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Organocatalytic Asymmetric Mannich-Type Reactions: an Easy Approach to Optically Active Amine Derivatives.

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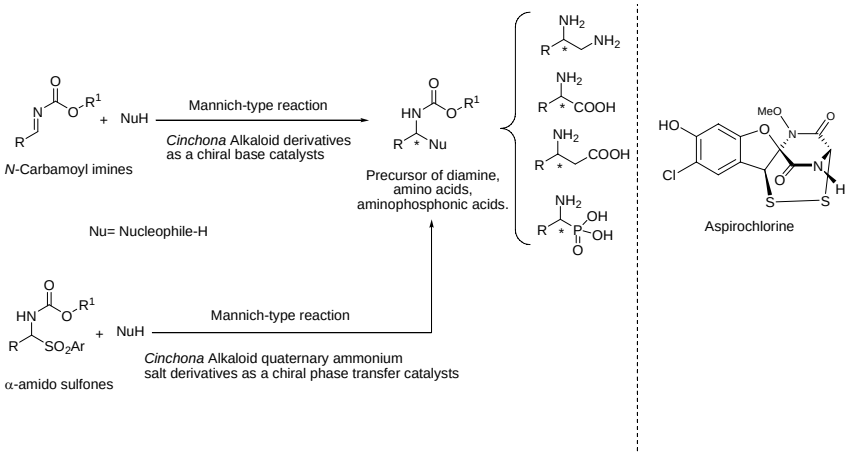
Esame finale anno 2008

Ai miei genitori
e a Lucia

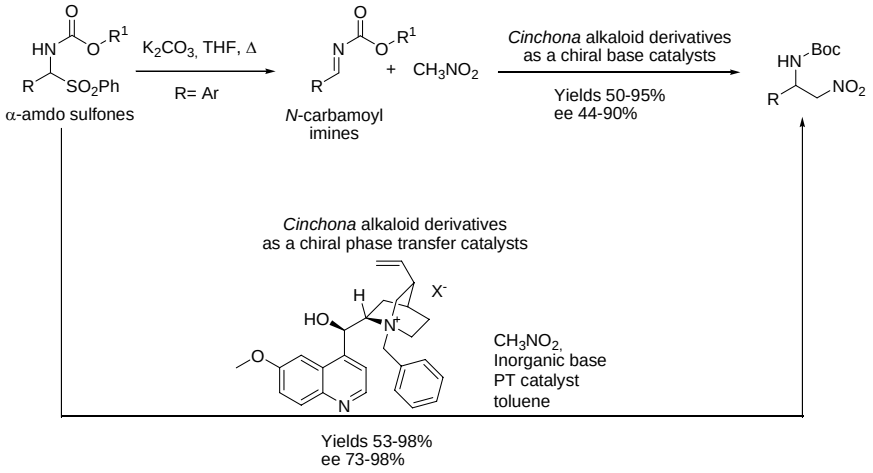
Preface

The topics I came across during the period I spent as a Ph.D. student are mainly two. The first concerns new organocatalytic protocols for Mannich-type reactions mediated by *Cinchona* alkaloids derivatives (Scheme I, left); the second topic, instead, regards the study of a new approach towards the enantioselective total synthesis of Aspirochlorine, a potent gliotoxin that recent studies indicate as a highly selective and active agent against fungi (**Scheme I**, right).



Scheme I

At the beginning of 2005 I had the chance to join the group of Prof. Alfredo Ricci at the Department of Organic Chemistry of the University of Bologna, starting my PhD studies. During the first period I started to study a new homogeneous organocatalytic aza-Henry reaction by means of *Cinchona* alkaloid derivatives as chiral base catalysts with good results. Soon after we introduced a new protocol which allowed the *in situ* synthesis of *N*-carbamoyl imines, scarcely stable, moisture sensitive compounds. For this purpose we used α-amido sulfones, bench stable white crystalline solids, as imine precursors (**Scheme II**).

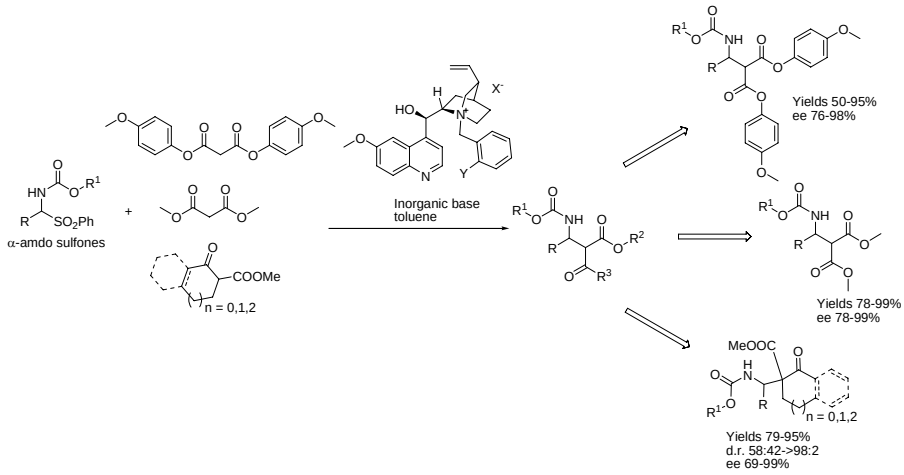


Scheme II

In particular we were able to obtain the aza-Henry adducts, by using chiral phase transfer catalysis, with a broad range of substituents as R-group and excellent results, unprecedented for Mannich-type transformations (Section 1, Chapter 2).

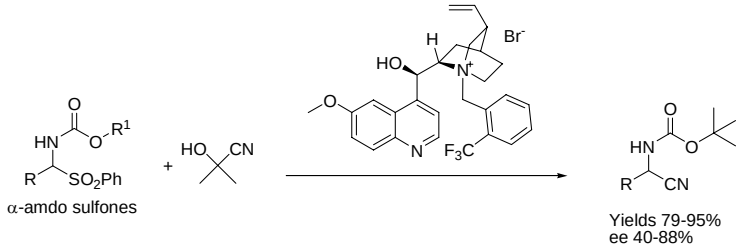
With the optimised protocol in hand we have extended the methodology to the other Mannich-type reactions. We applied the new method to the Mannich, Strecker and Pudovik (hydrophosphonylation of imines) reactions with very good results in terms of enantioselections and yields, broadening the usefulness of this novel protocol.

The Mannich reaction was certainly the most extensively studied work in this thesis (Section 1, Chapter 3). Initially we developed the reaction with α-amido sulfones as imine precursors and non-commercially available malonates with excellent results in terms of yields and enantioselections. In this particular case we recorded 1 mol% of catalyst loading, very low for organocatalytic processes. Then we thought to develop a new Mannich reaction by using simpler malonates, such as dimethyl malonate. With new optimised condition the reaction provided slightly lower enantioselections than the previous protocol, but the Mannich adducts were very versatile for the obtainment of β^3-amino acids. Furthermore we performed the first addition of cyclic β-ketoester to α-amido sulfones obtaining the corresponding products in good yield with high level of diastereomeric and enantiomeric excess. (**Scheme III**)



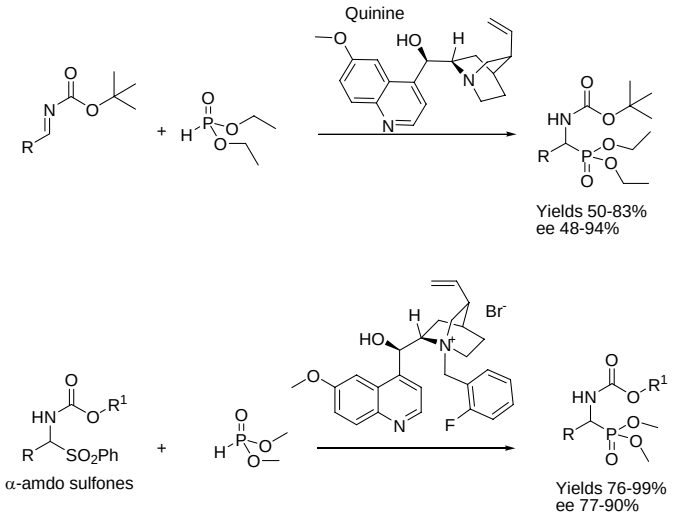
Scheme III

In Chapter 4 is reported that *Cinchona* Alkaloid phase-transfer quaternary ammonium salt derivatives can also mediated the Strecker reaction, using acetone cyanohydrin, a relatively harmless cyanide source. The reaction proceeded very well providing the corresponding α-amino nitriles in good yields and enantiomeric excesses (**Scheme IV**).



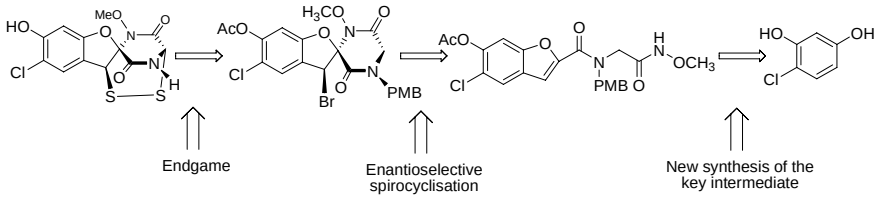
Scheme IV

Finally, we developed two new complementary methodologies for the hydrophosphonylation of imines (Section 1, Chapter 5). As a result of the low stability of the products derived from aromatic imines, we performed the reactions in mild homogeneous basic condition by using quinine as a chiral base catalyst giving the α-aryl-α-amido phosphonic acid esters as products. On the other hand, we performed the addition of dialkyl phosphite to aliphatic imines by using chiral *Cinchona* alkaloid phase transfer quaternary ammonium salt derivatives using our methodology based on α-amido sulfones. The results were good for both procedures covering a broad range of α-amino phosphonic acid ester (**Scheme V**).



Scheme V

During the second year Ph.D. studies, I spent six months in the group of Prof. Steven V. Ley, at the Department of Chemistry of the University of Cambridge, in United Kingdom. During this fruitful period I have been involved in a project concerning the enantioselective synthesis of Aspirochlorine (Section 2). We provided a new route for the synthesis of a key intermediate, reducing the number of steps and increasing the overall yield. Then we introduced a new enantioselective spirocyclisation for the synthesis of a chiral building block for the completion of the synthesis (**Scheme VI**).



Scheme VI

Francesco, Bologna 2006

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List of abbreviations

δ	Chemical shift
Ac	acetyl
Alk	Alkyl
Ar	Aryl
BINOL	1,1′-Bi(2-naphthol)
Bn	Benzyl
Boc	*Tert*-Butyloxycarbonyl
Bz	Benzoyl
N-BnCD$^+$Cl$^-$	*N*-benzylcinchonidinium chloride
N-BnCN$^+$Cl$^-$	*N*-benzylcinconinium chloride
Cbz	Benzyloxycarbnyl
Cy	Cyclohexyl
Co-Salen	Co-bis(salicylidene)ethylenediamine
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DMP	dimethylperiodinane
DPP	Diphenylphosphinoyl
ee	enantiomeric excess
Et	ethyl
et al.	*et alia*
FMOC	9-Fluorenylmethyloxycarbonyl
h	hours
HOBt	1-Hydroxybenzotriazole
i-Bu	iso-butyl
i-Pr	*Iso*-propyl
m	*meta*
Me	methyl
MOM	methoxymethyl
NBS	N-bromosuccinic amide
NCS	N-chlorosuccinic amide
o	*ortho*
OMP	*ortho*-Methoxyphenyl
p	*para*
pKa	$-\log_{10} K_a$
Ph	Phenyl

PG	Protecting Group
P-T	Phase transfer
PMP	*para*-Methoxyphenyl
PTC	Phase transfer catalysis
p-tol	*para*-tolyl
Py	pyridine
Ph	phenyl
PMB	p-methoxybenzyl
Ppm	Parts per million
S/C	Substrate catalyst ratio
TADDOL	trans-α,α'-(Dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol)
t-Bu	*Tert*-Butyl
TBABr	Tetrabutylammonium Bromide
Tol	Tolyl
THF	Tetrahydrofuran
TMSCN	Trimethylsilylcyanide
VAPOL	2,2'-Diphenyl-3,3'-(4-biphenanthrol)
vic	vicinal

Section 1

Organocatalytic Asymmetric Mannich-Type Reactions[1]

[1] Part of the results presented in this section has been published: a) L. Bernardi, F. Fini, R. P. Herrera, A. Ricci, V. Sgarzani *Tetrahedron* **2006**, *62*, 375; b) F. Fini, V. Sgarzani, D. Pettersen, R. P. Herrera, L. Bernardi, A. Ricci *Angew. Chem. Int. Ed.* **2005**, *44*, 7975; c) F. Fini, L. Bernardi, R. P. Herrera, D. Pettersen, A. Ricci, V. Sgarzani *Adv Synth. Catal.* **2006**, *248*, 2043; d) O. Marianacci, G. Micheletti, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani, A. Ricci *Chem. Eur. J.* **2007**, *13*, 8338; e) R. P. Herrera, V. Sgarzani, L. Bernardi, F. Fini, D. Pettersen, A. Ricci *J. Org.Chem.* **2006**, *71*, 9869; f) D. Pettersen, M. Marcolini, L. Bernardi, F. Fini, R. P. Herrera, V. Sgarzani, A. Ricci *J. Org.Chem.* **2006**, *71*, 6269.

1. General Introduction

1.1. Asymmetric Organocatalysis

Asymmetric organocatalysis is a branch of catalysis that uses chiral small organic molecules in sub-stoichiometric quantities to promote organic reactions.[2] Furthermore it is possible to obtain chiral organic products in enantioenriched form. Obviously the value of the reaction is determined by the optical purity of the product itself.

In the last 30 years asymmetric catalysis has literally exploded and three of the major chemists in 2001 have received the Nobel Prize in Chemistry for their contributions in asymmetric catalysis (Knowles, Sharpless, and Noyori).[3] A recent general classification of asymmetric catalysis places organocatalysis between metal catalysis and enzymatic transformations, giving three fields that at the present time are complementary one to another.[4]

It is possible to highlight enormous differences between the three classes of catalysts. The most obvious difference is the mode of action: a metal catalyst has a transition metal as the active centre, while an organocatalyst has a particular carbon-heteroatom skeleton that gives individual characteristics to the active site (thioureas, strong Brønsted acids, rigid tertiary amines, cyclic secondary amines etc.). Finally, an enzyme is the sum of hundreds of amino acids; however, only two or three of them are active in the catalytic sites.

Each type of catalysis has positive and negative features: metal catalysts are usually expensive and moisture/oxygen sensitive and give some concerns in the purification process, as the products for pharmaceuticals tolerate only small amounts of metals contaminants;[5] however the catalysts loadings are often very low (up to 1000000/1 in S/C). Organocatalysts have opposite characteristics; they are usually harmless in small

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[2] a) *Asymmetric Organocatalysis*, A. Berkessel, H. Gröger, Eds.; Wiley-VCH, Weinheim, **2005**; b) *Enantioselctive Organocatalysis*, P. I. Dalko, Ed.; Wiley-VCH, Weinheim, **2007**; c) P. I. Dalko, L. Moisan *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; d) P. I. Dalko, L. Moisan *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; e) *Organocatalysis*, B. List, Ed. *Chem. Rev.* **2007**, *107*, Nr 12; f) *Asymmetric Organocatalysis* K. N. Houk and B. List, Eds. *Acc. Chem. Res.* **2004**, *37*, Nr 8.

[3] W. S. Knowles *Angew. Chem. Int. Ed.* **2002**, *41*, 1998 (Nobel lecture). R. Noyori *Angew. Chem. Int. Ed.* **2002**, *41*, 2008 (Nobel lecture). K. B. Sharpless *Angew. Chem. Int. Ed.* **2002**, *41*, 2022 (Nobel lecture).

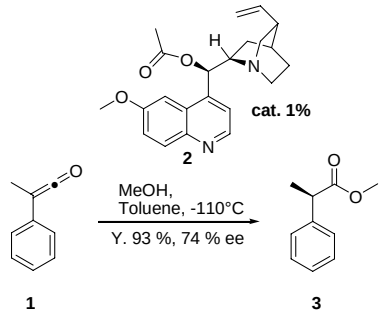
[4] *Asymmetric Organocatalysis*, A. Berkessel, H. Gröger, Eds.; Wiley-VCH, Weinheim, **2005**, xi-xiv, 1-8.

[5] The European Agency for Evaluation of Medicinal Products (EMEA) sets the Oral Concentration Limit in active components for Pt, Pd, Ru, Rh, Ir and Os as 5 ppm: *Note for Guidance on Specification Limits for Residues of Metal Catlysts*, CPMP/SWP/QWP/4446/00, London, **2002**.

amounts and often allow mild reaction conditions and trivial operative procedures, although the catalysts loadings are typically under 100/1 in S/C. A common feature for both catalysts is the opportunity to obtain both the enantiomers of the catalytic product without many problems. Finally, enzymes have no toxicity at all, low catalysts loadings are required but are active only in particular and strict conditions. Furthermore in this case the synthesis of both enantiomers is difficult.

The term "organocatalysis" was coined up by David MacMillan in 2000 to summarise several classes of organic catalysts that had been used during the last fifty years.[6] At the beginning this type of catalysis was mainly used as mechanistic/biomimetic branch of enzymatic catalysis with scarce synthetic application.[4] Indeed, in the first half of 1900s a small number of examples were reported and all of them were with low enantiomeric excess (less than 20%), therefore without any synthetic utility.[7]

A dramatic change occurred in the second half of 1900s, when two pioneering works with different kinds of catalysts appeared. First Pracejus *et al.* in 1960 reported that *Cinchona* alkaloid derivative **2** catalysed the addition of methanol to phenylmethylketene **1**, affording the (–)-α-phenyl methylpropionate **3** with 74 % *ee* (**Scheme 1**).[8]



Scheme 1 *Cinchona* alkaloid-catalysed addition of CH_3OH to a prochiral ketene.

The second milestone in the history of organocatalysis was the L-proline **4** mediated highly enantioselective Robinson annulation reported by Eder, Sauer, Wiechert and Hajos, Parrish, in the 1970s.[9] The results were very impressive, and the products obtained in up to 93% *ee*, have been used as important key intermediates in the synthesis of some natural products (**Scheme 2**).

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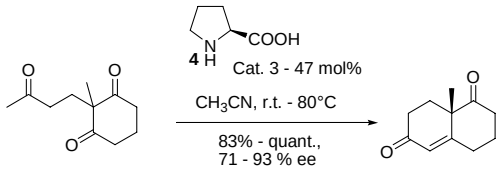
[6] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan *J. Am. Chem. Soc.* **2000**, *122*, 4243.
[7] For a detailed discussion about organocatalytic examples reported before 1960 see: *Enantioselctive Organocatalysis*, P. I. Dalko, Ed.; Wiley-VCH, Weinheim, **2007**, 2-6.
[8] a) H. Pracejus *Justus Liebis Ann. Chem.* **1960**, *634*, 9. b) H. Pracejus, H. Mätje *J. Prakt. Chem.* **1964**, *24*, 195.
[9] a) U. Eder, G. Sauer, R. Wiechert *Angew. Chem. Int. Ed.* **1971**, *10*, 496. b) Z. G. Hajos, D. R. Parrish *J. Org. Chem.* **1974**, *39*, 1615.



Scheme 2 L-Proline catalysed Robinson annulation.

Albeit these remarkable results, organocatalysis remained relatively unexplored for the next twenty years. Only in the 2000s there was a big bang, and the number of publications increased dramatically in less than five years becoming more than four hundred per year in 2007.[10] Considering the enormous number of reports of the last decade based on different types of catalytic system, a clarification is necessary. A possible simplification is the classification of the organocatalysts based on the covalent and non-covalent mode of interactions with the reagents.[11] Here it is proposed a very short overview in organocatalysis based on the mode of action of the organocatalysts as shown in **Chart 1**.[12]

A first class of catalysts, giving a covalent interaction with the reagents, is based on the enamine-iminium ion mechanism, and started predominantly at the beginning of 2000s. Barbas III, List and Lerner published the first highly enantioselective L-proline **4** catalysed aldol reaction.[13] Subsequently, from **4**, several catalysts were synthesised, among the most important are the silyl prolinol derivative **5** and the proline tetrazole derivative **6**, introduced respectively by Jørgensen and co-workers,[14] and Ley and co-workers.[15] Another very successful class of organocatalyst was developed by MacMillan.[16] He used an imidazolidinone catalyst **7** especially useful for the iminium-ion catalysis.[6,17]

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[10] B. List *Chem. Rev.* **2007**, *107*, 5413.
[11] A. Berkessel, H. Gröger *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**, 9-12.
[12] For a very exhaustive reviews about different types of organocatalysts, see note 2e and 2f.
[13] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395; b) For a review, see: B. List, *Tetrahedron* **2002**, *58*, 5573; c) for its versatility in aldol related reactions, proline has been named "the simplest enzyme", see: d) M. Movassaghi, E. N. Jacobsen *Science* **2002**, *298*, 1904.
[14] a) M. Marigo, D. Fielenbach, A. Braunton, A. Kjœrsgaard, K. A. Jørgensen *Angew. Chem. Int. Ed.* **2005**, *44*, 3703. b) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabniz, A. Kjœrsgaard, K. A. Jørgensen *J. Am. Chem. Soc.* **2005**, *127*, 18296 and references cited therein.
[15] a) A. J. A. Cobb, D. M. Shaw, S. V. Ley *Synlett* **2004**, 558. b) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley *Org. Biomol. Chem.* **2005**, *3*, 84. c) K. Knudsen, C. E. T. Mitchell, S. V. Ley *Chem. Commun.* **2005**, 66. d) S. Kumarn, D. M. Shaw, S. V. Ley *Chem. Commun.* **2006**, 3211.
[16] For a review of MacMillan catalysts, see: G. Lelais, D.W. C. MacMillan *Aldrichimica Acta* **2006**, *39*, 79.
[17] a) W. S. Jen, J. J. M. Wiener, D.W. C. MacMillan *J. Am. Chem. Soc.* **2000**, *122*, 9874; b) A. B. Northrup, D. W. C. MacMillan *J. Am. Chem. Soc.* **2002**, *124*, 2458; c) R. K. Kunz, D. W. C. MacMillan *J. Am. Chem. Soc.* **2005**, *127*, 3240.

A second class of organocatalysts involves a nucleophilic activation with a formation of a covalent bond. Usually these catalysts have a chiral scaffold and a highly nucleophilic nitrogen, oxygen, sulphur or carbon atom, as shown in **Chart 1**. For example phosphoramides like **8** were introduced by Denmark and co-workers in 2001. These compounds catalyse, among others, the highly enantioselective addition of silyl enolates to aldehydes.[18] A catalyst comprising an oxygen nucleophile like **9** was reported by Kočovský *et al.* in 2002.[19] It has an *N*-oxide moiety that can activate an allylsilane for the addition to an aldehyde. The class of nitrogen-based nucleophiles is represented by the chiral DMAP derivative **10**, and the two *Cinchona* alkaloid derivatives **11** and **12**. Catalyst **10** was utilised for example in a chiral acylation, developed by Fu *et al.* with excellent results.[20] The *Cinchona* catalyst **11** was utilised instead by the Hatakeyama group in a successful Baylis-Hillman reaction,[21] while catalyst **12** was used by Gaunt, Ley and co-workers for a highly asymmetric cyclopropanation reaction.[22] A sulphur nucleophile (catalyst **13**) was employed by Metzner for the synthesis of epoxides from aldehydes and benzyl bromides.[23] Finally, the very important class of carbon nucleophiles, usually based on carbenes, is represented in **Chart 1** by the carbene precursor **14** which was used by Rovis and co-workers for a highly enantio- and diasteroselective Stetter reaction.[24]

[18] S. E. Denmark, S. Ghosh, *Angew. Chem. Int. Ed.* **2001**, *40*, 4759.
[19] a) A. V. Malkov, M. Orsini, D. Pernazza, K. W. Muir, V. Langer, P. Meghani, P. Kočovský *Org. Lett.* **2002**, *4*, 1047; A. Malkov, M. Bell, M. Orsini, D. Pernazza, A. Massa, P. Herrmann, P. Meghani, P. Kočovský *J. Org. Chem.* **2003**, *68*, 9659.
[20] For a review, see: G. C. Fu *Acc. Chem. Res.* **2000**, *33*, 412. Compound **10** contains an iron atom yet is generally regarded as an organocatalyst since the ferrocene is a structural element and not a functional group involved in the catalysis.
[21] Y. Iwabuchi, M. Nakatami, N. Yokoyama, S. Hatakeyama *J. Am. Chem. Soc.* **1999**, *121*, 10219.
[22] a) C. D. Papageorgiou, M. A. Cubillo de Dios, S. V. Ley, M. J. Gaunt *Angew. Chem. Int. Ed.* **2004**, *43*, 4641; b) N. Bremeyer, S. C. Smith, S. V. Ley, M. J. Gaunt *Angew. Chem. Int. Ed.* **2004**, *43*, 2681; c) C. C. C. Johansson, N. Bremeyer, S. V. Ley, D. R. Owen, S. C. Smith, M. J. Gaunt *Angew. Chem. Int. Ed.* **2006**, *45*, 6024.
[23] a) J. Zanardi, C. Leriverend, D. Aubert, K. Julienne, P. Metzner *J. Org. Chem.* **2001**, *66*, 5620; b) K. Julienne, P. Metzner, V. Henryon, A. Greiner *J. Org. Chem.* **1998**, *63*, 4532; c) K. Julienne, P. Metzner, V. Henryon, *J. Chem. Soc. Perkin Trans. 1* **1999**, 731.
[24] J. Read de Alaniz, T. Rovis *J. Am. Chem. Soc.* **2005**, *127*, 6289.

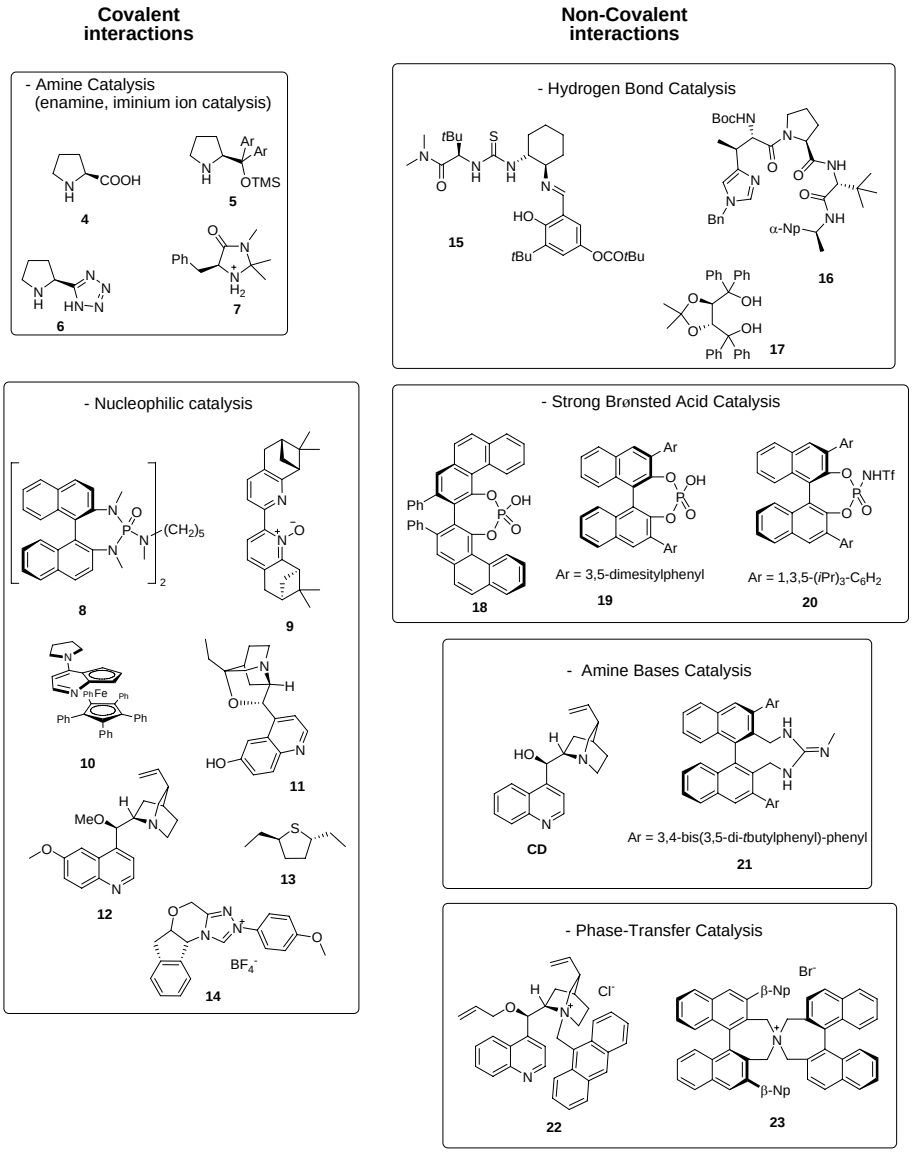

Chart 1 Some common types of chiral organocatalysts.

In the second part of **Chart 1** are shown some of the most important non-covalent organocatalysts: inside this category there are predominantly two types of interactions: hydrogen bonds and ion pairs. Jacobsen and Sigman in 1998 introduced the thiourea **15** in the first highly enantioselective transformation based on a H-bond activation, a Strecker reaction (reaction discussed deeper in chapter 1.4).[25] Miller and co-workers used instead the small peptide **16** for the 1,4 addition of azide to unsaturated ketones with

[25] M. S. Sigman, E. N. Jacobsen *J. Am. Chem. Soc.* **1998**, *120*, 4901.

excellent results in terms of catalyst loading, yields and enantiomeric excesses.[26] Another great achievement was the catalytic, enantioselective hetero Diels-Alder developed by Rawal *et al.*.[27] They used TADDOL **17** to catalyse a [4+2] cycloaddition reaction between a Danishefsky type diene and aldehydes with excellent yields and ees. A more recently developed class of organocatalysts uses a phosphoric acid moiety combined with chiral binaphtyl systems to mediate organic reactions. These catalysts, developed by Terada and Akiyama, are strong acids ($pK_a < 1$) and very efficient organocatalysts for the activation of imines through protonation. For example, Antilla and co-workers used the VAPOL derived phosphoric acid **18** in the enantioselective amidation of *N*-Boc imines for the synthesis of highly valuable building blocks.[28] Another significant example is the asymmetric addition of 2-methoxyfuran to *N*-Boc imines mediated by **19** with good results in terms of yields and enantioselections developed by Terada *et al.*[29] A more acidic organocatalyst (pKa < -1) able to activate less basic carbonyl compounds, such as ketones, was recently made by Yamamoto and co-workers; they synthesised the BINOL derived *N*-triflyl phosphoramide **20** that activated the carbonyl group in the cycloaddition of 1-substituted 2-siloxy-dienes with ethyl vinyl ketone obtaining very good results.[30]

Chiral bases are another very useful class of organocatalysts, and *Cinchona* alkaloids are certainly the most representative members of this class. A pioneering example was done by Wynberg and Hiemstra in 1981; they used cinchonidine **CD** in the addition of some thiophenol derivatives to cyclic α,β unsaturated ketones.[31] A different base catalyst was introduced by Terada and co-workers. They synthesised, by similarity with axial phosphoric acids, the binaphthyl derived guanidine **21** that was able to catalyse the additions of various β-dicarbonyl compounds to aromatic and aliphatic nitroolefins with high performance in term of catalyst loading and enantioselection.[32]

Finally, but not less important, the phase-transfer catalysis is a powerful method in organocatalysis based on ion pair interactions between a nucleophilic anion and a positively charged catalyst, often an ammonium salt. One of the most significant catalyst is the cinchonidine derived phase transfer catalyst **22**, independently developed by Corey and by Lygo and used for several transformations.[33] Few years later, Maruoka and co-workers introduced a new class of C2-symmetric chiral phase-transfer catalysts with

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[26] D. J. Guerin, S. J. Miller *J. Am. Chem. Soc.* **2002**, *124*, 2134.
[27] Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal *Nature* **2003**, *424*, 146.
[28] G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla *J. Am. Chem. Soc.* **2005**, *127*, 15696.
[29] D. Uraguchi, K. Sorimachi, Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804.
[30] D. Nakashima, H. Yamamoto *J. Am. Chem. Soc.* **2006**, *128*, 9626.
[31] H. Hiemstra, H. Wynberg *J. Am. Chem. Soc.* **1981**, *103*, 417.
[32] M. Terada, H. Ube, Y. Yaguchi *J. Am. Chem. Soc.* **2006**, *128*, 1454.
[33] B. Lygo, P. G. Wainright *Tetrahedron Lett.* **1998**, *39*, 1599; b) B. Lygo, P. G. Wainright *Tetrahedron* **1999**, *55*, 6289; c) E. J. Corey, F.-Y. Zhang *Org. Lett.* **1999**, *1*, 1287.

excellent results in many reactions. For example catalyst **23** was used by Maruoka in the alkylation of glycine Schiff base with very good results.[34]

Recently a different concept in organocatalysis arised. During the studies of different organocatalysts it was found that some of them work in a dual fashion. These catalysts, indeed, are able to activate not only one of the two partners of the reaction, but both the nucleophilic and the electrophilic species. These types of catalysts are named *bifunctional*.[35]

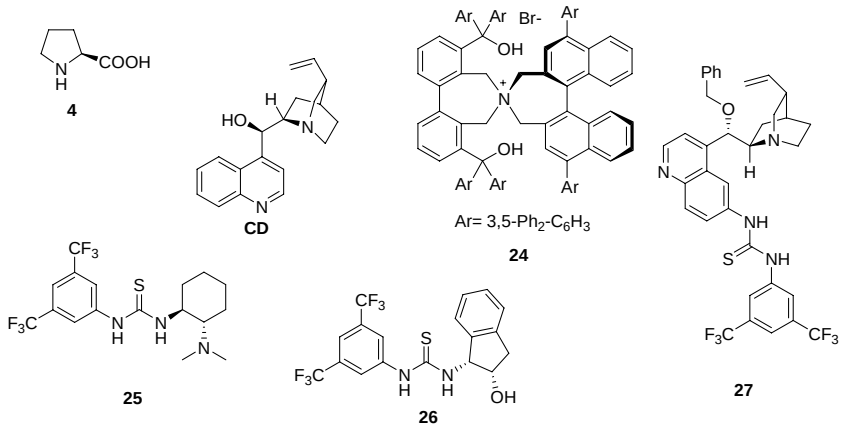

Chart 2 Some selected bifunctional organocatalysts.

In **Chart 2** a small number of bifunctional organocatalysts is shown. L-Proline **4** and cinchonidine **CD**, already reported in **Chart 1**, can also be considered bifunctional organocatalysts. These two molecules, besides the moiety that activates the nucleophile (by means of enamine and carbanion formation) present also a second moiety that usually activates the electrophile (by means of hydrogen bond).[13,31] Another interesting example of bifunctional catalyst was presented by Maruoka *et al.*. In 2004 they reported a highly asymmetric epoxidation of aromatic and aliphatic chalcones by means of catalyst **24**.[36] However, the most common motif which emerged in the last few years in the design of bifunctional organocatalysts, is certainly the thiourea moiety flanked by a group possessing basic properties. For example Takemoto and co-workers introduced **25** in the highly enantioselective additions of malonates to nitrolefins.[37] **25** showed the same characteristics mentioned above for **4** and **CD**; it has a thiourea moiety (electrophilic activation) and a basic tertiary nitrogen (basic activation). Ricci and co-workers showed instead that catalyst **26** catalysed the Friedel-Crafts alkylation of indoles with

[34] T. Ooi, M. Kameda, K. Maruoka *J. Am. Chem. Soc.* **1999**, *121*, 6519.
[35] L. Bernardi, F. Fini, M. Fochi, A. Ricci *Chimia* **2007**, *61*, 224.
[36] T. Ooi, D. Ohara, M. Tamura, K. Maruoka *J. Am. Chem. Soc.* **2004**, *126*, 6844.
[37] T. Okino, Y. Hoashi, Y. Takemoto *J. Am. Chem. Soc.* **2003**, *125*, 12672.

nitroalkenes in a enantioselective fashion, demonstrating that the catalyst activates both the electrophile and the nucleophile.[38] Another successful example was reported in 2005 by Hiemstra, who developed the first highly enantioselective organocatalytic Henry reaction by using the bifunctional catalyst **27**.[39]

[38] R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci *Angew. Chem. Int. Ed.* **2005**, *44*, 6576.
[39] T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra *Angew. Chem. Int. Ed.* **2006**, *45*, 929.

1.2. Large-Scale Applications of Organocatalysis

In the last twenty years the importance of enantiomeric purity increased dramatically, as most of the molecules used as active compounds in pharmaceutical, agrochemical, flavour industries are chiral and enantiopure. For this reason enantiomerically pure compounds (more than 95% *ee*) are strongly required and chemo- or biocatalytic processes become competitive against traditional technologies (chiral pool or resolution of racemates).[40] Moreover organocatalysed reactions might be even more convenient than the metal catalysed ones,[41] if the absence of metal contaminants is strictly required.[5] Nowadays there are already several chemical and pharmaceutical industries that use organocatalysts in their processes. Here, some topics in large scale reactions are reported.

Many commercially applications were performed with the Julia-Colonna epoxidation. Some of the biggest chemical industries in the world tried to use this process in the epoxidation of chalcone. The original epoxidation takes place in a three phase system with hydrogen peroxide giving the products in high yield and ee (>95%); however the reaction time was too long (1-5 days), catalyst loading was very high (>200% w/w) and a pre-activation was needed.[42] Surely this process was not economically valid for the industries. Bayer AG optimised the process introducing substantial changes in the original protocol. They optimised the catalyst preparation reducing the time of catalyst formation to 3 h with high efficiency (no activation is needed at all). The catalyst loading was decreased dramatically down to 10-20 % w/w (0.35-0.7 mol%) changing the original catalyst with poly-L-Leu. The result was quite good (yield 75 %, 97.6% *ee*) and could be preformed on a 100-g scale (**Scheme 3**).[43]

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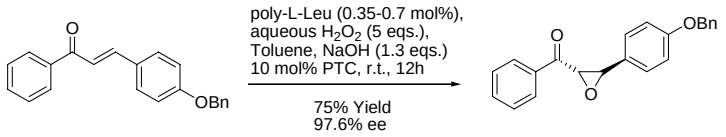
[40] H. U. Blaser, E. Schmidt *Asymmetric Catalysis on Industrial Scale*, Wiley-VCH, Weinheim, **2004**.

[41] For selected examples of recent organocatalytic patent applications, see: a) M. J. O'Donnel, S. Wu, I. Esikova, A. Mi US Pat. 5554753, **1996**; b) E. N. Jacobsen, M. S. Sigman PCT Int. Appl. WO 9951546, **1999**; c) D. W. C. MacMillan PCT Int. Appl. WO 2003002491, **2003**; d) N. Halland, K. A. Jørgensen, T. Hansen PCI Int. Appl. WO 20030619, **2003**.

[42] a) S. Julia, J. Masana, J. Vega, *Angew. Chem. Int. Ed.* **1980**, *19*, 929; b) S. Julia, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata, H. Molinari *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317.

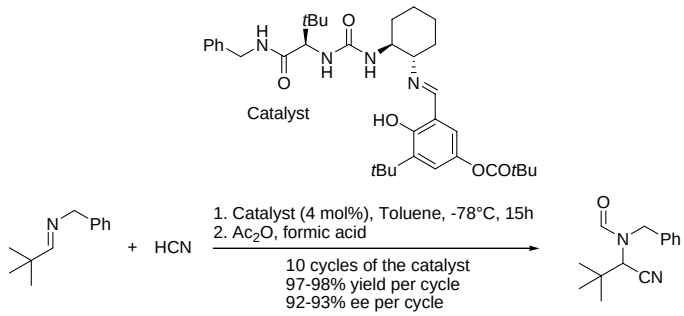
[43] a) T. Geller, A. Gerlach, C. M. Kruger, H.-C. Militzer *Tetrahedron Lett.* **2004**, *45*, 5065; b) T. Geller, C. M. Kruger, H.-C. Militzer EP Pat. 1279670, 2004; c) T. Geller, C. M. Kruger, H.-C. Militzer US Pat. 6770766, 2004; d) T. Geller, C. M. Kruger, H.-C. Militzer DE Pat. 10136132, 2003. e) T. Geller, C. M. Kruger, H.-C. Militzer *Tetrahedron Lett.* **2004**, *45*, 5069.



Scheme 3 Industrial Julia-Colonna-type epoxidation of a chalcone derivative.

Degussa AG introducing chemzyme membrane reactor (CMR) (the same technology used for the enzymatic resolution of α-amino acids on an industrial scale) built up a continuous epoxidation process. The catalyst was an oligo(L-Leu) polymer supported and the result was quite impressive; with 50 residence times the process was able to furnish 90-95 % ee and complete conversion.[44]

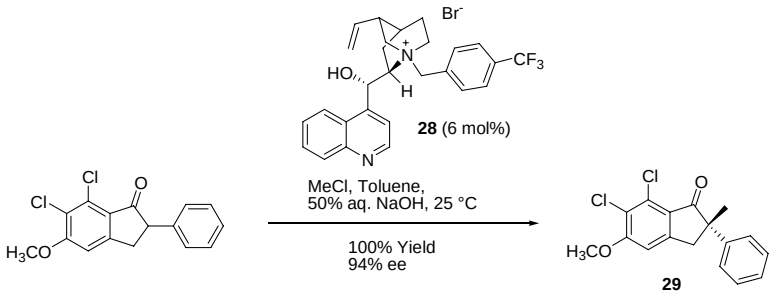
The Strecker reaction is one of the most powerful tools for the synthesis of α-amino acids (see chapter 4). Rodia ChiRex exploits the Jacobsen organocatalytic hydrocyanation of imines for the synthesis of L-*tert*-Leu in a bulk (**Scheme 4**).[45]



Scheme 4 Synthesis of L-*tert*-Leu by means of Jacobsen urea.

In the mid-1980s Merck chemists developed a very good process for the asymmetric alkylation of cyclic ketones in the presence of the *Cinchona* alkaloid ammonium salt derivative **28**.

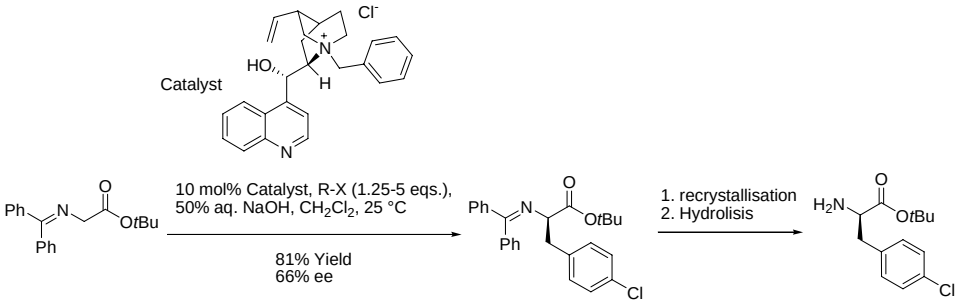
[44] S. B. Tsogoeva, J. Wöltinger, C. Jost, D. Reichert, A. Kuhnle, H.-P. Krimmer, K. Drauz *Synlett* **2002**, 707.
[45] http://www.Rhodiachirex.com/techpages/amino_acid_technology.htm



Scheme 5 Merk process by means of a phase transfer catalyst.

Using **28** as catalyst in 6 mol% loading it was possible to obtain **29** in quantitative yield and 94% *ee* at 25°C. In these conditions the process is more convenient than the resolution of the racemate. It was performed as a technical application on a pilot-plant reactor (**Scheme 5**).

Another very useful phase-transfer process is the alkylation of glycinate developed by O'Donnell and co-workers and subsequently optimised by Jew, Park *et al.* for a large scale reaction. It is possible to obtain hundreds grams of unnatural α-amino acids with satisfactory levels of ees and yields (**Scheme 6**).[41a,46]



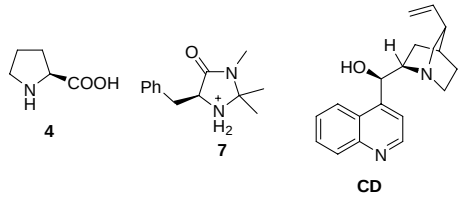
Scheme 6 Synthesis of D-*p*-chloro-phenylalanine by using PTC alkylation of glycine derivative.

After these few examples a general consideration is reported, clarifying the common characteristics of the organocatalysts.

Among the main criteria which must be discussed when assessing an organocatalytic reaction as a potential solution for a large-scale process are the price/availability and

[46] a) S. S. Jew, H. G. Park, B. S. Jeong, M. S. Yoo, S. H. Lee WO 2002083670, **2002**; b) S. S. Jew, H. G. Park, B. S. Jeong, M. S. Yoo, S. H. Lee, D. H. Cho WO 2003045948, **2003**; c) G. K. Mulholland, M. J. O'Donnel, F. T. Chin, F. Delgado WO 2002044144, **2002**; d) K. Fujita, Y. Taguchi, A. Oishi JP 3459986, **2003**.

stability of the catalyst, potential immobilisation, and finally, but not less important, catalyst loading, enantioselectivity and conversion of the final product.



Scheme 7 Some economically attractive organocatalysts

One of the major advantages of organocatalysis is the economy of the catalyst. Many organocatalysts are readily available and inexpensive raw materials from the chiral pool or are simple derivatives thereof. Representative examples of the many organocatalysts of economic interest are alkaloids and their derivatives (e.g. cinchonidine **CD**), or L-proline **4**, and natural amino acids, which function, for example as starting materials for MacMillan-type catalysts like **7** (**Scheme 7**). The economically attractive price of these catalysts might also "justify" the higher catalytic loadings occasionally required.

Other advantages of organocatalysts lie in their stability and handling. For most organocatalysts there are no concerns with regard to moisture sensitivity, which can be a serious issue for chiral metal complexes. Thus, special equipment for handling organocatalysts is often not required. Taking L-proline, MacMillan catalysts and alkaloid catalysts as representative examples, these compounds are stable and work well in the presence of moisture and air.

The possibility to recycle the catalyst is an important issue, as it would make possible to cut the cost dramatically, especially for the catalysts that are made by several steps, using expensive reagents. To facilitate the re-use, one of the most important techniques is the immobilisation of the catalyst in a solid support, typically polymeric arrays.

A problem of organocatalysis nowadays is that despite impressive results, the enantioselectivity obtained does not often exceed 98% *ee*. Because enantiomeric purity of >99% *ee* is required for pharmaceutical purposes, subsequent work-up and refining steps must be added to improve enantioselectivity. To avoid such subsequent purifications, further fine tuning of many catalysts is desirable. Besides asymmetric induction, conversion and productivity are also important.

1.3. *Cinchona* Alkaloids in Asymmetric Organocatalysis

Cinchona alkaloids are a large class of compounds extracted from the bark of homonym trees. The trees are cultivated above 1400 m in equatorial climatic zones, between Bolivian and Venezuelan Andes, and Indonesia (isle of Java). In the extract of the bark are present more than 30 alkaloids (5-15% w/w). Four of them represent 50 % of all the alkaloids: quinine (**QN**), quinidine (**QD**), cinchonidine (**CD**), cinchonine (**CN**). They have been quite important for all human kind. Quinine, the most known alkaloid, was the antimalarial drug of choice for over 400 years (it was abandoned in favour of chloroquine, less citotoxic).[47] Moreover it is used as bitter flavouring agent in food industry (e.g. tonic water or soft drinks).[48] Quinidine is employed in medicine as an antiarrhythmic agent. In chemistry, quinine and cinchonidine are utilised in the racemic resolution of Naproxen (very important FANS agent). For all these uses the production of these alkaloids is quite impressive (700 t/years). Not surprisingly, **QN**, **QD**, **CD**, **CN** are used in chemistry as chiral sources, as they are very cheap.

In 1820 Pasteur used a quinine derivative for resolution of a racemic tartaric acid,[49] and for many years remained the chiral resolving agentof choice.[50] The first example in asymmetric catalysis was reported in 1912 by Breding and Fiske; they catalysed the hydrocyanation of aldehyde with quinine and quinidine, obtaining poor enantiodiscrimination (ee <10%).[51] Another milestone in *Cinchona* catalysis was made by Pracejus et al. *O*-Acetyl quinine catalyses the methanolysis of phenylmethylketene **1** to (–)-α-phenyl methylpropionate **3** with 74 % *ee* (see **Scheme 1**, chapter 1.1).

A considerable improvement in the *Cinchona* chiral catalysis in was done in 1970s. Wynberg, Hiemstra and co-workers studied several reactions catalysed by quinine and its derivatives, obtaining excellent results and a quantity of mechanistic data for the addition of thiophenol to cycloexenone (**Scheme 8**).[31,52]

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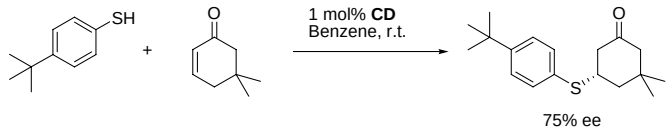
[47] T. S. Kaufman, E. A. Rúveda *Angew. Chem. Int. Ed.* **2005**, *144*, 854.
[48] a) D. C. McHale *The Biologist* **1986**, *33*, 45; b) F. Eiden *Pharmazie in unserer Zeit* **1998**, *27*, 257; c) P. M. Dewick *Medicinal Natural Products*, John Wiley & Sons, Chichester, New York, **1997**, 335; d) J. Herrmann *Pharm. Ztg.* **2001**, *146*, 1486.
[49] L. C. R. Pasteur *Acad. Sci.* **1853**, *37*, 162.
[50] a) P. Newman *Optical Resolution Procedures for Chemical Compounds*, Acids, Vol.2; Optical Resolution Information Center, Manhattan College, Riverdale; New York: **1981**, 7; b) J. Jacques, A. Collet, S. H. Wilen *Enantiomers, Racemates and Resolutions* Wiley, New York, **1981**, p.254; c) J. Jacques, A. Collet, S. H. Wilen *Enantiomers, Racemates and Resolutions* Wiley, New York, **1981**, p.257; d) R. A. Sheldon *Chirotechnology* Marcel Dekker, New York, **1993**, Chap. 6; e) *Chirality in Industry* Vol. 1: A. N. Collins, G. N. Sheldrake, J. Crosby Wiley, Chichester, **1992**; f) *Chirality in Industry* Vol. 2: A. N. Collins, G. N. Sheldrake, J. Crosby, Wiley, Chichester: **1997**.
[51] G. Brending, P. S. Fiske *Biochem. Z.* **1912**, *46*, 7.
[52] For a review see: a) H. Wynberg *Top. Stereochem.* **1986**, *16*, 87; b) K. Kacprzak, J. Gawroñski, *Synthesis* **2001**, 961.



Scheme 8 The enantioselective Michael of thiophenols to enones.

Dramatic enhancements were done in 1980s and 1990s. Indeed, *Cinchona* alkaloids derivatives were used in a phase transfer alkylation of glycine derivatives,[53] and in the Sharpless asymmetric dihydroxylation.[54] After all these successful and significant results *Cinchona* alkaloids are now recognised as a privileged class of chiral catalyst.[55]

The structures of the four alkaloids are quite interesting. It is possible to identify three different parts: the quinoline ring, the *vic*-amino function and the bicyclic moiety (**Figure 1**).

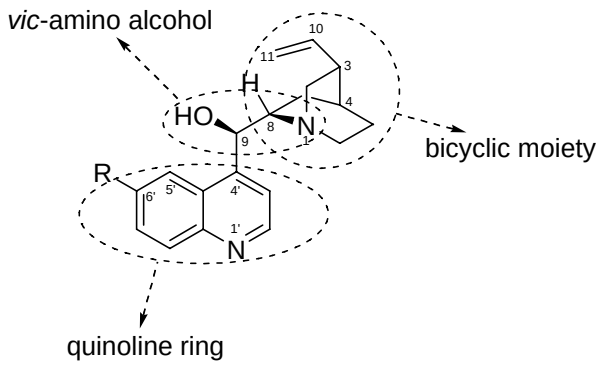
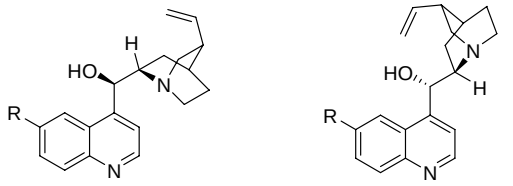


Figure 1. *Cinchona* alkaloids structure.

In all these bases are present five stereogenic centers, and the chiral quinuclidinic nitrogen is the most important as it is responsible of the direct transfer of chirality in catalysis. The four bases are diastereoisomers but are considered pseudo-enantiomers. Indeed, the N-C(8)-C(9)-O is usually the centre of the catalytic activity. Quinine *vs.* quinidine and cinchonidine *vs.* cinchonine have opposite absolute configuration this means that very often these pairs of diastereoisomers act as enantiomers (**Figure 2**). Furthermore, as mentioned above, in the molecules both Brønsted acid (C(9)OH) and base coexist, so it is possible to activate both the nucleophile and the electrophile. This behaviour makes several *Cinchona* alkaloid derivatives bifunctional organocatalysts.

[53] For a review, see: M. J. O'Donnell *Acc. Chem. Res.* **2004**, *37*, 506.
[54] For a review, see: H.C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless *Chem. Rev.* **1994**, *94*, 2483.
[55] T. P. Yoon, E. N. Jacobsen *Science* **2003**, *299*, 1691.



Quinine, **QN**, R= OMe,
Cinchonidine, **CD**, R= H

Quinidine, **QD**, R= OMe
Cinchonine, **CN**, R= H

Figure 2. A pseudoenantiomeric relationship.

The mentioned alkaloids are very flexible structures, there are many functional groups suitable for derivatizations. They can be used to synthesise a large number of catalysts.

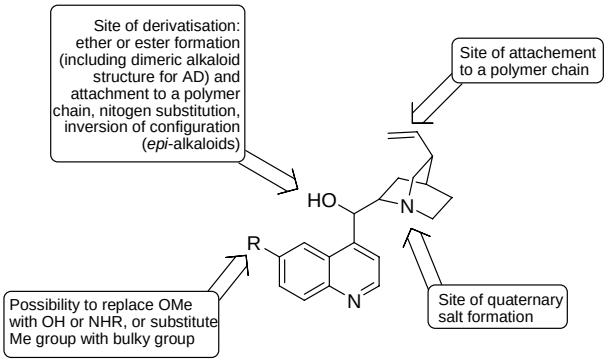
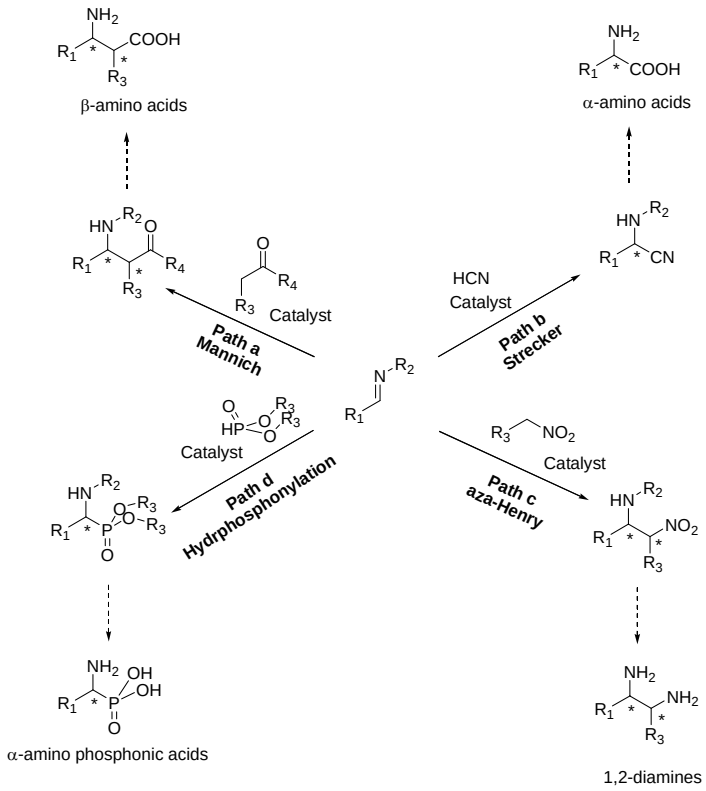


Figure 3 Preferred sites of derivatizations.

In general, the C(9)-OH, quinolinic OMe and quinuclidinic nitrogen are the preferred functional groups for the derivatizations. The C(9)-OH can be alkylated, the quinolinic OMe can be replaced in favour of a free hydroxyl group or an amino group, re-alkylated with bulky substituents; finally, but probably more important, the tertiary nitrogen can be alkylated to obtain a quaternary ammonium salt, used very often for phase-transfer catalysis (PTC). Moreover, there is another important modification in the *Cinchona* alkaloids chemistry, as the catalysts could be anchored in a solid support by different processes: polymerisation of the double bond, anchoring the catalyst alkylating the C(9)-OH, or the quinuclidinic nitrogen for the *P-T* catalysts (**Figure 3**).

1.4. Mannich-type Reactions

Chiral nitrogen-containing compounds are widely distributed in nature and include many biologically important molecules. In these compounds, the nitrogen-containing units are known to play important roles for their bioactivities. For the synthesis of these chiral nitrogen-containing building blocks, the use of imines as electrophiles is one of the most promising and convenient routes.[56] Indeed, Mannich-type reactions are certainly among the most important in organic chemistry (**Scheme 9**)[57]



Scheme 9 Mannich-type reactions.

Besides the proper Mannich reaction (**Scheme 9**, **Path a**), but also other very important transformations can be considered as part of this class: Strecker (**Scheme 9**, **Path b**), aza-

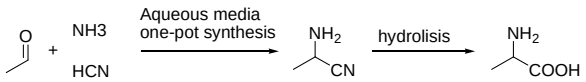
[56] a) R. A. Volkmann, *Comprehensive Organic Synthesis*, S. L. Schreiber, Ed., Pergamon: Oxford, **1991**, Vol. 1, p 355; b) D. Enders, U. Reinhold *Tetrahedron: Asymmetry* **1997**, *8*, 1895; c) R. Bloch *Chem. Rev.* **1998**, *98*, 1407; d) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069.

[57] For a review of catalytic enantioselective Mannich type reactions, see: S. Kobayashi, M. Ueno *Comprehensive Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Eds., Springer: Berlin, Germany, **2003**, Supp. 1, Chapter 29.5.

Henry (nitro-Mannich) (**Scheme 9**, **Path c**), hydrophosphonylation of imines (**Scheme 9**, **Path d**). Although the last reaction does not involve a carbon nucleophile, it can be considered as a Mannich-type taking into consideration its similarity with the more classical Mannich transformation.

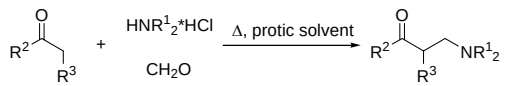
This thesis will focus on the organocatalytic version of these four reactions, mainly used for the synthesis of highly important building blocks: α-amino acids, β-amino acids, 1,2-diamines, α-amino phosphonic acids (**Scheme 9**).

According to a historical overview of these reactions, the Strecker reaction came first; indeed, already in 1850 Adolph Strecker reported the first example of the reaction that took his name.[58] It consists of a condensation of an aldehyde, ammonia, and cyanide source, followed by subsequent hydrolysis of the resulting α-amino nitrile (**Scheme 10**). When using amines instead of ammonia, the preformation of imines, followed by hydrocyanation instead of the one-pot synthesis represents a popular and widely used alternative route.



Scheme 10. Original Strecker reaction.

In 1912 Carl Mannich reported the first reaction that took his name.[59] He was also the first chemist that understood the importance of this new carbon-carbon bond forming reaction, doing a systematic research for a broad synthetic methodology. The reaction he reported was the condensation of formaldehyde with ammonia to form the corresponding iminium ion and a subsequent addition of a carbon nucleophile (enol). The product was a β-amino carbonyl compound and was named Mannich base (**Scheme 11**).

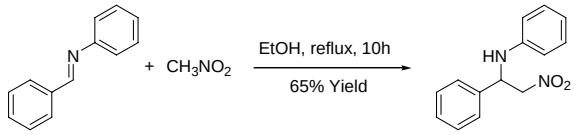


Scheme 11. Mannich reaction.

The aza-Henry or nitro-Mannich reaction has a different history. It was discovered as a direct consequence of Henry reaction (by replacing aldehyde with imines) and Mannich reaction (by replacing enols with nitro-paraffins). Only in 1950 Hurd and Strong reported the first example of aza-Henry, obtaining β-nitroamines in high yields (**Scheme 12**).[60]

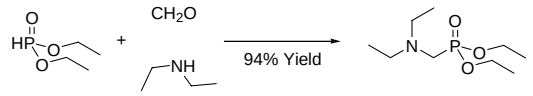
[58] A. Strecker *Ann. Chem. Pharm* **1850**, *75*, 27.
[59] C. Mannich, W. Krosche *Archiv der Pharmazie* **1912**, *250*, 647.
[60] C. D. Hurd, J. S. Strong *J. Am. Chem. Soc.* **1950**, *72*, 4813.

Although in 1943 it was reported a reaction with the same starting material, nitroolefins were obtained instead of β-nitroamines, probably due to harsh reaction condition.[61]



Scheme 12. The first aza-Henry reaction.

The general hydrophosphonylation of electrophilic double bond (alkenes, alkynes, carbonyl, and imines), forming a new carbon-phosphorous bond, is classified as Pudovik reaction.[62] The specific addition of dialkyl phosphite to in situ formed imines is named Kabachnik-Fields reaction, since these were the first researchers that studied this particular condensation.[63] They were contemporary to Pudovik. Kabachnik and Fields used an aldehyde, an amine and dialkyl phosphite as reagents, the formation of imines the intermediate for the subsequent addition. Contrary to the Mannich reaction this procedure resulted rather clean, and the crude product was quite pure even before distillation (**Scheme 13**).



Scheme 13. First addition of diethyl phosphite to an imine.

All the reactions that are mentioned in this thesis use aldimines as electrophilic partner, and for this reason a discussion about these fascinating compounds could be helpful. Imines are aza-analogues of aldehydes, with a carbon-nitrogen double bond. A nitrogen substituent is required for their stability. Their main characteristic is the electrophilicity of the carbon that could be adjusted by using different electronic features at the nitrogen substituent (**Figure 4**).[64]

[61] H. B. Hass, E. F. Riley *Chem. Rev.* **1943**, *32*, 409.
[62] A. N. Pudovik *Dokl. Akad. Nauk. SSSR* **1952**, *83*, 865; *Chem. Abstr.* **1953**, *47*, 4300.
[63] a) M. I. Kabachnic, T. Y. Medve *Dokl. Akad. Nauk. SSSR* **1952**, *83*, 689; *Chem. Abstr.* **1953**, *47*, 2724b; b) E. K. Fields *J. Am. Chem. Soc.* **1952**, *74*, 1528.
[64] M. Petrini *Chem. Rev.* **2005**, *105*, 3949 and references therein.

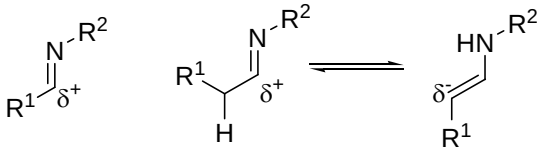


Figure 4 Imines

The utilization of aliphatic imines has a serious side process, i.e. an enolisation tautomerism could occur, mining the electrophilicity of the azomethine carbon.

It is also necessary to consider the synthetic utility of the product. Indeed, frequently, primary amines are required and the cleavage of the nitrogen substituent should be easily achieved. In addition, the nitrogen-linked group should activate the imines, be chiral or bulky, favouring highly enantio- or diastereo- control of the final product. Considering these tasks together, only few nitrogen substituents can be useful (**Chart 3**).[64]

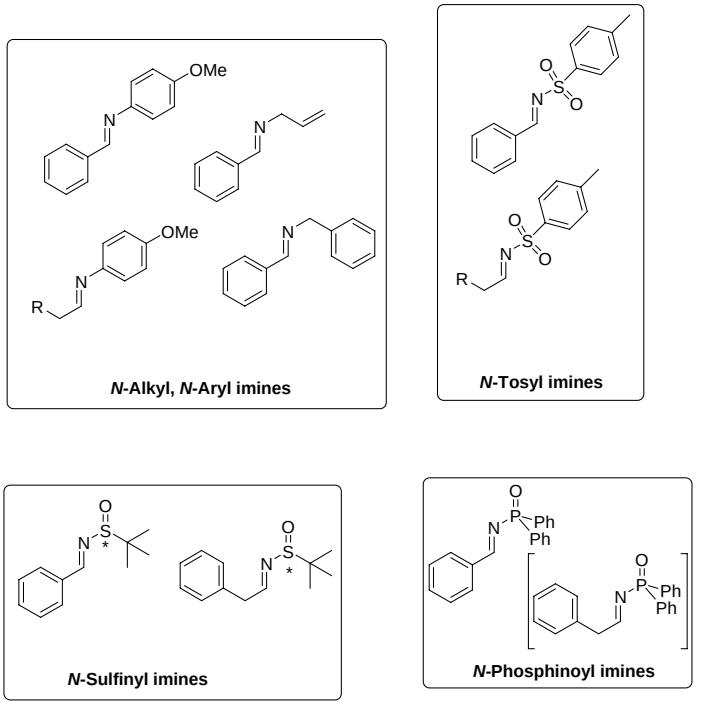


Chart 3 Different *N*-protected imines.

N-Alkyl imines (**Chart 3**, upper left) are often used in synthetic organic chemistry, and some alkyl groups frequently used are also easily removable. These azomethines with α enolisable hydrogens cannot be isolated. *N*-Aryl imines, (**Chart 3**, upper left) in particular with strong electron-donating group as *p*-methoxyphenyl, are usually more stable and even enolisable chains can be isolated without many problems. The cleavage of these

groups is quite difficult and very harsh conditions are required. A typical example could be the Birch reaction, sometimes using scavengers. Both mentioned groups do not activate the C-N double bond. This means that an iminium ion activation, mediated by Lewis or Brønsted acid, is a prerequisite for a good asset of the reaction.[64]

N-Tosyl imines (**Chart 3**, upper right), obtained from aromatic aldehydes are quite stable compounds, while the same derivatives obtained from aliphatic aldehydes must be freshly prepared before use. These imines have a strong electrophilicity, higher than the corresponding aldehyde but it is not trivial to remove the *N*-tosyl group.[64]

Another peculiar group is the *N*-sulfinyl (**Chart 3**, bottom left), having a stereogenic center and good electron–withdrawing properties. It is used as an auxiliary carrying the chiral information in a highly efficient way. Moreover both *C*-alkyl and *C*-aryl imines can be synthesised in high yield and the cleavage is not so difficult.[64]

Recently, *N*-phosphinoyl imines (**Chart 3**, bottom right) have gained a particular importance in a number of processes. This is an easily removable and bulky group, good for the diastereo- and enantio-discrimination in a nucleophilic addition reactions.[64]

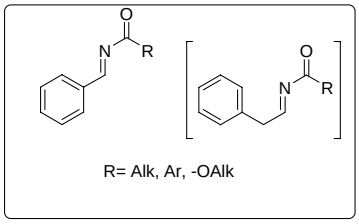
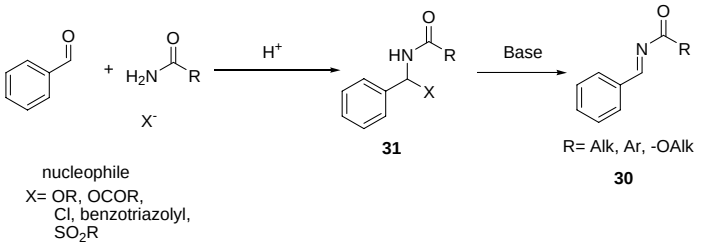


Chart 4 *N*-Acyl imines.

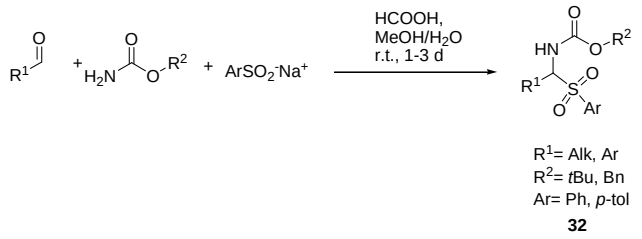
Finally, a very important class of imines is the substituted by *N*-acyl imines (**Chart 4**). They are quite electrophilic, the corresponding substituents are easy to cleave but are too unstable for a long storage, especially when bearing α enolisable hydrogens. However they are very useful and are one of the most used imines in organic synthesis, and also in this thesis they will be presented in many varieties (**Chart 4**).[64] The imines **30** are usually obtained in two steps. Firstly a precursor **31** is synthesised from an aldehyde, an amide or a carbamate and a suitable nucleophile by the intermediacy of a Brønsted acid. Usually the right nucleophile should give stability at the precursor, and be a good leaving group. In fact X^- should be easily eliminated if treated with base generating the required imines (**Scheme 14**).[64]



Scheme 14. General strategy for the synthesis of *N*-acyl imines.

During the last twenty years many examples were reported to overcome the instability of *N*-acyl imines. The most powerful tool is the in situ formation of imines through the treatment of a precursor **31** with a base. In this manner they are formed and immediately consumed in the nucleophilic addition. Many leaving groups have been used during the time but only few are good asset for both the imine formation and addition process. Although oxygenated groups are the most exploited and studied precursors, the sulfonyl group is probably better, as besides being a good leaving group, gives a superior stability to the intermediate **31**. Indeed, the α-amido sulfones **32** are bench stable white crystalline solids. Although numerous types of acyl groups could be synthesised, only carbamates, usually, are really used. Beside they, in fact *N*-carbamoyl substituents are quite stable, can also be easy removed under selected conditions. Especially *tert*-butyl carbamate, easily cleaved by using acidic conditions (pH< 4), or benzyl carbamate, cleaved by means of hydrogenolytic conditions, are intensely employed in organic synthesis.[64]

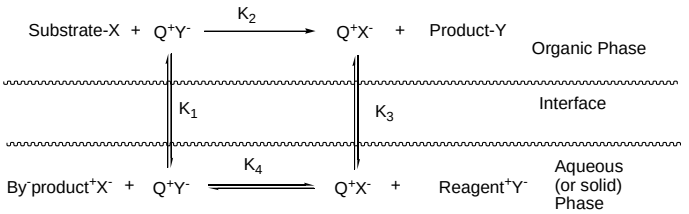
In general α-amido sulfones **32** can be easily synthesised in grams scale starting from the aldehyde and the corresponding carbamate, formic acid and arylsufinic acid sodium salt. The yields are generally good and the work-up consists in a filtration of the crude. They are frequently used without any further purification (**Scheme 15**).



Scheme 15. General synthesis of α-amido sulfones.

1.5. Phase-Transfer Catalysis

Phase-transfer catalysts (PTCs) are chemical agents that facilitate the transfer of a molecule or ion from one reaction phase to another and in doing so can greatly accelerate the rate of heterogeneous (polyphasic) reaction processes.[65] The simplest examples of these processes are "normal" biphasic phase-transfer reactions in which the catalyst facilitates reaction by solublizing a reagent or substrate ion in the organic phase (**Scheme 16**)



Scheme 16 Hypothetic phase transfer mechanism.

The most commonly used PTCs in reactions of this type are quaternary ammonium salts, and it has been shown that a number of subtly distinct mechanistic schemes are operative in these systems.[66] These variations relate to whether the ion exchange process takes place mainly in the aqueous phase (as implied in **Scheme 16**), the interfacial region, or in the organic phase.

Irrespective of the mechanistic detail, these processes often offer a number of advantages over homogeneous alternatives. The reactivity of the reagent anion (Y^-) in the organic phase is usually enhanced since the Q^+Y^- ion pair tends to have greater charge separation and reduced hydration compared to aqueous solutions of the precursor salt ($Reagent^+Y^-$). Consequently intrinsic reaction rates (k_2) tend to be significantly higher than those obtained in homogeneous media. Moreover the reactions are generally more selective (less side reactions) than homogeneous reactions due to controlled delivery of the reagent into the substrate-containing phase. The reaction conditions are usually

[65] a) M. E. Halpern *Phase Transfer Catalysis, Mechanisms and Synthesis*, American Chemical Society: Washington, DC, **1997**; b) *Handbook of Phase Transfer Catalysis* Y. Sasson, R. Neumann Eds., Blackie: London, **1997**; c) C. M. Starks, C. L. Liotta, M. C. Halpern, *Phase-Transfer Catalysis: Fundamentals, Applications, and Industrial Perspectives* Chapman & Hall, New York, **1994**; d) *Phase Transfer Catalysis* E. V. Dehmlow, S. S. Dehmlow Eds., VCH, Weinheim, **1993**; e) B. Lygo, Phase-Transfer Reactions, *Rodd's Chemistry of Carbon Compounds, Vol. V: Asymmetric Catalysis*, Elsevier Science Ltd., Oxford, **2001**, 101; f) R. A. Jones *Quaternary Ammonium Salts. Their Use in Phase-Transfer Catalysis*, Academic Press, London, **2001**.

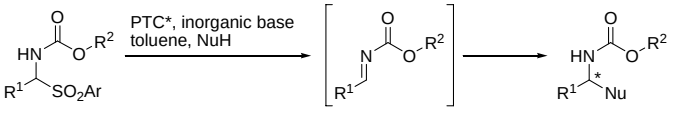
[66] See, for example: a) S. S. Yufit, S. S. Zinovyev *Tetrahedron* **1999**, *55*, 6319; b) D. Landini, A. Maia, F. Montanari *J. Chem. Soc., Chem. Commun.* **1977**, 112; c) M. Makosza, E. Bialecka *Tetrahedron Lett.* **1977**, *18*, 183; d) C. M. Starks, R. M. Owens *J. Am. Chem. Soc.* **1973**, *95*, 3613.

compatible with a wide variety of (water-immiscible) organic solvents. This allows the opportunity to select a solvent that is optimal for recovery or reuse or both in prior or subsequent synthetic steps. In addition, it is sometimes possible to utilize the substrate itself as the organic phase, thus eliminating the need for any organic solvent.

The biphasic nature of the processes greatly simplifies reagent and byproduct separation and hence product isolation. The catalysts (quaternary ammonium salts) are usually inexpensive and are biodegradable. This makes PTC reactions highly attractive alternatives than the processes that use polar, water-miscible solvents.

Because of these advantages, phase-transfer reactions have been recognized as "green" alternatives to many homogeneous reaction processes, and they have found widespread application in synthetic organic chemistry.[65,67] In the last 25 years, increasing attention has focused on the development of asymmetric phase-transfer processes.[68] Our own work in this area has centered on the use of *Cinchona* alkaloid derived quaternary ammonium salts in enantioselective Mannich-type reactions.

In this thesis we will present aspects of this work that relate to the use of chiral phase transfer catalysis in Mannich-type reactions, forming of *N*-carbamoyl imines in situ from α-amido sulfones. This is a novel protocol that will change the philosophy of the imine use (**Scheme 17**).



32

Scheme 17. Enantioselective nucleophilic additions to α-amido sulfones 32 by using chiral phase transfer catalysis.

[67] M. Makosza *Pure Appl. Chem*. **2000**, *72*, 1399.
[68] a) M. J. O'Donnell, Asymmetric Phase-Transfer Reactions, *Catalytic Asymmetric Synthesis*, 2nd ed.; I. Ojima, Ed., Verlag Chemie, New York, **2000**; b) T. Shioiri, Chiral Phase-Transfer Catalysts, *Handbook of Phase-Transfer Catalysis*, Y. Sasson, R. Neumann, Eds., Blackie, London, **1997**.

2. Aza-Henry

2.1. Introduction

The addition of nitroalkanes to imines, known as aza-Henry (nitro-Mannich) reaction, allows a straightforward entry to a variety of nitrogen-containing chiral buildings blocks. Indeed, the products β-nitroamines can undergo different manipulations, giving 1,2-diamines by means of the nitro group reduction or α-amino carbonyl compounds by using the Nef reaction. However, considering the harsh conditions needed for the Nef reactions, the most useful manipulation of β-nitroamines is the reduction, as it requires usually very mild reactions conditions, providing 1,2-diamines in high yields.

1,2-Diamines are highly valuable building blocks in organic synthesis,[69] and display an interesting biological activity.[70] For instance many antiarrhythmics,[71] antidepressants,[72] antihypertensives, antipsychotics, analgesics, antianxiety agents, anticancer drugs,[73] and antiparasitic agents, all contain the 1,2-diamino moiety in their structure.

Besides their applications in medicinal chemistry, in recent years the use of vicinal diamines has increased considerably also in organic synthesis, being the key structural unit of a series of chiral auxiliaries and ligands for metal catalysed reactions.[69]

Although the first report was published in 1950,[74] only in the last 10 years the aza-Henry reaction was studied in its catalytic asymmetric version. Here some significant results are reported during these years.

[69] For a review, see: D. Lucet, T. Le Gall, C. Mioskowski *Angew. Chem. Int. Ed.* **1998**, *37*, 2580.
[70] For a review on medicinal agents incorporating the 1,2-diamino unit: E. T. Michalson, J. Szmuszkovicz *Prog. Drug Res.* **1989**, *21*, 370.
[71] Z. Zubovics, L. Toldy, A. Varró, G. Rablokzky, M. Kürthy, P. Dvortsák, G. Jerkovich, E. Tomori *Eur. J. Med. Chem. Chim. Ter.* **1986**, *21*, 370.
[72] J. Szmuszkovicz, P. F. Von Voigtlander, M. P. Kane *J. Med. Chem.* **1981**, *24*, 1230.
[73] a) H. Brunner, P. Hankofer, U. Holzinger, B. Trettinger, H. Schönenberger *Eur. J. Med. Chem.* **1990**, *25*, 35; b) H. Brunner, P. Hankofer, U. Holzinger, B. Trettinger *Chem. Ber.* **1990**, *123*, 1029; c) R.Gust, T. Burgemeister, A. Mannschreck, H. Schönenberger *J. Med. Chem.* **1990**, *33*, 2535; d) L. R. Kelland, G. Abel, M. J. McKeage, M. Jones, P. M. Goddard, M. Valenti, B. A. Murrer, K. R. Harrap *Cancer Res.* **1993**, 2581; e) D.-K. Kim, Y.-W. Kim, H.-T. Kim, K.-H. Kim *Bioorg. Chem. Lett.* **1996**, *6*, 643; f) A. R. Khokhar, S. Al-Baker, S. Shamsuddin, Z. K. Siddik *Bioorg. Chem. Lett.* **1997**, *40*, 112; g) J. Reedijk *Chem. Commun.* **1996**, 801.
[74] For detailed information about the history of aza-Henry reaction, See chapter 1.4.

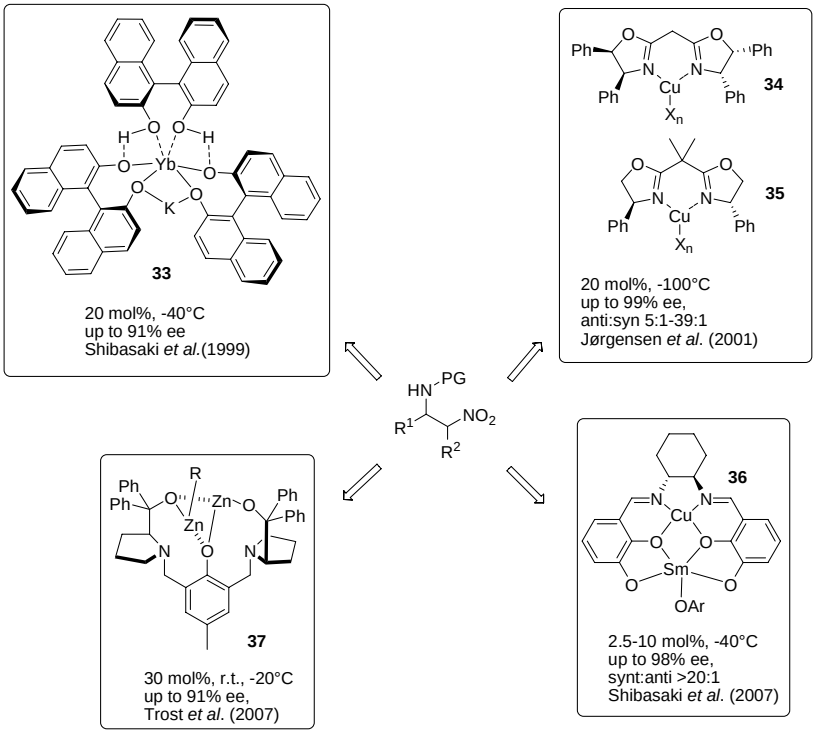


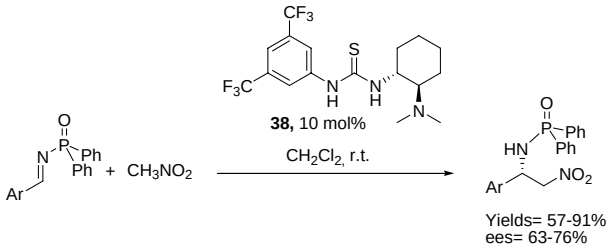
Chart 5 Some highly enantioselective metal catalysts for the aza-Henry reaction

The first example of a catalytic enantioselective aza-Henry reaction was reported by Shibasaki and co-workers and was based on a heterobimetallic BINOL-based catalyst **33**.[75] This catalyst contains both Lewis acidic (ytterbium) and basic (potassium alkoxide) sites in an asymmetric environment (**Chart 5**, upper left). The group of Jørgensen showed later that simple Cu-bisoxazolines complexes **34**, **35** are highly attractive catalyst for the aza-Henry reaction: high enantiomeric excess were obtained in THF at -100°C (**Chart 5**, upper right).[76] Very recently Shibasaki *et al.* developed a new samarium-copper complex **36** for the aza-Henry reaction, obtaining for the first time the diasteromeric syn adducts with high enantioselection (**Chart 5**, bottom right).[77] Finally Trost *et al.* developed the bimetallic zinc complex **37** which allowed the reactions to be carried out at a somewhat higher temperature but with a higher catalyst loading (**Chart 5**, bottom left).[78]

The use of metal-free catalysis for the aza-Henry reaction has probably met the same success. However, before we started our investigations only three examples could be found in the literature.

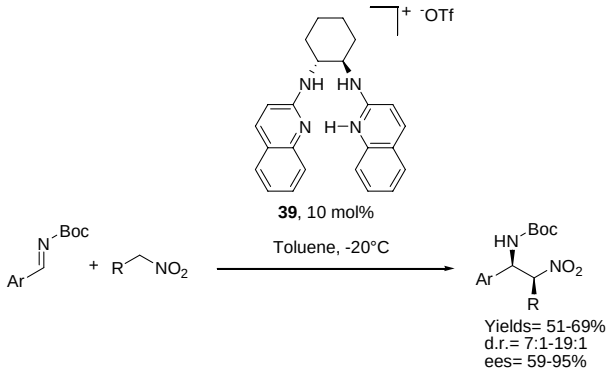
[75] K.-i. Yamada, S. J. Harwood, H. Gröger, M. Shibasaki *Angew. Chem. Int. Ed.* **1999**, *38*, 3504.
[76] K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, K. A. Jørgensen *J. Am. Chem. Soc.* **2001**, *123*, 5843.
[77] S. Handa, V. Gnanadesikan, S. Matsunaga, M. Shibasaki *J. Am. Chem. Soc.* **2007**, *129*, 4900.
[78] B. M. Trost, D. W. Lupton *Org. Lett.* **2007**, *9*, 2023.

In 2004, the Takemoto thiourea-tertiary amine catalyst **38** was applied to the addition of nitroalkanes to aromatic *N*-phosphinoyl imines.[79] Working at r.t. and with 10 mol% catalyst loading good enantiomeric excesses and high yields were achieved (**Scheme 18**).



Scheme 18 Aza-Henry reaction mediated by Takemoto's bifunctional organocatalyst.

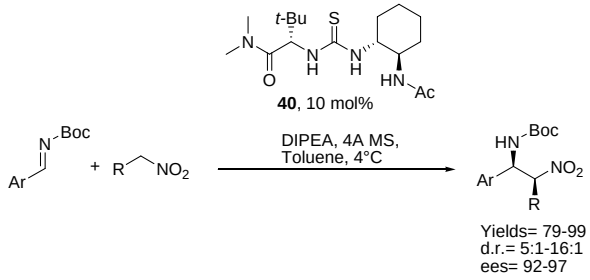
Johnston and co-workers almost simultaneously applied the chiral bisamidine triflic acid salt **39** to the enantioselective addition of nitromethane and nitroethane to electron-deficient aromatic *N*-Boc imines.[80] Also in this case, very good results in terms of enantioselection and yield were obtained (**Scheme 19**).



Scheme 19 Johnston's chiral bisamidine 39 catalysed enantioselective aza-Henry reaction.

Soonafter, at the beginning of 2005 Jacobsen *et al.* using the thiourea derivative **40** were able to promote the highly stereoselective addition of a range of nitroalkanes to aromatic *N*-Boc imines (**Scheme 20**).[81]

[79] T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto *Org. Lett.* **2004**, *6*, 625.
[80] B. M. Nugent, R. A. Yoder, J. N. Johnston *J. Am. Chem. Soc.* **2004**, *126*, 3418.
[81] T. P. Yoon, E. N. Jacobsen *Angew. Chem. Int. Ed.* **2005**, *44*, 466.



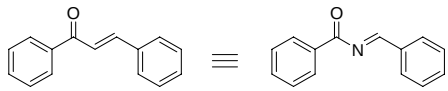
Scheme 20 Jacobsen thiourea derivative for the asymmetric aza-Henry reaction.

Albeit appreciable results were achieved in the aza-Henry reactions mentioned above, they are restricted to aromatic imines, as a consequence at least in part of the instability of *N*-Carbamoyl imines derived from enolisable aldehyde.

2.2. Results and Discussion

Considering the background of information acquired from the group, in the aza-Henry reactions during the past few years,[82] we decided to explore this reaction using an organocatalytic protocol mediated by *Cinchona* alkaloid derivatives.

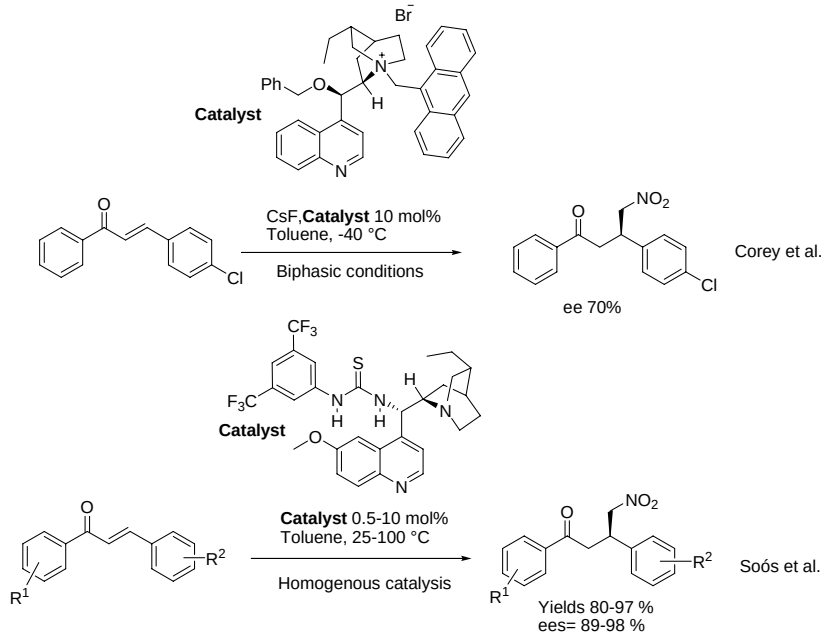
For this purpose we planned to use *N*-carbamoyl imines as a highly versatile azomethine electrophile.[83] In this context it was considered that *N*-acyl aromatic imines possess an intriguing analogy with chalcones (**Scheme 21**).



Scheme 21 Analogy between N-acyl imines and chalcones.

Two different conditions for the highly enantioselective addition of nitromethane to chalcones were reported in the literature. Corey and co-workers in 1999-2000 developed the *Cinchona* alkaloid quaternary ammonium derivative catalysed addition of nitromethane to various chalcones (**Scheme 22**, top).[84] Soós *et al.* developed more recently the highly enantioselctive addition of nitromethane to chalcones by using a *Cinchona* alkaloid derivative as a chiral base catalyst (**Scheme 22**, bottom).[85]

[82] L. Bernardi, B. F. Bonini, E. Capitò, G. Dessole, M. Comes-Franchini, M. Fochi, A. Ricci *J. Org. Chem.* **2004**, *69*, 8168.
[83] For more detail see Chapter 1.5.
[84] a) S. Colonna, H. Hiemstra, H. Wynberg, *J. Chem. Soc. Chem. Commun.* **1978**, 238; b) E. J. Corey, F.-Y. Zhang *Org. Lett.* **2000**, *2*, 4257; c) E. J. Corey, F.-Y. Zhang *Angew. Chem. Int. Ed.* **1999**, *38*, 1931.
[85] B. Vakulya, S. Varga, A Csampái, and T. Soós *Org. Lett.* **2005**, *7*, 1967.



Scheme 22. Different additions of nitromethane to chalcones by means of homogeneous and biphasic conditions.

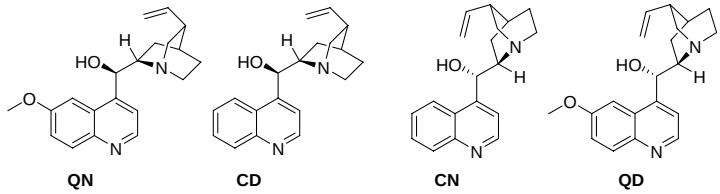
For this reason we started an investigation trying both these two types of conditions: homogenous and biphasic, by using *Cinchona* alkaloid derived catalysts.

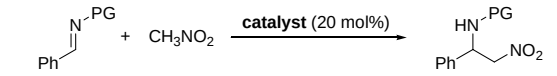
The first attempt was done under homogeneous conditions. At the outset of these studies a broad screening of reagents, catalysts and reaction parameters was done. Firstly the type of imine was taken in consideration, a particular focus was addressed towards the group installed at the nitrogen), in combination with the four natural *Cinchona* alkaloids as catalysts, and using toluene as a solvent at room temperature (**Table 1**).

The β-nitroamines **44a**, **45a**, **46a**, were obtained in fairly good yields with moderate enantioselectivities from Cbz-, Boc-, and Fmoc- *N*-protected benzaldehyde imines **41a**, **42a**, **43a** in the presence of quinine (**QN**) (**Table 1**, entries 1–4) and of quinidine (**QD**) (**Table 1**, entries 10 and 11). In the case of the (diphenylphosphinoyl) DPP-, Ts-, and *t*-BuCO- benzaldehyde imines **43b**,**c**,**e** a drop of the ee was noticed (**Table 1**, entries 5, 6, and 9) accompanied in the case of the former by a sizeable decrease in the chemical yield. Even more disappointing were the results with (*p*-methoxyphenyl) PMP imine **43d**, which gave even under forcing conditions (**Table 1**, entry 7) poor conversion and no ee at all. However, by running the reaction in the presence of 20% TFA a significant improvement was observed in terms both of conversion and ee (**Table 1**, entry 8). We

speculated that the reaction on an electron rich imine can proceed efficiently only if the imine is activated by protonation with a Brønsted acid such as TFA.[86]

Table 1. Results from the screening of various imines 41, 42, 43 using unmodified cinchona alkaloids as catalysts.[a]





41a: PG= Cbz
42a: PG= Boc
43a: PG= Fmoc
b: PG= Ts
c: PG= DPP
d: PG= PMP
e: PG= *t*-BuCO

44a: PG= Cbz
45a: PG= Boc
46a: PG= Fmoc
b: PG= Ts
c: PG= DPP
d: PG= PMP
e: PG= *t*-BuCO

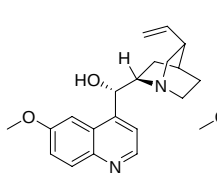
Entry	Imine	PG	Adduct	Catalyst	Conversion (%)[b]	*ee* (%)[c]
1	**41a**	Cbz	**44a**	**QN**	>95	53
2	**41a**	Cbz	**44a**	**QN**	90	61[d]
3	**42a**	Boc	**45b**	**QN**	>95	51
4	**43a**	Fmoc	**46a**	**QN**	>95	48
5	**43b**	DPP	**46b**	**QN**	50	12
6	**43c**	Ts	**46c**	**QN**	>95	30
7	**43d**	PMP	**46d**	**QN**	10[e]	rac
8	**43d**	PMP	**46d**	**QN**	>95[e,f]	40
9	**43e**	*t*-BuCO	**46e**	**QN**	>95	27
10	**43a**	Fmoc	**46a**	**QD**	>95	52
11	**41a**	Cbz	**44a**	**QD**	80	55
12	**41a**	Cbz	**44a**	**CN**	15	25
13	**41a**	Cbz	**44a**	**CD**	15	40

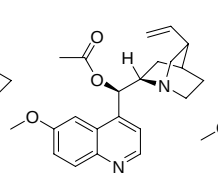
[a] Unless noted, reactions were run at 20°C, for 18 h in toluene (0.1 M). [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral stationary phase HPLC. [d] Reaction performed in mesitylene as the solvent. [e] Reaction performed in CH_3NO_2 (0.25 M). [f] Reaction performed in the presence of TFA (20 mol%).

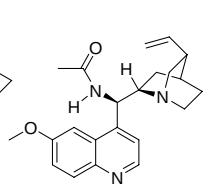
[86] H. Adams, J. C. Anderson, A. M. K. Pennel *J. Org. Chem* **1998**, *63*, 9932.

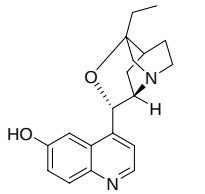
On changing the nature of the organocatalysts, cinchona alkaloids **CD** and **CN** not bearing any oxygen-based substituent at position 6' in the quinoline ring were found to afford (**Table 1**, entries 12 and 13) the desired adduct **44a** in poor yields and with enantioselectivities significantly lower than those bearing a 6'-methoxyquinoline moiety. Next, the influence of modifications on the natural *Cinchona* bases was studied using Cbz-, Boc-, and Fmoc- imines **41a, 42a, 43a**, (**Table 2**) which had shown the most promising results in the previous screening. However these protecting groups and give some added value to the products, for their synthetical usefulness.

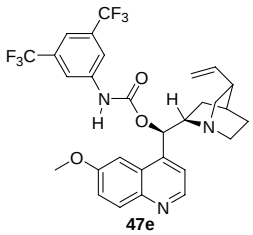
Table 2. Modified cinchona bases screened for the aza-Henry reaction using imines 41a, 42a, 43a.[a]

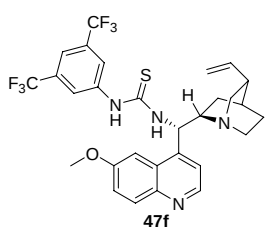


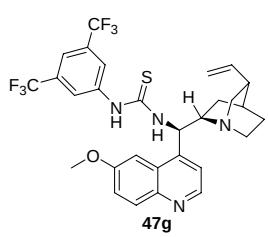


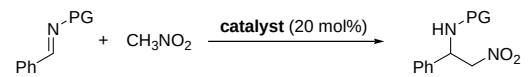












41a: PG= Cbz
42a: PG= Boc
43a: PG= Fmoc

44a: PG= Cbz
45a: PG= Boc
46a: PG= Fmoc

Entry	Imine	PG	Adduct	Catalyst	T (°C)	t (h)	Conversion (%)[b]	*Ee* (%)[c]
1	**41a**	Cbz	**44a**	**QN**	20	18	>95	53
2	**41a**	Cbz	**44a**	**47b**	20	120	<10	-
3	**41a**	Cbz	**44a**	**47e**	20	120	<10	-
4	**41a**	Cbz	**44a**	**47d**	20	120	20	37
5	**41a**	Cbz	**44a**	**47f**	20	22	46[d]	61
6	**41a**	Cbz	**44a**	**47f**	-24	22	64[d]	84
7	**42a**	Boc	**45a**	**QN**	20	18	>95	51
8	**42a**	Boc	**45a**	**47a**	20	18	45	56

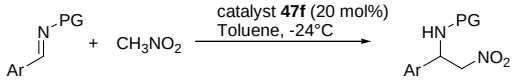
9	**42a**	Boc	**45a**	**47c**	20	120	<10	-
10	**42a**	Boc	**45a**	**47g**	20	18	30	19
11	**42a**	Boc	**45a**	**47f**	20	18	60[d]	76
12	**42a**	Boc	**45a**	**47f**	0	20	58[d]	81
13	**42a**	Boc	**45a**	**47f**	-24	20	52[d]	86
14	**42a**	Boc	**45a**	**47f**	-24	23	63[d,e]	85
15	**42a**	Boc	**45a**	**47f**	-24	18	72[d,f]	88
16	**43a**	Fmoc	**46a**	**47f**	-24	43	60[d,f]	90

[a] Unless noted, reactions were run 0.1 M in toluene. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral stationary phase HPLC. [d] Yield of product isolated after silica gel chromatography. [e] Reaction (0.05 M). [f] Reaction (0.2 M).

As shown in **Table 2**, unlike the catalytic efficiency shown by **QN** catalyst (entry 1), derivatives **47b** and **47e**, in which the OH of the quinine moiety has been protected via acetylation or carbamate formation, and derivative **47c** with the alcoholic function replaced by a benzamido moiety, did not give rise to the formation of the desired adducts in significant yields (**Table 2**, entries 2, 3, and 9). Neither the presence of a newly formed N-H bond in **47c** and **47e** seemed to convey to these modified *Cinchona* alkaloids any catalytic activity. Modest catalytic efficiency, accompanied by moderate enantioselectivity, was observed (**Table 2**, entry 4) on the other hand in the case of the conformationally more rigid catalyst **47d** bearing a phenolic moiety, which could eventually provide a site for hydrogen bonding.[21] To explore the influence, in terms of catalytic efficiency and enantioselectivity, of the quinine-epiquinine change,[31] epiquinine **47a** catalysed addition of nitromethane to the *N*-Boc protected imine **42a** was examined. Even though the conversion in the reaction was lower, the comparable enantioselectivities (**Table 2**, compare entries 7 and 8) suggested that the proper conformation of the *Cinchona* derivatives as such may not be crucial in the case for successful catalysis. Within the range of enantioselectivities observed, the best results were obtained with catalysts bearing methoxy and hydroxy functionalities. These findings prompted us to apply to the aza-Henry reaction the bifunctional *Cinchona*-based catalysts **47f** and **47g** bearing a stronger Lewis acid thiourea moiety.[85] By running the reaction with quinine-derived catalyst **47f** under the standard conditions adducts **45a** and **45a** were obtained (**Table 2**, entries 5 and 11) in satisfactory isolated yields and with ee's up to 76%, whereas organocatalyst **47g** with the natural configuration, derived from epiquinine turned out to be much less efficient (**Table 2**, entry 10). These results are in line with our previous consideration on the analogy between chalcones and *N*-acyl imines; also in the case of chalcones, catalysts bearing a thiourea moiety were the most efficient in terms of *ee* for the addition of CH_3NO_2.[85] Next, the influence of two

experimental parameters (temperature and concentration) was evaluated using the most efficient catalyst **47f**. Very good levels of enantioselectivity were observed on lowering the temperature (**Table 2**, entries 6, 11–13), and at -24°C with an increase of the imine concentration to 0.2 M, adducts **45a** and **46a** were obtained (**Table 2**, entries 15 and 16) with up to 90% *ee*. Adduct **45a** in **Table 2** was determined to have the (*S*) configuration by comparison with the literature data.[80,81]

Table 3. Scope of the aza-Henry reaction using imines 41, 42 and catalysts 47f.



41: PG= Cbz
42: PG= Boc

44: PG= Cbz
45: PG= Boc

Entry	Ar	PG	Imine	Adduct	t (h)	Yield (%)[a]	*ee* (%)[b]
1	1-Napht	Boc	**42b**	**45b**	20	87	88
2	2-Napht	Boc	**42c**	**45c**	23	95	85
3	2-Napht	Boc	**42c**	**45c**	38	82	94[c]
4	4-ClC_6H_4	Boc	**42d**	**45d**	68	77	94
5	4-ClC_6H_4	Cbz	**41b**	**44b**	45	58	90
6	2-BrC_6H_4	Boc	**42e**	**45e**	24	66	80
7	2-BrC_6H_4	Boc	**42e**	**45e**	72	82	88[c]
8	4-$MeOC_6H_4$	Boc	**42f**	**45f**	45	65	82
9	2-Thienyl	Boc	**42g**	**45g**	40	50	82
10	2-Furyl	Boc	**42h**	**45h**	40	70	44
11	2-Furyl	Boc	**42h**	**45h**	48	58	63[c]

[a] Yield of product isolated after silica gel chromatography [b] Determined by chiral stationary phase HPLC. [c] Reaction performed at -40°C.

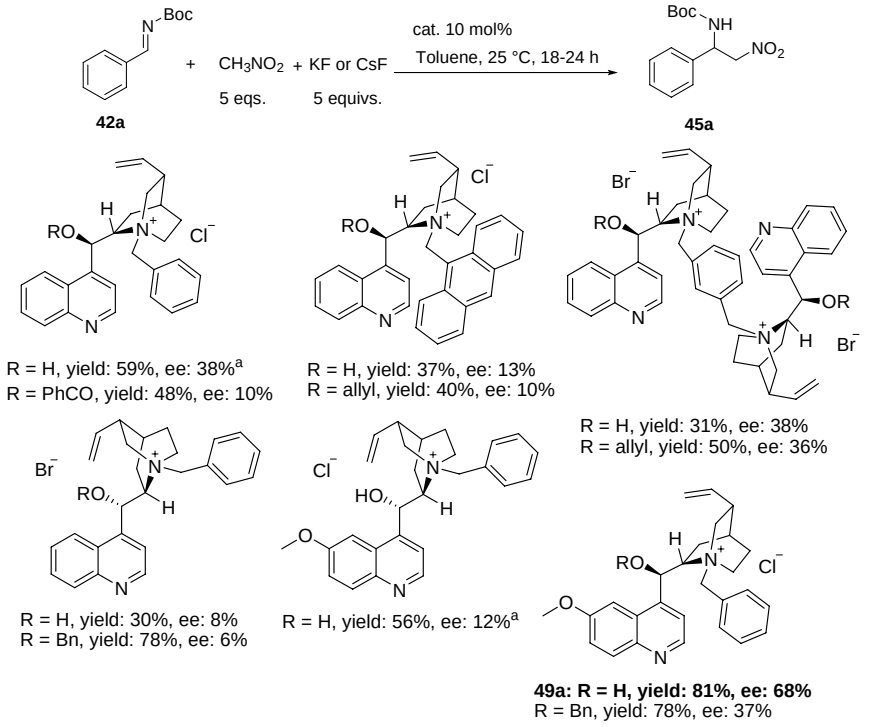
To establish the generality of this reaction in substrate scope we finally examined the aza-Henry reaction with representative *N*-Boc imines under catalysis by **47f** and the results are reported in **Table 3**. *N*-Fmoc imines were not taken into consideration due to their more tedious synthesis, compared with *N*-Boc and *N*-Cbz imines. The reaction appeared tolerant with respect to the nature of the imine and the benefits of catalyst **47f** extended over a wide range of substrates. The desired adducts were isolated in satisfactory to good yields and synthetically useful levels of enantioselectivity, with 1- and 2-naphthaldehyde-derived imines **42b-c** (**Table 3**, entries 1–3) and with benzaldimine derivatives **42d-f**, **41b** bearing both electron donating and electron withdrawing substituents (**Table 3**, entries 4–8). The good results obtained using the Cbz-protected

imine **41b** further confirm the tolerance of this catalytic reaction to different *N*-acyl protecting groups (**Table 3**, entry 5). Among the aromatic heterocyclic aldimines, the 2-thiophenecarboxyaldehyde derived imine **42g** (**Table 3**, entry 9) gave better results with respect to the oxygenated analogue **42h** (**Table 3**, entry 10 and 11).

Summarising first part of this project, we have developed a highly enantioselective organocatalysed aza-Henry reaction using nitromethane and a range of aromatic and heteroaromatic differently protected imines, by means of *Cinchona* alkaloids derivative as a chiral base catalyst, under homogeneous conditions.

As in the previous examples of catalytic asymmetric aza-Henry reaction, the reaction was limited to aromatic imines due to the instability of the enolisable aliphatic counterparts.

The second attempt was done using phase-transfer conditions. For this purpose, *N*-Boc imine **42a** was treated in the presence of catalytic amounts of several *Cinchona*-derived quaternary ammonium salts and KF as a base (**Scheme 23**), under the solid-liquid PTC conditions used by Corey and co-workers for the enantioselective addition of nitromethane to chalcones (**Scheme 22**, top).[84] Among the catalysts tested, the commercially available *N*-benzyl quininium chloride **49a** proved to be the most effective, furnishing the corresponding β-nitroamine **45a** after 18 h in good yield of isolated product and with moderate, but promising, enantiomeric excess (**Scheme 23**).



[a] Reaction carried out on the corresponding α-amido sulfone **48a**, see **Scheme 24**

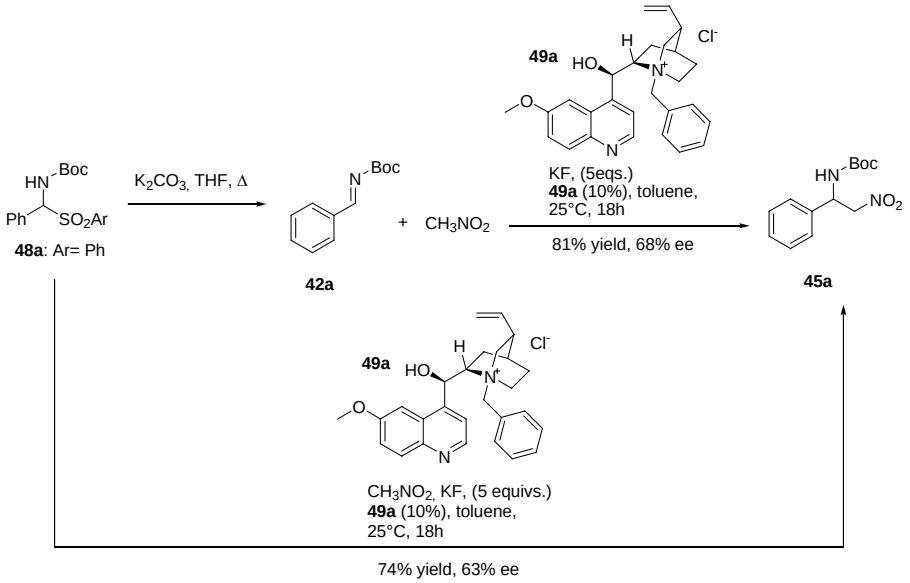
Scheme 23 Representative results from the screening of different catalysts in the addition of nitromethane to imine 42a.

During our studies we noticed that both phase transfer catalysis and *N*-carbamoyl imines synthesis use almost the same reaction conditions (biphasic ones by means of solid or aqueous inorganic base).[87] We therefore decided to try to synthesise the imine in situ, using directly the α-amido sulfones in the reaction.[88] Indeed, two reports, not dealing with asymmetric transformation, indicated the feasibility of this approach.[89]

[87] A method for the synthesis of aromatic *N*-Boc imines involves the treatment of α-amido sulfones with K_2CO_3 in THF at reflux for several hours: A. M. Kanazawa, J.-N. Denis, A. E. Greene, *J. Org. Chem.* **1994**, *59*, 1238.

[88] J. Morton, A. Rahim, E. R. H. Walker, *Tetrahedron Lett.* **1982**, *23*, 4122; b) N. Hermanns, S. Dahmen, C. Bolm, S. Bräse *Angew. Chem. Int. Ed.* **2002**, *41*, 3692; c) D. Enders, S. Oberbörsch, *Synlett* **2002**, 471; d) C. Palomo, M. Oiarbide, A. Landa, M. C. González-Rego, J. M. García, A. González, J. M. Odriozola, M. Martin-Pastor, A. Linden *J. Am. Chem. Soc.* **2002**, *124*, 8637; e) C. Palomo, M. Oiarbide, C. González-Rego, A. K. Sharma, J. M. García, A. González, C. Landa, A. Linden *Angew. Chem. Int. Ed.* **2000**, *39*, 1063; f) M. Petrini, R. Profeta, P. Righi *J. Org. Chem.* **2002**, *67*, 4530; g) N. Giri, M. Petrini, R. Profeta, *J. Org. Chem.* **2004**, *69*, 7303, and references therein.

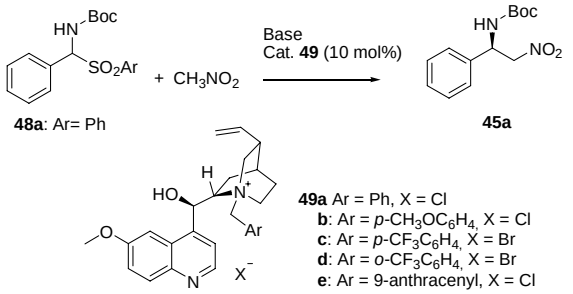
[89] R. Kimura, T. Nagano, H. Kinoshita *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2517; b) V. Banphavichit, S. Chaleawlertumpon, W. Bhanthumnavin, T. Vilaivan *Synth. Commun.* **2004**, *34*, 3147.



Scheme 24. Comparison between two different approaches for the aza-Henry reaction: the use of preformed imines and the direct use of α-amido sulfones 48a.

As shown in **Scheme 24** we were pleased to find that the catalytic asymmetric aza-Henry reaction performed by means of α-amido sulfones under PTC conditions provided β-nitroamine **45a** in good yield and enantiomeric excess. More importantly was the comparison of the two processes: in fact the one-step process, that uses directly α-amido sulfones without any isolation of the intermediate gave practically the same results in term of enantioselction than the reaction carried out with the preformed imines. This demonstrated for the first time that the formation of the *N*-Boc imine under PTC condition can be combined with an asymmetric addition of a nucleophile, such as nitromethane.

Table 4. Enantioselective reaction of nitromethane with α-amido sulfone 48a catalysed by quinine derived salts 49a-e under different reaction conditions.



Entry	Cat. **49**	Solvent	Base	T (°C)	t (h)	Yield (%)[a]	ee (%)[b]
1	**49a**	Toluene	KF	25	18	74	63
2	**49a**	THF	KF	25	18	85	30
3	**49a**	$CHCl_3$	KF	25	16	58[c]	54
4	**49a**	Toluene	K_2CO_3	25	18	81[c]	53
5	**49b**	Toluene	KF	25	18	80	60
6	**49c**	Toluene	KF	25	18	52	48
7	**49d**	Toluene	KF	25	18	84	48
8	**49e**	Toluene	K_2CO_3	25	18	>90[d,e]	46
9	**49a**	Toluene	KF	-20	18	<20[d,f]	nd
10	**49a**	Toluene	CsF	-20	22	84[c]	60
11	**49a**	Toluene	KOH	-45	40	95[g]	84

[a] Isolated yield after chromatography on silica gel. [b] Determined by chiral stationary phase HPLC. [c] The use of the corresponding cesium salts (CsF, Cs_2CO_3) gave comparable results. [d] Conversion, as determined by ^{1}H NMR analysis of the crude mixture. [e] The reaction with KF as a base furnished the product in very poor yield (<20%) after 48 h at 25 °C. [f] α-Amido sulfone **48a** was recovered unchanged. [g] Reducing the amount of either nitromethane, base or catalyst caused a dramatic decrease in the reaction efficiency.

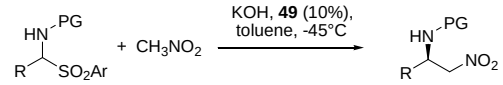
Starting from these results we have done a further screening of different reaction conditions. As shown in **Table 4**, the β-nitroamine **45a** could be obtained in satisfactory yield and with a moderate level of enantioselectivity (63% ee) from **48a** using **49a** in toluene (**Table 4**, entry 1). The use of other solvents such as THF or CH_2Cl_2, or K_2CO_3 as the base, caused a slight erosion of the enantioselectivity (**Table 4**, entries 2-4).[90] Then we shortly investigated the effect of the structure of catalyst **49** by varying the substituent on the quinuclidine nitrogen still keeping the quinine structure with the free hydroxy moiety in line with the optimisation coming from the screening done on the imines. However, we

[90] The use of the corresponding cesium salts (CsF, Cs_2CO_3) gave comparable results.

found an electron donating group in *para* position of the phenyl ring having little effect on the enantioselectivity of the reaction (**Table 4**, entry 5), whereas an electron withdrawing trifluoromethyl substituent in *ortho* or *para* position was detrimental (**Table 4**, entries 6,7). We also tried catalyst **49e**, with a (9-anthracenyl)methyl substituent, as *Cinchona* derivatives bearing this group often give improved results in PTC enantioselective reactions,[33] but also this catalyst, in combination with K_2CO_3 as the base,[91] furnished the β-nitroamine **45a** with slightly lower enantioselectivity with respect to **49a** (entry 8). At -20°C, KF in combination with **49a** was not able to promote the formation of the imine (**Table 4**, entry 9), whereas the corresponding cesium salt gave good conversion of the starting α-amido sulfone **48a** at the same temperature, but no improvement in the enantioselectivity was observed (**Table 4**, entry 10). Considering that a stronger base might be necessary for the reaction to proceed efficiently at low temperature, solid KOH was used, furnishing at –45 °C the product **45a** in good yield and with useful enantiomeric excess (**Table 4**, entry 11).[92]

We next investigated the generality of this new catalytic enantioselective addition of nitromethane to *N*-carbamoyl imines generated in situ from **50** by varying both the substituent of the starting compound **48** and the protecting group (PG) on the nitrogen atom (**Table 5**).

Table 5 Catalytic asymmetric addition of nitromethane to *N*-carbamoyl imines generated in situ from α-amidosulfones 48a-l under PTC.[a]



48a-h: Ar= Ph
i-m: Ar= *p*-tol
50a,c: Ar=*p*-tol

45a-m
44a,c

Entry	48	R group	PG	**44**,**45**	t (h)	Yield (%)[b]	Ee (%)[c]
1	**48a**	Ph	Boc	**45a**	40	95	84 (>99)[e]
2	**48e**	*o*-BrC_6H_4	Boc	**45b**	64	70	76
3	**48f**	*p*-$MeOC_6H_4$	Boc	**45c**	60	75[d]	88 (>99)[e]
4	**48b**	1-naphtyl	Boc	**45d**	44	95	84
5	**48h**	2-furyl	Boc	**45e**	25	81	75
6	**48i**	$PhCH_2CH_2$	Boc	**45f**	40	98	95
7	**48j**	Cy	Boc	**45g**	42	84	98
8	**48k**	*i*-Pr	Boc	**45h**	40	95	95

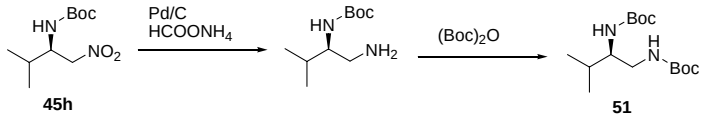
[91] The reaction with KF as a base furnished the product in very poor yield (<20%) after 48 h at r.t.
[92] Reducing the amount of either nitromethane, base or catalyst caused a dramatic decrease in the reaction efficiency.

9	**48l**	Et	Boc	**45i**	40	92	94
10	**48m**	Me	Boc	**45j**	43	86	92
11	**50a**	Ph	Cbz	**44a**	44	53[f]	73
12	**50c**	Cy	Cbz	**44c**	40	96[f]	93

[a] Experimental conditions: finely ground KOH (0.5 mmol) was added to a cooled mixture (-45°C) of 50 (0.1 mmol), **48** (0.01 mmol), and CH_3NO_2 (0.5 mmol) in toluene (1 mL), and the reaction mixture vigorously stirred for the stated time. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral stationary-phase HPLC. [d] aqueous KOH (50% w/w) was used in the reaction. [e] After single crystallisation. [f] A mixture of toluene/CH_2Cl_2 (1:1) was used as the solvent.

A few α-amido sulfones **48a-h** derived from aromatic and heteroaromatic aldehydes were treated with nitromethane under the optimized reaction conditions, furnishing the corresponding optically active *N*-Boc β-nitroamines **49a-e** in fairly good yield and enantiomeric excess (entries 1-5). It is worthy to note that **45a** and **45c** could be obtained in essentially enantiopure form after a single crystallization (entries 1 and 3). Moreover, we found that this new strategy for the catalytic enantioselective aza-Henry reaction was particularly effective for the synthesis of *N*-Boc α-alkyl β-nitroamines, which could not be obtained by the previously reported methods. As a matter of fact, **48i-m**, derived from both linear and branched aliphatic aldehydes, all gave the corresponding β-nitroamines **45f-j** in very good yields and enantioselectivities (entries 6-10). The efficiency of the present method for this class of substrates is well accounted for by the high enantiofacial discrimination in the imine derived from **48m** (entry 10) bearing a proton and a small methyl group. Variation of the protecting group on the nitrogen atom was then shortly investigated using **50a** and **50c** bearing a Cbz moiety (entries 11 and 12), thus demonstrating that the present method is not restricted to obtaining *N*-Boc-protected β-nitroamines. Also in this case, **50c**, derived from an aliphatic aldehyde, gave better results with respect to **50a**.

The absolute configuration of the products was determined by comparison of the HPLC retention time and optical rotation of **45a** with reported values[80,81] and by reduction of **45h** to the known diamine derivative **51** (**Scheme 25**).[93]



45h **51**

Scheme 25. Mild reduction of β-nitroamine 45h to a *N*,*N*'-diBoc derivative 51.

[93] D. Enders, J. Wiedemann *Synthesis* **1996**, 1443.

Attack on the *Si* face of the intermediate imine by the nitronate and quininium ion pair accounts for the R configuration at the stereogenic centre observed in both cases.

In summary, in the second part of this project we have developed a new catalytic enantioselective approach to the asymmetric nucleophilic addition of nitromethane to *N*-carbamoyl imines generated in situ from α-amido sulfones. The chiral phase-transfer catalyst acts in a dual fashion,[94] first promoting the formation of the imine under mild reaction conditions and then activating the nucleophile for asymmetric addition. This was the first demonstration that it is possible to use the highly versatile *N*-Boc, *N*-Cbz imines demonstrated for the aliphatic enolisable aldehydes as a azomethine electrophile. The potential of this approach was confirmed in the reaction of nitromethane with α-amido sulfones, which could be efficiently catalysed by a simple and commercially available quininium salt. Besides the mild reaction conditions and the operational simplicity, this method allowed *N*-carbamoyl imines derived from enolisable aldehydes to be used for the first time in a catalytic asymmetric aza-Henry reaction, thus extending the generality of this asymmetric transformation.

[94] For another example of two sequential processes carried out using a cinchona-derived phase-transfer catalyst, see: B. Lygo, D. C. M. To *Chem. Commun.* **2002**, 2360.

2.3. Experimental Section

General Methods. All reactions were carried out in test tubes. ^{1}H and ^{13}C NMR spectra were measured on a Varian AS 400 spectrometer running at 400 and 100 MHz respectively in $CDCl_3$ as the solvent. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H NMR and to the central line of $CDCl_3$ (77.0 ppm) for ^{13}C NMR. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES^+) ionisation techniques. Flash column chromatography (FC) was carried out using Merck silica gel 60 (230-400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 22°C. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H or AS). Melting points are uncorrected. Imines **41a**, **43a, 41b**,[95] **42a-h**,[104] as well as catalyst **47f**[85] were prepared following literature procedures. All commercially available solvents and reagents were used as received. α-Amido sulfones **48** and **50** were obtained following literature procedures.[96] Racemic samples were obtained using tetrabutylammonium bromide as the catalyst.

***Cinchona* alkaloids derivative catalyse Homogeneous aza-Henry reaction**

Optimised General Procedure for the Catalytic Enantioselective Aza-Henry Reaction. Table 3. In a test tube, to a cooled (-24 °C) solution of the imine **1** (0.1 mmol) and catalyst **VI** (11.9 mg, 0.02 mmol) in toluene (500 μL), nitromethane (27 μL, 0.5 mmol) was added in one portion. The test tube was placed in a freezer at –24 °C for the time reported in **Table 2**, **Table 3**, then the products **44a,b**, **45b-h**, **46a** were obtained by FC on silica gel (CH_2Cl_2).

2-Nitro-1-phenylethyl carbamic acid benzyl ester (44a). Following the general procedure, compound **44a** was obtained as a yellow solid in 64% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{major} = 17.1 min; τ_{minor} = 24.9 min). R_f 0.41 (*n*-hexane: EtOAc, 7:3); mp 67-70 °C; ^{1}H NMR δ 4.65 (dd, J = 4.6, 12.6 Hz, 1H), 4.72-4.88 (br s, 1H), 5.04 (s, 2H), 5.33-5.42 (br s, 1H), 5.46-5.57 (br s, 1H), 7.17-7.35 (m, 10H); ^{13}C NMR δ 53.2, 67.4, 78.6, 126.3, 128.2, 128.4, 128.6, 128.9, 129.2, 135.8, 136.4, 155.4; ESIMS *m/z* 323 [M + Na^+]**;** $[\alpha]^{22}_D$ +5 (c = 0.348, $CHCl_3$), 84% ee.

(*S*)-2-Nitro-1-phenylethyl carbamic acid *t*-butyl ester (45a). Following the general procedure, compound **45a** was obtained as a white solid in 72% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, τ_{major} = 36.0 min; τ_{minor} = 38.2 min). $[\alpha]^{22}_D$ +14 (c = 0.578, $CHCl_3$), 88% ee. The ^{1}H and ^{13}C NMR spectra and mp are consistent with values previously reported in the literature.[80]

(9-*H*-Fluoren-9-yl)methyl 2-nitro-1-phenylethylcarbamate (46a). Following the general procedure, compound **46a** was obtained as a white solid in 60% yield. The ee of

[95] J. Vidal, S. Damestoy, L. Guy, J.-C Hannachi, A. Aubry, A. Collet *Chem. Eur. J.* **1997**, *3*, 1691.
[96] a) W. H. Pearson, A. C. Lindbeck, J. W. Kampf *J. Am. Chem. Soc.* **1993**, *115*, 2622; b) E. Bernacka, A. Klepacz, A. Zwierzak *Tetrahedron Lett.* **2001**, *42*, 5093; c) A. G. Wenzel, E. N. Jacobsen *J. Am. Chem. Soc.* **2002**, *124*, 12964.

the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{major} = 23.7 min; τ_{minor} = 42.3 min). R_f 0.51 (*n*-hexane: EtOAc, 7:3); mp 148-150 ºC; ^{1}H NMR δ 4.20 (t, J = 6.6 Hz, 1H), 4.38-4.62 (br s, 2H), 4.62-4.94 (br s, 2H), 5.36-5.60 (br s, 2H), 7.22-7.64 (m, 11H), 7.66 (d, J = 7.6 Hz, 2H); ^{13}C NMR δ 47.1, 53.1, 67.1, 78.4, 120.0, 124.9, 126.3, 127.1, 127.8, 128.8, 129.3, 136.4, 141.3, 143.6, 155.4; ESIMS *m/z* 411 [M + Na^+]; $[\alpha]^{22}_D$ +11 (c = 0.675, $CHCl_3$), 90% ee.

1-(1-Naphthyl)-2-nitroethyl carbamic acid *t*-butyl ester (45b). Following the general procedure, compound **45b** was obtained as a white solid in 87% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, τ_{major} = 17.0 min; τ_{minor} = 25.7 min). R_f 0.64 (*n*-hexane: EtOAc, 7:3); mp 174-177 ºC; ^{1}H NMR δ 1.43 (s, 9H), 4.80-4.98 (br s, 2H), 5.24-5,38 (br s, 1H), 6.22-6.34 (br s, 1H), 7.44-7.48 (m, 2H), 7.52-7.58 (m, 1H), 7.60-7.64 (m, 1H), 7.84-7.86 (m, 1H), 7.88-7.92 (m, 1H), 8.11-8.13 (m, 1H); ^{13}C NMR δ 28.2, 49.2, 78.2, 80.8, 122.2, 123,2, 125.2, 126.3, 127.3, 129.2, 129.5, 130.3, 132.6, 134.1, 154.7; ESIMS *m/z* 339 [M + Na^+]**;** $[\alpha]^{22}_D$ +7 (c = 0.498, $CHCl_3$), 88% ee.

1-(2-Naphthyl)-2-nitroethyl carbamic acid *t*-butyl ester (45c). Following the general procedure, performing the reaction at –40 °C, compound **45c** was obtained as a white solid in 82% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, τ_{major} = 17.8 min; τ_{minor} = 21.5 min). R_f 0.79 (*n*-hexane: EtOAc, 7:3); mp 144-146 ºC; ^{1}H NMR δ 1.45 (s, 9H), 4.80 (dd, J = 5.5, 12.6 Hz, 1H), 4.88-5.00 (br s, 1H), 5.34-5.46 (br s, 1H), 5.50-5.60 (br s, 1H), 7.40 (dd, J = 1.8, 8.5 Hz, 1H), 7.48-7.54 (m, 2H), 7.76 (m, 1H), 7.82-7.88 (m, 3H); ^{13}C NMR δ 28.3, 53.0, 78.8, 80.8, 123.7, 125.6, 126.7, 126.7, 127.7, 128.0, 129.2, 133.2, 133.2, 134.2, 154.8; ESIMS *m/z* 339 [M + Na^+]; $[\alpha]^{22}_D$ +38 (c = 0.505, $CHCl_3$), 94% ee.

1-(*p*-Chlorophenyl)-2-nitroethyl carbamic acid *t*-butyl ester (45d). Following the general procedure, compound **45d** was obtained as a white solid in 77% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, τ_{major} = 12.8 min; τ_{minor} = 16.1 min). R_f 0.68 (*n*-hexane: EtOAc, 7:3); mp 128-131 ºC; ^{1}H NMR δ 1.44 (s, 9H), 4.68 (dd, J = 5.0, 12.6 Hz, 1H), 4-76-4.9 (br s, 1H), 5.28-5.40 (br s, 2H), 7.23-7.27 (m, 2H), 7.34-7.37 (m, 2H); ^{13}C NMR δ 28.2, 52.2, 78.6, 80.9, 127.7, 129.4, 134.6, 135.4, 154.6; ESIMS *m/z* 323 [M + Na^+]; $[\alpha]^{22}_D$ +20 (c = 0.790, $CHCl_3$), 94% ee.

1-(*p*-Chlorophenyl)-2-nitroethyl carbamic acid benzyl ester (44b). Following the general procedure, compound **2k** was obtained as a yellow oil in 58% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 90:10, flow rate 0.75 mL/min, τ_{major} = 36.7 min; τ_{minor} = 59.0 min). R_f 0.45 (*n*-hexane: EtOAc, 7:3); ^{1}H NMR δ 4.68 (dd, J = 5.1, 12.7 Hz, 1H), 4.76-4.89 (br s, 1H), 5.10 (s, 2H), 5.36-5.45 (br s, 1H), 5.63-5.71 (br s, 1H), 7.20-7.41 (m, 9H)**;** ^{13}C NMR δ 52.6, 67.5, 78.3, 127.7, 128.4, 128.6, 128.9, 129.4, 129.9, 134.8, 135.7, 155.3; ESIMS *m/z* 357 [M + Na^+]**;** $[\alpha]^{22}_D$ +8 (c = 0.160, $CHCl_3$), 90% ee.

1-(*o*-Bromophenyl)-2-nitroethyl carbamic acid *t*-butyl ester (45e). Following the general procedure, performing the reaction at –40 °C, compound **45e** was obtained as a white solid in 82% yield. The ee of the product was determined by HPLC using a Daicel

Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1 mL/min, τ_{major} = 18.4 min; τ_{minor} = 12.9 min). R_f 0.60 (*n*-hexane: EtOAc, 7:3); mp 130-133 ºC; ^{1}H NMR δ 1.43 (s, 9H), 4-72-4.92 (br s, 2H), 5.64-5.76 (br s, 2H), 7.20 (dt, J_d = 8.0 Hz, J_t = 4.5 1H), 7.34 (d, J = 4.2 Hz, 2H), 7.59 (dt, J_d = 7.9 Hz, J_t = 0.9 Hz, 1H); ^{13}C NMR δ 28.2, 52.4, 77.5, 80.8, 122.7, 127.9, 128.1, 130.1, 133.6, 135.9, 154.5; ESIMS *m/z* 367 [M + Na^+]; $[\alpha]^{22}_D$ -8 (*c* = 0.402, $CHCl_3$), 88% ee.

1-(*p*-Methoxyphenyl)-2-nitroethyl carbamic acid *t*-butyl ester (45f). Following the general procedure, compound **45f** was obtained as a white solid in 65% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 98:2, flow rate 1 mL/min, τ_{major} = 91.6 min; τ_{minor} = 97.5 min). R_f 0.53 (*n*-hexane: EtOAc, 7:3); mp 141-144°C; ^{1}H NMR δ 1.44 (s, 9H), 3.80 (s, 3H), 4.66 (dd, J = 5.9, 12.4 Hz, 1H), 4.75-4.9 (br s, 1H), 5.14-5.24 (br s, 1H), 5.25-5.35 (br s, 1H), 6.89 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H); ^{13}C NMR δ 28.2, 52.4, 55.3, 78.9, 80.6, 114.5, 127.6, 128.8, 154.7, 159.8; ESIMS *m/z* 319 [M + Na^+]; $[\alpha]^{22}_D$ +28 (*c* = 0.693, $CHCl_3$), 82% ee.

2-Nitro-1-(thiophen-2-yl)ethyl carbamic acid *t*-butyl ester (45g). Following the general procedure, compound **45g** was obtained as a yellow oil in 50% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 98:2, flow rate 1 mL/min, τ_{major} = 54.0 min; τ_{minor} = 57.4 min). R_f 0.52 (*n*-hexane: EtOAc, 7:3); ^{1}H NMR δ 1.46 (s, 9H), 4.75 (dd, J = 5.6, 12.9 Hz, 1H), 4.84-4.98 (br s, 1H), 5.22-5.36 (br s, 1H), 5.56-5.70 (br s, 1H), 6.97-7.02 (m, 2H), 7.27-7.29 (m, 1H); ^{13}C NMR δ 28.2, 48.9, 77.3, 78.6, 81.0, 125.7, 127.3, 140.0, 154.4; ESIMS *m/z* 295 [M + Na^+]; $[\alpha]^{22}_D$ +12 (*c* = 0.445, $CHCl_3$), 82% ee.

1-(Furan-2-yl)-2-nitro-ethyl carbamic acid *t*-butyl ester (45h). Following the general procedure, performing the reaction at –40 °C, compound **2o** was obtained as a yellow oil in 58% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 97:3, flow rate 0.75 mL/min, τ_{major} = 33.8 min; τ_{minor} = 31.2 min). R_f 0.67 (*n*-hexane: EtOAc, 7:3); ^{1}H NMR δ 1.46 (s, 9H), 4.72, (dd, J = 6.0, 12.9 Hz, 1H), 4.84, (dd, J = 6.0, 12.9 Hz, 1H), 5.08-5.26 (br s, 1H), 5.38-5.50 (br s, 1H), 6.28-6.36 (m, 2H), 7.34-7.40 (m, 1H); ^{13}C NMR δ 28.2, 47.2, 80.9, 88.1, 107.8, 110.7, 142.9, 149.4, 154.6; ESIMS *m/z* 279 [M + Na^+]; $[\alpha]^{22}_D$ +11 (*c* = 0.305, $CHCl_3$), 63% ee.

***P-T* catalysed aza-Henry reaction by using α-amido sulfones 48.**

General procedure for the catalytic enantioselective reaction of nitromethane with α-amido sulfones 48. In a test tube, to a mixture of an α-amido sulfone **48** (0.1 mmol), *N*-benzyl quininium chloride **48a** (4.4 mg, 0.01 mmol) and CH_3NO_2 (26 μL, 0.5 mmol) in toluene (1 mL), cooled to -45 °C, finely ground solid KOH (28 mg, 0.5 mmol) was added in one portion. The reaction mixture was then vigorously stirred at –45°C without any precaution to exclude moisture or air. After the stated reaction time, the mixture was poured onto sat. $NaHCO_3$ (3 mL), extracted with CH_2Cl_2 (3 x 3 mL), dried over Na_2SO_4 and filtered. After evaporation of the solvent, the residue was purified by chromatography on silica gel (CH_2Cl_2).

(2*R*)-2-(*tert*-Butoxycarbonylamino)-2-phenyl-1-nitro ethane (45a). Following the general procedure, compound **45a** was obtained after 40 h as a white solid in 95% yield.

The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, τ_{major} = 51.6 min; τ_{minor} = 44.9 min); ESIMS *m/z* 289 [M + Na^+]**;** $[\alpha]^{rt}_D$ +13 (*c* = 0.578, $CHCl_3$), 84% ee. The ^1H and ^{13}C NMR spectra are consistent with values previously reported, see above.

(2*R*)-2-(*o*-Bromophenyl)-2-(*tert*-butoxycarbonylamino)-1-nitro ethane (45b). Following the general procedure, compound **45b** was obtained after 64 h as a white solid in 70% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, τ_{major} = 14.0 min; τ_{minor} = 20.3 min); mp 130-133 ºC; $[\alpha]^{rt}_D$ -7 (*c* = 0.402, $CHCl_3$), 76% ee. The ^1H and ^{13}C NMR spectra are consistent with values previously reported, see above.

(2*R*)-2-(*tert*-Butoxycarbonylamino)-2-(*p*-methoxyphenyl)-1-nitro ethane (45c). Following the general procedure and using a KOH 50% w/w solution as the base, compound **45c** was obtained after 60 h as a white solid in 75% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AS column (*n*-hexane/*i*-PrOH = 90:10, flow rate 0.75 mL/min, τ_{major} = 28.1 min, τ_{minor} = 20.4 min); mp 141-144 °C; $[\alpha]^{rt}_D$ +30 (*c* = 0.693, $CHCl_3$), 88% ee. The ^1H and ^{13}C NMR spectra are consistent with values previously reported, see above.

(2*R*)-2-(*tert*-Butoxycarbonylamino)-2-(1-naphthyl)-1-nitro ethane (45d). Following the general procedure, compound **45d** was obtained after 44 h as a white solid in 95% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, τ_{major} = 44.1 min, τ_{minor} = 24.3 min); mp 174-177 ºC; $[\alpha]^{rt}_D$ +7 (*c* = 0.498, $CHCl_3$), 84% ee. The ^1H and ^{13}C NMR spectra are consistent with values previously reported, see above.

(2*S*)-2-(*tert*-Butoxycarbonylamino)-2-(furan-2-yl)-1-nitro ethane (45e). Following the general procedure, compound **45e** was obtained after 25 h as a yellow oil in 81% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 97:3, flow rate 0.75 mL/min, τ_{major} = 45.3 min; τ_{minor} = 51.3 min); $[\alpha]^{rt}_D$ +13 (*c* = 0.305, $CHCl_3$), 75% ee. The ^1H and ^{13}C NMR spectra are consistent with values previously reported, see above.

(2*R*)-2-(*tert*-Butoxycarbonylamino)-4-phenyl-1-nitro butane (45f). Following the general procedure, compound **45f** was obtained after 40 h as a white solid in 98% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, τ_{major} = 19.6 min; τ_{minor} = 21.8 min); mp 109-111 °C; ^1H NMR δ 7.38-7.18 (m, 5H), 4.90 (br d, *J* = 6.9 Hz, 1H), 4.60 (br s, 2H), 4.20-4.10 (m, 1H), 2.85-2.62 (m, 2H), 2.02-1.80 (m, 2H), 1.42 (s, 9H); ^{13}C NMR δ 155.0, 140.3, 128.6, 128.3, 126.4, 80.3, 78.3, 48.2, 33.4, 32.2, 28.3; ESIMS *m/z* 295 [M + H^+]; $[\alpha]^{rt}_D$ +22 (*c* = 0.743, $CHCl_3$), 95% ee.

(2*R*)-2-(*tert*-Butoxycarbonylamino)-2-cyclohexyl-1-nitro ethane (45g). Following the general procedure, compound **45g** was obtained after 42 h as a white solid in 84% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, τ_{major} = 7.5 min; τ_{minor} = 9.5 min); mp 136-138 °C; ^1H NMR δ 4.85 (br d, *J* = 10.0 Hz, 1H), 4.59 (dd, *J* = 12.6, 6.0 Hz, 1H), 4.52 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.00-3.88 (m, 1H), 1.84-1.50 (m, 5H), 1.42 (s, 9H),

1.32-1.00 (m, 6H); ^{13}C NMR δ 155.3, 80.0, 76.7, 53.9, 39.4, 29.8, 29.0, 28.3, 25.9, 25.7; ESIMS *m/z* 273 [M + H$^+$]; $[\alpha]^{rt}_D$ +19 (*c* = 0.963, $CHCl_3$), 98% ee.

(2*R*)-2-(*tert*-Butoxycarbonylamino)-3-methyl-1-nitro butane (45h). Following the general procedure, compound **45h** was obtained after 40 h as a white solid in 95% yield. A reaction performed on a 1.0 mmol scale gave the product in 96% yield and identical enantioselectivity. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 90:10, flow rate 0.75 mL/min, τ_{major} = 9.1 min; τ_{minor} = 13.0 min); mp 86-88 °C; ^{1}H NMR δ 4.83 (br d, *J* = 7.7 Hz, 1H), 4.57 (dd, *J* = 12.8, 7.1 Hz, 1H), 4.51 (dd, *J* = 12.2, 4.1 Hz, 1H), 4.03-3.90 (m, 1H), 1.88 (oct, *J* = 7.0 Hz, 1H), 1.44 (s, 9H), 0.99 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR δ 155.2, 80.1, 78.1, 54.7, 30.0, 28.2, 19.4, 18.6; ESIMS *m/z* 255 [M + Na$^+$]; $[\alpha]^{rt}_D$ +29 (*c* = 0.700, $CHCl_3$), 95% ee.

(2*R*)-(*tert*-Butoxycarbonylamino)-1-nitro butane (45i). Following the general procedure, compound **45i** was obtained after 40 h as a white solid in 92% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, τ_{major} = 10.0 min; τ_{minor} = 11.8 min); mp 70-72 °C; ^{1}H NMR δ 4.81 (br s, 1H), 4.54 (br s, 2H), 4.02 (ddt, J_t = 5.5 Hz, J_d = 13.0, 8.0Hz, 1H), 1.68-1.54 (m, 2H), 1.44 (s, 9H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 155.1, 80.1, 78.0, 50.7, 28.3, 24.9, 10,4; ESIMS *m/z* 241 [M + Na$^+$]; $[\alpha]^{rt}_D$ +37 (*c* = 0.600, $CHCl_3$), 94% ee.

(2*R*)-(*tert*-Butoxycarbonylamino)-1-nitro propane (45j). Following the general procedure, compound **45j** was obtained after 43 h as a white solid in 86% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AS column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, τ_{major} = 13.2 min; τ_{minor} = 15.4 min); mp 98-100 °C; ^{1}H NMR δ 4.82 (br s, 1H), 4.51 (br s, 2H), 4.30-4.19 (m, 1H), 1.44 (s, 9H), 1.29 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR δ 154.9, 80.2, 79.4, 44.9, 28.3, 17.8; ESIMS *m/z* 205 [M + H$^+$]; $[\alpha]^{rt}_D$ +30 (*c* = 0.650, $CHCl_3$), 92% ee.

(2*R*)-(Benzyloxycarbonylamino)-1-nitro-2-phenyl ethane (44a). Following the general procedure and performing the reaction in a toluene/CH_2Cl_2 1:1 mixture, compound **44a** was obtained after 44 h as a white solid in 53% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 80:20, flow rate 0.75 mL/min, τ_{major} = 22.8 min; τ_{minor} = 16.5 min); $[\alpha]^{rt}_D$ +4 (*c* = 0.348, $CHCl_3$), 73% ee. The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported, see above.

(2*R*)-(Benzyloxycarbonylamino)-2-cyclohexyl-1-nitro ethane (44b). Following the general procedure and performing the reaction in a toluene/CH_2Cl_2 1:1 mixture, compound **44b** was obtained after 40 h as a white solid in 96% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, τ_{major} = 27.2 min; τ_{minor} = 23.0 min); mp 99-101 °C; ^{1}H NMR δ 7.40-7.28 (m, 5H), 5.14 (br s, 1H), 5.10 (s, 2H), 4.60 (dd, *J* = 12.7, 6.3 Hz, 1H), 4.53 (dd, *J* = 12.9, 4.5 Hz, 1H), 4.08-3.98 (m, 1H), 1.87-1.48 (m, 7H), 1.32-0.93 (m, 6H); ^{13}C NMR δ 155.9, 136.1, 128.6, 128.3, 128.1, 76.5, 67.1, 54.4, 39.3, 29.7, 29.0, 25.9, 25.7; ESIMS *m/z* 307 [M + H$^+$]; $[\alpha]^{rt}_D$ +22 (*c* = 0.260, $CHCl_3$), 93% ee.

(2*R*)-*N*^{2}-(*tert*-Butoxycarbonyl)-3-methyl-1,2-butanediamine. To a cooled (0°C), stirred solution of β-nitroamine **45h** (0.1 mmol, 23 mg) in MeOH (1 mL) was added Pd/C 10% (10 mg) and $HCOONH_4$ (1.0 mmol, 63 mg). The mixture was stirred overnight at room temperature, then filtered on a plug of celite. The solvent was removed by evaporation under reduced pressure affording the crude diamine in quantitative yield as a thick colourless oil. ^{1}H NMR δ 4.60 (br d, J = 8.9 Hz, 1H), 3.38 (br s, 1H), 2.81 (dd, J = 13.0, 3.9 Hz, 1H), 2.64 (dd, J = 13.2, 7.9 Hz, 1H), 2.12 (br s, 2H), 1.74 (oct, J = 7.5 Hz, 1H), 1.44 (s, 9H), 0.91 (t, J = 7.5 Hz, 6H).

(2*R*)-*N*^{1},*N*^{2}-Di(*tert*-butoxycarbonyl)-3-methyl-1,2-butandiamine (51). To a cooled (0 °C) solution of crude (2*R*)-N^2-(tert-butoxycarbonyl)-3-methyl-1,2-butanediamine (0.1 mmol) in CH_2Cl_2 (0.6 mL) $(Boc)_2O$ (33 mg, 0.15 mmol) and Et_3N (16 μL, 0.12 mmol) were sequentially added. The reaction mixture was stirred overnight at room temperature and then was directly purified by chromatography on silica gel (CH_2Cl_2/AcOEt mixture) affording **51** as a thick colourless oil in 43% yield. The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[93] $[\alpha]^{rt}_D$ +28 (c = 1.000, $CHCl_3$).

3. Mannich

3.1. Introduction

The Mannich reaction is a classic method for the preparation of β-amino carbonyl compounds, and therefore a very important carbon-carbon bond forming reaction in organic synthesis. The versatility and potential to create both functional and structural diversity using this reaction have long stimulated the creativity of chemists.[97] For example, the Mannich reaction has been employed numerous times successfully as a key step in natural product synthesis as well as in medicinal chemistry.[56] In particular β-amino acids are one of the most important products that can be synthesised by Mannich reactions.[98] In the free form they often show interesting pharmacological properties. For instance, hypoglycaemic and anti-ketogenic activities were observed in rats after oral intake of emeriamine,[99] and cispentacin is an antifungal antibiotic (**Chart 6**, top).[98] β-Amino acids are also key components of a variety of bioactive molecules such as taxol, one of the most active antitumor agents, which contains phenylisoserine as its side chain,[98] and antibiotics cyanovinfin RR, nodularin, as well as microcystin LR where the unsaturated β-amino acid ADDA is part of their structure (**Chart 6**, bottom).[100]

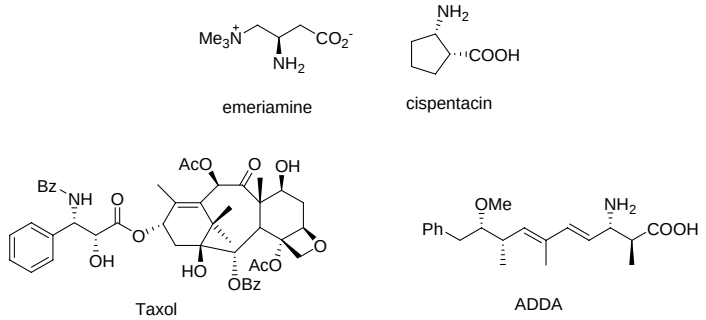


Chart 6. Some examples of free β-amino acids and as key components of a variety of bioactive molecules.

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[97] The first example of the application of the Mannich reaction to natural product synthesis is attributed to Robinson in his synthesis of tropinone: R. Robinson *J. Chem. Soc.* **1917**, 762.

[98] For a discussion of the synthesis and biology of β-amino acids see: *Enantioselective Synthesis of β-Amino Acids* E. Juaristi Ed., Wiley–VCH, New York **1997**.

[99] a) S. Shinagawa, T. Kanamaru, S. Harada, M. Asai, H. Okazaki *J. Med. Chem.* **1987**, *30*, 1458; b) T. Kanamaru, S. Shinagawa, M. Asai, H. Okazaki, Y. Sugiyama, T. Fujita, H. Iwatsuka, M. Yoneda *Life Sci.* **1985**, *37*, 217.

[100] M. Namikoshi, K. L. Rinehart, A. M. Dahlem, V. R. Beasley, W. W. Carmichael *Tetrahedron Lett.* **1989**, *30*, 4349, and references cited therein.

Although the Mannich reaction has been known from about a century, only recently the first successful examples of catalytic asymmetric additions of preformed enolates to imines were reported by the groups of Kobayashi,[101] Sodeoka,[102] Lectka,[103] and Jacobsen.[104] However, a disadvantage of these stereoselective Mannich reactions can be the preparation and instability of the preformed enolates used, typically silyl ketene acetals and silyl enol ethers.

For this reason, recently, direct catalytic asymmetric Mannich-type reactions where the nucleophilic enolate is instead generated in the catalytic cycle, were reported. The transformations are catalyzed by both organometallic complexes and metal-free organic catalysts. The different catalysts are complementary in their applicability and selectivity. Here, we highlight the recent developments in and contributions to this research.

Shibasaki in 1999 reported the first examples of direct catalytic asymmetric Mannich reaction by AlLibis(binaphthoxide) (ALB) **52**,[105] obtaining modest enantioselection using acetophenone as donors and an iminium ion as electrophile (**Chart 7**, upper left). Jørgensen and co-workers developed later a direct asymmetric reaction catalysed by a chiral bisoxazoline copper(II) complex.[106] By means of **53**, they were able to obtain the Mannich products from the addition of pyruvate derivatives to imines derived from glyoxalate, with good yields and high stereoselection (**Chart 7**, right). In 2003 Trost *et al.* used dinuclear zinc complex **54** in the direct Mannich reaction between α-hydroxy acetophenone and *N*-PMP imine of glyoxalate,[107] obtaining good diastereoselectivity and excellent enantiomeric excesses (**Chart 7**, bottom left).

[101] a) H. Ishitani, M. Ueno, S. Kobayashi *J. Am. Chem. Soc*. **1997**, *119*, 7153; b) S. Kobayashi, T. Hamada, K. Manabe *J. Am. Chem. Soc*. **2002**, *124*, 5640; c) H. Ishitani, S. Ueno, S. Kobayashi *J. Am. Chem. Soc*. **2000**, *122*, 8180.
[102] a) E. Hagiwara, A. Fujii, M. Sodeoka *J. Am Chem. Soc.* **1998**, *120*, 2474; b) A. Fujii, E. Hagiwara, M. Sodeoka *J. Am Chem. Soc.* **1999**, *121*, 545.
[103] D. Ferraris, B. Young, T. Dudding, T. A. Lectka *J. Am. Chem. Soc.* **1998**, *120*, 4548; b) D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. III Drury, L. Ryzhkov, T. Taggi, T. A. Lectka *J. Am Chem. Soc.* **2002**, *124*, 67; and references therein.
[104] A.G. Wenzel, E. N. Jacobsen *J. Am Chem. Soc.* **2002**, *124*, 12964.
[105] S. Yamasaki, T. Iida, M. Shibasaki *Tetrahedron Lett.* **1999**, *40*, 307.
[106] K. Juhl, N. Gathergood, K. A. Jørgensen *Angew. Chem. Int. Ed.* **2001**, *40*, 2995.
[107] B. T. Trost, L. M. Terrell *J. Am. Chem. Soc.* **2003**, *125*, 338.

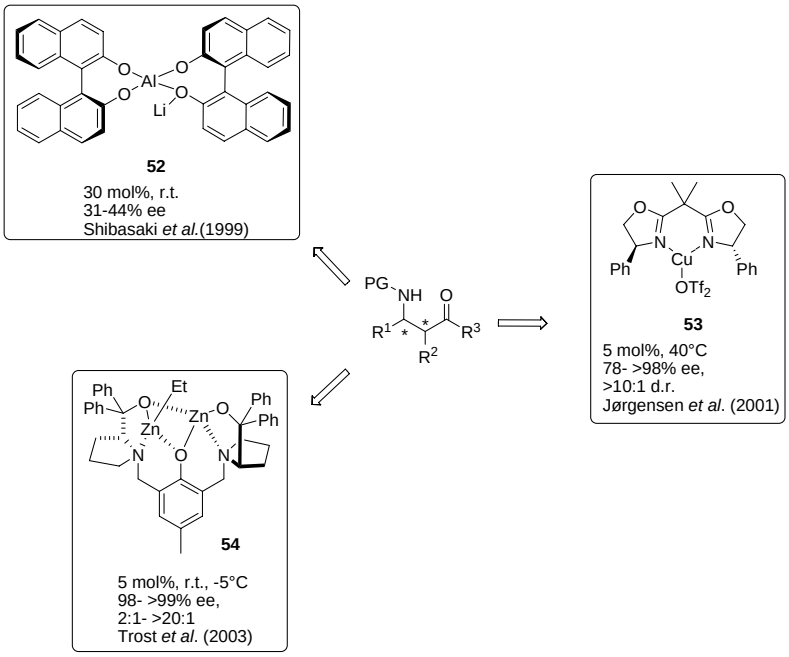
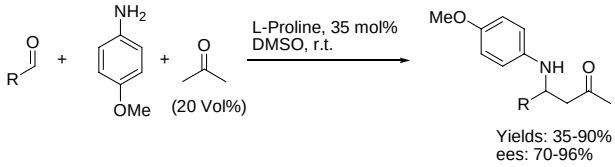


Chart 7 Metal-catalysed direct asymmetric Mannich reaction.

The use of metal-free catalysis for the Mannich reaction started in 2000 when List reported the first example of organocatalytic direct Mannich reaction by using L-proline (**Scheme 26**).[108]

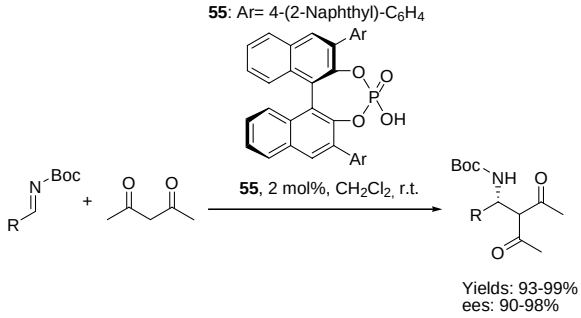


Scheme 26 Proline catalysed enantioselective direct Mannich reaction.

Although the catalytic loading was 35 mol%, good yields and enantioselctivity were obtained. In this three component reaction, the catalyst forms a nucleophilic enamine combining with acetone, wich reacts with an electrophilic imine preformed in situ.

In 2004 the Terada chiral Brønsted acid **55** was applied to the addition of acetylacetone to *N*-Boc imines (**Scheme 27**).[109]

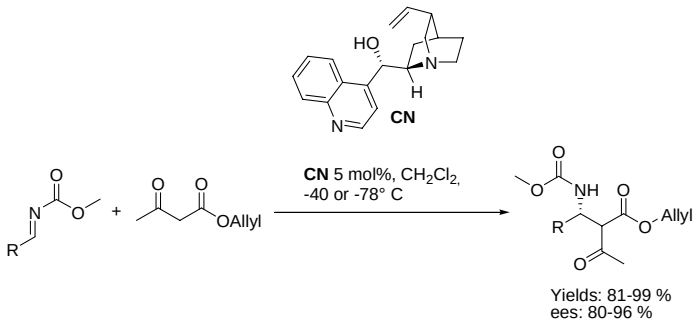
[108] a) B. List *J. Am. Chem. Soc.* **2000**, *122*, 9336. b) B. List, P. Porjalev, W. T. Biller, H. J. Martin *J. Am. Chem. Soc.* **2002**, *124*, 827.
[109] D. Uraguchi, M. Terada *J. Am. Chem. Soc.* **2004**, *126*, 4356.



Scheme 27 Phosphoric-acid-catalysed direct Mannich reaction.

The results were remarkable, and high yields and enantioselections could be achieved with low catalyst loading (2 mol% of **55**). In this case, the catalyst coordinates the azomethine nitrogen through H-bonding, activating the imine for the nucleophilic addition of the easily enolisable acetylacetone.

Schaus and co-workers reported the highly enantioselective cinchonine-catalysed diastereoselective Mannich of β-ketoesters with aryl methyl carbamate imines (**Scheme 28**).[110]



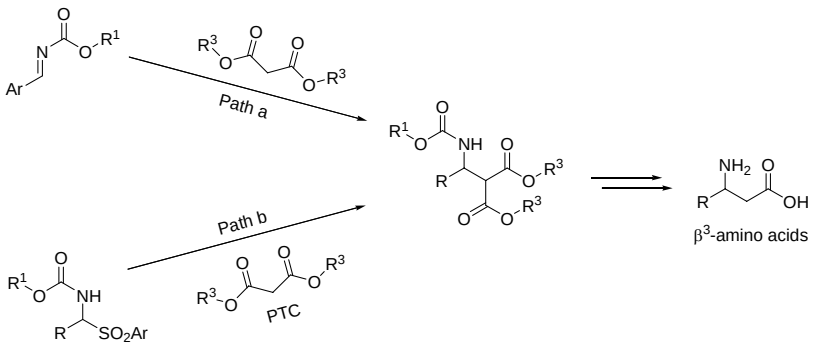
Scheme 28 Mannich reactions catalysed by *Cinchona* alkaloid.

The chiral base is able to deprotonate the β-ketoester, generating a chiral ion pair which then reacts with the highly electrophilic imine. High yields and ees could be obtained even with cheap and commercially available **CN**, and furthermore, the reaction with **CD** gave the opposite enantiomers with good stereoselections.

Although excellent results were reported during these years, surprisingly when we started to study the Mannich reaction we did not find any catalytic direct Mannich reaction of malonates with simple imines (**Scheme 29**, path a). In fact, the Mannich

[110] S. Lou, B. M. Taoka, A. Ting, S. E. Schaus *J. Am. Chem. Soc.* **2005**, *127*, 11256.

reaction with malonates is of great importance, as the products of the reaction are the direct precursors of β^3-amino acids (**Scheme 29**, right).[111]



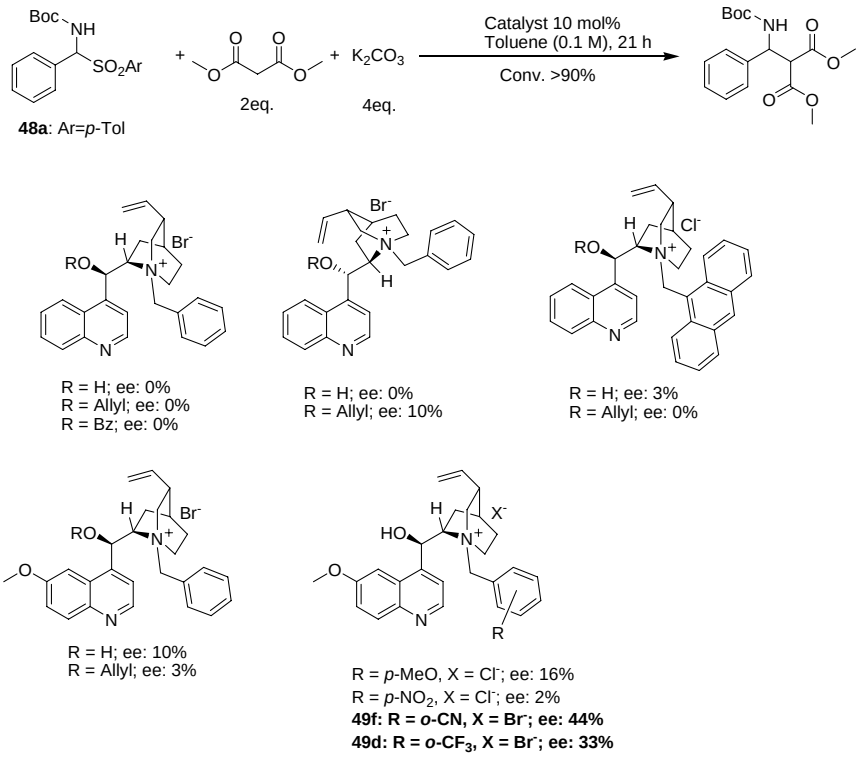
Scheme 29 Catalytic direct Mannich reaction of malonates.

Having developed a new and efficient procedure for the addition of nitromethane to α-amido sulfones through the in situ synthesis of *N*-carbamoyl imines,[112] we thought to apply this convenient methodology using malonates as nucleophiles in combination with α-amido sulfones for novel organocatalysed Mannich reactions (**Scheme 29**, path b). Indeed, we envisioned that the synthesis of a broad collection of aliphatic and aromatic β^3-amino acid precursors could be realised by means of the new flexible phase transfer protocol (**Scheme 29**, right)

[111] For the importance and usefulness of β-amino acid derivatives in organic and pharmaceutical chemistry, see: a) reference 98; b) T. Hintermann, D. Seebach *Chimia* **1997**, *51*, 244; c) J.-A. Ma *Angew. Chem. Int. Ed.* **2003**, *42*, 4290; d) M. Liu, M. Sibi, *Tetrahedron* **2002**, *58*, 7991; e) S. Abele, D. Seebach *Eur. J. Org. Chem.* **2000**, 1; f) R. P. Cheng, S. H. Gellman, W. F. DeGrado *Chem. Rev.* **2001**, *101*, 3219.
[112] See chaprter 2.2.

3.2. Results and Discussion

The initial screening of several chiral quaternary ammonium salts in the PTC Mannich reaction between dimethyl malonate and α-amido sulfone **48a**, was informative in that only quinine derivatives exhibited a significant though modest enantioselectivity (**Scheme 30**).

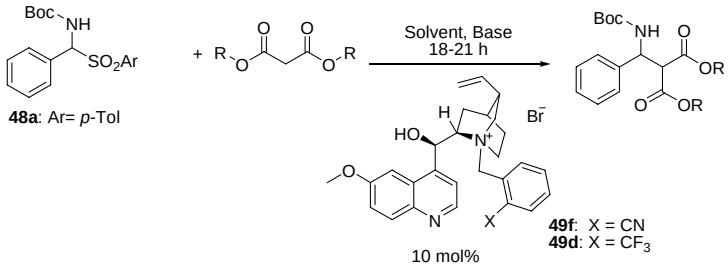


Scheme 30. Screening of different catalysts in the addition of dimethyl malonate to α-amido sulfone 48a.

Additional observations gave further insight into the requirements of the catalyst, indicating the crucial importance of the hydroxy function since the catalyst, whose alcohol group has been protected in the form of allyl ether, did not show any significant asymmetric induction. To examine the role of the electronic and steric factors present in the quinuclidinic nitrogen substituent, various *N*-benzyl quininium derivatives were prepared from quinine and benzyl bromides bearing various functional groups at *ortho*- and *para*-positions. A significant difference in asymmetric induction was noticed between *para*- and *ortho*-substituted derivatives and notably among the latters electron-

withdrawing functional groups, like CN and CF_3, gave higher enantioselectivity (catalyst **49f** and **49d**, **Scheme 30**), and were selected fo further studies.

Table 6. Screening of different malonates with α-amido sulfone 48a catalysed by 49f and 49d, under various reaction conditions.



Entry	R	Cat.	Base	Solvent	Conc.[c]	Conv.[a]	*ee*[b]
1	Me (2 eq.)	**49f**	K_2CO_3[d]	Toluene	0.1	>95%	44%
2	Me (2 eq.)	**49d**	K_2CO_3[d]	Toluene	0.1	>95%	33%
3	Et (2 eq.)	**49f**	K_2CO_3[d]	Toluene	0.1	>95%	37%
3	*t*-Bu (2 eq.)	**49f**	K_2CO_3[d]	Toluene	0.1	>95%	0
4	Bn (2 eq.)	**49f**	K_2CO_3[d]	Toluene	0.1	>95%	46%
5	Ph (2 eq.)	**49f**	K_2CO_3[d]	Toluene	0.1	>95%	50%
6	Ph (1.2 eq.)	**49f**	K_2CO_3[e]	Toluene	0.05	90%	62%
7	Ph (1.2 eq.)	**49f**	K_2CO_3[e]	CH_2Cl_2	0.05	>95%	0
8	Ph (1.2 eq.)	**49f**	K_2CO_3[e]	MTBE	0.05	85%	13%
9	Ph (1.2 eq.)	**49f**	Na_2CO_3[e]	Toluene	0.05	50%	16%
10	Ph (1.2 eq.)	**49f**	Li_2CO_3[e]	Toluene	0.05	0	-
11	Ph (1.2 eq.)	**49f**	Cs_2CO_3[e]	Toluene	0.05	>95%	53%
12	**56a**, PMP (1.2 eq.)	**49f**	K_2CO_3[e]	Toluene	0.05	60%	76%
13	**56a**, PMP (1.2 eq.)	**49d**	K_2CO_3[e]	Toluene	0.05	70%	67%
14	OMP (1.2 eq.)	**49f**	K_2CO_3[e]	Toluene	0.05	30%	40%

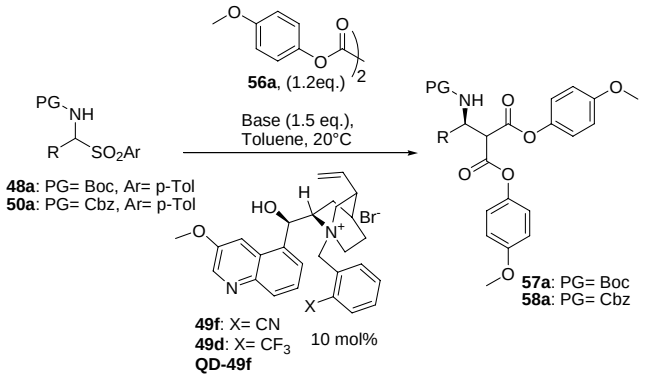
[a] Determined by ^{1}H NMR spectroscopy; [b] Determined by chiral stationary phase HPLC; [c] Molar concentration; [d] 4 eqs.of base were used; [e] 1.5 eqs. of base were used.

As shown in **Table 6**, in general the size of the ester moiety of the malonates did not affect to a substantial extent the chemical and stereochemical outcome. Conversely aryl malonates and especially the *p*-methoxy phenyl (PMP) derivative **56a** afforded an increase in stereoselectivity up to 76% *ee* (**Table 6**, compare entries 1-5 and 12-14). Toluene and potassium carbonate were determined to be the best solvent and base respectively and running the reaction under dilute conditions (0.05 M) afforded better

enantioselectivities, probably due to a polarity change of the reaction medium (**Table 6**, compare entries 5-11).[113]

These observations encouraged us to pursue in finding the optimised conditions. As shown in **Table 7**, variously *N*-protected α-amido sulfones were screened using catalysts **49f** and **49d**, and though excellent conversion yields and fairly good enantioselectivities were uniformly attained, the Cbz protection provided a further beneficial effect (compare entries 1,3 and entries 2,4)

Table 7 Optimization of the Catalyst, base and protecting group at Nitrogen in the Reaction of malonate 58a with α-Amido Sulfones 50a and 51a.[a]



Entry	Cat.	Base	PG	Product	Time (h)	Conv. (%)[b]	*ee* (%)[c]
1	**49f**	K_2CO_3 (s)	Boc	**57a**	21	60	76
2	**49d**			**57a**		70	67
3	**49f**		Cbz	**58a**		85	84
4	**49d**			**58a**		80	83
5	**49f**	K_2CO_3 (aq.)[d]	Boc	**57a**	5	>95	72
6	**49d**			**57a**		>95	64
7	**49f**		Cbz	**58a**		>95	93
8	**49d**			**58a**		>95	93
9	**QD-49f**			**58a**	7	50	87[e]
10	**49f**			**58a**	48	>95	98[f]

[a] Reactions conducted on a 0.1 mmol scale. [b] Determined by ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis. [d] Aqueous K_2CO_3 (50% w/w) was used. [e] The reaction performed with catalyst **QD-49f** gave the opposite enantiomer of **58a** [f] Reaction conducted at -20 °C with 1 mol % catalyst.

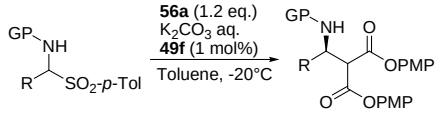
[113] U. H. Dolling, P. Davis, E. J. J. Grabowski *J. Am. Chem. Soc.* **1984**, *106*, 446.

Next we attempted the Mannich reaction using 50% (w/w) aqueous K_2CO_3 (entries 5-10). Under these conditions the rate was markedly enhanced and gratifyingly the enantioselectivity was substantially improved with respect to the anhydrous conditions when using the *N*-Cbz protected α-amido sulfone **50a** (compare entries 3,7 and 4,8 in **Table 7**), though the enantioinduction in the case of *N*-Boc protected α-amido sulfone **48a** resulted unaffected (compare entries 1,5 and 2,6). The effect of water could be explained by internal hydrogen bonding of the *ortho* substituents and the OH group in **49f** and **49d** with water, which might contribute to maintain a more rigid catalyst conformation; however an interaction of the imine moiety and the OH function of the catalyst with the water cannot be ruled out at this stage.[114] Bearing in mind the possibility to synthesize the opposite enantiomer with high enantioselectivity, we performed the reaction with *N*-(*o*-cyanobenzyl)quinidinium bromide **QD-49f** as catalyst: the enantioselectivity was slightly lower, though still acceptable, but the reaction rate decreased considerably (entry 9, **Table 7**).

Finally an enantioselectivity/temperature profile documented that the optimal enantiocontrol was available by lowering the temperature: cooling the reaction had a remarkably positive effect as the enantioselectivity rose to 98% (entry 9) at –20 °C. Noteworthy this superior level of asymmetric induction and efficiency was maintained even with a catalyst loading reduced to 1 mol% (entry 10).

The optimized conditions outlined in **Table 7** were selected for exploring the substrate scope of this Mannich reaction (**Table 8**).

Table 8 Scope of the organocatalyzed Mannich reaction of malonate 56a with azomethines generated in situ From α-amido sulfones 48, 50 under PTC.[a]



48a,c,j: PG= Boc
50a-j: PG= Cbz

57a,c,j: PG= Boc
58a-j: PG= Cbz

Entry	Sulfones	R	PG	Product	Yield (%)[b]	*ee* (%)[c]
1	**48a**	Ph	Boc	**57a**	92	90
2	**50a**	Ph	Cbz	**58a**	81	98
3	**48c**	2-Naphthyl	Boc	**57c**	90	84
4	**50d**	1-Naphthyl	Cbz	**58d**	94	95
5	**50e**	*p*-MeO-C_6H_4	Cbz	**58e**	85	98

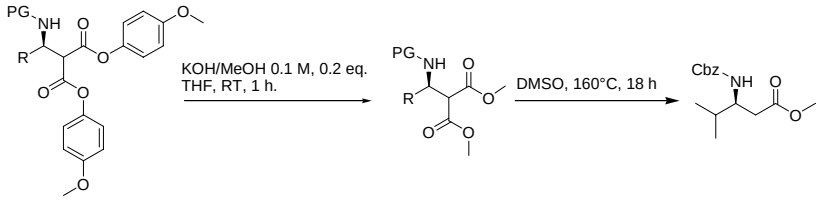
[114] M.-S., Yoo, B.-S. Jeong, J.-H. Lee, H.-g. Park, S.-s. Jew *Org. Lett.* **2005**, *7*, 1129; and references cited therein.

6	**50f**	*o*-Br-C_6H_4	Cbz	**58f**	95	98
7	**50b**	*p*-Cl-C_6H_4	Cbz	**58b**	90	96
8	**50g**	Me	Cbz	**58g**	93	86
9	**50h**	Et	Cbz	**58h**	90	86
10	**50i**	$PhCH_2CH_2$	Cbz	**58i**	90	96
11	**50j**	*i*-Pr	Cbz	**58j**	80	86[d]
12	**48j**	Cy	Boc	**57j**	50	76
13	**50c**	Cy	Cbz	**58c**	80	95

[a] Reactions conducted on a 0.1 mmol scale at -20°C for 48 h, using **48** or **50**: **56a**: **49f**: K_2CO_3 aq. in a 1: 1.2: 0.01: 1.5 molar ratio. [b] Isolated yields after column chromatography. [c] Determined by chiral HPLC analysis. [d] Determined by chemical correlation with compound **61j**.

As listed in **Table 8** the adducts were generally obtained in very good chemical yields using **49f** as the catalyst (1 mol%). With the aryl-substituted α-amido sulfones **48a,c** and **50a,b,d-f** the reaction proceeded smoothly with excellent enantioselectivity irrespective of the electronic nature of the aromatic ring (entries 1-7). Most remarkably also alkyl α-amido sulfones **48j** and **50c,g-j**, precursors of enolizable azomethines, gave the corresponding adducts **57j** and **58c,g-j** with enantiomeric excesses in the 76-96% range (entries 8-13).

Finally, a decarboxylation/transesterification sequence delineated the synthetic utility of this catalytic process to construct β-amino acid moieties bearing a synthetically useful protecting groups at nitrogen such as Cbz, allowing at the same time the determination of the absolute configuration of the adducts (**Scheme 31**)



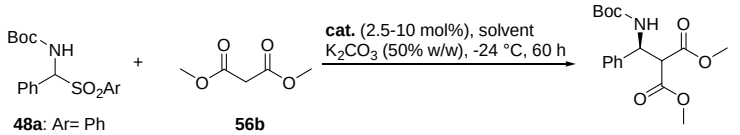
Scheme 31 Determination of absolute configuration by transesterification/decarboxylation sequence.

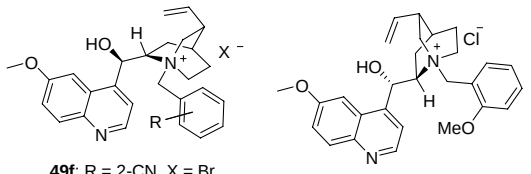
Although excellent results could be achieved, even with low catalyst loadings, the use of malonate **56a** for targeting optically active β^3-amino acid derivatives posed some concerns owing to the requirement for two additional synthetic steps, that is, the preparation of **56a** and a transesterification prior to decarboxylation. Therefore, we

thought it would be of interest to continue our investigations into the development of new catalytic systems and/or reaction conditions that are able to accommodate simpler malonates, and possibly different β-dicarbonyl derivatives. We therefore decided to further explore the Mannich reaction with dimethyl malonate **56b**.

An initial experiment with catalyst **49f** using the condition optimised for the malonate **56a** and a higher catalyst loading, strongly indicated the possibility of developing an asymmetric Mannich reaction with malonate **56b** (**Table 9**, entry 1) because product **59a** was obtained with a moderate conversion and a promising enantioselectivity. Following our working hypothesis, other quaternary ammonium salts **49g-i** were screened in the reaction. Whereas catalysts **49g,h**, which contain electron-withdrawing groups at the *ortho* position of the *N*-benzylic substituent, gave slightly worse or similar results to those obtained with **49f** (**Table 9**, entries 2-3), catalyst **49i** with a methoxy substituent[115] on the aromatic ring proved to be superior and resulted in the formation of product **59a** with full conversion and a satisfactory enantioselectivity (**Table 9**, entry 4).

Table 9 Representative results from the screening of different catalysts and reaction conditions for the catalytic asymmetric Mannich reaction between dimethyl malonate 56b and α-amido sulfone 48a.[a]





49f: R = 2-CN, X = Br
49g: R = 2,5-F_2, X = Br
49h: R = 2-NO_2, X = Cl
49i: R = 2-MeO, X = Cl

QD-49i

Entry	Catalyst	Solvent	Conversion (%)[b]	*ee* (%)[c]
1	**49f** (10 mol%)	toluene	80	81
2	**49g** (10 mol%)	toluene	90	79
3	**49h** (10 mol%)	toluene	>95	82
4	**49i** (10 mol%)	toluene	>95	91
5	**49i** (10 mol%)	toluene/CH_2Cl_2 7:1	>95[d]	81
6	**49i** (10 mol%)	*o*-xylene	75	85

[115] A) E. J. Park, M. H. Kim, D. Y. Kim *J. Org. Chem.* **2004**, *69*, 6897; b) R. Ceccarelli, S. Insogna, M. Bella *Org. Biomol. Chem.* **2006**, *4*, 4281.

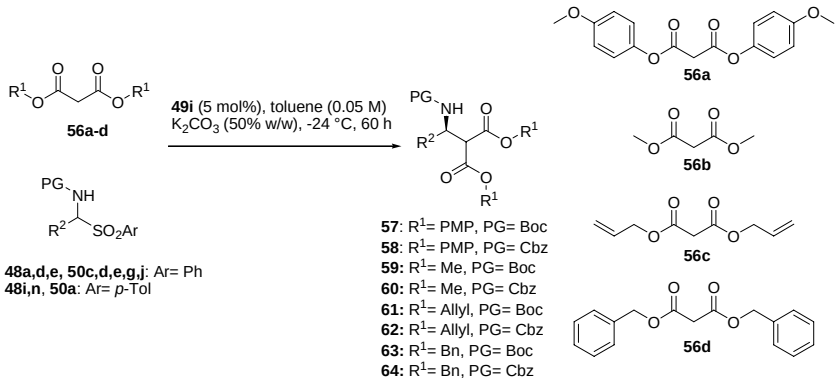
7	**49i** (10 mol%)	mesitylene	65	73
8[e]	**49i** (5 mol%)	toluene	>95	90
9	**49i** (2.5 mol%)	toluene	>95	83
10	**QD-49i** (10 mol%)	toluene	>95	45[f]

[a] Reactions carried out using **48a** (0.10 mmol), **56b** (0.12 mmol), catalyst **49f-i** (2.5-10 mol%), in the stated solvent (2 mL) with K_2CO_3 50% w/w (27μL, 0.15 mmol) at -24 °C for 60 h. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral stationary phase HPLC. [d] 22 h reaction time. [e] 6 equivs. of K_2CO_3 50% w/w were used. [f] *ent*-**59a** was obtained.

By using this catalyst, different solvents were then tested in an attempt to increase the reaction rate (**Table 9**, entries 5-7). Only the reaction performed in a mixture of toluene/CH_2Cl_2 gave **59a** with full conversion in a shorter time (**Table 9**, entry 5), however, the enantioselectivity was considerably lower compared with the reaction in toluene. By using toluene as the organic phase, the catalyst loading could be reduced to 5 mol% without affecting the enantioselectivity, although a further decrease to 2.5 mol % had a negative effect on the enantiomeric excess of the product (**Table 9**, entries 8 and 9). It was also found that performing the reaction with a larger excess of base (6 equivs.) improved the reproducibility of the reaction in terms of conversion without affecting the enantioinduction in the product (**Table 9**, entry 8). Unfortunately, the use of quasienantiomeric catalyst **QD-49i** derived from quinidine gave the corresponding enantiomeric product *ent*-**59a** with reduced enantiopurity (**Table 9**, entry 10).

Having established an efficient protocol for the enantioselective Mannich reaction of **56b** with **48a**, we investigated the generality of the reaction, first focusing on possible variations on the α-amido sulfone partner (**Table 10**, entries 1-11).

Table 10 Scope of the catalytic asymmetric Mannich reaction of malonates 56a-d with α-amido sulfones 48,50.[a]



Entry	56	48,50	R^2	PG	Yield (%)[b]	*ee* (%)[c]
1	**56b**	**48a**	Ph	Boc	**59a**-85[d]	90[e]
2	**56b**	**50a**	Ph	Cbz	**60a**-97	94[e]
3	**56b**	**48e**	*o*-BrC_6H_4	Boc	**59e**-98	90
4	**56b**	**48d**	*p*-ClC_6H_4	Boc	**59d**-97	83
5	**56b**	**50e**	*p*-$MeOC_6H_4$	Cbz	**60e**-99	94
6	**56b**	**50d**	1-naphthyl	Cbz	**60d**-97	91
7	**56b**	**48i**	$PhCH_2CH_2$	Boc	**59i**-80	78
8	**56b**	**48n**	*i*-Bu	Boc	**59n**-78	83
9	**56b**	**50g**	Me	Cbz	**60g**-99	81
10	**56b**	**50j**	*i*-Pr	Cbz	**60j**-88	85[f]
11	**56b**	**50c**	Cyclohexyl	Cbz	**60c**-90	97
12	**56c**	**48a**	Ph	Boc	**61a**-97	90
13	**56c**	**50a**	Ph	Cbz	**62a**-95	92
14	**56c**	**50c**	Cyclohexyl	Cbz	**62c**-84	94
15	**56d**	**48a**	Ph	Boc	**63a**-96	92[e]
16	**56d**	**50a**	Ph	Cbz	**64a**-92	93
17	**56d**	**48n**	*i*-Bu	Boc	**63n**-77	91
18[g]	**56a**	**48a**	Ph	Boc	**57a**-90	98[e]
19[g]	**56a**	**50a**	Ph	Cbz	**58a**-96	99[e]

[a] Reactions carried out using **48** or **50** (0.10 mmol), **56** (0.12 mmol), catalyst **49i** (5 mol%), in toluene (2 mL) with K_2CO_3 50% w/w (108 μL, 0.60 mmol) at -24 °C for 60 h. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC. [d] Reaction performed on a 1.0 mmol scale. [e] Absolute configuration determined as *S*. [f] Absolute configuration determined as *R*. [g] 1.5 equivs. of K_2CO_3 50% w/w were used.

Aside from the reaction with **48a**, which could also be performed with identical results on a preparative scale (**Table 10**, entry 1), its Cbz-protected counterpart **50a** was found to be a competent substrate for this transformation to give the corresponding product **60a** in a very good yield (97%) and enantioselectivity (94% *ee*) (**Table 10**, entry 2). The tolerance of the catalytic reaction to these two different protecting groups on the nitrogen atom of the α-amido sulfones is of considerable interest when considering the possibility of obtaining the corresponding *N*-protected β^3-amino acid derivatives (see below). The catalytic asymmetric reaction of **56b** with α-amido sulfones **48e,d**, **50e,d**, which were derived from aromatic aldehydes (**Table 10**, entries 3-6), further demonstrated the possibility of using different substrates and/or protecting groups with the present system.

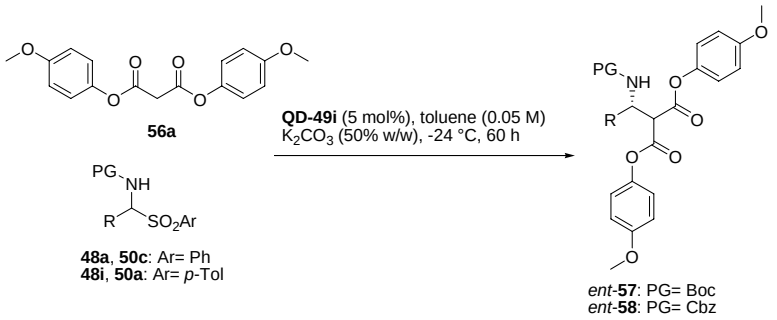
The corresponding products **59e,d**, **60e,f** were in fact obtained in very good yields (97-99%) and enantioselectivities (83-94% *ee*), irrespective of the electronic and/or steric properties of the substituents at the aromatic ring and the protecting group on the nitrogen atom. Sulfones **48i,n**, **50c,g,j**, which were derived from aliphatic, enolisable aldehydes, were then tested in the catalytic reaction (**Table 10**, entries 7-11) because a major advantage of the present method is the avoidance of the isolation of the corresponding, somewhat unstable, imines. By using catalyst **49i** under standard reaction conditions, the corresponding products **59i,n**, **60c,g,j**, were obtained in good yields (78-99%) and enantioselectivities (78-97% *ee*, entries 7-11), although in most cases the optical purity of **59i,n**, **60c,g,j** was not as high as for their aromatic counterparts **59e,d**, **60e,f**.

Exploring the possibility of using other malonates in the catalytic reaction, we focused our attention on diallyl malonate **56c** and dibenzyl malonate **56d** because the Mannich adducts that result from these compounds can be transformed into the corresponding *N*-Boc protected β^3-amino acids without the use of acidic or basic hydrolytic conditions.[116] Good yields (77-97%) and enantioselectivities (90-94% *ee*) for products **61a**, **62a,c**, **63a,n**, **64a** were obtained (**Table 10**, entries 12-17), with results that were comparable to that obtained for **58b**. For the sake of comparison, we also tested **56a** in the catalytic reaction with the newly developed catalyst **49i** (**Table 10**, entries 18-19). Catalyst **49i** was also found to be superior to our previously employed catalyst **49f**, to give the corresponding products **57a** and **58a** in very high yields (90 and 96%, respectively) and outstanding enantioselectivities (98 and 99% *ee*, respectively).

As anticipated in **Table 9**, (entry 10), unfortunately the present system does not allow the preparation of the opposite enantiomer of the products derived from dimethyl malonate **56b** with satisfactory levels of enantioselectivity, as the quasienantiomeric catalyst **QD-49i** derived from quinidine (**Table 9**) was found to be much less efficient.

[116] J. Song, Y. Wang, L. Deng *J. Am. Chem. Soc.* **2006**, *128*, 6048.

Table 11 Catalytic asymmetric Mannich reaction of malonate 58a using catalyst QD-49i derived from quinidine giving enantiomeric products ent-57, ent-58.[a]

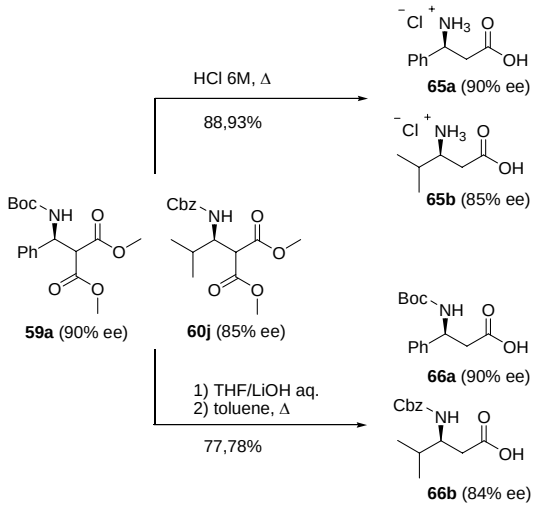


Entry	**48, 50**	R	PG	Yield (%)[b]	*ee* (%)[c]
1	**48a**	Ph	Boc	*ent*-**57a**-98	93
2	**50a**	Ph	Cbz	*ent*-**58a**-95	99
3	**48i**	$PhCH_2CH_2$	Boc	*ent*-**57i**-88	77
4	**50c**	Cyclohexyl	Cbz	*ent*-**58c**-89	93

[a] Reactions carried out using **48**, **50** (0.10 mmol), **58a** (0.12 mmol), catalyst **QD-49i** (5 mol%), in toluene (2 mL) with K_2CO_3 50% w/w (27 μL, 0.15 mmol) at -24 °C for 60 h. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC.

However, access to the antipodal Mannich adducts can be gained using malonate **56a** (**Table 11**). Exploiting the superior affinity of this malonate for this class of catalysts, it was indeed possible to prepare some representative products with the opposite absolute configuration with good results, in terms of both yields (88-98%) and enantioselectivities (77-99% *ee*) (**Table 11**, entries 1-4). As we have previously demonstrated the possibility of transforming these types of adducts into the corresponding dimethyl ester derivatives (**Scheme 31**), also the opposite enantiomer of the Mannich adducts derived from dimethyl malonate **56b** are thus available using the present method, although an additional transesterification step is required.

As stated at the beginning of this section, β-Amino acids and their derivatives are key compounds in organic and pharmaceutical chemistry. Besides being present in a variety of natural products, they are finding increasing use as pharmaceutically active agents, often incorporated into peptides and β-peptides, because of the promise shown by β-peptides as biostable peptidomimetics.[98,111]



Scheme 32. Preparation of unprotected and protected β^3-amino acids 65a,b, 66a,b from the Mannich adducts 59a, 60j.

The asymmetric Mannich reaction of malonates is conceivably a very direct route to optically active β^3-amino acids. In particular, our approach involving the use of simple malonates and easily removable protecting groups at nitrogen, allows the straightforward transformation of either *N*-Boc or *N*-Cbz protected Mannich adducts into the corresponding β^3-amino acid hydrochlorides (**Scheme 32**, top). For example, treatment of **59a** and **60j** with 6M HCl for a few hours[117] gave malonate hydrolysis, decarboxylation as well as nitrogen deprotection in a single step, furnishing cleanly the corresponding β^3-amino acid hydrochlorides **65a** and **65b** (**Scheme 32**, top), irrespective of the nature of the side chain and the protecting group at nitrogen. Mild basic hydrolysis followed by thermal decarboxylation afforded instead the analogous *N*-protected β^3-amino acids **66a** and **66b** (**Scheme 32**, bottom), thus showing the possibility of obtaining both β-aryl and β-alkyl-amino acids with orthogonal carbamate protecting groups suitable for peptide synthesis.[118]

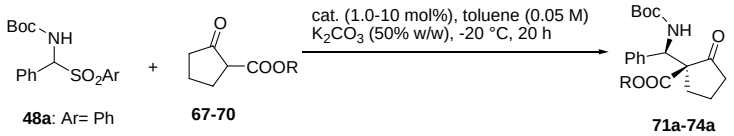
We then proceeded to evaluate the possibility of extending the catalytic asymmetric Mannich reaction of α-amido sulfones **48**, **50** to a different class of β-dicarbonyl compounds, namely β-ketoesters. The catalytic asymmetric Mannich reaction of these compounds has received a great deal of attention in recent times, due to their obvious synthetic utility as masked ketone donors.[118,119] However, catalytic asymmetric versions

[117] M. Nejman, A. Śliwińska, A. Zwierzak *Tetrahedron* **2005**, *61*, 8536.
[118] A. L. Tillman, J. Ye, D. J. Dixon *Chem. Commun.* **2006**, 1191.
[119] M. Marigo, A. Kjærsgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359; b) Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umebayashi, M. Sodeoka *Angew.*

of the Mannich reaction of β-ketoesters using α-amido sulfones were still unexplored. We therefore thought to develop an efficient protocol for this transformation based on our approach. In the search for the suitable parameters enabling an enantioselective transformation, we began our investigations performing the catalytic reaction with some cyclopentanone derived β-ketoesters **67-70** and α-amido sulfone **48a**, using catalysts **49f,h,i**. At first instance, we attempted the reaction using conditions similar to the corresponding transformation with malonates **56**. As shown in Table 4, we realised already from the first experiments with the ethyl β-ketoester **67** that an enantioselective reaction with β-ketoesters could be developed under these conditions, as the corresponding product **71** was obtained with excellent diastereoselectivity and with promising levels of enantioselectivity (**Table 12**, entries 1-3). Also in this case, catalyst **49i** with an *ortho*-methoxy substituent at the benzyl moiety of the quinuclidinic nitrogen was found to be more effective (**Table 12**, entry 3) than the other *ortho* substituted catalysts **49f,h** tested (**Table 12**, entries 1-2). A short inspection of the influence of the steric hindrance of the ester group revealed that an increase in the bulkiness of this moiety using benzyl or *tert*-butyl β-ketoesters **68**, **69** was detrimental to the enantioselectivity of the products (**Table 12**, entries 4-5), whereas the least bulky methyl β-ketoester **70** gave the best results (**Table 12**, entry 6). Using this β-ketoester **70** under these conditions, the catalyst loading could be decreased to 2.5 mol% with only marginal effects on the optical purity of the product **74a** (**Table 12**, entry 7), although a further reduction to 1 mol% gave a more significant decrease in the enantioselectivity observed (**Table 12**, entry 8). Unfortunately, also for this reaction the quasienantiomeric catalyst **QD-49i** derived from quinidine was found to be much less efficient in terms of enantioinduction (**Table 12**, entry 9).

Chem. Int. Ed. **2005**, *44*, 1525; c) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen *Angew. Chem. Int. Ed.* **2005**, *44*, 2896; d) S. Lou, B. Taoka, A. Ting, S. E. Schaus *J. Am. Chem. Soc.* **2005**, *127*, 11256; e) A. Ting, S. Lou, S. E. Schaus, *Org. Lett.* **2006**, *8*, 2003; f) C. M. Bode, A. Ting, S. E. Schaus *Tetrahedron* **2006**, *62*, 11499; g) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048.

Table 12 Representative results from the screening of different catalysts and reaction conditions for the catalytic asymmetric Mannich reaction between β-ketoesters 67-71 and α-amido sulfone 48a.[a]



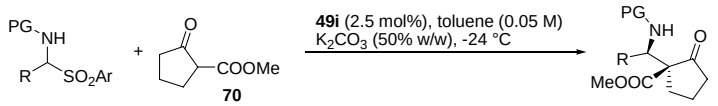
48a: Ar= Ph **67-70** **71a-74a**

Entry	β-Ketoesters	R	Catalyst	Conv. (%)[b]	d.r.[b]	*ee* (%)[c]
1	**67**	Et	**49f** (10 mol%)	**71a**->90	98:2	80
2	**67**	Et	**49h** (10 mol%)	**71a**->90	98:2	84
3	**67**	Et	**49i** (10 mol%)	**71a**->90	98:2	88
4	**68**	Bn	**49i** (10 mol%)	**72a**->90	87:13	87
5	**69**	*t*-Bu	**49i** (10 mol%)	**73a**-77	95:5[d]	71[d]
6	**70**	Me	**49i** (10 mol%)	**74a**->90	>98:2	93
7	**70**	Me	**49i** (2.5 mol%)	**74a**->90	>98:2	91
8	**70**	Me	**49i** (1.0 mol%)	**74a**->9o	97:3	88
9	**70**	Me	**QD-49i** (2.5 mol%)	*ent*-**74a**->90	98:2	54

[a] Reactions carried out using **48a** (0.10 mmol), **67-70** (0.12 mmol), catalyst **49i** (1.0-10 mol%), in toluene (2 mL) with K_2CO_3 50% w/w (27 μL, 0.15 mmol) at -20 °C for 20-29 h. [b] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c] *ee* of the major isomer, determined by chiral stationary phase HPLC. [d] Relative and absolute configuration determined by comparison of ^{1}H NMR spectrum and HPLC retention times with literature values. See ref. [119b]

We then explored the possibility of using different α-amido sulfones with the representative β-ketoester **70** under the optimised reaction conditions. As shown in Table 5, besides the *N*-Boc protected α-amido sulfone **48a**, also its analogous *N*-Cbz sulfone **50a** gave the corresponding product **75a** with excellent yield, diastereo- and enantioselectivity (**Table 13**, entries 1,2, 85-90% yield, 92-95% *ee*). Having proved the tolerance of the reaction to both Boc and Cbz protecting groups, other aromatic and aliphatic α-amido sulfones were subsequently tried in the catalytic reaction with β-ketoester **70** (**Table 13**, entries 3-11). The Mannich adducts **74-75** were obtained in moderate to good yields (50-98%), generally good diastereomeric ratios but variable enantiopurities (69-99% *ee*). Compared to the model reaction with **48a** and **50a** the enantioselectivities observed for these products were generally lower; however the possibility of reaching excellent levels of enantiopurity in some cases (**Table 13**, entries 8 and 11) must be recognised.

Table 13 Scope of the catalytic asymmetric Mannich reaction of β-keto esters 71d with α-amido sulfones 48, 50: variation of the α-amido sulfone partner.[a]



48a, **50a,c,j**: Ar= Ph
48e,i, **50b,d,e,f,g**: Ar= *p*-Tol

74: PG= Boc
75: PG= Cbz

Entry	**48, 50**	R	PG	Yield (%)[b]	d.r.[c]	*ee* (%)[d]
1	**48a**	Ph	Boc	**74a**-98	>98:2	95
2	**50a**	Ph	Cbz	**75a**-90	>98:2	92
3	**48e**	*o*-BrC_6H_4	Boc	**74e**-60	94:6	69
4	**50f**	*o*-BrC_6H_4	Cbz	**75f**-85	96:4	77
5	**50b**	*p*-ClC_6H_4	Cbz	**75b**-98	96:4	73
6	**50e**	*p*-$MeOC_6H_4$	Cbz	**75e**-70	95:5	77
7	**50d**	1-naphthyl	Cbz	**75d**-50	90:10	85
8	**48i**	$PhCH_2CH_2$	Boc	**74i**-55	97:3	90
9	**50g**	Me	Cbz	**75g**-70	97:3	75
10	**50j**	*i*-Pr	Cbz	**75j**-74	96:4	74
11	**50c**	Cyclohexyl	Cbz	**75c**-77	>98:2	99

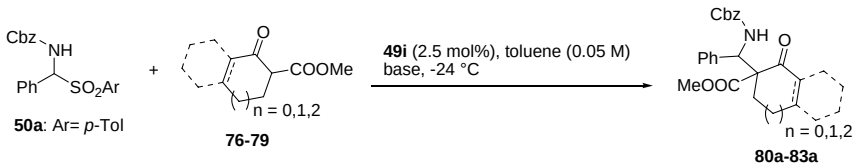
[a] Reactions carried out using **48**, **50** (0.12 mmol), **71d** (0.10 mmol), catalyst **49i** (2.5 mol%), in toluene (2 mL) with K_2CO_3 50% w/w (27 μL, 0.15 mmol) at -24 °C for 21-84 h. [b] Isolated yield of the diastereomeric mixture. [c] Determined by ^1H NMR spectroscopy on the crude reaction mixture. [d] *Ee* of the major isomer, determined by chiral stationary phase HPLC.

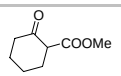
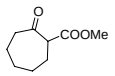
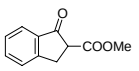
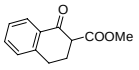
Finally, we investigated the behaviour of some other different cyclic β-ketoesters in the reaction with the representative α-amido sulfone **50a**. A practical asset of the present method is the use of methyl β-ketoesters as donors. The synthesis of these compounds is straightforward, especially the cyclic, ring-fused ones, if compared to other β-ketoesters bearing more bulky ester groups such as *tert*-butyl, often used in catalytic asymmetric transformations.[120] Accordingly, a few cyclic β-ketoesters **76-79** with different ring sizes and/or ring fused were readily synthesised and tested in the reaction (**Table 14**). In line with previous reports,[120,121] the different reactivity of these compounds reflected in the

[120] For a discussion, see: T. B. Poulsen, L. Bernardi, J. Alemán, J. Overgaard, K. A. Jørgensen *J. Am. Chem. Soc.* **2007**, *129*, 441.
[121] a) T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi, K. Maruoka *Angew. Chem. Int. Ed.* **2003**, *42*, 3796; b) M. Bella, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 3670; c) S. Kobbelgaard, M. Bella, K. A. Jørgensen, *J. Org. Chem.* **2006**, *71*, 4980; d) T. B. Poulsen, L. Bernardi, M. Bell, K. A. Jørgensen *Angew. Chem. Int. Ed.* **2006**, *45*, 6551; e) L. Bernardi, J. López-Cantarero, B. Niess, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 5772; f) E. J. Park, M. H. Kim, D. Y. Kim, *J. Org. Chem.* **2004**, *69*, 6897.

necessity of a tuning of the strength inorganic base and/or reaction temperature employed in the catalytic reaction. For example, the cyclohexanone and cycloheptanone derived β-ketoesters **76** and **77** did not furnish the expected Mannich adducts under the conditions used with the more reactive cyclopentanone derivative **70** (K_2CO_3 50% w/w, -24 °C). However, using a stronger base (K_3PO_4 50% w/w) it was possible to obtain the corresponding products **80a** and **81a** in satisfactory yields (77, 96%) and enantioselectivities (91, 95% *ee*) (**Table 14**, entries 1,2). The ring-fused β-keto esters **78** and **79** proved to be instead more reactive, as the reactions performed with aqueous K_2CO_3 as the base gave the Mannich products **82a** and **83a** with good results (**Table 13**, entries 3,4, 95-96% yield, 87-92% *ee*). In the former case, a less concentrated K_2CO_3 solution (30% w/w instead of 50% w/w) resulted in a slight improvement of the enantioselectivity of the product **82a**, presumably due to a background reaction, although the low diastereomeric ratio was unchanged. Non-cyclic β-ketoesters were also tried in the reaction, but, not surprisingly,[120,121] gave the corresponding products with low enantioselectivity with the present catalytic system.

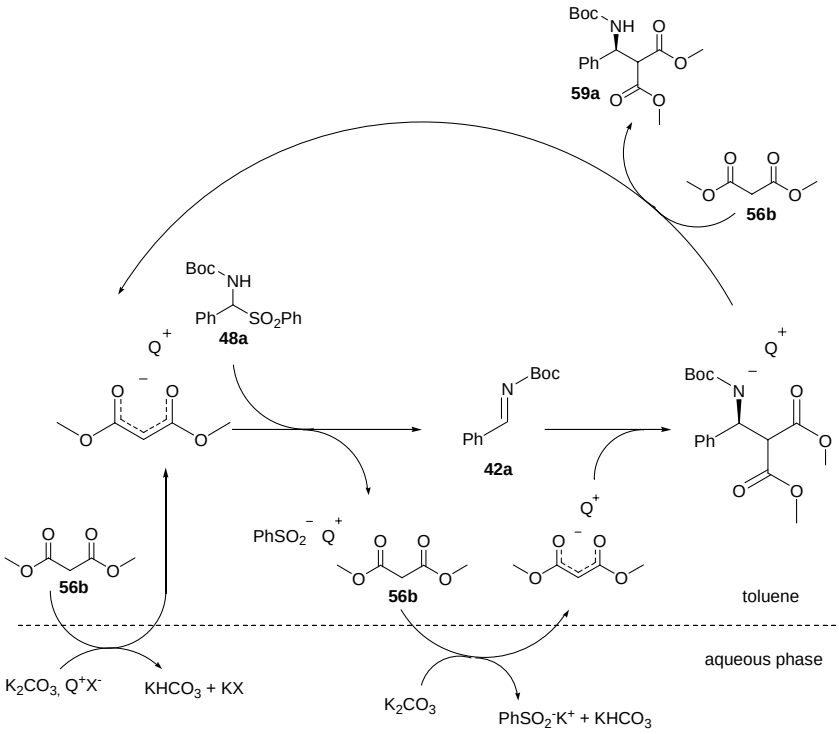
Table 14 Scope of the catalytic asymmetric Mannich reaction of β-keto esters 76-79 with α-amido sulfones 50a: variation of the β-keto ester partner.[a]



Entry	β-Keto ester		Base	Yield [%][b]	d.r.[c]	*ee* [%][d]
1[e]		**76**	K_3PO_4 50% w/w	**80a**-77[f]	85:15	91
2		**77**	K_3PO_4 50% w/w	**81a**-96[f]	96:4	95
3		**78**	K_2CO_3 30% w/w	**82a**-95	58:42	87[g]
4		**79**	K_2CO_3 50% w/w	**83a**-96	80:20	92

[a] Reactions carried out using **50a** (0.12 mmol), **76-79** (0.10 mmol), catalyst **49i** (2.5 mol%), in toluene (2 mL) with the stated base (1.5-5 equivs.) at -24 °C for 24-71 h. [b] Isolated yield of the diastereomeric mixture. [c] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [d] *ee* of the major isomer, determined by chiral stationary phase HPLC. [e] Reaction performed at 0 °C using 10 mol% catalyst **49i**. [f] Isolated yield of the enriched major diastereoisomer. [g] Minor diastereoisomer 85% *ee*, determined by chiral stationary phase HPLC.

A few ancillary experiments were then carried out using dimethyl malonate **56b** in order to get some insights into the possible reaction pathways. These can be summarised as follows: i) under the standard reaction conditions but in the absence of either malonate **56b** or catalyst **49i**, the formation of the imine **42a** from α-amido sulfone **48a** proceeded only sluggishly (<60% after 84h); ii) a reaction with the pre-formed *N*-Boc imine **42a** derived from **48a** gave very similar results, both in terms of yield and enantioselectivity, to the reaction performed with **48a**; iii) a sterically demanding α-amido sulfone derived from pivalaldehyde did not furnish the expected Mannich product in the reaction, presumably for steric reasons, though providing substantial amounts of the corresponding imine. On these grounds we propose the following catalytic cycle (**Scheme 33**), wherein the malonate, deprotonated by the inorganic base at the interface, combines with the quaternary ammonium salt giving an organic soluble anion, which acts first as a base, promoting the formation of the imine from the α-amido sulfone. The sulfinate formed can be solubilised into the aqueous phase, whereas the malonate can be deprotonated again to give a chiral ion pair with the catalyst, adding in an enantioselective fashion to the formed imine. An anionic carbamate adduct is then formed bearing the catalyst as the counterion. This highly basic species presumably deprotonates the most acidic compound in the reaction mixture, i.e. another molecule of malonate, thus restoring the catalytic cycle. However the quench of this anionic Mannich adduct by water owing to bulk effects, or the use of this anionic adduct as a basic promoter for the formation of imine, cannot be totally excluded.



Scheme 33. Proposed reaction pathway. (Q^+X^- = 49i).

The absolute configuration of the adducts **57-64** and **74**, **75** has been determined in a few cases by comparison of their optical and/or HPLC properties with literature values (see **Table 10**, **Table 13**). The simple diastereoselectivity observed in the asymmetric Mannich reaction of β-ketoesters **74**, **75** can be explained by an open transition state,[119b] whereas the absolute configuration of the adducts results in all cases from attack of the ion pair catalyst-enolate on the *Re*-face of the intermediate imine, when catalysts **49** derived from quinine were used. Previous reports based on X-ray structures of this class of catalysts showed the importance of the presence of a molecule of water in rigidifying the structure of these ammonium salts.[114] This conformational control, given by hydrogen bond interactions between the oxygen atom at the 9-position of the cinchona scaffold, a molecule of water and the *ortho* group of the quinuclidinic benzyl substituent, was found to be essential in attaining optimal enantioselectivities in the alkylation of the benzophenone imine derived from *tert*-butyl glycine ester. Accordingly we tried the catalytic reaction between dimethyl malonate **56b** and **48a** with catalyst **49i** under anhydrous conditions, using dry K_2CO_3 as the base. Besides a lowering in the conversion, presumably due to a less efficient interfacial exchange of the enolate anion, we observed also a dramatic decrease in the enantioselectivity of the product **59a**, which was obtained in 27% *ee*, instead of 90% *ee* when aqueous K_2CO_3 was employed. This result suggests

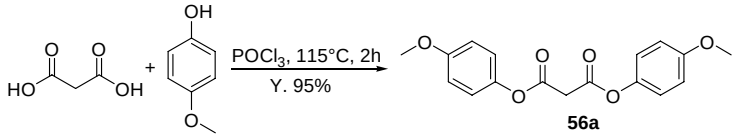
that the presence of water is also in our case a requirement for the obtainment of high enantioselectivity using this class of catalysts. The higher efficiency of catalyst **49i** bearing a methoxy moiety at the *ortho* position with respect to the other catalysts **49** may be therefore attributed to a more efficient contribution in this hydrogen bond interaction, thus giving a better conformational control resulting in a better recognition of the *Re*-face of the imine by the chiral ion pair

In summary, in the second part of this project we have developed a new catalytic system allowing the asymmetric Mannich reaction of simple, generally available malonates and β-keto esters with *N*-Boc and *N*-Cbz protected α-amido sulfones. The reaction makes use of a simple phase transfer catalyst, easily obtainable from quinine in a single step. The Mannich adducts are generally obtained in good yields, as well as diastereo- and enantioselectivities. The synthetic relevance of the present asymmetric transformation is shown by the straightforward conversion of the catalytic adducts into *N*-Boc and *N*-Cbz β^3-amino acids, suitable for peptide synthesis. Unprotected β^3-amino acids can be also readily obtained in a single step by acidic hydrolysis. Mild and user-friendly reaction conditions, as well as the avoidance of the need of isolation of *N*-Boc and *N*-Cbz imines are good assets of this organocatalytic asymmetric Mannich reaction. As demonstrated by control experiments, the catalyst-enolate ion pair first acts as a base promoting the elimination of sulfinic acid, and then adds to the formed imine in an enantioselective fashion. The presence of water in the reaction was also found to be essential in the obtainment of high enantioselectivities, presumably influencing the conformational rigidity of the catalyst through hydrogen bond interactions.

3.4. Experimental Section

General Methods. All reactions were carried out in test tubes. ^{1}H and ^{13}C NMR spectra were measured on a Varian AS 400 spectrometer running at 400 and 100 MHz respectively in $CDCl_3$ as the solvent. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H NMR and to the central line of $CDCl_3$ (77.0 ppm) for ^{13}C NMR. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES^+) ionisation techniques. Flash column chromatography (FC) was carried out using Merck silica gel 60 (230-400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 22°C. The enantiomeric excess (*ee*) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H or AS). Melting points are uncorrected. Imines **41a**, **43a, 41b**,[122] **42a-h**,[104], **47f**[85] as well as β-ketoesters **67-70**, **76-79**[123] were prepared following literature procedures. All commercially available solvents and reagents were used as received. α-Amido sulfones **48** and **50** were obtained following literature procedures.[124] Racemic samples were obtained using tetrabutylammonium bromide as the catalyst.

Preparation of malonic acid bis-(4-methoxyphenyl) ester (3).



56a

To a mixture of malonic acid (5.5 g, 53 mmol) and *p*-methoxy phenol (13.14 g, 106 mmol) was slowly added, at 0°C, $POCl_3$ (6 ml, 61.5 mmol) and was heated at 115°C until strong release of HCl ceased (about 2 h). The reaction mixture was poured into 100 ml of water and extracted with ether (3 x 100 ml), the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was recrystallized from Et_2O-AcOEt to afford 15.9 g (95% yield) of desired products as a white solid. ^{1}H NMR δ 7.11-7.03 (m, 4H), 6.94-6.87 (m, 4H), 3.80 (s, 8H); ^{13}C NMR δ 165.2, 157.6, 143.8, 122.1, 114.5, 55.6, 41.5; ESIMS *m/z* 339 $[M + Na]^+$

Preparation of *N*-(2-cyanobenzyl)-quininium bromide

A mixture of (-)-quinine (648 mg, 2 mmol) with *o*-cyanobenzyl bromide (431 mg, 2.2 mmol) in a solution of THF (1.8 ml), ethanol (1.5 ml), and chloroform (0.6 ml), was stirred at 100°C for 3 h. After cooling to room temperature, the crude was evaporated under reduced pressure and the crude product was purified by chromatography on silica gel (CH_2Cl_2/MeOH 90:10) to afford 925 mg (89% yield) of **49f** as a pale yellow solid.

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[123] a) S. B. Chavan, R. R. Kale, K. Shivasankar, S. I. Chandake, S. B. Benjamin, *Synthesis* **2003**, 2695; b) M. E. Bunnage, S. G. Davies, R. M. Parkin, P. M. Roberts, A. D. Smith, J. M. Withey, *Org. Biomol. Chem.* **2004**, *2*, 3337; c) H. O. House, C. B. Hudson, *J. Org. Chem.* **1970**, *35*, 647; d) F. Bennett, G. Fenton, D. W. Knight, *Tetrahedron* **1994**, *50*, 5147.
[124] a) W. H. Pearson, A. C. Lindbeck, J. W. Kampf *J. Am. Chem. Soc.* **1993**, *115*, 2622; b) E. Bernacka, A. Klepacz, A. Zwierzak *Tetrahedron Lett.* **2001**, *42*, 5093; c) A. G. Wenzel, E. N. Jacobsen *J. Am. Chem. Soc.* **2002**, *124*, 12964.

^{1}H NMR δ 8.64 (d, J = 4.5 Hz, 1H), 8.23 (d, J = 7.79 Hz, 1H), 7.92 (d, J = 9.27 Hz, 1H), 7.75-7.66 (m, 3H), 7.55 (t, J = 7.88 Hz, 1H), 7.27 (dd, J = 9.24, 2.36 Hz, 1H), 7.09 (d, J = 2.40 Hz, 1H), 6.65 (d, J = 5.61 Hz, 1H), 6.40 (d, J = 6.01 Hz, 1H), 6.31 (d, J = 12.82 Hz, 1H), 5.55-5.44 (m, 1H), 5.03-4.93 (m, 2H), 4.88-4.77 (m, 1H), 4.70 (d, J = 12.88 Hz, 1H), 3.95 (s, 3H), 3.75 (br t, J = 8.41 Hz, 1H), 3.49-3.40 (m, 1H), 3.31-3.16 (m, 2H), 2.65-2.55 (m, 1H), 2.26-2.11 (m, 2H), 1.97 (br s, 1H), 1.79 (br t, J = 12.36 Hz, 1H), 1.35 (br t, J = 12.36 Hz, 1H); ^{13}C NMR δ 158.2, 147.1, 143.6, 142.9, 135.9, 135.7, 134.1, 133.5, 131.5, 131.3, 129.7, 125.3, 122.0, 120.3, 117.8, 117.6, 115.5, 99.9, 70.6, 63.6, 61.7, 60.7, 55.9, 51.3, 37.3, 25.9, 24.4, 21.4; ESIMS m/z 440 $[(M - Br) + H]^+$; $[\alpha]^{20}_D$ = - 244 (c = 0.5, $CHCl_3$).

General procedure for the catalytic enantioselective reaction of malonate 56a with α-amido sulfones 48, 50.

A solution of *N*-(*o*-cyanobenzyl)quininium bromide **6** in toluene (2 mL, 5.0 x 10^{-4} M, 1.0 μmol) was added to a test tube containing a mixture of α-amido sulfone **48**, **50** (0.1 mmol) and malonic acid bis-(4-methoxyphenyl) ester **3** (38 mg, 0.12 mmol). After the resulting solution was cooled to -20°C, K_2CO_3 aq. 50% w/w (28 μl, 0.15 mmol) was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without any precaution to exclude moisture or air. After 48 h, the reaction product was directly purified by chromatography on silica gel (CH_2Cl_2).

(*S*)-2-(*tert*-Butoxycarbonylamino-phenyl-methyl)-malonic acid bis-(4-methoxyphenyl) ester (57a).

Following the general procedure, compound **57a** was obtained as a white solid in 92% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 47.5 min, τ_{min} = 77.0 min); m.p. 144-146 °C; ^{1}H NMR δ 7.45-7.31 (m, 5H), 7.06-7.03 (m, 2H), 6.90-6.87 (m, 2H), 6.83 (br s, 4H), 6.18 (br s, 1H), 5.82 (br s, 1H), 4.40 (br s, 1H), 3.80 (s, 3H), 3.77 (s, 3H) 1.44 (s, 9H); ^{13}C NMR δ 166.8, 166.0, 157.6, 155.1, 143.8, 143.5, 139.0, 128.8, 127.9, 126.4, 122.1, 122.0, 114.4, 80.0, 57.1, 55.6, 53.4, 28.3; ESIMS m/z 544 $[M + Na]^+$; $[\alpha]^{20}_D$ = + 2.8 (c = 0.7, $CHCl_3$), 90% ee.

(*S*)-2-(Benzyloxycarbonylamino-phenyl-methyl)-malonic acid bis-(4-methoxyphenyl) ester (58a).

Following the general procedure, compound **58a** was obtained as a white solid in 81% yield. The ee of the product was determined by HPLC using a Daicel Chiralcel OD column (*n*hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, τ_{maj} = 30.9 min, τ_{min} = 26.5 min); m.p. 161-163 ºC; ^{1}H NMR δ 7.45-7.34 (m, 10H), 6.97-6.95 (m, 4H), 6.86-6.84 (m, 4H), 6.48 (d, J = 10.1 Hz, 1H), 5.88 (br s, 1H), 5.20 (d, J = 12.4 Hz, 1H), 5.10 (d, J = 12.4 Hz, 1H), 4.43 (d, J = 4.1 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H); ^{13}C NMR δ 166.7, 165.8, 157.6, 157.6, 143.7, 143.4, 138.6, 128.8, 128.5, 128.1, 126.4, 122.0, 121.9, 114.5, 114.5, 67.0, 56.9, 55.6, 55.5, 54.0; ESIMS m/z 578 $[M + Na]^+$; $[\alpha]^{20}_D$ = + 3 (c = 0.7, $CHCl_3$), 98% ee.

(*S*)-2-(*tert*-Butoxycarbonylamino-naphthalen-2-yl-methyl)-malonic acid bis-(4-methoxyphenyl) ester (57c).

Following the general procedure, compound **57c** was obtained as a colourless oil in 90% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 85.3 min, τ_{min} = 96.7 min); ^{1}H NMR δ 7.91-7.82 (m, 4H), 7.58-7.47 (m, 3H), 7.06 (d, J = 9.8 Hz, 2H), 6.92-6.85 (m, 2H), 6.83-6.75 (m, 4H), 6.34 (d, J = 9.0 Hz, 1H), 5.98 (br s, 1H), 4.50 (d, J

= 5.0 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H) 1.46 (s, 9H); ^{13}C NMR δ 166.8, 166.0, 157.7, 155.1, 143.8, 143.5, 139.0, 136.5, 133.2, 132.9, 128.7, 128.1, 127.6, 126.4, 126.3, 125.5, 124.3, 122.1, 122.0, 114.5, 114.4, 80.1, 57.0, 55.6, 53.7, 28.3; ESIMS *m/z* 594 $[M + Na]^+$; $[\alpha]^{20}_D$ = + 0.6 (c = 0.73, $CHCl_3$), 84% ee.

(*S*)-2-(Benzyloxycarbonylamino-naphthalen-1-yl-methyl)-malonic acid bis-(4-methoxyphenyl) ester (58d).

Following the general procedure, compound **58b** was obtained as a white solid in 94% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 127.6 min, τ_{min} = 92.2 min); m.p. 149-151 ºC; ^{1}H NMR δ 8.28 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.72-7.45 (m, 4H), 7.41-7.27 (m, 4H), 7.06-6.95 (m, 3H), 6.93-6.65 (m, 8H), 5.21 (d, *J* = 12.4 Hz, 1H), 5.10 (d, *J* = 12.1 Hz, 1H), 4.59 (d, *J* = 3.8 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C NMR δ 166.9, 166.0, 157.7, 157.6, 155.7, 143.7, 143.3, 136.3, 134.0, 133.9, 130.0, 129.3, 129.0, 128.5, 128.0, 127.2, 126.0, 125.2, 124.1, 122.1, 121.9, 114.5, 114.4, 67.0, 55.7, 55.6, 55.5, 50.7; ESIMS *m/z* 628 $[M + Na]^+$; $[\alpha]^{20}_D$ = – 8.5 (c = 1.15, $CHCl_3$), 96% ee.

(*S*)-2-[Benzyloxycarbonylamino-(4-methoxyphenyl)-methyl]-malonic acid bis-(4-methoxyphenyl) ester (58e)

Following the general procedure, compound **58e** was obtained as a white solid in 85% yield. The ee of the product was determined by HPLC using a Daicel Chiralcel OD column (*n*hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, τ_{maj} = 49.7 min, τ_{min} = 39.6 min); m.p. 139-131 ºC; ^{1}H NMR δ 7.45-7.23 (m, 7H), 6.98-6.81 (m, 10H), 6.42 (d, *J* = 9.3 Hz, 1H), 5.81 (br s, 1H), 5.19 (d, *J* = 12.6 Hz, 1H), 5.09 (d, *J* = 12.6 Hz, 1H), 4.38 (d, *J* = 4.9 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H); ^{13}C NMR δ 166.7, 165.8, 159.3, 157.6, 157.5, 155.7, 152.2, 143.7, 143.5, 136.3, 130.7, 128.4, 128.0, 127.7, 122.0, 121.9, 114.5, 114.4, 114.1, 67.0, 57.1, 55.5, 55.3, 53.6 ;ESIMS *m/z* 608 $[M + Na]^+$; $[\alpha]^{20}_D$ = – 8.0 (c = 1.31, $CHCl_3$), 98% ee.

(*S*)-2-[Benzyloxycarbonylamino-(2-bromophenyl)-methyl]-malonic acid bis-(4-methoxyphenyl) ester (58f).

Following the general procedure, compound **58f** was obtained as a colourless oil in 95% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 110.4 min, τ_{min} = 62.7 min); ^{1}H NMR δ 7.64 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.39-7.28 (m, 6H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.90-6.78 (m, 7H), 6.14 (dd, *J* = 3.8, 9.6 Hz, 1H), 5.19 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 4.68 (d, *J* = 3.9 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H); ^{13}C NMR δ 166.9, 165.7, 157.7, 157.6, 155.5, 143.7, 143.3, 137.4, 136.2, 133.4, 130.8, 129.8. 128.8, 128.6, 128.1, 127.8, 122.7, 122.0, 121.9, 114.5, 114.4, 67.1, 55.6, 55.5, 54.1, 53.9; ESIMS *m/z* 658 $[M + Na]^+$; $[\alpha]^{20}_D$ = + 9.3 (c = 0.48, $CHCl_3$), 98% ee.

(*S*)-2-[Benzyloxycarbonylamino-(4-chlorophenyl)-methyl]-malonic acid bis-(4-methoxyphenyl) ester (58b).

Following the general procedure, compound **58b** was obtained as a white solid in 90% yield. The ee of the product was determined by HPLC using a Daicel Chiralcel OD column (*n*hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, τ_{maj} = 39.3 min, τ_{min} = 28.3 min); m.p. 151-153 ºC; ^{1}H NMR δ 7.37-7.33 (m, 9H), 6.96-6.94 (m, 4H), 6.86-6.84 (m, 4H), 6.48 (d, *J* = 9.4 Hz, 1H), 5.82 (br s, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.09 (d, *J* = 12.1 Hz,

1H), 4.36 (d, J = 5.0 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H); ^{13}C NMR δ 166.6, 165.6, 157.7, 143.6, 143.4, 137.2, 136.1, 134.0, 129.0, 128.5, 128.2. 127.9, 122.0, 121.9, 114.8, 114.6, 114.5, 67.2, 56.7, 55.6, 53.5; ESIMS m/z 612 $[M + Na]^+$; $[\alpha]^{20}_D$ = – 6.2 (c = 0.61, $CHCl_3$), 96% ee.

(*R*)-2-(1-Benzyloxycarbonylamino-ethyl)-malonic acid bis-(4-methoxyphenyl) ester (58g).

Following the general procedure, compound **58g** was obtained as a colourless oil in 93% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 62.6 min; τ_{min} = 55.2 min); ^{1}H NMR δ 7.36-7.31 (m, 5H), 7.07-7.00 (m, 4H), 6.92-6.85 (m, 4H), 5.70 (d, J = 11.1 Hz, 1H), 5.15 (d, J = 12.4 Hz, 1H), 5.10 (d, J = 12.4 Hz, 1H), 4.77-4.70 (m, 1H), 4.07 (d, J = 4.3 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 1.47 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 166.9, 166.4, 157.6, 157.6, 155.6, 143.6, 136.4, 128.5, 128.1, 128.0, 122.1, 122.0, 114.5, 114.5, 66.8, 56.0, 55.6, 46.6, 19.3; ESIMS m/z 516 $[M + Na]^+$; $[\alpha]^{20}_D$ = + 36.8 (c = 0.93, $CHCl_3$), 86% ee.

(*R*)-2-(1-Benzyloxycarbonylamino-propyl)-malonic acid bis-(4-methoxyphenyl) ester (58h).

Following the general procedure, compound **58h** was obtained as a white solid in 90% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 67.0 min; τ_{min} = 59.7 min); m.p. 107-109 °C; ^{1}H NMR δ 7.36-7.30 (m, 5H), 7.08-6.96 (m, 4H), 6.92-6.81 (m, 4H), 5.72 (d, J = 10.3 Hz, 1H), 5.16 (d, J = 12.6 Hz, 1H), 5.10 (d, J = 12.6 Hz, 1H), 4.53 (m, 1H), 4.10 (d, J = 4.1 Hz, 1H), 3.80 (s, 6H), 1.78 (quint, J = 7.8 Hz, 2H), 1.07 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 167.1, 166.6, 157.7, 157.6, 156.1, 143.8, 143.6, 136.5, 128.5, 128.0, 127.9, 122.1, 122.0, 114.53, 114.48, 66.8, 55.60, 55.57, 54.9, 52.4, 27.0, 10.9; ESIMS m/z 530 $[M + Na]^+$; $[\alpha]^{20}_D$ = + 30 (c = 1.47, $CHCl_3$), 86% ee.

(*R*)-2-(1-Benzyloxycarbonylamino-3-phenyl-propyl)-malonic acid bis-(4-methoxyphenyl) ester (58i).

Following the general procedure, compound **58i** was obtained as a white solid in 90% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 64.4 min, τ_{min} = 79.8 min); m.p. 133-135 ºC; ^{1}H NMR δ 7.36-7.21 (m, 10H), 7.03-7.00 (m, 4H), 6.89-6.84 (m, 4H), 5.78 (d, J = 10.0 Hz, 1H), 5.15 (d, J = 12.6 Hz, 1H), 5.12 (d, J = 12.6 Hz, 1H), 4.74-4.62 (m, 1H), 4.09 (d, J = 4.0 Hz, 1H), 3.80 (s, 6H), 2.88-2.71 (m, 2H), 2.19-1.99 (m, 2H); ^{13}C NMR δ 167.0, 166.4, 157.7, 157.6, 156.1, 143.7, 143.6, 140.8, 136.4, 128.5, 128.4, 128.1, 128.0, 126.2, 122.1, 122.0, 114.5, 66.9, 55.6, 55.3, 50.7, 35.6, 32.7; ESIMS m/z 606 $[M + Na]^+$; $[\alpha]^{20}_D$ = + 26 (c = 2.5, $CHCl_3$), 96% ee.

(*R*)-2-(1-Benzyloxycarbonylamino-2-methyl-propyl)-malonic acid bis-(4-methoxyphenyl) ester (58j).

Following the general procedure, compound **58j** was obtained as a colourless oil in 80% yield. The ee of the product was determined by chemical and stereochemical correlation with compound **61j**; ^{1}H NMR δ 7.35-7.29 (m, 5H), 7.07-6.80 (m, 8H), 5.87 (d, J = 10.8 Hz, 1H), 5.16 (d, J = 12.4 Hz, 1H), 5.09 (d, J = 12.4 Hz, 1H) 4.44-4.40 (m, 1H), 4.20 (d, J = 4.2 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.06-1.90 (m, 1H), 1.10 (d, J = 10.4 Hz, 3H), 1.07 (d, J = 10.4 Hz, 3H); ^{13}C NMR δ 167.3, 166.9, 157.7, 157.5, 156.3, 143.8, 143.6, 136.5, 128.4, 127.9, 127.8, 122.1, 122.0, 114.52, 114.46, 66.7, 56.7, 55.6,

55.5, 53.3, 32.1, 20.0, 19.4; ESIMS *m/z* 544 $[M + Na]^+$; $[\alpha]^{20}_D$ = + 45.2 (c = 1.73, $CHCl_3$), 86% ee.

(*R*)-2-(*tert*-Butoxycarbonylamino-cyclohexyl-methyl)-malonic acid bis(4-methoxyphenyl) ester (57j).

Following the general procedure, compound **57j** was obtained as a colourless oil in 50% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, τ_{maj} = 20.5 min; τ_{min} = 30.1 min); ^{1}H NMR δ 7.11-7.05 (m, 4H), 6.92-6.85 (m, 4H), 5.56 (d, *J* = 10.5 Hz, 1H), 4.37-4.28 (m, 1H), 4.19 (d, *J* = 4.0 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 1.94-1.05 (m, 11H), 1.42 (s, 9H); ^{13}C NMR δ 167.5, 167.4, 157.7, 157.6, 155.7, 143.9, 143.7, 122.3, 122.1, 114.5, 114.4, 79.3, 55.6, 55.2, 53.0, 41.4, 30.4, 29.6, 28.3, 26.0, 25.9, 25.8; ESIMS *m/z* 550 $[M + Na]^+$; $[\alpha]^{20}_D$ = + 31.8 (c = 0.70, $CHCl_3$), 76% ee.

(*R*)-2-(Benzyloxycarbonylamino-cyclohexyl-methyl)-malonic acid bis-(4-methoxyphenyl) ester (58c).

Following the general procedure, compound **58c** was obtained as a colourless oil in 80% yield. The ee of the product was determined by HPLC using a Daicel Chiralcel OD column (*n*hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, τ_{maj} = 13.9 min; τ_{min} = 11.1 min); ^{1}H NMR δ 7.34-7.30 (m, 5H), 7.07-6.80 (m, 8H), 5.85 (d, *J* = 10.4 Hz, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.08 (d, *J* = 12.4 Hz, 1H) 4.40 (dt, *J* = 3.9, 9.6 Hz, 1H), 4.22 (d, *J* = 3.9 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 1.95-1.60 (m, 6H), 1.29-1.09 (m, 5H); ^{13}C NMR δ 167.5, 167.1, 157.7, 157.5, 156.3, 143.8, 143.6, 136.5, 128.4, 128.0, 127.9, 122.1, 114.5, 114.5, 66.7, 55.8, 55.6, 55.5, 52.8, 41.3, 30.3, 29.6, 26.0, 25.9, 25.7; ESIMS *m/z* 584 $[M + Na]^+$; $[\alpha]^{20}_D$ = + 13 (c = 0.97, $CHCl_3$), 95% ee.

(*R*)-Dimethyl 2-(1-(benzyloxycarbonylamino)-2-methylpropyl)malonate (60j)

To a solution of **58j** (0.8 mmol) in THF (8 ml) were added 1.6 ml of a KOH solution in MeOH (0.1 M, 0.2 mmol) and the resulting mixture was stirred for one hour. The reaction was then quenched with saturated NH_4Cl (10 ml) and the product extracted with Et_2O (3 x 10ml); the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using CH_2Cl_2/Et_2O 95:5 as the eluant, giving **60j** (253 mg) as a colourless oil in 94% yield. ^{1}H NMR δ 7.38-7.26 (m, 5H), 5.76 (d, *J* = 10.2 Hz, 1H), 5.11 (d, *J* = 12.6 Hz, 1H), 5.06 (d, *J* = 12.6 Hz, 1H) 4.09-4.01 (m, 1H), 3.76-3.71 (m, 4H), 3.63 (s, 3H), 1.82-1.71 (m, 1H), 1.10 (d, *J* = 9.7 Hz, 3H), 1.07 (d, *J* = 9.7 Hz, 3H); ^{13}C NMR δ 168.9, 168.4, 156.2, 152.2, 136.7, 128.4, 128.0, 66.6, 56.6, 52.8, 52.7, 52.5, 31.9, 19.8, 19.3.

(*S*)-methyl 3-(benzyloxycarbonylamino)-4-methylpentanoate (61j)

A solution of **60j** (0.75 mmol) in DMSO (4 ml) was stirred for 18 h at 160°C. After cooling to room temperature, saturated NaCl (4 ml) was added and the aqueous layer was extracted with Et_2O (3 x 10 ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using CH_2Cl_2/Et_2O 95:5 as the eluant, giving **61j** (188 mg) as a colourless oil in 90% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak ADH column (*n*hexane/*i*PrOH = 90:10, flow rate 0.75 mL/min, τ_{maj} = 21.4 min; τ_{min} = 17.3 min). The ^{1}H and ^{13}C NMR spectra are consistent with values

previously reported in the literature. $[\alpha]^{20}_D$ = + 22.3 (c = 1.12, $CHCl_3$), [Lit (*R* enantiomer)[125]: $[\alpha]^{20}_D$ = – 24.6 (c = 1.4, $CHCl_3$)], 86% ee.

The absolute configuration of aromatic compound **57a** and **58a** was determined by comparison of the optical rotation of compound **59a** and **60a** with published values.[126]

(S)-dimethyl 2-[(tert-butoxycarbonylamino)(phenyl)methyl]malonate (59a)
(S)-dimethyl 2-[(benzyloxycarbonylamino)(phenyl)methyl]malonate (60a)

To a solution of **57a** (**58a**) (0.2 mmol) in THF (2 mL) were added 0.4 mL of a KOH solution in MeOH (0.1 M, 0.04 mmol). After the mixture was stirred for 30 min at room temperature, the reaction was quenched with saturated NH_4Cl (4 mL) and the poduct extracted with Et_2O (3 x 10 mL); the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC using CH_2Cl_2/Et_2O 95:5 as the eluant. Yield: **59a**, 87%, (**60a**, 91%). The ^1H and ^{13}C NMR spectra of compounds **59a** and **60a** are consistent with values previously reported in the literature.

59a: $[\alpha]^{20}_D$ = + 15 (c = 0.24, $CHCl_3$), [Lit (*S* enantiomer): $[\alpha]^{20}_D$ = + 17 (c = 1.14, $CHCl_3$)]

60a: $[\alpha]^{20}_D$ = + 8.5 (c = 1.55, $CHCl_3$), [Lit (*S* enantiomer): $[\alpha]^{20}_D$ = + 9.4 (c = 1.0, $CHCl_3$)]

Preparative-Scale reaction (2 mmol).

(*S*)-2-(Benzyloxycarbonylamino-naphthalen-1-yl-methyl)-malonic acid bis-(4-methoxyphenyl) ester (58d)

To a solution of α-amido sulfone **2b** (891 mg, 2.0 mmol) and malonic acid bis-(4-methoxyphenyl) ester **3** (758 mg, 2.4 mmol) in toluene (40 ml) *N*-(*o*-cyanobenzyl)quininium bromide **6** (10.4 mg, 0.02 mmol) was added. After the resulting solution was cooled to -20°C, K_2CO_3 aq. 50% w/w (540 µl, 3 mmol) was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without any precaution to exclude moisture or air. After 48 h, the reaction was quenched with saturated NH_4Cl (30 ml) and the aqueous layer was extracted with CH_2Cl_2 (4 x 20 ml). The combined organic phases were then washed with saturated NaCl (30 ml), dried over Na_2SO_4, filtered and concentrated under reduce pressure. The crude product was purified by chromatography on silica gel (CH_2Cl_2), giving 1.14 g of compound **58d** (94% yield) in 96% ee.

Preparation of *N*-(2-methoxybenzyl)-quininium chloride (49i): Quinine (648 mg, 2.0 mmol) was added to a solution of *o*-methoxybenzyl chloride (360 µL, 2.6 mmol) in toluene (6 mL). The resulting mixture was heated to 80°C with stirring. After 5 h the reaction mixture was allowed to cool to room temperature and evaporated in vacuo. The residue was purified by chromatography (CH_2Cl_2/MeOH mixtures) giving the title compound as a pale red solid (63% yield). M.p. >120°C (dec.); $[\alpha]_D^{20}$=-166 (*c*=0.31 in $CHCl_3$); ^1H NMR: δ=8.76 (d, *J*=4.7 Hz, 1H), 8.07-7.99 (m, 2H), 7.79 (d, *J*=4.5 Hz, 1H), 7.51-7.44 (m, 2H), 7.37 (dd, *J*=9.5, 2.8 Hz, 1H), 7.16 (d, *J*=2.8 Hz, 1H), 7.09 (dt, J_t=7.3

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[126] A. L. Tillman, J. Ye, D. J. Dixon *Chem. Commun.* **2006**, *11*, 1191.

Hz, J_d=1.2 Hz, 1H), 6.98 (d, J=7.7 Hz, 1H), 6.70 (br s, 1H), 6.23 (d, J=11.7 Hz, 1H), 5.63-5.49 (m, 1H), 5.25-5.12 (m, 1H), 5.08-4.93 (m, 2H), 4.67 (d, J=11.9 Hz, 1H), 3.96 (s, 3H), 3.86 (s, 3H), 3.64 (dd, J=10.2-6.3 Hz, 1H), 3.31-3.12 (m, 2H), 3.04 (ddd, J=13.1, 6.5, 3.0 Hz, 1H), 2.60-2.48 (m, 1H), 2.48-2.25 (m, 2H), 2.05-1.98 (m, 1H), 1.82-1.69 (m, 1H), 1.52-1.38 (m, 1H); ^{13}C NMR: δ =158.4, 158.0, 147.8, 144.2, 143.6, 136.7, 136.1, 132.6, 132.3, 125.6, 121.9, 121.6, 120.4, 117.7, 115.3, 111.1, 100.4, 71.1, 63.3, 60.6, 58.7, 55.7, 55.6, 50.8, 38.1, 26.4, 24.8, 21.2; ESIMS: *m/z* 445 [M^+].

General procedure for the catalytic reaction of malonate 56 with α-amido sulfones 48, 50: Malonate **1** (0.12 mmol) was added to a test tube containing a mixture of α-amido sulfone **2** (0.10 mmol) and catalyst **4e** (2.3 mg, 0.005 mmol) in toluene (2 mL). After the resulting mixture had been cooled to -24 °C, a pre-cooled 50% aqueous K_2CO_3 solution (w/w, 108 μL, 0.60 mmol) was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without any precaution to exclude moisture or air. After 60 h, the reaction product was directly isolated by chromatography on silica gel.

2-((*S*)-*tert*-Butoxycarbonylamino-phenyl-methyl)-malonic acid dimethyl ester (59a): Following the general procedure and performing the reaction on a 1.0 mmol scale, the title compound was obtained as a white solid in 85% yield, after chromatography on silica gel (Petroleum ether/Et_2O mixtures). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 15.9 min; t_{min} = 20.2 min; 90% *ee*). M.p. 102-103°C; $[\alpha]_D^{20}$=+15 (c=1.10 in $CHCl_3$); ^{1}H NMR: δ =7.35-7.22 (m, 5H), 6.14 (br s, 1H), 5.49 (br s, 1H), 3.92 (br s, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 1.42 (s, 9H); ^{13}C NMR: δ=168.4, 167.5, 155.1, 139.4, 128.6, 127.6, 126.2, 79.8, 56.7, 53.4, 52.8, 52.5, 28.3; ESIMS: *m/z* 360 [M^++Na]. The absolute configuration of **59a** was assigned as (*S*) by comparison of its optical rotation with a literature value (lit.:[118] $[\alpha]_D^{25}$=+17 (c=1.14 in $CHCl_3$), for the (*S*)-isomer 89% *ee*).

2-((*S*)-Benzyloxycarbonylamino-phenyl-methyl)-malonic acid dimethyl ester (60a): Following the general procedure, the title compound was obtained as a white waxy solid in 97% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 50.7 min; t_{min} = 73.5 min; 94% *ee*). $[\alpha]_D^{20}$=+11 (c=0.97 in $CHCl_3$); ^{1}H NMR: δ=7.39-7.24 (m, 10H), 6.46 (br d, J=8.5 Hz, 1H), 5.56 (dd, J=9.1, 4.4 Hz, 1H), 5.10 (d, J=12.6 Hz, 1H), 5.06 (d, J=12.2 Hz, 1H), 3.95 (br d, J=3.4 Hz, 1H), 3.70 (s, 3H), 3.63 (s, 3H); ^{13}C NMR: δ=168.3, 167.3, 155.7, 139.0, 136.4, 128.7, 128.4, 128.1, 127.8, 126.2, 66.9, 56.5, 53.9, 52.9, 52.6; ESIMS: *m/z* 394 [M^++Na]. The absolute configuration of **60b** was assigned as (*S*) by comparison of its optical rotation with a literature value (lit.: [118] $[\alpha]_D^{25}$=+9 (c=1.0 in $CHCl_3$), for the (*S*)-isomer, 92% *ee*).

2-[(*S*)-(2-Bromo-phenyl)-*tert*-butoxycarbonylamino-methyl]-malonic acid dimethyl ester (59e): Following the general procedure, the title compound was obtained as a colourless thick oil in 98% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 8.9 min; t_{min} = 10.9 min; 90% *ee*). $[\alpha]_D^{20}$=+37 (c=0.80 in $CHCl_3$); ^{1}H NMR: δ=7.53 (dd, J=7.9, 1.2 Hz, 1H), 7.37 (dd, J=7.7, 1.5 Hz, 1H), 7.28 (dt, J_t=7.5 Hz, J_d=1.2 Hz, 1H), 7.13 (dt, J_t=7.8 Hz, J_d=1.7 Hz, 1H), 6.52 (br d, J=9.2 Hz, 1H), 5.76 (br dd, J=8.8, 2.8 Hz, 1H), 4.16 (br d, J=3.0 Hz, 1H), 3.79

(s, 3H), 3.60 (s, 3H), 1.41 (s, 9H); ^{13}C NMR: δ=168.5, 167.5, 154.9, 138.1, 133.1, 129.3, 128.2, 127.5, 122.6, 79.9, 53.7, 53.3, 52.9, 52.4, 28.2; ESIMS: *m/z* 438 [M^++Na].

2-[(*S*)-*tert*-Butoxycarbonylamino-(4-chloro-phenyl)-methyl]-malonic acid dimethyl ester (59d): Following the general procedure, the title compound was obtained as a white solid in 97% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 21.8 min; t_{min} = 18.0 min; 83% *ee*). M.p. 94-96°C; $[\alpha]_D^{20}$=+10 (*c*=0.97 in $CHCl_3$); ^{1}H NMR: δ=7.31-7.22 (m, 4H), 6.13 (br s, 1H), 5.44 (br s, 1H), 3.87 (br d, *J*=3.4 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 1.40 (s, 9H); ^{13}C NMR: δ=168.2, 167.3, 154.9, 138.0, 133.5, 128.7, 127.6, 80.0, 56.4, 52.9, 52.6, 28.2; ESIMS: *m/z* 394 [M^++Na].

2-[(*S*)-Benzyloxyamino-(4-methoxy-phenyl)-methyl]-malonic acid dimethyl ester (60e): Following the general procedure, the title compound was obtained as white solid in 99% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 76.5 min; t_{min} = 63.9 min; 94% *ee*). M.p. 108-110°C; $[\alpha]_D^{20}$=+1 (*c*=0.95 in $CHCl_3$); ^{1}H NMR: δ=7.39-7.26 (m, 5H), 7.24-7.19 (m, 2H), 6.87-6.83 (m, 2H), 6.38 (br d, *J*=8.3 Hz, 1H), 5.49 (br dd, *J*=9.4, 4.9 Hz, 1H), 5.11 (d, *J*=12.5 Hz, 1H), 5.08 (d, *J*=12.5 Hz, 1H), 3.90 (br d, *J*=4.1 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.65 (s, 3H); ^{13}C NMR: δ=168.4, 167.3, 159.0, 155.6, 136.4, 131.1, 128.4, 128.0, 127.4, 114.0, 66.8, 56.6, 55.2, 53.5, 52.7, 52.5; ESIMS: *m/z* 424 [M^++Na].

2-((*S*)-Benzyloxycarbonylamino-naphthalen-1-yl-methyl)-malonic acid dimethyl ester (60d): Following the general procedure, the title compound was obtained as a waxy white solid in 97% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 30.2 min; t_{min} = 38.3 min; 91% *ee*). $[\alpha]_D^{20}$=+38 (*c*=0.80 in $CHCl_3$); ^{1}H NMR: δ=8.14 (d, *J*=8.8 Hz, 1H), 7.88 (d, *J*=8.8 Hz, 1H), 7.78 (d, *J*=8.2 Hz, 1H), 7.60 (t, *J*=6.4 Hz, 1H), 7.56-7.46 (m, 2H), 7.43 (t, *J*=7.7 Hz, 1H), 7.39-7.27 (m, 5H), 6.88 (br d, *J*=10.0 Hz, 1H), 6.38 (br dd, *J*=9.4, 3.9 Hz, 1H), 5.15 (br d, *J*=12.4 Hz, 1H), 5.08 (d, *J*=12.4 Hz, 1H), 4.13 (br d, *J*=3.3 Hz, 1H), 3.78 (s, 3H), 3.55 (s, 3H); ^{13}C NMR: δ=168.5, 167.6, 155.6, 136.4, 134.4, 133.8, 129.9, 129.2, 128.7, 128.5, 128.0, 126.9, 125.8, 125.2, 123.6, 122.1, 66.9, 55.2, 53.1, 52.4, 50.7; ESIMS: *m/z* 444 [M^++Na].

2-((*R*)-1-*tert*-Butoxycarbonylamino-3-phenyl-propyl)-malonic acid dimethyl ester (59i): Following the general procedure, the title compound was obtained as a colourless oil in 80% yield, after chromatography on silica gel (Petroleum ether/Et_2O mixtures). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AS column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 29.3 min; t_{min} = 35.3 min; 78% *ee*). $[\alpha]_D^{20}$=+31 (*c*=0.70 in $CHCl_3$); ^{1}H NMR: δ=7.31-7.24 (m, 2H), 7.21-7.15 (m, 3H), 5.39 (br d, *J*=10.4 Hz, 1H), 4.34-4.24 (m, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.62 (br d, *J*=4.2 Hz, 1H), 2.80-2.70 (m, 1H), 2.68-2.58 (m, 1H), 1.98-1.85 (m, 1H), 1.85-1.74 (m, 1H), 1.44 (s, 9H); ^{13}C NMR: δ=168.6, 168.2, 155.4, 141.2, 128.4, 128.3, 126.0, 79.4, 55.1, 52.6, 52.4, 50.1, 35.5, 32.7, 28.3; ESIMS: *m/z* 388 [M^++Na].

2-((*R*)-1-*tert*-Butoxycarbonylamino-3-methyl-butyl)-malonic acid dimethyl ester (59n): Following the general procedure, the title compound was obtained as a colourless

oil in 78% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 98:2, flow rate 0.75 mL/min, t_{maj} = 26.3 min; t_{min} = 30.7 min; 83% *ee*). $[\alpha]_D^{20}$=+44 (*c*=0.80 in $CHCl_3$); ^{1}H NMR: δ=5.26 (br d, *J*=10.2 Hz, 1H), 4.37-4.24 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.59 (br d, *J*=4.4 Hz, 1H), 1.64-1.44 (m, 1H), 1.41 (s, 9H), 1.32-1.18 (m, 2H), 0.91 (d, *J*=4.2 Hz, 3H), 0.89 (d, *J*=5.0 Hz, 3H); ^{13}C NMR: δ=168.7, 168.4, 155.3, 79.3, 55.2, 52.6, 52.4, 48.5, 42.7, 28.3, 25.0, 23.0, 21.9; ESIMS: *m/z* 340 [M^++Na].

2-((*R*)-1-Benzyloxycarbonylamino-ethyl)-malonic acid dimethyl ester (60g): Following the general procedure, the title compound was obtained as a colourless oil in 99% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 18.2 min; t_{min} = 15.9 min; 81% *ee*). $[\alpha]_D^{20}$=+29 (*c*=0.97 in $CHCl_3$); ^{1}H NMR: δ=7.37-7.28 (m, 5H), 5.61 (br d, *J*=8.7 Hz, 1H), 5.08 (br s, 2H), 4.49-4.37 (m, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.62 (br d, *J*=4.1 Hz, 1H), 1.28 (d, *J*=7.1 Hz, 3H); ^{13}C NMR: δ=168.4, 167.9, 155.5, 136.4, 128.4, 128.0, 127.9, 66.6, 55.6, 52.6, 52.5, 46.5, 19.0; ESIMS: *m/z* 332 [M^++Na].

2-((*R*)-1-Benzyloxycarbonylamino-2-methyl-propyl)-malonic acid dimethyl ester (60j): Following the general procedure, the title compound was obtained as a colourless oil in 88% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 22.7 min; t_{min} = 10.6 min; 85% *ee*). $[\alpha]_D^{20}$=+56 (*c*=0.97 in $CHCl_3$); ^{1}H NMR: δ=7.37-7.28 (m, 5H), 5.75 (br d, *J*=9.8 Hz, 1H), 5.11 (d, *J*=12.3 Hz, 1H), 5.06 (d, *J*=12.3 Hz, 1H), 4.09-4.01 (m, 1H), 3.74 (s, 3H), 3.72 (br d, *J*=4.1 Hz, 1H), 3.63 (s, 3H), 1.83-1.68 (m, 1H), 0.95 (d, *J*=6.8 Hz, 3H), 0.91 (d, *J*=6.7 Hz, 3H); ^{13}C NMR: δ=168.9, 168.4, 156.2, 136.7, 128.4, 127.9, 66.6, 56.6, 52.8, 52.5, 52.4, 31.9, 19.8, 19.2; ESIMS: *m/z* 360 [M^++Na]. The absolute configuration of **60j** was assigned as (*R*) after the transformation in the corresponding *N*-Cbz protected acid **66b** (*vide infra*).

2-((*R*)-1-Benzyloxycarbonylamino-cyclohexyl-methyl)-malonic acid dimethyl ester (60c): Following the general procedure, the title compound was obtained as a colourless oil in 90% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 20.6 min; t_{min} = 16.3 min; 97% *ee*). $[\alpha]_D^{20}$=+50 (*c*=1.03 in $CHCl_3$); ^{1}H NMR: δ=7.37-7.26 (m, 5H), 5.76 (br d, *J*=10.7 Hz, 1H), 5.10 (d, *J*=12.1 Hz, 1H), 5.04 (d, *J*=12.1 Hz, 1H), 4.08 (dt, J_t=9.8 Hz, J_d=4.0 Hz, 1H), 3.76 (d, *J*=4.1 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 1.88-1.56 (m, 5H), 1.47-1.35 (m, 1H), 1.22-0.95 (m, 5H); ^{13}C NMR: δ=169.0, 168.6, 156.2, 136.7, 128.3, 127.9, 66.6, 55.7, 52.6, 52.5, 52.3, 40.9, 30.1, 29.5, 26.0, 25.8, 25.7; ESIMS: *m/z* 400 [M^++Na].

2-((*S*)-*tert*-Butoxycarbonylamino-phenyl-methyl)-malonic acid diallyl ester (61a): Following the general procedure, the title compound was obtained as a white solid in 97% yield, after chromatography on silica gel (Petroleum ether/Et_2O mixtures). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 19.0 min; t_{min} = 14.8 min; 90% *ee*). M.p. 77-79°C; $[\alpha]_D^{20}$=+10 (*c*=1.17 in $CHCl_3$); ^{1}H NMR: δ=7.34-7.21 (m, 5H), 6.17 (br s, 1H), 5.94-5.82 (m, 1H), 5.79-5.68 (m, 1H), 5.52 (br s, 1H), 5.31 (dq, J_d=17.1 Hz, J_q=1.3 Hz, 1H), 5.24 (dq, J_d=10.4 Hz, J_q=1.1 Hz, 1H), 5.20-5.11 (m, 2H), 4.69-4.59 (m, 2H),

4.58-4.47 (m, 2H), 3.97 (br s, 1H), 1.41 (s, 9H); ^{13}C NMR: δ=167.6, 166.7, 155.0, 139.4, 131.2, 131.1, 128.5, 127.6, 126.2, 118.9, 118.7, 79.7, 66.4, 66.1, 56.8, 53.4, 28.2; ESIMS: *m/z* 412 [M^++Na].

2-((*S*)-Benzyloxycarbonylamino-phenyl-methyl)-malonic acid diallyl ester (62a): Following the general procedure, the title compound was obtained as a white solid in 95% yield, after chromatography on silica gel (Petroleum ether/Et_2O mixtures). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 70:30, flow rate 0.50 mL/min, t_{maj} = 41.9 min; t_{min} = 40.0 min; 92% *ee*). M.p. 88-89°C; $[\alpha]_D^{20}$=+8 (*c*=0.92 in $CHCl_3$); ^{1}H NMR: δ=7.39-7.23 (m, 10H), 6.47 (br d, *J*=9.5 Hz, 1H), 5.89-5.79 (m, 1H), 5.78-5.67 (m, 1H), 5.59 (br dd, *J*=9.0, 5.0 Hz, 1H), 5.29 (dq, J_d=17.2 Hz, J_q=1.4 Hz, 1H), 5.21 (dq, J_d=10.4 Hz, J_q=1.3 Hz, 1H), 5.18-5.15 (m, 1H), 5.15-5.12 (m, 1H), 5.12-5.05 (m, 2H), 4.62-4.58 (m, 2H), 4.58-4.48 (m, 2H), 3.99 (br d, *J*=4.4 Hz, 1H); ^{13}C NMR: δ=167.6, 166.5, 155.6, 138.9, 136.4, 131.2, 131.0, 128.6, 128.4, 128.1, 127.8, 126.2, 119.1, 118.8, 66.9, 66.5, 66.2, 56.7, 53.9; ESIMS: *m/z* 446 [M^++Na].

2-((*R*)-Benzyloxycarbonylamino-cyclohexyl-methyl)-malonic acid diallyl ester (62c): Following the general procedure, the title compound was obtained as colourless oil in 84% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 15.4 min; t_{min} = 10.4 min; 94% *ee*). $[\alpha]_D^{20}$=+37 (*c*=0.83 in $CHCl_3$); ^{1}H NMR: δ=7.37-7.27 (m, 5H), 5.95-5.75 (m, 3H), 5.34 (dq, J_d=17.1 Hz, J_q=1.2 Hz, 1H), 5.28 (dq, J_d=9.2 Hz, J_q=1.2 Hz, 1H), 5.26-5.24 (m, 1H), 5.19 (dq, J_d=10.4 Hz, J_q=1.0 Hz, 1H), 5.09 (d, *J*=12.6 Hz, 1H), 5.05 (d, *J*=12.6 Hz, 1H), 4.68-4.63 (m, 2H), 4.57-4.47 (m, 2H), 4.12 (dt, J_t=9.7 Hz, J_d=3.7 Hz, 1H), 3.80 (d, *J*=3.7 Hz, 1H), 1.89-1.54 (m, 5H), 1.48-1.36 (m, 1H), 1.22-0.92 (m, 5H); ^{13}C NMR: δ=168.3, 167.7, 156.1, 136.7, 131.4, 131.3, 128.4, 127.9, 119.0, 118.9, 66.6, 66.4, 66.0, 55.7, 52.5, 41.1, 30.1, 29.5, 25.9, 25.8, 25.7; ESIMS: *m/z* 452 [M^++Na].

2-((*S*)-*tert*-Butoxycarbonylamino-phenyl-methyl)-malonic acid dibenzyl ester (63a): Following the general procedure, the title compound was obtained as a white solid in 96% yield, after chromatography on silica gel (Petroleum ether/Et_2O mixtures). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AS column (hexane/*i*PrOH = 98:2, flow rate 1.5 mL/min, t_{maj} = 12.6 min; t_{min} = 10.8 min; 92% *ee*). M.p. 56-57°C; $[\alpha]_D^{20}$=+23 (*c*=1.00 in $CHCl_3$); ^{1}H NMR: δ=7.37-7.21 (m, 13H), 7.13-7.08 (m, 2H), 6.20 (br s, 1H), 5.56 (br s, 1H), 5.18 (d, *J*=12.6 Hz, 1H), 5.13 (d, *J*=12.6 Hz, 1H), 5.06 (s, 2H), 4.02 (br s, 1H), 1.41 (s, 9H); ^{13}C NMR: δ=167.8, 166.8, 155.0, 139.3, 135.0, 134.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.6, 126.2, 79.7, 67.6, 67.3, 56.9, 53.5, 28.3; ESIMS: *m/z* 512 [M^++Na]. The absolute configuration of **63a** was assigned as (*S*) by comparison of its optical rotation with a literature value (lit.:[118] $[\alpha]_D^{25}$=+14 (*c*=0.98 in $CHCl_3$), for the (*S*)-isomer, 96% *ee*).

2-((*S*)-Benzyloxycarbonylamino-phenyl-methyl)-malonic acid dibenzyl ester (64a): Following the general procedure, the title compound was obtained as a white solid in 92% yield, after chromatography on silica gel (Petroleum ether/Et_2O mixtures). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 89.5 min; t_{min} = 68.2 min; 93% *ee*). M.p. 85-87°C; $[\alpha]_D^{20}$=+13 (*c*=1.12 in $CHCl_3$); ^{1}H NMR: δ=7.40-7.23 (m, 18H), 7.13-7.08 (m, 2H), 6.48 (br d, *J*=8.3 Hz, 1H), 5.63 (br dd, *J*=9.1, 4.3 Hz, 1H), 5.13 (d, *J*=12.1

Hz, 1H), 5.10 (d, *J*=12.1 Hz, 1H), 5.08 (br s, 2H), 5.05 (br s, 2H), 4.04 (br d, *J*=5.0 Hz, 1H); ^{13}C NMR: δ =167.8, 166.6, 155.9, 138.9, 136.4, 134.9, 134.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 126.2, 67.7, 67.4, 66.9, 56.8, 53.7; ESIMS: *m/z* 546 [M^++Na].

2-((*R*)-1-*tert*-Butoxycarbonylamino-3-methyl-butyl)-malonic acid dibenzyl ester (63n): Following the general procedure, the title compound was obtained as a colourless oil in 77% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 95:5, flow rate 0.75 mL/min, t_{maj} = 27.9 min; t_{min} = 30.8 min; 91% *ee*). $[\alpha]_D^{20}$=+40 (*c*=0.75 in $CHCl_3$); ^{1}H NMR: δ =7.37-7.28 (m, 10H), 5.26 (br d, *J*=9.6 Hz, 1H), 5.21 (d, *J*=11.4 Hz, 1H), 5.18 (d, *J*=12.8 Hz, 1H), 5.16 (d, *J*=11.4 Hz, 1H), 5.10 (d, *J*=12.8 Hz, 1H), 4.41-4.31 (m, 1H), 3.70 (d, *J*=4.4 Hz, 1H), 1.65-1.44 (m, 2H), 1.41 (s, 9H), 1.29-1.18 (m, 1H), 0.87 (d, *J*=6.6Hz, 6H); ^{13}C NMR: δ =168.0, 167.7, 155.2, 135.1, 128.5, 128.4, 128.3, 128.2, 79.2, 67.3, 67.2, 55.3, 48.6, 42.2, 28.3, 25.0, 22.9, 21.8; ESIMS: *m/z* 492 [M^++Na].

2-((*S*)-*tert*-Butoxycarbonylamino-phenyl-methyl)-malonic acid bis-(4-methoxy-phenyl) ester (57a): Following the general procedure and using 1.5 equivalents 50% aqueous K_2CO_3 solution (w/w, 27 μL, 0.15 mmol), the title compound was obtained as a white solid in 90% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 47.5 min; t_{min} = 77.0 min; 98% *ee*); $[\alpha]_D^{20}$=+3 (*c*=0.700 in $CHCl_3$);. The absolute configuration of **57a** has been assigned as (*S*) *vide supra*.

2-((*S*)-Benzyloxycarbonylamino-phenyl-methyl)-malonic acid bis-(4-methoxy-phenyl) ester (58a): Following the general procedure and using 1.5 equivalents 50% aqueous K_2CO_3 solution (w/w, 27 μL, 0.15 mmol), the title compound was obtained as a white solid in 96% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, t_{maj} = 30.9 min; t_{min} = 26.5 min; 99% *ee*); $[\alpha]_D^{20}$=+3 (*c*=0.70 in $CHCl_3$);. The absolute configuration of **58a** has been assigned as (*S*) *vide supra*.

2-((*R*)-*tert*-Butoxycarbonylamino-phenyl-methyl)-malonic acid bis-(4-methoxy-phenyl) ester (*ent*-57a): Following the general procedure and using quinidine derived catalyst **QD-49i** and 1.5 equivalents 50% aqueous K_2CO_3 solution (w/w, 27 μL, 0.15 mmol), the title compound was obtained as a white solid in 98% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 77.0 min; t_{min} = 47.5 min; 93% *ee*). M.p. 147-149°C; $[\alpha]_D^{20}$=-4 (*c*=1.10 in $CHCl_3$); spectral data were identical to compound **57a**.

2-((*S*)-Benzyloxycarbonylamino-phenyl-methyl)-malonic acid bis-(4-methoxy-phenyl) ester (*ent*-58a): Following the general procedure and using quinidine derived catalyst **QD-49i** and 1.5 equivalents 50% aqueous K_2CO_3 solution (w/w, 27 μL, 0.15 mmol), the title compound was obtained as a white solid in 95% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, t_{maj} = 26.5 min; t_{min} = 30.9 min; 99% *ee*). M.p. 166-168°C; $[\alpha]_D^{20}$=-2 (*c*=0.96 in $CHCl_3$); spectral data were identical to compound **58a**.

2-((*S*)-*tert*-Butoxycarbonylamino-3-phenyl-propyl)-malonic acid bis-(4-methoxy-phenyl) ester (*ent*-57i): Following the general procedure and using quinidine derived catalyst **5** and 1.5 equivalents 50% aqueous K_2CO_3 solution (w/w, 27 μL, 0.15 mmol), the title compound was obtained as a white solid in 88% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, t_{maj} = 10.6 min; t_{min} = 8.9 min; 77% *ee*). M.p. 114-116°C; $[\alpha]_D^{20}$=-32 (*c*=0.76 in $CHCl_3$); ^{1}H NMR: δ=7.33-7.27 (m, 2H), 7.25-7.19 (m, 3H), 7.09 (br d, *J*=9.6 Hz, 2H), 7.05 (br d, *J*=8.6 Hz, 2H), 6.88 (br d, *J*=8.2 Hz, 4H), 5.50 (d, *J*=10.2 Hz, 1H), 4.66-4.56 (m, 1H), 4.08 (d, *J*=3.9 Hz, 1H), 3.80 (s, 6H), 2.89-2.79 (m, 1H), 2.79-2.67 (m, 1H), 2.17-1.96 (m, 2H), 1.46 (s, 9H); ^{13}C NMR: δ=167.1, 166.6, 157.6, 157.5, 155.5, 143.8, 143.6, 141.1, 128.5, 128.4, 126.1, 122.2, 122.1, 114.5, 114.4, 79.7, 55.6, 55.4, 50.2, 35.8, 32.7, 28.3; ESIMS: *m/z* 572 [M^++Na].

2-((*S*)-1-Benzyloxycarbonylamino-cyclohexyl-methyl)-malonic acid bis-(4-methoxy-phenyl) ester (*ent*-58c): Following the general procedure and using quinidine derived catalyst **5** and 1.5 equivalents 50% aqueous K_2CO_3 solution (w/w, 27 μL, 0.15 mmol), the title compound was obtained as a white solid in 89% yield, after chromatography on silica gel (CH_2Cl_2). The *ee* of the product was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH = 80:20, flow rate 1.0 mL/min, t_{maj} = 11.1 min; t_{min} = 13.9 min; 93% *ee*). $[\alpha]_D^{20}$=-54 (*c*=0.64 in $CHCl_3$); spectral data were identical to compound **58c**.

Preparation of the β^3-amino acid hydrochlorides:[127] Malonic acid dimethyl ester **59a** or **60j** (0.20 mmol) was suspended in HCl 6M (0.80 mL), and the mixture then heated at 100°C for 1h30min for **59a** and 5h for **60j**. After cooling to room temperature, the solution was evaporated to dryness under reduced pressure. Crude β^3-amino acid hydrochlorides were then purified by trituration with Et_2O.

(*S*)-3-Amino-3-phenyl-propionic acid hydrochloride (65a): Following the above procedure, the title compound was obtained as a white solid in 93% yield. The *ee* of the product was determined on the corresponding *N*-Boc ethyl ester, (prepared by esterification ($SOCl_2$, EtOH)[127] followed by Boc protection (Boc_2O, EtOAc/Na_2CO_3 aq.)) using a Daicel Chiralcel OD column (hexane/*i*PrOH = 98:2, flow rate 1.5 mL/min, t_{maj} = 8.6 min; t_{min} = 7.5 min; 90% *ee*), and was found to be consistent with the *ee* of the starting Mannich adduct **59a** (90% *ee*). M.p. 204-205°C; $[\alpha]_D^{20}$=+3 (*c*=0.47 in H_2O); ^{1}H NMR (D_2O):δ=7.54-7.48 (m, 5H), 3.19 (dd, *J*=17.2, 7.9 Hz, 1H), 3.11 (dd, *J*=17.2, 6.9 Hz, 1H), [C*H*N signal below the residual solvent peak]; ^{13}C NMR (D_2O): δ=177.0, 138.4, 132.8, 132.6, 130.2, 54.8, 41.1; ESIMS: *m/z* 166 [M^+].

(*S*)-3-Amino-4-methyl-pentanoic acid hydrochloride (65b): Following the above procedure, the title compound was obtained as a white solid in 88% yield. The *ee* of the product was determined on the corresponding *N*-Cbz methyl ester, (prepared by Cbz protection (CbzCl, NaOH 1M) followed by esterification with trimethylsilyldiazomethane)[128] using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 90:10, flow rate 0.75 mL/min, t_{maj} = 21.4 min; t_{min} = 17.3 min; 85% *ee*), and was found to

[127] M. Nejman, A. Śliwińska, A. Zwierzak, *Tetrahedron* **2005**, *61*, 8536.
[128] C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E. Gómez-Bengoa, J. M. García, *J. Am. Chem. Soc.* **2004**, *126*, 9188..

be consisten with the *ee* of the starting mannich adduct **60j** (85% *ee*). M.p. 180-181°C; $[\alpha]_D^{20}$=-24 (*c*=0.55 in H_2O); ^{1}H NMR (D_2O):δ=3.55-3.49 (m, 1H), 2.86 (dd, *J*=17.8, 4.1 Hz, 1H), 2.69 (dd, *J*=17.4, 9.0 Hz, 1H), 2.08-1.99 (m, 1H), 1.03 (d, *J*=6.6 Hz, 3H), 1.01 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (D_2O): δ=177.9, 56.6, 36.5, 32.9, 20.3, 19.9; ESIMS: *m/z* 132 [M^+].

Preparation of the *N*-protected β^3-amino acids: A 1M solution of LiOH in H_2O (0.4 mL) was added to a cooled (0°C) solution of malonic acid dimethyl ester **59a** or **60j** (0.10 mmol) in THF (0.4 mL). The solution was stirred at 0°C for 2h, then at room temperature for additional 4h. H_2O was then added, and the mixture acidified to pH≈2 using a 0.5M $KHSO_4$ solution. The malonic acid was then extracted with EtOAc (3x), the organic phases dried over Na_2SO_4, filtered and evaporated. The obtained malonic acid was then suspended in toluene (4 mL) and then heated to reflux for 2h30min. After cooling to room temperature, the solvent was evaporated and the residue purified by chromatography on silica gel.

(*S*)-3-*tert*-Butoxycarbonylamino-3-phenyl-propionic acid (66a): Following the above procedure, the title compound was obtained as a white solid in 77% yield, after chromatography on silica gel (hexane/EtOAc/AcOH 80:20:1). The *ee* of the product was determined on the corresponding methyl ester, (prepared by esterification with trimethylsilyldiazomethane)[128] using a Daicel Chiralcel OD column (hexane/*i*PrOH = 95:5, flow rate 1.5 mL/min, t_{maj} = 7.4 min; t_{min} = 6.1 min; 90% *ee*), and was found to be consistent with the *ee* of the starting **3a** (90% *ee*). M.p. 127-129°C; $[\alpha]_D^{20}$=-26 (*c*=0.50 in CH_3OH); ^{1}H NMR (CD_3OD):δ=7.35-7.20 (m, 6H), 5.02 (br s, 1H), 2.75 (dd, *J*=15.4, 8.3 Hz, 1H), 2.66 (dd, *J*=15.9, 13.4 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (CD_3OD): δ =174.4, 157.5, 134.6, 129.5, 128.3, 127.4, 80.3, 52.9, 42.3, 28.7; ESIMS: *m/z* 288 [M^++Na].

(*S*)-3-Benzyloxycarbonylamino-4-methyl-pentanoic acid (66b): Following the above procedure, the title compound was obtained as a white solid in 78% yield, after chromatography on silica gel (CH_2Cl_2/CH_3OH 95:5). The *ee* of the product was determined on the corresponding methyl ester, (prepared by esterification with trimethylsilyldiazomethane)[128] using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 90:10, flow rate 0.75 mL/min, t_{maj} = 21.4 min; t_{min} = 17.3 min; 84% *ee*), and was found to be consistent with the ee of the starting **60j** (85% *ee*). M.p. 82-84°C; $[\alpha]_D^{20}$=+24 (*c*=0.20 in $CHCl_3$); ^{1}H NMR (CD_3OD): δ =7.38-7.23 (m, 5H), 6.97 (br d, *J*=8.0 Hz, 1H), 5.07 (s, 2H), 3.91-3.82 (m, 1H), 2.51 (dd, *J*=15.4, 5.8 Hz, 1H), 2.39 (dd, *J*=15.4, 8.9 Hz, 1H), 1.79 (oct, *J*=6.5 Hz, 1H), 0.93 (d, *J*=6.6 Hz, 3H), 0.91 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (CD_3OD): δ =175.4, 158.6, 138.5, 129.4, 128.9, 128.6, 67.3, 55.0, 38.0, 33.5, 19.5, 18.4; ESIMS: *m/z* 288 [M^++Na]. The absolute configuration of **66b** was assigned as (*S*) by comparison of its optical rotation with a literature value (lit.:[129] $[\alpha]_D^{25}$=-33 (*c*=0.2 in $CHCl_3$), for the (*R*)-isomer).

General procedure for the catalytic reaction of β-ketoesters 67-70, 76-79 with α-amido sulfones 48, 50: β-Ketoester **67-70, 76-79** (0.10 mmol) was added to a test tube containing a mixture of α-amido sulfone **48, 50** (0.12 mmol) and catalyst **49i** (1.2 mg, 0.025 mmol) in toluene (2 mL). After the resulting mixture had been cooled to -24 °C, a pre-cooled 50% aqueous K_2CO_3 solution (w/w, 27 μL, 0.15 mmol) was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without

[129] A. Sutherland, C. L. Willis, *J. Org. Chem.* **1998**, *63*, 7764.

any precaution to exclude moisture or air. After the time stated, the reaction product was filtered through a short plug of silica, the plug washed with CH_2Cl_2 and Et_2O, and the solvent evaporated. The crude product was analysed by ^1H NMR spectroscopy to determine the diastereomeric ratio, and then purified by chromatography on silica gel.

(*S*)-1-[(*R*)-*tert*-Butoxycarbonylamino-phenyl-methyl]-2-oxo-cyclopentanecarboxylic acid methyl ester (74a): Following the general procedure (21 h reaction time), the title compound was obtained as a colourless oil in 98% yield after chromatography on silica gel (hexane/Et_2O 1:1) and as a single diastereoisomer, as determined on the crude mixture. The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 98:2, flow rate 0.75 mL/min, t_{maj} = 118.0 min; t_{min} = 36.2 min, 95% *ee*). $[\alpha]_D^{20}$=+25 (*c*=0.85 in CH_2Cl_2); ^1H NMR: δ=7.33-7.21 (m, 5H), 5.95 (br s, 1H), 5.20 (d, *J*=9.7 Hz, 1H), 3.67 (s, 3H), 2.57-2.25 (m, 1H), 2.37-2.25 (m, 2H), 2.05-1.82 (m, 3H), 1.38 (s, 9H); ^{13}C NMR: δ 210.9, 170.0, 155.2, 138.3, 128.4, 128.1, 127.8, 79.8, 64.9, 55.7, 52.7, 37.5, 30.6, 28.2, 18.8; ESIMS: *m/z* 370 [M^++Na].

(*S*)-1-((*R*)-Benzyloxycarbonylamino-phenyl-methyl)-2-oxo-cyclopentanecarboxylic acid methyl ester (75a): Following the general procedure (28 h reaction time), the title compound was obtained as a colourless oil in 90% yield after chromatography on silica gel (hexane/Et_2O 6:4) and as a single diastereoisomer, as determined on the crude mixture. The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 49.3 min; t_{min} = 19.4 min, 92% *ee*). $[\alpha]_D^{20}$=+30 (*c*=0.88 in CH_2Cl_2); ^1H NMR:δ=7.40-7.20 (m, 10H), 6.23 (br d, *J*=8.3 Hz ,1H), 5.23 (br d, *J*=8.3 Hz, 1H), 5.05 (s, 2H), 3.65 (s, 3H), 2.57-2.46 (m, 1H), 2.42-2.22 (m, 2H), 2.07-1.80 (m, 3H), ^{13}C NMR: δ 210.5, 169.7, 155.8, 138.2, 136.5, 128.5, 128.4, 128.1, 127.9, 66.9, 64.6, 56.8, 52.6, 37.6, 30.4, 18.9; ESIMS: *m/z* 404 [M^++Na].

1-[(2-Bromo-phenyl)-*tert*-butoxycarbonylamino-methyl]-2-oxo-cyclopentanecarboxylic acid methyl ester (74e): Following the general procedure (73 h reaction time), the title compound was obtained as a colourless oil in 60% yield after chromatography on silica gel (CH_2Cl_2) and as a mixture of diastereoisomers (94:6 diastereomeric ratio, as determined on the crude mixture). The *ee* of the products was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 90:10, flow rate 0.75 mL/min, major diastereoisomer: t_{maj} =16.1 min; t_{min} = 18.3 min, 69% *ee*, enantiomers of the minor diastereoisomer not separated). ^1H NMR [signals of the major diastereoisomer]:δ 7.59-7.50 (t, *J*=8.3 Hz, 2H), 7.30-7.22 (t, *J*=7.3 Hz, 1H), 7.14-7.08 (t, *J*=7.3 Hz, 1H), 6.22 (br s, 1H), 5.62 (br d, *J*=7.8 Hz, 1H), 3.66 (s, 3H), 2.65-2.50 (m, 1H), 2.49-2.33 (m, 2H), 2.33-2.18 (m, 1H), 2.15-2.05 (m, 1H), 2.05-1.91 (m, 1H), 1.39 (s, 9H); ^{13}C NMR [signals of the major diastereoisomer]: δ 210.7, 170.3, 155.4, 138.6, 133.2, 129.4, 129.3, 127.9, 125.1, 79.8, 64.3, 54.0, 52.6, 37.5, 31.3, 28.3, 19.1; ESIMS: *m/z* 448 [M^++Na].

1-(1-Benzyloxycarbonylamino-(2-bromo-phenyl)-methyl)-2-oxo-cyclopentanecarboxylic acid methyl ester (75f): Following the general procedure (73 h reaction time), the title compound was obtained as a colourless oil in 85% yield after chromatography on silica gel (hexane/EtOAc 8:2) and as a mixture of diastereoisomers (96:4 diastereomeric ratio, as determined on the crude mixture). The *ee* of the products was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH =

90:10, flow rate 0.75 mL/min, major diastereoisomer: t_{maj} =33.2 min; t_{min} = 26.0 min, 77% *ee*, minor diastereoisomer: t_{maj} =27.0 min; t_{min} = 30.1 min, 47% *ee*). ^{1}H NMR [signals of the major diastereoisomer]: δ=7.60-7.51 (m, 2H), 7.38-7.22 (m, 5H), 7.12 (t, *J*=7.6 Hz, 1H), 6.55 (br d, *J*=8.7 Hz, 1H), 5.65 (d, *J*=8.7 Hz, 1H), 5.05 (s, 2H), 3.66 (s, 3H), 2.69-2.50 (m, 1H), 2.50-2.34 (m, 2H), 2.14-1.89 (m, 3H); ^{13}C NMR [signals of the major diastereoisomer]: δ=210.7,170.1, 155.7, 138.3, 136.3, 133.2, 129.4, 129.3, 128.4, 128.0, 125.1, 67.0, 64.0, 54.6, 52.7, 37.6, 31.4, 19.2; ESIMS: *m/z* 482 [M^++Na].

1-(1-Benzyloxycarbonylamino-(4-chloro-phenyl)-methyl)-2-oxo-cyclopentanecarboxylic acid methyl ester (75b): Following the general procedure (21 h reaction time), the title compound was obtained as a colourless oil in 98% yield after chromatography on silica gel (hexane/EtOAc 85:15) and as a mixture of diastereoisomers (96:4 diastereomeric ratio, as determined on the crude mixture). The *ee* of the products was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, major diastereoisomer: t_{maj} = 51.0 min; t_{min} = 16.2 min, 73% *ee*, minor diastereoisomer: t_{maj} = 99.6 min; t_{min} = 25.6 min, 61% *ee*). ^{1}H NMR [signals of the major diastereoisomer, 50°C]: δ=7.40-7.21 (m, 9H), 6.08 (br s, 1H), 5.20 (d, *J*=8.8 Hz, 1H), 5.08 (d, *J*=11.8 Hz, 2H), 5.03 (d, *J*=11.8 Hz, 1H), 3.81 (s, 3H), 2.56-2.47 (m, 1H), 2.43-2.32 (m, 2H), 2.04-1.84 (m, 3H); ^{13}C NMR [signals of the major diastereoisomer]: δ=210.8, 169.7, 155.8, 136.6, 136.1, 133.9, 129.7, 128.7, 128.6, 128.5, 128.1, 67.0, 64.5, 55.9, 52.9, 37.6, 30.9, 19.0; ESIMS: *m/z* 438 [M^++Na].

1-(1-Benzyloxycarbonylamino-(4-methoxy-phenyl)-methyl)-2-oxo-cyclopentanecarboxylic acid methyl ester (75e): Following the general procedure (65 h reaction time), the title compound was obtained as a colourless oil in 70% yield after chromatography on silica gel (hexane/EtOAc 80:20) and as a mixture of diastereoisomers (95:5 diastereomeric ratio, as determined on the crude mixture). The *ee* of the products was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 95:5, flow rate 0.75 mL/min, major diasteroisomer: t_{maj} = 50.3 min; t_{min} = 20.7 min, 77% *ee*, minor diastereoisomer: t_{maj} = 87.1 min; t_{min} = 32.9 min, 53% *ee*); ^{1}H NMR [signals of the major diastereoisomer]: δ=7.41-7.19 (m, 7H), 6.85-6.80 (m, 2H), 6.18 (br s, 1H), 5.18 (br d, *J*=9.2 Hz, 1H), 5.05 (s, 2H), 3.78 (s, 3H), 3.65 (s, 3H), 2.51 (dt, J_d=13.6 Hz, J_t=6.6 Hz, 1H), 2.40-2.23 (m, 2H), 2.05-1.86 (m, 3H);.^{13}C NMR [signals of the major diastereoisomer]: δ=211.0, 169.8, 159.2, 155.8, 136.3, 130.1, 129.3, 128.4, 128.0, 113.8, 66.9, 64.8, 55.9, 55.2, 52.7, 37.5, 29.2, 18.9, ESIMS: *m/z* 434 [M^++Na].

1-(1-Benzyloxycarbonylamino-naphthalen-1-yl-methyl)-2-oxo-cyclopentanecarboxylic acid methyl ester (75d): Following the general procedure (40 h reaction time), the title compound was obtained as a colourless oil in 50% yield after chromatography on silica gel (hexane/Et_2O 80:20) and as a mixture of diastereoisomers (90:10 diastereomeric ratio, as determined on the crude mixture). The *ee* of the products was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 95:5, flow rate 0.75 mL/min, major diatstereoisomer: t_{maj} = 55 min; t_{min} = 57 min, 85% *ee*, enantiomers of the minor diastereoisomer not separated). ^{1}H NMR: δ=8.28 (d, *J* =7.7 Hz, $1H_{maj}$, $1H_{min}$), 7.85 (d, *J*=8.0 Hz, $1H_{maj}$, $1H_{min}$), 7.79 (d, *J*=8.0 Hz, $1H_{maj}$, $1H_{min}$), 7.68-7.45 (m, $3H_{maj}$, $3H_{min}$), 7.41 (t, *J*=8.2 Hz, $1H_{maj}$, $1H_{min}$), 7.36-7.21 (m, $5H_{maj}$, $5H_{min}$), 6.42 (d, *J*=9.7 Hz, $1H_{min}$), 6.20 (br d, *J*=9.4 Hz, $1H_{maj}$), 6.08 (d, *J*=9.4 Hz, $1H_{maj}$, $1H_{min}$), 5.12 (d, *J*=12.4 Hz, $1H_{maj}$), 5.06 (d, *J*=12.4 Hz, $1H_{maj}$, $1H_{min}$), 4.96 (d, *J*=12.4 Hz, $1H_{min}$), 3.76 (s, $3H_{min}$), 3.63 (s, $3H_{maj}$), 2.69-2.26 (m, $3H_{maj}$, $3H_{min}$), 2.22-1.87 (m, $3H_{maj}$, $3H_{min}$); ^{13}C NMR [signals of the major diastereoisomer]: δ=211.4, 171.2, 156.2, 136.5, 134.5, 133.9,

131.9, 128.8, 128.4, 128.0, 127.9, 126.8, 125.8, 125.3, 125.0, 123.3, 67.0, 64.4, 52.7, 50.9, 37.7, 32.8, 19.2; ESIMS: *m/z* 454 [M^++Na].

(*S*)-1-((*R*)-1-*tert*-Butoxycarbonylamino-3-phenyl-propyl)-2-oxo-cyclopentanecarboxylic acid methyl ester (74i): Following the general procedure (45 h reaction time), the title compound was obtained as a colourless oil in 55% yield after chromatography on silica gel (CH_2Cl_2) and as a mixture of diastereoisomers (97:3 diastereomeric ratio, as determined on the crude mixture). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, major diastereoisomer: t_{maj} = 8.1 min; t_{min} = 7.4 min, 90% *ee*, enantiomers of the minor diastereoisomer not separated). ^{1}H NMR [signals of the major diastereoisomer]: δ =7.28 (t, *J*=7.8 Hz, 2H), 7.22-7.14 (m, 3H), 5.12 (d, *J*=10.3 Hz, 1H), 3.96 (t, *J*=11.0 Hz, 1H), 3.69 (s, 3H), 2.99-2.73 (m, 1H), 2.63-2.23 (m, 4H), 1.99-1.83 (m, 4H), 1.76-1.65 (m, 1H), 1.44 (s, 9H); ^{13}C NMR [signals of the major diastereoisomer]: δ =211.9, 170.6, 156.2, 141.4, 128.5, 128.4, 126.0, 79.5, 64.5, 52.5, 52.1, 37.7, 33.7, 33.0, 31.8, 28.3, 18.9; ESIMS: *m/z* 398 [M^++Na].

1-(1-Benzyloxycarbonylamino-ethyl)-2-oxo-cyclopentanecarboxylic acid methyl ester (75g): Following the general procedure (47 h reaction time), the title compound was obtained as a colourless oil in 70% yield after chromatography on silica gel (CH_2Cl_2) and as a mixture of diastereoisomers (97:3 diastereomeric ratio, as determined on the crude mixture). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 90:10, flow rate 0.75 mL/min, major dastereoisomer: t_{maj} = 13.1 min; t_{min} = 18.4 min, 75% *ee*, enantiomers of the minor disastereoisomer not separated). ^{1}H NMR [signals of the major diastereoisomer]: δ =7.38-7.27 (m, 5H), 5.38 (br d, *J*=8.5 Hz ,1H), 5.16-4.97 (m, 2H), 4.24-4.12 (m, 1H), 3.71 (s, 3H), 2.61-2.47 (m, 1H), 2.43-2.30 (m, 2H), 2.10-1.84 (m, 3H), 1.25 (d, *J*=6.9 Hz, 3H); ^{13}C NMR [signals of the major diastereoisomer]: δ =212.1, 170.4, 156.0, 136.4 ,128.4, 128.03, 128.00, 66.7, 64.1, 52.6, 48.8, 37.8, 31.7, 19.1, 17.4, ESIMS: *m/z* 342 [M^++Na].

1-(1-Benzyloxycarbonylamino-2-methyl-propyl)-2-oxo-cyclopentanecarboxylic acid methyl ester (75j): Following the general procedure (64 h reaction time), the title compound was obtained as a colourless oil in 74% yield after chromatography on silica gel (hexane/Et_2O 70:30) and as a mixture of diastereoisomers (96:4 diastereomeric ratio, as determined on the crude mixture). The *ee* of the products was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, major diastereoisomer: t_{maj} = 10.3 min; t_{min} = 9.5 min, 74% *ee*; minor diastereoisomer: t_{maj} = 13.3 min; t_{min} = 15.6 min, 67% *ee*). ^{1}H NMR [signals of the major diastereoisomer]: δ =7.43-7.24 (m, 5H), 5.59 (d, *J*=10.7 Hz, 1H), 5.12 (d, *J*=12.2 Hz, 1H), 5.06 (d, *J*=12.2 Hz, 1H), 3.92 (dd, *J*=10.5, 4.7 Hz, 1H), 3.69 (s, 3H), 2.62 (dt, J_d=14.3 Hz, J_t=6.5 Hz, 1H), 2.51-2.23 (m, 2H), 2.13-1.84 (m, 4H), 0.95 (d, *J*=6.5 Hz, 3H), 0.85 (d, *J*=6.5 Hz, 3H); ^{13}C NMR [signals of the major diastereoisomer]: δ = 210.9, 170.2, 156.9, 136.6, 128.4, 128.0, 127.9, 66.8, 63.5, 57.7, 52.6, 37.5, 31.9, 30.5, 21.8, 19.1, 18.1; ESIMS: *m/z* 370 [M^++Na].

(*S*)-1-((*R*)-1-Benzyloxycarbonylamino-cyclohexyl-methyl)-2-oxo-cyclopentanecarboxylic acid methyl ester (75c): Following the general procedure (84 h reaction time), the title compound was obtained as a colourless oil in 77% yield after chromatography on silica gel (hexane/Et_2O 80:20) and as a single diastereoisomer, as determined on the crude mixture. The *ee* of the product was determined by HPLC using a

Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, t_{maj} = 14.4 min; t_{min} = 17.1 min, 99% *ee*). $[\alpha]_D^{20}$=+43 (*c*=0.0.87 in $CHCl_3$); ^{1}H NMR: δ=7.38-7.27 (m, 5H), 5.57 (br d, *J*=10.8 Hz, 1H), 5.13-5.03 (m, 2H), 3.94-3.82 (m, 1H), 3.68 (s, 3H), 2.66-2.54 (m, 1H), 2.49-2.37 (m, 1H), 2.37-2.25 (m, 1H), 2.13-1.84 (m, 3H), 1.81-1.67 (m, 2H), 1.66-1.49 (m, 3H), 1.32-0.97 (m, 6H), ^{13}C NMR: δ=211.1, 170.4, 156.8, 136.6 ,128.4, 128.0, 66.8, 66.7, 64.1, 57.3, 40.7, 37.5, 32.1, 31.7, 28.7, 26.4, 25.9, 25.3, 19.1; ESIMS: *m/z* 410 [M^++Na].

1-(1-Benzyloxycarbonylamino-phenyl-methyl)-2-oxo-cyclohexanecarboxylic acid methyl ester (80a): Following the general procedure (24 h reaction time), using K_3PO_4 50% w/w as the base (5 equiv.) and performing the reaction at 0°C, the title compound was obtained as a colourless oil in 77% yield after chromatography on silica gel (hexane/Et_2O 70:30) and as a mixture of diastereoisomers (97:3 diastereomeric ratio after chromatography, 85:15 diastereomeric ratio determined on the crude mixture). The *ee* of the products was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 95:5, flow rate 0.75 mL/min, major diastereoisomer: t_{maj} = 74.4 min; t_{min} = 39.7 min, 91% *ee*, minor diastereoisomer: t_{maj} = 48.2 min; t_{min} = 42.0 min, 9% *ee*). ^{1}H NMR [signals of the major diastereoisomer]: δ=7.40-7.22 (m, 10H), 6.52 (br d, *J*=9.9 Hz ,1H), 5.25 (d, *J*=9.9 Hz, 1H), 5.10-4.99 (m, 2H), 3.52 (s, 3H), 2.66-2.55 (m, 1H), 2.55-2.39 (m, 2H), 2.05-1.79 (m, 4H), 1.74-1.60 (m, 1H); ^{13}C NMR [signals of the major diastereoisomer]: δ=208.4, 170.9, 155.9, 138.1, 136.2, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 66.9, 66.8, 58.4, 52.2, 40.8, 34.8, 27.7, 27.8; ESIMS: *m/z* 418 [M^++Na].

1-(1-Benzyloxycarbonylamino-phenyl-methyl)-2-oxo-cycloheptanecarboxylic acid methyl ester (81a): Following the general procedure (71 h reaction time), the title compound was obtained as a white solid in 96% yield after chromatography on silica gel (hexane/Et_2O 80:20) and as a single diastereoisomer (96:4 diastereomeric ratio determined on the crude mixture). The *ee* of the product was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 90:10, flow rate 0.75 mL/min, t_{maj} = 62.3 min; t_{min} = 35.1 min, 95% *ee*). M.p. 113-115°C; $[\alpha]_D^{20}$=+22 (*c*=0.95 in $CHCl_3$); ^{1}H NMR: δ=7.37-7.22 (m, 10H), 6.73 (d, *J*=10.2 Hz, 1H), 5.23 (d, *J*=10.2 Hz, 1H), 5.02 (d, *J*=12.1 Hz, 1H), 4.98 (d, *J*=12.2 Hz, 1H), 3.66 (s, 3H), 2.82- (t, *J*=13.3 Hz, 1H), 2.52-2.42 (m, 1H), 2.13-2.03 (m, 1H), 1.93-1.72 (m, 3H),1.73-1.60 (m, 1H), 1.56-1.32 (m, 3H); ^{13}C NMR: δ =208.6, 171.8, 155.6, 137.8, 136.2, 128.7, 128.4, 128.3, 127.98, 127.94, 66.8, 60.4, 53.4, 52.1, 40.6, 33.5, 30.2, 26.4, 25.5; ESIMS: *m/z* 432 [M^++Na].

2-(1-Benzyloxycarbonylamino-phenyl-methyl)-1-oxo-indan-2-carboxylic acid methyl ester (82a): Following the general procedure (39 h reaction time), and using K_2CO_3 30% w/w as the base (1.5 equiv.), the title compound was obtained after chromatography on silica gel (hexane/Et_2O 80:20) as a colourless oil in 95% yield and as a mixture of diastereoisomers (58:42 diastereomeric ratio, as determined on the crude mixture). The *ee* of the products was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 85:15, flow rate 0.6 mL/min, major diastereoisomer: t_{maj} = 205.6 min; t_{min} = 58.3 min, 87% *ee*; minor diastereoisomer: t_{maj} = 221.9 min; t_{min} = 90.3 min, 85% *ee*). ^{1}H NMR [signals of the two diastereoisomers]: δ=7.76-7.69 (m, 1H), 7.57 (t, *J*=7.0 Hz, 1H), 7.49 (t, *J*=7.0 Hz, 1H), 7.41-7.20 (m, 12H), 7.19-7.10 (m, 1H), 7.04 (br, d, *J*=8.8 Hz, 1H), 6.38 (br, s, 1H), 5.52 (d, *J*=9.2 Hz, 1H), 5.31 (br, s, 1H), 5.14-4.98 (m, 1H), 3.78 (d, *J*=17.4 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.47 (d, *J*=17.4 Hz, 1H), 3.26-3.17 (m, 2H); ^{13}C NMR [signals of the two diastereoisomers]: δ =198.4, 171.1, 155.7, 151.9, 138.4, 137.2, 136.4, 136.3, 135.7, 135.5, 134.3, 128.5, 128.4, 128.3, 128.2,

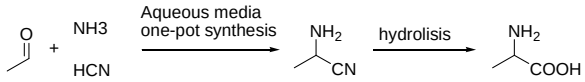
128.03, 128.00, 127.9, 126.1, 126.0, 125.1, 124.4, 66.9, 66.8, 58.8, 58.3, 53.0, 36.1, 34.7; ESIMS: *m/z* 452 [M^++Na].

2-(Benzyloxycarbonylamino-phenyl-methyl)-1-oxo-1,2,3,4-tetrahydro-naphthalene-2-carboxylic-acid methyl ester (83a): Following the general procedure (63 h reaction time), the title compound was obtained as a colourless oil in 96% yield after chromatography on silica gel (hexane/ EtOAc 80:20) and as a mixture of diastereoisomers (93:7 diastereomeric ratio, as determined on the crude mixture). The *ee* of the products was determined by HPLC using a Daicel Chiralpak AD-H column (hexane/*i*PrOH = 80:20, flow rate 0.75 mL/min, major diastereoisomer: t_{maj} = 70.6 min; t_{min} = 76.5 min, 92% *ee*, enantiomers of the minor diastereoisomer not separated); ^{1}H NMR [signals of the major diastereoisomer]: δ=8.01 (dd, *J*=7.9, 1.1 Hz, 1H), 7.56-7.18 (m, 13H), 6.30 (br d, *J*=10.5 Hz, 1H), 5.38 (d, *J*=10.5 Hz, 1H), 5.04 (d, *J*=12.4 Hz, 1H), 5.00 (d, *J*=12.4 Hz, 1H), 3.47 (s, 3H), 3.11-3.02 (m, 2H), 2.78-2.66 (m, 1H), 2.36-2.26 (m, 1H); ^{13}C NMR [signals of the major diastereoisomer]: δ=194.5, 170.3, 155.8, 142.3, 138.5, 136.2, 133.8, 132.2, 128.76, 128.70, 128.4, 128.25, 128.20, 128.0, 127.8, 126.9, 125.7, 66.9, 63.0, 58.7, 52.5, 30.7, 25.9; ESIMS: *m/z* 466 [M^++Na].

4. Strecker

4.1. Introduction

The Strecker reaction, which was reported already in 1850, is the oldest known synthesis of α-amino acids.[130] This reaction comprises a condensation of an aldehyde, ammonia, and cyanide source, followed by subsequent hydrolysis of the resulting α-amino nitrile (**Scheme 34**).



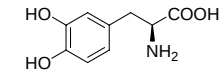
Scheme 34 Original Strecker reaction

In addition, the Strecker reaction represents one of the simplest and most economical methods for the preparation of α-amino acids on lab scale as well on a technical scale. Furthermore, the substrates are very cheap and available in commercial quantities. In industry, the Strecker reaction is applied widely due to those economically favorable properties.

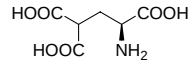
When using amines instead of ammonia, the preformation of imines, followed by hydrocyanation instead of the one-pot synthesis represents a popular and widely used alternative route.

There has also been considerable interest to extend this reaction toward an asymmetric process for the production of optically active α-amino acids, in particular, non-proteinogenic and unnatural α-amino acids. The importance of these products is rapidly increasing since they are often used for examples as key building blocks in pharmaceuticals, agrochemicals and food chemistry system. In particular many non-proteinogenic α-amino acids are known, often playing important roles as for example *S*-adenosyl-L-methionine, an important "supplier of cellular methyl group" in the synthesis of methylated species. Another important α-amino acid in this category is L-dopa, the precursor of dopamine in the brain, which is used for treatment of affliction such as Parkinson's disease (**Chart 8**).

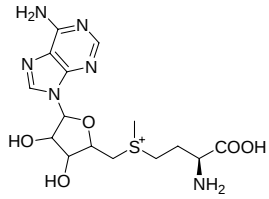
[130] For an overview about the stereoselective synthesis of α-amino acids in general, see a) R. O. Duthaler *Tetrahedron* **1994**, *50*, 1539; b) R. M. Williams, J. A. Hendrix *Chem. Rev.* **1992**, *92*, 889.



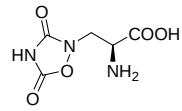
L-Dopa



γ-Carboxy-L-glutamic acid



S-Adenosyl-Lmethionine



Quisqualic acid

Chart 8 Some non-proteinogenic α-amino acids.

γ-Carboxy-L-glutamic acid is another non-standards amino acid found in the blood-clotting protein prothrombine and in certain other proteins that bind Ca^{2+} as part of their biological function. Quisqualic acid, a derivative of aspartic acid, has a special neurological importance indeed is active against Alzheimer's disease (**Chart 8**).

As for the aza-Henry and Mannich reactions also the first asymmetric versions of the Strecker was reported only in the middle of 1990s by several different goups (**Chart 9**).[131]

[131] a) H. Gröger *Chem. Rev.* **2003**, *103*, 2795; b) L. Yet *Angew. Chem. Int. Ed.* **2001**, *40*, 875. c) see reference 56d

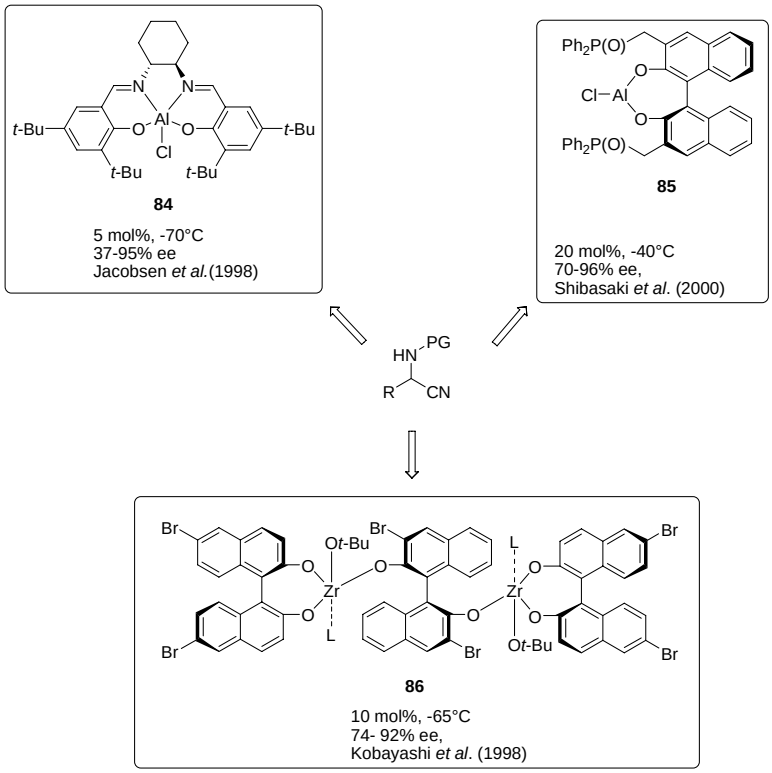


Chart 9 Some chiral metal catalysts for the asymmetric Strecker reaction.

Jacobsen group successfully reported the first metal-catalysed asymmetric Strecker reaction by using catalyst **84** and HCN as cyanide source (**Chart 9**, upper left).[132] In general, good yields accompanied by enantioselectivities in a moderate to excellent range were obtained for aromatic imines. In contrast, the asymmetric hydrocyanation of alkyl imines resulted in the formation of the corresponding amino nitrile products with considerably lower yields and enantioselectivities. Shibasaky *et al.* applied catalyst **85** to the Strecker reaction synthesising a broad variety of α-amino nitriles (**Chart 9**, upper right).[133] Both aromatic and aliphatic imines gave good results in term of yields and enantioslections by means of TMSCN as cyanide source. In 1998 Kobayashi group used a chiral zirconium(IV) complex **86** as a catalyst for the asymmetric Strecker reaction (**Chart 9**, bottom).[134] In the presence of 10 mol% of this very stable catalyst, the reaction was carried out with numerous substrates comprising aromatic as well as aliphatic

[132] M. S. Sigman, E. N. Jacobsen *J. Am. Chem. Soc.* **1998**, *120*, 5315.
[133] a) M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki *Angew. Chem. Int. Ed.* **2000**, *39*, 1650; b) M. Takamura, Y. Hamashima, H. Usuda, M. Kanai, M. Shibasaki *Chem. Pharm. Bull.* **2000**, *48*, 1586.
[134] H. Ishitani, S. Komiyama, S. Kobayashi *Angew. Chem. Int. Ed.* **1998**, *37*, 3186.

imines, with good results in terms of yields and enantiomeric excesses. In this case Bu_3SnCN was used as source of cyanide (**Chart 9**, bottom).

In addition to the metal-catalysed asymmetric cyanations several versions of this process based on the use of organocatalysts have been developed so far. A short survey of these organocatalysts is given in **Chart 10**.

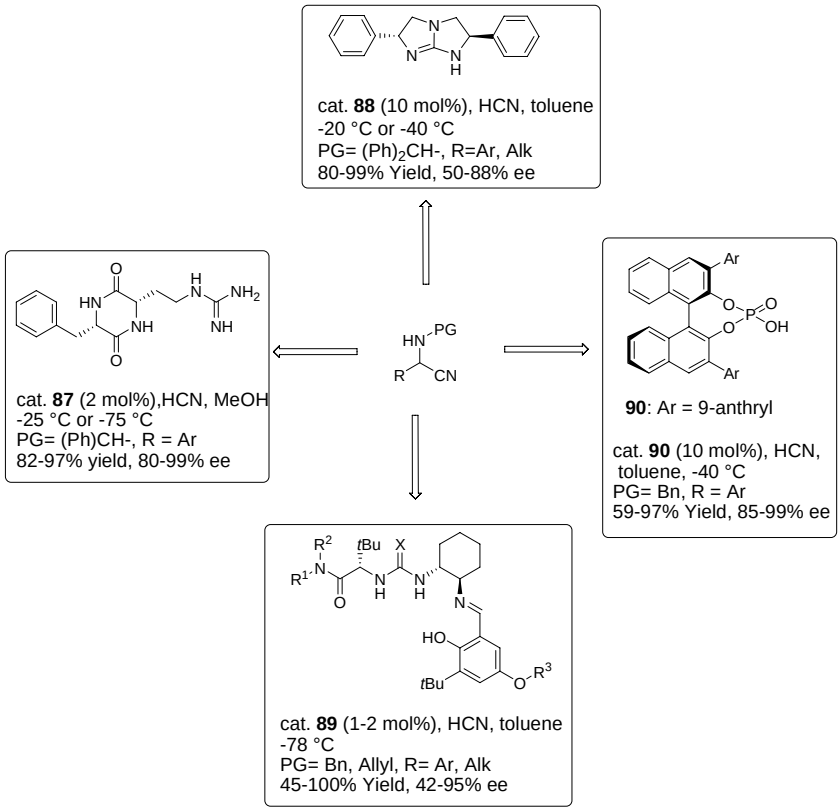


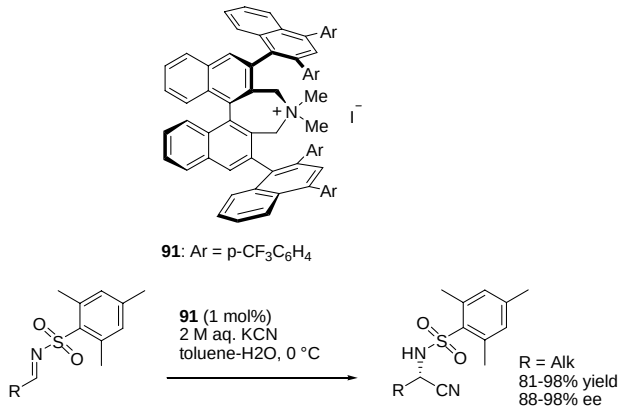
Chart 10 Common organocatalysts used in the Strecker reaction.

Most significantly, the first catalytic asymmetric Strecker reaction, reported by Lipton, employed an organic molecule as the catalyst, specifically the diketopiperazine **87** (**Chart 10**, left).[135] The reaction which is carried out with a low catalyst amount of 2 mol% of **87**, was studied intensively with a broad variety of *N*-benzydryl-sustituted imines. For examples, good to excellent enantioselectivities were obtained when starting from imines derived from benzaldehyde. In contrast to electron-deficient aromatic imines, heteroatom-substituted aromatic and aliphatic imines gave considerably lower enantioselectivities. In 1999 Corey reported an organocatalytic asymmetric Strecker reaction by using guanidine **88** as a catalyst and HCN as a cyanide source (**Chart 10**,

[135] M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton *J. Am. Chem. Soc.* **1996**, *118*, 4910.

top).[136] In the presence of 10 mol% of **88** the aromatic and aliphatic benzhydrylimines were converted in the corresponding α-amino nitriles with good results in terms of yields and enantioselectivities. Another type of catalyst was introduced by Jacobsen and co-workers in 1998.[137] They used urea **89** to catalyse the conversion of *N*-benzyl and *N*-allyl imines to the corresponding α-amino nitriles by means of 2 mol% of catalyst loading and HCN as cyanide source (**Chart 10**, bottom). The catalyst was able to afford aliphatic and aromatic imines in excellent yields and enantioselections. A different type of catalyst, applied in the catalytic asymmetric Strecker reaction, was introduced by Rueping *et al.* in 2006.[138] The reaction was performed with **90** in 10 mol% amount converting a broad variety of *N*-benzyl aromatic imines in the corresponding nitriles with good to excellent yields and enantiomeric excesses, by using HCN as cyanide source (**Chart 10**, right).

Although all these elaborated catalytic asymmetric methodologies rely on the use of anhydrous hydrogen cyanide, this cyanide source posesimportant problems to be addressed particularly when large-scale applications are considered due to the high toxicity. Recently the possibility of employing KCN as a cyanide source has also been taken into consideration and very recently successfully applied, among the others, to PTC asymmetric Strecker reaction developed by Maruoka (**Scheme 35**).[139]



Scheme 35 Strecker reaction performed with potassium cyanide under PTC condition

Using sing *N*-Mesityl sulfonyl imines, catalyst **91** promoted the reaction with *N*-alkyl imines with excellent yields and enantioselection by using KCN as the cyanide source (**Scheme 35**).

Taking into consideration the previous results obtained using α-amido sulfones as a imine surrogates in the aza-Henry and Mannich reaction, we envisioned that also Strecker

[136] E. J. Corey, M. J. Grogan *Org. Lett*. **1999**, *1*, 157.
[137] M. S. Sigman, E. N. Jacobsen *J. Am. Chem. Soc.* **1998**, *120*, 4901;
[138] M. Rueping, E. Sugiono, C. Azap *Angew. Chem. Int. Ed*. **2006**, *45*, 2617.
[139] T. Ooi, Y. Uematsu, K. Maruoka *J. Am. Chem. Soc.* **2006**, *128*, 2548.

transormation could be feasible using our approach. We planed to use acetone cyanohydrine as a cyanide source, as one of the simplest, most soluble, cheap and on large scale commercially available cyanide sources.[140] To date its use as cyanide source has been described for the regiospecific opening of 1,2-epoxides under mild basic conditions[141] and as a new Mitsunobu reagent in the cyanation of alcohols.[142] Furthermore more recently a convenient procedure for the Pd-catalyzed cyanation of aryl halides has been reported.[143]

[140] R. J. H. Gregory *Chem. Rev*. **1999**, *99*, 3649.
[141] D. Mitchell, T. M. Koenig *Tetrahedron Lett*, **1992**, *33*, 3281.
[142] T. Tsunoda, K. Uemoto, C. Nagino, M. Kawamura, H. Kaku, S. Ito *Tetrahedron Lett*. **1999**, *40*, 7355.
[143] M. Sundermeier, A. Zapf, M. Beller *Angew. Chem. Int. Ed.* **2003**, *42*, 1661.

4.2. Results and Discussion

In this project we disclosed the first example of the use of cyanohydrins as a CN^- source in a organocatalysed Strecker reaction performed under phase transfer conditions and employing *N*-Boc protected α-amido sulfones as imine precursors.[144]

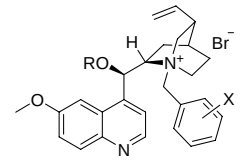
We initiated our search for an appropriate reaction system (**Table 15**) with the α-amido sulfone of 3-phenylpropionaldehyde **48i**[145] and acetone cyanohydrins **92a-c** as model substrates in order to develop the cyanation under biphasic conditions (K_2CO_3, organic solvent). Several chiral quaternary ammonium salts derived from *Cinchona* alkaloids were screened as potential organocatalysts together with the effect of the imine nitrogen substituent and of the addition of water.

The key elements for the success of the reaction were the easily available quinine-derived catalyst **49c,d,j** and the presence in it of an electron withdrawing group such as CF_3 at the *ortho* position of the benzyl group, which afforded the expected product **93i** in excellent yield and 60% *ee* (entry 1, **Table 15**). On the contrary **49c**, in which the same functional group was installed at the *para* position, resulted significantly less efficient (16% *ee*, entry 2). Also the free hydroxyl group at the position 9 plays a significant role in the substrate activation since the corresponding catalyst **49j**, whose OH group had been protected in the form of benzyl ether, led to a racemic mixture (entry 3).

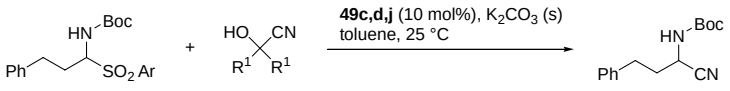
[144] During our studies in PTC Strecker reaction a work on the use of an NEt_3/acetone cyanohydrin as a catalytic system for the three-component Strecker-type α-amino nitrile synthesis is appeared: A. S. Paraskar, A. Sudalai *Tetrahedron Lett*. **2006**, *47*, 5759.

[145] For the preparation of α-amido sulfones see: a) note 96a; b) Mecozzi, T; Petrini, M. *J. Org. Chem*. **1999**, *64*, 8970.

Table 15 Initial Screening and Optimization of Reaction Conditions.[a]



49d X = *o*-CF_3, R = H
49c X = *p*-CF_3, R = H
49j X = *o*-CF_3, R = CH_2Ph



48i: Ar= *p*-Tol **92a-c** **93i**

Entry	Cyanohydrin	R^1	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	**92a**	Me	**49d**	5	95	60
2	**92a**	Me	**49c**	5	89	16
3	**92a**	Me	**49j**	5	90	0
4	**92b**	Ph	**49d**	18	80	20
5	**92c**	-(9-fluorenyl)-	**49d**	42	83	26
6	**92a**	Me	**49d**	42	95	68[d]

[a] The reactions were carried out at 25 °C using 0.1 mmol of α-amido sulfone **48i**, 0.2 mmol of cyanohydrin **92**, 0.5 mmol of K_2CO_3 (s) and 0.01 mmol of catalyst **49c,d,j** in 2 mL toluene. [b] Yields are given for isolated products. [c] The enantiomeric excess was determined by chiral HPLC. [d] Reaction performed at -20 °C with 5 mL toluene and aqueous K_2CO_3 (50% w/w).

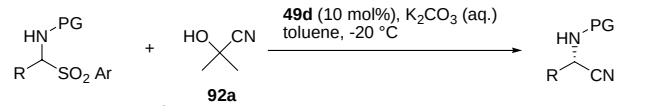
Increasing steric hindrance in the cyanide source, such as in benzophenone (**92b**) and fluorenone (**92c**) cyanohydrins, resulted detrimental for the enantioselection (compare entries 1, 4 and 5, **Table 15**). Finally, it was possible to further improve the enantioselectivity of the reaction by careful optimization of the reaction conditions. For example, the ee of product **93i** could be enhanced to 68% *ee* (entry 6) by simply using more dilute conditions in conjunction with aqueous base and lower temperature (-20 °C). The occurrence of an effective catalytic behaviour promoted by **49d**, was ascertained by the eightfold rate enhancement in the reaction with a catalytic loading of 10 mol%, run under the conditions shown in **Table 15**, with respect to the uncatalyzed reaction[146] and highlighted the minor role played by the background reaction. Interestingly the presence of the *in situ* generated imine was never detected, thus suggesting that deprotonation followed by sulfinate ion release may occur in the rate determining step.

With these insights into the optimised reaction conditions we explored the scope of the reaction using a range of aliphatic α-amido sulfones and acetone cyanohydrin **92a** as starting materials (**Table 16**). Catalyst **49d** proved to be highly effective for the

[146] The uncatalyzed reaction goes through itself in 40 hours.

hydrocyanation of a variety of *N*-Boc α-amido sulfones. The (*S*)-configured α-aminonitriles[147] were obtained throughout with excellent yields and high ee's and the size of the aliphatic group did appear to slightly dictate the levels of enantioselectivity (entries 1-9, **Table 16**). No changes in the products ee's were observed even after prolonged times, thus supporting the suitability of the reaction conditions employed. *N*-Boc proved to be the most suitable protection since the reaction run with *N*-Cbz α-amido sulfone **50i** led to a sizeable decrease of the enantioselection (compare entries 1 and 10, **Table 16**).

Table 16 Asymmetric Catalytic Strecker Reactions with Cyanohydrin 92a and Catalyst 49d.[a]



48i-q: PG= Boc, Ar= *p*-Tol
50i: PG= Cbz, Ar= *p*-Tol

93i-q: PG= Boc
94i: PG= Cbz

Entry	α-Amido sulfone	R	PG	Product	Yield (%)[b]	*ee* (%)[c]
1	**48i**	$Ph(CH_2)_2$	Boc	**93i**	95	68
2	**48o**	$PhCH_2$		**93o**	95	79
3	**48m**	Me		**93m**	85	78
4	**48l**	Et		**93l**	88	80
5	**48k**	*i*-Pr		**93k**	92	82
6	**48p**	*t*-Bu		**93p**	85	88
7	**48q**	$CH_3(CH_2)_5$		**93q**	95	72
8	**48n**	*i*-Bu		**93n**	90	68
9	**48j**	Cy		**93j**	95	50
10	**50i**	$Ph(CH_2)_2$	Cbz	**94i**	79	40

[a] The reactions were carried out at -20 °C for 42 h using 0.1 mmol of α-amido sulfone, 0.2 mmol of cyanohydrin, 0.5 mmol of aqueous K_2CO_3 (50% w/w) and 0.01 mmol of catalyst in 5 mL toluene. [b] Yields are given for isolated products. [c] The enantiomeric excess was determined by chiral HPLC or GC.

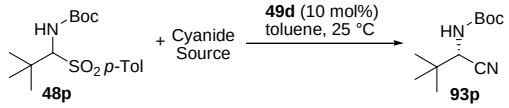
Catalyst **49d** displays a remarkably substrate scope in the asymmetric hydrocyanation of aldimines since accommodates substrates bearing α-substituents ranging from methyl to *tert*-alkyl moieties. This would enable, among the others, a straightforward synthesis of enantiomerically enriched *tert*-leucine, a target of considerable utility as chiral

[147] The absolute configuration of the optically active compounds **93o** and **93n** was determined by comparison of the measured optical rotation with literature values: A. Boeijen, R. M. J. Liskamp *Eur. J. Org. Chem.* **1999**, 2127; the remaining absolute configurations were assigned by analogy to further adducts.

building block, by simultaneous *N*-Boc deprotection and CN hydrolysis in acidic medium.[89b]

As shown in **Table 17**, a few ancillary experiments carried out on **48p** at room temperature revealed that in all cases the enantiomeric excesses, using more conventional CN^- ion sources like KCN (entry 2) and TMSCN (entry 4), resulted substantially lower with respect to the value obtained with cyanohydrin **92a** (entry 1). Undoubtedly in these reactions the operativity of other pathways leading to the Strecker product formation without recognition of the catalytic species is likely and a direct transfer of the nucleophile to the imine will probably compete with that occurring via **49d**/CN^- ion pair (entries 2 and 4, **Table 17**), as suggested by the moderate enantioselection observed.

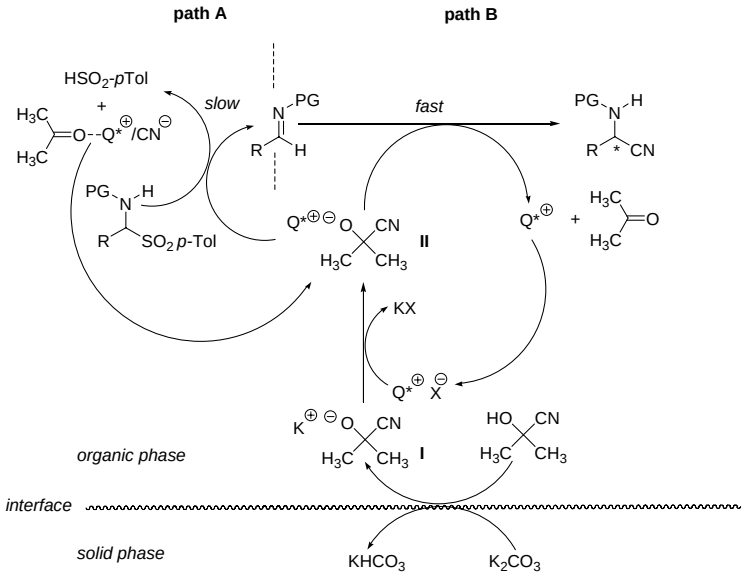
Table 17 Supplementary Experiments with Different Cyanide Sources.[a]



Entry	Cyanide source	Base (5 eq.)	Acetone	Time (h)	Conversion (%)[b]	*ee* (%)[c]
1	**92a**	K_2CO_3 (s)	-	3	>95	70
2	KCN	-	-	5	>95	40
3	KCN	-	2.5 eq.	5	>95	54
4	TMSCN	K_2CO_3 (s)	-	2	>95	35
5	TMSCN	K_2CO_3 (s)	2.5 eq.	2	>95	52

[a] The reactions were carried out at 25 °C for the stated time using 0.1 mmol of α-amido sulfone **48p**, 0.2 mmol of cyanide source, 0.01 mmol of catalyst **49d** in 2 mL toluene. [b] Conversions determined by ^{1}H NMR. [c] The enantiomeric excess was determined by chiral GC.

Furthermore most interestingly addition of 2.5 equivalents acetone produced a remarkable enhancement of the enantioselection (compare entries 2, 3 and 4, 5, **Table 17**). This prompted us to shed some light on the mechanism of this PTC reaction. The focus was firstly addressed towards the reaction pathway in which α-amido sulfones are converted into imines: in the presence of K_2CO_3 and 10 mol% of phase transfer catalyst this reaction took place after more than one day whereas the combination K_2CO_3/cyanohydrin/PTC afforded complete disappearance of the precursor within 3 hours. A cyanohydrin-derived anionic species, generated at the interface, might therefore act as the effective base in the α-amido sulfone-imine transformation. A sketch of a mechanistic proposal is shown in **Scheme 36**.



Scheme 36 Hypothetical Mechanism for the Strecker Reaction of α-Amido Sulfones and Cyanohydrin 92a Catalysed by 49d.

According to this proposal the conjugate base of the cyanohydrin **I** might form with the chiral quaternary ammonium salt a lipophilic ion pair **II** that in path **A** releases the CN^- ion promoting deprotonation of the precursor and its conversion into an imine. The already mentioned catalysis promoted by **49d**, is strongly suggestive of an intervention of the organocatalytic species in this rate-determining step.[148] In the presence of the *in situ* formed imine, **II** will then deliver in path **B** the CN^- ion to the electrophilic carbon. The possibility that in ion pair **II** the catalyst might accommodate in its chiral pocket a more complex anionic species than CN^-, is supported by the lowering of both yields and enantioselectivity observed with cyanohydrins **92b** and **92c** (**Table 15**), since one could easily assume that the accommodation of these bulkier systems would result much more difficult. Furthermore the beneficial effect on the enantioselection due to addition of acetone to the reactions in the presence of KCN or TMSCN (**Table 17**), most likely leading to *in situ* generation of **I**, provides further support to the above reported interpretation of the reaction pathways. According to this mechanism, the CN^- will thus play the sequential role of catalytic base and stoichiometric nucleophile. This is also consistent with the fact that the reaction described in **Table 16** for **48p**, performed with only 1.1 equivalents of cyanohydrin **92a**, afforded the expected α-amino nitrile **93p** in 85% yield and 89% ee without any erosion of efficiency and enantioselectivity.

[148] HPLC analysis performed on several samples at various reaction times did not show evidences in favour of enantiomeric enrichment of the unreacted α-amido sulfone.

In conclusion we have accomplished the first organocatalysed phase-transfer enantioselective cyanation of *in situ*-generated aliphatic imines using acetone cyanohydrin **92a** as a cyanide ion source. The ready preparation and stability of the simple chiral quininium salt, the convenient experimental procedure and the easy access to the α-amino acids in the natural (*S*)-form are good assets of the enantioselective Strecker process described herein.

4.4 Experimental Section.

General procedure for the catalytic enantioselective Strecker reaction of α-amido sulfones 48, 50 with cyanohydrin 92a.

To a solution of α-amido sulfone **48, 50** (0.1 mmol) in toluene (5 mL) was added *N*-(*o*-trifluoromethyl)quininium bromide **49d** (0.01 mmol, 5.6 mg) followed by acetone cyanohydrin (0.2 mmol, 18 μL). After the resulting solution was cooled to -20 °C, K_2CO_3 (aq.) 50% w/w (0.5 mmol, 90 μL) was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without any precaution to exclude moisture or air. After 42 h, the reaction was quenched with saturated $NaHCO_3$ and the aqueous layer extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was then purified by chromatography on silica gel (CH_2Cl_2).

Products **93i**, **93o**, **93l**, **93k**, **93p**, **93n**, **93j** are known compounds in literature and spectroscopical data are consistent with previously reported values.[89b] The absolute configuration of the optically active compounds 4b, 4h was determined by comparison of the measured optical rotation with literature values.[149] All other absolute configurations were assigned by analogy to further adducts.

(*S*)-*tert*-Butyl 1-cyano-3-phenylpropylcarbamate (93i).[89b] Obtained as a white solid in 95% yield (24.7 mg). The ee of the product was determined by HPLC using an AD-H column (*n*-hexane/*i*-PrOH = 98:2, flow rate 0.75 mL/min, λ = 254 nm, τ_{maj} = 42.7 min, τ_{min} = 38.8 min); $[\alpha]^{25}_D$ -11.4 (c = 0.38, dioxane), 68% ee.

(*S*)-*tert*-Butyl 1-cyano-2-phenylethylcarbamate (93o).[89b] Obtained as a white solid in 95% yield (23.4 mg). The ee of the product was determined by HPLC using an AD-H column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, λ = 254 nm, τ_{maj} = 22.7 min, τ_{min} = 21.3 min); $[\alpha]^{25}_D$ -11.5 (c = 0.42, dioxane), 79% ee. [Lit. (*S* enantiomer): $[\alpha]^{25}_D$ -16.4 (c = 0.98, dioxane)].[149]

(*S*)-*tert*-Butyl 1-cyanoethylcarbamate (93m). Obtained as a white solid in 85% yield (14.4 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 130 ºC, injector temp. = 235 °C, detector temp. = 250 °C, using N_2 as carrier gas, τ_{maj} = 17.0 min, τ_{min} = 17.5 min); m.p. 101-103 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.78 (br s, 1H), 4.62 (br s, 1H), 1.54 (d, *J* = 7.2 Hz, 3H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.4, 109.9, 81.1, 29.6, 28.2, 19.7; ESIMS *m/z* 193 $[M + Na]^+$; Anal. Calcd. for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.34; H, 8.31; N, 16.50. $[\alpha]^{25}_D$ -54.3 (c = 0.36, dioxane), 78% ee.

(*S*)-*tert*-Butyl 1-cyanopropylcarbamate (93l).[89b] Obtained as a white solid in 88% yield (16.2 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 150 ºC, injector temp. = 235 °C, detector temp. = 250 °C,

[149] The absolute configuration of the optically active compounds **93o** and **93n** was determined by comparison of the measured optical rotation with literature values: A. Boeijen, R. M. J. Liskamp, *Eur. J. Org. Chem.* **1999**, 2127.

using N_2 as carrier gas, τ_{maj} = 9.7 min, τ_{min} = 9.9 min); $[\alpha]^{25}_D$ -50.5 (c = 0.49, dioxane), 80% ee.

(*S*)-*tert*-Butyl 1-cyano-2-methylpropylcarbamate (93k).[89b] Obtained as a white solid in 92% yield (18.2 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 150 ºC, injector temp. = 235 °C, detector temp. = 250 °C, using N_2 as carrier gas, τ_{maj} = 9.7 min, τ_{min} = 10.0 min); $[\alpha]^{25}_D$ -44.2 (c = 0.55, dioxane), 82% ee.

(*S*)-*tert*-Butyl 1-cyano-2,2-dimethylpropylcarbamate (93p).[89b] Obtained as a white solid in 85% yield (18.0 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 150 ºC, injector temp. = 235 °C, detector temp. = 250 °C, using N_2 as carrier gas, τ_{maj} = 9.0 min, τ_{min} = 9.4 min); $[\alpha]^{25}_D$ -48.8 (c = 0.57, dioxane), 88% ee.

(*S*)-*tert*-Butyl 1-cyanoheptylcarbamate (93q). Obtained as a colourless oil in 95% yield (22.8 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 150 ºC, injector temp. = 235 °C, detector temp. = 250 °C, using N_2 as carrier gas, τ_{maj} = 53.0 min, τ_{min} = 55.1 min); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.78 (br s, 1H), 4.56 (br s, 1H), 1.82-1.73 (m, 2H), 1.46 (s, 9H), 1.36-1.25 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 154.1, 119.0, 81.2, 42.3, 33.4, 31.4, 28.4, 28.2, 25.2, 22.4, 14.0; ESIMS *m/z* 263 $[M + Na]^+$; Anal. Calcd. for $C_{13}H_{24}N_2O_2$: C, 64.97; H, 10.07; N, 11.66. Found: C, 64.83; H, 10.05; N, 11.62. $[\alpha]^{25}_D$ -26.6 (c = 0.88, dioxane), 72% ee.

(*S*)-*tert*-Butyl 1-cyano-3-methylbutylcarbamate (93n).[89b] Obtained as a white solid in 90% yield (19.1 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 140 ºC, injector temp. = 235 °C, detector temp. = 250 °C, using N_2 as carrier gas, τ_{maj} = 25.9 min, τ_{min} = 27.4 min); $[\alpha]^{25}_D$ -34.4 (c = 0.68, dioxane), 68% ee. [Lit. (*S* enantiomer): $[\alpha]^{25}_D$ - 58.9 (c = 0.98, dioxane)].[149]

(*S*)-*tert*-Butyl cyano(cyclohexyl)methylcarbamate (93j).[89b] Obtained as a white solid in 95% yield (22.6 mg). The ee of the product was determined by GC using a RT-BetaDEX-sm chiral column (isothermal 180 ºC, injector temp. = 235 °C, detector temp. = 250 °C, using N_2 as carrier gas, τ_{maj} = 17.5 min, τ_{min} = 17.7 min); $[\alpha]^{25}_D$ -13.8 (c = 0.68, dioxane), 50% ee.

Benzyl 1-cyano-3-phenylpropylcarbamate (94i). Obtained as a white solid in 79% yield (23.2 mg). The ee of the product was determined by HPLC using an AD-H column (*n*-hexane/*i*-PrOH = 95:5, flow rate 0.75 mL/min, λ = 254 nm, τ_{maj} = 30.4 min, τ_{min} = 36.4 min); m.p. 81-83 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.38-7.17 (m, 10H), 5.14 (s, 2H), 5.00 (br s, 1H), 4.57 (br s, 1H), 2.82 (dt, J = 7.3, 1.9 Hz, 2H), 2.18-2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.0, 138.9, 135.5, 128.8, 128.6, 128.5, 128.4, 128.3, 126.8, 118.3, 67.8, 42.3, 34.8, 31.4; ESIMS *m/*z 317 $[M+ Na]^+$; Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.57; H, 6.18; N, 9.50. $[\alpha]^{25}_D$ -10.0 (c = 0.12, dioxane), 40% ee.

5. Hydrophosphonylation of imines

5.1. Introduction

The Pudovik reaction is one of the most versatile pathways for the formation of carbon-phosphorous bonds and involves the additions of compounds containing a labile P–H bond to unsaturated systems, for examples alkenes, alkynes, carbonyls and imines.[150] The products of the reaction find significant industrial, biological, and chemical synthetic uses.[151]

Although the Pudovik reaction takes in consideration a wide range of electrophiles, among them the imines are certainly the most important. Indeed, the addition of phosphonic acid ester to imines is a powerful tool for the synthesis of α-amino phosphonic acids key compounds in pharmaceutical and medicinal chemistry.[152] These molecules are generally considered as α-amino acid analogues, bearing a tetrahedral phosphonic acid group in place of the planar and less bulky carboxylic acid, and have been found to possess a broad spectrum of biologically activity. Often incorporated into peptides (phosphono-peptides) α-amino phosphonic acids have shown, among others, very promising and useful anticancer,[153] antiinflammatory,[153] antirheumatic,[153a,154] antibacterial[155] and antifungal properties.[156]

This striking biological activity stems in several instances from the efficient inhibition of different protease or synthetase enzymes, which is usually rationalised considering the mimicking of the tetrahedral intermediate of enzymatic peptide bond hydrolisis (or formation) by the phosphonoamide or phosphonate moiety in phosphono-peptides.[157]

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[150] a) A.J. Kirby, S. G. Warren *The Organic Chemistry of Phosphorus*, Elsevier Publishing Co., New York, **1967**; b) J. Emsley, D. Hall *The Chemistry of Phosphorus*, Harper & Row Publishers, New York, **1976**; c) V. W. Wolfsberger *Chem. Zeit.* **1988**, 53; d) A. N. Pudovik, I. V. Konovalova *Synthesis* **1979**, 81.

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[152] a) *Aminophosphonic and Aminophosphinic Acids* V. P. Kukhar, H. R. Hudson Eds., John Wiley & Sons, **2000**; b) P. Kafarski, B. Lejczak *Phosphorous, Sulfur and Silicon* **1991**, *63*, 193.

[153] a) PCT Int. Appl. WO 2007045496, **2007**; b) PCT Int. Appl. WO 2004004658, **2004**.

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[155] a) J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassal, S. W. Holmes, R. W. Lambert, L. J. Nisbet, P. S. Ringrose *Nature* **1978**, *272*, 56.; b) F. R. Atherton, C. H. Hassal, R. W. Lambert *J. Med. Chem.* **1986**, *29*, 29; c) Z. Wu, C. T. Walsh *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 11603.

[156] W. W. Smith, P. A. Bartlett *J. Am. Chem. Soc.* **1998**, *120*, 4622.

[157] a) J. E. Hanson, A. P. Kaplan, P. A. Bartlett *Biochemistry* **1989**, *28*, 6294; b) A. P. Kaplan, P. A. Bartlett *Biochemistry* **1991**, *30*, 8165; c) P. A. Bartlett, C. K. Marlowe *Science* **1987**, *235*, 569; d) for an excellent review, see: J. Hiratake, J. Oda, *Biosc. Biotechnol. Biochem.* **1997**, *61*, 211.

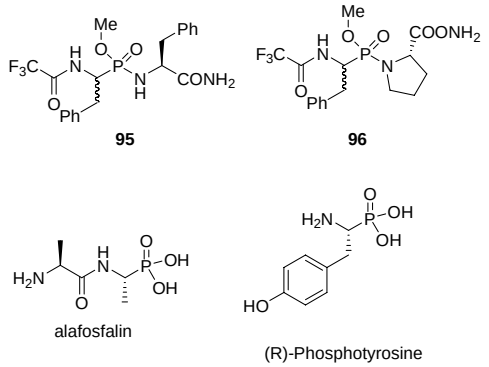

Chart 11. Some examples of α-aminophosphonic acid derivatives.

Some biologically relevant α-amino phosphonic acid derivatives are illustrated in **Chart 11**. **95** and **96** are transition-state-analogue inhibitors of proteolytic enzymes,[152a,154,158] and alafosfalin is an antibacterial agent.[155b] (*R*)-Phosphotyrosine occurs naturally as a component of two hypotensive tripeptides.[159] Interestingly, this example embodies the L configuration of the encoded α-amino carboxylic acids. Due to the different biological response of the two antipodes, a number of different routes have been devised for the asymmetric synthesis of α-amino phosphonic derivatives,[160] with a specal focus on catalytic methodologies.[161]

In particular, the hydrophosphonylation of imines, due to its practicity and simplicity, has been studied in great detail, leading to the development of a few efficient asymmetric catalytic protocols, relying first on the use of metal catalysis and later on organocatalytic concepts.

[158] D. A. McLeod, R. I. Brinkworth, J. A. Ashley, K. D. Janda, P. Wirsching *Bioorg. Med. Chem. Lett.* **1991**, *1*, 653.
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[160] V. P. Kukhar, V. A. Soloshonok, V. A. Solodenko *Phosphorous, Sulfur and Silicon* **1994**, *92*, 239; b) O. I. Kolodiazhnyi *Tetrahedron: Asymmetry* **1998**, *9*, 1279.
[161] a) H. Gröger, B. Hammer *Chem. Eur. J.* **2000**, *6*, 943; b) J.-A. Ma *Chem. Soc. Rev.* **2006**, *35*, 630.

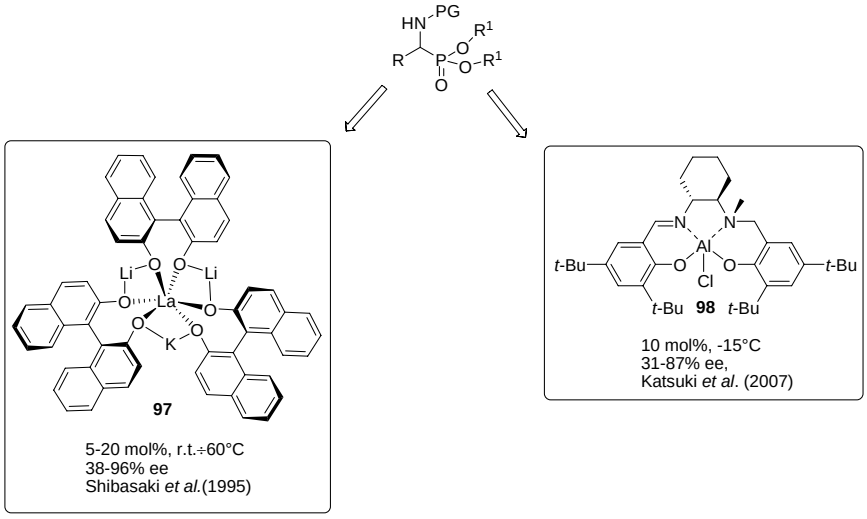


Chart 12. Some highly enantioselective metal catalysts for the Pudovik reaction.

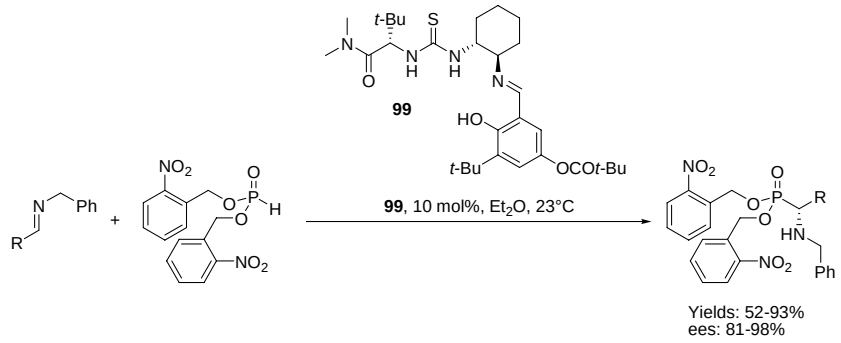
The first example of chiral metal-catalysed hydrophosphonylation of imines was reported by Shibasaki *et al.*.[162] They used a lanthanium-potassium heterobimetallic BINOL-based catalyst **97** for the addition to aliphatic imines, obtaining, in general, modest to good yields accompanied by enantioselectivities in a moderate to excellent range (**Chart 12**, left). Immediately after the same group reported a hydrophosphonylation of cyclic imines in high yields and enantiomeric excesses by using a slightly different ytterbium-potassium heterobimetallic BINOL-based catalyst.[163] In 2007 Katsuki's group reported the highly enantioselective aluminium(salalen) **98** catalysed hydrophosphonylation of imines.[164] In the presence of 10 mol% of catalyst the reactions were carried out with numerous substrates comprising preformed aromatic as well as in situ formed aliphatic imines, with good results in terms of yields and enantiomeric excesses (**Chart 12**, right).

Before our studies on the hydrophosphonylation of imines only two remarkable processes concerning organocatalysis had been reported.

The Jacobsen's thiourea-derivative **99** was applied to the addition of *ad hoc*-made phosphite to *N*-Benzyl imines.[165] With 10 mol% of catalyst loading and most remarkably at 23°C **99** was able to convert aromatic and branched aliphatic imines to the

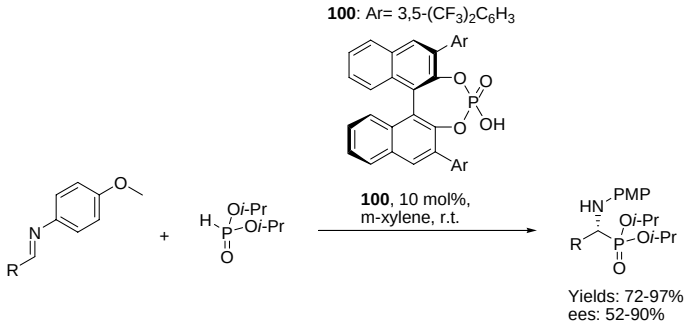
[162] H. Sasai, S. Arai, Y. Tahara, M. Shibasaki *J. Org. Chem.* **1995**, *60*, 6656.
[163] H. Groger, Y. Saida, H. Sasai, K. Yamaguchi, J. Martens, M. Shibasaki *J. Am. Chem. Soc.* **1998**, *120*, 3089.
[164] B. Saito, H. Egami, T. Katsuki *J. Am. Chem. Soc.* **2007**, *129*, 1978.
[165] G. D. Joly, E. N. Jacobsen *J. Am. Chem. Soc.* **2004**, *126*, 4102.

corresponding *N*-protected α-amino phosphonic acid esters, with astonishing results in terms of both yields and enantiomeric excesses (**Scheme 37**).



Scheme 37 Jacobsen's chiral thiourea 99 catalysed enantioselective Pudovic reaction.

In 2005, Akiyama and co-workers applied the chiral binaphthyl phosphoric acid **100** to the enantioselective addition of the simple phosphonic acid di-*i*-propyl ester to *N*-*p*-methoxyphenyl imines.[166] By using 10 mol% of **100** they obtained α-aryl-α-amino phosphonic acid ester with modest to good yields and enantioselections (**Scheme 38**).



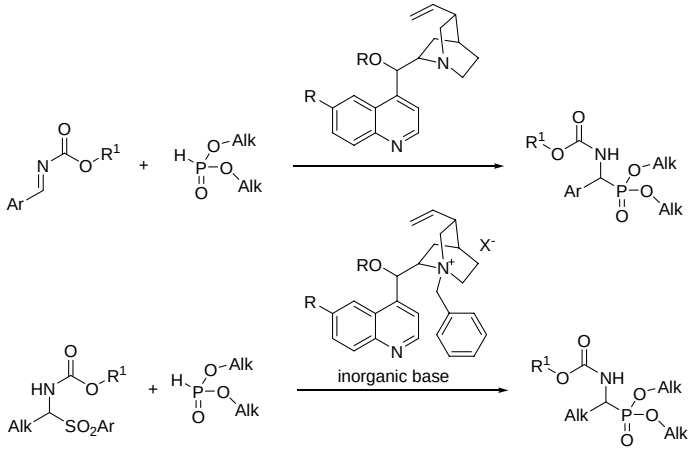
Scheme 38 Catalytic asymmetric hydrophosphonylation of imines by means of 100.

Bearing these few background reactions in mind and considering our experience on imine chemistry, we tried to develop a catalytic asymmetric hydrophosphonylation of imines. During our early studies on the reaction we discovered that *N*-carbamoyl-α-amido phosphonic acid dialkyl esters were not configurationally stable in basic conditions. In fact α-aryl-α-amido phosphonic acid ester racemise in the typical phase transfer conditions even with the use of a weak base, such as carbonate.

For this reason we planed to developed the catalytic, asymmetric hydrophosphonylation of imines by using two complementary approaches: firstly, we used homogeneous catalysis conditions, with simple *Cinchona* alkaloid derivatives as

[166] T. Akiyama, H. Morita, J.Itoh, K. Fuchibe *Org. Lett.* **2005**, *7*, 2583.

chiral base catalysts and preformed aromatic *N*-carbamoyl imines (**Scheme 39**, top) giving access to optically active phospho aryl glycine derivatives. Secondly, we used biphasic conditions associated with *Cinchona* alkaloid chiral quaternary ammonium salt derivatives for the addition of phosphonic acid esters to aliphatic imines generated *in situ* from α-amido sulfones (**Scheme 39**, bottom), providing a convenient route to enantioenriched α-alkyl α-amino phosphonic acids.



Scheme 39. Complementary route for the synthesis of α-amino phosphonic acid dialkyl esters.

5.2. Results and Discussion

At the outset of the study with chiral bases catalysts, an initial screening of *Cinchona* derivatives **47e,h**, **QN, QD** in the addition of diethyl phosphite **101** to *N*-tosyl protected imine **43b** in toluene revealed the key role played by the free hydroxyl group in the *Cinchona* catalysts. Therefore using ester **47h** or carbamate **47e**, lacking the free hydroxyl group, as catalysts resulted (**Table 18**, entries 1-2) in significantly lower efficiency (conversion typically <10%). In contrast, commercially available quinine **QN**, or its "pseudoenantiomer", quinidine **QD** afforded quantitative conversion of the starting imine **43b**, but only moderate enantioselectivities (**Table 18**, entries 3-4, 48% and 46% *ee*, respectively) were achieved.[167] Further optimization revealed that the enantioselectivity could be raised to a more satisfactory level by changing the imine **43b** into *N*-Boc protected imine **42a** (**Table 18**, entry 5, 68% *ee*).[168] Finally a screening of solvents[169] suggested a significant solvent dependence with xylene affording products (*S*)-**103a**[170] with improved enantioselectivity (80% *ee*) and good conversion, when using quinine **QN** as the organocatalyst (**Table 18** ,entry 7).[171]

[167] Several *Cinchona* derived catalysts with an acidic proton moiety were tested and found to be inferior to quinine and quinidine.

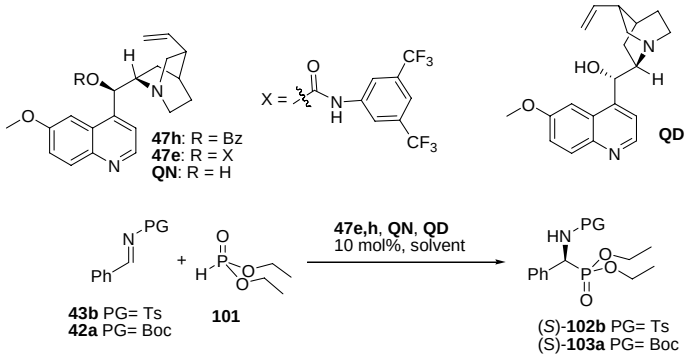
[168] Using a *N*-Cbz protected imine gave a product with lower enantioselectivity compared to the analogous Boc protected imine. This observation in combination with the more tedious preparation of *N*-Cbz imines resulted in no further consideration of *N*-Cbz imines as substrates.

[169] A screening of solvents showed that xylene gave better results than e.g. toluene and polar protic and aprotic solvents. Use of fluorobenzene or mesitylene lowered the selectivity with respect to xylene. No difference could be observed between using a mixture of xylenes or *p*-xylene as solvent.

[170] Deprotection of the *N*-Boc moiety by treatment with TFA gave the free amine having (*S*)-configuration with $[\alpha]^{25}_{D}$= -15.8° (c=1.0, $CHCl_3$) by comparison of literature data [amine having (*R*)-configuration; $[\alpha]^{25}_{D}$=17.2° (c=1.0, $CHCl_3$): F. A. Davis, S. Lee, H. Yan, D. D. Titus *Org. Lett* **2001**, *3*, 1757].

[171] Changing the nucleophile to diisopropyl phosphite lowered the reactivity and selectivity of the reaction whereas dimethyl phosphite was unreactive.

Table 18. Initial Screening of Catalysts, Solvents and Protecting Groups.[a]

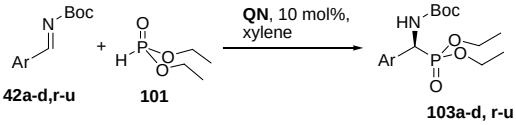


Entry	PG	Imines	Cat.	Solvent	Time (h)	Conv (%)[b]	ee (%)[c]
1	Ts	**43b**	**47h**	Toluene	42	<10	-
2	Ts	**46b**	**47e**	Toluene	77	0	-
3	Ts	**43b**	**QN**	Toluene	24	>95	48
4	Ts	**43b**	**QD**	Toluene	24	>95	46[d]
5	Boc	**42a**	**QN**	Toluene	48	>95	68
6	Boc	**42a**	**QD**	Toluene	48	>95	48[d]
7	Boc	**42a**	**QN**	Xylene	72	>95	80

[a] The reactions were carried out at 20 °C using 0.1 mmol imines **43b** or **42a**, 0.2 mmol phosphite **101** and 0.01 mmol catalysts **47e,h**, **QN**, **QD**, in 1 mL of solvent. [b] Conversions were determined by ^{1}H-NMR. [c] The enantiomeric excess was determined by chiral HPLC. [d] The reactions performed by quinidine **QD** gave the opposite enantiomer (*R*)-**102b** and (*R*)-**103b**.

With these informations in hand we proceeded to evaluate the quinine catalysed addition of diethyl phosphite to a representative selection of substituted *N*-Boc aromatic imines **42**. As shown in **Table 19**, both electron-donating (-Me, -OMe) and electron-withdrawing (-Cl) substituents on the aromatics ring, were applicable and gave the corresponding products with acceptable yields within 2 or 3 reaction days at 20°C. Some effect of the substitution pattern in the aromatic substituent of the imines could be observed in the case of imines **42b** (1-naphthyl) and **42c** (2-naphthyl), wherein the former afforded the corresponding α-amino phosphonate **103b** with a considerably poorer asymmetric induction (72% *ee*), with respect to the adduct **103c** obtained from **42c** in 85% *ee* (**Table 19**, compare entries 2 and 3). Using methyl and methoxy substituted imines **42d-g** resulted in enantiomeric excess in the range of 78-88% (**Table 19**, entries 4-7), whereas the 3-pyridinyl and *p*-Cl substituted imine **42h**, **42i** gave the product with 48% and 77% *ee* respectively (**Table 19**, entries 8, 9), indicating that also an electronic effect is involved in the enantiodiscrimination process (**Table 19**, compare entries 4-7 and 8-9).

Table 19. Enantioselective hydrophosphonylation of imines.[a]



42a-d,r-u **101** **103a-d, r-u**

Entry	Product	Ar	Time (d)	Temp (°C)	Yield (%)[b]	*ee* (%)[c]
1	**103a**	C_6H_5	3	20	83	80
2	**103b**	1-naphthyl	2	20	76	72
3	**103c**	2-naphthyl	2	20	82	85
4	**103r**	*m*-MeC_6H_4	3	20	71[d]	78
5	**103s**	*p*-MeC_6H_4	3	20	65[d]	86
6	**103t**	2,5-diMeC_6H_3	3	20	50	86
7	**103g**	*p*-$MeOC_6H_4$	2	20	50[d]	88
8	**103u**	3-pyridyl	3	20	72	48
9	**103d**	*p*-ClC_6H_4	2	20	57	77
10	**103a**	C_6H_5	3	-20	52	88
11	**103c**	2-naphthyl	4	-20	69	92
12	**103r**	*m*-MeC_6H_4	6	-20	61[d]	94
13	**103s**	*p*-MeC_6H_4	6	-20	62[d]	93
14	**103g**	*p*-$MeOC_6H_4$	7	-20	57[d]	94
15	**103d**	*p*-ClC_6H_4	4	-20	62	89

[a] The reactions were carried out using 0.1 mmol imine **42**, 0.2 mmol phosphite **103a** and 0.01 mmol catalyst in 1 ml of solvent. [b] Yields are given for isolated products. [c] The enantiomeric excess was determined by chiral HPLC. [d] Reactions carried out on a 0.3 mmol scale.

Finally, an enantioselectivity/temperature profile documented that in all cases enhanced enantioselectivities were available after prolonged reaction time (**Table 19**, entries 10-15), by running the reactions at -20 °C. Under these conditions α-amino phosphonates **103r** and **103g** were obtained with enantiomeric excesses up to 94% ee (**Table 19**, entries 12, 14).

A mechanistic proposal for the role of quinine **QN** as the catalyst in the hydrophosphonylation is shown in **Figure 5**. As the initial screening of catalysts showed the importance of the acidic hydroxyl group we believe that the imines are activated by a

hydrogen bonding from the catalyst.[52a,172] Regarding the phosphorous nucleophile, it is known that it is the phosphite and not the phosphonate form that is the actual nucleophilic species.[173] This equilibrium, which under neutral conditions is completely shifted towards the unreactive phosphonate, can be influenced by the presence of a base.[174] Therefore, it cannot be ruled out that the basic quinuclidinic nitrogen in the catalyst might shift the phosphite-phosphonate equilibrium towards the phosphite form and that its attack to the electrophilic azomethine carbon could be affected by the chiral environment generated by the catalyst.

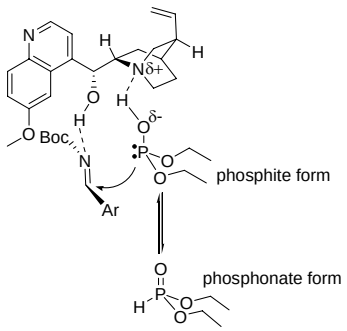


Figure 5 Proposed mechanism for the hydrophosphonylation of *N*-Boc imines catalysed by quinine.

After these successful results regarding catalytic enantioselective hydrophosphonylations of preformed *N*-carbamoyl aryl imines we took in consideration the second part of the project: biphasic conditions associated with *Cinchona* alkaloid chiral quaternary ammonium salt derivatives for the addition of phosphonic acid ester to α-amido sulfones.

At the beginning of the project we noticed that in the previous works, including the work described above on the hydrophosphonylation on *N*-Boc imines by means of quinine **QN**, it was not possible to use the reported protocols to prepare some very simple though of great importance α-amino phosphonic acids, such as phosphoalanine (Ala^p), phosphophenylalanine (Phe^p), and their substituted derivatives (see for example Tyr^P in **Chart 11**),[153-157] due to the sensitivity and instability of the corresponding linear unbranched imines.[165,166]

For this reason we thought that the addition of phosphonic acid dialkyl ester to aliphatic imines generated in situ from the corresponding α-amido sulfones could give a considerable improvement in term of reaction scope to this transformation.

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[172] a) H. Wynberg, A. A. Smaardijk *Tetrahedron Lett.* **1983**, *24*, 5899; b) A. A. Smaardijk, S. Noorda, F. van Bolhuis, H. Wynberg *Tetrahedron Lett.* **1985**, *26*, 493.
[173] D. F.Weimer *Tetrahedron* **1997**, *53*, 16609.
[174] B. Springs, P. Haake *J. Org. Chem.* **1977**, *42*, 472.

At the outset of our investigations concerning the reaction performed in biphasic conditions, we tested the behaviour of a few commercially available phosphites **101**, **104-107** in the reaction with α-amido sulfone **48i** (**Table 20**), in combination with different phase transfer catalysts **49a** (**Figure 6**) easily obtained from inexpensive quinine.[52b] Preliminary experiments carried out at room temperature with diethyl phosphite **101** confirmed our expectations of the tolerance of this system to linear, unbranched imines, as the product **103i** was obtained with very good levels of purity in the crude reaction mixture. These experiments showed also the beneficial effect exerted on the enantioselectivity of the reaction by a substituent at the *ortho* position of the benzylic moiety of the catalyst (**Table 20**, entries 1-2, 13% and 23% *ee*), in line with previous reports.[1c,1d,1e] A drop in enantioselectivity was observed decreasing the amount of base or using an aqueous base solution (**Table 20**, entry 3,4, 7% *ee*).

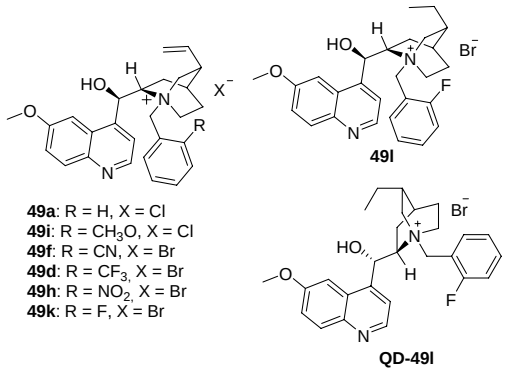
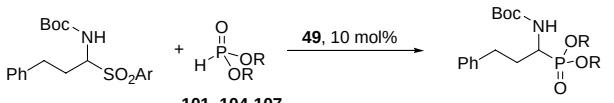


Figure 6. *Cinchona* alkaloid *P-T* catalysts for the optimisation process.

Table 20. Representative optimisation results in the addition of dialkyl phosphonate 101 to α-amido sulfones.[a]



Entry	Phosphite **101** (R)	Cat. **49**	Base (equivs.)	T (°C)	Conv.[b]	*ee* (%)[c]
1	**101** (Et)	49a	K_2CO_3 (5)	r.t.	>90 (**103i**)	13
2	**101** (Et)	49i	K_2CO_3 (5)	r.t.	>90 (**103i**)	23
3	**101** (Et)	49i	K_2CO_3 (1)	r.t.	45 (**103i**)	7
4	**101** (Et)	49i	K_2CO_3 aq.50% (5)	r.t.	>90 (**103i**)	7
5	**104** (Ph)	49i	K_2CO_3 (5)	r.t.	>90 (**108i**)	0
6	**105** (*i*-Pr)	49i	K_2CO_3 (5)	r.t.	55 (**109i**)	0
7	**106** (Bn)	49i	K_2CO_3 (5)	r.t.	>90 (**110i**)	37
8	**107** (Me)	49i	K_2CO_3 (5)	r.t.	>90 (**111i**)	40
9	**107** (Me)	49i	CsF (5)	-30	>90 (**111e**)	69
10	**107** (Me)	49f	CsF (5)	-30	>90 (**111i**)	79
11	**107** (Me)	49d	CsF (5)	-30	>90 (**111i**)	45
12	**107** (Me)	49h	CsF (5)	-30	>90 (**111i**)	75
13	**107** (Me)	49k	CsF (5)	-30	>90 (**111i**)	83
14	**106** (Bn)	49k	Cs_2CO_3 (5)	-30	>90 (**110i**)	80
15[d]	**107** (Me)	49k	KOH (3)	-78	>90 (**111i**)	87
16[d]	**106** (Bn)	49k	CsOH (1.5)	-78	>90 (**110i**)	82
17[d]	**107** (Me)	49l	KOH (3)	-78	>90 (**111i**)	90
18[d,e]	**107** (Me)	49l	KOH (3)	-78	>90 (**111i**)	89

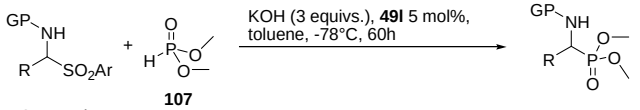
[a] Conditions: 0.10 mmol **48i**, 0.15 mmol **101**, **104-107**, 0.010 mmol cat. **49**, toluene (0.05 M), base, 18-48 h. [b] Determined by ^{1}H NMR spectroscopy or estimated by TLC. [c] Determined by chiral stationary phase HPLC. [d] 0.1 M reaction. [e] 5 mol% catalyst.

Among the different phosphites tested under these conditions (**Table 20**, entries 5-8), diphenyl and diisopropyl phosphites **104** and **105** furnished the products **108i** and **109i** in racemic form, whereas their dibenzyl and dimethyl derivatives **106** and **107** gave an encouraging improvement in terms of enantioselectivity (37-40% *ee*), with respect to diethyl phosphite **101**, and were thus selected for further investigations. Cooling the reaction temperature to -30 °C proved to be beneficial for the enantioselectivity, although the type of inorganic base had to be carefully optimised. It was eventually found that the

reaction could be carried out with good conversion using 5 equivalents of CsF as the base (**Table 20**, entry 9). Under these conditions, a few catalysts **49f,i,h,k** (**Figure 6**) all bearing an *ortho* substituent at the benzylic quinuclidinic moiety were tested (**Table 20**, entries 10-13), with the 2-fluoro substituted **49k** giving the best asymmetric induction (**Table 20**, entry 13, 83% ee). We found at this stage, in line with our previous experience with this type of transformations, that the free alcoholic group, as well as a single *ortho* substituent at the quinuclidinic benzylic moiety, were necessary requisites in the catalysts structure in order to obtain acceptable enantioselectivites (data not shown). Similar results were obtained using dibenzyl phosphite **92d** at -30 °C, although in this latter case the inorganic base had to be changed to Cs_2CO_3, to achieve a good level of conversion (**Table 20**, entry 14, 78% *ee*). Switching to the use of hydroxides as inorganic bases allowed to perform the reaction at a lower temperature (-78 °C), giving the α-amido dimethyl phosphonate **111i** with a satisfactory level of enantioselectivity (**Table 20**, entry 16, 87% *ee*), whereas the improvement in the case of the dibenzyl derivative **110i** was less pronounced (**Table 20**, entry 17, 82% *ee*). Again, the type and the amount of the inorganic base had to be carefully optimised, with KOH (3 equivalents) and CsOH (1.5 equivalents) giving the best results with **106** and **107**, respectively. Pursuing the reaction with dimethyl phosphite **107**, an additional small yet remarkable improvement in the enantioselectivity was observed when catalyst **49l**, derived from hydroquinine (**Figure 6**), was used in the reaction, even at lower (5 mol%) catalyst loading (**Table 20**, entries 17-18, 89-90% *ee*).

Having in hand a catalytic procedure able to furnish the corresponding α-aliphatic-α-amido phosphonic acid dimethyl esters **94e** with satisfactory levels of enantioinduction, we then proceeded to evaluate the generality of the present method, testing a few different α-amido sulfone **48, 50** (**Table 21**).

Table 21 Scope of the Pudovik reaction by using a-amindo sulfones 48,50[a]



48, Ar= Ph
50, Ar= *p*-Tol

107

111

Entry	Product	PG	R	Yield (%)[b]	*ee* (%)[c]
1	**111i**	Boc	$PhCH_2CH_2$	99	90
2	**111j**	Boc	Cy	94	82
3	**112c**	Cbz	Cy	93	89
4	**111m**	Boc	Me	84	77
5	**112g**	Cbz	Me	76	85

[a] The reactions were carried out using 0.1 mmol α-amido sulfones **48**, **50**, 0.15 mmol phosphite **107** and 5.0 μmol catalyst **49l** in 1 ml of solvent. [b] Yields are given for isolated products. [c] The enantiomeric excess was determined by chiral HPLC.

As shown in **Table 21**, both the Boc and Cbz as a protecting groups at the nitrogen were applicable in the reaction and gave the corresponding products with excellent yields, within 60 h at -78°C. In this case could not be observed any effect of the alkyl substituent and with both branched and unbranched ones with our delight the reaction provided the corresponding products in good enantiomeric excess.

In conclusion we have accomplished the first organocatalysed phase-transfer enantioselective hydrophosphonylation of *in situ*-generated aliphatic imines using commercially available dimethylphosphite as phosphite source. The ready preparation and stability of the simple chiral quininium salt, the convenient use of dimethyl phosphite and the easy access to the α-amino phosphonic acids, such as Ala^P are good assets of the enantioselective Pudovik process described.

5.4. Experimental Section

General procedure for the enantioselective hydrophosphonylation.

To a solution of imine **42** (0.1 mmol) in xylene (900 μl) was added quinine **QN** (0.01 mmol, 100 μl, 0.1 M stock solution in xylene) followed by diethyl phosphite (0.2 mmol, 26 μl). The reaction was stirred at 20 °C or -20 °C for the time stated, after which the α-amino phosphonate (**103**) was obtained through direct purification of the reaction mixture by column chromatography on silica gel (ethyl acetate/*n*-hexane 2:3).

(*S*)-Diethyl (*t*-butoxycarbonylamino-phenyl-methyl) phosphonate (103a). Following the general procedure, compound **103a** was obtained after 3 d at 20° C as white solid in 83% yield (28.3 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.12 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H), 3.74 (m, 1H), 3.95 (m, 1H), 4.12 (m, 2H), 5.11 (dd, J = 9.7, 21.8 Hz, 1H), 5.51 (br s, 1H), 7.24-7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4 (d, J = 5.7 Hz), 16.6 (d, J = 5.7 Hz), 28.5, 52.1 (d, J = 154.4 Hz), 63.3 (d, J = 7.3 Hz), 63.4 (d, J = 6.9 Hz), 80.6, 128.0 (d, J = 5.8 Hz), 128.2 (d, J = 2.9 Hz), 128.8 (d, J = 2.0 Hz), 135.7, 155.1; ^{31}P NMR (161 MHz, $CDCl_3$): δ 23.0. Chiral HPLC analysis (Chiralpak AD-H, 95:5 *n*-hexane:*i*-PrOH 0.75 mL/min, λ = 254 nm) indicated 80% ee, t_R(minor) = 31.1 min, t_R(major) = 22.4 min. $[\alpha]^{20}_D$= -11.8 (c = 0.97, $CHCl_3$). HRMS calcd for $C_{16}H_{26}NO_5P$ m/z 343.1549, found 343.1547.

(*S*)-Diethyl (*t*-butoxycarbonylamino-1-naphthyl-methyl) phosphonate (103b). Following the general procedure, compound **103b** was obtained after 2 d at 20° C as a white solid in 76% yield (29.9 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.83 (t, J = 7.4 Hz, 3H), 1.37 (t, J = 8.0 Hz, 3H), 1.42 (s, 9H), 3.45 (m, 1H), 3.80 (m, 1H), 4.21 (m, 2H), 5.64 (br s, 1H), 6.01 (dd, J = 9.3, 22.2 Hz, 1H), 7.60-7.45 (m, 3H), 7.76-7.70 (m, 1H), 7.89-7.79 (m, 2H), 8.25-8.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.1 (d, J = 5.6 Hz), 16.7 (d, J = 5.6 Hz), 28.5, 47.6 (d, J = 155.2 Hz), 63.3 (d, J = 7.8 Hz), 63.4 (d, J = 7.5 Hz), 80.6, 155.1. The aromatic carbons showed the following signals and are given without consideration of splitting; 123.7, 125.5, 126.0, 126.1, 126.8, 129.0, 131.47, 131.54, 132.3, 134.0; ^{31}P NMR (161 MHz, $CDCl_3$): δ 22.9. Chiral HPLC analysis (Chiralpak AD-H, 90:10 *n*-hexane:*i*-PrOH 0.75 mL/min, λ = 254 nm) indicated 72% ee, t_R(minor) = 22.6 min, t_R(major) = 15.4 min. $[\alpha]^{20}_D$= +11.5 (c = 0.87, $CHCl_3$). HRMS calcd for $C_{20}H_{28}NO_5P$ m/z 393.1705, found 393.1702.

(*S*)-Diethyl (*t*-butoxycarbonylamino-2-naphthyl-methyl) phosphonate (103c). Following the general procedure, compound **103c** was obtained after 4 d at -20° C as a white solid in 69% yield (27.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.10 (t, J = 6.8

Hz, 3H), 1.32 (t, *J* = 6.9 Hz, 3H), 1.44 (s, 9H), 3.75 (m, 1H), 3.95 (m, 1H), 4.15 (m, 2H), 5.29 (dd, *J* = 9.3, 22.0 Hz, 1H), 5.65 (br s, 1H), 7.43-7.60 (m, 3H), 7.78-7.93 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4 (d, *J* = 5.7 Hz), 16.6 (d, *J* = 5.6 Hz), 28.5, 52.3 (d, *J* = 156.1 Hz), 63.3 (d, *J* = 7.3 Hz), 63.5 (d, *J* = 6.8 Hz), 80.7, 155.2. The aromatic carbons showed the following signals and are given without consideration of splitting; 125.8, 126.3, 126.5, 127.1, 127.1, 127.9, 128.3, 128.5, 133.0, 133.3 (d, *J* = 20.6 Hz); ^{31}P NMR (161 MHz, $CDCl_3$): δ 22.4̃ Chiral HPLC analysis (Chiralpak AD-H, 90:10 *n*-hexane:*i*-PrOH 0.75 mL/min, λ = 254 nm) indicated 92% ee, t_R(minor) = 31.0 min, t_R(major) = 22.1 min. $[\alpha]^{20}_D$= -27.1 (c = 0.89, $CHCl_3$). HRMS calcd for $C_{20}H_{28}NO_5P$ m/z 393.1705, found 393.1702.

(*S*)-Diethyl (*t*-butoxycarbonylamino-3-methylphenyl-methyl) phosphonate (103r). Following the general procedure and performing the reaction on a 0.3 mmol scale, compound **5d** was obtained after 6 d at -20° C as a white solid in 61% yield (57.2 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.12 (t, *J* = 7.0 Hz, 3H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.42 (s, 9H), 2.35 (s, 3H), 3.74 (m, 1H), 3.95 (m, 1H), 4.12 (m, 2H), 5.07 (dd, *J* = 9.9, 21.4 Hz, 1H), 5.45 (br s, 1H), 7.24-7.47 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.1 (d, *J* = 5.8 Hz), 16.4 (d, *J* = 6.0 Hz), 21.4, 28.2, 51.7 (d, *J* = 152.8 Hz), 63.0 (d, *J* = 7.3 Hz), 63.2 (d, *J* = 7.2 Hz), 80.2, 124.8 (d, *J* = 6.0 Hz), 128.4, 128.5 (d, *J* = 5.5 Hz), 128.8 (d, *J* = 2.3 Hz), 135.3, 138.2, 154.8 (d, *J* = 11.2 Hz); ^{31}P NMR (161 MHz, $CDCl_3$): δ 22.6. Chiral HPLC analysis (Chiralpak AD-H, 95:5 *n*-hexane:*i*-PrOH 0.75 mL/min, λ = 254 nm) indicated 94 % ee, t_R(minor) = 20.9 min, t_R(major) = 16.7 min. $[\alpha]^{20}_D$= -30.1 (c = 0.12, $CHCl_3$). HRMS calcd for $C_{17}H_{28}NO_5P$ m/z 357.1705 found 357.1703.

(*S*)-Diethyl (*tert*-butoxycarbonylamino-4-methylphenyl-methyl) phosphonate (103s). Following the general procedure and performing the reaction on a 0.3 mmol scale, compound **5e** was obtained after 5 d at -20° C as a white solid in 62% yield (58.4 mg). ,^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.12 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.41 (s, 9H), 2.32 (s, 3H), 3.80-3.69 (m, 1H), 3.99-3.88 (m, 1H), 4.16-4.04 (m, 2H), 5.06 (dd, *J* = 9.7, 21.9 Hz, 1H), 5.48 (br s, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.1 (d, *J* = 5.8 Hz), 16.4 (d, *J* = 5.8 Hz), 21.1, 28.2, 51.5 (d, *J* = 154.9 Hz), 62.9 (d, *J* = 6.7 Hz), 63.1 (d, *J* = 6.7 Hz), 80.2, 127.6 (d, *J* = 6.0 Hz), 129.2 (d, *J* = 2.3 Hz), 132.4, 137.7 (d, *J* = 2.7 Hz), 154.8 (d, *J* = 9.7 Hz); ^{31}P NMR (161 MHz, $CDCl_3$): δ 23.2. Chiral HPLC analysis (Chiralpak AD-H, 80:20 *n*-hexane:*i*-PrOH 0.75 mL/min, λ = 254 nm) indicated 93% ee, t_R(minor) = 18.8 min, t_R(major) = 10.5 min. $[\alpha]^{20}_D$= -1.9 (c = 1.1, $CHCl_3$). HRMS calcd for $C_{17}H_{28}NO_5P$ m/z 357.1705 found 357.1704.

(*S*)-Diethyl (*t*-butoxycarbonylamino-2,5-dimethylphenyl-methyl) phosphonate (103t). Following the general procedure, compound **103t** was obtained after 3 d at 20° C as a pale yellow solid in 50% yield (18.6 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.06 (t, J = 7.3 Hz, 3H), 1.33 (t, J = 7.3 Hz, 3H), 1.42 (s, 9H), 2.31 (s, 3H), 2.41 (s, 3H), 3.67-3.56 (m, 1H), 3.94-3.83 (m, 1H), 4.20-4.09 (m, 2H), 5.36 (dd, J = 9.9, 21.8 Hz, 1H), 5.52 (br s, 1H), 6.99 (d, J = 8.0 Hz, 1H) 7.05 (d, J = 8.0 Hz, 1H), 7.20 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.1 (d, J = 5.2 Hz), 16.4 (d, J = 5.2 Hz), 19.2, 21.1, 28.3, 47.8 (d, J = 154.7 Hz), 62.9 (d, J = 7.0 Hz), 63.2 (d, J = 7.0 Hz), 80.2, 127.9, 128.7, 130.4, 133.4, 133.9, 135.7, 154.8 (d, J = 8.1 Hz); ^{31}P NMR (161 MHz, $CDCl_3$): δ 23.4. Chiral HPLC analysis (Chiralpak AD-H, 95:5 *n*-hexane:*i*-PrOH 0.75 mL/min, λ = 254 nm) indicated 86% ee, t_R(minor) = 11.6 min, t_R(major) = 9.2 min. $[\alpha]^{20}_D$= -18.6 (c = 1.0, $CHCl_3$). HRMS calcd for $C_{18}H_{30}NO_5P$ m/z 371.1862 found 371.1860.

(*S*)-Diethyl (*t*-butoxycarbonylamino-4-methoxyphenyl-methyl) phosphonate (103g). Following the general procedure and performing the reaction on a 0.3 mmol scale, compound **103g** was obtained after 7 d at -20° C as a pale yellow solid in 57 % yield (63.7 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.13 (t, J = 6.9 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.42 (s, 9H), 3.77 (m + s, 1H + 3H), 3.94 (m, 1H), 4.12 (m, 2H), 5.05 (dd, J = 9.4, 21.0 Hz, 1H), 5.44 (br s, 1H), 6.83-6.91 (m, 2H), 7.29-7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4 (d, J = 5.8 Hz), 16.6 (d, J = 5.8 Hz), 28.5, 51.4 (d, J = 153.4 Hz), 63.2 (d, J = 67.1), 63.4 (d, J = 6.5), 80. 4, 114.2, 127.8, 129.2, 129.3, 155.1 (d, J = 9.7 Hz), 159.6; ^{31}P NMR (161 MHz, $CDCl_3$): δ 22.8. Chiral HPLC analysis (Chiralpak AD-H, 80:20 *n*-hexane:*i*-PrOH 0.75 mL/min, λ = 254 nm) indicated 94% ee, t_R(minor) = 21.0 min, t_R(major) = 12.0 min. $[\alpha]^{20}_D$= -24.6 (c = 1.25, $CHCl_3$). HRMS calcd for $C_{17}H_{28}NO_6P$ m/z 373.1654, found 373.1652.

(*S*)-Diethyl (*t*-butoxycarbonylamino-pyridin-3-yl-methyl) phosphonate (103u). Following the general procedure, compound **103u** was obtained after 3 d at 20° C as a colourless oil in 72% yield (24.8 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.19 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.0 Hz, 3H), 1.45 (s, 9H), 3.90 (m, 1H), 4.03 (m, 1H), 4.16 (m, 2H), 5.14 (dd, J = 8.7, 23.2 Hz, 1H), 5.52 (br s, 1H), 7.33 (m, 1H), 7.80 (m, 1H), 8.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4 (d, J = 5.6 Hz), 16.6 (d, J = 5.5 Hz), 28.5, 50.1 (d, J = 155.9 Hz), 63.6 (d, J = 5.0 Hz), 63.6 (d, J = 5.0 Hz), 80.9, 132.5, 135.6, 149.4, 155.0; ^{31}P NMR (161 MHz, $CDCl_3$): δ 21.8. Chiral HPLC analysis (Chiralpak AD-H, 55:45 *n*-hexane:*i*-PrOH 0.5 mL/min, λ = 254 nm) indicated 48% ee, t_R(minor) = 9.4 min, t_R(major) = 10.8 min. $[\alpha]^{20}_D$= -14.2 (c = 0.80, $CHCl_3$). HRMS calcd for $C_{15}H_{25}N_2O_5P$ m/z 344.1501, found 344.1503.

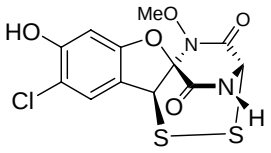
(*S*)-Diethyl (*t*-butoxycarbonylamino-4-chlorophenyl-methyl) phosphonate (103d). Following the general procedure, compound **103d** was obtained after 4 d at -20° C as a white solid in 62% yield (26.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.15 (t, J = 6.9 Hz, 3H), 1.30 (t, J = 6.9 Hz, 3H), 1.41 (s, 9H), 3.81 (m, 1H), 3.97 (m, 1H), 4.11 (m, 2H), 5.06 (dd, J = 9.2, 21.6 Hz, 1H), 5.47 (br s, 1H), 7.29-7.47 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4 (d, J = 6.0 Hz), 16.6 (d, J = 6.0 Hz), 28.5, 51.5 (d, J = 155.1 Hz), 63.4 (d, J = 7.6 Hz), 63.5 (d, J = 7.3 Hz), 80.8, 128.9, 129.3, 134.3 (d, J = 33.0 Hz), 155.0; ^{31}P NMR (161 MHz, $CDCl_3$): δ 22.4. Chiral HPLC analysis (Chiralpak AD-H, 90:10 *n*-hexane:*i*-PrOH 0.75 mL/min, λ = 254 nm) indicated 89% ee, t_R(minor) = 17.1 min, t_R(major) = 13.0 min. $[\alpha]^{20}_{D}$= -13.9 (c = 1.28, $CHCl_3$). HRMS calcd for $C_{16}H_{25}NO_5PCl$ m/z 377.1159, found 377.1156.

Section 2

Towards the Enantioselective Synthesis of Aspirochlorine

1. Introduction

Aspirochlorine **1** belongs to the epipolythiodioxopiperazines (EPTs) class which consists of a large group of fungal toxins (gliotoxins).[175] It has been isolated from *Aspergillus tamari* species in 1976,[176] and the structure has been determined by X-ray analysis ten years later.[177] Then the natural product was later also found to be an active ingredient in different other species of *aspergillus* strain. It shows an unusual 7-membered disulfide bridge in a bicyclic ring system and a unique *N*-methoxyl moiety in a diketopiperazine ring (**Figure 7**).



1

Figure 7. Aspirochlorine.

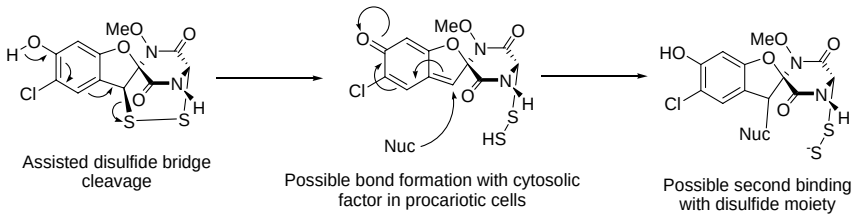
The molecule shows the usual activity of all gliotoxins, confirming antifungal, antibacterial, antitumor and antiviral activity. In general EPTs inhibit viral RNA-directed, RNA and DNA polymerases as well as RNA synthesis in HeLa cells (an important immortal tumor cell).[178] In particular aspirochlorine **1** is active against several yeasts, *Staphylococcus aureus*, the Newcastle disease virus, and the Ehrlich ascites tumor in mice, demonstrating that the compound is bioavailable in vivo.[176,179]

While these properties were closely related to other gliotoxins and due to the lower activity resulted not particularly interesting, a recent disclosure indicates that aspirochlorine **1**, instead, is a highly selective and active agent against fungi: specifically inhibits fungal protein synthesis but simultaneously does not inhibit protein synthesis in bacteria or higher eukaryotes.[180] Moreover aspirochlorine exhibits exceptional potency

[175] P. Waring, R. D. Eichner, A. Mullbacher *Med. Res. Rev.* **1988**, *8*, 499.
[176] D. H. Berg, R. P. Massing, M. M. Hoehn, L. D. Boeck, R. L. Hamill *J. Antibiot.* **1976**, *29*, 394.
[177] The structure was determined by X-ray analysis of a semisynthetic derivative: K. Sakata, M. Maruyama, J. Uzawa, A. Sakurai, H. S. M. Lu, J. Clardy *Tetrahedron Lett.* **1987**, *28*, 5607.
[178] a) A. Mullbacher, P. Waring, U. Tiwari-Palni, R. D. Eichner *Mol. Immunol.* **1986**, *23*, 231. b) A. Mullbacher, D. Hume, A. W. Braithwaite, P. Waring, R. D. Eichner *Proc. Natl. Acad. Sci.* **1987**, *84*, 3822. c) T. W. Jordan, S. J. Cordiner *TIPS* **1987**, *81*, 144.
[179] A. Kato, T. Saeki, S. Suzuki, K. Ando, G. Tamura *J Antibiot.* **1969**, *22*, 322.
[180] F. Monti, F. Ripamonti, S. P. Hawser, K. Islam *J. Antibiot.* **1999**, *52*, 311.

against an azole-resistant strain of *Candida Albicans* (IC_{50} 0.028 μM) and yet is relatively nontoxic to human CEM-SS lymphocytes (IC_{50} 0.58 μM).[181]

After 20 years of extensive research, however, the exact mechanism of action of this potent antifungal agent is not well known. One assumed mode of action is shown in **Scheme 40**, where the C-S bond in benzylic position, assisted by the stabilizing effect of the hydroxyl group is cleaved to generate an electrophilic acceptor that could interact and block the receptor binding site (**Scheme 40**).



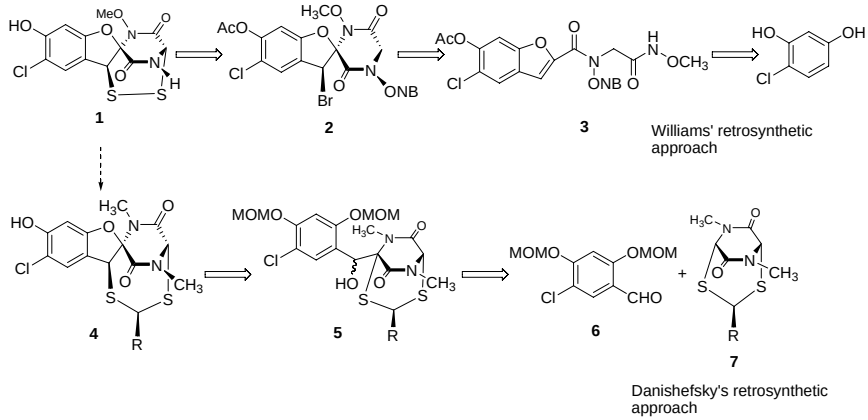
Scheme 40. Possible mechanism of action.

For further evaluation of the biological activity and mode of action of aspirochlorine, it is necessary to find a good synthetic approach to synthesise both the natural product and the structurally related compounds.

Considering the interesting properties of **1**, there are only three works related to the total synthesis of this natural product.[182]

The syntheses are all racemic and differ significally in the formation of the spiro centre. Only the oldest one by Williams leads to the natural product,[182a] whereas the others form structurally related compounds of aspirochlorine **1**.[182b,c] The second one is a recent synthesis of a close precursor of **1** made by Danishefsky in the 2000, in 25 % overall yield.[182b]

[181] P. Klausmeyer, T. G. McCloud, K. D. Tucker, J. H. Cardellina II, R. H. Shoemaker *J. Nat. Prod.* **2005**, *68*, 1300.
[182] a) G. F. Miknis, R. M. Williams *J. Am. Chem Soc.* **1993**, *115*, 536; b) Z. Wu, L. J. Williams, S. J. Danishefsky *Angew. Chem. Int. Ed.* **2000**, *39*, 3866; c) K. Itoh, M. Kasami, R. Yamada, K. Toshiaki, A. Honda, Sera *Heterocycles* **1997**, *45*, 1345.

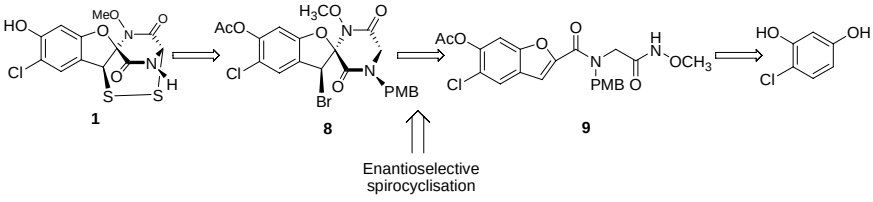


Scheme 41. Previous racemic synthesis of aspirochlorine.

The Williams' approach is based on the synthesis of *O*-methyl-hydroxamic acid ester **3**, a key intermediate for the subsequent spirocyclisation to form **2**, and a final disulfide bridge formation in 13 linear steps and 0.4 % overall yield.[182a] Danishefsky, instead, uses a convergent approaches forming **6** and **7**, which are then coupled them to the corresponding fragment **5**. The key step of the synthesis is the formation of the spirocentre by a sulphur rearrangement giving **4**, in 3 steps and 25% overall yield. Compound **4** is closely related to aspirochlorine **1** but has a different substitution pattern at the nitrogen atoms.[182b]

Both approaches present some drawbaks. The Williams' synthesis is quite long and the yield is low. Danishefsky's synthetic sequence, using a convergent strategy, is able to increase the yield and efficiency of the process but does not lead to the aspirochlorine. Furthermore the synthesis of **7** is not trivial.

Based on the known syntheses,[182] it was envisaged to find an enantioselective route for the formation of aspirochlorine **1**. For this ambitious project we used the Williams' approach as a suitable starting point.

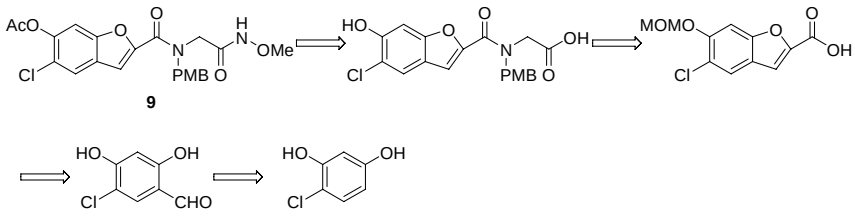


Scheme 42. Retrosynthesis of the enantioselective synthesis of aspirocholrine.

Following the first step of the Williams' route, the spirocyclisation should then be performed in an enantio- and diastereoselective fashion to obtain enantiomerically enriched material (**Scheme 42**).

2. Results and Discussion

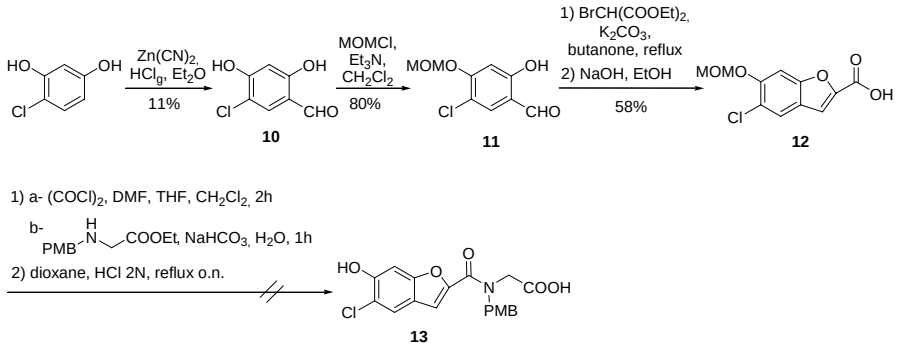
In the earlier study of this project intermediate **9** was obtaining using a slightly modified Williams' procedure. Instead of the *o*-nitrobenzyl protecting group, in the present work a more versatile and light stable *p*-methoxybenzyl was used.[183] Analysing the retrosynthesis of the first part of the total synthesis reveals the long sequence of transformations to get the desired intermediate (**Scheme 43**).



Scheme 43. Williams' retrosynthetic approach.

This synthesis started with a Gattermann reaction on the 4-chlororesorcinol leading to the formylated product **10**. This reaction gave several problems. The reproducibility and the yield were very low (**Scheme 44**). Furthermore, starting from a huge amounts of resorcinol and a dangerous combination of zinc cyanide and gaseous hydrogen chloride, just a few grams of **10** could be obtained. The 4-hydroxyl group of the formed benzaldehyde was then regioselectively protected with MOMCl, yielding **11** in 80% yield. The subsequent multi step benzofuran formation gave **12** in moderate yields. The following amide formation turned out to be more difficult than expected. After the acidic cleavage of both the MOM protecting group and the ethyl ester, only a brown oil could be obtained and no the desired glycine acid derivative **13** could be found, suggesting decomposition under these harsh conditions (**Scheme 44**).

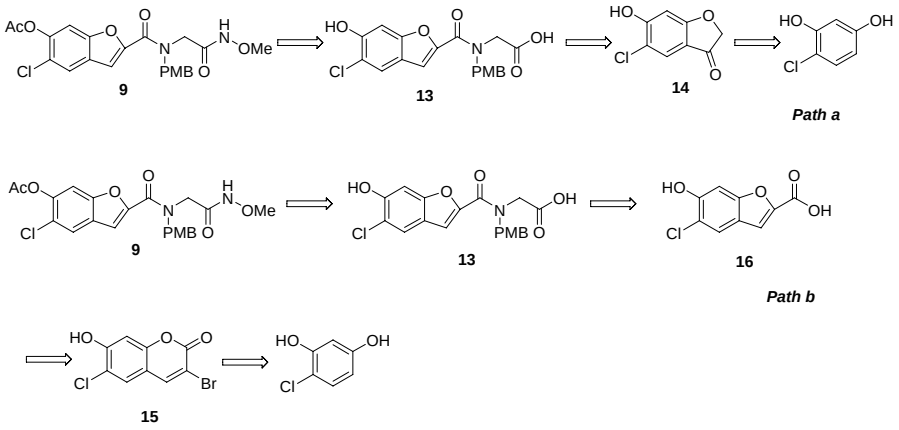
[183] *o*-Nitrobezyl protecting group could be easily removed by ultraviolet light.



Scheme 44.The modified Williams' approach.

These results indicated that this sequence was not efficient and needed improvement for the total synthesis. For this purpose we envisaged two new pathways to get the hydroxamic acid ester **9**.

As mentioned above, after the first unsuccessful efforts, we decided to modify the synthesis of **9**, proposing two different pathways.

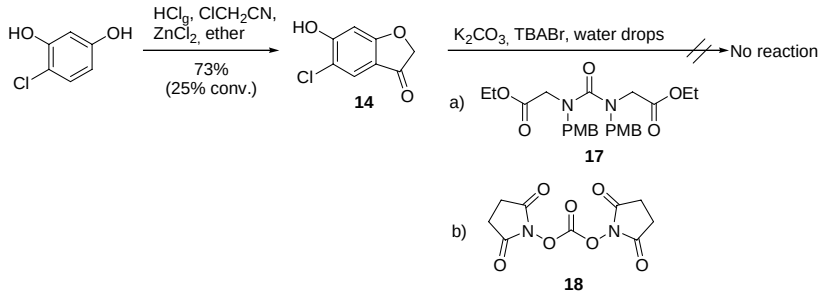


Scheme 45. Two novel approaches for the synthesis of 3.

Path a is clearly a very short route that implies the synthesis of benzofuranone **14**, a subsequent coupling with a carbamic chloride fragment and reduction of ketone moiety to give **13**. Protection of the phenol and amide coupling should give **9** (**Scheme 45, Path a**). ***Path b*** has one step more than ***a*** but is still convenient and avoids several dangerous reagents. This path requires the synthesis of 3-bromo-6-chloro-7-hydroxycoumarin **15** from 4-chlororesorcinol, which undergoes ring contraction to give **16**. After the coupling with a protected glycine fragment, acylation of the phenol group and a final amide formation with methoxylamine should lead to the formation of **9** (**Scheme 45, Path b**).

Path a: The benzofuranone route

To obtain the chloro-substituted benzofuranone **14** chloroacetonitrile was reacted with 4-chlororesorcinol (**Scheme 46**). To perform the intramolecular aromatic electrophilic substitution strong acidic conditions, using gaseous hydrogen chloride and zinc chloride, were needed. The conversion of the reaction was only 25% but the yield of the converted product was high (73%, **Scheme 46**).[184] The reactions of **14** with different activated carbonyl compounds to form the new C-C bond failed. It was found that, instead of the carbamic chloride, the urea **17** was formed and therefore was not suitable to undergo the bond formation (**Scheme 46**, try a).[185] Alternatively, *N*,*N*'-Disuccinimidyl carbonate **18** was used but also gave no conversion (**Scheme 46**, try b).[186] As a result of more promising data obtained from the other pathway (**Scheme 45**, **Path b**), it was decided not to proceed further on this route.



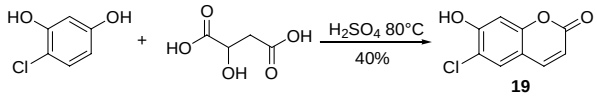
Scheme 46. Unsuccessful attempts for the synthesis of 13.

Path b: The coumarin route.

For this attempt, it was proposed to synthesise **15** by a Pechmann condensation followed by a bromination (or chlorination) of the pyranone double bond, starting from 4-chlororesorcinol and malic acid. The condensation proceeded in concentrated sulphuric acid at 80°C to give 6-chloro-7-hydroxycoumarin **19** in 40% yield without further optimization. The reaction is easily scalable and the crude material could be easily purified by recrystallisation from ethanol (**Scheme 47**).[187]

---

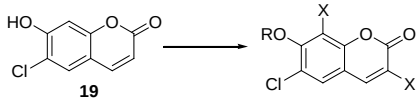
[184] E. C. Horning, D. B. Reisner *J. Am. Chem. Soc.* **1948**, *70*, 3619.
[185] For some examples of stable *N*-chlorocarbonyl moieties in a glycine scaffold see: a) T. M. V. D Phino e Melo, *et al. Tetrahedron* **2004**, *60*, 3949; b) K. Drauz, A. Kleemann, J. Martens, P. Scherberich, F. Effenberger *J. Org. Chem.* **1986**, *51*, 3494.
[186] A. K. Ghosh, T. T. Duong, S. P. McKee, W. J. Thompson *Tetrahedron Lett.* **1992**, *33*, 2781.
[187] a) H. von Pechmann *Ber.* **1884**, *17*, 929; b) D. N. Shah, N. M. Shah *J. Org. Chem.* **1954**, *19,* 1681; c) A. G. Osborne, S. J. Andrews, R. Mower *J. Chem. Res. (S)* **2003**, 114; and reference therein.



Scheme 47. Pechmann condensation

For the bromination (or chlorination) of **19** different reaction conditions were tested, but all attempts resulted in an over-halogenation of coumarin **19**,[188] which sometimes proceeded very cleanly (**Table 22**).

Table 22. Halogenation of 19.

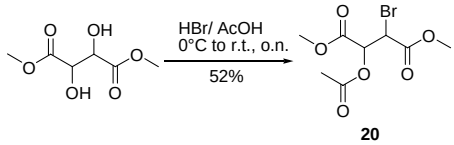


Entry	Reagent	Product	t	Conv.	Note
1[189]	$PhI(OAc)_2$, TBABr, dry CH_2Cl_2, r.t.	R=Ac, X=Br	2h	100%	clean reaction
2[189]	$PhI(OAc)_2$, TBABr, dry CH_2Cl_2, 0 °C → r.t.	R=Ac, X=Br	4h	100%	clean reaction
3[189]	$PhI(OAc)_2$, TBABr, dry CH_2Cl_2, -78 °C	R=Ac, X=Br	8h	100%	clean reaction
4[190]	1) Oxone, CH_2Cl_2, HCl 2N, r.t.; 2) Et_3N	R=H, X=Cl	1) 1h 2) o.n.	100%	clean reaction
5[191]	DMP, TBABr, dry CH_2Cl_2	Decomposed	24h	50%	complete mess

After these unsuccessful attempts it was considered to install the halogen prior to the cyclisation directly in the malic acid, and try the Pechmann condensation with this new substrate.

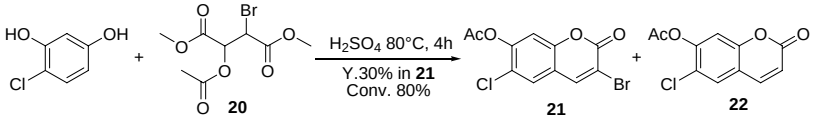
Following a literature procedure, the bromine bond was formed starting from (+)-dimethyl l-tartrate using hydrogen bromide in glacial acetic acid.[192]

[188] The haloganation occurs also at the 8 position , probably due to the activation of this position by two oxygens in the *ortho*- positions.
[189] S. H. Rho, B.-S. Ko, H. K. Kim, Y.-S Ju *Synth. Commun.* **2002**, *32*, 1303.
[190] Kim, K.-M.; Park, I.-N. *Synthesis* **2004**, 2641.
[191] Ramanarayanan, G. V.; Shukla, V. G.; Akamanchi, K. G. *Synlett* **2002**, 2059.
[192] S. Saito, T. Ishikawa, A. Kuroda, K. Koga, T. Moriwake *Tetrahedron* **1992**, *48*, 4067.



Scheme 48. Installation of bromine directly in the starting material.

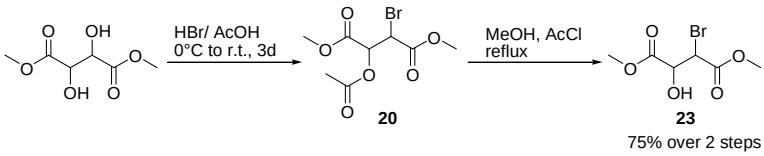
This procedure gave **20** in 52% yield after column chromatography (**Scheme 48**). The product was immediately used for the Pechmann condensation using the conditions previously tested and gave a mixture of **21** and **22** in a 5:1 ratio. Finally, 30% of coumarin **21** (80 % conversion of 4-chlororesorcinol) could be obtained after recrystallization (**Scheme 49**).



Scheme 49. Synthesis of coumarin 21 with bromine already installed.

Because of the low yield of the reaction and the formation of a large amount of the debrominated compound **22** this approach required an adjustment.

To improve the procedure, **20** was modified and the reaction conditions optimised. It was found that the deacetylated product **23** was more active in the condensation reaction than **20**.

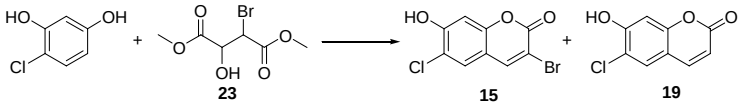


Scheme 50. Synthesis of 23 from dimethyl tartrate.

The optimized reaction gave 75% yield of **23** in two steps after column chromatography. The reaction was easily scalable to give up to 160 grams of **23** (**Scheme 50**).[192]

With a good amount of **23** in hand we started to optimise the Pechmann condensation by modifying the reaction conditions.

Table 23. Short optimization of Pechmann condensation using 23 as substrate.

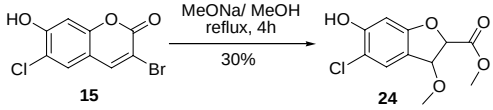


Entry	H_2SO_4 conc.	T	Isomeric ratio (15/19)	Yield[a]
1	3.7 eq.	80°C	8:1	15%
2	3.7 eq.	105°C	8:1	35%
3	5.6 eq.	105°C	9:1	42%
4	7.5 eq.	105°C	12:1	60%

[a] Estimated yield based on crude material.

Remarkably, in this short sequence the temperature and of the amount of sulphuric acid play a crucial role, showing that both factors were important for the transformation that **23** could undergoes (loss of carbon monoxide, two molecules of methanol and water).[187c] Moreover, with the optimized conditions (**Table 23**, entry 4) the crude material was pure enough to be used in the next step.

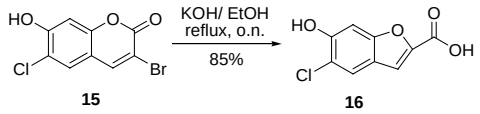
For the subsequent ring contraction, sodium methoxide in boiling methanol was initially used. The procedure gave compound **24**, having the right ring size but containing one more methanol unit, in poor yield (**Scheme 51**).[193]



Scheme 51. Ring contraction by sodium methoxide.

Encouraged from this result methoxide was replaced by potassium hydroxide, and good results was already obtained in the first attempt.[194] Additionally, this procedure leads directly to the free coumarilic acid derivative **16** and therefore shortens the synthetic route as no ester saponifications is required afterwards.

[193] M. Newman, C. K. Dalton *J. Org. Chem.* **1965**, *30*, 4126.
[194] a) W. H. Perkin *J. Chem. Soc.* **1870**, *23*, 368; b) W. H. Perkin *J. Chem. Soc.* **1871**, *24*, 37; c) R. C. Fuson, J. W Kneisley, E. W. Kaiser *Org. Synth.* **1955**, *Coll. Vol III*, 209.



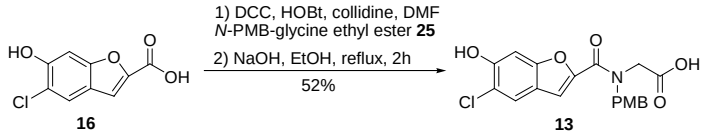
15 **16**

Scheme 52. Ring contraction performed in a Perkin fashion.

The ring contraction worked very well giving **16** in 85% yield. After work-up the crude material could be used for the following step without further purification (purity >95 %).[195]

Now, after optimization, both steps, the coumarin formation (**Table 23**, entry 4) and the ring contraction (**Scheme 52**) were performed without further purification of the crude materials affording **16** in 50 % overall yield in high purity (>95%) using up to 12 grams of 4-chlororesorcinol andaffording 8.5 g of **16**.

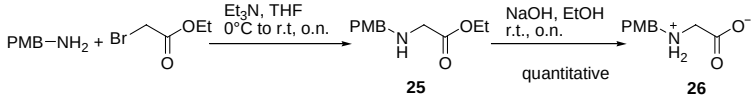
With a faster and better procedure for the synthesis of **16** in hand we started to look into the glycine unit coupling with the coumarilic acid moiety. At the beginning the Williams strategy was used performing the coupling with *N*-PMB-glycine ethyl ester unit **25** and a subsequent saponification to give **13**.[182a] In this particular reaction we chose HOBt/DCC for the coupling and a NaOH/EtOH combination for the saponification. This two steps procedure gave only 52 % yield of isolated product **13** (**Scheme 53**).



16 **13**

Scheme 53. Synthesis of 13 using Williams' strategy.

After several unsuccessful attempts to improve the yield we decided to change the strategy and we use directly the free glycine-derived carboxylic acid **26**, avoiding the harsh reaction conditions necessary for the the saponification. For this purpose, the *N*-PMB-glycine ethyl ester **25** was synthesised first and subsequently hydrolysed giving the free acid **26**.



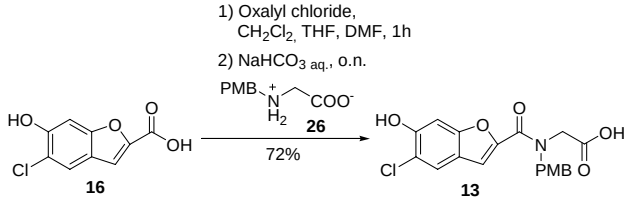
25 **26**

Scheme 54. Synthesis of 26 on a multi-gram scale.

[195] For a detailed study about the mechanism see note 19.

Both reactions also worked well on a multi-gram scale and it was possible to isolate **26** in quantitative yield after column chromatography (**Scheme 54**).

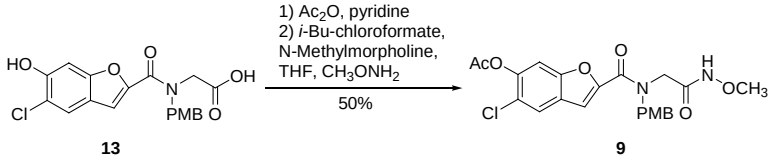
Trying to couple **26** with **16**, fortunately gave a excellent results in the first attempt, using the Schotten-Baumann conditions.



Scheme 55. Coupling of 16 with 26 under Schotten-Baumann conditions.

The reaction was performed in a two-pot procedure: the coumarilic acid **16** was converted into the corresponding acid chloride by oxalyl chloride and subsequently transferred dropwise to a mixture of **26** and aqueous sodium bicarbonate. The biphasic mixture was stirred overnight and afforded the amide **13** in 72% yield after work-up. The raw material showed an high purity (>90%) and was used in to the next step without further purification (**Scheme 55**).

For the next two steps the procedure utilized by Williams was used. The free phenolic OH was protected with an acetyl group, using an excess of acetic anhydride in pyridine. The following coupling with methoxylamine by a mixed anhydride formation (isobutyl chloroformate, *N*-methylmorpholine) afforded the hydroxamic acid ester **9** in only 50% yield over two steps.[182a] At this stage it is not clear why the yield is so poor The reaction proceeded "spot to spot" and no byproducts in the reaction were observed (**Scheme 56**).

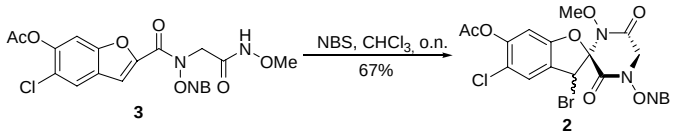


Scheme 56. Protection of the free hydroxyl group and methoxylamine coupling sequence.

In summary, a new strategy to form the *O*-Me hydroxamic acid ester **9** in 5 steps and in 18 % overall yield starting from 4-chlororesorcinol has been developed, performing easily scalable reactions without the use of highly toxic agents like $Zn(CN)_2$, gaseous HCl or MOMCl. This is a drastic improvement in the synthesis of this important precursor, in comparison to the Williams' route, that affords the *O*-Me-hydroxamic acid ester **3** in 9 steps and in 8 % yield.

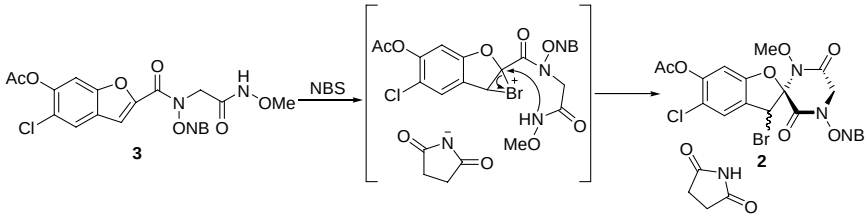
The formation of the spiro centre was the next focus of this project. Considering the reported results of the cyclisation from Williams attempts were made to perform the spirocyclisation in an enantioselective fashion.

Williams reported the spirocyclisation using NBS in chloroform, obtaining the bromo-substituted product **2** in 67% yield as a mixture of diastereoisomers (cis/trans 1:4) (**Scheme 57**).



Scheme 57. Reported spirocyclisation by Williams.

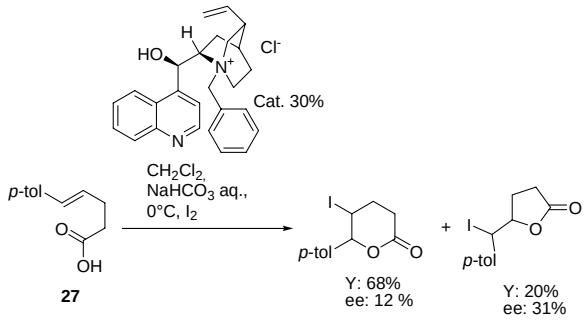
The key step is the formation of the bromonium intermediate and the consequent intramolecular nucleophilic attack of the amide nitrogen to close the ring and to afford the desired product (**Scheme 58**).



Scheme 58. Hypothetic reaction mechanism.

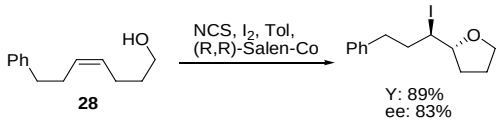
According to the others results reported by Williams, the reaction needs a bulky protecting group on the amide and a protecting group at the phenolic hydroxyl function. Otherwise, the yield of the cyclisation drops. All these data, taken together, can be considered as an evidence for the formation of this intermediate.

To clarify the planned reaction, some closely related examples of enantioselective spirocyclisations are presented in the following scheme.



Scheme 59. Lactonisation mediated by cinchona alkaloid phase-transfer catalyst.

The example described in **Scheme 59** shows a iodolactonisation mediated by a *Cinchona* alkaloid-derived phase-transfer catalyst that proceeds in good yield and low enantioselectivity. The unsaturated carboxylic acid **27** has significant similarities to the hydroxamic acid ester **9** (Compare 9 in **Scheme 56** with 27 in **Scheme 59**).[196]



Scheme 60. Enantioselective iodocyclisation mediated by Co-Salen complex.

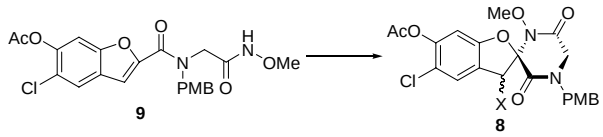
The substrate in **Scheme 60** is a little different than the previous one. Under Co-Salen catalysis the authors report the highly enantioselective iodocyclisation of **28** and related compounds.[197]

Inspired by these catalytic enantioselective intramolecular cyclisations it was decided to start the exploration of the spirocyclisation mediated by *Cinchona* alkaloid phase-transfer catalysts. This type of chemistry is quite flexible and powerful, it is possible to adjust the reactivity of the process using different inorganic bases as well as the solvent and the type of catalyst. Furthermore, there is a wide array of commercially available catalysts whose synthesis is usually quite easy.[198]

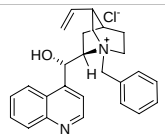
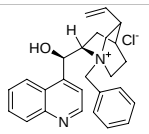
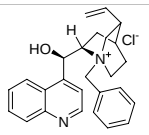
Only a few attempts for the enantioselective spirocyclisation step were done, but nevertheless they showed some encouraging results.

[196] M. Wang, L. X. Gao, W. P Mai, A. X. Xia, F. Wang, S. B. Zhang *J. Org. Chem.* **2004**, *69*, 2874.
[197] S. H. Kang, S. B. Lee, C. M. Park *J. Am. Chem. Soc.* **2003**, *125*, 15748.
[198] For a recent review of phase transfer catalysis see: a) Nelson, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 1583; b) K. Maruoka, T. Ooi *Chem. Rev.* **2003**, *103*, 3013; c) B. Lygo, B. I. Andrews *Acc. Chem. Res.* **2004**, *37*, 518; d) M. J. O'Donnell *Acc. Chem. Res.* **2004**, *37*, 506.

Table 24. Firsts attempts for the enantioselective spirocyclisation.



9 **8**

Entry	Catalyst	Base	Solvent	Reagent	t	Conv.	d.r.	*ee*
1	 *N*-Bn**CN**$^+$Cl$^-$	$NaHCO_3$ aq.	CH_2Cl_2	NCS	<2h	100 %	-	-
2	 *N*-Bn**CD**$^+$Cl$^-$	$NaHCO_3$ aq.	CH_2Cl_2	NCS	<2h	100 %	-	-
3[a]	-	-	$CHCl_3$	NCS	18h	0	-	-
4	 *N*-Bn**CD**$^+$Cl$^-$	$NaHCO_3$ aq.	Tol	NBS	<2h	100 %	1:5	23%
5	-	-	$CHCl_3$	NBS	18h	Y.67 %	1:4	-
6[a]	-	-	benzene	NBS	18h	Y. 30 %	1:4	-

[a] Entry carried out by Dr. Stephan Knauer.

In **Table 24** are outlined the first results of the spirocyclisation using *Cinchona*-derived phase transfer catalysis (**Table 24** , entries 1,3 and 4). Surprisingly, the reaction gave full conversion of the starting material when NCS was used as the electrophile within 2 hours (**Table 24**, entries 1 and 2). The reaction is highly accelerated under the applied conditions whereas using Williams' procedure no conversion was observed at all (**Table 24**, entry 3). The resulting product of this reaction could not be obtained in pure form.

Performing the spirocyclisation with NBS and the *N*-benzylcinchonidinium chloride (*N*-Bn**CD**$^+$Cl$^-$) as catalyst yielded the bromo-substituted cyclised product **8** (**Table 24**, entry 4). It was found that the diastereomeric ratio is 5:1 (trans product favored) higher than in the racemic approach, 1:4 (**Table 24**, entries 5 and 6). Analysing the HPLC chromatogram of the product from the phase transfer-catalysed reaction (**Table 24**, entry 4) and comparising that with the racemic chromatogram (**Table 24**, entry 5) revealed an enantiomeric excess of 23% (36% of the minor diastereoisomer).

Based on these initial results it should be possible to further improve both the diastereomeric and the enantiomeric excess of this bromospirocyclisation.

In conclusion a new synthetic sequence for the formation of *O*-Me-hydroxamic acid ester **9** has been developed. The new route avoids the use of highly toxic reagents and can be easily scaled up. In comparison to Williams' approach it cuts out four steps (out of nine !) and more than doubles the overall yield of the sequence to obtain the hydroxamic acid ester **9**.

Moreover, a new spirocyclisation mediated by a *cinchona* alkaloid phase transfer catalyst has been introduced, obtaining an encouraging 23 % (36 %) of enantiomeric excess. Certainly this new methodology requires further optimization of all reaction conditions and employed components. An extensive screening of catalysts, favouring the members of the cinchonidinium and quininium ammonium salt series, amount and type of bromine source, as well as solvent system and temperature is strongly suggested.

3. Experimental Section

3.1. General information

Unless otherwise noted, all reagents were obtained from commercial suppliers and were used without further purifications. All solvents were reagent grade. Tetrahydrofuran was freshly distilled from calcium hydride and lithium aluminium hydride; acetonitrile, dichloromethane, methanol and toluene were freshly distilled from calcium hydride. All other solvents were anhydrous grade and used as received. All reactions were carried out under argon conditions using oven-dried glassware unless otherwise stated.

Analytical thin layer chromatography was carried out on Merck 60 F254 silica gel plates and visualized by UV irradiation (254 nm) or by staining with aqueous acidic ammonium hexamolibdate or aqueous basic potassium permanganate solutions followed by heating as appropriate. Flash column chromatography was carried out using Silica Gel 60 (0.040-0.063 mm) 230-400 mesh under pressure.

^{1}H NMR spectra were recorded on Bruker DPX 400 spectrometer in DMSO, deuterochloroform, MeOD, operating at 400 MHz. All signals are reported in ppm with solvents residual peaks HD_2CSOCD_3, HD_2COD, $CHCl_3$ as the internal reference (δ_c= 2.50, 3.31, 7.26 ppm). Abbreviations are defined as follows: s= singlet; d= doublet; t= triplet; q= quartet; m= multiplet or unresolved; br= broad.

^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometers operating at 100 MHz. All signals are reported in ppm with the central peak of DMSO, MeOD, $CDCl_3$, as internal reference (δ_c = 39.5, 49.0, 77.0 ppm).

COSY, DEPT 135, HMQC and HMBC were used to support assignments where appropriate.

High resolution mass spectra (HRMS) analyses were measured on a Micromass Q-TOF spectrometer using EI (electron impact) or ESI (electrospray ionisation) techniques.

The enantiomeric excess (*ee*) of product **8** was determined by chiral stationary phase SFC (supercritical fluid chromatography), using racemic sample for comparison.

3.2. Experimental procedures

5-Chloro-2,4-dihydroxybenzaldehyde 10

In a 1-L, 3-necked flask equipped with an overhead stirrer and condenser was added 25 g (0.14 mol, 1 eq.) of 4-chlororesorcinol and 40.0 g (0.34 mol, 2.0 eq.) of $Zn(CN)_2$, 200 ml of diethyl ether was added and the reaction was cooled to 0 °C. Dry gaseous HCl was passed through the rapidly stirred solution for 2 h until a solid mass formed. The ether was decanted and, 250-300 ml of water was added. The reaction was heated and any residual ether was distilled off. The reaction was refluxed until the solid mass dissolved entirely. Upon cooling the product crystallized as a red solid and was collected. Recrystallization from water gave **9** as yellow needles in 11 % yield.

^{1}H NMR ($CDCl_3$) δ 11.2 (s, 1H), 9.7 (s, 1H), 7.5 (s, 1H), 6.6 (s, 1H), 6.2 (s, 1H).

5-Chloro-2-hydroxy-4-(methoxymethoxy)benzaldehyde 11

A solution containing 3.42 g (19.8 mmol, 1.0 eq.) of 5-chloro-2,4-dihydroxybenzaldehyde **10** in 140 ml of THF was cooled to 0 °C and 2.77 ml (20.8 mmol, 1.05 eq.) of Et_3N was added in one portion. After that 2.26 ml (29.8 mmol, 1.5

eq.) of MOMCl was added over 15 minutes and the reaction mixture was warmed to room temperature and stirred for 3 h. The suspension was filtered through a Celite plug, diluted with ether and extracted three times with 0.2 M NaOH. The aqueous layer was carefully acidified with H_2SO_4 (1 M) in an ice bath until pH 5 and extracted with ethyl acetate (3 x 100 ml). The organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated, obtaining 3.45g of **11** as an orange solid (yield 80 %). The crude material was used for the next step without further purification.

^{1}H NMR ($CDCl_3$) δ 11.27 (s, 1H), 9.70 (s, 1H), 7.52 (s, 1H), 6.76 (s, 1H), 5.30 (s, 2H), 3.51 (s, 3H).

5-Chloro-6-(methoxymethoxy)benzofuran-2-carboxylic acid 12

A slurry consisting of 2.333 g (10.8 mmol, 1eq.) of 11, 2.3 ml (11.85 mmol, 1.1 eq.) of diethyl bromomalonate, and 2.32 g (16.1 mmol, 1.5 eq.) of dry potassium carbonate in 9.7 ml of 2-butanone were heated under reflux for 5 h. After that the reaction was concentrated to a thick brown oil which was added 20.3 ml of ethanol and 16.1 ml (32.31 mmol, 3 eq.) of NaOH 2 M and refluxed again for 2 h and 30 minutes. The aqueous solution was taken up in dilute NaOH, washed with ether, carefully acidified to pH 5 and the precipitated collected, getting 1.611 g of 12 as a pale yellow solid (yield 58 %) which was used without further purification.

^{1}H NMR (DMSO) δ 13.5 (br s, 1H), 7.87 (s, 1H), 7.57 (s, 1H), 7.55 (s, 1H), 5.37 (s, 2H), 3.42 (s, 3H).

5-Chloro-6-hydroxybenzofuran-3(2H)-one 14.

Dry Hydrogen chloride was passed for 35 minutes through a stirred mixture of 6.0 g (41.7 mmol, 1.0 eq.) of 4-chlororesorcinol, 3.4 ml (53.0 mmol, 1.3 eq.) of chloroacetonitrile, 29.4 ml (29.4 mmol, 0.7 eq.) of $ZnCl_2$ (1 M in ether) and 10 ml ether. After that, 150 ml of water were added. The aqueous solution was extracted with ether (3x70 ml), the organic phases were dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. The crude product showed 25% conversion of 4-chlororesorcinol and was purified by column chromatography, using a CH_2Cl_2/Et_2O mixture, affording 1.4 g of **14** as a pale yellow solid (yield 73%).

^{1}H NMR ($CDCl_3$) δ 11.94 (s, 1H), 7.70 (s, 1H), 6.65 (s, 1H), 6.14 (s, 1H), 4.57 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 194.7, 164.8, 158.9, 130.5, 112.7, 112.1, 105.4, 44.9. ESI-MS m/z 183.56 $[M-H]^-$, EI-MS m/z 184.2 $[M]^+$.

6-Chloro-7-hydroxy-2H-chromen-2-one 19.

To a mixture of 2.2 g (15 mmol, 1.0 eq.) of 4-chlororesorcinol and 2.0 g (15 mmol, 1.0 eq.) of L-(-)-malic acid well mixed was drop wise added 5 ml (94 mmol, 6.3 eq.) of concentrated sulphuric acid dropwise at r.t.. The mixture was heated to 80 °C until the frothing ceased. The reaction mixture was poured into 5 g crushed ice and the solid collected. The crude was recrystallized from ethanol (60 ml) obtaining 1.2 g of **19** as a pale pink solid (yield 41 %).

^{1}H NMR (DMSO) δ 11.26 (br s, 1H), 7.79 (d, J = 12.0 Hz, 1H), 7.66 (s, 1H), 6.83 (s, 1H), 6.23 (d, J = 12.0 Hz, 1H). ^{13}C NMR (DMSO) δ 160.3, 156.6, 154.0, 143.7, 129.1, 117.2, 113.0, 112.3, 103.6. ESI-MS m/z 197.38 $[M+H]^+$.

Dimethyl 2-acetoxy-3-bromosuccinate 20.

To 8.9 g (50 mmol, 1.0 eq.) of (+)-dimethyl L-tartrate was added 42 ml (231 mmol, 4.6 eq.) of hydrogen bromide (45% w/v in glacial acetic acid) at 0°C and the reaction was left

at r.t. for 18 h. After that the reaction mixture was poured onto 50 g crushed ice and extracted into Et_2O (5x100 ml). The organic layer was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude was purified by column chromatography using a CH_2Cl_2/AcOEt mixture as eluent, affording 7.42 g of **20** as a colourless viscous oil (yield 52%), that solidified upon standing.

^{1}H NMR ($CDCl_3$) δ 5.60 (d, J = 8.0 Hz, 1H), 4.84 (d, J = 8.0 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 169.7, 167.3, 166.7, 72.9, 54.0, 53.3, 43.5, 20.7. ESI-MS m/z 284.89 $[M+H]^+$.

3-Bromo-6-chloro-2-oxo-2H-chromen-7-yl acetate 21

To a mixture of 288 mg (2 mmol, 1.0 eq.) 4-chlororesorcinol and 566 mg (2 mmol, 1.0 eq.) of dimethyl 2-acetoxy-3-bromosuccinate **20** was added dropwise 0.6 ml (11 mmol, 5.6 eq.) of concentrated sulphuric acid at r.t.. The mixture was heated to 80°C until the frothing ceased. The crude material was poured onto 1 g ice and the solid collected. The crude product showed 80 % conversion and 20 % regioisomer 22, and was recrystallized from ethanol obtaining 150 mg (30 % yield) of **21** as a pale yellow solid.

^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.44 (s, 1H), 7.01 (s, 1H), 2.17 (s, 3H). ESI-MS m/z 275.29 $[M-Ac]^-$

Dimethyl 2-bromo-3-hydroxysuccinate 23

To 159 g (0.89 mol, 1.0 eq.) (+)-dimethyl L-tartrate were added 500 ml (2.75 mol, 3.1 eq.) of hydrogen bromide (45% w/v in glacial acetic acid) at 0°C and the reaction was left at r.t. for 3 days. After that the reaction mixture was poured onto 300 g ice and extracted with Et_2O (10 x 250 ml). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The crude product was taken up into 900 ml methanol, 17 ml acetyl chloride were added and refluxed for 18 h. The solvent was removed and the crude product purified by column chromatography using a CH_2Cl_2/AcOEt mixture as eluent, affording 160.5 g of **23** as colourless viscous oil (yield 75%).

^{1}H NMR ($CDCl_3$) δ 4.70 (d, J = 4.0 Hz, 1H), 4.66 (dd, J = 4.0, 8.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.43 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 171.1, 167.7, 73.0, 53.9, 53.6, 47.0. EI-MS m/z 181 (100 %), 183 (98 %) $[M-Me-CO_2]^+$.

3-Bromo-6-chloro-7-hydroxy-2H-chromen-2-one 15

To a mixture of 12 g (83 mmol, 1.0 eq.) 4-chlororesorcinol and 20 g (83 mmol, 1.0 eq.) of dimethyl 2-bromo-3-hydroxysuccinate **23** were added dropwise 33 ml (620 mmol, 7.5 eq.) concentrated sulphuric acid at 10 °C. The mixture was heated to 105°C for 4 h. The crude material was poured into 80 g ice and heatedto reflux. Ethanol was added until all solid was dissolved. After 18 h crystallisation at r.t. the solid was collected and dried to obtain 14 g of crude material, that was used for the next step without further purification (60% crude yield). The ^{1}H NMR spectrum showed 8 % impurity of the isomer **19**.

^{1}H NMR (DMSO) δ 11.45 (br s, 1H), 8.36 (s, 1H), 7.68 (s, 1H), 6.86 (s, 3H). ^{13}C NMR (DMSO) δ 157.0, 156.8, 153.3, 144.7, 128.5, 117.8, 112.8, 107.1, 103.5. ESI-MS m/z 274.91 $[M-H]^-$

5-Chloro-6-hydroxybenzofuran-2-carboxylic acid 16.

To 14 g of crude 3-bromo-6-chloro-7-hydroxy-2H-chromen-2-one **15** in 50 ml ethanol was added a solution of 36 g potassium hydroxide in 250 ml ethanol. The reaction was refluxed for 18 h. The solvent was removed under reduced pressure and 200 ml sodium

hydroxide (0.2 M) was added. The aqueous layer was washed with ether (2 x 100 ml) and the last traces of ether were carefully removed under reduced pressure. The solid formed upon acidification to pH 2-3 (HCl 3 N) was collected and dried, affording 8.75 g of **16** as a light brown solid (yield 85 %); (50 % yield from 4-chlororesorcinol), purity >95%.

^{1}H NMR (MeOD) δ 7.65 (s, 1H), 7.44 (s, 1H), 7.07 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 162.7, 157.2, 155.3, 147.5, 124.5, 121.9, 120.8, 115.1, 100.1. ESI-MS m/z 167.55 $[M\text{-}CO_2]^-$; EI-MS m/z 168.3 $[M\text{-}CO_2]^+$.

2-(4-Methoxybenzylamino)acetic acid 26.

To 14.5 ml (75.7 mmol, 1.05 eq.) of *p*-methoxylamine in 40 ml THF were added 20 ml (144 mmol, 2 eq.) triethylamine. After cooling to 0°C 8 ml (72, 1 eq.) ethyl bromoacetate were added dropwise. After 18 h the reaction was filtered through a Celite pad and the solvent removed under reduced pressure. The crude product was taken up in 20 ml ethanol and a solution of 5.8 g (144 mmol, 2 eq.) sodium hydroxide in 120 ml ethanol were added. After 18 h the solution was acidified to pH 6-7 (HCl 3 N), the solvent was removed. The crude was purified by column chromatography using CH_2Cl_2/MeOH/H_2O mixture as eluent, affording 13.80 g of **26** as pale yellow solid (quantitative yield).

^{1}H NMR (D_2O) δ 7.39 (d, J = 12.0 Hz, 1H), 7.00 (d, J = 12 Hz, 1H), 4.15 (s, 2H), 3.80 (s, 3H) 3.55 (s, 2H). ^{13}C NMR (D_2O) δ 171.7, 160.1, 132.0, 123.6, 115.1, 55.9, 50.6, 48.7. ESI-MS m/z 194.19 $[M\text{-}H]^-$.

2-(5-Chloro-6-hydroxy-N-(4-methoxybenzyl)benzofuran-2-carboxamido)acetic acid 13.

To 5 g (23.6 mmol, 1 eq.) 5-chloro-6-hydroxybenzofuran-2-carboxylic acid **16** in 240 ml CH_2Cl_2 and 176 ml THF were added 0.5 ml (6.5 mmol, 0.27 eq.) DMF and 2.4 ml (28.3 mmol, 1.2 eq.) oxalyl chloride at r.t.. After an hour, half amount of solvent was removed under reduced pressure and the resulting solutions was added to a well stirred solution of 5.5 g (28.3 mmol, 1.2 eq.) 2-(4-methoxybenzylamino)acetic acid **26** and 2.9 g (35.4 mmol, 1.5 eq.) sodium bicarbonate in 70 ml of water at r.t.. After 18 h the reaction was diluted with 100 ml ethyl acetate, and acidified to pH 2-3 using 3 N HCl. The organic layer was washed with water (2x50 ml, containing 0.5 ml of 3 N HCl), and brine, dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure, 6.59 g of **13** as brown solid was obtained (yield 72%), that was used for the next step without further purification.

^{1}H NMR (DMSO) δ 12.80 (br s, 1H), 10.62 (br s, 1H), 7.72 (s, 1H), 7.23 (br s, 2H), 7.08 (s, 1H), 6.90 (br s, 2H), 4.84 (br s, 1H) 4.60 (br s, 1H), 4.28 (br s, 1H), 3.97 (br s, 1H), 3.73 (s, 3H). ^{13}C NMR (DMSO) δ 160.2, 159.0, 154.1, 153.7, 153.1, 130.0, 129.1, 123.4, 123.0, 120.0, 119.6, 118.3, 114.4, 114.3, 112.1, 99.15, 99.0, 55.4. ESI-MS m/z 388.04 $[M\text{-}H]^+$

5-Chloro-2-((2-(methoxyamino)-2-oxoethyl)(4-methoxybenzyl)carbamoyl)benzofuran-6-yl acetate 9.

To 5.03 g (12.93 mmol, 1 eq.) 2-(5-Chloro-6-hydroxy-N-(4-methoxybenzyl)benzofuran-2-carboxamido)acetic acid **13** in 13 ml pyridine was added 13 ml acetic anhydride (at least 10 eq.) r.t.. After 4 h the solution was diluted with 50 ml ethyl acetate, washed with hydrogen chloride 3 N HCl (3x25 ml), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was codistilled with 20 ml toluene and 20 ml CH_2Cl_2 respectively to obtain dry crude material

that was used for the next step without further purification (the yield of the acetylation was considered >98 %).

^{1}H NMR (DMSO) δ 12.69 (br s, 1H), 7.97 (s, 1H), 7.70 (d, J = 20. Hz, 1H), 7.40 (d, J = 20.0 Hz, 1H), 7.28 (br s, 2H), 6.91 (br s, 2H), 4.82 (br s, 1H) 4.62 (br s, 1H), 4.31 (br s, 1H), 3.99 (br s, 1H), 3.73 (s, 3H), 2.34 (s, 3H).

To 431 mg (1.0 mmol, 1.0 eq.) of the acetylated crude product in **25** ml THF was added 0.13 ml (1.2 mmol, 1.2 eq.) *N*-methylmorpholine, followed by dropwise addition of 0.15 ml (1.2 mmol, 1.2 eq.) of isobutyl chloroformate. After 1 hour 0.11 ml (2.0 mmol, 2.0 eq.) of methoxylamine was added and the reaction was stirred at r.t. for 1.5 h. The reaction mixture was poured in 25 ml water and extracted with ethyl acetate (2 x 25 ml). The organic layer was washed twice with 15 ml 3 N HCl, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography, using a CH_2Cl_2/AcOEt mixture as eluent, affording 213 mg of **3** as a yellow solid (yield 50 %).

^{1}H NMR (DMSO) δ 11.23 (br s, 1H), 7.98 (s, 1H), 7.71 (d, J = 12.0 Hz, 1H), 7.39 (d, J = 12.0 Hz, 1H), 7.26 (br s, 2H) 6.91 (br s, 2H), 4.83 (br s, 1H) 4.58 (br s, 1H), 4.07 (br s, 1H), 3.84 (br s, 1H), 3.73 (br s, 3H), 3.54 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (DMSO) δ 168.8, 159.1, 152.7, 145.4, 130.0, 129.2, 128.5, 126.0, 123.1, 122.5, 114.3, 110.9, 108.3, 63.71, 55.45, 20.73. ESI-MS m/z 461.00 $[M+H]^+$.

3-Bromo-5-chloro-1'-methoxy-4'-(-4-methoxybenzyl)-3',6'-dioxo-3H-spiro[benzofuran-2,2'-piperazine]-6-yl acetate 8.

Racemic sample

To a solution of 20 mg (43 μmol, 1.0 eq.) 2-(5-chloro-6-hydroxy-N-(4-methoxybenzyl)benzofuran-2-carboxamido)acetic acid **13** in 1.29 ml $CHCl_3$ were added 10 mg (52 μmol, 1.2 eq.) NBS at r.t.. After 18 h stirring in th dark the crude material was directly purified by a column chromatography using a CH_2Cl_2/AcOEt mixture, affording 15 mg of **8** as a white solid (yield 65 %).

^{1}H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.27 (d, J = 8.0 Hz, $2H_{maj}$), 7.23 (d, J = 8.0 Hz, $2H_{min}$), 6.91 (d, J = 8.0 Hz, $2H_{min}$), 6.88 (d, J = 8.0 Hz, $2H_{maj}$), 6.78 (s, 1H), 5.97 (s, $1H_{maj}$, $1H_{min}$), 4.71 (d, J = 16.0 Hz, $1H_{maj}$, $1H_{min}$), 4.53 (d, J = 16.0 Hz, $1H_{min}$), 4.47 (d, J = 16.0 Hz, $1H_{maj}$), 3.98 (s, $3H_{maj}$, $3H_{min.}$), 3.92 (s, $3H_{maj}$, $3H_{min.}$), 3.81 (t, J = 4 Hz, $2H_{maj}$, $2H_{min}$), 2.36 (s, $3H_{maj}$, $3H_{min.}$). ^{13}C NMR (DMSO) δ 168.5, 162.1, 160.8, 160.3, 157.3, 149.3, 131.0, 126.8, 126.1, 125.1, 121.1, 114.8, 106.3, 102.2, 66.2, 55.7, 47.8, 48.7, 48.4, 21.0. ESI-MS m/z 540.97 $[M+H]^+$.

Chiral sample

To a solution of 20 mg (43 μmol, 1.0 eq.) 2-(5-chloro-6-hydroxy-N-(4-methoxybenzyl)benzofuran-2-carboxamido)acetic acid **13** in 0.5 ml of toluene was sequentially added 3.6 mg (8.6 mmol, 0.2 eq.) N-benzylcinchonidinium chloride, 0.11 ml (86 μmol, 2.0 eq.) of saturated aqueous sodium bicarbonate and 15 mg (86 μmol, 2.0 eq.) NBS. After 2 h stirring in the dark, the reaction mixture was filtered through a plug of silica. The ^{1}H NMR shows a 5:1 diastereomeric ratio. The crude product was purified by a column chromatography using a CH_2Cl_2/AcOEt mixture, affording 17 mg of **8** as a white solid (yield 73 %). The ee of the product was determined by SFC using a Daicel chiralcel OD-H column (SF-CO_2/i-PrOH = 90:10, flow rate = 3 ml/min, dia_{maj} τ_{maj} = 33.9 min, τ_{min} = 37.1 min, dia_{min} τ_{maj} = 45.32 min, τ_{min} = 48.6 min; λ = 210 nm).dia_{maj} 23 % ee, dia_{min} 36 % ee.

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