SYNTHESIS OF AMINO KETONES USING *N*-HETEROCYCLIC CARBENE-CATALYZED TRANSFORMATIONS

A Thesis Submitted to the College of
Graduate and Postdoctoral Studies
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy
in the Department of Chemistry
University of Saskatchewan
Saskatoon, Canada

By
Pouyan Haghshenas

PERMISSION TO USE

In presenting this thesis/dissertation in partial fulfillment of the requirements for a postgraduate degree from the University of Saskatchewan, I agree that the Libraries of this University may make it freely available for inspection. I further agree that permission for copying of this thesis/dissertation in any manner, in whole or in part, for scholarly purposes may be granted by the professor or professors who supervised my thesis/dissertation work or, in their absence, by the Head of the Department or the Dean of the College in which my thesis work was done. It is understood that any copying or publication or use of this thesis/dissertation or parts thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of Saskatchewan in any scholarly use which may be made of any material in my thesis/dissertation.

Requests for permission to copy or to make other uses of materials in this thesis/dissertation in whole or part should be addressed to:

Head of the Department of Chemistry
165-110 Science Place
University of Saskatchewan
Saskatoon, Saskatchewan S7N 5C9
Canada

Abstract

This thesis describes the development of methodologies using *N*-heterocyclic carbene (NHC)-catalyzed reactions for synthesis of amino ketones and aims to demonstrate the usefulness of the developed methodologies in syntheses of structurally relevant complex molecules.

The first strategy towards the synthesis amino ketones involves the use of NHC-catalyzed aza-benzoin reactions. Efforts on a chiral auxiliary approach towards the NHC-catalyzed aza-benzoin transformation are discussed. It was investigated whether enantio-enriched α-aminoketones could be obtained using *tert*-butanesulfinamides under NHC-catalyzed aza-benzoin reaction conditions. Moderate yields and diastereomeric ratios are obtained between furfural-derived aldehydes and aldimines using this method.

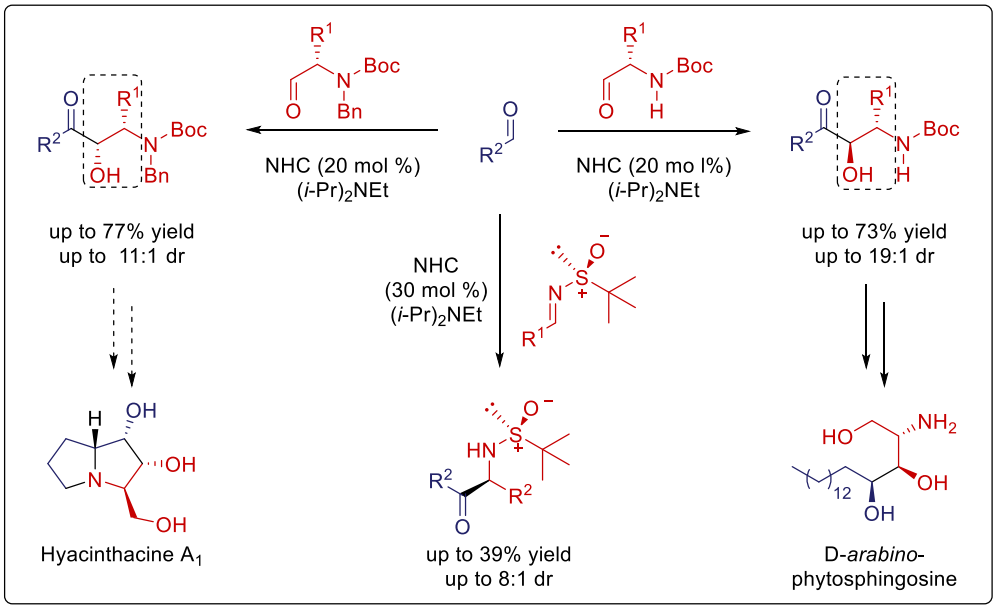
The second strategy for the synthesis of amino ketones utilizes NHC-catalyzed cross-benzoin reactions of two aliphatic aldehydes. *N*-Protected α-amino aldehydes, owing to a synergistic balance between their electronic and steric properties were used to address the chemoselectivity issues associated with NHC-catalyzed cross-benzoin reactions. This study describes the first examples of NHC-catalyzed chemo- and diastereoselective cross-benzoin reactions between two aliphatic aldehydes. The optimized reaction conditions can deliver a variety of enantio-enriched α-hydroxy-β-amino ketones with excellent chemoselectivity and good to excellent diastereoselectivity.

Further investigation on the effects of protecting groups in the NHC-catalyzed cross-benzoin reactions using *N*-*bis*-protected-α-amino aldehydes revealed that the diastereoselectivity could be reversed by altering the nature of the nitrogen protecting groups. Optimization reactions were carried out to obtain excellent chemoselectivity and good diastereoselectivity.

Having developed viable methodologies to access enantio-enriched amino triols, the application of these methods was investigated in the synthesis of two natural products. By combining straightforward transformations with the developed methodology using *N*-Boc-*α*-amino aldehydes, a synthesis of D-*arabino*-phytosphingosine was accomplished in 6 steps.

The synthetic utility of *N*-*bis*-protected amino aldehydes is demonstrated in a unique strategy towards hyacinthacine A_1. A highly diastereoselective NHC-catalyzed reaction between 2-furaldehyde and *tris*-protected-D-serinal is used as the key step affording the required enantio-enriched amino triol backbone in an efficient sequence. Photooxygenation of the furan moiety followed by cyclization using the pendant primary amine delivers the bicyclic framework of hyacinthacine A_1. Progress towards completion of the synthesis as well as future directions are discussed.

With an emphasis on expanding the scope of the application of *α*-amino aldehydes in NHC-catalyzed transformations, this thesis concludes with a general discussion and proposal for future directions.



Scheme 1.0 NHC-catalyzed transformations and applications in multistep synthesis

Acknowledgements

Firstly, I would like to express my sincere gratitude to my supervisor Dr. Michel Gravel for the continuous support throughout my PhD study and related research, for his patience, motivation, and immense knowledge. Not only he has been a great leader but also a great role model, both professionally and personally.

Secondly, in addition to my supervisor, I would like to thank my Advisory Committee: Professors, J. R. Dimmock, J. Müller, and M. S. C. Pedras for their insightful comments and guidance throughout my studies.

I would also like to acknowledge Professor D. Ward for insightful discussions on various research subjects during my PhD. A special thanks to Dr. W. Quail for acquiring the X-ray crystallography data and for useful discussions on the related subjects.

I would like to thank the Gravel Groups' previous and present members for all their support, useful discussions, and encouragement during my PhD program. I would like to specially thank Mr. S. M. Langdon for reviewing this thesis and my other manuscripts, and for his friendship throughout our time together in graduate school.

I thank all the staff at the Department of Chemistry and Saskatchewan Structural Sciences Centre (SSSC), especially Ms. L. Hildebrandt, and Dr. K. Brown for all their help during my PhD.

I would like to acknowledge the financial support from the Natural Science and Engineering Research Council of Canada (NSERC) and the Department of Chemistry of University of Saskatchewan.

Finally, I like to thank my spouse, Azam for all her emotional, professional, and financial support.

Table of Contents

List of Figures

List of Schemes

List of Tables

List of Abbreviations

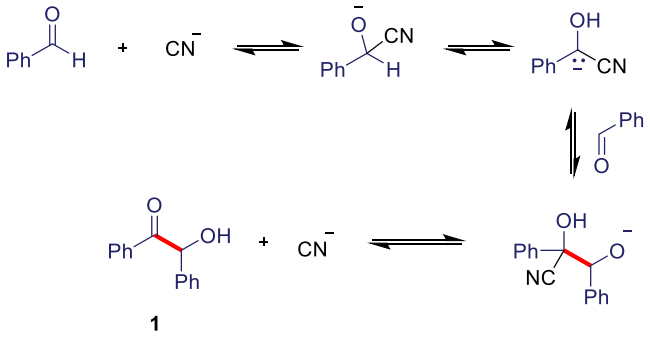
Ac – Acetyl
Alk – Alkyl
Ar – Aryl
BI – Breslow Intermediate
Bn – Benzyl
Boc – tert-Butyloxycarbonyl
BOM – Benzyloxymethyl acetal
Bz – Benzoyl
CAN – Ceric ammonium nitrate
DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF – Dimethylformamide
dr – Diastereomeric ratio
ee – Enantiomeric excess
Et – Ethyl
EWG – Electron Withdrawing Group
Fmoc – Fluorenyl methyloxycarbonyl
Het-Ar – Hetero Aryl
IBX – 2-Iodoxybenzoic acid
i-Pr – Isopropyl
M.S. – Molecular Sieves
Me – Methyl
Mes – Mesityl
MIP – Methoxyisopropyl
N.D. – Not Detected
NHC – N-Heterocyclic Carbene
obs. – Observed
PG – Protecting Group
Ph – Phenyl
PMB – para-Methoxybenzyl
red. – Reduction
rt – Room temperature
TBAF – tetra-*n*-Butyl Ammonium Fluoride
TBME – *tert*-Butyl Methyl Ether
TBS – *tert*-Butyldimethylsilyl
Tf – Triflate
TFA – Trifluoroacetic acid
TFAA – Trifluoroacetic anhydride
TFac – Trifluoroacetyl
TFMB – 4-(Trifluoromethyl)benzyl
THF – Tetrahydrofuran
TMS – Tetramethyl silane
Tol – Toluyl
Tr –Trityl
Ts – Toluenesulfonyl

CHAPTER 1: BACKGROUND

1.1. NHC-Catalyzed Cross-Benzoin Reactions

1.1.1. Introduction

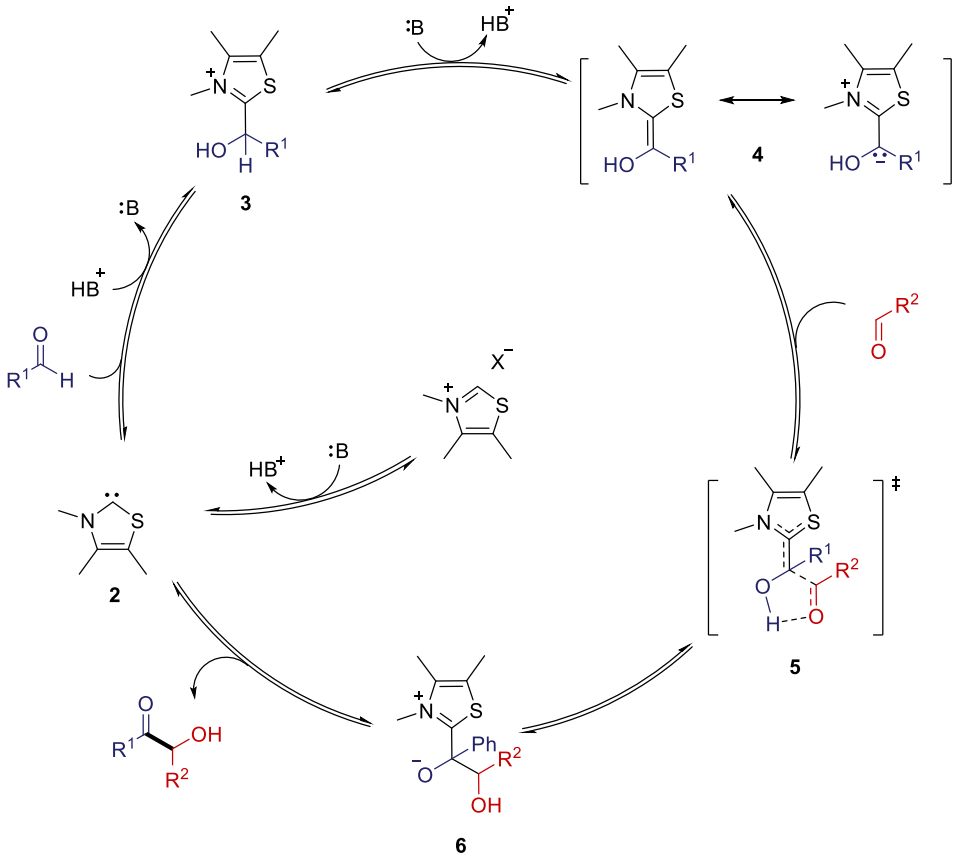
Early reports of the benzoin reaction date back to 1832 in which Wöhler and Liebig reported the isolation of benzoin (**Scheme 1.1,** compound **1**).[1] This product was obtained by treating a concentrated solution of potassium carbonate with oil extracts from bitter almonds over several days. In 1903, Lapworth proposed that the formation of such products can be explained by the involvement of a carbanion species which is obtained from the addition of a cyanide anion to the carbonyl center.[2] This intermediate could serve as a nucleophile towards another molecule of aldehyde in the subsequent step (**Scheme 1.1**). In 1979, Seebach coined the term '*umpolung*' for this type of behavior using Lapworth's mechanism as an example of the reversal of reactivity in carbonyl species.[3]



Scheme 1.1 The proposed mechanism for the benzoin reaction between two aldehydes in the presence of cyanide anion

In 1943, *N*-heterocyclic carbenes were found to catalyze the same transformation.[4] However, the underlying mechanistic principles of this transformation were not completely understood until

the late 1950's. The currently accepted mechanism for the NHC-catalyzed benzoin transformations is based on Breslow's[5] 1958 proposal (**Scheme 1.2**).



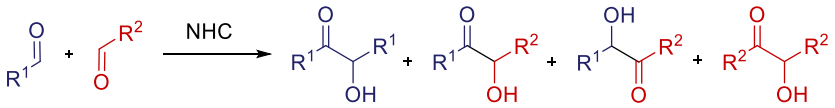
Scheme 1.2 Commonly accepted catalytic cycle for NHC-catalyzed benzoin reactions

According to the proposed catalytic cycle, deprotonation of the azolium-based pre-catalyst generates a reactive carbene species (**2**). Interestingly, the use of strong bases (such as NaHMDS) do not generally lead to higher yields and mild bases such as $(i\text{-Pr})_2\text{NEt}$ or Cs_2CO_3 are generally preferred. This may be related to the additional role of the conjugate acid in facilitating NHC-catalyzed transformations.[6] Attack of carbene **2** on an aldehyde with concomitant proton transfer results in a tetrahedral intermediate (**3**). Deprotonation then leads to a hydroxyl enamine intermediate (**4**) also known as the "Breslow intermediate". Since his initial proposal, a number of reports regarding the isolation and characterization of Breslow intermediates have surfaced.[7–10]

The C–C bond is established *via* the addition of **4** to another molecule of aldehyde. Although according to the original proposal, **6** is obtained from the formation of the C–C bond and a subsequent proton-transfer, recent computational studies suggest that the C–C bond formation and proton-transfer steps can occur through a concerted 5-membered transition state (**5**).[11] Furthermore, a recent study has reported evidence of involvement of radicals in the C–C bond formation step.[12] The resulting tetrahedral intermediate (**6**) collapses, expelling the benzoin product and regenerating the NHC to re-enter the catalytic cycle. With the presence of one type of aldehyde species in the reaction mixture (*i.e.* $R^1 = R^2$) the reaction is termed 'homo-benzoin', while in instances where two different aldehydes participate in the reaction (*i.e.* $R^1 \neq R^2$) the reaction is referred to as a 'cross-benzoin' reaction.

1.1.2. Chemoselectivity Challenges in the NHC-Catalyzed Cross-Benzoin Reactions

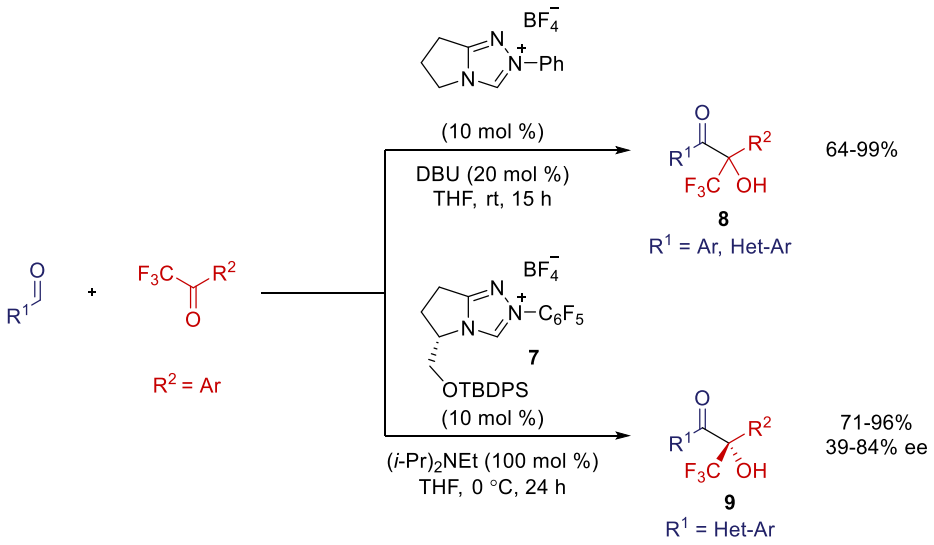
Almost a century after its discovery, controlling the chemoselectivity in the NHC-catalyzed cross-benzoin reaction remains among the most important challenges facing this reaction.[13–21] Without effective control over the chemoselectivity, a mixture of all four possible products (two homo-benzoin and two cross-benzoin) will be obtained (**Scheme 1.3**).



Scheme 1.3 Statistical product distribution in the absence of chemoselectivity

To address this issue a variety of strategies have been devised which strongly rely on the properties of the substrates. One approach relies on the application of reactive ketones in NHC-catalyzed cross benzoin reactions (**Scheme 1.4**).[6,22–30] In such systems, the ketone can only participate as the electrophile during C–C bond formation and the Breslow intermediate is formed exclusively with the aldehyde. Using this strategy, Enders and co-workers utilized trifluoromethyl

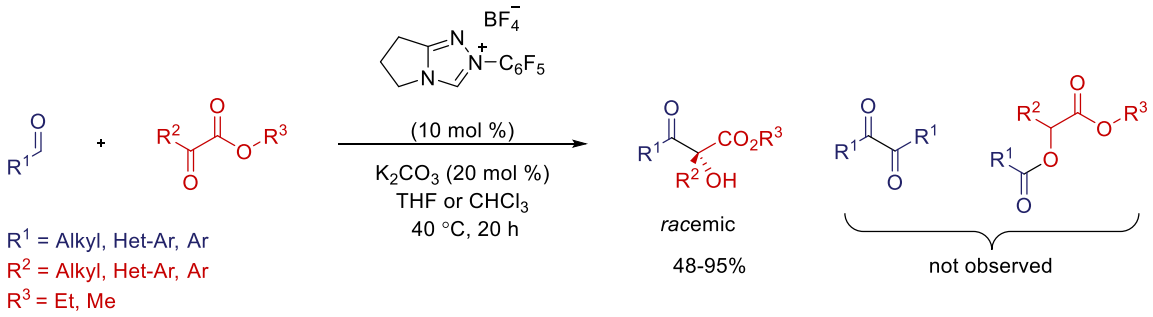
ketones and aromatic or heteroaromatic aldehydes in NHC-catalyzed cross-benzoin reactions.[27] The corresponding α-hydroxy ketones (**8** and **9**) were obtained in good to excellent yields and chemoselectivity. Later, the same group reported the enantioselective variant of this reaction using chiral triazolium salt **7**.[24] Their method can deliver enantio-enriched α-hydroxy ketones through NHC-catalyzed cross-benzoin reactions between a number of heteroaromatic aldehydes and aryl trifluoromethyl ketones with moderate to good enantioselectivity (**9** in Scheme **1.4**). Despite this success, the poor substrate scope arising from the requirement for the trifluoromethyl fragment renders the method unattractive.



Scheme 1.4 Use of reactive ketones in chemoselective NHC-catalyzed cross-benzoin reactions

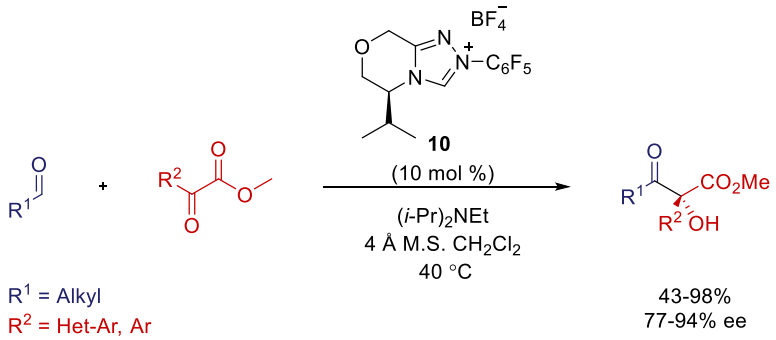
A similar strategy consists of using α-keto esters in chemoselective NHC-catalyzed cross-benzoin reactions.[30] Connon and Zeitler showed that a library of α-hydroxy ketones can be accessed through the reaction between non-Sterically sterically hindered α-keto esters with aromatic, hetero-aromatic, or aliphatic aldehydes in good to excellent yields (**Scheme 1.5**). It is noteworthy that the use of such substrates effectively inhibits the homo-benzoin and hydride

transfer pathways. Additionally, an example of the enantioselective variant using a chiral catalyst was reported with moderate enantioselectivity (not shown).



Scheme 1.5 Use of α-keto esters in chemoselective NHC-catalyzed cross-benzoin reactions

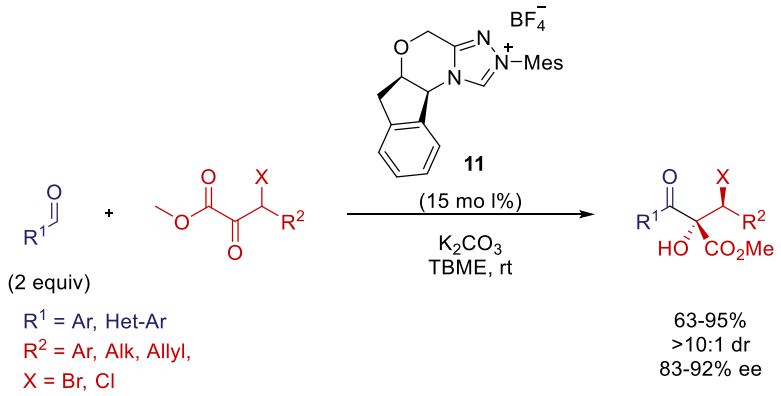
Shortly after, Gravel and co-workers reported the enantioselective NHC-catalyzed cross-benzoin reactions between aliphatic aldehydes and *α*-keto esters using chiral pre-catalyst **10**.[6]



Scheme 1.6 Chemo- and enantioselective NHC-catalyzed cross-benzoin reactions using *α*-keto esters

Johnson and co-workers have devised a strategy based on the dynamic kinetic resolution (DKR) of *β*-halo-*α*-keto esters and aldehydes.[31] Enantio-enriched *β*-halo *α*-glycolic acid derivatives are obtained with high chemo-, diastereo- and enantioselectivities using NHCs. In this case, the DKR process is comprised of a rapid equilibration between the two enantiomers corresponding to *racemic β*-halo-*α*-keto esters and the enantio-induction from a chiral triazolium pre-catalyst **11**. Although this method features an elegant strategy for accessing enantio-enriched products, the

substrate scope remains limited to the use of non-Sterically sterically hindered aromatic or heteroaromatic aldehydes (**Scheme 1.7**). Nevertheless, upon analysis of a crude reaction mixture, only trace amounts (9%) of the homo-benzoin product was detected, attesting to the excellent chemoselectivity.

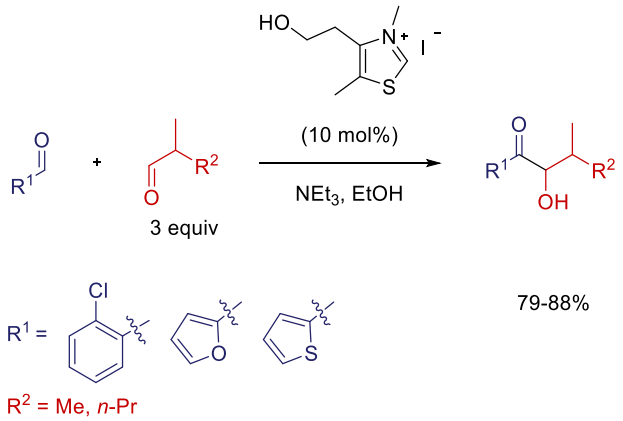


Scheme 1.7 Dynamic kinetic resolution of *β*-halo-*α*-keto esters and aldehydes under NHC catalysis

In another approach, Scheidt and co-workers utilized pre-formed catalyst adducts and aldehydes to deliver the cross-benzoin products.[32] Such approaches have proven effective in circumventing the issue of product distribution. However, the direct coupling of two aldehydes under NHC catalysis is an inherently more challenging task. This complexity originates from the fact that any factor that leads to one aldehyde being preferred in the Breslow intermediate formation, such as steric and electronic environment, could result in that aldehyde being preferred in the C–C bond formation as well. In order to obtain high chemoselectivity in the cross-benzoin reaction between two aldehydes, one should be selected for formation of the Breslow intermediate while the other aldehyde should act as an electrophile towards this intermediate.

A limited number of studies have addressed the chemoselectivity issues in cross-benzoin reactions of two aldehydes. These studies rely on the use of an excess of one of the aldehyde partners and/or the use of different substrates to alter the distribution of products. In 1977, Stetter

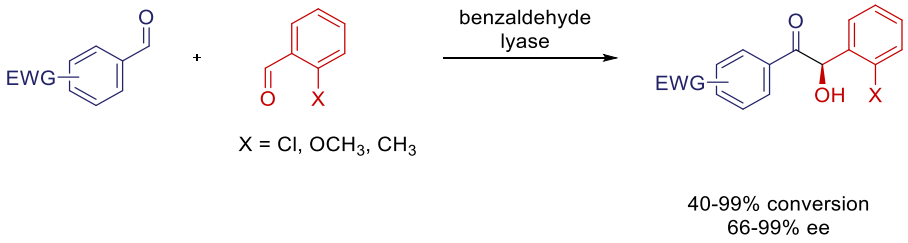
and co-workers demonstrated that *ortho*-chloro aromatic aldehydes, 2-heteroaromatic aldehydes and sterically Sterically sterically hindered aliphatic aldehydes can be coupled chemoselectively (**Scheme 1.8**).[33] In 2011, attempts to reproduce these results proved futile; Connon and Zeitler claimed that the chemoselectivity reported by Stetter was widely over-estimated and in at least one case the opposite cross-benzoin adduct was identified as the major product.[34]



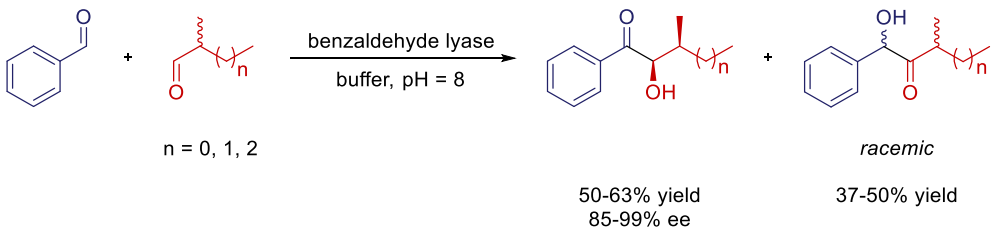
Scheme 1.8 Chemoselective NHC-catalyzed reactions using Sterically sterically hindered aliphatic aldehydes

In 2002, Müller and co-workers utilized a thiamine-dependent enzyme to deliver cross-benzoin products between *ortho*-substituted aromatic aldehydes and electron-deficient aromatic aldehydes with high chemo- and enantioselectivity (**Scheme 1.9**).[35]

Later, Domínguez de María and co-workers utilized the same enzyme to carry out diastereo- and enantioselective benzoin reactions between benzaldehyde and branched aliphatic aldehydes.[36] This method delivers moderate chemoselectivity and good to excellent diastereo- and enantioselectivity. However, the substrate scope remains limited to the use of benzaldehyde (**Scheme 1.10**). It is important to note that only a few examples of diastereoselective cross-benzoin reactions have been reported in the literature.[36,37]

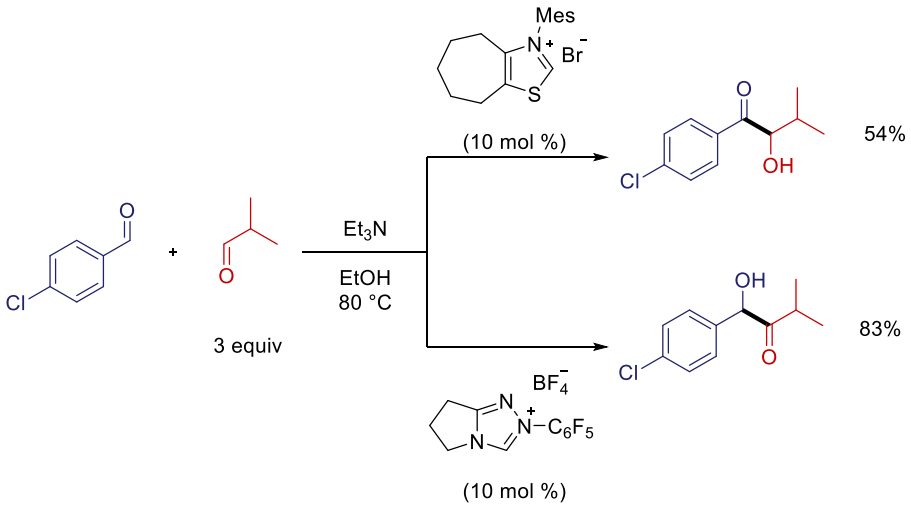


Scheme 1.9 Chemoselective cross-benzoin reactions catalyzed by benzaldehyde lyase



Scheme 1.10 Chemoselective enzyme mediated cross-benzoin reactions between Sterically sterically hindered aliphatic aldehydes and aromatic aldehydes

During their investigations on thiazolium-derived NHCs, Glorius and co-workers[38] found that cross-benzoin reactions similar to those by Müller and co-workers[35] could be replicated using NHCs. Moreover, it was discovered that under similar reaction conditions, thiazolium- and triazolium-derived pre-catalysts lead to opposite cross-benzoin products. This was exemplified in the NHC-catalyzed reaction between isobutyraldehyde and *para*-chloro benzaldehyde (**Scheme 1.11**). This reversal of chemoselectivity is postulated to stem from the nature of the pre-catalysts; thiazolium-based NHCs prefer a more thermodynamically stabilized Breslow intermediate (aromatic aldehydes) while triazolium-based catalysts are believed to be more sensitive to the steric environment of the aldehydes and prefer less sterically hindered aliphatic aldehydes. However, the authors do not provide evidence for their claim.

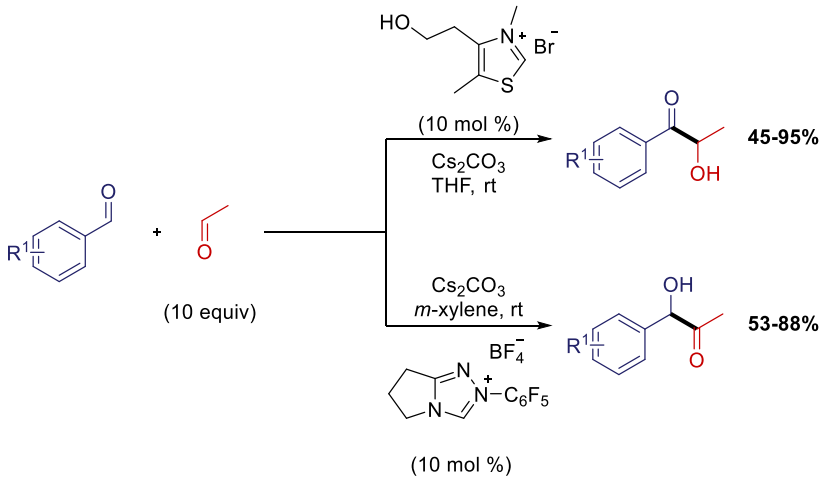


Scheme 1.11 Chemoselective NHC-catalyzed cross-benzoin reaction between isobutyraldehyde and aromatic aldehydes

Later that year Han, Ryu, and Yang reported a number of chemoselective cross-benzoin reactions relying on the use of an excess of one of the partner aldehydes (**Scheme 1.12**).[39] In a study similar to that of Glorius and co-workers,[38] it was shown that a judicious selection of the NHC pre-catalyst can directly influence the ratio of products in the cross-benzoin reaction between aromatic aldehydes and acetaldehyde. Again, the reversal of chemoselectivity is postulated to stem from the favoured formation of resonance-stabilized Breslow intermediates between thiazolium-derived NHCs and aromatic aldehydes, while the relatively sterically demanding triazolium-derived NHC prefers to react with the non-sterically hindered aldehyde partner (*i.e.* acetaldehyde).

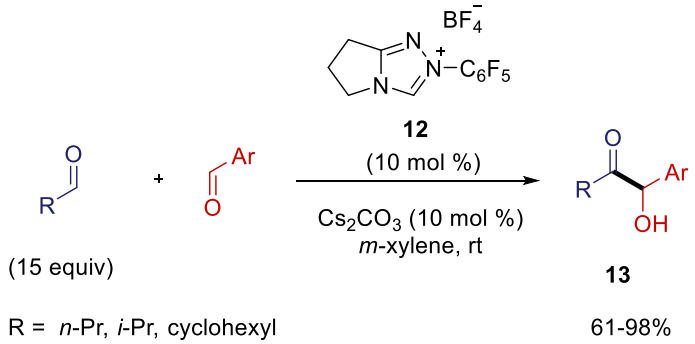
Ryu and co-workers also demonstrated that pre-catalyst **12** can be employed to obtain exclusive formation of cross-benzoin products (**13**) from aromatic aldehydes and a variety of sterically hindered- and non-sterically hindered aliphatic aldehydes (**Scheme 1.13**).[40] These results coincide with an earlier report by Glorius and co-workers[38] (**Scheme 1.11**). Furthermore, the chemoselectivity seems to be governed by a substantial difference in the molar ratio of the

aldehyde partners (1:15), which renders this approach unsuitable for aldehydes that are expensive or not readily available.

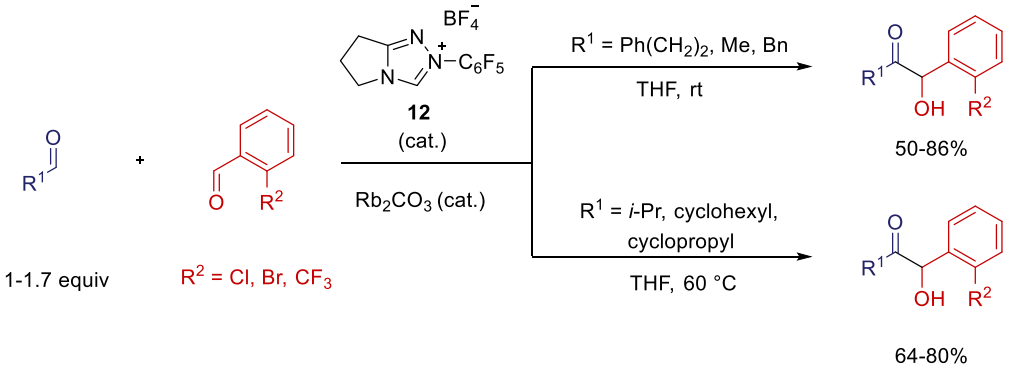


Scheme 1.12 Chemoselective NHC-catalyzed cross-benzoin reaction between acetaldehyde and aromatic aldehydes

Connon and Zeitler have highlighted the remarkable role of triazolium salt **12** in cross-benzoin reactions of aliphatic aldehydes and aromatic aldehydes, particularly *ortho*-halogenated ones (**Scheme 1.14**).[30,34] Interestingly, and in contrast Stetter's method,[33] it was observed that increased amounts (3 equiv) of the aliphatic partners are not required for obtaining synthetically useful amounts of the cross-benzoin products. Furthermore, it was shown that elevated temperatures are crucial for a successful cross-benzoin reaction between *ortho*-halogenated aromatic aldehydes and α-substituted aliphatic aldehydes. Despite these advances, the requirement for an *ortho*-substituent dramatically decreases the scope of this reaction.



Scheme 1.13 Chemoselective NHC-catalyzed cross-benzoin reaction between aliphatic and aromatic aldehydes using an excess of one partner



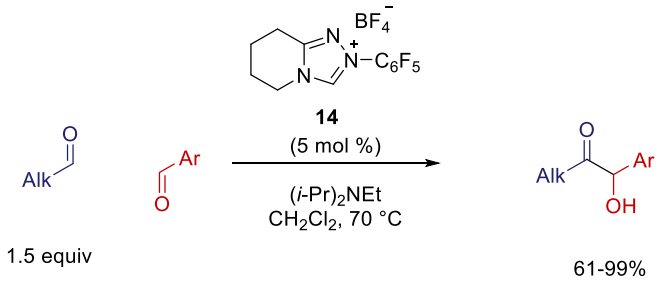
Scheme 1.14 Chemoselective NHC-catalyzed cross-benzoin reaction between aliphatic and *ortho*-substituted benzaldehyde derivatives

Connon and Zeitler have hypothesized that the chemoselectivity is influenced more dramatically by the steric requirements of the substrate-catalyst adduct rather than the electronic properties of the substrate.[34] Although a series of competition experiments were carried out to support this justification, this study does not elucidate the underlying mechanistic principles of such systems.

Recent kinetic studies by Smith and co-workers suggest that *ortho*-substituted aromatic aldehydes are especially reactive towards Breslow intermediates comprised of non-sterically hindered aromatic aldehydes.[41] It is postulated that the steric interaction between the *ortho*-

substituent and the oxygen of the aldehyde group forces the aromatic ring to twist out of conjugation with the carbonyl group. This results in destabilisation and hence activation of these aldehyde during the C–C bond formation step. However, this study does not rule out the fact that the subsequent step (*i.e.* ejection of the catalyst), might in fact be the rate-limiting step.

Gravel and co-workers have shown that catalyst-controlled chemoselectivity can be obtained using slightly sterically hindered triazolium pre-catalyst **14**.[42] It was shown that a variety of aromatic and aliphatic aldehydes could undergo chemoselective cross-benzoin reactions using this sterically hindered triazolium pre-catalyst at elevated temperature (**Scheme 1.15**). Consecutive computational modeling studies were carried out, elucidating the reaction pathways leading to each possible benzoin product and the modulating role of the fused ring on the product distribution.[43]



Scheme 1.15 Catalyst-controlled chemoselectivity in NHC-catalyzed cross-benzoin reaction between aliphatic and aromatic aldehydes

Factors affecting the chemoselectivity of the NHC-catalyzed cross-benzoin reactions are quite complex. Some studies have pinpointed the role of steric interactions between the NHC and the aldehyde as the most influential factor[34] while others suggest that electronic effects[38] are more crucial. In addition to the structure of the catalyst and that of the substrates, the potential reversibility of each step of the catalytic cycle can play an important role in the product distribution.[43] During their modeling studies, Gravel and co-workers found that in the reaction

between propionaldehyde and benzaldehyde in the presence of catalyst **14**, the rate-limiting (and presumably the chemoselectivity-determining) step leading to cross-benzoin products is the C–C bond formation step.[43] This is in sharp contrast to reports by Glorius and co-workers, which seem to suggest that the chemoselectivity is determined by the Breslow intermediate formation step.[38] Despite these discrepancies, it seems logical to assume that the synergistic interplay between steric interactions, the electronic nature of the substrates as well as the catalyst cumulatively determine the final product distribution.

1.2. NHC-Catalyzed Aza-Benzoin Reactions

Breslow's proposed mechanism for the NHC-catalyzed benzoin reaction is not exclusive to aldehydes; *α,β*-unsaturated ketones,[44–46] ketones,[6,28,47] and imines[48–50] have been successfully employed as electrophiles with aldehyde-derived Breslow intermediates. Notably, the direct coupling of aldehydes and imines through an aza-benzoin reaction has received comparatively little attention.[13]

The steric and electronic properties of imines are easily tuned using different protecting groups, rendering such substrates versatile reaction partners in many transformations. Furthermore, the resulting *α*-amino ketones are found in many compounds of high biological interest and serve as suitable surrogates for amino diols, ubiquitous motifs present in many natural products (*vide infra*)

1.2.1. Significance of *α*-Amino Ketones

α-Amino ketones are important structural motifs shown to exhibit interesting biological activities.[51–54] In particular, *α*-amino ketones are found in a number of psychoactive compounds and drugs,[55] such as those used for treatment of diabetes (**Figure 1.1**).[56]

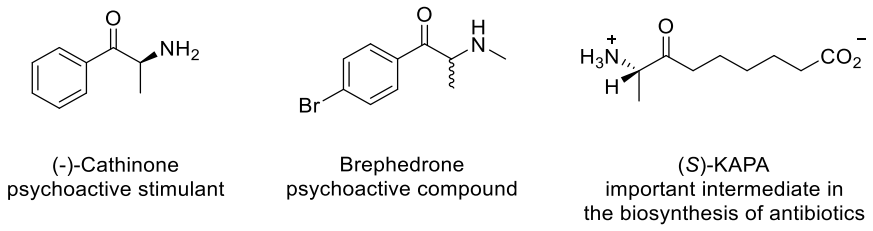
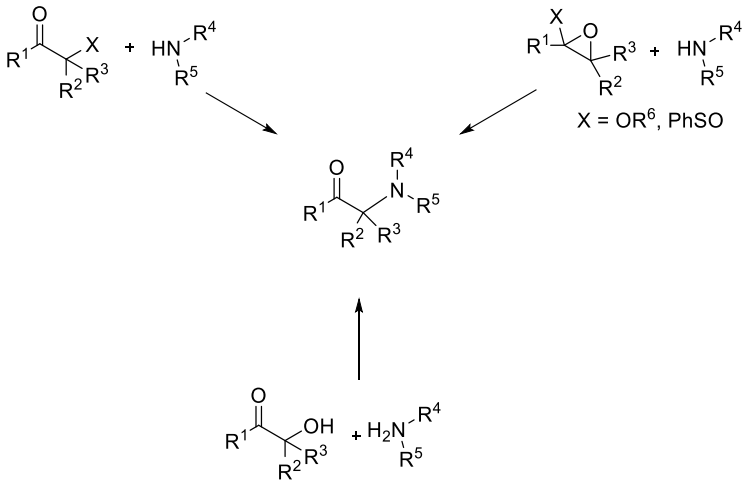


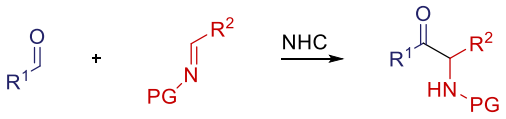
Figure 1.1 Examples of biologically active *α*-amino ketones

With such high biological importance, a variety of methods for the synthesis of *α*-amino ketones have been developed.[57–59] Scheme 1.16 outlines some common synthetic methods for obtaining *α*-amino ketones.



Scheme 1.16 Common strategies towards the synthesis of α-amino ketones[59]

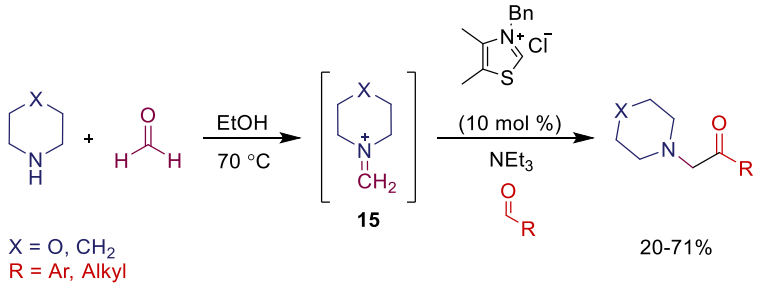
The NHC catalyzed aza-benzoin reaction is a potentially useful method for assembling these motifs through the direct reaction of aldehydes and imines (**Scheme 1.17**).



Scheme 1.17 Access to α-amino ketones using NHC-catalyzed aza-benzoin reactions

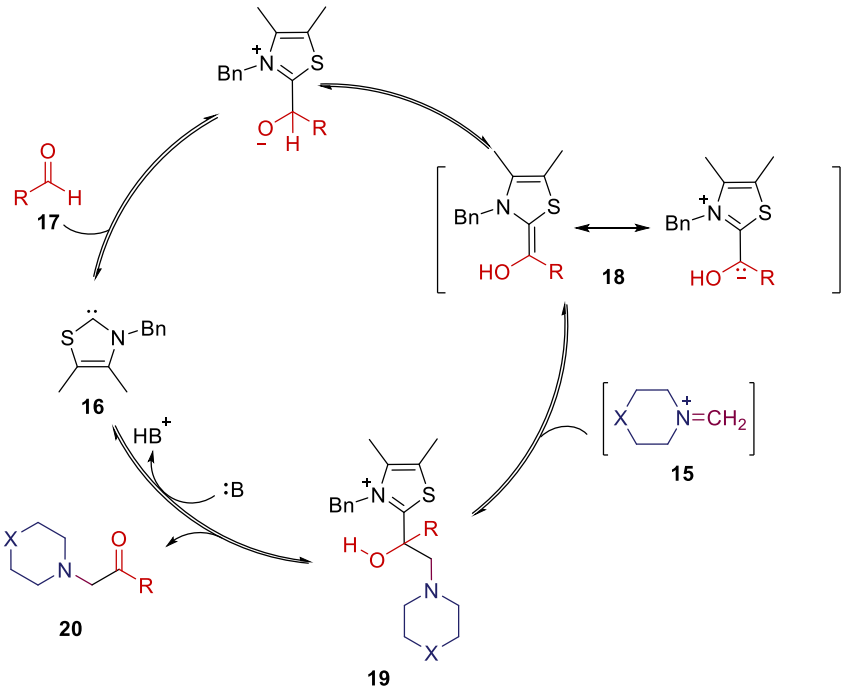
1.2.2. Reported NHC-Catalyzed Aza-Benzoin Reactions

The first example of NHC-catalyzed aza-benzoin reactions were reported by López-Calahorra and co-workers in which *in situ* prepared iminium ions **15** were utilized as aza-benzoin acceptors (**Scheme 1.18**).[60] Thiazolium-based pre-catalysts and electron-rich aromatic aldehydes are well-suited for this reaction whereas the use of aliphatic aldehydes results in low yields.



Scheme 1.18 NHC-catalyzed aza-benzoin reaction of cyclic iminium salts and aldehydes

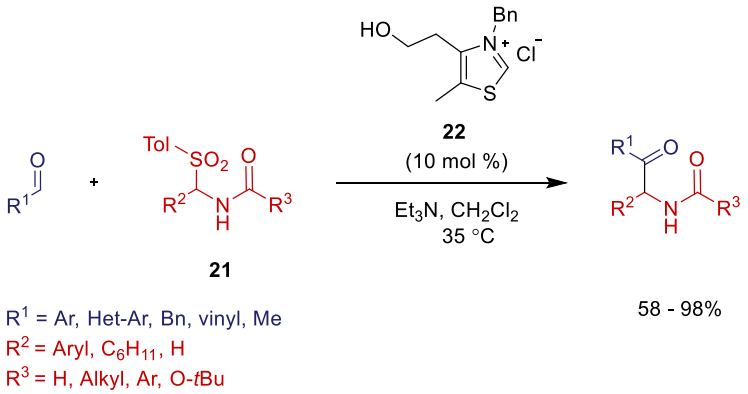
Similarly to the proposed mechanism for the benzoin reaction, Breslow intermediate **18** is formed from the nucleophilic addition of **16** to aldehyde **17** followed by a number of proton transfers (**Scheme 1.19**). This intermediate reacts with iminium ion **15** (generated *in situ* from the condensation between secondary amines and formaldehyde) to generate adduct **19**. Proton transfer followed by expulsion of α-amino ketone **20** results in regeneration of the NHC (**16**).



Scheme 1.19 Proposed catalytic cycle for the NHC-catalyzed aza-benzoin reaction of cyclic iminium salts and aldehydes

Despite the early report, the direct aza-benzoin reaction between aldehydes and imines remained elusive until the early 2000s. Murry and co-workers reported the NHC-catalyzed aza-

benzoin reaction between a variety of aldehydes and imines masked as arylsulfonylamides (**21**) in the presence of a thiazolium-based catalyst (**22**) (**Scheme 1.20**).[50] The use of aliphatic sulfonylamides (**21**, R^2=alkyl) proved unsuccessful which is believed to stem from the tendency of imines to form the corresponding enamides under the basic reaction conditions. Nevertheless, this study sparked renewed attention towards this transformation.

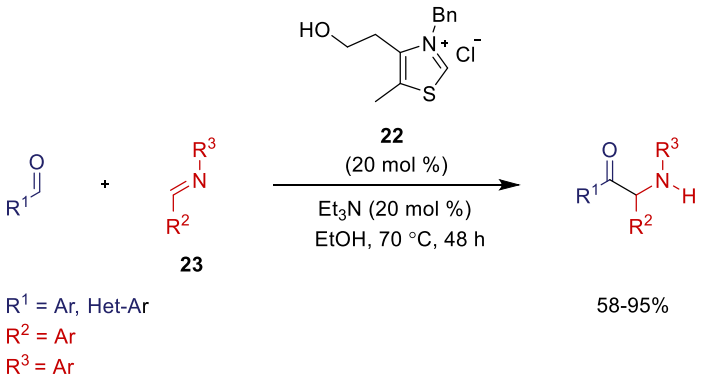


Scheme 1.20 NHC-catalyzed aza-benzoin reaction between aldehydes and imines masked as arylsulfonylamides

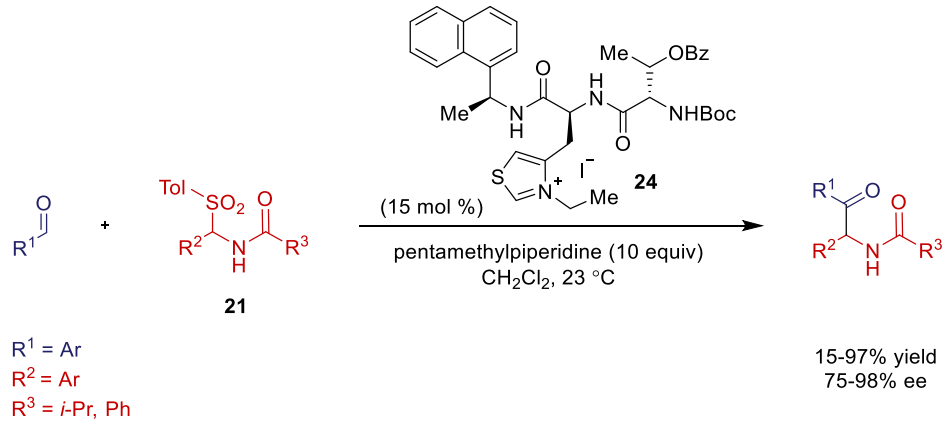
In 2007, You and co-workers studied the NHC-catalyzed aza-benzoin transformation using unactivated imines **23** and aryl or heteroaryl aldehydes (**Scheme 1.21**).[61] The reaction conditions were chosen based on those previously reported by Murry and co-workers. However, prolonged reaction times and elevated temperatures seem necessary for obtaining useful yields.

Using the same bench-stable imine precursors (arylsulfinyl amides) and a chiral thiazolium tripeptide pre-catalyst (**24**), the first enantioselective version of the aza-benzoin reaction utilizing aromatic aldehydes was investigated by Miller and co-workers in 2005 (**Scheme 1.22**).[62] Despite their success in obtaining highly enantio-enriched α-amino alcohols, the substrate scope is limited to electron-deficient aldehydes and electron-rich arylsulfinyl amides. Furthermore, deuterium-labelling studies revealed the detrimental role of post-reaction epimerization on the enantiomeric

ratio over time. This effect is pronounced in the case of electron-deficient aromatic aldehydes leading to low enantioselectivities.

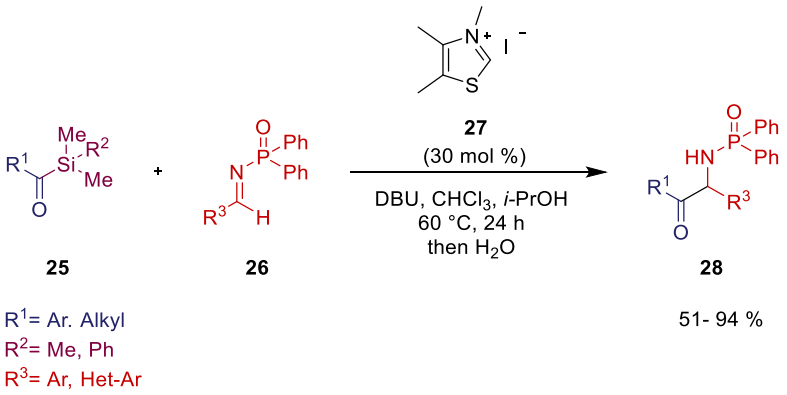


Scheme 1.21 NHC-catalyzed aza-benzoin transformation using aldehydes and unactivated imines



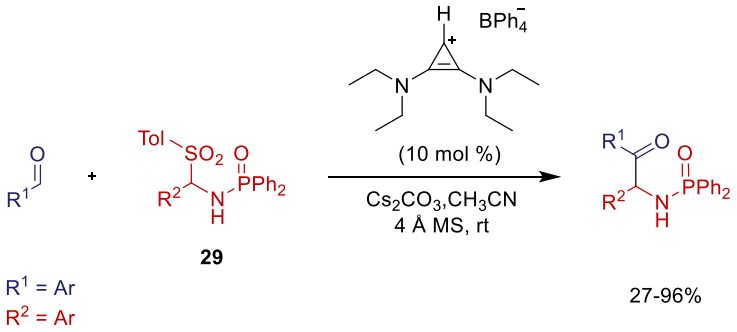
Scheme 1.22 Enantioselective NHC-catalyzed aza-benzoin reaction using arylsulfonylamides

Scheidt and co-workers investigated the formation of *N*-phosphinoyl amino ketones (**28**) by utilizing an aza-benzoin reaction (**Scheme 1.23**).[63] Thiazolium salt **27** was employed to catalyze efficient reactions between aliphatic or aromatic acylsilanes (**25**) and *N*-arylphosphinoylimines (**1.26**). The use of acylsilanes is crucial for the observed reactivity and suppression of the homo-benzoin pathway. The latter is an inherent result of using acyl silanes instead of aldehydes.



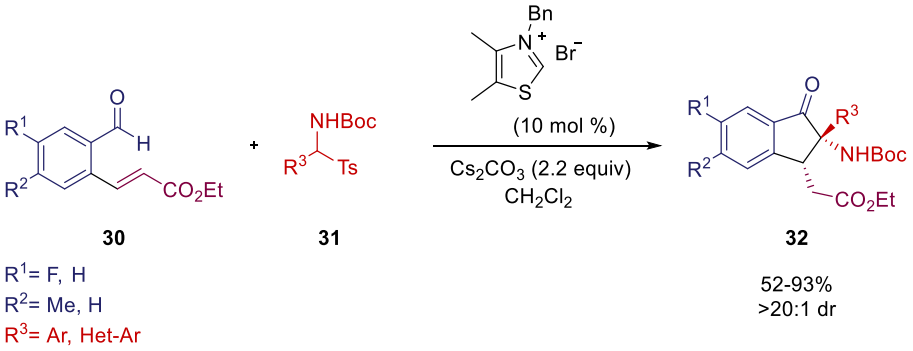
Scheme 1.23 NHC-catalyzed aza-benzoin reactions using *N*-arylphosphinoylimines

In 2014 Gravel and co-workers utilized bis(amino)cyclopropenylidenes (BACs) as catalysts for aza-benzoin reactions between aromatic aldehydes and phosphinoyl imines (**29**) (**Scheme 1.24**).[49] Interestingly, BACs effectively inhibit the benzoin reaction pathway. The application of these types of carbenes leads to fewer side products and more facile purification processes.



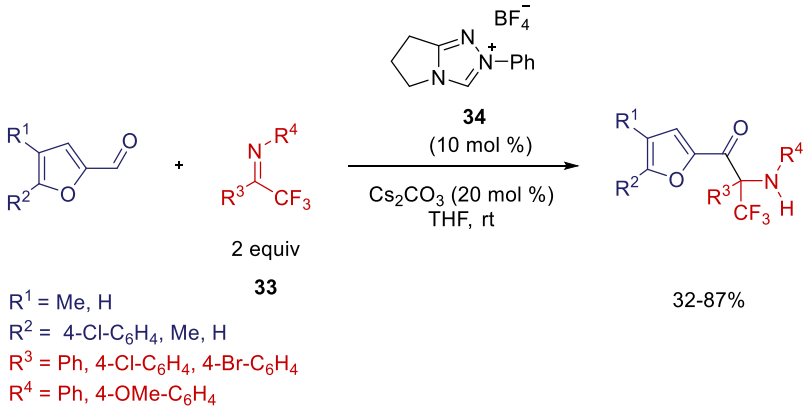
Scheme 1.24 BAC-catalyzed aza-benzoin reaction aldehydes and phosphinoyl imines

You and co-workers reported a cascade aza-benzoin/Michael reaction utilizing *tert*-butyl aryl(tosyl)methylcarbamates (**31**) as imine surrogates to generate indanones (**32**) (**Scheme 1.25**).[47] This method affords high yields and diastereoselectivity for a variety of *tert*-butyl aryl(tosyl)methylcarbamates. Interestingly, the use of pre-formed *N*-Boc-imines also delivers the desired products albeit in lower yield. However, it seems that the scope of the reaction is limited to using (*E*)-ethyl 3-(2-formylphenyl)acrylates (**30**) bearing alkyl or fluoro substituents.



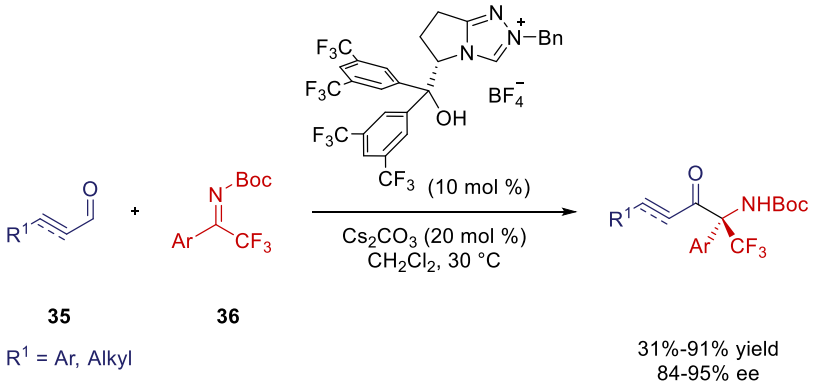
Scheme 1.25 NHC-catalyzed aza-benzoin/Michael cascade reaction

In 2009, Enders and co-workers reported the first application of ketimines in a cross aza-benzoin reaction using a triazolium pre-catalyst (**34**) (**Scheme 1.26**).[64] The scope of the reaction remained limited to 2-furyl aldehyde derivatives and trifluoromethyl aryl ketimines (**33**). It is also noteworthy that an excess of **33** was necessary for obtaining useful yields of the α-amino ketone adducts.



Scheme 1.26 NHC-catalyzed aza-benzoin reactions using trifluoromethyl ketimines

Shortly after Enders' report, Ye and co-workers reported the enantioselective version of this reaction using enals (**35**) and *N*-Boc-ketimines (**36**) (**Scheme 1.27**).[65] Although limited to α-β-unsaturated aldehydes, the reaction proved general for a variety of substitution patterns and functional groups on the aryl ketimine partner.

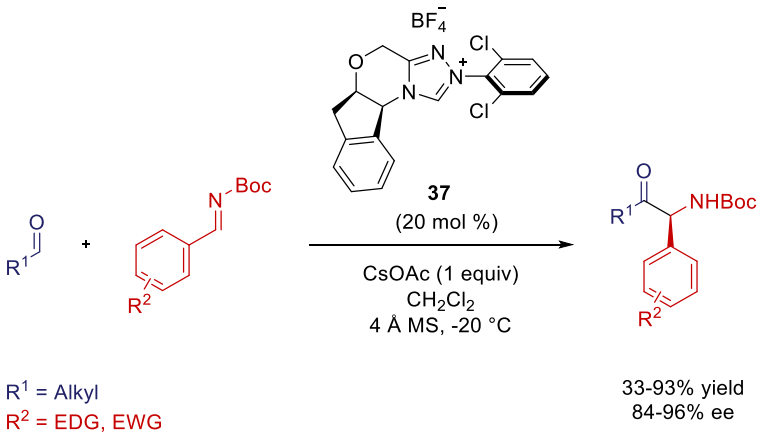


Scheme 1.27 Enantioselective NHC-catalyzed aza-benzoin reactions using ketimines and conjugated aldehydes

In 2012, in line with their studies on the aza-benzoin reaction, Rovis and co-workers isolated and characterized stable adducts formed between reactive imines and NHCs.[66] This seems relevant to Scheidt's earlier hypothesis that stable adducts could form between highly reactive imines and NHCs, effectively eliminating them from the catalytic cycle and resulting in low yields. Interestingly, Rovis and co-workers showed that although formation of such species is possible under the reaction conditions, this undesired reaction pathway can be reversed by using weak acids as additives. Additionally, prior to their study, it was believed that *in situ* generation of the imine using their arylsulfonyl adducts is a necessity for suppression of this unwanted side reaction. However, the reversible formation of such adducts disproves this hypothesis.

Later that year, Rovis and co-workers reported the enantioselective NHC-catalyzed cross aza-benzoin reaction between aliphatic or heteroaromatic aldehydes and *N*-Boc-imines (**Scheme 1.28**).[48] A chiral triazolium-derived NHC pre-catalyst (**37**) to access *N*-Boc-α-amino ketones under mild reaction conditions. A combination of tertiary amine such as *N*,*N*-diisopropylethyl amine (Hünig's base) and acetic acid (*i.e.* a buffer solution) or stoichiometric amounts of cesium acetate can be used to deliver satisfying results. Enantioenriched α-amino ketones were obtained in high yields and with high enantioselectivity for a variety of non-sterically hindered aliphatic aldehydes.

Substrates with a variety of functional groups including thioethers, imides, and esters are well-tolerated. However, the use of heteroaromatic aldehydes such as 2-furyl aldehyde affords lower yields and enantioselectivities. Although the electronic nature of the aryl substituent has little effect of the outcome of the reaction, the reaction proved sensitive to the steric properties of both reaction partners. This is demonstrated by the poor reactivity of *ortho*-substituted *N*-Boc-aryl imines and sterically hindered aliphatic aldehydes under the reaction conditions.



Scheme 1.28 Enantioselective NHC-catalyzed aza-benzoin reactions between aliphatic aldehydes and *N*-Boc-imines

1.3. Syntheses of D-*arabino*-phytosphingosine

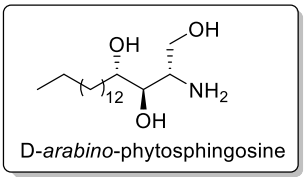
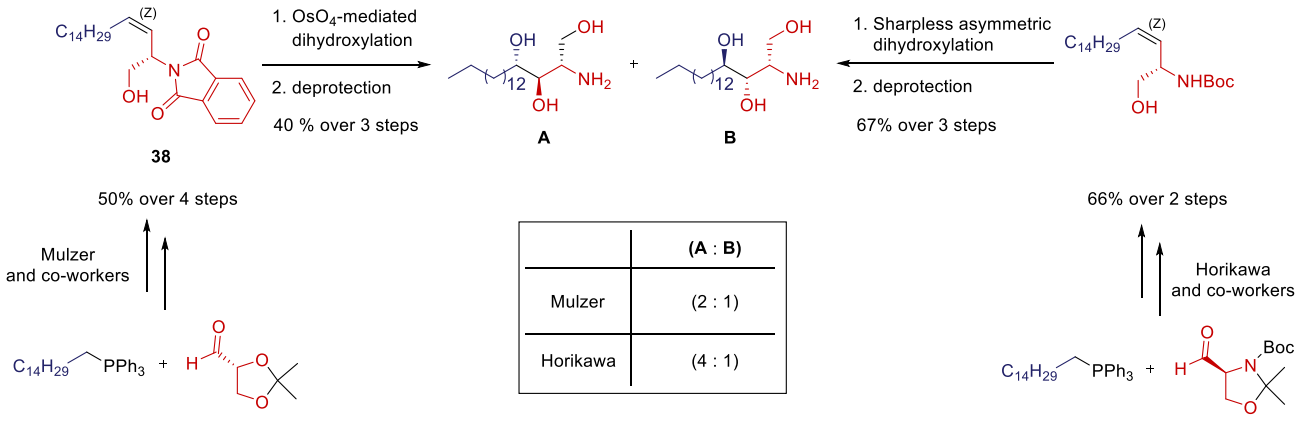


Figure 1.2 Structure of D-*arabino*-phytosphingosine

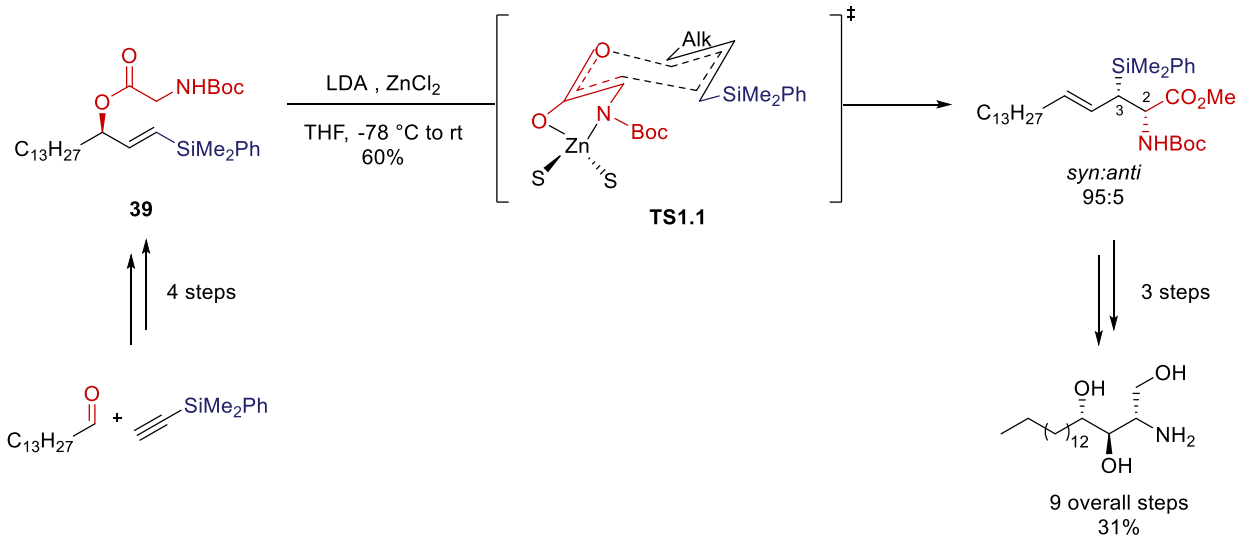
Early reports on the synthesis of D-*arabino*-phytosphingosine (**Figure 1.2**) utilize dihydroxylation reactions of (*Z*)-olefins to deliver the products featuring the appropriate configuration at the C_3 and C_4 secondary alcohols. Mulzer[67] and Horikawa[68] have independently adopted this synthetically straightforward approach using different enantio-enriched aldehydes (**Scheme 1.29**). Muzler's strategy involved the dihydroxylation of **38** using osmium oxide which affords a 2:1 mixture of diastereomers under the reaction conditions. Later, Horikawa and co-workers utilized a Sharpless asymmetric dihydroxylation instead. However, the diastereoselectivity remained poor, rendering this approach non-desirable. In a different study, the cyclic acetonide adduct of the olefin was subjected to osmium-mediated dihydroxylation conditions.[69] This modification results in a 2:1 mixture in favour of the desired diastereomer.



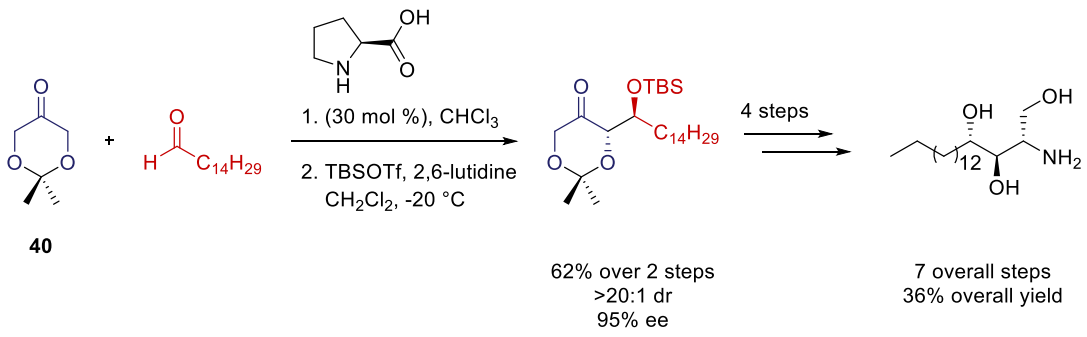
Scheme 1.29 Traditional approaches towards the synthesis of D-*arabino*-phytosphingosine

In 2005 Kim and co-workers reported the synthesis of acetylated D-*arabino*-phytosphingosine utilizing the Claisen rearrangement of vinylsilane (**39**) in 9 overall steps and 31% overall yield (**Scheme 1.30**).[70] In this study, C_2 and C_3 stereocentres are installed by relay of stereochemical information from the enantio-enriched vinyl silane (**39**). This strategy makes use of a method reported by Kazmaier,[71] who rationalized that the observed Claisen rearrangement step proceeds through a chair-like zinc enolate chelated transition state (**TS1.1**), leading to excellent diastereoselectivity. The silane was converted to the secondary alcohol using a Fleming-Tamao oxidation during a subsequent step (not shown).

Enders and co-workers used (*S*)-proline to catalyze the aldol reaction between commercially available 2,2-dimethyl-1,3-dioxan-5-one (**40**) and pentadecanal (**Scheme 1.31**).[72] This elegant approach was successful in installing two of the three stereocenters in a single step from racemic starting material. In addition to the observed high enantio- and diastereoselectivity, this reaction can also deliver the corresponding enantiomer of the aldol adduct by using (*R*)-proline.



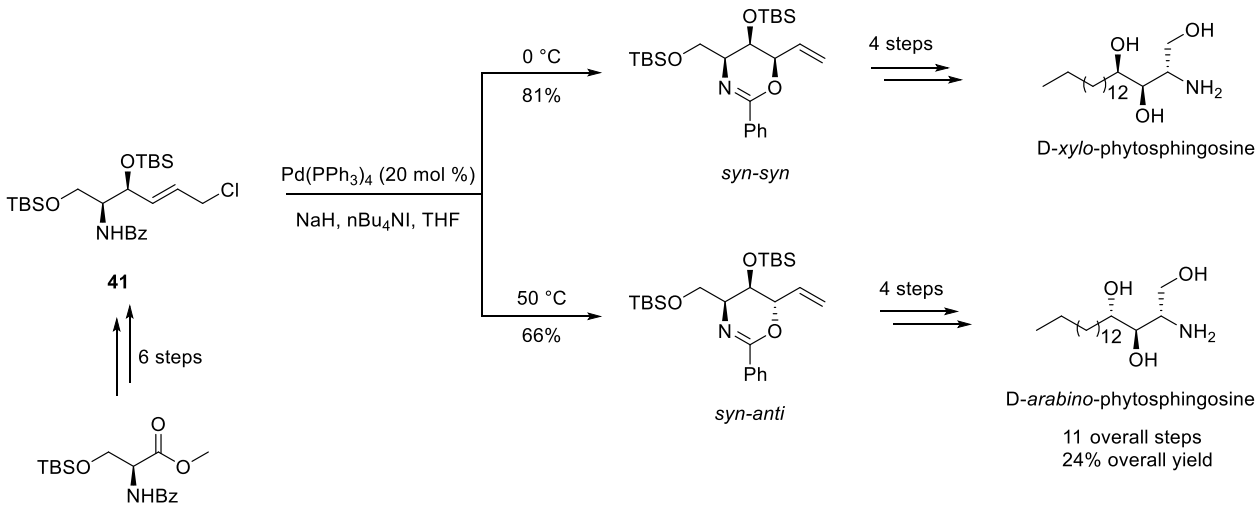
Scheme 1.30 Synthesis of protected D-*arabino*-phytosphingosine *via* the Claisen rearrangement of enantio-enriched vinyl silanes



Scheme 1.31 Enantioselective organocatalytic approach towards total synthesis of D-*arabino*-phytosphingosine

In 2012, Ham and co-workers found that in the presence of a palladium source, allylic chloride **41** undergoes a stereoselective intramolecular cyclization (**Scheme 1.32**).[73] The reaction showed a high degree of temperature dependence; low temperatures afford *syn-syn* products of kinetic control while higher temperatures provide the more thermodynamically stable *syn-anti* product. To establish the relative configuration, each diastereomer was converted to its corresponding phytosphingosine and the spectra were compared to the reported diastereomers of

phytosphingosines. Although, this approach features a high yielding and diastereoselective key step, the overall synthesis requires extensive functional and protecting group manipulations evidenced by the extended step count (11 overall steps).



Scheme 1.32 Diastereoselective Pd-catalyzed intramolecular cyclization of allyl chlorides for the synthesis of phytosphingosines

1.4. Syntheses of Hyacinthacine A_1

Isolated from *Muscari armeniacum*, hyacinthacines are polyhydroxylated bicyclic pyrrolizidine alkaloids bearing four contiguous stereocenters.[74] This family of alkaloids features a rare C3-hydroxy methyl substitution at C_3 (**Figure 1.3**).

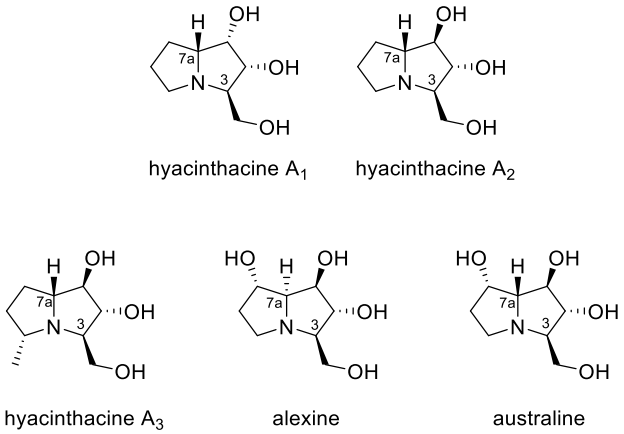
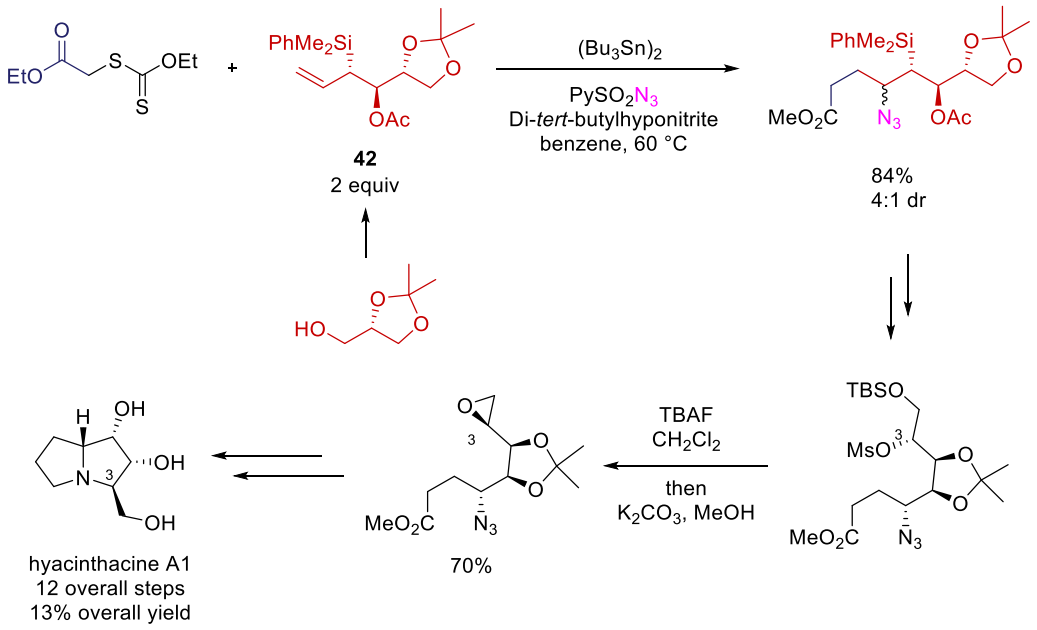


Figure 1.3 Chemical structure of polyhydroxylated pyrrolizidines

Among the family of hyacinthacines, hyacinthacine A_1 demonstrates potent inhibition towards amyloglucosidase from *Aspergillus niger* (IC_{50}=2.3 μM),[75] and *β*-glucosidase from rat intestinal lactase (IC_{50}=4.4 μM)[74] rendering this natural product suitable for the treatment of tumor metastasis, viral infections, and diabetes.[76] However, the isolation of hyacinthacine A_1 from its natural sources has proven inefficient (<0.0005% yield)[74,77] and therefore access to useful quantities of this compound necessitates the use of chemical synthesis.

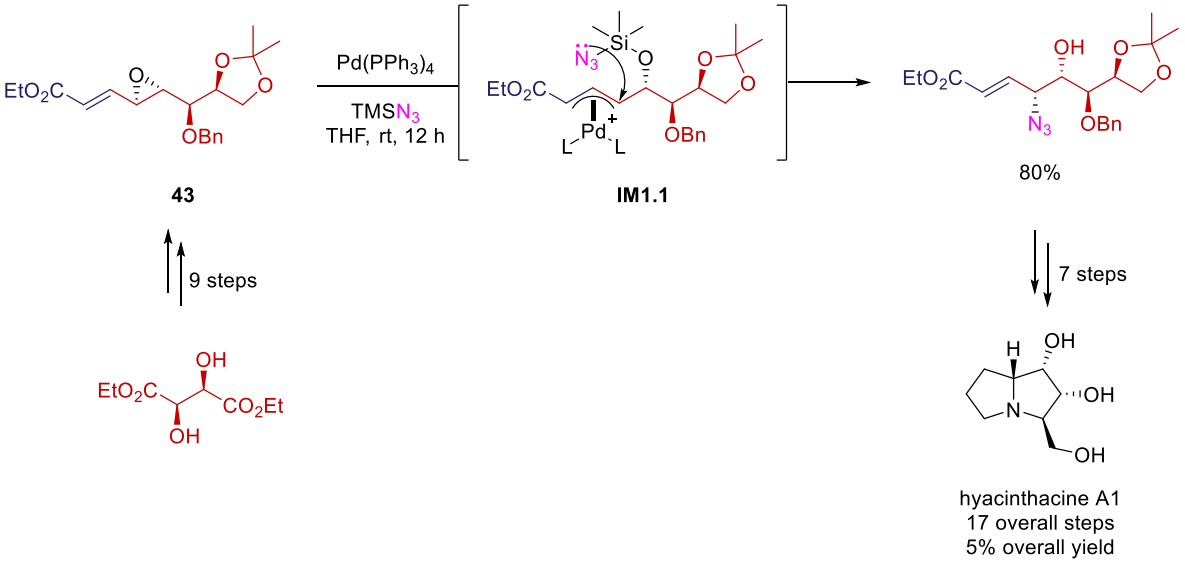
Unlike other members of the hyacinthacine family, reports on the synthesis of hyacinthacine A_1 are scant in the literature.[75,78–83] In 2005, the group of Landais and Renaud reported the first total synthesis of hyacinthacine A_1,[83] while confirming the absolute configuration reported by Asano *et al.*[74] A free-radical carboazadation of a D-*mannitol*-derived allyl silane (**42**) was utilized as the key step. While this strategy was successful in installing the correct relative configuration

at C_1 and C_2, it only delivers moderate diastereoselectivity (**Scheme 1.33**) and requires the use of excess allylsilane **42** (2 equiv). Furthermore, to obtain the correct stereochemistry at C_3, a double inversion of this stereocentre through an amine-assisted ring opening of the corresponding epoxide is required.



Scheme 1.33 Total synthesis of hyacinthacine A_1 by carboazadation of a chiral allylsilane

In a an approach similar to that of described above, Chandrasekhar and co-workers utilized a silyl azide tether to deliver the azide functional group (**Scheme 1.34**).[80] This was achieved through a Pd-catalyzed azide substitution of a γ,δ-epoxy ester (**43**). The tethered silyl azide delivers the nucleophile from the less sterically hindered side of the bulky π-allyl palladium complex (**IM1.1**) resulting in excellent diastereoselectivity. Furthermore, the configuration at C_3 is conveniently pre-installed by using a (+)-diethyl-L-tartarate-derived silyl azide, eliminating the necessity of double inversion of this stereocentre. However, the use of multiple protecting group manipulations render the step-count extensive (17 overall steps).

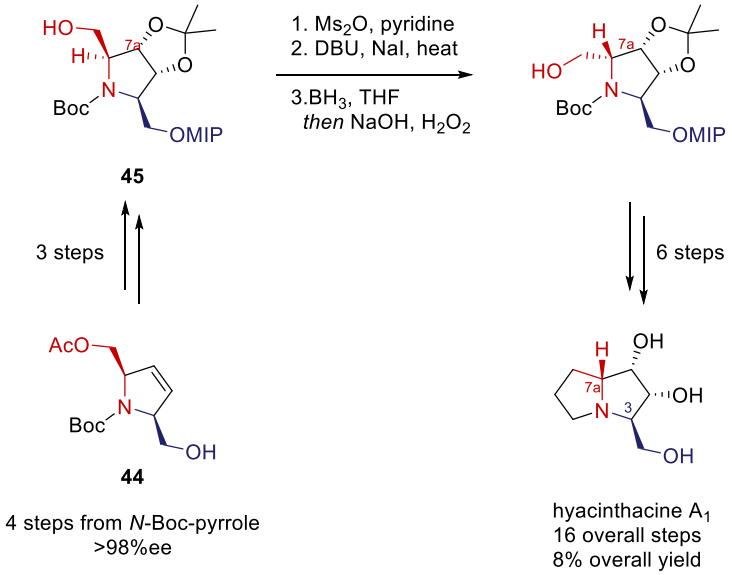


Scheme 1.34 Total synthesis of hyacinthacine A_1 using Pd-catalyzed azide substitution of γ,δ-epoxy esters

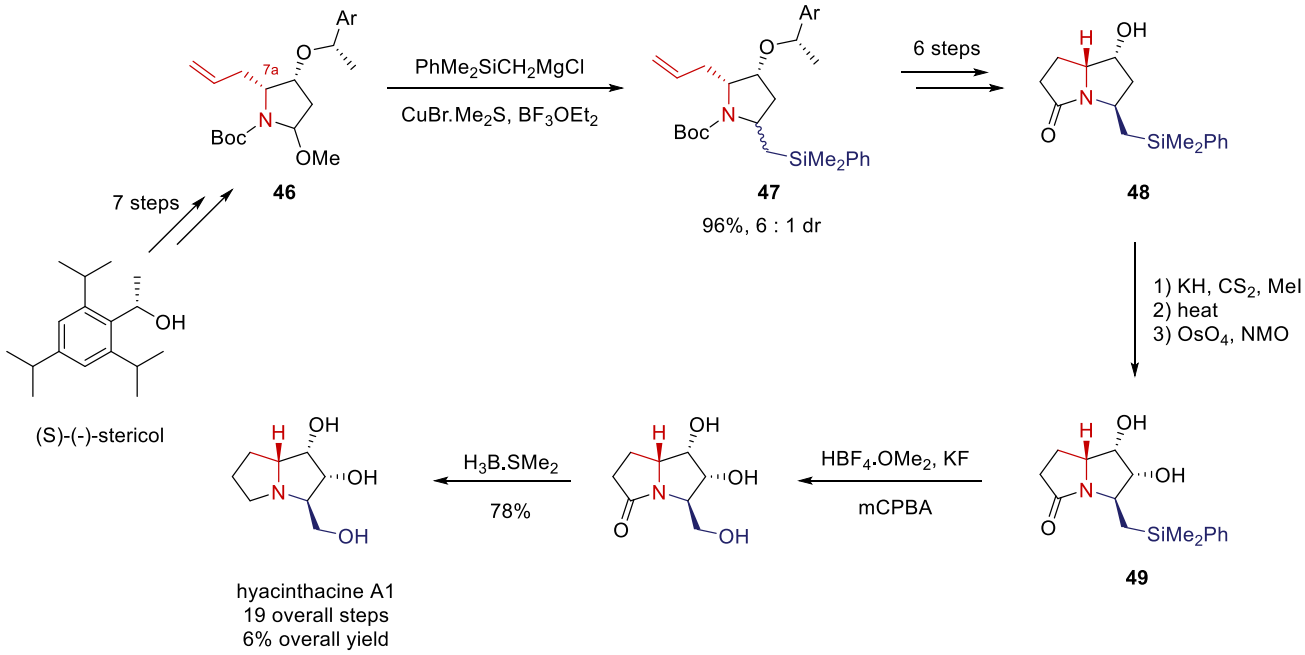
Earlier reports on the synthesis of hyacinthacine A_1 include a stepwise diastereoselective assembly of the fused five-membered rings. While this guarantees the correct configuration at the ring junction, such approaches require the use of many steps. Following a previously reported non-enantioselective synthesis of hyacinthacine A_1,[84] Donohoe and co-workers utilized **44** obtained from enzymatic desymmetrization of a dihydropyrrole derivative (**Scheme 1.35**).[85] The enzymatic process installs the C_3 stereocentre while the pyrrole backbone serves as a suitable surrogate for one of the two fused rings of the natural product. Although this strategy affords intermediate **45** through an efficient and concise sequence, this compound bears the wrong substitution pattern at the ring junction (C_{7a}). The inversion of this stereocentre is accomplished by the elimination of an activated hydroxyl group and hydroboration of the resulting alkene in three steps.

Later, Delair and co-workers devised a similar strategy; installation of the C_{7a} ring junction using (*S*)-(-)-stericol-derived intermediate (**46**) prior to the final cyclization (**Scheme 1.36**).[78,79] A moderately diastereoselective reductive alkylation was utilized as the key step delivering a highly substituted bicyclic pyrrolidinone core (**47**). Dihydroxylation of the alkene obtained from

elimination of the hydroxyl group in **48** installs the *cis*-vicinal diols at C_4 and C_5. Interestingly, while the pyrrolidinone backbone delivers excellent diastereoselectivity during the dihydroxylation step, the corresponding pyrrolizine affords poor diastereoselectivity. This was attributed to the flat nature of the fused pyrrolidinone rings resulting in a more dominant stereocontrol induced by the bulky silyl group. Hyacinthacine A_1 was obtained using the Tamao-Fleming oxidation of the silyl intermediate (**49**) followed by reduction of the amide functionality in 19 overall steps.



Scheme 1.35 Synthesis of hyacinthacine A_1 using an enantio-enriched dihydropyrrole derivative



Scheme 1.36 Synthesis of hyacinthacine A_1 through the reductive alkylation of (*S*)-(-)-stericol-derived pyrrolidines

The primary objective of this thesis is to describe the synthesis of amino ketones using direct *umpulong* reactions of aldehydes with aldehydes, or imines using NHC catalysis. The secondary objective is to demonstrate the application of the developed methodologies in the synthesis of amino ketone-derived natural products.

Chapter 2 describes a chiral auxiliary approach towards the synthesis of amino ketones: reactions between *tert*-butanesulfinimines and heteroaromatic aldehydes under NHC catalyzed aza-benzoin reaction conditions could deliver enantioenriched α-amino ketones. Chapters 3 and 4 of this thesis describe methodologies that were developed to access α-hydroxy-β-amino ketones. These methodologies target one of the most difficult challenges in NHC-catalyzed cross-benzoin reactions, *i.e.* the chemoselective coupling of two aliphatic aldehydes. A proposed hypothesis followed by optimization of the reaction conditions and mechanistic studies are presented in these chapters. Finally, chapter 5 describes the application of the developed methodologies from

chapters 3 and 4. A concise total synthesis of D-*arabino*-phytosphingosine and efforts towards the synthesis of hyacinthacine A_1 are presented in detail. Chapter 6 of this dissertation is dedicated to a discussion on each of the methods and proposal for future studies.

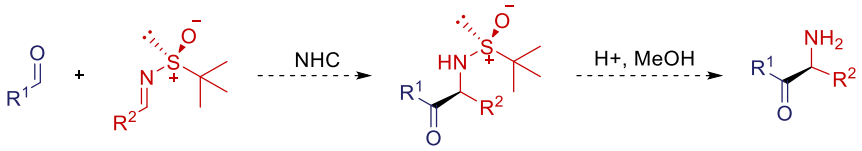
Chapter 2: A Chiral Auxiliary Approach Towards the *N*-Heterocyclic Carbene (NHC)-Catalyzed Aza-Benzoin Reaction

2.1. Research Objectives

α-Aminoketones are important structural motifs found in a number biologically active compounds (see **Section 1.2**). In light of such interesting activities, the goal was to develop a general method to access a variety of enantiomerically enriched *α*-aminoketones using diastereoselective NHC-catalyzed aza-benzoin transformations. The aza-benzoin reaction provides straightforward access to such motifs through the direct coupling of aldehydes and imines. At the onset of the investigation, the reported enantioselective variant of this transformation was associated with several limitations. A narrow scope of the aldehyde reaction partner as well as the necessity of using activated imines (or imine surrogates) for obtaining useful yields are among such drawbacks.[86,87] Additionally, moderate to good enantioselectivities were obtained in most cases, attesting to the necessity for developing new methods in the area. Also, the use of unactivated imines generally results in low yields as a result of their low electrophilicity towards the nucleophilic attack from the Breslow intermediate. Hence, the reported aza-benzoin reactions utilized nitrones,[88] *N*-sulfonyl ketimines,[50] and *N*-diarylphosphinoylimines [63] as activated substrates.

To address these drawbacks, a chiral auxiliary approach was devised towards this transformation. *tert*-Butanesulfinamides (Ellman's auxiliaries) were chosen as suitable candidates for this purpose (**Scheme 2.1**).[89–92] Facile accessibility and cleavage of *tert*-butanesufinimines renders such substrates suitable for inducing diastereoselectivity in a wide array of transformations. These auxiliaries have been frequently used with nucleophilic organo

-magnesuim, -lithium, -zinc, -silicon, -indium, -cerium, and -boron reagents for accessing enantio-enriched amines. The strong stereo-differentiating ability of the *tert*-butanesufinimides as well as their ability to enhance the electrophilicity of imines, through the electron-withdrawing sulfinyl substituent, are among the reasons for their widespread application.[90]



Scheme 2.1 A chiral auxiliary approach towards α-aminoketones

The conformational analysis of *tert*-butanesulfinimines is key to predicting the stereochemical outcome of nucleophilic additions to these substrates. A conformational study carried out by Bharatam and co-workers suggests that conformation **50a** is more stable than 50**b** with an energy difference of ca. 30 kJ mol^{-1} (**Figure 2.1**).[93] The most stable conformer features the lone pair of nitrogen and the S-O bond as antiperiplanar (**50a**). Destabilizing repulsion between the oxygen and nitrogen's electron cloud in **50b** and the favourable $n_N \rightarrow \sigma^* S^+–O^-$ stereoelectronic as well as the C-H$\cdots$O electrostatic interaction in **50a** are believed to be linked to the overall relative stability of **50a** over **50b**.

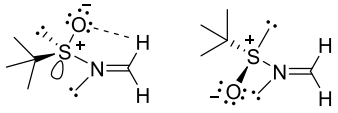


Figure 2.1 Two of the most stable conformers of (*R*)-2-methyl-*N*-methylenepropane-2-sulfinamide

In a separate study, the rotational barrier towards *Z*/*E* isomerization of **51a** and **51b** was calculated at the B3LYP\6-31+G* level of theory (**Figure 2.2**).[93] Results suggest a ca. 100 kJ mol^{-1} barrier for this isomerization, indicating a semi-rigid system at room temperature.[94]

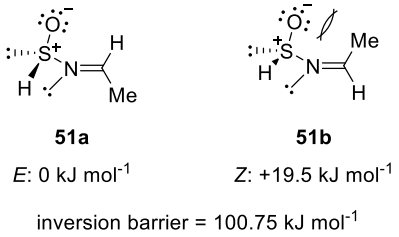
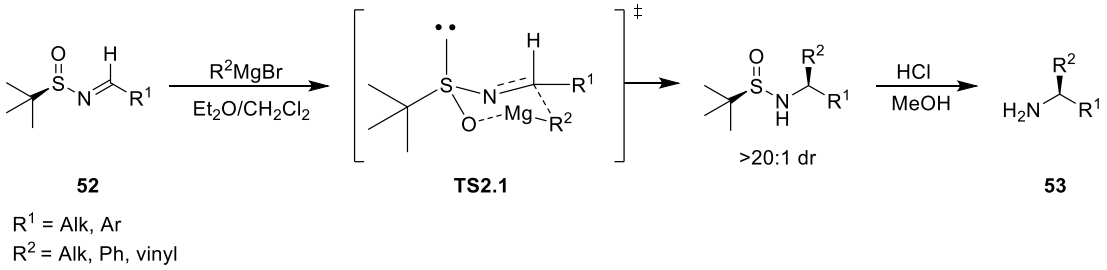


Figure 2.2 Calculated inversion barrier for *Z*/*E* isomerization of a simple sulfinimine

Synthesis of α-branched amines using Grignard reagents is a common example of highly diastereoselective reactions using *tert*-butanesulfinimines (**52**) (**Scheme 2.2**). A rigid six-membered transition state (**TS2.1**) is postulated to be responsible for the observed selectivity.[92] Finally, the chiral auxiliary can be cleaved using mild acidic conditions affording enantio-enriched amines (**53**).



Scheme 2.2 Synthesis of enantio-enriched amines using Ellman's auxiliary

2.2. Results and Discussion

2.2.1. Optimization of Reaction Conditions

Initial reaction conditions were chosen according to reactions developed during Gravel and co-workers' previous studies on Stetter[95] and benzoin[6] reactions. 2-Furaldehyde (**54**), frequently

reported for its superior reactivity in benzoin transformations, was chosen as the partner aldehyde. (*S*)-(*E*)-*N*-benzylidene-2-methylpropane-2-sulfinamide (**55**) was synthesized according to a known literature procedures (see **Section 7.1**). Diisopropylethylamine, a moderate base capable of deprotonating triazolium and thiazolium salts, was chosen as the base and activated molecular sieves were employed to prevent moisture from interfering with the reaction. Optimization reactions were carried out using a 1:1:1 molar ratio of aldehyde, imine, and base respectively and under nitrogen atmosphere unless noted otherwise. Reactions were quenched using 0.5 mL of acetic acid and the crude reaction mixtures were analyzed by ^{1}H NMR spectroscopy by using $CDCl_3$ as the solvent. The consumption of starting materials and diastereomeric ratios were calculated according to the ^{1}H NMR spectra of the crude reaction mixtures. Conversions in all reactions were measured by ^{1}H NMR spectroscopy. The conversion was calculated using the signals from the NH (ca. δ 8.60 ppm) of the corresponding *tert*-butanesulfinimine and the C*H*-OH of the products (ca. 6.40–6.50 ppm).

2.2.1.1. Screening of Various NHC Pre-Catalysts

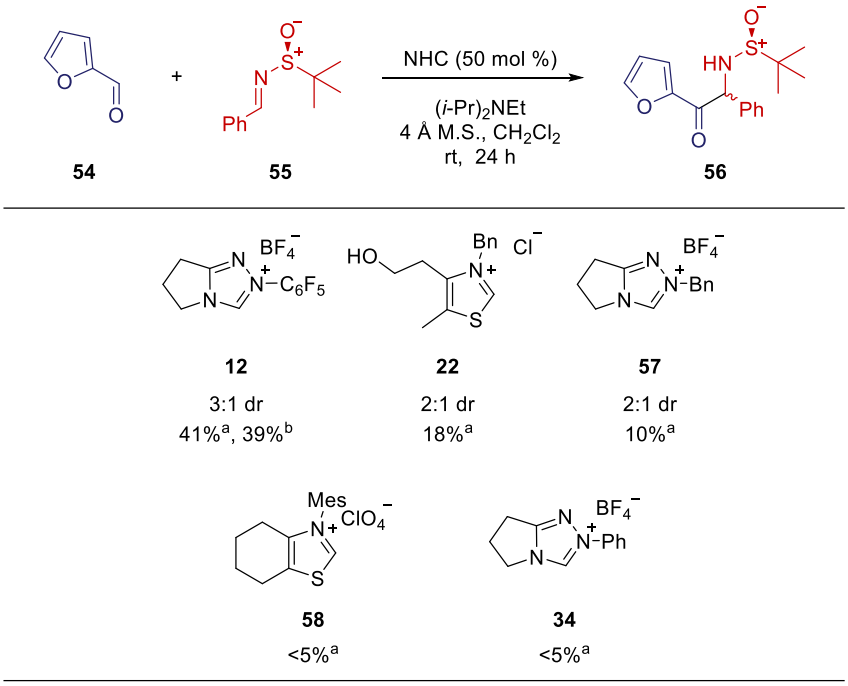
A number of known triazolium- and thiazolium-based pre-catalysts were screened as NHC surrogates under the reaction conditions described in Section 2.2.1 (**Table 2.1**).

Results show that **12** can best deliver the desired product (**56**) with moderate yield and diastereoselectivity[i] and therefore was chosen as the optimal pre-catalyst. Inspection of the crude reaction mixture shows clean conversion and hence the efficiency of the optimization reactions was assessed based on the conversion of the *tert*-butanesulfinimine to the desired products.

[i] It is unclear which of the diastereomers is preferentially formed under the reactions conditions. Additionally, the relative configuration of the diastereomers were not assigned

Interestingly, thiazolium salt **22** is also suited for this reaction albeit affording relatively lower yield and diastereoselectivity. Other triazolium- and thiazolium-based pre-catalysts (**57, 58,** and **34**) failed to deliver **56** in synthetically useful yields.

Table 2.1 Screening of various NHC pre-catalysts



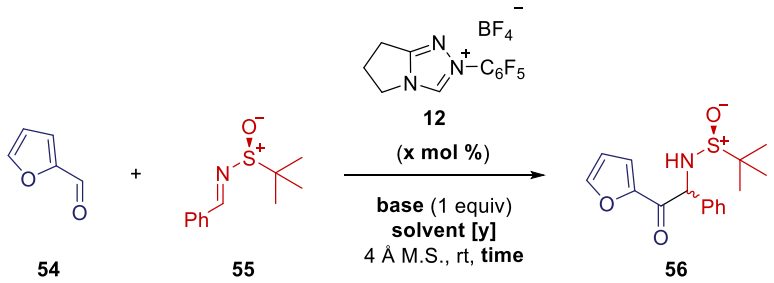
[a] Conversion; [b] Isolated yield of major diastereomer

2.2.1.2. Effects of Base, Solvent, Concentration, and Temperature

Using the triazolium salt **12**, a survey of reaction conditions was performed by varying the base, solvent, concentration, and the temperature (**Table 2.2**).

A survey of different protic and aprotic solvents (**entries 1-5**) revealed that the reaction is best performed in dichloromethane (**entry 1**). Interestingly, the use of ethanol affords comparable diastereoselectivity, although with reduced conversion (**entry 2**).

Table 2.2 Optimization of reaction conditions



entry	pre-catalyst x mol %	base	solvent	[y][a]	time (h)	conversion (%)	diastereomeric ratio
1	50	(*i*-Pr)$_2$NEt	CH_2Cl_2	0.2 M	24	41	4 : 1
2	50	(*i*-Pr)$_2$NEt	EtOH	0.2 M	24	26	4 : 1
3	50	(*i*-Pr)$_2$NEt	toluene	0.2 M	24	<5	N.D.
4	50	(*i*-Pr)$_2$NEt	THF	0.2 M	24	<5	N.D.
5	50	(*i*-Pr)$_2$NEt	CH_3CN	0.2 M	24	<5	N.D.
6	30	(*i*-Pr)$_2$NEt	CH_2Cl_2	0.2 M	24	26	3: 1
7	30	Cs_2CO_3	CH_2Cl_2	0.2 M	24	11	4 : 1
8	30	DBU	CH_2Cl_2	0.2 M	24	<5	N.D.
9	30	NaOAc	CH_2Cl_2	0.2 M	24	<5	N.D.
10	30	NaOAC+HOAc	CH_2Cl_2	0.2 M	24	<5	N.D.
11	30	(*i*-Pr)$_2$NEt	CH_2Cl_2	0.6 M	24	34	4 : 1
12	30	(*i*-Pr)$_2$NEt	CH_2Cl_2	0.6 M	5	40	3 : 1
13	30	(*i*-Pr)$_2$NEt	CH_2Cl_2	2.4 M	5	49	11: 1
14	30	(*i*-Pr)$_2$NEt	CH_2Cl_2	5.0 M	5	34	19 : 1
15	30	(*i*-Pr)$_2$NEt	N/A	neat	5	22	13 : 1
16[b]	30	(*i*-Pr)$_2$NEt	CH_2Cl_2	2.4 M	5	19	3: 1

[a] Concentration was determined based on **55**
[b] Reaction carried out at 60 °C

Reducing the catalytic loading of the NHC-precursor (from 50 mol % to 30 mol %) did not significantly affect the outcome of the reaction (**entry 6**). Screening of various commonly used bases and a NaOAc/HOAc buffer followed (**entries 7-10**). Among these, the use of (*i*-Pr)$_2$NEt (or Hünig's base) affords a higher yield. This superior reactivity could be linked to the additional role of its conjugated acid in activating the *tert*-butanesulfinimine towards the nucleophilic attack. A possible mode of activation is depicted in Figure 2.3.[96]

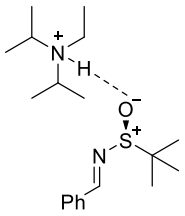


Figure 2.3 Proposed activation of (*S*)-(*E*)-*N*-benzylidene-2-methylpropane-2-sulfinamide through the conjugated acid of Hünig's base

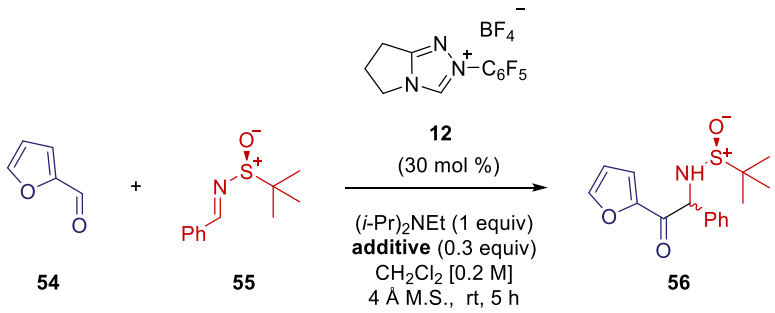
The use of DBU affords a mixture of unidentified side products (**entry 8**), while the use of sodium acetate/acetic acid buffer suggested by Xu and co-workers,[97] affords no detectible product (**entry 10**). Decreasing the reaction time to 5 hours led to a slight increase in the conversion while increasing the time led to a lower conversion (**entries 11-12**)**.** Reactions were then performed in parallel, varying the concentration of the reactants (**entries 13-15**). A correlation between concentration, conversion and diastereoselectivity was observed. The optimal concentration seems to lie between 2.4 M and 5.0 M. Note that conversion is reduced as the concentration is increased beyond a certain point (**entries 14** and **15**). This is possibly due to inefficient stirring of the viscous mixture at higher concentrations. Additionally, increasing temperature led to lower conversion and diastereoselectivity (**entry 16**).

2.2.1.3. Application of Lewis Acids to Facilitate the Reaction Outcome

Despite promising results from the optimization reactions, further attempts at improving the reaction outcome by varying the amount of 2-furaldehyde (**54**) and Hünig's base proved futile. Inspection of crude reaction mixtures from Table 2.1 using ^{1}H NMR indicates significant *tert*-butanesulfinimine (**55**) left over after workup. The poor electrophilicity of this reaction partner is believed to be linked to this observation. It was intriguing to investigate whether enhancement of the electrophilicity of **54** could be achieved by using an external additive.

At the onset of this study, Scheidt and co-workers had shown that different Lewis acid co-catalysts can facilitate NHC-catalyzed *umpolung* reactions. Their studies have shown that Mg(O*t*-Bu)$_2$ and Ti(O*i*-Pr)$_4$ can effectively facilitate homoenolate reactions (a^1, d^3) between Breslow intermediates and a number of electrophiles.[98,99] However, such activation was not known for (a^1, d^1) *umpolung* additions.[ii]

Table 2.3 Activation of (*S*)-(*E*)-*N*-benzylidene-2-methylpropane-2-sulfinamide using Lewis acids



entry	additive	conversion (%)	diastereomeric ratio
1	none	26	3 : 1
2	Mg(*Ot*-Bu)$_2$	26	3 : 1
3	Ti(O*i*-Pr)$_4$	<5	N/A

Results showed that Mg(O*t*-Bu)$_2$ did not affect the reaction outcome while Ti(O*i*-Pr)$_4$ inhibited product formation (**Table 2.3**, **entries 1-3**). The latter observation is believed to be linked to the irreversible reaction between the NHC and the titanium-based Lewis acid.

2.2.1.4. *H*-Bond Activation of *tert*-Butanesulfinimines with Thioureas

The role of thiourea derivatives as *H*-bond donors has been well-established throughout the literature.[100] It was hypothesized that in the presence of suitable *H*-bond donors such as thioureas,

[ii] Since these studies, other Lewis acids such as, Sc(OTf)$_3$, La(OTf)$_3$, Yb(OTf)$_3$, and Fe(OTf)$_3$ have been shown to facilitate NHC-catalyzed transformations[238]

tert-butanesulfinimines could be activated towards the nucleophilic attack from the Breslow intermediate. Figure 2.4. depicts two of the possible activation modes.

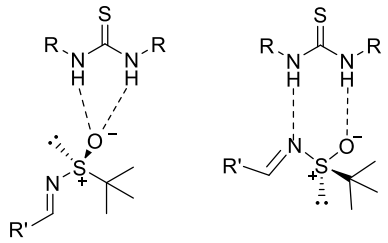


Figure 2.4 Plausible modes of activation of *tert*-butanesulfinimines using thioureas

A number of thiourea derivatives (**Figure 2.5**) were synthesized according to a reported procedure (see **Section 7.1**) and used as additives under the reaction conditions (**Table 2.4**).

Additives **59** and **60** were effective in increasing the conversion, and good diastereomeric ratios were maintained by using these additives (**entries 1-3**). Other thiourea additives led to either decrease in yield or were ineffective (**entries 4-5**). accuracy of these experiments was evaluated using dimethyl terephthalate as the internal standard for a quantitative ^{1}H NMR analysis. It was disappointing to learn that the conversion did not correspond to the NMR yield. The major diastereomer from the reaction corresponding to the use of **59** (**entry 2**) was isolated using flash chromatography. The poor isolated yield (40%) may be attributable to the hydrolysis (or decomposition) of the starting material (**55**). Such pathways could be facilitated in the presence of thiourea derivatives.

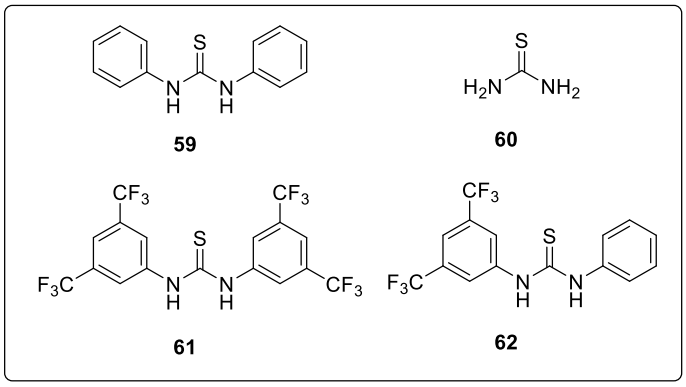
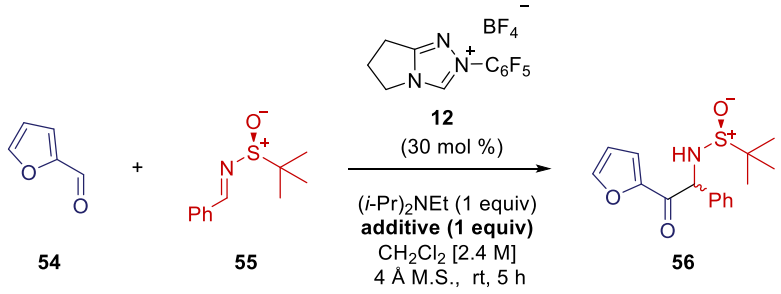


Figure 2.5 Thiourea-derived additives for the NHC-catalyzed aza-benzoin reaction

Table 2.4 Screening of thiourea-derived additives in the aza-benzoin reaction



entry	additive	conversion (%)	diastereomeric ratio
1	none	49	11 : 1
2	**59**	82	10 : 1
3	**60**	64	9 : 1
4	**61**	38	10 : 1
5	**62**	50	10 1

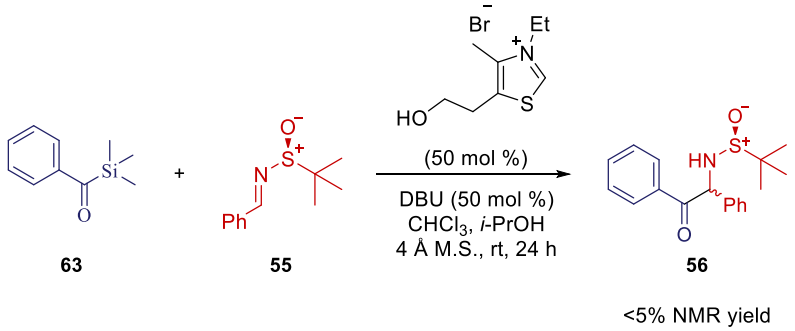
2.2.2. Identification of Competing Pathways

2.2.2.1. The Homo-Benzoin Pathway

The unsatisfactory results prompted investigation of the alternative reaction pathways that could contribute to decreasing the yields. ^{1}H NMR analyses of the crude reaction mixtures showed evidence of formation of homo-benzoin (furoin) and oxidized homo-benzoin (furyl) products. Although the reversibility of both homo-benzoin and aza-benzoin reactions are well established,[61]

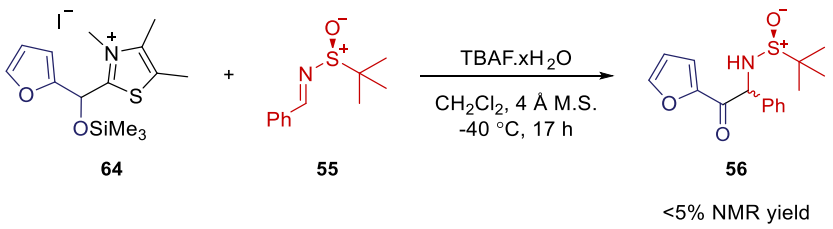
the oxidized homo-benzoin product may be responsible for the decrease in yields; oxidation of furoin effectively removes an essential source of the 2-furaldehyde-derived Breslow intermediate from the catalytic cycle, lowering the yield of the aza-benzoin product.

Scheidt and co-workers have shown that the use of acylsilanes can effectively inhibit the homo-benzoin pathway.[63] Acylsilane **63** was synthesized according to a known literature procedure (see **Section 7.1**) and utilized under the reaction conditions reported by Scheidt and co-workers (**Scheme 2.3**).[63] Unfortunately, this modification failed to deliver detectible amounts of the desired product.



Scheme 2.3 Efforts towards inhibition of undesired homo-benzoin side-products using an acylsilane

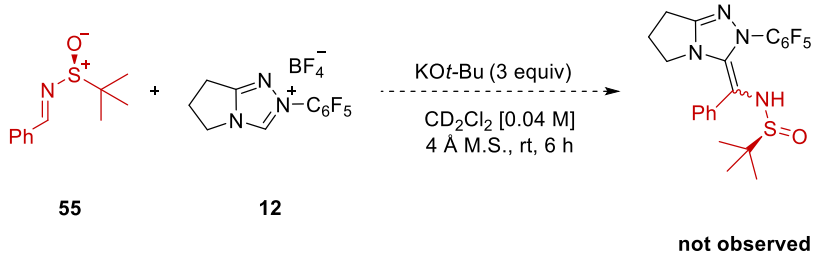
A similar strategy utilizes *O*-silyl protected carbinols as means of inhibiting the homo-benzoin pathway.[101] In such reactions, the pre-formed Breslow intermediate is activated through the deprotection of the silyl group using a mild fluorine source. Although non-catalytic, this method has demonstrated usefulness in addressing the chemoselectivity issues in cross-benzoin reactions. However, when **64** and **55** were subjected to the reaction conditions, no detectible amounts of the desired products (**56**) or the homo-benzoin products were observed (**Scheme 2.4**).



Scheme 2.4 Efforts towards inhibition of side-products using an *O*-silyl protected carbinol

2.2.2.2. NHC-Imine Adducts

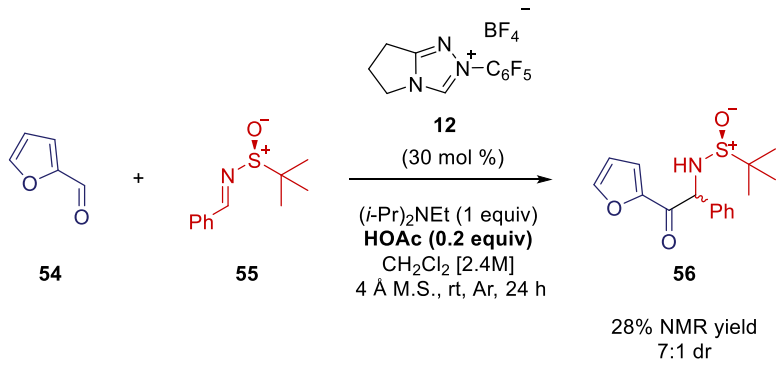
In 2012, Rovis and co-workers isolated stable adducts formed between imines and triazolium-based NHCs.[8] In a later study, adducts comprised of NHCs and *N*-Boc imines were identified in crude ^{1}H NMR mixtures.[102] In order to identify the adducts formed between the NHC and *tert*-butanesulfinimines, a ^{1}H NMR experiment was carried out following the procedure by Rovis and co-workers (**Scheme 2.5**). A reaction was performed in an NMR tube containing potassium *tert*-butoxide and equimolar amounts of the NHC precursor (**12**) and **55**. Careful ^{1}H NMR analysis of the crude reaction mixture showed no formation of NHC-imine adduct over the course of 6 hours.



Scheme 2.5 ^{1}H NMR monitoring experiment aimed towards identifying possible imine-NHC adducts

Although the ^{1}H NMR study showed no indication of the catalyst-imine adduct using potassium *tert*-butoxide, the existence of such often short-lived species under the model reaction conditions, can not be ruled out. Studies by Rovis and co-workers have shown that using a buffer solution could successfully reverse the formation of the catalyst-imine adducts.[102] It was interesting to investigate whether such buffers could act in the same manner in the aza-benzoin reaction of *tert*-

butanesulfinimines, leading to higher yields. This was examined by using $(i\text{-Pr})_2NEt_2$/HOAc buffer under the reaction conditions (**Scheme 2.6**). However, the use of catalytic amounts of acetic acid led to a slight decrease in yield. This is possibly due to less efficient deprotonation of the NHC precursor resulting in lower concentration of the Breslow intermediate and a slower reaction rate.



Scheme 2.6 Attempted use of Hünig's base/acetic acid buffer to improve the reaction outcome

2.2.3. Inconsistencies in Diastereomeric Ratios

While attempting to reproduce earlier results from Table 2.2, inconsistencies in the diastereomeric ratio of the products were observed. In order to identify the source of such discrepancies, parallel reactions were performed by varying the reaction atmosphere (argon, nitrogen, and air). Surprisingly, it was observed that the reactions which were carried out under argon atmosphere afford lower diastereomeric ratios compared to those carried out under nitrogen atmosphere. Furthermore, aliquots taken at different intervals from a reaction carried out in air showed that the ratio of the diastereomers increases over time while the overall NMR yield decreases. It is possible that both diastereomers of the *α*-amino ketone product are susceptible to oxygen-assisted degradation, with decomposition of the minor diastereomer proceeding faster than the major. With the higher oxygen-displacement ability of argon compared to nitrogen, the higher diastereomeric ratios observed with the latter also support such a degradation.

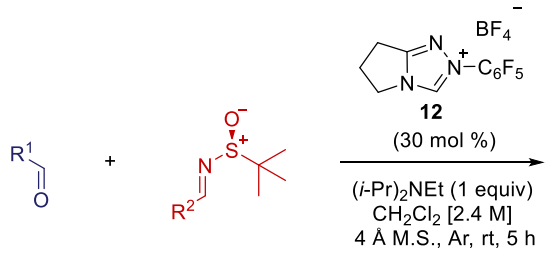
2.2.4. Scope of the NHC-Catalyzed Aza-Benzoin Reaction

The scope of the reaction was explored using the set of conditions obtained from Table 2.2 under argon atmosphere (**Table 2.5**). 2-Furaldehyde, 4-methyl-2-furaldehyde, and substituted *tert*-butanesulfimines were used to furnish *α*-aminoketones in moderate yields[iii] and diastereomeric ratios (**56a**, **65**, and **66**). The scope of the reaction is limited to the use of electron-rich *tert*-butanesulfinimines and 2-furaldehyde derivatives (**67** and **68**). Additionally, the use of 3-methoxyphenyl substituted acceptor led to poor yield and diastereoselectivity (**69**).

Interestingly, the use of cinnamaldehyde with stoichiometric amounts of catechol led to formation of **72** in moderate diastereomeric ratios.[103] Unfortunately, the use of aliphatic imines or aldehydes (not shown) as well as, heteroaromatic imines (not shown), and aromatic aldehydes (**70** and **71**) are not tolerated under the reaction conditions. Given the unsatisfactory yields and diastereomeric ratios, the isolation of the products was not attempted.

[iii] Yield was determined based on ^{1}H NMR analysis of crude reaction mixtures by using dimethyl terephthalate as the internal standard

Table 2.5 Scope of NHC-catalyzed aza-benzoin reactions



56a 4:1 dr 45%[a], 36%[b]	**65** 4:1 dr 52%[a]	**66** 3:1 dr 31%[a]
67 3:1 dr 18%[a]	**68** 2:1 dr 12%[a]	**69** 3:1 dr 24%[a]
70 < 5%[a]	**71** <5%[a]	**72** 3:1 27%[a, c]

[a] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard; [b] Isolated yield of the major diastereomer; [c] Modification to reaction conditions: 1 equiv of catechol was used as additive, reaction was carried out at room temperature for 24 h

2.3. Conclusion

Despite promising initial results, the competitive oxidation and/or degradation pathways, limited scope, and the poor reactivity of *tert*-butanesulfinimines renders this approach unattractive. Results indicate that a selective degradation of the minor diastereomer could be responsible for the discrepancies in the diastereomeric ratios encountered throughout the study. This degradation can be avoided by carrying out the reaction under argon atmosphere. However, attempts at improving the product ratios under argon atmosphere could only deliver moderate diastereoselectivities. ^{1}H NMR analyses of crude reaction mixtures show significant amounts of residual *tert*-butanesulfinimine. One of the factors influencing such poor reactivity could be attributed to the low electrophilicity of the imine reaction partner. Strategies to activate this reactant in the NHC-catalyzed aza-benzoin reaction proved futile either due to incompatibility with the reaction conditions or insufficient reactivity enhancement. Despite these drawbacks, these results could be utilized as an entry point for the intramolecular variant of the NHC-catalyzed aza-benzoin reaction using *tert*-butanesulfinimines (see **Section 6.1**).

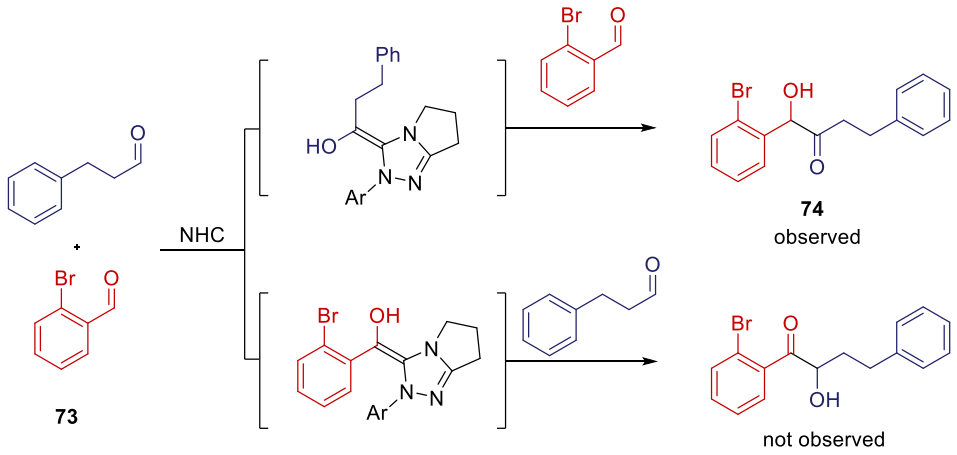
Chapter 3: Chemo- and Diastereoselective NHC-Catalyzed Cross-Benzoin Reactions using *N*-Boc-*α*-Amino Aldehydes

3.1. Research Objectives

Targeting the chemoselectivity issues associated with NHC-catalyzed cross-benzoin reactions has been among the most important challenges associated with these reactions (see **Section 1.2**). Involvement of multiple species in the catalytic cycle, as well as the similar electronic and steric properties of reactants are believed to be linked to such complexities; *i.e.* both aldehydes could participate as electrophiles towards the NHC or the Breslow intermediate.[104] Studies have shown that product distribution in the NHC-catalyzed cross-benzoin reaction of two distinctly different aldehydes can be altered (see, **Section 1.2**). Some mechanistic studies have elucidated the underlying principles of NHC-catalyzed cross-benzoin reactions: kinetic studies carried out by Smith and co-workers[41] as well as computational studies by Gravel and co-workers[43] showed that the steric and electronic properties of the aldehyde substrates have a significant effect on the chemoselectivity. However, this study only describes NHC-catalyzed cross-benzoin reactions involving two aromatic aldehydes or one aromatic and one aliphatic aldehyde were discussed. At the onset of this investigation, a general method for coupling two distinct aliphatic aldehydes using *N*-heterocyclic carbene catalysis had not been reported. The primary objective was to develop a synthetic methodology that could successfully address the chemoselectivity issues associated with the use of two aliphatic aldehydes in NHC-catalyzed cross-benzoin reactions.

Stetter[33], and Connon and Zeitler[34] separately reported chemoselective NHC-catalyzed cross-benzoin reactions between aliphatic aldehydes and 2-halo-substituted benzaldehyde derivatives. In all cases, the major product (**74**) is derived from a reaction between the NHC and the aliphatic

aldehyde, while the *ortho*-substituted aromatic aldehyde (**73**) serves as the electrophile towards the Breslow intermediate (**Scheme 3.1**). Computational calculation carried out by Gravel and co-workers suggest that (*Z*)-Breslow intermediates are preferred for aliphatic aldehydes while aromatic aldehydes adopt an *E* geometry.[43]



Scheme 3.1 Chemoselective NHC-catalyzed cross-benzoin reactions using *ortho*-halo-aromatic aldehydes

Connon and Zeitler link the observed chemoselectivity to the steric bulk of **73** rendering its reaction with the NHC unfavourable. In other words, the selection between the two reaction partners for formation of the Breslow intermediate possibly influences the final product distribution.

For NHC-catalyzed cross-benzoin reaction between aliphatic aldehydes, it was speculated that during the formation of the Breslow intermediate, the carbene catalyst would react more slowly with sterically hindered aldehydes compared to unhindered ones. However, such sterically congested aldehydes are less reactive toward a nucleophilic attack from the Breslow intermediate and require electrophilic activation in order to obtain the desired chemoselectivity. Installation of an electron-withdrawing group could inductively activate such electrophiles, increasing their propensity to undergo a nucleophilic attack by the Breslow intermediate (**Figure 3.1**). In such a

scenario, this aldehyde would be sterically sterically hindered enough to prevent formation of its corresponding Breslow intermediate, but electrophilic enough to be favoured in the C–C bond formation step.

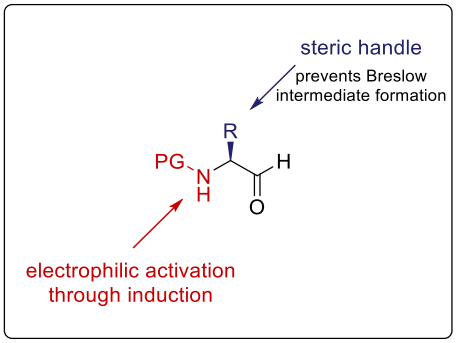
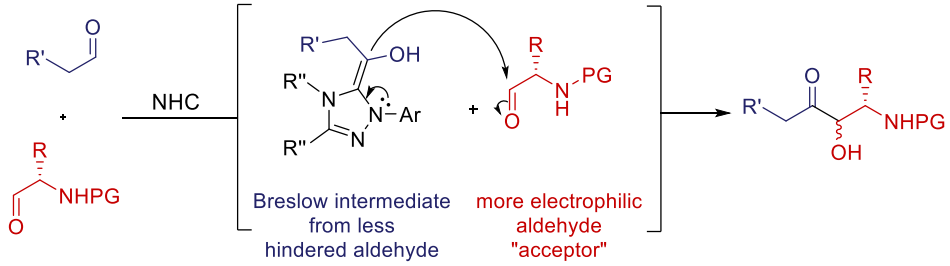


Figure 3.1. Proposed substrate design for chemoselective NHC-catalyzed cross-benzoin reactions

Amino acid-derived *N*-protected-*α*-amino aldehydes were chosen as suitable substrates for this purpose. The branched nature of these aldehydes would inhibit formation of the corresponding Breslow intermediate, while the electron-withdrawing carbamate group would activate the aldehyde for the subsequent electrophilic attack. Additionally, the *α*-stereogenic center would serve as a steric modulator for facial selectivity on the aldehyde during C–C bond formation (**Scheme 3.3**).



Scheme 3.2 Proposed reaction design for controlling chemo- and diastereoselectivity

3.2. Results and Discussion

3.2.1. Optimization of Reaction Conditions

Initial screening was carried out using hydrocinnamaldehyde (**75**), *N*-Boc-L-alaninal (**76**), and reaction conditions according to Gravel and co-workers (**Table 3.1**).[42] *N*-Boc-L-alaninal (**76**) was synthesized according to known literature procedures (see **Section 7.2**). Diisopropylethylamine, a moderate base capable of deprotonating triazolium and thiazolium salts,[13] was chosen as the base. After 4 hours, the reactions were quenched using 1M HCl (aq). The crude reaction mixture was extracted with dichloromethane (×3) and the combined organic layers were dried over Na_2SO_4. The crude reaction mixtures were analyzed *via* ^{1}H NMR spectroscopy by using dimethyl terephthalate as the internal standard.

3.2.1.1. Screening of Various NHC Pre-Catalysts

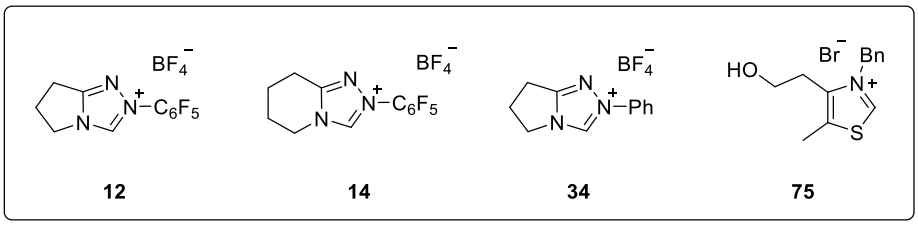
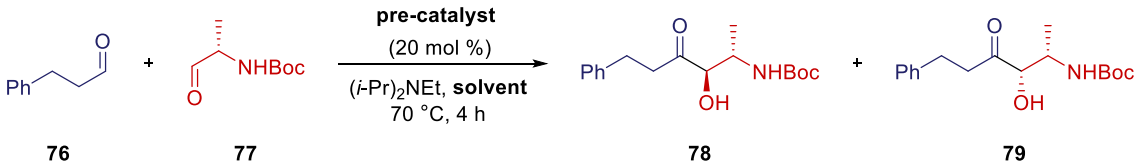


Figure 3.2 Common pre-catalysts for NHC-catalyzed cross-benzoin reactions

Table 3.1 Initial optimization reactions using hydrocinnamaldehyde and *N*-Boc-L-alaninal



entry	pre-catalyst	solvent	yield (%)[a]	diastereomeric ratio (78 : 79)
1	**12**	CH_2Cl_2	47 (30)[b]	3:1
2	**14**	CH_2Cl_2	45	2:1
3	**34**	CH_2Cl_2	<5	N.D.
4	**75**	CH_2Cl_2	<5	N.D.
5	**12**	THF	52	2: 1
6	**12**	toluene	47	3:1
7	**12**	MeOH	19	2:1
8	**12**	TBME	10	N.D.

[a] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard
[b] Isolated yield of major diastereomer

The use of pre-catalysts **12** and **14** affords useful yields of the desired α-hydroxy ketone product (**Table 3.1, entries 1-2**). Pre-catalyst **12** was chosen as the optimal catalyst, affording a good yield and a relatively higher diastereomeric ratio. In contrast, the use of the *N*-phenyl-substituted analog (**34**) and a thiazolium-derived pre-catalyst (**75**) proved unsuccessful (**entries 3-4**). The former coincides with Connon and Zeitler's report,[34] in which the pentafluorophenyl moiety was deemed crucial for the observed reactivity. Subsequent solvent optimization reactions revealed that this reaction could successfully be carried out in THF, toluene, or dichloromethane (**entries 5-8**). Among these variants, toluene was chosen based on the its successful application in the previous study (see Chapter 2) (**entry 6**).

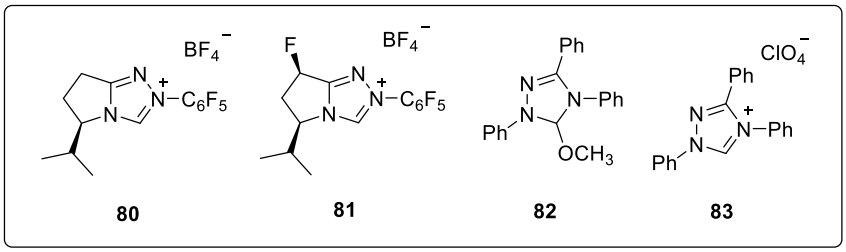
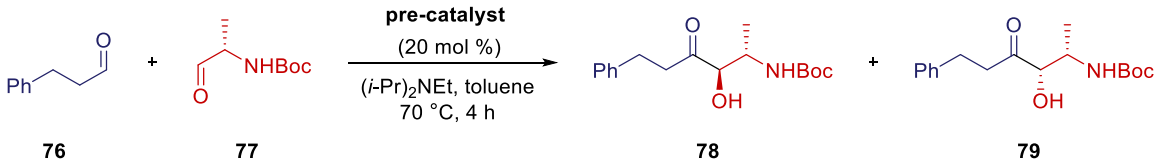


Figure 3.3 Other NHC pre-catalysts used for the optimization reactions

Table 3.2. Further Optimization reactions carried out using hydrocinnamaldehyde and *N*-Boc-L-alaninal



entry	pre-catalyst	yield (%)[a]	diastereomeric ratio (78 : 79)
1	**80**	50	5 : 1
2	**8q**	49	2 : 1
3	**82**[b]	18	2 : 1
4	**83**	<5	N.D.

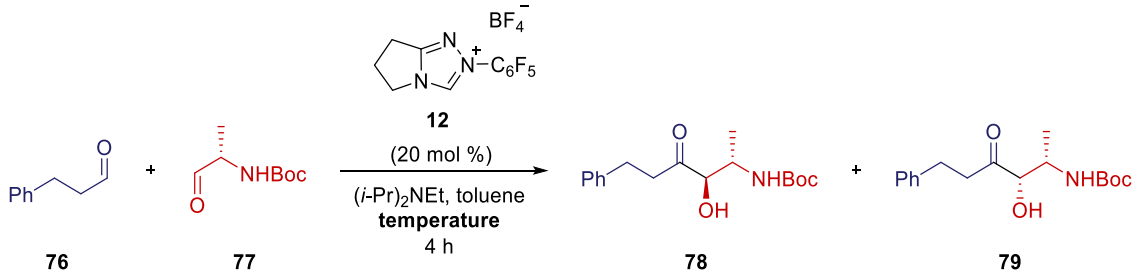
[a] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.
[b] Reaction carried out in the absence of base.

With the optimal solvent identified, further catalyst screenings were carried out using a number other NHC pre-catalysts (**Table 3.2**). Chiral *N*-pentafluorophenyl triazolium pre-catalysts performed well under the reaction conditions (**entries 1–2**). A slight increase in the diastereoselectivity was observed with the non-fluorinated variant (**entry 1**). However, this slight enhancement does not warrant the use of such chiral pre-catalysts due to their non-trivial and expensive syntheses. Interestingly, the use of **82** also delivers the desired product albeit in lower yields, while the application of **83** affords no detectible cross-benzoin products (**entries 3–4**).

3.2.1.2. Optimization of Reaction Temperature

In view of improving the reaction outcome, the model reaction was carried out at different temperatures (**Table 3.3**). Results show that these temperature variations do not lead to an improvement of the diastereomeric ratio or yields (**entries 1-4**). In fact, the reaction carried out at 23 °C resulted in a sluggish reaction and poor yield of the desired product. For these reasons 70 °C was chosen as the optimal temperature (**entry 4**).

Table 3.3 Effect of temperature on the reaction outcome



entry	temperature (°C)	NMR yield (%)[a]	diastereomeric ratio (78 : 79)
1	22	23	2 : 1
2	40	31	2 : 1
3	70	47	3 : 1
4	110	44	2 : 1

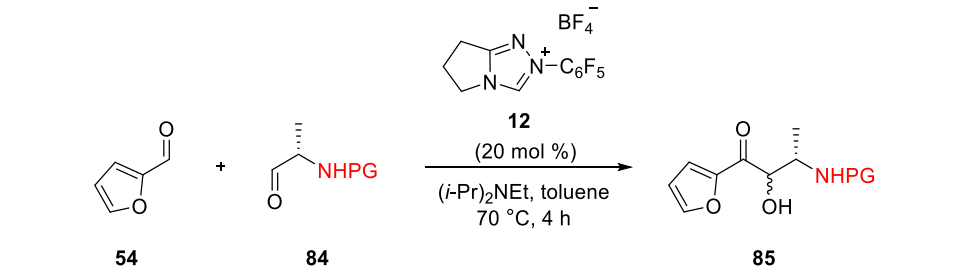
[a] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.

3.2.1.3. Effects of *N*-Protecting Groups

The remarkable reactivity of 2-furaldehyde (**54**) in NHC-catalyzed cross-benzoin reactions prompted investigation in using this aldehyde under previously optimized conditions. Gratifyingly, cleaner conversions and higher yields were obtained compared to reactions involving hydrocinnamaldehyde. For this reason, 2-furaldehdye was used for the subsequent optimization reactions.

In order to examine the effect of the nitrogen's protecting group on the yield and diastereoselectivity of the reaction, a series of *N*-mono-protected-L-alaninal derivatives were synthesized and subjected to the reaction conditions with 2-furaldehyde (**Table 3.4**).

Table 3.4 Use of various L-alaninal-derivatives under optimized reaction conditions



84a	84b	84c	84d
2:1	2:1	1:1	<5% [a]
72%[a]	50%[a]	28%[a]	

[a] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.

Carbamate protecting groups (**84a–84b**) are well-suited for this transformation with higher yields obtained from the use of *N*-Boc-L-alaninal. It seems that the diastereoselectivity is unaffected by the nature of the nitrogen-protecting group and remained poor for the examined substrate. Additionally, the application *N*-tosyl- and *N*-trityl-protected-L-alaninal proved disappointing (**84c–84d**).

The poor diastereoselectivity was addressed by modification of the α-substituent of the *N*-Boc-α-amino aldehyde. It was hypothesized that increasing the steric bulk on the amino aldehyde should lead to higher facial selectivities during the C–C bond formation step. To this end, *N*-Boc-L-valinal was synthesized and subjected to reaction conditions. It was interesting to discover that while maintaining excellent chemoselectivity, the use of this substrate successfully addresses the

diastereoselectivity issue (*vide infra*). To establish optimized conditions, this reactant was used to re-optimize the reaction conditions.

3.2.1.4. Re-Optimization of Reaction Using *N*-Boc-L-Valinal

Starting from the conditions established earlier (see **Sections 3.2.1.1**, **3.2.1.2**, and **3.2.1.3**), the reaction conditions were optimized for *N*-Boc-L-valinal (**86**) and **54** (**Table 3.5**).

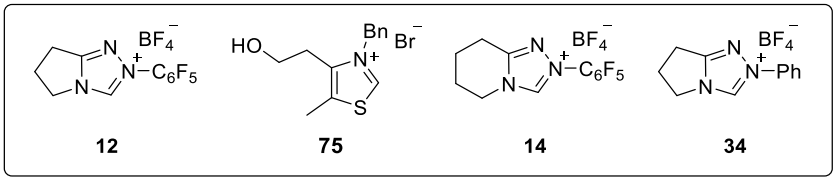
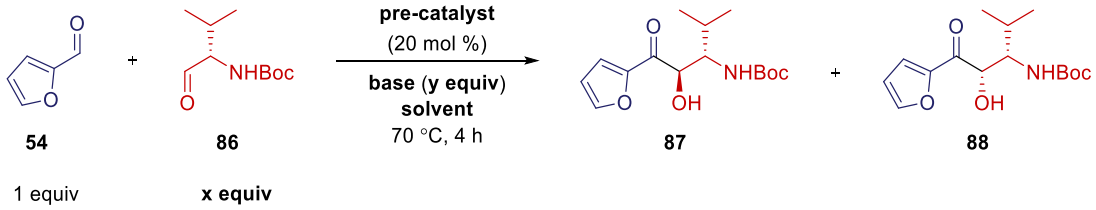


Figure 3.4 NHC-precatalysts used for screening reactions using *N*-Boc-L-valinal

Table 3.5 Optimization of reaction conditions using 2-furaldehyde and *N*-Boc-L-valinal

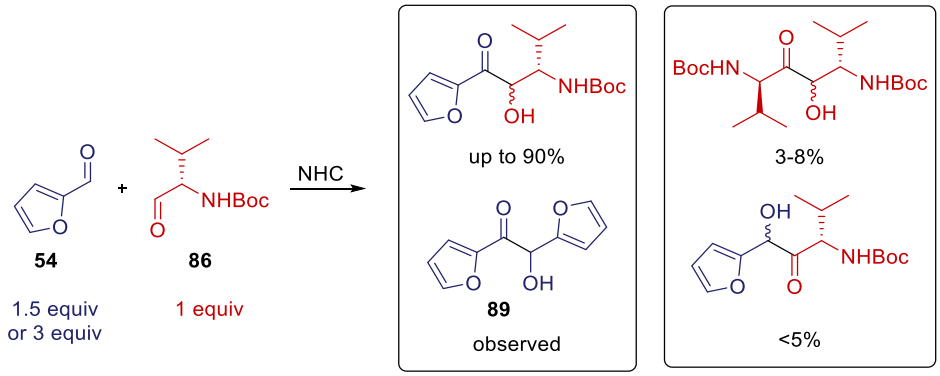


entry	pre-catalyst	solvent	base	x equiv	y equiv	yield (%)	diastereomeric ratio (87 : 88)
1	**12**	CH_2Cl_2	$(i\text{-Pr})_2NEt$	1.5	1	74	7 : 1
2	**75**	CH_2Cl_2	$(i\text{-Pr})_2NEt$	1.5	1	64	6 : 1
3	**14**	CH_2Cl_2	$(i\text{-Pr})_2NEt$	1.5	1	38	7 : 1
4	**34**	CH_2Cl_2	$(i\text{-Pr})_2NEt$	1.5	1	38	5 : 1
5	1	toluene	$(i\text{-Pr})_2NEt$	1.5	1	72	6 : 1
6	1	MeOH	$(i\text{-Pr})_2NEt$	1.5	1	71	7 : 1
7	1	THF	$(i\text{-Pr})_2NEt$	1.5	1	55	3 : 1
8	1	CH_2Cl_2	DBU	1.5	0.2	84	4 : 1
9	1	CH_2Cl_2	CsOAc	1.5	1	71	5 : 1
10	1	CH_2Cl_2	Cs_2CO_3	1.5	1	41	5 : 1
11[b]	1	CH_2Cl_2	$(i\text{-Pr})_2NEt$	1.5	1	75	9 : 1
12	1	CH_2Cl_2	$(i\text{-Pr})_2NEt$	1.5	2	80	7 : 1
13	1	CH_2Cl_2	$(i\text{-Pr})_2NEt$	3	2	83	7: 1

[a] Combined yield of the two diastereomers determined by analysis of ^1H NMR spectra and by using dimethyl terephthalate as the internal standard. [b] Reaction carried out at 40 °C for 16 hours.

A number of known pre-catalysts were utilized in the reaction in order to identify the optimal azolium salt (**Figure 3.4**). While the use of **12** affords the highest yields and diastereomeric ratios, thiazolium-derived pre-catalyst **75** was also a competent NHC source (**entries 1-2**). This contrasts with the earlier observations; when **75** was subjected to a reaction containing hydrocinnamaldehyde, no detectible cross-benzoin product was observed (**Table 3.1**, **entry 4**). This could be attributed to the lower reactivity of aliphatic aldehydes compared to heteroaromatic aldehydes in the presence of thiazolylidene in cross-benzoin transformations.[33] Furthermore, the use of triazolium salts **14** and **16** affords comparatively lower yields and good diastereomeric ratios (**entries 3-4**).

Analysis of the crude reaction mixtures revealed that the undesired cross-benzoin and *N*-Boc-L-alaninal homo-benzoin reaction pathways had been effectively suppressed (**Scheme 3.3**). Later in the study, a side product corresponding to the homo-benzoin product of *N*-Boc-L-valinal was identified. However, this undesired side product was only produced in limited amounts (3-8%) in all examined mixtures. Additionally, the homo-benzoin by product of 2-furaldehyde (furoin, **89**) could easily be removed using flash chromatography.



Scheme 3.3 Product distribution in NHC-catalyzed cross-benzoin reactions using *N*-Boc-amino aldehydes

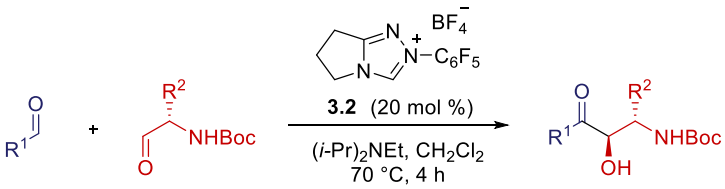
Solvent screening revealed that the reaction is best carried out in dichloromethane or toluene (**Table 3.5**, **entries 5-7**). A survey of various bases showed that tertiary amines continue to out perform carbonate or acetate bases (**entries 8-10**). Interestingly, catalytic amounts of DBU can deliver the cross-benzoin products in higher yield (**entry 8**). However, due to the susceptibility of enantio-enriched *N*-Boc-amino aldehydes towards racemization, Hünig's base was selected as the optimal base. Lower temperature with prolonged reaction times did not significantly affect the reaction outcome (**entry 11**). Finally, using excess amounts of the base and 2-furaldehyde led to an improvement in yield (**entry 13**). It is noteworthy that a large excess of the heteroaromatic aldehyde is not a requirement for the observed chemoselectivity; good yield (80%) of the cross-benzoin product could also be obtained by using only 1.5 equivalents of this substrate (**entries 12–13**).

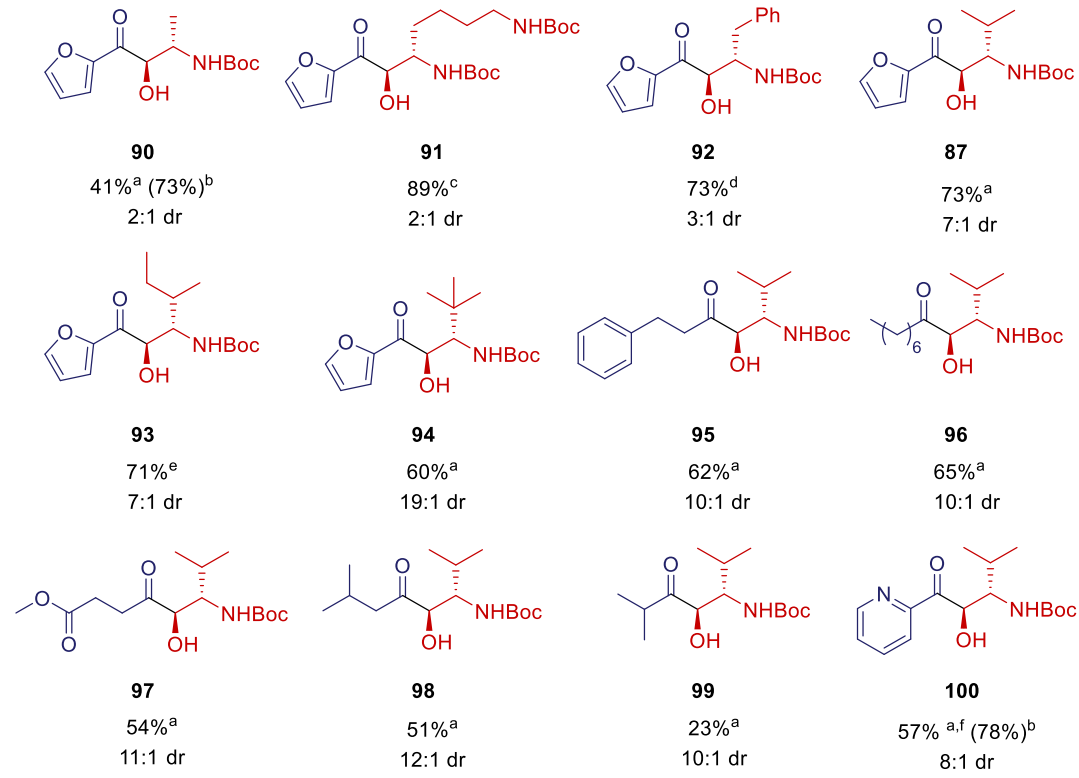
3.2.2. Scope of the NHC-Catalyzed Cross-Benzoin Reaction Using *N*-Boc-*α*-Amino Aldehydes

Having established optimized conditions, the substrate scope was examined using different *N*-Boc-*α*-amino aldehydes and aliphatic or heteroaromatic aldehydes (**Table 3.6**). As anticipated,

non-sterically hindered *N*-Boc-*α*-amino aldehydes such as *N*-Boc-L-alaninal, *N*-Boc-L-phenylalaninal, and *N*,*N*'-bis-Boc-L-lysinal afforded the corresponding *α*-hydroxy-*β*-amino ketones in good yields and moderate diastereoselectivity (**90**-**92**). Increasing the steric bulk on the *β*-substituent of the amino aldehyde reaction partner led to higher diastereomeric ratios (**87**, **93**-**94**). This effect is enhanced in the case of a sterically congested *tert*-L-leucine-derived *α*-amino aldehyde affording excellent diastereoselectivity (**94**). Importantly, good yields were obtained by using aliphatic aldehydes as coupling partners, including one bearing an ester functionality (**95**-**99**). Interestingly, higher diastereoselectivities were observed when using aliphatic aldehydes compared to heteroaromatic aldehydes. The reasons for the somewhat better diastereoselectivities observed for these substrates are unclear at this point. The presence of *α*-branching on both aldehyde partners seems to be detrimental to the yield due to increased steric bulk (**99**). The unsuccessful use of electron-poor 4-bromo-benzaldehyde indicates that benzaldehyde and its derivatives perform poorly under these reaction conditions resulting in a mixture of unidentified products (not shown). In contrast, the use of 2-pyridine carboxaldehyde affords a good yield and diastereomeric ratio (**100**). In some cases, the separation of diastereomers *via* chromatography proved laborious, highlighting the significance of diastereoselectivity in such reactions. The problem can be circumvented by using a subsequent hydroxyl-directed reduction of the ketone functionality, affording readily separable amino diols (*vide infra*).

Table 3.6 Substrate scope of NHC-catalyzed cross-benzoin reactions using *N*-Boc-*α*-amino aldehydes





90	**91**	**92**	**87**
41%[a] (73%)[b]	89%[c]	73%[d]	73%[a]
2:1 dr	2:1 dr	3:1 dr	7:1 dr
93	**94**	**95**	**96**
71%[e]	60%[a]	62%[a]	65%[a]
7:1 dr	19:1 dr	10:1 dr	10:1 dr
97	**98**	**99**	**100**
54%[a]	51%[a]	23%[a]	57% [a,f] (78%)[b]
11:1 dr	12:1 dr	10:1 dr	8:1 dr

Reaction conditions: 1 equiv *N*-Boc-amino aldehyde, 3 equiv aliphatic, heteroaromatic or aromatic aldehyde, 2 equiv Hünig's base. [a] Isolated yield of major diastereomer. [b] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard [c] Isolated yield of a 2:1 mixture of diastereomers. [d] Isolated yield of a 3:1 mixture diastereomers. [e] Isolated yield of a 13:1 mixture of the two diastereomers. [f] Product is air-sensitive.

3.2.3. Racemization of *N*-Boc-*α*-Amino Aldehydes Under the Reaction Conditions.

The undesired racemization of *N*-protected-*α* amino aldehydes under basic reaction conditions is well-documented in the literature.[105–107] Therefore, it was essential to examine whether the reaction conditions lead to epimerization. Gratifyingly, comparison of a representative cross-

benzoin product (**95** in **Table 3.6**) with a racemic sample showed no erosion of the enantiomeric ratio (>98:2) during the reaction (see **Section 7.2**).

3.2.4. Assignment of Relative Configuration

The relative configuration of the *α*-hydroxy-*β*-amino ketone products was assigned using various methods.

Computational modeling has been frequently used as means of predicting ^{1}H NMR and ^{13}C NMR spectra and is a powerful tool for structure elucidation. The ^{1}H NMR chemical sifts corresponding to the (2*S*,3*R*)- and (2*S*,3*S*)- *tert*-butyl [4-(furan-2-yl)-3-hydroxy-4-oxobutan-2-yl]carbamate (**Scheme 3.4**, **3.21** and **3.22**) were predicted at the B3LYP\6-311+G(2d,p)\\M062X\6-31+G(d,p) level of theory by Michel Gravel.[108] Graphs were constructed by plotting the difference in chemical shifts between the predicted and experimental values versus the hydrogen atom (**Figure 3.5**, for raw data see **Section 7.2**). Comparison between the predicted and experimental spectra show a close fit to two of the data sets.

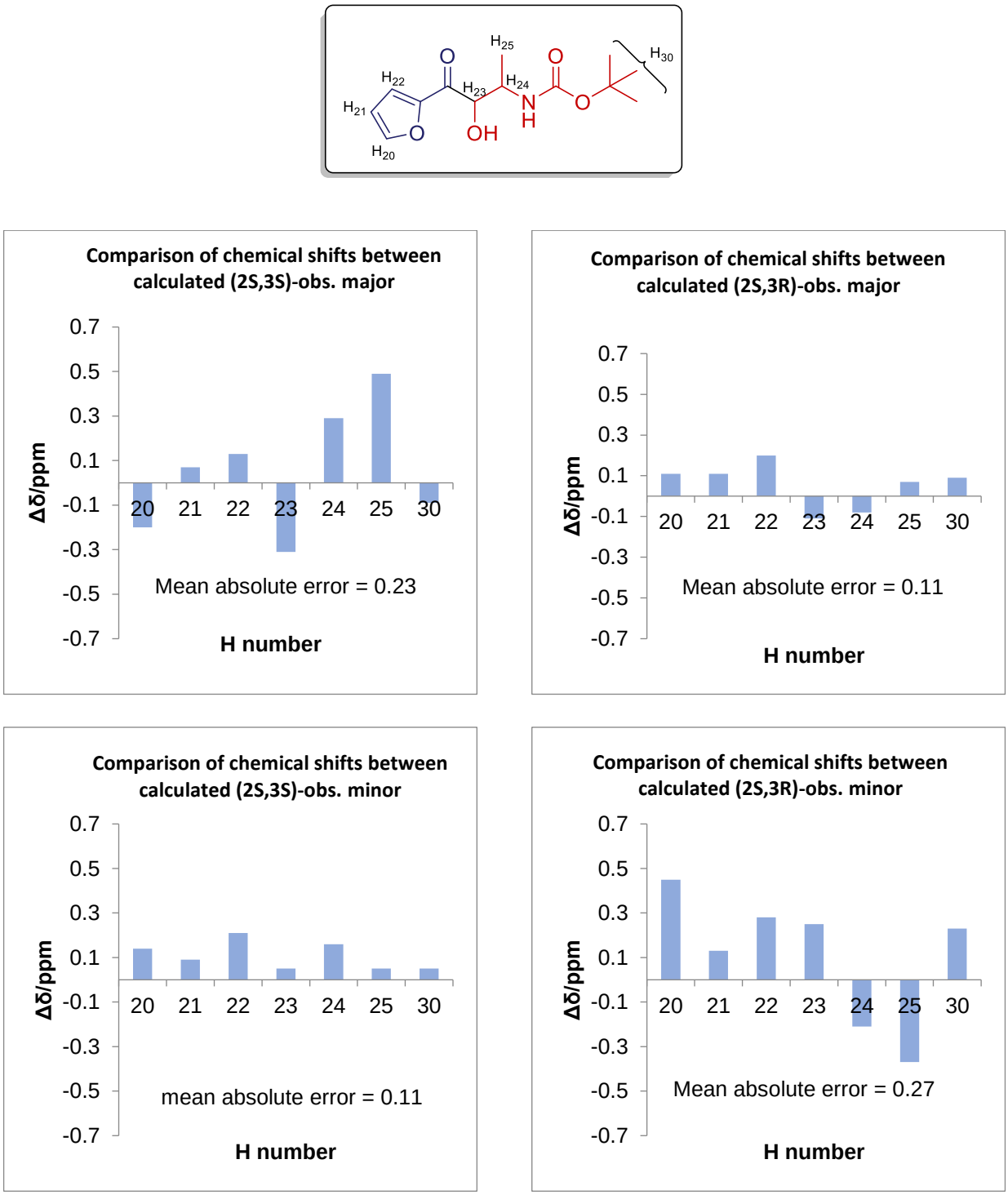
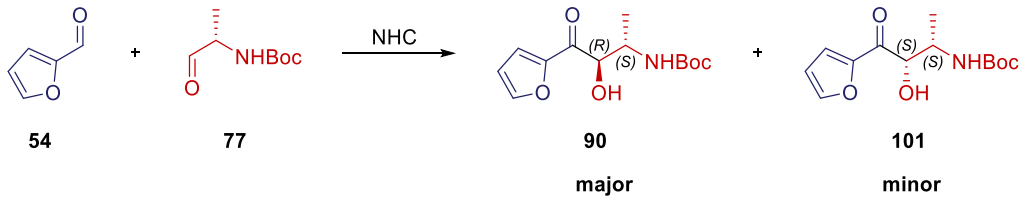


Figure 3.5 Comparison of predicted and experimental ^{1}H NMR shifts

Based on these predictions and the known absolute configuration of amino acid derived substrates, the absolute and relative configurations of the diastereomers were assigned as depicted

in Scheme 3.4. The assignments were later confirmed using X-ray crystallography of a closely related compound and synthesis of a configurationally known natural product (*vide infra*).



Scheme 3.4 Assignment of absolute and relative configuration of cross-benzoin products

A model featuring a hydrogen bond could be used to predict the diastereoselectivity of the reactions. According to this model, a hydrogen bond between the carbamate and aldehyde functional groups results in a semi-rigid transition state with the aldehyde poised for nucleophilic attack from the *Si* face (**Figure 3.6**). The steric properties of the R^2 substituent directly influence the facial selectivity and the final distribution of diastereomers. Additionally, this model could be successfully employed to rationalize the observed diastereoselectivity differences of L-alanine-, L-valine-, and *tert*-L-leucine-derived substrates.

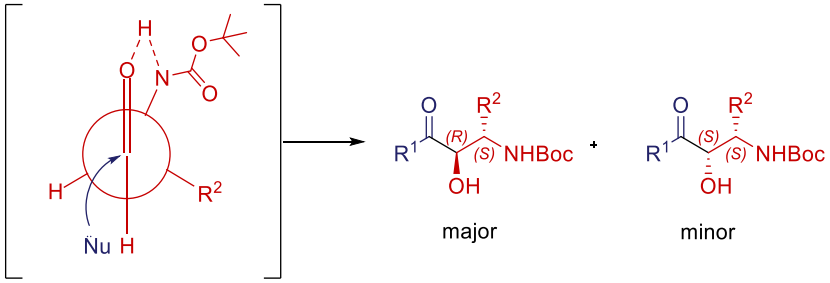
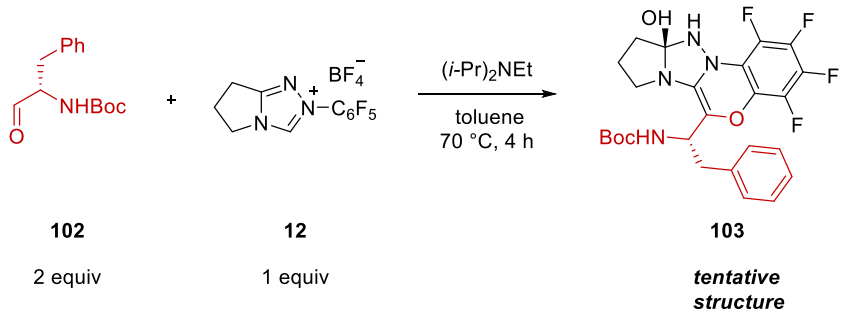


Figure 3.6 Proposed model for prediction of diastereoselectivity

3.2.5. NHC-Amino Aldehyde Adducts

In order to identify the alternative pathways involved in the NHC-catalyzed cross-benzoin reactions, **102** was subjected to the reaction conditions in the absence of a second aldehyde. After chromatography, an NHC-substrate adduct similar to S_NAr adducts isolated by Rovis and co-

workers was obtained in moderate yield (**Scheme 3.5**).[109] The isolation of this "trapped" Breslow intermediate highlights an important point: the formation of Breslow intermediate with the *N*-Boc-amino aldehydes is possible but possibly less favoured under the reaction condition. Nevertheless, the isolation of this adduct is another step towards validating the mechanism put forth by Breslow in 1958.[5]



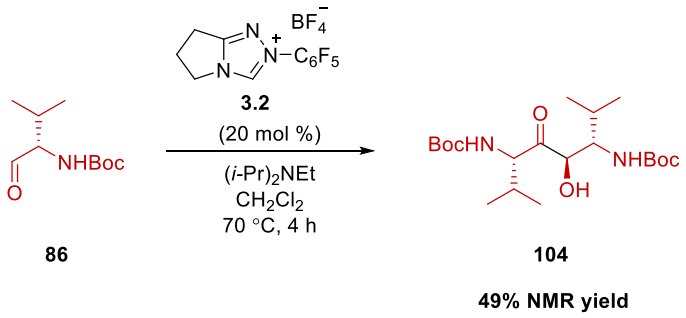
Scheme 3.5 Isolation of an NHC-aldehyde adduct

Detection of **102** confirms that the reaction of the NHC with sterically hindered amino aldehyde is possible, despite the proposed hypothesis. It was then examined whether the homo-benzoin product of the *N*-Boc-amino aldehyde is formed under the reaction conditions. When *N*-Boc-L-valinal (**86**) was subjected to standard reaction conditions without the partner aldehyde, the homo-benzoin product (**104**) was obtained in 49% yield[iv] and no NHC-amino aldehyde adduct was detected (**Scheme 3.6**). This may be attributed to the larger steric hindrance of L-valine- derived aldehydes compared to *N*-Boc-L-phenylalaninal inhibiting the adduct formation pathway.

To determine the importance of this homo-benzoin pathway, the crude mixtures from previous reactions (**Table 3.6**) were carefully analyzed by ^{1}H NMR spectroscopy. Only trace quantities (3-

[iv] Yield was determined based on ^{1}H NMR analysis of crude reaction mixtures by using dimethyl terephthalate as the internal standard

8%) of **104** were detected. This brings about another possibility: Breslow intermediate formation may not impact the final product distribution and a subsequent step is rate-limiting and responsible for the observed chemoselectivity.



Scheme 3.6 Formation of homo-benzoin product of *N*-Boc-L-valinal

3.2.6. ^{1}H NMR monitoring experiments

In order to gain a better mechanistic insight into the NHC-catalyzed cross-benzoin transformations using *N*-Boc-amino aldehydes, two ^{1}H NMR experiments were carried out. In these experiments, a 1:1 ratio between the two aldehydes was used and the species were monitored by ^{1}H NMR spectroscopy at 50 °C over time. Dimethyl terephthalate was used as internal standard for both experiments.

Monitoring the coupling of hydrocinnamaldehyde (**76**) and *N*-Boc-L-valinal (**86**) provided a wealth of information (**Figure 3.7**). Based on this experiment the reaction is highly chemoselective even with a 1:1 ratio of the two aldehydes. The formation of the desired product (**95**) was faster than that of the homo-benzoin by-product (**105**), suggesting a kinetically favoured reaction pathway. To examine this, **95** was purified, re-subjected to reaction conditions, and the reaction mixture was analyzed by ^{1}H NMR spectroscopy. No detectible amounts of the minor diastereomer, homo-benzoin products, or the starting aldehydes were observed. This suggests that the desired cross-benzoin pathway is irreversible under these conditions.

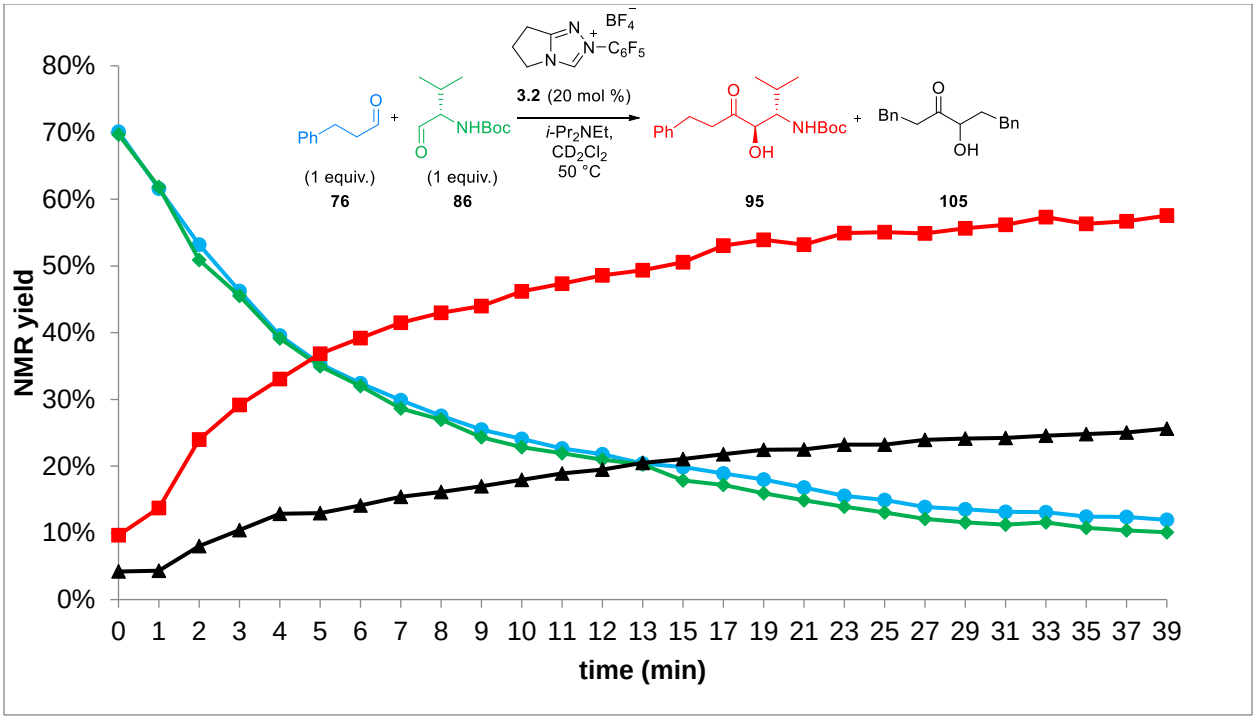


Figure 3.7 ^{1}H NMR monitoring results for the NHC-catalyzed cross-benzoin reactions between hydrocinnamaldehyde and *N*-Boc-L-valinal

The NHC-catalyzed cross-benzoin reaction between **54** and **86** contrasts the earlier study as the rate of formation of the homo-benzoin product (**89**) is faster than that of the desired cross-benzoin product (**87**) (**Figure 3.8**).

It is probable that after partial formation of the homo-benzoin product (**89**) a retro-benzoin reaction results in the re-generation of the corresponding Breslow intermediate (**106**) (**Scheme 3.7**). This intermediate then attacks the *N*-Boc-*α*-amino aldehyde (**86**) and leads to the steady formation of the desired cross-benzoin product (**87**) over time.

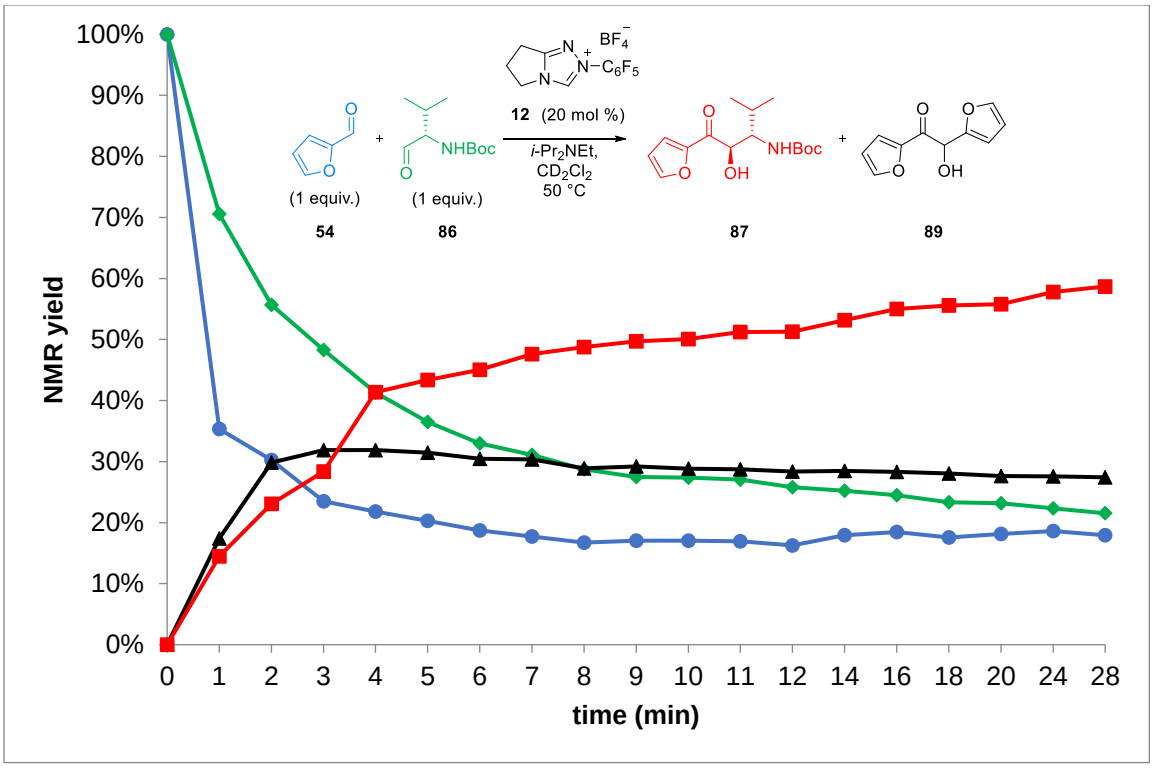
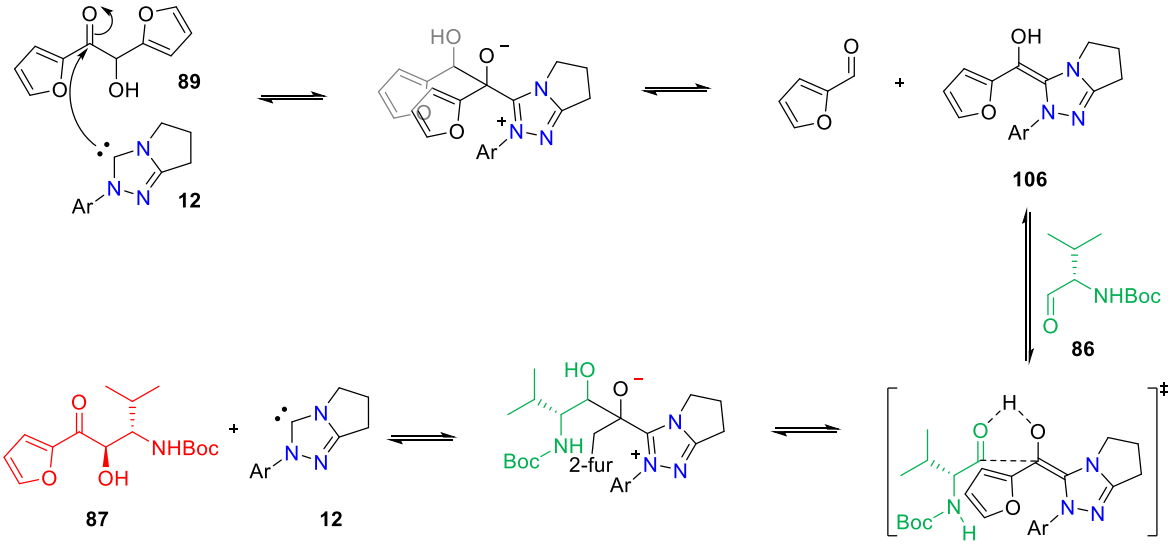


Figure 3.8 ^{1}H NMR monitoring experiment for the reaction between 2-furaldehyde and *N*-Boc-L-valinal

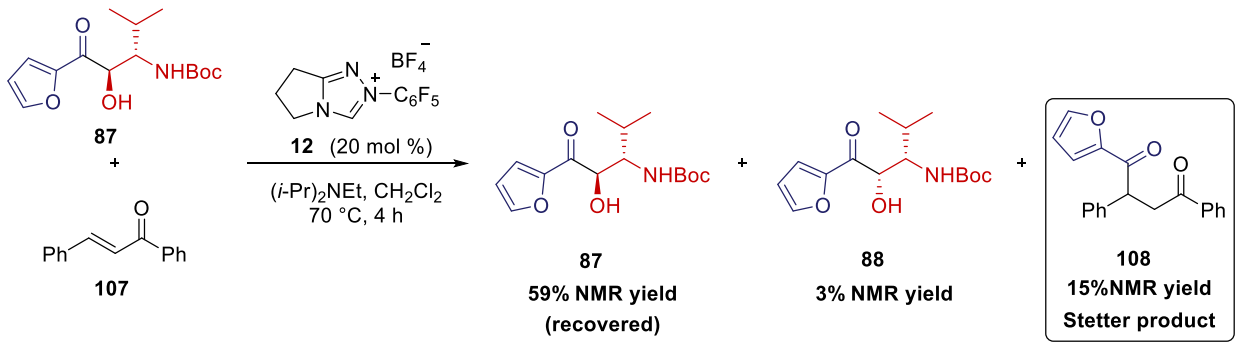


Scheme 3.7 Formation of the desired product through the retro-benzoin reaction of furoin and free NHC

This highlights an important detail: chemoselectivity at every step of the mechanism is not necessary to obtain high yields of cross-benzoin product. In this case, a presumably unfavourable

formation of the Breslow intermediate with the amino aldehyde combined with reversibility of the homo-benzoin reaction of 2-furaldehyde leads to formation of the desired cross-benzoin product (**87**) over time.

In order to evaluate the reversibility of this pathway, the major diastereomer (**87**) was subjected to reaction conditions in the presence of a stoichiometric amount of *trans*-chalcone (**107**) (**Scheme 3.8**). If the formation of the product is reversible, the retro-benzoin reaction would lead to re-formation of the Breslow intermediate with furfural. This intermediate could be trapped by the *α,β*-unsaturated ketone to form the Stetter product (**108**). It was found that under these conditions, **108** is observed in 15% yield[v] along with 3% of the minor diastereomer (**88**) and 59% recovered major diastereomer (**87**). These results confirm that the pathway leading to the formation of the major diastereomer is reversible.



Scheme 3.8 Cross over experiment with *trans*-chalcone

[v] Yield was determined based on ^{1}H NMR analysis of crude reaction mixtures by using dimethyl terephthalate as the internal standard

3.3. Conclusion

Complex chemoselectivity issues associated with NHC-catalyzed cross-benzoin reactions have thwarted their wide spread application. In addition, catalytic variants in which two aliphatic aldehydes are joined together through a chemoselective reaction are scarce. It was hypothesized that subtle steric and electronic properties of the reaction partners could influence the selection of the aldehydes during each step of the mechanism: a less sterically hindered aldehyde would be selected for the formation of Breslow intermediate while the more sterically hindered, but more electronically activated aldehyde would be preferred during C–C bond formation. α-Amino acid-derived *N*-Boc-amino aldehydes were shown to possess properties that could deliver high chemoselectivity in NHC-catalyzed cross-benzoin reactions. The α-substituent was shown to serve as a suitable modulator of the facial selectivity during the C–C formation step and moderate to good diastereoselectivities are obtained. The developed method can successfully deliver a variety of enantioenriched α-hydroxy-β-amino ketones rendering it a suitable synthetic tool for multi-step syntheses of biologically relevant molecules. However, the scope of the aldehydes that could successfully be employed in the reaction remains poor: unsterically hindered *N*-Boc-amino aldehydes afford poor diastereoselectivities. To address such limitations a complementary method was later developed (see **Chapter 4**).

Chapter 4: Reversal of Diastereoselectivity in NHC-Catalyzed Cross-Benzoin Reactions Using Doubly *N*-Protected-*α*-Amino Aldehydes

4.1. Research Objectives

α-Hydroxy ketones are convenient building blocks for a variety of synthetic transformations as well as important structural features present in a wide array of natural products (**Figure 4.1**).[110,111] Interest in such compounds stems not only from their alluring biological activities but also from their versatility in synthetic transformations; enantio-enriched *α*-hydroxy ketones can be easily transformed into other synthetically useful functional groups such as amino diols.[112–114]

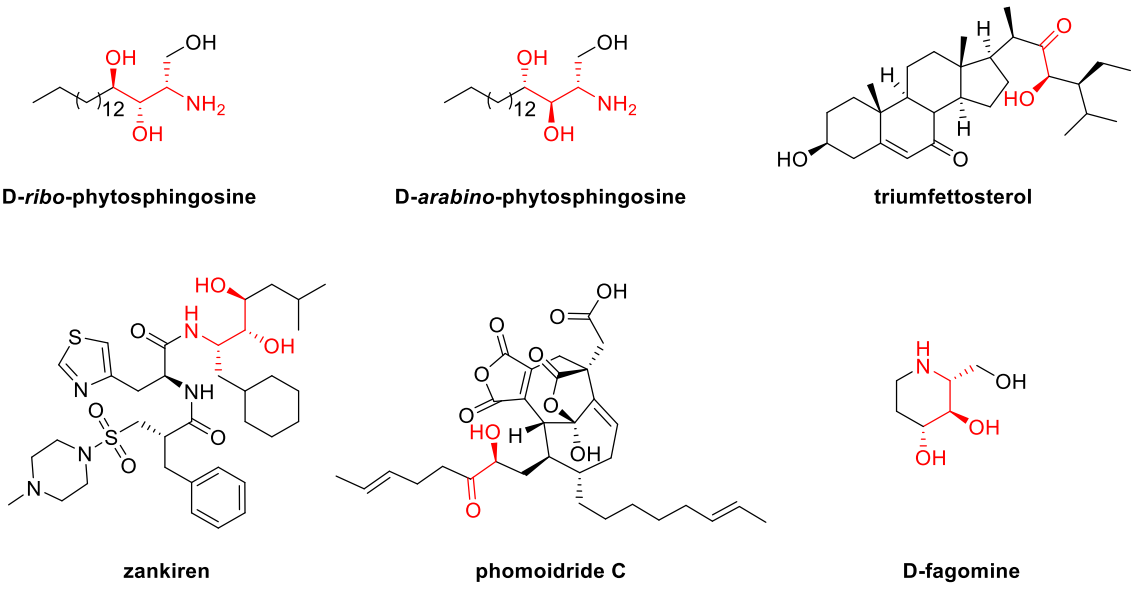
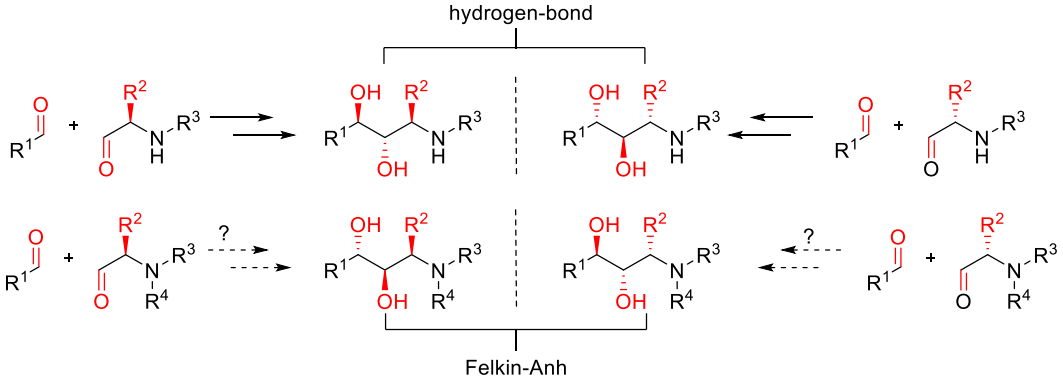


Figure 4.1 Examples of bioactive compounds containing *α*-hydroxy ketone and 1,2- diol moieties

The initial study on chemoselective cross-benzoin reactions using *N*-Boc-amino aldehydes shows excellent chemoselectivity for the (2*S*, 3*R*) diastereomer (see **Chapter 3**). By combining this methodology with a highly diastereoselective reduction (*vide infra*), a powerful synthetic tool is obtained which can be used to target various enantio-enriched amino diols.

By employing either enantiomer of the *α*-amino aldehyde followed by the stereoselective reduction of the resulting ketone, two out of eight possible diastereomers of the corresponding amino diols could be obtained (**Scheme 4.1**). However, in order to access a larger number of diastereomers (*i.e.* products from Felkin-Anh cross-benzoin reactions), a method that leads to the selective formation of the opposite diastereomer during the C–C bond formation step is sought.[115]



Scheme 4.1 Access to four stereoisomers using the NHC-catalyzed cross-benzoin reaction followed by diastereoselective reduction

The reversal of diastereoselectivity from Cram-chelate to Felkin-Anh selectivity using protecting group modifications is well-documented.[107,116,117] *N*,*N*-Dibenzylamino aldehydes,[117] Garner's aldehyde,[118] and *N*-Bn-*N*-Boc-amino aldehydes[107] have been shown to be suited for this purpose, In the context of nucleophilic addition reactions,. The diastereoselectivity of these reactions could be predicted using the Felkin-Anh type transition state model (**Figure 4.2**).[119]

In line with efforts towards expanding the scope of the NHC-catalyzed cross-benzoin reaction, It was intriguing to investigate whether protecting group modifications on the *α*-amino aldehyde reaction partner could lead to opposite diastereoselectivity. This modification could also serve as a test for the proposed hydrogen bond model (see **Section 3.2.4**). For this purpose, a variety of *N*,*N*-*bis*-protected amino aldehydes would be employed as coupling partners with heteroaromatic

and aliphatic aldehydes in NHC catalyzed cross-benzoin reactions. The reaction conditions would be re-optimized for the new substrates, and the diastereomers would be derivatized and compared to the diastereomers obtained from the previous method using ^{1}H NMR spectroscopy. If successful, this would confirm the relative configuration of the two diastereomers. With a general methodology to access a variety of enantio-enriched amino diols at hand, the long-term goal was to demonstrate its utility in the total synthesis of natural products (see **Chapters 5** and **6**).

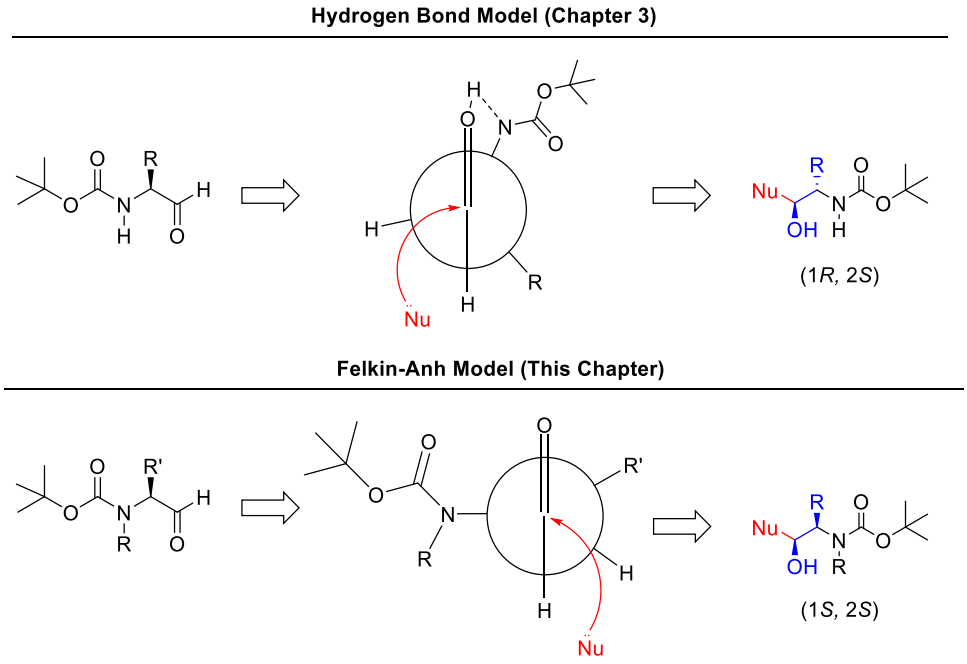


Figure 4.2 Different transition states leading to opposite diastereomers during the C-C bond forming step.

4.2. Results and Discussion

4.2.1. Optimization of Reaction Conditions

4.2.1.1. Exploring the Effects of *N*,*N*-Bis-Protecting Groups

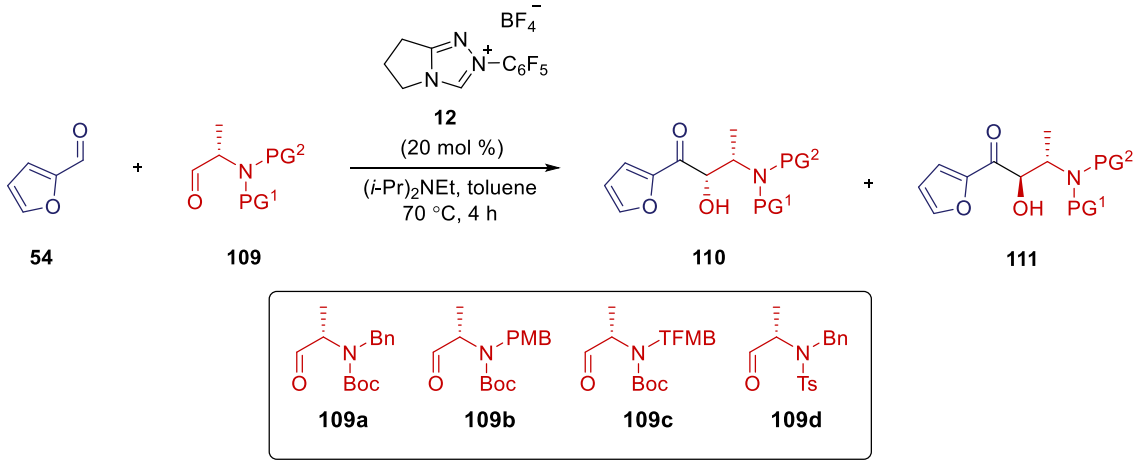
A number of protecting groups were installed on the nitrogen atom of L-alaninal and the resulting *N*,*N*-bis-protected-*α*-amino aldehydes (**109a-109d**) were utilized as reaction partners under the previously optimized reaction conditions (**Table 4.1**). The preferential formation of the

(*S*,*S*) diastereomer is expected using these substrates. The effects of the nitrogen's electron density on the outcome of the reaction was examined by using an electron-rich (**entry 2**) and an electron-poor (**entry 3**) protecting group. It was observed that the nature of the protecting group has limited impact on the diastereoselectivity of the reaction. *N*-Boc-*N*-Bn-protected α-amino aldehydes were chosen for future use due to their simple preparation and to the higher yield observed in the model reaction (**entry 1**). Although the use of substrate **109d** affords a relatively good yield,[vi] it was not selected for further optimization as the *N*-tosyl group may facilitate racemization of the corresponding α-amino aldehyde under the reaction conditions (**entry 4**).[i]

In order to establish the relative configuration of the products, *N*-Boc-*N*-Bn-L-alaninal (**109a**) was subjected to previously optimized conditions with furfural (**54**) (**Scheme 4.2**). The two diastereomers of the α-hydroxy-β-amino ketone product were separated *via* chromatography and a crystal corresponding to the major diastereomer (**112**) was analyzed by X-ray crystallography (**Figure 4.3**). The relationship between substituents on C_1 and C_2 was established using this method. Using the known configuration of the starting enantio-enriched α-amino aldehyde, the absolute configuration of the major diastereomer was assigned as (2*S*,3*S*).

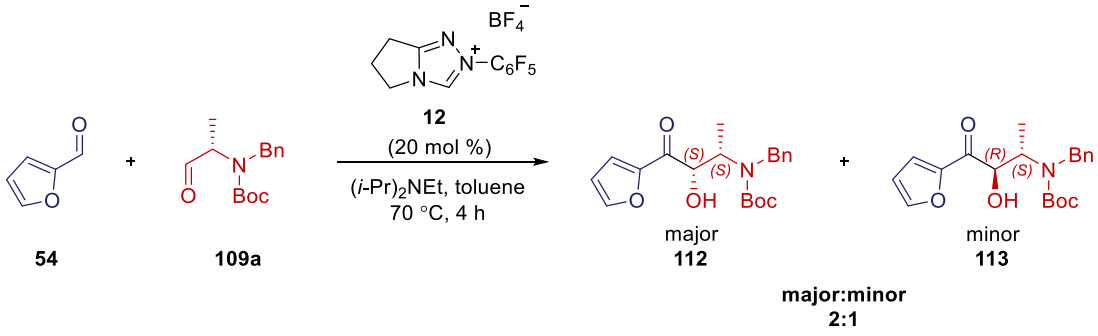
[vi] Yield was determined based on ^{1}H NMR analysis of crude reaction mixtures by using dimethyl terephthalate as the internal standard

Table 4.1 Screening of *N*,*N*-bis-protecting groups in NHC-catalyzed cross-benzoin reactions



entry	substrate	yield (%)[a]	diastereomeric ratio (110 : 111)
1	**109a**	93	2:1
2	**109b**	85	2:1
3	**109c**	79	3:1
4	**109d**	88	2:1

[a] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard



Scheme 4.2 NHC-catalyzed cross-benzoin reaction between 2-furaldehyde and *N*-Boc-*N*-Bn-L-alaninal

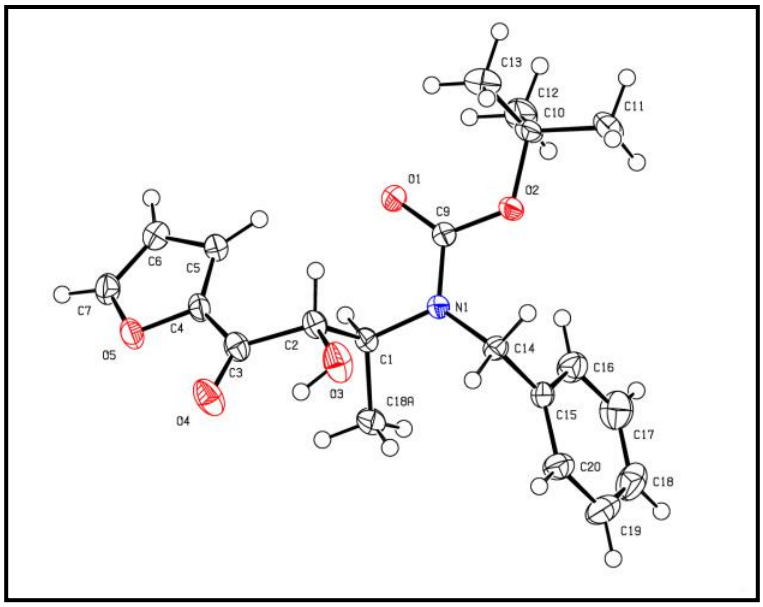


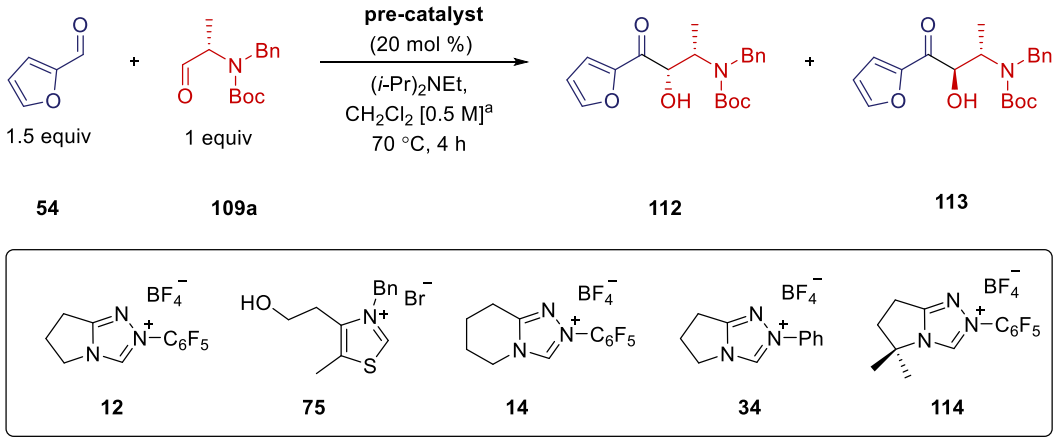
Figure 4.3 X-ray crystal structure of an α-hydroxy-β-amino ketone. Thermal ellipsoids are represented at the 30% probability level

4.2.1.2. Effects of NHC Pre-Catalyst and Solvent

Initial reaction conditions were chosen according to the previous study (see **Section 3.2.1**). Compound (**109a**) was chosen as the model α-amino aldehyde substrate and 2-furaldehyde (**54**) as the other reaction partner. Reactions were carried out using a 1:1.5 ratio of substrates unless otherwise noted. In some cases, peak broadening and the presence of rotamers renders the identification of the two diastereomers challenging. Acquiring the ^{1}H NMR spectra at elevated temperatures in DMSO-d_6 (80 °C) successfully addressed most of such issues.

A comparison of common NHC pre-catalysts showed that **12** is superior over other examined NHC precursors (**Table 4.2, entry 1**). As before, the use of **75** also delivers the cross-benzoin products in good yield, albeit with slightly lower diastereomeric ratios (**entry 2**). This contrasts with the use of **14**, **34,** and **114** which deliver the desired products in poor yields (**entries 3-5**).

Table 4.2 Screening of common NHC pre-catalysts under reaction conditions



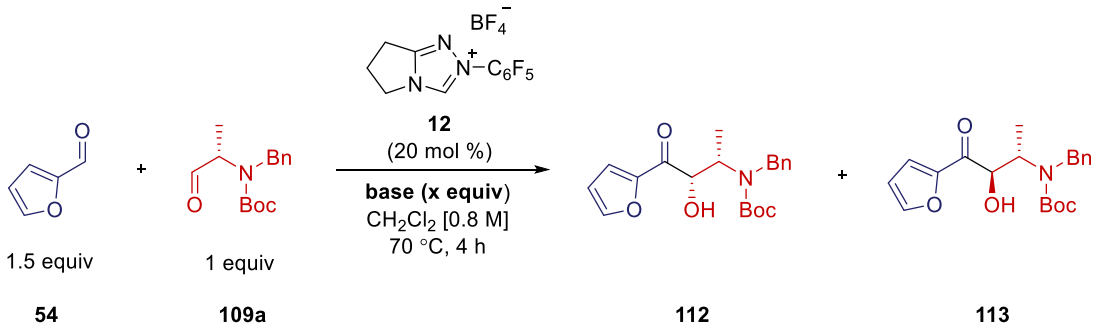
entry	pre-catalyst	yield (%)[a]	diastereomeric ratio (112 : 113)
1	**12**	93	(4 : 1)
2	**75**	85	(2 : 1)
3	**14**	30	(2 : 1)
4	**34**	<5	N.D.
5	**114**	<5	N.D.

[a] Concentration was determined with respect to the α-amino aldehyde.
[b] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.

A survey of different bases, at slightly higher concentration,[vii] showed that the use of Hünig's base and catalytic amounts of DBU furnish the cross-benzoin products in good yields and moderate diastereomeric ratios (**Table 4.3**, **entries 1-2**). However, due to the susceptibility of enantio-enriched amino aldehydes towards racemization, the former was chosen as the optimal base. It is noteworthy that cesium acetate and cesium carbonate afforded the desired product in comparatively lower yields (**entries 3-4**).

[vii] Concentration was determined with respect to **109a**

Table 4.3 Screening of various bases under the reaction conditions



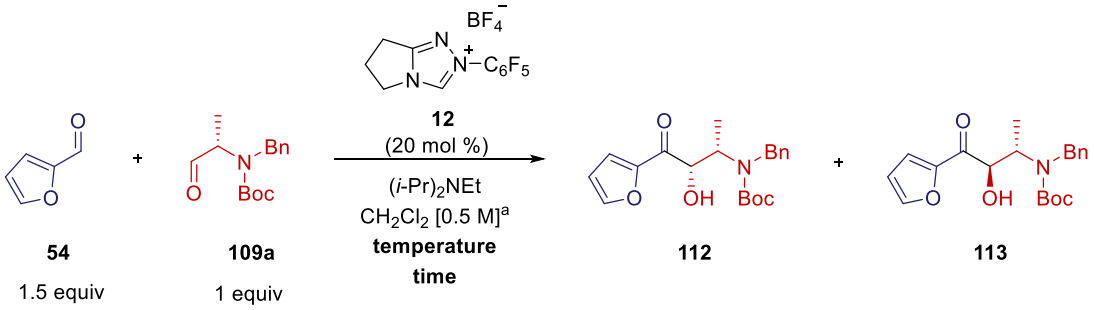
entry	base	x equiv	yield (%)[b]	Diastereomeric ratio (112 : 113)
1	(*i*-Pr)$_2$NEt	1	79	(4 : 1)
2	DBU	0.2	77	(4 : 1)
3	CsOAc	1	47	(2 : 1)
4	Cs_2CO_3	1	11	(1 : 1)

[a] Concentration was determined with respect to the α-amino aldehyde.
[b] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.

4.2.1.3. Variation of Temperature and Reaction Time

Initial optimization reactions were successful in affording good yields of the cross-benzoin products. However, the diastereomeric ratio remained moderate in all cases. In order to address this issue, a series of experiments were carried out by varying the reaction temperature and time (**Table 4.4**). Lowering the temperature (from 70 °C to 40 °C) led to a slight improvement in the diastereomeric ratio (**entries 1-2**) as did the reduction of reaction time (**entry 4**). It is noteworthy that further decrease in temperature led to a lower yield and moderate diastereomeric ratio (**entry 3**).

Table 4.4 Effects of temperature and reaction time variations on the diastereomeric ratio



entry	temperature	time (h)	yield (%)[a]	diastereomeric ratio (112 : 113)
1	70	4	93	(4 : 1)
2	40	4	91	(5 : 1)
3[c]	23	4	49	(4 : 1)
4	40	1	81	(6 : 1)

[a] Concentration was determined with respect to the *α*-amino aldehyde.
[b] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.
[c] Reaction carried out at [0.8 M].

4.2.2. Scope of the Reaction

The substrate scope was explored using a variety of *N*-Boc-*N*-Bn-*α*-amino aldehydes, in combination with heteroaromatic and aliphatic aldehydes using the conditions established in the optimization study. Interestingly, good diastereoselectivities are obtained by using non-sterically hindered amino aldehydes (**112, 115-117**). Again, there is a trend toward greater diastereoselectivity with increasing substituent size. Use of cyclic substrates such as *N*-Boc-L-prolinal results in lower diastereomeric ratio (**119**). The reaction exhibits good functional group tolerance as demonstrated by application of a L-glutamic acid-derived amino aldehyde (**120**) and *N*-Boc-*N*-Bn-*O*-BOM-L-serinal (**121**). With the exception of **116**, all products in Table 4.5 are obtained from enantiomerically-enriched amino aldehydes. Thus, it was important to examine the possibility of undesired erosion of enantiomeric ratio of *N*-Boc-*N*-Bn-*α*-amino aldehydes under

the reaction conditions. Gratifyingly, comparison of HPLC chromatograms of **118** to those of a racemic sample showed no erosion of enantiomeric ratio during the reaction (see **Section 7.3**). The use of benzofuran-2-carboxaldehyde affords moderate yields and diastereomeric ratio under these reaction conditions (**124**).

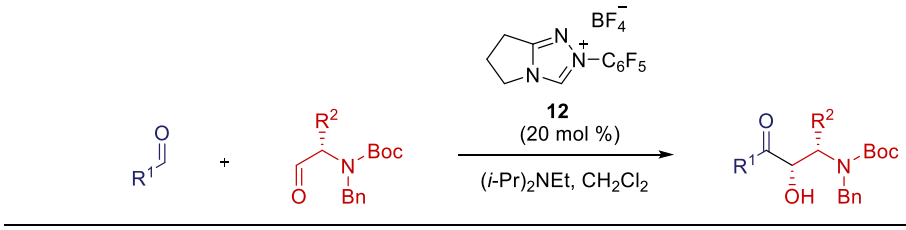
A brief re-optimization revealed that successful application of highly reactive hetereoaromatic aldehydes[120] necessitates the use of lower temperatures and shorter reaction times (**122-124**, see **Section 4.2.3** for optimization of reaction conditions). Pyrazine-2-carboxaldehyde is an extreme example for which even lower temperatures and reaction times are required to obtain significant amounts of the cross-benzoin products (**123**, see **Section 4.2.3.2** for optimization of reaction conditions). The modified conditions also improve the diastereomeric ratio for these substrates.[viii] These observations could be rationalized by considering the faster rates in both the forward and reverse direction using these reactive aldehydes. Lowering the temperature thus minimizes the thermodynamic equilibration between the two energetically similar diastereomers and leads to higher diastereomeric ratios.[11] Although the yields obtained using 1.5 equivalent of heteroaromatic aldehyde are generally good, it was found that they could be increased by using a larger excess (**116**, **121-123**). Analogous to earlier observations (see **Section 3.2.2**), aromatic aldehydes perform poorly under the reaction conditions (**125**). The use of thiophene-2-carboxaldehyde is not tolerated as only a minimal amount of the homo-benzoin adduct was detected after the reaction (**126**). The use of 3-pyridinecarboxaldehyde, 4-pyrimidinecarboxaldehyde, and 4-methylthiazole-2-carbaldehyde deliver poor yields and diastereomeric ratios (**127-129**). Analysis of crude reaction

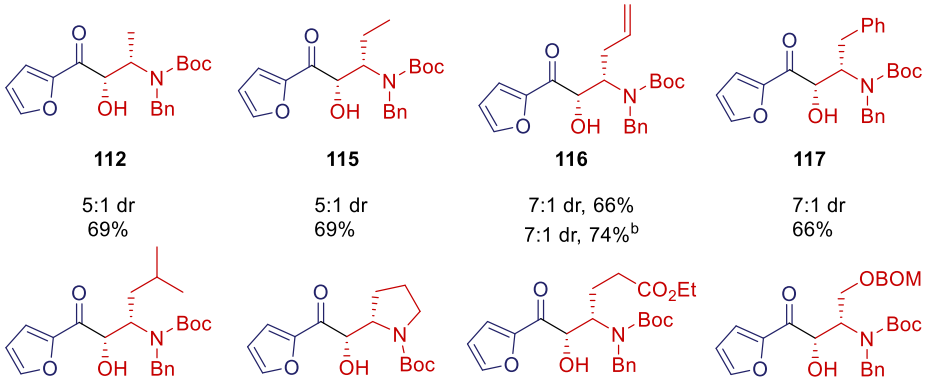
[viii] The NHC-catalyzed cross-benzoin reaction to form **118** under the modified conditions (CH_2Cl_2 (0.15 M), 0 °C, 30 min) was very low yielding.

mixtures containing such aldehydes indicates the presence of significant amounts of the starting *N*-Boc-*N*-Bn-α-amino aldehyde.

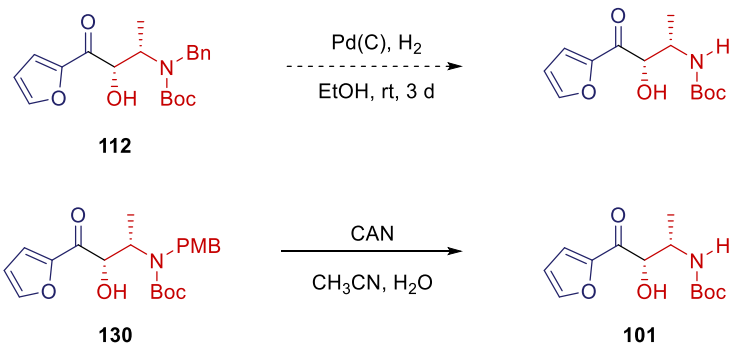
In order to further confirm the relative configuration of the products obtained from the earlier method (**Chapter 3**), **112** was subjected to various catalytic hydrogenation conditions (**Scheme 4.3**). However, efforts towards the removal of the *N*-benzyl protecting group proved futile. In order to circumvent this problem, *N*-Boc-*N*-PMB-L-alaninal was prepared and subjected to reaction conditions with 2-furaldehyde. The major product (**130**) was isolated and the PMB group was cleaved using ceric ammonium nitrate (CAN). The ^{1}H NMR spectrum of the corresponding carbamate (**101**) was found to be identical to that of the minor diastereomer obtained from the former study. This provides further evidence for the assignment of relative and absolute configuration of the cross-benzoin products obtained from the two methods.

Table 4.5 Substrate scope of the chemo- and diastereoselective NHC-catalyzed cross-benzoin reaction using *N*-Boc-*N*-Bn-amino aldehydes[a]





[a] Reaction conditions: 1 equiv of *N*-Boc-*N*-Bn-amino aldehyde, 1.5 equiv of hetereoaromatic aldehyde, 1 equiv of Hünig's base, CH_2Cl_2 (0.5 M with respect to the α-amino aldehyde), 40 °C, 1 h. Reported yield is that of the isolated major diastereomer. [b] 3 equiv of hetereoaromatic aldehyde, 30 minutes. [c] Modifications to reaction conditions: CH_2Cl_2 (0.15 M with respect to the α-amino aldehyde), 0 °C, 30 min. [d] Modifications to reaction conditions: CH_2Cl_2 (0.15 M with respect to the α-amino aldehyde), −15 °C, 15 min. [e] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.

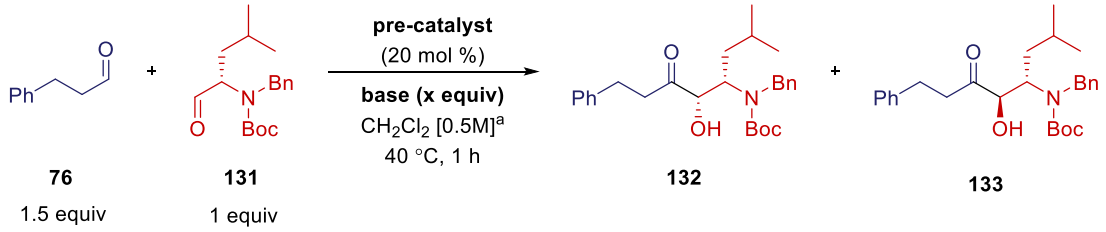


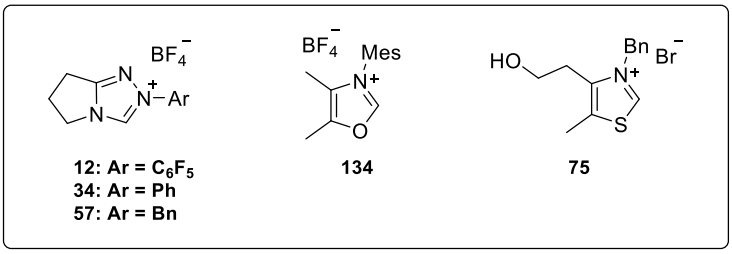
Scheme 4.3 Deprotection of the amine functional group

4.2.2.1. Use of Aliphatic Aldehydes under Optimized Reaction Conditions

The use of aliphatic aldehydes affords poor yields of the corresponding α-hydroxy-β-amino ketones under previously optimized reaction conditions. To address this issue re-optimization of reaction conditions was attempted using hydrocinnamaldehyde and **76** (**Table 4.6**). Initially, a number of NHC pre-catalysts were examined along with a base known for efficient deprotonation of the NHC precursor under the reaction conditions. The use of **12** proved more effective than the other examined pre-catalysts (**entry 1**). Interestingly, the use of oxazolium-derived pre-catalyst (**134**) also delivers the corresponding cross-benzoin product albeit in poor yield (**entry 2**). Additionally, the use of other triazolium- and thiazolium-derived pre-catalysts led to a loss of reactivity (**entries 3-5**).

Table 4.6 Catalyst and base optimization of aliphatic aldehydes in NHC-catalyzed cross-benzoin reactions involving hydrocinnamaldehyde



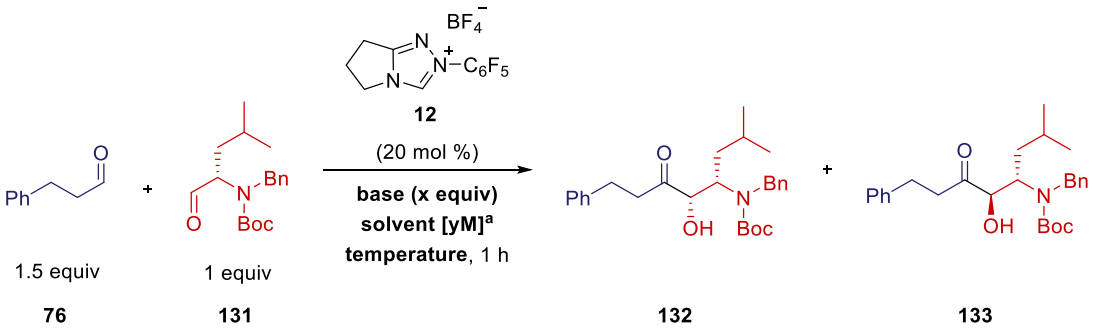


entry	pre-catalyst	base	x equiv	yield (%)[a]	diastereomeric ratio (132 : 133)
1	**12**	(*i*-Pr)$_2$NEt	1	29	10:1
2	**134**	DBU	0.2	8	N.D.
3	**34**	DBU	0.2	<5	N.D.
4	**57**	(*i*-Pr)$_2$NEt	1	<5	N.D.
5	**75**	(*i*-Pr)$_2$NEt	1	<5	N.D.

[a] Concentration with respect to the α-amino aldehyde.
[b] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.

With a suitable NHC pre-catalyst at hand, the optimization was continued by varying the base, solvent, temperature, and reaction concentration (**Table 4.7**). Application of different bases under the reaction conditions showed that DBU and Hünig's base are well-suited for the reaction (**entries 1-4**). A survey of various solvents also showed no significant improvement in the yield, with the use of THF and EtOH leading to lower diastereomeric ratios (**entries 5-8**). Similarly, the yields were not significantly improved by variations in reaction concentration and temperature (**entries 9-11**).

Table 4.7 Optimization of reaction conditions using an aliphatic aldehyde

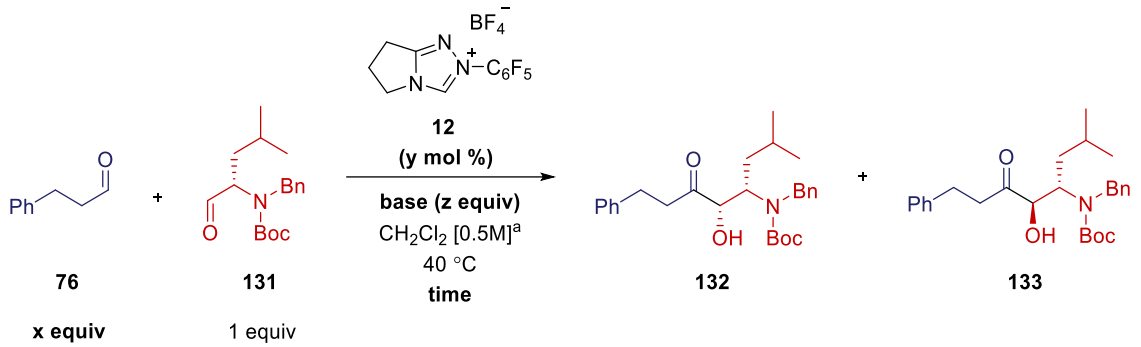


entry	base	x equiv	solvent	[yM][a]	temperature (°C)	yield (%)[b]	diastereomeric ratio (132 : 133)
1	(*i*-Pr)$_2$NEt	1	CH_2Cl_2	[0.5M]	40	32	10 : 1
2	DBU	0.2	CH_2Cl_2	[0.5M]	40	27	10 : 1
3	Cs_2CO_3	1	CH_2Cl_2	[0.5M]	40	6	N.D.
4	NaOAc	1	CH_2Cl_2	[0.5M]	40	<5	N.D.
5	(*i*-Pr)$_2$NEt	1	toluene	[0.5M]	40	33	10 : 1
6	(*i*-Pr)$_2$NEt	1	THF	[0.5M]	40	18	8 : 1
7	(*i*-Pr)$_2$NEt	1	EtOH	[0.5M]	40	14	2 : 1
8	(*i*-Pr)$_2$NEt	1	DMF	[0.5M]	40	<5	N.D.
9	(*i*-Pr)$_2$NEt	1	CH_2Cl_2	[0.07M]	40	20	4 : 1
10	(*i*-Pr)$_2$NEt	1	CH_2Cl_2	[0.7M]	40	36	8 : 1
11	(*i*-Pr)$_2$NEt	1	CH_2Cl_2	[0.5M]	70	35	10 : 1

[a] Concentration with respect to the *α*-amino aldehyde.
[b] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.

The optimization of reactions using *N*-Boc-*α*-amino aldehydes revealed that yields could be increased by changing the stoichiometry of reactants and base (see **Section 3.2.1.4**). Considering the similarities between the two methods, a number of experiments were carried out to examine such effects in this study (**Table 4.8**). Increasing the reaction time to 2 hours led to a slight increase in the yield (**entries 1-2**). Similarly, increasing the catalytic loading leads to an increase in yield, culminating with 30% mol loading (**entries 3-4)**. It is postulated that at higher catalytic loadings (>30 mol %), side reactions such as those described in Section 3.2.5 are responsible for lower yields of the cross-benzoin products. Additionally, increasing the equivalents of hydrocinnamaldehyde or Hünig's base has no effect on the reaction outcome (**entries 5-6**).

Table 4.8 Optimization of reaction conditions using an aliphatic aldehyde: variation in stoichiometry



entry	x equiv	y mol %	z equiv	time (h)	yield (%)[b]	diastereomeric ratio (132 : 133)
1	1.5	20	1	1	32	10 : 1
2	1.5	20	1	2	36	10 : 1
3	1.5	30	1	1	39	10 : 1
4	1.5	40	1	1	32	10 : 1
5	3	20	1	1	35	10 : 1
6	1.5	30	2	1	31	10 : 1

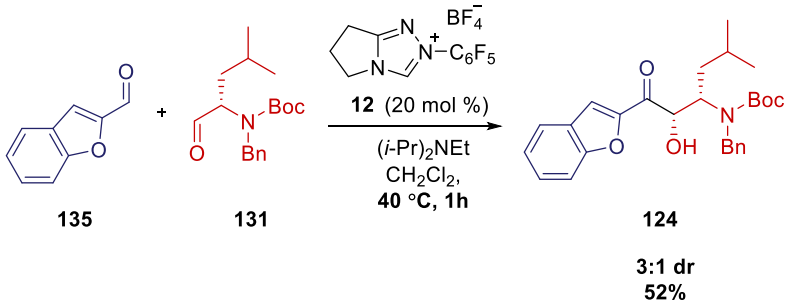
[a] Concentration with respect to the α-amino aldehyde.
[b] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.

These reactions showed that only moderate yield (≤39%) of the desired cross-benzoin products could be achieved with aliphatic aldehydes and hence, these substrates are not well-suited for this reaction.

4.2.3. ^{1}H NMR Monitoring Experiments of the Cross-Benzoin Reactions

4.2.3.1. Optimization of Reaction Conditions Involving Benzofuran-2-Carboxaldehyde

Optimization reactions using **135** and **131** yielded the cross-benzoin products in a 3:1 diastereomeric ratio (favouring the 2*S*, 3*S* diastereomer) in 1 hour at 40 °C (**Scheme 4.4**).



Scheme 4.4 Unoptimized reaction between benzofuran-2-carboxaldehyde and *N*-Boc-*N*-Bn-L-leucinal

It is possible that the poor diastereomeric ratio is due to a thermodynamic equilibration under the reaction conditions. This could occur either through a retro-benzoin reaction pathway, reversing the C–C bond formation (see **Section 3.2.6**), or by base-assisted post-reaction epimerization. In either case, it may be possible to improve the diastereomeric ratio by quenching the reaction before a substantial reduction in the diastereomeric ratio occurs.

To gain a better understanding of the dynamic profile of the reaction, a ^{1}H NMR monitoring experiment was carried out using a 1.5:1 ratio of benzofuran-2-carboxaldehyde and amino aldehyde **135** (**Figure 4.4**).

Similarly to the previous observations (**Section 3.2.6**), the formation of homo-benzoin product **137** is faster than that of the desired cross-benzoin products (**124** and **136**). When the combined yields[ix] of the two diastereomers were plotted against their ratio, an interesting observation was made: the reaction provides a good yield (70% yield) and excellent diastereomeric ratio (ca. 11:1) at ca. 7 min (**Figure 4.5**).

[ix] Yield was determined based on ^{1}H NMR analysis of crude reaction mixtures by using dimethyl terephthalate as the internal standard

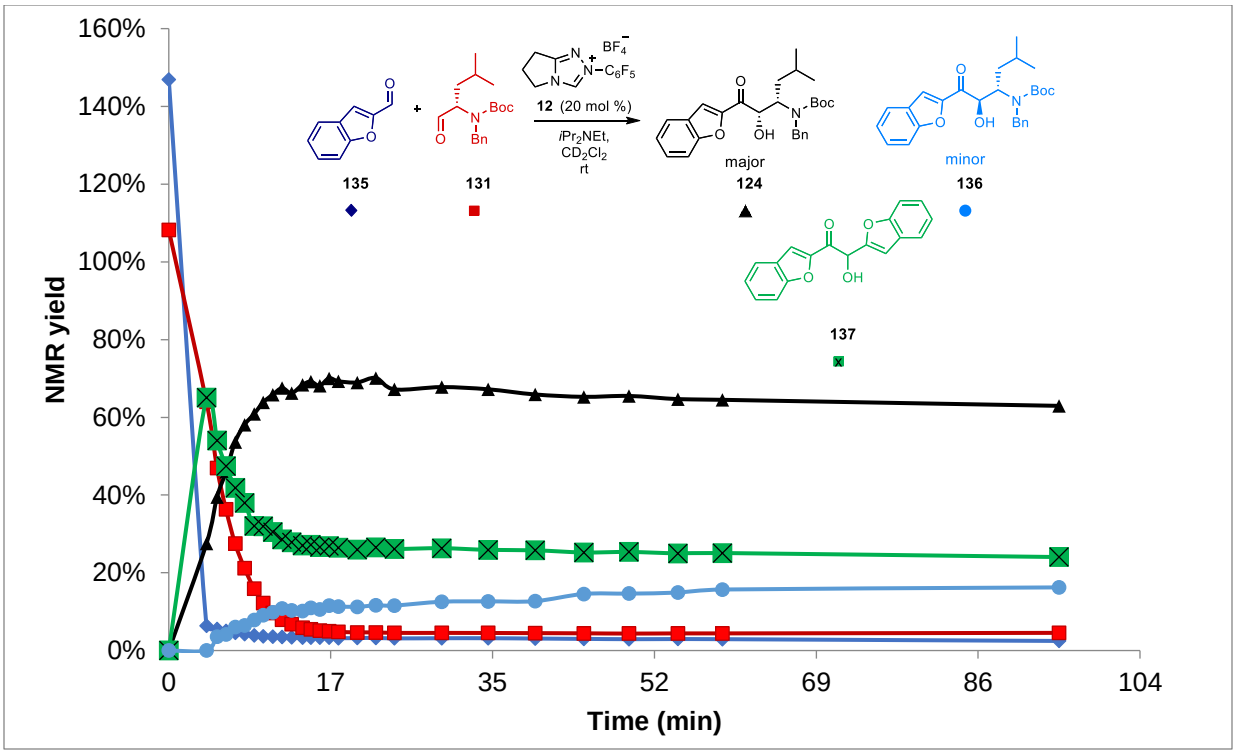


Figure 4.4 ^{1}H NMR monitoring experiment for the reaction between benzofuran-2-carboxaldehyde and *N*-Boc-*N*-Bn-L-leucinal

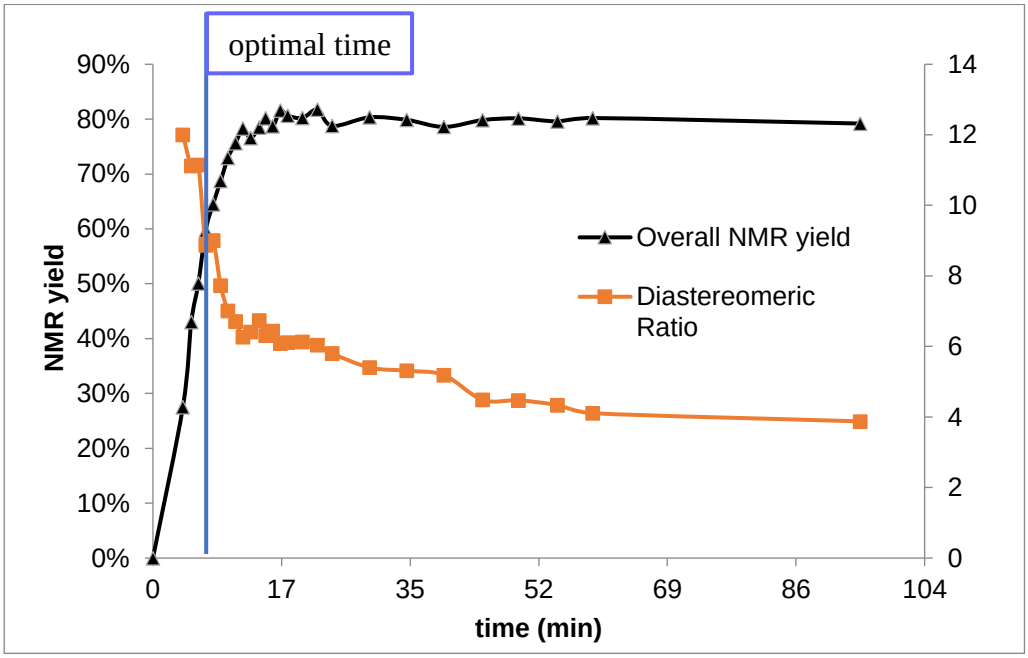
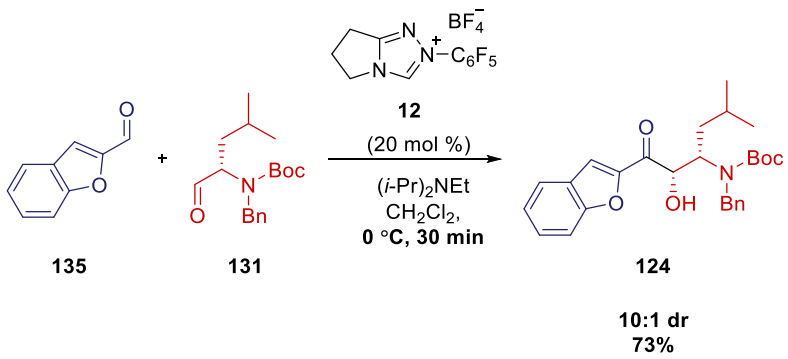


Figure 4.5 Yield and diastereomeric ratio profile over time in the formation of cross-benzoin product

It is postulated that following the rapid and reversible formation of **137**, selective formation of the major diastereomer (**124**) occurs. However, over time a thermodynamic equilibration between the two diastereomers results in a decrease of the diastereomeric ratio. It was thus desirable to terminate the reaction at an earlier time in which good yields and diastereomeric ratios are obtained. To obtain reproducible results, the temperature was adjusted to 0 °C and the reaction time was increased to 30 minutes. Under these modified conditions, the cross-benzoin products were obtained in a 10:1 diastereomeric ratio and the major diastereomer (**124**) was isolated in 73% yield (**Scheme 4.5**).

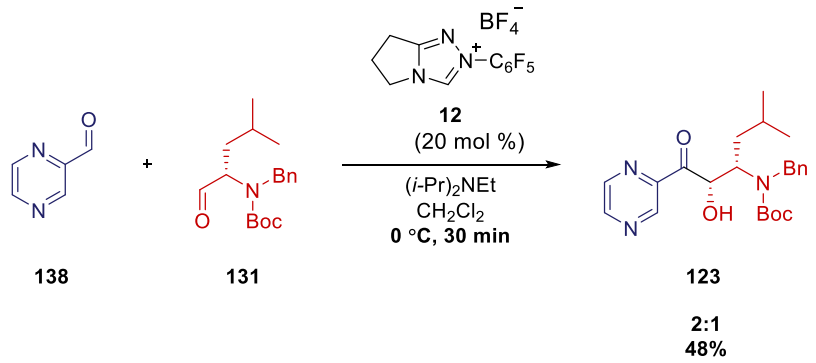


Scheme 4.5 Re-optimized reaction between benzofuran-2-carboxaldehyde and *N*-Boc-*N*-Bn-L-leucinal

Reactions involving 2-pyridinecarboxaldehyde, when carried out under similar conditions, also afford improved results (**122** in **Table 4.5**).

4.2.3.2. Optimization of Reaction Conditions involving Pyrazine-2-Carboxaldehyde

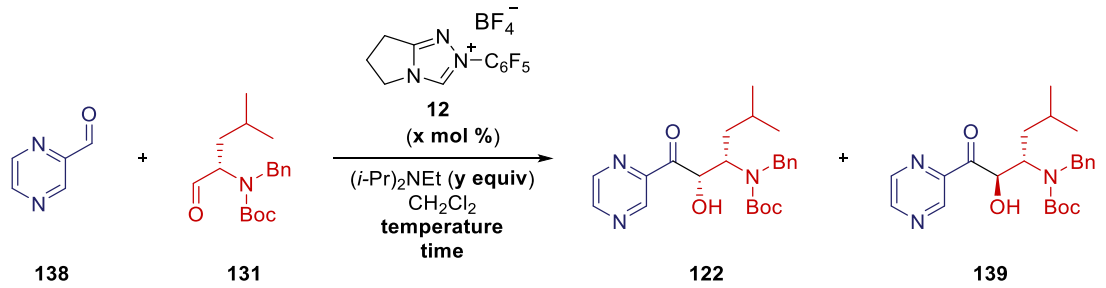
The use of pyrazine-2-carboxaldehyde (**138**) leads to a low diastereomeric ratio under previously modified conditions (**Scheme 4.6**).



Scheme 4.6 Unoptimized Reaction between pyrazine-2-carboxaldehyde and *N*-Boc-*N*-Bn-L-leucinal

Based on the previous observations on benzofuran-2-carboxaldehyde, it was sought to stop the reaction before a thermodynamic equilibrium was established. Initially this possibility was examined by lowering the amount of the free carbene in the reaction solution. To address the low yield and diastereomeric ratio a variety of reaction conditions were examined (**Table 4.9**). A more desirable outcome could be achieved by decreasing the amount of the pre-catalyst or Hünig's base (**entries 1-3**). Although a good yield was achieved using such modifications, the results were not reproducible. NHC-catalyzed cross-benzoin transformations at sub-zero temperatures are rare, possibly due to a low concentration of active carbene. The effect of such temperature variations was examined (**entries 4-6**). Interestingly, the product was formed at low temperatures, with the moderate diastereoselectivity attesting to a very rapid NHC-catalyzed reaction. However, the rate plummets at -40 °C (**entry 6**). Conditions capable of reproducibly delivering a good yield and diastereoselectivity were met by adjusting the temperature to -15 °C and reducing the reaction time to 15 minutes (**entry 7**).

Table 4.9 Optimization reactions using 2-pyrazine-carboxaldehyde and *N*-Boc-*N*-Bn-L-leucinal



entry	x mol %	y equiv	temperature (°C)	time (min)	yield (%)[a]	diastereomeric ratio (122 : 139)
1	20	1	0	30	48 (32)[b]	2 : 1
2	5	1	0	30	58	7 : 1
3	5	0.2	0	30	64	5 : 1
4	20	1	-20	30	65	5 : 1
5	20	1	-40	2 h	16	22 : 1
6	20	1	-40	4 h	17	19 : 1
7	20	1	-15	15	56 (50)[b]	8 : 1

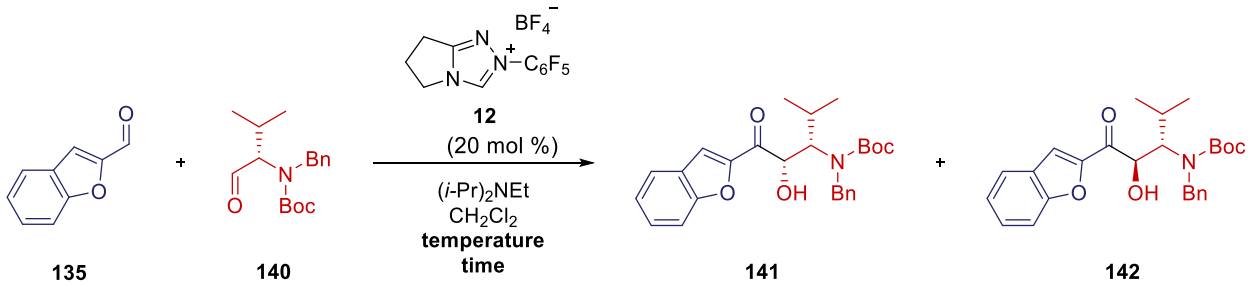
[a] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.
[b] Isolated yield of the major diastereomer.

4.2.4. NHC-Catalyzed Cross-Benzoin Reactions involving *N*-Boc-*N*-Bn-L-Valinal

Preliminary results obtained from the reaction of **140** and 2-furaldehyde under previously established reaction conditions only led to recovery of starting materials (not shown). When **140** was subjected to reaction conditions containing benzofuran-2-carboxaldehyde, cross-benzoin products were obtained in poor yield (**Table 4.10, entry 1**). Although under relatively forcing conditions, the yield[x] increased to 54% (**entry 2**), the low diastereomeric ratio renders such substrates unsuitable for a diastereoselective reaction.

[x] Yield was determined based on ^{1}H NMR analysis of crude reaction mixtures by using dimethyl terephthalate as the internal standard

Table 4.10 Optimization of reaction conditions using benzofuran-2-carboxaldehyde and *N*-Boc-*N*-Bn-L-valinal



entry	temperature (°C)	time (min)	yield (%)[a]	diastereomeric ratio (141 : 142)
1	0	30	5	N.D.
2	40	60	54	1 : 1

[a] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.

4.3. Conclusion

In summary, a complementary method was developed which can be employed to further expand the scope of NHC-catalyzed cross-benzoin reactions using α-amino aldehydes. This was accomplished through modification of the protecting groups which allows access to enantio-enriched α-hydroxy-β-amino ketones *via* a Felkin-Anh transition state model. Optimization of reaction conditions revealed that the reaction could be successfully carried out using a variety of non-sterically hindered α-amino aldehydes. However, the use of heteroaromatic aldehydes other than 2-furaldehyde requires slight modification to the reaction conditions. Noting the rapid rates of reactions associated with such substrates, ^{1}H NMR monitoring experiments were carried out to obtain synthetically useful yields and diastereomeric ratios. Substrates for this variant of the methodology remain limited to heteroaromatic aldehydes. Some heteroaromatic aldehydes such as 4-pyrimidine-2-carboxaldehyde are not suited for this transformation due to a rapid equilibration between the two diastereomers. This is believed to stem from the reversible cross-benzoin reaction pathways and not base-assisted epimerization. Despite these drawbacks, this method is believed

to be of particular synthetic value given the continued interest of heteroaromatic building blocks in medicinal chemistry as well as the synthetic potential of the furan moiety.

Chapter 5: Application of Chemo- and Diastereoselective NHC-Catalyzed Cross-Benzoin Reactions in Total Synthesis

5.1. Concise Total Synthesis of D-*arabino*-phytosphingosine

5.1.1. Background and Biological Activity

D-*arabino*-Phytosphingosine (**144**) is a sphingoid base, a wide spread family of natural products found in plants,[121] yeasts,[122] fungi,[123] and mammalian tissues[123] (**Figure 5.1**).[124] Sphingoids are long chain amino diols and -triols, and are key constituents of sphingolipids which are involved in the regulation of several biological processes.[125–127] The breakdown products of sphingolipids such as ceramide, sphingosine, and sphingosine-l-phosphate are involved in cell regulation and their role in signal transduction has been identified.[128] Among the members of this family, D-*ribo*-phytosphingosine (**143**) has demonstrated strong cytotoxity against murine B16 melanoma cells[129] and D-*arabino*-phytosphingosine exhibits growth inhibition of yeast cell lines.[130] The biological importance of phytosphingosines and their difficult isolation has spurred wide interest in their chemical synthesis.[68–70,72,72,73,124,130,131]

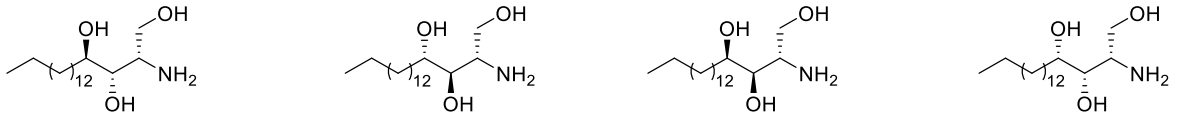


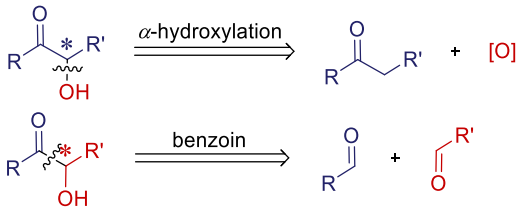
Figure 5.1 Chemical structures of phytosphingosines

Phytosphingosines (**143-146**) are 18-carbon skeleton amino triols featuring three contiguous stereogenic centers (C_2–C_4). Among this class of compounds, the synthesis of D-*arabino*-phytosphingosine has attracted considerable attention.

5.1.2. Research Objectives

Enantio-enriched α-hydroxy ketones are convenient building blocks for a variety of synthetic transformations as well as important structural features present in a wide array of natural products.

Typical synthetic approaches toward this motif rely on pre-formation of a ketone's C-C bond followed by α-hydroxylation (**Scheme 5.1**).[132–136] However, achieving desirable enantio- and/or diastereoselectivity in such reactions has remained a challenge.[137–140] In addition, controlling the regioselectivity of hydroxylation in the case of aliphatic ketones is particularly problematic. In contrast to the α-hydroxylation of ketones, disconnection at the central carbon-carbon bond represents a more efficient approach to α-hydroxy ketones as it introduces the stereogenic center while assembling the carbon chain. *N*-Heterocyclic carbene (NHC)-catalyzed cross benzoin reactions are potentially useful for such purposes.



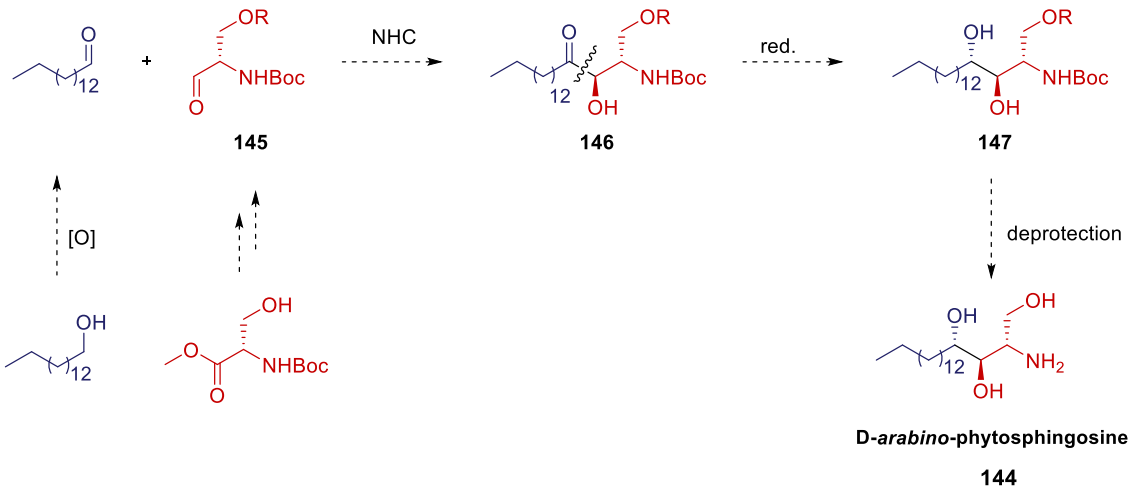
Scheme 5.1 Retrosynthetic approaches for accessing α-hydroxy ketones

Chemo- and diastereoselective NHC-catalyzed cross-benzoin reactions using *N*-Boc-α-amino aldehydes can successfully deliver a variety of enantio-enriched α-hydroxy-β-amino ketones (**Chapter 3**). To determine its synthetic utility, the application of this method as a key step in the total synthesis of a configurationally-known natural product was sought. As a secondary goal, the completion of this synthesis serves as a tool for establishing the absolute and relative configuration of other products obtained from similar substrates.

5.1.3. Results and Discussion

5.1.3.1. Synthetic Strategy

A chemo- and diastereoselective cross-benzoin reaction between pentadecanal and **145** using NHC catalysis could be employed as the key step (**Scheme 5.2**). This strategy assembles the carbon skeleton while concurrently establishing the desired configuration. This may be accomplished by the judicious selection of the corresponding *N*-Boc-α-amino aldehyde (**145**), postulated to deliver the product through the hydrogen bond transition state (see **Section 3.2.4**). It is noteworthy that the starting aldehydes could be obtained using simple functional group manipulations starting from amino acid-derived, and/or readily available commercial sources. To install the desired stereocentre at C4, a diastereoselective reduction of the enantio-enriched α-hydroxy-β-amino ketone (**146**) is sought. Finally, D-*arabino*-phytoshingosine (**144**) could be obtained from the deprotection of 1,2-amino triol **147**.

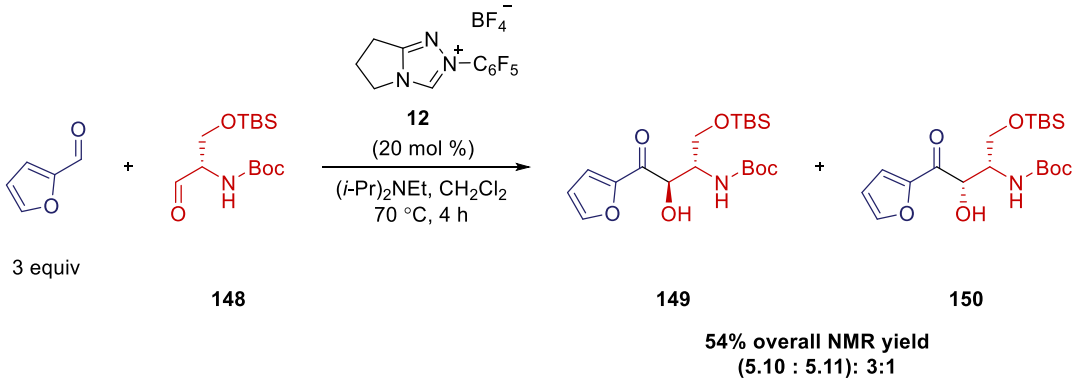


Scheme 5.2 Proposed **s**ynthetic strategy for the synthesis of D-*arabino*-phytosphingosine

5.1.3.2. Synthesis

5.1.3.2.1. Selection of Alcohol Protecting Group

Initially, *N*-Boc-*O*-TBS-L-serinal (**148**) was used under previously optimized NHC-catalyzed cross-benzoin reaction conditions (**Scheme 5.3**). Moderate yield and diastereoselectivity is obtained using these conditions. While the latter may be attributed to the poor facial selectivity induced by the small *β*-substituent, it is possible that the moderate yield is due to the inductive effect of the oxygen atom. In such a scenario, the presence of a *β*-heteroatom enhances the electrophilicity of the amino aldehyde, increasing the substrate's propensity to undergo side reactions. It was interesting to observe that the bulky TBS group has limited impact on the diastereoselectivity and the observed ratio is similar to that obtained from the use of *N*-Boc-L-phenylalaninal (**Section 3.2.2**, **117** in **Table 3.6**).



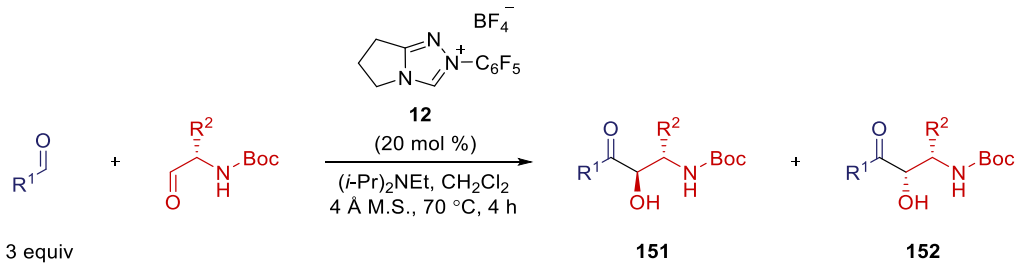
Scheme 5.3 NHC-catalyzed cross-benzoin reaction between *N*-Boc-*O*-TBS-L-serinal and 2-furaldehyde

It was previously observed that the use of aliphatic aldehydes results in higher diastereomeric ratios compared to 2-furaldehyde (**Section 3.2.2**, **Table 3.6**). Although the reasons behind such enhancement is unclear, application of pentadecanal could have a similar enhancing effect. However, it was still unclear whether the nature of the protecting group of the oxygen atom could influence the diastereoselectivity. Given the unsatisfying results obtained using *N*-Boc-*O*-TBS-L-serinal (**148**), efforts shifted to using the *O*-benzylated variant (**Table 5.1**). The commercial availability of *O*-benzyl-protected-L-serine derivatives was the basis for this selection. Pentadecanal was obtained through the IBX-mediated oxidation of the corresponding alcohol (see **Section 7.4**). Disappointingly, *O*-benzyl-protected-L-serinal and pentadecanal perform poorly under the NHC-catalyzed cross-benzoin reaction conditions (**entry 1**). A survey of substrates was carried out to identify the reaction partner responsible for the poor results (**entries 2-3**).

Earlier studies suggest that *N*-Boc-L-valinal is well-suited for NHC-catalyzed cross-benzoin reactions with hydrocinnamaldehyde (see **Section 3.2.1.4**). Similarly, when *N*-Boc-L-valinal was employed under the reaction conditions with pentadecanal, a good yield and diastereomeric ratio are obtained (**entry 2**). This suggests that pentadecanal behaves similarly to hydrocinnamaldehyde and therefore is not the reaction partner responsible for the poor reactivity. However, when *N*-Boc-

O-Bn-L-serinal was subjected to the reaction conditions with hydrocinamaldehyde, the diastereomeric ratio and yield decreased significantly (**entry 3**). This indicates that the low yield and diastereomeric ratio is due to *N*-Boc-*O*-Bn-L-serinal and not pentadecanal.

Table 5.1 Evaluation of reactivity of different substrates under the cross-benzoin reaction conditions

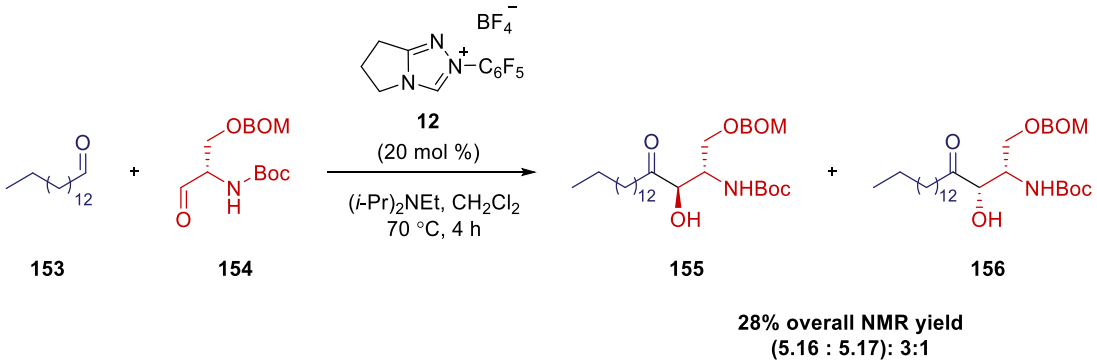


entry	R^1	R^2	yield (%)[a]	diastereomeric ratio (151 : 152)
1	$C_{14}H_{29}$	CH_2-OBn	26	4:1
2	$C_{14}H_{29}$	*i*-Pr	71	7:1
3	C_2H_4Ph	CH_2-OBn	34	3:1

[a] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.

Methoxymethyl (MOM) and benzyloxymethyl (BOM) protecting groups have been extensively used for the protection of alcohols in the presence of a carbamate group under mild basic conditions.[141] Their facile removal under mild acidic conditions is strategically important for the proposed route towards D-*arabino*-phytosphingosine; both the carbamate and acetal protecting groups could be cleaved in a single step, minimizing the step count. To further evaluate the effects of *O*-protecting groups on the yield and diastereomeric ratio, attention was focused on *N*-Boc-*O*-BOM-L-serinal (**154**). Compound **154** was synthesized from commercially available *N*-Boc-L-serine methyl ester (see **Section 7.4**). The use of **154** and pentadecanal (**153**) under the previous reaction conditions affords moderate yield of the desired product and diastereomeric ratios with no major side product detected (**Scheme 5.4**). This could be caused by degradation of the starting material prior to a productive cross-benzoin reaction. Despite the low yield, given the possibility

of concurrent removal of Boc and BOM protecting groups, this protecting group was chosen for the synthesis.

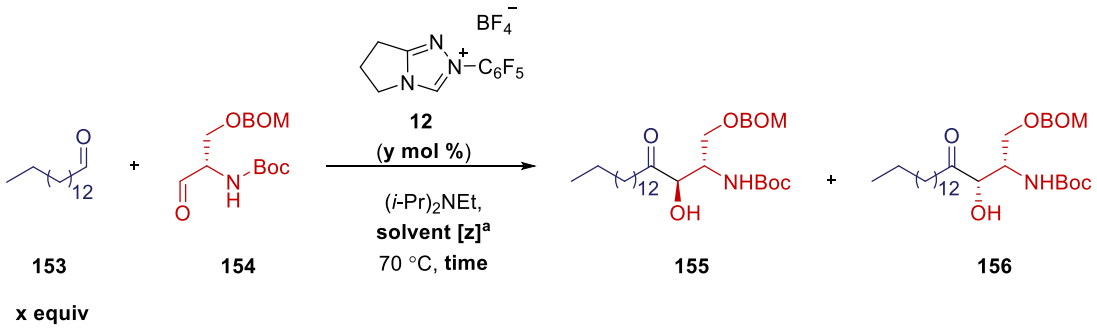


Scheme 5.4 NHC-catalyzed cross-benzoin reaction between *N*-Boc-*O*-BOM-L-serinal and 2-furaldehyde under unoptimized reaction conditions

5.1.3.2.2. Optimization of the Key Step

To establish optimized conditions several reactions were carried out using **154** and pentadecanal (**153**) (**Table 5.2**). Initially, the effects of solvent on the reaction outcome were examined (**entries 1-4**). Limited difference was observed using several solvents. However, the use of THF and toluene were marginally superior to that of other solvents. Decreasing the concentration of **154** to [0.03 M] led to a drop in the overall yield and a slight increase in the diastereomeric ratio (**entry 5**). Gratifyingly, increasing the catalytic loading and lowering the reaction time led to a noticeable improvement in the reaction outcome. Further increasing the catalytic loading did not improve the results (**entries 6-7**). Optimized conditions were met by increasing the amount of pentadecanal used under the reaction conditions (**entry 8**).

Table 5.2 Optimization of reaction conditions using pentadecanal and *N*-Boc-*O*-BOM-L-serinal



entry	x equiv	y mol%	solvent	[z][a]	time (h)	yield (%)[b]	diastereomeric ratio (155 : 156)
1	3	20	CH_2Cl_2	[0.07 M]	16	32	3:1
2	3	20	THF	[0.07 M]	16	37	4:1
3	3	20	benzene	[0.07 M]	16	36	5:1
4	3	20	toluene	[0.07 M]	16	38	4:1
5	3	20	toluene	[0.03 M]	16	35	6:1
6	3	30	toluene	[0.07 M]	4	55	5:1
7	5	40	toluene	[0.07 M]	4	54	4:1
8	5	30	toluene	[0.07 M]	4	60	4:1

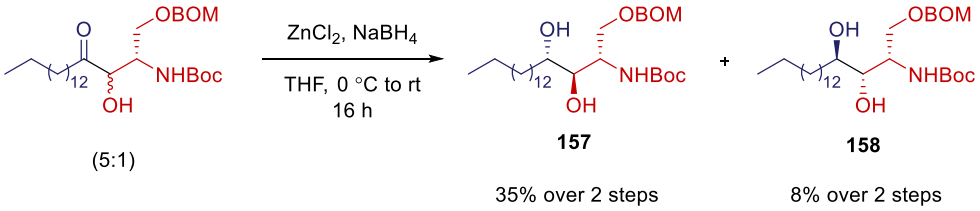
[a] Concentration with respect to the *α*-amino aldehyde.
[b] Combined yield of the two diastereomers determined by analysis of ^{1}H NMR spectra and by using dimethyl terephthalate as the internal standard.

Unfortunately, when the reaction was carried out on a larger scale, the yield of the desired *α*-hydroxy-*β*-amino ketone decreases (ca. 40% yield). Despite this drawback, a good diastereomeric ratio (5:1) was obtained. The inseparable mixture of diastereomers was carried to the subsequent step.

5.1.3.2.3. Diastereoselective Reduction of *α*-Hydroxy-*β*-Amino Ketones

The reduction of *α*-hydroxy ketones using $ZnCl_2$ and $NaBH_4$ is well-precedented in the literature.[112,113] Furthermore, owing to the remarkable coordination of this functional group to Zn species, this reaction affords excellent diastereoselectivity. The diastereomeric mixture obtained from the NHC-catalyzed cross-benzoin step was subjected to $ZnCl_2$/$NaBH_4$ (**Scheme 5.5**). As

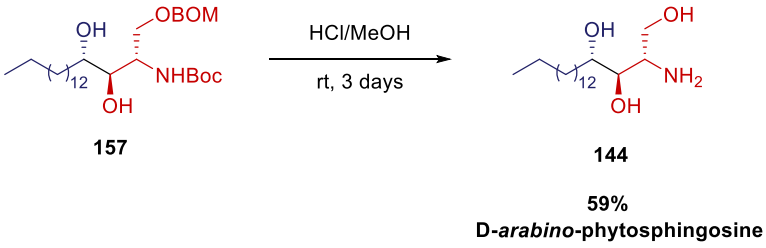
expected, high diastereoselectivity is obtained; only two diastereomers are observed and the major diastereomer (**157**) was isolated in moderate yield (35% over 2 steps). Additionally, this reaction allows for the separation of the diastereomers obtained from the previous step.



Scheme 5.5 Diastereoselective hydroxyl-directed reduction of *α*-hydroxy-*β*-amino ketones

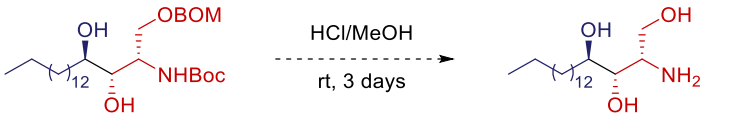
5.1.3.2.4. Global Deprotection for Accessing Phytosphingosines

The synthesis of D-*arabino*-phytosphingosine (**144**) was accomplished by simultaneous removal of Boc and BOM protecting groups using HCl/MeOH (**Scheme 5.6**).



Scheme 5.6 Acidic, simultaneous removal of protecting groups

It is noteworthy that the minor diastereomer (**158**) is a protected form of D-*ribo*-phytosphingosine (**143**), another important member of the phytosphingosine family. However, attempts to remove of its protecting groups under similar reaction conditions led to decomposition of the starting material (**Scheme 5.7**).



158 **143**

D-*ribo*-phytosphingosine

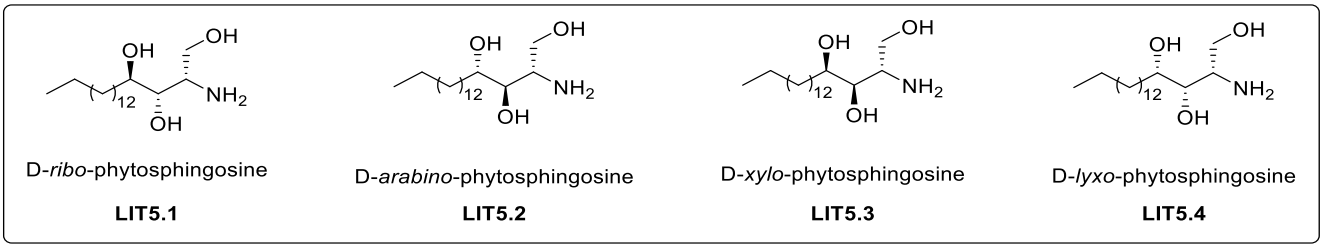
Scheme 5.7 Attempted deprotection of the minor diastereomer

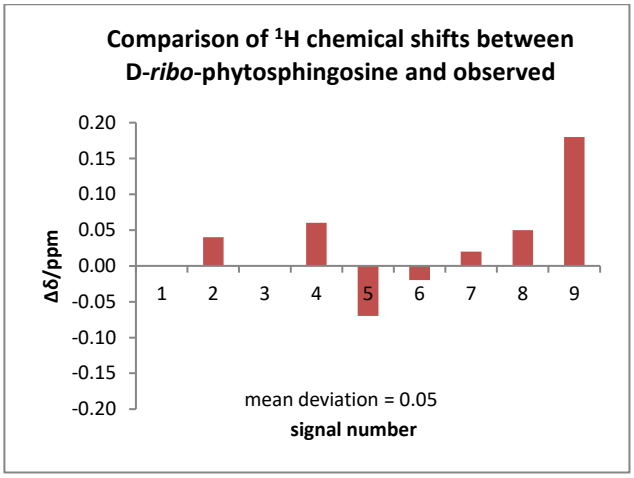
5.1.3.2.5. Identification of Isolated Product

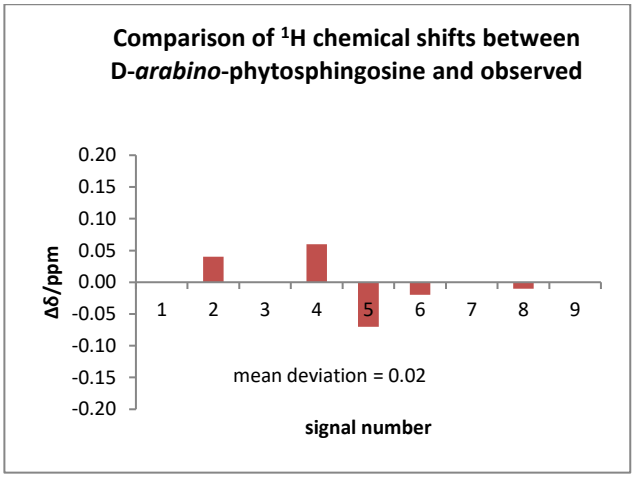
Difficulties were encountered when analysing NMR data; the chemical shifts corresponding to CH-OH peaks changed as a function of concentration, rendering the identification of the isolated product ambiguous. For a meaningful comparison, the experimental ^{1}H NMR and ^{13}C NMR data were compared to the reported data corresponding to all four diastereomers of the phytosphingosine family (see **Section 7.4**).[142] Graphs were constructed by plotting the difference in the chemical shifts for each signal in the ^{1}H NMR spectrum (**Figures 5.2** and **5.3**, for raw data see **Section 7.4**).[xi]

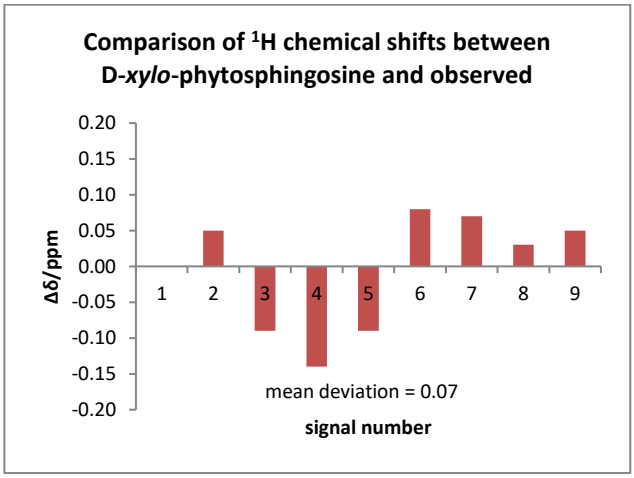
The obtained spectroscopic data most closely fit to that for D-*arabino*-phytosphingosine. The optical rotation and the melting point of the isolated product are also in close agreement with literature reports (melting range: 78–82 °C (lit: 82-83)[73]; $[\alpha]_D^{28\ °C}$ = -8 (*c* 0.4, pyridine), (lit: $[\alpha]_D^{23\ °C}$ = -3.79 (*c* 0.6, pyridine))[143]. This is particularly important as it confirms the previous assignment of relative and absolute configuration of *α*-hydroxy-*β*-amino ketones (**Section 3.2.4**).

[xi] The position number was assigned solely from the position on the NMR spectrum and is not related to IUPAC numbering









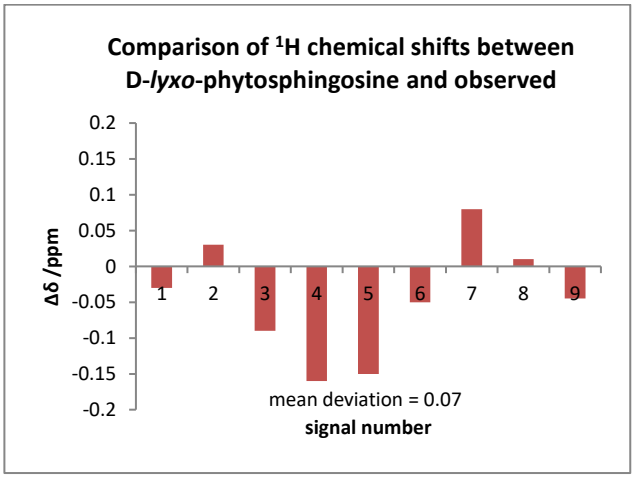


Figure 5.2 Comparison of ^{1}H NMR data for reported phytosphingosines and obtained product in CD_3OD

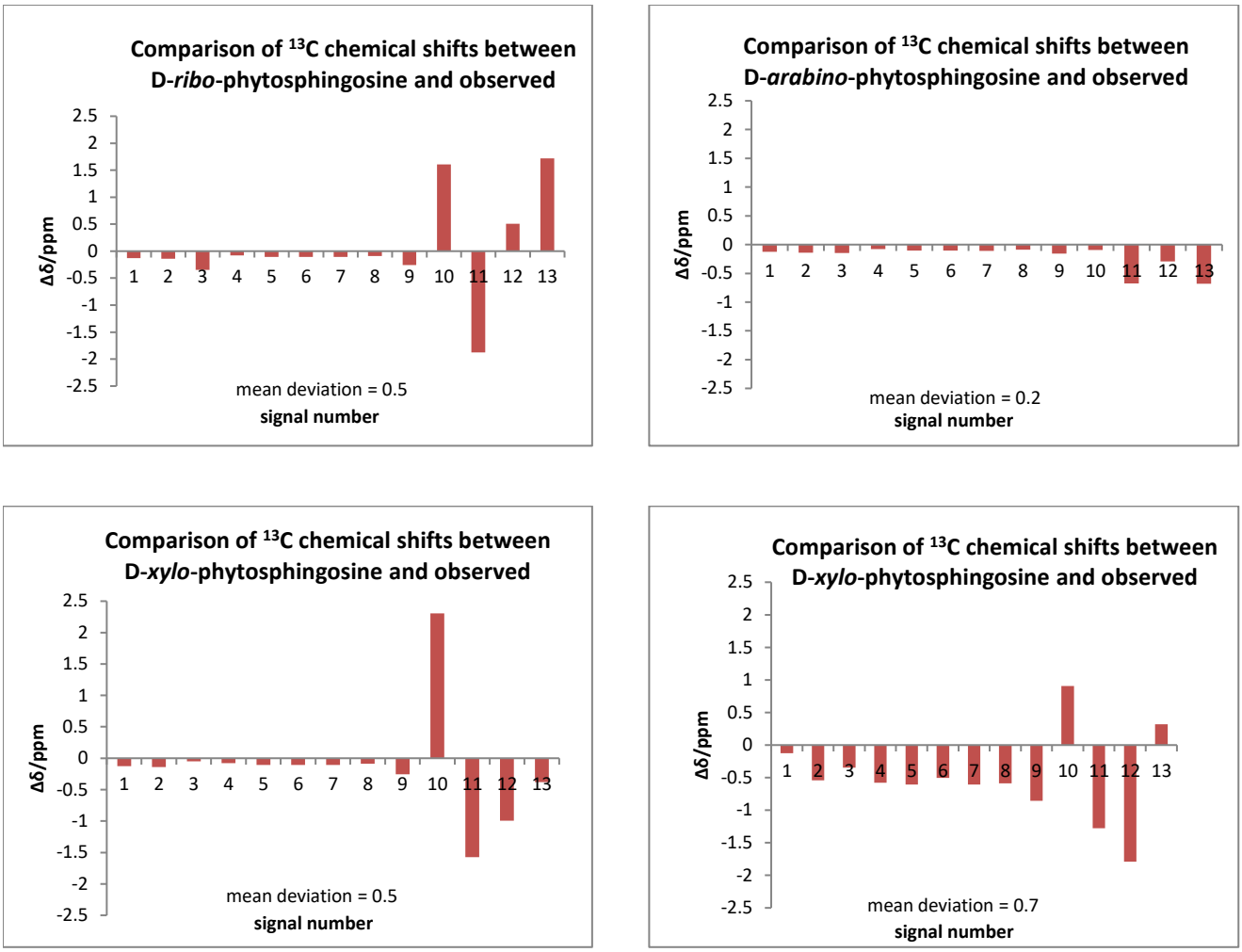


Figure 5.3 Comparison of ^{13}C NMR data for reported phytosphingosines and obtained product in CD_3OD

5.1.4. Conclusion

In summary, a concise route towards D-*arabino*-phytosphingosine was accomplished using a chemo- and diastereoselective NHC-catalyzed cross-benzoin reaction. This synthesis marks the shortest route towards this natural product to date (7 overall steps). NHC-catalyzed cross-benzoin reactions using L-serine-derived amino aldehydes afford good yields and diastereomeric ratios of the desired products. However, issues were encountered when the reaction was carried out on large

scale (>50 mg).[xii] The relatively lower yields using pentadecanal and *N*-Boc-*O*-BOM-L-serinal are hypothesized to derive from their greater electrophilicity; the inductive effect of the oxygen atom contribute to further enhancing its electrophilicity. Presumably, this leads to degradation of the starting material through pathways such as those described in Section 3.2.5, lowering the yield of the reaction. Nevertheless, brevity of this synthetic route attests to the usefulness of the developed method. The assignment of absolute configuration of previously assigned products was verified using the comprehensive comparison of spectroscopic data with reported data corresponding to this natural product.

[xii] The reasons behind such scale-up issue are unclear.

5.2. Total Synthesis of Hyacinthacine A_1

5.2.1. Isolation and Biological Activity

Enzymes involved in the processing of carbohydrates (*i.e.* glycosidases) have been linked to several human diseases such as AIDS, diabetes, cancer, and malaria.[144–146] Thus, there is a great deal of interest in exploring inhibitors aiming towards their treatment. A number of alkaloids, including ones derived from imino sugars,[147] have demonstrated utility in this regard. In particular, poly-hydroxylated pyrrolizines have emerged as useful candidates for inhibition of glycosidase enzymes.[148,149] Isolated from *Muscari armeniacum*,[74] hyacinthacine A_1 (**Figure 5.4**) is a relatively recently discovered natural product which exhibits strong and selective inhibition towards rat intestinal lactase (IC50 4.4 μM)[74] and amyloglucosidase from *Aspergillus niger* (IC50 2.3 μM).[75]

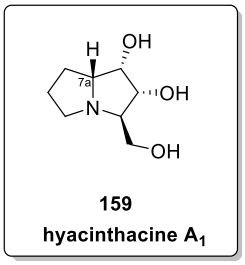
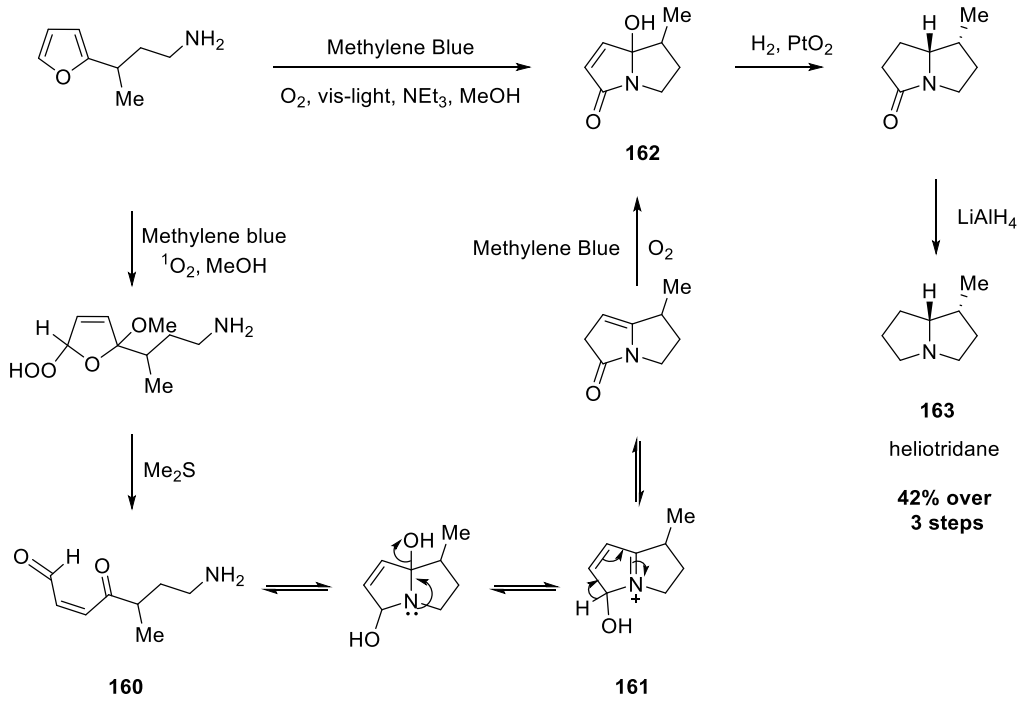


Figure 5.4 Structure of hyacinthacine A_1

The biological importance and interesting structural features of this natural product have spurred efforts towards its synthesis, the majority of which employ numerous steps and often expensive starting materials for their syntheses (see **Section 1.4**).[75,78–81,83–85] To address these drawbacks and demonstrate the synthetic utility of the developed NHC-catalyzed cross-benzoin transformations, the synthesis of hyacinthacine A_1 was investigated using the method described in **Chapter 4**.

5.2.2. Photooxygenation of Furans Using Singlet Oxygen

Furans obtained from the dehydration of sugars are abundant and useful building blocks for chemical synthesis. In this regard, a number of studies demonstrated the synthetic utility of compounds that bear such motifs.[150–154] Among other researchers, Vassilikogiannakis and co-workers have developed several methods for trapping reactive intermediates resulting from photooxygenation of furans.[153,155–159] It is well known that furans undergo a facile [4+2] cycloaddition reaction with *in situ*-prepared singlet oxygen obtained from the reaction of O_2 and photosensitizers in the presence of a powerful visible light source.[160] The immediate products of this reaction are intermediates that can undergo further cascade reactions affording complex bicyclic compounds. Recently it was reported that such intermediates can be intercepted with an amine functionality inter-[153] or intramolecularly.[159] The latter variant was successfully employed in the construction of a number of 5,5- and 6,5- fused pyrrolidinones in a concise sequence (**Scheme 5.8**). The mechanism of the photooxygenation reaction was suggested to involve diaminal **160** which undergoes selective dehydration affording iminium **161**. Proton transfer followed by proton-coupled electron transfer (PCET) facilitated by methylene blue and oxygen results in formation of **162**. Finally, sequential reduction of the hemiaminal and the lactam affords heliotridane (**163**) in good overall yield.



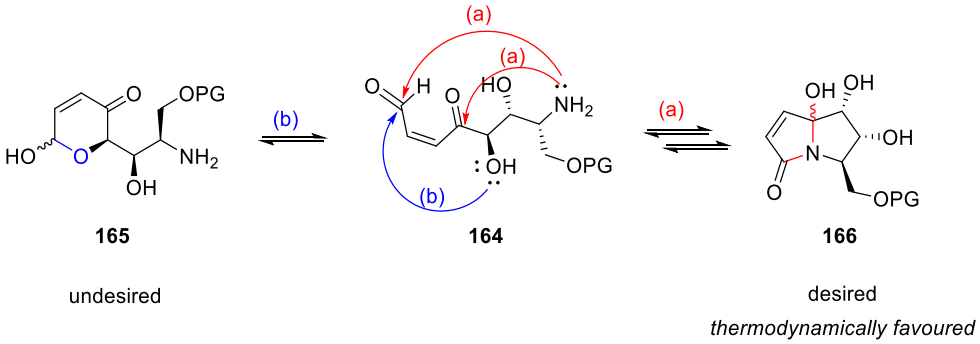
Scheme 5.8 Synthesis of heliotridane *via* photooxygenation of furylalkylamines

5.2.3. Research Objectives

NHC-catalyzed cross-benzoin reactions using *N*-Boc-*N*-Bn-*α*-amino aldehydes proved successful in delivering enantio-enriched amino ketones with excellent chemo- and diastereoselectivities (**Chapter 4**). The scope of the reaction demonstrated tolerance towards a variety of heteroaromatic aldehydes including 2-furaldehyde. With a viable methodology at hand, the synthesis of hyacinthacine A_1 was sought utilizing this method as the key step.

Although photooxygenation reactions of furans using singlet oxygen have been employed to deliver simple, non-functionalized scaffolds, to the best of the author's knowledge, none of the existing methods utilize highly functionalized surrogates. However, constructing the poly-hydroxylated bicyclic core of hyacinthacine A_1 using this strategy could introduce some complications: in addition to the amine, the pendant hydroxyl groups could intercept the diaminal moiety leading to the undesired formation of **165** (**Scheme 5.9**). Nevertheless, under the mildly

basic reaction conditions this pathway may be reversible. Additionally, the cyclization using the pendant amine group should provide a suitable thermodynamic driving force towards the desired product. Despite these uncertainties, it was intriguing to examine whether this strategy could be used towards the synthesis of hyacinthacine A_1.

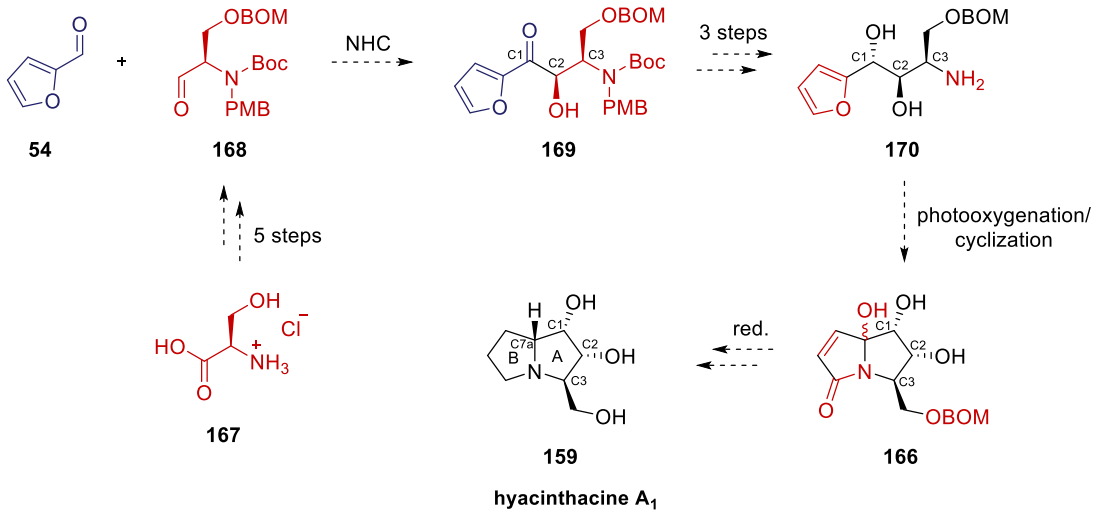


Scheme 5.9 Possible pathways involved in the photooxygenation of dihydroxy furyl alkyl amines

5.2.4. Results and Discussion

5.2.4.1. Synthetic Strategy

Compound **168** could be obtained through simple and/or known functional group manipulations starting from commercially available D-serine methyl ester salt (**167**) (**Scheme 5.10**). The poly-hydroxylated backbone bearing the desired configuration between C_2 and C_3 (**169**) could be constructed using a chemo- and diastereoselective cross-benzoin reaction between *O*-BOM-*N*-Boc-*N*-PMB-D-serinal (**168**) and 2- furaldehyde (**54**). The diastereoselective *syn* reduction of **169** could be accomplished using a strategy similar to the one described before (**Section 5.1.3.2.3**). Ring B could be constructed *via* photooxygenation of the furan moiety followed by cyclization using the pendant amine, delivering the bicyclic framework (**166**) in a single step. Finally, sequential reduction of alkene, hemiaminal, and amide functionalities would afford hyacinthacine A_1 (**159**).

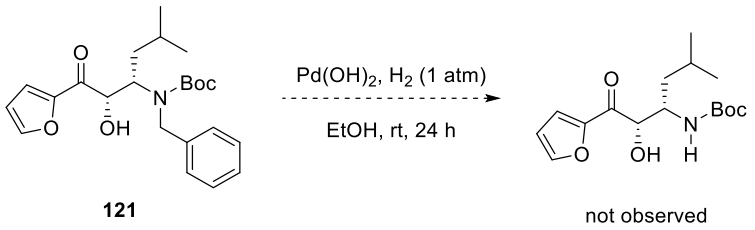


Scheme 5.10 Synthetic strategy for the total synthesis of hyacinthacine A_1

5.2.4.2. Synthesis of an Advanced Intermediate Toward Hyacinthacine A_1

5.2.4.2.1. Key Step: NHC-Catalyzed Cross-Benzoin Reaction

Earlier studies show that *N*-Boc-*N*-Bn-L-serinal and 2-furaldehyde (**54**) undergo a smooth NHC-catalyzed cross-benzoin transformation with high diastereoselectivity (**Section 4.2.2**, **121** in **Table 4.5**). However, for application in a multi-step sequence, full deprotection of the nitrogen is required. Earlier studies confirmed that the *N*-Boc protecting group could be readily cleaved under acidic conditions (see **Section 5.1.3.2.4**). To investigate the propensity of the *N*-benzyl towards deprotection, **121** was subjected to a $Pd(OH)_2$-catalyzed hydrogenation reaction (**Scheme 5.11**). Unfortunately, the removal of the *N*-benzyl protecting group under these conditions could not be achieved. Analysis of the reaction mixture indicates the loss of furyl proton signals, suggesting that the furan moiety is reduced faster than the benzyl group under the reaction conditions.



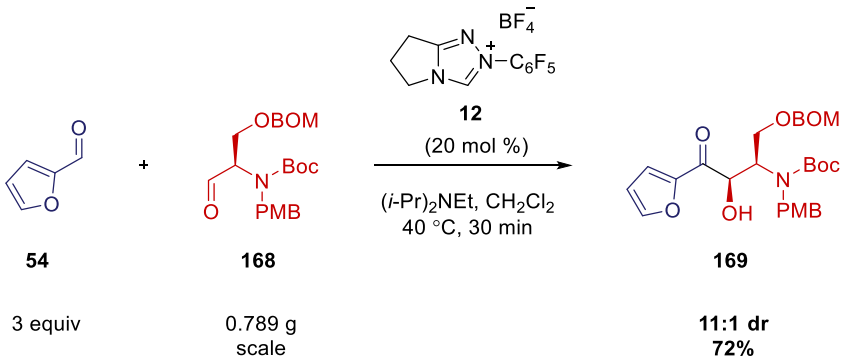
121

not observed

Scheme 5.11 *N*-benzyl deprotection of **121** using $Pd(OH)_2$

It was thus necessary to substitute the *N*-alkyl protecting group for a more readily cleavable one. *para*-Methoxy benzyl (PMB) protected substrates have been frequently used as proxies for *N*-benzyl protected substrates.[141] The advantage of using this protecting group lies in versatility in its removal; the *N*-PMB group can be cleaved under hydrogenative, acidic, or oxidative conditions. However, it was not clear whether this modification would influence the outcome of the NHC-catalyzed cross-benzoin reaction.

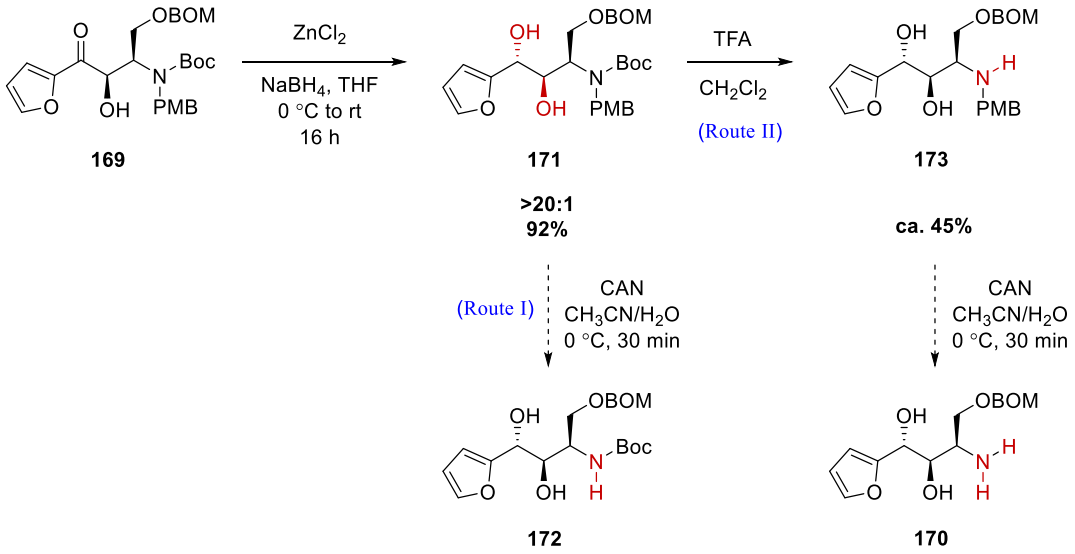
D-Serine-methyl ester hydrochloride (**167**) was transformed into *N*-Boc-*N*-PMB-D-serinal (**168**) using simple, scalable, and known functional group manipulations in 24% yield over 5 steps (see **Section 7.4**). Subjecting **168** and 2-furaldehyde (**54**) to previously optimized reaction conditions afforded the corresponding α-hydroxy-β-amino ketone in good yield and diastereomeric ratio (0.100 g scale, 68%, 8:1 dr). Additionally, all products could be easily separated using column chromatography. Increasing the scale of the reaction (0.789 g) led to an interesting observation: both the yield the diastereomeric ratio are improved on a larger scale (72% yield, 11:1 dr) (**Scheme 5.12**).



Scheme 5.12 NHC-catalyzed cross-benzoin reaction of **168** and 2-furaldehyde

5.2.4.2.2. Deprotection and Reduction Sequences

In order to obtain the required framework for the photooxygenation reaction, three subsequent reactions were necessary: the diastereoselective reduction of the α-hydroxy ketone, removal of the *N*-PMB group, and removal of the *N*-Boc group. Initially, the sequence was carried out according to **Scheme 5.13**. The hydroxyl-directed reduction of the alpha hydroxy ketone was achieved using the same strategy employed in the previous synthesis (see **Section 5.1.3.2.3**). Compound **171** was obtained in excellent yield and diastereoselectivity using $ZnCl_2/NaBH_4$. However, subsequent deprotection of the *N*-PMB group using CAN proved unfruitful, leading to decomposition of the starting material (**Route 1**). When DDQ was used for the deprotection, only small amounts of the desired product (**172**) could be detected after 18 hours. To circumvent this issue, attempts were made to remove the *N*-Boc protecting group prior to the *N*-PMB (**Route II**). Parallel reactions were carried out to identify a suitable deprotection method. *N*-Boc deprotection using HCl/MeOH,[161] TBSOTf followed by TBAF,[141] thermal deprotection (up to 250 °C),[162] and heating in water[163] proved unsatisfactory, either due to insufficient conversion or decomposition of the starting material. Gratifyingly, treatment of **171** with TFA in CH_2Cl_2 afforded the corresponding secondary amine (**173**) in moderate yield. However, oxidative cleavage of **173** using CAN results in decomposition of the starting material rendering this route non-viable.



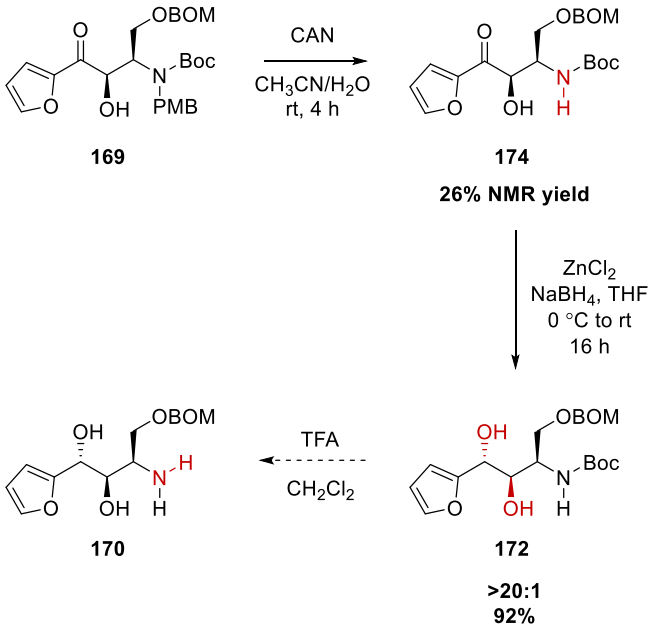
Scheme 5.13 Preliminary attempts towards the synthesis of **170**

In order to gain a better understanding of the oxidative removal of the PMB group, attention was focused on optimizing this step (**Scheme 5.13**, **Route I**). A careful inspection of the ^{1}H NMR spectrum of the crude reaction mixture corresponding to this route revealed the loss of the furan signals. This was suspected to be due to an incompatibility of the hydroxy furan functional group with *N*-PMB; the electron-rich furan ring competes with the PMB group towards oxidation using Ce (IV). Having a neighbouring carbonyl group could remove some of the electron density from the furan ring, lowering its propensity towards oxidation. To examine whether this modification could improve the reaction outcome, the deprotection was attempted using **169** (**Scheme 5.14**).

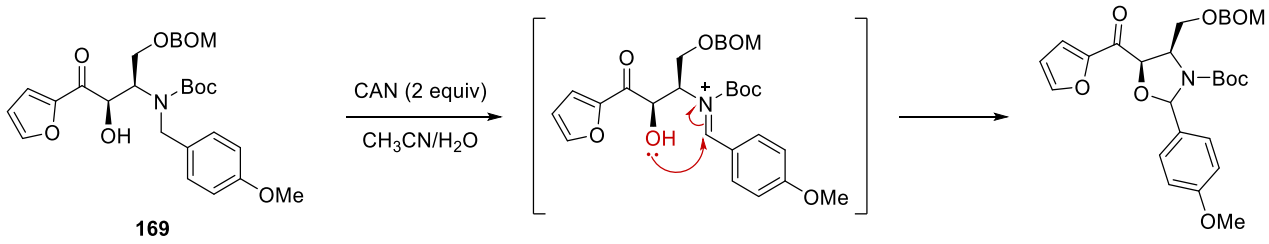
When **169** was subjected to known reaction conditions, 26% yield[xiii] of the product along with 14% of an unknown side-product were detected. Although speculative, this side product could be

[xiii] Yield was determined based on ^{1}H NMR analysis of crude reaction mixtures by using dimethyl terephthalate as the internal standard

a result of intramolecular reactions of the adjacent hydroxyl group with a radical cation or iminium intermediate involved in the reaction (**Scheme 5.15**).

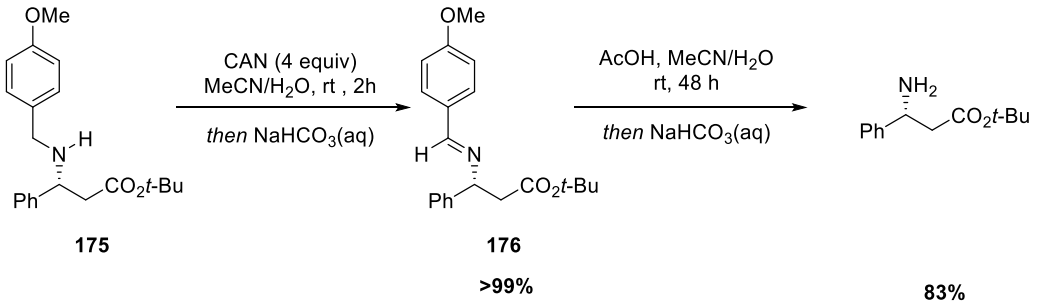


Scheme 5.14 Alternative route towards **170**



Scheme 5.15 Proposed pathway for formation of side product from oxidative deprotection of the *N*-PMB group

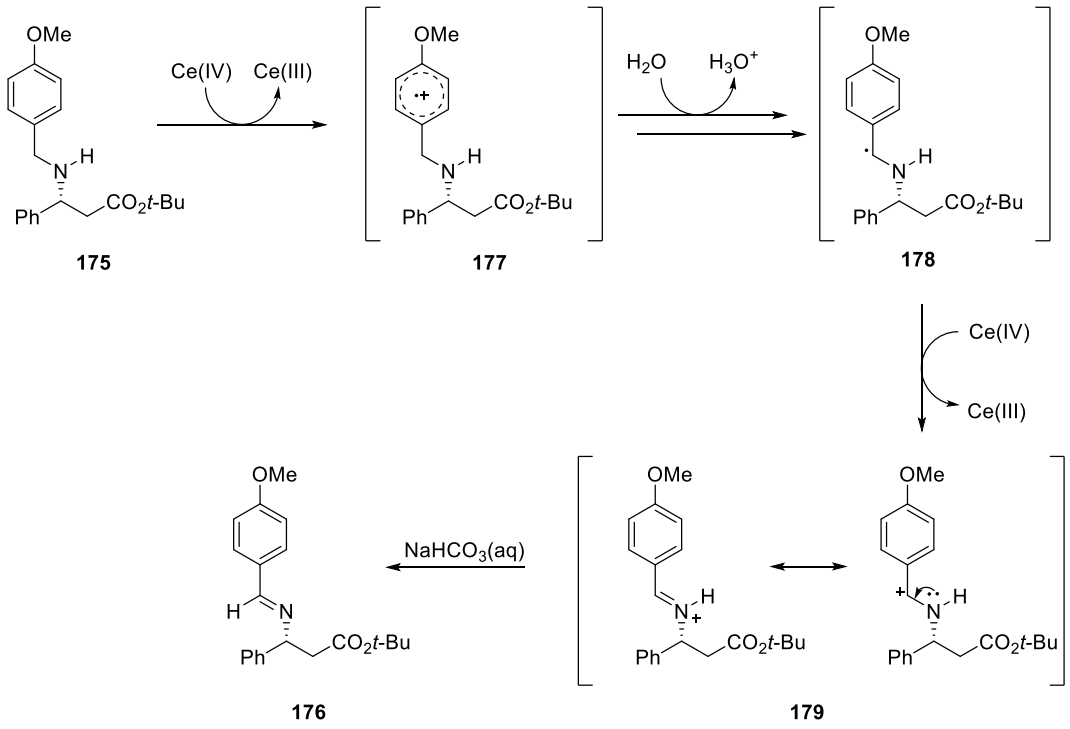
Bull and co-workers have proposed a two-step procedure for cleavage of *N*-PMB-*β*-amino esters (**175**): isolation of the imine intermediate followed by a subsequent acidic hydrolysis step (**Scheme 5.16**).[164]



Scheme 5.16 Two-step deprotection of *N*-PMB-*β*-amino esters according to Bull and co-workers[164]

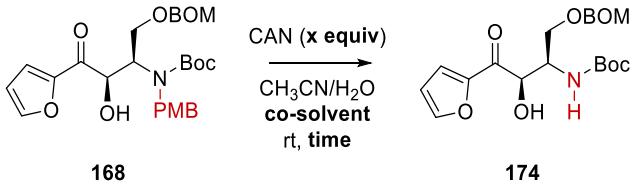
According to their proposed mechanism, the electron-rich aryl ring is initially oxidised to the corresponding radical cation (**177**) using cerium (IV) in water (**Scheme 5.17**). The resulting intermediate (**177**) undergoes deprotonation and a second oxidation, affording benzylic cation **179**. This iminium species is isolated as its corresponding imine (**176**) after basic workup. Similarly, highly reactive iminium species could arise from the reaction of **169** and two equivalents of CAN. In the presence of neighbouring hydroxyl groups, an intramolecular cyclization can result in the formation of an undesired side product (**Scheme 5.15**). Bull and co-workers found that such intermediates (*i.e.* **176**) could be hydrolyzed in the presence of acetic acid to afford the desired primary amine.

In order to minimize the formation of any undesired side product arising from such pathways, the deprotection procedure was modified to include acetic acid (**Table 5.3)** This additive proved effective, and good yield of the corresponding carbamate (**172**) was obtained **(entries 1–2**). Optimized reaction conditions were obtained by decreasing the amount of CAN and reaction time, affording the product (**174**) in excellent yield (**entry 3**).



Scheme 5.17 Proposed mechanism for the formation of imines in the CAN-mediated deprotection of *N*-PMB-*β*-amino esters

Table 5.3 CAN-mediated deprotection of PMB group in the presence of acetic acid

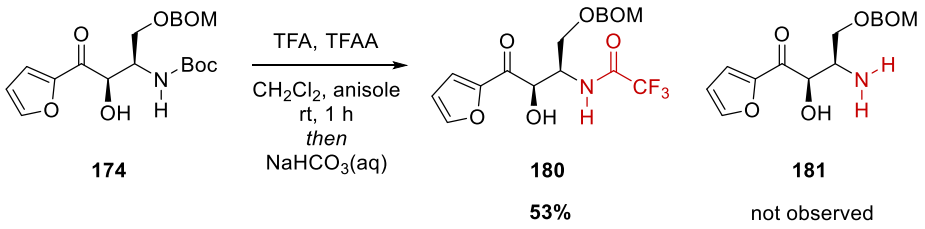


entry	x equiv	co-solvent [0.1 M]	time (min)	yield (%)[a]
1	5	none	240	26[b]
2	5	AcOH	60	56[a]
3	3	AcOH	10	80[a], 84[b]

[a] Yield determined by analysis of ^{1}H NMR spectra and by using trichloroethylene as the internal standard.
[b] Isolated yield of product.

Compound **174** was then subjected to *N*-Boc deprotection conditions using TFA in dichloromethane. Anisole was added to quench the *tert*-butyl cation produced as by-product and

trifluoroacetic anhydride (TFAA) was added in an effort to remove trace amounts water. After completion of the reaction, the crude reaction mixture was carefully neutralized using sat. $NaHCO_3$(aq). However, the crude reaction mixture contained no detectible amounts of the desired product (**181**) and **180** was isolated instead (**Scheme 5.18**).



Scheme 5.18 Conversion of protecting groups in the presence of TFA/ TFAA

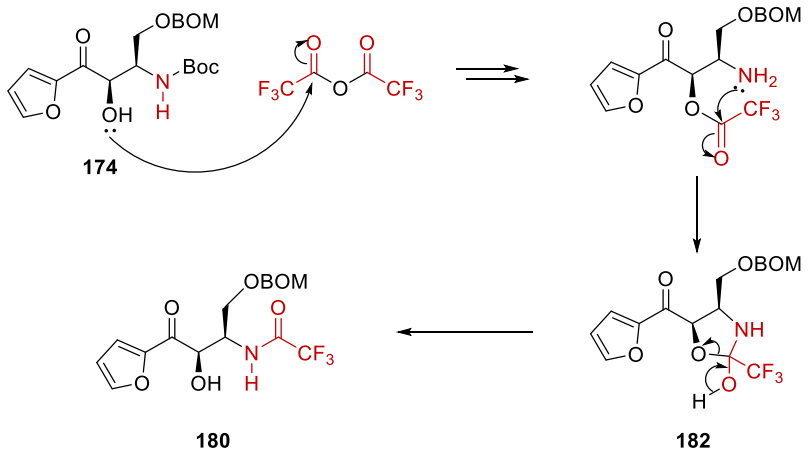
Examples of a single-step conversion of *N*-Boc group to other protecting groups are scarce in the literature.[141] This observation is particularly interesting as it allows for the replacement of an acid-labile protecting group with a base-labile one in one step.

It is speculated that, in the presence of TFAA, esterification of the hydroxyl group occurs rapidly under the acidic reaction conditions (**Scheme 5.19**). Upon neutralization, the ester undergoes a nucleophilic attack from the adjacent amine resulting in **182**. This cyclic-tetrahedral intermediate collapses to afford **180** under the basic workup conditions.

It is possible that **181** is in fact produced under the reaction conditions, however, it may undergo a rapid degradation initiated by a retro-Mannich reaction (*vide infra*) and hence it may not be detected after workup.

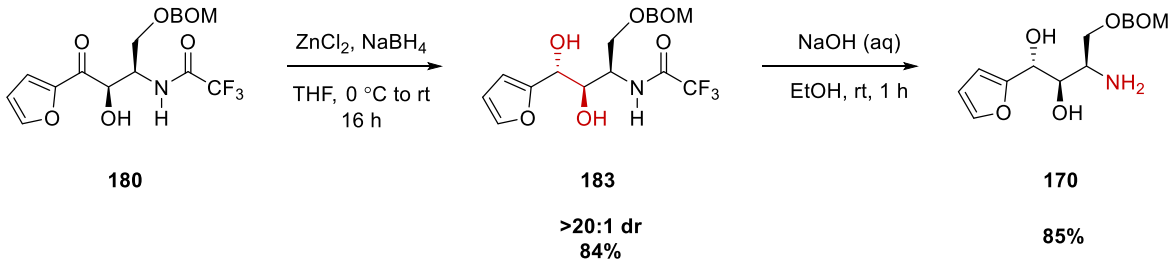
Although the use of **180** would require additional deprotection of *N*-Tfac at a later stage, its easy removal renders this reaction viable for accessing **170**. Later attempts at reproducing this

reaction at slightly larger-scale (ca. 200 mg) results in a lower yield (38%), which led to the investigation of alternative routes towards **170** (*vide infra*).



Scheme 5.19 Proposed mechanism for the protecting group exchange

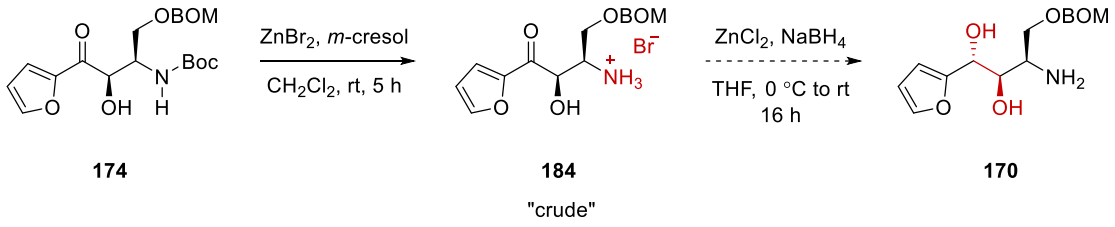
The hydroxyl-directed diastereoselective reduction of **180** was carried out in the presence of $ZnCl_2/NaBH_4$ (**Scheme 5.20**). The reaction affords **182** in good yield and diastereoselectivity. Interestingly, the *N*-Tfac protecting group remains intact under the reaction conditions. Compound **164** was obtained in good yield after basic hydrolysis.



Scheme 5.20 Reduction followed by basic hydrolysis for obtaining the corresponding amino diol

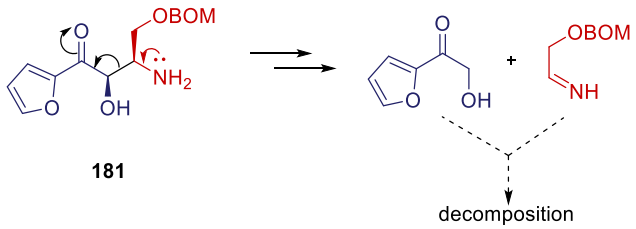
Although it was demonstrated that small quantities of **170** could be accessed through the above sequence, in order to obtain useful amounts of this substrate an alternative method for *N*-Boc

deprotection was sought. In their synthesis of hyacinthacine A_1, Donohoe and co-workers utilized a mild, late-stage *N*-Boc deprotection using $ZnBr_2$ and *p*-cresol.[165] A similar protocol was used for the deprotection of **174** (**Scheme 5.21**). The cleavage of the Boc moiety in the presence of $ZnBr_2$ proceeds cleanly to the bromide salt **183**. However, attempts to neutralize **183** under mild basic conditions resulted in its immediate decomposition. Similarly, decomposition occurred when the crude reaction mixture was subjected to $ZnCl_2/NaBH_4$. This degradation could possibly be initiated by the retro-Mannich reaction depicted in Scheme 5.22.



174 **184** "crude" **170**

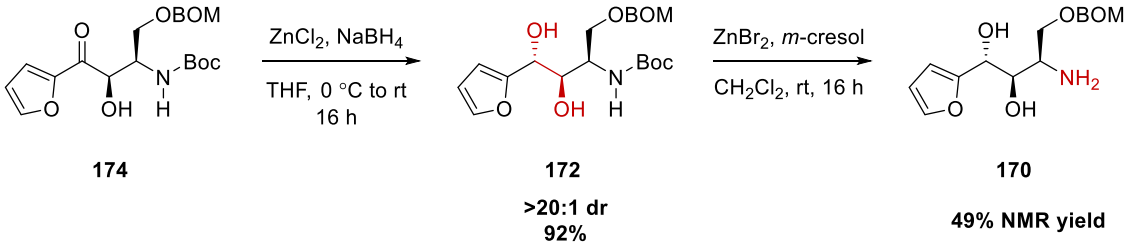
Scheme 5.21 $ZnBr_2$-mediated *N*-Boc deprotection followed by diastereoselective reduction to access **170**



Scheme 5.22 Proposed decomposition through a retro-Mannich reaction

Efforts towards isolation of the intermediates involved in the retro-Mannich reaction pathway remained fruitless. However, if such a pathway is responsible for the degradation of **181**, reduction of the carbonyl group prior to the deprotection step should inhibit this undesired pathway. In order to examine this possibility, the order of these two reactions was reversed (**Scheme 5.23**). The hydroxyl-directed diastereoselective reduction of **174** affords the corresponding diol (**172**) in excellent yield and diastereoselectivity. Gratifyingly, when **172** was subjected to deprotection

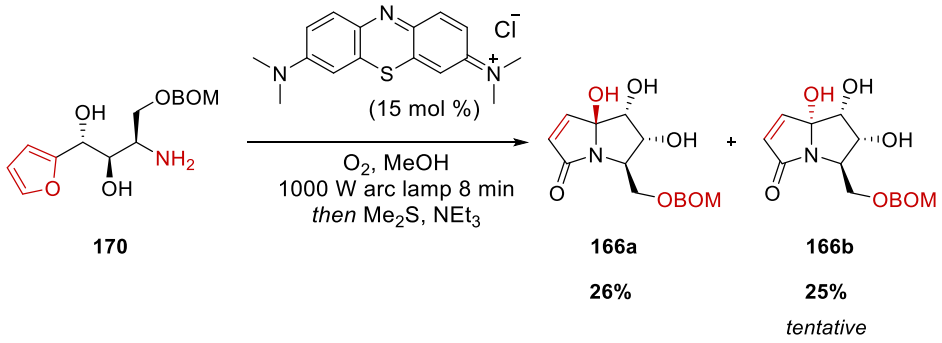
conditions, **170** was isolated in good yield. Importantly, the product was stable to neutralization and chromatography but required immediate use in the next step (storage at 8 °C leads to its decomposition within 16 h).



Scheme 5.23 Route towards **170** using diastereoselective reduction followed by *N*-Boc deprotection

5.2.4.2.3. Photooxygenation of Furan and Cyclization

The photooxygenation reaction of **170** in the presence of oxygen and methylene blue was carried out according to conditions suggested by Vassilikogiannakis and co-workers[159] (**Scheme 5.24**) with the following modifications: a 1000 W arc lamp was used instead of the suggested xenon Variac Eimac Cermax 300 W light source and increased catalytic loading (15 mol % instead of 3 mol %).



Scheme 5.24 Photooxygenation of **170** using methylene blue and oxygen

The major diastereomer of the desired product (**166a**) was obtained in moderate yield along with an unknown impurity, tentatively assigned as the minor diastereomer (**166b**). It is noteworthy

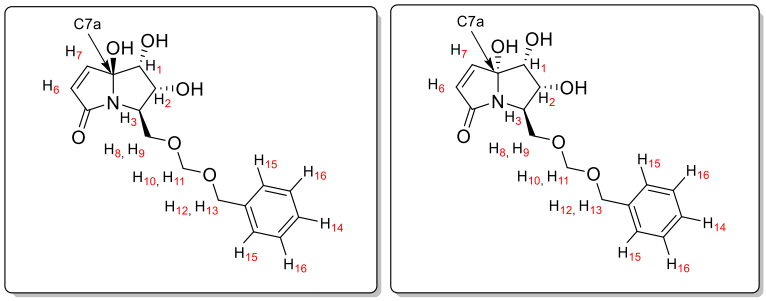
that separation of the diastereomers is not necessary as the poor diastereomeric ratio could be improved at a later stage: Vassilikogiannakis and co-workers have shown that when a 2:1 mixture of similar diastereomers were subjected to the subsequent reduction of the hemiaminal, a 10:1 mixture of diastereomers is obtained which are epimeric at the ring junction. Additionally, the hemiacetal arising from cyclization of a pendant hydroxyl on to the aldehyde was not observed (**Scheme 5.25**).

164 **165**

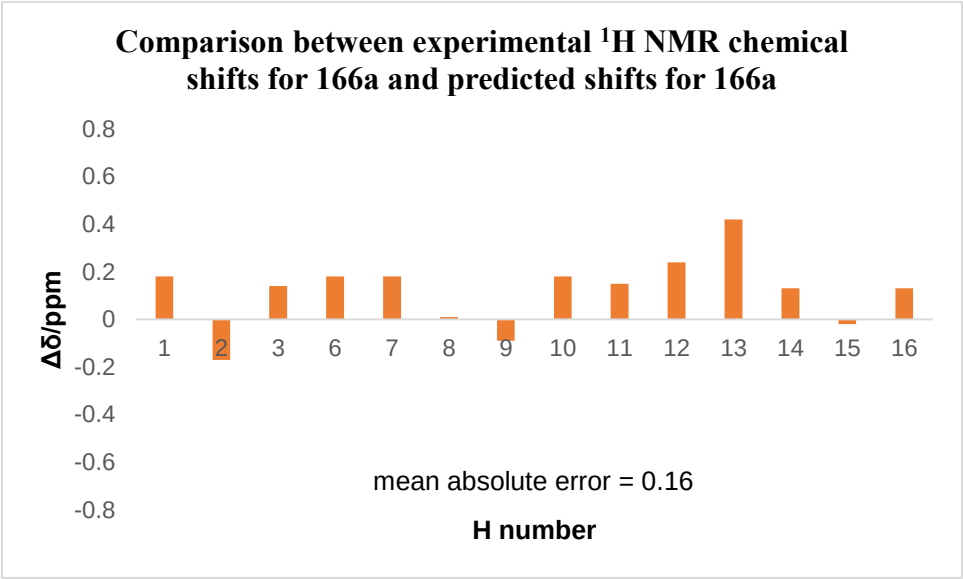
Scheme 5.25 Undesired formation of a side-product during the photooxygenation

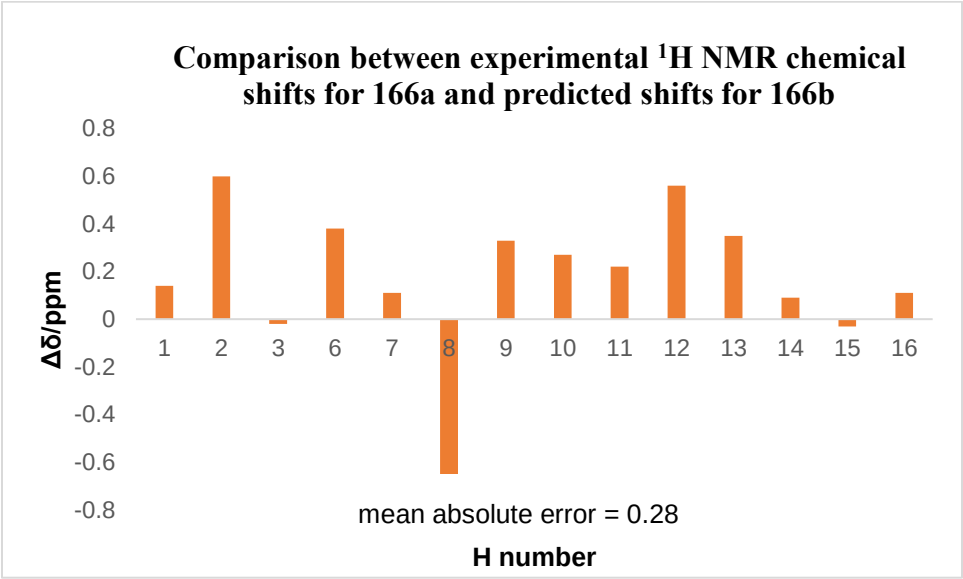
To verify the structure of the product (**166a** in **Scheme 5.24**), the ^{1}H NMR and ^{13}C NMR shifts corresponding to **166a** were predicted at the B3LYP/6-311+G(2d,p)\\M062X/6-31+G(d,p) level of theory by Michel Gravel.[108] Gratifyingly, comparison between the predicted and experimental shifts shows a close fit to the obtained major diastereomer (**166a** in **scheme 5.24)** (**Figure 5.5**, for raw data see **Section 7.4**).

The isolation of **166a** is particularly interesting as it underscores the usefulness of this method in delivering good yield even without the protection of the adjacent secondary alcohols. Although the photooxygenation step requires further optimization, preliminary results attest to its ability to rapidly form the pyrrolizine core for the synthesis of hyacinthacine A_1.

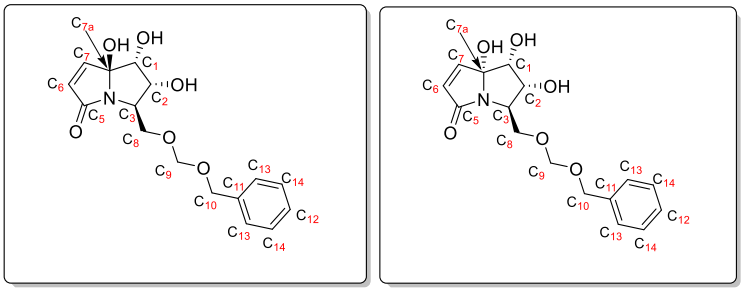


166a **166b**

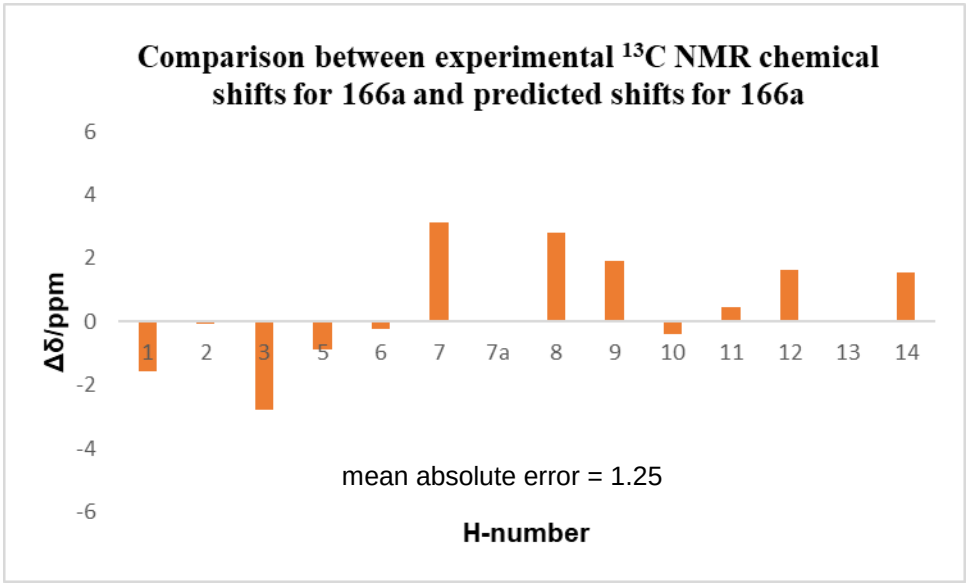




Continued on next page



166a **166b**



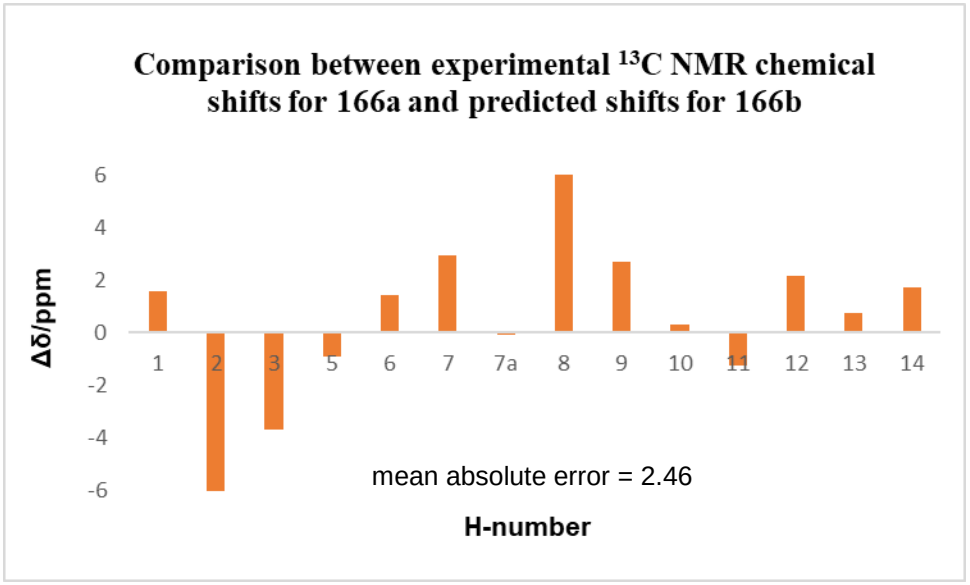


Figure 5.5 Comparison between observed and predicted NMR chemical shifts for C7a epimers of 166

5.2.5. Conclusion

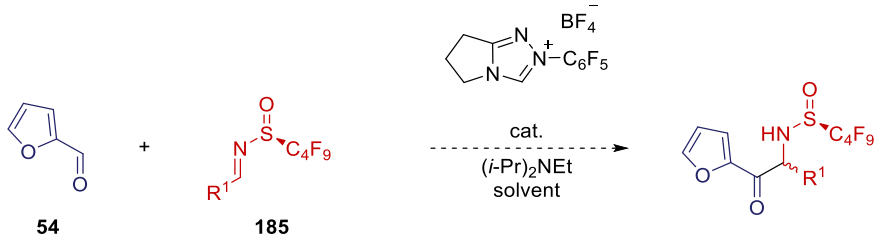
In summary, a concise route towards hyacinthacine A_1 has been shown. The NHC-catalyzed cross-benzoin reaction between 2-furaldehdye and *N*-Boc-*N*-PMB-D-serinal is utilized as the key step, installing two out of the four stereogenic centres present in hyacinthacine A_1. The use of an abundant and affordable enantio-enriched amino aldehyde renders this approach suitable for large scale synthesis of this natural product. A reliable three-step reduction/deprotection sequence was developed that can be used to access large quantities of the polyhydroxylated backbone. The photooxygenation of a 1,2-amino diol affords the bicyclic pyrrolizine core in a single step. However, in order to proceed further with the proposed route, optimization of the photooxygenation step is necessary for accessing useful amounts of the natural product's framework.

Chapter 6: Discussion and Future Work

6.1. Amino Ketones *via* NHC-Catalyzed Aza-Benzoin Reactions

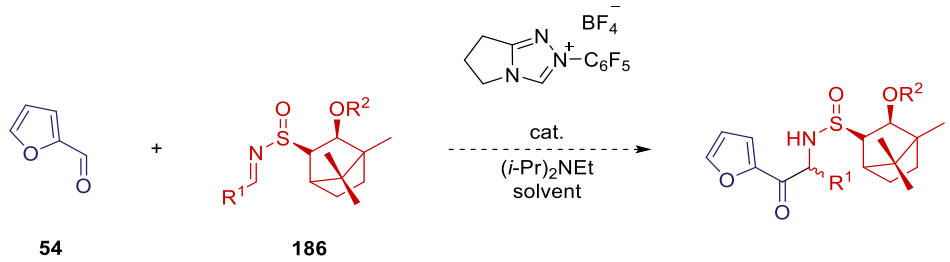
NHC-catalyzed cross-benzoin and aza-benzoin reactions provide rapid access to enantio-enriched amino ketones by directly joining two aldehydes or an aldehyde and an imine respectively. The first strategy presented in this thesis towards the synthesis of these motifs involved NHC-catalyzed aza-benzoin reactions using *tert*-butanesulfinimides as chiral auxiliaries. Reactions between 2-furaldehyde and *tert*-butanesulfinimines afford enantio-enriched α-amino ketones in poor yields with moderate diastereoselectivity. It is possible that the poor diastereomeric ratio is a result of an equilibration between the two diastereomers. To evaluate this, a ^{1}H NMR monitoring experiment similar to those described in **Sections 3.2.6** and **4.2.3** is desirable.

Liu and co-workers have successfully developed a method for accessing (*S*)-nonafluorobutanesulfinamides (**185** in **Scheme 6.1**) in high enantioselectivity.[166] Additionally, when the corresponding imine adducts were employed in Strecker reactions, good to excellent yields and diastereoselectivities were obtained. The authors suggest that the inductive electron-withdrawing effect of the polyfluoroalkyl group renders their imine adducts more electrophilic than the non-fluorinated variants. Based on this precedent, it would be interesting to investigate whether the application of nonafluorobutanesulfinimines (**185**) to NHC-catalyzed aza-benzoin transformations could lead to an improvement in the yield of the reaction (**Scheme 6.1**).



Scheme 6.1 Application of (*S*)-nonafluorobutanesulfinimines in NHC-catalyzed aza-benzoin reactions

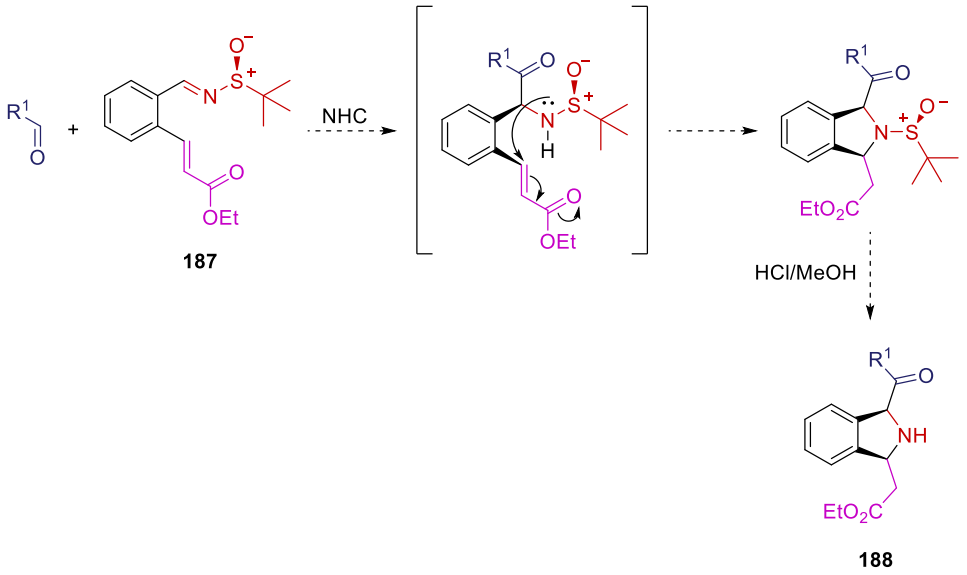
Alternatively, the low diastereomeric ratio may stem from an inherently poor facial selectivity imparted by the chiral auxiliary. Yang and co-workers have applied (+)-camphor-derived sulfinimines[167–169] (**186** in **Scheme 6.2**) as electrophiles towards Grignard reagents with great success.[169] Despite their relatively difficult preparation, an investigation into the use of **186** could lead to a more effective facial selectivity and hence improvement in the diastereomeric ratio under the reaction conditions (**Scheme 6.2**). However, the application of this bulky chiral auxiliary is not expected to improve the yield of the reaction.



Scheme 6.2 Application of (+)-camphor-derived sulfinimines in NHC-catalyzed aza-benzoin reactions

Alternatively, the chiral auxiliary strategy could be employed for obtaining synthetically useful enantio-enriched products in an intramolecular reaction. Fustero *et al.* investigated the intramolecular aza-Michael reaction of *tert*-butanesulfinimines using fluorinated nucleophiles.[170] It is hypothesized that **187** and aldehydes could undergo a domino reaction involving an NHC-catalyzed aza-benzoin reaction followed by an intramolecular Michael cyclization (**Scheme 6.3**).

Finally, removal of the chiral auxiliary would lead to synthetically useful scaffolds (**188**) found in a number of biologically-relevant molecules.[171,172]

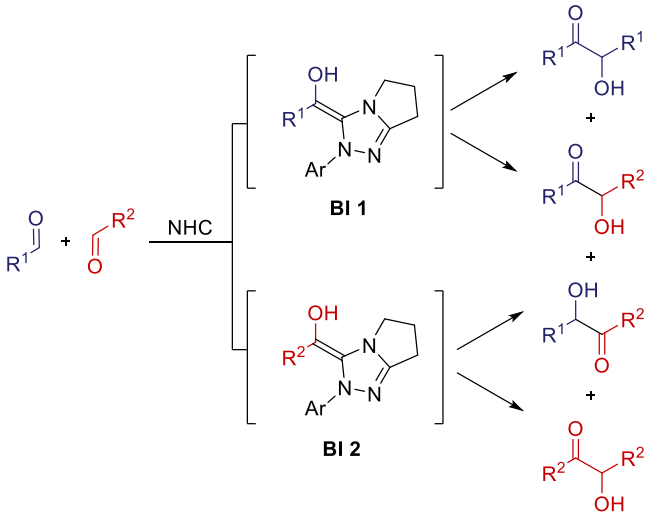


Scheme 6.3 Proposed domino aza-benzoin-Michael reactions using a tethered chiral auxiliary

6.2. Amino Ketones *via* NHC-Catalyzed Cross-Benzoin Reactions

Chemo- and diastereoselective cross-benzoin reactions involving *α*-amino aldehydes serve as powerful tools for accessing *α*-hydroxy-*β*-amino ketones. Traditionally, the chemoselectivity issues related to the direct coupling of two aldehydes have thwarted widespread application of the benzoin reaction in organic synthesis (**Scheme 6.4**).

Despite many efforts, a universal predictive model for chemoselectivity has not been proposed to this date. This is due to the fact that the nature of the substrates, catalyst, solvent, and base cumulatively influence the rates of the competing pathways, and ultimately the final product distribution. This thesis describes chemoselective NHC-catalyzed cross-benzoin reactions, either between two aliphatic aldehydes or an aliphatic and a heteroaromatic aldehyde.

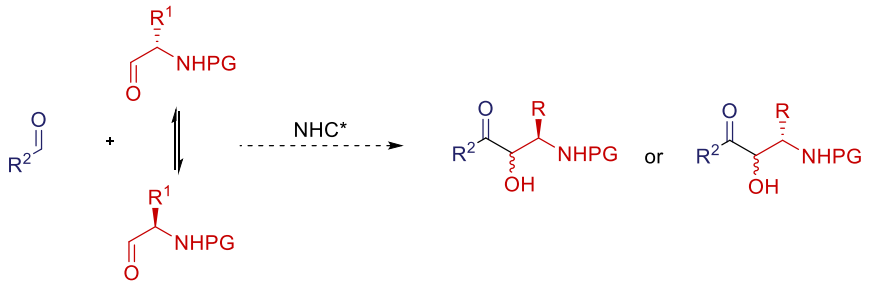


Scheme 6.4 The chemoselectivity issue in intermolecular NHC-catalyzed cross-benzoin reactions of aldehydes

It was hypothesized that application of substrates that possess activation *via* an adjacent heteroatom concurrent with steric hindrance induced by an alkyl substituent could influence the final product distribution. According to this hypothesis the selection between the aldehydes occurs during formation of the Breslow intermediate. Results confirm that chemoselectivity could be successfully achieved using this substrate design. However, in various instances the homo-benzoin products of α-amino aldehydes were detected. This indicates that the initial hypothesis was not entirely accurate as the Breslow intermediates deriving from amino aldehydes are formed under the reaction conditions. It is possible that the selection of aldehydes does not occur during Breslow intermediate formation and a subsequent step may be responsible for the observed chemoselectivity. Thorough mechanistic and/or computational studies are required to further elucidate the underlying mechanistic principles using these reaction partners.

Enantio-enriched α-hydroxy-β-amino ketones from naturally occurring amino acid derivatives can be obtained using the methods described in Chapters 3 and 4. Conventional methods for the synthesis of non-naturally occurring amino aldehydes are generally non-enantioselective, ultimately affording *racemic* aldehydes that are unsuitable for the synthesis of enantio-enriched α-

hydroxy-β-amino ketones. In order to expand the scope of the NHC catalyzed cross-benzoin to non-natural α-amino aldehydes, a dynamic kinetic resolution (DKR) strategy is sought.[173,174] Enantio-enriched α-hydroxy-β-amino ketones could be obtained from a combination of a rapid equilibration between the enantiomers of the amino aldehyde and kinetic resolution *via* an enantioselective cross-benzoin reaction (**Scheme 6.5**). It is important to note that only a few examples of DKR reactions involving amino aldehydes have been reported.[175] This strategy is currently being pursued by a co-worker in the Gravel research group.

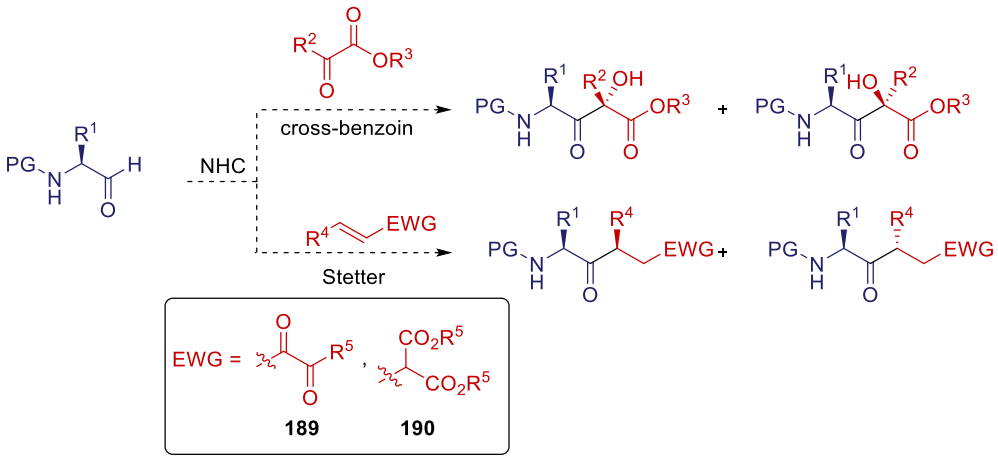


Scheme 6.5 Dynamic kinetic resolution of *racemic* α-amino aldehydes in NHC-catalyzed cross-benzoin reactions

6.2.1. Other NHC-Catalyzed Cross-Benzoin and Stetter Reactions using α-Amino Aldehydes

Based on the observed formation of Breslow intermediates with amino aldehydes, it would be worthwhile to investigate whether *N*-protected amino aldehydes could be used in Stetter or other cross-benzoin reactions (**Scheme 6.6**). In the absence of a competing aldehyde, the NHC would attack the amino aldehyde to form the corresponding Breslow intermediate. This intermediate would add to the electrophile to deliver either the cross-benzoin or Stetter product. It would be crucial to use substrates that are inherently incapable of reacting with the NHC, as the desired formation of a Breslow intermediate would be slow for the sterically hindered amino aldehyde.

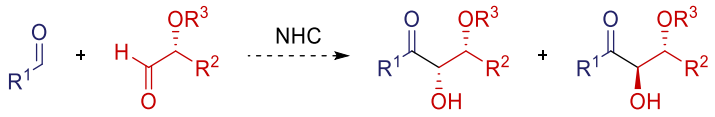
Activated acceptors such as α-keto esters (**189**)[6,95] or arylidenemalonates (**190**)[176] are suitable candidates for this purpose.



Scheme 6.6 NHC-catalyzed cross-benzoin reactions using α-amino aldehydes and activated electrophiles

6.2.2. α-Hydroxy Aldehydes in NHC-Catalyzed Cross-Benzoin Reactions

A prudent balance of the electronic and steric properties of the *N*-protected amino aldehydes is believed to lead to the excellent observed chemoselectivity. Additionally, when *N*,*N*-bis-protected amino aldehydes are employed, high diastereoselectivities are obtained for Felkin-Anh products. Thus, it should be examined whether replacement of the amine with a protected α-hydroxy aldehyde could deliver the corresponding cross-benzoin products with high chemo- and diastereoselectivity. Enantio-enriched *O*-protected-α-hydroxy aldehydes can be readily accessed from chiral-pool derived starting material. Alternatively, a DKR strategy, similar to that outlined above could be used to access enantio-enriched cross-benzoin products from *racemic O*-protected-α-hydroxy aldehydes. It is important to note that the desired products could easily be transformed into moieties that are present in a wide array of biologically active compounds (**Scheme 6.7**).

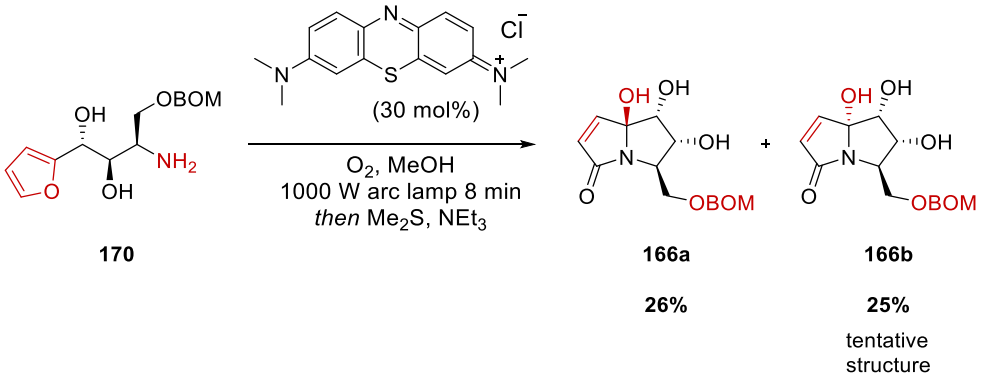


Scheme 6.7 NHC-catalyzed cross-benzoin reactions of protected α-hydroxy aldehydes

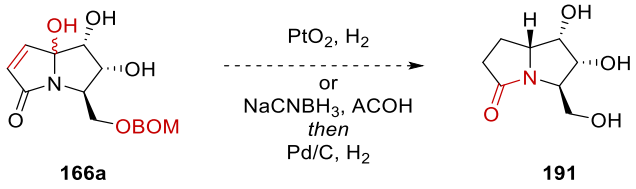
6.3. Synthesis of Hyacinthacine A_1: Completion

Efforts towards the synthesis of hyacinthacine A_1 feature a successful key NHC-catalyzed cross-benzoin step. Subsequent reduction and deprotection steps were optimized to afford reproducible yields of **170** (**Scheme 6.8**). Preliminary results from the photooxygenation reaction indicate that the major diastereomer of the desired product (**166a**) could be obtained in modest yield along with an unidentified impurity. NMR, HRMS and FTIR data suggest that the major impurity in this reaction is the minor diastereomer (epimeric at C7a, **166b**). However, the computed ^{1}H NMR chemical shifts do not correspond to the experimentally observed ones, rendering its identification ambiguous. Structure elucidation of this intermediate using derivatization is an alternative solution to this problem. As a future direction, linear optimization of this step is desirable. The goal of such optimizations is to explore conditions that can deliver the desired product(s) in good yield.

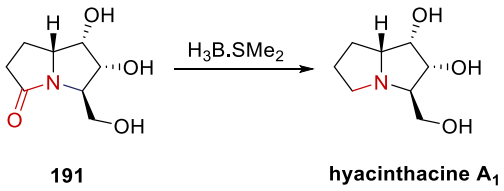
Reduction of both the hemiaminal and alkene,[159] as well as removal of BOM from **166a** could be accomplished using Adam's catalyst and hydrogen. Although the simultaneous reduction of the cyclic hemi-aminal and the alkene is well-known,[159] a two-step reduction sequence using $NaCNBH_3$ and acetic acid followed by Pd/C and hydrogen might also afford the desired outcome (**Scheme 6.9**).[177,178] The synthesis would then be completed by reduction of **191** using a known literature procedure (**Scheme 6.10**).[79]



Scheme 6.8 Photooxygenation reaction in presence of methylene blue and oxygen



Scheme 6.9 Proposed reduction and deprotection of cyclic pyrrolidinone **166a**



Scheme 6.10 Completion of the synthesis of hyacinthacine A_1

Chapter 7: Experimental Section

General Methods

Anhydrous CH_2Cl_2, diethyl ether, toluene, and THF were dried using a Braun Solvent Purification System and stored under argon over 4 Å molecular sieves. DMF was dried *via* distillation over CaH_2. Unless otherwise noted, all reactions were performed under an inert atmosphere of argon.

Preparative thin layer chromatography (PTLC) was carried out on glass plates (20 × 20 cm) pre–coated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phosphomolybdic acid (5%) containing a trace of ceric sulfate in aq. sulfuric acid (5% *v*/*v*), or with basic $KMnO_4$ [$KMnO_4$ (1.5 g), K_2CO_3 (10 g), 10% aq. NaOH (1.25 mL), in H_2O (200 mL)], followed by charring with a heat gun. Analytical TLC was carried out on glass plates (4 × 3 cm) pre–coated (0.25 mm) with silica gel 60 F_{254} and was visualized in the same manner as described for preparative TLC.

Flash column chromatography (FCC) was performed according to Still *et al.*[179] with Merck silica gel 60 (0.040–0.063 mm). All mixed solvents eluents are reported as *v*/*v* solutions. Unless otherwise noted, all reported compounds were homogenous by thin layer chromatography (TLC) and by ^{1}H NMR spectroscopy.

Concentration refers to removal of volatiles with a rotary evaporator under vacuum supplied by vacuum pump (ca. 30 Torr). Evacuation at ca. 0.5 Torr with a vacuum pump generally followed rotary evaporation. ^{1}H NMR and ^{13}C NMR calculations were performed according to reported procedures.[108,180]

Spectral Data

High resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were obtained on a VG 70E double focusing high resolution spectrometer; only partial data are reported. Electron impact (EI) ionization was accomplished at 70 eV, chemical ionization (CI) at 50 eV with ammonia as the reagent gas. Alternatively, HRMS was obtained on a LC–MS/MS time–of–flight high resolution spectrometer with electrospray ionization (ESI) from acetonitrile solution.

Infrared spectra were recorded on a Fourier transform interferometer using a diffuse reflectance cell (DRIFT); only diagnostic peaks and/or intense peaks are reported. Unless otherwise noted, all experiments used DRIFT.

Unless otherwise noted, NMR spectra were measured in $CDCl_3$ solution at 500 MHz or 600 MHz for ^{1}H and 125 or 150 MHz for ^{13}C. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard: $CDCl_3$ (7.26 δ_H, 77.16 δ_C); C_6D_6 (7.16 δ_H, 128.39 δ_C); CD_3OD (3.31 δ_H, 49.00 δ_C); DMSO-d_6 (2.50 δ_H, 39.52 δ_C). The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), sep (septet), m (multiplet), br (broad), ap (apparent); the list of coupling constants (*J*) corresponds to the order of the multiplicity assignment. Coupling constants are reported to the nearest 0.5 Hz (digital resolution ca, 0.1 Hz/pt) or the nearest 0.1 Hz (digital resolution ca. 0.03 Hz/pt.). The ^{13}C NMR assignments were made on the basis of the chemical shifts. In cases where rotamers are present, the chemical shifts corresponding to the minor rotamer are marked with an asterisk.

Specific rotations ($[\alpha]_D$) are the average of five determinations at ambient temperature using 1 mL, 10 dm cell; the units are 10^{-1} deg. cm^2 g^{-1} and the concentrations (*c*) are reported in g/100 mL. The values reported are rounded to reflect the accuracy of the measured concentrations (the major source of error). Enantiomeric purity was determined by chiral HPLC analysis. In all cases, the analysis was calibrated with a sample of the racemate. HPLC analyses were carried out using an Agilent Technologies 1200 series liquid chromatograph.

Materials

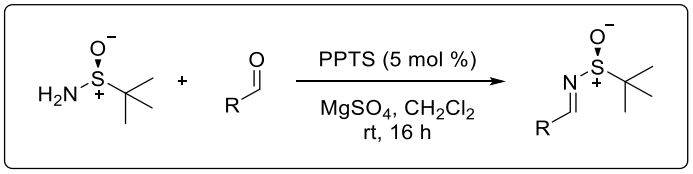
All commercially available aldehydes were purified by bulb–to–bulb distillation prior to use. 2-Iodoxybenzoic acid (IBX) was synthesized according to a literature procedure.[181] Triazolium precatalyst **12, was** synthesized following a reported procedure.[43,182] $ZnCl_2$ was dried by heating to 350 °C under vacuum (0.5 Torr) for a period of 16 h. Compound **2.15** was synthesized by Sida Zhou. Compounds **80** and **81** were synthesized by Eduardo Sanchez-Larios. Compounds **34** and **57** were synthesized by Steven Langdon, **14** was prepared by Myron Wilde, and **134** was synthesized by Venkata Krishna Garapati.

Unless otherwise noted, all other reagents were purchased and used without further purification.

7.1. A Chiral Auxiliary Approach Towards the NHC-Catalyzed Aza-Benzoin Reaction

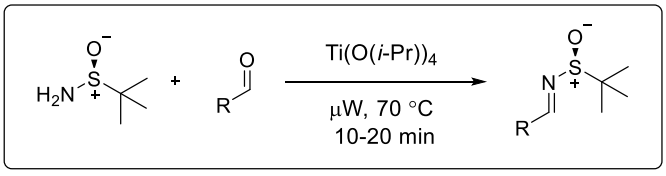
Synthesis of *tert*-butanesulfinimines

General Procedure A



Following a reported procedure,[183] to a solution of (S)-*t*-butanesulfinamide (1.0 equiv) and CH_2Cl_2 [0.5 M] under nitrogen atmosphere was added pyridinium *p*-toluenesulfonate (0.05 equiv) and anhydrous magnesium sulfate (5.0 equiv) followed by the corresponding freshly-distilled aldehyde (3.0 equiv). The reaction mixture was stirred at room temperature for 16 hours and the reaction completion was judged by TLC analysis. The crude reaction mixture was filtered through a pad of Celite® and washed with EtOAc (×3). The crude reaction mixture was purified using column chromatography.

General Procedure B

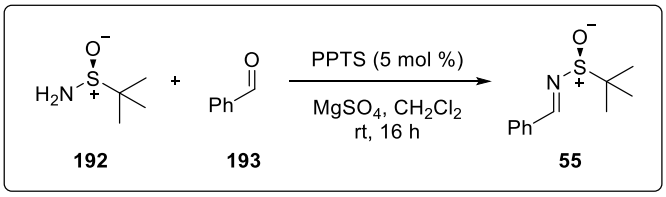


Following a modified literature procedure,[184] a microwave vial was charged with (S)-*t*-butanesulfinamide (1.0 equiv), the corresponding aldehyde (1.0 equiv), and $Ti(O(i\text{-}Pr))_4$ (2.0 equiv) under nitrogen atmosphere. The reaction mixture was capped and stirred for 5 min at room

temperature. The reaction vessel was placed in a microwave reactor and was heated to 70 °C for 10-12 minutes. Upon completion, the reaction was cooled to room temperature, diluted with EtOAc (ca. 10 mL), and poured into brine (2 mL). The reaction mixture was filtered through Celite® and the filtrate was washed with EtOAc (×3). The combined organic layers were dried on Na_2SO_4 and concentrated. The crude reaction mixture was purified using column chromatography.

(*S*,*E*)-*N*-Benzylidene-2-methylpropane-2-sulfinamide (**55**)

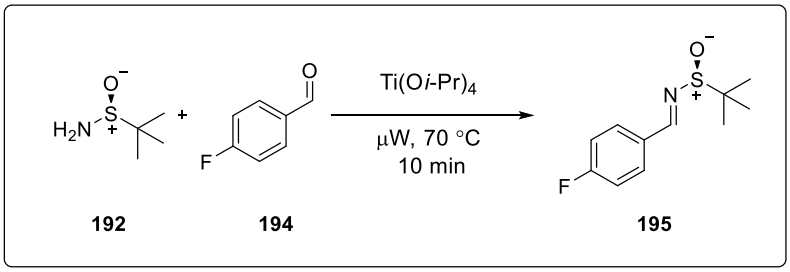
Prepared according to **general procedure A**



Isolated by column chromatography (7:1 hexane/EtOAc, R_f =0.10) as a light-yellow oil (0.311 g, 90%). Spectral data match the previously reported values.[185] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.60 (s, 1 H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.57–7.42 (m, 3H), 1.27 (s, 9H).

(*S*,*E*)-*N*-(4-Fluorobenzylidene)-2-methylpropane-2-sulfinamide (**195**)

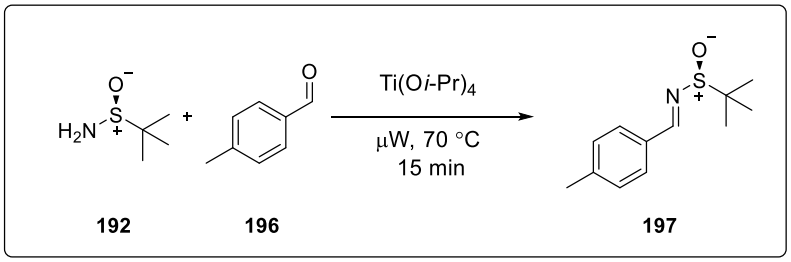
Prepared according to **general procedure B**



Isolated by column chromatography (7:1 hexane/EtOAc, R_f =0.21) as a white solid (0.299 g, 76%). Spectral data match the previously reported values.[185] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.55 (s, 1 H), 7.87 (dd, *J* = 5.5, 2.0 Hz, 2H), 7.17 (ap t, *J* = 8.5, 8.5 Hz, 2H), 1.27 (s, 9H).

(*S*,*E*)-2-Methyl-*N*-(4-methylbenzylidene)propane-2-sulfinamide (**197**)

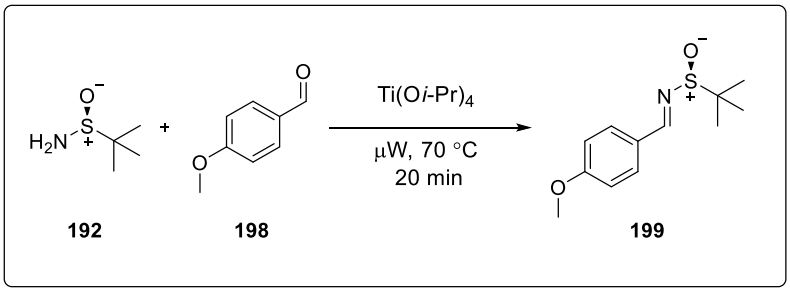
Prepared according to **general procedure B**



Isolated by column chromatography (4:1 hexane/EtOAc, R_f =0.26) as a white solid (0.103 g, 70%). Spectral data match the previously reported values.[186] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 2.42 (s, 3H), 1.26 (s, 9H).

(*S*,*E*)-*N*-(4-Methoxybenzylidene)-2-methylpropane-2-sulfinamide (**199**)

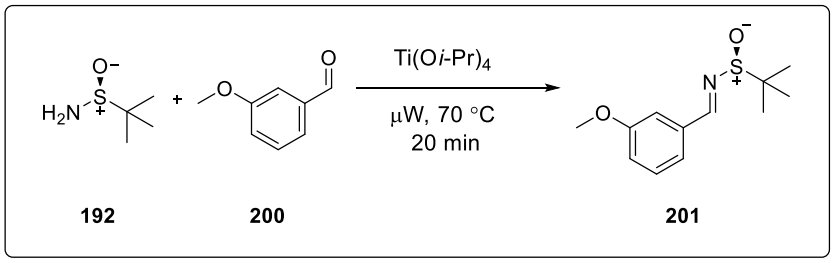
Prepared according to **general procedure B**



Isolated by column chromatography (3:1 hexane/EtOAc, R_f =0.26) as a white solid (0.103 g, 70%). Spectral data match the previously reported values.[185] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.55 (s, 1 H), 7.75 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.83 (s, 3H), 1.21 (s, 9H).

(*S*,*E*)-*N*-(3-Methoxybenzylidene)-2-methylpropane-2-sulfinamide (**201**)

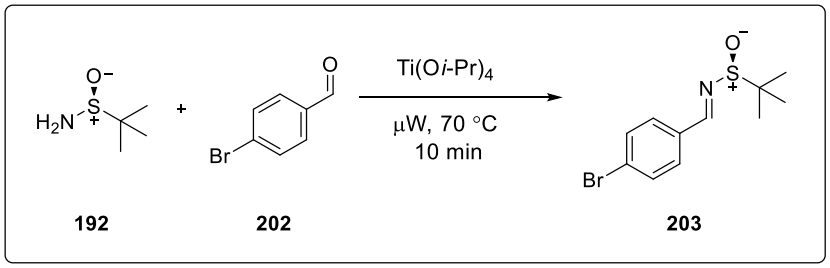
Prepared according to **general procedure B**



Isolated by column chromatography (5:1 hexane/EtOAc) as a white solid (0.181 g, 82%). Spectral data match the previously reported values.[187] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.56 (s, 1 H), 7.50–7.35 (m, 3H), 7.15–7.03 (m, 1H), 3.86 (s, 3H), 1.28 (s, 9H).

(*S*,*E*)-*N*-(4-Bromobenzylidene)-2-methylpropane-2-sulfinamide (**203**)

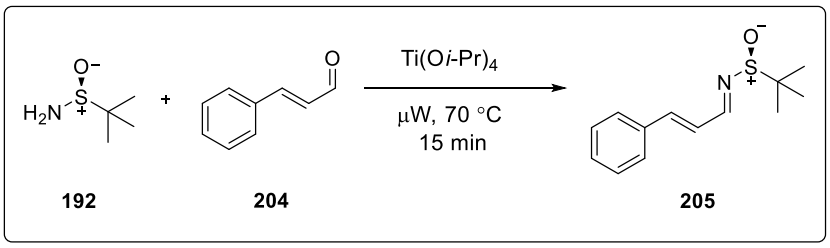
Prepared according to **general procedure B**



Isolated by column chromatography (9:1 hexane/EtOAc) as a white solid (0.219 g, 94%). Spectral data match the previously reported values.[185] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 1.26 (s, 9H).

(*S*)-2-Methyl-*N*-[(1*E*,2*E*)-3-phenylallylidene]propane-2-sulfinamide (**205**)

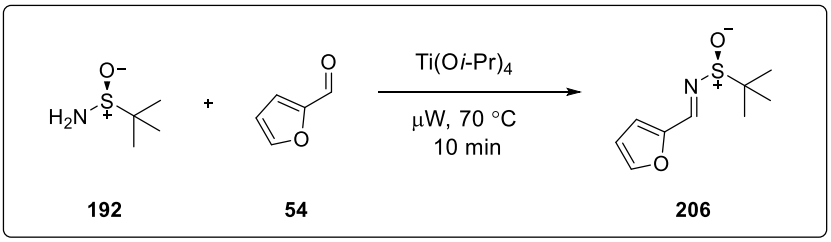
Prepared according to **general procedure B**



Isolated by column chromatography (9:1 hexane/EtOAc, R_f = 0.28) as pale yellow solids (0.187 g, 80%). Spectral data match the previously reported values.[188] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.38 (d, *J* = 9.2 Hz, 1H), 7.55 (dd *J* = 8.0, 1.8 Hz, 2H), 7.45–7.35 (m, 3H), 7.26–7.22 (m, 1H), 7.09 (dd, *J* = 16.0, 9.3 Hz, 1H), 1.24 (s, 9H).

(*S*,*E*)-*N*-(Furan-2-ylmethylene)-2-methylpropane-2-sulfinamide (**206**)

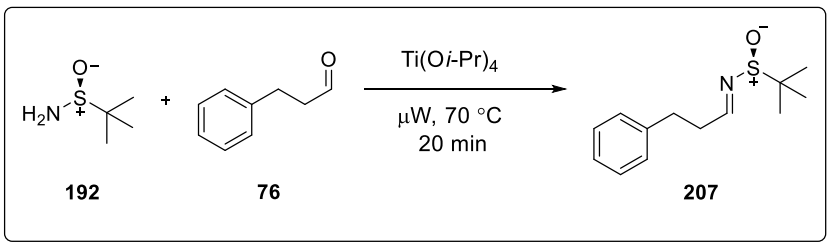
Prepared according to **general procedure B**



Isolated by column chromatography (3:1 hexane/EtOAc, R_f = 0.34) as a white solid (0.080 g, 98%). Spectral data match the previously reported values.[188] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.64 (s, 1H), 7.00 (d, *J* = 3.4 Hz, 1H), 6.57 (br s, 1H), 1.26 (s, 9H).

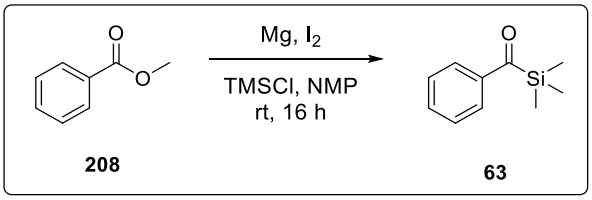
(*S*,*E*)-2-Methyl-*N*-(3-phenylpropylidene)propane-2-sulfinamide (**207**)

Prepared according to **general procedure B**



Isolated by column chromatography (5:1 hexane/EtOAc, R_f = 0.32) as a white solid (0.233 g, 98%). Spectral data match the previously reported values.[188] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.12 (t, *J* = 4.2 Hz, 1H), 7.32–7.27 (m, 2H), 7.23–7.16 (m, 3H), 3.02–2.93 (m, 2H), 2.91–2.83 (m, 2H), 1.13 (s, 9H).

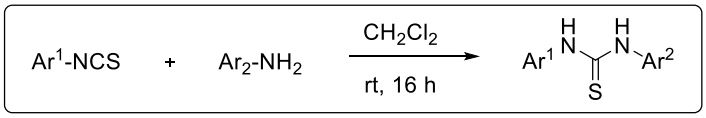
Phenyl(trimethylsilyl)methanone (**63**)



Following a reported procedure,[189] methyl benzoate (0.63 mL, 5 mmol) was added dropwise to a mixture of magnesium powder (10 mmol, 0.240 g,), iodine (1.6 mmol, 0.407 g), and chlorotrimethylsilane (5.1 mL) in NMP (12 mL) under nitrogen atmosphere. The reaction mixture was stirred overnight (16 h) and quenched with addition of sat. NH_4Cl (aq). The stirring was continued for an additional 2 hours. Distilled water added and the mixture was extracted with pentane (3 × 40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The semi-volatile crude product was purified using column chromatography (15:1 hexane:EtOAc) to afford the title compound as a yellow oil along with small amounts of unknown impurities. Spectral data match the previously reported values.[189] This mixture was used in the next step without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.91–7.79 (m, 2H), 7.57–7.51 (m, 1H), 7.51–7.45 (m, 2H), 0.37 (s, 9H). Unknown impurities **^{1}H NMR** (500 MHz, $CDCl_3$): 8.04 (d, *J* = 7.3 Hz), 7.44 (d, *J* = 9.3 Hz), 7.32–7.27 (m), 7.17 (d, *J* = 7.3 Hz), 7.16–7.11 (m), 5.89–5.81 (m), 5.70–5.64 (m), 3.96–3.91 (m), 3.73 (s), 3.69 (s), 3.42 (s), 3.29 (s), 2.12 (d, *J* = 8.7 Hz), 0.03 (s).

Synthesis of Thioureas

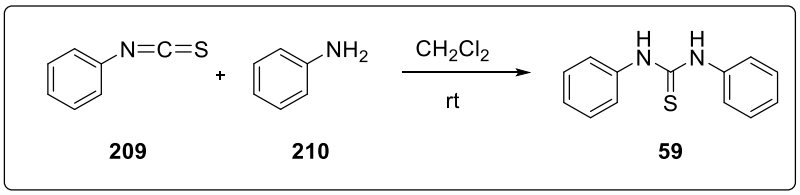
General Procedure C



Following a reported procedure,[190] to a stirred solution of the corresponding amine (1.0 equiv) and CH_2Cl_2 [0.2M], the appropriate phenylisothiocyanate (1.0 equiv) was added (dropwise). The reaction mixture was stirred over night (16 h) and volatiles were removed after this period. The crude reaction mixture was diluted with CH_2Cl_2 and washed with water (×1). The organic layer was dried over Na_2SO_4 and concentrated to afford the corresponding pure product.

1,3-Diphenylthiourea (**59**)

Prepared according to **general procedure C**

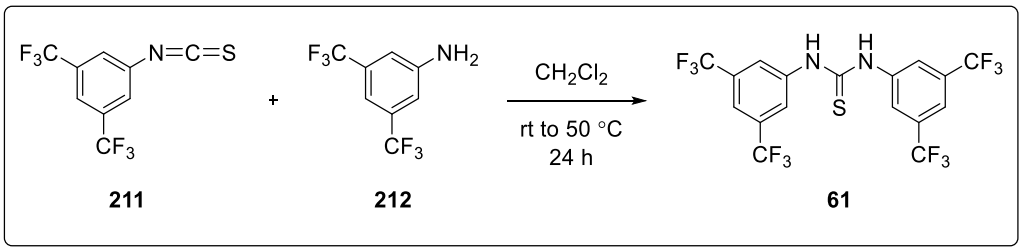


Isolated as a white solid (0.087 g, 78%). Spectral data match the previously reported values.[190]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (br s, 2H), 7.46–7.36 (m, 8H), 7.33–7.28 (m, 2H).

1,3-bis[3,5-bis(Trifluoromethyl)phenyl]thiourea (**61**)

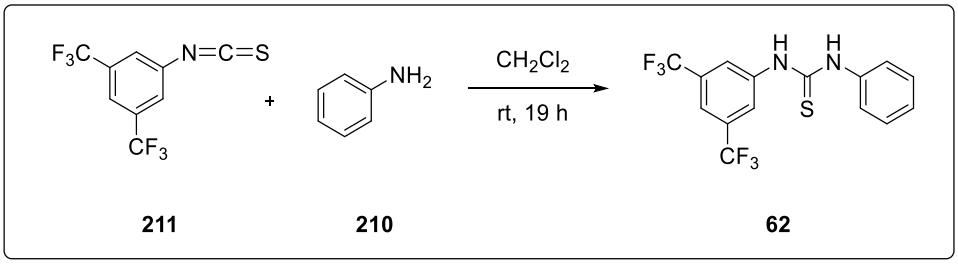
Prepared according to **general procedure C** with the following modifications: a pressure vessel was used instead of a round-bottomed flask and the reaction mixture was heated to 50 °C for 24 hours in an oil bath.



Isolated as a white solid (0.065 g, 46%). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 10.64 (br s, 2H), 8.20 (s, 4H), 7.86 (m, 2H).

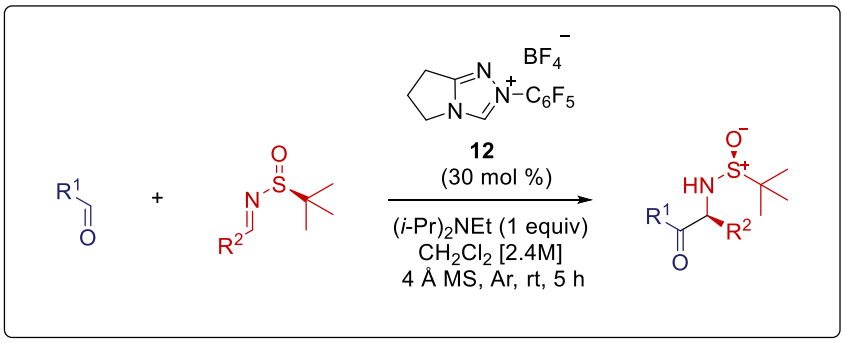
1-[3,5-bis(Trifluoromethyl)phenyl]-3-phenylthiourea (**62**)

Prepared according to **general procedure C**



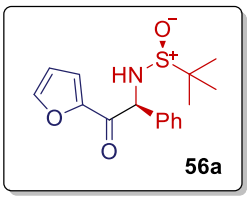
Isolated as a white solid (0.148 g, 84%). **^{1}H NMR** (500 MHz, DMSO-d_6): δ 10.29 (s, 1H), 10.20 (s, 1H), 8.25 (s, 2H), 7.79 (s, 1H), 7.45 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.7 Hz, 2H), 7.19 (t, J = 7.4 Hz, 1H).

General Procedure for NHC–Catalyzed Aza–Benzoin Reactions



The corresponding *tert*-butanesulfinimine (1.0 equiv) and triazolium salt **12** (0.3 equiv), and freshly prepared 4 Å molecular sieves were added to an oven–dried test tube with a Schlenk take–off and fitted with a septum. The vessel was placed under vacuum and re–filled with argon three times to ensure inert atmosphere. The heteroaromatic aldehyde (1.0 equiv) and CH_2Cl_2 [2.4 M] were added sequentially. Lastly (*i*-Pr)$_2$NEt (1.0 equiv) was added and the septum was then quickly exchanged for a plastic stopper. The reaction mixture was stirred at room temperature for 5 hours. The crude reaction mixture was quenched by addition of 1M HCl (2 mL) and CH_2Cl_2 (2 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 2 mL) and dried over Na_2SO_4. The crude product was purified by column chromatography to afford the corresponding aza–benzoin product.

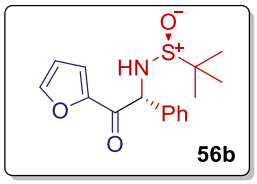
(*S*)-*N*-[(*S*)-2-(Furan-2-yl)-2-oxo-1-phenylethyl]-2-methylpropane-2-sulfinamide (**56a**)



Prepared according to **general procedure D**. Column chromatography (7:1 hexane/acetone) afforded the major product as a white solid (26 mg, 36%). R_f = 0.14 (14% EtOAc in hexane); $[\alpha]_D^{27}$ = +268 (*c* 0.53, $CHCl_3$); melting range: 173.5–174.5 °C; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3264, 3111, 3098, 2964, 1652 1466,

1455, 1396, 1387, 1073, 728; **^{1}H NMR** (500 MHz, $CDCl_3$); δ 7.54 (s, 1H), 7.39 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 3.5 Hz, 1H), 6.47 (br s, 1H), 5.77 (d, *J* = 4.2 Hz, 1H), 5.03 (br d, *J* = 1.8 Hz, 1H), 1.21 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) 184.9, 150.6, 147.2, 137.8, 129.0, 128.6, 128.6, 119.7, 112.8, 63.2, 56.1, 22.7; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{16}H_{19}NO_3SNa$; 328.0978 Found 328.0967.

The minor diastereomer (**56b**) was also isolated as a white solid (5.7 mg, 8%). R_f = 0.17 (14% EtOAc in hexane); **^{1}H NMR** (500 MHz, $CDCl_3$); δ 7.57 (s, 1H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.26–7.24 (m, 1H), 6.49 (br s, 1H), 5.85 (d, *J* = 7.1 Hz, 1H), 4.74 (br d, *J* = 6.9 Hz, 1H), 1.20 (s, 9H).

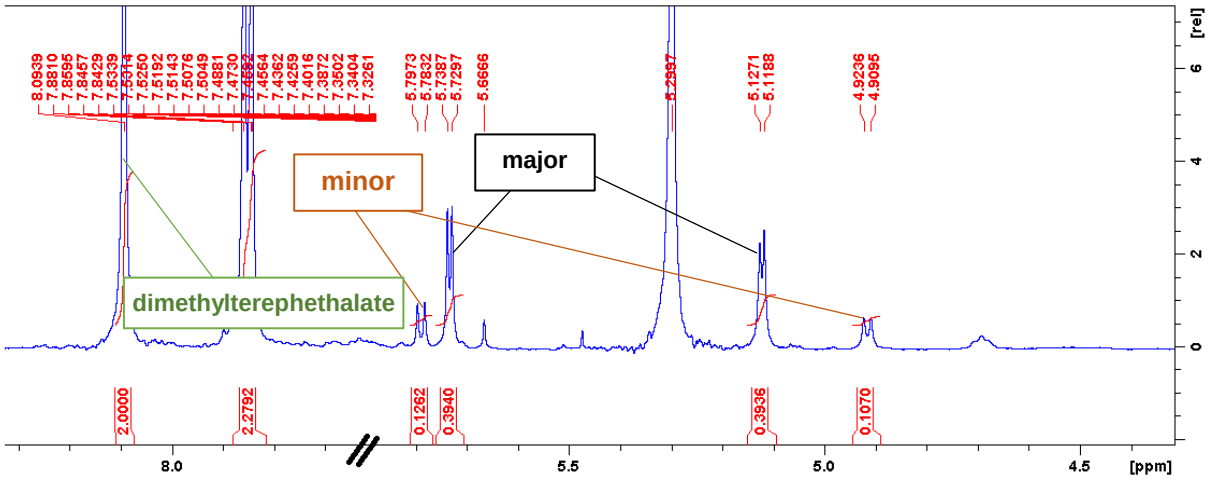


56b

Determination of NMR yields and Diastereomeric Ratios from Crude Reaction Mixtures

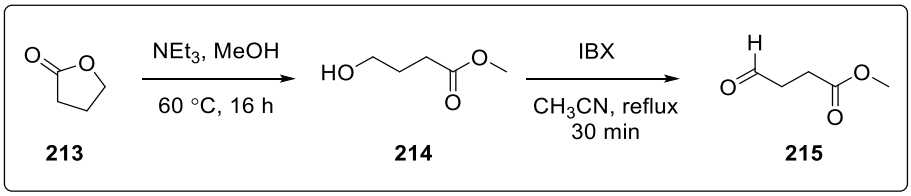
Yields were determined based on ^{1}H NMR spectra by using dimethyl terephthalate (0.5 equiv) as the internal standard. Diastereomeric ratios were determined based on ^{1}H NMR spectra of the crude reaction mixtures. A typical example is shown below:

(*S*)-2-Methyl-*N*-[2-(5-methylfuran-2-yl)-2-oxo-1-phenylethyl]propane-2-sulfinamide (**65**)



7.2. Chemo- and Diastereoselective NHC-Catalyzed Cross-Benzoin Reactions using *N*-Boc-*α*-Amino Aldehydes

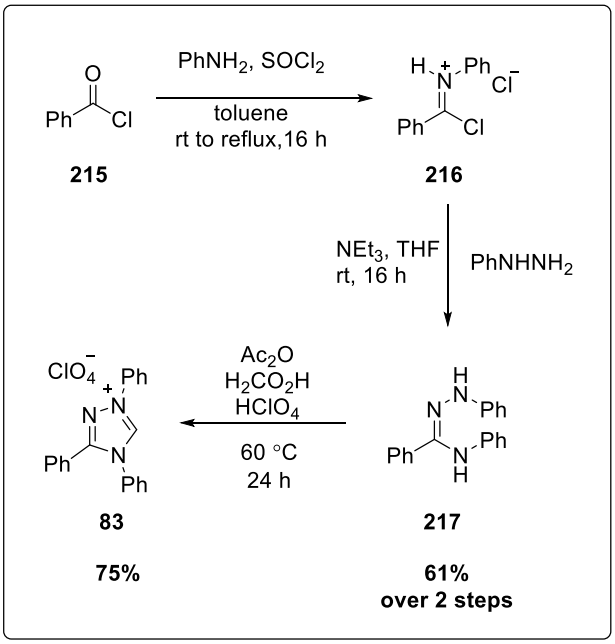
Methyl 4-oxobutanoate (**215**)



Methyl 4-hydroxybutanoate (**214**) was prepared according to a previously reported procedure[191] and carried to the next step without further purification. To a suspension of **214** (7.46 mmol, 1.0 equiv) in CH_3CN (37 mL) was added IBX (11.2 mmol, 1.5 equiv) and heated to reflux. The reaction was monitored *via* TLC analysis. After consumption of starting material (*i.e.* 30 min), the reaction was cooled to room temperature and filtered through a pad of Celite® and then washed with EtOAc (3×10 mL). The resulting solution was concentrated and the crude product was purified by chromatography (5:1 hexane:acetone $R_f = 0.22$) to afford **215** as a clear colourless oil (552 mg, 64%). Spectral data match the previously reported values.[192]

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.82 (s, 1H), 3.70 (s, 3H), 2.80 (t, J = 6.6 Hz, 2H), 2.64 (t, J = 6.7 Hz, 2H).

1,3,4-Triphenyl-4*H*-1,2,4-triazol-1-ium perchlorate (**83**)



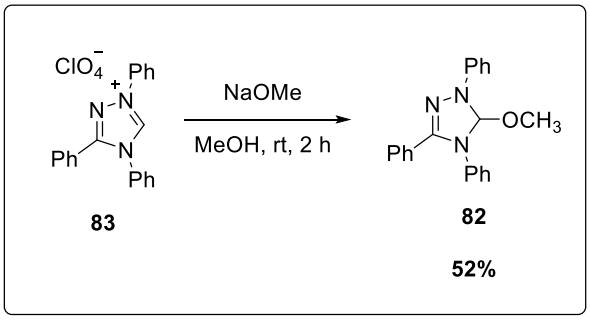
Following a reported procedure,[193] to a solution of benzoyl chloride (**215**) (10 mmol, 1.2 mL) and dry toluene (10 mL) at 0 °C was added aniline (10 mmol, 0.9 mL) dropwise over 10 minutes. The reaction mixture was warmed to room temperature and then heated to reflux for 16 h. After this period, the reaction flask was cooled to room temperature and $SOCl_2$ (30 mmol, 2.2 mL) was added. The slurry was once again heated to reflux for 7 h, then cooled to room temperature, and the volatiles were removed *in vacuo*. The reaction mixture was taken to the next step without further purification.

Crude **216** was dissolved in THF (10 mL) and NEt_3 (15 mmol, 2.1 mL) was added. To this solution, phenylhydrazine (10 mmol, 1.0 mL) was added dropwise over 10 minutes and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was treated with 2% AcOH solution (100 mL) upon which a white solid precipitated. The slurry was filtered and the cake was sequentially washed with water (10 mL) and methanol (10 mL) to yield the

corresponding *N*,*N'*-diphenylbenzohydrazonamide (**217**) (1.76 g, 61% over two steps). Spectral data match the previously reported values.[194] **^{1}H NMR** (500 MHz, DMSO-d_6): δ 9.15 (s, 1 H), 8.02 (s, 1H), 7.59 (d, *J* = 7.1 Hz, 2H), 7.38–7.24 (m, 3H), 7.24–7.04 (m, 6H), 7.78–7.68 (m, 2H), 6.60 (d, *J* = 7.9 Hz, 2H).

A round-bottomed flask containing Ac_2O (10 mL) and H_2CO_2H (5 mL) was stirred at 60 °C for 15 minutes and cooled to room temperature. To this mixture, **217** (6.14 mmol, 1.76 g) was added in one portion and the reaction mixture was stirred at room temperature for an additional 24 h. The volatiles were removed *in vacuo* and the resulting slurry was treated with $HClO_4$ (35% aqueous solution) and stirred at room temperature for additional 2 hours. To the crude reaction mixture was added water (5 mL) and the white precipitate was filtered. The cake was washed sequentially with H_2O (10 mL), MeOH (10 mL), and Et_2O (10 ml). The white crystals were collected and dried under reduced pressure to afford **83** as a white solid (1.74 g, 75%). Spectral data match the previously reported values.[193] **^{1}H NMR** (500 MHz, DMSO-d_6): δ 11.34 (s, 1H), 8.09 (d, *J* = 8.2 Hz, 2H), 7.78 (t, *J* = 7.8 Hz, 2H), 7.75–7.67 (m, 6H), 7.67–7.60 (m, 1H), 7.54 (d, *J* = 4.5 Hz, 4H).

5-methoxy-1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazole (**82**)

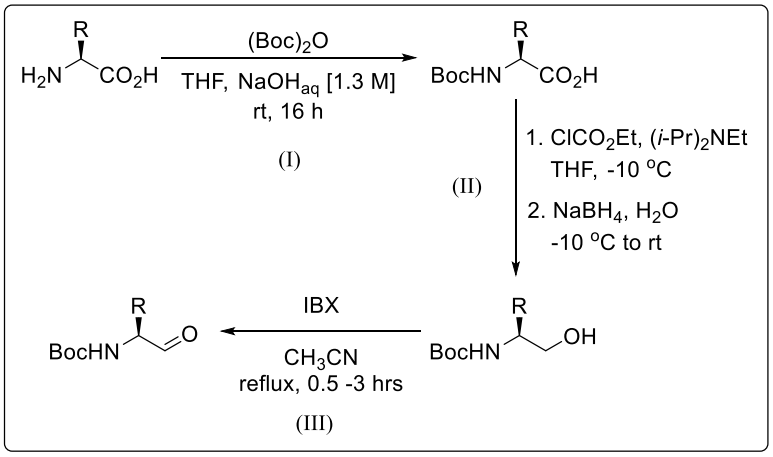


Following a reported procedure,[193] To a stirring solution of **83** (1.30 mmol, 0.500 g) and methanol (8 mL), a solution of NaOMe in methanol (30% w/w, 0.34 mL) was added. The reaction mixture was stirred for 2 hours at room temperature and the resulting slurry was filtered and

washed with cold methanol (5 mL). The crude was recrystallized using methanol to afford **82** as a white solid (0.223 g, 52%). Spectral data match the previously reported values.[193] **^{1}H NMR** (500 MHz, DMSO-d_6): δ 7.68–7.58 (m, 4H), 7.33–7.22 (m, 3H), 7.03–6.98 (m, 4H), 6.95–6.86 (m, 3H), 6.85–6.78 (m, 1H), 6.58 (s, 1H), 3.02 (s, 3H), 3.00 (br s, 1H).

Synthesis of *N*-Boc-*α*-Amino Aldehydes

General Procedure A



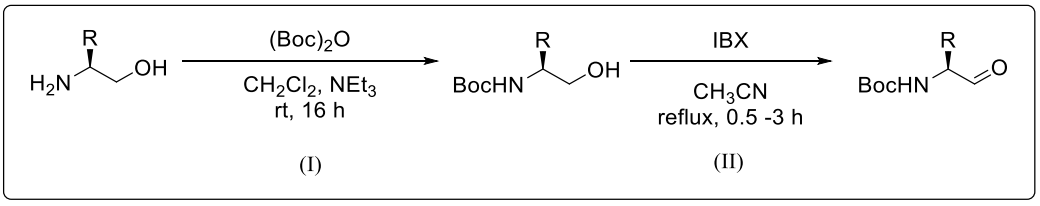
A (I): Using a modified procedure from Nair and co–workers,[195] the corresponding amino acid (1.0 equiv) was suspended in THF [0.4 M] and an aqueous solution of NaOH (3.0 equiv [1.3 M]) was added to this suspension at 0 °C. This is followed by the addition of Boc_2O (1.1 equiv). The ice bath was removed and the mixture was stirred overnight at ambient temperature. After 16 hours, the reaction was cooled to 0 °C and acidified to pH=3 using HCl_{aq} [1 M]. The reaction mixture was extracted with ethyl acetate (×3) and the organic layers were combined and dried over anhydrous $MgSO_4$. The resulting suspension was filtered and concentrated *in vacuo*. Depending on the ratio of impurities to the product, the crude product was either taken to the next step without further purification or was purified by chromatography using a mixture of ethyl acetate and hexanes to afford the desired *N*-Boc-amino acid.

A (II): The reduction of the corresponding amino acids was accomplished by using a modified procedure by Yudin and co–workers [196] The corresponding *N*-Boc amino acid was dissolved in THF [1 M] and cooled to –10 °C. To this solution was added *N*,*N*–diisopropylethylamine (1.0

equiv) followed by ethyl chloroformate (1.0 equiv). The mixture was stirred at this temperature for 15 minutes and the suspension was filtered and washed with THF (×3). The filtrate was once again cooled to –10 °C and $NaBH_4$ (1.5 equiv) was added in one portion followed by addition of water [3 M]. The mixture was stirred for an additional 30 minutes and the crude product was extracted with EtOAc (×3). The combined organic layers were washed with brine and dried over $MgSO_4$. The resulting solution was concentrated *in vacuo* and purified by FCC using a mixture of EtOAc and hexanes to afford the desired *N*-Boc-amino alcohol.

A (III): The oxidation process was carried out according to the previously reported procedure.[6] IBX (1.5 equiv) was added to a solution of *N*-Boc–amino alcohol (1.0 equiv) in acetonitrile [0.2 M]. The reaction was monitored for complete consumption of starting material (typical reaction time = 45 minutes). After completion, the contents were cooled to room temperature, filtered through a pad of Celite® and washed with EtOAc (×3). The resulting solution was concentrated and purified by chromatography.

General Procedure B



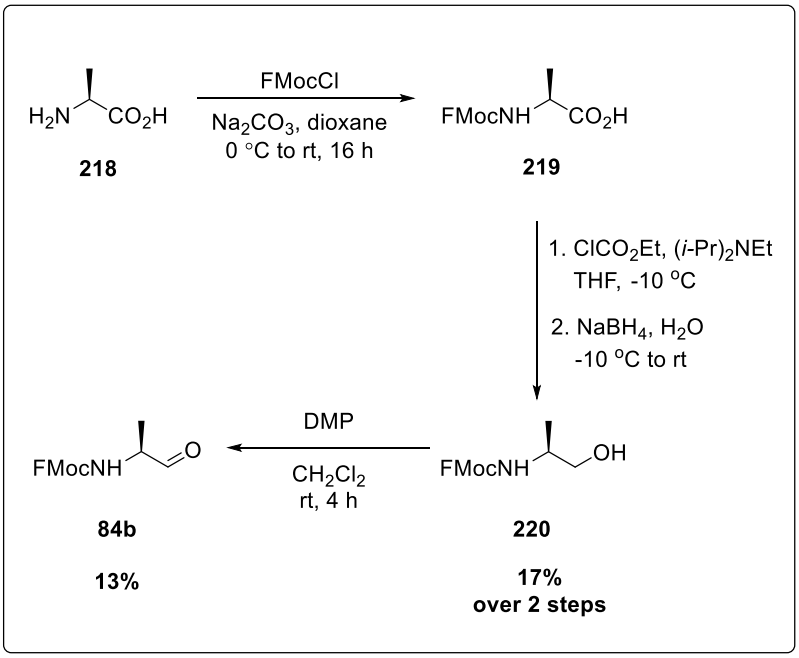
B (I): The Boc protection of amino alcohols was accomplished using a modified procedure.[197]

To a solution of amino alcohol (1.0 equiv) in CH_2Cl_2 [0.6 M] was added triethylamine (1.1 equiv) at room temperature. To this solution was added di-*tert*-butyl dicarbonate (Boc_2O) (1.1 equiv) and stirred at ambient temperature for 16 hours. The reaction was quenched with addition of HCl [1

M] and extracted with CH_2Cl_2 (×3). The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography using a mixture of EtOAc and hexanes.

B (II): The oxidation process was carried out according to the previously reported procedure.[6] IBX (1.5 equiv) was added to a solution of *N*-Boc-amino alcohol (1.0 equiv) in acetonitrile [0.2 M]. The reaction was monitored for complete consumption of starting material (typical reaction time = 45 minutes). After completion, the contents were cooled to room temperature, filtered through a pad of Celite® and washed with EtOAc (×3). The resulting solution was concentrated and purified by chromatography.

(9*H*-Fluoren-9-yl)methyl (*S*)-(1-oxopropan-2-yl)carbamate (**84b**)



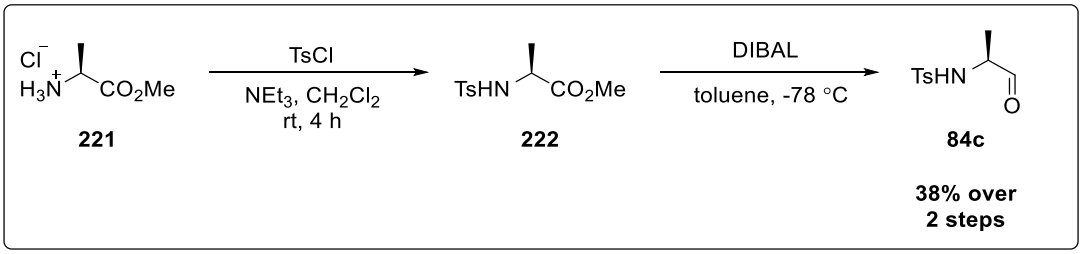
Based on a reported procedure,[198] to a stirred solution of L-alanine (**218**) (10.6 mmol, 2.00 g), Na_2CO_3 (aq) (10% *w*/*w*, 28 ml), and dioxane (40 mL) at 0 °C was added FmocCl (12.7 mmol, 3.29

g). The reaction mixture was stirred at room temperature for 16 h. The crude mixture was acidified with [1M] HCl (pH = 2) and the precipitate was collected. The crude reaction mixture was taken to next step without further purification.

The reduction of the corresponding acid was accomplished using the **General Procedure A(II)**. Compound **219** was isolated by column chromatography (1:1 hexane/EtOAc, R_f =0.17) as a white solid (0.437 g, 17% over two steps). Spectral data match the previously reported values.[196]

According to a modified literature report,[106] to a solution of **219** (1.40 mmol, 0.417 g) in CH_2Cl_2 (9 mL) was added DMP (2.95 mmol, 1.46 g) in one portion. The reaction mixture was stirred at room temperature for 2 h. A 1:1 mixture of sat. $NaHCO_3$(aq) (5 mL) and sat. Na_2SO_3 (aq) (5 mL) was added to the reaction mixture and stirred for 2 hours at room temperature. Solids were filtered and washed sequentially with sat. $NaHCO_3$(aq) (10 mL) and sat. Na_2SO_3(aq) (10 mL) to afford the title compound as a white solid (0.054 g, 13%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.57 (s, 1H), 7.77 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 5.37 (br s, 1H), 4.48–4.39 (m, 2H), 4.36–4.29 (m, 1H), 4.27–4.20 (m, 1H), 1.40 (d, *J* = 7.2 Hz, 2H).

(*S*)-4-Methyl-N-(1-oxopropan-2-yl)benzenesulfonamide (**84c**)

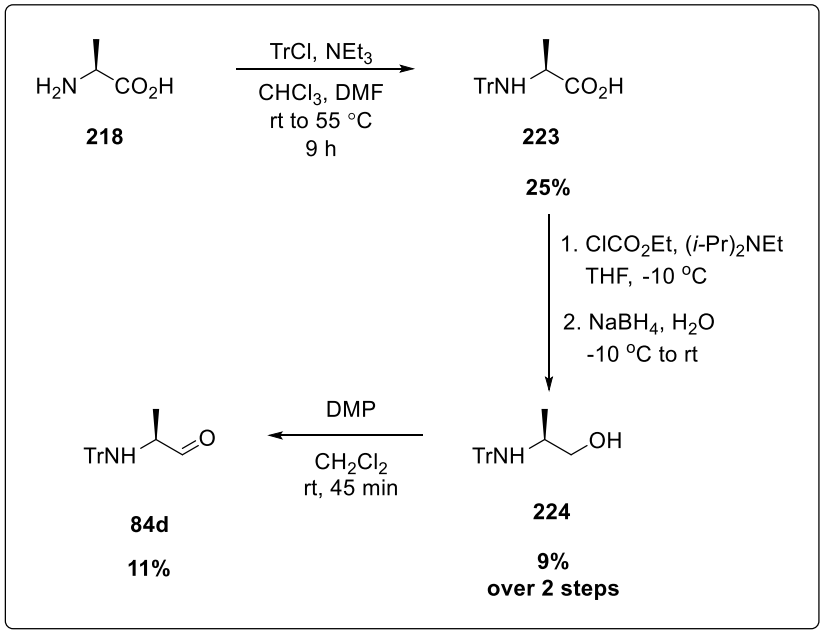


Following a known literature procedure,[199] to a suspension of L-alanine methyl ester hydrochoride (**221**) (7.16 mmol, 1.00 g) in CH_2Cl_2 (70 mL) was added NEt_3 (21.5 mmol, 3.0 mL) followed by TsCl (7.16 mmol, 1.37 g). The reaction mixture was stirred at room temperature for 4 hours and quenched with the addition of 1M HCl (aq) (pH=2). The resulting mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were washed with sat. $NaHCO_3$ (aq) (3 ×100 mL) and dried on $MgSO_4$. The crude reaction mixture was concentrated *in vacuo* and **222** along with small amounts of unknown impurities were carried to the next step without further purification.

To dry toluene (3.9 mL) was added crude **222** (1.0 g) in toluene (3 mL) and cooled to -78 °C. This mixture was stirred for 30 min at this temperature and DIBAL-H (1.0 M in hexane, 9.47 mmol, 9.5 mL) was added to the reaction slowly by maintaining -78 °C. After consumption of the starting material as judged by TLC analysis, the reaction was quenched with careful addition of MeOH (5 mL) and warmed gradually to room temperature. The reaction mixture was treated with Rochelle's salt (aq) (0.5 M,10 mL) and stirred vigorously at room temperature for an additional 1 hour. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried on $MgSO_4$. Removal of volatiles followed by chromatography (2:1 hexane/EtOAc, R_f =0.20) afforded the title compound as a white solid (0.354 g, 38% over two steps). Spectral data match the previously reported values.[200] ^{1}**H NMR** (500 MHz, $CDCl_3$): δ 9.46 (s, H), 7.76 (d, *J* = 8.2 Hz,

2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.93 (d, *J* = 6.1 Hz, 1H), 3.84 (dq, *J* = 7.1, 6.9 Hz, 1H), 2.41 (s, 3H), 1.26 (d, *J* = 7.4 Hz, 3H).

(*S*)-2-(Tritylamino)propanal (**84d**)



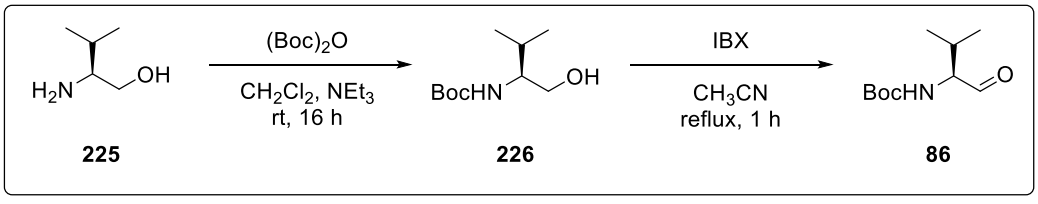
Following a modified reported procedure,[201] to a solution of Ph_3CCl (49.4 mmol, 13.8 g) in $CHCl_3$:MeOH (2:1, 155 mL) was added L-alanine (**218**) (22.5 mmol, 2.00 g) at room temperature. The reaction mixture was stirred at this temperature for an additional 2 h and NEt_3 (89.8 mmol, 12.5 mL) in $CHCl_3$:MeOH (2:1, 25 mL) was added dropwise to the reaction over 45 minutes. Stirring was continued for 2 hours before methanol (110 mL) was added, the reaction vessel was equipped with a condenser and heated to 55 °C for 2 hours. The volatiles were removed under reduced pressure and the crude reaction mixture was added Et_2O (50 mL) and washed sequentially with citric acid (aq) (10% *w*/*w*, 3 × 50 mL) and water (2 × 50 mL). The organic layer was dried using $MgSO_4$ and volatiles were removed *in vacuo*. Column chromatography (3:2 hexane/EtOAc,

R_f =0.16) afforded **223** along with unknown impurities (1.88 g). This mixture was taken to the next step without further purification

The reduction of the corresponding acid was accomplished using the **General Procedure A(II)**. Isolated by column chromatography (3:1 hexane/EtOAc, R_f =0.30) as a white solid (0.162 g, 9% over 2 steps). Spectral data match the previously reported values.[196]

According to a modified literature report,[106] to a solution of **223** (0.511 mmol, 0.162 g) in CH_2Cl_2 (2 mL) was added DMP (1.07 mmol, 0.455 g) in one portion. The reaction mixture was stirred at room temperature for 45 min. A 1:1 mixture of sat. $NaHCO_3$(aq) (2 mL) and sat. Na_2SO_3(aq) (2 mL) was added to the reaction mixture and stirred for 2 hours at room temperature. Solids were filtered and washed sequentially with $NaHCO_3$(aq) (5 mL) and sat. Na_2SO_3(aq) (5 mL) and the crude reaction mixture was dried over Na_2SO_4. Column chromatography (6:1 hexane:EtOAc, R_f =0.25) followed by re-crystallization in EtOAc/hexane afforded the title compound as a white solid (0.017 g, 11%). Spectral data match the previously reported values.[202] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.02 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 6H), 7.31–7.26 (m, 6H), 7.20 (t, *J* = 7.2 Hz, 3H), 3.35 (dq, *J* = 7.9, 7.1 Hz, 1H), 2.69 (d, *J* = 7.6 Hz, 1H), 1.06 (d, *J* = 7.2 Hz, 3H).

(*S*)–*tert*–Butyl (3–methyl–1–oxobutan–2–yl)carbamate (**86**)

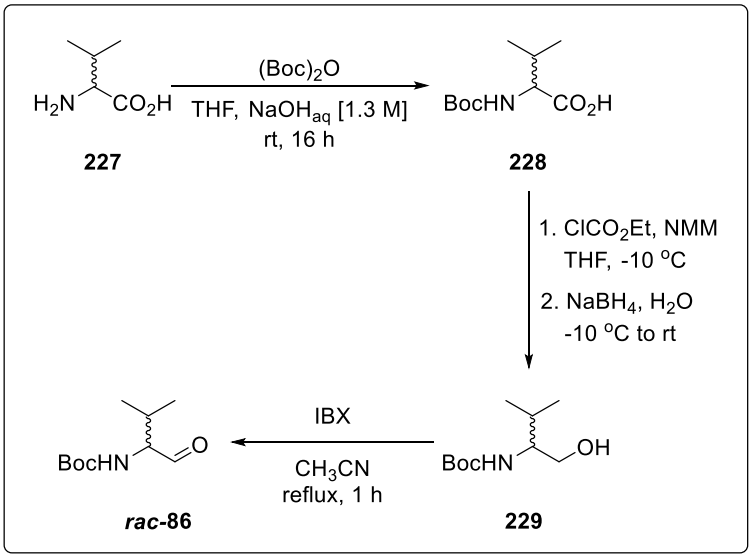


[(*S*)–*tert*–Butyl 1–hydroxy–3–methylbutan–2–yl]carbamate (*N*–Boc–L–valinol) (**226**) was prepared according to **general procedure B (I)**. Isolated by column chromatography (3:1

hexane/EtOAc, R_f =0.22) as a colorless oil (2.85 g, 72%). Spectral data match the previously reported values.[194] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.62 (br s, 1 H), 3.74–3.67 (m, 1 H), 3.64–3.57 (m, 1 H), 3.48–3.39 (m, 1 H), 2.26–2.19 (m, 1 H), 1.88–1.79 (m, 1H), 1.45 (s, 9 H), 0.96 (d, *J* = 5.7 Hz, 3H), 0.93 (d, *J* = 5.7 Hz, 3H).

(*S*)–*tert*–Butyl (3–methyl–1–oxobutan–2–yl)carbamate (*N*–Boc–L–valinal) (**86**) was prepared according to **general procedure B (II).** Isolated by column chromatography (6:1 hexane/EtOAc, R_f = 0.30) followed by recrystallization from hexane overnight at –20 °C afforded the title compound as a white powder (2.44 g, 83%). Spectral data match the previously reported values.[203] **^{1}H NMR** (600 MHz, $CDCl_3$): mixture of rotamers; δ 9.65 (s, 1 H), 5.07 (br s, 0.9H), 4.76 (br s, 0.1H), 4.25 (br s, 0.9H), 3.95 (br s, 0.1H), 2.35–2.23 (m, 1H), 1.45 (s, 9 H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H).

rac-tert-Butyl (3-methyl-1-oxobutan-2-yl)carbamate (***rac*-86**)



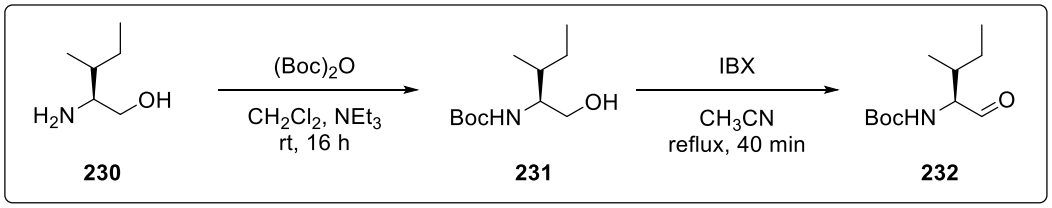
rac-2-[(*tert*-Butoxycarbonyl)amino]-3-methylbutanoic acid (*rac*-*N*-Boc-L-valine) (**228**) was prepared according to **general procedure B (I).** The crude mixture was carried to next step without further purification.

rac-tert-Butyl (1-hydroxy-3-methylbutan-2-yl)carbamate (*rac*-*N*-Boc-L-valinol) (**229**) was prepared according to a modified **general procedure B (II)** by replacing $(i\text{-Pr})_2$NEt with 4-methyl morpholine (NMM). Isolated by recrystallization from a mixture of EtOAc/hexane at -20 °C overnight as a white solid (1.66 g, 89%).

rac-tert-Butyl (3-methyl-1-oxobutan-2-yl)carbamate (*rac*-*N*-Boc-L-valinal) (***rac*-86**) was prepared according to **general procedure B (II).** Isolated by column chromatography (5:1 hexane/EtOAc, R_f = 0.24) followed by recrystallization from EtOAc/hexanes overnight at –20 °C as a white solid (700 mg, 71%). Spectral data match the previously reported values.[203]

^{1}H NMR (600 MHz, $CDCl_3$): mixture of rotamers; δ 9.65 (s, 0.9H), 9.57 (s, 0.1H), 5.09 (d, *J* = 4.6 Hz, 0.9H), 4.77 (br s, 0.1H), 4.25 (dd, *J* = 7.7, 4.2 Hz, 0.9H), 3.96 (br s, 0.1H), 2.29 (m, 0.9H), 2.20 (m, 0.1H), 1.45 (s, 9 H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H).

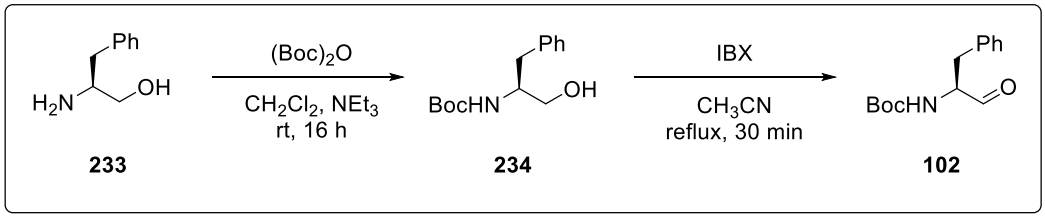
(*S*,*S*)–*tert*–butyl (3–methyl–1–oxobutan–2–yl)carbamate (*N*–Boc–L–isoleucinal) (**232**)



tert–Butyl [(2S,3S)–3–methyl–1–oxopentan–2–yl]carbamate (*N*–Boc–L–isoleucinol) (**230**) was prepared according to **general procedure B (I).** Isolated by column chromatography (3:1 hexane/acetone, R_f =0.21) as a colorless oil (732 mg, 79%). Spectral data match the previously reported values.[204] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.65 (br s, 1H), 3.74–3.67 (m, 1H), 3.66–3.56 (m, 1H), 3.51 (br, s, 1H), 2.31 (br s, 1H), 1.62–1.55 (m, 1H), 1.54–1.47 (m. 1H), 1.45 (s, 9), 1.20–1.10 (m, 1H), 0.92 (d, *J*= 6.4 Hz, 3H), 0.91 (t, *J*= 7 Hz, 3H).

(*S*,*S*)–*tert*–Butyl (3–methyl–1–oxobutan–2–yl)carbamate (*N*–Boc–L–isoleucinal) (**231**) was prepared according to **general procedure B (II).** Isolated by column chromatography (9:1 hexane/EtOAc, R_f =0.30) colourless viscous oil (276 mg, 70%). Spectral data match the previously reported values.[205] **^{1}H NMR** (500 MHz, $CDCl_3$); mixture of rotamers; δ 9.66 (s, 1H), 5.11 (br s, 0.9H), 4.78 (br s, 0.1H), 4.29 (br s, 0.9H), 4.01 (br s, 0.1H), 2.02 (br s, 1H), 1.52–1.45 (m, 1H), 1.45 (s, 9 H), 1.33–1.21 (m, 1H) 0.98 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 7.4 Hz, 3H).

(*S*)–*tert*–Butyl (1–oxo–3–phenylpropan–2–yl)carbamate (*N*–Boc–L–phenyl–alaninal) (**102**)



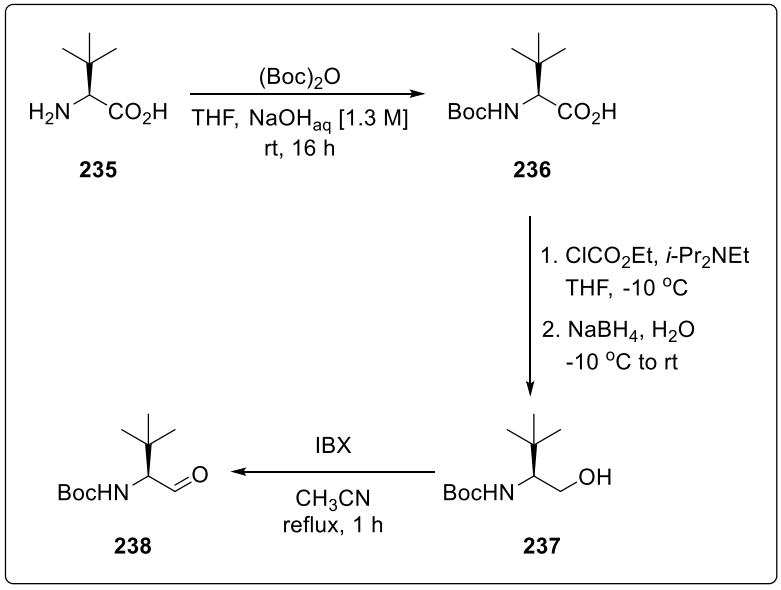
(*S*)–*tert*–Butyl (1–hydroxy–3–phenylpropan–2–yl)carbamate (*N*–Boc–L–phenylananinol) (**233**) was prepared according to **general procedure A(I).** Isolated by re–crystallization from a mixture of EtOAc: hexanes at –20 °C as off white solid (680 mg, 82%). Spectral data match the previously reported values.[206]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.28 (m, 2H), 7.25–7.20 (m, 3H), 4.71 (br s, 1H), 3.87 (br s, 1H), 3.71–3.63 (m, 1H), 3.58–3.51 (m, 1H), 2.84 (d, *J* = 7.1, 2H), 2.22 (br s, 1H), 1.42 (s, 9 H).

(*S*)–*tert*–Butyl (1–oxo–3–phenylpropan–2–yl)carbamate (*N*–Boc–L–phenylalaninal) (**102**) was prepared according to **general procedure A (II).** Isolated by column chromatography (5:1 hexanes:EtOAc, R_f = 0.2) followed by recrystallization from a mixture of EtOAc/hexane overnight at –20 °C as a white powder (343 mg, 51%). Spectral data match the previously reported values.[207]

^{1}H NMR (500 MHz, $CDCl_3$); mixture of rotamers; δ 9.64 (s, 1H), 7.34–7.28 (m, 2H), 7.27–7.24 (m, 1H), 7.19–7.15 (d, *J* = 7.1, 2H), 5.03 (br s, 0.9H), 4.73 (br s, 0.1H), 4.47–4.39 (m, 0.9H), 4.22–4.15 (m, 0.1H), 3.12 (d, *J* = 6.4 Hz, 1.8H), 2.99–2.91 (m, 0.2H), 1.44 (s, 9H).

(*S*)–*tert*–Butyl (3,3–dimethyl–1–oxobutan–2–yl)carbamate (*N*–Boc–*tert*–leucinal) (**238**)



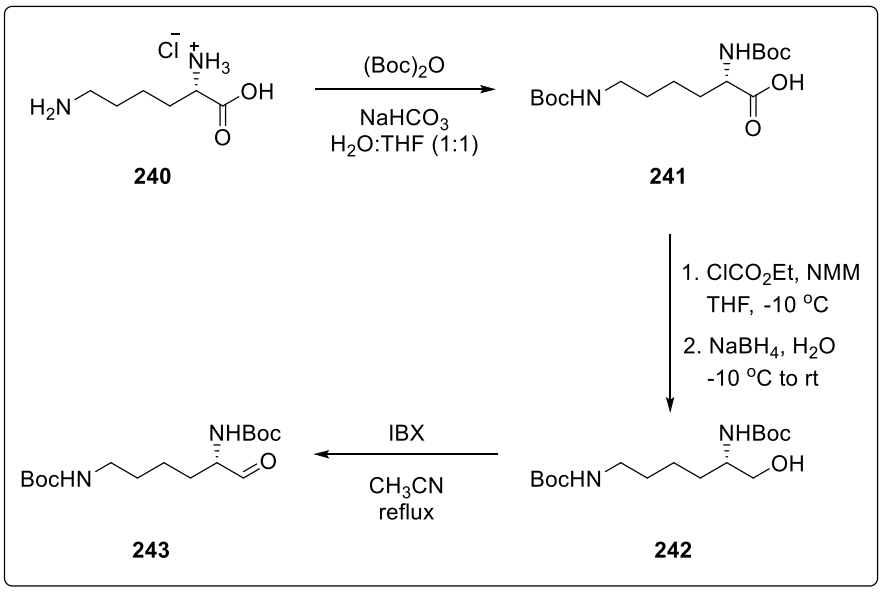
(S)–2–[(*tert*–Butoxycarbonyl)amino]–3,3–dimethylbutanoic acid (*N*–Boc–L–*tert*–leucine) (**236**) was prepared according to general procedure **A (I)**. The crude reaction mixture was carried to next step without further purification.

(*S*)–*tert*–Butyl (1–hydroxy–3,3–dimethylbutan–2–yl)carbamate (*N*–Boc–L–*tert*–leucinol) (**237**) was prepared according to general procedure **A (II)**. Isolated a mixture of product and unknown impurity by chromatography (4:1 hexanes/EtOAc, R_f =0.2) as a white solid. This mixture was carried to the next step without further purification.

(*S*)–*tert*–butyl (3,3–dimethyl–1–oxobutan–2–yl)carbamate (*N*–Boc–*tert*–leucinal) (**238**) was prepared according to **general procedure A (III).** Isolated by column chromatography (6:1 Hex/EtOAc, R_f = 0.28) followed by re–crystallization from a mixture of EtOAc:hexanes overnight at –20 °C as a white needle–like crystals (95 mg, 6% yield over 3 steps). Spectral data match the previously reported values.[208]

^{1}H NMR (600 MHz, $CDCl_3$); mixture of rotamers; δ 9.83 (s, 0.8H), 9.71 (s, 0.2H), 5.14 (s, 0.8H), 4.82 (s, 0.2H), 4.42 (d, *J* = 10.2 Hz, 0.2H), 3.95 (d, *J* = 8.6 Hz, 0.8H), 1.46 (s, 2.7H), 1.44 (s, 7.3H), 1.06 (s, 2.7H), 1.05 (s, 7.3H).

(*S*)-di-*tert*-Butyl (6-oxohexane-1,5-diyl)dicarbamate [N_α,N_ε-Bis(Boc)lysinal] (**243**)



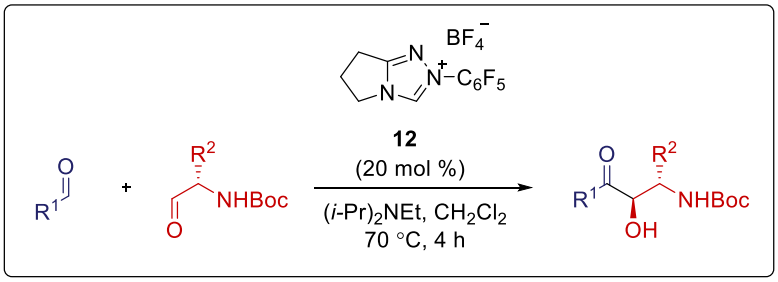
(*S*)-2,6-bis[(*tert*-Butoxycarbonyl)amino)hexanoic acid [Boc-Lys(Boc)-OH] (**241**) was prepared according to a literature procedure.[209] The crude reaction mixture was carried to next step without further purification.

(*S*)-di-*tert*-Butyl (6-hydroxyhexane-1,5-diyl)dicarbamate [N_α,N_ε-Bis(Boc)lysinol] (**242**) was prepared according to a modified **general procedure B (II)** by replacing *i*-Pr_2NEt with 4-methyl morpholine (NMM). Column chromatography (3:1 hexanes: EtOAc, R_f = 0.20) afforded the title compound as a viscous colourless oil (99% purity, clalcd. 0.547g, 64% over 2 steps). Spectral data match the previously reported values.[210]

^{1}H NMR (500 MHz, $CDCl_3$); δ 4.76 (br s, 1H), 4.56 (br s, 1H), 3.71–3.51 (m, 3H), 3.24–3.14 (m, 1H), 3.13–3.02 (m, 1H), 2.52 (br s, 1H), 1.64–1.56 (m, 1H), 1.53–1.47 (m, 2H), 1.45 (s, 9H), 1.44 (s, 9H), 1,41–1.30 (m, 2H).

(*S*)-di-*tert*-Butyl (6-oxohexane-1,5-diyl)dicarbamate [N_α,N_ε-Bis(Boc)lysinal] (**243**) was prepared according to **general procedure B (III).** Isolated by column chromatography (5:1 hexane:EtOAc, R_f = 0.16) followed by re–crystallization from a mixture of EtOAc:hexanes overnight at –20 °C as a white crystals (202 mg, 68%). Spectral data match the previously reported values.[211] **^{1}H NMR** (500 MHz, $CDCl_3$); Mixture of rotamers; δ 8.57 (s, 1H), 5.19 (s, 0.9H), 4.83 (s, 0.1H), 4.58 (s, 0.9H), 4.19 (ap d, *J* = 4.2 Hz, 0.9H), 3.93 (s, 0.1H), 3.21–2.99 (m, 2H), 1.96–1.75 (m, 1H), 1.68–1.55 (m, 1H), 1.56–1.47 (m, 2H), 1.45 (s, 9H), 1.44 (s, 9H), 1,42–1.34 (m, 2H).

General Procedure for NHC–Catalyzed Cross–Benzoin Reactions

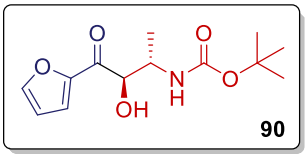


The corresponding *N*–Boc–amino aldehyde (0.24 mmol, 1.0 equiv) and triazolium salt **12** (0.048 mmol, 0.2 equiv) were added to an oven–dried test tube with a Schlenk take–off and fitted with a septum. The vessel was placed under vacuum and re–filled with argon three times to ensure inert atmosphere. The aliphatic or hetereoaromatic aldehyde (0.72 mmol, 3.0 equiv) and CH_2Cl_2 (0.3 mL, 0.8 M) were added sequentially. Lastly (*i*-Pr)$_2$NEt (0.48 mmol, 2.0 equiv) was added and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re–established

the flask was sealed and heated to 70 °C for 4 hours. (WARNING: when performed on a larger scale, it is advised to use a water condenser instead of a cold finger to avoid the small pressure buildup that occurs when using a cold finger. The crude reaction mixture was cooled to room temperature and quenched by addition of 1M HCl (2 mL). The reaction crude was extracted with CH_2Cl_2 (3 × 2 mL) and dried over Na_2SO_4. The reaction mixture was purified by column chromatography followed by preparative thin layer chromatography to afford the corresponding cross–benzoin product.

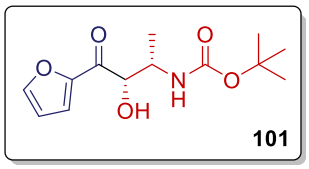
tert-Butyl [(*2S*,*3R*)-4-(furan-2-yl)-3-hydroxy-4-oxobutan-2-yl]carbamate (**90**)

Column chromatography (4:1 hexanes: EtOAc) followed by PTLC (7:1 toluene: EtOAc) afforded the major product as a white solid (26 mg, 41%). Melting range = 136.2–136.8 °C, R_f = 0.20 (20% acetone in hexanes); $[\alpha]_D^{25\ °C}$ = +82 (*c* 1.3, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3435, 3375, 2977, 2932, 1703, 1680, 1571, 1502, 1466,1366, 1246, 1166, 1109, 1059, 768; **^{1}H NMR** (500 MHz, $CDCl_3$) Mixture of rotamers: δ 7.65 (s, 1H), 7.31 (br s, 1H,), 6.59 (br s, 1H), 4.73 (s, 1H), 4.66 (br d, *J* =8.3 Hz 1H), 4.46–4.33 (m, 1H), 3.80 (br s, 1H), 1.36 (d, *J* = 6.9 Hz, 3H), 1.33 (s, 7.8H), 1.18 (s, 1.2H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 188.2, 155.2, 150.7, 147.2, 118.9, 112.9, 79.5, 76.6, 50.0*, 49.1, 28.3, 28.0*, 19.7*, 19.0; **HRMS** (CI) *m/z*: $[M+1]^+$ Calcd for $C_{13}H_{20}NO_5$ 270.1342; Found 270.1337.



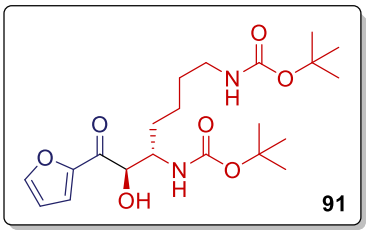
The minor diastereomer was also isolated, along with an unidentified impurity:

tert-Butyl [(*2S*,*3S*)-4-(furan-2-yl)-3-hydroxy-4-oxobutan-2-yl]carbamate (**101**)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H). 7.65 (d, *J* = 3.4 Hz, 1H), 6.62 (d, *J* = 1.9 Hz, 1H), 5.07–4.90 (m, 2H), 4.28 (ap t, *J* = 6.8 Hz, 1H), 3.68 (br s, 1H), 1.47 (s, 9H), 0.93 (t, *J* = 5.3 Hz, 3H).

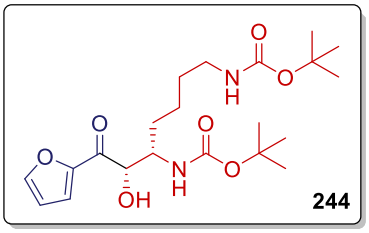
di-*tert*-butyl [(5*S*,6*R*)-7-(furan-2-yl)-6-hydroxy-7-oxoheptane-1,5-diyl)dicarbamate (**91**)



Column chromatography (3:1 hexanes:Acetone R_f = 0.15 (25% acetone in hexanes) followed by PTLC (7:3 toluene: EtOAc) afforded varying mixtures (6:1–9:1) of the two diastereomers (major= 57.4 mg, minor=33.6 mg, 89%). An analytically pure sample of the major diastereomer was prepared by subjecting a 9:1 mixture of diastereomers to PTLC (6:2:1:1 toluene:hexane:EtOAc:acetone) as a yellow oil; $[\alpha]_D^{26\ °C}$ = -105 (*c* 0.24, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3364, 2977, 2932, 1685, 1570, 1391, 1366, 1249,. 1170,768 ; **^{1}H NMR** (500 MHz, $CDCl_3$) Mixture of rotamers: δ 7.66 (s, 1H), 7.31 (s, 0.1H), 7.30 (s, 0.9H), 6.60 (s, 0.1H), 6.59 (s, 0.9H), 4.81 (d, *J* = 6.9 Hz, 0.9H), 4.75 (s, 0.1H), 4.62 (d, *J* = 10 Hz, 0.9H) 4.56 (br s, 1H), 4.33 (d, *J* = 11 Hz, 0.1H), 4.29–4.17 (m, 1H), 3,81 (d, *J* = 5.3 Hz, 0.9H), 3.78–3.74 (m, 0.1H), 3.23–3.05 (m, 2H), 1.81–1.65 (m, 2H), 1.61–1.52 (m, 2H), 1.52–1.46 (m, 2H), 1.44 (s, 9H), 1.32 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 188.2, 156.2, 155.5, 150.6, 147.3, 118.9, 112.9, 79.5, 75.3, 53.0, 40.5, 32.9, 29.8, 28.6, 28.3, 27.9*, 23.4.; **HRMS** (TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{21}H_{34}N_2O_7Na$ 449.2258; Found 449.2260.

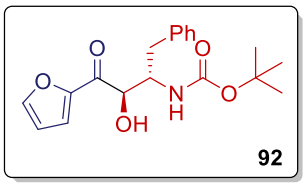
The minor diastereomer was also isolated along with an unknown impurity:

di-*tert*-Butyl [(5*S*,6*S*)-7-(furan-2-yl)-6-hydroxy-7-oxoheptane-1,5-diyl]dicarbamate (**244**)



^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers: δ 7.72 (s, 1H), 7.65 (br s, 1H), 7.63 (br s, 1H), 4.97 (br s, 2H), 4.50 (br s, 1H), 4.15 (ap t, *J* = 10 Hz, 1H), 1.69 (br s, 1H), 3.10–2.90 (m, 2H), 1.47 (s, 9H), 1.44–1.41 (m, 10H), 1.39–1.26 (m, 3H), 1.25–1.14 (m, 1H), 1.14–1.03 (m, 1H).

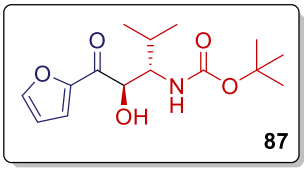
tert-Butyl [(*2S*,*3R*)-4-(furan-2-yl)-3-hydroxy-4-oxo-1-phenylbutan-2-yl]carbamate (**92**)



Column chromatography (7:1 toluene: EtOAc) afforded an inseparable 3:1 mixture of two diastereomers (60 mg, 73% yield). R_f = 0.23 (14% EtOAc in toluene); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3437, 2977, 2930, 1699, 1570, 1497, 1466, 1391, 1367, 1169, 1018, 912, 883, 764; **^{1}H NMR** (600 MHz, $CDCl_3$) Mixture of two diastereomers and rotamers. Major diastereomer: δ 7.69 (s, 0.2H), 7.69 (s, 0.8H), 7.49–7.39 (m, 4.3H),7.38–7.33 (m, 0.7H), 7.29–7.24 (m, 0.8H), 7.14–7.09 (m, 0.8H), 6.80–6.56 (m, 1H), 4.96 (d, *J* = 9.7 Hz, 0.9H), 4.83–4.74 (m, 1.3H), 4.61–4.52 (m, 1H,), 3.98 (br s, 1H), 3.14 (dd, , *J* = 13.4, 6.2 Hz, 1H,), 3.08 (dd, , *J* = 13.0, 9.6 Hz, 1H,), 1.41 (s, 8.4H), 1.19 (s, 1.6H); Minor diastereomer: δ 7.64 (s, 1H,), 7.61 (d, *J* = 3.3 Hz, 1H,), 7.49–7.39 (m, 1H),7.38–7.19 (m, 3H), 7.24–7.09 (m, 2H), 6.74–6.63 (m, 1H), 5.19 (d, *J* = 9.1 Hz, 1H,), 5.11 (s, 0.9H), 5.06–5.01 (m, 0.1H), , 4.69–4.62 (m, 1H,), 4.06 (s, 1H), 2.82 (dd, , *J* = 14.3, 9.1 Hz, 1H,), 2.71 (dd, , *J* = 14.3, 5.5 Hz, 1H,), 1.48 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) major diastereomer as a mixture of rotamers (minor rotamer indicated by asterisk): δ 188.2, 155.2, 150.1, 147.3, 146.9*,

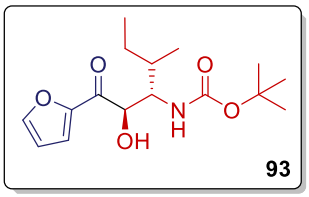
137.9, 129.7, 129.6, 128.7, 126.8, 119.0, 118.8*, 112.7, 112.6, 79.6, 76.1, 73.2, 56.1*, 55.0, 39.9, 39.2, 28.3; minor diastereomer: δ 187.2, 155.6, 150.0, 147.9, 137.1, 129.3. 128.3, 126.5, 120.6, 112.8, 177.36, 79.8, 74.1, 55.3, 34.7, 28.4, 27.8; **HRMS** (TOF) *m/z*: [M+ Na]$^{+}$ Calcd for $C_{19}H_{23}NO_5NO_5$ 368.1468; Found 368.1467.

tert–Butyl [(*2R,3S*)–1–(furan–2–yl)–2–hydroxy–4–methyl–1–oxopentan–3–yl]carbamate (**87**)



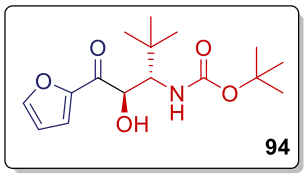
Column chromatography (4:1 hexanes: EtOAc) followed by PTLC (3:1 hexanes: EtOAc) afforded the major product as a colourless oil (52 mg, 73%). R_f = 0.20 (30% acetone in hexanes); $[\alpha]_D^{23\ °C}$ = +65 (*c* 0.8, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3446, 3377, 2973, 1710, 1682, 1469, 1390, 1366, 1172, 1020,769; **^{1}H NMR** (600 MHz, $CDCl_3$) Mixture of rotamers: δ 7.65 (s, 0.2H), 7.64 (s, 0.8H),7.32 (d, *J* = 3.4 Hz, 0.2H), 7.28 (d, *J* = 3.6 Hz, 0.8H), 6.64–6.61 (m, 0.2H), 6.58 (dd, *J* = 3.5, 1.6 Hz, 0.8H), 5.02 (dd, *J* = 5.2, 1.3 Hz, 0.8H), 4.97 (d, *J* = 4.7 Hz, 0.2H), 4.69 (d, *J* = 10.2 Hz, 0.8H), 4.47 (d, *J* = 10.5 Hz, 0.2H), 3.93 (dd, *J* = 9,8, 1.3 Hz, 0.8H), 3.86–3.81 (m, 0.2H), 3.81 (d, *J* = 5.2 Hz, 0.8H), 3.79 (d, *J* = 5.3 Hz, 0.2H), 2.02–1.90 (m, 1H), 1.31 (s, 7.7H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.14 (s, 1.3H), 1.01 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 188.9, 188.6*, 155.6 , 155.02*, 150.8*, 150.5, 147.1, 146.7, 118.7, 118.6*, 112.8, 112.8*, 79.7*, 79.3, 73.7, 60.0*, 58.8, 31.6*, 31.2, 28.3, 28.0*, 20.1*, 19.9, 19.7*, 19.6; **HRMS** (TOF) *m/z*: [M + Na]$^{+}$ Calcd for $C_{15}H_{23}NO_5Na$ 320.1468; Found 320.1473.

tert-Butyl [(*2R*,*3S*,*4R*)-1-(furan-2-yl)-2-hydroxy-4-methyl-1-oxohexan-3-yl]carbamate (**93**)



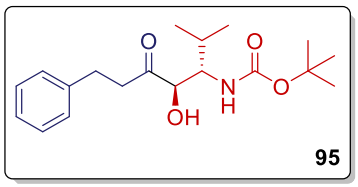
Column chromatography (5:1 hexane:acetone) followed by PTLC (7:1 toluene: EtOAc) afforded the major product as a 13:1 mixture of diastereomers as a colourless oil (58 mg, 71%). An analytically pure sample was prepared by further purification by PTLC (75:25:0.25 hexanes:EtOAc:MeOH). R_f = 0.20 (20% acetone in hexanes); $[\alpha]_D^{27\,°C}$ = +59 (*c* 1.0, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3447, 3378, 2967, 2932, 1706, 1683, 1468, 1390, 1366, 1172, 1018, 768; **^{1}H NMR** (600 MHz, $CDCl_3$) mixture of rotamers: δ 7.65 (s, 0.2H), 7.64 (s, 0.8H),7.32 (d, *J* = 2.7 Hz, 0.2H,), 7.28 (d, *J* = 3.5 Hz, 0.8H), 6.64–6.61 (m, 0.2H), 6.58 (dd, *J* = 3.5, 1.6 Hz, 0.8H), 5.02 (d, *J* = 4.1 Hz, 0.8H), 4.98 (d, *J* = 4.3 Hz, 0.2H), 4.68 (d, *J* = 10.2 Hz, 0.8H), 4.46 (d, *J* = 10.3 Hz, 0.2H), 4.00 (dd, *J* = 10.2, 1.3 Hz, 0.8H), 3.92 (t, *J* = 9.9, 0.2H), 3.80 (d, *J* = 5.1 Hz, 0.8H), 3.77 (d, *J* = 5.0 Hz, 0.2H), 1.77–1.68 (m, 1H), 1.68–1.68 (m, 1H), 1.31 (s, 7.5H), 1.24–1.17 (m, 1H), 1.13 (s, 1.5H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 7.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ mixture of rotamers (minor rotamer indicated by asterisk): 189.0, 188.7*, 155.5, 154.9*, 150.8*, 150.6, 147.1, 146.7, 118.7, 118.5*, 112.8*, 112.8, 79.7*, 79.3, 73.6, 73.6*, 58.1*, 57.3, 37.4, 28.3, 27.9*, 25.8, 25.5*, 16.03, 15.5*, 11.35, 10.72*; **HRMS** (TOF) *m/z*: $[M + 1]^+$ Calcd for $C_{16}H_{26}NO_5$ 312.18110; Found 312.18178.

tert-Butyl [(*2R,3S*)-1-(furan-2-yl)-2-hydroxy-4,4-dimethyl-1-oxopentan-3-yl]carbamate (**94**)



Column chromatography (4:1 hexanes: EtOAc) followed by PTLC (7:1 toluene: EtOAc) afforded the major product as a white solid (52 mg, 73%). Melting range = 84.2–85.6 °C, R_f = 0.24 (20% acetone in hexanes); $[\alpha]_D^{27\,°C}$ = +1.5 (*c* 0.5, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3450, 3134, 2965, 1703, 1679, 1571, 1493, 1468,1367, 1232, 1171, 1059, 768; **^{1}H NMR** (600 MHz, $CDCl_3$) Mixture of rotamers: δ 7.64 (s, 0.2H), 7.62 (s, 0.8H),7.32 (d, *J* = 3.2 Hz, 0.2H), 7.28 (d, *J* = 3.5 Hz, 0.8H), 6.64–6.60 (m, 0.2H), 6.60–6.54 (m, 0.8H), 5.10 (d, *J* = 4.9 Hz, 0.8), 5.07 (d, *J* = 4.8 Hz, 0.2H), 4.89 (d, *J* = 10.5 Hz, 0.8H), 4.75 (d, *J* = 10.3 Hz, 0.2H), 3.95 (d, *J* = 10.7 Hz, 0.8H), 3.88 (d, *J* = 10.9 Hz, 0.2H), 3.81 (d, *J* = 5.2 Hz, 0.2H), 3.78 (d, *J* = 5.2 Hz, 0.8H), 1.33 (s, 7.3H), 1.14 (s, 1.8H), 1.08 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 189.1, 188.9*, 155.7, 155.0*, 150.6*, 150.3, 147.1, 146.7, 118.9, 118.6*, 112.9, 112.8*, 79.6*, 79.3, 72.8*, 72.5, 60.9*, 59.6, 38.8*, 35.9, 28.3, 27.9, 27.3; **HRMS** (TOF) *m/z*: $[M]^+$ Calcd for $C_{16}H_{26}NO_5$ 312.1806; Found 312.1801.

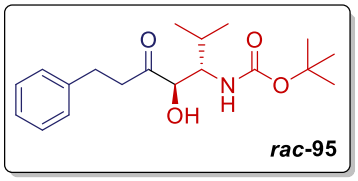
tert-Butyl [(3S,4R)-4-hydroxy-2-methyl-5-oxo-7-phenylheptan-3-yl]carbamate (**95**)



Column chromatography (3:2 hexanes:Et_2O) followed by PTLC (3:2 hexanes:Et_2O) afforded the major product as a colourless oil (50 mg, 62%). R_f = 0.19 (43% Et_2O in hexanes); $[\alpha]_D^{24\,°C}$ = -62 (*c* 1.4, $CHCl_3$); HPLC analysis – Chiralcel IC column, 5% isopropanol in hexanes, 0.1 mL/min. Major:

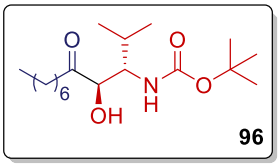
21.9 min, minor: 8.80 min. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3445, 3394, 2967, 2931, 1710, 1497, 1391, 1366, 1242, 1168, 1018, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32–7.25 (m, 2H), 7.23–7.17 (m, 3H), 4.66 (d, *J* = 10.3 Hz, 0.9H), 4.45(d, *J* = 10.2 Hz, 0.1H), 4.25 (d, *J* = 3.1 Hz, 0.9H), 4.22 (s, 0.1H), 3.83–3.71 (m, 2H), 3.64 (t, *J* = 9.9 Hz, 0.1H), 3.17 (ddd, *J* = 14.8, 9.1, 5.7 Hz, 1H), 3.00–2.85 (m, 2H), 2.74 (ddd, *J* = 16.2, 9.0, 6.8 Hz, 1H), 1.95–1.83 (m, 1H), 1.41 (s, 9H), 1.04 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 210.5, 155.9, 140.7, 128.7, 128.4, 126.3, 79.7, 76.6, 58.1, 39.3, 31.0, 29.6, 28.4, 20.0, 19.6; **HRMS** (CI) *m/z*: [M+1] Calcd for $C_{19}H_{30}NO_4$ 336.2175; Found 336.2178.

rac-tert-Butyl [(3S,4R)-4-hydroxy-2-methyl-5-oxo-7-phenylheptan-3-yl]carbamate (***rac*-95**)



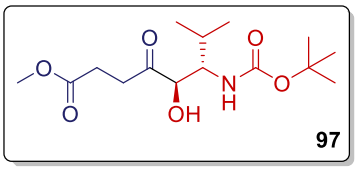
Column chromatography (3:1 hexanes:Et_2O) followed by PTLC (3:2 hexanes:Et_2O) afforded the major product as a colourless oil (36 mg, 44% yield). R_f = 0.19 (43% Et_2O in hexanes); HPLC analysis – Chiralcel IC column, 5% isopropanol in hexanes, 0.1 mL/min. 22.5 min and 8.84 min. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.22–7.17 (m, 3H), 4.66 (d, *J* = 10.3 Hz, 0.9H), 4.45 (d, *J* = 10.5 Hz, 0.1H), 4.25 (d, *J* = 2.5 Hz, 0.9H), 4.21 (s, 0.1H), 3.82–3.71 (m, 2H), 3.63 (t, *J* = 9.7 Hz, 0.1H), 3.16 (ddd, *J* = 14.8, 9.2, 5.6 Hz, 1H), 2.99–2.85 (m, 2H), 2.73 (ddd, *J* = 16.2, 8.9, 6.8 Hz, 1H), 1.94–1.83 (m, 1H), 1.40 (s, 9H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H).

tert-Butyl [(*3S*,*4R*)-4-hydroxy-2-methyl-5-oxododecan-3-yl]carbamate (**96**)



Column chromatography (8:1 hexanes:Et_2O) afforded the major product as a colourless oil (51 mg, 65%). R_f = 0.20 (13% Et_2O in hexanes); $[\alpha]_D^{24\ °C}$ = -83 (*c* 2.5, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3448, 3358, 2960, 2930, 2873, 2858, 1713, 1500, 1391, 1366, 1244, 1172, 1099, 1018, 780; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers δ 4.64 (d, *J* = 10.3 Hz, 0.9H), 4.43(d, *J* = 10.1 Hz, 0.1H), 4.28 (s, 0.9H), 4.24 (s, 0.1H), 3.86–3.70 (m, 1.8H), 3.63 (t, *J* = 9.7 Hz, 0.1H), 2.72 (dt, *J* = 17.5, 7.4 Hz, 0.9H), 2.61–2.51 (m, 0.1H), 2.44 (dt, *J* = 17.5, 7.4 Hz, 1H), 1.96–1.80 (m, 1H), 1.71–1.66 (m, 0.1H), 1.64–1.50 (m, 1.9H), 1.36 (s, 9H), 1.32–1.15 (m, 8H) 1.05 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.90–0.82 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) mixture of rotamers (minor rotamer indicated by asterisk) δ 211.5, 155.8, 79.5, 79.5*, 76.3, 76.2*, 59.1*, 57.8, 37.6, 37.5*, 31.9*, 31.7, 31.1, 39.4, 29.4*, 29.1, 28.4*, 28.3, 23.5, 22.7, 20.0*, 20.0, 19.6, 14.2; **HRMS** (FD) *m/z*: [M+1] Calcd for $C_{18}H_{36}NO_4$ 330.26443; Found 330.26529.

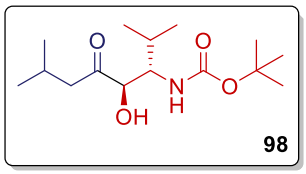
(5*R*,6*S*)-Methyl 6-[(*tert*-butoxycarbonyl)amino]-5-hydroxy-7-methyl-4-oxooctanoate (**97**)



Column chromatography (5:1 hexanes:acetone) followed by PTLC (3:2 hexanes:Et_2O) afforded major as a colourless oil (41 mg, 54%). R_f = 0.26 (25% acetone in hexanes); $[\alpha]_D^{28\ °C}$ = -99 (*c* 1.5, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3450,3373, 2971, 2875, 1740, 1712, 1509, 1367, 1241, 1173, 1083, 1045, 748; **^{1}H NMR** (500 MHz, $CDCl_3$) Mixture of rotamers δ 4.66 (d, *J* = 10.2 Hz, 0.9H), 4.45 (d, *J* = 9.5 Hz, 0.1H), 4.39 (d, *J* = 2.5 Hz, 0.8H), 4.33 (s, 0.1H), 3.75 (dd, *J* = 10.4, 1.0 Hz, 0.8H),

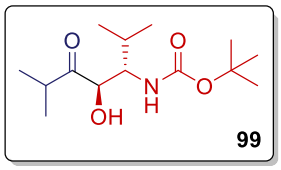
3.71–3.55 (m, 4H), 3.05–2.92 (m, 1H), 2.87–2.69 (m, 2H), 2.57–2.45 (m, 1H), 1.97–1.82 (m, 1H), 1.43 (s, 0.7H), 1.37 (s, 8.3H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 209.9, 173.1, 155.9. 79.7, 76.6, 59.2, 57.9, 52.0, 32.6, 32.3*, 31.8*, 30.9, 28.3, 27.9, 20.0, 19.7; **HRMS** (TOF) *m/z*: [M+Na] Calcd for $C_{15}H_{27}NO_6Na$ 340.1731; Found 340.1723.

tert-Butyl [(*3S,4R*)-4-hydroxy-2,7-dimethyl-5-oxooctan-3-yl]carbamate (**98**)



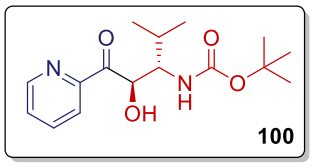
Column chromatography (8:1 hexanes:Et_2O) afforded the major product as a white solid (35.5 mg, 56%). R_f = 0.21 (13% Et_2O in hexanes); melting range: 96.1–97.2 °C; $[\alpha]_D^{24\,°C}$ = -110 (*c* 1.3, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3505, 3314, 2962, 2939, 2872, 1706, 1638,1529, 1389, 1370, 1287, 1171, 1092, 1019, 949; **^{1}H NMR** (600 MHz, $CDCl_3$) Mixture of rotamers δ 4.64 (d, *J* = 10.3 Hz, 0.9H), 4.42 (d, *J* = 10.6 Hz, 0.1H), 4.26 (d, *J* = 2.3 Hz, 0.9H), 4.19 (br s, 0.1H), 3.81 (d, *J* = 3.7 Hz, 0.9H),), 3.77 (dt, *J* = 9.2, 1.3 Hz, 0.9H), 3.62 (t, *J* = 10.0 Hz, 0.1H), 2.59 (dd, *J* = 7.0, 17.2 Hz, 0.9 H), 2.44 (dd, *J* = 6.6, 17.0 Hz, 0.1H), 2.38 (dd, *J* = 6.7, 17.1 Hz, 0.9H), 2.22–2.09 (m, 1H), 1.93–1.83 (m, 1H), 1.43 (s, 0.7H), 1.36 (s, 8.3H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 4.0 Hz, 3H), 0.90 (d, *J* = 4.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk); δ 211.0, 209.8*, 155.7, 154.9*, 80.3*, 79.5, 76.5, 59.0*, 57.8, 46.4*, 46.4, 32.0*, 31.3, 28.4*, 28.3, 24.6, 24.5*, 22.9*, 22.7, 22.6, 20.0*, 20.0, 19.6*, 19.6; **HRMS** (TOF) *m/z*: [M+1] Calcd for $C_{15}H_{30}NO_4$ 288.2169; Found 288.2170.

tert-Butyl [(*3S*,*4R*)-4-hydroxy-2,6-dimethyl-5-oxoheptan-3-yl]carbamate (**99**)



Column chromatography (6:1 hexanes:Et_2O) afforded the major product as a white solid (15 mg, 23%). R_f = 0.12 (17% Et_2O in hexanes); melting range: 135.4–138.7 °C; $[\alpha]_D^{24\,°C}$ = -113 (*c* 0.8, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3505, 3320, 2974, 2941, 2873, 1710, 1676, 1529, 1384, 1246, 1171, 1099, 1032, 1017, 969; **^{1}H NMR** (500 MHz, $CDCl_3$) Mixture of rotamers δ 4.64 (d, *J* = 10.1 Hz, 0.9H), 4.50 (d, *J* = 2.7 Hz, 0.9H), 4.44 (s, 0.1H), 4.62 (br s, 0.1H), 3.82–3.70 (m, 1.9H), 3.64 (t, *J* = 9.8 Hz, 0.1H), 3.04 (sep, *J* = 6.9 Hz, 0.9H), 2.96–2.89 (m, 0.1H), 1.96–2.85 (m, 1H), 1.45 (s, 0.7H), 1.43 (s, 8.3H), 1.14 (d, *J* = 7.2 Hz, 3H), 1.08 (dd, *J* = 7.1, 6.9 Hz, 6H), 1.00 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk); δ 215.1, 155.7, 79.6, 74.4, 58.9*, 57.7, 35.7, 35.5, 32.3*, 31.3, 28.5*, 28.3, 20.0, 20.0*, 19.6, 17.3*, 17.0; **HRMS** (TOF) *m/z*: [M+1] Calcd for $C_{14}H_{28}NO_4$ 274.201285; Found 274.2025.

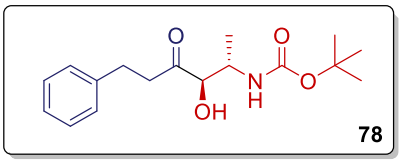
tert-Butyl [(2*R*,3*S*)-2-hydroxy-4-methyl-1-oxo-1-(pyridin-2-yl)pentan-3-yl]carbamate (**100**)



Column chromatography (5:1 hexanes:acetone) afforded the major product with unknown impurity, as a colourless oil (40 mg, 57% yield (54% calculated yield)). An analytically pure sample was prepared by PTLC (85:15:1 hexanes:acetone:NEt_3) R_f = 0.28 (20% acetone in hexanes); $[\alpha]_D^{24\,°C}$ = +19 (*c* 0.6, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3447, 3385, 2973, 2931, 2874, 1704, 1585, 1499, 1391, 1366, 1244, 1172, 1002, 799; **^{1}H NMR** (600 MHz, $CDCl_3$) Mixture of rotamers δ 8.70 (d, *J* = 4.4 Hz, 0.2H), 8.67 (d, *J* = 4.6 Hz, 0.8H), 8.08 (d, *J* = 7.8 Hz, 0.2H), 7.97 (d, *J* = 7.8 Hz, 0.8H), 7.89 (dd, *J* = 7.6, 7.6 Hz, 0.2H), 7.83 (ddd *J* = 7.8, 7.8, 1.2 Hz, 0.8H), 7.53 (dd, *J* = 7.2, 4.8 Hz, 0.2H),

7.49 (dd, *J* = 7.2, 4.8 Hz, 0.8H), 5.63 (d, *J* = 5.1 Hz, 0.8H), 5.51 (d, *J* = 4.6 Hz, 0.2H), 4.66 (d, *J* = 10.3 Hz, 0.8H), 4.43 (d, *J* = 10.6 Hz, 0.2H), 4.05 (t, *J* = 9.9 Hz, 0.2H), 3.98 (t, *J* = 9.3 Hz, 0.8H), 3.87 (d, *J* = 5.4 Hz, 0.2H), 3.79 (d, *J* = 5.6 Hz, 0.2H), 2.02–1.91 (m, 1H), 1.29 (s, 7.5H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.00 (s, 1.5H), 0.99 (d, *J* = 6.5 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk); δ 201.4, 155.6, 151.6, 149.1*, 149.1, 137.2*, 137.1, 127.8*, 127.8, 123.1*, 123.0, 79.3*, 79.1, 74.3*, 74.0, 59.9*, 58.5, 31.8*, 31.2, 28.3, 27.9*, 20.0*, 20.0, 19.7; **HRMS** (TOF) *m/z*: [M+1] Calcd for $C_{14}H_{28}NO_4$ 274.201285; Found 274.2025.

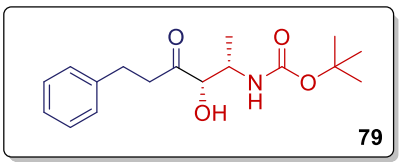
tert-Butyl [(2*S*,3*R*)-3-hydroxy-4-oxo-6-phenylhexan-2-yl]carbamate (**78**)



Carried out using *N*-Boc-L-alaninal (0.12 mmol, 0.021 g, limiting reagent). The amount of other reagents were adjusted accordingly. Column chromatography (3:1 hexane:acetone R_f = 0.26) followed by PTLC (7:1 toluene:EtOAc) afforded the major product as a white solid (7.2 mg, 23% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ ,7.31–7.26 (m, 2H), 7.20 (m 3H), 4.62 (d, *J* = 9.5 Hz, 1H), 4.31 (dq, *J* = 7.3, 7.0 Hz, 1H), 3.99 (s, 1H), 3.74 (d, *J* = 3.8 Hz, 1H), 3.24–3.08 (m, 1H), 3.02–2.83 (m, 2H), 2.83–2.67 (m, H), 1.40 (s, 9H), 1.30 (d, *J* = 6.8 Hz, 3H).

The minor diastereomer was also isolated:

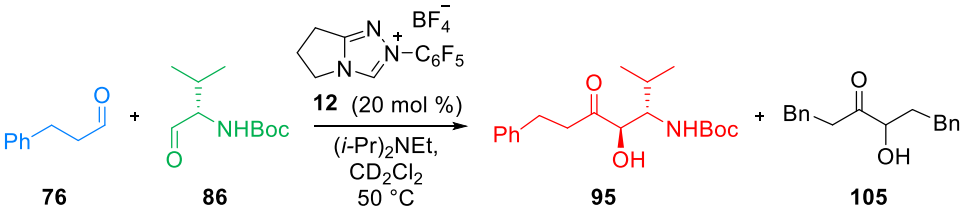
tert-Butyl [(2*S*,3*S*)-3-hydroxy-4-oxo-6-phenylhexan-2-yl]carbamate (**79**)



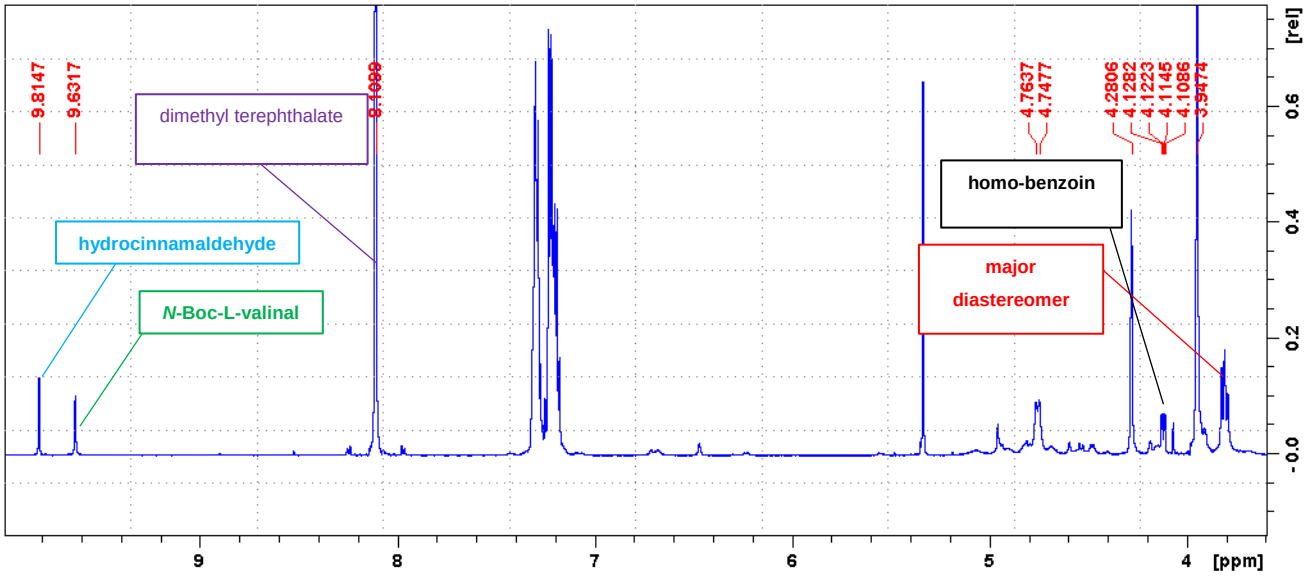
^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers: δ 7.32–7.26 (m, 2H), 7.23–7.11 (m, 3H), 4.88 (d, *J* = 6.7 Hz, 0.9H), 4.66–4.55 (m, 0.1H), 4.32 (s, 1H), 4.17–4.05 (m, 0.9H), 4.01–3.97

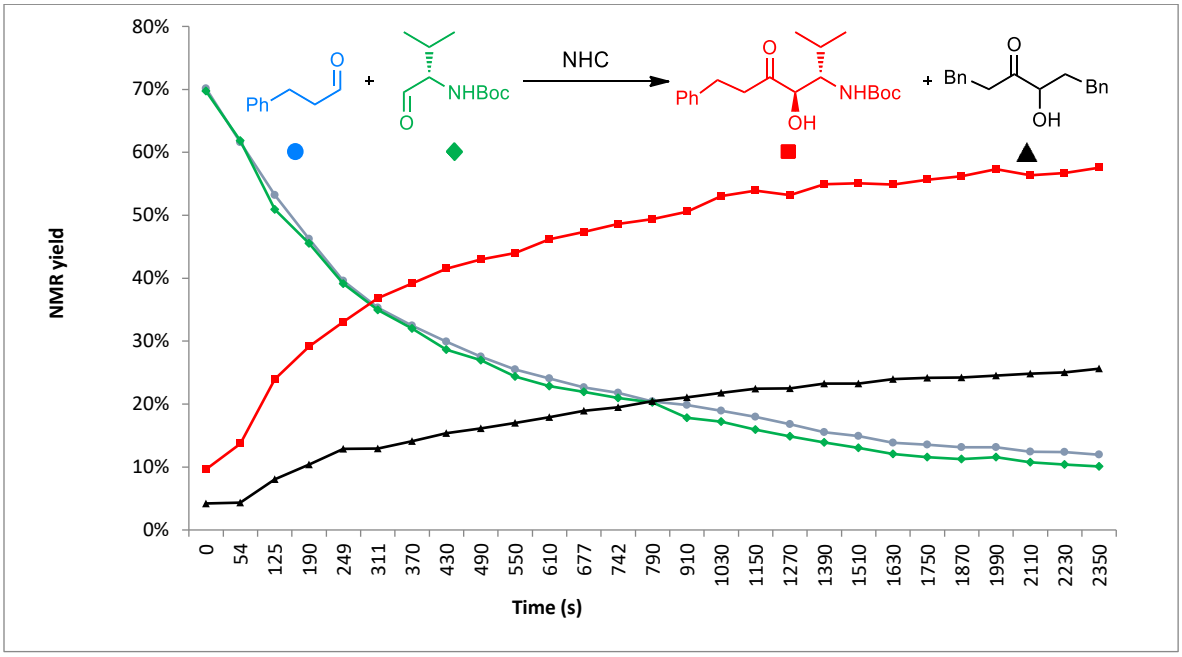
(m, 0.1H), 3.76–3.72 (m, 0.1H), 3.62 (d, *J* = 4.3 Hz, 0.9H). 3.06–2.90 (m, 2H), 2.90–2.77 (m, 2H), 1.55 (s, 1H), 1.44 (s, 8H).

^{1}H NMR Monitoring Experiment for the Reaction Between 76 and 86

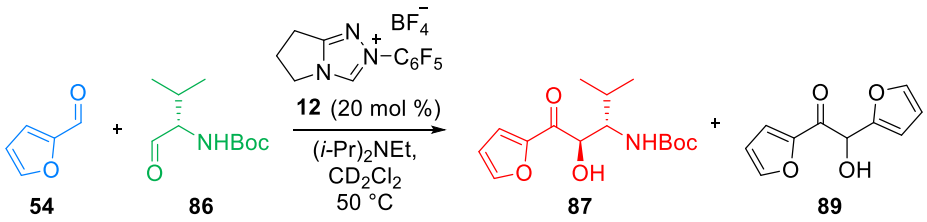


An oven-dried NMR tube was charged with triazolium salt **12** (3 mg, 0.008 mmol, 0.2 equiv), **86** (0.0053 mL, 0.04 mmol, 1 equiv), and dimethylterephthalate (7.8 mg, 0.04 mmol, 1 equiv) and equipped with Schlenk take–off adapter. The NMR tube was placed under vacuum and re–filled with argon three times to ensure inert atmosphere. Compound **76** (0.04 mmol, 1 equiv) and CH_2Cl_2 (0.5 mL, 0.08 M) were added sequentially under argon atmosphere. Lastly *i*-Pr_2NEt (0.08 mmol, 2 equiv) was added and the NMR tube was immediately inserted into a pre–heated NMR apparatus (50 °C). Spectra were acquired once per minute for the first 15 minutes and every 2 minutes for the remaining 45 minutes. A typical reaction spectrum (41 min.) is shown below:

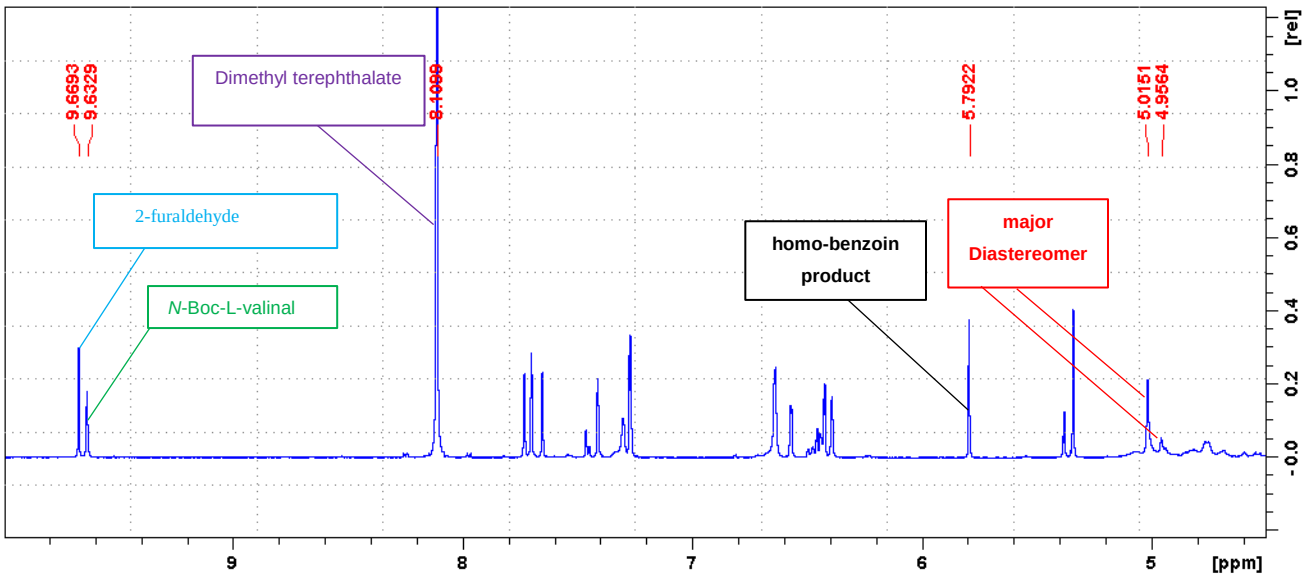

9.8147
9.6317
9.1699
4.7637
4.7477
4.2806
4.1282
4.1223
4.1145
4.1086
3.9474
dimethyl terephthalate
hydrocinnamaldehyde
N-Boc-L-valinal
homo-benzoin
major
diastereomer
[rel]
0.6
0.4
0.2
-0.0
9
8
7
6
5
4
[ppm]

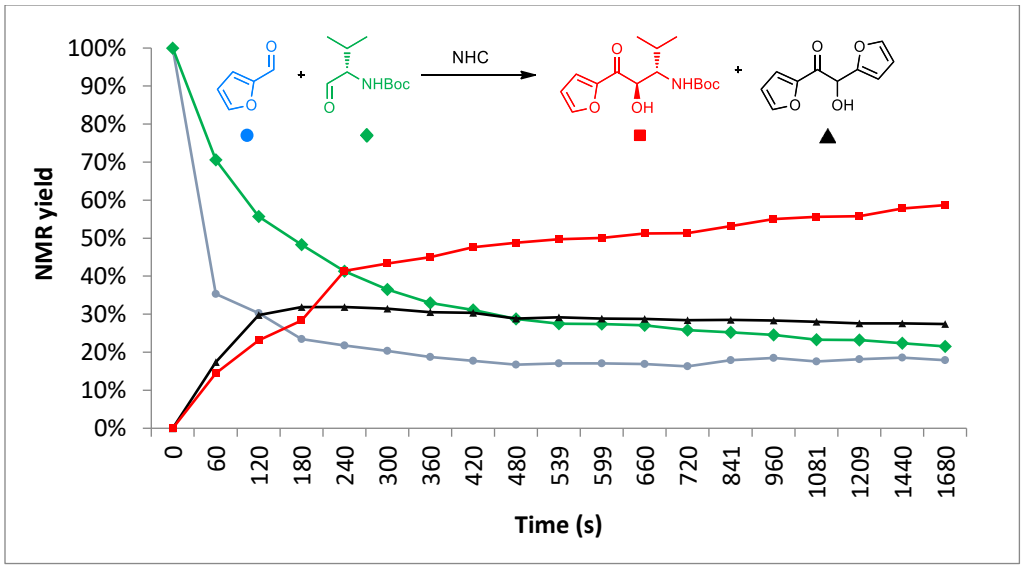

NHC
Ph
NHBoc
OH
Bn
NMR yield
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
54
125
190
249
311
370
430
490
550
610
677
742
790
910
1030
1150
1270
1390
1510
1630
1750
1870
1990
2110
2230
2350
Time (s)

^{1}H NMR Monitoring Experiment for the Reaction Between 54 and 86

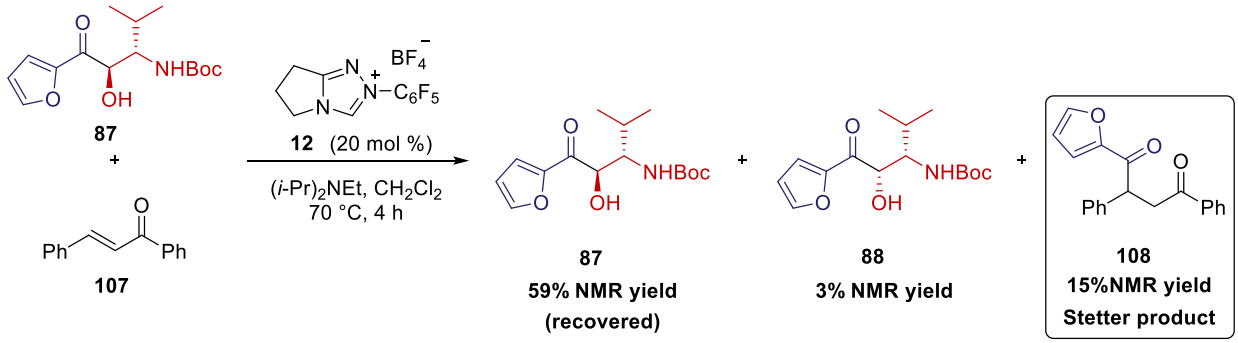


An oven-dried NMR tube was charged with triazolium salt **12** (3 mg, 0.008 mmol, 0.2 equiv), **86** (0.0053 mL, 0.04 mmol, 1 equiv), and dimethylterephthalate (7.8 mg, 0.04 mmol, 1 equiv) and equipped with Schlenk take–off adapter. The NMR tube was placed under vacuum and re–filled with argon three times to ensure inert atmosphere. Compound **54** (0.04 mmol, 1 equiv) and CH_2Cl_2 (0.5 mL, 0.08 M) were added sequentially under argon atmosphere. Lastly *i*-Pr_2NEt (0.08 mmol, 2 equiv) was added and the NMR tube was immediately inserted into a pre–heated NMR apparatus (50 °C). Spectra were acquired once per minute for the first 15 minutes and every 2 minutes for the remaining 45 minutes. A typical reaction spectrum (28 min.) is shown below:





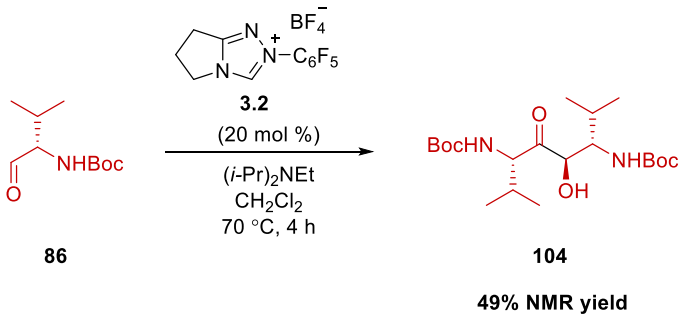
Crossover Experiment of Major Cross-Benzoin Diastereomer 87 and *trans*-Chalcone



Compound **87** (0.0875 mmol, 0.026 g), triazolium salt **12** (0.0175 mmol, 0.0064 g), and *trans*-chalcone (**107**) (**3.35**) (0.0875 mmol, 0.018 mg) were added to an oven–dried test tube with a Schlenk take–off and fitted with a septum. The vessel was placed under vacuum and re–filled with argon three times to ensure inert atmosphere. Addition of CH_2Cl_2 (0.1 mL, 0.8 M) was followed by $(i\text{-Pr})_2NEt$ (0.175 mmol, 0.0305 mL) was added and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re–established the flask was sealed and heated to 70

°C for 4 hours. The crude reaction mixture was cooled to room temperature and quenched by addition of HCl [1M] (2 mL). The reaction crude was extracted with CH_2Cl_2 (3 × 2 mL) and dried over Na_2SO_4. The reaction mixture was analyzed by ^1H NMR spectroscopy and by using dimethyl terephthalate as the internal standard.

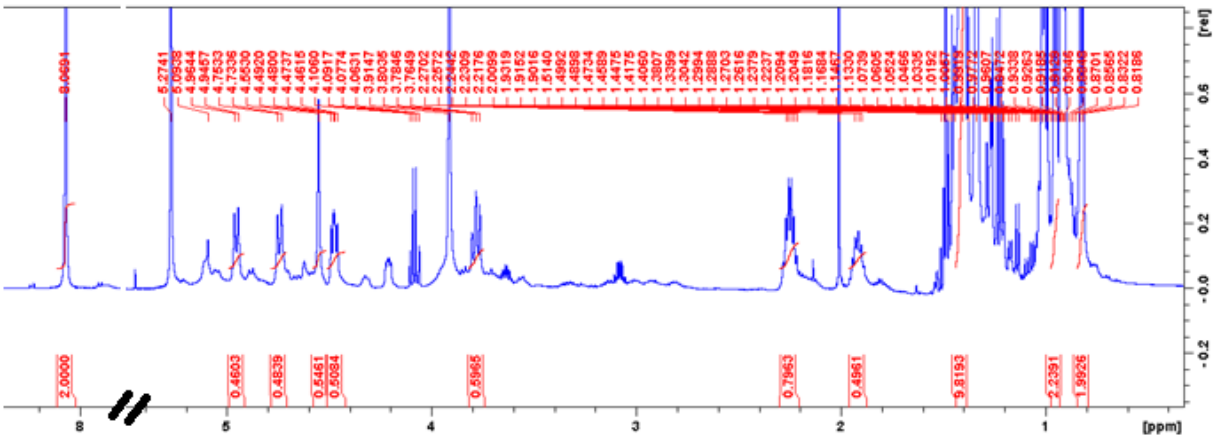
Homo-Benzoin Reaction of *N*-Boc-L-valinal



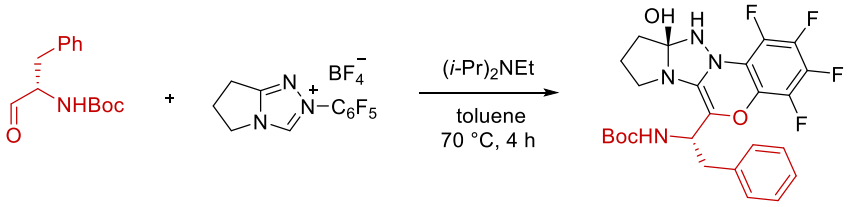
86 **104**

49% NMR yield

N–Boc–L-valinal (**86**) (0.24 mmol, 48 mg) and triazolium salt **12** (0.048 mmol, mg) were added to an oven–dried test tube with a Schlenk take–off and fitted with a septum. The vessel was placed under vacuum and re–filled with argon three times to ensure inert atmosphere. CH_2Cl_2 (0.3 mL, 0.8 M) and (*i*-Pr)$_2$NEt (0.48 mmol, 2.0 equiv) were added and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re–established the flask was sealed and heated to 70 °C for 4 hours. The crude reaction mixture was cooled to room temperature and quenched by addition of 1M HCl (2 mL). The reaction crude was extracted with CH_2Cl_2 (3 × 2 mL) and dried over Na_2SO_4. The reaction mixture was analyzed by ^1H NMR spectroscopy and by using dimethyl terephthalate as the internal standard.



S_NAr Reaction Between *N*-Boc-L-valinal and the NHC



102 2 equiv

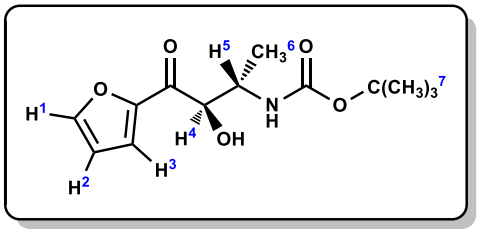
12 1 equiv

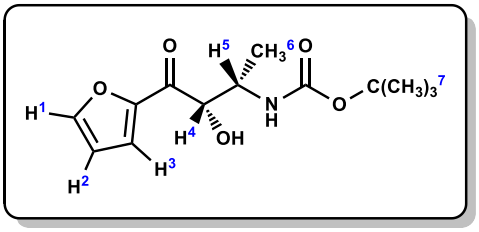
103 ***tentative structure***

Compound **102** (0.120 mmol, 0.030 g) and triazolium salt **12** (0.060 mmol, 0.022 g) were added to an oven–dried test tube with a Schlenk take–off and fitted with a septum. The vessel was placed under vacuum and re–filled with argon three times to ensure inert atmosphere. Addition of toluene (0.12 mL, 0.8 M) was followed by (*i*-Pr)$_2$NEt (0.120 mmol, 0.021 mL) was added and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re–established the flask was sealed and heated to 70 °C for 4 hours. The crude reaction mixture was cooled to room temperature and quenched by addition of HOAc (2 mL). Purification using column chromatography (3:1 hexane:EtOAc, R_f = 0.32) followed by PTLC (3:2 EtOAc:hexane) afforded

the title compound as white semi-solids (10 mg).); $[\alpha]_D^{27\ °C}$ = +158 (*c* 0.21, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3320, 2979, 2890, 1702, 1637, 1518, 1344, 1313, 1078, 1061; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37-7.30 (m, 2H), 7.29-7.22(m, 3H), 6.66 (br s, 1H), 4.73 (s, 1H), 4.48 (dd, *J* = 7.9, 7.7 Hz, 1H), 4.29 (br d, *J* = 6.8 Hz, 1H), 3.57 (dd, *J* = 14.9, 8.0 Hz, 1H), 3.40 (dd, *J* = 14.2, 8.0 Hz, 1H), 3.02 (dd, *J* = 14, 8.1 Hz, 1H), 3.01 (dd, *J* = 14, 8.1 Hz, 1H), 2.83-2.70 (m, 1H), 2.69-2.56 (m, 1H), 2.22-2.03 (m, 2H), 1.26 (s, 9H); **^{19}F NMR** (470 MHz, $CDCl_3$): -152.54 (dd, *J* = 21.0, 6.0 Hz), -162.99 (t, *J* = 21.7 Hz), -163.29 (ap d, *J* = 21.1 Hz), -166.98 (t, *J* = 21.2 Hz); **^{13}C NMR** (500 MHz, $CDCl_3$): δ 170.8, 159.4, 156.0, 136.0, 129.3, 129.1, 127.4, 81.0, 79.1, 54.3, 46.0, 38.1, 29.6, 28.2, 22.2; **HRMS** (TOF) *m/z*: [M+1] Calcd. for $C_{25}H_{27}N4O_4F_4$ 523.1963; Found 523.1960.

Comparison between predicted and experimental ^{1}H NMR chemical shifts for isomers 90 and 101





anti ***syn***

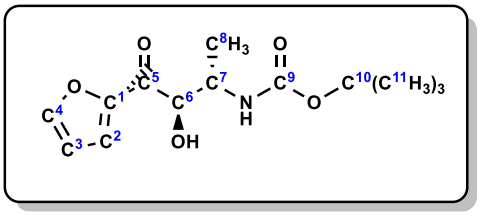
Major Isomer (90)

signal number	observed shift (ppm)		calculated shift – anti (ppm)	Δδ obs. vs. calc. anti (ppm)		calculated shift – syn (ppm)	Δδ obs. vs. calc. syn (ppm)
1	7.65		7.44	0.21		7.51	0.14
2	6.59		6.49	0.10		6.53	0.06
3	7.31		7.20	0.11		7.51	-0.20
4	4.66		4.75	-0.09		4.95	-0.29
5	4.40		4.49	-0.09		4.12	0.28
6	1.36		1.30	0.06		0.88	0.48
7	1.33		1.24	0.09		1.42	-0.09
mean deviation				**0.11**			**0.22**

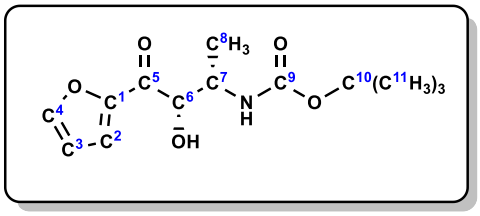
Minor Isomer (101)

signal number	observed shift (ppm)	calculated shift –anti (ppm)	Δδ obs. vs. calc. anti (ppm)	calculated shift – syn (ppm)	Δδ obs. vs. calc. syn (ppm)
1	7.72	7.44	0.28	7.51	0.21
2	6.62	6.49	0.13	6.53	0.09
3	7.65	7.20	0.45	7.51	0.14
4	4.99	4.75	0.24	4.95	0.04
5	4.28	4.49	-0.21	4.12	0.16
6	0.93	1.30	-0.37	0.88	0.05
7	1.47	1.24	0.23	1.42	0.05
mean deviation			**0.27**		**0.11**

Comparison between predicted and experimental ^{13}C NMR chemical shifts for isomer 90 and 101



anti



syn

Major Isomer (90)

signal number	observed shift (ppm)		calculated shift – anti (ppm)	Δδ obs. vs. calc. anti (ppm)	calculated shift – syn (ppm)	Δδ obs. vs. calc. syn (ppm)
1	150.8		149.2	1.6	147.9	2.9
2	118.9		117.2	1.7	119.3	-0.4
3	112.9		111.1	1.8	111.1	1.8
4	147.3		144.1	3.2	145.5	1.8
5	188.3		185.0	3.3	184.7	3.6
6	76.7		75.5	1.2	74.1	2.6
7	49.2		50.3	-1.1	50.7	-1.5
8	19.1		16.5	2.6	11.8	7.3
9	155.3		152.4	2.9	152.7	2.6
10	79.6		77.3	2.3	77.5	2.1
11	28.4		29.9	-1.5	25.2	3.2
mean deviation				**2.1**		**2.7**

7.3. Reversal of Diastereoselectivity in NHC-Catalyzed Cross-Benzoin Reactions using *N*,*N*-Bis-Protected-*α*-Amino Aldehydes

X-ray crystal structure and refinement data for compound 112

A clear colourless irregular-like specimen of $C_{20}H_{25}NO_5$, approximate dimensions 0.300 mm x 0.300 mm x 0.400 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured.

Axis	dx/mm	2θ/°	ω/°	φ/°	χ/°	Width/°	Frames	Time/s	Wavelength/Å	Voltage/kV	Current/mA	Temperature/K
Omega	39.478	-29.50	-34.28	-159.51	-95.32	0.50	120	40.00	0.71073	50	30.0	173
Phi	39.478	-24.50	-30.05	-133.91	96.96	0.50	276	40.00	0.71073	50	30.0	173
Phi	39.478	-24.50	-12.05	-55.29	-88.84	0.50	357	40.00	0.71073	50	30.0	173
Phi	39.478	-24.50	25.74	-172.81	-88.84	0.50	253	40.00	0.71073	50	30.0	173
Phi	39.478	-19.50	15.51	-22.07	-48.26	0.50	739	40.00	0.71073	50	30.0	173
Omega	39.478	8.00	-51.91	-206.56	50.73	0.50	132	40.00	0.71073	50	30.0	173
Omega	39.478	10.50	-37.36	-33.34	79.42	0.50	106	40.00	0.71073	50	30.0	173

A total of 1983 frames were collected. The total exposure time was 22.03 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using an orthorhombic unit cell yielded a total of 35007 reflections to a maximum θ angle of 28.30° (0.75 Å resolution), of which 4709 were independent (average redundancy 7.434, completeness = 99.8%, R_{int} = 2.36%, R_{sig} = 1.37%), and 4507 (95.71%) were greater than $2\sigma(F^2)$.

The final cell constants of a = 10.1471(4) Å, b = 10.2402(4) Å, c = 18.2370(7) Å, volume = 1894.98(13) $Å^3$, are based upon the refinement of the XYZ-centroids of 9129 reflections above 20 σ(I) with 5.652° < 2θ < 56.58°. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.929. The calculated minimum and maximum transmission coefficients (based on crystal size)

are 0.9650 and 0.9730.

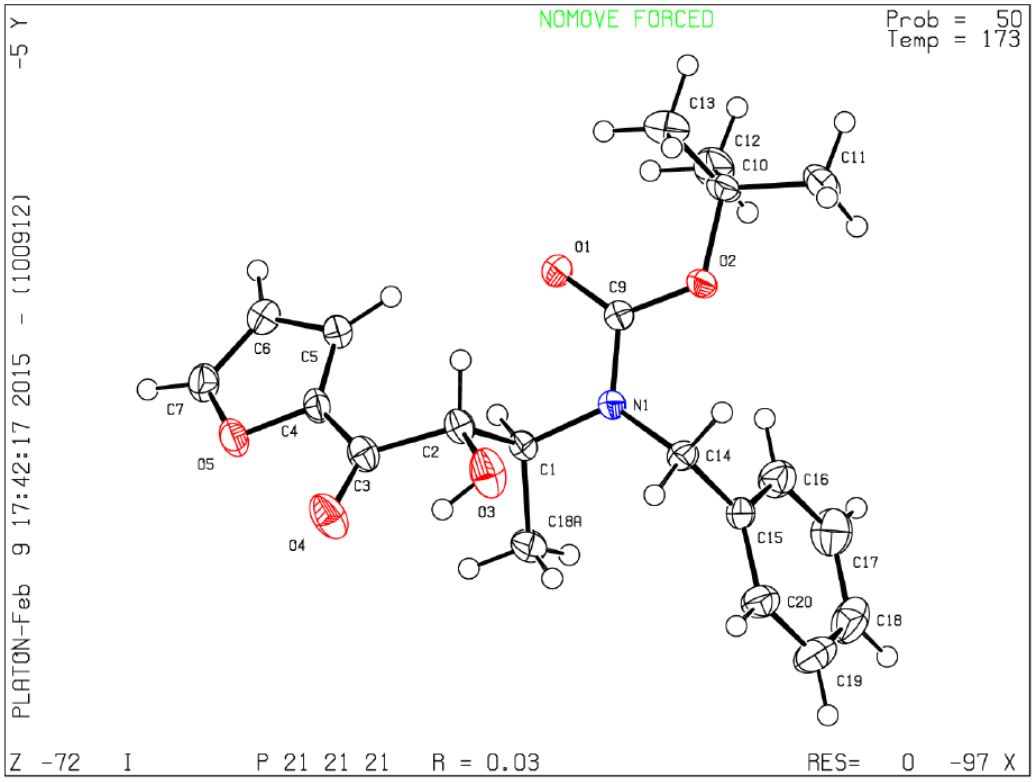
The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group P 21 21 21, with Z = 4 for the formula unit, $C_{20}H_{25}NO_5$. The final anisotropic full-matrix least-squares refinement on F^2 with 242 variables converged at R1 = 2.91%, for the observed data and wR2 = 7.65% for all data. The goodness-of-fit was 1.028. The largest peak in the final difference electron density synthesis was 0.230 $e^-/Å^3$ and the largest hole was -0.162 $e^-/Å^3$ with an RMS deviation of 0.031 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.260 g/cm^3 and F(000), 768 e^-.

Table 2. Sample and crystal data for compound 112

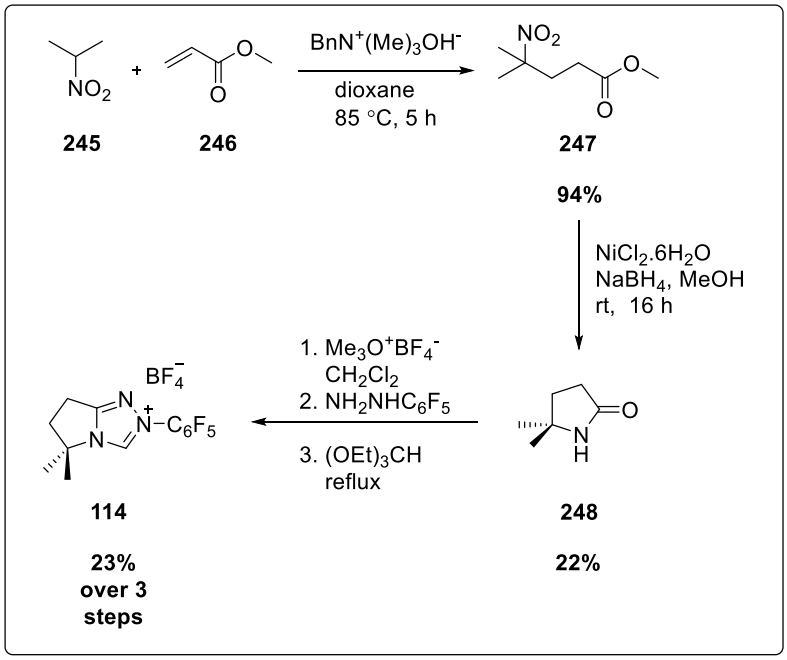
Identification code	1497d	
Chemical formula	$C_{20}H_{25}NO_5$	
Formula weight	359.41 g/mol	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal size	0.300 x 0.300 x 0.400 mm	
Crystal habit	clear colourless irregular	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.1471(4) Å	α = 90°
	b = 10.2402(4) Å	β = 90°
	c = 18.2370(7) Å	γ = 90°
Volume	1894.98(13) $Å^3$	
Z	4	
Density (calculated)	1.260 g/cm^3	
Absorption coefficient	0.090 mm^{-1}	
F(000)	768	

Table 3. Data collection and structure refinement for compound 6

Theta range for data collection	2.99 to 28.30°	
Index ranges	-12<=h<=13, -13<=k<=13, -24<=l<=23	
Reflections collected	35007	
Independent reflections	4709 [R(int) = 0.0236]	
Coverage of independent reflections	99.8%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9730 and 0.9650	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014/6 (Sheldrick, 2014)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	4709 / 0 / 242	
Goodness-of-fit on F^2	1.028	
Δ/σ_{max}	0.001	
Final R indices	4507 data; $I>2\sigma(I)$	R1 = 0.0291, wR2 = 0.0753
	all data	R1 = 0.0308, wR2 = 0.0765
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0449P)^2+0.2226P]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	-0.1(2)	
Largest diff. peak and hole	0.230 and -0.162 eÅ^{-3}	
R.M.S. deviation from mean	0.031 eÅ^{-3}	


NOMOVE FORCED
Prob = 50
Temp = 173
-5 Y
PLATON-Feb 9 17:42:17 2015 - (100912)
Z -72 I P 21 21 21 R = 0.03 RES= 0 -97 X
C13
C12
C10
C11
O1
O2
C9
C6
C5
C7
C4
O5
C3
C2
C1
N1
C14
C16
O3
O4
C18A
C15
C17
C20
C18
C19

5,5-Dimethyl-2-(perfluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-c][1,2,4]triazol-2-ium tetrafluoroborate (**114**)



According to a reported procedure,[212] a three-neck flask was equipped with a thermometer and condenser. 2-Nitropropane (**245**) (20 mmol, 1.8 mL), *N*,*N*,*N*-trimethyl-1-phenylmethanaminium hydroxide (aq) (40% *w*/*w*, 0.2 mL), and dioxane (1 mL) were added to the reaction flask and heated to 70 °C. Methylacrylate (**246**) (20 mmol, 1.8 mL) was added to the reaction mixture and the temperature was increased to 85 °C. Upon completion of the reaction, as judged by ^{1}H NMR analysis (*i.e.* 5 h), the reaction was quenched with the addition of 1M HCl (10 mL) and the reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed sequentially with water (20 mL) and brine (20 mL), and dried over Na_2SO_4. Removal of volatiles under reduced pressure followed by fractional distillation (2 torr, 90 °C) afforded **247** as a light-yellow oil (3.29 g, 94%). Spectral data match the previously reported values.[212] ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.68 (s, 3H), 2.40–2.30 (m, 2H), 2.30–2.20 (m, 2H), 1.59 (s, 6H).

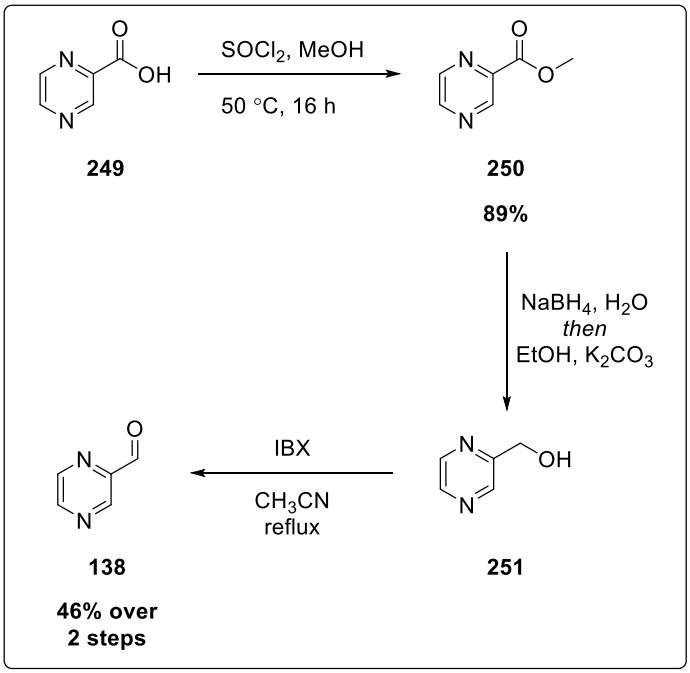
Following a reported procedure,[213] to a solution of $NiCl_2.6H_2O$ (50 mmol, 11.90 g) in methanol (750 mL) was added $NaBH_4$ (501 mmol, 18.95 g) in three portions at 0 °C. This mixture was stirred at room temperature for 30 minutes and then a solution of **247** (100 mmol, 17.5 g) in methanol (250 mL) was added to the reaction mixture. This was followed by addition of excess $NaBH_4$ (333 mmol, 12.6 g) and the reaction was stirred at room temperature for an additional 16 h. The reaction mixture was filtered through Celite® and washed with MeOH (3 × 50 mL) and volatiles were removed under reduced pressure. The crude reaction mixture was diluted with H_2O (250 mL) and extracted sequentially with CH_2Cl_2 (3 × 200 mL) and EtOAc (2 × 100 mL). The organic layers were combined and dried over Na_2SO4. Sublimation (1.5 torr, 110 °C) using a cold finger afforded **248** as a white solid (2.54 g, 22%). Spectral data match the previously reported values.[213] ^{1}H NMR (600 MHz, $CDCl_3$): mixture of rotamers; δ 5.56 (br s, 1H), 2.41 (t, *J* = 8.0 Hz, 2H), 1.94 (t, *J* = 7.9 Hz, 2H), 1.28 (s, 6H).

According to a previously published procedure,[214] to a solution of 5,5-dimethylpyrrolidin-2-one (**148**) (17.7 mmol, 2.00 g) in dry CH_2Cl_2 (90 mL) was added trimethyloxonium tetrafluoroborate (17.7 mmol, 2.62 g) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at this temperature for 16 h. Perfluorophenyl hydrazine (26.5 mmol, 5.26 g) was added to the reaction and the contents were stirred for an additional 3 days. The volatiles were thoroughly removed under reduced pressure and trimethyl orthoformate (29 mL) was added. The reaction was stirred at room temperature for 3 days. Volatiles were removed *in vacuo* and the crude product purified by recrystallization using EtOAc and Et_2O to afford **114** as light brown solids (0.330 g, 23% over three steps). melting range = 164.8–167.1 °C; **FTIR** (KBr pallet) ν_{max} (cm^{-1}): 2993, 1671, 1603, 1527, 1499, 1353, 1071, 798; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.25 (s, 1H), 3.36 (t, *J* = 7.5 Hz, 2H), 2.79 (t, *J* = 7.6 Hz, 2H), 1.83 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.5, 142.4,

69.0, 42.0, 27.3, 21.9; **HRMS** (ESI-TOF) *m*/*z*: $[M]^+$ Calcd. for $C_{13}H_{11}F_5$ 304.0867; Found 304.0879.

Synthesis of Hetero-Aromatic Aldehydes

Pyrazine-2-carboxaldehyde (**138**)



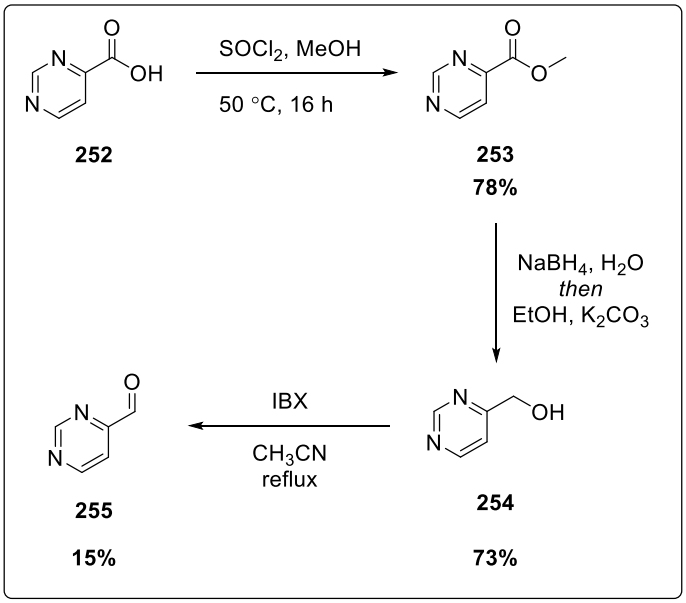
To a solution of pyrazine-2-carboxylic acid (**249**) (80.5 mmol, 10.0 g), in MeOH (200 mL) was added $SOCl_2$ (88.7 mmol, 6.4 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature and then heated to 50 °C. The reaction was stirred at this temperature for 16 h and the volatiles were removed under reduced pressure. The crude reaction mixture was re-dissolved in water (100 mL) and the pH was adjusted to 8.5 using sat. $NaHCO_3$ (aq). The solution was extracted with EtOAc (3 × 300 mL) and the combined organic layers were dried on $MgSO_4$. Complete removal of volatiles *in vacuo* afforded **250** as yellow solids (9.33 g, 89%). Spectral data match the

previously reported values.[215] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.77 (s, 1H), 8.72 (s, 1H), 4.04 (s, 3H).

According to reported procedure,[216] to a solution of methyl pyrazine-2-carboxylate (**250**) (40.3 mmol, 5.00 g) in H_2O (135 mL) was added $NaBH_4$ (181.3 mmol, 6.86 g) in three portions at room temperature. The stirring was continued for an additional 1 h. EtOH (47 mL) and sat. K_2CO_3 (90 mL) were added to the reaction and stirred for 1 h. The crude reaction mixture was extracted with EtOAc (3 × 200 mL) and the combined organic layers were dried using $MgSO_4$. Removal of volatiles under reduced pressure afforded **251** along with an unknown impurity as light-yellow solids. This mixture was carried to next step without further purification.

Following a known procedure,[161] IBX (28.5 mmol, 7.99 g) was added to a solution of crude pyrazin-2-ylmethanol (**251**) (1.57 g) in acetonitrile (20 mL) and heated to reflux. The reaction was monitored for complete consumption of starting material (80 min). After completion, the contents were cooled to room temperature, filtered through a pad of Celite® and washed with EtOAc (3 × 20 mL). The resulting mixture was concentrated and purified by bulb-to-bulb distillation (50 torr, 115 °C) to afford pyrazine-2-carboxaldehyde (**138**) along with acetonitrile as a yellow oil (0.87 mL, calculated 46% over two steps.) Spectral data match the previously reported values.[215] **^{1}H NMR** (600 MHz, $CDCl_3$); δ 10.16 (s, 1H), 9.18 (s, 1H), 8.81 (d, J = 2.5 Hz, 1H), 8.76 (t, J = 1.6 Hz, 1H).

Pyrimidine-4-carboxaldehyde (**255**)

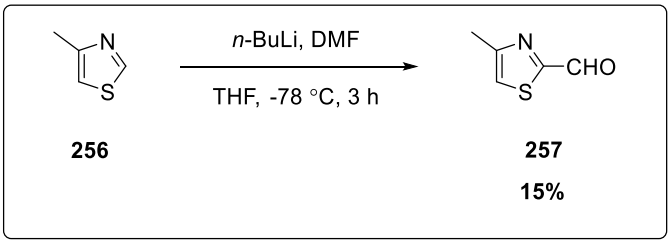


Synthesized according to the sequence described for pyrazine-2-carboxaldehyde. Methyl pyrimidine-4-carboxylate (**253**); isolated as yellow solids (3.45 g, 78%). Spectral data match the previously reported values.[217] **^{1}H NMR** (500 MHz, $CDCl_3$); δ 9.42 (d, *J* = 1.2 Hz, 1H), 9.01 (d, *J* = 5.1 Hz, 1H), 8.04 (dd, *J* = 5.1, 1.5 Hz, 1H).

Pyrimidin-4-ylmethanol (**254**); isolated as amber solids (1.75 g, 73%). Spectral data match the previously reported values.[218] **^{1}H NMR** (500 MHz, $CDCl_3$); δ 9.18 (s, 1H), 8.71 (d, *J* = 5.2 Hz, 1H), 7.35 (d, *J* = 5.2 Hz, 1H), 4.78 (s, 2H), 3.29 (br s, 1H).

Pyrimidine-4-carboxaldehyde (**255**) (0.256 g, 15%). Spectral data match the previously reported values.[218] **^{1}H NMR** (500 MHz, $CDCl_3$); δ 10.08 (s, 1H), 9.47 (s, 1H), 9.03 (d, *J* = 4.9 Hz, 1H), 7.84 (dd, *J* = 4.9, 1.3 Hz, 1H).

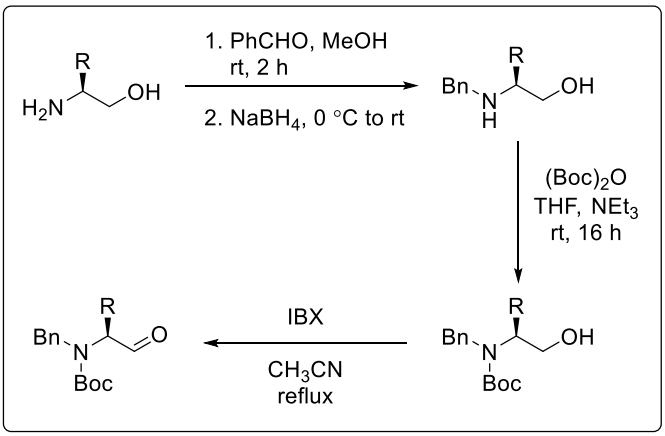
4-Methylthiazole-2-carboxaldehyde (**257**)



Following a reported procedure,[219] a dry round-bottomed flask was charged with 4-methylthiazole (**256**) (20.2 mmol, 1.8 mL) and dry THF (80 mL) under argon and cooled to -70 °C. *n*-BuLi (0.94 M in THF, 24.2 mmol, 26 mL) was added dropwise to the reaction mixture. The stirring was continued for an additional 1 hour and DMF (40.3mmol, 3.1 mL) was added dropwise to the reaction. The reaction was stirred for 3 hours and then warmed to 0 °C and poured on (wet) ice. The pH was adjusted to 4 using 1M HCl (aq). The reaction mixture was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed sequentially with water (100 mL) and brine (100 mL). Drying over $MgSO_4$ and volatiles were removed under reduced pressure. Column chromatography (5:1 pentane:EtOAc, $R_f = 0.10$) afforded the title compound as a yellow oil (0.380 g, 15%). Spectral data match the previously reported values.[219] **^{1}H NMR** (500 MHz, $CDCl_3$); δ 9.96 (d, *J* = 0.9 Hz, 1H), 7.33 (s, 1H), 2.57 (s, 3H).

Synthesis of *N*-Boc-*N*-Bn-amino aldehydes:

General procedure (A);



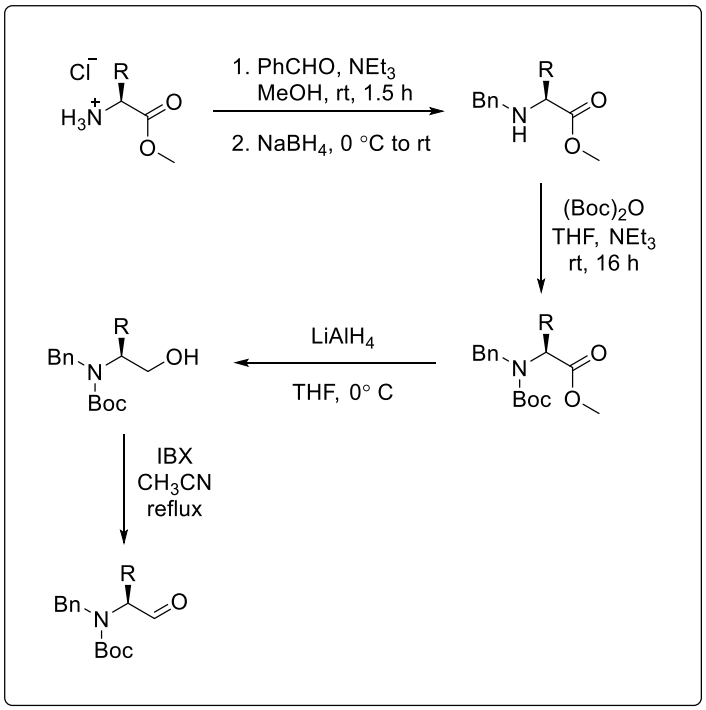
A(I) *N*-Benzyl protection: Following a modified procedure;[220] to a solution of the corresponding α-amino alcohol (1 equiv) in dry MeOH [0.25 M] freshly distilled benzaldehyde (1 equiv) was added at room temperature. The resulting solution was stirred for 2 hours before being cooled to 0 °C using an ice bath. $NaBH_4$ (5 equiv) was slowly added to the mixture in three portions. The resulting suspension was warmed to room temperature and stirred for one hour. The suspension was once again cooled to 0 °C and quenched with the addition of sat. $NH_4Cl_{(aq.)}$ The reaction mixture was extracted with EtOAc (×3) and the combined organic layers were dried over $MgSO_4$. The crude mixture was reduced *in vacuo* and carried to next step without further purification.

A(II) *N*-Boc protection:[221] To a solution of *N*-Bn-amino alcohol (1.0 equiv) in THF [0.3 M] was added triethylamine (1 equiv) at room temperature. To this solution was added di–*tert*–butyl dicarbonate (Boc_2O) (1.1 equiv) and stirred at ambient temperature for 16 hours. The reaction was quenched with addition of HCl [1 M] and extracted with Et_2O (×3). The combined organic

layers were washed with brine and dried over $MgSO_4$. The crude product was purified by column chromatography.

A(III) oxidation:[161] IBX (1.5 equiv) was added to a solution of *N*–Boc-*N*-Bn–amino alcohol (1.0 equiv) in acetonitrile [0.2 M] and heated to reflux. The reaction was monitored for complete consumption of starting material (typical reaction time = 30 minutes). After completion, the contents were cooled to room temperature, filtered through a pad of Celite® and washed with EtOAc (×3). The resulting mixture was concentrated and purified by column chromatography.

General procedure (B);



B(I) *N*-Benzyl protection:[222] Following a modified procedure, to a solution of amino ester HCl salt (1 equiv) in dry MeOH [0.7 M], triethylamine (1 equiv) followed by freshly distilled benzaldehyde (1.5 equiv) were added at room temperature. The resulting solution was stirred for 1.5 h before being cooled to 0 °C using an ice bath. $NaBH_4$ (2 equiv) was slowly added to the

mixture in three portions. The resulting suspension was warmed to rt and stirred for two hours. The volatiles were removed under reduced pressure and the crude reaction mixture was partitioned between H_2O and EtOAc. The layers were separated and the aqueous layer was further extracted with EtOAc (×2). The organic layers were combined, dried over $MgSO_4$, and volatiles were removed under reduced pressure. The crude product was purified by column chromatography.

B(II) *N*-Boc protection:[221] To a solution of *N*-benzyl-amino ester (1.0 equiv) in THF [0.3 M] was added triethylamine (1 equiv) at room temperature. To this solution was added di–*tert*–butyl dicarbonate (Boc_2O) (1.1 equiv) and stirred at ambient temperature for 16 hours. The reaction was quenched with addition of HCl [1 M] and extracted with Et_2O (×3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography.

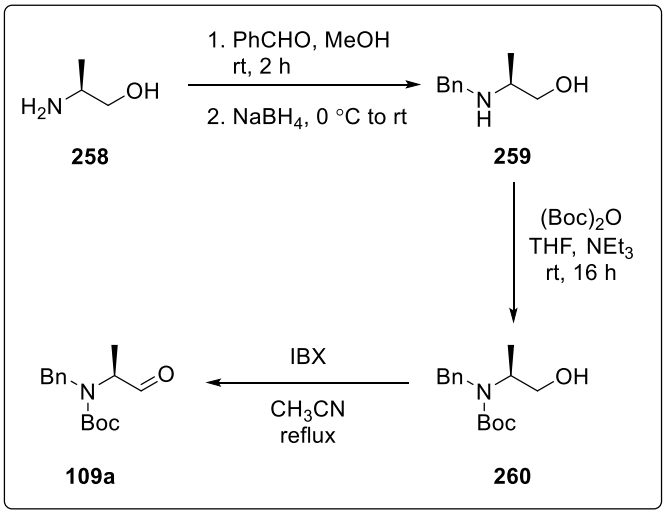
B(III) $LiAlH_4$ reduction:[161] To a suspension of $LiAlH_4$ (3 equiv) in THF [0.2 M] was added the crude ester from the previous step (1 equiv) in dry THF [0.2 M] at 0 °C. After the reaction was completed (as judged by TLC analysis) an aqueous solution of Rochelle's salt [0.5 M] was slowly added to the mixture at 0 °C. The reaction was vigorously stirred at room temperature for two hours. The reaction mixture was diluted in EtOAc and the layers were separated. The aqueous phase was extracted using EtOAc (×2) and the combined organic layers were dried over $MgSO_4$. The resulting mixture was concentrated *in vacuo* and purified by column chromatography.

B(IV) oxidation:[161] IBX (1.5 equiv) was added to a solution of *N*–Boc-*N*-Benzyl amino alcohol (1.0 equiv) in acetonitrile [0.2 M] and heated to reflux. The reaction was monitored for complete consumption of starting material (typical reaction time = 30 minutes). After completion, the

contents were cooled to room temperature, filtered through a pad of Celite® and washed with EtOAc (×3). The resulting mixture was concentrated and purified by column chromatography.

tert-Butyl (*S*)-benzyl(1-oxopropan-2-yl)carbamate (**109a**)

Prepared according to **general procedure A**;



A(I): (*S*)-2-(Benzylamino)propan-1-ol (**259**)

Isolated as a mixture of product and benzyl alcohol. This mixture was carried to the next step without further purification.

A (II): *tert*-Butyl (*S*)-benzyl(1-hydroxypropan-2-yl)carbamate (**260**)

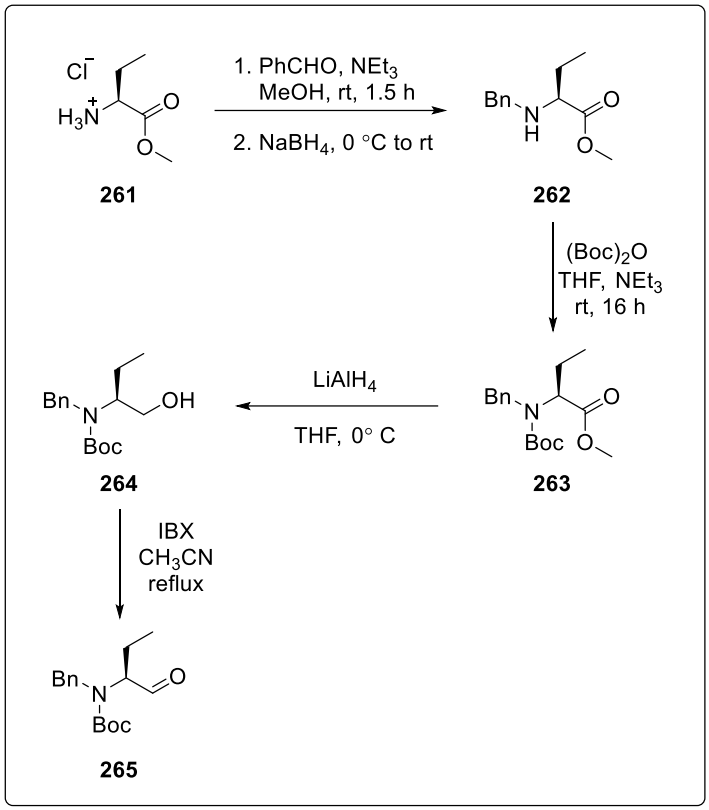
Isolated by column chromatography (9:1 hexanes: EtOAc) as a clear colourless oil (9.56 g, 90% over two steps). R_f = 0.21 (25% EtOAc in hexanes). Spectral data match the previously reported values.[223] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.35–7.26 (m, 4H), 7.26–7.22 (m, 1H), 4.39 (br s, 2H), 4.05–3.90 (m, 1H), 3.73–2.85 (m, 1H), 2.93 (br s, 1H), 1.43 (s, 9H), 1.14 (br d, *J* = 4.9 Hz, 3H).

A(III): *tert*-Butyl (*S*)-benzyl(1-oxopropan-2-yl)carbamate (**109a**)

Isolated by column chromatography (6:1 hexane/Et_2O, R_f =0.26 [11% EtOAc in hexane]) as a clear colorless oil (0.455 g, 92%). Spectral data match the previously reported values.[223] **^{1}H NMR** (500 MHz, $CDCl_3$): mixture of rotamers; δ 9.49 (s, 0.4H), 9.43 (s, 0.6 H), 7.38–7.26 (m, 5H), 4.85 (d, *J* = 15.0 Hz, 0.6H), 3.79–3.68 (m, 0.4H), 3.51–3.40 (m, 0.6H), 1.46 (s, 9H), 1.34–1.23 (m, 3H).

tert-Butyl (*S*)-benzyl(1-oxobutan-2-yl)carbamate (**265**)

Prepared according to **general procedure B**;



B(I): Methyl (*S*)-2-(benzylamino)butanoate (**262**)

Isolated a mixture of product benzyl alcohol. This mixture was carried to the next step without further purification.

B (II): Methyl (*S*)-2-[benzyl(*tert*-butoxycarbonyl)amino]butanoate (**263**)

Isolated with small amounts of an unknown impurity by column chromatography (9:1 hexanes/EtOAc). R_f = 0.15 (10% EtOAc in hexanes). This mixture was carried to the next step without further purification.

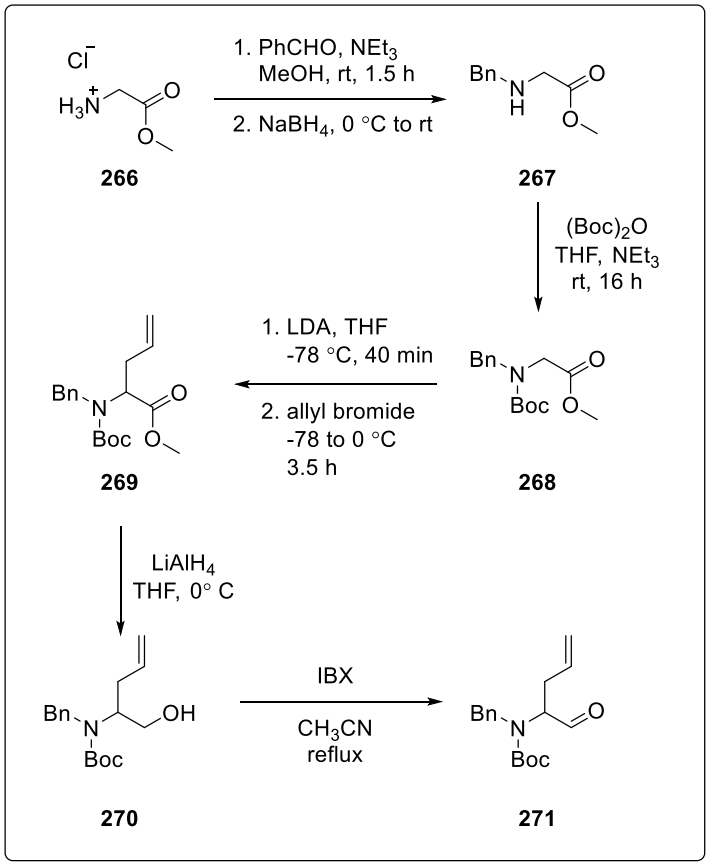
B(III): *tert*-Butyl (*S*)-benzyl(1-hydroxybutan-2-yl)carbamate (**264**)

Isolated by column chromatography (3:1 hexane/EtOAc) as a clear colorless oil (0.550 g, 38% over 3 steps). R_f =0.17 (25% EtOAc in hexane). $[\alpha]_D^{26}$ = -33 (*c* 1.1, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3445, 2972, 2877, 1690, 1496, 1454, 1366, 1251, 1048; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.40–7.26 (m, 4H), 7.26–7.22 (m, 1H), 4.76–4.51 (m, 0.3H), 4.51–4.11 (m, 1.7H), 3.87–3.70 (m, 3H), 3.16–2.91 (m, 1H), 1.74–1.59 (m, 1H), 1.50 (br s, 2.8H), 1.42 (br s, 9H), 0.96–0.78 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 157.2, 139.3, 128.6, 127.7*, 127.2, 127.2, 80.4, 64.3, 61.6, 50.0, 48.2*, 28.5, 22.6*, 21.8, 11.2; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{16}H_{25}NO_3Na$ 302.1727; Found 302.1722.

B(IV): *tert*-Butyl (*S*)-benzyl(1-oxobutan-2-yl)carbamate (**265**)

Isolated by column chromatography (8:1 hexanes/EtOAc) as a clear colourless oil (0.360 g, 91%). R_f = 0.17 (11% EtOAc in hexanes). $[\alpha]_D^{27}$ = -161 (*c* 2.0, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3369, 2976, 2934, 1695, 1497, 1455, 1367, 1250, 1166, 1049, 897, 742, 701; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 9.46 (s, 0.4H), 9.35 (s, 0.6H), 7.40–7.26 (m, 5H), 5.02 (d, *J* = 15.0 Hz, 0.6H), 4.71 (d, *J* = 15.6 Hz, 0.4H), 4.22 (d, *J* = 15.8 Hz, 0.4H), 4.13 (d, *J* = 15.0 Hz, 0.6H), 3.75–3.60 (m, 0.4H), 3.35 (dd, *J* = 7.2, 5.0 Hz, 0.6H), 2.01 (ddq, *J* = 13.9, 7.3, 7.3 Hz, 1H), 1.85–1.63 (m, 1H), 1.45 (s, 9H), 0.94 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 199.7, 155.7*, 155.3, 138.3*, 137.8, 128.9, 128.8*, 128.5, 127.9*, 127.7, 81.7, 81.2*, 67.4*, 67.3, 52.3, 51.7*, 28.4*, 28.3, 21.6, 20.5*, 11.1, 11.0*; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{16}H_{23}NO_3Na$ 300.1570; Found 300.1552.

tert-Butyl benzyl(1-oxopent-4-en-2-yl)carbamate (**271**)



Benzylglycinate (**267**):

To a solution of ethyl glycinate.HCl salt (**266**) (21.5 mmol, 3.0 g) in dry MeOH (33 mL, [0.7 M], triethylamine (21.49 mmol, 3.0 mL) followed by freshly distilled benzaldehyde (32.2 mmol, 3.3 mL) were added at room temperature. The resulting solution was stirred for 1.5 hr before cooling to 0 °C using an ice bath. Sodium borohydride (43.0 mmol, 1.63 g) was added slowly to the mixture in three portions. The resulting suspension was warmed to rt and stirred for additional 2 hr. The volatiles were removed under reduced pressure and the crude reaction mixture was partitioned between H_2O (ca. 75 mL) and CH_2Cl_2 (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined, dried

over $MgSO_4$, and volatiles were removed under reduced pressure. Crude **267** was carried to next step without further purification.

tert-Butyl ethyl *N*-benzyl-*N*-(tert-butoxycarbonyl)glycinate (**268**):

To a solution of crude **267** (21.5 mmol) in THF (72 mL, [0.3 M]) was added triethylamine (21.5 mmol, 3.0 mL) at room temperature. To this solution was added di–*tert*–butyl dicarbonate (Boc_2O) (23.6 mmol, 5.15 g) and the reaction was stirred at ambient temperature for 16 hours. The reaction was quenched with addition of HCl [1 M] and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was concentrated *in vacuo* and purified by column chromatography (7:1 hexanes: EtOAc). *tert*-Butyl ethyl *N*-benzyl-*N*-(tert-butoxycarbonyl)glycinate (**268**) was obtained as a clear colourless oil (4.37g, 85% over two steps). Spectral data match the previously reported values.[224] **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers: δ 7.36–7.29 (m, 1H), 7.29–7.19 (m, 4H), 4.55 (s, 1H), 4.51 (s, 1H), 4.16 (q, *J* = 4.8, 1H), 4.15 (q, *J* = 7.0, 1H), 3.92 (s, 1H), 1.47 (s, 4.1H), 1.47 (s, 4.9H), 1.24 (t, *J* = 1.5 Hz, 3H).

Ethyl 2-[benzyl(*tert*-butoxycarbonyl)amino]pent-4-enoate (**269**)

According to literature precedence,[225] to a flame-dried flask was added diisopropyl amine (1.05 mmol, 0.150 mL) followed by THF (1.4 mL) under inert atmosphere. This solution is cooled to 0 °C using an ice bath and *n*-BuLi [2.5 M] in THF (0.962 mmol, 0.385 mL) was added dropwise. The reaction mixture was stirred at this temperature for additional 15 min. The reaction was cooled to -78 °C and a solution of **268** (0.837 mmol, 0.200 g) in THF (2.8 mL) was added dropwise to this solution. Stirring was continued for additional 40 minutes and allyl bromide (1.26 mmol, 0.110 mL) was added to the reaction mixture. The reaction was stirred at -78 °C for additional 3.5 h and then allowed to warm to 0 °C. The reaction was quenched with the addition of sat. NH_4Cl_{aq} and

extracted with Et_2O (3 × 3 mL). The organic layers were combined, washed with HCl [1 M] (1 × 3 mL), and dried over sodium sulphate. The crude product was concentrated *in vacuo* and purified by column chromatography (9:1 hexanes: Et_2O). Ethyl 2-[benzyl(*tert*-butoxycarbonyl)amino]pent-4-enoate[225] (**269**) was isolated along with small amounts of an unknown impurity. This mixture was taken to next step without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$): mixture of rotamers δ 7.36–7.27 (m, 4H), 7.26–7.20 (m, 1H), 5.80–5.56 (m, 1H), 5.08–5.00 (m, 1H), 5.08–4.95 (m, 2H), 4.68 (d, *J* = 15.5 HZ, 0.5H), 4.52 (*J* = 15.8 Hz, 0.5H), 4.44–4.36 (m, 0.5H), 4.35–4.27 (m, 1H), 4.12–3.94 (m, 2H), 3.90–3.80 (m, 0.5H), 2.71 (dt, *J* = 14.4, 6.3 Hz, 1H), 2.62–2.41 (m, 1H), 1.47 (s, 5H), 1.39 (s, 4H), 1.19 (t, *J* = 7.1 Hz, 3H).

Ethyl benzyl(1-hydroxypent-4-en-2-yl)carbamate (**270**)

To a suspension of $LiAlH_4$ (4.66 mmol, 0.177g) in THF (7 mL) was added the crude (**269**) (1.55 mmol) in dry THF (10.5 mL) at 0°C. After the reaction is complete (judged by TLC analysis) aqueous solution of Rochelle's salt [0.5 M] (ca. 20 mL) was slowly added to the mixture at 0 °C. The reaction was vigorously stirred at room temperature for an additional 2 hours. The reaction mixture was diluted in EtOAc (30 mL) and the layers were separated. The aqueous phase was extracted using EtOAc (2 × 30 mL) and the combined organic layers were dried over $MgSO_4$. The crude product was concentrated *in vacuo* and purified by column chromatography (4:1 hexanes/EtOAc) ethyl benzyl(1-hydroxypent-4-en-2-yl)carbamate (**270**) was obtained as a clear colourless oil (0.350, 36% over two steps); R_f = 0.10 (25% EtOAc in hexane. **FTIR** (KBr film) ν_{max} (cm^{-1}): 3442, 3066, 1683, 1496, 1367, 1167, 1030; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.37–7.22 (m, 5H), 5.73 (br s, 1H), 5.16–4.93 (m, 2H), 3.96–3.46 (m, 3H), 3.36 (br s, 0.6H), 2.54–2.20 (m, 2H), 1.86–1.32 (m, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 156.9, 139.2, 150.3, 135.0, 128.6, 127.7*, 127.2, 117.3,

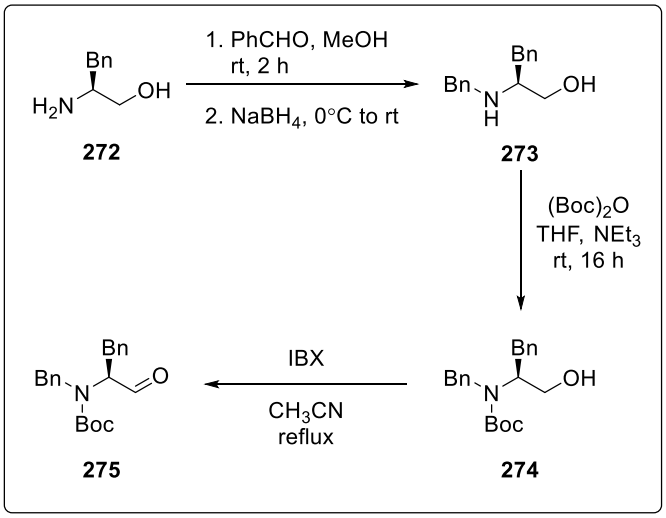
80.5, 64.2, 63.8*, 60.0, 59.6*, 50.8, 48.9*, 34.5*, 33.4, 28.4; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{17}H_{25}NO_3Na$ 314.1727; Found 314.1737.

Ethyl benzyl(1-hydroxypent-4-en-2-yl)carbamate (**271**)

IBX (2.30 mmol, 0.642g) was added to a solution of **270** (1.15 mmol, 0.350g) in acetonitrile (5.8 mL, [0.2 M]) and heated to reflux. The reaction was monitored for complete consumption of starting material. After 40 minutes, the contents were cooled to room temperature, filtered through a pad of Celite® and washed with EtOAc (3 × 5 mL). The resulting solution was concentrated and purified by chromatography. (5:1 hexanes/ Et_2O) *tert*-butyl benzyl(1-oxopent-4-en-2-yl)carbamate (**271**) was obtained as a clear colourless oil (0.298, 86%); R_f =0.21 (16% Et_2O in hexane. **FTIR** (KBr film) ν_{max} (cm^{-1}): 2979, 2816, 1738, 1703, 1454, 1422, 1250, 1165; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 9.45 (s, 0.4H), 9.35 (s, 0.6H), 7.39–7.27 (m, 5H), 5.89–5.68 (m, 1H), 5.16–5.06 (m, 1H), 5.05 (d, *J* = 15.2 Hz, 0.4H), 4.77 (d, *J* = 15.9 Hz, 0.6H), 4.16 (d, *J* = 14.7 Hz, 0.4H), 4.07 (d, *J* = 15.0 Hz, 0.6H), 3.67 (dd, *J* = 9.2, 5.2 Hz, 0.4H), 3.46 (dd, *J* = 8.9, 5.2 Hz, 0.6H), 2.81–2.68 (m ,1H), 2.56 (ddd, *J* = 14.0, 7.1, 7.1 Hz 0.4H), 2.44 (ddd, *J* = 14.0, 7.1, 7.1 Hz, 0.4H), 1.47 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 198.9*, 198.8, 155.6*, 155.0, 138.0*, 137.7, 134.5*, 134.2, 128.9, 128.8*, 128.5, 127.9*, 127.8, 118.3, 118.1*, 81.9, 81.3*, 65.7*, 65.5, 52.3, 52.2*, 32.9, 31.9*, 28.4*, 28.3; **HRMS** (FD-TOF) *m*/*z*: [M] Calcd. for $C_{17}H_{23}NO_3$ 289.1678; Found 396.1683.

tert-Butyl (*S*)-benzyl(1-oxo-3-phenylpropan-2-yl)carbamate (**275**)

Prepared according to **general procedure A**;



A(I): (*S*)-2-(Benzylamino)-3-phenylpropan-1-ol (**273**)

Obtained as a mixture with benzyl alcohol. This mixture was carried to the next step without further purification.

A (II): *tert*-Butyl (*S*)-benzyl(1-hydroxy-3-phenylpropan-2-yl)carbamate (**274**)

Isolated along with small amounts of an unknown impurity by column chromatography (3:1 hexanes: acetone). This mixture was carried to next step without further purification. **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.34–7.26 (m, 3H), 7.26–7.18 (m, 2H), 4.49–4.29 (m, 1H), 3.86 (d, *J* = 14.5 Hz, 0.5H), 3.78–3.59 (m, 2.5H), 3.10–2.88 (m, 1H), 1.44 (s, 7.5H), 1.29–1.24 (m, 1.5H).

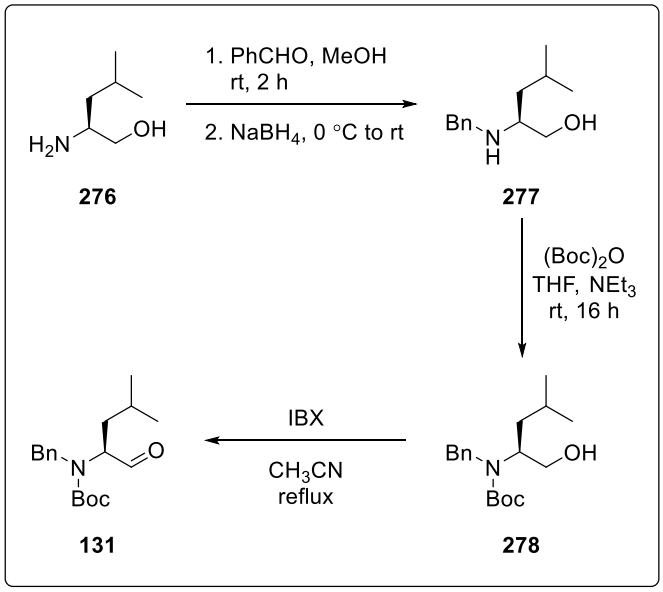
A(III): *tert*-Butyl (*S*)-benzyl(1-oxo-3-phenylpropan-2-yl)carbamate (**275**)

Isolated by column chromatography (8:1 hexane/EtOAc, R_f =0.28 [11% EtOAc in hexane]) as a light yellow oil (0.756 g, 22% over three steps). Spectral data match the previously reported

values.[223] **^{1}H NMR** (500 MHz, $CDCl_3$): mixture of rotamers; δ 9.46 (s, 0.4H), 9.36 (s, 0.6H), 7.37–7.27 (m, 4H), 7.26–7.22 (m, 2.2H), 7.17 (d, *J* = 7.3 Hz, 0.8H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 7 Hz, 2H), 4.89 (d, *J* = 15.0 Hz, 0.6H), 4.40 (d, *J* = 15.5 Hz, 0.4H), 3.61 (dd, *J* = 10.1, 4.5 Hz, 0.4H), 3.53 (dd, *J* = 10.0, 4.3 Hz, 0.6H), 3.33 (t, *J* = 6.3 Hz, 0.4H), 3.31 (t, *J* = 4.5 Hz, 0.6H), 3.22 (d, *J* = 15.6 Hz, 0.4H), 3.12 (dd, *J* = 13.9, 10.2 Hz, 0.4H), 3.05 (d, *J* = 15.1 Hz, 0.6H), 2.96 (dd, *J* = 13.9, 10.0 Hz, 0.6H), 1.51 (s, 5H), 1.50 (s, 4H).

tert-Butyl (*S*)-benzyl(4-methyl-1-oxopentan-2-yl)carbamate (**131**)

Prepared according to **general procedure A**;



A(I): (*S*)-2-(Benzylamino)-4-methylpentan-1-ol (**277**)

Obtained as a mixture with benzyl alcohol. This mixture was carried to the next step without further purification.

A(II): *tert*-Butyl (*S*)-benzyl(1-hydroxy-4-methylpentan-2-yl)carbamate (**278**)

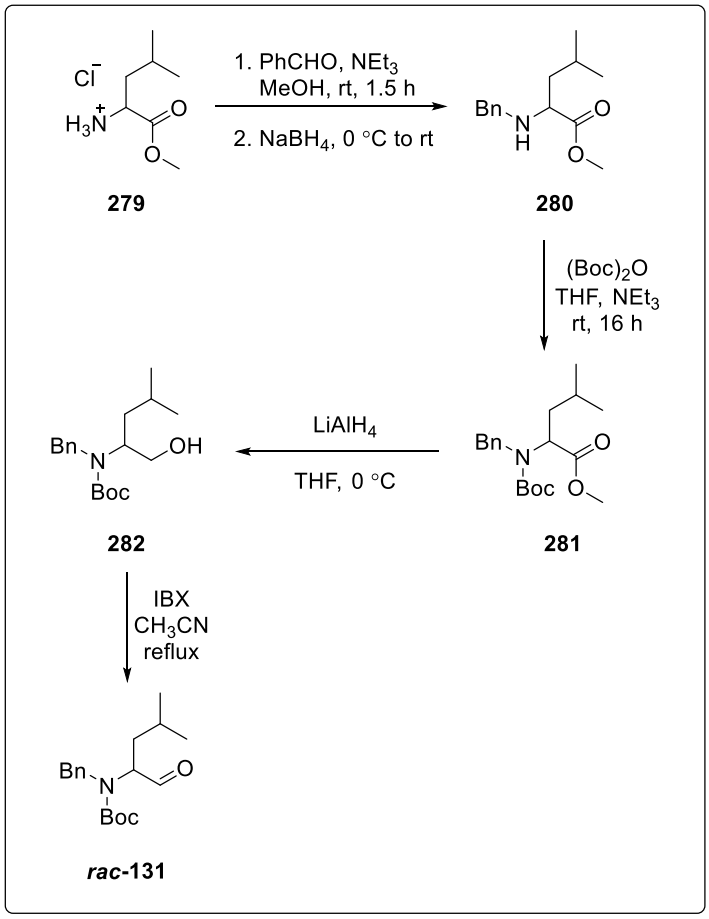
Isolated by column chromatography (6:1 hexanes/acetone) the corresponding as a clear colourless oil (2.37g, 90% over two steps). R_f = 0.11 (24% acetone in hexanes). Spectral data match the previously reported values.[223] **^{1}H NMR** (500 MHz, $CDCl_3$): mixture of rotamers; δ 7.35–7.20 (m, 10H), 4.69–4.47 (m, 0.4H), 4.47–4.35 (m, 0.6H), 4.35–4.18 (m, 1H), 4.12–3.97 (m, 0.4H), 3.96–3.78 (m, 0.6H), 3.69–3.35 (m, 2H), 2.97–2.81 (m, 1H), 1.54–1.32 (m, 11H), 1.30–1.07 (m, 1H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H).

A(III): *tert*-Butyl (*S*)-benzyl(4-methyl-1-oxopentan-2-yl)carbamate (**131**)

Isolated by column chromatography (9:1 hexane/EtOAc). R_f = 0.26 (10% EtOAc in hexane) as a clear colorless oil (0.451 g, 91%). Spectral data match the previously reported values.[223] **^{1}H NMR** (500 MHz, $CDCl_3$): mixture of rotamers; δ 9.44 (s, 0.4H), 9.34 (s, 0.6H), 7.37–7.27 (m, 5H), 5.01 (d, *J* = 14.8 Hz, 0.6H), 4.71 (d, *J* = 15.5 Hz, 0.4H), 4.19 (d, *J* = 15.5 Hz, 0.4H), 4.10 (d, *J* = 15.0 Hz, 0.6H), 3.94–3.85 (m, 0.4H), 4.54 (dd, *J* = 7.0, 5.0 Hz, 0.6H), 1.90–1.76 (m, 1H), 1.67–1.55 (m, 2H), 1.46 (s, 9H), 0.94–0.88 (m, 3H), 0.86 (d, *J* = 6.6 Hz, 3H).

rac-*tert*-Butyl benzyl(4-methyl-1-oxopentan-2-yl)carbamate (***rac*-131**)

Prepared according to **general procedure B**;



B(I): *rac*-Methyl benzylleucinate (**280**)

Obtained as a mixture with benzyl alcohol. This mixture was carried to the next step without further purification.

B (II): *rac*-Methyl *N*-benzyl-*N*-(*tert*-butoxycarbonyl)leucinate (**281**)

Isolated by column chromatography (9:1 hexanes: EtOAc) as a clear colourless oil (2.17 g, 59% over two steps). R_f = 0.23 (10% EtOAc in hexanes). Spectral data match the previously reported values.[223] **^{1}H NMR** (500 MHz, $CDCl_3$): mixture of rotamers; δ 7.41–7.26 (m, 3.6H), 7.26–7.20

(m, 1.4H), 4.79–4.65 (m, 0.5H), 4.59 (d. *J* = 14.9 Hz, 0.5H), 4.52 (d, *J* = 16.5 Hz, 0.5H), 4.39 (d, *J* = 14.8 Hz, 0.5H), 4.30 (d, *J* = 14.9 Hz, 0.5H), 4.22–4.04 (m, 0.5H), 3.58 (s, 3H), 1.81–1.69 (m, 1H), 1.64–1.57 (m, 1H), 1.48 (s, 5H), 1.43–1.32 (m, 5H).

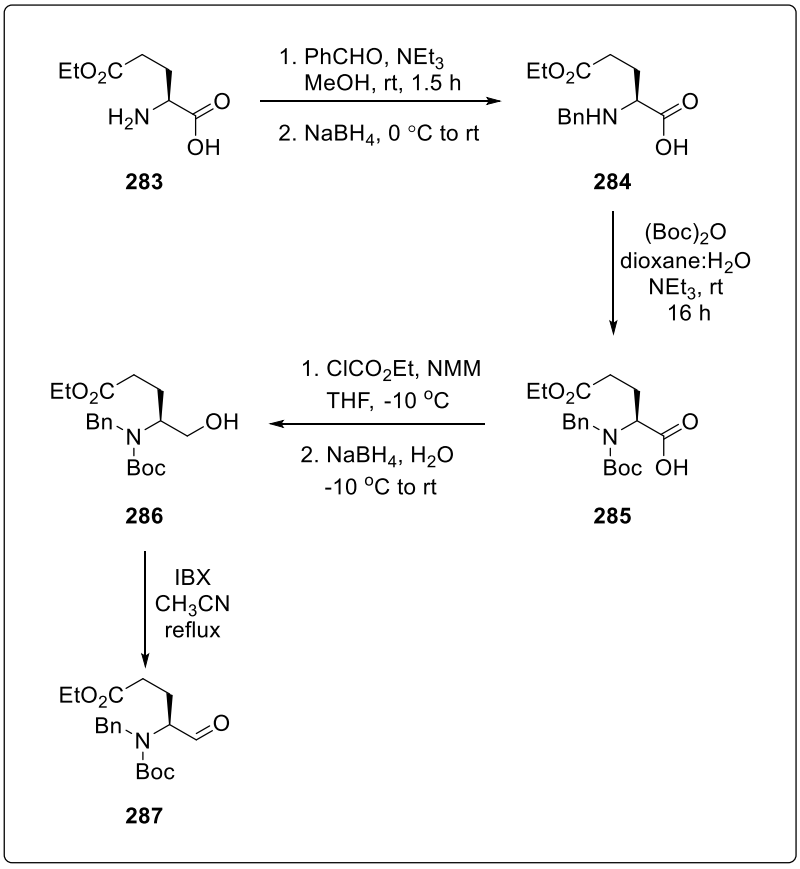
B(III): *rac*-*tert*-Butyl benzyl(1-hydroxy-4-methylpentan-2-yl)carbamate (**282**)

Isolated by column chromatography (3:1 hexane/EtOAc). as a clear colorless oil (0.858 g, 93%). R_f =0.20 (25% EtOAc in hexane). **^{1}H NMR** spectrum was identical to **278**.

B(IV): *tert*-Butyl benzyl(4-methyl-1-oxopentan-2-yl)carbamate (***rac*-131**)

Isolated by column chromatography (9:1 hexanes/EtOAc) as a clear colourless oil (0.455 g, quantitative). R_f = 0.26 (10% EtOAc in hexanes); **^{1}H NMR** spectrum was identical to **131**.

Ethyl (*S*)-4-[benzyl(*tert*-butoxycarbonyl)amino]-5-oxopentanoate (**287**)



(*S*)-2-(Benzylamino)-5-ethoxy-5-oxopentanoic acid (**284**)

To a solution of (*S*)-2-amino-5-ethoxy-5-oxopentanoic acid (**283**) (11.4 mmol, 2.00 g) in dry MeOH (23 mL, [0.5 M]), triethylamine (22.8 mmol, 3.2 mL) followed by freshly distilled benzaldehyde (17.13 mmol, 1.8 mL) were added at room temperature. The resulting solution was stirred for 1 h before cooled to 0 °C using an ice bath. Sodium borohydride (34.3 mmol, 1.30g) was added to the mixture in three portions. The resulting suspension was warmed to room temperature and stirred for additional 2 h. The volatiles were removed under reduced pressure and the crude reaction mixture was partitioned between H_2O (ca. 75 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 100 mL). The organic layers were combined, dried over $MgSO_4$, and volatiles were removed under reduced pressure to

afford **284** and benzyl alcohol as white crystals. The crude reaction mixture was carried to the next step without further purification.

(*S*)-2-[Benzyl(*tert*-butoxycarbonyl)amino]-5-ethoxy-5-oxopentanoic acid[22] (**285**)

To a solution of **284** (3.78 mmol) in (1:1 *v*/*v*) dioxane:H_2O (13 mL, [0.3 M]) was added triethylamine (11.4 mmol, 1.6 mL) at room temperature. To this solution was added di–*tert*–butyl dicarbonate (Boc_2O) (3.79 mmol, 0.826 g) and stirred at ambient temperature for 16 hours. The reaction was quenched with addition of HCl [1 M] and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was concentrated *in vacuo* and purified by column chromatography (1:1 hexane/EtOAc). **285**[226] and benzyl alcohol were obtained as a mixture which were carried to the next step without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers: δ 7.36–7.26 (m, 5H), 4.70–4.61 (m, 0.4H), 4.61–4.48 (m, 0.6H), 4.35 (d, *J* = 15.6 Hz, 1H), 4.28–4.14 (m, 0.6H), 4.12–4.01 (m, 1.8H), 4.00–3.88 (m, 0.6H), 2.40–2.15 (m, 3H), 2.15–1.97 (m, 1H), 1.46 (s, 9H), 1.22 (t, *J* = 7.2Hz, 3H).

Ethyl (*S*)-4-[benzyl(*tert*-butoxycarbonyl)amino]-5-hydroxypentanoate (**286**)

Crude **285** (1.01 mmol, 0.369 g) was dissolved in THF (5.1 mL, [0.2 M]) and cooled to –10 °C. To this solution was added 4-methyl morpholine (NMM) (2.03 mmol, 0.22 mL) followed by ethyl chloroformate (1.52 mmol, 0.14 mL). The mixture was stirred at this temperature for 1 h, then $NaBH_4$ (3.04 mmol, 0.115g) was added in one portion followed by addition of MeOH (10.2 mL). The mixture was stirred for an additional 30 minutes and the crude product was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The resulting solution was concentrated *in vacuo* and purified by column chromatography (1:1 hexane/EtOAc) (**286**) was obtained as a clear colourless oil (0.239g, 27% over three steps); R_f

=0.18 (50% EtOAc in hexane. $[\alpha]_D^{27}$ = -122 (*c* 1.1, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3458, 2978, 1735, 1690, 1496, 1392, 1366, 1249, 1165; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.36–7.27 (m, 4H), 7.26–7.23 (m, 1H), 4.56–4.39 (m, 1H), 4.39–4.21 (m, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.77–3.50 (m, 3H), 3.23–3.15 (m, 1H), 2.47–2.18 (m, 2H), 2.08–1.83 (m, 2H), 1.44 (br s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 173.3, 156.9, 139.1, 128.7, 127.4, 127.4, 80.8, 64.4, 60.6, 59.4, 59.1, 50.8, 48.4, 31.0, 28.5, 25.6*, 23.6, 14.3; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{19}H_{29}NO_5Na$ 374.1937; Found 374.1945.

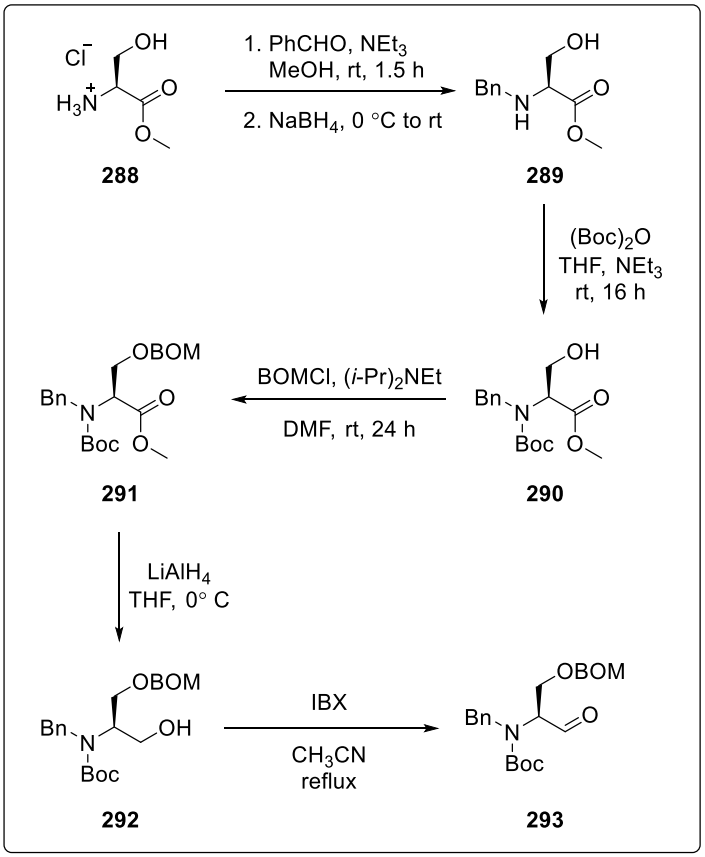
Ethyl (*S*)-4-[benzyl(*tert*-butoxycarbonyl)amino]-5-oxopentanoate (**287**)

IBX (2.30 mmol, 0.642 g) was added to a solution of **286** (0.595 mmol, 0.209 g) in acetonitrile (6 mL, [0.1 M]) and heated to reflux. The reaction was monitored for complete consumption of starting material. After 1 h, the contents were cooled to room temperature, filtered through a pad of Celite® and washed with EtOAc (3 × 5 mL). The resulting solution was concentrated and purified by chromatography (7:1 hexane/ EtOAc). Compound **287** was obtained as a clear colourless oil (0.179, 86%); R_f =0.16 (13% EtOAc in hexane). $[\alpha]_D^{27}$ = -120 (*c* 3.2, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3389, 2993, 1738, 1703, 1497, 1250, 1163, 1030; **^{1}HNMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 9.38 (s, 0.4H), 9.27 (s, 0.6H), 7.36–7.26 (m, 5H), 5.04 (d, *J* = 14.9 Hz, 0.6H), 4.77 (d, *J* = 15.5 Hz, 0.4H), 4.18 (d, *J* = 15.5 Hz, 0.6H), 4.15–4.08 (m, 2H), 4.06 (d, *J* = 14.9 Hz, 0.6H), 3.77–3.67 (m, 0.4H), 3.56 (app t, *J* = 6.3 Hz, 0.6H), 2.45–2.25 (m, 3H), 2.08–1.90 (m, 1H), 1.47 (s, 3H), 1.44 (s, 6H), 1.24, (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 199.0, 190.0*, 173.1*, 173.0, 155.5*, 155.1, 138.0*, 137.7, 128.9, 128.6, 128.0*, 127.8, 82.0, 81.4*, 64.8*, 64.5, 60.6, 60.6*, 51.9,

51.8*, 30.5, 28.4*, 28.2, 23.6, 22.6*, 14.3; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{19}H_{27}NO_5Na$ 372.1781; Found 372.1795.

tert-Butyl (*S*)-benzyl{1-[(benzyloxy)methoxy]-3-oxopropan-2-yl}carbamate (**293**)

Prepared according to **general procedure B**;



B(I): Methyl benzyl-L-serinate (**289**)

Obtained as a mixture with benzyl alcohol. This mixture was carried to the next step without further purification.

B (II): Methyl *N*-benzyl-*N*-(*tert*-butoxycarbonyl)-L-serinate (**290**)

Isolated by column chromatography (9:1 hexane/ EtOAc) as a clear colourless oil (2.11 g, 53% over two steps). Spectral data match the previously reported values.[227] **^{1}H NMR** (500 MHz, $CDCl_3$): mixture of rotamers; δ 7.37–7.27 (m, 5H), 4.58–4.51 (m, 1.5H), 4.47–4.39 (m, 0.5H), 4.15–4.02 (m, 1.5H), 3.87–3.73 (m, 1H), 3.70 (s, 3H), 3.52–3.43 (m, 0.5H), 3.13–3.04 (m, 0.5H), 2.43–2.34 (m, 0.5H), 1.45 (s, 9H).

Methyl *N*-benzyl-*O*-[(benzyloxy)methyl]-*N*-(*tert*-butoxycarbonyl)-L-serinate (**291**)

To a solution of **290** (1.90 g, 6.15 mmol) in dry DMF (6.2 mL [1 M]) was added $(i\text{-Pr})_2$NEt (3.4 mL, 19.7 mmol) at room temperature under argon. This was followed by the addition of BOMCl (70% purity *w*/*w*) (4.11 g, 18.4 mmol). After 24 hours, the reaction mixture was diluted in EtOAc (150 mL) and washed sequentially with sat. NH_4Cl_{aq} (150 mL), distilled water (150 mL), and brine (150 mL). The organic layer was dried over $MgSO_4$ and concentrated. The volatiles were removed *in vacuo* and the reaction mixture was purified by chromatography (7:1 hexane/ EtOAc) to afford methyl **291** as light yellow oil (2.00 g, 76%). R_f = 0.17 (13% EtOAc in hexane). Spectral data match the previously reported values.[227] **^{1}H NMR** (500 MHz, $CDCl_3$): mixture of rotamers; δ 7.38–7.26 (m, 8.8H), 7.26–7.20 (m, 1.2H), 4.77 (d, *J* = 15.3 Hz, 0.5H), 4.72–4.66 (m, 1H), 4.66–4.63 (m, 0.5H), 4.61–4.55 (m, 1.5H), 4.52–4.39 (m, 3H), 4.11–4.04 (m, 1H), 4.03–3.95 (m, 1H), 3.84 (app t, 9.4 Hz, 0.5H), 3.69 (s, 1.5H), 3.65 (s, 1.5H), 1.44 (s, 4.5H), 1.39 (s, 4.5H).

B(III): *tert*-Butyl (*R*)-benzyl{1-[(benzyloxy)methoxy]-3-hydroxypropan-2-yl}-carbamate (**292**)

Isolated by column chromatography (2:1 hexane/EtOAc) as a clear colorless oil (0.346 g, 74%). R_f =0.22 (33% EtOAc in hexane). Spectral data match the previously reported values.[227] **^{1}H NMR**

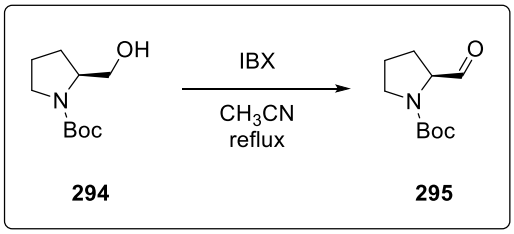
(500 MHz, $CDCl_3$) mixture of rotamers; δ 7.39–7.26 (m, 8.2H), 7.26–7.22 (m, 1.8H), 4.74–4.64 (m, 2H), 4.64–4.58 (m, 0.7H), 4.54 (dd, *J* = 12.1, 2.5Hz, 2.3H), 4.43-4.30 (m, 1H),3.96–3.62 (m, 5H), 3.40 (br s, 1H), 1.54–1.37 (m, 9H).

B(IV): *tert*-Butyl (*S*)-benzyl{1-[(benzyloxy)methoxy]-3-oxopropan-2-yl}carbamate (**293**)

Isolated by column chromatography (5:1 hexanes: acetone) as a clear colourless oil (0.271 g, 79%). Rf = 0.20 (17% acetone in hexanes). Spectral data match the previously reported values.[227] **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 9.44 (s, 0.4H), 9.33 (s, 0.6H), 7.39–7.27 (m, 10H), 5.11 (d, *J* = 15.0 Hz, 0.6H), 4.88 (d, *J* = 15.5 Hz, 0.4Hz), 4.74 (app t, *J* = 6.9 Hz, 0.8H), 4.71 (app t, *J* = 6.0 Hz, 1.2H), 4.60–4.52 (m, 2H), 4.29 (d, *J* = 15.6 Hz, 0.4H), 4.22 (d, *J* = 15 Hz, 0.6H), 4.18–4.09 (m, 1H), 3.98 (app t, 7.8Hz, 0.4H), 3.91–3.79 (m, 1H), 3.69 (app t, *J* = 6.9 Hz, 0.6H), 1.46 (s, 4H), 1.43 (s, 5H).

Synthesis of Other Doubly *N*,*N*- Protected Amino Aldehydes

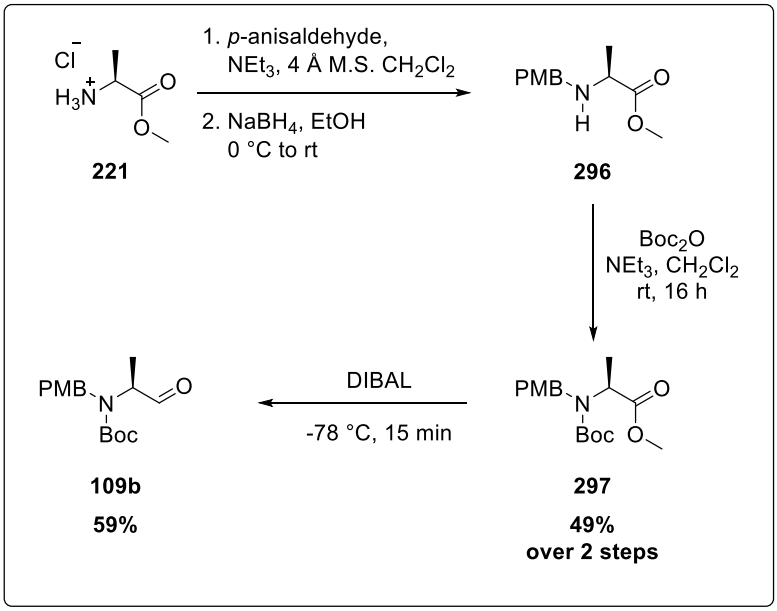
tert-Butyl (*S*)-2-formylpyrrolidine-1-carboxylate (*N*-Boc-L-Prolinal) (**295**)



IBX (3.74 mmol, 1.05 g) was added to a solution of *N*–Boc-prolinol (**294**) (2.49 mmol, 0.500 g) in acetonitrile (12.5 mL, [0.2 M]) and heated to reflux. The reaction was monitored for complete

consumption of starting material. After 30 minutes the contents were cooled to room temperature, filtered through a pad of Celite® and washed with EtOAc (3 × 10 mL). The resulting mixture was concentrated and purified by column chromatography. Compound **295** was isolated by column chromatography (8:1 hexane/EtOAc, R_f =0.10 [11% EtOAc in hexane]) as clear colourless oil (0.413 g, 83%). Spectral data match the previously reported values.[228] **^{1}H NMR** (500 MHz, $CDCl_3$): mixture of rotamers; δ 9.56 (s, 0.4H), 9.46 (d, *J* = 2.8 Hz, 0.6H), 4.25–4.14 (m, 0.4H), 410–3.99 (m, 0.6H), 3.61–3.52 (m, 0.gH), 3.52–3.39 (m, 1.4H), 2.17–2.09 (m, 0.6H), 2.08–2.01 (m, 0.4H), 2.01–1.91 (m, 1H), 1.91–1.82 (m, 2H), 1.48 (s, 3H), 1.43 (s, 6H).

tert-butyl (*S*)-(4-methoxybenzyl)(1-oxopropan-2-yl)carbamate (**109b**)



Following a reported procedure,[229] to a solution of L-alanine methyl ester hydrochloride salt (**221**) (14.3 mmol, 2.00 g) in CH_2Cl_2 (42 mL), NEt_3 (25.8 mmol, 3.6 mL) followed by freshly distilled *p*-anisaldehyde (14.3 mmol, 1.7 mL) were added at room temperature. The resulting

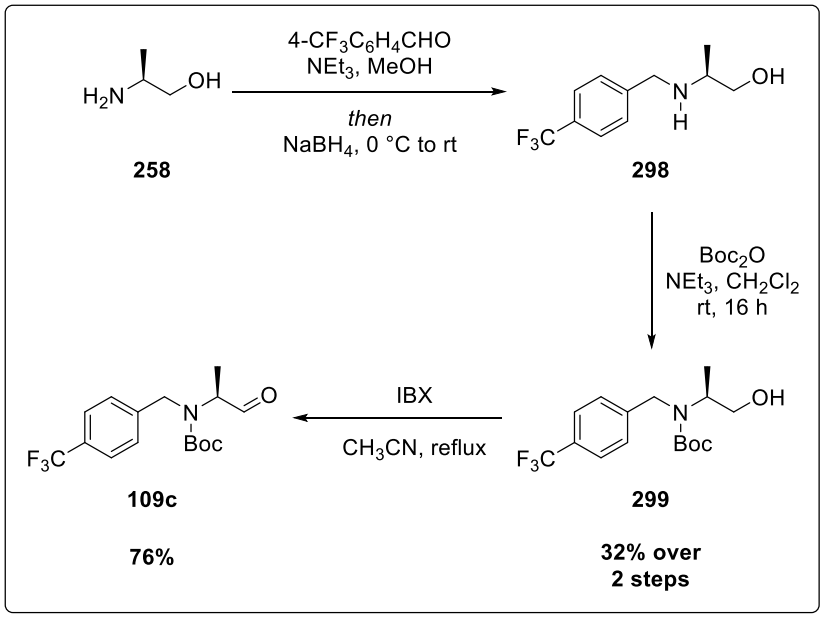
solution was stirred for 18 h before EtOH (14 mL) was added and the reaction mixture was cooled to 0 °C using an ice bath. Sodium borohydride (22.9 mmol, 0.868 g) was added to the mixture in three portions. The resulting suspension was warmed to room temperature and stirred for additional 17 hours. The reaction mixture was treated with 1M HCl (aq) (pH=2) and the pH was re-adjusted to neutral using 0.5M NaOH (aq). The mixture was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were washed sequentially with sat. NH_4Cl (aq) (50 mL) and H_2O (50 mL), and dried using $MgSO_4$. The volatiles were removed under reduced pressure. Column chromatography (4:1 hexane:acetone R_f = 0.10) afforded **296**[230] along with 4% (4-methoxyphenyl)methanol. This mixture was taken to the next step without any further purification.

To **296** (4.30 mmol, 1.00g, [96% purity]) in CH_2Cl_2 (6.5 mL), was added NEt_3 (4.74 mmol, 0.66 mL). Boc_2O (1.24 mmol, 12.2 mL) was added to this mixture at room temperature and the reaction was stirred for 16 hours. Removal of volatiles under reduced pressure followed by column chromatography (7:1 hexane:EtOAc, Rf = 0.25) afforded **297** as a colourless oil (1.13 g, 49% over 2 steps). **^{1}H NMR** (500 MHz, $CDCl_3$); mixture of rotamers; δ 7.25-7.13 (m, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 4.56–4.38 (m, 2H), 4.36–4.21 (m, 0.5H), 3.92–3.84 (m, 0.5H), 3.80 (s, 3H), 3.65 (s, 3H), 1.47–1.39 (m, 9H), 1.38–1.27 (m, 3H).

To dry toluene (10 mL) was added **297** (0.500 g, 1.55 mmol) in toluene (18 mL) and the reaction flask was cooled to -78 °C. This mixture was stirred for 10 min at this temperature and DIBAL-H (1.0 M in hexane, 4.09 mmol, 4.1 mL) was added dropwise to the reaction by maintaining -78 °C. After consumption of the starting material as judged by TLC analysis (15 min), the reaction was quenched with careful addition of MeOH (10 mL) and warmed gradually to room temperature. The reaction mixture was treated with citric acid (aq) (10% *v/v*) (10 mL) and stirred vigorously at room temperature for an additional 2 hours. Volatiles were removed *in vacuo* and the crude

reaction mixture was partitioned between H_2O:EtOAc (1:1, 50 mL each). The layers were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The organic layers were combined and dried using $MgSO_4$. Removal of volatiles followed by chromatography (8:1 hexane/EtOAc, R_f =0.26) afforded **109b** as a white solid (0.294 g, 59%). **^{1}H NMR** (500 MHz, $CDCl_3$): mixture of rotamers; δ 9.44 (s, 0.4H), 9.40 (s, 0.6H), 7.25–7.15 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.76 (d, *J* = 14.9 Hz, 0.6H), 4.59 (d, *J* = 15.3 Hz, 0.4H), 4.25 (d, *J* = 15.1 Hz, 1H), 3.80 (s, 2.9H), 3.72–3.66 (m, 0.4H), 3.65 (s, 0.1H), 3.48-3.40 (m, 0.6H), 1.48 (s, 3H), 1.45 (s, 6H), 1.32–1.21 (m, 3H).

tert-butyl (*S*)-(1-oxopropan-2-yl)[4-(trifluoromethyl)benzyl]carbamate (**109c**)

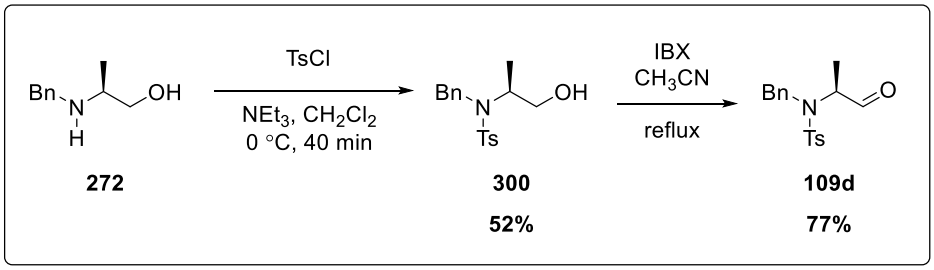


Following a modified reported procedure,[222] to a solution of the L-alaninol (**258**) (6.66 mmol, 0.91 mL) in dry MeOH (26 mL) freshly distilled 4-(trifluoromethyl)benzaldehyde (6.66 mmol, 0.518 mL) was added at room temperature. The resulting solution was stirred for 2 hours before

being cooled to 0 °C using an ice bath. $NaBH_4$ (33.3 mmol, 1.26 g) was slowly added to the mixture in three portions. The resulting suspension was warmed to room temperature and stirred for one hour. The suspension was once again cooled to 0 °C and quenched with the addition of sat. $NH_4Cl_{(aq.)}$ (50 mL). The reaction mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$. The crude mixture (**298**) was concentrated *in vacuo* and carried to next step without further purification.

N-Boc protection was carried out according to **General Procedure A(II)**. Column chromatography (2:1 hexane:EtOAc, R_f = 0.24) afforded **299** as a clear colourless oil (0.674 g, 32% over two steps) **^{1}H NMR** (600 MHz, $CDCl_3$); mixture of rotamers; δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 7.6 Hz, 2H), 4.48 (d, *J* = 15.4 Hz, 1.3H), 4.43–4.33 (m, 0.7H), 4.03–4.16 (m, 1H), 3.63–3.72 (m, 0.7H), 3.55–3.63 (m, 1.3H), 2.66 (br s, 1H), 1.24–1.29 (m, 9H), 1.13 (br s, 3H). Oxidation of **299** to **109c** was carried out according to **General Procedure A(III)**. Column chromatography (8:1 hexane:EtOAc R_f = 0.30) afforded **4.2c** as a clear colourless oil (0.378g, 76%). **^{1}H NMR** (600 MHz, $CDCl_3$): mixture of rotamers; δ 9.54 (s, 0.4H), 9.47 (s, 0.6H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.50–7.35 (m, 2H), 4.85 (d, *J* = 15.0 Hz, 0.6H), 4.70 (d, *J* = 17.2 Hz, 0.4H), 4.41–4.26 (m, 1H), 3.88 (s, 0.4H), 3.50 (s, 0.6H), 1.46 (s, 9H), 1.37–1.22 (m, 3H).

(*S*)-*N*-benzyl-4-methyl-*N*-(1-oxopropan-2-yl)benzenesulfonamide (**109d**)



According to a modified literature procedure,[231] to a solution of **272** (3.03 mmol, 0.500g) in CH_2Cl_2 (10 mL) was added NEt_3 (3.63 mmol, 0.51 mL) and the reaction flask was cooled in an ice-bath. A solution of TsCl (3.33 mmol, 0.636 g) in CH_2Cl_2 was added to reaction mixture over 20 minutes and the contents were stirred at 0 °C for an additional 20 minutes. The reaction was quenched with the addition of water (10 mL) and the crude reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with sat. $NaHCO_3$ (aq) and dried over MgSO4. Column chromatography (3:2 hexane:acetone, R_f = 0.31) afforded **300** as a white solid (0.502 g, 52%). Spectral data match the previously reported values.[231] **^{1}H NMR** (500 MHz, $CDCl_3$); δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.45–7.38 (m, 2H), 7.38–7.27 (m, 5H), 4.68 (d, *J* = 15.7 Hz, 1H), 4.15 (d, *J* = 15.7 Hz, 1H), 4.02 (ap. sex, *J* = 9.7, 9.7, 9.7 Hz, 1H), 3.31–3.20 (m, 2H), 2.43 (s, 3H), 1.66 (dd, *J* = 7.3, 5.3 Hz, 1H), 0.90 (d, *J* = 7.0 Hz, 3H).

IBX (1.41 mmol, 0.392 g) was added to a mixture of **300** (0.940 mmol, 0.300 g) in acetonitrile (4.7 mL) and heated to reflux. The reaction was monitored for complete consumption of starting material upon which the contents were cooled to room temperature, filtered through a pad of Celite® and washed with EtOAc (3 × 10 mL). The resulting mixture was concentrated and purified by column chromatography (8:1 hexane/acetone, R_f =0.25) to afford **109d** as a yellow viscous oil (0.229 g, 77%). Spectral data match the previously reported values.[232] **^{1}H NMR** (600 MHz,

$CDCl_3$): δ 9.30 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.32–7.29 (m, 5H), 4.56 (d, *J* = 14.8 Hz, 1H), 4.22–4.14 (m, 2H), 2.46 (s, 3H), 1.48 (d, *J* = 7.1 Hz, 3H).

General Procedures for the Cross-Benzoin Reaction

General Procedure C

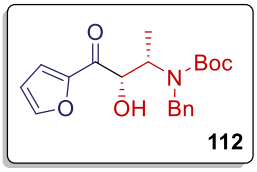
The corresponding *N*–Boc-*N*-Bn–amino aldehyde (0.152 mmol, 1.0 equiv) and triazolium salt **12** (0.0304 mmol, 0.2 equiv) were added to an oven–dried test tube with a Schlenk take–off and fitted with a septum. The vessel was placed under vacuum and re–filled with argon three times to ensure inert atmosphere. The hetereoaromatic aldehyde (0.228 mmol, 1.5 equiv) and CH_2Cl_2 (0.3 mL, [0.5 M]) were added sequentially. Lastly (*i*-Pr)$_2$NEt (0.152 mmol, 1 equiv) was added and the septum was then quickly exchanged for a cold finger. Once inert atmosphere was re–established the flask was sealed and heated to 40 °C for 1 hour. (WARNING: when performed on a larger scale, it is advised to use a water condenser instead of a cold finger to avoid the small pressure buildup). The crude reaction mixture was cooled to room temperature and quenched by addition of HCl (2 mL, [1 M]). The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and dried over Na_2SO_4. The crude product was purified by column chromatography followed by preparative thin layer chromatography to afford the corresponding cross–benzoin product.

General procedure D

The corresponding *N*–Boc-*N*-Bn–amino aldehyde (0.152 mmol, 1.0 equiv) and triazolium salt **12** (0.0304 mmol, 0.2 equiv) were added to an oven–dried test tube with a Schlenk take–off and fitted with a septum. The vessel was placed under vacuum and re–filled with argon three times to

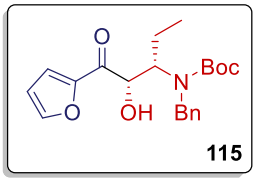
ensure inert atmosphere. The hetereoaromatic aldehyde (0.228 mmol, 1.5 equiv) and CH_2Cl_2 (1.0 mL, 0.15 M) were added sequentially. The reaction was cooled to 0 °C and $(i\text{-Pr})_2NEt$ (0.152 mmol, 1 equiv) was added. After 30 minutes the reaction mixture was warmed to room temperature and quenched by addition of 1M HCl (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) and dried over Na_2SO_4. The crude product was purified by column chromatography followed by preparative thin layer chromatography to afford the corresponding cross–benzoin product.

tert-butyl benzyl[(2*S*,3*S*)-4-(furan-2-yl)-3-hydroxy-4-oxobutan-2-yl]carbamate (**112**)



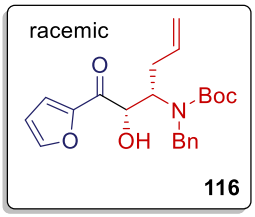
Prepared according to **general procedure C**; Column chromatography (5:1 hexane/acetone) followed by PTLC (7:1 toluene: EtOAc) afforded the major product as a white solid (38 mg, 69%). Rf = 0.22 (17% acetone in hexanes); melting point = 121.1 °C, $[\alpha]_D^{26}$ = -30 (*c* 1.9, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3457, 3123, 2978, 1678, 1466, 1392, 1367, 1166, 1034, 921, 769, 733, 700; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.89 (br s, 1H), 7.70 (s, 1H), 7.33–7.27 (m, 2H), 7.24–7.17 (m, 3H), 6.62 (dd, *J* = 3.7, 1.7 Hz, 1H), 5.09 (app d, *J* = 3.7 Hz, 1H), 4.73–4.60 (m, 2H), 4.49 (d, *J* = 16.8 Hz, 1H), 4.05 (d, *J* = 5.3 Hz, 0.8H), 3.58 (br s, 0.2H), 1.57 (s, 1.5H), 1.38 (s, 7.5H), 0.98 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 187.5, 156.4, 148.2, 147.7*, 140.5, 128.3, 126.8, 126.4, 122.08, 120.0*, 112.8, 80.5, 77.4, 76.7*, 55.4, 54.9*, 48.7, 28.7*, 28.4, 13.5*, 11.5*; **HRMS** (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{20}H_{25}NO_5Na$ 382.1625; Found 382.1620.

tert-Butyl benzyl[(2*S*,3*S*)-1-(furan-2-yl)-2-hydroxy-1-oxopentan-3-yl]carbamate (**115**)



Prepared according to **general procedure C**; Column chromatography (7:1 hexane/acetone) followed by PTLC (7:1 toluene: EtOAc) afforded the major product as a clear colourless oil (39 mg, 69%). Rf = 0.18 (13% acetone in hexanes); $[\alpha]_D^{26}$ = +31 (*c* 1.3, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3452, 2934, 1679, 1568, 1496, 1367, 1297, 1250, 1165; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.81 (br s, 1H), 7.67 (s, 1H), 7.39–7.28 (m, 4H), 7.25–7.17 (m, 1H), 6.60 (s, 1H), 5.00 (dd, *J* = 5.2, 2.2 Hz, 1H), 4.62 (d, *J* = 15.8 Hz, 1H), 4.43 (d, *J* = 16.0 Hz, 1H), 4.35 (br s, 1H), 3.49 (br s, 0.2H), 1.84–1.67 (m, 1H), 1.56–1.45 (m, 2H), 1.39 (s, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 187.9, 157.0, 149.9, 147.9, 139.9, 128.3, 127.9*, 127.2, 126.9, 121.8, 120.1*, 112.8, 80.6, 78.2, 62.6, 50.0*, 28.7*, 28.4, 19.3, 11.2, 10.8*; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{21}H_{27}NO_5Na$ 396.1781; Found 396.1789.

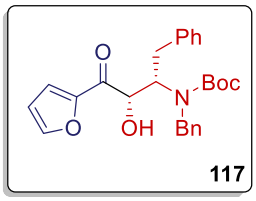
tert-Butyl [1-(benzofuran-2-yl)-2-hydroxy-1-oxohex-5-en-3-yl](benzyl)carbamate (**116**)



Prepared according to **general procedure C**; Column chromatography (4:1 hexane/EtOAc) followed by PTLC (7:1 toluene/EtOAc) afforded the major product as a clear colourless oil (1.5 equiv of 2-furaldehyde: 40 mg, 66%; 3 equiv of 2-furaldehyde: 45 mg, 74%). Rf = 0.45 (13% EtOAc in toluene); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3444, 2978, 1679, 1568, 1465, 1367, 1165, 1033, 914; **^{1}H NMR** (600 MHz,

$CDCl_3$) mixture of rotamers; δ 7.70 (br s, 1H), 7.66 (s, 1H), 7.33–7.26 (m, 3H), 7.26–7.20 (m, 2H), 6.58 (br s, 1H), 5.48 (dddd, *J* = 16.0, 7.4, 7.4, 7.4 Hz, 0.8H), 5.44–5.33 (m, 0.2H), 4.99 (s, 1H), 4.94 (d, *J* = 17.0 Hz, 0.7H), 4.90 (d, *J* = 10.2 Hz, 1 H), 4.87–4.81 (m, 0.3H), 4.61 (d, *J* = 16.0 Hz, 1.7 H), 4.43 (br s, 1H), 4.35 (d, *J* = 16.1 Hz, 1H), 3.53 (br s, 0.2H), 2.62–2.50 (m, 0.9H), 2.50–2.39 (m, 0.1H), 2.18 (ddd, *J* = 14.4, 6.9, 6.9 Hz, 1H), 1.52 (s, 2H), 1.39 (s, 7H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 187.6, 156.9, 150.1, 147.9, 139.4, 134.5, 128.3, 127.9*, 127.3, 127.0, 121.7, 120.1*, 118.0, 117.7*, 112.7, 80.7, 77.9, 70.0, 50.9, 30.9, 28.6*, 28.39; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{22}H_{27}NO_5Na$ 408.1781; Found 408.1798.

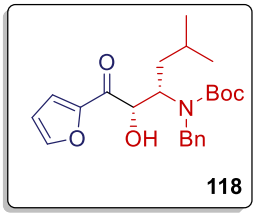
tert-Butyl benzyl-[(2*S*,3*S*)-4-(furan-2-yl)-3-hydroxy-4-oxo-1-phenylbutan-2-yl]carbamate (**117**)



Prepared according to **general procedure C**; Column chromatography (4:1 hexane/acetone) followed by PTLC (7:1 toluene: EtOAc) afforded the major product as a light-yellow oil (43 mg, 66%). Rf = 0.25 (20% acetone in hexanes); $[\alpha]_D^{26}$ = -34 (*c* 2.2, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3446, 3029, 1679, 1569, 1496, 1367, 1249, 1165; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.69–7.51 (m, 2H), 7.37–7.26 (m, 0.7H), 7.26–7.09 (m, 6H), 7.09–6.98 (m, 3H), 6.90–6.82 (m, 0.3H), 6.58 (s, 0.2H), 6.52 (s, 0.8H), 5.08–4.91 (m, 1.3H), 4.71–4.43 (m, 0.7H), 4.48 (d, *J* = 15.4 Hz, 1H), 4.04–3.76 (m, 0.7H), 3.76 –3.60 (m, 0.3 H), 3.28–3.04 (m, 0.8H), 2.99–2.87 (m, 0.2H), 2.79 (dd, *J* = 14.2, 4.9 Hz, 0.9H), 2.73–2.58 (m, 0.1H), 1.45–1.28 (m, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 187.3, 157.0, 150.2, 147.6, 146.9, 138.9, 138.0,

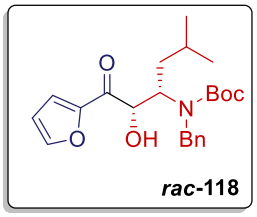
129.5*, 129.4, 128.6, 128.5*, 128.3, 127.3, 126.9, 126.5, 121.4, 119.8*, 112.8*, 112.6, 80.9, 78.0, 63.3, 52.1*, 32.6, 31.7*, 28.4; **HRMS** (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{26}H_{29}NO_5Na$ 458.1938; Found 458.1927.

tert-Butylbenzyl[(2*S*,3*S*)-1-(furan-2-yl)-2-hydroxy-5-methyl-1-oxohexan-3-yl]carbamate (**118**)



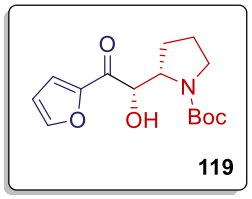
Prepared according to **general procedure C**; Column chromatography (5:1 hexane/acetone) followed by PTLC (7:1 toluene: EtOAc) afforded the major product as a clear colourless oil (49 mg, 77%). Rf = 0.25 (20% acetone in hexanes); $[\alpha]_D^{26}$ = +5.9 (*c* 1.6, $CHCl_3$); HPLC analysis – Chiralcel IC column, 2% isopropanol in hexanes, 0.1 mL/min. Major: 20.0 min, minor: 33.0 min **FTIR** (KBr film) ν_{max} (cm^{-1}): 3452, 2958, 1679, 1496, 1390, 1366, 1165, 991; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.84 (br s, 1H), 7.68 (s, 1H), 7.41–7.26 (m, 4H), 7.24–7.16 (m, 1H), 6.61 (s, 1H), 5.03 (s, 1H), 4.81–4.54 (m, 2H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.14 (br s, 0.8H), 3.57 (br s, 0.2H), 1.76–1.57 (m, 1H), 1.31–1.22 (m, 1H), 1.52 (s, 2.2H), 1.38 (s, 6.8H), 1.00–0.77 (m, 1H), 0.69–0.41 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 187.7, 156.9, 149.7, 148.1, 147.7*, 140.2, 128.3, 127.6*, 127.0, 126.8, 121.8, 120.0*, 112.9, 111.1*, 80.5, 78.5, 58.2, 49.2*, 34.9, 28.6*, 28.4, 24.8, 24.2*, 23.14, 21.7, 21.4*; **HRMS** (ESI-TOF) *m/z*: $[M+1]^+$ Calcd. for $C_{23}H_{32}NO_5$ 402.2275; Found 402.2271.

rac-tert-Butyl benzyl-(furan-2-yl)-2-hydroxy-5-methyl-1-oxohexan-3-ylcarbamate (***rac*-118**)



Prepared according to **general procedure C**; Column chromatography (5:1 hexane/EtOAc) afforded the major diastereomer as a clear colourless oil (48 mg, 77%). Rf = 0.21 (16% EtOAc in hexanes); HPLC analysis – Chiralcel IC column, 2% isopropanol in hexanes, 0.1 mL/min. Major: 20.0 min, minor: 32.9 min; **^{1}H NMR** spectrum was identical to **118**.

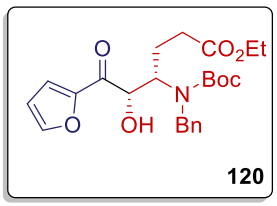
tert-Butyl-(*S*)-2-[(*S*)-2-(furan-2-yl)-1-hydroxy-2-oxoethyl]pyrrolidine-1-carboxylate (**119**)



Prepared according to **general procedure C**; Column chromatography (3:1 hexane/acetone) followed by (7:1 toluene: EtOAc) afforded the product along with small amounts of impurities. This mixture was re-crystallized in hexanes to afford the major diastereomer as a white solid (38 mg, 43%). Rf = 0.28 (25% acetone in hexanes); melting point = 91.0 °C, $[\alpha]_D^{26}$ = +120 (*c* 1.9, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3460, 2976, 1683, 1466, 1394, 1168, 1084, 771; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.81 (d, *J* = 3.4 Hz, 0.7H), 7.70 (s, 0.7H), 7.67 (s, 0.3H), 7.35 (br s, 0.3H), 6.64–6.56 (m, 1H), 5.37 (dd, *J* = 6.4, 1.7 Hz, 0.7H), 5.20–5.10 (m, 0.3H), 4.30–4.21 (m, 0.7H), 4.21–4.12 (m, 0.3H), 3.82 (d, *J* = 6.4 Hz, 0.7H), 3.59–3.55 (m, 0.3H), 3.55–3.50 (m, 0.2H), 3.47–3.32 (m, 1.8H), 2.08–1.96 (m, 1H), 1.82–1.62(m, 3H), 1.48 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 188.4*, 188.2, 155.1, 154.1*, 150.6*, 149.8, 148.11, 147.6*, 122.0, 119.9*, 112.8*, 112.8, 80.2*, 79.7, 74.9*, 74.7, 61.5, 60.4*, 47.3, 47.1*, 28.6,

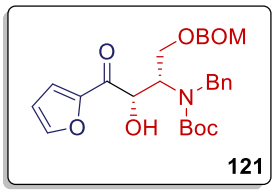
26.3*, 24.8, 24.8, 23.7; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{15}H_{21}NO_5Na$ 318.1312; Found 318.1318.

Ethyl (4*S*,5*S*)-4-[benzyl(*tert*-butoxycarbonyl)amino]-6-(furan-2-yl)-5-hydroxy-6-oxohexanoate (**120**)



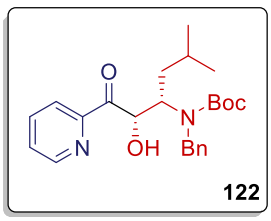
Prepared according to **general procedure A**; Column chromatography (4:1 hexanes: acetone) followed by PTLC (7:3 toluene/ EtOAc) afforded the major product as a light-yellow oil (43 mg, 64%). Rf = 0.18 (20% acetone in hexane); $[\alpha]_D^{27}$ = +17 (*c* 2.2, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3451, 2979, 1733, 1683, 1496, 1392, 1251, 1164; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.71 (br s, 1H), 7.66 (d, *J* = 1.1 Hz, 1H), 7.40–7.27 (m, 4H), 7.25–7.17 (m, 1H), 6.59 (s, 1H), 5.00 (dd, *J* = 5.1, 2.2 Hz, 1H), 4.63 (d, *J* = 16.0 Hz, 1H), 4.43 (d, *J* = 15.7 Hz, 1H), 4.34 (br s, 0.7H), 3.97 (q, *J* = 7 Hz, 2H), 3.59 (br s, 0.2H), 2.14–1.85 (m, 3H), 1.71–1.59 (m, 1H), 1.50 (s, 2H), 1.40 (s, 7H), 1.13 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 187.4, 172.7, 156.8, 149.9, 147.8, 139.5, 128.4, 127.9*, 127.3, 127.0, 121.8, 120.0*, 112.8, 80.9, 77.8, 60.4, 60.0, 50.0*, 31.0, 30.5*, 28.4, 22.5*, 21.7, 14.2; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{24}H_{31}NO_7Na$ 468.1993; Found 468.2005.

tert-Butyl benzyl{(2*S*,3*S*)-1-[(benzyloxy)methoxy]-4-(furan-2-yl}-3-hydroxy-4-oxobutan-2-yl)carbamate (**121**)



Prepared according to **general procedure D** with the following modifications: in place of 1.5 equiv heteroaromatic aldehyde, 3 equiv of that reagent was used. Column chromatography (4:1 hexane/acetone) followed by PTLC (7:1 toluene/EtOAc) afforded the major product as a light yellow wax (51 mg, 68%). Rf = 0.24 (20% acetone in hexane); $[\alpha]_D^{27}$ = +3.1 (*c* 2.0, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3442, 2976, 1681, 1497, 1391, 1250, 1165, 1047; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.71 (br s, 1H), 7.65 (d, *J* = 0.9 Hz, 1H), 7.38–7.27 (m, 5.5H), 7.26–7.16 (m, 4.5H), 6.58 (s, 1H), 5.03 (br s, 1H), 4.72 (m, 2H), 4.52–4.40 (m, 3H), 4.37 (s, 2H), 3.82–3.72 (m, 1H), 3.72–3.63 (m, 0.8H), 3.63–3.54 (m, 0.2 H), 1.54 (s, 2H), 1.39 (s, 7H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 187.0, 156.6, 150.1, 147.5, 139.6, 137.8, 128.5, 128.4, 128.0, 127.8, 126.9, 126.8, 120.9, 112.6, 94.5, 80.9, 76.4, 69.4, 64.5, 60.1, 50.6*, 28.4; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{28}H_{33}NO_7Na$ 518.2149; Found 518.2159.

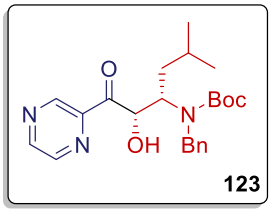
tert-Butyl benzyl[(2*S*,3*S*)-2-hydroxy-5-methyl-1-oxo-1-(pyridin-2-yl)hexan-3-yl]-carbamate (**122**)



Prepared according to **general procedure D**; Column chromatography (7:1 hexane/acetone) followed by PTLC (7:1 toluene: EtOAc) to afford the major product as a clear colourless oil (1.5 equiv 2-pyridinecarboxaldehyde: 38 mg, 61%; 3 equiv 2-pyridinecarboxaldehyde: 44 mg, 71%). Rf = 0.17

(17% EtOAc in hexane); $[\alpha]_D^{27}$ = -22 (*c* 1.2, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3470, 2958, 1690, 1584, 1496, 1347, 1244, 1166; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 8.68 (d, *J* = 3.8 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.88 (s, 1H), 7.52 (s, 1H), 7.40–7.26 (m, 3H), 7.26–7.06 (m, 1H), 5.41–5.09 (m, 2H), 4.79–4.49 (m, 2H), 4.49–4.37 (m, 1H), 1.67–1.53 (m, 1H), 1.40–1.32 (m, 4H), 1.29 (s, 6H), 1.19–0.98 (m, 0.7H), 0.95–0.85 (m, 0.3H), 0.71–0.43 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 199.7*, 199.3, 156.3, 152.3, 152.0, 148.7, 140.2, 137.7, 137.5, 128.2, 127.8, 127.2, 126.7, 123.4, 123.3, 80.0, 79.0, 78.6, 57.8, 49.5*, 36.5, 28.3, 28.2*, 24.8, 24.2*, 23.2, 21.8, 21.4*; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{24}H_{32}N_2O_4Na$ 435.2254; Found 435.2267.

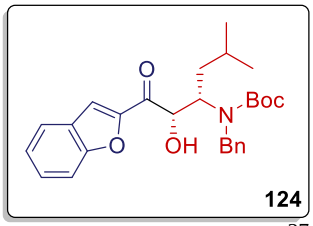
tert-Butyl benzyl[(2*S*,3*S*)-2-hydroxy-5-methyl-1-oxo-1-(pyrazin-2-yl)hexan-3-yl]-carbamate (**123**)



Prepared according to **general procedure D** with the following modifications: in place of 1.5 equiv heteroaromatic aldehyde, 3 equiv of that reagent was used, in place of an ice batch, a brine ice bath (ca. -15 °C) was used. The reaction was quenched at 15 minutes. Column chromatography (3:1 hexane/EtOAc) followed by PTLC (3:1 toluene/acetone) afforded a mixture. The mixture was washed with cold hexanes and the filtrate was concentrated *in vacuo* to afford the major diastereomer as a light-yellow oil (37 mg, 50%). Rf = 0.24 (25% acetone in hexane); $[\alpha]_D^{27}$ = +11 (*c* 0.9, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3439, 2958, 1690, 1407,1497, 1166, 1052, 1018; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 9.29 (s, 0.1H), 9.22 (s, 0.9H), 8.86–8.76 (m, 0.9H), 8.74 (s, 0.1H), 8.70 (s, 0.1H), 8.64 (s, 0.9H), 7.41–7.28 (m , 3.1H), 7.25–7.02 (m, 1.9H), 5.47–5.41 (m, 0.1H), 5.38 (dd, *J* = 9.9, 4.8 Hz, 0.9H), 4.75–4.34 (m, 3.7H), 3.74 (br s, 0.3H), 1.69–

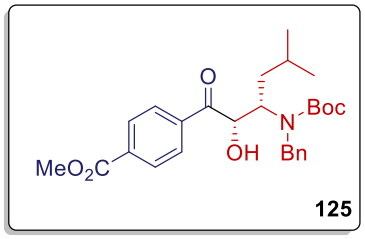
1.60 (m, 1H), 1.42 (s, 3H), 1.33 (s, 6H), 0.71–0.46 (m, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 200.1*, 199.4, 156.4, 148.6*, 148.3, 146.7, 144.8, 143.3, 139.8, 128.3, 127.7*, 127.3, 126.9, 80.5*, 78.1, 58.1, 50.3*, 36.5, 28.4*, 28.3, 28.2, 24.8, 24.2*, 23.1, 22.7*, 21.9, 21.5*; **HRMS** (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{23}H_{31}N_3O_4Na$ 436.2207; Found 436.2226.

tert-Butyl [(2*R*,3*R*)-1-(benzofuran-2-yl)-2-hydroxy-5-methyl-1-oxohexan-3-yl](benzyl)carbamate (**124**)



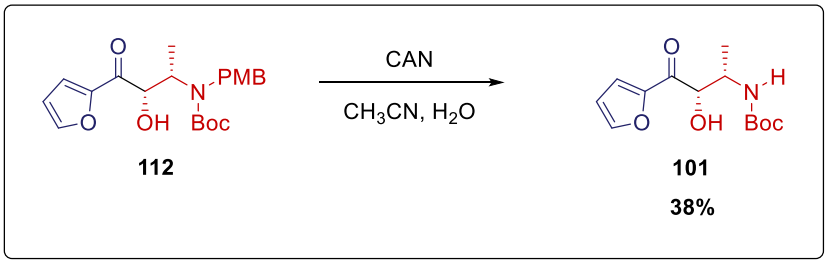
Prepared according to **general procedure D**; Column chromatography (5:1 hexane/Et_2O) followed by PTLC (7:1 toluene: EtOAc) afforded the major product as a clear colourless oil (50 mg, 73%). Rf = 0.18 (25% Et_2O in hexanes); $[\alpha]_D^{27}$ = -30 (*c* 2.5, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3455, 2958, 1678, 1550, 1496, 1367, 1165, 1030; **^{1}H NMR** (500 MHz, CDCl3) mixture of rotamers; δ 8.13 (br s, 1H), 7.79 (d, *J* = 7.4 Hz, 0.8H), 7.76–7.71 (m, 0.2H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.55–7.46 (m, 1H), 7.41–7.28 (m, 5H), 7.26–7.19 (m, 1H), 5.16 (s, 1H), 4.72 (d, *J* = 16.0 Hz, 1H), 6.63 (br s, 0.9H), 4.45 (d, *J* = 16.0 Hz, 1H), 3.59 (br s, 0.1H), 1.85–1.62 (m, 1H), 1.51 (s, 2H), 1.41 (s, 7H), 1.36–1.24 (s, 1H), 1.10–0.98 (s, 1H), 0.68–0.48 (m, 6H); **^{13}C NMR** (125 MHz, CDCl3) Mixture of rotamers (minor rotamer indicated by asterisk): δ 189.9, 157.00, 156.0, 149.7, 139.9, 129.2, 128.37, 127.7*, 127.1, 124.2, 124.2, 123.6*, 117.5, 115.9*, 112.7, 80.7, 79.0, 77.9*, 59.0, 50.1*, 35.07. 28.6*, 28.4, 24.8, 24.1*, 23.14, 21.9, 21.5*; **HRMS** (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{27}H_{33}NO_5Na$ 474.2262; Found 474.2260.

Methyl 4-{(2*S*,3*S*)-3-[benzyl(*tert*-butoxycarbonyl)amino]-2-hydroxy-5-methylhex-anoyl}benzoate (**125**)



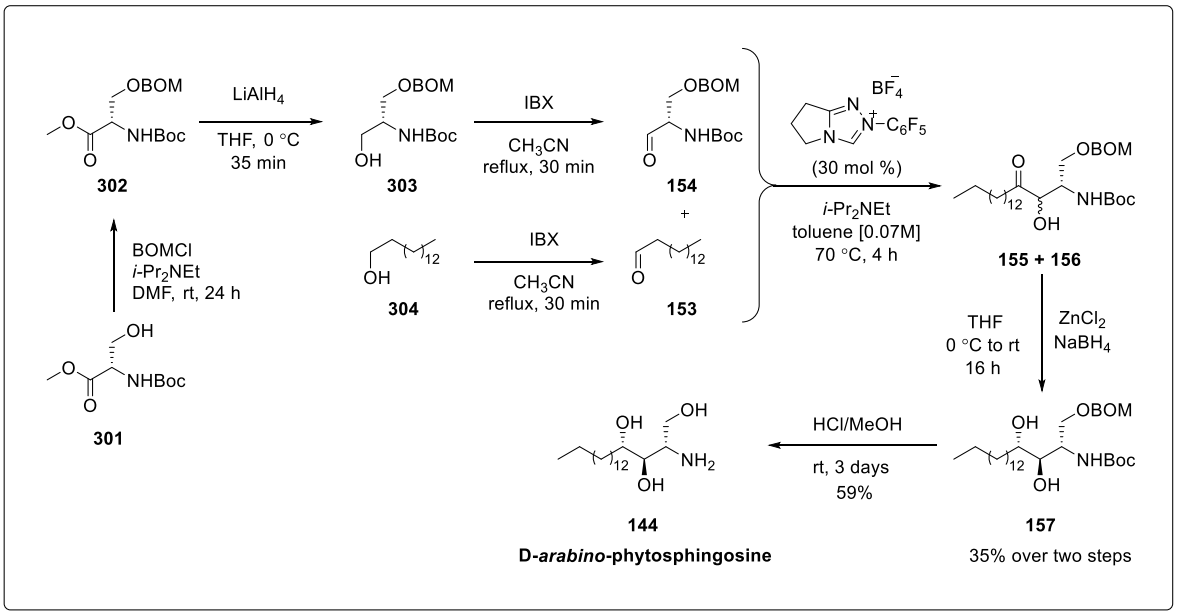
Prepared according to **general procedure C**; Column chromatography (9:1 hexanes/EtOAc) followed by PTLC (4:1 hexane/acetone) afforded the major product as a clear colourless oil (13 mg, 18%). Rf = 0.20 (10% EtOAc in hexanes); $[\alpha]_D^{27}$ = -28 (*c* 1.3, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3461, 2957, 1730, 1683, 1496, 1367, 1281, 1164; **^{1}H NMR** (500 MHz, CDCl3) mixture of rotamers; δ 8.26–8.12 (m, 3.4H), 8.07–7.96 (m, 0.6H), 7.39–7.27 (m, 4H), 7.24–7.17 (m, 1H), 5.34 (s, 0.7H), 5.29 (s, 0.3H), 7.72 (d, *J* = 16.1 Hz, 1H), 4.65 (br s, 1H), 4.46 (d, *J* = 15.8 Hz, 1H), 4.12 (br s, 0.6H), 2.96 (s, 3H), 3.72 (br s, 0.2H), 1.70–1.58 (m, 1H), 1.48 (s, 3H), 1.38 (s, 6H), 1.23–1.12 (m, 1H), 0.83–0.71 (m, 0.7H), 0.69–0.61 (m, 0.3H), 0.57–0.42 (m, 6H); **^{13}C NMR** (125 MHz, CDCl3) Mixture of rotamers (minor rotamer indicated by asterisk): δ 200.1, 166.2, 256.8, 140.3, 136.8, 134.8, 130.2, 129.2, 128.8*, 128.3, 127.5*, 126.9, 126.7, 80.5, 78.6, 78.1*, 56.8, 52.7*, 48.9, 39.9, 28.7,*, 28.4, 24.7, 24.0*, 23.1, 21.7, 21.3*; **HRMS** (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{27}H_{35}NO_6Na$ 492.2357; Found 492.2351.

Removal of *N*-PMB Protecting Group

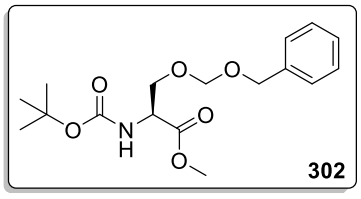


According to a known procedure,[233] to a solution of **112** (0.437 mmol, 0.017 g) in wet CH_3CN (80% *v/v*, 1.0 mL) was added ceric ammonium nitrate (0.245 mmol, 0.134 g). After 30 minutes, the reaction mixture was diluted with EtOAc:hexane (1:1, 5 mL). The organic m was washed sequentially with Sat. $NaHCO_3$ (aq) (20 mL) and water (20 mL) and the combined aqueous phases were back extracted with EtOAc:hexane (1:1, 50 mL). The organic layers were combined and dried over Na_2SO_4. PTLC (2:1 hexane:EtOAc) afforded **101** as a white solid (0.045 g, 38%). Characterization data match those reported compound (**101**).

7.4. Total Synthesis of D-*arabino*-Phytosphingosine

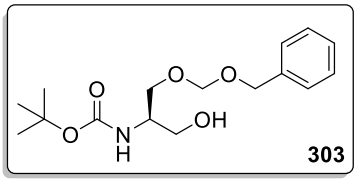


(*S*)-Methyl-3-[(benzyloxy)methoxy]-2-[(*tert*-butoxycarbonyl)amino]propanoate (*N*-Boc-*O*-BOM-L-serine ester) (**302**)



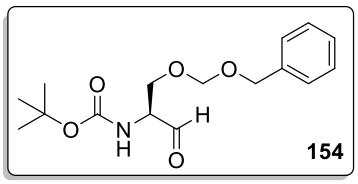
To a solution of *N*-Boc-L-serine ester (**301**) (2.34 g, 10.7 mmol) in dry DMF (11 mL) was added $(i\text{-Pr})_2$NEt (6 mL, 34.2 mmol) at room temperature under argon. This was followed by the addition of BOMCl (70% purity) (7.17 g, 32.05 mmol). The mixture was stirred at this temperature for 24 hours. The mixture was diluted in EtOAc (300 mL) and washed sequentially with sat. NH_4Cl_{aq} (200 mL), distilled water (200 mL), and brine (200 mL). The organic layer was dried over $MgSO_4$ and concentrated. The resulting solution was purified by chromatography (5:1 hexane:EtOAc) to afford a mixture of **302** and an unknown impurity as clear colourless oil. R_f = 0.20 (5:1 hexane:EtOAc. The mixture was carried to next step without further purification.

(*R*)-*tert*-Butyl {1-[(benzyloxy)methoxy]-3-hydroxypropan-2-yl}carbamate (*N*-Boc-O-BOM-L-serinol) (**303**)



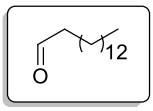
To a suspension of $LiAlH_4$ in THF (20 mL) was added the crude ester (**302**) (2.01 g, 5.93 mmol) in dry THF (20 mL) at 0°C. The reaction mixture was stirred at this temperature for 35 minutes and quenched with addition of an aqueous solution of Rochelle's salt [0.5 M] (ca. 20 mL). The reaction was vigorously stirred at room temperature for an additional 2 hours. The reaction mixture was diluted in EtOAc (150 mL) and the layers were separated. The aqueous phase was extracted using EtOAc (2×150 mL) and the combined organic layers were dried over $MgSO_4$. The resulting solution was concentrated and purified by chromatography (3:2 hexane:EtOAc) to afford **303** as a clear colourless oil (1.46 g, 41% yield over 2 steps). R_f = 0.20 (3:2 hexane:EtOAc); $[\alpha]_D^{26\,°C}$ = -1 (*c* 0.9, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3438, 3065, 2976, 2934, 2883, 1694, 1499, 1455, 1367, 1248, 1170, 1046, 738, 699; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39–7.33 (m, 4H), 7.33–7.28 (m, 1H), 5.10 (s, 1H), 4.77 (dd, *J* = 11.0, 6.7 Hz, 2H), 4.61 (s, 2H), 3.85–3.73 (m, 3H), 3.73–3.64 (m, 2H), 2.24 (s, 1H), 1.45 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.2, 137.6, 137.6, 128.6, 128.0, 128.0, 95.1, 79.8, 69.9, 68.2, 63.5, 51.8, 28.5; **HRMS** (TOF) *m/z*: [M+Na] Calcd for $C_{16}H_{25}NO_5Na$ 334.162495; Found 334, 1641.

(*S*)-*tert*-Butyl {1-[(benzyloxy)methoxy]-3-oxopropan-2-yl}carbamate (*N*-Boc-*O*-BOM-L-serinal)(**154**)



To a suspension of **303** (1.28 g, 4.1 mmol) in CH_3CN (41 mL) was added IBX (1.73 g, 6.17 mmol) and heated to reflux. The reaction was monitored for consumption of starting material (30 min). The reaction was cooled to room temperature and filtered through a pad of Celite® and washed with EtOAc (3×50 mL). The resulting solution was concentrated and purified by chromatography (3:1 hexane:EtOAc) to afford **154** as a clear colourless oil (1.21 g, 95% yield). R_f = 0.28 (3:1 hexane:EtOAc); $[\alpha]_D^{26\ °C}$ = -1 (*c* 0.9, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3349, 2977, 2944, 2887, 1712, 1498, 1368, 1167, 1116, 1048, 748, 699; **^{1}H NMR** (600 MHz, $CDCl_3$) Mixture of rotamers: δ 9.52 (s, 1H), 7.31–7.16 (m, 5H), 5.35 (d, *J* = 5.1 Hz, 0.8H), 5.12–4.97 (m, 0.2H), 4.64 (dd, *J* = 7.5, 7.4 Hz, 2H), 4.66 (s, 2H), 4.26 (s, 0.8H), 4.08 (d, *J* = 9.9 Hz, 0.8H), 4.04–3.93 (m, 0.2H), 3.72 (d, *J* = 9.5 Hz, 0.8H), 3.64–3.54 (m, 0.2H), 1.38 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk); δ 199.0, 155.7, 137.5, 128.6, 128.1, 128.1, 95.1, 80.4, 70.1, 66.0, 60.9*, 60.1, 28.4; **HRMS** (FD) *m/z*: [M+1] Calcd for $C_{16}H_{24}NO_5$ 310.16545; Found 310.16431.

Pentadecanal (153)

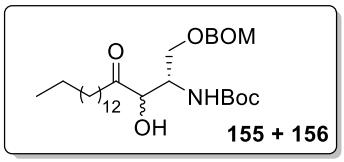


To a solution of pentadecan-1-ol (**304**) (2.1 g, 9.21 mmol) in CH_3CN (28 mL) was added IBX (3.87g, 13.82 mmol) and heated to reflux. The reaction was monitored for consumption of starting material (50 min). The reaction was cooled to room temperature and filtered through a pad of Celite® and washed with EtOAc (3×50 mL). The resulting solution was concentrated and purified by chromatography (9:1 hexane:EtOAc) to afford **153** as a clear

colourless oil that solidifies upon refrigeration (1.81 g, 87%) (R_f = 0.31 (9:1 hexane:EtOAc). Spectral data match the previously reported values.[234]

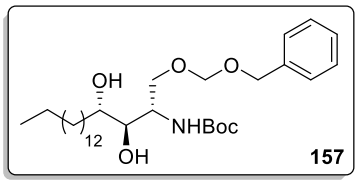
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.76 (s, 1H), 2.42 (t, *J* = 7.3, 2H), 1.70–1.58 (m, 2H), 1.40–1.16 (m, 24 H), 0.88 (t, *J* = 5.7, 3H).

tert-Butyl {(2*S*)-1-[(benzyloxy)methoxy]-3-hydroxy-4-oxooctadecan-2-yl}carbamate (**155**)

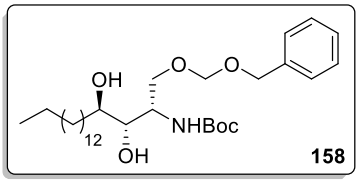


N-Boc-O-BOM-L-serinal (**154**) (0.3 g, 0.97 mmol.) and triazolium salt **12** (0.106 g, 0.29 mmol) were added to a Schlenk flask and fitted with a septum. The vessel was placed under vacuum and re–filled with argon three times to ensure inert atmosphere. Pentadecanal (**304**) (1.32 mL, 4.85 mmol) and dry toluene (14 mL) were added sequentially. Lastly *i*-Pr_2NEt (0.34 mL, 1.94 mmol) was added and the septum was then quickly exchanged for a water condenser. The mixture was heated to 70 °C for 4 hours. The reaction was cooled to room temperature and quenched by addition of 1M HCl (15 mL). The bi-phasic mixture was extracted with CH_2Cl_2 (3x20 mL) and dried over Na_2SO_4. This mixture was purified by column chromatography (7:1 hexane:EtOAc) to afford a 5:1 mixture of diastereomers. R_f = 0.20 (7:1 hexane:EtOAc). The resulting mixture was carried to the next step without further purification.

tert-Butyl {(2*S*,3*R*,4*S*)-1-[(benzyloxy)methoxy]-3,4-dihydroxyoctadecan-2-yl}carbamate (**157**)

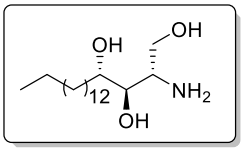


To a pre-cooled (0 °C) dry round-bottomed flask containing $NaBH_4$ (0.44 mmol, 1 equiv) in THF (1 mL) was added a solution of $ZnCl_2$ (0.44 mmol, 1 equiv) in dry Et_2O (0.88 mL) under argon. This mixture was stirred at 0°C for 5 minutes and a solution of **155** and **156** (5:1) (0.44 mmol, 1 equiv) in THF (3.5 mL) was added. The mixture was gradually warmed to room temperature and stirred at this temperature for 16 h. The reaction was quenched with the slow addition of water at 0°C. The crude mixture was diluted in Et_2O (40 mL) and the layers were separated. The aqueous phase was washed with Et_2O (2×40mL) and the combined organic layers were dried over Na_2SO_4 and then concentrated. Column chromatography (7:1 hexane:acetone) afforded **157** as a white wax (183 mg, 35% over two steps). R_f = 0.21 (7:1 hexane:acetone); $[\alpha]_D^{27\ °C}$ = -47 (*c* 0.9, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3430, 2921, 2853, 1683, 1515, 1455, 1361, 1169, 734, 698; **^{1}H NMR** (600 MHz, C_6D_6) Mixture of rotamers: δ 7.24 (d, *J* = 7.5 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 5.44–5.36 (m, 1H), 4.43 (s, 2H), 4.38 (s, 2H), 4.37–4.30 (m, 2H), 3.64–3.53 (m, 4H), 3.01 (d, *J* = 3.2 Hz, 0.8H), 3.07 (d, *J* = 2.8 Hz, 0.2H), 2.04–1.95 (m, 1H), 1.87–1.76 (m, 1H), 1.69–1.52 (m, 2H), 1.88–1.34 (m, 14H), 1.32–1.21 (m, 19 H), 0.90 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (150 MHz, C_6D_6) Mixture of rotamers (minor rotamer indicated by asterisk); δ 158.1, 138.7, 129.0, 128.4, 128.7, 128.2, 95.4, 80.3, 76.5, 70.4*, 70.4, 70.2, 51.0, 35.3*, 34.0, 32.7*, 32.7, 32.3*, 30.8, 30.7, 30.6, 30.6, 30.6, 30.6, 30.5, 30.2, 30.2*, 28.7, 26.8, 23.5, 23.4*, 14.7, 14.7*; **HRMS** (TOF) *m/z*: [M+Na] Calcd for $C_{31}H_{55}NO_6Na$ 560.39216; Found 560.3914.



The minor diastereomer (**158**) was also isolated as a clear colourless oil (42 mg, 8%). $[\alpha]_D^{27\,°C}$ = -32 (*c* 0.7, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3335, 2924, 2853, 1678, 1528, 1456, 1390, 1366, 1170, 1051, 699; **^{1}H NMR** (600 MHz, C_6D_6) δ 7.29 (d, *J* = 7.4 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 5.32 (d, *J* = 8.6 Hz, 1H), 4.49–4.34 (m, 4H), 4.20 (ap d, *J* = 3.8 Hz, 1H), 3.97 (dd, *J* = 9.6, 3 Hz, 1H), 3.74–3.60 (m, 3H), 3.10 (br s, 1H), 2.60 (br s, 1H), 1.89–1.78 (m, 1H), 1.71–1.61 (m, 1H), 1.58–1.48 (m, 1H), 1.43 (s, 10H), 1.37–1.23 (m, 22H), 0.92 (t, *J* = 6.7 Hz, 3H); **^{13}C NMR** (150 MHz, C_6D_6) Mixture of rotamers (minor rotamer indicated by asterisk); δ 155.9, 138.0, 128.4*, 128.1*, 128.0, 127.8*, 127.8, 127.6, 94.8, 79.2, 75.7, 73.3, 69.5, 67.9, 51.6, 33.4, 32.1, 30.0, 29.9*, 29.6, 28.2, 26.2, 22.9, 14.1; **HRMS** (TOF) *m/z*: [M+Na] Calcd. for $C_{31}H_{55}NO_6Na$ 560.39216; Found 560.3908.

D-*arabino*-phytosphingosine (**144**)

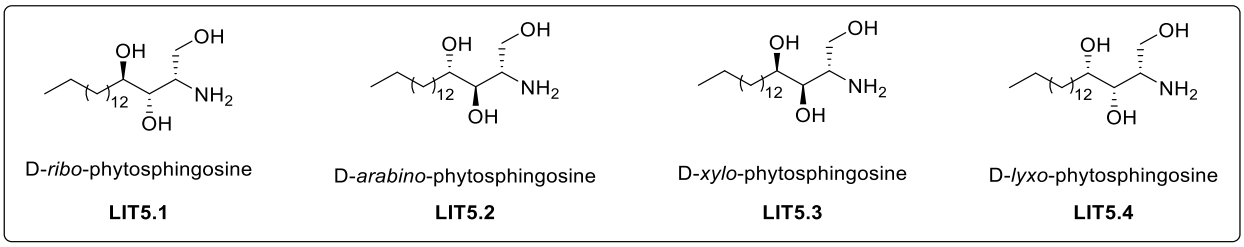


To a mixture of **157** (0.04 mmol, 1 equiv) in THF (0.6 mL) and MeOH (0.3 mL) was added a freshly prepared solution of acyl chloride (1.12 mmol, 30 equiv) in MeOH (1 mL) at 0°C. The reaction mixture was sealed and gradually warmed to room temperature. After 3 days, the reaction was quenched by addition of sat. $NaHCO_{3aq.}$ (1 mL). The solids were filtered and washed with EtOAc (3×5 mL) and concentrated *in vacuo.* The crude was partitioned between in EtOAc (5 mL) and H_2O (2 mL). The layers were separated and the organic layer was washed with water (2×2 mL) The aqueous phase was back extracted with EtOAc (2x3 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by column chromatography (4:1:0.1 $CHCl_3$:MeOH:NH_4OH) afforded D-*arabino*-phytosphingosine (**144**) as a white solid (7 mg, 59%, 6 LLS, 8% overall yield). R_f = 0.50 (4:1:0.1

$CHCl_3$:MeOH:NH_4OH); Melting range: 78–82 °C (lit: 82-83)[73]; $[\alpha]_D^{28\ °C}$ = -8 (*c* 0.4, pyridine), (lit: $[\alpha]_D^{23\ °C}$ = -3.79 (*c* 0.6, pyridine))[73]; **FTIR** (KBr film) ν_{max} (cm^{-1}): 3464, 2985, 2086, 1743, 1374, 1241, 1047, 938, 847; **^{1}H NMR** (500 MHz, CD_3OD) δ 3.60 (dd, *J* = 10.8, 7.0 Hz, 1H), 3.58–3.51 (m, 1H), 3.53 (dd, *J* = 11.0, 6.4 Hz, 1H), 3.39 (dd, *J* = 7.0, 2.2 Hz, 1H), 3.09 (ddd, *J* = 7.0, 7.9, 2.2 Hz, 1H), 1.73–1.63 (m, 1H), 1.60–1.52 (m, 1H), 1.40–1.26 (m, 26H), 0.90 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (150 MHz, CD_3OD) δ 74.4, 73.8, 65.4, 54.3, 35.1, 33.2, 31.0, 30.9, 30.9, 30.6, 26.9, 23.8, 14.5; **HRMS** (TOF) *m/z*: [M+1] Calcd for $C_{18}H_{40}NO_3$ 318.300271; Found 318.2994.

^{1}H NMR and ^{13}C NMR Spectral Data Comparison of Phytosphingosines and observed 144

^{1}H NMR Data for Phytosphingosines and observed 144 in CD_3OD



signal number	δ 144 (ppm)		δ LIT5.1[a] (ppm)	Δδ LIT5.1 vs. 144 (ppm)		δ LIT5.2[a] (ppm)	Δδ LIT5.2 vs. 144 (ppm)		δ LIT5.3[a] (ppm)	Δδ LIT5.3 vs. 144 (ppm)		δ LIT5.4[a] (ppm)	Δδ LIT5.4 vs. 144 (ppm)
1	0.90		0.90	0.00		0.90	0.00		0.90	0.00		0.87	-0.03
2	1.29		1.33	0.04		1.33	0.04		1.34	0.05		1.32	0.03
3	1.56		1.56	0.00		1.56	0.00		1.47	-0.09		1.47	-0.09
4	1.68		1.74	0.06		1.74	0.06		1.54	-0.14		1.52	-0.16
5	3.09		3.02	-0.07		3.02	-0.07		3.00	-0.09		2.94	-0.15
6	3.39		3.37	-0.02		3.37	-0.02		3.47	0.08		3.34	-0.05
7	3.56		3.58	0.02		3.56	0.00		3.63	0.07		3.64	0.08
8	3.53		3.58	0.05		3.52	-0.01		3.56	0.03		3.54	0.01
9	3.60		3.78	0.18		3.60	0.00		3.65	0.05		3.74	-0.05
mean deviation				**0.05**			**0.02**			**0.07**			**0.07**

[a] Reported literature values. [130]

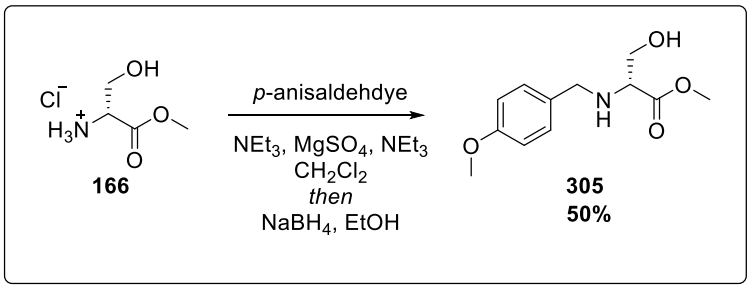
^{13}C NMR Data for Phytosphingosines and observed 144 in CD_3OD

signal number	δ 144 (ppm)		δ LIT5.1[a] (ppm)	Δδ LIT5.1 vs. 144 (ppm)		δ LIT5.2[a] (ppm)	Δδ LIT5.2 vs. 144 (ppm)		δ LIT5.3[a] (ppm)	Δδ LIT5.3 vs. 144 (ppm)		δ LIT5.4[a] (ppm)	Δδ LIT5.4vs. 144 (ppm)
1	14.5		14.4	-0.1		14.4	0.0		14.4	0.0		14.4	0.0
2	23.8		23.7	-0.1		23.7	-0.1		23.7	-0.1		23.3	-0.5
3	26.9		26.6	-0.3		26.8	-0.1		26.9	0.0		26.6	0.3
4	30.6		30.5	-0.1		30.5	-0.1		30.5	-0.1		30.0	-0.6
5	30.9		30.8	-0.1		30.8	-0.1		30.8	-0.1		30.3	-0.6
6	30.9		30.8	-0.1		30.8	-0.1		30.8	-0.1		30.4	-0.5
7	31.0		30.9	-0.1		30.9	-0.1		30.9	-0.1		30.4	-0.6
8	33.2		33.1	-0.1		33.1	-0.1		33.1	-0.1		32.6	-0.6
9	35.1		34.8	-0.3		34.9	-0.2		34.8	-0.3		34.2	-0.9
10	54.3		55.9	1.6		54.2	-0.1		56.6	2.3		55.2	0.9
11	65.4		63.5	-1.9		64.7	-0.7		63.8	-1.6		64.1	-1.3
12	73.8		74.3	0.5		73.5	-0.3		72.8	-1.0		72.0	-1.8
13	74.4		76.1	1.7		73.7	-0.7		74.0	-0.4		74.7	0.3
mean deviation				**0.5**			**0.2**			**0.5**			**0.7**

[a] Reported literature values. [130]

7.5. Total Synthesis of Hyacinthacine A_1

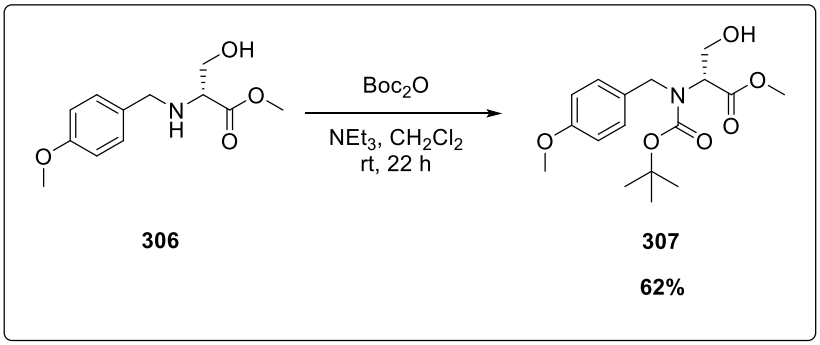
Methyl (4-methoxybenzyl)-D-serinate (**305**)



According to a modified literature procedure,[235] to a solution of D-serine methyl ester hydrochloride salt (**166**) ((32.3 mmol, 5.00 g) and $MgSO_4$ (10 g) in CH_2Cl_2 (64 mL), was added

NEt_3 (56.1 mmol, 8.1 mL) followed by freshly distilled *p*-anisaldehyde (32.3 mmol, 4.0 mL) at room temperature under argon atmosphere. The resulting solution was stirred for 18 h and EtOH (25 mL) was added and the reaction mixture was cooled to 0 °C using an ice bath. Sodium borohydride (51.6 mmol, 1.95 g) was added to the mixture in three portions. The resulting suspension was warmed to room temperature and stirred for additional 6 hours. The reaction mixture was cooled using an ice-bath and treated with sat. NH_4Cl (aq) and the pH was basified using sat. $NaHCO_3$ (aq). The mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried using $MgSO_4$. The volatiles were removed under reduced pressure. Column chromatography (4:2:1 hexane:acetone:toluene R_f = 0.15) afforded the title compound as a light yellow oil (4.19 g, 50%). Spectral data match the previously reported values.[235] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 3.85–3.79 (m, 4H), 3.79–3.75 (m, 1H), 3.75 (s, 3H), 3.67 (d, *J* = 12.8 Hz, 1H), 3.59 (dd, *J* = 10.5, 6.6 Hz, 1H), 3.43 (dd, *J* = 6.6, 4.6 Hz, 1H).

Methyl *N*-(*tert*-butoxycarbonyl)-*N*-(4-methoxybenzyl)-D-serinate (**307**)



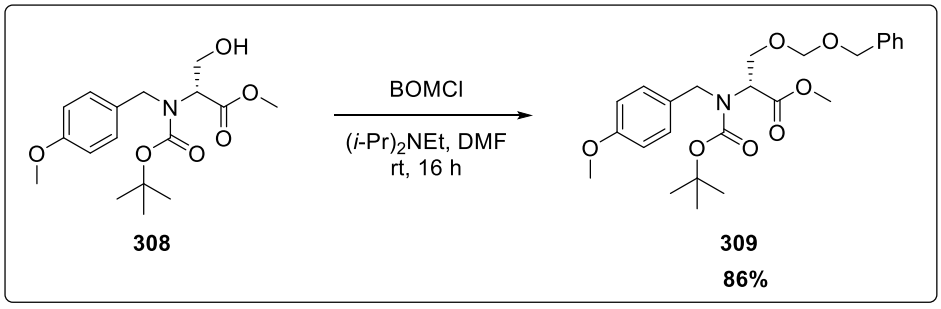
306 **307**

62%

N-Boc protection accomplished using a reported procedure.[197] To a solution of Methyl (4-methoxybenzyl)-D-serinate (**306**) (17.5 mmol, 4.19 g) in CH_2Cl_2 (27 mL) was added triethylamine (19.28 mmol, 2.7 mL) at room temperature. To this solution was added di-*tert*-butyl dicarbonate

(Boc_2O) (21.7 mmol, 4.75 g) and stirred at ambient temperature for 22 hours. The reaction was quenched with addition of 1M HCl (aq) and extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Column chromatography (3:1 hexane:acetone, R_f = 0.26) afforded the title compound as a clear colourless oil (3.66 g, 62%). $[\alpha]_D^{26}$ = +19 (*c* 1.7, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3370, 2976, 1742, 1695, 1514, 1367, 1247, 1163. 1036;; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.25–7.19 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.54–4.43 (m, 1.5H), 4.42–4.32 (m, 0.5H), 4.16–3.97 (m, 1.5 H), 3.84–3.87 (m, 3.5 H), 3.70 (m, 3H), 3.46 (br s, 0.5H), 3.07 (br s, 0.5H), 2.37 (br s, 1H), 1.46 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 172.3, 171.3*, 159.3, 129.9, 129.5, 129.0, 114.1, 81.3, 61.8, 61.7*, 60.9, 55.4, 52.2, 51.9*, 51.6, 28.4; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{17}H_{25}NO_6Na$ 362.1574; Found 362.1557.

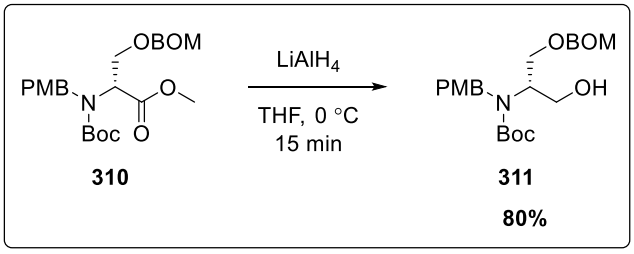
Methyl *O*-[(benzyloxy)methyl]-*N*-(*tert*-butoxycarbonyl)-*N*-(4-methoxybenzyl)-D-serinate (**309**)



According to a reported procedure,[161] To a solution of *N*-(*tert*-butoxycarbonyl)-*N*-(4-methoxybenzyl)-D-serinate (**308**) (5.57mmol, 1.89 g) in dry DMF (5.6 mL) was added (*i*-Pr)$_2$NEt (17.8 mmol, 3.1 mL) at room temperature under argon. This was followed by the addition of BOMCl (70% purity) (16.7 mmol, 3.1 mL). The mixture was stirred at this temperature for 24

hours. The mixture was diluted in EtOAc (100 mL) and washed sequentially with sat. NH_4Cl ($aq_)$ (100 mL), distilled water (100 mL), and brine (100 mL). The organic layer was dried over $MgSO_4$ and concentrated. The resulting solution was purified by chromatography (4:1 hexane:EtOAc, R_f = 0.22) to afford the title compound as a clear colourless oil (2.19 g, 86%). $[\alpha]_D^{27}$ = +39 (*c* 2.3, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3031, 2975, 2951, 1746, 1698, 1514, 1367, 1302 1165, 1048, 607; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.39–7.27 (m, 5H), 7.25–7.17 (m, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.78–4.54 (m, 3.5H), 4.54–4.36 (m, 2H), 4.39 (t, *J* = 16.2 Hz, 1H), 4.12–3.92 (m 2H), 3.86–3.80 (m, 0.5H), 3.77 (s, 3H), 3.70–3.60 (m, 3H), 1.47–1.37 (m, 9H); **^{13}C NMR** (125 MHz, CDCl3) Mixture of rotamers (minor rotamer indicated by asterisk): δ 171.4, 159.1, 158.7*, 155.8*, 155.1, 137.8, 131.0*, 129.9, 128.6*, 128.5, 127.9, 127.8, 113.8, 113.7*, 94.7, 91.9*, 90.1, 81.0, 80.8*, 69.4, 67.4, 66.6*, 59.4, 59.2*, 55.3, 52.1*, 52.1, 51.4, 50.61, 28.4 ; **HRMS** (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{25}H_{33}NO_7Na$ 482.2149; Found 482.2164.

tert-Butyl (*S*)-{1-[(benzyloxy)methoxy]-3-hydroxypropan-2-yl}(4-methoxy-benzyl)carbamate (**311**)

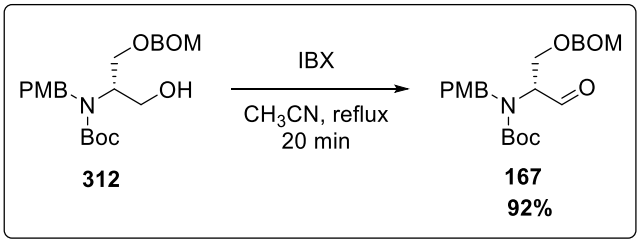


310 **311** **80%**

To a suspension of $LiAlH_4$ (3.3 mmol, 0.125 g) in THF (5 mL) was added a solution of **310** (1.10 mmol, 0.509 g) in dry THF (6 mL) at 0 °C. After the reaction was completed (as judged by TLC analysis) an aqueous solution of 0.5 M Rochelle's salt was slowly added to the mixture at 0 °C. The reaction was vigorously stirred at room temperature for two hours. The reaction mixture

was diluted in EtOAc (30 mL) and the layers were separated. The aqueous phase was extracted using EtOAc (2 × 50) and the combined organic layers were dried over $MgSO_4$. The resulting mixture was concentrated *in vacuo*. Purification using column chromatography (4:1 hexane:acetone, R_f = 0.21) afforded the title compound as a clear colourless oil (0.396 g, 80%). $[\alpha]_D^{26}$ = -19 (*c* 3.0, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3451, 2934, 2886, 1669, 1613, 1513, 1555, 1391, 1247, 1166, 1084, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.39–7.28 (m, 5H), 7.24–7.14 (m, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.75–4.65 (m, 2H), 4.59–4.49 (m, 3H), 4.36–4.21 (m, 0.5H), 3.92–3.82 (m, 1.3H), 3.82–3.77 (m, 3.7H), 3.77–3.63 (m, 3H), 3.51–3.41 (m, 0.5H), 1.46 (s, 9H); **^{13}C NMR** (125 MHz, CDCl3) Mixture of rotamers (minor rotamer indicated by asterisk): δ 158.9, 156.8, 137.8, 131.0, 128.6, 128.5, 128.5, 127.9, 127.8, 127.0*, 114.0, 94.8, 92.2*, 80.7, 69.5, 67.5*, 66.2*, 63.2, 62.8*, 59.9, 59.2*, 55.3, 51.4, 49.6*, 28.5; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{24}H_{33}NO_6Na$ 454.2200; Found 454.2211.

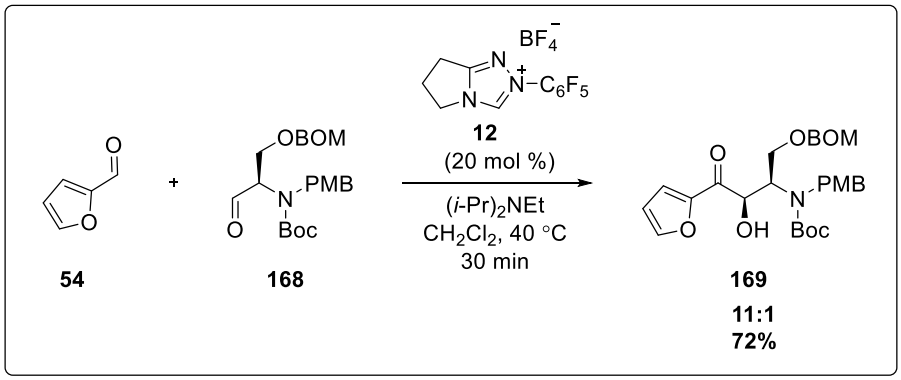
tert-Butyl (*R*)-{1-[(benzyloxy)methoxy]-3-oxopropan-2-yl}(4-methoxybenzyl)carbamate (**168**)



According to a known procedure,[161] IBX (1.74 mmol, 0.487 g) was added to a solution of **312** (1.16 mmol, 0.500 g) in acetonitrile (5.8 mL) and heated to reflux. The reaction was monitored for complete consumption of starting material (20 min). After completion, the contents were cooled to room temperature, filtered through a pad of Celite® and washed with EtOAc (3 × 20 mL). The

resulting mixture was concentrated. Purification using column chromatography (5:1 hexane:acetone, R_f = 0.30) afforded the title compound as a clear colourless oil (0.458 g, 92%). $[\alpha]_D^{27}$ = +7.5 (*c* 1.3, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 2977, 2936, 1737, 1704, 1683, 1613, 1514, 1368, 1249, 1164, 1040; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 9.39 (s, 0.4H), 9.29 (s, 0.6H), 7.38–7.27 (m, 5H), 7.25–7.19 (m, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.04 (d, *J* = 14.7 Hz, 0.6H), 4.82 (d, *J* = 15.9 Hz, 0.4H), 4.78–4.73 (m, 1H), 4.73–4.68 (m, 1H), 4.60–4.53 (m, 2H), 4.23 (d, *J* = 15.2 Hz, 0.6H), 4.18–4.08 (m, 1.4H), 3.96 (ap t, *J* = 9.3 Hz, 0.4H), 3.86–3.77 (m, 4H), 3.67 (ap t, *J* = 5.5 Hz, 0.6H), 1.48 (s, 4H), 1.43 (s, 5H); **^{13}C NMR** (125 MHz, CDCl3) Mixture of rotamers (minor rotamer indicated by asterisk): δ 158.9, 156.8, 137.8, 131.0, 128.6, 128.5, 128.5, 127.9, 127.8, 127.0*, 114.0, 94.8, 92.2*, 80.7, 69.5, 67.5*, 66.2*, 63.2, 62.8*, 59.9, 59.2*, 55.3, 51.4, 49.6*, 28.5; **HRMS** (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{24}H_{31}NO_6Na$ 452.2044; Found 452.2060.

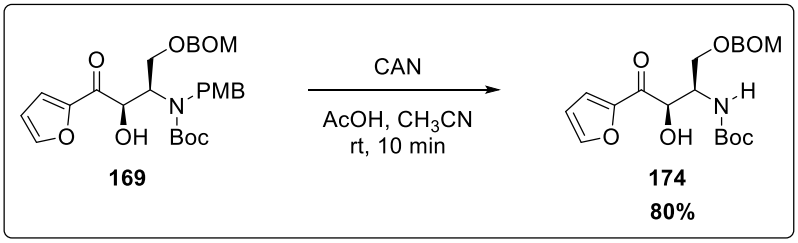
tert-Butyl [(2*R*,3*R*)-5-(benzyloxy)-1-(furan-2-yl]-2-hydroxy-1-oxopentan-3-yl)(4-methoxybenzyl)carbamate (**169**)



Compound **168** (1.84 mmol, 0.789 g) and triazolium salt **12** (0.368 mmol, 0.134 g) were added to an oven–dried test tube with a Schlenk take–off and fitted with a septum. The vessel was placed

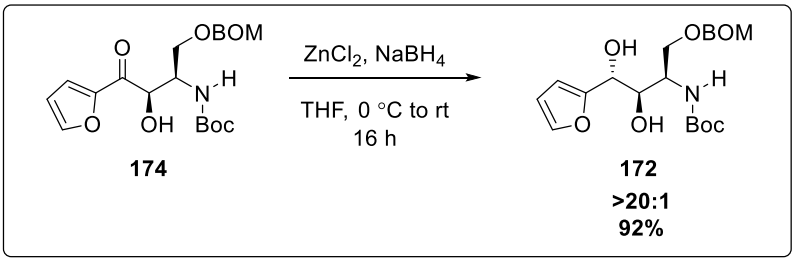
under vacuum and re–filled with argon three times to ensure inert atmosphere. Freshly distilled 2-furaldehyde (**54**) (5.52 mmol, 0.46 mL) and CH_2Cl_2 (3.7 mL) were added sequentially. Lastly (*i*-Pr)$_2$NEt (1.84 mmol, 0.32 mL) was added and the septum was then quickly exchanged for a cold finger immersed into a pre-heated oil bath (40 °C). Note: the side-arm was left open with a gentle flow of argon. After 30 minutes, the crude reaction mixture was cooled to room temperature and quenched by addition of 1M HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and dried over Na_2SO_4. The crude product was purified by column chromatography (4:1 hexane:acetone, R_f = 0.28) to afford the title compound as a yellow wax (0.694g, 72%). $[\alpha]_D^{26}$ = +58 (*c* 0.5, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3439, 2975, 2934, 1681, 1513, 1465, 1406, 1301, 1165, 1042; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.69 (br s, 1H), 7.64 (s, 1H), 7.36–7.26 (m, 3H), 7.22 (d, *J* = 7.0Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 6.57 (s, 1H), 4.99 (s, 1H), 4.72–4.50 (m, 3H), 4.49–4.40 (m, 2.5H), 4.40–4.31 (m, 2.5H), 3.84–3.71 (m, 4H), 3.71–3.62 (m, 0.8H), 3.62–3.52 (m, 0.2H), 1.53 (s, 1.5H), 1.42 (s, 7.5H); **^{13}C NMR** (125 MHz, CDCl3) Mixture of rotamers (minor rotamer indicated by asterisk): δ 187.0, 158.7, 156.6, 150.2, 147.5, 147.3*, 137.8, 131.6, 128.5, 128.3, 128.0, 127.8, 121.0, 119.2*, 113.8, 112.6, 94.5, 80.9, 76.5, 69.4, 65.6*, 64.5*, 60.3, 55.4, 50.3, 48.4*, 28.5; **HRMS** (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd. for $C_{29}H_{35}NO_8Na$ 548.2255; Found 548.2236.

tert-Butyl {(2*R*,3*R*)-1-[(benzyloxy)methoxy]-4-(furan-2-yl}-3-hydroxy-4-oxobuta-n-2-yl)carbamate (**174**)



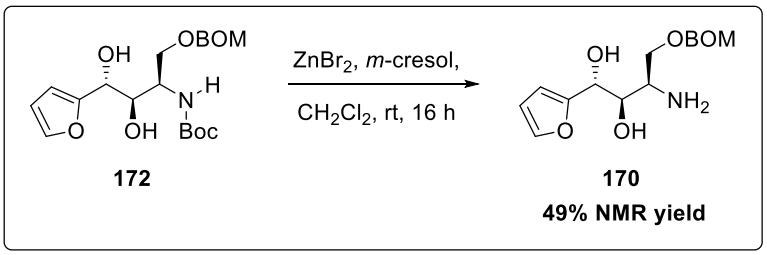
According to a modified procedure,[164] to a solution of **169** (0.166 mmol, 0.087g) in wet acetonitrile (80%, 0.8 mL) and glacial acetic acid (0.8 mL) was added ceric ammonium nitrate (CAN) (0.497 mmol, 0.272 g) in one portion. The reaction was stirred at room temperature for 10 minutes and cooled to 0 °C using an ice-bath. The reaction was quenched with the careful addition of sat. NaHCO3 (aq) (pH = 8). The reaction mixture was extracted with EtOAc (3 × 30 mL) and the combined organic layers were dried using MgSO4. The volatiles were removed *in vacuo* and the crude product was purified using column chromatography (3:1 hex:acetone, R_f = 0.16) to afford the title compound as a white solid (0.054g, 80%). Meting Range (91.3–93.3 °C); $[\alpha]_D^{25}$ = +57 (*c* 0.5, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3375, 3032, 2933, 2886, 1709, 1677, 1499, 1467, 1367, 1168, 1403, 699; **^{1}H NMR** (500 MHz, $CDCl_3$) mixture of rotamers; δ 7.67 (s, 1H), 7.48 (d, *J* = 3.5 Hz, 1H), 7.36–7.27 (m, 5H), 4.58 (dd, *J* = 3.5, 1.6 Hz, 1H), 5.24 (d, *J* = 9.3 Hz, 1H), 4.94 (dd, *J* = 6.2, 3.4 Hz, 1H), 4.56 (d, *J* = 6.7 Hz, 1H), 4.52 (d, *J* = 6.8 Hz, 1H), 4.50–4.43 (m, 2H), 3.87 (d, *J* = 6.4 Hz, 1H), 3.62 (dd, *J* = 10.0, 4.8 Hz, 1H), 3.56 (dd, *J* = 9.8, 7.1 Hz, 1H), 1.44 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) Mixture of rotamers (minor rotamer indicated by asterisk): δ 187.1, 155.4, 150.5, 147.5, 137.6, 128.5, 128.1, 127.9, 119.6, 113.5*, 112.7, 94.5, 80.0, 74.6, 69.6, 65.8, 53.5, 28.5; **HRMS** (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd. for $C_{21}H_{27}NO_7Na$ 428.1680; Found 428.1683.

tert-Butyl {(2*R*,3*R*,4*R*)-1-[(benzyloxy)methoxy]-4-(furan-2-yl}-3,4-dihydroxybuta-n-2-yl)carbamate (**172**)



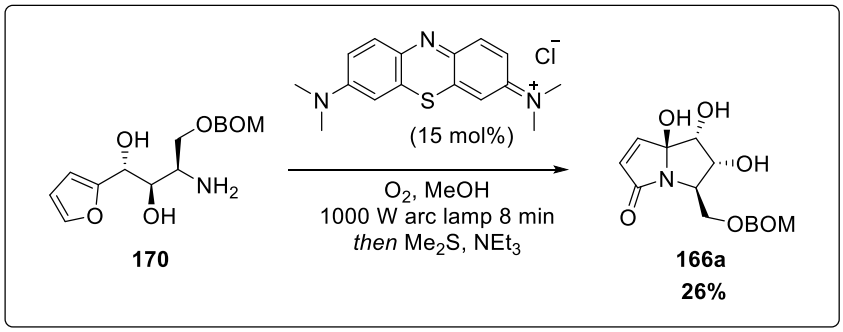
According to a reported procedure,[161] to a pre-cooled (0 °C) dry round-bottomed flask containing $NaBH_4$ (0.320 mmol, 0.012 g) in THF (2 mL) was added a 0.5 M solution of $ZnCl_2$ (in Et2O, 0.320 mmol, 0.64 mL) under argon. This mixture was stirred at 0°C for 10 minutes and a solution of **174** (0.320 mmol, 0.168 g) in THF (1.2 mL) was added. The mixture was gradually warmed to room temperature and stirred at this temperature for 16 h. The reaction was quenched with the slow addition of water at 0 °C. The crude mixture was diluted in Et_2O (40 mL) and the layers were separated. The aqueous phase was washed with Et_2O (2 × 40 mL) and the combined organic layers were using $MgSO_4$ and then concentrated. Column chromatography (3:1 hexane:acetone) afforded the title compound as a clear colourless oil (0.154 mg, 92%). $[\alpha]_D^{26\,°C}$ = -37 (*c* 1.1, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3412, 2977, 2933, 2887, 1689, 1506, 1367, 1249, 1169, 1046, 737; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.38 (br s, 1H), 7.37–7.34 (m, 4H), 7.34–7.28 (m, 1H), 6.34 (s, 2H), 5.12 (d, *J* = 8.3 Hz, 1H), 4.83–4.75 (m, 3H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.14 (dd, *J* = 12.8, 6.0 Hz, 1H), 4.01 (ap d, *J* = 9.5 Hz, 1H), 3.96–3.86 (m, 1H), 3.73 (dd, *J* = 10.0, 4.2 Hz, 1H), 3.30 (d, *J* = 7.5 Hz, 1H), 3.83 (d, *J* = 7.9 Hz, 1H), 1.41 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) ; δ 156.1, 154.0, 142.3, 137.5, 128.6, 128.0, 128.0, 110.5, 1105, 107.4, 95.2, 80.1, 73.9, 70.1, 67.9, 51.4, 28.5; **HRMS** (TOF) *m/z*: [M+Na] Calcd for $C_{21}H_{29}NO7Na$: 430.1836; Found 430.1839.

(1*R*,2*R*,3*R*)-3-Amino-4-[(benzyloxy)methoxy]-1-(furan-2-yl)butane-1,2-diol (**164**)



Following a modified procedure,[81] an oven–dried test tube with a Schlenk take–off was charged with **172** (0.332 mmol, 0.135 g). The vessel was placed under vacuum and re–filled with argon three times to ensure inert atmosphere. CH_2Cl_2 (1.7 mL), *m*-cresol (3.32 mmol, 0.35 mL), and $ZnBr_2$ (1M in Et_2O, 2.49 mmol, 2.5 mL) were added to the reaction vessel and stirred at room temperature for 16 hours. The reaction was quenched by the addition of sat. Rochelle's salt (aq) (10 mL) and stirred vigorously at room temperature. The solids were filtered and the cake was washed with EtOAc (2 × 50 mL). Removal of volatiles under reduced pressure followed by purification by column chromatography (9:1:01 CH_2Cl_2:MeOH:NH_4OH (aq)) afforded the title compound as a clear colourless oil. CAUTION: this compound is acid and moisture sensitive. The yield was determined bases on the ^1H NMR spectra by using trichloro ethylene as the internal standard (49% NMR yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.32 (s, 0.2H), 7.42 (s, 0.8H), 7.38–7.32 (m, 3H), 7.32–7.27 (s, 1H), 6.41 (d, *J* = 3.2 Hz, 0.2H), 6.39 (d, *J* = 3.1 Hz, 0.8H), 6.38–6.33 (m, 1H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.80 (d, *J* = 6.9 Hz, 1H), 4.74 (d, *J* = 8.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 3.81 (dd, *J* = 9.8, 4.8 Hz, 1H), 3.76 (ap t, *J* = 8.3, 1H), 3.66 (dd, *J* = 9.7, 3.5 Hz, 1H), 3.05 (dt, *J* = 8.4, 4.3 Hz, 1H).

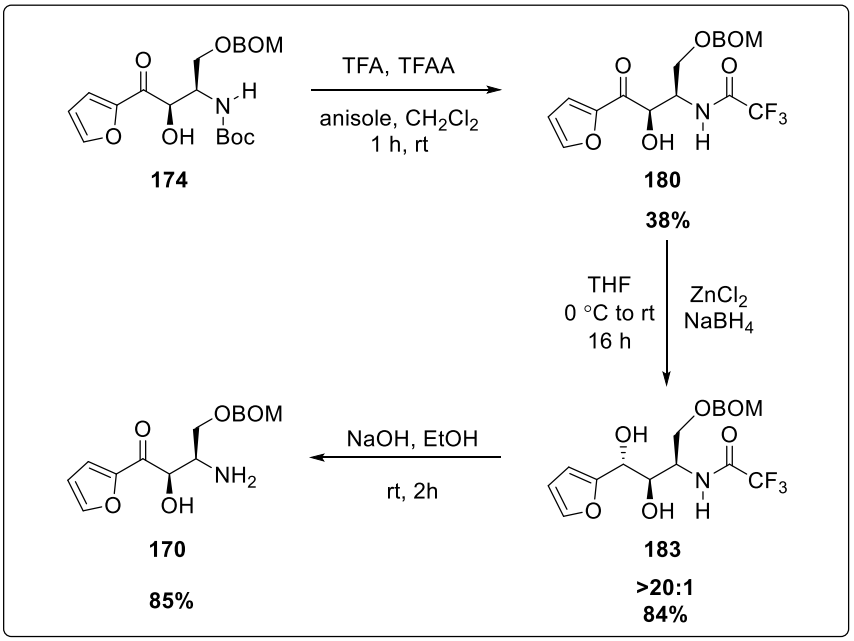
(5*R*,6*R*,7*R*,7a*S*)-5-{[(Benzyloxy)methoxy]methyl}-6,7,7a-trihydroxy-5,6,7,7a-tetrahydro-3*H*-pyrrolizin-3-one (**166a**)



According to a modified procedure,[236] a solution of **170** (0.0375 mmol, 0.0115 g) and methylene blue (0.0056 mmol, 0.002 g) in MeOH (0.5 mL) was cooled to 0 °C using an ice-bath. Oxygen was gently bubbled into the solution and the reaction mixture was irradiated with a Xe-Hg 1000W arc lamp light for 2 minute intervals. After consumption of starting material (as judged by TLC analysis, typically 6-9 minutes), Me_2S (0.0375 mmol, 0.0030 mL) and NEt_3 (0.0375 mmol, 0.0052 mL) was added to the reaction mixture and stirring was continued at room temperature under air. After 16 hours, charcoal was added to the reaction mixture and the contents were stirred for an additional 10 minutes. The reaction mixture was filtered through Celite® and washed with EtOAc (3 ×2 mL). The organic layer was washed with H_2O (2 × 5 mL) and dried over Na_2SO_4. Removal of volatiles under reduce pressure afforded the crude product. Purification using PTLC (3:1 acetone:hexane, R_f = 0.45) afforded the title compound as a yellow oil (0.0031 g, 26%). $[\alpha]_D^{24\ °C}$ = -11 (*c* 0.23, $CHCl_3$); **FTIR** (KBr film) ν_{max} (cm^{-1}): 3365, 2917, 2849, 1692, 1384, 1043, 734; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5H), 6.98 (d, *J* = 5.8 Hz, 1H), 6.18 (d, *J* = 5.8 Hz, 1H), 4.84 (s, 2H), 4.72 (dd, *J* = 6.7, 4.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.11 (d, *J* = 3.6 Hz, 1H), 3.92 (dd, *J* = 9.8, 3.2 Hz, 1H), 3.82–3.75 (m, 1H), 3.74–3.70 (m, 1H), 3.06 (br s, 1H), 2.57 (br s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.09, 146.6, 137.7, 130.3,

128.7, 128.2, 128.0, 98.8, 95.4, 77.4, 74.0, 70.4, 68.5, 59.8,; **HRMS** (TOF) *m/z*: [M+Na] Calcd for $C_{16}H_{19}NO_6Na$: 344.1106; Found 344.1118.

Alternative Synthesis of (1*R*,2*R*,3*R*)-3-Amino-4-[(benzyloxy)methoxy]-1-(furan-2-yl)butane-1,2-diol (**170**)



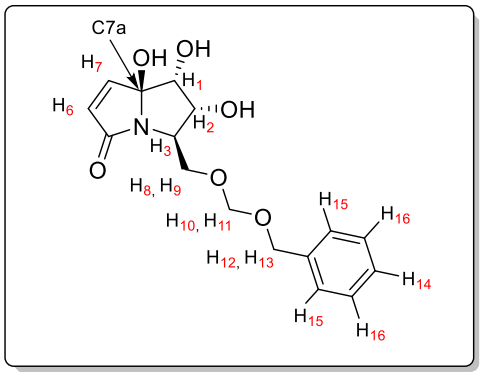
To a solution of **174** (0.279 mmol, 0.113 g) in dry CH_2Cl_2 (2.8 mL) was added anisole (1.40 mmol, 0.26 mL) followed by trifluoroacetic anhydride (TFAA) (2.79 mmol, 0.39 mL) under argon was added freshly distilled trifluoroacetic acid (TFA) (6.98 mmol, 0.53 mL). After 1 h, the reaction was cooled to in an ice-bath and basified with the addition of sat. $NaHCO_3$ (aq) (pH = 8). The reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried using $MgSO_4$. Purification using column chromatography (4:1 hexane:acetone, R_f = 0.15) afforded **179** as a clear colourless oil (0.043g, 38%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.46 (d, *J* = 3.6 Hz, 1H), 7.39–7.32 (m, 2H), 7.32–7.27 (m, 3H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.28 (dd,

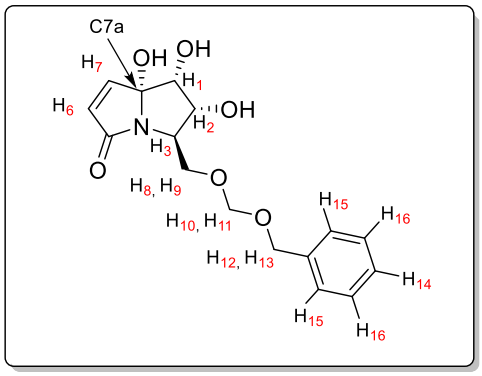
J = 3.6, 1.6 Hz, 1H), 4.98 (ap s, 1H), 4.84–4.76 (m, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.55 (d, *J* = 6.8 Hz, 1H), 4.51 (d, *J* = 12.3 Hz, 1H), 4.48 (d, *J* = 12.3 Hz, 1H), 3.91 (br s, 1H), 3.68 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.60 (dd, *J* = 10.2, 6.6 Hz, 1H).

The diastereoselective reduction of **180** was carried out according to the procedure described for the synthesis of **172**. Column chromatography (2:1 hexane:acetone, R_f = 0.18) afforded **183** as a clear colourless oil (0.054 g, 84%). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40–7.30 (m, 5H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.39–6.33 (m, 2H), 6.81–6.74 (m, 3H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 11.9 Hz, 1H), 4.33 (ddt, *J* = 9.0, 5.1, 3.9 Hz, 1H), 14.15 (dd, *J* = 6.3, 13.4 Hz, 1H), 4.08 (dd, *J* = 3.5, 10.6 Hz, 1H), 3.77 (dd, *J* = 10.6, 4.0 Hz, 1H), 2.94 (d, *J* = 6.4 Hz, 1H), 2.87 (d, *J* = 7.8 Hz, 1H).

According to a reported procedure,[237] to a solution of **183** (0.0126 mmol, 0.0051 g) in EtOH (2.5 mL) was added 2M NaOH (aq) (2.1 mL) and the reaction mixture was stirred at room temperature for 2 hours and extracted with EtOAc (2 ×3 mL). The combined organic layers were dried on MgSO4 and concentrated *in vacuo*. Purification using column chromatography (9:1:01 CH_2Cl_2:MeOH:NH_4OH (aq)) afforded the title compound as a clear colourless oil (0.0032 g, 85%). ^{1}H NMR spectrum corresponds to that of previously reported for **170**.

Predicted ^{1}H NMR Shifts Versus Experimental ^{1}H NMR Shifts for Compound 166a

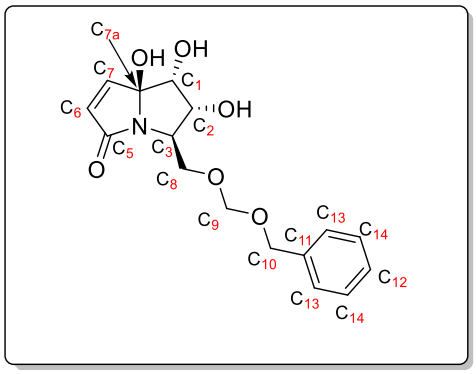




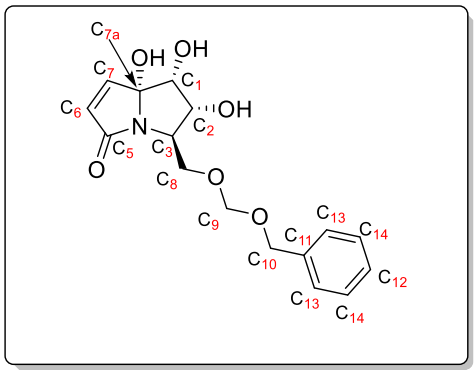
166a **166b**

Major isomer (166a)

signal number	observed ^{1}H NMR shift (ppm)	calculated ^{1}H NMR shift – 166a (ppm)	Δδ obs. vs. calc. (ppm)	calculated ^{1}H NMR shift – 166b (ppm)	Δδ obs. vs. calc. (ppm)
1	4.11	3.93	0.18	3.97	0.14
2	4.72	4.89	-0.17	4.12	0.6
3	3.72	3.58	0.14	3.74	-0.02
6	6.18	6.00	0.18	5.80	0.38
7	6.98	6.80	0.18	6.87	0.11
8	3.92	3.91	0.01	4.57	-0.65
9	3.79	3.88	-0.09	3.46	0.33
10	4.66	4.48	0.18	4.39	0.27
11	4.61	4.46	0.15	4.39	0.22
12	4.85	4.61	0.24	4.29	0.56
13	4.85	4.43	0.42	4.50	0.35
14	7.30	7.17	0.13	7.21	0.09
15	7.35	7.37	-0.02	7.38	-0.03
16	7.35	7.22	0.13	7.24	0.11
mean deviation			0.16		0.28



166a



166b

signal number	observed ^{13}C NMR shift (ppm)	calculated ^{13}C NMR shift – 166a (ppm)	Δδ obs. vs. calc. (ppm)	calculated ^{13}C NMR shift – 166b (ppm)	Δδ obs. vs. calc. (ppm)
1	74.0	75.57	-1.57	72.42	1.58
2	77.4	77.46	-0.06	83.99	-6.59
3	59.0	61.77	-2.77	62.69	-3.69
5	146.6	147.48	-0.88	147.51	-0.91
6	130.3	130.54	-0.24	128.88	1.42
7	174.1	170.94	3.15	171.16	2.93
7a	98.8	98.81	-0.01	98.88	-0.08
8	70.4	67.61	2.79	62.09	8.31
9	95.4	93.47	1.93	92.71	2.69
10	68.5	68.90	-0.4	68.20	0.3
11	137.7	137.25	0.45	138.93	-1.23
12	128.0	126.35	1.65	125.84	2.16
13	128.7	128.71	-0.01	127.94	0.76
14	128.2	126.65	1.55	126.46	1.74
mean deviation			1.25		2.46

References

(1) Wöhler, F.; Liebig, J. *Ann. Der. Pharm.* **1832**, *3*, 249–287.

(2) Lapworth, A. *J. Chem. Soc. Trans.* **1903**, *83*, 995–1005.

(3) Seebach, D.; Locher, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 957–958.

(4) Ukai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn* **1943**, *63*, 296–300.

(5) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.

(6) Thai, K.; Langdon, S. M.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2013**, *15*, 2214–2217.

(7) Berkessel, A.; Elfert, S.; Yatham, V. R.; Neudörfl, J. M.; Schlörer, N. E.; Teles, J. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 12370–12374.

(8) Dirocco, D. A.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 6143–6145.

(9) Maji, B.; Mayr, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 10408–10412.

(10) Jordan, F.; Kudzin, Z. H.; Rios, C. B. *J. Am. Chem. Soc.* **1987**, *109*, 4415–4416.

(11) Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5770–5775.

(12) Rehbein, J.; Ruser, S.-M.; Phan, J. *Chem. Sci.* **2015**, *6*, 6013–6018.

(13) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307–9387.

(14) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314–325.

(15) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511–3522.

(16) Thai, K.; Sánchez-Larios, E.; Gravel, M. In Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions, and Applications; Wiley−VCH: Weinheim, **2013**; 495−522.

(17) O'Bryan, E. A.; Scheidt, K. A. *Acyloin Coupling Reactions*, In *Comprehensive Organic Synthesis II*; Marek, I.; Knochel, P., Eds.; Elsevier: Amsterdam, **2014**, 2nd ed., Vol. 3, 621–655.

(18) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485–496.

(19) Yetra, S.; Patra, A.; Biju, A. *Synthesis* **2015**, *47*, 1357–1378.

(20) Izquierdo, J.; Hutson, G. E.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11686–11698.

(21) Bugaut, X. *Benzoin and Aza-benzoin*, In *Comprehensive Organic Synthesis II*; Marek, I.; Knochel, P., Eds.; Elsevier: Amsterdam, **2014**, 2nd ed., Vol. 1, 424–470.

(22) Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432–8433.

(23) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492–3494.

(24) Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. *Chem. Commun.* **2010**, *46*, 6282–6284.

(25) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431–2434.

(26) Li, Y.; Feng, Z.; You, S.-L. *Chem. Commun.* **2008**, 19, 2263–2265.

(27) Enders, D.; Henseler, A. *Adv. Synth. Catal.* **2009**, *351*, 1749–1752.

(28) Ema, T.; Oue, Y.; Akihara, K.; Miyazaki, Y.; Sakai, T. *Org. Lett.* **2009**, *11*, 4866–4869.

(29) Takada, A.; Hashimoto, Y.; Takikawa, H.; Hikita, K.; Suzuki, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2297–2301.

(30) Rose, C. A.; Gundala, S.; Fagan, C.-L.; Franz, J. F.; Connon, S. J.; Zeitler, K. *Chem. Sci.* **2012**, *3*, 735–740.

(31) Goodman, C. G.; Johnson, J. S. *J. Am. Chem. Soc.* **2014**, *136*, 14698–14701.

(32) Mathies, A. K.; Mattson, A. E.; Scheidt, K. A. *Synlett* **2009**, 377–383.

(33) Stetter, H.; Dambkes, G. *Synthesis* **1977**, 403–404.

(34) O'Toole, S. E.; Rose, C. A.; Gundala, S.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2011**, *76*, 347–357.

(35) Demir, A. S.; Şeşenoglu, Ö.; Eren, E.; Hosrik, B.; Pohl, M.; Janzen, E.; Kolter, D.; Feldmann, R.; Dünkelmann, P.; Müller, M. *Adv. Synth. Catal.* **2002**, *344*, 96–103.

(36) Müller, C. R.; Pérez-Sánchez, M.; Domínguez de María, P. *Org. Biomol. Chem.* **2013**, *11*, 2000–2004.

(37) Stockton, K. P.; Greatrex, B. W.; Taylor, D. K. *J. Org. Chem.* **2014**, *79*, 5088–5096.

(38) Piel, I.; Pawelczyk, M. D.; Hirano, K.; Fröhlich, R.; Glorius, F. *Eur. J. Org. Chem.* **2011**, 5475–5484.

(39) Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W. *Org. Lett.* **2011**, *13*, 880–883.

(40) Jin, M. Y.; Kim, S. M.; Mao, H.; Ryu, D. H.; Song, C. E.; Yang, J. W. *Org. Biomol. Chem.* **2014**, *12*, 1547–1550.

(41) Collett, C. J.; Massey, R. S.; Maguire, O. R.; Batsanov, A. S.; O'Donoghue, A. C.; Smith, A. D. *Chem. Sci.* **2013**, *4*, 1514.

(42) Langdon, S. M.; Wilde, M. M. D.; Thai, K.; Gravel, M. *J. Am. Chem. Soc.* **2014**, *136*, 7539–7542.

(43) Langdon, S. M.; Legault, C. Y.; Gravel, M. *J. Org. Chem.* **2015**, *80*, 3597–3610.

(44) de Alaniz, J. R.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033–2040.

(45) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Giovannini, P. P.; Massi, A.; Pacifico, S. *Org. Biomol. Chem.* **2011**, *9*, 8437–8444.

(46) Sánchez-Larios, E.; Holmes, J. M.; Daschner, C. L.; Gravel, M. *Org. Lett.* **2010**, *12*, 5772–5775.

(47) Wu, K.-J.; Li, G.-Q.; Li, Y.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2011**, *47*, 493–495.

(48) Dirocco, D. A.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5904–5906.

(49) Wilde, M. M. D.; Gravel, M. *Org. Lett.* **2014**, *16*, 5308–5311.

(50) Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696–9697.

(51) Rogers, D. F.; Barnes, P. J. *Trends Pharmacol. Sci.* **1999**, *20*, 352–354.

(52) Béguin, C.; Andurkar, S. V; Jin, A. Y.; Stables, J. P.; Weaver, D. F.; Kohn, H. *Bioorg. Med. Chem.* **2003**, *11*, 4275–4285.

(53) Haustein, K. O. *Int. J. Clin. Pharmacol. Ther.* **2003**, *41*, 56–66.

(54) Di Gioia, M. L.; Leggio, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. *J. Org. Chem.* **2001**, *66*, 7002–7007.

(55) Goodnick, P.; Dominguez, R.; DeVane, C. L.; Bowden, C. *Biol. Psychiatry* **1998**, *44*, 629–632.

(56) Demuth, H. U.; Heiser, U.; Niestroj, A.; Hoffmann, T. Substituted amino ketone compounds. US20050014946, May 15, 2003.

(57) Muñiz, K.; Hövelmann, C. H.; Villar, A.; Vicente, R.; Streuff, J.; Nieger, M. *J. Mol. Catal. A Chem.* **2006**, *251*, 277–285.

(58) Myers, A. G.; Yoon, T. *Tetrahedron Lett.* **1995**, *36*, 9429–9432.

(59) Katritzky, A. R.; Musgrave, R. P. *Heterocycles* **1996**, *42*, 273–280.

(60) Castells, J.; López-Calahorra, F.; Bassedas, M.; Urrios, P. *Synthesis* **1988**, 314–315.

(61) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Chem. Commun.* **2007**, 852–854.

(62) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654–1655.

(63) Mattson, A. E.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 4363–4366.

(64) Enders, D.; Henseler, A.; Lowins, S. *Synthesis* **2009**, 4125–4128.

(65) Sun, L. H.; Liang, Z. Q.; Jia, W. Q.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 5803–5806.

(66) DiRocco, D. A.; Oberg, K. M.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 6143–6145.

(67) Mulzer, J.; Brand, C. *Tetrahedron* **1986**, *42*, 5961–5968.

(68) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657–10670.

(69) Azuma, H.; Tamagaki, S.; Ogino, K. *J. Org. Chem.* **2000**, *65*, 3538–3541.

(70) Jung, D. Y.; Kang, S.; Chang, S. B.; Kim, Y. H. *Synlett* **2005**, 2183–2186.

(71) Kazmaier, U. *J. Org. Chem.* **1996**, *61*, 3694–3699.

(72) Enders, D.; Paleček, J.; Grondal, C. *Chem. Commun.* **2006**, *55*, 655–657.

(73) Mu, Y.; Jin, T.; Kim, G.-W.; Kim, J.-S.; Kim, S.-S.; Tian, Y.-S.; Oh, C.-Y.; Ham, W.-H. *Eur. J. Org. Chem.* **2012**, 2614–2620.

(74) Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1–8.

(75) D'Adamio, G.; Goti, A.; Parmeggiani, C.; Moreno-Clavijo, E.; Robina, I.; Cardona, F. *Eur. J. Org. Chem.* **2011**, *1*, 7155–7162.

(76) Asano, N. *Glycobiology* **2003**, *13*, 93R–104R.

(77) Chandrasekhar, S.; Parida, B. B.; Rambabu, C. *J. Org. Chem.* **2008**, 7826–7828.

(78) Veyron, A.; Reddy, P. V.; Koos, P.; Bayle, A.; Greene, A. E.; Delair, P. *Tetrahedron: Asymmetry* **2015**, *26*, 85–94.

(79) Reddy, P. V.; Veyron, A.; Koos, P.; Bayle, A.; Greene, A. E.; Delair, P. *Org. Biomol. Chem.* **2008**, *6*, 1170–1172.

(80) Chandrasekhar, S.; Parida, B. B.; Rambabu, C. *J. Org. Chem.* **2008**, *73*, 7826–7828.

(81) Donohoe, T. J.; Thomas, R. E.; Cheeseman, M. D.; Rigby, C. L.; Bhalay, G.; Linney, I. D. *Org. Lett.* **2008**, *10*, 3615–3618.

(82) Tsou, E. L.; Yeh, Y. T.; Liang, P. H.; Cheng, W. C. *Tetrahedron* **2009**, *65*, 93–100.

(83) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587–2590.

(84) Donohoe, T. J.; Sintim, H. O.; Hollinshead, J. *J. Org. Chem.* **2005**, *70*, 7297–7304.

(85) Donohoe, T. J.; Rigby, C. L.; Thomas, R. E.; Nieuwenhuys, W. F.; Bhatti, F. L.; Cowley, A. R.; Bhalay, G.; Linney, I. D. *J. Org. Chem.* **2006**, *71*, 6298–6301.

(86) Mennen, S. M.; Gipson, J. D.; Kim, Y. R.; Miller, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 1654–1655.

(87) Sun, L.; Liang, Z.; Jia, W.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 5803–5806.

(88) Garrett, M. R.; Tarr, J. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 12944–12945.

(89) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162–1186.

(90) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600–3740.

(91) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.

(92) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995.

(93) Bharatam, P. V; Kaur, A.; Kaur, D. *J. Phys. Org. Chem.* **2002**, *15*, 197–203.

(94) Bharatam, P. V.; Uppal, P.; Kaur, A.; Kaur, D. *J. Chem. Soc. Perkin Trans. 2* **2000**, 43–50.

(95) Sánchez-Larios, E.; Thai, K.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2011**, *13*, 4942–4945.

(96) Ling, K. B.; Smith, A. D. *Chem. Commun.* **2011**, *47*, 373–375.

(97) Liu, G.; Wilkerson, P. D.; Toth, C. A.; Xu, H. *Org. Lett.* **2012**, *14*, 858–861.

(98) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53–57.

(99) Raup, D. E. A.; Cardinal-David, B.; Holte, D.; Scheidt, K. A. *Nat. Chem.* **2010**, *2*, 766–771.

(100) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543.

(101) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheldt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932–4933.

(102) DiRocco, D. A.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5904–5906.

(103) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *133*, 10402–10405.

(104) Haghshenas, P.; Langdon, S. M.; Gravel, M. *Synlett* **2017**, *28*, 542–559.

(105) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236–239.

(106) Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359–1362.

(107) Gryko, D.; Chałko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514–541.

(108) Willoughby, P. H.; Jansma, M. J.; Hoye, T. R. *Nat. Protoc.* **2014**, *9*, 643–660.

(109) Zhao, X.; Glover, G. S.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *Synlett* **2013**, *24*, 1229–1232.

(110) Hanessian, S. *Total Synthesis of Natural Products, the "Chiron" Approach*; Pergamon Press Oxford, 1983; Vol. 3.

(111) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2012**, *41*, 4150–4164.

(112) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653–2656.

(113) Husain, S. M.; Stillger, T.; Dünkelmann, P.; Lödige, M.; Walter, L.; Breitling, E.; Pohl, M.; Bürchner, M.; Krossing, I.; Müller, M.; Romano, D.; Molinari, F. *Adv. Synth. Catal.* **2011**, *353*, 2359–2362.

(114) Jahn, E.; Smrček, J.; Pohl, R.; Císařová, I.; Jones, P. G.; Jahn, U. *Eur. J. Org. Chem.* **2015**, *2015*, 7785–7798.

(115) Haghshenas, P.; Quail, J. W.; Gravel, M. *J. Org. Chem.* **2016**, *81*, 12075–12083.

(116) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531–1546.

(117) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121–1162.

(118) Passiniemi, M.; Koskinen, A. M. *Beilstein J. Org. Chem.* **2013**, *9*, 2641–2659.

(119) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *47*, 556–569.

(120) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066–14067.

(121) Carter, H. E.; Celmer, W. D.; Lands, W. E. M.; Mueller, K. L.; Tomizawa, H. H. *J. Biol. Chem.* **1954**, *206*, 613–623.

(122) Thorpe, S. R.; Sweeley, C. C. *Biochemistry* **1967**, *6*, 887–897.

(123) Oda, T. *J .Pharm. Soc. Jpn.* **1952**, *72*, 142.

(124) Kim, S.; Lee, N.; Lee, S.; Lee, T.; Lee, Y. M. *J. Org. Chem.* **2008**, *73*, 1379–1385.

(125) Howell, A.; Ndakala, A. *Curr. Org. Chem.* **2002**, *6*, 365–391.

(126) Brodesser, S.; Sawatzki, P.; Kolter, T. *Eur. J. Org. Chem.* **2003**, 2021–2034.

(127) Liao, J.; Tao, J.; Lin, G.; Liu, D. *Tetrahedron* **2005**, *61*, 4715–4733.

(128) Lee, D. H.; Kim, S. H.; Ahn, K. H.; Kim, S. K.; Choi, J. M.; Ji, J. E.; Won, J. H.; Park, Y. H.; Lim, C.; Kim, S.; Kim, D. K. *Arch. Pharm. Res.* **2011**, *34*, 229–236.

(129) Rives, A.; Baudoin-Dehoux, C.; Saffon, N.; Andrieu-Abadie, N.; Génisson, Y. *Org. Biomol. Chem.* **2011**, *9*, 8163–8170.

(130) Mormeneo, D.; Casas, J.; Llebaria, A.; Delgado, A. *Org. Biomol. Chem.* **2007**, *5*, 3769–3777.

(131) Mulzer, J.; Brand, C. *Tetrahedron* **1986**, *42*, 5961–5968.

(132) Dong, D.-Q.; Hao, S.-H.; Wang, Z.-L.; Chen, C. *Org. Biomol. Chem.* **2014**, *12*, 4278–4289.

(133) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917–958.

(134) Adam, W.; Lazarus, M.; SahaMoller, C. R.; Schreier, P. *Acc. Chem. Res.* **1999**, *32*, 837–845.

(135) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893–2903.

(136) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919–934.

(137) Kawasaki, M.; Li, P.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3795–3797.

(138) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080–1081.

(139) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463–8464.

(140) Basdevant, B.; Legault, C. Y. *Org. Lett.* **2015**, *17*, 4918–4921.

(141) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons, 2006.

(142) Chang, S.; Hur, S.; Britton, R. *Chem. Eur. J.* **2015**, *21*, 16646–16653.

(143) Mu, Y.; Jin, T.; Kim, G.-W.; Kim, J.-S.; Kim, S.-S.; Tian, Y.-S.; Oh, C.-Y.; Ham, W.-H. *Eur. J. Org. Chem.* **2012**, 2614–2620.

(144) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.

(145) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683–4696.

(146) Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *Mini-Reviews Med. Chem.* **2006**, *6*, 1043–1052.

(147) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077–3092.

(148) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773–781.

(149) Yoda, H. *Curr. Org. Chem.* **2002**, *6*, 223–243.

(150) Ghogare, A. A.; Greer, A. *Chem. Rev.* **2016**, *116*, 9994–10034.

(151) Deska, J.; Thiel, D.; Gianolio, E. *Synthesis* **2015**, *47*, 3435–3450.

(152) Gollnick, K.; Griesbeck, A. *Tetrahedron* **1985**, *41*, 2057–2068.

(153) Kalaitzakis, D.; Kouridaki, A.; Noutsias, D.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 6283–6287.

(154) Montagnon, T.; Kalaitzakis, D.; Sofiadis, M.; Vassilikogiannakis, G. *Org. Biomol. Chem.* **2016**, *14*, 8636–8640.

(155) Kalaitzakis, D.; Montagnon, T.; Antonatou, E.; Vassilikogiannakis, G. *Org. Lett.* **2013**, *15*, 3714–3717.

(156) Kalaitzakis, D.; Montagnon, T.; Antonatou, E.; Bardají, N.; Vassilikogiannakis, G. *Chem. Eur. J.* **2013**, *19*, 10119–10123.

(157) Kalaitzakis, D.; Montagnon, T.; Alexopoulou, I.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 8868–8871.

(158) Kalaitzakis, D.; Antonatou, E.; Vassilikogiannakis, G. *Chem. Commun.* **2014**, *50*, 400–402.

(159) Kalaitzakis, D.; Triantafyllakis, M.; Sofiadis, M.; Noutsias, D.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2016**, *55*, 4605–4609.

(160) DeRosa, M. C.; Crutchley, R. J. *Coord. Chem. Rev.* **2002**, *233–234*, 351–371.

(161) Haghshenas, P.; Gravel, M. *Org. Lett.* **2016**, *18*, 4518–4521.

(162) Krakowiak, K. E.; Bradshaw, J. S. *Synth. Commun.* **1996**, *26*, 3999–4004.

(163) Wang, J.; Liang, Y.-L.; Qu, J. *Chem. Commun.* **2009**, 5144–5146.

(164) Archer, R. M.; Hutchby, M.; Winn, C. L.; Fossey, J. S.; Bull, S. D. *Tetrahedron* **2015**, *71*, 8838–8847.

(165) Donohoe, T. J.; Rigby, C. L.; Thomas, R. E.; Nieuwenhuys, W. F.; Bhatti, F. L.; Cowley, A. R.; Bhalay, G.; Linney, I. D. *J. Org. Chem.* **2006**, *71*, 6298–6301.

(166) Liu, L.-J.; Chen, L.; Li, P.; Li, X.; Liu, J. *J. Org. Chem.* **2011**, *76*, 4675–4681.

(167) Li, Y.; Zhu, W.; Cheng, Z.; Yang, G. *Synth. Commun.* **1999**, *29*, 2645–2656.

(168) Zhu, W.; Li, Y.; Chen, Z.; Li, D.; Yang, G. *Synth. Commun.* **2000**, *30*, 1075–1081.

(169) Yang, T.; Chen, R.-Y.; Lee, D.-S.; Peng, W.-S.; Jiang, Y.-Z.; Mi, A.; Jong, T.-T. *J. Org.*

Chem. **1994**, *59*, 914–921.

(170) Fustero, S.; Moscardó, J.; Sánchez-Roselló, M.; Rodríguez, E.; Barrio, P. *Org. Lett.* **2010**, *12*, 5494–5497.

(171) Pandey, G.; Varkhedkar, R.; Tiwari, D. *Org. Biomol. Chem.* **2015**, *13*, 4438–4448.

(172) Solé, D.; Serrano, O. *J. Org. Chem.* **2010**, *75*, 6267–6270.

(173) Li, P.; Hu, X.; Dong, X.-Q.; Zhang, X. *Molecules* **2016**, *21*, 1327.

(174) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 659–676.

(175) Rein, T.; Kreuder, R.; von Zezschwitz, P.; Wulff, C.; Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1023–1025.

(176) Enders, D.; Han, J. *Synthesis* **2008**, 3864–3868.

(177) Kim, S. H.; Kim, S. I.; Lai, S.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 6771–6775.

(178) Kise, N.; Inoue, Y.; Sakurai, T. *Tetrahedron Lett.* **2013**, *54*, 3281–3285.

(179) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(180) Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. *Chem. Rev.* **2012**, *112*, 1839–1862.

(181) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.

(182) Vora, H. U., Lathrop, S. P., Reynolds, N. T., Kerr, M. S., de Alaniz, J. R., Rovis, T. *Org. Synth.* **2010**, *87*, 350.

(183) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.

(184) Collados, J. F.; Toledano, E.; Guijarro, D.; Yus, M. *J. Org. Chem.* **2012**, *77*, 5744–5750.

(185) Zhang, W.; Gilbertson, S. R. *Tetrahedron Lett.* **2017**, *58*, 2175–2177.

(186) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092–1093.

(187) Petrone, D. A.; Yoon, H.; Weinstabl, H.; Lautens, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 7908–7912.

(188) Collados, J. F.; Toledano, E.; Guijarro, D.; Yus, M. *J. Org. Chem.* **2012**, *77*, 5744–5750.

(189) Tongco, E. C.; Wang, Q.; Surya Prakash, G. K. *Synth. Commun.* **1997**, *27*, 2117–2123.

(190) Kasmi-Mir, S.; Djafri, A.; Paquin, L.; Hamelin, J.; Rahmouni, M. *Molecules* **2006**, *11*, 597–602.

(191) Allegretti, P. A.; Ferreira, E. M. *Org. Lett.* **2011**, *13*, 5924–5927.

(192) Brasholz, M.; Johnson, B. a.; Macdonald, J. M.; Polyzos, A.; Tsanaktsidis, J.; Saubern, S.; Holmes, A. B.; Ryan, J. H. *Tetrahedron* **2010**, *66*, 6445–6449.

(193) Enders, D.; Breuer, K.; Kallfass, U.; Balensiefer, T. *Synthesis* **2003**, 1292–1295.

(194) Jadhav, S. V.; Bandyopadhyay, A.; Benke, S. N.; Mali, S. M.; Gopi, H. N. *Org. Biomol.*

Chem. **2011**, *9*, 4182.

(195) Khatik, G. L.; Kumar, V.; Nair, V. A. *Org. Lett.* **2012**, *14*, 2442–2445.

(196) Rotstein, B. H.; Yudin, A. K. *Synthesis* **2012**, *44*, 2851–2858.

(197) Mansueto, M.; Frey, W.; Laschat, S. *Chem. Eur. J.* **2013**, *19*, 16058–16065.

(198) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404–3409.

(199) De Marco, R.; Di Gioia, M. L.; Liguori, A.; Perri, F.; Siciliano, C.; Spinella, M. *Tetrahedron* **2011**, *67*, 9708–9714.

(200) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051–6064.

(201) Tae Bo Sim; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 2532–2536.

(202) Albeck, A.; Persky, R. *J. Org. Chem.* **1994**, *59*, 653–657.

(203) Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742–15745.

(204) Rapireddy, S.; Nhon, L.; Meehan, R. E.; Franks, J.; Stolz, D. B.; Tran, D.; Selsted, M. E.; Ly, D. H. *J. Am. Chem. Soc.* **2012**, *134*, 4041–4044.

(205) Moore, C. L.; Leatherwood, D. D.; Diehl, T. S.; Selkoe, D. J.; Wolfe, M. S. *J. Med. Chem.* **2000**, *43*, 3434–3442.

(206) Kano, T.; Shirozu, F.; Maruoka, K. *J. Am. Chem. Soc.* **2013**, *135*, 18036–18039.

(207) Norsikian, S.; Beretta, M.; Cannillo, A.; Martin, A.; Retailleau, P.; Beau, J.-M. *Chem. Commun.* **2015**, *51*, 9991–9994.

(208) Morita, T.; Nagasawa, Y.; Yahiro, S.; Matsunaga, H.; Kunieda, T. *Org. Lett.* **2001**, *3*, 897–899.

(209) Ghosh, C.; Manjunath, G. B.; Akkapeddi, P.; Yarlagadda, V.; Hoque, J.; Uppu, D. S. S. M.; Konai, M. M.; Haldar, J. *J. Med. Chem.* **2014**, *57*, 1428–1436.

(210) Schon, I.; Szirtes, T.; Uberhardt, T.; Csehi, A. *J. Org. Chem.* **1983**, *48*, 1916–1919.

(211) Salvino, J. M.; Mervic, M.; Mason, H. J.; Kiesow, T.; Teager, D.; Airey, J.; Labaudiniere, R. *J. Org. Chem.* **1999**, *64*, 1823–1830.

(212) Moffett, R. B. *Org. Synth.* **1952**, *32*, 59–60.

(213) Coyle, J. P.; Kurek, A.; Pallister, P. J.; Sirianni, E. R.; Yap, G. P. A.; Barry, S. T. *Chem. Commun.* **2012**, *48*, 10440–10442.

(214) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725–5728.

(215) Ligiero, C. B. P.; Visentin, L. C.; Giacomini, R.; Filgueiras, C. A. L.; Miranda, P. C. M. L. *Tetrahedron Lett.* **2009**, *50*, 4030–4032.

(216) Bradbury, R. H.; Kettle, J. G. 4-anilino-quinazoline derivatives as antiproliferative agents. WO2004093880 A1, CA2526897A1, November 4, 2004.

(217) Lefker, B. A.; Brodney, M. A.; Sakya, S. M.; Hay, B. A.; Wessel, M. D.; Conn, E. L. Pyrimidone Compounds As GSK-3 Inhibitors. US20100292205 A1, CA2661334A1, 2010.

(218) Abarca, B.; Ballesteros, R.; Chadlaoui, M.; Miralles, J.; Murillo, J. V.; Colonna, D. *Tetrahedron* **2001**, *57*, 10111–10117.

(219) Lohre, C.; Fröhlich, R.; Glorius, F. *Synthesis* **2008**, 2221–2228.

(220) Breuning, M.; Winnacker, M.; Steiner, M. *Eur. J. Org. Chem.* **2007**, 2100–2106.

(221) Márquez, F.; Montoro, R.; Llebaria, A.; Lago, E.; Molins, E.; Delgado, A. *J. Org. Chem.* **2002**, *67*, 308–311.

(222) Dondoni, A.; Perrone, D. *Synthesis* **1993**, 1162–1176.

(223) Hormuth, S.; Reißig, H.-U.; Dorsch, D. *Liebigs Ann. der Chemie* **1994**, 121–127.

(224) Ugarriza, I.; Uria, U.; Carrillo, L.; Vicario, J. L.; Reyes, E. *Chem. Eur. J.* **2014**, *20*, 11650–11654.

(225) Joosten, A.; Lambert, E.; Vasse, J.-L.; Szymoniak, J. *Org. Lett.* **2010**, *12*, 5128–5131.

(226) Yoon, U. C.; Jin, Y. X.; Oh, S. W.; Park, C. H.; Park, J. H.; Campana, C. F.; Cai, X.; Duesler, E. N.; Mariano, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 10664–10671.

(227) Golebiowski, A.; Gorins, G.; Johnson, C. R.; Kiciak, K. *Pol. J. Chem.* **1993**, *67*, 685–690.

(228) Molnár, I.; Holland, M.; Daniliuc, C.; Houk, K.; Gilmour, R. *Synlett* **2016**, *27*, 1051–1055.

(229) Atkinson, R. C.; Leonard, D. J.; Maury, J.; Castagnolo, D.; Volz, N.; Clayden, J. *Chem. Commun.* **2013**, *49*, 9734–9736.

(230) Niethe, A.; Fischer, D.; Blechert, S. *J. Org. Chem.* **2008**, *73*, 3088–3093.

(231) Chong, H.-S.; Chen, Y. *Org. Lett.* **2013**, *15*, 5912–5915.

(232) Arndt, H.-D.; Welz, R.; Müller, S.; Ziemer, B.; Koert, U. *Chem. Eur. J.* **2004**, *10*, 3945–3962.

(233) Marcoux, D.; Bindschädler, P.; Speed, A. W. H.; Chiu, A.; Pero, J. E.; Borg, G. A.; Evans, D. A. *Org. Lett.* **2011**, *13*, 3758–3761.

(234) Paul, B.; Das, D.; Ellington, B.; Marsh, E. N. G. *J. Am. Chem. Soc.* **2013**, *135*, 5234–5237.

(235) Geden, J. V.; Clark, A. J.; Coles, S. R.; Guy, C. S.; Ghelfi, F.; Thom, S. *Tetrahedron Lett.* **2016**, *57*, 3109–3112.

(236) Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001–1011.

(237) Schaffert, D.; Badgujar, N.; Wagner, E. *Org. Lett.* **2011**, *13*, 1586–1589.

(238) Wang, M. H.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912–14922.

LIST OF PUBLICATIONS

- **Haghshenas, P**; Langdon, S. M.; Gravel, M. "Carbene Organocatalysis for Stetter, Benzoin, and Ring-Expansion Reactions" *Synlett*, **2017**, *28*, 542–559.
- **Haghshenas, P**; Quail, J. W; Gravel, M. "Substrate-Controlled Diastereoselectivity Reversal in NHC-Catalyzed Cross-Benzoin Reactions Using *N*-Boc-*N*-Bn-Protected-*α*-Amino Aldehydes", *The Journal of Organic Chemistry*, **2016**, *81*, 12075–12083.
- **Haghshenas, P**; Gravel, M. "Chemo- and Diastereoselective NHC-Catalyzed Cross-Benzoin Reactions using *N*-Boc-*α*-amino Aldehydes", *Organic Letters*, **2016**, *18*, 4518−4521.
- **Haghshenas, P;** Gravel, M. **2016**, 3-Benzyl-5-(2-hydroxyethyl)-4-methyl-1,3-thiazolium Chloride. e-EROS Encyclopedia of Reagents for Organic Synthesis, 1–3.