Department of Chemistry

Substrate Controlled Synthesis of 1,2-Amino Alcohols

Oskari Karjalainen

Aalto University

DOCTORAL DISSERTATIONS

Aalto University publication series
DOCTORAL DISSERTATIONS 159/2013

Substrate Controlled Synthesis of 1,2-Amino Alcohols

Oskari Karjalainen

A doctoral dissertation completed for the degree of Doctor of Science (Technology) to be defended, with the permission of the Aalto University School of Chemical Technology, at a public examination held at the Komppa Auditorium of the school on 16 November 2013 at 12.

Aalto University
School of Chemical Technology
Department of Chemistry
Koskinen Research Group

Supervising professor
Professor Ari Koskinen

Thesis advisor
Professor Ari Koskinen

Preliminary examiners
Professor Marcus A. Tius, University of Hawaii at Manoa, United States
Professor Peter Somfai, Lund University, Sweden

Opponent
Professor Mathias Christmann, Freie Universität Berlin, Germany

Aalto University publication series
DOCTORAL DISSERTATIONS 159/2013

ISBN 978-952-60-5369-1
ISBN 978-952-60-5370-7 (pdf)
ISSN-L 1799-4934
ISSN 1799-4934 (printed)
ISSN 1799-4942 (pdf)
http://urn.fi/URN:ISBN:978-952-60-5370-7

Unigrafia Oy
Helsinki 2013

Finland

441 697
Printed matter

Aalto University

Abstract

Aalto University, P.O. Box 11000, FI-00076 Aalto www.aalto.fi

Author
Oskari Karjalainen

Name of the doctoral dissertation
Substrate Controlled Synthesis of 1,2-Amino Alcohols

Publisher School of Chemical Technology

Unit Department of Chemistry

Series Aalto University publication series DOCTORAL DISSERTATIONS 159/2013

Field of research Organic Chemistry

Manuscript submitted 5 April 2013 **Date of the defence** 16 November 2013

Permission to publish granted (date) 18 June 2013 **Language** English

☐ **Monograph** ☒ **Article dissertation (summary + original articles)**

Abstract

1,2-Amino alcohols are a very common structural motif in a range of natural products. These 1,2-amino alcohol containing compounds range from important physiological constituents of human body, like the hormone epinephrine and the amino acid serine, to peculiar secondary metabolites, like amaminol and calyculin, encountered in deep sea creatures. Consequently these molecules display a range of interesting biological responses. This fact has spawned plethora of pharmaceuticals sporting the said moiety intended for treating conditions from asthma to HIV.

Given the importance of the 1,2-amino alcohol motif the synthetic methods to access them are well developed. This thesis aims to give an overview of possible synthetic strategies in the context of substrate controlled, eg. diastereoselective, synthesis with the emphasis on amino acid derived starting materials. In substrate controlled synthesis the fate of the forming stereocenters is controlled by the existing stereocenters in the molecule as opposed to enantioselective synthesis where chiral information is brought to achiral substrate by the action of an external source of chirality such as chiral catalyst. These strategies include additions to reagents to amino acid derived aldehydes, additions to amino acid derived ketones and oxidation of allyl amine. The total syntheses of 1-deoxyaltronojirimycin and trans-3-hydroxypipecolic acid described here demonstrate the first strategy.

It is also important to open up hitherto inaccessible portions of chemical space, that is develop new synthetic methods to hard-to-prepare compounds. Described herein is the synthesis of pentasubstituted 3-oxo-pyrrolidines via a palladium catalyzed diastereoselective allylative formal 5-endo-trig heterocyclization of in situ generated enones. The pyrrolidinones could also be further reduced *in situ* to the corresponding 1,2-amino alcohols or reacted with organometallic reagents to obtain pyrrolidinols with two consecutive quaternary stereocenters. These demonstrate the second strategy.

The cyclization mechanism was shown to be complex and not to conform to any known reaction mechanism. The cursory mechanistic studies in this thesis suggest an interrupted Nazarov reaction to be the most likely reaction mode. Amine additives were shown to affect the reaction mechanism in peculiar way and a plausible mechanistic proposal to account for their effect is given.

Keywords amino alcohols, amino acids, palladium catalysis, diastereoselective synthesis, total synthesis

ISBN (printed) 978-952-60-5369-1 **ISBN (pdf)** 978-952-60-5370-7

ISSN-L 1799-4934 **ISSN (printed)** 1799-4934 **ISSN (pdf)** 1799-4942

Location of publisher Helsinki **Location of printing** Helsinki **Year** 2013

Pages 154 **urn** http://urn.fi/URN:ISBN:978-952-60-5370-7

Aalto-yliopisto

Tiivistelmä

Aalto-yliopisto, PL 11000, 00076 Aalto www.aalto.fi

Tekijä
Oskari Karjalainen

Väitöskirjan nimi
Substraattiohjattu 1,2-aminoalkoholien synteesi

Julkaisija Kemian tekniikan korkeakoulu

Yksikkö Kemian laitos

Sarja Aalto University publication series DOCTORAL DISSERTATIONS 159/2013

Tutkimusala Orgaaninen kemia

Käsikirjoituksen pvm 05.04.2013 **Väitöspäivä** 16.11.2013

Julkaisuluvan myöntämispäivä 18.06.2013 **Kieli** Englanti

☐ **Monografia** ☒ **Yhdistelmäväitöskirja (yhteenveto-osa + erillisartikkelit)**

Tiivistelmä

1,2-Aminoalkoholit ovat erittäin yleinen rakenneosa, joka löytyy monenlaisista luonnonaineista aina ihmisen elitoiminnoille tärkeistä yhdisteistä, kuten hormoni epinefriini tai aminohappo seriini, erikoisiin syvänmeren eliöissä esiintyviin aineenvaihduntatuotteisiin kuten amaminoli tai calyculiini. Täten ei ole ihme, että tämän yhdisteluokan molekyyleillä esiintyy monenlaisia biologisia vasteita, joita on hyödynnetty monissa lääkeaineissa aina astman hoidosta HI-virusta vastaan taisteluun.

1,2-Aminoalkoholiosasen tärkeydestä johtuen synteesitekniikat sen valmistamiseksi ovat pitkälle kehittyneitä. Yhtenä tämän väitöskirjan tavoitteista on antaa yleiskuva 1,2-aminoalkoholien synteesistrategioista diastereoselektiivisen synteesin puitteissa keskittyen erityisesti aminohapoista johdettuihin lähtöaineisiin. Diastereoselektiivisessä, eli substraattikontrolloidussa, synteesissä molekyylissä jo olevia stereokeskuksia käytetään ohjaamaan syntyvien stereokeskuksien stereokemiaa. Enantioselektiivisessä synteesissä taas kiraalinen informaatio tuodaan jostain erillisestä lähteestä, kuten katalyytistä, akiraaliseen substraattiin. Väitöskirjassa käsitellyt strategiat ovat additiot aminohapoista johdettuihin aldehydeihin, additiot aminohapoista johdettuihin ketoneihin sekä allyyliamiinien hapetus. Näistä ensimmäistä strategiaa edustavat väitöskirjassa esitetyt 1-deoksialtronojirimysiinin ja 3-hydroksipipekolihapon kokonaissynteesit.

Tässä väitöskirjassa esitetään *in situ* muodostettujen enonien palladiumkatalysoitu diastereoselektiivinen allyloiva 5-endo-trig hetorosyklisointi joka johtaa pentasubstituoituihin 3-okso-pyrrolidiineihin. Pyrrolidinonit voitiin edelleen pelkistää *in situ* vastaaviksi 1,2-aminoalkoholeiksi tai antaa reagoida organometallireagenssien kanssa, jolloin syntyi kaksi peräkkäistä stereokeskusta omaavia pyrrolidinoleja. Tämä menetelmä edustaa toista väitöskirjassa käsiteltyä synteesistrategiaa.

Syklisointimekanismin näytettiin olevan monimutkainen ja ennennäkemätön. Alustavien mekanististen tutkimusten perusteella eräänlainen keskeytetty Nazarov-reaktio vastaa parhaiten kokeellista dataa. Amiinilisäaineiden osoitettiin vaikuttavan reaktiomekanismiin erikoisella tavalla ja mahdollinen reatiomekanismi, joka selittää tämän vaikutuksen on esitetty.

Avainsanat aminoalkoholit, aminohapot, palladiumkatalyysi, diastereoselektiivinen syntheesi, kokonaissynteesi

ISBN (painettu) 978-952-60-5369-1 **ISBN (pdf)** 978-952-60-5370-7

ISSN-L 1799-4934 **ISSN (painettu)** 1799-4934 **ISSN (pdf)** 1799-4942

Julkaisupaikka Helsinki **Painopaikka** Helsinki **Vuosi** 2013

Sivumäärä 154 **urn** http://urn.fi/URN:ISBN:978-952-60-5370-7

Acknowledgements

The work reported in this thesis was carried out in the Aalto University School of Chemical Technology during 2010-2013. The work was financed by the National Graduate School Organic Chemistry and Chemical Biology, for which I am deeply grateful. The generously long continuous funding period enabled me to focus on the matters at hand instead of the constant battle for grants.

First and foremost I will give my earnest thanks to my supervisor Professor Ari Koskinen for all the help and advice during the years, and for the freedom to pursue my own research interest. Without the freedom to try out even the most harebrained idea the work presented herein wouldn't have been possible.

Tiia Juhala and Johanna Mareta are gratefully acknowledged for timely HRMS analyses as is Dr. Jari Koivisto for keeping the NMR facility in such a good shape.

Big thanks to the Koskinen group in general; Antti, Essi, Annika, Christopher, Aino and Andrejs, you have made our group a wonderful place to work in! Without you guys it just wouldn't have been the same! I would also like to extend my thanks to the former colleagues Dr. Peter Huy, Dr. Esa Kumpulainen, Dr. Mikko Myllymäki, Dr. Antti Pohjakallio, M.Sc. Aki Abe and especially to my Master's supervisor M.Sc. Mikko Passiniemi for good times in the olden days.

I am grateful for the Professors Peter Somfai and Marcus Tius for taking the time to review this thesis. Your comments and suggestions are deeply appreciated.

I would also like to thank all the undergraduate students that I have had the privilege to teach, especially Jemina Deldicque and Harry Eastman who had the misfortune of having to work with me for a better part of a year.

Outside the labs my warmest thanks go to my loving wife Maaret and our two sons for just being for me through this long journey. Also to my parents, brother and friends - you have given me the perfect counterbalance to the strenuous life a lab rat.

Table of Contents

List of Publications

The thesis consists of an overview of the authors work and related literature and of the following publications. The publications are referred to in the text by their Roman numerals.

I Karjalainen, O. K.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2012**, *10*, 4321-4326.

II Karjalainen, O. K.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2011**, *9*, 1231-1236.

III Karjalainen, O. K.; Koskinen, A. M. P. *Synlett* **2013**, *Submitted manuscript.*

IV Karjalainen, O. K.; Nieger, M.; Koskinen, A. M. P. *Angew. Chem. Int. Ed.* **2013**, *52*, 2551-2554.

Author's Contribution

The author has contributed to the publications as stated below.

I	The author wrote the article with the co-author.
II	The author designed and carried out the experiments and analyses. The article was written with the co-author.
III	The author designed and carried out the experiments and analyses. The article was written with the co-author.
IV	The author designed and carried out the experiments and analyses except for the crystal structure which was measured and elucidated by co-author (M. N.). The article was written with the co-authors with M. N. being responsible for the crystallography related notions.

Abbreviations and Symbols

Ac	acetyl
Alloc	allyloxycarbonyl
API	active pharmaceutical ingredient
BAIB	bis(acetoxy)iodobenzene
Boc	*t*-butyloxycarbonyl
Bt	benzotriazolyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
CDI	1,1-carbonyldiimidazole
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DGJ	deoxygalactonojirimycin
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	*N,N*-dimethylaminopyridine
DMFDMA	dimethylformamide dimethylacetal
DMSO	dimethylsulfoxide
DNJ	deoxynojirimycin
dppb	1,1-bis(diphenylphosphino)butane
dppm	1,1-bis(diphenylphosphino)methane
dr	diastereomeric ratio
ee	enantiomeric excess
Fmoc	fluorenylmethyloxycarbonyl
HFIP	hexafluoroisopropanol
HMDS	hexamethyldisilazane or bis(trimethylsilyl)amine
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high pressure liquid chromatography
HWE	Horner-Wadsworth-Emmons reaction

*m*CPBA	*m*-chloroperbenzoic acid
Ms	methanesulfonyl
MS	molecular sieves
MTBE	methyl *t*-butyl ether
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
Pg	protecting group
Piv	pivaloyl
PMB	*p*-methoxybenzyl
Py	pyridine
TBAI	tetrabutylammonium iodide
TBS	*t*-butyldimethylsilyl
TC	thiophene-2-carboxylate
TEA	triethylamine
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
Tr	trityl (triphenylmethyl)
Ts	*p*-toluenesulfonyl

1. Introduction

β-Amino alcohols (or 1,2-amino alcohols) are a very common structural motif in a range of natural products. Several diverse examples are presented in Figure 1. The first rows contain six common molecules found in the human body and other organisms. Threonine and serine are common amino acids and thus found in proteins. Epinephrine (also known as adrenaline) is a hormone and a neurotransmitter. Sphingoids (such as sphingosine) are encountered in the cell membranes and are also important in regulating cell events such as apoptosis.[1] Neuraminic acid is a crucial part of the gangliosides (glycosylated sphingoids) found in neuronal membranes. Finally, we have acetylcholine; the first ever neurotransmitter to be characterized by mankind by Otto Loewi in 1921, a feat which was awarded with a Nobel Prize in Physiology or Medicine in 1936.

The next two rows represent molecules isolated elsewhere from Nature. The piperidinol febrifugine has antimalarial properties[2] and amaminol (also considered to be a sphingoid with the C18 skeleton) has some potent anti-cancer activity.[3] The sugar-like nojirimycin inhibits glycosidases[4] and quinine is one of the oldest anti-malarial agents. The last compound in the series is the highly complex spiroketal calyculin C, a very potent protein phosphatase inhibitor.[5]

Given all these diverse types of the 1,2-amino alcohol moiety found in Nature coupled with the plethora of biological responses they effect it is not surprising that the pharmaceutical industry has capitalized on this enormously. The last two rows of Figure 1 show examples of marketed APIs sporting the 1,2-amino alcohol domain. Beginning with some simple compounds, salbutamol is reminiscent of epinephrine and consequently affects the same receptors, in this case the β_2 adrenergic receptor, where it acts as an agonist providing relief from the symptoms of asthma. Metoprolol, another epinephrine look-alike, also affects the same system but the β_1 adrenergic receptor present in the cardiovascular system where it acts as an antagonist. Metoprolol is used to treat conditions such as hypertension and the heart failure. Tiotropium is an antagonist of the muscarinic acetylcholine receptors (mAChR) and is used to treat chronic obtrusive pulmonary disease. Note that tiotropium is a lot more complex than the native agonist acetylcholine. Zanamavir is structurally related to the sialic acid neuraminic acid. Its function is to inhibit the enzyme neuraminidase, which is necessary for contraction of influenza

virus. Consequently it is used to treat the avian flu. The last example on the marketed drugs shows an unusual tripeptide with all unnatural amino acids. Atazanavir is a protease inhibitor antiretroviral and is used to treat HIV.

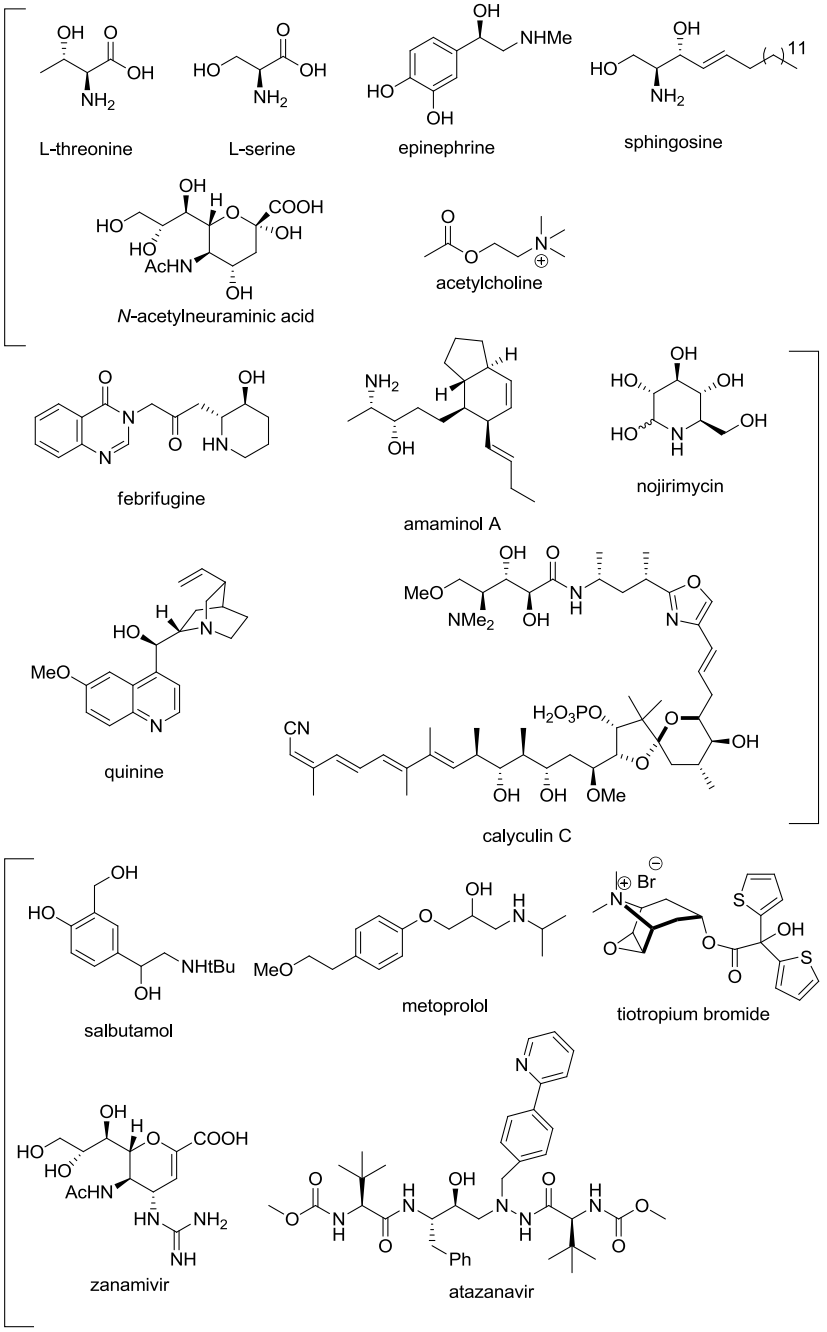


Figure 1. Examples of biologically relevant amino alcohols.

Due to the importance of the amino alcohol moiety its synthesis has been studied extensively. Enantioselective synthesis relies on the introduction of chiral information into an achiral substrate through the use of a chiral catalyst, auxiliary or reagent.[6] In the context of β-amino alcohols the most straightforward enantioselective methods are arguably the asymmetric Henry-reaction[7] (i.e. aldol reaction between an aldehyde and a nitro compound, Figure 2 A) and the asymmetric Mannich-reaction[8] (i.e. aldol reaction between an aldimine and in this case a hydroxyl ketone, Figure 2 B). While becoming more and more important, asymmetric methods often require expensive catalysts or suffer from narrow substrate scope.

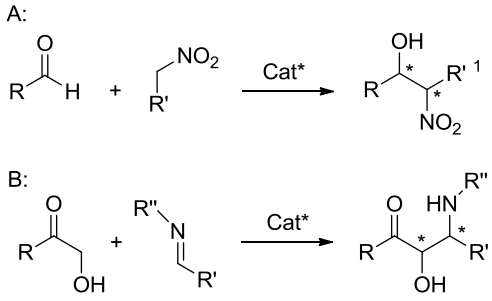


Figure 2. Enantioselective methods for construction of the 1,2-aminoalcohol moiety.

On the other hand, substrate controlled synthesis uses the existing chiral information within the molecule itself to control the fate of the forming stereocenters.[6a,] This approach capitalizes on the use of simple naturally occurring chiral compounds such as amino acids, sugars and some terpenes as inexpensive starting points for synthesis. This reservoir of naturally occurring, readily available materials is known as the chiral pool. When 1,2-amino alcohols are concerned, amino acids provide the ideal starting material; the often difficult to introduce amino functionality is already in place together with at least one functional handle. Natural L-amino acids are very affordable and today also many of the D-amino acids are available in bulk quantities. As far as chemists are concerned, the chiral pool based on solely natural products is rather obsolete as many unnatural enantiopure compounds are being produced on industrial scale today. For example, BASF sells many enantiopure phenethylamines and alkyl amines under the trade name ChiPros® in large quantities. This gives the chemists access to a broader "chiral pool" than ever before. The emphasis of this thesis will be solely on the substrate controlled synthesis.

Figure 3 summarizes the three conceptually different methods commonly used to synthesize 1,2-amino alcohols from amino acid derivatives. The first one is the addition of nucleophiles, such as organometallics to amino acid derived amino aldehydes. The second one uses a nucleophile to attack amino acid derived ketones. Most commonly the nucleophile is the hydride ion or equivalent and results in reduction. The overall outcome of the additions depends heavily, and sometimes unpredictably, on the actual nature of the substrate, protecting groups used (R' and R'') and the nature of the nucleophile as well as on external conditions. The third common strategy is the oxidation of an amino acid derived (often synthesized *via* a Wittig type reaction from the corresponding aldehyde) allyl amine to give an epoxide or a diol. These approaches have been reviewed in a recent paper by the author and shall be only briefly looked at.[I] Instead, the aforementioned review will act as a "glue" to bind the humble bits of knowledge produced by the author into a coherent Thesis.

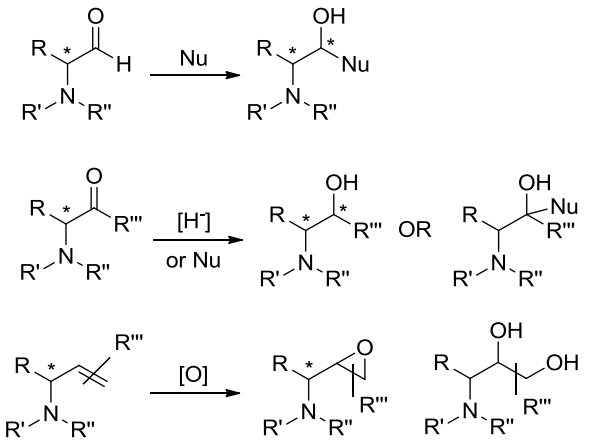


Figure 3. Conceptualizations of common methods for 1,2-amino alcohol synthesis.

This thesis culminates in the brief glance into the synthesis of highly substituted 3-oxo-pyrrolidines via an allylative formal 5-*endo-trig* heterocyclization. This novel transformation enables facile access to this hitherto restricted part of the chemical space. The pyrrolidinones in turn can be transformed into pyrrolidin-3-ols, a cyclic version of the 1,2-amino alcohol moiety. Finally, the mechanism of the hetero cyclization is examined in some detail and a plausible proposition is given.

2. Additions to Aminoaldehydes

The most important selectivity deciding factor in the addition of organometallic reagents to α-amino aldehydes is arguably the type of protection on the nitrogen atom. Consequently, the aldehydes are divided roughly into the three classes pictured in Figure 4. The first class corresponds to singly protected aldehydes. Most often the protecting group is a carbamate like *tert*-butyloxycarbonyl (Boc) or sulfonamide like *p*-toluenesulfonate (Ts). Type I amino aldehydes are notoriously unstable and usually cannot be isolated in enantiomerically pure form. Type II amino aldehydes correspond to doubly, often bis-benzyl, protected aldehydes. Such aldehydes are significantly more stable than type I ones, but still tend to epimerize during purification.[9] The type III amino aldehydes are a special case of the doubly protected aldehyde where a cyclic molecule is formed. The molecule in the figure is the serinal derivative known as Garner's aldehyde, but analogous structures have been made from threonine and cysteine as well.[10,11] We have made extensive use of Garner's aldehyde and found it to be configurationally stable even after years of storage.

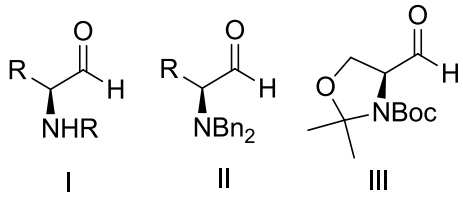


Figure 4. The three types of amino aldehydes.

The additions can be rationalized using the Felkin-Anh/Cram-chelate models (Figure 5). In the Felkin-Anh model the electronegative substituent is placed perpendicular to the carbonyl axis because of favourable orbital interaction (n → $C{=}O^{\pi^*}$). The nucleophile approaches the carbonyl from the least hindered face along the Bürgi-Dunitz angle. This leads to the formation of the *anti*- or Felkin-product. In the Cram-chelate model the nitrogen and the carbonyl oxygen are chelated together by some agent, usually a metal cation. Now the addition must take place from the other face of the carbonyl group to give the *syn*- or *anti*-Felkin

product. Thus, it is easy to rationalize the large effect of the nitrogen protecting groups on the selectivity.

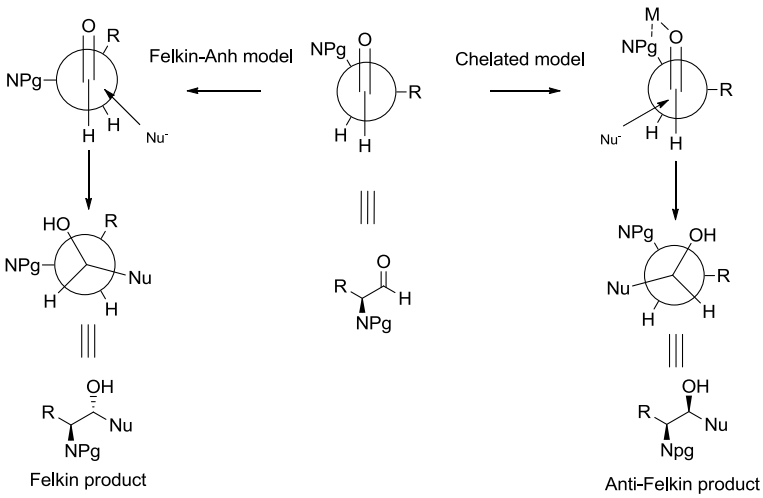
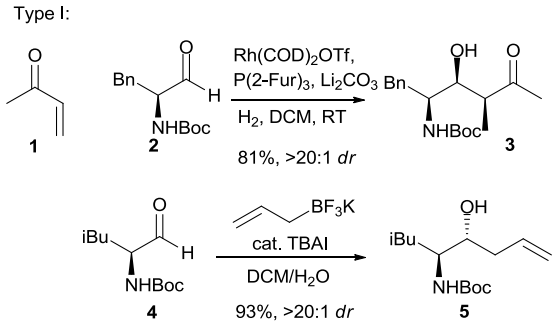


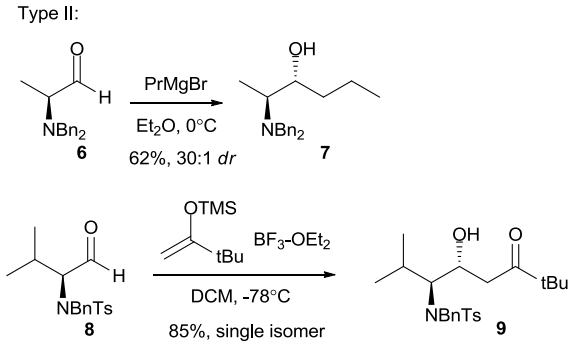
Figure 5. Models used to explain the stereochemistry of nucleophilic additions to aldehydes.

Type I amino aldehydes normally exhibit low to mediocre diastereoselectivity when reacted with typical organometallics such as Grignard reagents or organolithium compounds. However, under specific conditions very good results can be obtained. As shown in Scheme 1, type I aldehydes can be made to react under chelate control or under Felkin control. Krische *et al.* showed that under rhodium catalysis enones such as **1** react with Boc protected amino aldehydes **2** with excellent *syn* selectivity.[12] If run in the presence of an alcohol the selectivity was eroded, thus supporting the chelate model. Tetrabutylammonium iodide catalyzed addition of potassium allyl trifluoroborate to a similar aldehyde (**4**) on the other hand proceeded with high *anti* selectivity.[13] However, as stated before, the usefulness of such compounds is limited as they usually cannot be synthesized in enantiopure form.



Scheme 1. Additions to type I aldehydes.

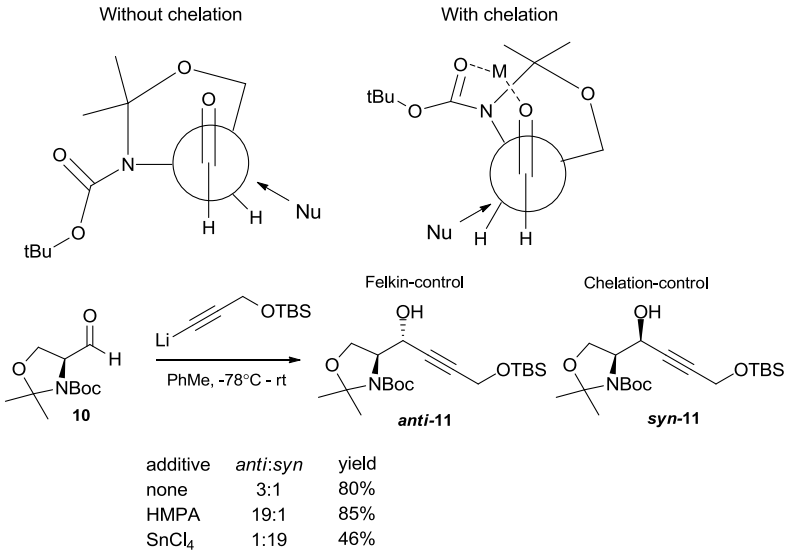
Type II amino aldehydes typically react with excellent *anti* selectivity. Even in the presence of chelating metals such as titanium the selectivity cannot be effectively reversed. Scheme 2 displays two examples: a Grignard addition[14] and a Mukaiyama aldol.[15] Both proceed with near complete Felkin-control. Reportedly, the selectivity can be reversed under Sakurai conditions, albeit this limits the scope to allylic nucleophiles and the obtained yields were moderate.[14]



Scheme 2. Additions to type II aldehydes.

The type III amino aldehydes tend to exhibit moderate *anti* selectivity towards most Grignard reagents and lithium nucleophiles. However, the exact conditions can affect the overall selectivity tremendously. In Scheme 3 the two addition modes are exemplified by addition of a lithium acetylide under two different conditions to **10**. Without any additives a mediocre *anti*-preference is observed. However, in the presence of HMPA, which breaks up the lithium aggregates, almost complete *anti*-selectivity is achieved. In the presence of a chelating metal *syn*-addition product is obtained and as shown, the chelation is thought to involve the carbamate oxygen.[16]

Type III:



Scheme 3. Addition to a type III aldehyde.

We have used the Garner's aldehyde to access nojirimycin analogues. Nojirimycins are a diverse class of polyhydroxylated piperidine alkaloids which, due to their sugar mimicking structure, inhibit glycosidase enzymes.[17] The two best known derivatives are probably *N*-butyl-1-deoxynojirimycin (miglustat) which is sold under the trade name Zavesca® for the treatment of Gaucher's disease and *N*-hydroxyethyl-1-deoxynojirimycin (miglitol), an antidiabetic (Figure 6). In Gaucher's disease glycosphingolipids accumulate in cells due to either mutation in or lack of glucosylceramidase enzyme. Zavesca slows down the biosynthesis of glycosphingolipids by inhibiting glycosylceramide synthase thus bringing the sphingolipid metabolism into balance. Miglitol works by inhibiting glycosidases in the intestinal tract thus lowering sugar intake.

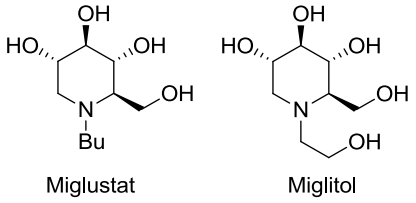
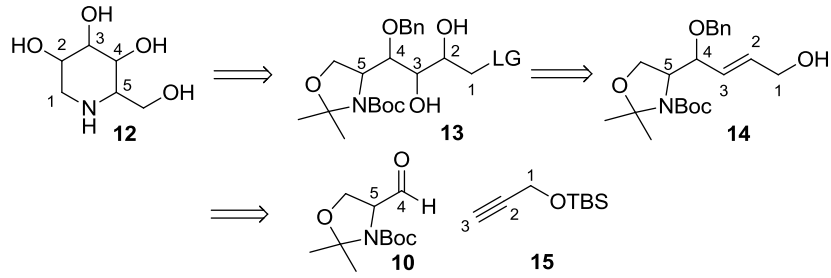


Figure 6.Two marketed nojirimycin derivatives.

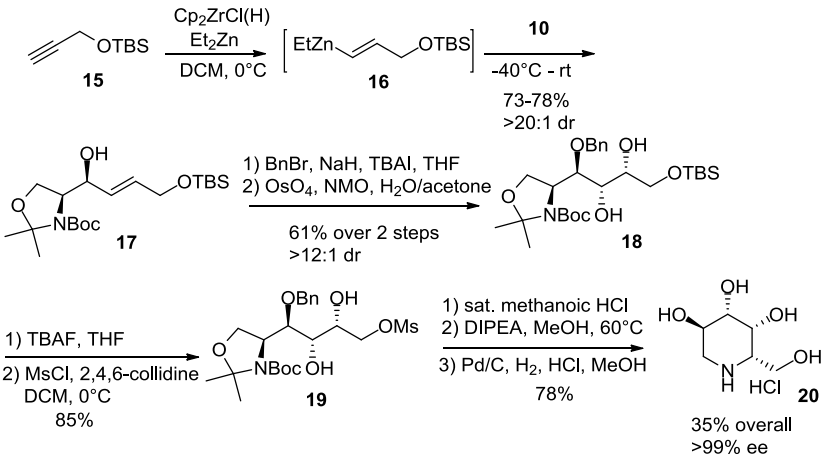
Our retrosynthesis for the 1-deoxynojirimycin scaffold is shown in Scheme 4. Scission of the N-C1 bond in **12** leads to structure **13**, which in turn can be envisioned to arise from dihydroxylation of the allyl alcohol **14**. According to the Kishi model, the addition should take place *anti* with respect to the C4 stereocenter.[18] Thus, controlling the addition of a propargyl equivalent to Garner's aldehyde (**10**), which generates the C4 stereocenter, becomes paramount for the success of the syntheses. Garner's aldehyde is an ideal starting point for the synthesis of the nojirimycin scaffold as it contains two of the hydroxy groups, half of the nojirimycin carbons and can be readily accessed in multi-decagram scale. Using this general retrosynthesis we targeted two specific 1-deoxynojirimycins, one which would require *syn*-addition (1-deoxygalactonojirimycin) and one which would require *anti*-addition (1-deoxyaltronojirimycin) of the propargyl moiety.



Scheme 4. Retrosynthetic analysis for deoxynojirimycins.

To access the *syn*-diastereomer we opted to use a vinyl zinc reagent as *per* a promising literature precedent (Scheme 5).[19] The zinc nucleophile **16** was generated from silyl protected propargyl alcohol **15** via hydrozirconation followed by transmetallation to zinc.[20] The vinyl zinc species then added to the aldehyde with virtually full chelation control to deliver the allylic diol **17**. This formal reductive coupling was found to be scalable and was later proven to be mild enough to completely preserve the labile α-stereocenter. The secondary alcohol was benzyl protected and the resulting compound was subjected to dihydroxylation to give the tetraol **18** in good yield and high selectivity. Chemoselective installation of the leaving group at the terminal hydroxyl proved to be surprisingly simple; after silyl group removal mesylation using collidine as base furnished the primary mesylate **19** in 85% yield over 2 steps. Next the acetonide and Boc protections were removed and the cyclization was brought about using DIPEA in hot methanol. Finally, hydrogenolysis of the benzyl group furnished the target

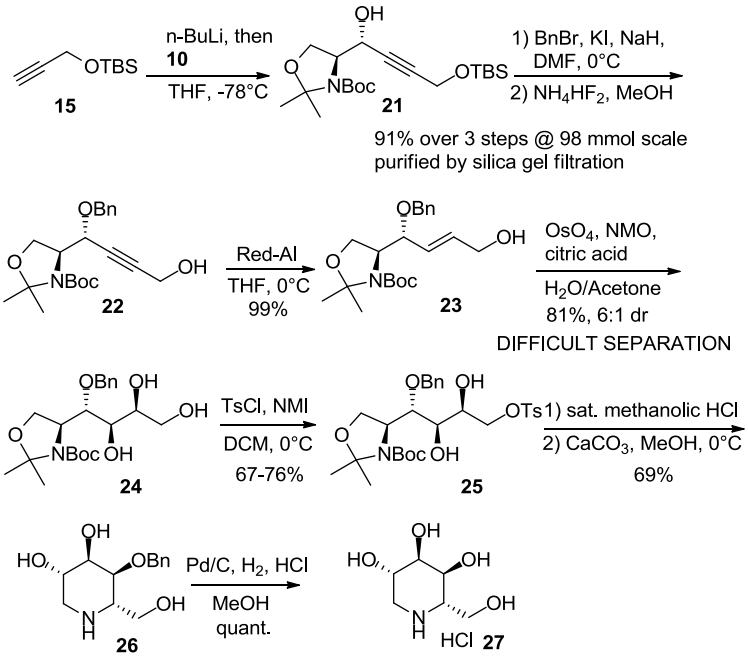
compound (-)-1-deoxygalactonojirimycin (**20**) as a crystalline hydrochloride salt in 78% yield over 3 steps and in 35% overall yield from Garner's aldehyde.[21]



Scheme 5. The total synthesis of (-)-1-deoxygalactonojirimycin.

Next, we tackled 1-deoxyaltronojirimycin **27**.[II] The synthesis should proceed using the same sequence as above, except that we needed to achieve a Felkin controlled addition of the vinyl zinc species. Despite careful experimentation we were unable to reverse the selectivity of the addition. Alongside with this issue, we wanted to improve the now so typical academic synthesis by seriously cutting down on the number of chromatographic purifications, the number of which amounted to 5 in the DGJ synthesis. To rectify the selectivity problem we started off with the results reported by Jurczak on the addition of TBS protected propargyl alcohol to Garner's aldehyde (Scheme 3). First of all, we wanted to replace the HMPA with something less toxic and to our delight simply running the reaction in THF provided the alkynol **21** in high yield, purity and diastereoselectivity (>15:1). Attempted partial reduction of the alkyne with Red-Al produced an unexpected side product: an allene resulting from the elimination of TBSO. The Red-Al reduction requires a coordinating group in order to work, so we simply changed the order of the reactions. We first benzyl protected the secondary alcohol under improved conditions: the solvent was changed to DMF (although NaH and DMF are known to react violently,[22] we encountered no problems when the mixture was kept below room temperature) to improve solubility of NaH and the iodide source was changed to the cheaper KI. This way the reaction proceeds at lower temperature and with cleaner outcome with excess BnBr as the only impurity. The desilylation conditions were also changed: the relatively expensive TBAF was substituted with ammonium bifluoride, which is an inexpensive glass etching

chemical. This way the tetrabutylammonium residues, which can be difficult to remove on scale, are avoided. The three step sequence was readily scaled up to nearly 100 mmol. Satisfyingly, treatment of **22** with Red-Al provided the *E*-alkene in quantitative yield without need to resort to chromatography. Dihydroxylation of **23** under modified Upjohn conditions[23] provided the tetraol in good yield and with the selectivity expected on the basis of the Kishi model. However, separation of the diastereomeric mixture proved to be very difficult with multiple consecutive chromatographic purifications needed to provide a sample of diastereopure material. Although this route was clearly not up to the standards set at the start, we continued to validate the rest of the sequence. While the mesylation chemistry worked admirably well in the *galacto*-series, mesylation of **24** only led to decomposition. The corresponding tosylate (**25**) on the other hand was isolatable, and after some experimentation reproducible conditions for its installment could be established. The key here was to use *N*-methyl imidazole as the base. All other bases tested gave inferior yields, most likely due to the fragile nature of the compound.

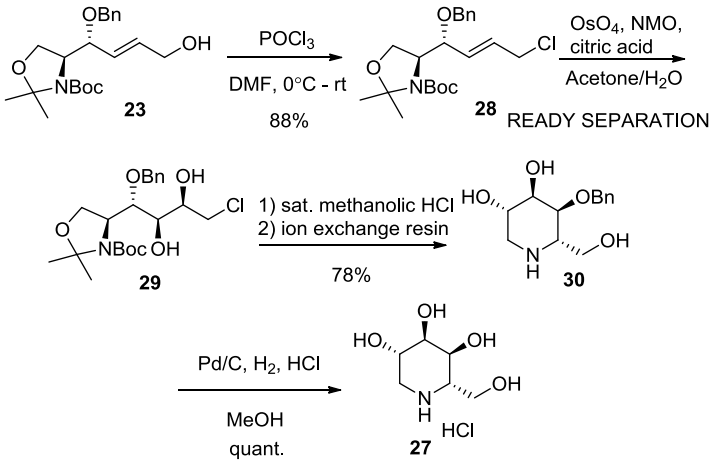


Scheme 6. The total synthesis of (-)-1-deoxyaltronojirimycin.

While the deprotection with methanolic HCl worked smoothly, the cyclization using the method established during the DGJ synthesis provided a new surprise: after benzyl group cleavage we were left with a yellow oil and no means to remove

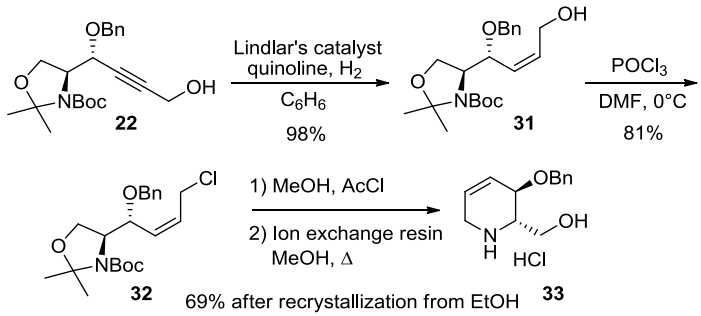
the impurities. Thus, severe tinkering was required to deliver the end product in adequate purity. First we changed the organic base to an inorganic one, but this only partly dealt with the problem. Although clean by ^{1}H-NMR, the crude product was contaminated with inorganic impurities. The key improvement came from the tosylation reaction; a side product was often detected on TLC, which was later confirmed to be the chloride **29** (Scheme 7). The chloride appeared to be much more stable and its cyclization should be much cleaner as there would be no tosylate impurities to deal with. Indeed, **29** was taken through the cyclization step and proved to be a viable alternative to the tosylate. Thus, a new route was conceived to access this new key intermediate.

It turned out that the allylic alcohol **23** could be readily chlorinated under various conditions (Scheme 7). After some experimentation phosphorous oxychloride in DMF proved to be the best alternative delivering the allylic chloride **28** in one chromatography free operation. Pleasingly, dihydroxylation of the electron deficient alkene went smoothly without any erosion of selectivity or yield. The diastereomers were also now much easier to separate. Final improvement was made to the cyclization procedure by substituting the base with a basic ion exchange resin. This way the crude free base **30** was of much higher quality and could be further upgraded by eluting through a short silica column. After hydrogenolysis in the presence of hydrochloric acid (-)-1-deoxyaltronojirimycin was obtained as the hydrochloride salt in excellent purity. Thus, the number of chromatographic purifications from the previous synthetic route were diminished from 5 to two. The final purification can be omitted if a suitable crystalline salt is discovered.



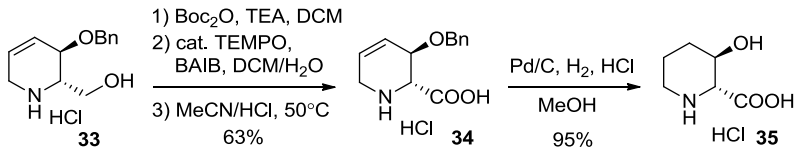
Scheme 7. Improved endgame for the synthesis of (-)-1-deoxyaltronojirimycin.

As a part of one of our projects we required a scalable access to the tetrahydropyridine **33**. This type of building block is highly useful and has been used to access nojirimycins and sialic acid derivatives. Consequently the *altro*-DNJ synthesis provided the means to do this (Scheme 8).[III] Starting from intermediate **22** a *cis*-hydrogenation under Lindlar conditions furnished the *Z*-alkene in high yield together with some (<5%) *E*-alkene. This impurity turned out to be of no consequence as it was readily purged during crystallization of **33**. Allylic chlorination with $POCl_3$ gave the allylic chloride **32**, which was subjected to the deprotection-cyclization procedure established above. The crude product was then crystallized from ethanol to furnish **33** as colorless needles in a completely chromatography free sequence. This synthesis was used to deliver over 10 g of the target compound in a single batch.



Scheme 8. Synthesis of the tetrahydropyridine **33**.

The usefulness of **33** was quickly demonstrated by converting it in 4 steps to *trans*-3-hydroxy pipecolic acid[24] (**35**) as described in scheme 9. Initially **33** was Boc-protected under standard conditions. This protection proved absolutely necessary, as the oxidation of **33** failed under a multitude of conditions. It should be noted that the Boc carbamate was the only stable carbamate. The other carbamates tended to form the intramolecular cyclic carbamate over time. The primary alcohol was cleanly oxidized using the mild TEMPO/BAIB system.[25] Then Boc was cleaved and the intermediate amino acid was obtained as a solid. The solid was purified by slurrying it in *i*PrOH/heptane to give the acid in 63% yield over 3 steps on 9 mmol scale. It proved critical to remove all traces of iodobenzene at this stage as it proved to inhibit the final hydrogenolysis. With pure **34** the hydrogenolysis in MeOH proceeded without problems. The final product was decolorized by slurrying it in EtOH/$CHCl_3$ to give the pure **35** in 95% yield.

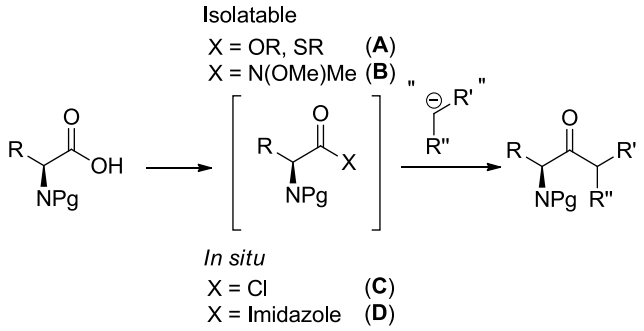


Scheme 9. Synthesis of *trans*-hydroxypipecolic acid.

3. Amino Ketones

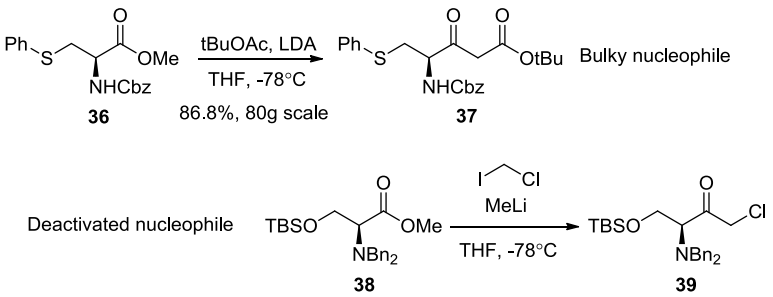
3.1 Synthesis of acyclic amino ketones

Simply put, amino ketones are synthesized from amino acids by addition of a carbanion or its equivalent to an activated form of the acid. The enantiopurity of the product ketone is highly dependent on the type of nucleophile and the optimal method of activation must in most cases be determined for each substrate individually. Scheme 10 displays four common activation methods used widely today and have been roughly devided into two distinct classes: Isolatable (**A**, **B**) and non-isolatable intermediates (**C**, **D**).



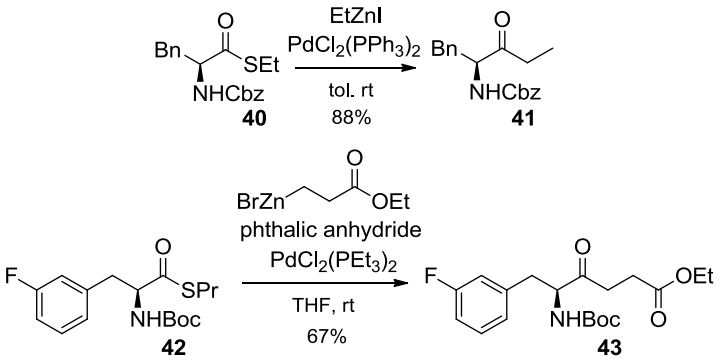
Scheme 10. Synthesis of ketones *via* activated amino acids.

A very convenient activated form of an acid is the corresponding ester (**A**). However, normal esters are often too reactive towards most organometallic reagents and therefore prone to over react. Nevertheless, deactivated or bulky hard nucleophiles can give good results, like in the preparation of a β-ketoester by cross-Claisen condensation or in the preparation of chloroketones (Scheme 11).[26,27]



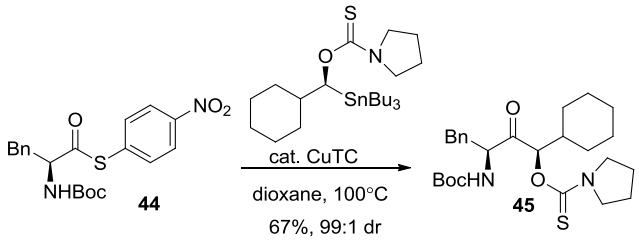
Scheme 11. Ester as an activated amino acid.

Esters typically are too reactive towards most organometallics since the product ketone is more reactive than the ester itself. Using less reactive organometallic species which do not readily react with ketones in conjunction with highly reactive esters is a workaround for this problem. As demonstrated in Scheme 12 alkyl zinc reagents readily add to thioesters under palladium catalysis. Fukuyama reported that the additions take place without any epimerization (top of Scheme 12) with zinc iodides.[28] Li *et al.* from Pfizer on the other hand reported that under their conditions (lower portion of Scheme 12) complete racemization occured.[29] This was completely avoided by adding three equivalents of phthalic anhydride to scavenge the propyl thiolate from the mixture.



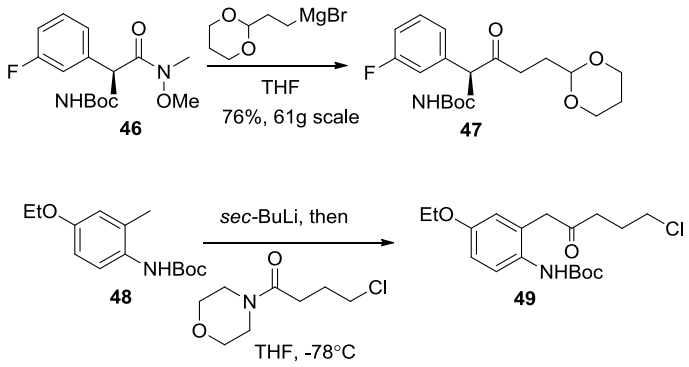
Scheme 12. Palladium catalyzed additions of alkyl zinc reagents to thioesters.

Liebeskind has reported a highly diastereoselective addition of α-hydroxystannanes to nitrothiophenyl esters (Scheme 13) under copper catalysis. The homochiral stannanes undergo transmetallation to copper species which add to the thioester. The tin residue traps the thiolate from the copper thiolate and regenerates the copper. No racemization was detected.[30]



Scheme 13. Copper catalyzed addition of α-hydroxystannane to the thioarylester **44**.

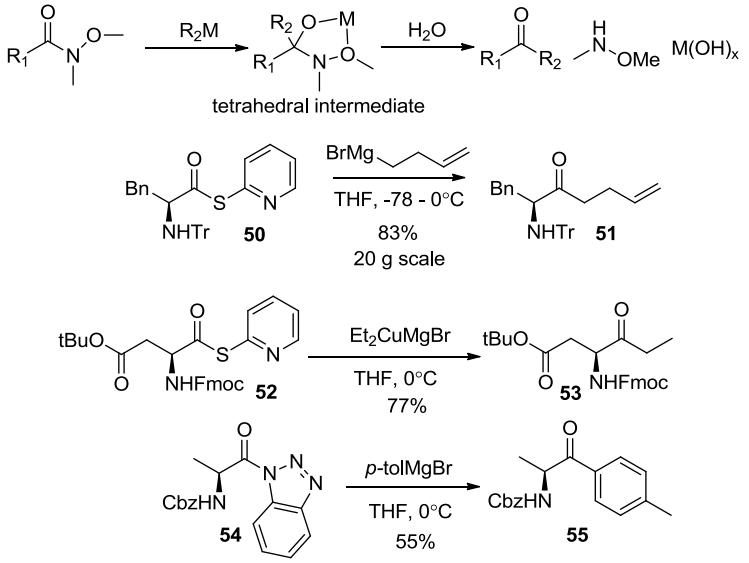
Probably the most common activated intermediate is the Weinreb amide (**B**).[31] The amide itself can be synthesized using many of the methods available for amide synthesis, or it can be synthesized from the corresponding ester (**A**). Weinreb amides are almost unique as they can be made to react with most hard nucleophiles with ease. This is demonstrated on the top portion of Scheme 14 with an addition of an alkyl Grignard to the amino acid derived Weinreb amide **46**. [32] Morpholine amides have been reported to have similar reactivity as Weinreb amides in certain cases.[33] A representative example is shown in the bottom of Scheme 14. Here the toluidine derivative **48** was lithiated and allowed to react with the morpholine amide to produce ketone **49**.[34]



Scheme 14. Addition to a Weinreb amide and its equivalent.

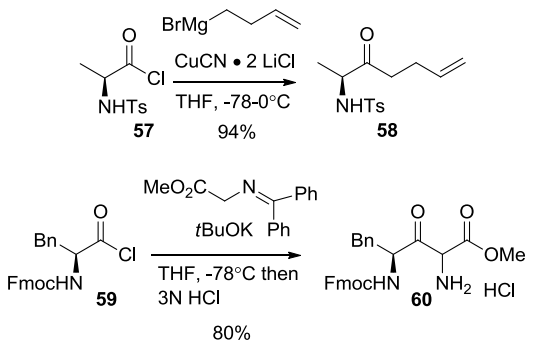
It has been shown that the reason why Weinreb amides are able to react with hard organometallic species without significant overreaction is that the Weinreb amide forms a stable tetrahedral intermediate, which only collapses to the product upon workup (Scheme 15, top).[35] This effect is not only capitalized by the morpholine amide but by several other species as well. The 2-thiopyridinyl ester is an old (it in fact predates the Weinreb amide itself)[36] method which works similarly to the two amides above. The trityl protected phenylalanine derivative **50** was treated with

homoallyl Grignard to produce the corresponding ketone **51** in good yield albeit at cryogenic conditions.[37] Grignard derived cuprates have been shown to react with 2-pyridinylesters such as **52** at more convenient temperatures.[38] Of more modern take on the field is the benzotriazolyl (Bt) moiety introduced by Katritzky. The alanine derivative **54** was reacted with an aryl Grignard to afford the corresponding ketone **55** without racemization.[39]



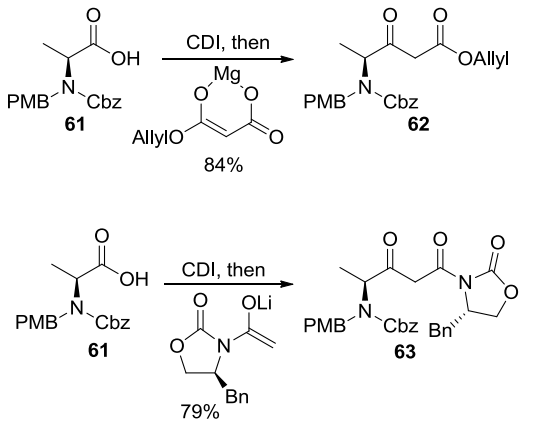
Scheme 15. The stable tetrahedral intermediate and application to 2-thiopyridinyl esters.

Of the *in situ* methods the acid chloride (**C**) is one of the oldest. Simple acid chlorides like benzoyl chloride can be isolated and stored for extended periods of time. However, amino acid chlorides are usually not isolated due to their instability The methods for generation of acid chlorides are rather harsh which limits the scope and can lead to partial racemization or decomposition if the nitrogen atom is not properly protected. Furthermore, the acid chlorides tend to overreact with most carbanion equivalents for the same reason as the corresponding esters. In Scheme 16 two successful couplings of acid chlorides are shown. The upper one describes the addition of an organocopper species to **57**, an acid chloride derived from alanine.[40] Without the copper the reaction was sluggish and low yielding. The lower reaction of Scheme 16 shows the addition of a glycine ester enolate to phenylalanine derived acid chloride **59** to give an α-amino β-ketoester.[41] No comment was made about the diastereoselectivity of the reaction or the integrity of the stereocenter.



Scheme 16. Successful additions to acid chlorides.

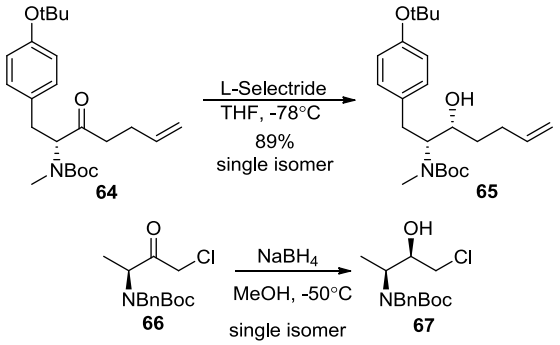
The acyl imidazole (D) represents a "modern" alternative to the acid chloride. As with acid chlorides, the acyl imidazolides can often be isolated, but for practical reasons most of the time they are not. The method of preparation using CDI is simple and mild and the byproducts are harmless and water soluble. Consequently, this activation method has become the method of choice especially in amide couplings. However, in the context of ketone synthesis, acyl imidazole is mostly compatible with relatively “soft” nucleophiles such as ester enolates. In the first example monoallyl malonate was coupled with CDI activated alanine derivative **61** as its magnesium enolate in good yield (Scheme 17). In the second example, a lithium enolate was added to the same substrate in similar yield.[42]



Scheme 17. Activation of amino acids with CDI.

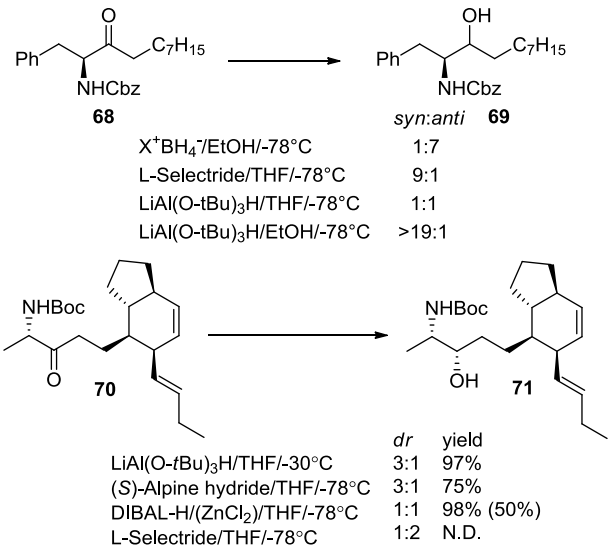
3.2 Reduction of acyclic amino ketones with hydride sources

The reactivity of ketones towards hydride sources is very sensitive to the protecting groups employed. *N*-Bisprotected amino ketones typically give high Felkin- or *syn*-selectivity irrespective of the reducing agent as exemplified in Scheme 18.[43,44] It should be noted that in both cases the carbamate functionality does not interfere. This would suggest that the carbamate carbonyl is not strongly involved in chelation.



Scheme 18. Reduction of *N*-bisprotected amino ketones.

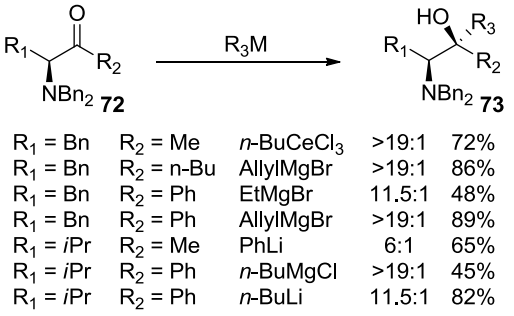
Monoprotected amino ketones are much more reagent sensitive, but as a rule of thumb *anti*-selectivity prevails when using chelating reducing agents like borohydrides. As in the example in top portion of Scheme 19 the reduction of the simple amino ketone **68** is moderately *anti*-selective with different borohydrides and completely *syn*-selective with the bulky $LiAl(O\text{-}tBu)_3H$ in a protic solvent.[45] However, in a more complex case presented in the lower portion of Scheme 19 only modest selectivity could be achieved despite extensive experimentation.[46]



Scheme 19. Reduction of monoprotected amino ketones.

3.3 Additions to acyclic amino ketones

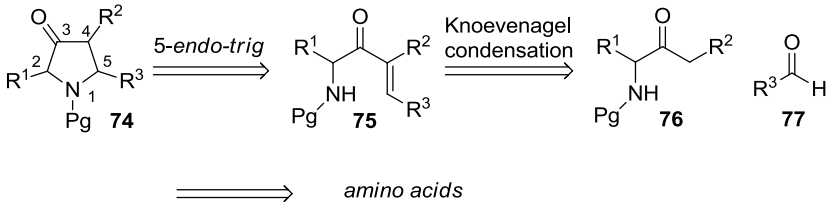
Additions of common organometallic reagents to acyclic amino ketones most frequently involve bis-*N*-protected substrates. These additions have been exhaustively covered by Reetz *et al*. (Scheme 20).[47] High *syn*-selectivity is achieved in each case with higher yields being obtained with the softer reagents (organocerium and allyl Grignard). The increase in yield was attributed to the lesser propensity of the softer reagents to undergo *β*-hydride elimination.



Scheme 20. Addition of organometallic reagents to *N*-bisprotected amino ketones.

3.4 Cyclic, non-lactam amino ketones

As expected, most of the synthetic methods targeting functionalized 3-oxo-pyrrolidines begin from the amino acid 4-hydroxy proline. Some examples of such functionalizations are presented in schemes in later sections. At the outset of this study, to our surprise, there were no *de novo* syntheses, substrate controlled or otherwise, to substituted 3-oxo-pyrrolidines like **74**. Given their potential usefulness, we were prompted to devise a modular route to access them.



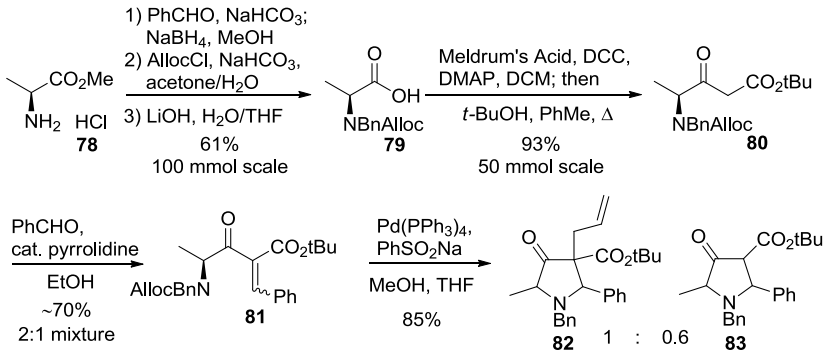
Scheme 21. Retrosynthetic analysis of pyrrolidinones **74**.

As a retrosynthesis, we came up with the rather bold plan pictured in Scheme 21. Disconnection of the N-C5 bond of **74** would lead to much simplified enone system **75**. However, in synthetic sense this disconnection would call for a 5-*endo-trig* cyclization which is "forbidden" according to the Baldwin guidelines.[48] Besides annealing the ring, we hoped to control the stereochemistry at the 4 and 5 positions using the lone stereocenter at the 2-position during this single transformation. The enone can be disassembled to ketone **76** and aldehyde **77** bearing the R^3-substituent *via* Knoevenagel disconnection. This would allow late stage introduction of various substituents R^3 into the molecule. For the Knoevenagel reaction to work efficiently the R^2 substituent must be an electron withdrawing functionality. The ketone **76** can be then traced back to amino acids from which it can be synthesized using the many methods for ketone synthesis described above. All in all, this would sum up to a modular, short and redox conservative synthesis.

For the initial studies we decided that R^2 should be an ester as β-ketoesters are simple to synthesize and should participate in the Knoevenagel condensation. The choice of the *N*-protecting groups, a choice which would become important later, were the Alloc (allyloxycarbonyl) and benzyl. This would enable us to test various cyclization conditions since Alloc can be cleaved under basic, neutral and acidic

conditions using palladium catalysis and benzyl amines are nucleophilic. An encouraging example was set by Thompson *et al.* where a benzyl and Alloc protected amine undergoes intramolecular hetero annulation, albeit 5-*exo*, under deprotection.[49]

The required ketoester was synthesized in 4 steps from alanine methyl ester (Scheme 22). The benzyl group was installed by reductive amination and the resulting *N*-benzyl adduct was Alloc-protected. Final saponification of the ester delivered the bis-*N*-protected alanine free acid **79** in 61% overall yield at 100 mmol scale in exquisite purity without chromatography. Next, **79** was condensed with Meldrum's acid with the help of DCC and the resulting tricarbonyl compound was decomposed in the presence of *t*BuOH to give the ketoester **80** in excellent yield and purity after silica gel filtration. This sequence does NOT provide **80** in enantiopure form as some optical integrity is lost during saponification and some is lost during the DCC coupling. However, such an enantiopurity preserving sequence was developed by us in conjunction of a related project and will be discussed later.



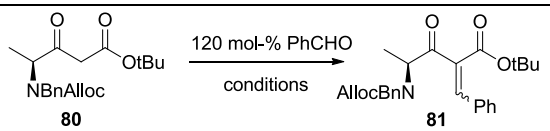
Scheme 22. Proof-of-concept: β-ketoester.

Knoevenagel condensation of **80** with benzaldehyde proved to be sluggish with roughly 70% yield obtained after stirring in EtOH in the presence of catalytic pyrrolidine. Now, exposure of **81** to the Thompson conditions ($Pd(PPh_3)_4$ with 2-ethylhexanoic acid as allyl trap) gave a very complicated mixture. When exposed to conditions reported by Nagakura,[50] an interesting mixture of products consisting of **82** and its des-allyl counterpart **83** was obtained. We quickly recognized this to be a novel transformation in two ways; first of all, it represents the first ever productive use of Alloc as the allyl cation source and secondly it is a remarkably facile 5-*endo* cyclization. Suspiciously, the product distribution seemed to mirror

the *E*:*Z* ratio of the enone. Since it is virtually impossible to control the geometry of the double bond the observation raised serious concerns. Despite this very exciting proof-of-concept, we were forced to look back at the poorly performing Knoevenagel condensation before going any further with the investigation.

The Knoevenagel reaction was investigated (Table 1) in some detail, but no improvement over the initial conditions was ever achieved. Although heating does drive the reaction to completion, such conditions were deemed to be too harsh given the nature of the enone to be implemented in the final route and were thus disregarded (entries 7 and 8). Use of desiccants did not provide any significant improvements and even the relatively harsh Lewis acid mediated[51] conditions failed (entries 9 and 10). Since the Knoevenagel reaction is basically an aldol condensation followed by dehydration, the soft enolization techniques[52] used in direct aldol reactions were tested to no avail (entries 11-13).

Table 1. Investigation of Knoevenagel conditions.



80 **81**

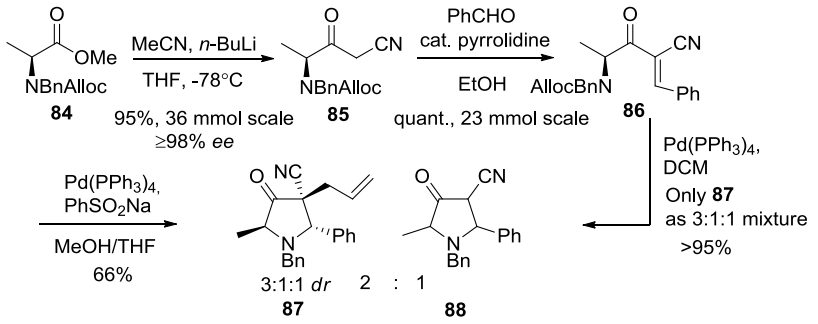
Entry	Solvent	Base	Additive	81:80	NOTES
1	DMSO	20% pyrrolidine		1:1	
2	EtOH	20% pyrrolidine		4:1	
3	HFIP	20% pyrrolidine		1:2.5	
4	DCM	20% pyrrolidine	20% TFA, 3Å sieves	no rxn	
5	DCM	20% pyrrolidine	4Å sieves	1:1	
6	toluene	20% diphenylprolinol		no rxn	60°C
7	MTBE	20% pyrrolidine		full conv.	Dean-Stark
8	toluene	20% pyrrolidine	150% DMFDMA	full conv.	60°C, side products
9	DCM	150% DIPEA	150% $TiCl_4$	no rxn	
10	DCM	150% DIPEA	150% $SnCl_4$	no rxn	
11	toluene	150% NMM	20% $MgBr_2 OEt_2$, 150% TMSCl	ND	low conversion
12	MeCN	150% NMM	20% $MgBr_2 OEt_2$, 150% TMSCl	ND	low conversion
13	DCM	150% DIPEA	20% $Sc(OTf)_3$, 150% TMSCl	1:4	

To a stirred mixture of **80** was added base and PhCHO (120 mol-%) followed by the additive. Stirred until complete or for 16h and then concentrated and the crude analyzed by NMR.

It was clear that the substrate **80** was not sufficiently active in the Knoevenagel condensation. Therefore other types of electron withdrawing group (EWG) were considered. It was also thought that judicious selection of the EWG could also

solve the *E*:*Z* selectivity issue and thereby simplify the analysis. Indeed, tentative molecular modeling suggested that a cyano group would produce >20 kJ/mol difference[a] between *Z* and *E* isomers (favoring the Z isomer) as compared to *t*-butyl ester (4 kJ/mol difference, a very good agreement with experimental data). Calculation with a nitro group gave similar results to *t*-butyl ester. Thus, we chose the ketonitrile as our prime substrate candidate.

The ketonitrile **85** was readily synthesized form the corresponding ester by addition of lithiated acetonitrile followed by silica gel filtration (Scheme 23). We were happy to see that this potentially harsh addition completely conserved the optical integrity of the starting material. Now the Knoevenagel condensation with PhCHO went to completion in less than an hour to furnish the enone **86** in quantitative yield as a single geometrical isomer. Subjection to the previous conditions formed **87** and its des-allyl counterpart **88** in 66% yield and 2:1 mixture. Compound **87** was obtained as an inseparable 3:1:1 diastereomeric mixture and **88** as a single isomer. The geometry of the major diastereomer was established through NOE studies, but the relative stereochemistry of the des-allyl **88** remained elusive. Treatment of **86** with Pd(0) in DCM without any allyl trapping agent produced only **87** as the very same diastereomeric mixture as before. This proved that double bond geometry does not affect the chemical or stereochemical outcome. Despite the miserable diastereomeric mixture obtained, we were extremely happy about the highly efficient Knoevenagel reaction.



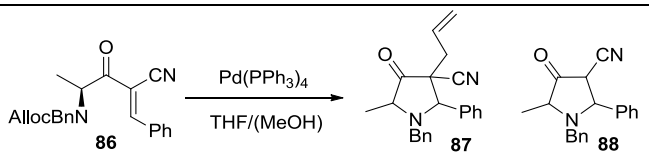
Scheme 23. Proof-of-concept: β-ketonitrile.

The fact that **88** was obtained as a single isomer prompted us to look into its selective synthesis. We tested a lot of different trapping agents for the allyl cation, with one promising hit (Table 2). Potassium thiosalicylate was a very efficient

[a] All calculations were perfomed using Schrödinger Maestro 9.0 software package. OPLS2005 forcefield was employed with full conformational search (500 steps in $CHCl_3$).

cation trap with no **87** being formed. A short salt screen (Na, K, Cs, Ba, NEt_3) showed Na, K and Cs to perform in identical manner. Ba salt was too insoluble and the amine salt was very slow and was an oil instead of a solid. Despite this promising screening hit, the isolated yields were low in each case (*ca*. 30%). A series of reactions showed that the yield is time dependent. In fact, the isolated samples quickly turned into glassy, insoluble substances in the presence of air, thus rendering these compounds virtually useless as intermediates. This finding made us return to investigate the novel allylative cyclization.

Table 2. Screen for potential trapping agents for the allyl cation.

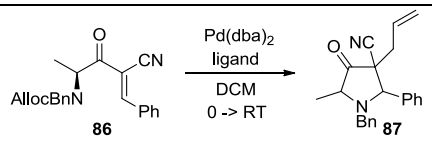


Entry	Trapping agent	87:88
1	benzenesulfonamide	1:0
2	2-mercaptothiazole	no rxn
3	thiophenol	no rxn
4	diethylmalonate	decomposition
5	morpholine	1:0
6	*N*-hydroxysuccinimide	1:0
7	*N*-hydroxyphthalimide	1:0
8	HOBt	no rxn
9	BH_3-$NHMe_2$	decomposition
10	thiosalicylic acid	decomposition
11	potassium thiosalicylate	0:1

Conditions: 0.27 mmol (100 mg) **86**, 0.29 mmol of trapping agent, 9 mg $Pd(PPh_3)_4$ (3 mol-%), in 1 mL THF + 0.25 mL of MeOH if the agent is insoluble in THF (entries 10, 11).

A ligand screen was conducted to assess the ligand effect on the cyclization (Table 3). Ligands with small bite angles (entries 1 and 2) performed poorly conversion-wise and alkyl phosphine did not work at all (entry 7). All the other ligands produced roughly the same result, which would indicate that the transition state is essentially free from the influence of the ligand. Based on these results nothing dissuaded us from the use of cheap triphenylphosphine as the ligand.

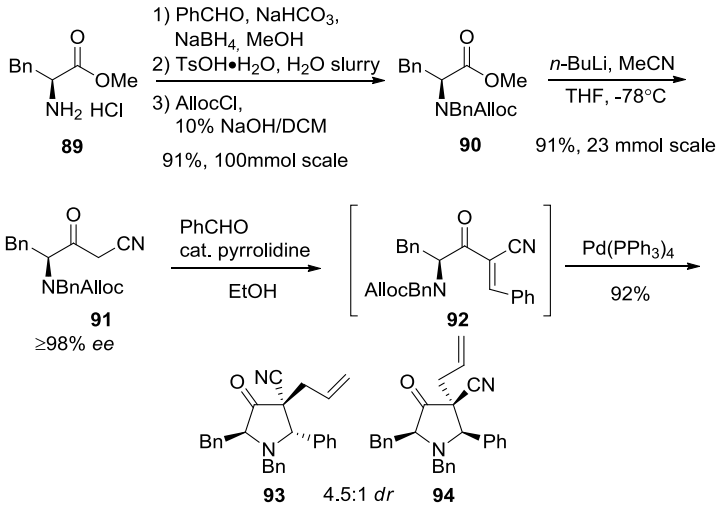
Table 3. Ligand screen for the transformation of **86** to **87**.



Entry	ligand	dr1	dr2	dr3	dr1:(dr2+dr3)	notes
1	dppm	3,0	1,0	0,8	1,7	50% conv
2	1,2-(PPh_2)Ph	3,2	1,0	0,9	1,7	35% conv
3	P(*o*-tolyl)$_3$	3,5	1,0	1,3	1,5	
4	TPP	3,0	1,0	0,8	1,7	
5	dppb	3,2	1,0	1,0	1,6	
6	P(2-furyl)$_3$	2,3	1,0	0,7	1,4	
7	P(*c*-hex)$_3$	-	-	-	-	no rxn
8	nothing	-	-	-		no rxn

Conditions: A solution of **86** (100 mg/mL, 1 mL) in DCM was added to a premixed solution of $Pd(dba)_2$ (3 mol-%) and the ligand (6 mol-% for bidantate ligands and 12 mol-% for monodentate) in DCM (0.5 mL) under Ar. Stirred until complete or 48h and then filtered through a pad of silica. Analyzed by ^{1}H-NMR.

We then investigated the effect of the R^1-substituent by synthesizing the ketonitrile substrate from a different amino acid. Phenylalanine was chosen as the amino acid, and that substrate became our workhorse for the rest of the study for its high sensitivity to reaction conditions. The protection chemistry was adjusted slightly by introducing a slurrying stage as tosylate salt after the reductive amination (Scheme 24). This considerably increases the robustness of the route as all the impurities are effectively removed at this point. The Alloc protection could then be done in a biphasic mixture of DCM and 10% NaOH without a separate salt break, i.e. the liberation of the amine free base, to give the protected ester **90** in high yield and impeccable purity after phase separation. This was also found to affect downstream chemistry by making the cyanomethylation much more consistent. As was the case for alanine, the phenylalanine derived ketonitrile **91** was also of uncompromised optical purity. Due to the fragile nature of the enones we decided to use them *in situ* by simply adding the catalyst mixture after the Knoevenagel reaction was complete, as judged by TLC. This produced an inseparable mixture of two diastereomers in 4.5:1 ratio. The relative configurations of the products were established through NOE experiments.

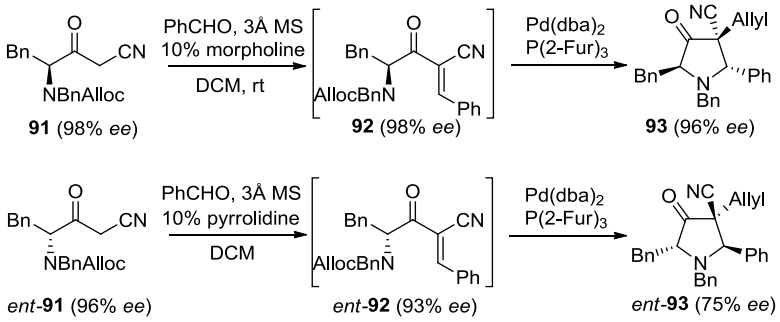


89 **90** **91** ≥98% *ee* **92** **93** **94**

Scheme 24. Synthesis and evaluation of the phenylalanine derived substrate.

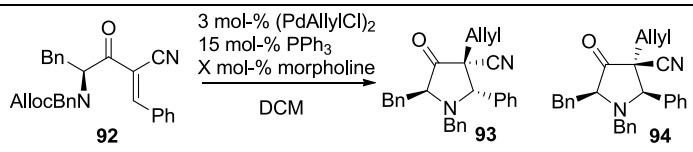
Solvent screening revealed DCM to be the optimal solvent for the cyclization and thus it became imperative to be able to run the whole sequence in it. Fortunately, the Knoevenagel condensation worked nicely in DCM in the presence of molecular sieves. One more major obstacle was left to be overcome before the exploration of the reaction could begin in earnest, and that was the erratic enantiomeric excesses measured for the pyrrolidinones. The ee's of the isolated products fluctuated between 70 and 85%. It was deemed important to establish racemization free conditions *prior* to reaction optimization, as it effectively sets the constraints on the reaction conditions. The culprit was identified to be the pyrrolidine; simply switching to less basic amine catalyst worked wonders as illustrated in Scheme 25. In the presence of pyrrolidine a slight erosion of ee was noted in the Knoevenagel adduct *ent*-**92** and major erosion in the cyclized product *ent*-**93**. In the presence of morpholine, no racemization was detected in the Knoevenagel adduct **92** and only slight decrease of ee was noted in the annulated product (**93**). The racemization could be completely eliminated when the reaction was run at 0˚C.

It later became apparent that morpholine had an unexpected beneficial effect on the diastereoselectivity of the reaction (Table 4), an effect which was pronounced when the reactions were run at 0°C. It was observed that the diastereoselectivity increased with increasing morpholine loading and at the same time the reactions became faster and lower yielding. The effect of the additive is discussed further in the next chapter. These discoveries lead to the realization of a new synthetically useful method, the scope of which is summarized in Table 5.[IV]



Scheme 25. The effect of the amine catalyst on enantiomeric excess.

Table 4. The effect of morpholine on reaction performance.



Entry	Morpholine (mol-%)	T (˚C)	dr (93:94)	Yield (%)
1	0	0	6.2	91
2	0	20	5.9	94
3[a]	0	35	4.8	89
4	15	20	7.0	93
5	15	0	9.4	86
6	25	0	16.0	78
7	50	0	17.5	58
8[b]	23	0	15.5	82

Condtions: To a solution of **92** (200 mg) in CH_2Cl_2 (4 mL) at rt was added morpholine followed by $(PdAllylCl)_2$ (3 mol-%) together with PPh_3 (15 mol-%). After reaction completion the the products were absorbed on silica and chromatographed. [a] $P(4\text{-}OMe\text{-}Ph)_3$ was used as ligand instead. [b] On 1.5 g scale.

In almost all cases the *trans-trans* isomer **B** was obtained as the major product with varying degrees of selectivity with higher selectivities obtained with bulkier R-groups. It should be noted that when a 2,6-disubstituted aldehyde was used virtually complete diastereoselectivity was observed, but for the *syn-trans* isomer **C** (entries 5 and 6). Also, with the ortho disubstituted aldehydes the cyclization reactions were abnormally fast, even with the highly electron deficient 2,6-dichlorobenzaldehyde, and proceeded with partial racemization. Thankfully the 2,6-dichlorobenzaldehyde adduct of the alanine derived substrate was crystalline, and we were able to obtain a crystal structure to confirm our structures that had been assigned by NOE (Figure 7).

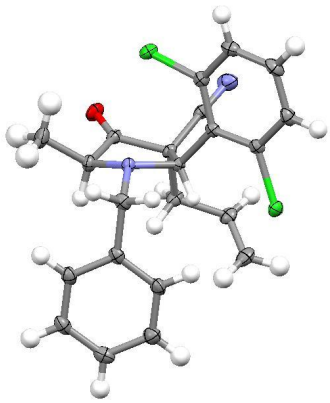
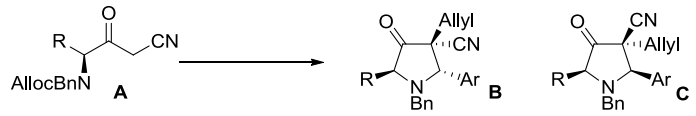


Figure 7. Crystal structure of 2,6-dichlorobenzaldehyde adduct of the alanine derived substrate.

Table 5. Scope of the allylative 5-*endo* heteroannulation.



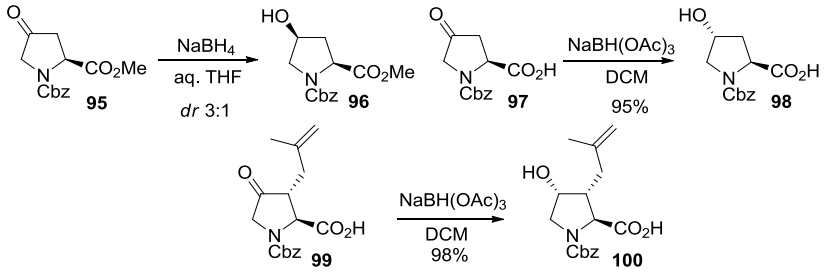
Entry	R	Ar	dr (B:C)[a]	Yield[b]
1	Bn	Ph	14.3:1	82
2	Bn	2-Me-Ph	11.1:1	83
3	Bn	2-OMe-Ph	6.5:1	80
4	Bn	2-Cl-Ph	3.2:1	71
5	Bn	2,4,6-Me-Ph	>1:20	54
6	Bn	2,6-Cl-Ph	>1:20	81
7	Bn	3-Me-Ph	8.7:1	85
8	Bn	3-OMe-Ph	7.7:1	80
9	Bn	3-Cl-Ph	2.6:1	71
10	Bn	3-CN-Ph	1:1	51
11	Bn	3,5-OMe-Ph	11.0:1	75
12	Bn	Piperonal	12:1	75
13	Bn	4-Me-Ph	7.5:1	93
14	Bn	4-*t*-Bu-Ph	7.4:1	77
15	Bn	4-OMe-Ph	6.5:1	84
16	Bn	4-Cl-Ph	5.4:1	81
17	Bn	Furfural	8.8:1	89
18[c]	Me	Ph	4.9:1.3:1	84
19	Me	Ph	6.2:1.3:1	70
20[c]	*i*-Bu	Ph	6.5:1	99
21	*i*-Bu	Ph	>20:1	76
22[c]	*i*-Pr	Ph	>20:1	89
23	*i*-Pr	Ph	>20:1	79
24[d]	Bn	Ph	7.5:1	75

To a solution of **A** in DCM (0.5 M) under argon at rt was added 4 Å MS (100 w-%) followed by the aryl aldehyde (120 mol-%) and morpholine (23 mol-%). After being judged complete by TLC the reaction was cooled to 0°C and diluted with DCM (0.11 M). Then $(AllylPdCl)_2$ (3 mol-%) was added together with PPh_3 (15 mol-%). After reaction completion the products were absorbed on silica and chromatographed. [a] Determined by ^{1}H-NMR. [b] Isolated yield after chromatography. [c] No morpholine. [d] PMB protecting group instead of Bn. PMB = *para*-methoxybenzyl.

As such, the pyrrolidinones have no clear application in natural product synthesis, an expected effect of a novel skeleton. However, the molecules exhibit several orthogonally reactive functionalities (an amine, a ketone, a nitrile and an alkene) which provide versatility and enable further processing of the scaffold. With this logic the molecules are well suited for medicinal chemistry related endeavors involving analogue generation. As a matter of fact, related highly functionalized pyrrolidines have recently been described by Hoffman-La Roche researchers[53] and others[54] as MDM2 antagonists.

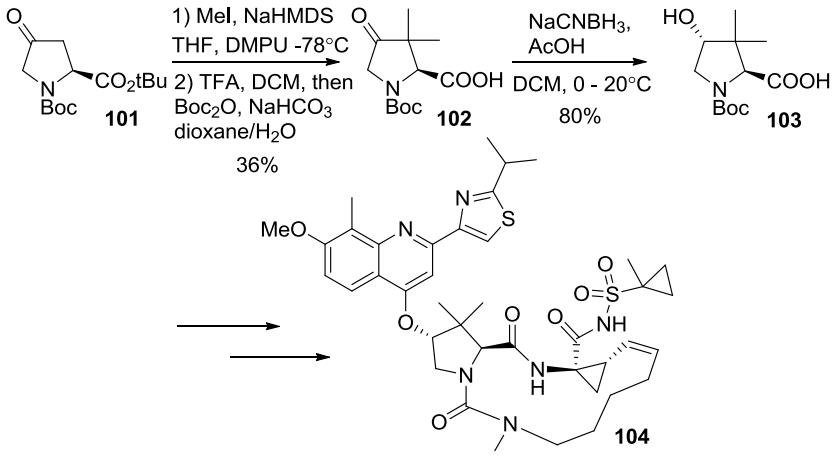
3.5 Reduction of cyclic, non-lactam pyrrolidinones

Reduction of oxoproline methylester **95** with sodium borohydride produced a 57:13 mixture of diastereomers together with 30% of over reduced *syn*-isomer (Scheme 26). On the other hand, chelation controlled reduction of the free acid **97** with sodium tris(acetoxy)borohydride gave the *trans*-isomer **98** in excellent yield. Analogously, the 3-isobutene substituted analog **99** was reduced under the same conditions with flawless selectivity.[55]



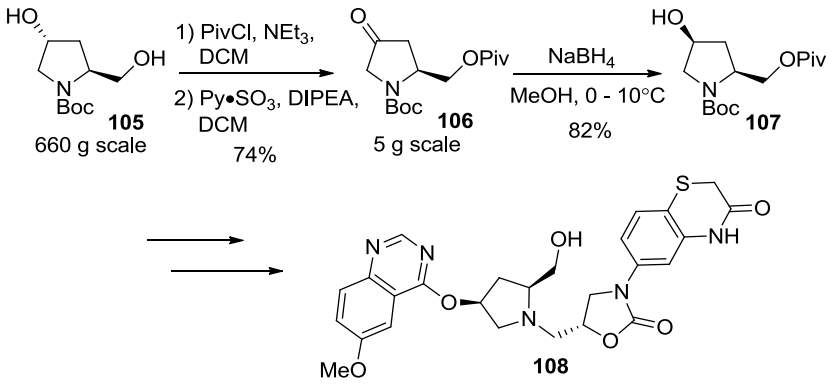
Scheme 26. Reduction of 4-oxoprolines.

During the synthesis of hepatitis C replication inhibitors such as **104**, the researchers at Intermune required access to 3,3-dimethyl substituted hydroxyproline **103** which would act as the core of the molecule (Scheme 27). The required building block was accessed by low yielding dimethylation of a 4-oxoproline derivative **101** followed by stereoselective reduction with sodium cyanoborohydride to give exclusively the *trans*-isomer. A good yield is obtained, despite the gem-dimethyl substitution at 3-position.[56]



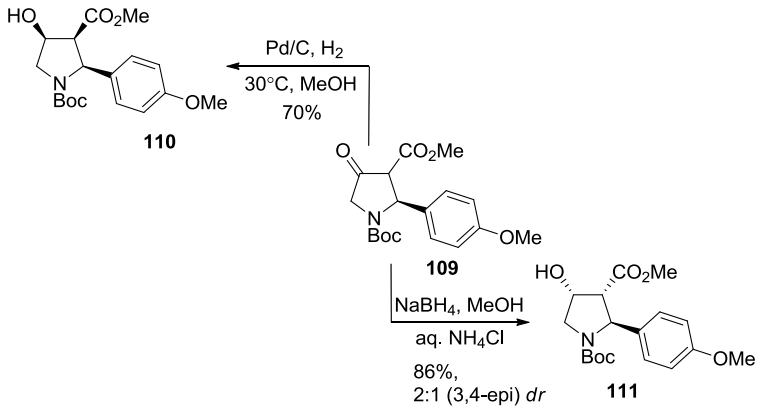
Scheme 27. Chelation controlled reduction of 3,3-dimethyl-4-oxoproline **102**.

As a part of research into novel antibacterial compounds the researchers at Actelion required ready access to *syn*-4-hydroxy prolinol **107** (Scheme 28). Protection of the primary alcohol of hydroxy prolinol **105** as the pivalate ester followed by Parikh-Doering oxidation furnished the oxoprolinol **106** in 74% yield on 660 g scale. Reduction with sodium borohydride delivered the *syn*-hydroxyprolinol in good yield.[57]



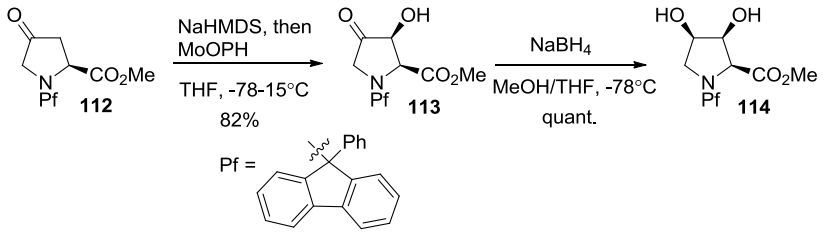
Scheme 28. Synthesis of syn 4-hydroxy prolinol **107**.

Hydrogenation of an enolizable keto-ester **109** provided the all-*syn* hydroxyl ester **110** in 70% yield, albeit after 3 d reaction time (Scheme 29). Reduction of the same substrate using sodium borohydride provided the 3,4-epimer **111** as the major product, although the selectivity was low.[58]



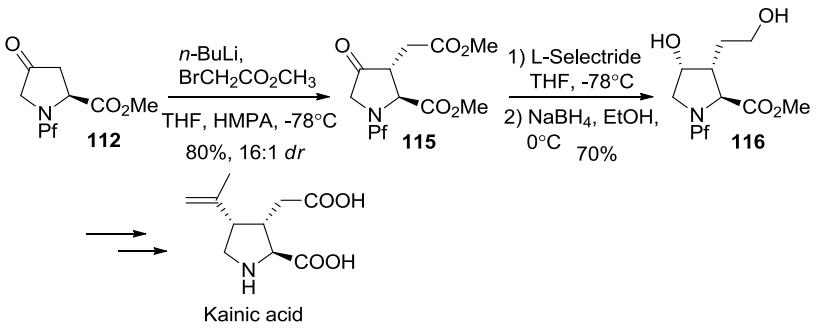
Scheme 29. Reduction of an enolizable keto-ester.

Sardina *et al*. have used the phenyl fluorenyl (Pf) group to prevent epimerization during α-oxidation of a ketone enolate derived from **112** with oxodiperoxymolybdate-HMPA-pyridine complex (Scheme 30). Reduction of the resulting α-hydroxy ketone (**113**) gave the all-s*yn* isomer as the only product. Same stereochemical outcome was reported for reduction of **113** with $LiEt_3BH$.[59]



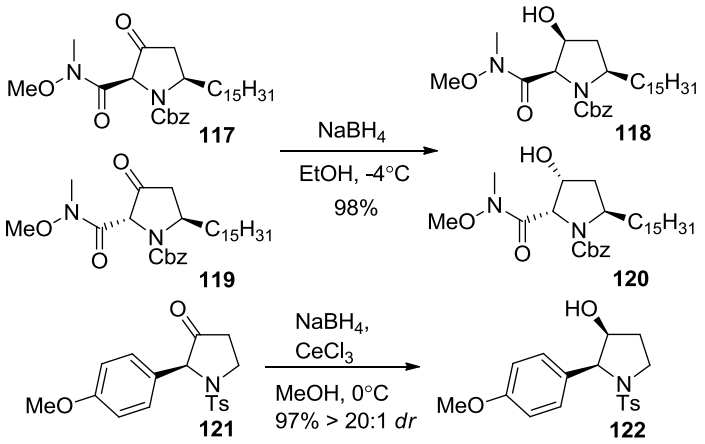
Scheme 30. Reduction of the α-hydroxyketone **113**.

In their route to kainic acid Greene and co-workers used a similar strategy for 3-functionalization as Sardina's group above (Scheme 31). Again, the Pf group was used to prevent enolization towards the amino group. Now the enolate was quenched with methyl bromoacetate to install the masked hydroxyethyl substituent in a highly diastereoselective manner. Treatment of **115** with L-Selectride then produced a lactol which was further reduced to the diol using $NaBH_4$ to produce the 3,4-*syn* pattern. The authors report that direct treatment of **115** with $NaBH_4$ produces the wrong isomer at the 4-position.[60]



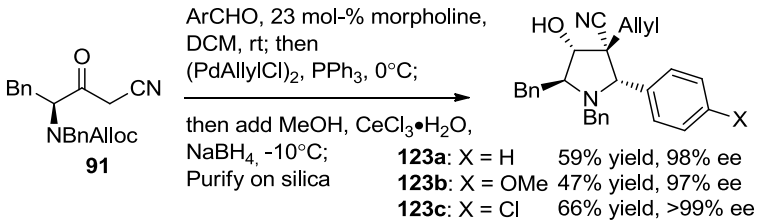
Scheme 31. Substrate controlled synthesis of Kainic acid.

Ma *et al*. have shown an interesting effect the substituent at the 2-position of 3-oxopyrrolidine analogues produces (Scheme 32) as the reductions appear to be completely controlled by it. In both cases the substrates **117** and **119** are reduced in 98% yield with full control of the 2,3-*cis* relationship.[61] A similar result was described by Liu and co-workers when reducing the nicotinoid **121** under Luche conditions.[62]



Scheme 32. The effect of substituent at 2-position of 3-oxopyrrolidine analogues.

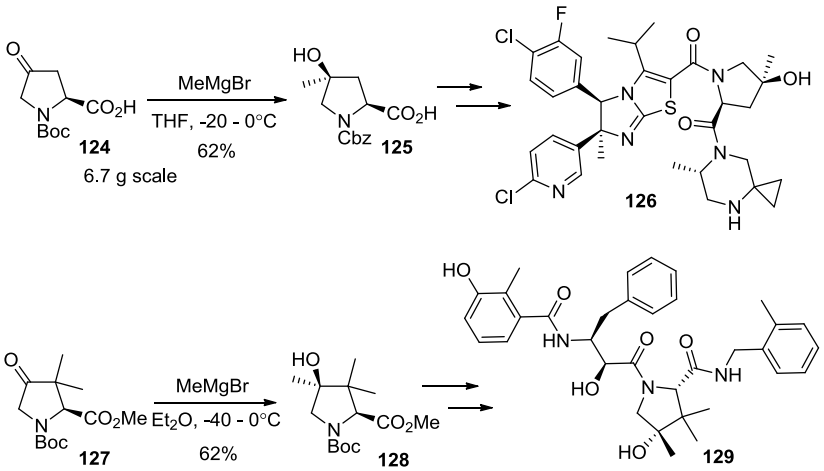
We found out that our heavily substituted pyrrolidinones could be reduced *in situ* under Luche conditions to provide the pyrrolidinols **123** in passable yield but excellent diastereoselectivity over 3 steps (Scheme 33).[IV] If the lanthanoid was omitted, the diastereoselectivity decreased considerably to about 3:1.



Scheme 33. One-pot sequence to obtain complex pyrrolidinols from keto-nitriles **91**.

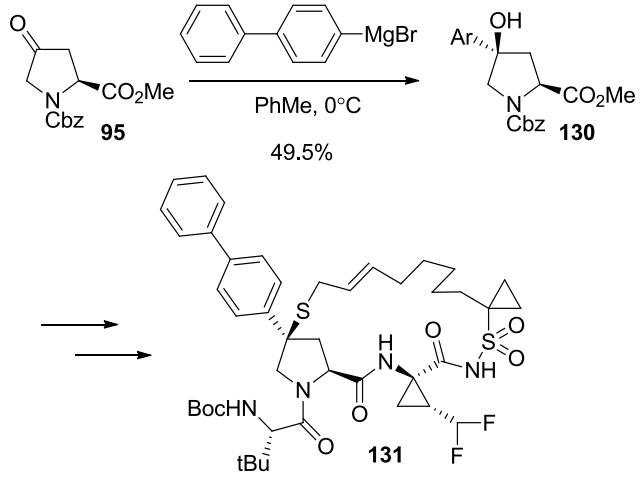
3.6 Additions to cyclic, non-lactam amino ketones

As part of a program to develop mdm2/p53 inhibitors like **126** for cancer treatment the researchers at Daiichi company required access to the pyrrolidinol building block **125** (Scheme 34). It was readily synthesized as a single isomer by treating the Boc protected oxoproline **124** with MeMgBr. It was then advanced to the drug candidate **126** which was reported to have IC_{50} value of <0.2μM towards mdm2/p53.[63] A similar outcome is seen when the 3,3-dimethyl derivative **127** is reacted with methyl Grignard. This product was then advanced to the potential HIV protease inhibitor **129**.[64]



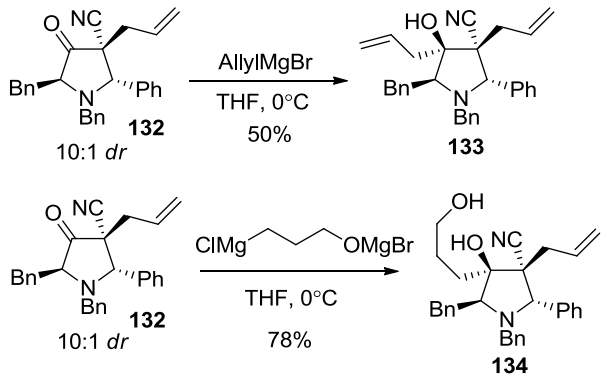
Scheme 34. Addition of methyl Grignard to oxo-prolines **124** and **127**.

Bristol-Myers Squibb chemists reacted the protected oxoproline **95** with biphenyl Grignard to obtain the tertiary alcohol **130** (Scheme 35). This piece was a part of a Hepatitis C virus replication inhibitor **131**, which has an IC_{50} of 2 nM.[65]



Scheme 35. Addition of biphenyl Grignard to oxoproline **131**.

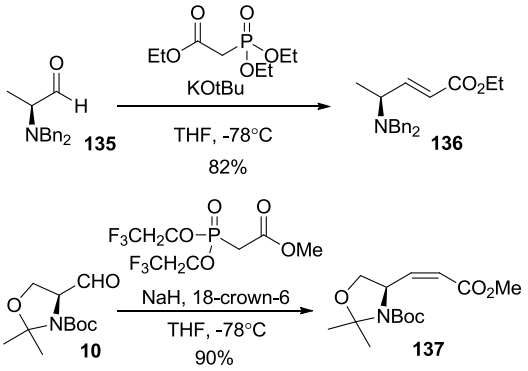
We briefly experimented with additions of organometallic reagents to the piperidinone **132** (Scheme 36). Aryl Grignards gave no product at all. Instead only 2-*epi*-**132** could be isolated in low yield. On the other hand, the softer allyl Grignard gave the expected product **133** as a single isomer at moderate yield. The deactivated Grignard derived from chloropropanol worked even better, giving **134** as a single isomer and good yield. These results are in line with Reetz's report on organometallic additions to amino ketones.



Scheme 36. Reactions of Grignard reagents with the highly substituted piperidinone **132**.

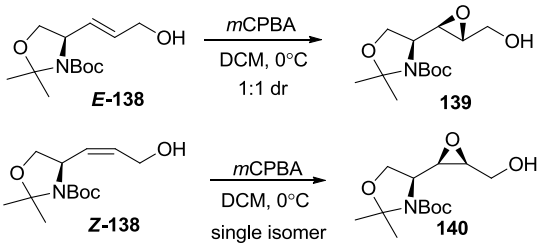
4. Oxidation of Allyl Amines

The required allyl amines are readily available through Horner-Wadsworth-Emmons (HWE) or similar Wittig-type transformations from the corresponding amino aldehydes. On the top portion of Scheme 37 is shown a traditional HWE reaction between the alaninal **135** and a phosphonate to give **136** in a highly *E*-selective manner.[66]



Scheme 37. Examples of *E* and *Z*-selective allyl amine syntheses.

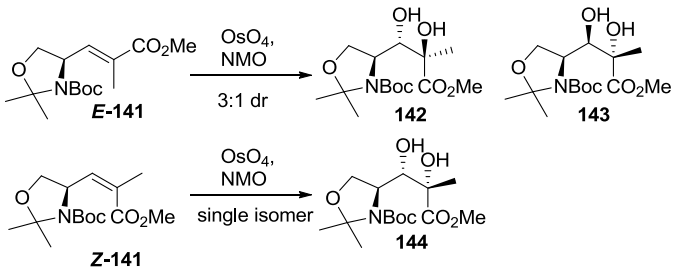
The lower portion of Scheme 37 showcases a *Z*-selective variant of the HWE reaction.[67] The key is to use a trifluoroethyl phosphonate (the Still-Gennari modification).[68] In both cases the products were obtained with minimal racemization.



Scheme 38. Epoxidation of allyl amines with *m*CPBA.

Treatment of ***E***- and ***Z*-138** under identical conditions led to a 1:1 mixture of diastereomers in the case of the *E*-isomer and to a single isomer in the case of the *Z*-isomer. [69]

A similar outcome was seen with dihydroxylations (Scheme 39). Treatment of ***E*-141** with catalytic osmium tetroxide and *N*-methyl morpholine *N*-oxide produced a 3:1 mixture of diols **142** and **143** while ***Z*-141** under identical conditions produced only **144**.[70]



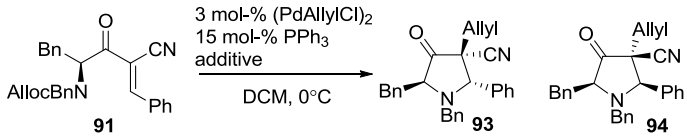
Scheme 39. Dihydroxylation of allyl amines.

The effect can be explained by considering allylic $A^{1,3}$-strain. The *Z*-alkenes take up larger amount of space than their *E*-configured counterparts and thus the rotational barrier around the single bond is higher. The more rapid rotation of the *E*-alkenes enable the oxidant to approach the alkene from either face thus leading to mixtures of products.

5. On the Mechanism of the Allylative 5-*endo* Heterocyclization

5.1 Kinetic studies with additives

One of the most important and perplexing aspects of the newly discovered reaction was undoubtedly the amine additive. To gain some insight into the role of the amine, we recorded reaction the profile for the conversion of **91** to **93**/**94** using HPLC in the presence of various additives (see experimental section for details). Figure 8 shows the conversions with a selection of conditions.



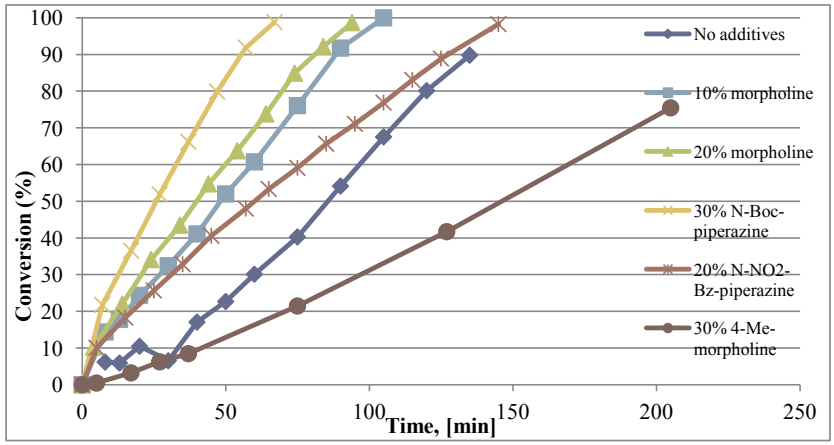


Figure 8. Conversion of **91** to **93**/**94** in the presence of various amine additives.

There are several important observations that can be gleaned from this dataset. First of all, the reaction is zero-order as can be seen from the linear conversion. Secondly, the reaction is strongly inhibited by tertiary amines, but accelerated by electron rich secondary amines. Thirdly, there appears to be an initiation period, which is effectively removed by the amine additive. To more effectively compare the data, the rate profiles were reduced into single values obtained from the slopes

of the linear portions. The complete dataset in reduced form is presented in Table 6.

Table 6. Reaction rates for the conversion of **91** into **93**/**94**. The uncertainties presented are at 95% confidence level.

Entry	Additives/deviations	rate [SM%/min]	Rel rate
1	30% *N*-Me-Morph	0.401 ±0.040	0.50
2	20% *N*-*p*-NO_2Bz piperazine	0.6644 ±0.067	0.83
3	no additives	0.7570 ±0.081	1.00
4	2xPd, 2xPPh_3	0.9346 ±0.094	1.16
5	10% morpholine	0.9365 ±0.094	1.17
6	20% *N*-Boc piperazine	1.0048 ±0.101	1.25
7	20% morpholine	1.0299 ±0.103	1.28
8	$Pd(dba)_2$ + 20% morpholine	1.0752 ±0.108	1.34
9	20% *N*-Me-piperazine	1.325 ±0.133	1.65
10	30% *N*-Boc piperazine	1.4139 ±0.142	1.76
11	20% DMAP	1.5038 ±0.151	1.87
12	20% DABCO	1.6632 ±0.167	2.07

Despite the lack of statistically significant data on repeats we can evaluate the error in the rate constants through simple rationale. The rate constants k are derived from the linear portions of the plots where the square of the residual variance $R^2 > 0.99$ and the k values are represented by the following equation

$$k = \frac{Conv}{t} \quad (1)$$

where *Conv* is the conversion relative to the initial value in respect to the internal standard (*trans*-stilbene) and *t* is time in minutes. Thus, it follows that the relative uncertainty *u*(k)/*k* is:

$$\frac{u(k)}{k} = \sqrt{\left(\frac{u(Conv)}{Conv}\right)^2 + \left(\frac{u(t)}{t}\right)^2} \quad (2)$$

The uncertainty for the time domain is easy to evaluate as a clock with minute resolution was used, uncertainty of *u*(t) = ±0.5 min is more than reasonable. The conversion term is slightly trickier to evaluate, as it comprises of many factors including sampling, detector performance, weighing etc. However, it is quite logical to use the uncertainty of the response factor (RF) between the substrate and the internal standard in this context. The response factor is defined as

$$RF = \frac{R_S * c_{iSTD}}{R_{iSTD} * c_S} \quad (3)$$

Where R_s and R_{iSTD} are the detector responses corresponding to substrate and internal standard, correspondingly, and c_S and c_{iSTD} are the substrate and internal standard concentrations. The reactions were run under identical conditions in respect to substrate and internal standard loadings as well as concentration. Therefore, the uncertainty of the RF will intrinsically include at least an estimate of all the aforementioned uncertainties. Since a large number of runs were made, the standard uncertainty can be calculated for the RF. For the entries in the above table 6 we obtain

$$u(RF) = \frac{s(RF)}{\sqrt{12}} = 0.003804 \qquad (4)$$

The mean of the RFs is 0.7875. For a typical experimental run the reaction is sampled at 10 minute intervals. Thus, for the extended uncertainty at 95% confidence level we obtain:

$$U(k)_{95\%} = u(k) * 2k = \sqrt{\left(\frac{u(RF)}{RF}\right)^2 + \left(\frac{u(t)}{t}\right)^2} * 2k$$

$$= \sqrt{\left(\frac{0.003804}{0.7875}\right)^2 + \left(\frac{0.5\ min}{10\ min}\right)^2} * 2k = 0.100465k \qquad (5)$$

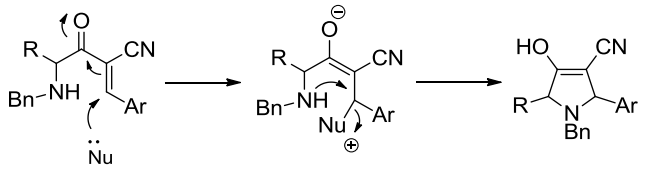
The extended uncertainty is reasonable (10%) although through this treatment huge majority of the uncertainty originates from the time domain.

Doubling catalyst concentration (entry 4) only modestly increases the reaction rate (16%). This might suggest that the catalyst is present in the transition state complex, but does not affect the rate determining step. Using Pd(0) source instead of Pd(II) has no measurable effect on the reaction rate, and more importantly the profile (entry 8). Thus, a similar complex is formed from both Pd sources.

Using an electron deficient amine or a tertiary amine (entries 1 and 2) one effectively slows down the reaction. Using a more electron rich secondary amine than morpholine has a more profound accelerating effect (entry 9). In this context the Boc-piperazine turned out to be a very handy replacement for morpholine since it is an easily weighable solid yet has similar performance (entry 6 versus entry 7).

The stronger bases DMAP and DABCO both had great accelerating effect (entries 11 and 12). Both bases are highly nucleophilic and are in fact used as nucleophilic catalysts in many reactions such as acylations and Baylis-Hillman reactions in which they act to activate the electrophile. This result raises the question of whether the mechanism is in fact the addition of the nucleophile to the enone system followed by 5-*exo*-*tet* displacement by the intramolecular amine

(Scheme 40). However, this model is not supported by the fact that electron withdrawing aryl groups make the reaction *slower* and less selective, which is the opposite to what would be expected in the nucleophilic catalysis scenario. Also, using chiral amines had no measurable effect on the diastereomeric ratio.



Scheme 40. Possible activation of an enone system towards formal 5-*endo-trig* cyclization through nucleophilic catalysis.

The kinetics were also recorded for other trapping agents besides amines such as sulfinates and thiophenolates. The kinetics showed no change from the data recorded without any additives (entry 3) although they were very effective in trapping the allyl cation. With sulfinates product started to form only after the trapping agent was spent. We took this as evidence that these compounds do not interact with palladium.

The relative rates seem to roughly correlate with calculated HOMO-orbital energies of the bases within the morpholine/piperazine series (Figure 9).[a] The model obviously does not take into account steric effects nor different contributions to the HOMO energy and thus cannot be expanded outside the morpholine/piperazine skeleton.

[a] The calculations were done on B3LYP(6-311G**+) level of theory using the Schrödinger Maestro 9.0 software package. The energies are single point energies obtained after structure minimization.

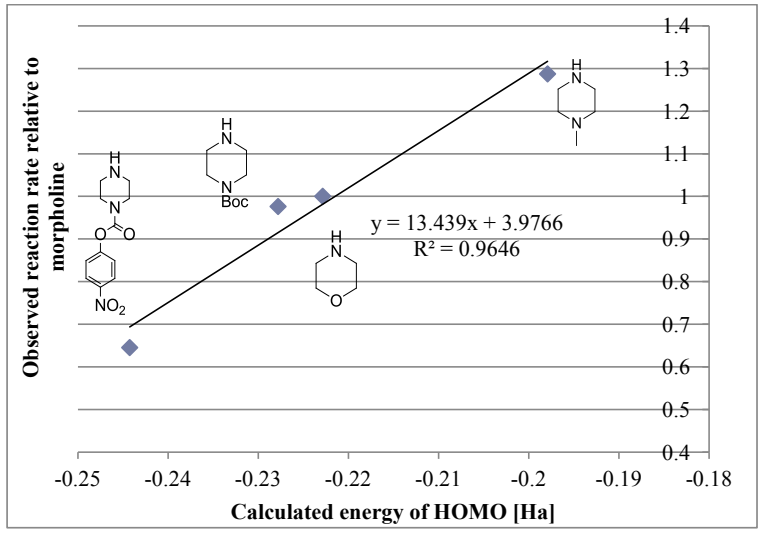


Figure 9. The effect of the amine HOMO energy on reaction rate in the conversion of **91** into **93**/**94**.

Besides the reaction rate, the diastereomeric ratio was monitored during these transformations (Figure 10) and confirmed by NMR from the crude product. This data has a lot of variation, since it incorporates the product of error from two separately measured components. Moreover, it seemed that too highly basic additives interfered with the HPLC conditions. In these cases it was not possible to monitor the dr despite all efforts to moderate the pH of the HPLC eluent. Nevertheless, it is apparent that without amine additive (or with a poor one) the dr stays low at about 6:1 throughout the reaction. With amine additives the dr starts up very high, but decays with time apparently towards the same limit.

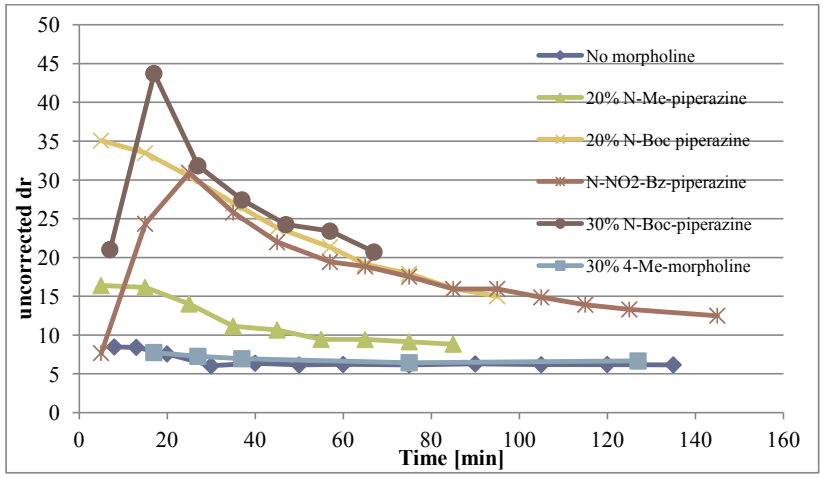


Figure 10. Diastereomeric ratio during the conversion of **91** into **93**/**94** with various additives.

As was stated, the key word is indeed time, as the epimerization can be separated from reaction progress. If we look at Figure 11 where conversion and dr plots of two reactions are shown we can see that at 95 minute mark the Boc piperazine reaction (square marker) is >99% complete and the nitrobenzoyl piperazine reaction (X marker) is 70% complete. However, the dr's of the reactions are essentially the same. This means, that the reaction mixtures are not stable and in fact there is epimerization of the 2-position even *after* all starting material has been consumed. Palladium appears to be necessary component, as stirring of the worked up reaction mixture in the presence of morpholine did not change the diastereomeric ratios.

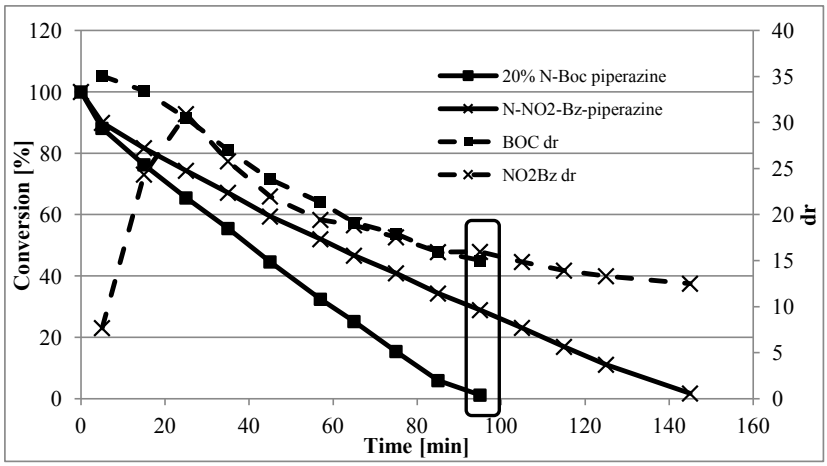


Figure 11. Comparison of conversions and dr's with two different additives in the reaction of **91** to **93**/**94**.

5.2 The effect of the aryl substituent

The fact that a thermodynamically unfavorable diastereomer is formed as the major product in the reaction indicates that the reaction is under kinetic control. Thus the data in table 4 can be used to construct a Hammett plot to probe any underlying electronic effects (Figure 12).[IV] Two domains of reactivity were revealed. In the electron rich domain the dr increases at modest rate ($\rho = +0.62$) as a function of Hammett constant. In the electron deficient domain the dr rapidly decreases ($\rho = -2.08$) as more and more electronegative substituents are introduced.

Clearly a positive charge is being formed during the rate determining step. The abrupt change in the plot might indicate a change in the rate determining step.

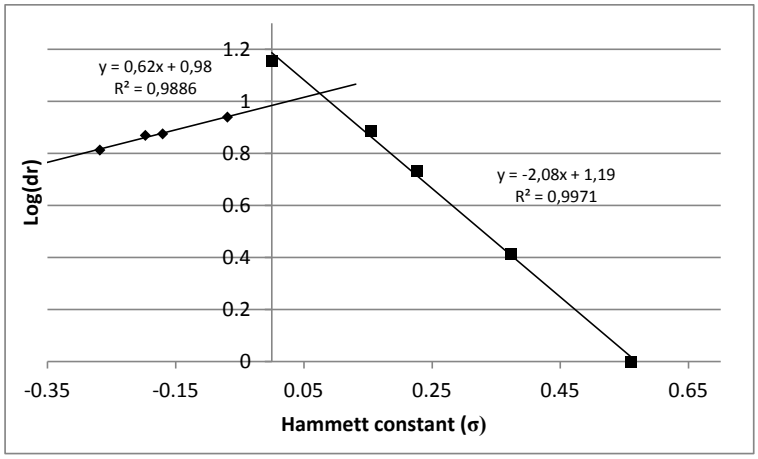
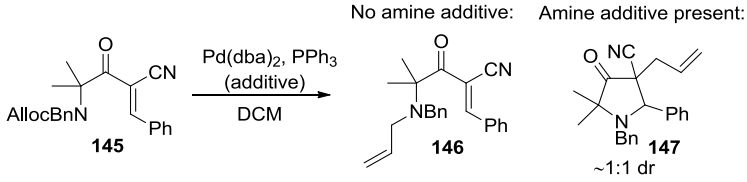


Figure 12. Hammett plot constructed from the data in table 4.

5.3 Studies concerning achiral substrate

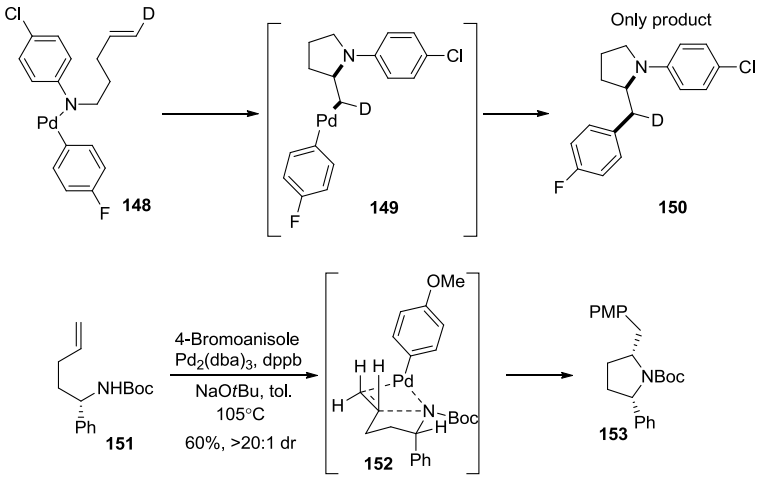
A piece of evidence about the mechanism comes from our studies on the reactions of the achiral substrate **145** derived from 2-aminoisobutyric acid (Scheme 41).



Scheme 41. Heteroannulation of **145**.

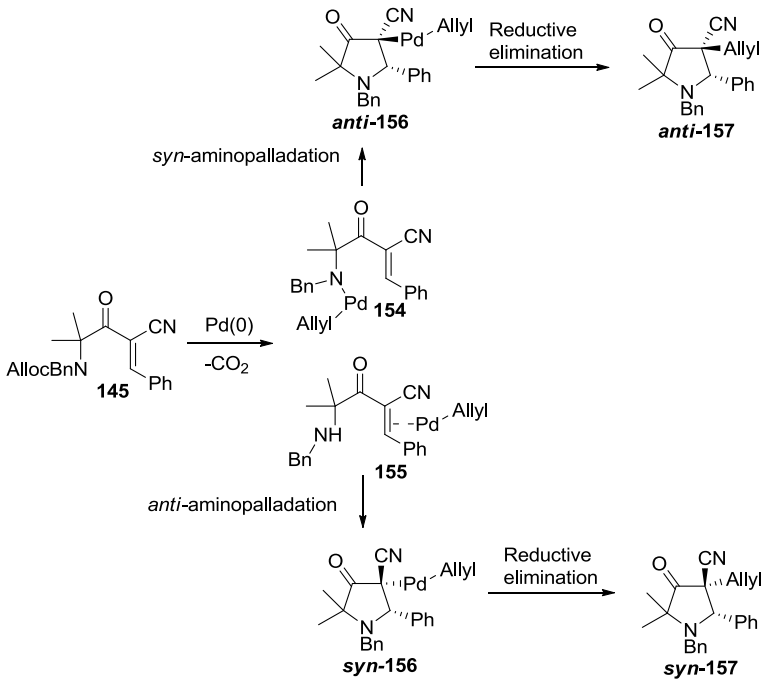
Without amine additives *no* cyclisized product **147** formed. Instead only the *N*-allylated product **146** was isolated. This clearly indicates that the amine is deeply involved in the mechanism. We also concluded that it is not necessary to have an amine, but several other additives were able to promote the formation of the desired product over the open-chain form. For example, thiophene (but not pyrrole or anillines) and tetrahydrothiophene cleanly gave the desired cyclic product.

Wolfe *et al.* have shown that Pd-N complexes such as **148** undergo *syn*-aminopalladation, and that the reductive elimination of the resulting complex **149** happens with retention of stereochemistry to give **150** as a single isomer (Scheme 42).[71] A diastereoselective carbopalladation of **151** was proposed to proceed *via* transition state structure **152** to deliver the 2,5-*trans* substituted pyrrolidine with virtually complete control.[72] The authors propose that in the transition state the $A^{1,3}$ strain between the phenyl group and Boc is minimized. A similar type of intermediate to **149** is most likely obtained from the deprotection of the Alloc group (**154**, Scheme 43), which must be the first step of the catalytic cycle. If it were to proceed similarly to the Wolfe chemistry the intermediate ***anti*-156** from *syn*-aminopalladation would indeed deliver the observed major product. However, the poor diastereoselectivity speaks against the concerted aminopalladation.



Scheme 42. Reactions of a Pd-N complexes according to Wolfe *et al.*

Wacker-type *anti*-activation by palladium(II)[73] is unlikely as formation of a complex like **155** requires a relatively nucleophilic π-system, which our system most certainly is not. This mode of reactivity would deliver *syn*-**157** as the major product. Thus, we have come to conclusion that the ring closure and the allyl transfer are two distinct steps and that the annulation does not proceed *via* the typical activation modes.



Scheme 43. Stereochemical outcomes of the known alkene activation modes.

The proposition that the annulation and the allyl transfer are separate events is also supported by the results obtained with chiral ligands. The majority of chiral phosphine ligands commercially available today are bidentate in order to produce configurationally stable complexes by eliminating Berry pseudorotation.[74] When applied to our reaction, the bidentate ligands failed utterly. Reactions did not proceed at all or became extremely slow (Scheme 44). We tested ligands with many different characteristics such as various BINAP derivatives, BIPHEP derivatives, DIOP, Josiphos, and a Trost ligand (scheme 26). The only bidentate ligands to show any activity at all were the basic BINAP (21/38% ee, 1:1 *dr*), DIOP (<10/10% ee, 1:1 *dr*) and the Trost ligand (10/5% *ee*, 6:1 *dr*). It should be noted that only the reactions with DIOP and the trost ligand reached completion within 48h. We concluded that now the rate determining step of the reaction was the dissociation of the Pd from one of the phosphorus centers slowing the reaction down considerably. This prompted us to take a look at "mono"dentate ligands, such as the PHOX series and the phosphoramidites.

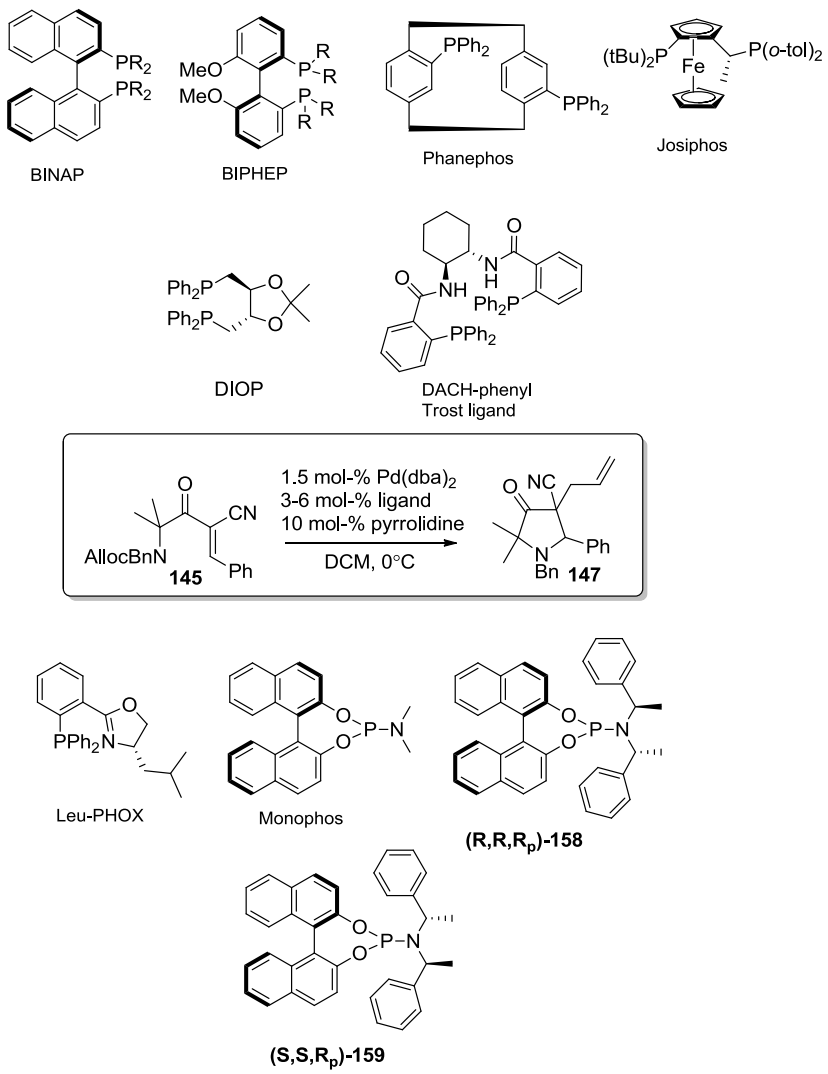
Of the monodentate ligands we tested leucine derived PHOX ligand, the prototypical phosphoramidite Monophos and two diastereomers of the bis(phenethylamine) derivative thereof. Leu-PHOX did not give any activity at all

whereas Monophos gave full conversion very swiftly but with no effect on stereochemistry at all. The two diastereomeric phosphoramidites **158** and **159** were able to impart some stereogenic information to the products, but to different degrees (Table 7). The effect of temperature is also interesting, with the peak selectivity seen at 0˚C. These results show that it is in principle possible to turn this into an enantioselective reaction, but the need for a monodentate ligand imparts significant challenges for ligand design since the ligand has to be able to control both of the steps effectively in order to gain good selectivity.

Table 7. The effect of temperature on stereoselectivity.

	(S,S,R)-159				(R,R,R)-158		
T [˚C]	dr	ee_{major}	ee_{minor}		dr	ee_{major}	ee_{minor}
20	1.70	0	26		3.75	0	10
0	1.75	15	33		6.1	28	14
-15	1.69	14	35		5.8	18	15
-20	1.55	12	36		4.8	9	13

We also tested the effect of several chiral amines in place of pyrrolidine including Jørgensen's O-TMS diphenylprolinol, a MacMillan's imidazolidinone catalyst, *R*-phenethylamine and bis(*R*-phenethylamine). However, these amines failed to induce any selectivity, thus we think it unlikely for the amine to interact with the ketone or be involved in any addition-elimination type chemistry.



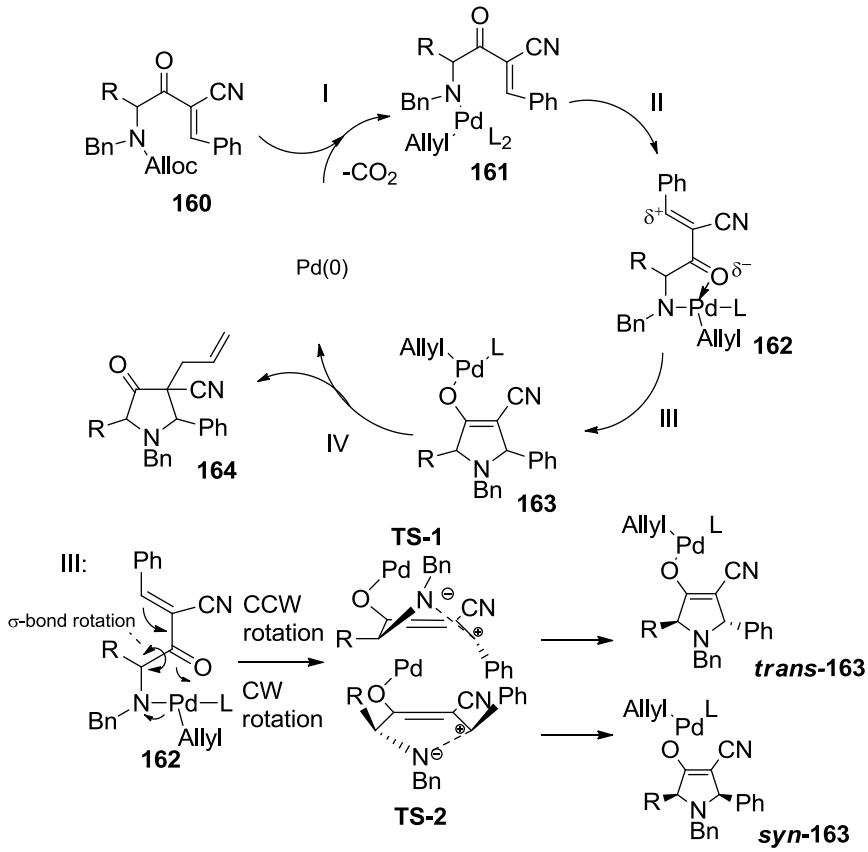
Scheme 44. The stereoselective variant and ligand structures.

5.4 Proposed mechanism

The findings disclosed herein prompted us to propose the catalytic cycle presented in Scheme 45. The step I must be the decomposition of the Alloc-group with release of CO_2 and generation of the *N*-bound allyl palladium(II) complex **161**. The palladium coordinates to the ketone oxygen (**162**), most likely in intramolecular fashion, drawing electrons from the enone system thereby generating considerable cationic character into the benzylic position and disrupting

the enone geometry. This activation mode resembles the palladium catalyzed Nazarov-reactions wherein the palladium acts as a Lewis acid by coordinating to the carbonyl oxygen.[75] The generation of complex **162** also explains the observed Hammett-plot. We propose that the step II is in fact the rate determining step in the electron poor regime of the Hammett plot; the palladium is involved in the transition state complex but does not dictate the reaction rate, at least not as much as the electronic properties of the enone system. The disruption of the enone geometry allows the formal 5-*endo*-*trig* cyclization to occur leading to the palladium enolate **163**. The soft nucleophile is ideal for intramolecular trapping of the allyl cation and thereby regeneration of the catalyst and release of product **164**.

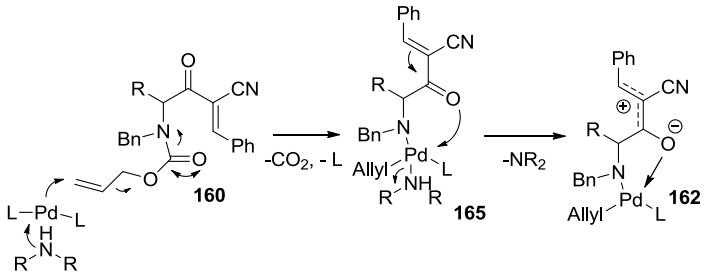
Step III is further broken down in Scheme 45 to explain the observed stereochemistry. The complex **162** undergoes the proposed N to O Pd shift alongside with simultaneous σ-bond rotation. The transition states **TS-1** and **TS-2** are thus results from the σ-bond rotating in opposite directions. Therefore, the rotational barrier around the σ-bond is an important factor determining the diastereoselectivity, an effect which is readily seen when substrates derived from different amino acids are compared. **TS-1** has the nitrogen approaching the cation from the top face. In this case the substituent R would be pseudo equatorial and lead to the kinetic product ***trans*-163**. In **TS-2** the substituent is pseudo axial. This would generate a potential steric clash with the phenyl group which would also have to adapt pseudo axial disposition as the N-C bond starts to form. This model would also explain the observed ligand effect. To generate the proposed intermediate **162** the palladium center can only accommodate one ligand. This together with the distal location of the Pd nucleus rules out all tight binding bidentate ligands and explains the relative difficulty of achieving enantioselectivity through chiral ligands.



Scheme 45. Proposed catalytic cycle.

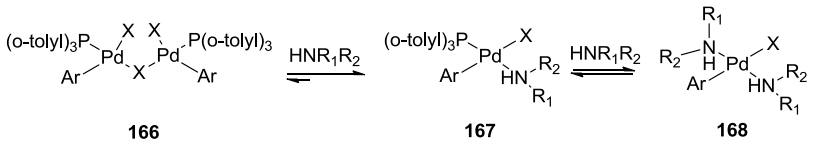
Based on the studies with the achiral substrate **145** together with the kinetic studies the amine (or other sigma donor) additive seems to enable the cyclization somehow. Most likely the amine is involved in the initial oxidative insertion step by donating electron density to the palladium nucleus. The fact that **129** refuses to cyclize without it indicates that it is also present during step II but most likely not during the annulation itself as no chiral induction was ever detected with chiral amines. Therefore, we propose the mechanism in Scheme 46. First the amine activates the palladium towards oxidative insertion by donating electron density to palladium and thereby generating complex **165**. This is not terribly important as the oxidative insertion is not the rate determining step but it does eliminate the incubation period from the beginning of the reaction. We propose that the reason why the amine activates the system towards cyclization is twofold. First of all, it discourages reductive elimination from the **165** for the same reason it encourages oxidative insertion. This buys the time needed for the generation of complex **162**.

Secondly, and more importantly, it acts as an easily displaceable ligand which is less sterically congested than the phosphine ligands. This is important when the cyclization site is crowded as it is in the case of **145**.



Scheme 46. Proposed role of the amine.

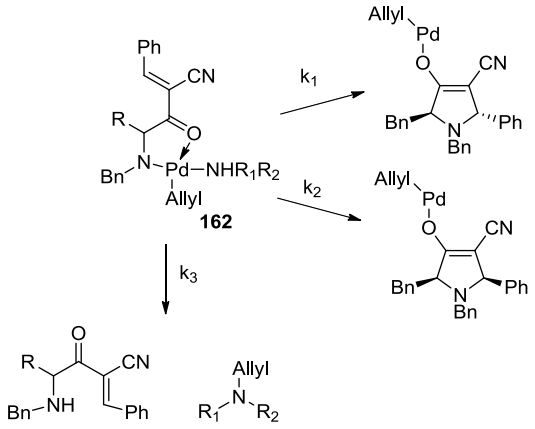
The amine complexes presented herein are not unprecedented. In fact, Buchwald has studied reactions of Pd(II) halide dimers with amines in the context of the Buchwald amination.[76,77] These studies have shown that treatment of Pd(II) halide dimers **166** with secondary or primary amines readily form the Pd-N complexes **167** and many such complexes were isolated in high yield (scheme 47). The mono amine complexes could even be converted to the bis(amine) complexes **168** in the presence of excess amine.



Scheme 47. Reactions of Pd(II) halide with benzylamine according to Buchwald *et al.*

The mode suggests that the diastereoselectivity is dictated by the steric bulk of the substituent R. The enhancement of diastereoselectivity and simultaneous decrease in yield observed in the presence of suitable amines might be due to selective destruction of complexes **162** or **163** by the amine through a kinetic resolution process (Scheme 48.). Resolution of complexes **163** is unlikely as no des-allyl products were detected in the crude reaction mixtures. However, given the instability of the des-allyl compounds it is not outright impossible. The most profound selectivity enhancement is seen with compounds which have electroneutral aryl substituent. This seems to give the perfect balance of the reaction rates, that is when $k_1>k_3>k_2$. We have shown that in the electron rich

regime (in which the rough order of rate constants is $k_1>k_2>k_3$) actually slightly raising the reaction temperature brings improvements to diastereoselectivity suggesting that the rate for the reductive elimination can be tweaked. In the end of the electron poor regime of the Hammett plot (Figure 12) apparently $k_3 \geq k_1 \approx k_2$ as seen with *m*-CN-PhCHO derivative with which the stereochemical outcome was 1:1.



Scheme 48. Kinetic resolution of complex **162**.

5.5 Conclusions

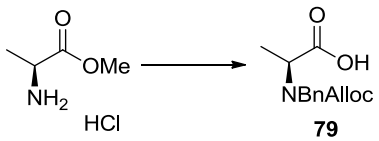
Although we have successfully demonstrated the usefulness of this novel transformation, the details of the reaction are still largely clouded. It is quite apparent that the mechanism does not follow one of the traditionally accepted pathways but instead follows a novel amine enabled mechanism for which a tentative proposition is given. The amine additive plays a key role in the mechanism, however the highly complicated interaction of the substrate properties and the amine properties need thorough investigation. Also, more work is still needed to establish the true scope of the reaction which conceivably can be extended outside the nitrile/ester-type substrates.

The experiments on the enantioselective variant suggest that inducing chiral information efficiently through the use of chiral ligands is very difficult at best. This trait is reflected on and derives from the mechanism.

6. Experimental Section

This section contains data for all the compounds not reported in any publications and that are relevant to this thesis.

Dry dichloromethane and tetrahydrofuran were obtained from a solvent drier (MB SPS-800, neutral alumina). Dimethyl formamide was from a freshly opened bottle. Other solvents used in reactions and in chromatography were of p.a. quality. Reagents were obtained from Sigma-Aldrich, from TCI or from Acros Organics (*n*-BuLi) and used as such, unless otherwise stated. TLC monitoring was performed on Merck silica gel 60 F_{254} (230 – 400 mesh, aluminum) plates. Stains used to visualize the plates were permanganate (3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 1 M NaOH, diluted to 300 mL with water), vanillin (3 g vanillin, 2.5 mL conc. H_2SO_4, 1.5 mL acetic acid, 125 mL EtOH) and UV-light (λ = 254 nm). Flash chromatography was performed on Merck Silica Gel 60 silica. The Celite used in filtrations was either Fluka Celite 501 or Sigma-Aldrich Celite 535 Coarse. NMR spectra were recorded on a Bruker Avance 400 spectrometer. The spectra were calibrated either to TMS (^{1}H: δ 0.00 ppm), MeOD (^{1}H: TMS, ^{13}C δ: 49.86 ppm), $CDCl_3$ (^{13}C: δ 77.0 ppm), $Cl_2CDCDCl_2$ (^{1}H: δ 6.00 ppm, ^{13}C δ: 73.8), toluene-d8 (^{1}H: δ 2.09 ppm, ^{13}C δ: 20.4) or to D_2O (^{1}H: δ 4.70 ppm, ^{13}C: δ 49.5 ppm, MeOH as internal standard) depending on the solvent. Spectra were recorded at 25 °C, unless otherwise stated. Heating of the NMR-samples was performed using a probe heater. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR machine. Optical rotations were measured with a Perkin-Elmer 343 polarimeter using a sodium lamp and a 10 cm quartz cuvette. Melting points were measured with a Stuart SMP30 melting point apparatus. HRMS spectra were recorded on a Waters Micromass LCT Premier (ESI / TOF) mass spectrometer.

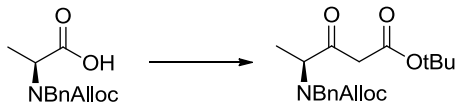


79

To a suspension of L-alanine methylester hydrochloride (14.0 g, 100 mmol, 100 mol-%) in dichloromethane (170 mL) under argon was added triethylamine (14.0

mL, 100 mmol, 100 mol-%). To the thick slurry thus formed was added benzaldehyde (11.2 mL, 110 mmol, 110 mol-%) and the mixture was stirred for 18 h. The mixture was filtered through a pad of Celite and the solvent was swapped for MeOH (150 mL). Then $NaBH_4$ (4.2 g, 110 mmol, 110 mol-%) was added in four portions while cooling with an ice bath. The mixture was stirred for 3 h after which 1M NaOH (80 mL) was added, and the methanol was evaporated. The aqueous solution was extracted with ether (2x100 mL) and the organic extracts were dried and concentrated. The residue was dissolved in acetone/water (100 mL, 50:50) and cooled with an ice bath. To the resulting colorless solution was added $NaHCO_3$ (8.4 g, 100 mmol, 100 mol-%) followed by slow addition of allyl chloroformate (11.2 mL, 105 mmol, 105 mol-%). After 1 h (little or no gas evolution) the solution was taken to rt and stirred for further 2 h. Then acetone was evaporated and the aqueous solution was extracted with ether (2x100 mL). Organic extracts were dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (100 mL) and 150 mL of 1M aq. LiOH was added. The solution was stirred until complete consumption of starting material. THF was evaporated and replaced with EtOAc. The organic layer was discarded, and the aqueous layer was acidified with 1M HCl. After extraction with EtOAc (2x 80 mL) the organic layer was dried over Na_2SO_4 and concentrated to give 16.0 g (61%) of the title product (**79**) as colorless oil.

R_f : 0.15 (70% EtOAc/Hex)
$[\alpha]_D^{20}$: -34.4 (c = 1.0, dichloromethane)
HRMS : Calculated for 264.1236 ($C_{14}H_{18}NO_4$, M + H), found 264.1235
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.42 - 7.21 (m, 5 H), 5.91 (brs, 1 H), 5.40 - 5.12 (m, 2 H), 4.72 - 4.20 (m, 5 H), 1.47 - 1.34 (m, 3 H)
^{13}C-NMR : 176.8, 156.4, 137.9, 132.4, 128.5, 127.8, 127.3, 127.1, 117.6, 66.6, 55.5, 55.0, 50.9, 50.1, 15.8, 15.1 (includes rotameric species)
IR : 1705, 1472, 1453, 1415, 1245 (film)

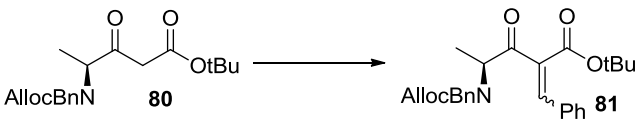


79 **80**

To a solution of **79** (14.0g, 53.3 mmol, 100 mol-%) in dry dichloromethane (130 mL) was added Meldrum's acid (8.45 g, 58.6 mmol, 110 mol-%) followed by DMAP (9.8 g, 80 mmol, 150 mol-%) under argon. The resulting solution was cooled to 0 °C and then *N,N*-dicyclohexylcarbodiimide (12.1 g, 58.6 mmol, 110 mol-%) was added over 45 minutes as a dichloromethane solution (40 mL). After

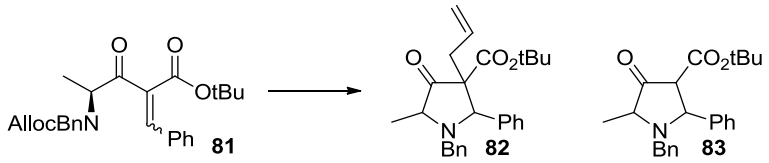
the addition the resulting slurry was stirred for 1h and then taken to rt and stirred for further 1h. Then the slurry was filtered through a pad of Celite and the filtrate was washed with 5% $KHSO_4$ solution (2x120 mL, 1x 80 mL). The organic phase was dried over sodium sulfate and concentrated (crystals of dicyclohexylurea will appear in the crude). The residue was dissolved in 50% EtOAc/hexanes (50 mL) and filtered second time, thus removing all traces of dicyclohexylurea and providing the desired Meldrum adduct in high purity after evaporation (22.0 g, assumed quantitative). The crude Meldrum adduct was dissolved in dry toluene (100 mL) and 20 mL of *t*BuOH and the solution was heated to 80 °C under argon atmosphere. After 1.5h the bubbling had ceased thus signaling the end of reaction. The mixture was concentrated, loaded on a short pad of silica and eluted with 30% EtOAc/Hex until no more organics passed through. After concentrating 17.9 g (93%, > 95% pure by NMR) of clear, slightly yellow oil was obtained.

R_f : 0.8 (50% EtOAc/Hex)
$[\alpha]_D^{20}$: -41.4 (c = 1.0, dichloromethane)
HRMS : Calculated 362.1967 ($C_{20}H_{28}NO_5$, M+H), found 362.1967
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.38 - 7.24 (m, 5 H), 5.98 - 5.84 (m, 1 H), 5.33 - 5.18 (m, 2 H), 4.75 - 4.56 (m, 3 H), 4.50 - 4.25 (m, 1.5 H), 4.01 (d, *J* = 6.2 Hz, 0.5 H), 3.48 - 3.12 (m, 2 H), 1.43 (s, 9 H), 1.30 - 1.23 (m, 3 H)
^{13}C-NMR : 200.7, 166.2, 165.9, 153.1, 151.7, 135.9, 128.5, 128.4 128.2, 128.0, 127.6, 82.2, 67.7, 67.2, 65.8, 65.5, 65.0, 64.7, 48.1, 47.3, 28.2, 27.9, 25.9, 25.1
IR : 3430, 1743, 1713, 1455, 1417, 1369, 1324, 1244, 1149 (film)

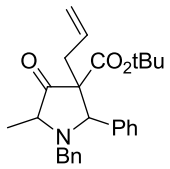


To a solution of **80** (725 mg, 2.0 mmol, 100 mol-%) in EtOH (4 mL) was added benzaldehyde (300 µL, 3.0 mmol, 150 mol-%) followed by pyrrolidine (164 µL, 2.0 mmol, 100 mol-%). The flask was sealed with a cap and stirred for 16h prior to concentration. The crude product was purified on silica gel (10% MTBE/hexane) to give 600 mg (66%) of **81**.

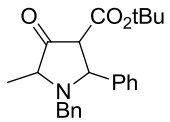
R_f : 0.55 (30% MTBE/Hex)
HRMS : Calculated for 450.2280 ($C_{27}H_{32}NO_5$, M+H), found 450.2293
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.79 - 7.70 (m, 1 H), 7.58 – 7.09 (m, 10H), 6.04 – 5.72 (m, 1 H), 5.53 – 4.48 (m, 3 H), 4.80 – 3.99 (m, 5 H), 1.33 – 1.20 (m, 3 H)



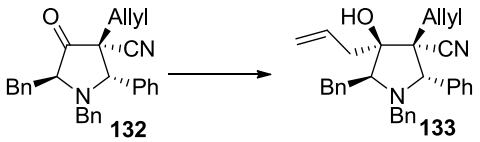
To a solution of **81** (600 mg, 1.33 mmol, 100 mol-%) and $PhSO_2Na$ (230 mg, 1.40 mmol, 105 mol-%) in MeOH/THF (1:2, 4 mL) was added $Pd(PPh_3)_4$ (30 mg, 0.026 mmol, 2 mol-%). The resulting orange mixture was stirred for 35 min and then concentrated *in vacuo*. The mixture was transferred to an extraction funnel using Et_2O and 1M HCl. The organic phase was separated, dried over sodium sulfate and concentrated. Flash chromatographic purification (10 -> 30% MTBE/hexanes) afforded 440 mg of the title compounds **82** and **83** as a 1:0.6 mixture by NMR.



R_f : 0.56 (15% MTBE/Hex)
HRMS : Calculated for 406.2382 ($C_{26}H_{32}NO_3$, M+H), found 406.2380
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.61 – 7.13 (m, 10 H), 5.86 – 5.72 (m, 1 H), 5.33 – 5.26 (m, 2 H), 4.32 (s, 1 H), 3.97 (d, *J* = 14.6 Hz, 1 H), 3.82 (d, *J* = 7.1 Hz, 1 H), 3.41 (d, *J* = 14.6 Hz, 1 H), 2.85 – 2.77 (m, 1 H), 2.62 (dd, *J* = 14.5, 8.8 Hz, 1 H), 1.27 (s, 9 H), 1.13 (d, *J* = 7.1 Hz, 3 H)

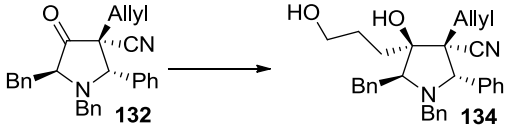


R_f : 0.56 (15% MTBE/Hex)
HRMS : Calculated for 366.2069 ($C_{23}H_{28}NO_3$, M+H), found 366.2082
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.61 – 7.13 (m, 10 H), 4.20 (d, *J* = 10.2 Hz, 1 H), 3.97 (d, *J* = 14.1 Hz, 1 H), 3.57 (d, *J* = 14.3 Hz, 1 H), 3.22 (d, *J* = 10.2 Hz, 1 H), 3.01 (dd, *J* = 13.2, 6.6 Hz, 1 H), 1.40 (s, 9 H), 1.19 (d, *J* = 6.6 Hz, 3 H)



To a solution of **132** (320mg, 0.78 mmol, 100 mol-%) in dry THF (5 mL) under argon at 0°C was added allylmagnesium bromide (0.94 mL, 0.94 mmol, 125 mol-%, 1M in Et_2O). After 30 min the reaction was quenched with sat. NH_4Cl. The aqueous layer was extracted with Et_2O. The combined organic layers were dried over sodium sulfate and concentrated. The crude was purified on silica and then crystallized from MTBE/hexane to give 180 mg (50%) of **133** as clear colorless sheets.

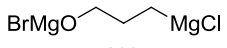
R_f : 0.38 (40% Et_2O/Hex)
$[\alpha]_D^{20}$: -47.5 (c = 1.0, dichloromethane)
HRMS : Calculated for 449.2593 ($C_{31}H_{33}N_2O$, M + H), found 449.2575
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.71 – 7.55 (m, 2 H), 7.46 – 7.25 (m, 9 H), 7.21 – 7.09 (m, 3 H), 6.88 (d, *J* = 7.3 Hz, 1 H), 5.85 – 5.73 (m, 1 H), 5.37 – 5.24 (m, 1 H), 5.23 – 5.10 (m, 2 H), 4.99 – 4.91 (m, 2 H), 4.18 (s, 1 H), 3.91 (d, *J* = 14.6 Hz, 1 H), 3.75 (dd, *J* = 8.8 Hz, 4.6 Hz, 1 H), 3.53 (d, *J* = 14.6 Hz, 1 H), 3.04 – 2.93 (m, 2 H), 2.81 (dd, *J* = 14.3 Hz, 7.1 Hz, 1 H), 2.64 (dd, *J* = 13.9 Hz, 7.9 Hz, 1 H), 2.56 (dd, *J* = 13.9 Hz, *J* = 7.0 Hz, 1 H), 2.45 (dd, *J* = 14.3 Hz, 7.1 Hz, 1 H), 2.06 (s, 1 H)
^{13}C-NMR : 140.1, 138.4, 136.3, 133.4, 132.1, 129.4, 129.2, 128.8, 128.4, 128.3, 127.8, 126.9, 125.8, 121.3, 120.4, 119.2, 80.1, 72.4, 67.3, 58.0, 49.8, 45.3, 37.1, 29.5
IR : 3425, 3080, 3024, 2914, 2244, 1640, 1602, 1493, 1454, 1434, 924 (KBr tablet)



To a solution of **132** (100 mg, 0.25 mmol, 100 mol-%) in dry THF (2.5 mL) under argon was added **169** (1.25 mL, ~0.2M in THF, see below for preparation) at 0°C. After the addition the mixture was taken to rt and quenched after 30 min with sat. NH_4Cl. The mixture was diluted with Et_2O (5 mL) and the layers were separated. The aq. phase was extracted with Et_2O and the combined organic layers were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (Et_2O) to give 90 mg (78%) of **134** foamy white solid.

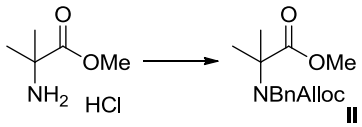
R_f : 0.08 (40% Et_2O/Hex)
$[\alpha]_D^{20}$: -68.4 (c = 0.5, dichloromethane)
HRMS : Calculated for 467.2699 ($C_{31}H_{35}N_2O_2$, M + H), found 467.2680

^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.68 – 7.51 (m, 2 H), 7.46 – 7.23 (m, 8 H), 7.20 – 7.09 (m, 3 H), 6.98 – 6.90 (m, 2 H), 5.93 – 5.79 (m, 1 H), 5.28 – 5.11 (m, 2 H), 4.15 (s, 1 H), 3.97 – 3.98 (m, 1 H), 3.86 (d, *J* = 14.5 Hz, 1 H), 3.66 (dd, *J* = 8.1, 4.2 Hz, 1 H), 3.52 (d, *J* = 14.5 Hz, 1 H), 3.48 – 3.43 (m, 2 H), 3.06 (dd, *J* = 13.5, 8.2 Hz, 1 H), 2.99 (dd, *J* = 13.5, 4.2 Hz, 1 H), 2.88 (ddt, *J* = 14.3, 7.0, 1.3 Hz, 1H), 2.54 – 2.45 (m, 1 H), 2.22 – 2.12 (m, 1 H), 2.09 – 1.98 (m, 1 H), 1.82 – 1.61 (m, 2 H), 1.53 – 1.21 (m, 3 H), 0.97 – 0.85 (m, 1 H)
^{13}C-NMR : 140.9, 138.5, 136.7, 133.8, 129.4, 129.3, 128.7, 128.32, 128.29, 128.1, 127.8, 126.8, 125.6, 120.9, 119.1, 80.8, 72.5, 67.3, 62.8, 58.2, 50.0, 38.8, 38.1, 29.2, 26.6
IR : 3436, 3025, 2960, 2243, 1601, 1494, 1454, 1432, 922 (KBr tablet)



169

To a solution of 3-chloropropanol (2.0 mL, 24 mmol, 100 mol-%) in dry THF (80 mL) under argon at 0°C was added methylmagnesium bromide (8.8 mL, 24 mmol, 100 mol-% 2.74M in Et_2O). Then magnesium turnings (1.17 g, 48.0 mmol, 200 mol-%) were added followed by 240 µL of 1,2-dibromoethane. The mixture was taken to room temperature for 10 minutes and then heated to reflux for 45 minutes. The mixture was then allowed to cool to room temperature and titrated to be 0.16 - 0.22M.



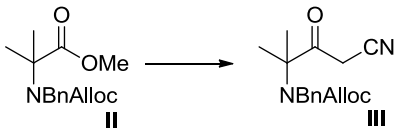
II

To a solution of dimethylglycine methyl ester hydrochloride (3.6 g, 24.0 mmol, 100 mol-%) in MeOH (25 mL) was added sodium bicarbonate (2.21 g, 24.4 mmol, 110 mol-%) followed by PhCHO (2.5 mL, 24 mmol, 100 mol-%). The vessel was sealed and stirred overnight. To the white suspension thus formed was added $NaBH_4$ (0.9 g, 24 mmol, 100 mol-%) is several portions. The mixture was stirred for 1 h and then acidified with 2M HCl. Methanol was evaporated *in vacuo* and the residue was washed 2x20 mL Et_2O. The aqueous layer was basified with 2M NaOH and extracted 3x20 mL Et_2O. The organic phase was dried over sodium sulfate and concentrated to give 3.58g clear colorless oil.

The oil was dissolved in acetone/H_2O (9/9 mL). To the solution was added sodium bicarbonate (1.6 g, 18.6 mmol, 110 mol-%) followed by AllocCl (2.24 mL, 18.6 mmol, 110 mol-%). The mixture was stirred for 16 h. Acetone was evaporated and

the aqueous layer extracted 3x10 mL Et_2O. The organic phase was dried over sodium sulfate and concentrated to give 4.84 g (69%) of clear colorless oil.

R_f : 0.44 (30% EtOAc/Hex)
HRMS : Calculated 292.1549 (C16H22NO4, M+H), found 292.1555
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.40 – 7.31 (m, 4 H), 7.28 – 7.23 (m, 1 H), 5.90 (ddd, *J* = 22.6 Hz, *J* = 10.5 Hz, *J* = 5.4 Hz, 1 H), 5.34 – 5.10 (m, 2 H), 4.77 (s, 2 H), 4.63 (dt, *J* = 5.5 Hz, 1.5 Hz, 2 H), 3.74 (s, 3 H), 1.44 (s, 6 H)
^{13}C-NMR : 175.1, 156.0, 139.4, 132.5, 128.4, 126.8, 126.5, 117.5, 66.4, 61.8, 52.3, 47.1, 24.5



To a solution of *n*-BuLi (24.4 mL, 48.7 mmol, 2.0M in hexane, 195 mol-%) in THF (50 mL) was added MeCN (2.44 mL, 49.9 mmol, 200 mol-%) dropwise at -78°C under argon. The suspension was then stirred for 20 min prior to addition of **II** (7.3 g, 25.0 mmol, 100 mol-%) as a THF solution (45 + 5 mL) *via* cannula. The mixture was warmed to -50°C, at which temperature the color of the mixture changed from light yellow to orange. TLC indicated complete conversion. The reaction was quenched by pouring it into 50 mL of 1M HCl. The mixture was diluted with Et_2O (35 mL). The organic layer was separated and washed with water and brine, then dried over sodium sulfate and concentrated. The residue was purified by filtering it through a pad of silica (eluted with 30% EtOAc/Hex) to give 5.7 g (76%) of an colorless oil.

R_f : 0.31 (30% EtOAc/Hex)
HRMS : Calculated 301.1552 ($C_{17}H_{21}N_2O_3$, M+H), found 301.1550
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.41 – 7.28 (m, 5 H), 6.00 – 5.88 (m, 1 H), 5.38 – 5.22 (m, 2 H), 4.69 (dt, *J* = 5.9 Hz, *J* =1.3 Hz, 2 H), 4.66 (s, 2 H), 3.56 (s, 2 H), 1.36 (s, 6 H)
^{13}C-NMR : 206.9, 156.5, 138.4, 131.9, 128.8, 127.6, 127.0, 118.8, 114.4, 67.2, 66.7, 47.2, 26.2, 22.8
IR : 2990, 1734, 1683, 1403, 765, 750 (film)

To a solution of **III** (5.7 g, 18.9 mmol, 100 mol-%) in DCM (31 mL) was added molecular sieves (4Å, 6 g), PhCHO (2.31 mL, 22.7 mmol, 120 mol-%) and morpholine (380 µL, 4.3 mmol, 23 mol-%). The mixture stirred until complete by TLC (1.5 h). 25 g of silica was added to the mixture which was then concentrated to a free-flowing powder *in vacuo*. The powder was loaded on a silica column and carefully eluted with 10% to 20% Et_2O/Hexanes to give 4.9 g (67%) of slightly yellow solid.

R_f : 0.56 (30% EtOAc/Hex)
HRMS : Calculated 389.1865 ($C_{24}H_{25}N_2O_3$, M+H), found 389.1866
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 8.45 – 8.32 (broad s, 1 H), 8.05 – 7.98 (m, 2 H), 7.59 – 7.48 (m, 3 H), 7.41 – 7.27 (m, 5 H), 5.99 – 5.77 (m, 1 H), 5.29 (broad d, *J* = 17.4 Hz, 1 H), 5.14 (ddd, *J* = 10.4 Hz, 2.6 Hz, 1.3 Hz, 1 H), 4.86 (s, 2 H), 4.66 (s, 2 H), 1.49 (s, 6 H)
^{13}C-NMR : 192.3, 156.0, 138.4, 136.4, 134.4, 132.8, 132.2, 131.2, 129.7, 129.1, 128.6, 127.7, 127.4, 118.1, 105.7, 66.8, 65.9, 47.5, 23.2
IR : 2987, 2206, 1708, 1673, 1584, 1402, 1228, 1083 (KBr disk)

Procedure for the reaction progress kinetics:

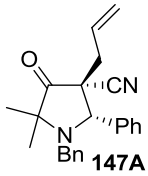
A 5 mL round bottom flask equipped with a magnetic stir bar was charged with **91** (200.0 mg, 0.444 mmol, 100 mol-%) and *trans*-stilbene (40.2 mg) as internal standard. The flask was flushed with argon, sealed with a septum and equipped with an argon balloon. The contents were then dissolved in DCM (4.0 mL, 0.111M) and the vial was placed in an ice bath. To the solution thus formed were added the additive in appropriate quantity. The 0 sample was taken by withdrawing a 13µL aliquot through the septum and immediately injecting it into a vial containing 1.0 mL of the HPLC eluent. This sample was used to calculate the response factor and to confirm the HPLC-system stability. If significant drift was noticed in the retention times a standard prepared from a mixture of **93** and **94** was run to make sure there was complete separation of the products within the allotted analytical timeframe (10 minutes). Finally $(allylPdCl)_2$ (4.9 mg, 3 mol-%, unless otherwise stated) was added together with PPh_3 (15.1 mg, 15 mol-%) as solids. The reaction was sampled 5 minutes after introduction of the catalyst system and in about 10 minute intervals after that using the procedure described above.

The HPLC system:

Waters 501 pump together with Waters 2487 UV-detector at 220 nm was used. A Phenomenex Kinetex 5µ C18 100Å (250 x 4.60 mm) column was used with eluent system being 66:34 MeCN/Water at 1.0 mL/min. Retention times for the monitored species: *trans*-stilbene (6.3 min), **91** (7.1 min), **94** (8.9 min), **93** (9.3 min). Total analysis time: 10 minutes.

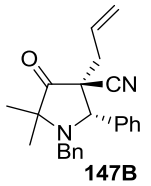
Chiral ligand screen:

A vial was charged with of **145** (50 mg, 0.13 mmol, 100 mol-%), $Pd(dba)_2$ (2.2 mg, 3 mol-%) and the appropriate ligand (3 mol-% for bidentate ligands and 6 mol-% for monodentate ligands). The vial was flushed with argon and sealed with a septum. The vial was then heated or cooled to the appropriate temperature, 1 mL of DCM was added followed by 1µL of pyrrolidine. The reaction was run until complete and then filtered through a pad of silica. The crude product was analyzed by HPLC (Chiralpak 1A, 5% iPrOH/Hex, 1mL/min). **147A** retention 5.2 min and 8.4 min. **147B** retention 5.75 min and 6.6 min.



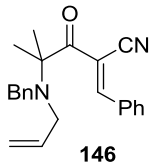
147A

R_f : 0.42 (40% Et_2O/Hex)
HRMS : Calculated 345.1967 ($C_{23}H_{25}N_2O$, M+H), found 345.1950
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.82 – 7.16 (m, 10 H), 5.75 – 5.62 (m, 1 H), 5.32 – 5.24(m, 2 H), 4.05 (s, 1 H), 3.80 (d, *J* = 14.5 Hz, 1 H), 3.49 (d, *J* = 14.5 Hz, 1 H), 2.77 (ddt, *J* = 14.3, 6.2, 1.4 Hz, 1 H), 2.53 (ddt, *J* = 14.3, 8.3, 0.9 Hz, 1 H), 1.22 (s, 3 H), 1.09 (s, 3 H)
^{13}C-NMR : 209.1, 139.2, 135.2, 129.1, 129.0, 128.8, 128.63, 128.58, 128.3, 128.2, 127.2, 121.3, 116.3, 68.9, 66.1, 53.9, 50.7, 35.8, 27.8, 16.6



147B

R_f : 0.42 (40% Et_2O/Hex)
HRMS : Calculated 345.1967 ($C_{23}H_{25}N_2O$, M+H), found 345.1950
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.82 – 7.16 (m, 10 H), 5.61 – 5.48 (m, 1 H), 5.15 – 5.10 (m, 1 H), 5.03 (ddd, *J* = 16.8, 2.7, 1.3 Hz, 1 H), 4.53 (s, 1 H), 3.98 (d, *J* = 14.5 Hz, 1 H), 3.56 (d, *J* = 14.5 Hz, 1 H), 2.61 (ddt, *J* = 14.3, 7.7, 0.9 Hz, 1 H), 2.12 (ddt, *J* = 14.4, 6.9, 1.1 Hz, 1 H), 1.34 (s, 3 H), 0.97 (s, 3 H)
^{13}C-NMR : 208.3, 138.9, 133.9, 130.2, 129.1, 129.0, 128.8, 128.63, 128.58, 128.3, 128.2, 127.4, 120.4, 117.5, 70.6, 66.4, 52.4, 51.3, 35.3, 27.3, 17.6



146

To a solution of **145** (115 mg, 0.29 mmol, 100 mol-%) in DCM (2.6 mL) was added $Pd(dba)_2$ (5 mg, 0.9 µm, 3 mol-%) together with PPh_3 (8 mg, 0.03 mmol, 10 mol-%) at rt. The reaction was monitored by TLC and after completion the reaction mixture was absorbed on silica gel and purified by column chromatography to give 89 mg (88%) of the title compound.

R_f : 0.24 (40% Et_2O/Hex)
HRMS : Calculated 344.1967 ($C_{23}H_{25}N_2O$, M+H), found 345.1952
^{1}H-NMR : (400MHz ,$CDCl_3$) δ = 7.90 – 7.83 (m, 2 H), 7.66 (s, 1 H), 7.54 – 7.47 (m, 3 H), 7.40 – 7.28 (m, 5 H), 5.97 (qd, *J* = 17.2, 5.3 Hz, 1 H), 5.34 (ddd, *J* = 17.2, 3.3, 1.6 Hz, 1 H), 5.23, (ddd, *J* = 10.4, 2.9, 1.5 Hz, 1 H), 4.52 (d, *J* = 16.1 Hz, 1 H), 4.44 (d, *J* = 16.1 Hz, 1 H), 4.29 (ddt, *J* = 12.8, 5.3, 1.6 Hz), 4.13 (ddt, *J* = 12.8, 5.5, 1.6 Hz, 1 H), 1.50 (s, 3 H), 1.12 (s, 3 H)
^{13}C-NMR : 220.1, 154.5, 147.5, 137.5, 133.2, 131.79, 131.75, 129.6, 129.1, 128.7, 127.7, 127.4, 117.2, 116.1, 105.5, 105.1, 66.2, 64.9, 44.2, 24.3, 20.2

7. References

[1] Pettus, B. J.; Chalfant, C. E.; Hannun, Y. A. *Biochimica et Biophysica Acta* **2002**, *1585*, 114-125.

[2] Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. *Angew. Chem.,Int. Ed.* **2003**, *42*, 5274.

[3] Kumpulainen, E. *Total synthesis of Amaminols*, Doctoral dissertation **2010**, TKK Dissertations 219, ISBN 978-952-60-3092-0.

[4] Niwa, T.; Inouye, S.; Tsuruoka, T.; Niida, T.; Koaze Y. *Agrig. Biol. Chem.*, **1970**, *34*, 966-967.

[5] Habrant, D.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2010**, *8*, 4364-4373.

[6] For general discussion on enantioselective synthesis, see e.g. a) Koskinen, A. M. P. *Asymmetric Synthesis of Natural Products*, Wiley, 2nd Ed. **2012**; b) Corey, E. J.; Kűrti, L. *Enantioselective Chemical Synthesis,* Direct Book Publishing, LLC, 1st ed, **2010**; c) Walsh, P.; Kowzlowski, M. *Fundamentals of Asymmetric Catalysis*, University Science Books, **2008**.

[7] a) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326; b) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574; c) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem.* **2004**, *116*, 5558; *Angew. Chem. Int. Ed.* **2004**, *43*, 5442–5444

[8] For examples featuring a-hydroxy ketones see: a) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712-471;. b) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777-8785; c) Trost, B. M., Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778-2779. For a review on Mannich reaction in general, see: Kobayashi, S.; Mori, Y.; Fossey, S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626-2704.

[9] Adia, M.; Hénaff, N.; Whiting A. *Tetrahedron Lett.* **1997**, *38*, 3101-3103.

[10] Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361-2364.

[11] Duthaler, R. O. *Angew. Chem.* **1991**, *103*, 729-731.

[12] Young, C.-K.; Krische, M. J, *J. Am. Chem. Soc.* **2006**, *128*, 17051-17056.

[13] Cella, R.; Venturoso, R. C.; Stefani, H. A. *Tetrahedon Lett.* **2008**, *49*, 16-19.

[14] Nicholas, G. M.; Molinski, T. F. *J. Am. Chem. Soc.* **2000**, *122*, 4011-4019.
[15] Restorp, P.; Somfai, P *Org. Lett.* **2005**, *7*, 893-895.

[16] Gruza, H.; Kiciak, K.; Krasinski, A.; Jurczak, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2627-2631.

[17] Kato, A.; Kato, N.; Kano, E.; Adachi, I.; Ikeda, K.; Yu, L.; Okamoto, T.; Banba, Y.; Ouchi, H.; Takahata, H.; Asano, N. *J. Med. Chem.* **2005**, *48*, 2036-2044.

[18] Cha, K. J.; Christ, W. G. ; Kishi, Y. *Tetrahedron Lett.* **1983**, *37*, 3943-1946.

[19] Murakami, T.; Furusawa, K. *Tetrahedron* **2002**, *58*, 9257-9263.

[20] Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197-5200.

[21] Karjalainen, O. K.; Passiniemi, M.; Koskinen, A. M. P. *Org. Lett.* **2010**, *12*, 1145-1147.

[22] Bernard, M. *Chemical Risk Analysis: A Practical Handbook*, Butterworth-Heinemann **2004**, p. 342.

[23] Dupau, P.; Epple, R.; Thomas, A.A.; Fokin, V.V.; Sharpless, K.B. *Adv. Synth. Catal.* **2002**, *344*, 421-433.

[24] For recent reviews see: a) Cant, A. A.; Sutherland, A. *Synthesis* **2012**, *44*, 1935-1951; b) Cochi, A.; Pardo, D. G.; Cossy, J. *Eur. J. Org. Chem.* **2013**, 809-829.

[25] Epp, B. J.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293.

[26] Ajinomoto Co. Inc., US Patent: US5767316 A1, **1998**.

[27] Concellon, L. M.; Riego, E.; Rodriguez-Solla, H.; Plutin, A. M. *J. Org. Chem.* **2001**, *66*, 8661-8665.

[28] Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189 - 3192.

[29] Li, B.; Buzon, R. A.; Chiu, C. K.-F.; Colgan, S. T.; Jorgensen, M. L.; Kasthurikrishnan, N. *Tetrahedron Lett.* **2004**, *45*, 6887-6890.

[30] Li, H.; He, A,; Falck, J. R.; Liebeskind, L. S. *Org. Lett.* **2011**, *13*, 3682-3685.

[31] Nahm, S.; Weinreb, S. *Tetrahedron Lett* **1981**, *22*, 3815-3818.

[32] Pfizer Products Inc., Patent: WO2003095439 A1, **2003**.

[33] a) Sengupta, S.; Modal, S.; Das, D. *Tetrahedron Lett.* **1999**, *40*, 4107-4110; b) Clark, C. T.; Milgram, B. C.; Scheidt K. A. *Org. Lett.* **2004**, *6*, 3977-3980.

[34] Peters, R.; Waldmeier, P.; Joncour A. *Org. Proc. Res. Dev.* **2005**, *9*, 508-512.

[35] Qu, B.; Collum, D. B. *J. Org. Chem.* **2006**, *71*, 7117-7119.

[36] In the context of amino acid derivatives the earliest example is Almquist, R. G.; Chao, W.-R.; Ellis, M. E.; Johnson, H. W. *J. Med. Chem.* **1980**, *23*, 1392 - 1398. The seminal publication describing the use of 2-thiopyridyl esters is: Mukaiyama, T.; Araki, M.; Takei, H. *J. Am. Chem. Soc.* **1973**, *95*, 4763 - 4765.

[37] Almquist, R. G.; Chao, W.-R.; Judd, A. K.; Mitoma C.; Rossi, D. J.; Panasevich, R. E.; Matthews R. J. *J. Med. Chem.* **1988**, *31*, 561-567.

[38] Vázquez, J.; Albericio, F. *Tetrahedron Lett.* **2002**, *43*, 7499-7502.

[39] Katritzky, A. R.; Le, K. N. B,; Khelashvili, L.; Mohapatra, P. P. *J, Org. Chem.* **2006**, *71*, 9861-9864.

[40] Schrey, A.; Osterkamp, F.; Straudi, A.; Rickert, C.; Wagner, H.; Koert, U.; Herrschaft, B.; Harms, K. *Eur. J. Org. Chem.* **1999**, 2977-2990.

[41] Mann, E.; Kessler, H. *Org. Lett.* **2003**, *5*, 4567-4570.

[42] Lin, W.; Theberge, C. R.; Henderson, T. J.; Zercher, C. K.; Jasinski, J.; Butcher, R. J. *J. Org. Chem.***2009**, *74*, 645-651.

[43] Tae, H. S.; Hines, J.; Schneekloth, A. R.; Crews, C. M. *Org Lett.* **2010**, *12*, 4308-4311.

[44] Pells, A.; Koskinen, A. M. P, unpublished results.

[45] Hoffman, R.V.; Maslouh, N. and Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045 – 1056.

[46] Kumpulainen, E. *Total synthesis of Amaminols*, Doctoral dissertation **2010**, TKK Dissertations 219, ISBN 978-952-60-3092-0.

[47] Reetz, M. T.; Schmitz, A. *Tetrahedron Lett.* **1999**, *40*, 2737-2740.

[48] Baldwin, J. E. *J. Chem Soc., Chem. Commun.* **1976**, 734-736.

[49] Thompson, C. M.; Frick, J. A.; Green, D. L. C. *J. Org. Chem.* **1990**, *55*, 111-116.

[50] Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932-8936.

[51] Lehnert, W. *Tetrahedron Lett.* **1970**, *11*, 4723-4724.

[52] Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392-393.

[53] Shu, L.; Li, Z., Fishlock, D. *Org. Process Res. Dev.* **2013**, *17*, 247-256.

[54] Zhao, Y.; Liu, L.; Sun, W.; Lu, J.; McEachern, D.; Li, X.; Yu, S.; Bernard, D.; Ochsenbein, P.; Ferey, V.; Carry, J.-C.; Deschamps, J. R., Sun, D.; Wang, S. *J. Am. Chem. Soc.* **2013**, ASAP: DOI: 10.1021/ja3125417

[55] Liu, Y.-T. L.; Wong, J. K.; Tao, M.; Osterman, R.; Sannigrahi, M.; Girijavallabhan, V. M.; Saksena, A. *Tetrahedron Lett.* **2004**, *45*, 6097-6100.

[56] Buckman, B.; Nicholas, J. B.; Serebryany, V.; Seivert, S. D. Intermune Inc., Patent WO2012/40242 A1.

[57] Actelion Pharmaceuticals LTD, Patent WO2009077989 A1.

[58] Wang, Y.; Ma, D. *Tetrahedron: Asymmetry* **2001**, *12*, 725-730.

[59] Blanco, M.-J.; Sardina, F. J. *J. Org. Chem.* **1996**, *61*, 4748-4755.

[60] Poisson, J.-F.; Orellana, A.; Greene, A. E., *J. Org. Chem.* **2005**, *70*, 10860-10863.

[61] Wang, Y.; Ma, D. *Tetrahedron: Asymmetry* **2001**, *12*, 725-730.

[62] Cai, S.; Gorityala, B. K.; Ma, J.; Leow, M. L.; Liu, X.-W. *Org. Lett* **2011**, *13*, 1072-1075.

[63] Daiichi Sankyo Company, LTD, Patent: EP2298778 A1, 2011, example 68.

[64] Pfizer Inc., Patent WO2005/26114 A1.

[65] Bristol-Myers Squibb Company, Patent: US2010/150866 A1.

[66] Stanway, S. J.; Thomas, E. J. *Tetrahedron* **2012**, *68*, 5998-6009.

[67] Koskinen, A.M.P.; Chen, J.S. *Tetrahedron Lett.* **1991**, *32*, 6977–6980.

[68] Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.

[69] Sakai, N. and Ohfune, Y. *J. Am. Chem. Soc.* **1992**, *114*, 998-1010.

[70] Kauppinen, P. M.; Koskinen, A. M. P. *Tetrahedron Lett.* **1997**, *38*, 3103-3106.

[71] Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 6276-6277.

[72] Lemen, G. S.; Wolfe, J. P. *Org Lett.* **2010**, *12*, 2322-2325.

[73] a) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.***2006**, *128*, 3130-3131. b) W. He, K.-T. Yip, N.-Y. Zhu, D. Yang, Org. Lett. 2009, 11, 5626–5628; c) Weinstein, A. B.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 11505-11509.

[74] Berry, R. S. *J. Org. Phys.* **1960**, *32*, 933-939.

[75] a) Shimada, N.; Stewart, C.; Bow, W. F.; Jolit, A.; Wong, K.; Zhou, Z.; Tius, M. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 5727 – 5729. b) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.*, **2003**, *5*, 4927 - 4930.

[76] Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755 - 2763.

[77] Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534 - 3542.

Aalto-DD 159/2013

ISBN 978-952-60-5369-1
ISBN 978-952-60-5370-7 (pdf)
ISSN-L 1799-4934
ISSN 1799-4934
ISSN 1799-4942 (pdf)

Aalto University
School of Chemical Technology
Department of Chemistry
www.aalto.fi

BUSINESS +
ECONOMY

ART +
DESIGN +
ARCHITECTURE

SCIENCE +
TECHNOLOGY

CROSSOVER

**DOCTORAL
DISSERTATIONS**