Off the Beaten Path:

Atypical Products of Ugi and Passerini Reactions

Răzvan Costin Cioc

2017
The research leading to these results has received funding from the Innovative Medicines Initiative Joint Undertaking project CHEM21 under Grant Agreement No. 115360, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

Printed by Paswerk
Cover design by Mihai Lefter

ISBN: 978-90-9030342-0
Off the Beaten Path:

Atypical Products of Ugi and Passerini Reactions

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
prof.dr. V. Subramaniam,
in het openbaar te verdedigen
ten overstaan van de promotiecommissie
van de Faculteit der Exacte Wetenschappen
op vrijdag 16 juni 2017 om 11.45 uur
in de aula van de universiteit,
De Boelelaan 1105

door

Răzvan Costin Cioc
geboren te Brașov, Roemenië
promotor: prof.dr.ir. R.V.A. Orru

copromotor: dr. E. Ruijter
Părinților mei

“An idea won’t work unless you do”
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of Abbreviations</td>
<td>9</td>
</tr>
<tr>
<td>Preface</td>
<td>11</td>
</tr>
<tr>
<td><strong>Chapter 1</strong> <em>Passerini and Ugi Reactions</em></td>
<td>13</td>
</tr>
<tr>
<td><strong>Chapter 2</strong> <em>Synthesis of β-Amino Alcohols from Aldehydes and Isocyanides</em></td>
<td>31</td>
</tr>
<tr>
<td><strong>Chapter 3</strong> <em>Versatility of Trityl Isocyanide in Ugi-type Reactions</em></td>
<td>57</td>
</tr>
<tr>
<td><strong>Chapter 4</strong> <em>Brønsted Acid-Catalyzed Cyanotritylation of Aldehydes by Trityl Isocyanide</em></td>
<td>83</td>
</tr>
<tr>
<td><strong>Chapter 5</strong> <em>An Ugi Approach towards Racetams</em></td>
<td>107</td>
</tr>
<tr>
<td><strong>Chapter 6</strong> <em>Diastereoselective Passerini Reactions with Ketoacids</em></td>
<td>127</td>
</tr>
<tr>
<td><strong>Chapter 7</strong> <em>Future Research Directions</em></td>
<td>147</td>
</tr>
<tr>
<td>Summary</td>
<td>159</td>
</tr>
<tr>
<td>Samenvatting</td>
<td>165</td>
</tr>
<tr>
<td>Acknowledgement</td>
<td>171</td>
</tr>
<tr>
<td>List of publications</td>
<td>175</td>
</tr>
</tbody>
</table>
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>nCR</td>
<td>(n)-component reaction</td>
</tr>
<tr>
<td>4C-3CR</td>
<td>four center three component reaction</td>
</tr>
<tr>
<td>Å</td>
<td>Ångström</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>concn</td>
<td>concentration</td>
</tr>
<tr>
<td>CPA</td>
<td>chiral phosphoric acid</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicycloundec-7-ene</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DMC</td>
<td>dimethyl carbonate</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>DPP</td>
<td>diphenyl phosphate</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>e.g.</td>
<td>exempli gratia (for example)</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>et al.</td>
<td>et alii (and others)</td>
</tr>
<tr>
<td>GBB</td>
<td>Groebke-Blackburn-Bienaymé</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>i.e.</td>
<td>id est (that is)</td>
</tr>
<tr>
<td>IMCR</td>
<td>isocyanide based multicomponent reaction</td>
</tr>
<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>M</td>
<td>molar (concentration)</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>MCR</td>
<td>multicomponent reaction</td>
</tr>
<tr>
<td>MeTHF</td>
<td>2-methyl tetrahydrofuran</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>MTBE</td>
<td>methyl tert-butyl ether</td>
</tr>
<tr>
<td>MW</td>
<td>microwave</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>P 3CR</td>
<td>Passerini three component reaction</td>
</tr>
<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium (p)-toluenesulfonate</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>(p)-toluenesulfonic acid</td>
</tr>
<tr>
<td>quant</td>
<td>quantitative</td>
</tr>
<tr>
<td>TFE</td>
<td>2,2,2-trifluoroethanol</td>
</tr>
<tr>
<td>Method</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>$S_{N}1$</td>
<td>unimolecular nucleophilic substitution</td>
</tr>
<tr>
<td>$S_{N}2$</td>
<td>bimolecular nucleophilic substitution</td>
</tr>
<tr>
<td>$S_{N}Ar$</td>
<td>nucleophilic aromatic substitution</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethylsulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
</tbody>
</table>
The 100th anniversary of the Passerini reaction (P 3CR), the first isocyanide-based multicomponent reaction, is just a few years away; its even more famous descendent, the Ugi four component reaction (U 4CR), was also discovered already more than half a century ago. Since then, these two reactions have been exhaustively explored, and highly sophisticated as well as purely applied synthetic chemistry has emerged from the research in this field. So is there anything left to discover in Ugi and Passerini chemistry or have these two reactions already revealed all their secrets?

In this work the classical Ugi and Passerini reactions are given an upgrade: these valuable reactions are reinterpreted based on a rational design to afford atypical products for this chemistry. Thus, after introducing the reader with the notions and concepts of the classical Ugi and Passerini reactions in Chapter 1, this thesis exemplifies in the following chapters how old chemistry can be reinvented and improved for the synthesis of valuable molecules. Chapter 2 describes the combinatorial synthesis of β-amino alcohols from aldehydes and isocyanides. This Passerini-based protocol is a convenient way to prepare libraries of (enantioenriched) medicinally relevant β-amino alcohols in a straightforward and general manner, circumventing well-known limitations of conventional synthetic approaches. The next two chapters detail the versatile application of triphenylmethyl (trityl) isocyanide in Ugi and Passerini reactions. Known for more than half a century, this reagent is applied in multicomponent reactions for the first time herein. Intriguingly, together with the expected reactivity, this simple isocyanide exhibits distinctive chemical behavior in interactions with imines and aldehydes, respectively, and under determined conditions it allows the preparation of atypical Ugi and Passerini products: α-amino nitriles, N-acyl aminoacids, free imidazo[1,2-α]pyridin-3-amines (Chapter 3) and (enantioenriched) O-trityl cyanohydrins (Chapter 4). Next, the Ugi 3CR with γ-aminobutyric acid is employed for the first time to prepare compounds of the racetam
class via a single-reaction process (Chapter 5). Similarly to Chapter 2, this work enables the
direct and general preparation of bioactive molecules from simple starting materials
under a generic protocol. Another reaction employing a bifunctional input is described in
Chapter 6: the diastereoselective Passerini 2CR with substituted ketoacids yielding bicyclic
lactones. Interestingly, these typical MCR products can isomerize to an uncommon α-
hydroxy imide scaffold under certain conditions. Finally, Chapter 7 provides opportunities
to expand the concepts and ideas developed in the previous chapters towards novel
isocyanide-based multicomponent reactions.

Scheme 1. Thesis outline.
Abstract: Multicomponent reactions are important synthetic tools in modern organic chemistry. Among them, isocyanide-based reactions like the Passerini 3CR and the Ugi 4CR are widely used nowadays to efficiently prepare complex molecules, both in target-oriented synthetic projects and in combinatorial and diversity-oriented applications. The defining features and latest developments in Passerini and Ugi chemistry are presented in this Chapter.

Parts of this chapter are published in Green Chem. 2014, 16, 2958-2975.
Chapter 1

Introduction

Organic synthesis of valuable molecules has come a long way since Wöhler first synthesized urea in 1828.\cite{1} Yet, synthetic organic chemists today are just as passionate as their predecessors from those times in pursuing the challenging task of creating molecules with advanced properties and exciting chemical structures. This has served as the motivation for the discovery of novel reactivity, reagents and catalysts that enabled synthetic chemists to design sequences of reactions to access compounds of whatever complexity.\cite{2} *Getting there* has been for many years synonymous with indisputable success, but in the last 30 years chemists have become more and more preoccupied about how they are getting there. Attributes like “concise”, “efficient”, “convergent”, now frequent in the titles of (total) synthesis papers,\cite{3} are surely not only catchwords but also defining criteria that chemists consider when planning their synthetic approach.

An excellent solution to meet these efficiency criteria is brought by multicomponent reactions (MCRs). In contrast with conventional multistep sequential synthesis, multicomponent reactions combine at least three reactants in the same pot to generate a product containing most (preferably all) atoms of the starting materials (Scheme 1).\cite{4}

Scheme 1. Classical sequential synthesis vs. multicomponent reactions.

Intrinsically, multicomponent reactions feature high convergence and step economy which has a great positive impact on the resource side (namely the starting materials utilization and time) of a chemical synthesis route. Moreover, MCRs bring additional advantages in term of mildness of reaction conditions and compatibility with green chemistry principles (e.g. atom economy, waste prevention, benign solvents, less hazardous synthesis)\cite{5} which improve the sustainability side of the process. All these
justify a central position of multicomponent reactions in the toolbox of modern synthetic organic methodologies.

Not surprisingly, MCRs have been extensively applied, particularly in the past two decades, in natural product synthesis, medicinal chemistry and drug discovery programmes, combinatorial chemistry, agrochemistry and polymer chemistry. This is not only due to their high efficiency as described earlier, but also to their unmatched ability to rapidly produce large collections of compound libraries. Indeed, the exploitation of the different variation points in the input materials (at least three) dramatically condenses the synthetic effort to assemble libraries of analogues of the desired dimension. For instance, for a four component condensation (4CR), starting with sets of just 10 inputs for each of the components allows the preparation of a library with $10^4$ members in a minimum number of experiments performed under identical reaction conditions!

Among the many classes of MCRs, multicomponent reactions involving isocyanides as one of the components (IMCRs) have seen tremendous progress in the last decades and are nowadays extensively studied both at the fundamental and applied level.

**General Aspects of Passerini and Ugi Chemistry**

The key reagents in IMCR chemistry are the isocyanides. These compounds are generally well known in the synthetic organic community but mostly because of their foul smell rather than their unique reactivity. In fact, the isocyanide is an extraordinary functional group, with peculiar structure and remarkable behavior in organic reactions. Compared to their structural isomers, the more common nitriles, they also contain a cyano/nitrile functionality (CN) but the connectivity in isocyanides (also called isonitriles) is via the nitrogen atom and not the carbon center. This implies that the carbon atom in isocyanides is formally divalent, which is a rare structural feature in organic chemistry, encountered only in carbon monoxide and carbenes. However unlike in typical carbenes, the carbon atom of the isocyanide functionality is formally sp and not sp$^2$-hybridized, as the structure is better described as the zwitterionic form with a triple bond between the carbon and nitrogen as shown in Figure 1.
This makes isocyanides unique in comparison with common classes of organic compounds, including the related nitriles, as both the electrophilic and nucleophilic center in the molecule are located at the same position, i.e. the isocyanide carbon atom. Most of the reactions involving isocyanides are indeed the expression of this structural feature: isocyanides react via ionic pathways with both electrophilic and nucleophilic partners, typically sequentially (generally in this order), but concerted mechanisms are also possible. Reactions with radicals, stemming from their carbenoid nature, are also an important part of isocyanide chemistry. Furthermore, rich chemistry has been developed around the acidic character of the proton(s) available at the isocyanide α-position.

Due to their ability to engage in multiple-bond forming reactions, isocyanides have found wide applications in multicomponent chemistry. Numerous important reactions have been developed in the nearly one hundred years of IMCR chemistry which debuted in 1921 with the Passerini reaction. This is a classical showcase of isocyanide ambident reactivity, in which highly valuable α-acyloxyamides are prepared in a three component condensation with carbonyl compounds (electrophiles) and carboxylic acids (nucleophiles). The upgrade to the four component reaction, achieved by Ugi forty years later by introducing amines as additional reactants, represents the foundation on which a remarkably rich variety of novel reactions has been developed further throughout the years. This research area is still in expansion nowadays; a few representative old and recent examples of IMCRs are given in Scheme 2. In this thesis several novel interpretations of Passerini and Ugi chemistry will be described in Chapters 2-6.
### Ugi and Passerini Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Structure 1</th>
<th>Structure 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Passerini 3CR</strong></td>
<td><img src="https://example.com/structure1.png" alt="Structure" /></td>
<td><img src="https://example.com/structure2.png" alt="Structure" /></td>
</tr>
<tr>
<td><strong>Ugi 4CR</strong></td>
<td><img src="https://example.com/structure3.png" alt="Structure" /></td>
<td><img src="https://example.com/structure4.png" alt="Structure" /></td>
</tr>
<tr>
<td><strong>Ugi-azide 4CR</strong></td>
<td><img src="https://example.com/structure5.png" alt="Structure" /></td>
<td><img src="https://example.com/structure6.png" alt="Structure" /></td>
</tr>
<tr>
<td><strong>Ugi-Smiles 4CR</strong></td>
<td><img src="https://example.com/structure7.png" alt="Structure" /></td>
<td><img src="https://example.com/structure8.png" alt="Structure" /></td>
</tr>
<tr>
<td><strong>Ugi-oxazole 3CR</strong></td>
<td><img src="https://example.com/structure9.png" alt="Structure" /></td>
<td><img src="https://example.com/structure10.png" alt="Structure" /></td>
</tr>
<tr>
<td><strong>Groebke-Blackburn-Bienaymé 3CR</strong></td>
<td><img src="https://example.com/structure11.png" alt="Structure" /></td>
<td><img src="https://example.com/structure12.png" alt="Structure" /></td>
</tr>
<tr>
<td><strong>Ugi-Dömling 3CR</strong></td>
<td><img src="https://example.com/structure13.png" alt="Structure" /></td>
<td><img src="https://example.com/structure14.png" alt="Structure" /></td>
</tr>
<tr>
<td><strong>Orru 3CR</strong></td>
<td><img src="https://example.com/structure15.png" alt="Structure" /></td>
<td><img src="https://example.com/structure16.png" alt="Structure" /></td>
</tr>
</tbody>
</table>

**Scheme 2.** Isocyanide-based multicomponent reactions.

### Reaction Mechanism

**Passerini 3CR**

The generally accepted mechanism of the Passerini 3CR is depicted in Scheme 3. The carbonyl compound and the carboxylic acid associate in a hydrogen-bonded complex into which the isocyanide inserts in a concerted fashion. This leads to an acyl-imidate intermediate (the α-adduct) which undergoes intramolecular acyl transfer (the so-called Mumm rearrangement) to afford the final Passerini 3CR product. There is ample experimental and theoretical evidence supporting this mechanism. The reaction proceeds in relatively nonpolar aprotic solvents (dichloromethane, toluene, THF) at high molarities, whereas in protic solvents like methanol the conversions are poor. Under the optimal conditions, the formation of the hydrogen bond-associated complex is favored while ionic pathways including the nitrilium ion as intermediate are unlikely. The final rearrangement step has received less attention but recently it was suggested that an additional carboxylic...
acid molecule may be involved as a catalyst for this step.\textsuperscript{[18]} Although the nitrilium ion is not generally considered a relevant intermediate for the Passerini reaction, a recent theoretical study revealed the contrary,\textsuperscript{[19]} and consequently there is a certain controversy around the P 3CR mechanism. In Chapter 4 additional (indirect) evidence for the concerted mechanism will be presented.

\textbf{Scheme 3.} Mechanism of the Passerini 3CR.

\textit{Ugi 4CR}

Since the Ugi 4CR reaction is an extension of the P 3CR, it is expected that these two reactions are mechanistically related. Indeed, the U 4CR can be regarded as a Passerini reaction with an imine as the electrophilic component instead of an aldehyde/ketone. However, the solvent profiles of the two reactions are distinct, with the Ugi reaction performing best in alcoholic solvents; furthermore, a complete proton transfer from the carboxylic acid to the imine is more likely than a hydrogen bond association (although this is strongly dependent on the acidity/basicity of the inputs involved). Therefore an ionic profile is anticipated for the Ugi reaction and most (recent) experimental and computational data support this premise.\textsuperscript{[20]} The nitrilium ion seems to be a viable intermediate in the Ugi 4CR reaction, as postulated by Ugi more than half a century ago. Its formation by the isocyanide addition to the iminium ion is the rate-determining step of the process and is irreversible; the subsequent trapping of this reactive intermediate by the carboxylate counterion situated in the proximity is a fast and highly exothermic step. The resulting α-adduct undergoes the Mumm rearrangement in analogy with the Passerini reaction; this is also a fast, thermodynamically favored step. This mechanism is depicted in Scheme 4.

Alternative mechanisms, for instance isocyanide insertion into hemiaminal species have also been proposed but are generally considered less relevant for the Ugi 4CR. Notably, the Ugi reaction likely proceeds via a series of related mechanisms with the favorable pathway being strongly dependent on the structural particularities of the inputs. Thus, in
some instances the reaction does not show a clear preference for polar protic solvents and dichloromethane is preferred; a theoretical study by Fleurat-Lessard et al. demonstrated that in contrast to methanol, the reaction pathway computed in toluene circumvents the nitrilium ion and leads to the α-adduct by a concerted addition of the isocyanide.\textsuperscript{[20c]} The subtleties of the Ugi 4CR reaction and the complete mechanistic picture are yet not fully understood; interesting mechanistic observations are presented in Chapter 3 where trityl isocyanide is employed as mechanistic probe for the nitrilium ion intermediate.

\begin{center}
\textbf{Scheme 4.} Mechanism of the Ugi 4CR.
\end{center}

\textit{Ugi-type reactions}

Mechanistically, most variants of IMCRs (\textit{e.g.} Ugi-azide 4CR, Groebke-Blackburn-Bienaymé 3CR, Ugi-oxazole 3CR, Ugi-Smiles 4CR) resemble the Ugi 4CR reaction as they are centered around the addition of the isocyanide to an iminium species and subsequent trapping of the resulting nitrilium ion intermediate by various nucleophiles, both intra- and intermolecularly. In the classical Ugi 4CR, as already discussed, a carboxylate anion adds to the nitrilium intermediate and this α-adduct rearranges towards the more stable dipeptidic structure; when hydrazoic acid is used instead of the carboxylic acid a similar α-adduct is formed which then undergoes cyclization towards the tetrazole.\textsuperscript{[21]} The Ugi-Smiles reaction makes use of an acidic phenol and closely resembles the parent condensation; in this case the Mumm rearrangement is replaced by a Smiles rearrangement.\textsuperscript{[20a]} The Groebke-Blackburn-Bienaymé (GBB)\textsuperscript{[22]} reaction is yet another version of the Ugi reaction with an amidine/pyridinamine component in which the internal nitrogen nucleophile captures the nitrilium ion to yield the imidazo[1,2-\textalpha]pyridine heterocyclic system after deprotonation/tautomerization. A similar trapping of the nitrilium ion by an internal nucleophile leads to oxazole derivatives when the isocyanide bears a secondary carboxamide functionality at the α-position.\textsuperscript{[23]} These mechanisms are depicted in Scheme 5.
Single Reactant Replacement

Reactions like the Ugi 4CR and the Passerini 3CR are highly versatile, in the sense that the generic components can be replaced with surrogates without compromising performance, while the scope thus becomes significantly larger. This approach towards novel MCR variants is known as the \textit{single reactant replacement} strategy.\footnote{24} The Ugi 4CR itself, derived by replacing the carbonyl component with an imine in the Passerini 3CR, is perhaps the best illustration of this concept. At another level, many variants of the Ugi reaction are based on the utilization of carboxylic acid surrogates (water, monocarbonates, acidic phenols, isocyanic acid, hydrazoic acid, etc.)\footnote{25} as shown in Scheme 6. The Passerini reaction, although somewhat less flexible than the Ugi 4CR, is also amenable to the single reactant replacement strategy. The carboxylic acid is the component that allows this type of diversification; interesting examples of Passerini-type reactions include the use of water,\footnote{26} alcohols,\footnote{27} silicon tetrachloride,\footnote{28} triphenylsilanol,\footnote{29} acidic phenols (Passerini-Smiles),\footnote{30} sulfinic acids,\footnote{31} phosphinic acids\footnote{32} and hydrazoic acid\footnote{33} (Scheme 7). The Passerini reaction with silicon tetrachloride as one of the components is used in Chapter 2 in a novel synthesis of β-amino alcohols.
Post-condensation Modification

As previously mentioned, IMCRs are particularly suitable for generating chemical diversity. This is due to the numerous variation points in intrinsically available in a multicomponent condensation as well as the opportunity for a myriad of follow-up transformations based on judicious design of starting components with appropriate reactivity handles. Thus, the products of the IMCR can rapidly evolve towards structures that bear little resemblance to the initial scaffold, producing molecules with the desired properties for the envisaged application (for instance heterocycles for the pharmaceutical industry). The MCR condensation-modification protocol typically consists of two simple steps, but one-pot transformations are also possible. With the right choice of the functional groups in the inputs, Ugi and Passerini reactions can be combined with further elaboration of the
primary scaffold via deprotection-cyclization, cycloadditions, $S_{N}$Ar, ring closing metathesis, metal-catalyzed couplings, etc. A few representative examples of this approach are shown in Scheme 8.

Interesting tricyclic lactams 6 can be prepared in a single pot by a combination of the Ugi 4CR with the Himbert arene/allene Diels–Alder cycloaddition when the carboxylic acid component has an allene-based structure 3. The second example showcases the high degree of complexity that can be achieved starting from very simple inputs: when using $p$-anisidine 10 as the amine component and propargylic carboxylic acids, the Ugi reaction can be coupled in the same pot with an interesting ipso-cyclization/detertbutylation/conjugate addition cascade to deliver alkaloid-like products 12 in high yields and (stereo)selectivities. Finally, a Pd-catalyzed cyclization cascade was used to modify Ugi products into benzopyrrolizidine derivatives 18 with antioxidant properties.

The MCR/post-condensation modification strategy enables the efficient synthesis of relatively complex molecules and greatly expands the chemical space accessible by multicomponent reactions. This concept is a key element of MCR chemistry and is applied in various forms in all chapters of this thesis.

Scheme 8. Examples of post-condensation modification of Ugi products.
Bifunctional Inputs

The utilization of bifunctional inputs is also commonly used in MCRs to enhance the diversity of the Ugi and Passerini reactions, particularly in the case of the former where the possibility for combinations is greater.\[38\] Such reactions typically yield cyclic products with interesting tridimensional shapes which represents an important advantage for medicinal applications. Furthermore, the transition state leading to the α-adduct has by definition less freedom degrees and it is often that the stereocentrol that can be achieved in IMCRs with bifunctional component is high.\[39\] Finally, it is also common that these reactions are relatively fast processes that show improved flexibility in solvent requirements which makes them attractive in designing applications. In Scheme 9 a few examples of Ugi chemistry with bifunctional inputs are highlighted.

![Scheme 9. Ugi reactions with bifunctional inputs.](image)

The first example demonstrates the unmatched potential of Ugi reactions to generate diversity and complexity starting from simple premises: α-amino acids can be successfully employed as bifunctional components in Ugi reactions, only in this case the Mumm rearrangement is kinetically inhibited.\[40\] Nevertheless, the α-adduct remains a reactive intermediate and evolves towards the thermodynamic sink by reaction with external nucleophiles instead, for instance secondary amines, affording peptoid scaffolds 23 in a remarkably efficient and general way. Secondly, the use of oxoacid components 24\[41\] or cyclic imines 29 (oxoamines)\[42\] respectively enables highly diastereoselective isocyanide...
additions in the synthesis of biologically-interesting (polycyclic) scaffolds. Finally, another interesting combination is the inclusion of the isocyanide and carboxylic acid functionalities in the same precursor \textbf{34}, which is an elegant way to generate macrocyclic products with Ugi chemistry.\(^{[43]}\) In \textbf{Chapter 6} a diastereoselective Passerini reaction with a bifunctional input (ketoacid) will be described.

\textbf{Convertible Isocyanides}

The diversity of Ugi-type chemistry can be pushed further by the utilization of convertible isocyanides. These rationally-designed reagents enable post-condensation manipulation of the primary scaffolds at the amide bond originating from the isocyanide component. This concept represents an attractive manner to expand the chemical space and rapidly assemble large collections of compound analogues required for (pharmaceutical) applications; furthermore, convertible isocyanides have great potential in the synthesis of natural products. A good number of such designer isocyanides have been developed over the last twenty years; three representative examples are depicted in the scheme below.\(^{[44]}\)

\begin{center}
\textbf{Scheme 10.} The concept of convertible isocyanide.
\end{center}

Convertible isocyanides can be compared based on several features, such as availability, stability, generality in the MCR condensation, mildness of conversion of primary adducts, generality of further elaboration, recyclability, etc. In \textbf{Chapter 3} we will present the advantages of trityl isocyanide as a novel convertible isocyanide.

\textbf{Catalytic Enantioselective Passerini and Ugi-type Reactions}

The development of catalytic asymmetric multicomponent reactions has received great interest in the synthetic organic community, particularly in the last decades.\(^{[45]}\) Both the Passerini and Ugi reactions lead to the formation of a new chiral center and therefore stereocontrol in this transformations is highly desirable. Since the asymmetry arises from the attack of the isocyanide, a relatively small nucleophile (due to its linear geometry), the
discrimination between the enantiotopic faces of the electrophile is particularly challenging. Furthermore, the lack of a general mechanistic understanding of Passerini and Ugi reactions represents another important complication. Nevertheless, the intense efforts in the development of catalytic enantioselective protocols for these reactions have been rewarded with outstanding results. Various catalytic systems (45, 46) have been shown successful in asymmetric Passerini-type reactions\(^{28,46}\) as well as the classical three component condensation itself (Scheme 11).\(^{47}\) In Chapter 4, a novel catalytic asymmetric Passerini-type reaction (cyanotritylation) will be described.

On the other hand, despite intensive efforts and promising results in the development of enantioselective Ugi-type reactions,\(^{48}\) the race for the first asymmetric variant of the most versatile of MCRs continues. The group of Wulff made an important step forward by developing a highly efficient enantioselective Ugi 3CR in which water plays the role of the acid component.\(^{49}\) A laborious systematic catalyst screening process concluded with the selection of a boroxinate species as the optimal promotor for the asymmetric multicomponent coupling (Scheme 12) and α-amino amides 50 were obtained in good yields with ee’s up to 90%. The scope included diversely substituted aromatic aldehydes 47, dibenzyl amine 48 and a number of isocyanides 49. The stereochemical outcome of the reaction strongly correlates with the bulk of the isocyanide, as the tert-butyl derivative lead to the best ee. Extending this interesting concept to the long-sought parent four-component condensation resulted in racemic products (the uncatalyzed background reaction outcompetes the catalytic pathway because the carboxylic acid readily protonates the imine). The catalytic enantioselective Ugi 4CR remains an endeavor for the future.
Passerini and Ugi Reactions in the Pharmaceutical Industry

The application area that benefits the most from the advantages of multicomponent reactions (and of Passerini and Ugi chemistry in particular) is certainly pharmaceutical research. MCRs are privileged tools for chemists involved in drug discovery and are ideally suited for various medicinal applications, like structure-activity relationship studies, lead optimization, novel scaffold synthesis for bioactivity screening projects, functionalization of bioactive molecules (including natural products), etc. Indeed, when it comes to the generation of compound libraries, MCRs are superior to any other class of reactions as they can supply a plethora of scaffolds with large numbers of derivatives in a concise, general and efficient manner. For instance, the Ugi 4CR has a very large scope and exists in several variants (developed by single reactant replacement for example); the primary dipeptidic scaffold can be further elaborated by post-condensation modifications and the simple nature of the inputs (typically commercially available in a great number of derivatives) enables the exploitation of the many variation points (Figure 2).

Figure 2. Diversity accessed via the Ugi 4CR reaction.
If their application at the medicinal chemistry stage is widespread, reactions like the Passerini 3CR and the Ugi 4CR remain on the other hand severely underexploited in process chemistry. Despite certain benefits, particularly on the sustainability side (high atom economy, mild reaction conditions, green solvents) the uptake of this technology from academic laboratories in this industrial setting is limited to the best of our knowledge to a single report!\textsuperscript{50} Rossen \textit{et al.} recently described the 50 kg scale preparation of the antiepileptic drug Lacosamide 56 via an Ugi 4CR with a chiral auxiliary (53) with comparable efficiency to previously reported process (Scheme 13).

As this research provides valuable insight in critical upscaling issues (the synthesis and handling of the foul-smelling benzyl isocyanide 55, order and rate of addition of the reagents, etc.) it may pave the way towards a more general adoption of the Ugi reaction in process chemistry, especially since several such routes towards commercial drugs have been already validated at lab scale (Scheme 14).\textsuperscript{51}
Chapter 1

Conclusions

Multicomponent reactions are valuable tools for the synthetic organic chemist. Featuring convergence, step economy and compatibility with the principles of green chemistry, MCRs are highly useful in target-directed synthesis. On the other hand, their generality, versatility and ease of combination with various (one-pot) transformations recommend MCRs as the best approach in combinatorial applications, diversity-oriented synthesis and exploration of chemical space. Among the many MCR classes, isocyanide-based multicomponent reactions like the Passerini and Ugi reactions have been extensively studied and applied. This chapter briefly discussed key features of these highly important reactions, notions and concepts that form the basis of the research work described in this thesis.
Ugi and Passerini Reactions

References


29
Chapter 1

Synthesis of β-Amino Alcohols from Aldehydes and Isocyanides

Abstract: A practical two-stage one-pot synthesis of N-substituted β-amino alcohols using aldehydes and isocyanides as starting materials has been developed. Based on a less common central carbon-carbon bond disconnection, this protocol complements traditional approaches. Medicinally relevant products can be prepared in a concise and efficient way from simple building blocks, as demonstrated in the synthesis of the anti-asthma drug Salbutamol.

Introduction

The β-amino alcohol moiety is a privileged structural motif in the pharmaceutical industry. Salbutamol (1) and Propranolol (2) are on the World Health Organization List of Essential Medicines\cite{1} and represent the most important examples of therapeutic agents bearing this structural feature. Numerous others have been released on the market for the treatment of various circulatory, respiratory and other diseases (Figure 1). In addition to their high relevance in drug discovery,\cite{2} N-substituted β-amino alcohols are important building blocks in the preparation of added value chemicals\cite{3} and ligands for catalysis.\cite{4}

![Figure 1. Examples of drugs based on the N-substituted β-amino alcohol motif.](image)

The construction of the β-amino alcohol fragment is almost invariably achieved by the nucleophilic attack of an amine on a suitable electrophilic reaction partner, such as an epoxide, α-haloketone or β-halohydrin (Scheme 1). Although robust, there are many drawbacks associated with this synthetic strategy. First, the required starting materials are typically not commercial and their multistep preparation is highly wasteful and time-consuming. Second, the substitution approach poses important selectivity issues (e.g., regioselectivity in the epoxide opening), double alkylation of the (unprotected) primary amine and low reactivity of poorly nucleophilic and bulky amines which thus need to be employed in large excess.\cite{2c, 5} In this respect, the tert-butyl substituent on the amine has particular importance in drug design as it contributes both to the drug metabolic stability and selectivity for a (specific) β-adrenergic receptor.\cite{6} A general alternative strategy circumventing these problems and employing readily available building blocks would therefore be a valuable tool for medicinal as well as process chemistry.
Synthesis of β-Amino Alcohols from Aldehydes and Isocyanides

Scheme 1. Synthetic approaches towards N-substituted β-amino alcohols.

With this goal in mind, we envisioned the construction of the N-substituted β-amino alcohol motif via a less straightforward central C-C bond retrosynthetic disconnection through addition rather than substitution, using aldehydes and isocyanides as building blocks. Aldehydes are good starting points for (combinatorial) synthesis since a remarkable variety of derivatives is available from numerous suppliers, whereas isocyanides are readily accessible from the corresponding amines. Combining these two inputs with carboxylic acids leads to α-acyloxy amides (via the well-known Passerini three-component reaction) which upon ester hydrolysis and amide reduction would afford the target β-amino alcohols. This approach was demonstrated in the 1970s but has severe limitations in scope and productivity due to the need for three distinct operations, intermediary purifications and harsh reaction conditions. Alternatively, SiCl₄ can be used as the acid component in a Passerini-type addition leading to α-trichlorosilyloxy imidoyl chlorides as shown by Denmark and Fan. We envisioned that the reduction of the imidoyl chloride functionality can be achieved in the same pot with a mild reducing agent delivering the desired β-amino alcohol in a faster and potentially more general way than the existing methods.

Scheme 2. Passerini-type additions towards N-substituted β-amino alcohols.
Results and Discussion

We started our optimization efforts with 4-methylbenzaldehyde and tert-butyl isocyanide as convenient benchmark inputs considering the relevance of tert-butyl substitution in the pharmacology of β-amino alcohols. Initial experiments focused on the optimization of the SiCl$_4$-mediated isocyanide addition in which the formation of α-trichlorosilyloxy imidoyl chloride derivative 3a (Scheme 2, Stage 1) was studied under various conditions. The analysis of 3a could not be performed directly due to its chemical lability; instead, the corresponding α-hydroxyamide which forms from 3a upon aqueous work-up was monitored (by NMR analysis using internal standard). A preliminary round of experiments showed that the SiCl$_4$-mediated isocyanide addition step can be performed at 0-5 °C in a variety of solvents (dichloromethane, toluene, THF, MeTHF, ethyl acetate, dimethyl carbonate). Ethyl acetate was chosen for further optimization in view of its green credentials.$^{[11]}$

Next, several Lewis bases were screened as catalysts for the reaction. Lewis bases are known to activate SiCl$_4$ by complexation$^{[10]}$ and in the particular case of a Passerini-type addition, the introduction of a Lewis base catalyst may dramatically increase both the rate and selectivity of the process. Upon complexation to a Lewis base, a chloride ion is expelled from SiCl$_4$ generating a cationic silylium species.$^{[12]}$ This greatly enhances the Lewis acid capabilities of SiCl$_4$ and thus the propensity of its adduct with the aldehyde to undergo nucleophilic addition. Furthermore, the nitrilium ion generated by the isocyanide addition is preferentially trapped by the chloride counterion, improving the reaction selectivity (Scheme 3).

Scheme 3. Mechanism of HMPA-catalyzed isocyanide addition to aldehydes (methyl groups omitted for clarity).
Synthesis of β-Amino Alcohols from Aldehydes and Isocyanides

The screen of Lewis bases established HMPA as the best catalyst for this reaction (at 10 mol% loading), with nearly quantitative conversion of aldehyde 1a to N-(tert-butyl)-2-hydroxy-2-(p-tolyl)acetamide after basic aqueous work-up of imidoyl chloride 3a (compared to the uncatalyzed reaction with a 57% yield). Other Lewis bases can also be used as catalysts but their performance is somewhat lower: triphenylphosphine oxide (71%); N,N'-dimethylpropyleneurea (70%); pyridine oxide (76%).

Having established convenient conditions for the generation of intermediate 3a, we next investigated the one-pot reduction of the imidoyl chloride functionality to yield the desired β-amino alcohol. For this purpose several boronhydride reagents were screened as shown in Table 1. Ammonia borane complex was the most promising choice, mostly due to its good compatibility with the organic solvent used as medium for the generation of 3a. In addition, this reagent is an air-stable solid that is convenient to handle and thus we focused on improving the initial yield (entry 6). The reduction is reasonably fast and prolonged reaction times did not improve the outcome (entry 7); however, increasing the stoichiometry to 1.5 equiv afforded a delightful 95% yield of 4a. Next, technical grade BH₃NH₃, which has a considerably reduced price compared to the high purity reagent, performed even better (entry 9), even under non-rigorously dry conditions (entry 10). Importantly, the reaction is robust and delivers the β-amino alcohol target in good yields in solvents other than AcOEt (entries 11-13).

With the optimized reaction conditions at hand (entry 10), we next explored the synthetic potential of this novel method. To our delight, diverse aldehydes 1 (aromatic, heteroaromatic and aliphatic) reacted with tert-butyl isocyanide affording the corresponding β-amino alcohols 4 in high yields without additional optimization. The results are summarized in Table 2. With the exception of aliphatic aldehydes and electron-rich aromatic aldehydes, the isocyanide addition step proceeds to near completion for all substrates within one hour. A lower rate in the reduction of the imidoyl chloride functionality was observed for sterically hindered and electron-deficient substrates (1d, 1f, 1j, 1k, 1t), but even in these cases the desired products were obtained in satisfactory yield. Notably, the reaction tolerates a variety of functional groups, including halogens, nitro groups, (thio)ethers, nitriles, esters, amides, alkenes, alkynes, etc. Interestingly, N-tert-butyl 1-arylaziridine formation was observed as minor side reaction pathway (up to 20%) for electron-rich aromatic aldehydes, accounting for the slightly lower yields of products 4p, 4q, 4v (entries 16, 17 and 22). In this case the C-OSiCl₃ bond is most likely elongated and the resulting partial positive charge at the benzylic position favors aziridine formation (Scheme 4). This structure-reactivity relationship indicates that the mechanism has substantial S_N1 character but the exact nature of this side reaction was not
established. Importantly, this undesired reaction pathway can be minimized by increasing the borane concentration and shortening the reaction time in the imidoyl chloride reduction stage.

### Table 1. Optimization of β-amino alcohol synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Reducing agent</th>
<th>Equiv</th>
<th>Time</th>
<th>Yield 4a&lt;sup&gt;[b]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOEt</td>
<td>NaBH&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1</td>
<td>3 h</td>
<td>4%</td>
</tr>
<tr>
<td>2</td>
<td>AcOEt</td>
<td>NMe&lt;sub&gt;3&lt;/sub&gt;BH&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1</td>
<td>3 h</td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td>AcOEt</td>
<td>BH&lt;sub&gt;3&lt;/sub&gt;-THF</td>
<td>1</td>
<td>3 h</td>
<td>82%&lt;sup&gt;[c]&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>AcOEt</td>
<td>BH&lt;sub&gt;3&lt;/sub&gt;NMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1</td>
<td>3 h</td>
<td>50%&lt;sup&gt;[d]&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>AcOEt</td>
<td>BH&lt;sub&gt;3&lt;/sub&gt;NMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1</td>
<td>3 h</td>
<td>24%&lt;sup&gt;[d]&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>AcOEt</td>
<td>BH&lt;sub&gt;3&lt;/sub&gt;NH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1</td>
<td>3 h</td>
<td>86%</td>
</tr>
<tr>
<td>7</td>
<td>AcOEt</td>
<td>BH&lt;sub&gt;3&lt;/sub&gt;NH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.5</td>
<td>3 h</td>
<td>95%</td>
</tr>
<tr>
<td>8</td>
<td>AcOEt</td>
<td>BH&lt;sub&gt;3&lt;/sub&gt;NH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.5</td>
<td>3 h</td>
<td>99%&lt;sup&gt;[e]&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>AcOEt</td>
<td>BH&lt;sub&gt;3&lt;/sub&gt;NH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.5</td>
<td>3 h</td>
<td>98%&lt;sup&gt;[f]&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>AcOEt</td>
<td>BH&lt;sub&gt;3&lt;/sub&gt;NH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.5</td>
<td>3 h</td>
<td>98%&lt;sup&gt;[f]&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>BH&lt;sub&gt;3&lt;/sub&gt;NH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.5</td>
<td>3 h</td>
<td>82%&lt;sup&gt;[g]&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>THF</td>
<td>BH&lt;sub&gt;3&lt;/sub&gt;NH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.5</td>
<td>3 h</td>
<td>95%&lt;sup&gt;[h]&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>MeTHF</td>
<td>BH&lt;sub&gt;3&lt;/sub&gt;NH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1.5</td>
<td>3 h</td>
<td>98%&lt;sup&gt;[h]&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>[a]</sup> Standard conditions: 4-methylbenzaldehyde (0.5 mmol), catalyst (10 mol%), SiCl<sub>4</sub> (1.1 equiv) and tert-butyl isocyanide (1.2 equiv) in solvent (1 mL) for 1 h at 0-5 °C, then reducing agent at room temperature; <sup>[b]</sup> yields based on crude NMR using mesitylene as internal standard; <sup>[c]</sup> added as THF – AcOEt 1:1 solution (1 mL); <sup>[d]</sup> borane added as solution (AcOEt, 1 mL); <sup>[e]</sup> technical BH<sub>3</sub>NH<sub>3</sub> (90%); <sup>[f]</sup> performed in normal grade AcOEt under air atmosphere; <sup>[g]</sup> side product formation (N-tert-butyl 1-(p-tolyl)aziridine, 12%); <sup>[h]</sup> impurities from THF-ring opening due to activation by SiCl<sub>4</sub> were observed.
**Synthesis of β-Amino Alcohols from Aldehydes and Isocyanides**

Table 2. Aldehyde scope for one-pot N-tert-butyl β-amino alcohol synthesis\[^{[a]}\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>R</th>
<th>Product</th>
<th>Yield[^{[b]}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>4-MeC₆H₄⁻</td>
<td>4a</td>
<td>74%</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>Ph</td>
<td>4b</td>
<td>83% (93%[^{[c-d]}])</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2-Naphthyl</td>
<td>4c</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>Mesityl</td>
<td>4d</td>
<td>70%</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>4-ClC₆H₄⁻</td>
<td>4e</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>2-BrC₆H₄⁻</td>
<td>4f</td>
<td>78%</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>4-NCC₆H₄⁺</td>
<td>4g</td>
<td>90%</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>4-MeOCOC₆H₄⁻</td>
<td>4h</td>
<td>80%</td>
</tr>
<tr>
<td>9</td>
<td>1i</td>
<td>4-CF₃C₆H₄⁻</td>
<td>4i</td>
<td>82%</td>
</tr>
<tr>
<td>10</td>
<td>1j</td>
<td>2-F₃CC₆H₄⁻</td>
<td>4j</td>
<td>71%</td>
</tr>
<tr>
<td>11</td>
<td>1k</td>
<td>4-O₂NC₆H₄⁺</td>
<td>4k</td>
<td>68%[^{[d]}]</td>
</tr>
<tr>
<td>12</td>
<td>1l</td>
<td></td>
<td>4l</td>
<td>88%[^{[d]}]</td>
</tr>
<tr>
<td>13</td>
<td>1m</td>
<td>4-MeSC₆H₄⁻</td>
<td>4m</td>
<td>77%</td>
</tr>
<tr>
<td>14</td>
<td>1n</td>
<td>3-HC≡CHCH₂OC₆H₄⁻</td>
<td>4n</td>
<td>89%</td>
</tr>
<tr>
<td>15</td>
<td>1o</td>
<td>3,5-(MeO)₂C₆H₃⁻</td>
<td>4o</td>
<td>76%</td>
</tr>
<tr>
<td>16</td>
<td>1p</td>
<td>4-AcNHCC₆H₄⁺</td>
<td>4p</td>
<td>73%[^{[d]}]</td>
</tr>
<tr>
<td>17</td>
<td>1q</td>
<td></td>
<td>4q</td>
<td>67%</td>
</tr>
<tr>
<td>18</td>
<td>1r</td>
<td>PhCH₂CH₂⁻</td>
<td>4r</td>
<td>83%</td>
</tr>
<tr>
<td>19</td>
<td>1s</td>
<td>Cy</td>
<td>4s</td>
<td>78%</td>
</tr>
<tr>
<td>20</td>
<td>1t</td>
<td>Cl₃C⁻</td>
<td>4t</td>
<td>44%</td>
</tr>
<tr>
<td>21</td>
<td>1u</td>
<td></td>
<td>4u</td>
<td>58%</td>
</tr>
</tbody>
</table>
A typical distribution of products is shown for substrate 1q in Scheme 5. A simple adjustment of the time parameter leads to a significant improvement in the conversion of 1q to 4q from 77% under the standard conditions to 95%. In this way we were able to prepare the antiasthmatic drug Salbutamol acetate 4z from the protected aldehyde 1z in a 75% yield upon acetal cleavage under acidic conditions (Scheme 6).[16]
A noteworthy benefit of our method is the reduced reaction time, which is in the order of a few hours, compared to conventional options that need at least two separate operations and an intermediate purification. Moreover, the productivity can be improved at the expense of a slight loss in yield: for example, product 4b was synthesized in a 71% yield in only 10 minutes of reaction time for each of the two stages. Next, chromatographic purification can be successfully replaced with precipitation of the products 4 as the corresponding hydrochloride salts from ethereal solvents, as demonstrated for the more polar products (4k, 4l, 4p)\textsuperscript{[17]} and the 5 mmol scale synthesis of 4b. Combined with the broad substrate scope, this makes our method ideal for rapid generation of large libraries of compounds required for bioactivity screening in a lead optimization project, especially in cases where extensive variation in the aldehyde moiety is required.

![Scheme 6. Synthesis of Salbutamol acetate.](image)

Importantly, this new approach efficiently converts commercial starting materials to products that are challenging targets for methods based on the conventional C-N disconnection. Bulky aldehydes such as 2,4,6-trimethylbenzaldehyde 1d and chloral 1t work satisfactorily; thioethers and alkenes (inputs 1m and 1u), incompatible with epoxide formation via oxidation (required for the traditional approach) as well as nucleophile-sensitive inputs (aldehyde 1l with a reactive C\textsubscript{Ar}-F bond) are well tolerated in our reaction, whereas regioselectivity issues of epoxide opening with styrene derivatives are avoided. On the other hand, nicotinic aldehyde was found incompatible with this methodology (entry 24), possibly due to the competing nucleophilicity of the pyridine nitrogen atom, while the 3-amino-1-alkoxy-propan-2-ol motif represents another synthetic challenge (entry 25). Ketones are also poor substrates for the reaction: the isocyanide addition to cyclopentanone afforded only traces of the desired product.

Regarding the N-substitution, bulky substituents which typically reduce the amine propensity for nucleophilic attack in the classical approach are not problematic in our reaction, as the bulk is further away from the reacting center in isocyanides (the ‘divalent’ carbon atom). Bearing this in mind, we investigated other bulky tertiary isocyanides to generalize this feature of our approach (Table 3). Thus, tert-octyl isocyanide displayed similar reactivity to its lower molecular weight homologue; cumyl isocyanide\textsuperscript{[18]} also
afforded the expected products in good yields, both for aliphatic and aromatic aldehydes (products 9a, 9b). These results have significance in a medicinal chemistry context since in recent years it has been demonstrated that α,α-dimethylbenzyl substitution (and variations) on the nitrogen atom of β-amino alcohols represents an attractive handle to optimize bioactivity and pharmacological properties.\textsuperscript{[19]}

Reactions employing cyclohexyl isocyanide, another frequently used benchmark isocyanide, gave only slightly lower yields than tertiary isocyanides (compounds 10a and 10b, Table 3). In contrast, we were surprised to note a significant difference in the reaction outcome when isopropyl isocyanide was employed. Due to side reactions, a modest yield (35%) was obtained under the standard conditions for dichloroisoprenaline (DCI, 11a), the first clinically used beta-blocking agent.\textsuperscript{[20]} We identified double isocyanide addition as the major undesired pathway. Most likely, unproductive consumption of the isocyanide upon activation by SiCl$_4$ also accounts for the lower yield. A noteworthy improvement in the reaction selectivity was achieved by resorting to a less polar solvent, dichloromethane, and lowering the temperature for the isocyanide addition to -20 °C: DCI could be isolated in a pleasing 78% yield using this modified procedure. This protocol allowed the general application of secondary isocyanides, with both aromatic and aliphatic aldehyde inputs. Chiral isocyanides such as (S)-α-methylbenzyl isocyanide also reacted satisfactorily (however with no asymmetry induction\textsuperscript{[7e, 10a]}). Naphthyl isocyanide gave a complex reaction mixture most likely due to oligomerization processes which are facile for unhindered aromatic isocyanides. A notable exception is the 2,6-dimethylphenyl derivative which reacted cleanly, albeit with lower rate in the imidoyl chloride reduction stage (compounds 14a and 14b, Table 3). This extension represents an important synthetic advantage, since bulky aromatic substituents are generally incompatible with conventional approaches towards β-amino alcohols due to the poor reactivity of the corresponding amines.\textsuperscript{[21]}

At this stage it became evident that the steric properties of the isocyanide markedly influence the outcome of the reaction. Consistent with our previous observations, less bulky primary isocyanides proved more problematic leading to extensive side product formation even under the modified conditions. Presumably, multiple coordination of sterically unencumbered isocyanides to SiCl$_4$ initiates unproductive events.\textsuperscript{[22]} To counteract this problem, we resorted to a stronger Lewis base to minimize competition of the isocyanide for the silicon center. Accordingly, the use of catalytic pyridine N-oxide instead of HMPA in the n-pentyl isocyanide addition gave the desired 2-(n-pentylamino)-1-phenylethanol in a synthetically useful yield (compound 15, Table 3). On the other hand,
sterically similar but α-acidic isocyanoacetate gave complications in the imidoyl chloride reduction and the desired product could not be isolated.

The substrate scope evaluation demonstrates the generality of our method, which ideally complements the chemical space of readily available N-substituted β-amino alcohols with bulky derivatives both at the carbinol side as well as the amine position.

### Table 3. Isocyanide scope for one-pot N-substituted β-amino alcohol synthesis\[^{[a,b]}\]

<table>
<thead>
<tr>
<th>Isocyanide</th>
<th>Isolated Yield</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>35%[^{[b]}](78%[^{[d]}])</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15%[^{[e]}]</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>50%[^{[f]}]</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>49%[^{[g]}]</td>
<td></td>
</tr>
</tbody>
</table>

\[^{[a]}\] Standard conditions: aldehyde (1 mmol), HMPA (10 mol%), SiCl<sub>4</sub> (1.1 equiv) and isocyanide (1.2 equiv) in AcOEt (2 mL) for 1 h at 0-5 °C, then BH<sub>3</sub>·NH<sub>3</sub> (technical, 1.5 equiv) for 3 h at room temperature; \[^{[b]}\] isolated yield after chromatography; \[^{[c]}\] isolated by precipitation as HCl salt; \[^{[d]}\] isocyanide addition performed in CH<sub>2</sub>Cl<sub>2</sub> at -20 °C for 4 h; \[^{[e]}\] 1:1 mixture of diastereoisomers; \[^{[f]}\] pyridine oxide instead of HMPA under conditions \[^{[d]}\]; \[^{[g]}\] crude yield based on NMR using internal standard.
For adrenergic agents the (R)-enantiomer is typically responsible for the biological effect, but most often the drug is marketed as the racemate. Nevertheless, rapid access to both enantiomers in high optical purity is of utmost importance for the complete biological profiling of drug candidates and therefore intensive research has been conducted towards enantioselective arylethanolamine preparation. Our protocol can be conveniently upgraded to an asymmetric synthesis by resorting to commercially available bisphosphoramidate catalyst 17 as chiral HMPA analogue in the isocyanide addition. This simple modification applied to benzaldehyde as benchmark aldehyde input allowed the isolation of (R)-2-(tert-butyramino)-1-phenylethanol in 79% yield with 99% ee.

Scheme 7. Asymmetric variant using chiral bisphosphoramidate 17.

**Conclusion**

In conclusion, we have developed an efficient two-stage one-pot synthesis of pharmaceutically important N-substituted β-amino alcohols from aldehydes and isocyanides based on a SiCl₄-mediated Passerini-type addition and subsequent ammonia borane reduction. This method has high functional group tolerance and broad aldehyde and isocyanide scope. Furthermore, the best performance is achieved in challenging circumstances for conventional approaches: oxidation-sensitive functional groups, nucleophilic substitution-sensitive substrates and non-nucleophilic amines. The good availability of the required building blocks, the reduced reaction time and the easy extension to a catalytic asymmetric version recommend this method for both combinatorial and medicinal chemistry applications.
Experimental Section

General Remarks

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Dichloromethane was distilled over CaH₂. Cyclohexane was distilled prior to use. Other solvents were used as purchased. Silicon tetrachloride was stored in a Schlenk under nitrogen. HMPA was stored in a Schlenk on 4Å molecular sieves under nitrogen. 4-methylbenzaldehyde was distilled before use in the reaction optimization. All reactions were performed in oven dried glassware (125 °C) under an inert atmosphere of dry N₂ unless stated otherwise.

3-(2-propynyloxy)benzaldehyde 1n was prepared by alkylation of 3-hydroxybenzaldehyde. 1-tosyl-indole-3-carbaldehyde 1v was prepared by tosylation of 3-formylindole as reported. Acetal protected aldehyde 1z was prepared according to literature procedure. 1-methyl-1-phenylethyl isocyanide was prepared via dehydration of the formamide as reported.

Infrared (IR) spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm⁻¹. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 (125.78 MHz for ¹³C) or Bruker Avance 400 (100.62 MHz for ¹³C) using the residual solvent as internal standard (¹H: δ 8.26 ppm, ¹³C{¹H}: δ 77.16 ppm for CDCl₃, ¹H: δ 2.50 ppm, ¹³C{¹H}: δ 39.52 ppm for DMSO-d₆ and ¹H: 4.80 ppm for D₂O). Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), br (broad singlet) and m (multiplet) or combinations thereof. Melting points were recorded on a Büchi M-565 melting point apparatus and are uncorrected. Electrospray Ionization (ESI) high-resolution mass spectrometry was carried out using a Bruker microTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Optical rotation was measured on an Optical Activity AA-10 polarimeter. Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 μm, pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO₂, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator).

General synthetic procedures

Reaction optimization

Tert-butyl isocyanide (68 µL, 0.6 mmol, 1.2 equiv) was added to a solution (1 mL AcOEt, anhydrous) of 4-methylbenzaldehyde (59 µL, 0.5 mmol), catalyst (0.05 mmol, 0.1 equiv), and SiCl₄ (63 µL, 0.55 mmol, 1.1 equiv) at 0-5 °C. After stirring for one hour at 0-5 °C, the reducing agent was added as solid unless stated otherwise. After stirring for the indicated reaction time at room temperature, the mixture was diluted (in three portions) with 10 mL CH₂Cl₂ and transferred (cautiously, gas evolution!) to an aqueous solution of Na₂CO₃ 10 wt% (20 mL). The mixture was stirred for 30 minutes at room temperature. The solution was filtered and the filter was washed with another 10 mL CH₂Cl₂. The layers were separated and the aqueous layer was extracted once more with 10 mL CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The yield was determined by ¹H-NMR analysis of the crude reaction mixture using mesitylene as internal standard.

General procedure

An isocyanide (1.2 mmol, 1.2 equiv) was added to a solution (2 mL AcOEt, normal grade) of aldehyde (1 mmol), hexamethylphosphoramide (17.4 µL, 0.1 mmol, 0.1 equiv), and SiCl₄ (126 µL, 1.1 mmol, 1.1 equiv) at 0-5 °C. After stirring for one hour at 0-5 °C, technical grade BH₃NH₃ (46 mg, 1.5 mmol, 1.5 equiv) was added. The cooling bath was removed and the reaction mixture was stirred for another 3 h at ambient temperature. Next, the mixture
was diluted (in three portions) with 10 mL CH$_2$Cl$_2$ and transferred (cautiously, gas evolution!) to an aqueous solution of Na$_2$CO$_3$ 10 wt% (20 mL). The mixture was stirred for 30 minutes at room temperature. The solution was filtered and the filter was washed with another 10 mL CH$_2$Cl$_2$. The layers were separated and the aqueous layer was extracted with 20 mL CH$_2$Cl$_2$ in two portions. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The product was purified by column chromatography on silicagel or by precipitation as hydrochloride salt from methyl tert-butyl ether.

**Modified procedure**

An isocyanide (1.2 mmol, 1.2 equiv) was added to a solution of aldehyde (1 mmol, 1 equiv), hexamethylphosphoramide (17.4 µL, 0.1 mmol, 0.1 equiv), and SiCl$_4$ (126 µL, 1.1 mmol, 1.1 equiv) in 2 mL dry dichloromethane cooled to -20 °C. After stirring for 4 h at -20 °C, BH$_3$NH$_2$ (46 mg, 1.5 mmol, 1.5 equiv) was added. The cooling bath was removed and the reaction mixture was stirred for another 3 h. Next, the mixture was diluted (in three portions) with 10 mL CH$_2$Cl$_2$ and transferred (cautiously, gas evolution!) to an aqueous solution of Na$_2$CO$_3$ 10 wt% (20 mL). The mixture was stirred for 30 minutes at room temperature. The solution was filtered and the filter was washed with another 10 mL CH$_2$Cl$_2$. The layers were separated and the aqueous layer was extracted with 20 mL CH$_2$Cl$_2$ in two portions. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The product was purified by column chromatography on silicagel.

**Characterization of compounds**

2-(tert-butylamino)-1-(p-tolyl)ethan-1-ol 4a
Prepared from 4-toluualdehyde (120 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (cyclohexane/AcOEt/Et$_2$N 75/25/5, R$_f$ = 0.10). Isolated as a white solid. Yield: 154 mg, 0.74 mmol, 74%.

m.p.: 102.7-104.6 °C; $^1$H-NMR (CDCl$_3$, 400 MHz): δ 7.25 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 4.60 (dd, J = 8.8, 3.6 Hz, 1H), 2.80 (dd, J = 12.0, 3.6, 1H), 2.60 (dd, J = 12.0, 8.8 Hz, 1H), 2.34 (s, 3H), 1.08 (s, 9H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): δ 140.5 (C), 136.9 (C), 129.0 (CH), 125.8 (CH), 72.1 (CH), 50.4 (C), 50.3 (CH$_3$), 29.0 (CH$_3$), 21.2 (CH$_3$) ppm; IR (neat): νmax (cm$^{-1}$) = 2972 (m), 2910 (w), 2845 (w), 1225 (m), 1078 (s), 810 (s) ppm; HRMS (ESI): m/z calculated for C$_{13}$H$_{22}$NO [M+H]$^+$ 208.1696, found 208.1688.

2-(tert-butylamino)-1-phenylethan-1-ol 4b
Prepared from benzaldehyde (106 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (cyclohexane/AcOEt/Et$_2$N 75/25/5, R$_f$ = 0.20). Isolated as an off-white solid. Yield: 160 mg, 0.83 mmol, 83%.

m.p.: 86.1-87.0 °C; $^1$H-NMR (CDCl$_3$, 400 MHz): δ 7.33-7.40 (m, 4H), 7.26-7.30 (m, 1H), 4.65 (dd, J = 8.8, 3.6 Hz, 1H), 2.86 (dd, J = 11.6, 3.6 Hz, 1H), 2.63 (dd, J = 11.6, 8.8 Hz, 1H), 1.10 (s, 9H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): δ 143.4 (C), 128.4 (CH), 127.4, 125.9 (CH), 72.3 (CH), 50.4 (C), 50.4 (CH$_3$), 29.1 (CH$_3$) ppm; IR (neat): νmax (cm$^{-1}$) = 2970 (w), 1474 (w), 1223 (m), 1088 (m), 754 (m), 700 (s), 629 (m), 561 (s); HRMS (ESI): m/z calculated for C$_{13}$H$_{18}$NO [M+H]$^+$ 194.1540, found 194.1543.

2-(tert-butylamino)-1-(1-naphthalen-2-yl)ethan-1-ol 4c
Prepared from 2-naphthaldehyde (156 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (AcOEt/Et$_2$N/MeOH 100/5/0.5, R$_f$ = 0.27). Isolated as a light brown solid. Yield: 190 mg, 0.78 mmol, 78%.
Synthesis of β-Amino Alcohols from Aldehydes and Isocyanides

m.p.: 121.0-124.5 °C; 1H-NMR (CDCl$_3$, 400 MHz): δ 7.82-7.86 (m, 4H), 7.46-7.50 (m, 3H), 4.84 (dd, J = 8.0, 3.6 Hz, 1H), 2.97 (dd, J = 11.6, 3.6 Hz, 1H), 2.72 (dd, J = 11.6, 8.0 Hz, 1H), 1.12 (s, 9H) ppm; 13C($^H$)-NMR (CDCl$_3$, 125 MHz): δ 140.7 (C), 133.4 (C), 133.0 (C), 128.1 (CH), 128.0 (CH), 127.8 (CH), 126.1 (CH), 125.8 (CH), 124.6 (CH), 124.1 (CH), 72.2 (CH), 50.7 (C), 50.2 (CH$_2$), 29.1 (CH$_3$) ppm; IR (neat): vmax (cm$^{-1}$) = 2966 (w), 1429 (w), 1367 (m), 1221 (m), 1078 (s), 864 (s), 824 (s), 750 (s); HRMS (ESI): m/z calculated for C$_{16}$H$_{22}$NO [M+H]$^+$ 244.1694, found 244.1694.

2-(tert-butylamino)-1-mesitylethan-1-ol 4d
Prepared from 2,4,6-trimethylbenzaldehyde (148 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silica gel (AcOEt/Et$_3$N/MeOH 100/5/0.5, Rf = 0.26). Isolated as a white solid. Yield: 165 mg, 0.70 mmol, 70%.

m.p.: 127.3-131.0 °C; 1H-NMR (CDCl$_3$, 400 MHz): δ 6.82 (s, 2H), 5.01 (dd, J = 10.8, 3.5 Hz, 1H), 2.89 (t, J = 11.4 Hz, 1H), 2.71 (dd, J = 12.0, 3.5 Hz, 1H), 2.41 (s, 6H), 2.25 (s, 3H), 1.13 (s, 9H) ppm; 13C($^H$)-NMR (CDCl$_3$, 125 MHz): δ 136.6 (C), 136.5 (C), 134.8 (C), 130.2 (CH), 70.3 (CH), 50.6 (C), 46.2 (CH$_2$), 29.2 (CH$_3$), 21.0 (CH$_3$), 20.8 (CH$_3$) ppm; IR (neat): vmax (cm$^{-1}$) = 2962 (w), 1474 (m), 1364 (m), 1223 (m), 1082 (s), 847 (s), 727 (m), 582 (m); HRMS (ESI): m/z calculated for C$_{16}$H$_{22}$NO [M+H]$^+$ 236.2009, found 236.2019.

2-(tert-butylamino)-1-(4-chlorophenylethan-1-ol 4e
Prepared from 4-chlorobenzaldehyde (141 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silica gel (AcOEt/Et$_3$N/MeOH 100/5/0.5, Rf = 0.24). Isolated as a yellow solid. Yield: 182 mg, 0.80 mmol, 80%.

m.p.: 130.0-133.1 °C; 1H-NMR (CDCl$_3$, 400 MHz): δ 7.31 (s, 4H), 4.55 (dd, J = 8.8, 3.6 Hz, 1H), 2.89 (dd, J = 12.0, 3.6 Hz, 1H), 2.52 (dd, J = 12.0, 8.8 Hz, 1H), 1.10 (s, 9H); 13C($^H$)-NMR (CDCl$_3$, 125 MHz): δ 141.6 (C), 133.1 (C), 128.6 (CH), 127.3 (CH), 71.6 (CH), 50.7 (C), 50.3 (CH$_2$), 29.2 (CH$_3$) ppm; IR (neat): vmax (cm$^{-1}$) = 2970 (w), 1487 (w), 1223 (m), 1078 (s), 1013 (m), 820 (s), 565 (m), 527 (m); HRMS (ESI): m/z calculated for C$_{16}$H$_{16}$NO [M+H]$^+$ 228.1150, found 228.1139.

1-(2-bromophenyl)-2-(tert-butylamino)ethan-1-ol 4f
Prepared from 2-bromobenzaldehyde (185 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silica gel (cyclohexane/AcOEt/Et$_3$N 90/10/5, Rf = 0.09). Isolated as a white solid. Yield: 213 mg, 0.78 mmol, 78%.

m.p.: 80.7-84.0 °C; 1H-NMR (CDCl$_3$, 400 MHz): δ 7.63 (dd, J = 7.8, 1.2 Hz, 1H), 7.49 (dd, J = 7.8, 1.2 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 7.11 (td, J = 7.8, 1.4 Hz, 1H), 4.95 (dd, J = 8.8, 3.6 Hz, 1H), 3.03 (dd, J = 12.0, 3.6 Hz, 1H), 2.45 (dd, J = 12.0, 8.8 Hz, 1H), 1.09 (s, 9H) ppm; 13C($^H$)-NMR (CDCl$_3$, 125 MHz): δ 142.4 (C), 132.5 (CH), 128.7 (CH), 127.8 (CH), 127.7 (CH), 121.8 (C), 71.1 (CH), 50.6 (C), 48.2 (CH$_2$), 29.1 (CH$_3$) ppm; IR (neat): vmax (cm$^{-1}$) = 2964 (w), 1458 (m), 1431 (m), 1364 (m), 1221 (m), 1082 (s), 1020 (m), 746 (s); HRMS (ESI): m/z calculated for C$_{16}$H$_{15}$BrNO [M+H]$^+$ 272.0645, found 272.0654.

4-(2-(tert-butylamino)-1-hydroxyethyl)benzonitrile 4g
Prepared from 4-formylbenzonitrile (131 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silica gel (AcOEt/Et$_3$N/MeOH 100/5/0.5, Rf = 0.21). Isolated as a light brown solid. Yield: 196 mg, 0.90 mmol, 90%.

m.p.: 104.5-105.8 °C; 1H-NMR (CDCl$_3$, 400 MHz): δ 7.60 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 4.65 (dd, J = 8.8, 3.6 Hz, 1H), 2.86 (dd, J = 12.0, 3.6 Hz, 1H), 2.51 (dd, J = 12.0, 8.8 Hz, 1H), 1.06 (s, 9H) ppm; 13C($^H$)-NMR (CDCl$_3$, 125 MHz): δ 148.8 (C), 132.2 (CH), 126.5 (CH), 119.0 (C), 111.0 (C), 71.4 (CH), 50.6 (C), 49.9 (CH$_3$), 29.0 (CH$_3$) ppm; IR (neat): vmax (cm$^{-1}$) = 2972 (w), 2228 (w), 1223 (m), 1080 (m), 908 (m), 829 (s), 573 (s); HRMS (ESI): m/z calculated for C$_{16}$H$_{15}$N$_2$O [M+H]$^+$ 219.1492, found 219.1499.

45
Chapter 2

Methyl 4-(2-tert-butylamino)-1-hydroxyethyl)benzoate 4h
Prepared from methyl 4-formylbenzoate (164 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (AcOEt/EtOAc/MeOH 100/5/0.5, Rf = 0.24). Isolated as a white solid. Yield: 201 mg, 0.80 mmol, 80%.

2-(tert-butylamino)-1-(4-trifluoromethyl)phenyl)ethan-1-ol 4i
Prepared from 2-(trifluoromethyl)benzaldehyde (174 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (AcOEt/EtOAc/MeOH 100/5/0.5, Rf = 0.30). Isolated as an off-white solid. Yield: 214 mg, 0.82 mmol, 82%.

2-(tert-butylamino)-1-(2-(trifluoromethyl)phenyl)ethan-1-ol 4j
Prepared from 2-(trifluoromethyl)benzaldehyde (174 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (cyclohexane/AcOEt/EtOAc/N/MeOH 80/20/5, Rf = 0.26). Isolated as an off-white solid. Yield: 185 mg, 0.71 mmol, 71%.

2-(tert-butylamino)-1-(4-nitrophenyl)ethan-1-ol (chloride salt) 4k
Prepared from 4-nitrobenzaldehyde (151 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: precipitation as hydrochloride salt with HCl (4N in dioxane) from methyl tert-butyl ether. Isolated as a brown solid. Yield: 187 mg, 0.68 mmol, 68%.

2-(tert-butylamino)-1-(4-fluoro-3-nitrophenyl)ethan-1-ol (chloride salt) 4l
Prepared from 4-fluoro-3-nitrobenzaldehyde (169 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: precipitation as hydrochloride salt with HCl (4N in dioxane) from methyl tert-butyl ether. Isolated as an orange solid. Yield: 258 mg, 0.88 mmol, 88%.
m.p.: 220 °C (decomposition); ¹H-NMR (DMSO-d₆, 400 MHz): δ 9.54 (br, 1H), 8.72 (br, 1H), 8.21 (dd, J = 7.3, 2.1 Hz, 1H), 7.87-7.93 (m, 1H), 7.63 (dd, J = 11.1, 8.8 Hz, 1H), 6.56 (br, 1H), 5.17 (d, J = 9.0 Hz, 1H), 3.14 (d, J = 11.0 Hz, 1H), 2.98 (t, J = 10.0 Hz, 1H), 1.32 (s, 9H) ppm; ¹³C(¹H)-NMR (DMSO-d₆, 125 MHz): δ 154.0 (d, J = 260 Hz, C), 139.4 (d, J = 4 Hz, C), 136.7 (d, J = 9 Hz, C), 134.2 (d, J = 9 Hz, CH), 123.7 (d, J = 1 Hz, CH), 118.5 (d, J = 21 Hz, CH), 67.4 (CH), 56.5 (C), 48.0 (CH₂), 25.0 (CH₃) ppm; IR (neat): vmax (cm⁻¹) = 2968 (w), 1535 (s), 1346 (s), 1244 (m), 1080 (m), 841 (m); HRMS (ESI): m/z calculated for C₂₃H₂₃F₃O₅ [M+H]+ 257.1296, found 257.1288.

2-(tert-butylamino)-1-(4-(methylthio)phenyl)ethan-1-ol 4m
Prepared from 4-(methylthio)benzaldehyde (152 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (AcOEt/Et₂O/MeOH 100/5/0.5, Rf = 0.30). Isolated as a yellow solid. Yield: 184 mg, 0.77 mmol, 77%.

m.p.: 116.0-122.5 °C; ¹H-NMR (CDCl₃, 400 MHz): δ 7.28 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 4.59 (dd, J = 8.8, 3.6 Hz, 1H), 2.84 (dd, J = 12.0, 3.6 Hz, 1H), 2.58 (dd, J = 12.0, 8.8 Hz, 1H), 2.47 (s, 3H), 1.09 (s, 9H) ppm; ¹³C(¹H)-NMR (CDCl₃, 125 MHz): δ 140.1 (C), 137.3 (C), 126.7 (CH), 71.8 (CH), 50.6 (C), 50.3 (CH₂), 29.1 (CH₃), 16.1 (CH₃) ppm; IR (neat): vmax (cm⁻¹) = 3304 (w), 2964 (w), 1281 (s), 1231 (s), 1148 (s), 1080 (m), 841 (m); HRMS (ESI): m/z calculated for C₁₃H₁₃NOS [M+H]+ 240.1417, found 240.1423.

N-(4-(2-tert-butylamino)-1-hydroxyethyl)phenyl)acetamide (chloride salt) 4p
Prepared from 4-acetamidobenzaldehyde (163 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: precipitation as hydrochloride salt with HCl (4N in dioxane) from methyl tert-butyl ether. Isolated as a light brown solid (hygroscopic). Yield: 210 mg, 0.73 mmol, 73%.

¹H-NMR (D₂O, water suppression test, 400 MHz): δ 7.38-7.45 (m, 4H), 4.93 (dd, J = 9.6, 3.2 Hz, 1H), 3.28 (dd, J = 12.5, 3.2 Hz, 1H), 3.19 (dd, J = 12.5, 9.6 Hz, 1H), 2.13 (s, 3H), 1.35 (s, 9H) ppm; ¹³C(¹H)-NMR (D₂O, 125 MHz): δ 173.0 (C), 137.0 (C), 136.6 (C), 126.7 (CH), 122.2 (CH), 69.0 (CH), 57.4 (C), 47.3 (CH₃), 24.7 (CH₃), 22.7 (CH₃) ppm;
1-(benzof[d][1,3]dioxol-5-yl)-2-(tert-butylamino)ethan-1-ol 4q
Prepared from piperonal (150 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silica gel (cyclohexane/AcOEt/Et2O 75/25/5, Rf = 0.18). Isolated as an off-white solid. Yield: 158 mg, 0.67 mmol, 67%.

m.p.: 96.0-98.0 °C; 1H-NMR (CDCl3, 400 MHz): δ 6.87 (d, J = 0.8 Hz, 1H), 6.79 (d, J = 8 Hz, 1H), 6.74 (d, J = 8 Hz, 1H), 5.91 (s, 2H), 4.54 (dd, J = 9.2, 3.6 Hz, 1H), 2.76 (dd, J = 11.6, 3.6 Hz, 1H), 2.56 (dd, J = 11.6, 9.2 Hz, 1H), 1.07 (s, 9H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz): δ 147.7 (C), 146.8 (C), 137.5 (C), 119.1 (C), 108.1 (C), 106.5 (C), 101.0 (CH3), 72.0 (CH), 50.5 (C), 50.4 (CH2), 29.0 (CH3) ppm; IR (neat): vmax (cm−1) = 2966 (w), 1367 (m), 1223 (m), 1116 (m), 750 (m), 723 (m), 658 (m), 478 (s); HRMS (ESI): m/z calculated for C22H29NO3 [M+H]+ 322.1853, found 322.1864.

1-(tert-butylnamido)-4-phenylbutan-2-ol 4r
Prepared from 3-phenylpropanal (134 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silica gel (cyclohexane/AcOEt/Et2O 80/20/5, Rf = 0.26). Isolated as a yellow oil. Yield: 181 mg, 0.83 mmol, 83%.

1H-NMR (CDCl3, 400 MHz): δ 7.16-7.30 (m, 5H), 3.53-3.57 (m, 1H), 2.66-2.86 (m, 5H), 2.40 (dd, J = 11.6, 3.6 Hz, 1H), 1.73-1.79 (m, 2H), 1.08 (s, 9H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz): δ 142.3 (C), 128.5 (CH), 128.3 (CH), 125.7 (CH), 69.3 (CH), 50.4 (C), 48.2 (CH2), 37.1 (CH3), 32.1 (CH3), 29.0 (CH3) ppm; IR (neat): vmax (cm−1) = 2962 (m), 1545 (w), 1364 (w), 1221 (w), 700 (w), 633 (s), 538 (s), 498 (s); HRMS (ESI): m/z calculated for C14H18NO [M+H]+ 222.1864.

2-(tert-butylnamido)-1-cyclohexylethan-1-ol 4s
Prepared from cyclohexanecarboxaldehyde (112 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silica gel (cyclohexane/AcOEt/Et2O 90/10/5, Rf = 0.19). Isolated as a yellow solid. Yield: 156 mg, 0.78 mmol, 78%.

1H-NMR (CDCl3, 400 MHz): δ 3.19 (ddd, J = 3.4, 3.2, 3.0 Hz, 1H), 2.75 (ddd, J = 11.6, 3.2 Hz, 1H), 2.36 (dd, J = 11.6, 3.0 Hz, 1H), 1.89-1.92 (m, 1H), 1.65-1.77 (m, 4H), 1.12-1.36 (m, 4H), 1.09 (s, 9H), 0.82-1.05 (m, 2H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz): δ 74.3 (CH), 50.4 (C), 45.5 (CH2), 42.5 (CH), 29.4 (CH3), 29.1 (CH3), 28.9 (CH2), 26.7 (CH2), 26.3 (CH2) ppm; IR (neat): vmax (cm−1) = 2924 (m), 2853 (w), 1258 (m), 1072 (bm), 1011 (bs), 791 (s); HRMS (ESI): m/z calculated for C12H20NO [M+H]+ 200.2009, found 200.2005.

3-(tert-butylnamido)-1,1,1-trichloropropan-2-ol 4t
Prepared from chloral (147 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silica gel (cyclohexane/AcOEt/Et2O 66/33/5, Rf = 0.27). Isolated as a light brown solid. Yield: 98 mg, 0.44 mmol, 44%.1H-NMR (CDCl3, 400 MHz): δ 5.05 (t, J = 5.6 Hz, 1H), 3.05 (dd, J = 5.6 Hz, J = 13.6 Hz, 1H), 2.96 (dd, J = 13.6, 5.6 Hz, 1H), 1.14 (s, 9H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz): δ 103.1 (C), 79.1 (C), 51.4 (C), 42.5 (CH3), 29.2 (CH3) ppm; IR (neat): vmax (cm−1) = 3254 (w), 2970 (m), 1317 (m), 1217 (m), 1117 (m), 962 (m), 789 (s), 623 (s), 550 (s); HRMS (ESI): m/z calculated for C16H14Cl3NO [M+H]+ 234.0214, found 234.0207.

(E)-1-(tert-butylnamido)-3-methylpent-3-en-2-ol 4u
Prepared from tiglic aldehyde (84 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silica gel (cyclohexane/AcOEt/Et2O 50/50/5, Rf = 0.21). Isolated as a colorless oil. Yield: 99 mg, 0.58 mmol, 58%.
1H-NMR (CDCl3, 400 MHz): δ 5.55 (dd, J = 12.0, 6.0 Hz, 1H), 3.90 (dd, J = 8.5, 3.5 Hz, 1H), 2.68 (dd, J = 11.5, 3.5 Hz, 1H), 2.50 (dd, J = 11.5, 9.0 Hz, 1H), 1.62 (s, 3H), 1.61 (s, 3H), 1.09 (s, 9H) ppm; 13C{1H}-NMR (CDCl3, 125 MHz): δ 136.1 (C), 120.7 (CH), 75.4 (CH), 50.3 (C), 46.5 (CH2), 29.3 (CH3), 13.2 (CH3), 12.0 (CH3) ppm; IR (neat): v_max (cm⁻¹) = 3242 (w), 2920 (m), 1448 (m), 1227 (s), 1018 (s), 860 (w), 743 (w), 561 (w); HRMS (ESI): m/z calculated for C16H23NO [M+H]+ 240.1594, found 240.1589.

2-(tert-butylamino)-1-(1-tosyl-1H-indol-3-yl)ethan-1-ol 4v
Prepared from 1-tosyl-indole-3-carbaldehyde (299 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (AcOEt/EtO/MeOH 100/5/0, Rf = 0.23). Isolated as an orange gummy solid. Yield: 213 mg, 0.55 mmol, 55%.

2-(tert-butylamino)-1-(1-methyl-1H-imidazol-2-yl)ethan-1-ol 4w
Prepared from 1-methyl-2-imidazolecarboxaldehyde (110 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (AcOEt/EtO/MeOH 100/5/10, Rf = 0.19). Isolated as a yellow oil. Yield: 130 mg, 0.66 mmol, 66%.

Salbutamol acetate 4z
Tert-butyl isocyanide (136 µL, 1.2 mmol, 1.2 equiv) was added to a solution (2 mL AcOEt, normal grade) of aldehyde 1z (192 mg, 1 mmol, 1 equiv), hexamethylphosphoramide (0.1 equiv, 0.1 mmol, 17.4 µL), and SiCl4 (1.1 equiv, 1.1 mmol, 126 µL) at 0-5 °C. After stirring for 2 h at 0-5 °C, technical grade BH3·NH3·CH2Cl (62 mg, 2 mmol, 2 equiv) was added. The ice bath was removed and the reaction mixture was stirred for another 20 minutes at room temperature. Next, the mixture was diluted (in three portions) with 10 mL CH2Cl2 and transferred (cautiously, gas evolution!) to a vigorously stirring saturated Na2CO3 solution (20 mL) at 0-5 °C. The mixture was then stirred for 30 minutes at room temperature. The solution was filtered and the filter was washed with another 10 mL CH2Cl2. The layers were separated and the aqueous layer was extracted with 20 mL CH2Cl2 in two portions. The combined organic layers were dried over Na2SO4 and concentrated under reduced pressure. The crude product was redissolved in 2 mL AcOH/H2O (1:1) and stirred for 5 h at 60 °C. The solvents were then removed in vacuo and the resulting powder was triturated with AcOEt (2x20 mL) and dried to give the pure product. Isolated as a white solid. Yield: 225 mg, 0.75 mmol, 75% (over the two steps).
Chapter 2

1-(4-bromophenyl)-2-((2,4,4-trimethylpentan-2-yl)amino)ethan-1-ol 5a
Prepared from 4-bromobenzaldehyde (185 mg, 1 mmol, 1 equiv) and tert-octyl isocyanide (167 mg, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (cyclohexane/AcOEt/Et₂O 80/20/5, Rₚ = 0.15). Isolated as an off-white solid. Yield: 263 mg, 0.80 mmol, 80%.

m.p.: 87.4–89.0 °C; ¹H-NMR (CDCl₃, 400 MHz): δ 7.45 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.54 (dd, J = 8.4, 3.6 Hz, 1H), 2.83 (dd, J = 11.6, 3.6 Hz, 1H), 2.53 (dd, J = 11.6, 8.4 Hz, 1H), 1.38 (s, 2H), 1.11 (s, 6H), 0.98 (s, 9H) ppm; ¹³C{¹H}-NMR (CDCl₃, 125 MHz): δ 142.4 (C), 131.4 (CH), 127.6 (CH), 121.1 (C), 71.6 (CH), 54.3 (C), 53.8 (C), 49.8 (CH₃), 31.8 (CH₃), 31.7 (CH₃), 29.0 (CH₃), 28.7 (CH₃) ppm; IR (neat): v_max (cm⁻¹) = 2947 (w), 1456 (m), 1364 (m), 1227 (w), 1090(w), 891 (m), 469 (m); HRMS (ESI): m/z calculated for C₂₃H₂₉BrNO [M+H]^⁺ 328.1271, found 328.1259.

1-cyclohexyl-2-((2,4,4-trimethylpentan-2-yl)amino)ethan-1-ol 5b
Prepared from cyclohexanecarboxaldehyde (112 mg, 1 mmol, 1 equiv) and tert-octyl isocyanide (167 mg, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (cyclohexane/AcOEt/Et₂O 80/20/5, Rₚ = 0.4). Isolated as a colorless oil. Yield: 204 mg, 0.80 mmol, 80%.

¹H-NMR (CDCl₃, 400 MHz): δ 3.17 (dd, J = 9.0, 4.5 Hz, 1H), 2.75 (dd, J = 11.5, 3.0 Hz, 1H), 2.35 (t, J = 10.5 Hz, 1H), 1.80-1.95 (m, 1H), 1.60-1.75 (m, 4H), 1.41 (s, 2H), 1.29-1.33 ppm (m, 4H), 1.12 (s, 6H), 1.01-1.07 (m, 2H), 1.01 (s, 9H); ¹³C{¹H}-NMR (CDCl₃, 125 MHz): δ 74.3 (CH), 54.2 (C), 54.0(CH₂), 45.0 (CH₂), 44.2 (CH), 31.9 (CH₃), 31.7 (C), 29.3 (CH₃), 29.0 (CH₃), 28.9 (CH₃), 28.7 (CH₃), 26.6 (CH₃), 26.3 (CH₃), 26.2 (CH₃) ppm; IR (neat): v_max (cm⁻¹) = 2922 (s), 2851 (m), 1448 (m), 1364 (m), 1227 (w), 1090(w), 891 (m), 469 (m); HRMS (ESI): m/z calculated for C₂₅H₃₈NO [M+H]^⁺ 256.2635, found 256.2622.

1-(4-nitrophenyl)-2-((2-phenylpropan-2-yl)amino)ethan-1-ol (chloride salt) 6a
Prepared from 4-nitrobenzaldehyde (151 mg, 1 mmol, 1 equiv) and 1-methyl-1-phenylethyl isocyanide (174 mg, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: precipitation as hydrochloride salt with HCl (4N in dioxane) from methyl tert-butyl ether. Isolated as a yellow solid. Yield: 175 mg, 0.52 mmol, 52%.

m.p.: 213 °C (decomposition); ¹H-NMR (DMSO-d₆, 400 MHz): δ 10.36 (br, 1H), 9.28 (br, 1H), 8.16 (d, J = 8.8 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.42 (t, J = 7.2 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 6.50 (d, J = 2.8 Hz, 1H), 5.18 (d, J = 9.2 Hz, 1H), 2.70-2.85 (m, 1H), 2.45-2.60 (m, 1H), 1.78 (d, J = 7.2 Hz, 6H) ppm; ¹³C{¹H}-NMR (DMSO-d₆, 125 MHz): δ 149.1 (C), 147.0 (C), 139.5 (C), 128.8 (CH), 128.5 (CH), 127.2 (CH), 126.5 (CH), 123.5 (CH), 68.0 (CH), 61.2 (C), 49.6 (CH₃), 25.8 (CH₃), 24.9 (CH₃) ppm; IR (neat): v_max (cm⁻¹) = 3137 (w), 2764 (w), 1516 (s), 1348 (s), 1080 (m), 854 (m), 696 (s); HRMS (ESI): m/z calculated for C₁₇H₁₄N₂O₃ [M+H]^⁺ 301.1537, found 301.1537.

1-((2-phenylpropan-2-yl)amino)octan-2-ol 6b
Prepared from heptanal (114 mg, 1 mmol, 1 equiv) and 1-methyl-1-phenylethyl isocyanide (174 mg, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silicagel (cyclohexane/AcOEt/Et₂O 80/10/5, Rₚ = 0.25). Isolated as a yellow gummy solid. Yield: 163 mg, 0.62 mmol, 62%.

¹H-NMR (CDCl₃, 400 MHz): δ 7.43 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 3.47-3.55 (m, 1H), 2.47 (dd, J = 11.6, 3.2 Hz, 1H), 2.16 (dd, J = 11.6, 9.2 Hz, 1H), 1.48 (d, J = 5.6 Hz, 6H), 1.25-1.37 (m, 10H), 0.89 (t, J = 6.5 Hz, 3H) ppm; ¹³C{¹H}-NMR (CDCl₃, 125 MHz): δ 147.4 (C), 128.3 (CH), 126.4 (CH), 125.7 (CH), 70.6 (CH), 55.6 (C), 48.9 (CH₂), 35.2 (CH₂), 31.8 (CH₃), 29.8 (CH₃), 29.4 (CH₃), 29.4 (CH₃), 25.7 (CH₃), 22.6 (CH₃), 14.1 (CH₃) ppm; IR (neat): v_max (cm⁻¹) = 2926 (w), 1458 (m), 1234 (w), 1076 (m), 1030 (m), 764 (m), 698 (s); HRMS (ESI): m/z calculated for C₁₇H₂₁NO [M+H]^⁺ 264.2322, found 264.2314.
Synthesis of β-Amino Alcohols from Aldehydes and Isocyanides

2-(cyclohexyamino)-1-(4-fluorophenyl)ethan-1-ol 7a
Prepared from 4-fluorobenzaldehyde (124 mg, 1 mmol, 1 equiv) and cyclohexyl isocyanide (131 mg, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silica gel (AcOEt/Et2N/MeOH 100/5/0.5, Rt = 0.26). Isolated as a white solid. Yield: 142 mg, 0.60 mmol, 60%.

m.p.: 90.5-95.0 °C; 1H-NMR (CDCl3, 400 MHz): δ 7.30 (dd, J = 8.4, 5.2 Hz, 2H), 7.02 (t, J = 8.4 Hz, 2H), 4.63 (dd, J = 9.4, 3.6 Hz, 1H), 2.87 (dd, J = 12.0, 3.6 Hz, 1H), 2.60 (dd, J = 12.0, 9.4, 1H), 2.35-2.44 (m, 1H), 1.80-1.89 (m, 2H), 1.64-1.73 (m, 2H), 1.55-1.62 (m, 1H), 1.00-1.23 (m, 5H) ppm; 13C¹H-NMR (CDCl3, 125 MHz): δ 162.2 (d, J = 244 Hz, C), 139.0 (C), 127.5 (d, J = 8 Hz, CH), 115.1 (CH), 71.4 (CH), 56.7 (CH), 54.4 (CH3), 33.6 (CH3), 33.5 (CH3), 26.1 (CH3), 25.1 (CH3), 25.0 (CH3) ppm; IR (neat): νmax (cm⁻¹) = 2932 (w), 285 (w), 1508 (s), 1223 (m), 1215 (m), 1070 (m), 939 (m), 833 (s), 822 (s), 546 (s); HRMS (ESI): m/z calculated for C22H23FNO [M+H]⁺ 327.1603, found 327.1603.

1-(cyclohexyamino)-4-phenylbutan-2-ol 7b
Prepared from 3-phenylpropanol (134 mg, 1 mmol, 1 equiv) and cyclohexyl isocyanide (131 mg, 1.2 mmol, 1.2 equiv) according to the general procedure. Purification: column chromatography on silica gel (AcOEt/Et2N/MeOH 100/5/0.5, Rt = 0.30). Isolated as a white solid. Yield: 161 mg, 0.65 mmol, 65%.

m.p.: 59.5-61.7 °C; 1H-NMR (CDCl3, 400 MHz): δ 7.15-7.29 (m, 5H), 3.50-3.65 (m, 1H), 2.68-2.83 (m, 3H), 2.38-2.45 (m, 2H), 1.62-1.88 (m, 7H), 0.98-1.28 (m, 5H) ppm; 13C¹H-NMR (CDCl3, 125 MHz): δ 142.4 (C), 128.5 (CH), 128.4 (CH), 125.8 (CH), 69.2 (CH), 56.7 (CH), 52.5 (CH3), 37.0 (CH3), 34.1 (CH3), 33.7 (CH3), 32.2 (CH3), 26.2 (CH3), 25.1 (CH3) ppm; IR (neat): νmax (cm⁻¹) = 3273 (w), 2928 (m), 1456 (m), 1047 (m), 937 (s), 746 (s), 528 (s); HRMS (ESI): m/z calculated for C22H25NO [M+H]⁺ 328.1603, found 328.1603.

1-(3,4-dichlorophenyl)-2-(isopropylamino)ethan-1-ol 8a
Prepared from 3,4-dichlorobenzaldehyde (175 mg, 1 mmol, 1 equiv) and isopropyl isocyanide (113 µL, 1.2 mmol, 1.2 equiv) according to the modified procedure. Purification: column chromatography on silica gel (AcOEt/Et2N 100/5, Rt = 0.30). Isolated as a white solid. Yield: 193 mg, 0.78 mmol, 78%.

m.p.: 80.3-85 °C; 1H-NMR (CDCl3, 400 MHz): δ 7.46 (d, J = 1.6 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 8.4, 1.6 Hz, 1H), 4.59 (dd, J = 8.8, 3.6 Hz, 1H), 2.88 (dd, J = 12.4, 3.6 Hz, 1H), 2.80-2.95 (m, 1H), 2.55 (dd, J = 12.0, 8.8 Hz, 1H), 1.00-1.10 (m, 6H) ppm; 13C¹H-NMR (CDCl3, 125 MHz): δ 143.5 (C), 132.6 (C), 131.2 (C), 130.4 (CH), 127.9 (CH), 125.2 (CH), 70.8 (CH), 54.5 (CH3), 48.8 (CH), 23.3 (CH3), 21.3 (CH3) ppm; IR (neat): νmax (cm⁻¹) = 2966 (w), 1464 (s), 1074 (s), 1032 (m), 897 (m), 824 (s), 708 (m), 604 (m); HRMS (ESI): m/z calculated for C13H12Cl2NO [M+H]⁺ 248.0909, found 248.0909.

1-(isopropylamino)-4-(phenylbutan-2-ol 8b
Prepared from 3-phenylpropanol (134 mg, 1 mmol, 1 equiv) and isopropyl isocyanide (113 µL, 1.2 mmol, 1.2 equiv) according to the modified procedure. Purification: column chromatography on silica gel (Cyclohexane/AcOEt/Et2N 50/50/5, Rt = 0.14). Isolated as a white solid. Yield: 135 mg, 0.65 mmol, 65%.

m.p.: 39.5-43.9 °C; 1H-NMR (CDCl3, 400 MHz): δ 7.22-7.26 (m, 2H), 7.12-7.18 (m, 3H), 3.45-3.60 (m, 1H), 2.66-2.80 (m, 4H), 2.39 (dd, J = 12.0, 9.6 Hz, 1H), 600-1.75 (m, 2H), 1.02 (d, J = 6.4 Hz, 6H) ppm; 13C¹H-NMR (CDCl3, 125 MHz): δ 142.3 (C), 128.5 (CH), 128.4 (CH), 125.8 (CH), 69.1 (CH), 53.0 (CH3), 48.8 (CH), 37.1 (CH3), 32.1 (CH3), 23.2 (CH3), 23.0 (CH3) ppm; IR (neat): νmax (cm⁻¹) = 3281 (w), 2968 (w), 1452 (m), 1371 (m), 1088 (m), 1046 (m), 743 (m), 696 (s); HRMS (ESI): m/z calculated for C14H16N2O [M+H]⁺ 208.1666, found 208.1666.

1-phenyl-2-((S)-1-phenylethylamino)ethan-1-ol 9
Prepared from benzaldehyde (106 mg, 1 mmol, 1 equiv) and (S)-α-methylbenzyl isocyanide (162 µL, 1.2 mmol, 1.2 equiv) according to the modified procedure. Purification: column chromatography on silica gel (Cyclohexane/AcOEt/Et2N 50/50/5,
Chapter 2

R_\text{T} = 0.39). Isolated as a white solid (mixture of ~1:1 \((S,S)\) and \((R,S)\) diastereoisomers). Yield: 181 mg, 0.75 mmol, 75%.

NMR signals assigned based on reported spectral data [27]

\((S,S)\) diastereoisomer: \(^{1}H\)-NMR (CDCl\(_3\), 400 MHz): \(\delta 7.38-7.21\) (m, 10H), 4.56 (dd, \(J = 9.0, 3.5\) Hz, 1H), 3.76 (q, \(J = 6.5\) Hz, 1H), 2.76 (dd, \(J = 12.2, 3.5\) Hz, 1H), 2.62 (dd, \(J = 12.2, 9.0\) Hz, 1H), 1.38 (d, \(J = 6.5\) Hz, 3H) ppm; \(^{13}C\)-NMR (CDCl\(_3\), 125 MHz): 145.4 (C), 141.9 (C), 130.2 (C), 129.0 (CH), 128.6 (CH), 127.9 (CH), 125.9 (CH), 122.4 (CH), 73.3 (CH), 55.6 (CH\(_2\)), 18.5 (CH\(_3\)) ppm; IR (neat): v\(_{\text{max}}\) (cm\(^{-1}\)) = 3370 (m), 2850 (w), 1473 (s), 1454 (m), 1215 (w), 1099 (w), 758 (s), 698 (s), 536 (m); HRMS (ESI): m/z calculated for C\(_{13}\)H\(_{20}\)NO \([M+H]^+\) 242.1439, found 242.1527.

\(2\)-(\((2,6\text{-dimethylphenyl})amino\)-1-phenylethan-1-ol 11a
Prepared from benzaldehyde (106 mg, 1 mmol, 1 equiv) and 2,6-dimethylphenyl isocyanide (157 mg, 1.2 mmol, 1.2 equiv) according to the modified procedure. Purification: column chromatography on silicagel (Cyclohexane/AcOEt/MeOH 87:13:1 R\(_T = 0.23\)). Isolated as a colorless oil. Yield: 120 mg, 0.50 mmol, 50%.

\(^{1}H\)-NMR (CDCl\(_3\), 400 MHz): \(\delta 7.29-7.40\) (m, 5H), 7.02 (d, \(J = 7.5\) Hz, 2H), 6.87 (t, \(J = 1.6\) Hz, 1H), 4.81 (dd, \(J = 8.8, 3.7\) Hz, 1H), 3.50 (br, 1H), 3.27 (dd, \(J = 12.6, 3.7\) Hz, 1H), 3.14 (dd, \(J = 12.6, 8.8\) Hz, 1H), 2.29 (s, 6H) ppm; \(^{13}C\)-NMR (CDCl\(_3\), 125 MHz): \(\delta 145.2\) (C), 142.3 (C), 129.9 (C), 129.0 (CH), 128.6 (CH), 127.9 (CH), 125.9 (CH), 122.4 (CH), 73.3 (CH), 55.6 (CH\(_2\)), 18.5 (CH\(_3\)) ppm; IR (neat): v\(_{\text{max}}\) (cm\(^{-1}\)) = 3370 (m), 2850 (w), 1473 (s), 1454 (m), 1099 (m), 1061 (m), 764 (s), 741 (m), 702 (s); HRMS (ESI): m/z calculated for C\(_{13}\)H\(_{20}\)NO \([M+H]^+\) 242.1439, found 242.1527.

\(1\)-(\((2,6\text{-dimethylphenyl})amino\)-4-phenylbutan-2-ol 11b
Prepared from 3-phenylpropanal (134 mg, 1 mmol, 1 equiv) and 2,6-dimethylphenyl isocyanide (157 mg, 1.2 mmol, 1.2 equiv) according to the modified procedure. Purification: column chromatography on silicagel (Cyclohexane/AcOEt/MeOH 80:20:1 R\(_T = 0.37\)). Isolated as a colorless oil. Yield: 132 mg, 0.49 mmol, 49%.

\(^{1}H\)-NMR (CDCl\(_3\), 400 MHz): \(\delta 7.32\) (t, \(J = 7.6\) Hz, 2H), 7.20-7.25 (m, 3H), 7.04 (d, \(J = 8.0\) Hz, 2H), 6.89 (t, \(J = 8.0\) Hz, 1H), 3.82 (sept, \(J = 3.5\) Hz, 1H), 3.10 (dd, \(J = 3.0\) Hz, \(J = 12.3\) Hz, 1H), 2.68-2.92 (m, 4H), 2.32 (s, 6H), 1.77-1.91 (m, 2H) ppm; \(^{13}C\)-NMR (CDCl\(_3\), 125 MHz): \(\delta 145.5\) (C), 141.9 (C), 130.2 (C), 129.0 (CH), 128.6 (CH), 128.5 (CH), 126.0 (CH), 122.6 (CH), 70.7 (CH), 54.3 (CH\(_2\)), 36.8 (CH\(_3\)), 32.1 (CH\(_2\)), 18.5 (CH\(_3\)) ppm; IR (neat): v\(_{\text{max}}\) (cm\(^{-1}\)) = 3380 (w), 2927 (m), 1473 (s), 1454 (s), 1215 (w), 1099 (w), 764 (s), 748 (m), 698 (s); HRMS (ESI): m/z calculated for C\(_{13}\)H\(_{20}\)NO \([M+H]^+\) 270.1852, found 270.1862.

\(2\)-(pentylamino)-1-phenylethan-1-ol 12
n-pentyl isocyanide (151 \(\mu\)L, 1.2 mmol, 1.2 equiv) was added to a solution of benzaldehyde (106 mg, 1 mmol, 1 equiv), pyridine oxide (9.5 mg, 0.1 mmol, 0.1 equiv), and SiCl\(_4\) (126 \(\mu\)L, 1.1 mmol, 1.1 equiv) in 2 mL dry dichloromethane cooled at -20 °C. After stirring for 4 h at -20 °C, BH\(_3\)NH\(_2\) (46 mg, 1.5 mmol, 1.5 equiv) was added. The cooling bath was removed and the reaction mixture was stirred for another 3 hours. Next, the mixture was diluted (in three portions) with 10 mL CH\(_2\)Cl\(_2\) and transferred (cautiously, gas evolution) to an aqueous solution of Na\(_2\)CO\(_3\) 10 wt% (20 mL). The mixture was stirred for 30 minutes at room temperature. The solution was filtered and the filter was washed with another 10 mL CH\(_2\)Cl\(_2\). The layers were separated and the aqueous layer was extracted with 20 mL CH\(_2\)Cl\(_2\) in two portions. The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Purification: column chromatography on silicagel (AcOEt/MeOH 100/5/0.5, R\(_T = 0.45\)). Isolated as an off-white solid. Yield: 108 mg, 0.52 mmol, 52%.
Synthesis of β-Amino Alcohols from Aldehydes and Isocyanides

m.p.: 53.4-59.4 °C; 1H-NMR (CDCl₃, 400 MHz): δ 7.22-7.33 (m, 5H), 4.70 (dd, J = 8.8, 3.6 Hz, 1H), 2.75 (dd, J = 12.0, 3.6 Hz, 1H), 2.66 (dd, J = 12.0, 8.8 Hz, 1H), 2.47-2.60 (m, 2H), 2.13-2.14 (m, 3H), 0.85 (t, J = 7.2 Hz, 3H) ppm; 13C{1H}-NMR (CDCl₃, 125 MHz): δ 143.4 (C), 128.4 (CH), 127.4 (CH), 125.9 (CH), 71.8 (CH), 57.4 (CH₂), 49.6 (CH₂), 29.7 (CH₃), 29.5 (CH₃), 22.6 (CH₃), 14.1 (CH₃) ppm; IR (neat): νmax (cm⁻¹) = 2922 (w), 2820 (w), 1450 (m), 1421 (m), 1113 (m), 1088 (m), 872 (m), 752 (m), 696 (s), 552 (s); HRMS (ESI): m/z calculated for C₁₃H₂₂NO [M+H⁺]⁺ 208.1696, found 208.1687.

2-(tert-butylamino)-1-phenylethan-1-ol (chloride salt) 4b
Prepared from benzaldehyde (531 mg, 5 mmol, 1 equiv) and tert-butyl isocyanide (680 µL, 6 mmol, 1.2 equiv) according to the general procedure. Purification: precipitation as hydrochloride salt with HCl (4N in dioxane) from methyl tert-butyl ether. Isolated as a white solid. Yield: 1070 mg, 0.93 mmol, 93%.

m.p.: decomposes upon heating; 1H-NMR (DMSO-d₆, 400 MHz): δ 9.40 (m, 1H), 8.52 (m, 1H), 7.34-7.41 (m, 4H), 7.28 (m, 1H), 4.97 (dd, J = 10.0, 2.0 Hz, 1H), 2.97 (m, 1H), 2.86 (m, 1H), 2.47 (m, 1H), 1.28 (s, 9H) ppm; 13C{1H}-NMR (DMSO-d₆, 125 MHz): δ 141.9 (C), 128.4 (CH), 127.8 (CH), 126.1 (CH), 88.8 (CH), 56.3 (CH), 48.4 (CH₂), 25.0 (CH₃) ppm; IR (neat): νmax (cm⁻¹) = 2970 (w), 1541 (w), 1474 (w), 1223 (m), 1088 (m), 754 (m), 700 (s), 629 (m), 561 (s); HRMS (ESI): m/z calculated for C₁₂H₂₀NO [M+H⁺]⁺ 194.1540, found 194.1539.

(R)-2-(tert-butylamino)-1-phenylethan-1-ol 4b
Tert-butyl isocyanide (75 µL, 0.6 mmol, 1.2 equiv) was dissolved in 0.5 mL dry dichloromethane and added via syringe pump over 4 h to a solution of benzaldehyde (53 mg, 0.5 mmol, 1 equiv), (S,S)-14 (21 mg, 0.025 mmol, 0.05 equiv), and SiCl₄ (63 µL, 0.55 mmol, 1.1 equiv) in 0.5 mL dry dichloromethane cooled to -78 °C. When the addition was over, the mixture was let to stir at -78 °C for another 2 h. BH₃NH₃ (31 mg, 1 mmol, 2 equiv) was then added and the cooling bath was removed. The mixture was stirred for 1 h at room temperature. Next, the mixture was diluted (in three portions) with 10 mL CH₂Cl₂ and transferred (cautiously, gas evolution!) to an aqueous solution of Na₂CO₃ 10 wt% (20 mL). The mixture was stirred for 30 minutes at room temperature. The solution was filtered and the filter was washed with another 10 mL CH₂Cl₂. The layers were separated and the aqueous layer was extracted with 20 mL CH₂Cl₂ in two portions. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. Purification: column chromatography on silicagel (cyclohexane/CHCl₃/Et₃N 75/25/5, Rf = 0.20). Isolated as an off-white solid. Yield: 76 mg, 0.38 mmol, 79%.

Spectral data corresponds to that of racemic 4b. [α]D²⁰ = - 76.5 °C (c = 1.0, CHCl₃), lit. [α]D²⁰ = - 80 °C (c = 1.0, CHCl₃) for (R)-4b. RP-HPLC (Chirobiotic T column, MeCN/MeOH/CH₂Cl₂/Et₃N 70/30/0.5/2, flow rate 1.8 mL/min, UV detection at 256 nm, t₀ (R) = 8.15 min, t₀ (S) = 9.05 min, ee = 99%)
References and Notes


[11] D. Prat, J. Hayler, A. Wells, Green Chem. 2014, 16, 4546-4551. Since solvents have a major impact on the sustainability of a chemical process, the use of ethyl acetate is certainly a green advantage. On the other hand, the use of stoichiometric SiCl₄ which does not contribute any atoms to the product is detrimental from the sustainability perspective.


[13] Ammonia borane has been extensively studied as hydrogen storage material and it is less known as reducing agent in organic synthesis but it shows several advantages for this purpose, including good

[14] Assuming all three hydrogen atoms are available for the reaction and since two hydrides are required for the imidoyl chloride reduction this corresponds to 2.25 fold excess.

[15] Unreacted aldehydes are converted to the corresponding alcohols by BH$_3$NH$_3$.


[17] Purification of these compounds on silicagel column proved difficult.


Versatility of Trityl Isocyanide in Ugi-type Reactions

Abstract: In this chapter we describe the versatile application of triphenylmethyl (trityl) isocyanide in multicomponent chemistry. This reagent can be employed as cyanide source in the Strecker reaction and as a convertible isocyanide in the preparation of N-acyl amino acids via Ugi 4CR/detritylation and free imidazo[1,2-a]pyridin-3-amines via Groebke-Blackburn-Bienaymé 3CR condensation/deprotection.

Introduction

Multicomponent reactions (MCRs) – reactions in which three or more reagents are combined to selectively form a product containing the majority of atoms in the starting materials – represent an important tool in modern organic synthesis.\[1\] Although multicomponent chemistry dates back to the early days of organic chemistry, it is a field in continuous evolution, as the improvement of existing MCRs and the development of novel reactions remain active areas of research.\[2\] Among MCRs, isocyanide-based reactions (IMCRs) occupy a central position because of their remarkable diversity and high potential for applications. This chemistry flourished on the unique ability of isocyanides, reagents with a formally divalent carbon atom, to engage in multi-bond formation processes with both nucleophilic and electrophilic reaction partners.

Mechanistically, numerous variants of IMCRs (e.g. Ugi 4CR, Ugi-azide 4CR, Groebke-Blackburn-Bienaymé 3CR, etc.) are centered around the addition of an isocyanide to an iminium species and subsequent trapping of the resulting nitrilium ion intermediate by various nucleophiles, both intra- and intermolecularly (Figure 1).\[3\] In the classical Ugi 4CR reaction,\[4\] a carboxylate anion adds to the nitrilium intermediate and this α-adduct rearranges towards the more stable dipeptidic structure; the Groebke-Blackburn-Bienaymé (GBB)\[5\] reaction is a version of the Ugi reaction with an amidine/pyridinamine component in which the internal nitrogen nucleophile captures the nitrilium ion to yield the imidazo[1,2-\alpha]pyridine heterocyclic system after deprotonation/tautomerization. It is interesting to note that Ugi-type chemistry is closely related to the very first discovered multicomponent reaction, the Strecker synthesis combining amines, aldehydes and HCN to give α-amino nitriles.\[6\] In fact, Ugi reactions can be regarded as higher homologue Strecker processes involving N-substituted cyanide addition to iminium species; initially, N-substituted Strecker products are generated from this interaction and these positively charged reactive intermediates evolve towards more stable structures by nucleophilic addition.

With this perspective in mind, we wondered whether we could unify the Ugi and Strecker reactions by exploiting a disregarded reaction pathway of the common nitrilium ion intermediate in Ugi-type additions: fragmentation by $\equiv N^+–R$ heterolytic bond cleavage in an α-amino nitrile and a carbocationic species. The prerequisites for this atypical reactivity would be a labile N–R bond and a relatively stable R$^+$ fragment. We hypothesized that the triphenylmethyl (trityl) substituent would comply with these requirements and decided to explore the various reaction pathways of the N-triphenylmethyl nitrilium ion resulting from the interaction of trityl isocyanide (TrNC) with imines.
Results and Discussion

Reports describing trityl isocyanide and its use in organic synthesis are scarce\[^7\] and to the best of our knowledge there are no applications of this reagent in multicomponent chemistry. Remarkably, trityl isocyanide exhibits distinct favorable physical properties (high stability, crystallinity and absence of unpleasant odor) which combined with straightforward options for follow-up chemistry recommend it as a convenient reagent for synthesis.

While performing the Ugi condensation between trityl isocyanide, imine 1 and acetic acid under typical reaction conditions, we were pleased to observe the formation of the Strecker product 2a in roughly the same amount as the Ugi product 3i, together with the corresponding amount of trityl ethyl ether (Table 1, entry 2). This initial result confirmed the viability of the nitrilium ion fragmentation pathway in the case of N-trityl substitution.

Next, we pursued complete chemoselectivity control by tuning the reaction conditions. With the more acidic trifluoroacetic acid leading to a slight preference for the α-amino nitrile (66% selectivity, entry 3)\[^8\] we reasoned that a non-nucleophilic counterion for the iminium would provide the Strecker product exclusively. Indeed, strong Brønsted acids such as p-TsOH give the Strecker product almost exclusively within 1 h, with only traces of the Ugi 3CR product 3iii (resulting from capture of the nitrilium ion by water) as a side product.\[^9\] Importantly, the acid can now be used in catalytic amounts (10 mol%) since the α-cyano substitution significantly reduces the basicity of the N-aryl amine product compared to that of the starting imine and turnover is favorable. Other similar acids (HClO\(_4\), HCl, MeSO\(_3\)H) give comparable performance; interestingly, even weak Brønsted acid such as pyridinium p-toluenesulfonate (PPTS) can catalyze the reaction. Since we anticipated that for less basic substrates the reaction would require a relatively stronger...
We chose p-TsOH as the catalyst for studying the scope. It was found beneficial to preform the imine before the isocyanide addition since the one-stage three component condensation is slower and less clean (entry 6). In our hands, preforming the imine overnight in CH$_2$Cl$_2$ with powdered 3Å MS gave the best result for the sequential (two-stage) three component condensation. Other solvents can be used for the reaction, but the isocyanide dissolves best in CH$_2$Cl$_2$. A scavenger for the trityl cation is mandatory (EtOH).

To our delight, this reactivity could be extended to a diverse set of inputs and good yields were obtained for a series of Strecker products (Table 2). Substituted (hetero)aromatic aldehydes, aliphatic aldehydes (including bulky pivalaldehyde) and even ketones were accepted as carbonyl components in the reaction. Enolizable aldehydes were found to be problematic as isobutyraldehyde gave a complex reaction mixture in combination with 4-bromoaniline (entry 2h); however, with 2-amino-6-chloropyridine the imine appeared to be more stable and the Strecker product was isolated in good yield (entry 2l). Notably, the α-amino nitrile of 2-nitrobenzaldehyde cyclodehydrates to the indazole N-oxide 2c as
Versatility of Trityl Isocyanide in Ugi-type Reactions

previously reported. The amine scope includes both electron-rich and electron-poor anilines. In the latter case, the reaction is slow and ethanol addition to the imine is a competing process; heating was found to be beneficial for conversion. The use of aliphatic amines (benzylamine) was also validated, but in this case the Strecker product 2n is more basic and the catalyst turnover is reduced. Bulky anilines (mesidine) and secondary amines gave poor conversions to the expected products (entries 2m and 2o).

We propose the following mechanism for the Strecker synthesis using trityl isocyanide, depicted in Scheme 1. The isocyanide adds to the protonated imine generating the

Table 2. Scope of the Strecker reaction using trityl isocyanide

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Reaction Conditions</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>85%</td>
</tr>
<tr>
<td>Me</td>
<td>N</td>
<td>Me</td>
<td>Me</td>
<td>--</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>88%</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>n.d. [a]</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>64% [a]</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>64% [a]</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>64% [a]</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>72% [a]</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>--</td>
<td>trace [%]</td>
</tr>
</tbody>
</table>

[a] Standard conditions: aldehyde and amine in CH₂Cl₂ with 3Å MS for 20 h, then (diluted in EtOH) p-TsOH·H₂O (10 mol%) and TrNC (1.1 equiv) for 3-24 h at room temperature; [b] isolated yields; [c] yield based on crude NMR analysis; [d] reaction performed at 50 °C; [e] isolated yield; product not stable on silica gel column.
nitrilium ion. This intermediate undergoes C-N fragmentation releasing the Strecker product and the trityl cation as a byproduct. This reactive species is trapped by ethanol to form trityl ethyl ether regenerating the acid catalyst.

The existence of the nitrilium ion as a key intermediate in the reaction is evidenced by the minor impurity 3iii which corresponds to its trapping by a water molecule. This side reaction depends mostly on the availability of water: if the imine is preformed in the presence of molecular sieves only traces of 3iii are observed. Secondly, when an internal nucleophile is present the nitrilium ion can be trapped intramolecularly, as observed in the series of pyridine-2-amines (which will be discussed in a following section). In this case, as we will show, the fragmentation pathway is still viable for less nucleophilic pyridines (due to steric and/or electronic reasons).

Importantly, this mechanism implies the stoichiometric generation of trityl ethyl ether as byproduct. This correlation is indeed observed with relatively basic imines, whereas in the case of less basic substrates we saw a full conversion of the isocyanide to this byproduct (including the 10 mol% excess). We attribute this fact to the relatively high acidity of the protonated Strecker products (which buffers the p-TsOH catalyst at the end of the reaction) that can promote an S_N1-type solvolysis of trityl isocyanide with release of HCN as depicted in the bottom section of Scheme 1. This acid-catalyzed process was investigated in further details, as shown in Table 3. We found a good correlation of the extent of solvolysis with the pK_a of the acid catalyst to support our premises.

### Table 3. Stability of Ph_3C-NC^{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Approx. pK_a</th>
<th>Conversion^{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>-</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>PPTS</td>
<td>5.1</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>4-CF_3-C_6H_4NH_3Cl</td>
<td>2.6</td>
<td>9%</td>
</tr>
<tr>
<td>4</td>
<td>4-CF_3-C_6H_4NH_3Cl</td>
<td>2.6</td>
<td>25%^{[d]}</td>
</tr>
<tr>
<td>5</td>
<td>2a • p-TsOH</td>
<td>&lt;2.6^{[d]}</td>
<td>22%</td>
</tr>
</tbody>
</table>

{[a] Standard conditions: trityl isocyanide (0.22 mmol), catalyst (0.02 mmol) in 0.4 mL EtOH – CH_2Cl_2 (1:1) for 1 h at room temperature; [b] conversion based on crude NMR using mesitylene as internal standard; [c] performed at 50 °C; [d] based on NMR analysis of a mixture of 4-CF_3-C_6H_4NH_3Cl and 2a.}
Given the fact that PPTS promotes the model Strecker reaction with N-benzylideneaniline but not the isocyanide solvolysis, we conclude that the nitrilium fragmentation is the major reaction pathway. The isocyanide solvolysis and slow release of HCN is a minor pathway which is relevant only for relatively non-basic substrates, at high conversions of imine.

Numerous variations of the Strecker reaction have been reported, but all procedures invariably rely on toxic reagents (KCN, CuCN, Zn(CN)₂, TMSCN, etc.). Trityl isocyanide is a convenient and safe cyanide surrogate and the possibility to recover and recycle trityl ethyl ether in the isocyanide synthesis makes it an attractive novel cyanation reagent in Strecker reactions.

Scheme 1. Mechanism of the Strecker reaction with trityl isocyanide.

After identifying reaction conditions to bias the fragmentation pathway of the nitrilium ion, we turned our attention to the classical Ugi 4CR condensation. Pleasingly, by resorting to a less polar solvent (CH₂Cl₂) we were able to switch the selectivity in favor of the Ugi products (stoichiometric carboxylic acids were used instead of catalytic p-TsOH) and acceptable yields were obtained with all possible combinations of aliphatic/aromatic inputs (Table 4). The moderate yields are due to slow reactions; the nitrilium ion...
fragmentation was not observed by NMR analysis of the crude product, although it cannot be excluded for the low-yielding examples with anilines as the amine component (products 3b and 3c). This is in accordance with the nucleophilicity of the carboxylate anions that are able to trap the nitrilium ion before fragmentation.\textsuperscript{[13]} Noteworthy is the improved yield (90% vs. 77%) obtained for the bicyclic product 3d with the less nucleophilic trityl isocyanide as compared with t-BuNC; the greater steric bulk of this isocyanide is in this case reflected in a better \textit{dr}, 33:1 (compared to 13:1 for the reported t-butyl substituted derivative).\textsuperscript{[14]}

While studying the cleavage of the trityl group under acidic conditions we observed the surprisingly facile hydrolysis of the initially forming primary amide to the carboxylic acid and decided to pursue this more interesting transformation. Stirring the Ugi products at room temperature in TFA for 4 h with the addition of 5 equiv of water is sufficient for complete conversion, whereas the ratios carboxylic acid/primary amide in the series accurately follow the ease of formation of a Münchnone intermediate (Scheme 2).\textsuperscript{[15]} less electron-dense tertiary amide groups (\textit{e.g.} \(R^2\) is Ar, 3b and 3c) are less able to assist the hydrolysis of the primary amide, whereas the conformationally restricted bicyclic scaffold hampers this transformation altogether.

Diluting the reaction mixture with ethanol before quenching allows for the isolation of the ethyl ester (shown for carboxylic acid 4a). This demonstrates the convenience and versatility of trityl isocyanide as convertible reagent in the Ugi 4CR to afford carboxylic acid derivatives by detritylation (Table 2).\textsuperscript{[16]}

\textbf{Scheme 2.} Mechanism of detritylation of Ugi products via the Münchnone.
Having established trityl isocyanide as a useful convertible reagent in Ugi condensations, we envisaged the extension of its application towards the synthesis of imidazo[1,2-a]pyridin-3-amines via a Groebke-Blackburn-Bienaymé/deprotection strategy. The imidazo[1,2-a]pyridine core is a widely employed scaffold in medicinal applications\textsuperscript{17} and the GBB reaction combining amidines, aldehydes and isocyanides is undoubtedly the most
straightforward way to access this framework, particularly in a combinatorial chemistry context. The 3- amino substituent serves as an ideal handle for further derivatization and for this reason several convertible isocyanides have been developed to allow the isolation of free imidazo[1,2-a]pyridin-3-amine derivatives by deprotecting GBB products.\[^{18}\] However, these methods generally employ harsh conditions, expensive and/or hazardous reagents and are not compatible with library synthesis. For instance, tert-octyl isocyanide (Walborsky’s isocyanide) leads to a GBB product than can be deprotected under relatively mild acidic conditions (TFA – CH₂Cl₂ 1:1, room temperature), but it is rather expensive and cannot be regenerated after the MCR deprotection sequence.\[^{18a}\]

We reasoned that trityl isocyanide would be a superior alternative in all aspects – cost, ease of deprotection and recyclability. The success of this strategy relies on the fate of the nitrilium ion intermediate, which should undergo intramolecular trapping by the pyridine nitrogen rather than fragmentation. Since the 6-chloro-2-aminopyridine input in the Strecker reaction with trityl isocyanide exclusively provided the α-amino nitrile over the imidazo[1,2-a]pyridine (Table 2, product 2I), we anticipated that the nucleophilicity of the pyridine would be the determining factor in the Groebke-Blackburn-Bienaymé MCR with this isocyanide. Thus, applying the optimized Strecker protocol to a series of 2-aminopyridines and aromatic and aliphatic aldehydes showed that the cyclization to the GBB products is favored (in most cases exclusively) for all tested inputs, with the anticipated exception of 6-substituted pyridines (Table 2, product 2I and Table 6, entry 6). Significant fragmentation of the nitrilium ion (GBB product to Strecker product ratio 5:1) was also observed for the electron-deficient 5-fluoropyridine. These results are in complete accordance with the propensity of the pyridine to engage in nucleophilic addition, influenced by both electronics and steric.\[^{19}\] As expected, the detritylation of the GBB products was facile (3 equiv of TFA, 3-24 h at 65 °C)\[^{20}\] and good yields were obtained for the overall preparation of imidazo[1,2-a]pyridin-3-amines.\[^{21}\] The exception was the use of anisaldehyde (entry 2; the reduced electrophilicity makes imine formation and isocyanide addition difficult) and pyrimidinamine (entry 5; the imine forms a stable hemiaminal with ethanol),\[^{11}\] respectively.
Finally, after investigating the selectivity of Strecker vs. Ugi reactions and GBB vs. Strecker reactions involving trityl isocyanide, we were curious to see which product would predominate in a system in which all three pathways are possible. We thus performed the Ugi 4CR with 5-fluoropyridine, pivalaldehyde, acetic acid and trityl isocyanide under our standard conditions.

Interestingly, this reaction was fully selective towards the GBB product with no evidence of the Strecker and Ugi products based on NMR analysis of the crude product. Not surprisingly, the addition of an external nucleophile (acetate) cannot compete with the intramolecular trapping of the nitrilium ion by the pyridine nitrogen even if it is relatively electron-deficient. Furthermore, the mild activation of the imine by a carboxylic acid instead of a strong Brønsted acid (possibly via hydrogen bonding rather than protonation) completely suppresses the nitrilium ion fragmentation towards the Strecker product (Scheme 3).
**Table 6. Scope of the GBB 3CR/deprotection sequence**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Main product, 6 or 2</th>
<th>Yield&lt;sup&gt;[b]&lt;/sup&gt;</th>
<th>6:2&lt;sup&gt;[c]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>65%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image" /></td>
<td>~20%</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image" /></td>
<td>71%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image" /></td>
<td>63%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image" /></td>
<td>~10%</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Image" /></td>
<td>50%</td>
<td>&lt;1:20</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Image" /></td>
<td>75%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8.png" alt="Image" /></td>
<td>56%</td>
<td>5:1</td>
</tr>
<tr>
<td>9</td>
<td><img src="image9.png" alt="Image" /></td>
<td>68%</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

[a] Standard conditions: preformed imine, p-TsOH•H₂O and TrNC (1.1 equiv) in CH₂Cl₂ and EtOH (1:1) for 2 days at room temperature, then TFA (3 equiv) for 3-24 h at 65 °C; [b] isolated overall yields; [c] ratio based on crude NMR analysis before deprotection of the GBB products.
Versatility of Trityl Isocyanide in Ugi-type Reactions

Scheme 3. Fate of the nitrilium ion intermediate in an Ugi 4CR with trityl isocyanide, pivalaldehyde, acetic acid and 5-fluoropyridine.

Trityl isocyanide can be easily synthesized via the formamide dehydration method.\textsuperscript{[22]} In our hands, POCl\(_3\) -mediated dehydration worked best, with 88% yield on a 10 g scale. In contrast with most other convertible isocyanides,\textsuperscript{[23]} our reagent can be regenerated in two simple steps, since both triphenylmethanol and trityl ethyl ether can be recovered after the multicomponent reaction/deprotection sequence and converted back to N-trityl formamide. Indeed, trityl ethyl ether was recovered after the Strecker reaction (2g) and the GBB/deprotection protocol (6i) in 85% and 83% yields, respectively, whereas after detritylation of Ugi product 3d, triphenylmethanol was recovered (90%) as depicted in Scheme 4. Overall, the C and N atoms that are delivered from the isocyanide to the multicomponent products originate from H\(_2\)NCHO.

Scheme 4. Regeneration of trityl isocyanide after MCR-deprotection sequence.
Conclusion

In summary, trityl isocyanide is a convenient, versatile reagent in multicomponent chemistry. It can be employed as a benign cyanide source in a formally cyanide-free Strecker synthesis and as a recyclable convertible isocyanide in the efficient preparation of N-acyl amino acids via Ugi 4CR/detritylation and free imidazo[1,2-a]pyridin-3-amine after GBB-3CR condensation/deprotection under mild conditions. The mechanisms of these three classical MCRs intersect at the common N-trityl nitrilium ion intermediate whose predictable reactivity can be exploited towards chemoselective transformations.

Experimental Section

General Remarks

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Cyclohexane was distilled prior to use. Dry dichloromethane was distilled over CaH$_2$ and stored under nitrogen on 4Å molecular sieves. All other solvents were used as purchased. All reactions were performed under air unless stated otherwise.

Melting points were recorded on a Büchi M-565 melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 (125.78 MHz for $^{13}$C) or Bruker Avance 400 (100.62 MHz for $^{13}$C) using the residual solvent as internal standard ($^1$H: δ 7.26 ppm, $^{13}$C($^1$H): δ 77.16 ppm for CDCl$_3$, $^1$H: δ 2.50 ppm, $^{13}$C($^1$H): δ 39.52 ppm for DMSO-d$_6$ and $^1$H: 3.31 ppm, $^{13}$C($^1$H): δ 49.00 ppm for CD$_3$OD). Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), sep (septet), br (broad singlet) and m (multiplet) or combinations thereof. Infrared (IR) spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm$^{-1}$. Electrospray Ionization (ESI) high-resolution mass spectrometry (HRMS) was carried out using a Bruker microTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Chiral SFC analysis of 3d was recorded using an Acquity UPC2 system with
Versatility of Trityl Isocyanide in Ugi-type Reactions

TrefoilTM column and MS Full Scan ESI detection from Waters. Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 μm, pore diameter 60Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO₂, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator).

1-tosyl-indole-3-carbaldehyde was prepared by tosylation of 3-formylindole as reported.⁴¹ Enantioenriched (99% ee) 1-pyrroline derivative used in the synthesis of 3d was generously provided by Dr. G. Barreca (Chemessentia)

General synthetic procedures

N-Trityl formamide
Triphenylmethanol (38 mmol, 1 equiv), formamide (76 mmol, 2 equiv), and acetic anhydride (38 mmol, 1 equiv) were dissolved in 100 mL acetic acid. Catalytic amount of sulfuric acid (250 µL) was added and the reaction mixture was stirred at 70 °C for 4 h. The mixture was allowed to cool to room temperature and poured into ice. The precipitate was filtered and washed with H₂O (2x 200 mL) and MTBE (2x 200 mL). The white solid was dried to afford the pure product. Yield: 9.66 g, 33.6 mmol, 88% yield.

Trityl isocyanide
Tritylformamide (32 mmol, 1 equiv) and triethylamine (192 mol, 6 equiv) were dissolved in 100 mL dry CH₂Cl₂ and cooled to -78 °C under N₂ atmosphere. Phosphorousoxychloride (40 mmol, 1.25 equiv) was diluted in 5 mL CH₂Cl₂ and added dropwise at -78 °C. The reaction mixture was allowed to warm to -30 °C and stirred for 3 h at this temperature. During the reaction the color of the mixture turned brown. The solution was then transferred to an extraction funnel and washed with 150 mL of saturated NaHCO₃ solution and the aqueous layer was extracted with CH₂Cl₂ (2x 150 mL). The solvent was evaporated and the resulting solid was triturated with methanol. The filtrate was concentrated and a second batch of product was obtained after column chromatography on silicagel (cyclohexane/MTBE 100/3, Rf = 0.5). Isolated as an off-white solid. Yield: 7.76 g, 28.9 mmol, 88%.

Procedure Strecker reaction (Procedure A)
The amine (0.5 mmol, 1 equiv) and aldehyde (0.5 mmol, 1 equiv) were dissolved in 0.5 mL CH₂Cl₂. 3Å powdered molecular sieves were added (250 mg) and the mixture was stirred at room temperature for 20 h. Then, the mixture was diluted with EtOH (0.5 mL). p-toluenesulfonic acid hydrate (0.05 mmol, 0.1 equiv) was added and the mixture was stirred for 10 min before adding trityl isocyanide (0.55 mmol, 1.1 equiv). The mixture was then stirred for 1-24 h at room temperature. The reaction was quenched with NEt₃ (0.5 mmol, 1 equiv). The molecular sieves were removed by filtration over Celite, the filter was thoroughly washed with CH₂Cl₂ and the solution was concentrated under reduced pressure. The product was purified by chromatography on silicagel column.

Notes: conversion of the isocyanide to Ph₃C-OEt was monitored by TLC; if the reaction was not complete in 3 h, it was left to stir overnight (24 h total reaction time); some α-amino nitriles have limited stability under the isolation protocol (2n; likely 2f and 2d).

Procedure Ugi reaction (Procedure B)
The amine (0.5 mmol, 1 equiv) and aldehyde (0.5 mmol, 1 equiv) were dissolved in 0.5 mL CH₂Cl₂. 3Å powdered molecular sieves were added (250 mg) and the mixture was stirred at room temperature for 20 h. Then, the carboxylic acid (0.55 mmol, 1 equiv) and trityl isocyanide (0.55 mmol, 1.1 equiv) were added and the mixture was stirred for 72 h at room temperature. The molecular sieves were removed by filtration over Celite, the filter was thoroughly washed with CH₂Cl₂ and the solution was concentrated under reduced pressure. The product was purified by chromatography on silicagel column.
Procedure for deprotecting Ugi products (Procedure C)
The Ugi product (0.2 mmol) was dissolved in 0.4 mL trifluoroacetic acid. Water (1 mmol, 5 equiv) was then added and the intense yellow solution was stirred at room temperature for 4 hours. The solution was diluted in CH₂Cl₂ and quenched in 2M NaOH solution. The organic layer was separated and the aqueous layer was washed again with CH₂Cl₂. The aqueous layer was then acidified to pH = 1 with HCl 1M and extracted twice with AcOEt. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to give the pure N-acyl amino acid.

Procedure for Groebke-Blackburn-Bienaymé/detritylation (Procedure D)
The amine (0.5 mmol, 1 equiv) and aldehyde (0.5 mmol, 1 equiv) were dissolved in 0.5 mL CH₂Cl₂. 3Å powdered molecular sieves were added (250 mg) and the mixture was stirred at room temperature for 20 h. Then, the mixture was diluted with EtOH (0.5 mL). p-toluenesulfonic acid hydrate (0.05 mmol, 0.1 equiv) was added and the mixture was stirred for 10 min before adding trityl isocyanide (0.55 mmol, 1.1 equiv). The mixture was stirred for 48 h at room temperature. The molecular sieves were removed by filtration over Celite, the filter was thoroughly washed with CH₂Cl₂ and the solution was concentrated under reduced pressure. The crude mixture was redissolved in EtOH (2 mL) and trifluoroacetic acid (1.5 mmol, 3 equiv) was added. This solution was stirred at 65 °C for 3-24 h (reaction time based on TLC). The solution was diluted with CH₂Cl₂ and neutralized with 2M NaOH. The aqueous layer was extracted twice with CH₂Cl₂. The combined organic extract was dried over Na₂SO₄ and concentrated under reduced pressure. The product was purified by chromatography on silicagel column.

Note: compounds 6c and 6g coelute with N-trityl formamide (sideproduct resulting from the hydrolysis of unreacted isocyanide during the deprotection of the GBB products) and were further purified by acid-base extraction (with 1M KHSO₄ and 2M NaOH respectively).

Characterization of compounds

- **N-Trityl formamide**[^25]
  - m.p.: 198.7-201.4 °C; ¹H-NMR (CDCl₃, 400 MHz; rotamers observed in a 5:1 ratio): δ 8.37 (d, J = 2.0 Hz, 1H, R₂), 8.07 (d, J = 12.0 Hz, 1H, R₁), 7.39-7.28 (m, 10H, R₁ and 10H, R₂), 7.16 (dd, J = 8.0, 1.8 Hz, 5H, R₁ and 5H, R₂), 6.82 (d, J = 12.1 Hz, 1H, R₁), 6.66 (d, J = 2.0 Hz, 1H, R₂) ppm; ¹³C{¹H}-NMR (CDCl₃, 125 MHz): δ 169.3 (CH, R₁), 166.2 (CH, R₂), 144.6 (C, R₁), 144.4 (C, R₂), 128.8 (CH, R₁), 128.5 (CH, R₂), 128.0 (CH, R₁), 127.8 (CH, R₂), 127.3 (CH, R₁), 127.1 (CH, R₂), 70.6 (C, R₂), 69.8 (C, R₁) ppm; IR (neat): νmax (cm⁻¹) = 3226 (m), 3062 (s), 2910 (s), 1672 (w), 1442 (s), 1299 (m), 757 (s), 730 (s), 698 (s); HRMS (ESI): m/z calculated for C₂₀H₁₇NO [M+Na]⁺ 310.1202, found: 310.1198.

- **Trityl isocyanide**[^22b]
  - m.p.: 134.7-136.7 °C; ¹H-NMR (CDCl₃, 500 MHz): δ 7.38-7.32 (m, 9H), 7.26-7.21 (m, 6H) ppm; ¹³C{¹H}-NMR (CDCl₃, 125 MHz): δ 157.7 (C), 141.7 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 75.2 (C) ppm; IR (neat): νmax (cm⁻¹) = 3064 (s), 3049 (s), 2124 (m), 1490 (m), 1444 (m), 750 (m), 696 (s), 638 (s); HRMS (ESI): m/z calculated for C₂₀H₁₅N [M-NC]⁺ 243.1174, found: 243.1184.

- **2-phenyl-2-(phenylamino)acetonitrile 2a**[^24]
  - Prepared from benzaldehyde (53 mg, 0.5 mmol), aniline (47 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (3 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 15/1, Rf = 0.35). Isolated as a white solid. Yield: 88 mg, 0.425 mmol, 85%.
Versatility of Trityl Isocyanide in Ugi-type Reactions

m.p.: 82-83.7 °C; 1H-NMR (CDCl₃, 500 MHz): δ 7.62 (d, J = 6.8 Hz, 2H), 7.47 (d, J = 6.8 Hz, 3H), 7.30 (t, J = 7.8 Hz, 2H), 6.92 (t, J = 7.4 Hz, 1H), 6.79 (d, J = 8.0 Hz, 2H), 5.44 (s, 1H), 4.08 (br, 1H) ppm; 13C{1H}-NMR (CDCl₃, 125 MHz): δ 144.8 (C), 134.0 (C), 129.7 (CH), 129.6 (CH), 129.4 (CH), 127.3 (CH), 120.3 (CH), 118.3 (CN), 114.2 (CH), 50.2 (CH) ppm; IR (neat): v max (cm⁻¹) = 3334 (s), 3029 (s), 2196 (m), 1697 (s), 1598 (m), 1515 (s), 1488 (w), 1438 (s), 1346 (m), 1287 (m), 1244 (s), 923 (s), 750 (m), 690 (m), 598 (s); HRMS (ESI): m/z calculated for C₁₄H₂₁N₂ [M+H]^+ 209.1073, found: 209.1082.

2-(phenylamino)-2-(4(trifluoromethyl)phenyl)acetonitrile 2b

Prepared from 4-trifluoromethylbenzaldehyde (87 mg, 0.5 mmol), aniline (47 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (2 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 12/1, Rf = 0.2). Isolated as a yellow solid. Yield: 128 mg, 0.463 mmol, 93%.

m.p.: 80.2-88.8 °C; 1H-NMR (CDCl₃, 500 MHz): δ 7.74 (d, J = 14.6, 8.3 Hz, 4H), 7.29 (t, J = 7.5 Hz, 2H), 6.94 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 7.8 Hz, 2H), 5.53 (d, J = 8.6 Hz, 1H), 4.16 (d, J = 8.6 Hz, 1H) ppm; 13C{1H}-NMR (CDCl₃, 125 MHz): δ 144.3 (C), 137.9 (C), 131.9 (C, J CF₂ = 32.8 Hz), 129.8 (CH), 127.8 (CH), 126.4 (CH, J CF₂ = 3.6 Hz), 123.8 (C, J CF₂ = 273.5 Hz), 120.9 (CH), 117.7 (CN), 114.5 (CH), 49.9 (CH) ppm; IR (neat): v max (cm⁻¹) = 3334 (s), 3058 (s), 2255 (s), 1689 (s), 1604 (m), 1500 (m), 1326 (w), 1164 (m), 1128 (m), 1106 (m), 844 (s), 757 (s), 692 (w), 624 (s), 501 (s). HRMS (ESI, negative ion mode): m/z calculated for C₁₅H₁₄F₂N₂ [M-H]^− 275.0802, found: 275.0811.

3-cyano-2-(p-tolyl)-2H-indazole 1-oxide 2c

Prepared from 2-nitrobenzaldehyde (76 mg, 0.5 mmol), p-toluidine (54 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (1 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 3/1, Rf = 0.24). Isolated as a yellow solid. Yield: 115 mg, 0.46 mmol, 92%.

m.p.: 201.1-203.2 °C; 1H-NMR (CDCl₃, 400 MHz): δ 7.84 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.47-7.37 (m, 4H), 2.48 (s, 3H) ppm; 13C{1H}-NMR (CDCl₃, 125 MHz): δ 142.2 (C), 130.5 (CH), 129.1 (C), 128.7 (CH), 128.5 (C), 127.5 (CH), 126.9 (CH), 122.7 (C), 118.9 (CH), 114.7 (CH), 110.8 (C), 92.1 (C), 21.6 (CH₃) ppm; IR (neat): v max (cm⁻¹) = 3334 (s), 3068 (s), 2196 (m), 1697 (s), 1598 (m), 1515 (s), 1488 (w), 1438 (s), 1346 (m), 1242 (m), 808 (s), 744 (m), 688 (s), 584 (s); HRMS (ESI): m/z calculated for C₁₅H₁₄F₂N₂O [M+H]^+ 275.0976, found: 250.0976.

2-(4-methoxyphenyl)-2-(p-tolylamino)acetonitrile 2d

Prepared from anisaldehyde (68 mg, 0.5 mmol), toluidine (54 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (24 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 10/1, Rf = 0.26). Isolated as an orange solid. Yield: 81 mg, 0.32 mmol, 64% (co-elutes with the corresponding imine, reported yield is corrected for 93 wt% purity).

m.p.: 97-102.5 °C; 1H-NMR (CDCl₃, 500 MHz): δ 7.51 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 7.9 Hz, 2H), 6.96 (d, J = 7.9 Hz, 2H), 6.70 (d, J = 7.7 Hz, 2H), 5.34 (d, J = 8.3 Hz, 1H), 3.87 (d, J = 6.1 Hz, 1H), 3.84 (s, 3H), 2.30 (s, 3H) ppm; 13C{1H}-NMR (CDCl₃, 125 MHz): δ 160.4 (C), 142.5 (C), 130.1 (CH), 129.8 (C), 128.7 (CH), 126.2 (C), 118.7 (CN), 114.7 (CH), 114.5 (CH), 55.5 (CH₃), 50.1 (CH), 20.6 (CH₃) ppm; IR (neat): v max (cm⁻¹) = 3348 (s), 2956 (s), 2298 (s), 2196 (m), 1679 (s), 1601 (m), 1510 (w), 1261 (m), 1231 (m), 1180 (s), 1027 (s), 811 (m), 611 (w), 509 (m); HRMS (ESI): m/z calculated for C₂₃H₂₈NO₂ [M-CN]^− 326.1226, found: 226.1240.
Chapter 3

2-[(3-iodophenyl)amino]-2-[(1-tosyl-1H-indol-3-yl)acetonitrile 2e
Prepared from N-tosyl-3-indolecarboxaldehyde (149 mg, 0.5 mmol), 3-iodoaniline (110 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (24 h reaction time). Purification: column chromatography on silicagel (cyclohexane/ACOEt 8/1, Rf = 0.25). Isolated as a yellow solid. Yield: 232 mg, 0.44 mmol, 88%.

m.p.: 164.2-168.2 °C; 1H-NMR (DMSO-d6, 500 MHz): δ 7.97 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 7.9 Hz, 1H), 7.46-7.39 (m, 3H), 7.34 (t, J = 7.6 Hz, 1H), 6.28 (d, J = 9.2 Hz, 1H), 2.32 (s, 3H) ppm; 13C{1H}-NMR (DMSO-d6, 125 MHz): δ 147.2 (C), 146.0 (C), 134.4 (C), 133.8 (C), 131.1 (CH), 130.5 (CH), 127.5 (C), 126.9 (CH), 125.7 (CH), 125.1 (CH), 123.7 (CH), 121.9 (CH), 121.8 (CH), 120.4 (CH), 118.4 (CN), 116.1 (C), 113.4 (CH), 113.2 (CH), 95.6 (C), 41.0 (CH), 21.1 (CH3) ppm; IR (neat): νmax (cm⁻¹) = 3402 (s), 2986 (s), 2227 (s), 1604 (m), 1508 (w), 1313 (s), 1130 (s), 1031 (s), 746 (m), 693 (m); HRMS (ESI): m/z calculated for C23H18INO3 [M-CN]⁺ 501.0128, found: 501.0154.

2-[(4-chlorophenyl)amino]-2-[(4-methoxyphenyl)acetonitrile 2f
Prepared from 4-chlorobenzaldehyde (70 mg, 0.5 mmol), p-anisidine (62 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (3 h reaction time). Purification: column chromatography on silicagel (cyclohexane/ACOEt 8/1, Rf = 0.25). Isolated as a pale yellow solid. Yield: 60 mg, 0.22 mmol, 44%.

m.p.: 85-87.2 °C; 1H-NMR (CDCl3, 500 MHz): δ 7.53 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 6.74 (d, 8.9 Hz, 2H), 5.32 (d, J = 6.4 Hz, 1H), 3.85 (d, J = 6.4 Hz, 1H), 3.76 (s, 3H) ppm; 13C{1H}-NMR (CDCl3, 125 MHz): δ 154.3 (C), 138.3 (C), 135.5 (C), 132.7 (C), 129.5 (CH), 128.7 (CH), 118.2 (CN), 116.6 (CH), 115.1 (CH), 55.7 (CH3), 51.1 (CH) ppm; IR (neat): νmax (cm⁻¹) = 3334 (s), 3035 (s), 1697 (s), 1598 (m), 1494 (w), 1244 (m), 1029 (s), 923 (s), 750 (m), 690 (m) 597 (s); HRMS (ESI): m/z calculated for C15H13ClN2O [M-CN]⁺ 246.0700, found: 246.0685.

3,3-dimethyl-2-(phenylamino)butanenitrile 2g
Prepared from pivalaldehyde (43 mg, 0.5 mmol), aniline (47 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (1 h reaction time). Purification: column chromatography on silicagel (cyclohexane/ACOEt 12/1, Rf = 0.44). Isolated as a white solid. Yield: 84 mg, 0.445 mmol, 89%.

m.p.: 72.4-74.7 °C; 1H-NMR (CDCl3, 500 MHz): δ 7.26 (t, J = 7.9 Hz, 2H), 6.87 (t, J = 7.9 Hz, 1H), 6.74 (d, J = 8.3 Hz, 2H), 3.94 (s, 1H), 1.19 (s, 9H) ppm; 13C{1H}-NMR (CDCl3, 125 MHz): δ 145.5 (C), 129.7 (CH), 120.2 (CH), 118.9 (CN), 114.4 (CH), 56.7 (CH), 34.8 (C), 26.3 (CH3) ppm; IR (neat): νmax (cm⁻¹) = 3402 (s), 2986 (s), 2228 (w), 1605 (s), 1508 (s), 1313 (m), 1130 (m), 874 (m), 750 (s), 692 (s) 507 (m); HRMS (ESI): m/z calculated for C12H14N2 [M-H]⁻ 189.1386, found: 189.1399.

1-(phenylamino)cyclohexane-1-carbonitrile 2i
Prepared from cyclohexanone (49 mg, 0.5 mmol), aniline (47 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (1 h reaction time). Purification: column chromatography on silicagel (cyclohexane/ACOEt 10/1, Rf = 0.35). Isolated as a pale yellow solid. Yield: 88 mg, 0.445 mmol, 89%. 
Versatility of Trityl Isocyanide in Ugi-type Reactions

m.p.: 70.2-72.8 °C; ^1H-NMR (CDCl_3, 500 MHz): δ 7.25 (t, J = 6.8 Hz, 2H), 6.95-6.86 (m, 3H), 3.59 (br, 1H), 2.38-2.31 (m, 2H), 1.83-1.76 (m, 2H), 1.75-1.61 (m, 5H), 1.37-1.28 (m, 1H) ppm; ^13C([H]-NMR (CDCl_3, 125 MHz): δ 143.5 (C), 129.4 (CH), 121.2 (CN), 120.8 (CH), 117.8 (CH), 54.6 (C), 36.8 (CH_3), 25.0 (CH_3), 22.3 (CH_3) ppm; IR (neat): vmax (cm⁻¹) = 3350 (s), 2929 (s), 2856 (s), 2227 (s), 1598 (m), 1473 (w), 1278 (m), 1205 (s), 1149 (m), 1051 (s), 813 (w), 676 (s), 574 (s); HRMS (ESI): m/z calculated for C_{13}H_{16}N_2 [M+H]^+ 201.1386, found: 201.1401.

2-[[4-chlorophenyl]amino]-2-(3,5-dimethoxyphenyl)acetonitrile 2i
Prepared from 3,5-dimethoxybenzaldehyde (78 mg, 0.5 mmol), 4-chloroaniline (64 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (24 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 8/1, R_f = 0.15). Isolated as a white solid. Yield: 125 mg, 0.415 mmol, 83%.

m.p.: 126.4-129.5 °C; ^1H-NMR (CDCl_3, 500 MHz): δ 7.22 (d, J = 8.2 Hz, 2H), 6.72-6.67 (m, 4H), 6.49 (s, 1H), 5.31 (s, 1H), 4.10 (br, 1H), 3.81 (s, 6H) ppm; ^13C([H]-NMR (CDCl_3, 125 MHz): δ 161.6 (C), 143.3 (C), 135.7 (C), 129.6 (CH), 125.3 (C), 117.9 (CN), 115.5 (CH), 105.3 (CH), 101.4 (CH), 55.7 (CH), 50.4 (CH_3) ppm; IR (neat): vmax (cm⁻¹) = 3350 (s), 2966 (s), 2239 (s), 1598 (m), 1458 (w), 1325 (m), 1166 (s), 961 (s), 746 (s), 692 (m); HRMS (ESI): m/z calculated for C_{16}H_{17}ClN_2O [M+H]^+ 325.1071, found: 325.1073.

2-[[4-(methylthio)phenyl]-2-[[4-(trifluoromethyl)phenyl]amino]acetonitrile 2k
Prepared from 4-(methylthio)benzaldehyde (76 mg, 0.5 mmol), 4-trifluoromethylaniline (81 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (with heating at 50 °C for 3 h). Purification: column chromatography on silicagel (cyclohexane/AcOEt 10/1, R_f = 0.1). Isolated as a yellow solid. Yield: 103 mg, 0.32 mmol, 64%.

m.p.: 141-146 °C; ^1H-NMR (CDCl_3, 400 MHz): δ 7.52 (d, J = 7.5 Hz, 2H), 7.50 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 7.5 Hz, 2H), 6.79 (d, J = 8.3 Hz, 2H), 5.42 (d, J = 7.5 Hz, 1H), 4.34 (d, J = 7.5 Hz, 1H), 2.51 (s, 3H) ppm; ^13C([H]-NMR (CDCl_3, 125 MHz): δ 147.2 (C), 141.5 (C), 129.5 (C), 127.9 (CH), 127.1 (CH, J_C,F = 3.5 Hz), 126.9 (CH), 124.6 (C, J_C,F = 270.0 Hz), 122.1 (C, J_C,F = 33.0 Hz), 117.6 (CN), 113.5 (CH), 49.3 (CH), 15.5 (CH_3) ppm; IR (neat): vmax (cm⁻¹) = 3360 (m), 1616 (m), 1533 (w), 1334 (m), 1091 (s), 1062 (s), 820 (s), 802 (m); HRMS (ESI): HRMS (ESI, negative ion mode): m/z calculated for C_{15}H_{15}F_2S [M-Na]^− 321.0679, found: 321.0688.

2-[[6-chloropyridin-2-yl]amino]-3-methylbutanenitrile 2l
Prepared from isobutyraldehyde (36 mg, 0.5 mmol), 2-amino-6-chloropyridine (64 mg, 0.55 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (24 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 8/1, R_f = 0.2). Isolated as a white solid. Yield: 75 mg, 0.36 mmol, 72% (contains an unknown impurity <5%, reported yield is uncorrected).

m.p.: 90.2-92.4 °C; ^1H-NMR (CDCl_3, 500 MHz): δ 7.41 (t, J = 7.7 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 6.40 (d, J = 8.1 Hz, 1H), 4.78-4.72 (m, 2H), 2.14 (m, 1H), 1.16 (d, J = 6.9 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H) ppm; ^13C([H]-NMR (CDCl_3, 125 MHz): δ 156.3 (C), 149.7 (C), 140.1 (CH), 118.8 (CN), 114.5 (CH), 106.6 (CH), 49.2 (CH), 31.6 (CH), 19.0 (CH_3), 18.3 (CH_3) ppm; IR (neat): vmax (cm⁻¹) = 3350 (m), 2966 (s), 2239 (s), 1598 (m), 1458 (w), 1325 (m), 1166 (s), 961 (s), 783 (s), 696 (s), 536 (w); HRMS (ESI): m/z calculated for C_{16}H_{15}ClN_2 [M+H]^+ 210.0793, found: 210.0803.


**Chapter 3**

2-(benzylamino)-2-(3,4-dichlorophenyl)acetonitrile 2n
Prepared from 3,4-dichlorobenzaldehyde (88 mg, 0.5 mmol), benzylamine (54 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure A (24 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 10/1, Rf = 0.24). Isolated as an off-white solid. Yield: 40 mg, 0.137 mmol, 28%.

m.p.: 56-60.5 °C; 1H-NMR (CDCl₃, 400 MHz): 7.67 (d, J = 1.5 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.43-7.28 (m, 6H), 4.72 (d, J = 4.3 Hz, 1H), 4.05 (d, J = 13.2 Hz, 1H), 3.95 (d, J = 13.2 Hz, 1H), 1.92 (br, 1H) ppm; 13C{¹H}-NMR (CDCl₃, 125 MHz): δ 137.7 (C), 134.9 (C), 133.5 (C), 133.4 (C), 131.0 (CH), 129.4 (CH), 128.9 (CH), 128.6 (CH), 128.0 (CH), 126.7 (CH), 118.0 (CN), 52.4 (CH), 51.3 (CH₂) ppm; IR (neat): νmax (cm⁻¹) = 3295 (m), 2830 (w), 2228 (w), 1473 (s), 1450 (s), 1095 (m), 1029 (m), 866 (s), 820 (s), 727 (s), 693 (s); HRMS (ESI): m/z calculated for C₁₄H₁₂Cl₂N [M-CN]⁺ 264.0341, found: 264.0337.

2-(4-chlorophenyl)-2-(N-phenethylacetamido)-N-tritylacetamide 3a
Prepared from phenethylamine (61 mg, 0.5 mmol), 4-chlorobenzaldehyde (70 mg, 0.5 mmol), acetic acid (28.6 µL, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure B. Purification: column chromatography on silicagel (cyclohexane/AcOEt 4/1, Rf = 0.15). Isolated as a white solid. Yield: 163 mg, 0.285 mmol, 57%.

m.p.: 218.1-220.1 °C; 1H-NMR (CDCl₃, 500 MHz): δ 7.33 (d, J = 8.3 Hz, 2H), 7.31-7.19 (m, 17H), 7.19-7.13 (m, 4H), 6.78 (d, J = 7.0 Hz, 2H), 6.10 (s, 1H), 3.38-3.24 (m, 2H), 2.46 (dt, J = 12.1, 5.8 Hz, 1H), 2.19 (s, 3H), 2.07 (dt, J = 12.7, 5.6 Hz, 1H) ppm; 13C{¹H}-NMR (CDCl₃, 125 MHz): δ 171.9 (C), 168.3 (C), 144.2 (C), 138.1 (C), 135.0 (C), 133.1 (C), 131.6 (CH), 129.1 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.1 (CH), 126.6 (CH), 70.8 (C), 61.5 (CH), 48.4 (CH₃), 36.3 (CH₂), 21.9 (CH₃) ppm; IR (neat): νmax (cm⁻¹) = 3287 (s), 3025 (s), 1692 (m), 1616 (w), 1525 (m), 1488 (s), 1346 (s), 1116 (s), 1014 (s), 902 (s), 744 (s), 700 (w), 545 (s); HRMS (ESI): m/z calculated for C₃₇H₃₃ClN₂O₂ [M+Na]⁺ 595.2123, found: 595.2116.

2-(3,5-dimethoxyphenyl)-2-(N-(p-tolyl)acetamido)-N-tritylacetamide 3b
Prepared from p-toluidine (54 mg, 0.5 mmol), 3,5-dimethoxybenzaldehyde (83 mg, 0.5 mmol), acetic acid (28.6 µL, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure B. Purification: column chromatography on silicagel (cyclohexane/AcOEt 2/1, Rf = 0.18). Isolated as a white solid. Yield: 142 mg, 0.25 mmol, 50%.

m.p.: 210-213 °C; 1H-NMR (CDCl₃, 400 MHz): δ 7.30-7.18 (m, 17H), 6.99 (s, 1H), 6.90 (d, J = 6.8 Hz, 2H), 6.26 (t, J = 2.1 Hz, 1H), 6.14 (d, J = 2.1 Hz, 2H), 6.10 (s, 1H), 3.52 (s, 6H), 2.23 (s, 3H), 1.84 (s, 3H) ppm; 13C{¹H}-NMR (CDCl₃, 125 MHz): δ 171.5 (C), 168.5 (C), 160.3 (C), 144.5 (C), 138.1 (C), 135.0 (C), 133.1 (C), 131.6 (CH), 129.1 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.1 (CH), 126.6 (CH), 70.8 (C), 61.5 (CH), 48.4 (CH₃), 36.3 (CH₂), 21.9 (CH₃) ppm; IR (neat): νmax (cm⁻¹) = 3375 (s), 3023 (m), 1689 (s), 1596 (m), 1512 (s), 1492 (s), 1296 (s), 1202 (s), 750 (m), 698 (m), 553 (s); HRMS (ESI): m/z calculated for C₃₇H₃₄N₂O₄ [M+H]⁺ 585.2748, found: 585.2758.

2-(N-(4-bromophenyl)acetamido)-4-methyl-N-tritylpentanamide 3c
Prepared from 4-bromoaniline (86 mg, 0.5 mmol), 3-methylbutanal (43 mg, 0.5 mmol), acetic acid (28.6 µL, 0.5 mmol), and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure B. Purification: column chromatography on silicagel (cyclohexane/AcOEt 8/1, Rf = 0.18). Isolated as a white solid. Yield: 142 mg, 0.25 mmol, 50%.
Versatility of Trityl Isocyanide in Ugi-type Reactions

= 0.25). Isolated as a white solid. Yield: 89 mg, 0.16 mmol, 32%.
m.p.: 76.6-81.2 °C; 1H-NMR (CDCl3, 500 MHz): δ 8.18 (s, 1H), 7.26 (d, J = 7.6 Hz, 6H), 7.28 (t, J = 7.7 Hz, 9H), 7.21 (t, J = 7.1 Hz, 4H), 5.27 (dd, J = 9.6, 5.4 Hz, 1H), 1.73 (s, 3H), 1.56 (appsept, J = 6.7 Hz, 1H), 1.40-1.32 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H, overlaps with m, 1H), 0.86 (d, J = 6.7 Hz, 3H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz): δ 171.7 (C), 168.7 (C), 144.6 (C), 137.9 (C), 132.2 (CH), 131.2 (CH), 128.6 (CH), 128.0 (CH), 126.9 (CH), 122.5 (C), 70.4 (C), 56.1 (CH), 37.2 (CH3), 25.1 (CH3), 23.3 (CH3), 22.4 (CH3) ppm; IR (neat): vmax (cm⁻¹) = 3145 (m), 2954 (s), 1697 (m), 1637 (m), 1487 (m), 1379 (s), 1317 (s), 1012 (s), 700 (w), 626 (s); HRMS (ESI): m/z calculated for C33H33BrN2O2 [M+H]^+ 569.1798, found: 569.1787.

Ugi product 3d
Prepared from bicyclic imine (55 mg, 0.5 mmol), benzoic acid (61 mg, 0.5 mmol), and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure B. Diastereoisomeric ratio determined by SFC-ESI MS analysis of the crude reaction mixture (Acquity Trefoil CEL1 column, 2.1 x 150mm, 2.5 μm; MeOH/IPA 1:1 + 0.2% TFA as modifier; tminor = 2.85 min, tmajor = 3.46 min, ratio 33:1). Purification: column chromatography on silicagel (cyclohexane/AcOEt 5/1, R = 0.15). Isolated as a white solid. Yield: 225 mg, 0.45 mmol, 90% (major diastereoisomer isolated in pure form).
m.p.: 152-153 °C; 1H-NMR (CDCl3, 500 MHz; rotamers observed in a 14:1 ratio, signals reported for the major rotamer only): δ 8.16 (br, 1H), 7.35-7.18 (m, 5H), 7.34-7.19 (m, 15 H), 4.83 (d, J = 2.5 Hz, 1H), 3.56 (dd, J = 11.0, 8.0 Hz, 1H), 3.28 (dd, J = 11.0, 2.5 Hz, 1H), 3.14-3.06 (m, 1H), 2.65 (quint, J = 6.5 Hz, 1H), 1.97 (sex, J = 7.0 Hz, 1H), 1.81 (sex, J = 6.1 Hz, 1H), 1.74-1.50 (m, 3H), 1.26 (sept, J = 6.1 Hz, 1H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz): 170.6 (C), 169.4 (C), 144.9 (C), 136.2 (C), 130.2 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.0 (CH), 70.4 (C), 67.2 (CH), 55.9 (CH3), 44.2 (CH), 43.3 (CH), 33.0 (CH3), 32.9 (CH3), 26.3 (CH3), ppm; IR (neat): vmax (cm⁻¹) = 2950 (w), 1734 (m), 1695 (s), 1612 (s), 1491 (s), 1240 (s), 1043 (m), 698 (s); HRMS (ESI): m/z calculated for C34H34N2O2 [M+H]^+ 501.2537, found: 501.2524.

2-(4-chlorophenyl)-2-(N-phenylacetamido)acetic acid 4a
Prepared from Ugi product 3a (130 mg, 0.227 mmol) according to Procedure C. Purification: acid-base extraction. Isolated as a white solid. Yield: 68 mg, 0.20 mmol, 90%.
m.p.: 175-183 °C; 1H-NMR (DMSO-d6, 500 MHz; rotamers observed in a 5:1 ratio): δ 12.85 (br, 1H, R1 and R2), 7.53 (d, J = 7.0 Hz, 2H, R2), 7.49-7.40 (m, 4H, R1, 2H, R2), 7.25 (t, J = 6.8 Hz, 2H, R1), 7.22-7.11 (m, 1H, R1, 3H, R2), 7.07 (d, J = 7.3 Hz, 2H, R1), 6.86 (d, J = 7.4 Hz, 2H, R2), 5.82 (s, 1H, R2), 5.60 (s, 1H, R1), 3.54-3.13 (m, 2H, R1, 1H, R2, overlap with water from DMSO-d6), 3.05 (td, J = 12.0, 4.3 Hz, 1H, R2), 2.74-2.57 (m, 1H, R1, 1H, R2), 2.49-2.41 (m, 1H, R1), 2.14 (s, 3H, R2), 2.03 (s, 3H, R1), 1.92-1.84 (m, 1H, R2) ppm; 13C(1H)-NMR (DMSO-d6, 125 MHz): 171.4 (C, R2), 170.8 (C, R1), 170.3 (C, R2), 170.2 (C, R1), 139.1 (C, R2), 138.5 (C, R1), 135.1 (C, R2), 134.5 (C, R2), 133.0 (C, R2), 132.7 (C, R1), 131.5 (CH, R1), 131.3 (CH, R2), 128.7 (CH, R1), 128.6 (CH, R2), 128.4 (CH, R1 and R2), 128.2 (CH, R1 and R2), 126.4 (CH, R1), 126.0 (CH, R2), 63.5 (CH, R2), 61.5 (CH, R1), 49.6 (CH2, R1), 46.3 (CH2, R2), 35.1 (CH2, R1), 34.2 (CH2, R2), 22.2 (CH3, R2), 21.4 (CH3, R1) ppm; IR (neat): vmax (cm⁻¹) = 1735 (m), 1601 (s), 1485 (m), 1202 (s), 1095 (m), 878 (m), 740 (s); HRMS (ESI): m/z calculated for C18H16ClINaO3 [M+Na]^+ 354.0867, found: 354.0854.
Chapter 3

**ethyl 2-(4-chlorophenyl)-2-(N-phenethylacetamido)acetate**
Prepared from Ugi product 3a (60 mg, 0.10 mmol) according to Procedure C (Ethanol was added and the reaction was stirred for 1 h at room temperature before quenching). Purification: column chromatography on silicagel (cyclohexane/AcOEt 3/1, R_f = 0.15). Isolated as a gummy white solid. Yield: 25 mg, 0.07 mmol, 70%.

^1H-NMR (CDCl_3, 500 MHz; rotamers observed in a 10:1 ratio, signals reported for the major rotamer only): δ 7.43 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.29-7.18 (m, 3H), 6.92 (d, J = 7.3 Hz, 2H), 6.03 (s, 1H), 4.25 (q, J = 7.3 Hz, 2H), 3.52-3.44 (m, 1H), 3.43-3.35 (m, 1H), 2.71-2.62 (m, 1H), 2.31-2.22 (m, 1H), 2.18 (s, 3H), 1.28 (t, J = 7.3 Hz, 3H) ppm; ^13C(H)-NMR (CDCl_3, 125 MHz): 171.6 (C), 170.3 (C), 138.0 (C), 135.0 (C), 133.5 (C), 131.2 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 126.7 (CH), 61.7 (CH), 48.8 (CH), 36.7 (CH), 21.8 (CH), 14.2 (CH_2) ppm; IR (neat): νmax (cm^-1) = 1740 (s), 1647 (s), 1408 (m), 1205 (w), 1030 (w), 702 (m), 631 (m), 530 (s); HRMS (ESI): m/z calculated for C_{20}H_{19}BrNO_3 [M+H]^+ 382.1180, found: 382.1163.

**2-(3,5-dimethoxyphenyl)-2-(N-p-tolylacetamido)acetic acid 4b**
Prepared from Ugi product 3b (92 mg, 0.157 mmol) according to Procedure C. Purification: acid-base extraction. Isolated as a gummy brown solid. Yield: 33 mg, 0.096 mmol, 60%.

^1H-NMR (CD_2OD, 500 MHz): δ 7.33-6.75 (s, 4H), 6.27 (t, J = 2.0 Hz, 1H), 6.21 (d, J = 2.0 Hz, 2H), 5.97 (s, 1H), 3.60 (s, 6H), 2.27 (s, 3H), 1.83 (s, 3H) ppm; ^13C(H)-NMR (CD_2OD, 125 MHz): δ 173.7 (2C), 162.0 (C), 139.6 (C), 138.8 (C), 137.1 (C), 131.1 (CH), 130.5 (CH), 109.7 (CH), 101.4 (CH), 65.5 (CH), 55.7 (CH), 23.1 (CH_2), 21.1 (CH_3) ppm; IR (neat): vmax (cm^-1) = 1717 (s), 1697 (s), 1683 (s), 1560 (m), 800 (m), 780 (s), 532 (s); HRMS (ESI): m/z calculated for C_{19}H_{17}NO_5 [M+H]^+ 344.1483, found: 344.1492.

**N-acetyl-N-(4-bromophenyl)leucine 4c**
Prepared from Ugi product 3c (86 mg, 0.15 mmol) according to Procedure C. Purification: acid-base extraction. Isolated as a gummy white solid. Yield: 26 mg, 0.08 mmol, 52%.

^1H-NMR (CD_2OD, 400 MHz): δ 7.63 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 4.93 (dd, J = 9.5, 5.0 Hz, 1H, partly overlaps with water from CD_2OD), 1.84 (s, 3H), 1.74-1.47 (m, 3H), 0.88 (d, J = 6.0, 3H), 0.85 (d, J = 6.3 Hz, 3H) ppm; ^13C(H)-NMR (CD_2OD, 125 MHz): δ 174.8 (C), 173.4 (C), 141.4 (C), 133.8 (CH), 132.2 (CH), 123.5 (C), 59.8 (CH), 39.5 (CH), 26.1 (CH_2), 23.2 (CH_2), 23.1 (CH_3), 22.2 (CH_3) ppm; IR (neat): vmax (cm^-1) = 2959 (w), 1717 (s), 1647 (s), 1488 (s), 1384 (s), 1134 (s), 1070 (m), 1015 (m), 723 (m), 524 (m); HRMS (ESI): m/z calculated for C_{14}H_{13}BrNO_3 [M+H]^+ 328.0543, found: 328.0535.

**1R,3aR,6aS)-2-benzoyloctahydrocyclopenta[c]pyrrole-1-carboxamide 5d**
Prepared from Ugi product 3d (78 mg, 0.156 mmol) according to Procedure C. Purification: column chromatography on silicagel (AcOEt, R_f = 0.18). Isolated as a gummy white solid. Yield: 36 mg, 0.14 mmol, 89%.

^1H-NMR (CDCl_3, 500 MHz; rotamers observed in a 7:1 ratio, signals reported for the major rotamer only): δ 7.48 (d, J = 6.8 Hz, 2H), 7.44-7.32 (m, 3H), 6.92 (br, 1H), 5.83 (br, 1H), 4.65 (d, J = 2.5 Hz, 1H), 3.77 (dd, J = 11.0, 8.0 Hz, 1H), 3.32 (dd, J = 11.0, 2.5 Hz, 1H), 3.13-3.04 (m, 1H), 2.70 (quint, J = 6.5 Hz, 1H), 2.17-2.06 (m, 1H), 2.00-1.90 (m, 1H), 1.87-1.75 (m, 1H), 1.73-1.63 (m, 1H), 1.62-1.50 (m, 1H, overlaps with water from CDCl_3), 1.30-1.19 (m, 1H) ppm; ^13C(H)-NMR (CDCl_3, 400 MHz): 173.9 (C), 170.5 (C), 136.0 (C), 130.4 (CH), 128.8 (CH), 127.2 (CH), 66.0 (CH), 56.0 (CH_2), 45.4 (CH), 43.4 (CH), 33.0 (CH_2), 32.5 (CH_2), 26.1 (CH_3) ppm; IR (neat):
Versatility of Trityl Isocyanide in Ugi-type Reactions

vmax (cm\(^{-1}\)) = 1660 (s), 1616 (s), 1576 (m), 1417 (s), 783 (m), 723 (m); HRMS (ESI): m/z calculated for C\(_{15}\)H\(_{13}\)N\(_2\)O\(_2\) [M+\(\text{H}\)]\(^+\) 259.1441, found: 259.1429.

2-phenylimidazo[1,2-\(a\)]pyridin-3-amine 6a\(^{[29]}\)

Prepared from pyridin-2-amine (47 mg, 0.5 mmol), benzaldehyde (53 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure D. Purification: column chromatography on silicagel (cyclohexane/AcOEt 2/1 with 0.5% NEt\(_3\), R\(_f\) = 0.19). Isolated as a yellow solid. Yield: 68 mg, 0.325 mmol, 65%.

m.p.: 185-193 °C (decomposition); \(^1\)H-NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 8.25 (d, \(J = 7.0\) Hz, 1H), 8.06 (d, \(J = 7.5\) Hz, 2H), 7.43-7.39 (m, 3H), 7.23 (t, \(J = 7.0\) Hz, 1H), 7.04 (t, \(J = 7.5\) Hz, 1H), 6.83 (t, \(J = 6.7\) Hz, 1H), 5.2 (br, 2H) ppm; \(^{13}\)C\(^{[1}\)H\)-NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 138.8 (C), 135.2 (C), 128.3 (C), 127.4 (C), 126.5 (C), 126.2 (C), 125.9 (CH), 122.5 (CH), 121.1 (CH), 116.4 (CH), 110.9 (CH) ppm; IR (neat): \(\nu_{\text{max}}\) (cm\(^{-1}\)) = 3200-3000 (w), 1560 (m), 1489 (m), 1445 (m), 1198 (m), 777 (s), 748 (s), 694 (s); HRMS (ESI): m/z calculated for C\(_{16}\)H\(_{14}\)N\(_2\) [M+\(\text{H}\)]\(^+\) 210.1026, found: 210.1036.

7-methyl-2-(4-(trifluoromethyl)phenylimidazo[1,2-\(a\)]pyridin-3-amine 6c

Prepared from 4-methylpyridin-2-amine (54 mg, 0.5 mmol), 4-trifluoromethylbenzaldehyde (87 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure D. Purification: column chromatography on silicagel (cyclohexane/AcOEt 2/1 with 0.5% NEt\(_3\), R\(_f\) = 0.17). Isolated as a yellow solid. Yield: 103 mg, 0.355 mmol, 71% (contains 1 wt% CH\(_2\)Cl\(_2\), reported yield is corrected).

m.p.: 185-200 °C (decomposition); \(^1\)H-NMR (DMSO-d\(_6\), 500 MHz): \(\delta\) 8.25 (d, \(J = 7.0\) Hz, 2H), 8.18 (d, \(J = 7.0\) Hz, 1H), 7.72 (d, \(J = 8.4\) Hz, 2H), 7.20 (s, 1H), 6.68 (dd \(J = 7.0, 1.7\) Hz, 1H), 5.37 (br, 2H), 2.30 (s, 3H) ppm; \(^{13}\)C\(^{[1}\)H\)-NMR (DMSO-d\(_6\), 125 MHz): \(\delta\) 139.5 (C), 133.0 (C), 127.8 (C), 126.0 (CH), 125.7 (C, \(J_{CF} = 20\) Hz), 125.1 (CH, \(J_{CF} = 4\) Hz), 124.8 (C), 124.7 (C, \(J_{CF} = 270\) Hz), 122.1 (CH), 115.0 (CH), 113.8 (CH), 20.8 (CH\(_3\)) ppm; IR (neat): \(\nu_{\text{max}}\) (cm\(^{-1}\)) = 3350(w), 3200 (w), 1637 (w), 1619 (w), 1491 (w), 1448 (w), 1319 (m), 1157 (s), 1105 (s), 1059 (s), 841 (s), 785 (s), 748 (s), 690 (s); HRMS (ESI): m/z calculated for C\(_{16}\)H\(_{14}\)F\(_3\)N\(_2\) [M+\(\text{H}\)]\(^+\) 292.1056, found: 292.1071.

2-isobutylimidazo[1,2-\(a\)]pyridin-3-amine 6d

Prepared from pyridin-2-amine (47 mg, 0.5 mmol), 3-methylbutanal (43 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure D. Purification: column chromatography on silicagel (AcOEt with 0.5% NEt\(_3\), R\(_f\) = 0.19). Isolated as a yellow oil. Yield: 60 mg, 0.315 mmol, 63% (co-elutes with pyridin-2-amine, reported yield is corrected for 94 wt% purity).

\(^1\)H-NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.91 (d, \(J = 7.0\) Hz, 1H), 7.36 (d, \(J = 8.5\) Hz, 1H), 6.96 (t, \(J = 8.0\) Hz, 1H), 6.66 (t, \(J = 7.0\) Hz, 1H), 3.15 (br, 2H), 2.53 (dd \(J = 8.0\) Hz, 2H), 2.07 (appsept, \(J = 6.5\) Hz, 1H), 0.88 (d, \(J = 6.5\) Hz, 6H) ppm; \(^{13}\)C\(^{[1}\)H\)-NMR (CDCl\(_3\), 125 MHz): \(\delta\) 140.6 (C), 135.6 (C), 122.7 (C), 122.4 (CH), 121.9 (CH), 116.6 (CH), 111.1 (CH), 36.3 (CH\(_3\)), 29.2 (CH), 22.6 (CH\(_3\)) ppm; IR (neat): \(\nu_{\text{max}}\) (cm\(^{-1}\)) = 3400-3200 (w), 2952 (m), 1684 (w), 1636 (w), 1501 (w), 1489 (s), 1319 (m), 1157 (s), 1105 (s), 1059 (s), 841 (s), 785 (s), 748 (s), 690 (s); HRMS (ESI): m/z calculated for C\(_{16}\)H\(_{13}\)F\(_3\)N\(_2\) [M+\(\text{H}\)]\(^+\) 292.1056, found: 292.1071.

3,3-dimethyl-2-((6-methylpyridin-2-yl)amino)butanenitrile 6f

Prepared from 6-methylpyridin-2-amine (54 mg, 0.5 mmol), pivaldehyde (43 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure D. Purification: column chromatography on silicagel (cyclohexane/AcOEt 10/1, R\(_f\) = 0.22). Isolated as a colorless oil.
Chapter 3

Yield: 51 mg, 0.255 mmol, 50% (product co-elutes with 6-methyl-N-tritylpyridin-2-amine, reported yield is corrected for 54 wt% purity).

$^1$H-NMR (CDCl$_3$, 500 MHz): δ 7.40-7.34 (t, 1H, overlaps with impurity), 6.58 (d, J = 7.1 Hz, 1H), 6.33 (d, J = 7.5 Hz, 1H), 4.87 (d, J = 9.7 Hz, 1H), 4.63 (d, J = 9.7 Hz, 1H), 2.42 (s, 3H), 1.17 (s, 9H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): δ 157.3 (C), 157.0 (C), 138.0 (CH), 119.4 (CN), 114.2 (CH), 105.2 (CH), 52.8 (CH), 34.7 (C), 24.3 (CH$_3$) ppm; IR (neat): ν$_{max}$ (cm$^{-1}$) = 3000 (w), 1597 (m), 1320 (m), 1213 (m), 1043 (s), 806 (m); HRMS (ESI): m/z calculated for C$_{10}$H$_{18}$N$_3$ [M+H$^+$] = 204.1495, found: 204.1507.

**2-isobutyl-7-(trifluoromethyl)imidazo[1,2-$\alpha$]pyridin-3-amine 6g**

Prepared from 4-(trifluoromethyl)pyridin-2-amine (81 mg, 0.5 mmol), 3-methylbutanal (43 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure D. Purification: column chromatography on silicagel (cyclohexane/AcOEt 4/1 with 0.5% NEt$_3$, R$_f$ = 0.11). Isolated as a yellow solid. Yield: 96 mg, 0.375 mmol, 75%.

m.p.: 105-109 °C (decomposition); $^1$H-NMR (CDCl$_3$, 500 MHz): δ 8.05 (d, J = 7.0 Hz, 1H), 7.71 (s, 1H), 6.90 (t, J = 7.0 Hz, 1H), 3.24 (br, 2H), 2.60 (d, J = 7.5 Hz, 2H), 2.11 (appsept, J = 6.5 Hz, 1H), 0.92 (d, J = 6.5 Hz, 6H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): δ 138.4 (C), 137.9 (C), 124.6 (C), 124.0 (C, J$_{CF}$ = 34 Hz), 123.8 (C, J$_{CF}$ = 270 Hz), 122.4 (CH), 114.7 (CH, J$_{CF}$ = 4.5 Hz), 107.3 (CH), 36.4 (CH$_2$), 29.3 (CH) ppm; IR (neat): ν$_{max}$ (cm$^{-1}$) = 3150(w), 1555 (m), 1489 (m), 1450 (m), 1339 (m), 1157 (m), 1107 (s), 1052 (s), 748 (s), 694 (s); HRMS (ESI): m/z calculated for C$_{12}$H$_{18}$F$_3$N$_3$ [M+H$^+$] = 208.1218, found: 208.1212.

**2-(tert-butyl)-6-fluoroimidazo[1,2-$\alpha$]pyridin-3-amine 6h**

Prepared from 3-fluoropyridin-2-amine (56 mg, 0.5 mmol), pivalaldehyde (43 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure D. Purification: column chromatography on silicagel (cyclohexane/AcOEt 4/1 with 0.5% NEt$_3$, R$_f$ = 0.11). Isolated as a light-brown solid. Yield: 58 mg, 0.28 mmol, 56% (co-elutes with 5-fluoropyridin-2-amine, reported yield is corrected for 94 wt% purity).

m.p.: 110-113 °C (decomposition); $^1$H-NMR (CDCl$_3$, 400 MHz): δ 7.91 (s, 1H), 7.44 (dd, J = 9.5, 4.7 Hz, 1H), 6.94 (t, J = 9.0 Hz, 1H), 3.08 (br, 2H), 1.47 (s, 9H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): δ 154.3 (C), 144.8 (C, J$_{CF}$ = 1880 Hz), 145.5 (C), 121.9 (C), 117.4 (CH, J$_{CF}$ = 9 Hz), 114.4 (CH, J$_{CF}$ = 26 Hz), 108.3 (CH, J$_{CF}$ = 42 Hz), 33.0 (C), 30.3 (CH$_3$) ppm; IR (neat): ν$_{max}$ (cm$^{-1}$) = 3150(w), 2950 (w), 1647 (w), 1541 (m), 1473 (m), 1450 (m), 1321 (m), 1213 (m), 791 (s); HRMS (ESI): m/z calculated for C$_{15}$H$_{15}$F$_3$N$_3$ [M+H$^+$] = 208.1245, found: 208.1255.

**2-phenethyl-6-(trifluoromethyl)imidazo[1,2-$\alpha$]pyridin-3-amine 6i**

Prepared from 5-(trifluoromethyl)pyridin-2-amine (81 mg, 0.5 mmol), 3-phenylpropanal (67 mg, 0.5 mmol) and trityl isocyanide (148 mg, 0.55 mmol) according to Procedure D. Purification: column chromatography on silicagel (cyclohexane/AcOEt 2/1 with 0.5% NEt$_3$, R$_f$ = 0.25). Isolated as a yellow solid. Yield: 104 mg, 0.34 mmol, 68%.

m.p.: 149-152 °C (decomposition); $^1$H-NMR (CDCl$_3$, 500 MHz): δ 8.32 (s,1H), 7.54 (d, J = 7.0 Hz, 1H), 7.36-7.03 (m, 6H), 3.07 (s, 4H), 2.61 (br, 2H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): δ 141.8 (C), 140.6 (C), 138.0 (C), 128.6 (CH), 128.5 (CH), 126.2 (CH), 124.0 (C), 124.0 (C, J$_{CF}$ = 270 Hz), 121.4 (CH, J$_{CF}$ = 7 Hz), 118.6 (CH), 117.4 (C), 115.7 (C, J$_{CF}$ = 34 Hz), 35.7 (CH$_2$), 29.7 (CH$_3$) ppm; IR (neat): ν$_{max}$ (cm$^{-1}$) = 3140 (w), 1647 (w), 1583 (m), 1315 (m), 1165 (m), 1119 (s), 1043 (s), 806 (m); HRMS (ESI): m/z calculated for C$_{16}$H$_{15}$F$_3$N$_3$ [M+H$^+$] = 306.1213, found: 306.1219.
Versatility of Trityl Isocyanide in Ugi-type Reactions

References and Notes


[8] Since we observed that acetic acid does not protonate this imine under these conditions it is possible that the mechanism is not entirely identical when using trifluoroacetic acid as acid component.


[11] A similar problem was observed by Bienaymé in the related imidazo[1,2-a]pyridine synthesis: see ref. 5c.


[13] This can also imply a different mechanism bypassing the nitriﬁon ion intermediate; the mechanism of the Ugi reaction was calculated to circumvent charged intermediates in toluene: (a) N. Chéron, R. Ramozzi, L. El Kaim, L. Grimaud, P. Fleurat-Lessard, J. Org. Chem. 2012, 77, 1361-1366; we wish to point out that there is no consensus on the general Ugi reaction mechanism and most likely several mechanisms operate depending on conditions and substrates, see also ref. 3 and: (b) G. A. Medeiros, W. A. da Silva, G. A. Bataglion, D. A. C. Ferreira, H. C. B. de Oliveira, M. N. Eberlin, B. A. D. Neto, Chem. Commun. 2014, 50, 338-340; (c) Iacobucci, S. Reale, J. F. Gal, F. De Angelis, Eur. J. Org. Chem. 2014, 32, 7087-7090.


Interestingly, t-BuNC can also be used for this purpose: the t-butyl analogue of 3a was deprotected directly to give 4a in a 52% yield, but in this case the reaction was not clean.


For a survey of convertible isocyanides, see: H. Ghafuri, M. Roshani, RSC Adv. 2014, 4, 58280-58286.


Brønsted Acid-Catalyzed Cyanotritylation of Aldehydes by Trityl Isocyanide

Abstract: In this chapter we report a novel cyanide-free synthesis of O-trityl protected cyanohydrins via a catalytic Passerini-type reaction involving aldehydes and trityl isocyanide. The possibility for a catalytic enantioselective upgrade is demonstrated using chiral phosphoric acid catalysis. Conventional Passerini products can be obtained with excellent selectivity by subtle changes in the reaction conditions.

Published in *Org. Lett.* 2016, 18, 3562-3565.
Introduction

The cyanohydrin functionality is often encountered in biologically active compounds[1] and represents a versatile handle for further synthetic elaboration, e.g. into α-hydroxy carboxylic acids, β-amino alcohols, and α-amino acids (Scheme 1). Cyanohydrin formation by nucleophilic addition of cyanide to carbonyl compounds is a key C-C bond forming process frequently employed in the synthesis of natural products, pharmaceuticals and agrochemicals.[2] Consequently, this chemical transformation has received considerable attention, and numerous protocols have been developed to access cyanohydrins and their O-protected derivatives which are usually more stable and more convenient to manipulate. However, these methods invariably rely on highly toxic cyanide sources (HCN, metal cyanides, TMSCN, cyanoformate esters, cyanophosphate esters, etc.) and often undesirable metal catalysts. Notably, the (bio)catalytic enantioselective synthesis of cyanohydrin derivatives, which has seen remarkable progress in the past decade,[3] suffers from similar drawbacks as all protocols employ toxic cyanide reagents as well.

Scheme 1. Conventional cyanohydrin synthesis and applications.

In the previous chapter we showed that triphenylmethyl (trityl) isocyanide can function as cyanide donor in Strecker reactions following an interrupted Ugi reaction pathway, i.e. the C-N fragmentation of the key N-trityl nitrilium ion intermediate.[4] As trityl isocyanide is a readily available, hydrolytically stable[5] crystalline solid we consider this reagent as a viable benign alternative to traditional cyanide sources; additionally, in contrast with conventional cyanation reagents, the synthesis of trityl isocyanide does not involve metal cyanides (it is based on conversion of triphenylmethanol to trityl formamide followed by dehydration). We therefore investigated the utility of trityl isocyanide in the synthesis of cyanohydrin derivatives via an interrupted Passerini-type mechanism, in which the
cyanohydrin functionality is generated upon addition of trityl isocyanide to an activated aldehyde and subsequent fragmentation of the resulting N-trityl nitrilium ion intermediate (Scheme 2). This mechanism confers an important advantage in the synthesis of cyanohydrins as both the hazardous handling of cyanide reagents and the generation of toxic cyanide species in solution can be circumvented. Additionally, instead of conventional transition metal catalysis, this process relies on simple Brønsted acid catalysis which to the best of our knowledge has not been applied before in cyanohydrin synthesis.\textsuperscript{[6]}

\begin{center}
Scheme 2. Cyanohydrin synthesis via an interrupted Passerini-type reaction.
\end{center}

**Results and Discussion**

We began our optimization using isovaleraldehyde as the benchmark substrate. Initial experiments revealed several important facts: the desired reactivity was possible, interestingly with concomitant tritylation of the free cyanohydrin product; the major competitive pathway was the isomerization of trityl isocyanide 2 to triphenylacetonitrile 2b (see also the mechanistic discussion).\textsuperscript{[7]} Both these events indicated the presence of the trityl cation as a reactive intermediate and served as preliminary validation of our mechanistic hypothesis. A small screen of Brønsted acids established diphenyl phosphate (DPP) as the optimal catalyst for the reaction (Table 1, entry 5). The reaction performed best in toluene while other solvents intriguingly gave (moderate) selectivity for the free cyanohydrin 4a (entries 6-11).\textsuperscript{[8]} We considered the O-trityl protected derivative 3a the more interesting target\textsuperscript{[9]} and pursued the optimization for this product. The use of one of the reactants in excess did not seem to improve the outcome and we then investigated the temperature effect. Intriguingly, the reaction was cleaner at increased temperatures (50 °C) rather than at 0 °C (entry 15 vs. entry 14); an additional improvement was
obtained by diluting the reaction to a 0.125 M solution (entry 16). Notably, normal grade solvent is preferable over rigorously anhydrous conditions (entries 17-19); the role of water traces in the reaction will be detailed in the mechanistic discussion.

**Table 1. Optimization of reaction conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Temp.</th>
<th>Conc.</th>
<th>1:2</th>
<th>Time</th>
<th>Yield[^b]</th>
<th>3a:4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>none</td>
<td>rt</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>24 h</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>TFA</td>
<td>rt</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>24 h</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>PTSA</td>
<td>rt</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>24 h</td>
<td>48</td>
<td>22:26</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>PhP(OH)2</td>
<td>rt</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>24 h</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>DPP</td>
<td>rt</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>24 h</td>
<td>74</td>
<td>61:13</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>DPP</td>
<td>rt</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>24 h</td>
<td>7</td>
<td>3:4</td>
</tr>
<tr>
<td>7</td>
<td>CHCl₃</td>
<td>DPP</td>
<td>rt</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>24 h</td>
<td>68</td>
<td>8:60</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>DPP</td>
<td>rt</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>24 h</td>
<td>43</td>
<td>12:31</td>
</tr>
<tr>
<td>9</td>
<td>MeTHF</td>
<td>DPP</td>
<td>rt</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>24 h</td>
<td>33</td>
<td>6:27</td>
</tr>
<tr>
<td>10</td>
<td>MTBE</td>
<td>DPP</td>
<td>rt</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>24 h</td>
<td>44</td>
<td>14:30</td>
</tr>
<tr>
<td>11</td>
<td>Dioxane</td>
<td>DPP</td>
<td>rt</td>
<td>0.25 M</td>
<td>1:2</td>
<td>24 h</td>
<td>75</td>
<td>69:6</td>
</tr>
<tr>
<td>12</td>
<td>Toluene</td>
<td>DPP</td>
<td>rt</td>
<td>0.25 M</td>
<td>2:1</td>
<td>24 h</td>
<td>70</td>
<td>53:17</td>
</tr>
<tr>
<td>13</td>
<td>Toluene</td>
<td>DPP</td>
<td>0 °C</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>24 h</td>
<td>79</td>
<td>72:7</td>
</tr>
<tr>
<td>14</td>
<td>Toluene</td>
<td>DPP</td>
<td>50 °C</td>
<td>0.25 M</td>
<td>1:1.1</td>
<td>5 h</td>
<td>85</td>
<td>79:6</td>
</tr>
<tr>
<td>15</td>
<td>Toluene</td>
<td>DPP</td>
<td>50 °C</td>
<td>0.125 M</td>
<td>1:1.1</td>
<td>5 h</td>
<td>79[^c]</td>
<td>72:7</td>
</tr>
<tr>
<td>16</td>
<td>Toluene</td>
<td>DPP</td>
<td>50 °C</td>
<td>0.125 M</td>
<td>1:1.1</td>
<td>5 h</td>
<td>91[^d]</td>
<td>53:38</td>
</tr>
<tr>
<td>17</td>
<td>Toluene</td>
<td>DPP</td>
<td>50 °C</td>
<td>0.125 M</td>
<td>1:1.1</td>
<td>5 h</td>
<td>65[^e]</td>
<td>57:8</td>
</tr>
</tbody>
</table>

[^a] Standard conditions: isovaleraldehyde (0.25 mmol) in toluene, DPP (10 mol%) and trityl isocyanide (1.1 equiv) stirred at the indicated temperature for 2-24 h (isocyanide conversion monitored by TLC);[^b] combined yield of 3a and 4a based on NMR analysis using mesitylene as internal standard;[^c] using freshly distilled toluene and anhydrous conditions;[^d] with addition of 3Å molecular sieves;[^e] with addition of MgSO₄.

With this optimized protocol in hand, we began to explore the aldehyde scope of the reaction. A good efficiency of the reaction was achieved using aliphatic inputs with diverse substitution patterns (linear, branched, α-heteroatom substituted, etc.). Benchmark
isovaleraldehyde 1a yielded 69% of the desired product (59% on gram scale) after chromatographic purification. Aldehydes 1d and 1j gave reduced yields presumably due to side reactions arising from their propensity to enolize under acidic conditions. Similarly, N-Boc-derivative 3h most likely undergoes Boc deprotection under the reaction conditions, leading to a basic site that quenches the catalyst. Hence, the desired product was obtained in low yield compared to the structurally related product 3g. Notably, bulky inputs were accepted (pivalaldehyde, 1k). A complex reaction mixture that hampered the isolation of the desired product was observed for the highly functionalized input 1l, whereas aromatic aldehydes performed modestly due to extensive conversion of trityl isocyanide to triphenylacetonitrile. This behavior was also observed for chloral (1n). Finally, α,β-unsaturated aldehydes (tiglic aldehyde, 1o) and ketones (cyclohexanone, 1p) proved incompatible substrates for the reaction due to their reduced electrophilicity.

O-trityl cyanohydrins are highly stable, typically crystalline compounds, which makes them easy to handle and further manipulate in synthetic transformations. Notably, in contrast with all other readily accessible O-protected cyanohydrins, the trityl derivatives are base stable, which is a complementary feature that can be beneficial in follow-up reactions. If required, the deprotection to free cyanohydrins is straightforward (stirring for 1 h at room temperature in TFA with 1 equiv Et3SiH) and can be performed in the same pot, without intermediate purification of the tritylated product (as shown for 4b, 4g and 4m). This protocol is not only simpler but also higher yielding than the sequential cyanotritylation-detritylation since it includes the minor amounts of 4 resulting from the first step (up to 10%) and circumvents purification issues of 3.[10]

The observations made during the reaction optimization and the evaluation of the substrate scope allowed us to draw the following mechanistic picture (Scheme 3). The electrophilicity of the aldehyde is enhanced by hydrogen-bond activation by the acid catalyst DPP. In the absence of this activation (if the reaction is performed in the absence of the catalyst or with DPP premixed with excess Na2CO3) no conversion is observed. Thus, the role of the acid catalysis is critical. The aldehyde activated by DPP I undergoes nucleophilic addition by trityl isocyanide leading to nitrilium ion intermediate II. This key intermediate fragments at the labile N-Tr bond into the free cyanohydrin 4 and the reactive trityl cation which combine to afford the final product 3 and regenerate the catalyst. The trityl group transfer is an essential step and deserves additional comment. Most likely, this process occurs from a tight ion pair III; control experiments showed that product 3 cannot be formed by tritylation of the free cyanohydrin 4 with triphenylmethanol (TrOH) under the reaction conditions (pathway C).[11] The exact nature of the interaction between diphenyl phosphate and tritylum is uncertain (electrostatic or
covalent) but the formation of 3 necessarily has the free carbocation as intermediate (an $S_{N}1$ mechanism from the covalent organic phosphate). This covalent compound, diphenyl trityl phosphate, although labile hydrolytically, can be prepared and stored as a toluene solution; in contrast with TrOH, the reaction between 4a and this trityl source is complete within minutes at room temperature, suggesting the viability of intermediate III. If the trityl cation diffuses in solution (possibly as the neutral phosphate) it initiates the isomerization of trityl isocyanide to trityl cyanide 2b via an ionic chain mechanism involving nitrilium ion intermediate IV (pathway B).

Table 2. Reaction scope$^{[a,b]}$

<table>
<thead>
<tr>
<th>$R_{1}$</th>
<th>$R_{2}$</th>
<th>$R_{3}$</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>CN</td>
<td>Ph</td>
<td>69%</td>
</tr>
<tr>
<td></td>
<td>CN</td>
<td>Ph</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td>CN</td>
<td>Ph</td>
<td>65%</td>
</tr>
<tr>
<td>Ph</td>
<td>O</td>
<td>Ph</td>
<td>42%</td>
</tr>
<tr>
<td>Ph</td>
<td>O</td>
<td>Ph</td>
<td>69%</td>
</tr>
<tr>
<td>Ph</td>
<td>O</td>
<td>Ph</td>
<td>69%</td>
</tr>
<tr>
<td>Ph</td>
<td>O</td>
<td>Ph</td>
<td>72%</td>
</tr>
<tr>
<td>Ph</td>
<td>O</td>
<td>Ph</td>
<td>45%</td>
</tr>
<tr>
<td>Ph</td>
<td>O</td>
<td>Ph</td>
<td>54%</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>26%</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>15%</td>
</tr>
<tr>
<td>Cl</td>
<td>Cl</td>
<td>Cl</td>
<td>4%</td>
</tr>
</tbody>
</table>

[a] Standard conditions: aldehyde (0.5 mmol) in toluene (0.125 M), DPP (10 mol%) and trityl isocyanide (1.1 equiv) stirred at 50 °C for 2-24 h (isocyanide conversion monitored by TLC); [b] isolated yields for O-trityl cyanohydrins 3; [c] isolated yield for free cyanohydrin 4 after deprotection with TFA-Et$_3$SiH without purification of 3; [d] yield based on NMR analysis using mesitylene as internal standard.
Since this unproductive consumption of trityl isocyanide is catalytic in the trityl cation it represents an important limiting factor for the reaction. This becomes particularly problematic with inputs for which the trityl transfer to the free cyanohydrin is more difficult due to reduced nucleophilicity (benzaldehyde, chloral, see Table 2) and/or steric factors (1p). Notably, the reaction performs better if traces of water are present, since the trityl cation is rapidly quenched (traces of triphenylmethanol are consistently detected during the reaction) and the extent of isomerization of 2 is reduced. Indeed, when the reaction is run with the addition of 0.5 equiv of water, no isomerization is detected; interestingly, α-hydroxyamide 5 is also observed (7% crude NMR yield, 9% selectivity). The selectivity for 5 (which is the product of the capture of nitrilium ion II by water) is enhanced at room temperature compared to 50 °C (35% vs. 9%) plausibly due to the stronger temperature dependence of the rate of the fragmentation pathway (II→III) that the addition of water (A).[14]

An alternative mechanism based on tritylium Lewis acid catalysis[12,15] can also be imagined, but since trityl isocyanide is rapidly isomerized in the presence of traces of the trityl cation this pathway is unlikely. Similarly, a mechanism involving fragmentation of the isocyanide prior to the addition (protonation of 2 and release of HCN to add to 1) can be ruled out as the isocyanide is essentially stable under the reaction conditions.[16] The experimental data are in good agreement with the Passerini/fragmentation mechanism which implies that this novel approach towards cyanohydrins is essentially cyanide-free.

Scheme 3. Reaction mechanism.
With this knowledge in hand we attempted the asymmetric synthesis of O-tritylated cyanohydrins using chiral phosphoric acid (CPA) catalysis. In the past decade, CPAs have been extensively employed as catalysts for an impressive array of asymmetric transformations.\textsuperscript{[17]} However, reactions involving isocyanides as reagents are rare: to the best of our knowledge, there are only two reports describing asymmetric Passerini-type chemistry under CPA catalysis.\textsuperscript{[18]} As a proof of concept, the reaction with \((R)\)-TRIP as the catalyst affords enantioenriched cyanohydrin derivatives \(3a\) and \(3m\) in good yields and reasonable ee’s as shown in Scheme 4. Interestingly, TRIP performed slightly better in terms of yield and selectivity than DPP, primarily due to an improved trityl transfer from \(\text{III}\) to \(\text{3}\) over the isocyanide isomerization via \(\text{IV}\). The absolute configuration of \(3m\) was determined both by single crystal XRD and chiral HPLC; the stereochemical outcome is identical as in the mechanistically-related \(\alpha\)-addition of \(\alpha\)-isocyanoacetamides to aldehydes.\textsuperscript{[18a]} Thus, \((S)\)-O-trityl mandelonitrile \(3m\) could be obtained in good yield and 79% ee, whereas a less bulky substrate \((1a)\) leads to a significantly reduced enantioselectivity. Optimization of these initial results is currently underway in our laboratories.

Having established trityl isocyanide as a reagent that stands out in its class,\textsuperscript{[19]} we pursued the more conventional Passerini three-component reaction involving \(2\), an aldehyde and a carboxylic acid. This reaction is mechanistically closely related to the DPP-catalyzed cyanohydrin synthesis (nucleophilic addition of the isocyanide to the acid-activated aldehyde as the initiating event, see Scheme 1) and thus chemoselectivity is an important issue here. Notably, the Passerini reaction with trityl isocyanide proceeds with complete selectivity for the \(\alpha\)-acyloxyamides \(6\) with all possible combinations of inputs (aromatic/aliphatic aldehyde and carboxylic acid respectively, Scheme 5). This represents valuable mechanistic information for the Passerini reaction which most likely proceeds...
with the concerted formation of the imidate α-adduct rather than having a true nitrilium ion as intermediate.\textsuperscript{[20]} Furthermore, the trityl substituent can be readily removed yielding primary α-acyloxyamides 7 which are useful building blocks for the synthesis of natural products and bioactive compounds.\textsuperscript{[2c, 2d, 21]}

\textbf{Scheme 5.} Scope of the Passerini-deprotection sequence.

\section*{Conclusion}

In this chapter we report the synthesis of $O$-trityl cyanohydrin derivatives under Brønsted acid catalysis\textsuperscript{[22]} using trityl isocyanide as a convenient cyanating reagent. The trityl substituent is a convenient protecting group, making these products useful building blocks for follow-up chemistry. Its removal is readily achieved and can also be performed in the same pot; the byproduct triphenylmethane can be converted back to the isocyanide in three simple steps.\textsuperscript{[4,23]} Importantly, this approach is mechanistically different than conventional cyanohydrin syntheses and the Passerini addition/fragmentation mechanism does not involve toxic cyanide species. Finally, enantioenriched $O$-trityl cyanohydrins can be obtained by means of chiral phosphoric acid organocatalysis.
Experimental Section

General Remarks

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Cyclohexane was distilled prior to use. Dry toluene was distilled over sodium and stored under nitrogen on 4Å molecular sieves. All other solvents were used as purchased. All reactions were performed under nitrogen atmosphere.

Melting points were recorded on a Büchi M-565 melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 (125.78 MHz for $^{13}$C) or Bruker Avance 400 (100.62 MHz for $^{13}$C) using the residual solvent as internal standard ($^1$H: δ 7.26 ppm, $^{13}$C($^1$H): δ 77.16 ppm for CDCl$_3$, $^1$H: δ 2.50 ppm, $^{13}$C($^1$H): δ 39.52 ppm for DMSO-d$_6$). Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), sep (septet), br (broad singlet) and m (multiplet) or combinations thereof. Infrared (IR) spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm$^{-1}$. Electrospray Ionization (ESI) high-resolution mass spectrometry (HRMS) was carried out using a Bruker microTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 μm, pore diameter 60Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO$_2$, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator). Chiral HPLC was recorded using a LC10VP with a SCL-10A VP system controller, LC-10AT VP liquid chromatograph, SPD-M10A VP diode array detector and CTO-10AC VP column oven from Shimadzu. X-ray analysis was performed on an Agilent SuperNova diffractometer with Cu K(α) microsource, mirror monochromator and Atlas CCD detector. The data were reduced and corrected for absorption with CrysAlisPro, Agilent Technologies, Version 1.171.37.35 (release 13-08-2014 CrysAlis171 .NET). The structure was solved with SHELXD (Sheldrick, 2008) and refined with SHELXL (Sheldrick, 2008) and the ShelxLE graphical interface (Hübschle, 2011).

Aldehydes 1e and 1l were prepared by oxidation of the corresponding alcohols.$^{[24]}$ Spectra were in accordance with literature reports.$^{[25]}$ Trityl isocyanide was synthesized as previously reported.$^{[4]}$

General synthetic procedures

Reaction optimization

To a solution of isovaleraldehyde (0.25 mmol, 1 equiv) in toluene was added the diphenyl phosphoric acid catalyst (0.025 mmol, 0.1 equiv). Then, trityl isocyanide (0.275 mmol, 1.1 equiv) was added and the resulted pale yellow solution was stirred at room temperature for 1-24 h (isocyanide consumption monitored by TLC). The reaction was then quenched with triethylamine (0.05 mmol, 0.2 equiv) and concentrated in vacuo. The crude yield was determined by NMR analysis using mesitylene as internal standard.

Procedure A. Synthesis of O-trityl cyanohydrins

To a solution of aldehyde (0.5 mmol, 1 equiv) in toluene (4 mL) was added the diphenyl phosphoric acid catalyst (0.05 mmol, 0.1 equiv). Then, trityl isocyanide (0.55 mmol, 1.1 equiv) was added and the resulted pale yellow solution was stirred at 50 °C for 5-24 h (isocyanide consumption monitored by TLC). The reaction was then quenched with triethylamine (0.1 mmol, 0.2 equiv) and concentrated in vacuo. The product was purified by column chromatography on silicagel.
Brønsted Acid-Catalyzed Cyanotritylation of Aldehydes by Trityl Isocyanide

Note: in some instances the product co-elutes with impurities (generally triphenylacetonitrile). Gradient elution was employed (starting with cyclohexane/AcOEt 100/1).

Procedure B. One-pot synthesis of cyanohydrins

To a solution of aldehyde (0.5 mmol, 1 equiv) in toluene (4 mL) was added the diphenyl phosphoric acid catalyst (0.05 mmol, 0.1 equiv). Then, trityl isocyanide (0.55 mmol, 1.1 equiv) was added and the resulted pale yellow solution was stirred at 50 °C for 5-24 h (isocyanide consumption monitored by TLC). The reaction mixture was concentrated in vacuo and redissolved in trifluoroacetic acid (1 mL). Then, Et$_3$SiH (0.75 mmol, 1.5 equiv) was added slowly. Upon addition, the intense yellow color disappeared within seconds and a white precipitate was formed. The mixture was stirred for 1 h at room temperature. The volatiles were removed and the product was purified by column chromatography on silicagel.

Procedure C. Passerini reaction

The aldehyde (0.5 mmol, 1 equiv), carboxylic acid (0.5 mmol) and trityl isocyanide (0.55 mmol, 1.1 equiv) were dissolved in dichloromethane (1 mL) and the solution was stirred at reflux for 24-48 h (isocyanide consumption monitored by TLC). The reaction was concentrated in vacuo and the product was purified by column chromatography on silicagel.

Procedure D. Deprotection of Passerini products

The Passerini product (0.2 mmol, 1 equiv) was dissolved in a mixture of TFA-dichloromethane (4:1, 0.4 mL). Then, Et$_3$SiH was added (0.3 mmol, 1.5 equiv) and the solution was stirred at room temperature for 1-20 h. The mixture was then quenched in saturated NaHCO$_3$ solution (10 mL), and the product was extracted in dichloromethane (two times). Subsequently, the organic layers were combined and dried over Na$_2$SO$_4$. The solvents were removed in vacuo and the product was purified by column chromatography on silicagel or trituration with pentane.

Procedure E. Synthesis of enantioenriched O-trityl cyanohydrins

To a solution of aldehyde (0.25 mmol, 1 equiv) in toluene (0.25 mL) was added the (R)-TRIP (19 mg, 0.025 mmol, 0.1 equiv). Then, trityl isocyanide (0.275 mmol, 1.1 equiv) in toluene (1 mL) was added dropwise over 1 h and the resulted clear solution was stirred at room temperature for 48 h. The reaction was then quenched with triethylamine (0.05 mmol, 0.2 equiv) and concentrated in vacuo. The product was purified by column chromatography on silicagel. The ee was determined by chiral HPLC analysis.

Determination of optical configuration of 3m

Enantioenriched 3m (10 mg) was dissolved in dichloromethane-methanol (1:1, 0.4 mL). Amberlyst® 15 (20 mg) was then added and the suspension was stirred at 60 °C for 4 h. The mixture was cooled, Amberlyst was filtered off and the solvents were removed in vacuo. Chiral HPLC analysis of the crude reaction mixture indicated that the major enantiomer is the S enantiomer (comparison with a commercial sample of (R)-3m). This result is consistent with the configuration established by X-ray analysis.

Chiral HPLC (Chiracel OD-H, heptane/isopropanol = 95/5, $v$ = 1.0 mL/min, column temperature: 20 °C, $\lambda$ = 214 nm) $t$ (S)-3m = 19.6, $t$ (R)-3m = 20.6 min.
Note: 3a and 3m appear to have a different order of elution of enantiomers in the chiral HPLC. It is difficult to determine whether this is due to a different interaction with the chiral stationary phase during the analysis or the selectivity of the reaction changes with the aliphatic/aromatic nature of the aldehyde (particularly since the ee obtained for 3a was moderate). Herein we assume the selectivity of the reaction with 1a and 1m to be consistent, i.e. (S)-enantiomer is the major one in both cases.

X-ray analysis

XRD-quality single crystals were obtained by slow evaporation of a CDCl₃ solution. A single crystal of 3m was mounted on a kapton loop and placed in a 100.0(1)K cold nitrogen stream on the diffractometer. Via ω scans, 116883 reflections were collected, of which 4227 were unique. Rint was 8.8%.

The enantiopure source material crystallized in the chiral space group P2₁, and the resulting atomic distances and angles are unremarkable. The Flack parameter was determined using 1811 Friedel pair quotients to 0.04(12), confirming the absolute configuration to be S. In the crystal packing there is a non-classical hydrogen bond with an unexpectedly short distance, between the hydrogen on the chiral carbon and the cyano nitrogen.

Stability of trityl isocyanide

Trityl isocyanide (27 mg, 0.1 mmol) was dissolved in THF (0.2 mL). To this solution, water/HCl 1M/NaOH 2M (0.2 mL) was added. Upon mixing the isocyanide partly precipitated out. After 2 h, ethyl acetate was added to dissolve all solids. TLC analysis indicated utmost traces of TrOH.

Mechanistic studies

E1. Control experiment of trityl isocyanide stability in the reaction conditions

Trityl isocyanide (37 mg, 0.138 mmol, 1.1 equiv) was stirred in toluene (1 mL) with DPP (2.5 mg, 0.01 mmol, 0.1 equiv) at 50 °C for 5 h. The reaction was then quenched with triethylamine (14 μL, 0.1 mmol, 1 equiv) and concentrated in vacuo. ¹H-NMR and ¹³C-NMR analysis using mesitylene as internal standard indicated 5% conversion to TrOH. TrCN was not observed.

Performing this experiment in dichloromethane showed only traces of TrOH but complete conversion of trityl isocyanide to TrCN within 1.5 h (TLC analysis).
The release of HCN from trityl isocyanide is a slow process (in toluene) and cannot account for the conversions obtained in the tritylative cyanation reaction. In dichloromethane the initially formed DPP-Tr by loss of HCN induces the trityl isocyanide isomerization via the tritylium chain mechanism.

E2. Influence of base on the reaction

Prestirring DPP with Na₂CO₃ (10 equiv) under the optimal reaction conditions suppresses the reactivity completely (TLC analysis).

E3. Hydrolysis of 3a under the reaction conditions

3a (71 mg, 0.2 mmol, 1 equiv) was stirred in toluene (1.6 mL) with DPP (5 mg, 0.02 mmol, 0.1 equiv) and H₂O (7.2 μL, 0.4 mmol, 2 equiv) at 50 °C for 5 h. The reaction was then quenched with triethylamine (28 μL, 0.2 mmol, 1 equiv) and concentrated in vacuo. ¹H-NMR analysis using mesitylene as internal standard indicated 2% conversion to 4a and TrOH.

During the tritylative cyanation of 1a, 4a is formed mostly by isocyanide addition to 1a and fragmentation of II. Formation of 4a by hydrolysis of 3a (pathway C) is not favored kinetically.

E4. Reaction in the presence of water

Reaction was done according to Procedure A with the addition of 0.5 equiv H₂O. The reaction outcome was analyzed by NMR using mesitylene as internal standard.
Chapter 4

experiments the isomerization to TrCN was completely suppressed). A minor amount of $5a$ is also formed by the trapping of the nitrilium ion with water (stage II). When the reaction is performed at room temperature, the selectivity towards $5a$ increases to 35% compared to 9% at 50 °C (this allowed the isolation and characterization of $5a$). We reason that the nitrilium ion has a longer lifetime at room temperature and water addition occurs at a comparable rate with the fragmentation whereas at higher temperatures the rate of fragmentation is greatly enhanced and only a minor amount of $5a$ is formed.

**E5. Tritylation of 4a to 3a with TrOH**

![Diagram](image)

$4a$ (11 mg, 0.1 mmol, 1 equiv) was stirred in toluene (0.8 mL) with DPP (2.5 mg, 0.01 mmol, 0.1 equiv) and TrOH (26 mg, 0.1 mmol, 1 equiv) at 50 °C for 5 h. TLC analysis indicated no reaction.

Formation of $3a$ by tritylation of $4a$ with TrOH (pathway C) is not possible (thermodynamically). The formation of $3a$ does not have TrOH as intermediate. Once the tritylium is intercepted by water traces it does not take part in the reaction.

**E6. Tritylation of 4a to 3a with DPP-Tr**

*Synthesis of DPP-Tr*

\[
\begin{align*}
\text{DPP} & \quad \text{AgOAc} \\
\text{PhO} & \quad \text{MeCN, rt, o/n} \\
\text{O} & \quad \text{PhO} \\
\text{OH} & \quad \text{PhO} \\
\text{Tol-NaOH} & \quad \text{rt, 3 h} \\
\text{PhO} & \quad \text{PhO} \\
\text{O} & \quad \text{PhO} \\
\text{OAg} & \quad \text{DPP-Tr} \\
\end{align*}
\]

DPP (250 mg, 1 mmol, 1.3 equiv) and AgOAc (167 mg, 1 mmol, 1.3 equiv) were dissolved in anhydrous MeCN (2 mL) under a nitrogen atmosphere. Upon stirring overnight, a white solid precipitated. The volatiles were removed in vacuo and the solid was suspended in toluene-d8 (2 mL). Then, trityl bromide (242 mg, 0.75 mmol, 1 equiv) was added portionwise. The mixture was stirred at room temperature for 3 h and then filtered. The filter was washed with toluene-d8 (1 mL). $^{31}$P-NMR indicated complete conversion of DPP (-10 ppm) to DPP-Tr (-18 ppm); $^{13}$C-NMR analysis indicated complete conversion of TrBr. DPP-Tr was found hydrolytically unstable upon storage in toluene (~50% hydrolysis to DPP and TrOH over 3 days). For this reason, DPP-Tr was not isolated but used as a toluene solution directly.

**Tritylation of 4a with DPP-Tr**

![Diagram](image)
A solution of DPP-Tr (0.1 mmol, 1 equiv) in toluene-d8 (0.6 mL) was added over a solution of 4a (0.1 mmol, 1 equiv) in toluene-d8 (0.2 mL). Upon mixing of the two colorless solutions, an intense yellow color appeared which persisted for a few seconds. After 5 min, the NMR of the solution was recorded. $^{31}$P-NMR indicated complete conversion of DPP-Tr to DPP; $^1$H-NMR indicated a 63% conversion of 4a to 3a.

The trityl cation released upon isocyanide fragmentation (III) is rapidly trapped by neighboring nucleophiles. The reaction with 4 is fast, particularly since 4 is in the proximity (as it is in III), leading to observed product 3. If tritylium diffuses in solution (potentially as covalently bound to diphenylphosphate, DPP-Tr) it becomes available to other nucleophiles (water, trityl isocyanide).

**Characterization of compounds**

4-methyl-2-(trityloxy)pentanenitrile 3a
Prepared from isovaleraldehyde (43 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/ACOEt 100/1, $R_f = 0.30$ in cyclohexane/ACOEt 10:1). Isolated as a white solid. Yield: 122 mg, 0.345 mmol, 69% (co-elutes with triphenylacetonitrile, reported yield is corrected for 90 wt% purity).

Large scale reaction: prepared from isovaleraldehyde (517 mg, 6.0 mmol, 1 equiv) and trityl isocyanide (1777 mg, 6.6 mmol, 1.1 equiv) according to Procedure A (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/ACOEt 100/1, $R_f = 0.30$ in cyclohexane/ACOEt 10:1). Isolated as a white solid. Yield: 1258 mg, 3.5 mmol, 59% (co-elutes with triphenylacetonitrile, reported yield is corrected for 90 wt% purity).

m.p.: 71-85 °C; $^1$H-NMR (CDCl$_3$, 500 MHz): $\delta$ 7.54-7.47 (m, 6H), 7.39-7.27 (m, 9H), 4.09 (dd, $J = 8.5$, 6.0 Hz, 1H), 1.90-1.81 (m, 1H), 1.80-1.73 (m, 1H), 1.57-1.50 (m, 1H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.79 (d, $J = 6.3$, 3H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): $\delta$ 143.0 (C), 128.9 (CH), 128.3 (CH), 127.9 (CH), 119.0 (CN), 89.1 (C), 62.2 (CH), 43.4 (CH$_2$), 24.4 (CH$_3$), 22.9 (CH$_3$), 22.1 (CH$_3$) ppm; IR (neat): $\nu_{\text{max}}$ (cm$^{-1}$) = 2957 (m), 1489 (s), 1448 (s), 1221 (m), 1059 (s), 1032 (s), 978 (m), 899 (m), 746 (s), 696 (s), 630.7 (s); HRMS (ESI): $m/z$ calculated for C$_{25}$H$_{25}$NNaO [M+Na]$^+$ 378.1828, found: 378.1823.

Enantioselective reaction: prepared from isovaleraldehyde (17 mg, 0.20 mmol, 1 equiv) and trityl isocyanide (60 mg, 0.22 mmol, 1.1 equiv) according to Procedure E. Purification: column chromatography on silicagel (cyclohexane/ACOEt 15/1, $R_f = 0.30$ in cyclohexane/ACOEt 10:1). Isolated as a white solid. Yield: 37 mg, 0.104 mmol, 52% (co-elutes with triphenylacetonitrile, reported yield is corrected for 90 wt% purity).

Chiral HPLC (Chiracel OD-H, heptane/isopropanol = 95/5, $v = 0.5$ mL/min, column temperature: 20 °C, $\lambda = 214$ nm) $t$ (minor)-3a = 9.3, $t$ (major)-3a = 10.1 min, 55% ee.

2-(trityloxy)octanenitrile 3b
Prepared from heptaldehyde (57 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/ACOEt 50/1, $R_f = 0.58$ in cyclohexane/ACOEt 10:1). Isolated as a colorless oil. Yield: 117 mg, 0.305 mmol, 61% (co-elutes with triphenylacetonitrile, reported yield is corrected for 92 wt% purity).

$^1$H-NMR (CDCl$_3$, 500 MHz): $\delta$ 7.58-7.51 (m, 6H), 7.43-7.36 (m, 6H), 7.33 (tt, $J = 7.3$, 2.5 Hz, 3H), 4.17 (dd, $J = 7.6$, 4.7 Hz, 1H), 1.88-1.79 (m, 1H), 1.74-1.66 (m, 1H), 1.66-1.56 (m, 1H), 1.50-1.39 (m, 1H), 1.38-1.24 (m, 6H), 0.93 (t, 3H).
J = 6.9 Hz, 3H ppm; $^{13}$C{¹H}-NMR (CDCl₃, 125 MHz): δ 143.0 (C), 128.8 (CH), 128.2 (CH), 127.9 (CH), 118.7 (CN), 88.9 (C), 63.3 (CH), 34.6 (CH₂), 31.6 (CH₂), 28.8 (CH₂), 24.4 (CH₂), 22.6 (CH₂), 14.1 (CH₃) ppm; IR (neat): v_max (cm⁻¹) = 2955 (m), 2930 (m), 1489 (s), 1447 (m), 1221 (m), 1061 (s), 1032 (s), 899 (m), 748 (s), 696 (s), 644 (s); HRMS (ESI): m/z calculated for C₂₇H₂₉NNaO [M+Na]⁺ 406.2141, found: 406.2137.

3-(benzylxylo)-2-(trityloxy)propanenitrile 3c
Prepared from (benzylxylo)acetaldehyde (75 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 100/1, Rf = 0.31 in cyclohexane/AcOEt 10:1). Isolated as a colorless oil. Yield: 136 mg, 0.325 mmol, 65% (co-elutes with triphenylacetonitrile, reported yield is corrected for 96 wt% purity).

$^1$H-NMR (CDCl₃, 500 MHz): δ 7.58-7.51 (m, 6H), 7.43-7.30 (m, 14H), 4.62 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.37 (t, J = 6.0 Hz, 1H), 3.71 (dd, J = 10.4, 6.3 Hz, 1H), 3.62 (dd, J = 10.4, 6.0 Hz, 1H) ppm; $^{13}$C{¹H}-NMR (CDCl₃, 125 MHz): δ 142.6 (C), 137.3 (C), 128.9 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 117.4 (CN), 89.3 (C), 73.7 (CH₂), 70.5 (CH₂), 63.0 (CH) ppm; IR (neat): ν_max (cm⁻¹) = 3059 (m), 2966 (m), 2177 (s), 1489 (s), 1447 (s), 1250 (s), 1084 (s), 837 (s), 750 (s), 706 (s), 633 (s); HRMS (ESI): m/z calculated for C₂₉H₂₅NNaO₂ [M+Na]⁺ 442.1773, found: 442.1778.

3-phenyl-2-(trityloxy)propanenitrile 3d
Prepared from 2-phenylacetaldehyde (60 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 100/1, Rf = 0.39 in cyclohexane/AcOEt 10:1). Isolated as a white solid. Yield: 82 mg, 0.210 mmol, 42% (co-elutes with triphenylacetonitrile, reported yield is corrected for 98 wt% purity).
m.p.: 135-139 °C; $^1$H-NMR (CDCl₃, 500 MHz): δ 7.53-7.45 (m, 6H), 7.39-7.27 (m, 12H), 7.18 (dd, J = 7.9, 1.6 Hz, 2H), 4.32 (dd, J = 7.9, 5.4 Hz, 1H), 2.54 (ddd, J = 17.3, 7.9, 6.0 Hz, 1H), 2.43 (dt, J = 17.3, 7.9 Hz, 1H), 2.12-2.00 (m, 2H), 0.10 (s, 9H) ppm; $^{13}$C{¹H}-NMR (CDCl₃, 125 MHz): δ 142.8 (C), 134.4 (C), 130.0 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 118.4 (CN), 89.4 (C), 64.8 (CH), 41.2 (CH₂) ppm; IR (neat): ν_max (cm⁻¹) = 3028 (m), 1489 (s), 1450 (s), 1339 (m), 1157 (s), 1068 (s), 997 (s), 903 (m), 754 (s), 696 (s), 635 (s); HRMS (ESI): m/z calculated for C₂₈H₂₃NNaO [M+Na]⁺ 412.1672, found: 412.1658.

6-(trimethylsilyl)-2-(trityloxy)hex-5-ynenitrile 3e
Prepared from 5-(trimethylsilyl)pent-4-ynal (93 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (5.5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 100/1, Rf = 0.45 in cyclohexane/AcOEt 10:1). Isolated as a white solid. Yield: 146 mg, 0.345 mmol, 69%.
m.p.: 100-106 °C; $^1$H-NMR (CDCl₃, 500 MHz): δ 7.52-7.48 (m, 6H), 7.36 (tt, J = 7.6, 1.6 Hz, 6H), 7.32 (tt, J = 6.9, 2.2 Hz, 3H), 4.29 (dd, J = 6.9, 5.4 Hz, 1H), 2.54 (ddd, J = 17.3, 7.9, 6.0 Hz, 1H), 2.43 (dt, J = 17.3, 7.9 Hz, 1H), 2.12-2.00 (m, 2H), 0.10 (s, 9H) ppm; $^{13}$C{¹H}-NMR (CDCl₃, 125 MHz): δ 142.7 (C), 128.8 (CH), 128.3 (CH), 128.0 (CH), 118.1 (CN), 104.4 (C), 89.2 (C), 86.3 (C), 62.2 (CH), 33.7 (CH₂), 15.7 (CH₂), 0.1 (CH₃) ppm; IR (neat): ν_max (cm⁻¹) = 3059 (m), 2996 (m), 2177 (s), 1489 (s), 1447 (s), 1250 (s), 1084 (s), 905 (s), 837 (m), 750 (s), 706 (s); HRMS (ESI): m/z calculated for C₂₈H₂₃NNaO₂Si [M+Na]⁺ 446.1911, found: 446.1912.
Brønsted Acid-Catalyzed Cyanotritylation of Aldehydes by Trityl Isocyanide

2-cyclopropyl-2-(trityloxy)acetonitrile 3f
Prepared from cyclopropenecarboxaldehyde (35 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (6 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 100/1, Rf = 0.39 in cyclohexane/AcOEt 10:1). Isolated as a white solid. Yield: 85 mg, 0.250 mmol, 50%.

m.p.: 106 - 111 °C; 1H-NMR (CDCl₃, 500 MHz): δ 7.58 - 7.53 (m, 6H), 7.40 - 7.35 (m, 6H), 7.32 (tt, J = 7.3, 2.5 Hz, 3H), 3.96 (d, J = 6.9 Hz, 1H), 1.40 - 1.32 (m, 1H), 0.75 - 0.65 (m, 2H), 0.57 - 0.51 (m, 1H), 0.43 - 0.37 (m, 1H) ppm; 13C{1H}-NMR (CDCl₃, 125 MHz): δ 142.9 (C), 128.9 (CH), 128.2 (CH), 127.9 (CH), 117.3 (CN), 88.8 (C), 66.7 (CH), 14.9 (CH), 4.6 (CH₂), 2.5 (CH₂) ppm; IR (neat): νmax (cm⁻¹) = 3057 (m), 3026 (m), 1489 (s), 1448 (s), 1339 (m), 1157 (m), 1067 (s), 999 (s), 756 (s), 696 (s), 635 (s); HRMS (ESI): m/z calculated for C₂₄H₂₁NNaO [M+Na]⁺ 362.1515, found: 362.1516.

2-cyclohexyl-2-(trityloxy)acetonitrile 3g
Prepared from cyclohexanecarbaldehyde (56 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 100/1, Rf = 0.33 in cyclohexane/AcOEt 10:1). Isolated as a white solid. Yield: 97 mg, 0.255 mmol, 51% (co-elutes with triphenylacetonitrile, reported yield is corrected for 85 wt% purity).

m.p.: 103 - 130 °C; 1H-NMR (CDCl₃, 500 MHz): δ 7.60 - 7.53 (m, 6H), 7.42 - 7.36 (m, 6H), 7.34 (tt, J = 7.3, 2.5 Hz, 3H), 3.97 (d, J = 4.4 Hz, 1H), 2.16 - 2.09 (m, 1H), 1.90 - 1.83 (m, 1H), 1.83 - 1.67 (m, 2H), 1.64 - 1.54 (m, 2H), 1.39 - 1.12 (m, 5H) ppm; 13C{1H}-NMR (CDCl₃, 125 MHz): δ 143.1 (C), 128.8 (CH), 128.2 (CH), 127.8 (CH), 117.8 (CN), 88.7 (C), 68.1 (CH), 42.0 (CH), 28.5 (CH₂), 27.6 (CH₂), 26.1 (CH₂), 25.8 (CH₂), 25.7 (CH₂), ppm; IR (neat): νmax (cm⁻¹) = 2926 (s), 2854 (s), 1489 (s), 1447 (s), 1228 (m), 1045 (s), 980 (s), 899 (s), 767 (s), 756 (s), 694 (s); HRMS (ESI): m/z calculated for C₂₇H₂₇NNaO [M+Na]⁺ 404.1985, found: 404.1976.

tert-butyl 4-(cyano(trityloxy)methyl)piperidine-1-carboxylate 3h
Prepared from tert-butyl 4-formylpiperidine-1-carboxylate (110 mg, 0.51 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (24 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 100/1, Rf = 0.20 in cyclohexane/AcOEt 10:1). Isolated as a colorless oil. Yield: 57 mg, 0.117 mmol, 23%.

1H-NMR (CDCl₃, 500 MHz): δ 7.53 - 7.47 (m, 6H), 7.39 - 7.27 (m, 9H), 4.40 (br, 2H), 3.95 (d, J = 4.7 Hz, 1H), 2.60 (br, 2H), 1.98-1.87 (m, 1H), 1.72-1.58 (m, 1H), 1.57-1.39 (m, 2H), 1.46 (s, 9H), 1.39-1.22 (m, 1H). ppm; 13C{1H}-NMR (CDCl₃, 125 MHz): δ 154.7 (CO), 142.8 (C), 128.8 (CH), 128.3 (CH), 128.0 (CH), 117.3 (CN), 89.0 (C), 79.7 (C), 67.1 (CH), 40.6 (CH), 39.0 (CH₂), 29.8 (CH₂), 28.5 (CH₂), 27.5 (CH₂), 27.0 (CH₂) ppm; IR (neat): νmax (cm⁻¹) = 2926 (s), 1684 (s), 1489 (s), 1449 (s), 1053 (s), 978 (s), 901 (s), 767 (s), 698 (s), 644 (s), 631 (s); HRMS (ESI): m/z calculated for C₃₁H₃₄N₂NaO [M+Na]⁺ 505.2462, found: 505.2452.

Note: most likely conformational changes (ring flip, N-Boc rotation) occur on the NMR time scale which determine the broadening of some signals in 1H-NMR and lower the intensity of some signals in 13C-NMR.

3-methyl-2-(trityloxy)butanenitrile 3i
Prepared from isobutyraldehyde (36 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 100/1, Rf = 0.39 in cyclohexane/AcOEt 10:1). Isolated as a white solid. Yield: 81 mg, 0.244 mmol, 55%.
chromatography on silicagel (cyclohexane/AcOEt 100/1, R<sub>f</sub> = 0.38 in cyclohexane/AcOEt 10:1). Isolated as a white solid. Yield: 123 mg, 0.360 mmol, 72%.

m.p.: 105-109 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz): δ 7.58-7.52 (m, 6H), 7.42-7.36 (m, 6H), 7.33 (tt, J = 7.3, 2.5 Hz, 3H), 4.02 (d, J = 4.4 Hz, 1H), 2.01-1.90 (m, 1H), 1.22 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H) ppm; <sup>13</sup>C<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 125 MHz): δ 143.0 (C), 128.8 (CH), 128.2 (CH), 127.8 (CH), 117.3 (CN), 88.8 (C), 68.8 (CH), 32.7 (CH), 18.2 (CH<sub>3</sub>) ppm; IR (neat): νmax (cm<sup>-1</sup>) = 2934 (m), 1489 (s), 1447 (s), 1354 (s), 1213 (s), 1053 (s), 1030 (s), 980 (s), 901 (s), 766 (s), 631 (s); HRMS (ESI): m/z calculated for C<sub>24</sub>H<sub>23</sub>NaO [M+Na]<sup>+</sup> 364.1672, found: 364.1667.

3-phenyl-2-(trityloxy)butanenitrile 3j
Prepared from 2-phenylpropanal (67 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 100/1, R<sub>f</sub> = 0.30 in cyclohexane/AcOEt 10:1). Diastereoisomers (formed in ~1:1 ratio) were only partly resolved. Isolated as white amorphous solids. Combined yield: 122 mg, 0.345 mmol, 69% (co-elutes with triphenylacetonitrile, reported yield is corrected for 90 wt% purity).

Fraction 1 (20:1 ratio, relative configuration not assigned): <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz): δ 7.53-7.49 (m, 6H), 7.44-7.17 (m, 12H), 7.10-7.05 (m, 2H), 4.24 (dd, J = 5.0 Hz, 1H), 2.86-2.77 (m, 1H), 1.56 (d, J = 6.9 Hz, 3H) ppm; <sup>13</sup>C<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 125 MHz): δ 143.0 (C), 139.6 (C), 128.9 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 117.4 (CN), 89.5 (C), 69.6 (CH), 43.3 (CH), 14.5 (CH<sub>3</sub>) ppm; IR (neat): νmax (cm<sup>-1</sup>) = 2926 (s), 2854 (s), 1489 (s), 1448 (s), 1340 (m), 1223 (s), 1045 (s), 978 (s), 899 (s), 694 (s); HRMS (ESI): m/z calculated for C<sub>29</sub>H<sub>25</sub>NaO [M+Na]<sup>+</sup> 426.1828, found: 426.1823.

Fraction 2 (1:5 ratio, relative configuration not assigned): <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz): δ 7.44-7.27 (m, 20H), 4.21 (dd, J = 5.0 Hz, 1H), 3.07-3.00 (m, 1H), 1.40 (d, J = 7.3 Hz, 3H) ppm; <sup>13</sup>C<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 125 MHz): δ 142.8 (C), 139.9 (C), 128.9 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.6 (CH), 117.6 (CN), 89.0 (C), 68.2 (CH), 43.3 (CH), 16.1 (CH<sub>3</sub>) ppm;

IR (neat): νmax (cm<sup>-1</sup>) = 2968 (m), 1595 (m), 1489 (s), 1445 (s), 1182 (m), 1063 (s), 1030 (s), 978 (s), 910 (s), 748 (s), 696 (s), 642 (s); HRMS (ESI): m/z calculated for C<sub>25</sub>H<sub>25</sub>NaO [M+Na]<sup>+</sup> 378.1828, found: 378.1819.

3,3-dimethyl-2-(trityloxy)butanenitrile 3k
Prepared from pivaldehyde (43 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 100/1, R<sub>f</sub> = 0.47 in cyclohexane/AcOEt 10:1). Isolated as a white solid. Yield: 96 mg, 0.270 mmol, 54% (co-elutes with triphenylacetonitrile, reported yield is corrected for 90 wt% purity).

m.p.: 90-105 °C; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 500 MHz): δ 7.55-7.50 (m, 6H), 7.35-7.30 (m, 6H), 7.27 (tt, J = 7.6 Hz, 1.6 Hz, 3H), 3.29 (s, 1H), 1.07 (s, 9H) ppm; <sup>13</sup>C<sup>1</sup>H-NMR (CDCl<sub>3</sub>, 125 MHz): δ 143.1 (C), 129.0 (CH), 128.1 (CH), 127.8 (CH), 118.1 (CN), 88.5 (C), 71.4 (CH), 36.3 (C), 26.0 (CH<sub>3</sub>) ppm; IR (neat): νmax (cm<sup>-1</sup>) = 2968 (m), 1595 (m), 1489 (s), 1445 (s), 1182 (m), 1063 (s), 1030 (s), 901 (s), 748 (s), 696 (s), 642 (s); HRMS (ESI): m/z calculated for C<sub>25</sub>H<sub>25</sub>NaO [M+Na]<sup>+</sup> 378.1828, found: 378.1819.

2-phenyl-2-(trityloxy)acetonitrile 3m
Prepared from benzaldehyde (53 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure A (7 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 100/1, R<sub>f</sub> = 0.36 in cyclohexane/AcOEt 10:1).
**Brønsted Acid-Catalyzed Cyanotritylation of Aldehydes by Trityl Isocyanide**

Isolated as a white solid. Yield: 49 mg, 0.130 mmol, 26%.

m.p.: 116-118 °C; ¹H-NMR (CDCl₃, 500 MHz): δ 7.58-7.51 (m, 6H), 7.48-7.29 (m, 14H), 5.16 (s, 1H) ppm; ¹³C{¹H}-NMR (CDCl₃, 125 MHz): δ 142.7 (C), 135.6 (C), 129.4 (CH), 129.1 (CH), 128.9 (CH), 128.3 (CH), 128.0 (CH), 127.1 (CH), 118.0 (CN), 90.0 (C), 65.2 (CH) ppm; IR (neat): νmax (cm⁻¹) = 3059 (m), 2177 (m), 1489 (s), 1448 (s), 1217 (m), 1082 (s), 1051 (s), 972 (s), 905 (s), 839 (s), 694 (s); HRMS (ESI): m/z calculated for C₂₇H₂₁NNaO [M+Na]⁺ 398.1515, found: 398.1499.

**Enantioselective reaction:** prepared from benzaldehyde (27 mg, 0.25 mmol, 1 equiv) and trityl isocyanide (135 mg, 0.5 mmol, 2 equiv) according to Procedure E. Purification: column chromatography on silicagel (cyclohexane/AcOEt 30/1, Rf = 0.2 in cyclohexane/AcOEt 30:1). Isolated as a white solid. Yield: 47 mg, 0.125 mmol, 50%.

Chiral HPLC (Chiracel OD-H, heptane/isopropanol = 95/5, v = 0.5 mL/min, column temperature: 20 °C, λ = 214 nm) t (major) - 3m = 14.0, t (minor) - 3m = 15.2 min, 79% ee.

2-hydroxyoctanenitrile 4b
Prepared from heptaldehyde (57 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure B (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 10/1, Rf = 0.16). Isolated as a pale yellow oil. Yield: 49 mg, 0.350 mmol, 70%. Spectra in accordance to literature report.[²⁶]

¹H-NMR (CDCl₃, 500 MHz): δ 4.48 (t, J = 7.0 Hz, 1H), 3.43 (br, 1H), 1.86-1.82 (m, 2H), 1.54-1.43 (m, 2H), 1.39-1.24 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H) ppm;
¹³C{¹H}-NMR (CDCl₃, 125 MHz): δ 119.9 (CN), 61.4 (CH), 35.3 (CH₂), 31.6 (CH₂), 28.6 (CH₂), 24.5 (CH₂), 22.5 (CH₂), 14.2 (CH₃) ppm.

2-cyclohexyl-2-hydroxyacetonitrile 4g
Prepared from cyclohexanecarbaldehyde (56 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure B (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 10/1, Rf = 0.37). Isolated as a colorless oil. Yield: 63 mg, 0.450 mmol, 90% (co-elutes with triethylsilanol, reported yield is corrected for 97 wt% purity). Spectra in accordance to literature report.[²⁶]

¹H-NMR (CDCl₃, 500 MHz): δ 4.28 (t, J = 6.0 Hz, 1H), 3.55 (br, 1H), 1.92-1.70 (m, 6H), 1.33-1.03 (m, 5H) ppm;
¹³C{¹H}-NMR (CDCl₃, 125 MHz): δ 119.0 (CN), 66.5 (CH), 42.4 (CH), 28.1 (CH₂), 27.8 (CH₂), 26.0 (CH₂), 25.5 (CH₂), 25.5 (CH₂) ppm.

2-phenyl-2-hydroxyacetonitrile 4m
Prepared from benzaldehyde (53 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure B (5 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 7/1, Rf = 0.13). Isolated as a colorless oil. Yield: 20 mg, 0.15 mmol, 30%. Spectra in accordance to literature report.[²⁶]

¹H-NMR (CDCl₃, 500 MHz): δ 7.55-7.51 (m, 2H), 7.48-7.43 (m, 3H), 5.52 (s, 1H), 3.50 (br, 1H) ppm; ¹³C{¹H}-NMR (CDCl₃, 125 MHz): δ 135.3 (C), 129.9 (CH), 128.3 (CH), 126.7 (CH), 119.0 (CN), 63.6 (CH) ppm.
4-methyl-1-oxo-1-(tritylamino)pentan-2-yl acetate 6a
Prepared from isovaleraldehyde (43 mg, 0.5 mmol, 1 equiv), acetic acid (30 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure C (24 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 10/1). Isolated as a white amorphous solid. Yield: 172 mg, 0.415 mmol, 83%.

\[
\begin{align*}
\text{H-NMR (CDCl}_3, 500 MHz): & \quad \delta 7.37-7.31 (m, 6H, 6H), 7.29 (tt, J = 7.3, 2.2 Hz, 3H), 7.27-7.21 (m, 7H), 5.27 (dd, J = 9.1, 3.8 Hz, 1H), 2.19 (s, 3H), 1.82-1.66 (m, 3H), 0.97 (d, J = 6.3 Hz, 3H); \\
\text{C}{\text{H}}-\text{NMR (CDCl}_3, 125 MHz): & \quad \delta 170.0 (CO), 168.8 (CO), 144.4 (C), 128.5 (CH), 128.0 (CH), 127.2 (CH), 73.4 (CH), 70.2 (C), 40.3 (CH), 24.5 (CH), 23.1 (CH), 21.7 (CH), 20.9 (CH); \\
\text{IR (neat):} & \quad \nu_{\text{max}} (\text{cm}^{-1}) = 2957 (m), 1740 (s), 1697 (s), 1489 (m), 1447 (w), 1369 (s), 1215 (s), 1068 (s), 750 (s), 696 (s); \\
\text{HRMS (ESI):} & \quad m/z \text{ calculated for C}_{27}H_{29}NNaO}_3 [M+Na]^+ 438.2040, \text{found: } 438.2031.
\end{align*}
\]

1-(3-nitrophenyl)-2-oxo-2-(tritylamino)ethyl benzoate 6b
Prepared from 3-nitrobenzaldehyde (76 mg, 0.5 mmol, 1 equiv), benzoic acid (61 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure C (24 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 10/1 to 3:1, Rf = 0.50 in cyclohexane/AcOEt 3:1). Isolated as a white solid. Yield: 201 mg, 0.370 mmol, 74%.

m.p.: 82-83.7 °C; \text{H-NMR (CDCl}_3, 500 MHz): \delta 8.41 (s, 1H), 8.25 (dd, J = 8.2, 1.3 Hz, 1H), 8.21 (d, J = 7.5 Hz, 2H), 7.93 (s, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.72 (t, J = 7.3 Hz, 1H), 7.61-7.25 (m, 15H), 6.50 (s, 1H); \text{C}{\text{H}}-\text{NMR (CDCl}_3, 125 MHz): \delta 166.0 (CO), 164.6 (CO), 148.2 (C), 144.0 (C), 137.2 (C), 134.2 (CH), 129.8 (CH), 129.7 (CH), 128.8 (CH), 128.5 (CH), 128.1 (CH), 127.3 (CH), 123.8 (CH), 122.2 (CH), 75.0 (CH), 70.7 (C); \text{IR (neat):} \nu_{\text{max}} (\text{cm}^{-1}) = 1701 (s), 1680 (s), 1528 (s), 1489 (s), 1349 (s), 1244 (s), 1026 (m), 698 (s); \text{HRMS (ESI):} m/z \text{ calculated for C}_{34}H_{26}NNO_5 [M+Na]^+ 565.1734, \text{found: } 565.1708.

Note: two quaternary carbon signals overlap.

1-(4-chlorophenyl)-2-oxo-2-(tritylamino)ethyl acetate 6c
Prepared from p-chlorobenzaldehyde (71 mg, 0.5 mmol, 1 equiv), acetic acid (30 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure C (23 h reaction time). Purification: column chromatography on silicagel (cyclohexane/AcOEt 10/1 to 4:1, Rf = 0.32 in cyclohexane/AcOEt 4:1). Isolated as a white solid. Yield: 139 mg, 0.295 mmol, 59%.

m.p.: 57.3-75.5 °C; \text{H-NMR (CDCl}_3, 400 MHz): \delta 7.42-7.28 (m, 14H), 7.18 (d, J = 7.7 Hz, 6H), 6.05 (s, 1H), 2.24 (s, 3H); \text{C}{\text{H}}-\text{NMR (CDCl}_3, 125 MHz): \delta 169.4 (CO), 166.2 (CO), 144.2 (C), 135.1 (C), 133.6 (C), 129.0 (CH), 128.9 (CH), 128.6 (CH), 127.3 (CH), 75.4 (CH), 70.6 (C), 21.1 (CH); \text{IR (neat):} \nu_{\text{max}} (\text{cm}^{-1}) = 3315 (s), 3044 (s), 2388 (s), 1755 (m), 1682 (w), 1496 (w), 1244 (w), 1166 (m), 7.54 (m), 698 (w), 623 (s); \text{HRMS (ESI):} m/z \text{ calculated for C}_{29}H_{24}ClNO_3 [M+H]^+ 470.1517, \text{found: } 470.1497.

Passerini product 6d
Prepared from aldehyde 1 (142 mg, 0.5 mmol, 1 equiv), benzoic acid (62 mg, 0.5 mmol, 1 equiv) and trityl isocyanide (148 mg, 0.55 mmol, 1.1 equiv) according to Procedure C (48 h reaction time). Purification: column chromatography on silicagel
(cyclohexane/AcOEt 1/1, \( R_f = 0.16 \)). Diastereoisomers (formed in 1.5:1 ratio) were not resolved. Isolated as a white solid. Combined yield: 215 mg, 0.320 mmol, 64%.

\[ \text{m.p.: 127-153 °C; } ^1\text{H-NMR (CDCl}_3, 500 MHz; D1:D2 ratio 1.5:1): } \delta \text{ 9.8 (s, NH, D1), 9.7 (s, NH, D2), 8.10-8.03 (m, 2H, D1, 2H, D2), 7.70 (s, NH, D1), 7.67-7.58 (m, 1H, D1, 1H, D2), 7.56 (s, NH, D2), 7.52-7.44 (m, 2H, D1, 2H, D2), 7.35 (d, } J = 7.9 \text{ Hz, 1H, D1), 7.31-7.18 (m, 15H, D1, 15H, D2), 7.16 (d, } J = 8.20 \text{ Hz, 1H, D2), 5.85-5.78 (m, 2H, D1, 2H, D2), 5.57 (d, } J = 7.9 \text{ Hz, 1H, D1), 5.52 (dd, } J = 6.3, 3.5 \text{ Hz, 1H, D2), 5.01 (dd, } J = 6.3, 3.8 \text{ Hz, 1H, D1), 4.96 (dd, } J = 6.3, 3.2 \text{ Hz, 1H, D2), 4.88 (dd, } J = 6.3, 2.8 \text{ Hz, 1H, D1), 4.73 (t, } J = 3.8 \text{ Hz, 1H, D1), 4.65 (t, } J = 3.8 \text{ Hz, 1H, D2), 1.61 (s, 3H, D2), 1.60 (s, 3H, D1), 1.37 (s, 3H, D2), 1.36 (s, 3H, D1) ppm; } ^{13}\text{C}[^1\text{H}]-\text{NMR (CDCl}_3, 125 MHz): } \delta \text{ 165.6 (CO, D1), 165.5 (CO, D2), 93.0 (CH, D1), 85.3 (CH, D2), 127.8 (CH, D1), 128.5 (CH, D1), 128.4 (C, D1), 128.1 (CH, D1), 128.0 (CH, D2), 127.3 (CH, D1), 127.2 (CH, D2), 115.1 (C, D2), 114.8 (C, D1), 103.1 (CH, D2), 102.7 (CH, D1), 93.7 (CH, D2), 93.0 (CH, D1), 85.3 (CH, D1), 85.0 (CH, D2), 84.1 (CH, D1), 83.3 (CH, D2), 81.3 (CH, D2), 80.3 (CH, D1), 73.4 (CH, D2), 73.3 (CH, D1), 70.8 (C, D2), 70.7 (C, D1), 27.2 (CHs, D1 and D2), 25.4 (CHs, D1), 25.3 (CHs, D2) ppm; IR (neat): v\text{max (cm}^{-1}) = 3059 (w), 1678 (br), 1491 (s), 1448 (s), 1419 (s), 1379 (s), 1246 (br), 1084 (s), 1067 (s), 905 (m), 810 (m), 698 (s); HRMS (ESI): m/z calculated for C_{15}H_{12}N_{2}NaO_4 [M+Na]^+ 263.0618, found: 264.0618.

\[ \text{2-amino-1-(4-chlorophenyl)-2-oxoethyl acetate 7c} \]
Prepared from 6c (130 mg, 0.28 mmol) according to Procedure D (1 h reaction time). The crude reaction mixture was dried over a stream of nitrogen. Purification: column chromatography on silica gel (cyclohexane/AcOEt 1/1, \( R_f = 0.17 \)). Isolated as a white solid. Yield: 49 mg, 0.216 mmol, 77%.
m.p.: 111-114 °C; 1H-NMR (CDCl₃, 400 MHz): δ 7.38 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 6.33 (br, 1H), 6.27 (br, 1H), 6.02 (s, 1H), 2.18 (s, 3H) ppm; 13C(1H)-NMR (CDCl₃, 125 MHz): δ 170.8 (CO), 169.2 (CO), 135.2 (C), 133.8 (C), 129.1 (CH), 128.9 (CH), 74.6 (CH), 21.1 (CH₃) ppm; IR (neat): v max (cm⁻¹) = 3311 (m), 3178 (m), 2967 (s), 1735 (m), 1632 (w), 1488 (s), 1409 (m), 1367 (s), 1222 (w), 1093 (s), 1039 (m), 821 (s), 661 (w), 544 (m); HRMS (ESI): m/z calculated for C₁₃H₁₇NO₃ [M+Na]⁺ 250.0241, found: 250.0246.

2-hydroxy-4-methyl-N-tritylpentanamide 5a

Isolated from experiment E4 in the mechanistic section (cyclohexane/AcOEt 6/1, Rᵢ = 0.15 in cyclohexane/AcOEt 1:1). Isolated as a white solid.

m.p.: 171-172 °C; 1H-NMR (CDCl₃, 500 MHz): δ 7.77 (br, 1H), 7.36-7.25 (m, 9H), 7.21 (d, J = 7.0 Hz, 6H), 4.13 (dd, J = 9.5, 2.3 Hz, 1H), 2.77 (br, 1H), 1.88-1.77 (m, 1H), 1.71-1.54 (m, 2H), 0.97 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H) ppm; 13C(1H)-NMR (CDCl₃, 125 MHz): δ 173.2 (CO), 144.7 (C), 128.7 (CH), 128.1 (CH), 127.2 (CH), 71.3 (CH), 70.0 (C), 43.9 (CH₃), 24.7 (CH), 23.6 (CH₃), 21.4 (CH₃) ppm; IR (neat): v max (cm⁻¹) = 3238 (w), 1664 (s), 1564 (s), 1500 (s), 1492 (s), 1350 (s), 1286 (m), 1191 (m), 1139 (s), 1013 (s), 941 (w), 821 (s), 752 (m), 661 (w), 544 (m); HRMS (ESI): m/z calculated for C₁₃H₁₇NO₃ [M+Na]⁺ 250.0246, found: 250.0246.

References and Notes


[5] Trityl isocyanide was found to be stable in water, 2 M NaOH and 1 M HCl; see the Supporting Information for details.


[8] A different mechanism may operate in this case.


[10] Triphenylacetoneitrile coelutes with some O-trityl cyanohydrins. Purity of all isolated products is > 90 wt%.

[11] 3a was found to be stable to hydrolysis under the reaction conditions (10 mol% DPP, toluene, 50 °C, 5 h with 2 equiv water), so 4a must originate exclusively from isocyanide addition and fragmentation.

[12] Trityl phosphates have been recently shown to be potent tritylium sources, see: J. Lv, Z. Zhang, X. Zhong, S. Luo, J. Am. Chem. Soc. 2015, 137, 15576-15583.

[13] 100% conversion of DPP-Tr to DPP (based on ³¹P-NMR) and 62% conversion of 4a to 3a (hydrolysis of DPP-Tr also occurs).
Brønsted Acid-Catalyzed Cyanotritylation of Aldehydes by Trityl Isocyanide


[16] Only 5% hydrolysis to TrOH was observed while stirring trityl isocyanide with catalytic DPP at 50 °C for 5 h (no TrCN).


[19] This is also reflected in physical properties: in contrast with most other isocyanides that have a foul smell, trityl isocyanide is odorless.


[22] Although theoretically possible, Lewis acid catalysis applied to reactions with trityl isocyanide is limited by the fast metal ion-mediated isomerization of the reagent.


Chapter 5

An Ugi Approach towards Racetams

Abstract: In this chapter the Ugi 4C-3CR synthesis of racetam derivatives is described. For the first time, γ-aminobutyric acid is employed as bifunctional input in the Ugi reaction. This protocol is simple, general and allows one-pot access to various drugs and bioactive small molecules.

Published in Synthesis 2017, 49, 1664-1674.
Introduction

Racetams are a broad class of drugs that feature a pyrrolidone ring. Of particular importance are the 2-oxo-1-pyrrolidino acetamide derivatives (Figure 1), which find widespread use in the treatment of various medical conditions, such as epilepsy, dementia, depression, anxiety, hypoxia, etc.\(^1\) Despite more than 50 years of clinical significance, the 2-oxo-1-pyrrolidino acetamide remains an interesting pharmacophore for medicinal chemistry and novel applications of racetam derivatives continue to be developed.\(^2\)

![Figure 1. Commercial drugs of the racetam class.](image)

Structurally, the bioactive 2-oxo-1-pyrrolidino acetamides are relatively simple small molecules; their synthesis is straightforward and invariably relies on an S\(_{N}\)2 reaction with pyrrolidone to introduce the γ-lactam unit. In the context of drug design, this approach, although reliable and robust, has certain drawbacks, such as: it is time-consuming (linear, multistep synthesis), it provides a reduced variability at the α-position of the acetamide (due to the limited availability of precursors) and it features S\(_{N}\)2-specific scope limitations (substrates with base-sensitive functionalities, additional electrophilic centers, bulky substituents). Therefore, for the combinatorial synthesis of novel racetam analogues, a chemoselective convergent/multicomponent approach would be more suited.

![Scheme 1. Conventional vs. multicomponent synthesis of racetams.](image)
Recognizing the general 2-oxo-1-pyrrolidino acetamide structure as an Ugi scaffold,[3] we envisaged to prepare racetam derivatives via this multicomponent condensation. Ugi approaches towards racetam derivatives have been reported before, but these methods graft the pyrrolidone core indirectly, by subsequent manipulation (i.e. xanthate cyclization,[4] olefin metathesis[5]) of Ugi adducts with proper reactivity handles. Instead, we decided to pursue the direct synthesis, in which γ-aminobutyric acid is combined with a carbonyl compound and an isocyanide to afford the 2-oxo-1-pyrrolidino acetamide scaffold in one simple step.

Amino acids have been intensively applied in Ugi chemistry (Scheme 2). In the case of α-amino acids, the typical Mumm rearrangement is kinetically blocked and the α-adduct undergoes reactions with external nucleophiles (alcohols,[6] amines[7]) or internal nucleophiles (alcohols[8]) instead. On the other hand, β-amino acids, unless sterically constrained[9] do follow the complete Ugi pathway, including the final rearrangement leading to β-lactam derivatives.[10] Remarkably, the use of γ-amino acids and higher homologues[11] has not been thoroughly investigated in the Ugi reaction. Extrapolating the behavior of the first members of the series, it is expected that γ-amino acids would react in an Ugi condensation by the contraction of the eight-membered ring α-adduct to a pyrrolidone derivative upon Mumm rearrangement. This hypothesis was just recently validated by Darehkordi et al. who showed that 2-(1-aminomethyl)cyclohexylacetic acid (gabapentin) can be successfully applied in Ugi 3CR condensations;[12] however, this bifunctional input is strongly biased by the Thorpe-Ingold effect towards cyclization and one should be cautious when generalizing this reactivity to linear un-branched amino acids.

Scheme 2. Ugi reactions with amino acids.
Although deceptively simple, the use of γ-amino acids in the Ugi reaction faces a number of challenges. The formation of the α-adduct, an 8-membered ring, is plausibly a slow process;\textsuperscript{[13]} competition with the intermolecular Ugi reaction is anticipated. Furthermore, the lactamization of γ-aminobutyric acid (possibly isocyanide-mediated\textsuperscript{[14]}) is also a kinetically relevant transformation, particularly at elevated temperatures. Finally, the ring-contraction trans-annulation (the Mumm rearrangement) in this medium-sized ring may also be problematic and lead to undesired side reactions (solvolyis, addition of external nucleophiles).

**Results and Discussion**

Indeed, when performing the reaction between γ-aminobutyric acid, tert-butyl isocyanide and an aldehyde (aliphatic or aromatic) under typical Ugi conditions – methanolic solution, 1 M concentration, room temperature – the yield of the desired product was very low as the anticipated side-reactions occur as well. Extensive optimization efforts\textsuperscript{[15]} were rewarded with a significantly improved selectivity and a satisfactory yield for the expected 2-oxo-1-pyrrolidino acetamide derivative using 2,2,2-trifluoroethanol (TFE) as solvent at relatively high dilutions.\textsuperscript{[16]} With the optimized protocol in hand, we set out to explore the scope of this reaction (Table 1).

The key (and rate-determining) step in the Ugi-type reactions is believed to be the addition of the isocyanide to the iminium ion;\textsuperscript{[17]} in this sense, we observe that in general the yield of the product in this reaction correlates well with the relevant reactivity parameters of the inputs, \textit{i.e.} aldehyde electrophilicity and isocyanide nucleophilicity (except in specific cases that will be outlined below). The aldehyde scope is broad, including both aliphatic and aromatic inputs, with the former generally performing better than the latter (\textit{i.e.} entries 4i vs. 4s); α,β-unsaturated tiglic aldehyde gave no conversion due to reduced electrophilicity (entry 4p). In the series of aliphatic aldehydes, the yield is slightly higher for branched inputs (products 4d-f vs. 4a-c), possibly due to side reactions initiated by enamine formation in the case of linear aldehydes; in this respect, pivalic aldehyde appears to perform the best (examples 4i, 4k). This feature of our method nicely complements the conventional approach towards racetams for which the introduction of bulky substituents at this position in the molecule is challenging (neopentylic halides are poor S\textsubscript{N}2 electrophiles). Formaldehyde on the other hand does not follow the general trend: the yield is somewhat lower than expected (formaldehyde is the most electrophilic aldehyde considering both electronic and steric properties and it does not enolize) but can be improved by performing the reaction at reflux (shown for 4n).\textsuperscript{[18]} Next, (hetero)aromatic aldehydes can also be employed (4q-v), though the yield is slightly lower
than for aliphatic homologues (the decrease is significant particularly for electron-rich anisaldehyde, entry 4r). Finally, (relatively reactive) ketones are also suitable carbonyl components in this reaction (4x); again, this is an important complementary feature to conventional methods based on S\textsubscript{N}2 substitution which would require here a tertiary halide electrophile.

Secondly, regarding the isocyanide scope, the reaction is quite flexible, without notable reactivity differences between various isocyanides. Aliphatic (linear or branched, entries 4a, 4d, 4h, 4i, 4n, 4p, 4q, etc), aromatic (4c, 4f) or α-acidic isocyanides (4g, 4k) are well tolerated in the reaction. To our delight, the convertible reagent 2-bromo-6-isocyanopyridine,\textsuperscript{19} which is somewhat less nucleophilic than other isocyanides, can also be employed in this transformation (4f, 4o). On the other hand, 2-morpholinoethyl isocyanide (and the related 2-(diisopropylamino)ethyl isocyanide envisaged for 4m) most likely displayed the peptide coupling reactivity rather than Ugi addition;\textsuperscript{20} in these two examples, the desired products were formed in low yields at best.\textsuperscript{21}

Although γ-aminobutyric acid is the component relevant to the family of racetams, we also investigated the amino acid scope of our reaction. Thus, product 5a was obtained in good yield (as a mixture of diastereoisomers\textsuperscript{22} starting from a NH-Boc-substituted γ-aminobutyric acid (Boc-Dab-OH). On the other hand, the introduction of a 3-hydroxyl group on the amino acid proved to be a problematic variation as a complex mixture resulted in the attempted synthesis of Oxiracetam derivatives 5b and 5c.\textsuperscript{23} A similar result was obtained when 5-aminovaleric acid was employed:\textsuperscript{24} when the desired product 5d was formed in only about 10% yield (based on crude NMR). It thus seems that this protocol is restricted to the formation of γ-lactam derivatives and we decided not to further pursue the exploration of the lactam space accessible via this Ugi reaction.

Next, we probed the utility of this novel Ugi reaction in the synthesis of clinically important racetam derivatives (Scheme 3). Piracetam 4aa and Etiracetam 4bb were prepared in good yields via a one-pot Ugi condensation using 1,1,3,3-tetramethylbutyl isocyanide (Walborski’s isocyanide) and subsequent acid deprotection to the primary amide. Etiracetam enriched in the bioactive enantiomer ((S)-Levetiracetam, Keppra) can be obtained by a crystallization-induced dynamic resolution of the diastereoisomeric mixture of Ugi adduct 4cc,\textsuperscript{25} though this was obtained in a relatively low yield (typical for the employment of an enolizable linear aldehyde, propionaldehyde). Another racetam drug, Nefiracetam 4dd can be obtained directly via the multicomponent condensation, albeit in moderate yield plausibly due to the utilization of a less-nucleophilic isocyanide, 2,6-dimethylphenyl isocyanide (see also 4j vs. 4i in Table 1).
Table 1. Racetam derivatives accessible via an Ugi 3CR approach\textsuperscript{[a,b]}

<table>
<thead>
<tr>
<th>Formula</th>
<th>4a</th>
<th>4b</th>
<th>4c</th>
<th>4d</th>
<th>4e</th>
<th>4f</th>
<th>4g</th>
<th>4h</th>
<th>4i</th>
<th>4j</th>
<th>4k</th>
<th>4l</th>
<th>4m</th>
<th>4n</th>
<th>4o</th>
<th>4p</th>
<th>4q</th>
<th>4r</th>
<th>4s</th>
<th>4t</th>
<th>4u</th>
<th>4v</th>
<th>4w</th>
<th>4x</th>
<th>4y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yields</td>
<td>62%</td>
<td>36%</td>
<td>49%</td>
<td>60%</td>
<td>69%</td>
<td>66%</td>
<td>49%</td>
<td>45%</td>
<td>71%</td>
<td>46%</td>
<td>65%</td>
<td>n.d.</td>
<td>58%\textsuperscript{[d]}</td>
<td>48%</td>
<td>0%</td>
<td>42%</td>
<td>34%</td>
<td>41%</td>
<td>46%</td>
<td>40%</td>
<td>50%</td>
<td>41%</td>
<td>~15%\textsuperscript{[e]}</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Standard conditions: \(\gamma\) amino-butyric acid (1 mmol), aldehyde (1 mmol) and isocyanide (1 mmol) in TFE (10 mL) at 40 °C for 24 h; \textsuperscript{[b]} isolated yields; \textsuperscript{[c]} n.d. = not determined, complex reaction mixture; \textsuperscript{[d]} performed at reflux; \textsuperscript{[e]} crude NMR yield, product not isolated.
Finally, this novel Ugi-type reaction can be exploited to synthesize racetams in combination with the convertible isocyanide 2-bromo-6-isocyanopyridine. Pramiracetam 4ee can be obtained by heating Ugi product 4o with the required primary amine, while ester 6, the general intermediate in the preparation of racetams, is accessed by acid-mediated solvolysis of 4o. Given the high versatility of the conversion of Ugi products derived from the convertible isocyanide, this approach provides rapid access to a large number of racetam derivatives, allowing extensive variation at the α-position of the 2-oxo-pyrrolidino acetamide as well as the primary amide side (see also Table 1 product 4f).

Scheme 3. Synthesis of clinically important racetams.

Conclusion

In summary, we disclose a novel multicomponent synthesis of racetam derivatives. The Ugi 4C-3CR condensation with γ-aminobutyric acid is a simple, resource-efficient and general way to access clinically relevant small molecules in a single step or via short reaction sequences. Typical problems of the conventional route are circumvented allowing the generation of a broad range of racetam derivatives, including examples that are challenging for the traditional methods.
Experimental Section

General Remarks

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Cyclohexane was distilled prior to use. 2,2,2-Trifluoroethanol was flushed with nitrogen upon storing. Reactions were performed under nitrogen atmosphere.

Melting points were recorded on a Büchi M-565 melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 (125.78 MHz for $^{13}$C) or Bruker Avance 400 (100.62 MHz for $^{13}$C) using the residual solvent as internal standard ($^1$H: δ 7.26 ppm, $^{13}$C($^1$H): δ 77.16 ppm for CDCl$_3$, $^1$H: δ 2.50 ppm, $^{13}$C($^1$H): δ 39.52 ppm for DMSO-d$_6$ and $^1$H: 3.31 ppm, $^{13}$C($^1$H): δ 49.00 ppm for CD$_3$OD). Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), sep (septet), br (broad singlet) and m (multiplet) or combinations thereof. Infrared (IR) spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm$^{-1}$. Electrospray Ionization (ESI) high-resolution mass spectrometry (HRMS) was carried out using a Bruker microTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 μm, pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO$_2$, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator).

N-(2-(diisopropylamino)ethyl)formamide was synthesized by reacting N,N-diisopropylethane-1,2-diamine with ethyl formate; N-(2-isocyanoethyl)-N-isopropylpropan-2-amine was synthesized by dehydrating the corresponding formamide with POCl$_3$/NEt$_3$. 2-bromo-6-isocyanopyridine was prepared in a similar manner, as described.$^{[19]}$

General synthetic procedures

Reaction optimization

To a solution of γ-aminobutyric acid (0.5 mmol, 1 equiv) in 2,2,2-trifluoroethanol were added the aldehyde (0.5 mmol, 1 equiv) and tert-butyl isocyanide (0.5 mmol, 1 equiv). After stirring the reaction mixture at the indicated temperature for the indicated time, the solution was concentrated and the crude yield was determined by NMR analysis using mesitylene as internal standard.

Procedure A.

To a solution of γ-aminobutyric acid (1.0 mmol, 1 equiv) in 2,2,2-trifluoroethanol (10 mL) were added the aldehyde (1.0 mmol, 1 equiv) and the isocyanide (1.0 mmol, 1 equiv). Unless otherwise indicated, the mixture was stirred at 40 °C for 24 h. The solution was then concentrated in vacuo and the product was purified by column chromatography on silicagel.

Procedure B.

To a solution of γ-aminobutyric acid (1.0 mmol, 1 equiv) in 2,2,2-trifluoroethanol (10 mL) were added the aldehyde (1.0 mmol, 1 equiv) and the isocyanide (1.0 mmol, 1 equiv). The mixture was heated at reflux for 3 h, then concentrated and redissolved in 3 mL of trifluoroacetic acid. This solution was refluxed for 1 h. The reaction mixture was then concentrated in vacuo and the product was purified by column chromatography on silicagel.
An Ugi Approach towards Racetams

Reaction optimization

![Reaction scheme]

Table 2. Reaction optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc.</th>
<th>Temp.</th>
<th>Time</th>
<th>1:2:3</th>
<th>Yield 4[^[a]]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 M</td>
<td>25 °C</td>
<td>24 h</td>
<td>1:1:1</td>
<td>14%</td>
</tr>
<tr>
<td>2</td>
<td>0.5 M</td>
<td>25 °C</td>
<td>24 h</td>
<td>1:1:1</td>
<td>27%</td>
</tr>
<tr>
<td>3</td>
<td>0.2 M</td>
<td>25 °C</td>
<td>24 h</td>
<td>1:1:1</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>0.1 M</td>
<td>25 °C</td>
<td>72 h</td>
<td>1:1:1</td>
<td>50%</td>
</tr>
<tr>
<td>5</td>
<td>0.1 M</td>
<td>40 °C</td>
<td>24 h</td>
<td>1:1:1</td>
<td>53%</td>
</tr>
<tr>
<td>6</td>
<td>0.1 M</td>
<td>50 °C</td>
<td>24 h</td>
<td>1:1:1</td>
<td>53%</td>
</tr>
<tr>
<td>7</td>
<td>0.1 M</td>
<td>80 °C</td>
<td>24 h</td>
<td>1:1:1</td>
<td>58%</td>
</tr>
<tr>
<td>8</td>
<td>0.1 M</td>
<td>100 °C[^[b]]</td>
<td>24 h</td>
<td>1:1:1</td>
<td>51%</td>
</tr>
<tr>
<td>9</td>
<td>0.1 M</td>
<td>120 °C[^[b]]</td>
<td>24 h</td>
<td>1:1:1</td>
<td>50%</td>
</tr>
<tr>
<td>10</td>
<td>0.1 M</td>
<td>40 °C</td>
<td>24 h</td>
<td>1.5:1:1</td>
<td>58%</td>
</tr>
<tr>
<td>11</td>
<td>0.1 M</td>
<td>40 °C</td>
<td>24 h</td>
<td>1:1.5:1</td>
<td>55%</td>
</tr>
<tr>
<td>12</td>
<td>0.1 M</td>
<td>40 °C</td>
<td>24 h</td>
<td>1:1:1.5</td>
<td>50%</td>
</tr>
<tr>
<td>13[^[c]]</td>
<td>0.1 M</td>
<td>40 °C</td>
<td>24 h</td>
<td>1:1:1</td>
<td>84%</td>
</tr>
</tbody>
</table>

[^[a]] Crude yield based on NMR analysis using mesitylene as internal standard; [^[b]] sealed vial; [^[c]] isovaleraldehyde used instead of p-methylbenzaldehyde.

Initial experiments indicated that TFE was a superior solvent to MeOH or EtOH in which the product was formed in small amounts. Typical concentrations for the Ugi 4CR (1 M) delivered the product in a poor yield, most likely due to intermolecular condensations (entry 1). A dilution to 0.1 M allowed for a significant improvement of the yield to 50% (entry 4). In an attempt to improve the rate and the yield heating was employed but the results were comparable; particularly at higher temperatures, additional side reactions become relevant (identified sideproducts are shown in the scheme above). Nevertheless, performing the reaction at 40 °C allowed for the reduction of the reaction time to 24 h (optimal conditions, entry 5). Attempts to further improve the yield by changing the stoichiometry of the components were unsuccessful (entries 10-12); the addition of drying agents (molecular sieves, Na₂SO₄) or preforming the imine before isocyanide addition had also no significant effect on the reaction (results not shown). A much better performance of aliphatic aldehydes over aromatic derivatives was observed (yield of 84%, entry 13) and we thus set out to evaluate the reaction scope under these conditions.
**Chapter 5**

**Characterization of compounds**

---

**N-(tert-buty1)-4-methyl-2-(2-oxopyrrolidin-1-yl)pentanamide 4a**

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), 3-methylbutanal (86 mg, 1.0 mmol, 1 equiv) and tert-butyl isocyanide (83 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/AcOEt 10:1 to 1:1, Rf = 0.29 in cyclohexane/AcOEt 1:1). Isolated as a white solid. Yield: 167 mg, 0.621 mmol, 62%.

m.p.: 148-151 °C; 
\[ \text{H-NMR (CDCl}_3\text{, 500 MHz): 6.00 (br, 1H), 4.45 (dd, } J = 9.1 \text{ Hz, } J = 6.6 \text{ Hz, 1H), 3.43-3.27 (m, 2H), 2.41-2.26 (m, 2H), 2.02-1.87 (m, 2H), 1.66-1.50 (m, 2H), 1.43-1.32 (m, 1H), 1.24 (s, 9H), 0.87 (d, } J = 6.6 \text{ Hz, 3H), 0.84 (d, } J = 6.6 \text{ Hz, 3H), ppm; } \text{13C}^{(1)}{\text{H)-NMR (CDCl}_3\text{, 125 MHz): } \delta 175.6 \text{ (C), 169.5 \text{ (C), 165.9 \text{ (C), 53.7 \text{ (CH), 51.2 \text{ (C, 43.8 (CH}, \text{3}, 36.6 \text{ (CH}, \text{3}, 31.3 \text{ (CH}, \text{3}, 28.7 \text{ (CH}, \text{3}, 24.8 \text{ (CH), 23.0 \text{ (CH}, \text{3}, 22.0 \text{ (CH}, \text{3}, 18.3 \text{ (CH}, \text{3}, \text{31.2 (CH}, \text{3}, 28.7 \text{ (CH}, \text{3}, 21.3 \text{ (CH}, \text{3}, 18.3 \text{ (CH}, \text{3}, 10.6 \text{ (CH}, \text{3}, ppm; IR (neat): vmax (cm}^{-1} \text{) = 3300 (s), 2952 (m), 2871 (m), 2362 (m), 1651 (s), 1552 (s), 1444 (s), 1388 (s), 1290 (s), 1224 (s); HRMS (ESI): m/z calculated for C_{16}H_{27}N_{2}Na_{2}O_{2} [M+Na]^+ 277.1886, found: 277.1873.}

---

**N-(tert-buty1)-2-(2-oxopyrrolidin-1-yl)butanamide 4b**

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), propionaldehyde (58 mg, 1.0 mmol, 1 equiv) and tert-butyl isocyanide (83 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/AcOEt 10:1 to 100% AcOEt, Rf = 0.19 in cyclohexane/AcOEt 1:1). Isolated as a white solid. Yield: 80 mg, 0.355 mmol, 36%.

m.p.: 99-104 °C; 
\[ \text{H-NMR (CDCl}_3\text{, 500 MHz): 6.06 (br, 1H), 4.25 (dd, } J = 8.5 \text{ Hz, } J = 6.9 \text{ Hz, 1H), 3.44-3.37 (m, 1H), 3.36-3.29 (m, 1H), 2.41-2.27 (m, 2H), 2.01-1.90 (m, 2H), 1.89-1.79 (m, 1H), 1.63-1.52 (m, 1H), 1.24 (s, 9H), 0.80 (t, } J = 7.6 \text{ Hz, 3H), ppm; } \text{13C}^{(1)}{\text{H)-NMR (CDCl}_3\text{, 125 MHz): } \delta 175.8 \text{ (C), 169.3 \text{ (C), 57.1 \text{ (CH), 51.2 \text{ (C, 43.8 (CH}, \text{3}, 31.2 \text{ (CH}, \text{3}, 28.7 \text{ (CH}, \text{3}, 21.3 \text{ (CH}, \text{3}, 18.3 \text{ (CH}, \text{3}, 10.6 \text{ (CH}, \text{3}, ppm; IR (neat): vmax (cm}^{-1} \text{) = 3294 (s), 3074 (m), 2958 (s), 2360 (m), 1649 (s), 1550 (s), 1444 (s), 1390 (s), 1357 (s), 1303 (s); HRMS (ESI): m/z calculated for C_{14}H_{22}N_{2}Na_{2}O_{2} [M+Na]^+ 249.1573, found: 249.1563.}

---

**3-(benzoxo1y)-N-(napthalen-2-yl)-2-(2-oxopyrrolidin-1-yl)propanamide 4c**

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), benzoxycetone (150 mg, 1.0 mmol, 1 equiv) and 2-napthyl isocyanide (156 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/AcOEt 10:1 to 100% AcOEt, Rf = 0.30 in cyclohexane/AcOEt 1:1). Isolated as a brown solid. Yield: 191 mg, 0.492 mmol, 49%.

m.p.: 101-111 °C; 
\[ \text{H-NMR (CDCl}_3\text{, 500 MHz): 9.65 (s, 1H), 8.31 (d, } J = 2.0 \text{ Hz, 1H), 7.80-7.71 (m, 3H), 7.53 (dd, } J = 8.8 \text{ Hz, } J = 1.9 \text{ Hz, 1H), 7.48-7.27 (m, 7H), 5.25 (dd, } J = 8.2 \text{ Hz, } J = 6.0 \text{ Hz, 1H), 4.62 (d, } J = 11.7 \text{ Hz, 1H), 4.52 (d, } J = 11.7 \text{ Hz, 1H), 4.03-3.92 (m, 2H), 3.76-3.68 (m, 1H), 3.53-3.45 (m, 1H), 2.52-2.45 (m, 2H), 2.14-1.96 (m, 2H), ppm; } \text{13C}^{(1)}{\text{H)-NMR (CDCl}_3\text{, 125 MHz): } \delta 176.7 \text{ (C), 167.1 \text{ (C), 137.4 \text{ (C), 135.4 \text{ (C), 133.7 \text{ (C, 130.5 \text{ (C, 128.5 \text{ (CH), 128.4 \text{ (CH), 127.9 \text{ (CH), 127.8 \text{ (CH), 127.6 \text{ (CH), 126.4 \text{ (CH), 124.9 \text{ (CH), 120.0 \text{ (CH), 116.7 \text{ (CH), 73.1 \text{ (CH}, \text{3}, 66.8 \text{ (CH}, \text{3}, 55.2 \text{ (CH), 44.8 \text{ (CH}, \text{3}, 31.0 \text{ (CH}, \text{3}, 18.2 \text{ (CH}, \text{3}, ppm; IR (neat): vmax (cm}^{-1} \text{) = 3263 (m), 2900 (m), 2868 (m), 2358 (s), 1666 (s), 1631 (s), 1585 (s), 1544 (s), 1502 (s), 1433 (s); HRMS (ESI): m/z calculated for C_{24}H_{21}N_{2}O_{3} [M+Na]^+ 411.1679, found: 411.1665.}

---

**N-benzyl-3-methyl-2-(2-oxopyrrolidin-1-yl)butanamide 4d**

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), isobutyraldehyde (72 mg, 1.0 mmol, 1 equiv) and benzyl isocyanide (117 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silicagel
An Ugi Approach towards Racetams

3-methyl-N-(naphthalen-2-yl)-2-(2-oxopyrrolidin-1-yl)butanamide 4e
Prepared from N-(6-bromopyridin-2-yl)-3-methyl-2-(2-oxopyrrolidin-1-yl)butanamide 4f.

N-(6-bromopyridin-2-yl)-3-methyl-2-(2-oxopyrrolidin-1-yl)butanamide 4f
Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv) and 2-bromo-6-isocyanoypyridine (92 mg, 0.5 mmol, 1 equiv) according to procedure A. Purification: column chromatography on silicagel (cyclohexane/ACOEt 1:1 to 100% ACOEt). Yield: 112 mg, 0.329 mmol, 66%.

m.p.: 147-152 °C; 1H-NMR (CDCl3, 500 MHz): δ 9.51 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 4.51 (d, J = 11.0 Hz, 1H), 3.71-3.60 (m, 1H), 3.53-3.39 (m, 1H), 2.62-2.43 (m, 2H), 2.42-2.27 (m, 1H), 2.14-1.95 (m, 2H), 1.04 (d, J = 6.0, 3H), 0.92 (d, J = 6.0 Hz, 3H) ppm; 13C{1H}-NMR (CDCl3, 125 MHz): δ 176.6 (C), 168.9 (C), 151.5 (C), 140.3 (CH), 139.5 (C), 123.6 (CH), 112.5 (CH), 62.6 (CH), 44.5 (CH), 31.3 (CH), 26.9 (CH), 19.6 (CH), 19.0 (CH), 18.5 (CH) ppm; IR (neat): v max (cm⁻¹) = 3209 (w), 2964 (w), 1650 (s), 1568 (s), 1529 (s), 1472 (s), 1388 (s), 1214 (s), 784 (s); HRMS (ESI): m/z calculated for C14H13BrN4O2 [M+Na]+ 362.0475, found: 362.0469.

methyl (2-cyclopropyl-2-(2-oxopyrrolidin-1-yl)acetyl)glycinate 4g
Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), cyclopropanecarboxaldehyde (70 mg, 1.0 mmol, 1 equiv) and methyl isocyanocacetate (99 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/ACOEt 1:1 to AcOEt/MeOH 9:1). Isolated as an orange solid. Yield: 126 mg, 0.494 mmol, 49%.

m.p.: 104-115 °C; 1H-NMR (CDCl3, 500 MHz): 7.02 (t, J = 4.7 Hz, 1H), 3.99 (dd, J = 18.0 Hz, J = 5.7 Hz, 1H), 3.88 (dd, J = 18.0 Hz, J = 5.7 Hz, 1H), 3.75 (d, J = 10.4 Hz, 1H), 3.66 (s, 3H), 3.58-3.53 (m, 2H), 2.36 (t, J = 7.9 Hz, 2H), 2.08-1.93 (m, 2H), 1.36-1.24 (m, 1H), 0.74-0.66 (m, 1H), 0.55-0.42 (m, 2H), 0.26-0.19 (m, 1H) ppm; 13C{1H}-NMR (CDCl3, 125 MHz): δ 175.8 (C), 170.2 (C), 190.1 (C), 59.8 (CH), 52.3 (CH), 44.5 (CH), 41.0 (CH), 30.9 (CH), 18.1 (CH).
10.2 (CH), 5.3 (CH), 2.9 (CH) ppm; IR (neat): vmax (cm\(^{-1}\)) = 3186 (m), 2939 (s), 2362 (s), 1753 (s), 1651 (s), 1546 (s), 1440 (s), 1400 (s), 1359 (s), 1309 (s); HRMS (ESI): m/z calculated for C\(_{15}\)H\(_{26}\)N\(_{2}\)NaO\(_{4}\) [M+Na\(^{+}\)] = 277.1159, found: 277.1150.

**N-[(1H-benzo[d][1,2,3]triazol-1-yl)methyl]-2-cyclohexyl-2-[2-oxopyrrolidin-1-yl]acetamide 4h**

Prepared from \(\gamma\)-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), cyclohexanecarboxaldehyde (112 mg, 1.0 mmol, 1 equiv) and 1H-benzotriazol-1-ylmethyl isocyanide (159 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silica gel (cyclohexane/AcOEt 1:2 to AcOEt/MeOH 9:1, \(R_r = 0.13\) in cyclohexane/AcOEt 1:2). Isolated as a yellow solid. Yield: 158 mg, 0.445 mmol, 45%.

m.p.: 88-93 °C; \(^1\)H-NMR (CDCl\(_3\), 500 MHz): 8.99 (t, \(J = 6.3\ Hz\), 1H), 7.97 (d, \(J = 8.2\ Hz\), 1H), 7.82 (d, \(J = 8.5\ Hz\), 1H), 7.45-7.40 (m, 1H), 7.34-7.29 (m, 1H), 6.09 (dd, \(J = 13.9\ Hz\), \(J = 6.9\ Hz\), 1H), 5.95 (dd, \(J = 13.9\ Hz\), \(J = 6.9\ Hz\), 1H), 4.29 (d, \(J = 11.0\ Hz\), 1H), 3.46-3.38 (m, 1H), 3.35-3.28 (m, 1H), 2.37-2.28 (m, 1H), 2.24-2.15 (m, 1H), 1.97-1.78 (m, 3H), 1.63-1.43 (m, 3H), 1.42-1.32 (m, 2H), 1.15-1.04 (m, 2H), 1.03-0.92 (m, 1H), 0.79-0.65 (m, 2H) ppm; \(^{13}\)C{\(^1\)H}-NMR (CDCl\(_3\), 125 MHz): \(\delta\) 176.1 (C), 170.3 (C), 146.0 (C), 132.2 (C), 127.6 (CH), 124.2 (CH), 119.6 (CH), 110.7 (CH), 60.0 (CH), 50.9 (CH\(_3\)), 44.4 (CH\(_3\)), 35.3 (CH), 31.0 (CH\(_3\)), 29.6 (CH\(_3\)), 29.0 (CH\(_3\)), 26.1 (CH\(_3\)), 25.4 (CH\(_3\)), 25.3 (CH\(_3\)), 18.2 (CH\(_3\)) ppm; IR (neat): vmax (cm\(^{-1}\)) = 3271 (m), 2923 (s), 2850 (s), 2362 (s), 1658 (s), 1546 (s), 1492 (s), 1421 (s), 1286 (s), 1271 (s); HRMS (ESI): m/z calculated for C\(_{15}\)H\(_{26}\)N\(_{2}\)NaO\(_{4}\) [M+Na\(^{+}\)] = 378.1900, found: 378.1885.

**3,3-dimethyl-2-[2-oxopyrrolidin-1-yl]-N-pentylbutanamide 4i**

Prepared from \(\gamma\)-aminobutyric acid (104 mg, 1.0 mmol, 1 equiv), pivalaldehyde (86 mg, 1.0 mmol, 1 equiv) and 1-pentyl isocyanide (97 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silica gel (cyclohexane/AcOEt 20:1 to cyclohexane/AcOEt 1:1, \(R_r = 0.18\) in cyclohexane/AcOEt 1:1). Isolated as a white solid. Yield: 189 mg, 0.705 mmol, 71%.

m.p.: 42-48 °C; \(^1\)H-NMR (CDCl\(_3\), 500 MHz): 7.22 (t, \(J = 5.0\ Hz\), 1H), 4.40 (s, 1H), 3.76-3.68 (m, 1H), 3.66-3.58 (m, 1H), 3.21-3.12 (m, 1H), 3.00-2.91 (m, 1H), 2.31-2.14 (m, 2H), 1.86 (quint, \(J = 7.6\ Hz\), 2H), 1.37 (quint, \(J = 7.3\ Hz\), 2H), 1.24-1.12 (m, 4H), 0.94 (s, 9H), 0.76 (t, \(J = 6.9\ Hz\), 3H) ppm; \(^{13}\)C{\(^1\)H}-NMR (CDCl\(_3\), 125 MHz): \(\delta\) 175.8 (C), 168.7 (C), 62.4 (CH), 47.4 (CH\(_3\)), 39.0 (CH), 34.7 (C), 30.9 (CH\(_3\)), 29.0 (CH\(_3\)), 28.9 (CH\(_3\)), 27.6 (CH\(_3\)), 22.2 (CH\(_3\)), 19.0 (CH\(_3\)), 13.9 (CH\(_3\)) ppm; IR (neat): vmax (cm\(^{-1}\)) = 3305 (m), 2956 (s), 2931 (s), 2871 (s), 2360 (m), 1651 (s), 1546 (s), 1421 (s), 1365 (s), 1284 (s); HRMS (ESI): m/z calculated for C\(_{15}\)H\(_{24}\)N\(_{2}\)NaO\(_{2}\) [M+Na\(^{+}\)] = 291.2043, found: 291.2031.

**N-(2,6-dimethylphenyl)-3,3-dimethyl-2-[2-oxopyrrolidin-1-yl]butanamide 4j**

Prepared from \(\gamma\)-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), pivalaldehyde (86 mg, 1.0 mmol, 1 equiv) and 2,6-dimethylphenyl isocyanide (131 mg, 1.0 mmol, 1 equiv) according to procedure A. Purification: column chromatography on silica gel (cyclohexane/AcOEt 2:1, \(R_r = 0.17\)). Isolated as a white solid. Yield: 139 mg, 0.46 mmol, 46%.

m.p.: 147-155 °C; \(^1\)H-NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.98 (s, 1H), 7.10-6.97 (s, 3H), 4.73 (s, 1H), 3.86-3.65 (m, 2H), 2.46-2.23 (m, 2H), 2.18 (s, 6H), 2.04-1.85 (m, 2H), 1.16 (s, 9H) ppm; \(^{13}\)C{\(^1\)H}-NMR (CDCl\(_3\), 125 MHz): \(\delta\) 176.3 (C), 167.6 (C), 135.2 (C), 134.0 (C), 128.2 (CH), 127.1 (CH), 62.6 (CH), 47.3 (C), 35.2 (CH\(_3\)), 30.9 (CH\(_3\)), 27.8 (CH\(_3\)), 19.3 (CH\(_3\)), 18.7 (CH\(_3\)) ppm; IR (neat): vmax (cm\(^{-1}\)) = 3169 (w), 2957 (w), 1655 (s), 1533 (m), 1161 (m), 770 (s); HRMS (ESI): m/z calculated for C\(_{18}\)H\(_{26}\)N\(_{2}\)NaO\(_{2}\) [M+Na\(^{+}\)] = 325.1886, found: 325.1879.
An Ugi Approach towards Racetams

3,3-dimethyl-2-(2-oxopyrrolidin-1-yl)-N-(tosylmethyl)butanamide 4k
Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), pivalaldehyde (86 mg, 1.0 mmol, 1 equiv) and tosylmethyl isocyanide (195 mg, 1.0 mmol, 1 equiv) according to procedure A. Purification: column chromatography on silicagel (cyclohexane/AcOEt 1:1; Rf = 0.36). Isolated as a white solid. Yield: 238 mg, 65%.

m.p.: 182-192 °C; 1H-NMR (CDCl3, 500 MHz): δ 8.81 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.94 (dd, J = 14.0 Hz, J = 7.0 Hz, 1H), 4.70 (s, 1H), 4.43 (dd, J = 14.0 Hz, J = 7.0 Hz, 1H), 3.53-3.47 (m, 1H), 3.11-3.05 (m, 1H), 2.56-2.47 (m, 1H), 2.44-2.35 (m, 1H), 2.40 (s, 3H), 1.95-1.86 (m, 1H), 1.86-1.77 (m, 1H), 0.93 (s, 9H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz): δ 176.8 (C), 167.1 (C), 151.1 (C), 140.7 (C), 129.2 (CH), 129.2 (CH), 112.6 (CH), 49.6 (CH2), 47.3 (CH2), 35.7 (C), 30.8 (CH2), 27.5 (CH2), 21.8 (CH3), 18.8 (CH3) ppm; IR (neat): vmax (cm⁻¹) = 3200 (w), 2959 (w), 1659 (s), 1551 (m), 920 (w), 731 (m); HRMS (ESI): m/z calculated for C18H23N2O2S [M+H]+ 367.1686, found: 367.1683.

2-(2-oxopyrrolidin-1-yl)-N-(2,4,4-trimethylpentan-2-yl)acetamide 4n
Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), paraformaldehyde (30 mg, 1.0 mmol, 1 equiv) and 1,1,3,3-tetramethylbutyl isocyanide (139 mg, 1.0 mmol, 1 equiv) according to procedure A (reflux, 3 h reaction time). Purification: column chromatography on silicagel (100% AcOEt to AcOEt/MeOH 19:1; Rf = 0.52 in AcOEt/MeOH 19:1). Isolated as a colorless oil. Yield: 148 mg, 0.582 mmol, 58%.

1H-NMR (CDCl3, 500 MHz): δ 6.14 (s, 1H), 3.72 (s, 2H), 3.41 (t, J = 7.0 Hz, 2H), 2.31 (t, J = 8.0 Hz, 2H), 1.96 (quint, J = 7.0 Hz, 2H), 1.62 (s, 2H), 1.72 (s, 6H), 0.87 (s, 9H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz): δ 175.7 (C), 166.9 (C), 55.1 (C), 51.2 (CH3), 48.4 (CH3), 48.0 (CH3), 31.5 (C), 31.3 (CH3), 30.4 (CH3), 29.1 (CH3), 17.9 (CH3) ppm; IR (neat): vmax (cm⁻¹) = 3310 (w), 2951 (w), 1659 (s), 1551 (m), 920 (w), 731 (m); HRMS (ESI): m/z calculated for C14H22N2O2 [M+Na]+ 277.1886, found: 277.1893.

N-(6-bromopyridin-2-yl)-2-(2-oxopyrrolidin-1-yl)acetamide 4o
Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), paraformaldehyde (30 mg, 1.0 mmol, 1 equiv) and 1-bromo-3-isocyanopyridine (183 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/AcOEt 1:1 to cyclohexane/AcOEt 1:3; Rf = 0.13). Isolated as a green solid. Yield: 143 mg, 0.48 mmol, 48%.

m.p.: 168-170 °C; 1H-NMR (CDCl3, 500 MHz): δ 8.82 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 4.16 (s, 2H), 3.55 (t, J = 7.0 Hz, 2H), 2.52 (t, J = 8.0, 2H), 2.14 (quint, J = 7.5 Hz, 2H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz): δ 176.8 (C), 167.1 (C), 151.1 (C), 140.7 (CH), 139.5 (C), 124.0 (CH), 112.6 (CH), 48.6 (CH2), 47.7 (CH3), 30.4 (CH3), 18.1 (CH3) ppm; IR (neat): vmax (cm⁻¹) = 3034 (w), 2945 (w), 1672 (s), 1571 (s), 1427 (s), 1288 (s), 1126 (s), 791 (s); HRMS (ESI): m/z calculated for C13H12BrN2O2 [M+Na]+ 320.0005, found: 320.0004.

N-isopropyl-2-(2-oxopyrrolidin-1-yl)-2-phenylacetamide 4q
Prepared from γ-aminobutyric acid (104 mg, 1.0 mmol, 1 equiv), benzaldehyde (106 mg, 1.0 mmol, 1 equiv) and isopropyl isocyanide (69 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/AcOEt 10:1 to 100% AcOEt). Isolated as a white solid. Yield: 109 mg, 0.417 mmol, 42%.

m.p.: 148-151 °C; 1H-NMR (CDCl3, 500 MHz): 7.35-7.21 (m, 5H), 6.50 (d, J = 7.3 Hz, 1H), 5.86 (s, 1H), 4.08-3.97 (m, 1H), 3.83-3.74 (m, 1H), 2.99-2.91 (m, 1H), 2.42-2.22 (m, 2H), 2.02-1.91 (m, 1H), 1.84-1.73 (m, 1H), 1.07 (d, J = 6.3 Hz, 3H), 1.05 (d, J = 6.3 Hz, 3H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz): δ 175.3 (C), 167.9 (C), 151.1 (C), 140.7 (CH), 139.5 (C), 124.0 (CH), 112.6 (CH), 48.6 (CH2), 47.7 (CH3), 30.4 (CH3), 18.1 (CH3) ppm; IR (neat): vmax (cm⁻¹) = 3203 (w), 2945 (w), 1672 (s), 1571 (s), 1427 (s), 1288 (s), 1126 (s), 791 (s); HRMS (ESI): m/z calculated for C13H12BrN2O2 [M+Na]+ 320.0005, found: 320.0004.
128.7 (CH), 128.3 (CH), 58.4 (CH), 45.0 (CH$_2$), 41.6 (CH$_3$), 31.1 (CH$_2$), 22.4 (CH$_3$), 18.1 (CH$_2$) ppm; IR (neat): vmax (cm$^{-1}$) 3265 (s), 2970 (s), 2360 (m), 1666 (s), 1643 (s), 1556 (s), 1431 (s), 1417 (s), 1365 (s), 1284 (s); HRMS (ESI): m/z calculated for C$_{19}$H$_{20}$N$_2$O$_2$ [M+Na]$^+$ 283.1417, found: 283.1411.

**N-cyclohexyl-2-(4-methoxyphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide 4r**

Prepared from γ-aminobutyric acid (104 mg, 1.0 mmol, 1 equiv), p-methoxybenzaldehyde (136 mg, 1.0 mmol, 1 equiv) and cyclohexyl isocyanide (109 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/AcOEt 10:1 to 100% AcOEt, R$_f$ = 0.12 in cyclohexane/AcOEt 1:1). Isolated as a white solid. Yield: 111 mg, 0.336 mmol, 34%.

m.p.: 139-143 °C; $^1$H-NMR (CDCl$_3$, 500 MHz): 7.21 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.22 (d, J = 7.9 Hz, 1H), 5.77 (s, 1H), 3.75 (s, 3H), 3.79-3.66 (m, 2H), 2.97 (qd, J = 8.8 Hz, J = 5.7 Hz, 1H), 2.32-2.33 (m, 1H), 2.03-2.16 (m, 1H), 1.87-1.76 (m, 3H), 1.67-1.57 (m, 2H), 1.53 (t, J = 12.6 Hz, J = 3.5 Hz, 1H), 1.34-1.21 (m, 2H), 1.12-0.96 (m, 3H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): 6 175.3 (C), 168.5 (C), 159.5 (C), 130.2 (CH), 127.1 (C), 114.1 (CH), 55.3 (CH$_3$), 48.5 (CH), 44.9 (CH$_3$), 32.7 (CH$_3$), 31.2 (CH$_3$), 25.5 (CH$_3$), 24.8 (CH$_3$), 18.1 (CH$_3$) ppm; IR (neat): vmax (cm$^{-1}$) = 3255 (s), 2931 (s), 2852 (s), 2358 (m), 1651 (s), 1608 (s), 1546 (s), 1512 (s), 1438 (s), 1365 (s); HRMS (ESI): m/z calculated for C$_{20}$H$_{22}$N$_2$O$_2$ [M+Na]$^+$ 353.1836, found: 353.1820.

**2-(2-oxopyrrolidin-1-yl)-N-pentyl-2-(4-trifluoromethyl)phenyl)acetamide 4s**

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), p-trifluoromethylbenzaldehyde (174 mg, 1.0 mmol, 1 equiv) and 1-pentyl isocyanide (97 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/AcOEt 15:1 to 100% AcOEt, R$_f$ = 0.47 in cyclohexane/AcOEt 1:1). Isolated as a white solid. Yield: 145 mg, 0.466 mmol, 41%.

m.p.: 84-88 °C; $^1$H-NMR (CDCl$_3$, 500 MHz): 7.57 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H), 7.08 (t, J = 5.0 Hz, 1H), 6.00 (s, 1H), 3.86-3.77 (m, 1H), 3.29-3.20 (m, 1H), 3.19-3.11 (m, 1H), 3.08-3.01 (m, 1H), 2.44-2.27 (m, 2H), 2.08-1.97 (m, 1H), 1.93-1.82 (m, 1H), 1.44 (pentyl) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): 6 175.7 (C), 168.5 (C), 139.2 (C), 130.5 (q, J$_{CF}$ = 33 Hz, C), 129.1 (CH), 125.8 (q, J$_{CF}$ = 4, CH), 124.0 (q, J$_{CF}$ = 270, C), 58.0 (CH$_3$), 45.1 (CH$_2$), 39.7 (CH$_2$), 31.0 (CH$_3$), 29.1 (CH$_3$), 29.0 (CH$_3$), 22.3 (CH$_3$), 18.2 (CH$_3$), 14.0 (CH$_3$) ppm; IR (neat): vmax (cm$^{-1}$) = 3253 (m), 2927 (m), 2360 (m), 1679 (s), 1672 (s), 1649 (s), 1552 (s), 1421 (s), 1325 (s), 1286 (s); HRMS (ESI): m/z calculated for C$_{18}$H$_{19}$F$_3$N$_2$O$_2$ [M+Na]$^+$ 379.1588.

**N-cyclohexyl-2-(2-oxopyrrolidin-1-yl)-2-(2-(trifluoromethyl)phenyl)acetamide 4t**

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), 2-trifluoromethylbenzaldehyde (174 mg, 1.0 mmol, 1 equiv) and cyclohexyl isocyanide (109 mg, 1.0 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/AcOEt 1:1 to cyclohexane/AcOEt 1:2, R$_f$ = 0.26 in 1:1). Isolated as a white solid. Yield: 169 mg, 0.46 mmol, 46%.

m.p.: 160-165 °C; $^1$H-NMR (CDCl$_3$, 500 MHz): 6 7.70 (t, J = 8.0 Hz, 2H), 7.55 (t, J = 7.0 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 5.97 (s, 1H), 5.74 (d, J = 6.5 Hz, 1H), 3.80-3.68 (m, 1H), 3.68-3.57 (m, 1H), 2.91-2.78 (m, 1H), 2.48-2.29 (m, 2H), 2.08-1.94 (m, 1H), 1.92-1.76 (m, 3H), 1.71-1.45 (m, 3H), 1.36-0.87 (m, 5H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): 6 175.1 (C), 168.1 (C), 133.1 (C), 132.1 (CH), 131.2 (CH), 129.8 (q, J$_{CF}$ = 30 Hz, C), 129.0 (CH), 126.8 (q, J$_{CF}$ = 6 Hz, CH), 124.0 (q, J$_{CF}$ = 275 Hz, C), 55.5 (CH), 48.9 (C), 45.7 (CH$_2$), 32.8 (CH$_3$), 32.6 (CH$_3$), 31.0 (CH$_3$), 25.5 (CH$_3$), 24.8 (CH$_3$), 24.7 (CH$_3$), 18.3 (CH$_3$) ppm; IR (neat): vmax (cm$^{-1}$) = 3254 (w), 2932 (w), 1664 (s), 1439 (m), 1313 (m), 1124 (s) 1040 (m), 779 (m); HRMS (ESI): m/z calculated for C$_{18}$H$_{19}$F$_3$N$_2$O$_2$ [M+H]$^+$ 369.1784, found: 369.1785.
An Ugi Approach towards Racetams

**methyl (2-[2-oxopyrrolidin-1-yl]-2-(pyridin-3-yl)acetyl)glycinate 4u**
Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), nicotinaldehyde (107 mg, 1.0 mmol, 1 equiv) and methyl isocyanoacetate (99 mg, 1.0 mmol, 1 equiv) according to procedure A. Purification: column chromatography on silicagel (AcOEt/MeOH 9:1, Rf = 0.23). Isolated as a gummy yellow solid. Yield: 118 mg, 0.404 mmol, 40%.

$^1$H-NMR (CDCl$_3$, 500 MHz): δ 8.56-8.48 (m, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.38 (br, 1H), 7.30 (t, J = 5.0 Hz, 1H), 6.0 (s, 1H), 4.10-3.96 (m, 2H), 3.80-3.64 (m, 4H), 3.10-3.00 (m, 1H), 2.50-2.29 (m, 2H), 2.14-2.00 (m, 1H), 2.00-1.84 (m, 1H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): δ 176.0 (C), 170.1 (C), 168.8 (C), 150.4 (CH), 149.8 (CH), 136.9 (CH), 130.5 (CH), 123.7 (CH), 52.5 (CH$_3$), 44.9 (CH$_3$), 41.3 (CH$_3$), 30.9 (CH$_3$); IR (neat): v$_\text{max}$ (cm$^-1$) = 3294 (w), 2955 (w), 1749 (m), 1659 (s), 1416 (m), 1204 (s) 714 (m); HRMS (ESI): m/z calculated for C$_8$H$_{13}$N$_3$NaO$_4$ [M+Na]$^+$ 314.1108, found: 314.1104.

**2-[2-oxopyrrolidin-1-yl]-2-(pyridin-4-yl)-N-{(2,4,4-trimethylpentan-2-yl)acetamide 4v**
Prepared from γ-aminobutyric acid (104 mg, 1.0 mmol, 1 equiv), 4-pyridinecarboxaldehyde (107 mg, 1.0 mmol, 1 equiv) and 1,1,3,3-tetramethylbutyl isocyanide (119 mg, 1.0 mmol, 1 equiv) according to procedure A. Purification: column chromatography on silicagel (cyclohexane/ACOEt 1:2, to AcOEt/MeOH 9:1, Rf = 0.45 in AcOEt/MeOH 9:1). Isolated as a white solid. Yield: 165 mg, 0.499 mmol, 50%.

m.p.: 165-173 °C; $^1$H-NMR (CDCl$_3$, 500 MHz): 8.51 (d, J = 6.0 Hz, 2H), 7.18 (d, J = 6.0 Hz, 2H), 6.73 (br, 1H), 5.83 (s, 1H), 3.79-3.71 (m, 1H), 3.09-3.02 (m, 1H), 2.41-2.26 (m, 2H), 2.05-1.95 (m, 1H), 1.92-1.83 (m, 1H), 1.81 (d, J = 14.8 Hz, 1H), 1.53 (d, J = 14.8 Hz, 1H), 1.35 (s, 3H), 1.32 (s, 3H), 0.87 (s, 9H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): δ 175.5 (C), 166.7 (C), 150.2 (CH), 144.2 (C), 123.4 (CH), 57.9 (CH), 55.8 (C), 51.4 (CH$_3$), 45.1 (CH$_3$), 31.6 (CH$_3$), 31.3 (CH$_3$), 30.8 (C), 29.2 (CH$_3$), 28.7 (CH$_3$), 18.3 (CH$_2$)$_2$ ppm; IR (neat): v$_\text{max}$ (cm$^-1$) = 3276 (s), 2964 (s), 2362 (m), 1654 (s), 1598 (s), 1556 (s), 1436 (s), 1382 (s), 1359 (s), 1259 (s); HRMS (ESI): m/z calculated for C$_{19}$H$_{29}$N$_3$NaO$_2$ [M+Na]$^+$ 354.2152, found: 354.2137.

**N-isopropyl-(2-oxopyrrolidin-1-yl)cyclohexane-1-carboxamide 4x**
Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), cyclohexanone (98 mg, 1.0 mmol, 1 equiv) and isopropyl isocyanide (69 mg, 1.0 mmol, 1 equiv) according to procedure A. Purification: column chromatography on silicagel (cyclohexane/ACOEt 1:4, Rf = 0.23). Isolated as a colorless oil. Yield: 97 mg, 0.385 mmol, 38%.

$^1$H-NMR (CDCl$_3$, 500 MHz): δ 6.65 (d, J = 8.0 Hz, 1H), 3.97 (sep, J = 7.5 Hz, 1H), 3.41 (t, J = 7.0 Hz, 2H), 2.35 (t, J = 8.0 Hz, 2H), 2.30-2.17 (m, 2H), 2.03-1.85 (m, 4H), 1.62-1.50 (m, 2H), 1.49-1.30 (m, 4H), 1.08 (d, J = 6.5 Hz, 6H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz): δ 177.7 (C), 172.2 (C), 63.6 (C), 46.3 (CH$_3$), 41.4 (CH$_3$), 33.1 (CH$_3$), 32.4 (CH$_3$), 25.3 (CH$_2$), 22.7 (CH$_2$), 22.6 (CH$_2$), 18.1 (CH$_2$) ppm; IR (neat): v$_\text{max}$ (cm$^-1$) = 3300 (w), 2930 (m), 1668 (s), 1639 (s), 1535 (m), 1256 (m), 642 (w); HRMS (ESI): m/z calculated for C$_{12}$H$_{26}$N$_2$O$_2$ [M+Na]$^+$ 275.1730, found: 275.1724.

**Racemate derivative 5a**
Prepared from Na-Boc-L-2,4-diaminobutyric acid (218 mg, 1.0 mmol, 1 equiv), isobutyraldehyde (72 mg, 1.0 mmol, 1 equiv) and cyclohexyl isocyanide (109 mg, 1.0 mmol, 1 equiv) according to Procedure A. Diastereoisomers formed in ratio ~1:1. Purification: column chromatography on silicagel (cyclohexane/ACOEt 2:1 to cyclohexane/ACOEt 1:1, Rf = 0.29 and Rf = 0.14 for the two diastereoisomers respectively in cyclohexane/ACOEt 1:1). Diastereoisomers were not resolved. Isolated as a white solid. Yield: 174 mg, 0.466 mmol, 46%. Spectrum is complicated by the existence of rotamers and/or unidentified impurities.
Chapter 5

1H-NMR (CDCl3, 500 MHz): δ 6.50 (br, 1H, D1), 6.28 (d, J = 7.0 Hz, 1H, D2), 5.25 (d, J = 5.0 Hz, 1H, D1), 5.18 (br, 1H, D2), 4.23-4.07 (m, 1H, D1, 1H, D2), 4.00 (d, J = 10.4 Hz, 1H, D2), 3.93 (d, J = 11.3 Hz, 1H, D1), 3.71-3.59 (m, 2H, D1, 1H, D2), 3.42-3.21 (m, 1H, D1, 2H, D2), 2.64-2.37 (m, 2H, D1, 2H, D2), 2.34-2.19 (m, 1H, D1, 1H, D2), 1.90-1.50 (m, 5H, D1, 5H, D2), 1.40 (s, 9H, D1, 9H, D2), 1.35-1.03 (m, 4H, D1, H, D2), 0.93 (d, J = 7.0 Hz, 3H, D2), 0.91 (d, J = 7.0 Hz, 3H, D2), 0.80 (d, J = 7.0 Hz, 3H, D1), 0.78 (d, J = 7.0 Hz, 3H, D1) ppm; 13C-1H)-NMR (CDCl3, 125 MHz): δ 173.2 (C, D2), 173.0 (C, D1), 168.2 (C, D1), 167.8 (C, D2), 155.7 (C, D1 and D2), 79.9 (C, D1 and D2), 62.8 (CH, D1), 62.1 (CH, D2), 52.9 (CH, D2), 52.3 (CH, D1), 48.3 (CH, D1 and D2), 41.6 (CH2, D2), 41.4 (CH2, D1), 32.8 (CH1, D1), 32.7 (CH2, D2), 29.7 (CH2, D2), 29.7 (CH3, D1), 28.3 (CH3, D1 and D2), 27.1 (CH, D1), 26.1 (CH, D2), 25.5 (CH2, D1), 25.5 (CH2, D2), 24.9 (CH2, D1), 24.8 (CH2, D2), 19.5 (CH3, D2), 19.3 (CH3, D1), 19.1 (CH3, D1), 18.7 (CH3, D2) ppm; IR (neat): vmax (cm−1) = 3327 (w), 3274 (w), 2927 (m), 1670 (s), 1533 (s), 1435 (m), 1283 (m), 1160 (s), 1047 (w), 707 (w); HRMS (ESI): m/z calculated for C19H33N3NaO4 [M+Na]+ 404.2520, found: 404.2503.

2-(oxopyrrolidin-1-yl)acetamide 4aa[27]

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), paraformaldehyde (30 mg, 1.0 mmol, 1 equiv) and 1,1,3,3-tetramethylbutyl isocyanide (139 mg, 1.0 mmol, 1 equiv) according to procedure B. Purification: column chromatography on silicagel (100% AcOEt to AcOEt/MeOH 9:1, Rf = 0.21 in AcOEt/MeOH 9:1). Isolated as an off-white solid. Yield: 82 mg, 0.58 mmol, 58%.

m.p.: 136-141 °C; 1H-NMR (CDCl3/DMSO-d6, 500 MHz): δ 6.72 (br, 1H, D1), 6.22 (br, 1H), 3.27 (s, 2H), 2.86 (t, J = 7.0 Hz, 2H), 1.75 (t, J = 8.0 Hz, 2H), 1.45 (quint, J = 7.5 Hz, 2H); 13C-1H)-NMR (CDCl3/DMSO-d6, 125 MHz): δ 174.0 (C), 169.1 (C), 46.6 (CH2), 44.2 (CH2), 29.2 (CH2), 16.4 (CH2) ppm; IR (neat): vmax (cm−1) = 3333 (m), 3160 (m), 2958 (w), 1688 (s), 1651 (s), 1406 (s), 1306 (s), 1290 (s), 1163 (m), 1032 (w), 613 (s); HRMS (ESI): m/z calculated for C9H15N2NaO3 [M+Na]+ 165.0634, found: 165.0627.

2-(oxopyrrolidin-1-yl)butanamide 4bb[28]

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), propionaldehyde (58 mg, 1.0 mmol, 1 equiv) and 1,1,3,3-tetramethylbutyl isocyanide (139 mg, 1.0 mmol, 1 equiv) according to procedure B. Purification: column chromatography on silicagel (AcOEt/MeOH, 9:1, Rf = 0.31). Isolated as brown crystals. Yield: 90 mg, 0.53 mmol, 53%.

m.p.: 63-90 °C; 1H-NMR (CDCl3, 500 MHz): δ 6.55 (s, 1H), 5.88 (s, 1H), 4.45 (q, J = 6.0 Hz, 1H), 3.50-3.31 (m, 2H), 2.49-2.32 (m, 2H), 2.10-2.00 (m, 2H), 2.00-1.86 (m, 1H), 1.73-1.59 (m, 1H), 0.88 (t, J = 7.0 Hz, 3H) ppm; 13C-1H)-NMR (CDCl3, 125 MHz): δ 176.3 (C), 172.7 (C), 56.2 (CH3), 44.0 (CH2), 31.2 (CH3), 21.2 (CH2), 18.3 (CH2), 10.7 (CH3) ppm; IR (neat): vmax (cm−1) = 3379 (m), 2966 (w), 1650 (s), 1421 (m), 1269 (m), 1204 (m), 1130 (m), 611 (m); HRMS (ESI): m/z calculated for C7H13N2NaO3 [M+Na]+ 193.0954, found: 193.0954.

2-(oxopyrrolidin-1-yl)-(S)-(S)-phenylethyl)butanamide 4cc[29]

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), propionaldehyde (58 mg, 1.0 mmol, 1 equiv) and (S)-α-methylbenzyl isocyanide (131 mg, 1.0 mmol, 1 equiv) according to Procedure A. Diastereoisomers formed in ratio ~1:1. Purification: column chromatography on silicagel (cyclohexane/AcOEt 1:2 to cyclohexane/AcOEt 1:4, Rf = 0.22 and Rf = 0.15 for the two diastereoisomers respectively in cyclohexane/AcOEt 1:2). Diastereoisomers were not resolved. Isolated as a pale yellow oil. Yield: 55 mg, 0.20 mmol, 20%.

1H-NMR (CDCl3, 500 MHz): 7.39-7.15 (m, 5H, D1, 5H, D2), 6.67 (br, 1H, D2), 6.64 (br, 1H, D1), 5.05 (quint, J = 7.0 Hz, 1H, D1, 1H, D2), 4.43 (t, J = 7.0 Hz, 1H, D1), 4.40 (t, J = 7.0 Hz, 1H, D2), 3.56-3.48 (m, 1H, D2), 3.45-3.39 (m, 1H, D2), 3.34-3.27 (m, 1H, D1), 3.20-3.13 (m, 1H, D1), 2.48-2.36 (m, 1H, D1, 2H, D2), 2.27 (ddd, J = 16.0 Hz, J = 10.0 Hz, J = 6.5 Hz, 1H, D1), 2.10-1.80 (m, 3H, D1, 3H, D2), 1.74-1.60 (m, 1H, D1, 1H, D2), 1.46 (d, J = 7.0 Hz, 3H, D1), 1.44 (d, J = 7.0 Hz, 3H, D2), 0.90 (t, J = 7.3 Hz, 3H, D1), 0.85 (t, J = 7.3 Hz, 3H, D2) ppm; 13C-1H)-NMR (CDCl3,
An Ugi Approach towards Racetams

125 MHz): δ 176.2 (C, D2), 176.1 (C, D1), 169.3 (C, D2), 169.0 (C, D1), 143.7 (C, D1), 143.2 (C, D2), 128.7 (CH, D1), 127.4 (CH, D2), 127.3 (CH, D1), 126.1 (CH, D2), 126.0 (CH, D1), 56.9 (CH, D2), 56.6 (CH, D1), 49.0 (CH, D2), 49.0 (CH, D1), 44.1 (CH, D2), 43.8 (CH, D1), 31.3 (CH, D2), 31.2 (CH, D1), 22.2 (CH, D1), 22.2 (CH, D2), 21.4 (CH2, D2), 20.9 (CH2, D1), 18.4 (CH2, D2), 18.2 (CH2, D1), 10.7 (CH2, D2), 10.6 (CH2, D1) ppm; IR (neat): νmax (cm−1) = 3299 (w), 2969 (w), 1651 (s), 1533 (m), 1449 (m), 1287 (m), 1213 (w), 700 (s); HRMS (ESI): m/z calculated for C16H22N2NaO2[M+Na]+ 297.1573, found: 297.1570.

N-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide 4dd[29]

Prepared from γ-aminobutyric acid (103 mg, 1.0 mmol, 1 equiv), paraformaldehyde (30 mg, 1.0 mmol, 1 equiv) and 2,6-diethylphenyl isocyanide (131 mg, 1.0 mmol, 1 equiv) according to Procedure A (reflux, 6 h reaction time). Purification: column chromatography on silica gel (100% AcOEt to AcOEt/MeOH 19:1, RF = 0.14 in 100% AcOEt). Isolated as a white solid. Yield: 97 mg, 0.392 mmol, 39%.

m.p.: 139-142 °C; 1H-NMR (CDCl3, 500 MHz): 8.05 (br, 1H), 7.10-6.97 (m, 3H), 4.02 (s, 2H), 3.51 (t, J = 6.9 Hz, 2H), 2.34 (t, J = 8.2 Hz, 2H), 2.14 (s, 6H), 2.03 (quint, J = 7.6 Hz, 2H) ppm; 13C{1H}-NMR (CDCl3, 125 MHz): δ 176.2 (C), 167.0 (C), 135.2 (C), 133.5 (C), 128.1 (CH), 127.3 (CH), 48.5 (CH2), 47.2 (CH2), 30.4 (CH2), 18.4 (CH3), 18.1 (CH2) ppm; IR (neat): νmax (cm−1) = 3257 (s), 2920 (m), 2364 (m), 1697 (s), 1662 (s), 1529 (s), 1467 (s), 1438 (s), 1425 (s), 1406 (s); HRMS (ESI): m/z calculated for C14H18N2O2[M+Na]+ 269.1260, found: 269.1256.

N-(2-(diisopropylamino)ethyl)-2-(2-oxopyrrolidin-1-yl)acetamide 4ee[30]

To Ugi product 4o (20 mg, 0.065 mmol, 1 equiv) was added N,N-diisopropylethyl-1,2-diamine (0.1 mL) and the mixture was stirred at 110 °C for 11 h (under N2 atmosphere). Crude NMR analysis indicated the complete conversion of 4o to 4ee and 2-amino-6-bromo pyridine. The product 4ee was not isolated.

1H-NMR (CDCl3, 500 MHz): 3.93 (s, 2H), 3.47 (t, J = 7.0 Hz, 2H), 3.28 (q, J = 5.5 Hz, 2H), 3.08 (sept, J = 7.0 Hz, 2H), 2.65 (t, J = 5.5 Hz, 2H), 2.43 (t, J = 8.0 Hz, 2H), 2.03 (quint, J = 7.5 Hz, 2H), 1.05 (d, J = 7.5 Hz, 2H) ppm; 13C{1H}-NMR (CDCl3, 125 MHz): δ 175.9 (C), 168.2 (C), 48.4 (CH2), 48.1 (CH), 47.1 (CH2), 37.8 (CH2), 36.5 (CH2), 30.4 (CH2), 20.9 (CH2), 18.1 (CH2) ppm; HRMS (ESI): m/z calculated for C14H28N3O2[M+H]+ 270.2176, found: 270.2171.

ethyl 2-(2-oxopyrrolidin-1-yl)acetate 6[30]

To a solution of 4o (34 mg, 0.11 mmol, 1 equiv) in 0.3 mL ethanol was added acetyl chloride (44 mg, 0.56 mmol, 5 equiv) and the mixture was stirred at room temperature for 22 h. Then, ethanol was removed in vacuo and the crude mixture was redissolved in diethyl ether. A solution of HCl in cyclopentylmethyl ether (3 M, 0.2 mL) was then added precipitating the hydrochloride salt of 2-amino-6-bromopyridine. This byproduct was filtered off and concentration of the filtrate afforded the product as a colorless oil. Yield: 14 mg, 0.08 mmol, 70%.

1H-NMR (CDCl3, 500 MHz): 4.17 (q, J = 7.0 Hz, 2H), 4.03 (s, 2H), 3.47 (t, J = 7.0 Hz, 2H), 2.41 (t, J = 8.0 Hz, 2H), 2.06 (quint, J = 7.2 Hz, 2H) ppm; 13C{1H}-NMR (CDCl3, 125 MHz): δ 175.8 (C), 168.8 (C), 61.4 (CH2), 47.8 (CH2), 44.2 (CH2), 30.4 (CH2), 18.0 (CH2), 14.2 (CH2) ppm.
References and Notes


[15] see Supporting Information for details.


[18] The need for depolymerization of paraformaldehyde could be the problem here; however, the use of a stabilized monomeric manehanolic solution did not improve the yield.


[21] The formation of product 4m was observed in the HRMS spectrum, but the NMR analysis of the crude reaction showed a complex mixture that hampered its isolation.

Possibly due to competing N,O-acetal formation.


This reaction occurred with quantitative conversion based on crude NMR analysis but the purification of 4ee from the reaction mixture proved troublesome.


This reaction occurred with quantitative conversion based on crude NMR analysis but the purification of 4ee from the reaction mixture proved troublesome.
Diastereoselective Passerini Reactions with Ketoacids

Abstract: In this chapter we describe the use of bifunctional inputs (ketoacids) in a diastereoselective Passerini reaction. The study of the reaction scope reveals the structural features required for high stereoselectivity in the isocyanide addition. In this system, an interesting isomerization of the primary Passerini scaffold – the α-carboxamide lactone – to an atypical product, an α-hydroxy imide, occurs under acidic conditions. Furthermore, enantioenriched Passerini products can be obtained by employing a biocatalytically-generated ketoacid.

Isocyanide-based multicomponent reactions (IMCRs) are essential tools in combinatorial and diversity-oriented synthesis applications. Based on the unique reactivity of the formally divalent isocyanide carbon atom, this chemistry facilitates the exploration of the chemical space generating rapid complexity from simple inputs. Importantly, the primary MCR products provide numerous opportunities for further synthetic elaboration, for instance into planar heterocycles as well as sp\(^3\)-rich structures.\(^1\) The first discovered IMCR, the Passerini reaction combining an oxo-compound, a carboxylic acid and an isocyanide,\(^2\) still represents one of the most used IMCRs in various applications.\(^3\) Its advantages (convergence, atom economy, simple operation, broad scope)\(^4\) as well as its most important limitation - the poor control over the newly formed stereocenter - are well recognized in the multicomponent reactions community.\(^5\)

Notably, despite great efforts to address this issue, the success in the development of asymmetric Passerini reactions is still limited to just a few examples of catalytic enantioselective variants\(^6\) and diastereoselective reactions (with chiral isocyanides,\(^7\) chiral carboxylic acids\(^8\) or chiral aldehydes/ketones,\(^9\) respectively). Some representative examples of diastereoselective Passerini reactions are depicted in Scheme 1. A relatively simple strategy to improve the modest stereocontrol is the use of bifunctional inputs – oxoacids – as the intramolecular reaction benefits from a more sterically constrained transition state for the isocyanide addition. The bifunctional nature of oxoacid components has been strategically exploited in isocyanide chemistry to create a broad spectrum of heterocycles via the Ugi reaction (Scheme 2);\(^10\) however, similar examples of the Passerini reaction are scarce\(^11\) (last two examples of Scheme 1).

Herein we report a novel diastereoselective Passerini reaction with simple oxoacids as starting inputs; by employing cyclic starting components, the reaction follows a fused bicyclic transition state with additional steric constraints, thus providing a good bias for stereoselectivity. Furthermore, we show the unusual rearrangement of these Passerini products towards unprecedented α-hydroxy bicyclic imides.
**Diastereoselective Passerini Reactions with Ketoacids**

**Scheme 1.** Diastereoselective Passerini reactions.

**Scheme 2.** Use of oxoacids in Ugi reactions.
Chapter 6

Results and Discussion

We began our investigation with the reaction between 2-(2-oxocyclohexyl)acetic acid 1a and tert-butyl isocyanide 2a (1.5 equiv). Under standard Passerini conditions (CH$_2$Cl$_2$, rt), the reaction proceeded smoothly to afford the desired product with already good diastereoselectivity (85:15) in favor of the trans-fused isomer (Table 1, entry 1). The stereochemistry corresponds to an axial attack of the isocyanide (expected for a non-stERICALLY demanding nucleophile$^{[12]}$) to yield a cis-fused O-acyl imidate α-adduct which upon Mumm rearrangement affords trans-fused bicyclic lactone 3a (see also Scheme 3). This structure was unambiguously confirmed by XRD analysis, as depicted in Figure 1.

![Figure 1. X-ray structure of major trans diastereoisomer 3a (some H atoms omitted for clarity).](image)

Encouraged by this initial result, we attempted to improve the diastereomeric ratio of the isocyanide addition by varying the solvent. The reaction was found to proceed in most solvents investigated (toluene, dimethyl carbonate, tert-butanol, methanol and even water) but with lower stereoselectivity. We then resorted to Lewis acid catalysis under the hypothesis that the coordination of both carbonyl groups (and possibly the isocyanide as well) to a metal center would lead to a more rigid transition state.$^{[9c]}$ A small screen identified Zn(OTf)$_2$ as promising candidate for an improved diastereoselectivity (Table 1, entry 3). Since the Lewis acid also led to an enhanced rate we repeated the solvent screen and focused on the solvent with the slowest background (uncatalyzed) reaction. Thus, the reaction with 20 mol% Zn(OTf)$_2$ in dimethylcarbonate (DMC)$^{[13]}$ gave complete conversion and a diastereomeric ratio of 9:1 (entry 9). While performing the reaction at 0 °C was detrimental for both yield and selectivity (possibly due to catalyst insolubility) we observed that we could significantly reduce both the catalyst loading (to 10 mol%) and reaction time (to 2 h) without adverse effects. These conditions turned out to be optimal, as a further reduction in the isocyanide stoichiometry (entry 14) or in the catalyst loading (entry 15) did not lead to improved results.
Diastereoselective Passerini Reactions with Ketoacids

Table 1. Optimization of the intramolecular Passerini reaction with 1a\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Cat. load</th>
<th>Time</th>
<th>Yield(^{[b]})</th>
<th>3a:3a'(^{[c]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH(_2)Cl (_2)</td>
<td>0%</td>
<td>20 h</td>
<td>100%</td>
<td>85:15</td>
</tr>
<tr>
<td>2</td>
<td>DMC</td>
<td>0%</td>
<td>20 h</td>
<td>73%</td>
<td>72:18</td>
</tr>
<tr>
<td>3</td>
<td>CH(_2)Cl (_2)</td>
<td>20%</td>
<td>20 h</td>
<td>100%</td>
<td>88:12</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>20%</td>
<td>20 h</td>
<td>95%</td>
<td>86:14</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>20%</td>
<td>20 h</td>
<td>100%</td>
<td>83:17</td>
</tr>
<tr>
<td>6</td>
<td>t-BuOH</td>
<td>20%</td>
<td>20 h</td>
<td>93%</td>
<td>81:19</td>
</tr>
<tr>
<td>7</td>
<td>AcOEt</td>
<td>20%</td>
<td>20 h</td>
<td>98%</td>
<td>87:13</td>
</tr>
<tr>
<td>8</td>
<td>MeCN</td>
<td>20%</td>
<td>20 h</td>
<td>100%</td>
<td>89:11</td>
</tr>
<tr>
<td>9</td>
<td>DMC</td>
<td>20%</td>
<td>20 h</td>
<td>100%</td>
<td>90:10</td>
</tr>
<tr>
<td>11</td>
<td>DMC</td>
<td>20%</td>
<td>2 h</td>
<td>100%</td>
<td>90:10</td>
</tr>
<tr>
<td>12</td>
<td>DMC</td>
<td>20%</td>
<td>2 h</td>
<td>56(^{[d]})</td>
<td>50:50</td>
</tr>
<tr>
<td>13</td>
<td>DMC</td>
<td>10%</td>
<td>2 h</td>
<td>100%</td>
<td>90:10</td>
</tr>
<tr>
<td>14</td>
<td>DMC</td>
<td>10%</td>
<td>2 h</td>
<td>90%(^{[e]})</td>
<td>90:10</td>
</tr>
<tr>
<td>15</td>
<td>DMC</td>
<td>5%</td>
<td>2 h</td>
<td>93%</td>
<td>75:25</td>
</tr>
</tbody>
</table>

[a] Standard conditions: ketoacid 1a (0.5 mmol) and t-BuNC 2a (0.75 mmol, 1.5 equiv) in solvent (1 mL) at room temperature for the indicated time; [b] crude yield based on NMR using mesitylene as internal standard; [c] based on crude NMR; [d] performed at 0 °C; [e] with 1.1 equiv of t-BuNC, ~10% of intermolecular Passerini 3CR observed.

With the optimal protocol in hand, we investigated the isocyanide scope of this reaction. Gratifyingly, all classes of isocyanide reagents are accepted in this reaction (Table 2): aliphatic (tertiary [products 3a, b], secondary [products 3c, d], primary [products 3e, f]), aromatic (including the bulky 2,6-dimethylphenyl derivative, product 3h) and α-acidic (products 3i, j). In general, the diastereoisomers can be easily resolved by column chromatography and the isolated yields of the pure trans-fused Passerini products 3a-j are moderate to high. As expected for relatively small linear nucleophiles like isocyanides, the diastereoselectivity is well conserved across the series (around 9:1, as in the parent example 3a).
Next, we were interested in extending this intramolecular Passerini reaction to other oxoacids in order to rationalize the structural features required for high diastereoselectivity. We focused on several elements: ring size, relationship between the two reacting centers (C=O and COOH) and conformational flexibility of the oxoacid 1. First, the introduction of a carbamate group in the cyclohexanone ring (input 1b) lead to a drastic reduction in reaction rate (Table 3, entry 1), possibly due to preferential binding of the Zn ions to this additional coordinating group. Then, an input with the 1,5-disposition of the keto and carboxylic groups reacts somewhat slower (the imidate α-adduct is a seven-membered ring in this case) but still delivers the product in a good yield under the standard conditions (with t-BuNC, entry 2 and TsCH2NC, entry 3). The diastereoselectivity is reduced to 3:1 but the direction of isocyanide attack is preserved (trans-fused product predominates). Next, the reaction is unfortunately not tolerant to a variation in the nature of the cyclic ketone, as inputs based on a cyclopentanone (1d), cycloheptanone (1e) or tetralone (1f) motif respectively gave slow conversions and side reactions (entries 4-7). Due to ring strain, the carbonyl group is particularly reactive in the cyclohexanone system compared to the C₅ and C₇ homologues; conjugation with the aromatic ring drastically
Diastereoselective Passerini Reactions with Ketoacids

reduces the reactivity of 1f. Furthermore, side reactions (for instance multiple isocyanide addition) may take place as a result of conformational/strain effects disfavoring the formation of the usual intermediates. Indeed, in input 1d a more ionic mechanism (i.e. sequential isocyanide addition to generate a nitrilium ion[^14]) can be expected since the nucleophilic attack would presumably take place from the least hindered diastereotopic face of the carbonyl leading to a strained trans-fused α-adduct,[^15] which may be difficult to form and may not evolve cleanly towards a single product. Additionally, intermolecular reactions can take place if the transition state is not favorable for the intramolecular condensation. Spectral evidence for these side reactions was obtained in the reaction of 1d with t-BuNC under the standard conditions; a complex mixture of products was observed (entry 4). Moreover, in the case of the less reactive isocyanide TsCH₂NC the conversion was low and product formation could not be confirmed. In the case of the 7-membered homologue 1e, HRMS analysis indicated the formation of the desired product 3p, but we were unable to isolate it from the complex product mixture. A similar outcome was observed for tetralone-based acid 1f. On the other hand, the simple acyclic derivative 1g reacted cleanly, albeit slow and with no stereoselectivity (entry 8). Extending the reaction time to 24 h allowed the isolation of the expected Passerini product of 1g and TsCH₂NC in 82% yield (entry 9), but with this scaffold the diastereoisomers could not be resolved anymore on silicagel column. As a control experiment, the Passerini three-component reaction between cyclohexanone, acetic acid and tert-butyl isocyanide proceeded to near completion within 24 h even in the absence of the Lewis acid (entry 10), confirming the particularly high electrophilicity of cyclohexanone. On the other hand, the addition of catalytic Zn(OTf)₂ gave a much reduced yield (~50%, entry 11) due to side reactions, indicating that the Lewis acid not only enhances the rate of the desired pathway but also that of alternative pathways, possibly by a switch in the reaction mechanism.

Thus, the success of the reaction depends on a fine balance between the rigidity of the transition state required for good diastereoselectivity (1a vs. 1g, 1c vs. 1g) and some degree of conformational flexibility to prevent side reactions (1g vs. 1d).

Upon crystallization of Passerini product 3j from ethanol, we were intrigued to observe that the structure revealed by XRD analysis corresponded to a rearrangement of the scaffold to an α-hydroxy imide 4j (Figure 2). We then investigated this unusual transformation further and found out that it is amenable to Brønsted acid catalysis. Surprisingly, the conditions required to drive this rearrangement (1 equiv of MeSO₃H, 80 °C) are not as mild as expected from the crystallization experiment[^16] whereas the rate varies significantly and relatively inconsistently with the type of secondary amide substituent.
Table 3. Ketoacid scope\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Ketoacid</th>
<th>R</th>
<th>Time</th>
<th>Yield(^{[b]})</th>
<th>3:3(^{[c]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3k</td>
<td>1b</td>
<td>t-Bu</td>
<td>6 h</td>
<td>23%</td>
<td>5:1</td>
</tr>
<tr>
<td>2</td>
<td>3l</td>
<td>1c</td>
<td>t-Bu</td>
<td>2 h</td>
<td>58%</td>
<td>3:1</td>
</tr>
<tr>
<td>3</td>
<td>3m</td>
<td>1c</td>
<td>TsCH(_2)</td>
<td>2 h</td>
<td>50%</td>
<td>3:1</td>
</tr>
<tr>
<td>4</td>
<td>3n</td>
<td>1d</td>
<td>t-Bu</td>
<td>2 h</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>3o</td>
<td>1d</td>
<td>TsCH(_2)</td>
<td>2 h</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>3p</td>
<td>1e</td>
<td>t-Bu</td>
<td>24 h</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>3q</td>
<td>1f</td>
<td>t-Bu</td>
<td>24 h</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>3r</td>
<td>1g</td>
<td>t-Bu</td>
<td>2 h</td>
<td>11%(^{[d]})</td>
<td>~1:1</td>
</tr>
<tr>
<td>9</td>
<td>3s</td>
<td>1g</td>
<td>TsCH(_2)</td>
<td>24 h</td>
<td>82%(^{[d]})</td>
<td>~1:1</td>
</tr>
<tr>
<td>10</td>
<td>3t</td>
<td>-</td>
<td>t-Bu</td>
<td>24 h</td>
<td>95%(^{[b, f]})</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>3t</td>
<td>-</td>
<td>t-Bu</td>
<td>24 h</td>
<td>50%(^{[e]})</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Standard conditions: ketoacid 1 (1 mmol) and isocyanide 2 (1.5 mmol, 1.5 equiv) in DMC (2 mL) with Zn(OTf)\(_2\) (10 mol%) at room temperature for the indicated time; \(^{[b]}\) isolated yield of the major diastereoisomer unless indicated otherwise; \(^{[c]}\) based on crude NMR; \(^{[d]}\) combined yield of diastereoisomers; \(^{[e]}\) crude yield using mesitylene as internal standard; \(^{[f]}\) without catalyst.

Nevertheless, this transformation is general in the series of Passerini products 3a-j and can be pushed to near completion over 24 h (Table 4). The tertiary derivatives 3a and 3b represent a particular case as they undergo dealkylation under these conditions: for 3a, the conversion was slow and lead to a mixture of products, whereas for the tert-octyl derivative 3b the corresponding free α-hydroxy imide (4b, R = H) could be isolated in a good yield (Table 4, entry 2).
Diastereoselective Passerini Reactions with Ketoacids

Figure 2. X-ray structure of 4j (some H atoms omitted for clarity).

Table 4. Rearrangement of Passerini products to α-hydroxyimides[^a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>3</th>
<th>R</th>
<th>Time</th>
<th>Yield[^b]</th>
<th>3:4[^c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>t-Bu</td>
<td>24 h</td>
<td>n.d.[^d]</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>t-Oct</td>
<td>7 h</td>
<td>60%^[^a]</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>Cy</td>
<td>24 h</td>
<td>89%</td>
<td>94:6</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>iPr</td>
<td>24 h</td>
<td>96%</td>
<td>95:5</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>n-pentyl</td>
<td>2 h</td>
<td>75%</td>
<td>94:6</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>benzyl</td>
<td>4 h</td>
<td>93%</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>2-naphthyl</td>
<td>24 h</td>
<td>64%^[^f]</td>
<td>91:9</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>2,6-Me₂C₆H₄</td>
<td>3 h</td>
<td>99%</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>TsCH₂</td>
<td>1 h</td>
<td>83%</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>10</td>
<td>3j</td>
<td>MeO₂CCH₂</td>
<td>3 h</td>
<td>76%^[^f]</td>
<td>&gt;95:5</td>
</tr>
</tbody>
</table>

[^a] Standard conditions: Passerini product (0.1 mmol) and MeSO₃H (1 equiv) in CHCl₃ (0.3 mL) at 80 °C for the indicated time;[^b] isolated yield of 3 with minor amounts of 4;[^c] based on crude NMR;[^d] complex product mixture;[^e] free imide (4, R = H) isolated after column chromatography;[^f] minor impurity observed.

We hypothesize that in this rearrangement (which corresponds to a formal 1,3(O-N) acyl transfer in the Passerini α-adduct instead of the acyl migration to the OH group) ring strain plays an important part. Most likely the thermodynamic driving force for this isomerization is the release of strain from the bicyclic *trans*-fused [4.3.0] system to the more relaxed *cis* hexahydroisoquinolinedione scaffold. This premise is supported by
negative control experiments: the minor diastereoisomer $3h'$ is stable under the rearrangement conditions whereas homologue $3m$ and monocyclic lactone $3r$ gave low conversions over 24 h (Scheme 3).

![Scheme 3. Negative control experiments in the formal 1,3(O-N) Mumm rearrangement of scaffold 3.](image)

Finally, we attempted to control not only the diastereoselectivity but also the absolute stereochemistry during our intramolecular Passerini reaction. Thus, the intramolecular isocyanide addition can be coupled with the biocatalytic preparation of non-racemic keto acid $1a$\(^1\) to deliver enantioenriched Passerini products,\(^2\) as exemplified for $3a$ in Scheme 4.

![Scheme 4. Chemoenzymatic preparation of enantioenriched Passerini products.](image)

**Conclusion**

In conclusion, we report a novel diastereoselective intramolecular Passerini reaction with cyclic ketoacids leading to interesting $sp^3$-rich bicyclic lactone derivatives. The structural features required for high stereoselectivity in the isocyanide addition were identified and discussed. Interestingly, these Passerini 2CR products can isomerize to $\alpha$-hydroxy imide derivatives as formal 1,3(O-N) Mumm rearrangement products of the $\alpha$-adduct. Furthermore, complete stereocontrol can be ultimately achieved by combining this diastereoselective isocyanide addition with a biocatalytic preparation of the non-racemic ketoacid building block.
Experimental Section

General Remarks

Unless stated otherwise, all solvents and commercially available reagents were used as purchased.

Melting points were recorded on a Büchi M-565 melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 500 (125.78 MHz for $^{13}$C) or Bruker Avance 400 (100.62 MHz for $^{13}$C) using the residual solvent as internal standard ($^1$H: δ 7.26 ppm, $^{13}$C($^1$H): δ 77.16 ppm for CDCl$_3$, $^1$H: δ 2.50 ppm, $^{13}$C($^1$H): δ 39.52 ppm for DMSO-d$_6$). Chemical shifts (δ) are given in ppm and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sextet), sep (septet), br (broad singlet) and m (multiplet) or combinations thereof. Infrared (IR) spectra were recorded neat using a Shimadzu FTIR-8400s spectrophotometer and wavelengths are reported in cm$^{-1}$. Electrospray Ionization (ESI) high-resolution mass spectrometry (HRMS) was carried out using a Bruker microTOF-Q instrument in positive ion mode (capillary potential of 4500 V). Chiral GC analysis was performed on a Shimadzu GC-2010 Plus chromatograph. Flash chromatography was performed on Silicycle Silia-P Flash Silica Gel (particle size 40-63 μm, pore diameter 60 Å) using the indicated eluent. Thin Layer Chromatography (TLC) was performed using TLC plates from Merck (SiO$_2$, Kieselgel 60 F254 neutral, on aluminium with fluorescence indicator).

The ketoacids 1a, 1c-f are known compounds and were prepared according to common procedures: 1a, 1c, 1d, 1e, 1f, 1g is commercially available.

General synthetic procedures

Reaction optimization

To a solution of ketoacid 1a (0.5 mmol, 1 equiv) in solvent (1 mL) was added Zn(OTf)$_2$ (0.05 mmol, 0.1 equiv) and the isocyanide 2a (0.75 mmol, 1.5 equiv). The solution was stirred at room temperature for 2-20 h. Then the mixture was diluted with CH$_2$Cl$_2$ and quenched in a saturated NaHCO$_3$ solution. The organic layer was separated and the aqueous layer was extracted again with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, concentrated in vacuo and the crude yield of 3a and the ratio 3a:3a' were determined by NMR analysis using mesitylene as internal standard.

Procedure A. Intramolecular Passerini reaction

To a solution of ketoacid 1 (1 mmol, 1 equiv) in dimethyl carbonate (2 mL) was added Zn(OTf)$_2$ (0.1 mmol, 0.1 equiv) and the isocyanide 2 (1.5 mmol, 1.5 equiv). The solution was stirred at room temperature for 2 h. Then the mixture was diluted with CH$_2$Cl$_2$ and quenched in a saturated NaHCO$_3$ solution. The organic layer was separated and the aqueous layer was extracted again with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, concentrated in vacuo and the crude product 3 was purified by column chromatography on silica gel.

Procedure B. Rearrangement of Passerini products

To a solution of Passerini product 3 (0.1 mmol) in CHCl$_3$ was added CH$_2$SO$_2$H (0.1 mmol, 1 equiv) and the solution was heated at 80 °C in a sealed vial for 1 – 24 h (conversion monitored by TLC). The solution was then diluted with CH$_2$Cl$_2$ and quenched in a saturated NaHCO$_3$ solution. The organic layer was separated and the aqueous layer was extracted again with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$. After concentration in vacuo, the yield and the ratio of 4 to 3 were determined.
Chapter 6

Characterization of compounds

Passerini products 3a-s

**N-(tert-butyl)-2-oxohexahydrobenzofuran-7a(2H)-carboxamide 3a**

Prepared from 2-(2-oxocyclohexyl)acetic acid 1a (156 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (170 µl, 1.5 mmol, 1.5 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/ethyl acetate, 4/1); diastereoisomers could be separated (Rf = 0.50 (major) and Rf = 0.34 (minor)).

Major diastereoisomer (trans)

Isolated as a slowly crystallizing solid. Yield: 182 mg, 0.76 mmol, 76%.

m.p.: 50-54 °C; 1H-NMR (CDCl3, 500 MHz) δ 6.08 (br, 1H), 2.52 (qd, J = 12.5 Hz, J = 3.5 Hz, 1H), 2.46-2.34 (m, 2H), 2.18-2.06 (m, 2H), 2.01-1.87 (m, 2H), 1.78 (d, J = 13.0 Hz, 1H), 1.76-1.66 (m, 2H), 1.47-1.37 (m, 1H), 1.35 (s, 9H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz): δ 175.9 (C), 170.2 (C), 86.5 (C), 51.6 (C), 48.5 (CH), 34.6 (CH2), 33.8 (CH2), 28.7 (CH3), 25.3 (CH3), 24.0 (CH2), 22.1 (CH2) ppm; IR (neat): vmax (cm⁻¹) = 3396 (m), 2924 (w), 2868 (w), 1700, 1665 (s), 1522 (s), 1452 (m), 1188 (s), 1024 (s), 901 (m), 881 (m), 552 (m); HRMS (ESI): m/z calculated for C13H13NO3 [M+H]+ 240.1595, found 240.1594.

Minor diastereoisomer (cis)

Isolated as a white solid. Yield: 14 mg, 0.06 mmol, 6%.

m.p.: 93-105 °C; 1H-NMR (CDCl3, 500 MHz) δ 6.15 (br, 1H), 2.88-2.77 (m, 1H), 2.51 (dd, J = 17.0 Hz, J = 7.0 Hz, 1H), 2.19 (dd, J = 17.0 Hz, J = 2.0 Hz, 1H), 1.97-1.87 (m, 3H), 1.73-1.57 (m, 2H), 1.47-1.34 (m, 2H), 1.32 (s, 9H), 1.21-1.10 (m, 1H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz) δ 171.8 (C), 87.2 (C), 51.6 (C), 48.5 (CH), 34.6 (CH2), 33.8 (CH2), 28.7 (CH3), 25.3 (CH3), 24.0 (CH2), 22.1 (CH2) ppm; IR (neat): vmax (cm⁻¹) = 3354 (m), 2951 (w), 1780 (s), 1736 (s), 1670 (s), 1533 (m), 1414 (m), 1188 (s), 1011 (s), 935 (s), 885 (s), 710 (m), 548 (m).

**N-((2,4,4-trimethylpentan-2-yl)-2-oxohexahydrobenzofuran-7a(2H)-carboxamide 3b**

Prepared from 2-(2-oxocyclohexyl)acetic acid 1a (156 mg, 1 mmol, 1 equiv) and 1,1,3,3-tetramethylbutyl isocyanide (263 µl, 1.5 mmol 1.5 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/ethyl acetate, 4/1); diastereoisomers could be separated (Rf = 0.50 (major) and Rf = 0.37 (minor)).

Major diastereoisomer (trans)

Isolated as a white solid. Yield: 200 mg, 0.68 mmol, 68%.

m.p.: 59-67 °C; 1H-NMR (CDCl3, 500 MHz) δ 6.11 (br, 1H), 2.52 (qd, J = 12.7 Hz, J = 4.0 Hz, 1H), 2.42-2.32 (m, 2H), 2.13-2.04 (m, 2H), 1.94-1.82 (m, 2H), 1.79-1.61 (m, 5H), 1.39-1.31 (m, 1H), 1.35 (s, 6H), 0.96 (s, 9H) ppm; 13C(1H)-NMR (CDCl3, 125 MHz) δ 175.7 (C), 169.6 (C), 86.3 (C), 55.4 (C), 55.8 (CH2), 48.3 (CH), 34.2 (CH3), 33.6 (CH3), 31.6 (C), 31.4 (CH), 28.8 (CH3), 25.0 (CH3), 23.7 (CH2), 21.8 (CH2) ppm. IR (neat): vmax (cm⁻¹) = 3394 (m), 2948 (w), 2868 (w), 1788 (s), 1675 (s), 1522 (s), 1454 (m), 1177 (s), 1018 (s), 878 (m), 718 (m); HRMS (ESI): m/z calculated for C17H20NO3 [M+H]+ 296.2220, found 296.2215.

Minor diastereoisomer (cis)

Isolated as a white solid. Yield: 180 mg, 0.68 mmol, 68%.

m.p.: 111-114 °C; 1H-NMR (CDCl3, 500 MHz) δ 6.19 (br, 1H), 3.75-3.64 (m, 1H), 2.49 (qd, J = 12.0 Hz, J = 4.0 Hz, 1H), 2.42-2.28 (m, 2H), 2.17-2.06 (m, 2H), 1.90-1.62 (m, 9H), 1.62-1.53 (m, 1H), 1.44-1.27 (m, 3H), 1.20-1.06 (m,
Diastereoselective Passerini Reactions with Ketoacids

3H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz) δ 175.9 (C), 169.8 (C), 86.5 (C), 48.5 (CH), 34.5 (CH$_3$), 33.7 (CH$_3$), 33.1 (CH$_3$), 32.8 (CH$_3$), 31.1 (CH), 25.5 (CH$_3$), 25.3 (CH$_3$), 24.9 (CH$_3$), 24.9 (CH$_3$), 23.9 (CH$_3$), 22.1 (CH$_3$) ppm; IR (neat): vmax (cm$^{-1}$) = 3323 (w), 2930 (m), 1784 (s), 1653 (s), 1522 (s), 1427 (m), 1194 (m), 1183 (m), 1021 (s), 938 (m), 885 (m), 733 (s), 693 (s), 557(s); HRMS (ESI): m/z calculated for C$_{16}$H$_{23}$NO$_3$ [M+H]$^+$ 266.1751, found 266.1751.

**N-isopropyl-2-oxohexahydrobenzofuran-7a(2H)-carboxamide 3d**

Prepared from 2-(2-oxocyclohexyl)acetic acid 1a (156 mg, 1 mmol, 1 equiv) and isopropyl isocyanide (141 µL, 1.5 mmol 1.5 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/ethyl acetate, 3/1); diastereoisomers could be separated (R$_f$ = 0.5 (major) and R$_f$ = 0.25 (minor)).

Major diastereoisomer (trans)

Isolated as a white solid. Yield: 124 mg, 0.55 mmol, 55%.

m.p.: 84-86 °C; $^1$H-NMR (CDCl$_3$, 500 MHz) δ 6.19 (d, J = 12.0 Hz, 1H), 4.04-3.96 (m, 1H), 2.49 (qd, J = 12.6 Hz, J = 3.8 Hz, 1H), 2.44-2.30 (m, 2H), 2.16-2.07 (m, 2H), 1.98-1.84 (m, 2H), 1.80-1.65 (m, 3H), 1.43-1.31 (m, 1H), 1.11 (d, J = 6.5 Hz, 6H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz) δ 175.6 (C), 169.5 (C), 86.1 (C), 48.1 (CH), 41.1 (CH), 34.1 (CH$_3$), 33.4 (CH$_3$), 24.9 (CH$_3$), 23.6 (CH$_3$), 22.4 (CH$_3$), 22.2 (CH$_3$), 21.7 (CH$_3$) ppm; IR (neat): vmax (cm$^{-1}$) = 3310 (w), 2927 (m), 1784 (s), 1645 (s), 1521 (s), 1450 (m), 1196 (m), 1026 (s), 906 (m), 883 (m), 696 (s); HRMS (ESI): m/z calculated for C$_{16}$H$_{23}$NO$_3$ [M+H]$^+$ 226.1438, found 226.1437.

**N-pentyl-2-oxohexahydrobenzofuran-7a(2H)-carboxamide 3e**

Prepared from 2-(2-oxocyclohexyl)acetic acid 1a (156 mg, 1 mmol, 1 equiv) and n-pentyl isocyanide (188 µL, 1.5 mmol, 1.5 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/ethyl acetate, 5/1); diastereoisomers could be separated (R$_f$ = 0.30 (major)).

Major diastereoisomer (trans)

Isolated as a white solid. Yield: 177 mg, 0.70 mmol, 70%.

m.p.: 55-57 °C; $^1$H-NMR (CDCl$_3$, 500 MHz) δ 6.33 (br, 1H), 3.25-3.14 (m, 2H), 2.50 (dq, J = 12.6 Hz, J = 3.9 Hz, 1H), 2.44-2.29 (m, 2H), 2.18-2.09 (m, 2H), 1.99-1.83 (m, 2H), 1.81-1.64 (m, 3H), 1.50-1.33 (m, 3H), 1.32-1.19 (m, 4H), 0.87 (t, J = 6.9 Hz, 3H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz) δ 175.7 (C), 170.5 (C), 86.5 (C), 48.4 (CH), 39.1 (CH$_3$), 34.3 (CH$_3$), 33.5 (CH$_3$), 29.0 (CH$_3$), 28.9 (CH$_3$), 25.1 (CH$_3$), 23.7 (CH$_3$), 22.2 (CH$_3$), 21.8 (CH$_3$), 13.9 (CH$_3$) ppm; IR (neat): vmax (cm$^{-1}$) = 3312 (w), 2928 (m), 2866 (w), 1788 (s), 1651 (s), 1533 (s), 1439 (m), 1194 (m), 1184 (m), 1026 (s), 943 (m), 881 (m), 704 (m), 561 (w); HRMS (ESI): m/z calculated for C$_{16}$H$_{23}$NO$_3$ [M+H]$^+$ 254.1751.751, found 254.1745.

**N-benzyl-2-oxohexahydrobenzofuran-7a(2H)-carboxamide 3f**

Prepared from 2-(2-oxocyclohexyl)acetic acid 1a (156 mg, 1 mmol, 1 equiv) and benzyl isocyanide (183 µL, 1.5 mmol 1.5 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/ethyl acetate, 4/1); diastereoisomers could be separated (R$_f$ = 0.5 (major) and R$_f$ = 0.3 (minor)).

Major diastereoisomer (trans)

Isolated as a yellowish solid. Yield: 200 mg, 0.73 mmol, 73%.

m.p.: 56-66 °C; $^1$H-NMR (CDCl$_3$, 500 MHz) δ 7.32-7.29 (m, 2H), 7.27-7.25 (m, 1H), 7.20 (d, J = 7.3, 2H), 6.78 (br, 1H), 6.33 (dd, J = 14.8 Hz, J = 5.5 Hz, 1H), 4.45 (dd, J = 14.8 Hz, J = 6.1 Hz, 1H), 2.51 (dq, J = 12.7 Hz, J = 4.0 Hz, 1H), 2.44-2.34 (m, 2H), 2.17-2.10 (m, 2H), 1.98-1.88 (m, 2H), 1.80-1.78 (m, 1H), 1.74-1.69 (m, 2H), 1.42-1.35 (m, 1H) ppm; $^{13}$C($^1$H)-NMR (CDCl$_3$, 125 MHz) δ 175.6 (C), 170.5 (C), 137.7 (C), 128.7 (CH), 127.5 (CH), 127.3 (CH), 86.5 (C), 48.3 (CH), 34.2 (CH$_3$), 33.5 (CH$_3$), 29.6 (CH$_3$), 25.0 (CH$_3$), 23.7 (CH$_3$), 21.8 (CH$_3$) ppm. IR (neat): vmax (cm$^{-1}$) = 3315 (w), 2930 (m), 1782 (s), 1653 (s), 1522 (s), 1427 (m), 1194 (m), 1183 (m), 1021 (s), 938 (m), 885 (m), 733 (s), 693 (s), 557 (s); HRMS (ESI): m/z calculated for C$_{16}$H$_{23}$NO$_3$ [M+H]$^+$ 274.1438, found 274.1435.
**Chapter 6**

**N-(2-naphthyl)-2-oxohexahydrobenzofuran-7a(2H)-carboxamide 3g**

Prepared from 2-(2-oxocyclohexyl)acetic acid 1a (78 mg, 0.5 mmol, 1 equiv) and 2-naphthyl isocyanide (115 mg, 0.75 mmol, 1.5 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/ethyl acetate, 7:1); diastereoisomers could be partly separated (R₁ = 0.20 (major) and R₁ = 0.18 (minor)).

Major diastereoisomer (trans)

Isolated as a white solid. Yield: 77 mg, 0.25 mmol, 50%.

m.p.: 115-129 °C (dec.); 1H-NMR (CDCl₃, 500 MHz) δ 8.23 (br, 1H), 8.22 (d, J = 13.5 Hz, 1H), 7.78 (t, J = 8.0 Hz, 3H), 7.46 (t, J = 8.0 Hz, 1H), 7.42 (t, J = 7.0 Hz, 2H), 2.65 (qd, J = 13.0 Hz, J = 4.2 Hz, 1H), 2.54-2.46 (m, 2H), 2.37-2.29 (m, 1H), 2.28-2.17 (m, 1H), 2.07-1.92 (m, 2H), 1.91-1.75 (m, 3H), 1.52-1.40 (m, 1H) ppm; 13C(1H)-NMR (CDCl₃, 125 MHz) δ 175.5 (C), 169.2 (C), 134.5 (C), 133.8 (C), 131.0 (C), 129.0 (CH), 127.8 (CH), 127.6 (CH), 126.7 (CH), 125.4 (CH), 120.2 (CH), 117.2 (CH), 86.7 (C), 48.5 (CH), 34.4 (CH₂), 33.7 (CH₃), 25.2 (CH₃), 23.9 (CH₂), 22.0 (CH₃) ppm; IR (neat): v max (cm⁻¹) = 3332 (w), 2937 (w), 1772 (s), 1684 (s), 1540 (m), 1223 (m), 1021 (s), 810 (m); HRMS (ESI): m/z calculated for C₂₀H₁₉NNaO₅ [M+MeOH+Na⁺]: 364.1519, found 364.1564.

**N-(2,6-dimethylphenyl)-2-oxohexahydrobenzofuran-7a(2H)-carboxamide 3h**

Prepared from 2-(2-oxocyclohexyl)acetic acid 1a (156 mg, 1 mmol, 1 equiv) and 2,6-dimethylphenyl isocyanide (196 mg, 1.5 mmol, 1.5 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/ethyl acetate, 4:1); diastereoisomers could be separated (R₁ = 0.21 (major) and R₁ = 0.10 (minor)).

Major diastereoisomer (trans)

Isolated as a white solid. Yield: 194 mg, 0.68 mmol, 68%.

m.p.: 157-159 °C; 1H-NMR (CDCl₃, 500 MHz) δ 7.61 (br, 1H), 7.14-7.04 (m, 3H), 2.58 (qd, J = 13.0 Hz, J = 3.5 Hz, 1H), 2.51 (d, J = 10.5 Hz, 2H), 2.36 (d, J = 12.5 Hz, 1H), 2.28-2.18 (m, 1H), 2.18 (s, 6H), 2.01-1.83 (m, 4H), 1.74 (d, J = 12.5 Hz, 1H), 1.50-1.38 (m, 1H) ppm; 13C(1H)-NMR (CDCl₃, 125 MHz) δ 175.7 (C), 169.3 (C), 135.3 (C), 132.9 (C), 128.4 (CH), 127.7 (CH), 87.1 (C), 48.5 (CH), 34.7 (CH₂), 33.8 (CH₃), 25.3 (CH₃), 23.9 (CH₂), 22.1 (CH₃), 18.5 (CH₃) ppm; IR (neat): v max (cm⁻¹) = 3294 (w), 2922 (w), 1782 (s), 1655 (m), 1499 (m), 1190 (m), 1020 (s), 912 (m), 883 (m), 770 (m), 706 (m), 519 (m); HRMS (ESI): m/z calculated for C₁₇H₁₃NO₃ [M+H⁺]: 288.1595, found 288.1594.

Minor diastereoisomer (cis)

Isolated as a white solid. Yield: 23 mg, 0.08 mmol, 8%. (contains 10% of the trans diastereoisomer)

1H-NMR (CDCl₃, 500 MHz) δ 7.71 (br, 1H), 7.15-7.03 (m, 3H), 3.02-2.92 (m, 1H), 2.68 (dd, J = 17.0 Hz, J = 7.0 Hz, 1H), 2.29 (d, J = 17.0 Hz, 1H), 2.21-2.14 (m, 1H), 2.16 (s, 6H), 2.09-1.93 (m, 2H), 1.80-1.65 (m, 2H), 1.56-1.35 (m, 2H), 1.28-1.17 (m, 1H) ppm; 13C(1H)-NMR (CDCl₃, 125 MHz) δ 176.0 (C), 171.0 (C), 135.3 (C), 132.7 (C), 128.4 (CH), 127.8 (CH), 87.7 (C), 36.6 (CH₂), 36.3 (CH), 31.5 (CH₃), 28.1 (CH₃), 22.3 (CH₂), 20.3 (CH₃), 18.4 (CH₃) ppm; IR (neat): v max (cm⁻¹) = 3288 (w), 2924 (w), 1782 (s), 1655 (m), 1499 (m), 1190 (m), 1020 (s), 912 (m), 883 (m), 770 (m), 706 (m), 519 (m).

**N-(tosylmethyl)-2-oxohexahydrobenzofuran-7a(2H)-carboxamide 3i**

Prepared from 2-(2-oxocyclohexyl)acetic acid 1a (156 mg, 1 mmol, 1 equiv) and tosylmethyl isocyanide (196 mg, 1 mmol, 1 equiv) according to Procedure A. Purification: column chromatography on silicagel (cyclohexane/ethyl acetate, 3:1 to cyclohexane/ethyl acetate, 1:2); diastereoisomers could be separated (R₁ = 0.15 (major) in cyclohexane/ethyl acetate, 3:1).

Major diastereoisomer (trans)

Isolated as a gummy white solid. Yield: 280 mg, 0.80 mmol, 80%.

1H-NMR (CDCl₃, 500 MHz) δ 7.71 (d, J = 7.5 Hz, 2H), 7.53 (t, J = 6.3 Hz, 1H), 7.28 (d, J = 7.5 Hz, 2H), 2.36 (s, 3H), 2.33-2.11 (m, 2H), 2.11-2.93 (m, 3H), 1.76-1.50 (m, 4H), 1.40-1.17 (m, 2H) ppm; 13C(1H)-NMR (CDCl₃, 125 MHz) δ 175.4 (C), 170.1 (C), 145.3 (C), 133.8 (C), 129.9 (CH), 128.9 (CH), 86.4 (C), 59.6 (CH₂), 47.9 (CH), 33.8 (CH₃), 33.3 (CH₂), 24.7 (CH₃), 23.4 (CH₂), 22.6 (CH₂), 22.5 (CH₃) ppm; IR (neat): v max (cm⁻¹) = 3377 (w), 2935 (w), 1786 (s), 1686 (s), 1597 (w), 1499 (m), 1321 (m), 1286 (m), 1140 (s), 1018 (s), 925 (m), 727 (s); HRMS (ESI): m/z calculated for C₁₈H₁₈NNaO₅S [M+MeOH+Na⁺]: 406.1295, found 406.1341.
**Diastereoselective Passerini Reactions with Ketoacids**

methyl (2-oxooctahydrobenzofuran-7a-carbonyl)glycinate 3j

Prepared from 2-(2-oxocyclohexyl)acetic acid 1a (156 mg, 1 mmol, 1 equiv) and methyl isocyanatoacetate (136 µL, 1.5 mmol, 1.5 equiv) according to Procedure A. Purification: column chromatography on silica gel (cyclohexane/ethyl acetate, 4/1); diastereoisomers could be separated (Rf = 0.07 (major)).

Major diastereoisomer (trans)

Isolated as a colorless oil. Yield: 217 mg, 0.85 mmol, 85%.

1H-NMR (CDCl3, 500 MHz) δ 6.79 (s, 1H), 3.99 (d, J = 5.5 Hz, 2H), 3.74 (s, 3H), 2.52-2.38 (m, 3H), 2.27-2.12 (m, 2H), 1.96-1.85 (m, 2H), 1.84-1.67 (m, 3H), 1.50-1.35 (m, 1H) ppm; 13C(H)-NMR (CDCl3, 125 MHz) δ 175.7 (C), 171.5 (C), 169.8 (C), 86.6 (CH), 52.6 (CH2), 48.5 (CH3), 41.0 (CH2), 34.2 (CH2), 33.6 (CH2), 25.2 (CH2), 23.9 (CH2), 21.9 (CH3) ppm; IR (neat): v probe (cm⁻¹) = 3356 (m), 2951 (w), 1780 (m), 1736 (s), 1672 (s), 1531 (m), 1414 (s), 1188 (s), 1011 (s), 935 (s), 885 (s); HRMS (ESI): m/z calculated for C12H13NO5 [M+H]+ = 256.1180, found 256.1179.

**tert-Butyl 7a-(tert-butylcarbamoyl)-2-oxohexahydrofuro[3,2-c]pyridine-5(4H)-carbamate 3k**

Prepared from 2-(1-(tert-butoxycarbonyl)-4-oxopiperidin-3-yl)acetic acid 1b (132 mg, 0.51 mmol, 1 equiv) and tert-butyl isocyanide (87 µL, 0.77 mmol, 1.5 equiv) according to Procedure A (reaction time 6 h). Purification: column chromatography on silica gel (cyclohexane/ethyl acetate, 3/1); diastereoisomers could be separated (Rf = 0.40 (major) and Rf = 0.23 (minor)).

Major diastereoisomer (trans)

Isolated as a white solid. Yield: 40 mg, 0.12 mmol, 23%.

m.p.: 132-144 °C. 1H-NMR (CDCl3, 500 MHz) δ 6.15 (s, 1H), 4.42-3.74 (m, 3H), 3.55-3.25 (m, 1H), 2.49 (dd, J = 16.2 Hz, J = 6.4 Hz, 2H), 2.43-2.32 (m, 3H), 2.31-2.21 (m, 1H), 1.96-1.84 (m, 1H), 1.45 (s, 9H), 1.33 (s, 9H) ppm; 13C(H)-NMR (CDCl3, 125 MHz) δ 174.5 (C), 169.3 (C), 155.0 (C), 84.1 (C), 80.1 (C), 51.8 (C), 46.7 (CH), 41.8 (CH3), 39.6 (CH3), 33.8 (CH3), 31.3 (CH3) 28.5 (CH2), 28.3 (CH2) ppm; IR (neat): v max (cm⁻¹) = 3342 (w), 2972 (w), 1793 (s), 1664 (s), 1526 (m), 1418 (s), 1163 (s), 1015 (s), 974 (w), 849 (m); HRMS (ESI): m/z calculated for C16H23NO6 [M+H]+ = 373.2333, found 373.2330.

**N-(tert-butyl)-2-oxooctahydro-8aH-chromene-8a-carboxamide 3l**

Prepared from 3-(2-oxocyclohexyl)propanoic acid 1c (170 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (124 µL, 1.1 mmol, 1.1 equiv) according to Procedure A (reaction time 2 h). Purification: column chromatography on silica gel (cyclohexane/ethyl acetate, 6/1); diastereoisomers could be separated (Rf = 0.22 (major) and Rf = 0.13 (minor)).

Major diastereoisomer (trans)

Isolated as a white solid. Yield: 148 mg, 0.58 mmol, 58%.

m.p.: 101-104 °C. 1H-NMR (CDCl3, 500 MHz) δ 6.00 (br, 1H), 2.69-2.65 (m, 2H), 2.23 (qd, J = 13.5 Hz, J = 3.5 Hz, 1H), 2.01 (d, J = 9.0 Hz, 1H), 1.93-1.58 (m, 9H), 1.33 (s, 9H) ppm; 13C(H)-NMR (CDCl3, 125 MHz) δ 171.6 (C), 171.1 (C), 185.0 (C), 51.4 (C), 42.2 (CH), 37.4 (CH2), 29.8 (CH2), 29.0 (CH2), 28.9 (CH2), 25.3 (CH3), 23.0 (CH3), 21.8 (CH2) ppm; IR (neat): v max (cm⁻¹) = 3327 (w), 2932 (m), 2868 (w), 1744 (s), 1666 (s), 1537 (m), 1450 (m), 1354 (m), 1244 (m), 1157 (m), 1059 (m), 1032 (s), 989 (m), 631 (w), 542 (m), 488 (m); HRMS (ESI): m/z calculated for C14H13NO6 [M+H]+ = 254.1751, found 254.1751.

**N-(tosylmethyl)-2-oxooctahydro-8aH-chromene-8a-carboxamide 3m**

Prepared from 3-(2-oxocyclohexyl)propanoic acid 1c (85 mg, 0.5 mmol) and tosylmethyl isocyanide (148 mg, 0.75 mmol, 1.5 equiv) according to Procedure A (reaction time 2 h). Purification: column chromatography on silica gel (cyclohexane/ethyl acetate, 1/1); diastereoisomers could be partly separated. Major diastereoisomer contains a small amount of the minor diastereoisomer.

Major diastereoisomer (trans)

Isolated as a gummy white solid. Yield: 91 mg, 0.50 mmol, 50%.

1H-NMR (CDCl3, 500 MHz) δ 7.75 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.0 Hz, 1H), 7.32 (d, J = 7.6 Hz, 2H), 4.80-4.70 (m, 1H), 4.68-4.58 (m, 1H), 2.57 (t, J = 6.2 Hz, 2H), 2.40 (s, 3H), 2.05-1.93 (m, 1H), 1.88 (d, J = 12.5 Hz, 1H), 1.80-1.47 (m, 7H), 1.30-1.05 (m, 2H) ppm; 13C(H)-NMR (CDCl3, 125 MHz) δ 171.0 (C), 171.0 (C), 145.4 (C), 134.1 (C), 130.0 (C).
N-(tert-butyl)-2,3-dimethyl-5-oxotetrahydrofuran-2-carboxamide 3

Prepared from 3-methyl-4-oxopentanoic acid 1g (130 mg, 1 mmol, 1 equiv) and tert-butyl isocyanide (170 μL, 1.5 mmol, 1.5 equiv) according to Procedure A (reaction time 2 h). Diastereoisomers were not resolved by chromatographic purification. Isolated as a colorless oil. Yield: 24 mg, 0.11 mmol, 11%.

1H-NMR (CDCl₃, 500 MHz) δ 6.26 (br, 1H, D1), 6.19 (br, 1H, D1), 2.88 (dd, J = 10.0 Hz, 8.0 Hz, 1H, D1), 2.75-2.57 (m, 1H, D1/D2, 1H, D2), 2.57-2.49 (m, 1H, D2/D1), 2.28-2.15 (m, 1H, D1, 1H, D2), 1.53 (s, 3H, D2), 1.42 (s, 3H, D1), 1.33 (s, 9H, D1), 1.32 (s, 9H, D2), 1.20 (d, J = 7.0 Hz, 3H, D3), 1.04 (d, J = 7.0 Hz, 3H) ppm; 13C(1H)-NMR (CDCl₃, 125 MHz) δ 175.2 (C, D1/D2), 174.8 (C, D2/D1), 171.6 (C, D1/D2), 169.2 (C, D2/D1), 88.5 (C, D2), 87.6 (C, D1), 51.7 (C, D1), 51.3 (C, D2), 38.2 (CH, D1), 37.1 (CH, D2), 36.7 (CH₂, D2), 36.3 (CH₂, D1), 28.7 (CH₃, D1), 28.7 (CH₃, D2), 24.0 (CH₂, D2), 18.9 (CH₂, D2), 16.4 (CH₃, D1/D2), 15.2 (CH₃, D2/D1) ppm; IR (neat): vmax (cm⁻¹) = 2972 (w), 1784 (s), 1670 (s), 1521 (m), 1456 (m), 1365 (m), 1223 (s), 1194 (m), 1123 (s), 1059 (m), 1010 (w), 926 (m), 768 (w); HRMS (ESI): m/z calculated for C₁₇H₂₃N₂O₄ [M+Na]+ 388.1189, found 388.1181.

N-tosylmethyl)-2,3-dimethyl-5-oxotetrahydrofuran-2-carboxamide 3s

Prepared from 3-methyl-4-oxopentanoic acid 1g (130 mg, 1 mmol, 1 equiv) and tosylmethyl isocyanide (294 mg, 1.5 mmol, 1.5 equiv) according to Procedure A (reaction time 2 h). Purification: column chromatography on silicagel (cyclohexane/ethyl acetate, 2/1 to cyclohexane/ethyl acetate, 1/1); diastereoisomers could not be separated (Rᵣ = 0.32 and Rᵣ = 0.27). Isolated as a gummy white solid. Contains 2 wt% AcOEt. Yield (corrected): 266 mg, 0.82 mmol, 82%.

1H-NMR (CDCl₃, 500 MHz) δ 7.76 (d, J = 8.0 Hz, 2H, D1, 2H, D2), 7.70 (t, J = 6.6 Hz, 1H, D1/D2), 7.69 (t, J = 7.0 Hz, 1H, D2/D1), 7.30 (d, J = 8.0 Hz, 2H, D1, 2H, D2), 4.73-4.53 (m, 2H, D1, 2H, D2), 2.80 (dd, J = 17.0 Hz, J = 9.0 Hz, 1H, D1), 2.57 (dd, J = 17.0 Hz, J = 9.0 Hz, 1H, D1), 2.50-2.38 (m, 1H, D1, 1H, D2), 2.37 (s, 3H, D1), 2.37 (s, 3H, D2), 2.23-2.14 (m, 1H, D1, 1H, D2), 1.40 (s, 3H, D2), 1.26 (s, 3H, D1), 1.00 (d, J = 7.5 Hz, 3H, D1), 0.81 (d, J = 7.5 Hz, 3H, D2) ppm; 13C(1H)-NMR (CDCl₃, 125 MHz) δ 174.9 (C, D2), 174.6 (C, D1), 171.9 (C, D1), 171.0 (C, D2), 145.4 (C, D1), 143.9 (C, D2), 133.8 (C, D1), 129.9 (CH, D2), 129.8 (CH, D2), 129.0 (CH, D1), 88.4 (C, D2), 87.3 (C, D1), 59.9 (CH₂, D1), 59.8 (CH₂, D2), 38.5 (CH₂, D1), 37.1 (CH, D1), 36.2 (CH₂, D2), 35.6 (CH₂, D1), 23.9 (CH₂, D2/D1), 21.7 (CH₂, D1, 2H, D2), 18.2 (CH₃, D2/D1), 15.9 (CH₃, D2), 14.3 (CH₃, D1) ppm; IR (neat): vmax (cm⁻¹) = 3354 (w), 1784 (s), 1676 (s), 1518 (s), 1294 (s), 1220 (m), 1148 (s), 1088 (s), 1053 (m), 926 (m), 750 (m); HRMS (ESI): m/z calculated for C₁₇H₂₃N₂O₄ [M+MeOH+Na]+ 380.1138, found 380.1178.

Rearranged Passerini products 4a-l

Note: due to cyclohexane ring flip some peaks in the ¹³C-NMR appear broad and of low intensity.

8a-hydroxyhexahydroisouquinoline-1,3(2H,4H)-dione 4b

Prepared from 3b (6 mg, 0.2 mmol) according to Procedure B (reaction time 7 h). Purification: column chromatography on silicagel (cyclohexane/ethyl acetate, 4/1 to cyclohexane/ethyl acetate, 2/1; Rᵣ = 0.13); Isolated as a white solid. Yield: 22 mg, 0.12 mmol, 60%.

m.p.: 150-158 °C; ¹H-NMR (CDCl₃/DMSO-d₆, 500 MHz) δ 9.32 (br, 1H), 4.73 (br, 1H), 2.76 (d, J = 16.6 Hz, 1H), 2.20 (d, J = 16.6 Hz, 1H), 2.11-1.97 (m, 1H), 1.95-1.84 (m, 1H), 1.67-1.45 (m, 2H), 1.43-1.31 (m, 1H), 1.28-0.95 (m, 4H) ppm; ¹³C(1H)-NMR (CDCl₃/DMSO-d₆, 125 MHz) δ 172.5 (C), 71.4 (C), 37.5 (CH), 34.4 (CH₂), 32.8 (CH₂), 29.5 (CH₂), 22.6 (CH₂), 22.2 (CH₂) ppm; IR (neat): vmax (cm⁻¹) = 3166 (m), 2923 (m), 1722 (s), 1668 (s), 1358 (s), 1209 (s), 1068 (s), 1041 (m), 840 (m), 732 (m); HRMS (ESI): m/z calculated for C₁₉H₁₃N₂O₄ [M+Na]+ 335.0788, found 335.0786.

Chapter 6

(CH), 128.9 (CH), 85.0 (C), 59.7 (CH₂), 42.0 (CH), 37.8 (CH₃), 29.7 (CH₃), 28.4 (CH₂), 25.0 (CH₃), 22.6 (CH₃), 21.7 (CH₃), 21.3 (CH₃) ppm; IR (neat): vmax (cm⁻¹) = 3315 (w), 2938 (w), 1742 (s), 1686 (s), 1501 (m), 1448 (m), 1321 (s), 1286 (m), 1229 (m), 1140 (s), 1084 (s), 1030 (s), 914 (w), 727 (s); HRMS (ESI): m/z calculated for C₁₈H₁₉N₂O₄ [M+Na]+ 388.1189, found 388.1181.
Diastereoselective Passerini Reactions with Ketoacids

2-cyclohexyl-8a-hydroxyhexahydroisquinoline-1,3(2H,4H)-dione 4c
Prepared from 3c (27 mg, 0.1 mmol) according to Procedure B (reaction time 24 h). Isolated as a white solid. Yield: 24 mg, 0.089 mmol, 89%.

m.p.: 110-117 °C; 1H-NMR (CDCl$_3$, 500 MHz) δ 4.48 (tt, J = 12.5 Hz, J = 4.0 Hz, 1H), 3.25 (br, 1H), 2.82-2.64 (m, 2H), 2.28-2.08 (m, 3H), 1.97-1.40 (m, 12H), 1.37-1.06 (m, 4H) ppm; 13C($^1$H)-NMR (CDCl$_3$, 125 MHz) δ 171.9 (C), 72.4 (C), 53.9 (CH), 35.2 (CH$_2$), 34.5 (CH), 32.6 (CH$_2$), 29.3 (CH$_2$), 28.7 (CH$_3$), 26.4 (CH$_2$), 26.4 (CH$_2$), 25.6 (CH), 25.3 (CH$_2$), 21.0 (CH$_3$), 20.4 (CH$_2$) ppm; IR (neat): v$_{max}$ (cm$^{-1}$) = 3377 (w), 2927 (m), 1719 (m), 1654 (m), 1538 (s), 1225 (s), 1136 (m), 1043 (m), 729 (m); HRMS (ESI): m/z calculated for C$_{13}$H$_{16}$NaO$_3$ [M+Na]$^+$ 288.1570, found 288.1572.

2-isopropyl-8a-hydroxyhexahydroisquinoline-1,3(2H,4H)-dione 4d
Prepared from 3d (23 mg, 0.1 mmol) according to Procedure B (reaction time 24 h). Isolated as a white solid. Yield: 22 mg, 0.075 mmol, 75%.

m.p.: 81-89 °C; 1H-NMR (CDCl$_3$, 500 MHz) δ 4.90 (sep, J = 7.9 Hz, 1H), 2.82-2.64 (m, 2H), 2.22-2.12 (m, 1H), 1.97-1.70 (m, 3H), 1.55-1.42 (m, 4H), 1.41-1.28 (m, 1H), 1.36 (d, J = 7.0 Hz, 3H), 1.34 (d, J = 7.0 Hz, 3H) ppm; 13C($^1$H)-NMR (CDCl$_3$, 125 MHz) δ 177.5 (C), 171.9 (C), 72.4 (C), 45.4 (CH), 35.2 (CH$_2$), 34.4 (CH), 32.6 (CH$_2$), 25.6 (CH$_2$), 21.0 (CH$_3$), 20.4 (CH$_2$), 19.8 (CH), 19.4 (CH$_2$) ppm; IR (neat): v$_{max}$ (cm$^{-1}$) = 3400 (w), 2935 (m), 1719 (m), 1668 (s), 1346 (m), 1244 (m), 1221 (m), 1116 (w), 1045 (w); HRMS (ESI): m/z calculated for C$_{12}$H$_{15}$NaO$_3$ [M+Na]$^+$ 248.1257, found 248.1249.

2-pentyl-8a-hydroxyhexahydroisquinoline-1,3(2H,4H)-dione 4e
Prepared from 3e (25 mg, 0.1 mmol) according to Procedure B (reaction time 2 h). Isolated as a colorless oil. Yield: 19 mg, 0.075 mmol, 75%.

1H-NMR (CDCl$_3$, 500 MHz) δ 4.83-3.63 (m, 2H), 2.90-2.70 (m, 3H), 2.24-2.12 (m, 1H), 1.99-1.65 (m, 3H), 1.57-1.40 (m, 6H), 1.38-1.15 (m, 5H), 0.87 (t, J = 7.0 Hz, 3H) ppm; 13C($^1$H)-NMR (CDCl$_3$, 125 MHz) δ 171.9 (C), 72.2 (C), 40.4 (CH$_2$), 34.8 (CH), 34.7 (CH$_2$), 32.7 (CH$_2$), 29.1 (CH), 27.7 (CH$_2$), 25.9 (CH$_2$), 22.4 (CH$_2$), 21.6 (CH$_3$), 20.7 (CH$_2$), 14.1 (CH$_2$) ppm; IR (neat): v$_{max}$ (cm$^{-1}$) = 3411 (w), 2932 (m), 1724 (m), 1653 (s), 1346 (s), 1254 (m), 1176 (s), 1118 (s), 1047 (m), 734 (w); HRMS (ESI): m/z calculated for C$_{16}$H$_{18}$NaO$_3$ [M+Na]$^+$ 276.1570, found 276.1558.

2-benzyl-8a-hydroxyhexahydroisquinoline-1,3(2H,4H)-dione 4f
Prepared from 3f (28 mg, 0.1 mmol) according to Procedure B (reaction time 4 h). Isolated as a pale yellow oil. Yield: 26 mg, 0.093 mmol, 93%.

1H-NMR (CDCl$_3$, 500 MHz) δ 7.34-7.19 (m, 5H), 4.95 (d, J = 13.5 Hz, 1H), 4.93 (d, J = 13.5 Hz, 1H), 3.01 (br, 1H), 2.86 (dd, J = 19.0 Hz, J = 4.5 Hz, 1H), 2.74 (dd, J = 19.0 Hz, J = 9.0 Hz, 1H), 2.21 (sex, J = 5.0 Hz, 1H), 1.98-1.85 (m, 2H), 1.85-1.73 (m, 1H), 1.55-1.37 (m, 4H), 1.33-1.25 (m, 4H) ppm; 13C($^1$H)-NMR (CDCl$_3$, 125 MHz) δ 171.5 (C), 136.9 (C), 128.6 (CH), 128.5 (CH), 127.6 (CH), 72.3 (C), 43.5 (CH$_2$), 34.8 (CH), 34.7 (CH$_2$), 32.7 (CH$_2$), 26.0 (CH), 21.2 (CH$_2$), 20.7 (CH$_2$) ppm; IR (neat): v$_{max}$ (cm$^{-1}$) = 3445 (w), 2929 (m), 1726 (m), 1670 (s), 1346 (s), 1173 (m), 1076 (w), 733 (w); HRMS (ESI): m/z calculated for C$_{16}$H$_{18}$NaO$_3$ [M+Na]$^+$ 296.1257, found 296.1249.

2-(naphthalen-2-yl)-8a-hydroxyhexahydroisquinoline-1,3(2H,4H)-dione 4g
Prepared from 3g (31 mg, 0.1 mmol) according to Procedure B (reaction time 24 h). Isolated as a brown solid. Contains 15% 2-naphthyl amine. Yield (corrected): 20 mg, 0.064 mmol, 64%.

m.p.: 141-147 °C; 1H-NMR (CDCl$_3$, 500 MHz) δ 7.93 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.60 (s, 1H), 7.56-7.46 (m, 2H), 7.16 (dd, J = 8.5 Hz, J = 2.0 Hz, 1H), 3.06 (dd, J = 18.5 Hz, J = 5.0 Hz, 1H), 2.93 (dd, J = 18.5 Hz, J = 10.0 Hz, 1H), 2.41 (sex, J = 4.0 Hz, 1H), 2.16 (t, J = 11.0 Hz, 1H), 2.10-2.01 (m, 1H), 1.92-1.80 (m, 1H), 1.71-1.44 (m, 6H) ppm; 13C($^1$H)-NMR (CDCl$_3$, 125 MHz) δ 171.9 (C), 133.5 (C), 133.2 (C), 132.3 (C), 129.4 (CH), 128.2 (CH), 128.0...
(CH), 127.4 (CH), 127.0 (CH), 126.7 (CH), 125.8 (CH), 34.8 (CH), 34.7 (CH2), 32.7 (CH2), 26.0 (CH2), 21.2 (CH2), 20.7 (CH3) ppm; IR (neat): νmax (cm⁻¹) = 3446 (w), 2936 (w), 1734 (m), 1680 (s), 1370 (m), 1202 (m), 1073 (w), 746 (w); HRMS (ESI): m/z calculated for C20H23NaO3 [M+MeOH+Na⁺] 364.1519, found 364.1564.

2-(2,6-dimethylphenyl)-8a-hydroxyhexahydroisoquinoline-1,3(2H,4H)-dione 4h
Prepared from 3h (29 mg, 0.1 mmol) according to Procedure B (reaction time 3 h). Isolated as a colorless oil. Yield: 29 mg, 0.01 mmol, 99%.

1H-NMR (CDCl₃, 500 MHz) δ 7.21 (t, J = 7.5 Hz, 1H), 7.16-7.10 (m, 2H), 3.08 (dd, J = 18.5 Hz, J = 5.0 Hz, 1H), 2.65 (dd, J = 18.5 Hz, J = 7.0 Hz, 1H), 2.28 (br, 1H), 2.16 (m, 1H), 1.94-1.98 (m, 1H), 2.06 (s, 3H), 1.92-1.80 (m, 1H), 1.68-1.44 (m, 5H) ppm; 13C¹H]-NMR (CDCl₃, 125 MHz) δ 175.8 (C), 171.0 (C), 135.4 (C), 135.1 (C), 133.3 (C), 129.0 (CH), 128.7 (CH), 128.6 (CH), 35.5 (CH), 26.7 (CH), 21.8 (CH) ppm; IR (neat): νmax (cm⁻¹) = 3390 (w), 2927 (m), 1734 (m), 1670 (s), 1364 (s), 1238 (s), 1186 (s), 1132 (m), 1003 (m), 768 (m) 725 (m); HRMS (ESI): m/z calculated for C₂₀H₂₁N₂O₃ [M⁺] 344.1444, found 344.1510.

2-tosylmethyl-8a-hydroxyhexahydroisoquinoline-1,3(2H,4H)-dione 4i
Prepared from 3i (29 mg, 0.1 mmol) according to Procedure B (reaction time 3 h). Isolated as a white solid. Yield: 24 mg, 0.083 mmol, 83%.

m.p.: 149-163 °C; 1H-NMR (CDCl₃, 500 MHz) δ 7.76 (d, J = 7.5 Hz, 2H), 7.34 (d, J = 7.5 Hz 2H), 5.26 (s, 2H), 3.08 (br, 1H), 2.99 (dd, J = 18.5 Hz, J = 5.0 Hz, 1H), 2.65 (dd, J = 18.5 Hz, J = 7.0 Hz, 1H), 2.44 (s, 3H), 2.21-2.12 (m, 2H), 1.94-1.64 (m, 2H), 1.65-1.27 (m, 5H) ppm; 13C¹H]-NMR (CDCl₃, 125 MHz) δ 170.3 (C), 145.4 (C), 136.0 (C), 130.0 (CH), 128.6 (CH), 72.7 (C), 59.4 (CH₃), 35.7 (CH₃), 34.5 (CH₂), 33.5 (CH₂), 27.1 (CH₂), 21.9 (CH₂), 19.8 (CH₃), 21.8 (CH₃) ppm; IR (neat): νmax (cm⁻¹) = 3420 (w), 2939 (m), 1734 (m), 1686 (s), 1586 (s), 1298 (s), 1138 (s), 1043 (m), 927 (m), 820 (m), 735 (m); HRMS (ESI): m/z calculated for C₂₁H₂₂N₂O₄ [M⁺] 374.1033, found 374.1025.

methyl 2-(8a-hydroxy-1,3-dioxoocthahydroisoquinolin-2(1H)-yl)acetate 4j
Prepared from 3j (26 mg, 0.1 mmol) according to Procedure B (reaction time 3 h). Isolated as a white solid. Yield: 20 mg, 0.076 mmol, 76%.

m.p.: 122-126 °C; 1H-NMR (CDCl₃, 500 MHz) δ 4.57 (d, J = 16.5 Hz, 1H), 4.52 (d, J = 16.5 Hz, 1H), 3.73 (s, 3H), 2.96 (dd, J = 19.0 Hz, J = 5.5 Hz, 1H), 2.80 (br, 1H), 2.75 (dd, J = 19.0 Hz, J = 8.0 Hz, 1H), 2.28-2.19 (m, 1H), 2.16-2.05 (m, 1H), 1.98-1.88 (m, 1H), 1.86-1.75 (m, 1H), 1.64-1.40 (m, 5H) ppm; 13C¹H]-NMR (CDCl₃, 125 MHz) δ 171.3 (C), 168.5 (C), 72.4 (C), 52.5 (CH₂), 40.8 (CH₂), 35.6 (CH), 34.5 (CH₂), 33.3 (CH₂), 26.7 (CH), 21.7 (CH₃), 21.8 (CH₃) ppm; IR (neat): νmax (cm⁻¹) = 3404 (w), 2948 (w), 1753 (s), 1720 (m), 1664 (s), 1594 (s), 1380 (s), 1239 (s), 1218 (s), 1173 (s), 1130 (s), 1070 (s), 1022 (s), 940 (m), 744 (m); HRMS (ESI): m/z calculated for C₁₃H₁₇N₂O₄ [M⁺] 278.0999, found 278.0989.

(3aR,7aS)-N-[(ter-butyl)-2-oxohexahydrobenzofuran-7a(2H)]-carboxamide (3aR,7aS)-3a
To a solution of (R)-1a (17 mg, 0.11 mmol, 1 equiv) in dimethyl carbonate (0.45 mL) was added Zn(OTf)₂ (4 mg, 0.011 mmol, 1 equiv) and tert-butyl isocyanide (18.5 µL, 0.165 mmol 1.5 equiv). The solution was stirred at room temperature for 6 hours. Then the mixture was diluted with CH₂Cl₂ and quenched with saturated NaHCO₃ solution. The organic layer was separated and the aqueous layer was extracted again with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, concentrated in vacuo and the crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate, 6/1). Yield: 18 mg, 0.075 mmol, 68%.

Spectral data in accordance to the racemic compound 3a. Enantiomeric ratio determined by chiral-GC on the chiral phase ChiraSil Dex CB (25x0.25); temperature program 130 °C, hold for 60 min. Retention times: tᵣₘajo r = 23.5 min, tᵣₘino r = 25.6 min, e.r. 92:8. [α]D²⁰ = -54 (c = 0.67, CHCl₃).
References


[13] Dimethyl carbonate is one of the most environmentally benign aprotic solvents. For a recent discussion on the sustainability aspects of MCRs, see ref. 4.


[15] In an Ugi reaction, ketoacid 1d does indeed preferentially (3:1 ratio) afford the cis-bicyclic lactam corresponding to an anti addition, see ref. 10c.

[16] Crystal packing forces may be relevant in the isomerization-crystallization of 3j to 4j.


[18] Chiral oxoacid 1a was observed to slowly epimerize upon prolonged storage.


Abstract: In this final chapter we elaborate on few of the possibilities to extend the knowledge acquired in the previous six chapters towards new applications in methodology development and target-oriented synthesis.
Introduction

In Chapter 1 the virtues of isocyanides in applied organic chemistry were presented. The Passerini 3CR and Ugi 4CR, certainly two of the most famous reactions involving isocyanides, represent highly potent tools to generate (depsipeptide)-containing molecules. Since this chemistry has been extensively explored in the past decades, our research has focused on less conventional products of isocyanide chemistry, in an attempt to move away from the classical Ugi and Passerini conversion of the isocyano group into primary amides. Thus, functionalities like secondary amines, nitriles, carboxylic acids, esters, imides are new entries in the chemical space of products accessible via isocyanide addition. Accordingly, the repertoire of scaffolds and targets that can be reached using isocyanide chemistry is greatly expanded and some of the possibilities for future research will be described in this Chapter.

Silicon tetrachloride-mediated isocyanide additions

In Chapter 2 the one-pot synthesis of β-amino alcohols from aldehydes and isocyanides was described. This transformation proceeds via an imidoyl chloride derivative resulting from a Passerini-type addition of an isocyanide to an aldehyde using silicon tetrachloride as carboxylic acid surrogate. This electrophilic intermediate can engage in reactions with various nucleophiles leading to interesting structures in a multicomponent fashion. Notably, the reaction with an external hydride source (BH$_3$NH$_3$) results in the double reduction of the imidoyl chloride functionality. The selective monoreduction is also of particular interest since this would provide an aldimine which can be reacted further with nucleophiles increasing the (stereo)complexity of the products. A potentially viable approach would be the use of HSiCl$_3$ as Lewis acid for the isocyanide addition step generating a α-(dichlorosilyloxy) imidoyl chloride that can subsequently undergo internal hydride transfer forming 4 (Scheme 1). Finally, this imine species can be hydrolyzed towards α-amino ketones 6 or reacted with a suitable nucleophile (e.g. indole) to generate vicinal amino-alcohol compounds 7 upon aqueous workup. This latter idea would be particularly valuable if control at the two stereogenic centers could be achieved (i.e. enantioselective isocyanide addition, for instance by using Denmark’s bisphosphoramidate catalyst$^{[1]}$ and diastereoselective imine trapping).
Future Research Directions

Scheme 1. Versatility of the α-trichlorosilyloxy imidoyl chloride 3.

Importantly, HSiCl₃ displays the required reactivity for both stages of this process. It has sufficient Lewis acidity for a fast isocyanide addition, as it proved to be even stronger than SiCl₄ in a related aldehyde allylation protocol.[2] HSiCl₃ is also a well-known reagent for hydrosilylation of imines, particularly in combination with Lewis-base activation.[3] However, this domino transformation is challenging as numerous alternative reactions are possible: reduction of the aldehyde starting material, overreduction of the product to the β-amino alcohol, hydrosilylation of the isocyanide, etc. A proof of concept is provided by the reaction shown in Scheme 2, where α-amino ketone 6a was formed in a 42% yield in this model system.

Scheme 2. HSiCl₃-mediated α-amino ketone synthesis from aldehydes and isocyanides.

Following a related strategy, the imidoyl chloride derivative 3 (generated this time with SiCl₄) can undergo addition by a nucleophile, for instance an electron-rich heterocycle, in a Friedel-Crafts-type reaction. This would lead to interesting α-amino ketone derivatives upon aqueous work-up (and eventually tautomerization) and the overall transformation would be a one-pot, two-stage three-component process. Indeed, this idea proved feasible in our initial experiments using N-methyl pyrrole as third reaction component. After the generation of intermediate 3a in standard conditions, N-methyl pyrrole (1 equiv) and catalytic Sc(OTf)₃ were added and product 5a was isolated in a 91% yield upon aqueous workup (Scheme 3). Interestingly, this structure appears to undergo facile oxidation under air to the corresponding α-imino ketone, which brings additional diversity to this novel multicomponent process.
Scheme 3. Friedel-Crafts-type trapping of the α-trichlorosilyloxy imidoyl chloride.

This overall transformation of an isocyanide building block into an amine functionality can be rendered useful in the synthesis of natural products. An interesting target would be the isoquinoline alkaloid noscapine, widely employed as over-the-counter antitussive medication. The silicon tetrachloride-mediated isocyanide addition involving building blocks 1b and 2b would lead to the imidoyl chloride derivative 3b which upon activation can undergo a Bischler-Napieralski-type cyclization (regioselectivity is relevant here), whereas the lactone would form most likely upon aqueous workup. The imine 8 can be diastereoselectively reduced and N-methylation would complete the route (Scheme 4). The control of absolute stereochemistry can be achieved by performing the enantioselective isocyanide addition employing Denmark’s catalyst.

Scheme 4. Proposed route towards noscapine.

Cyanations with trityl isocyanide

In Chapters 3 and 4 we showed the utility of trityl isocyanide as a relatively benign cyanide source in the synthesis of α-amino nitriles and O-trityl cyanohydrins. The understanding of the mechanistic aspects of trityl isocyanide chemistry enables the design of other applications. For example, trityl isocyanide can be an advantageous reagent for the synthesis of benzonitrile derivatives, from either aryl halides or diazonium salts. In both cases, the specific reactivity of trityl isocyanide can be strategically exploited to improve well-established protocols.
The transition-metal catalyzed cross-coupling between aryl halides and cyanide sources has been thoroughly studied over the last decades and nowadays numerous protocols are available. An impressive range of catalysts (heterogenous or homogenous) and various cyanide sources were shown to be applicable in this important transformation, yet there are still challenges to overcome, such as toxicity of cyanide donors, solubility issues, safety upon scale-up, harsh reaction conditions and, perhaps most relevant, the poisoning of the catalyst by the cyanation reagents. Indeed, the most commonly used catalyst for the synthesis of benzonitriles from aryl halides is palladium, which is very susceptible to poisoning by cyanide as the metal forms strong bonds with this ligand.\[^5\] In this respect, trityl isocyanide can be employed as a slow-release cyanide donor which would circumvent catalyst poisoning.\[^6\] This idea is based on the generation of palladium (0)-cyanide active species upon initial binding of trityl isocyanide to the metal center and fragmentation around the N-Tr bond, as seen in Chapters 3 and 4. This type of reactivity is preceded in literature: silver ions are known to catalyze the isomerization of trityl isocyanide to triphenylacetonitrile which is based on this mechanism.\[^7\] The palladium-cyanide complex can undergo oxidative addition of the aryl halide to provide a palladium (II) intermediate which upon reductive elimination liberates the product benzonitrile and the catalyst. A simplistic representation of this mechanism is represented in Scheme 5. Importantly, a trityl cation scavenger (e.g. alcoholic solvent, see Chapter 3) is mandatory, otherwise this reactive species will decompose trityl isocyanide via the chain-isomerization mechanism. Alternatively, the L\(_n\)Pd(Ar)CN species could form by a related pathway (different order in the occurrence of main events): oxidative addition of Pd(0) into ArX, TrNC insertion into the Pd-Ar bond and cleavage at the N-Tr bond. Such a mechanism would provide a completely cyanide-free synthesis of benzonitrile derivatives.

**Scheme 5.** Proposed mechanism for Pd-catalyzed cyanation of aryl halides with trityl isocyanide.
Alternatively, diazonium salts (readily available from anilines) are important precursors of benzonitriles: the Sandmeyer reaction using stoichiometric CuCN is a well-established methodology for this purpose.\[^8\] The obvious disadvantage of this reaction is however the generation of large amounts of metal waste. A potential way to circumvent this problem would be the use of trityl isocyanide as cyanide donor in a metal-free process. This idea is inspired by recent syntheses of N-substituted benzamide derivatives from diazonium salts and isocyanides.\[^9\] The mechanism of this transformation is presumably of radical nature: the diazonium salt $\text{11}$ is the source of the aryl radical $\text{12}$ which adds to the isocyanide to form an imidoyl radical $\text{13}$ which is further oxidized and trapped by water to form the final product $\text{15}$. Interestingly, fragmentation of this imidoyl radical does not seem to be a competitive pathway in these systems, even if substituted with the relatively labile tert-butyl group. The trityl analogue however is expected to be more susceptible to fragmentation (see Chapters 3 and 4) and the preparation of benzonitrile derivatives may be possible with our reagent (Scheme 6). Alternatively, the benzonitrile can be produced upon oxidation of the imidoyl radical to the nitrilium ion $\text{14}$, a species more prone to fragmentation. Therefore, such a transformation would be interesting both from the fundamental perspective (exploring the radical chemistry of trityl isocyanide for the first time) and the practical side (metal-free Sandmeyer reaction).

![Scheme 6](image)

**Scheme 6.** Proposed synthesis of benzonitriles from diazonium salts and trityl isocyanide.

**Catalytic asymmetric cyano-functionalization using trityl isocyanide**

In Chapter 4 the chiral phosphoric acid–catalyzed $\text{O}$-trityl cyanohydrin asymmetric synthesis was described. Although these preliminary results leave room for improvement, they do demonstrate the compatibility of trityl isocyanide with enantioselective organocatalysis. This reagent has good potential for the asymmetric synthesis of various nitrile-containing compounds, as it is relatively bulky (especially within the class of isocyanides) – a property useful in the discrimination of the enantiotopic faces of a prochiral substrate; furthermore it could engage in non-covalent interactions with a chiral catalyst ($\pi$-$\pi$ stacking for instance) providing a strong preference for a particular direction of nucleophilic attack. Therefore, it would be interesting to further exploit the catalytic enantioselective addition of trityl isocyanide in the preparation of chiral nitrile derivatives.
Thus, closely related to the O-trityl cyanohydrip synthesis described in Chapter 4, a preparation of β-cyanohydrin derivatives can be envisaged by employing epoxides as electrophilic substrates. Numerous catalysts (including for instance chiral phosphoric acids) and protocols are available for the asymmetric opening of meso-epoxides with different nucleophiles. Preliminary attempts to react epoxide 16 with trityl isocyanide under Brønsted-acid catalysis (diphenyl phosphate, 10 mol%) showed no conversion, suggesting an insufficient activation of the epoxide by the catalyst. The reaction has not been performed with other (chiral) analogues; a thorough catalyst screen – within the class of chiral Brønsted acids (disulfonimides, N-sulfonyl phosphoramides, etc.) or using other systems (Lewis acids, thioureas) – is required to validate the feasibility of this envisaged transformation.

Scheme 7. Epoxide opening with trityl isocyanide under Brønsted-acid catalysis.

Another interesting application of trityl isocyanide would be the hydrocyanation of α,β-unsaturated derivatives. This transformation implies the Michael addition of the isocyanide 2c to the catalyst-activated substrate 18 followed by N-Tr fragmentation of the intermediate 19 and quench (internal or with external additives) of the resulting enolate and tritylium species respectively (Scheme 8). An encouraging precedent is the racemic hydrocyanation of enones with tert-butyl isocyanide which relies on activation by TiCl₄.[10] However, catalytic enantioselective additions of isocyanides to activated alkenes are rare, therefore it is difficult to assess the viability of this idea. A good starting point in the catalyst screen would be the N,N'-dioxide/Mg²⁺ system developed by Feng et al. to construct polycyclic spiroindolines from 2-isocynoethylindoles and alkylidene malonates via a related mechanism.[11] The Lewis acid should be selected bearing in mind the propensity of trityl isocyanide to isomerize under the catalytic action of metal ions with affinity for isocyanide ligands; alkali or alkaline earth metals are most likely compatible with this requirement.

Scheme 8. β-Cyanation with trityl isocyanide.
Natural product synthesis exploiting trityl isocyanide as convertible reagent

In Chapter 3, the properties of trityl isocyanide as a convertible reagent were shown. This chemical behavior can be advantageously exploited in the convergent synthesis of various targets. Two interesting molecules that could be synthesized with the use of convertible isocyanide chemistry are the natural products schulzeine B and kainic acid.

Schulzeine B is part of a family of marine natural products that have antiviral activity.\textsuperscript{[12]} It consists of two units: a tricyclic 3-aminobenzo[a]quinolizidin-4-one ring and a sulfated fatty acid chain, connected via an amide bond. For the synthesis of this target, we envisage to use as the key step an Ugi 4CR reaction between chiral aldehyde 23, ammonia\textsuperscript{[13]} (or an equivalent\textsuperscript{[14]}), a protected precursor of carboxylic acid 27\textsuperscript{[15]} and trityl isocyanide. Upon acidic treatment, all cleavable groups (Me, Boc, Tr) would be removed and the δ-lactam unit installed. Finally, this precursor 25 would require only protecting group manipulations and sulfatation to afford the target schulzeine B 26.

The stereochemistry in this route can be controlled by the use of imine reductases (IREDS)\textsuperscript{[16]} to prepare the (S)-configured amine 22; the second stereocenter would be the result of the Ugi reaction and a long range induction is improbable in this case. Nevertheless, the efficiency of the route can benefit from the facile resolution of the diastereoisomers and the possibility to epimerize the undesired stereoisomer at the lactam stage as shown by Uenishi et al.\textsuperscript{[17]}

\begin{center}
\textbf{Scheme 9.} Proposed route for the synthesis of schulzeine B using trityl isocyanide.
\end{center}
Another interesting target for this methodology would be the marine small molecule kainic acid. This natural product has attracted considerable interest in neuroscience due to its neuroexcitatory properties: kainic acid binds strongly to glutamate receptors and for this reason it is widely used in medical research.\textsuperscript{[18]} (-)-α-Kainic acid is also highly interesting for the synthetic community, as it is a densely functionalized and stereochemically complex compound.\textsuperscript{[19]}

The envisioned approach towards kainic acid is based again on the union of biocatalysis and multicomponent reactions.\textsuperscript{[20]} Thus, enantioenriched imine 28 can be prepared via a monoamine oxidase-N-catalyzed oxidative desymmetrization of the \textit{meso}-pyrrolidine precursor as described (with 98\% ee).\textsuperscript{[21]} This intermediate can be subjected to an Ugi (or Ugi-type) reaction involving trityl isocyanide followed by reductive ozonolysis to afford diol 31. Next, the properties of trityl isocyanide as a convertible reagent can be strategically exploited to enable the selective manipulation of only one of the primary alcohols into the bicyclic lactone 32. Then, standard chemistry can be used to transform the second 2-hydroxyethyl group into a isopropenyl substituent and further processing (protecting group manipulation, oxidation) furnishes the final product 35 (Scheme 10).

\textit{Scheme 10}. Proposed route for the synthesis of kainic acid using trityl isocyanide.

The most interesting feature of this route (which does have a rather poor redox economy) would be the symmetry breaking of the \textit{C}_\textsubscript{5}-starting material 28. Secondly, the three contiguous stereocenters would be generated with high stereocontrol: the enzymatic desymmetrization delivers 98\% ee (in favor of the desired enantiomer) whereas the subsequent Ugi-Joullié reaction is also expected to provide the required diastereoisomer with good selectivity.\textsuperscript{[22]}
Finally, a viable back-up option for both syntheses of schulzeine B and kainic acid is the use of 2-bromo-6-isocyanopyridine as convertible isocyanide with complementary cleavage properties (base-promoted conversion compared with the trityl amide which is removed in acidic conditions). [23]

Conclusion

In this chapter several research ideas to develop further the chemistry elaborated in the previous chapters of this thesis were presented. New methodology can be derived from the SiCl₄-mediated Passerini-type addition described in Chapter 2, to furnish for instance α-amino (α-substituted) ketone derivatives. This class of compounds is highly versatile in the synthesis of more complex molecules and a route towards the alkaloid noscapine is suggested. Next, the cyanation reactions using trityl isocyanide (Chapter 3 and 4) can be generalized by the investigation of other substrates (epoxides, Michael acceptors, aryl halides, diazonium salts). The mechanistic studies shown in this part of the thesis can direct the screening for (novel) catalytic enantioselective cyanation protocols. Finally, the convertible nature of trityl isocyanide enables the design of novel routes towards interesting natural product targets. Schulzeine B and kainic acid are addressed herein, but the synthesis of many other targets can benefit from the tremendous versatility and synthetic power of isocyanides.
Future Research Directions

References and Notes

Off the Beaten Path:

Atypical Products of Ugi and Passerini Reactions
In 1921 Mario Passerini performed the reaction between acetone, acetic acid and p-isocyanooazobenzene, in what turned out to be the first isocyanide-based multicomponent reaction. Almost four decades later, Ivar Ugi took this reaction further by introducing a fourth component, the amine. Nowadays, these old reactions (Scheme 1) are recognized as essential synthetic tools and are widely applied in combinatorial and diversity-oriented synthesis, natural product synthesis, polymer science, etc.

In this work the classical Ugi and Passerini reactions are given an upgrade: these valuable reactions are reinterpreted based on a rational design to afford atypical products for this chemistry. Several key concepts in the field of (isocyanide-based) multicomponent reactions have been used to access unconventional scaffolds: single-reactant replacement, post-condensation modification, bifunctional inputs, convertible isocyanides. Furthermore, based on sound mechanistic considerations, the normal course of the Passerini 3CR and Ugi 4CR has been manipulated towards different reaction pathways, and this only with subtle changes in reaction conditions and/or isocyanide design. Ultimately, the primary focus of this research was to move away from the classical conversion of the isocyanide group into a primary amide moiety and to provide access to other functionalities: primary amines, nitriles, carboxylic acids, esters, imides (Scheme 2).

Thus, after introducing the reader with the notions and concepts of the classical Ugi and Passerini reactions in Chapter 1, this thesis exemplifies in the following chapters how old chemistry can be reinvented for the improvement of the synthesis of valuable molecules. Chapter 2 describes the combinatorial synthesis of medicinally relevant β-amino alcohols from aldehydes and isocyanides. This protocol combines a Passerini-type reaction (in which the carboxylic acid component is replaced by silicon tetrachloride) with the one-pot ammonia-borane reduction to afford directly bioactive compounds in a straightforward
and general manner (Scheme 3). We demonstrated that this unusual retrosynthetic disconnection allows easy access to targets that are challenging for the conventional approaches based on substitution: the reaction tolerates steric bulk, unsaturated bonds and various functional groups. Importantly, the process can be upgraded by the introduction of a chiral catalyst to enable the catalytic enantioselective synthesis of β-amino alcohols through isocyanide addition. Finally, this new methodology was showcased by the preparation of the highly important anti-asthma drug Salbutamol.

**Scheme 3.** Synthesis of β-amino alcohols from aldehydes and isocyanides.

Next, in Chapters 3 and 4 the multicomponent chemistry of triphenylmethyl (trityl) isocyanide 2a was explored for the first time. Intriguingly, together with the expected reactivity, this simple isocyanide exhibits distinctive chemical behavior in interactions with imines or aldehydes and under determined conditions it allows the preparation of atypical Ugi and Passerini products. Thus, trityl isocyanide can be used as cyanide donor in the Strecker reaction (product 4) and cyanohydrin (7) synthesis and serves as convenient convertible isocyanide in Ugi, Passerini and Groebke-Blackburn-Bienaymé reactions (Scheme 4).

**Scheme 4.** Ugi and Passerini-type additions with trityl isocyanide.

The mechanisms of these classical MCRs intersect in the common trityl nitrilium ion intermediate whose predictable reactivity can be exploited towards chemoselective
transformations. Specifically, this reactive species can undergo fragmentation (Strecker pathway), intramolecular addition (Groebke-Blackburn-Bienaymé pathway) or intermolecular addition (Ugi/Passerini pathways), as shown in Scheme 5. A great variety of products is thus accessible from simple inputs in a divergent way, particularly since the N-trityl amide derivative can be transformed further into interesting scaffolds.

This unique chemical behavior of trityl isocyanide can be exploited in many other ways; some suggestions were provided in Chapter 7.

Continuing on the topic of combinatorial synthesis of bioactive compounds, Chapter 5 describes the direct Ugi four center-three component reaction involving γ-aminobutyric acid 9 towards racetam derivatives 10. These compounds find wide application in the treatment of various medical conditions and represent therefore highly relevant targets for synthesis. Substantial optimization efforts were required to improve the selectivity for the desired product in this novel Ugi reaction but gratifyingly under the optimal conditions the transformation proved to be general. Thus, this method provides rapid access towards novel racetam derivatives as well as commercial drug molecules: no less than four clinically important racetams were prepared using this approach (Scheme 6).
Finally, in Chapter 6 we returned to the Passerini reaction and attempted to tackle a difficult problem in isocyanide chemistry, namely the stereocontrol of the isocyanide addition. Thus, we were able to add a new entry to the brief list of diastereoselective Passerini reactions by employing a bifunctional input, keto acid 11. Trans-fused bicyclic lactones 12 can be generated with dr of up to 90:10 and the isocyanide scope of this intramolecular Passerini reaction is broad. Interestingly, this scaffold was shown to rearrange towards α-hydroxy imide 13 under acidic conditions, which is unprecedented in Passerini chemistry.

Scheme 7. Diastereoselective intramolecular Passerini reaction.

In summary, the work described in this thesis represents an attempt to expand the highly diverse chemistry of isocyanides in new directions, going beyond the classical primary amide products. Building on well-established concepts of isocyanide chemistry and reaction mechanisms, novel transformations were designed to access unconventional products. Thus, the new entries added to the list of Passerini and Ugi products are the β-amino alcohols, α-amino nitriles, O-trityl cyanohydrins, 2-pyrrolidone-1-acetamides and α-hydroxy imides. The protocols towards these structures generally feature attractive characteristics for applications in organic synthesis: high atom economy, high selectivity, mild reaction conditions, short reaction times, broad scope. Moreover, the chemistry developed herein is divergent, in the sense that typically both the classical (i.e. Passerini and Ugi) as well as the novel reactivity can be pursued in the same system, under rationally adapted conditions.

In conclusion, isocyanides are highly versatile building blocks for synthesis and this thesis testifies that despite the decades of intense exploration, the possibilities of developing novel chemistry with these reagents are far from exhausted.
Samenvatting

Buiten de gebaande paden:

Atypische Reactieproducten van Ugi en Passerini Chemie
Samenvatting

In 1921 voerde Mario Passerini de eerste reactie uit tussen aceton, azijnzuur en p-isocyanooazobenzeen, in wat uiteindelijk de eerste isocyanide-gebaseerde multicomponent reactie bleek te zijn. Bijna vier decennia later ontwikkelde Ivar Ugi deze reactie verder door er een vierde component aan toe te voegen, een amine. Tegenwoordig worden deze oude reacties (Schema 1) gezien als essentiële synthetisch gereedschap en worden ze veelvuldig gebruikt in combinatoriën en op diversiteit gerichte syntheses, natuurproduct synthese, polymeer wetenschap, etc.

![Schema 1. Isocyanide-gebaseerde multicomponent reacties: Ugi en Passerini.](image)

In dit onderzoek krijgen de klassieke Ugi en Passerini reacties een nieuw jasje: gebaseerd op rationeel ontwerp hebben we de reacties opnieuw tegen het licht gehouden om zo tot atypische producten te komen voor deze chemie. Uitgaande van verschillende ontwerp principes in het veld van multicomponent reacties hebben we toegang gekregen tot vaak onconventionele scaffolds: we hebben gebruik gemaakt van reactant vervanging, post-condensatie bewerkingen, bifunctionele inputs en converteerbare isocyanides. Gebaseerd op mechanistische overwegingen is bovendien het normale verloop van de Passerini 3CR en de Ugi 4CR gestuurd over verschillende reactiepaden door subtiel aangebrachte aanpassingen in reactiecondities en/of het isocyanide. Uiteindelijk was de primaire focus van dit onderzoek om af te wijken van de klassieke conversie van het isocyanide tot een primaire amide groep en om toegang te krijgen tot andere functionaliteiten zoals primaire amines, nitrilen, carbonzuren, esters, imides (Schema 2).

![Schema 2. Conventionele en nieuwe conversies van isocyanides.](image)

Na het introduceren van de begrippen en concepten van de klassieke Ugi en Passerini reacties in Hoofdstuk 1, licht dit manuscript in de daarop volgende hoofdstukken hoe de oude chemie heruitgevonden kan worden voor de synthese van waardevolle moleculen. Hoofdstuk 2 beschrijft de combinatoriën synthese van medisch relevante β-amino alcoholen 3 vanuit aldehyden en isocyanides. Dit protocol combineert een Passerini-type...
reactie (waarin het carbonzuur component vervangen is door silicium tetrachloride) met de een-pots ammoniak-boraan reductie om op een eenvoudige en algemene manier direct bioactieve verbindingen te verkrijgen. We hebben gedemonstreerd dat deze ongewone retrosynthetic disconnectie makkelijk toegang geeft tot targets die uitdagend zijn voor de conventionele benaderingen gebaseerd op substitutie: de reactie tolerert sterisch grote groepen, onverzadigde bindingen en verschillende andere functionele groepen. Van groter belang is echter dat het proces uitgebreid kan worden door de introductie van een chirale katalysator om de enantioselectieve synthese van β-amino alcoholen mogelijk te maken via isocyanide additie. Deze nieuwe methodologie werd gebruikt in de bereiding van het zeer belangrijke anti-astma medicijn Salbutamol.


Vervolgens is in Hoofdstukken 3 en 4 de multicomponent chemie van triphenylmethyl (trityl) isocyanide 2a voor de eerste keer onderzocht. Samen met de verwachte reactiviteit demonstreerde dit simpele isocyanide intrigerend en tamelijk bijzonder kenmerkend chemisch gedrag in interacties met imines of aldehyde en onder bepaalde condities konden zo atypische Ugi en Passerini producten worden verkregen. Trityl isocyanide kan dus gebruikt worden als cyanide donor in de Strecker reactie (product 4) en cyanohydrin (7) synthese en kan ook dienst doen als geschikt converteerbaar isocyanide in Ugi, Passerini en Groebe-Blackburn-Bienaymé reacties (Schema 5).

Schema 4. Ugi en Passerini-type addities met trityl isocyanide.
Het mechanisme van de klassieke MCRs verlopen steeds via een gemeenschappelijk trityl nitrilium ion intermediair waarvan de voorspelbare reactiviteit vervolgens kon worden benut voor chemoselectieve vervolg transformaties. In de beschreven reactie kan fragmentatie (Strecker reactiepad), intramoleculaire additie (Groebke-Blackburn-Bienaymé reactiepad) of intermoleculaire additie (Ugi/Passerini reactiepaden) plaatsvinden zoals getoond wordt in Schema 5. Een grote variëteit van producten is zo dus toegankelijk vanuit simpele inputs op een divergente manier, voornamelijk aangezien het N-trityl amide derivaat verder omgezet kan worden in interessante scaffolds.

Dit unieke chemische gedrag van trityl isocyanide kan verder toegepast worden op vele andere manieren; enkele suggesties zijn voorgesteld in Hoofdstuk 7.

Schema 5. Reactiviteit van de N-trityl nitrilium ion.

Voortgaande op het onderwerp van combinatoriële synthese van bioactieve stoffen beschrijft Hoofdstuk 5 de directe Ugi vier center-drie component reactie door gebruik te maken van γ-aminobutaanzuur naar racetam derivaten. Deze componenten kunnen breed ingezet worden in de behandeling van verschillende medische aandoeningen en vertegenwoordigen daarom tal van relevante doelmoleculen voor organische synthese. Substantiële optimalisatie bleek nodig om selectieve vorming van de gewenste producten in deze ongewone Ugi reactie voor elkaar te krijgen. Gelukkig bleken de geoptimaliseerde condities breed toepasbaar te zijn. Deze methode biedt dus snelle toegang naar nieuwe racetam derivaten, waaronder commercieel verkrijgbare: niet minder dan vier klinisch belangrijke racetams zijn bereid met behulp van deze methode (Schema 6).
Samenvatting


Tot slot keren we in de **Hoofdstuk 6** terug naar de Passerini reactie. In dit hoofdstuk beschrijven we onze inspanningen om een moeilijk probleem in isocyanide chemie aan te pakken, namelijk de stereocontrole van de isocyanide additie. We hebben een nieuw voorbeeld toegevoegd aan de korte lijst van diastereoselectieve Passerini reacties door gebruik te maken van een bifunctionele input, ketozuur 11. **Trans**-gefuseerde bicyclische lactonen 12 kunnen gegenereerd worden met *dr* tot 90:10 en de isocyanide scope van deze intramoleculaire Passerini reactie is breed. Interessant te noemen is dat het gemaakte scaffold omgezet bleek te worden naar α-hydroxy imide 13 onder zure condities, een omzetting nog niet eerder waargenomen in Passerini chemie.

Samengevat is het werk zoals beschreven in dit manuscript een poging om de zeer diverse chemie van isocyanides uit te breiden in nieuwe richtingen, en om voorbij de klassieke primaire amide producten te gaan. Voortbordurend op gevestigde concepten in isocyanide chemie en reactiemechanismes zijn nieuwe transformaties ontworpen om toegang te krijgen tot onconventionele producten. De nieuwe toevoegingen aan de lijst van Passerini en Ugi producten zijn de β-amino alcoholen, α-amino nitrilen, O-trityl cyanohydrines, 2-pyrrolidone-1-acetamides en α-hydroxy imides. De protocollen voor deze structuren bevatten over het algemeen aantrekkelijke kenmerken voor toepassingen in organische synthese: hoge atoomeconomie, hoge selectiviteit, milde reactiecondities, korte reactietijden, brede scope. Bovendien wijkt de chemie die hier is ontwikkeld af, in
die zin dat doorgaans gestuurd kan worden naar zowel de klassieke (*i.e.* Passerini en Ugi) als de nieuwe reactiviteit in hetzelfde systeem, afhankelijk van de condities.

Isocyanides zijn zeer veelzijdige bouwstenen voor organische synthese. Het werk beschreven in dit proefschrift laat heel mooi zien dat ondanks de decennia van intense onderzoeken naar isocyanides, de mogelijkheden om met deze reagentia nieuwe chemie te ontwikkelen nog lang niet verzadigd zijn.
Acknowledgement

It was the summer of 2010, seven years before writing the final pages of this book, that I was introduced for the first time to the chemistry going on in the labs of Romano Orru. On the eve of packing for my big Dutch adventure, I browsed through the Synthetic and Bio-organic Chemistry webpage to find out what the group’s research focus was. A reoccurring theme over there was isocyanide chemistry, most notably the Ugi reactions. At that time, I knew just a couple of things about isocyanides and had never heard of the Ugi reaction before. With curiosity, enthusiasm and confidence in my organic chemistry capabilities, I tried to ‘solve’ the mechanism on paper. I did not get very far.

Now, seven years later, after almost five years of working with isocyanides, reading about isocyanides, talking about isocyanides and thinking (too much) about isocyanides, I still feel reluctant in writing down the mechanism and pinpointing: ‘this is it!’ So, yes, there are still open questions and there will always still be, but one thing’s for sure: I have certainly enjoyed the journey! The journey and the people that were at my side along the way. It is you that made this time of my life truly special and it is the good moments that we’ve shared that I look at as my biggest achievements of these years. For all that I am deeply grateful.

I would first like to thank Romano, my promotor, for providing me a working environment that allowed me to develop myself and grow. From the very beginning and throughout the years, you showed me openness, trust, respect and appreciation. You’ve always given me the freedom to pursue my own ideas and the support (in many forms) to make them work. Thank you for all that!

I am also very grateful to my daily supervisor, Eelco, for the tremendous contribution to my projects, all the way from the design and idea stage to the manuscript preparation and submission. Thank you for the countless tips, suggestions and constructive comments that brought improvements not only to how I performed the work but also to how I made use
of it. I have certainly learned a lot from our collaboration and that goes far beyond chemistry.

Thank you Elwin for all the technical support. It’s incredible how much work is sometimes hidden behind a simple number: 99% (ee)...Your expertise, and most importantly your positive attitude and commitment to help out have certainly made (some) of the PhD problems simpler. I am also very happy to have shared so many good times and I am certainly proud that I am part of one of your many red pin flags on the world map.

I would now like to thank the members of the thesis examination and/or promotion defense committee for reading my thesis and taking part in this important final stage of my PhD experience: Prof. Dr. Tom Grossmann, Prof. Dr. Laurent El Kaïm, Prof. Dr. Francesco Mutti, Prof. Dr. Tom Wennekes, Prof. Dr. Syuzanna Harutyunyan and Prof. Dr. Floris Rutjes.

During my PhD I was fortunate to be involved in a number of collaborations with research groups from other universities. This has been an enjoyable experience with very fruitful results. For that I am grateful to the group of Prof. Dr. Kurt Faber (with Mélanie Hall and Nikolaus Turrini) at the University of Graz and the group of Prof. Dr. Nicholas Turner (with Friedemann Leipold) at the University of Manchester. I would also like to acknowledge Dr. Christophe Vande Velde (University of Antwerp) for his valuable help in stereochemistry confirmation by means of XRD analysis.

This thesis and the whole PhD experience would have not been the same without the contribution of students. Supervising students was certainly the best investment I could make, and this was something that I had already realized early in my PhD; however, towards the end, when it was the time of reflection and inventory (of notebooks, projects, nmr spectra and vials with compounds) I was really amazed at how much we could achieve together in these years! For that, but also for the good times in the lab and beyond, I am grateful to you Floor, Arthur, Wesley, Daan, Daniel, Sjaak, Xander, Peter, Lola and Imme.

I would now like to thank all my colleagues at SyBOrCh. During four years, we shared success and struggle, ideas and plans, expertise and experience, both in the lab as well as in the real world. Tjøstil, Guido, Corien, Matthijs, Sanne, Art, Esther, Veronica, Gydo, Jordy, Jurrien, John, thank you for the help, support and encouragements, the serious talks and especially the less serious ones, the laughs, the music and the drinks and most of all the gezelligheid!
Acknowledgement

I would also like to acknowledge my colleagues from the various research groups on the 3\textsuperscript{rd} floor of the W&N building and later on in the O|2 labs. Thank you neighbors from the ‘Phosphorous group’, Analytical Chemistry, Medicinal Chemistry and the Biomimetic Synthesis for Molecular Complexity for the lively discussions and sharing your own perspective over the PhD journey (and not only that), I greatly appreciate those memories!

În egală măsură vă sunt foarte recunoscător vouă, prietenilor mei din afara universității, pentru interes, sprijin și încredere, dar mai ales pentru multele momente frumoase pe care le-am împărtășit în ultimii ani, în cele mai diverse (sau banale) locuri și împrejurări. Mulțumesc prietenilor mei din Olanda (Andrei și Lidia, Cristina, Iulia și Mihai, Radu și Silvia, Alex și Oana, Anca și Luci, Dragoș, Nadina și Roshan, Flori, Vladimir, Laurian, Ionică, Cristi, Max și Dacilor din echipa de fotbal) sau de prin alte părți ale lumii (Andreea, Vali, Andrei și Alina, Ştefan). Mulțumesc și prietenilor mei dragi din Brașov, întotdeauna e o mare bucurie să vă văd și să stăm la povești sau la șah (Roxana și Sorin, Sergiu, Horea, Victor, Vlădu, Valentina, Maria, Octa, Ramo și Ionuț).

Mulțumesc familiei mele (Raluca, Ionuț, mama, tata, bunica, bunicu, tatamare) voi sunteți reperul meu dintâi.

Roxana, mulțumesc pentru că mi-ai însoțit fiecare pas pe cărările nemaiumbrate.
List of publications

Stereoselective Synthesis of Functionalized Bicyclic Scaffolds by Passerini 3-Center-2-Component Reactions of Cyclic Ketoacids

Ugi 4-Center-3-Component Reaction as a Direct Approach to Racetams

Biocatalytic Access to Nonracemic γ-Oxo Esters via Stereoselective Reduction Using Ene-Reductases

Brønsted Acid-Catalyzed Cyanotritylation of Aldehydes by Trityl Isocyanide

Trityl Isocyanide as a Mechanistic Probe in Multicomponent Chemistry: Walking the Line between Ugi- and Strecker-type Reactions

One-pot Synthesis of N-substituted β-Amino Alcohols from Aldehydes and Isocyanides

Multicomponent Reactions: Advanced Tools for Sustainable Organic Synthesis
Synthesis of Polycyclic Spiroindolines by Highly Diastereoselective Interrupted Ugi Cascade Reactions of 3-(2-isocyanoethyl)indoles

Asymmetric Synthesis of Tetracyclic Pyrroloindolines and Constrained Tryptamines by a Switchable Cascade Reaction

Sustainable Synthesis of Diverse Privileged Heterocycles by Palladium-Catalyzed Aerobic Oxidative Isocyanide Insertion