UNIVERSITÀ DI PISA

DIPARTIMENTO DI CHIMICA E CHIMICA INDUSTRIALE

A Dissertation Submitted to the

GALILEO GALILEI Ph.D. SCHOOL XXIV CYCLE (2009-2011)

In Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY IN CHEMICAL SCIENCES

SUPPORTED LIGANDS AND ORGANOCATALYSTS FOR ENANTIOSELECTIVE TRANSFORMATIONS: A PRACTICAL FEASIBILITY PERSPECTIVE

By

Ravindra Panjabrao Jumde

Supervisors

Prof. Dario Pini

Dr. Alessandro Mandoli

External Supervisor

Prof. Maurizio Benaglia

Dedicated to

My Sister (Kiran)

All truths are easy to understand once they are discovered; the point is to discover them.

-Galileo Galilei-

Acknowledgement

First and foremost, I offer my sincerest gratitude to my esteemed supervisors Professor Dario Pini and Dr. Alessandro Mandoli for their erudite and scrupulous supervision and long-lasting patience which gave me constant encouragement and guidance. Their painstaking efforts, immense insight, inspiring attitude, enthusiasm and in particular the provided friendly atmosphere in the lab made this task much easier and joyful than expected.

The thought provoking comments by Dr. Alessandro Mandoli and keen insight in identifying various facets of problems have been a source of enduring patience to me without which this work could neither gather substance nor assume the present form. His scholarship, humanity made my task a joy. His efficacy led to broadcasting and deepening of my understanding of the research problem. It is a great pleasure and privilege for me for being associated with both of my supervisors. I shall always remain beholden to them.

I would also like to show my gratitude to my external supervisor Prof. Maurizio Benaglia for his attentive corrections and comments in the Thesis.

The collaborative help from Prof. Gloria Uccello-Barretta and Dr. Federica Balzano for the NMR studies, Dr. Angela Cuzzola for mass- and Dr. Antonella Manariti for IR-measurements is gratefully acknowledged.

I sincerely thank Ms. Anila Di Pietro, Mr. Alessio Stefanini, Ms. Federica De Lorenzi and Mr. Damiano Cancogni, for their initial contribution in this Thesis work. I would also like to thank Prof. Anna Iuliano for her encouragement and cheerful presence in the lab.

I wish to express my acknowledgment to Galileo Galilei PhD School, University of Pisa for the financial support unless otherwise this Thesis would not have been possible.

I am also greatly indebted to my teachers in past: Dr. P. G. Rohankar and Ms. Deshmukh (Jagadamba Mahavidyalaya, Achalpur City, S.G.B. Amravati university, India), and Prof. V.G. Deshmukh and Prof. P. R. Mandlik (Master degree, Shri Shivaji Science College, Amravati, S.G.B. Amravati university, India) who have taught me the basic chemistry and inspired me to perceive my doctoral degree in chemistry.

I would like to especially thank my previous mentors Mr. S. S. Joshi, Dr. R. Jaganathan, (National Chemical Laboratory, Pune, India) who had developed my interest in

research by allowing me to carry out work of my interest (organic synthesis) and Dr. T. Raja for encouraging me to perceive doctoral degree abroad.

Special thanks to all my friends, Pappu and Mintu (friends from my childhood), Sushil M., Sunil, Krishna, Avinash, Suresh, Amol D. T., Amol D. Shailesh (college friends) Dr. Yogesh V., Dr. Pravin U., Mr. Rajendra, Dr. Nishant for supporting me through all the ups and downs and helping me whenever I needed it.

I do not have words to express my feelings towards my family: Mammy, Papa, Kiran (my sister) who have constantly encouraged and supported for my higher studies, and waiting long enough for my return, thank you very much. I would specially thank my sister who boosts my interest in Chemistry and insists me to take master degree in Chemistry.

Lastly and by no means least Varsha (my friend/wife/labmate), it is equally difficult to put into words my gratitude and love to you, we started on this journey almost together three years ago and throughout that time you became my morale booster. Thank you firstly for your friendship over the years; for your love, support, and encouragement and for being by my side through thick and thin.

Ravindra P. Jumde

TABLE OF CONTENTS

ABBREVIATIONS

AA	Asymmetric aminohydroxylation
AD	Asymmetric dihydroxylation
AIBN	Azobisisobutyronitrile
AMST	Azidomethyl styrene
aq.	Aqueous
AQN	Anthraquinone-1,4-diyl-
Ar	Aryl group
BET	Brunauer Emmett Teller surface area
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl group
Boc	tert-Butyloxycarbonyl group
Cat.	Catalyst
CBz	Benzyloxy carbonyl group
CD	Cinchonidine or 9-O-cinchonidinyl
CN	Cinchonine or 9-O-cinchoninyl
CSP	Chiral stationary phase
CuAAC	Copper-catalyzed azide-alkyne cycloaddition
DCDPH	*N,N'*-dichlorodiphenylhydantoin
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DHQD	10,11-Dihydroquinidine or 9-O-10,11-Dihydroquinidinyl
DHQN	10, 11-Dihydroquinine or 9-O-10,11-Dihydroquininyl
DIAD	Diisopropyl azodicarboxylate
DIPEA	Diisopropylethylamine
DKR	Dynamic kinetic resolution
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
DVB	Divinylbenzene
eCD	Epicinchonidine
eCN	Epicinchonine
ee	Enantiomeric excess

EGDMA	Ethylene glycol dimethacrylate
eQD	Epiquinidine
eQN	Epiquinine
Equiv.	Equivalent
ESI-MS	Electron spray ionization mass spectrometry
Et.	Ethyl
FMOC	Fluoren-9-ylmethoxycarbonyl
GC	Gas chromatography
GLC	Gas liquid chromatography
HEMA	Hydroxyethylmethacrylate
HIPE	High-internal phase emulsion
HPLC	High-pressure liquid chromatography
IED-DA	Inverse electron-demand Diels-Alder reaction
IL’s	Ionic liquids
IPB	Insoluble polymer bound
IR	Infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
KR	Kinetic resolution
MCM-41	Mobil Catalytic Material Number 41
MMA	Methyl methacrylate
MTBE	Methyl tert-butyl ether
NMO	*N*-Methylmorpholine-N-oxide
NMP	*N*-Methylpyrrolidone; solvent
NMR	Nucler magnetic resonance spectroscopy
PEG	Poly(ethylene glycol)
PHAL	Phthalazine-1,4-diyl-
PMHS	Poly(methylhydrosiloxane)
PS	Polystyrene
PTC	Phase transfer catalyst
PVA	Poly(vinyl alcohol)
PYZ	Pyridazine
QD	Qunidine or 9-O-Qunidinyl
QN	Quinine or 9-O-Quininyl

(QD)P	Propargyl quinidine
(QD)P	Propargyl quinine
R_f	Retention factor
ROESY	Rotating-frame Overhauser enhancement spectroscopy
RTILs	Room temperature ionic liquids
SPAN-80	Sorbitan monooleate emulsion stabilizer
SPPS	Solid-phase peptide synthesis
TBHP	Tert-butylhydroperoxide
TCCA	Trichloroisocyanuric acid
TLC	Thin layer chromatography
TMS	Tetramethylsilane, also Trimethylsilyl
UV	Ultra violet
VBC	Vinylbenzyl chloride

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

CHAPTER -1- INTRODUCTION

General introduction

Asymmetric synthesis[1] is continuously performed by Nature in a very clean manner with the help of enzymes.[2] From the research and development (R&D) and organic chemical industry point of view, the challenge is often to replace enzymes with compounds (catalysts) that are available from natural sources, or can be easily prepared in the laboratory, and that may display similar selectivity but higher stability, lower cost, and wider substrate scope than the former.

Historically, this goal has been pursued since the beginning of 20th century, with *Cinchona* alkaloids used as early as 1913 in a pioneering example (formation of enantioenriched cynohydrins)[3a] of what has then become known as 'organocatalysis'.[4,8] Afterwards, the 50's of the past century witnessed the first serious attempts to exploit chirally modified metal catalysts,[5] and through the admirable efforts in the 70's, 80's, and 90's, opened the way to the establishment of asymmetric catalysis as a key technology for satisfying the increasing demand of enantiopure compounds from the pharmaceutical industry as well as from the agrochemicals, fragrances and flavors fields.[6]

These achievements, culminating in the Nobel Prize shared by William S. Knowles, Ryoji Noyori, and K. Barry Sharpless in 2001 in recognition of their work on homogeneous asymmetric hydrogenation and oxidation reactions,[7] render asymmetric catalysis a mature but still growing branch of science, with hundreds of new catalytic systems and applications reporting each year.

---

[1] Asymmetric synthesis is a reaction or reaction sequence that selectively creates one configuration of one or more new stereogenic elements by action of chiral reagents or auxiliary, acting on heterotopic faces, atoms, or groups of a given substance. Gawley, R. E.; Aube, J.; Editors. *Principles of Asymmetric Synthesis.*; Elsevier, **1996**

[2] **a)** Schmid, R. D.; Verger, R. *Angewandte Chemie International Edition* **1998**, *37*, 1608-1633; **b)** Kazlauskas, R. J.; Bornscheuer, U. T. *Hydrolases in Organic Chemistry*, Wiley-VCH, Weinheim, Germany, **1999**; **c)** Boichem, Z.; Faber, K. *Biotransformations in Organic Chemistry*, Springer, Berlin, 4th Ed. **2000.**

[3] Bredig, G.; Fiske, P. S. *Biochemische Zeitschrift* **1913**, *46*, 7–23.

[4] **a)** Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481-2495; **b)** Dalko, P. I.; Moisan, L. *Angewandte Chemie, International Edition* **2004**, *43*, 5138-5175; **c)** Berkessel, A.; Groerger, H. *Asymmetric Organocatalysis.*; Wiley-VCH Verlag GmbH, **2005**; **d)** Buckley, B. R.; Farah, M. M. *Annual Reports Section "B" (Organic Chemistry)* **2011**, *107*, 102-117.

[5] **a)** Akabori, S.; Sakurai, S.; Izumi, Y. *Nature*, **1956**, *178*, 323-324; **b)** Izumi, Y. *Advances in Catalysis* **1983**, *32*, 215-271; **c)** Tai, A.; Harada, T. *in Thailand Metal Catalysts*, Editor; Y. D. Iwasawa, Reidel, Dordrecht,The Netherlands, **1986**, 265-285

[6] **a)** Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons Inc.: New York, **1994**; **b)** Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, **1999**; Vol. 1-3; **c)** Ojima, I.; Editor. *Catalytic Asymmetric Synthesis, Third Edition.*; John Wiley & Sons, Inc., **2010**; **d)** See Ref.14c; **d)** Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Advanced Synthesis & Catalysis* **2011**, *353*, 1825-1864.

[7] **a)** Knowles, W. S. *Angewandte Chemie International Edition* **2002**, *41*, 1999-2007; **b)** Noyori, R. *Angewandte Chemie International Edition* **2002**, *41*, 2008-2022; **c)** Sharpless, K. B. *Angewandte Chemie International Edition* **2002**, *41*, 2024-2032.

However, when the attention is focused on the practical outcome of these continuing efforts, it can be concluded that just a very small fraction of known catalytic systems actually meet the requirements for large-scale use.[8] In many cases the origin of this discrepancy can be traced back to the relatively high loading of the reported catalysts that, depending on the specific application, can be as large as 10-50 mol%. In a real production environment this often raises problems that range from the need of complex schemes for the purification of the product, to the mandatory recovery of the expensive components of catalytic system (e.g. chiral ligands or metal compounds).

In general, these problems tend to be less severe in the case of heterogeneous asymmetric catalysts that, according to Blaser, can be classified as:[9]

(a) Heterogeneous achiral catalysts made enantioselective by modification with a chiral auxiliary.

The most representative and extensively studied examples from this class are the Raney-nickel modified with tartaric acid (TA-MRNi, Izumi's catalyst)[10] and Pt modified with alkaloids (mainly *Cinchona* systems, Orito's catalyst).[11] Both systems find use in the asymmetric hydrogenation of carbonyl compounds, with the former mainly indicated for β-dicarbonyl substrates and the latter for α-ketoderivatives. Besides, a few reports on the use of chirally modified metal oxides for other applications have also appeared.[12]

(b) Insoluble enantioselective systems with no heterogeneous or homogeneous precedent.

Generally, these are the macromolecular systems where activation and stereocontrol are connected to supramolecular effect. This is the case, e.g., of the polyaminoacids for the Julià-Colonna epoxidation of electron-poor olefins or the cyclic dipeptides for the asymmetric hydrocyanation of aldehydes, both of which appear to work well only in a gelled state.[13] Chirally-imprinted organic polymers have also been studied as

[8] Cole-Hamilton, D. J. *Science* **2003** *299* 1702-1706.
[9] Blaser , H. U.; Pugin. B.; Studer, M. in Ref. 14a, pp 1-17.
[10] **a)** Osawa, T.; Harada, T.; Tai, A. *Catalysis Today* **1997**, *37*, 465-480; **b)** Tai, A.; Sugimura, T. in Ref. 14a, pp 173-209.
[11] **a)** Blaser, H.-U.; Jalett, H.-P.; Muller, M.; Studer, M. *Catalysis Today* **1997**, *37*, 441-463; **b)** Baiker, A. in Ref. 14a, pp 155-171.
[12] **a)** Choudari, B. M.; Valli, V. L. K.; Durga Prasad, A. *Chemical Communications* **1990**, 1186-1187; **b)** Meunier, D.; Piechaczyk, A.; de Mallmann, A.; Basset, J.-M. *Angewandte Chemie* **1999**, *111*, 3738-3741; **c)** Hutchings, G. J. *Chemical Communications* **1999**, 301-306.
[13] **a)** North, M. *Synlett* **1993**, 807-820; **b)** Berkessel, A.; Gasch, N.; Glaubitz, K.; Koch, C. *Organic Letters* **2001**, *3*, 3839-3842; **c)** Whitcombe, M. J.; Alexander, C.; Vulfson, E. N. *Synlett* **2000**, 911-923; **d)** Wulff, G. *Chemical Review* **2002**, *102*, 1-27.

enantioselective catalysts (*plastic antibodies*), together with chiral footprints on silica surfaces and the use of zeolite β, partially enriched in 'polymorph A'.[13c,d]

Despite the easy separation and sometimes, the possibility of re-use, these truly heterogeneous asymmetric catalysts possess however a scope that is very limited in comparison with the large number of known homogeneous systems. In order to conjugate the favorable features of either approach to asymmetric catalysis, since the 70's a very active research topic in the field has hence been the implementation of strategies for the simplified separation and recovery of soluble catalysts and ligands.[14,15] Broadly speaking, these efforts can be subdivided into two main groups, depending on whether the modified catalyst retains its solubility in the reaction medium during the catalysis phase or, on the contrary, is made insoluble.

1.1 Soluble systems[15]

In general, these kind of systems have been developed by introducing functionalities in the original homogeneous catalyst that provide some distinctive feature (e.g. high molecular mass, water or fluorous phase solubility, etc.) in comparison to the other components of the reaction mixture.[15d] By using this approach, the asymmetric transformation can be carried out in a homogeneous manner, often leading to comparable activity and stereoselectivity as the unmodified system. At the end of the reaction, the

[14] For general catalyst recovery, see books: **a)** De Vos, D. E.; Vankelecom, I. F. J.; Jacobs, P. A. Editors. *Chiral Catalyst Immobilization and Recycling, Wiley-VCH: Weinheim*, **2000**; **b)** Benaglia, M.; Editor. *Recoverable And Recyclable Catalysts.*; John Wiley & Sons Ltd., **2009**; **c)** Giacalone, F.; Gruttadauria, M. Editors. *Catalytic Methods in Asymmetric Synthesis*; John Wiley & Sons, Inc., **2011**; for insoluble systems, see: **d)** Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. *Chemical Reviews* **2002**, *102*, 3385-3466; **e)** Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chemical Reviews* **2002**, *102*, 3325-3344; **f)** Salvadori, P.; Mandoli, A.; Pini, D. *XXVII Summer School "A. Corbella"* **2002,** June 17-21, 211-232; **g)** Benaglia, M.; Puglisi, A.; Cozzi, F. *Chemical Reviews* **2003**, *103*, 3401-3430; **h)** Corma, A.; Garcia, H. *Chemical Reviews* **2003**, *103*, 4307-4366; **i)** McMorn , P.; Hutchings, G. J. *Chemical Society Reviews* **2004,** 33 , 108–122; **j)** Cozzi, F. *Advanced Synthesis & Catalysis* **2006**, *348*, 1367-1390; **k)** Benaglia, M. *New Journal of Chemistry* **2006**, *30*, 1525-1533; **l)** Heitbaum, M.; Glorius, F.; Escher, I. *Angewandte Chemie International Edition* **2006**, *45*, 4732-4762; **m)** Trindade, A. F.; Gois, P. M. P.; Afonso, C. A. M. *Chemical Reviews* **2009**, *109*, 418-514; **n)** Kristensen, T. E.; Vestli, K.; Jakobsen, M. G.; Hansen, F. K.; Hansen, T. *Journal of Organic Chemistry* **2010**, *75*, 1620-1629; **o)** *Heterogenized Homogeneous Catalysts for Fine Chemicals Production* **2010**, *Vol. 33*, P. Barbaro, F. Liguori, Editors, Springer Netherlands, Dordrecht; **p)** Kristensen, T. E.; Hansen, T. *European Journal of Organic Chemistry* **2010**, *2010*, 3179-3204.

[15] For soluble systems, see: **a)** Bayer, E.; Mutter, M. *Nature* **1972**, *237*, 512-513; **b)** Toy, P. H.; Janda, K. D. *Accounts of Chemical Research* **2000**, *33*, 546-554; **c)** Bergbreiter, D. E.; Sung, S. D. *Advanced Synthesis & Catalysis* **2006**, *348*, 1352-1366; **d)** Bergbreiter, D. E.; Tian, J.; Hongfa, C. *Chemical Reviews* **2009**, *109*, 530-582; **e)** Chinnusamy, T.; Hilgers, P.; Reiser, O. In Ref. 14a; pp 77-100; **f)** Astruc, D.; Chardac, F. *Chemical Reviews* **2001**, *101*, 2991-3024; **g)** Méry, D.; Astruc, D. *Coordination Chemistry Reviews* **2006**, *250*, 1965-1979; **h)** Astruc, D. *Tetrahedron: Asymmetry* **2010**, *21*, 1041-1054; **i)** Pu, L. *Chemistry - A European Journal* **1999**, *5*, 2227-2232; **j)** Pu, L. *Macromolecular Rapid Communications* **2000**, *21*, 795-809; **k)** Madhavan, N.; Jones, C. W.; Weck, M. *Accounts of Chemical Research* **2008**, *41*, 1153-1165; **l)** Sakthivel, S.; Punniyamurthy, T. *Tetrahedron: Asymmetry* **2010**, *21*, 2834-2840; **m)** Bergbreiter, D.E.; Liu, Y.-S.; Osburn, P.L. *Journal of American Chemical Society* **1998**, 120, 4250–4251; **n)** Bergbreiter, D. E. In Ref. 14a; pp 117-153.

distinctive property can then be exploited for aiding the separation and recovery of the modified catalyst. The main strategies depending on this concept are briefly summarized below.

1.1.1. ***Molecularly enlarged soluble systems:*** [15a-e] Soluble polymers have been used as catalyst 'supports' since the pioneering work of Bayer and Mutter in the early 1970's.[15a] Most of the work in this direction has involved the use of poly(ethylene glycol) (PEG) or polystyrene (PS) as the macromolecular material,[14h,15a-e] but dendrimers,[15f-h] linear chiral polymers,[15i-l] and thermomorphic polymers[15m,n] have also been used. As anticipated, these molecularly enlarged catalysts may have a solution-like behavior under appropriate conditions, but can nonetheless be separated at the end of the reaction by solvent precipitation, membrane filtration, size exclusion chromatography, or temperature-dependant phase separation.

1.1.2. ***Liquid biphasic systems and non conventional reaction media****:* The use of aqueous biphasic systems,[16] ionic liquids (IL's),[17] supercritical fluids,[18] and fluorous solvents[16b,19] are all recovery strategies of current interest. The switch to any of these techniques often involves some drastic modifications in the reaction conditions with respect to the original catalytic procedures. Nonetheless, as far these changes can be tolerated and the confinement of the engineered catalyst realized in a phase different from the one containing the reaction products, an effective separation – normally by using of two immiscible liquids - may result. As in the previous case, the advantage of these approaches is that the catalyst actually operates as a homogeneous one. Even here, however, a satisfactory phase distribution usually requires some extensive modification of the original catalytic system by, e.g., introducing suitable hydrophilic, polar, ionic, or fluorous tag groups.

1.2 Insoluble systems

At variance with the strategies discussed in the previous paragraph, frequently needing dedicated instrumentation (e.g. a membrane reactor) or changes in the reaction

[16] **a)** Cornils, B.; Herrmann, W. A.; *Aqueous-Phase Organometallic Catalysis, 2nd Ed;* Wiley-VCH Verlag GmbH&Co. KGaA, Weinheim, Germany, **2004**; **b)** Pozzi, G.; Shepperson, I. *Coordination Chemistry Reviews* **2003**, *242*, 115-124.

[17] **a)** Malhotra, S. V.; Kumar, V.; Parmar, V. S. *Current Organic Synthesis* **2007**, *4*, 370-380; **b)** Xu, L.; Xiao, J. In Ref. 14b, pp 259-300; **c)** Ni, B.; Headley, A. D. *Chemistry - A European Journal* **2010**, *16*, 4426-4436.

[18] **a)** Jessop, P. G.; Ikariya, T.; Noyori, R. *Chemical Reviews* **1999**, *99*, 475-494; **b)** Leitner, W. *Accounts of Chemical Research* **2002**, *35*, 746-756; **c)** Cole-Hamilton, D. J. *Advanced Synthesis & Catalysis* **2006**, *348*, 1341-1351; **d)** Ogawa, C.; Kobayashi, S. In Ref. 6c; pp 1-35.

[19] **a)** Fish, R. H. *Chemistry - A European Journal* **1999**, *5*, 1677-1680; **b)** P. Barthel-Rosa, L.; A. Gladysz, J. *Coordination Chemistry Reviews* **1999**, *190-192*, 587-605; **c)** Soos, T. In Ref. 14b; pp 179-198.

conditions, the separation, and recovery of insoluble catalyst can be attained by much simpler and more general procedures, like decantation, filtration, or centrifugation. These techniques correspond to standard unit operations in the chemical industry and appear, therefore, particularly appealing for large-scale asymmetric synthesis. Moreover, insoluble systems are potentially well fit for continuous-flow processes, as an alternative to the traditional 'round-bottom flask' concept.[20]

Not surprisingly, these features stimulated a great deal of work on the *immobilization* of soluble systems onto (or within) insoluble supports, which resulted into a large number of heterogenised homogeneous catalysts reported in the literature to date.[14] In addition to the two cases discussed above, these *heterogenized* systems can be considered a third class of insoluble enantioselective catalyst, with the same favorable recovery properties of the truly heterogeneous ones but a comparatively large versatility.[11]

In this respect, it should be noted that the concept of heterogenizing a soluble catalyst is apparently a very simple and general one and, as such, should prove effective in a number of circumstances. Nonetheless, the experience accumulated in the course of more than four decades demonstrated that the successful implementation of this strategy requires to pay attention to several issues, the most important of which are briefly discussed in the next paragraphs.

1.2.1. *Support type*

In any case of immobilization, the support material needs to be thermally, chemically, and mechanically stable under the conditions of the catalytic process. Moreover, its structure should not interfere with the catalyzed reaction[21] and the active sites should be easily accessible, and usually also well dispersed. Generally, this requires the support to have a reasonably high surface area and an appropriate three-dimensional structure to allow the unhindered diffusion to and from the active sites.[22]

[20] Mak, X. Y.; Laurino, P.; Seeberger, P. H. *Beilstein Journal of Organic Chemistry* **2009**, *5*, 19.

[21] In some cases a favorable interaction with the support was observed: see for example **a)** Johnson, B. F. G.; Raynor, S. A.; Shephard, D. S.; Mashmeyer, T.; Mashmeyer, T.; Thomas, J. M.; Sankar, G.; Bromley, S.; Oldroyd, R.; Gladden, L.; Mantle, M. D. *Chemical Communications* **1999**, 1167-1168; **b)** Song, C. E.; Lim, J. S.; Kim, S. C.; Lee, K.-J.; Chi, D. Y. *Chemical Communications* **2000**, 2415-2416; **c)** Raynor, S. A.; Thomas, J. M.; Raja, R.; Johnson, B. F. G.; Bell, R. G.; Mantle, M. D. *Chemical Communications* **2000**, 1925-1926; **d)** Fan, Q.-H.; Wang, R.; Chan, A. S. C. *Bioorganic & Medicinal Chemistry Letters* **2002**, *12*, 1867-1871.

[22] **a)** Song, C. E.; Lee, S.-g. *Chemical Reviews* **2002**, *102*, 3495-3524; **b)** Leadbeater, N. E.; Marco, M. *Chemical Reviews* **2002**, *102*, 3217-3274; **c)** Vankelecom, I. F. J.; Jacobs, P. A. In Ref. 14a; p 19; **d)** Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. *Chemical Reviews* **2002**, *102*, 3385-3466.

Inorganic supports such as silica, zeolites, alumina, zirconia, ZnO, clays, etc[22] often meet the latter requirements as, normally, they posses a very large surface area and do not require to swell in the reaction medium. However, stability may be a problem under reaction conditions and, as discussed also in 1.4.1, the highly polar oxidic structure of these materials can cause unwanted interactions with the catalytic system.[23]

In contrast, cross-linked organic polymers posses somewhat worse mechanical and thermal characteristics,[22a] but they are readily available in a range of structures and can be easily modified and tailored to attain specific properties and functions.[14g,p 24] Moreover, the nature of the macromolecular backbone may be usually chosen as to behave like an innocent spectator in the catalyzed reaction. On the contrary, the main concerns with this kind of supports may include the chemical stability of ill-designed materials [25] or, more commonly, limitations in the accessibility of the catalytic sites.

In order to solve the latter problem two general strategies can be pursued, relying on the use of either a gel-type support (like chloromethylated PS containing 1-2% of divinylbenzene, known as Merrifield's resin) or a macroporous material, respectively.[26] In the former case, the slightly cross-linked resin has to swell in the reaction medium in order to bring the polymer chains apart and to allow the free diffusion of reactants and products in the three-dimensional structure; in turn, this requires the choice of a material backbone with a good compatibility with the reaction solvent. In contrast, macroporous resins are normally highly cross-linked materials, with a permanent and relatively high surface area even in the dry state. As such, they do not need to swell for permitting the unhindered access to the supported catalytic sites and can therefore be used also in solvents that are non compatible with the polymer material.

1.2.2. *Nature of the catalyst-support linkage.*

Also on dependence on the nature of the support, four distinct methodologies have been developed for the heterogenization of homogeneous catalysts (Figure 1).[27]

[23] Rechavi, D.; Albela, B. n.; Bonneviot, L.; Lemaire, M. *Tetrahedron* **2005**, *61*, 6976-6981.
[24] **a)** Hodge, P. *Industrial & Engineering Chemistry Research* **2005**, *44*, 8542-8553; **b)** Wang, Z.; Yang, R. L.; Zhu, J. D.; Zhu, X. X. *Science China: Chemistry* **2010**, *53*, 1844-1852.
[25] Mandoli, A.; Pini, D.; Fiori, M.; Salvadori, P. *European Journal of Organic Chemistry* **2005**, *2005*, 1271-1282.
[26] Sherrington, D. C. *Chemical Communications* **1998**, 2275-2286.
[27] **a)** Trewyn, B. G.; Chen, H.-T.; Lin, V. S.-Y. In Ref. 14b, pp 15-47; **b)** McMorn, P.; Hutchings, G. J. *Chemical Society Reviews.* **2004**, *33*, 108-122.

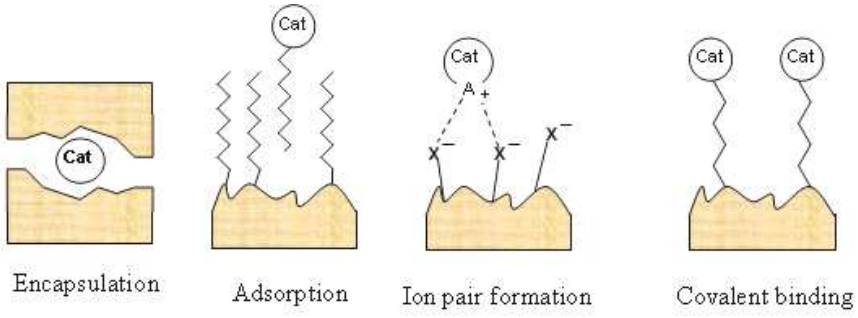


Figure 1. General methodologies for catalyst immobilization

Encapsulation. Encapsulation is the only technique in which no attractive interaction between the catalyst and the support is needed.[27] In this kind of materials, the catalyst is trapped within a three-dimensional insoluble structure, whose exit windows have a smaller size than the catalyst itself and thus prevent its outward diffusion into the bulk of the solution.

The supported system can be prepared by either *i*) assembling the catalyst within the pores of the preformed support ("ship in the bottle" technique) or *ii*) assembling the support around the catalyst ("Van der Waals wrapping"). Generally, the first approach is used when the catalyst can be prepared by joining smaller sub-units (e.g. formation of a metal-salen complex in the cages of a zeolite) and the support is stable under the conditions required for this latter task. By contrast, the second technique may be chosen when the catalyst is stable under the conditions used for preparing the support, which may consist in the vulcanization of silicone prepolymers or in the formation of a siliceous matrix.[28]

Although this kind of systems are in principle mimic of the corresponding homogeneous catalysts, as they are not chemically bound to the support, restricted diffusion of reactants and products (especially in the case of the former approach) or leaching (in the case of the latter) can be serious drawbacks here.

Adsorption. The anchoring by non-covalent interactions of a chiral ligand or metal complex onto the surface of a support is arguably one of the most straightforward methods for achieving the heterogenization of an asymmetric catalyst.[27a] However, as long as the immobilization depends on weak interactions - which may range from Van der Waals forces

[28] **a)** Ogunwumi, S. B.; Bein, T. *Chemical Communications* **1997**, 901-902; b) Blum, J.; Avnir, D.; Schumann, H. *ChemTech* **1999**, *29*, 32-38; c) Janssen, K. B. M.; Laquiere, I.; Dehaen, W.; Parton, R. F.; Vankelecom, I. F. J.; Jacobs, P. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3481-3487.

to hydrogen bonding-leaching is normally a major problem of the technique.[29] This drawback limits the recycling of the catalyst and determines the contamination of the crude product. [27]

In a variation of the direct adsorption outlined above and the liquid biphasic systems discussed in the paragraph 1.1.2, the concept of "supported liquid phase" has been introduced recently.[30] This approach, that represents a hybrid of homogeneous and heterogeneous catalysis, relies on the confinement of the catalyst within a thin film of a suitable liquid phase adsorbed onto a porous support. As expected, also in this case the main limitations are caused by the need of preventing the leaching of both the supported liquid and the catalyst into the bulk of the reaction mixture. It is therefore not surprising that the examples reported to date appear essentially restricted to the immobilization of highly polar or ionic catalysts (e.g. Box-Cu and sulfonated BINAP-Ru) in similarly polar supported films (e.g. ionic liquids, water, and ethylene glycol).[31]

Ion pairing. Besides resins like some Amberlyst (sulfonated PS) and Nafion (sulfonated perfluoroalkyl polymer), many porous solids like zeolites, zeotypes, ordered mesoporous silicates and layered materials, including clays and hydrotalcites, can act as ion exchangers. This allows the immobilization of enantioselective catalysts, either by exploiting the ionic nature of the chiral substance itself (e.g. a cationic metal complex, an ammonium salt, etc.) or by introducing a suitable ionic group into the structure of an otherwise neutral compound.

Whilst there are some successful examples of heterogeneous enantioselective catalysts prepared by this methodology that exhibited significantly improved catalytic performances with respect to their homogeneous counterparts,[27,32] the main disadvantage of this immobilization strategy is the high mobility of the catalyst within the support. Even if

[29] The stability of the supported catalyst has been sometimes improved by modifying the catalyst and the support to allow strong hydrogen bonding (Ref. 27b). This technique did not seem to find, however, a broad application.

[30] **a)** Riisager, A.; Fehrmann, R.; Haumann, M.; Wasserscheid, P. *Topics in Catalysis* **2006**, *40*, 91-102; **b)** Riisager, A.; Fehrmann, R.; Haumann, M.; Wasserscheid, P. *European Journal of Inorganic Chemistry* **2006**, 695-706 **c)** Van, D., Charlie; Wahlen, J.; Mertens, P.; Binnemans, K.; De, V., Dirk. *Dalton Transactions* **2010**, *39*, 8377-8390; **d)** Steinrueck, H.-P.; Libuda, J.; Wasserscheid, P.; Cremer, T.; Kolbeck, C.; Laurin, M.; Maier, F.; Sobota, M.; Schulz, P. S.; Stark, M. *Advanced Materials* **2011**, *23*, 2571-2587.; **e)** Jutz, F.; Andanson, J.-M.; Baiker, A. *Chemical Reviews* **2011**, *111*, 322-353;

[31] **a)** Wan, K. T.; Davis, M. E. *Journal of Catalysis* **1995**, *152*, 25-30; **b)** Evans, D. A.; Johnson, J. S.; Olhava, E. J. *Journal of the American Chemical Society* **2000**, *122*, 1635-1649

[32] Selke, R.; Haeupke, K.; Krause, H. W. *Journal of Molecular Catalysis* **1989**, *56*, 315-28; **b)** Selke, R.; Capka, M. *Journal of Molecular Catalysis* **1990**, *63*, 319-34; **c)** Langham, C.; Piaggio, P.; Bethell, D.; Lee, D. F.; McMorn, P.; Page, P. C. B.; Willock, D. J.; Sly, C.; Hancock, F. E.; King, F.; Hutchings, G. J. *Chemical Communications* **1998**, 1601-1602.

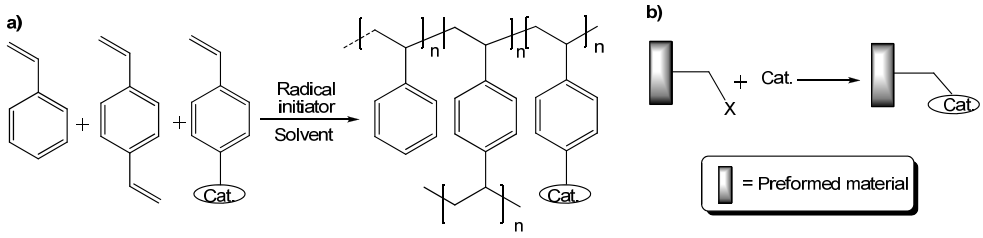
the ion-exchanged materials tend to be more stable than the adsorbed ones, described above, this can still lead to the leaching of active species or to aggregation problems (in particular with metal complexes) that eventually may result in the deactivation of the catalyst.[33]

Covalent anchoring. The covalent binding of a catalyst or a ligand to an insoluble support is one of the most explored and popular approach for designing stable heterogenised asymmetric catalyst. The success of this route, deeply rooted in the Merrifield's idea of solid phase synthesis,[34] can be justified on the basis of the ability of the chiral derivative to bind unalterably to the support regardless of the actual composition of the reaction medium. Thus, properly design insoluble polymer bound (IPB) systems are virtually exempt from leaching of the catalyst (or, in the case of metal complexes, at least of the chiral ligand), without requiring major changes in the reaction conditions. In addition to the possible reduction of activity or stereoselectivity, sometimes observed with heterogenised catalysts, the main disadvantage of this technique is probably the synthetic overhead required for their preparation. This topic will be discussed in more detail in the paragraph 1.5.

1.2.3. *Immobilization techniques for IPB systems*

In the case of encapsulation, adsorption, and ion pairing the preparation procedure is largely dictated by the immobilization strategy itself. On the contrary, the goal of obtaining an IPB system can be tackled by two alternative routes, namely *i*) the (co)polymerization of a 'monomer' bearing the chiral catalyst or ligand (usually with suitable achiral 'diluting monomer' and cross-linking agent, see for example Scheme 1a or *ii*) the anchoring of the chiral derivative onto a preformed insoluble support (Scheme 1b). Interestingly, even if the former approach has been largely employed for the preparation of materials with an organic polymeric backbone, some examples have been also reported where inorganic IPB systems were obtained by this strategy (see for instance the paragraph 1.4).[35]

[33] Andrew J., S. *Journal of Molecular Catalysis A* **2001**, *177*, 105-112.
[34] Merrifield, R. B. *Journal of American Chemical Society* **1963**, *85*, 2149–2154.
[35] See ref. no. 70, 71, 72, 73, 77, 88



Scheme 1. a) Catalyst prepared by radical copolymerization of styrene monomers. b) Anchoring on to the preformed support

Either of the two options has its own merits and drawbacks. For example, the copolymerization route often allows to obtain precisely tailored materials, but it normally requires to work with sensitive 'monomers' and may lead to the burial of some chiral units inside highly cross-linked regions. On the contrary, the anchoring approach generally results in chiral units that are well accessible by the reagents in solution, but it is somewhat limited by the availability of suitable functionalized supports and by the efficiency of the anchoring step itself.[14i, 36]

1.2.4. *Use of a spacer group, grafting, and tethering.*

Another design element that has to be taken into consideration when planning the IPB heterogenization of an asymmetric catalyst is the opportunity of spacing the chiral units from the support surface. The aim here would be to provide the catalyst with an optimal solution-like behaviour by reducing any possible adverse effect of the polymeric support backbone. In general, this goal is pursued by placing a suitable 'tethering' (or 'spacer') group between the chiral unit and the actual linking site on the support. This can be done either by embedding the spacer into the structure of the functional monomer, in the case of a copolymerization route, or by introducing it in the course of the anchoring sequence.[37]

In conclusion, it has to be noted that most of the aspects discussed above are well documented when the specific case of IPB *Cinchona* derivatives is considered.[27b] Given the central interest of these topics for the present Thesis, after a brief outline of the importance of *Cinchona* alkaloids in organic chemistry they will be discussed in more detail in the 1.4.

[36] Itsuno, S.; Sakurai, Y.; Ito, K.; Maruyama, T.; Nakahama, S.; Frechet, J. M. J. *Journal of Organic Chemistry* **1990**, *55*, 304-310.

[37] In the case of the anchoring strategy, a distinction has been made in the literature between *grafting* and *tethering*, depending on whether the chiral derivative is linked to the support directly or through a spacer group, respectively. See for example: **a)** Maschmeyer, T.; Rey, F.; Sankar, G.; Thomas, J. M. *Nature (London)* **1995**, *378*, 159-62; **b)** Burch, R.; Cruise, N.; Gleeson, D.; Tsang, S. C. *Chemical Communications* **1996**, 951-952; **b)** Subba Rao, Y. V.; E. De Vos, D.; Bein, T.; A. Jacobs, P. *Chemical Communications*, **1997**, 355-356; **c)** Tian, Z.-R.; Tong, W.; Wang, J.-Y.; Duan, N.-G.; Krishnan, V. V.; Suib, S. L. *Science* **1997** *276* 926-930; **d)** Abramson, S. b.; Bellocq, N.; Lasperas, M. *Topics in Catalysis* **2000**, *13*, 339-345 (and ref. cited therein).

1.3 *Cinchona* Alkaloids in Chemistry: A brief overview

The *Cinchona* alkaloids (Figure 2) are intriguing organic compounds obtained from the bark of *Cinchona* trees (Figure 3). These substances have a comprehensive history, dating back to the early 17th century when bark extracts were first introduced into the European market following the discovery of their antimalarial properties.[38]

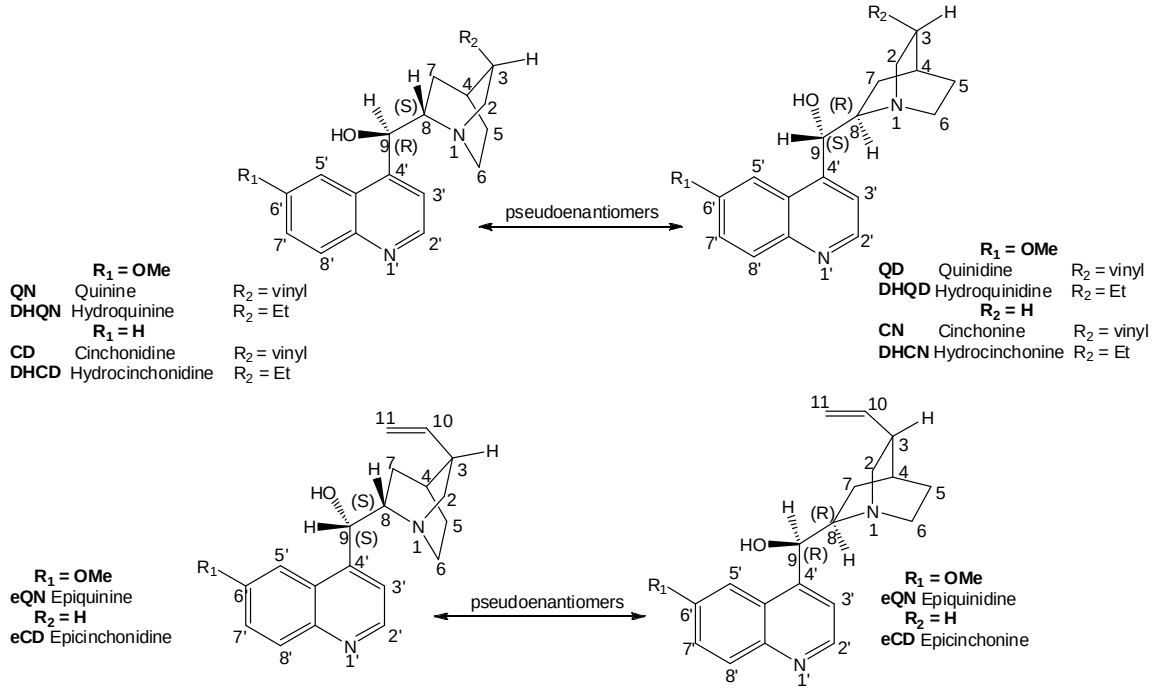


Figure 2. Structure and numbering scheme of *Cinchona* alkaloids.

Figure 3. *Cinchona* tree a) Flowering *Cinchona* tree, b) Bark of *Cinchona* tree, c) Flowers of *Cinchona* tree

[38] **a)** Tropical plants database at http://www.rain-tree.com/plants.htm. *Raintree Nutrition*: Carson City; **b)** Yeboah, E. M. O.; Yeboah, S. O.; Singh, G. S. *Tetrahedron* **2011**, *67*, 1725-1762; **c)** Yang, F.; Hanon, S.; Lam, P.; Schweitzer, P. *The American Journal of Medicine* **2009**, *122*, 317-321; **d)** Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, *2001*, 961-998.

Today, approximately 700 metric tons of *Cinchona* alkaloids are extracted annually from the bark of *Cinchona ledgeriana*[39] and find applications as anticancer, analgesic, germicide, fungicide, insecticide and antibacterial agents, as well as digestion stimulants and bitter flavoring agents for some drinks. Quinidine (QD), is also employed in modern medicine in the treatment of abnormal heartbeat and for relieving leg cramps.[38]

The interest of the organic chemists for *Cinchona* alkaloids began in 1820 when Pelletier and Caventou isolated the basic chemical that provides the highest antimalarial effect of the bark extracts and named it 'Quinine' (QN).[38,39] Shortly after (1853) Pasteur discovered the potential of these compounds as chiral resolving agent[40] and opened the way to a large number of studies where the *Cinchona* alkaloids were employed for this purpose.[39]

As anticipated at the beginning of the Chapter, another major chemical application of these natural chiral derivatives followed in 1913, when Bredig and Fiske first reported the use of the alkaloids for promoting an enantioselective transformation.[3] In particular, the German chemists demonstrated that in the presence of QN as catalyst the addition of HCN to benzaldehyde gave optically active cyanohydrins. Although the optical yields were just in the range of < 10%, they also observed that the reaction in the presence of QD afforded a prevalence of the opposite cyanohydrin product, thus highlighting the occurrence of *Cinchona* alkaloids as pseudoenantiomeric pairs (*vide infra*).

Since then many other catalytic uses of *Cinchona* alkaloids have been disclosed in the literature, including their use as chiral Pt modifiers in the Orito's heterogeneous hydrogenation system[41] and as organocatalysts for asymmetric conjugate additions and ketene [2+2] cycloaddition reactions, developed by Wynberg and co-workers.[42a,b]

However, it was in last twenty years that these chiral auxiliaries experienced an explosive growth of applications, milestoned in the late 80's by the introduction of 9-*O*

[39] Song, C. E. In *Cinchona Alkaloids in Synthesis and Catalysis*; Wiley-VCH Verlag GmbH & Co. KGaA, **2009**; pp 1-10
[40] **a)** Pasteur, L. *Academie des Sciences* **1853**, 37, 162-165; **b)** Pasteur, L. *Justus Liebigs Annalen der Chemie* **1853**, *88*, 209-214.
[41] **a)** Orito, Y.; Imai, S.; Niwa, S. *Journal of Chemical Society of Japan* **1979**, 1118–1120; **b)** Orito, Y.; Imai, S.; Niwa, S. *Journal of Chemical Society of Japan*, **1980**, 4, 670-672.
[42] **a)** Wynberg, H.; Helder, R. *Tetrahedron Letters* **1975**, *16*, 4057-4060; **b)** Wynberg, H.; Staring, E. G. J. *Journal of the American Chemical Society* **1982**, *104*, 166-8.

derivatives as ligands in the Os-catalyzed asymmetric dihydroxylation of olefins (AD)[43] and, since 2000, by the renewed interest in their use as organocatalysts.[38b,44, 45]

In fact, while the former process had a great impact on the field of asymmetric synthesis, eventually leading to the already mentioned award of the Nobel Prize to Sharpless,[7c] most of the present efforts appear focused on metal-free applications of the *Cinchona* alkaloids. These investigations include examples where the pristine alkaloids or their derivatives act as chiral Lewis acid, Bronsted base, or nucleophilic catalysts in a wealth of mechanistically diverse asymmetric transformations.[38b,44,45]

The reasons of the success of this class of natural compounds, that let them ranking amongst the so-called 'privileged chiral auxiliaries',[38b,45f] are deeply buried inside their structure. In this respect, a first distinctive feature is the occurrence of the alkaloids in pair of stereoisomers that share the same configuration at N1, C3, and C4 but mirror each other at C8 and C9 (i.e. QD and QN; CD and CN). In spite of diastereomeric relationship, the fact that the catalytic properties are mainly associated with the C8/C9 region almost invariably leads to the pseudoenantiomeric behavior noted above, *i.e.* the attainment of an opposite sense of asymmetric induction when, e.g., QD or QN are alternatively used as catalysts or ligands. The judicious choice of the alkaloid pseudoenantiomer in a given asymmetric transformation allows therefore to obtain either of the two possible enantiomeric products. Although the enantiomeric purity of the latter may vary somewhat in dependence of which particular pseudoenantiomer is used (because of the diastereomeric -and not enantiomeric- relationship between the alkaloid cores),[46] this feature is nonetheless a clear advantage over most of the other chiral auxiliaries from natural sources, which are typically available as one stereoisomer only.

The second favorable attribute of the *Cinchona* alkaloids is a multifunctional structure that embeds:

[43] **a)** VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Letters* **1976**, *23*, 1973-1976; **b)** Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *Journal of the American Chemical Society* **1988**, *110*, 1968-1970; **c)** Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chemical Reviews* **1994**, *94*, 2483-2547.

[44] **a)** Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 7, 961-998; **b)** Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, 299, 1691-1693.

[45] **a)** Houk, K.N. and List, B. *Accounts of Chemical Research* **2004**, 37, 487; **b)** *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH Verlag GmbH, Weinheim, **2005**; **c)** *Enantioselective Organocatalysis*, Wiley-VCH Verlag GmbH, Weinheim, **2007**; **d)** List, B. *Chemical Reviews* **2007**, 107, 5413; **e)** Lee, J. W.; Jang, H. B.; Lee, J. E.; Song, C. E. In *Cinchona Alkaloids in Synthesis and Catalysis*; Wiley-VCH Verlag GmbH & Co. KGaA, 2009; pp 325-357; **f)** Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 8, 1229-1279.

[46] Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *Journal of the American Chemical Society* **1989**, *111*, 8069-8076.

- a Bronsted acidic site, represented by the 9-*O* hydroxyl group;
- a quinoline ring that, besides providing steric hindrance, can get involved in π-π interactions;
- a very basic and nucleophilic quinuclidine nitrogen atom (N1) that, despite the presence of bulky groups nearby, appears to be implicated in the catalysis of most of the reactions promoted by the pristine alkaloids or their derivatives.

On the other hand, the same multifunctional nature of the native alkaloids allows also a number of structural changes. Normally exploited for the fine-tuning of the alkaloid architecture for specific catalysis applications, these modifications may include:[45f]

- derivatization at 9-*O*, most often with conversion into ether and ester monomeric derivatives (Figure 4a), or aromatic ether bridged dimers (Figure 4b).[45f] The latter type of compounds, introduced by the Sharpless group for the AD reactions, are particularly interesting as they are finding growing applications as organocatalysts. For instance, the phthalazine (**6**) and pyridazine (**7**) ethers have been used in metal-free oxindoles α-amination,[47] halolactonization,[48] conjugate addition,[49] etc. Similarly the anthraquinone derivatives (**8**) proved highly effective in various 'dynamic kinetic resolution' (DKR) reactions,[50] *meso*-anhydride alcoholysis,[51] allylic alkylation,[52] etc. (for the details of most of these reactions, see the Chapter 5).

[47] **a)** Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Organic Letters* **2009**, *11*, 3874-3877; **b)** Bui, T.; Borregan, M.; Barbas, C. F. *The Journal of Organic Chemistry* **2009**, *74*, 8935-8938.
[48] Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *Journal of the American Chemical Society* **2010**, *132*, 3298-3300.
[49] Bella, M.; Jorgensen, K. A. *Journal of the American Chemical Society* **2004**, *126*, 5672-5673.
[50] Tang, L.; and Deng, L. *Journal of American Chemical Society* **2002**, 124, 2870–2871
[51] **a)** Hiratake, J.; Yamamoto, Y.; Oda, J. *Journal of the Chemical Society, Chemical Communications* **1985**, 1717-1719; **b)** Aitken, R. A.; Gopal, J.; Hirst, J. A. *Journal of the Chemical Society, Chemical Communications* **1988**, 632-634; **c)** Yang, W.; Wei, X.; Pan, Y.; Lee, R.; Zhu, B.; Liu, H.; Yan, L.; Huang, K.-W.; Jiang, Z.; Tan, C.-H. *Chemistry A European Journal* **2011**, *17*, 8066-8070.
[52] Cui, H.-L.; Peng, J.; Feng, X.; Du, W.; Jiang, K.; Chen, Y.-C. *Chemistry A European Journal* **2009**, *15*, 1574-1577.

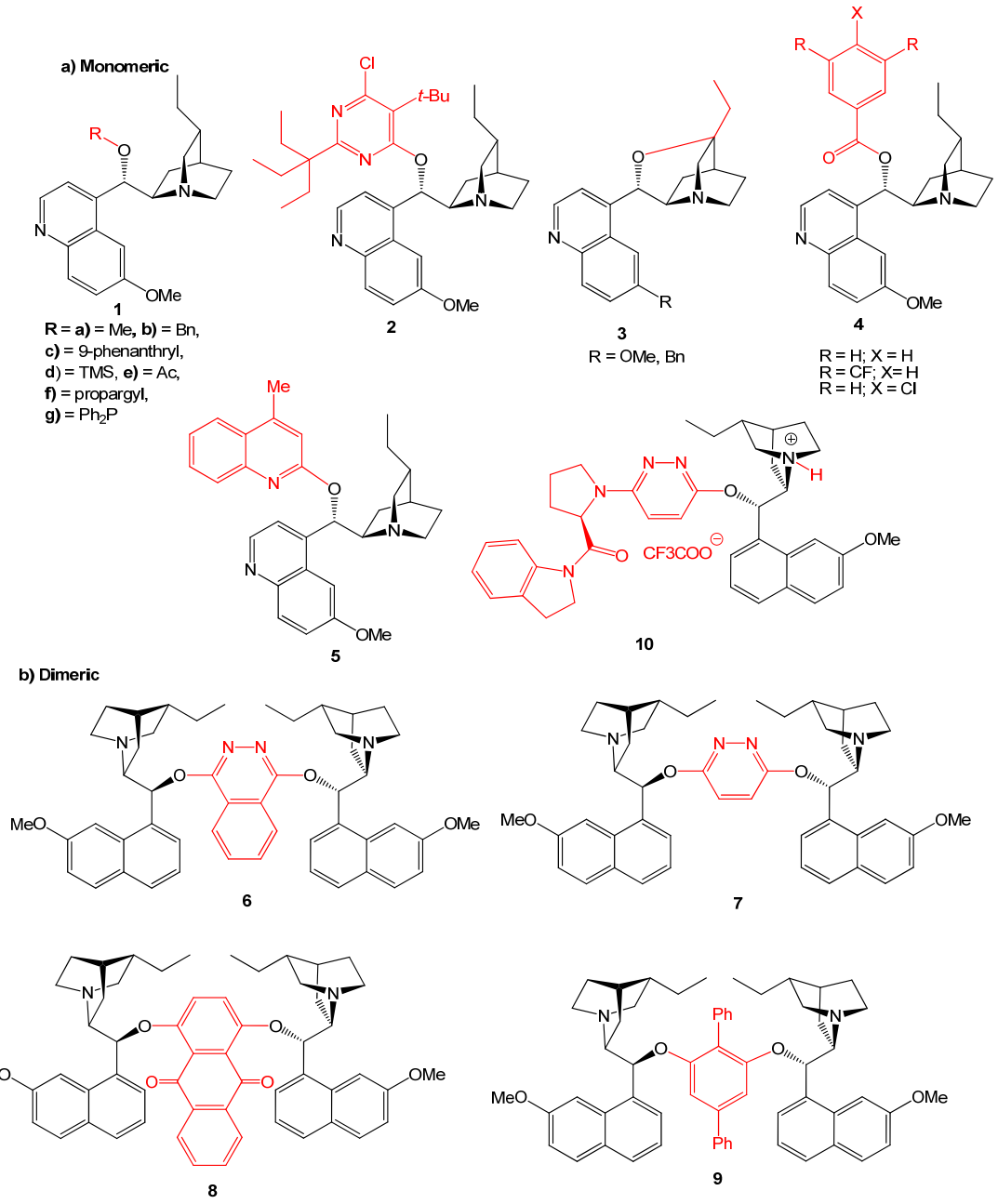


Figure 4. Representative 9-O ether and ester derivatives

- inversion of the OH group at C-9 for obtaining the corresponding alkaloid epimers or, more frequently, conversion into 9-amino(9-deoxy) analogs (**11**). The latter (Figure 5) can be used as catalysts themselves or be further transformed into, e.g., amide or thiourea derivatives (**12-18**) with wide applicability in organocatalyzed asymmetric reactions.[45f,53]

[53] Mukherjee, S.; Yang, J.W.; Hoffmann, S.; List, B. *Chemical Review* **2007,** 107, 5471-5569.

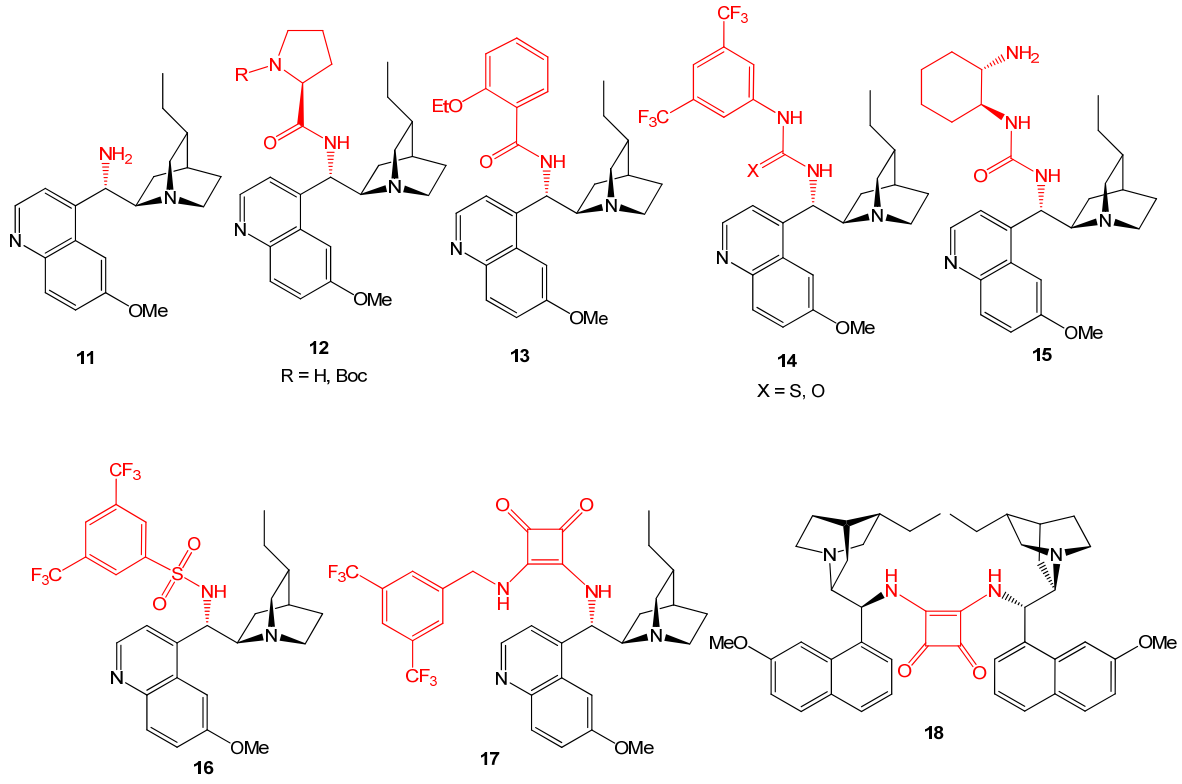


Figure 5. Epi- or nat-9-Amino(9-deoxy)alkaloids and other bifunctional derivatives.

- alkylation of the quinuclidine nitrogen atom (Figure 6) for obtaining monomeric (**19**-**27**) or sometimes dimeric (**28**-**30**) quaternary ammonium salts. Derivatives of this class have generally[54] found use as IPB chiral phase-transfer catalysts (PTC) in the alkylation of carbonyl compounds, epoxidation of enones, Michael addition reactions, etc.[38d; 55]

[54] For a case where a *Cinchona* quaternary ammonium salt was used as a catalyst apparently devoid of any PTC role (asymmetric cyanoformilation of 3,5-dimehoxybenzaldehyde in a monophasic CH_2Cl_2 system), see for example: Chinchilla, R.; Najera, C.; Ortega, F. J.; Tari, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2279-2286.

[55] **a)** Hashimoto, T.; Maruoka, K. *Chemical Review*, **2007**, 107, 5656-5682; **b)** Maruoka, K. *Asymmetric Phase Transfer Catalysis*, Wiley-VCH Verlag GmbH, Weinheim. **2008.**

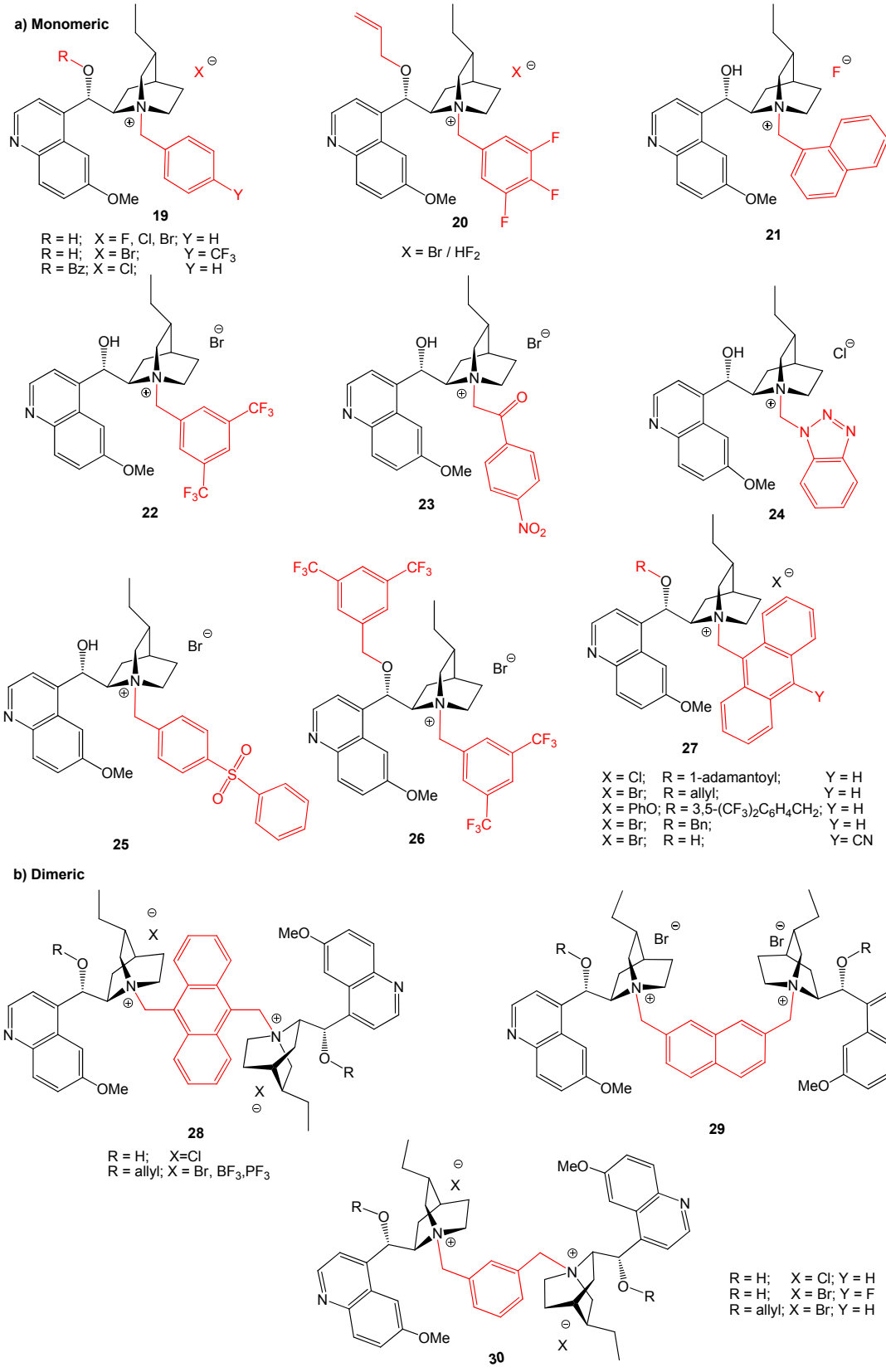


Figure 6. Alkaloid quaternary ammonium salts

- demethylation of the 6'-OMe group (Figure 7) in order to provide an additional Bronsted acidic site (as in **31**) or the opportunity to introduce a strategically placed thiourea or amide group (**32** and **33**). These modified alkaloids have been successfully employed in various asymmetric transformation,[56] like the Henry reaction,[56a] the cyclization of various α-substituted chalcones,[56b] the formation of carbon-sulfur bonds,[56c] and the Aza-Morita–Baylis–Hillman reaction.[56d]

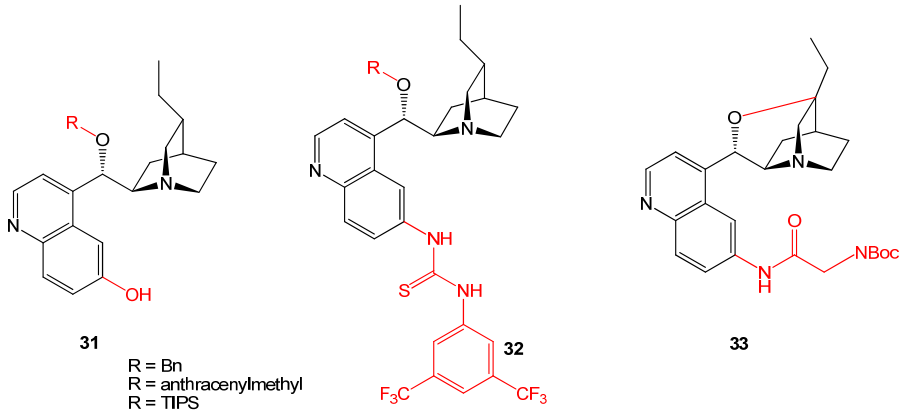


Figure 7. Thiourea and amide C6'-derivatives.

1.4. IPB *Cinchona* alkaloid derivatives

Even if the cost of several *Cinchona* alkaloids is relatively low in comparison with other chiral auxiliaries [e.g. QN, 665 € / mol; QD, 2,060 € / mol (Aldrich 2011 prices)], the same can be hardly said for many commercial derivatives [e.g. $(DHQD)_2PHAL$, ~ 70,000 € / mol; $(DHQD)_2AQN$, ~100,000 € / mol] and for most of those compounds that have to be synthesized in the lab.

Together with the rather high loading required in most of the disclosed applications (e.g. 1 – 20 mol%), this makes the recovery of the chiral auxiliary mandatory for any large scale use. Given the basic nature of the alkaloid core, this task has been often accomplished by a trivial acidic work-up that, when practicable, normally proves quite effective in separating *Cinchona* derivatives from the neutral organic products in the reaction mixture.[57]

[56] **a)** Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angewandte Chemie International Edition* **2006**, *45*, 929-931; **b)** Dittmer, C.; Raabe, G.; Hintermann, L. *European Journal of Organic Chemistry* **2007**, *2007*, 5886-5898; **c)** Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *Journal of the American Chemical Society* **2008**, *131*, 418-419;**d)** Abermil, N.; Masson, G. r.; Zhu, J. *Journal of the American Chemical Society* **2008**, *130*, 12596-12597.

[57] **a)** Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455-3467; **b)** Hang, J.; Li, H.; Deng, L. *Organic Letters* **2002**, *4*, 3321-3324.

Nonetheless, this simple strategy cannot be considered an universal solution for the problem at hand as it turns out to fail under several circumstances.

A first problem in this regard is represented by the high solubility in common organic solvents of the ammonium salts of some alkaloid derivatives, especially of the monomeric type.[58] In a real production environment, this feature has sometimes imposed the adoption of complex purification schemes of the crude product, with multiple extractions being used for reducing the concentration of the alkaloid contaminant to an acceptable level.[59]

Moreover, in some specific transformations the possibility of an acidic work-up is simply precluded by the high sensitivity of the reaction product itself. This is the case, for instance, with the β-lactam products obtained by alkaloid-catalyzed [2+2] ketene-imine addition (see 1.4.2), or the β-ketoamides prepared by the Calter's protocol discussed in more detail in the Chapter 5. Under these conditions, as well as in other conceivable cases where the water solubility or the basic properties of the product would prevent the simple strategy outlined above, the separation and recovery of the alkaloid catalyst or ligand is much less straightforward, with chromatography often remaining as the only viable option.

Given these problems, as well as the general interest in developing continuous-flow process,[60] it is not surprising that the study of more easily recoverable variants of *Cinchona* alkaloids and their derivatives has a long established tradition.[61] Indeed, besides modified soluble systems, excellently reviewed elsewhere,[15,16-19] the history of IPB *Cinchona* catalysts began in 1977 when Hermann and Wynberg covalently bound QN to 2% DVB cross-linked PS and used the resulting materials for catalyzing a Michael addition reaction.[61d,62] Even if a very low optical purity (≤ 11%) was obtained in this pioneering study, the work unequivocally demonstrated the possibility of preparing an enantiomerically enriched product by using a supported alkaloid derivative. This conclusion opened the way

[58] For instance, the partitioning of some alkaloid derivatives (e.g. **1c**) between CH_2Cl_2 and 5% HCl causes the former to be extracted almost completely into the organic layer! See: Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *Journal of Organic Chemistry* **1993**, *58*, 844-849.

[59] See for example: Vittuli, M. *Laurea Thesis*, University of Pisa, **2003**

[60] **a)** Mak, X. Y.; Laurino, P.; Seeberger, P. H. *Beilstein Journal of Organic Chemistry* **2009**, *5*, No. 19; **b)** Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chemical Reviews* **2007**, *107*, 2300-2318; **c)** Jas, G.; Kirschning, A. *Chemistry-A European Journal* **2003**, *9*, 5708-5723.

[61] **a)** Grubhofer, N.; Schleith, L. *Naturwissenschaften* **1953**, *40*, 508; **b)** Yamamuchi, K.; Kinoshita, M.; Imoto, M. *Bulletin of Chemical Society of Japan* **1971**, 44, 3186-3187; **c)** Yamashita, T.; Yasueda, H.; Nakamura, N. *Chemistry Letters* **1974**, 585-588; **d)** Hermann, K.; Wynberg, H. *Helvetica Chimica Acta* **1977**, *60*, 2208-2212.; **e)** Yamashita, T.; Yasueda, H.; Miyauchi, Y.; Nakamura, N. *Bulletin of Chemical Society of Japan* **1977**, 50, 1532-1534.

[62] Actually, the first example of a soluble PS bound *Cinchona* alkaloi dates back to 1953 (ref. 61a), while the first IPB derivative was reported in 1971 (ref.61b). However, none of the two materials was intended to be used for catalysis.

to a wealth of successive studies that, by taking full advantage of the polyfunctional nature of the alkaloid core, of the choice of alternative anchoring techniques, and of the selection of different support materials, eventually led the large family of IPB alkaloid derivatives known today.

With the aim of illustrating state of art at the beginning of the present Thesis, the most representative of these supported ligands and catalysts are briefly described in the following paragraphs. For the purposes of this discussion, the examples will be mainly organized on the basis of the position in the alkaloid core (Figure 8) where the anchoring to the insoluble support actually takes place.

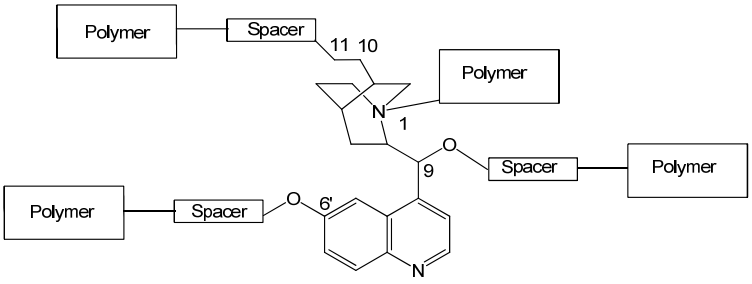


Figure 8. Anchoring sites in the alkaloid core and general architectures of IPB materials.

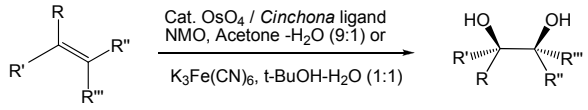
1.4.1. IPB- Cinchona alkaloid derivatives linked at the 10 or 11 position

The vinyl group of the native alkaloids is probably the most frequently exploited site for effecting the attachment to an insoluble support. In general, this choice has the advantage of maintaining the 9-*O* group free for any derivatization may be required, leaving at the same time much flexibility for what it concerns the choice of the immobilization procedure. Indeed, a survey of the literature easily reveals that IPB derivatives anchored through the position 10 or 11 of the alkaloid core have been obtained by all the main covalent strategies discussed in the 1.2. In order to outline the important aspects of the preparation and use in catalysis of the supported *Cinchona* alkaloid, the most representative examples are summarized below.

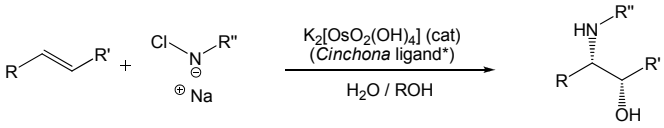
Direct copolymerization of the vinyl group (Figure 10). Despite the reluctance of simple alkenes to undergo radical polymerization, the vinyl group of the *Cinchona* alkaloids can be effectively copolymerized if a suitable electron-poor alkene, like acrylonitrile, is present in the feed mixture. The resulting copolymers (e.g. **34**) are not cross-linked but nevertheless prove sparingly soluble in most of the common organic solvents.[63] This characteristic

[63] **a)** Pini, D.; Rosini, C.; Nardi, A.; Salvadori, P. *Fifth IUPAC Symposium on Organometallic Chemistry Directed Towards Organic Synthesis* (Florence, Oct. 1-6, 1989), Abstract PS1-67; **b)** Moon Kim, B.; Sharpless, K. B.

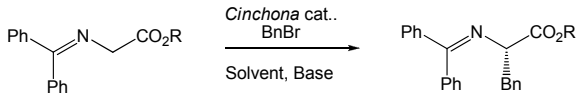
allowed the preparation of the first 9-*O* acyl alkaloid derivatives used as filtration-recoverable ligands in the osmium-catalyzed AD reaction (Figure 9 eq.1) under the original Upjohn conditions (*N*-methylmorpholine-*N*-oxide – NMO- as the terminal oxidant, in acetone:H_2O = 9: 1).[43a]



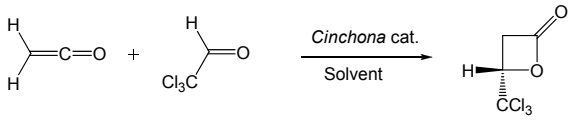
Eq. 1 Asymmetric dihydroxylation



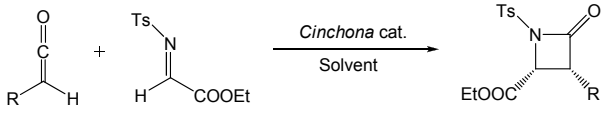
Eq. 2 Asymmetric aminohydroxylation



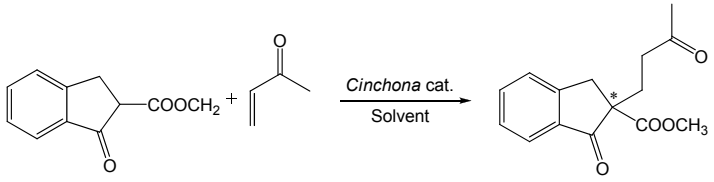
Eq. 3 Asymmetric Lygo-Corey benzylation reaction



Eq. 4 Asymmetric [2+2] cycloaddition reaction between ketene and chloral



Eq. 5 Asymmetric [2+2] cyclo addition reaction between monosubstituted ketenes and the N-tosylimine of ethyl glyoxylate



Eq. 6 Asymmetric Michael addition reaction

Figure 9. Some asymmetric reactions catalyzed by *Cinchona* alkaloid derivatives.

Interestingly, even if the diol products were obtained with only modest enantiomeric excess (*ee*) values (≤86%),[63] several observations could be made in the course of these early studies. The first of these remarks concerns the influence on the catalytic properties of the

Tetrahedron Letters **1990**, *31*, 3003-3006; **c)** Pini, D.; Petri, A.; Nardi, A.; Rosini, C.; Salvadori, P. *Tetrahedron Letters* **1991**, *32*, 5175-5178.

alkaloid content in the material: only the copolymers with a low loading (10-15 mol%) of chiral units could afford high yields of the diol; in contrast, with a higher alkaloid content no product was formed at all in the AD reaction.[63c] These results were explained on the basis of the inhibition of the catalytic cycle when the high alkaloid concentration in the polymer increased the likelihood of finding two chiral units in close proximity along the macromolecular chain. Under these conditions the proximal quinuclidine fragments can form a very stable osmium(VI) chelate complex, which is known to be refractory to hydrolysis and represents therefore a dead-end for the catalytic cycle.[64] The second general observation that emerged from this work was the unsuitability of acrylonitrile as the 'diluting' monomer in the preparation of IPB alkaloids for AD. This conclusion was confirmed by control experiments which revealed that the nitrile groups of bare polyacrylonitrile themselves can catalyze the dihydroxylation reaction, to give the racemic diol product.

Copolymers of the same general structure **34** were also employed as organocatalysts, in the asymmetric [2+2] cycloaddition between ketene and chloral (Figure 9. eq. 4). [65] In this case, the low optical purity of the resulting β-lactone adduct was related to the poorly swollen state of the material in the reaction solvent (toluene) or to an unfavorable influence of the highly polar polyacrylonitrile backbone.

Moreover, *N*-alkylation of an analogous CN containing copolymer afforded the insoluble PTC **35**, which was used in the Lygo-Corey asymmetric benzylation of the *iso*-propyl ester of *N*-diphenylmethyleneglycine (Figure 9, eq. 3).[66] Even if **35** proved more effective than other supported phase-transfer agents, the best results (up to 71% *ee*) lagged behind those provided by other optimized materials for this reaction (see 1.4.2 and 1.4.3).

In order to solve the problems raised by the necessity of using acrylonitrile as the 'diluting' monomer, the elaboration of the vinyl group of the native alkaloids into more easily polymerizable styrene or acrylate units has been generally pursued (*vide infra*). Nonetheless, attempts further to exploit the vinyl direct copolymerization strategy outlined above continued to appear in the course of the years.[67] In general, all these studies claimed the radical copolymerization of the alkaloid derivatives (usually of the dimeric type) with a

[64] Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *Journal of the American Chemical Society* **1989**, *111*, 737-739.
[65] Song, C. E.; Ryu, T. H.; Roh, E. J.; Kim, I. O. *Tetrahedron : Asymmetry* **1994**, *5*, 1215-1218.
[66] Chinchilla, R.; Mazon, P.; Najera, C. *Molecules* **2004**, *9*, 349-364.
[67] **a)** Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron Letters* **1994**, *35*, 6559-6562; **b)** Song, C. E.; Yang, J. W.; Ha, H. J.; Lee, S.-g. *Tetrahedron: Asymmetry* **1996**, *7*, 645-648; **c)** Nandanan, E.; Sudalai, A.; Ravindranathan, T. *Tetrahedron Letters* **1997**, *38*, 2577-2580.

methacrylate hydrophilic monomer (e.g. methyl methacrylate, MMA, or hydroxyethylmethacrylate, HEMA) and cross-linking agent (e.g. ethylene glycol dimethacrylate, EGDMA). However, subsequent studies by Sherrington and by this group demonstrated that, instead of the assumed architectures **36a – 36c**, these materials consisted of a cross-linked methacrylate network containing some physically-trapped chiral monomers.[68] This conclusion was confirmed by the observation of a continuous and significant alkaloid leaching from the purported materials that, arguably, can also explain the high *ee*'s obtained in the AD reaction with these (encapsulated and not IPB) derivatives.

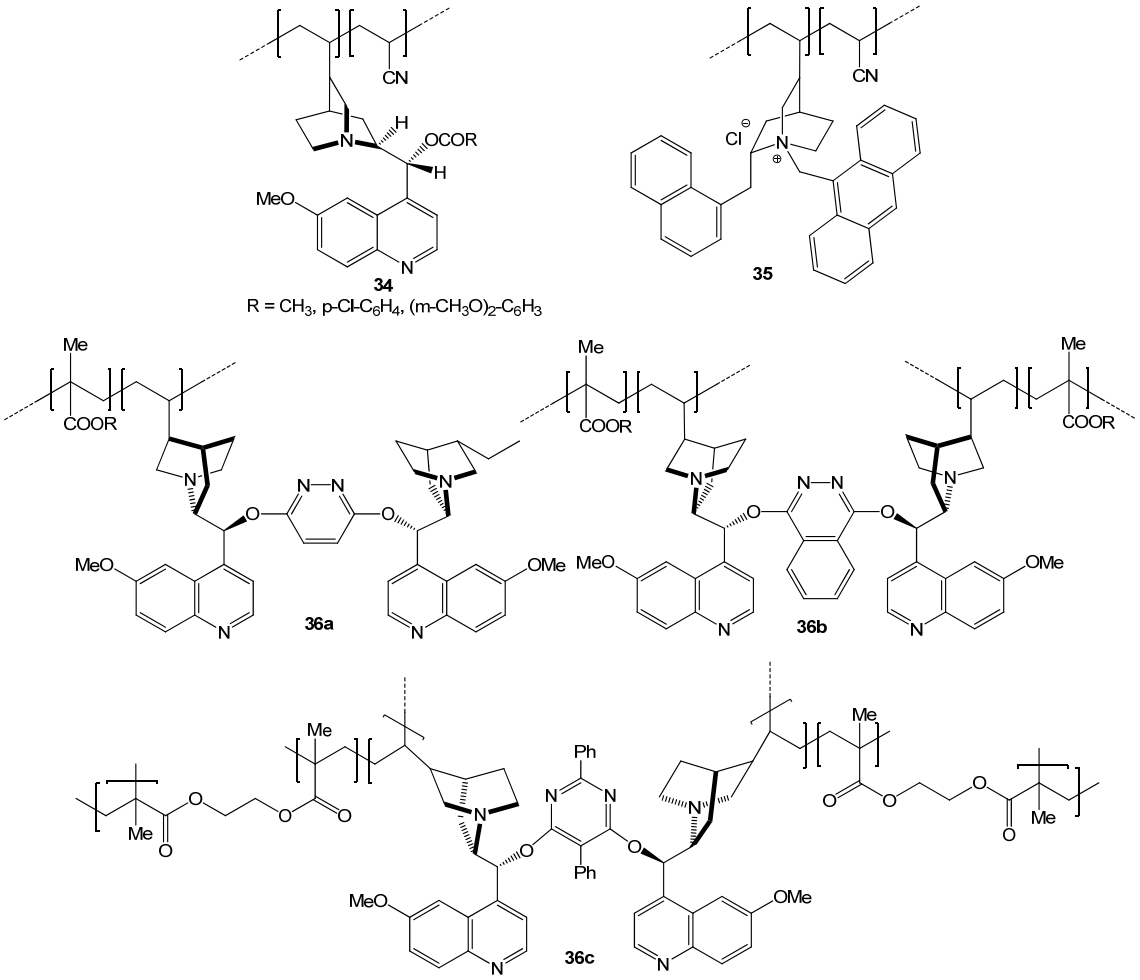


Figure 10. Purported structures (see text) of IPB materials obtained by direct copolymerization of alkaloid derivatives.

Direct grafting or tethering at C10 or C11 (Figure 11). Since early work on the preparation of HPLC chiral stationary phases (CSP),[69] the anti-Markownikov radical addition of supported thiol units to the alkaloid's vinyl group proved a suitable method for effecting the

[68] **a)** Canali, L.; Song, C. E.; Sherrington, D. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1029-1034; **b)** Salvadori, P.; Pini, D.; Petri, A. *Synlett* **1999**, 1181-1190.

[69] Rosini, C.; Altemura, P.; Pini, D.; Bertucci, C.; Zullino, G.; Salvadori, P. *Journal of Chromatography A* **1985**, *348*, 79-87.

grafting/tethering of the latter. With this aim, various mercaptopropylsilanized inorganic materials, including amorphous silica-gel (e.g. KG-60),[70] ordered mesoporous aluminosilicates (MCM-41),[71] or silica foams (SBA-15),[72] were used for obtaining IPB alkaloid derivatives. Given the orthogonal nature of the chemistry involved in this approach, an advantage of the method is that different soluble precursors could be immobilized without having to resort to any protection/deprotection scheme. This allowed, for instance, the direct preparation of IPB alkaloids containing the free hydroxyl group (**37**)[71a] as well as a number of other dimeric 9-*O* ether derivatives (**38**-**40**).[70a,72,73]

Despite its simplicity, this route may nevertheless present some problems due to the potential instability of the underlying inorganic matrix or the interference of the highly polar support surface in the catalyzed reaction. The former problem was observed (**39**) in the AD reaction carried out with the highly effective ferricyanide oxidant system ($K_3Fe(CN)_6$ – K_2CO_3 in a biphasic *t*BuOH:H_2O 1:1 mixture).[43] Under the strongly alkaline aqueous conditions of this procedure (pH ~ 12 in the water phase), the leaching of up to 0.5% of the supported phthalazine derivative was noted.[25] Besides contaminating the product and limiting the recycling, such a large degree of dissolution of the ligand made even the nature of the catalysis (heterogeneous *vs.* homogeneous*)* to be at question in this case.

Another general shortcoming of this approach is the frequently low chemical efficiency of the immobilization technique. For instance, in the cases where the pertinent data are available it can be estimated that no more than 15.9% [70a] (an sometimes as little as 6 % and 0.08 $mmolg^{-1}$) [70c,72a] of the soluble alkaloid precursor was actually bound to the support and, hence, recovered with the purified IPB material.

An approach that makes use of a completely different chemistry but still relies on the direct grafting at the alkaloid's vinyl group has been described by DeClue and Siegel.[73] In this case a non-symmetric phthalazine dimeric derivative was reacted with poly(methylhydrosiloxane) (PMHS) in the presence of a Pt catalysts to afford a material (**40)** where the chiral unit were linked to the macromolecular chain by hydrosilylation.

[70] **a)** Song, C. E.; Yang, J. W.; Ha, H.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 841-844; **b)** Song, C. E.; Lee, S. G. *Chemical Reviews* **2002**, *102*, 3495-3524; **c)** Kim, H. S.; Song, Y.-M.; Choi, J. S.; Yang, J. W.; Han, H. *Tetrahedron* **2004**, *60*, 12051-12057.

[71] **a)** Bigi, F.; Carloni, S.; Maggi, R.; Mazzacani, A.; Sartori, G.; Tanzi, G. *Journal of Molecular Catalysis A: Chemical* **2002**, *182-183*, 533-539; **b)** Choudary, B. M.; Chowdari, N. S.; Jyothi, K.; Kantam, M. L. *Catalysis Letters* **2002**, *82*, 99-102.

[72] **a)** Lee, H. M.; Kim, S.-W.; Hyeon, T.; Kim, B. M. *Tetrahedron: Asymmetry* **2001**, *12*, 1537-1541; **b)** Lee, D.; Lee, J.; Lee, H.; Jin, S.; Hyeon, T.; Kim, B. M. *Advanced Synthesis & Catalysis* **2006**, *348*, 41-46.

[73] DeClue, M. S.; Siegel, J. S. *Organic & Biomolecular Chemistry* **2004**, *2*, 2287-2298.

Despite the linear structure of the polymer and at variance with similar materials containing long achiral side arms, also evaluated in the study, (**40**) proved insoluble in the solvent mixture used in the AD with either the NMO or ferricianyde oxidant systems. This allowed the recovery of the polymeric ligand by filtration and its use in the course of four successive cycles, without major changes in the reaction outcome (in the AD of *trans*-stilbene: > 90% yield and ~ 95% *ee* in 24-26 h). In this regard it should be noted, however, that the initial amount of chiral ligand was ten times larger (10 mol%) than used in the standard homogeneous AD conditions, making the proof of its economic convenience rather problematic.[43c] Moreover, given the capacity of even minute amounts of soluble second-generation phthalazine derivatives to promote the AD of different olefins with high *ee*'s[25,43] and the lack in the study under exam of any evidence for catalyst heterogeneity, the inclusion of **(40)** in the family of IPB alkaloid derivatives appears equally questionable.

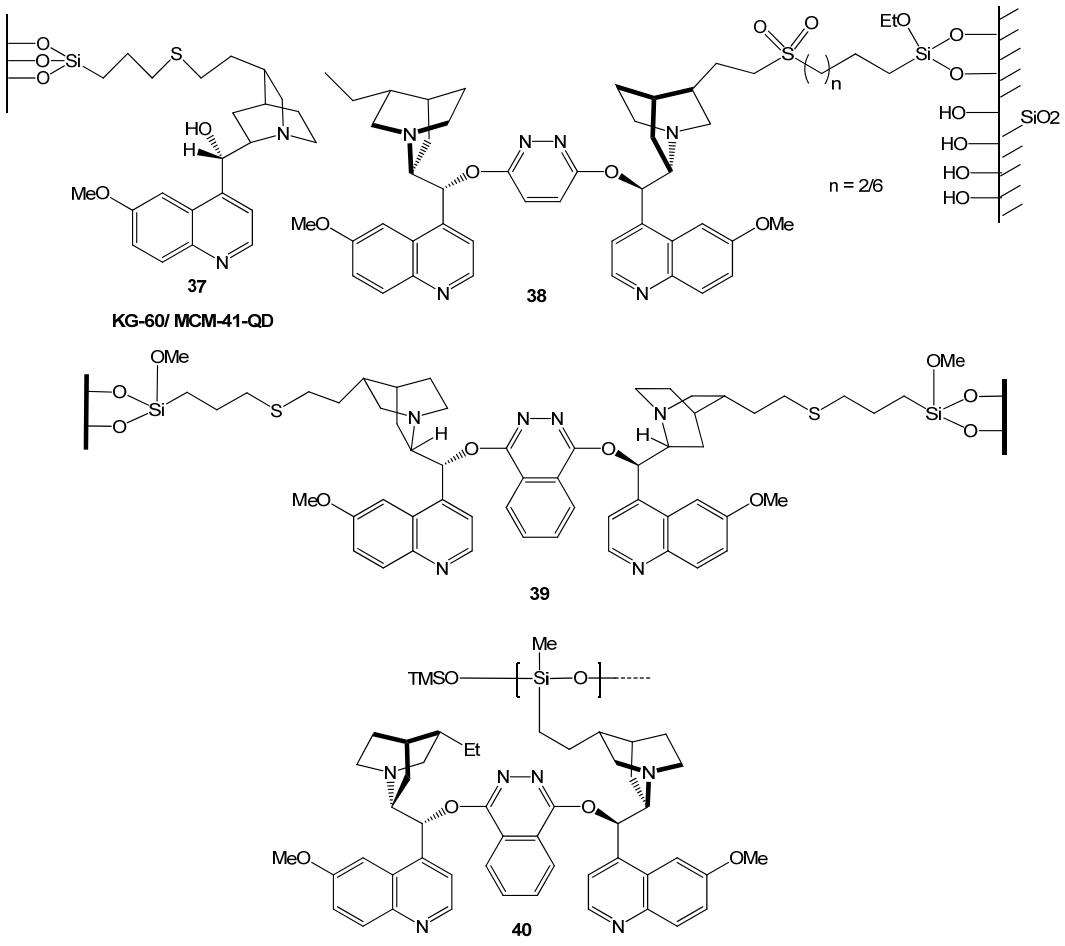


Figure 11. IPB alkaloid derivatives obtained by grafting/tethering at C10 or C11

Elaboration of the 10,11-double bond and 'copolymerization' (Figure 12). Due to the said limitations of the direct radical copolymerization of the alkaloid's vinyl group, attempts to

elaborate the latter have long been pursued.[74] In the case of the AD reaction, these approaches relied on the radical addition of a soluble functional thiol (e.g. 2-mercaptoethanol) to the double bond, followed by the oxidation of the sulfide linkage (to prevent any interference in the catalysis), and then the introduction of an easily polymerized monomer unit of the (meth)acrylate or styrene type.[63c, 74, 75,] By these means not only the alkaloid derivatives could be effectively polymerized with various achiral co-monomers like acrylonitrile (**41a-d** and **42**), styrene/DVB (**43**), or HEMA/EGDMA (**45**), but the spacing of the chiral units from the macromolecular support was also achieved at the same time. As expected, this latter structural feature proved beneficial in terms of catalytic performances in the AD reaction, as confirmed by the better *ee* values provided by **41b,c** (87% *ee*)[63a,b] and especially **42** (89% *ee*),[75] in comparison with the corresponding not spaced polyacrylonitrile materials **34** discussed before. In the case of **41a** the attainment of a recycle run was reported, albeit with some reduction of the activity and of the *ee* values.

However, due to the already mentioned interference of the nitrile groups in the AD,[68a] a substantial improvement of the enantioselectivity for olefins other than *trans*-stilbene (60-87% *ee*) had to wait the introduction of materials possessing an inert cross-linked PS architecture (**43**). Interestingly, the latter proved effective, however, only in the reactions carried out under the original Upjohn condition.[43a] On the contrary, when **43** was tested with the generally more effective ferricyanide protocol, the outcome was disappointing as the formation of only traces of the diol product was observed. This result was related to the a compatibility issue between the PS backbone of **43** and the reaction medium: while in the relatively apolar acetone:H_2O (9:1) solvent of the former procedure the polymeric material is well swollen and the supported alkaloid-OsO_4 sites freely accessible for the olefin substrate, under the alternative AD condition the hydrophilic *t*BuOH:H_2O (1:1) mixture causes the macromolecular skeleton to collapse and thence prevents the explication of the catalytic activity of the IPB system.

In order to solve the problem, further developments involved the preparation of hydrophilic HEMA/EGDMA co-monomers. The resulting materials (general structure **45**) proved highly compatible with both acetone:H_2O and *t*BuOH:H_2O solvent mixtures and

[74] Pini, D.; Petri, A.; Mastantuono, A.; Salvadori, P. in *Chiral Reactions in Heterogeneous Catalysis*, Jannes G and Dubois V (Eds.), Plenum Press: New York, 1995; p. 155-176.

[75] **a)** Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2351-2354; **b)** Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron* **1994**, *50*, 11321-11328; **c)** Song, C. E.; Roh, E. J.; Lee, S.-g.; Kim, I. O. *Tetrahedron: Asymmetry* **1995**, *6*, 2687-2694; **d)** Athawale, V.; Manjrekar, N. *Tetrahedron Letters* **2001**, *42*, 4541-4543.

afforded good results (up to 95% *ee*) in the AD under the alternative reaction conditions.[75b] Applications to the asymmetric aminohydroxylation of olefins (AA) were also reported.[76]

Nonetheless, a successive study by this group demonstrated that under the basic aqueous condition of the ferricyanide AD process the IPB derivatives like **45** suffered from a serious leaching problem (~ 2%).[25] Analogously to the siliceous systems discussed above, this made difficult to ascertain if the reported AD results had to be referred to a heterogeneous type of catalysis or, more likely, to the homogeneous contribution due to the dissolved alkaloid.

In order to answer this question, the preparation was decided of new materials with a much reduced alkaloid leaching. With this aim an optimized architecture was imagined where all the obvious base-sensitive sites of **45** (i.e. any ester and β-oxysulfone units) had to be carefully replaced by stable linkages. Starting from this idea, two IPB phthalazine derivatives (**44a**,**b**) were designed that contained only ether and isolated sulfone fragments. Even if the preparation of the necessary functional styrene monomers was somewhat involved, requiring four or five synthetic steps and repeated chromatographic purifications, their radical polymerization with and hydrophilic comonomer and cross-linking agent smoothly afforded the expected IPB materials. By these means the first clear demonstration of a *heterogeneous* and highly enantioselective AD reaction with the ferricyanide oxidant system could be attained.[25] Indeed, not only **44a**,**b** proved compatible with the hydrophilic solvent mixture and afforded high yields and enantioselectivities (87-99% *ee*) in the AD of various olefins, but they also displayed a very low alkaloid leaching (in the 1-5‰ range), which made the homogeneous contribution to the reaction largely negligible. Moreover, these new IPB alkaloids resulted rather robust, leading to the complete conversion of the alkene substrate and an unchanged enantiomeric purity of the diol product even after being exposed to the AD reaction conditions for more than 20 times.

From the strategy point of view, it is interesting to note that the general scheme outline above is not necessarily limited to the preparation of organic type of materials. In fact, in a very recent example a conceptually similar approach was applied for obtaining IPB alkaloid derivatives immobilized within an inorganic support of zirconium phosphonate (**46**).[77] In this case, the chiral 'monomer' was obtained by radical addition to the vinyl group

[76] Mandoli, A.; Pini, D.; Agostini, A.; Salvadori, P. *Tetrahedron: Asymmetry* **2000**, *11*, 4039-4042.
[77] Ma, X.; Wang, Y.; Wang, W.; Cao, J. *Catalysis Communications* **2010**, *11*, 401-407.

of CD of different thiols containing a diethylphosphonate ester group and subsequent saponification of the latter.

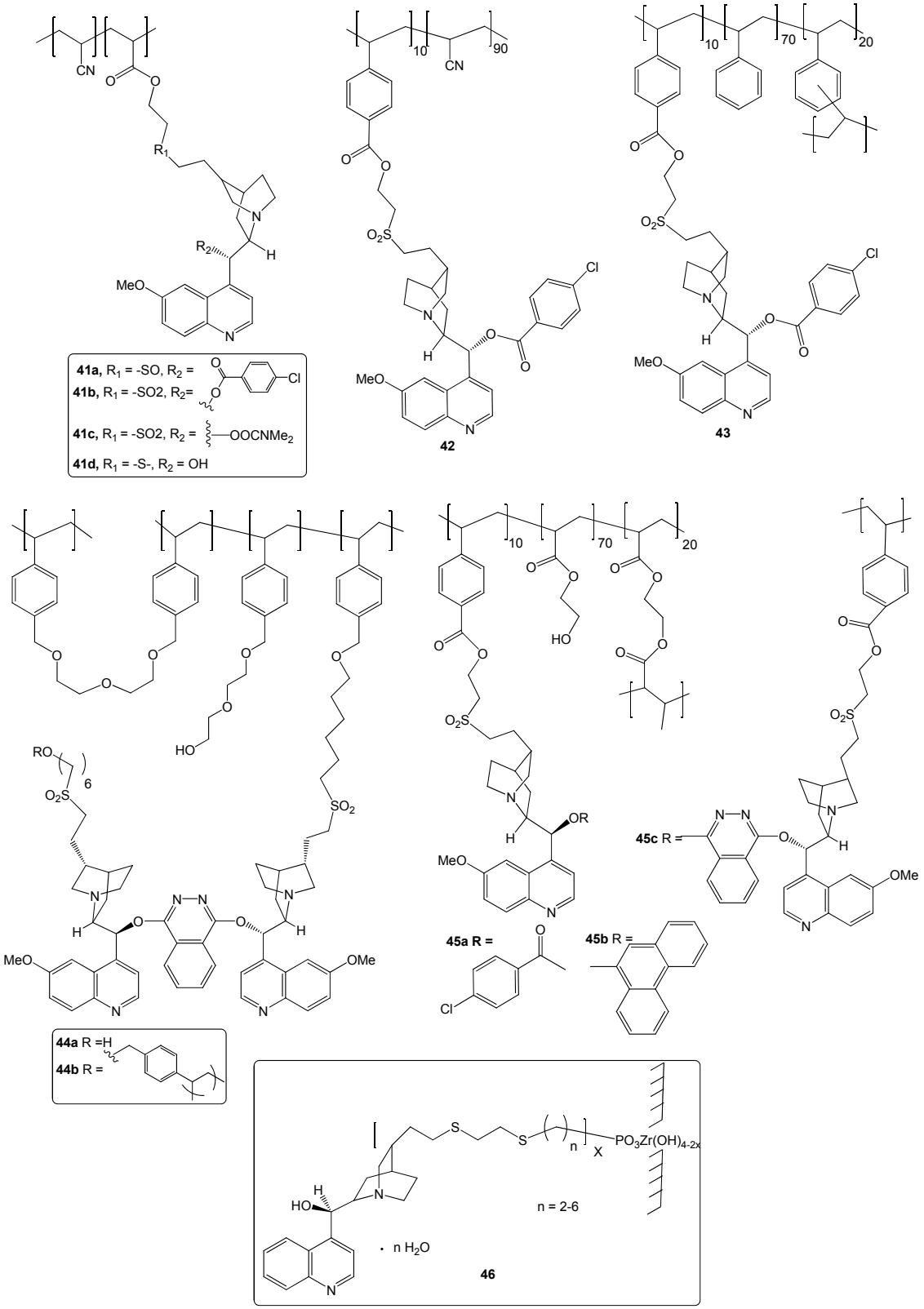


Figure 12. Spaced IPB alkaloid derivatives obtained by copolymerization.

Then, the combination of the resulting phosphonic acid derivative with zirconium oxychloride gave rise to the 'copolymerization' of the mixture that in this case consisted in the formation of a network of insoluble zirconium phosphonate carrying the covalently-bound alkaloid fragments. The resulting materials were tested in the asymmetric addition of diethylzinc to various aldehydes: although the enantiomeric purity of the alcohol products (35-62% *ee*) were only modest, the yields were fair to good (68-92%) and the catalyst could be reused effectively ten times.

Elaboration of the 10,11-double bond and grafting/tethering (Figure 13). The possibility of functionalize the vinyl group of the native alkaloids by introducing different spacer groups allowed the exploration of anchoring strategies, alternative to the direct addition of supported thiol units (*vide supra*). In an early example, the radical addition of β-mercaptoethanol to a pyridazine dimeric alkaloid ether afforded a soluble derivative that was tethered to chloropropylsilanized silica-gel under Williamson conditions.[78] The resulting material (**47**) was used as an IPB ligand in the AD reaction with the ferricyanide oxidant system, leading to diol products with comparable yields but lower enantioselectivity (14 - 80% *ee*) than the corresponding homogeneous reactions.

In a related approach 3-mercaptopropionic acid or the corresponding methyl ester were radically added to the vinyl group of an alkaloid phthalazine dimeric ether.[79] The carboxy group of the resulting derivatives was then used for tethering to TentaGel-NH_2 (cross-linked PS, with amino-terminated PEG grafts), in the former case by standard peptide coupling chemistry, in the latter by simply heating the resin at 100°C with a *N*,*N*-dimethylformamide (DMF) solution of the ester compound. After end-capping of the unreacted amine groups, to prevent possible interferences, the IPB ligands (**48**) were tested in the AD reaction of various styrenes. Interestingly, while the reaction NMO as the terminal oxidant afforded disappointing results (25% *ee*), the use of the ferricyanide system provided better enantioselectivities (63-96% *ee*); the IPB ligand could be also reused, even if just three recycles were documented in this case.

Besides the radical addition of thiol derivatives, the oxidation of the vinyl group provides another opportunity for setting-up an anchoring point into the alkaloid core. Resting on this idea, 9-*O*-TBDMS QN and QD were converted by hydroboration-oxidation

[78] Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron: Asymmetry* **1996**, *7*, 2805-2808.
[79] Achkar, J.; Hunt, J. R.; Beingessner, R. L.; Fenniri, H. *Tetrahedron: Asymmetry* **2008**, *19*, 1049-1051.

into the corresponding C11 primary alcohols and the newly introduced function was then exploited for the anchoring.[80] This task was accomplished by two alternative procedures, i.e. by the direct Williamson reaction of the modified alkaloid with a Merrifield resin or by first grafting carboxy-terminated side arms to the resin and then effecting the esterification of the chiral derivative. The grafted/tethered materials obtained by these routes (**49** and **50a-b**, respectively) were subjected to the cleavage of the TBDMS protecting group with *n*Bu_4NF to give the corresponding 9-*O* unprotected derivatives (**49** and **50a-b**, respectively). The latter were studied as IPB organocatalysts in the asymmetric Michael addition of 2-(methoxycarbonyl)indane-1-one to methyl vinyl ketone. This screening revealed that all the prepared materials could catalyze the benchmark reaction, albeit with a largely variable stereochemical efficiency.

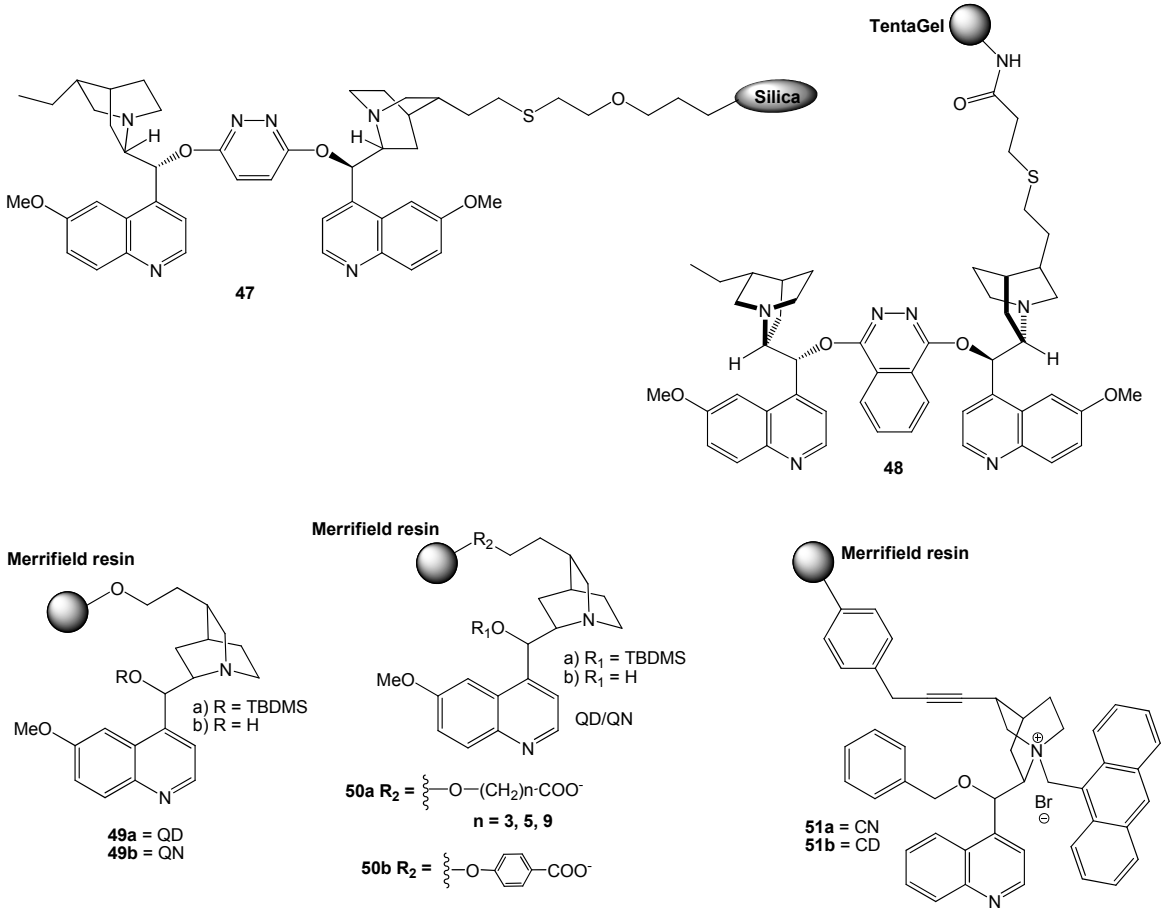


Figure 13. Spaced IPB alkaloid derivatives obtained by grafting/tethering.

For the QN derivatives best results (87% *ee*) were obtained when the chiral unit was linked to the resin through a seven atom spacer [**50a** (n = 5)], while the grafted material (**49**)

[80] Alvarez, R.; Hourdin, M.-A.; Cave, C.; d'Angelo, J.; Chaminade, P. *Tetrahedron Letters* **1999**, *40*, 7091-7094.

and those with shorter or longer tethers [**50a** (n = 3 or 9), **50b**] led to a much lower enantioselectivity (≤ 31% *ee*). In the corresponding QD series the results were generally worse (12-45% *ee*), with the highest *ee* provided by the grafted organocatalyst **49**. Surprisingly enough, the configuration of the prevailing enantiomer of the Michael adduct turned out to be the same (*R*), regardless of the use of QN or QD-derived materials. This rather unexpected result was deemed to be caused by the C11 substituent whose steric bulk in proximity of C3 and C4 would magnify the influence of this alkaloid region, up to override the control on the asymmetric induction normally provided by the C8 and C9 stereocenters. Because the configuration of the former molecular fragment is conserved on switching between QN and QD, this could explain the observed departure from the usual pseudoenantiomeric behavior. Unfortunately, no recycling data of the IPB organocatalyst were provided in this study.

The conversion of the vinyl group of *Cinchona* alkaloids into a terminal acetylene one opens several possibilities of further elaboration.[81] For the purposes of alkaloid anchoring, this opportunity was exploited in the preparation of the IPB quaternary ammonium salts **51a**,**b**.[82] These materials were obtained in relatively low yields (31-34%) by deprotonation with *n*BuLi of the corresponding 10,11-didehydro CN or CD derivatives, followed by the coupling of the resulting lithium acetylides with a commercial Merrifield resin. Both supported systems were tested as chiral PTC in the Lygo-Corey asymmetric benzylation (Figure 9, eq. 3), obtaining much better results with the CN derivative (63-73% *ee*, depending on the actual reaction conditions) than with the CD one (11% *ee*). Also in this case, no attempt to re-use the IPB organocatalyst was reported.

1.4.2. *IPB- Cinchona alkaloid derivative linked at 9-O position.*

Provided the free hydroxyl group is not required for effective catalysis, the immobilization of *Cinchona* alkaloid derivatives through the 9-*O* position is another viable and extensively practiced route. Also in this case, numerous examples exist, that differ in the technique adopted for the preparation of the IPB system.

Copolymerization of 9-O monomers (Figure 14). Together with the direct use of the alkaloid's vinyl group, described in the previous paragraph, the radical copolymerization of 9-*O* monomer derivatives has been employed since the beginning of the studies in the field.

[81] Hoffmann, H. M. R.; Frackenpohl J. *European Journal of Organic Chemistry* **2004**, 4293-4312 (and ref. cited therein)
[82] Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Molecular Diversity* **2005**, *9*, 277-290.

One of the first examples in this direction involved the copolymerization of the 9-*O* acryloyl derivatives of CN and QN with some acryalmide cross-linkers.[61c] The resulting insoluble materials (**52a**,**b**) were employed to catalyze the addition of methanol to methylphenyl ketene at -78°C, giving methyl 2-phenylpropionate of fairly low enantiomeric purity (11-34% *ee*).

In addition to cross-linked materials, 9-*O* alkaloid monomers were also embedded into some linear copolymers that, as already noted, can display a very poor solubility in organic solvents. An example of this approach is provided by the copolymer between the 9-*O*-(undec-10-enoyl) ester of DHQD and acrylonitrile (**53**), prepared in an effort to avoid the steric congestion around the alkaloid units of the previously discussed IPB ligand **34** (see 1.4.1).[63c] Even if the preparation of **53** was poorly efficient (13% yield), in the AD of *trans*-stilbene the material performed much better than **34** and, to some extent, of **41a-c**. Interestingly, good results were obtained using either NMO (87% yield, 82% *ee*) or ferricyanide (91% yield, 86% *ee*) terminal oxidant, but no recycling attempt was reported in this case.

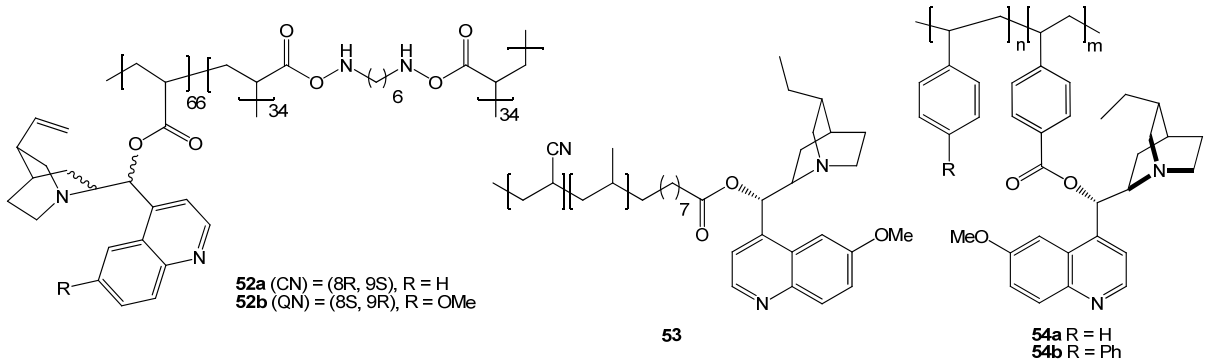


Figure 14. IPB alkaloid derivatives obtained by copolymerization of 9-O monomers.

Similarly, some PS-supported alkaloid derivatives (**54a**,**b**) were prepared by radical copolymerization of styrene or 4-phenylstyrene with the 9-*O*-(4-vinylbenzoate) of DHQD or DHQN.[83] The materials obtained by this route were tested in the AD of various olefins in MeCN : H_2O (8:2) or *t*BuOH : H_2O (1:1), the terminal oxidant being NMO and $K_3Fe(CN)_6$, respectively. Besides confirming the adverse effect of a high concentration of alkaloid units in the macromolecular chain (see 1.4.1), these runs demonstrated that even the optimized ligands (**54a**,**b** with 10% alkaloid incorporation) could deliver a high enantioselectivity in

[83] Lohray, B. B.; Thomas, A.; Chittari, P.; Ahuja, J. R.; Dhal, P. K. *Tetrahedron Letters* **1992**, *33*, 5453-5456

the AD of *trans*-stilbene only (≤ 85% *ee*). On the contrary, the dihydroxylation of terminal or other *trans*-disubstituted olefins provided diols of lower enantiomeric purity (22-69% *ee*). Moreover, the observation was made in this study that the initial suspension of the polymeric ligand in MeCN : H_2O gradually changed into a homogeneous solution as the AD reaction proceeded. Although the alkaloid derivative could be precipitated by diluting the mixture with water and used again in a single recycle run, no evidence was provided at this stage about the nature (heterogeneous or homogeneous) of the catalysis at work.

Grafting/tethering through the 9-O oxygen atom (Figure 15). After the pioneering work of Hermann and Wynberg mentioned before (materials **55a,b**)[61d] the anchoring through the 9-*O* position has been employed more and more times. Provided the preparation of a simple 9-*O* derivative is aimed, the direct reaction of the native alkaloid's OH group with a functional support can prove one of the most efficient methods for obtaining IPB systems of this class. A remarkable example of this approach was described by Lectka and co-workers for the preparation of QN ester derivatives (**56**,**57a-c**).[84] Initially, the direct esterification of the alkaloid with a carboxypolystyrene resin was attempted but, due to the relatively poor diastereoselectivity afforded by the material **56** in the catalysis runs (*vide infra*), a different route was eventually chosen. The latter involved the reaction of the benzyl alcohol moieties of a high loading Wang resin with a bis(carboxylic acid chloride), followed by the use of the pendant chlorocarbonyl residual groups for the grafting of the native alkaloid. By this approach three materials were prepared (**57a-c**) that differed in the structure of the tether linking the chiral units to the support. This design element proved rather important when the IPB organocatalyst were employed for promoting the [2+2] addition between monosubstituted ketenes and the *N*-tosylimine of ethyl glyoxylate: while all of the materials afforded the *β*-lactam products in similar yield (62-64%) and enantiomeric purity (87-95%), only those containing an aromatic spacer (**57a**,**b**) also lead to a satisfactory diastereomeric purity (*cis* : *trans* ≥ 10 : 1). Interestingly, the runs of this study were carried out under flow conditions into sequentially linked columns, demonstrating that the generation of the ketene and *N*-tosylimine reactants, their organocatalyzed asymmetric reaction, and the scavenging of any unreacted ketene and imine byproducts could all be performed in a 'synthesis

[84] Hafez, A. M.; Taggi, A. E.; Dudding, T.; Lectka, T. *Journal of the American Chemical Society* **2001**, *123*, 10853-10859.

machine'.[85] In turn, this allowed the direct recrystallization of the crude without requiring any preliminary purification of the sensitive *β*-lactam compound.

Probably due to some alkaloid leaching, freshly prepared **57a-c** required 5-10 initial runs before affording consistent results. After proper 'ageing' the resins proved nevertheless rather robust, in the case of a (unspecified) batch of IPB organocatalyst allowing the preservation of its catalytic efficiency over 60 reaction cycles. In spite of this quite impressive result it has been noted, however, that in each catalysis run the IPB alkaloid was employed in undisclosed amounts, but anyway much larger than 100 mol%.[86] Under these conditions, the increase of productivity over the use of the corresponding homogeneous organocatalyst is clearly not as large as the number of recycles might suggest.

Supported chiral PTC (**58a**,**b**) were prepared in low overall yields (24-30%) by direct esterification of the hydroxy group of quaternary ammonium salt of CN and CD with carboxypolystyrene resin.[82] The materials were tested in the asymmetric Lygo-Corey benzylation but, due to the long reaction times (96-120 h) and the moderate enantioselectivity (30-65% *ee*), they proved scarcely effective. On the contrary, the grafting of CN, CD, QN, and QD quaternary ammonium salts to a Merrifield resin resulted much more convenient, leading to the corresponding PTC (**59a-d**) in good to excellent yields (71-90%). Screening of the materials in the same benchmark reaction as above showed the expected pseudoenantiomeric effect, albeit with a strong dependence of the *ee*'s on the catalyst structure. In particular, while the CD derivative (**59b**) afforded an excellent enantioselectivity under optimized conditions (93-96% *ee*), the other materials (**59a,c-d**) led to significantly worse results (≤ 79% *ee*). In the same study, attempts were also made for improving the catalytic performances of (**59b**) and for addressing its unsatisfactory recycling profile (14% yield decrease and 7% *ee* loss in 4 cycles). In order to tackle the former issue, a material embedding a longer tether group was studied (**60**) but this actually resulted in a reduced enantioselectivity (81% *ee*). Instead, on the assumption that the mechanical wearing would be the reason of catalysis degradation on recycling, the use of SynPhase^{TM} lanterns (chloromethylated PS stacked disk) was explored as a mean for solving the latter problem. The resulting materials (which should be chemically similar to **59b**) afforded essentially constant results over three cycles, but the enantioselectivity

[85] For another application of this concept, see: France, S.; Bernstein, D.; Weatherwax, A.; Lectka, T. *Organic Letters* **2005**, *7*, 3009-3012.
[86] Oliver Gleeson, Renata Tekoriute, Yurii K. Gun'ko, Stephen J. Connon *Chemistry A European Journal* **2009**, 15, 5669 – 5673

attained in these runs was substantially lower (77-78% *ee*) than in the case of the standard Merrifield type of support.

For the sake of completeness, it is worth mentioning that three monomeric alkaloid derivatives containing an allyloxy side arm were linked to linear PMHS by the same approach described for **40** (see 1.4.1).[73] The resulting materials (**61a,b,c**) were screened in the AD but afforded relatively low enantioselectivity values (≤ 83% *ee*), even if the test olefin (*trans*-stilbene) is arguably the best substrate for the reaction under exam. Also in this case, no evidence was provided that could support the actual heterogeneity of the catalytic system.

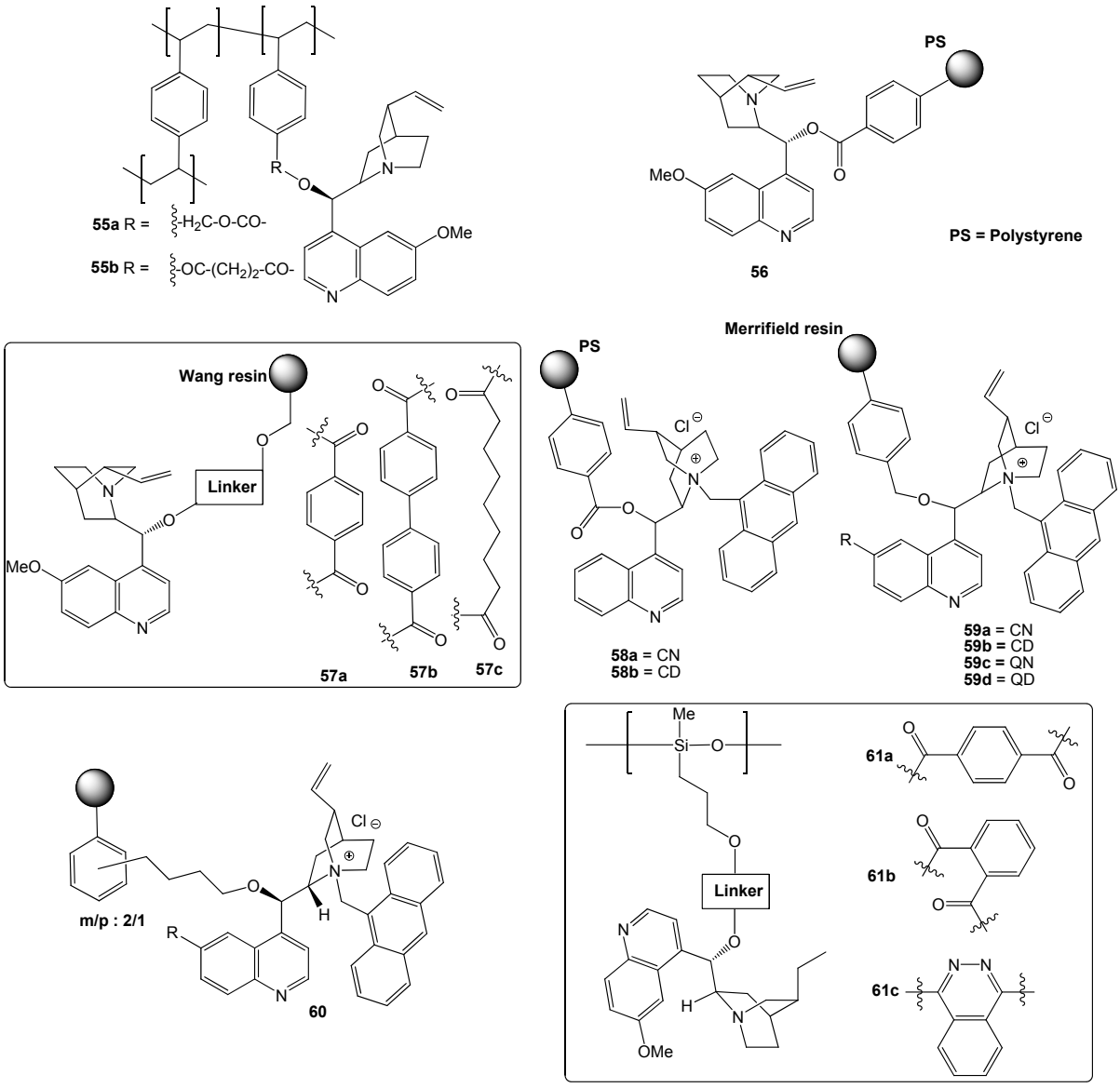


Figure 15. IPB alkaloid derivatives prepared by grafting/tethering through the 9-O position.

Dimeric alkaloid ethers linked through the central (hetero)aromatic spacer group (Figure 16). In the case of soluble 9-*O* derivatives whose preparation involves a clean and high yielding reaction (e.g. esters and simple ethers), most of the examples discussed above demonstrate that a similar procedure can be also performed 'in the solid phase', so as to allow a straightforward and reasonably effective anchoring route.

Unfortunately, a similar approach falls generally short in the immobilization of other derivatives for which, already in the homogeneous phase, the introduction of the 9-*O* substituent requires harsh conditions or leads to reduced yields or byproducts. This kind of limitations are typically encountered in the specific case of second-generation dimeric ethers like **6-9** (see 1.3), where the formation of a bond between the native alkaloid's 9-*O* oxygen atom and a -hypothetical- (hetero)aromatic supported substrate appears hardly practicable as an efficient immobilization technique. Considering also the synthetic difficulties encountered in preparing alkaloid derivatives with the anchoring site localized in the (hetero)aromatic spacer between the chiral units (e.g., see 2.1), it is therefore not surprising that the heterogeneization of this class of expensive, yet very versatile ligands or organocatalysts has been largely tackled by other approaches (most notably by taking advantage of the alkaloid's vinyl group, see 1.4.1).

Besides a soluble PS-supported anthraquinone derivative,[87] which lays outside the scope of this overview but will be discussed again in the paragraphs 2.4 and 4.3, an exception in this sense is represented by the dimeric IPB alkaloid ligands **62a-c**, **63a-b**, and **64** developed by Bolm and co-workers.[88] In general, all these materials were prepared by first synthesizing a ligand bearing a bromine atom on the spacer core, then introducing a 4-hydroxyphenyl group by a Suzuki-Miyaura cross-coupling, and finally exploiting the phenol portion of the resulting derivative for linking to functional silica-gel. The IPB ligands were tested in the AD reaction of various olefins with the ferricyanide oxidant system. In the case of standard AD substrates (e.g. styrene and *trans*-stilbene) the materials **62a**, **62b** and **62c** performed quite well, affording the corresponding diols with a high enantioselectivity (97-99% *ee*).[88a] Interestingly, while **62b** showed some evident drop in the asymmetric induction ability already after four cycles, **62a** could also be used seven times without any significant degradation of performances. This difference was believed to be due

[87] **a)** Wöltinger, J.; Krimmer, H.-P.; Drauz, K. *Tetrahedron Letters* **2002**, *43*, 8531-8533; **b)** Woeltinger, J.; Henniges, H.; Bolm, C.; Maischak, A.; Burkhardt, O.; Reichert, D.; Karau, A.; Philippe, J.-L.; Bommarius, A.; Drauz, K.; Krimmer, H.-P. In *Degussa AG, Germany*, DE 10036328A1, **2002**; pp 28.

[88] **a)** Bolm, C.; Gerlach, A. *Chemical Communications* **1997**, 2353-2354; **b)** Bolm, C.; Gerlach, A. *Angewandte Chemie International Edition in English* **1997**, *36*, 741-743; **c)** Bolm, C.; Maischak, A. *Synlett* **2001**, 93-95.

to the saponification of the ester linkage of **62b** under the strongly basic reaction conditions. At variance with **62a**,**b**,**c**, the other three materials (**63a**,**b** and **64**) were specifically designed for tackling the AD of notoriously 'difficult' substrates, like terminal aliphatic or *cis*-1,2-disubstituted olefins. Accordingly, the IPB pyrimidine derivatives **63a**,**b** were tested in the AD of 1-decene (61-84% *ee*),[69,88a] while the anthraquinone ether **64** was employed for the dihydroxylation of allyl iodide or indene (73 and 47% *ee*, respectively).[88b] Even if the magnitude of the enantioselectivity in these examples is not impressive, it is worth noting that the results reflect to a large extent those provided by the analogous soluble chiral ligands under comparable conditions (89, 83, and 63% *ee*, respectively).[43]

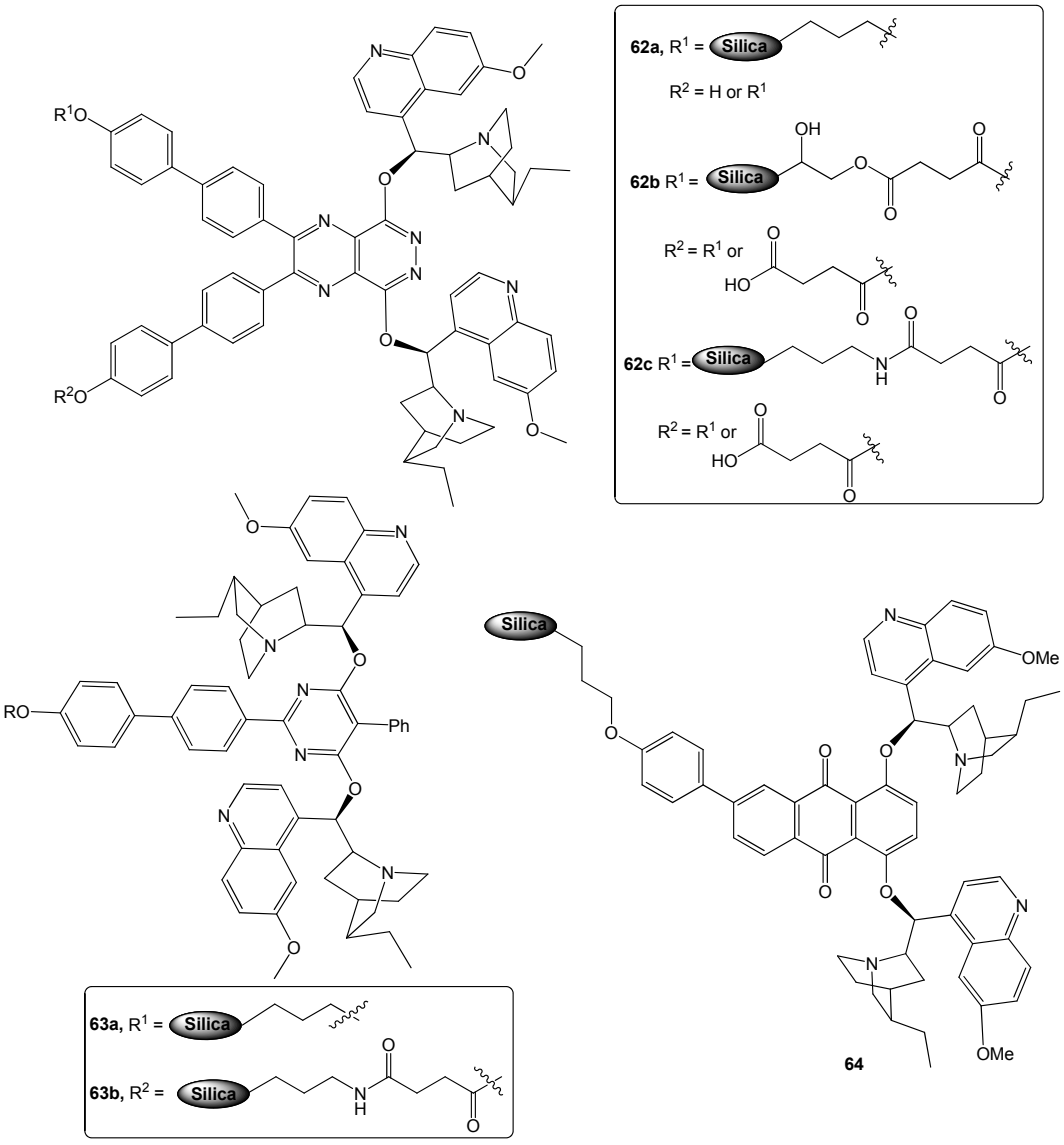


Figure 16. IPB dimeric alkaloid derivatives anchored through the (hetero)aromatic spacer.

1.4.3. *IPB- Cinchona alkaloid derivatives linked at the quinuclidine nitrogen.*

With a few exceptions,[54] the *Cinchona* quaternary ammonium salts obtained by alkylation of the quinuclidine nitrogen atom (N1) (Figure 17) have a catalyst scope that is limited to the field of chiral PTC. Provided this is the aim, the immobilization through such position can nonetheless prove quite effective and generally obtained by grafting.

This latter observation is confirmed, amongst the others,[89] by the extensive work carried out independently by Cahard and co-workers and Nàjera and co-workers.[66,82,90,91] These groups comprehensively examined alternative approaches for the preparation of IPB quaternary ammonium derivatives, some of which are also discussed in the sections dedicated to other anchoring positions (see 1.4.1, 1.4.2, and 1.4.4). In this context a distinction of the IPB derivatives into first and second generation was made,[90a] but, as this organization reflects more the historical development of the materials than actual differences in the preparation procedure, it will not be followed here.

Arguably, the alkylation of N1 by a polymeric alkyl halide is the most direct way for synthesizing IPB quaternary ammonium salts. Therefore it is not surprising that most of the reported examples made use of this strategy, with the main variations deriving from changes in the structure of the alkaloid core (stereochemistry, presence of 6' methoxy group, and nature of 9-*O* substituent) and of the insoluble support.

A first series of derivatives of this class (**65-66**) was introduced by Nàjera and coworkers,[66,92] by grafting of CN or QD onto commercial resins containing alkylating side arms. In addition to standard Merrifield beads, this study included PS-bound trityl chloride, chloromethylated JandaJel™ [PS cross-linked with 1,4-bis(4-vinylphenoxy)butane],[93] Wang-Br resin [cross-linked PS with (4-bromomethylphenoxy)methyl grafts], and

[89] **a)** Shi, Q.; Lee, Y.-J.; Song, H.; Cheng, M.; Jew, S.-S.; Park, H.-G.; Jeong, B.-S. *Chemistry Letters* **2008**, *37*, 436-437; **b)** Qin, Y.; Yang, G.; Yang, L.; Li, J.; Cui, Y. *Catalysis Letters* **2011**, *141*, 481-488.

[90] For more contributions from the Cahard group: **a)** Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Tetrahedron: Asymmetry* **2001**, *12*, 983-986; **b)** Thierry, B.; Perrard, T.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Synthesis* **2001**, *2001*, 1742-1746.

[91] For more contributions from the Nàjera group: **a)** Chinchilla, R.; Mazon, P.; Najera, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3277-3281; **b)** Chinchilla, R.; Mazon, P.; Najera, C. *Advanced Synthesis & Catalysis* **2004**, *346*, 1186-1194.

[92] One of the first example of quaternary CD and CN (of the same structure **65)** grafted on chloromethylated crosslinked polystyrene (2-20% crosslinking) was reported in **1983** for catalyzing Michael addition of 1-oxoindan-2-carboxylate to methyl vinyl ketone, however, by using different catalysts the products were isolated with quantitative yields but with very low enantiomeric purities (upto 27%): Hodge, P.; Khoshdel, E.; Waterhouse, J. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999)* **1983**, 2205-2209.

[93] Toy, P. H.; Reger, T. S.; Janda, K. D. *Aldrichimica Acta* **2000**, *33*, 87-93.

ArgoGel-Cl™ [a proprietary architecture of former Argonaut Technologies Inc., probably made of a cross-linked PS core with pendant (4-chloromethylphenoxy)PEG grafts].[94]

In an attempt of further tuning the catalytic properties of the supported PTC's, the development of tailor-made resins was also explored. With this aim Cahard and co-workers prepared a family of IPB derivatives (**67a-l**), which differed in the nature of the alkaloid moiety and the length of the tethering group between the chiral units and the cross-linked PS support.[82] On the contrary, the transformation of a standard Merrifield resin into the corresponding mercapto form, followed by reaction with 9,10-bis(chloromethyl)anthracene, allowed Nàjera and co-workers to eventually tether CN through N1 (see the material **70**) without having to renounce to the highly effective 9-anthrylmethyl substituent.[66]

All of the IPB derivatives discussed above were tested as chiral PTC in different Lygo-Corey reactions (most of which were nonetheless carried out with benzyl bromide as the alkylating agent).[66,82,90,91] Without entering into much details, that may be found in the cited literature, it can be said that in the case of the Spanish group the only supported catalyst capable of providing at least 90% *ee* in the benchmark asymmetric alkylation of glycinate imines was the simple CN derivative anchored onto a standard Merrifield resin (**65a**). By contrast, the alkylation of 9-*O* (**65b**), the switch to an alkaloid core of the QD series (**65c**), the change of the support (**65d**), the use of different spacers (**66**, **68**, **69**), and even the use of the 9-anthrylmethyl derivative (**70**) afforded enantioselectivity levels that did not surpass 74% *ee*.

Similarly, the French group found that while the enantioselectivity of the materials in the studied set was only moderately dependent on the length of the tethering group in **61a-l**, the structure of the alkaloid core exerted a very strong influence. In particular, the CN-based PTC (**61a-c**, 64-81% *ee*) performed significantly better than the CD (**61d-f**, 6-29% *ee*) and, especially, the QN/QD ones (**67g-l**, 4-10% *ee*). Interestingly, also in this case a departure from the usual pseudoenantiomeric behaviour between CN and CD (or QN and QD) was observed, leading to speculate that the "superstructure" generated by configurationally-specified polymer domains could have some influence in the asymmetric induction process. Overall, the best results provided by **61a-c** could not reach, however, the performances of the CD derivative **59b** (see 1.4.2).

[94] Labadie, J. W.; Deegan, T. L.; Gooding, O. W.; Heisler, K.; Newcomb, W. S.; Porco, J. A., Jr.; Tran, T. H.; Van, E., P. *Polymeric Materials Science and Engineering* **1996**, *75*, 389-390.

Even if the anchoring through 9-*O* and N1 can be considered two equally viable routes for the immobilization of alkaloid PTC, the comparison between the results attained by the Spanish and the French groups suggest that the optimal solution in terms of enantioselectivity has probably to be found case by case.

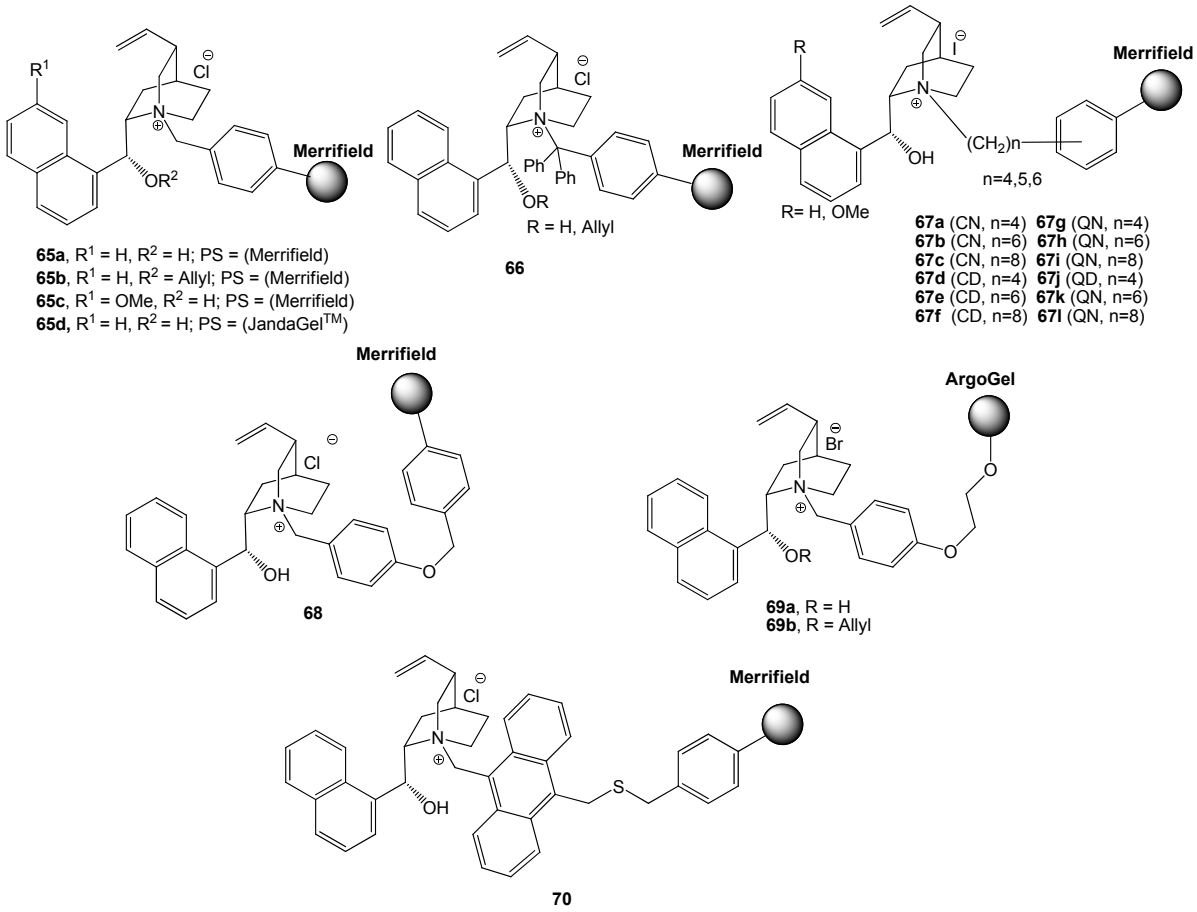


Figure 17. IPB alkaloid derivatives obtained by grafting/tethering through N1.

1.4.4. *IPB- Cinchona alkaloid derivatives linked at the 6'-O position.*

As a matter of facts, the 6'-*O* site of the *Cinchona* alkaloids QD and QN (Figure 18) is the less frequently used position for the attachment to an insoluble support. Probably, the reasons of this limited popularity have to be searched in the necessity of preparing derivatives suitable for anchoring (e.g. *dihydrocupreine*, the 6'*des*-methyl analog of DHQN) by demethylation of the commercially available DHQD or DHQN, as well as in the fact that no significant advantage for this strategy seems to have been reported to date for IPB materials.[95]

[95] For an application to soluble derivatives, see for example: Danelli, T.; Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. *Tetrahedron: Asymmetry* **2003**, *14*, 461-467

In fact, a very early example of this approach was already provided in the anticipated work by Hermann and Wynberg, where dihydrocupreine was anchored to cross-linked chloromethylPS to give **71**.[61d] However, this material afforded an almost racemic product in the benchmark Michael reaction (Figure 9, eq. 6) and, therefore, proved even less effective than the IPB organocatalysts anchored through 9-*O* (**55a** and **55b**).

More recently, the same approach has been briefly examined in the cited study Cahard and co-workers for the preparation of a supported PTC.[82] After anchoring dihydrocupreine to a Merrifield resin (60% yield), the resulting IPB alkaloid was *N*-alkylated with 9-chloromethylanthracene to give **72** in low yield (25%). Even if the conversion and yield in a standard Lygo-Corey benzylation were good, also in this case a practically racemic compound was unfortunately obtained. This led to the conclusion that in the case under exam the anchoring through 9-*O* or N1 can be more effective, in terms of enantioselectivity, than linking at 6'-*O* or C11 (see also **51a**,**b** in the see 1.4.1).

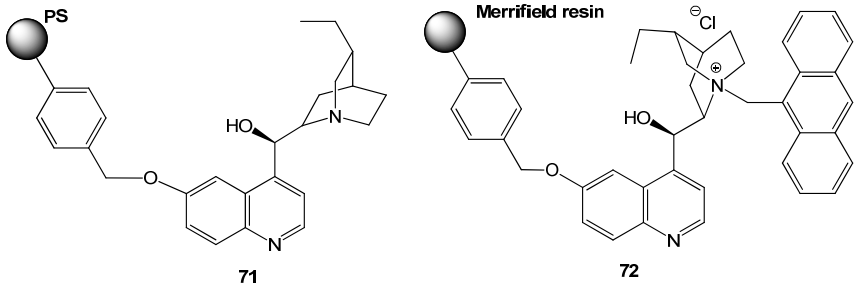


Figure 18. IPB alkaloid derivatives linked through the 6'-O position.

1.4.5. *Anchoring of amino and thiourea Cinchona alkaloid derivatives.*

Although the present Thesis is mainly focused on ligands and organocatalysts prepared by simple alkylation or acylation of the natural alkaloids, it has been mentioned (see 1.3) that their conversion into *epi*- or *nat*-9-amino(9-deoxy) analogs can often lead to more powerful amino or bifunctional derivatives. For the sake of completeness, a few examples of IPB systems belonging to this category (Figure 19) will be discussed in this paragraph.

The organocatalysts (**73a,b**) were prepared by direct grafting onto a Merrifield resin of amino eQN bearing two different amino-terminated spacer groups.[89b] The materials were then tested in the asymmetric conjugate addition of 1, -dicarbonyl compounds to *N*-benzylmaleimide and showed only poor performances (21-38% yield, 10-49% *ee*).

The bifunctional polymer-supported sulfonamide catalyst **74** was obtained by first synthesizing the corresponding chiral monomer and then embedding it by suspension radical copolymerization into a cross-linked PS network. The material was successfully employed in the methanolic desymmetrization of *meso* cyclic anhydrides to give enantioenriched chiral hemiesters (~99% yield, 89-97% *ee*). Recycling gave also reproducible results of up to 10 successive runs.[96]

In order to have the primary amino group free for derivatization, the IPB organocatalyst **75** was prepared by resorting to the radical addition of mercaptopropylsilanized SBA-15 to the vinyl group of the preformed *N*-[3,5-bis(trifluoromethyl)phenyl]thiourea chiral derivative. When employed in the Friedel-Crafts reaction of imines with indoles, **75** smoothly provided products with excellent results (65-79% yield, 89-99% *ee* after 5 days). The material could be also reused for three times with stable enantioselectivity, but a significant erosion of yield (up to 20%) observed in the last cycle. [97]

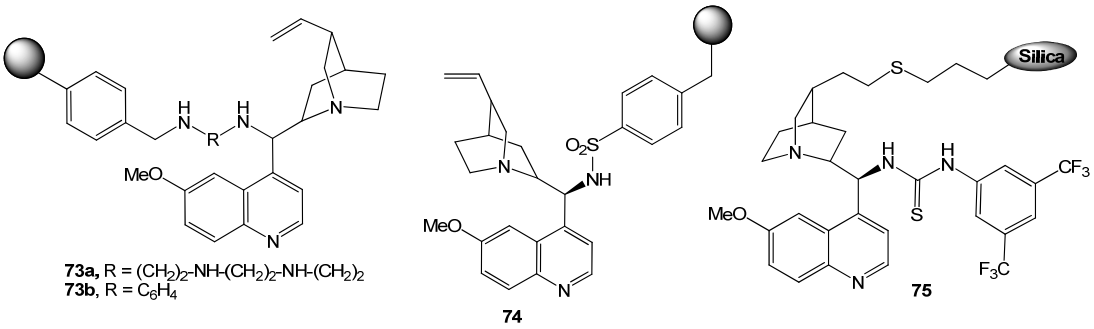


Figure 19. IPB amino and bifunctional alkaloid derivatives.

[96] Youk, S. H.; Oh, S. H.; Rho, H. S.; Lee, J. E.; Lee, J. W.; Song, C. E. *Chemical Communications.* **2009**, 2220-2222.
[97] Yu, P.; He, J.; Guo, C. X. *Chemical Communications* **2008**, *9*, 2355-2357.

1.5. A critical evaluation of known IPB *Cinchona* derivatives and assessment of open questions.

From the discussion in the previous paragraphs, it should be clear that the much efforts have been devoted in the last four decades to the development of IPB variants of the alkaloids of *Cinchona* and their derivatives. Overall, this body of work appears largely paradigmatic of recoverable enantioselective catalysts, in general, and allows therefore to draw some conclusions about the present state of advancement of the field.

In this respect, the first observation that can be made concerns the goals of the studies reported so far. With very few exceptions, these have been strongly focused on the attainment of high catalytic performances and, just to a much lesser extent, to the problem of whether the recoverable catalyst could actually find any application beyond and above the proof-of-concept level. On the one hand this emphasis was important because it allowed to outline the prominent design elements required for preparing covalently immobilized catalysts with satisfactory activity and enantioselectivity, and helped to demystify the belief that IPB systems would be irremediably ill-performing in comparison with the original homogeneous catalysts (as well as with respect to other recovery strategies).[14i, 22, 96]

On the other hand, however, limiting the attention to this single aspect appears largely unsatisfactory nowadays, when a more resolute thrust seems urgently needed for making the IPB asymmetric catalysts a common tool for work on preparatory scale in the synthetic organic chemist's laboratory. [14p]

In addition to the performance issue noted above, for any given homogeneous catalyst this paradigm shift requires to take into account two additional aspects (Figure 20): (*i*) how to develop an economic and scalable preparation of the IPB variant and (*ii*) how long the supported system can be recycled effectively.

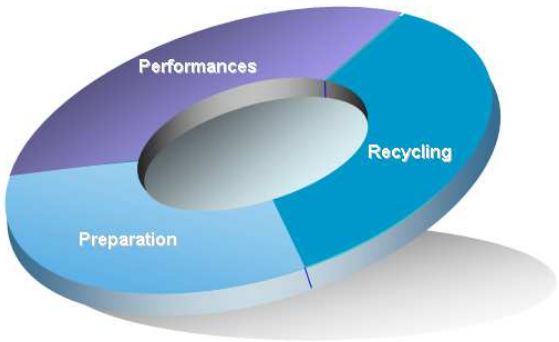


Figure 20. The three mandatory aspects for practical applications of IPB systems

As anticipated, these questions have been frequently neglected in the studies reported so far and, in many cases, implicitly deferred to an eventual scale-up stage (which, incidentally, practically never followed). However, when one considers that the preparation, performance, and durability goals often require conflicting solutions, it is evident that tackling just one or two of these aspects at time is not expected to lead to much progress. On the contrary, the design of IPB systems that comprehensively settle of all of the three issues simultaneously could only be the proper answer for the problem at hand.

Therefore it is not surprising that even in a recent review on the impact of catalysis in the pharmaceutical industry,[6d] just an example was reported for 'large-scale' applications of IPB chiral catalysts (*i.e.* the PS-supported Schiff base, (Figure 21) used at Chirex for the synthesis of enantioenriched amino nitriles).

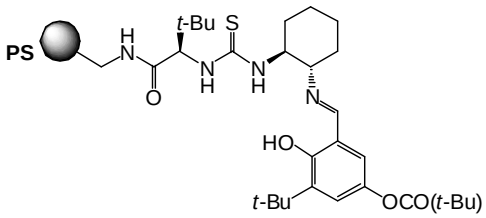


Figure 21. A polystyrene-supported Schiff base catalyst.

Before proceeding further with the discussion, it is worth considering a bit more in detail what 'practical applications' could mean in this context. In fact, the potential scenarios where the IPB systems may conceivably find a routine use are quite ample, ranging from high throughput R&D investigations to the actual production of fine chemical. Given the large variability of typical working scales in these applications (milligrams to kilos to tons)[9b] widely different requirements can also be expected for what it concerns the characteristics of the IPB system.

For the purposes of the present work, a practically relevant IPB enantioselective catalyst will be considered a material for which: (*i*) no obvious limit exists for scaling-up at least to gram quantities, (*ii*) affords ≥ 90% *ee* in one or more asymmetric transformations, and (*iii*) can be recovered and reused ≥ 20 times without any significant reduction of the activity and enantioselectivity.

Albeit rather arbitrary as a definition, this choice has the merit of including as a minimal target for the preparation problem, the packaging sizes of the few IPB chiral derivatives that already found a way to commercialization (*e.g.* polymer-bound TADDOL,

pseudoephedrine, and tartaric acid from Sigma-Aldrich)[98]. Moreover, although the limits set may look largely conservative, it is interesting to note that nearly all of the IPB *Cinchona* derivatives discussed in the previous paragraph would strive in meeting even these loose requirements.

Concerning the preparation, the main problems appear to arise in either the synthesis of a soluble derivative suitable for anchoring, or in the immobilization step itself. The former case is typical for IPB systems obtained by copolymerization (*i.e.* **34**, **42-45**, **52** and **53**), where the synthesis of functional monomers (normally styrene or methacrylate type) requires several steps and repeated chromatographic purifications.[63c,74-77, 61b, 83] By contrast, the latter problem is often met when anchoring of the alkaloid derivative to a preformed insoluble support is attempted. In particular, this appears to be the case when the rather popular addition of thiol groups supported onto siliceous materials to the alkaloid' C10-C11 double bond is used (*i.e.* **37**, **39**), because the straightforward preparation of the anchorable derivative is made vain by the low grafting yield and alkaloid loading [0.28 mmol g^{-1} and 0.49 mmol $g^{-1}$for **38** and 15.9 wt% loading for **39**] in the final material.[71a,70a] Instead, the alternative use of chloromethylated PS or chloropropyl silica-gel for grafting neutral derivatives by Williamson-type chemistry (**71** and **47**, respectively)[61,72f] is somewhat questionable due to the presence of very nucleophilic nitrogen atoms in the chiral cores, which could lead to unwanted alkylation reactions.[99, 100]

Hence, the sole IPB alkaloid systems that appeared reasonably scalable at the beginning of this work were those linked through the quinuclidine nitrogen (**65-70**)[54,66,82,90,91] or the simple 9-*O* esters obtained by the Lectka approach (**56**,**57**).[84,85] In both cases, the final IPB materials could be prepared by combining the native alkaloids, or simple derivatives thereof, with commercial resins, sometimes using a suitable linker/spacer reagent. However, the former class of materials essentially finds use as chiral phase-transfer catalysts only and the latter seems equally limited in catalysis scope to the excellent results provided by the American group.

[98] To give an idea of the commercial availability and the cost of these IPB catalyst precursors, the following figures from the Sigma-Aldrich catalog can be mentioned: *L*-tartaric acid polymer-bound,~ 1 mmol g^{-1}, 274 € for 5 g; (−)-2,3-O-benzylidene-1,1,4,4-tetraphenyl-*L*-threitol (TADDOL) polymer-bound,~ 0.4 mmol g^{-1}, 200 € for 250 mg; (*1R,2R*)-pseudoephedrine polymer-bound,1-2 mmol g^{-1}, 535 € for 25 g (2011 prices).

[99] **a)** O'Donnell, M. J. *Accounts of Chemical Research* **2004**, *37*, 506-517; **b)** Lygo, B.; Andrews, B. I. *Accounts of Chemical Research* **2004**, *37*, 518-525.

[100] Ishii, Y.; Fujimoto, R.; Mikami, M.; Murakami, S.; Miki, Y.; Furukawa, Y. *Organic Process Research & Development* **2007**, *11*, 609-615.

Besides a few specific cases where the simplified separation alone could be a sufficient reason for developing an IPB chiral catalyst, it is clear that the justification of the efforts required for preparing a recoverable system should normally come from the attainment of extended recycling. In this respect, the customary description of a few reaction runs only (typically 3-5 cycles, with "nearly unchanged catalysis results") appears therefore unsatisfactory, as it leaves largely unanswered the question whether the durability of the supported system could pay back for its –often rather onerous- preparation.

As before, the decision where to set the boundary that discriminates practical recyclability is somewhat a matter of an arbitrary choice, which involves the definition of both (*i*) the maximum acceptable extent of catalyst performance degradation and (*ii*) the minimum number of reaction cycles that the catalyst should survive before reaching the said limit. Although a meaningful decision in this sense could probably require a case-by-case analysis, the latter aspect has been recently discussed by Gun'ko, Connon, and co-workers. [86] These Authors proposed 20 cycles as the minimum level, that would encourage the synthesis of an IPB system "by the practitioner interested only in its use as a tool".

By adopting this perspective, the only IPB *Cinchona* alkaloid derivatives that could be taken as satisfactorily recyclable at the beginning of this Thesis were the phthalazine **44** (20 successive AD runs with 87-99% *ee*, depending on the alkene structure)[25] and the ester **57** (60 successive ketene-imine addition cycles, with 87-99% *ee*). [84]

As noted above, the synthesis of **44** was however too complicated for any reasonable practical application, thereby lacking in one of the three mandatory requirements outlined at the beginning of this paragraph. On the contrary, the preparation of **57** was arguably scalable and the number of recycles quite impressive but the fact that "the catalyst was employed at undisclosed loadings (yet considerably higher than 100 mol%)"[86] is likely to lead more to 'polymer-facilitated synthesis' than to true 'catalysis'.

Overall, forty years of research were then apparently insufficient for providing a single example of an IPB *Cinchona* derivative that could satisfy all the criteria dictated by the current trends in the field.

This last observation is at the origin of the present Thesis work, whose objectives and strategies are briefly outlined in the next paragraph.

1.6. Aims, contents and plot of the Thesis.

Given the previous discussion, the general goal of this Thesis was the development of procedures for the preparation of *Cinchona* IPB systems, which could nicely conjugate in a single architecture the three main requirements for practical applications, noted above (Figure 20). Due to the number of variables that could come into play, some strategic decision had to be taken at the onset. These may be summarized as follows:

- *Support type*. Even if the inorganic supports (*e.g.* silica-gel, mesoporous silicates, etc.) have often been claimed to be superior to the organic ones in terms of mechanical and thermal stability,[22] their use for catalyst immobilization can present problems that range from strong leaching[25] to unwanted interactions with the highly polar oxidic surface.[23] For this reason, in the present work organic polymers only were studied as support materials. Moreover, the further assumption was made that a right balance between chemical and mechanical stability and minimal perturbation of the anchored chiral units could be achieved by the selection of PS resins, whose use has been then thoroughly pursued in this Thesis.
- *Immobilization technique*. The covalent immobilization of any derivative onto (or within) an insoluble support is an inherently two-step procedure, composed by the preparation of a proper anchorable derivative to which the actual anchoring step follows. For the whole sequence to be reasonably convenient, no significant bottleneck (or efficiency loss) should then occur at any of the two stages. From this point of view, the (co)polymerization strategy can provide finely-tailored insoluble materials, usually in high yields, but it suffers from the need of preparing and handling sensitive functional monomers, usually by multistep synthetic schemes that start from the expensive alkaloid precursor. A further point of concern with this approach is the possible occurrence of chiral units deeply buried inside the macromolecular network and, hence, lost for catalysis. Grafting or tethering, as defined in 1.2 (Covalent binding), look therefore more appealing in principle, but still require the attainment of a sufficient efficiency and the avoidance of ambiguities due to the chemistry involved in the anchoring step. In consideration of the state of the art and the experience gained in our group, in this Thesis the hypothesis was then made that a convenient approach could be based on the generalized use of copper-catalyzed alkyne-azide dipolar cycloaddition as the method for ligating suitable alkaloid

derivatives to preformed resins. Besides providing the precise chemistry and the high efficiency desired for the immobilization step (Chapter 4), this choice was indeed expected to greatly simplify also the preparation of proper anchorable derivatives (Chapter 2).

- *Structure of the alkaloid derivative*. Generally speaking, the focus of this work was put on the immobilization of neutral 9-*O* ether derivatives of the pseudoenantiomeric alkaloids (hydro)quinine and (hydro)quinidine (Figure 2). Due to their large scope as enantioselective organocatalysts as well as the rather unsatisfactory preparation methods reported to date, a particular attention was dedicated to the immobilization of dimeric alkaloid derivatives that, in the panorama of IPB alkaloids, appeared to be the most challenging but, potentially, also the most rewarding ones.
- *Type of catalysis*. Even though the *Cinchona* alkaloids have a well established track as ligands in metal-catalyzed asymmetric transformations, the growing interest towards metal-free processes and the expectation that organocatalysts could be easier to recycle [38b,45b,101] suggested to substantially limit the scope of this Thesis to the latter class of reactions only. This led to explore a number of mechanistically diverse transformations (Chapter 5) with the ultimate goal to define the scope of the prepared IPB derivatives and, at least in a few cases, their recycling potential.

[101] **a)** Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481-2495; **b)** Dalko, P. I.; Moisan, L. *Angewandte Chemie, International Edition* **2004**, *43*, 5138-5175; **c)** Berkessel, A.; Groerger, H. *Asymmetric Organocatalysis.*; Wiley-VCH Verlag GmbH, **2005**.

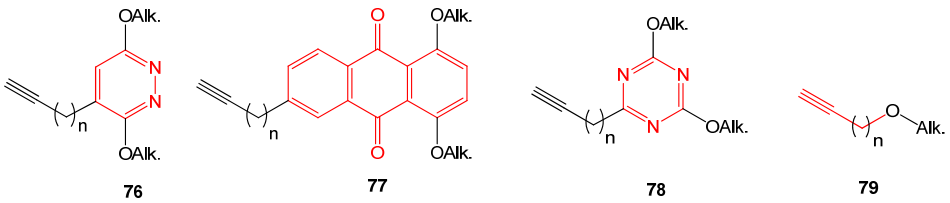
CHAPTER -2- DESIGN AND SYNTHESIS OF CLICKABLE *CINCHONA* ALKALOID DERIVATIVES

2.1 Synthetic strategy

The first objective of this work was to design synthetic schemes for the preparation of *Cinchona* alkaloid derivatives suitable for immobilization by Copper(I)-catalyzed azide-alkyne 1,3-dipolar 'click' cycloaddition (chapter-4). Given the anticipated interest in large-scale (multi-gram) applicability, the attention was primarily focused on procedures that made use of cheap chemicals and reliable transformations. In order to reduce chemicals waste and to increase the likelihood of scale-up, the avoidance of chromatographic purification steps was also considered highly desirable at this stage.

Having chosen the Huisgen reaction as the immobilization technique, two different strategies could emerge, *i.e.* the use of alkaloid derivatives with a terminal acetylene group and polymer supports bearing azido units, or vice versa.

On the assumption that it could significantly simplify the preparation of the anchorable chiral derivatives and avoid the hazard of handling low molecular-weight azides, the first approach was adopted in the present Thesis. With this initial decision, four general types of *Cinchona* alkaloid 9-O ether derivatives (Figure 22) were considered of potential interest for this work in view of the similarity to known effective ligands or organocatalysts (**76** and **77**), the possibility of devising a simple preparation route (**78**), or the already demonstrated suitability for kilo-scale applications (**79**).[102]



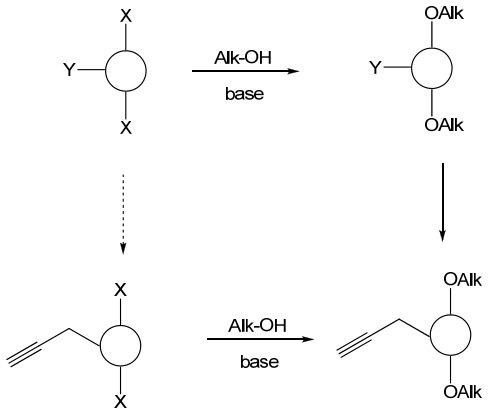
Alk-OH	R	Configuration
QD	vinyl	8R, 9S
DHQD	Et	8R, 9S
QN	vinyl	8S, 9R
DHQN	Et.	8S, 9R

Figure 22. Different types of *Cinchona* alkaloid derivatives planned to be synthesized.

Generally speaking, all of the selected derivatives, either monomeric or dimeric, could be reconducted retrosynthetically to a 9-O alkylation or arylation of the corresponding commercial alkaloid precursor with a proper halide. In this regard, it is worth noting that, in principle, the terminal acetylene unit needed for the subsequent 'click-chemistry' anchoring

[102] Ishii, Y.; Fujimoto, R.; Mikami, M.; Murakami, S.; Miki, Y.; Furukawa, Y. *Organic Process Research & Development* **2007**, *11*, 609-615.

could be introduced either before or after 9-O derivatization of the alkaloid had taken place (Scheme 2). Even though in the case of anthraquinone derivatives the latter approach was eventually followed by analogy with literature precedents, the former one was generally deemed preferable in this work as it was expected to lead to a more efficient synthetic use of the relatively expensive alkaloid precursor.



Scheme 2 Preparation of clickable *Cinchona* alkaloid derivatives

The detailed description of the synthesis of different 'clickable' *Cinchona* alkaloid derivatives belonging to the four general classes noted above is given in the rest of this chapter.

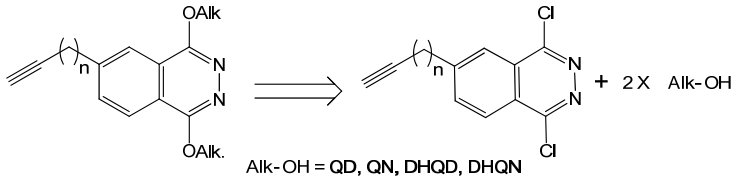
2.2. Preparation of clickable pyridazine-core dimeric *Cinchona* alkaloid-derivatives.

As anticipated, several studies have been reported in the literature describing phthalazine- and pyridazine-core dimeric *Cinchona* alkaloid derivatives on polymer supports (see 1.4). However, it has been already noted that most of them missed to tackle important aspects like the stability of the supported ligand/catalyst, with the associated leaching and recycling problems. Even when this was done, as in the case of the ligand **44** prepared in our group (chapter-1),[25] the sensitivity of the styrenic comonomers involved in the preparation of the material and need of repeated chromatographic purification steps, made the approach difficult to apply on a reasonably large scale.

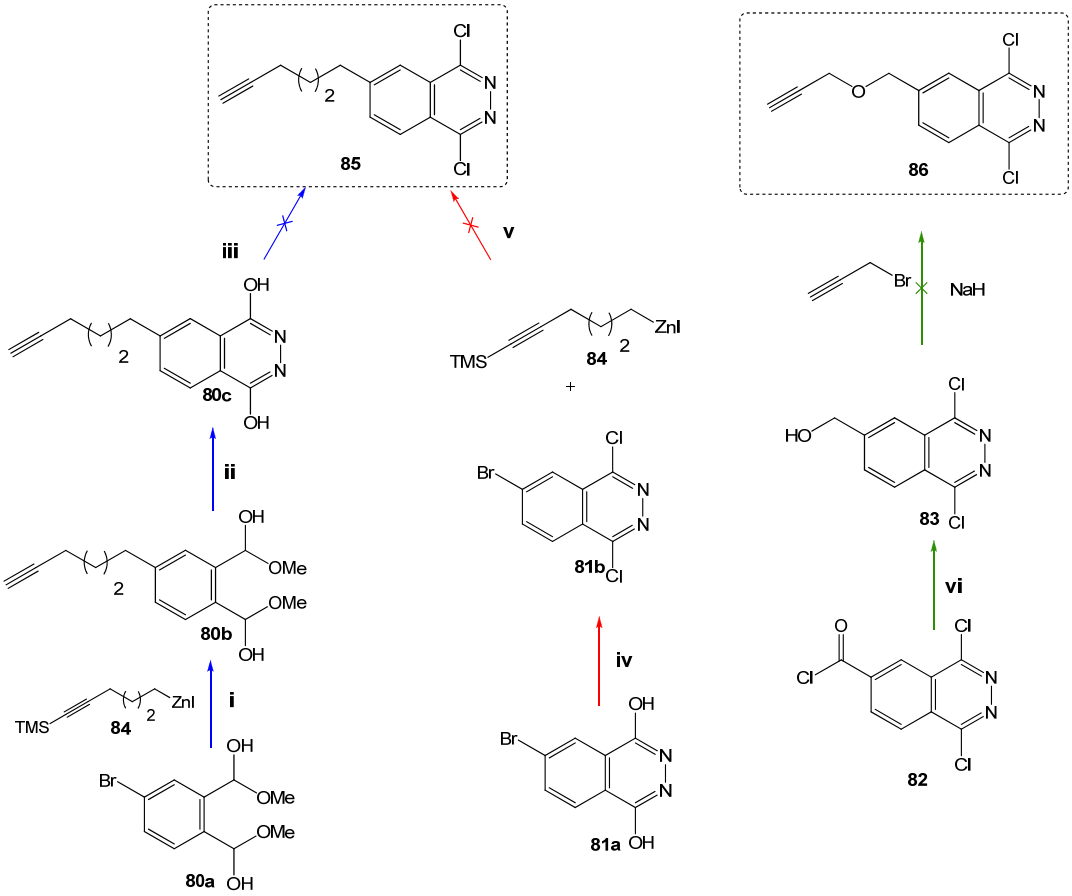
For this reason, in a previous Doctoral Thesis an attempt was made for obtaining 'clickable' phthalazine ethers by the strategy outlined in the Scheme 3.[103] Unfortunately,

[103] Lessi, M. *Ph.D. Thesis, XX-cycle*, Universita di Pisa, **2007**

several efforts to prepare 1,4-dichlorophtalazine derivatives provided with a terminal acetylene unit faced however a constant lack of success due to the mutual incompatibility of the conditions needed for introducing on the heterocyclic nucleus the alkyne-terminated spacer and the chlorine substituents (for an idea of some of the explored routes, see Scheme 4).



Scheme 3. Retrosynthetic approach for the synthesis of 'clickable phthalazine derivative'.



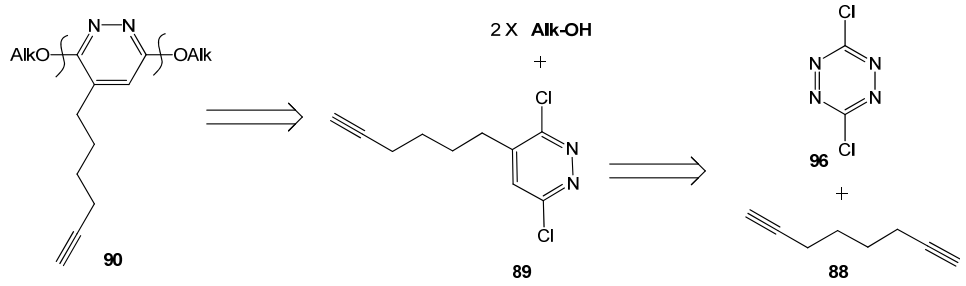
Scheme 4. Routes tried for synthesis of 'modified dichlorophthalazine derivatives' (85, 86)

i) a: Pd(dppf)Cl_2(5mol%), THF, Δ; **b**: TBAF,THF (deprotection); PCl_5/ DMF_{cat}/ 145°C. ; **ii)** $NH_2NH_2.H_2O$, MeOH/H_2O; **iii)** PCl_5/DMF_{cat}, Δ; **iv)** PCl_5/ DMF_{cat}/ 145°C. ; **v)** Pd(dppf)Cl_2, Dioxane; **vi)** $NaBH_4$, Dioxane, 55°C.

For these reasons, at the onset of the present work the attention was shifted towards dimeric alkaloid derivatives belonging to the pyridazine class (general structure **76**). In this respect it is worth noting that, on the one hand, the catalytic performances of pyridazine

chiral ligands have generally proven comparable to those of the corresponding phthalazine ethers, at least as far as their use in the AD reaction was examined.[104] On the other hand, the possibility of obtaining 4-substitued-3,6-dichloropyridazines by a tandem inverse electron-demand Diels-Alder (IED-DA) nitrogen extrusion-reaction [105] between 3,6-dichloro-1,2,4,5-tetrazine (**96**) and a suitable acetylene compound seemed to offer an especially simple solution for the problem at hand. Indeed, by following the analysis shown in the

Scheme 5 the synthesis of the 'clickable' alkaloid derivatives **90** could be traced back to the preparation of the pyridazine derivative **89** that, in turn, could be conceivably obtained by the mentioned reaction sequence between **96** and 1,7-octadiyne (**88**).



Scheme 5. Retrosynthetic hypothesis for synthesis of clickable pyridazine derivative 90

As discussed in following paragraphs, this hypothesis proved correct and eventually allowed the preparation of a range of chiral derivatives **90**, suitable for immobilization by the anticipated 'click' strategy.

2.2.1 Preparation of 3,6-dichloro-1,2,4,5-tetrazine (96)

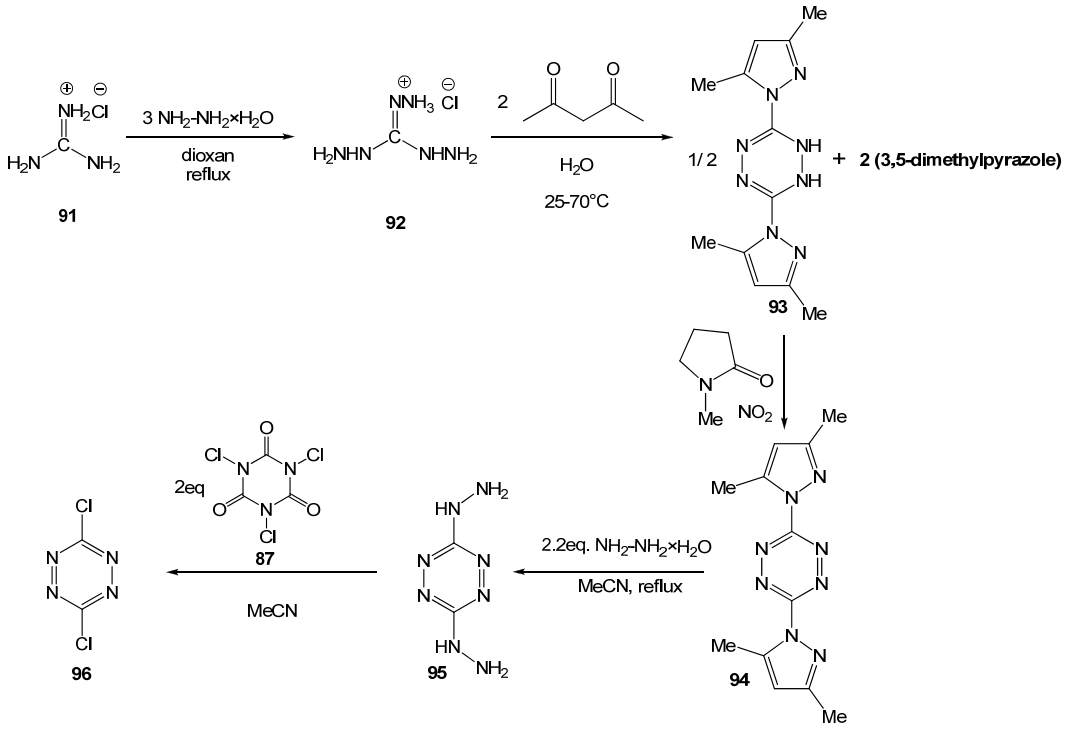
As described in the literature, the needed tetrazine **96** can be obtained in five steps from cheap commercial chemicals (Scheme 6).[106,107] As the different reactions appeared to be simple and required no chromatographic purification at any stage, for the preparation of **96** the published procedures were followed with the minor changes discussed below.

In the first step guanidine hydrochloride (**91**) was reacted with 3.5 equivalents of hydrazine monohydrate in 1,4-dioxane to give the hydrochloride of triamminoguanidine

[104] Corey, E. J.; Noe, M. C.; Sarshar, S. *Journal of American Chemical Society* **1993**, 115, 3828 –3829.
[105] **a)** Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th Edition*; John Wiley & Sons, Ltd., **2000.** Chapter 15, p. 1062; **b)** Boger, D. L. *Chemical Reviews* **1986**, *86*, 781-794; **c)** Sparey, T. J.; Harrison, T. *Tetrahedron Letters* **1998**, *39*, 5873-5874.
[106] **a)** Coburn, M. D.; Ott, D. G. *Journal of Heterocyclic Chemistry* **1990**, *27*, 1941-1945; **b)** Coburn, M. D.; Buntain, G. A.; Harris, B. W.; Hiskey, M. A.; Lee, K.-Y.; Ott, D. G. *Journal of Heterocyclic Chemistry* **1991**, *28*, 2049-2050.
[107] **a)** Schirmer, U.; Wuerzer, B.; Meyer, N.; Neugebauer, F. A.; Fischer, H. (*BASF A.-G.; Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V.*) Ger. Offen. DE 350821411 **1986** [*Chemical Abstract* **1987**, *106*, 45718p]; **b)** Helm, M. D.; Plant, A.; Harrity, J. P. A. *Organic & Biomolecular Chemistry* **2006**, *4*, 4278-4280.

(**92**). After separation by filtration, washing with dioxane and drying under reduced pressure, the product (96% yield) was characterized by determining the melting point, which was in agreement with the literature value. [106b]

The second step of the sequence consisted in heating a solution of **92** in water with two equivalent of acetylacetone. Under these conditions **92** condensed with the diketone to afford the desired dihydrotetrazine derivative **93** and two equivalents of 3,5-dimethylpyrazole. Remarkably, the formation of a mixture was not a serious problem here because, on cooling, **93** separated as nice crystals while the more soluble 3,5-dimethylpirazole (largely present as its hydrochloride salt) remained in the aqueous solution. After filtration, washing with little water and drying at 60°C under vacuum (or in a dessiccator over P_4O_{10}), the intermediate **93** was obtained in 66% yield, with melting point and spectroscopic constants in agreement with those reported in the literature. [106b]



Scheme 6. Sequence of reactions for the preparation of 3.6-dichloro-1,2,4,5-tetrazine (96)

Based on literature, the oxidation of the heterocycle **93** to the corresponding aromatic derivative **94** can be conducted with a variety of reagents, including nitrogen dioxide. With NO_2, the reaction is virtually instantaneous, quantitative, and clean, and can be easily carried out by first condensing a stoichiometric amount of the oxidant, for measuring its volume, and then vaporizing the liquid and by bubbling it through a suspension of the substrate **93** in *N*-methylpyrrolidone (NMP). [106b]

In this work, the small amount of needed NO_2 was prepared through the thermal decomposition of lead(II) nitrate. In practice, a mixture of $Pb(NO_3)_2$ and sand was placed in a Pyrex glass tube connected to the vessel containing the substrate by way of an intermediate empty washing bottle. The Pyrex tube was heated with a flame to start the NO_2 production and the brownish fumes were forwarded to the suspension of **93** in NMP with the aid of an air stream. The consumption of **93** was easily followed by the colour change, from yellow to deep orange, and by TLC. The product was then isolated by pouring the reaction mixture in water, filtering and washing with water. After drying under vacuum over P_4O_{10}, the compound **94** was obtained as a deep red solid (78% yield), with melting point and spectroscopic constants identical to those reported in the literature.[106b]

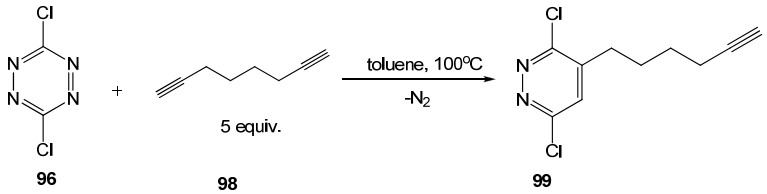
For the conversion of **94** into **95**, the published procedure was followed.[106a] Accordingly, **94** was treated with two equivalents of hydrazine monohydrate in acetonitrile under reflux condition. The desired product **95** was formed together with two equivalents of 3,5-dimethylpyrazole. The latter, being soluble in acetonitrile, was easily removed from the desired product which, on the contrary, is sparingly soluble in the common organic solvents. The filtration residue was washed with acetonitrile and dried under vacuum to give **95** as a red-brown solid (83% yield). Characterization of product was primarily based on its melting point (which was in agreement with literature),[106a] as the NMR spectra of the compound were not described in the literature. Nonetheless, it may be noted that the ^{13}C NMR spectrum of a diluted sample of **95** in DMSO-d_6 showed a single significant resonance at 163.3 ppm, a value similar to that observed in the ^{13}C spectrum of the final dichlorotetrazine product **96** (168.1 ppm).

The last stage of the sequence was the oxidation/chlorination of **95** to **96**. This reaction can be performed with chlorine or, more conveniently, with trichloroisocyanuric acid.[107] In this work, **95** was transformed into **96** by treating its suspension in acetonitrile with a solution of trichloroisocyanuric acid in the same solvent. As **96** is very soluble in the reaction medium in contrast to the reduction product of trichloroisocyanuric acid, the latter could be largely removed by filtration. After evaporation of the filtrate, the literature procedure of sublimation in a nitrogen flow was initially followed for the purification of the product (51% yield).[107] Afterwards, a more convenient satisfactory procedure for the large-scale purification of **96** was however found, which consists in the dissolution of the crude product in boiling *n*-heptane, filtration under an inert atmosphere to remove any undissolved materials and then cooling of the filtrate to room temperature. The crystallized

product was separated by filtration under nitrogen, washed with a small amount of *n*-pentane and dried under reduced pressure to provide bright orange crystals of **96**. By concentration of the mother liquors to a small volume and a new crystallization, two additional crops of the product were obtained (73% combined yield). For all the crops, the melting point and the ^{1}H and ^{13}C NMR spectra were consistent with the literature data.[107]

2.2.2 Preparation of 3,6-dichloro-4-(hex-5-ynyl)pyridazine.

Once the dichlorotetrazine **96** was prepared, its IED-DA reaction with the commercially available 1,7-octadiyne (**98**) could be investigated. Since the reaction between the compounds under exam was not described in the literature, standard conditions for reacting **96** with monoalkynes were chosen.[105c] Hence, a toluene solution of **96** and **98** in 1:5 molar ratio was heated at 110-120°C (Scheme 7), monitoring the consumption of **96** by the colour fading and by GC. After 4 hours the analysis of a sample showed the complete disappearance of the tetrazine substrate **96** and one new GC peak at higher retention time. The resulting yellow-brownish solution was filtered through a glass frit to remove some insoluble dark impurities and the filtrate was fractionally distilled under vacuum, for recovering the excess of diyne **98** as a toluene solution that was employed in further preparations. The pale-brown residue was dried under vacuum and treated with warm *n*-heptane. After decantation for removing some insoluble materials, a practically pure product **99** was obtained by placing the filtrate in ice bath. Concentration of the mother liquors afforded two more crops of **99** as a clear solid (76% combined yield). The structure of the new compound was corroborated by ^{1}H NMR, ^{13}C NMR, ESI-MS and elemental analysis.

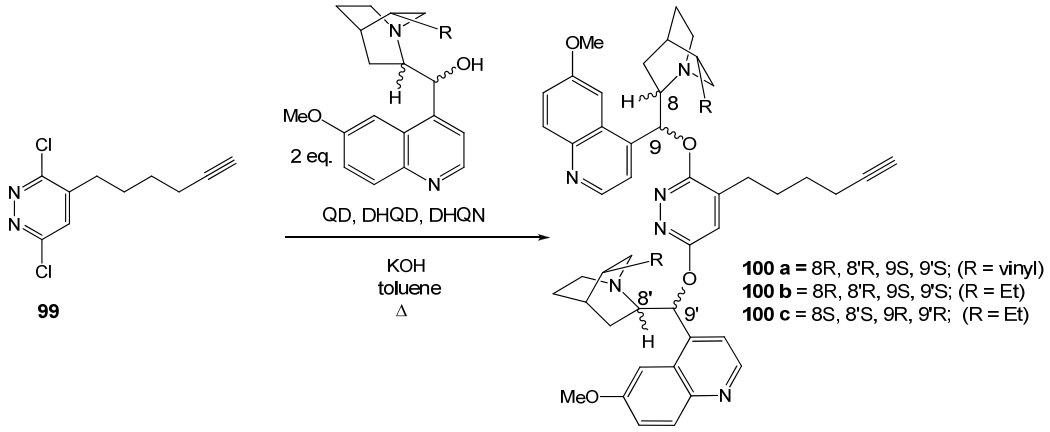


Scheme 7. Synthesis of functionalized aromatic spacer 99

2.2.3. Preparation of clickable ligands 100 a,b,c.

For the synthesis of the dimeric *Cinchona* alkaloid derivatives **100** the procedure originally used by Corey and co-workers for the preparation of the unsusbstituted PYR ligands **7** was chosen.[104] Therefore (Scheme 8) a toluene solution of the dichlorophthalazine

substrate **99** and two equivalents of the alkaloid (QD, DHQD, or DHQN) was heated at reflux in the presence of KOH, with azeotropic removal (Dean-Stark) of the formed water. In this regard, it should be noted that the use of an excess of base (as described for the parent derivatives **7**) did not prove suitable here because of the formation of byproducts, probably resulting from the alkyne-allene isomerization of the pyridazine side chain. However, the reduction of the amount of KOH to nearly the stoichiometric value was sufficient for circumventing the problem, eventually allowing the formation of **100a-c** in high yields. In fact, ^{1}H NMR analysis of the crude products obtained after extractive work-up revealed the presence of minor amounts (≈ 10 wt%) of toluene and the starting alkaloid as the sole significant contaminants (see the Experimental Section). Thanks to the possibility of washing away from the resin any compound that, being devoid of acetylene units, could not participate in the 'click'-process with the azide-functionalized support, these findings prompted the use of the crude **100a-c** in the subsequent anchoring step. However, for the purpose of confirming the identity of the newly synthesized compounds, small samples were purified by flash chromatography and characterized by ^{1}H NMR, ^{13}C NMR, ESI-MS, and determination of the optical rotatory power (Experimental Section).



Scheme 8. Synthesis of modified dimeric pyridazine ligand

In the course of preparations of **100a**, TLC analysis revealed the transient presence of a less retained compound **101** that, given its lower polarity, was likely to be one of the two possible regioisomeric mono-alkaloid intermediates *en route* to the final bis-alkaloid product. To isolate such an intermediate and determine its actual structure, a regular preparation of **100** was stopped before complete conversion and a sample of the resulting mixture was separated by column chromatography. By these means **101** (17%) could be obtained as a TLC homogeneous fraction, alongside with the expected derivative **100a**

(80%). To probe its identity, the compound **101** was subjected to ESI-MS and ^{1}H NMR analyses. Both techniques confirmed the introduction of a single alkaloid unit on the pyridazine core and, in the case of the latter, also the presence of one product regioisomer only. A preliminary rotating-frame Overhauser enhancement spectroscopy (ROESY) experiment revealed a close spatial proximity of the quinoline H_1 and pyridazine H_a protons, as well as the lack of any strong dipolar interaction between the acetylene side chain and the alkaloid moiety (for the numbering, see Figure 23). These results are therefore consistent with the depicted structure for **101** that, unsurprisingly, may form through nucleophilic displacement of the least hindered chlorine atom of the starting compound **99**.

As described in the chapter-5, the isolation of **101** allowed performing some control catalysis runs aimed at highlighting the possible effect of minor amounts of immobilized monomeric units in the IPB materials obtained from the crude precursor's **100a-c.**

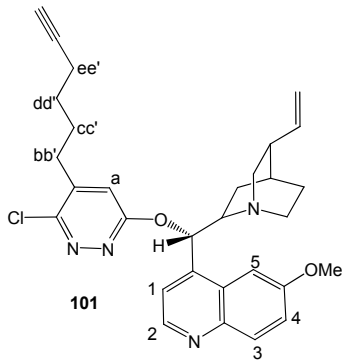


Figure 23. Numbering scheme of the alkaloid derivative 101.

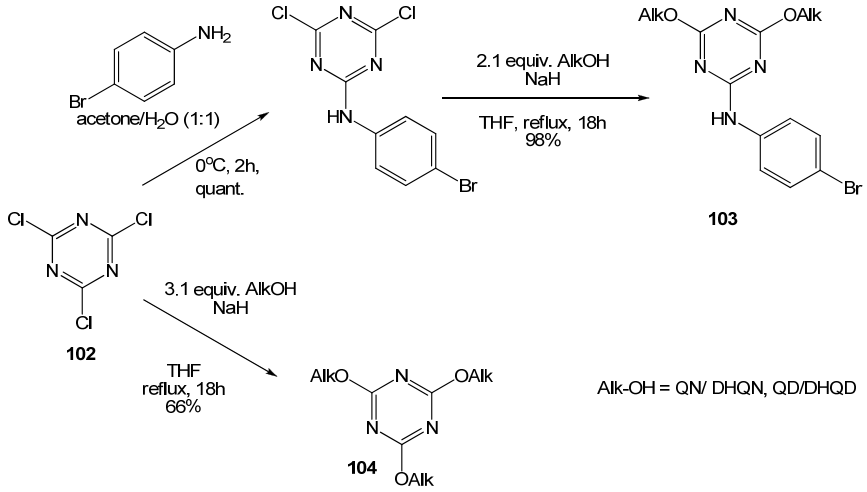
Overall, the route devised for preparing **100a-c** appears to meet the first of the general aims set out at the beginning of this work. In fact, not only the 'clickable' alkaloid derivatives could be obtained without the need of chromatographyc purifications at any stage, but the procedure proved also simple and, apparently, thoroughly scalable. In fact, in the course of this Thesis the whole sequence was carried out several times, preparing up to ~ 3 g of the tetrazine **96** and 14 g of the alkaloid derivative **100**: Given the excellent reproducibility of all the steps involved, no obstacle seems however present for a substantial increase of the synthetic scale.

As these findings encouraged to further implementation of the strategy and the exploration of the other alkaloid derivative structures, shown in the Figure 22, followed.

2.3. Preparation of clickable triazine-core dimeric *Cinchona* alkaloid-derivative.

As anticipated, the dimeric 9-O derivatives of the *Cinchona* alkaloids **6**-**9** (Figure 4) are finding more and more applications as powerful chiral organocatalysts. While this success certainly stems from specific structural features, their popularity and widespread use is undoubtedly connected also with the fact that these compounds have been commercially available since the introduction by Sharpless in the 90's as chiral ligands.

Because the central aromatic spacer between two alkaloid units often exerts a strong influence on catalytic performances, it cannot be excluded, however, that better organocatalysts could be discovered by exploring alkaloid derivatives other than the commercial ones. In this respect, compounds with a strongly electron poor central spacer, like the 1,3,5-triazine one, have been almost entirely neglected. Indeed, despite the straightforward preparation of dimeric (**103**) and trimeric (**104**) triazine derivatives (Scheme 9),[108] just a few examples have been reported to date where this sort of alkaloid structures were used in either metal-catalyzed [108] or organocatalyzed reactions.[47,109]



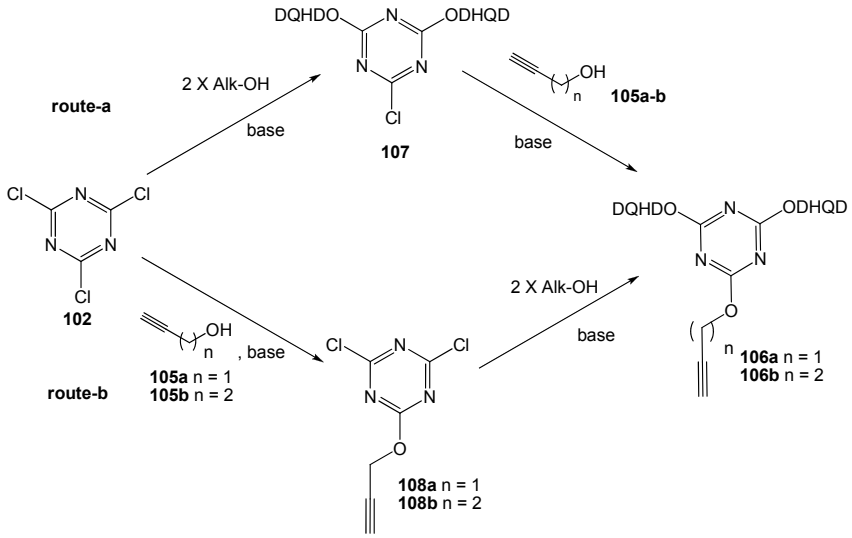
Scheme 9. Preparation of 1,3,5-triazine derivative 102, 103

Taking into account these facts, the development of new organocatalysts with a 1,3,5-triazine central spacer looked interesting for the purposes of the present work, in at least two aspects: first, to evaluate in asymmetric synthesis some derivatives whose

[108] McNamara, C. A.; King, F.; Bradley, M. *Tetrahedron Letters* **2004**, *45*, 8527-8529
[109] Chen, H.; Jiang, R.; Wang, Q.-F.; Sun, X.-L.; Zhang, S.-Y. *Acta Chimica Slovenica* **2009**, *56*, 694-697.

structure and stereoelectronic characteristics differ from those of most of the compounds studied so far; second, to exploit the possibility of selectively replacing the three chlorine atoms of 2,4,6-trichloro-1,3,5-triazine (**102**) for promptly accessing dimeric alkaloids provided with a pending acetylene group.

On this ground, a preliminary screening of organocatalysts possessing the anticipated general structure **78** was therefore decided. The practical implementation of this idea led to the design of the new compounds **106a,b**, whose synthesis (Scheme 10) could be plausibly reconducted to **102**, DHQD, and a suitable acetylenic alcohol like **105a** or **105b**.



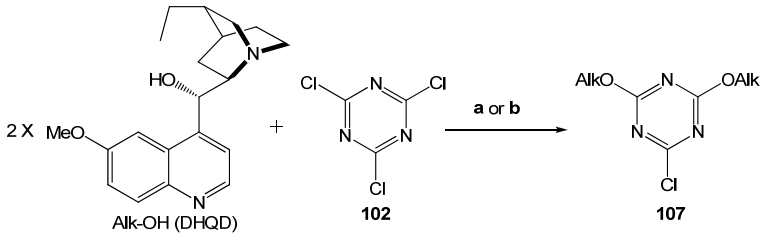
Scheme 10. Synthetic routes explored for the preparation of 106a-b

Because the order of introduction of the chiral and achiral substituents in the triazine nucleus of **102** could lead to a different overall efficiency of the synthetic scheme, the problem was tackled by exploring both of the two alternative approaches (*route a* and *b*) shown in the Scheme 10.[110] As discussed in the next paragraphs, only the second strategy proved however feasible and, also in this case, the procedure permitted a reasonable preparation of the derivative **106b** only.

[110] This work was done in collaboration with Ms. Anila Di Pietro [A. Di Pietro, *Laurea Triennale in Chimica*, University of Pisa (2010)].

2.3.1. Route-a: Preparation of 2,4-bis(10,11-dihydro-9-O-quinidinyl)-6-chloro-1,3,5-triazine (107).

Because **107** had not been previously reported in the literature, an initial attempt for its preparation was made by adopting the very same conditions already used for the synthesis of the dimeric derivatives of the pyridazine series (see 2.2.3). Unfortunately, heating a toluene solution of **102** with two equivalents of **DHQD** and a slight excess of KOH, with azeotropic removal of water (Scheme 11), led to a complex mixture containing at least 6 different alkaloids species by ^{1}H NMR



Scheme 11. Reagents and conditions: a. KOH (2.05 equiv.), Toluene, reflux (Dean-Stark), 4h.

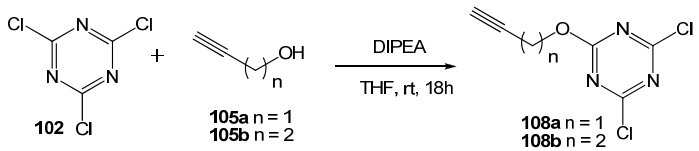
Searching for alternative conditions, the procedure by McNamara (see Scheme 9)[108] was explored next. Hence, **DHQD** was heated with a slight excess of NaH in THF and then the solution of the resulting chiral alcoholate was reacted with **102**. Also in this case, however, the ^{1}H NMR analysis of the crude product isolated after 18 h at reflux provided a poor spectrum, featuring much broadened peaks. Therefore, a further attempt was made by preparing the alkaloid sodium salt as described above, but avoiding heating in the subsequent reaction with the trichlorotriazine **102**. After stirring at room temperature until disappearance of **DHQD**, the ^{1}H NMR spectrum of the isolated product did not show a much improved quality with respect to the previous run. In spite of this, the crude was subjected to chromatographic purification to give two main fractions showing single spot by TLC. However, neither ^{1}H NMR nor ESI-MS analysis revealed the presence of the desired product **107**: The former afforded again broad signals, while the latter provided peaks at m/z values not compatible with the structure depicted for **107** (Experimental Section).

Even if no explanation can be provided at present for the outcome of these runs, it is worth noting that the high reactivity of **102** allows sometimes the dealkylative *N*-arylation of tertiary amines (see 2.3.2). Given the strong nucleophilic character of the quinuclidine nitrogen atom of the *Cinchona* alkaloids, it is therefore tempting to speculate that the attack of **102** at N_1 could trigger the formation of the unexpected and poorly characterized

products described above. In any case, these difficulties prompted us to abandon this way and to focus onto the alternative *route b* strategy.

2.3.2. Route-b: Preparation of 2,4-dichloro-6-(prop-2-ynyloxy)-1,3,5-triazine (108a) and Preparation of 2,4-dichloro-6-(but-3-ynyloxy)-1,3,5-triazine (108b).

The first step of this approach required the preparation of the dichlorotriazine derivatives **108a** and **108b**. Both compounds were obtained by the procedure already reported in the literature for the synthesis of **108a**,[111] consisting in the reaction of **102** with an equivalent of the required acetylenic alcohol **105a** or **105b** and an excess of N,N-diisopropylethylamine (DIPEA) (Scheme 12).



Scheme 12. Synthesis of the 108a

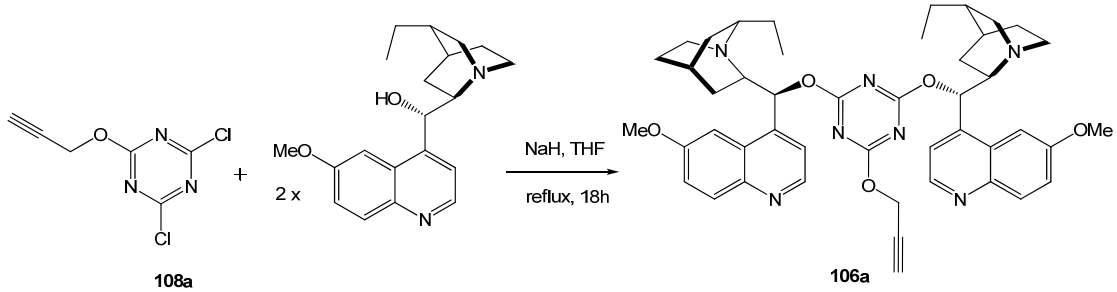
Under these conditions, the reactions proceeded smoothly, affording the desired products **108a** and **108b** in fair to excellent yields (50% and 92%, respectively) after chromatographic purification. In the case of **108a**, the chemical identity of the product was confirmed by comparison of the ^{1}H NMR and ^{13}C NMR spectroscopic constants with those reported in the literature.[111] On the contrary, since **108b** had not been described before its identity was proved by a detailed ^{1}H NMR, ^{13}C NMR, GC-MS and ESI-MS characterizations (Experimental Section).[112]

On the basis of the planned strategy (Scheme 13), the next synthetic step consisted in the double nucleophilic substitution on **108a,b** by deprotonated **DHQD**. The conditions selected for this purpose were those reported by McNamara and co-workers for the synthesis of **103** (Scheme 9) and already discussed in the attempted preparation of **107**. Therefore, **DHQD** was converted into the corresponding sodium alcoxide by heating with

[111] Ghini, G.; Lascialfari, L.; Vinattieri, C.; Cicchi, S.; Brandi, A.; Berti, D.; Betti, F.; Baglioni, P.; Mannini, M. *Soft Matter* **2009**, *5*, 1863-1869.

[112] As anticipated, the chromatographic purification of **108a,b** afforded also significant amounts (8-21%) of a less-retained component. GC-MS and 1D- and 2D-NMR characterization of the compound revealed it was *N*-ethyl-*N*-isopropyl-2-amino-4,6-dichloro-1,3,5-triazine, *i.e.* the product of the reaction between **102** and DIPEA, with loss of an isopropyl group. Even if this reaction had been reported in toluene at 110°C [Reddy, N.; Elias, A.; Vij, A. *Journal of Chemical Research (Synopses)* **1998**, 504-505], its occurrence was not mentioned under the mild conditions of the preparation of **108a**.

NaH in THF and the resulting solution was added to the functionalized triazine **108a** and heated to reflux for 18 h (Scheme 13).

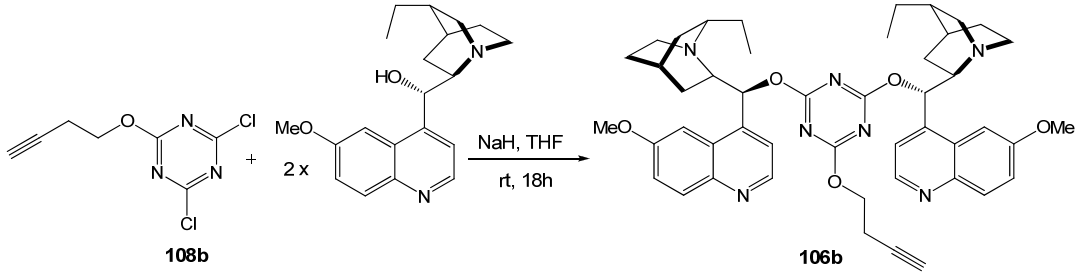


Scheme 13. Synthesis of the 106a

After extractive isolation the ^{1}H NMR spectrum of the crude product proved rather complex, showing at least four different alkaloid species (one being probably the **DHQD** precursor). Moreover, two resonances were observed that could be attributed to the propargyl unit (2.24 and 2.39 ppm, J = 2.4 Hz) but their intensities proved very low in comparison with the other alkaloid signals in the spectrum.

After chromatographic purification, the NMR analysis of the main fraction (23% yield, single spot by TLC) indicated the presence of two alkaloid derivatives in ~ 2 : 1 ratio. In this case, the intensity of the acetylene proton triplet (2.24 ppm) proved consistent with the alkaloid signals of the major component, thereby suggesting the presence of the desired acetylenic derivative **106a** in the mixture. Nonetheless, the low yield and the difficulties in separating the accompanying alkaloid byproduct discouraged further attempts to prepare **106a**. In this regard it is worth noting that the observation in the ^{1}H NMR spectrum of the isolated product of an apparent doublet (J = 1.8 Hz) at 4.51 ppm suggested that the minor component in the mixture could arise from the base-catalyzed alkyne-allene isomerisation of the propargyl unit of **106a**.[113] Reasoning that the removal of acetylene unit away from the triazineoxy substituent would allow a significant reduction in acidity of propargylic protons and, therefore, of the tendency to isomerisation, the use of the alternative derivative **108b** was examined next. The procedure for the synthesis of **106b** from **108b** was similar to that described for the preparation of **106a**, with the difference that the reaction was conducted at room temperature (Scheme 14).

[113] In support of this hypothesis, it can be said that the alkyne-allene isomerization of several 3-aryloxypropyne derivatives has been recently reported to occur under much milder conditions (*t*BuOK or NaH in THF at r.t.) than those employed for the synthesis of **106a**. See: Gonzales-Gomez, A.; Anorhbe, L.; Poblador, A.; Doninguez, G.; Perez-Castells, J. *European Journal of Organic Chemistry* **2008**, 1370-1377.



Scheme 14. Preparation of the 106b

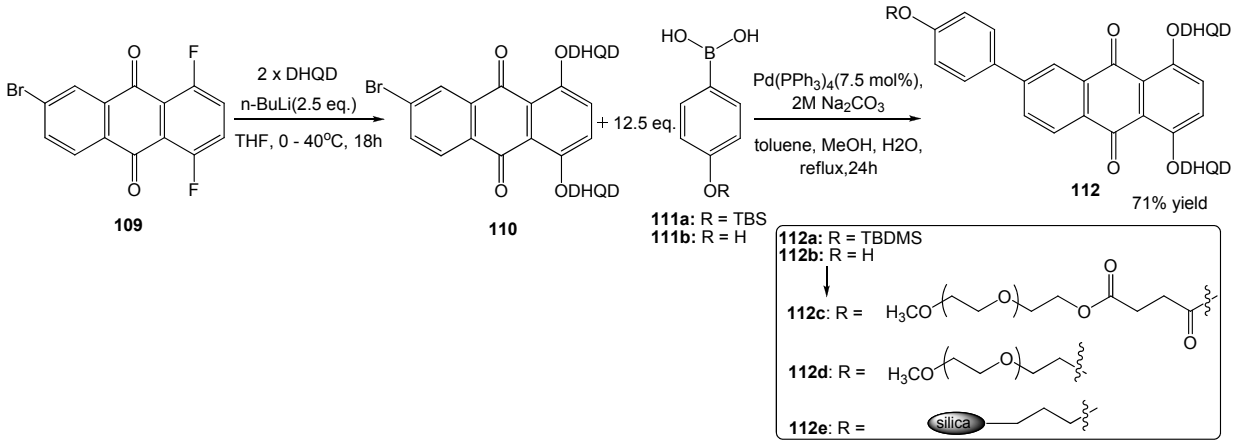
Unlike the synthesis of **106a**, in this case ^{1}H NMR analysis of the crude product showed the presence of a signal for the acetylene proton, whose intensity was compatible with the expected structure **106b**. Because two minor alkaloid components (5-10%) were present (probably the unreacted **DHQD** and the monosubstituted intermediate *en route* to **106b**), the crude mixture was subjected to purification by flash chromatography. By these means, a fraction showing a single TLC spot could be obtained (39% yield) that by ^{1}H NMR, ^{13}C NMR, and ESI-MS (see Experimental Section) proved to be the expected product **106b**.

Although the yield of **106b** was not particularly high and column chromatography was required for obtaining analytical samples, also in this case (compare section **2.2.3**) a possibility existed of using the crude product in subsequent click step, without the need of any purification. However, because the model compound obtained from **106b** did not prove particularly advantageous over other *Cinchona* alkaloid catalyst, no further effort was put in this work in trying to optimize the synthesis of triazine derivatives of the kind discussed above.

2.4. Preparation of clickable anthraquinone-core dimeric *Cinchona* alkaloid-derivative.

The dimeric *Cinchona* alkaloid derivatives provided with an antraquinone core (**8**, Figure 4) were first introduced in 1996 by Sharpless and co-workers as ligands for the AD reaction.[114] Afterwards their use was extensively explored not only in other metal-catalyzed reaction, but also in various organocatalyzed asymmetric transformations,[50-52] some of which have been disclosed very recently.[115]

Recoverable variants of **8** on linear polystyrene, PEG and silica-gel were also reported in the literature,[87,88] though, to the best of our knowledge, no example of immobilization onto crosslinked-polystyrene appeared to have been described to date. In this respect, an approach that seemed to potentially fit the aims of the present Thesis work was that of Bolm and co-workers, shown in the Scheme 15.[88c] In fact, as the route of the literature study required precious-metal catalysis and a further synthetic step (**110→112**) after the introduction of the alkaloid units in the aromatic spacer, this approach could be considered a bit more involved of those described in the previous sections. Nonetheless, it was speculated that with a few modifications (*vide infra*) of the published route to **112**, a scalable procedure could be obtained for the preparation of a dimeric anthraquinone derivative **114**, suitable for immobilization by click-chemistry (Figure 24).



Scheme 15. Literature preparation of recoverable anthraquinone derivatives of *Cinchona* alkaloids.

[114] Becker, H.; Sharpless, K. B. *Angewandte Chemie International Edition* **1996**, 35, 448-451.
[115] **a)** Yang, W.; Wei, X.; Pan, Y.; Lee, R.; Zhu, B.; Liu, H.; Yan, L.; Huang, K.-W.; Jiang, Z.; Tan, C.-H. *Chemistry-A European Journal* **2011**, *17*, 8066-8070; **b)** Zhu, B.; Yan, L.; Pan, Y.; Lee, R.; Liu, H.; Han, Z.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *Journal of Organic Chemistry* **2011**, *76*, 6894-6900.

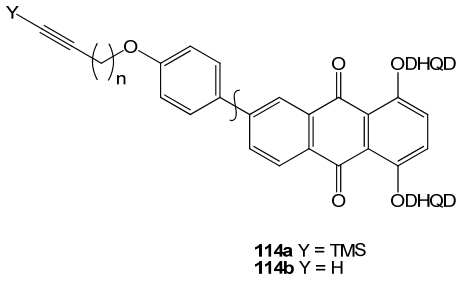
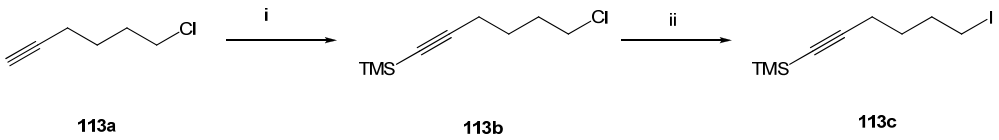


Figure 24. Clickable anthraquinone-core dimeric *Cinchona* alkaloid-derivative.

2.4.1. Preparation of (6-iodohex-1-ynyl)trimethylsilane (113c)

By following the literature method,[116a] the compound **113c** was easily obtained in two steps (Scheme 16) starting from the commercially available 6-chloro-hex-1-yne (**113a**).



Scheme 16. **a**: EtMgBr, THF/Et_2O, Δ ; **b** : TMSCl ; ii) NaI, acetone, reflux.

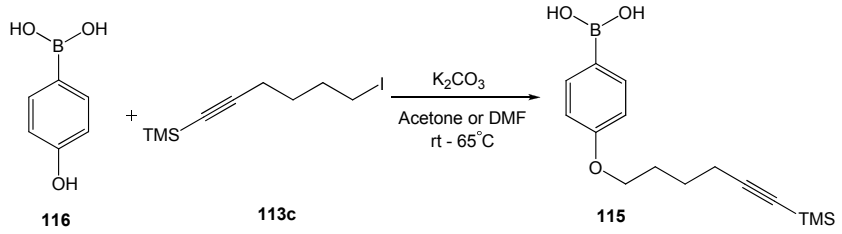
The reaction progress was monitored by gas chromatographic analysis (GC) of the reaction mixture until disappearance of significant presence of the substrate **113a** (16 hours). After dilution with *n*-pentane and filtration of the reaction mixture through glass frit, to remove the salts formed, the crude product **113b** was obtained with adequate purity (^{1}H NMR) and directly used in the next step. After refluxing **113b** with NaI in acetone for 30 h, the isolated product **113c** was characterized by ^{1}H NMR and ^{13}C NMR, providing spectral data consistent with the literature.[116b]

2.4.2. Preparation of 4-(6-trimethylsilylhex-5-ynyloxy)phenylboronic acid (115).

The phenylboronic acid derivative **115** was obtained by aliphatic nucleophilic substitution on **113c** with commercially available 4-hydroxyphenylboronic acid (**116**). The synthesis of this specific compound was not reported in literature, hence a general procedure was initially employed, which consisted in refluxing an acetone solution of **113c** and **116** (1 equiv.) with a stoichiometric amount of K_2CO_3 (Scheme 17). However, TLC and ^{1}H NMR analyses revealed that, under these conditions, the reaction was largely incomplete

[116] **a)** Van der Louw, J.; Komen, C. M. D.; Knol, A.; De Kanter, F. J. J.; Van der Baan, J. L.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron Letters* **1989**, *30*, 4453-4456; **b)** Knochel, P.; Singer, R. D. *Chemical Reviews* **1993**, *93*, 2117-88, (and ref. cited therin).

even after 36 h heating. Addition of an excess of **113c** and base did not improve the conversion to any significant extent, as confirmed also by the fair yield of **115** (54%) obtained after isolation and chromatographic purification of the crude product.

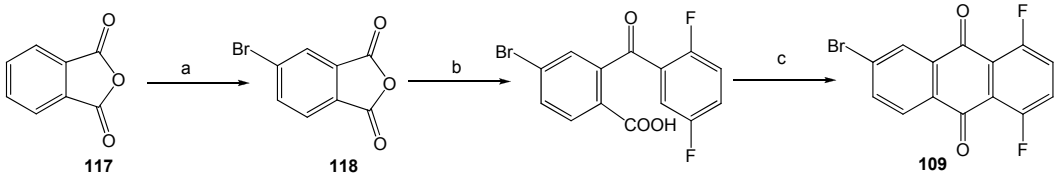


Scheme 17: Synthesis of 115

Therefore, a larger scale preparation of **115** was carried out by using DMF, as a more polar replacement for acetone, and heating the mixture up to 65°C. With these changes the reaction between **113c** and **116** turned out to smoothly proceed to complete conversion (117 h), eventually leading to a mixture showing a single spot by TLC. After extractive work-up, several washings with water to remove the DMF solvent, and evaporation of the volatiles at reduced pressure, the crude product was dissolved in methyl *t*-butyl ether (MTBE) and filtered to eliminate some insoluble impurities. Drying with a rotary evaporator furnished the product **115** (83% yield) in a form that was sufficiently pure (^{1}H NMR) to be used directly in the subsequent Suzuki-coupling step without the need of further treatments. The structure of the new compound **115** (which turned out to be identical to the product obtained in the previous preparation) was confirmed by ESI-MS and by ^{1}H and ^{13}C NMR (Experimental Section).

2.4.3. Preparation of 6-bromo-1,4-bis(10,11-dihydro-9-O-quinidinyl)-anthracene-9,10-dione (110)

With the purpose of having the dimeric *Cinchona* alkaloid derivative **110** (vide infra) for Suzuki coupling reaction, its intermediate compound **109** was prepared from phthalic-anhydride **117** as described in the literature (Scheme 18).[88c, 117]



Scheme 18. a: i)NaOH, H_2O, Br_2, 90ºC; ii) $SOCl_2$; **b**: 1,4-difluorobenzene(**119**) (11.6 eq.), $AlCl_3$ (4 eq.); **c**: polyphosphoric acid.

[117] **a)** Norman, M. H.; Kelley, J. L.; Hollingsworth, E. B. *Journal of Medicinal Chemistry* **1993**, *36*, 3417-3423; **b)** Krapcho, A. P.; Getahun, Z. *Synthetic Communications* **1985**, *15*, 907-910.

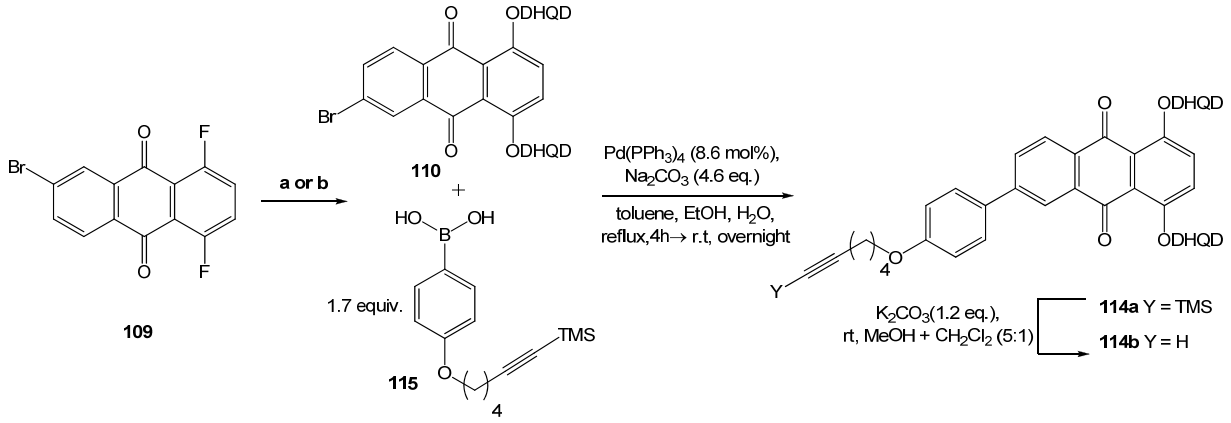
2.4.4. Preparation of 1,4-bis(10,11-dihydro-9-O-quinidinyl)-6-(4-(hex-5-ynyloxy) phenyl)anthracene-9,10-dione (114b)

For the synthesis of **110**, the original conditions by Bolm were initially chosen.[88c] Accordingly, **DHQD** in THF was first converted into the corresponding lithium salt with *n*BuLi and then used to replace the fluorine atoms of **109** (Scheme 19). Unfortunately, ^{1}H NMR and TLC monitoring of the reaction progress showed an incomplete conversion even after 18-36 h, with the presence of at least three main alkaloid derivatives (probably **110**, the corresponding monosusbtituted intermediates, and unreacted **DHQD**). Not surprisingly, this eventually led to a low yield of **110** (39%) after isolation and chromatographic purification of the product.

Reasoning that the problem in reproducing the published procedure could be related to the difficulty in dosing *n*BuLi accurately, the use of NaH in DMF was examined next. As monitored by ^{1}H NMR and TLC, under these condition the conversion of **109** was completed in 18 h and afforded a mixture that gave a single intense spot by TLC. After extractive workup followed by drying under reduced pressure, crude **110** was obtained in high yield (95%) and with spectroscopic constants matching those reported in the literature.[87b] Because ^{1}H NMR spectroscopy showed the presence of unreacted **DHQD** and residual DMF as the major contaminants, crude **110** (87% purity) was directly employed in the subsequent Suzuki coupling.

The Suzuki-Miyaura cross-coupling between the alkaloid intermediate **110** and the boronic acid **115** was carried out under conditions similar to those described by Bolm and co-workers for the synthesis of **112b** (see Scheme 15).[88c] However, unlike the published procedure where a large excess (12.5 equiv.) of the phenylboronic acid derivative **111** was employed, in this work just 1.7 equiv. of **115** were used and MeOH was replaced by EtOH (Scheme 19). Under these conditions the reaction smoothly proceeded to completion in 18 hours and afforded a single product by TLC analysis. For the purification, the reaction mixture was washed with water, to remove the inorganic salts, and then subjected to acidic treatment with 10% HCl, to extract alkaloid derivatives in the aqueous phase. However, subsequent neutralization of the latter with sodium bicarbonate and back-extraction of the basic organic compounds with ethyl acetate afforded a very little amount of material; by ^{1}H NMR this fraction turned out to be **DHQD** (present in crude **110**) and not the expected cross-coupling product **114a**. Nonetheless, on standing the neutralized aqueous phase separated a white precipitate, which was isolated by extraction with CH_2Cl_2. After

evaporation of the volatiles a solid form was obtained in substantial amounts (72% yield), whose ESI-MS and NMR spectra (Experimental Section) matched those expected for the structure **114a**.



Scheme 19. a) DHQD (2.5 equiv.), *n*BuLi (2.5 equiv.), THF, r.t. (18h) and 40ºC (18h); b) DHQD (2.05 equiv.), NaH (2.1 equiv.), DMF, r.t., 18 h.

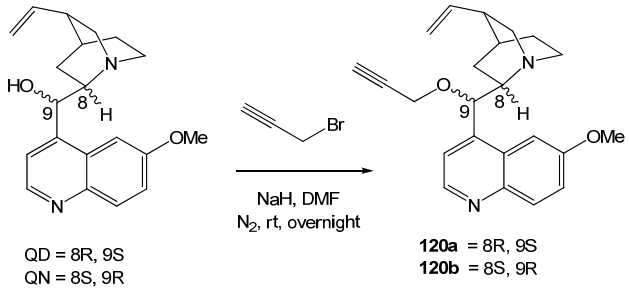
Deprotection of the alkyne group of **114a** was achieved by treating the compound with K_2CO_3 (1.2 equiv.) in MeOH:CH_2Cl_2 (5:1). After 64 hours stirring at room temperature, extractive isolation and evaporation of the volatiles afforded **114b** in an essentially quantitative yield with respect to **114a**. ESI-MS and NMR analyses (Experimental Section) confirmed the identity of the compound and demonstrated the absence of significant product contaminants.

In conclusion, a very straightforward procedure could be developed for the preparation of clickable *Cinchona* alkaloid ethers provided with an anthraquinone core. As anticipated at the beginning of the paragraph, the overall synthetic scheme may be considered a variant of the Bolm strategy for linking dimeric derivatives of this class to soluble polymers or insoluble inorganic supports. Nonetheless, the findings in this Thesis represent an advance over the literature precedents because, in addition to demonstrate the preparation of novel anthraquinone derivatives suitable for click-chemistry anchoring, eventually resulted in a complete sequence where all of the major bottlenecks towards scaling-up were effectively removed by careful optimization of the single reaction steps.

2.5. Preparation of clickable propargyl alkaloid derivatives.

In some cases, monomeric *Cinchona* alkaloid derivatives may display similar or even superior catalytic activity and stereoselectivity than analogous dimeric counterparts. One example in this sense is provided by the enantioselective kinetic resolution of urethane-protected amino acid *N*-carboxyanhydrides and the desymmetrization of *meso*-anhydrides, where simple organocatalysts like 9-*O*-propargyl quinidine (**120a**) and 9-*O*-propargyl quinine (**120b**) performed quite well on a multikilogram scale. [118, 119]

Taking into account that **120a** and **120b** can be easily obtained on a large scale by a simple one-step procedure (Scheme 20)[119] and that, expectedly, their terminal acetylene group could be exploited for the immobilization onto an azido-functionalized resin, this kind of derivatives were included in the set of 'clickable' alkaloid precursors examined in this Thesis work. Clearly, after the click step the propargyl group of **120a** and **120b** was going to be converted into a triazol-1-ylmethyl unit, thus leading to a completely new class of potential alkaloid organocatalysts.



Scheme 20. Preparation of 120a and 120b

2.5.1. Preparation of propargyl QN/QD.

According to the reported procedure,[119] **120a** and **120b** were obtained by deprotonation of **QN** or **QD** with NaH in DMF, followed by addition of slight excess (1.2 equiv.) of propargyl bromide at 0ºC and stirring overnight at room temperature. After extractive workup, the crude product was dissolved in ethanol, filtered through a pad of activated charcoal, and concentrated to dryness.

[118] Dai, H.-F.; Chen, W.-X.; Zhao, L.; Xiong, F.; Sheng, H.; Chen, F.-E. *Advanced Synthesis & Catalysis* **2008**, *350*, 1635-1641.
[119] Ishii, Y.; Fujimoto, R.; Mikami, M.; Murakami, S.; Miki, Y.; Furukawa, Y. *Organic Process Research & Development* **2007**, *11*, 609-615.

In the case **120a**, an attempt to purify the product by the literature procedure (recrystallization from EtOAc:*n*Hex) failed to provide a crystalline material. Nonetheless, the simple filtration through small pad of silica-gel was sufficient for obtaining a pure enough product in 91% yield.

In contrast, crude **120b** was first treated with boiling *n*-hexane, for removing the undissolved neutral contaminants by filtration, the filtrate was treated with 2N HCl; the aqueous phase was separated, followed by akalinization with $NaHCO_3$ and back-extraction in CH_2Cl_2 of the precipitated product, eventually afforded **120b** in high purity and nearly quantitative yield.

The ^{1}H and ^{13}C NMR spectroscopic data for **120a** and **120b** were identical to those reported in literature.

2.6 Conclusions

In conclusion, the synthesis of four different types of *Cinchona* alkaloid derivatives provided with terminal acetylene groups has been described. With the exception of **106a** and **106b**, where no particular effort was made in optimizing the synthetic sequence, the products were generally obtained with very straightforward procedures. Remarkably, in these cases the purification of the final product and all of the synthetic intermediates could be reduced to a minimum, in particular avoiding tedious and expensive chromatographic purifications.

In turn, this allowed to demonstrate for the first time the possibility of easily preparing anchorable dimeric alkaloid ethers (**100a,b**) on a multigram-scale and to define procedures for other derivatives (**106a**,**b** and **114b**) that appear similarly scalable. Together with the literature precedents for monomeric propargyl ethers (**120a**,**b**), these findings confirmed that the combination of the click-chemistry strategy with a careful optimization of the single synthetic steps could fulfil the first aim of this work, *i.e.* to prepare anchorable derivatives by procedures that present no obvious bottleneck in a scale-up perspective.

With the availability of four different types of *Cinchona* alkaloid ethers suitable for click anchoring, the immobilization onto insoluble supports was examined next.

CHAPTER -3- PREPARATION OF POLYMER SUPPORTS

3.1 Introduction

Due to the anticipated influence of the polymer architecture on the catalytic properties of IPB alkaloid derivatives (Chapter 1, section 1.4), as well as the potential interest in developing continuous-flow systems, the use of different polystyrene supports was briefly explored in the course of this Thesis. Besides converting commercial chloromethyl-polystyrene resins of the gel (Merrifield) and macroporous (ArgoPore^{TM}) type into the corresponding azidomethyl materials, the in-house preparation of a few other azido functionalized-crosslinked polymers was therefore investigated. The latter include resins with oligo(ethylene oxide) side chains and cross-linking agents and PS monoliths with a macroporous or *high internal-phase emulsion* structure (Poly-HIPE).

After providing in each case a brief introduction about the literature and the properties of the materials of concern, the next paragraphs will describe in detail the preparation and the characterization of these resins.

3.2 Azidomethyl poly(styrene-*co*-divinylbenzene) resins (Merrifield and ArgoPore^{TM} type).

Cross-linked chloromethylpolystyrene has a long history in the field of polymer-assisted organic chemistry, begun in the early 1960's with the pioneering work of Merrifield on solid-phase peptide synthesis (SPPS).[34] Afterwards, the same type of materials have been used more and more times in postmodification strategies for chiral catalyst immobilization,[14] even when a relatively large number of alternative organic supports become commercially available in the course of the years. The reasons of this popularity can be searched in the comparatively low cost of chloromethylpolystyrene,[120] the good compatibility of the PS backbone with all but the most of the polar organic solvents, and its availability in different morphological forms.

In fact, depending upon the level of cross-linking the polymer resin beads may show two distinct morphologies, *i.e.* a micropourous or a macropourous one.[121] Microporous

[120] Depending on the chlorine content, mesh size, cross-linking degree and morphology, different chloromethylpolystyrene resins can be purchased from Sigma-Aldrich at a cost that varies between ~ 3 and 7.5 € g^{-1}. For the sake of comparison, the price of the analogous brominated Wang resin is ~65 € g^{-1}.

[121] Sherrington, D. C. *Chemical Communications* **1998**, 2275-2286.

polymers (Figure 25a) are often referred to as *gel-type* materials because their swelling in a compatible solvent is accompanied by a significant expansion of the macromolecular network, up to forming a fully solvated state with gel properties. This behavior is normally possible only with low levels of cross-linking in the resin (*e.g.* 1-2%) and additionally it requires that the liquid medium has a good solvation capability for the polymer chains.

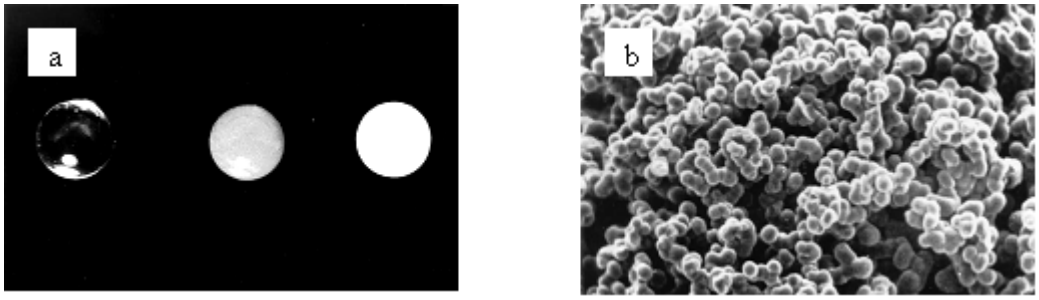


Figure 25. a) Optical photograph of (left) gel-type bead, (right) macroporous bead, and (centre) mixed morphology; b) Scanning electron micrograph of a macroporous resin fracture section (taken from ref. 121).

In contrast, the macroporous resins (Figure 25b) have a high degree of cross-linking (up to 50% or more) and are prepared in the presence of a suitable solvent or solvent mixture (the *porogen*), which causes phase-separation in the course the copolymerization process. By these means, materials can be prepared with a permanent porosity and high surface area (*e.g.* ~50-1000 $m^2 g^{-1}$) that is retained even in the dry state or in the presence of an incompatible solvent.[121]

Even in the case of a similar chemical composition, the actual resin morphology can strongly influence the material properties, there including advantages and shortcomings in the use as catalyst support.

Indeed, while gel-type resins often allow higher loadings and the attainment of a solution-like behaviour of the supported units, they tend to be mechanically fragile and, more important, their use is precluded into poorly compatible reaction media that cause the collapse of the macromolecular architecture. In this regard, it is also worth noting that if a gel-type resin is fully swollen with a good solvent and then introduced into an excess of bad solvent, the shrinking of beads starts from the outside and causes a very high mechanical stress (‘osmotic shock’) that can lead to the crack or burst of the polymer particles (Figure 26). Moreover, gel-type beads are soft and compressible and prove hence difficult to be used in packed-column continuous-flow systems.[121]

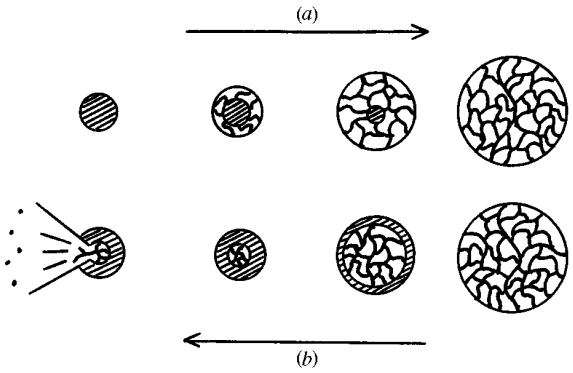


Figure 26. Solvent response of gel-type resins: *a*) swelling of the glassy core to form an expanded gel in a good solvent; *b*) contraction of swollen gel on addition of a bad solvent with bursting of the resin due to osmotic shock. (taken from ref. 121).

Unlikely microporous resins, the macroporous (or *macroreticular*) ones do not need to swell in a solvent in order to allow the access to their interior. In fact, thanks to the permanent porous structure and high surface area, this class of resins can be used even in solvents that are totally incompatible with the polymer backbone (*e.g.*, sulfonated macroporous polystyrene is commonly employed as an ion-exchange resin in water).

However, the much-reduced swelling capability with respect to gel-type resins leads the side effect that only the catalytic sites placed onto the exposed surface can be actually accessed by the reactants in solution. From the catalysis point of view, this tends to result in reduced loading capacities of such support materials. Moreover, while the high degree of cross-linking renders the macroporous resins much more rigid and well suited for packing flow reactors, the breaking of the brittle polymer beads under magnetic stirring can be still an issue. For this reason, suspension polymerization techniques are frequently employed in the preparation of resins of this class, in an effort to obtain nearly spherical polymer particles that show a reduced wearing tendency. Dedicated stirring techniques during the catalysis runs (*e.g.* the *tea-bag* approach)[122] have been also explored as a mean for circumventing this problem.

[122] With this technique, the IPB catalyst is placed inside a permeable polymer bag (or another container), which is then placed into the magnetically stirred solution. By these means the diffusion to and from the polymer beads is allowed, yet preventing the latter to be damaged by the magnetic follower. The strategy, originally developed for solid phase syntheses of peptides (Houghten, R. A. *Proceedings of the National Academy of Sciences of the United States of America* **1985**, *82*, 5131-5135.), in the field of heterogeneous catalyst has been named "tea-bag catalyst" by J. M. Thomas (Thomas, J. M. *Philosophical Transactions of the Royal Society of London, Series A: Mathematical, Physical and Engineering Sciences* **1990**, *333*, 173-207.

For some applications, see: a) Comina, P. J.; Beck, A. K.; Seebach, D. *Organic Process Research & Development* **1998**, *2*, 18-26; b) Berger, A.; Gebbink, R. J. M. K.; van, K., Gerard. *Topics in Organometallic Chemistry* **2006**, *20*, 1-38 (metallodendrimers); c) Rueping, M.; Sugiono, E.; Steck, A.; Theissmann, T. *Advanced Synthesis & Catalysis* **2010**, *352*, 281-287.

3.2.1. Preparation of gel-type and macroporous azidomethylpolystyrene resins.

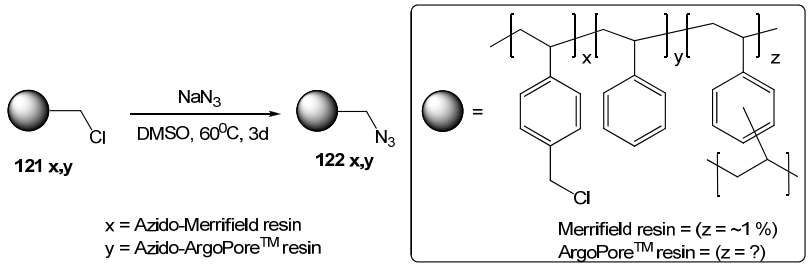
Considering that microporous (Merrifield) and macroporous (ArgoPore^{TM}-Cl) chloromethylpolystyrene resins are commercially available and that the chlorine group can be easily displaced by nucleophilic reagents, the materials, **121x** and **121y** were chosen as the initial candidates in the preparation of the azido supports required by the 'click' strategy pursued herein.

In order to convert **121x** or **121y** into the corresponding azidomethyl materials, literature conditions were adopted that involve heating of a Merrifield resin with an excess sodium azide in dry DMSO (Scheme 21).[123] In the present work, the reactions were carried out for some longer times under a nitrogen atmosphere, at slow stirring for avoiding mechanical damage of the polymer beads. After filtration of the suspension and thorough washing with water, MeOH, CH_2Cl_2 followed by drying under reduced pressure (0.5 mmHg), the materials **122x** and **122y** were obtained as off-white solids in 95% and 98% recovery yield, respectively.

The introduction of azido group in **122x** and **122y** was confirmed by the presence of 9.3 and 3.7% of nitrogen respectively by elemental analysis as well as by the observation of the strong IR azide stretching at 2095 cm^{-1},[124] and a positive colour test with PPh_3/ninhydrin (Kaiser test).[125] In the case of Merrifield resin (**122x)** as calculated by elemental analysis the N_3 substitution was almost complete (2.2 mmol g^{-1}) over initial chlorine content of **121x** (2.3 mmol g^{-1}). On the other hand, not surprisingly, in case of ArgoPore^{TM} resin (**122y**) the lower degree of substitution (0.9 mmol g^{-1}) was observed over (1.46 mmol g^{-1}) initial chlorine content of ArgoPore^{TM}-Cl (**121y**), which could be explain by burial of some chlorine atoms inside the polymeric network, depending upon the copolymerization technique used for the preparation of these type of resins. At the same time, the disappearance of the 1265 cm^{-1} $-CH_2Cl$ wagging[126] and negative 4-(4-nitrobenzyl)pyridine colour tests[127] indicated the substantial conversion of the chloromethyl groups of the starting resins.

[123] Lober, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Organic Letters* **2003**, *5*, 1753-1755.
[124] Oyelere, A. K.; Chen, P. C.; Yao, L. P.; Boguslavsky, N. *Journal of Organic Chemistry* **2006**, *71*, 9791-9796.
[125] Gaggini, F.; Porcheddu, A.; Reginato, G.; Rodriquez, M.; Taddei, M. *Journal of Combinatorial Chemistry* **2004**, *6*, 805-810.
[126] Mannion, J. J.; Wang, T. S. *Spectrochimica Acta* **1964**, *20*, 45-49.
[127] Galindo, F.; Altava, B.; Burguete, M. I.; Gavara, R.; Luis, S. V. *Journal of Combinatorial Chemistry* **2004**, *6*, 859-861.

Besides confirming the literature precedents for gel-type materials,[123] the possibility of an effective transformation of the macroporous ArgoPore™-Cl resin could be therefore demonstrated.



Scheme 21. Preparation the azidomethyl resins

3.3 Azido-functionalized PS supports with oligo(ethylene oxide) cross-linkers.

Even if poly(styrene-*co*-divinylbenzene) supports are in some way the work-horse of polymer-assisted chemistry,[14p] the intimate properties of the macromolecular backbone can render them less effective when the fast diffusion through the polymer network or the use in protic solvents is sought. In order to overcome these limitations, modified polystyrene materials have been proposed that embed longer/more polar cross-linking agents and, sometimes, polar side arms.

An early example in this direction was reported in the late 80's by Itsuno and co-workers,[128] who obtained spherical beads of the polymers **123a** or **123b** (Figure 27) by the suspension copolymerization of styrene or styrene and *p*-chloromethylstyrene with α,ω-bis(*p*-vinylbenzyl)-terminated cross-linking agents, embedding oligo(ethylene oxide) chains of different lengths. These insoluble materials performed nicely as achiral PTC in Williamson reactions, thus suggesting a rather unhindered access to the crown ether-like sites.

[128] **a)** Itsuno, S.; Moue, I.; Ito, K. *Polymer Bulletin* **1989**, *21*, 365-370; **b)** Itsuno, S.; Moue, I.; Ito, K. *Journal of the Chemical Society, Chemical Communications* **1991**, 1599-1601

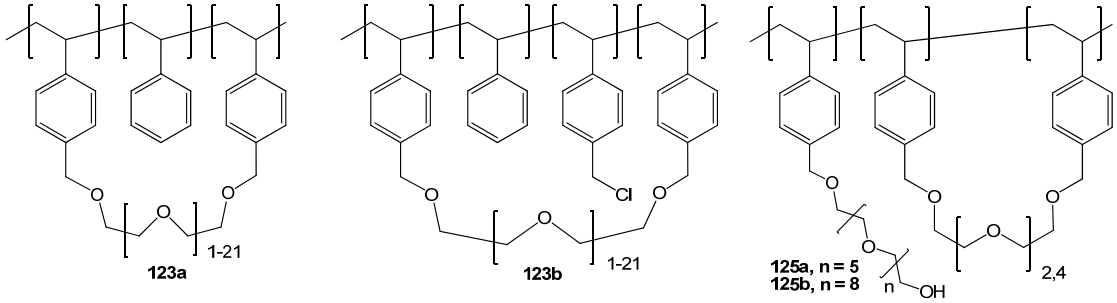


Figure 27. Preparation of PS resins with oligo(ethylene oxide) cross-linkers.

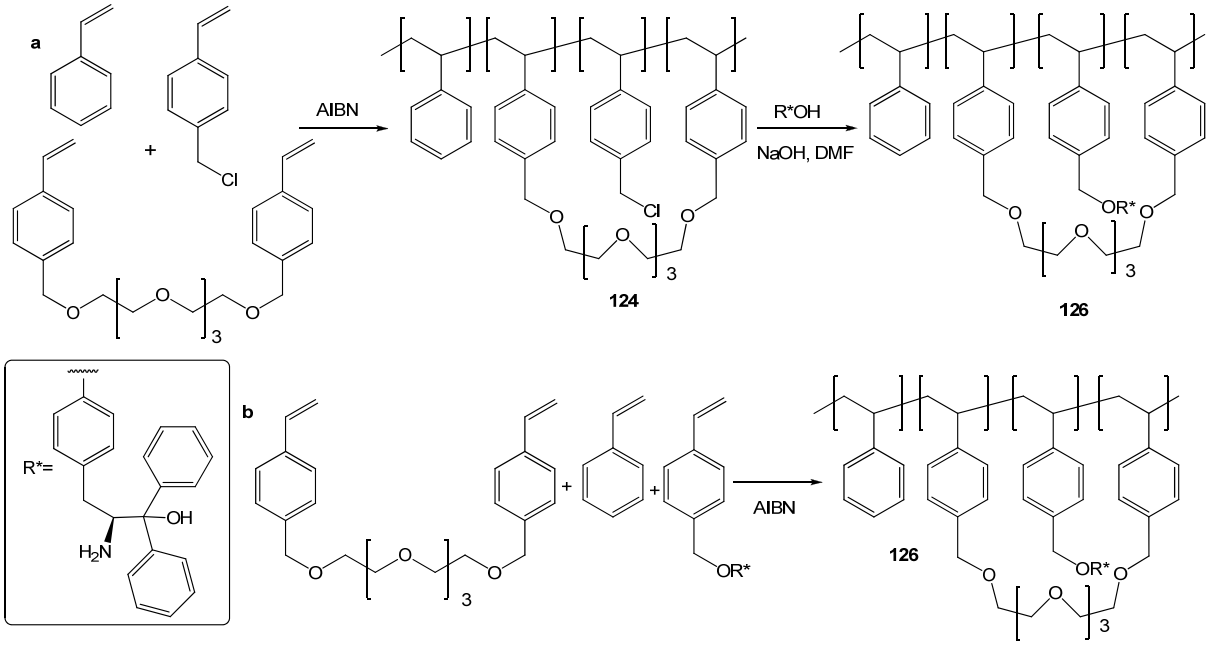
Similarly, Janda and co-workers introduced PS resins cross-linked with bis(styrene) derivatives in order to prepare materials (*e.g.* JandaJel^{TM}) with a superior swelling capability.[93]

However, studies by Kurth and co-workers demonstrated that while crosslinked styrene copolymers containing oxyethylene chains (including those of type **123a** and **123b**) swell better in various organic aprotic solvents and allow a faster diffusion than poly(styrene-*co*-divinylbenzene), their compatibility with aqueous media is still at question.[129]

In order to solve this issue, the introduction of oligo(ethylene oxide) grafts has been often pursued. For instance, in 2002 Sutherland and co-workers reported the preparation of the materials **125a**, **125b** and demonstrated their high compatibility with polar and aqueous media.[130]

In the field of IPB chiral derivatives, an early example was reported by Itsuno and Fréchet who described in 1990 the preparation of tailored PS with pendant aminoalcohol units (**126**).[131] The materials were obtained either by anchoring of the chiral derivative to a resin containing chloromethyl groups (Scheme 22a), or by the direct copolymerization of the aminoalcohol-bearing monomer with styrene and an oligo(ethylene oxide) cross-linker (Scheme 22b). The resins were used as chiral IPB catalyst precursors in the addition of $ZnEt_2$ to aldehydes, to afford optically active secondary alcohols in very good *ee*'s.

[129] Wilson, M. E.; Paech, K.; Zhou, W.-J.; Kurth, M. J. *Journal of Organic Chemistry* **1998**, *63*, 5094-5099.
[130] McCairn, M. C.; Tonge, S. R.; Sutherland, A. J. *Journal of Organic Chemistry* **2002**, *67*, 4847-4855.
[131] Itsuno, S.; Sakurai, Y.; Ito, K.; Maruyama, T.; Nakahama, S.; Frechet, J. M. J. *Journal of Organic Chemistry* **1990**, *55*, 304-310.



Scheme 22. Preparation of IPB aminoalcohol derivatives onto PS resins embedding oligo(ethylene oxide) cross-linkers.

In a combination of the two latter examples, this research group also reported in 2005 the IPB *Cinchona* alkaloid derivatives (**44**) that contain oligo(ethylene oxide) units both as cross-link bridges and side arms; the preparation of these materials by copolymerization and their effective use in the AD reaction have been already discussed in the paragraph 1.4.1.

3.3.1. Synthetic strategy

In view of the possibility of using the IPB alkaloid derivatives in reactions involving polar media (*e.g.* the alcoholysis of *meso* anydrides, paragraph 5.2), the preparation was decided of 'click' supports more hydrophilic than ordinary PS resins.

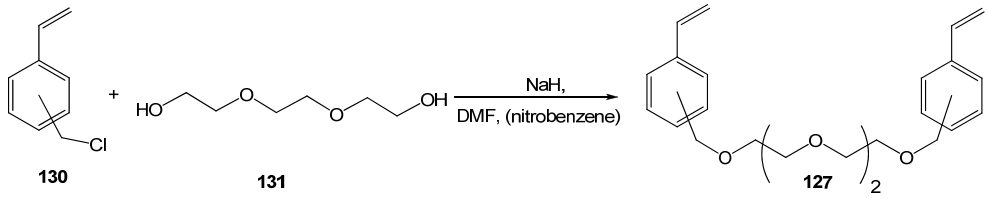
Given the literature precedents outlined above, a conceivable route could involve the synthesis of chloromethyl resins analogous to **123b** or **124** and their subsequent 'solid-phase' conversion into the corresponding azidomethyl supports. Nonetheless, the reports in the literature about the effective radical copolymerization of azidomethylstyrene (**129**)[132] suggested a more straightforward approach, based on the direct combination of the latter with suitable polar co-monomer and cross-linking agents.

[132] a) Mason, B. P.; Bogdan, A. R.; Goswami, A.; McQuade, D. T. *Organic Letters* **2007**, *9*, 3449-3451; b) Rodionov, V.; Gao, H.; Scroggins, S.; Unruh, D. A.; Avestro, A.-J.; Frechet, J. M. J. *Journal of the American Chemical Society* **2010**, *132*, 2570-2572.

With this aim, the achiral styrene derivatives 1,12-bis(4-vinylphenyl)-2,5,8,11-tetraoxadodecane (**127**) and 1-((2-(2-methoxyethoxy)ethoxy)methyl)-4-vinylbenzene (**128**) were selected as the polar components.

3.3.2. Synthesis of the monomers

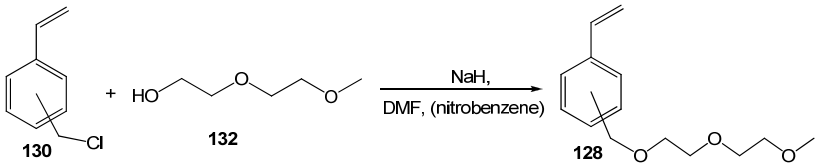
The syntheses of **127** (Scheme 23) and **128** (Scheme 24) were performed as published,[128,131] with only minor experimental changes in the isolation procedure.



130 131 127

Scheme 23. Preparation of the cross-linker 127

In the case of the cross-linker **127**, the product was obtained by reacting triethyleneglycol (**131**) in DMF with an excess of sodium hydride, followed by the halide **130**. After stirring at r.t. for 44h, an extractive work-up and the evaporation of volatiles gave a residue that was purified by a quick filtration through silica-gel, with 3/1 *n*-hexane/ CH_2Cl_2 as the eluent. The removal of the solvents under reduced pressure provided the desired product (92% yield), as an amber-coloured oil with NMR constants identical to those reported in the literature.[131]

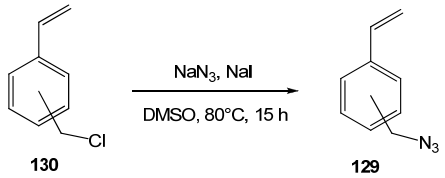


130 132 128

Scheme 24. Preparation of the polar monomer 128

Similarly, the synthesis of **128** was achieved by reacting first di(ethylene glycol) monomethyl ether **132** with sodium hydride, followed by a Williamson reaction of the alcoholate with the halide **130**. After the aqueous work-up and evaporation of the volatiles, the filtration through a pad of silica with $CHCl_3$ as the eluent afforded the polar monomer **128** (96% yield), as an amber-oil whose NMR data prove identical to the literature ones.[25] Due to the tendency of these styrene derivatives to homopolymerize no further purification attempt was made. Instead, the monomers were kept under nitrogen at -20ºC, until its use.

Similarly, the synthesis of azidomethylstyrene (**129**) was performed by a literature method (Scheme 25).[133]



Scheme 25. Preparation of the azidomethyl monomer 129

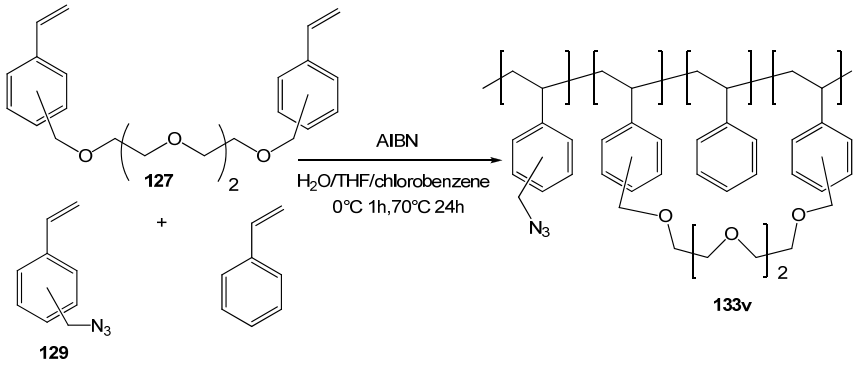
Accordingly, the commercial chloromethylstyrene *meta*/*para* = 70/30 mixture (**130**) in dry DMSO was treated with two equivalents of sodium azide and 10 mol% of sodium iodide and allowed to react at 80ºC for 15 h. After extractive work-up and evaporation of the volatiles, ^{1}H NMR analysis of the crude residue (~ 92% yield) confirmed the identity of the product[133] and indicated purity greater than ~95%. Analogously to the literature,[133] its direct use in the copolymerization runs was hence decided, with the only additional purification step being the filtration through neutral alumina for removing some polymer material.

3.3.3. Synthesis of cross-linked azidomethylpolystyrene supports

Even though the copolymerization of azidomethylstyrene with polar monomers and cross-linkers like **127** and **128** appeared unprecedented in the literature, the preparation of the two different insoluble supports, **133v** and **133z**, was decided in this Thesis.

The material **133v**, which can be considered an azido-Merrifield resin containing triethylene glycol cross-links, was obtained (Scheme 26) by the suspension radical copolymerization of a feed mixture of **127**, **129** and styrene (molar ratio of 15/25/60 respectively). For this purpose, the comonomers were dissolved in chlorobenzene and THF and the organic phase was dispersed in an aqueous solution of polyvinylalcohol (PVA), as a suspension stabilizer. After the addition of azo-bis(isobyronitrile) (AIBN) radical initiator, the degassed mixture was stirred vigorously at 70°C for 24 hours in the apparatus shown in (Figure 28).

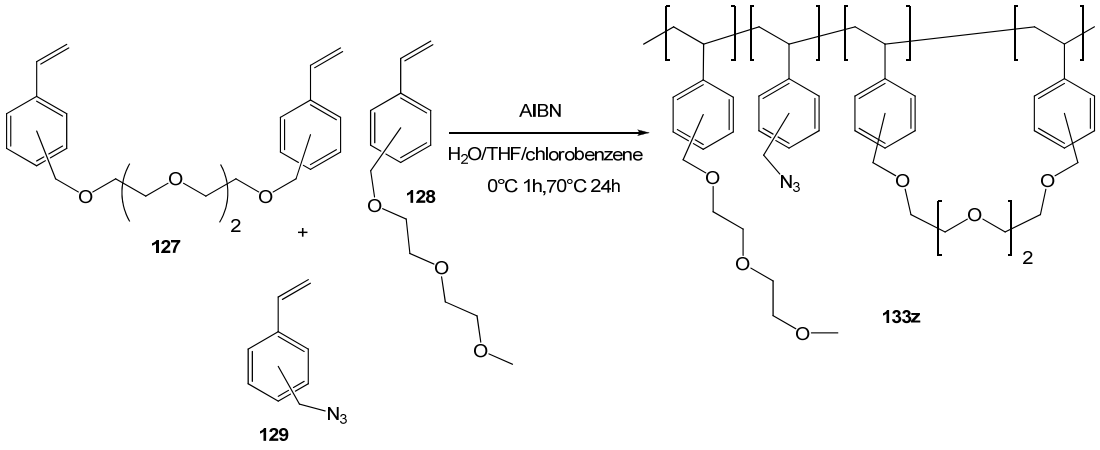
[133] Malagu, K.; Guerin, P.; Guillemin, J.-C. *Synlett* **2002**, 316-318.



Scheme 26. Synthesis of polymer support 133v.

Figure 28. Apparatus for suspension polymerization

Similarly, the material **133z** containing diethylene glycol monomethylether pending groups (Scheme 27) was prepared under the same experimental conditions, but starting with a mixture of the comonomers **127**, **128** and **129** (molar ratio 14/43/43, respectively).



Scheme 27. Synthesis of polymer support 133z.

After polymerization, **133v** and **133z** were isolated by filtration through medium porosity glass frit, repeatedly washed with hot water, CH_3OH, THF and finally with CH_2Cl_2 and dried under vacuum (0.01 mmHg) to constant weight. The mass recovery of the materials **133v** and **133z** was greater than 95% of the feed mixture weight.

The two different insoluble supports were obtained as free-flowing powders (Figure 29a), whose observation under optical magnification (Figure 29b) revealed the presence of

small aggregates of spherical polymer particles with diameters ranging between ~70 μm and 160 μm. Moreover, the IR spectroscopic analysis of both materials showed the 2095 cm^{-1} azido group stretching that, as expected on the basis of the respective azidomethylstyrene contents, proved stronger for **133v** than for **133z**.

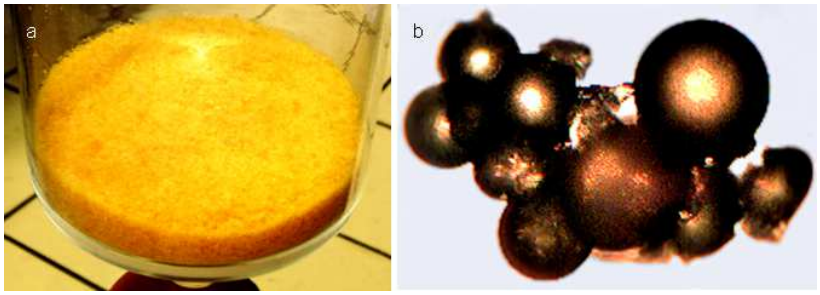


Figure 29 a) Materials 133v and 133z, formed by suspension polymerization b) magnified image of polymer 133z from an optical microscope.

The swelling behaviour of the new materials was also briefly characterized by a literature method consisting in the measure of volume increase of the dry polymer beads on exposure to a given solvent.[129] By these means, it was possible to establish that, despite the relatively high cross-linking degree, both materials underwent a volume expansion up to 200-300% of the original one when equilibrated with CH_2Cl_2, THF or toluene. On the contrary the swelling was negligible (~10%) in the homogeneous *t*BuOH:H_2O (1:1) mixture. In striking contrast with the literature materials **125a-b** discussed above, the polar cross-linker and (for **133z**) the diethylene glycol monomethyl ether grafts appeared therefore not sufficient for providing the resins of this work with high compatibility towards the most polar solvents. While this problem could probably be mitigated by replacing the terminal methyl ether groups in the pendant arms of **133z** with free hydroxyl ones, the resulting material architecture was judged not compatible with the organocatalyzed reactions of interest in this work (Chapter 5).

Finally, in view of the practically quantitative mass recovery in the copolymerization process, no direct determination of the azide content in the prepared resins was deemed necessary. Instead, the nominal values of 1.6 mmol g^{-1} (**133v**) and 2.0 mmol g^{-1} (**133z**) were directly assumed as a reasonable estimation of the $–N_3$ group loading of the two supports.

3.4. Porous monolithic polymer supports.

Especially in the perspective of industrial applications, the use of IPB catalysts in continuous-flow devices is a particularly appealing opportunity.[60,134] In this type of system, the reagents are flushed through the reactor containing the heterogeneous or heterogenised catalyst and the product is collected at the outlet. By attaining catalysis and product/catalyst separation at the same time, the downstream treatments can be reduced in principle, which makes the whole process potentially more economical and environmentally friendly.[135]

Depending upon the properties of the insoluble catalyst, different implementations of the continuous-flow concept have been explored, *i.e.* the use of stirred-tanks with stepwise addition of the reactants and removal of the products (actually a semicontinous process), the packing of tubular reactors with bead-type insoluble catalysts, or the selection of porous monoliths as the supporting structure.[135]

Regarding the latter approach, monoliths are single continuous polymeric objects that, for the purposes of the present work, can be taught as filling completely the flow-reactor volume (for an example in capillary reactor, see the Figure 30b).[136c] Provided the material posses a permanent porous structure with interconnected channels at least in the macropore region and the architecture is rigid enough to avoid mechanical collapse and excessive swelling, the monolith can be flown rather freely by liquids. With respect to the use of packed-bed systems, this solution can present the advantage of avoiding the stagnation of the fluid flow, thereby improving the contact between reactants in the liquid phase and any supported 'active' site. For this reason, monolithic supports (either organic or inorganic) have been utilized in different applications,[136] *e.g.* separation of heavy metals[136a] and catalysts (including the enantioselective one).[136b-e]

Organic monoliths can be prepared by a 'molding' process described by Frechet and coworkers (Figure 30a).[137] The procedure consists of filling a tube (the *mold*) with

[134] **a)** Sherrington, D. C. *Chemistry of Waste Minimization*, Blackie: London, **1995**; Chapter 6, p 141; **b)** de Miguel, Y. R.; Brule, E.; Margue, R. G. *Journal of the Chemical Society, Perkin Transactions 1* **2001**, 3085-3094; **c)** Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637-4662.

[135] In 14c, Rasheed, M.; Elmore, S. C.; Wirth, T. pp 345-371.

[136] **a)** Sherrington, D. C.; Hodge, P. *Syntheses and Separations Using Functional Polymers*, John Wiley & Sons, **1988**; **b)** Burguete, M. I.; Garcia-Verdugo, E.; Vicent, M. J.; Luis, S. V.; Pennemann, H.; von, K., Nikolai Graf; Martens, J. *Organic Letters* **2002**, *4*, 3947-3950; **c)** Peters, E. C.; Svec, F.; Frechet, J. M. J. *Advanced Materials* **1999**, *11*, 1169-1181; **d)** Burguete, M. I.; Cornejo, A.; Garcia-Verdugo, E.; Garcia, J.; Jose, G., Maria; Luis, S. V.; Martinez-Merino, V.; Mayoral, J. A.; Sokolova, M. *Green Chemistry* **2007**, *9*, 1091-1096; **e)** Buchmeiser, M. R. *Polymer* **2007**, *48*, 2187-2198.

[137] Peters, E. C.; Svec, F.; Frechet, J. M. J. *Advanced Materials* **1999**, *11*, 1169-1181 (and ref. cited therin).

monomers, cross-linking agents, initiators, and porogens and, after sealing from both sides, triggering the polymerization (*e.g.* by heating or UV irradiation). Flushing with a suitable solvent is then carried out in order to remove the porogens and any soluble material, leaving the mold filled with the insoluble monolith phase.

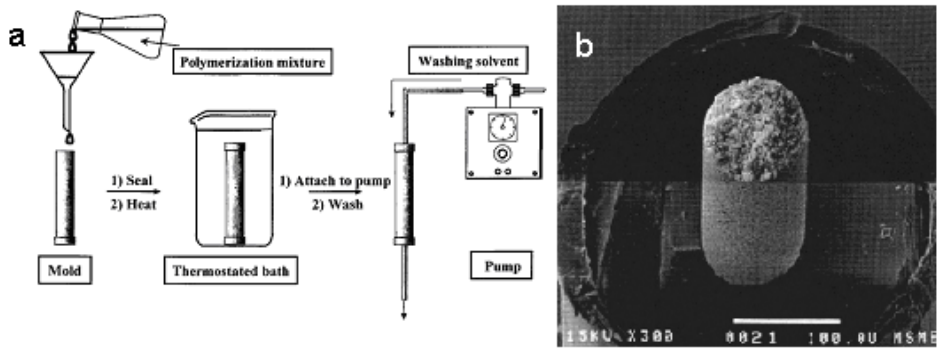


Figure 30. a) Preparation of macroporous monolith by 'molding' process (taken from ref. 137), b) capillary column cross-section (taken from ref. 136c)

Similarly, to the preparation of macroporous polymer beads discussed before, the attainment of the continuous porous network rests critically on the phase-behaviour of the mixture subjected to the copolymerization process. In turn, the latter depends on various parameters, the most important being the nature of the comonomers and the porogens, the feed mixture quantitative composition, and the polymerization temperature (sometimes the relationship between feed composition and polymer morphology is shown as an isothermal *pseudo-phase diagram*).[138]

Even if a macroporous monolith can oppose a relatively low resistance to flow, its porosity in the sub-μm range can still raise concerns about clogging or hindered passage of the most viscous liquids. For lifting these problems, high internal phase emulsion polymers (Poly-HIPE) were first introduced in 1982.[139] This type of materials can be obtained by a polymerization process in a water-in-oil emulsion, in which the water represents at least 76% by volume. In this reverse emulsion, the oil phase, containing the vinyl monomers and cross-linker, surrounds the water droplets: On polymerizing a highly interconnected open-cell resin structure forms around the water templating phase that, after washing and drying, eventually results in the attainment of a cross-linked polymer foam (see for example Figure 31). The much larger void fraction in Poly-HIPE materials than in the ordinary macroporous

[138] Sherrington, D. C. *Chemical Communications* 1998, 2275-2286.
[139] **a)** Barby, D., Haq, A. *European Patent Application* 0,060,138,Al **1982**; **b)** Barby, D.; Haq, Z. In *Unilever PLC, UK; Unilever N. V., U. S. Pat*. 4522953 **1985**.

monoliths, noted above allows a much easier flow through the channels. For this reason, monoliths obtained by the HIPE approach have been studied in a flow-through manner as scavengers,[140] reagents,[141] catalyst supports[142] and chromatography supports.[143]

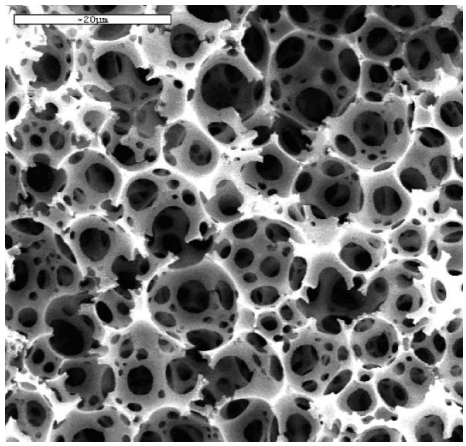
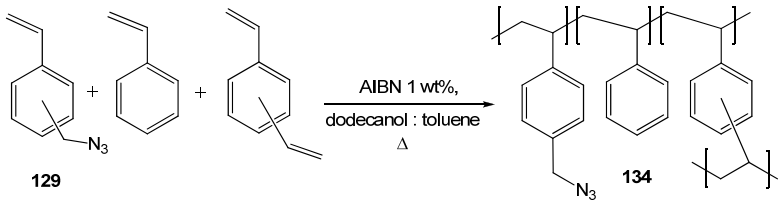


Figure 31. Scanning electron micrograph of VBC/DVB Poly-HIPE monolith (taken from ref. 140).

3.4.1. Attempts to prepare azidomethyl PS macroporous monoliths.

While many efforts have been devoted to the study of PS monoliths embedding chloromethylstyrene as the functional monomer,[144] no comparable data is available for similar materials containing azidomethyl groups. Hence, an attempt was made in this work for preparing porous supports by the direct radical copolymerization of styrene, azidomethylstyrene, and divinylbenzene (DVB) (Scheme 28).



Scheme 28. Preparation of monoliths containing azidomethyl group.

[140] **a)** Krajnc, P.; Brown, J. F.; Cameron, N. R. *Organic Letters* **2002**, *4*, 2497-2500; **b)** Lucchesi, C. l.; Pascual, S.; Dujardin, G.; Fontaine, L. *Reactive and Functional Polymers* **2008**, *68*, 97-102.
[141] Mercier, A.; Deleuze, H.; Mondain-Monval, O. *Reactive and Functional Polymers* **2000**, *46*, 67-79.
[142] Mercier, A.; Deleuze, H.; Maillard, B.; Mondain-Monval, O. *Royal Society of Chemistry* **2001**, *266*, 125-132.
[143] Krajnc, P.; Leber, N.; Å tefanec, D.; Kontrec, S.; Podgornik, A. *Journal of Chromatography A* **2005**, *1065*, 69-73.
[144] **a)** Gagne, M. R.; Korotchenko, V. N. *Polymer Preprints* **2005**, *46*, 1188; **b)** Urban, J.; Svec, F.; Frechet, J. M. J. *Journal of Chromatography A* **2010**, *1217*, 8212-8221.

The experimental conditions were based on those of Frechet and co-workers for similar PS materials,[145] with a solution of toluene and 1-dodecanol as the porogen medium and a stainless steel HPLC column as the mold.[136b,d]

Because of the subtle effect often caused by changes in the working parameters on the properties (pore distribution and surface area) of the final resin, different polymerization experiments were carried out (Table 1).

In general, all these runs resulted in well-formed monoliths that appeared to fill completely the mold volume and showed the spectroscopic (IR) and chemical features (Kaiser test) of an azido-containing material. Unfortunately, when the flushing of the column with the THF washing solvent was attempted a high back-pressure was however observed in all cases (*e.g.* > 100 Kg cm^{-2} at 0.5 ml min^{-1}). Irrespective of the feed and porogen composition or the polymerization temperature (Table 1), no monolithic bed suitable for flow-through applications could be therefore obtained by this route. On the contrary, in the initial runs performed by Frechet approach, (*i.e.* preparation of monolith using vinylbenzyl chloride (VBC) and DVB) provided flushable monolith with modest backpressure (30 - 50 Kg cm^{-2}), followed by chlorine/azide exchange by passing LiN_3/DMF, a positive color test with PPh_3/ninhydrin (Kaiser test) confirmed the azide substitution.

Table 1. Preparation of cross-linked polymer monoliths with different compositions.

	Monomers			Porogens			
Entry	AMST [%]	Styrene [%]	DVB [%]	Toluene [%]	Dodecanol[%]	Temp. [ºC]	Time [h]
1	10	10	20	15	45	80	24
2	6	14	20	15	45	80	24
3	16	0	24	20	40	80	24
4	10	0	20	10	60	60	24
5	10	0	20	10	60	70	24
6	11.7	0	23.3	9.3	55.7	75– 80	24

Except few satisfactory results obtained in preliminary runs by VBC/DVB polymerization followed by chlorine/azide substitution, the solution of the problems described above would conceivably require much efforts, largely trespassing the aims of this Thesis, in a final attempt to obtain a porous material apt as a ‘click’ monolithic support the resort to Poly-HIPE was evaluated instead.

[145] Viklund, C.; Svec, F.; Frechet, J. M. J.; Irgum, K. *Chemistry of Materials* **1996**, *8*, 744-750.

3.5. Preparation of Poly-HIPE materials

By taking inspiration from a literature procedure for similar chloromethylstyrene materials,[146] the copolymerization of **129** and DVB (20 : 80) was carried out in a reverse emulsion made up by a water phase (76% by volume) containing sorbitan monooleate (SPAN 80, emulsion stabilizer), $K_2S_2O_8$ (radical polymerization initiator) and NaCl. Due to the high viscosity of the emulsion, the different components were directly mixed together (300 rpm) in a 2 × 15 cm glass mold equipped with a stopcock on both sides (Figure 32). After sealing under nitrogen, the stable suspension so obtained was placed in oven at 60°C and kept heating for two days. The resulting polymeric monolith was then washed several times with water, to remove the inorganic components, followed by THF and acetonitrile until disappearance of UV absorbing substances in the washings. Finally, the freely-flushable Poly-HIPE column was characterized by IR and by the Kaiser test, which confirmed the presence of the azido function within the highly cross-linked polymer architecture which having 90 m^2 g^{-1} surface area calculated by BET method.

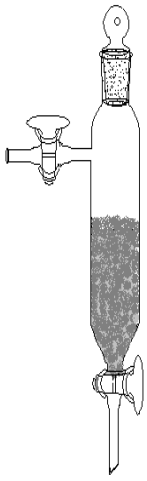


Figure 32. Glass mold for PolyHIPE preparation.

[146] Barbetta, A.; Cameron, N. R.; Cooper, S. J. *Chemical Communications* **2000**, 221-222.

3.6 Conclusions

The preparation of five different azide-functionalized polymer supports was explored in this work, starting either from commercial resins (Merrifield and ArgoPore^{TM}-Cl beads) or by forming the insoluble material through the copolymerization of suitable monomers.

Apart from the problems encountered in obtaining macropourous monoliths with proper permeability properties, this led to a set of insoluble supports which differed in the chemical composition (nature of the cross-linker and grafts, degree of functionalization) as well as in their morphology (gel-type or macroporous, including the Poly-HIPE type).

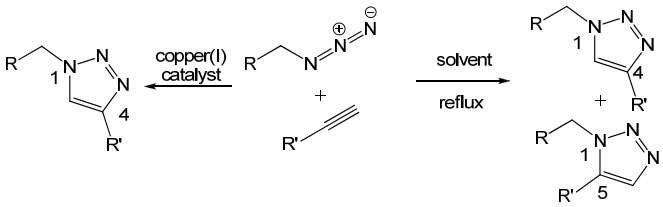
Being provided with pending azidomethyl groups, these new materials were investigated next as supports in the preparation of IPB alkaloid derivatives by the anticipated ‘click-chemistry’ strategy.

CHAPTER -4- IMMOBILIZATION OF ALKALOID DERIVATIVES ON TO POLYMER SUPPORTS AND PREPARATION OF MODEL COMPOUNDS

4.1 Introduction

As anticipated, the copper-catalyzed azide-alkyne dipolar cycloaddition was thoroughly employed in this work as the tool for the covalent immobilization of alkaloid derivatives onto insoluble organic polymers.

The 1,3-dipolar cycloaddition between organic azides and alkynes has been known for more than 100 years[147] and investigated in detail by Huisgen and co-worker in the 60's of the past century.[148] Although the process offers a simple access to 1,2,3-triazoles, the uncatalyzed reaction had the disadvantage of requiring high temperatures and to lead to a mixture of regioisomeric products (Scheme 29).[149] For this reason, the independent introduction in 2001-2002 of Cu(I) catalysts, by the groups of Meldal[150] and Sharpless,[151] represented a major improvement: Under these conditions the reaction of terminal alkynes can usually proceed at room temperature, with almost exclusive formation of 1,4-disubstituted triazoles.



Scheme 29. Azide-alkyne cycloaddition under thermal and catalytic conditions

Since then many catalytic system for the copper-catalyzed cycloaddition reaction (CuAAC) have been described, including simple halide salts (normally in the presence of a teriary amine) or more sophisticated complexes with chelating ligands. *In situ* reduced Cu(II) salts (*e.g.* $CuSO_4$ with sodium ascorbate) or Cu(0) nanoparticles proved also effective in a number of circumstances, while the addition of a weak reducing agent to the

[147] Michael, A. *Journal fuer Praktische Chemie (Leipzig)* **1893**, *48*, 94-95.
[148] **a)** Hueisgen, R. *Proceedings of the Chemical Society, London* **1961**, 357-369; **b)** Huisgen, R.; Szeimies, G.; Moebius, L. *Chemische Berichte* **1967**, *100*, 2494-2507.
[149] Kirmse, W.; Horner, L. *Justus Liebigs Annalen der Chemie* **1958**, *614*, 1-3.
[150] **a)** Tornoe, C. W.; Meldal, M.; *American Peptide Society*, **2001**; 263-264; **b)** Tornoe, C. W.; Christensen, C.; Meldal, M. *Journal of Organic Chemistry* **2002**, *67*, 3057-3064.
[151] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angewandte Chemie, International Edition* **2002**, *41*, 2596-2599.

reaction mixture was shown to allow the reaction to be carried out under open-air conditions.[152]

CuAAC can stand wide variations in the structure of the reaction partners (including the presence of many functional groups) and changes in reaction conditions, like the solvent or the pH.[153] Moreover, the triazole product is often obtained in quantitative yield and without the formation of significant amounts of side- or byproducts.

With all these characteristics, CuAAC was rapidly recognized as the tool of choice for ligating organic molecules in a number of fields, including material and polymer science,[154,155,156] organic, combinatorial, and supramolecular chemistry,[157] medicinal chemistry and biochemistry.[158,159] This led to the introduction of the idea of 'click-chemistry' and 'click-reaction',[160] *i.e.* synthetic methodologies possessing the mildness, versatility, and atom-economy features discussed above for CuAAC (which, in fact, if often referred to as the 'click-reaction' *tout court*).

The postulated mechanism for CuAAC (Scheme 30)[151,161] involves the formation of a copper(I)-acetylide **136** as the first step. According to theoretical studies, the coordination of the azide reactant would then take place (**138**), followed by evolution to the triazole **140**

[152] However, open air conditions cannot be generally recommended due to potential oxidative side reactions of the substrates. See: **a**) Angell, Y.; Burgess, K. *Angewandte Chemie International Edition* 2007, *46*, 3649-3651; **b)** Meldal, M. *Macromolecular Rapid Communications* **2008**, *29*, 1016-1051.

[153] Pachon, L. D.; Van Maarseveen, J. H.; Rothenberg, G. *Advanced Synthesis & Catalysis* **2005**, *347*, 811-815

[154] **a)** Lutz, J.-F. *Angewandte Chemie, International Edition* **2007**, *46*, 1018-1025; **b)** Diaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *Journal of Polymer Science, Part A: Polymer Chemistry* **2004**, *42*, 4392-4403.

[155] **a)** Joralemon, M. J.; O'Reilly, R. K.; Matson, J. B.; Nugent, A. K.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **2005**, *38*, 5436-5443; **b)** Dave, P. R.; Duddu, R.; Yang, K.; Damavarapu, R.; Gelber, N.; Surapaneni, R.; Gilardi, R. *Tetrahedron Letters* **2004**, *45*, 2159-2162; **c)** Lee, J. W.; Kim, B.-K. *Synthesis* **2006**, 615-618; **d)** Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angewandte Chemie, International Edition* **2004**, *43*, 3928-3932.

[156] **a)** Tsarevsky, N. V.; Sumerlin, B. S.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 3558-3561; **b)** Opsteen, J. A.; van, H., Jan C. M. *Chemical Communications* **2005**, 57-59; **c)** van, S., Dirk Jan V. C.; David, O. R. P.; van, S., Gino P. F.; van, M., Jan H.; Reek, J. N. H. *Chemical Communications* **2005**, 4333-4335.

[157] **a)** Aucagne, V.; Haenni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B. *Journal of the American Chemical Society* **2006**, *128*, 2186-2187; **b)** Aucagne, V.; Berna, J.; Crowley, J. D.; Goldup, S. M.; Haenni, K. D.; Leigh, D. A.; Lusby, P. J.; Ronaldson, V. E.; Slawin, A. M. Z.; Viterisi, A.; Walker, D. B. *Journal of the American Chemical Society* **2007**, *129*, 11950-11963; **c)** Aprahamian, I.; Dichtel, W. R.; Ikeda, T.; Heath, J. R.; Stoddart, J. F. *Organic Letters* **2007**, *9*, 1287-1290; **d)** Mobian, P.; Collin, J.-P.; Sauvage, J.-P. *Tetrahedron Letters* **2006**, *47*, 4907-4909.

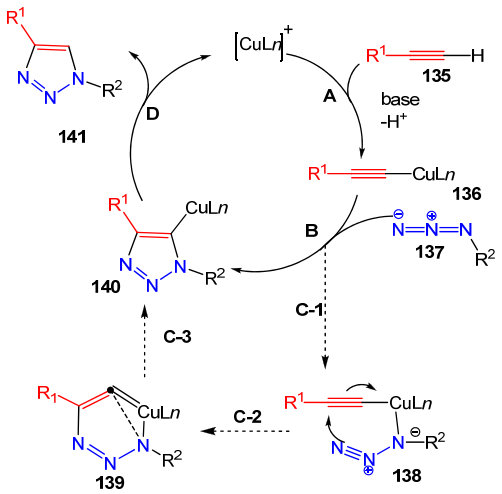
[158] **a)** Lewis, W. G.; Magallon, F. G.; Fokin, V. V.; Finn, M. G. *Journal of the American Chemical Society* **2004**, *126*, 9152-9153; **b)** Gommermann, N.; Gehrig, A.; Knochel, P. *Synlett* **2005**, 2796-2798; **c)** Wu, Y.-M.; Deng, J.; Li, Y.; Chen, Q.-Y. *Synthesis* **2005**, 1314-1318; **d)** Yang, D.; Fu, N.; Liu, Z.; Li, Y.; Chen, B. *Synlett* **2007**, 278-282.

[159] **a)** Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angewandte Chemie, International Edition* **2002**, *41*, 1053-1057; (b) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V; Sharpless, K. B.; Finn, M. G. *Journal of the American Chemical Society* **2003**, *125*, 3192-3193; **c)** Mocharla, V. P.; Colasson, B.; Lee, L. V.; Roeper, S.; Sharpless, K. B.; Wong, C.-H.; Kolb, H. C. *Angewandte Chemie, International Edition* **2005**, *44*, 116-120.

[160] Moses, J. E.; Moorhouse, A. D. *Chemical Society Reviews* **2007**, *36*, 1249-1262

[161] **a)** Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *Journal of the American Chemical Society* **2005**, *127*, 210-216; **b)** Bock, V. D.; Hiemstra, H.; Van Maarseveen, J. H. *European Journal of Organic Chemistry* **2006**, *2006*, 51-68.

through an intriguing metallacycle intermediate **139** (path-C), rather than by direct cycloaddition **137** (path-B).



Scheme 30. Proposed mechanism for the Cu(I) catalyzed Reaction between organic azides and terminal alkynes

Regarding to the topic most relevant to the present Thesis work, *i.e.* the use of 'click'- chemistry for the preparation of supported chiral ligands or catalysts, several examples had been reported in the literature at the beginning of this work (Figure 33).

In 2006 Pericas and co-workers described the immobilization of chiral amino alcohol onto azidomethyl PS-DVB resins and the use of the resulting IPB ligands **142** in the asymmetric phenylation of aldehydes.[162] Under these conditions, high catalytic activity was observed, together with moderate to high levels of enantioselectivity (up to 82% *ee*).

Shortly after, the groups of Moeberg and Levacher reported a similar strategy for the immobilization pyridine-bisoxazoline (pybox) ligands on PS resin.[163] The resulting material **143** was then used for preparing IPB metal complexes for the ring-opening of cyclohexene oxide or silylcyanation of benzaldehyde with TMSCN [Yb(III) or Lu(III) catalysts] and for the alkynylation of imines [Cu(I) catalysts]. While the former two transformations afforded only moderate *ee* values (≤78% *ee*), better results (mostly in the 80-90% *ee* range) could be attained in the latter. The lower *ee*'s obtained in the transformations catalyzed by the lanthanide complexes were ascribed to achiral adducts between the metal precursors and the 1,2,3-triazole nucleus, whose presence would allow a non enantioselective pathway for the

[162] Bastero, A.; Font, D.; Pericas, M. A. *Journal of Organic Chemistry* **2007**, *72*, 2460-2468.
[163] Tilliet, M. l.; Lundgren, S.; Moberg, C.; Levacher, V. *Advanced Synthesis & Catalysis* **2007**, *349*, 2079-2084.

reaction. A few reaction cycles (≤ 5) were also described, but in the case of the opening of cyclohexene oxide a significant loss of performance was noted.

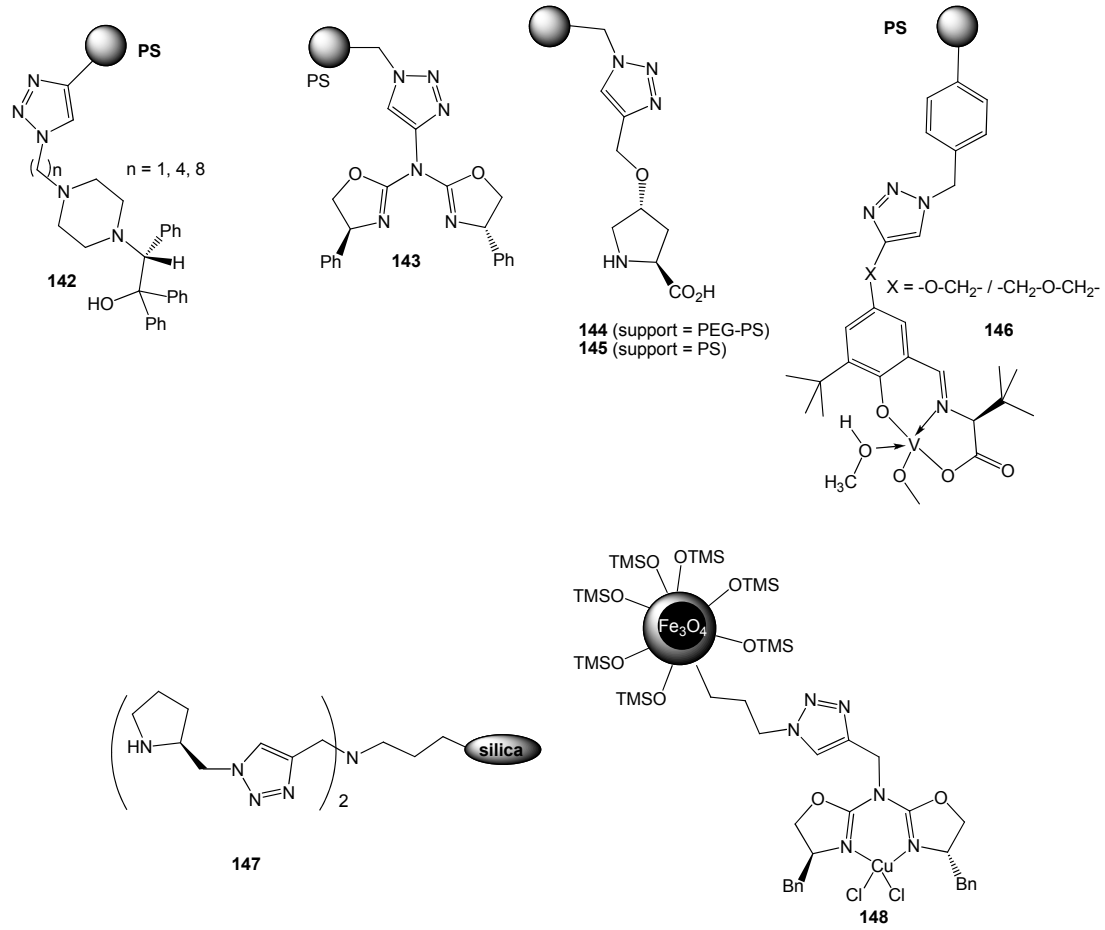


Figure 33. IPB enantioselective ligands or catalysts obtained by 'click-chemistry'.

Interestingly, this did not seem to be a problem for metal-free asymmetric reactions. For instance, the PEG-polystyrene supported 4-hydroxyproline **144** was successfully applied by Pericas and co-workers to the direct aldol reactions of aryl aldehydes with cyclic and acyclic ketones in water.[164] In this case, the IPB system provided similar or even better performance than its soluble counterparts (up to 96% *ee*) and the catalyst was recovered by simple filtration and reused for three times without loss of activity and stereoselectivity.

[164] Font, D.; Jimeno, C.; Pericas, M. A. *Organic Letters* **2006**, *8*, 4653-4655.

Subsequently, the same group described also an analogous IPB derivative on PS (**145**) for the highly stereoselective Mannich reaction of aldehydes and ketones with the *N*-(*p*-methoxyphenyl) ethyl glyoxylate imine.[165]

Recently Chen and co-workers reported the synthesis by 'click' chemistry of chiral *N*-salicylidene vanadyl(V) *tert*-leucinate complex (**146)** onto azide-functionalized PS. This catalyst promoted the aerobic oxidation of a broad range of α-hydroxy carboxylic acid derivatives with excellent enantioselectivities (up to 99% *ee*). The catalyst could be reused effectively four times, although 9% vanadium leaching was observed.[166]

'Click-chemistry' has been sometimes applied also to the immobilization of chiral ligand/catalyst onto inorganic supports (mainly silica).

Zhao and co-workers reported the 'click' preparation of the silica-supported dimeric-pyrrolidine organocatalyst **147** and its successful application to the asymmetric Michael addition of ketones to nitroalkenes.[167] Products were obtained in high yields, excellent diastereoselectivity (*syn/anti* ratio up to 20:1), and excellent enantioselectivity (up to 93% *ee*). The catalyst could also be recycled effectively 4 times.

In 2009, Reiser and co-workers developed a short route for grafting Cu(II)-azabis(oxazoline)-complexes onto different magnetite nanoparticles coated with amorphous silica (Fe_3O_4 @ SiO_2).[168] The resulting 'clicked' heterogeneous catalyst **148** was then tested in the asymmetric benzoylation of 1,2-diols with moderate yields and excellent *ee* values (up to 98% *ee*). The catalyst was separated by magnetic decantation and reused 5 times without loss of activity and selectivity.

For the sake of completeness, it can be mentioned that 'click' strategies have been used also for the development of recoverable enantioselective catalysts of the soluble type. As shown in Figure 34, these include, *e.g.*, PEG-supported proline (**149**),[169] perfluorinated bis-oxazoline ligands (**150**),[170] dendritic systems (**151**),[171] and ionically tagged organocatalyst (**152**).[172]

[165] Alza, E.; Rodriguez-Escrich, C.; Sayalero, S.; Bastero, A.; Pericas, M. A. *Chemistry-A European Journal* **2009**, *15*, 10167-10172.
[166] Salunke, S. B.; Babu, N. S.; Chen, C.-T. *Advanced Synthesis & Catalysis* **2011**, *353*, 1234-1240.
[167] Zhao, Y.-B.; Zhang, L.-W.; Wu, L.-Y.; Zhong, X.; Li, R.; Ma, J.-T. *Tetrahedron: Asymmetry* **2008**, *19*, 1352-1355.
[168] Schaetz, A.; Hager, M.; Reiser, O. *Advanced Functional Materials* **2009**, *19*, 2109-2115.
[169] Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericas, M. A. *Organic Letters* **2008**, *10*, 337-340.
[170] Rasappan, R.; Olbrich, T.; Reiser, O. *Advanced Synthesis & Catalysis* **2009**, *351*, 1961-1967.
[171] Lv, G.; Jin, R.; Mai, W.; Gao, L. *Tetrahedron: Asymmetry* **2008**, *19*, 2568-2572.
[172] Wu, L.-Y.; Yan, Z.-Y.; Xie, Y.-X.; Niu, Y.-N.; Liang, Y.-M. *Tetrahedron: Asymmetry* **2007**, *18*, 2086-2090.

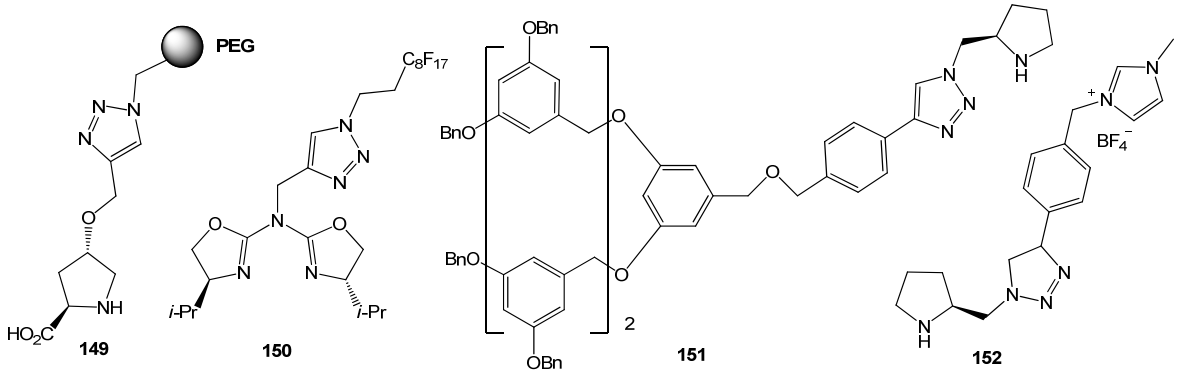


Figure 34. Examples of recoverable enantioselective ligands and catalysts obtained through 'click-chemistry'

In conclusion, the immobilization of chiral catalyst/ligands using 'click-chemistry' appears well precedented for a number of systems. To the best of our knowledge, however, no application of this technique had been reported at the beginning of this Thesis for the specific case of *Cinchona* alkaloids in catalytic applications. Actually, two examples could be found, where simple alkyne-functionalized *Cinchona* alkaloid derivatives were covalently bound to azide-functionalized silica gel. Nonetheless, the resulting materials were meant for chromatographic uses and not catalysis.[173]

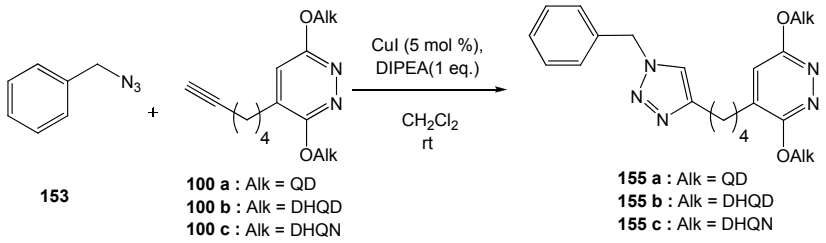
4.2. Immobilization of *Cinchona* alkaloid derivatives onto polymer supports

From the overview given above it should be clear that 'click-chemistry' proved already effective in providing a number of excellent IPB systems. Nonetheless, the presence of 1,2,3-triazole nucleus formed at the 'click' stage has been occasionally associated with poor performance in asymmetric catalysis.[163] Therefore, in this work the preparation and use of supported systems was constantly accompanied by the synthesis of proper soluble models of the supported chiral units. In general, these soluble compounds were obtained by 'click' addition of benzylazide (**153**) to the same alkaloid derivatives employed for polymer immobilization. Their use in selected asymmetric transformations allowed then the preliminary screening of the local organocatalyst structure on catalytic performance and, in particular, to assess the effect of the modification introduced in literature systems for allowing their immobilization.

[173] **a)** Kacprzak, K. M.; Maier, N. M.; Lindner, W. *Tetrahedron Letters* **2006**, *47*, 8721-8726; **b)** Kacprzak, K. M.; Lindner, W. *Journal of Separation Science* **2011,** *34*, 2391-2396.

4.2.1 Preparation of pyridazine-core *Cinchona* alkaloid soluble model compounds 155a,b,c and 154.

According to the line of reasoning drawn above, the synthesis of soluble models of pyridazine-types *Cinchona* alkaloid derivatives **155a-c** was carried out as shown in Scheme 31. After some initial optimization tests, good results were obtained with the CuI-DIPEA catalytic system, which proved the most effective in promoting the 'click' reaction of the alkaloid derivatives.

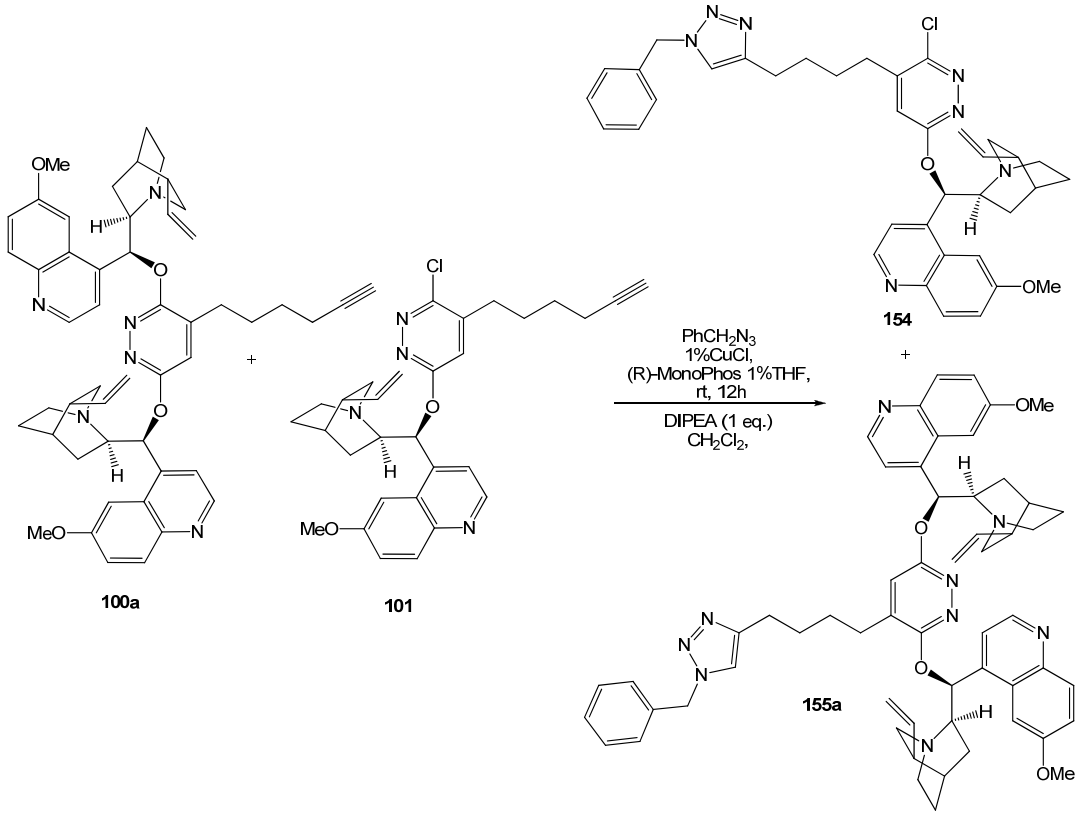


Scheme 31. Preparation of the dimeric soluble model compounds 155a-c

After mixing solvents, reagents and catalyst components, the resulting solution was kept stirring at room temperature until TLC and ^{1}H NMR analysis revealed the complete conversion, of the starting alkaloid (24-48h). The crude products were subjected to flash chromatography purification, giving **155a**, **155b**, and **155c** in 73, 66 and 74% yields, respectively. The compounds were characterized by MS, ^{1}H NMR, ^{13}C NMR analyses, and optical rotatory power measurement (see Experimental Section).

Similarly, the mixture of the monomeric and dimeric alkaloid derivatives **101** and **100a** was subjected to analogous reaction conditions (Scheme 32).[174] After chromatographic separation, the compound **154** could be obtained (75% yield, based on the initial composition of mixture) together wth **155a** (53% yield).

[174] Campbell-Verduyn, L. S.; Mirfeizi, L.; Dierckx, R. A.; Elsinga, P. H.; Feringa, B. L. *Chemical Communications* **2009**, 2139-2141.



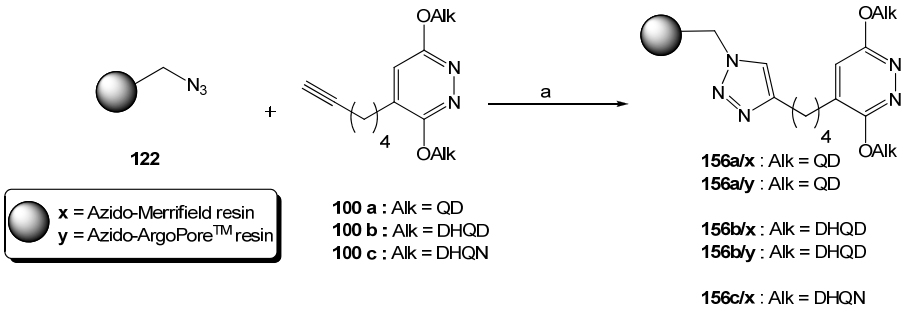
Scheme 32. Preparation of monomeric soluble model compound 154

The characterization of **154** was carried out as described for **155a**, confirming the structure of the derivative (see Experimental Section).

4.2.2. Preparation of immobilized pyridazine-core *Cinchona* alkaloid derivatives 100a, 100b, 100c on azido-polystyrene resins 122x and 122y.

After successful preparation of the soluble model compounds (section 4.2.1), the next goal was to prepare their insoluble counterpart by immobilizing them on azide-functionalized polymers. For the initial studies, azido-Merrifield resin **122x** and azido-ArgoPore^{TM} resin **122y** were chosen as support.

The supported pyridazine-core 1,2,3-triazole alkaloid derivatives **156a/x**, **156a/y**, **156b/x**, **156b/y** and **156c/x**, were prepared by reacting directly the unpurified alkyne-functionalized alkaloid derivatives **100a,b,c** (reason described in section 2.1.3) with excess of gel-type or macroporous azide-functionalized resins **122x** or **122y** in presence of CuI catalyst under the typical 'click'-reaction conditions described in Scheme 33.



Scheme 33. Immobilization of pyridazine-core *Cinchona* alkaloid derivatives on azide-functionalized polymers. Reagents and conditions: (a) CuI (5 mol%), DIPEA, CH_2Cl_2, rt

After proper time (from 48 to 71h), the functionalized resins were filtered and thoroughly washed with ammonia solution (to remove copper salts), water, methanol, dry THF and finally CH_2Cl_2. After drying to constant weight under vacuum (0.05 mmHg), the recovered pale yellow insoluble materials **156a/x**, **156a/y**, **156b/x**, **156b/y** and **156c/x** were characterized by IR analysis (Experimental Section) and the alkaloid loading was determined by the weight increase over the starting azidomethyl resins (Table 2).

Table 2. Loading of alkaloid on to the polymer supports

Entry	Resin	Alkaloid loading [mmol·g^{-1}]	Anchoring Yield [%]
1	**156a/x**	0.41 – 0.70	87
2	**156a/y**	0.26	47
3	**156b/x**	0.54	87
4	**156b/y**	0.22	39
5	**156c/x**	0.25	27

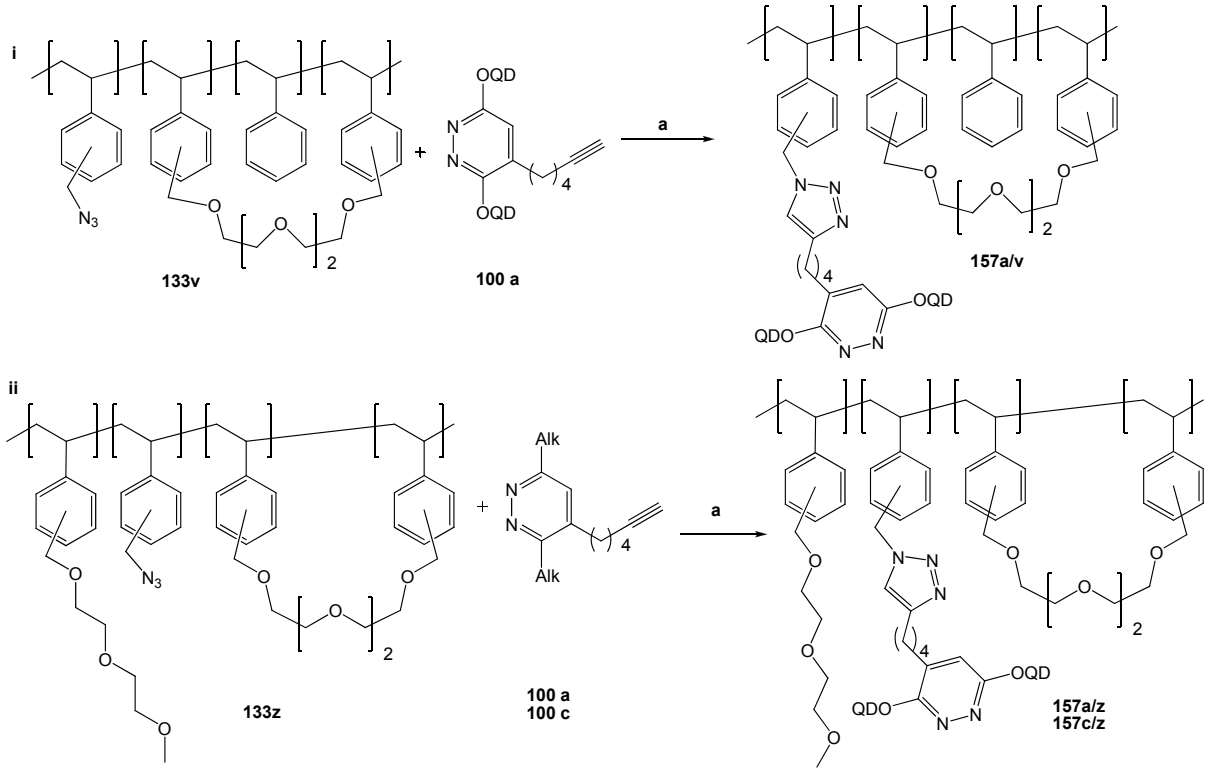
Both kinds of data confirmed the successful immobilization of the chiral derivatives, albeit to an extent clearly dependant on the polymeric support. In particular, **122x** proved much more effective than **122y** in the click capture of **100a** or **100b**, as demonstrated by the roughly two to three-fold increase in the alkaloid loading and anchoring yield attained in the preparation of **156a/x** and **156b/x** (Table 2**,** entries 1 and 3) in comparison with **156a/y** and **156b/y** (Table 2, entries 2 and 4).

4.2.3. Preparation of immobilized *Cinchona* alkaloid derivatives on polymer beads 133v and 133z

The new types of polymer **133v** and **133z** in the form of beads, bearing oxyethylene crosslinking chain, were also used as a support for anchoring the *Cinchona* alkaloid

derivatives **100a**,**b** and **c**, by 'click'-reaction. The procedure for the preparation and isolation of immobilized 1,2,3-triazole pyridazine-core *Cinchona* alkaloids derivatives **157a/v** and **157a/z**, **157c/z** (Scheme 34) was the same as followed before for the derivatization of the azido-resins **122** (see Scheme 33).

The recovered yellow insoluble beads, washed and dried in the usual way, were characterized by IR and alkaloid loading estimated by weight increase over the starting azido-beads. The efficient immobilization was confirmed for all the three materials both by decrease in intensity of the absorption IR band (2095 cm^{-1}) due to azide-stretching and by the weight increase. Both the resins **133v** and **133z** were equally effective in click capture of alkaloid derivative **100a** (Table 3, entries 1 and 2), even if almost a two-fold decrease in loading of *Cinchona* alkaloid **100c** on polymer beads **133z** was observed.



Scheme 34. i) Immobilization of $(QD)_2$PYZ-alkyne onto beads 133v, ii) Immobilization of pyridazine-core alkaloid derivatives onto beads 133z. Reagents and conditions: a) as in Scheme 33.

Table 3. Loading of *Cinchona* alkaloid derivative on polymer beads 133v and 133z.

Entry	Resins	Alkaloid loading [mmol·g^{-1}]	Anchoring yield [%]
1	**157a/v**	0.41	80
2	**157a/z**	0.50	81
3	**157c/z**	0.23	80

4.3. Anthraquinone-core *Cinchona* alkaloid derivative 114b.

After the successful immobilization of the pyridazine-core *Cinchona* alkaloid derivatives **100a,b,c** on to the four different polymer supports **122x,y** and **133v,z** by 'click'-chemistry, the same strategy described in Section 4.2 was applied for supporting the anthraquinone-core *Cinchona* alkaloid derivative **114b**. Same as in the previous cases initially a model compound of **114b** was prepared in order to compare the performances of the two systems in enantioselective reactions under homogeneous and heterogeneous phases.

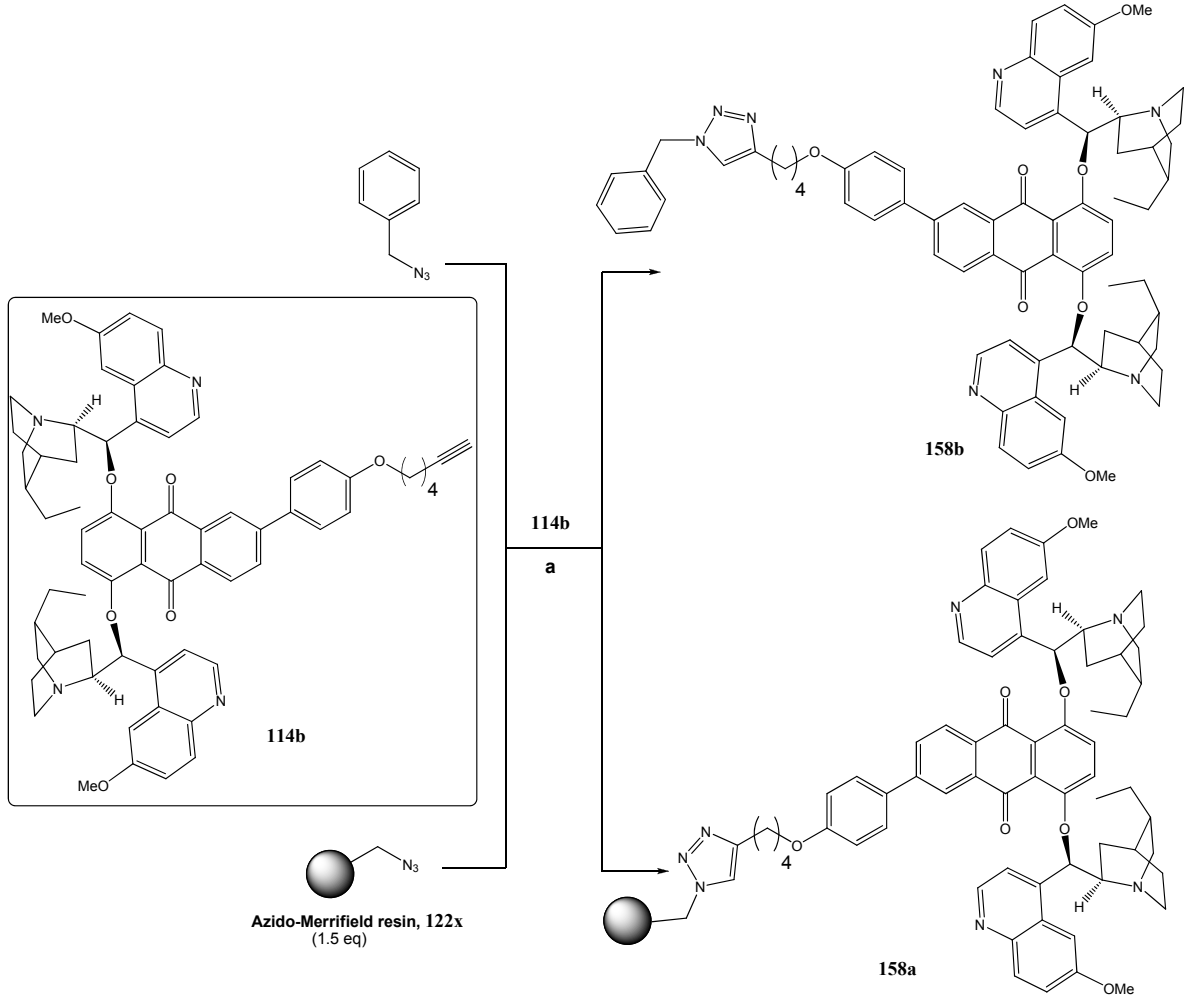
4.3.1. Preparation of the soluble 158b and the immobilized 158a anthraquinone-core *Cinchona* alkaloid derivative

The soluble 1,2,3-triazole derivative of the antraquinone-core model compound **158b** and the corresponding anchored one **158a** were prepared by reacting the alkyne-functionalized antraquinone-core derivative **114b** under typical click-reaction conditions, as reported in Scheme 35.

In the synthesis of **158b** the reaction was stopped after complete conversion of **114b**, as monitored by TLC and confirmed by ^{1}H NMR analysis (complete disappearance of acetylene signal). The isolated crude was subjected to the flash chromatographic purification, giving pure product **158b** (81% yield), which structure was attested by ^{1}H NMR, ^{13}C NMR and MS measurements.

As the effective immobilization of pyridazine-core alkyne-functionalized *Cinchona* alkaloid derivatives to form the insoluble catalysts **156a/x** and **156b/x** was achieved by using azido-Merrifield resin **122x** (Table 2, entries 1 and 3), it was initially decided to use the same support for immobilizing anthraquinone-core alkyne-functionalized *Cinchona* alkaloid **114b**.

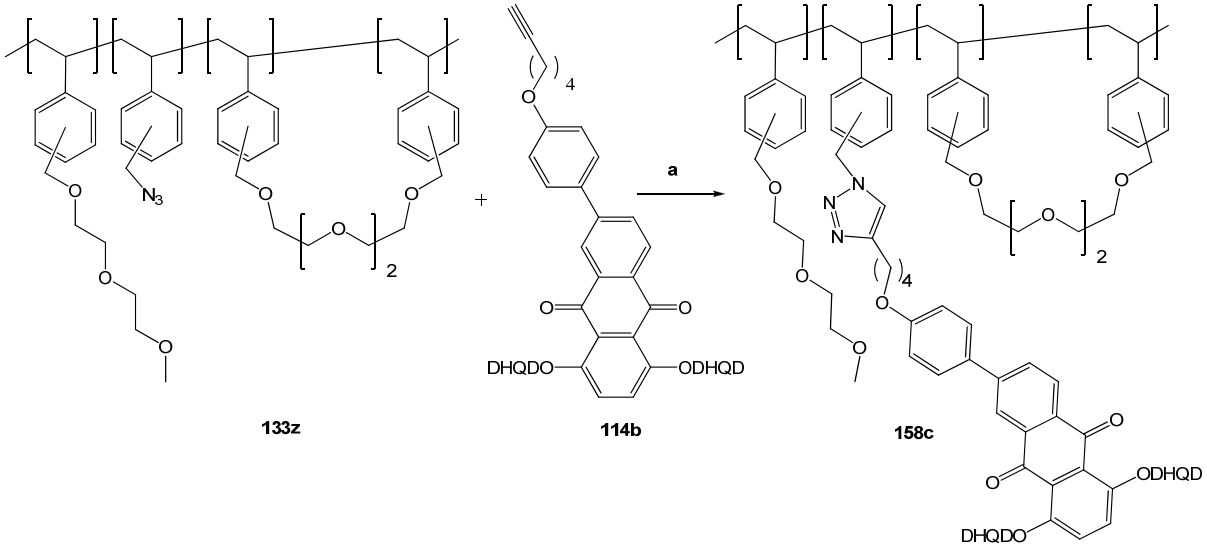
After reaction the isolated insoluble yellow resin was thoroughly washed and dried by same technique mentioned in Section 4.2.2, the immobilization of **114b** on polymer support to form **158a** was confirmed by slight decrease in intensity of absorption band at 2095 cm^{-1} in its IR spectrum (azide stretching) along with slight weight increase. Nevertheless the immobilization of alkaloid derivative **114b** on polymer support occurred with a low anchoring yield (17%) and a modest alkaloid loading (0.18 $mmol.g^{-1}$).



Scheme 35. Preparation of soluble and insoluble antraquinone-care quinidine derivatives. Reagents and conditions: (a) as in Scheme 33.

4.3.2. Preparation of immobilized *Cinchona* alkaloid derivative 158c.

Because of the modest loading of alkaloid derivative **114b** by using azido-Merrifield resin as support, it was decided to switch to oxyethylene-crosslinked azide-functionalized support **133z**, in beads form, as it had been proven the better support for the efficient immobilization of pyridazine-core derivative (see Table 3, entry 2). The polymer (beads) supported derivative **158c** (Scheme 36) was prepared by linking **114b** on 1.5 equivalent of **133z** using the standard 'click'-reaction conditions.



Scheme 36 Immobilization of $(DHQD)_2AQN$-alkyne onto beads 133z. Reagents and conditions: a) as in Scheme 33.

After stirring the reaction mixture for 5 days, the isolated yellow polymer beads (by the washing and drying techniques mentioned in section 4.2.2) were characterized by IR and weight increase, indicating a considerable loading of the alkaloid derivative **114b (**0.23 $mmol \cdot g^{-1}$) with 44% anchoring yield.

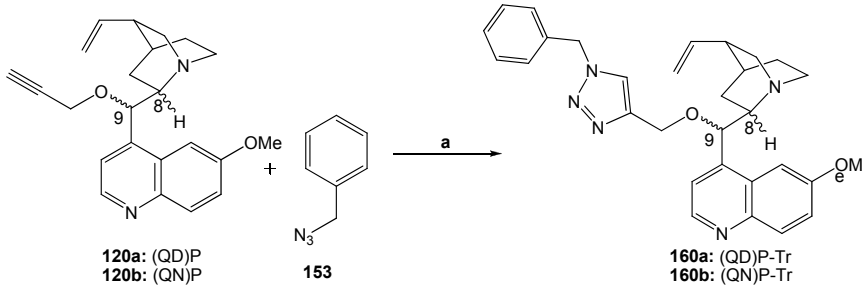
4.4. Propargyl alkaloid derivatives.

As shown in the following paragraphs, the most easily accessible modified soluble *Cinchona* alkaloid derivatives, prepared in this Thesis work, have been the propargyl quinine (QN)P and quinidine (QD)P, which could be easily adapted to the ongoing immobilization strategy. With this assumption, the syntheses of such soluble and insoluble derivatives have been planned.

4.4.1. Preparation of soluble model compounds 160a and 160b.

Low molecular weight 1,2,3-triazole soluble model derivatives of alkaloid (QD)P-Tr **160a** and (QN)P-Tr **160b** were prepared by the 'click'-reaction of propargyl derivatives (QD)P **120a** and (QN)P **120b** with an excess of benzyl azide **153** under the usual reaction conditions (Scheme 37). As monitored by TLC and ^1H NMR the reaction was complete in 48h, showing both by TLC the appearance of a new component slightly less retained than

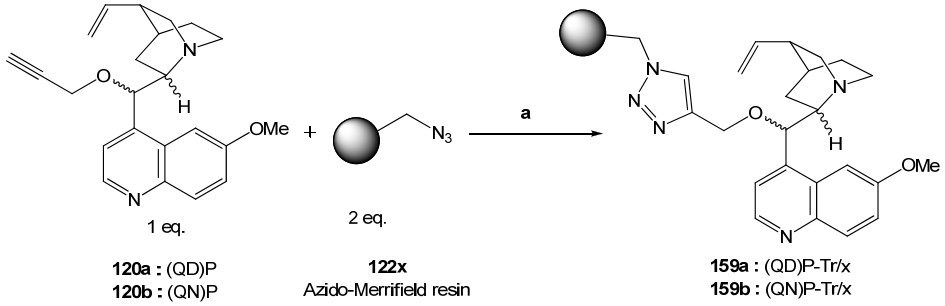
starting alkaloids and by ^{1}H NMR complete disappearance of propargyl proton signal at 2.45 ppm. The crudes obtained after extractive isolation as described (section 4.2.1) were subjected to the flash chromatographic purification, providing products **160a** and **160b** in 78 and 64% yields, respectively. Newly prepared compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass spectral measurements and optical rotatory power.



Scheme 37. Preparation of soluble model compounds (QD)P-Tr and (QN)P-Tr. Reagents and conditions: (a) as in Scheme 33.

4.4.2. Preparation of the immobilized *Cinchona* alkaloid propargyl derivatives 159a and 159b.

Propargyl quinine and quinidine **120a** and **120b** were clicked on to the azido-Merrifield resin support **122x** by following the 'click'-reaction conditions (Scheme 33) After 3 days the resins were thoroughly washed and dried (as described before). The isolated pale-yellow resins (QD)P-Tr/x **159a** and (QN)P-Tr/x **159b** confirmed effective immobilization of alkaloid **120a** and **120b**, as characterized by IR and weight increase of the resins (see Table 4).



Scheme 38. Preparation of the immobilized *Cinchona* alkaloid derivatives (QD)P-Tr/x and (QN)P-Tr/x. Reagents and conditions: (a) as in Scheme 33.

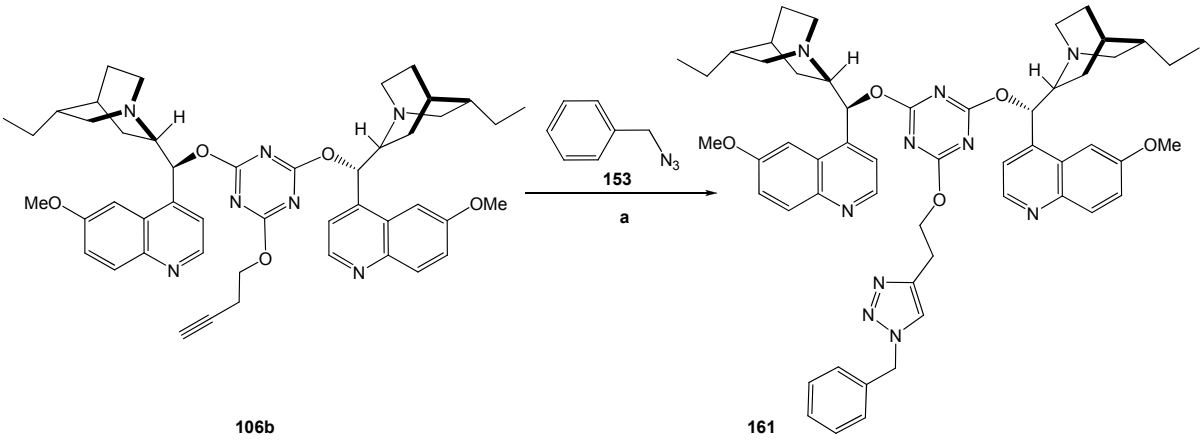
Table 4. Loading of *Cinchona* alkaloid derivatives 120a,b on resin 122x.

Entry	Resin	Alkaloid loading [mmol·g^{-1}]	Anchoring yield [%]
1	**159a**	0.77	97
2	**159b**	0.69	64

In summary, very effective immobilization of monomeric propargyl *Cinchona* alkaloid derivatives **120a** and **120b** on azide-functionalized gel-type Merrifield resin (0.77 and 0.69 mmol g^{-1}, respectively) was attained by simple 'click'-reaction. It is worth noting that the anchoring yields of these monomeric alkaloid derivatives are very high, especially for **159a** (Table 4, entry 1).

4.5. Preparation of the soluble model compound of 1,3,5-triazine-core *Cinchona* alkaloid derivative.

The 1,2,3-triazole soluble model derivative (**161)** was synthesized by 'click'-reaction as described in the previous paragraphs. The starting alkyne alkaloid derivative **106b** was subjected to cycloaddition reaction with two equivalents of benzylazide **153** under reaction conditions described in Scheme 39.

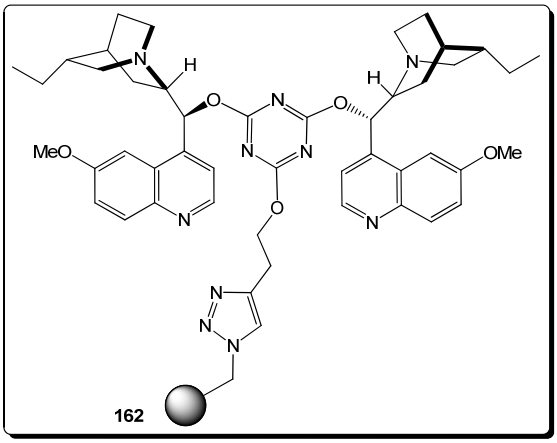


Scheme 39. Preparation of soluble model compound 1,3,4-triazine-core (DHQD)$_2$TZ (161). Reagents and conditions: a) as in Scheme 33.

The mixture of solvent, reagent and catalyst was kept stirring at room temperature for 20 hours, observing the disappearance of the substrate **106b** by TLC analysis and the formation of a new compound, slightly more retained. The ^{1}H NMR analysis of the crude

confirmed the formation of desired product by disappearance of acetylene unit of starting alkaloid **106b** and the presence on new signal related to the 1,3,5-triazole unit. The crude product was then subjected to flash chromatographic purification, giving **161** as colourless solid foam with 71% yield, which provided a single spot on TLC analysis. The compound was characterized by MS, ^{1}H NMR and ^{13}C NMR analyses and measurement of optical rotatory power (see Experimental Section).

The immobilization study of substrate **106b** to prepare insoluble 1,3,5-triazole core *Cinchona* alkaloid derivative (**162**) is in progress.



4.6. Attempt to immobilize the alkaloid derivative 100a onto the azido functionalized PolyHIPE material.

In order to obtained *Cinchona* alkaloid functionalized PolyHIPE monolith, we have decided to attempt to immobilize, through CuAAC, an alkyne-functionalized dimeric pyridazine-core quinidine derivative (**100a**) on to the azide-functionalized PolyHIPE monolith (Figure 35a). The same reaction conditions were employed as described in Scheme 33, except the preparation of the mixture of alkaloid derivative (**100a**) (equivalent to the moles of azide group in the PolyHIPE), catalyst and DIPEA in acetonitrile separately followed by its introduction under nitrogen into the glass-mold containing polymer. The collected unbound alkaloid from the sealed mold (Figure 35b) after 24h, by flushing the reaction mixture and subsequent washings with the solvent revels minute loading of alkaloid (**100a**) as estimated based on the reduction of recovered alkaloid amount over initial. Even by repeating the reaction on same polyHIPE (mold) for three times did not improve the loading of **100a** to the acceptable level, which was also evident from

comparing the IR of polyHIPE material before and after reaction, where no noticeable change was observed in the intensity of azide stretching at 2095 cm^{-1}. Technically, the negligible loading of alkaloid on polyHIPE precluded its further use in continuous flow processes.

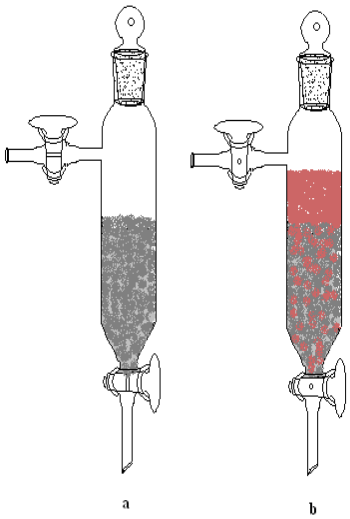


Figure 35. a) PolyHIPE monolith, b) PolyHIPE mold filled with reaction mixture

4.7. Conclusions

Respect to the traditional approaches mentioned in Chapter 1, section 1.4, in most of the investigated cases the ‘click’-reaction proved a very efficient tool for the immobilization of different soluble *Cinchona* alkaloid derivatives onto insoluble macromolecular backbones. By the above-cited technique, three different types of soluble *Cinchona* alkaloid derivatives (pyridazine-core; anthraquinone-core and propargyl-type) were immobilized on four types of polymer supports, by giving twelve different IPB-*Cinchona* alkaloid derivatives pending from the main polymeric matrix. In addition, the immobilization of the soluble dimeric 1,3,5-triazole-core dihydroquinidine alkyne derivative onto the organic polymer supports is in evaluation.

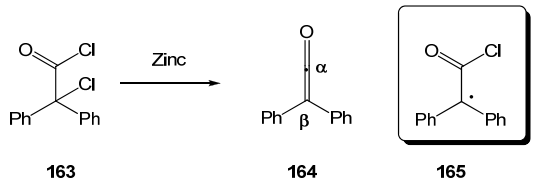
These immobilized *Cinchona* alkaloid derivatives will be employed as heterogeneous organocatalysts in some catalytic asymmetric transformations by comparing their performances with the representative soluble model derivatives.

In this regards, the next chapter is devoted to demonstrate the scope of these chiral organocatalysts and, in the case of the supported materials, their possible recycling in few cases.

CHAPTER -5- ASYMMETRIC TRANSFORMATIONS USING POLYMER SUPPORTED *CINCHONA* ALKALOID ORGANOCATALYSTS

5.1. Asymmetric dimerization of ketenes

The first ketene was serendipitously discovered in 1905 when Hermann Staudinger attempted the synthesis of radical species **165** by the reaction of α-chlorodiphenylacetyl chloride **163** with zinc (Scheme 40). Surprisingly, a dehalogenated closed-shell product was formed which was eventually identified as diphenylketene **164**.[175] Highly reactive ketenes are characterized by unusual 'heteroallenic' bond structure, having significant negative charge on both oxygen and β-carbon atom. Instead, the positive charge is localized on α-carbon atom that, in fact, preferentially undergoes nucleophilic attack.[176] These properties make ketenes highly useful and versatile organic reactive intermediates for numerous applications, nicely reviewed elsewhere.[176]



163 **164** **165**

Scheme 40. Historic discovery of ketene

Over the years different approaches emerged to prepare this reactive intermediate **164b** (Figure 36), including pyrolysis of homodimers or anhydrides (route-1 and route-2) and photolysis of phenyldiazoacetate (route-3). A more popular method for ketene generation is the dehydrohalogenation of di- or mono-substituted acid chlorides with tertiary amines (route-4).

Following the latter approach, the group of Calter developed an interesting enantioselective dimerization of monosubstituted ketenes, generated in situ by dehydrohalogenation of the acid chlorides **166** with DIPEA. The reactions were carried out at room temperature, in presence of 5% of different 9-*O* alkaloid derivatives (**205**) (*e.g.* propanoyl, trimethylsilyl, *tert*-butyldimethylsilyl, etc.) as the chiral catalyst (Scheme 41).[177]

[175] Staudinger, H. *Berichte der Deutschen Chemischen Gesellschaft* **1905**, *38*, 1735-1739.
[176] **a)** Tidwell, T. T. *European Journal of Organic Chemistry* **2006**, *2006*, 563-576; **b)** Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771-6803.
[177] **a)** Calter, M. A.; Guo X. Journal of Organic Chemistry **1998**, 63, 5308 –5309 ; **b)** Calter, M. A.; Orr, R. K.; Song, W. *Organic Letters* **2003**, *5*, 4745 – 4748.

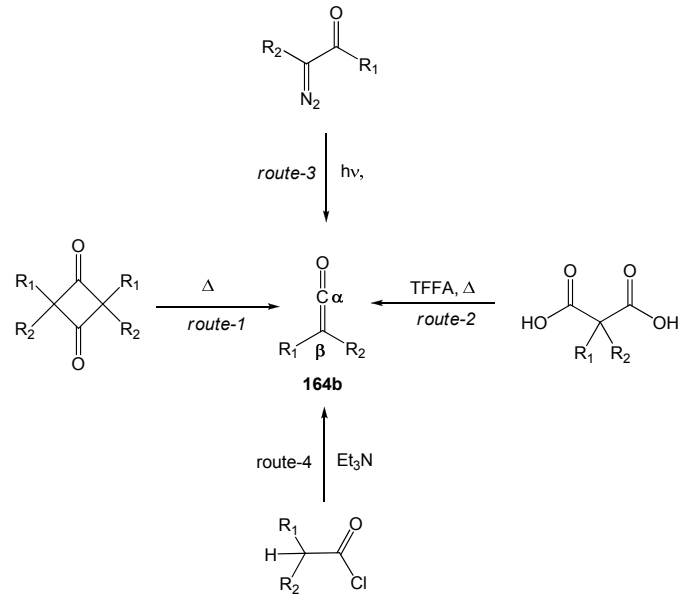
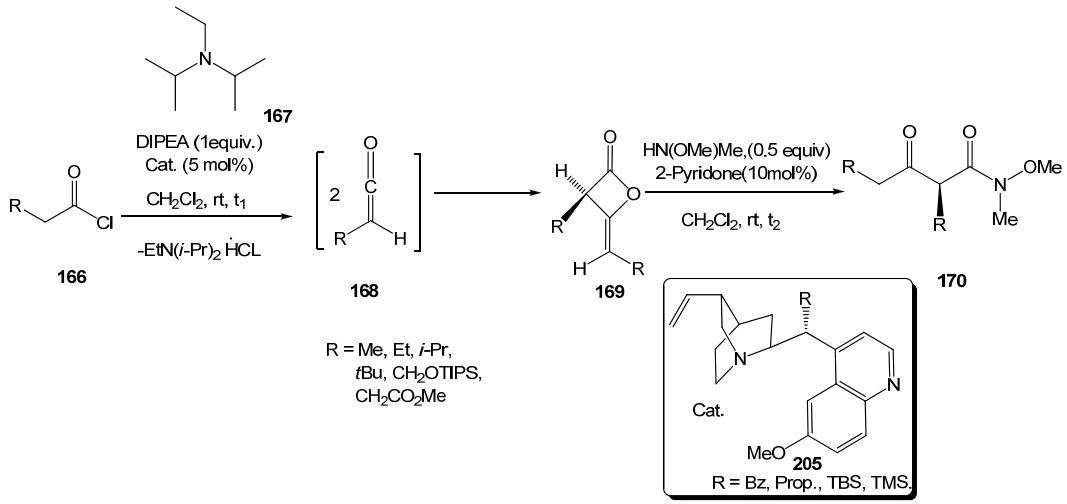


Figure 36 Different routes for ketenes generation

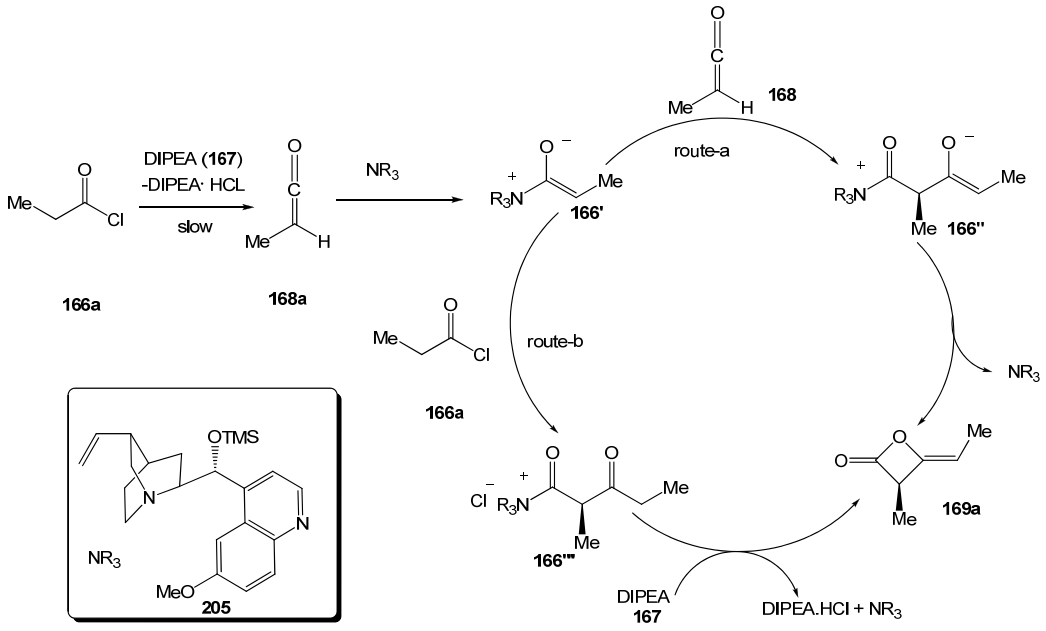


Scheme 41 Asymmetric ketene dimerization by Calter and coworkers

Under these mild conditions, the intermediate **168** has a low tendency to dimerize spontaneously or by action of the hindered amine **167**.[177b] On the contrary, if the solution contains a *Cinchona* alkaloid derivative, its very nucleophilic quinuclidine nitrogen atom can interact with the ketene **168** and promote the conversion to dimer **169**. In this way the dimerization occurs predominantly by the action of the *Cinchona* alkaloid organocatalyst that, being chiral, can induce enantioselectivity in the formation of **169** (for the mechanistic details see below). Finally, the rather volatile and unstable β-lactone product **169** was normally not isolated. Instead, it was reacted *in situ* with *N,O*-dimethyl hydroxylamine, in the presence of 2-pyridone as acylation catalyst, to give the corresponding Weinreb amides **170** products in fair to good yields (58-88%) and high enantiomeric purity (91-96% *ee*).

Amongst the different amides synthesized by this approach, **170** (R = Me) is particularly interesting, being able to provide a dipropionate chiral synthon that has been used in the preparation of various natural products.[176b]

From the mechanistic point of view (Scheme 42), kinetic measurements revealed that the rate-determining step is the dehydrohalogenation of **166a** to give **168a** while, in presence of alkaloid catalyst, its subsequent dimerization to give **169a** is faster. Regarding this last step, the author speculated that the quinuclidine nitrogen atom of the alkaloid organocatalyst attacks electrophilic carbon atom of ketene **168a**. The generated acyl ammonium enolate **166'** would then react with a second molecule of ketene **168a** (route-a) to give the intermediate **166"** or with the acid chloride **166a** (route-b) to give the intermediate **166"'**; either compound could eventually cyclise to the dimer **169a**, with regeneration the alkaloid organocatalyst.



Scheme 42. Proposed mechanism for the ketene dimerization reaction catalyzed by alkaloid derivative.

Because of the synthetic importance of chiral ketene derivatives[176b] and the apparently high tolerance to variations in the alkaloid 9-*O* substituent,[177b] the remarkable ketene dimerization of Calter and coworker was selected to evaluate the catalytic performances of the alkaloid derivatives prepared in this Thesis work.

5.1.1. Asymmetric dimerization of ketene using soluble model catalysts

To test the suitability of the different polymer supported *Cinchona* alkaloid derivatives (chapter-4) as IPB catalysts in the asymmetric ketene dimerization reaction, their low molecular weight models **154**, **155a-c**, **160a**,**b** and **161** (Scheme 35) were studied first.

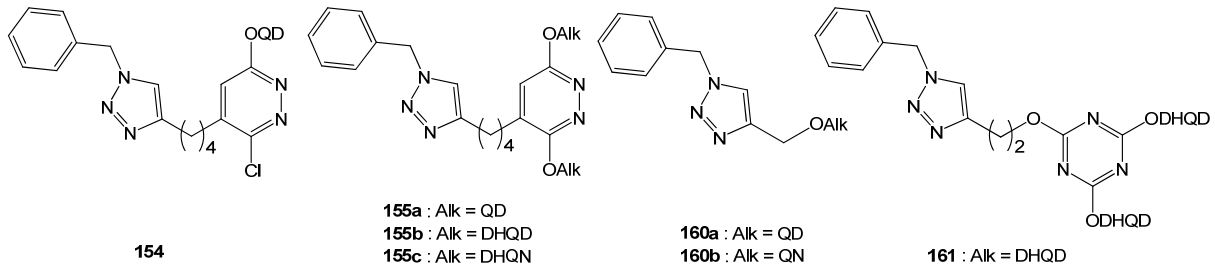


Figure 37. Soluble alkaloid derivatives employed in the asymmetric dimerization of ketenes.

The reactions (Table 5) were performed according to the protocol reported by Calter for the in situ formation of the ketenes by dehydrohalogenation of acid chlorides with DIPEA, followed by the one-pot ring opening of the intermediate β-lactone dimers to Weinreb amides.[177b]

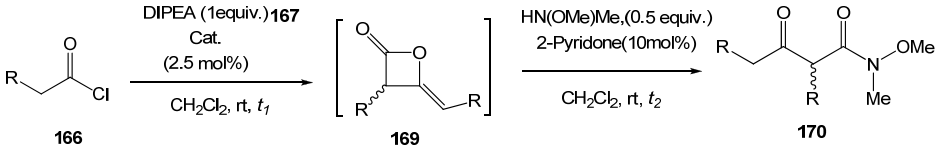
When **166** (R = Me) was reacted in the presence of 2.5 mol% of the soluble dimeric QD or DHQD pyridazine-core catalysts **155a** or **155b** (Table 5, entries 1 and 2), we were pleased to find that **170** (R = Me) was formed in good isolated yields and with high *ee* values. The absolute configuration of the product was also consistent with that reported by Calter for catalysts of the QD series.

By using the dimeric DHQD catalyst **161** with the 1,3,5-triazine core, a slight decrease of the *ee* of the product **170a** was observed (Table 5, entry 3). On the contrary, the monomeric pyridazine ether **154** (5 mol%) afforded the same yield and *ee* value as the corresponding dimeric derivative **155a** (compare entry 1 and 13 in Table 5)

In addition to the possible mechanistic implications, the latter findings appear significant for the purposes of this work. In particular, they supported the choice of using the crude pyridazine ethers **100a-c** in the preparation of the corresponding IPB systems (see **4.2.2**): Indeed, the presence of the monomeric intermediate (*e.g.* **154**) in the unpurified dimeric alkaloid derivatives and its subsequent immobilization onto the insoluble support were not expected to lead to any significant reduction of the catalytic performance.

Interestingly, similarly results were also obtained for the mechanistically unrelated alcoholysis of *meso*-anhydrides discussed below (see 5.2.1).

Table 5. Results in the asymmetric dimerization of ketenes with soluble alkaloid derivatives.



166 169 170

Entry	Cat.	R	t_1 [h]	t_2 [h]	Yield [%][a]	ee [%][b] (a.c.)
1	**155a**	Me	6	2	67	95 (S)
2	**155b**	Me	6	2	60	95 (S)
3	**161**	Me	6	2	69	92 (S)
4[c]	**160a**	Me	6	2	65	93 (S)
5[c]	**160a**	Et	6	2	69	95 (S)
6[c]	**160a**	i-Pr	24	24	70	95 (S)
7[c]	**160b**	Me	6	2	57	70 (R)
8[c]	**160b**	Et	6	2	55	70 (R)
9[c]	**160b**	i-Pr	24	24	70	68 (R)
10	**155c**	Me	6	2	65	77 (R)
11	**155c**	Et	6	2	68	88 (R)
12	**155c**	i-Pr	24	24	64	92 (R)
13	**154**	Me	6	2	62	95 (S)

a) Isolated yield after silica-gel filtration. b) Determined by HPLC on chiral stationary phase (CPS); absolute configuration of the prevailing enantiomer in parentheses. c) 5 mol% of catalyst used.

The use of 5 mol% of the monomeric compound **160a** in the reaction with propionyl chloride (entry 4) provided the final product **170** (R = Me) with yield and *ee* values analogous to those observed with the dimeric and monomeric derivatives discussed above. Together with results obtained in the reaction of homologous acid chlorides **166** (R = Et) and **166** (R = *i*Pr) (entries 5 and 6), these findings confirmed the anticipated high tolerance of the asymmetric transformation under exam to changes in the structure of 9-*O* substituent.

In order to evaluate the use of the alkaloid organocatalysts belonging to the QN series, the monomeric ether **160b** (5 mol%) and the dimeric one **155c** (2.5 mol%) were examined next (Table 5, entries 7-12). In general, all these runs afforded the Weinreb amides **170a-c** in good yields, with prevalence of the opposite enantiomer of that obtained in the experiments with QD organocatalysts. However, the *ee* values of the products were only moderate in most cases, reaching synthetically useful levels only in the reaction of the

butanoyl and *iso*-valeroyl acid chlorides catalyzed by **155c** (Table 5, entries 11 and 12). As already found for most of the organocatalyst examined in the study of Calter,[177b] for the alkaloid derivatives of the present work the pseudoenantiomeric effect seems therefore accompanied by a considerable change of the enantioselectivity level on switching between the QD and QN series.

Overall, the results provided by the model compounds described above demonstrated the suitability of all of the new alkaloid derivatives developed in this Thesis, for the catalysis of the asymmetric dimerization of ketenes. Nonetheless, given the generally better scalability and higher performance of the organocatalysts obtained from the 9-*O* propargyl alkaloids or embedding a pyridazine unit over those possessing a 1,3,5-triazine-core, only the former were further studied in their IPB version.

5.1.2. Heterogeneous asymmetric dimerization of ketenes using IPB *Cinchona* alkaloid derivatives.

The heterogeneous enantioselective dimerization of ketenes was generally carried out using the same conditions discussed above for the homogeneous reactions. The only modification required was the doubling of the solvent volume for better magnetic stirring. Moreover, because the alkaloid derivative is not involved in the conversion of the intermediate β-lactone **169** into the final product **170**,[177a] the overall transformation was not accomplished one pot. Instead, after the dimerization step was carried for the prescribed time t_1 the insoluble catalyst was removed by filtration under inert atmosphere and the filtrate treated with *N*,*O*-dimethylhydroxylamine and 2-pyridone for the time t_2, to effect the ring opening of **169**. With this change, the contamination of the IPB systems by the reactants involved in the second step could be prevented, thereby allowing the direct recycling of the recovered catalyst without the need of any regeneration procedure.

The screening of the supported organocatalysts of this Thesis in the ketene dimerization reaction involved the set materials summarized in Figure 38. These included either monomeric or dimeric derivatives of QD, DHQD, QN, or DHQN, immobilized onto Merrifield or ArgoPore™ polystyrene supports.

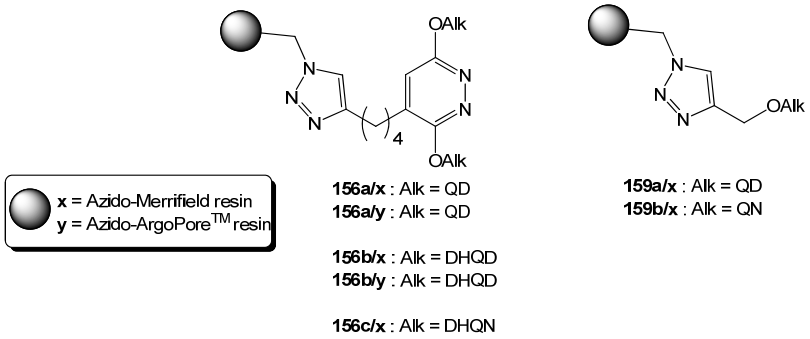
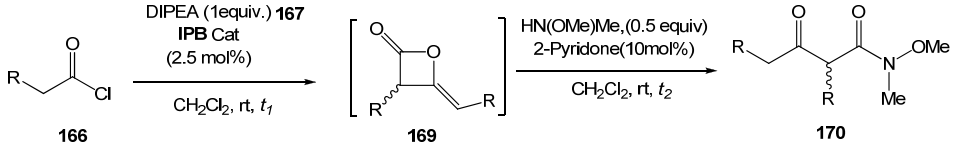


Figure 38. IPB-catalysts used in the asymmetric dimerization of ketenes.

Table 6. Results in the catalytic heterogeneous enantioselective dimerization of ketenes.



Entry	IPB-Cat.	Cycles	R	t_1 [h]	t_2 [h]	Yield [%][a]	ee [%][b,c]
1	**156a/x**	1	Me	6	2	60	97 (95)
2	**156a/x**	2	Et	6	2	56	97 (-)
3	**156a/x**	3	*i*-Pr	24	24	61	97 (-)
4	**156a/y**	1	Me	6	2	63	95 (95)
5	**156a/y**	2	Et	6	2	61	96 (-)
6	**156a/y**	3	i-Pr	24	24	64	97 (-)
7	**156b/x**	1	Me	6	2	60	96 (95)
8	**156b/y**	1	Me	6	2	56	96 (95)
9[d]	**159a/x**	1	Me	6	2	70	91 (93)
10[d]	**159a/x**	2	Et	6	2	63	95 (95)
11[d]	**159a/x**	3	i-Pr	24	24	61	93 (95)
12[d]	**159b/x**	1	Me	6	2	65	70 (70)[e]
13[d]	**159b/x**	2	Et	6	2	68	68 (70)[e]
14[d]	**159b/x**	3	i-Pr	24	24	63	62 (68)[e]
15	**156c/x**	1	Me	6	2	75	61 (77)[e]
16	**156c/x**	2	Et	6	2	81	82 (88)[e]
17	**156c/x**	3	i-Pr	24	24	42	89 (92)[e]

a) Isolated yield after silica-gel filtration; b) Determined by CSP-HPLC analysis; c) In parentheses, data obtained under comparable conditions with the corresponding soluble model catalyst; d) 5 mol% catalyst used; e) Opposite enantiomer with (*R*)-configuration was obtained.

When the dimeric (2.5 mol%) or the monomeric IPB catalysts (5 mol%) of the QD or DHQD series (**156a/x**, **156a/y**, **156b/x**, and **156b/y** or **159a/x**, respectively) were employed in the reaction of propanoyl chloride, the product **170** (R=Me) was eventually

isolated in good yield (56–70%) and with excellent enantiomeric purity (91–97% *ee*, Table 6, entries 1, 4, 7, and 9).[178] Under the same conditions, the pseudoenantiomeric QN-based IPB catalysts **159b/x** and **156c/x** afforded equally good yields (Table 6, entries 12 and 15) but, as already observed for their homogeneous counterparts (see 5.1.1), the *ee* of the product **170** (R = Me) was moderate for both catalysts.

These findings were confirmed by using the recovered materials for the dimerization of the ketenes obtained from the homologous acid chlorides **166** (R = Et) and **166** (R = *i*-Pr). By adopting the very same reaction times t_1 and t_2 reported by Calter for these substrates,[177b] the QD/DHQD-derived systems (**156a/x**, **156a/y**, and **159a/x**) allowed the eventual isolation of the (*S*)-configured Weinreb amides **170** (R = Et) and **170** (R = *i*-Pr) in good yields (56-64%) and with excellent *ee* values (93-97%; Table 6, entries 2, 3, 5, 6, 10, and 11). On the other hand, with pseudoenantiomeric IPB organocatalysts obtained form DHQN/QN (**156c/x** and **159b/x**) the expected inversion of the sense of asymmetric induction was accompanied, also in this case, by the anticipated reduction of the enantioselectivity levels (Table 6, entries 13, 14, 16, and 17). Thanks to the trend already observed with the corresponding soluble model **155c** (see 5.1.1), this effect did not preclude the possibility of obtaining the (*R*) enantiomers of **170** (R = Et) and **170** (R = *i*-Pr) in a substantial enantiomeric purity (82-89%), by the use of the IPB organocatalyst **156c/x**.

Interestingly, in the case of pyridazine derivatives belonging to the QD/DHQD series the outcome of the heterogeneous runs proved essentially independent from the support architecture. More in general, the yield and *ee* values afforded by the IPB organocatalysts of this screening appear to match quite well those provided by the corresponding soluble model compounds discussed in the previous paragraph. Taking also into account that the catalysis runs with the immobilized systems were carried out in a more diluted solution and with the same dimerization time t_1 as in the homogeneous ones, it could be concluded that neither the chemical efficiency, nor the asymmetric induction ability of the alkaloid fragments were dramatically impaired after linking to the insoluble support.[179] Overall, these results pointed to the absence of major immobilization effects in the IPB-catalysts suggesting that, irrespective of the ligand loading and support morphology, the

[178] Standard filtration experiments were carried out concurrently and demonstrated the lack of significant enantioselective catalytic activity in solution (Experimental section) Therefore, the results described in this Thesis may be safely related to a catalysis type which is largely heterogeneous in nature.

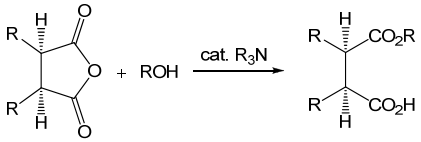
[179] In this respect, it should be noted, however, that under Calter's conditions the rate-limiting event is the dehydrochlorination of the acid chloride (**166**) by DIPEA, to give the corresponding ketene, and not the dimerization step itself (Ref. 177b): Variations of the alkaloid catalytic activity in the dimerization step could be, therefore, largely shadowed by this fact.

chiral units of these materials should experience a solution-like behaviour; at the same time any adverse site-site interaction or an active catalytic role of residual azide groups in the IPB systems of this work appears also unlikely.

In summary, the screening of some of the new IPB derivatives of the *Cinchona* alkaloids prepared in this Thesis in the asymmetric dimerization of ketenes allowed to achieve the first example of a highly enantioselective heterogeneous version of this metal-free reaction. While the yields were somewhat lower than reported by Calter for the reaction in homogeneous phase with simple alkaloid 9-*O* esters or silylethers,[177b] the *ee* values attained with the new chiral derivatives of this work were generally comparable or even slightly superior to the published ones. Given the possibility of obtaining valuable β-ketoamides of the Weinreb type with high enantiomeric purity and by a simple and economic transformation, the next obvious issue to be addressed in this Thesis was the recycling profile of the IPB organocatalysts. While promising indications in this respect could be gained from the screening runs of the homologous acid chlorides (Table 6), already carried out with recovered insoluble materials (see above), a more detailed investigation of this very important aspect for the purposes of the present work is presented in 5.6.1.

5.2. Asymmetric alcoholysis of cyclic *meso*-anhydrides

The desymmetrization of achiral *meso* compounds represents very useful strategy in asymmetric synthesis,[180] as it allows the preparation of polyfunctional chiral compounds. Often, the latter are valuable building blocks in the synthesis of natural products or biologically active substances.[181] Several attempts to develop methods for the stereoselective opening of *meso*-anhydrides have been described in the literature, including the use of enzymes,[182] enantiopure *chiral* nucleophiles (oxygen, nitrogen, carbon, or sulfur-based),[181] and *achiral* nucleophiles in combination with a chiral Lewis acid or base catalyst or a metal-free chiral mediator.[183] Amongst these strategies, the alcoholysis of *meso*-anhydrides in the presence of *chiral* tertiary amine catalysts (Scheme 43) appears remarkably convenient in terms of experimental simplicity, substrate scope, and synthetic versatility of the resulting hemiester products.[184]



Scheme 43. Asymmetric alcoholysis of *meso*-anhydrides

In this context, the use of *Cinchona* alkaloids and their derivatives[45e,f] has played a major role since the pioneering studies by Oda and Aitken's groups in the mid 80's.[185] Nonetheless, it was not until the turn of past century that this methodology gained a new momentum when Bolm and co-workers reported the attainment of synthetically useful *ee* values by the use of an excess of methanol and 1.1 equivalents of QD or QN, under

[180] **a)** Ward, R. S. *Chemical Society Reviews* **1990**, *19*, 1-19; **b)** Willis, M. C. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry* **1999**, 1765-1784; c) Spivey, A. C.; Andrews, B. I. *Angewandte Chemie, International Edition* **2001**, 40, 3131-3134.

[181] Atodiresei, I.; Schiffers, I.; Bolm, C. *Chemical Reviews* **2007**, *107*, 5683-5712.

[182] **a)** Wong, C. H. Whitesides G. M. in *Enzymes in Synthetic Organic Chemistry*, Editors: J. E. Baldwin, P. D. Magnus, Oxford: Elsevier, **1994**.

[183] Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455-3467. (and refs. cited therein)

[184] **a)** Chen, Y.; McDaid, P.; Deng, L. *Chemical Reviews* **2003**, *103*, 2965-2984; b) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chemical Reviews* **2003**, *103*, 2985-3012; **c)** Berkessel, A.; Groerger, H. *Asymmetric organocatalysis*. Weinheim: Wiley-VCH; **2005**, 347–355; **d)** Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Accounts of Chemical Research* **2004**, *37*, 621-631.

[185] **a)** Hiratake, J.; Yamamoto, Y.; Oda, J. i. *Journal of the Chemical Society, Chemical Communications* **1985**, 1717-1719; **b)** Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. i. *Journal of the Chemical Society, Perkin Transactions 1* **1987**, 1053-1058; **c)** Aitken, R. A.; Gopal, J.; Hirst, J. A. *Journal of the Chemical Society, Chemical Communications* **1988**, 632-634; **d)** Aitken, R. A.; Gopal, J. *Tetrahedron: Asymmetry* **1990**, *1*, 517-520.

carefully optimized conditions.[186] The same group succeeded also in carrying out the reaction with just catalytic amounts of the chiral organocatalyst QD,[185b] but the need of one equivalent of the expensive tertiary amine pimpedine (1,2,2,6,6-pentamethylpyperidine), as an achiral auxiliary base to help keeping the catalyst in the not-protonated form, limited the usefulness of the protocol to a large extent.

Nearly at the same time, Deng and coworkers gave another fundamental contribution to the field,[187] describing the organocatalytic use of some of the monomeric and dimeric alkaloid ligands originally developed for the Sharpless's osmium-mediated asymmetric dihydroxylation.[188] In particular, by using the phenanthrene and anthraquinone 9-*O* ether derivatives of the *Cinchona* alkaloids, an effective protocol could be disclosed whose landmarks are the wide substrate scope, mild reaction conditions, relatively short reaction times and, especially, the possibility of using just a limited amount (10 mol %) of the expensive alkaloid derivative in the absence of any added achiral base. Since then several improvements followed, including the use of different alcohol nucleophiles,[189] modified alkaloid organocatalysts (either monofunctional[189c, 190] or bifunctional),[191] recoverable variants,[192] and additives.[193]

Nonetheless, most of these efforts appear largely empirically-driven because the lack of a detailed mechanistic understanding of the reaction prevents a rational approach to the design of improved catalytic systems. In this respect it should be noted that two alternative scenario were emerged in the course of years, where the alkaloid catalyst would act either as a nucleophilic or general-base catalyst for the alcoholysis reaction (Figure 39).[180c, 184a] Both hypotheses received some degree of experimental support, with the latter preferentially credited at present as a satisfactory mechanistic rationale.[184a, 190, 194]

---

[186] **a)** Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, *1999*, 195,196; **b)** Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *The Journal of Organic Chemistry* **2000**, *65*, 6984-6991.

[187] Chen, Y.; Tian, S.-K.; Deng, L. *Journal of the American Chemical Society* **2000**, *122*, 9542-9543.

[188] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chemical Reviews* **1994**, *94*, 2483-2547.

[189] **a)** Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455-3467; **b)** Deng, L.; Chen, Y.; Tian, S. In *Brandeis University, USA* . **2004**; pp 33, Cont.-in-part of U.S. Pat. Appl. 2003 171,610; **c)** Ishii, Y.; Fujimoto, R.; Mikami, M.; Murakami, S.; Miki, Y.; Furukawa, Y. *Organic Process Research & Development* **2007**, *11*, 609-615.

[190] Li, H.; Liu, X.; Wu, F.; Tang, L.; Deng, L. *Proceedings of the National Academy of Sciences of the United States of America* **2010**, *107*, 20625-20629.

[191] **a)** Peschiulli, A.; Gun'ko, Y.; Connon, S. J. *Journal of Organic Chemistry* **2008**, *73*, 2454-2457; **b)** Connon, S. J. *Chemical Communications (Cambridge, United Kingdom)* **2008**, 2499-2510.

[192] **a)** Bigi, F.; Carloni, S.; Maggi, R.; Mazzacani, A.; Sartori, G.; Tanzi, G. *Journal of Molecular Catalysis A: Chemical* **2002**, *182-183*, 533-539; **b)** Woltinger, J.; Krimmer, H.-P.; Drauz, K. *Tetrahedron Letters* **2002**, *43*, 8531-8533; **c)** Kim, H. S.; Song, Y.-M.; Choi, J. S.; Yang, J. W.; Han, H. *Tetrahedron* **2004**, *60*, 12051-12057; **d)** Song, Y.-M.; Seok Choi, J.; Woon Yang, J.; Han, H. *Tetrahedron Letters* **2004**, *45*, 3301-3304.

[193] Ivasic, T.; Hamersak, Z. *Tetrahedron: Asymmetry* **2009**, 20, 1095-1098.

[194] Dedeoglu, B.; Catak, S.; Houk, K. N.; Aviyente, V. *ChemCatChem* **2010**, *2*, 1122-1129.

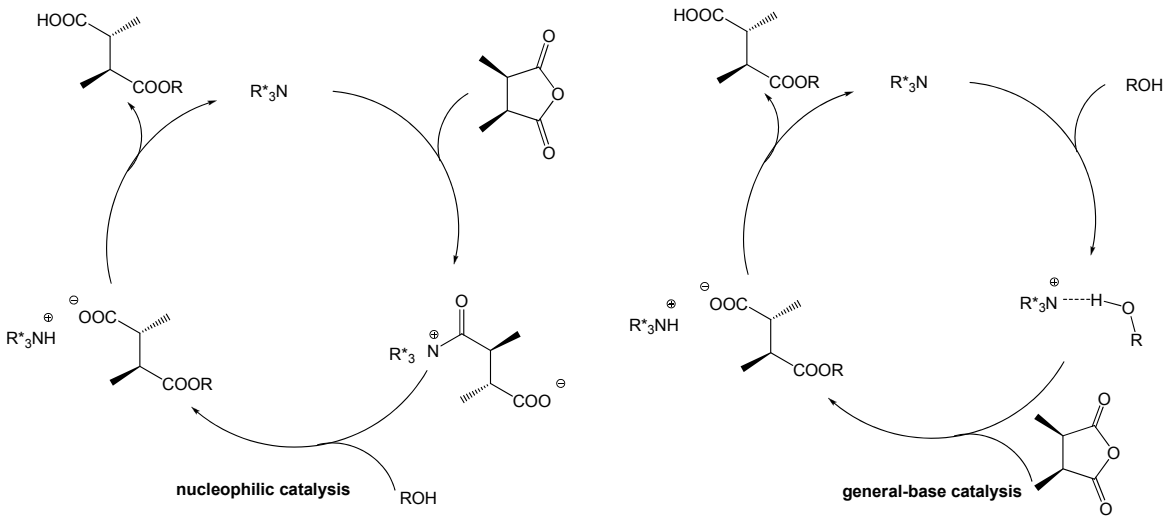


Figure 39. Proposed mechanism for catalytic *meso*-anhydride ring opening reaction

Said catalytic process was chosen as an extension of this Thesis work in the investigation of IPB *Cinchona* alkaloids performances in asymmetric transformations.

5.2.1. Asymmetric methanolysis of *cis*-1,2,3,6-tetrahydrophtalic anhydride using soluble model compounds

For testing the performances of catalysts prepared in this work, the methanolytic desymmetrization of *cis*-1,2,3,6-tetrahydrophtalic anhydride (**171**) was chosen as the benchmark (Scheme in Table 7). The conditions were those of Deng and coworkers,[187,190] with different alkaloid organocatalysts and a fixed reaction time of 48 h. For comparison purposes, runs with the commercial anthraquinone bis-hydroquinidyl ether **8** (10 mol%) were also carried out, providing the additional results summarized in the Table 7 (entries 2,[187] 5 and 6).

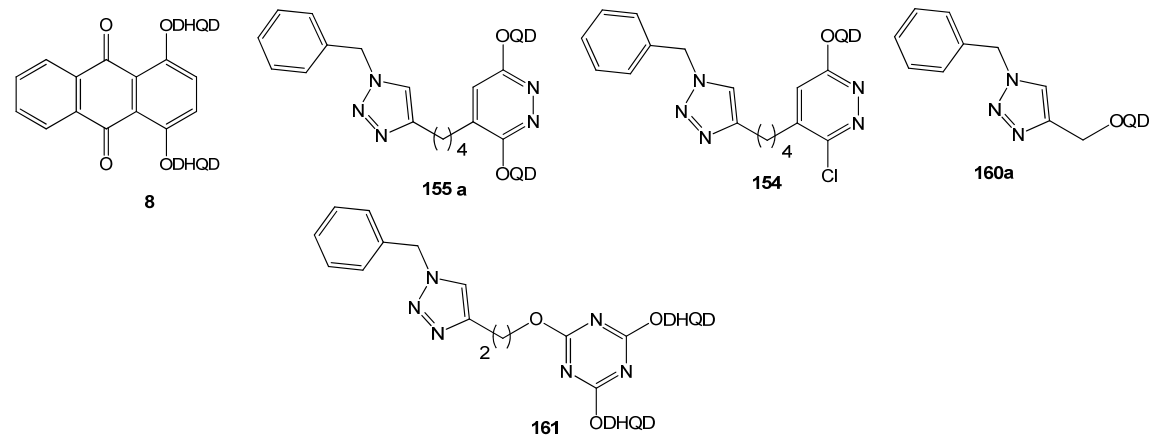


Figure 40. Soluble alkaloid derivatives employed in the methanolysis of *cis*-1,2,3,6-tetrahydrophtalic anhydride

Table 7. Asymmetric methanolysis of *cis*-1,2,3,6-tetrahydrophtalic anhydride

Entry	Cat. (mol%)	Solvent	Conversion (%)[a]	Yield (%)[b]	*ee* (%)[c,d]
1	**155a** (10)[e]	Et_2O	54	45	55
2	**8** (7)[f]	Et_2O	-	95	98
3	**155a** (10)	THF	25	18	67
4	**155a** (10)	Toluene	70	69	50
5	**8** (10)	THF	78	73	93
6	**8** (10)	Toluene	88	85	83
7	**155a** (50)	Toluene	>98	quant.	66
8	**154** (20)	Toluene	68	66	47
9	**160a** (10)	Toluene	-	quant	50
10	**160a** (100)	Toluene	-	quant	68
11	**161** (10)	Et_2O	-	quant	77
12	-	Toluene	6	~ 5	-

a) Determined on the crude product, by ^{1}H NMR, b) Isolated yield after flash chromatography, c) By CSP-HPLC (Chiralcel OJ, 1 ml min^{-1}, n-hexane:IPA = 95:5+0.1% trifluoroacetic acid, 210 nm), d) The major enantiomer of **172** had (1*R*;2*S*)configuration,[187] e) The catalyst was largely undissolved, f) from ref.[187].

Preliminary solvent screening using the soluble pyridazine derivative **155a** revealed a strong influence of the reaction medium on the methanolysis progress, with some notable differences in comparison with the literature derivative **8**. In fact, whilst diethyl ether and THF proved substantially superior to toluene in the reactions involving **8** (Table 7, entries 2,[187] 5, and 6), in the case of **155a** only the latter solvent could afford a reasonable compromise between activity and enantioselectivity (Table 7, entries 1, 3, and 4). For this reason additional catalyst screening experiments were carried out in toluene, with the aim of exploring the effect of catalyst loading, the influence of the structure of the different alkaloid derivative, and the rate of the background reaction.

The increase of the amount of the catalyst **155a** from 10 to 50 mol % led to an essentially complete conversion of **171** in the standard time and to a noticeable rise of the enantiomeric purity of the product **172** (Table 7, entries 4 and 7). In contrast, the use of the mono-alkaloid pyridazine ether **154** (20 mol %) afforded results that were not appreciably different from those provided by the corresponding dimeric derivative **155a** at the same *alkaloid unit* loading (10% mol; compare Table 7, entries 4 and 8).

The use of the propargyl quinidine derivative **160a** (10 mol%; Table 7, entry 9) furnished the product **172** in quantitative yield but with similar enantiomeric purity as provided by the pyridazine derivatives above. Also in this case, increasing the amount of **160a** from a catalytic to stoichiometric loading led to an enhancement in the enantiomeric excess of the product **172** (Table 7, entry 10). However, neither these conditions nor the use of the dimeric QD derivative **161** based on the 1,3,5-triazine-scaffold (Table 7, entry 11) allowed to attain synthetically useful *ee* values. Finally, a run carried out at -20°C in toluene, without any alkaloid catalyst, afforded the racemic product in ~ 5% yield after the standard 48 h reaction time.

Overall, the monomeric or dimeric nature of the chiral organocatalysts seems to have a minor impact on the catalytic performance in the transformation under exam (compare **154** and **155a**), resembling in the sense what previously found in the dimerization of methylketene (see 5.1.1).[195] On the contrary, the actual structure of the 9-*O* substituent turned out to have a much stronger impact here, with all the new catalysts tested in the screening providing substantially lower *ee* values than the optimal anthraquinone derivative reported in the literature.[196]

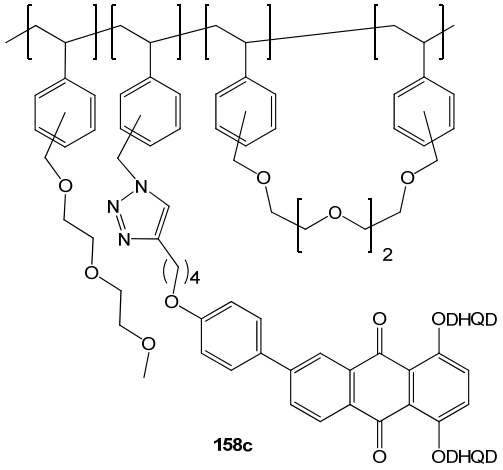
5.2.2. Asymmetric methanolysis of *cis*-1,2,3,6-tetrahydrophtalic anhydride using the IPB organocatalyst 158c.

Given the much better performance of anthraquinone organocatalyst in the homogeneous phase, only the material **158c** was selected for exploring the heterogeneous version of the reaction under exam. As described in 4.3, this IPB derivative could be obtained with a substantial higher loading than the analogous system **158a** immobilized onto a standard Merrifield resin. Moreover, the polar and flexible oligo(ethylene oxide) fragments embedded in the structure of **158c** (reported again in Figure 41 for the sake of

[195] To corroborate this hypothesis it can be mentioned also a recent B.Sc. training work carried out in this laboratory. In this study, the use of a monomeric anthraquinone organocatalyst (bearing a DHQD unit and a benzyloxy group on the aromatic scaffold) afforded the same *ee* in the benchmark methanolysis of *cis*-1,2,4,6-tetrahydrophtalic as provided by **8** under the same conditions [A. Del Grande, Laurea Triennale, Università di Pisa (2011)].

[196] **a)** The intriguing influence of the 9-*O* substituent on the catalytic performance of DHQD alkaloid derivatives was examined in collaboration with Prof. G. Uccello-Barretta from this Department, by combining catalysis experiments with mono- and bidimensional NMR measurements on pyridazine (**155a** and **154**) and anthraquinone (**8**) model compounds. Because this topic lays somewhat outside the scope of the present Thesis, no data will be presented here. Nonetheless, it can be said that, at variance with literature conclusions, the evidence gained in such a study pointed to a more specific role of the 9-*O* substituent than just enforcing a preferential reactive conformation of the alkaloid units. For further details, see: **b)** Balzano, F.; Jumde, R. P.; Mandoli, A.; Masi, S.; Pini, D.; Uccello-Barretta, G. *Chirality* **2011,** *23*, 784-795.

convenience) were supposed to be beneficial for a process taking place in a medium that contains a relatively large amount (2 vol%) of methanol.



158c

Figure 41. IPB-catalyst used in *meso*-anhydride ring opening

Considering that both PS and PEG materials are not compatible with Et_2O, the catalysis runs were carried out in THF or toluene. By using 20 mol% of the supported catalyst at -20°C, ^{1}H NMR analysis revealed a rather incomplete conversion of the *meso* substrate **171** after 48 h standard reaction time (51 and 62% for THF and toluene, respectively). As a consequence, after filtration of the supported catalysts the chromatographic purification of the crude product afforded the hemiester **172** in only fair yields (48 and 59%, respectively). Moreover, chiral HPLC analysis of purified **172** demonstrated that the enantiomeric purity of the product was significantly lower (70 and 72%, respectively) than attained with the commercial organocatalyst **8** under comparable conditions (93 and 83%, respectively; see Table 7, entries 5 and 6). Clearly, the not negligible background 'racemic' reaction observed in the process under exam (see Table 7, entry 12), combined with the reduced catalytic activity displayed by the supported catalyst, could be largely responsible for the diminished enantioselectivity provided by **158c** with respect to **8**. In this respect, it is interesting to note that enantioselectivity observed in the reaction catalyzed by **158c** in toluene (72% *ee*) is almost perfectly matching the result (74% *ee*) calculated by the superimposition of the background reaction to an enantioselective process catalyzed by an IPB anthraquinone derivative with an asymmetric induction ability analogous to **8**.[197] This latter observation suggested that from the point of view of both the

[197] Provided the two processes proceed independently, the result of the background reaction can be taken approximatively equal to the outcome of the blank run (see Table 7, entry 12), *i.e.* 6% conversion in 48 h, 0% *ee*. Therefore, the substrate conversion due to the IPB catalyst should amount to about (62 – 6)% = 56% in 48 h. By assuming for the supported

product yield and its enantiomeric purity, the use of a larger loading of the supported catalyst could be a possible approach for improving the outcome of the reaction under exam. Nonetheless, the practical shortcomings of this solution and some limitations in recycling (see 5.6.2, below) discouraged its adoption in this work.

In conclusion, a brief comparison with the IPB catalysts reported to date for the asymmetric methanolysis of *meso*-anhydrides seems appropriate. As a matter of facts, **158c** afforded results that are similar or somewhat better of those described by the groups of Sartori (native QD) and Deng (QN anthraquinone ether) with alkaloid derivatives anchored onto siliceous supports through the C_9-C_{10} position.[192a,d] Indeed, when the process was carried out in THF or Et_2O, for 16-72 h between -20 and -30°C, these literature IPB catalysts afforded variable conversions or yields (15-85%) and generally fair *ee* values (52-67% *ee*) in the opening of different bicyclic *meso*-anhydrides (including **171**). On the contrary, the material **158c** investigated in this Thesis proved less effective than the QD or QN anthraquinone ethers by Han and co-workers, immobilized on silica-gel through the C_9-C_{10} position.[192c] Despite the similarity with the Deng's IPB catalyst the latter materials provided up to 73% conversion and 92% *ee* in the methanolysis of **171** under optimized conditions (72 h at -10°C). Interestingly, in this latter work a strong influence of the solvent was also observed, *e.g.* with THF leading to substantially lower conversions (44 *vs.* 76%) but higher *ee* values (88 *vs.* 80%) than Et_2O, in the reactions carried out at -30°C for 72 h. Clearly, these literature precedents indicated the possibility of improving the results with **158c** by further optimizing the reaction medium. Nonetheless, the relatively narrow solvent compatibility window of PS materials suggested that future advances in this direction would probably require also some re-design of the support architecture, perhaps by reduction of the cross-linking degree of the macromolecular network.

units a chiral discrimination ability similar to that of the soluble catalyst **8** under the same conditions (83% *ee*, see Table 7, entry 6) the overall enantiomeric purity of the product can be estimated as: (0.56 × 83% + 0.06 × 0%)/(0.56 + 0.06) = 74% *ee*.

5.3. Dynamic kinetic resolution of mandelic acid derivatives

Despite of tremendous progress in the field of asymmetric synthesis, the kinetic resolution of the racemates is still the most important industrial approach to the synthesis of enantiomerically pure product.[198] According to the 1996 IUPAC recommendations, a *kinetic resolution* (KR) is defined as "The achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, etc.)".[199] In the simplest cases of KR, the enantiomers of the racemic mixture interact with a chiral reagent or catalyst to generate two diastereomeric transition states. The free energies of these competing transition states define the rate constants *k* for conversion of the fast-reacting and slow-reacting substrate enantiomers (*e.g.* S_R and S_S, respectively, Figure 42). Ideally, when the ratio k_{fast}/k_{slow} (equal to k_{rel} or the reaction enantioselectivity) is large enough, the transformation of S_R in the corresponding product P_R can be attained, while the latter substrate enantiomer (S_S) is recovered in the unchanged form. [200,201]

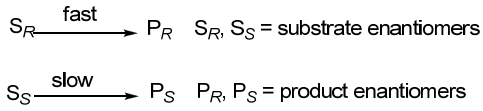


Figure 42. Classical Kinetic Resolution

The history of KR date back in 1858, when Pasteur observed that fermentation of racemic ammonium tartrate with *Penicillium glaucum* selectively destroys the dextrorotatory isomer.[202] Later in 1890, Fischer studied other enzymatic resolution of carbohydrates, and correctly realized that the natural *d*-hexoses are consumed upon fermentation with brewer's yeast, whereas the *l* enantiomers remain unchanged.[203]

The first example of the KR phenomenon with nonenzymatic reagents was reported a few years later. Marckwald and McKenzie observed enantioselective esterification of racemic mandelic acid by (-)-menthol upon heating the reactants, and were able to recover a

[198] Pellissier, H. *Tetrahedron* **2011**, *67*, 3769-3802.
[199] **a)** Moss, G. P. *Pure and Applied Chemistry* **1996**, *68*, 2193-2222; **b)** Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407-1446; **c)** Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stuermer, R.; Zelinski, T. *Angewandte Chemie International Edition* **2004**, *43*, 788-824; **c)** Vedejs, E.; Jure, M. *Angewandte Chemie International Edition* **2005**, *44*, 3974-4001.
[200] Pellissier, H. *Advanced Synthesis & Catalysis* **2011**, *353*, 659-676.
[201] Vedejs, E.; Jure, M. *Angewandte Chemie International Edition* **2005**, *44*, 3974-4001.
[202] M. L. Pasteur. *Comptes Rendus Hebdomadaires des Seances de l Academie des Sciences* **1858**, *46*, 615-618.
[203] Fischer, E. *Berichte der Deutschen Chemischen Gesellschaft* **1890**, *23*, 370-394.

small amount of the less-reactive *l*-mandelic acid in pure form after multiple crystallizations. [204] A milestone in the use of KR for the preparation of highly enantioenriched substances came in 1981 when Sharpless and co-workers reported the resolution of racemic allylic alcohol substrates with diisopropyl tartrate/tert-butylhydroperoxide (TBHP)/Ti(OiPr),[205]

The major limitation of classical KR is that the maximum theoretical yield with respect to the racemic mixture is 50%. Attempts to overcome this problem led to the evolution of classical KR into *dynamic kinetic resolution* (DKR), *i.e.* a process that combines the resolution step of KR with an *in situ* equilibration (racemization) of the stereochemically-labile substrate enantiomers (Figure 43). Provided the latter process is faster than the reaction of the slow-reacting substrate (S_S) with the chiral reagent or catalyst (Curtin–Hammett kinetics), S_S is no longer allowed to accumulate. Instead, it is continuously transformed into the fast-reacting enantiomer (S_R), whose further enantioselective transformation can eventually drive the whole process to the complete conversion of the racemic substrate. In principle, DKR has therefore the potential of combining a high yield (with respect to the substrate racemic mixture) with the attainment of a product P_R of high enantiomeric purity.

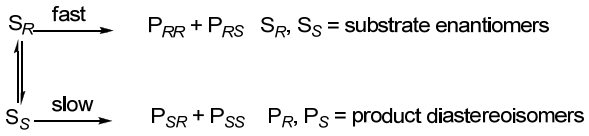
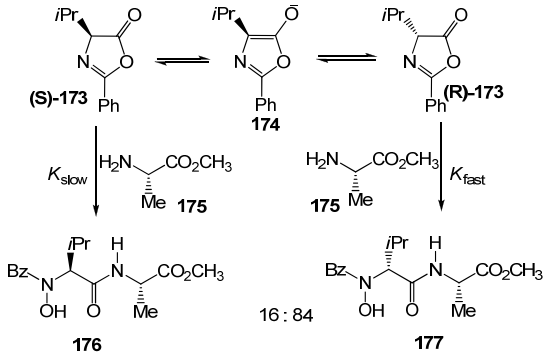


Figure 43. Enantioselective synthesis of diastereoisomer via DKR

Perhaps the first example of DKR appeared in a 1966 study by Weygand and co-workers, involving the reaction of racemic azlactones with chiral amino esters,[206] but it was not until the classic 1989 work by Noyori and co-workers on the asymmetric hydrogenation of racemic β-dicarbonyl compounds, that the term "dynamic kinetic resolution" appeared in the literature.[207]

[204] Marckwald, M.; Mc., K., Alex. *Berichte der Deutschen Chemischen Gesellschaft* **1899**, *32*, 2130-36.
[205] Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *Journal of the American Chemical Society* **1981**, *103*, 6237-40
[206] Weygand, F.; Steglich, W.; Barocio, d. l. L., X. *Tetrahedron, Supplement* **1966**, *No. 8*, 9-13.
[207] Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; et, a. *Journal of the American Chemical Society* **1989**, *111*, 9134-5.



Scheme 44. One of the first examples of DKR by Weygand et al.[206]

Since then the concept has been applied more and more times, both in enzymatic and nonenzymatic reactions.[208,209] Concerning the latter, a noteworthy advancement beyond the classical DKR with chiral metal complexes, involves the use of asymmetric organocatalyst.[198,201] In this respect, modified *Cinchona* alkaloids have played a major role since the 2001 seminal report by Deng and co-workers where the asymmetric cyanation of ketones was shown to involve a KR of cyanohidrin intermediates.[210] Shortly after, the same group described the alcoholytic DKR of *rac*-5-aryl-1,3-dioxolane-2,4-diones (**178**, Scheme 45).[211] Interestingly, in this study the commercially available anthraquinone ether $(DHQD)_2AQN$ was shown to perform a dual role, *i.e.* promoting both the KR of the substrate enantiomers, by the enantioselective ring opening, and the *in situ* racemization of the slow-reacting 5-aryl-1,3-dioxolane-2,4-dione antipode. Consequently, the α-hydroxy ester products **179** could be obtained in good yields (61-85%) and with high enantiomeric purity (up to 96% *ee*), opening the way to a host of other applications of *Cinchona* alkaloid derivatives in metal-free DKR processes.[198,212]

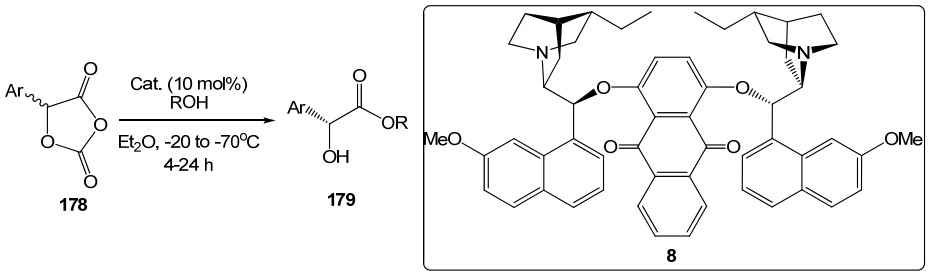
[208] **a)** Noyori, R.; Tokunaga, M.; Kitamura, M. *Bulletin of Chemical Society of Japan.* **1995**, *68*, 36-56; **b)** Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475-1490; **c)** Caddick, S.; Jenkins, K. *Chemical Society Review* **1996**, *25*, 447-456; **d)** Huerta, F. F.; Minidis, A. B. E.;. Backvall, J.-E *Chemical Society Review* **2001**, *30*, 321-331; e) Gihani, M. T. El.; Williams, J. M. J. *Current Opinion in Chemical Biology*. 1999, *3*, 11-15; f) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563-1601.

[209] **a)** Backvall, J.-E. in: *Asymmetric Synthesis – The Essentials, Wiley-VCH, Weinheim*, **2006**; **b)** Martin-Matute, B.; Backvall, J.-E. *Current Opinion in Chemical Biology* **2007**, *11*, 226-232; **c)** Kamal, A.; Azhar, M. A.; Krisnaji, T.; Malik, M. S.; Azeeza, S. *Coordination Chemistry Review* **2008**, *252*, 569-592; **d)** Ahn, Y.; Ko, S.-B.; Kim, M.-J.; Park, J. *Coordination Chemistry Review* **2008**, *252*, 647-658; **e)** Martin-Matute, B.; Backvall, J.-E. *in: Asymmetric Organic Synthesis with Enzymes, Wiley- VCH, Weinheim*, **2008**, 89-113; **f)** Karvembu, R.; Prabhakaran, R.; Tamizh, M. M.; Natarajan, K. *Comptes Rendus Chimie* **2009**, *12*, 951-962; **g)** Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *European Journal of Organic Chemistry* **2010**, 999-1015.

[210] Tian, S.-K.; Deng, L. *Journal of the American Chemical Society* **2001**, *123*, 6195-6196.

[211] Tang, L.; Deng, L. *Journal of the American Chemical Society* **2002**, 124, 2870-2871.

[212] **a)** Hang, J.; Li, H.; Deng, L. *Organic Letters* **2002**, *4*, 3321-3324; **b)** Hayakawa, Y.; Hyodo, M.; Kimura, K.; Kataoka, M. *Chemical Communications* **2003**, 1704-1705; **c)** Shibata, N.; Matsunaga, M.; Nakagawa, M.; Fukuzumi, T.; Nakamura, S.; Toru, T. *Journal of the American Chemical Society* **2005**, *127*, 1374-1375; **d)** Tian, S.-K.; Deng, L. *Tetrahedron* **2006**, *62*, 11320-11330; **e)** Peschiulli, A.; Quigley, C.; Tallon, S. n.; Gun'ko, Y. K.; Connon, S. J. *Journal*



Scheme 45. DKR of 5-aryl-1,3-dioxolane-2,4-diones.

Given the interest of enantioenriched mandelic acid analogs in the synthesis of biologically interesting natural and unnatural compounds,[198,213] the remarkable DKR transformation described above was also selected for screening the scope of the IPB alkaloid derivatives of this Thesis. It has however to be anticipated that several shortcomings were met already at the stage of the evaluation of alkaloid's soluble model derivatives. As described in the next paragraph, these problems discouraged the present study from actually reaching the heterogeneous catalysis phase.

5.3.1 Screening of soluble models 155a and 160a in the DKR of rac-5-phenyl-1,3-dioxolane-2,4-dione.

In order to benchmark the alkaloid derivative of this work in the said DKR process, *rac*-5-phenyl-1,3-dioxolane-2,4-dione (**181**) was selected as the reference substrate. Because the original conditions for the reaction (Et_2O, -78°C) seemed hardly compatible with IPB organocatalysts on PS supports, a preliminary screening in the homogeneous phase was decided in order to investigate the effect of adopting a higher reaction temperature (-20°C) or solvents with a better PS compatibility (CH_2Cl_2, THF). In this regard it is worth noting that an example was included in the Deng contribution, where the 4-(*iso*-propyl)phenyl derivative was reacted for 8 h at -20°C to provide the corresponding 4-substituted mandelate in 68% yield and 91% *ee*. Moreover, the use of THF was also mentioned in one case (DKR of 1-naphthyl derivative with *iso*-propyl alcohol at -40°C), but no systematic study of the solvent influence could be actually found in the published work.

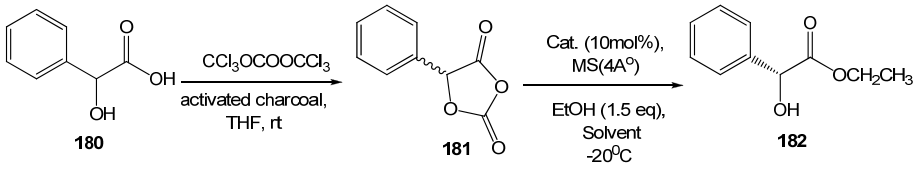
of Organic Chemistry **2008**, *73*, 6409-6412; **f)** Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angewandte Chemie International Edition* **2008**, *47*, 4177-4179; **g)** Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chemical Communications* **2009**, 7224–7226; **h)** Wakayama, M.; Ellman, J. A. *Journal of Organic Chemistry* **2009**, *74*, 2646-2650.

[213] Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Synthesis; VCH: Weinheim*, **1997**.

The racemic substrate **181** was prepared by the published procedure (Table 8),[211] consisting in the room temperature condensation of racemic mandelic acid (**180**) with triphosgene in THF, in the presence of activated charcoal. Filtration of reaction mixture followed by solvent evaporation afforded **181** that, according to the literature,[211] was used in the catalysis runs without any further purification.

The latter (Table 8) were carried out following the Deng protocol,[211] with 10 mol% of any of the new alkaloid catalyst **155a** or **160a**, dry ethanol (1.5 equiv.), and in the presence of 4Å molecular sieves. After stirring at -20ºC for 27-65 h, the acidic workup of the mixture and the *flash* chromatography purification of the crude provided the ester **182**. The identity of the compound was confirmed by NMR while its enantiomer composition was ascertained by CSP-HPLC

Table 8. Dynamic kinetic resolution of 5-phenyl-1,3-dioxolane-2,4-dione.



Entry	Catalyst	Solvent	Time	Yield [%][a]	Ee [%][b]
1	**155a**	Et_2O	62	32	46
2	**155a**	CH_2Cl_2	27	53	48
3	**155a**	THF	27	<5	Nr
4	**160a**	Et_2O-THF (3:0.24)	65	14	56
5	$(DHQD)_2AQN$	Et_2O	21	28	90

a) Isolated yield after flash chromatography b) By CSP-HPLC (Chiralcel OD-H, 1 ml min^{-1}, n-hexane:IPA = 95:5, 220 nm)

An initial run in Et_2O at -20°C with the QD dimeric pyridazine derivative **155a** led to a very slow reaction that, after 62 h stirring, eventually provided **182** in low yield and with only a modest enantiomeric purity (Table 8, entry 1). The switch to CH_2Cl_2 as the reaction medium afforded a comparatively faster reaction but no noticeable increase of the *ee* of the isolated product could be attained also under these conditions (Table 8, entry 2). On the contrary, repeated attempts of running the reaction in THF unexpectedly resulted in the isolation of only trace amounts of the product (Table 8, entry 3): In consideration of the literature precedent noted above, no reasonable explanation can be provided at the moment for this rather surprising finding.

The use of the monomeric alkaloid organocatalyst **160a** in a Et_2O-THF (3:0.24) mixture improved somewhat the enantioselectivity of the reaction (Table 8, entry 4). However, also in this case the product **182** could be isolated only in minute amounts after 65 h reaction time.

Overall, the new organocatalysts **152a** and **160a** appear therefore poorly fit for the catalysis of the DKR reaction under exam. Arguably, this result could be a consequence of the quite different structure of the 9-*O* substituent of the derivatives in this work, with respect to the anthraquinone unit in the literature $(DHQD)_2AQN$-**8** organocatalyst. In this regard, it is interesting to note that an additional run with commercial $(DHQD)_2AQN$ under the very same conditions employed in the first experiment described above (Et_2O, -20°C) confirmed the possibility of attaining a substantial enantioselectivity in the DKR of the benchmark substrate **181** (Table 8, entry 5). Not unexpectedly, the *ee* attained in this case appears to match that observed under the same reaction conditions in the DKR of the closely related 4-(*iso*-propyl)phenyl-1,3-dioxolane-2,4-dione derivative noted above.[211] While this result substantiates the superior asymmetric induction ability of the alkaloid derivatives embedding the anthraquinone core, it is worth stressing that, in our hands, the mandelate product was isolated in a much-reduced yield even in this run.

Although the latter result suggested the possibility of employing IPB alkaloid derivatives of the anthraquinone type in the reaction under exam, the difficulties encountered in attaining acceptable yields in the homogeneous phase prompted us to turn the attention to alternative transformations catalyzed by *Cinchona* alkaloid derivatives.

5.4. Asymmetric halolactonization reaction

The lactonization of unsaturated acids, mediated by electrophiles, is a powerful and long-standing process for the regio- and stereoselective functionalization of carbon-carbon double bonds.[214]

Although extensive efforts have been made to explore these cycloadditions under a variety of conditions,[215] very few examples of their enantioselective version were disclosed.

In 1992 the Taguchi group reported a first reagent-controlled enantioselective halolactonization (65% *ee*), where an alkenoic acid was cyclized under the action of iodine and a *stoichiometric* amount of a chiral titanium complex.[216] In 2003, Kang and co-workers described the asymmetric iodoetherification of alkenes and alkynes with *N*-chlorosuccinimide, in the presence of a cobalt–salen catalyst. [217]

After the disclosure of this work, a few more reports appeared describing the asymmetric halolactonization of unsaturated substrates.[218] Amongst these, several transformations involving *Cinchona* alkaloids were published,[219] most of which make use, however, of more than a stoichiometric amount of the chiral derivative. An exception in this regard is represented by the recent organocatalytic enantioselective chlorolactonization

[214] Reviews and books: **a)** Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321-3408; **b)** Mulzer, J.; Altenback, H. J.; Braun, M.; Krohn, K.; Reissig, H. U. *Organic Synthesis Highlights.*; VCH: Weinheim, **1991**; p 157; **c)** Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681-13736; Iodolactonization : **a)** Bougault, J. *Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences* **1904**, 139, 864-867; **b)** Bougault, J. *Annales de Chimie et de Physique* **1909**, 15, 296; **c)** Bougault, J. *Annales de Chimie et de Physique* **1911**, 22, 125-136; **d)** Linstead, R. P.; May, C. J. *Journal of the Chemical Society* **1927**, 2565-2579; **e)** Van, T., Eugene E.; Shamma, M. *Journal of the American Chemical Society* **1954**, 76, 2315-2317; **f)** Klein, J. *Journal of the American Chemical Society* **1959**, *81*, 3611-3614; **g)** Campos, M. d. M.; do, A., L. *Archiv der Pharmazie und Berichte der Deutschen Pharmazeutischen Gesellschaft* **1965**, 298, 92-100; Bromolactonization: **a)** Fittig, R.; Spenzer, J. G. *Justus Liebigs Annalen der Chemie* **1894**, *283*, 66-79 and 79-81; **b)** Fittig, R. *Justus Liebigs Annalen der Chemie* **1894**, *283*, 47-65; **c)** Hjelt, E. *Justus Liebigs Annalen der Chemie*, *216*, 52-77; **d)** Stobbe, H.; Kohlmann, P.; Noetzel, M. *Justus Liebigs Annalen der Chemie* **1899**, *308*, 89-114; Chlorolactonization :There are relatively few examples regarding the conversion of unsaturated acids into chlorolactones, see **a)** Berti, G. *Gazzetta Chimica Italiana* **1951**, *81*, 305-314; **b)** Berti, G. *Tetrahedron* **1958**, *4*, 393-402.

[215] Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. *Angewandte Chemie International Edition* **2011**, *50*, 2593-2596. (and ref. cited therin).

[216] Kitagawa, O.; Hanano, T.; Tanabe, K.; Shiro, M.; Taguchi, T. *Journal of the Chemical Society, Chemical Communications* **1992**, 1005-1007.

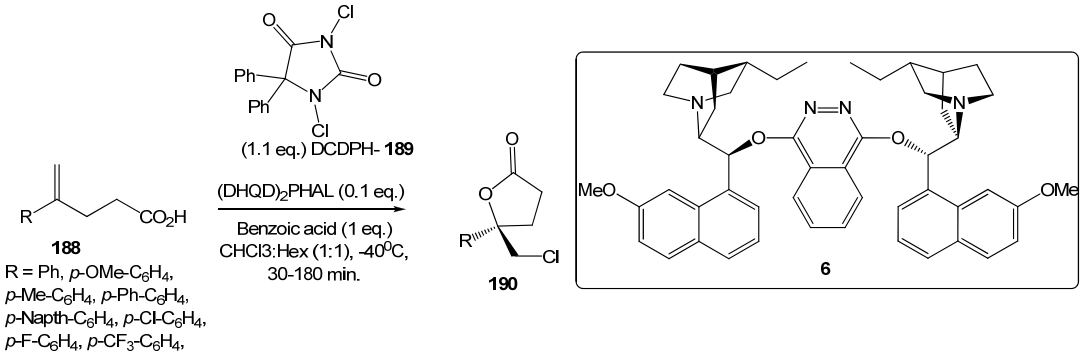
[217] Kang, S. H.; Lee, S. B.; Park, C. M. *Journal of the American Chemical Society* **2003**, *125*, 15748-15749.

[218] **a)** Chen, G.; Ma, S. *Angewandte Chemie International Edition* **2010**, *49*, 8306-8308; **b)** Murai, K.; Matsushita, T.; Nakamura, A.; Fukushima, S.; Shimura, M.; Fujioka, H. *Angewandte Chemie International Edition* **2010**, *49*, 9174-9177; **c)** Veitch, G. E.; Jacobsen, E. N. *Angewandte Chemie International Edition* **2010**, *49*, 7332-7335.

[219] **a)** Wilkinson, S. C.; Lozano, O.; Schuler, M.; Pacheco, M. C.; Salmon, R.; Gouverneur, V. r. *Angewandte Chemie International Edition* **2009**, *48*, 7083-7086; **b)** Zhang, W.; Zheng, S.; Liu, N.; Werness, J. B.; Guzei, I. A.; Tang, W. *Journal of the American Chemical Society* **2010**, *132*, 3664-3665; **c)** Zhou, L.; Tan, C. K.; Jiang, X.; Chen, F.; Yeung, Y.-Y. *Journal of the American Chemical Society* **2010**, *132*, 15474-15476.

described by Borhan and co-workers.[220] According to this protocol (Scheme 46), 4-substituted pent-4-enoic acids (**188**) undergo a smooth cyclization when treated with a source of electrophilic chlorine in the presence of a catalytic amount (1-10 mol%) of the commercial *Cinchona* alkaloid PHAL derivatives. Optimization experiments revealed that best results could be achieved at -40ºC, in the chlorolactonization of 4-arylpent-4-enoic acids devoid of electron-releasing substituents on the aromatic ring. Essential for the attainment of good yields (68-86%) and enantioselectivity values (74-90% *ee*) was also the use of *N,N'*-dichlorodiphenylhydantoin (DCDPH, **189**) as the achiral chlorine source, benzoic acid (1 equivalent) as an achiral additive, and *n*-hexane-$CHCl_3$ (1:1) as the reaction medium. Moreover, even though the use of as little as 1 mol% of $(DHQD)_2PHAL$ provided very similar results as the standard 10 mol% loading, the switch to the pseudoenantiomeric $(DHQN)_2PHAL$ organocatalyst afforded a much reduced enantioselectivity (*i.e.* 77% *ee vs.* 89% *ee* in the chlorolactonization of 4-phenylpent-4-enoic acid).

Besides allowing the preparation of an array of enantioenriched chlorolactones, that may find use as chiral building blocks in the synthesis of natural products,[221] one of the striking features of the reaction under exam was the very short reaction time: Most of the substrates were completely converted in 30-180 min, while for the 4-fluorophenyl derivative a reaction time as short as 2 min was reported!



Scheme 46. $(DHQD)_2PHAL$ mediated chlorolactonization

Given the similarity between the PHAL aromatic spacer of the literature organocatalyst and the pyridazine scaffold developed in this Thesis, the possibility was considered of employing the new IPB *Cinchona* alkaloid derivatives in the aforementioned reaction. As usual, before attempting to perform the actual heterogeneous catalysis

[220] Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. *Journal of the American Chemical Society* **2010**, *132*, 3298-3300.
[221] Gribble, G. W. *Accounts of Chemical Research* **1998**, *31*, 141-152.

experiments, a preliminary evaluation of the catalytic efficiency of a proper model compound (**155a**) was therefore decided. The results of this survey are summarized in the next paragraph.

5.4.1 Screening of the soluble model 155a in the asymmetric chlorolactonization of 4-(4-fluorophenyl)pent-4-enoic acid.

In order to evaluate the suitability of the pyridazine-scaffold for the promotion of asymmetric chlorolactonization reactions, the soluble QD derivative **155a** was selected as the representative organocatalyst structure. For benchmarking the performances of the latter, the optimized Borhan conditions were chosen with 4-(4-fluorophenyl)pent-4-enoic acid (**188**) as the substrate and DCDPH (**189**) as the chlorine source.

After preparation of both reagents (**189**, **191**) by literature methods,[222,223] the catalysis runs (Table 9) were carried out following the literature procedure.[220] Accordingly, the catalyst **155a** (0.1 equiv.) and the chlorinating agent **189** (1.1 equiv.) were stirred at -40º C for 30 min in an appropriate solvent (Table 9), followed by addition of the substrate **191** and benzoic acid (1 equiv.). The resulting solution was kept at same temperature until complete conversion of **191** (TLC monitoring).

Afterwards, the crude product was obtained by basic extraction of any acidic component, followed by silica-gel filtration and evaporation of the volatiles. The determination of the enantiomeric excess of the chlorolactone **190** was performed by CSP-HPLC as described.[220]

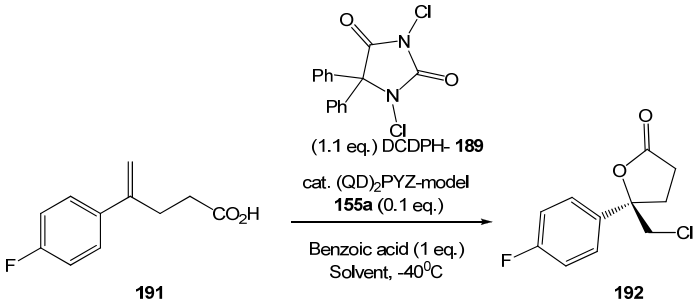
An initial run with the pyridazine organocatalyst **155a** under reaction conditions otherwise identical to the literature ones, afforded the product **190** in good isolated yield but only moderate enantiomeric excess (Table 9, entry 1).

Because the influence of the solvent nature was essentially unknown also for this reaction,[224] a brief evaluation of alternative reaction media was carried out. As before, **155a** was tested in a few solvents whose compatibility with PS materials could eventually facilitate the subsequent extension to IPB catalysts. With this aim four more runs were performed, using THF, toluene, CCl_4, and pure $CHCl_3$ (Table 9, entries 2-5).

[222] Takemiya, A.; Hartwig, J. F. *Journal of the American Chemical Society* **2006**, *128*, 6042-6043.
[223] Whitehead, D. C.; Staples, R. J.; Borhan, B. *Tetrahedron Letters* **2009**, *50*, 656-658.
[224] In the cited study (Ref. 220)an extensive parallel additive and cosolvent screening was mentioned, but no actual data were reported for solvents other than CH_2Cl_2, $CHCl_3$, and *n*-Hex-$CHCl_3$ (1:1). To highlight the importance of the solvent nature in this kind of reactions it can be noted, however, that switching from $CHCl_3$ to CH_2Cl_2 (the other conditions being the same) resulted in a ~13-26% *ee* drop.

Interestingly, while the reaction in THF afforded much reduced yield and *ee* values (Table 9, entry 2) and the use of CCl_4 or toluene (Table 9, entries 3-4) provided nearly the same enantioselectivity as in the initial run, a significant increase of the enantiomeric purity of **190** was observed in neat $CHCl_3$ (Table 9, entry 5). Even with this modification, the pyridazine organocatalyst **155a** proved however less effective than the commercial phthalazine ether $(DHQD)_2PHAL$. In this respect it is worth noting that a final control experiment carried out under the very same reaction conditions as in the Borhan work,[220] afforded in our hands the chlorolactone **190** with 83% *ee* (Table 9, entry 6).

Table 9. Chlorolactonization of 4-(4-fluorophenyl)pent-4-enoic acid



Entry	Catalyst	Solvent	Time [min.]	Yield [%][a]	Ee [%][b]
1	**155a**	*n*-Hex-$CHCl_3$ (1:1)	90	88	55
2	**155a**	THF	90	50	12
3	**155a**	Toluene	overnight	88	55
4 [c]	**155a**	CCl_4	90	66	52
5	**155a**	$CHCl_3$	120	79	70
6	$(DHQD)_2PHAL$	*n*-Hex-$CHCl_3$ (1:1)	90	96	83

a) Isolated yield after flash chromatography, b) By CSP-HPLC (Chiralcel OJ, 1mL/min, n-hexane:IPA = 95:5, 220nm), c) reaction run at r.t. because CCl_4 freezes at -40ºC.

Albeit somewhat lower than the 89% *ee* literature value,[220] these results suggested that the apparently modest structural changes on going from the 1,4-phthalazine heterocyclic spacer of the literature organocatalyst to the 1,4-pyridazine one in this work had a significant adverse effect on the chiral induction degree in the reaction under exam. Given the large gap between the best *ee* obtained in this exploratory screening and the levels currently deemed of synthetic interest, the decision was therefore taken to avoid the testing of IPB catalysts and, instead, to turn the attention to the more promising asymmetric α-amination of oxindoles described in the next paragraph.

5.5. Asymmetric α-amination of 2-oxindoles

2-Oxindoles are important building blocks for the preparation of biological active compounds and their structural motif is found in a wide array of natural products.[225] Amongst the many derivatives, 3-substituted 3-amino-2-oxindoles posses a particular interest in view of their potential pharmaceutical use.[226]

The preparation of the latter class of compounds has been achieved by various methods like the cyclization of *o*-chlorinated anilines,[227] the alkylation or addition to 2-oxindoles,[228] and others.[229] Moreover, enantioenriched 3-amino-2-oxindoles have been recently obtained by effective catalytic enantioselective α-amination reactions of racemic 3-substituted-2-oxindoles, in the presence of either chiral metal complexes[230] or *Cinchona* alkaloid derivatives.[231, 229c]

The latter approach, due to the independent work of the Chen,[231a] Zhou,[229c] and Barbas III [231b] groups is particularly interesting as it provides a general catalytic route for the construction of a stereo-defined C-N bond at the C3 quaternary carbon (Scheme 47). The protocols developed in these studies look rather similar in that they all involve the use of dimeric alkaloid derivatives as the chiral organocatalyst. Nevertheless, the catalyst, substrate, and reactant scopes appear also somewhat complementary: For instance, while in

[225] Marti, C.; Carreira, E. M. *European Journal of Organic Chemistry* **2003**, *2003*, 2209-2219.

[226] **a)** Heimgartner, H. *Angewandte Chemie International Edition in English* **1991**, *30*, 238-264; **b)** Malinakova, H. C.; Liebeskind, L. S. *Organic Letters* **2000**, *2*, 4083-4086; **c)** Ochi, M.; Kawasaki, K.; Kataoka, H.; Uchio, Y.; Nishi, H. *Biochemical and Biophysical Research Communications* **2001**, *283*, 1118-1123; **d)** Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Organic Letters* **2001**, *4*, 249-251; **e)** Hewawasam, P.; Erway, M.; Moon, S. L.; Knipe, J.; Weiner, H.; Boissard, C. G.; Post-Munson, D. J.; Gao, Q.; Huang, S.; Gribkoff, V. K.; Meanwell, N. A. *Journal of Medicinal Chemistry* **2002**, *45*, 1487-1499; **f)** Suzuki, H.; Morita, H.; Shiro, M.; Kobayashi, J. i. *Tetrahedron* **2004**, *60*, 2489-2495; **g)** Bernard, K.; Bogliolo, S. p.; Ehrenfeld, J. *British Journal of Pharmacology* **2005**, *144*, 1037-1050; **h)** Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qiu, S.; Ding, Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Tomita, Y.; Parrish, D. A.; Deschamps, J. R.; Wang, S. *Journal of the American Chemical Society* **2005**, *127*, 10130-10131; **i)** Abadi, A. H.; Abou-Seri, S. M.; Abdel-Rahman, D. E.; Klein, C.; Lozach, O.; Meijer, L. *European Journal of Medicinal Chemistry* **2006**, *41*, 296-305; **j)** Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *Journal of the American Chemical Society* **2008**, *130*, 2087-2100.

[227] For selected examples, see: **a)** Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kundig, E. P. *Chemical Communications* **2008**, 4040-4042; b) Marsden, S. P.; Watson, E. L.; Raw, S. A. *Organic Letters* **2008**, *10*, 2905-2908; **c)** Watson, E. L.; Marsden, S. P.; Raw, S. A. *Tetrahedron Letters* **2009**, *50*, 3318-3320.

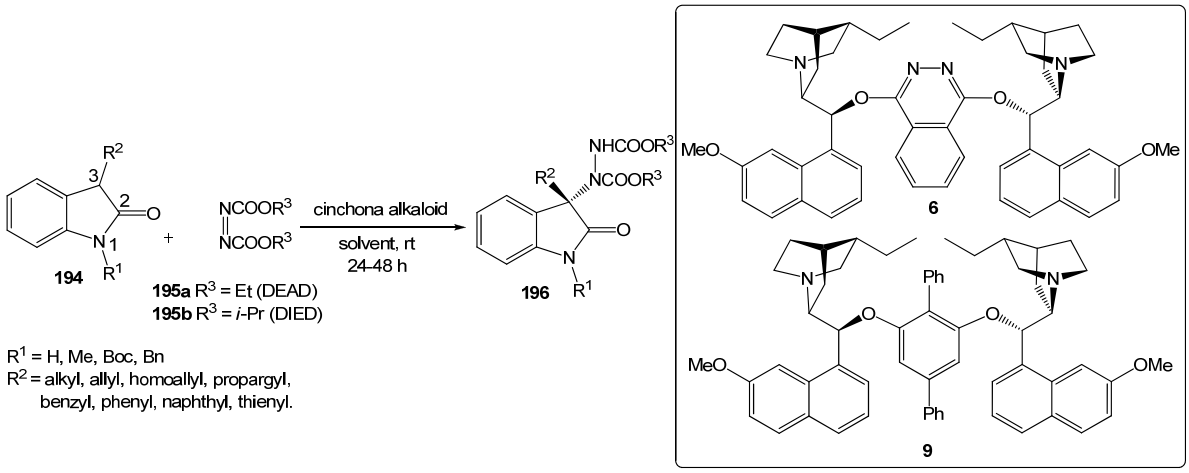
[228] For selected examples, see: **a)** Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *The Journal of Organic Chemistry* **2005**, *70*, 3324-3327; **b)** Emura, T.; Esaki, T.; Tachibana, K.; Shimizu, M. *The Journal of Organic Chemistry* **2006**, *71*, 8559-8564; **c)** Sun, C.; Lin, X.; Weinreb, S. M. *The Journal of Organic Chemistry* **2006**, *71*, 3159-3166.

[229] For selected examples see, **a)** O'Connor, S. J.; Liu, Z. *Synlett* **2003**, *2003*, 2135,2138; **b)** Bella, A. F.; Slawin, A. M. Z.; Walton, J. C. *The Journal of Organic Chemistry* **2004**, *69*, 5926-5933; **c)** Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Ding, M.; Zhao, X.-L.; Zhou, J. *Chemical Communications* **2009**, 6753-6755 (and references cited therein.)

[230] **a)** Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *Journal of the American Chemical Society* **2010**, *132*, 1255-1257; **b)**Yang, Z.; Wang, Z.; Bai, S.; Shen, K.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Chemistry A European Journal* **2010**, *16*, 6632-6637.

[231] **a)** Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Organic Letters.* **2009**, *11*, 3874-3877; **b)** Bui, T.; Borregan, M.; Barbas, C. F. *The Journal of Organic Chemistry* **2009**, *74*, 8935-8938.

the case of Zhou the best results (82-94% *ee*) were obtained in the α-amination of *N*-unprotected 2-oxindoles with diisopropyl azodicarboxylate (DIAD, **195b**) in the presence of PYR-type catalysts **(9)**, both Chen and Barbas III found that the PHAL ether **(6)** was far superior (76-99% *ee*) of other screened alkaloid derivatives. Moreover, while the former group focused again on the reaction of *N*-unprotected 2-oxindoles with DIAD, the latter found advantageous to use a Boc or Bn *N*-derivative of 2-oxindole, as the reaction substrate, and diethyl azodicarboxylate (DEAD, **195a**), as the aminating agent.

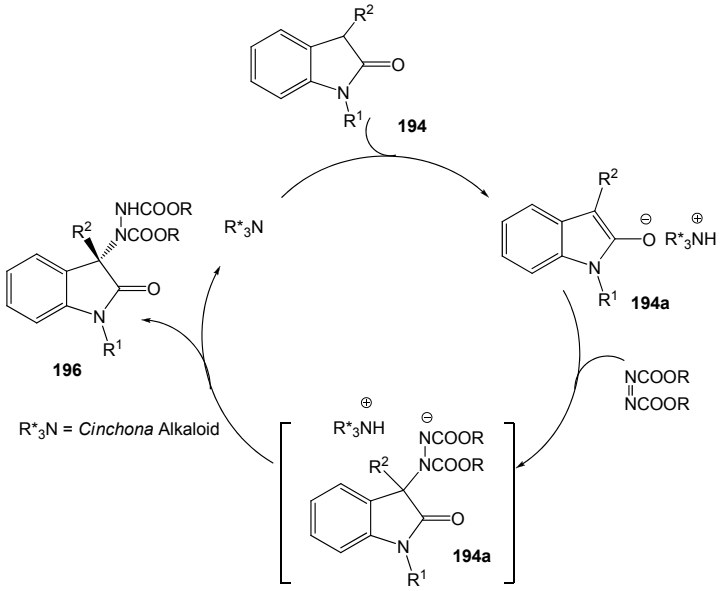


Scheme 47. Asymmeric α-amination of 3-substituted 2-oxindoles

Interestingly, the three investigations provided also different solutions for what it concerns the optimal solvent an reaction temperature: In the case of the Zhou work, best results were achieved in CH_2Cl_2 at -10°C, with toluene, Et_2O, THF, or *i*-PrOH leading to a large drop of the enantioselectivity. On the contrary, the conditions recommended in the Chen study required to run the reaction at r.t. in 1,1,2-trichloroethane, as the latter proved marginally superior to 1,2-dicloroethane as a solvent but much better than Et_2O, toluene, and hexane. Finally, in the Barbas III contribution an initial optimization screening led to the use of Et_2O at r.t. Surprisingly enough, in view of the poor results obtained in the other two studies, in this case ethereal solvents (Et_2O and, similarly, THF) proved in fact largely superior to toluene, MeCN, AcOEt, diglyme, and, especially, CH_2Cl_2.

The α-amination mechanism hypothesized by Barbas and Chen (Scheme 48),[231] involves the deprotonation of the racemic substrate **194** by the *Cinchona* alkaloid organocatalyst to give a zwitterionic enolate **194a.** The latter would exist as a tight contact ion pair with the chiral base, so that its reaction with the electrophilic azodicarboxylate could proceed with a strict control of the configuration of the newly forming quaternary

stereocentre. Upon protonation, the intermediate **194b** would then lead to the desired product **196** and release the catalyst back into the cycle.



Scheme 48. Proposed mechanism of the α-amination reaction

Overall, the aforementioned asymmetric transformation appears interesting not only because of the synthetic relevance of enantioenriched 3-amino-2-oxindoles with a quaternary stereocentre, but also in view of the experimental simplicity, the very mild reaction conditions, and the innocuous character of the postulated reactive intermediates.

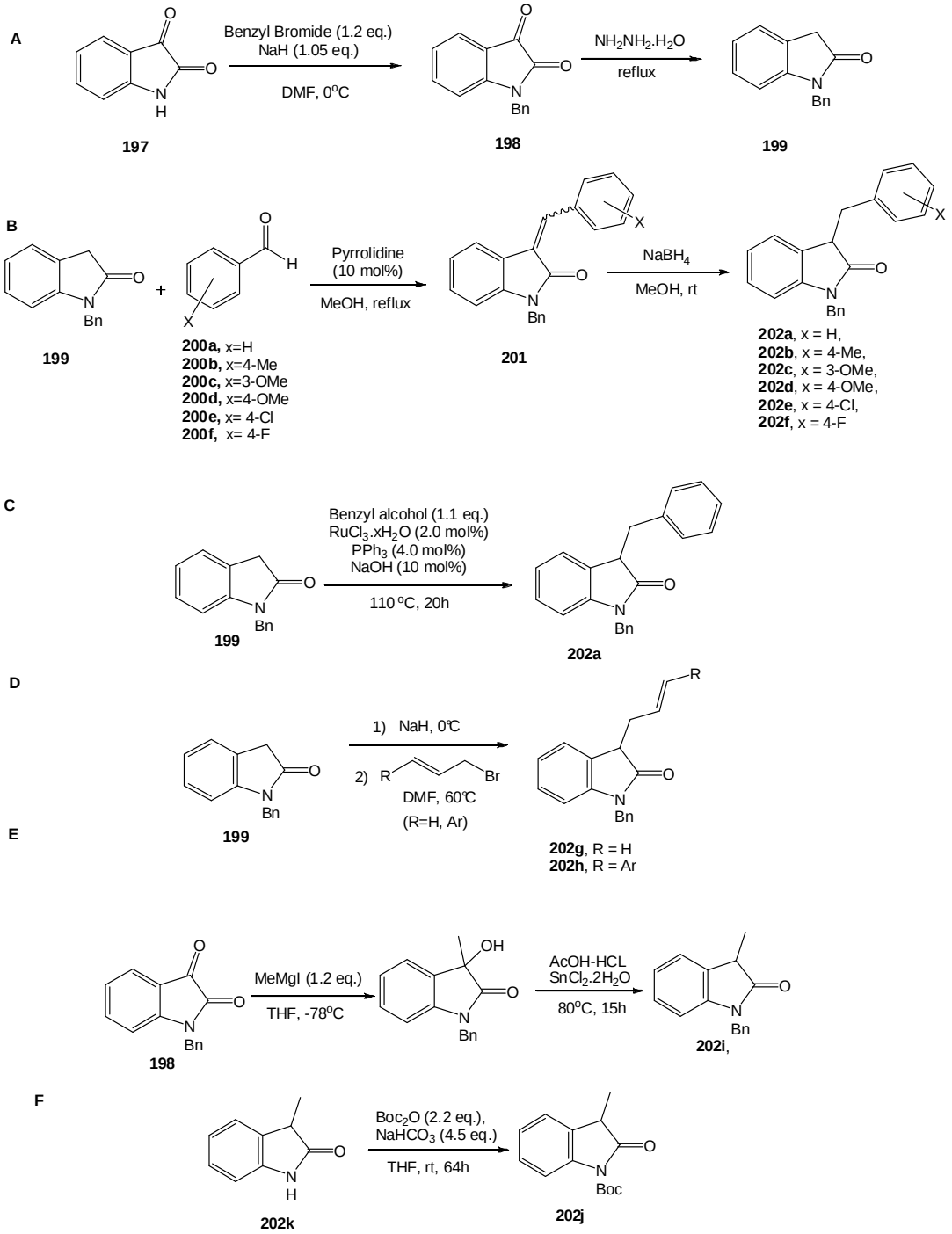
Considering also that at the beginning of this Thesis no example of an heterogeneous α-amination of 2-oxindoles could be found in the literature, this attractive enantioselective process was therefore selected for further screening the modified *Cinchona* alkaloid derivatives developed in the present work.

5.5.1. Asymmetric α-amination of 3-substituted-2-oxindoles.

Given the structural analogy with the most effective PHAL organocatalysts in the Chen and Barbas III studies, the pyridazine-scaffold was chosen as the most promising motif for to the development of a heterogeneous version of the reaction. With this aim, the usual preliminary screening in the homogeneous phase was carried out with the alkaloid derivatives **155a** as the soluble models of the supported chiral units in IPB materials.

In consideration of the somewhat higher *ee* values, the the Barbas III conditions were adopted for testing the modified alkaloid organocatalyst. In turn, this required to

prepare a set of 2-oxindole substrates that were obtained by the literature procedures summarized in the Scheme 49. [231,232,233]



Scheme 49. Preparation of 3-substituted-2-oxindole substrates

[232] Sano, D.; Nagata, K.; Itoh, T. *Organic Letters* **2008**, *10*, 1593-1595.

The *N*-benzylation of Isatin (**197**), followed by hydrazine reduction of the C3 carbonyl afforded the protected 2-oxindole **199** (Scheme 49A)[233] that was used as a common intermediate in the preparation of racemic substrates bearing at C3 a (substituted) benzyl group or a (substituted) allyl one. For the former series of derivatives, **199** was condensed with an aromatic aldehyde (**200a-f**) in presence of pyrrolidine and the resulting intermediate **201** was reduced with sodium borohydride to the corresponding 3-substitited oxindole **202a-f** (Scheme 49B).[231] Overall, this procedure proved more convenient than the direct ('hydrogen borrowing') benzylation of **199** with benzyl alcohol and catalytic amount of $RuCl_3$,[233] initially employed for the preparation of **202a** (Scheme 49C).

Starting from **199**, the 3-allyl and 3-cinnamyl derivatives of 1-benzyl-2-oxindole were prepared by deprotonation with NaH and alkylation of the resulting enolate with the competent allylic bromide (Scheme 49D).[232]

1-benzyl-3-methyl-2-oxindole (**202i**) was prepared by adding phenylmagnesium iodide to *N*-benzylisatin (**198**) followed by the reductive deoxygenation (Scheme 49E).[234] The 1-Boc-3-methyl-2-oxindole (**202j**) was obtained by N-benzylation of commercial racemic 3-methyl-2-oxindole (**202k**) (Scheme 49F).[235]

The initial testing of the QD alkaloid derivative **155a** in the asymmetric α-amination of 1,3-dibenzyl-2-oxindole (**202a**) was carried out under the original Barbas III conditions.[231b] In this respect it is worth noting that, due to the lack of precise data in the published procedure, a decision had to be taken at this stage about the substrate concentration. By comparison with other organocatalytic transformations involving *Cinchona* alkaloid derivatives,[187,190] this variable was set at 0.04 M in the initial experiments. Accordingly, racemic **202a** was stirred in Et_2O at r.t., with DEAD as the aminating agent and 10 mol% of the soluble organocatalyst (Table 10). Under these conditions, the product **203a** was isolated in good yield and with a high enantiomeric excess (Table 10, entry 1). Albeit slightly lower than reported for the $(DHQD)_2PHAL$ organocatalyst (96% yield, 99% *ee*),[231b] this result established the suitability of the pyridazine scaffold for the catalysis of the reaction under exam.

Because Et_2O is a solvent of low compatibility with PS materials, the next goal of this initial screening was to find an alternative reaction medium. On the basis of the

[233] Jensen, T.; Madsen, R. *Journal of Organic Chemistry* **2009**, *74*, 3990-3992.
[234] Huang, A.; Kodanko, J. J.; Overman, L. E. *Journal of the American Chemical Society* **2004**, *126*, 14043-14053.
[235] Rajeswaran, W. G.; Cohen, L. A. *Tetrahedron* **1998**, *54*, 11375-11380.

literature precedents (see previous paragraph), CH_2Cl_2 and THF were selected for this purpose.

In the former solvent, the benchmark reaction of **202a** showed a much slower rate together with some reduction of the product *ee* (Table 10, entry 2). At variance with Zhou and Chen studies with *N*-unprotected 2-oxindoles,[229c,231a] the use of a slightly polar, chlorinated solvent appeared therefore less effective than an ether one. While these findings resemble the conclusions of the Barbas III investigation, it is nonetheless worth noting that the only α-amination reaction in CH_2Cl_2 described in the latter work (1-Boc-3-methyl-2-oxindole as the substrate) resulted in a much lower enantioselectivity (2% *ee*)[231b] than found here.

The intriguing influence of the reaction medium on the catalysis outcome was confirmed in when the α-amination of **202a** was examined in THF (Table 10, entry 4). Under these conditions, the substrate conversion was faster than in CH_2Cl_2 but, rather disappointingly, the product **203a** was obtained in a substantially diminished *ee* than in the previous runs. While the enantioselectivity reduction could be somewhat anticipated on the basis of the Barbas III results, the *ee* drop on going from Et_2O to THF as the reaction solvent (compare entries 1 and 3 in Table 10) was three times larger than observed for the substrate/organocatalyst combination of the literature study.

However, further optimization of the reaction conditions led to the felicitous discovery that a reduction of the solvent volume had a beneficial effect on the catalytic reaction. Indeed, when the α-amination of **202a** was repeated with just half the amount of the THF used in the previous run (Table 10, entry 4), the expected increase in rate was accompanied by the complete recovery of the high asymmetric induction ability displayed by **155a** in the initial experiment in Et_2O (see Table 10, entry 1).

At present no supporting data can be put forward for providing a rationale of this quite strong influence of the reactant concentration. Moreover, the only literature precedent dealing with concentration effects in the reaction under exam could be found in the Chen paper.[231a] In that contribution, however, better *ee* values were actually achieved by diluting the reaction mixture from 1 M to 0.1 M.

For the time being, it is nonetheless tempting to speculate that the enantioselectivity increase in more concentrated solutions could be due to either the competition between the catalyzed enantioselective α-amination and the corresponding background (uncatalyzed) process or, alternatively, to association phenomena involving the reactants or the catalyst. In

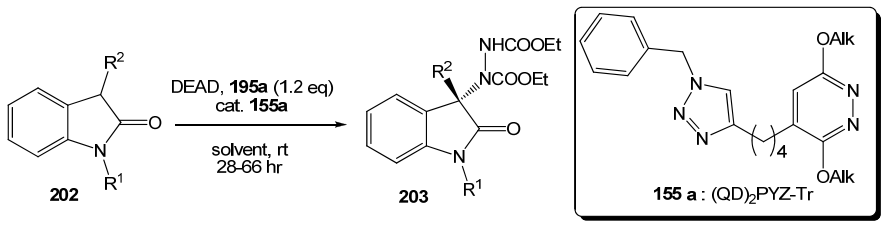
the former hypothesis, a stronger kinetic dependence on the solvent volume of the catalyzed reaction (*e.g.* first order in both the substrate and the catalyst concentration) over the uncatalyzed one (*e.g.* first order in the substrate concentration only) would suffice for accounting the higher *ee* obtained in the run with less solvent. Alternatively, the departure from the postulated catalytic cycle (Scheme 48) could be imagined, leading to a mechanistic scheme where more than one molecule of substrate or catalyst (and, possibly, product) were involved.[236]

Regardless of the exact reasons of the large enantioselectivity increase into concentrated THF solutions, the practical implication of this finding was the possibility of running the heterogeneous reactions in a solvent compatible with PS supports. Before moving to this final stage, the substrate scope was explored in more detail under the optimized reaction conditions. With this aim, the α-amination of various 3-subtituted-2-oxindoles in the presence of the soluble organocatalyst **155a** was studied. In general, these experiments were carried out as described above with the notable exception that, for a better comparison with the subsequent heterogeneous catalysis runs (*vide infra*), the catalyst loading was raised to 20 mol% and the reactions were performed in an even more concentrated manner (0.14 M).

The additional results obtained in this screening revealed that the modified pyridazine organocatalyst could induce a significant degree of enantioselectivity in the reaction of different substrates bearing a substituted benzyl group at C3 (, entries 5-9). The replacement of the latter with an allyl, cinnamyl, or even a simple methyl group was well tolerated, as confirmed by the attainment of > 85% *ee* in all cases (Table 10, entries 10-12). On the contrary, the α-amination of Boc-protected or unprotected 3-methyl-2-oxindole resulted in a reduction of the enantioselectivity (Table 10, entries 13-14), particularly evident in the case of the latter substrate. Similarly, the use of bulkier azodicarboxylic esters as DIAD led to 40% *ee* (Table 10, entry 15) and was therefore excluded from further screening runs.

[236] As anticipated, no supporting evidence for any of these hypotheses could be obtained in this work. In this respect it should be noted that, in the presence of minute amount (0.1%) any *Cinchona* catalyst ($(DHQD)_2PHAL$), the background reaction between **202a** and DEAD is extremely slow (<10% in 304h) and can therefore account for only a limited part of the observed *ee* changes. Similarly, attempts to evidence catalyst/substrate/azodicarboxylate/ product interactions by NMR did not provide conclusive results.

Table 10. Screening of soluble pyridazine organocatalysts in the asymmetric α-amination of 2-oxindole substrates.



Entry	Loading [mol%]	Substrate (R^1, R^2)	Solvent	*C* [M][a]	*t* [h]	Yield [%][b,c]	*ee* [%][c,d]
1	10	**202a** (Bn, Bn)	Et_2O	0.04	48	82 (96)	95 (99)
2	10	**202a** (Bn, Bn)	CH_2Cl_2	0.04	66	35	85
3	10	**202a** (Bn, Bn)	THF	0.04	48	72	77
4	10	**202a** (Bn, Bn)	THF	0.08	48	90	96
5	20	**202b** (Bn, 4-Me-benzyl)	THF	0.14	48	96 [f]	91(n.r.)[f]
6	20	**202c** (Bn, 3-MeO-benzyl)	THF	0.14	48	98 [f]	85 (n.r.)[f]
7	20	**202d** (Bn, 4-MeO-benzyl)	THF	0.14	48	~ quant [f]	89 (n.r.)[f]
8	20	**202e** (Bn, 4-Cl-benzyl)	THF	0.14	48	~ quant [f]	89 (n.r.)[f]
9	20	**202f** (Bn, 4-F-benzyl)	THF	0.14	48	~ quant [f]	92 (n.r.)[f]
10	20	**202g** (Bn, Allyl)	THF	0.14	48	~ quant	91 (94)
11	20	**202h** (Bn, Cinnamyl)	THF	0.14	48	~ quant	87 (91)
12	20	**202i** (Bn, Me)	THF	0.14	48	~ quant	86 (76)
13	20	**202j** (Boc, Me)	THF	0.14	48	75	73 (91)[e]
14	20	**202k** (H, Me)	THF	0.14	48	88	17 (78)
15	10	**202a** (Bn, Bn)	THF	0.14	48	70	40 (93)

a) Substrate concentration; b) Isolated yield after flash chromatography; c) In parentheses, best literature values with PHAL organocatalysts under comparable conditions [Refs. 231a and 231b]; d) By CSP-HPLC (Chiralcel OD-H, n-hexane:IPA = 97:3, 0.5mL/min, 254nm), the prevailing enantiomer had (*S*) configuration; e) The literature reaction was run at -20°C; 81% *ee* at 4°C; f) Not reported in the literature.

As summarized in the Table 10, the data collected in this screening appear to mirror quite well the results described by the Barbas III group. In most cases, the *ee* values attained with **155a** fell within a few percent of those provided by the PHAL organocatalyst and, in the reaction of the 3-methyl substituted substrate **202i** (Table 10, entry 12), a significant boost of the enantioselectivity could even be achieved over the literature result. On the contrary, the α-amination of the Boc protected derivative **202j** (Table 10, entry 13) proved less enantioselective than the reported one. In this case, it has to be considered, however, that the result included in Table 10 refers to the reaction run at -20°C; when the α-amination of **202j** was carried out at 4°C, the reported enantiomeric purity was 81% *ee*

only.[231b] Interestingly, the latter result was deemed to reflect the stronger tendency towards enolisation of the Boc protected derivatives,[237] which eventually leads to a relatively more significant background reaction.

Finally, the use of unprotected substrates was not examined in the Barbas III paper but some comparison is nevertheless possible with the work of the Chen group.[231a] In this respect, it can be noted that while the α-amination of **202k** under optimized conditions (10 mol% PHAL organocatalyst, DIAD, 0.1 M in 1,1,2-trichloroethane, r.t.) afforded **203k** with 79% *ee*, the same reaction with DEAD in CH_2Cl_2 or DIAD in Et_2O gave the product with 31-39% *ee* only. Considering the apparent difficulty of attaining synthetically useful *ee* values with unprotected and Boc-protected 2-oxindole derivatives (**202j** and **202k**), no further attempt was made in this work for exploring the α-amination of substrates bearing an *N*-substituent other than the benzyl group.

Having demonstrated the suitability of the pyridazine scaffold for building effective organocatalysts for the α-amination reaction, the use of IPB systems was examined next (Table 11). With this aim, the best conditions in THF were chosen as the starting point. Nevertheless, due to the significant concentration effect noted above, a brief preliminary optimization of the heterogeneous reaction of **202a** was carried out also in this case.[238]

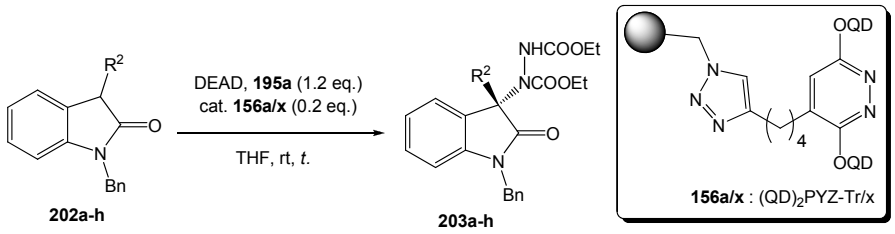
Starting at 0.08 M substrate concentration with 10 mol% of the insoluble QD derivative **156a/x**, the product **203a** was formed with good enantiomeric purity (Table 11, entry 1). However, even after some prolonged reaction time the yield turned out to be only moderate under these conditions. Therefore, a further run was carried out by doubling the catalyst loading (Table 11, entry 2). This simple change proved effective in increasing the conversion, which was further improved by progressively raising the substrate concentration first to 0.14 M (Table 11, entry 3) and then to 0.20 M (Table 11, entry 4). Considering that a 0.14 M a practically complete conversion could be attained in 48 and that the enantioselectivity was marginally superior than in the other runs,[239] these conditions (20 mol% catalyst, 0.14 M substrate concentration, and 48 h reaction time at r.t.) were adopted in the subsequent experiments.

[237] For the effect of the *N*-protecting group on the acidity of C3 methine proton of 2-oxindole, see Bui, T.; Syed, S.; Barbas, C. F. *Journal of the American Chemical Society* **2009**, *131*, 8758-8759.

[238] Heterogeneity tests by standard filtration experiments were carried out concurrently: In all cases no catalytic activity was found in the solution.

[239] It has to be noted that, due to some tailing of the enantiomer HPLC peaks, the reported *ee*'s are affected by an uncertainty of approx. ±1% of the stated value.

Table 11. Heterogeneous α-amination of 1-benzyl-2-oxindoles



Entry	Loading [mol%]	Substrate (R^2)	*C* [M][a]	*t* [h]	Yield [%][b,c]	*ee* [%][c,d]
1	10	**202a** (Bn)	0.08	64	51 (90)	92 (96)
2	20	**202a** (Bn)	0.08	48	72	92
3	20	**202a** (Bn)	0.15	48	81 (90)	95 (96)
4	20	**202a** (Bn)	0.20	48	96	93
5	20 [e]	**202b** (4-Me-benzyl)	0.14	48	84 (96)	91 (91)
6	20 [e]	**202c** (3-MeO-benzyl)	0.14	48	99 (98)	81 (85)
7	20 [e]	**202d** (4-MeO-benzyl)	0.14	48	93 (>99)	89 (89)
8	20 [e]	**202e** (4-Cl-benzyl)	0.14	48	>99 (>99)	89 (89)
9	20 [e]	**202f** (4-F-benzyl)	0.14	48	>99 (>99)	91 (92)
10	20 [e]	**202g** (Allyl)	0.14	48	92 (>99)	91 (91)
11	20 [e]	**202h** (Cinnamyl)	0.14	48	91 (>99)	89 (87)
12	20 [e]	**202i** (Me)	0.14	48	99 (>99)	85 (86)

a) Substrate concentration; b) Isolated yield after flash chromatography; c) In parentheses, data obtained under comparable conditions with the soluble model catalyst **155a**; d) By CSP-HPLC, the prevailing enantiomer had (*S*) configuration; e) Recycled organocatalyst was used.

The screening of the IPB organocatalysts **156a/x** in the asymmetric α-amination of 1-benzyl-2-oxindole substrates bearing different C3 substituents afforded the additional data shown in the Table 11 (entries 5-12).

In general, the results obtained in the heterogeneous phase proved very satisfactory both in terms of products yield (nearly quantitative in many cases) and enantiomeric purity (81-95% *ee*). For benzyl-substituted substrates the corresponding products were generally obtained in around 90% *ee*. The only exception in this regard was the 3-methoxybenzyl derivative **202c** (Table 11, entry 6) that, already in the homogeneous phase, had actually proved to afford a somewhat diminished enantioselectivity. Similarly, while the α-amination of the substrates **202g** and **202h**, with an unsaturated C3 substituent, led to approximately 90% *ee* (Table 11, entries 10-11), some reduction of the enantiomeric purity was observed for the product obtained from the less hindered 3-methyl substrate **203i** (Table 11, entry 12). Also in this case, however, the outcome of the heterogeneous reaction could be substantially anticipated from the result of the homogeneous one with the soluble

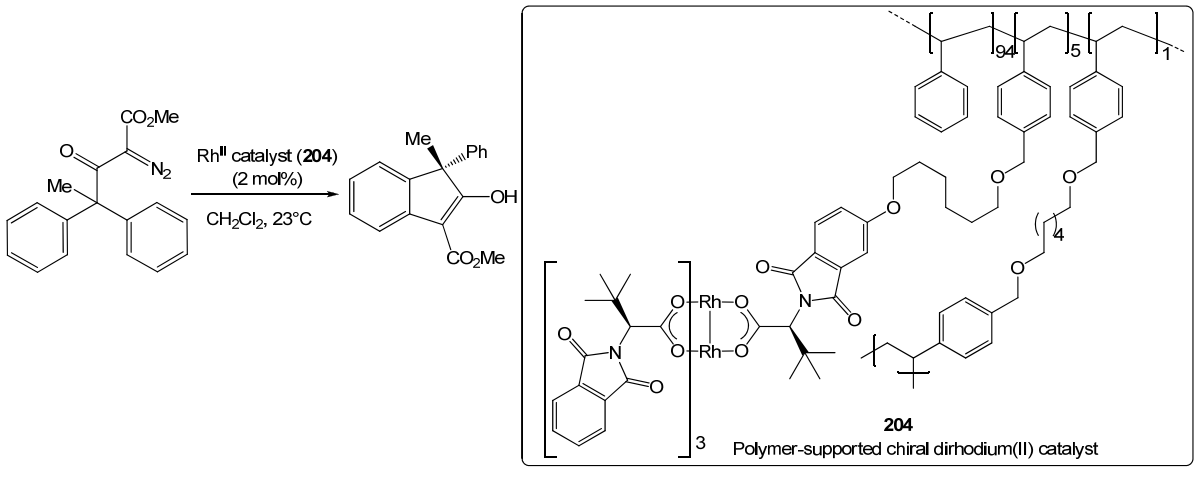
model **155a**. In this respect it interesting to note that, for all the cases examined, the *ee* values attained with the supported organocatalyst matched within the experimental uncertainties those provided by its soluble model compound.

In conclusion, this second part of the investigation confirmed the possibility of achieving for the first time a highly enantioselective α-amination of 3-substituted 1-benzyl-2-oxindoles by the use of an insoluble and recyclable organocatalyst. Concerning this last aspect, it is worth noting that eight of the entries of Table 11 were obtained by running the reaction with the IPB derivative recovered from a previous run. While these findings already suggest a good recyclability of the supported alkaloid derivative, this topic will be examined in more detail in the next paragraphs.

5.6. Recycling study of IPB-*Cinchona* alkaloid catalysts

Having established convenient routes for the preparation of a set of IPB-*Cinchona* alkaloid derivatives and their excellent performance in competent asymmetric transformations, the last goal of this Thesis was to explore the extent to which the supported organocatalysts could be actually reused. As noted at the onset of this work (see 1.5 and Figure 20), this -usually neglected- aspect is nonetheless very important in the perspective of large-scale applications of IPB catalysts. In this regard it should be stressed again that at the beginning of the present investigation the only example of substantial recycling of an immobilized asymmetric catalyst (60 reaction cycles) was that reported by Lectka and co-workers,[84] however, due to the use of more than stoichiometric amounts of the alkaloid derivative (**54a**,**b**), such a study essentially failed to demonstrate a clear-cut advantage in terms of catalyst productivity over the corresponding soluble organocatalysts.[86] While this Thesis was in progress, more convincing results were disclosed by Hashimoto and co-workers with the polymer supported $[Rh_2(S\text{-}PTTL)_4]$ complex **204**.[240]

By using an 'Argonaut quest-210' parallel synthesizer for easy separation and reuse of the polymer beads, the Japanese group was able of attaining 100 reaction cycles in the enantioselective C-H insertion of a diazo-β-ketoester (Scheme 50), with practically unchanged yield (86-90%) and *ee* values (91-92%) over the whole run series.



Scheme 50. Enantioselective C-H insertion with recyclable Rh(II) catalyst 204

[240] Takeda, K.; Oohara, T.; Anada, M.; Nambu, H.; Hashimoto, S. *Angewandte Chemie, International Edition* **2010**, *49*, 6979-6983

To the best of our knowledge, this study represent the most successful recycling reported to date for a recoverable asymmetric catalyst of any kind. As such, it undoubtedly set an important milestone in the field that, remarkably, appears to exceed by far the limits proposed by Connon and co-workers for attaining practical relevance (see 1.5).

Nevertheless, even these impressive results still leaved some unanswered questions, the most notable of which were (*a*) if a clear productivity increment over the homogeneous conditions could be achieved by the use of the IPB catalyst and how this could affect the product *ee* and (*b*) if catalyst immobilized onto cross-linked polymer-supports could be used longer than the ~34 h total reaction time achieved in the literature contribution. Given the interest of these issues for practical applications and because none of them could be easily solved on the basis of literature precedents, a detailed investigation was carried out in this Thesis work.

5.6.1. Recycling in the dimerization of ketenes.

As anticipated in 5.1.2, the preliminary screening of IPB alkaloid derivatives in the asymmetric dimerization of ketenes had already involved some limited recycling of the supported catalyst. Irrespective of the nature of the chiral derivative (either dimeric or monomeric) and the support material (either gel-type or macroporous), these experiments demonstrated that the IPB organocatalysts could be reused two times without any appreciable degradation of their activity or enantioselectivity (Table 6). Nonetheless, further recycling with the experimental set-up used in these initial runs proved difficult, because of the grinding of polymer beads under magnetic stirring. Especially for the gel-type materials, already after 2–3 cycles this led to exceedingly extended filtration times (>1 h) and to a poor retention of the worn particles by the glass frit.

For this reason, a new series of experiments were started with fresh batches of supported alkaloid derivatives, using an orbital shaking bench for reaction mixing (Figure 44). With this simple modification IPB catalyst damage was prevented to large extent, leading to a very fast filtration time (< 2min) in any case. Moreover, the replacement of magnetic stirring by gentle shaking did not appear to impact negatively on the catalyst efficiency, as confirmed by the analogous isolated yield and *ee* values recorded in the dimerization of methylketene under alternative conditions (compare Figure 44 and Table 6).

When the monomeric alkaloid derivative on the Merrifield support **159a** (5 mol%) was tested with this modified stirring set-up, the catalytic activity of the IPB system appeared to be largely preserved over five reaction cycles (Figure 44-a). However, especially after the fourth run a noticeable decrease of the product *ee* was observed (from 96% *ee* in the first run to 76% *ee* in the last one), which considerably limits the practical utility of this type of IPB organocatalyst.

From this point of view, the pyridazine derivatives performed significantly better. In the case of the organocatalyst **156a/y** immobilized onto the ArgoPore type of resin, a first series of experiments carried out at 2.5 mol% loading (Figure 44-b) provided a nearly constant product yield (around 50%) over nine reaction cycles. Even though also in this case a progressive reduction of the enantioselectivity was evidenced in the course of the successive runs (from 96 to 80% *ee*), increasing of the catalyst loading to 5 mol% (Figure 44-c) proved sufficient for maintaining the product enantiomeric purity at higher than 90% *ee* over eight reaction cycles.

When new set of experiments was started with the gel-type pyridazine derivative **156a/x** (2 mol%), an even better recycling profile was observed, which allowed to isolate the valuable of the polypropionate precursor **170** (R = Me) with good yield and excellent enantioselectivity in the course of 20 reaction cycles (Figure 44-d). In particular, this IPB organocatalyst showed no evidence of decrease in the product yield (56 ± 5%) and *ee* (96.6 ± 0.5%) up to the 13 run. Thereafter a slight negative trend in the catalytic performances began which, however, did not prevent the attainment of a respectable 48% yield and 90% *ee* even in the last run.[241]

From the above discussion, it is clear that the quinidine gel-type (Merrifield) bis-alkaloid material **156a/x** showed greater stability than analogous ArgoPore-type **156a/y**; on the contrary, the mono-alkaloid derivative **159a** turned out to perform substantially worse, in recycling, than the former class of IPB organocatalyst. Although no evidence can be provided at present for rationalizing these observations, it is worth observing that the relatively large difference in stability amongst the different derivatives could hardly be predicted on the basis of their structure alone.[242] Therefore, the importance of evaluating the IPB catalyst stability on a case by case basis has to be stressed.

[241] Standard filtration experiments excluded any significant catalytic activity in the solution (for details, see Experimental section)

[242] For the lower stability of the monomeric alkaloid derivative **159a**, it is tempting to speculate that the problem may be the 1,2,3-triazol-1-ylmethyl substituent at 9-*O*: The benzylic nature of the latter could prove particularly sensitive to the

Limiting the discussion to the best performing supported derivative **156a/x**, the repeated use of the recoverable organocatalyst appeared capable of leading to a definitive increase of productivity *P* (*vide infra*) over analogous soluble alkaloid derivatives.

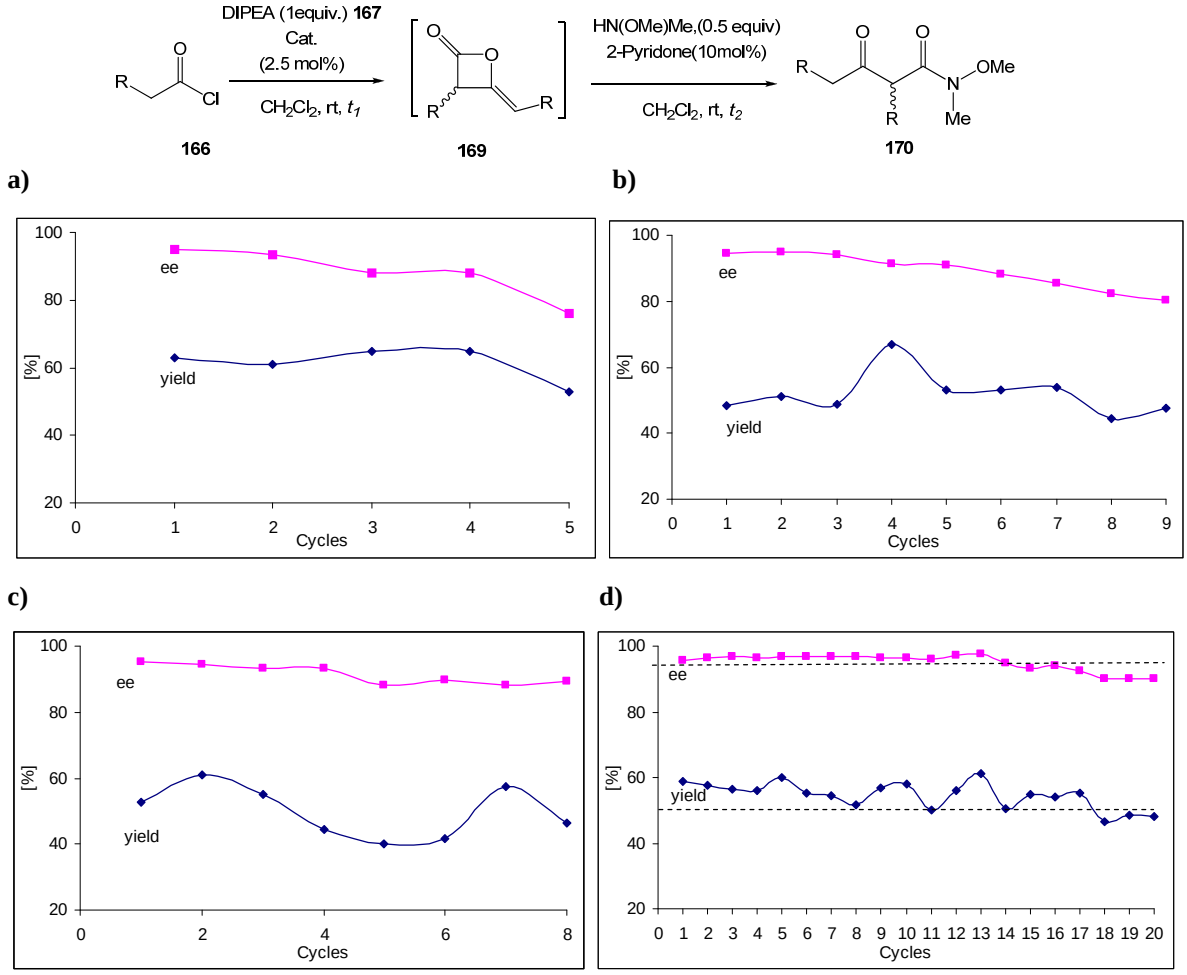


Figure 44. Catalyst recycling in the dimerization of ketenes with a) 159a (5 mol%); b) 156a/y (2.5 mol%); c) 156a/y (5 mol%) and d) 156a/x (2 mol%).

In particular, by making use of the results by Calter with 5 mol% of various monomeric alkaloid derivatives (see 5.1)[177b] it can be estimated that the best result in the homogeneous phase corresponded to the isolation of about 8 mol of the product **170** (R = Me) per mol of the chiral catalyst, with the former having an *ee* of 97% (*P*~8@97% *ee*).

presence of strong electrophiles (acid chloride, ketene) and nucleophiles (chloride ions) in the reaction mixture, which would lead to the progressive detachment of the chiral units from the resin. On the contrary, for what it concerns the different recycling profile of the same pyridazine derivative onto alternative PS supports (**156a/x** *vs.* **156a/y**), it can be thought that the fully swollen gel-type polymer beads would undergo a significantly reduced mechanical damage, as compare to the rigid ArgoPore material. Because of their brittleness, the latter could easily break down even under gentle shaking condition, eventually leading to the loss of significant amounts of the supported organocatalyst already after a few reaction cycles. Unfortunately, due to the difficult evaluation of the alkaloid loading in **156a/x**, **156a/y**, and **159a** by direct means (microanalysis or IR spectroscopy), no proof could be gained in the present Thesis in order to confirm or confute the hypotheses above.

By contrast, the repeated use of **156a/x** over 20 reaction cycles afforded over one order of magnitude more product per mol of alkaloid orgnocatalyst,[243] albeit with a somewhat reduced enantiomeric purity (see Figure 44-d). In principle the same result, *i.e.* increase of *P* and reduction of the product *ee*, could be attained in the homogeneous phase by reducing the loading of the soluble catalyst. Starting from this observation, a series of experiments were designed for exploring the relationship between catalyst amount and *P*/*ee* performance in the benchmark dimerization of methylketene.[244] With this aim the phthalazine ether **6** was initially selected as the soluble organocatalyst (Figure 45-a), prompted in this choice by its similarity with the IPB derivative **156a/x** and by its commercial availability. In order to make a comparison with the original Calter's catalysts, a second set of experiments were subsequently carried out with the simpler monomeric derivative **205**. Albeit not commercially available, **205** was easily prepared from DHQD,[177b] with the advantage of a much lower cost than **6**.

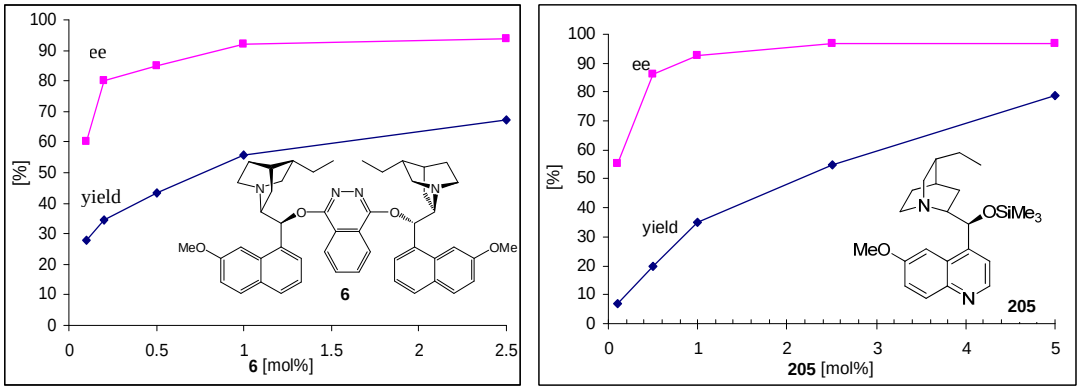


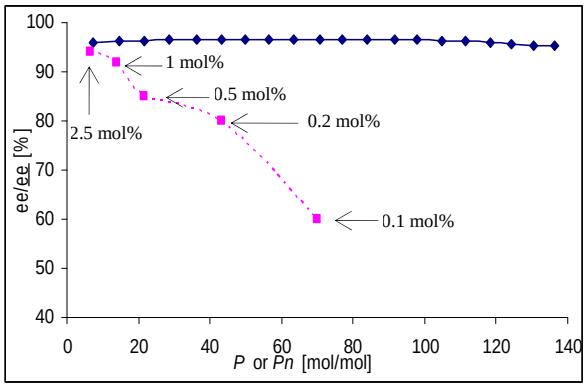
Figure 45. Asymmetric dimerization of methylketene in the presence of the soluble derivative 6.

The results of the tests with **6** revealed that the reaction of methylketene could tolerate a nearly twofold reduction of the catalyst loading below the 2.5 mol% level without any major erosion of the *ee* of the product **170** (R = Me). However, further lowering of the alkaloid amount resulted in a rapid degradation of performances, with an abrupt decrease of isolated yields and *ee* values when the loading was reduced below the 1 mol% level. Provided the different content in terms of alkaloid units is taken into account, a very similar trend was observed for **205**. Together with the results already discussed for the screening of alkaloid model compounds (see Table 5), these findings suggested that the nature of 9-*O*

[243] For the sake of comparison between monomeric and dimeric organocatalysts, in this section the *P* values were calculated with reference to 1 mol of alkaloid units.
[244] Cancogni, D.; Mandoli, A.; Jumde, R. P.; Pini, D. In press, *European Journal of Organic Chemistry* **2012**

substituent exerted a minor influence on the catalysis of the reaction under exam, both in terms of product yield and enantiomeric purity. Therefore, the productivity/enantioselectivity relationship at different loadings of the soluble catalyst was evaluated in the case of **6** only and, for the sake of comparison, plotted in a *ee*-*P* graph (Figure 46).[245]

The outcome of this analysis, shown as the broken curve in the Figure 46, revealed that the use of 2.5 mol% of the soluble commercial derivative **6** afforded results (*P*~6@94% *ee*) which appear similar to the literature data noted above. The reduction of the catalyst loading to 1 mol% led to some improvement of the productivity without a major penalty in terms of enantiomeric purity (*P*~12@92% *ee*). However, due to the anticipated relationship between alkaloid amount and catalytic performances (Figure 45), this favorable trend did not keep valid on moving to the loading low-end region. In this respect it is worth noting that, besides the enantioselectivity reduction, the relatively large *P* values scored by the use of 0.1 mol% of **6** (*P*~70@60% *ee*) actually corresponded to the isolation of unsatisfactory amounts (28% yield) of the product **170** (R = Me). Hence, in the reaction under exam a moderate reduction of the catalyst loading appears a viable option for increasing the productivity of the alkaloid derivative, which however cannot be pursued much below the 1 mol% threshold (where 56% isolated yield was obtained).[246]



[245] For the runs employing the soluble organocatalyst **6**, the productivity *P* was calculated as:

$$P = \frac{n_{\mathbf{170}}}{n_{\mathrm{Alk}}} = \frac{n_{\mathbf{166}}}{2 \cdot n_{\mathbf{6}}} \cdot \frac{y\%}{2 \cdot 100}$$

where, n_{Alk}, $n_{\mathbf{6}}$, and $n_{\mathbf{166}}$ are the amounts (moles) of alkaloid units, catalyst **6**, and the acid chloride **166** (R = Me) used in the homogeneous runs, while $n_{\mathbf{170}}$ and *y%* are the amount (moles) and the isolated yield of the purified Weinreb amide product **170** (R = Me), respectively.

[246] The monomeric TMS-ether **205** proved somewhat more effective than **6**, as it could provide *P*~11@97% *ee* (54% isolated yield) and *P*~17@93% *ee* (35% isolated yield) at 2.5 and 1 mol% loading, respectively. However, examination of the **Figure 45** revealed that the reduction of the catalyst loading below the 1 mol% was impractical also in this case. In this respect, it is worth noting that attempts to increase yield of **170** (R = Me) by prolonging the dimerization t_1 time were fruitless, possibly because of the evaporation loss of the volatile methylketene intermediate.

Figure 46. Enantioselectivity *vs.* productivity for soluble (6) and IPB (156a/x) catalysts (for the meaning of *P*, P_n, and *ee*, see the text).

The establishment of the *ee*-*P* relationship for the soluble catalyst **6** set the stage for a better assessment of the IPB material **156a/x**. For this purpose, the *ee* and yield data of the heterogeneous runs were converted into P_n@*ee* pairs, defined as the productivity (P_n) and weight-averaged enantiomeric excess (*ee*) for a virtual gross-sample of **170a** obtained by ideally pooling together those isolated up to the *n*-th run.[247]

By this approach, the cumulative productivity of the heterogeneous system was represented by the rightmost point of the solid curve in the

Figure **46** and turned out to be P_{20} ~136@95% *ee*. Comparison of these figures with the results for the soluble derivative revealed that the repeated use of the supported organocatalyst **156a/x** (2 mol%) was capable of affording larger than 20 times more product than **6** (2.5 mol%), the enantiomeric purity of the isolated amide being essentially the same (94-95% *ee*).[248]

Of course, the judgment whether the productivity increase attained with the IPB organocatalyst **156a/x** were sufficient for justifying its preparation in a real scenario is an issue that would require a comprehensive evaluation of many other aspects (*e.g.* cost of **156a/x**, overall reaction time, etc.). From this point of view, the *P@ee* analysis protocol described herein is not expected, therefore, to be a universal criterion for drawing this kind of conclusions. Nonetheless, in all the cases (like the present one) where the chiral organocatalyst is by far the most expensive chemical involved in the asymmetric transformation, it is unquestionable the capacity of increasing its productivity may be of prime importance in a practical perspective. Moreover, it is worth noting that the perhaps not impressive *P* enhancement was not the only advantage of the IPB approach described in this work: Because of the stereochemical lability of the β-dicarbonyl compounds **170**, the

[247] The cumulative productivity P_n and the averaged enantiomeric excess *ee* after *n* reaction cycles -carried out by using, in each run, the same amount ($n_{\mathbf{166}}$ moles) of the acid chloride substrate **166** (R = Me) and the recovered supported alkaloid derivative (initial amount $n_{\mathbf{156a/x}}$ moles) - were calculated as:

$$P_n = \frac{\sum_{i=1}^{n}(n_{\mathbf{170}})_i}{n_{\mathrm{Alk}}} = \frac{n_{\mathbf{166}}}{2 \cdot n_{\mathbf{156a/x}}} \cdot \frac{\sum_{i=1}^{n}(y\%)_i}{2 \cdot 100} \qquad \text{and } \underline{ee} = \frac{\sum_{i=1}^{n}(n_{\mathbf{170}})_i \cdot ee_i}{\sum_{i=1}^{n}(n_{\mathbf{170}})_i} = \frac{\sum_{i=1}^{n}(y\%)_i \cdot ee_i}{\sum_{i=1}^{n}(y\%)_i}$$

where, $n_{\mathbf{170}}$, ee_i, and $(y\%)_i$ are the amount (moles), the enantiomeric excess, and the percentage yield, respectively, of the purified Weinreb amide product **170** (R = Me) isolated in the *i*-th run.

[248] Comparison with the results provided by the monomeric TMS-ether **205** (Figure 45-b) as well as the model compound **155b** (*P*~*6*@95% *ee*, see Table 5, entry 2) confirmed that also for these soluble organocatalysts a one order of magnitude productivity increment could be attained by recycling the IPB derivative **156a/x**.

reaction under exam is one of those cases (see 1.4) where the separation and recovery of the alkaloid derivative by an acidic work-up is out of question. For this reason, in the published procedure a chromatographic separation was required for eliminating the chiral catalysts. Arguably, the latter constitutes the major contaminant in the crude product after removal of water-soluble co- and by-products by washing with a pH = 7 buffer solution. On the contrary, the use of the IPB organocatalysts of this work allowed the prompt separation of the alkaloid derivative, already after the ketene dimerization stage. Hence, practically pure Weinreb ketoamides could be obtained after the neutral work-up, without the need of further chromatographic purifications.

5.6.2. Recycling in the alcoholysis of *meso*-anhydrides.

Despite the preliminary screening of the anthraquinone-core alkaloid derivative **158c** in the asymmetric opening of *cis*-1,2,3,6-tetrahydrophthalic anhydride afforded only moderate *ee* values (see 5.2.2), its reuse was nonetheless briefly examined. With this aim, the recovered material was employed in three more runs to give the results summarized in the Figure 47.

Unfortunately, after the first run (which afforded **172** with 72% *ee*) the enantiomeric purity of the product dropped down to 62% *ee* and levelled around this value in the next two experiments. At present, no evidence can be presented for rationalizing this trend. Nevertheless, the observations above about the catalytic activity make the catalyst leaching an improbable cause of the observed phenomenon. Hence, the effect has to be related most likely to some modification of the alkaloid derivative, perhaps reflecting the unsolved question of how the basic organocatalyst could keep working in a reaction mixture that is accumulating progressively larger amounts of an acidic product (see 5.2). In this respect, it is interesting to note that control experiments revealed that the alkaloids immobilized onto PS resins had a strong tendency to scavenge from the solution a relatively large fraction (34%) of the product **172** formed in the reaction mixture.[196b] Even if treatment with an excess of triethylamine in toluene proved sufficient for releasing the captured hemiester,[196b] the procedure was not completely effective, however, for restoring the initial enantioselectivity.

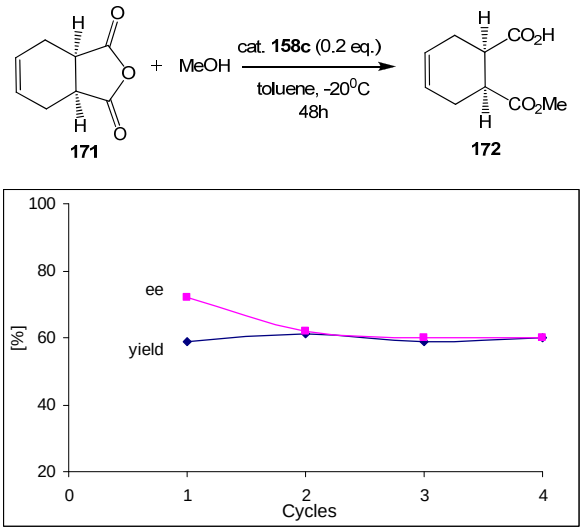


Figure 47. Recycling in *meso*-anhydride ring opening using catalyst 158c.

In conclusion, the IPB organocatalyst **158c** showed a reasonable recyclability and, also from this point of view, provided results that are very similar to those of the catalysts by Sartori and Deng groups (52-67% *ee* in the course of 3-5 reaction cycles),[192a,d] already discussed in 5.5.2. On the contrary, **158c** proved less effective than the Han IPB organocatalyst on silica-gel,[192c] which could provide 70-73% yield and 89-93% *ee* across five reaction cycles with *cis*-hexahydrophthalic anhydride. Given the limited recycling demonstrated also in such literature study, it may be therefore concluded that the development of a completely satisfactory recoverable alkaloid catalyst for the alcoholysis of *meso*-anhydrides remains, for the moment, an open problem.

5.6.3. Recycling in the asymmetric α-amination reaction

As anticipated, the supported pyridazine catalyst had showed their reusability potential already in the course of the substrate screening for the asymmetric α-amination of oxindoles (see 5.5.1). At variance with the methanolysis of *meso*-anhydrides, discussed in the previous paragraph, the *ee* values attained in the aforementioned process were also synthetically interesting. Hence, a detailed examination of recycling for the most effective IPB organocatalysts (**156a/x**) was decided, adopting for this purpose the *P@ee* analysis protocol described in 5.6.1. As for the dimerization of ketenes, this involved on one hand the study of the influence of the loading of the soluble organocatalyst **6** on the productivity and the enantioselectivity of the process; on the other hand, the extended recycling of the

immobilized alkaloid derivative. For benchmarking the results in the alternative scenarios, the α-amination of 1,3-dibenzyl-2-oxindole (**202a**) with DEAD (**195a**) under optimized conditions was selected (Figure 48).

Concerning the former aspect, the experiments with variable amounts of **6** (Figure 48) showed that the reaction could tolerate a twenty-fold reduction of the catalyst loading below the literature 10 mol% level,[231b] before any significant erosion of the *ee* of the product **203a** was observed. On the contrary, further lowering of the alkaloid amount below the 0.5 mol% limit resulted in a noticeable degradation of performance, with a sudden decrease of the *ee* value. As expected, the rate of the α-amination decreased progressively with the reduction of the catalyst amount; in the case of the lowest loadings, this resulted into a largely incomplete conversion of the substrate **202a** after the standard 48 h reaction time. In order to compensate for this effect, the runs with 0.1-5 mol% of **6** were extended up to 300 h: As shown in the Figure 48, this modification could only partially alleviate the problem, as only 61% product could be isolated even from the reaction carried out with 1 mol% of **6**.

Therefore, in the reaction under exam the simultaneous attainment of high product yields and *ee* values in a reasonable time seemed to require no less than 5 mol% of the soluble catalyst **6**.

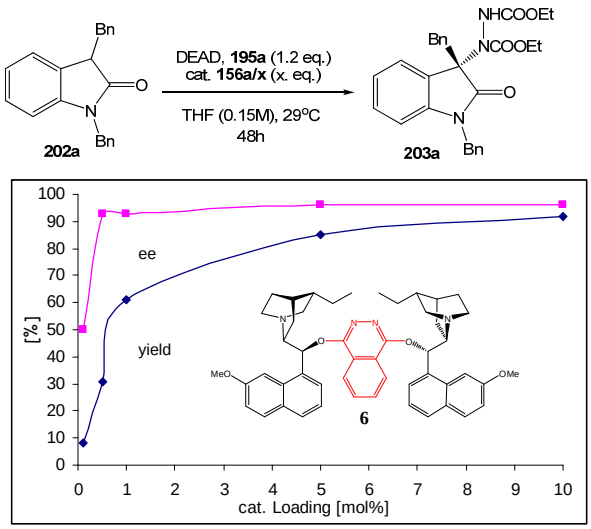


Figure 48. Asymmetric α-amination of 202a in the presence of variable amounts of the soluble derivative 6 (the data corresponding to 0.1-5 mol% of catalyst were obtained with 300 h reaction time)

Concerning the extended use of the supported catalyst, the decision was made to recycle **156a/x** as long as the *ee* of the product **203a** proved not less than 90%. As shown in

the Figure 49, much to our delight this event did not occur before the 100th reaction cycle. Moreover, while the initial experiments (cycles 1-30) afforded somewhat variable yield and *ee* values, probably because of fluctuations in the room temperature, thermostating the reaction mixture at 29°C (cycles 31-100) allowed the attainment of remarkably constant results. Under these conditions, a complete conversion of **202a** was obtained after 48 h (≈ 65 h in the weekends) and the product **203a** was obtained in a nearly quantitative yield and 93.5±1.5% *ee* throughout the recycle series.

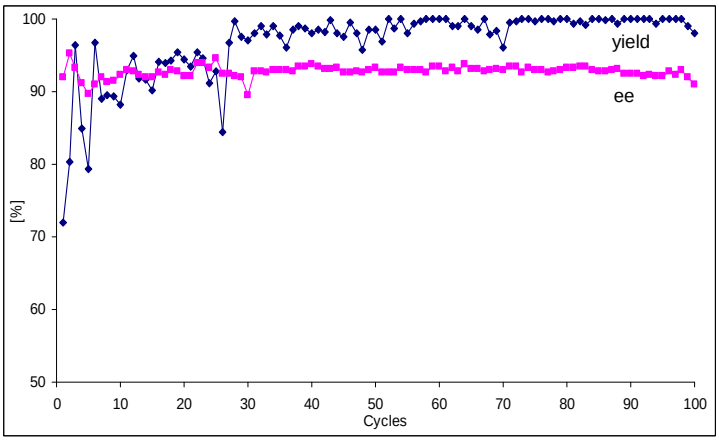


Figure 49. Recycling of 156a/x (20 mol%) in the α-amination reaction of 202a

Conversion of the results of the homogeneous (Figure 48) and heterogeneous runs (Figure 49) into *P@ee* and P_n@<u>*ee*</u> pairs by the same procedure described in 5.6.1,[249] led to the trends summarized in the Figure 50.

Examination of the enantioselectivity *vs.* productivity curves for **6** and **156a/x** revealed that, also in this case, the immobilized system could provide a definitively larger amount of product per mole of organocatalyst, than the soluble one. Interestingly, when the comparison was made at the same level of enantiomeric purity of **203a** (93% *ee* or <u>*ee*</u>), the enhancement of productivity was about one order of magnitude (*P*~60@93% *ee vs.* P_{100}~484@92% <u>*ee*</u> for **6** and **156a/x**, respectively). In this respect, it should be however pointed out that the reference results in the homogeneous phase correspond to the use of 0.5-1 mol% of the soluble catalysts **6**. As noted before, under these conditions the α-amination of **202a** was largely incomplete even after 300 h reaction time (31-61% yield, see Figure 48). On the contrary, the optimized use of the supported catalyst led to a complete conversion and nearly quantitative product yield in the standard reaction time of 48 h. In the

[249] Because only dimeric organocatalysts were examined for this reaction, the *P* and P_n productivity values reported in the present section are calculated with respect to the amount (moles) of **6** and of the chiral derivative contained in the material **156a/x**, respectively. The productivities per alkaloid unit are obviously one half of the stated *P* and P_n values.

process under exam, in addition to the larger productivity the IPB system appears therefore capable of a more effective use of the expensive reactants involved in the asymmetric transformation.

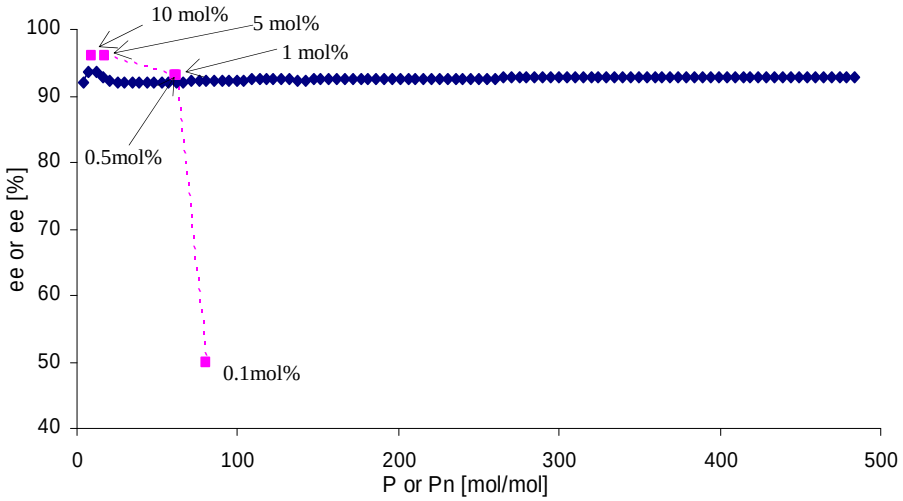


Figure 50. Enantioselectivity *vs.* productivity for 6 at various loadings (broken curve) and in the recycles of 156a/x (20 mol%; solid curve) in the asymmetric α-amination of 202a (for the conditions, see Figure 48; for the meaning of *P*, *Pn*, and *ee*, see the text).

Further examination of the Figure 50 showed that the productivity increase in heterogeneous runs was even larger (between 28 and 54-fold) when the homogeneous runs with 5-10 mol% of **6** were taken as the comparison term. However, in the case of the latter the enantiomeric purity of the product resulted slightly higher (95-96% *ee*) than in any of the heterogeneous runs. Overall, the commercial soluble phthalazine ether **6** appeared hence to posses somewhat better chiral discrimination ability than **156a/x** which, nevertheless, could not attain the 99% *ee* reported by Barbas III and co-workers for the reaction of **202a** in Et_2O.[231b]

Because the attainment of enantiomeric purities in the high-end region could be a very important issue for practical applications (especially in the pharmaceutical field), an attempt was made in this work to raise the *ee* of **203a** by recrystallization. With this aim, the combined samples from the 100 reaction cycles (93% *ee*, determined on the pooled fractions) were dissolved in hot MTBE and then allowed to cool to room temperature. Under these conditions a small amount of crystals were formed that, by chiral HPLC

analysis, turned out to be nearly racemic **203a**. On the contrary, evaporation of the mother liquors provided the product in 75% yield and >99% *ee*.[250]

Interestingly, a similar phenomenon had been observed before by Zhou and co-workers for unprotected 3-benzyl oxindole product,[229c] thus suggesting that the stereochemical purification of the kind described herein could be possible for a whole range of oxindole derivatives.

In closing, a comparison with the IPB Rh(II) complex **204** of Hashimoto and co-workers (p. 156),[240] seems appropriate. As anticipated, the supported metal catalyst of the Japanese group proved fully recyclable across 100 runs, without any noticeable decrease of activity (86-90% yield) or enantioselectivity (91-92% *ee*). In the published study, a homogeneous run with the corresponding soluble catalysts was also reported to provide very similar results (89% yield, 91% *ee*), which allow to estimate a 100-fold productivity increase by the use of the supported catalyst (all the experiments carried out with the same 2 mol% loading). Nonetheless, due to the lack of a punctual evaluation of the influence of the soluble Rh(II) complex amount on the catalysis performance, a comprehensive decision on the relative merits of homogeneous and heterogeneous catalytic systems seems hard to be reached in this case.[251]

In spite of the remarkable number of reaction cycles, a second observation that can be made concerns the overall operative time of IPB asymmetric catalysts. In the case of **204**, the relatively rapid reaction under exam allowed to complete each catalysis run in 20 min and the whole cycle series in less than two days (34 h). While the implementation of such a fast process may be undoubtedly convenient from a practical point of view, the limited time-span of the literature study makes it less than obvious if a "practitioner interested only in its use as a tool" (to use Connon's words)[86] could ever be convinced to prepare a recoverable catalyst with such a modest temporal horizon.

[250] It is interesting to note that the behavior of enantiomerically enriched **203a** upon crystallization does not seem to match to any of the limit phase-diagrams for enantiomeric mixtures (Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions.*; John Wiley and Sons, 1981). Indeed, while the *conglomerates* provide enantiomerically pure product as the crystalline material and the racemic mixture in the mother liquors, even in the alternative case (*true racemates* or *racemic compounds*) the mother liquors cannot contain a product purer than a given eutectic composition. Hence, for the compound under exam two explanations can be considered: (*a*) the behavior is that of a true racemate, with an eutectic composition very close to 100% *ee* (possibly, because of the much higher stability of racemic crystals over the enantiopure ones) or (*b*) the crystallization of the racemic product was much faster than for the enantiomerically pure and equilibrium was not actually attained under the working conditions.

[251] Thus, as noted at the beginning of this section, the use of less soluble catalyst could afford equally good results and, therefore, a potentially large increase of the productivity of the homogeneous system. In this respect, it is interesting to note that the heterogeneous runs were carried out with a four times larger reaction time (20 min) than for the homogeneous one (5 min).

From this point of view, the findings of this Thesis work appear by far more exhaustive, as the 100 cycles with the IPB organocatalyst **156a/x** actually correspond to more than 5300 h of operation time, over 10 months. Clearly, this result is a direct consequence of the long reaction times of the organocatalytic transformation examined in this work, *i.e.* a feature that can be considered more a nuisance than a practical advantage. As a matter of facts, this nonetheless allowed to demonstrate for the first time the multi-thousand hours flawless use of an IPB asymmetric catalysts. Considering that several factors can negatively affect the recycling of supported systems (*e.g.* leaching, chemical degradation, mechanical wearing, etc.), this result demonstrates that -in favourable cases and with proper condition optimization- an IPB organocatalyst can attain an operational life much longer than thought possible at the beginning of this Thesis.

Finally, it has to be remarked that the reported preparation of the IPB Rh(II) complex **204** was somewhat cumbersome, involving a low-yielding statistical preparation of the necessary unsymmetrical dirhodium precursor, the handling of a sensitive styrene monomers, and at least four chromatographic purification steps (two of which on metal-containing intermediates).[240] In spite of the excellent catalytic performance and recyclability, the literature system appears therefore hardly amenable of scale-up and so misses one of the three important features for practical usage. At present, the material **156a/x** seems therefore the only demonstrated case where satisfactory preparation, catalysis performance, and durability could be conjugated whitin a single IPB asymmetric catalyst architecture.

5.7 Conclusions

In summary, the different IPB alkaloid derivatives prepared in this Thesis work were tested as chiral catalysts in five different metal-free asymmetric transformations, *i.e.* dimerization of ketenes, alcoholysis of *meso*-anhydrides, dynamic kinetic resolution of 5-phenyl-1,3-dioxolane-2,4-dione, halolactonization reaction, and α-amination of 2-oxindoles. Even if satisfactory catalytic performance were not achieved in all cases, fair to excellent results could be attained at least in three of the examined transformations (methanolysis of *cis*-1,2,3,6-tetrahydrophthalic anhydride: >99 yield, 77% *ee*; dimerization of ketenes: 70 % yield, 97% *ee*; α-amination of 2-oxindoles: >99 % yield, 96% *ee*).

Recycling of the IPB organocatalyst was also studied in detail in the best cases, with results that turned out to be strongly dependant on the architecture of catalytic material and the nature of the catalyzed reaction. Overall, a pyridazine dimeric alkaloid ethers immobilized onto Merrifield resin (**156a/x**) proved the most effective and recyclable system: In addition of being efficiently reused 20 times in the dimerization of mehylketene, in the asymmetric α-amination of 1,3-dibenzyl-2-oxindole this kind of materials successfully underwent 100 reaction cycles over more than 5300 h of operation time.

To the best of our knowledge, these findings represent the longest recycling ever reported for an IPB asymmetric catalyst, which remarkably extend the temporal horizon of known recoverable systems by about two orders of magnitude.

Finally, a *P@ee* protocol was introduced in this work for the comparison of IPB asymmetric catalyst with their homogeneous counterparts. Basically this analysis involves the extensive recycling of the former and the study of the catalytic performance of the latter, at variable loadings. By these means, a productivity increase of about one order of magnitude could be demonstrated for the best IPB organocatalysts (the enantiomeric purity of the product being the same), over the alternative of merely reducing the amount of the soluble catalyst in the homogeneous process. As noted, this analysis is not expected to give the ultimate answer on which option would be chosen in a real scenario. Nonetheless, the approach takes the judgement between soluble and immobilized catalytic systems on a more meaningful, quantitative ground than the customary comparison between (a few) recycle runs and the results under standard (often unoptimized) homogeneous conditions. As such,

the proposed protocol will hopefully help to increase the interest and the credibility of the field of IPB asymmetric systems.

CHAPTER -6- CONCLUSIONS

Conclusions

As stated in the Introduction, the main theme of this Thesis was the development of *Cinchona* alkaloid derivatives covalently bound to insoluble supports (IPB systems) and their use in catalytic heterogeneous asymmetric transformations.

Even if this topic has been much explored in the last forty years, the ambition of the present work was to demonstrate the practical feasibility of this approach. Starting from an analysis of the state of the art in this field, this led to focus the efforts on the development of new IPB derivatives featuring a simple and scalable preparation, good catalytic performance, and an efficient recycling *within the same material architecture*. With this aim, three specific goals were outlined: *i*) The introduction of preparation procedures of the IPB systems devoid of obvious scale-up limitations (like, but not limited to, chromatographic purification steps); *ii*) the attainment of >90% *ee* in the catalyzed asymmetric process; *iii*) the demonstration of at least 20 reaction cycles with minimal or no reduction of the catalytic efficiency.

Overall, the insights gained in the course of the present Thesis appear to fulfil quite well the minimal requirements stated above. In fact, the main achievements of this work can be briefly summarized as follows:

i) Preparation of IPB Cinchona derivatives.

The initial hypothesis in this work was that the copper-catalyzed *click* addition between azides and alkynes could significantly improve the covalent linking of chiral derivatives onto organic insoluble supports. Based on this idea, the preparation of a set of *Cinchona* alkaloid provided with a terminal alkyne group was investigated. These included simple 9-*O* propargyl ethers, for which the scale-up to kilogram amounts had been already demonstrated in the literature, as well as new dimeric derivatives embedding a pyridazine, 1,3,5-triazine, or anthraquinone (hetero)aromatic spacer group between the two alkaloid units.

In general, all these anchorable compounds could be obtained by procedures that made use of cheap chemicals (the native alkaloid being in all cases the most expensive one) in reliable and, usually, rather high-yielding reactions. The purification of the anchorable derivatives, and all of the intermediates towards them, proved also generally straightforward: When the crude product was not directly used in the next step, or for

anchoring, it normally consisted in the recrystallization of the substance; in any case, chromatography purification could be avoided in the synthesis of all the alkaloid derivatives whose immobilization proved worthwhile. These features allowed the prompt preparation of different QD, QN, DHQD, and DHQN ethers of the propargyl, anthraquinone, and pyridazine type, with the actual demonstration of a multigram scale synthesis in the case of the latter. Taking into account the literature precedents for 9-*O* propargyl ethers, as well as the lack of any obvious bottleneck for the anthraquinone ones, these findings clearly indicated the possibility of scaling-up the first step of any covalent immobilization strategy of *Cinchona* alkaloids, *i.e.* the synthesis of derivatives suitable for anchoring.

In this regard, the dimeric 1,3,5-triazine ethers introduced in this work could be deemed an exception. Even in that case, however, the choice to subject the crude compounds to column chromatography was dictated more by the need of analytical samples, for characterization purposes, than by real purity issues. Due to the somewhat lower performance with respect to the other organocatalysts, no specific efforts were devoted herein to demonstrate their large-scale preparation. Nonetheless, if competent catalytic applications of alkaloid ethers belonging to this class were to be discovered in the future, the procedure outlined in this Thesis could already be employed as a basis for a convenient synthesis of anchorable derivatives of the new 1,3,5-triazine type.

Concerning the insoluble supports, the attention was mainly focused on the use of Merrifield resins. In addition to solvent compatibility considerations, this choice was prompted by the widespread use of this type of materials, their low cost, and the easy introduction of the azide groups required for the *click* anchoring. Because the support architecture can have a significant effect on the activity of the immobilized catalyst, polystyrene beads with macroporous morphology (ArgoPore^{TM} resin) or with oligo(ethylene oxide) crosslinks were also examined. While the latter had to be prepared in house, the use of materials of the former two kinds proved particularly handy and allowed to obtain *click* supports in a fully scalable manner from the commercial chloromethyl resins.

Finally, the last step of the immobilization sequence confirmed the initial hypothesis about the convenience of the *click* strategy: By simply shaking the alkaloid derivatives with the azido resins in the presence of Cu(I) salts, satisfactory results were generally attained, which became excellent in the immobilization of some of the chiral derivatives onto Merrifield and polar cross-linked materials. In best cases, this allowed to score

unprecedented anchoring yields and alkaloid loadings, which represent a substantial improvement of the present possibilities in the field.

ii) Performance of IPB Cinchona alkaloids

Guided by literature precedents, a number of organocatalytic enantioselective transformations were considered in order to find applications of the new materials developed in this Thesis. After a preliminary screening with soluble model compounds, the attention was mainly focused on two reactions that, in addition to provide synthetically useful chiral products, could match the >90% *ee* performance criterion stated above. These were the asymmetric dimerization of ketenes and the α-amination of 2-oxindoles.

Much to our delight, the pyridazine-type of organocatalysts on Merrifield resins proved effective in both transformations and allowed to obtain up to 81% yield and 97% *ee*, in the case of the former, and up to >99% yield and 95% *ee*, in the latter.

In addition to represent the first example of heterogeneous versions of the said reactions, thoroughly performed comparison experiments revealed that the supported alkaloid derivatives could display very similar results (especially enantioselectivity) as their soluble model compounds (or similar homogeneous organocatalysts from the literature). Therefore, the choice of *click* chemistry as the anchoring technique can be judged, *a posteriori*, to provide materials well fit for high catalytic performance in metal-free transformations.

Fulfilling the second goal outlined at the onset of the work, these findings provided a suitable playground where to tackle the third, but equally important, issue of catalyst recycling.

iii) Recovery and recycling of the IPB Cinchona alkaloid organocatalysts.

Reuse of some of the IPB organocatalysts in the asymmetric dimerization of ketenes revealed some interesting structure-dependent behaviour, with best results (20 reaction cycles with ≥ 90% *ee*) attained in the case of a pyridazine derivative onto the Merrifield resin.

While these findings can be considered noteworthy, also in view of the current standards in the field of IPB asymmetric catalysts, even better results were possible in the α-amination of 2-oxindoles: In this case, 100 consecutive cycles could be effectively performed for this reaction, still obtaining the expected product in high yield and

enantiomeric purity. Remarkably, these experiments were carried out over 10 months, with the catalyst exposed to reaction conditions for more than 5300 h!

In our opinion this last result stands as one of the most important achievements of the present Thesis because it demonstrates that, at least in favourable cases, an IPB asymmetric catalyst can keep working effectively for much longer (about two orders of magnitude) than believed at the beginning of this work. In this respect, it should be noted that, besides witnessing high chemical stability under the reaction conditions, this result showed that optimization of the stirring technique could be a key point in order to obtain extended serviceability, even with polystyrene materials.

In summary, a class of IPB alkaloid organocatalysts could be eventually developed (the pyridazine ethers onto the Merrifield resin), which appear to nicely combine within a single material architecture easy and scalable preparation, high catalytic performance, and sustained recycling.

From this point of view, the general goals of this work, as stated in the Introduction, were undoubtedly met. Moreover, because the basic requirements for IPB systems were set with the aim to push significantly ahead the limitations of the materials reported to date, these findings can be considered advancements in the field. Further developments in this direction can be foreseen, including the use of the most durable supported organocatalysts under continuous mini- and micro-flow conditions.

Of course, whether the aims and the results of this Thesis can be considered an appropriate answer to the needs of practical applications, in general, is a conclusion that goes well beyond the scope of the present study. In this regard, it was already noted that the choice of specific limits for performance and recycling bears some great deal of arbitrariness. In a real scenario, many other factors would come also into play: Some (the more onerous preparation, the somewhat lower catalytic activity) disfavouring the IPB approach, other (the simplified purification, the higher overall productivity) that could let the balance to lean decisively in favour of it.

Finally, it could be argued that the achievements described herein are likely to depend largely on the specific catalyst’s structure and the chemistry involved in the catalyzed reactions. This is certainly true and the prediction can be made that the exciting results obtained in selected organocatalytic asymmetric transformations with *Cinchona* alkaloid derivatives could not be extended, by large and far, to any catalytic system or enantioselective process.

Nonetheless, we hope that the methods and the insights gained in this work will help to boost the interest towards IPB asymmetric catalysts and to increase the general appreciation of this field.

Publications

Part of this Thesis work is collected in the following articles:

Journals:

- Silicone-supported Cinchona alkaloid derivatives as insoluble organocatalysts in the enantioselective dimerization of ketenes.
  Damiano Cancogni, Alessandro Mandoli, Ravindra P. Jumde, Dario Pini
  In press, *European Journal of Organic Chemistry* **2012**

- Mono- and bis-Quinidine Organocatalysts in the Asymmetric Methanolysis of Cis-1,2,3,6-Tetrahydrophthalic Anhydride: A Conformational and Mechanistic NMR Study.
  Balazano Federica, Jumde Ravindra P., Mandoli Alessandro, Masi Sofia, Pini Dario, Uccello Barretta Gloria, *Chirality* **2011**, *23*, 784-795.

- Simple Preparation of Dimeric Cinchona Alkaloid Derivatives on Polystyrene Supports and a Highly Enantioselective Catalytic Heterogeneous Dimerization of Ketenes.
  Ravindra P. Jumde, Alessandro Mandoli, Federica De Lorenzi, Dario Pini, Piero Salvadori, *Advanced Synthesis & Catalysis*, **2010**, *352*, 9, 1434-1440

Congresses:

- (Oral): A scalable strategy for the preparation of polymer-supported alkaloid derivatives and application to asymmetric organocatalysis
  Jumde Ravindra P., Mandoli Alessandro, Delorenzi Federica, Cancogni Damiano, Pini Dario, Salvadori Piero
  SISOC VIII-**2010**, pp OC16-OC16, Padova, Italy.

- (Oral and Poster): A convenient and scalable strategy for the preparation of polymer-supported alkaloid derivatives and application to asymmetric organocatalysis.

Jumde Ravindra P., Mandoli Alessandro, Pini Dario, De lorenzi Federica, Cancogni Damiano.
IASOC-**2010,** pp P28, Ischia (Naples), Italy.

- (Poster): A convenient and scalable strategy for the preparation of polymer-supported alkaloid derivatives and application to asymmetric organocatalysis.
  Jumde Ravindra P., Mandoli Alessandro, Pini Dario, De lorenzi Federica, Cancogni Damiano.
  ICCTCB-**2009**, pp 51-51, Bangalore-India.

CHAPTER -7- EXPERIMENTAL SECTION

7.1. General Methods and Materials

All the reactions involving sensitive compounds were carried out under dry N_2, in flame-dried glassware. Solvents were freshly distilled before the use from the proper drying agent.[252] If not noted otherwise, the compounds were commercially available and used as received. For the heterogeneous reactions carried out under shaking conditions, a Scienceware Spindrive® orbital shaking platform was used.

TLC analyses were carried out with Merck 60 F_{254} plates (0.2 mm) and chromatography purifications with Macherey-Nagel flash grade silica-gel (230-400 mesh). Melting points (uncorrected) were measured with a Reichert hot stage apparatus.

Unless otherwise noted ^1H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions on a Varian XL 300 instrument and are reported in ppm relative to TMS (^1H) or to the solvent (^{13}C, $CDCl_3$ at 77.16 ppm).[253] Data were reported as follows: chemical shift, multiplicity, coupling constants and integration, (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, td = triplet of doublets and br = broad).

Electron ionization mass analyses [MS (EI)] were performed on a Varian Saturn 2000 spectrometer, interfaced with a Varian 3800 gaschromatograph. IR spectra were recorded using a Perkin-Elmer Spectrum GX FT-IR; the wavenumber of the principal peaks are reported in cm^{-1}. Electrospray mass analyses were carried out in the positive ion mode [MS(ESI^+)] on methanolic solutions, with a Perkin-Elmer-Sciex Api 3000 spectrometer.

For the GC analyses a BP-1 column (25 m) on a Perkin-Elmer Autosystem gas chromatograph was used, with nitrogen as the carrier gas. HPLC analyses were carried out on a Jasco PU-1580 chromatograph, equipped with an UV-1575 detector. Optical rotation were measured as solutions in 1 dm cells at the sodium D line, using a Jasco DIP360 polarimeter.

Elemental analyses were performed in duplicates by the microanalytical laboratory of the Dipartimento di Scienze e Tecnologie Chimiche dell'Universita degli Studi di Udine (Italy).

[252] Armarego, W. L. F.; Chai, C. *Purification of Laboratory Chemicals, 5th Edition.*; Butterworth-Heinemann, 2003.
[253] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *The Journal of Organic Chemistry* **1997**, *62*, 7512-7515

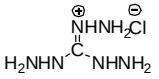
N,O-dimethylhydroxylamine[254] was obtained by literature methods. The resins **121a** (2% cross-linking, 2.3 mmol Cl g^{-1}) and **121b** (1.46mmol Cl g^{-1}) were purchased from Aldrich.

7.2. Experimental section for chapter-2

7.2.1 Preparation of clickable pyridazine-core *Cinchona* alkaloid-derivatives (100a,b,c and 101).

7.2.1.a Preparation of 3,6-dichloro-1,2,4,5-tetrazine (96)

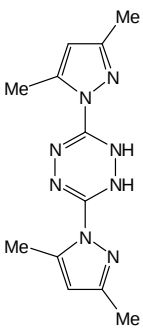
Step-I. Preparation of 92.



To a 500 mL three-necked round bottom flask, equipped with a reflux condenser were introduced 200 mL of 1,4-dioxane, 38.2 g (0.4 mol) of guanidine hydrochloride **91** and 68.2 g (1.36 mole) of hydrazine monohydrate. The mixture was heated to reflux under magnetic stirring for 2 hours. A formed plentiful pinkish-white precipitate, after cooling, was filtered through medium porosity glass frit, washed with dioxane and dried under reduced pressure on P_4O_{10}. Mobile white powder was obtained 54 g (96% yield).

mp 228-230°C [Lit 230°C][106b]

Step-II. Preparation of 93.



To a 1L three-necked round bottom flask, equipped with a reflux condenser and dropping funnel were introduced 54 g (0.38 mol) of **92** and 383 mL of water. The apparatus was flushed with nitrogen, the suspension was vigorously stirred until complete dissolution of the solids, then 78.6 g (0.76 mol) of 2,4-pentanedione (acetylacetone) were added dropwise in the course of 1 h, at the end obtaining a clear yellow solution. After 30 minutes of stirring at room temperature, the mixture was heated to 70°C for 4 h, during which time light yellow solid was precipitated from the solution, which, after cooling the mixture was separated by filtration through G3 glass frit. After washing with portions of water and

[254] Beak, P.; Basha, A.; Kokko, B.; Loo, D. *Journal of the American Chemical Society* **1986**, *108*, 6016-6023

drying at 60°C (0.05 mmHg) for 5 h with Kugelrohr apparatus, the product was isolated as pale-yellow solid 38.5g (66% yield).

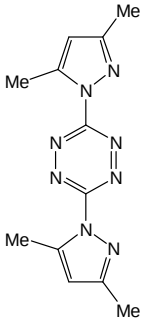
mp 145-149°C [Lit 150°C] [106b]

TLC R_f = 0.40 (silica gel, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (s, 2H), 5.97 (br q, *J* = 0.84 Hz, 2H), 2.48 (d, *J* = 0.84 Hz, 6H), 2.22 (s, 6H).

^{13}C NMR (75 MHz,$CDCl_3$): δ = 150.0, 145.8, 142.4, 109.9, 13.9, 13.6.

Step-III. Preparation of 94.



A mixture of $Pb(NO_3)_2$, (48 g) and sand (36 g) is placed in a Pyrex tube (a) of typical assembly (Figure 51) used for NO_2 production. The tube (a) was heated with flame, NO_2 production was started by decomposition of $Pb(NO_3)_2$ with red-brown fumes which was forwarded towards Schlenk tube (c) through trap (b) by a slow stream of compressed air. The reaction proceeded with the bubbling of NO_2 in a Schlenk tube containing a suspension of 50 g (0.18 mol) of **93** in 134 mL of N-methyl-pyrrolidone**:** after few seconds the gradual change in colour of suspension to bright red was observed. The heating was stopped after almost complete decomposition of $Pb(NO_3)_2$ indicated by the ceasing of red-brown fumes. The reaction was monitored on TLC, observing a complete conversion by disappearance of starting **93**.

The red suspension was introduced in 500 mL water, the solid precipitated was filtered and washed with water and dried under vacuum over $P_4O_{10.}$ The product was isolated as red solid 37 g (76 % yield).

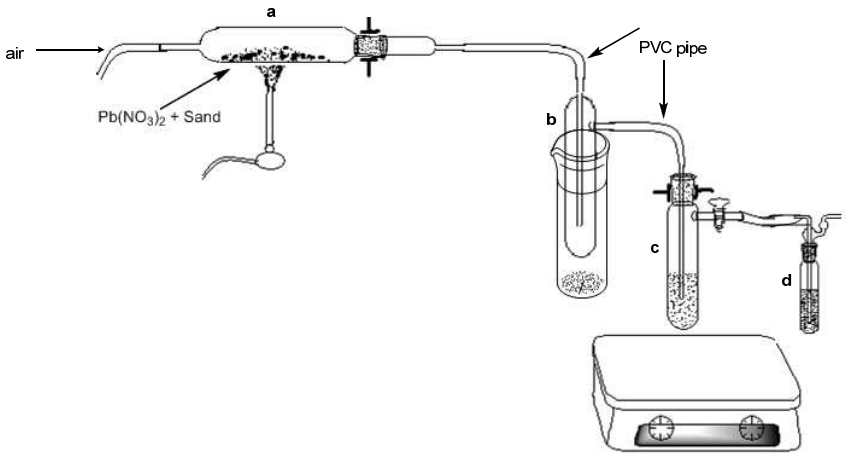


Figure 51 Typical assembly for NO_2 production

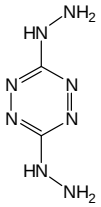
mp 226-229 ° C [Lit 226°C][106b]

TLC R_f = ~ 0 (silica gel, CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.17 (s, 2H), 2.68 (s, 6H), 2.36 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.2, 154.4, 143.7, 111.8, 14.6, 13.8.

Step-IV Preparation of 95.



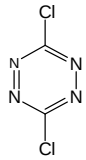
In a 500 ml three-necked round bottom flask, equipped with a reflux condenser and dropping funnel, 36 g (0.133 mol) of **94** and 350 mL of CH_3CN were introduced under nitrogen flow. Under vigorous stirring to the resulting red solution was added, dropwise, 14.25 mL of hydrazine hydrate. After the addition, the brown mixture was refluxed for 20 minutes and then allowed to cool to room temperature. The solid formed was separated by filtration, washed with small portions of CH_3CN and then dried at 0.05 mmHg, obtaining 15.7 g (83 % yield) of **95** as a red-brown solid.

mp 150-156°C [Lit 146-147°C, 160-162°C][255]

^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.3.

[255] Marcus, H. J.; Remanick, A. *Journal of Organic Chemistry* **1963**, *28*, 2372-1375.

Step-IV Preparation of 96.

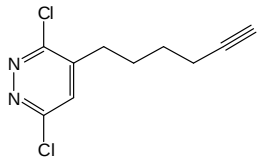


In a 1L two-neck round bottom flask, fitted with a dropping funnel, were introduced under nitrogen flow 15.7 g (0.11 mol) of **95** and 450 mL of CH_3CN. After cooling to 0ºC in an ice bath, to the resulting red suspension was added, over 30 minutes, a solution of 51.13 g (0.22 mol) of trichloroisocyanuric acid (TCCA) in 300 mL of CH_3CN. The solution turned to orange colour and a white solid was precipitated. The suspension was allowed to warm to room temperature and the solid was removed by filtration. The filtrate, carefully concentrated by the rotary evaporator, was purified by dissolving, under N_2, in minimum amount of boiling heptane (100 mL) and filtered in a hot condition to remove small amounts of undissolved brown material. After cooling to room temperature, bright orange crystals were formed which was separated by filtration, washed with small portions of *n*-pentane and dried briefly at about 10 mmHg, obtaining 9.3 g of **96** as a bright orange solid. By concentrating the mother liquor and repeating the recrystallization, two more crops of crystals were recovered, 2.77 g with 73 % overall yield.

mp 130-149°C [Lit 146-147°C][107a]

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1.

7.2.1.b. Preparation of 3,6-dichloro-4-(hex-5-ynyl)pyridazine (99)



A Schlenk tube was charged under nitrogen with 4.00 g (26.5 mmol) of **96**, 17.5 mL (132 mmol, 5 equiv.) of 1,7-octadiyne **98** and dry toluene (55 mL). The resulting orange solution was heated at 100 ºC, following the consumption of **96** from the color fading and by GC. After full conversion (6 h), the dark-yellow solution was filtered through a medium porosity glass frit to remove small amounts of dark insoluble material which on the frit was rinsed with 3 × 3 mL of toluene. The combined filtrates were distilled under reduced pressure (10 mmHg) to recover the toluene and excess of 1,7-octadiyne. The pale brown residue was dried under high vacuum (0.05 mmHg) and then purified by recrystallization from boiling *n*-heptane (55 mL, cooling into an ice bath was required for obtaining a solid product). The clear crystals were separated by filtration, washed with little pentane, and dried under vacuum (0.05 mmHg) to provide **99** as a pale orange solid 4.65 g (76% yield).

mp 38-40°C;

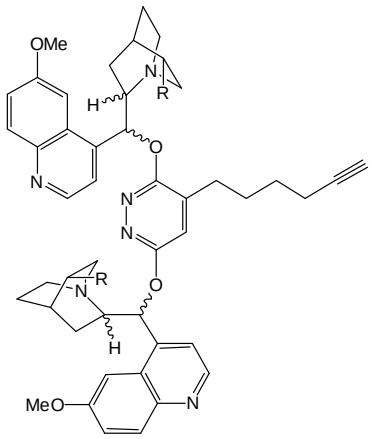
TLC R_f = 0.52 (SiO_2, CH_2Cl_2);

^{1}H NMR ($CDCl_3$, 300 MHz): δ =7.49 (s, 1H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.30 (dt, J_a = 6.9 Hz, J_b = 2.7 Hz, 2H), 2.01 (t, *J* = 2.7 Hz, 1H); 1.91-1.77 (m, 2H), 1.73-1.61 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 156.8, 155.7, 144.0, 129.0, 83.3, 69.0, 31.6, 27.5, 26.4, 17.9. MS (EI): *m/z* (%) = 230 (10), 228 (15), 195 (66), 193 (100), 39 (35).

anal. calcd. for $C_{10}H_{10}Cl_2N_2$: C 52.42, H 4.40, Cl 30.95, N 12.23. found: C 52.65, H 4.45, Cl 30.65, N 12.14.

7.2.1.c. Preparation of 4-(Hex-5-yn-1-yl)-3,6-bis(alkaloid)pyridazine (100a,b and c).



100a, b, c

General procedure: A 500-mL three-necked flask, fitted with a Dean–Stark apparatus, was charged under nitrogen with 4.40 g (19.2 mmol) of **99**, 12.5 g (~38.5 mmol, 2 equiv.) of QD/DHQD/DHQN, 2.21 g (39.4 mmol, 2.05 equiv.) of KOH pellets and 250 mL of toluene. The mixture was refluxed for 4 h with azeotropic removal of water, cooled to room temperature, and then treated with water (200 mL). The organic components were extracted with Et_2O (3 × 200 mL) and the organic phase was washed with brine (3 × 100 mL). After drying (Na_2SO_4) the volatiles were removed with a rotary evaporator to give **100a**, **b** or **c** as a brownish solid foams, containing (^{1}H NMR analysis) small amount of solvent and starting alkaloid. These crude materials were directly employed in the subsequent anchoring step. For characterization purposes, small samples (ca. 0.5 g) were purified by flash chromatography (SiO_2, AcOEt : MeOH= 7:3+1% Et_2NH), obtaining **100a**, **b** or **c** as colourless solid foams.

4-(Hex-5-yn-1-yl)-3,6-bis(9-O-quinidinyl)pyridazine (100a): 14.20 g crude (85% pure by ^{1}H

NMR, 78% yield);

TLC R_f = 0.37 (SiO_2, AcOEt : MeOH = 7 : 3 + 0.5% Et_2NH);

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.64 (d, *J* = 4.6 Hz, 2H), 7.95 (d, *J* = 9.3 Hz, 2H), 7.47 (d, *J* = 2.3 Hz, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.30-7.39 (m, 4H), 6.89-6.68 (m, 3H), 6.03-5.83 (m, 2H), 5.05-4.93 (m, 4H), 3.87 (s, 3H), 3.86 (s, 3H), 3.43-3.20 (m, 2H), 3.03-2.57 (m,

10H), 2.30 (dt, J_a = 6.6 Hz, J_b = 2.6 Hz, 2H), 2.26-2.14 (m, 2H), 2.01 (t, J= 2.7 Hz, 1H), 1.96-1.73 (m, 6H), 1.73-1.62 (m, 2H) 1.60-1.37 (m, 6H).

^{13}C NMR (150 MHz, $CDCl_3$,) δ = 160.8, 159.5, 158.9, 157.6, 157.5, 147.1, 144.8, 144.56, 144.51, 140.2, 139.8, 135.5, 131.3, 127.3, 127.1, 121.7, 121.5, 118.7, 118.3, 114.6, 114.5, 102.0, 101.7, 83.6, 75.7, 68.8, 59.9, 59.7, 55.5, 55.4, 49.7, 49.5, 49.2, 49.1, 39.7, 39.6, 28.7, 27.8, 26.2, 23.8, 22.9.

MS (ESI$^+$) *m/z* = 827.4 [M+Na$^+$], 805.6 [M+H$^+$].

$[\alpha]_D^{25}$ = -120 (c = 1.0, CH_2Cl_2).

3,6-Bis(10,11-dihydro-9-O-quinidinyl)-4-(hex-5-yn-1-yl)pyridazine (100b): 16.13 g crude (80% pure by ^{1}H NMR, 85% yield).

TLC R_f = 0.27 (SiO_2, AcOEt : MeOH = 7 : 3 + 0.5% Et_2NH)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.69 (d, J = 4.4 Hz, 2H), 8.00 (d, J = 9.2 Hz, 2H), 7.52 (d, J = 2.6 Hz, 1H), 7.47 (d, J = 2.6 Hz, 1H), 7.41-7.33 (m, 4H), 6.82-6.70 (m, 3H), 3.88 (s, 3H), 3.87 (s, 3H), 3.42-3.18 (m, 2H), 3.02-2.45 (m, 10H), 2.30 (dt, J_a = 6.6 Hz, J_b = 2.6 Hz, 2H), 2.01 (t, J = 2.6 Hz, 1H), 1.94-1.21 (m, 20H), 0.89-0.76 (m, 6H)

^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.2, 159.9, 157.7, 147.5, 145.4, 145.2, 144.92, 144.87, 135.7, 131.7, 127.8, 127.6, 121.9, 121.7, 119.0, 118.8, 102.6, 102.3, 83.9, 76.3, 75.5, 69.0, 60.5, 60.3, 55.8, 55.7, 51.1, 50.2, 50.0, 37.71, 37.65, 29.0, 28.2, 27.6, 27.5, 26.8, 26.4, 26.3, 25.5, 24.4, 23.6, 18.4, 12.1.

MS (ESI$^+$) *m/z* = 832.0 [M+Na$^+$], 809.9 [M+H$^+$]

$[\alpha]_D^{30}$ = -66.9 (c = 0.80, CH_2Cl_2).

3,6-Bis(10,11-dihydro-9-O-quininyl)-4-(hex-5-yn-1-yl)pyridazine (100c): 2.2g crude (92% pure by ^{1}H NMR, 89% yield).

TLC R_f = 0.39 (SiO_2, AcOEt : MeOH = 7 : 3 + 1% Et_2NH)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.65 (dd, J = 4.5, 2.6 Hz, 2H), 7.98 (dd, J = 9.2, 1.7 Hz, 2H), 7.51 (dd, J = 4.3, 2.8 Hz, 2H), 7.44 – 7.31 (m, 4H), 6.87 – 6.68 (m, 3H), 3.87 (s, 6H), 3.45 – 3.25 (m, 2H), 3.15 – 2.88 (m, 4H), 2.65 (td, J = 7.1, 1.6 Hz, 2H), 2.59 – 2.42 (m, 2H), 2.34 – 2.19 (m, 4H), 2.00 (t, J = 2.6 Hz, 1H), 1.90 – 1.53 (m, 12H), 1.50 – 1.20 (m, 10H), 0.84 – 0.77 (t, 6H).

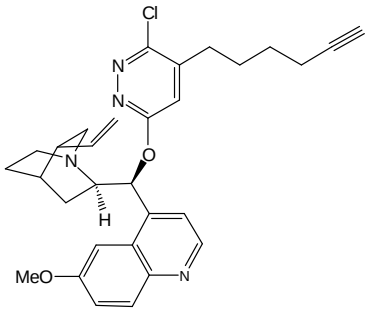
^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.2, 159.8, 157.8, 157.7, 147.6, 147.4, 145.0, 144.9, 144.8, 144.8, 135.8, 131.5, 127.5, 127.4, 121.9, 121.8, 119.1, 118.9, 118.8, 118.6, 102.3,

102.2, 101.3, 83.8, 77.3, 77.1, 76.4, 69.0, 60.1, 60.0, 58.5, 58.5, 55.8, 55.8, 42.8, 42.8, 37.6, 29.0, 28.7, 28.5, 28.2, 27.8, 27.8, 26.9, 25.5, 24.2, 23.9, 18.4, 12.2.

MS (ESI$^+$) *m/z* = 810 [M+H$^+$], 405.4 [M+2H$^+$]

$[\alpha]_D^{27}$ = +106.76 (c = 0.5, CH_2Cl_2)

***6-Chloro-4-(Hex-5-yn-1-yl)-3-(9-O-quinidinyl)pyridazine (101)*:** (0.053 g, 17% yield)



TLC R_f = 0.75 (SiO_2, AcOEt : MeOH = 7 : 3 + 0.5% Et_2NH).

^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.66 (d, *J* = 4.6 Hz, 1H), 7.98 (d, *J* = 6.7 Hz, 1H), 7.52 (d, *J* = 2.6 Hz, 1H), 7.37 (d, *J* = 4.6 Hz, 1H), 7.35 (dd, J_a = 6.7 Hz, J_b = 2.6 Hz, 1H), 7.11 (d, J_a = 4.4 Hz, 1H), 6.91 (s, 1H), 6.05 (ddd, J_a = 17.4 Hz, J_b = 10.4 Hz, J_c = 7.3 Hz, 1H), 5.12 (m, 1H), 5.09 (ddd, J_a = 17.4 Hz $J_{b=c}$ = 1.6 Hz, 1H), 3.97 (s, 3H), 3.39 (m, 1H), 3.06 (m, 1H), 2.95 (m, 1H), 2.86 (m, 1H), 2.78 (m, 1H), 2.65 (m, 2H), 2.27 (m, 1H), 2.25 (m, 2H), 2.06 (m, 1H), 1.97 (t, $J_{a=b}$ = 2.7 Hz, 1H), 1.84 (m, 1H), 1.76 (m, 2H), 1.61 (m, 2H), 1.60–1.58 (m, 2H), 1.54 (m, 1H).

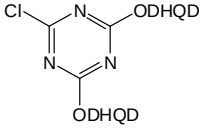
^{13}C NMR (150 MHz, $CDCl_3$) δ = 163.7, 157.9, 152.6, 147.3, 144.7, 144.3, 143.6, 140.3, 131.7, 127.2, 121.9, 118.5, 118.1, 114.9, 101.7, 83.6, 76.5, 69.0, 59.7, 55.7, 49.9, 49.3, 39.7, 31.9, 27.9, 27.7, 26.7, 26.6, 23.1, 18.1.

MS (ESI$^+$) *m/z* = 517.3 [M+H$^+$].

$[\alpha]_D^{25}$ = -85.7 (c = 1.28, CH_2Cl_2).

7.2.2 Preparation of clickable triazine-core dimeric *Cinchona* alkaloid-derivatives (106a,b).

7.2.2-a. Attempts to prepare the 2,4-bis(10,11-dihydro-9-O-quinidinyl)-6-chloro-1,3,5-triazine (107).



a) With KOH in toluene: A 100 mL three necked round bottom flask, equipped with Dean-Stark apparatus were charged under N_2 flow with 1.33 g (4.05 mmol) of DHQD, 0.23 g (4.05 mmol) of KOH pellets, 0.37 g (2.00 mmol) of triclorotriazine **102** and 30 mL of anhydrous toluene. The suspension was heated to reflux for 4 h, resulting in a yellow-brown mixture. A sample of the suspension was treated with H_2O, extracted with AcOEt, dried over Na_2SO_4, evaporated at reduced

pressure and analyzed by ^{1}H NMR. Since the recorded spectrum showed the presence of at least 6-7 different alkaloids species, whose signals attributable to the methoxy group with overlapping of broad resonances, the reaction mixture was not processed further.

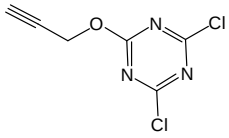
b) With NaH in THF: In a 50 mL two-necked round bottom flask, fitted with a reflux condenser, were introduced under N_2 flow 1.33 g (4.05 mmol) of DHQD, 10 mL of anhydrous THF followed by 0.1880 g (~ 4.5 mmol) of NaH (55%, dispersed in mineral oil). The suspension was vigorously stirred until dissolution of most of the solid and the gas evolution ceased (15-30 min). After addition of 0.37 g (2.00 mmol) of triclorotriazine **102**, the resulting cloudy solution was heated to reflux for 18 h or in a subsequent trial, kept at room temperature for 90 h. In both cases, samples of reaction mixtures were treated with H_2O, extracted with AcOEt, dried over Na_2SO_4, evaporated under reduced pressure and analyzed by ^{1}H NMR. The spectra of the two tests showed essentially identical results and signals of the main alkaloids different from those of the precursor DHQD. The reaction mixture was treated with 10 mL of H_2O, extracted with 4×25 mL AcOEt, dried over Na_2SO_4 and volatiles were removed to the rotary evaporator. Thus was obtained 1.56 g of crude product as a yellow solid foam, which was subjected to flash chromatography (SiO_2, AcOEt: CH_3OH = 8:2 → 6:4, then CH_3OH: CH_2Cl_2 = 1: 1). Two main fractions were collected, which provided a single spot by TLC analysis. One at R_f = 0.42 (0.440 g) showed broadening of the NMR peaks and very low intensity of most of the characteristic signals of the alkaloid units which were expected to fall in the area (2-9 ppm). The other at R_f = 0.16 (0.500 g) provided a more resolved spectrum but, however, still characterized by the overlapping and broadening of signals, also the MS (ESI^+) spectrum of the both samples did not showed the m/z values expected for the desired product.

TLC: R_f = 0.16 (SiO_2, AcOEt : CH_3OH = 7:3 + 1% Et_2NH).

^{1}H NMR (300 MHz, $CDCl_3$, major resonances) δ = 8.60 (d, *J* = 11.0 Hz), 7.99 (dd, *J* = 9.2, 3.7 Hz), 7.26 (ddd, *J* = 47.2, 23.8, 3.5 Hz), 6.28 (s, 8H), 4.11 (q, *J* = 7.1 Hz), 4.05 – 2.86 (m), 3.18 (s), 2.03 (s, 11H), 1.83 (d, *J* = 6.8 Hz), 1.67 (s), 3.21 – -0.99 (m, 315H), 1.42 (s, 17H), 1.35 (s), 1.25 (t, *J* = 7.1 Hz), 2.46 – -0.99 (m).

MS(ESI^+) *m/z* = 309.4, 327.3, 347.4, 782.9.

7.2.2-b. Preparation of 2,4-dichloro-6-(prop-2-ynyloxy)-1,3,5-triazine(108a).



In a 25 mL two-necked round bottom flask, equipped with a reflux condenser, were introduced under N_2 flow 2.25 g (12.0 mmol) of TCT **102**, 12 mL of anhydrous THF and 2.8 mL (17 mmol) in DIPEA. The resulting solution was vigorously stirred at room temperature for 5 min and then added with 0.54 mL (9.4 mmol) of propargyl alcohol **105a**, observing a distinct turbidity in a few minutes. The resulting suspension was left under stirring for 18 h and then filtered through a pad Celite, washing the residue with three portions of THF. The solvent was removed on the rotary evaporator and the yellow oil obtained (2.56 g) was subjected to flash chromatography (SiO_2, petroleum ether: AcOEt = 6:1). From the chromatographic separation two components were recovered which showed, respectively, individual spots at R_f = 0.59 and 0.69. After evaporation of the solvent from the more retained fractions the desired product **108a** 0.963 g (50.4%) was obtained, as a clear solid having physical constants and spectroscopic properties in agreement with those of literature.[111]

From the fractions of less retained compound was obtained 0.602 g of a colourless solid, which by NMR and MS analyses, proved to be the 4,6-dichloro-N-ethyl-N-isopropyl-1,3,5 -triazine-2-amine(**108c**).

Product **108a**:

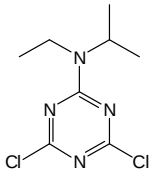
mp 41°C [Lit. mp = 40-41°C][111]

TLC, R_f = 0.59 (SiO_2, petrolium ether : AcOEt = 6:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.09 (d, *J* = 2,4 Hz, 2H), 2.58 (t, *J* = 2.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.8, 170.5, 77.0, 75.7, 57.4.

Product **108c**:



mp 57-58°C.

TLC, R_f = 0.69 (SiO_2, petrolium ether : AcOEt = 6:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.90 (hetp, *J* = 6.8 Hz, 1H), 3.49 (q, *J* = 7.1 Hz, 2H); 1,23 (d, *J* = 6.8 Hz, 6H), 1.22 (t, *J* = 7.0 Hz, 3H).

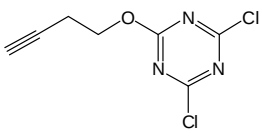
^{13}C NMR (50 MHz, $CDCl_3$) δ = 169.9, 169.6, 163.8, 47.9, 37.8, 20.1, 14.0.

GC (DB-1701, N_2 15 psi, 100°C for 2 min, then 10°C min^{-1} up to 280°C) t_R, area%: 13.4 min, > 98%.

GC-MS *m/z* (intensity): 94.2 (15), 191.2 (30), 193.2 (19), 205.2 (17), 219.3 (100), 221.1 (85), 234.0 (17), 235.1 (12), 235.9 (12).

MS(ESI$^+$) *m/z* = 235.1, 237.1 [M+H$^+$].

7.2.2-c. Preparation of 2,4-dichloro-6-(but-3-ynyloxy)-1,3,5-triazine (108b)



In a 25 mL two-necked round bottom flask, equipped with a reflux condenser, were introduced under N_2 flow, 2.25 g (12 mmol) of TCT **102**, 12 mL of anhydrous THF and 2.80 mL (17 mmol) in DIPEA. The resulting solution was vigorously stirred at room temperature for 5 min and then added with 0.66 g (9.4 mmol) of alcohol **105b**, observing a marked turbidity in a few minutes. The resulting suspension was left under stirring for 18 h and then filtered through a pad of Celite, washing the residue with three portions of THF. The solvent was removed on rotary evaporator and the yellow oil obtained (2.73 g) was subjected to flash chromatography (SiO_2, petroleum ether: AcOEt = 6:1). The fractions containing only one component at R_f = 0.45 were combined and evaporated, giving 1.9 g (92.0%) of the desired product **108b** as a clear solid having a purity GC> 98%. From the chromatographic separation were also retrieved 0.22 g of a compound that was identical to the product **108c** isolated in the preparation of **108a**.

mp 50-54°C.

TLC, R_f = 0.45 (SiO_2, petroleum ether: AcOEt = 6:1).

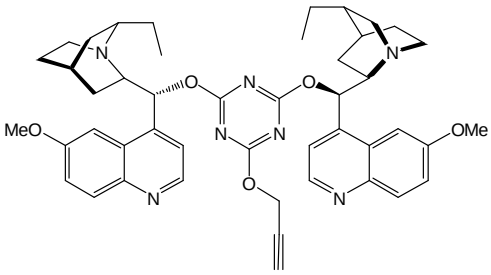
^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.58 (t, *J* = 6.9, 2H), 2.72 (dt, J_a = 6.9, J_b = 2.7, 2H), 2.03 (t, *J* = 2.7, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ = 172.74, 170.86, 78.78, 70.97, 67.71, 18.89.

GC (DB-1701, 15 psi N_2 100°C for 2 min, then 10°C min^{-1} up to 280°C) t_R, area%: 12.1 min, > 98%.

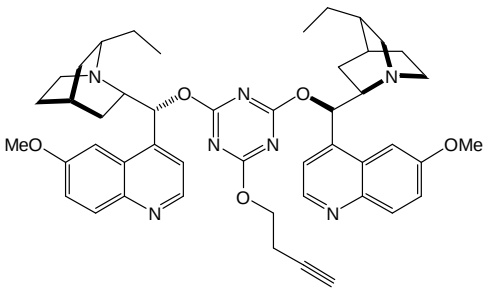
GC-MS *m/z* (intensity) = 50.2 (24), 51.2 (25), 52.3 (60), 53.2 (38), 154.1 (37), 182.1 (60), 184.1 (21), 218.0 (100), 219.9 (65).

7.2.2-d. Preparation of 2,4-bis(10,11-dihydro-9-O-quinidinyl)-6-(prop-2-ynyloxy)-1,3,5-triazine (106a).



In a 25 mL two-neck round bottom flask, fitted with a reflux condenser, were introduced under N_2 flow 0.67 g (2.05 mmol) DHQD, 10 mL of THF and 0.01 g (2.05 mmol) of NaH 55% (w/w) in mineral oil. The resulting suspension was heated to reflux, until the dissolution of most of the solid and cessation of gas evolution (about 15 min). After cooling to room temperature, were added 0.2 g (1.00 mmol) of the heterocyclic spacer **108a** and the almost clear yellow solution stirred and heated at reflux, for 18h. After verifying by TLC the disappearance of the precursor **108a**, the yellow-brown mixture was carefully hydrolyzed with 10 mL of water and extracted with 4 × 20 mL of AcOEt (due to the formation of emulsions was useful to add 5 mL of brine to the aqueous phase). After drying on Na_2SO_4, the solvent was removed by rotary evaporator to obtain crude product (0.672 g) as solid foam. TLC analysis of crude showed several major spots and NMR spectrum was rather complex. Therefore, the purification was attempted by flash chromatography (SiO_2, AcOEt : CH_3OH = 80:20 + 0.5% Et_2NH, then AcOEt : CH_3OH : CH_2Cl_2 = 60:30:10 + 0.5% Et_2NH), obtaining 4 fractions of major components at R_f = 0.13 (0.117 g), 0.15 (0.180 g), 0.21 (0.156 g) and 0.85 (0.181 g), none of these fractions showed, however, a ^{1}H NMR spectrum consistent with the structure of the compound **106a**.

7.2.2-e. Preparation of 2,4-bis(10,11-dihydro-9-O-quinidinyl)-6-(but-3-ynyloxy)-1,3,5-triazine (106b)



In a two-necked round bottom flask, 25 mL, fitted with a reflux condenser, were introduced under N_2 flow 0.69 g (2.1 mmol) DHQD, 10 mL of THF and 0.08 g (2.0 mmol) of NaH 55% (w/w) in mineral oil. The resulting suspension was heated to reflux, for 30 minutes, until the solution is pale yellow, slightly opalescent. After cooling at room temperature were added 0.22 g (1.0 mmol) of heterocyclic spacer **108b**, and the solution was kept stirring for 48 h at same temperature.

The resulting suspension was treated with 10 mL of water and organic compounds were extracted with 4×20 mL AcOEt. After drying on Na_2SO_4, the volatile components were removed on the rotary evaporator, getting the crude product (0.65 g) as yellow-brown solid foam. Purified by flash chromatography (SiO_2, CH_2Cl_2:CH_3OH = 95:5 + 0.2% Et_2NH) has provided a fraction of **106b** 0.31 g (38.8%) as a pale-yellow solid foam, which TLC analysis gave single spot.

TLC, R_f = 0.52 (SiO_2, CH_2Cl_2 : CH_3OH = 90:10 + 0.5% Et_2NH).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.66 (d, *J* = 4.5 Hz, 2H), 8.00 (d, *J* = 9.2 Hz, 2H), 7.39 (Br s , 2H), 7.35 (dd, J_a = 9.1, J_b = 2.6 Hz, 2H), 7.29 (d, *J* = 4.6 Hz, 2H), 6.61 (d Br, *J* = 4.3 Hz, 2H), 3.85-4.12 (m, 2H), 3.90 (s, 6H), 3.15-3.35 (m, 2H), 2.50-2 , 95 (m, 8H), 2.15-2.40 (m, 2H), 1.91 (t, *J* = 2.7 Hz, 1H), 1.65-1.90 (m, 4H); 1.30-1.60 (m, 12H), 0.88 (t, *J* = 6.9 Hz, 6H).

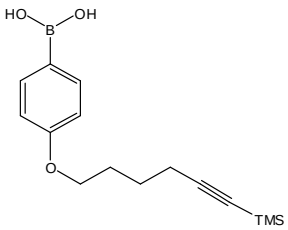
^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.5, 172.3, 157.7, 147.3, 144.5, 143.3, 131.6, 126.6, 121.8, 118.5, 101.3, 78.8, 77.9, 70.2, 65.6, 59.4, 55.5, 50.8, 49.9, 37.1, 29.5, 26.9, 25.7, 25.1, 22.9, 18.4, 11.9.

MS(ESI$^+$) *m/z* = 309.2, 399.5 [M+2H$^+$], 798.5 [M+H$^+$].

$[\alpha]_D^{27}$ = -74.4 (c = 1.0, CH_2Cl_2).

7.2.3 Preparation of the clickable anthraquinone-core dimeric *Cinchona* alkaloid-derivatives (114b).

7.2.3-a. Preparation of the 4-(6-(trimethylsilyl)hex-5-ynyloxy)phenylboronic acid (115)



***a) With K_2CO_3 in acetone*:** In a 50 mL two-necked round bottom flask, fitted with refluxed condenser, were introduced under N_2 flow 150 mg (1.09 mmol) of hydroxyphenylboronic acid **116**, 152 mg (1.1 mmol, 1 equiv.) of K_2CO_3, 5 mL acetone and 294.5 mg (1.09 mmol, 1 equiv.) **113c**. The resulting suspension heated to reflux for 20h, excess of base K_2CO_3 76.1 mg (0.55 mmol, 0.5 equiv.) and **113c** 58.9 mg (0.218 mmol, 0.2 equiv.) was added to improve the conversion and kept running at same conditions for additional 16 h. As no further improvement in conversion was observed by ^{1}H NMR, reaction was cooled to room temperature, volatiles were removed in vacuo, the resulting crude was treated with 20 mL of HCL-diluted and organic components were

extracted with 3 × 20 mL of AcOEt, combined organic layers were dried over Na_2SO_4, solvents were removed on rotary evaporator and off-white crude (400 mg) obtained was purified by flash chromatography (SiO_2, Hex:EtOAc = 2:1) providing pure fractions of product **115** (170 mg, 54% yield).

b) With K_2CO_3 in DMF: A 100 mL Schlenk tube, were charged under N_2 flow with 0.8 g (5.8 mmol) 4-hydroxyphenylboronic acid **116**, 0.963 g (6.96 mmol, 1.2 equiv.) K_2CO_3, 10 mL anhydrous DMF and 1.706 g (6.09 mmol, 1.05 equiv.) **113c**, 2 mL DMF was used to wash the walls of Schlenk tube. The resulting suspension kept stirring at room temperature (24 h), followed by heating at 50-65ºC until complete consumption of **116** (117h) as monitored by TLC and confirmed by ^{1}H NMR. The resulting reaction mixture was treated with 75 mL HCL diluted and extracted with 4 × 25 mL AcOEt. After drying over Na_2SO_4 the volatiles were removed on rotary evaporator to give muddy crude **115** (~ 3 g). ^{1}H NMR analysis of the crude showed the presence of residual DMF. The crude was further treated with water (50 mL) and extracted with 3 × 25 mL CH_2Cl_2, combined organic phases were washed with brine, after drying over Na_2SO_4 solvents were removed on rotary evaporator and dried thoroughly under reduced pressure (0.5 mmHg). The crude was dissolved in MTBE and filtered from G4 glass frit to remove undissolved material, after removal of solvent, the product **115** obtained in almost pure form by ^{1}H NMR as off-white solid (1.4 g, 83 % yield)

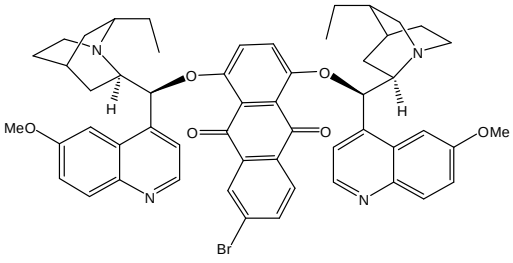
TLC, R_f = 0.21 (SiO_2, Hex : EtOAc = 2:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 4.08 (t, *J* = 6.2 Hz, 2H), 2.34 (t, *J* = 7.0 Hz, 2H), 2.08 – 1.84 (m, 2H), 1.83 – 1.63 (m, 2H), 0.16 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.8, 137.6, 135.3, 114.1, 107.0, 85.1, 67.4, 28.5, 25.3, 19.8, 0.3.

MS(ESI$^-$) *m/z* = 335.1 [M+HCOO$^-$]

7.2.3-b. Preparation of the 6-bromo-1,4-bis(10,11-dihydro-9-O-quinidinyl)-anthracene-9,10-dione (110)



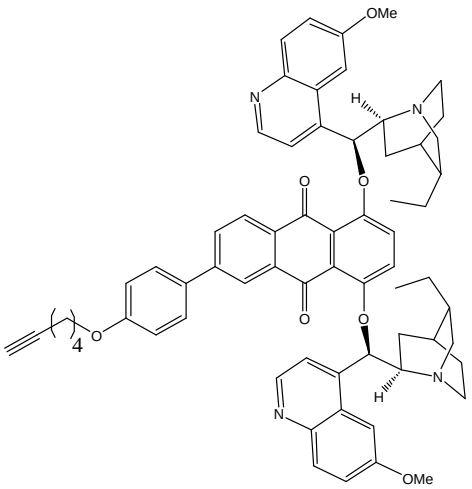
a) With nBuLi in THF: A typical procedure of Bolm was followed. In a 100 mL Schlenk tube, were introduced under N_2 flow 1.34 g (4.1 mmol,

2.5 equiv.) DHQD and 40 mL anhydrous THF, the solution was cooled to -18ºC and 1.8 mL (4.1 mmol, 2.5 equiv.) of 1.9 M *n*BuLi in hexane was added slowly over 15 min (solution became dark red in colour at the end of *n*BuLi addition). To this solution then 0.53 g (1.64 mmol) of 6-bromo-1,4-difluoroanthracene-9,10-dione **109** was added and reaction mixture was warmed to room temperature, stirred for 18 h, warmed to ca. 40ºC and stirred for another 2 h. With this procedure as judged from TLC and ^{1}H NMR, reaction was largely incomplete even after 36 h at 40ºC. The THF was removed from the reaction mixture on rotary evaporator, added CH_2Cl_2 + water (25 + 25 mL), organic phase was separated and aqueous phase was washed 4 × 20 mL of CH_2Cl_2. Combined organic phases were washed with brine and dried over Na_2SO_4, volatiles were removed in vacuo and brown crude obtained was subjected to flash chromatography (SiO_2, CH_2Cl_2:MeOH = 10:1 + 0.5% Et_2NH then CH_2Cl_2:MeOH = 8:2 + 0.5% Et_2NH) has provided a fractions of **110** as yellow solid (0.6 g, 39 % yield), which NMR data was in agreement with those reported in literature.[87b]

***b) With NaH in DMF*:** In a 100 mL Schlenk tube, were introduced under N_2 flow 1.09 g (3.17 mmol, 2.05 equiv.) DHQD (95%) and 20 mL DMF, stirred until complete dissolution (15 min). The resulting solution was cooled to 0ºC and 0.156g (3.25 mmol, 2.1 equiv.) of NaH (50 % in mineral oil) was added in one portion and stirred for 10 min at same temperature→ 10 min at rt →15 min at 50ºC and 15 min at 60ºC to obtained almost clear solution (reaction mixture turned light red after addition of NaH and became pale-yellow in color after complete dissolution). To the solution at room temperature was added 6-bromo-1,4-difluoroanthracene-9,10-dione **109** (the solution turned green in colour after addition of **109** and remained brown after 30 min) and kept stirring at same temperature. Complete conversion to a single spot was observed on TLC after 18h, which was confirmed by ^{1}H NMR. The reaction was quenched by adding 50 mL water and extracted with 4 × 25 mL EtOAc, combined organic phases were dried over Na_2SO_4, and volatiles were removed on rotary evaporator, thus providing gummy crude, which was stripped by CH_2Cl_2 and thoroughly dried under high vacuum 0.5 mmHg (to remove excess of DMF) to give foamy yellow product **110** in crude form, containing small amount of residual DMF and unreacted DHQD (87% pure by ^{1}H NMR, 95% yield).

The spectroscopic data of product **110** was in agreement with those reported in literature,[87b] this crude material was directly employed in the subsequent Suzuki-coupling step.

7.2.3-c. Preparation of the 1,4-bis(10,11-dihydro-9-O-quinidinyl)-6-(4-(hex-5-ynyloxy) phenyl)anthracene-9,10-dione (114b)



Step-I, A two-necked round bottom flask, 100 mL, equipped with refluxed condenser was subjected to six vacuum/nitrogen cycle and charged with 700 mg (0.695 mmol) of **110** (87% purity), 348.9 mg (1.202 mmol, 1.72 equiv.) of boronic acid derivative **115**, 339.8 mg (3.206 mmol, 4.6 equiv.) Na_2CO_3 and 69.45 mg (0.0601 mmol, 8.6 mol%).

The reaction vessel with all solids was again degassed by six vacuum/nitrogen cycle and added solvents (dry toluene 35 mL, EtOH 3.5 mL and H_2O 3.5 mL). The resulting reaction mixture heated to reflux for 4h, overnight at rt, as monitored by TLC the complete conversion was observed by disappearance of **110** (R_f = 0.35) and new spot was emerged just above starting (R_f = 0.38) in 4h. The reaction was quenched by adding 100 mL water, aqueous layer was removed and organic layer was washed with 5 × 50 mL of HCL (10%), combined HCL washing were neutralized ($NaHCO_3$) and extracted with 5 × 50 mL of EtOAc, obtaining small amount of compound which was revealed as DHQD by ^{1}H NMR (present in starting **110**).

The white precipitate formed in the neutralized aqueous layer was extracted with 2 × 25 mL CH_2Cl_2, combined organic layers were dried over Na_2SO_4, volatiles were removed on rotary evaporator and drying under reduced pressure (0.5 mmHg) provided product **114a** in essentially pure form by ^{1}H NMR (550 mg, 72 % yield). The crude material directly employed to subsequent deprotection step. For characterization purposes small amount of sample was purified by flash chromatography (SiO_2, EtOAc:MeOH = 9:1 + 0.5 % Et_2NH), obtaining **114a** as a yellow powder.

TLC, R_f = 0.38 (SiO_2, CH_2Cl_2 : MeOH = 9:1 + 0.5 % Et_2NH)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.58 (d, *J* = 4.2 Hz, 2H), 8.38 (s, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 8.09 – 7.85 (m, 3H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.56 – 7.20 (m, 6H), 6.98 (d, *J* = 8.3 Hz, 2H), 6.72 (s, 2H), 6.14 (br s, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 3.86 (s, 6H), 3.30 – 3.05 (m, 2H), 3.03 – 2.65 (m, 6H), 2.65 – 2.39 (m, 4H), 2.29 (t, *J* = 6.9 Hz, 2H), 1.98 – 1.81 (m, 2H), 1.80 – 1.64 (m, 4H), 1.65 – 1.21 (m, 12H), 0.76 (t, *J* = 7.0 Hz, 6H), 0.12 (s, 9H).
^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.0, 182.5, 159.7, 158.2, 151.18, 151.14, 147.5, 145.7, 144.62, 142.65, 142.5, 134.7, 132.3, 131.9, 131.4, 131.0, 128.3, 127.0, 126.4 123.8, 123.6, 122.0, 120.7, 120.5, 119.1 (br), 115.0, 106.8, 100.8, 84.9, 79.4 (br), 67.5, 60.1, 55.8, 50.7, 49.9, 42.8, 39.9, 37.6, 28.3, 26.8, 26.5, 25.1, 24.4, 19.5, 12.06, 12.02, 0.17.
MS(ESI$^+$) *m/z* = 550.8 [M+2H$^+$], 791.5 [M–DHQD$^{\bullet+}$], 1028.0 [M–TMS+H$^+$], 1103.8 [M+H$^+$]
$[\alpha]_D^{27}$ = -530.02 (c = 0.525, CH_2Cl_2).

***Step-II-deprotection*-** In a 100 mL two-necked round bottom flask, under N_2 flow were introduced 550 mg (0.499 mmol) $(DHQD)_2$AQN-TMS-**114a**, MeOH : CH_2Cl_2 = 25:5 mL, stirred vigorously until complete dissolution (10 min). To the resulting solution was added 82.8 mg (0.599 mmol, 1.2 equiv.) K_2CO_3. Complete deprotection to single spot slightly more retained (R_f = 0.22) than starting on TLC was achieved in 64 h.
The solvents were removed on rotary evaporator, resulting crude was dissolved in 20 mL CH_2Cl_2 and treated with 20 mL H_2O, organic phase separated and aqueous phase was washed 3 × 10 mL CH_2Cl_2. Combined organic phases were washed with brine, dried over Na_2SO_4 and volatiles were removed on rotary evaporator followed by thorough drying under reduced pressure (0.5 mmHg), provided deprotected product **114b** in almost pure form by ^{1}H NMR (> 99% yield).

TLC, R_f = 0.22 (SiO_2, EtOAc : MeOH = 7:3 + 1 % Et_2NH)
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.62 (d, *J* = 4.4 Hz, 2H), 8.40 (s, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.18 – 7.88 (m, 3H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.59 – 7.27 (m, 6H), 7.00 (d, *J* = 8.6 Hz, 2H), 6.72 (s, 2H), 6.01 (s, 2H), 4.02 (t, *J* = 6.2 Hz, 2H), 3.90 (s, 6H), 3.31 – 3.08 (m, 2H), 2.99 – 2.72 (m, 6H), 2.73 – 2.58 (m, 2H), 2.47 (br s, 2H), 2.26 (td, *J* = 6.8, 2.4 Hz, 2H), 1.98 (t, *J* = 2.1 Hz, 1H), 1.96 – 1.83 (m, 2H), 1.82 – 1.64 (m, 4H), 1.65 – 1.29 (m, 12H), 0.81 (t, *J* = 7.1 Hz, 6H).

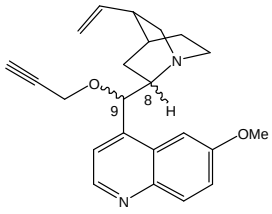
^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.1, 182.6, 159.7, 158.2, 151.3, 151.2, 147.6, 145.7, 144.72, 143.07, 143.03, 134.8, 132.5, 132.0, 131.5, 131.1, 128.4, 127.1, 126.6, 123.9, 123.7, 122.0, 120.7, 120.5, 119.3 (br), 101.0, 84.0, 79.9 (br), 68.8, 67.5, 60.5, 55.9, 51.0, 50.2, 37.8, 29.7, 28.3, 27.2, 26.6, 25.1, 24.6, 18.2, 12.16, 12.13.

MS(ESI$^+$) *m/z* = 514.7 [M+2H^{2+}], 719.3 [M–DHQD$^{\bullet+}$], 1029.7 [M+H$^+$].

$[\alpha]_D^{25}$ = -341.88 (c = 0.5, CH_2Cl_2).

7.2.4. Preparation of the clickable propargyl *Cinchona* alkaloid-derivatives (120a and 120b).

Preparation of clickable propargyl alkaloid (120a and 120b).



120a, OPQD = 8R, 9S
120b, OPQN = 8S, 9R

A 100 mL Schlenk tube, under N_2 atmosphere, were charged with 1.62 g (5 mmol) of QN/QD, dry DMF 30 mL and stirred at 0ºC until complete dissolution of solid (~ 20 min). To the cooled reaction mixture (0ºC) was added 0.48 g NaH (10 mmol, 50% in mineral oil). After cessation of H_2 evolution (2.5 h), 0.71 g (6 mmol) of propargyl bromide was added dropwise over a period of 30 min, while maintaining the temperature below 0°C, followed by stirring overnight at room temperature. Water (50 mL) was added to quench the reaction, followed by extraction with toluene (50 mL). The toluene layer was washed with brine (20 mL), concentrated, and in case of QD, crude was stirred with activated charcoal in toluene and filtered through G4 glass frit, rinse with small amount of toluene and concentrated on rotary evaporator, as crystallization attempt of crude **120a** (as reported) was failed, crude was passed through small pad of silica with (EtOAc:MeOH = 8:2 + 1% Et_2NH), providing product **120a** (propargyl quinidine) in essentially pure form (1.64g, 91% yield). In case of QN, crude was dissolved in minimum amount of boiling hexane, filtered to remove insoluble materials, resulting reaction mixture was treated with 2N HCL, organic phase was separated, aqueous phase was made basic ($NaHCO_3$) and extracted with 4 × 30 mL CH_2Cl_2, combined organic phases were dried over Na_2SO_4, filtered, concentrated on rotary evaporator followed by thorough drying under vacuum (0.5 mmHg), provided product **120b** (propargyl quinine) (1.8 g, quant. yield). Spectroscopic data for **120a** and **120b** (^{1}H NMR, ^{13}C NMR) were identical to those reported in literature.[119]

7.3. Experimental section for chapter-3

7.3.1. Preparation of azidomethyl Merrifield (122x) and ArgoPore™ (122y) resins

The conditions of Lober were adopted:[123] a Schlenk tube was charged with the resin **121a** or **121b** (9.2 mmol Cl), 2.99 g (46 mmol, 5 eq.) of NaN_3, and dry DMSO (40 mL). After briefly evacuating at 5 mmHg for degassing the solids, the resulting pale-yellow suspension (containing some undissolved NaN_3) was heated for 64 h at 60°C, under nitrogen and with slow magnetic stirring. The mixture was cooled to r.t., diluted with water (20 mL), and filtered through a medium porosity glass frit. The polymer residue was washed with water (2×20 mL), MeOH (4×20 mL), dry-THF (4×20mL) and dry-CH_2Cl_2 (4×20 mL). After drying to constant weight under vacuum (0.05 mmHg), the materials **121a** and **121b** were obtained as a white solid and a yellow light powder, respectively. The resins were characterized by IR as KBr disks (showing azide stretching at 2095 cm^{-1}) and by elemental analysis.

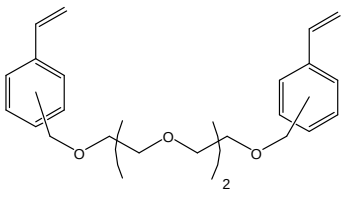
121a. 95% recovery yield; anal. found: C 81.02 ± 0.13, H 6.72 ± 0.13, N 9.27 ± 0.06. (2.20 ± 0.013 mmol N3 g^{-1}).

121b. 98% recovery yield; anal. found: C 86.09 ± 0.12, H 7.41 ± 0.13, N 3.77 ± 0.05. (0.90 ± 0.010 mmol N3 g^{-1}).

7.3.2 Synthesis of azidomethylstyrene and of oligo(ethylene oxide) polar monomers and cross-linker.

Preparation of the monomers:

7.3.2-a. Synthesis of 1,12-bis(4-vinylphenyl)-2,5,8,11-tetraoxadodecane (127)



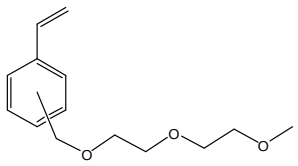
In a three-necked round bottom flask, 500 mL, equipped with dropping funnel 25 mL, under N_2 flow, were introduced 5.4 mL (6.1g, 40 mmol) triethyleneglycol **131**, 4.4 g (92 mmol, 50% w/w in mineral oil) of NaH, 0.15 mL of nitrobenzene in 80 mL of dry DMF.

The resulting suspension stirred at 0°C for 30 min, followed by 2.5 h at room temperature, through dropping funnel 13.2 mL (14.2g, 92 mmol) of chloromethylstyrene **130** was

introduced dropwise over a period of 5 min at 0ºC. The reaction mixture kept stirring at same temperature for 1h and room temperature for 44 h. After completion, as monitored by TLC analysis (SiO_2, CH_2Cl_2:*n*-hexane = 1:3), reaction was quenched by adding 20 mL of ice-cold water. The organic phase was separated and aqueous phase was extracted with 40 mL of CH_2Cl_2. The combined organic phases were washed with water and dried over Na_2SO_4, volatiles were removed on rotary evaporator, the oily crude obtained was purified by filtration through small pad of silica with (CH_2Cl_2 : *n*-hexane = 1:3, → AcOEt), obtaining 14:13 g (37 mmol) of product **127** (*meta*/*para* = 70/30 mixture) as amber oil (92% yield).

TLC R_f = 0.24 (SiO_2, CH_2Cl_2 : *n*-hexane = 1:3)
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25 (m, 8H), 6.65 (m, 2H), 5.71 (m, 2H), 5.19 (m, 2H), 4.47 (s, 4H), 3.57 (m, 12H).
^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.3, 137.7, 137.3, 136.5, 136.4, 136.2, 128.2, 127.5, 126.8, 125.9, 125.1, 113.6, 113.4, 72.7, 72.5, 70.3, 69.2, 69.1.

7.3.2-b. Synthesis of 1-((2-(2-methoxyethoxy)ethoxy)methyl)-4-vinylbenzene (128)

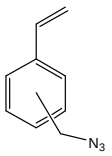


In a three-necked round bottom flask, 500 mL, equipped with dropping funnel 25 mL, under N_2, were introduced 4.7 mL (4.84 g, 40 mmol) of ethylene glycol)-methyl-ether **132**, 2.6 g (52 mmol, 50% w/w in mineral oil) of NaH, 0.15 mL of nitrobenzene in 80 mL of dry DMF. The resulting suspension stirred at 0°C for 30 min, followed by 2.5 h at room temperature, through dropping funnel 6.7 mL (46 mmol) of chloromethylstyrene **130** was introduced dropwise over a period of 5 min at 0ºC. The reaction mixture kept stirring at same temperature for 1h and room temperature for 88 h.After completion, as monitored by TLC analysis (SiO_2, $CHCl_3$), reaction was quenched by adding 20 mL of ice-cold water. The organic phase was separated and aqueous phase was extracted with 40 mL of CH_2Cl_2. The combined organic phases were washed with water and dried over Na_2SO_4, volatiles were removed on rotary evaporator, the oily crude obtained was purified by filtration through small pad of silica with (CH_2Cl_2:*n*-hexane = 1:2, → $CHCl_3$→ AcOEt), obtaining 9.11 g (38.5 mmol) of product **128** (*meta*/*para* = 70/30 mixture) as amber oil (96% yield).

TLC R_f = 0.26 (SiO_2, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33 (m, 4H), 6.70 (m, 2H), 5.78 (m, 1H), 5.25 (m, 1H), 4.55 (m, 1H), 3.65 (m,6H), 3.55 (d, *J* = 5.4 Hz, 1H), 3.54 (d, *J* = 6.6 Hz, 1H), 3.38 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.29, 137.64, 137.26, 136.50, 136.43, 136.22, 128.18, 127.53, 126.79, 125.83, 125.12, 125.08, 113.55, 113.30, 72.66, 72.50, 71.59, 70.30, 70.19, 69.13, 69.09, 58.58.

7.3.2-c. Synthesis of azidomethyl styrene (129)

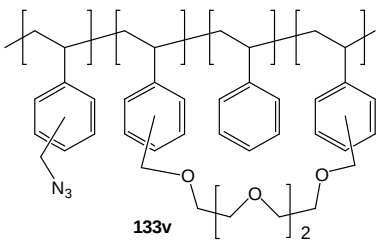


In a 250 mL round bottom flask, under N_2 flow, were introduced, 0.89 g (5.9 mmol) of sodium iodide and dissolved in 90 mL of (DMSO). To the resulting solution were added 7.4 mL (52 mmol) of chloromethylstyrene **130**, and 6.8 g (104 mmol) NaN_3. Reaction kept stirring at 80°C for 15 h. After completion, as monitored on TLC, the reaction was cooled to room temperature and quenched by adding 20 ml of water and organic components were extracted with 50 mL of Et_2O, the separated organic phase was dried over Na_2SO_4, filtered and volatiles were removed on rotary evaporator. After thorough drying the product **129** obtained as clear oil in almost pure form 7.63 g (47.9 mmol, 92 % yield). The product was used as such without further purification in subsequent steps.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 8.1, 2H), 7.25 (d, *J* = 8.1, 2H), 6.71 (dd, *J* = 10.7, 17.8, 1H), 5.75 (d, *J* =17.8, 1H), 5.25 (d, *J* = 10.7, 1H), 4.29 (s, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.3, 136.9, 135.4, 129.1, 127.3, 115.1, 55.2.

7.3.3 Preparation azido-functionalized polystyrene supports with oligo(ethylene oxide) cross linkers (133v and 133z).

7.3.3-a. Synthesis of polymer (133v)



133v

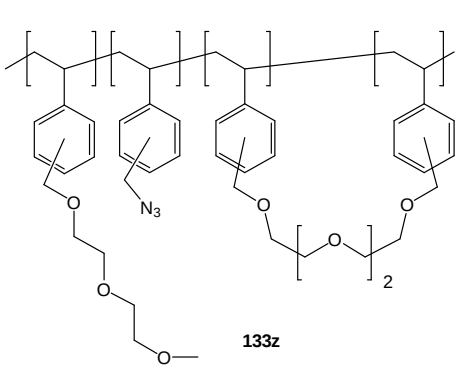
In a Schlenk tube, 200 mL, equipped with magnetic stirrer, was introduced 0.5 g of polyvinylalcohol (PVA) and dissolved in 120 mL of H_2O, the resulting reaction mixture was degassed by bubbling nitrogen at 80°C for 3 h, providing perfectly clear solution, which was allowed to return to room temperature. In another Schlenk tube, 100 mL, were introduced under N_2 flow, 0.30 g of AIBN, 5.53 g (14.5 mmol) of 1,12-bis(4-vinylphenyl)-2,5,8,11-

tetraoxadodecane **127** and dissolved in 10 mL of THF. To this mixture while stirring, were added a solution of 3.85 g (24.2 mmol) azidomethylstyrene **129** in 30 mL of chlorobenzene. Complete reaction mixture was degassed by Freeze-Pump-Thaw technique and kept under N_2.

The suspension polymerization apparatus was subjected to several vacuum-nitrogen cycles and while maintained it under N_2, the mixture of comonomers from the second Schlenk and 6.7 mL (58 mmol) of styrene were introduced and with the vigorous stirring, the aqueous solution of PVA was added slowly through the dropping funnel. After complete addition, the assembly was cooled to 0ºC and reaction mixture was stirred vigorously for 1 h, and heated to 80°C for 24 h. After cooling the polymerized material was filtered through a G2 glass frit and washed successively with H_2O at room temperature, 70°C H_2O, CH_3OH, THF and CH_2Cl_2, and dried under vacuum (0.1 mmHg). The polymer **133v** was obtained 14.7 g (95% yield) in the form of yellow beads.

IR: 2095 cm^{-1} stretching of azido group.

7.3.3-b. Synthesis of polymer (133z)



133z

In a Schlenk tube, 200 mL, equipped with magnetic stirrer, was introduced 0.52 g of polyvinylalcohol (PVA) and dissolved in 120 mL of H_2O, the resulting reaction mixture was degassed by bubbling nitrogen at 80°C for 3 h, providing perfectly clear solution, which was allowed to return to room temperature.

In another Schlenk tube, 100 mL, were introduced under N_2 flow, 0.31 g of AIBN, 3.82 g (10 mmol) of 1,12-bis(4-vinylphenyl)-2,5,8,11-tetraoxadodecane 127 and dissolved in 7 mL of dry THF. To this mixture while stirring, were added a solution of 4.78 g (30 mmol) azidomethylstyrene 129 and 7.1 g (30 mmol) of 1-((2-(2-methoxyethoxy)ethoxy)methyl)-4-vinylbenzene **128** in 35 mL of chlorobenzene. Complete reaction mixture was degassed by Freeze-Pump-Thaw technique and kept under N_2.

The suspension polymerization apparatus was subjected to several vacuum-nitrogen cycles and while maintained it under N_2, the mixture of comonomers from the first Schlenk was introduced and with the vigorous stirring, the aqueous solution of PVA was added

slowly through dropping funnel. After complete addition, the assembly was cooled to 0ºC and reaction mixture was stirred vigorously for 1 h and heated to 80°C for 24 h. After cooling, the polymerized material was filtered through a G2 glass frit and washed successively with H_2O at room temperature, 70°C H_2O, CH_3OH, THF and CH_2Cl_2, and dried under vacuum (0.1 mmHg). The polymer **133z** was obtained 15.2 g (97% yield) in the form of yellow beads.

IR: 2095 cm^{-1} stretching of azido group.

7.4.4. Preparation of polymeric monolith (134)

The polymerization mixtures containing 1 wt% initiator (AIBN), monomers (azidomethyl styrene **129**, styrene, and divinylbenzene) and porogenic solvents (toluene and dodecanol) with different compositions (Table 1) were purged with N_2 for 15 min in order to remove oxygen. The stainless steel column (HPLC) were sealed at one end, filled with the mixture under N_2, then sealed on the other end, and placed in a vertical position into a preheated oven or oil bath at temperature (60-80ºC). The polymerization was allowed to proceed for 24 h. The seals were removed, the tube was provided with fittings, attached to the high-pressure pump, and tried to remove the porogenic solvents and any other soluble compound remained in the polymer rod after polymerization, by passing THF. In most of the cases, very high backpressure and low permeability of solvent through polymer rod were noted.

7.4.5. Preparation of poly-HIPE

A dropping funnel equipped with stopcock sidearm (Figure 52) and overhead stirrer (fitted with a D-shaped PTFE paddle) was charged under N_2 with, 0.210 g (20 wt%) of AMST **129**, 0.840 g (80 wt%) of DVB and 0.205 g (25% of organic monomers) of sorbitan monooleate Span-80, and stirred at 300 rpm. The aqueous solution prepared separately by dissolving 0.256 g (0.95 mmol) of the initiator 'potassium persulfate'($K_2S_2O_8$) and 0.384 g (6.57 mmol) of NaCl in 25 mL of de-ionized water 25 mL was purged with N_2 for 10 min and added slowly in organic phase by syringe (10 min). After complete addition of the aqueous phase, the stirring continued at same speed for 1 h to produce homogeneous emulsion. The glass mold was closed under N_2 and kept in preheated oven at 60ºC for 2 d. After cooling, the column was washed with water several times followed by THF (200 mL) and CH_3CN.

IR: 2095 cm^{-1} stretching of azido group.

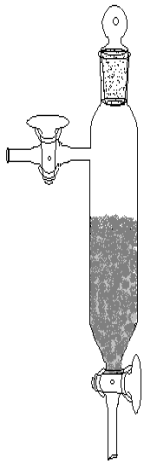


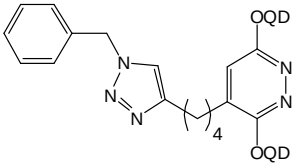
Figure 52: polyHIPE glass mold.

7.4. Experimental section for chapter-4

7.4.1 Preparation of pyridazine-core dimeric-*Cinchona* alkaloid soluble model compounds (155a,b,c).

General procedure: A Schlenk tube was charged under N_2 with (1.20 mmol) of crude **100a**, **100b** or **100c**, 0.33 g (2.4 mmol, 2 equiv.) of benzyl azide [256], 11.4 mg (0.06 mmol, 5 mol%) of CuI, 0.19 ml (1.20 mmol, 1 eq.) of DIPEA and (20 mL) of dried CH_2Cl_2. The resulting solution was kept stirring overnight at r.t and then treated with 30% ammonia solution (10 mL) to remove the copper salt. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic extracts were dried (Na_2SO_4) and then concentrated with rotary evaporator. The dark residue was purified by flash chromatography (SiO_2, AcOEt : MeOH = 7 : 3 + 1% Et_2NH), obtaining the products **155a**, **155b** and **155c** as solid foams.

4-(4-(1-Benzyl-1H-1,2,3-triazol-4-yl)butyl)-3,6-bis(9-O-quinidinyl) pyridazine (155a): 73% yield;

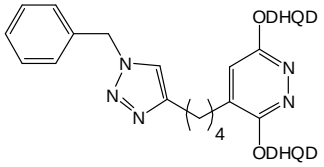


155a : $(QD)_2$PYZ-Tr

TLC R_f = 0.26 (SiO_2, AcOEt : MeOH = 7 : 3 + 0.5% Et_2NH);
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.66 (d, *J* = 4.2 Hz, 1H), 8.65 (d, *J* = 4.2 Hz, 1H), 7.98 (d, *J* = 9.3 Hz, 1H), 7.97 (d, *J* = 9.3 Hz, 1H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.43 (d, *J* = 2.3 Hz, 1H), 7.41-7.23 (m, 9H), 7.20 (s, 1H), 6.83-6.73 (m, 3H), 6.14-5.77 (m, 2H), 5.51 (s, 2H), 5.00-4.85 (m, 4H), 3.87 (s, 3H), 3.84 (s, 3H), 3.38-3.15 (m, 2H), 3.00-2.50 (m, 12H), 2.33-2.06 (m, 2H), 2.02-1.58 (m, 6H), 1.59-1.29 (m, 6H), 1.26-1.00 (m, 2H);
^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.1, 159.8, 157.8, 157.7, 148.1, 147.5, 145.2, 145.0, 144.8, 144.7, 140.6, 140.2, 135.97, 135.98, 131.6, 129.2, 128.8, 128.1, 127.6, 127.4, 121.9, 121.8, 120.7, 119.0, 118.6, 114.9, 114.7, 102.4, 102.0, 76.1, 60.6, 60.0, 55.8, 55.7, 54.1, 50.0, 49.8, 49.5, 40.0, 39.0, 29.3, 29.2, 28.1, 27.9, 27.4, 26.6, 26.5, 25.6, 24.2, 23.4;
MS (ESI$^+$) m/z = 938.8 [M+H$^+$]; $[\alpha]_D^{25}$ = -101 (c = 0.75, CH_2Cl_2).

[256] Antoni, P.; Hed, Y.; Nordberg, A.; Nystrom, D.; von, H., Hans; Hult, A.; Malkoch, M. *Angewandte Chemie, International Edition* **2009**, *48*, 2126-

4-(4-(1-Benzyl-1H-1,2,3-triazol-4-yl)butyl)-3,6-bis(10,11-dihydro-9-O-quinidinyl) pyridazine (155b): 66% yield;



155b : $(DHQD)_2PYZ$-Tr

TLC R_f = 0.24 (SiO_2, AcOEt : MeOH = 7 : 3 + 0.5% Et_2NH);

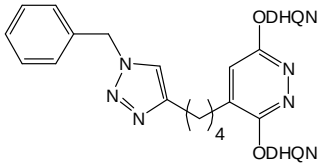
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.65 (d, *J* = 4.5 Hz, 1H), 8.64 (d, *J* = 4.5 Hz, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.49 (d, *J* = 2.6 Hz, 1H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.39-7.22 (m, 9H), 7.19 (s, 1H), 6.84-6.69 (m, 3H), 5.49 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.41-3.19 (m, 2H), 2.95-2.50 (m, 12H), 1.95-1.61 (m, 7H), 1.61-1.26 (m, 13H), 0.86-0.72 (m, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.1, 159.9, 157.9, 157.7, 148.2, 147.6, 145.2, 144.9, 144.8, 136.0, 135.1, 131.7, 129.3, 128.9, 128.2, 127.7, 127.5, 122.1, 121.9, 120.8, 118.9, 118.8, 102.48, 102.07, 89.4, 76.2, 75.7, 66.1, 60.4, 60.2, 56.0, 55.9, 54.3, 51.0, 50.2, 50.1, 37.6, 37.4, 29.36, 29.32, 27.4, 27.3, 26.4, 26.2, 25.7, 25.5, 24.2, 23.2, 15.5, 12.2, 12.1.

MS (ESI$^+$) m/z = 943.2 [M+H$^+$];

$[\alpha]_D^{25}$ = -88.1 (c = 1.0, CH_2Cl_2).

4-(4-(1-Benzyl-1H-1,2,3-triazol-4-yl)butyl)-3,6-bis(10,11-dihydro-9-O-quininyl) pyridazine (155c): (crude sample) 74% yield;



155c : $(DHQN)_2PYZ$-Tr

TLC R_f = 0.37 (SiO_2, AcOEt : MeOH = 7 : 3 + 1% Et_2NH);

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.65 (m, 2H), 7.96 (d, *J* = 9.2 Hz, 2H), 7.50 (m, 2H), 7.42 – 7.28 (m, 6H), 7.28 – 7.20 (m, 2H), 7.18 (s, 1H), 6.86 – 6.64 (m, 3H), 5.48 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.48 – 3.21 (m, 2H), 3.14 – 2.86 (m, 4H), 2.81 – 2.69 (m, 2H), 2.69 – 2.58 (m, 2H), 2.57 – 2.41 (m, 2H), 2.36 – 2.19 (m, 2H), 1.88 – 1.47 (m, 12H), 1.46 – 1.19 (m, 9H), 0.79 (t, *J* = 7.0 Hz, 6H).

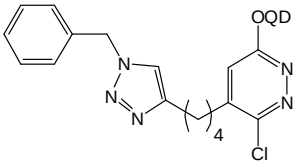
^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.2, 159.8, 157.7, 157.7, 148.0, 147.4, 145.0, 144.9, 144.8, 144.8, 136.0, 134.9, 131.5, 129.1, 128.7, 128.0, 127.4, 121.8, 121.7, 120.6, 119.0, 118.9, 118.7, 102.3, 102.2, 76.3, 60.0, 58.5, 58.4, 55.8, 55.7, 54.1, 42.8, 42.7, 37.6, 29.2, 29.1, 28.6, 28.5, 27.8, 27.7, 27.4, 25.5, 25.5, 24.1, 23.8, 12.1.

MS (ESI$^+$) *m/z* = 943.3 [M+H$^+$], 471.8 [M+2H$^+$]

$[\alpha]_D^{27}$ = +123.82 (c = 0.5, CH_2Cl_2)

7.4.2. Preparation of the pyridazine-core monomeric-*Cinchona* alkaloid soluble model compound (154).

4-(4-(1-benzyl-1H-1,2,3-triazol-4-yl)butyl)-6-chloro-3-(9-O-quinidinyl)pyridazine (154)



154 : (QD)PYZ-Tr

A 25-ml Schlenk tube was charged under dry nitrogen with 1.00 g of the crude mixture of **100a** and **101** (~1.1 and 0.23 mmol, respectively), 0.33 g (2.4 mmol) benzyl azide, 0.0013 g (13 μmol, ~1 mol %) of CuCl, 0.0048 g (13 μmol, 1 mol %) of (R)-Mono-Phos and THF (11 ml). After stirring overnight at r.t., the solution was concentrated with a rotary evaporator and the dark residue (1.123 g) directly subjected to *flash*-chromatography (SiO_2, AcOEt : MeOH = 8 : 2 + 0.5% Et_2NH) to give **155a** (0.112 g, ~75%) and **154** (0.556 g, ~54%) as colorless solid foams. The chromatographic and spectral properties of **155a** were identical to the previously reported ones. (See, **6.4.1**)

For **154**: **TLC** R_f = 0.53 (SiO_2, AcOEt : MeOH = 8 : 2 + 0.5% Et_2NH).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.65 (d, *J* = 4.50 Hz, 1H); 7.97 (d, *J* = 9.21 Hz, 1H) ; 7.52 (d, *J* = 2.44 Hz, 1H); 7.40–7.29 (m, 5H); 7.27–7.17 (m, 2H); 7.13–7.04 (m, 1H); 6.89 (s, 1H); 6.05 (ddd, J_a = 17.32, J_b = 10.45, J_c = 7.24 Hz, 1H); 5.46 (s, 2H); 5.14–5.03 (m, 2H); 3.95 (s, 3H); 3.51–3.32 (m, 1H); 3.11–2.78 (m, 4H); 2.78–2.67 (m, 3H); 2.63 (t, *J* = 7.38 Hz, 1H) 2.63 (m, 1H); 2.28 (q, $J_{a=b}$ = 7.66 Hz, J_c = 7.48 Hz, 1H); 2.03 (dd, J_a = 12.52 Hz, J_b = 9.43 Hz, 1H); 1.89–1.79 (m, 1H), 1.79–1.62 (m, 4H), 1.62–1.52 (m, 3H); 1.35–1.15 (m, 1H).

^{13}C NMR (75 MHz,$CDCl_3$) δ = 163.8, 157.9, 152.5, 147.8, 147.3, 144.6, 144.4, 143.8, 140.3,

134.8, 131.6, 129.0, 128.6, 127.9, 127.2, 121.9, 120.7, 118.3, 114.9, 101.6, 77.5, 77.1, 76.7, 59.7, 55.7, 54.0, 49.9, 49.4, 39.7, 32.2, 28.9, 27.9, 27.3, 26.4, 25.2, 23.4, 23.4.

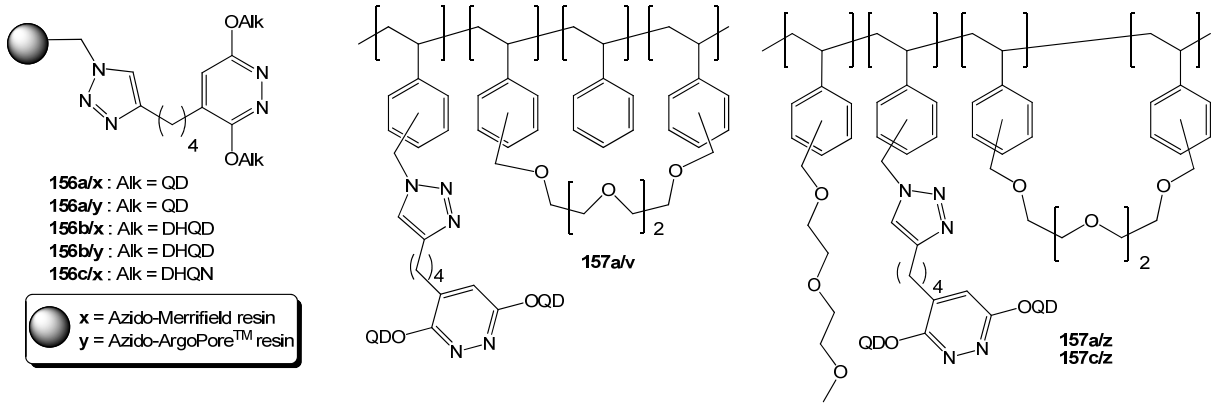
MS (ESI$^+$) *m/z* = 651.3 [M+H$^+$].

$[\alpha]_D^{25}$ = -77.6 (c = 0.75, CH_2Cl_2).

7.4.3. Preparation of IPB pyridazine-core *Cinchona* alkaloid derivatives (156a/x, 156a/y, 156b/x, 156b/y, 156c/x, 157a/v, 157a/z, 157c/z).

General Procedure: A Schlenk tube was charged with the resin **122x, 122y, 133v or 133z** (2 equiv. of N_3). After evacuation at 5 mmHg for 5 min, for degassing the solids, freshly distilled CH_2Cl_2 was added under nitrogen, followed by a solution of crude **100a** or **100b** or **100c** (*C* = 0.5M, 1 equiv.) and CuI (5 mol%) and DIPEA (1 equiv.) in CH_2Cl_2. The Schlenk tube was closed under nitrogen and kept on an orbital shaking platform or at slow stirring for two-five days at room temperature. The mixture was filtered under air through a medium porosity glass frit and washed several times with portions of CH_2Cl_2, 30% ammonia-THF, methanol, THF, and CH_2Cl_2. After drying to constant weight under vacuum (0.05 mmHg), the pale yellow resin was characterized by IR and the alkaloid loading was determined by the mass difference between the recovered material (**156a**/**x**, **156a**/**y**, **156b**/**x**, **156b**/**y**, **156c**/**x**, **157a**/**v**, **157a**/**z**, **157c**/**z**) and the starting azidomethyl resins (see Table 12).

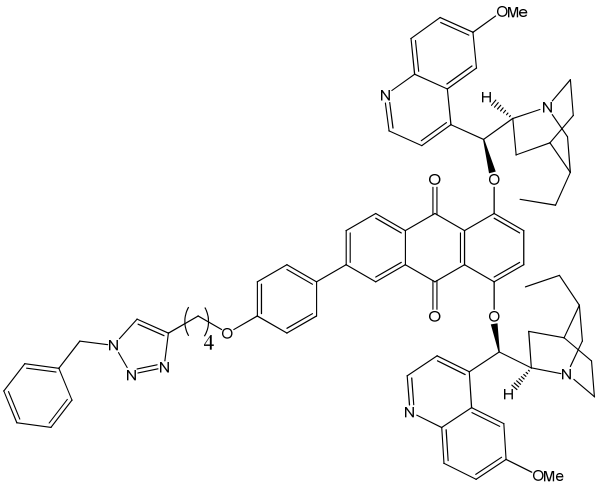
Table 12: Preparation of immobilized pyridazine-core *Cinchona* alkaloids on to the resins.



Alkyne-alkaloid	Azido-resins	Functionalized polymer	Alkaloid loading [mmol·g^{-1}]	Anchoring yield [%]
100a	**122x**	**156a/x**	0.41 – 0.70	87
100a	**122y**	**156a/y**	0.26	47
100b	**122x**	**156b/x**	0.54	87
100b	**122y**	**156b/y**	0.22	39
100c	**122x**	**156c/x**	0.25	27
100a	**133v**	**157a/v**	0.41	80
100a	**133z**	**157a/z**	0.50	81
100c	**133z**	**157c/z**	0.23	80

7.4.4. Preparation of the anthraquinone-core *Cinchona* alkaloid soluble model compound (158b).

Preparation of 1,4-bis(10,11-dihydro-9-O-quinidinyl)-6-(4-(4-(1-benzyl-1H-1,2,3-triazol-4-yl)butoxy)phenyl)anthracene-9,10-dione (158b)



A Schlenk tube was charged under N_2 with 1.38 mg (0.0073 mmol, 5 mol%) of CuI, 0.15 g (0.146 mmol) of crude **114b**, after degassing were added dried CH_2Cl_2 (2 mL), 25.5 μL (0.146 mmol, 1 equiv.) DIPEA and stirred for 15 min at rt. To the resulting brownish-yellow reaction mixture was added 0.039 g (0.292 mmol, 2 equiv.) of benzyl azide and second portion of dried CH_2Cl_2 (3 mL). The resulting solution was kept stirring overnight at r.t and then treated with 30% ammonia solution (10 mL) to remove the copper salt. The two phases were separated and the aqueous layer was extracted with CH2Cl2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and then concentrated with rotary evaporator. The dark residue was purified by flash chromatography (SiO_2, CH_2Cl_2 : MeOH = 10 : 1 + 0.5% Et_2NH), obtaining the product **158b** (0.136 g, 81% yield) as yellow solid.

TLC R_f = 0.40 (SiO_2, CH_2Cl_2 : MeOH = 9 : 1 + 0.5% Et_2NH)

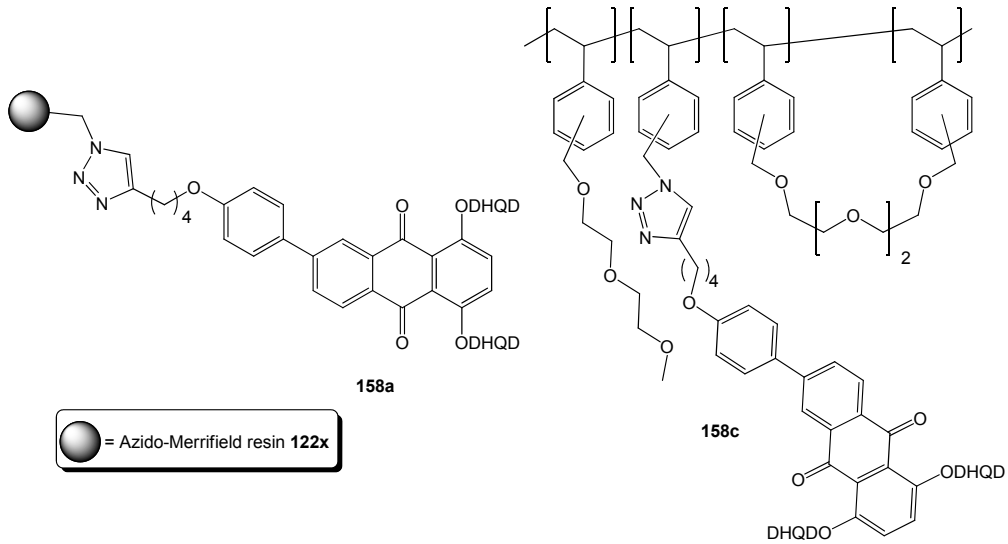
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.65 (d, *J* = 4.4 Hz, 2H), 8.41 (d, *J* = 1.6 Hz, 1H), 8.26 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 9.3 Hz, 2H), 7.97 (dd, J_a = 8.2, J_b = 1.8 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 4.5 Hz, 2H), 7.46 – 7.33 (m, 7H), 7.29 – 7.21 (m, 4H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.68 (s, 2H), 5.94 (br. s, 2H), 5.50 (s, 2H), 4.06 (t, *J* = 5.3 Hz, 2H), 3.92 (s, 6H), 3.33 – 3.16 (m, 2H), 2.93 – 2.61 (m, 10H), 2.44 (s, 2H), 1.97 – 1.83 (m, 3H), 1.78 (s, 2H), 1.67 – 1.34 (m, 12H), 0.83 (td, J_a = 7.2, J_b = 2.1 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ =183.2, 182.7, 159.8, 158.2, 151.3, 148.4, 147.8, 145.8, 144.8, 143.2, 135.0, 134.9, 132.5, 132.2, 132.2, 131.6, 131.2, 129.2, 128.7, 128.5, 128.5, 128.1, 127.2, 126.7, 126.7, 124.0, 123.8, 122.1, 120.7, 120.5, 119.4, 115.2, 101.0, 80.2, 70.7, 67.8, 60.6, 60.6, 55.9, 54.1, 51.2, 50.3, 37.9, 29.8, 28.9, 27.3, 26.7, 26.7, 26.1, 25.5, 24.7, 12.2, 12.2.

MS (ESI$^+$) *m/z* = 581.6 [M+2H^{2+}], 852.5 [M - DHQD$^{\bullet+}$], 1161.8 [M+H$^+$]

$[\alpha]_D^{27}$ = -371.43 (c = 0.51, CH_2Cl_2)

7.4.5. Preparation of IPB anthraquinone-core *Cinchona* alkaloid derivatives (158a, 158c).

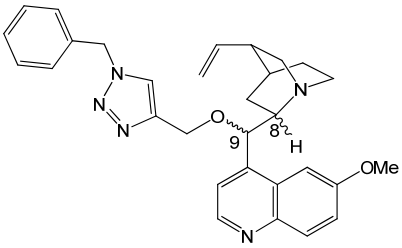


Schlenk tube was charged with the 0.242 g (0.437 mmol, 1.5 equiv. of N_3) of resin **122x**. After evacuation at 5 mmHg for 5 min, for degassing the solids, freshly distilled CH_2Cl_2 (3 mL) was added under nitrogen, followed by brownish-yellow reaction mixture of crude **100b** 0.3 g (0.291 mmol, 1 equiv.) and 2.8 mg (0.0145mmol, 5 mol%) of CuI and 54 μL (0.291 mmol, 1 equiv.) of DIPEA in dried-CH_2Cl_2 (4 mL). The Schlenk tube was closed under nitrogen and kept stirring (slow) for five days at room temperature. The mixture was filtered under air through a medium porosity glass frit and washed several times with portions of CH_2Cl_2, 30% ammonia-THF, methanol, THF, and CH_2Cl_2. After drying to constant weight under vacuum (0.05 mmHg), the yellow resin was characterized by IR and the alkaloid loading was determined by the mass difference between the recovered material (**158a**) and starting azido-Merrifield resin **122x** (17 % anchoring yield, 0.18 mmol.g^{-1} loading of alkaloid).

Material **158c** was prepared by same procedure described above apart from varied molar ratios between azido-resin **133z** 0.145 g (0.29 mmol, 3 equiv.) and alkaloid derivative **100b** 0.1 g (0.097 mmol, 1equiv.). The material **158c** was isolated as described above (44% anchoring yield, 0.22 mmol.g^{-1} loading of alkaloid **100b**).

7.4.6. Preparation of propargyl *Cinchona* alkaloid soluble model derivatives (160a and 160b)

Preparation of 1-benzyl-4-(quinidinyl/quininyl)-1H-1,2,3-triazole (160a/160b)



160a: (QD)P-Tr (8R, 9S)
160b: (QN)P-Tr (8S, 9R)

(QD)P-Tr (160a): A Schlenk tube was charged under N_2 with 13.2 mg (6.9 μmol, 5 mol%) of CuI, 0.5 g (1.38 mmol) of **120a** ((QD)P), after degassing were added dried CH_2Cl_2 (5 mL), 0.24 mL (1.38 mmol, 1 equiv.) of DIPEA and stirred for 15 min at rt. To the resulting brownish solution were added 0.367 g (2.76 mmol, 2 equiv.) of benzyl azide and second portion of dried CH_2Cl_2 (15 mL). The resulting solution was kept stirring for 22 h at r.t and then treated with 30% ammonia solution (25 mL) to remove the copper salt. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic extracts were dried (Na_2SO_4) and then concentrated with rotary evaporator. The dark residue was purified by flash chromatography (SiO_2, EtOAc : MeOH = 7 : 3 + 1% Et_2NH), obtaining the product **160a** (0.389 g, 78 % yield) as a colorless solid.

TLC R_f = 0.29 (SiO_2, EtOAc : MeOH = 8 : 2 + 1 % Et_2NH)

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.74 (d, *J* = 4.5 Hz, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.53 – 7.41 (m, 2H), 7.41 – 7.30 (m, 5H), 7.29 – 7.19 (m, 2H), 5.90 (ddd, J_a = 17.5, J_b = 10.3, J_c = 7.5 Hz, 1H), 5.51 (s, 2H), 5.31 (d, *J* = 3.1 Hz, 1H), 5.05 – 4.82 (m, 2H), 4.56 (dd, J_a = 25.6, J_b = 12.0 Hz, 2H), 3.91 (s, 3H), 3.17 (m, 1H), 3.04 (m, 1H), 2.94 – 2.60 (m, 4H), 2.19 (dd, J_a = 16.9, J_b = 8.1 Hz, 1H), 1.96 (br. dd, *J* = 13.2, 9.0 Hz, 1H), 1.71 (br. s, 1H), 1.59 – 1.35 (m, 2H), 1.34 – 1.09 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.8, 147.7, 145.3, 144.7, 144.3, 140.7, 134.6, 131.9, 129.2, 128.8, 128.0, 127.4, 122.5, 121.8, 119.0, 114.4, 101.2, 81.1, 63.0, 59.9, 55.7, 54.2, 50.2, 49.5, 40.0, 28.1, 26.5, 22.0.

MS (ESI$^+$) *m/z* = 496.3 [M+H$^+$].

$[\alpha]_D^{25}$ = 128.2 (c = 1.015, CH_2Cl_2)

(QN)P-Tr (160b): The soluble model derivative **160b** was prepared by same procedure reported above for **160a**, with an exception of running reaction on reduced scale (1.1 mmol of (QN)P (**120b)** and the loading of other components corresponding to **120b**).

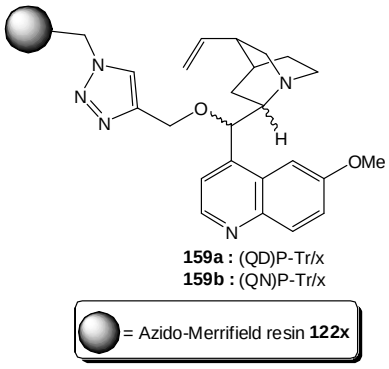
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.73 (d, *J* = 4.4 Hz, 1H), 8.03 (d, *J* = 9.7 Hz, 1H), 7.45 (d, *J* = 4.3 Hz, 1H), 7.41 – 7.30 (m, 6H), 7.28 – 7.17 (m, 2H), 5.70 (ddd, J_a = 17.6, J_b = 10.0, J_c = 7.8 Hz, 1H), 5.51 (s, 2H), 5.29 (s, 1H), 4.92 (dd, J_a = 13.2, J_b = 9.4 Hz, 2H), 4.53 (dd, J_a = 31.2, J_b = 12.1 Hz, 2H), 3.92 (s, 3H), 3.42 – 3.22 (m, 1H), 3.22 – 2.94 (m, 2H), 2.73 – 2.49 (m, 2H), 2.26 (br. s, 1H), 1.76 (s, 1H), 1.72 – 1.54 (m, 3H), 1.54 – 1.34 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.9, 147.6, 144.9, 144.7, 144.1, 141.5, 134.6, 131.9, 129.1, 128.8, 128.1, 127.4, 122.7, 121.9, 119.3, 114.5, 101.4, 80.4, 62.6, 60.2, 56.9, 56.1, 54.2, 43.1, 39.7, 27.7, 27.5, 22.8.

MS (ESI$^+$) *m/z* = 496.9 [M+H$^+$].

$[\alpha]_D^{27}$ = - 53.4 (c = 1.02, CH_2Cl_2)

7.4.7. Preparation of IPB propargyl *Cinchona* alkaloid derivatives (159a and 159b)



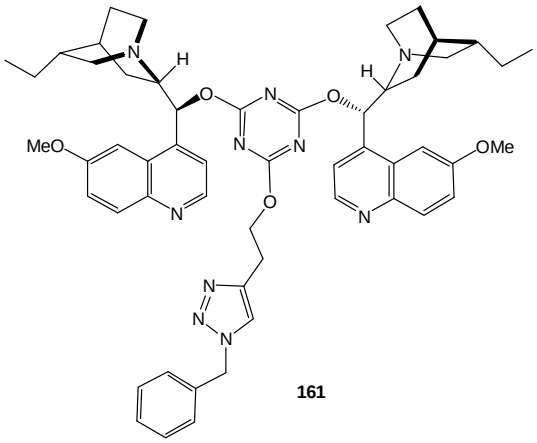
(QD)P-Tr/x (159a): Schlenk tube was charged with the 0.5 g (1.1 mmol, 2 equiv. of N_3) of resin **122x**. After evacuation at 5 mmHg for 5 min, for degassing the solids, freshly distilled CH_2Cl_2 (5 mL) was added under nitrogen, followed by brownish solution of propargyl alkaloid (**120a** or **120b**) 0.2 g (0.55 mmol), 5.3 mg (2.3 μmol, 5 mol%) of CuI and 95 μL (0.55 mmol, 1 equiv.) of DIPEA in dried-CH_2Cl_2 (5 mL). The Schlenk tube was closed under nitrogen and kept stirring (slow) for four days at room temperature. The mixture was filtered under air through a medium porosity glass frit and washed several times with portions of CH_2Cl_2, 30% ammonia-THF, methanol, THF, and CH_2Cl_2. After drying to constant weight under vacuum (0.05 mmHg), the yellow resin was characterized by IR and the alkaloid loading was determined by the mass difference between the recovered material (**159a)** and starting azido-Merrifield resin (**122x)**. The pale-yellow functionalized resin (**159a**) was recovered with 97 % anchoring yield and 0.77 mmol.g^{-1} loading of alkaloid).

(QN)P-Tr/x (159b): The IPB catalyst **159b** was prepared using the above reported procedure for **159a**, with an exception of running reaction on comparatively large-scale (1.52 mmol of (QN)P (**120b**) and loading of other components corresponding to **120b**). The

pale-yellow functionalized resin (**159b**) was recovered with 64% anchoring yield and 0.69 mmol.g^{-1} loading of alkaloid).

7.4.8. Preparation of the 1,3,5-triazine-core *Cinchona* alkaloid soluble model derivative (161).

Preparation of 2,4-bis(10,11-dihydro-9-O-quinidinyl)-6-(2-(1-benzyl-1H-1,2,3-triazol-4-yl)ethoxy)-1,3,5-triazine (161)



161

A Schlenk tube was charged under N_2 with 2 mg (10 μmol, ~5 mol%) of CuI, 0.1352 g (0.17 mmol) of **106b**, after degassing were added dried CH_2Cl_2 (2 mL), followed by 27 μL (0.16 mmol, ~1 eq.) of DIPEA and 50 μL (0.34 mmol, 2 equiv.) of benzyl azide. The resulting yellow solution was kept stirring for 20 h at rt. After complete conversion of **106b** as confirmed by TLC, the reaction mixture was directly loaded on silica column and the crude was purified by *flash*-chromatography (SiO_2, CH_2Cl_2, then CH_2Cl_2:CH_3OH = 8:2 → 7:3 + 0,5% Et_2NH) obtaining 0.1125 g (71,1%) of product (**161)** as a colorless solid foam which provided single spot on TLC.

TLC R_f = 0.55 (SiO_2, CH_2Cl_2: CH_3OH = 7:3 + 0.5% Et_2NH).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.63 (d, *J* = 4.2 Hz, 2H), 7.94 (t, *J* = 9.2 Hz, 2H), 7.40 (br. d, *J* = 2.4 Hz, 2H), 7.10-7.36 (m, 9H), 6.99 (s, 1H), 6.57 (br. s, 2H), 5.39 (s, 2H), 4.20-4.35 (m, 1H), 3.87-4.02 (m, 1H), 3.85 (s, 6H), 3.15-3.35 (m, 2H), 2.50-2.95 (m, 10H), 1.65-1.90 (m, 4H), 1.30-1.60 (m, 12H), 0.85 (t, *J* = 7, 0 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.6, 172.5, 157.8, 147.5, 144.5, 143.8, 134.8, 131.7, 129.0, 128.7, 128.6, 127.9, 127.3, 126.9, 121.7, 121.7, 118.7, 101.6, 78.1, 66.9, 59.7, 55.6, 53.9, 50.9, 50.1, 37.4, 27.2, 25.8, 25.3, 23.3, 12.1.

MS (ESI$^+$) *m/z*: 466.9 [M+2H^{2+}], 931.8 [M+H$^+$], 954.0 [M+Na$^+$].

$[\alpha]_D^{27}$ = - 62.8 (c = 1.0, CH_2Cl_2).

7.5. Experimental section for chapter-5

7.5.1. Catalytic asymmetric dimerization of ketenes.

7.5.1-a. Homogeneous catalytic asymmetric dimerization of ketene.

General procedure: To any of the soluble model-alkaloid derivatives **155a-c**, **161** (0.025 mmol) or **154**, **160a**,**b** (0.05 mmol) in anhydrous CH_2Cl_2 (10 mL) under nitrogen was added DIPEA (1.0 mmol), followed by the appropriate acid chloride **166** (5.0 mmol). After stirring for time t_1 at room temperature, 37 μL (0.50 mmol) of HN(OMe)Me and 0.0047 g (0.05 mmol) of 2-hydroxypyridine were added to the reaction mixture. The mixture was then stirred for time t_2 at room temperature, after which pH 7 buffer solution concentrate (5 mL) was added. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated on rotary evaporator, and the residue was purified by filtration through small pad of silica (EtOAc/hexanes, 2:1). The evaluation of enantiomeric composition of the isolated products **170** (R = Me) and **170** (R = Et) were carried out according to the Calter's conditions.[177b] A direct enantiomer separation method by chiral HPLC could be developed also for the compound **170** (R = i-Pr): [220 nm, Phenomenex Lux Cellulose-2 column, 0.5 mL min^{-1} of *n*-hexane : 2-propanol = 99 : 1, (R)-enantiomer = 32.1 min, (S)-enantiomer = 35.2 min].

7.5.1-b. Heterogeneous catalytic asymmetric dimerization of ketenes.

General Procedure: A Schlenk tube fitted with a medium porosity glass frit and stopcock side arm (Figure 53), was charged under nitrogen with IPB-catalyst (**156a/x-y**, **156b/x-y** or **156c/x**: 0.025 mmol supported bis-alkaloid derivative, 2.5 mol%) or (**159a-b/x**: 0.05 mmol supported mono-alkaloid derivative, 5 mol%) and dry CH_2Cl_2 (10 mL), followed by 170 μL (1.0 mmol) of DIPEA and acid chloride (distilled prior to use) **166** (1.0 mmol). The Schlenk was closed under nitrogen and kept on an orbital shaking platform, at room temperature, for the time t_1 (Table 6). Then the mixture was filtered through the enclosed frit, collecting the filtrate and CH_2Cl_2 rinses (2 × 2.5 mL) into a dry Schlenk tube. The combined filtrates were treated under nitrogen with 37 μL (0.50 mmol) of HN(OMe)Me and 0.0047 g (0.05 mmol) of 2-hydroxypyridine and the resulting solution was stirred at room temperature for the time t_2 (Table 6). For *ee* determination, a sample of the reaction mixture (0.20 mL) was passed through small pad of silica gel with *n*-hexane:AcOEt = 2:1 (3 × 1 mL), evaporated with a

nitrogen flow and dissolved in 2-propanol for HPLC analysis. The remaining part of the solution was worked-up as described above,[177b] purifying the product **170** by filtration through silica gel. After brief drying under vacuum (5 mmHg), the frit-retained polymeric material was returned into the flask and directly used in further catalysis cycles.

Figure 53. Schlenk tube used for heterogeneous asymmetric transformations.

7.5.1-c Catalytic activity control experiments.

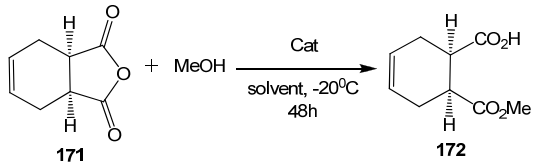
To confirm the heterogeneous nature of the catalysis, two sets of filtration experiments were carried out:

Heterogeneity test-I: A 50 mL flask fitted with a medium porosity glass frit and stopcock side arm, was charged under nitrogen with **156a-b/x** or **156a-b/y** (0.025 mmol supported alkaloid derivative, 2.5 mol%) and dry CH_2Cl_2 (10 mL), sealed under nitrogen and kept for 1 day, at room temperature, on an orbital shaking platform. Then the mixture was filtered under nitrogen through the enclosed frit, collecting the filtrate into a dry Schlenk tube where it was treated with 166 (R = Me) (87 μL, 1 mmol) and DIPEA (170 μL, 1 mmol). After stirring for 6 h at room temperature, NH(OMe)Me (37 μL, 0.50 mmol) and 2-hydroxypyridine (0.0047g, 0.05 mmol) were added and the resulting solution was stirred for 2 h at room temperature. The isolation of 170 (R = Me) and the ee determination were performed as described above, obtaining the product in low yields (0.017-0.027 g , 20-31%) and enantiomeric purity (< 1% ee). If magnetic stirring was employed in the first stage, a larger enantioselectivity was observed in the filtrate (57% ee).

Heterogeneity test-II: A 25 mL Schlenk tube fitted with a medium porosity glass frit and stopcock side arm, was charged under nitrogen with **156a-b/x** or **156a-b/y** (0.025 mmol

supported alkaloid derivative, 2.5 mol%), dry CH_2Cl_2 (10 mL), 166 (R = Me) (87 μL, 1 mmol), and DIPEA (170 μL, 1 mmol). The tube was sealed under nitrogen and kept for 1 h at room temperature, on an orbital shaking platform. Then the mixture was filtered under nitrogen through the enclosed frit, collecting the filtrate into a dry Schlenk tube where it was stirred for further 5 h at room temperature. After addition of NH(OMe)Me (37 μL, 0.50 mmol) and 2-hydroxypyridine (0.0047g, 0.05 mmol), the resulting solution was stirred for 2 h at room temperature. The isolation of **170** (R = Me) and the ee determination were performed as described above, obtaining the product with 91-98% ee, but in much reduced yield (0.017-0.020 g, 20-23%) in comparison with regular heterogeneous catalysis runs. (Table 6).

7.5.2. Asymmetric methanolysis of cis-1,2,3,6-tetrahydrophthalic anhydride.



7.5.2-a. Homogeneous catalytic asymmetric methanolysis of cis-1,2,3,6-tetrahydrophthalic anhydride.

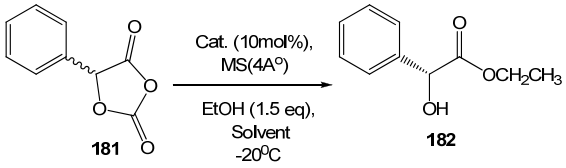
General procedure: A 25-ml Schlenk tube was charged under nitrogen with the soluble alkaloid catalyst **8**, **154**, **155a**, **160**, or **161** (for the exact amounts see Table 7) and 0.0761 g (0.50 mmol) of **171**. After cooling to -20ºC, the dry solvent (10 ml) was added and the mixture was kept stirring for 15 min, whereupon the complete dissolution of the solids was generally observed. 202 μL (5 mmol, and 10 equiv.) of dry MeOH was added and the resulting solution was stirred at the same temperature for 48 h. The reaction was quenched by adding 2N HCl (4 ml) and, after separation of the layers, the organic one was washed with a second portion of 2N HCl (4 ml). The aqueous washings were back-extracted with AcOEt (2 × 5 ml) and the combined organic phases dried (Na_2SO_4). The volatiles were removed with a rotary evaporator, and the reaction conversion was determined by ^{1}H NMR of the residue. The crude product was then purified by flash chromatography (SiO_2, petrolium ether:AcOEt = 3:1 + 0.5% trifluoroacetic acid) to give product (+)-(1R; 2S)-**172** as a viscous oil that solidified on standing. The absolute configuration of the product was confirmed by comparing its optical rotatory power with the literature value.[187] After

dissolution in *iso*-propyl alcohol (IPA, 0.1 ml), the enantiomeric composition of the sample was determined by HPLC analysis [210 nm, Daicel Chiralcel OJ, 1 ml min^{-1}, (*n*-hexane:IPA = 95:5+0.1% trifluoroacetic acid): t_R[(1*R*; 2*S*)-**172**] = 10.7 min; t_R[(1*S*; 2*R*)-**172**] = 16.2 min.]

7.5.2-b. Heterogeneous catalytic asymmetric methanolysis of cis-1,2,3,6-tetrahydrophthalic anhydride.

General procedure: A Schlenk tube fitted with a medium porosity glass frit and stopcock side arm (Figure 53), was charged with 0.149 g (0.033 mmol, 0.2 equiv.) of IPB-catalyst (**158c**) and 0.025 g (0.164 mmol) of anhydride **171**, after evacuation, at 5 mmHg for degassing the solids, dry toluene (5 mL) was added under nitrogen and kept stirring at slow speed until complete dissolution of **171** (10 min). The Schlenk tube was cooled to -20ºC and then added in one portion 33 μL (0.821 mmol, 5 equiv.) of dry MeOH followed by second portion of toluene (1.6 mL) from the walls, the Schlenk tube was closed under nitrogen and kept stirring at slow speed at same temperature for 48 h. Then the mixture was filtered through the enclosed frit in a conical flask containing water and the catalyst washed by CH_2Cl_2 (3 × 5 mL). Organic phase was removed and aqueous phase was washed with CH_2Cl_2 (2 × 5 mL) and combined organic phases dried (Na_2SO_4). The volatiles were removed with a rotary evaporator, the reaction conversion was determined by ^{1}H NMR of the residue. The crude product was then purified by *flash* chromatography (SiO_2, petrolium ether: AcOEt = 3:1 + 0.5% trifluoroacetic acid) to give product (+)-(1R; 2S)-**172** as a viscous oil that solidified on standing. Enantiomeric composition of the product was evaluated as described before. After drying under vacuum (5 mmHg), the frit-retained IPB-catalyst was returned into the flask and directly used in further catalysis cycles.

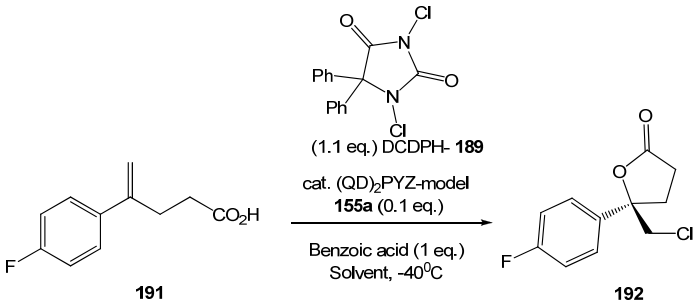
7.5.3. General procedure for soluble model-*Cinchona* alkaloid-catalyzed dynamic kinetic resolution of 5-phenyl-1,3-dioxolane-2,4-dione.



In a Schlenk tube a mixture of 0.089 g (0.5 mmol) of 5-phenyl-1,3-dioxolane-2,4-diones (**181**) and 4 Å molecular sieves (50 mg) in anhydrous solvent (Table 8) (25 mL) was stirred at room temperature for 15 minutes, then cooled to -20ºC, after which the soluble

model-*Cinchona* alkaloid derivatives **8, 155a** or **160** (0.05 mmol, 0.1 equiv.) was added to the mixture. The resulting mixture was stirred for another 5 minutes and then 44 μL (0.75 mmol, 1.5 equiv.) of ethanol was added in one portion. The resulting reaction mixture was stirred at same temperature for time given in Table 8. Reaction was quenched by adding HCl (2N, 5.0 mL) dropwise. The resulting mixture was allowed to warm to room temperature. The organic phase was collected, washed with aqueous HCl (2 N, 2 x 5.0 mL) and the aqueous phase was extract with CH_2Cl_2 (2 × 5.0 mL). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The residue was subjected to *flash* chromatography (SiO_2, *n*-hexane:AcOEt = 4:1) to give the final product **182**. The enantiomeric composition of the sample was determined by CSP-HPLC analysis [220 nm, Chiralcel OD-H, 1 mL min^{-1}, *(n*-hexane:IPA = 95:5): t_R = 17.18 min (major), t_R = 8.8 min (minor).]

7.5.4. General procedure for soluble model-*Cinchona* alkaloid-catalyzed chlorolactonization of 4-(4-fluorophenyl)-pent-4-enoic acid.



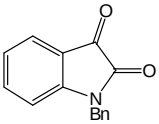
General procedure: To a Schenk tube was added 0.0094 g (0.01 mmol, 0.1 equiv) of catalyst **155a**, 32 mg (0.11 mmol, 1.1 equiv) of DCDPH (**189**), and 12 mg (0.1 mmol, 1 equiv) of benzoic acid. These reagents were dissolved in appropriate solventc(2 mL) (see Table 9 for solvents used) and cooled to -40°C (acetone/liq. N_2). The resulting -40°C solution was stirred for ca. 20-30 minutes at which time 0.018 g (0.1 mmol, 1 equiv) of the alkenoic acid (**191**) was added in one portion. The resulting mixture was stirred at -40°C and monitored by TLC (see Table 9 for reaction times). The reaction mixture was poured into a 60 mL separatory funnel and diluted with CH_2Cl_2 (10 mL). The organics were then washed with 0.1 M aq. NaOH (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organics were dried (Na_2SO_4) and concentrated by rotary evaporation. The crude isolate was then purified by *flash* chromatography (SiO_2, *n*-hexane:AcOEt = 8:2). The enantiomeric excess of the products was determined by CSP-HPLC analysis [220nm,

Chiralcel OJ, 1mL/min, (*n*-hexane:IPA = 95:5): t_R = 30.41 min (major), t_R = 39.73 min (minor)]

7.5.5. α-Amination of 2-oxindoles.

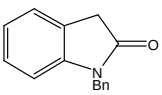
7.5.5-a. Synthesis of substrates.

1-Benzyl isatin (198).[233]



To a three-necked round bottom flask (250 mL) were added under nitrogen, 11.04 g (75 mmol) of isatin (**197**) and DMF (150 mL) stirred until complete dissolution of **197**. The resulting bright orange solution was cooled to 0°C by the use an ice/water bath, 3.78 g (78.7 mmol, 1.05 equiv.) of NaH (50% dispersion in mineral oil) was added portionwise resulting in a deep purple solution. The solution was stirred until any effervescence had ceased (~50 min). To this, 10.71 mL (90 mmol, 1.2 equiv.) of benzyl bromide was added in a dropwise manner and the resulting red-brown mixture was stirred for an additional 50 min at 0°C. 1 L of H_2O was added to precipitate the product. The product was filtered through glass frit dried under reduced pressure (0.5 mmHg) and recrystallized from 125 mL EtOH. Title product (**198**) was obtained as bright orange needles 13.9 g, additional crop of product was obtained from mother liquor 0.67 g of, (combined yield = 82%).

1-Benzyl-1,2-dihydroindol-2-one (199).[233]

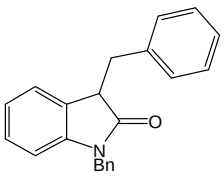


To a 100 mL round bottom flask were added 10 g (44 mmol) of **198** and 46.5 mL of hydrazine hydrate. The resulting suspension was heated to reflux until the gas evolution had stopped (5 h). The reaction mixture went from orange via green to yellow within this time. The reaction mixture was allowed to cool to ambient temperature treated with H_2O (75 mL) and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure (0.5 mmHg). The yellow crude was recrystallized from Et_2O. 7.3 g of product **199** was obtained as heavy off-white needles (75% yield)

General procedure for 3-alkylation of N-Bn oxindoles:

a) By 'borrowing hydrogen' method (with [$RuCl_3 \cdot xH_2O$]):[233] In a 7-mL thick-walled screw-cap vial were added, 0.00954 g (0.046 mmol, 0.02 equiv.) of [$RuCl_3 \cdot \times H_2O$], 0.024 g (0.092 mmol, 0.04 equiv.) of PPh_3, 0.0115 (0.23 mmol, 0.1 equiv.) of NaOH, 0.512 g (2.3 mmol, 1 equiv.) of **199**, and 0.26 mL (2.53 mmol, 1.1 equiv.) of the benzyl alcohol. The vial was purged with nitrogen and sealed with a screw-cap. The mixture was placed in a preheated oil bath to 110°C and stirred for 39 h or until ^{1}H NMR of the crude reaction mixture showed complete consumption of the oxindole. The reaction mixture was allowed to cool to room temperature followed by dilution with CH_2Cl_2 (10 mL). SiO_2 was added and the suspension was concentrated under reduced pressure to afford a powder that was purified by use of *flash* chromatography (SiO_2, *n*-Hexane:EtOAc = 7:3). The product 1,3-dibenzylindolin-2-one (**202a**) was obtained as brownish solid (0.44 g, 61% yield).

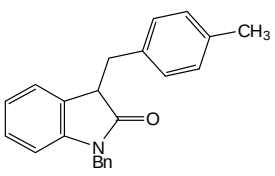
1,3-dibenzylindolin-2-one(202a).[233]



*b) By condensation of **199** with an aromatic aldehyde followed by reduction with ($NaBH_4$)*: In a round bottom flask (100 mL), under nitrogen were added, 2.0 g (8.96 mmol, 1 equiv.) of **199** and methanol (18 mL), stirred until complete dissolution of **199**. To the resulting solution were added 90 µL (0.896 mmol, 0.1 equiv.) of pyrrolidine and 0.9l mL (8.96 mmol, 1 equiv.) of benzaldehyde and the mixture was heated to reflux for 2 h (until complete consumption of **199**, by TLC) and cooled to room temperature. To this yellow solution was added 1.69 g (44.79 mmol, 5 equiv.) of $NaBH_4$ in portions and the color faded and disappeared in 1 hour. The reaction was quenched by water and extracted with ethyl acetate (2 × 50 mL). The organic layer was dried (Na_2SO_4), filtered, and dried to give a white crude product (**202a**) which was almost pure by ^{1}H NMR (2.48 g, 88% yield).

Oxindoles **202b-f** were synthesized analogously, all these products were purified by flash chromatographic technique.

1-benzyl-3-(4-methylbenzyl)indolin-2-one (202b): (>99% yield)



TLC R_f = 0.77 (SiO_2, petrolium ether: EtOAc = 3:1).

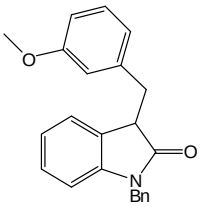
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.28 – 7.18 (m, 3H), 7.16 – 7.07 (m, 1H), 7.04 (s, 4H), 7.02 – 6.90 (m, 4H), 6.57 (d, *J* = 7.8 Hz, 1H), 5.09 (d, *J* = 15.8 Hz, 1H), 4.64 (d, *J* = 15.8 Hz, 1H), 3.86 (dd, J_a =

7.9, J_b = 4.3 Hz, 1H), 3.50 (dd, J_a = 13.6, J_b =4.3 Hz, 1H), 3.15 (dd, J_a = 13.6, J_b = 8.0 Hz, 1H), 2.35 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.9, 143.4, 136.0, 135.6, 134.3, 129.5, 128.9, 128.5, 128.3, 127.8, 127.3, 127.0, 124.4, 122.0, 109.0, 47.1, 43.5, 36.1, 21.1.

MS (ESI$^+$) m/z = 328.2 [M+H$^+$].

1-benzyl-3-(3-methoxybenzyl)indolin-2-one (202c): (77% yield).



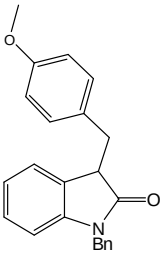
TLC R_f = 0.5 (SiO_2, petrolium ether: EtOAc = 3:1),

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.29 – 7.18 (m, 3H), 7.18 – 7.06 (m, 2H), 7.04 – 6.90 (m, 4H), 6.77 (m, 2H), 6.68 – 6.62 (m, 1H), 6.57 (d, J = 7.8 Hz, 1H), 5.06 (d, J = 15.8 Hz, 1H), 4.64 (d, J = 15.8 Hz, 1H), 3.86 (dd, J_a = 8.1, J_b = 4.3 Hz, 1H), 3.65 (s, 3H), 3.50 (dd, J_a = 13.6, J_b = 4.3 Hz, 1H), 3.12 (dd, J_a = 13.6, J_b = 8.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.6, 159.4, 143.4, 138.8, 135.6, 129.0, 128.5, 128.2, 127.7, 127.1, 126.8, 124.3, 121.9, 114.7, 112.6, 108.8, 54.9, 46.8, 43.4, 36.4.

MS (ESI$^+$) m/z = 344.1 [M+H$^+$]

1-benzyl-3-(4-methoxybenzyl)indolin-2-one (202d): (88% yield).



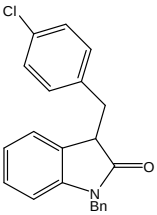
TLC R_f = 0.42 (SiO_2, *n*-hexane: ethyl acetate = 3:1),

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30 – 7.16 (m, 3H), 7.16 – 6.95 (m, 5H), 6.95 – 6.82 (m, 2H), 6.81 – 6.68 (m, 2H), 6.56 (d, J = 7.7 Hz, 1H), 5.11 (d, J = 15.9 Hz, 1H), 4.58 (d, J = 15.9 Hz, 1H), 3.83 (dd, J_a = 7.4, J_b = 4.2 Hz, 1H), 3.76 (s, 3H), 3.46 (dd, J_a = 13.7, J_b = 4.2 Hz, 1H), 3.20 (dd, J_a = 13.7, J_b = 7.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.6, 158.2, 143.3, 135.4, 130.5, 129.0, 128.3, 128.1, 127.7, 127.1, 126.7, 124.2, 121.9, 113.4, 108.8, 54.9, 47.1, 43.2, 35.3.

MS (ESI$^+$) m/z = 344.0 [M+H$^+$]

1-benzyl-3-(4-chlorobenzyl)indolin-2-one (202e): (40% yield).



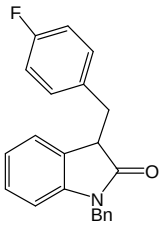
TLC R_f = 0.26 (SiO_2, *n*-hexane: ethyl acetate = 6:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.30 – 7.18 (m, 3H), 7.18 – 7.06 (m, 4H), 7.02 (d, J = 8.2 Hz, 3H), 6.86 (dd, J_a = 6.7, J_b =2.1 Hz, 2H), 6.56 (d, J = 8.1 Hz, 1H), 5.10 (d, J = 15.9 Hz, 1H), 4.55 (d, J = 15.9 Hz, 1H), 3.85 (dd, J_a = 6.9, J_b = 4.4 Hz, 1H), 3.34 (ddd, J_a = 20.7, J_b =13.6, J_c = 5.7 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.3, 143.5, 135.6, 135.5, 132.5, 131.0, 128.5, 128.2, 128.0, 127.7, 127.3, 126.8, 124.2, 122.1, 109.0, 46.8, 43.5, 35.5.

MS (ESI^+) m/z = 348.1 [$M+H^+$]

1-benzyl-3-(4-fluorobenzyl)indolin-2-one (202f): (89% yield)



TLC R_f = 0.29 (SiO_2, petroleum ether: ethyl acetate = 6:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.28 – 7.17 (m, 3H), 7.17 – 6.96 (m, 5H), 6.95 – 6.80 (m, 4H), 6.62 – 6.52 (m, 1H), 5.09 (d, *J* = 15.9 Hz, 1H), 4.57 (d, *J* = 15.8 Hz, 1H), 3.84 (dd, J_a = 7.0, J_b =4.3 Hz, 1H), 3.35 (ddd, J_a = 20.8, J_b = 13.7, J_c = 5.7 Hz, 2H).

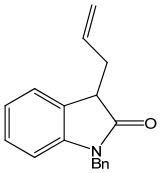
^{13}C NMR (75 MHz, CDCl3) δ = 176.4, 163.3, 160.0, 143.4, 135.4, 132.7, 132.6, 131.1, 131.0, 128.4, 127.9, 127.7, 127.2, 126.7, 124.1, 122.0, 115.0, 114.7, 108.9, 46.9, 43.3, 35.3.

MS (ESI^+) m/z = 332.0 [$M+H^+$].

General procedure of the synthesis of 3-allyl and 3-cinnamyl oxindole derivatives:[129]

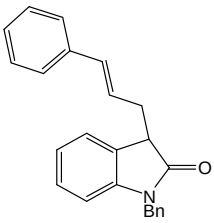
In a Schenk tube under nitrogen were added 0.446 g (2 mmol) of benzyl-1,2-dihydroindol-2-one (**199**) and DMF (8 mL), after stirring to the solution was added at 0°C, 0.106 g (2.2 mmol, 1.1 equiv.) of NaH (50 % dispersion in mineral oil) and the mixture was stirred for 5 minutes at same temperature. After, allyl- or cinnamyl-bromide (1.0 equiv.) was added to the solution at -60°C, the mixture was further stirred for overnight. The reaction was quenched by the addition of H_2O, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent was removed by evaporation. The residue was purified by *flash* chromatography (SiO_2, *n*-hexane: ethyl acetate = 6:1 for **202g** and 3:1 for **202h**) to give the corresponding alkylated compounds **202g** and **202h** (13% and 50% yield respectively).

3-allyl-1-benzylindolin-2-one (202g):[257] (13% yield)



1-benzyl-3-cinnamylindolin-2-one (202h): (50% yield).

[257] Thomson, J. E.; Kyle, A. F.; Ling, K. B.; Smith, S. R.; Slawin, A. M. Z.; Smith, A. D. *Tetrahedron* **2010**, *66*, 3801-3813.



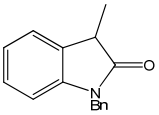
TLC R_f = 0.4 (SiO_2, *n*-hexane: ethyl acetate = 3:1),

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.40 – 7.02 (m, 13H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.26 – 5.99 (m, 1H), 5.20 (d, *J* = 15.8 Hz, 1H), 4.71 (d, *J* = 15.7 Hz, 1H), 3.75 (t, *J* = 5.6 Hz, 1H), 3.27 – 2.80 (m, 2H).

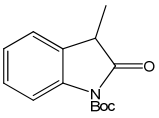
^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.9, 143.3, 136.9, 135.6, 133.4, 128.5, 128.4, 128.2, 127.8, 127.3, 127.2, 126.9, 126.1, 124.9, 124.0, 122.2, 108.9, 45.6, 43.5, 34.0.

MS (ESI$^+$) m/z = 340.1 [M+H$^+$]

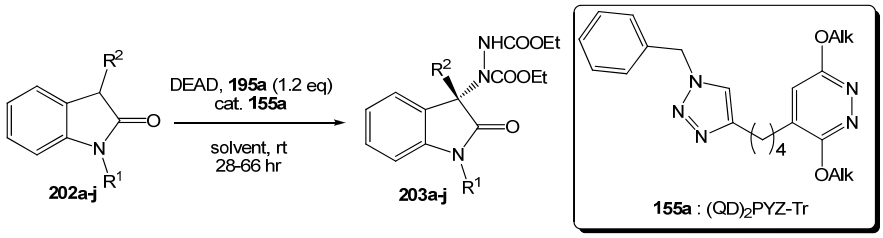
1-benzyl-3-methylindolin-2-one (202i):[234]



1-boc-3-methylindolin-2-one (202j):[235]

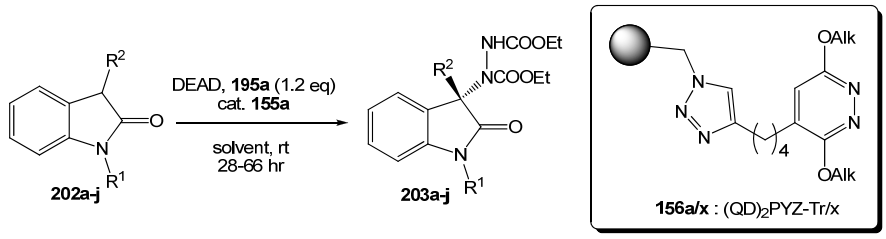


7.5.5-b. General procedure for soluble model-*Cinchona* alkaloid-catalyzed α-amination of oxindoles (homogeneous).



A Schlenk tube was charged under nitrogen atmosphere with 18.8 mg (0.02 mmol, 0.2 equiv.) of model soluble catalyst $(QD)_2PYZ$ (**155a**), 3-substituted oxindole (0.1 mmol), and 0.75 mL of dried-THF, after was added 57.5 μL (0.12 mmol, 1.2 equiv.) of DEAD (40% in toluene). The resulting solution was stirred at rt for 48 h. and then directly purified by flash column chromatography (SiO_2, petroleum ether: ethyl acetate = 3:1) to afford the desired products. Structure was confirmed by ^{1}H NMR, ^{13}C NMR, [MS (ESI+)]. Enantiomeric excess were calculated by use of CSP-HPLC analysis.

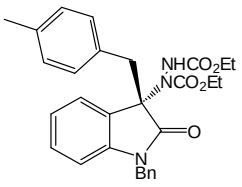
7.5.5-c. General procedure for IPB *Cinchona* alkaloid-catalyzed α-amination of oxindoles (heterogeneous):



A 10 mL Schlenk tube fitted with a medium porosity glass frit and stopcock side arm (Figure 53), was charged under nitrogen with 28.6 mg (0.02 mmol, 0.2 equiv) of IPB-catalyst (**156a/x,** 0.7 mmol g^{-1} of supported alkaloid derivative), 3-substituted oxindole (0.1 mmol) in 0.75 mL THF. To this stirred mixture added 57.5 μL (0.12 mmol, 1.2 equiv.) of DEAD (**195a**, 40% in toluene) and reaction was stirred at very slow speed at 29ºC for 48 h. The reaction mixture was filtered through frit, collected into a test-tube and rinses with (2 x 5 mL) THF. Combined filtrate were concentrated to approx. 1mL and directly purified by *flash* column chromatography (SiO_2, petroleum ether: ethyl acetate = 3:1). The polymer material retained by frit was dried briefly under reduced pressure 5 mmHg and was used for subsequent reactions.

The detailed characterizations of new compounds are given below:

(*S*)-diethyl1-(1-benzyl-3-(4-methylbenzyl)-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (203b):



White solid, **TLC** R_f = 0.25 (SiO_2, *n*-hexane: ethyl acetate = 3:1), **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 6.6 Hz, 1H), 7.32 (s, 1H), 7.14 (m, 2H), 7.10 – 7.04 (m, 2H), 6.79 (d, *J* = 7.9 Hz, 2H), 6.76 – 6.70 (m, 2H), 6.60 (d, *J* = 8.0 Hz, 2H), 6.25 (d, *J* = 7.4 Hz, 1H), 4.59 (dd, J_a = 69.3, J_b = 16.0 Hz, 2H), 4.41 – 4.19 (m, 2H), 4.07 – 3.84 (m, 2H), 3.32 (dd, J_a = 62.7, J_b = 12.1 Hz, 2H), 2.25 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H).

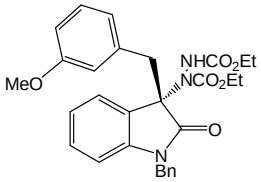
^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.2, 157.3, 154.1, 143.0, 136.4, 135.4, 130.5, 129.8, 129.7, 128.7, 128.5, 128.4, 127.1, 126.9, 124.5, 122.8, 108.8, 70.0, 62.7, 62.4, 44.30, 41.25, 21.21, 14.6, 14.1.

MS (ESI$^+$) *m/z* = 502.3 [M+H$^+$]

$[\alpha]_D^{25}$ = + 47.54 (c = 1, CH_2Cl_2).

CSP-HPLC (254 nm, Chiralpak OD-H, flow rate = 0.5 mL/min, 30ºC, hexane/*i*-PrOH = 97:3): t_R = 19.12 min (major), t_R = 27.57 min (minor).

(*S*)-diethyl-1-(1-benzyl-3-(3-methoxybenzyl)-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (203c):



TLC R_f = 0.19 (SiO_2, petrolium ether : ethyl acetate = 3:1),

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 7.0 Hz, 1H), 7.40 – 7.21 (m, 1H), 7.24 – 7.00 (m, 5H), 6.94 (t, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 3H), 6.45 (d, *J* = 7.4 Hz, 1H), 6.26 (d, *J* = 7.2 Hz, 1H), 6.11 (s, 1H), 4.59 (dd, J_a = 50.2, J_b = 16.1 Hz, 2H), 4.45 – 4.12 (m, 2H), 4.14 – 3.83 (m, 2H), 3.44 (s, 3H- Ome + d, 1H), 3.23 (d, *J* = 12.0 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 6.4 Hz, 3H).

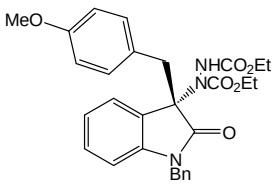
^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.0, 158.9, 157.4, 154.1, 143.1, 135.4, 134.3, 129.9, 128.7, 128.7, 128.5, 127.1, 126.7, 124.5, 123.1, 122.8, 114.8, 114.1, 108.9, 70.0, 62.8, 62.4, 55.0, 44.2, 41.7, 14.6, 14.1.

MS (ESI$^+$) m/z = 518.2 [M+H$^+$]

$[\alpha]_D^{25}$ = +18.43 (c = 1.005, CH_2Cl_2).

CSP-HPLC (254 nm, Chiralpak OD-H, flow rate = 0.5 mL/min, 30ºC, hexane/*i*-PrOH = 97:3) t_R = 23.39 min (major), t_R = 37.37 min (minor).

(*S*)-diethyl-1-(1-benzyl-3-(4-methoxybenzyl)-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (203d):



TLC R_f = 0.16 (SiO_2, petrolium ether : ethyl acetate = 3:1),

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.97 (d, *J* = 7.3 Hz, 1H), 7.45 (s, 1H), 7.24 – 6.96 (m, 5H), 6.84 – 6.40 (m, 6H), 6.27 (d, *J* = 6.9 Hz, 1H), 4.61 (dd, J_a = 76.9, J_b = 16.2 Hz, 2H), 4.41 – 4.14 (m, 2H), 4.09 – 3.87 (m, 2H), 3.70 (s, 3H), 3.31 (dd, J_a = 66.2, J_b = 12.2 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.12 – 0.82 (m, 3H).

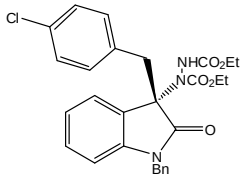
^{13}C NMR (75 MHz, $CDCl_3$) δ 182.1, 176.2, 158.7, 157.3, 154.1, 142.9, 135.3, 131.6, 129.8, 128.7, 128.4, 127.1, 126.8, 124.7, 124.5 122.9, 113.2, 108.9, 70.0, 62.7, 62.4, 55.0, 44.2, 40.8, 14.6, 14.1.

MS (ESI$^+$) m/z = 540.5 [M+Na], 518.2 [M+H$^+$].

$[\alpha]_D^{27}$ = + 48.64 (c = 1.005, CH_2Cl_2).

CSP-HPLC (254 nm, Chiralpak OD-H, flow rate = 0.5 mL/min, 30ºC, hexane/*i*-PrOH = 97:3) t_R = 30.80 min (major), t_R = 54.15 min (minor).

(*S*)-diethyl-1-(1-benzyl-3-(4-chlorobenzyl)-2-oxoindolin-3-yl)hydrazine-1,2 dicarboxylate (203e):



TLC R_f = 0.21 (SiO_2, petroleum ether: ethyl acetate = 3:1),

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.16 – 7.81 (m, 1H), 7.33 (s, 1H), 7.24 – 7.11 (m, 3H), 7.16 – 7.00 (m, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 6.81 – 6.67 (m, 2H), 6.63 (d, *J* = 8.3 Hz, 2H), 6.31 (dd, J_a = 5.6, J_b = 2.8 Hz, 1H), 4.75 (d, *J* = 16.0 Hz, 1H), 4.47 (d, *J* = 16.0 Hz, 1H), 4.32 (ddq, J_a = 20.9, J_b = 10.4, J_c = 7.0 Hz, 2H), 4.13 – 3.81 (m, 2H), 3.32 (dd, J_a = 65.1, J_b = 12.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 6.7 Hz, 3H).

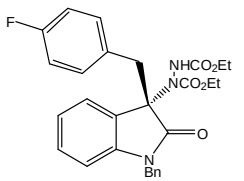
^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.9, 157.3, 154.1, 143.1, 135.4, 133.2, 132.1, 131.9, 131.6, 129.6, 129.0, 128.5, 127.9, 127.3, 127.0, 124.6, 123.0, 109.0, 69.8, 62.8, 62.5, 44.4, 41.0, 14.6, 14.1.

MS (ESI$^+$) *m/z* = 522.1 [M+H$^+$]

$[\alpha]_D^{25}$ = + 47.97 (c = 0.995, CH_2Cl_2).

CSP-HPLC (254 nm, Chiralpak OD-H, flow rate = 0.5 mL/min, 30ºC, hexane/*i*-PrOH = 97:3) t_R = 22.26 min (major), t_R = 32,19 min (minor).

(*S*)-diethyl-1-(1-benzyl-3-(4-flurobenzyl)-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (203f):



TLC R_f = 0.24 (SiO_2, petrolium ether: ethyl acetate = 3:1),

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.06 – 7.87 (m, 1H), 7.34 (s, 1H), 7.24 – 7.11 (m, 3H), 7.13 – 6.93 (m, 2H), 6.85 – 6.71 (m, 2H), 6.65 (d, *J* = 7.1 Hz, 4H), 6.39 – 6.22 (m, 1H), 4.58 (dd, J_a = 41.7, J_b =16.0 Hz, 2H), 4.44 – 4.21 (m, 2H), 4.08 – 3.86 (m, 2H), 3.32 (dd, J_a = 67.8, J_b = 12.2 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 8.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 175.9, 163.7, 160.5, 157.3, 154.1, 142.8, 135.3, 132.1, 132.0, 129.5, 128.9, 128.5, 127.3, 126.9, 124.5, 123.0, 114.7, 114.5, 108.9, 69.8, 62.8, 62.5, 44.2, 40.8, 14.6, 14.1.

MS (ESI$^+$) m/z = 506.4 [M+H$^+$]

$[\alpha]_D^{27}$ = + 5.52 (c = 1.0, CH_2Cl_2).

CSP-HPLC (254 nm, Chiralpak OD-H, flow rate = 0.5 mL/min, 30ºC, hexane/*i*-PrOH = 97:3) t_R = 23.65 min (major), t_R = 32.92 min (minor).