CHAPTER 7
1,3-DIPOLAR CYCLOADDITIONS TOWARDS C2-ARYLATED 2-IMIDAZOLINES

Summary
Explorative investigations on 1,3-dipolar cycloadditions of imines with α-acidic imidoyl chlorides is presented, which proceeds both under base and TMSOTf promoted conditions. Optimization of the reaction conditions and a multicomponent approach are discussed. Additionally, assignment of the diastereoisomers is presented.
C2-functionalized 2-imidazolidines and 2-imidazolines – Multicomponent Synthesis and Synthetic Potential
7.1 Introduction

In chapter 1 the biological activity and synthesis of C2 functionalized 2-imidazolines is discussed, including C2-arylated and C2-alkylated 2-imidazolines. These scaffolds have drawn considerable attention as they are known for a wide variety of interesting biological properties. In this category, compounds are the nutlin-like structures with a C2-aryl decorated cis imidazoline heterocyclic core, which show MDM-p53 PPI inhibitory activity. In addition the reported synthetic routes towards this class of compounds were discussed. They are often multi-step routes that do not allow for much control over scaffold decoration. In chapter 4, we introduced a 2-step synthetic approach consisting of (1) an MCR using α-acidic isothiocyanates in combination with in situ formed imines to generate the initial heterocyclic core, and (2) a follow-up Liebeskind-Srogl cross coupling reaction to introduce the C2 aryl function (Scheme 1).

Although effective we aimed to develop an even more efficient route. We envisioned that 1,3-dipolar cycloadditions of nitrile ylides (1) with (in situ-generated) imines should facilitate synthesis of C2-arylated 2-imidazolines (2) in a single synthetic step (Scheme 2).

This approach was inspired by the work of Bunge et al., who demonstrated easy access to C2-arylated imidazoles (3) employing a cycloaddition protocol starting from benzonitrile benzylides (Scheme 3). The reported cycloadditions reactions combine nitrile ylides 1
and commercially available imine using 10 equivalents of the imine (both as reagent and solvent) and purification by distillation. It is our strong believe that under these conditions, (high temperature and air-atmosphere) the C2-arylated imidazoles are isolated rather than their 2-imidazoline counterparts. Therefore we set out to further optimize the synthetic procedure towards the C2-arylated 2-imidazoline scaffold.

Scheme 3  Synthesis of C2-arylated imidazoles by Bunge et al.

### 7.1.1 The 1,3-Dipolar Cycloaddition
The 1,3-dipolar cycloaddition, also known as the Huisgen cycloaddition, is a reaction between a 1,3-dipole and a double or triple bond (Scheme 4), in which, from the dipole a-b-c and the dipolarophile d-e, two new σ-bonds in a pericyclic suprafacial fashion are formed with preservation of stereochemistry. Generally, the 1,3-dipolar cycloaddition proceeds through a concerted mechanism, proved by the following observations: (1) ground state stabilization by additional carbonyl groups on the 1,3-dipole, (2) minor solvent effects; no improved reaction rate is observed with increased solvent polarity, (3) cis-addition through simultaneous bond formation.

Scheme 4  The 1,3-dipolar cycloaddition

A large variety of 1,3-dipoles and dipolarophiles (Table 1) can be utilized in this reaction, making this one of the most important methods to construct five-membered heterocyclic rings, creating a maximum of four potential stereocenters in one single step.
Table 1  

<table>
<thead>
<tr>
<th>1,3-Dipoles</th>
<th>Dipolarophile</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image.png" alt="Diagram" /></td>
<td><img src="image.png" alt="Diagram" /></td>
</tr>
</tbody>
</table>

### 7.1.2 Nitrile Ylide synthesis

Two general methods for the synthesis of nitrile ylides are known: treatment of imidoyl chlorides (2) with (1) an organic base to afford a nitrile ylide (6), or (2) the use of TMSOTf for *in situ* generation of a nitrilium triflate (7), to afford nitrile ylide (6) upon deprotonation (Scheme 5). Synthesis of the imidoyl chlorides from the corresponding amides can be accomplished through application of various conditions and/or reagents such as (1) PCl₅,⁴⁰ (2) C₂O₂Cl₂/2,6-lutidine,⁴¹ (3) CCl₄/PPh₃/NEt₃⁴² or (4) COCl₂.⁴³ However, this transformation is most straightforwardly accomplished in quantitative yield utilizing SOCl₂ under reflux conditions.⁴⁴

**Scheme 5**  
Nitrile ylide (6) and nitrile ylide triflate synthesis
However, also some more specific procedures have been reported in literature. For example, Marquart et al.\textsuperscript{45} report the \textit{in situ} formation of a nitrilium ion 9 from the corresponding amide 8 by treatment with PPSE, to afford endocyclic imine 10 upon intramolecular cyclization (Scheme 6). Interestingly, this method avoids synthesis of the imidoyl chloride intermediate.

**Scheme 6 \textbf{In situ nitrilium ion synthesis}**

7.1.3 Synthetic strategy

The C2-arylated 2-imidazolines could be obtained from a 1,3-dipolar cycloaddition of imines (\textit{in situ} formed from amines and aldehydes or ketones) and nitrile ylides, \textit{in situ} formed from the corresponding imidoyl chlorides (Scheme 7). The imidoyl chlorides are afforded from a reaction of the corresponding amides with SOCl\textsubscript{2}, which in turn are derived from a condensation reaction of the corresponding amines and acid chlorides.

**Scheme 7 \textbf{Synthetic strategy}**
7.2 Results

7.2.1 Imidoyl chloride synthesis

The imidoyl chlorides utilized in the reaction are basically derived from the corresponding amines and acid chlorides via amide intermediates. Therefore, the amides were synthesized according to literature procedure, by a reaction of the appropriate amine and acid chloride (Table 2), performed in EtOAc utilizing NEt₃ as base. Generally, the amides (4) were obtained in good to excellent yield (77 – 95%).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image of amide 4a" /></td>
<td>95%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Image of amide 4b" /></td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Image of amide 4c" /></td>
<td>84%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Image of amide 4d" /></td>
<td>77%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Image of amide 4e" /></td>
<td>90%</td>
</tr>
</tbody>
</table>

Next, the corresponding imidoyl chlorides were synthesized by a reaction of the corresponding amides in refluxing SOCl₂, a method described by von Braun et al. (Table 3), of which progress can be easily monitored by ¹H NMR. Application of this method afforded all imidoyl chlorides in quantitative yields.
7.2.2 Base promoted 1,3-cycloadditions
As a first attempt towards synthesis of C2-arylated 2-imidazolines an adapted version of the conditions of Bunge et al. were applied. The modifications include: (1) use of an organic solvent (DCM) and, (2) reduction of the amount of utilized imine (large excess (used as both reagent and solvent) → (10 eq). Thus, to a stirred solution of imidoyl chloride (2a-e) and imine (11) in DCM at room temperature, the base was added. Then the reacting mixture was stirred for seven days. Application of triethylamine as base (Table 4, entries 1 – 3) afforded 2-imidazolines 2a and 2c in ~70% isolated yield, although the reaction towards 2-imidazoline 2b proved unsuccessful, indicating the necessity of a strong electronic withdrawing group on R2. In an effort to reduce the reaction time, lutidine as organic base (Table 3, entries 4 and 5) was employed in this procedure. While synthesis of 2b proved still unsuccessful, 2a was again afforded, albeit in a lower 58% yield.

Table 3  Imidoyl chloride synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imidoyl Chloride</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Imidoyl Chloride 5a" /></td>
<td>quant.</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Imidoyl Chloride 5b" /></td>
<td>quant.</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Imidoyl Chloride 5c" /></td>
<td>quant.</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Imidoyl Chloride 5d" /></td>
<td>quant.</td>
</tr>
</tbody>
</table>
Table 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>R₂</th>
<th>Base</th>
<th>2-imidazoline</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>PNP</td>
<td>Et₃N</td>
<td>2a</td>
<td>71%</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph</td>
<td>Et₃N</td>
<td>2b</td>
<td>n.r.</td>
</tr>
<tr>
<td>3</td>
<td>PNP</td>
<td>PNP</td>
<td>Et₃N</td>
<td>2c</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>PNP</td>
<td>Lutidine</td>
<td>2a</td>
<td>&gt;58%</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Ph</td>
<td>Lutidine</td>
<td>2b</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

Noteworthy is the fact that all products were obtained in a 1 : 3 cis : trans diastereomeric ratios. Although we were unable to assign the relative stereochemistry through NOESY NMR experiments due to the rather flexible 5-membered ring, the respective diastereomers could be assigned by their relative oxidation rates towards imidazoles, discussed in detail in the ensuing paragraph.

7.2.3 Oxidation of 2-imidazolines to imidazoles

In contrast to our work, Bunge et al. originally isolated C2-arylated imidazoles, most probably a result of the rather harsh purification methodology, which includes distillation at 220 – 260 °C. This may well result in subsequent oxidation of the initially formed C2-arylated 2-imidazoline (Scheme 8).

Scheme 8 Synthesis of C2-arylated imidazole 3a

In analogy to this observation, we have reported the oxidation of mono C-4 and C-5 substituted imidazolines to the corresponding imidazoles in the presence of air. These oxidation reactions are instantaneous during work-up for the cis-imidazoline diastereomer. However, storage of a purified trans-imidazoline for six months under air led to 75% of the corresponding imidazole oxidation product (Scheme 9).
In order to obtain information on the relative stereochemistry, pure samples of diastereoisomers were stored under air and subjected to \(^1\)H-NMR analysis during set time intervals. The results of this study are depicted in table 5. In all examples shown, the less polar isomer (l.p.i.) exhibits more stability towards air oxidation than the more polar isomer (m.p.i.). Hence, in analogy with the work of Bon et al., \(^{47}\) the l.p.i.’s are assigned as the trans diastereoisomers whereas the m.p.i.’s were assigned as being cis.

### Table 5

**Relative oxidation rates of the more and less polar isomers m.p.i. and l.p.i., respectively**

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-imidazoline</th>
<th>Isomer</th>
<th>Period</th>
<th>Oxidized</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>l.p.i.</td>
<td>3 months</td>
<td>partially</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>m.p.i.</td>
<td>3 months</td>
<td>fully</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>l.p.i.</td>
<td>3 months</td>
<td>fully</td>
</tr>
<tr>
<td>4</td>
<td>3c</td>
<td>m.p.i.</td>
<td>2 days</td>
<td>fully</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>l.p.i.</td>
<td>3 months</td>
<td>partially</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>m.p.i.</td>
<td>3 months</td>
<td>fully</td>
</tr>
</tbody>
</table>

### 7.2.4 Multicomponent reaction towards C2 Imidazolines

Parallel to optimization of the reaction conditions discussed earlier in this chapter, an attempt was undertaken to expand the scope of this reaction utilizing *in situ* formed imines. This would result in a novel multicomponent reaction. Thus imidoyl chloride 5a was added at room temperature to a stirred solution of \(n\)-butyl amine and 4-chlorobenzaldehyde (*in situ* preformed imine) and triethylamine (Scheme 10). This gave 14 in 34% isolated yield after 7 days. In analogy with the other obtained C2-arylated 2-imidazolines, 14 was obtained in a ~ 1 : 3 cis : trans mixture of diastereoisomers. Although
delighted with this result, due to time limitation further investigations into this direction were ceased and were focused on the optimization of the 1,3-dipolar cycloaddition reaction itself.

Scheme 10  MCR approach towards C2-arylated 2-imidazoline (14)

7.2.5 TMSOTf promoted 1,3-cycloadditions

Next, in order to further reduce reaction times, we turned our attention to the use of TMSOTf to promote these reactions. The thus generated corresponding (in situ generated) nitrilium ions are known for their enhanced reactivity towards dipolarophiles. At -78°C imine 11 was added to stirred mixture of TMSOTf and the imidoyl chloride 2 (Scheme 11).

Scheme 11  TMSOTf promoted 1,3-cycloadditions

Application of these conditions gave major products in a 45 and 60% isolated yield, utilizing imidaoly chlorides 2a and 2b respectively. Unexpectedly, 1H-NMR analysis of the product showed that the distinct two doublets from the C4 and C5 protons are shifted about one ppm further upfield than anticipated for the product 2a. This indicates that a phenyl ring is present on C4 of the reaction product. Since mass analysis provided the correct mass for the desired product, formation of regioisomeric product 2a-iso (Scheme 12) can explain the observed 1H-NMR chemical shifts.
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Scheme 12 Possible formation of regioisomer 2-iso

![Scheme 12](image)

This reversed regioselectivity could be, as suggested by Bunge et al., a result of the equilibrium between nitrile ylide isomers as a consequence of a formal hydride shift, affording both amides 4 and 4-iso, through basic hydrolysis of either imidoyl chlorides 5 of 5-iso (Scheme 13).

Scheme 13 Nitrile ylide interconversion

![Scheme 13](image)

For the interconversion, two mechanistic pathways were proposed (Scheme 14): (1) via a four-membered transition state (16), which is formally forbidden because of orbital symmetry and thus very unlikely, or (2) via the interconversion of two 2H-azirines (17/17-iso), which was refuted by heating 17 (R= Ph, R= 2,4-(NO2)-Ph) to 80 °C, which did not yield either 6 or 6-iso.

Scheme 14 Proposed mechanism for hydride shift interconversion of nitrile ylides

![Scheme 14](image)
Alternatively, interconversion from 6 to 6-iso could occur through protonation of nitrile ylide 6 via aza-allene cation 18, of which the tetraphenyl substituted antimony hexachloride salt 19 is reported in literature (Scheme 15).\textsuperscript{48, 50}

**Scheme 15** Interconversion of nitrile ylides via aza-allene cations

Moreover, this type of interconversion was also observed by Yoo et al. in the reaction of imidoyl chloride 5a and 5a-iso with \(N, N\)-dimethylacrylamide (20),\textsuperscript{51} in which the reaction of imidoyl chloride 5a solely yields stereoisomers 21 whereas the reaction of imidoyl chloride 2a-iso with \(N, N\)-dimethylacrylamide yields both regioisomers, 21 and 21-iso respectively (Scheme 16). These results indicate some sort of interconversion during the reaction pathway.

**Scheme 16** Interconversion of imidoyl chlorides 5a and 5a-iso with \(N, N\)-dimethylacrylamide (20)

### 7.3 Conclusions

A novel route towards C2-arylated 2-imidazolines from 1,3-dipolar cycloadditions of imines with imidoyl chlorides was established, which proceeds both under base and TMSOTf promoted conditions. Although the latter is slightly more tolerant of utilization of less \(\alpha\)-acidic imidoyl chorides, formation of regioisomers through nitrile ylide interconversion is suspected. Additionally, careful conclusions can be made on the assignment of respective diastereoisomers in analogy to the work of Bon et al. Moreover, although still in its infancy, a MCR protocol was established.
7.4 Acknowledgements

M. C. Smoluch and F. J. J. de Kanter are kindly acknowledged for HRMS and NMR measurements, respectively.

7.5 Experimental

Materials and Instrumentation

All reactions were carried out under atmospheric conditions, unless stated otherwise. $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 250 (250.13 MHz for $^1$H and 62.90 MHz for $^{13}$C), Bruker Avance 400 (400.13 MHz for $^1$H and 100.62 MHz for $^{13}$C) or Bruker Avance 500 (500.23 MHz for $^1$H and 125.70 MHz for $^{13}$C) with chemical shifts (δ) reported in ppm, internally referenced to residual solvent resonances for CDCl$_3$ ($^1$H δ: = 7.26 ppm; $^{13}$C($^1$H) δ: = 77.00 ppm), and coupling constants (J) are reported in Hz. Infrared (IR) spectra were obtained from neat samples utilizing a Shimadzu FTIR-8400S spectrophotometer and with wavelengths (ν) reported in cm$^{-1}$. Electrospray Ionization (ESI) mass spectrometry was carried out with a micrOTOF-Q instrument in positive ion mode unless stated otherwise. Chromatographic purification refers to flash chromatography using the indicated solvent (mixture) and Baker 7024-02 silica gel (40 μ, 60 Å). Thin layer chromatography was performed using silica plates from Merck (Kieselgel 60 F254 on aluminium with fluorescence indicator. Compounds on TLC were visualized by UV detection and I$_2$-staining unless stated otherwise. Dichloromethane (DCM) was dried and freshly distilled from CaH$_2$ prior to use.

General procedure I for the formation of amides: To a flame dried flask charged with EtOAc, amine (0.2 M) and Et$_3$N (0.28 M), on slow addition of a solution of benzoyl chloride (1.2 eq) in EtOAc (0.28 M), a precipitate was formed. The reaction mixture was stirred at room temperature overnight and the solvent was removed in vacuo, washed with c-hex and washed twice with cooled c-hex : EtOAc (5 : 1).

$N$-benzylbenzamide 4a: According to General procedure I, the reaction between (4-nitrophenyl)ethanaminium chloride (1.89 g, 10.0 mmol) and benzoyl chloride (1.39 mL, 12.0 mmol) in the presence of Et$_3$N (3.46 mL, 25.0 mmol) in EtOAc (80 mL) afforded 4a as a yellow solid (2.44 g, 9.5 mmol, 95%). $^1$H NMR (250 MHz, CDCl$_3$) δ (ppm) 8.18 (d, 2H, J = 7.3), 7.81 (d, 2H, J = 8.0), 7.49 (m, 5H), 6.68 (s, 1H), 4.74 (d, 2H, J = 6.0).
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**N-benzylbenzamide 4b:** According to General procedure I, the reaction between benzylamine (5.47 mL, 50.0 mmol) and benzoyl chloride (6.97 mL, 60.0 mmol) in the presence of Et$_3$N (10.39 mL, 75.0 mmol) in EtOAc (250 mL), which was subsequently washed with saturated NaHCO$_3$(aq) and NaCl(aq), afforded 4b as a yellow solid (10.02 g, 47.5 mmol, 95%). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ (ppm) 7.79 (d, 2H, $J = 8.2$), 7.41 (m, 8H), 6.48 (s, 1H), 4.64 (d, 2H, $J = 8.2$).

**N-benzylbenzamide 4c:** According to General procedure I, the reaction between (4-nitrophenyl)methanaminium chloride (0.47 mg, 2.5 mmol) and 4-nitrobenzoyl chloride (0.56 mg, 3 mmol) in the presence of Et$_3$N (0.87 mL, 6.3 mmol) in EtOAc (12.5 mL), which was subsequently washed with DCM, afforded 4c as a yellow solid (0.63 g, 2.1 mmol, 84%). $^1$H NMR (250 MHz, DMSO) $\delta$ (ppm) 9.55 (t, 1H, $J = 5.8$), 8.21 (m, 6H), 7.62 (dt, 2H, $J = 8.7$; 3.3), 4.65 (d, 2H, $J = 5.9$).

**N-benzylbenzamide 4d:** According to General procedure I, the reaction between (4-nitrophenyl)methanaminium chloride (1.89 g, 10.0 mmol) and 4-methoxybenzoyl chloride (1.65 mL, 12.0 mmol) in the presence of Et$_3$N (3.47 mL, 25.0 mmol) in EtOAc (50 mL), which was subsequently washed with saturated NaHCO$_3$(aq) and NaCl(aq), afforded 4d as a yellow solid (2.63 g, 7.7 mmol, 77%). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ (ppm) 8.10 (d, 2H), 7.65 (d, 2H), 6.72 (d, 2H), 6.40 (d, 2H), 4.38 (s, 2H), 3.68 (s, 3H).

**N-benzylbenzamide 4e:** According to General procedure I, the reaction between methyl 2-amino-2-(4-chlorophenyl)acetate (1.99 g, 10.0 mmol) and benzoyl chloride (1.4 mL, 12.0 mmol) in the presence of Et$_3$N (2.0 mL, 14.0 mmol) in EtOAc (75 mL), which was subsequently washed with saturated NaHCO$_3$(aq) and NaCl(aq), afforded 4e as a yellow solid (1.03 g, 3.4 mmol, 34%). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ (ppm) 7.86 (d, 2H), 7.44 (m, 7H), 5.79 (d, 1H, $J = 6.9$ Hz), 3.77 (s, 3H).

**N-(benzyl)acetamide 4f:** According to General procedure I, the reaction between (4-nitrophenyl)methanaminium chloride (1.89 g, 10.0 mmol) and acetyl chloride (0.86 mL, 12.0 mmol) in the presence of Et$_3$N (3.47 mL, 25.0 mmol) in EtOAc (50 mL), which was subsequently washed with saturated NaHCO$_3$(aq) and NaCl(aq), afforded 4f as a yellow solid (1.90 g, 9.0 mmol, 90%). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ (ppm) 7.99 (d, 2H, $J = 8.7$), 7.30 (d, 2H, $J = 8.5$), 4.32 (d, 2H, $J = 6.1$), 2.47 (s, 3H).

**N-benzylbenzamide 4g:** According to General procedure I, the reaction between benzylamine (1.09 mL, 10.0 mmol) and 4-nitrobenzoyl chloride (2.228 g, 12.0 mmol) in the presence of Et$_3$N (2.08 mL, 15.0 mmol) in EtOAc (80 mL), which was subsequently washed with saturated NaHCO$_3$(aq) and NaCl(aq), afforded 4g as a yellow solid (2.20 g, 8.6 mmol, 86%). $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ (ppm) 8.28 (d, 2H, $J = 8.7$), 7.95 (d, 2H, $J = 8.7$), 7.34 (m, 5H), 6.45 (s, 1H), 4.67 (d, 2H, $J = 5.6$).

**General procedure II for converting amides into imidoyl chlorides:** In a flame dried flask amide was dissolved in thionyl chloride (large excess) and refluxed for 4 hrs. The solvent was removed *in vacuo* and the product was used without further purification.
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**N-benzylbenzimidoyl chloride 5a**: According to General procedure II, the reaction between 4a (770 mg, 3.0 mmol) and thionylchloride (0.5 mL, excess) afforded 5a as a yellow solid (quant.). ¹H NMR (250 MHz, CDCl₃) δ (ppm) 8.17 (m, 2H), 8.08 (m, 2H), 7.48 (m, 5H), 4.94 (s, 2H).

**N-benzylbenzimidoyl chloride 5b**: According to General procedure II, the reaction between 4b (5.0 g, 21.8 mmol) and thionylchloride (10.0 mL, excess) afforded 5b as a yellow liquid (quant.). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.14 (dd, 2H, J = 8.5, 1.0 Hz), 7.49 (tt, 2H, J = 7.5; 1.0), 7.37 (m, 4H), 7.17 (m, 3H), 4.95 (s, 2H).

**N-benzylbenzimidoyl chloride 5c**: According to General procedure II, the reaction between 4c (603 mg, 2.0 mmol) and thionylchloride (2.0 mL, excess) afforded 5c as a yellow solid (quant.). ¹H NMR (250 MHz, CDCl₃) δ (ppm) 8.09 (m, 6H), 7.47 (d, 2H, J = 8.5), 4.87 (s, 2H).

**N-benzylbenzimidoyl chloride 5d**: According to General procedure II, the reaction between 4d (2.63 g, 9.2 mmol) and thionylchloride (6.0 mL, excess) afforded 5d as a yellow solid (quant.). ¹H NMR (250 MHz, CDCl₃) δ (ppm) 8.18 (dd, 4H, J = 20.9; 8.8), 7.65 (d, 2H, J = 8.6), 6.97 (d, 2H, J = 8.9 Hz), 5.03 (s, 2H), 3.88 (s, 3H).

**General procedure III for the reaction towards imidazolines**: To a flame dried flask charged with DCM, imidoyl chloride (0.6 or 2.0 M) and base (0.22 M) was added imine (0.2 M). The reaction mixture was stirred for 3-7 days after which the solvent was removed in vacuo and the crude product was purified by silica gel flash column chromatography (c-hex:EtOAc = 9:1 → gradient).

**2-Aryl-2-imidazoline 2a**: According to General procedure III, the reaction between N-benzylidenemethanamine (1.24 mL, 10.0 mmol) and 5a (0.256 g, 1.0 mmol) in the presence of NEt₃ (0.15 mL, 1.1 mmol) in DCM (5.0 mL) afforded 2a in a 8 : 2 mixture of diastereoisomers as a yellow solid (271.0 mg, 71%). Analysis: (l.p.i) ¹H NMR (250 MHz, CDCl₃) δ (ppm) 8.23 (dt, 2H, J = 8.8; 2.0), 7.77 (m, 2H), 7.44 (m, 10 H), 7.44 (m, 2H, J = 10.2), 2.76 (s, 3H); ¹³C NMR (100.61 MHz, CDCl₃) δ (ppm) 168.3 (C), 151.1 (C), 147.6 (C), 140.5 (C), 129.5 (2x CH), 128.9 (2x CH), 128.8 (4x CH), 128.0 (2x CH), 127.8 (2x CH), 127.5 (2x CH), 127.1 (CH), 124.1 (2x CH), 78.6 (CH), 77.1 (CH), 35.0 (CH₃); HRMS 358.1536. (m.p.i.) ¹H NMR (250 MHz, CDCl₃) δ (ppm) m.p.i. 7.87 (d, 2H, J = 8.8), 7.75 (m, 2H), 7.49 (m, 5H), 7.09 (m, 3H), 6.93 (m, 2H), 5.67 (d, 1H, J = 11.2), 5.05 (d, 1H, J = 11.3), 2.79 (s, 3H).
2-Aryl-2-imidazoline 2b: According to General procedure III, the reaction between N-benzylidenemethanamine (0.37 mL, 3.0 mmol) and 5c (0.319 g, 1.0 mmol) in the presence of NEt₃ (1.5 mL, 1.1 mmol) in DCM (5.0 mL) afforded 2c in a 95 : 5 mixture of diastereoisomers as a yellow solid (70%). ¹H NMR (250 MHz, CDCl₃) δ (ppm) l.p.i. 8.35 (d, 2H, J = 9.0), 8.20 (d, 2H, J = 9.0), 7.95 (d, 2H, J = 9.0), 7.45 – 7.34 (m, 7H), 5.13 (d, 1H, J = 11.0), 4.27 (d, 1H, J = 11.0), 2.74 (s, 3H); ¹³C NMR (100.61 MHz, CDCl₃) δ (ppm) l.p.i. 166.2 (C), 150.2 (C), 149.1 (C), 147.5 (C), 139.7 (C), 137.2 (C), 129.8 (2x CH), 129.4 (2x CH), 128.8 (CH), 127.8 (2x CH), 127.3 (2x CH), 123.97 (2x CH), 78.6 (CH), 77.4 (CH), 34.8 (CH₃); HRMS l.p.i 403.1388; HRMS m.p.i 403.1392

2-Aryl-2-imidazoline 14: A flame dried flask was charged with freshly dried mol. sieves (3 Å), DCM (5 ml), p-chlorobenzaldehyde (0.703 g, 5.0 mmol) and n-butylamine (0.494 mL, 5.0 mmol) and stirred overnight. After addition of 2a (0.274 g, 5.0 mmol) in the presence of NEt₃ (0.15 mL, 1.1 mmol), the reaction mixture was stirred for 7 days. The solvent was removed in vacuo after which the crude product was purified by silica gel flash column chromatography (c-hex:EtOAc = 9:1 → gradient) to afford 14 in a 7:3 mixture of diastereoisomers as a yellow solid (0.147 g, 34%). Analysis: (l.p.i.) ¹H NMR (250 MHz, CDCl₃) δ (ppm) 8.26 – 7.31 (m, 13H), 5.05 (d, 1H, J = 9.0), 4.38 (d, 1H, J = 9.0), 3.20 – 3.14 (m, 1H), 3.05 – 3.01 (m, 1H), 1.34 – 1.03 (m, 4H), 0.69 (t, 3H, J = 7.0); ¹³C NMR (100.61 MHz, CDCl₃) δ (ppm) 167.8 (C), 151.0 (C), 147.2 (C), 140.3 (C), 133.9 (C), 130.8 (C), 130.3 (CH), 129.3 (2x CH), 128.5 (2x CH), 128.2 (2x CH), 128.1 (2x CH), 127.4 (2x CH), 123.9 (2x CH), 77.3 (CH), 73.9 (CH), 46.6 (CH₂), 29.7 (CH₃), 19.6 (CH₃), 13.4 (CH₃); HRMS l.p.i 434.1608. (m.p.i.) ¹H NMR (250 MHz, CDCl₃) δ (ppm) 7.93 – 6.89 (m, 13H), 5.72 (d, 1H, J = 11.0), 5.18 (d, 1H, J = 11.0), 3.37 – 3.27 (m, 1H), 2.93 – 2.83 (m, 1H), 1.42 – 1.06 (m, 4H), 0.73 (t, 3H, J = 7.0); ¹³C NMR (100.61 MHz, CDCl₃) δ (ppm) 168.8 (C), 147.7 (C), 146.8 (C), 135.7 (C), 133.7 (C), 131.2 (C), 130.8 (CH), 129.3 (2x CH), 129.1 (2x CH), 129.0 (2x CH), 128.8 (2x CH), 128.6 (2x CH), 123.1 (2x CH), 123.3 (2x CH), 72.8 (CH), 69.1 (CH₂), 45.9 (CH₃), 30.3 (CH₃), 20.1 (CH₃), 13.9 (CH₃).

General procedure V for the reaction towards imidazolines via nitrilium ions: To a flame dried flask charged with DCM, imidoyl chloride (0.2 M) and imine (0.6 M) was added TMSOTf (1.2 eq) in DCM (0.24 M) at -78˚C. The reaction mixture was stirred for 3 hours after which temperature was slowly raised to RT, in two hrs. TLC and crude ¹H NMR showed no starting material and probable product formation, but isolation and thus characterization was unsuccessful.
References


11. C.-functionalized 2-imidazolidines and 2-imidazolines – Multicomponent Synthesis and Synthetic Potential


22. E. Ware, *Chemical Reviews*, 1950, 46, 403-470.


