



HAL
open science

Dual organocatalysis for the development of Michael-initiated enantioselective organocascades

Yajun Ren

► **To cite this version:**

Yajun Ren. Dual organocatalysis for the development of Michael-initiated enantioselective organocascades. Catalysis. Ecole Centrale Marseille; Ecole centrale de Marseille; Ecole centrale de Marseille, 2015. English. NNT : 2015ECDM0005 . tel-02927957

HAL Id: tel-02927957

<https://theses.hal.science/tel-02927957>

Submitted on 2 Sep 2020

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 CENTRALE MARSEILLE

THÈSE

Dual organocatalysis for the development of Michael-initiated enantioselective organocascades

Présentée et soutenue publiquement par

Yajun Ren

Pour obtenir le grade de **Docteur en Sciences** de l'École Centrale Marseille
Discipline: **Chimie Organique**

Ecole doctorale 250 "Sciences Chimiques"
Institut des Sciences Moléculaires de Marseille (iSm2 – UMR CNRS 7313)
Equipe Synthèse Totale et Réactivité Organique (STeRéO)

Soutenue le 27 octobre 2015 devant le Jury composé de :

Prof. Jacques Rouden
Dr. Françoise Dumas
Dr. Michel Miesch
Prof. Alexandre Martinez
Prof. Jean Rodriguez
Dr. Yoann Coquerel

ENSICAEN
Université Paris-Sud
Université de Strasbourg
Ecole Centrale Marseille
Aix-Marseille Université
Aix-Marseille Université

Rapporteur
Rapporteur
Examineur
Président
Co-Directeur
Directeur

ÉCOLE CENTRALE MARSEILLE

THÈSE

Dual organocatalysis for the development of Michael-initiated enantioselective organocascades

Présentée et soutenue publiquement par

Yajun Ren

Pour obtenir le grade de **Docteur en Sciences** de l'École Centrale Marseille
Discipline: **Chimie Organique**

Ecole doctorale 250 "Sciences Chimiques"
Institut des Sciences Moléculaires de Marseille (iSm2 – UMR CNRS 7313)
Equipe Synthèse Totale et Réactivité Organique (STeRéO)

Soutenue le 27 octobre 2015 devant le Jury composé de :

Prof. Jacques Rouden
Dr. Françoise Dumas
Dr. Michel Miesch
Prof. Alexandre Martinez
Prof. Jean Rodriguez
Dr. Yoann Coquerel

ENSICAEN
Université Paris-Sud
Université de Strasbourg
Ecole Centrale Marseille
Aix-Marseille Université
Aix-Marseille Université

Rapporteur
Rapporteur
Examineur
Président
Co-Directeur
Directeur

To my family,
岳晓花(Xiaohua Yue), 任沛(Pei Ren), 任霄杰(Xiaojie Ren)

To my beloved,
李明浩(Minghao Li)

ACKNOWLEDGMENT

Firstly, I would like to express my sincere gratitude to my two advisors Dr. Yoann Coquerel and Prof. Jean Rodriguez for the continuous support of my Ph.D study, for their patience, inspirational and timely advice and constant encouragement. Their guidance helped me not only in my research and writing of this thesis, but also in fulfilling one thing with perseverance and careful. I have learned a lot from the discussion of my project with them and their perspectives on research. I cannot finish my project without their immense knowledge and encouragement to me. I could not have imagined having better advisors and mentors over the past three years.

I would like to thank China scholarship council and École centrale de Marseille for the financial support to enable my study and life in France.

I also would like to thank Dr. Cyril Bressy, Dr. Damien Bonne, Dr. Xavier Bugaut, Prof. Thierry Constantieux, Dr. Adrien Quintard, Dr. Jacques Viala, Dr. Gaëlle Chouraqui, Dr. Olivier Chuzel, Dr. Laurent Commeiras, Dr. Virginie Heran, Dr. Jean-Luc Parrain to give me many good advises and help to my research.

I would like to thank the most beautiful and kindly lady Sylvie Bernard to do me many favors in daily life, without her help, my life will be difficult in France.

I would like to thank Mr. Fabien PEREZ who give helps me a lot (a good translator, a funny guy...), also Dr. Yirong Zhou, Mme Ophélie Quinonero, Dr. Carole Guyon, Mr. Julien Botton, Mr. Maxime Dousset, Mr. Yohan Dudognon, Mr. Muhammad Idham Darussalam Mardjan, Mr. Jérémy Merad, Mme Mylène Roudier, Mme Cecilia Sassodelia, Dr. Juan Carlos Castillo, Dr. Diana Karina, Mme Paola Andrea Acosta Guzman, Dr. Vivek Raut Dr. David Pierrot and other lovely people in STEREO supply me a friendly and warmly environment for laboratory life.

I would like to thank Dr. Roseline Rosas, Dr. Gaëtan Herbette and Dr. Stéphane Viel for NMR, Dr. Valérie Monnier and Mr. Christophe Chendo for high resolution mass spectrometry, Dr. Michel Giorgi for the X-ray diffraction analysis, Dr. Nicolas Vanthuyne

and Mme Marion Jean for detection of HPLC; Prof. Clément Mazet and Dr. Houhua Li for one test of isomerization.

Finally, I would like to thank my friends, my parents, my brother and my boyfriend Minghao Li for the spiritual support.

Table of Contents

Résumé du travail	1
Chapter 1 Dual organocatalysis in enantioselective synthesis of bicyclo[3.2.1]octanes	7
1.1. Introduction	8
1.1.1. Organocatalysis: concepts, main activation modes & multi-catalysis	8
1.1.2. Objective of the research project.....	25
1.1.3. Single step enantioselective construction of bicyclo[3.2.1]octanes	26
1.2. Original enantioselective bi-organocatalytic synthesis of bicyclo[3.2.1]octanes	30
1.2.1. Preparation of substrates	30
1.2.2. Early work	31
1.2.3. Enantioselective synthesis of bicyclo[3.2.1]octanes	34
1.2.4. Conclusion.....	40
Chapter 2 Total synthesis of quadrane sesquiterpenes	41
2.1. Introduction	42
2.1.1. Quadrane natural products	42
2.1.2. Total syntheses of quadranes.....	45
2.1.3. Retrosynthetic analysis for (–)-isishippuric acid B (VI)	50
2.2. Synthetic approach to (–)-isishippuric acid B (VI)	52
2.2.1. Construction of the bicyclo[3.2.1]octane	52
2.2.2. Functionalization at C2	55
2.3. Total synthesis of (+)-suberosanone (IV) and formal synthesis of (+)-suberosenone (III)	66
2.3.1. Retrosynthetic analysis.....	66
2.3.2. The Arndt–Eistert homologation.....	67
2.3.3. Completion of the syntheses	72
2.4. Summary and conclusion	78
Chapter 3 Enantioselective synthesis of glutarimides	80
3.1. Introduction	81
3.1.1. Glutarimides in drugs and natural products	81
3.1.2. Enantioselective routes to glutarimides.....	82
3.1.3. Our approach	85
3.2. Enantioselective synthesis of glutarimides	87
3.2.1. The racemic series	87

3.2.2. The optically active series	88
3.3. Conclusion.....	92
General conclusion	93
Experimental part	99
ES.0. General experimental information	100
ES.1. Chemistry of bicyclo[3.n.1]octanes	102
ES.2. Total synthesis of quadrane sesquiterpenes	113
ES.3. Chemistry of glurarimides	139

Abbreviation

AIBN	Azobisisobutyronitrile
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DIPEA	N,N-diisopropylethylamine
dr	Diastereomeric ratio
er	Enantiomeric ratio
EA	Ethyl acetate
HMPA	Hexamethylphosphoramide
IBX	2-Iodoxybenzoic acid
IDipp	1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene
LDA	Lithium diisopropylamide
NHC	N-heterocyclic carbene
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
Nu	Nucleophile
[Ox]	Oxidation
P-BEMP	2-Tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine supported on polystyrene
PCC	Pyridinium chlorochromate
PE	Petroleum ether
TFA	Trifluoroacetic acid
THF	Tetrahedron furan

Résumé du travail

Le travail décrit dans ce manuscrit est centré sur l'organocatalyse énantiosélective, tant au niveau du développement méthodologique qu'au niveau des applications en synthèse totale de produits naturels.

L'organocatalyse énantiosélective, qui implique de petites molécules organiques chirales comme catalyseurs dans des transformations énantiosélectives, est un domaine de recherche en chimie organique conceptualisé en 2000 et aujourd'hui plutôt mature. Récemment, et en capitalisant sur le savoir acquis au cours des quinze années passées, des stratégies de multi-organocatalyse, c'est à dire des stratégies impliquant des combinaisons de plusieurs organocatalyseurs au sein du même milieu réactionnel, ont été développées pour permettre la réalisation de processus réactionnels complexes, souvent très difficiles à réaliser autrement.

Par exemple, le groupe de Rovis a décrit en 2009 une cascade bi-catalytique impliquant la combinaison d'un aminocatalyseur avec un carbène N-hétérocyclique (NHC) pour la synthèse énantiosélective de cyclopentanones (Schéma 1, haut). Inspirés par ce travail, et dans la continuité des travaux de recherche de notre équipe sur les propriétés des NHCs comme bases de Brønsted organocatalytiques, nous avons imaginé une organocascade divergente à partir des même substrats pour la préparation de molécules bicycliques pontées (Schéma 1, bas).

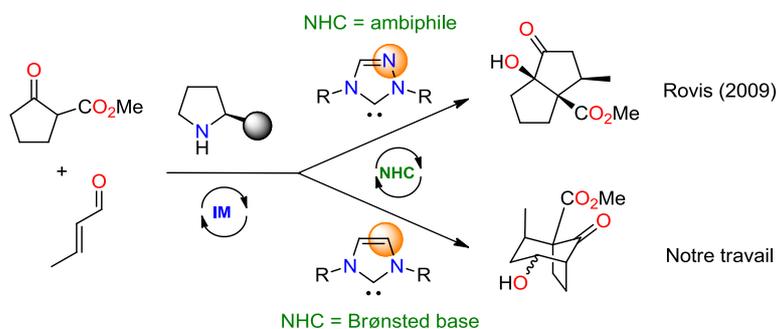


Schéma 1. Organocascades bi-catalytiques combinant aminocatalyse et catalyse par les NHCs

Ainsi, nous avons développé une méthode bi-organocatalytique pour la synthèse énantiosélective directe de molécules bicycliques pontées, essentiellement des bicyclo[3.2.1]octanes (Schéma 2 et Chapitre 1). L'originalité de ce travail repose sur l'utilisation d'un NHC de la classe des 1,3-imidazol-2-ylidènes comme base de Brønsted organocatalytique. Une partie importante de ce travail a consisté à limiter la réversibilité des processus mis en jeu lors de la cascade réactionnelle (addition de Michael et aldolisation) pour assurer un bon contrôle de la stéréosélectivité.

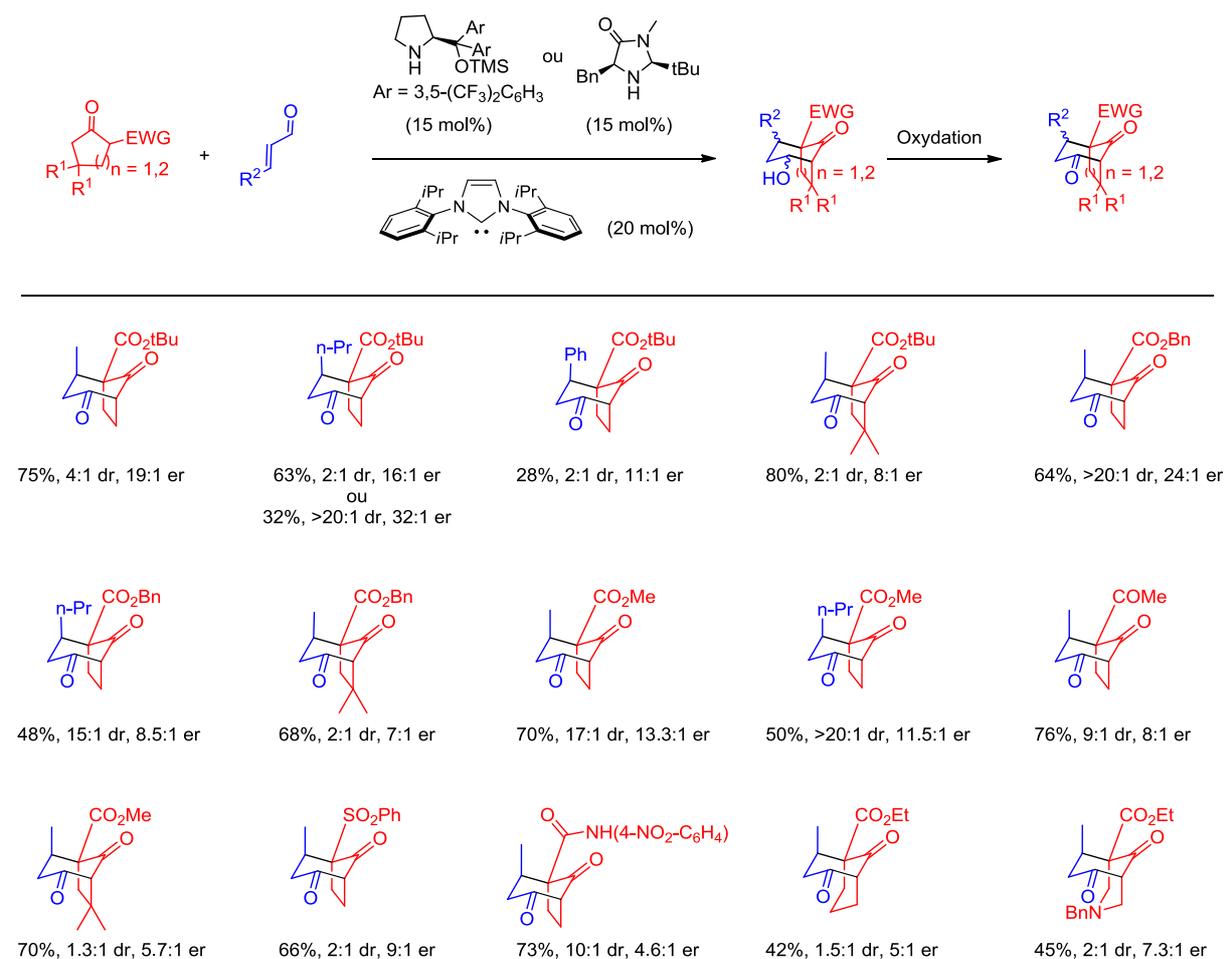


Schéma 2. Organocascade bi-catalytique énantiosélective: synthèse de bicyclo[3.n.1]alcanes

La méthode s'est révélée suffisamment générale et efficace pour envisager son application à la synthèse totale énantiosélective de produits naturels. Nos efforts dans le domaine se sont concentrés sur la synthèse des sesquiterpènes de la famille des quadranes, et en particulier la (+)-suberosanone et la (+)-suberosenone, deux molécules naturelles d'origine marine montrant des activités biologiques prometteuses (Schéma 3 et Chapitre 2). Nous avons obtenu la (+)-suberosanone (er > 99:1) avec un rendement global de 8% pour 15 étapes, ce qui représente la première synthèse totale énantiosélective d'un produit naturel de cette famille. Ce travail constitue également une synthèse totale formelle de la (+)-suberosenone. La stratégie développée est suffisamment flexible pour permettre la synthèse de nombreux analogues.

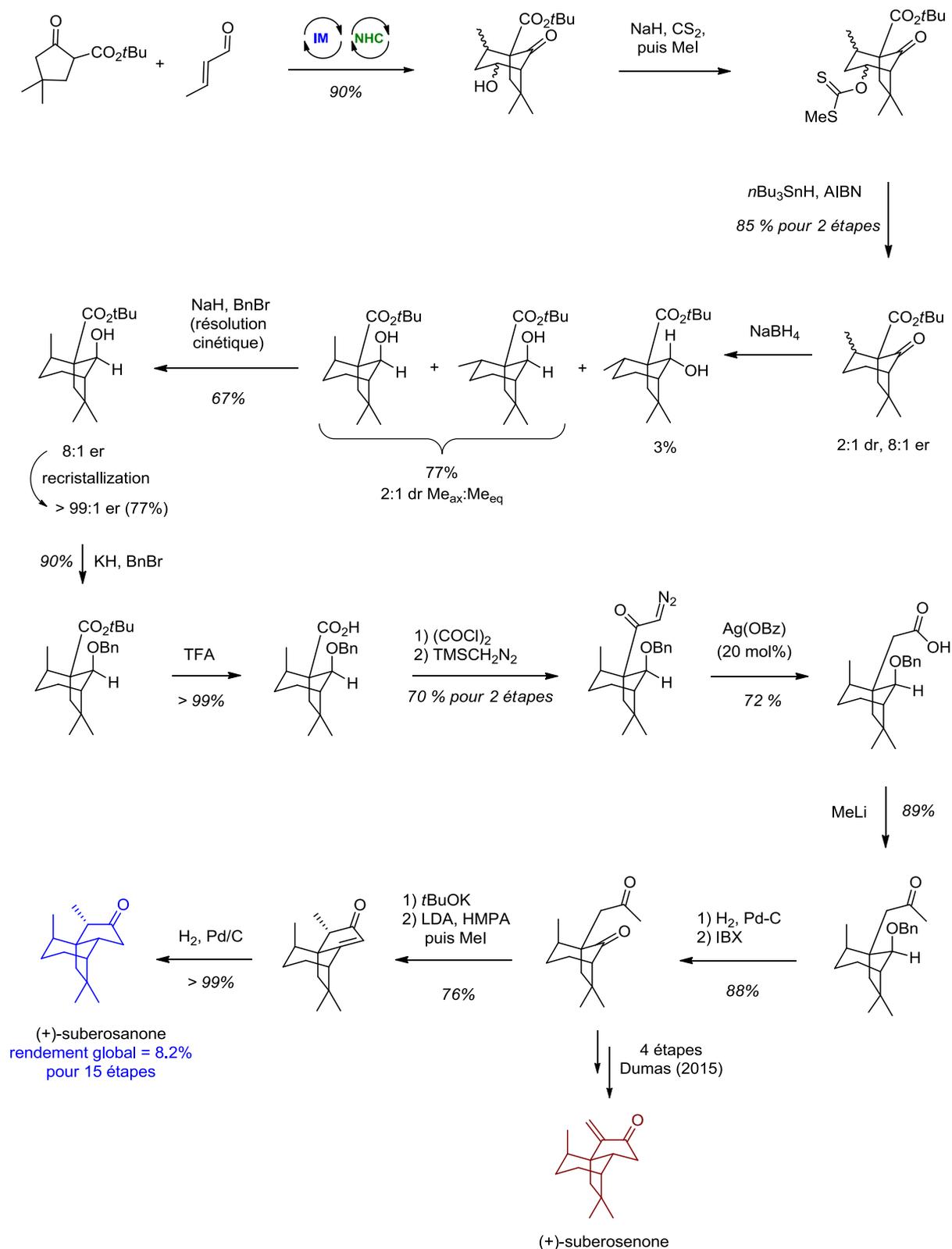


Schéma 3. Synthèse totale de la (+)-suberosanone, synthèse formelle de la (+)-suberosenone

Enfin, le troisième chapitre de ce manuscrit détaille notre travail préliminaire sur une autre organocascade énantiosélective bicatalytique pour la préparation de glutarimides

(Schéma 4 et Chapitre 3). Le motif glutarimide est présent dans de nombreuses molécules naturelles biologiquement actives et plusieurs médicaments, mais il n'existe que très peu de méthodes énantiosélectives pour leur préparation. Sur la base de travaux antérieurs de notre équipe, l'approche étudiée repose sur une addition de Michael organocatalytique énantiosélective à partir de cyclobutanones activées par une fonction amide secondaire suivie d'un réarrangement de cycle catalysé par une base de Lewis comme les NHCs. Nous avons obtenu la preuve du concept pour la faisabilité de cette nouvelle organocascade et identifié plusieurs systèmes catalytiques performants. Faute de temps, l'optimisation et la généralisation de la réaction restent à effectuer.

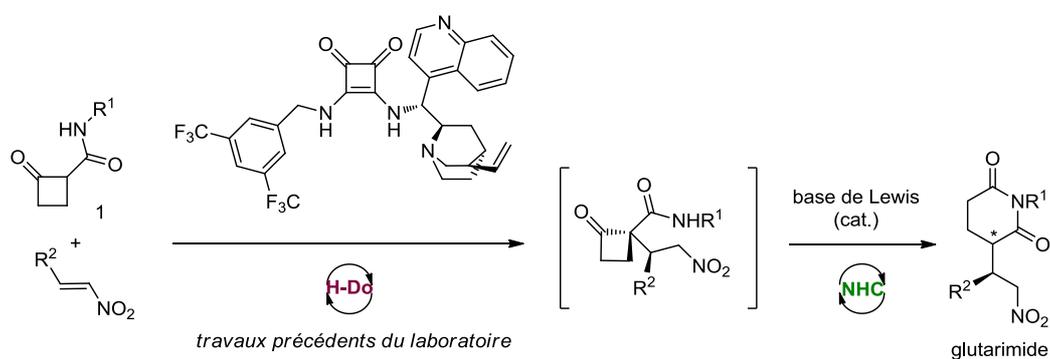


Schéma 4. Organocascade bi-catalytique énantiosélective : synthèse de glutarimides

Chapter 1

Dual organocatalysis in enantioselective synthesis of bicyclo[3.2.1]octanes

1.1. Introduction

1.1.1. Organocatalysis: concepts, main activation modes & multi-catalysis

In its editorial of the 2007 thematic issue of *Chemical Reviews* on organocatalysis, Benjamin List defined organocatalysis as “catalysis with small organic molecules, where an inorganic element is not part of the active principle”.¹ Although well represented in Nature for centuries,² this field gained an identity only in 2000 with the work of List³ and MacMillan⁴ on enantioselective aminocatalysis, while examples of organocatalytic transformations can be traced back to 1859 with the work of Justus von Liebig on the catalytic properties of acetaldehyde.⁵ The first enantioselective organocatalytic reaction was reported in 1971 with the Hajos & Parrish proline-catalyzed enantioselective aldol reaction,⁶ but it took almost three decades before the method was regarded as a general concept rather than an isolated specific case. Nowadays, organocatalysis is firmly established as the third pillar of enantioselective catalysis, together with biocatalysis and metal catalysis.⁷ Organocatalysis offers several attractive features: it generally tolerates aerobic conditions, do not require rigorous exclusion of water, and organocatalysts are usually stable and have a reduced toxicity when compared to metal-based catalytic systems. Most often, organocatalysts are obtained from naturally occurring chiral molecules (the so-called “chiral pool”) but can also be prepared in their optically pure form by desymmetrization. Naturally occurring Cinchona alkaloids and amino acids have become the principal source of organocatalysts, together with synthetic *trans*-cyclohexane-1,2-diamine and binol derivatives. Organocatalytic

¹ List, B. *Chem. Rev.* **2007**, *107*, 5413.

² (a) March, J. J.; Leberherz, H. G. *TIBS* **1992**, *17*, 110. (b) Rutter, W. J. *Fed. Proc. Am. Soc. Exp. Biol.* **1964**, *23*, 1248. (c) Lai, C. Y.; Nakai, N.; Chang, D. *Science* **1974**, *183*, 1204. (d) Morris, A. J.; Tolan, D. R.; *Biochemistry* **1994**, *33*, 12291.

³ List, B.; Lerner, R. A.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

⁴ Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

⁵ von Liebig, J. *Ann. der Chem. and Pharm.* **1860**, *113*, 246.

⁶ (a) Hajos, Z. G.; Parrish, D. R. German patent DE 2102623, **1971**. (b) Eder, U.; Sauer, G. R.; Wiechert, R. German patent DE 2014757, **1971**.

⁷ A number of reviews, books and thematic issues exist of the topic. For select contributions: (a) *Organocatalysis*, see reference 1. (b) *Asymmetric Organocatalysis*, List, B. Ed., *Top Curr. Chem.* **2009**, *291*, 1–460. (c) *Enantioselective Organocatalyzed Reactions*; Mahrwald, R., Ed.; Springer: Berlin, 2011. (d) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703. (e) *Stereoselective Organocatalysis*, Rios Torres, R. Ed.; John Wiley & Sons: Hoboken NJ, 2013. (f) *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications*, Dalko, P. I. Ed.; Wiley-VCH: Weinheim, 2013.

transformations can be categorized according to the activation mode involved.⁸ In the following, a brief summary of the main organocatalytic activation modes is presented.

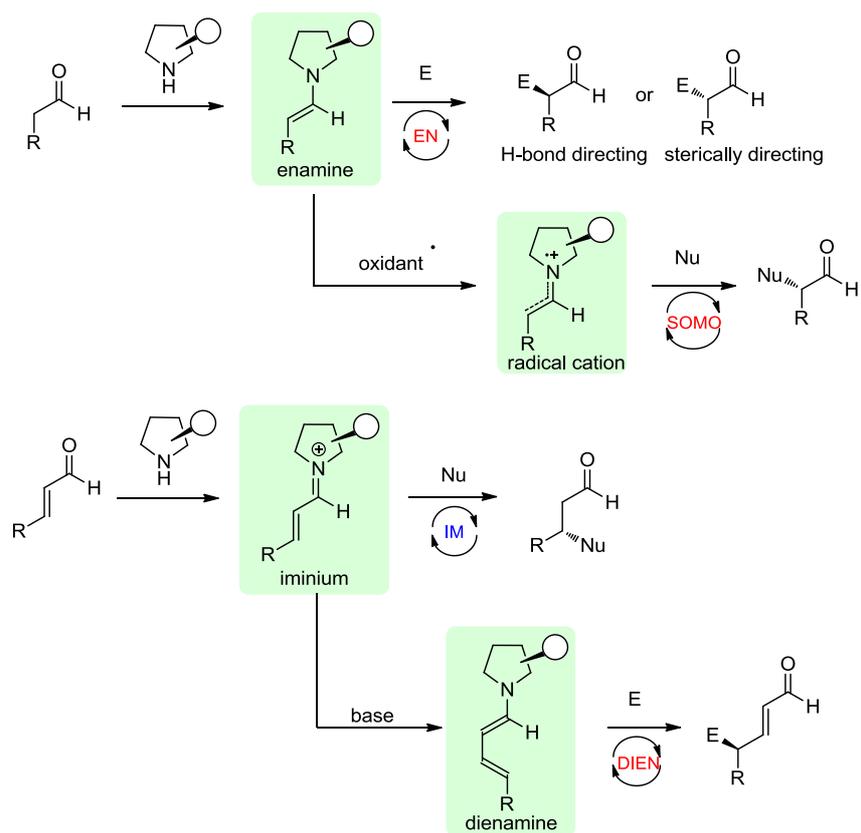
Aminocatalysis

The term aminocatalysis embraces three distinct organocatalytic activation modes, namely enamine (and dienamine) activation, iminium activation, and SOMO activation (Scheme 1), all proceeding through the formation of a covalent bond between a primary or secondary amine catalyst and a carbonyl moiety in the substrate.⁹ Enamine activation builds on the capacity of amines to react with enolisable carbonyl compounds to form an enamine that can in turn react with electrophiles for the α -functionalization of the carbonyl compound [Highest Occupied Molecular Orbital (HOMO)-activation]. If the catalytically generated enamine is submitted to a one-electron oxidation, it produces a reactive radical cation amenable to react with nucleophiles for the α -functionalization of the carbonyl compound [Single Occupied Molecular Orbital (SOMO)-activation]. With non-enolisable α,β -unsaturated carbonyl compounds (essentially aldehydes), the situation is different. Indeed, their reactions with amine catalysts produce iminium ions amenable to react with nucleophiles for the β -functionalization of the carbonyl compound *via* a conjugate addition [Lowest Unoccupied Molecular Orbital (LUMO)-activation]. Finally, the reaction of catalytically generated enolisable α,β -unsaturated iminium ions with Brønsted bases produces dienamines (γ -deprotonation) that can in turn react with electrophiles for the γ -functionalization of the carbonyl compound (HOMO-activation). Representative commercially available aminocatalysts are depicted in Figure 1, and the iminium activation mode is illustrated in Scheme 2.¹⁰

⁸ MacMillan, D. W. C. *Nature* **2008**, *455*, 304.

⁹ For an excellent review on the topic, see: Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Comm.* **2011**, *47*, 632.

¹⁰ (a) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305. For related reactions: (b) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1101. (c) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun.* **2006**, 4928. (d) Rueping, M.; Sugiono, E.; Merino, E. *Chem. Eur. J.* **2008**, *14*, 6329. (e) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 3699.



Scheme 1. Principles of aminocatalysis

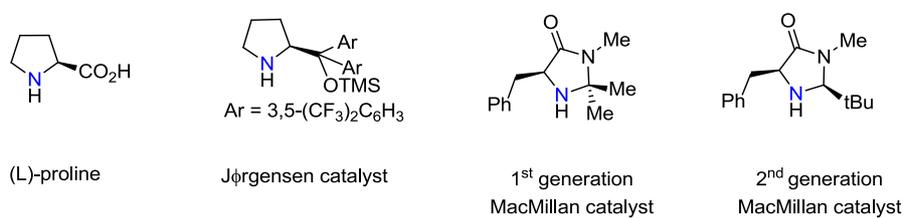
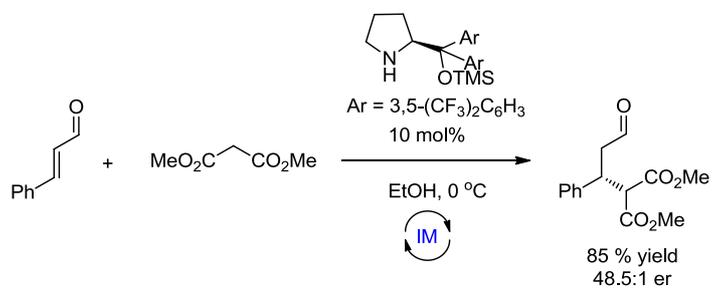


Figure 1. Representative popular chiral aminocatalysts



Scheme 2. Iminium activation for the enantioselective Michael addition of dimethyl malonate to cinnamaldehyde^{10a}

Lewis base catalysis

Lewis bases such as tertiary amines, pyridines and phosphines are well known to catalyze some organic reactions. Representative Lewis base catalysts are depicted in Figure 2. In recent years, N-heterocyclic carbenes (NHCs) have also been identified as potent Lewis base organocatalysts (vide infra for NHC catalysis). Famous examples of Lewis base catalysis in the enantioselective series include the Morita–Baylis–Hillman reaction¹¹ and acyl transfer reactions (Scheme 3).¹² The Lewis base activation involves the formation of a covalent bond between the Lewis base catalyst and an electrophilic substrate to form a zwitterionic reactive intermediate.

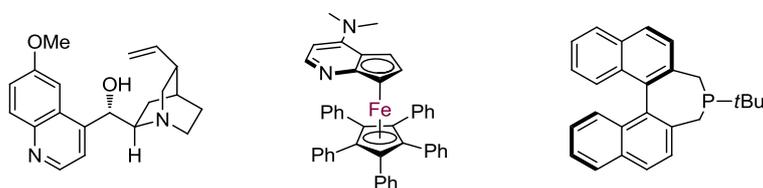
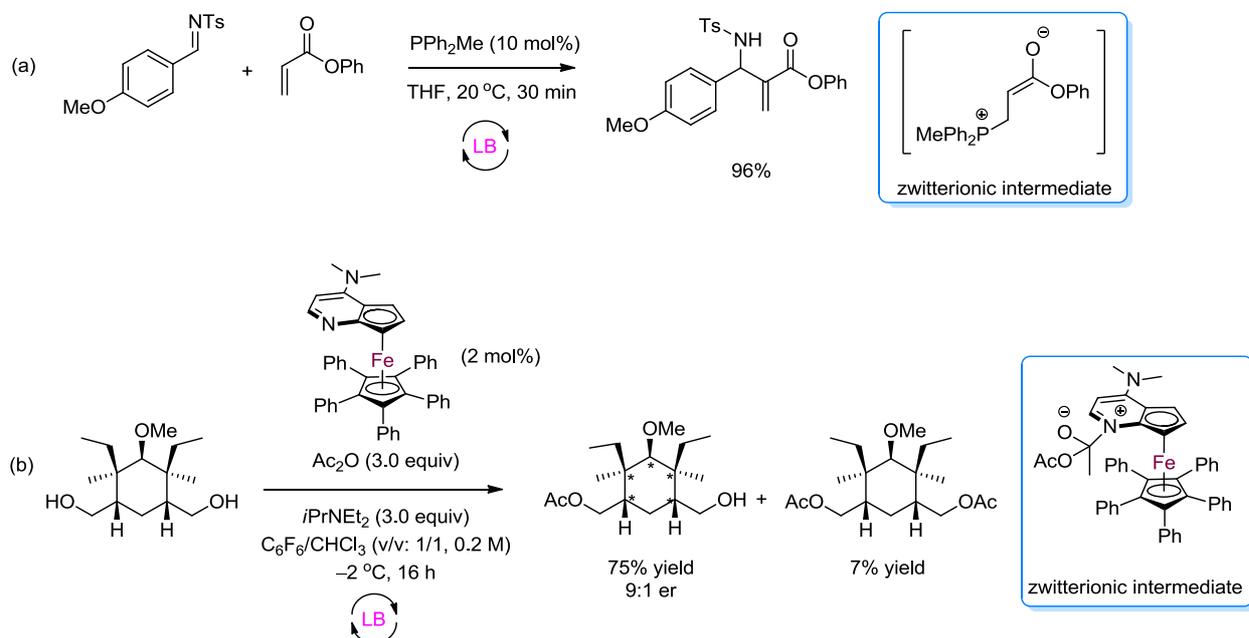


Figure 2. Representative popular chiral Lewis base organocatalysts



Scheme 3. (a) Examples of a phosphine-catalyzed MBH reaction;¹¹ (b) Example of a pyridine-catalyzed acyl transfer reaction^{12a}

¹¹ (a) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem Rev.* **2010**, *110*, 5447. (b) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659.

¹² Phosphine catalysis: (a) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174. Pyridine catalysis: (b) Roux, C.; Chuzel, O.; Bressy, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 766. (c) Yunmi Lee, S.; Murphy, J. M.; Ukai, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15149 and references therein.

Brønsted acid catalysis

Acidic hydrogen atoms can be regarded as the simplest Lewis acids. Consequently, small organic molecules containing one or several acidic hydrogen atom(s) are able to catalyze organic transformations in an analogous manner than traditional metal-based Lewis acids (LUMO-activation).¹³ Depending on their Brønsted acidity, this large class of organocatalysts operates either by non-covalent hydrogen-bonding interactions for weak Brønsted acids (e.g. thioureas, $pK_{a\text{DMSO}} = 8.5\text{--}19.6$),¹⁴ or by covalent interaction, that is protonation, with stronger Brønsted acids (e.g. phosphoric acids, $pK_{a\text{DMSO}} = 2.4\text{--}4.2$).^{15,16} The pioneer realizations in the field are depicted in Scheme 4.¹⁷

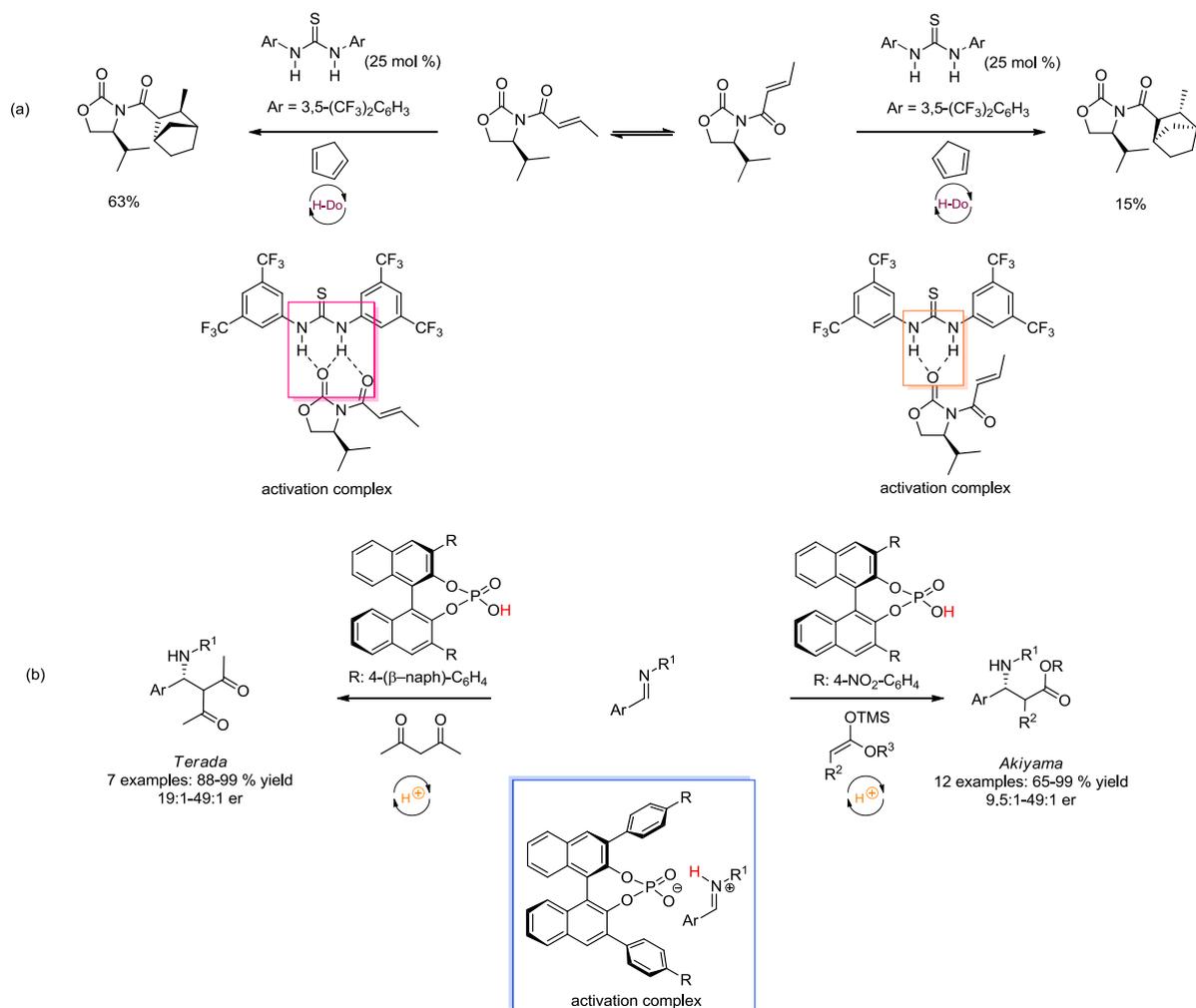
¹³ Reviews: (a) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (b) Terada, M. *Synthesis* **2010**, 1929. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.

¹⁴ Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724.

¹⁵ (a) Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudörfl, J.-M.; Berkessel, A.; O'Donoghue, A. C. *Chem. Eur. J.* **2011**, *17*, 8524. (b) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 11569.

¹⁶ For a study on the H-bond vs ion pairing activation of imines with phosphoric acids: Fleischmann, M.; Rueping, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 6364

¹⁷ (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (b) Akiyama, T.; Itoh, J.; Yokota, K.; Fichibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566 (c) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.



Scheme 4. (a) First example of H-bonding catalysis with a thiourea. (b) First examples of enantioselective organocatalysis with phosphoric acids.

N-Heterocyclic carbene (NHC) catalysis

Since their isolation as stable free carbenes by Arduengo in 1991,¹⁸ *N*-heterocyclic carbenes (NHCs) have found a plethora of applications in organic chemistry,¹⁹ initially in the field of organometallic chemistry²⁰ and more recently as a class of organocatalysts with unique properties.²¹ The four most common classes of NHCs are depicted in Figure 3.

¹⁸ Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

¹⁹ Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485.

²⁰ Select reviews: (a) Hahn, F. E.; Jahnke, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3122. (b) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612.

²¹ Select reviews: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307.

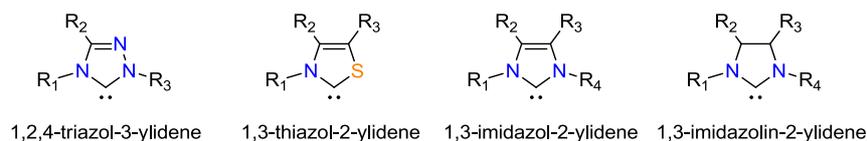
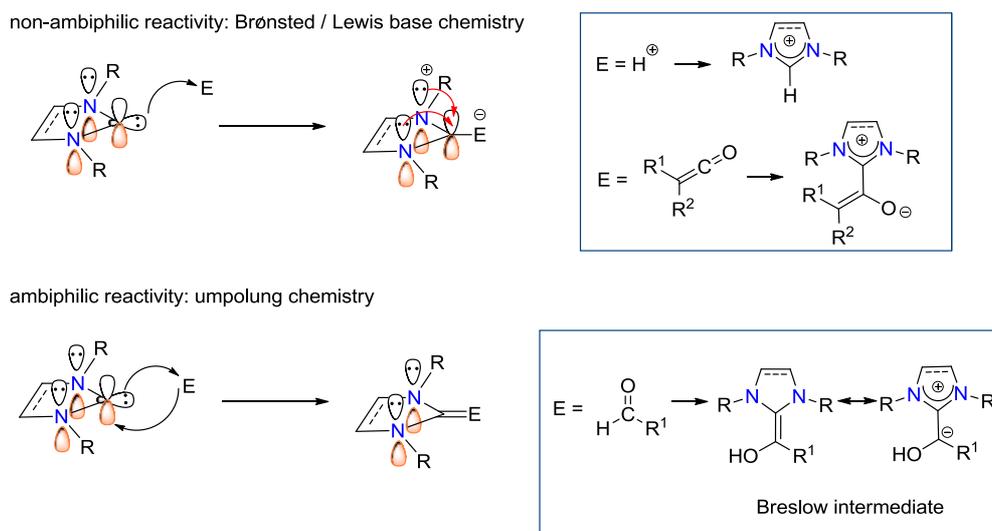


Figure 3. The four common classes of NHCs

On the one side, applications of NHCs in organometallic chemistry, especially 1,3-imidazol(in)-2-ylidenes, result from their excellent σ -donor properties as ancillary transition metal ligands, allowing for strong metal–ligand bonds, as for example, in the late-generations Grubbs precatalysts for olefin metathesis.²² On the other side, the applications of NHC in organocatalysis can involve three distinct activation modes depending on the nature of the NHC and the substrates: two non-ambiphilic activation modes, namely Brønsted base activation and Lewis base activation,²³ and an ambiphilic activation mode via a resonance-stabilized enaminol-type intermediate, the so-called Breslow intermediate, to trigger umpolung reactivity (**Scheme 5**).²⁴



Scheme 5. Activation modes in organocatalysis with NHCs

In the past few years, our laboratory has been actively involved in the field of NHC catalysis, especially involving the Brønsted base properties of stable (and bottleable)

²² Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.

²³ Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906.

²⁴ Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511.

1,3-imidazol-2-ylidenes. The relative Brønsted basicities of NHCs follow the order shown in Figure 4.²⁵

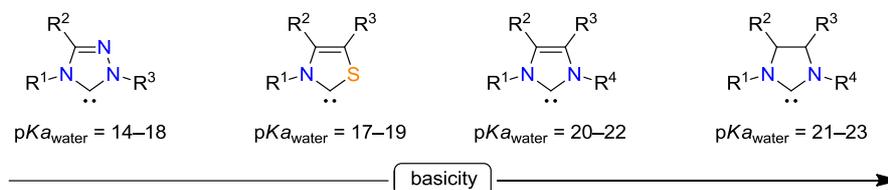


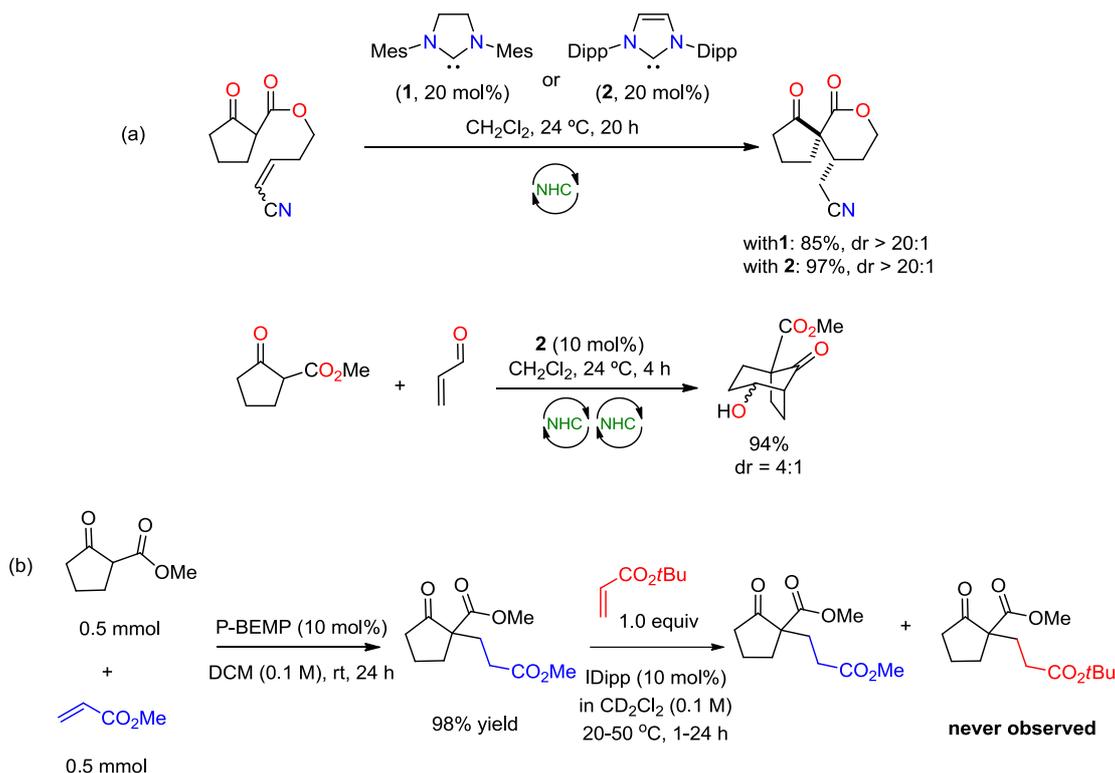
Figure 4. Relative Brønsted basicities of NHCs. The $\text{p}K_{\text{a}}$ values are for the corresponding azolium salts, and are of course highly dependent on the nature of the R^i substituents.

The work of our group in this area of research was initiated by the serendipitous discovery that the NHCs SIMes (**1**) and IDipp (**2**) are excellent catalysts for Michael additions and Michael / aldol organocascades (Scheme 6a).²⁶ Importantly for the following, it was demonstrated that NHC-catalyzed Michael additions performed at room temperature or below are not or slowly reversible.^{26b} This was also proven more recently by simple cross-experiments using methyl and tert-butyl acrylates (Scheme 6b).²⁷

²⁵ (a) Amyes, T. L.; Diver, S. T.; Richard, J. P.; Rivas, F. M.; Toth, K. *J. Am. Chem. Soc.* **2004**, *126*, 4366. (b) Higgins, E. M.; Sherwood, J. A.; Lindsay, A. G.; Armstrong, J.; Massey, R. S.; Alder, R. W.; O'Donoghue, A. C. *Chem. Commun.* **2011**, *47*, 1559. (c) Massey, R. S.; Collett, C. J.; Lindsay, A. G.; Smith, A. D.; O'Donoghue, A. C. *J. Am. Chem. Soc.* **2012**, *134*, 20421.

²⁶ (a) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Adv. Synth. Catal.* **2009**, *351*, 1744. (b) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Chem. Eur. J.* **2011**, *17*, 2266. (c) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2011**, 5061.

²⁷ Unpublished results.



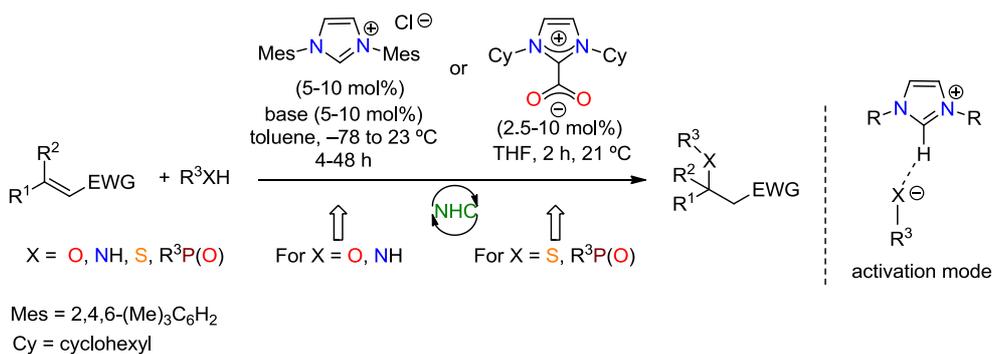
Scheme 6. (a) Examples of NHC-catalyzed Michael addition and Michael / aldol cascade.²⁶
(b) Cross-experiments probing the non-reversibility of the NHC-catalyzed Michael addition.

Contemporaneously, the groups of Scheidt and Zhang reported NHC-catalyzed oxa-Michael and aza-Michael additions, respectively, using closely related NHC catalysts (Scheme 7).²⁸ By analogy with the carba- series, the oxa-Michael addition was also found irreversible at 20 °C, and slowly reversible at 70 °C.^{28a} More recently, and in collaboration with Prof. Lionel Delaude from the University of Liege, our group reported the complementary NHC-catalyzed sulfa- and phospho-Michael additions using zwitterionic NHC•CO₂ adducts precatalysts (Scheme 7).²⁹ Very recently, the group of Huang has reported some enantioselective NHC-catalyzed Michael and sulfa-Michael additions.³⁰

²⁸ (a) Phillips, E. M.; Riedrich, M.; Scheidt, K. A. *Jd. Am. Chem. Soc.* **2010**, *132*, 13179. (b) Kang, Q.; Zhang, Y. *Org. Biomol. Chem.* **2011**, *9*, 6715.

²⁹ Hans, M.; Delaude, L.; Rodriguez, J.; Coquerel, Y. *J. Org. Chem.* **2014**, *79*, 2758.

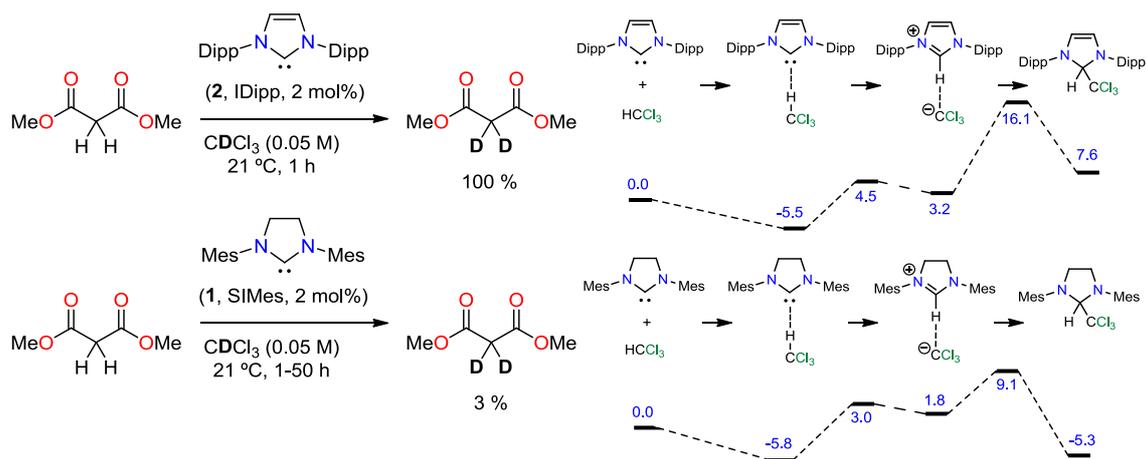
³⁰ (a) Chen, J.; Huang, Y. *Nat. Commun.* **2014**, *5*, 3437. (b) Chen, J.; Meng, S.; Huang, Y. *Chem. Sci.* **2015**, *6*, 4184.



Scheme 7. NHC-catalyzed hetero-Michael additions^{28,29}

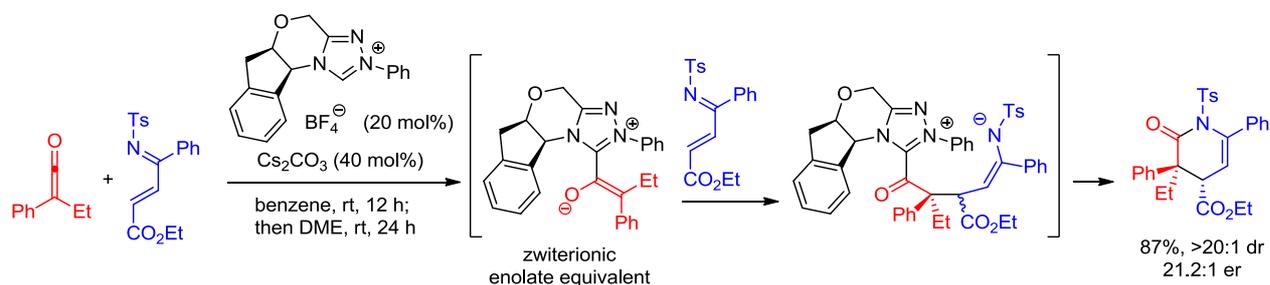
Lately, our group reported some NHC-catalyzed hydrogen / deuterium exchange reactions between pseudo-acids ($pK_{a\text{DMSO}} = 14\text{--}19$) and deuterated chloroform (Scheme 8).³¹ I have been involved in this work as a side-project of my main PhD project. The excellent organocatalytic activity of the NHC IDipp (**2**) in these reactions was attributed to its ideal “proton shuttling” properties involving a stable azolium cation / trichloromethyl anion Brønsted pair. Surprisingly, the parent NHC SIMes (**1**) exhibiting a very similar Brønsted basicity than the NHC IDipp (**2**, $\Delta pK_{a\text{water}} = 0.2$) was an incompetent catalyst in these reactions. A combined experimental and theoretical study [DFT, B3LYP 6-311++G(d,p)] allowed rationalizing this sharp difference of reactivity. It was found that the reaction of the NHC SIMes (**1**) with chloroform produces an unstable azolinium cation / trichloromethyl anion Brønsted pair that rapidly rearranges into the formal insertion product of the NHC **1** in the C–H bond of chloroform, resulting in a rapid loss of the catalytic activity.

³¹ Perez, F.; Ren, Y.; Boddaert, T.; Rodriguez, J.; Coquerel, Y. *J. Org. Chem.* **2015**, *80*, 1092.



Scheme 8. NHC-catalyzed H/D exchange reactions, and detailed mechanism and energy profiles of the reaction of NHCs SIMes (**1**) and IDipp (**2**) with chloroform. The energy profile was obtained by DFT calculations at the B3LYP-6-311++G(d,p) level of theory (free energies at 25 °C including ZPE correction in kcal/mol with the IEFPCM solvation model)

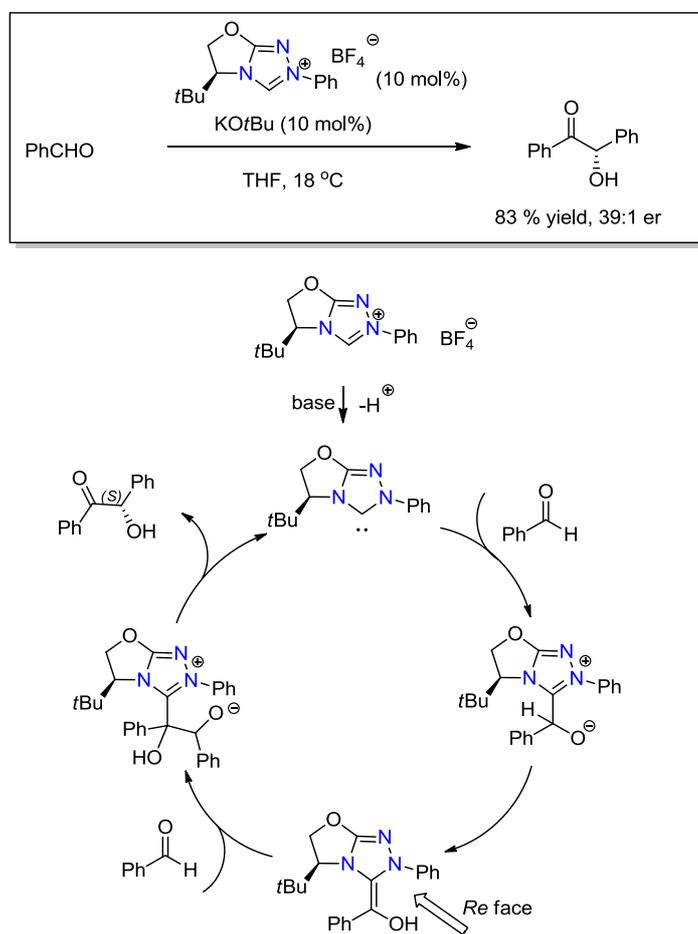
The recently developed chemistry of zwitterionic enolate-type intermediates is a nice example of the Lewis base activation with NHCs. The principle of these reactions is illustrated below in the case of the NHC-catalyzed reaction of a ketene with a 1-aza-diene recently reported by Ye (Scheme 9).^{32a} In this Lewis base-catalyzed reaction, the nucleophilic catalyst adds first to the ketene to form a zwitterionic azolium enolate intermediate. This catalytically generated species then undergoes a conjugated nucleophilic addition to the 1-aza-diene to give a zwitterionic intermediate, precursor of the δ -lactam product by nucleophilic substitution at the carbonyl group regenerating the catalyst.



Scheme 9. NHC-catalyzed formal [4 + 2] cycloaddition between 1-azadienes and ketenes

³² (a) Jian, T.-Y.; Shao, P.-L.; Ye, S. *Chem. Commun.* **2011**, 47, 2381. See also: (b) Duguet, N.; Campbell, C. D.; Slawin, A. M. Z.; Smith, A. D. *Org. Biomol. Chem.* **2008**, 6, 1108. (c) Jian, T.-Y.; He, L.; Tang, C.; Ye, S. *Angew. Chem., Int. Ed.* **2011**, 50, 9104. (d) Wang, X.-N.; Shen, L.-T.; Ye, S. *Org. Lett.* **2011**, 13, 6382.

Probably the most spectacular applications of NHCs as organocatalysts involve their ambiphilic character leading to umpolung reactions of carbonyl compounds.²⁴ The archetypal and first developed enantioselective NHC-catalyzed umpolung transformation was the benzoin condensation (Scheme 10).³³ This reaction proceeds via the catalytic formation of an enamino intermediate, the so-called Breslow intermediate, from benzaldehyde and the NHC catalyst. As illustrated above in **Scheme 5**, both the nucleophilic σ and electrophilic π orbitals of the carbene atom are involved in the formation of the Breslow intermediate. This nucleophilic species (equivalent to a d^1 -synthon in the terminology of Seebach for umpolung reactions³⁴) can add to a second molecule of benzaldehyde to finally produce benzoin and liberate the NHC catalyst.



Scheme 10. The enantioselective NHC-catalyzed benzoin condensation

³³ (a) Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743. For the current state of the art catalyst for the benzoin condensation of benzaldehyde: (b) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214.

³⁴ Seebach, D. *Angew. Chem. Int. Ed.* **1979**, *18*, 239.

Multi-catalysis

With the advent of organocatalysis, it has nowadays become easier to imagine multi-catalytic systems that combine several catalytic activation modes to achieve complex chemical transformations. In the last decade, a number of multi-catalytic processes have been described combining activation modes from a vast array of catalysts, including of course metal-based catalysts.³⁵ In an excellent *Perspective* article, MacMillan recently proposed a categorization of bi-catalytic processes.³⁶ The definitions and terminology proposed by MacMillan have been reproduced hereafter (Figure 5).

(A) Bifunctional catalysis: “both the nucleophile and electrophile are activated separately by discrete functional groups *on the same catalyst*”;

(B) Double activation catalysis: “both catalysts work in concert to activate only one of the reacting partners”;

(C) Cascade catalysis: “both catalysts activate the same reacting partner, but *in a sequential fashion* (i.e. an activated substrate produces an intermediate, which is further activated by the second catalyst)”;

(D) Synergistic catalysis: “two catalysts and two catalytic cycles work in concert to create a single new bond.” “In its simplest form, synergistic catalysis involves the concurrent activation of both a nucleophile and an electrophile using distinct catalysts.”

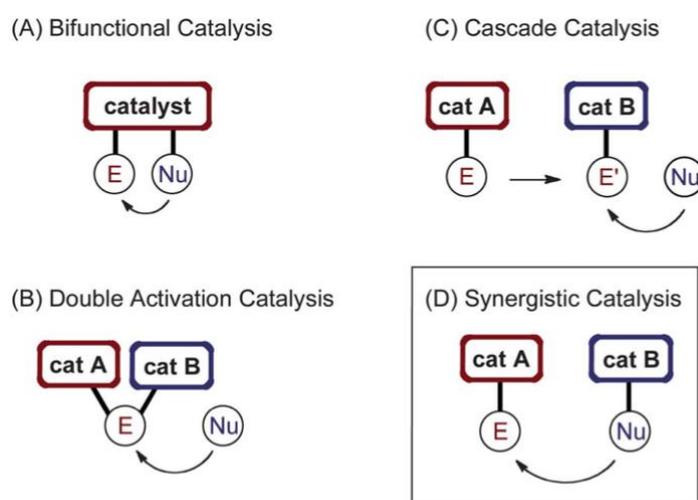
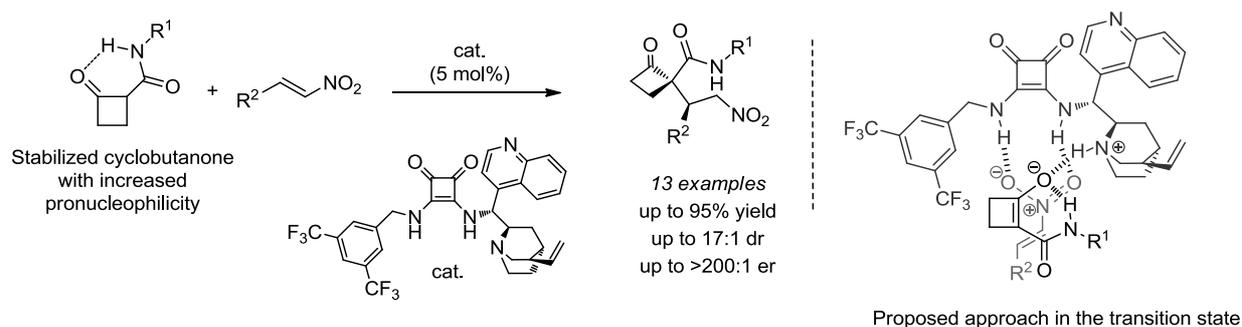


Figure 5. Classification of catalytic systems involving two catalysts. Reproduced from ref 36.

³⁵ Reviews: (a) Zhou, J. *Chem. Asian J.* **2010**, *5*, 422. (b) Piovesana, S.; Schietroma, D. M. S.; Bella, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6216. (c) Wende, R. C.; Schreiner, P. R. *Green Chem.* **2012**, *14*, 1821.

³⁶ Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633, and the references therein.

A selection of illustrative examples is presented below. In 2012, our group described enantioselective Michael additions of activated cyclobutanones to nitroalkenes using the bifunctional catalyst developed by Rawal (Scheme 11).³⁷ This bifunctional catalyst operates by simultaneous Brønsted base activation of the cyclobutanone pronucleophile and Brønsted acid activation (H-bonding) of the electrophilic nitroalkene, affording to the Michael adducts in high yields and stereoselectivities.³⁸



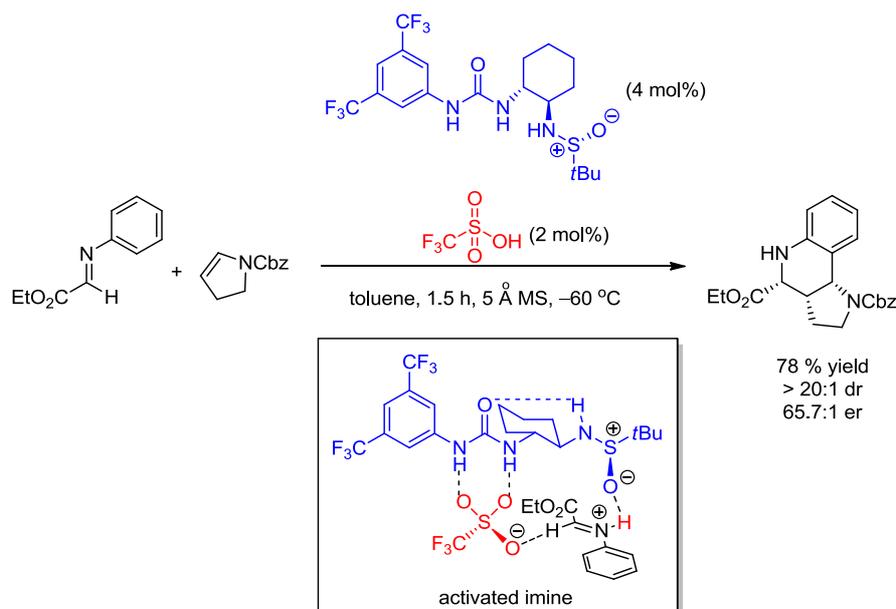
Scheme 11. Enantioselective organocatalytic Michael addition of cyclobutanones to nitroalkenes³⁷

In 2010, Jacobsen and co-workers reported a beautiful example of double activation catalysis in the case of the Povarov reaction between furan and N-phenyl aldimimines (Scheme 12).³⁹ A detailed experimental and computational analysis has revealed that the two catalysts, namely triflic acid (2 mol%) and the bifunctional sulfinamido urea derivative (4 mol%), are simultaneously activating the imine substrate in a well stereodefined environment, allowing for a high stereocontrol.

³⁷ Mailhol, D.; Sanchez Duque, M. M.; Raimondi, W.; Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. *Adv. Synth. Catal.* **2012**, *354*, 3523.

³⁸ For benchmark work on this type of bifunctional organocatalysis: (a) Tomotaka, O.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. For reviews: (b) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 7496. (c) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (d) Serdyuk, O.V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051. (e) Fang, X.; Wang, C. *J. Chem. Commun.* **2015**, *51*, 1185.

³⁹ Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986.



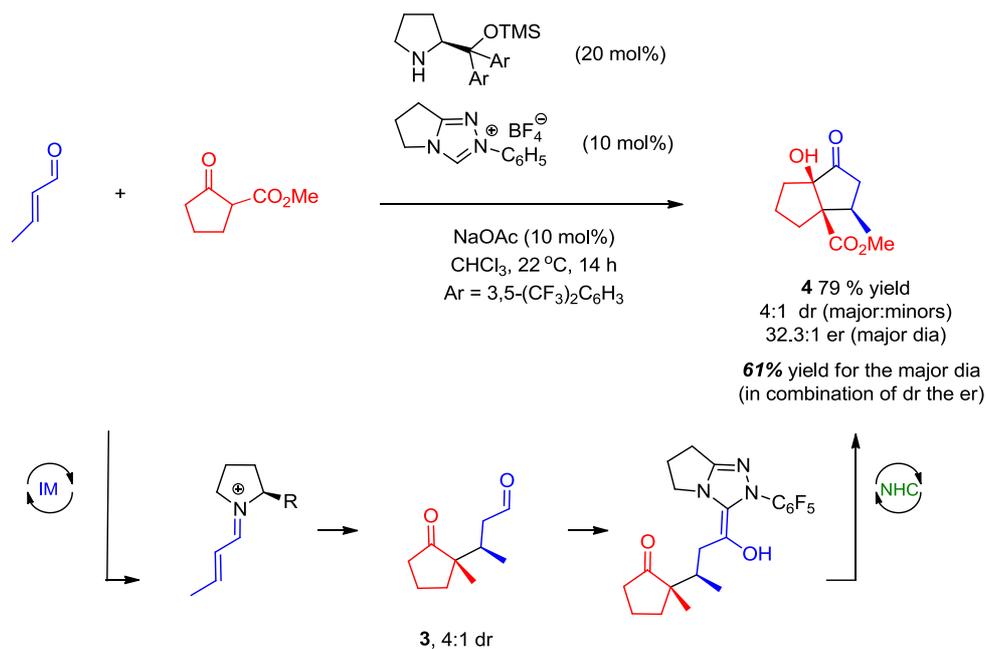
Scheme 12. Double activation catalysis in the Povarov reaction

In 2009, Lathrop and Rovis reported a beautiful example of cascade catalysis.^{40,41} They described an enantioselective Michael / benzoin organocascade between 1,3-dicarbonyl compounds and α,β -unsaturated aldehydes to give stereo-defined cyclopentanol derivatives (Scheme 13). The reaction proceeds by an initial enantioselective Michael addition under aminocatalytic iminium activation to afford the corresponding intermediate adduct **3**. The latter then undergoes an intramolecular NHC-catalyzed diastereoselective benzoin condensation in the presence of a suitable achiral NHC catalyst to afford the fused bicyclic product **4** in good yield as a 4:1 mixture of diastereomers with an excellent enantioselectivity. For comparison purpose (see below), it can be noted that the diastereo- and enantio-pure product **4** was obtained in 61 % yield. The work from the group of Rovis and other groups on the combination of aminocatalysis with NHC catalysis in cascade processes⁴² has been very inspiring for the research work described in this thesis.

⁴⁰ Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628.

⁴¹ Reviews on cascade organocatalysis: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (b) Grossmann A.; Enders D. *Angew. Chem. Int. Ed.* **2012**, *51*, 314. (c) Volla, C. M. R.; Atodiressei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390. (d) Wang, Y.; Lu, H.; Xu, P.-F. *Acc. Chem. Res.* **2015**, *48*, 1832.

⁴² (a) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (b) Ozboya, K. E.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1835. (c) Enders, D.; Grossmann, A.; Huang, H.; Raabe, G. *Eur. J. Org. Chem.* **2011**, 4298. (d) Jacobsen, C. B.; Jensen, K. L.; Udmark, J.; Jørgensen, K. A. *Org. Lett.* **2011**, *13*, 4790. (e) Deiana, L.; Dziedzic, P.; Zhao, G.-L.; Vesely, J.; Ibrahim, I.; Rios, R.; Sun, J.; Cór dova, A. *Chem. Eur. J.* **2011**, *17*, 7904. (f) Liu, Y.-Z.; Zhang, J.; Xu, P.-F.; Luo, Y.-C. *J. Org. Chem.* **2011**, *76*, 7551. (g) Liu, Y.; Nappi, M.; Escudero-Adan, E. C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 1310. (h) Ma, C.; Jia, Z.-J.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2013**, *52*, 948. (i) Youn, S. W.; Song, H. S.; Park, J. H. *Org. Lett.* **2014**, *16*, 1028. (j) He, G.; Wu, F.; Huang, W.; Zhou, R.; Ouyanga, L.; Han, B. *Adv. Synth. Catal.* **2014**, *356*, 2311. (k) Hong,

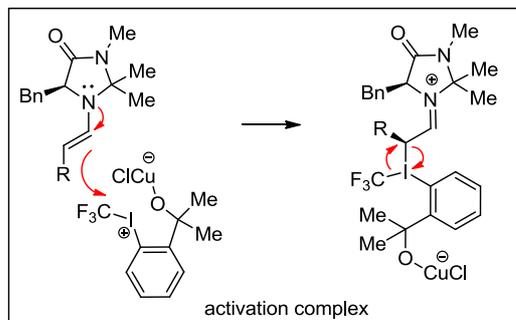
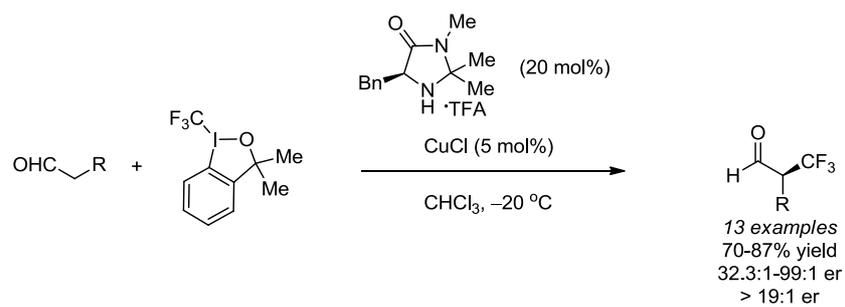


Scheme 13. Michael / benzoin organocascade under iminium / NHC activation

Finally, a beautiful example of synergistic catalysis was provided by the group of MacMillan with their work on the enantioselective α -trifluoromethylation of aldehydes (Scheme 14).⁴³ In this catalytic system, the copper(I) catalyst operates by Lewis acid activation of the electrophilic trifluoromethylation agent, while the nucleophile is activated through the enamine mode of action.

B.-C.; Dange, N. S.; Hsu, C.-S.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 4812. (l) Hong, B.-C.; Dange, N. S.; Hsu, C.-S.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2011**, *13*, 1338.

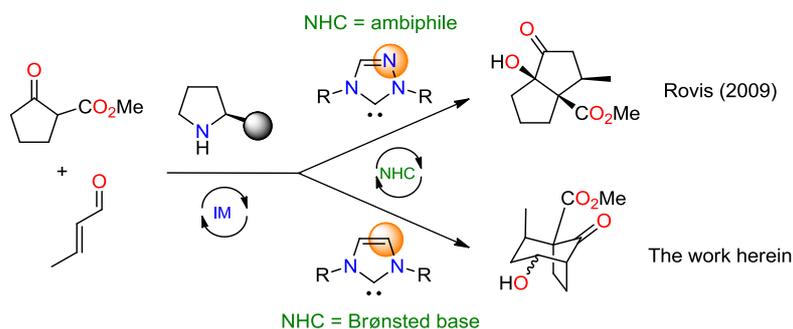
⁴³ Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986.



Scheme 14. Synergistic catalytic enantioselective α -trifluoromethylation of aldehydes

1.1.2. Objective of the research project

As explained above, our group has a strong interest for the use of NHCs in catalysis and cascade reactions. When I joined the group in fall 2012, I have been proposed to develop an enantioselective Michael / aldol organocascade for the preparation of bicyclo[3.2.1]octane derivatives. The envisioned catalytic system was forged on an enantioselective Michael addition step under aminocatalytic iminium activation, followed by a diastereoselective NHC-catalyzed aldol ring closure reaction operating by Brønsted base activation to afford the desired bicyclic product (see Scheme 6 for the NHC-catalyzed racemic version of this reaction). Thus, the prospected organocascade would use the same substrates as in the Rovis study highlighted in Scheme 13 and the same classes of organocatalysts, namely an aminocatalyst and a NHC, but affording a different product. As illustrated below in Scheme 15, the divergence point would be due to the ability of imidazolylidene-type NHCs to operate preferentially as catalytic Brønsted bases rather than ambiphilic catalysts as it is the case with triazolylidene NHCs. This part of my work is detailed in the following of this chapter.

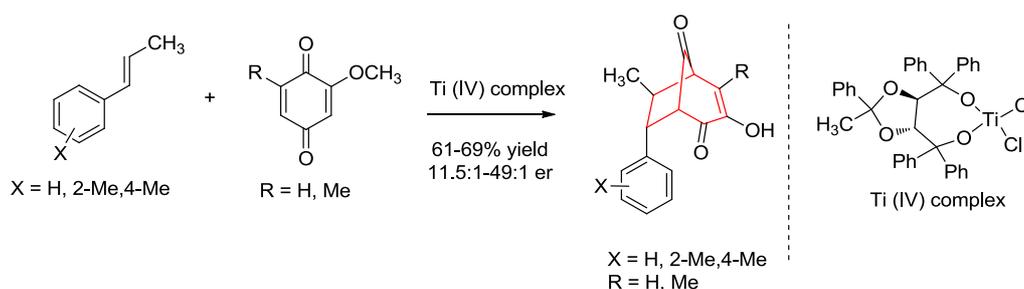


Scheme 15. A divergence point in dual iminium / NHC organocatalytic activation

1.1.3. Single step enantioselective construction of bicyclo[3.2.1]octanes

A highlight-type article from our group has recently appeared in the literature on this topic,⁴⁴ and only a synopsis of the work described therein, together with the most recent work will be described here.

Although several approaches to optically active bicyclo[3.2.1]octane derivatives have been described from the chiral pool or by multi-step synthesis,⁴⁵ only a few approaches are available for their single-step enantioselective synthesis. Among these, we can mention the early work of Engler and co-workers, who achieved enantioselective 6π (5+2) cycloadditions of 1,4-benzoquinones with aromatic olefins using a titanium-TADDOLate complex catalyst (Scheme 16).⁴⁶ A few other metal-catalyzed transformations were also developed.⁴⁴



Scheme 16. Titanium(IV)-catalyzed enantioselective 6π (5+2) cycloaddition

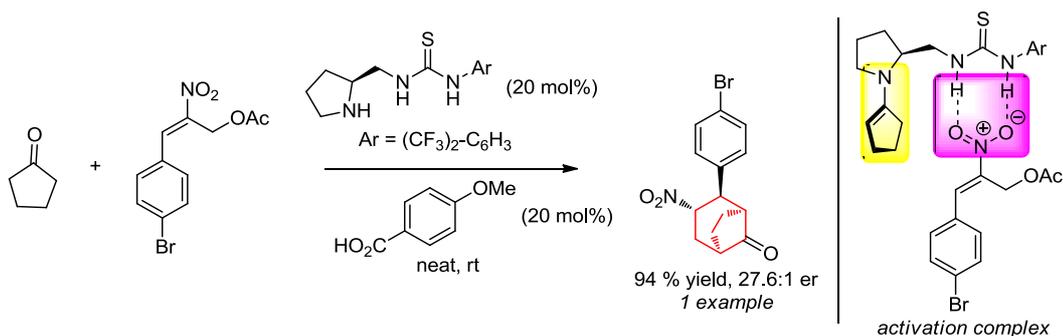
As to organocatalytic approaches, a few systems were described early on over the 2000–2007 period, but none of these were found both general and efficient. A significant step further was accomplished in 2009 with the work of Tang, Li and their co-workers who described a general approach to bicyclo[3.n.1] derivatives involving an interesting Michael / elimination / Michael cascade sequence catalyzed by a bifunctional aminocatalyst operating by enamine / H-bonding activation (Scheme 17).⁴⁷ Although a single example of a bicyclo[3.2.1]octane product was reported in the study, it was obtained in high yield, diastereo- and enantio-selectivity.

⁴⁴ Passet, M.; Coquerel, Y.; Rodriguez, J. *ChemCatChem* **2012**, *4*, 172.

⁴⁵ Passet, M.; Coquerel, Y.; Rodriguez, J. *Chem. Rev.* **2013**, *113*, 525.

⁴⁶ Enders, T. A.; Letavic, M. A. *J. Org. Chem.* **1999**, *64*, 2391.

⁴⁷ Cao, C.-L.; Zhou, Y.-Y.; Zhou, J.; Sun, X.-L.; Tang, Y.; Li, Y.-X.; Li, G.-Y.; Sun, J. *Chem. Eur. J.* **2009**, *15*, 11384.



Scheme 17. Enantioselective Michael / elimination / Michael organocascade

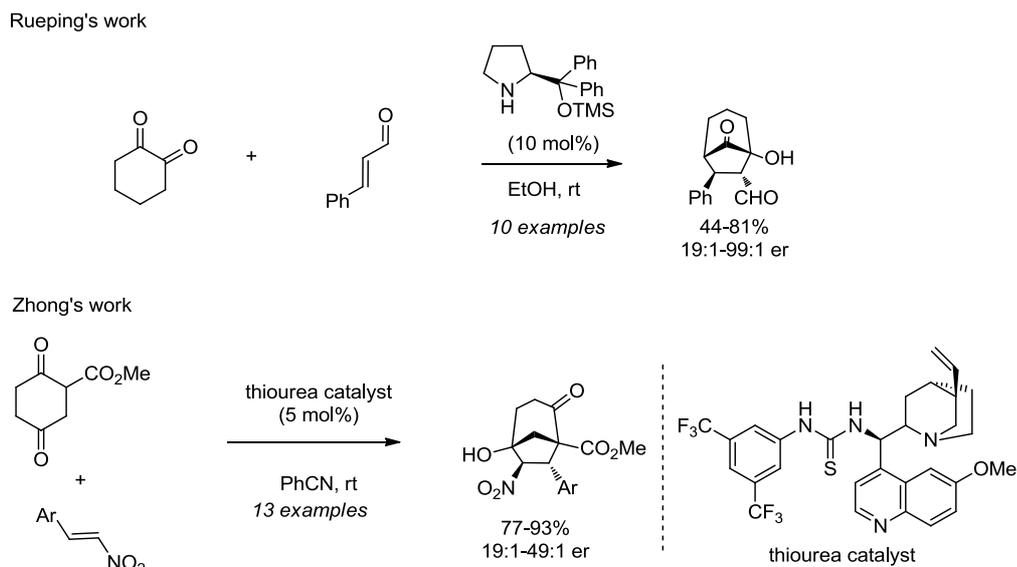
The same year, the Rueping group developed a different clever approach based on a Michael / aldol organocascade from cyclohexane-1,2-dione and α,β -unsaturated aldehydes using the Hayashi–Jørgensen aminocatalyst (Scheme 18, top).⁴⁸ A remarkable feature of the reaction is that cyclohexane-1,2-dione reacts successively as a nucleophile and an electrophile involving an iminium / enamine cascade activation with the same aminocatalyst. Shortly after, and contemporaneously with Zhao and coworkers,⁴⁹ the Rueping group reported a conceptually similar enantioselective organocatalytic Michael–Henry cascade from cyclohexan-1,2-dione and nitrostyrene derivatives, using a bifunctional Brønsted base/H-bond donor catalyst.⁵⁰ In a closely related study, Zhong and coworkers used 2-carbomethoxy cyclohexan-1,4-dione for the efficient construction of the bridged products and more recently Kokotos and co-workers developed a complementary sequence with simple cyclohexan-1,4-dione (Scheme 18, bottom).⁵¹

⁴⁸ Rueping, M.; Kuenkel, A.; Bats, J. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 3699.

⁴⁹ Ding, D.; Zhao, C.-G.; Guo, Q.; Arman, H. *Tetrahedron* **2010**, *66*, 4423.

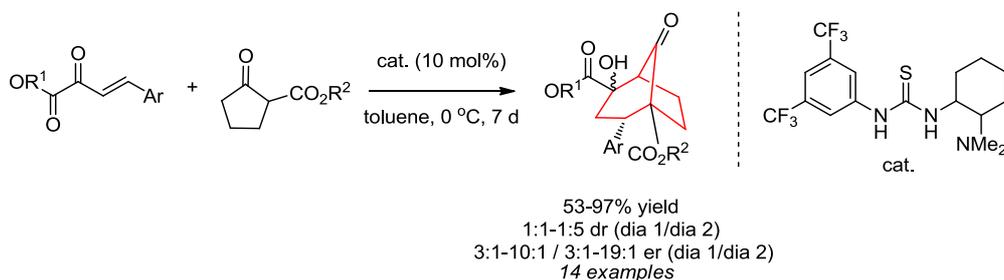
⁵⁰ Rueping, M.; Kuenkel, A.; Fröhlich, R. *Chem. Eur. J.* **2010**, *16*, 4173.

⁵¹ (a) Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682 (erratum: *ibid Org. Lett.* **2010**, *12*, 2892). (b) Tsakos, M.; Elsegood, M. R. J.; Kokotos, C. G. *Chem. Commun.* **2013**, *49*, 2219.



Scheme 18. Enantioselective Michael / aldol organocascades for the synthesis of bicyclo[3.2.1]octanes

Finally, the Alexakis group recently reported an approach to the bicyclo[3.2.1] ring system based on a distinct Michael / aldol cascade, also using a bifunctional Brønsted base/H-bond donor bifunctional catalyst (Scheme 19).⁵² In this work, and in analogy with the work we plan to develop, a 2-oxo-cyclopentane carboxylic acid derivative is used as bis-pronucleophile in combination with an activated α,β -unsaturated ketone acting as a bis-electrophile. Although the method was found relatively general and efficient in terms of isolated yields of the product, it suffers from stereoselectivity issues.



Scheme 19. Enantioselective Michael / aldol organocascade for the synthesis of bicyclo[3.2.1]octanes

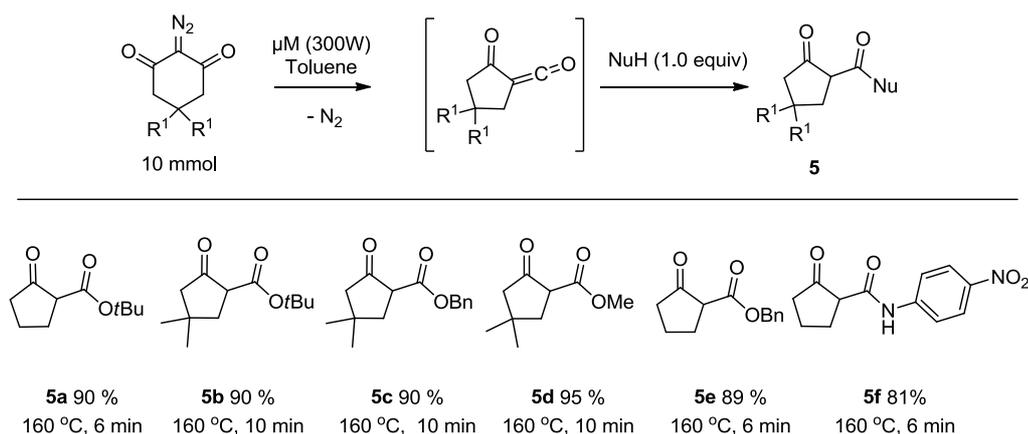
⁵² (a) Lefranc, A.; Gremaud, L.; Alexakis, A. *Org. Lett.* **2014**, *16*, 5242. For an early comparable approach: (b) Cao, C.-L.; Sun, X.-L.; Kang, Y.-B.; Tang, Y. *Org. Lett.* **2007**, *9*, 4151.

The recent work summarized above for the single step synthesis of optically active bicyclo[3.2.1]octane derivatives highlights, if necessary, the advantages of enantioselective metallic or organic catalysis over the chiral auxiliary and chiral pool approaches. However, and despite the recent progresses in the field, a general efficient enantioselective catalytic approach is still highly desirable, especially for applications in the synthesis of natural products. Our own approach is detailed in the next section of this manuscript.

1.2. Original enantioselective bi-organocatalytic synthesis of bicyclo[3.2.1]octanes

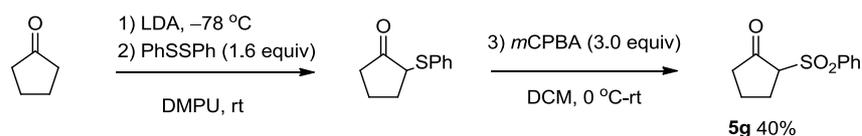
1.2.1. Preparation of substrates

Most of the substrates, reagents and catalysts used for the work were obtained by commercial sources. The non-commercially available cyclic β -ketoesters and β -ketoamides of type **5** were easily prepared from the corresponding 2-diazo-cyclopentan-1,3-diones⁵³ and one equivalent of alcohols or amines (Scheme 20).⁵⁴ The method involves a microwave-assisted Wolff rearrangement of the diazo substrate to produce an α -oxo-ketene intermediate, which is trapped by the nucleophilic alcohol or amine substrate to give the product **5**.



Scheme 20. Microwave-assisted synthesis of β -ketoesters and β -ketoamides

The β -ketosulfone **5g** was previously prepared in the laboratory and was obtained by oxidation of the corresponding sulfide using described methods (Scheme 21).⁵⁵



Scheme 21. Synthesis of the β -ketosulfone **1g**

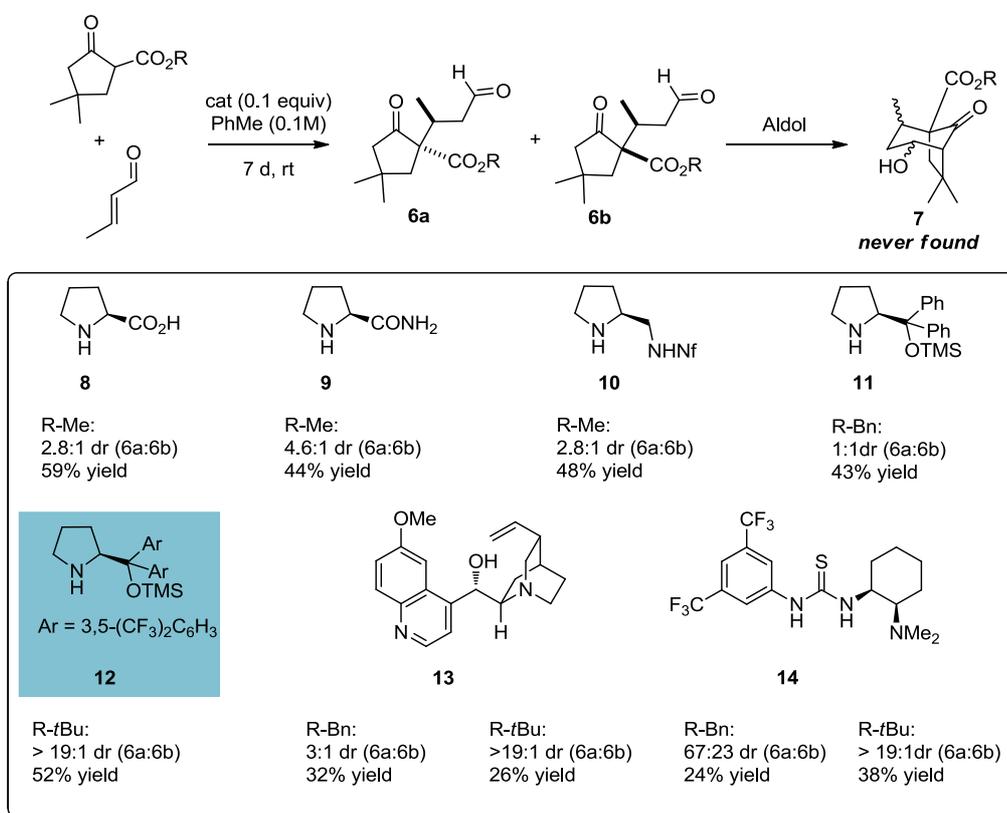
⁵³ Presset, M.; Mailhol, D.; Coquerel, Y.; Rodriguez, J. *Synthesis* **2011**, *16*, 2549.

⁵⁴ Presset, M.; Coquerel, Y.; Rodriguez, J. *J. Org. Chem.* **2009**, *74*, 415.

⁵⁵ Trost, B.M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287

1.2.2. Early work

In our group, the first trial for enantioselective organocatalytic Michael / aldol organocascades leading to optically active bicyclo[3.2.1]octane derivatives dates back to 2008 with the PhD thesis of Dr. Marc Presset.⁵⁶ At that time, a series of organocatalysts known to catalyze Michael addition reactions were tested in the model reaction depicted below (Scheme 22). Regrettably, and despite the fact that some Michael / aldol cascades were found to be catalyzed by a single organocatalyst (iminium then enamine activation),^{10d} none of the tested catalysts was able to promote the desired organocascade, and only the Michael adducts were obtained in moderate yields (24–59%) with poor to excellent diastereoselectivities. The enantioselectivity of the reactions was not examined during this work.



Scheme 22. Evaluation of catalysts for Michael-Aldol reaction

⁵⁶ Dr. Marc Presset, PhD thesis Aix-Marseille Université 2010, DOI: 2010AIX30033

From this series of preliminary results, it was concluded the following:

- The Michael addition works nicely under iminium activation, the most promising catalyst being the so-called Jørgensen proline derivative **12**.⁵⁷ Although enantioselectivities were not determined, some previous work made us confident on this matter.^{10a-d}
- The aldol elemental step would probably require an additional activation by a second catalyst with Brønsted base properties in a bi-catalytic process. Importantly, this second catalyst should not interact with the aminocatalyst used for the Michael addition elemental step, and of utmost importance, it should not promote a retro-Michael addition in order to maintain the stereochemical integrity of the intermediate Michael adduct.

It was previously demonstrated in our group that standard Brønsted bases, K₂CO₃ or DBU for example, were suitable promoters for the desired Michael / aldol cascade in the racemic series.⁵⁸ It was also demonstrated that these reactions are under thermodynamic control, involving a complete reversibility of both the Michael addition and aldol steps. Thus, none of the previously used Brønsted bases would be applicable in the targeted enantioselective organocascade. Based on the previous work of our group on the Brønsted base properties of NHCs (see above), and particularly the slow reversibility of the Michael addition under NHC catalysis, it was hypothesized that NHCs would be suitable Brønsted base catalysts to achieve the desired aldol elemental step of the cascade.

This idea was tested during the laboratory internship of M. Jeremy Godemert during his Master 2.⁵⁹ In short, the proof of concept for our hypothesis was obtained with the reaction depicted in Scheme 23. In that case, the Michael addition step catalyzed by the aminocatalyst **12** introduced in 20 mol% required 2 hours at room temperature in relatively concentrated methanolic solution as determined by TLC analysis. Then, the NHC catalyst **2** (20 mol%) was added to the reaction mixture in order to achieve the aldolization step of the sequence. The desired bicyclic product **7a** was obtained in 56% yield as a relatively complex and difficult to analyze mixture of four diastereomers. For simplification, the secondary alcohol in **7a** was oxidized using IBX in ethyl acetate,⁶⁰ affording the diketone **16a** in 77% yield, with a dr of 3:1 and an er of 11:1 for the major diastereomer. The relative configuration of the methyl group C7 in the major diastereomer of **16a** was determined to be axial by ¹³C NMR. Indeed,

⁵⁷ (a) Jensen, K. L.; Dickmeiss, K. L.; Jiang, H.; Albrecht, L. Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.

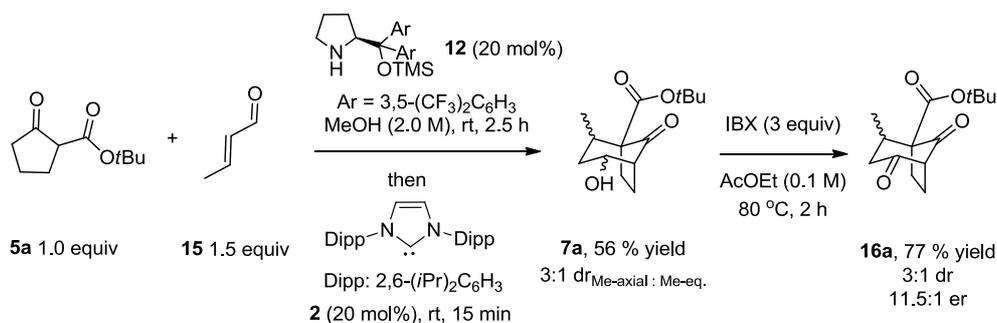
(b) Meninno, S; Lattanzi, A. *Chem. Commun.* **2013**, *49*, 3821.

⁵⁸ Coquerel, Y.; Filippini, M.-H.; Bensa, D.; Rodriguez, J. *Chem. Eur. J.* **2008**, *14*, 3078 and references therein.

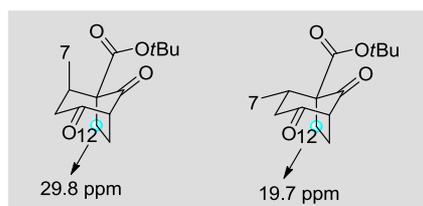
⁵⁹ Godemert, J., M.Sc. report, Aix-Marseille Université, 2012.

⁶⁰ More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.

in the case of the diastereomer with the axial methyl substituent, the carbon at C12 is deshielded by about 10-12 ppm relative to the same carbon atom in the other diastereomer due to the absence of γ -effect (Scheme 24).⁶¹ This method has largely been used in the past in our group for the determination of the relative configurations of these kinds of bicyclic systems.⁶²



Scheme 23. The first enantioselective Iminium / NHC Michael aldol organocascade



Scheme 24. Determination of the diastereoselectivity by ¹³C NMR

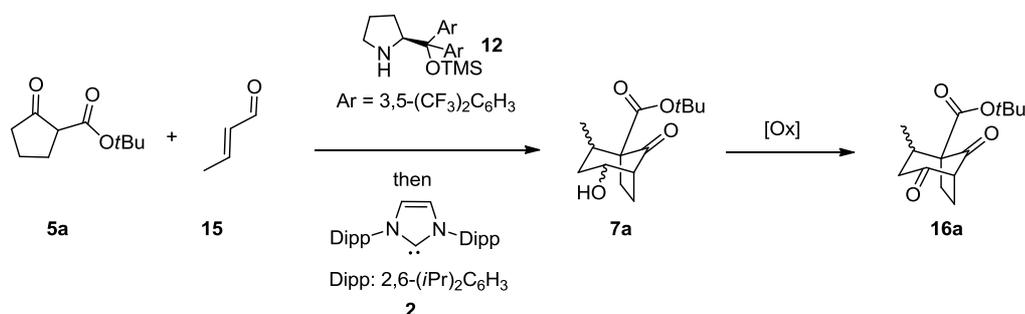
Overall, the preliminary work exposed above allowed obtaining the proof of concept for the methodology we plan to develop. However, many problems (yields, catalysts loading, stereoselectivities) were to be solved before the method could be generalized and ultimately become a useful synthetic tool for enantioselective catalysis.

⁶¹ Grant, D. M.; Vernon Cheney, B. *J. Am. Chem. Soc.* **1967**, *89*, 5315.

⁶² Filippini, M.-H.; Faure, R.; Rodriguez, J. *J. Org. Chem.* **1995**, *60*, 6872.

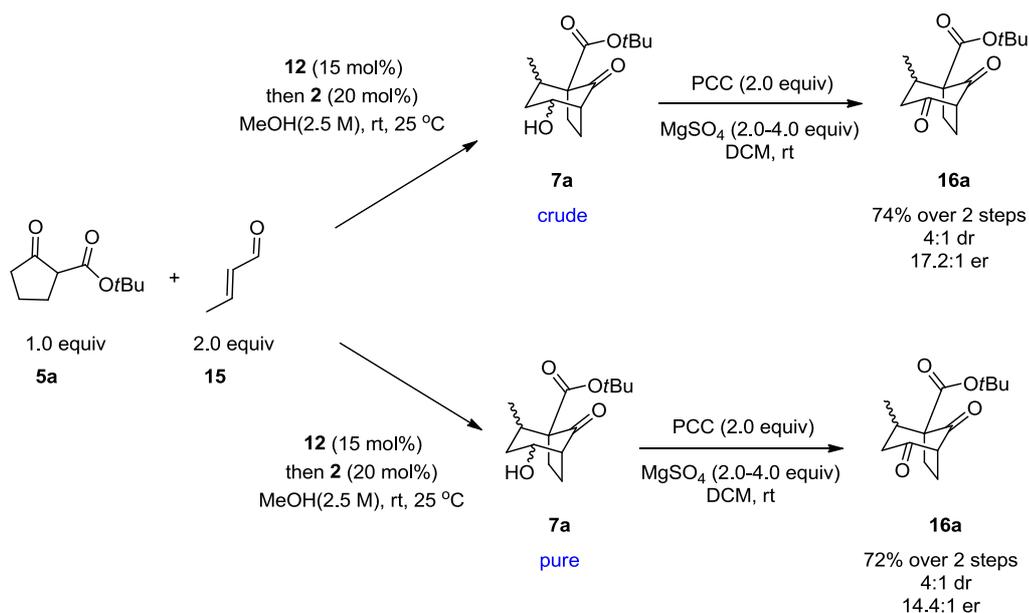
1.2.3. Enantioselective synthesis of bicyclo[3.2.1]octanes

From the above preliminary results, we selected the reaction between tert-butyl 2-oxo-cyclopentane carboxylate and crotonaldehyde with the Jørgensen catalyst **12** and the NHC catalyst IDipp (**2**) for the optimization study (Scheme 25).



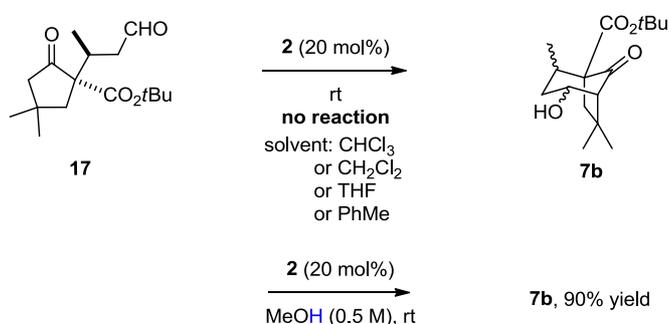
Scheme 25. The model reaction for optimization studies

As shown above, an oxidation step of the bicyclo[3.2.1]octanol product **7a** into the diketone **16a** is required to facilitate the stereochemical analyses. Previous conditions for this reaction using IBX (Scheme 23) were not satisfactory, affording only a moderate yield of the diketone product **16a**. So, I started my work with the optimization of this oxidation reaction. Obviously, neutral or moderately acidic conditions are required to avoid the base-promoted epimerization of the product **7** by retro-aldol / retro-Michael processes. For this purpose, we selected pyridinium chlorochromate (PCC) as a potential oxidant candidate. We have rapidly found that in the presence of anhydrous magnesium sulfate, the desired diketone **16a** could be obtained in nearly quantitative yield from the corresponding alcohol **7a** (Scheme 26). Also, we have checked if the crude product **7a** could be used directly in this reaction in order to save time and solvents. A comparison of the results obtained from crude and purified **7a** afforded very similar results with a little preference for the reaction performed directly from crude **7a** (Scheme 26).



Scheme 26. Optimization of the oxidation step

This being done, we could embark on the optimization study of the bicatalytic enantioselective reaction. We first examined the influence of the nature of the solvent on the aldolization step in the racemic series. Many common organic solvents are suitable for this NHC-catalyzed aldolization reaction, except in the challenging cases in which the aldolization is occurring at a neopentyl position as in the gem-dimethyl containing Michael adduct **17** (Scheme 27). We thus selected **17** as a model substrate. The aldehyde **17** (dr > 19:1) was treated with 20 mol% of the NHC IDipp in representative organic solvents (Scheme 27). Unsurprisingly, this series of test showed that a protic solvent is necessary to achieve the aldolization, probably involving a Lewis acid activation of the aldehyde carbonyl group with the solvent (H-bonding).



Scheme 27. Selection of the solvent (racemic series)

Then, we examine the influence of the reaction time and temperature with both the Jørgensen and MacMillan catalysts **12** and **18**, respectively, in the reaction of the β -ketoester **5a** and crotonaldehyde (**15**) (Table 1). In this case, it was rapidly confirmed that the Jørgensen catalyst **12** exhibit superior activity when compared to the MacMillan catalyst **18** (compare entries 1 with 2, and 6 with 7). A reaction performed in hexafluoroisopropanol did not improve the result (entry 3), but the reaction was found sensitive to the concentration with an optimum at 2.5 M (compare entries 1, 4 and 5). The influence of the temperature was also examined: while slightly better results were obtained at 0 °C (entry 6), longer reaction time was observed at lower temperature (compare with entry 8). Overall, the best conditions identified for the studied reaction involve a reaction in 2.5 M methanol with the Jørgensen catalyst **12** at 0 °C (entry 6). In this case, and following oxidation, the desired diketone **16a** could be obtained in 75% yield as a 4:1 mixture of diastereomers with an excellent enantiomeric ratio for the major diastereomer (er = 19:1).

Table 1. Optimization of reaction time and temperature with catalysts **12** and **18**

Reaction scheme: **5a** (1.0 equiv) + **15** (2.0 equiv) $\xrightarrow[\text{then IDipp (20 mol\% MeOH)}]{\text{12 (15 mol\%) or 18 (20 mol\%)}}$ **7a** (without purification) $\xrightarrow[\text{MgSO}_4 (2.0-4.0 \text{ equiv}), \text{DCM, rt}]{\text{PCC (2.0 equiv)}}$ **16a**

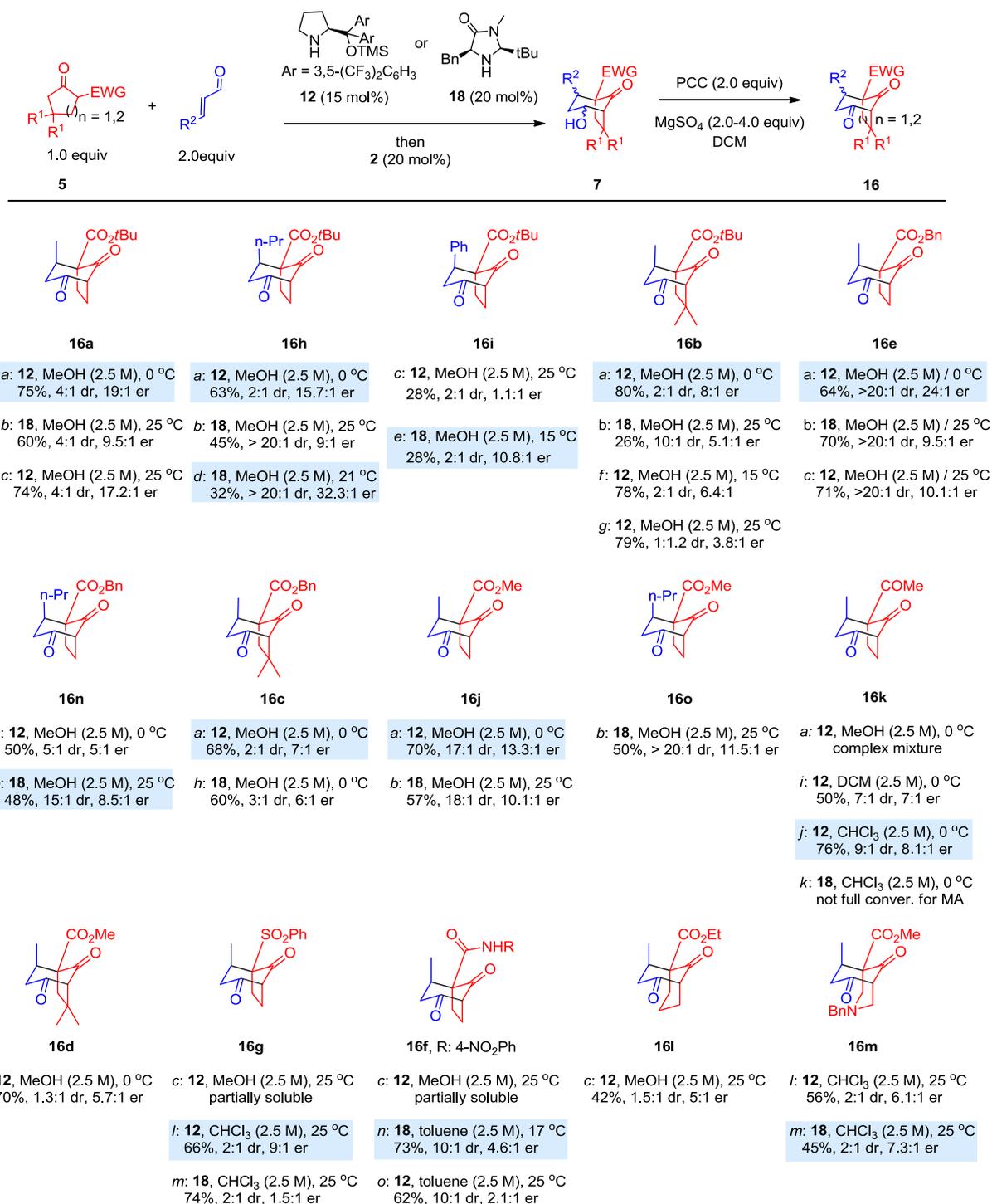
entry	cat	T.(°C)	reaction time of MA (h)	product (%)	dr (ax : eq.)	er ^e
1 ^a	12	25	18	74	4:1	17.2:1
2 ^a	18	25	72	60	4:1	9.5:1
3 ^b	12	25	72	55	4:1	7.3:1
4 ^c	12	25	120	20	3:1	4:1
5 ^d	12	25	72	70	3:1	7:1
6 ^a	12	0	22	75	4:1	19:1
7 ^a	18	0	96	–	–	–
8 ^a	12	-10	64	72	4:1	19:1

(a) The reaction was carried out in 2.5 mol/L MeOH, the reaction time of aldolization is 2–10 h; (b) The reaction was carried out in 2.5 mol/L (CF₃)₂CHOH, the reaction time of aldolization is 5 h; (c) The reaction was carried out in 10.0 mol/L MeOH, the reaction time of aldolization is 5 h.; (d) The reaction was carried out in 0.5 mol/L

MeOH, the reaction time of aldolization is 5 h; (e) The enantiomeric ratio was determined by HPLC on a chiral stationary phase for the major diastereomer having the axial methyl group (see experimental section).

With good reaction conditions in hand, we embarked on the investigation of the scope of the reaction (Scheme 28). Rapidly after the beginning of this part of my work, it was clear that optimum reaction conditions identified above for the product **16a** [conditions (a)] were not directly transposable to other cases, affording the desired bridged bicyclic products in low to moderate yields and/or stereoselectivities. In many cases, it was thus necessary to re-optimize the conditions (solvent, temperature, and catalyst for the Michael addition) as a function of the couple of substrates used. For example, when crotonaldehyde is replaced by hex-2-enal, conditions (a) delivered the product **16h** in lower yield and stereoselectivities when compared to the product **16a**. In this case, the MacMillan catalyst **18** was found much more selective although the product **16h** was only obtained in 32% yield. The reaction was also found possible but not efficient with an α,β -unsaturated aldehyde having an aromatic group at the β position, cinnamaldehyde for instance, affording the product **16i** in quite low yield and stereoselectivities. In this case, a significant amount of the intermediate Michael adduct could be isolated even after prolonged reaction time using the aminocatalyst **12** (or **18**), while catalyst **18** (or **12**, verify) afforded the product **16i** in very low stereoselectivities. The introduction of a gem-dimethyl substituent onto the starting β -ketoester as in the case of the product **16b** did not affect the yield of the reaction, but had a deleterious effect on the stereoselectivity. Notably, the aminocatalyst **12** was found significantly superior to **18** in this case (very slow Michael addition with **18**). A rationale for the observed decrease in stereoselectivity is that the aldolization step of the cascade is kinetically disfavored due to an increased steric effect, which resulted in a longer life-time of the intermediate Michael adduct and ultimately to more NHC-catalyzed retro-Michael / Michael processes responsible for the loss of diastereoselectivity and enantioselectivity. Benzyl and methyl β -ketoesters could also be used, sometimes leading to better results than tert-butyl β -ketoesters as in the case of the product **16e**. Also, the reaction leading to the product **16j** is interesting. It uses the exact same substrates as the previously reported reaction of Rovis⁴⁰ (Scheme 13) with just a subtle difference in the structures of the NHC catalyst to afford a very different product. Other activating groups than esters could also be used. For example, the reaction with 2-acetyl cyclopentanone afforded the corresponding triketone **16k**. However, in this case the reaction required a non-nucleophilic solvent to avoid the retro-Dieckmann-type fragmentation of the intermediate Michael adduct, and dichloromethane and chloroform afforded acceptable

results. A β -ketosulfone and a secondary β -ketoamide (partially soluble in MeOH in this case) were also productive substrates to afford the products **16g** and **16f**, respectively. Finally, the reaction could also be extended to six-membered β -ketoester substrates to produce the bicyclo[3.3.1]nonane derivatives **16l** and **16m**, although with somewhat reduced efficiency and stereoselectivity. This can be explained by a relatively slow and difficult to drive to completion Michael addition, with an introduction of the NHC catalyst when some substrates are still present in the reaction mixture leading to racemic reactions (NHC-catalyzed Michael addition).



Scheme 28. Enantioselective Michael / aldol organocascade for the synthesis of bicyclo[3.n.1]alkanes. All reactions were conducted on a 0.5 mmol scale; diastereomers ratio were determined by NMR of the crude reaction mixtures; the enantiomers ratio of the major diastereomer (axial C8 substituent) was determined by HPLC on a chiral stationary phase.

1.2.4. Conclusion

We have developed an original organocascade for the enantioselective synthesis of bridged, essentially bicyclo[3.2.1]octanes, compounds. The reaction features an enantioselective Michael addition step under aminocatalytic iminium activation, followed by a diastereoselective NHC-catalyzed aldol ring closure reaction operating by Brønsted base activation to afford the desired bicyclic product. Very interestingly, the studied organocascade is not the first to combine iminium activation with NHC activation with these substrates (see the Rovis work in Scheme 13), and we have identified a divergence point in iminium / NHC cascade catalysis controlled by the nature of the selected NHC. One notable difference between the two studies is that we cannot introduce the two catalysts simultaneously at the beginning of the reaction as in the Rovis work.

Of course, our new methodological tool is not perfect and there is plenty of room for its improvement, but we estimated that it was good enough for applications in synthesis. In order to demonstrate the synthetic value of our method, we decided to embark on its application to a concrete case with the total synthesis of a natural product. This part of my work is the topic of the next chapter.

Chapter 2

Total synthesis of quadrane sesquiterpenes

2.1. Introduction

2.1.1. Quadranes natural products

Quadranes form a small class of 18 sesquiterpene natural products belonging to the larger family of polyquinanes.⁶³ Quadranes are also sometimes referred to as suberosanes or terrecyclanes. They generally exhibit interesting but not exceptional biological activities, especially as antimicrobial agents and anticancer agents. The structural features of this class of compounds include a diquinane ring system (*cis*-fused AB rings) bridged with a three carbon tether forming the bicyclo[3.2.1]octane ring system (BC rings), an axial one-carbon substituent at C8, a gem-dimethyl group at C13, and a one-carbon substituent at C5 that can exist in both relative configurations (Figure 6). Naturally occurring quadranes have been isolated from two kinds of sources, terrestrial ones in fungi, and marine ones in gorgonians.⁶³

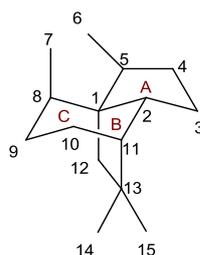


Figure 6. Structural features of quadranes

The first isolated quadrane is (–)-quadrone (**I**), which was isolated in 1978 by Calton and Ranieri from the fermentation of broth of the fungus *Aspergillus terreus* (Figure 7).⁶⁴ (–)-Quadrone (**I**) is the only known tetracyclic quadrane. Very soon after the isolation of (–)-quadrone (**I**), (+)-terrecyclic acid A (**II**) was isolated from the same fungus by the group of Isogai (Figure 7).⁶⁵ It can already be noted that the natural products **I** and **II** are structurally closely related, and actually Isogai and co-workers were able to convert **II** into **I** (oxa-Michael addition under pyrolytic conditions). The absolute configurations of (–)

⁶³ Review: Passet, M.; Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2010**, 2247.

⁶⁴ (a) Calton, G. J.; Ranieri, R. L.; Espenshade, M. A. *J. Antibiot.* **1978**, *31*, 38. (b) Ranieri, R. L.; Calton, G. J. *Tetrahedron Lett.* **1978**, *19*, 499.

⁶⁵ (a) Nakagawa, M.; Hirota, A.; Isogai, A. *J. Antibiot.* **1982**, *35*, 778. (b) Nakagawa, M.; Hirota, A.; Sakai, H.; Isogai, A. *J. Antibiot.* **1982**, *35*, 783. (c) Hirota, A.; Nakagawa, M.; Sakai, H.; Isogai, A. *J. Antibiot.* **1984**, *37*, 475. (d) Hirota, A.; Nakagawa, M.; Hirota, H.; Takahashi, T.; Isogai, A. *J. Antibiot.* **1986**, *39*, 149.

-)quadrone (**I**) and (+)-terrecyclic acid A (**II**) were determined in 1984 by the groups of Isoe⁶⁶ and Smith, III⁶⁷ by diastereoselective total syntheses: (+)-fenchone (terpene chiral pool) served as starting material for the synthesis of (+)-**II**, and (+)-**I** was obtained following a kinetic resolution of an advanced intermediate using (*S*)-*O*-methyl mandelic acid as the chiral auxiliary.

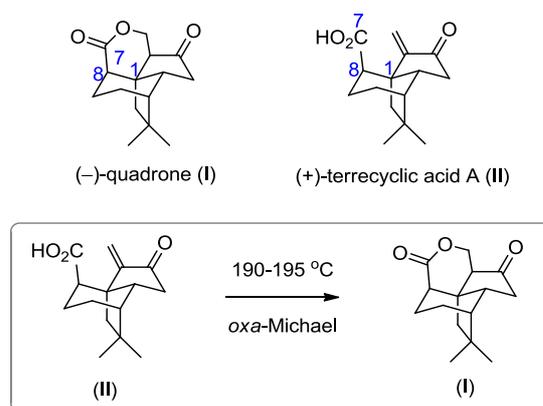


Figure 7: Two representative quadranes isolated from terrestrial sources

In 1996, the Boyd group reported the isolation of (+)-suberosenone (**III**) from the gorgonian *Subergorgia suberosa* (Figure 8).⁶⁸ It was the first time that a quadrane sesquiterpene could be isolated from a marine organism. Remarkably, (+)-suberosenone (**III**) exhibits a completely reduced carbon atom at C7 (methyl group), a feature later found in all naturally occurring quadranoids isolated from marine sources. Following this discovery, the group of Sheu reported the isolation of the closely related (-)-suberosanone (**IV**),⁶⁹ as well as the two bicyclic quadranes (-)-isishippuric acid A (**V**) and (-)-isishippuric acid B (**VI**)⁷⁰ from the gorgonian *Isis hippuris*. Interestingly, the natural products **V** and **VI** exhibit a bicyclic BC ring system biosynthetically obtained by oxidative ring fragmentation of the A ring of their biosynthetic precursors. Also, it can be noted that compound **VI** is actually a norquadrane with only 14 carbon atoms.

⁶⁶ Kon, K.; Ito, K.; Isoe, S. *Tetrahedron Lett.* **1984**, *25*, 3739.

⁶⁷ (a) Smith, III, A. B.; Konopelski, J. P. *J. Org. Chem.* **1984**, *49*, 4094. (b) Smith, III, A. B.; Konopelski, J. P.; Sprengeler, P. A. *J. Am. Chem. Soc.* **1991**, *113*, 3533.

⁶⁸ Bokesch, H. R.; McKee, T. C.; Boyd, M. R. *Tetrahedron Lett.* **1996**, *37*, 3259.

⁶⁹ Sheu, J.-H.; Hung, K.-C.; Duh, C.-Y. *J. Nat. Prod.* **2000**, *63*, 1603.

⁷⁰ Sheu, J.-H.; Chao, C.-H.; Wu, C.-C. *Tetrahedron Lett.* **2004**, *45*, 6413.

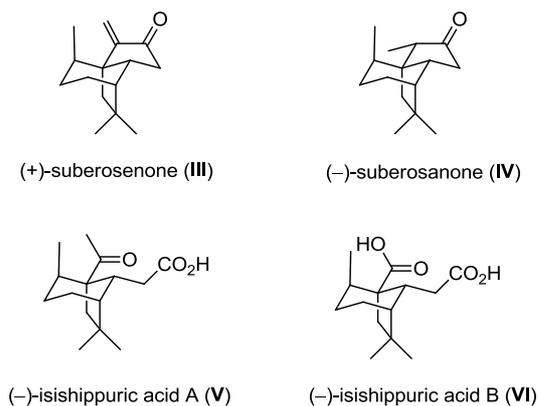


Figure 8: Four representative quadranes isolated from marine sources

Importantly for the following, only the absolute configurations of (-)-quadrone (**I**), (+)-terrecyclic acid A (**II**), (-)-isishippuric acid A (**V**), (-)-isishippuric acid B (**VI**), and more recently (+)-suberosenone (**III**),⁷⁵ have been unambiguously established by chemical synthesis to be (1*R*) as depicted in Figure 7 and Figure 8 (see above).⁶³ Some studies directed towards the prediction of the absolute configurations of compounds **I**, **III**, and **IV** through DFT calculations based on their $[\alpha]_D$ values indicated that their absolute configurations at C1 are likely to be (1*R*) as depicted in Figure 7 and Figure 8.⁷¹ While this is true and confirmed in the cases of compounds **I**, **III**, **V** and **VI**, the absolute configuration of naturally occurring **IV** remains to be unambiguously demonstrated (see discussion below).

⁷¹ Stephens, P. J.; McCann, D. M.; Devlin, F. J.; Smith, III, A. B. *J. Nat. Prod.* **2006**, *69*, 1055.

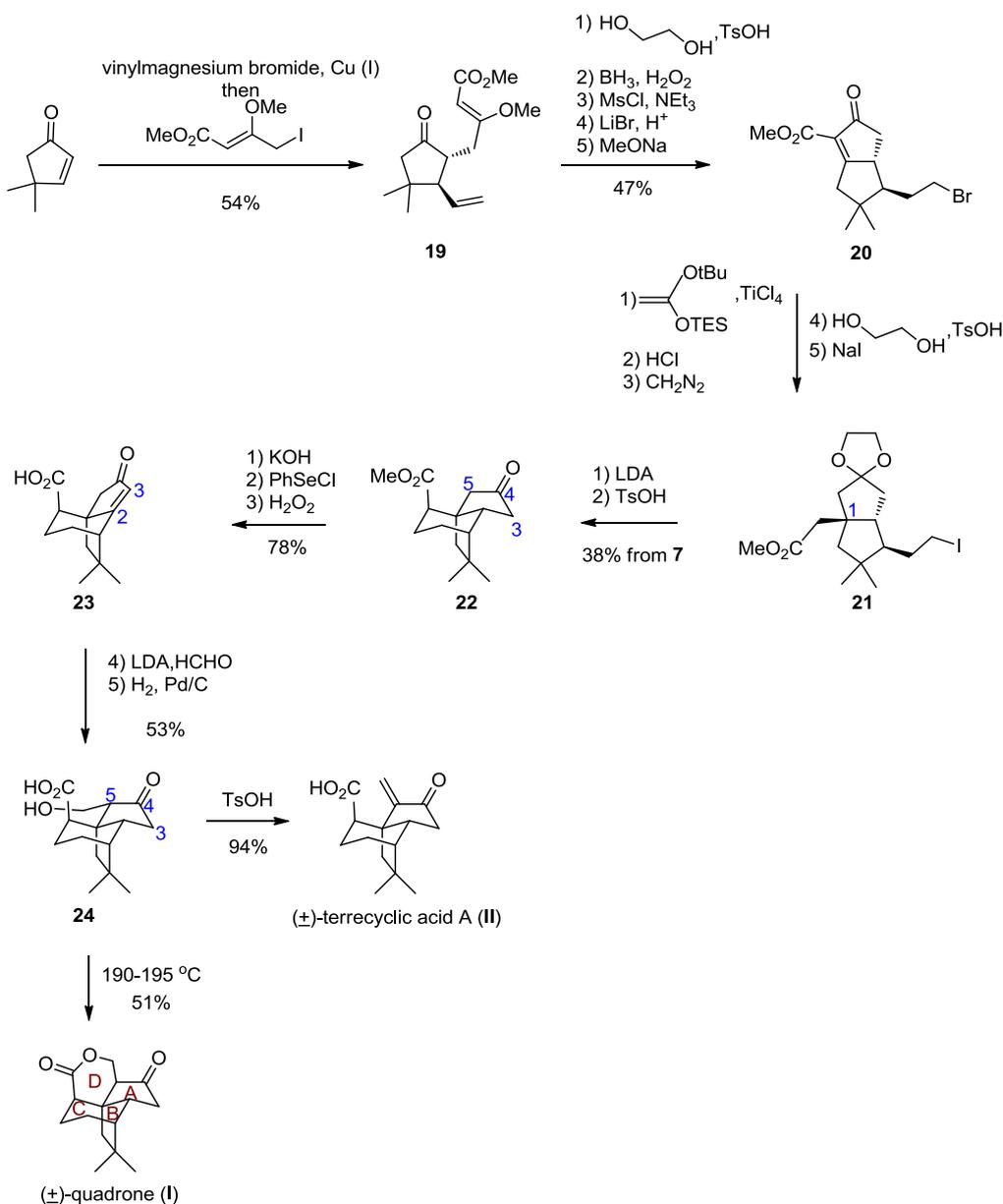
2.1.2. Total syntheses of quadranes

Due to their potent biological activities and challenging molecular architectures, quadrane sesquiterpenes have soon attracted great attention from the synthetic community. This area of research was comprehensively reviewed recently,⁶³ and only the most important work will be highlighted here.

Danishefsky first reported the total synthesis of (\pm)-quadrone (**I**) in 1980, just two years after its isolation (Scheme 29)⁷². The synthesis started from 4,4-dimethylcyclopentenone as the precursor of ring B with a consecutive copper(I)-promoted conjugate addition of a vinyl Grignard / enolate trapping with a functionalized alkyl iodide to give intermediate **19**. Five additional steps were required to prepare the AB ring system **20**, notably involving a base-promoted aldolization / crotonization sequence for the construction of ring A. The quaternary carbon atom at C1 was installed by a conjugate addition of a silyl ketene acetal, and some functional groups manipulations afforded intermediate **21**. The elaboration of the six-membered C ring ensued from a remarkably diastereoselective cyclization of the lithium enolate derived from **21** to give the ABC ring system of quadranes, and a deprotection step afforded intermediate **22**. The α -alkylation at C5 of the ketone group in **22** proved very difficult due to regioselectivity issues, the $\Delta_{3,4}$ enolate being formed preferentially. This problem was circumvented by the temporary introduction of the $\Delta_{2,3}$ unsaturation with concomitant saponification of the methyl ester at C8 to give the enone intermediate **23**. Then the desired $\Delta_{4,5}$ enolate could be generated and trapped by formaldehyde, and the $\Delta_{2,3}$ double bond diastereoselectively hydrogenated from the β face to give the hydroxyacid intermediate **24**. Amusingly, compound **24** was later isolated as a naturally occurring quadrane.⁷³ The dehydration of **24** afforded (\pm)-terrecyclic acid A (**II**), while (\pm)-quadrone (**I**) was obtained under thermolytic conditions directly from **24**. Overall, this total synthesis of (\pm)-quadrone (**I**) was achieved in 19 steps and 3.1% yield from 4,4-dimethylcyclopentenone.

⁷² Danishefsky, S.; Vaughan, K.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 4262.

⁷³ Wijeratne, E. M. K.; Turbyville, T. J.; Zhang, Z.; Bigelow, D.; Pierson, III, L. S.; VanEtten, H. D.; Whitesell, L.; Canfield, L. M.; Gunatilaka, A. A. L. *J. Nat. Prod.* **2003**, *66*, 1567.

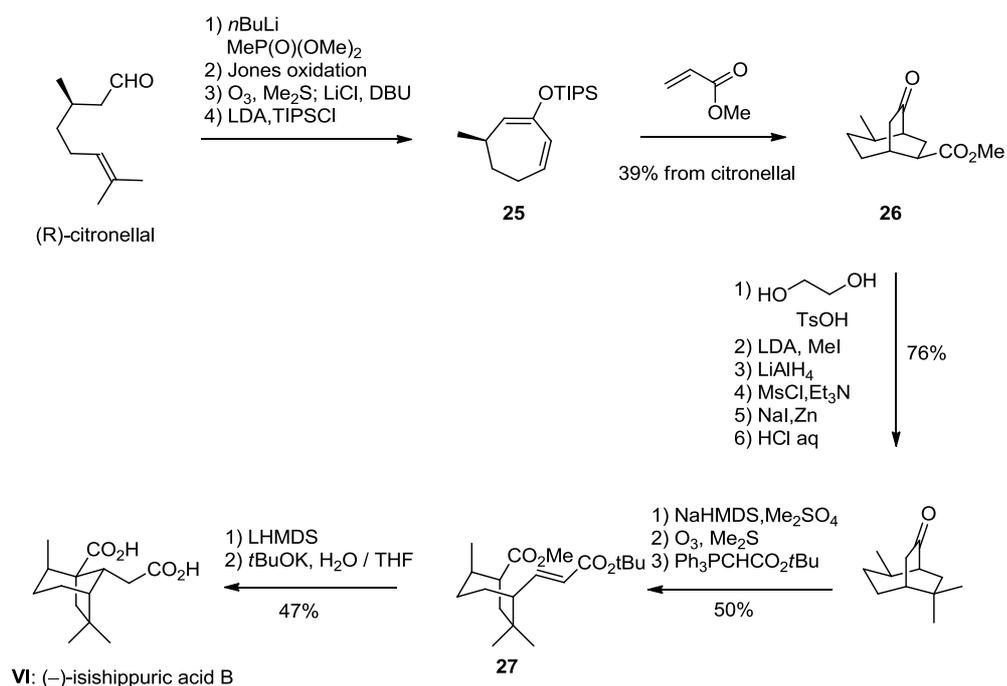


Scheme 29: Danishefsky's total synthesis of (±)-quadrone (**I**)

Inspired by Danishefsky's work, improved synthetic routes to quadrone (**I**) and other quadranes emerged.⁶³ Importantly, most of the existing total syntheses of quadranes are in the racemic series, and only a restricted number of non-racemic diastereoselective syntheses have been reported. These include approaches based on the chiral pool, either used as starting material or temporary chiral auxiliary, or on kinetic resolution. It must be underlined here that, to date, *no enantioselective total synthesis of a quadrane sesquiterpene has been reported*. In the following, two recent diastereoselective non-racemic total syntheses based on

the chiral pool are highlighted. The first one uses (*R*)-citronellal as the starting material, while the second one exploits (*R*)-1-phenylethylamine as a chiral auxiliary.

In 2007, Kuwahara realized the first and only total synthesis of (–)-isishippuric acid **VI** from (*R*)-citronellal (Scheme 30).⁷⁴ The cycloheptadienol silyl ether **25** was obtained from (*R*)-citronellal in four steps including an intramolecular Horner–Wadsworth–Emmons reaction. The latter then served as an electron-rich diene in a regioselective Diels–Alder reaction with methyl acrylate to afford the bicyclic intermediate **26**. After some chemical manipulations, the key diester intermediate **27** could be obtained. The bicyclo[3.2.1]octane ring system of the natural product was next elaborated by an elegant intramolecular Michael addition, regrettably performing with a moderate diastereoselectivity (dr = 2.3:1), and the saponification of the resulting material afforded (–)-isishippuric acid **VI**. Overall, this total synthesis of (–)-isishippuric acid **VI** was achieved in 16 steps and 6.9% yield from (*R*)-citronellal, which allowed establishing the absolute configuration of naturally occurring (–)-**VI** as (1*R*).

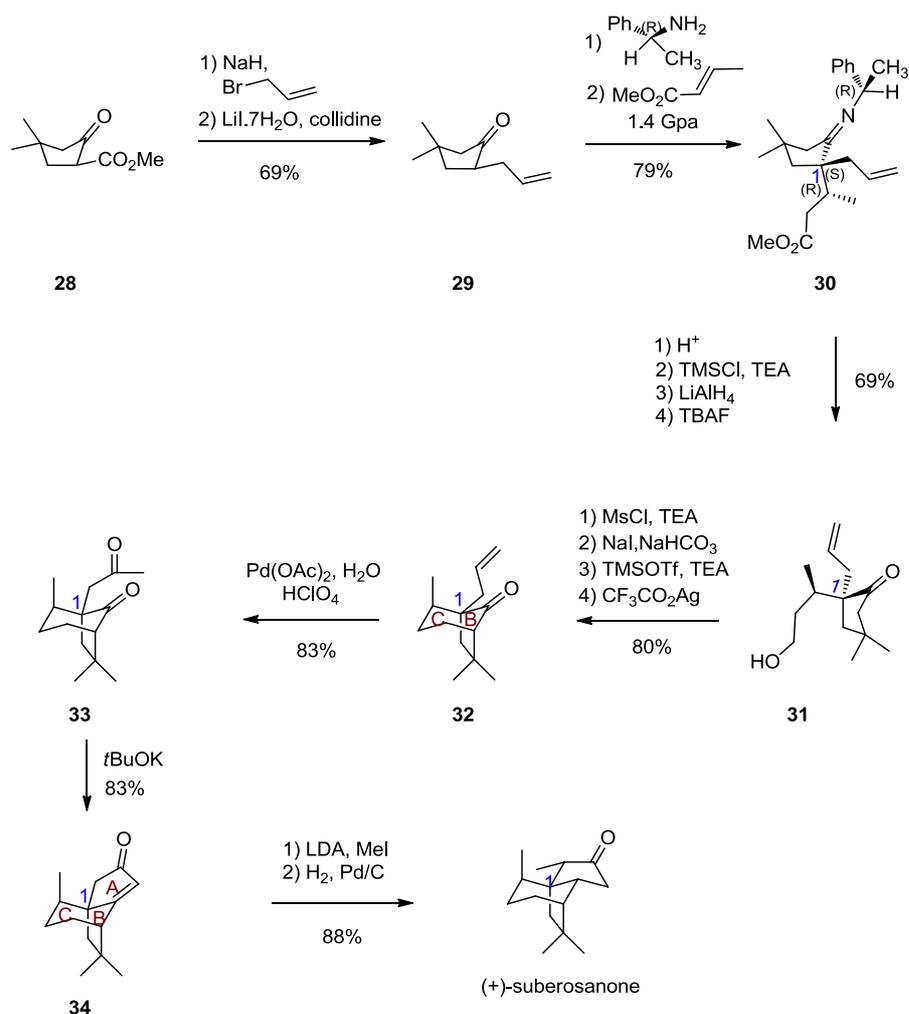


Scheme 30: Kuwahara's synthesis of (–)-isishippuric acid **VI**

⁷⁴ Torihata, M.; Nakahata, T.; Kuwahara, S. *Org. Lett.* **2007**, *9*, 2557.

In 2015, the group of Dumas reported the total syntheses of (+)-suberosenone (**III**) and (+)-suberosanone (**IV**) (Scheme 31).⁷⁵ This work is of importance to us because we have achieved an independent total synthesis of (+)-**IV**. The pivotal step of the Dumas' approach relies on a highly regio- and diastereo-selective hyperbaric Michael addition of the chiral enantiopure imine derived from the cyclopentanone **29** with methyl crotonate using (*R*)-1-phenylethylamine as the chiral auxiliary to afford the product **30** as a single diastereomer (dr > 39:1 as determined by NMR), thereby fixing the absolute configuration at C1. Notably, this reaction can be conducted on a gram-scale. Some functional group manipulations were then necessary to obtain the primary alcohol **31**, which was converted to the corresponding iodide and engaged in a ring-closing α -alkylation sequence via a silyl enol ether intermediate to give the BC ring system in **32**. A Wacker-type oxidation of the olefin in **32** afforded the diketone **33**. From there, the end-game strategy more or less follows previous approaches to quadranes⁶³ including a base-promoted aldolization / crotonization sequence, and a regio- and diastereoselective alkylation / hydrogenation sequence to afford (+)-suberosanone (**VI**). Overall, this total synthesis of (+)-suberosanone (**VI**) was achieved in 16 steps with a remarkable 18.2% yield from the β -ketoester **28**. In the same study, the authors were able to convert the enone **34** into (+)-suberosenone (**III**) in three steps (35% yield from **34**, not shown). Of importance for the following, this study allowed establishing the absolute configuration of naturally occurring (+)-suberosenone (**III**) as (1*R*,2*R*,8*R*,11*R*). In the case of suberosanone (**IV**), the situation is significantly more complex. It is important to note that the synthetic products (+)-suberosenone (**III**) and (+)-suberosanone (**IV**) were obtained from the same intermediate **34** and thus have identical absolute configuration. Also, the synthetic sample of (+)-suberosanone (**IV**) prepared by Dumas and co-workers shows an opposite sign for its optical rotation when compared to the reported one for the isolated natural product (–)-suberosanone (**IV**). Providing that the sign of the optical rotation for the isolated natural product is really (–) as reported by Sheu and co-workers,⁶⁹ the results of Dumas and co-workers point out a possible occurrence of both absolute configurations for quadranes in nature.

⁷⁵ Kousara, M.; Ferry, A.; Le Bideau, F.; Serré, K. L.; Chataigner, I.; Morvan, E.; Dubois, J.; Cheron, M.; Dumas, F. *Chem. Commun.* **2015**, *51*, 3458.

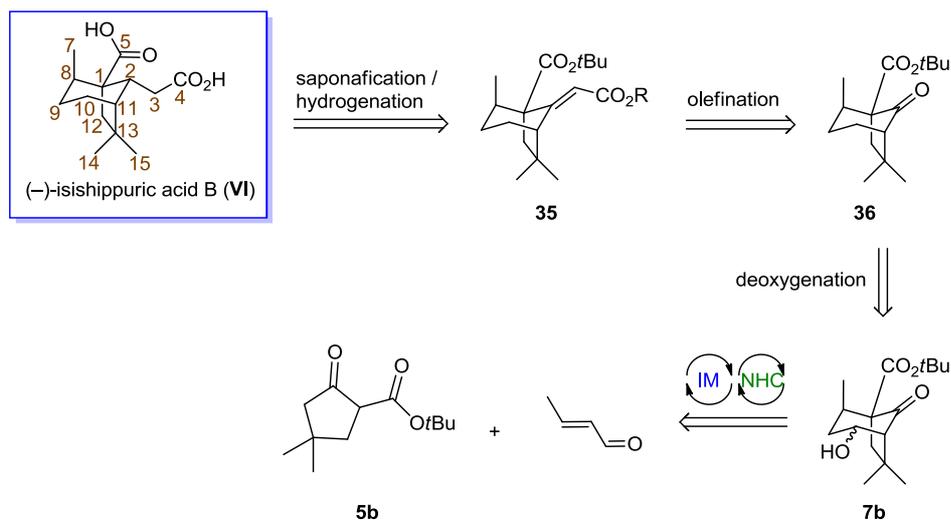


Scheme 31: Dumas' synthesis of (+)-suberosanone (IV).

In order to test the synthetic value of the methodology presented in Chapter 1, we decided to apply it to a concrete case through the total synthesis of a quadrane sesquiterpene. Because of its apparent structural simplicity and resemblance with some of the products prepared during our work on the enantioselective organocascade presented in Chapter 1 (e.g. compound **16b**), (–)-isishippuric acid B (**VI**) was selected as the target compound. As the reader will see in the following section, the realization of this project revealed a number of unforeseen difficulties and surprises.

2.1.3. Retrosynthetic analysis for (-)-isishippuric acid B (VI)

It was initially devised that (-)-isishippuric acid B (VI) could be obtained from the unsaturated diester **35** by a saponification / hydrogenation sequence (Scheme 32). Intermediate **35** would be obtained directly from the ketone **36** by a Wittig-like olefination, and the ketone **36** would derive from the product **7b** obtained during the methodological studies presented in Chapter 1.



Scheme 32. Retrosynthetic analysis for (-)-Isishippuric acid B (VI)

While the above retrosynthetic analysis is very seducing on the paper, several of its features should be highlighted:

- the ketone group at C2 is α to a quaternary center resulting in kinetically disfavored nucleophilic additions to this moiety,
- a severe 1,3-diaxial interaction exists between the methyl group at C8 and the electrophilic carbon atom at C2 rendering very difficult nucleophilic additions at C2 from the β face,
- a bulky gem-dimethyl is present at C13 rendering very difficult nucleophilic additions at C2 from the α face,
- the bicyclic ring system in **36** is rigid and shows no conformational flexibility.

Dr. Marc Presset, a former Ph.D. student in our group, has extensively studied the synthetic route presented in Scheme 32 in the racemic series.⁵⁶ For the reasons mentioned above, all attempts to perform a Wittig-type olefination at C2 on intermediate **36** and its analogs failed, leaving the starting material unchanged in most cases. After considerable

efforts several analogs of the unsaturated intermediate **35** could be prepared. Again, the reduction of the $\Delta_{2,3}$ double bond in **35** and its analogs proved extremely challenging, and no conditions could be identified at the time to perform this reaction. Some nucleophilic substitutions at C2 were also examined from the activated alcohol (e.g. the corresponding mesylate) derived from **36**, and in this case again, no suitable conditions could be identified.

From this accumulated knowledge, and despite the many unsuccessful attempts, it was decided to push forward our work on the total synthesis of (-)-isishippuric acid B (**VI**) taking advantage of some recently described methods for the manipulation of the sterically hindered double bonds as the $\Delta_{2,3}$ double bond in **35** and its analogs. Our efforts in this direction are detailed in the next section.

2.2. Synthetic approach to (–)-isishippuric acid B (VI)

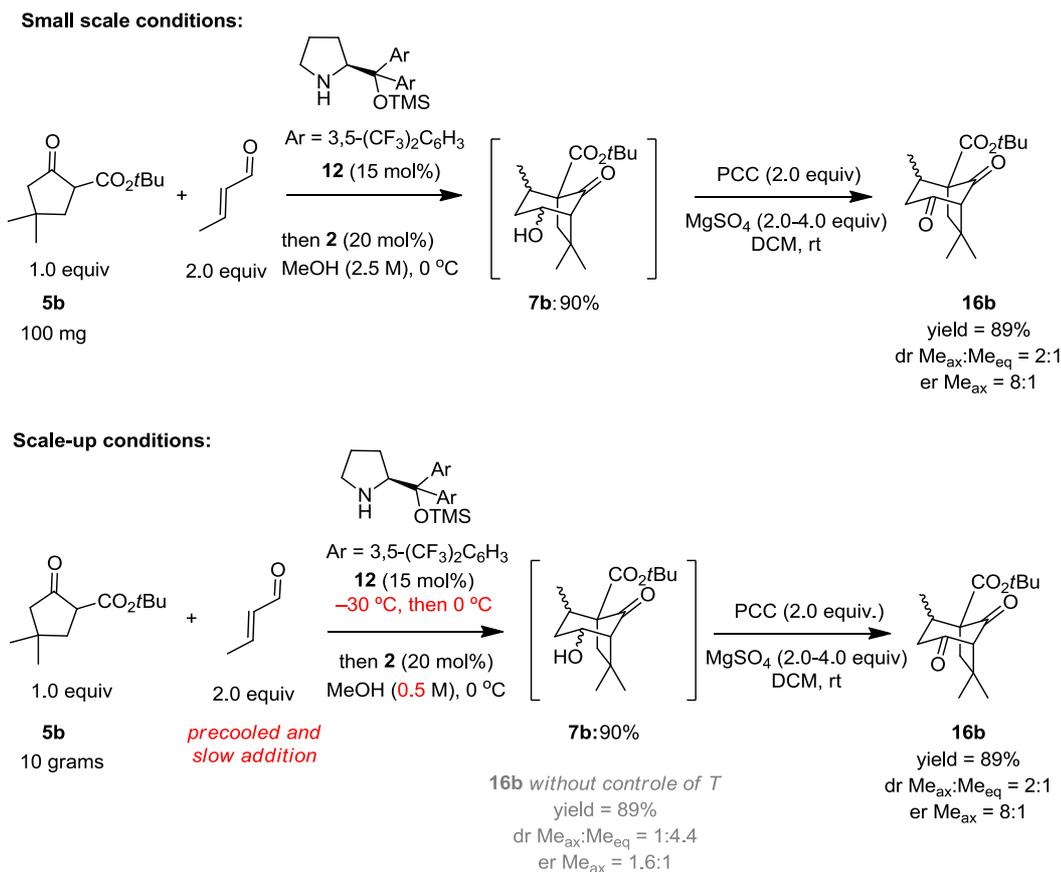
2.2.1. Construction of the bicyclo[3.2.1]octane

The bicatalytic Michael / aldol organocascade

As detailed in Chapter 1, we have developed a method to prepare optically active bicyclo[3.2.1]octane derivatives based on a bicatalytic enantioselective organocascade combining iminium activation with NHC activation. Using this method on a 10-gram scale with the previously developed conditions, we were able to obtain compound **7b** in 90% yield from the β -ketoester **5b** and crotonaldehyde using a combination of catalyst **12** and the NHC IDipp **2** in methanol (Scheme 33). The determination of the diastereoselectivity and enantioselectivity of the reaction was realized as before on the diketone product **16b** obtained in 89% from **7b** (80% over the two steps). Surprisingly, the diketone **16b** was obtained as a mixture of two diastereomers with a reverse diastereoselectivity ($dr = 1:4.4 Me_{ax}:Me_{eq}$), the diastereomer with the equatorial methyl group being largely major. Moreover, the desired diastereomer with the axial methyl group (the minor one in this case) proved almost racemic ($er = 1.6:1$). This unexpected difference between the results obtained on a 50–100 mg scale and on a 10 g scale forced us to look deeper to the reaction conditions, especially the evolution of the internal temperature during the reaction. It was rapidly found that the Michael addition step is relatively exothermic, and the observed loss of stereoselectivity was attributed to the uncontrolled elevation of the temperature during the early stages of the reaction producing less stereoselective Michael additions and probably some NHC-catalyzed retro-Michael / Michael processes leading to racemization. Accordingly, we modified our protocol as follow:

- the reaction mixture containing **5b** and catalyst **12** was diluted to 0.5 M instead of 2.5 M, cooled down to $-30\text{ }^{\circ}\text{C}$, and vigorously stirred to dissipate efficiently the evolved heat,
- the crotonaldehyde was added dropwise over 1h at $-30\text{ }^{\circ}\text{C}$ and the resulting reaction mixture was kept at that temperature for 4 h and then allowed to warm slowly to $0\text{ }^{\circ}\text{C}$.

Using this modified protocol on a 10-gram scale, we could reproducibly obtain the same results with small scale reactions, and the product **16b** was obtained in good yield (80% over two steps) with acceptable stereoselectivities ($dr Me_{ax}:Me_{eq} = 2:1$, $er Me_{ax} = 8:1$) to continue the synthesis.



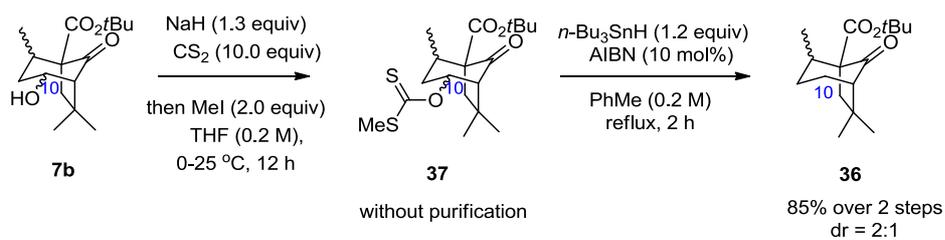
Scheme 33. Scale-up for the bicatalytic Michael / aldol organocascade

Deoxygenation at C10

With in hand a protocol for the preparation of compound **7b** on a multi-gram scale, we examined its deoxygenation using the conditions found earlier by Dr. Marc Presset in the racemic series.⁵⁶ To do so, the Barton–McCombie reduction⁷⁶ proved very useful.

The clean crude xanthate **37** was obtained following classic conditions and directly used for the next step (Scheme 34). In the presence of small amount of the radical initiator AIBN (5 mol%) and a stoichiometric amount of tributyltin hydride (1.1 equiv) in refluxing toluene for 2 hours, the xanthate **37** could be converted into the corresponding deoxygenated product **36** in 85% yield over the two steps.

⁷⁶ (a) Barton, D. H. R.; McCombie, S. W. J. *Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Barrett, A. G. M.; Barton, D. H. R. *Chem. Soc., Chem. Commun.* **1979**, 24, 1175. (c) Barton, D. H. R.; Motherwell, W.B. *Synthesis* **1981**, 743. (d) Barton, D. H. R.; Tse, C. L. *Tetrahedron Lett.* **1993**, 34, 2733. (e) Oba, M.; Nishiyama, K. *Tetrahedron* **1994**, 50, 10193.

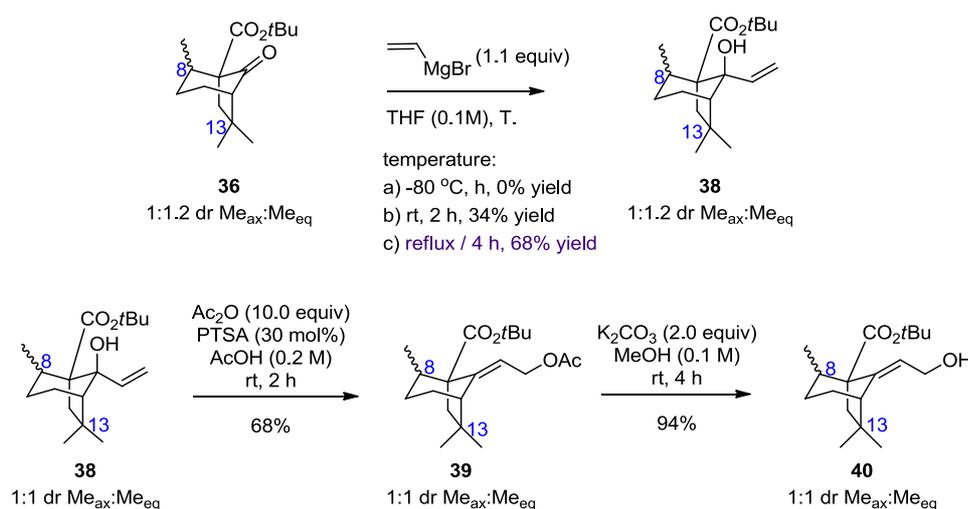


Scheme 34: Barton–McCombie deoxygenation

Because the formation of the xanthate **37** is performed under basic conditions, base-promoted retro-Michael / Michael processes leading to the racemization of **37** cannot be excluded in the non-racemic series. The analysis of the secondary alcohol intermediate **57** obtained from **36** confirmed that no racemization occurred during the overall Barton–McCombie deoxygenation process (see section 2.3.2).

2.2.2. Functionalization at C2

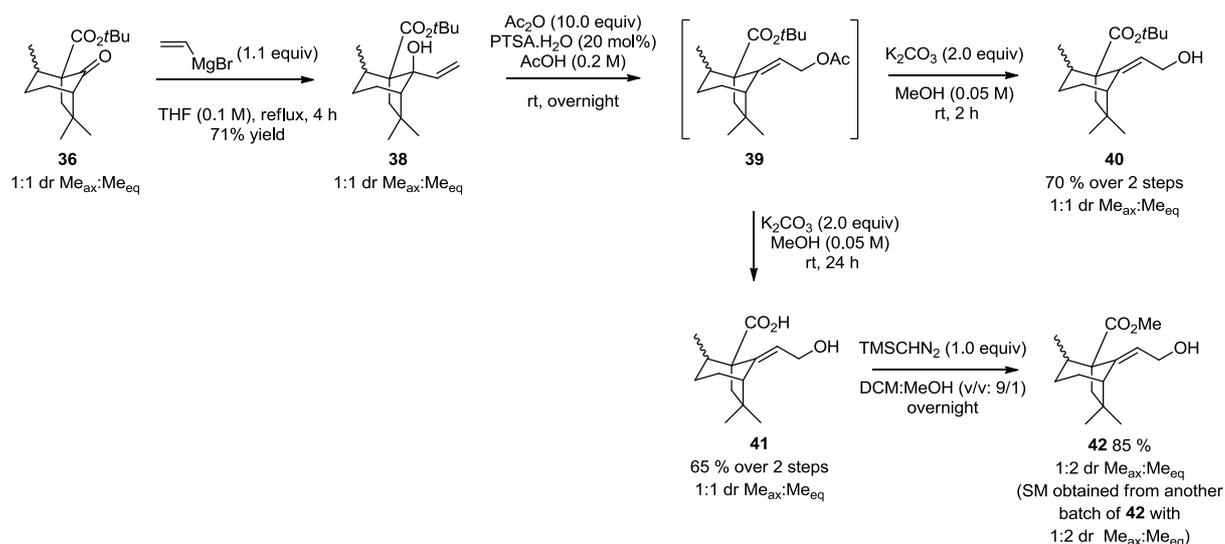
As mentioned above, Dr. Marc Presset has already accomplished a large body of work on these transformations in the racemic series,⁵⁶ and my work builds up on his findings. Notably, it was previously found that the ketone group at C2 in **36** could undergo diastereoselective nucleophilic additions with vinyl Grignard reagents from the α face to give the corresponding adduct **38** (Scheme 35, top). Surprisingly, and in apparent contradiction with earlier results (see for example the hydrogenation step in Scheme 29), this reaction indicates that the gem-dimethyl group at C13 induces less steric effect than the axial methyl group at C8. The reaction however required some thermal activation to proceed efficiently. Next, an allylic transposition from **38** allowed installing the desired double bond $\Delta_{2,3}$ as in the products **39** and **40** (Scheme 35, bottom). A number of conditions were then tested to perform the diastereoselective hydrogenation, or more generally the reduction, of the double bond in **39** and its derivatives. A few attempts were also performed for the rhodium-catalyzed isomerization of the allylic alcohol moiety in **40** into the corresponding saturated aldehyde. Regrettably, no suitable conditions could be identified, compound **39** and its derivatives being extremely stable. This chemical inertness of these compounds toward hydrogenation and isomerization reactions was attributed, again, to the very crowded environment of the $\Delta_{2,3}$ double bond.



Scheme 35. Early results in the racemic series (from the PhD thesis of Dr. Marc Presset)

For the present work, I have used the route developed by Dr. Marc Presset for the preparation of the allylic alcohols **40**, **41** and **42** (Scheme 36). First, we reproduced the

addition of vinyl magnesium bromide to the ketone **36**, which afforded the tertiary allyl alcohol **38** in 71% yield. Then, the allylic transposition of **38** under the previously developed conditions afforded the primary allyl alcohol **40** in 70% yield over the 2 steps. If the reaction time of saponification step of the intermediate allylic acetate is prolonged, the tert-butyl ester was also saponified to afford the acid **41** in 65% yield over the 2 steps, and the latter could be esterified back with trimethylsilyldiazomethane to give the methyl ester **42**.



Scheme 36. Preparation of three analogous allylic alcohols (racemic series)

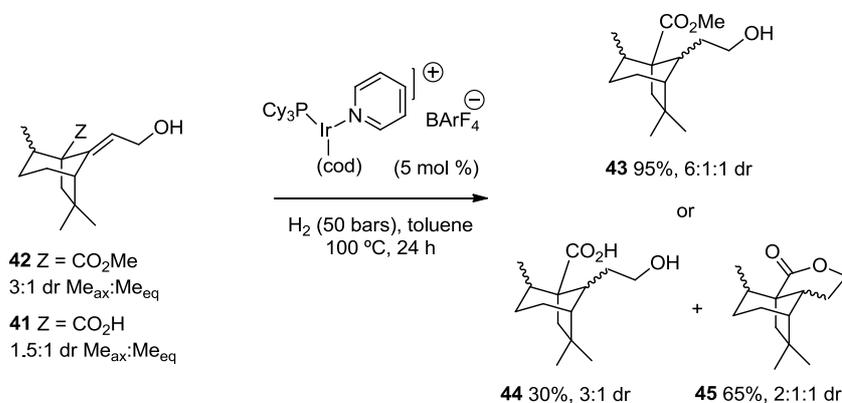
At first, we wanted to test the BArF analogue of the Crabtree catalyst⁷⁷ developed by Wuestenberg and Pfaltz⁷⁸ because of its superior activity, especially in difficult hydrogenation reactions.⁷⁹ Based on previous results (see Scheme 29 and Scheme 31), it was anticipated that, if occurring, the hydrogenation would proceed from the β face of the allylic alcohols **41** and/or **42**. In early trials, we attempted the hydrogenation of the unsaturated hydroxyester **42** in THF under 20 bars of H₂ at 25 °C, or in dichloromethane under 50 bars of H₂ at 40 °C, or in toluene under 2 bars of H₂ at 90 °C. Under none of these conditions could a hydrogenation product be detected after 24 hours. However, forcing a little the conditions, that is in toluene under 50 bars of H₂ at 100 °C, allowed for the first time the hydrogenation of the $\Delta_{2,3}$ double bond in **42** to afford **43** (Scheme 37). These conditions were also suitable for the hydrogenation of the parent unsaturated hydroxyacid **41** to give the products **44** and **45**. In both cases the isolated yield was excellent, producing three diastereomers, and in the case of

⁷⁷ Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331.

⁷⁸ Wuestenberg, B.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, *350*, 174.

⁷⁹ For an example, see: Shvartsbart, A.; Smith, III, A. B. *J. Am. Chem. Soc.* **2014**, *136*, 870.

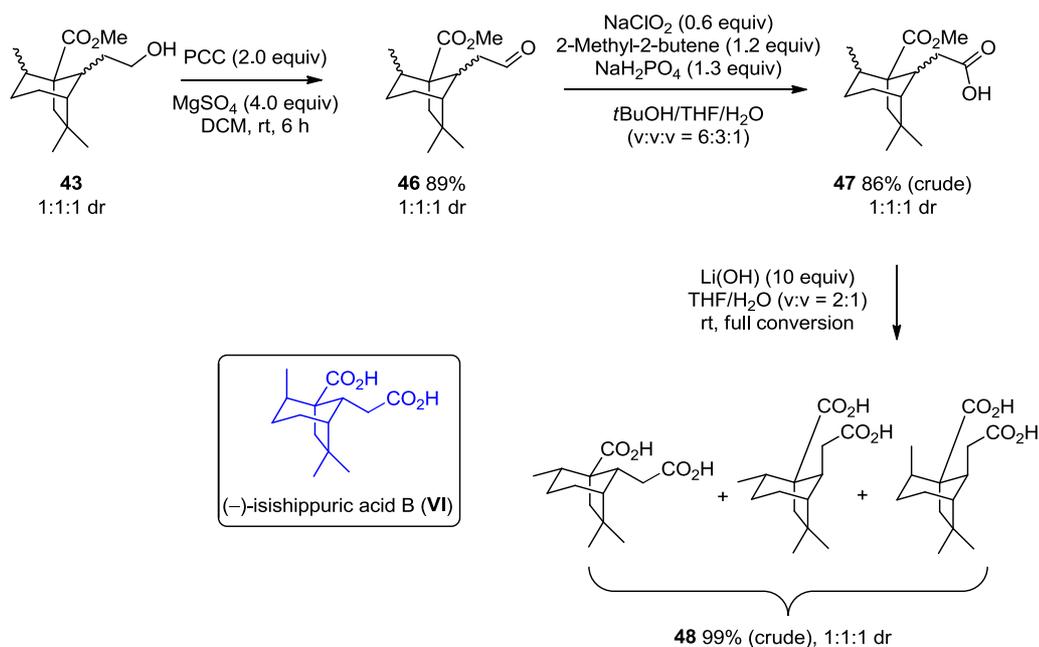
the acid-containing product some spontaneous lactonization was observed as in **45**. We were very happy with this result, but were unable to determine the relative configurations of the various diastereomers at this stage.



Scheme 37. Hydrogenation of the $\Delta_{2,3}$ double bond

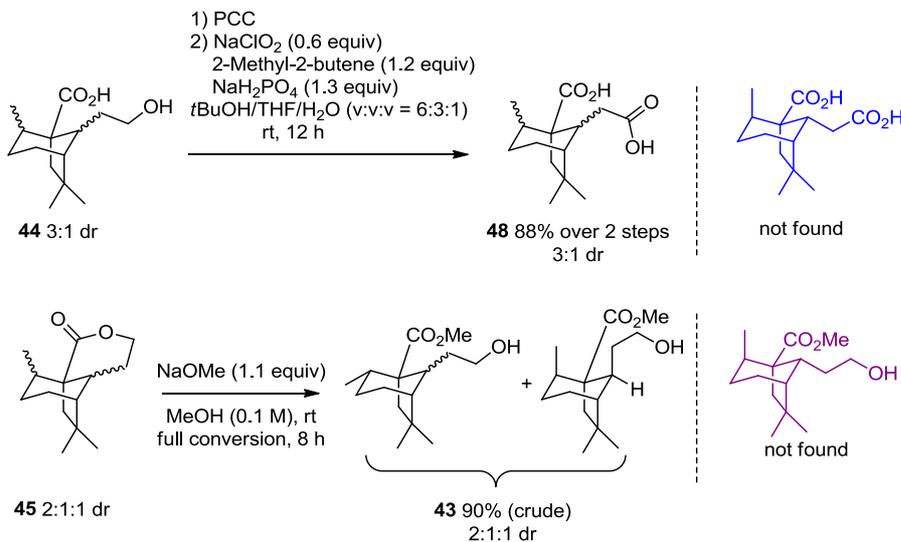
In order to do so, it was decided to convert a 1:1:1 mixture of the three diastereomers present in **43** (sample obtained by silica gel chromatography from the crude product) into the corresponding diacid **48** (1:1:1 dr) and compare the spectroscopic data of this material with those of the natural product **VI**. Thus, the primary alcohol group in **43** was converted into a carboxylic acid moiety in two steps,⁸⁰ and the methyl ester was saponified to afford the expected diacid **48** as a 1:1:1 mixture of diastereomers (Scheme 38). It was a great disappointment when we realized that none of the three diastereomers of **48** show comparable NMR data with the natural product **VI**. Actually, our sample of **48** contains all the possible non-natural diastereomers of the natural product.

⁸⁰ For the Lindgren–Pinnick oxidation: (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175. (c) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.



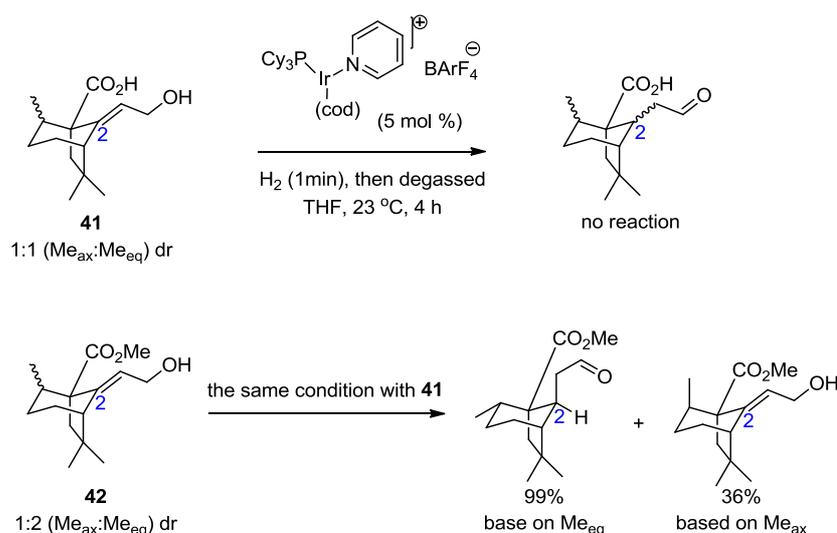
Scheme 38. A route to all non-natural diastereomers of **VI**

Similarly, the conversion of **44** into the corresponding diacid afforded two of the three diastereomers present in the sample of **48** (Scheme 39), and the ring opening of the lactone **45** with methanol afforded the corresponding hydroxyester as a mixture of the same three diastereomers present in **43** (Scheme 39).



Scheme 39. More non-natural diastereomers of **VI**

All combined together, these results indicate that the diastereoselective hydrogenation of the retrosynthetic intermediate **35** and/or its analogs from the β face is very unlikely to occur. Aware of the recent work of Prof. Clément Mazet in Geneva on the iridium-catalyzed isomerization of allylic alcohols into aldehydes,⁸¹ we initiated collaboration with him to test his method on our challenging substrates. We selected the representative substrates **41** and **42** for these tests, which were sent to Prof. Mazet in Geneva. M. Hou-hua Li, a PhD student in the Mazet group performed the isomerization reactions. It was found that the acid-containing substrate **41** is inert under the reaction conditions, probably due to chemical incompatibility of the carboxylic acid moiety with the cationic iridium catalyst (Scheme 40). However, substrate **42** (1:2 Me_{ax}:Me_{eq} dr) did undergo some isomerization reaction, but only the undesired diastereomer with the equatorial methyl group could be converted into the corresponding aldehyde, moreover with the wrong relative configuration at C2 (Scheme 40). The unreacted diastereomer with the axial methyl group in **42** was recovered (in part), and the rest of the material could not be identified.

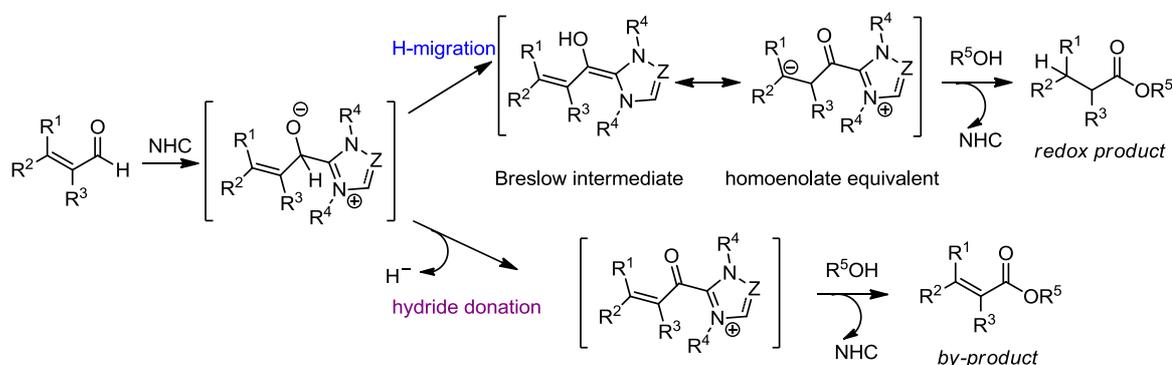


Scheme 40. Iridium-catalyzed isomerization reactions (performed in the Mazet group)

At that stage of our studies, it was decided to stop the hydrogenation strategy to obtain the targeted natural product (–)-isishippuric acid B (**VI**). As demonstrated above, the severe steric effect observed on the retrosynthetic intermediate **35** and its analogs precludes the approach of large entities to C2 from the β face. It was hypothesized that may be a simple

⁸¹ (a) Mantilli, L.; Mazet, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5143. (b) Mantilli, L.; Mazet, C. *Eur. J. Inorg. Chem.* **2012**, 3320. (c) Mazet, C. *CHIMIA*, **2011**, *65*, 802.

proton would be able to do so. However, the C2 position in **35** is electrophilic, and an umpolung at C2 would be necessary in order to achieve such a transformation. As mentioned in Chapter 1, NHCs are capable of catalyzing umpolung reactions of aldehydes via the Breslow intermediate. With α,β -unsaturated aldehydes, conjugated Breslow intermediates are formed, and these species are at the core of the chemistry of homoenolates.⁸² More specifically, the groups of Scheidt and Bode simultaneously reported that catalytically generated homoenolates react with alcohols to afford the corresponding saturated esters, thereby providing a method for the NHC-catalyzed conversion of α,β -unsaturated aldehydes into saturated esters (Scheme 41).⁸³ The main side-product observed during these reactions is the oxidized α,β -unsaturated ester. The latter is believed to result from a Cannizzaro-like generation of a hydride equivalent from the aldehyde.



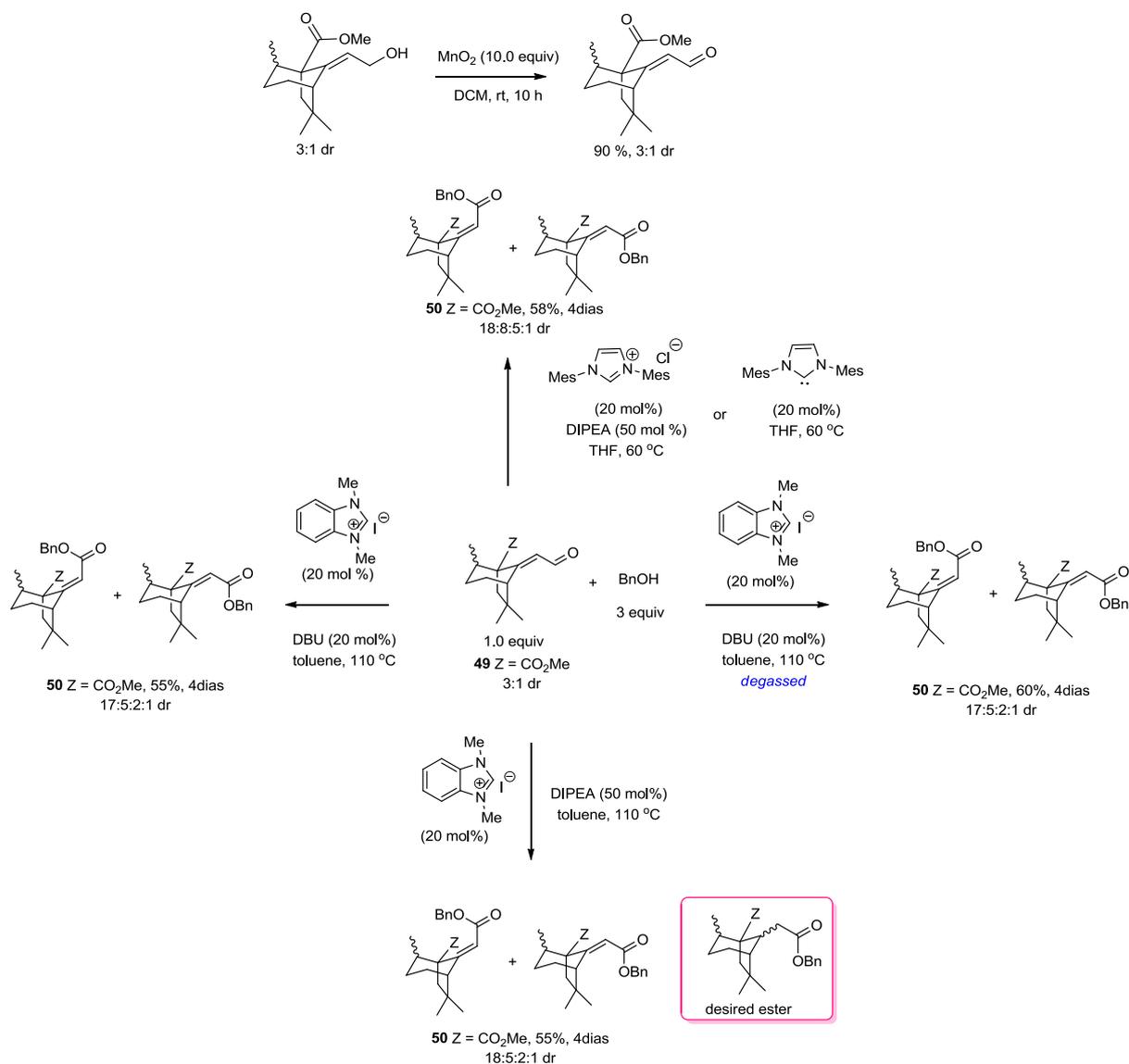
Scheme 41. Homoenate generation and protonation by Scheidt and Bode

This seducing transformation was attempted with our substrates, and the required α,β -unsaturated aldehyde **49** was easily prepared from the corresponding alcohol **42** using manganese dioxide as an oxidant (Scheme 42). Compound **49** was then treated under the standard conditions described by Scheidt and Bode (Scheme 42).⁸³ In all cases, only the undesired α,β -unsaturated ester **50** was obtained as mixtures of the four possible diastereomers (Me_{ax}/Me_{eq} and E/Z double bond). A reaction performed under rigorous exclusion of dissolved oxygen did not improve the result. The nature of the base was earlier found to have some impact of the formation of the undesired α,β -unsaturated ester,^{83a} but no

⁸² For a recent review: Menon, R. S.; Biju, A. T.; Nair, V. *Chem. Soc. Rev.* **2015**, *44*, 5040.

⁸³ (a) Maki, B.; Scheidt, K. *Synthesis* **2008**, 1306. (b) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873. (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905.

beneficial effect was observed in our case with the best base identified (*N,N*-diisopropylethylamine [DIPEA]). After these trials, the strategy was abandoned.

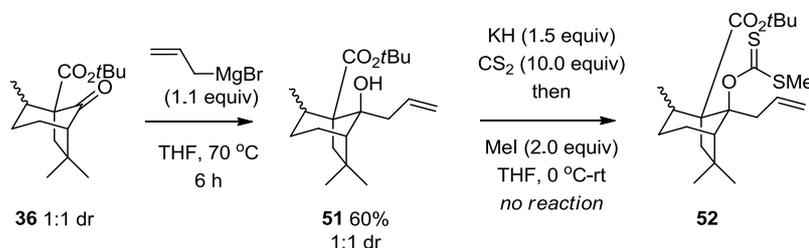


Scheme 42. NHC-catalyzed redox reactions of **50**

Ultimately, we explored some radical-mediated transformations for the reduction at C2. Dr. Marc Presser already explored some related routes during his thesis.⁵⁶ In 1993, Sir Barton reported a study on the stability and radical deoxygenation of tertiary xanthates.⁸⁴ Following the described conditions, we tried to prepare the tertiary xanthate **52** from the tertiary alcohol **51** derived from the nucleophilic addition of allyl magnesium bromide to the ketone **36**

⁸⁴ Barton, D. H.; Tse, C. H. *Tetrahedron Lett.* **1993**, 34, 2733.

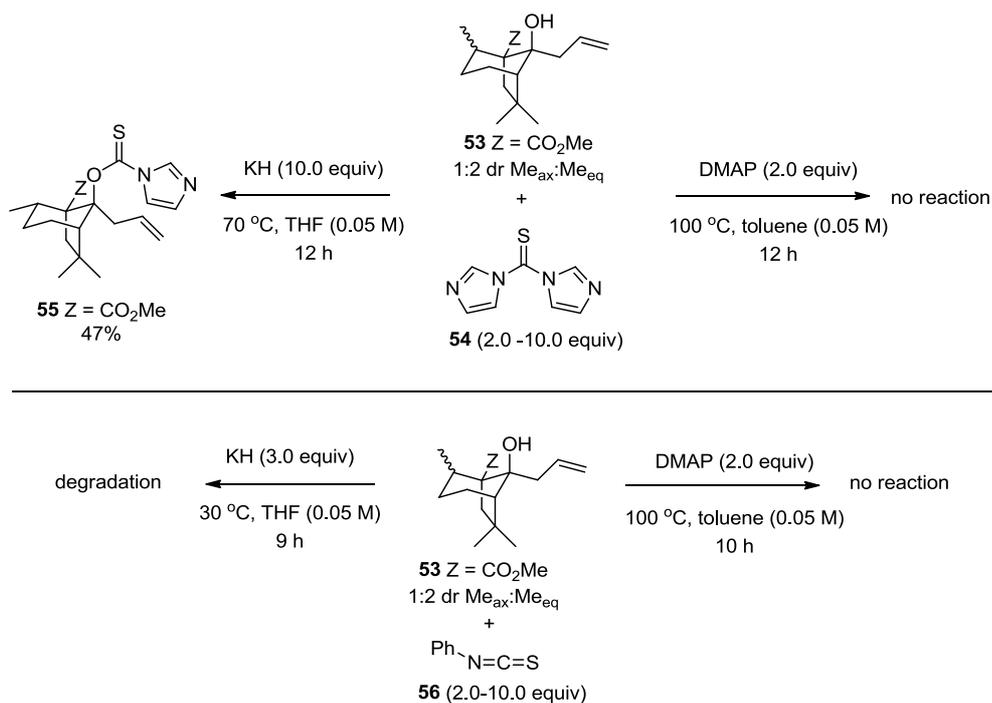
(Scheme 43). Using the previously developed conditions (see above), we could prepare the desired tertiary alcohol **51** in 60% yield. However, the corresponding xanthate **52** could not be obtained under the conditions described by Barton using KH as the base and CS₂/MeI as the trapping agent, leaving the substrate **51** unreacted.



Scheme 43. Attempts for the radical deoxygenation of a tertiary xanthate

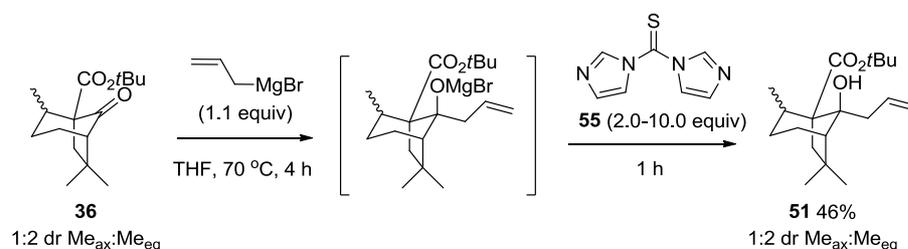
Alternatively, we tried to prepare the corresponding tertiary thiocarbamate from **53**, which should be reducible under radical conditions.⁸⁵ Two different electrophiles were tested in these reactions, namely di(1*H*-imidazol-1-yl)methanethione **54** and phenyl isothiocyanate **56**, using two sets of conditions (Scheme 44). In most cases, no reaction occurred. And when something happened, the reaction led to degradation, or in the best case, to the isolation of the undesired diastereomer with the equatorial methyl group as in **55** (the diastereomer of **53** with the axial methyl group was recovered unchanged).

⁸⁵ (a) Yadav, J. S.; Sridhar, B. *Org. Lett.*, **2013**, *15*, 3782. (b) Yamashita, S.; Hiram, M. *Tetrahedron Lett.* **2009**, *50*, 3277. (c) Yamashita, S.; Hiram, M. *J. Org. Chem.* **2011**, *76*, 2408.



Scheme 44. Attempts for the radical deoxygenation of a tertiary thiocarbamate

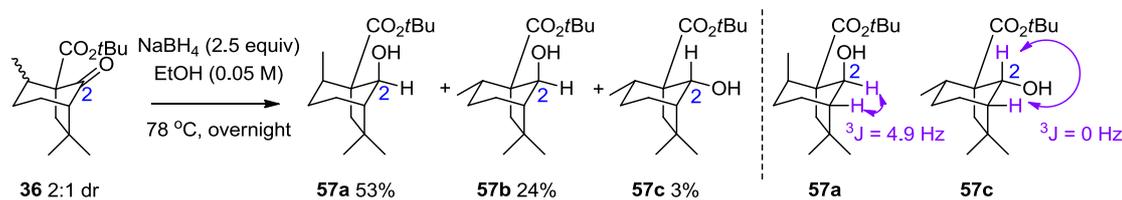
We also tried to trap the magnesium tertiary alcoholate intermediate obtained after the nucleophilic addition of the Grignard reagent with **36** without more success, the tertiary alcohol **51** being isolated in 46% yield under these conditions (Scheme 45).



Scheme 45. Attempts for the preparation of a tertiary thiocarbamate

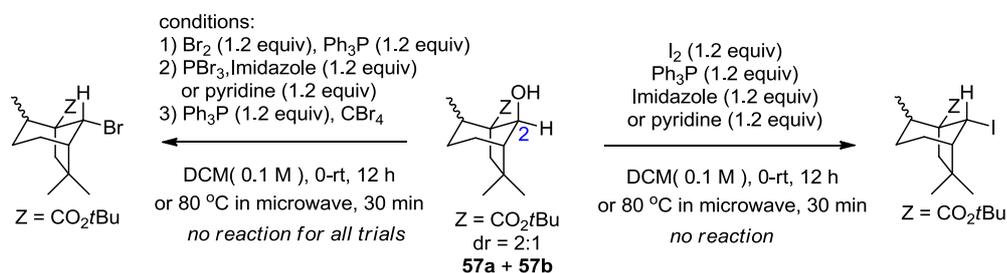
From the above, it was concluded that the desired tertiary radical would be very difficult to generate. It was then decided to study the generation of the corresponding secondary radical at C2. During his thesis, Dr. Marc Presset identified that sodium borohydride could add to the ketone group at C2 in **36** to afford the corresponding secondary alcohol (Scheme 46).⁵⁶ Interestingly, it was found that the diastereomer of **36** with the axial methyl group diastereoselectively underwent hydride addition from the α face affording the axial alcohol **57a**, while the diastereomer of **36** with the equatorial methyl group underwent a much less

diastereoselective reaction to afford the diastereomer alcohols **57b** and **57c**. Practically, **57c** showing an equatorial hydroxyl group could be separated from the two other diastereomers by silica gel chromatography, but **57a** and **57b** could not be separated at this stage.



Scheme 46. Reduction at C2 with sodium borohydride (from Dr. Marc Presset PhD thesis)

Based on the work of Oshima on the radical-mediated allylation of primary, secondary and tertiary alkyl halides,⁸⁶ we tried to generate the secondary alkyl bromide or iodide from the mixture of diastereomer alcohols **57a** and **57b** (Scheme 47). Several halogen sources were tested, including iodine, bromine, phosphorus tribromide, and carbon tetrabromide in Appel-like reactions, but in no case a reaction was observed and the starting alcohols were recovered in full.



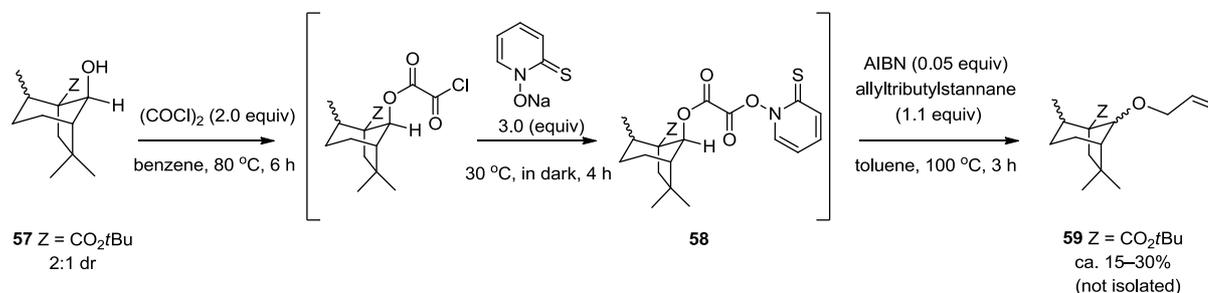
Scheme 47. Attempts for Appel-type reactions at C2

Finally, we also attempted the generation of the desired secondary radical at C2 using the remote system developed by Barton, Newcomb and Crich via a *N*-(alkoxyoxalyloxy)pyridine-2-thione.⁸⁷ The reaction must be conducted in a one-pot manner without isolating any intermediate. After some optimization on model compounds, we succeeded in preparing the desired radical precursor **58** (not isolated because unstable), but its reaction in the presence of a radical initiator and allyltributyltin only led to complex mixtures

⁸⁶ Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4137.

⁸⁷ (a) Simakov, P.; Newcomb, M. *J. Org. Chem.* **1998**, *63*, 1226. (b) Barton, D.; Zard, S. *Tetrahedron* **1985**, *41*, 5507. (c) Crich, D.; Fortt, S. *Synthesis* **1987**, *1*, 35.

of products (degradation) from which we could not identify the desired allylated product. However, ca. 15–30% of the allyl ether product **59** (not isolated) could be identified. A plausible explanation for this unexpected outcome would involve the formation of an alkoxy (and not alkyl as desired) radical from the precursor **58**.



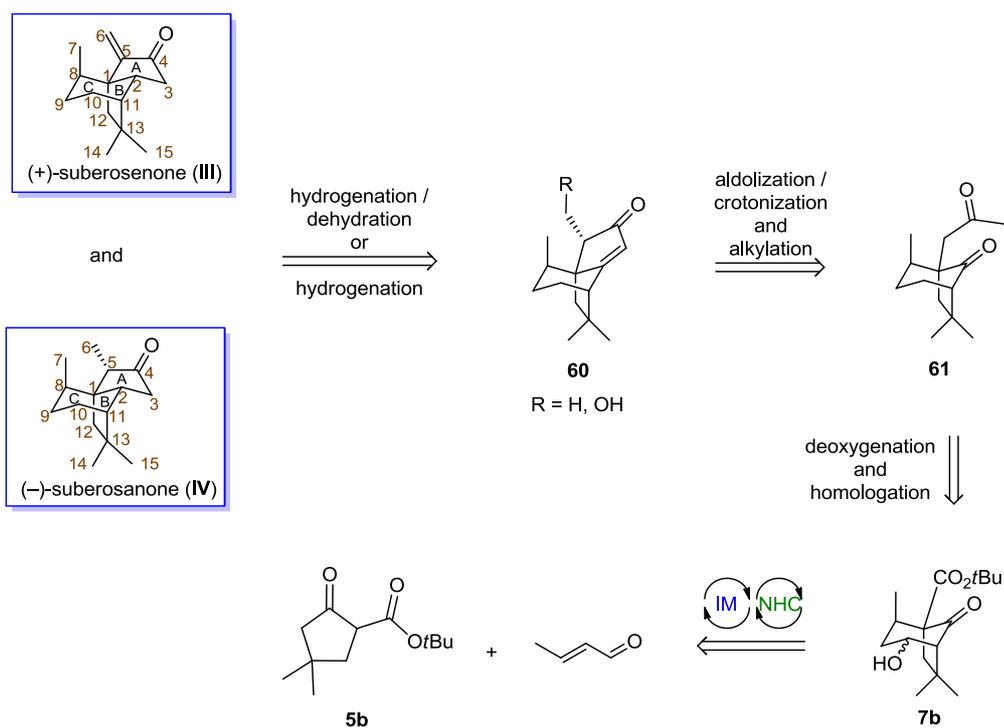
Scheme 48. Generation of a radical at C2 via a *N*-(alkoxyoxalyloxy)pyridine-2-thione

From all the above, it was concluded that our retrosynthetic analysis for (–)-isishippuric acid B (**VI**) presented in Scheme 32 has very few chances to be correct. Indeed, and after considerable efforts, the diastereoselective manipulation of the retrosynthetic intermediates **35** and **36** at C2 was found very difficult, and when possible, it afforded the wrong relative configuration. For example, we could prepare all the non-natural diastereomers of the natural product **VI** by this approach, but not the only desired naturally occurring one. At this stage of my work, it was decided to change the natural product synthetic target from (–)-isishippuric acid B (**VI**) to (+)-suberosenone (**III**) and/or (–)-suberosanone (**IV**). This part of my work is detailed in the next section.

2.3. Total synthesis of (–)-suberosanone (IV) and formal synthesis of (+)-suberosenone (III)

2.3.1. Retrosynthetic analysis

Based on the work of Danishefsky⁷² and others⁶³ on the total synthesis of quadrone (I), it was postulated that a diastereoselective hydrogenation of the cyclopentenone **60** would be possible from the β face to afford the tricyclic ring system of (+)-suberosenone (III) and (–)-suberosanone (IV, Scheme 49). Similarly, based on the approach of Kende,⁸⁸ Smith,⁸⁹ and others⁶³ to quadrone (I), the cyclopentenone **60** would be obtained from the diketone **33**, the latter being available from the product **7b** obtained during the methodological studies presented in Chapter 1. It can already be noted that our retrosynthetic plan shows some similarities with the recent work of Dumas and co-workers.⁷⁵



Scheme 49. Retrosynthetic analysis for (+)-suberosenone (III) and (–)-suberosanone (IV)

⁸⁸ Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808.

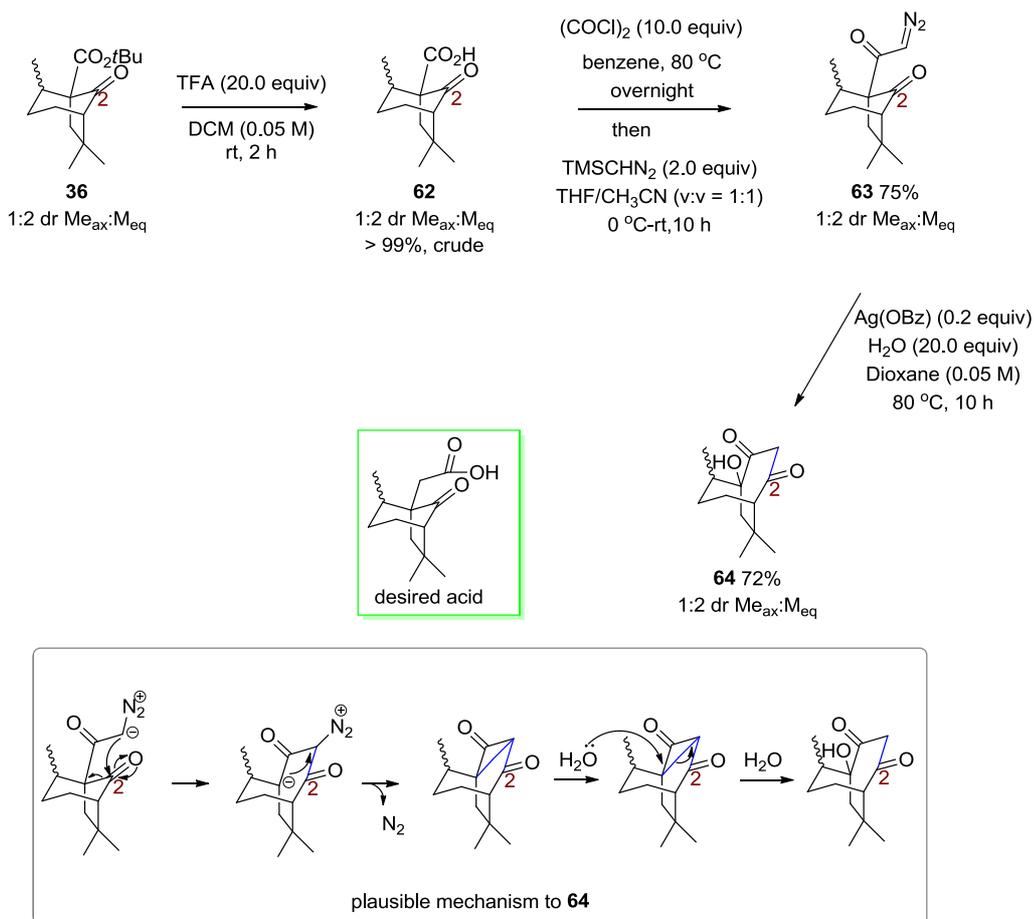
⁸⁹ Smith, III, A.; Slade, J. *Tetrahedron Lett.* **1982**, *23*, 1631.

2.3.2. The Arndt–Eistert homologation

The synthesis started with the ketone **36** obtained as described above (Scheme 34). The preparation of the retrosynthetic intermediate **61** from **36** requires the homologation of the ester moiety together with its conversion into a methyl ketone moiety. The Arndt–Eistert homologation,⁹⁰ involving the reaction of an activated carboxylic acid with diazomethane and subsequent Wolff rearrangement⁹¹ of the intermediate diazoketone in the presence of a nucleophile, was selected for this purpose. Thus, the tert-butyl ester in **36** was saponified under acidic conditions to give the corresponding carboxylic acid **62** quantitatively (Scheme 50). The resulting clean crude material was then converted into the corresponding acyl chloride and allowed to react in situ with trimethylsilyldiazomethane to afford the diazoketone **63** in 75% yield. The silver catalyzed Wolff rearrangement of **63** at 80 °C (no reaction occurred at lower temperature) in the presence of water unexpectedly afforded the ring-expanded bicyclic product **64** and not the desired homologated carboxylic acid. A plausible mechanism for the formation of **64** is depicted in Scheme 50.

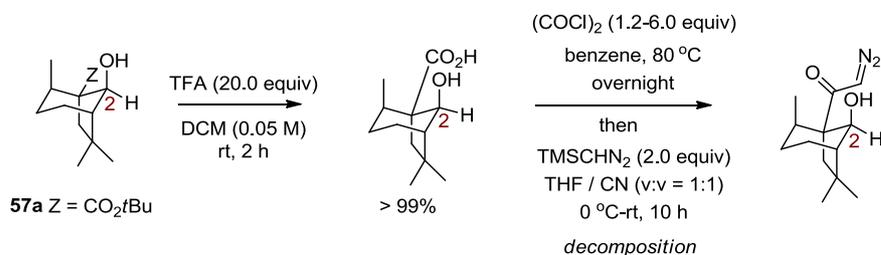
⁹⁰ (a) Arndt, F.; Eistert, B. *Ber. Dtsch. Chem. Ges.* **1935**, *68*, 200. For recent examples: (b) Tam, N. T.; Jung, E.-J.; Cho, C.-G. *Org. Lett.* **2010**, *12*, 2012. (c) Xu, W.; Wu, S.; Zhou, L.; Liang, G. *Org. Lett.* **2013**, *15*, 1978.

⁹¹ Reviews: (a) Coquerel, Y.; Rodriguez, J. in *Molecular Rearrangements in Organic Synthesis*, Rojas, C. M. Ed., 2015, John Wiley & Sons, Chap. 3, pp. 59–84. (b) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, DOI: 10.1021/acs.chemrev.5b00121.



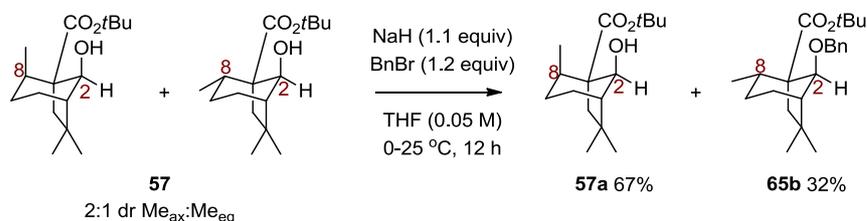
Scheme 50. Early trials for the Arndt–Eistert homologation

It thus seems that the ketone group at C2 is responsible for the unusual reactivity observed during the attempted Wolff rearrangement of the diazoketone **63**. It was decided to try the same reaction from a diazoketone substrate having a secondary alcohol at C2. Regrettably, we were not able to prepare the required diazoketone in the presence of the free alcohol under the same conditions as above (Scheme 51).



Scheme 51. Toward the Arndt–Eistert homologation with a free alcohol

As demonstrated above, the nucleophilic addition to the ketone group at C2 in substrate **36** is very difficult, meaning that its protection, for example as an acetal, would also be very challenging. So we decided to mask this ketone group as a benzyl ether. Although this strategy is step-demanding (4 steps are required to protect/deprotect the ketone), we finally got a little lucky with this idea. As mentioned above, the two diastereomers of **57** cannot be separated by silica gel chromatography. When **57** (dr Me_{ax}:Me_{eq} = 2:1, er Me_{ax} = 8:1) was treated with sodium hydride (2.5 equiv) / benzyl bromide (2.2 equiv) in order to prepare the corresponding benzyl ether as a mixture of diastereomers, we had a good surprise to observe that the diastereomer with the equatorial methyl group was totally etherified to give the product **65b**, and that only a fraction of the diastereomer with the axial methyl group was converted into the corresponding benzyl ether. However, when the same reaction was conducted with 10 equiv of sodium hydride, most of the two diastereomers of **57** were converted into the corresponding benzyl ethers **65**. We saw here an opportunity to separate the two diastereomers of **57** taking advantage of this difference of kinetic. And indeed, after several trials, we have found some good conditions to achieve the selective etherification of the diastereomer of **57** with the equatorial methyl group, allowing for the quantitative recovery of the diastereochemically pure product **57a** having an axial methyl group (Scheme 52).



Scheme 52. Separation of **57**

The above kinetically driven separation was a big step further and a great relief for us. Indeed, it may not have been realized yet that all the work described above was conducted using mixtures of diastereomers (moreover in various amounts depending on batches), which complicated a lot the purification, analysis and structural determination of our products. In the following, only diastereomerically pure compounds will be used.

In order to make sure that no racemization occurred during the Barton–McCombie deoxygenation (Scheme 34), the enantiomeric ratio of **57a** was measured. As expected, we

have found 8:1 er, a value identical to the one measured on compound **16b** (see Scheme 33) before the Barton–McCombie deoxygenation, thereby attesting that no racemization occurred.

Luckily, compound **57a** was obtained as a white solid after its chromatographic separation from the benzyl ether **65b**. At this stage we attempted a recrystallization of **57a** (8:1 er) with the idea to obtain some material with higher er for the completion of the syntheses. The compound **57a** was found soluble in all the tested organic solvents, going from non-polar hydrocarbons (e.g. pentane) to polar and/or protic solvents (e.g. THF, MeOH). After some unsuccessful trials and optimization, it was found that 0.16 M solution of **57a** in acetonitrile stored at 0 °C for 10 days reproducibly afforded beautiful large colorless needles. The analysis of these crystals by HPLC on chiral stationary phase showed that this material is enantiopure (>99:1 er), the minor enantiomer being undetectable (Figure 9). Also, we examined the er of the mother liquor and we had the good surprise to find that it was racemic (1.02:1 er) after a single recrystallization. We have thus identified extremely efficient conditions for the enantiomeric enrichment of compound **57a** by recrystallisation, allowing obtaining crystalline enantiopure material and racemic mother liquor in a single operation.

The enantiopure crystalline **57a** was analyzed by X-ray diffraction technique, which allowed confirming its structure, but also its absolute configuration to be as depicted [Flack parameter = 0.05(6), see Supporting Information] and as desired for the projected synthetic applications (Figure 9).

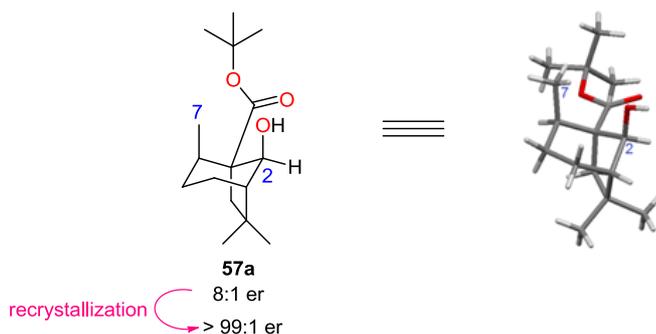
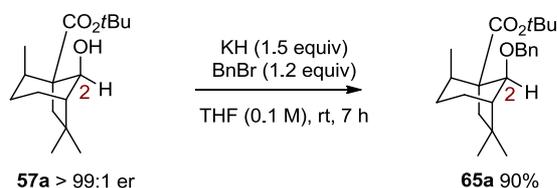


Figure 9. Enantiomeric enrichment and X-ray diffraction analysis of **57a**

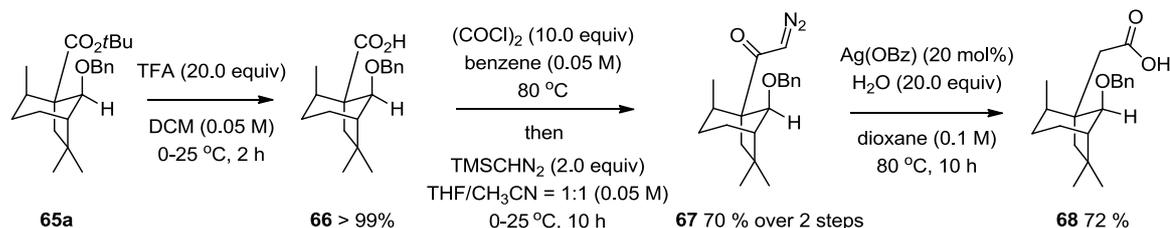
With the diastereo- and enantio-pure product **57a** in hand, we moved on its homologation by the planned Arndt–Eistert homologation. As shown above, the free hydroxyl group is not compatible with the projected chemistry, and it was converted into the corresponding benzyl ether using KH as a base in the presence of benzyl bromide (Scheme

53). The reaction afforded the protected product **65a** in good yield. It can be noted that a simple switch from sodium hydride to potassium hydride dramatically changed the reactivity of the alcoholate corresponding to **57a** (compare with Scheme 52).



Scheme 53. Protection of the free hydroxyl group in **57a**

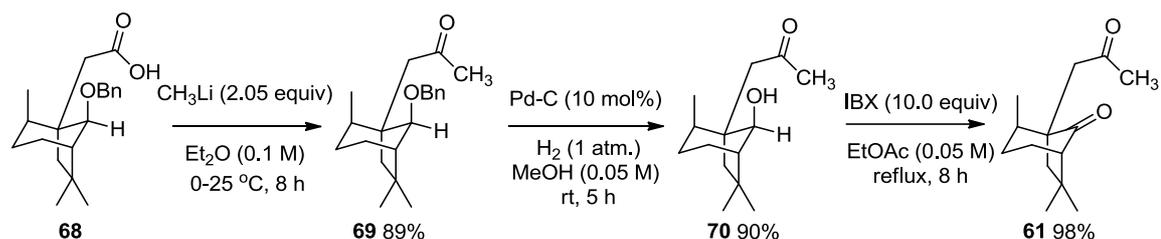
As before, the tert-butyl ester moiety in **65a** was quantitatively hydrolyzed under acidic conditions, and this time, the resulting carboxylic acid **66** could successfully be converted into the desired diazoketone **67** in good yield (Scheme 54). Under silver(I) catalysis conditions, the Wolff rearrangement proceeded smoothly, affording the expected homologated carboxylic acid **68** in 72% yield (Scheme 54).



Scheme 54. Arndt–Eistert homologation of **66**

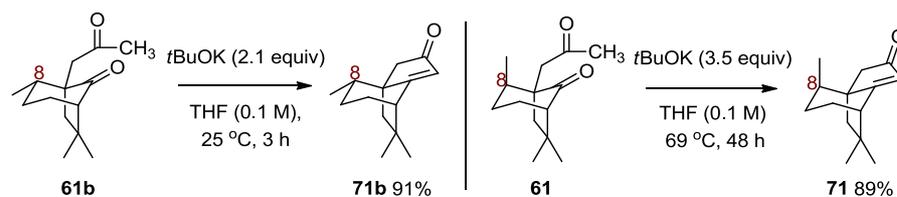
2.3.3. Completion of the syntheses

Following our synthetic plan, the carboxylic acid moiety in **68** was converted into the corresponding methylketone by treatment with an excess of methyllithium to afford compound **69** (Scheme 55).⁹² Then, the hydrogenolysis of the benzyl ether group followed by the oxidation of the resulting secondary alcohol⁶⁰ in **70** afforded the targeted diketone **61** in good overall yield (Scheme 55).



Scheme 55. Synthesis of the diketone **61**

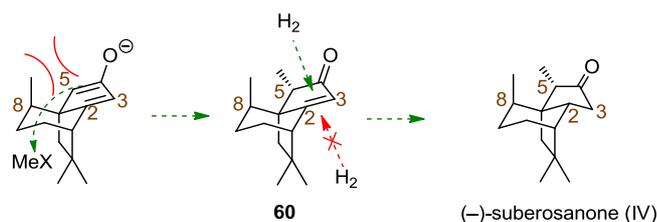
The projected formation of ring A by an aldolization / crotonization sequence paralleling the work of Kende,⁸⁸ Smith,⁸⁹ and others⁶³ was next attempted. Potassium tert-butoxide being identified as the best base in the previously reported closely related transformations, we logically focused our efforts in this direction. The optimization studies were performed on the undesired diastereomer **61b** (obtained from **65b**), which required 2.1 equiv of *t*-BuOK in THF at 25 °C for 3 hours to reach full conversion, and the enone **71b** was isolated in 91% yield (Scheme 56). When the same conditions were employed with the correct diastereomer **61** having an axial methyl group, no reaction occurred, demonstrating, again if necessary, the strong steric effect induced by the axial methyl substituent at C8. Finally, increasing the temperature to 69 °C and using 3.5 equiv of *t*-BuOK afforded the desired product **71** in good yield after prolonged reaction time (Scheme 56).



Scheme 56. Construction of the A ring

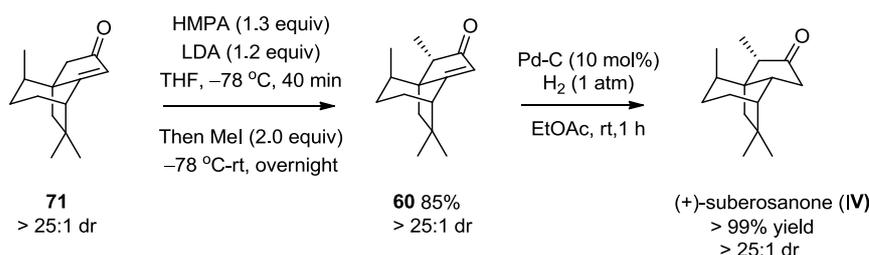
⁹² Genna, D. T.; Posner, G. H. *Org. Lett.* **2011**, *13*, 5358

Based on the work of Danishefsky⁷² (and others⁶³) illustrated in Scheme 29 (see **23** → **24**), we planned to rely on a diastereoselective α -methylation of the enolate derived from the enone **71** followed by a diastereoselective hydrogenation of the double bond to complete the total synthesis of (–)-suberosanone (**IV**) (Scheme 57). Indeed, the steric effect from the axial methyl at C8 should induced a methylation of the enolate derived from **71** from the α face, and with this additional methyl group on the α face, the hydrogenation should then occur from the β face.



Scheme 57. End-game stereoselectivities

In practice, the treatment of a THF solution of enone **71** with LDA and then iodomethane in the presence of HMPA at low temperature afforded the alkylated product **60** in good yield as the only observable diastereomer in the ¹H NMR spectrum of the crude reaction product (> 25:1 dr) (Scheme 58). Ultimately, a palladium-catalyzed hydrogenation of **60** afforded the target compound (+)-**IV** quantitatively, again as the only detectable diastereomer by NMR spectroscopy (> 25:1 dr), which completed the total synthesis.



Scheme 58. Completion of the total synthesis of (+)-suberosanone (**IV**)

In order to ascertain the identity of our synthetic sample of (+)-**IV**, its spectroscopic data were carefully compared with the data reported by Sheu and co-workers at the time of the isolation and structural identification of (–)-**IV** from the gorgonian *Isis hippuris*.⁶⁹ Two notable differences were found: 1) in the ¹H NMR data, the chemical shift for the C14 methyl

group of natural **IV** was reported at 1.04 ppm while our synthetic sample of **IV** showed a signal at 1.14 ppm; and 2) the $[\alpha]_D$ value of natural **IV** was reported at $[\alpha]_D^{25} = -60$ ($c = 0.1$, CHCl_3), while we measured $[\alpha]_D^{25} = +17$ ($c = 0.1$, CHCl_3) for our synthetic sample. Two puzzling and anxiety-provoking observations!

Research programs aiming at the total synthesis of never-prepared natural products are a risky activity. Indeed, one may, for example, end up with the finding that the proposed structure is actually wrong, turning down most of the synthetic efforts. Or eventually, just a few days before you obtain the long-desired first milligram of the targeted product, one may discover in the literature that another group was working on the same synthesis and published before you. And this is exactly what happened to us one morning of January 2015 when we saw the Dumas paper in the asap of *Chemical Communications*.⁷⁵ The story could have been sad, but actually, the contribution from Dumas and co-workers was more a blessing than a problem to us.

As to the ^1H NMR chemical shift of the C14 methyl group, Dumas and co-workers have reported a signal at 1.13 ppm for their synthetic sample of **IV**, a value nicely comparable with the one we observed on our own synthetic sample ($\delta = 1.14$ ppm). This was reassuring but not enough. On March 5, 2015, we contacted Prof. Sheu, who isolated naturally occurring **IV**, and informed him on the different chemical shift values reported and/or measured for the hydrogen atoms at C14 for natural and synthetic **IV**. Very kindly, Prof. Sheu has send to us a copy of the original ^1H NMR spectrum obtained for the natural sample of **IV**, on which the signal for the hydrogen atoms at C14 is clearly visible at 1.14 ppm, and not at 1.04 ppm as reported in the original paper due to a simple typographical error (Figure 10). We would like to express here our deepest gratitude to Prof. Sheu for making that information available to us.

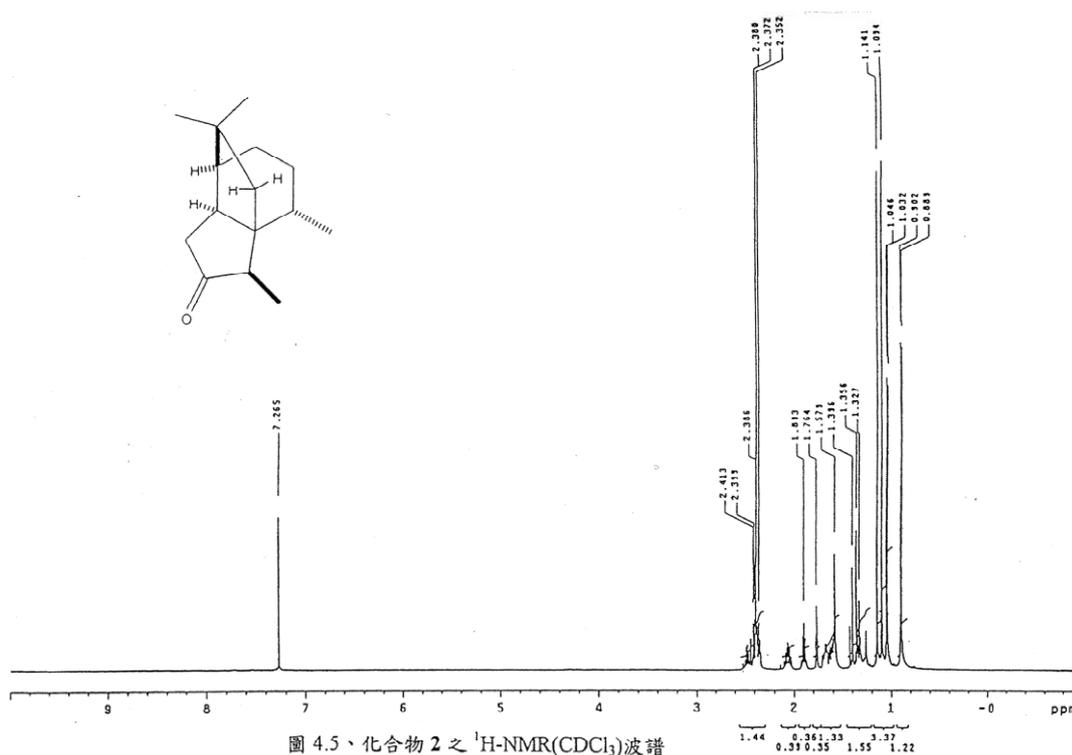


Figure 10. The ^1H NMR spectrum of naturally occurring (–)-**IV** (courtesy of Prof. J.-H. Sheu)

The issue on the structural identification of our synthetic sample of **IV** being solved, we next turned our attention to the different optical rotation values reported for the three samples of **IV** (Figure 11). The most striking fact is that both synthetic samples of **IV**, independently prepared and confirmed to exhibit a (1*R*,2*R*,5*S*,8*R*,11*R*) absolute configuration, show an opposite sign of their $[\alpha]_{\text{D}}$ value when compared to the naturally occurring material. Based on the fact that the actual $[\alpha]_{\text{D}}$ of the natural product is (–) as reported by Sheu,⁶⁹ Dumas and co-workers have assigned the absolute configuration of the naturally occurring (–)-**IV** to be (1*S*,2*S*,5*R*,8*S*,11*S*), raising the question for the existence of two enantiodivergent biosynthetic routes for quadranes.⁷⁵ Indeed, in all other known cases, the absolute configuration of quadranes was determined as (1*R*). Providing that the reported $[\alpha]_{\text{D}}$ value of naturally occurring **IV** is correct,⁶⁹ our work on the total synthesis of (+)-(1*R*)-**IV** confirms the findings of Dumas and co-workers for the occurrence of two enantiodivergent biosynthetic pathways⁹³ for quadrane sesquiterpenes in the gorgonian *Isis hippuris*. As shown in Scheme 30, the Kuwahara group reported in 2007 the total synthesis of the natural product (–)-isishippuric

⁹³ The biogenesis of terrecyclene, the generally accepted biosynthetic precursor for quadranes (see ref. 63), has recently been examined computationally: Barquera-Lozada, J. E.; Cuevas, G. *J. Org. Chem.* **2011**, *76*, 1572.

acid B (**VI**) from (*R*)-citronellal, thereby establishing its absolute configuration as (*1R*).⁷⁴ In a follow-up article, the absolute configuration of naturally occurring (–)-isishippuric acid A (**V**) could also be confirmed as (*1R*).⁹⁴ And it should be noted that the three natural products (–)-suberosanone (**IV**) possibly (*1S*)-configured, (–)-isishippuric acid A (**V**) and (–)-isishippuric acid B (**VI**) both confirmed (*1R*)-configured have been isolated from the same sample of the gorgonian *Isis hippuris* collected by hand using scuba at Green Island, located on the southeast coast of Taiwan, in February 1999, at depths of 25 m.^{69,70}

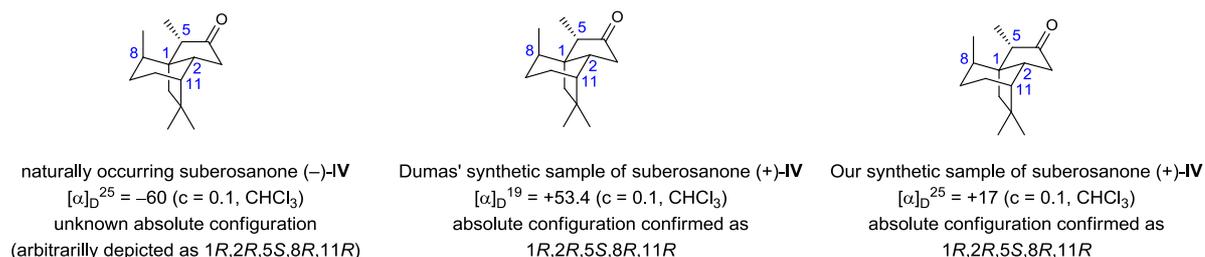


Figure 11. The different [α]_D values reported for **IV**

This being said, the discrepancies observed in the absolute value of our synthetic sample of (+)-**IV** with the two other known samples cannot be ignored (Figure 11). The different HPLC traces obtained from our sample of (+)-**IV** are reproduced in Figure 12. As can be seen from the bottom DAD-recorded trace at 290 nm, our sample of (+)-suberosanone (**IV**), although obtained on a 20 mg scale after silica gel chromatography, is not free from impurities, especially some chiral species detected at ca. 10.5 minutes on the chromatograms. These impurities are not visible of the ¹H and ¹³C NMR spectra of our sample of (+)-**IV** (see Supporting Information). Because of the strong absorption observed for the impurities @ 290 nm and the apparent purity of the sample by NMR, it was hypothesized that the impurities exhibit a high molar extinction coefficient ε @ 290 nm, indicating a conjugated system as, for example, in the enone **71**. The observed variation in the absolute value of the [α]_D in our sample of (+)-**IV** was attributed to these impurities. The preparative HPLC purification of our synthetic sample of (+)-**IV** is on going in order to solve this issue.

⁹⁴ Torihata, M.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 1628.

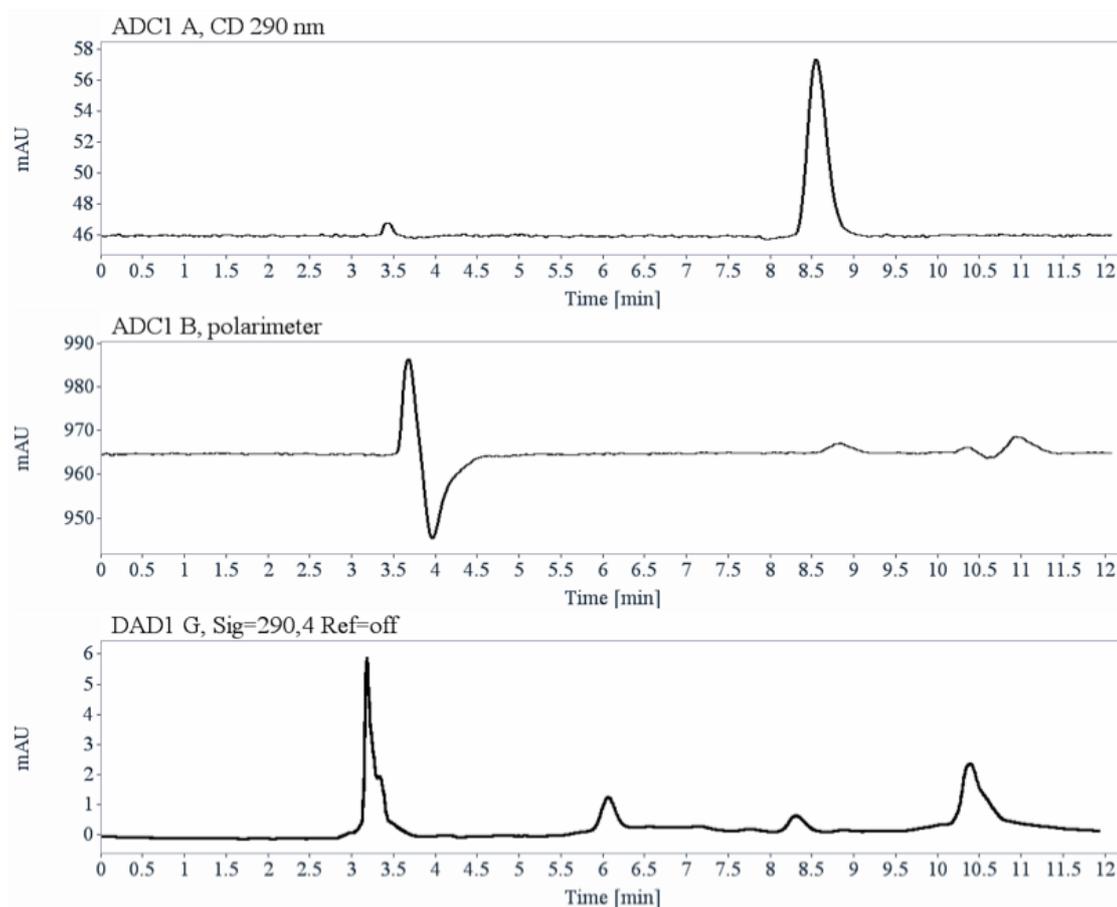


Figure 12. HPLC traces of our sample of (+)-**IV**. Top: detector = circular dichroism @ 290 nm; Middle = on line polarimeter equipped with a Hg(Xe) lamp; Bottom: detector = UV detector @ 290 nm. For details see ref ⁹⁵.

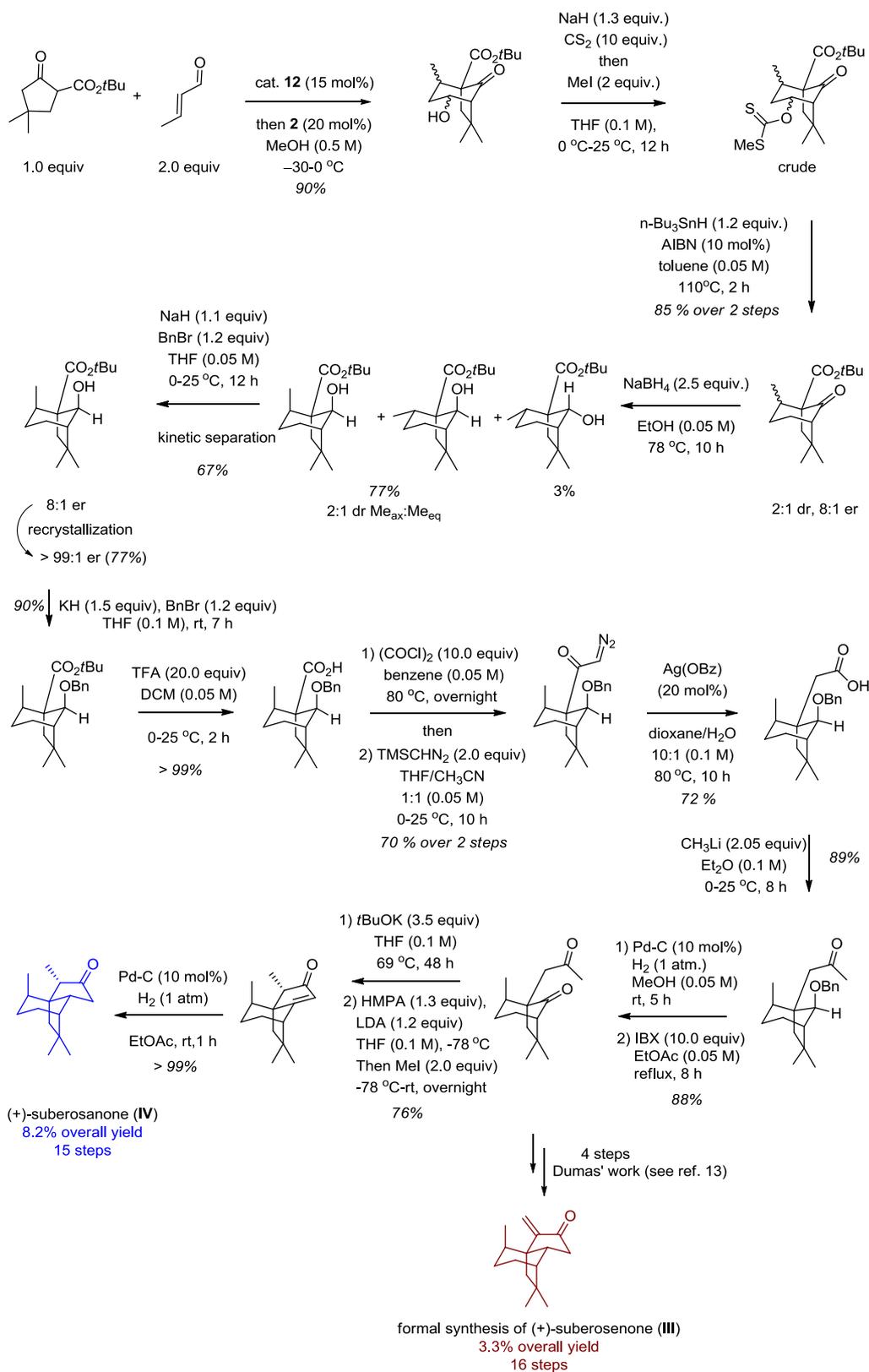
As can be seen from Scheme 31 and Scheme 55, the diketone **61** we have prepared is the first common intermediate with the Dumas syntheses of the optically pure quadranes (+)-suberosenone (**III**) and (+)-suberosanone (**IV**), **61** being the same compound as **33** in Scheme 31.⁷⁵ The spectroscopic data for (–)-**61** were in all respect identical to the reported data for (–)-**33**. The measurement of the optical rotation of our sample of **61** gave $[\alpha]_D^{25} = -67.1$ ($c = 0.5$, EtOH), which nicely matches with the value reported by Dumas for **33**: $[\alpha]_D^{20} = -60.2$ ($c = 1.03$, EtOH_{abs}). Overall, and in the light of Dumas' work, we have also achieved the formal enantioselective synthesis of (+)-suberosenone (**III**).

⁹⁵ Vanthuyne, N.; Roussel, C. *Top. Curr. Chem.* **2013**, *340*, 107

2.4. Summary and conclusion

Quadranes are sesquiterpene natural products belonging to the larger family of polyquinanes, the biological properties and total syntheses of which have been long studied.⁶³ In this section of the manuscript, and after considerable difficulties, we are pleased to report the first enantioselective total and formal syntheses of two quadranes, namely (+)-suberosanone (**IV**) and (+)-suberosenone (**III**), respectively (Scheme 59). Among the difficulties we faced, we have notably learned what steric effect means to kinetics, and how risky it is to embark on a total synthesis project.

The work described confirmed the recent findings of Dumas and co-workers that (+)-suberosanone-(**IV**) is (1*R*)-configured, questioning the occurrence for two enantiodivergent biosynthetic routes to quadranes. In our eyes, further investigations are required to ascertain this point, including the confirmation of the optical rotation of naturally occurring **IV** and the determination of the absolute configuration of the other quadranes present in the studied sample of *Isis hippuris*.



Scheme 59. Overview of the work

Chapter 3

Enantioselective synthesis of glutarimides

3.1. Introduction

The results summarized in this Chapter are preliminary, and accordingly, briefly introduced and presented. I actually ran out of time to complete this study.

3.1.1. Glutarimides in drugs and natural products

Glutarimides, that is to say piperidine-2,6-dione derivatives, can be found in numerous biologically active natural products and drugs (Figure 13). Famous examples include cycloheximide (**72**, a strong protein synthesis inhibition agent) and migrastatin (**73**, an antimetastatic drug lead) for the natural products,⁹⁶ and pomalidomide (**74**, a thalidomide analog with immunomodulator and anti-angiogenic properties),⁹⁷ and aminoglutethimide (**75**, an anti-steroid synthesis drug)⁹⁸ for the synthetic compounds.

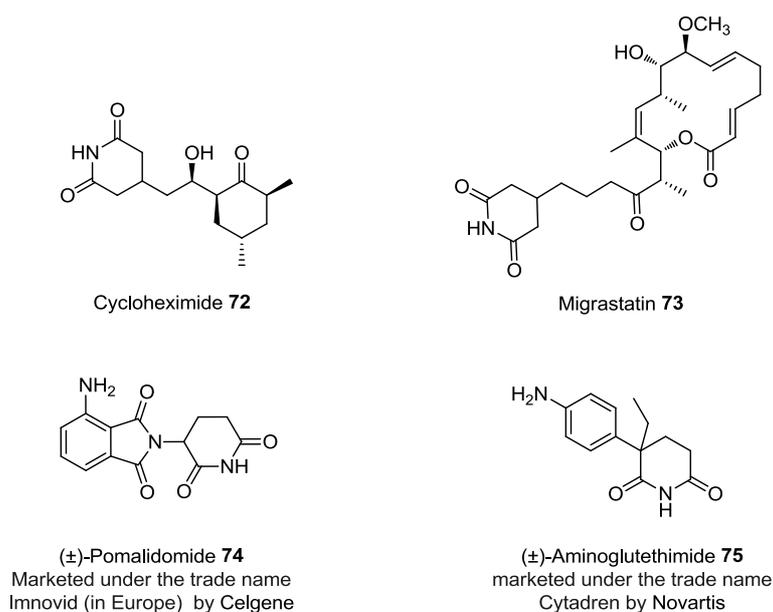


Figure 13. Naturally occurring and synthetic drugs with a glutarimide moiety

⁹⁶ Schneider-Poetsch, T.; Ju, J.; Eyler, D. E.; Dang, Y.; Bhat, S.; Merrick, W. C.; Green, R.; Shen, B.; Liu, J. O. *Nat. Chem. Biol.* **2010**, *6*, 209 and references therein.

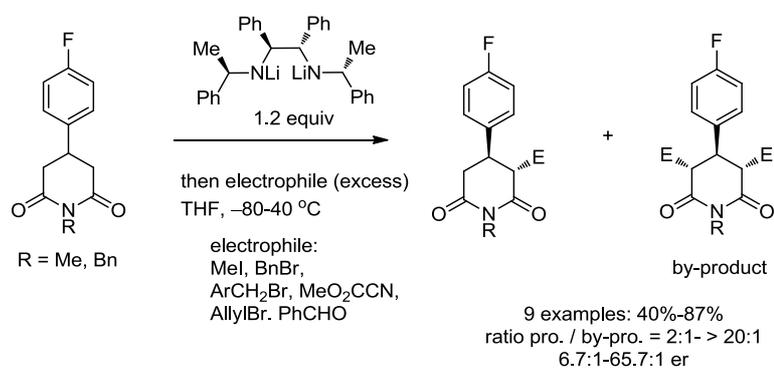
⁹⁷ <http://www.pomalyst.com>

⁹⁸ [http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20\(General%20Monographs-%20C\)/CYTADREN.html](http://www.rxmed.com/b.main/b2.pharmaceutical/b2.1.monographs/CPS-%20Monographs/CPS-%20(General%20Monographs-%20C)/CYTADREN.html)

3.1.2. Enantioselective routes to glutarimides

As illustrated above, some structurally simple chiral glutarimides have important biological applications, and of course, the control of their absolute configuration is crucial. The well-known case of thalidomide is a perfect illustration for this.⁹⁹ In sharp contrast with the importance of non-racemic glutarimides in chemistry, biology and medicine, there are only a very limited number of studies available on the enantioselective synthesis of glutarimides.

In 2002, Simpkins has reported the desymmetrization of prochiral 4-aryl-glutarimides using a stoichiometric amount of a chiral lithium-amide base and various electrophiles (Scheme 60).¹⁰⁰



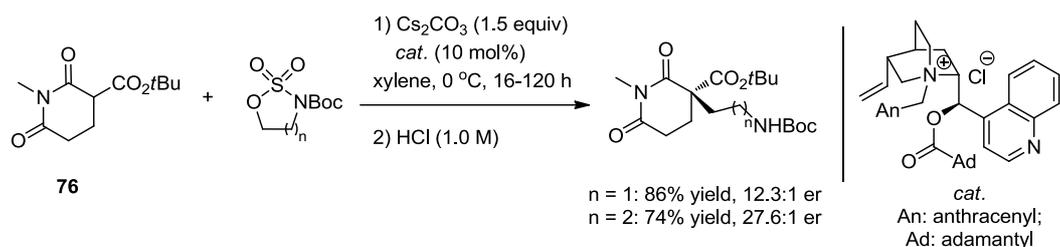
Scheme 60. Enantioselective desymmetrization of glutarimides

More recently, the Dixon group has reported enantioselective alkylation reactions of various activated carbonyl compounds with cyclic sulfamidates under phase-transfer organocatalytic conditions, including two examples with the glutarimide **76** (Scheme 61).¹⁰¹

⁹⁹ The interested reader may consult: *Dark Remedy: The Impact of Thalidomide and its Revival as a Vital Medicine*, Brynner, R.; Stephens T. 2001, Basic Books, Cambridge MA.

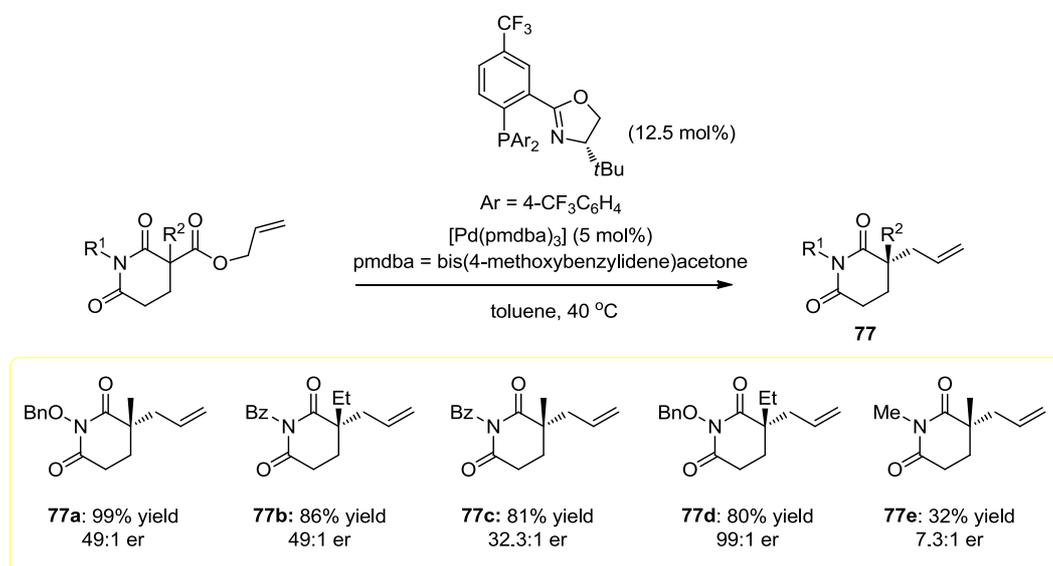
¹⁰⁰ Greenhalgh, D. A.; Simpkins, N. S. *Synlett* **2002**, 2074-2076

¹⁰¹ Moss, T. A.; Barber, D. M.; Kyle, A. F.; Dixon, D. J. *Chem. Eur. J.* **2013**, *19*, 3071.



Scheme 61. Dixon alkylation with cyclic sulfamidates

In a comparable approach, Stoltz and coworkers have prepared the closely related products **77a-e** using their palladium-catalyzed enantioselective allylic alkylation reaction (Scheme 62).¹⁰²

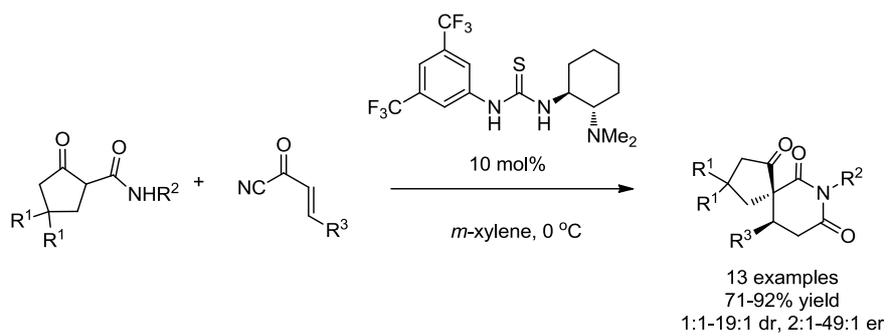


Scheme 62. Stoltz allylic alkylation reaction with glutarimides

Notably, in all the above approaches, a preformed and activated glutarimide moiety served as the substrate for functionalization reactions. Lately, Bonne and Rodriguez reported the first enantioselective synthetic methods for the synthesis of glutarimides, introducing α,β -unsaturated acyl cyanides as original bis-electrophiles in organocatalytic formal [3+3] spiroannulations (Scheme 63).¹⁰³

¹⁰² Bennett, N. B.; Duquette, D. C.; Kim, J.; Liu, W.-B.; Marziale, A. N.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2013**, *19*, 4414.

¹⁰³ Gouedranche, S.; Bugaut, X.; Constantieux, T.; Bonne, D.; Rodriguez, J. *Chem. Eur. J.* **2014**, *20*, 410.

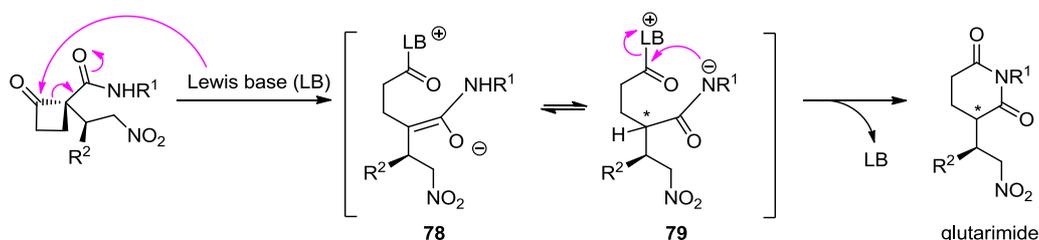


Scheme 63. Bonne / Rodriguez synthesis of non-racemic glutarimides

3.1.3. Our approach

A few years ago, our group reported some enantioselective organocatalytic Michael additions of activated cyclobutanones to nitroalkenes using bifunctional organocatalysts (Scheme 11).³⁷ The reaction performed best with cyclobutanone substrates activated by a secondary amide moiety, and a variety of cyclobutanone Michael adducts were obtained with high to excellent yields and stereoselectivities.

From these results, and because of the ring strain energy in cyclobutanones,¹⁰⁴ it was hypothesized that some Lewis base-catalyzed ring-rearrangement of the cyclobutanone products would be possible to afford glutarimides as depicted in Scheme 64. The Lewis base catalyst would first undergo a sp^2 -centered nucleophilic substitution at the cyclobutanone carbonyl group via a retro-Dieckmann-type ring opening to produce the zwitterionic intermediates **78** and then **79** (tautomers), and the latter would then cyclize back by a sp^2 -centered nucleophilic substitution of the nucleophilic nitrogen atom of the secondary amide to the carbonyl group bearing the positively charged Lewis base catalyst, affording both the glutarimide product and liberating the catalyst. As one can see from Scheme 64, some diastereoselectivity issues are anticipated due to a possible loss of chiral information during the process (**78** \rightarrow **79** should proceed with poor diastereoselectivity).

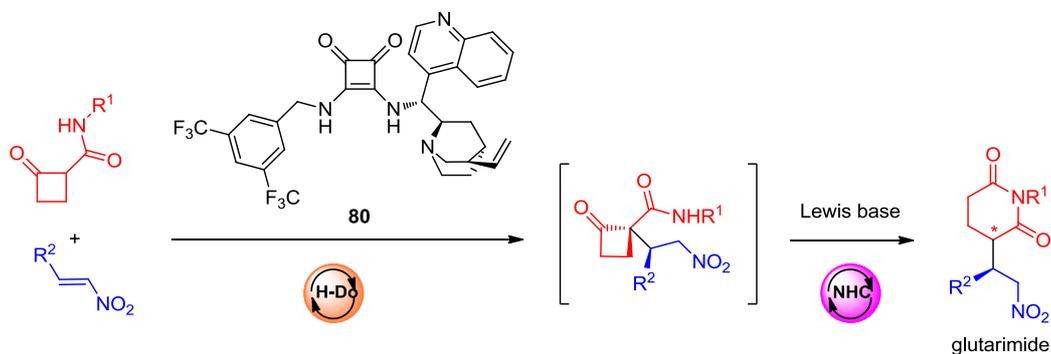


Scheme 64. Proposed stepwise approach to glutarimides

Ideally, both the enantioselective Michael addition and the ring rearrangement steps should be performed in a bi-organocatalytic cascade process comparable with the methodology detailed in Chapter 1, allowing for a *de novo* enantioselective synthesis of

¹⁰⁴ Reviews: (a) Bellus, D.; Ernst, B. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 797. (b) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449. (c) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485. (d) *The Chemistry of Cyclobutanes*, (Eds.: Z. Rappoport, J.F. Liebman), John Wiley & Sons, Chichester, 2005. (e) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 7740.

glutarimides (Scheme 65). More specifically, it was anticipated that NHCs could be suitable Lewis base catalysts for this purpose.

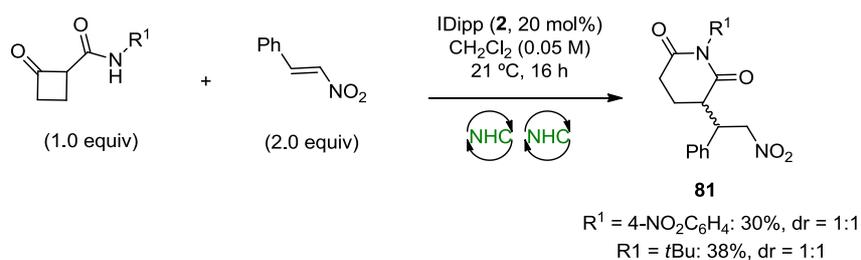


Scheme 65. Proposed enantioselective bicatalytic organocascade for the synthesis of glutarimides

3.2. Enantioselective synthesis of glutarimides

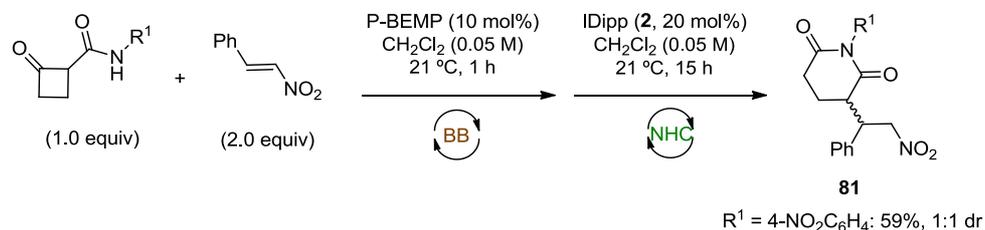
3.2.1. The racemic series

Of course, we needed a racemic synthesis of the targeted glutarimides. Because the NHC IDipp **2** is 1) a very good Brønsted base catalyst to perform Michael additions, and 2) a very good Lewis base (N parameter $\approx 22^{105}$), we surmised that both elemental steps of the cascade could be catalyzed by the NHC IDipp (**2**) acting successively as a Brønsted base and then as a Lewis base. In practice, this idea was evaluated in two model reactions, which indeed afforded the expected glutarimide products **81** but in somewhat low yields at full conversion, and virtually no diastereoselectivity (Scheme 66). The efficiency issue is probably due to the instability of the cyclobutanone substrates in the presence of the NHC IDipp (**2**). Nevertheless, these first examples validated the strategy.



Scheme 66. Early attempts for the racemic organocascade

In another version of the racemic Michael reaction, two distinct catalysts were used, namely the polystyrene-supported phosphazene base P-BEMP¹⁰⁶ and the NHC IDipp (**2**), in order to reach an acceptable degree of efficiency (Scheme 67).



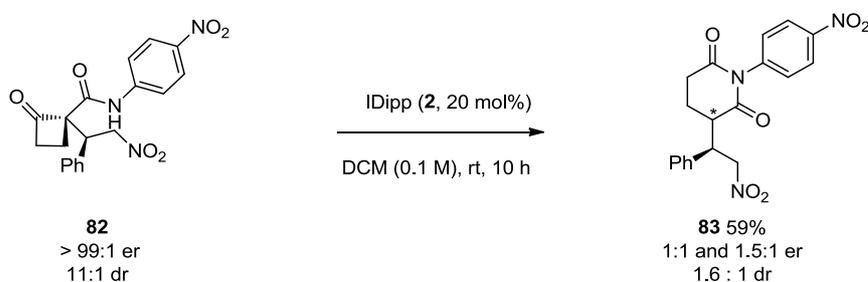
Scheme 67. Bi-organocatalytic racemic organocascade

¹⁰⁵ The nucleophilicity parameter N of the closely related NHC IMes was measured at 21.72. For comparison, the N parameter of triphenylphosphine is 13.59, and the one of DABCO is 18.80 See: (a) Maji, B.; Breugst, M.; Mayr, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 6915. (b) Baidya, M.; Kobayashi, S.; Brotzel, F.; Schmidhammer, U.; Riedle, E.; Mayr, H. *Angew. Chem. Int. Ed.* **2007**, *46*, 6176.

¹⁰⁶ Bensa, D.; Constantieux, T.; Rodriguez, J. *Synthesis* **2004**, 923.

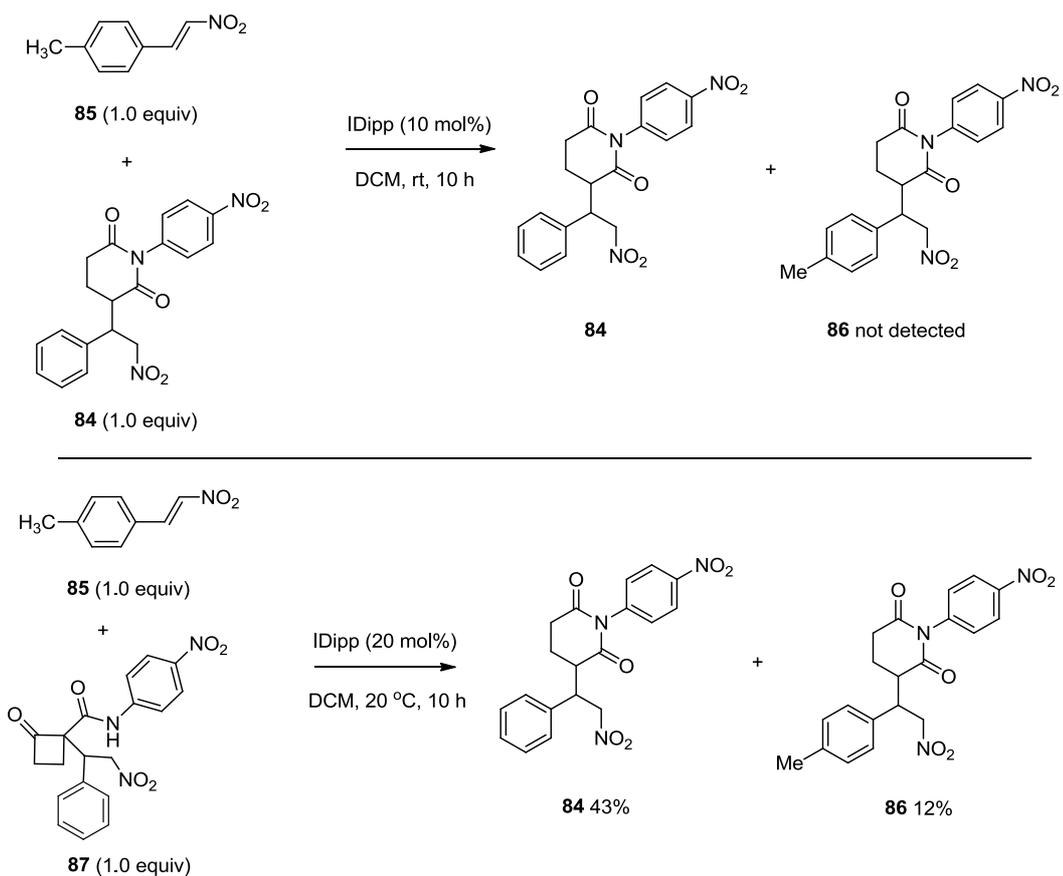
3.2.2. The optically active series

With in hand a method for the preparation of racemic glutarimides via the proposed cascade process, we turned our attention to its development in the enantioselective series. And before going into the overall cascade process, we examined the NHC-catalyzed ring rearrangement step individually. For this purpose, the enantiopure cyclobutanone Michael adduct **82** (11:1 dr, er > 99:1) was allowed to react with a catalytic amount of the NHC IDipp (**2**) in dichloromethane (Scheme 68). The desired glutarimide product **83** was obtained in 59% yield, but disappointingly, as a 1.6:1 mixture of two almost racemic diastereomers (er = 1:1 and 1.5:1, respectively). While the preparation of **83** as a mixture of two diastereomers was anticipated, its almost complete racemization was not.



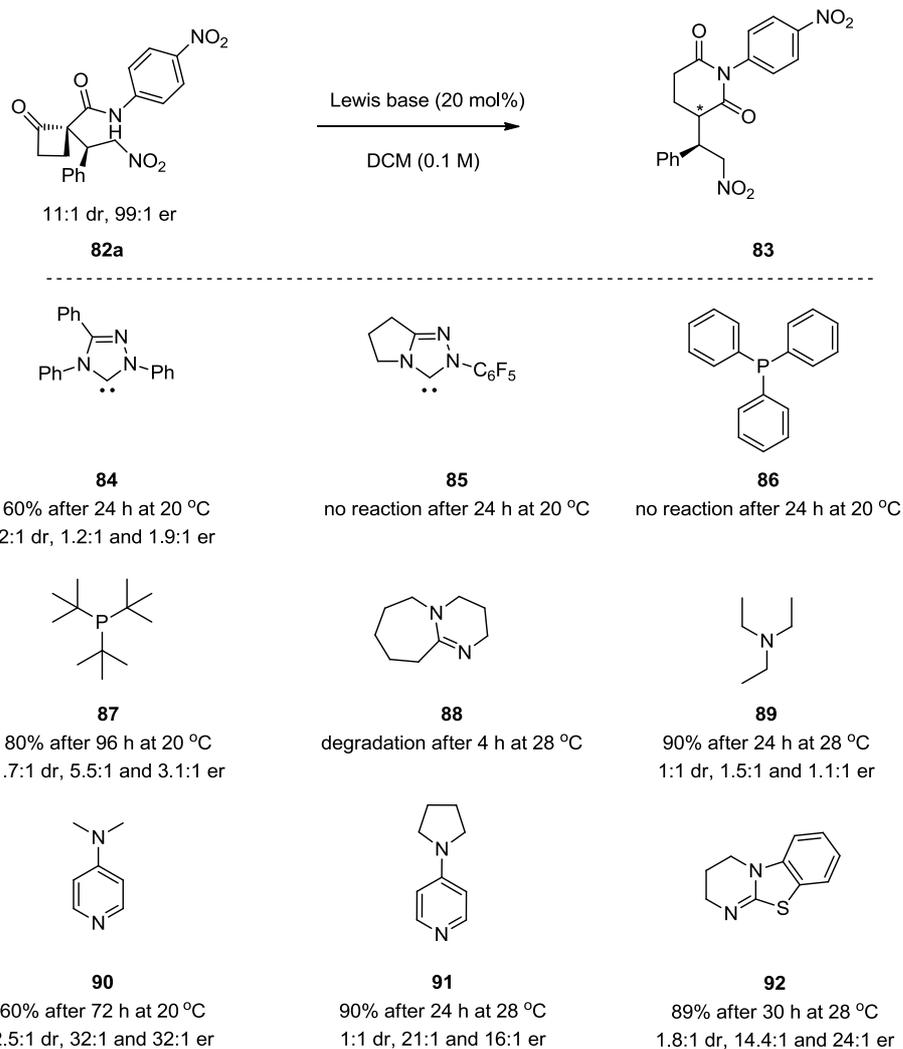
Scheme 68. NHC-catalyzed ring rearrangement

In order to determine at what stage the racemization occurred, two control cross-experiments were performed in the racemic series. In the first one (Scheme 69, top), the glutarimide **84** was allowed to react with the NHC IDipp **2** in the presence of the nitroalkene **85** having an extra methyl group. No cross-product **86** could be detected from this reaction, leading to the conclusion that no retro-Michael / Michael process is occurring on the glutarimide product under these conditions. Analogously, the second control experiment (Scheme 69, bottom) was performed from the cyclobutanone adduct **87**, still in the presence of the nitroalkene **85**. In this case, the glutarimide **84** was obtained in 43% together with the cross-product glutarimide **86** (12%), demonstrating the some retro-Michael / Michael processes occurred before the ring rearrangement.



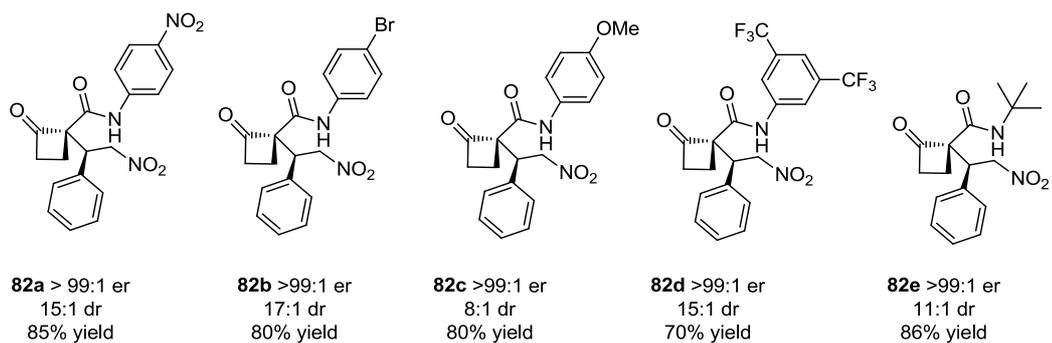
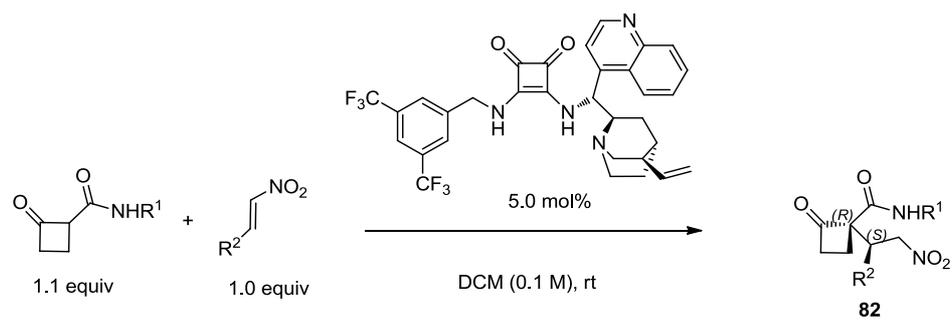
Scheme 69. Control experiments

From the above experiments, it was concluded that proposed enantioselective bicatalytic organocascade is possible, but we need to identify another catalyst showing comparable Lewis basicity and reduced Brønsted basicity when compared to the NHC IDipp (**2**) for the ring rearrangement step. We thus embarked on the evaluation of representative Lewis base organocatalysts on the model reaction depicted in Scheme 70. It was found that the 4-amino-pyridines **90** and **91**, as well as the isothiourea **92** afforded the desired glutarimides **83** in good yields and very acceptable enantiomeric ratio from 14.4:1 to 32:1 er.



Scheme 70. Lewis bases screening for the ring rearrangement

A small series of cyclobutanone Michael adducts **82** was prepared to evaluate the scope of the reaction (Scheme 71), but regrettably, time was lacking to perform these reactions and I had to stop my bench-work at this stage.



Scheme 71. Preparation of the cyclobutanone substrates

3.3. Conclusion

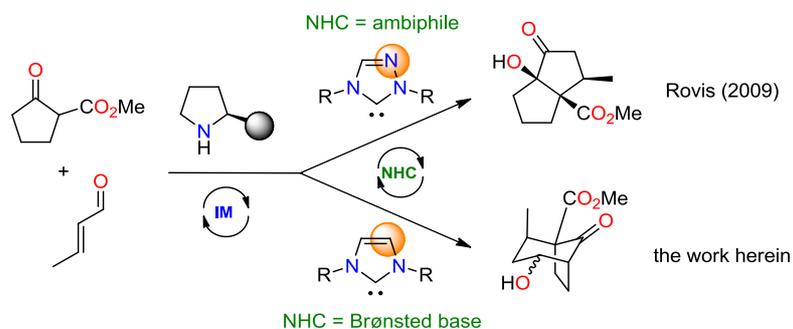
The preliminary work detailed in this Chapter has allowed obtaining the proof of concept for an enantioselective bi-organocatalytic cascade to convert prochiral cyclobutanones into glutarimides. Some good, but probably not yet best, catalysts have been identified, and the full enantioselective cascade remains to be demonstrated. This and related work is ongoing in our laboratory.

General conclusion

The work described in this manuscript is centered on enantioselective organocatalysis, including methodological developments and their application in the total synthesis of natural products.

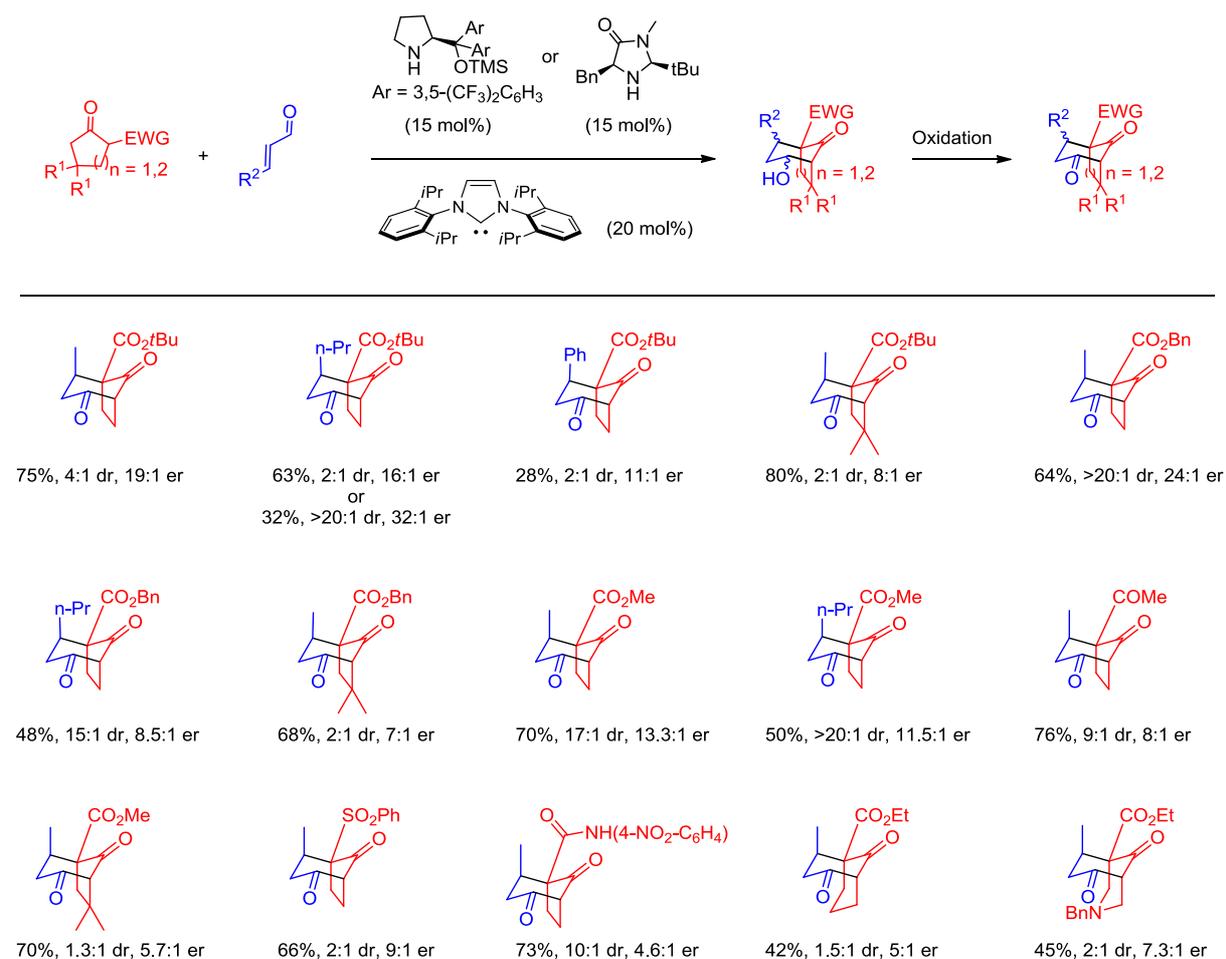
Enantioselective organocatalysis, which involves small chiral organic molecules as catalysts in enantioselective transformations, is a very active field of research in organic chemistry. It has been conceptualized back to 2000, and is now relatively mature. In recent years, the maturity of the field has translated into the emergence of the concept of multi-organocatalysis, involving combination of several organocatalysts in the same reaction mixture for the realization of complex transformations that would be difficult, if not impossible, to realize otherwise.

For example, the group of Rovis described in 2009 a bi-catalytic organocascade involving the combination of an aminocatalyst with a N-heterocyclic carbene (NHC) for the enantioselective synthesis of cyclopentanones (Scheme 72, top). Inspired by this work, and in the continuation of the research program of our group on the properties of NHCs as organocatalytic Brønsted bases, we have imagined a divergent organocascade from the same substrates for the preparation of bridged bicyclic compounds (Scheme 72, bottom).



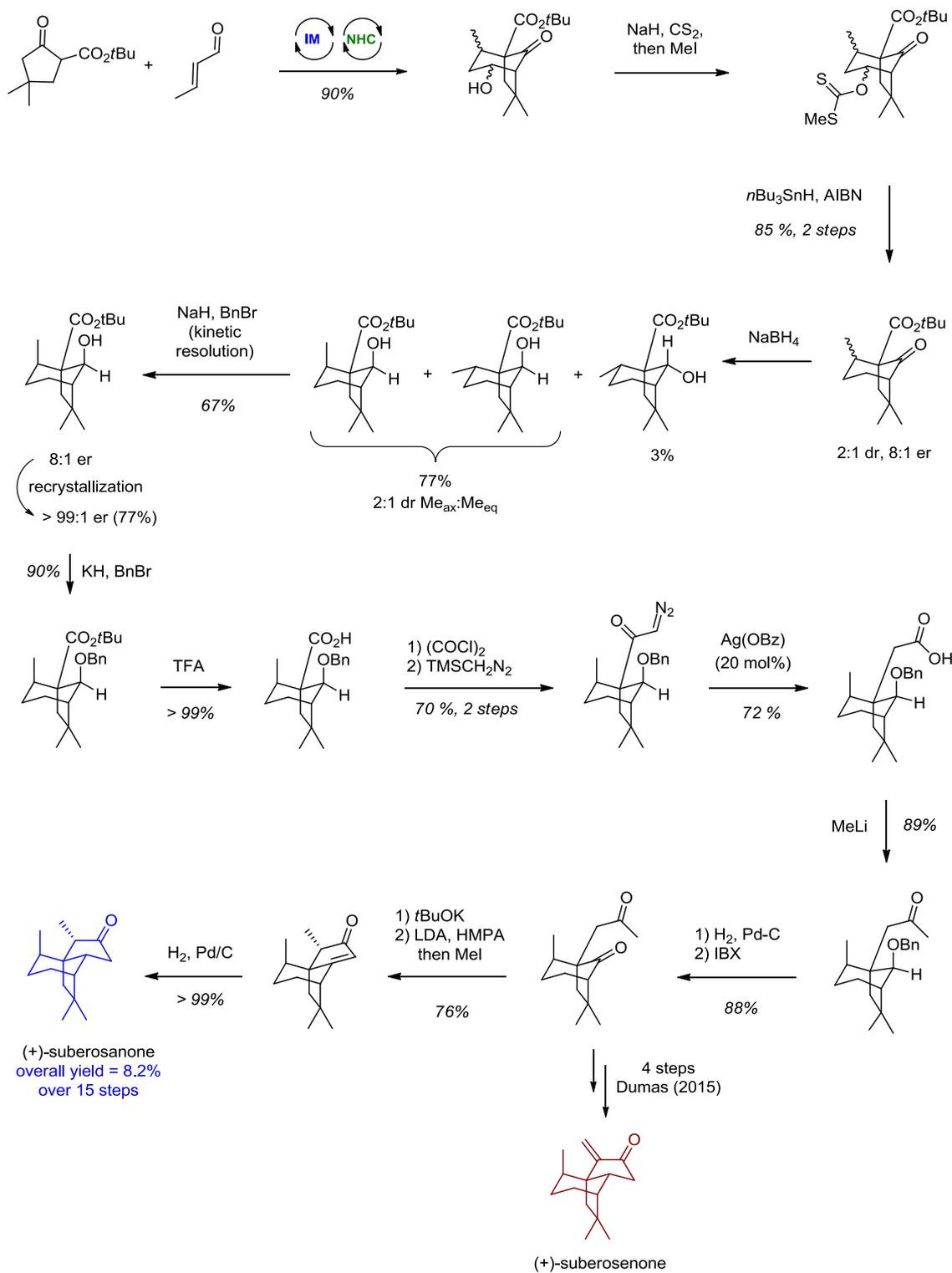
Scheme 72. Bi-catalytic organocascades combining aminocatalysis and NHC catalysis

We have thus developed an original bi-organocatalytic methodology for the direct and enantioselective synthesis of bridged bicyclic compounds, essentially bicyclo[3.2.1]octane derivatives (Scheme 73 and Chapter 1). The originality of the work lies on the use of a 1,3-imidazol-2-ylidene NHC as an organocatalytic Brønsted base (proton shuttle). A large part of the work has been directed at the optimization of the reaction to minimize the reversibility of the processes at hand (Michael addition & aldolization) in order to maintain a good control of the stereoselectivity.



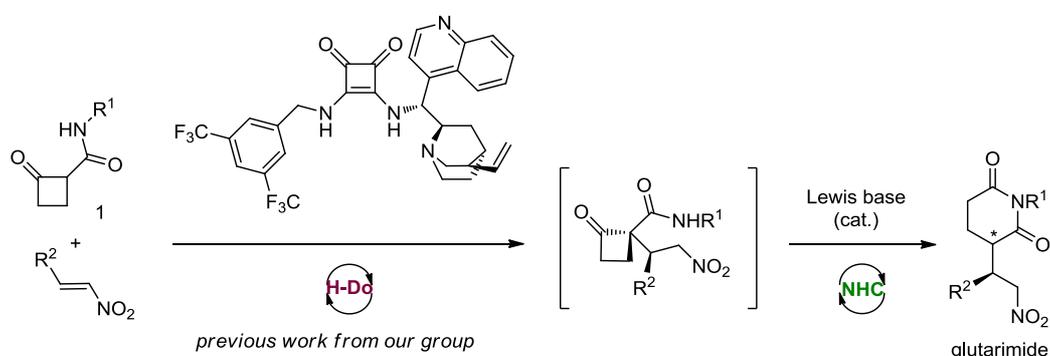
Scheme 73. Enantioselective bi-catalytic organocascade: synthesis of bicyclo[3.n.1]alkanes

The method was found general and efficient enough for its application to the enantioselective total synthesis of natural products. For this part of the work, we have focused on the synthesis of quadrane sesquiterpenes, and more specifically on the marine natural products (+)-suberosanone and (+)-suberosenone, two compounds with a promising biological profile (Scheme 74 and Chapter 2). Using our methodology as the key step, we could obtain (+)-suberosanone (ee > 99%) with an overall yield of 8% for 15 steps. Notably, this work represents the first enantioselective total synthesis of a quadrane sesquiterpene. A formal synthesis of (+)-suberosenone could also be achieved, and the overall synthetic strategy is believed to be flexible enough for the preparation of many analogs. Through this work, we have notably learned what steric effect means to kinetics, and how challenging it is to embark on a total synthesis project.



Scheme 74. Total synthesis of (+)-suberosanone, and formal synthesis of (+)-suberosenone

Finally, the third and last Chapter of this manuscript details our preliminary work on another enantioselective bi-catalytic organocascade for the preparation of glutarimides. The glutarimide moiety, i.e. the piperidine-2,6-dione moiety, can be found in biologically active natural products and synthetic drugs, but very few methods are available for their enantioselective synthesis. Capitalizing on earlier work from our group, we have examined a bi-catalytic approach based on an enantioselective Michael addition of cyclobutanones activated by a secondary amide moiety using a bifunctional catalyst, combined with a Lewis base catalyst, e.g. a NHC, capable of promoting a ring rearrangement of the intermediate Michael adduct into the desired glutarimide (Scheme 75 and Chapter 3). We have obtained the proof of concept for this original organocascade and identified several promising catalytic systems. This reaction should now be optimized and generalized.



Scheme 75. Enantioselective bi-catalytic organocascade: synthesis of glutarimides

In conclusion, the basic research work presented herein is anchored at the core of modern synthetic organic chemistry, and more specifically in the field of enantioselective multi-organocatalysis. During this work, we have identified two original organocascades and demonstrated the synthetic relevance of one of these through applications in total synthesis. More generally, our work adds to the arsenal of enantioselective multi-catalytic processes for the time-efficient synthesis of complex small molecules. It is the author's view that such modern synthetic processes are keys to unlock the availability of truly complex functional molecules.

Experimental part

ES.0. General experimental information

- All of commercial available reagents were used without further purification unless otherwise stated. Oxygen and/or moisture sensitive reactions and manipulations were performed under argon atmosphere, using syringes, cannula, oven-dried glassware, and dry solvents obtained from a solvent purification system. Anhydrous methanol was prepared by refluxing for 2 hours in the presence of magnesium turnings and distilled under argon.

- Reactions were monitored by TLC visualized by ultraviolet light (254 nm) and/or using an acidic *p*-anisaldehyde ethanolic solution. Flash chromatography was performed on 40-63 μm silica gel, generally eluted with EtOAc / petroleum ether (herein abbreviated PE, bp 40-60°C) or EtOAc / Et₂O.

- ¹H NMR data were generally recorded in CDCl₃ at 294 K at 300 MHz or 400 MHz using the residual nondeuterated solvent as an internal standard ($\delta = 7.26$ ppm). ¹³C{¹H} NMR spectra were generally recorded in CDCl₃ at 294 K at 75 MHz or 100 MHz using the deuterated solvent as an internal standard ($\delta = 77.16$ ppm). In some cases, CD₂Cl₂ or (CD₃)₂CO were used to record the NMR data, again using the residual nondeuterated solvent as an internal standards. Coupling constants (*J*) are in Hertz (Hz) and the classical abbreviations are used to describe the signal multiplicities.

- Melting points were measured with a Büchi B-540 apparatus.

- Specific rotations were recorded on an Anton Paar MCP 200 Polarimeter at 589 nm and at 25 °C or 20 °C and specific rotations are reported as follows: specific rotation (concentration in grams/100 mL of solution, solvent).

- Low resolution mass spectra (MS) were recorded on ion trap *Brucker Esquire 6000*, equipped with an electrospray source (ESI), methanol is used as solvent (Sigma Aldrich/HPLC grade). High resolution mass spectra (HRMS) were recorded at the spectropole (<http://fr-chimie.univ-amu.fr/spectropole/>) on a Waters Synapt G2 HDMS apparatus using a positive electrospray (ESI) ionization source.

- HPLC analyses for the determination of enantiomeric ratio were performed on a Merck-Hitachi system equipped with Chiralpak AD-H, Chiralcel OD-3, Chiralcel IF,

Lux-Cellulose-4, Chiralpak IA, Chiralpak AZ-H, and Lux-Cellulose-2. See <http://chirbase.u-3mrs.fr> for details.

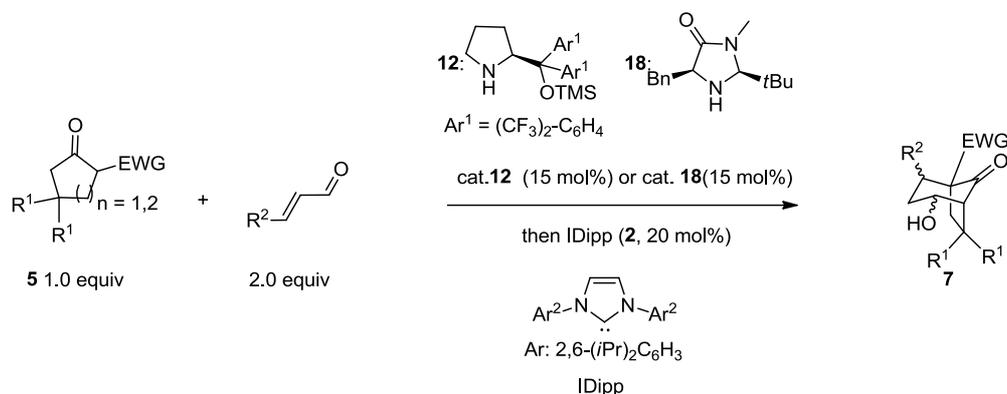
- Crotonaldehyde, *trans*-2-hexenal and cinnamaldehyde were freshly distilled under argon atmosphere.

- Cyclic 2-diazo-1,3-diketones were obtained by treatment of the corresponding 1,3-diketones with *p*-toluenesulfonyl azide according to the reported procedure in similar yields and purities.¹⁰⁷

- Unless otherwise stated, all dr (diastereomeric ratio) mentioned in the following account for the ratio of diastereomers at C7 as follow: C7(axial substituent):C7(equatorial substituent)

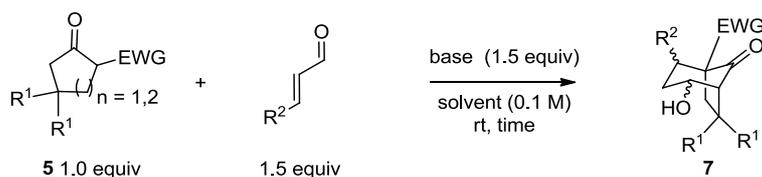
¹⁰⁷ Presset, M.; Mailhol, D.; Coquerel, Y.; Rodriguez, J. *Synthesis* **2011**, 2549

ES.1. Chemistry of bicyclo[3.n.1]octanes



General procedure: To a solution of α -activated cycloalkanone **5** (0.5 mmol) and α,β -unsaturated aldehyde (1.0 mmol) in dry solvent (0.2 mL) under argon atmosphere was added (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (Jørgensen catalyst **12**) (15 mol%) or (*2S,5S*)-(-)-2-tert-Butyl-3-methyl-5-benzyl-4-imidazolidinone (MacMillan catalyst **18**) (15 mol%). Then the mixture was stirred at 0 °C or room temperature, the reaction was monitored by TLC, after compound **5** was full converted, 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene (IDipp) (20 mol%) was added. The reaction mixture was concentrated in vacuum to afford compound **7** (purify or not depend on the followed reaction)

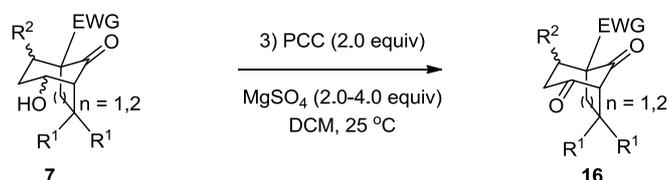
•preparation of racemate:



To a solution of α -carbonylated-cyclopentanone **5** (1.0 equiv) in dry solvent (0.1 M) under an argon atmosphere was added the appropriate base (1.5 equiv) and the mixture was stirred for 5 min at room temperature. α,β -unsaturated aldehyde (1.5 equiv) was then added dropwise and the reaction was stirred at room. After full conversion, when K_2CO_3 was used, simple filtration through a pad of Celite and concentration of the filtrate in vacuum gave the crude bicyclic compounds **7**, which were purified by flash chromatography. In the case of DBU, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted twice with EtOAc.

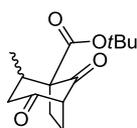
The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuum to afford the crude bicyclic compounds which were purified by flash chromatography.

•oxidation of compound **7**:



To a solution of compound **7** in dichloromethane was added pyridinium chlorochromate (PCC) (2.0 equiv) and magnesium sulfate (2.0 equiv), the reaction mixture was stirred at room temperature overnight. The resulting crude was filtered, then concentrated in vacuum and purified by flash chromatography to afford compound **16**.

Compound 16a



C₁₄H₂₀O₄
MW = 252.31

Following the general procedure, the reaction between **5a** (92.1 mg, 0.5 mmol) and *trans*-crotonaldehyde (83 μL, 1.0 mmol) at 0 °C using catalyst **12** in MeOH (2.5 M) afforded compound **16a** (94.6 mg, 75 %, 4:1 dr, 19:1 er) as a white solid after silica gel purification.

R_f (PE/EtOAc: 4/1) = 0.26;

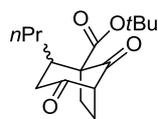
M.p. = 111-119 °C;

HRMS (ESI+) for C₁₄H₂₁O₄⁺: calcd. [M+H]⁺: 253.1434, found: 253.1428;

HPLC (Lux-Amylose-2, Heptane/ethanol 80/20, 1.0 mL/min, UV 220 nm): τ_{axial-Me} = 6.85 min and 7.29 min

¹³C NMR (100 MHz, δ ppm/CDCl₃): **axial-Me**: 205.1 (C), 200.4 (C), 169.6 (C), 82.1 (C), 65.7 (CH), 60.7 (C), 42.1 (CH₂), 32.5 (CH), 29.8 (CH₂), 28.1 (CH₃×3, *t*-Bu), 21.6 (CH₂), 16.8 (CH₃); **equatorial-Me**: 203.8 (C), 202.9 (C), 168.1 (C), 82.3 (C), 63.83 (CH), 62.6 (C), 42.9 (CH₂), 32.5 (CH), 28.1 (CH₃×3, *t*-Bu), 22.1 (CH₂), 19.7 (CH₂), 15.8 (CH₃). **¹H NMR** (400 MHz, δ ppm/CDCl₃): **axial-Me**: 3.18 (t, *J* = 5.1 Hz, 1H), 2.95 (dd, *J* = 16.1, 7.9 Hz, 1H), 2.69 – 2.50 (m, 1H), 2.50 – 2.33 (m, 1H), 2.25 (ddd, *J* = 13.1, 10.2, 4.3 Hz, 1H), 2.21 – 2.16 (m, 1H), 2.16 – 2.05 (m, 1H), 2.03 – 1.80 (m, 1H), 1.45 (s, 9H), 0.89 (d, *J* = 7.0 Hz, 3H); **equatorial-Me**: 3.18 (t, *J* = 5.1 Hz, 1H), 2.95 (dd, *J* = 16.1, 7.9 Hz, 1H), 2.69 – 2.50 (m, 1H), 2.50 – 2.33 (m, 1H), 2.25 (ddd, *J* = 13.1, 10.2, 4.3 Hz, 1H), 2.21 – 2.16 (m, 1H), 2.16 – 2.05 (m, 1H), 2.03 – 1.80 (m, 1H), 1.46 (s, 9H), 1.04 (d, *J* = 5.8 Hz, 3H)

Compound 16h



$C_{16}H_{24}O_4$
MW = 280.36

Following the general procedure, the reaction between **5a** (92.1 mg, 0.5 mmol) and *trans*-2-hexenal (116 μ L, 1.0 mmol) at 0 °C using catalyst **12** in MeOH (2.5 M). The product **16h** (88.3 mg, 63 %, 2:1 dr, 15.7:1 er) is a yellow-off solid after flash chromatography.

R_f (PE/EtOAc: 5/1) = 0.28

M.p. = 80-107 °C

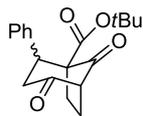
HRMS (ESI+) for $C_{16}H_{28}NO_4^+$: calcd. $[M+NH_4]^+$: 298.2013, found: 298.2013

HPLC ((S, S)-Whelk-O1, Heptane/ethanol 90/10, 1.0 mL/min, UV 220 nm): $\tau_{\text{axial-}n\text{Pr}}$ = 9.73 min and 10.56 min

^{13}C NMR (100 MHz, δ ppm/ CDCl_3): **axial-*n*Pr**: 205.3 (C), 200.3 (C), 169.7 (C), 82.0 (C), 65.7 (CH), 60.8 (C), 38.3 (CH₂). 37.4 (CH), 32.5 (CH₂), 29.8 (CH₂), 28.1 (CH₃×3, *t*-Bu), 21.6 (CH₂), 20.3 (CH₂), 13.8(CH₃); **equatorial-*n*Pr**: 204.0 (C), 202.8 (C), 168.2 (C), 82.2 (C), 64.3 (CH), 62.9 (C), 40.5 (CH₂), 36.7 (CH), 33.6 (CH₂), 22.1 (CH₂), 28.1 (CH₃×3, *t*-Bu), 21.3 (CH₂), 20.3 (CH₂), 13.9 (CH₃). ^1H NMR (400 MHz, δ ppm/ CDCl_3): **axial-*n*Pr**: δ 3.21 – 3.08 (m, 1H), 2.85 – 1.80 (m, 7H), 1.44 (s, 9H), 1.40 – 1.17 (m, 3H), 0.83 (t, J = 7.0 Hz, 3H), 0.76 – 0.69 (m, 1H)

Equatorial-*n*Pr: δ 3.21 – 3.08 (m, 1H), 2.85 – 1.80 (m, 7H), 1.46 (s, 9H), 1.40 – 1.17 (m, 3H), 0.88 (t, J = 6.9 Hz, 3H), 0.76 – 0.69 (m, 1H)

Compound 16i



$C_{19}H_{22}O_4$
MW = 314.38

Following the general procedure, the reaction between **5a** (92.1 mg, 0.5 mmol) and cinnamaldehyde (125 μ L, 1.0 mmol) at 15 °C using catalyst **18** in MeOH (2.5 M). The product **16i** (44.0 mg, 28 %, 2:1 dr, 10.8:1 er) is a white solid after flash chromatography.

R_f (PE/EtOAc: 4/1) = 0.24

M.p. = 115-179 °C

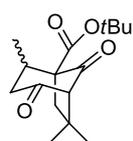
HRMS (ESI+) for $C_{19}H_{23}O_4^+$: calcd. $[M+H]^+$: 315.1591, found: 315.1591

HPLC (Chiralcel OD-3, Heptane/ethanol 80/20, 1.0 mL/min, UV 220 nm): $\tau_{\text{axial-ph}}$ = 5.85 min and 6.54 min

^{13}C NMR (75 MHz, δ ppm/ CDCl_3): **axial-Ph**: 206.2 (C), 200.2 (C), 168.6 (C), 140.2 (C), 128.4 (CH×2), 128.3 (CH×2), 127.6 (CH), 82.2 (C), 66.1 (CH), 59.9 (C), 44.9 (CH), 41.8 (CH₂), 30.6 (CH₂), 28.0 (CH₃×3, *t*-Bu), 21.8 (CH₂); **equatorial-Ph**: 203.3 (C), 202.1 (C), 167.5 (C), 138.4 (C), 128.6 (CH), 128.3 (CH×2), 127.8 (CH×2), 82.5 (C), 64.4 (CH), 62.7(C),

42.7 (CH), 42.7 (CH₂), 27.9 (CH₃×3, *t*-Bu), 22.31 (CH₂), 21.38 (CH₂). ¹H NMR (300 MHz, δ ppm/CDCl₃): **axial-Ph**: 7.34 – 7.27 (m, 2H), 7.25 – 7.16 (m, 2H), 7.05 – 6.95 (m, 1H), 3.76 – 3.58 (m, 1H), 3.44 (d, J = 6.8 Hz, 1H), 3.40 – 3.24 (m, 1H), 2.94 – 2.39 (m, 3H), 2.37 – 2.19 (m, 1H), 2.14 – 2.00 (m, 1H), 1.33 (s, 9H). **equatorial-Ph**: 7.34 – 7.27 (m, 2H), 7.25 – 7.16 (m, 2H), 7.05 – 6.95 (m, 1H), 3.76 – 3.58 (m, 1H), 3.40 – 3.24 (m, 1H), 3.03 (dd, J = 16.7, 13.4 Hz, 1H), 2.94 – 2.39 (m, 3H), 2.37 – 2.19 (m, 1H), 2.14 – 2.00 (m, 1H), 1.30 (s, 9H)

Compound 16b



C₁₆H₂₄O₄
MW = 280.36

Following the general procedure, the reaction between **5b** (106.1 mg, 0.5 mmol) and *trans*-crotonaldehyde (83 μL, 1.0 mmol) at 0 °C using catalyst **12** in MeOH (2.5 M) afforded compound **16b** (112.1 mg, 80 %, 2:1 dr, 8:1 er) as white solid after flash chromatography.

R_f (PE/EtOAc: 4/1) = 0.67

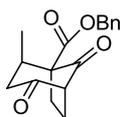
M.p. = 92-112 °C

HRMS (ESI+) for C₁₆H₂₈NO₄⁺: calcd. [M+NH₄]⁺: 298.2013, found: 298.2013

HPLC (Chiralpak AZ-H, Heptane/ethanol 80/20, 1.0 mL/min, UV 220 nm): τ_{axial-Me} = 7.13 min and 15.34 min

¹³C NMR (75 MHz, δ ppm/CDCl₃): **axial-Me**: 205.5 (C), 201.1 (C), 169.5 (C), 81.8 (C), 78.4 (CH), 62.3 (C), 45.7 (CH₂), 44.1 (CH₂), 35.5 (C), 31.9 (CH), 30.3 (CH₃), 27.9 (CH₃×3, *t*-Bu), 24.2 (CH₃), 17.4 (CH₃); **equatorial-Me**: 204.0 (C), 203.5 (C), 168.1 (C), 82.1 (C), 76.9 (CH), 63.9 (C), 44.6 (CH₂), 36.5 (CH₂), 36.0 (C), 32.3 (CH), 30.3 (CH₃), 28.0 (CH₃×3, *t*-Bu), 24.6 (CH₃), 16.10 (CH₃). ¹H NMR (300 MHz, δ ppm/CDCl₃): **axial-Me**: 2.84 – 2.33 (m, 3H), 2.22 (d, J = 17.8 Hz, 1H), 2.12 (d, J = 7.2 Hz, 1H), 1.98 (dt, J = 41.6, 9.8 Hz, 1H), 1.42 (s, 9H), 1.06 (s, 6H), 0.91 (d, J = 6.9 Hz, 3H); **equatorial-Me**: 2.84 – 2.33 (m, 3H), 2.22 (d, J = 17.8 Hz, 1H), 2.12 (d, J = 7.2 Hz, 1H), 1.98 (dt, J = 41.6, 9.8 Hz, 1H), 1.44 (s, 9H), 1.03 (s, 6H), 0.99 (d, J = 6.3 Hz, 3H)

Compound 16e



C₁₇H₁₈O₄
MW = 286.32

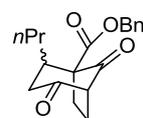
Following the general procedure, the reaction between **5e** (109.1 mg, 0.5 mmol) and *trans*-crotonaldehyde (83 μL, 1.0 mmol) at 0 °C using catalyst **12** in MeOH (2.5 M) afforded compound **16e** as a yellow oil (91.6 mg, 64 %, >20:1 dr, 24:1 er) after fresh chromatography purification.

R_f (PE/EtOAc: 4/1) = 0.24

HRMS (ESI+) for C₁₇H₁₉O₄⁺: calcd. [M+H]⁺: 287.1278, found: 287.1278

HPLC (Chiralpak IC, Heptane/Ethanol 80/20, 1.0 mL/min, DAD): $\tau = 7.20$ min and 7.95 min
 $^{13}\text{C NMR}$ (75 MHz, ppm/ CDCl_3): 204.6 (C), 200.0 (C), 170.4 (C), 135.5 (C), 128.7 (CH \times 2), 128.5 (CH), 128.2 (CH \times 2), 67.2 (CH $_2$), 65.6 (CH), 60.5 (C), 42.1 (CH $_2$), 32.5 (CH), 29.7 (CH $_2$), 21.7 (CH $_2$), 16.9 (CH $_3$). $^1\text{H NMR}$ (300 MHz, δ ppm/ CDCl_3): 7.36 – 7.26 (m, 5H), 5.29 – 5.18 (m, 2H), 3.26 (d, $J = 6.4$ Hz, 1H), 2.99 (dd, $J = 16.1, 7.8$ Hz, 1H), 2.66 (p, $J = 7.1$ Hz, 1H), 2.60 – 2.48 (m, 1H), 2.35 – 2.27 (m, 1H), 2.21 (dd, $J = 17.2, 9.0$ Hz, 2H), 2.05 – 1.90 (m, 1H), 0.94 (d, $J = 6.9$ Hz, 3H)

Compound 16n



$\text{C}_{19}\text{H}_{22}\text{O}_4$
 MW = 314.38

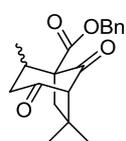
Following the general procedure, the reaction between **5e** (109.1 mg, 0.5 mmol) and *trans*-2-hexenal (116 μL , 1.0 mmol) at 25 °C using catalyst **18** in MeOH (2.5 M) afforded compound **16n** as a yellow oil (75.5 mg, 48 %, 15:1 dr, 8:1 er) after silica gel purification.

R_f (PE/EtOAc: 4/1) = 0.58

HRMS (ESI+) for $\text{C}_{19}\text{H}_{23}\text{O}_4^+$: calcd. $[\text{M}+\text{H}]^+$: 315.1591, found: 315.1591

HPLC (Chiralpak IC, Hexane/Ethanol 80/20, 1.0 mL/min, DAD): $\tau = 6.36$ min and 7.20 min
 $^{13}\text{C NMR}$ (75 MHz, δ ppm/ CDCl_3): 204.9 (C), 199.9 (C), 170.5 (C), 135.5 (C), 128.7 (CH), 128.5(CH \times 2), 128.3 (CH \times 2), 67.17 (CH $_2$), 65.6 (CH), 60.56 (C), 38.3 (CH $_2$), 37.5 (CH), 32.5 (CH $_2$), 29.7 (CH $_2$), 21.8 (CH $_2$), 21.3 (CH $_2$), 13.8 (CH $_3$). $^1\text{H NMR}$ (300 MHz, δ ppm/ CDCl_3): 7.46 – 7.28 (m, 5H), 5.24 (dd, $J = 30.6, 12.2$ Hz, 2H), 3.25 (d, $J = 6.1$ Hz, 1H), 2.95 – 2.73 (m, 1H), 2.57 – 2.33 (m, 3H), 2.35 – 2.14 (m, 2H), 2.05 – 1.92 (m, 1H), 1.47 – 1.30 (m, 2H), 1.29 – 1.10 (m, 2H), 0.81 (t, $J = 7.0$ Hz, 3H)

Compound 16c



$\text{C}_{19}\text{H}_{22}\text{O}_4$
 MW = 314.38

The reaction between **5c** (123.2 mg, 0.5 mmol) and *trans*-crotonaldehyde (83 μL , 1.0 mmol) at 0 °C using catalyst **12** in MeOH (2.5 M) afforded compound **16c** as a yellow solid (106.9 mg, 68 %, 2:1 dr, 7:1 er) after flash chromatography

R_f (PE/EtOAc: 4/1) = 0.47

M.p. = 62-64 °C

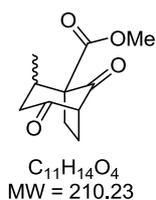
HRMS (ESI+) for $\text{C}_{19}\text{H}_{23}\text{O}_4^+$: calcd. $[\text{M}+\text{H}]^+$: 315.1591, found: 315.1591

HPLC (Chiralpak AD-H, Heptane/Ethanol (90/10), 1 mL/min, DAD): $\tau_{\text{axial-Me}} = 12.15$ min and 19.44 min

$^{13}\text{C NMR}$ (75 MHz, δ ppm/ CDCl_3): **axial-Me**: 205.0 (C), 200.8 (C), 170.2 (C), 135.6 (C), 128.7 (CH \times 2), 128.3 (CH \times 2), 127.9 (CH), 78.3 (CH), 67.0 (CH $_2$), 61.8 (C), 45.5 (CH $_2$), 44.0

(CH₂), 35.6 (C), 32.2 (CH₃), 30.5 (CH₃), 24.2 (CH₃), 17.6 (CH₃); **equatorial-Me**: 203.6 (C), 202.9 (C), 169.1 (C), 135.5 (C), 128.7 (CH×2), 128.4 (CH), 128.2 (CH×2), 76.7 (CH), 67.5 (CH₂), 63.7 (C), 44.5 (CH₂), 36.5 (C), 36.2 (CH₂), 32.6 (CH₃), 30.5 (CH₃), 24.6 (CH₃), 16.2 (CH₃); ¹H NMR (300 MHz, δ ppm/CDCl₃): 7.36 – 7.29 (m, 5H), 5.27 – 5.17 (m, 2H), 2.90 – 1.93 (m, 6H), 1.12 – 1.09 (m, 6H), 0.99 – 0.97 (m, 3H)

Compound 16j



Following the general procedure, the reaction between methyl-2-oxocyclopentanecarboxylate (75 mg (95% purity), 0.5 mmol) and *trans*-crotonaldehyde (83 μL, 1.0 mmol) at 0 °C using catalyst **12** in MeOH (2.5 M) afforded compound **16j** as a pale-yellow solid (73.5 mg, 70 %, 17:1 dr, 13.3:1 er) after silica gel purification.

R_f (PE/EtOAc: 4/1) = 0.21

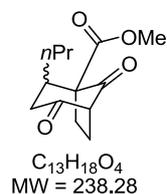
M.p. = 56-58 °C

HRMS (ESI+) for C₁₁H₁₅O₄⁺: calcd. [M+H]⁺: 211.0965, found: 211.0965

HPLC (Chiralpak AD-H, Heptane/ethanol 80/20, 1.0 mL/min, UV 220 nm): τ = 9.74 min and 11.25 min

¹³C NMR (100 MHz, δ ppm/CDCl₃): 204.6 (C), 200.2 (C), 170.9 (C), 65.4 (CH), 60.4 (C), 52.5 (CH₃), 42.0 (CH₂), 32.4 (CH), 29.8 (CH₂), 21.7 (CH₂), 16.9 (CH₃). ¹H NMR (400 MHz, δ ppm/CDCl₃): 3.78 (s, 3H), 3.24 (d, *J* = 6.4 Hz, 1H), 2.98 (dd, *J* = 16.1, 7.9 Hz, 1H), 2.70 – 2.59 (m, 1H), 2.58 – 2.49 (m, 1H), 2.29 (ddd, *J* = 12.1, 9.8, 4.2 Hz, 1H), 2.25 – 2.18 (m, 1H), 2.23 – 2.19 (m, 1H), 1.99 (ddd, *J* = 14.0, 7.9, 3.0 Hz, 1H), 0.91 (d, *J* = 7.0 Hz, 3H)

Compound 16o



Following the general procedure, the reaction between methyl 2-oxocyclopentanecarboxylate (75 mg (95% purity), 0.50 mmol) and *trans*-2-hexenal (116 μL, 1.0 mmol) at 25 °C using catalyst **18** in MeOH (2.5 M) afforded compound **16o** (56.5 mg, 50 %, >20:1 dr, 11.5:1 er) as pale-yellow solid after flash chromatography

R_f (PE/EtOAc: 5/1) = 0.35

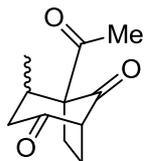
M.p. = 63-65 °C

HRMS (ESI+) for C₁₃H₁₉O₄⁺: calcd. [M+H]⁺: 239.1278, found: 239.1278

HPLC (Chiralpak AD-H, Hexane/ethanol 80/20, 1.0 mL/min, UV 220 nm): τ = 6.32 min and 8.81 min

^{13}C NMR (75 MHz, δ ppm/ CDCl_3): 204.9 (C), 200.1 (C), 171.3 (C), 65.5 (CH), 60.6 (C), 52.6 (CH_3), 38.3 (CH_2), 37.4 (CH), 32.5 (CH_2), 29.8 (CH_2), 21.8 (CH_2), 21.2 (CH_2), 13.8 (CH_2). ^1H NMR (300 MHz, δ ppm/ CDCl_3): 3.78 (s, 3H), 3.24 (d, $J = 6.3$ Hz, 1H), 2.82 (dd, $J = 16.2, 7.5$ Hz, 1H), 2.48 (ddd, $J = 22.5, 15.1, 3.9$ Hz, 3H), 2.33 – 2.16 (m, 2H), 2.04 – 1.94 (m, 1H), 1.44 – 1.31 (m, 2H), 1.24 (td, $J = 13.4, 4.9$ Hz, 2H), 0.85 (t, $J = 6.9$ Hz, 3H).

Compound 16k



Following the general procedure, the reaction between 2-acetylcyclopentanone (61.7, μL (98% purity), 0.5 mmol) and *trans*-crotonaldehyde (83 μL , 1.0 mmol) using catalyst **12** at 0 $^\circ\text{C}$ in CHCl_3 (2.5 M) afforded **16k** (73.8 mg, 76%, 9:1 dr, 8:1 er) as a white solid after flash chromatography.

$\text{C}_{11}\text{H}_{14}\text{O}_3$
MW = 194.23 R_f (PE/EtOAc: 4/1) = 0.20

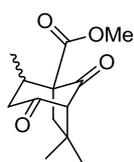
M.p. = 56-63 $^\circ\text{C}$

HRMS (ESI+) for $\text{C}_{11}\text{H}_{15}\text{O}_3^+$: calcd. $[\text{M}+\text{H}]^+$: 195.1016, found: 195.1016

HPLC (Chiralpak AS-H, Hexane/ethanol 80/20, 1.0 mL/min, DAD): $\tau = 6.475$ min and 8.186 min

^{13}C NMR (75 MHz, δ ppm/ CDCl_3): 205.2 (C), 205.1(C), 203.1(C), 65.8(C), 65.6(CH), 41.9 (CH_2), 31.7 (CH), 28.2 (CH_3), 28.1 (CH_2), 21.8 (CH_2), 16.6 (CH_3). ^1H NMR (300 MHz, δ ppm/ CDCl_3): 3.25 (d, $J = 6.1$ Hz, 1H), 2.96 (dd, $J = 16.1, 8.0$ Hz, 1H), 2.79 – 2.67 (m, 1H), 2.40-2.31 (m, 1H), 2.29 (s, 3H), 2.25 – 2.00 (m, 4H), 0.78 (d, $J = 7.0$ Hz, 3H).

Compound 16d



$\text{C}_{13}\text{H}_{18}\text{O}_4$
MW = 238.28 R_f (PE/EtOAc: 4/1) = 0.53

Following the general procedure, in the presence of catalyst **12**, the reaction between **5d** (85.0 mg, 0.5 mmol) and *trans*-crotonaldehyde (83 μL , 1.0 mmol) at 0 $^\circ$ in MeOH (2.5 M) gave product **16d** (83.4 mg, 70%, 1.3:1 dr, 5.7:1 er) as oil after flash chromatography.

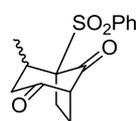
HRMS (ESI+) for $\text{C}_{13}\text{H}_{19}\text{O}_4^+$: calcd. $[\text{M}+\text{H}]^+$: 239.1278, found: 239.1278

HPLC (Chiralpak IE, Heptane/Ethanol 80/20, 1.0 mL/min, DAD): $\tau_{\text{axial-Me}} = 9.80$ min and 11.05 min

^{13}C NMR (75 MHz, δ ppm/ CDCl_3): **axial-Me**: 205.0 (C), 200.8 (C), 170.9 (C), 78.1 (CH), 61.7 (C), 52.5 (CH_3), 45.5 (CH_2), 43.9 (CH_2), 35.5 (C), 32.1 (CH), 30.5 (CH_3), 24.1 (CH_3), 17.5 (CH_3); **equatorial-Me**: 203.5 (C), 202.9 (C), 169.6 (C), 76.6 (CH), 63.7 (C), 52.7 (CH_3), 44.4 (CH_2), 36.4 (CH_2), 36.1 (C), 32.6 (CH), 30.5 (CH_3), 24.5 (CH_3), 16.2 (CH_3); ^1H NMR

(300 MHz, δ ppm/ CDCl_3): **axial-Me**: 3.73 (s, 3H), 2.84 – 2.43 (m, 3H), 2.27 – 1.88 (m, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.90 (d, $J = 6.9$ Hz, 3H); **equatorial-Me**: 3.75 (s, 3H), 2.84 – 2.43 (m, 3H), 2.27 – 1.88 (m, 3H), 1.07 (s, 3H), 1.03 (s, 3H), 0.97 (d, $J = 6.2$ Hz, 3H).

Compound 16g



$\text{C}_{15}\text{H}_{16}\text{O}_4\text{S}$
MW: 292.35

Following the general procedure, the reaction between **5g** (112.1 mg, 0.5 mmol) and *trans*-crotonaldehyde (83 μL , 1.0 mmol) at 25°C using catalyst **12** in CHCl_3 (2.5 M) afforded compound **16g** as pale-yellow solid (96.5 mg, 66%, 2:1 dr, 9:1 ee) after silica gel purification.

R_f (PE/EtOAc: 6/4) = 0.33

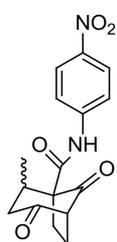
M.p. = 169-205 °C

HRMS (ESI+) for $\text{C}_{15}\text{H}_{20}\text{NO}_4\text{S}^+$: calcd. $[\text{M}+\text{NH}_4]^+$: 310.1108, found: 310.1108

HPLC (Chiralpak AS-H, Hexane/ethanol 50/50, 1 mL/min, UV 220 nm): $\tau_{\text{axial-Me}}$ = 6.27 min and 6.97 min

^{13}C NMR (75 MHz, δ ppm/ CDCl_3): **axial-Me**: 202.9 (C), 196.8 (C), 137.3 (C), 134.5 (CH), 130.2 (CH), 129.3 (CH), 75.2 (C), 65.4 (CH), 44.1 (CH_2), 32.8 (CH), 27.4 (CH_2), 21.4 (CH_2), 17.3 (CH_3); **equatorial-Me**: 201.8 (C), 200.0 (C), 136.8 (C), 134.5 (CH), 131.1 (CH), 128.9 (CH), 76.5 (C), 64.0 (CH), 44.1 (CH_2), 31.9 (CH), 21.8 (CH_2), 20.4 (CH_2), 16.4 (CH_3); ^1H NMR (300 MHz, δ ppm/ CDCl_3): **axial-Me**: 8.02 – 7.99 (m, 2H), 7.60 – 7.53 (m, 3H), 3.24 (d, $J = 6.3$ Hz, 1H), 3.03 (dd, $J = 16.1, 7.5$ Hz, 1H), 2.80 – 2.43 (3H), 2.27 (d, $J = 16.1$ Hz, 1H), 2.22 – 1.85 (2H), 1.24 (d, $J = 6.9$ Hz, 3H); **equatorial-Me**: 8.13 – 8.10 (m, 2H), 7.71 – 7.64 (m, 3H), 3.15 (d, $J = 7.0$ Hz, 1H), 2.80 – 2.43 (4H), 2.22 – 1.85 (3H), 1.42 (d, $J = 4.9$ Hz, 3H)

Compound 16f



$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5$
MW 316.31

Following the general procedure, the reaction between **5f** (124.1 mg, 0.5 mmol) and *trans*-crotonaldehyde (83 μL , 1.0 mmol) at 17°C using catalyst **18** in toluene (2.5 M) afforded compound **16f** as pale-yellow solid (115.5 mg, 73%, 10:1 dr, 4.6:1 er) after silica gel purification.

R_f (PE/Acetone: 3/1) = 0.48

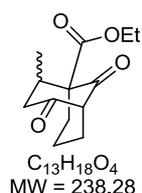
M.p. = 158-164 °C

HRMS (ESI+) for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_5$: calcd. $[\text{M}+\text{H}]^+$: 317.1132, found: 317.1132

HPLC (Chiralpak AZ-H, Heptane/ethanol 50/50, 1 mL/min, UV 220 nm): $\tau_{\text{axial-Me}}$ = 11.39 min and 17.53 min

^{13}C NMR (75 MHz, δ ppm/ CDCl_3): 207.6 (C), 203.8 (C), 169.1 (C), 144.0 (C), 142.9 (C), 125.2 (CH), 119.9 (CH), 65.7 (CH), 58.6 (C), 41.5 (CH_2), 35.8 (CH), 28.6 (CH_2), 21.0 (CH_2), 16.8 (CH_3); ^1H NMR (300 MHz, δ ppm/ CDCl_3): 10.06 (s, 1H), 8.21 (d, $J = 9.1$ Hz, 2H), 7.79 (d, $J = 9.1$ Hz, 2H), 3.41 (d, $J = 6.4$ Hz, 1H), 3.17 (dd, $J = 16.2, 8.2$ Hz, 1H), 2.89 – 2.79 (m, 1H), 2.62 – 2.41 (m, 2H), 2.31 (d, $J = 16.3$ Hz, 1H), 2.23 – 2.02 (m, 2H), 0.89 (d, $J = 7.1$ Hz, 3H)

Compound 16l



Following the general procedure, in the presence of catalyst **12**, the reaction between ethyl 2-oxocyclohexanecarboxylate (85.1 mg, 0.5 mmol) and *trans*-crotonaldehyde (83 μL , 1.0 mmol) at 25 ° in MeOH (2.5 M) afforded compound **16l** (50.0 mg, 42%, 1.5:1 dr, 5:1 er) as a yellow oil after flash chromatography

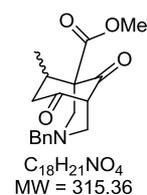
R_f (PE/EtOAc: 6/4) = 0.64

HRMS (ESI+) for $\text{C}_{13}\text{H}_{19}\text{O}_4^+$: calcd. $[\text{M}+\text{H}]^+$: 239.1278, found: 239.1278

HPLC (Chiralpak IE, Heptane/Ethanol 80/20, 1.0 mL/min, DAD): $\tau_{\text{axial-Me}}$ = 12.91 min and 16.13 min

^{13}C NMR (75 MHz, δ ppm/ CDCl_3): **axial-Me**: 208.2 (C), 206.6 (C), 170.5 (C), 62.5 (CH), 61.6 (C), 61.1 (CH_2), 48.6 (CH_2), 38.7 (CH_2), 34.7 (CH_2), 31.9 (CH), 19.0 (CH_2), 19.2 (CH_3), 14.2 (CH_3); **equatorial-Me**: 206.9 (C), 206.4 (C), 170.9 (C), 65.1 (CH), 61.9 (C), 61.6 (CH_2), 47.1 (CH_2), 34.4 (CH_2), 31.0 (CH_2), 30.5 (CH), 19.6 (CH_2), 16.6 (CH_3), 14.1 (CH_3); ^1H NMR (300 MHz, δ ppm/ CDCl_3): **axial-Me**: 4.26 – 4.16 (m, 2H), 3.08 (dd, $J = 4.5, 3.2$ Hz, 1H), 2.80 – 2.68 (m, 1H), 2.50 – 1.99 (m, 6H), 1.81 – 1.65 (m, 2H), 1.28 – 1.19 (m, 3H), 1.08 – 1.01 (m, 3H); **equatorial-Me**: 4.26 – 4.16 (m, 2H), 3.28 (t, $J = 3.3$ Hz, 1H), 2.80 – 2.68 (m, 1H), 2.50 – 1.99 (m, 6H), 1.81 – 1.65 (m, 2H), 1.28 – 1.19 (m, 3H), 1.08 – 1.01 (m, 3H).

Compound 16m



Following the general procedure, in the presence of catalyst **18**, the reaction between methyl 1-benzyl-4-oxopiperidine-3-carboxylate hydrochloride (neutralized with NaOH before using) (141.9 mg, 0.5 mmol) and *trans*-crotonaldehyde (83 μL , 1.0 mmol), at 25 °C in CDCl_3 (2.5 M) afforded compound **16m** (71.0 mg, 45%, 2:1 dr, 7.3:1 er) as a yellow solid after flash chromatography.

R_f (PE/EtOAc: 6/4) = 0.59

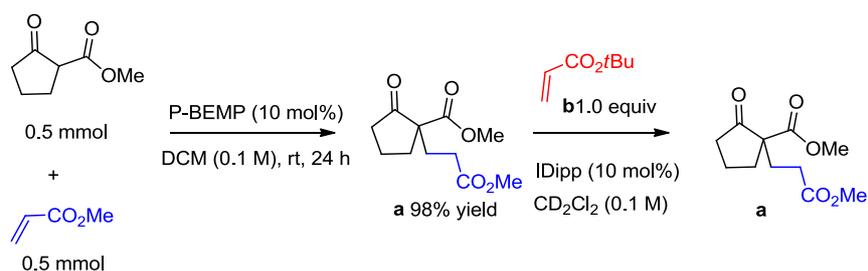
M.p. = 84-100 °C

HRMS (ESI+) for C₁₈H₂₂NO₄⁺: calcd. [M+H]⁺: 316.1543, found: 316.1543

HPLC (Chiralpak IC, Heptane/Ethanol 80/20, 1.0 mL/min, DAD): $\tau_{\text{axial-Me}}$ = 7.96min and 8.61 min

¹³C NMR (75 MHz, δ ppm/CDCl₃): **axial-Me**: 207.2 (C), 202.4 (C), 169.6 (C), 136.8 (C), 128.8 (CH \times 2), 128.8 (CH \times 2), 127.9 (CH), 64.8 (CH), 62.8 (CH₂), 62.4 (C), 61.2 (CH₂), 59.3 (CH₂), 52.3 (CH₃), 48.9 (CH₂), 32.8 (CH), 19.6 (CH₃); **equatorial-Me**: 206.2 (C), 203.4 (C), 170.1 (C), 137.1 (C), 129.2 (CH \times 2), 128.8 (CH \times 2), 128.0 (CH), 66.1 (CH), 62.6 (C), 61.5 (CH₂), 59.6 (CH₂), 56.4 (CH₂), 52.7 (CH₃), 47.9 (CH₂), 31.2 (CH), 16.4 (CH₃); **¹H NMR** (300 MHz, δ ppm/CDCl₃): **axial-Me**: 7.28 – 7.13 (m, 5H), 3.71 (s, 3H), 3.50 – 3.09 (m, 6H), 2.85 – 2.61 (m, 3H), 2.28 (dd, J = 16.0, 6.2 Hz, 1H), 0.92 (d, J = 7.1 Hz, 3H); **equatorial-Me**: 7.28 – 7.13 (m, 5H), 3.70 (s, 3H), 3.50 – 3.09 (m, 6H), 2.85 – 2.61 (m, 3H), 2.28 (dd, J = 16.0, 6.2 Hz, 1H), 0.87 (d, J = 6.2 Hz, 3H)

▪Cross experiment between *a* and *b*



To a solution of methyl-2-oxo-cyclopentanecarboxylate (65 μ L, 0.5 mmol, 95% purity) in DCM was added methyl acrylate (45 μ L, 0.5 mmol) and P-BEMP (11.4 mg, 10 mmol%, 2.2 mmol/g base loading on polystyrene). The reaction was stirred at room temperature for 24 h. P-bemp was removed by filtration, and the filtrate was concentrated in vacuum to afford pure Michael adduct (111.8 mg, 98%) without any purification.

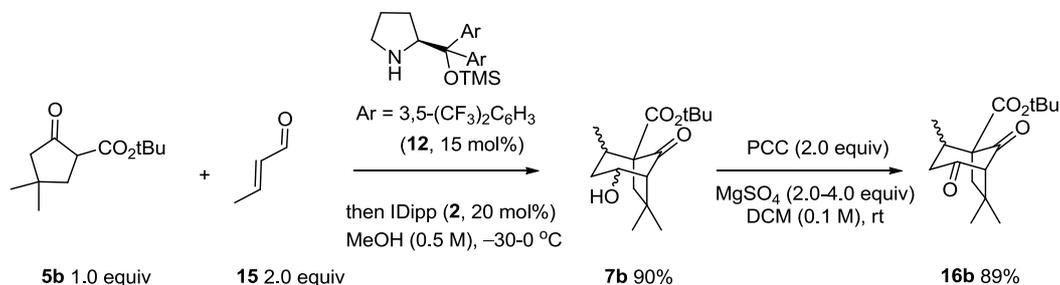
To a 20 mL round bottom flask with screwed cap was charged the generated Michael adduct (111.8 mg, 0.49 mmol) in CD₂Cl₂, and then was added *tert*-butyl-2-oxo-cyclopentanecarboxylate (72 μ L, 0.49 mmol) and IDipp (19 mg, 0.05 mmol) to the solution. the reaction was stirred for 1 h, 24 h at room temperature, 1 h and 24 h at 50 °C in order to track the cross behaviour.

Compound a: R_f (average) = 0.35 (PE:EtOAc = 4:1); **MS** (ESI+, m/z): 251 $[M+Na]^+$; **^{13}C NMR** (75 MHz, δ ppm/ $CDCl_3$): 214.3 (C), 173.4 (C), 171.4 (C), 59.3 (C), 52.6 (CH_3), 51.7 (CH_3), 37.9 (CH_2), 33.6 (CH_2), 29.6 (CH_2), 28.5 (CH_2), 19.6 (CH_2); **1H NMR** (300 MHz, δ ppm/ $CDCl_3$): 3.56 (s, 3H), 3.52 (s, 3H), 2.42 – 2.01 (m, 6H), 1.94 – 1.68 (m, 4H).

Tert-butyl acrylate b in the reaction crude: **^{13}C NMR** (75 MHz, δ ppm/ CD_2Cl_2): 165.7 (C), 130.8 (CH), 129.3 (CH_2), 80.7 (C), 28.2 (CH_3 , *t*Bu); **1H NMR** (300 MHz, δ ppm/ CD_2Cl_2): 6.26 (dd, $J = 17.3, 1.7$ Hz, 1H), 6.02 (dd, $J = 17.3, 10.3$ Hz, 1H), 5.71 (dd, $J = 10.3, 1.7$ Hz, 1H), 1.47 (s, 9H)

ES.2. Total synthesis of quadrane sesquiterpenes

•construction of the bicyclo[3.2.1]octane skeleton **7b** in 10-gram scale

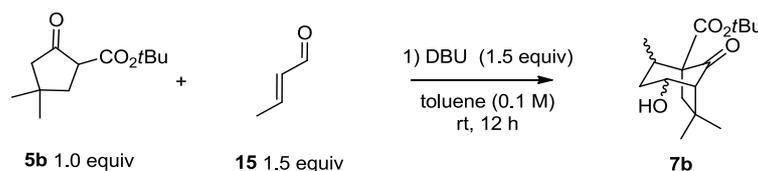


To a solution of *t*-butyl 4,4-dimethyl-2-oxocyclopentanecarboxylate **5b** (47.11 mmol, 10.0 g) in methanol (95 mL, 0.5 M) was added (*S*)- α,α -bis[3,5-bis (trifluoromethyl) phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **12** (7.07 mmol, 4352.0 mg, 97% purity). Once cooling down to -30 °C, crotonaldehyde **15** (94.22 mmol, 7.8 mL) was added dropwise under an argon atmosphere. The reaction solution was stirred at -30 °C for 24 h., and then the temperature was increased to 0 °C which was then stirred for 4 days. After compound **5b** was converted totally, 1,3-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene (IDipp, **2**) (9.42 mmol, 3773.7 mg, 97% purity) was added. The reaction was monitored by TLC. The reaction mixture was then concentrated in vacuum and purified by flash chromatography afforded compound **7b** (12.0 g, 90%, dia1: dia2: dia3: dia4 = 5.3:4.6:4:1 dr) as a yellow oil. In order to check the enantiomeric excess of **7b**, 50 mg of **7b** was oxidized into **16b** (44.8 mg, 89%, 4:1 dr), and 8:1 er (Me_{ax}:Me_{eq}) was obtained.

7b: R_f (average) = 0.20 (PE:EtOAc = 4:1); HRMS (ESI+) for C₁₆H₂₆NaO₄⁺: calcd. [M+Na]⁺: 305.1723, found: 305.1723; ¹³C NMR (75 MHz, δ ppm/CDCl₃): axial-Me (equatorial-OH and axial-OH): 211.4 (C), 209.6 (C), 170.7 (C), 170.6 (C), 81.1 (C), 81.0 (C), 76.4 (CH), 72.4 (CH), 65.8(CH), 65.3(CH), 62.1 (C), 62.0 (C), 47.4 (CH₂), 46.5 (CH₂), 42.5 (CH), 36.3 (CH₃), 34.6 (CH₂), 32.9 (CH), 32.8 (C), 32.0 (C), 31.9 (CH₃), 31.9 (CH₃), 28.0 (CH₃×3, *t*-Bu), 28.0 (CH₃×3, *t*-Bu), 23.4 (CH₃), 23.3 (CH₃), 18.0 (CH₃), 16.4 (CH₃); ¹H NMR (300 MHz, δ ppm/CDCl₃): axial-Me (equatorial-OH and axial-OH): 4.38 (t, J = 4.3 Hz, 1H, dia 1), 4.19 (ddd, J = 9.6, 7.0, 4.0 Hz, 1H, dia 3), 2.88 – 2.35 (m, 2H, dia 1), 2.88 – 2.35 (m, 2H, dia 3), 2.22 – 2.13 (m, 1H, dia 1), 2.22 – 2.13 (m, 1H, dia 3), 2.06 – 1.93 (m, 2H, dia 1), 2.06 – 1.93 (m, 2H, dia 3), 1.79 – 1.49 (m, 2H, dia 1), 1.79 – 1.49 (m, 2H, dia 3), 1.42 (s, 9H, dia 1), 1.41

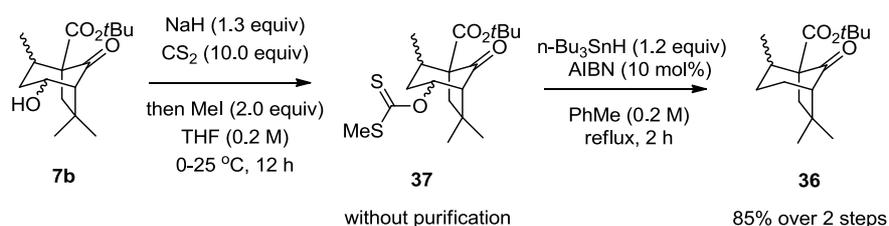
(s, 9H, dia 3), 1.16 (d, $J = 7.2$ Hz, 3H, dia 1), 1.33 (s, 3H, dia 1), 1.13 (s, 6H, dia 3), 0.97 (s, 3H, dia 1), 0.95 (d, $J = 7.0$ Hz, 3H, dia 3); ^{13}C NMR (75 MHz, δ ppm/ CDCl_3): **equatorial-Me (equatorial-OH and axial-OH)**: 212.3 (C), 212.3 (C), 169.0 (C), 169.0 (C), 81.4 (C), 81.4 (C), 72.8 (CH), 72.8 (CH), 64.5 (CH), 64.4 (C), 63.9 (CH), 63.8 (CH), 38.0 (CH₃), 37.3 (CH₂), 36.6 (CH₂), 35.9 (CH₂), 35.4 (CH), 35.2 (CH₂), 33.8 (C), 33.5 (C), 33.0 (CH₃), 32.0 (C), 28.2 (CH₃×3, *t*-Bu), 28.2 (CH₃×3, *t*-Bu), 25.1 (CH₃), 24.8 (CH₃), 16.6 (CH₃), 16.1 (CH₃); ^1H NMR (300 MHz, δ ppm/ CDCl_3): **equatorial-Me (equatorial-OH and axial-OH)**: 4.28 – 4.24 (m, 1H, dia 2), 4.06 – 3.94 (m, 1H, dia 4), 2.88 – 2.35 (m, 2H, dia 2), 2.88 – 2.35 (m, 2H, dia 4), 2.22 – 2.13 (m, 1H, dia 2), 2.22 – 2.13 (m, 1H, dia 4), 2.06 – 1.93 (m, 2H, dia 2), 2.06 – 1.93 (m, 2H, dia 4), 1.79 – 1.49 (m, 2H, dia 2), 1.79 – 1.49 (m, 2H, dia 4), 1.42 (s, 9H, dia 2), 1.41 (s, 9H, dia 4), 1.00 (s, 3H, dia 2), 1.00 (s, 3H, dia 4), 0.99 (s, 3H, dia 2), 0.99 (s, 3H, dia 4), 0.92 (d, $J = 6.7$ Hz, 3H, dia 2), 0.88 (d, $J = 6.4$ Hz, 3H, dia 4)

▪preparation of racemate **7b**



To a solution of α -carbonylated-cyclopentanone **5b** (10.0 grams, 47.1 mmol) in dry toluene (471 mL, 0.1 M) under an argon atmosphere was added 1,8-diazabicyclo[5.4.0]undec-7-ene (10.6 mL, 70.7 mmol), the mixture was stirred for 10 min at room temperature. Crotonaldehyde **15** (5.9 mL, 70.7 mmol) was then added dropwise and the reaction was stirred at room temperature for 12 h. After full conversion, the reaction mixture was poured into saturated aqueous NH_4Cl and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuum, purified by flash chromatography to afford bicyclic compound **7b** (12.0 grams, 90 %, 4 dias, ~1:1:1:1 dr).

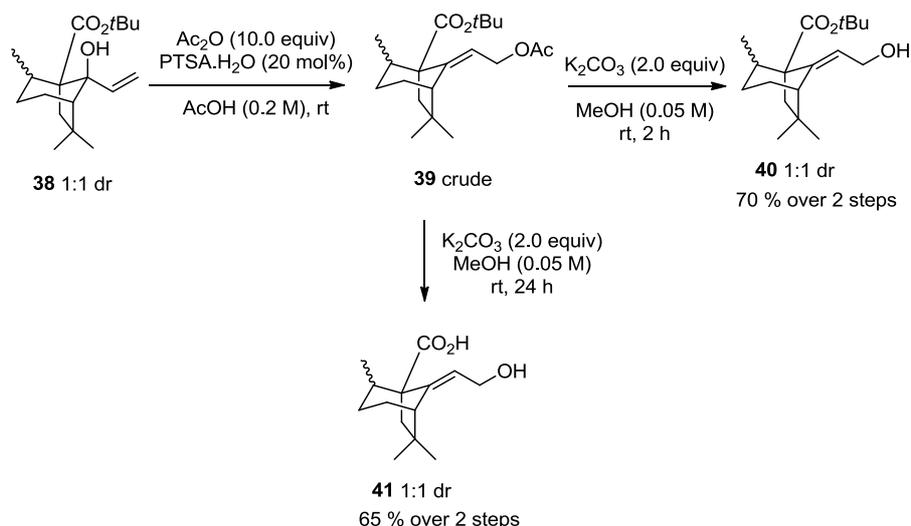
▪deoxygenation of **7b** to carboxylate **36**



To a suspension of NaH (52.94 mmol, 1270.6 mg) in THF (0.2 M, 203.6 mL) was added CS₂ (24.5 mL, 407.2 mmol) under an argon atmosphere and the mixture was cooled down to 0 °C. **7b** (40.72 mmol, 11.5 g, 5.3:4.6:4:1 dr) in THF was added and stirred for 45 min at 0 °C. Then, MeI (81.44 mmol, 5.1 mL) was added and the reaction solution was stirred for 15 h. The reaction mixture was poured into saturated NaCl, extracted with diethyl ether, dried over NaSO₄, and then concentrated in vacuum to afford xanthate **37** which was used without further purification.

To a solution of **37** in dry toluene under an argon atmosphere were successively added tributyltin hydride (13.1 mL, 48.86 mmol) and azobisisobutyronitrile (AIBN, 668.7 mg, 4.07 mmol). The reaction mixture was heated to 110 °C for 2 h in toluene (200 mL, 0.2M), which then was cooled down to room temperature, concentrated in vacuum. Purification by flash chromatography afforded compound **36** (9219.9 mg, 85%, 2:1 dr) as colorless oil. **R_f** (average) = 0.50 (PE:EtOAc/9:1); **HRMS** (ESI+) for C₁₆H₂₆NaO₃⁺: calcd. 289.1774 [M+Na]⁺; found: 289.1774; **¹³C NMR** (75 MHz, δ ppm/CDCl₃): **axial-Me**: 213.8 (C), 171.1 (C), 80.7 (C), 62.5 (C), 58.3 (CH), 46.8 (CH₂), 42.2 (CH), 32.5 (C), 31.8 (CH₃), 28.5 (CH₂), 28.0 (CH₃×3, *t*-Bu), 25.2 (CH₂), 22.8 (CH₃), 16.3 (CH₃); **equatorial-Me**: 215.6 (C), 169.2 (C), 81.0 (C), 64.5 (C), 56.9 (CH), 42.4 (CH), 37.0 (CH₂), 32.7 (C), 32.0 (CH₃), 29.9 (CH₂), 28.2 (CH₃×3, *t*-Bu), 27.1 (CH₂), 23.0 (CH₃), 17.0 (CH₃); **¹H NMR** (300 MHz, δ ppm/CDCl₃): **axial-Me**: 2.50 – 2.35 (m, 1H), 2.11 – 1.44 (m, 6H), 1.32 (s, 9H), 1.24 – 1.16 (m, 1H), 1.08 (s, 3H), 1.02 (d, J = 7.1 Hz, 3H), 0.91 (s, 3H); **equatorial-Me**: 2.50 – 2.35 (m, 1H), 2.11 – 1.44 (m, 6H), 1.35 (s, 9H), 1.24 – 1.16 (m, 1H), 1.07 (s, 3H), 0.88 (s, 3H), 0.77 (d, J = 6.9 Hz, 3H)

•1,3-allylic transposition to *10* and acid *11*

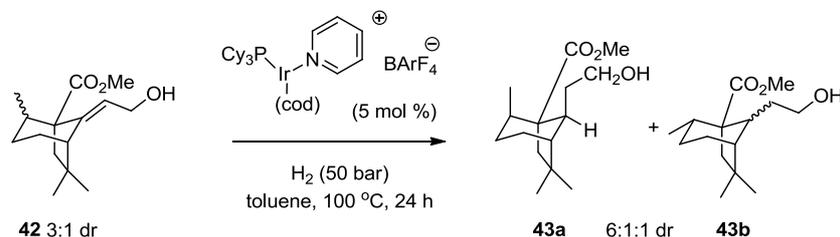


To a solution of **38** (294.4 mg, 1 mmol, 1:1 dr) (the preparation and spectrum details see Marc Pisset's thesis) in acetic acid (5.0 mL, 0.2 M) was added *p*-Toluenesulfonic acid (38.0 mg, 0.2 mmol) at room temperature overnight. The combined organic layers were washed with saturated aqueous Na_2HCO_3 and brine, dried over Na_2SO_4 and concentrated in vacuum. The crude acetate was used directly for saponification in the presence of K_2CO_3 (276.4 mg, 2.0 mmol) in methanol at room temperature. The reaction mixture was stirred for 2h, then poured into saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 , then concentrated in vacuum and purified by flash chromatography to afford ester alcohol **40** (206.1 mg, 70%, 1:1 dr) by flash chromatography purification. $R_f = 0.31$ (PE:EtOAc/6:1); **MS** (ESI+, *m/z*): 317 $[\text{M}+\text{Na}]^+$, 333 $[\text{M}+\text{K}]^+$; ^{13}C **NMR** (75 MHz, δ ppm/ CDCl_3): **axial-Me**: 174.2 (C), 148.3 (C), 120.3 (CH), 79.9 (C), 60.4 (C), 60.3 (CH_2), 50.1 (CH_2), 49.6 (CH), 39.1 (CH), 36.4 (C), 32.8 (CH_3), 29.9 (CH_2), 28.2 ($\text{CH}_3 \times 3$, *t*-Bu), 26.8 (CH_2), 23.0 (CH_3), 17.0 (CH_3), **equatorial-Me**: 172.4 (C), 155.3 (C), 115.1 (CH), 80.6 (C), 60.4 (CH_2), 58.7 (C), 48.7 (CH), 41.6 (CH), 39.4 (CH_2), 37.0 (C), 32.8 (CH_3), 28.4 ($\text{CH}_3 \times 3$, *t*-Bu), 28.3 (CH_2), 25.8 (CH_2), 23.0 (CH_3), 17.4 (CH_3), ^1H **NMR** (300 MHz, δ ppm/ CDCl_3): **axial-Me**: 5.66 (t, $J = 7.0$ Hz, 1H), 4.29 – 3.91 (m, 2H), 2.36 – 2.26 (m, 2H), 2.06 – 1.69 (m, 3H), 1.67 – 1.53 (m, 2H), 1.48 (s, 9H), 1.36 – 1.17 (m, 2H), 1.10 (s, 3H), 1.07 (s, 3H), 0.90 (d, $J = 6.9$ Hz, 3H); **equatorial-Me**: 5.52 (t, $J = 6.9$ Hz, 1H), 4.29 – 3.91 (m, 2H), 2.36 – 2.26 (m, 2H), 2.06 – 1.69 (m, 3H), 1.67 – 1.53 (m, 2H), 1.42 (s, 9H), 1.36 – 1.17 (m, 2H), 0.94 (s, 3H), 0.92 (s, 3H), 0.77 (d, $J = 6.4$ Hz, 3H).

The crude acetate was used directly for saponification in the presence of K_2CO_3 (276.4 mg, 2.0 mmol) in methanol at room temperature. The reaction mixture was stirred for 24h, then

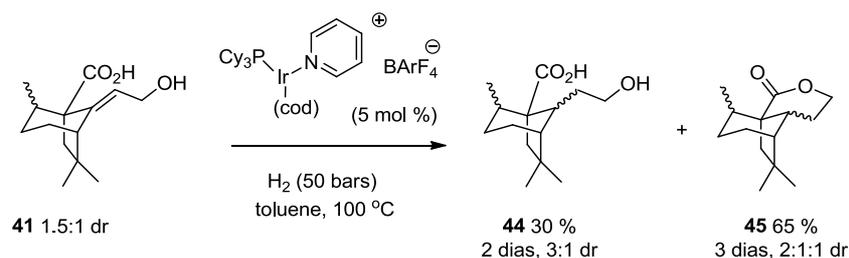
(m, 2H), 3.69 (s, 3H), 2.28 – 2.13 (m, 2H), 2.06 – 1.71 (m, 3H), 1.62 – 1.49 (m, 3H), 1.31 – 1.14 (m, 1H), 1.06 (s, 3H), 0.91 (s, 3H), 0.70 (d, $J = 6.4$ Hz, 3H).

▪reduction of the double bond from **42** to **43**



To a solution of **42** (80 mg, 0.32 mmol, 3:1 dr) in toluene (8.0 mL, 0.04 M) was added (1,5-Cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I)tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (25.4 mg, 0.016 mmol, 95% purity). The reaction was conducted in autoclave with 50 bars hydrogen at 100 °C. After 24h, it was concentrated in vacuum and purified by flash chromatography to afford **43** (77.4 mg, 95%, 6:1:1 dr). Part of the major product **43a** was able to be isolated. $R_f = 0.41$ (PE:EtOAc/6:4); **MS** (ESI+, m/z): 277 $[\text{M}+\text{Na}]^+$. ^{13}C NMR (75 MHz, δ ppm/ CDCl_3): **43a**: 178.4 (C), 63.1 (CH_2), 55.4 (C), 52.5 (CH_2), 51.8 (CH_3), 47.5 (CH), 40.8 (CH), 37.0 (C), 36.0 (CH), 33.7 (CH_3), 31.3 (CH_2), 25.2 (CH_2), 24.7 (CH_3), 20.7 (CH_3), 18.6 (CH_2); **43a** + **43b**: 178.3 (C, 14a), 177.0 (C, 14b), 176.3 (C, 14b), 63.0 (CH_2 , 14a), 62.2 (CH_2 , 14b), 61.7 (CH_2 , 14b), 61.0 (C, 14b), 56.8 (C, 14b), 55.4 (C, 14a), 52.5 (CH_2 , 14a), 41.0 (CH_2 , 14b), 39.3 (CH_2 , 14b), 51.7 (CH_3 , 14a), 53.9 (CH_3 , 14b), 51.5 (CH_3 , 14b), 51.4 (CH, 14b), 47.3 (CH, 14a), 48.1 (CH, 14b), 46.8 (CH, 14b), 40.8 (CH, 14a), 40.4 (CH, 14b), 44.7 (CH, 14b), 35.9 (CH, 14a), 36.9 (C, 14a), 37.7 ($\text{C}\times 2$, 14b), 35.1 (CH_2 , 14b), 33.6 (CH_3 , 14a), 34.4 (CH, 14b), 33.3 (CH_3 , 14b), 29.6 (CH_3 , 14b), 31.1 (CH_2 , 14a), 30.4 (CH_2 , 14b), 25.1 (CH_2 , 14a), 28.6 (CH_2 , 14b), 28.4 (CH_2 , 14b), 27.5 (CH_2 , 14b), 26.3 (CH_3 , 14b), 24.7 (CH_3 , 14a), 24.7 (CH_3 , 14b), 20.6 (CH_3 , 14a), 17.8 (CH_3 , 14b), 17.7 (CH_3 , 14b), 18.5 (CH_2 , 14a), 21.0 (CH_2 , 14b); ^1H NMR (300 MHz, δ ppm/ CDCl_3): **43a**: 3.68 (s, 3H), 3.67 – 3.55 (m, 2H), 2.57 – 2.54 (m, 1H), 2.19 (p, $J = 7.7$ Hz, 1H), 2.09 – 1.85 (m, 3H), 1.74 – 1.43 (m, 6H), 1.31 – 1.24 (m, 1H), 1.13 (s, 3H), 1.08 (s, 3H), 0.99 (d, $J = 7.4$ Hz, 3H); **43a** + **43b**: 3.65 (s, 3H, 14a), 3.64 (s, 3H, 14b), 3.63 (s, 3H, 14b), 3.61 – 3.50 (m, 2H $\times 3$, 3 dias), 2.53 – 2.49 (m, 1H, 14a), 2.33 – 2.11 (m, 1H, 14a), 2.33 – 2.11 (m, 2H $\times 2$, 14b), 2.05 – 1.81 (m, 3H $\times 3$, 3 dias), 1.76 – 1.41 (m, 6H $\times 3$, 3 dias), 1.28 – 1.13 (m, 1H $\times 3$, 3 dias), 1.13 (s, 3H, 14b), 1.11 (s, 3H, 14b), 1.09 (s, 3H, 14a), 1.05 (s, 3H, 14a), 1.05 (s, 3H $\times 2$, 14b), 0.96 (d, $J = 7.4$ Hz, 3H, 14a), 0.67 (dd, $J = 6.4, 4.4$ Hz, 3H $\times 2$, 14b);

hydrogenation of carboxylic-alcohol **41** to **44** and **45**



To a solution of **41** (60 mg, 0.25 mmol, 1.5:1 dr) in toluene (5.0 mL, 0.05 M) was added (1,5-Cyclooctadiene)(pyridine)(tricyclohexylphosphine)iridium(I)tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (20.0 mg, 0.0125 mmol, 95% purity). The reaction was conducted in autoclave with 50 bars hydrogen at 100 °C. After 24h, the reaction mixture was concentrated in vacuum and purified by flash chromatography to afford **44** (18.0 mg, 30%, 3:1 dr) and **45** (36.1 mg, 65%, 2:1:1 dr).

Compound **44**:

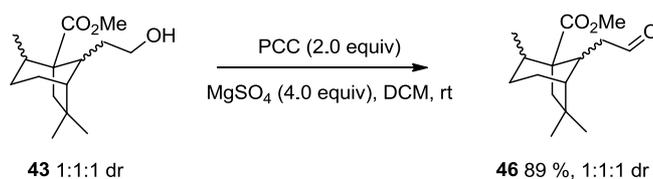
R_f = 0.19 (PE:EtOAc/7:3). **MS** (ESI⁻, m/z): 239 [M-H]. **¹³C NMR** (75 MHz, δ ppm/ $CDCl_3$): **major dia**: 183.5 (C), 63.0 (CH₂), 55.3 (C), 52.6 (CH₂), 47.3 (CH), 40.7 (CH), 37.1 (C), 35.8 (CH), 33.6 (CH₃), 30.9 (CH₂), 25.2 (CH₂), 24.7 (CH₃), 20.7 (CH₃), 18.5 (CH₂); **minor dia**: 182.4 (C), 62.1 (CH₂), 56.7 (C), 40.9 (CH₂), 46.8 (CH), 44.9 (CH), 37.9 (C), 33.2 (CH), 29.3 (CH₃), 28.3 (CH₂), 27.5 (CH₂), 24.7 (CH₃), 21.0 (CH₂), 17.7 (CH₃); **¹H NMR** (300 MHz, δ ppm/ $CDCl_3$): **major dia**: 7.31 (br. s, 1H), 3.71 – 3.54 (m, 2H), 2.54 – 2.50 (m, 1H), 2.23 – 2.14 (m, 1H), 2.05 – 1.89 (m, 4H), 1.78 – 1.56 (m, 1H), 1.77 (d, J = 13.5 Hz, 1H), 1.61 (d, J = 13.5 Hz, 1H), 1.52 – 1.41 (m, 2H), 1.28 (dd, J = 14.3, 6.4 Hz, 1H), 1.13 (s, 3H), 1.09 (s, 3H), 1.05 (d, J = 7.4 Hz, 3H); **minor dia**: 7.31 (br. s, 1H), 3.71 – 3.54 (m, 2H), 2.42 – 2.36 (m, 1H), 2.23 – 2.14 (m, 1H), 2.05 – 1.89 (m, 4H), 1.78 – 1.56 (m, 1H), 1.77 (d, J = 13.5 Hz, 1H), 1.61 (d, J = 13.5 Hz, 1H), 1.52 – 1.41 (m, 2H), 1.28 (dd, J = 14.3, 6.4 Hz, 1H), 1.11 (s, 3H), 1.07 (s, 3H), 0.76 (d, J = 6.4 Hz, 3H).

Compound **45**:

R_f = 0.60 (PE:EtOAc/7:3). **MS** (ESI⁺, m/z): 245 [M+Na]⁺. **¹³C NMR** (75 MHz, δ ppm/ $CDCl_3$): **major dia**: 174.3 (C), 70.5 (CH₂), 55.6 (C), 55.3 (CH), 49.6 (CH), 44.3 (CH₂), 40.2 (CH), 38.5 (C), 34.3 (CH₃), 30.4 (CH₂), 29.5 (CH₂), 28.4 (CH₂), 25.8 (CH₃), 18.2 (CH₃); **two minor dias**: 176.9 (C), 176.1 (C), 70.6 (CH₂), 70.0 (CH₂), 52.0 (C), 51.1 (C), 49.5 (CH₂), 46.0 (CH), 45.7 (CH), 41.4 (CH), 40.6 (CH), 40.0 (CH₂), 38.7 (C), 37.5 (C), 37.4 (CH), 33.6

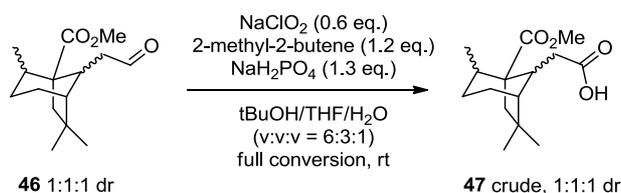
(CH), 33.4 (CH₃), 29.1 (CH₃), 27.0 (CH₂), 24.7 (CH₃), 24.7 (CH₂), 24.2 (CH₃), 21.9 (CH₃), 21.9 (CH₂), 21.4 (CH₂), 20.5 (CH₂), 18.7 (CH₂), 16.7 (CH₃); ¹H NMR (300 MHz, δ ppm/CDCl₃): **major dia**: 4.43 – 4.29 (m, 2H), 2.47 – 2.25 (m, 1H), 2.13 – 1.98 (m, 1H), 1.96 – 1.82 (m, 2H), 1.77 – 1.41 (m, 6H), 1.38 – 1.24 (m, 1H), 1.14 (s, 3H), 1.03 (s, 3H), 0.92 (d, J = 6.5 Hz, 3H), **two minor dias**: 4.57 – 4.49 (m, 2H), 4.18 – 4.10 (m, 2H), 2.47 – 2.25 (m, 1H×2), 2.13 – 1.98 (m, 1H×2), 1.96 – 1.82 (m, 2H×2), 1.77 – 1.41 (m, 6H×2), 1.38 – 1.24 (m, 1H×2), 1.14 (s, 3H), 1.12 (d, J = 7.7 Hz, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 1.03 (s, 3H), 0.71 (d, J = 6.5 Hz, 3H).

•oxidation of alcohol **43** to aldehyde **46**



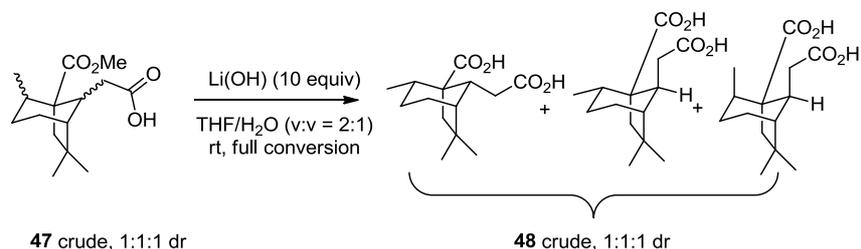
To a solution of **43** (38 mg, 0.15 mmol, ~ 1:1:1 dr) with 3 dias in dichloromethane was added anhydrous MgSO₄ (72.2 mg, 0.6 mmol) and pyridinium chlorochromate (64.7 mg, 0.3 mmol), sequentially. The reaction mixture was stirred at room temperature for 6h. Then, the filtrate was concentrated in vacuum and purified by flash chromatography to afford **46** (33.7 mg, 89 %, ~1:1:1 dr). $R_f = 0.61$ (PE:EtOAc/ 7:3). **MS** (ESI+, m/z): 275 [M+Na]⁺. ¹³C NMR (75 MHz, δ ppm/CDCl₃): **3 dias**: 202.7 (CH), 202.0 (CH), 202.0 (CH), 177.3 (C), 176.3 (C), 175.6 (C), 60.8 (C), 56.0 (C), 55.0 (C), 51.7 (CH₃), 51.6 (CH₃), 51.5 (CH₂), 51.3 (CH₃), 50.8 (CH), 50.7 (CH), 48.1 (CH₂), 47.7 (CH), 47.0 (CH), 42.8 (CH₂), 41.1 (CH), 41.1 (CH₂), 40.6 (CH₂), 40.5 (CH), 39.5 (C), 39.4 (CH), 37.7 (CH), 37.7 (C), 37.0 (C), 36.1 (CH), 34.2 (CH₃), 33.5 (CH₃), 33.2 (CH₃), 30.4 (CH₂), 29.8 (CH₂), 28.3 (CH₂), 27.3 (CH₂), 26.2 (CH₃), 24.8 (CH₂), 24.7 (CH₃), 24.6 (CH₃), 21.3 (CH₂), 20.4 (CH₃), 18.4 (CH₂), 17.7 (CH₃), 17.4 (CH₃); ¹H NMR (300 MHz, δ ppm/CDCl₃): **3 dias**: 9.72 – 9.60 (m, 1H×3), 3.66 (s, 3H), 3.61 (s, 3H), 3.57 (s, 3H), 3.01 – 2.85 (m, 1H×3), 2.79 – 2.59 (m, 1H×3), 2.54 – 2.39 (m, 1H×3), 2.24 – 1.93 (m, 2H×3), 1.75 – 1.45 (m, 5H×3), 1.24 – 1.20 (m, 1H×3), 1.15 – 1.07 (m, 6H×3), 0.94 (d, J = 7.5 Hz, 3H), 0.69 (d, J = 6.5 Hz, 3H), 0.67 (d, J = 6.3 Hz, 3H).

▪Pinnick oxidation from **46** to **47**



To a solution of **46** (33 mg, 0.13 mmol, 1:1:1 dr) in a mixture solvent (5 mL, *t*-BuOH/THF/H₂O with v:v:v = 6:3:1) was added monosodium phosphate (20.3 mg, 0.17 mmol), sodium chlorite (7.1 mg, 0.078 mmol) and 2-methyl-2-butene (16.5 μL , 0.16 mmol), the reaction was stirred at room temperature overnight. Then, the reaction mixture was poured into 5% aqueous chloric acid, extracted with ethyl acetate, dried over NaSO₄, concentrated in vacuum to afford **47** (30 mg, 86%, crude) without purification. $R_f = 0.40$ (PE:EtOAc/6:4). **MS** (ESI+, *m/z*): 267 [M-H]⁻. **¹³C NMR** (75 MHz, δ ppm/CDCl₃): **3 dias**: 179.5 (C), 179.5 (C), 178.9 (C), 176.3 (C), 175.8 (C), 175.8 (C), 60.6 (C), 55.9 (C), 55.1 (C), 53.0 (CH), 51.7 (CH₃), 51.7 (CH₂), 51.5 (CH₃), 51.5 (CH₃), 49.9 (CH), 47.7 (CH), 46.7 (CH), 43.1 (CH), 40.7 (CH₂), 40.5 (CH), 40.0 (CH), 39.5 (CH₂), 39.0 (C), 38.0 (CH₂), 37.4 (C), 36.8 (C), 36.0 (CH), 34.5 (CH), 33.4 (CH₃), 33.2 (CH₃), 32.8 (CH₂), 31.3 (CH₂), 30.3 (CH₂), 30.0 (CH₃), 28.3 (CH₂), 27.3 (CH₂), 26.3 (CH₃), 24.9 (CH₂), 24.7 (CH₃), 24.6 (CH₃), 20.4 (CH₃), 21.3 (CH₂), 18.3 (CH₂), 17.7 (CH₃), 17.5 (CH₃); **¹H NMR** (300 MHz, δ ppm/CDCl₃): **3 dias**: 9.24 (s, 1H \times 3), 3.67 (s, 3H), 3.63 (s, 3H), 3.62 (s, 3H), 2.93 – 2.54 (m, 2H \times 3), 2.22 – 1.96 (m, 3H \times 3), 1.75 – 1.45 (m, 6H \times 3), 1.16 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 1.07 (s, 3H), 1.07 (s, 3H), 0.94 (d, *J* = 7.4 Hz, 3H), 0.69 (d, *J* = 6.3 Hz, 3H), 0.67 (d, *J* = 6.1 Hz, 3H).

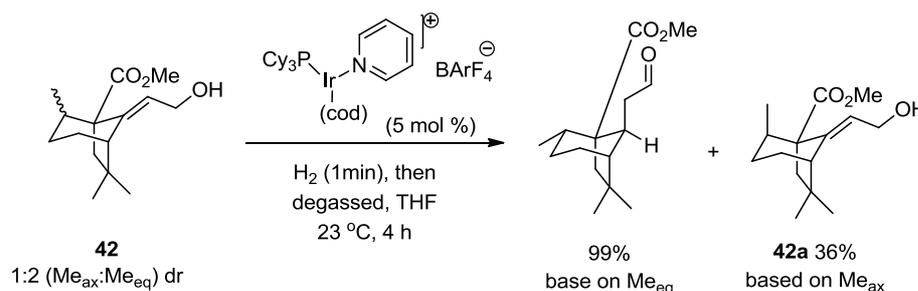
▪saponification of **47** to the undesired dias of (\pm)-isishippuric acid **B**



To a solution of acid **47** (30 mg, crude, \sim 0.11 mmol, 1:1:1 dr) in THF/H₂O (v:v = 2:1) was added lithium hydroxide (26.8 mg, 1.12 mmol). The reaction was stirred for 10h. Then, the reaction mixture was poured into 5% aqueous chloric acid, extracted with ethyl acetate, dried over NaSO₄, concentrated in vacuum to afford **48** (27 mg, 99%, crude) without purification.

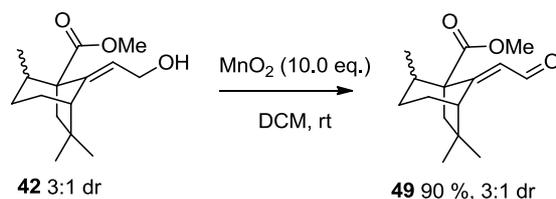
MS (ESI+, m/z): 239 [M-H]⁻, 238 [M-2H]⁻. **¹³C NMR** (75 MHz, δ ppm/ Pyridine-d₅): **3 dias**: 179.6 (C), 178.7 (C), 177.8 (C), 176.4 (C), 176.1(C), 175.5 (C), 61.2 (C), 57.0 (C), 55.8 (C), 54.4 (CH), 52.8 (CH₂), 49.6 (CH), 48.0 (CH), 47.5 (CH), 44.8 (CH), 41.7 (CH₂), 41.4 (CH), 40.9 (CH), 40.4 (CH₂), 39.3 (C), 38.7 (CH₂), 38.1 (C), 37.2 (C), 36.7 (CH), 35.3 (CH), 33.9 (CH₃), 33.9 (CH₂), 33.6 (CH₃), 32.3 (CH₂), 31.1 (CH₂), 30.5 (CH₃), 29.0 (CH₂), 28.1 (CH₃), 26.9 (CH₃), 25.8 (CH₂), 25.1 (CH₂), 25.1 (CH₃), 21.9 (CH₂), 21.3 (CH₃), 19.1 (CH₂), 18.5 (CH₃), 18.3 (CH₃); **¹H NMR** (300 MHz, δ ppm/ Pyridine-d₅): **3 dias**: 11.25 (br. s, 2H×3), 3.76 – 2.85 (m, 3H×3), 2.67 – 2.42 (m, 2H×3), 2.11 – 2.03 (m, 1H×3), 1.92 – 1.48 (m, 5H×3), 1.37 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 1.12 (s, 3H), 1.09 (s, 3H×2), 1.22 (d, J = 7.5 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.2 Hz, 3H);

•isomerization of allylic alcohol to aldehyde



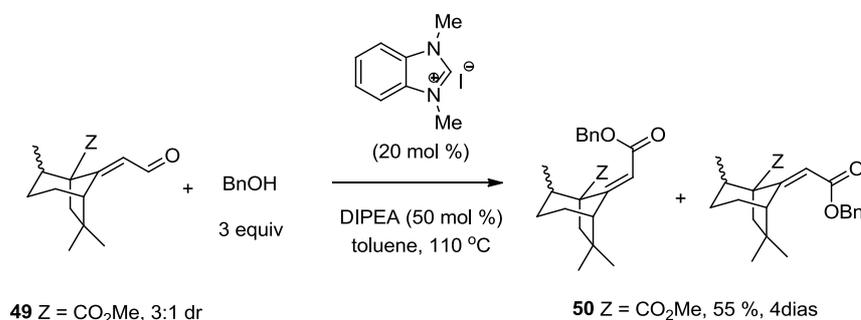
The isomerization of primary allylic alcohol **42** to corresponding aldehyde was conducted by Mazet's group according to the above reaction condition. **¹³C NMR** (100 MHz, δ ppm/CDCl₃): 201.9 (CH), 175.5 (C), 60.6 (C), 51.2 (CH₃), 50.7 (CH), 50.5 (CH), 47.9 (CH₂), 40.4 (CH), 39.4 (CH₂), 39.2 (C), 34.1 (CH₃), 30.2(CH₂), 28.1 (CH₂), 26.0 (CH₃), 17.6 (CH₃); **¹H NMR** (400 MHz, δ ppm/CDCl₃): 9.61 (dd, J = 2.8, 1.2 Hz, 1H), 3.58 (s, 3H), 2.49 – 2.43 (m, 4H), 2.11 (d, J = 14.8 Hz, 1H), 1.59 – 1.52 (m, 6H), 1.14 (s, 3H), 1.09 (s, 3H), 0.70 (d, J = 6.4 Hz, 3H).

•oxidation of alcohol to aldehyde **49**



To allylic alcohol **42** (252.3 mg, 1.0 mmol, 3:1 dr) in dichloromethane (10.0 mL, 0.1 M) was added manganese oxide (1022.8 mg, 10.0 equiv, activated 85%). The reaction was stirred at room temperature for 10h. When the reaction reached full conversion, MnO₂ was removed by filtration. The filtrate was concentrated in vacuum to afford **49** (225.3 mg, 90 %, 3:1 dr) without purification. **R_f** = 0.71 (PE:EtOAc/3:1); **MS** (ESI+, m/z): 273 [M+Na]⁺; **¹³C NMR** (75 MHz, δ ppm/CDCl₃): **axial-Me**: 191.0 (CH), 173.6 (C), 172.3 (C), 124.6 (CH), 60.0 (C), 51.9 (CH₃), 49.7 (CH), 48.7 (CH₂), 41.1 (CH), 36.6 (C), 32.7 (CH₃), 28.5 (CH₂), 25.0 (CH₂), 22.6 (CH₃), 16.8 (CH₃); **Equatorial-Me**: 191.5 (CH), 177.7 (C), 172.1 (C), 119.9 (CH), 61.8 (C), 52.0 (CH₃), 48.9 (CH), 38.6 (CH₂), 43.2 (CH), 37.4 (C), 32.6 (CH₃), 31.1 (CH₂), 27.4 (CH₂), 22.7 (CH₃), 17.4 (CH₃); **¹H NMR** (300 MHz, δ ppm/CDCl₃): **axial-Me**: 9.85 (d, *J* = 8.1 Hz, 1H), 6.10 (d, *J* = 8.1 Hz, 1H), 3.64 (s, 3H), 3.00 – 3.29 (m, 1H), 2.48 (p, *J* = 6.8 Hz, 1H), 2.12 – 1.57 (m, 5H), 1.23 (dd, *J* = 14.2, 5.7 Hz, 1H), 1.14 (s, 3H), 0.94 (s, 3H), 0.85 (d, *J* = 6.9 Hz, 3H); **Equatorial-Me**: 9.80 (d, *J* = 7.9 Hz, 1H), 5.94 (d, *J* = 8.0 Hz, 1H), 3.70 (s, 3H), 3.00 – 3.29 (m, 1H), 2.31 (td, *J* = 12.0, 5.9 Hz, 1H), 2.12 – 1.57 (m, 5H), 1.23 (dd, *J* = 14.2, 5.7 Hz, 1H), 1.12 (s, 3H), 0.92 (s, 3H), 0.75 (d, *J* = 6.5 Hz, 3H)

•redox reaction from aldehyde **49** to undesired ester **50**



To a mixture of aldehyde **49** (47.9 mg, 0.25 mmol, 3:1 dr) and benzyl aldehyde (81.1 mg, 0.75 mmol) in toluene (1.0 mL, 0.25 M) was added 1,3-Dimethyl-1H-benzimidazolium iodide (13.7 mg, 0.05 mmol) and N,N-diisopropylethylamine (22 μL, 0.125 mmol). The reaction mixture was stirred under argon atmosphere at 110 °C for 10h, then concentrated in vacuum and purified by flash chromatography to afford **50** (40.9 mg, 55%, 4 dias, 17:5:2:1 dr). **MS** (ESI+, m/z): 379 [M+Na]⁺; **¹³C NMR** (75 MHz, δ ppm/CDCl₃): only two diastereomers were observed. **major dia**: 174.4 (C), 167.5 (C), 166.5 (C), 136.5 (C), 128.6 (CH), 128.3 (CH), 128.2 (CH), 112.6 (CH), 65.8 (CH₂), 60.2 (C), 51.9 (CH₃), 50.4 (CH), 49.0 (CH₂), 41.2 (CH), 36.6 (C), 32.9 (CH₃), 27.3 (CH₂), 25.2 (CH₂), 22.8 (CH₃), 17.0 (CH₃); **minor dia**: 173.4 (C), 162.5 (C), 156.0 (C), 136.4 (C), 128.7 (CH), 128.3 (CH), 128.2 (CH), 108.1 (CH), 65.9

(CH₂), 62.0 (C), 52.1 (CH₃), 49.6 (CH), 43.7 (CH), 38.7 (CH₂), 37.4 (C), 32.9 (CH₃), 30.0 (CH₂), 27.7 (CH₂), 22.9 (CH₃), 17.5 (CH₃); ¹H NMR (400 MHz, δ ppm/CDCl₃): **four dias** (not all of the diastereomers are obvious sometimes): 7.41 – 7.32 (m, 5H×4, 4 dias), 6.00 (s, 1H, dia 1), 5.81 (s, 1H, dia 2), 5.37 (s, 1H, dia 3), 5.20 – 5.09 (m, 2H×4, 4 dias), 3.74 (s, 3H, dia 1), 3.69 (s, 3H, dia 2), 3.60 (s, 3H, dia 3), 3.56 (s, 3H, dia 4), 3.46 – 3.43 (m, 1H×4, for 4 dias), 2.47 (p, J = 6.8 Hz, 1H, dia 1), 2.28 (tt, J = 12.0, 6.1 Hz, 1H, dia 1), 2.12 – 1.43 (m, 6H×4, 4 dias), 1.33 – 1.19 (m, 1H×4, 4 dias), 1.15 (s, 3H, dia 1), 1.12 (s, 3H, dia 2), 0.95 (s, 3H, dia 1), 0.94 (s, 3H, dia 2), 0.89 (d, J = 6.9 Hz, 3H, dia 1), 0.77 (d, J = 6.5 Hz, 3H, dia 2), 0.68 (d, J = 6.5 Hz, 3H, dia 3), 0.67 (d, J = 6.4 Hz, 3H, dia 4).

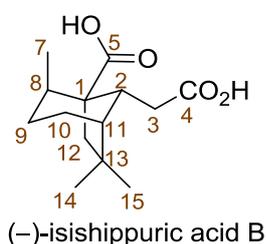
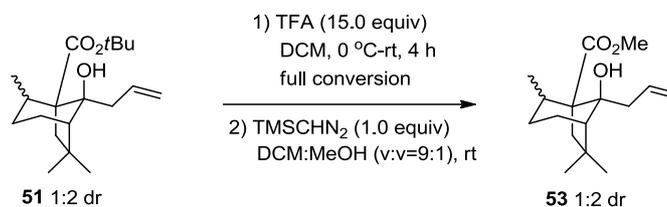


Table 1: comparison of ¹H chemical shifts of (-)-isishippuric acid B and compound **48**

proton	(-)-isishippuric acid B ⁷⁰ 500 MHz / Pyridine-d ₅	compound 48 (3 dias) 300 MHz / Pyridine-d ₅
2	3.16 (dd, J = 7.0, 7.0 Hz, 1H)	3.76 – 2.85 (m, 3H×3)
3	2.73 (dd, J = 16.0, 7.0 Hz, 1H) 3.65 (dd, J = 16.0, 7.0 Hz, 1H)	
7	1.36 (d, J = 7.0, 3H)	1.22 (d, J = 7.5 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.2 Hz, 3H)
8	2.40 (m, 1H)	2.67 – 2.42 (m, 2H×3),
9 _α	1.25 (m, 1H)	2.11 – 2.03 (m, 1H×3),
9 _β	2.09 (dd, J = 7.0, 7.0 Hz, 1H)	1.92 – 1.48 (m, 5H×3)
10 _α	1.61 (m, 1H)	
10 _β	1.78 (m, 1H)	
11	1.86 (br. s, 1H)	
12 _α	1.96 (d, J = 14.0 Hz, 1H)	
12 _β	2.45 (d, J = 14.0 Hz, 1H)	

To a solution of **36** (350 mg, 1.32 mmol, 1:2 dr) in THF was added allylmagnesium bromide (2.64 mL, 2.64 mmol, 1.0 M in diethyl ether) under an argon atmosphere. The reaction was stirred for 6 h under reflux. The resulting mixture was cooled down to room temperature and poured into saturated aqueous NH₄Cl. This mixture was extracted twice with EtOAc, washed with brine, dried over Na₂SO₄ and concentrated in vacuum. Purification by flash chromatography afforded product **51** (285.0 mg, 70 %, 1:2 dr). **R_f** = 0.42 (PE:Et₂O/9:1). **MS** (ESI+, m/z): 331 [M+Na]⁺. **¹³C NMR** (75 MHz, δ ppm/ CDCl₃): **axial-Me**: 174.7 (C), 134.4 (CH), 117.9 (CH₂), 81.6 (C), 80.7 (C), 59.1 (C), 49.1 (CH₂), 47.5 (CH), 43.0 (CH₂), 40.3 (CH), 33.5 (C), 33.0 (CH₃), 28.7 (CH₃), 28.2 (CH₃×3, *t*-Bu), 25.8 (CH₂), 22.3 (CH₃), 21.6 (CH₂), **equatorial-Me**: 174.8 (C), 134.0 (CH), 118.1 (CH₂), 81.0 (C), 80.8 (C), 61.6 (C), 47.8 (CH), 43.2 (CH₂), 38.4 (CH₂), 34.3 (C), 33.6 (CH), 33.4 (CH₃), 28.2 (CH₃×3, *t*-Bu), 27.9 (CH₃), 27.0 (CH₂), 22.9 (CH₂), 17.2 (CH₃) **¹H NMR** (300 MHz, δ ppm/ CDCl₃): **axial-Me**: 5.98 – 5.84 (m, 1H), 5.13 – 5.02 (m, 2H), 2.74 – 2.38 (m, 3H), 2.21 – 1.94 (m, 5H), 1.70 – 1.65 (m, 1H), 1.53 – 1.48 (m, 1H), 1.39 – 1.34 (m, 1H), 1.43 (s, 9H), 1.14-1.07 (m, 9H); **equatorial-Me**: 5.98 – 5.84 (m, 1H), 5.13 – 5.02 (m, 2H), 2.74 – 2.38 (m, 3H), 2.21 – 1.94 (m, 5H), 1.70 – 1.65 (m, 1H), 1.53 – 1.48 (m, 1H), 1.39 – 1.34 (m, 1H), 1.44 (s, 9H), 1.14-1.07 (m, 6H), 0.68 (d, *J* = 6.7 Hz, 3H).

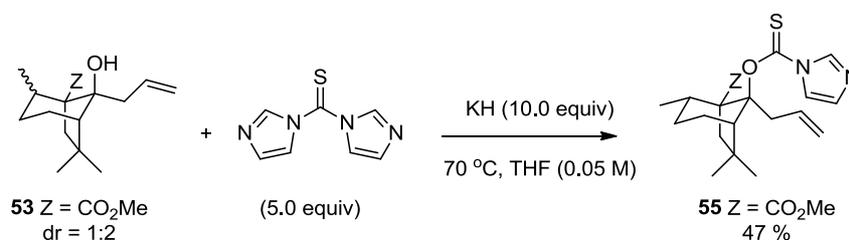
•preparation of methyl ester alcohol **53** from **51**



To a solution of **51** (150 mg, 0.49 mmol, 1:2 dr Me_{ax}:Me_{eq}) in DCM (10.0 mL, 0.05 M) was added TFA (563 μL, 7.35 mmol) dropwise using syringe at 0 °C, then the reaction mixture was allowed to warm to room temperature stirring for 4h. After completion, the reaction solution was concentrated by vacuum, and the generating acid was used directly for next step without purification. To the acid solution in a mixture solvents (DCM:MeOH / v:v = 9:1) was added trimethylsilyldiazomethane (245 μL, 2.0 M in hexane) under argon atmosphere. The reaction was stirred at room temperature for 10h. After completion, the reaction was concentrated in vacuum, purified by flash chromatography to afford **53** (108.3 mg, 83 %, 1:2 dr Me_{ax}:Me_{eq}). **R_f** = 0.63 (PE : EtOAc/ 6:1). **MS** (ESI+, m/z): 289 [M+Na]⁺. **¹³C NMR** (75 MHz, δ ppm/ CDCl₃): **axial-Me**: 175.7 (C), 134.1 (CH), 118.2 (CH₂), 81.5 (C), 59.0 (C), 51.1

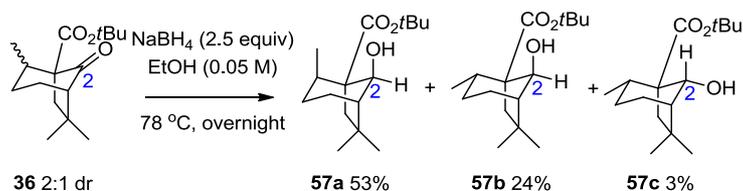
(CH), 48.8 (CH₂), 47.6 (CH), 43.1 (CH₂), 40.5 (CH₃), 33.7 (C), 33.3 (CH₃), 28.8 (CH₃), 25.6 (CH₂), 22.4 (CH₃), 21.6 (CH₂); **equatorial-Me**: 176.0 (C), 133.6 (CH), 118.5 (CH₂), 80.9 (C), 61.7 (C), 51.5 (CH), 48.3 (CH), 43.5 (CH₂), 38.5 (CH₂), 34.4 (C), 33.6 (CH₃), 32.9 (CH₃), 27.9 (CH₃), 26.9 (CH₂), 22.9 (CH₂), 17.4 (CH₃). **¹H NMR** (300 MHz, δ ppm/ CDCl₃): **axial-Me**: 5.98 – 5.82 (m, 1H), 5.10 (t, J = 15.1 Hz, 2H), 3.66 (s, 3H), 2.74 – 2.39 (m, 2H), 2.14 – 1.97 (m, 4H), 1.72 (t, J = 2.9 Hz, 1H), 1.56 (dt, J = 12.9, 7.3 Hz, 2H), 1.43 – 1.35 (m, 2H), 1.16 (s, 3H), 1.12 (s, 3H), 1.06 (d, J = 6.9 Hz, 1H); **equatorial-Me**: 5.98 – 5.82 (m, 1H), 5.10 (t, J = 15.1 Hz, 2H), 3.67 (s, 3H), 2.74 – 2.39 (m, 2H), 2.14 – 1.97 (m, 4H), 1.67 (t, J = 2.9 Hz, 1H), 1.56 (dt, J = 12.9, 7.3 Hz, 2H), 1.43 – 1.35 (m, 2H), 1.17 (s, 3H), 1.10 (s, 3H), 0.65 (d, J = 6.7 Hz, 2H).

•preparation of thiocarbamate **55**



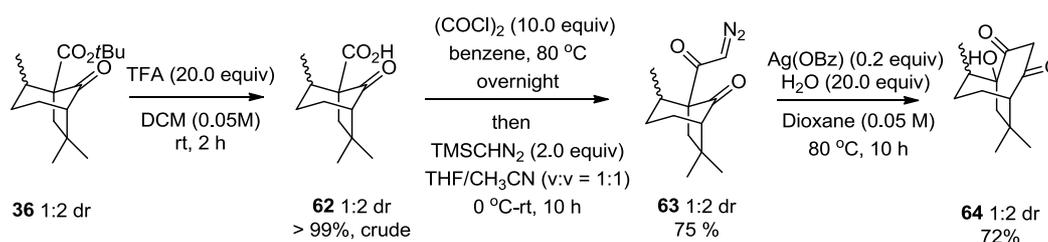
To a solution of **53** (25 mg, 0.09 mmol, 1:2 dr Me_{ax}:Me_{eq}) in THF (1.9 mL, 0.05 M) was added N,N'-thiocarbonyldiimidazole (80.2 mg, 0.45 mmol) and potassium hydride (36.1 mg, 0.9 mmol). The reaction was stirred under reflux and argon atmosphere. After 12h, the reaction mixture was poured into saturated aqueous NH₄Cl, and then dried over Na₂SO₄, concentrated in vacuum, purified by flash chromatography to afford the undesired **55** (15.9 mg, 47 %). **R_f** = 0.46 (PE:EtOAc = 7:3). **MS** (ESI+, m/z): 399 [M+Na]⁺. **¹³C NMR** (75 MHz, δ ppm/ CDCl₃): 181.3 (C), 173.7 (C), 137.2 (CH), 135.1 (CH), 131.5 (CH), 130.4 (CH), 119.0 (CH₂), 92.5 (C), 61.6 (C), 51.7 (CH), 51.4 (CH), 42.5 (CH₂), 37.4 (CH₂), 34.5 (C), 33.6 (CH₃), 32.2 (CH₃), 27.6 (CH₃), 26.1 (CH₂), 24.1 (CH₂), 17.2 (CH₃); **¹H NMR** (300 MHz, ppm/ δ CDCl₃): 8.18 (s, 1H), 7.45 (s, 1H), 7.08 (s, 1H), 5.66 – 5.37 (m, 1H), 4.96 (ddd, J = 13.5, 11.5, 1.2 Hz, 2H), 3.70 (s, 3H), 3.04 (dd, J = 14.8, 7.9 Hz, 1H), 2.87 – 2.59 (m, 2H), 2.54 (t, J = 2.4 Hz, 1H), 2.28 (d, J = 15.0 Hz, 1H), 1.72 – 1.47 (m, 5H), 1.28 (s, 3H), 1.19 (s, 3H), 0.75 (d, J = 6.6 Hz, 3H).

•preparation of alcohol **57**



To a solution of **36** (479.5 mg, 1.80 mmol, 2:1) in ethanol was added NaBH_4 (170.2 mg, 4.5 mmol). The reaction mixture was heated to 78°C for 10h. The reaction mixture was then poured into saturated aqueous NH_4Cl , extracted with diethyl ether, dried over Na_2SO_4 and concentrated in vacuum. Purification by flash chromatography afforded compound **57** (**57a** and **57b**: 372.0 mg, 77 %, 2:1 dr). $R_f = 0.53$ (PE:EtOAc/9:1). ^{13}C NMR (75 MHz, δ ppm/ CDCl_3): **axial-Me**: 177.0 (C), 80.1 (C), 74.2 (CH), 54.7 (C), 47.9 (CH), 47.8 (CH_2), 36.9 (CH), 33.8 (CH_3), 33.5 (C), 28.0 ($\text{CH}_3 \times 3$, *t*-Bu), 25.0 (CH_2), 24.8 (CH_3), 19.4 (CH_3), 17.4 (CH_2); **equatorial-Me**: 176.1 (C), 80.8 (C), 74.3 (CH), 56.5 (C), 47.4 (CH), 38.4 (CH_2), 34.3 (C), 33.5 (CH), 29.5 (CH_3), 28.1 ($\text{CH}_3 \times 3$, *t*-Bu), 27.2 (CH_2), 24.8 (CH_3), 20.3 (CH_2), 16.6 (CH_3); ^1H NMR (300 MHz, δ ppm/ CDCl_3): **axial-Me**: 4.43 (dd, $J = 5.0, 2.3$ Hz, 1H), 2.55 (d, $J = 2.3$ Hz, 1H), 2.38 – 1.84 (m, 3H), 1.72-1.42 (m, 3H), 1.36 (s, 9H), 1.32 – 1.19 (m, 2H), 1.08 (d, $J = 7.0$, 3H), 1.02 (s, 3H), 0.97 (s, 3H); **equatorial-Me**: 4.20 (d, $J = 4.7$ Hz, 1H), 2.82 (d, $J = 1.4$ Hz, 1H), 2.38 – 1.84 (m, 3H), 1.72 – 1.42 (m, 3H), 1.38 (s, 9H), 1.32 – 1.19 (m, 2H), 0.99 (s, 3H), 0.96 (s, 3H), 0.62 (d, $J = 6.7$ Hz, 3H)

■saponification of ester **36** to carboxylic acid **62** and Arndt-Ester reaction toward undesired diketone **64**

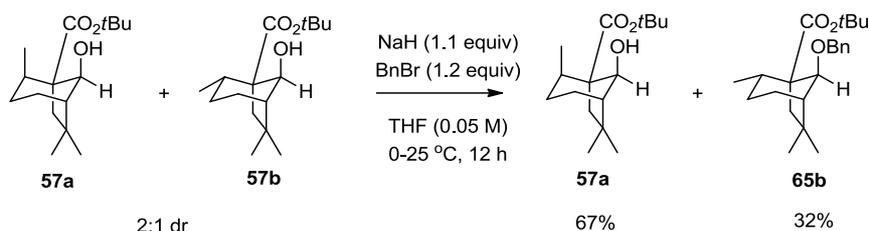


To a solution of *t*-butyl ester **36** (60 mg, 0.23 mmol, 1:2 dr $\text{Me}_{\text{ax}}:\text{Me}_{\text{eq}}$) in dichloromethane was added trifluoroacetic acid (345 μL , 4.6 mmol), the reaction was stirred under room temperature for 2h. The reaction mixture was poured into saturated aqueous NH_4Cl , extracted by ethyl acetate, dried over NaSO_4 . Then, the organic solution was concentrated in vacuum to afford acid **62** (crude) without purification. $R_f = 0.31$ (PE:EtOAc/6:4).

Crude acid **62** was subjected to benzene (5 mL, 0.05 M), and then oxalyl chloride (197.3 μ L, 2.3 mmol) was injected to the benzene solution. The reaction mixture was stirred under reflux and argon atmosphere overnight. After completion, benzene and excess oxalyl chloride was removed by vacuum to afford an acyl chloride which was used directly. To a solution of generating acyl chloride in mixture solvents of THF and acetonitrile (5 mL, v : v = 1:1) was added trimethylsilyldiazomethane (230 μ L, 2.0 M in hexane) at 0 °C, then the reaction solution was allowed to warm to room temperature and stirred for 10h to give diazoketone **63** (40.4 mg, 75%). R_f = 0.56 (PE:EtOAc/4:1). **MS** (ESI+, m/z): 257 [M+Na]⁺. **¹³C NMR** (75 MHz, δ ppm/ CDCl₃): **axial-Me**: 217.3 (C), 194.1 (C), 64.1 (C), 58.5 (CH), 54.8 (CH), 46.4 (CH₂), 44.6 (CH), 32.7 (CH₃), 31.9 (C), 28.9 (CH₂), 24.9 (CH₂), 22.8 (CH₃), 16.2 (CH₃); **equatorial-Me**: 218.1 (C), 191.6 (C), 66.5 (C), 57.8 (CH), 55.4 (CH), 46.1 (CH), 35.9 (CH₂), 32.5 (CH₃), 32.3 (C), 30.7 (CH₂), 27.3 (CH₂), 22.9 (CH₃), 16.6 (CH₃); **¹H NMR** (300 MHz, δ ppm/CDCl₃): **axial-Me**: 6.06 (s, 1H), 2.84 – 2.76 (m, 1H), 2.25 (d, J = 14.1 Hz, 1H), 2.03 – 1.80 (m, 3H), 1.71 (d, J = 14.4 Hz, 1H), 1.63 – 1.22 (m, 2H), 1.16 (s, 3H), 0.91 (s, 3H), 0.88 (d, J = 7.1 Hz, 3H); **equatorial-Me**: 5.86 (s, 1H), 2.25 (d, J = 14.1 Hz, 1H), 2.15 – 2.05 (m, 1H), 2.03 – 1.80 (m, 3H), 1.71 (d, J = 14.4 Hz, 1H), 1.63 – 1.22 (m, 2H), 1.13 (s, 3H), 0.90 (s, 3H), 0.81 (d, J = 6.5 Hz, 3H).

To a solution of diazoketone **63** (40.4 mg, 0.17 mmol) in dioxane (3.5 mL, 0.05 M) was added H₂O (61 μ L, 3.4 mmol) and silver benzoate (7.8 mg, 0.034 mmol). The reaction mixture was stirred at 80 °C for 10h. Then, the reaction solution was extracted with diethyl ether, dried over Na₂SO₄ and concentrated in vacuum. Purification by flash chromatography afforded compound **64** (27.5 mg, 72 %, 1:2 dr) as a white solid. R_f = 0.23 (PE : EtOAc = 5:1). **MS** (ESI+, m/z): 247 [M+Na]⁺. **¹³C NMR** (75 MHz, δ ppm/ CDCl₃): **axial-Me**: 215.6 (C), 209.2 (C), 66.7 (CH₂), 64.9 (C), 58.1 (CH), 45.6 (CH₂), 42.9 (CH), 32.6 (CH₃), 32.6 (C), 28.7 (CH₂), 24.7 (CH₂), 22.8 (CH₃), 16.2 (CH₃); **equatorial-Me**: 216.1 (C), 206.8 (C), 67.7 (C), 67.4 (CH₂), 56.9 (CH), 44.6 (CH), 35.4 (CH₂), 32.6 (C), 32.5 (CH₃), 30.3 (CH₂), 27.1 (CH₂), 22.9 (CH₃), 16.8 (CH₃); **¹H NMR** (300 MHz, δ ppm/CDCl₃): **axial-Me**: 4.76 – 4.58 (m, 1H), 4.37 – 4.25 (m, 1H), 3.14 (br. s, 1H), 2.89 – 2.80 (m, 1H), 2.13 – 1.96 (m, 3H), 1.94 – 1.89 (m, 1H), 1.75 (d, J = 14.0 Hz, 1H), 1.73 – 1.38 (m, 2H), 1.18 (s, 3H), 0.98 (s, 3H), 0.85 (d, J = 7.1 Hz, 3H); **equatorial-Me**: 4.76 – 4.58 (m, 1H), 4.37 – 4.25 (m, 1H), 3.21 (br. s, 1H), 2.52 (dp, J = 12.2, 6.3 Hz, 1H), 2.23 (d, J = 14.3 Hz, 1H), 2.13 – 1.96 (m, 2H), 1.94 – 1.89 (m, 1H), 1.74 (d, J = 14.3 Hz, 1H), 1.73 – 1.38 (m, 2H), 1.15 (s, 3H), 0.91 (s, 3H), 0.76 (d, J = 6.5 Hz, 3H)

•separation of **57a**

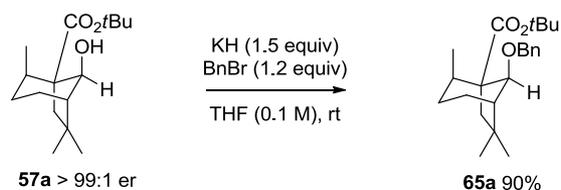


To a solution of **57** (**57a**, **57b**) (372.0 mg, 1.39 mmol, 2:1 dr) in THF was added benzyl bromide (198 μL , 1.67 mmol) and sodium hydride (36.7 mg, 1.53 mmol). The reaction mixture was stirred at room temperature for 12 h. The reaction solution was poured into saturated aqueous NH_4Cl , extracted with diethyl ether, dried over Na_2SO_4 and concentrated in vacuum. Purification by flash chromatography afforded compound **57a** (white solid, 250.0 mg, 67%, 77 % ee) and **42b** as white solid. $R_f = 0.38$ (PE:Et₂O/ 5:1). $\text{Mp} = 108 - 109$ °C; **HRMS** (ESI+) for $\text{C}_{16}\text{H}_{29}\text{O}_3^+$: calcd. $[\text{M}+\text{H}]^+$: 269.2111, found: 269.2117. After recrystallization, the enantiomeric excess was increased to >99 %, 192.5 mg **57a** was obtained. **HPLC** (chiralpak AZ-H, heptane/ethanol 80/20, 1.0 mL/min, UV 220 nm): $\tau_{\text{axial-Me}} = 6.30$ min; $[\alpha]_D^{25} = -32.0$ (c 0.8, EtOH_{absolute}). **¹³C NMR** (75 MHz, δ ppm/ CDCl_3): 177.2 (C), 80.3 (C), 74.4 (CH), 54.8 (C), 47.9 (CH), 47.9 (CH₂), 37.1 (CH), 34.0 (CH₃), 33.6 (C), 28.2 (CH₃×3, *t*-Bu), 25.1 (CH₂), 24.9 (CH₃), 19.5 (CH₃), 17.5 (CH₂); **¹H NMR** (300 MHz, δ ppm/ CDCl_3): 4.49 (d, $J = 4.3$ Hz, 1H), 2.44 (br. s, 1H), 2.05-1.98 (m, 3H), 1.64-1.49 (m, 3H), 1.43 (s, 9H), 1.38 – 1.22 (m, 2H), 1.15 (d, $J = 6.9$ Hz, 3H), 1.09 (s, 3H), 1.04 (s, 3H).

benzylic compound **65b**:

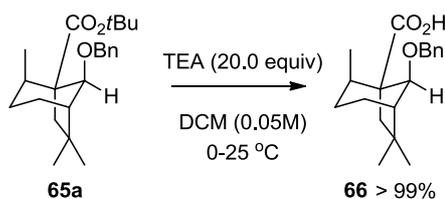
$R_f = 0.65$ (PE:EtOAc/ 20:1). **¹³C NMR** (75 MHz, δ ppm/ CDCl_3): 175.4 (C), 139.1 (C), 128.2 (CH×2), 127.4 (CH×2), 127.4 (CH), 83.9 (CH), 79.8 (C), 71.9 (CH₂), 57.3 (C), 46.5 (CH), 39.0 (CH₂), 34.6 (C), 33.3 (CH), 28.9 (CH₃), 28.2 (CH₃×3, *t*-Bu), 27.8 (CH₂), 25.1 (CH₃), 21.0 (CH₂), 17.0 (CH₃); **¹H NMR** (300 MHz, δ ppm/ CDCl_3): 7.30 – 7.15 (m, 5H), 4.45 (s, 2H), 3.96 (d, $J = 4.6$ Hz, 1H), 2.54 (p, 6.4 Hz, 1H), 1.89 (d, $J = 14.1$ Hz, 1H), 1.77 (dddd, $J = 13.3, 9.7, 6.5, 3.2$ Hz, 1H), 1.62-1.58 (m, 1H), 1.48-1.41 (m, 1H), 1.35 (s, 9H), 1.26 – 1.11 (m, 2H), 0.98 (s, 3H), 0.96 (s, 3H), 0.84-0.75 (m, 1H), 0.68 (d, $J = 6.5$ Hz, 3H).

•benzylation of **57a** to **65a**



To a solution of **57a** (192.5 mg, 0.72 mmol) in THF (7.2 mL, 0.1 M) was added benzyl bromide (103 μL , 0.86 mmol) and potassium hydride (43.3 mg, 1.08 mmol). The reaction mixture was stirred at room temperature for 7 h. The reaction solution was poured into saturated NH_4Cl , extracted with diethyl ether, dried over Na_2SO_4 and concentrated in vacuum. Purification by flash chromatography afforded compound **65a** (232.3 mg, 90 %) as colorless oil. $R_f = 0.63$ (PE:Et₂O/15:1). **HRMS** (ESI+) for $\text{C}_{23}\text{H}_{34}\text{NaO}_3^+$: calcd. $[\text{M}+\text{Na}]^+$: 381.2400, found: 381.2400. $[\alpha]_D^{25} = +15.1$ (*c* 1.0, EtOH_{absolute}). **¹³C NMR** (75 MHz, δ ppm/ CDCl_3): 175.8 (C), 139.7 (C), 128.2 (CH \times 2), 127.1 (CH \times 2), 127.1 (CH), 82.3 (CH), 79.7 (C), 72.6 (CH₂), 55.1 (C), 49.5 (CH₂), 46.5 (CH), 36.4 (CH), 33.9 (C), 33.7 (CH₃), 28.2 (CH₃ \times 3, *t*-Bu), 25.3 (CH₂), 25.0 (CH₃), 19.8 (CH₃), 18.3 (CH₂); **¹H NMR** (300 MHz, δ ppm/ CDCl_3): 7.29–7.13 (m, 5H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.33 (d, *J* = 4.6 Hz, 1H), 2.09 (p, *J* = 7.1 Hz, 1H), 2.01 – 1.79 (m, 2H), 1.63 (br. s, 1H), 1.53 (d, *J* = 13.7 Hz, 1H), 1.47 (d, *J* = 13.7 Hz, 1H), 1.37 (s, 9H), 1.32 – 1.16 (m, 2H), 1.12 (d, *J* = 7.3 Hz, 3H), 1.02 (s, 3H), 0.98 (s, 3H).

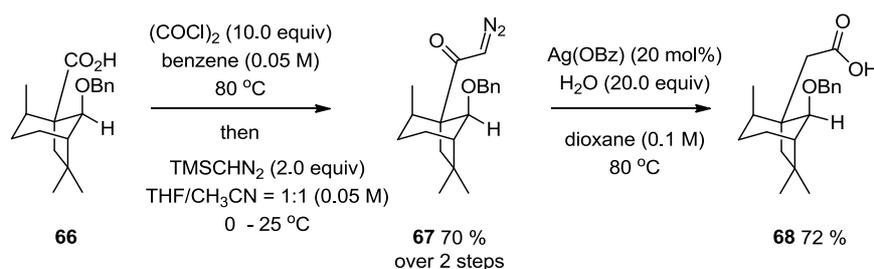
•saponification of *t*-butyl ester **65a** to acid **66**



To a solution of **65a** (232.3 mg, 0.65 mmol) in dichloromethane (12.9 mL, 0.05 M) was added trifluoroacetic acid (995 μL , 13.0 mmol) at 0 $^\circ\text{C}$, then the reaction solution was warmed to room temperature, stirred for 2 hours, concentrated in vacuum. Purification by flash chromatography afforded compound **66** (193.5 mg, 99 %) as a white solid. $R_f = 0.27$ (PE:EtOAc/4:1). $\text{Mp} = 134 - 135^\circ\text{C}$. **HRMS** (ESI+) for $\text{C}_{19}\text{H}_{27}\text{O}_3^+$: calcd. $[\text{M}+\text{H}]^+$: 303.1955, found: 303.1960; $\text{C}_{19}\text{H}_{30}\text{NO}_3^+$: calcd. $[\text{M}+\text{NH}_4]^+$: 320.2226, found: 320.2220; $[\alpha]_D^{25} = +10.3$ (*c* 1.0, EtOH_{absolute}). **¹³C NMR** (75 MHz, δ ppm/ $(\text{CD}_3)_2\text{CO}$): 177.6 (C), 140.4 (C), 128.9 (CH \times 2), 128.0 (CH \times 2), 127.9 (CH), 83.0 (CH), 73.0 (CH₂), 54.9 (C), 50.0 (CH₂), 46.9 (CH),

36.9 (CH), 34.5 (C), 33.8 (CH₃), 25.8 (CH₂), 25.1 (CH₃), 20.4 (CH₃), 18.8 (CH₂); ¹H NMR (300 MHz, δ ppm/CDCl₃): 10.91 (br. s, 1H), 7.40-7.28 (m, 5H), 4.63 (d, J = 11.8 Hz, 1H), 4.58 (d, J = 11.8 Hz, 1H), 4.44 (d, J = 4.6 Hz, 1H), 2.31 (p, J = 6.9 Hz, 1H), 2.08-2.01 (m, 2H), 1.83 (d, J = 13.8 Hz, 1H), 1.82-1.79 (m, 1H), 1.67 (d, J = 13.7 Hz, 1H), 1.45-1.36 (m, 2H), 1.28 (d, J = 7.2 Hz, 3H), 1.16 (s, 3H), 1.10 (s, 3H).

▪Arndt-Ester reaction toward carboxylic acid **66**

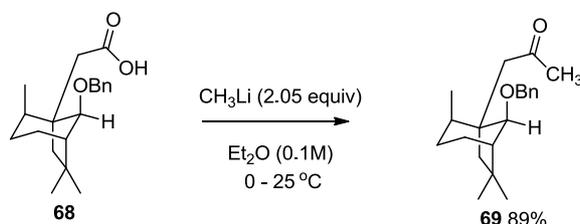


To a solution of acid **66** (193.5 mg, 0.65 mmol) in benzene (12.9 mL, 0.05 M) was injected oxalyl chloride (557 μL, 6.5 mmol). The reaction mixture was stirred under reflux and argon atmosphere overnight. After completion, benzene and excess oxalyl chloride was removed by vacuum to afford an acyl chloride which was used directly. To a solution of generating acyl chloride in mixture solvents of THF and acetonitrile (12.9 mL, v:v = 1:1, 0.05 M) was added trimethylsilyldiazomethane (650 μL, 2.0 M in hexane) at 0 °C, then the reaction solution was allowed to warm to room temperature and stirred for 10h to give diazoketone **67** (148.5 mg, 70%) as a yellowish oil. *R_f* = 0.42 (PE:EtOAc/9:1). **HRMS** (ESI+) for C₂₀H₂₇N₂O₂⁺: calcd. [M+H]⁺: 327.2067, found: 327.2067; [α]_D²⁵ = +64.3 (c 1.0, EtOH_{absolute}). ¹³C NMR (75 MHz, δ ppm/ CDCl₃): 200.3 (C), 138.8 (C), 128.5 (CH×2), 127.5 (CH), 127.4 (CH×2), 81.1 (CH), 72.0 (CH₂), 58.8 (C), 53.2 (CH), 48.6 (CH₂), 45.3 (CH), 37.9 (CH), 33.8 (CH₃), 33.6 (C), 25.6 (CH₂), 25.1 (CH₃), 19.7 (CH₃), 18.2 (CH₂); ¹H NMR (300 MHz, δ ppm/CDCl₃): 7.28-7.13 (m, 5H), 5.40 (s, 1H), 4.52 (d, J = 11.9 Hz, 1H), 4.34 (d, J = 11.9 Hz, 1H), 4.09 (d, J = 4.4 Hz, 1H), 1.93-1.84 (m, 3H), 1.76 - 1.74 (m, 1H), 1.54 (d, J = 13.9 Hz, 1H), 1.48 (d, J

= 14.0 Hz, 1H), 1.31 – 1.28 (m, 1H), 1.24 – 1.20 (m, 1H), 1.08 (d, $J = 7.0$ Hz, 3H), 1.01 (s, 3H), 0.92 (s, 3H).

To a solution of diazoketone **67** (148.5 mg, 0.45 mmol) in dioxane (4.5 mL, 0.1 M) was added H₂O (162 μ L, 9.0 mmol) and silver benzoate (20.6 mg, 0.09 mmol). The reaction mixture was stirred at 80 °C for 10h. Then, the reaction solution was extracted with diethyl ether, dried over Na₂SO₄ and concentrated in vacuum to afford compound **68** (102.5 mg, 72 %) as a white solid without purification, the crude is very clean. $R_f = 0.47$ (PE:EtOAc/ 4:1). $Mp = 108 - 109$ °C. **HRMS** (ESI+) for C₂₀H₂₈NaO₃⁺: calcd. $[M+Na]^+$: 339.1931, found: 339.1931; $[\alpha]_D^{25} = +24.5$ (c 1.0, EtOH_{absolute}). **¹³C NMR** (75 MHz, δ ppm/ CDCl₃): 178.9 (C), 139.3 (C), 128.4 (CH \times 2), 127.4 (CH), 127.2 (CH \times 2), 85.6 (CH), 72.2 (CH₂), 49.3 (CH₂), 46.0 (C), 44.9 (CH), 42.5 (CH₂), 37.3 (CH), 34.2 (C), 34.0 (CH₃), 26.5 (CH₂), 25.2 (CH₃), 19.0 (CH₃), 18.2 (CH₂); **¹H NMR** (300 MHz, δ ppm/CDCl₃): 11.43 (br. s, 1H), 7.27 – 7.17 (m, 5H), 4.51 (d, $J = 11.9$ Hz, 1H), 4.27 (d, $J = 11.9$ Hz, 1H), 3.71 (d, $J = 4.4$ Hz, 1H), 2.73 (d, $J = 14.4$ Hz, 1H), 2.18 (d, $J = 14.4$ Hz, 1H), 1.94 – 1.83 (m, 2H), 1.71 – 1.67 (m, 2H), 1.54 (d, $J = 14.0$ Hz, 1H), 1.48 (d, $J = 14.0$ Hz, 1H), 1.36-1.26 (m, 1H), 1.23 – 1.18 (m, 1H), 1.13 (d, $J = 7.4$ Hz, 3H), 1.05 (s, 3H), 0.95 (s, 3H)

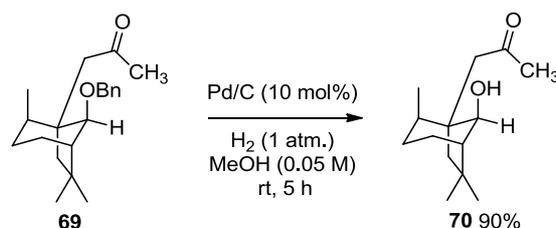
•methylation of carboxylic acid **68** to **69**



Under the argon atmosphere, to the carboxylic acid **68** (102.5 mg, 0.32 mmol) in Et₂O was added methyllithium (410 μ L, 1.6 M in diethyl ether) at 0 °C, after 30 mins, the reaction was allowed to warm to room temperature and stirred for 8 hours. Then, the reaction was quenched with saturated aqueous NH₄Cl, extracted with diethyl ether, dried over Na₂SO₄ and concentrated in vacuum. Purification by flash chromatography afforded compound **69** (89.6 mg, 89 %,.) as a clear-yellow oil. $R_f = 0.67$ (PE:EtOAc/9:1). **HRMS** (ESI+) for C₂₁H₃₁O₂⁺: calcd. $[M+H]^+$: 315.2319, found: 315.2319; $[\alpha]_D^{25} = +84.8$ (c 0.43, EtOH_{absolute}). **¹³C NMR** (75 MHz, δ ppm/ CDCl₃): 208.9 (C), 139.3 (C), 128.3 (CH \times 2), 127.3 (CH), 127.1 (CH \times 2), 86.0 (CH), 72.0 (CH₂), 50.8 (CH₂), 49.4 (CH₂), 46.1 (C), 44.5 (CH), 36.6 (CH), 34.3 (C), 34.0 (CH₃), 31.9 (CH₃), 26.3 (CH₂), 25.2 (CH₃), 19.1 (CH₃), 18.2 (CH₂); **¹H NMR** (300 MHz, δ

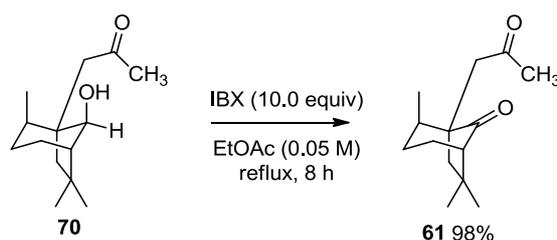
ppm/ CDCl_3): 7.18–7.30 (m, 5H), 4.60 (d, $J = 11.9$ Hz, 1H), 4.32 (d, $J = 11.9$ Hz, 1H), 3.72 (d, $J = 4.5$ Hz, 1H), 3.02 (d, $J = 16.1$ Hz, 1H), 2.25 (d, $J = 16.1$ Hz, 1H), 2.11 (s, 3H), 2.04 – 1.87 (m, 2H), 1.80 (p, $J = 7.4$ Hz, 1H), 1.74 – 1.73 (m, 1H), 1.65 (d, $J = 13.8$ Hz, 1H), 1.54 (d, $J = 13.9$ Hz, 1H), 1.40 – 1.36 (m, 1H), 1.25 (dd, $J = 13.6, 5.2$ Hz, 1H), 1.15 (d, $J = 7.4$ Hz, 3H), 1.13 (s, 3H), 1.03 (s, 3H).

▪deprotection of **69** to alcohol **70**



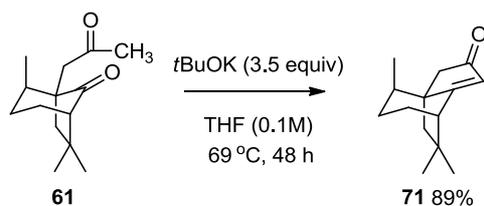
To the solution of ketone **69** (89.6 mg, 0.285 mmol) in MeOH was added Pd/C (30.9 mg, 0.029 mmol, 10 % Pd loading), then bubbled H_2 for 2 minutes. The reaction was stirred vigorously under hydrogen atmosphere (1.0 atm.) at room temperature. After 5 hours, the reaction reached full conversion. Pd/C was filtered, and the filtrate was concentrated in vacuum. Purification by flash chromatography afforded compound **70** (57.5 mg, 90 %) as yellow oil. $R_f = 0.25$ (PE:EtOAc/4:1). **HRMS** (ESI+) for $\text{C}_{14}\text{H}_{25}\text{O}_2^+$: calcd. $[\text{M}+\text{H}]^+$: 225.1849, found: 225.1849; for $\text{C}_{14}\text{H}_{24}\text{NaO}_2^+$: calcd. $[\text{M}+\text{Na}]^+$: 247.1669, found: 247.1669; $[\alpha]_D^{25} = +10.8$ (c 0.65, $\text{EtOH}_{\text{absolute}}$). **^{13}C NMR** (75 MHz, δ ppm/ CDCl_3): 209.9 (C), 78.3 (CH), 52.0 (CH_2), 51.2 (CH_2), 49.2 (CH), 46.3 (C), 37.7 (CH), 34.3 (C), 34.0 (CH_3), 32.0 (CH_3), 26.5 (CH_2), 25.0 (CH_3), 19.5 (CH_3), 17.7 (CH_2); **^1H NMR** (300 MHz, δ ppm/ CDCl_3): 4.13 (d, $J = 4.8$ Hz, 1H), 2.82 (d, $J = 16.3$ Hz, 1H), 2.55 (br. s, 1H), 2.43 (d, $J = 16.3$ Hz, 1H), 2.15 (s, 3H), 2.03 – 1.95 (m, 2H), 1.71 (p, $J = 7.3$ Hz, 1H), 1.60 (d, $J = 13.8$ Hz, 1H), 1.57 – 1.54 (m, 1H), 1.43 (d, $J = 13.8$ Hz, 1H), 1.40 – 1.35 (m, 1H), 1.29 – 1.21 (m, 1H), 1.11 (d, $J = 7.5$ Hz, 3H), 1.09 (s, 3H), 1.03 (s, 3H).

•oxidation of alcohol **70** to diketone **61**



To the solution of ketone **70** (57.5 mg, 0.26 mmol) in ethyl acetate (5.2 mL, 0.05 M) was added 2-iodoxybenzoic acid (728.1 mg, 2.6 mmol), then the reaction was stirred at 90 °C, monitored the reaction by TLC. After completion, the solid residue was discarded, and the filtrate was concentrated in vacuum. Purification by flash chromatography afforded compound **61** (56.6 mg, 98 %) as a yellow oil. $R_f = 0.59$ (PE:EtOAc/ 4:1). **MS** (ESI+): 245 $[M+Na]^+$. $[\alpha]_D^{25} = -67.1$ (c 0.5, EtOH_{absolute}). **¹³C NMR** (75 MHz, δ ppm/ CDCl₃): 219.8 (C), 207.0 (C), 57.2 (CH), 53.1 (C), 46.3 (CH₂), 44.8 (CH₂), 43.6 (CH), 32.7 (CH₃), 32.4 (C), 31.4 (CH₃), 28.5 (CH₂), 25.8 (CH₂), 23.2 (CH₃), 15.5 (CH₃); **¹H NMR** (300 MHz, δ ppm/CDCl₃): 2.73 (d, $J = 17.7$ Hz, 1H), 2.47 (d, $J = 17.7$ Hz, 1H), 2.35 (p, 7.0 Hz, 1H), 2.14 – 2.12 (m, 1H), 2.09 (s, 3H), 2.06 – 2.04 (m, 1H), 2.01 – 1.88 (m, 2H), 1.78 – 1.76 (m, 1H), 1.65 (d, $J = 13.6$ Hz, 1H), 1.21 – 1.18 (m, 1H), 1.15 (s, 3H), 0.92 (s, 3H), 0.83 (d, $J = 7.2$ Hz, 3H).

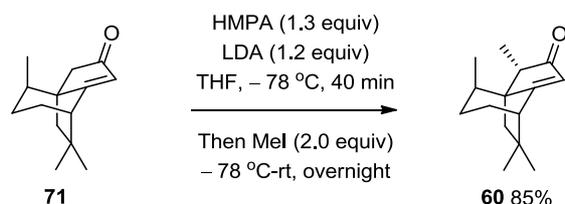
•aldol / dehydration of **61** to α,β -unsaturated ketone **71**



To a solution of diketone **61** (56.6 mg, 0.255 mmol) in THF (2.6 mL, 0.1 M) was added potassium *tert*-butoxide (100.1 mg, 0.89 mmol) promptly, then the reaction was stirred at 69 °C for 48h, after full conversion, cooled down the solution to room temperature, then poured the reaction mixture to saturated aqueous NH₄Cl, extracted with Et₂O, dried over Na₂SO₄, then concentrated in vacuum. Purification by flash chromatography afforded compound **71** (46.4 mg, 89 %, 0.23 mmol) as a yellow oil. $R_f = 0.29$ (PE:EtOAc/ 9:1). **MS** (ESI+): 227 $[M+Na]^+$. $[\alpha]_D^{25} = -21.0$ (c 0.15, EtOH_{absolute}). **¹³C NMR** (75 MHz, δ ppm/ CDCl₃): 211.2 (C), 191.9 (C), 121.8 (CH), 54.1 (C), 50.1 (CH₂), 48.9 (CH), 48.8 (CH₂), 40.7 (CH), 40.2 (C), 33.3 (CH₃), 25.7 (CH₂), 24.4 (CH₂), 23.2 (CH₃), 14.7 (CH₃); **¹H NMR** (400 MHz, δ

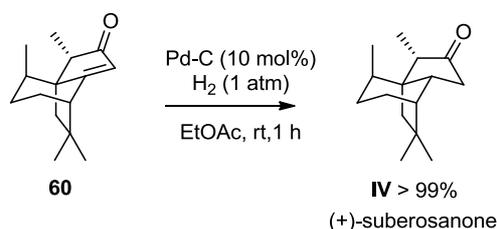
ppm/ CDCl_3): 5.82 (s, 1H), 2.36 (d, $J = 18.0$ Hz, 1H), 2.35 (t, $J = 3.2$ Hz, 1H), 2.06 (d, $J = 17.9$ Hz, 1H), 2.10 – 1.95 (m, 2H), 1.89 (d, $J = 13.2$ Hz, 1H), 1.81 – 1.75 (m, 2H), 1.35 (d, $J = 13.2$ Hz, 1H), 1.25 (ddd, $J = 14.0, 5.0, 2.0$ Hz, 1H), 1.20 (s, 3H), 0.89 (s, 3H), 0.74 (d, $J = 7.0$ Hz, 3H).

•methylation of **71** to **60**

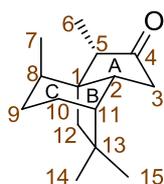


LDA was prepared by adding *n*-BuLi (172 μL , 0.28 mmol, 1.6 M in hexanes) to a solution of diisopropylamine (43 μL , 0.31 mmol) in 5 mL of THF, at -78°C . The solution was stirred 30 min at -30°C . To a stirred solution of ketone **71** (46.4 mg, 0.23 mmol) and hexamethylphosphoramide (52.0 μL , 0.30 mmol) in THF (5.8 mL, 0.04 M) was added the prepared LDA (0.28 mmol) by cannula, the reaction mixture was stirred for 40 minutes at -78°C . Iodomethane (28.6 μL , 0.46 mmol) was then added to the enolate solution. The solution was allowed to warm to room temperature overnight. Then the reaction was quenched by saturated NH_4Cl , extracted with Et_2O , dried over Na_2SO_4 , concentrated in vacuum. Purification by flash chromatography afforded compound **60** (42.7 mg, 85 %) as a colorless oil. $R_f = 0.49$ (PE:EtOAc/ 9:1). **MS** (ESI $^+$): 241 $[\text{M}+\text{Na}]^+$. $[\alpha]_D^{25} = -50.8$ (c 0.2, $\text{EtOH}_{\text{absolute}}$). ^{13}C NMR (75 MHz, δ ppm/ CDCl_3): 214.8 (C), 191.1 (C), 119.7 (CH), 57.8 (C), 49.2 (CH), 47.8 (CH), 42.2 (CH_2), 42.0 (CH), 39.6 (C), 32.4 (CH_3), 26.1 (CH_2), 24.9 (CH_2), 23.1 (CH_3), 15.7 (CH_3), 14.6 (CH_3); ^1H NMR (400 MHz, δ ppm/ CDCl_3): 5.78 (s, 1H), 2.35 (t, $J = 3.2$ Hz, 1H), 2.24 (q, $J = 7.7$ Hz, 1H), 2.08 – 2.02 (m, 2H), 1.81 – 1.76 (m, 2H), 1.60 (d, $J = 13.5$ Hz, 1H), 1.52 (d, $J = 13.5$ Hz, 1H), 1.26 (ddd, $J = 13.2, 5.3, 2.1$ Hz, 1H), 1.22 (s, 3H), 0.99 (d, $J = 7.7$ Hz, 3H), 0.87 (s, 3H), 0.75 (d, $J = 7.0$ Hz, 3H).

•hydrogenation of **60** to target molecule (+)-suberosanone **IV**



To a solution of ketone **60** (42.7 mg, 0.196 mmol) in ethyl acetate was added Pd/C (20.9 mg, 0.02 mmol, 10 % loading on carbon), then bubbled H₂ for 2 minutes. The reaction was stirred vigorously with a hydrogen balloon (1 atm.) at room temperature. After 1 hour, the reaction completed. Pd/C was filtered, and the filtrate was concentrated in vacuum to afford **IV** (42.8 mg, >99 %) without purification as a colorless oil which is not UV active and is not visible even though soaked by stains. **HRMS** (ESI+) for C₁₅H₂₄NaO⁺: calcd. [M+Na]⁺: 243.1719, found: 243.1719; [α]_D²⁵ = +17.0 (c 0.1, EtOH_{absolute}). **HPLC** (Lux-Cellulose-2, heptane/tertobutanol (98/2), 1.0 mL/min, CD 290 nm): τ_{axial-Me} = 8.56 min. **¹³C NMR** (100 MHz, δ ppm/ CDCl₃): 220.4 (C), 57.0 (C), 50.1 (CH), 49.8 (CH), 47.9 (CH₂), 44.0 (CH), 40.8 (CH₂), 39.3 (C), 35.8 (CH), 34.4 (CH₃), 28.4 (CH₂), 27.1 (CH₂), 27.1 (CH₃), 17.1 (CH₃), 8.2 (CH₃); **¹H NMR** (400 MHz, δ ppm/CDCl₃): 2.51 – 2.32 (m, 4H), 2.05 (ddd, *J* = 20.9, 14.1, 7.2 Hz, 1H), 1.88 (p, *J* = 7.2 Hz, 1H), 1.75 (br. t, *J* = 3.1 Hz, 1H), 1.70 – 1.55 (m, 2H), 1.40 (d, *J* = 14.5 Hz, 1H), 1.33 (d, *J* = 14.5 Hz, 1H), 1.32 (dd, *J* = 14.5, 6.0 Hz, 1H), 1.13 (s, 3H), 1.08 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).



(+)-suberosanone

Table 3: the comparison of ¹H chemical shifts of (+)-suberosanone

proton	literature ⁶⁹	compound IV
	500 MHz / CDCl ₃	400 MHz / CDCl ₃
2	2.38 (m, 1H)	
3α	2.48 (dd, <i>J</i> = 7.0, 1.5 Hz, 1H)	2.51 – 2.32 (m, 4H)
3β	2.35 (dd, <i>J</i> = 7.0, 3.0 Hz, 1H)	
5	2.39 (q, <i>J</i> = 7.0 Hz, 1H)	
6	0.90 (d, <i>J</i> = 7.0 Hz, 3H)	0.88 (d, <i>J</i> = 6.8 Hz, 3H)
7	1.04 (d, <i>J</i> = 7.0 Hz, 3H)	1.03 (d, <i>J</i> = 7.0 Hz, 3H)
8	1.89 (q, <i>J</i> = 7.0 Hz, 1H)	1.88 (p, <i>J</i> = 7.2 Hz, 1H)
9α	1.33 (dd, <i>J</i> = 7.0, 7.0 Hz, 1H)	1.32 (dd, <i>J</i> = 14.5, 6.0 Hz, 1H)
9β	2.06 (m, 1H)	2.05 (ddd, <i>J</i> = 20.9, 14.1, 7.2 Hz, 1H)
10α	1.62 (ddd, <i>J</i> = 13.5, 6.5, 2.5 Hz, 1H)	1.70 – 1.55 (m, 2H)
10β	1.68 (m, 1H)	

11	1.79 (br. t, J = 3.0)	1.75 (br. t, J = 3.1 Hz, 1H)
12 α	1.40 (d, J = 14.5Hz, 1H)	1.40 (d, J = 14.5 Hz, 1H)
12 β	1.33 (d, J = 14.5 Hz, 1H)	1.33 (d, J = 14.5 Hz, 1H)
14	1.04 (s, 3H) ¹⁰⁸	1.13 (s, 3H)
15	1.09 (s, 3H)	1.08 (s, 3H)

Table 4: the comparison of ¹³C chemical shifts of (+)-suberosanone

carbon	literature ⁶⁹	compound IV
	125 MHz / CDCl ₃	100 MHz / CDCl ₃
1	56.9 (C)	57.0 (C)
2	43.8 (CH)	44.0 (CH)
3	40.7 (CH ₂)	40.8 (CH ₂)
4	220.5 (C)	220.4 (C)
5	50.0 (CH)	50.1 (CH)
6	8.1 (CH ₃)	8.2 (CH ₃)
7	17.0 (CH ₃)	17.1 (CH ₃)
8	35.6 (CH)	35.8 (CH)
9	26.9 (CH ₂)	27.1 (CH ₂)
10	28.3 (CH ₂)	28.4 (CH ₂)
11	49.6 (CH)	49.8 (CH)
12	47.7 (CH ₂)	47.9 (CH ₂)
13	39.2 (C)	39.3 (C)
14	27.0 (CH ₃)	27.1 (CH ₃)
15	34.3 (CH ₃)	34.4 (CH ₃)

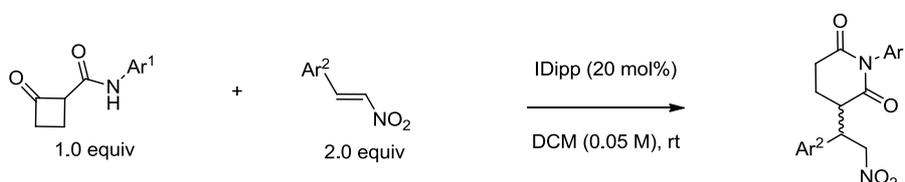
¹⁰⁸ The author made a mistake to write 1.14 into 1.04, and this has been confirmed by professor Sheu

ES.3. Chemistry of glutarimides

•preparation of catalyst **3** and α -substituted- β -oxocyclobutanecarboxamides

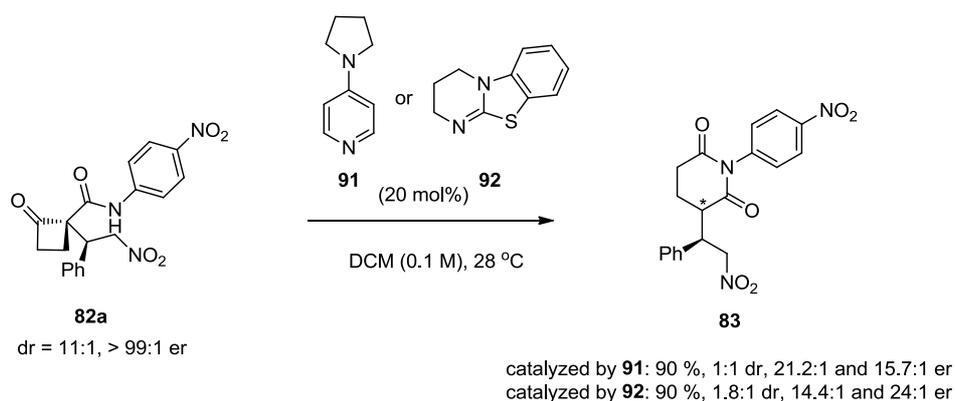
The preparation of squaramide catalyst **80** was according to Rawal¹⁰⁹ and He's¹¹⁰ methods using a (*S*)-quinindium as starting material via Mitsunobu reaction. α -substituted- β -oxocyclobutanecarboxamides were prepared according to one previous work of our lab, enantioselective Michael addition occurred between β -oxocyclobutanecarboxamides and nitrostyrenes under the catalysis of squaramide catalyst **80**.¹¹¹

•preparation of racemic glutarimides



To a solution of α -substituted- β -oxocyclobutanecarboxamides (1.0 equiv) in DCM (0.05 M) was added nitrostyrene (2.0 equiv) and IDipp **2** (0.2 equiv). The reaction mixture was stirred at room temperature under an argon atmosphere for 20h. The reaction solution was then concentrated in vacuum, purified by flash chromatography to afford glutarimides.

•enantioselective synthesis of glutarimide **83**



¹⁰⁹ Malerich, J.; Rawal, V. *J. Am. Chem. Soc.* **2008**, *130*, 14416; 2) Konishi, H.; Rawal, V. *Org. Lett.* **2010**, *12*, 2028.

¹¹⁰ Liu, Y.; He, L. *Org. Lett.* **2013**, *15*, 6090

¹¹¹ Mailhol, D.; Coquerel, Y.; Rodriguez, J. *Adv. Synth. Catal.* **2012**, *354*, 3523

To a solution of α -substituted- β -oxocyclobutanecarboxamides (50 mg, 0.13 mmol) in DCM (1.3 mL, 0.1 M) was added pyrrolidinopyridine **91** (3.9 mg, 0.026 mmol) or Smith catalyst **92** (4.9 mg, 0.026 mmol). The reaction mixture was stirred at 28 °C for 20h (catalyst **91**) or 34h (catalyst **92**). The reaction solution was then concentrated in vacuum, purified by flash chromatography to afford glutarimide **83** (under the catalysis of **91**: 90 %, 1:1 dr, 21.2:1 and 15.7:1 er; under the catalysis of **92**: 90 %, 1.8:1 dr, 14.4:1 and 24:1 er;) as a yellow solid which is slightly soluble in CDCl₃. **R_f** = 0.25 (PE:EtOAc/ 6:4). **HRMS** (ESI+) for C₁₉H₁₈N₃O₆⁺: calcd. [M+H]⁺: 384.1190, found: 384.1190; for C₁₉H₂₁N₄O₆⁺ calcd. [M+NH₄]⁺: 401.1456, found: 401.1456; **HPLC** (Chiralpak IC, heptane/ethanol (50/50), 1.0 mL/min, DAD): τ_{major} = 6.43 and 8.16 min, τ_{minor} = 7.03 and 9.20 min. **¹³C NMR** (75 MHz, δ ppm/CDCl₃): **major dia**: 172.9 (C), 171.3 (C), 147.8 (C), 140.9 (C), 136.2 (C), 130.0 (CH), 129.5 (CH), 128.8 (CH), 128.3 (CH), 124.6 (CH), 78.0 (CH₂), 44.9 (CH), 43.5 (CH), 31.1 (CH₂), 20.5 (CH₂); **minor dia**: 172.7 (C), 171.1 (C), 147.7 (C), 139.4 (C), 136.1 (C), 129.9 (CH), 129.4 (CH), 128.8 (CH), 128.8 (CH), 124.6 (CH), 77.6 (CH₂), 45.6 (CH), 45.5 (CH), 32.3 (CH₂), 21.3 (CH₂); **¹H NMR** (300 MHz, δ ppm/CDCl₃): **major dia**: 8.22 (d, J = 8.5 Hz, 2H), 7.29 – 7.08 (m, 7H), 5.09 (td, J = 13.7, 7.4 Hz, 1H), 4.69 (dd, J = 13.4, 7.4 Hz, 1H), 4.13 – 3.98 (m, 1H), 2.99 (dd, J = 13.1, 8.6 Hz, 1H), 2.82 – 2.78 (m, 1H), 2.70 – 2.56 (m, 1H), 1.97 – 1.90 (m, 2H); **minor dia**: 8.22 (d, J = 8.5 Hz, 2H), 7.29 – 7.08 (m, 7H), 5.09 (td, J = 13.7, 7.4 Hz, 1H), 4.95 (dd, J = 13.1, 7.9 Hz, 1H), 4.13 – 3.98 (m, 1H), 3.13 – 3.06 (m, 1H), 2.88 – 2.84 (m, 1H), 2.70 – 2.56 (m, 1H), 2.09 – 2.04 (m, 2H).

Dual organocatalysis for the development of Michael-initiated enantioselective organocascades

The basic research work presented herein is anchored at the core of modern synthetic organic chemistry, and more specifically in the field of enantioselective multi-organocatalysis. In this manuscript, we have identified two original organocascades and demonstrated the synthetic relevance of one of these through applications in total synthesis. The originality of the work lies on the use of a 1,3-imidazol-2-ylidene NHC as an organocatalytic Brønsted or Lewis base.

Keywords: enantioselectivity, multi-organocatalysis, total synthesis, NHC, Brønsted base, Lewis base

Double organocatalyse pour le développement de Michael-initié organocascades énantiosélectifs

Les travaux de recherche fondamentale présentés ici sont ancrés au cœur de la chimie organique de synthèse moderne, et plus particulièrement dans le domaine de la multi-organocatalyse énantiosélective. Dans ce manuscrit, nous avons identifié deux organocascades originales et démontré la pertinence synthétique de l'une d'elle par des applications en synthèse totale de produits naturels. L'originalité de ce travail repose sur l'utilisation d'un NHC de la classe des 1,3-imidazol-2-ylidènes comme base de Brønsted ou base de Lewis organocatalytique.

Mots-clés: énantiosélectivité, multi-organocatalyse, synthèse totale, NHC, base de Brønsted, base de Lewis