CHAPTER 1
GENERAL INTRODUCTION

C2-functionalized 2-imidazolidines and 2-imidazolines
Multicomponent Synthesis and Synthetic Potential

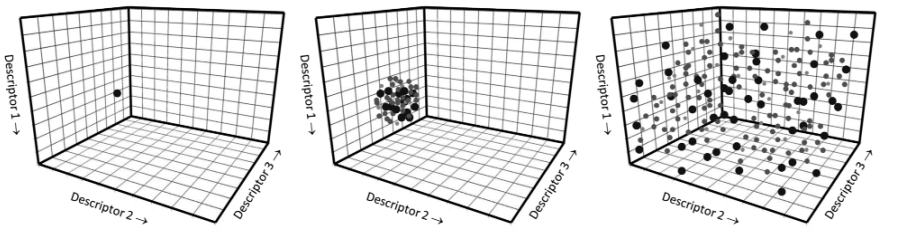
Summary

This chapter contains a brief introduction to some important topics presented in this thesis. First, the concept of Diversity-oriented synthesis is introduced (DOS). Then, multicomponent reactions (MCRs), as valuable tools for DOS strategies, are discussed. Next, comprehensive reviews of relevant literature, on the relevance and synthetic strategies towards the target compounds are presented. To conclude the scope of the thesis is outlined.

1.1 Diversity-Oriented Synthesis

Pharmacological screens and bio-assays have become important tools in the search for and discovery of novel drugs during last decades. Structurally, most of the biologically active pharmaceutically relevant compounds are still small organic molecules, often containing heterocyclic rings.[1] The complete theoretical array of small organic molecules has been estimated to comprise 10^{30} – 10^{200} distinct structures, each of which can be represented as a single point in chemical space. This chemical space is defined as multi-dimensional with each dimension defined by either computed or measured descriptor values of biological or chemical nature.[2] Obviously, although large compound libraries are inevitable, biological screening, let alone synthesis of all of these small molecules is unmanageable. Moreover, the universe does not consist of enough matter to facilitate synthesis of one single molecule of all conceivable structures.[1] Chemical reactions allow us to move through chemical space, however, the correlation of chemical space and molecular properties is often not unique; one point in can represent multiple distinct molecules that exhibit the same properties. Drug discovery, catalyst/ligand discovery and material design involve the exploration of chemical space. Generally, three general approaches are available in the synthetic chemist's toolbox, all of which address different volumes of chemical space: (1) Target-Oriented Synthesis (TOS), (2) Combinatorial Synthesis and (3) Diversity-Oriented Synthesis (DOS) (Figure 1). In TOS focus is on a specific region of chemical space, where often target assignment relies on the discovery of novel natural product structures. The combinatorial approach focuses on the close proximity of a well-defined point in chemical space, useful for creating structures with possible beneficial properties compared to a lead structure, originating either from a natural product, a known drug, or a rationally designed structure. DOS targets a much larger portion of chemical space,[2, 3, 4] since a wide array of small molecules displaying vast structural and complex diversity are created. Due to the non-focused nature of this approach, a vast spectrum of physical and biological properties is to be expected. Consequently, DOS enables fast discovery of structures suitable for lead optimization towards synthesis of novel biological probes or potential drugs. Due to the target oriented nature, both TOS and combinatorial chemistry require a 'retro-synthetic analysis', whereas DOS relies on 'forward synthetic planning'.[2, 3, 4]

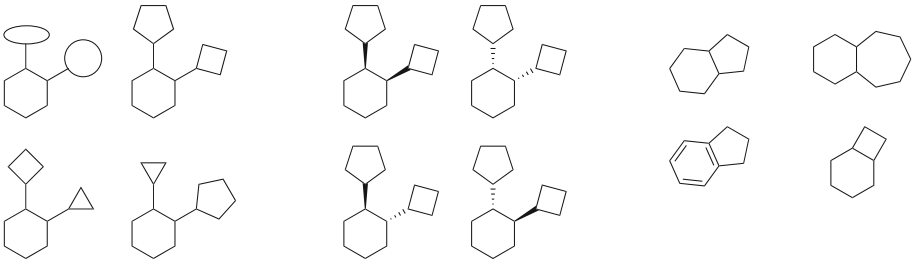
Figure 1 *Schematic representation of (1) TOS, (2) Combinatorial Chemistry and (3) DOS in chemical space*



(1) Target Oriented Synthesis (TOS) *(2) Combinatorial Chemistry* *(3) Diversity Oriented Synthesis (TOS)*

To cover the broadest volume of chemical space, DOS relies on the introduction molecular diversity, of which three fundamental levels can be distinguished (1) appendage diversity, (2) stereo chemical diversity and (3) scaffold diversity **(Figure 2)**.[3] Appendage diversity, most commonly applied in combinatorial chemistry, relies on the decoration of a common molecular skeleton; a scaffold. Consequently, sharing an identical scaffold, product structures will display similar biological activity. Stereo chemical diversity relies on stereo-specific reactions proceeding in high diastereo- and/or enantioselectivity. Scaffold diversity is achieved by either (1) a reagent based approach; transformation a common substrate into a collection of products, employing a suitable reagent or (2) a substrate based approach; transformation of a collection of diversely decorated substrates into a collection of products.

Figure 2 *General approaches towards molecular diversity*



(1) Appendage diversity *(2) Stereo chemical diversity* *(3) Scaffold diversity*

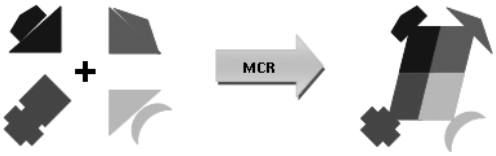
Due to the fact that DOS targets a vast amount of structures, versatile and robust methodologies are required, preferably with a maximum of 3 – 5 reaction steps in absence of undesired protective group manipulations. An important factor to maximize the potential of a DOS approach is to implement a 'complexity-generating reaction'. In this context, development of novel multicomponent reactions (MCRs),[5] a special class of tandem, domino or cascade reactions, has proven to be the seminal approach.[6, 7, 8, 9, 10, 11, 12, 13] The advantage of MCRs over traditional organic synthesis, where individual bonds are formed in stepwise procedures, is the possibility to obtain complex structures in one single step from readily available starting materials. Beneficial to the overall yield and efficiency of manufacture, long synthetic procedures, involving often inevitable isolation and purification steps of the intermediates, are avoided.[9]

1.1.1 Multicomponent reactions

Multicomponent Reactions (MCRs) are convergent reactions, in which product formation is achieved from a reaction of three or more initial components, including essentially all atoms of the starting components **(Figure 3)**.[9] Generally, product formation proceeds through a cascade of elementary reaction equilibria, followed by an irreversible step. The challenge is to conduct MCRs in such a way that the network of pre-equilibrated reactions channel into the main product in absence of any side products. This is dependent on the

reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of vital importance in connection with the design and discovery of novel MCRs.

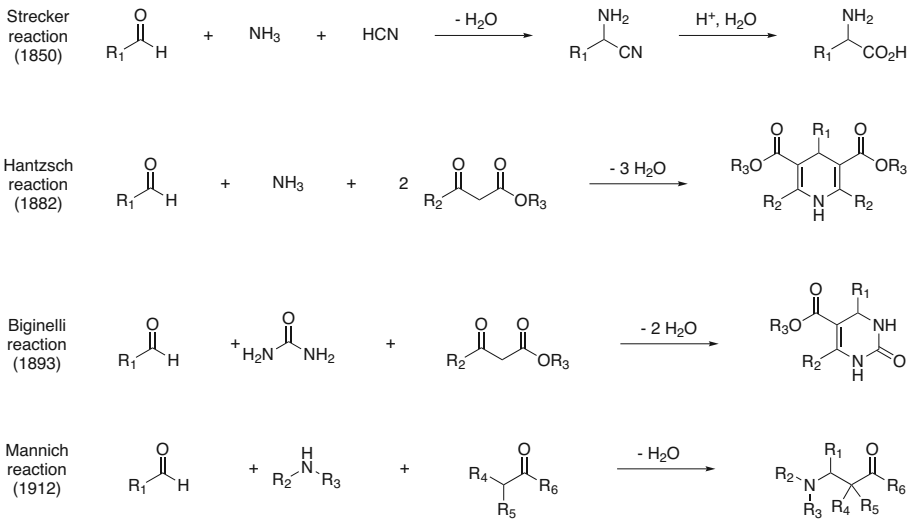
Figure 3 *Formation of a complex product by a multicomponent reaction*



1.1.2 History of MCRs

The first to report the development of a MCR was Strecker in 1850 (**Scheme 1**).[14] In this MCR an aldehyde, ammonia and hydrogen cyanide are combined to give α-amino nitriles, affording α-amino acids upon hydrolysis. In the Hantzsch reaction (1882),[15] hydrogen cyanide is exchanged for a β-ketoester, affording dihydropyridines. In the Biginelli reaction (1892),[16, 17] dihydropyrimidinones are formed from the combination of a β-ketoester with an aldehyde and urea. In the Mannich reaction (1912),[18] a non-enolizable aldehyde is combined with an amine to afford an intermediate Schiff base, affording β-amino carbonyls in a reaction with an α-acidic carbonyl component.

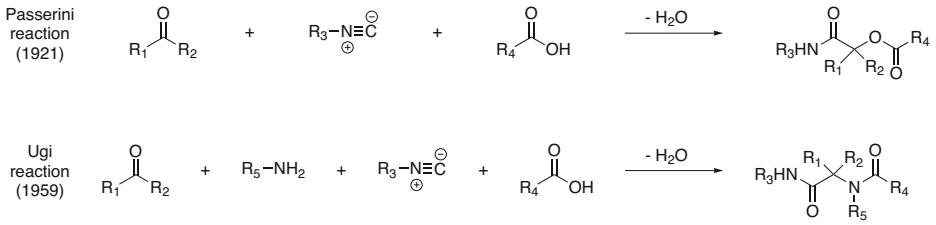
Scheme 1 *Some of the first reported MCRs*



In 1921, Passerini reported a novel MCR utilizing an isocyanide component, exploiting its ambivalent reactivity, both nucleophilic and electrophilic. This was the first report of what presently has become one of the renowned subclasses of MCRs; the isocyanide MCRs (IMCRs)

(**Scheme 2**). An additional famous example of this class is the Ugi reaction (1959).[19] In the Passerini-3CR, the isocyanide is combined with and ketone and a carboxylic acid to afford α-acyloxy amides, whereas, for the Ugi-4CR, an additional amine component is required to give α-acylamino amides.

Scheme 2 *Important isocyanide MCRs (IMCRs)*



1.1.3 MCR Classification

MCRs can be subdivided according to various aspects, such as (1) mechanism, (2) components involved or (3) exploratory power (E_N),[6] of which the latter contemplates the number of variable substituents and hence synthesizable structures. The Strecker reaction is an example of an MCR of low exploratory power: the sole synthesizable structure has only a single variable substituent, whereas the Mannich reaction, allowing decoration on six positions of the target scaffold, features high exploratory power.

Table 1 *Mechanistic assignment of MCRs*

MCR type	General Reaction Equation										
I	A	+	B	↔	C	↔	D	…	O	↔	P
II	A	+	B	↔	C	↔	D	…	O	→	P
III	A	+	B	→	C	→	D	…	O	→	P

Mechanistically, three types of MCRs can be distinguished (**Table 1**). Mechanisms of type I are characterized by a cascade of elementary reaction equilibria where product formation solely depends on thermodynamics. In mechanisms of type II, product formation proceeds through a cascade of elementary reaction equilibria followed by an irreversible step. Finally, the type III mechanism is a sequence of elementary irreversible sub-reactions. Most known MCRs in preparative chemistry, such as the Biginelli, Passerini and Ugi reactions, product formation proceed through a type II mechanism. Strecker and Mannich reactions are examples to proceed through a type I mechanism.[20] In 1960, Hellmann and Opitz[21] revealed that the majority of the MCRs can, alternatively, be divided into two groups; either α-aminoalkylations of nucleophiles (MCRs of mechanistic type I), or reactions of *bis*-functional reactants with intermediates, upon formation of a heterocycle (MCRs of mechanistic type II).

1.2 Imidazolidine-2-thiones, 2H-Imidazoliolium halides and C2-aryl-2-imidazolines

In the remaining part of this chapter, an overview of relevant literature on the relevance and synthetic procedures towards imidazolidine-2-thiones, 2-Imidazolinium halides and C2-aryl-2-imidazolines, the target scaffolds of this thesis is presented.

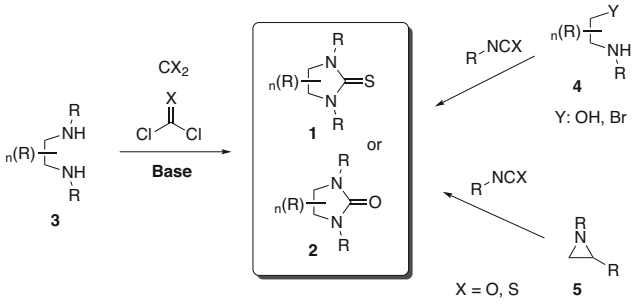
1.3 Imidazolidin-2-ones and imidazolidine-2-thiones

1.3.1 Relevance

Imidazolidine-2-thiones (**1**) and imidazolidin-2-ones (**2**) are important classes of heterocyclic scaffolds (**Scheme 3**). Imidazolidin-2-ones are known as NK1[22] or 5-HT_{2C}[23] receptor antagonists, BACE-1 inhibitors[24] and for their retinoidal activity.[25] Furthermore, imidazolidine-2-ones have been employed as chiral auxiliaries in asymmetric organic synthesis.[26, 27] On the other hand, imidazolidine-2-thiones have been reported as valuable intermediates in the synthesis of medicinally relevant compounds such as antibacterials,[28] and so-called 'nutloids',[29] nutlin[30] like structures which are promising leads for anticancer drugs as a result of their MDM2-p53 PPI inhibitory activity.[31] Furthermore, imidazlolidine-2-thiones are highly appreciated precursors of cyclic constrained guanidines[32, 33, 34, 35] and N-heterocyclic carbene (NHC) ligands, [36, 37, 38, 39, 40] which find widespread application in coordination chemistry and homogeneous catalysis.

1.3.2 Synthesis

Scheme 3 *Strategies for imidzolidine-2-(thi)one synthesis*



Common approaches towards synthesis of imidazolidine-2-(thi)one scaffolds **1** and **2** include condensation reactions of 1,2-diamines **(3)** and either CO_2, CS_2 or (thio)phosgene (analogues) under basic conditions in polar aprotic solvents.[22, 23, 24, 25, 27, 41, 42] Alternative approaches involve cyclization reactions of iso(thio)cyanates with 2-aminoalcohols, 2-bromoalkylamines, **(4)** or aziridines **(5)** (**Scheme 3**).[22, 23, 24, 25, 27, 28, 43, 44] However, due to

the limited commercial availability of diversely substituted derivatives of these 1,2-difunctionalized building blocks (and their precursors), simple and efficient synthesis of structurally diverse analogs of **1** and **2** is not straightforward. An alternative synthetic route to efficiently access diversely functionalized imidazolidine-2-(thi)ones[45] was recently reported by our group based on the Orru-3CR[46, 47, 48, 49] (discussed in further detail in chapter 2). Alternatively, imidazolidine-2-thiones **1** can be synthesized from the corresponding imidazolidin-2-ones **2** by application of Lawesson's reagent.[50, 51]

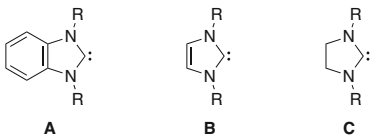
1.4 2*H*-Imidazoliolium halides as NHC precursors

2*H*-imidazolium halides are foremost known as versatile NHC precursors. Therefore, the following parts focus on NHC relevance and synthesis thereof.

1.4.1 Relevance

The distinct properties of NHCs make them suitable for application both as substrates[52, 53] and organocatalysts[54, 55, 56] in organic reactions. Mostly however, their utilization as valuable ligands in coordination chemistry and homogeneous catalysis is reported.[57, 58, 59, 60] A specific strength of these compounds is their universal capability to coordinate to metal centers, ranging from electron-rich transition metals including Pd(0) and Rh(I) to electron-poor main group metal cations (e. g. Be^{2+}) and high oxidation state metals such as Ti(IV), Nb(V), and Re(VII). Furthermore, other attractive features of NHCs include: (1) typically, stronger -donor capacity compared to the strongest phosphane donor ligands is displayed,[61, 62] with the exception of the very sterically demanding adamantyl carbenes, (2) little to no π-back-bonding is exhibited,[62] (3) due to the strong metal-carbenic bond of the NHC complex, tight binding is favored over ligand dissociation, (4) N-bound sterically hindering bulky groups facilitate relatively facile reductive product elimination, and (5) tunable ligand activity by (a) variation of the azole ring: benzimidazole > imidazole > imidazoline (in order of electron donating power) and (b) introduction of remotely situated electronic directing substituents.[63] The introduction of efficient chirality on the NHC is hampered by the basic structure of the carbene. While synthesis and application of some four-,[64, 65] six-[66, 67, 68] and seven-membered[69, 70] heterocycle derived NHCs are described in literature, commonly five-membered derivatives are reported (**Figure 4**), mostly benzimidazole- (**A**), imidazole- (**B**), imidazoline- (**C**) derived 2-ylidenes.

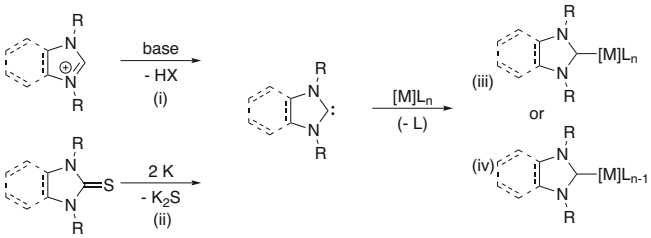
Figure 4 Commonly used five membered NHCs



1.4.2 Synthesis

The popularity of NHCs has resulted in the reports of countless complexes to nearly all metals across the periodic system. Generally they are afforded by **(Scheme 4)**; (i) deprotonation of (benz)imidazoli(ni)um halides by a base (generally non nucleophilic bases such as NaH, KH, LDA, KHDMS, although also the use of KO*t*Bu[48, 49, 71] has been reported) or (ii) reductive desulfurization of imidazoline-2-thiones,[71, 72] followed by (iii) either complexation of the free carbene to a coordinately saturated metal (complex) or (iv) replacement of one (or more) ligands of a metal complex by the free carbene. Generally, synthesis of NHC complexes via the imidazoline-2-thione route is disfavored because of the harsh conditions for desulfurization.

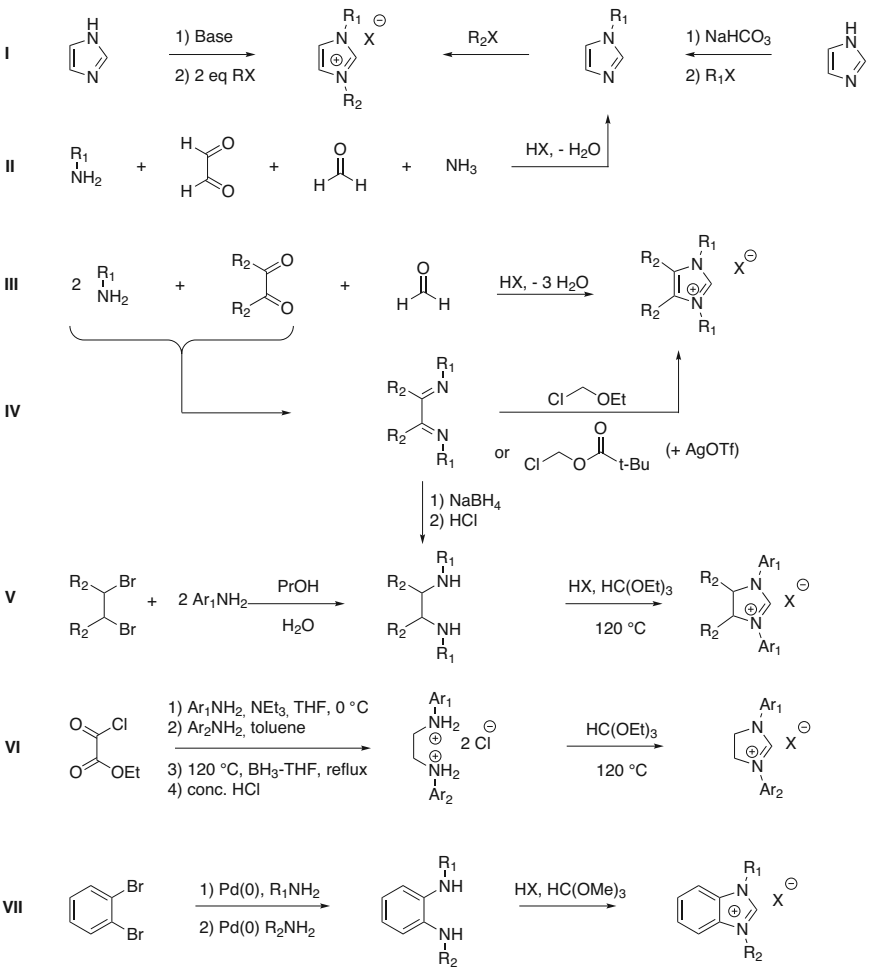
Scheme 4 *Synthesis of NHC-metal complexes from (benz)imidazoli(ni)um salts and imidazilodine-2-thiones*



In the stated strategy the (benz)imidazoli(ni)um species are presented as the pivotal NHC precursor. Not surprisingly since, in many cases, these NHC precursors possess excellent air and moisture stability.[73, 74, 75] Synthesis of the imidazolium scaffold can generally be achieved via two complementary synthetic strategies, (1) by nucleophilic substitution of appropriate electrophiles (generally halides) at the nitrogen atoms of an imidazole scaffold or (2) by construction of the scaffold from scratch via a suitable MCR (**Scheme 5**). Both methods enable either symmetrical or unsymmetrical functionalization of N1 and N3. Symmetrical functionalization by direct substitution (**Scheme 5**, procedure **I**) is achieved through a one-pot synthesis in which the imidazole with one equivalent of base in the presence of two equivalents of halide.[72] Alternatively, unsymmetrical functionalization of N1 and N3 can be afforded in a stepwise procedure.[76] Alternatively, unsymmetrically *N,N'*-functionalized imidazolium salts can be synthesized combining a MCR and a quaternization reaction (**Scheme 5**, procedure **II**).[77] Next to this strategy, a more versatile MCR provides access to a broad range of symmetrically *N,N'*-functionalized imidazolium salts, combining glyoxal derivatives, primary amines and formaldehyde in the presence of a Brønsted acid. (**Scheme 5**, procedure **III**).[78] Although some aryl functionalized imidazoles have been reported,[72] this method is generally applied for the introduction of primary alkyl groups. The initial condensation 1,2-diimine product, can be isolated before cyclization, which allows, via alternative ring-closing reactions utilizing either (chloromethoxy)ethane or chloromethyl pivalate in presence of AgOTf, the preparation of imidazolium salts with unusual or sterically very demanding nitrogen substituents (**Scheme 5**, procedure **IV**).[72] Furthermore, symmetrically functionalized 2-imidazolinium halides can be afforded by a cyclocondensation of 1,2-diamines with triethyl orthoformate (**Scheme 5**, procedure **V**).[79]

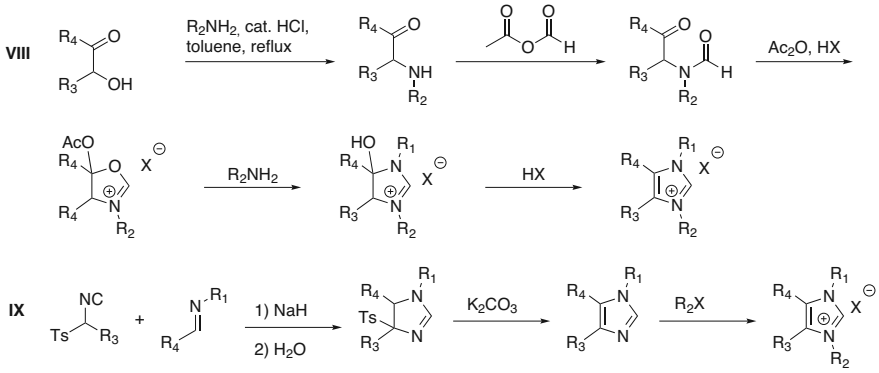
Generally, symmetrically functionalized 1,2-diamines can be afforded by reduction of 1,2-diimines with $NaBH_4$ or by amination of 1,2-dibromides. Alternatively, from ethyl oxalyl chloride, unsymmetrically *N,N'*-functionalized 2-imidazolinium halides can be synthesized by sequential introduction of the N-substituents as shown (**Scheme 5**, procedure **VI**). The initial 1,2-diamide is reduced to the unsymmetrical 1,2-diamine and subsequently acidified, after which the 2-imidazolinium halide is afforded by a reaction with triethyl orthoformate. Benzimidazolium halides can be obtained by two sequential Buchwald-Hartwig aminations to give 1,2-diaminobenzenes, followed by a reaction with trimethyl orthoformate (**Scheme 5**, procedure **VII**).[80] This procedure allows either symmetrical or unsymmetrical *N,N'*-functionalization.[81]

Scheme 5 *Synthesis of (benz)imidazoli(ni)um halides*



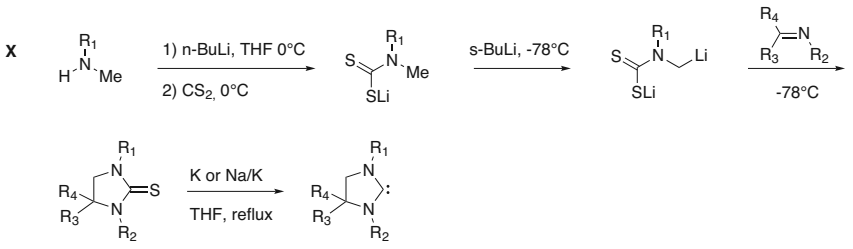
The procedures **I** – **VII** (**Scheme 5**) have proven to be powerful methods to access many different types of (un)symmetrical *N*,*N*'-functionalized (benz)imidazoli(ni)um halides. However, these approaches do not allow functionalization of the NHC carbon backbone. In the recent past, several procedures to address this problem were reported, for example, Furstner *et al.* described a procedure to access imidazolium halides containing diverse (backbone) substitution patterns (**Scheme 6**, procedure **VIII**).[82] In this procedure, starting from an α-hydroxyketone, a substituted oxazolium salt was synthesized followed by a heterocycle inter-conversion to afford the desired imidazolium halide scaffold containing up to four decorative groups. Alternatively, imidazolium halides can be afforded staring from tosylmethyl isocyanide (TosMIC) (**Scheme 6**, procedure **IX**).[83, 84] In this MCR, a combination of these α-acidic isocyanide components with *in situ* generated imines affords trisubstituted imidazoles. Subsequent alkylation of N3 affords the fully decorated imidazolium halide as the NHC precursor.

Scheme 6 *Sequential synthesis of unsymmetrical functionalized imidazolium halides*



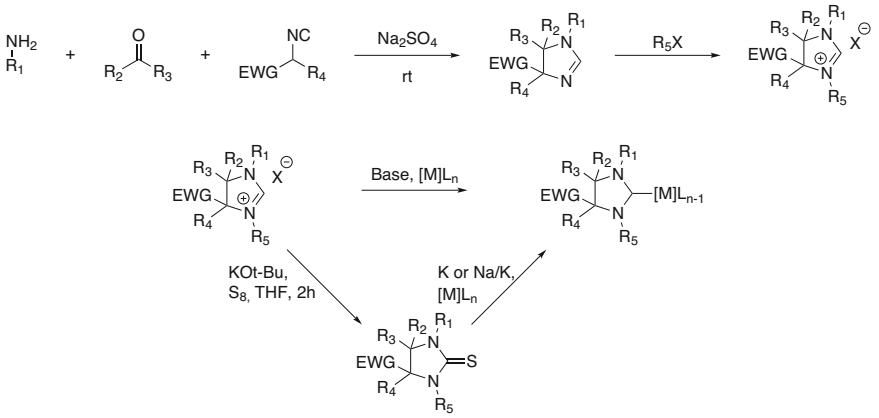
Contrary to the common 'azolium routes', a procedure towards 2-imidazoline derived NHC precursors via imidazoline-2-thiones was developed by Hahn *et al.* (**Scheme 7**, procedure **X**).[85] This three-step, one-pot sequence, allows control over both N-substituents and the C4 backbone substituents. Final treatment of the imidazoline-2-thione with Na/K affords the corresponding free NHC.

Scheme 7 *Synthesis of NHCs via imidazolidine-2-thiones*



As may become clear from this summary, the Achilles heel of wide-spread and full scale application of NHCs in catalysis, is the development of general synthetic protocols thereof. Although the methods presented above provide access to a broad range of NHC precursors, their synthetic potential is limited for their lengthy sequences and limited staring material flexibility. Moreover, methods for (unsymmetrical) backbone functionalization are scarce, which is a unfortunate since recent research on the use of NHCs in ruthenium-based olefin metathesis showed that both substitution on N1 and N2, and NHC-backbone substitution can be important for efficient reaction progress.[86]

Scheme 8 *Orru-3CR based approaches towards 2-imidazoline type NHCs*



In the recent past, based on the Orru-3CR,[46, 47, 87, 88] we have reported a simple, straightforward and inexpensive route towards two types of NHC precursors: (i) imidazolidine-2-thiones[29, 45, 71] and (ii) 2-imidazolinium halides **(Scheme 8)**.[48, 71] These strategies not only provide unsymmetrical *N,N'*-functionalization, they also allow for 'full' decorative control of the carbon backbone. This MCR approach allows building a vast variety of NHC precursors from scratch virtually instantly, facilitating a combinatorial approach for fast ligand optimization in hetero- and/or homogeneous catalysis.

1.5 The Orru-3CR in an MCR-PM combination

Although MCRs, and the Orru-3CR in particular, can be great tools for ligand optimization, it still can be like searching for a needle in a haystack, as factors contributing to ligand activity and effectivity are not always obvious. The use of computational power in e.g. predictive modeling (PM) can also be a great tool in ligand optimization studies. These PM methods can teach "catalytic intuition" to a computer[89] in order to help solve problems in catalysis. Virtual catalysts are synthesized in silico and their characteristics and performance predicted. The cycle is then closed by subsequent experimental validation. Such a PM approach may thus select active regions in the catalyst space,[90] provided that the following three conditions are met: (1) availability of sufficient experimental data to build

a predictive model, (2) accessibility to a large number of diverse ligand-metal complexes, and (3) availability of a robust model validation procedure. Normally experimental validation is the cycle's weak spot, while, contrary to experimental synthesis, generation of large virtual libraries in silico is relatively easy. We believe and have shown[49] that a combination of experimental MCR syntheses and PM provides a powerful tool for ligand optimization in catalysis studies; MCRs provide facile access to a vast variety of potential ligands, each of which can be synthesized in high yield and selectivity, whereas predictive modeling avoids the pursuit of "dead ends" highlighting "good regions" in the catalyst space. In PM, descriptor models can give high correlations even in situations where structure/activity relationships are elusive. Moreover, the combined 'MCR – PM' approach allows facile simultaneous variation of the scaffolds decoration, speeding up the process of catalyst optimization. Recently, we have published such an 'MCR – PM' approach towards furfural hydrogenation catalysts.[49]

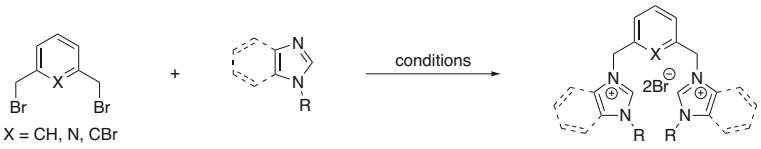
1.6 Saturated NHCs vs. unsaturated NHCs

The use of saturated imidazole based NHCs clearly dominates the literature over their unsaturated 2-imidazoline derived counterparts, most likely due to the facile synthetic access to their imidazolium halide precursors. However, it has been shown that saturated NHCs can be better metal binders. For example, in a study of the Suzuki-Miyaura coupling reaction;[91] a crossover experiment demonstrated dissociation of an unsaturated NHC ligand from the active bis-carbene palladium complexes, which was not observed for the corresponding saturated NHCs. Consequently, in this case, the latter NHC ligands appear to be better pre-catalysts.

1.6.1 Bis-NHCs

Apart from monodentate NHC ligands, a large number bi-, tri-, and tetradentate NHC donor-functionalized or pincer-type complexes, have been prepared and utilized as homogeneous catalysts, often exhibiting an increased catalytic activity. Particularly, chelated bis-NHC complexes[92, 93, 94, 95] have gained popularity over their mono-NHC counterparts for their outstanding stability even under harsh reaction conditions. Although mostly reported as ligands in Pd(0) complexes,[96] also a few analogous Pt,[97, 98] Ni,[99, 100] Rh[101] and Ru[102] complexes have been reported.

Figure 5 *Synthesis of 2H-(benz)imidazole based, chelating or pincer type bi- or tri-dentate bis NHCs*

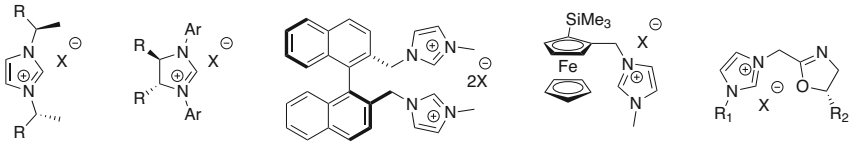


Synthesis of the bis-NHC precursors proceeds through bis-alkylation of lutidinyl- or xylenyl dibromides to (benz)imidazoles (**Figure 5**).[103, 104, 105] Surprisingly, only a handful of 2-imidazoline derived bis-NHCs of this kind have been reported, although even stronger binding and as a direct result more stable complexes can be expected for these bis-NHCs.

1.6.2 Chiral NHCs

Just as chiral phosphanes, NHCs can act as stereo-directing ligands in asymmetric synthesis. Generally chiral NHC ligands (or their precursors) can be classified in five major families according to the location or type of chirality; NHCs containing (1) chiral N-substituents,[106, 107] (2) chiral elements within the NHC backbone,[100, 107, 108] (3) an element of axial chirality,[109, 110] (4) a form of planar chirality,[111, 112] (5) chiral oxazoline units **(Figure 6)**.[113, 114] However, the development of efficient chiral NHC ligands for asymmetric catalysis remains a major challenge and reports hereof are scarce.

Figure 6 *Major families of chiral NHCs*

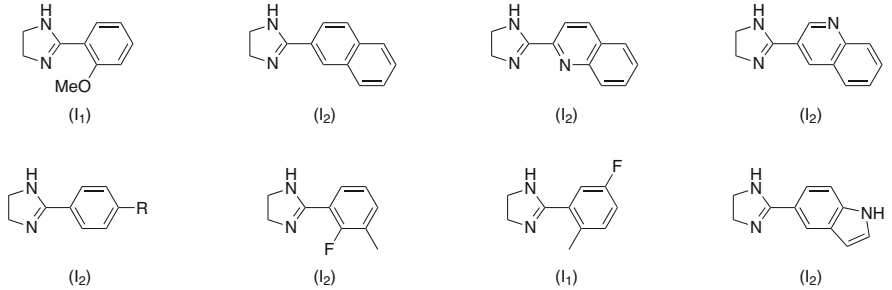


(1) (2) (3) (4) (5)

1.6.3 C2-aryalated 2-imidazolines

1.6.3.1 Relevance

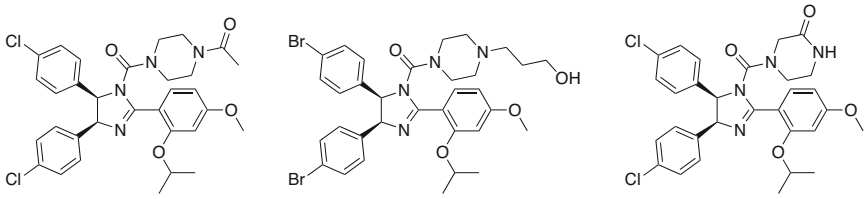
Figure 7 *Some relevant 2-aryl-2-imidazolines and preferred site of binding*



R = Me, n-Pr, i-Pr, Bu, t-Bu, OMe, OPh, SMe, CF_3, OCF_3

Since Bousquet *et al.* discovered the imidazoline binding sites (IBS) nearly three decades ago,[115] these receptors have been paid a great deal of attention.[116, 117, 118, 119] Although their exact structure remains unknown, based on their binding affinity for different radioligands, three subtypes, I_1, I_2 and I_3, have been characterized. While the I_1 receptor mediates the sympatho-inhibitory actions of 2-imidazolines to lower blood pressure, the I_2 receptor functions as an allosteric binding site of monoamine oxidase and is involved in pain modulation and neuroprotection. Finally, the I_3 receptor is involved in insulin secretion regulation from pancreatic beta cells.[116, 120] In **figure 7**, some C2-aryl-2-imidazolines and their receptor specificities are depicted.

Figure 8 *Nutlins*



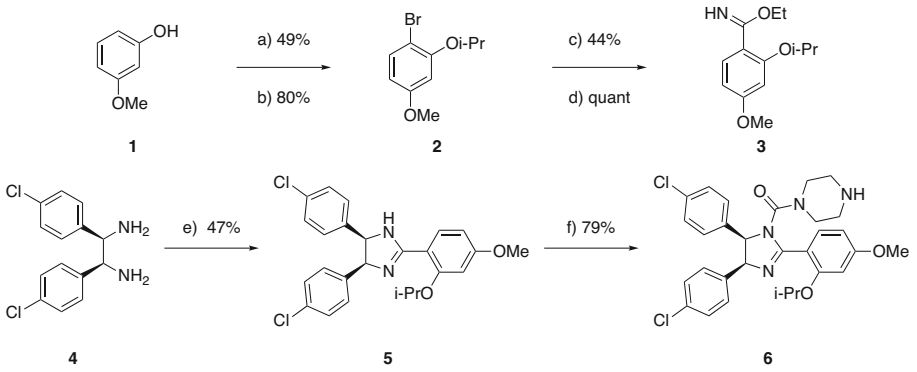
Nutlin-1 **Nutlin-2** **Nutlin-3**

Furthermore, there are so-called nutloids,[29] which are promising leads for anticancer drugs as a result of their MDM2-p53 PPI inhibitory activity (**Figure 8**).[30] For this reason Chapter 4 focuses on the synthesis of such compounds. The next part summarizes the various approaches to the scaffolds.

1.6.3.2 Synthesis

C2-aryl-2-imidazoline scaffolds have been synthesized by condensation of 1,2-diamines and imidates **(Scheme 9)**.[121] First, condensation partner of diamine **4**, benzimidate **3**, must be synthesized. Bromination of **1** followed by subsequent alkylation gives **2**. A palladium catalyzed cyanation reaction introduces a nitrile functionality from which benzimidate **3** is afforded by subsequent treatment with HCl in EtOH. Next, 2-imidazoline **5** is obtained by the condensation of diamine **4** and benzimidate **3** under basic conditions in EtOH. Subsequent treatment of **5** with phosgene and piperazine followed by acidic work up affords **6** in a 6% overall yield. Given this rather lengthy multi-step synthetic approach, efficient synthesis of structurally diverse libraries is not straightforward. Additionally, the method lacks flexibility through the limited commercial availability of 1,2-aryl-1,2-diamines. Moreover, those that are available are mostly symmetrically substituted. An additional weak point of this strategy is that it always affords *rac*-**6** from 2-imidazoline **5**, due to the latter's similar reactivity of N1 and N3 under basic conditions, decimating the overall yield of the desired isomer.

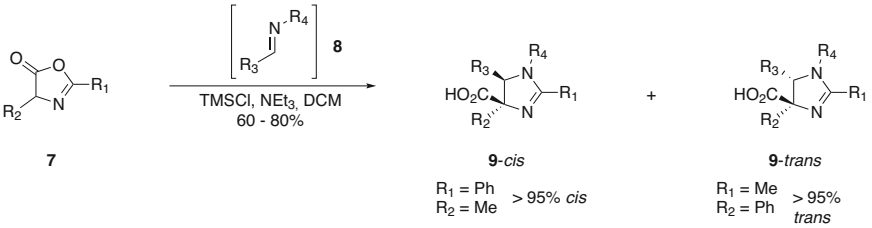
Scheme 9 *Nutlin synthesis from diamines*



a) NBS, THF; b) Cs_2CO_3, iPrOH; c) $Zn(CN)_2$, $Pd(PPh_3)_4$; d) HCl EtOH; e) **3**, NEt_3, EtOH; f) (1) $COCl_2$, NEt_3, DCM (2) Piperazine, DCM (3) HCl, Et_2O

Alternatively, synthesis via TMSCl mediated 1,3-dipolar cycloadditions of oxazol-5-ones with *in situ* formed imines under basic conditions have been reported (**Scheme 10**).[122, 123, 124, 125, 126] The diastereoselectivity in this reaction is directed by respective substituents R_1 and R_2 of oxazol-5-one **7**. However, while nutloids require *cis*-oriented hydrophobic C4 and C5 backbone substituents in combination with an aromatic group on C2, this method majorly yields (**9**-cis), in which the hydrophobic groups on C4 and C5 are *trans*-oriented.

Scheme 10 *Nutloid synthesis from oxazol-5-ones*



Recently, we have reported an approach towards nutloids, nutlin like structures, via Liebeskind-Srogl couplings of imidazolidine-2-thiones with arylboronic acids[29] based on the versatile Orru-3CR (see Chapter 3) towards 2-imidazolines (**Figure 9**).[46, 47]

Figure 9 *The Orru-3CR based sequence towards C2-arylated imidazolines (nutloids)*

Four structures synthesized by this method exhibited MDM2 binding in the micro molar range without precipitation in a NMR-based biological screening by the group of prof. Dömling (unpublished results), illustrating the potential of the method.

1.7 Scope of this thesis

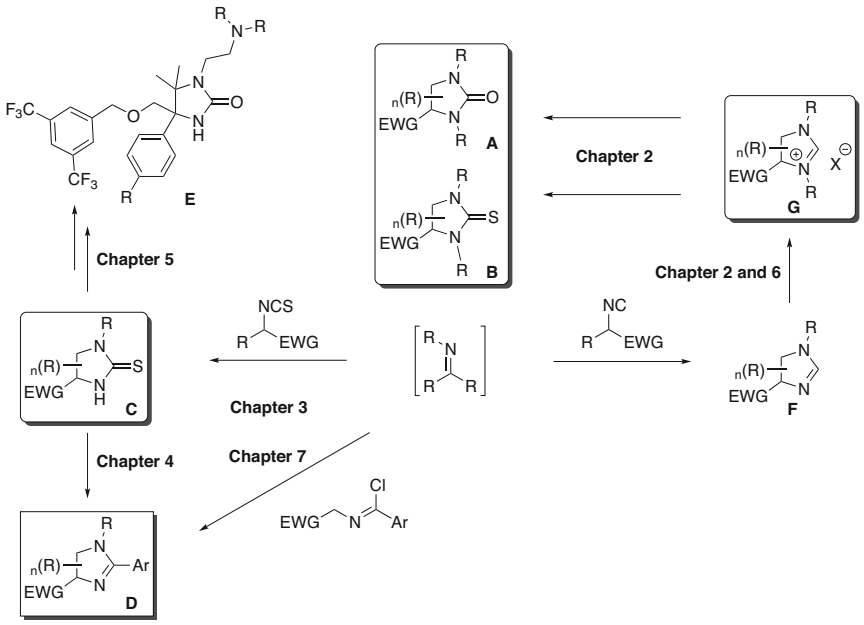
This thesis deals with synthesis of both 2-imidazolidines and C2-functionalized 2-imidazolines, of which all strategies were based on MCRs of *in situ* formed imines and α-acidic components **(Scheme 11)**.

In **Chapter 2**, respective selective C2-oxidation and C2-thionation protocols of 2-imidazolinium halides (**G**) towards imidazolidin-2-ones (**A**) and imidazolidine-2-thiones (**B**) are discussed, of which the synthetic sequence is based on the Orru-3CR.[46, 47, 88]

In **chapter 3** multicomponent synthesis of imidazolidine-2-thiones (**C**), utilizing α-acidic isothiocyanates, is presented. The research on this topic includes: (1) optimization of the reaction conditions, (2) library synthesis, (3) study the scope of the α-acidic isothiocyanate component, (3) experimental and computational mechanistic investigations.

In **chapter 4**, synthesis of C2-aryl-2-imidazolines (**D**) through Liebeskind-Srogl[127] reactions of arylboronic acids with imidazolidine-2-thions is presented. This chapter was directed towards synthesis of nutloids, potential MDM2-p53 PPI inhibitors.[30] The chapter commences with a comprehensive overview of this interaction.

Scheme 11 *Multicomponent approaches towards both C2-functionalized 2-imidazolidines and 2-imidazolines*



In **chapter 5** synthetic investigations towards synthesis of novel NK1 receptor antagonists **(E)**[22, 128] is discussed, of which the synthetic strategy was based on the α-acidic

isothiocyanate MCR. The chapter commences with a comprehensive overview of relevant NK1 literature.

Chapter 6 deals with the synthesis of imidazolium halides (**E**) from 2-imidazolines (**F**), contrary to chapter 3, this work was focused towards synthesis of NHC precursors.

Finally, in **chapter 7**, explorative investigations towards a single-step multicomponent synthesis of C2-aryl-2-imidazolines (**D**) is discussed. The chapter commences with a comprehensive overview of relevant 1,3-dipolar cycloaddition literature.

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