1H), 6.12 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.83 – 5.78 (m, 1H), 4.49 (d, *J* = 5.3 Hz, 1H), 4.14 – 4.07 (m, 2H), 4.07 – 3.97 (m, 2H), 3.39 (ddd, *J* = 13.4, 9.4, 4.4 Hz, 1H), 2.54 (s, 3H), 2.27 (ddd, *J* = 13.6, 3.2, 2.3 Hz, 1H), 2.08 (ddd, *J* = 13.6, 11.7, 6.0 Hz, 1H), 1.18 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.1 (C), 154.0 (C), 143.5 (C), 134.0 (C), 132.2 (C), 130.7 (CH), 129.4 (2 CH), 126.5 (CH), 118.9 (CH), 108.6 (CH), 103.1 (CH), 100.5 (C), 78.8 (C), 49.5 (CH), 45.2 (CH₂), 44.3 (CH₂), 35.9 (CH), 33.3 (CH₂), 28.2 (3 CH₃), 17.4 (CH₃).

HRMS (ESI) calc'd for [C₂₃H₂₆N₂O₂Cl₂+H]⁺: 433.1444, found: 433.1441.

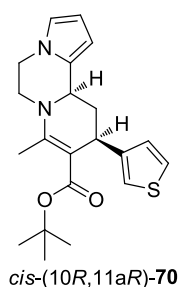
HPLC Chiralcel OD-3, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 5.96 min, τ_{minor} = 5.02 min.

[α]_D²⁰ = -192 (c 0.10, CHCl₃).

tert-Butyl 8-methyl-10-(thiophen-3-yl)-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a] pyrrolo [2,1-c] pyrazine-9-carboxylate 70

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-3-(3-thienyl)acrolein (41.5 mg, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 2:1 then PE/Et₂O/AcOH 2:1:0.025) afforded *cis*-(10*R*,11*aR*)-**70** as a yellow oil (20.0 mg, 0.054 mmol, 27% yield, 97% *ee*) and *trans*-(10*R*,11*aS*)-**70** as a yellow oil (12.6 mg, 0.034 mmol, 17% yield, 94% *ee*).

cis-(10*R*,11*aR*) diastereomer:



TLC (PE/Et₂O 2:1) *R_f* 0.48 (UV, vanillin).

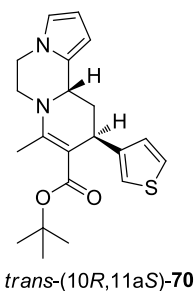
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.15 (dd, *J* = 4.5, 3.4 Hz, 1H), 6.97 – 6.89 (m, 2H), 6.56 – 6.49 (m, 1H), 6.11 (dd, *J* = 3.5, 2.9 Hz, 1H), 5.87 – 5.80 (m, 1H), 4.45 (dd, *J* = 10.8, 2.4 Hz, 1H), 4.16 (dd, *J* = 10.1, 6.5 Hz, 1H), 4.06 – 3.93 (m, 3H), 3.29 (ddd, *J* = 13.4, 9.9, 4.1 Hz, 1H), 2.54 (ddd, *J* = 13.5, 6.4, 2.8 Hz, 1H), 2.36 (d, *J* = 1.5 Hz, 3H), 2.00 (dt, *J* = 13.5, 11.1 Hz, 1H), 1.13 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.8 (C), 149.2 (C), 147.8 (C), 129.5 (C), 127.4 (CH), 124.9 (CH), 119.7 (CH), 118.6 (CH), 108.7 (CH), 106.3 (C), 103.1 (CH), 79.1 (C), 53.8 (CH), 45.4 (CH₂), 43.9 (CH₂), 39.4 (CH₂), 37.1 (CH), 27.9 (3 CH₃), 16.6 (CH₃).

HRMS (ESI) calc'd for [C₂₁H₂₆N₂O₂S+H]⁺: 371.1788, found: 371.1793.

HPLC Chiralcel OJ-H, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 8.62 min, τ_{minor} = 10.61 min.

$[\alpha]_{\text{D}}^{20}$ = -37.3 (c 0.04, CHCl₃).

trans-(10R,11aS) diastereomer 70:

TLC (PE/Et₂O 2:1) R_f 0.10 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.24 (dd, *J* = 4.9, 3.0 Hz, 1H), 6.99 (d, *J* = 5.1 Hz, 1H), 6.87 (d, *J* = 2.9 Hz, 1H), 6.56 – 6.54 (m, 1H), 6.13 (t, *J* = 3.1 Hz, 1H), 5.85 – 5.79 (m, 1H), 4.21 – 4.10 (m, 2H), 4.11 – 3.97 (m, 3H), 3.34 (ddd, *J* = 14.0, 9.7, 4.4 Hz, 1H), 2.47 (s, 3H), 2.33 (dt, *J* = 13.1, 2.7 Hz, 1H), 2.05 (ddd, *J* = 13.6, 11.7, 6.0 Hz, 1H), 1.26 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.7 (C), 152.0 (C), 148.7 (C), 129.8 (C), 127.5 (CH), 125.1 (CH), 120.9 (CH), 118.6 (CH), 108.4 (CH), 102.7 (CH), 102.5 (C), 78.5 (C), 49.8 (CH), 45.1 (CH₂), 44.2 (CH₂), 35.1 (CH₂), 34.5 (CH), 28.2 (3 CH₃), 17.5 (CH₃).

HRMS (ESI) calc'd for [C₂₁H₂₆N₂O₂S + H]⁺: 371.1788, found: 371.1794.

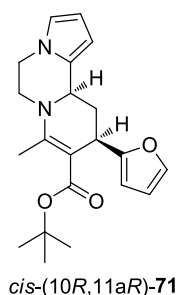
HPLC Chiralcel OD-3, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 7.75 min, τ_{minor} = 6.47 min.

[α]_D²⁰ = -52 (c 0.05, CHCl₃).

tert-Butyl 10-(furan-2-yl)-8-methyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo [2,1-c]pyrazine-9-carboxylate 71

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-3-(2-furyl)acrolein (36.6 mg, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 4:1 then PE/Et₂O/AcOH 4:1:0.025) afforded *cis*-(10*R*,11*aR*)-**71** as a pale yellow oil (9.9 mg, 0.028 mmol, 14% yield, 74% *ee*) and *trans*-(10*R*,11*aS*)-**71** as a pale yellow oil (12.0 mg, 0.034 mmol, 17% yield, 92% *ee*).

cis-(10*R*,11*aR*) diastereomer 71:



TLC (PE/Et₂O 4:1) *R_f* 0.40 (UV, vanillin).

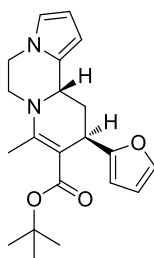
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.21 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.52 – 6.46 (m, 1H), 6.14 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.05 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.80 (d, *J* = 3.2 Hz, 1H), 5.77 – 5.74 (m, 1H), 4.49 (dd, *J* = 8.8, 3.4 Hz, 1H), 4.15 (dd, *J* = 8.1, 7.1 Hz, 1H), 4.01 (dt, *J* = 7.6, 3.4 Hz, 1H), 3.98 – 3.91 (m, 2H), 3.32 (ddd, *J* = 14.3, 8.8, 5.6 Hz, 1H), 2.49 (ddd, *J* = 13.5, 6.3, 3.5 Hz, 1H), 2.41 (d, *J* = 1.3 Hz, 3H), 2.25 (dt, *J* = 13.5, 9.1 Hz, 1H), 1.26 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.5 (C), 159.0 (C), 150.7 (C), 139.8 (CH), 129.3 (C), 118.4 (CH), 110.2 (CH), 108.5 (CH), 103.9 (CH), 102.9 (C), 102.9 (CH), 79.1 (C), 53.2 (CH), 45.0 (CH₂), 44.3 (CH₂), 35.3 (CH₂), 34.4 (CH), 28.1 (3 CH₃), 16.9 (CH₃).

HRMS (ESI) calc'd for [C₂₁H₂₆N₂O₃+H]⁺: 355.2016, found: 355.2016.

HPLC Chiralcel OD-3, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 9.52 min, τ_{minor} = 7.19 min.

$[\alpha]_{\text{D}}^{20}$ = -14 (c 0.10, CHCl₃).

trans-(10R,11aS) diastereomer 71:*trans*-(10R,11aS)-71

TLC (PE/Et₂O 4:1) *R_f* 0.16 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.31 (dd, *J* = 1.7, 0.7 Hz, 1H), 6.57 – 6.54 (m, 1H), 6.25 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.15 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.94 (d, *J* = 3.2 Hz, 1H), 5.88 (dt, *J* = 3.4, 1.3 Hz, 1H), 4.22 – 4.16 (m, 2H), 4.08 – 3.97 (m, 3H), 3.34 (ddd, *J* = 13.5, 9.0, 4.4 Hz, 1H), 2.51 (ddd, *J* = 13.2, 3.2, 2.2 Hz, 1H), 2.45 (d, *J* = 0.6 Hz, 3H), 1.95 (ddd, *J* = 13.2, 11.8, 5.4 Hz, 1H), 1.34 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.6 (C), 159.9 (C), 152.7 (C), 141.0 (CH), 129.8 (C), 118.8 (CH), 110.1 (CH), 108.6 (CH), 106.1 (CH), 103.0 (CH), 100.0 (C), 78.8 (C), 50.4 (CH), 45.3 (CH₂), 44.3 (CH₂), 33.1 (CH), 32.8 (CH₂), 28.4 (3 CH₃), 17.7 (CH₃).

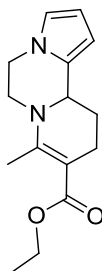
HRMS (ESI) calc'd for [C₂₁H₂₆N₂O₃+H]⁺: 355.2016, found: 355.2012.

HPLC Chiralcel OD-3, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 6.15 min, τ_{minor} = 5.32 min.

[α]_D²⁰ = -38.9 (c 0.18, CHCl₃).

Ethyl 8-methyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 72

Prepared according to the general procedure using ethyl acetoacetate **51** (26.0 mg, 25.3 μL , 0.200 mmol, 1 equiv), acrolein (16.8 mg, 19.7 μL , 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL , 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc 4:1) afforded **72** as a pale yellow oil (33.8 mg, 0.130 mmol, 65% yield, 0% *ee*).

**72**

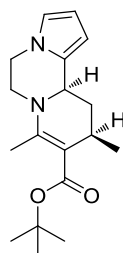
TLC (PE/EtOAc 4:1) R_f 0.47 (UV, vanillin).

^1H NMR (300 MHz, CDCl_3) δ (ppm) 6.56 (s, 1H), 6.19 – 6.12 (m, 1H), 5.94 (dd, $J = 2.0, 1.4$ Hz, 1H), 4.37 (dd, $J = 8.2, 3.6$ Hz, 1H), 4.18 – 4.01 (m, 3H), 3.99 – 3.89 (m, 2H), 3.45 – 3.22 (m, 1H), 2.57 – 2.46 (m, 1H), 2.42 (d, $J = 8.1$ Hz, 3H), 2.25 (ddd, $J = 17.5, 11.4, 6.9$ Hz, 1H), 2.04 – 1.88 (m, 1H), 1.26 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 169.2 (C), 152.6 (C), 130.3 (C), 118.8 (CH), 108.3 (CH), 102.5 (CH), 98.9 (C), 59.1 (CH_2), 54.2 (CH), 44.8 (CH_2), 44.7 (CH_2), 27.2 (CH_2), 22.0 (CH_2), 16.9 (CH_3), 14.6 (CH_3).

tert-Butyl 8,10-dimethyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 73

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-crotonaldehyde (21.0 mg, 24.9 μ L, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O/AcOH 3:1:0.025) afforded *cis*-(10*R*,11*aR*)-**73** as a yellow oil (19.9 mg, 0.066 mmol, 33% yield, 88% *ee*).



cis-(10*R*,11*aR*)-**73**

TLC (PE/Et₂O 3:1) *R_f* 0.20 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 6.60 – 6.54 (m, 1H), 6.17 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.95 – 5.89 (m, 1H), 4.30 (dd, *J* = 11.8, 3.3 Hz, 1H), 4.05 – 3.95 (m, 3H), 3.35 – 3.25 (m, 1H), 2.93 (quint, *J* = 6.1 Hz, 1H), 2.33 (s, 3H), 2.06 (ddd, *J* = 13.2, 3.3, 1.9 Hz, 1H), 1.84 (ddd, *J* = 13.2, 11.8, 5.4 Hz, 1H), 1.49 (s, 9H), 1.12 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 169.3 (C), 150.6 (C), 130.5 (C), 118.7 (CH), 108.5 (CH), 106.0 (C), 102.7 (CH), 78.7 (C), 49.7 (CH), 45.4 (CH₂), 44.3 (CH₂), 34.9 (CH₂), 28.6 (3 CH₃), 27.1 (CH), 22.8 (CH₃), 17.8 (CH₃).

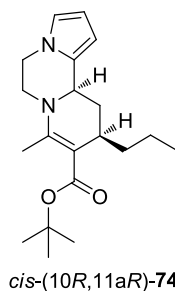
HRMS (ESI) calc'd for [C₁₈H₂₆N₂O₂+H]⁺: 303.2067, found: 303.2071.

HPLC Chiralcel OJ-H, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 7.28 min, τ_{minor} = 9.25 min.

$[\alpha]_{\text{D}}^{20}$ = -161 (c 0.10, CHCl₃).

**tert-Butyl 8-methyl-10-propyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo
[2,1-c]pyrazine-9-carboxylate 74**

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-2-hexan-1-al (29.4 mg, 34.8 μ L, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc/AcOH 4:1:0.025) afforded *cis*-(10*R*,11*aR*)-**74** as a yellow oil (25.7 mg, 0.078 mmol, 39% yield, 92% *ee*).



TLC (PE/EtOAc 4:1) *R_f* 0.33 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 6.58 – 6.55 (m, 1H), 6.17 (dd, *J* = 3.4, 2.9 Hz, 1H), 5.95 – 5.89 (m, 1H), 4.26 (dd, *J* = 11.9, 3.3 Hz, 1H), 4.06 – 3.95 (m, 3H), 3.30 (ddd, *J* = 13.2, 9.0, 5.7 Hz, 1H), 2.82 – 2.74 (m, 1H), 2.32 (s, 3H), 2.23 (ddd, *J* = 13.4, 3.3, 2.0 Hz, 1H), 1.72 (td, *J* = 12.7, 5.2 Hz, 1H), 1.49 (s, 9H), 1.41 – 1.18 (m, 4H), 0.94 (t, *J* = 7.0 Hz, 3H)

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 169.4 (C), 150.2 (C), 130.7 (C), 118.7 (CH), 108.5 (CH), 105.5 (C), 102.6 (CH), 78.7 (C), 50.0 (CH), 45.4 (CH₂), 44.4 (CH₂), 39.0 (CH₂), 31.8 (CH), 31.2 (CH₂), 28.6 (3 CH₃), 20.6 (CH₂), 17.8 (CH₃), 14.4 (CH₃).

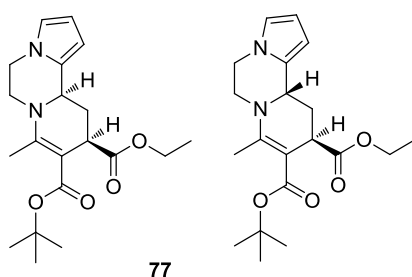
HRMS (ESI) calc'd for [C₂₀H₃₀N₂O₂+H]⁺: 331.2380, found: 331.2380.

HPLC Chiralcel OD-3, Hexane/EtOH 95/5, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 7.25 min, τ_{minor} = 5.16 min.

$[\alpha]_{\text{D}}^{20}$ = -82.7 (c 0.08, CHCl₃).

(10*R*)-9-*tert*-butyl 10-ethyl 8-methyl-6,10,11,11a-tetrahydro-5*H*-pyrido[1,2-*a*]pyrrolo [2,1-*c*]pyrazine-9,10-dicarboxylate 77

A reaction tube was charged with (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **VI** (6.6 mg, 0.020 mmol, 0.1 equiv), benzoic acid (4.9 mg, 0.040 mmol, 0.2 equiv), dry α,α,α -trifluorotoluene (2.5 mL), flushed with argon and placed at 0 °C. *tert*-Butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv) and (*E*)-ethyl 4-oxobut-2-enoate (30.8 mg, 28.9 μ L, 0.240 mmol, 1.2 equiv) were then added. After full conversion of *tert*-butyl acetoacetate **63** as monitored by TLC, followed by the addition of *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv), the mixture was stirred at 0 °C for another 24 h. After reaction, direct purification by flash chromatography (PE/EtOAc 4:1) afforded **77** as a mixture of diastereomers (\sim 1.2:1) yellow oil (32.4 mg, 0.090 mmol, 45% yield, 94% and 93% *ee*).



TLC (PE/EtOAc 4:1) R_f 0.18 (UV, vanillin).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) *major diastereomer*: 6.58 – 6.56 (m, 1H), 6.13 (t, $J = 3.2$ Hz, 1H), 5.96 – 5.93 (m, 1H), 4.36 (dd, $J = 11.5, 3.2$ Hz, 1H), 4.09 – 3.93 (m, 5H), 3.71 – 3.67 (m, 1H), 3.40 – 3.31 (m, 1H), 2.54 – 2.49 (m, 1H), 2.46 (s, 3H), 1.99 – 1.90 (m, 1H), 1.44 (s, 9H), 1.28 (t, $J = 7.1$ Hz, 3H); *minor diastereomer*: 6.55 – 6.53 (m, 1H), 6.17 (t, $J = 3.2$ Hz, 1H), 5.92 – 5.89 (m, 1H), 4.41 (dd, $J = 8.9, 3.2$ Hz, 1H), 4.23 – 4.09 (m, 3H), 4.09 – 3.93 (m, 2H), 3.67 – 3.62 (m, 1H), 3.40 – 3.31 (m, 1H), 2.54 – 2.49 (m, 1H), 2.49 (s, 3H), 2.20 – 2.11 (m, 1H), 1.42 (s, 9H), 1.19 (t, $J = 7.1$ Hz, 3H)

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ (ppm) *major diastereomer*: 175.8 (C), 168.1 (C), 153.3 (C), 129.3 (C), 118.9 (CH), 108.6 (CH), 103.1 (CH), 97.6 (C), 79.1 (C), 60.8 (CH_2), 50.8 (CH), 45.1 (CH_2), 44.2 (CH_2), 39.6 (CH), 30.7 (CH_2), 28.5 (3 CH_3), 17.2 (CH_3), 14.5 (CH_3); *minor diastereomer*: 175.3 (C), 167.6 (C), 153.7 (C), 128.8 (C), 119.0 (CH), 108.5 (CH), 103.5 (CH), 99.8 (C), 79.3 (C), 60.5 (CH_2), 52.9 (CH), 44.9 (CH_2), 44.2 (CH_2), 41.2 (CH), 32.4 (CH_2), 28.4 (3 CH_3), 17.0 (CH_3), 14.2 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_4+\text{H}]^+$: 361.2122, found: 361.2119.

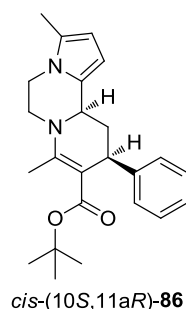
HPLC Chiralpak AD-H, Heptane/ethanol 90/10, 25 °C, 1 ml/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 6.90$ min, $\tau_{\text{minor}} = 10.82$ min.

Chiralcel OD-3, Heptane/ethanol 90:10, 25 °C, 1 ml/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 17.66$ min, $\tau_{\text{minor}} = 10.93$ min.

tert-Butyl 3,8-dimethyl-10-phenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 86

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-cinnamaldehyde **52** (39.7 mg, 37.8 μ L, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)-2-methylpyrrole **78** (24.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 4:1) afforded *cis*-(10*S*,11*aR*)-**86** as a pale solid (12.9 mg, 0.034 mmol, 17% yield, 97% *ee*) and *trans*-(10*S*,11*aS*)-**86** as a yellow oil (28.0 mg, 0.074 mmol, 37% yield, 93% *ee*).

cis-(10*S*,11*aR*) diastereomer 86:



TLC (PE/Et₂O 4:1) *R_f* 0.20 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.25 – 7.17 (m, 4H), 7.16 – 7.11 (m, 1H), 5.83 (dd, *J* = 3.4, 0.7 Hz, 1H), 5.75 (dd, *J* = 3.4, 1.0 Hz, 1H), 4.45 (dd, *J* = 11.1, 1.6 Hz, 1H), 4.05 – 3.92 (m, 2H), 3.93 – 3.77 (m, 2H), 3.26 (ddd, *J* = 13.6, 10.3, 4.2 Hz, 1H), 2.54 (ddd, *J* = 13.5, 6.3, 2.7 Hz, 1H), 2.40 (d, *J* = 1.5 Hz, 3H), 2.18 (s, 3H), 1.94 (dt, *J* = 13.5, 11.6 Hz, 1H), 1.02 (s, 9H).

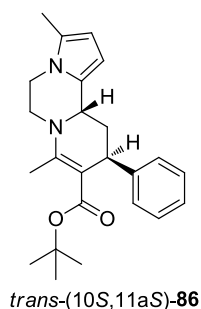
¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.8 (C), 145.0 (C), 147.5 (C), 128.8 (C), 128.3 (2 CH), 127.4 (2 CH), 126.6 (C), 125.9 (CH), 106.3 (CH), 106.2 (C), 102.2 (CH), 79.1 (C), 54.1 (CH), 43.9 (CH₂), 42.9 (CH₂), 42.1 (CH), 40.5 (CH₂), 27.8 (3 CH₃), 16.5 (CH₃), 11.5 (CH₃).

HRMS (ESI) calc'd for [C₂₄H₃₀N₂O₂+H]⁺: 379.2380, found: 379.2382.

HPLC Lux-Amylose-2, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 5.43 min, τ_{minor} = 4.69 min.

$[\alpha]_{\text{D}}^{20}$ = -28.7 (c 0.05, CHCl₃).

m.p. = 145-146 °C.

trans-(10S,11aS) diastereomer 86:

TLC (PE/Et₂O 4:1) *R_f* 0.13 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.30 – 7.09 (m, 5H), 5.82 (dd, *J* = 3.3, 1.5 Hz, 1H), 5.68 (dd, *J* = 3.4, 0.9 Hz, 1H), 4.18 – 4.07 (m, 3H), 3.91 – 3.78 (m, 2H), 3.35 (ddd, *J* = 14.0, 9.7, 4.4 Hz, 1H), 2.51 (s, 3H), 2.27 (dt, *J* = 13.2, 3.0 Hz, 1H), 2.16 (d, *J* = 10.8 Hz, 3H), 2.11 (ddd, *J* = 13.1, 11.4, 5.8 Hz, 1H), 1.17 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.7 (C), 152.8 (C), 147.9 (C), 129.1 (C), 128.12 (2 CH), 128.09 (2 CH), 126.7 (C), 125.8 (CH), 106.1 (CH), 101.8 (CH), 101.8 (C), 78.6 (C), 49.7 (CH), 44.4 (CH₂), 42.7 (CH₂), 39.0 (CH), 36.1 (CH₂), 28.2 (3 CH₃), 17.5 (CH₃), 11.5 (CH₃).

HRMS (ESI) calc'd for [C₂₄H₃₀N₂O₂+H]⁺: 379.2380, found: 379.2381.

HPLC Lux-Cellulose-2, Hexane/EtOH 95/5, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 7.46 min, τ_{minor} = 6.87 min.

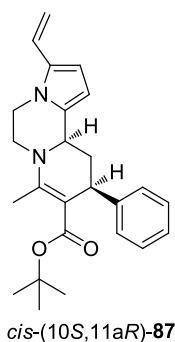
[α]_D²⁰ = -74 (c 0.10, CHCl₃).

m.p. = 146-147 °C.

tert-Butyl 8-methyl-10-phenyl-3-vinyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 87

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-cinnamaldehyde **52** (39.7 mg, 37.8 μ L, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)-2-vinylpyrrole **79** (27.2 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 4:1) afforded *cis*-(10*S*,11*aR*)-**87** as a pale solid (19.4 mg, 0.050 mmol, 25% yield, 92% *ee*) and *trans*-(10*S*,11*aS*)-**87** as a pale yellow oil (28.2 mg, 0.072 mmol, 36% yield, 94% *ee*).

***cis*-(10*S*,11*aR*) diastereomer 87:**



TLC (PE/Et₂O 4:1) R_f 0.36 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.34 – 7.17 (m, 5H), 6.59 (dd, *J* = 17.5, 11.3 Hz, 1H), 6.38 (d, *J* = 3.8 Hz, 1H), 5.91 (d, *J* = 3.7 Hz, 1H), 5.49 (dd, *J* = 17.5, 1.1 Hz, 1H), 5.08 (dd, *J* = 11.3, 1.1 Hz, 1H), 4.54 (dd, *J* = 11.5, 2.7 Hz, 1H), 4.15 – 3.98 (m, 4H), 3.33 (ddd, *J* = 13.3, 11.5, 5.6 Hz, 1H), 2.61 (ddd, *J* = 13.5, 6.3, 2.7 Hz, 1H), 2.47 (d, *J* = 1.4 Hz, 3H), 2.02 (dt, *J* = 13.5, 11.5 Hz, 1H), 1.10 (s, 9H).

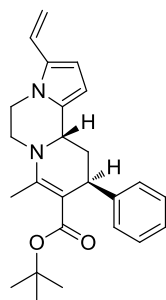
¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.7 (C), 149.90 (C), 147.3 (C), 130.9 (C), 130.3 (C), 128.3 (2 CH), 127.3 (2 CH), 125.9 (CH), 125.0 (CH), 110.5 (CH₂), 106.9 (CH), 106.4 (C), 104.0 (CH), 79.1 (C), 54.0 (CH), 43.6 (CH₂), 43.6 (CH₂), 42.1 (CH), 40.5 (CH₂), 27.8 (3 CH₃), 16.5 (CH₃).

HRMS (ESI) calc'd for [C₂₅H₃₀N₂O₂+H]⁺: 391.2380, found: 391.2386.

HPLC Chiralpak AD-H, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 5.68 min, τ_{minor} = 6.36 min.

$[\alpha]_{\text{D}}^{20}$ = -55 (c 0.06, CHCl₃).

m.p. = 164-165 °C.

trans-(10S,11aS) diastereomer 87:*trans*-(10S,11aS)-87

TLC (PE/Et₂O 4:1) R_f 0.33 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.32 – 7.13 (m, 5H), 6.51 (dd, *J* = 17.5, 11.3 Hz, 1H), 6.30 (d, *J* = 3.7 Hz, 1H), 5.78 (d, *J* = 3.7 Hz, 1H), 5.41 (dd, *J* = 17.5, 1.1 Hz, 1H), 5.01 (dd, *J* = 11.3, 1.1 Hz, 1H), 4.19 – 4.08 (m, 3H), 4.03 (dt, *J* = 11.8, 3.4 Hz, 1H), 3.94 (td, *J* = 11.0, 4.2 Hz, 1H), 3.35 (ddd, *J* = 14.0, 9.7, 4.4 Hz, 1H), 2.52 (s, 3H), 2.27 (ddd, *J* = 13.2, 3.2, 2.7 Hz, 1H), 2.11 (ddd, *J* = 13.1, 11.5, 5.8 Hz, 1H), 1.18 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.6 (C), 152.5 (C), 147.7 (C), 131.3 (C), 130.4 (C), 128.2 (2 CH), 128.1 (2 CH), 125.9 (CH), 125.0 (CH), 110.5 (CH₂), 106.8 (CH), 103.7 (CH), 101.9 (C), 78.6 (C), 49.7 (CH), 44.2 (CH₂), 43.4 (CH₂), 39.0 (CH), 36.2 (CH₂), 28.2 (3 CH₃), 17.4 (CH₃).

HRMS (ESI) calc'd for [C₂₅H₃₀N₂O₂+H]⁺: 391.2380, found: 391.2387.

HPLC Lux-Amylose-2, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 6.14 min, τ_{minor} = 5.47 min.

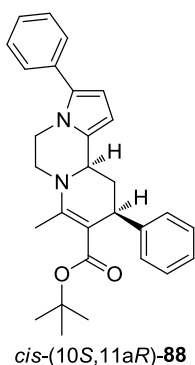
[α]_D²⁰ = -24 (c 0.03, CHCl₃).

m.p. = 165-166 °C.

tert-butyl 8-methyl-3,10-diphenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 88

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μL , 0.200 mmol, 1 equiv), *trans*-cinnamaldehyde **52** (39.7 mg, 37.8 μL , 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)-2-phenylpyrrole **80** (37.2 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 6:1) afforded *cis*-(10*S*,11*aR*)-**88** as a pale solid (31.0 mg, 0.051 mmol, 26% yield, 94% *ee*) and *trans*-(10*S*,11*aS*)-**88** as a pale solid (37.9 mg, 0.086 mmol, 43% yield, 93% *ee*).

cis-(10*S*,11*aR*) diastereomer 88:



TLC (PE/Et₂O 6:1) *R_f* 0.34 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.43 – 7.36 (m, 4H), 7.32 – 7.19 (m, 5H), 7.18 – 7.12 (m, 1H), 6.22 (d, *J* = 3.6 Hz, 1H), 5.96 (dd, *J* = 3.6, 0.9 Hz, 1H), 4.60 (dd, *J* = 11.2, 1.9 Hz, 1H), 4.13 – 4.00 (m, 3H), 3.89 (dt, *J* = 13.1, 3.9 Hz, 1H), 3.31 (ddd, *J* = 13.1, 9.4, 3.7 Hz, 1H), 2.58 (ddd, *J* = 13.4, 6.5, 2.6 Hz, 1H), 2.42 (d, *J* = 1.4 Hz, 3H), 2.06 – 1.96 (m, 1H), 1.05 (s, 9H).

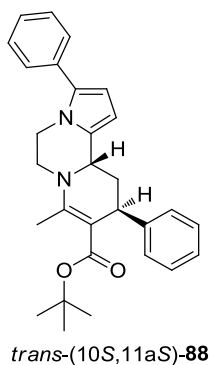
¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.7 (C), 150.3 (C), 147.4 (C), 132.9 (C), 132.8 (C), 131.1 (C), 128.6 (2 CH), 128.3 (2 CH), 128.3 (2 CH), 127.3 (2 CH), 126.8 (CH), 125.9 (CH), 108.6 (CH), 105.9 (C), 103.9 (CH), 79.0 (C), 54.0 (CH), 45.1 (CH₂), 44.0 (CH₂), 42.3 (CH), 41.0 (CH₂), 27.9 (3 CH₃), 16.8 (CH₃).

HRMS (ESI) calc'd for [C₂₉H₃₂N₂O₂+H]⁺: 441.2537, found: 441.2538.

HPLC Chiralcel OD-3, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 6.48 min, τ_{minor} = 5.07 min.

$[\alpha]_{\text{D}}^{20}$ = -48.8 (c 0.13, CHCl₃).

m.p. = 168-169 °C.

trans-(10S,11aS) diastereomer 88:

TLC (PE/Et₂O 6:1) R_f 0.21 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.42 – 7.33 (m, 4H), 7.32 – 7.22 (m, 5H), 7.22 – 7.15 (m, 1H), 6.21 (d, *J* = 3.6 Hz, 1H), 5.88 (dd, *J* = 3.6, 1.0 Hz, 1H), 4.28 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.17 (d, *J* = 5.1 Hz, 1H), 4.14 – 4.08 (m, 1H), 4.07 – 3.94 (m, 2H), 3.44 (ddd, *J* = 14.0, 9.7, 4.4 Hz, 1H), 2.54 (s, 3H), 2.36 – 2.28 (m, 1H), 2.18 (ddd, *J* = 13.0, 11.7, 5.8 Hz, 1H), 1.19 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 168.8 (C), 152.8 (C), 147.9 (C), 133.1 (C), 132.8 (C), 131.5 (C), 128.7 (2 CH), 128.3 (2 CH), 128.2 (2 CH), 128.1 (2 CH), 126.8 (CH), 125.9 (CH), 108.4 (CH), 103.6 (CH), 101.7 (C), 78.5 (C), 49.4 (CH), 44.8 (CH₂), 44.5 (CH₂), 39.2 (CH), 36.1 (CH₂), 28.2 (3 CH₃), 17.5 (CH₃).

HRMS (ESI) calc'd for [C₂₉H₃₂N₂O₂+H]⁺: 441.2537, found: 441.2538.

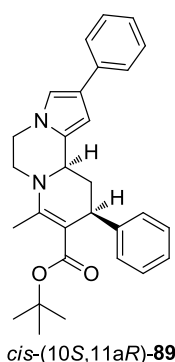
HPLC Chiralcel OD-3, Hexane/EtOH 80/20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 5.31 min, τ_{minor} = 6.23 min.

[α]_D²⁰ = +111.1 (c 0.23, CHCl₃).

m.p. = 167-168 °C.

tert-Butyl 8-methyl-2,10-diphenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo [2,1-c]pyrazine-9-carboxylate 89

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), *trans*-cinnamaldehyde **52** (39.7 mg, 37.8 μ L, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)-3-phenylpyrrole **81** (37.2 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc 4:1) afforded *cis*-(10*S*,11*aR*)-**89** as a pale yellow solid (15.1 mg, 0.034 mmol, 17% yield, 95% ee) and *trans*-(10*S*,11*aS*)-**89** as a pale yellow solid (15.0 mg, 0.034 mmol, 17% yield, 97% ee).

***cis*-(10*S*,11*aR*) diastereomer 89:**

TLC (PE/EtOAc 4:1) R_f 0.34 (UV, vanillin).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.37 – 7.34 (m, 4H), 7.22 – 7.18 (m, 1H), 7.16 – 7.11 (m, 2H), 7.07 – 7.00 (m, 3H), 6.59 (d, $J = 2.8$ Hz, 1H), 6.29 (d, $J = 2.8$ Hz, 1H), 5.04 (dd, $J = 10.9, 1.8$ Hz, 1H), 4.13 – 4.03 (m, 2H), 3.88 – 3.81 (m, 2H), 3.48 (ddd, $J = 12.7, 8.4, 4.1$ Hz, 1H), 2.43 (d, $J = 1.4$ Hz, 3H), 2.29 (ddd, $J = 13.5, 7.0, 1.9$ Hz, 1H), 1.63 (dt, $J = 13.3, 11.4$ Hz, 1H), 1.04 (s, 9H).

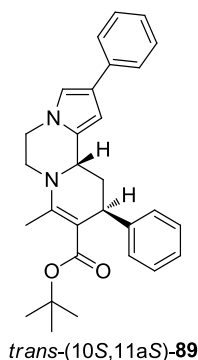
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ (ppm) 168.5 (C), 151.9 (C), 147.0 (C), 137.0 (C), 128.6 (2 CH), 128.1 (2 CH), 127.5 (2 CH), 127.1 (2 CH), 125.7 (CH), 125.6 (CH), 124.6 (C), 120.2 (C), 118.9 (CH), 109.4 (CH), 107.3 (C), 79.1 (C), 54.2 (CH), 46.0 (CH_2), 43.4 (CH), 43.2 (CH_2), 39.5 (CH_2), 27.9 (3 CH_3), 17.7 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{29}\text{H}_{32}\text{N}_2\text{O}_2+\text{H}]^+$: 441.2537, found: 441.2532.

HPLC Chiralcel OD-3, Hexane/EtOH 80/20, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 8.22$ min, $\tau_{\text{minor}} = 6.52$ min.

$[\alpha]_{\text{D}}^{20} = -20$ (c 0.27, CHCl_3).

m.p. = 166-167 $^\circ\text{C}$.

trans-(10S,11aS) diastereomer 89:

TLC (PE/EtOAc 6:1) R_f 0.26 (UV, vanillin).

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.32 – 7.22 (m, 3H), 7.14 – 7.07 (m, 2H), 7.00 (t, $J = 7.3$ Hz, 1H), 6.94 – 6.88 (m, 2H), 6.84 – 6.77 (m, 2H), 6.59 (d, $J = 2.8$ Hz, 1H), 6.30 (d, $J = 2.8$ Hz, 1H), 4.66 (dd, $J = 11.5, 2.0$ Hz, 1H), 4.15 – 4.00 (m, 3H), 3.96 (d, $J = 5.5$ Hz, 1H), 3.52 – 3.39 (m, 1H), 2.56 (s, 3H), 2.14 (dt, $J = 13.2, 2.0$ Hz, 1H), 1.73 (ddd, $J = 13.2, 11.6, 5.9$ Hz, 1H), 1.14 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 168.9 (C), 153.0 (C), 147.2 (C), 136.1 (C), 128.4 (2 CH), 128.3 (2 CH), 128.1 (2 CH), 127.1 (2 CH), 125.8 (CH), 125.0 (CH), 124.6 (C), 119.8 (C), 119.0 (CH), 109.3 (CH), 102.4 (C), 78.6 (C), 49.8 (CH), 46.2 (CH_2), 43.3 (CH_2), 39.9 (CH), 34.3 (CH_2), 28.1 (3 CH_3), 17.6 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{29}\text{H}_{32}\text{N}_2\text{O}_2+\text{H}]^+$: 441.2537, found: 441.2534.

HPLC Chiralcel OD-3, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 6.90$ min, $\tau_{\text{minor}} = 6.02$ min.

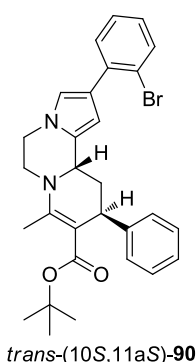
$[\alpha]_{\text{D}}^{20} = +20.4$ (c 0.23, CHCl_3).

m.p. = 167-168 °C.

(10S,11aR)-tert-butyl 2-(2-bromophenyl)-8-methyl-10-phenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 90

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μ L, 0.300 mmol, 1.5 equiv), 2-(3-(2-bromophenyl)-1*H*-pyrrol-1-yl)ethanamine **82** (52.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc 4:1 then PE/EtOAc/AcOH 6:1: 0.025) afforded *trans*-(10S,11aR)-**90** as a pale yellow powder (20.9 mg, 0.036 mmol, 18% yield, 92% ee)

***trans*-(10S,11aS) diastereomer 90:**



TLC (PE/EtOAc 4:1) *R*_f 0.34 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.41 (d, *J* = 7.8 Hz, 1H), 7.19 – 7.10 (m, 4H), 7.03 – 6.95 (m, 1H), 6.92 – 6.87 (m, 3H), 6.59 (d, *J* = 2.7 Hz, 1H), 6.19 (d, *J* = 2.7 Hz, 1H), 4.37 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.13 – 3.98 (m, 3H), 3.86 – 3.80 (m, 1H), 3.42 (ddd, *J* = 14.2, 11.4, 3.6 Hz, 1H), 2.51 (s, 3H), 1.77 – 1.63 (m, 2H), 1.13 (s, 9H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) 168.9 (C), 152.7 (C), 147.1 (C), 137.7 (C), 132.7 (CH), 131.4 (CH), 127.9 (2 CH), 127.8 (CH), 127.7 (2 CH), 127.1 (CH), 125.8 (C), 125.5 (CH), 124.2 (C), 119.0 (C), 117.9 (CH), 110.7 (CH), 102.5 (C), 78.6 (C), 50.2 (CH), 45.7 (CH₂), 43.7 (CH₂), 39.1 (CH), 34.8 (CH₂), 28.1 (3 CH₃), 17.4 (CH₃).

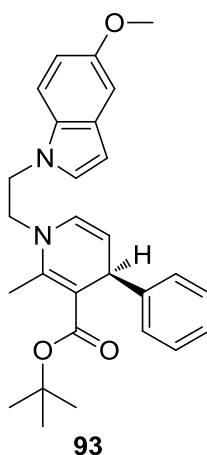
HRMS (ESI) calc'd for [C₂₉H₃₁N₂O₂Br+H]⁺: 519.1642, found: 519.1639.

HPLC Lux-Cellulose-2, Heptane/ethanol 95:5, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 8.94 min, τ_{minor} = 7.07 min.

$[\alpha]_{\text{D}}^{20}$ = +23.2 (c 0.19, CHCl₃).

Sequential reactions**(S)-tert-butyl 1-(2-(5-methoxy-1H-indol-1-yl)ethyl)-2-methyl-4-phenyl-1,4-dihydropyridine-3-carboxylate 93****and****(2S,13bS)-tert-butyl 11-methoxy-4-methyl-2-phenyl-2,6,7,13b-tetrahydro-1H-pyrido[2',1':3,4]pyrazino [1,2-a]indole-3-carboxylate 94**

A reaction tube was charged with (S)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **VII** (12.0 mg, 0.020 mmol, 0.1 equiv), dry α,α,α -trifluorotoluene (2.5 mL), flushed with argon and placed at 0 °C. *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv) and cinnamaldehyde **52** (39.7 mg, 37.8 μ L, 0.300 mmol, 1.5 equiv) were then added. After full conversion of *tert*-butyl acetoacetate **63** as monitored by TLC, followed by the addition of 2-(5-methoxy-1H-indol-1-yl)ethanamine **85** (38.0 mg, 0.200 mmol, 1 equiv), the mixture was stirred at 0 °C for another 24 h. After reaction, the solution was filtered through a short pad of silica gel, which was thoroughly washed with EtOAc. The solvent was evaporated by reduced pressure to obtain the crude compound, which was analyzed by ^1H NMR, which was identified as the dihydropyridine **93**. Purification by flash column chromatography (PE/EtOAc 6:1) on Aluminiumoxide 90 neutral provided the pure (S)-dihydropyridine **93** as pale yellow solid (26.3 mg, 0.060 mmol, 30% yield, 91% *ee*). Alternatively, purification by flash column chromatography (PE/EtOAc 4:1 and then PE/EtOAc/AcOH 4:1:0.025) on silica gel provided the pure *trans*-(2S,13bS)-indolopiperazine **94** as pale yellow solid (28.4 mg, 0.064 mmol, 32% yield, 85% *ee*).



TLC (PE/EtOAc 6:1) R_f 0.42 (UV, vanillin).

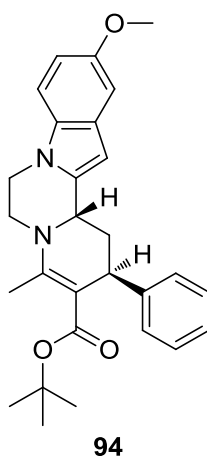
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.31 – 7.26 (m, 1H), 7.23 – 7.19 (m, 3H), 7.18 – 7.18 – 7.12 (m, 1H), 7.09 (d, $J = 2.3$ Hz, 1H), 6.98 (d, $J = 3.1$ Hz, 1H), 6.89 (dd, $J = 8.8, 2.3$ Hz, 1H), 6.43 (d, $J = 2.6$ Hz, 1H), 5.61 (d, $J = 7.8$ Hz, 1H), 4.83 (dd, $J = 7.8, 5.0$ Hz, 1H), 4.55 (d, $J =$

5.0 Hz, 1H), 4.35 – 4.14 (m, 2H), 3.85 (s, 3H), 3.84 – 3.73 (m, 2H), 3.60 (dt, $J = 15.0, 6.2$ Hz, 1H), 2.19 (s, 3H), 1.21 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 168.5 (C), 154.3 (C), 149.1 (C), 146.4 (C), 131.1 (C), 129.4 (C), 128.7 (CH), 128.3 (2 CH), 127.8 (CH), 127.6 (2 CH), 126.1 (CH), 112.4 (CH), 109.6 (CH), 108.5 (CH), 103.0 (CH), 102.7 (C), 101.8 (CH), 79.2 (C), 56.0 (CH_3), 49.7 (CH_2), 46.6 (CH_2), 41.1 (CH), 28.2 (3 CH_3), 15.5 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_3+\text{H}]^+$: 445.2486, found: 445.2487.

HPLC Chiralpak AZ-H, Heptane/ethanol 90:10, 25 °C, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 12.11$ min, $\tau_{\text{minor}} = 14.10$ min.



TLC (PE/EtOAc 4:1) R_f 0.53 (UV, vanillin).

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.34 – 7.27 (m, 2H), 7.27 – 7.17 (m, 3H), 7.15 (d, $J = 8.8$ Hz, 1H), 7.00 (d, $J = 2.3$ Hz, 1H), 6.82 (dd, $J = 8.8, 2.3$ Hz, 1H), 6.09 (s, 1H), 4.38 – 4.23 (m, 2H), 4.21 – 4.08 (m, 2H), 4.02 (td, $J = 11.3, 4.2$ Hz, 1H), 3.83 (s, 3H), 3.41 (ddd, $J = 13.9, 11.5, 3.7$ Hz, 1H), 2.55 (s, 3H), 2.40 (dt, $J = 13.3, 3.3$ Hz, 1H), 2.25 (ddd, $J = 13.2, 11.3, 5.7$ Hz, 1H), 1.18 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 168.5 (C), 154.6 (C), 152.5 (C), 147.5 (C), 137.9 (C), 131.3 (C), 128.7 (C), 128.3 (C), 128.3 (2 CH), 128.1 (2 CH), 126.0 (CH), 111.2 (CH), 109.3 (CH), 102.5 (CH), 96.1 (CH), 78.8 (C), 56.1 (CH_3), 50.2 (CH), 44.3 (CH_2), 42.6 (CH_2), 38.9 (CH), 36.1 (CH_2), 28.2 (3 CH_3), 17.5 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_3+\text{H}]^+$: 445.2486, found: 445.2485.

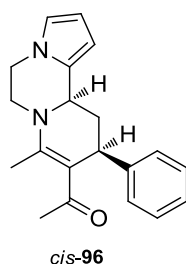
HPLC Chiralpak AZ-H, Heptane/ethanol 90:10, 25 °C, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 11.47$ min, $\tau_{\text{minor}} = 9.83$ min.

General procedure (reactions were carried out on a 0.2 mmol scale):

A tube was charged with (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **VI** (6.6 mg, 0.020 mmol, 0.1 equiv), benzoic acid (4.9 mg, 0.040 mmol, 0.2 equiv), dichloromethane (2.5 mL) flushed with argon and placed at $-10\text{ }^{\circ}\text{C}$. Diketone **95** (0.200 mmol, 1 equiv) was then added followed by freshly distilled α,β -unsaturated aldehyde (0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (0.200 mmol, 1 equiv). After 46 h, the solution was directly purified by flash column chromatography on silica gel to provide the product as two diastereoisomers.

1-(8-methyl-10-phenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazin-9-yl)ethanone 96

Prepared according to the general procedure using acetylacetone **95** (20.0 mg, 20.5 μL , 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μL , 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL , 0.200 mmol, 1 equiv), (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **VI** (6.6 mg, 0.020 mmol, 0.1 equiv) and benzoic acid (4.9 mg, 0.040 mmol, 0.2 equiv). Purification by flash chromatography (PE/Et₂O 1:2) afforded *cis*-(10*S*,11*aR*)-**96** as a pale solid (27.5 mg, 0.090 mmol, 45% yield, 94% *ee*) and *trans*-(10*S*,11*aS*)-**96** as a pale yellow oil (14.0 mg, 0.046 mmol, 23% yield, 90% *ee*).

***cis*-(10*S*,11*aR*) diastereoisomer 96:**

TLC (PE/Et₂O 1:2) *R_f* 0.36 (UV, vanillin).

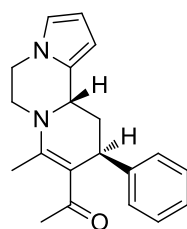
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.24 – 7.08 (m, 5H), 6.51 (d, *J* = 1.8 Hz, 1H), 6.05 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.73 (dt, *J* = 3.4, 1.4 Hz, 1H), 4.54 (dd, *J* = 9.7, 3.0 Hz, 1H), 4.12 – 3.99 (m, 4H), 3.37 (ddd, *J* = 10.3, 7.8, 4.3 Hz, 1H), 2.62 (ddd, *J* = 13.6, 6.4, 3.3 Hz, 1H), 2.45 (d, *J* = 1.0 Hz, 3H), 2.10 – 2.05 (m, 1H), 1.80 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 200.2 (C), 151.0 (C), 146.2 (C), 129.1 (C), 128.7 (2 CH), 127.2 (2 CH), 126.2 (CH), 118.6 (CH), 112.9 (C), 108.7 (CH), 103.4 (CH), 53.6 (CH), 45.2 (CH₂), 44.0 (CH₂), 41.8 (CH), 40.7 (CH₂), 30.6 (CH₃), 17.1 (CH₃).

HRMS (ESI) calc'd for [C₂₀H₂₂N₂O+H]⁺: 307.1805, found: 307.1802.

HPLC Lux-Amylose-2, Hexane/ethanol 80:20, 25 $^{\circ}\text{C}$, 1.0 mL/min, λ = 254 nm, τ_{major} = 11.43 min, τ_{minor} = 9.02 min.

$[\alpha]_{\text{D}}^{20}$ = -4.7 (c 0.05, CHCl₃)

trans-(10S,11aS) diastereoisomer 96:*trans*-96

TLC (PE/Et₂O 1:2) R_f 0.33 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.35 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 6.55 (d, *J* = 1.8 Hz, 1H), 6.11 (t, *J* = 3.0 Hz, 1H), 5.80 (dt, *J* = 3.5, 1.2 Hz, 1H), 4.19 – 4.07 (m, 3H), 4.08 – 3.95 (m, 2H), 3.42 (ddd, *J* = 13.7, 9.5, 4.4 Hz, 1H), 2.61 (s, 3H), 2.43 (ddd, *J* = 13.0, 3.5, 2.8 Hz, 1H), 2.18 (dd, *J* = 12.1, 5.0 Hz, 1H), 2.00 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 198.1 (C), 154.3 (C), 146.0 (C), 129.5 (C), 128.7 (2 CH), 128.1 (2 CH), 126.6 (CH), 118.9 (CH), 108.6 (CH), 107.8 (C), 103.0 (CH), 49.5 (CH), 45.0 (CH₂), 44.5 (CH₂), 39.8 (CH), 36.3 (CH₂), 29.6 (CH₃), 18.0 (CH₃).

HRMS (ESI) calc'd for [C₂₀H₂₂N₂O+H]⁺: 307.1805, found: 307.1801.

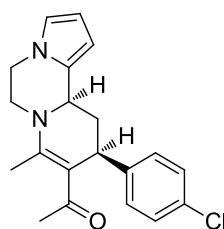
HPLC Lux-Amylose-2, Hexane/ethanol 90:10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 22,68 min, τ_{minor} = 18,58 min.

[α]_D²⁰ = -9.9 (c 0.03, CHCl₃)

1-(10-(4-chlorophenyl)-8-methyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]piazin-9-yl)ethanone 97

Prepared according to the general procedure using acetylacetone **95** (20.0 mg, 20.5 μL , 0.200 mmol, 1 equiv), 4-chlorocinnamaldehyde (50.0 mg, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL , 0.200 mmol, 1 equiv.), (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **VI** (6.6 mg, 0.020 mmol, 0.1 equiv.) and benzoic acid (4.9 mg, 0.040 mmol, 0.2 equiv). Purification by flash chromatography (PE/EtOAc 1:2) afforded *cis*-(10*S*,11*aR*)-**97** as a pale solid (25.8 mg, 0.076 mmol, 38% yield, 91% *ee*) and *trans*-(10*S*,11*aS*)-**97** as a pale yellow oil (19.8 mg, 0.058 mmol, 29% yield, 91% *ee*).

***cis*-(10*S*,11*aR*) diastereoisomer 97:**



cis-**97**

TLC(PE/EtOAc 1:2) R_f 0.36(UV, vanillin).

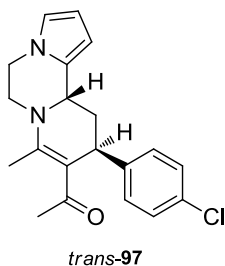
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.16 (d, $J = 8.4$ Hz, 2H), 7.03 (d, $J = 8.4$ Hz, 2H), 6.53 – 6.46 (m, 1H), 6.03 (dd, $J = 3.4, 2.8$ Hz, 1H), 5.65 (dt, $J = 3.4, 1.3$ Hz, 1H), 4.55 (dd, $J = 9.0, 3.3$ Hz, 1H), 4.13 – 4.06 (m, 2H), 4.03 – 3.95 (m, 2H), 3.43 – 3.31 (m, 1H), 2.58 (ddd, $J = 13.6, 6.4, 3.6$ Hz, 1H), 2.46 (d, $J = 0.9$ Hz, 3H), 2.13 – 2.03 (m, 1H), 1.82 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 199.6 (C), 151.6 (C), 144.7 (C), 131.8 (C), 128.76 (2 CH), 128.72 (2 C), 128.5 (2 CH), 118.6 (CH), 112.1 (C), 108.7 (CH), 103.4 (CH), 53.4 (CH), 45.1 (CH_2), 44.2 (CH_2), 41.0 (CH), 39.9 (CH_2), 30.5 (CH_3), 17.2 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{20}\text{H}_{21}\text{N}_2\text{OCl}+\text{H}]^+$: 341.1415, found: 341.1414.

HPLC Chiralpak AD-H, Hexane/ethanol 80:20, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 8.34$ min, $\tau_{\text{minor}} = 9.90$ min.

$[\alpha]_{\text{D}}^{20} = -3.3$ (c 0.09, CHCl_3)

trans-(10S,11aS) diastereoisomer 97:

TLC (PE/EtOAc 1:2) *R*_f 0.33(UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.36 – 7.24 (m, 2H), 7.17 – 7.13 (m, 2H), 6.61 – 6.55 (m, 1H), 6.14 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.85 – 5.79 (dt, *J* = 3.4, 1.4 Hz, 1H), 4.18 (dt, *J* = 13.5, 3.8 Hz, 1H), 4.14 – 3.98 (m, 4H), 3.44 (ddd, *J* = 13.7, 9.1, 4.7 Hz, 1H), 2.61 (s, 3H), 2.44 – 2.38 (m, 1H), 2.18 (ddd, *J* = 13.1, 12.0, 5.0 Hz, 1H), 2.01 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 197.7 (C), 154.5 (C), 144.5 (C), 132.4 (C), 129.5 (2 CH), 129.2 (C), 128.9 (2 CH), 119.0 (CH), 108.6 (CH), 107.5 (C), 103.1 (CH), 49.4 (CH), 44.9 (CH₂), 44.5 (CH₂), 39.3 (CH), 36.2 (CH₂), 29.6 (CH₃), 18.0 (CH₃).

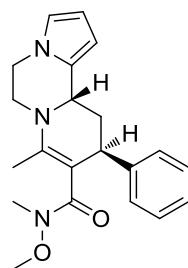
HRMS (ESI) calc'd for [C₂₀H₂₁N₂OCl+H]⁺: 341.1415, found: 341.1411.

HPLC Lux-Amylose-2, Hexane/ethanol 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 13.32 min, τ_{minor} = 10.93 min.

[α]_D²⁰ = +2.5 (c 0.07, CHCl₃)

(10*S*,11*aS*)-*N*-methoxy-*N*,8-dimethyl-10-phenyl-6,10,11,11*a*-tetrahydro-5*H*-pyrido[1,2-*a*]pyrrolo[2,1-*c*]pyrazine-9-carboxamide 102

Prepared according to the general procedure using *N*-methoxy-*N*-methyl-3-oxobutanamide **100** (29.0 mg, 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μ L, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). Purification by flash chromatography (CH₂Cl₂/MeOH 50:1 then CH₂Cl₂/MeOH/AcOH 50:1:0.025) afforded *trans*-(10*S*,11*aS*)-**102** as a yellow oil (19.7 mg, 0.056 mmol, 28% yield, 88% *ee*).



trans-**102**

TLC (CH₂Cl₂/MeOH 50:1) *R*_f 0.36 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.24 – 7.09 (m, 5H), 6.46 – 6.42 (m, 1H), 6.02 (t, *J* = 3.0 Hz, 1H), 5.72 (d, *J* = 2.9 Hz, 1H), 4.12 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.93 – 3.79 (m, 4H), 3.29 (s, 3H), 3.25 – 3.14 (m, 1H), 2.95 (s, 3H), 2.17 (dt, *J* = 18.7, 9.1, 5.0 Hz, 2H), 1.95 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ (ppm) 171.3 (C), 145.1 (C), 141.7 (C), 130.3 (C), 128.5 (2 CH), 128.3 (2 CH), 126.4 (CH), 118.9 (CH), 108.4 (CH), 106.4 (C), 102.4 (CH), 60.8 (CH₃), 50.7 (CH), 44.9 (CH₂), 44.7 (CH₂), 38.6 (CH), 35.2 (CH₂), 34.0 (CH₃), 17.3 (CH₃).

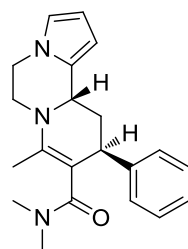
HRMS (ESI) calc'd for [C₂₁H₂₅N₃O₂+H]⁺: 352.2020, found: 352.2021.

HPLC Chiralpak AD-H, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 10.21 min, τ_{minor} = 7.59 min.

$[\alpha]_{\text{D}}^{20}$ = – 31.2 (c 0.02, CHCl₃).

(10S,11aS)-N,N,8-trimethyl-10-phenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxamide 103

Prepared according to the general procedure using *N,N*-dimethyl-3-oxobutanamide **101** (25.8 mg, 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μ L, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μ L, 0.200 mmol, 1 equiv). Purification by flash chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 50:1 then $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{AcOH}$ 50:1:0.025) afforded *trans*-(10S,11aS)-**103** as a yellow oil (16.8 mg, 0.050 mmol, 25% yield, 92% *ee*).



TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 50:1) R_f 0.5 (UV, vanillin).

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.29 – 7.16 (m, 4H), 7.12 – 7.08 (m, 1H), 6.49 – 6.44 (m, 1H), 6.05 (t, $J = 3.0$ Hz, 1H), 5.74 (d, $J = 2.7$ Hz, 1H), 4.16 (d, $J = 7.3$ Hz, 1H), 3.92 (dt, $J = 11.4, 8.2, 3.5$ Hz, 2H), 3.83 – 3.68 (m, 2H), 3.26 – 3.14 (m, 1H), 2.78 (s, 6H), 2.27 – 2.12 (m, 2H), 1.87 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 172.7 (C), 145.1 (C), 139.3 (C), 130.3 (C), 128.5 (2 CH), 128.2 (2 CH), 126.4 (CH), 118.9 (CH), 108.4 (CH), 107.2 (C), 102.4 (CH), 50.5 (CH), 45.2 (CH_2), 44.5 (CH_2), 39.5 (CH), 39.5 (2 CH_3), 35.3 (CH_2), 17.2 (CH_3).

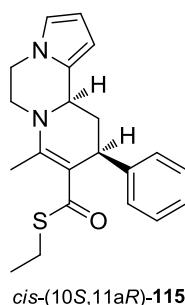
HRMS (ESI) calc'd for $[\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}+\text{H}]^+$: 336.2070, found: 336.2071.

HPLC Lux-Cellulose-4, Hexane/ethanol 90:10, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 26.36$ min, $\tau_{\text{minor}} = 24.29$ min.

$[\alpha]_{\text{D}}^{20} = -24.6$ (c 0.03, CHCl_3).

Ethyl 8-methyl-10-phenyl-6,10,11,11a-tetrahydro-5H-pyrido[1,2-a] pyrrolo [2,1-c] pyrazine-9-carbothioate 115

Prepared according to the general procedure using *S*-ethyl acetothioacetate **114** (29.2 mg, 26.8 μL 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μL, 0.300 mmol, 1.5 equiv), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 4:1 then PE/Et₂O/AcOH 4:1: 0.025) afforded *cis*-(10*S*,11*aR*)-**115** as a yellow oil (15.0 mg, 0.042 mmol, 21% yield, 49% *ee*) and *trans*-(10*S*,11*aS*)-**115** as a yellow oil (23.2 mg, 0.058 mmol, 29% yield, 54% *ee*).

***cis*-(10*S*,11*aR*)-diastereomer 115:**

TLC (PE/EtOAc 4:1) *R_f* 0.29 (UV, vanillin).

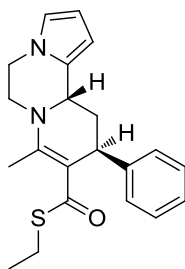
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.19 – 7.13 (m, 2H), 7.13 – 7.04 (m, 3H), 6.51 – 6.42 (m, 1H), 5.99 (dd, *J* = 3.5, 2.8 Hz, 1H), 5.63 (dt, *J* = 3.5, 1.4 Hz, 1H), 4.55 (dd, *J* = 8.6, 3.6 Hz, 1H), 4.26 – 4.18 (m, 1H), 4.07 (dt, *J* = 13.0, 3.4 Hz, 1H), 4.03 – 3.97 (m, 2H), 3.39 (ddd, *J* = 13.5, 8.9, 5.2 Hz, 1H), 2.74 – 2.57 (m, 3H), 2.42 (d, *J* = 1.1 Hz, 3H), 2.19 (dt, *J* = 13.6, 8.8 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 192.4 (C), 149.4 (C), 145.5 (C), 128.9 (C), 128.2 (2 CH), 127.5 (2 CH), 125.9 (CH), 118.5 (CH), 111.4 (C), 108.7 (CH), 103.4 (CH), 53.5 (CH), 45.2 (CH₂), 44.4 (CH₂), 40.9 (CH), 39.5 (CH₂), 23.5 (CH₂), 17.4 (CH₃), 15.0 (CH₃).

HRMS (ESI) calc'd for [C₂₁H₂₄N₂OS+H]⁺: 353.1682, found: 353.1681.

HPLC Lux-Amylose-2, Hexane/ethanol 80:20, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 7.15 min, τ_{minor} = 6.20 min.

[α]_D²⁰ = – 11.6 (c 0.02, CHCl₃).

trans-(10S,11aS)-diastereomer 115:*trans*-(10S,11aS)-115

TLC (PE/EtOAc 4:1) R_f 0.2 (UV, vanillin).

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.34 – 7.29 (m, 2H), 7.24 – 7.19 (m, 3H), 6.55 (tt, $J = 1.7, 0.6$ Hz, 1H), 6.12 (dd, $J = 3.6, 2.7$ Hz, 1H), 5.80 (dt, $J = 3.6, 1.4$ Hz, 1H), 4.37 (dd, $J = 4.9, 2.7$ Hz, 1H), 4.21 – 4.10 (m, 2H), 4.07 – 3.99 (m, 2H), 3.43 (ddd, $J = 13.8, 9.6, 4.4$ Hz, 1H), 2.86 – 2.77 (m, 1H), 2.67 (dt, $J = 13.3, 7.4$ Hz, 1H), 2.60 (s, 3H), 2.46 (ddd, $J = 13.1, 4.0, 2.7$ Hz, 1H), 2.17 (ddd, $J = 13.1, 12.0, 4.8$ Hz, 1H), 1.15 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 190.2 (C), 152.5 (C), 145.6 (C), 129.4 (C), 128.5 (2 CH), 127.9 (2 CH), 126.4 (CH), 118.9 (CH), 108.6 (CH), 106.2 (C), 103.0 (CH), 49.6 (CH), 44.9 (CH_2), 44.7 (CH_2), 38.6 (CH), 36.1 (CH_2), 23.5 (CH_2), 17.9 (CH_3), 15.1 (CH_3).

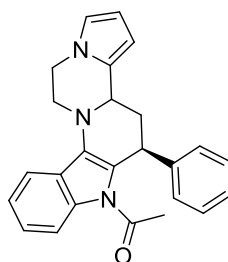
HRMS (ESI) calc'd for $[\text{C}_{21}\text{H}_{24}\text{N}_2\text{OS}+\text{H}]^+$: 353.1682, found: 353.1685.

HPLC Chiralpak AD-H, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 12.07$ min, $\tau_{\text{minor}} = 8.08$ min.

$[\alpha]_{\text{D}}^{20} = -28.9$ (c 0.02, CHCl_3).

1-((5S)-5-phenyl-4,5,12,13-tetrahydropyrrolo[2'',1'':3',4']pyrazino[1',2':1,6]pyrido[3,2-b]indol-6(3bH)-yl)ethanone 128

Prepared according to the general procedure at 0 °C using 1-acetylmindolin-3-one **120** (35.0 mg, 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μL, 0.300 mmol, 1.5 equiv.), *N*-(2-aminoethyl)pyrrole **32** (22.0 mg, 21.6 μL, 0.200 mmol, 1 equiv), (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (6.6 mg, 0.020 mmol, 0.1 equiv). Purification by flash chromatography (PE/Et₂O 4:1) afforded **128** as a white solid, as a ~1.5:1 mixture of two diastereoisomers (52.8 mg, 0.136 mmol, 68% yield, 88% *ee* and 87% *ee*).



128

TLC (PE/Et₂O 4:1) *R_f* 0.15 (UV, vanillin).

HRMS (ESI) calc'd for [C₂₅H₂₃N₃O+H]⁺: 382.1914, found: 382.1913.

diastereomer (major) 128:

¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.04 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.41 – 7.27 (m, 3H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.01 (d, *J* = 7.2 Hz, 2H), 6.62 – 6.57 (m, 1H), 6.17 (t, *J* = 3.1 Hz, 1H), 5.98 (d, *J* = 3.2 Hz, 1H), 4.70 (dd, *J* = 10.4, 7.5 Hz, 1H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.38 (d, *J* = 10.2 Hz, 1H), 4.19 – 4.07 (m, 1H), 3.79 (dt, *J* = 12.7, 3.9 Hz, 1H), 3.57 (ddd, *J* = 12.9, 9.7, 3.5 Hz, 1H), 2.50 – 2.42 (m, 1H), 2.36 (s, 3H), 2.04 – 1.91 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 169.6 (C), 144.7 (C), 136.1 (C), 134.1 (C), 129.3 (C), 128.9 (2 CH), 127.9 (2 CH), 127.0 (2 CH), 125.1 (CH), 124.6 (C), 123.0 (CH), 118.7 (CH), 118.4 (CH), 115.4 (CH), 108.4 (CH), 103.9 (CH), 54.6 (CH), 46.2 (CH₂), 45.7 (CH₂), 42.3 (CH), 39.0 (CH₂), 26.8 (CH₃).

HPLC Chiralpak AZ-H, Hexane/ethanol 50:50, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 14.25 min, τ_{minor} = 10.45 min.

diastereomer (minor) 128:

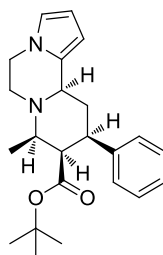
¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.12 (d, *J* = 8.2 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.40 – 7.27 (m, 3H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.11 (d, *J* = 7.3 Hz, 2H), 6.62 – 6.57 (m, 1H), 6.14 (t, *J* = 3.1 Hz, 1H), 5.77 (d, *J* = 3.3 Hz, 1H), 4.79 (d, *J* = 3.9 Hz, 1H), 4.35 – 4.26 (m, 2H), 4.19 – 4.07 (m, 1H), 3.71 (dt, *J* = 12.6, 4.2 Hz, 1H), 3.65 (dt, *J* = 7.6, 3.8 Hz, 1H), 2.56 (td, *J* = 13.4, 5.6 Hz, 1H), 2.48 (s, 3H), 2.12 (dt, *J* = 13.6, 2.0 Hz, 1H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 169.1 (C), 145.2 (C), 135.9 (C), 131.8 (C), 129.5 (C), 128.8 (2 CH), 126.7 (2 CH), 126.6 (2 CH), 125.0 (CH), 124.2 (C), 123.1 (CH), 118.8 (CH), 118.5 (CH), 116.3 (CH), 108.3 (CH), 103.6 (CH), 50.0 (CH), 46.9 (CH₂), 45.6 (CH₂), 40.1 (CH), 35.2 (CH₂), 27.2 (CH₃).

HPLC Chiralpak AZ-H, Hexane/ethanol 50:50, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 11.58 min, τ_{minor} = 7.09 min.

(8R,9R,10R,11aR)-tert-butyl 8-methyl-10-phenyl-6,8,9,10,11,11a-hexahydro-5H-pyrido[1,2-a]pyrrolo[2,1-c]pyrazine-9-carboxylate 133

To a flame-dried 25-mL round-bottom flask were placed PtO₂ (22.7 mg, 0.100 mmol, 0.5 equiv) and enaminoester *cis*-(10*S*,11*aR*)-**56** (72.9 mg, 0.200 mmol, 1 equiv) in MeOH (7 mL). The flask was filled with H₂ by balloon and the resulting suspension was stirred at room temperature for 16 h. TLC showed complete conversion of the starting material. The solution was filtered through Celite™ and concentrated in vacuum. Purification by flash chromatography on buffered silica gel (CH₂Cl₂) afforded **133** as a pale yellow solid (68.8 mg, 0.188 mmol, 94% yield, 92% ee).

**133**

TLC (CH₂Cl₂) R_f 0.50 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.33 – 7.27 (m, 4H), 7.25 – 7.17 (m, 1H), 6.58 – 6.48 (m, 1H), 6.13 (dd, *J* = 3.4, 2.8 Hz, 1H), 5.90 (dd, *J* = 3.1, 1.5 Hz, 1H), 4.16 (td, *J* = 11.8, 4.6 Hz, 1H), 3.95 (ddd, *J* = 11.6, 3.7, 1.5 Hz, 1H), 3.51 – 3.23 (m, 2H), 3.10 (ddd, *J* = 13.1, 4.9, 3.9 Hz, 1H), 2.87 – 2.75 (m, 2H), 2.68 (qd, *J* = 6.5, 4.0 Hz, 1H), 2.39 (td, *J* = 11.8, 4.0 Hz, 1H), 2.29 – 2.19 (m, 1H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.12 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 170.3 (C), 142.4 (C), 131.6 (C), 128.2 (2 CH), 127.8 (2 CH), 126.6 (CH), 118.3 (CH), 108.3 (CH), 102.0 (CH), 80.0 (C), 61.1 (CH), 59.3 (CH), 53.8 (CH), 47.5 (CH₂), 45.2 (CH₂), 43.2 (CH), 30.6 (CH₂), 28.0 (3 CH₃), 18.5 (CH₃).

HRMS (ESI) calc'd for [C₂₃H₃₀N₂O₂+H]⁺: 367.2380, found: 367.2379.

HPLC Chiralcel OD-3, Hexane/EtOH 90/10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 4.92 min, τ_{minor} = 7.58 min.

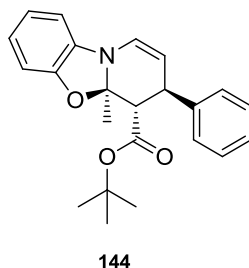
EXPERIMENTAL PART OF SYNTHESIS OF ENANTIOENRICHED POLYFUNCTIONALIZED HETEROCYCLES BY 3-CR OR 4-CR

General procedure (reactions were carried out on a 0.200-mmol scale):

A reaction tube was charged with (S)-(-)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **VI** (6.6 mg, 0.020 mmol, 0.1 equiv), dry α,α,α -trifluorotoluene (2.5 mL), flushed with argon and placed at 0 °C. *tert*-Butyl acetoacetate **63** (0.200 mmol, 1 equiv) was then added followed by freshly distilled cinnamaldehyde **52** (0.300 mmol, 1.5 equiv) and 2-aminophenol **142** (0.200 mmol, 1 equiv). After 2 days, the solution was directly purified by flash column chromatography on silica gel to provide the products **144**, **147**.

(3R,4S,4aR)-*tert*-butyl 4a-methyl-3-phenyl-4,4a-dihydro-3H-benzo[4,5]oxazolo[3,2-a]pyridine-4-carboxylate **144**

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μ L, 0.300 mmol, 1.5 equiv), 2-aminophenol **142** (21.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 10:1) afforded **144** as a pale yellow oil (18.2 mg, 0.050 mmol, 25% yield, 92% *ee*)



TLC (PE/Et₂O 10:1) R_f 0.45 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.26 – 7.16 (m, 5H), 6.82 – 6.77 (m, 1H), 6.73 – 6.66 (m, 2H), 6.63 – 6.59 (m, 1H), 6.54 (dd, *J* = 7.6, 2.1 Hz, 1H), 4.82 (dd, *J* = 7.6, 2.0 Hz, 1H), 3.81 (dt, *J* = 11.9, 2.0 Hz, 1H), 2.92 (d, *J* = 11.9 Hz, 1H), 1.70 (s, 3H), 1.21 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 170.3 (C), 149.8 (C), 141.7 (C), 134.6 (C), 128.5 (2 CH), 128.3 (2 CH), 127.3 (CH), 124.0 (CH), 121.4 (CH), 120.2 (CH), 108.9 (CH), 107.0 (CH), 106.9 (CH), 100.0 (C), 81.2 (C), 54.9 (CH), 43.4 (CH), 28.0 (3 CH₃), 20.8 (CH₃).

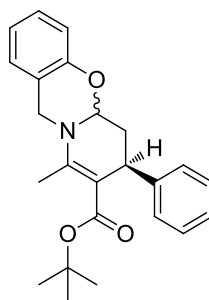
HRMS (ESI) calc'd for [C₂₃H₂₅NO₃+H]⁺: 364.1907, found: 364.1909.

HPLC Chiralpak IA, Hexane/isopropanol 95:5, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 4.99 min, τ_{minor} = 5.99 min.

$[\alpha]_{\text{D}}^{20}$ = - 11.3 (c 0.03, CHCl₃).

(7S)-tert-butyl 9-methyl-7-phenyl-5a,6,7,11-tetrahydrobenzo[e]pyrido[2,1-b][1,3]oxazine-8-carboxylate 147

Prepared according to the general procedure using *tert*-butyl acetoacetate **63** (31.6 mg, 32.9 μ L, 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μ L, 0.300 mmol, 1.5 equiv), 2-(aminomethyl)phenol **146** (24.6 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 10:1) afforded **147** as a 5:1 mixture pale yellow oil (57.3 mg, 0.152 mmol, 76% yield, 94% *ee*).



147

TLC (PE/Et₂O 10:1) R_f 0.51 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) *major diastereomer*: 7.34 – 7.15 (m, 6H), 7.10 – 7.03 (m, 1H), 6.95 (td, *J* = 7.5, 1.1 Hz, 1H), 6.88 (dd, *J* = 8.2, 0.8 Hz, 1H), 4.94 (dd, *J* = 6.9, 3.5 Hz, 1H), 4.78 (d, *J* = 16.1 Hz, 1H), 4.46 (d, *J* = 16.1 Hz, 1H), 4.11 (t, *J* = 6.4 Hz, 1H), 2.50 (d, *J* = 1.3 Hz, 3H), 2.42 (ddd, *J* = 13.4, 6.6, 6.1 Hz, 1H), 2.25 (ddd, *J* = 13.4, 7.6, 3.5 Hz, 1H), 1.15 (s, 9H); *minor diastereomer*: 7.34 – 7.15 (m, 6H), 7.10 – 7.03 (m, 1H), 6.92 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.52 (dd, *J* = 8.2, 0.8 Hz, 1H), 5.23 (dd, *J* = 6.9, 3.5 Hz, 1H), 4.76 (d, *J* = 16.1 Hz, 1H), 4.51 (d, *J* = 16.1 Hz, 1H), 4.11 (t, *J* = 6.4 Hz, 1H), 2.52 (d, *J* = 1.1 Hz, 3H), 2.47 (ddd, *J* = 13.4, 6.6, 6.1 Hz, 1H), 2.42 (ddd, *J* = 13.4, 7.6, 3.5 Hz, 1H), 1.17 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) *major diastereomer*: 168.2 (C), 154.1 (C), 149.5 (C), 146.2 (C), 128.4 (2 CH), 128.2 (CH), 127.6 (2 CH), 126.6 (CH), 126.1 (CH), 121.3 (CH), 120.6 (C), 117.0 (CH), 105.8 (C), 81.8 (CH), 79.2 (C), 47.0 (CH₂), 37.6 (CH), 35.9 (CH₂), 28.0 (3 CH₃), 16.4 (CH₃); *minor diastereomer*: 168.3 (C), 153.6 (C), 150.0 (C), 146.5 (C), 128.3 (CH), 128.0 (2 CH), 127.8 (2 CH), 126.4 (CH), 125.6 (CH), 120.7 (C), 120.5 (CH), 117.0 (CH), 105.3 (C), 83.0 (CH), 79.1 (C), 47.7 (CH₂), 37.6 (CH), 34.4 (CH₂), 28.0 (3 CH₃), 16.8 (CH₃).

HRMS (ESI) calc'd for [C₂₄H₂₇NO₃+H]⁺: 378.2064, found: 378.2060.

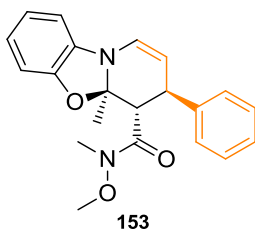
HPLC Chiralpak IF, Hexane/isopropanol 95:5, 25 °C, 1.0 mL/min, DAD + polarimeter, τ_{major} = 8.99 min, τ_{minor} = 13.64 min.

General procedure (reactions were carried out on a 0.200-mmol scale):

A reaction tube was charged with (*S*)-(-)- α,α -diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **VI** (13.0 mg, 0.040 mmol, 0.2 equiv), benzoic acid **154** (9.0 mg, 0.080 mmol, 0.4 equiv), CH₂Cl₂ (2.0 mL), flushed with argon and placed at +10 °C. Weinreb β -ketoamide **100** (29.0 mg, 0.200 mmol, 1 equiv) was then added followed by α,β -unsaturated aldehyde (0.300 mmol, 1.5 equiv) and 2-aminophenol (21.8 mg, 0.200 mmol, 1 equiv). After 60-70 h, the solution was quenched by adding a few drops of saturated NH₄Cl solution. The organic layer was pipetted out and the aqueous layer extracted with CH₂Cl₂ (3*2 mL). After drying of the combined organic layers on MgSO₄, filtration and concentration under vacuum, the crude reaction mixture was analyzed by ¹H NMR to measure the *dr*, which was always >20:1. Purification by flash column chromatography on silica gel provided the pure products **153**, **158-162**.

(3*R*,4*S*,4*aR*)-*N*-methoxy-*N*,4*a*-dimethyl-3-phenyl-4,4*a*-dihydro-3*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide **153**

Prepared according to the general procedure using Weinreb β -ketoamide **100** (29.0 mg, 0.200 mmol, 1 equiv), cinnamaldehyde **52** (39.7 mg, 37.8 μ L, 0.300 mmol, 1.5 equiv) and 2-aminophenol **142** (21.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/Et₂O 4:1) afforded **153** as a yellow solid (42.0 mg, 0.120 mmol, 60% yield, 94% *ee*).



TLC (PE/EtOAc 4:1) R_f 0.23 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.42 – 7.27 (m, 5H), 7.03 – 6.91 (m, 1H), 6.86 – 6.71 (m, 4H), 5.06 (dd, *J* = 7.6, 1.9 Hz, 1H), 4.13 (d, *J* = 11.5 Hz, 1H), 3.77 (d, *J* = 11.5 Hz, 1H), 3.38 (s, 3H), 3.13 (s, 3H), 1.88 (s, 3H).

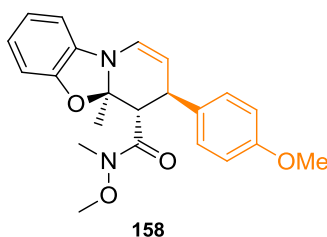
¹³C NMR (101 MHz, CDCl₃) δ (ppm) 171.3 (C), 149.5 (C), 142.0 (C), 134.7 (C), 128.5 (2 CH), 128.2 (2 CH), 127.2 (CH), 123.9 (CH), 121.5 (CH), 112.0 (CH), 108.5 (CH), 107.3 (CH), 106.7 (CH), 100.7 (C), 61.1 (CH₃), 48.8 (CH), 43.2 (CH₃), 32.1 (CH), 20.9 (CH₃).

HRMS (ESI) calc'd for [C₂₁H₂₂N₂O₃+H]⁺: 351.1703, found: 351.1704.

HPLC Chiralpak AZ-H, Hexane/Isopropanol 90:10, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 8.12 min, τ_{minor} = 7.35 min.

(3*R*,4*S*,4*aR*)-*N*-methoxy-3-(4-methoxyphenyl)-*N*,4*a*-dimethyl-4,4*a*-dihydro-3*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide 158

Prepared according to the general procedure using Weinreb β -ketoamide **100** (29.0 mg, 0.200 mmol, 1 equiv), 4-methoxycinnamaldehyde (48.7 mg, 0.300 mmol, 1.5 equiv) and 2-aminophenol **142** (21.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc 5:1) afforded **158** as a yellow solid (26.6 mg, 0.070 mmol, 35% yield, n.d. *ee*).



TLC (PE/EtOAc 4:1) R_f 0.26 (UV, vanillin).

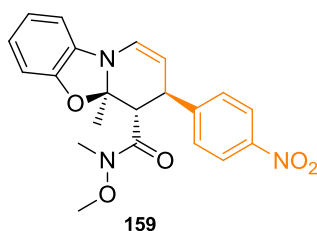
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.19 – 7.14 (m, 2H), 6.85 – 6.80 (m, 1H), 6.80 – 6.76 (m, 2H), 6.71 – 6.63 (m, 3H), 6.60 (dd, $J = 7.7, 2.0$ Hz, 1H), 4.90 (dd, $J = 7.6, 1.8$ Hz, 1H), 3.96 (d, $J = 11.5$ Hz, 1H), 3.76 (s, 3H), 3.62 (d, $J = 11.5$ Hz, 1H), 3.29 (s, 3H), 3.02 (s, 3H), 1.74 (s, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ (ppm) 171.4 (C), 158.7 (C), 149.5 (C), 134.7 (C), 133.9 (C), 129.2 (2 CH), 123.7 (CH), 121.4 (CH), 119.9 (CH), 113.8 (2 CH), 108.5 (CH), 107.7 (CH), 106.7 (CH), 100.7 (C), 61.1 (CH_3), 55.3 (CH_3), 48.9 (CH), 42.4 (CH_3), 32.1 (CH), 20.9 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4+\text{H}]^+$: 381.1809, found: 381.1805.

(3*R*,4*S*,4*aR*)-*N*-methoxy-*N*,4*a*-dimethyl-3-(4-nitrophenyl)-4,4*a*-dihydro-3*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide 159

Prepared according to the general procedure using Weinreb β -ketoamide **100** (29.0 mg, 0.200 mmol, 1 equiv), *trans*-4-nitrocinnamaldehyde (53.2 mg, 0.300 mmol, 1.5 equiv) and 2-aminophenol **142** (21.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc 4:1) afforded **159** as a yellow solid (46.5 mg, 0.118 mmol, 59% yield, 94% *ee*).



TLC (PE/EtOAc 5:1) R_f 0.24 (UV, vanillin).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 8.11 (d, $J = 8.8$ Hz, 2H), 7.44 (d, $J = 8.6$ Hz, 2H), 6.85 (td, $J = 7.5, 1.2$ Hz, 1H), 6.76 – 6.63 (m, 4H), 4.85 (dd, $J = 7.6, 1.7$ Hz, 1H), 4.14 (d, $J = 11.7$ Hz, 1H), 3.65 (d, $J = 11.7$ Hz, 1H), 3.39 (s, 3H), 3.00 (s, 3H), 1.74 (s, 3H).

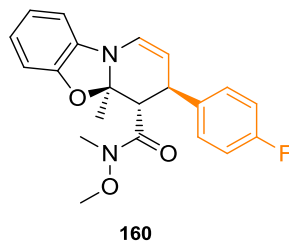
$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ (ppm) 170.6 (C), 150.1 (C), 149.3 (C), 147.2 (C), 134.1 (C), 129.2 (2 CH), 124.8 (CH), 123.7 (2 CH), 121.7 (CH), 120.4 (CH), 108.7 (CH), 107.0 (CH), 105.0 (CH), 100.2 (C), 61.2 (CH₃), 48.4 (CH), 43.0 (CH₃), 32.2 (CH), 20.9 (CH₃).

HRMS (ESI) calc'd for $[\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_5+\text{H}]^+$: 396.1554, found: 396.1552.

HPLC Chiralpak AD-H, Heptane/Isopropanol 80:20, 25 °C, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 12.00$ min, $\tau_{\text{minor}} = 7.42$ min.

(3R,4S,4aR)-3-(4-fluorophenyl)-N-methoxy-N,4a-dimethyl-4,4a-dihydro-3H-benzo[4,5]oxazolo[3,2-a]pyridine-4-carboxamide 160

Prepared according to the general procedure using Weinreb β -ketoamide **100** (29.0 mg, 0.200 mmol, 1 equiv), *trans*-4-fluorocinnamaldehyde (45.0 mg, 39.3 μ L, 0.300 mmol, 1.5 equiv) and 2-aminophenol **142** (21.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc 4:1) afforded **160** as a yellow solid (33.8 mg, 0.092 mmol, 46% yield, 91% *ee*).



TLC (PE/EtOAc 4:1) *R_f* 0.50 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.22 (dd, *J* = 8.3, 5.6 Hz, 2H), 6.93 (t, *J* = 8.7 Hz, 2H), 6.83 (td, *J* = 7.4, 1.6 Hz, 1H), 6.75 – 6.57 (m, 4H), 4.89 (dd, *J* = 7.6, 1.7 Hz, 1H), 3.99 (d, *J* = 11.6 Hz, 1H), 3.60 (d, *J* = 11.6 Hz, 1H), 3.32 (s, 3H), 3.01 (s, 3H), 1.74 (s, 3H).

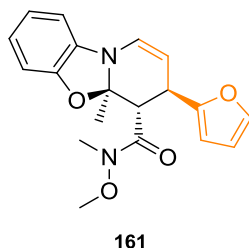
¹³C NMR (101 MHz, CDCl₃) δ (ppm) 171.2 (C), 162.0 (C, d, *J*_{C-F} = 245 Hz), 149.5 (C), 137.7 (C, d, *J*_{C-F} = 3.0 Hz), 134.5 (C), 129.7 (2 CH, d, *J*_{C-F} = 7.8 Hz), 124.0 (CH), 121.5 (CH), 120.1 (CH), 115.4 (CH), 115.2 (CH), 108.6 (CH), 106.8 (2 CH, d, *J*_{C-F} = 12.3 Hz), 100.6 (C), 61.2 (CH₃), 48.9 (CH), 42.5 (CH₃), 32.1 (CH), 21.0 (CH₃).

HRMS (ESI) calc'd for [C₂₁H₂₁N₂O₃F+H]⁺: 369.1609, found: 369.1606.

HPLC Chiralpak IF, Heptane/Isopropanol 95:5, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 7.65 min, τ_{minor} = 6.79 min.

**(3R,4S,4aR)-3-(furan-2-yl)-N-methoxy-N,4a-dimethyl-4,4a-dihydro-3H-benzo[4,5]oxazol-
o[3,2-a]pyridine-4-carboxamide 161**

Prepared according to the general procedure using Weinreb β -ketoamide **100** (29.0 mg, 0.200 mmol, 1 equiv), (*E*)-3-(furan-2-yl)acrylaldehyde (36.6 mg, 0.300 mmol, 1.5 equiv) and 2-aminophenol **142** (21.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc 10:1) afforded **161** as a yellow solid (~0.070 mmol, ~35% yield, n.d. *ee*).



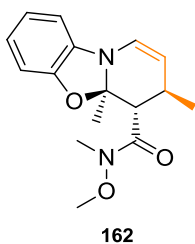
TLC (PE/EtOAc 4:1) R_f 0.26 (UV, vanillin).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 7.28 (d, $J = 1.0$ Hz, 1H), 6.85 – 6.77 (m, 1H), 6.69 (dd, $J = 8.5, 5.1$ Hz, 2H), 6.62 (d, $J = 7.7$ Hz, 1H), 6.58 (dd, $J = 7.7, 2.0$ Hz, 1H), 6.25 (dd, $J = 3.1, 1.9$ Hz, 1H), 6.11 (d, $J = 3.0$ Hz, 1H), 4.96 (dd, $J = 7.7, 1.8$ Hz, 1H), 4.15 (d, $J = 11.9$ Hz, 1H), 3.81 (d, $J = 11.7$ Hz, 1H), 3.49 (s, 3H), 3.16 (s, 3H), 1.70 (s, 3H).

HRMS (ESI) calc'd for $[\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4+\text{H}]^+$: 341.1496, found: 341.1494.

(3R,4S,4aR)-N-methoxy-N,3,4a-trimethyl-4,4a-dihydro-3H-benzo[4,5]oxazolo[3,2-a]pyridine-4-carboxamide 162

Prepared according to the general procedure using Weinreb β -ketoamide **100** (29.0 mg, 0.200 mmol, 1 equiv), crotonaldehyde (21.0 mg, 24.8 μ L, 0.300 mmol, 1.5 equiv) and 2-aminophenol (21.8 mg, 0.200 mmol, 1 equiv). Purification by flash chromatography (PE/EtOAc 4:1) afforded **162** as a yellow liquid (~0.060 mmol, ~30% yield, n.d. *ee*).



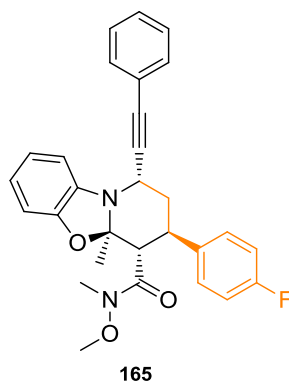
TLC (PE/EtOAc 4:1) R_f 0.28 (UV, vanillin).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 6.82 – 6.77 (m, 1H), 6.69 – 6.63 (m, 2H), 6.58 (d, $J = 7.7$ Hz, 1H), 6.43 (dd, $J = 7.6, 1.9$ Hz, 1H), 4.76 (dd, $J = 7.6, 1.6$ Hz, 1H), 3.65 (s, 3H), 3.27 (s, 3H), 3.26 – 3.20 (m, 1H), 2.88 – 2.73 (m, 1H), 1.63 (s, 3H), 0.99 (d, $J = 6.9$ Hz, 3H).

HRMS (ESI) calc'd for $[\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3+\text{H}]^+$: 289.1547, found: 289.1548.

(1*S*,3*R*,4*S*,4*aR*)-3-(4-fluorophenyl)-*N*-methoxy-*N*,4*a*-dimethyl-1-(phenylethynyl)-2,3,4,4*a*-tetrahydro-1*H*-benzo[4,5]oxazolo[3,2-*a*]pyridine-4-carboxamide 165

160 (73.6 mg, 0.200 mmol, 1 equiv, 91% *ee*), potassium alkynyltrifluoroborate **164** (49.9 mg, 0.240 mmol, 1.2 equiv), scandium (III) triflate (9.8 mg, 0.020 mmol, 10 mol%) were stirred in CH₂Cl₂ at 25 °C. After 4 h, the crude solution was filtrated through a short pad of Celite and the solvent concentrated under vacuum. Purification by flash chromatography (PE/EtOAc 8:1) afforded **165** as a yellow solid (quantitative yield, 91% *ee*).



TLC (PE/EtOAc 4:1) *R_f* 0.18 (UV, vanillin).

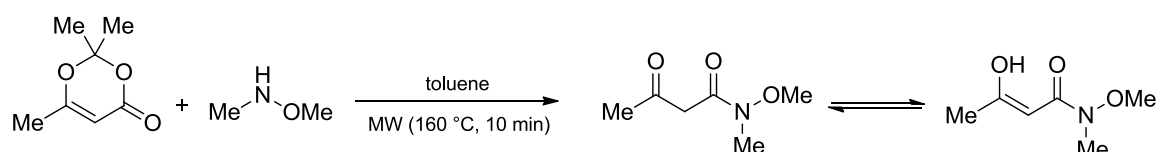
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.54 – 7.43 (m, 2H), 7.39 – 7.31 (m, 3H), 7.20 – 7.10 (m, 2H), 6.98 – 6.81 (m, 3H), 6.76 – 6.59 (m, 2H), 6.53 (d, *J* = 7.5 Hz, 1H), 5.00 (dd, *J* = 4.8, 2.1 Hz, 1H), 3.94 (d, *J* = 12.1 Hz, 1H), 3.76 (dd, *J* = 11.6, 4.1 Hz, 1H), 3.68 (s, 3H), 2.89 (s, 3H), 2.13 (s, 3H), 2.11 – 2.03 (m, 2H).

HPLC Chiralpak IA, Heptane/ethanol 80/20, 25 °C, 1.0 mL/min, DAD + polarimeter, τ_{major} = 4.76 min, τ_{minor} = 6.95 min.

IV. EXPERIMENTAL PART OF ORGANOCATALYTIC ENANTIO- AND DIASTEREOSELECTIVE CONJUGATE ADDITION OF β -KETOAMIDES TO NITROOLEFINS

IV.1 Preparation of β -Ketoamides

N-methoxy-*N*-methyl-3-oxobutanamide 100

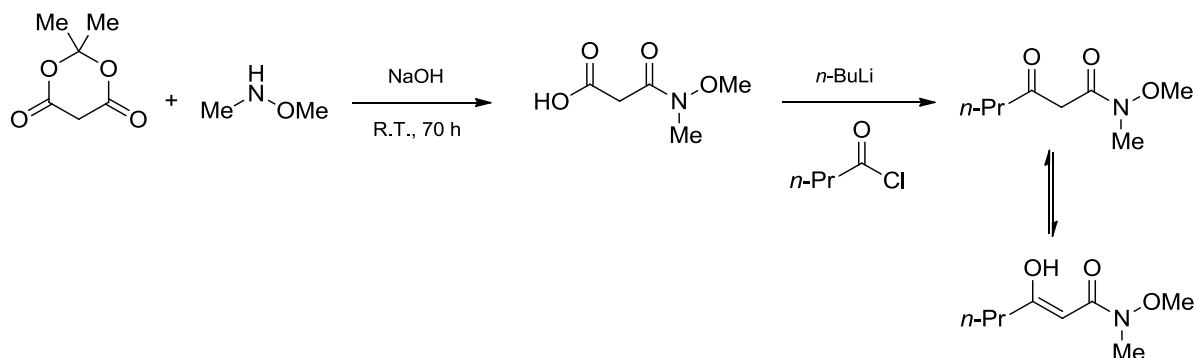


To a solution of triethylamine (1.67 mL, 12 mmol, 3 equiv) in toluene (8 mL) was added *N,O*-dimethylhydroxylamine (1.17 g, 12 mmol, 3 equiv). The resulting solution was stirred at room temperature for 12 h. After filtration and washing using toluene (8 mL), the obtained solution was mixed with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (531 μ L, 4 mmol, 1 equiv) in a closed glass container and subjected to microwave irradiation at 160 $^{\circ}$ C for 10 min. The resulting Weinreb β -ketoamide solution was directly purified by flash column chromatography on silica gel (PE/EtOAc 2:1) to provide the ketoamide as a mixture of tautomers as a pale yellow oil (372 mg, 2.56 mmol, 64% yield).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) *ketone/enol* 1:0.18; *ketone* 3.63 (s, 3H), 3.53 (s, 2H), 3.17 (s, 3H), 2.21 (s, 3H); *enol* 13.68 (s, 1H), 5.35 (s, 1H), 3.64 (s, 3H), 3.14 (s, 3H), 1.92 (s, 3H).

NMR data are in accordance with those reported in the literature.^[312]

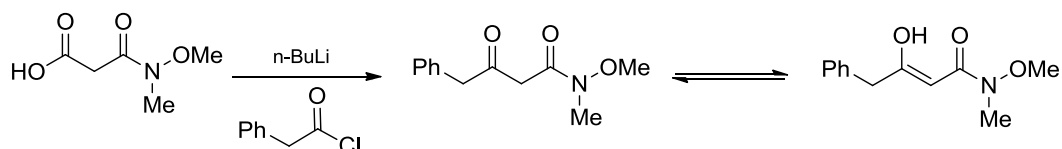
N-methoxy-*N*-methyl-3-oxohexanamide 167



N-methoxy-*N*-methyl-3-oxohexanamide was prepared according to the literature.^[274] Yield: 25% as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm) *ketone/enol 1:0.14*; *ketone* 3.67 (s, 3H), 3.56 (s, 2H), 3.21 (s, 3H), 2.51 (t, 3H, *J* = 7.2 Hz, 2H), 1.62–1.55 (m, 2H), 0.93 (t, 3H, *J* = 7.4 Hz); *enol* 13.70 (s, 1H), 5.39 (s, 1H), 3.69 (s, 3H), 3.19 (s, 3H), 2.15 (t, 2H, *J* = 7.6 Hz), 1.62–1.55 (m, 2H), 0.96 (t, 3H, *J* = 7.4 Hz).

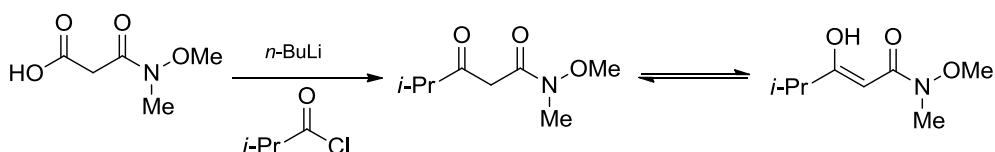
N-methoxy-*N*-methyl-3-oxo-4-phenylbutanamide 168



N-methoxy-*N*-methyl-3-oxo-4-phenylbutanamide was prepared according to the literature.^[274] Yield: 20% as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm) *ketone/enol 1:0.20*; *ketone* 7.38 – 7.17 (m, 5H), 3.81 (s, 2H), 3.57 (s, 2H), 3.52 (s, 3H), 3.17 (s, 3H); *enol* 13.78 (s, 1H), 7.38 – 7.17 (m, 5H), 5.38 (s, 1H), 3.63 (s, 3H), 3.47 (s, 2H), 3.17 (s, 3H).

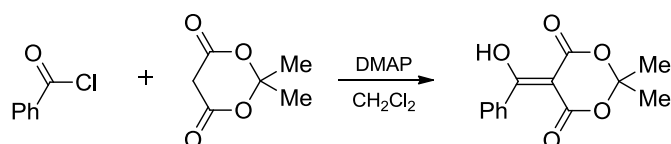
N-methoxy-*N*,4-dimethyl-3-oxopentanamide 169



N-methoxy-*N*,4-dimethyl-3-oxopentanamide was prepared according to the literature.^[274] Yield: 35% as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ (ppm) *ketone/enol 1:0.25*; *ketone* 3.65 (s, 3H), 3.62 (s, 2H), 3.20 (s, 3H), 2.71 (hept, *J* = 7.0 Hz, 1H), 1.13 – 1.03 (m, 6H); *enol* 13.76 (s, 1H), 5.37 (s, 1H), 3.68 (s, 3H), 3.18 (s, 3H), 2.40 (hept, *J* = 7.0 Hz, 1H), 1.13 – 1.03 (m, 6H).

5-(Hydroxyphenylmethylene)-2,2-dimethyl[1,3]dioxane-4,6-dione



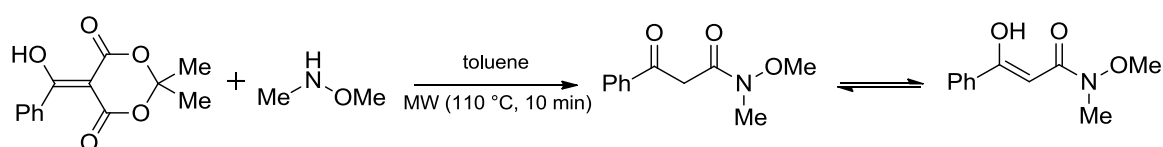
5-(Hydroxyphenylmethylene)-2,2-dimethyl[1,3]dioxane-4,6-dione was prepared according to the literature.^[275] A solution of benzoyl chloride (2.4 mL, 20.3 mmol, 1.13 equiv) in dry CH₂Cl₂ (20 mL) was added slowly during 1 h to a stirred solution of Meldrum's acid (2.6 g, 18.0 mmol, 1 equiv) and DMAP (4.31 g, 35 mmol, 1.94 equiv) in dry CH₂Cl₂ (40 mL) at –10 °C. The temperature was maintained for an additional 1 h, and then the resulting solution was allowed to attain room temperature and was then stirred for 3 h before being diluted with

CH₂Cl₂ and washed with aqueous KHSO₄ (2%), HCl (10%), water, and brine. The aqueous layers were extracted with CH₂Cl₂, and the combined organic layers were dried on Na₂SO₄, filtered, and concentrated under vacuum. The residue was recrystallized from acetone to give yield the pure product as a pale yellow solid (2.50 g, 10.1 mmol, 56%).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 15.47 (s, 1H), 7.70 – 7.66 (m, 2H), 7.63 – 7.57 (m, 1H), 7.51 – 7.43 (m, 2H), 1.84 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 189.4 (2 C), 133.5 (C), 132.8 (C), 129.6 (3 CH), 128.2 (2 CH), 105.2 (C), 91.1 (C), 26.94 (2 CH₃).

N-methoxy-*N*-methyl-3-oxo-3-phenylpropanamide 170



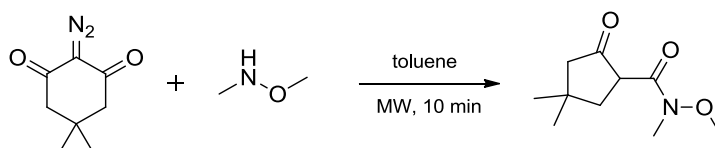
To a solution of triethylamine (242 μL, 1.80 mmol, 3 equiv) in toluene (3 mL) was added *N*,*O*-dimethylhydroxylamine (176 mg, 1.80 mmol, 3 equiv). The resulting solution was stirred at room temperature for 12 h. After filtration and washing using toluene (8 mL), the obtained solution was mixed with 5-(hydroxyphenylmethylene)-2,2-dimethyl[1,3]dioxane-4,6-dione (149 mg, 0.60 mmol, 1 equiv) in a closed glass container and subjected to microwave irradiation at 110 °C for 10 min. The resulting Weinreb β-ketoamide solution was directly purified by flash column chromatography on silica gel (PE/EtOAc 2:1) to provide a mixture of tautomers as a pale yellow oil (106 mg, 0.51 mmol, 85% yield).

¹H NMR (400 MHz, CDCl₃) δ (ppm) *ketone/enol* 1:0.55; *ketone* 7.97 (dd, *J* = 8.1, 0.9 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.38 (m, 2H), 4.13 (s, 2H), 3.66 (s, 3H), 3.24 (s, 3H); *enol* 14.25 (s, 1H), 7.83 – 7.79 (m, 2H), 7.51 – 7.38 (m, 3H), 6.08 (s, 1H), 3.76 (s, 3H), 3.27 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) *ketone* 193.6 (C), 171.6 (C), 136.5 (C), 133.8 (CH), 128.9 (2 CH), 128.6 (2 CH), 61.5 (CH₃), 44.6 (CH₂), 32.3 (CH₃); *enol* 172.9 (C), 168.6 (C), 134.6 (C), 131.0 (CH), 128.6 (2 CH), 126.2 (2 CH), 84.5 (CH), 61.6 (CH₃), 31.0 (CH₃).

HRMS (ESI) calc'd for [C₁₁H₁₃NO₃+H]⁺: 208.0968, found: 208.0967.

N-methoxy-*N*,4,4-trimethyl-2-oxocyclopentanecarboxamide 171

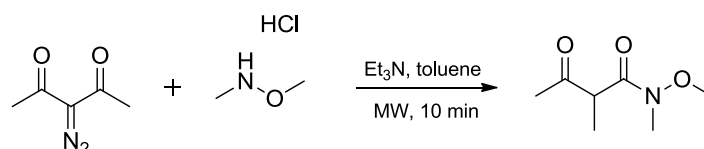


To a solution of triethylamine (1.67 mL, 12 mmol, 3 equiv) in toluene (8 mL) was added

N,O-dimethylhydroxyamine (1.17 g, 12 mmol, 3 equiv). The resulting solution was stirred at r.t. for 12 h. After filtration and washing use toluene (8 mL), obtained the solution, and then mixed with 2-diazo-5,5-dimethylcyclohexane-1,3-dione (664.7 mg, 4 mmol) in a closed glass container and subjected to microwave irradiation at 165 °C for 10 min. The resulting β -keto Weinreb amide solution was directly purified by flash column chromatography on silica gel (PE/EtOAc=2:1) to provide a pure product as a yellow oil (68% yield).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 3.99 – 3.80 (m, 1H), 3.73 (s, 3H), 3.25 – 3.13 (m, 3H), 2.30 – 2.08 (m, 3H), 2.00 – 1.91 (m, 1H), 1.20 (s, 3H), 1.02 (d, $J = 7.3$ Hz, 3H).

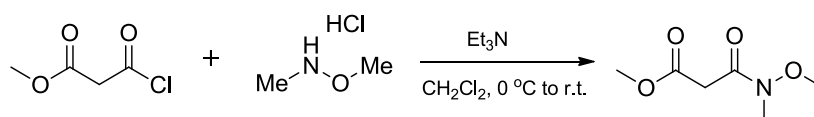
N-methoxy-*N*,2-dimethyl-3-oxobutanamide 172



To a solution of triethylamine (1.67 mL, 12 mmol, 3 equiv) in toluene (8 mL) was added *N,O*-dimethylhydroxyamine (1.17 g, 12 mmol, 3 equiv). The resulting solution was stirred at r.t. for 12 h. After filtration and washing use toluene (8 mL), obtained the solution, and then mixed with 3-diazopentane-2,4-dione (504 mg, 4 mmol) in a closed glass container and subjected to microwave irradiation at 165 °C for 10 min. The resulting Weinreb β -ketoamide solution was directly purified by flash column chromatography on silica gel (PE/EtOAc=2:1) to provide a pure product as a yellow oil (121.4 mg, 24% yield).

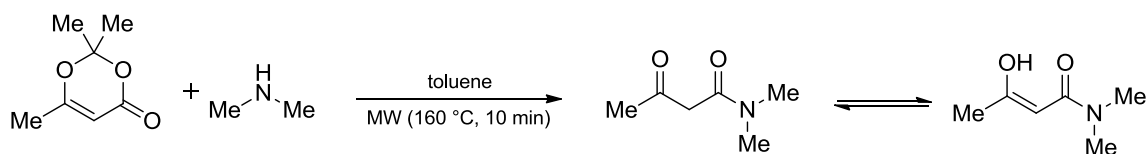
$^1\text{H NMR}$ (400 MHz, CDCl_3) δ (ppm) 3.75 (q, $J = 7.1$ Hz, 1H), 3.68 (s, 3H), 3.22 (s, 3H), 2.18 (s, 3H), 1.34 (d, $J = 7.1$ Hz, 3H).

Methyl 3-[methoxy(methyl)amino]-3-oxopropanoate 173



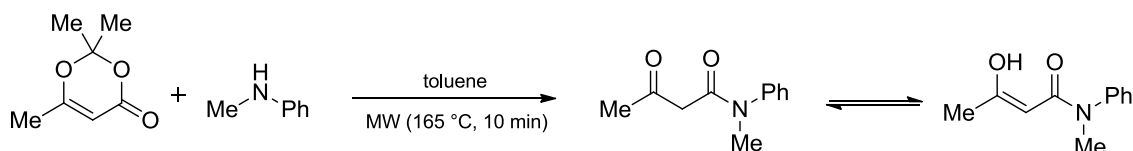
A solution of triethylamine (6.518 g, 73.2 mmol) in dry CH_2Cl_2 (11 mL) was added dropwise to a cold (0 °C) solution of methyl 3-chloro-3-oxopropanoate (5.00 g, 36.62 mmol) and *N,O*-dimethylhydroxyamine hydrochloride (3.57 g, 36.62 mmol) in dry CH_2Cl_2 (90 mL) under an argon atmosphere. The resulting yellow solution was stirred for 1 h at 0 °C and for 12 h at r.t.. Conversion was then complete (monitored by TLC), and the mixture was extracted with water (40 mL). The aqueous layer was re-extracted with CH_2Cl_2 (3×40 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 , and concentrated in vacuo to give a brown oil as the crude product. And then purified by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 100:1) to provide a yellow liquid (53% yield).^[276]

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 3.74 (s, 3H), 3.70 (s, 3H), 3.50 (s, 2H), 3.21 (s, 3H).

***N,N*-dimethyl-3-oxobutanamide 101**

To a solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (531 μ L, 4 mmol, 1 equiv) in toluene (16 mL) was added dimethylamine solution (2.0M in THF, 4 mL, 8 mmol, 2 equiv). The resulting solution was put in a closed glass container and subjected to microwave irradiation at 160 $^{\circ}$ C for 10 min. The resulting β -ketoamide solution was directly purified by flash column chromatography on silica gel (PE/EtOAc 1:1) to provide a mixture of tautomers as a pale yellow oil (475 mg, 3.68 mmol, 92% yield).

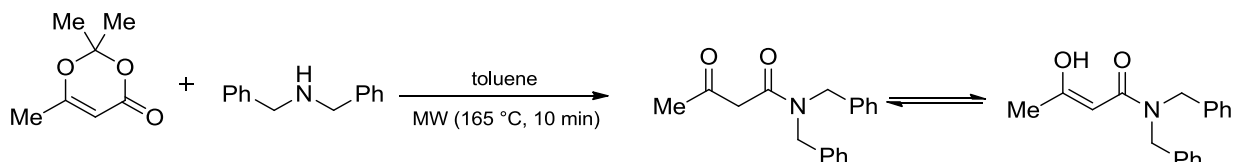
^1H NMR (400 MHz, CDCl_3) δ (ppm) *ketone/enol* 1:0.25; *ketone* 3.51 (s, 2H), 2.95 (s, 3H), 2.93 (s, 3H), 2.23 (s, 3H); *enol* 14.78 (s, 1H), 5.08 (s, 1H), 2.93 (s, 6H), 1.91 (s, 3H).

***N*-methyl-3-oxo-*N*-phenylbutanamide 174**

To a solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (531 μ L, 4 mmol, 1 equiv) in toluene (12 mL) was added *N*-methylaniline (867 μ L, 8 mmol, 2 equiv). The resulting solution was put in a closed glass container and subjected to microwave irradiation at 165 $^{\circ}$ C for 10 min. The resulting β -ketoamide solution was directly purified by flash column chromatography on silica gel (PE/EtOAc 1:1) to provide a mixture of tautomers as a pale yellow oil (581 mg, 3.04 mmol, 76% yield).

^1H NMR (400 MHz, CDCl_3) δ (ppm) *ketone/enol* 1:0.35; *ketone* 7.44 – 7.37 (m, 2H), 7.37 – 7.31 (m, 1H), 7.21 – 7.15 (m, 2H), 3.28 (s, 5H), 2.08 (s, 3H); *enol* 14.24 (s, 1H), 7.44 – 7.37 (m, 2H), 7.37 – 7.31 (m, 1H), 7.21 – 7.15 (m, 2H), 4.66 (s, 1H), 3.27 (s, 3H), 1.78 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) *ketone* 202.4 (C), 166.8 (C), 143.7 (C), 133.0 (2 CH), 128.4 (CH), 127.3 (2 CH), 50.0 (CH_2), 37.4 (CH_3), 30.4 (CH_3); *enol* 172.0 (C), 143.5 (C), 129.7 (2 CH), 127.7 (CH), 127.4 (2 CH), 89.0 (CH), 36.5 (CH_3), 21.7 (CH_3), one of the C could not be unambiguously attributed.

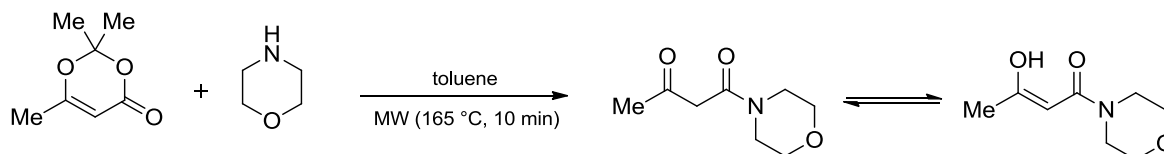
***N,N*-dibenzyl-3-oxobutanamide 175**

To a solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (531 μL , 4 mmol, 1 equiv) in toluene (12 mL) was added dibenzylamine (770 μL , 4 mmol, 1 equiv). The resulting solution was put in a closed glass container and subjected to microwave irradiation at 165 $^{\circ}\text{C}$ for 10 min. The resulting β -ketoamide solution was directly purified by flash column chromatography on silica gel (PE/EtOAc 1:1) to provide a mixture of tautomers as a pale yellow oil (1.00 g, 3.56 mmol, 89% yield).

^1H NMR (400 MHz, CDCl_3) δ (ppm) *ketone/enol* 1:0.55; *ketone* 7.43 – 7.12 (m, 10H), 4.64 (s, 2H), 4.42 (s, 2H), 3.63 (s, 2H), 2.29 (s, 3H); *enol* 14.85 (s, 1H), 7.43 – 7.12 (m, 10H), 5.22 (s, 1H), 4.62 (s, 2H), 4.33 (s, 2H), 1.94 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) *ketone* 202.3 (C), 167.5 (C), 136.3 (C), 136.0 (C), 128.9 (2 CH), 128.7 (2 CH), 128.1 (2 CH), 127.7 (CH), 127.5 (CH), 126.6 (2 CH), 50.6 (CH_2), 49.9 (CH_2), 48.4 (CH_2), 30.4 (CH_3); *enol* 175.8 (C), 172.6 (C), 137.2 (C), 136.4 (C), 129.0 (2 CH), 128.8 (2 CH), 128.2 (2 CH), 127.7 (CH), 127.6 (CH), 126.7 (2 CH), 87.0 (CH), 49.7 (CH_2), 47.8 (CH_2), 22.1 (CH_3).

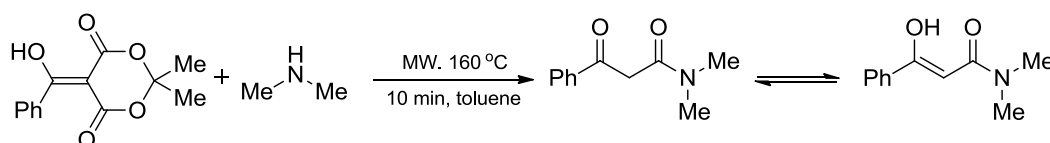
1-Morpholinobutane-1,3-dione 176



To a solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (531 μL , 4 mmol, 1 equiv) in toluene (12 mL) was added morpholine (700 μL , 8 mmol, 2 equiv). The resulting solution was put in a closed glass container and subjected to microwave irradiation at 165 $^{\circ}\text{C}$ for 10 min. The resulting β -ketoamide solution was directly purified by flash column chromatography on silica gel (PE/EtOAc 1:1) to provide a mixture of tautomers as a pale yellow oil (562 mg, 3.28 mmol, 82% yield).

^1H NMR (400 MHz, CDCl_3) δ (ppm) *ketone/enol* 1:0.17; *ketone* 3.70 – 3.61 (m, 6H), 3.55 (s, 2H), 3.45 – 3.37 (m, 2H), 2.27 (s, 3H); *enol* 14.59 (s, 1H), 5.10 (s, 1H), 3.70 – 3.61 (m, 8H), 1.95 (s, 3H). NMR data are in accordance with those reported in the literature.^[313]

N,N-dimethyl-3-oxo-3-phenylpropanamide 177



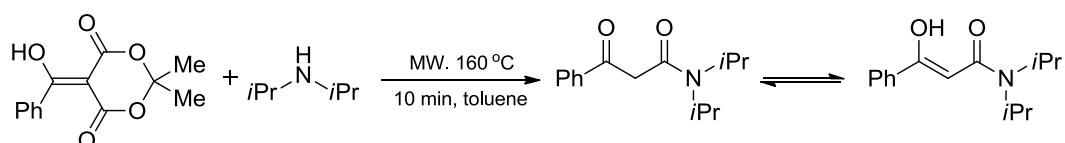
To a solution of 5-(hydroxyphenylmethylene)-2,2-dimethyl[1,3]dioxane-4,6-dione (148.8 mg,

0.60 mmol, 1 equiv) in toluene (3 mL) was added dimethylamine solution (2.0 M in THF, 0.9 mL, 1.80 mmol, 3 equiv). The resulting solution was put in a closed glass container and subjected to microwave irradiation at 160 °C for 10 min. The resulting β -ketoamide solution was directly purified by flash column chromatography on silica gel (PE/EtOAc 2:1) to provide a mixture of tautomers as a pale yellow oil (94.1 mg, 0.49 mmol, 82% yield).

^1H NMR (400 MHz, CDCl_3) δ (ppm) *ketone/enol 1:2.3 ketone* 8.03 (d, $J = 7.7$ Hz, 2H), 7.59 (t, $J = 7.7$ Hz, 1H), 7.47 (t, $J = 7.7$ Hz, 2H), 4.11 (s, 2H), 3.05 (s, 3H), 3.00 (s, 3H); *enol* 15.36 (s, 1H), 7.78 (dd, $J = 7.7, 1.7$ Hz, 2H), 7.44 – 7.36 (m, 3H), 5.79 (s, 1H), 3.08 (s, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) *ketone* 194.0 (C), 167.1 (C), 136.3 (C), 133.8 (CH), 128.82 (2 CH), 128.79 (2 CH), 46.1 (CH_2), 38.2 (2 CH_3); *enol* 172.4 (C), 171.3 (C), 135.1 (C), 130.7 (CH), 128.5 (2 CH), 126.0 (2 CH), 84.7 (CH), 35.7 (2 CH_3).

***N,N*-diisopropyl-3-oxo-3-phenylpropanamide 178**



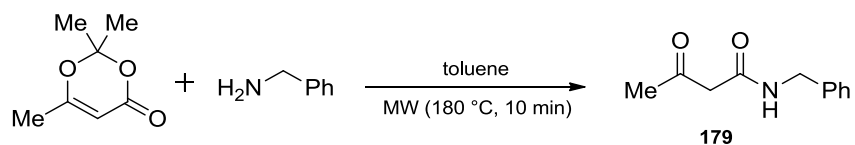
To a solution of 5-(hydroxyphenylmethylene)-2,2-dimethyl[1,3]dioxane-4,6-dione (148.8 mg, 0.60 mmol, 1 equiv) in toluene (3 mL) was added diisopropyl amine solution (252 μL , 1.80 mmol, 3 equiv). The resulting solution was put in a closed glass container and subjected to microwave irradiation at 160 °C for 10 min. The resulting β -ketoamide solution was directly purified by flash column chromatography on silica gel (PE/Et₂O 5:1) to provide a mixture of tautomers as a pale yellow oil (128.8 mg, 0.52 mmol, 87% yield).

^1H NMR (400 MHz, CDCl_3) δ (ppm) *ketone/enol 2:1 ketone* 8.04 – 7.99 (m, 2H), 7.59 – 7.52 (m, 1H), 7.48 – 7.42 (m, 2H), 4.12 – 3.88 (m, 4H), 1.38 (d, $J = 6.8$ Hz, 6H), 1.34 (br s, 6); *enol* 15.81 (s, 1H), 7.78 – 7.72 (m, 2H), 7.41 – 7.35 (m, 3H), 5.74 (s, 1H), 3.42 (hept, $J = 6.9$ Hz, 2H), 1.17 (d, $J = 6.9$ Hz, 6H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) *ketone* 194.6 (C), 165.8 (C), 136.5 (C), 133.5 (CH), 128.8 (2 CH), 128.7 (2 CH), 48.4 (CH_2), 46.2 (CH), 21.5 (2 CH_3), 20.5 (2 CH_3); *enol* 172.0 (C), 171.3 (C), 135.7 (C), 130.4 (CH), 128.5 (2 CH), 125.9 (2 CH), 86.9 (CH), 50.2 (CH), 20.8 (4 CH_3).

Acetoacetanilide 205 was purchased from Strem.

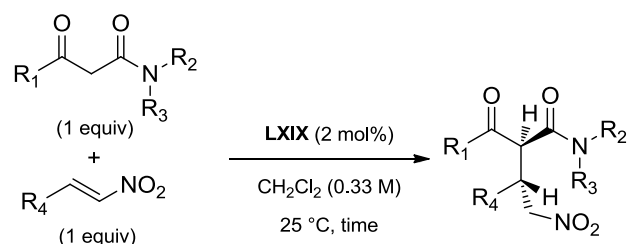
***N*-benzyl-3-oxobutanamide 179**



To a solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (531 μ L, 4 mmol, 1 equiv) in toluene (12 mL) was added benzylamine (436.9 μ L, 4 mmol, 1 equiv). The resulting solution was put in a closed glass container and subjected to microwave irradiation at 180 $^{\circ}$ C for 10 min. The resulting β -ketoamide solution was directly purified by flash column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 50:1 then $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 2.5:1) to provide the product as a pale yellow oil (498 mg, 2.60 mmol, 65% yield).

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.36 – 7.30 (m, 5H), 4.49 (d, J = 5.8 Hz, 2H), 3.48 (s, 2H), 2.29 (s, 3H).

IV.2 General Procedure, Synthesis and Characterization of Products

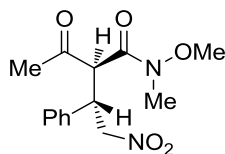


General procedure (reactions were carried out on 0.2 mmol of β -ketoamide):

To a solution of chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%) and β -ketoamide (0.200 mmol, 1.0 equiv) in dry CH_2Cl_2 (0.6 mL) under argon was added substituted nitroolefin (0.200 mmol, 1.0 equiv). The reaction mixture was stirred at 25°C until complete conversion of the β -ketoamide, checked by TLC. The solution was then filtered through a short pad of silica gel, which was thoroughly washed with CH_2Cl_2 . The solvent was evaporated under reduced pressure to obtain crude compound, which was analyzed by NMR to measure the diastereomeric ratio. Purification by flash column chromatography on silica gel provided the pure product. For products obtained with $>6:1$ *dr*, only the NMR description of the main diastereomer is given.

Racemates **184-192**, **194**, **195** and **197-207** were prepared by mixing the two starting materials in the presence of Et_3N and LiClO_4 .^[314]

Racemates **193**, **196** and **208** was prepared following the general procedure using TUC racemic catalyst. These racemic reactions were not diastereoselective.

(2*S*,3*S*)-2-Acetyl-*N*-methoxy-*N*-methyl-4-nitro-3-phenylbutanamide 184

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N*-methoxy-*N*-methyl-3-oxobutanamide **100** (29.0 mg, 0.200 mmol, 1 equiv) and (*E*)- β -nitrostyrene **121** (29.8 mg, 0.200 mmol, 1 equiv). Reaction run for 14 h and crude product obtained with 18:1 *dr*. Purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 50:1) afforded **184** (53.3 mg, 0.184 mmol, 92% yield, 98% *ee*).

TLC ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 50:1) *R_f* 0.57 (UV, vanillin).

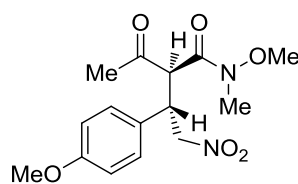
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.33 – 7.23 (m, 5H), 4.96 (dd, $J = 13.1, 9.2$ Hz, 1H), 4.87 (dd, $J = 13.1, 4.0$ Hz, 1H), 4.35 (d, $J = 8.4$ Hz, 1H), 4.28 (td, $J = 8.8, 4.0$ Hz, 1H). 3.45 (s, 3H), 3.21 (s, 3H), 1.98 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 201.3 (C), 168.4 (C), 137.0 (C), 129.3 (2 CH), 128.4 (CH), 128.2 (2 CH), 77.5 (CH_2), 61.3 (CH_3), 58.9 (CH), 42.9 (CH), 32.6 (CH_3), 29.5 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_5+\text{H}]^+$: 295.1288, found: 295.1289.

HPLC Chiralpak AS-H, Hexane/EtOH 90:10, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 220$ nm, $\tau_{\text{major}} = 8.10$ min, $\tau_{\text{minor}} = 14.56$ min.

$[\alpha]_{\text{D}}^{20} = -67.4$ (c 0.23, CHCl_3).

(2*S*,3*S*)-2-Acetyl-*N*-methoxy-3-(4-methoxyphenyl)-*N*-methyl-4-nitrobutanamide **185****185**

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N*-methoxy-*N*-methyl-3-oxobutanamide **100** (29.0 mg, 0.200 mmol, 1 equiv) and (*E*)-1-methoxy-4-(2-nitrovinyl)benzene (35.8 mg, 0.200 mmol, 1 equiv). Reaction run for 15 h and crude product obtained with 16:1 *dr*. Purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 50:1) afforded **185** (57.0 mg, 0.176 mmol, 88% yield, 94% *ee*).

TLC ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 50:1) *R*_f 0.47 (UV, vanillin).

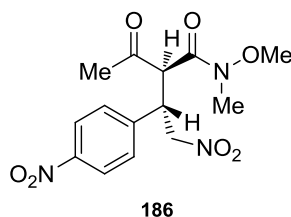
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.25 – 7.07 (m, 2H), 6.90 – 6.77 (m, 2H), 4.92 – 4.75 (m, 2H), 4.29 (d, *J* = 8.7 Hz, 1H), 4.21 (td, *J* = 8.7, 4.5 Hz, 1H), 3.75 (s, 3H), 3.49 (s, 3H), 3.20 (s, 3H), 1.96 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 201.5 (C), 168.4 (C), 159.5 (C), 129.3 (2 CH), 128.6 (C), 114.6 (2 CH), 77.9 (CH_2), 61.4 (CH_3), 59.0 (CH), 55.3 (CH_3), 42.3 (CH), 32.6 (CH_3), 29.5 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_6+\text{H}]^+$: 325.1394, found: 325.1396.

HPLC Chiralcel OD-3, Hexane/EtOH 90:10, 25 °C, 1.0 mL/min, λ = 220 nm, τ_{major} = 16.98 min, τ_{minor} = 24.24 min.

$[\alpha]_{\text{D}}^{20}$ = -58.8 (c 0.64, CHCl_3).

(2*S*,3*S*)-2-Acetyl-*N*-methoxy-*N*-methyl-4-nitro-3-(4-nitrophenyl)butanamide 186

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N*-methoxy-*N*-methyl-3-oxobutanamide **100** (29.0 mg, 0.200 mmol, 1 equiv) and (*E*)-1-nitro-4-(2-nitrovinyl)benzene (38.8 mg, 0.200 mmol, 1equiv). Reaction run for 15 h and crude product obtained with 18:1 *dr*. Purification by column chromatography (CH_2Cl_2) afforded **186** (57.0 mg, 0.168 mmol, 84% yield, 98% *ee*).

TLC (CH_2Cl_2) *R_f* 0.2 (UV, vanillin).

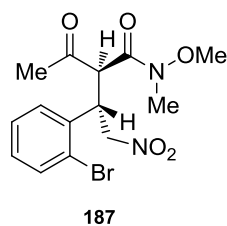
^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.23 – 8.12 (m, 2H), 7.52 – 7.39 (m, 2H), 4.99 (dd, *J* = 13.7, 9.5 Hz, 1H), 4.89 (dd, *J* = 13.7, 3.9 Hz, 1H), 4.47 – 4.36 (m, 1H), 4.34 (d, *J* = 7.9 Hz, 1H), 3.52 (s, 3H), 3.22 (s, 3H), 2.05 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 200.2 (C), 167.7 (C), 147.8 (C), 144.8 (C), 129.3 (2 CH), 124.3 (2 CH), 76.8 (CH_2), 61.5 (CH_3), 58.4 (CH), 42.4 (CH), 32.6 (CH_3), 29.4 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_7+\text{H}]^+$: 340.1139, found: 340.1140.

HPLC Chiralpak AD-H, Hexane/EtOH 70:30, 25 °C, 1.0 mL/min, λ = 220 nm, τ_{major} = 16.83 min, τ_{minor} = 21.34 min.

$[\alpha]_{\text{D}}^{20}$ = -103 (c 0.31, CHCl_3).

(2*S*,3*S*)-2-Acetyl-3-(2-bromophenyl)-*N*-methoxy-*N*-methyl-4-nitrobutanamide 187

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N*-methoxy-*N*-methyl-3-oxobutanamide **100** (29.0 mg, 0.200 mmol, 1 equiv) and (*E*)-1-bromo-2-(2-nitrovinyl)benzene (45.6 mg, 0.200 mmol, 1 equiv). Reaction run for 13 h and crude product obtained with 20:1 *dr*. Purification by column chromatography (CH_2Cl_2) afforded **187** (64.0 mg, 0.172 mmol, 86% yield, 99% *ee*).

TLC (CH_2Cl_2) R_f 0.24 (UV, vanillin).

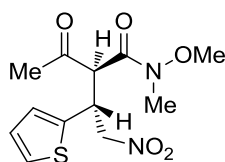
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.57 (d, $J = 7.8$ Hz, 1H), 7.30 – 7.20 (m, 2H), 7.14 – 7.08 (m, 1H), 5.21 (dd, $J = 14.1, 9.6$ Hz, 1H), 4.92 (dd, $J = 14.1, 3.8$ Hz, 1H), 4.78 (ddd, $J = 9.8, 6.2, 3.8$ Hz, 1H), 4.49 (d, $J = 6.1$ Hz, 1H), 3.29 (s, 3H), 3.12 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 200.9 (C), 168.2 (C), 136.2 (C), 133.8 (CH), 129.7 (CH), 128.6 (CH), 128.1 (CH), 124.9 (C), 75.3 (CH_2), 61.3 (CH_3), 56.8 (CH), 40.9 (CH), 32.4 (CH_3), 29.0 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_5\text{Br}+\text{H}]^+$: 373.0394, found: 373.0392.

HPLC Lux-Amylose-2, Hexane/EtOH 80:20, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 220$ nm, $\tau_{\text{major}} = 29.29$ min, $\tau_{\text{minor}} = 19.23$ min.

$[\alpha]_{\text{D}}^{20} = -125.6$ (c 0.38, CHCl_3).

(2*S*,3*R*)-2-Acetyl-*N*-methoxy-*N*-methyl-4-nitro-3-(thiophen-2-yl)butanamide 188**188**

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μ mol, 2 mol%), *N*-methoxy-*N*-methyl-3-oxobutanamide **100** (29.0 mg, 0.200 mmol, 1 equiv) and (*E*)-2-(2-nitrovinyl)thiophene (31.0 mg, 0.200 mmol, 1 equiv). Reaction run for 24 h and crude product obtained with 11:1 *dr*. Purification by column chromatography (CH_2Cl_2) afforded **188** (48.0 mg, 0.160 mmol, 80% yield, 99% and 88% *ee*).

TLC (CH_2Cl_2) R_f 0.23 (UV, vanillin).

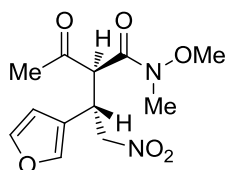
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.20 (dd, $J = 4.1, 2.2$ Hz, 1H), 6.95 – 6.89 (m, 2H), 4.94 (dd, $J = 13.4, 8.9$ Hz, 1H), 4.86 (dd, $J = 13.4, 4.0$ Hz, 1H), 4.58 (td, $J = 8.4, 4.0$ Hz, 1H), 4.39 (d, $J = 7.8$ Hz, 1H), 3.53 (s, 3H), 3.22 (s, 3H), 2.06 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 201.0 (C), 168.0 (C), 139.5 (C), 127.3 (CH), 126.8 (CH), 125.5 (CH), 78.2 (CH₂), 61.4 (CH₃), 59.4 (CH), 38.2 (CH), 32.5 (CH₃), 29.6 (CH₃).

HRMS (ESI) calc'd for $[\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_5\text{S}+\text{H}]^+$: 301.0853, found: 301.0852.

HPLC Chiralpak IE, Hexane/EtOH 50:50, 25 °C, 1.0 mL/min, DAD $\lambda = 220$ nm, *major diastereomer*: $\tau_{\text{major}} = 9.36$ min, $\tau_{\text{minor}} = 8.55$ min; *minor diastereomer*: $\tau_{\text{major}} = 11.14$ min, $\tau_{\text{minor}} = 10.33$ min.

$[\alpha]_{\text{D}}^{20} = -87.4$ (c 0.95, CHCl_3).

(2*S*,3*S*)-2-Acetyl-3-(furan-3-yl)-*N*-methoxy-*N*-methyl-4-nitrobutanamide 189**189**

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N*-methoxy-*N*-methyl-3-oxobutanamide **100** (29.0 mg, 0.200 mmol, 1 equiv) and (*E*)-3-(2-nitrovinyl)furan (27.8 mg, 0.200 mmol, 1 equiv). Reaction run for 72 h and crude product obtained with 14:1 *dr*. Purification by column chromatography (CH_2Cl_2) afforded **189** (43.7 mg, 0.154 mmol, 77% yield, 90% and 77% *ee*).

TLC (CH_2Cl_2) R_f 0.29 (UV, vanillin).

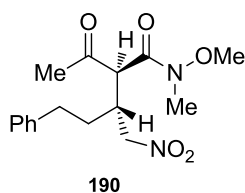
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.40 – 7.30 (m, 2H), 6.31 (dd, $J = 1.7, 0.9$ Hz, 1H), 4.80 (dd, $J = 13.0, 8.2$ Hz, 1H), 4.74 (dd, $J = 13.0, 4.2$ Hz, 1H), 4.28 (d, $J = 8.3$ Hz, 1H), 4.20 (td, $J = 8.3, 4.2$ Hz, 1H), 3.62 (s, 3H), 3.22 (s, 3H), 2.08 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 201.4 (C), 168.3 (C), 143.9 (CH), 140.8 (CH), 121.1 (C), 109.5 (CH), 77.8 (CH_2), 61.5 (CH_3), 58.3 (CH), 34.1 (CH), 32.6 (CH_3), 29.6 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_6+\text{H}]^+$: 285.1081, found: 285.1082.

HPLC Lux-Cellulose-4, Hexane/EtOH 80:20, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 220$ nm, *major diastereomer*: $\tau_{\text{major}} = 10.47$ min, $\tau_{\text{minor}} = 11.86$ min; *minor diastereomer*: $\tau_{\text{major}} = 12.96$ min, $\tau_{\text{minor}} = 14.14$ min.

$[\alpha]_{\text{D}}^{20} = -63.5$ (c 0.64, CHCl_3).

(2*S*,3*R*)-2-Acetyl-*N*-methoxy-*N*-methyl-3-(nitromethyl)-5-phenylpentanamide 190

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N*-methoxy-*N*-methyl-3-oxobutanamide **100** (29.0 mg, 0.200 mmol, 1 equiv) and (*E*)-(4-nitrobut-3-en-1-yl)benzene (35.4 mg, 0.200 mmol, 1 equiv). Reaction run for 20 h and crude product obtained with 13:1 *dr*. Purification by column chromatography (CH_2Cl_2) afforded **190** (48.9 mg, 0.152 mmol, 76% yield, 97% *ee*).

TLC (CH_2Cl_2) *R_f* 0.18 (UV, vanillin).

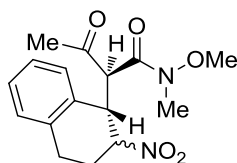
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.31 – 7.26 (m, 2H), 7.22 – 7.18 (m, 1H), 7.17 – 7.13 (m, 2H), 4.68 (d, *J* = 5.1 Hz, 2H), 4.09 (d, *J* = 7.0 Hz, 1H), 3.70 (s, 3H), 3.20 (s, 3H), 2.94 – 2.83 (m, 1H), 2.78 (ddd, *J* = 15.3, 9.1, 6.3 Hz, 1H), 2.65 (ddd, *J* = 13.8, 9.1, 7.0 Hz, 1H), 2.18 (s, 3H), 1.84 – 1.74 (m, 2H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 202.5 (C), 168.8 (C), 140.5 (C), 128.8 (2 CH), 128.4 (2 CH), 126.5 (CH), 76.7 (CH_2), 61.4 (CH_3), 57.2 (CH), 36.5 (CH), 33.2 (CH_2), 32.5 (CH_3), 31.6 (CH_2), 29.7 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_5+\text{H}]^+$: 323.1601, found: 323.1599.

HPLC Chiralcel OD-3, Hexane/EtOH 90:10, 25 °C, 1.0 mL/min, λ = 220 nm, τ_{major} = 13.28 min, τ_{minor} = 16.26 min.

$[\alpha]_{\text{D}}^{20}$ = +21.8 (c 0.55, CHCl_3).

(S)-N-methoxy-N-methyl-2-((S)-2-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)-3-oxobutanamide 191**191**

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N*-methoxy-*N*-methyl-3-oxobutanamide **100** (29.0 mg, 0.200 mmol, 1 equiv) and 3-nitro-2*H*-chromene (35.4 mg, 0.200 mmol, 1 equiv). Reaction run for 72 h and crude product obtained with 3:1 *dr*. Purification by column chromatography (CH_2Cl_2) afforded **191** (32.2 mg, 0.100 mmol, 50% yield, 86% and 69% *ee*).

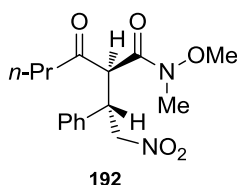
TLC (CH_2Cl_2) *R_f* 0.29 (UV, vanillin).

^1H NMR (400 MHz, CDCl_3) δ (ppm) *major diastereomer* 7.22 – 7.10 (m, 2H), 6.98 – 6.92 (m, 1H), 6.89 – 6.84 (m, 1H), 5.21 (dd, *J* = 5.0, 2.8 Hz, 1H), 4.87 – 4.79 (m, 1H), 4.53 (d, *J* = 6.6 Hz, 1H), 4.43 (d, *J* = 6.6 Hz, 1H), 4.31 (dd, *J* = 12.9, 3.1 Hz, 1H), 3.45 (s, 3H), 3.17 (s, 3H), 2.09 (s, 3H); *minor diastereomer* 7.22 – 7.10 (m, 2H), 6.98 – 6.92 (m, 1H), 6.89 – 6.84 (m, 1H), 5.17 (dd, *J* = 4.7, 2.6 Hz, 1H), 4.87 – 4.79 (m, 1H), 4.50 (d, *J* = 7.6 Hz, 1H), 4.35 (d, *J* = 7.6 Hz, 1H), 4.18 (dd, *J* = 13.0, 3.0 Hz, 1H), 3.42 (s, 3H), 3.16 (s, 3H), 2.07 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) *major diastereomer* 201.5 (C), 168.4 (C), 154.0 (C), 129.3 (CH), 129.1 (CH), 122.1 (CH), 119.2 (C), 117.8 (CH), 80.9 (CH), 64.7 (CH_2), 61.5 (CH_3), 59.3 (CH), 35.1 (CH), 32.6 (CH_3), 30.3 (CH_3); *minor diastereomer* 202.5 (C), 168.4 (C), 153.7 (C), 129.4 (CH), 129.2 (CH), 122.1 (CH), 119.0 (C), 117.7 (CH), 80.5 (CH), 64.2 (CH_2), 61.1 (CH_3), 59.7 (CH), 35.3 (CH), 32.5 (CH_3), 30.7 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_6+\text{H}]^+$: 323.1238, found: 323.1237.

HPLC Lux-Amylose-2, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, λ = 220 nm, *major diastereomer*: τ_{major} = 20.18 min, τ_{minor} = 18.16 min; *minor diastereomer*: τ_{major} = 29.57 min, τ_{minor} = 24.04 min.

(S)-N-methoxy-N-methyl-2-((S)-2-nitro-1-phenylethyl)-3-oxohexanamide 192

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N*-methoxy-*N*-methyl-3-oxohexanamide **167** (34.6 mg, 0.200 mmol, 1 equiv) and (*E*)- β -nitrostyrene **121** (29.8 mg, 0.200 mmol, 1 equiv). Reaction run for 14 h and crude product obtained with 12:1 *dr*. Purification by column chromatography (PE/Et₂O 2:1) afforded **192** (52.2 mg, 0.162 mmol, 81% yield, 99% *ee*).

TLC (PE/Et₂O 2:1) *R_f* 0.20 (UV, vanillin).

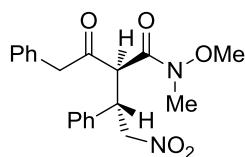
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.34 – 7.26 (m, 3H), 7.25 – 7.23 (m, 2H), 4.98 (dd, *J* = 13.2, 8.9 Hz, 1H), 4.88 (dd, *J* = 13.2, 3.7 Hz, 1H), 4.40 – 4.24 (m, 2H), 3.44 (s, 3H), 3.21 (s, 3H), 2.34 (dt, *J* = 17.9, 7.4 Hz, 1H), 2.15 (dt, *J* = 17.9, 7.4 Hz, 1H), 1.45 – 1.34 (m, 2H), 0.72 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 203.2 (C), 168.5 (C), 137.2 (C), 129.2 (2 CH), 128.3 (CH), 128.2 (2 CH), 77.6 (CH₂), 61.3 (CH₃), 58.5 (CH), 44.2 (CH₂), 42.9 (CH), 32.6 (CH₃), 16.6 (CH₂), 13.4 (CH₃).

HRMS (ESI) calc'd for [C₁₆H₂₂N₂O₅+H]⁺: 323.1601, found: 323.1603.

HPLC Chiralpak AZ-H, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, λ = 220 nm, τ_{major} = 14,12 min, τ_{minor} = 12,75 min.

$[\alpha]_{\text{D}}^{20}$ = -73.4 (c 0.59, CHCl₃).

(2*S*,3*S*)-*N*-methoxy-*N*-methyl-4-nitro-3-phenyl-2-(2-phenylacetyl)butanamide 193**193**

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N*-methoxy-*N*-methyl-3-oxo-4-phenylbutanamide **168** (44.3 mg, 0.200 mmol, 1 equiv) and (*E*)- β -nitrostyrene **121** (29.8 mg, 0.200 mmol, 1 equiv). Reaction run for 16 h and crude product obtained with 10:1 *dr*. Purification by column chromatography (CH_2Cl_2) afforded **193** (56.2 mg, 0.152 mmol, 76% yield, 99% *ee*).

TLC (CH_2Cl_2) *R*_f 0.35 (UV, vanillin).

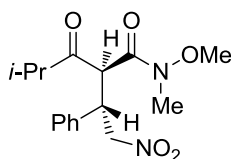
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.33 – 7.27 (m, 3H), 7.26 – 7.16 (m, 5H), 6.90 (dd, *J* = 7.3, 2.0 Hz, 2H), 4.99 (dd, *J* = 13.2, 9.3 Hz, 1H), 4.88 (dd, *J* = 13.2, 4.1 Hz, 1H), 4.45 (d, *J* = 8.3 Hz, 1H), 4.29 (td, *J* = 8.8, 4.1 Hz, 1H), 3.63 (d, *J* = 16.4 Hz, 1H), 3.52 (d, *J* = 16.4 Hz, 1H), 3.42 (s, 3H), 3.19 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 200.7 (C), 168.0 (C), 137.0 (C), 132.8 (C), 129.7 (2 CH), 129.3 (2 CH), 128.7 (2 CH), 128.4 (CH), 128.3 (2 CH), 127.3 (CH), 77.4 (CH_2), 61.3 (CH_3), 57.8 (CH), 49.2 (CH_2), 43.0 (CH), 32.6 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_5+\text{H}]^+$: 371.1601, found: 371.1602.

HPLC Chiralpak AD-H, Hexane/EtOH 80:20, 25 $^\circ\text{C}$, 1.0 mL/min, λ = 254 nm, τ_{major} = 13.86 min, τ_{minor} = 21.39 min.

$[\alpha]_{\text{D}}^{20}$ = +10.5 (c 0.21, CHCl_3).

(S)-N-methoxy-N,4-dimethyl-2-((S)-2-nitro-1-phenylethyl)-3-oxopentanamide 194**194**

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N*-methoxy-*N*,4-dimethyl-3-oxopentanamide **169** (34.6 mg, 0.200 mmol, 1 equiv) and (*E*)- β -nitrostyrene **121** (29.8 mg, 0.200 mmol, 1 equiv). Reaction run for 26 h and crude product obtained with 8:1 *dr*. Purification by column chromatography (CH_2Cl_2) afforded **194** (46.4 mg, 0.144 mmol, 72% yield, 96% and 37% *ee*).

TLC (CH_2Cl_2) *R_f* 0.35 (UV, vanillin).

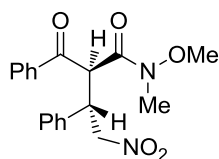
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.32 – 7.21 (m, 5H), 5.03 (dd, $J = 13.4, 9.8$ Hz, 1H), 4.89 (dd, $J = 13.4, 3.9$ Hz, 1H), 4.52 (d, $J = 7.1$ Hz, 1H), 4.37 – 4.25 (m, 1H), 3.35 (s, 3H), 3.20 (s, 3H), 2.63 (hept, $J = 6.8$ Hz, 1H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 207.1 (C), 168.3 (C), 137.8 (C), 129.2 (2 CH), 128.3 (CH), 128.2 (2 CH), 77.3 (CH_2), 61.3 (CH_3), 57.3 (CH), 42.8 (CH), 40.0 (CH_3), 32.6 (CH), 18.9 (CH_3), 18.3 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_5+\text{H}]^+$: 323.1601, found: 323.1603.

HPLC Chiralpak AD-H, Heptane/EtOH 90:10, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 220$ nm, *major diastereomer*: $\tau_{\text{major}} = 13.40$ min, $\tau_{\text{minor}} = 15.95$ min; *minor diastereomer*: $\tau_{\text{major}} = 11.24$ min, $\tau_{\text{minor}} = 17.39$ min.

$[\alpha]_{\text{D}}^{20}$ = -129.3 (c 0.30, CHCl_3).

(2*S*,3*S*)-2-benzoyl-*N*-methoxy-*N*-methyl-4-nitro-3-phenylbutanamide 195**195**

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N*-methoxy-*N*-methyl-3-oxo-3-phenylpropanamide **170** (41.4 mg, 0.200 mmol, 1 equiv) and (*E*)- β -nitrostyrene **121** (29.8 mg, 0.200 mmol, 1 equiv). Reaction run for 14 h and crude product obtained with 3:1 *dr*. Purification by column chromatography (CH_2Cl_2) afforded **195** (52.6 mg, 0.148 mmol, 74% yield, 92% and 75% *ee*).

TLC (CH_2Cl_2) R_f 0.34 (UV, vanillin).

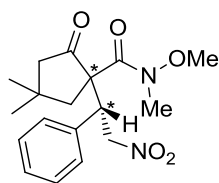
^1H NMR (400 MHz, CDCl_3) δ (ppm) *major diastereomer* 7.83 – 7.76 (m, 2H), 7.56 – 7.49 (m, 1H), 7.42 – 7.35 (m, 2H), 7.27 – 7.10 (m, 5H), 5.19 – 5.05 (m, 3H), 4.36 (ddd, $J = 9.6, 7.5, 4.1$ Hz, 1H), 3.30 (s, 3H), 3.15 (s, 3H); *minor diastereomer* 7.83 – 7.76 (m, 2H), 7.56 – 7.49 (m, 1H), 7.42 – 7.35 (m, 2H), 7.27 – 7.10 (m, 5H), 5.19 – 5.05 (m, 2H), 4.90 (dd, $J = 13.5, 10.3$ Hz, 1H), 4.53 (ddd, $J = 10.3, 6.8, 4.3$ Hz, 1H), 3.33 (s, 3H), 3.04 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) *major diastereomer* 194.4 (C), 168.9 (C), 137.2 (C), 136.3 (C), 133.6 (CH), 129.0 (2 CH), 128.8 (2 CH), 128.50 (2 CH), 128.47 (2 CH), 128.2 (CH), 77.4 (CH_2), 61.0 (CH_3), 54.1 (CH), 43.5 (CH), 32.8 (CH_3); *minor diastereomer* 194.3 (C), 168.9 (C), 137.2 (C), 136.6 (C), 133.8 (CH), 129.0 (2 CH), 128.8 (2 CH), 128.6 (2 CH), 128.3 (2 CH), 128.2 (CH), 76.8 (CH_2), 61.0 (CH_3), 54.5 (CH), 43.1 (CH), 32.8 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_5+\text{H}]^+$: 357.1445, found: 357.1447.

HPLC Chiralpak IE, Heptane/EtOH 70:30, 25 $^\circ\text{C}$, 1.0 mL/min, DAD $\lambda = 254$ nm, *major diastereomer*: $\tau_{\text{major}} = 20.51$ min, $\tau_{\text{minor}} = 13.03$ min; *minor diastereomer*: $\tau_{\text{major}} = 18.24$ min, $\tau_{\text{minor}} = 17.07$ min.

N-methoxy-N,4,4-trimethyl-1-(2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxamide
196



196

To a solution of chiral squaramide catalyst **LXIX** (2.6 mg, 2 mol%, 0.0040 mmol) and *N*-methoxy-*N*,4,4-trimethyl-2-oxocyclopentanecarboxamide **171** (39.9 mg, 1.0 equiv, 0.200 mmol) in CH₂Cl₂ (0.6 mL) was added *trans*-β-nitrostyrene **121** (29.8 mg, 1.0 equiv, 0.200 mmol). After 72 h, the reaction mixture was concentrated and checked the crude NMR as 3:1 mixture of diastereomers, and then purification by column chromatography (CH₂Cl₂) afforded **196** (25.8 mg, 0.074 mmol 37 % yield, 84% *ee*).

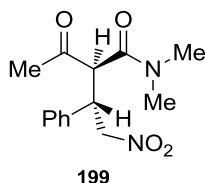
TLC (CH₂Cl₂) *R_f* 0.19 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.42 – 7.10 (m, 5H), 5.25 (dd, *J* = 13.5, 11.4 Hz, 1H), 4.79 (dd, *J* = 13.6, 3.2 Hz, 1H), 4.15 (dd, *J* = 11.3, 3.2 Hz, 1H), 3.33 (s, 3H), 3.19 (s, 3H), 2.18 (dd, *J* = 42.4, 17.1 Hz, 2H), 1.91 (dd, *J* = 41.7, 17.1 Hz, 2H), 1.00 (s, 3H), 0.32 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 214.6 (C), 173.1 (C), 135.7 (C), 130.5 (CH), 128.9 (CH), 128.6 (CH), 77.7 (CH₂), 64.0 (C), 59.1 (CH₃), 53.9 (CH₂), 48.9 (CH), 47.8 (CH₂), 34.1 (CH₃), 32.4 (C), 31.5 (CH₃), 30.9 (CH₃).

HRMS (ESI) calc'd for [C₁₈H₂₄N₂O₅+H]⁺: 349.1758, found: 349.1760.

HPLC Chiralpak AZ-H, Hexane/ethanol 80/20, 25 °C, 1.0 mL/min, UV 220 nm and CD 254 nm τ_{major} = 11.77 min, τ_{minor} = 9.75 min.

(2*S*,3*S*)-2-Acetyl-*N,N*-dimethyl-4-nitro-3-phenylbutanamide 199

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N,N*-dimethyl-3-oxobutanamide **101** (25.8 mg, 0.200 mmol, 1 equiv) and (*E*)- β -nitrostyrene **121** (29.8 mg, 0.200 mmol, 1 equiv). Reaction run for 35 h and crude product obtained with >20:1 *dr*. Purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 50:1) afforded **199** (46.7 mg, 0.168 mmol, 84% yield, 98% *ee*).

TLC ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ =50:1) *R_f* 0.30 (UV, vanillin).

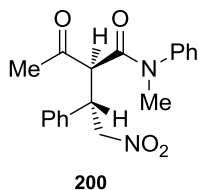
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.28 – 7.20 (m, 3H), 7.19 – 7.12 (m, 2H), 4.76 (dd, $J = 12.8, 4.6$ Hz, 1H), 4.71 (dd, $J = 12.8, 8.2$ Hz, 1H), 4.31 (td, $J = 8.5, 4.6$ Hz, 1H), 4.16 (d, $J = 8.9$ Hz, 1H), 2.94 (s, 3H), 2.84 (s, 3H), 1.97 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 201.8 (C), 166.7 (C), 136.5 (C), 129.3 (2 CH), 128.5 (CH), 128.1 (2 CH), 78.1 (CH_2), 60.0 (CH), 43.3 (CH), 37.8 (CH_3), 36.4 (CH_3), 27.4 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_4+\text{H}]^+$: 279.1339, found: 279.1341.

HPLC Chiralpak AS-H, Hexane/EtOH 90:10, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 220$ nm, $\tau_{\text{major}} = 7.93$ min, $\tau_{\text{minor}} = 11.89$ min.

$[\alpha]_{\text{D}}^{20} = +23.9$ (c 0.51, CHCl_3).

(2*S*,3*S*)-2-Acetyl-*N*-methyl-4-nitro-*N*,3-diphenylbutanamide 200

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μ mol, 2 mol%), *N*-methyl-3-oxo-*N*-phenylbutanamide **174** (41.0 mg, 0.200 mmol, 1 equiv) and (*E*)- β -nitrostyrene **121** (29.8 mg, 0.200 mmol, 1 equiv). Reaction run for 35 h and crude product obtained with >20:1 *dr*. Purification by column chromatography (CH₂Cl₂/EtOAc 50:1) afforded **200** (59.2 mg, 0.174 mmol, 87% yield, 99% *ee*).

TLC (CH₂Cl₂/EtOAc=50:1) *R_f* 0.50 (UV, vanillin).

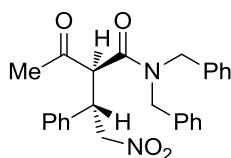
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.52 – 7.18 (m, 7H), 7.17 – 7.10 (m, 2H), 6.57 (br s, 1H), 5.12 (dd, *J* = 13.5, 10.4 Hz, 1H), 4.94 (dd, *J* = 13.5, 3.8 Hz, 1H), 4.23 (ddd, *J* = 10.4, 6.7, 3.8 Hz, 1H), 3.79 (d, *J* = 6.7 Hz, 1H), 3.27 (s, 3H), 1.92 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 201.7 (C), 167.4 (C), 142.7 (C), 137.1 (C), 130.2 (2 CH), 129.2 (2 CH), 128.7 (CH), 128.3 (CH), 128.1 (2 CH), 127.4 (2 CH), 76.8 (CH₂), 60.0 (CH), 43.3 (CH), 38.0 (CH₃), 29.2 (CH₃).

HRMS (ESI) calc'd for [C₁₉H₂₀N₂O₄+H]⁺: 341.1496, found: 341.1498.

HPLC Chiralpak IE, Hexane/EtOH 70:30, 25 °C, 1.0 mL/min, λ = 254 nm, τ_{major} = 14.13 min, τ_{minor} = 11.65 min.

$[\alpha]_{\text{D}}^{20}$ = -31.7 (c 0.12, CHCl₃).

(2*S*,3*S*)-2-Acetyl-*N,N*-dibenzyl-4-nitro-3-phenylbutanamide 201**201**

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N,N*-dibenzyl-3-oxobutanamide **175** (56.2 mg, 0.200 mmol, 1 equiv) and (*E*)- β -nitrostyrene **121** (29.8 mg, 0.200 mmol, 1 equiv). Reaction run for 23 h and crude product obtained with $>20:1$ *dr*. Purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 50:1) afforded **201** (76.6 mg, 0.178 mmol, 89% yield, 99% *ee*).

TLC (PE/EtOAc=5:1) R_f 0.50 (UV, vanillin).

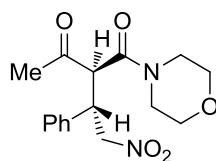
^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.42 – 7.30 (m, 6H), 7.28 – 7.18 (m, 5H), 7.12 – 7.03 (m, 4H), 4.87 (d, $J = 14.4$ Hz, 1H), 4.80 (dd, $J = 12.8, 3.9$ Hz, 1H), 4.60 – 4.40 (m, 4H), 4.06 (d, $J = 8.5$ Hz, 1H), 3.99 (d, $J = 17.2$ Hz, 1H), 1.99 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 201.9 (C), 167.6 (C), 136.6 (C), 136.22 (C), 136.19 (C), 129.4 (2 CH), 129.3 (2 CH), 129.0 (2 CH), 128.7 (2 CH), 128.5 (CH), 128.3 (CH), 128.2 (2 CH), 128.1 (CH), 126.6 (2 CH), 77.7 (CH_2), 61.0 (CH), 50.4 (CH_2), 50.2 (CH_2), 43.4 (CH), 27.5 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_4+\text{H}]^+$: 431.1965, found: 431.1968.

HPLC Chiralpak IE, Hexane/EtOH 70:30, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 254$ nm, $\tau_{\text{major}} = 8.57$ min, $\tau_{\text{minor}} = 9.61$ min.

$[\alpha]_{\text{D}}^{20} = -90.9$ (c 0.58, CHCl_3).

(S)-1-Morpholino-2-((S)-2-nitro-1-phenylethyl)butane-1,3-dione 202**202**

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), 1-morpholinobutane-1,3-dione **176** (34.2 mg, 0.200 mmol, 1 equiv) and (*E*)- β -nitrostyrene **121** (29.8 mg, 0.200 mmol, 1 equiv). Reaction run for 25 h and crude product obtained with >20:1 *dr*. Purification by column chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 50:1) afforded **202** (51.2 mg, 0.160 mmol, 80% yield, 95% *ee*).

TLC ($\text{CH}_2\text{Cl}_2/\text{EtOAc}=50:1$) *R_f* 0.29 (UV, vanillin).

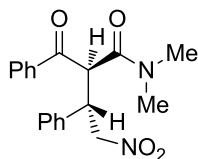
¹H NMR (400 MHz, CDCl_3) δ (ppm) 7.36 – 7.26 (m, 3H), 7.24 – 7.16 (m, 2H), 4.83 – 4.74 (m, 2H), 4.39 (dt, *J* = 9.3, 6.2 Hz, 1H), 4.23 (d, *J* = 9.3 Hz, 1H), 3.77 – 3.47 (m, 7H), 3.41 – 3.30 (m, 1H), 2.02 (s, 3H).

¹³C NMR (101 MHz, CDCl_3) δ (ppm) 201.5 (C), 165.2 (C), 136.1 (C), 129.3 (2 CH), 128.6 (CH), 128.0 (2 CH), 78.1 (CH_2), 66.7 (CH_2), 66.3 (CH_2), 59.4 (CH), 46.7 (CH_2), 42.3 (CH), 42.9 (CH_2), 27.1 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_5+\text{H}]^+$: 321.1445, found: 321.1442.

HPLC Chiralpak IA, Hexane/EtOH 50:50, 25 °C, 1.0 mL/min, λ = 220 nm, τ_{major} = 11.29 min, τ_{minor} = 7.19 min.

$[\alpha]_{\text{D}}^{20}$ = +5.2 (c 0.17, CHCl_3).

(2*S*,3*S*)-2-benzoyl-*N,N*-dimethyl-4-nitro-3-phenylbutanamide 203**203**

Prepared by modifying the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), *N,N*-dimethyl-3-oxo-3-phenylpropanamide **177** (38.2 mg, 0.200 mmol, 1 equiv) and (*E*)- β -nitrostyrene **121** (89.4 mg, 0.600 mmol, 3 equiv). Reaction run for 6 d and crude product obtained with 6:1 *dr*. Purification by column chromatography (CH_2Cl_2 then $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 50:1) afforded **203** (51.1 mg, 0.150 mmol, 75% yield, 95% and 69% *ee*).

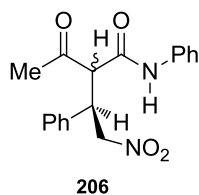
TLC (CH_2Cl_2) *R_f* 0.24 (UV, vanillin).

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.81 – 7.76 (m, 2H), 7.57 – 7.51 (m, 1H), 7.43 – 7.37 (m, 2H), 7.31 – 7.18 (m, 5H), 5.13 (dd, $J = 13.5, 4.0$ Hz, 1H), 5.01 (dd, $J = 13.5, 9.6$ Hz, 1H), 4.86 (d, $J = 7.2$ Hz, 1H), 4.49 (ddd, $J = 9.6, 7.2, 4.0$ Hz, 1H), 2.93 (s, 3H), 2.77 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) 194.2 (C), 167.0 (C), 137.3 (C), 136.3 (C), 133.7 (CH), 129.2 (2 CH), 129.0 (2 CH), 128.30 (2 CH), 128.29 (CH), 128.20 (2 CH), 77.4 (CH_2), 56.0 (CH), 43.8 (CH), 37.8 (CH_3), 36.3 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4+\text{H}]^+$: 341.1496, found: 341.1497.

HPLC Chiralpak AS-H, Hexane/EtOH 95:5, 25 °C, 2.0 mL/min, $\lambda = 254$ nm, *major diastereomer*: $\tau_{\text{major}} = 9.35$ min, $\tau_{\text{minor}} = 13.45$ min; *minor diastereomer*: $\tau_{\text{major}} = 10.67$ min, $\tau_{\text{minor}} = 15.37$ min.

(3R)-2-Acetyl-4-nitro-N,3-diphenylbutanamide 206

Prepared by modifying the general procedure with **chiral squaramide catalyst XXXII** (2.6 mg, 4.0 μmol , 2 mol%), 3-oxo-*N*-phenylbutanamide **205** (70.8 mg, 0.400 mmol, 2 equiv) and (*E*)- β -nitrostyrene **121** (29.8 mg, 0.200 mmol, 1 equiv). Reaction run for 43 h and crude product obtained with 2:1 *dr*. Purification by column chromatography (CH_2Cl_2) afforded **206** as a mixture of the diastereomers (47.6 mg, 0.146 mmol, 73% yield, 95% and 69% *ee*).

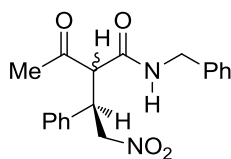
TLC (CH_2Cl_2) R_f 0.13 and 0.31 (UV, vanillin).

^1H NMR (400 MHz, CDCl_3) δ (ppm) *major diastereomer*: 8.30 (s, 1H), 7.52 (dd, $J = 8.5, 1.0$ Hz, 2H), 7.39 – 7.28 (m, 5H), 7.26 – 7.22 (m, 2H), 7.20 – 7.15 (m, 1H), 4.85 – 4.78 (m, 2H), 4.23 (ddd, $J = 11.0, 8.2, 5.9$ Hz, 1H), 3.99 (d, $J = 11.0$ Hz, 1H), 1.96 (s, 3H); *minor diastereomer*: 7.99 (s, 1H), 7.31 – 7.15 (m, 10H), 4.91 (dd, $J = 13.1, 5.9$ Hz, 1H), 4.85 – 4.78 (m, 1H), 4.29 – 4.17 (m, 1H), 4.04 (d, $J = 8.5$ Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) *major diastereomer*: 205.3 (C), 164.2 (C), 137.0 (C), 135.9 (C), 129.6 (2 CH), 129.3 (2 CH), 128.9 (CH), 128.0 (2 CH), 125.5 (CH), 120.3 (2 CH), 78.2 (CH_2), 64.9 (CH), 45.1 (CH), 30.7 (CH_3); *minor diastereomer*: 205.1 (C), 164.1 (C), 136.6 (C), 135.4 (C), 129.3 (2 CH), 129.1 (2 CH), 128.8 (CH), 128.1 (2 CH), 125.3 (CH), 120.7 (2 CH), 77.7 (CH_2), 63.4 (CH), 44.0 (CH), 30.4 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4+\text{H}]^+$: 327.1339, found: 327.1342.

HPLC (*S,S*)-Whelk-O1, Hexane/EtOH 80:20, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 220$ nm, *major diastereomer*: $\tau_{\text{major}} = 14.37$ min, $\tau_{\text{minor}} = 16.28$ min; *minor diastereomer*: $\tau_{\text{major}} = 12.19$ min, $\tau_{\text{minor}} = 16.98$ min.

(3R)-2-Acetyl-N-benzyl-4-nitro-3-phenylbutanamide 207**207**

Prepared by modifying the general procedure with **chiral squaramide catalyst XXXII** (2.6 mg, 4.0 μmol , 2 mol%), *N*-benzyl-3-oxobutanamide **179** (76.4 mg, 0.400 mmol, 2 equiv) and (*E*)- β -nitrostyrene **2a** (29.8 mg, 0.200 mmol, 1 equiv). Reaction run for 43 h and crude product obtained with 2:1 *dr*. Purification by column chromatography (CH_2Cl_2) allowed the only partial separation of both diastereomers of **3b** (53.1 mg, 0.156 mmol, 78 % yield, 69% and 58% *ee*).

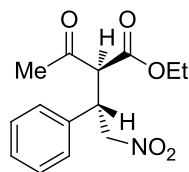
TLC (CH_2Cl_2) *R_f* 0.19 (UV, vanillin).

^1H NMR (400 MHz, CDCl_3) δ (ppm) *major diastereomer*: 7.28 – 7.06 (m, 10H), 6.66 (br s, 1H), 4.68 – 4.56 (m, 2H), 4.35 (dd, *J* = 5.8, 2.0 Hz, 2H), 4.06 (ddd, *J* = 10.6, 9.3, 4.9 Hz, 1H), 3.76 (d, *J* = 10.6 Hz, 1H), 1.84 (s, 3H); *minor diastereomer*: 7.38 – 7.14 (m, 5H), 6.67 – 6.60 (m, 2H), 6.14 (br s, 1H), 4.79 – 4.66 (m, 2H), 4.45 (dd, *J* = 5.7, 3.4 Hz, 1H), 4.27 – 4.10 (m, 2H), 3.91 (d, *J* = 9.6 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ (ppm) *major diastereomer*: 204.5 (C), 166.0 (C), 137.4 (C), 136.3 (C), 129.4 (2 CH), 129.0 (2 CH), 128.6 (CH), 128.0 (CH), 127.9 (2 CH), 127.8 (2 CH), 78.1 (CH_2), 64.2 (CH), 44.7 (CH), 44.2 (CH_2), 30.3 (CH_3); *minor diastereomer*: 204.1 (C), 165.6 (C), 137.1 (C), 136.0 (C), 129.3 (2 CH), 128.8 (2 CH), 128.6 (CH), 128.1 (2 CH), 128.0 (CH), 127.7 (2 CH), 78.0 (CH_2), 63.6 (CH), 44.0 (CH_2), 43.6 (CH), 30.0 (CH_3).

HRMS (ESI) calc'd for $[\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4+\text{H}]^+$: 341.1496, found: 341.1494.

HPLC Chiralpak ID, Hexane/EtOH 80:20, 25 °C, 1.0 mL/min, DAD λ = 220 nm, *major diastereomer*: τ_{major} = 9.67 min, τ_{minor} = 17.26 min; *minor diastereomer*: τ_{major} = 8.73 min, τ_{minor} = 12.45 min.

(2*S*,3*S*)-ethyl 2-acetyl-4-nitro-3-phenylbutanoate 208**208**

Prepared following the general procedure with chiral squaramide catalyst **LXIX** (2.6 mg, 4.0 μmol , 2 mol%), ethyl acetoacetate **51** (25.3 μL , 0.200 mmol, 1 equiv) and (*E*)- β -nitrostyrene **121** (89.4 mg, 0.600 mmol, 3 equiv). Reaction run for 4 h and crude product obtained with 1.2:1 *dr*. Purification by column chromatography (CH_2Cl_2) afforded **208** (46.3 mg, 0.166 mmol, 83% yield, 99% and 99% *ee*).

^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.34 – 7.24 (m, 3H), 7.23 – 7.18 (m, 2H), 4.89 – 4.80 (m, 1H), 4.77 – 7.73 (m, 1H), 4.28 – 4.16 (m, 2H), 4.12 (d, $J = 10.0$ Hz, 0.5H), 4.03 (d, $J = 10$ Hz, 0.5H), 3.96 (q, $J = 7.1$ Hz, 1H), 2.30 (s, 1.5H), 2.05 (s, 1.5H), 1.27 (t, $J = 7.1$ Hz, 1.5H), 1.00 (t, $J = 7.1$ Hz, 1.5H).

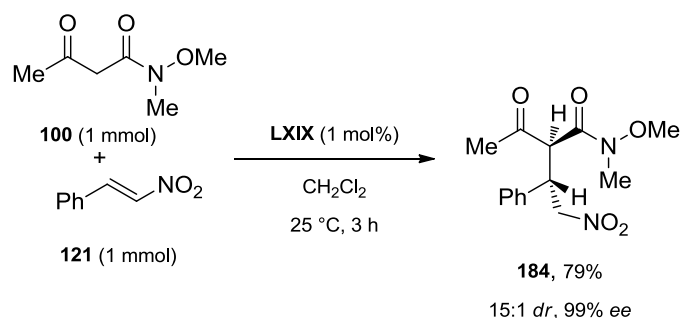
NMR data are in accordance with those reported in the literature.^[315]

HPLC Chiralpak IA, Heptane/EtOH 80:20, 25 $^\circ\text{C}$, 1.0 mL/min, $\lambda = 220$ nm, *major diastereomer*: $\tau_{\text{major}} = 6.73$ min, $\tau_{\text{minor}} = 10.13$ min; *minor diastereomer*: $\tau_{\text{major}} = 8.49$ min, $\tau_{\text{minor}} = 7.77$ min.

IV.3 Preparative-Scale Reactions and Post-Functionalizations:

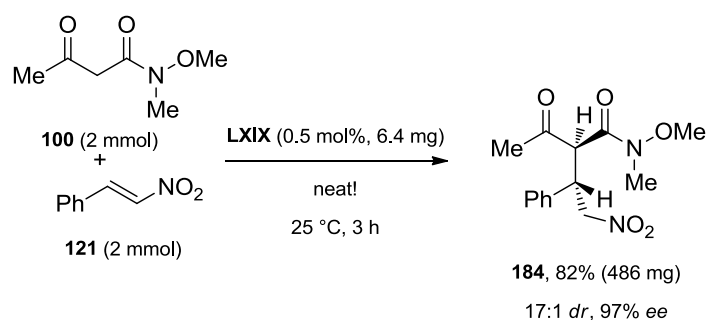
IV.3.1 Preparative-scale reactions:

IV.3.1.1 Preparative-scale reaction (1.00-mmol):



To a solution of chiral squaramide catalyst **LXIX** (6.4 mg, 10.0 μmol , 1 mol%) and *N*-methoxy-*N*-methyl-3-oxobutanamide **100** (145 mg, 1.00 mmol, 1.0 equiv) in dry CH_2Cl_2 (3.0 mL) under argon was added (*E*)- β -nitrostyrene **121** (149 mg, 1.00 mmol, 1.0 equiv). After 5 h of stirring at 25 °C, the solution was filtered through a short pad of silica gel, which was thoroughly washed with CH_2Cl_2 . The solvent was evaporated under reduced pressure to obtain crude compound, which was analyzed by NMR to measure the diastereomeric ratio (15:1 *dr*). Purification by column chromatography (CH_2Cl_2) afforded **184** (232 mg, 0.788 mmol, 79% yield, 99% *ee*). Analyses were in accordance with those obtained when the reaction was run on a 0.2-mmol scale in the standard reaction conditions.

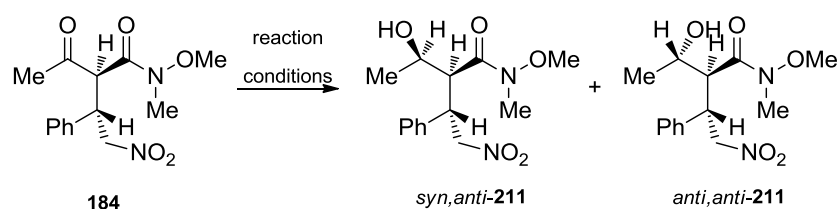
IV.3.1.2 Neat preparative-scale reaction (2.00-mmol):



Chiral squaramide catalyst **LXIX** (6.4 mg, 10.0 μmol , 0.5 mol%),

N-methoxy-*N*-methyl-3-oxobutanamide **100** (290 mg, 2.00 mmol, 1.0 equiv) and (*E*)- β -nitrostyrene **121** (298 mg, 2.00 mmol, 1.0 equiv) were mixed without solvent under argon. After 3 h of stirring at 25 °C, the reaction mixture had become completely solid and was analyzed by NMR to measure the diastereomeric ratio (17:1 *dr*). Purification by column chromatography (CH₂Cl₂) afforded **184** (486 mg, 1.64 mmol, 82% yield, 97% *ee*). Analyses were in accordance with those obtained when the reaction was run on a 0.2-mmol scale in the standard reaction conditions.

IV.3.2 Diastereoselective ketone reduction



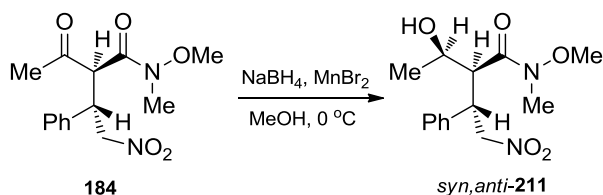
Entry	Reaction conditions	Yield ^a	<i>dr</i> ^b (<i>syn,anti/anti,anti</i>)
1	NaBH ₄ , MnBr ₂ , MeOH, 0 °C, 10 min	75% (<i>syn,anti</i>)	13:1
2	KBHET ₃ , Et ₂ O, -78 °C, 20 min	degradation	-
3	NaBH(OAc) ₃ , AcOH, r.t., 2.5 h	no reaction	-
4	NaBH ₄ , AcOH, r.t., 2.5 h	no reaction	-
5	NaBH ₄ , MeOH, 0 °C, 10 min	45% (<i>anti,anti</i>)	1:2.5
6	NaBH ₄ , CF ₃ CH ₂ OH, 0 °C, 10 min	not purified	3:1
7	NaBH ₄ , MeOH, -40 °C, 4 h	not purified	1:3
8	Me ₄ NBH ₄ , MeOH, 0 °C, 30 min	54% (<i>anti,anti</i>)	1:3
9	Me ₄ NBH ₄ , MeOH, -40 °C, 4 h	78% (<i>anti,anti</i>)	1:7

^aYields of isolated major diastereomer of the product after silica gel column chromatography.

^b*dr* determined by ¹H NMR of the crude reaction mixture.

Reduction of α -chiral β -dicarbonyl compounds by NaBH_4 in the presence of a Lewis acid is known to proceed with *syn,anti* selectivity. When **184** was placed in the presence of NaBH_4 and MnBr_2 in MeOH at 0 °C, the reaction proceeded with high diastereoselectivity (13:1 *dr*) and *syn,anti*-**211** was isolated with 75% yield (entry 1).

On related compounds, KHBEt_3 has been shown to deliver the other diastereomer of the product. However, exposing **184** to this reductant in Et_2O resulted in extensive degradation (entry 2). An alternative is to use $\text{NaBH}(\text{OAc})_3$ or NaBH_4 in AcOH, but **184** was found to be unreactive in these conditions, even at room temperature (entries 3 and 4). Coming back to the most classical conditions for the reduction of ketones to alcohols, i.e. NaBH_4 in MeOH, *anti* reduction could be favored over *syn* reduction, but only with a modest selectivity (1:2.5 *dr*) and product *anti,anti*-**211** was isolated with 45% yield (entry 5). Changing the solvent for 2,2,2-trifluoroethanol or decreasing the temperature to -40 °C was not successful for improving the diastereoselectivity (entries 6 and 7). Non-coordinating Me_4NBH_4 performed a slightly better than NaBH_4 at 0 °C (entry 8) and, in that case, decreasing the reaction temperature to -40 °C allowed to reach 1:7 *dr* (entry 9). After purification, product *anti,anti*-**211** was isolated in a synthetically useful 78% yield.

(2*S*,3*S*)-2-((*R*)-1-hydroxyethyl)-*N*-methoxy-*N*-methyl-4-nitro-3-phenylbutanamide***syn*-211**

Manganese (II) bromide (465 mg, 2.00 mmol, 2 equiv) was added to a solution of **184** (293 mg, 1.00 mmol, 1 equiv) in dry MeOH (10 mL) and the resulting clear solution was stirred for 30 min at 25 °C. The reaction mixture was cooled to 0 °C and NaBH₄ (40.0 mg, 1.00 mmol, 1 equiv) was added. Vigorous gas evolution occurred. After stirring for 10 min at 0 °C, the reaction mixture was poured into 1N HCl and extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. Analysis of the crude product by NMR gave a *syn,anti/anti,anti* ratio of 13:1. Purification by column chromatography (CH₂Cl₂ then CH₂Cl₂/EtOAc 4:1) afforded *syn,anti*-**211** as a white solid (222 mg, 0.750 mmol, 75% yield).

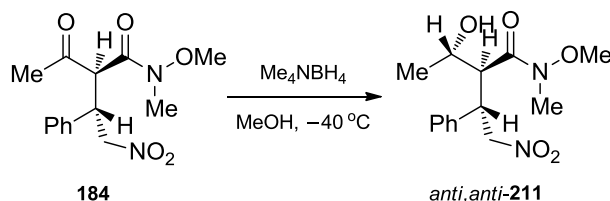
TLC (CH₂Cl₂/EtOAc 2:1) R_f 0.35 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.34 – 7.28 (m, 2H), 7.26 – 7.22 (m, 3H), 5.13 (dd, *J* = 13.3, 10.5 Hz, 1H), 5.06 (dd, *J* = 13.3, 4.5 Hz, 1H), 4.17 – 4.10 (m, 1H), 4.04 – 3.95 (m, 1H), 3.40 (t, *J* = 6.5 Hz, 1H), 3.11 (s, 6H), 2.30 (d, *J* = 3.9 Hz, 1H), 1.23 (d, *J* = 6.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 173.1 (C), 138.7 (C), 129.1 (2 CH), 128.02 (2 CH), 127.98 (CH), 77.0 (CH₂), 67.5 (CH), 61.0 (CH₃), 51.3 (CH), 42.6 (CH), 32.0 (CH₃), 21.3 (CH₃).

HRMS (ESI) calc'd for [C₁₄H₂₀N₂O₅+H]⁺: 297.1445, found: 297.1446.

(2*S*,3*S*)-2-((*S*)-1-hydroxyethyl)-*N*-methoxy-*N*-methyl-4-nitro-3-phenylbutanamide
anti-211



Me₄NBH₄ (17.8 mg, 0.200 mmol, 1 equiv) was added to a solution of **184** (58.5 mg, 0.200 mmol, 1 equiv) in dry MeOH (2 mL) at – 40 °C. After stirring for 4 h at the same temperature, the reaction mixture was poured into 1N HCl and extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. Analysis of the crude product by NMR gave a *syn,anti/anti,anti* ratio of 1:7. Purification by column chromatography (CH₂Cl₂ then CH₂Cl₂/ Et₂O 10:1) afforded *anti,anti*-**211** as a white solid (46.2 mg, 0.156 mmol, 78% yield) and *syn,anti*-**211** as a white solid (7.7 mg, 0.026 mmol, 13% yield).

TLC (CH₂Cl₂) R_f 0.32 (UV, vanillin).

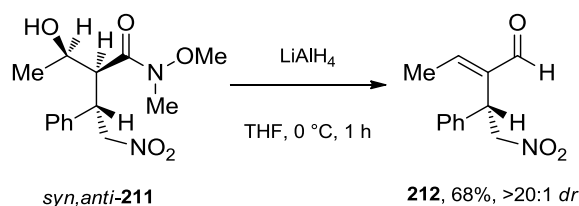
¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.35 – 7.25 (m, 5H), 4.81 (dd, *J* = 12.8, 11.3 Hz, 1H), 4.61 (dd, *J* = 12.8, 4.6 Hz, 1H), 4.14 (td, *J* = 10.6, 4.6 Hz, 1H), 3.61 (s, 3H), 3.60 (s, 1H), 3.58 – 3.53 (m, 1H), 3.24 (s, 3H), 3.17 (dd, *J* = 10.1, 2.3 Hz, 1H), 1.13 (d, *J* = 5.7 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 174.3 (C), 137.6 (C), 129.1 (2 CH), 128.16 (CH), 128.15 (2 CH), 78.2 (CH₂), 66.7 (CH), 61.5 (CH₃), 49.0 (CH), 44.3 (CH), 31.9 (CH₃), 22.5 (CH₃).

HRMS (ESI) calc'd for [C₁₄H₂₀N₂O₅+H]⁺: 297.1445, found: 297.1447.

[α]_D²⁰ = –3.90 (c 0.03, CHCl₃).

IV.3.3 Other post-functionalizations

(*R,E*)-2-(2-nitro-1-phenylethyl)but-2-enal 212

LiAlH₄ (32.3 mg, 0.850 mmol, 5.7 equiv) was added to a solution of *syn,anti*-**211** (44.5 mg, 0.150 mmol, 1 equiv, 99% *ee*) in dry THF (1.6 mL) at 0 °C. The reaction mixture was stirred for 1 h before quenching with EtOAc. After aqueous saturated potassium sodium tartrate was added, the reaction mixture was warmed to room temperature and stirred for 50 min. The layer were separated, and then the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. Analysis of the crude product by NMR gave a *syn,anti/anti,anti* ratio of 1:7. Purification by column chromatography (PE/EtOAc 5:1) afforded **212** as a colorless liquid (23.0 mg, 0.104 mmol, 68% yield, 99% *ee*).

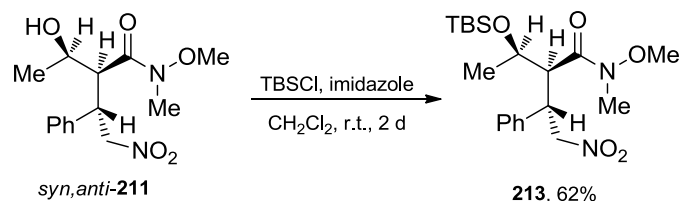
TLC (PE/EtOAc 5:1) R_f 0.48 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.37 (d, *J* = 1.2 Hz, 1H), 7.36 – 7.18 (m, 5H), 6.79 (q, *J* = 7.1 Hz, 1H), 5.31 (dd, *J* = 13.1, 9.0 Hz, 1H), 5.03 (dd, *J* = 13.1, 6.5 Hz, 1H), 4.75 – 4.70 (m, 1H), 2.12 (d, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 194.7 (CH), 154.8 (CH), 141.8 (C), 137.7 (C), 129.1 (2 CH), 127.9 (2 CH), 127.8 (CH), 76.6 (CH₂), 41.3 (CH), 15.3 (CH₃).

HPLC Chiralcel OD-3, Heptane/EtOH 70:30, 25 °C, 1.0 mL/min, λ = 220 nm, τ_{major} = 12.70 min, τ_{minor} = 8.17 min.

[α]_D²⁰ = −41.2 (c 0.05, CHCl₃).

(2*S*,3*S*)-2-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-*N*-methoxy-*N*-methyl-4-nitro-3-phenylbutanamide 213

Imidazole (463 mg, 6.88 mmol, 4 equiv) and TBSCl (769 mg, 5.16 mmol, 3 equiv) were successively added to a solution of alcohol *syn,anti*-**211** (502 mg, 1.72 mmol, 1 equiv) in dry CH₂Cl₂ (7 mL) at 0 °C. A white solid formed. The mixture was allowed to reach room temperature and stirred for 2 days. Filtration on a short pad of silica gel afforded crude product, which was purified by column chromatography (PE/EtOAc 9:1) to afford **213** as a white solid (433 mg, 1.06 mmol, 62% yield).

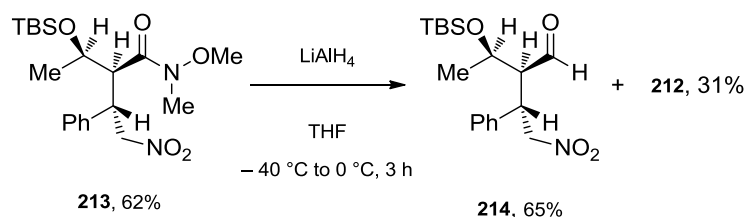
TLC (PE/EtOAc 9:1) R_f 0.12 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.32 – 7.27 (m, 2H), 7.24 – 7.20 (m, 3H), 5.43 – 5.22 (m, 1H), 4.87 (dd, *J* = 13.8, 3.5 Hz, 1H), 4.18 (dt, *J* = 12.0, 3.9 Hz, 1H), 4.01 (dq, *J* = 9.0, 6.0 Hz, 1H), 3.32 (dd, *J* = 9.0, 4.4 Hz, 1H), 3.07 (s, 3H), 2.89 (s, 3H), 1.14 (d, *J* = 6.0 Hz, 3H), 0.96 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 172.9 (C), 139.3 (C), 129.0 (2 CH), 127.9 (2 CH), 127.8 (CH), 75.8 (CH₂), 67.9 (CH), 60.7 (CH₃), 54.0 (CH), 42.2 (CH), 31.9 (CH₃), 26.0 (3 CH₃), 22.3 (CH₃), 18.1 (C), – 3.5 (CH₃), – 4.8 (CH₃).

HRMS (ESI) calc'd for [C₂₀H₃₄N₂O₅Si+H]⁺: 411.2310, found: 411.2310.

[α]_D²⁰ = –3.87 (c 0.01, CHCl₃).

(2*S*,3*S*)-2-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-nitro-3-phenylbutanal **214**

LiAlH₄ (11.3 mg, 0.300 mmol, 1.5 equiv) was added to a solution of **213** (82.0 mg, 0.200 mmol, 1 equiv) in dry THF (1.7 mL) at $-40\text{ }^\circ\text{C}$. The reaction mixture was stirred for 2 h, then warmed to $0\text{ }^\circ\text{C}$ and stirred on for 1 h before quenching with EtOAc. After aqueous saturated potassium sodium tartrate was added, the reaction mixture was warmed to room temperature and stirred for 50 min. The organic layer was separated, and then the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. Purification by column chromatography (PE/EtOAc 5:1) afforded **214** as a white solid (45.6 mg, 0.130 mmol, 65% yield) and **212** as a colorless liquid (14.0 mg, 0.062 mmol, 31% yield).

TLC (PE/Et₂O 5:1) R_f 0.28 (UV, vanillin).

¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.95 (d, *J* = 1.1 Hz, 1H), 7.38 – 7.26 (m, 3H), 7.21 – 7.17 (m, 2H), 4.90 (dd, *J* = 12.7, 4.1 Hz, 1H), 4.68 (dd, *J* = 12.7, 10.3 Hz, 1H), 3.84 (qd, *J* = 6.4, 4.6 Hz, 1H), 3.78 (td, *J* = 10.0, 4.1 Hz, 1H), 3.02 (ddd, *J* = 9.9, 4.5, 1.1 Hz, 1H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.85 (s, 9H), -0.01 (s, 3H), -0.05 (s, 3H).

¹³C NMR (101 MHz, CDCl₃) δ (ppm) 204.2 (CH), 137.3 (C), 129.3 (2 CH), 128.3 (CH), 128.0 (2 CH), 78.7 (CH₂), 68.0 (CH), 60.2 (CH), 40.9 (CH), 25.8 (3 CH₃), 19.8 (CH₃), 18.0 (C), -4.6 (CH₃), -5.0 (CH₃).

HRMS (ESI) calc'd for [C₁₈H₂₉NO₄Si+H]⁺: 352.1939, found: 352.1941.

[α]_D²⁰ = -0.82 (c 0.01, CHCl₃).

REFERENCES

REFERENCES

- [1] T. Komnenos, *Liebigs Ann. Chem.* **1883**, 218, 145-169.
- [2] A. Michael, *J. Prakt. Chem.* **1887**, 35, 349-356.
- [3] T. Tokoroyama, *Eur. J. Org. Chem.* **2010**, 2009-2016.
- [4] D. Rele, G. K. Trivedi, *J. Sci. Ind. Res.* **1993**, 52, 13-28.
- [5] J. Leonard, E. Díez-Barra, S. Merino, *Eur. J. Org. Chem.* **1998**, 2051-2061.
- [6] A. Berkessel, H. Gröger, in *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**, pp. 45-84.
- [7] B. D. Mather, K. Viswanathan, K. M. Miller, T. E. Long, *Prog. Polym. Sci.* **2006**, 31, 487-531.
- [8] R. R. Torres, *Stereoselective organocatalysis: Bond Formation Methodologies and Activation Modes* Wiley-VCH, Weinheim, **2013**.
- [9] P. I. Dalko, *Comprehensive Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2013**.
- [10] J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, *Organocatalytic Enantioselective Conjugate Addition Reactions: A powerful Tool for the Stereocontrolled Synthesis of Complex Molecules*, RSC, Cambridge, **2010**.
- [11] B. List, *Chem. Rev.* **2007**, 107, 5413-5415.
- [12] K. Mikami, M. Lautens, *New Frontiers in Asymmetric Catalysis*, Wiley-VCH, Weinheim, **2007**.
- [13] P. I. Dalko, *Enantioselective Organocatalysis: Reactions and Experimental Procedures*, Wiley-VCH, Weinheim, **2007**.
- [14] D. W. C. Macmillan, *Nature* **2008**, 455, 304-308.
- [15] X. Linghu, J. R. Potnick, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, 126, 3070-3071.
- [16] J. C. Ruble, H. A. Latham, G. C. Fu, *J. Am. Chem. Soc.* **1997**, 119, 1492-1493.
- [17] J. C. Ruble, J. Tweddell, G. C. Fu, *J. Org. Chem.* **1998**, 63, 2794-2795.
- [18] E. N. Jacobsen, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2010** 107, 20618-20619.

- [19] A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182-1195.
- [20] V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691-2698.
- [21] X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511-3522.
- [22] E. Marques-Lopez, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138-1167.
- [23] S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183-188.
- [24] M. J. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8-27.
- [25] G. Bredig, R. W. Balcom, *Ber. Deusch. Chem. Ger.* **1908**, *41*, 740-751.
- [26] G. Bredig, K. Fajans, *Ber. Deusch. Chem. Ger.* **1908**, *41*, 752-763.
- [27] W. Langenbeck, *Angew. Chem.* **1928**, *41*, 740-745.
- [28] G. Bredig, P. S. Fiske, *Biochem. Z.* **1912**, *46*, 7-23.
- [29] H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9-22.
- [30] B. Langström, G. Bergson, *Acta Chem. Scand.* **1973**, *27*, 3118-3119.
- [31] R. Helder, H. Wynberg, *Tetrahedron Lett.* **1975**, *16*, 4057-4060.
- [32] K. Hermann, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 2238.
- [33] H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417-430.
- [34] H. Wynberg, *Top. Stereochem.* **1986**, *16*, 87.
- [35] B. List, in *Asymmetric Organocatalysis I Lewis Base and Acid Catalysts*, Thieme, Stuttgart, **2012**.
- [36] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.
- [37] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615-1621.
- [38] B. List, R. A. Lerner, C. F. Barbas, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.
- [39] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.
- [40] T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744-5758.

- [41] D. Bonne, T. Constantieux, Y. Coquerel, J. Rodriguez, *Chem. Eur. J.* **2013**, *19*, 2218-2231.
- [42] X. Bugaut, D. Bonne, Y. Coquerel, J. Rodriguez, T. Constantieux, *Curr. Org. Chem.* **2013**, *17*, 1920-1928.
- [43] J. L. Vicarion, D. Badia, L. Carrillo, E. Reyes, in *RSC, Cambridge*, **2010**.
- [44] J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719-724.
- [45] J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, *14*, 2065-2092.
- [46] A. Kawara, T. Taguchi, *Tetrahedron Lett.* **1994**, *35*, 8805-8808.
- [47] M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520-3530.
- [48] N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 661-665.
- [49] N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 4955-4957.
- [50] K. R. Knudsen, C. E. T. Mitchell, S. V. Ley, *Chem. Commun.* **2006**, 66-68.
- [51] Z. Dong, L. Wang, X. Chen, X. Liu, L. Lin, X. Feng, *Eur. J. Org. Chem.* **2009**, 5192-5197.
- [52] X. Zhu, A. Lin, Y. Shi, J. Guo, C. Zhu, Y. Cheng, *Org. Lett.* **2011**, *13*, 4382-4385.
- [53] S. Brandau, A. Landa, J. Franzén, M. Marigo, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, *45*, 4305-4309.
- [54] X. Zhang, W. Yuan, Y. Luo, Q.-Q. Huang, W. Lua, *Heterocycles* **2012**, *85*, 73-84.
- [55] E. Adi Prasetyanto, S.-C. Lee, S.-M. Jeong, S.-E. Park, *Chem. Commun.* **2008**, 1995-1997.
- [56] O. V. Maltsev, A. S. Kucherenko, S. G. Zlotin, *Eur. J. Org. Chem.* **2009**, 5134-5137.
- [57] K. Dudzinski, A. M. Pakulska, P. Kwiatkowski, *Org. Lett.* **2012**, *14*, 4222-4225.
- [58] M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 5672-5673.
- [59] J. Hine, S. M. Linden, V. M. Kanagasabapathy, *J. Am. Chem. Soc.* **1985**, *107*, 1082-1083.
- [60] A. Lattanzi, *Tetrahedron: Asymmetry* **2006**, *17*, 837-841.
- [61] A. Lattanzi, C. De Fusco, A. Russo, A. Poater, L. Cavallo, *Chem. Commun.* **2012**, *48*, 1650-1652.

- [62] C. E. Song, *Cinchona Alkaloids in Synthesis and Catalysis Ligands Immobilization and Organocatalysis*, Wiley-VCH, Weinheim, **2009**.
- [63] F. Giacalone, M. Gruttadauria, P. Agrigento, R. Noto, *Chem. Soc. Rev.* **2012**, *41*, 2406-2447.
- [64] J.-W. Xie, L. Yue, W. Chen, W. Du, J. Zhu, J.-G. Deng, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 413-415.
- [65] J. Luo, L.-W. Xu, R. A. S. Hay, Y. Lu, *Org. Lett.* **2009**, *11*, 437-440.
- [66] P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 9748-9770.
- [67] H. Li, Y. Wang, L. Tang, L. Deng, *J. Am. Chem. Soc.* **2004**, *126*, 9906-9907.
- [68] F. Wu, R. Hong, J. Khan, X. Liu, L. Deng, *Angew. Chem. Int. Ed.* **2006**, *45*, 4301-4305.
- [69] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902.
- [70] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673.
- [71] T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119-125.
- [72] A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151-13160.
- [73] Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299-4306.
- [74] S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418-5427.
- [75] J. M. Andrés, R. Manzano, R. Pedrosa, *Chem. Eur. J.* **2008**, *14*, 5116-5119.
- [76] X. Jiang, Y. Zhang, X. Liu, G. Zhang, L. Lai, L. Wu, J. Zhang, R. Wang, *J. Org. Chem.* **2009**, *74*, 5562-5567.
- [77] X. Pu, P. Li, F. Peng, X. Li, H. Zhang, Z. Shao, *Eur. J. Org. Chem.* **2009**, 4622-4626.
- [78] P. Gao, C. Wang, Y. Wu, Z. Zhou, C. Tang, *Eur. J. Org. Chem.* **2008**, 4563-4566.
- [79] B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967-1969.
- [80] S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367-6370.
- [81] J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481-4483.
- [82] P. S. Hynes, P. A. Stupple, D. J. Dixon, *Org. Lett.* **2008**, *10*, 1389-1391.

- [83] J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713-4716.
- [84] F.-Z. Peng, Z.-H. Shao, B.-M. Fan, H. Song, G.-P. Li, H.-B. Zhang, *J. Org. Chem.* **2008**, *73*, 5202-5205.
- [85] Y. Gao, Q. Ren, L. Wang, J. Wang, *Chem. Eur. J.* **2010**, *16*, 13068-13071.
- [86] M. M. Sanchez Duque, O. Baslé, N. Isambert, A. Gaudel-Siri, Y. Génisson, J.-C. Plaquevent, J. Rodriguez, T. Constantieux, *Org. Lett.* **2011**, *13*, 3296-3299.
- [87] P. Jakubec, D. M. Cockfield, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 16632-16633.
- [88] X. Li, H. Deng, B. Zhang, J. Li, L. Zhang, S. Luo, J.-P. Cheng, *Chem. Eur. J.* **2010**, *16*, 450-455.
- [89] X. Han, J. Luo, C. Liu, Y. Lu, *Chem. Commun.* **2009**, 2044-2046.
- [90] P. Jakubec, D. M. Cockfield, P. S. Hynes, E. Cleator, D. J. Dixon, *Tetrahedron: Asymmetry* **2011**, *22*, 1147-1155.
- [91] X. Chen, W. Zhu, W. Qian, E. Feng, Y. Zhou, J. Wang, H. Jiang, Z.-J. Yao, H. Liu, *Adv. Synth. Catal.* **2012**, *354*, 2151-2156.
- [92] C.-Y. Jin, Y. Wang, Y.-Z. Liu, C. Shen, P.-F. Xu, *J. Org. Chem.* **2012**, *77*, 11307-11312.
- [93] N. Molleti, S. Allu, S. K. Ray, V. K. Singh, *Tetrahedron Lett.* **2013**, *54*, 3241-3244.
- [94] H.-H. Zou, J. Hu, J. Zhang, J.-S. You, D. Ma, D. Lu, R.-G. Xie, *J. Mol. Catal. A: Chem.* **2005**, *242*, 57-61.
- [95] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416-14417.
- [96] D.-Q. Xu, Y.-F. Wang, W. Zhang, S.-P. Luo, A.-G. Zhong, A.-B. Xia, Z.-Y. Xu, *Chem. Eur. J.* **2010**, *16*, 4177-4180.
- [97] Z. Dong, G. Qiu, H.-B. Zhou, C. Dong, *Tetrahedron: Asymmetry* **2012**, *23*, 1550-1556.
- [98] B. Liu, X. Han, Z. Dong, H. Lv, H.-B. Zhou, C. Dong, *Tetrahedron: Asymmetry* **2013**, *24*, 1276-1280.
- [99] D. Mailhol, M. M. Sanchez Duque, W. Raimondi, D. Bonne, T. Constantieux, Y. Coquerel, J. Rodriguez, *Adv. Synth. Catal.* **2012**, *354*, 3523-3532.
- [100] H. Y. Bae, S. Some, J. S. Oh, Y. S. Lee, C. E. Song, *Chem. Commun.* **2011**, *47*, 9621-9623.
- [101] J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890-6899.

- [102] B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631-5639.
- [103] D. Almasi, D. A. Alonso, E. Gómez-Bengoa, C. Nájera, *J. Org. Chem.* **2009**, *74*, 6163-6168.
- [104] E. Gómez-Torres, D. A. Alonso, E. Gómez-Bengoa, C. Nájera, *Org. Lett.* **2011**, *13*, 6106-6109.
- [105] M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454-1455.
- [106] C.-J. Wang, Z.-H. Zhang, X.-Q. Dong, X.-J. Wu, *Chem. Commun.* **2008**, 1431-1433.
- [107] P. Li, S. Wen, F. Yu, Q. Liu, W. Li, Y. Wang, X. Liang, J. Ye, *Org. Lett.* **2009**, *11*, 753-756.
- [108] J. Yang, W. Li, Z. Jin, X. Liang, J. Ye, *Org. Lett.* **2010**, *12*, 5218-5221.
- [109] C. M. Starks, *J. Am. Chem. Soc.* **1971**, *93*, 195-199.
- [110] T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107*, 5656-5682.
- [111] A. Loupy, J. Sansoulet, A. Zaparucha, C. Merienne, *Tetrahedron Lett.* **1989**, *30*, 333-336.
- [112] A. Loupy, A. Zaparucha, *Tetrahedron Lett.* **1993**, *34*, 473-476.
- [113] T. Perrard, J.-C. Plaquevent, J.-R. Desmurs, D. Hebrault, *Org. Lett.* **2000**, *2*, 2959-2962.
- [114] D. Y. Kim, S. C. Huh, S. M. Kim, *Tetrahedron Lett.* **2001**, *42*, 6299-6301.
- [115] R. T. Dere, R. R. Pal, P. S. Patil, M. M. Salunkhe, *Tetrahedron Lett.* **2003**, *44*, 5351-5353.
- [116] T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi, K. Maruoka, *Angew. Chem. Int. Ed.* **2003**, *42*, 3796-3798.
- [117] T. Ooi, D. Ohara, K. Fukumoto, K. Maruoka, *Org. Lett.* **2005**, *7*, 3195-3197.
- [118] T. B. Poulsen, L. Bernardi, M. Bell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2006**, *45*, 6551-6554.
- [119] T. B. Poulsen, L. Bernardi, J. Aleman, J. Overgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 441-449.
- [120] L. Bernardi, J. López-Cantarero, B. Niess, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 5772-5778.

- [121] P. Elsner, L. Bernardi, G. D. Salla, J. Overgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2008**, *130*, 4897-4905.
- [122] S. Tarí, R. Chinchilla, C. Nájera, *Tetrahedron: Asymmetry* **2009**, *20*, 2651-2654.
- [123] B. Pignataro, *New Strategies in Chemical Synthesis and Catalysis*, Wiley-VCH, Weinheim, **2012**.
- [124] R. Sheldon, A., I. Arends, U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, **2007**.
- [125] L. F. Tietze, H. P. Bell, G. Brasche, Eds., *Domino reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.
- [126] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115-136.
- [127] D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* **2007**, *46*, 1570-1581.
- [128] C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.* **2013**, *114*, 2390-2431.
- [129] X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037-2046.
- [130] T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951-6954.
- [131] A.-N. Alba, X. Companyo, M. Viciano, R. Rios, *Curr. Org. Chem.* **2009**, *13*, 1432-1474.
- [132] P. T. Franke, R. L. Johansen, S. Bertelsen, K. A. Jørgensen, *Chem. Asian J.* **2008**, *3*, 216-224.
- [133] H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886-10894.
- [134] R. Rios, H. Sundén, J. Vesely, G.-L. Zhao, P. Dziejczak, A. Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1028-1032.
- [135] X. Companyó, A.-N. Alba, F. Cárdenas, A. Moyano, R. Rios, *Eur. J. Org. Chem.* **2009**, 3075-3080.
- [136] R. Rios, J. Vesely, H. Sundén, I. Ibrahim, G.-L. Zhao, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 5835-5839.
- [137] L. Zu, H. Li, H. Xie, J. Wang, W. Jiang, Y. Tang, W. Wang, *Angew. Chem. Int. Ed.* **2007**, *46*, 3732-3734.
- [138] J. Wang, H. Li, H. Xie, L. Zu, X. Shen, W. Wang, *Angew. Chem. Int. Ed.* **2007**, *46*, 9050-9053.
- [139] P. G. McGarraugh, S. E. Brenner, *Org. Lett.* **2009**, *11*, 5654-5657.

- [140] A. Ma, D. Ma, *Org. Lett.* **2010**, *12*, 3634-3637.
- [141] N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 1272-1277.
- [142] M. Marigo, S. Bertelsen, A. Landa, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 5475-5479.
- [143] A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, 4928-4930.
- [144] S. Cabrera, J. Alemán, P. Bolze, S. Bertelsen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2008**, *47*, 121-125.
- [145] S. Bertelsen, R. L. Johansen, K. A. Jørgensen, *Chem. Commun.* **2008**, 3016-3018.
- [146] Y. Hayashi, M. Toyoshima, H. Gotoh, H. Ishikawa, *Org. Lett.* **2009**, *11*, 45-48.
- [147] Y.-K. Liu, C. Ma, K. Jiang, T.-Y. Liu, Y.-C. Chen, *Org. Lett.* **2009**, *11*, 2848-2851.
- [148] S. P. Lathrop, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13628-13630.
- [149] J. Franzén, A. Fisher, *Angew. Chem. Int. Ed.* **2009**, *48*, 787-791.
- [150] W. Zhang, J. Franzén, *Adv. Synth. Catal.* **2010**, *352*, 499-518.
- [151] G. Valero, J. Schimer, I. Cisarova, J. Vesely, A. Moyano, R. Rios, *Tetrahedron Lett.* **2009**, *50*, 1943-1946.
- [152] Z. Jin, H. Huang, W. Li, X. Luo, X. Liang, J. Ye, *Adv. Synth. Catal.* **2011**, *353*, 343-348.
- [153] Z. Jin, X. Wang, H. Huang, X. Liang, J. Ye, *Org. Lett.* **2011**, *13*, 564-567.
- [154] X. Wu, X. Dai, L. Nie, H. Fang, J. Chen, Z. Ren, W. Cao, G. Zhao, *Chem. Commun.* **2010**, *46*, 2733-2735.
- [155] M. Rueping, C. M. R. Volla, M. Bolte, G. Raabe, *Adv. Synth. Catal.* **2011**, *353*, 2853-2859.
- [156] M. Rueping, C. M. R. Volla, *RSC Adv.* **2011**, *1*, 79-82.
- [157] B. Bradshaw, C. Parra, J. Bonjoch, *Org. Lett.* **2013**, *15*, 2458-2461.
- [158] Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 9185-9188.
- [159] Y. Hoashi, T. Yabuta, P. Yuan, H. Miyabe, Y. Takemoto, *Tetrahedron* **2006**, *62*, 365-374.

- [160] S. H. McCooey, T. McCabe, S. J. Connon, *J. Org. Chem.* **2006**, *71*, 7494-7497.
- [161] Y.-N. Xuan, S.-Z. Nie, L.-T. Dong, J.-M. Zhang, M. Yan, *Org. Lett.* **2009**, *11*, 1583-1586.
- [162] B. Tan, Z. Shi, P. J. Chua, G. Zhong, *Org. Lett.* **2008**, *10*, 3425-3428.
- [163] B. Tan, P. J. Chua, X. Zeng, M. Lu, G. Zhong, *Org. Lett.* **2008**, *10*, 3489-3492.
- [164] T. Akiyama, T. Katoh, K. Mori, *Angew. Chem. Int. Ed.* **2009**, *48*, 4226-4228.
- [165] M. Rueping, A. Parra, U. Uria, F. Besselièvre, E. Merino, *Org. Lett.* **2010**, *12*, 5680-5683.
- [166] X. Dou, X. Han, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 85-89.
- [167] L. Wen, L. Yin, Q. Shen, L. Lu, *ACS Catalysis* **2013**, *3*, 502-506.
- [168] S. Gouedranche, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Chem. Eur. J.* **2014**, *20*, 410-415.
- [169] J. Zhu, H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**.
- [170] C. M. Marson, *Chem. Soc. Rev.* **2012**, *41*, 7712-7722.
- [171] H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321-3329.
- [172] R. C. Cioc, E. Ruijter, R. V. A. Orru, *Green Chem.* **2014**, *16*, 2958-2975.
- [173] B. M. Trost, *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259-281.
- [174] C. de Graaff, E. Ruijter, R. V. A. Orru, *Chem. Soc. Rev.* **2012**, *41*, 3969-4009.
- [175] S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2003**, *125*, 7825-7827.
- [176] A. Dömling, I. Ugi, *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.
- [177] I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückne, *Angew. Chem.* **1959**, *71*, 373-388.
- [178] M. Passerini, L. Simone, *Gazz. Chim. Ital.* **1921**, 126-129.
- [179] A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083-3135.
- [180] A. Hantzsch, *Chem. Ber.* **1881**, *14*, 1637-1638.
- [181] P. Biginelli, *Chem. Ber.* **1891**, *24*, 1317-1319.
- [182] F. Jaisli, A. Eschenmoser, M. Shibuya, *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 636-637.

- [183] C. Simon, J.-F. Peyronel, J. Rodriguez, *Org. Lett.* **2001**, *3*, 2145-2148.
- [184] C. Simon, F. Liéby-Muller, J.-F. Peyronel, T. Constantieux, J. Rodriguez, *Synlett* **2003**, 2301-2304.
- [185] F. Liéby-Muller, T. Constantieux, J. Rodriguez, *Synlett* **2007**, 1323-1325.
- [186] F. Liéby-Muller, T. Constantieux, J. Rodriguez, *J. Am. Chem. Soc.* **2005**, *127*, 17176-17177.
- [187] R. Noël, M.-C. Fargeau-Bellassoued, C. Vanucci-Bacqué, G. Lhommet, *Synthesis* **2008**, 1948-1954.
- [188] V. Sridharan, J. C. Menéndez, *Org. Lett.* **2008**, *10*, 4303-4306.
- [189] P. A. Suryavanshi, V. Sridharan, J. C. Menéndez, *Chem. Eur. J.* **2013**, *19*, 13207-13215.
- [190] D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861-863.
- [191] J. M. Betancort, K. Sakthivel, R. Thayumanavan, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 4441-4444.
- [192] Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, P.-F. Xu, D. J. Dixon, *Angew. Chem. Int. Ed.* **2009**, *48*, 9834-9838.
- [193] D. Enders, G. Urbanietz, E. Cassens-Sasse, S. Keeß, G. Raabe, *Adv. Synth. Catal.* **2012**, *354*, 1481-1488.
- [194] M. M. Sanchez Duque, O. Baslé, Y. Génisson, J.-C. Plaquevent, X. Bugaut, T. Constantieux, J. Rodriguez, *Angew. Chem. Int. Ed.* **2013**, *52*, 14143-14146.
- [195] D. Bonne, Y. Coquerel, T. Constantieux, J. Rodriguez, *Tetrahedron: Asymmetry* **2010**, *21*, 1085-1109.
- [196] S. Hayashibe, S. Yamasaki, N. Shiraishi, H. Hoshii, T. Tobe, in *PCT Int. Appl.*, Vol. WO 2009069610 A1 20090604, Japan, **2009**.
- [197] R. N. Schut, T. M. H. Liu, *J. Org. Chem.* **1965**, *30*, 2845-2847.
- [198] R. N. Schut, F. E. Ward, R. Rodriguez, *J. Med. Chem.* **1972**, *15*, 301-304.
- [199] R. N. Schut, Vol. US 3354161 19671121, U.S., **1967**.
- [200] J. G. Diaz, J. G. Ruiza, H. Werner, *Phytochemistry* **2005**, *66*, 837-846.
- [201] G. Valero, J. Schimer, I. Cisarova, J. Vesely, A. Moyano, R. Rios, *Tetrahedron Lett.* **2009**, *50*, 1943-1946.

- [202] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed.* **1971**, *10*, 496-497.
- [203] R. I. Storer, C. Aciro, L. H. Jones, *Chem. Soc. Rev.* **2011**, *40*, 2330-2346.
- [204] M.-H. Filippini, R. Faure, J. Rodriguez, *J. Org. Chem.* **1995**, *60*, 6872-6882.
- [205] J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 10954-10990.
- [206] I. L. Jirkovsky, *Vol. 4,188,389*, United States, **1980**.
- [207] A. J. Ratcliffe, R. J. A. Walsh, T. N. Majid, S. Thurairatnam, S. Amendola, D. J. Aldous, J. E. Souness, C. Nemecek, S. Wentzler, C. Venot, *Vol. WO 03/024967 A2*, **2003**.
- [208] J. P. Cain, A. V. Mayorov, M. Cai, H. Wang, B. Tan, K. Chandler, Y. Lee, R. R. Petrov, D. Trivedi, V. J. Hruby, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5462-5467.
- [209] B. Merla, T. Christoph, S. Oberbörsch, K. Schiene, G. Bahrenberg, R. Frank, S. Kühnert, W. Schröder, in *WO 2008/046582 A1*, **2008**.
- [210] W. Zhang, J. Bah, A. Wohlfarth, J. Franzén, *Chem. Eur. J.* **2011**, *17*, 13814-13824.
- [211] X. Dai, X. Wu, H. Fang, L. Nie, J. Chen, H. Deng, W. Cao, G. Zhao, *Tetrahedron* **2011**, *67*, 3034-3040.
- [212] X. Wu, H. Fang, Q. Liu, L. Nie, J. Chen, W. Cao, G. Zhao, *Tetrahedron* **2011**, *67*, 7251-7257.
- [213] X. Wu, Y. Zhang, X. Dai, H. Fang, J. Chen, W. Cao, G. Zhao, *Synthesis* **2011**, 3675-3679.
- [214] S. Lin, L. Deiana, A. Tseggai, A. Córdova, *Eur. J. Org. Chem.* **2012**, 398-408.
- [215] B.-C. Hong, W.-K. Liao, N. S. Dange, J.-H. Liao, *Org. Lett.* **2013**, *15*, 468-471.
- [216] M. Rueping, E. Merino, E. Sugiono, *Adv. Synth. Catal.* **2008**, *350*, 2127-2131.
- [217] Kindly provided by D. Wilhelm from Clariant Specialty Fine Chemicals.
- [218] T. A. Nigst, M. Westermaier, A. R. Ofial, H. Mayr, *Eur. J. Org. Chem.* **2008**, 2369-2374.
- [219] M. M. C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 4572-4573.
- [220] T. D. Lash, D. T. Richter, C. M. Shiner, *J. Org. Chem.* **1999**, *64*, 7973-7982.
- [221] Y. He, M. Lin, Z. Li, X. Liang, G. Li, J. C. Antilla, *Org. Lett.* **2011**, *13*, 4490-4493.

- [222] W. E. Noland, N. P. Lanzatella, L. Venkatraman, N. F. Anderson, G. C. Gullickson, *J. Heterocycl. Chem.* **2009**, *46*, 1154-1176.
- [223] W. Jie, X. Xiao-Yu, L. Ke-Liang, *Chin. J. Chem.* **2003**, *21*, 566-573.
- [224] N. D. Smith, D. Huang, N. D. P. Cosford, *Org. Lett.* **2002**, *4*, 3537-3539.
- [225] A. M. Cuadro, M. P. Matia, J. L. Garcia, J. J. Vaquero, J. Alvarez-Builla, *Synth. Commun.* **1991**, *21*, 535-544.
- [226] C. G. Evans, J. E. Gestwicki, *Org. Lett.* **2009**, *11*, 2957-2959.
- [227] M. Rueping, E. Sugiono, E. Merino, *Chem. Eur. J.* **2008**, *14*, 6329-6332.
- [228] M. d. M. Sanchez Duque, O. Baslé, N. Isambert, A. Gaudel-Siri, Y. Génisson, J.-C. Plaquevent, J. Rodriguez, T. Constantieux, *Org. Lett.* **2011**, *13*, 3296-3299.
- [229] V. K. Khlestkin, D. G. Mazhukin, *Curr. Org. Chem.* **2003**, *7*, 967.
- [230] S. Balasubramaniam, I. S. Aidhen, *Synthesis* **2008**, *23*, 3707-3738.
- [231] W. Ye, Z. Jiang, Y. Zhao, S. L. M. Goh, D. Leow, Y.-T. Soh, C.-H. Tan, *Adv. Synth. Catal.* **2007**, *349*, 2454-2458.
- [232] J. L. Marco, *J. Org. Chem.* **1997**, *62*, 6575-6581.
- [233] H. Yang, R. G. Carter, L. N. Zakharov, *J. Am. Chem. Soc.* **2008**, *130*, 9238-9239.
- [234] C. Cassani, L. Bernardi, F. Fini, A. Ricci, *Angew. Chem. Int. Ed.* **2009**, *48*, 5694-5697.
- [235] M. Nielsen, C. B. Jacobsen, M. W. Paixão, N. Holub, K. A. Jørgensen, *J. Am. Chem. Soc.* **2009**, *131*, 10581-10586.
- [236] S. Kiren, A. Padwa, *J. Org. Chem.* **2009**, *74*, 7781-7789.
- [237] J. Alemán, V. Marcos, L. Marzo, J. L. García Ruano, *Eur. J. Org. Chem.* **2010**, 4482-4491.
- [238] D. Enders, A. Grossmann, H. Huang, G. Raabe, *Eur. J. Org. Chem.* **2011**, 4298-4301.
- [239] N. Holub, H. Jiang, M. W. Paixão, C. Tiberi, K. A. Jørgensen, *Chem. Eur. J.* **2010**, *16*, 4337-4346.
- [240] S. Delarue-Cochin, J.-J. Pan, A. Dauteloup, F. Hendra, R. G. Angoh, D. Joseph, P. J. Stephens, C. Cavé, *Tetrahedron: Asymmetry* **2007**, *18*, 685-691.
- [241] Ł. Albrecht, B. Richter, C. Vila, H. Krawczyk, K. A. Jørgensen, *Chem. Eur. J.* **2009**, *15*, 3093-3102.

- [242] K. Hu, T. Liu, A. D. Lu, Y. Liu, Y. Wang, G. Wu, Z. Zhou, C. Tang, *Eur. J. Org. Chem.* **2011**, 3507-3513.
- [243] P. S. Baran, E. J. Corey, *J. Am. Chem. Soc.* **2002**, *124*, 7904-7905.
- [244] T. Kawasaki, A. Ogawa, Y. Takashima, M. Sakamoto, *Tetrahedron Lett.* **2003**, *44*, 1591-1593.
- [245] T. Kawasaki, M. Shinada, M. Ohzono, A. Ogawa, R. Terashima, M. Sakamoto, *J. Org. Chem.* **2008**, *73*, 5959-5964.
- [246] B. Guyen, C. M. Schultes, P. Hazel, J. Mann, S. Neidle, *Org. Biomol. Chem.* **2004**, *2*, 981-988.
- [247] T. Kawasaki, M. Shinada, D. Kamimura, M. Ohzono, A. Ogawa, *Chem. Commun.* **2006**, 420-422.
- [248] S. Takiguchi, T. Iizuka, Y.-s. Kumakura, K. Murasaki, N. Ban, K. Higuchi, T. Kawasaki, *J. Org. Chem.* **2010**, *75*, 1126-1131.
- [249] Y.-Z. Liu, R.-L. Cheng, P.-F. Xu, *J. Org. Chem.* **2011**, *76*, 2884-2887.
- [250] Y.-Z. Liu, J. Zhang, P.-F. Xu, Y.-C. Luo, *J. Org. Chem.* **2011**, *76*, 7551-7555.
- [251] W. Sun, L. Hong, R. Wang, *Chem. Eur. J.* **2011**, *17*, 6030-6033.
- [252] S. Torii, T. Yamanaka, H. Tanaka, *J. Org. Chem.* **1978**, *43*, 2882-2885.
- [253] X. Companyo, A. Zea, A.-N. R. Alba, A. Mazzanti, A. Moyano, R. Rios, *Chem. Commun.* **2010**, *46*, 6953-6955.
- [254] N. Bravo, I. Mon, X. Companyó, A.-N. Alba, A. Moyano, R. Rios, *Tetrahedron Lett.* **2009**, *50*, 6624-6626.
- [255] R. A. Jones, M. T. P. Marriott, W. P. Rosenthal, J. Sepulveda Arques, *J. Org. Chem.* **1980**, *45*, 4515-4519.
- [256] J. A. Marshall, W. S. Johnson, *J. Org. Chem.* **1963**, *28*, 421-423.
- [257] X. Wu, L. Nie, H. Fang, J. Chen, W. Cao, G. Zhao, *Eur. J. Org. Chem.* **2011**, 6755-6763.
- [258] G. Bartoli, C. Cimarelli, E. Marcantoni, G. Palmieri, M. Petrini, *J. Org. Chem.* **1994**, *59*, 5328-5335.
- [259] J. Jiang, J. Yu, X.-X. Sun, Q.-Q. Rao, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2008**, *47*, 2458-2462.
- [260] Y. Zhang, A. I. Gerasyuto, Q. A. Long, R. P. Hsung, *Synlett* **2009**, 237-240.

- [261] L. Shi, Z.-S. Ye, L.-L. Cao, R.-N. Guo, Y. Hu, Y.-G. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 8286-8289.
- [262] A. P. Kozikowski, G. L. Araldi, J. Boja, W. M. Meil, K. M. Johnson, J. L. Flippen-Anderson, C. George, E. Saiah, *J. Med. Chem.* **1998**, *41*, 1962-1969.
- [263] J. Takaya, K. Sasano, N. Iwasawa, *Org. Lett.* **2011**, *13*, 1698-1701.
- [264] H. Du, J. Rodriguez, X. Bugaut, T. Constantieux, *Adv. Synth. Catal.* **2014**, *356*, 851-856.
- [265] W.-Y. Han, Z.-J. Wu, X.-M. Zhang, W.-C. Yuan, *Org. Lett.* **2012**, *14*, 976-979.
- [266] S. Lou, S. E. Schaus, *J. Am. Chem. Soc.* **2008**, *130*, 6922-6923.
- [267] Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2009**, *38*, 2745-2755.
- [268] Z. Du, Z. Shao, *Chem. Soc. Rev.* **2013**, *42*, 1337-1378.
- [269] I. Ibrahem, A. Córdova, *Angew. Chem. Int. Ed.* **2006**, *45*, 1952-1956.
- [270] F.-L. Zhang, A.-W. Xu, Y.-F. Gong, M.-H. Wei, X.-L. Yang, *Chem. Eur. J.* **2009**, *15*, 6815-6818.
- [271] M. Presset, D. Mailhol, Y. Coquere, J. Rodriguez, *Synthesis* **2011**, 2549-2552
- [272] M. Presset, Y. Coquerel, J. Rodriguez, *J. Org. Chem.* **2009**, *74*, 415-418.
- [273] B. Miriyala, J. S. Williamson, *Tetrahedron Lett.* **2003**, *44*, 7957-7959.
- [274] Y. Chen, S. M. N. Sieburth, *Synthesis* **2002**, 2191-2194.
- [275] Y. Yamamoto, Y. Watanabe, S. Ohnishi, *Chem. Pharm. Bull.* **1987**, *35*, 1860-1870.
- [276] P. Dübon, M. Schelwies, G. Helmchen, *Chem. Eur. J.* **2008**, *14*, 6722-6733.
- [277] P. Elsner, H. Jiang, J. B. Nielsen, F. Pasi, K. A. Jørgensen, *Chem. Commun.* **2008**, 5827-5829.
- [278] P. T. Franke, B. Richter, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 6317-6321.
- [279] M.-K. Zhu, Q. Wei, L.-Z. Gong, *Adv. Synth. Catal.* **2008**, *350*, 1281-1285.
- [280] M. Rueping, E. Sugiono, E. Merino, *Angew. Chem. Int. Ed.* **2008**, *47*, 3046-3049.
- [281] J. Duschmalé, H. Wennemers, *Chem. Eur. J.* **2012**, *18*, 1111-1120.
- [282] W. Raimondi, M. M. Sanchez Duque, S. Gouedranche, A. Quintard, T. Constantieux, X. Bugaut, D. Bonne, J. Rodriguez, *Synthesis* **2013**, 1659-1666.

- [283] X. Ni, X. Li, Z. Wang, J.-P. Cheng, *Org. Lett.* **2014**, *16*, 1786-1789.
- [284] G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, *14*, 1724-1727.
- [285] H.-P. Deng, Y. Wei, M. Shi, *Eur. J. Org. Chem.* **2011**, 1956-1960.
- [286] R. Manzano, J. M. Andrés, R. Pedrosa, *Synlett* **2011**, 2205.
- [287] R. W. Taft, *J. Am. Chem. Soc.* **1953**, *75*, 4538-4539.
- [288] M. Charton, *J. Am. Chem. Soc.* **1975**, *97*, 1552-1556.
- [289] M. Charton, *J. Org. Chem.* **1976**, *41*, 2217-2220.
- [290] J. J. Miller, M. S. Sigman, *Angew. Chem. Int. Ed.* **2008**, *47*, 771-774.
- [291] M. S. Sigman, J. J. Miller, *J. Org. Chem.* **2009**, *74*, 7633-7643.
- [292] J. L. Gustafson, M. S. Sigman, S. J. Miller, *Org. Lett.* **2010**, *12*, 2794-2797.
- [293] K. H. Jensen, M. S. Sigman, *J. Org. Chem.* **2010**, *75*, 7194-7201.
- [294] L. Mantilli, D. Gérard, S. Torche, C. Besnard, C. Mazet, *Chem. Eur. J.* **2010**, *16*, 12736-12745.
- [295] A. Quintard, A. Alexakis, *Org. Biomol. Chem.* **2011**, *9*, 1407-1418.
- [296] K. C. Harper, M. S. Sigman, *J. Org. Chem.* **2013**, *78*, 2813-2818.
- [297] T. Azuma, Y. Kobayashi, K. Sakata, T. Sasamori, N. Tokitoh, Y. Takemoto, *J. Org. Chem.* **2014**, *79*, 1805-1817.
- [298] T. Lu, S. E. Wheeler, *Chem. Eur. J.* **2013**, *19*, 15141-15147.
- [299] H. Fujii, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1991**, *32*, 6147-6150.
- [300] D. A. Evans, K. T. Chapman, *Tetrahedron Lett.* **1986**, *27*, 5939-5942.
- [301] J. Vesely, R. Rios, A. Córdova, *Tetrahedron Lett.* **2008**, *49*, 1137-1140.
- [302] J. M. Andrés, R. Pedrosa, A. Pérez-Encabo, *Tetrahedron* **2000**, *56*, 1217-1223.
- [303] H. Yokoe, H. Sasaki, T. Yoshimura, M. Shindo, M. Yoshida, K. Shishido, *Org. Lett.* **2007**, *9*, 969-971.
- [304] C. Cook, X. Guinchard, F. Liron, E. Roulland, *Org. Lett.* **2012**, *12*, 744-747.
- [305] W. Raimondi, PhD thesis, Aix-Marseille Université (Marseille), **2012**.

- [306] H. Mitsunuma, S. Matsunaga, *Chem. Commun.* **2011**, 47, 469-471.
- [307] J. Liu, M. M. D. Numa, H. Liu, S.-J. Huang, P. Sears, A. R. Shikhman, C.-H. Wong, *J. Org. Chem.* **2004**, 69, 6273-6283.
- [308] H. Du, J. Rodriguez, X. Bugaut, T. Constantieux, *Chem. Eur. J.* **2014**, 20, 8458-8466.
- [309] B. R. Baker, E. E. Janson, N. M. J. Vermeulen, *J. Med. Chem.* **1969**, 12, 898-902.
- [310] G. E. Stokker, W. F. Hoffman, A. W. Alberts, E. J. Cragoe, A. A. Deana, J. L. Gilfillan, J. W. Huff, F. C. Novello, J. D. Prugh, *J. Med. Chem.* **1985**, 28, 347-358.
- [311] L. H. Kiem, K. W. Gopinath, *J. Heterocycl. Chem.* **1965**, 2, 225-227.
- [312] W. Li, X. Ma, W. Fan, X. Tao, X. Li, X. Xie, Z. Zhang, *Org. Lett.* **2011**, 13, 3876-3879.
- [313] D. S. Bose, M. Idrees, N. M. Jakka, J. V. Rao, *J. Comb. Chem.* **2010**, 12, 100-110.
- [314] M. R. Saidi, N. Azizi, E. Akbari, F. Ebrahimi, *J. Mol. Catal. A: Chem.* **2008**, 292, 44-48.
- [315] D. A. Evans, D. Seidel, *J. Am. Chem. Soc.* **2005**, 127, 9958-9959.