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Institute of Condensed Matter and Nanosciences
Molecules, Solids and Reactivity
Prof. R. Robiette

Development of a general and regioselective N-alkylation strategy of azoles and synthesis of original imidazole derivatives of chemical and biological interest

Dissertation présentée en vue de l'obtention du grade de docteur en sciences

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During this thesis the following publications were written:

Synthesis and Biological Evaluation of Novel Imidazole-Containing Macrocycles
Nshimyumukiza, P.; Van Den Berge, E.; Delest, B.; Mijatovic, T.; Kiss, R.; Marchand-Brynaert, J.; Robiette R.*
Tetrahedron **2010**, *66*, 4515-4520.

Planar Chirality of Imidazole-Containing Macrocycles - Understanding and Tuning Atropisomerism
Van Den Berge, E.; Pospíšil, J.; Tran, T.-V.; Collard, L.; Robiette R.*
Eur. J. Org. Chem. ***2011***, *6649-6655.*

Comprendre les réactions pour mieux les développer et les utiliser
Robiette, R.;* Caruano, J.; Rousseau, O.; Tran, T.-V.; Van Den Berge, E.
Chimie Nouvelle ***2013***, *113, 18-20.*

New 5-aryl-1H-imidazoles display in vitro antitumor activity against apoptosis-resistant cancer models, including melanomas, through mitochondrial targeting
Mathieu,V.;* Van Den Berge, E.; Ceusters, J.; Konopka, T.; Cops, A.; Bruyère, C.; Pirker, C.; Berger, W.; Trieu-Van, T.; Serteyn, D.; Kiss, R.; Robiette, R.*
J. Med. Chem. ***2013***, *56, 6626-6637.*

Synthesis and pharmacological evaluation of new 5-aryl-1H-imidazoles derivatives
Van Den Berge, E.; Robiette, R.
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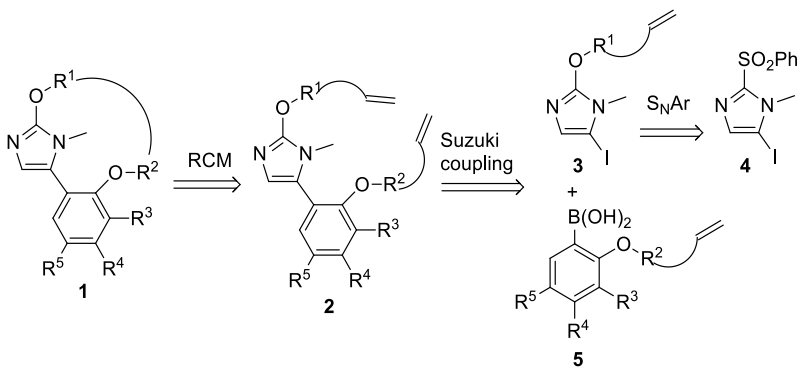
Development of a regioselective N-methylation of (benz)imidazoles providing the more sterically hindered isomer
Van Den Berge, E.; Robiette, R.
J. Org. Chem. ***2013****, submitted.*

Abstract

Imidazoles are key structures in medicinal chemistry. Numbers of imidazole derivatives have found applications in the treatment of parasites, infectious diseases, cancer, metabolic, cardiovascular, and CNS disorders as well as analgesic and inflammatory conditions.

One objective of our work is the synthesis and biological evaluation of a new family of macrocycles containing a 5-aryl-1*H*-imidazole motif. The envisioned structures **1** consist in large rings incorporating this motif by connection at C2 and *ortho*-aryl positions. Our strategy for the synthesis of these macrocycles begins with the regioselective formation of a key intermediate **4** using a methodology developed in our laboratory. Next, formation of the macrocycle is based on three steps: a S_NAr, a Suzuki coupling and a ring closing metathesis (RCM) reaction. Structural variations were introduced by R^1-R^5 groups. We studied the possibility of forming the corresponding 2-aminoimidazole derivatives (instead of 2-alkoxyimidazole).

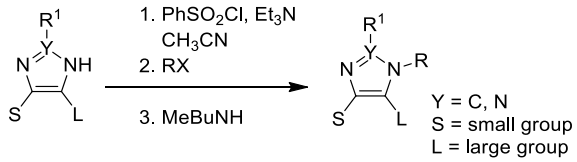
We found that our compounds possess cytostatic effects against cancers cells, including cell-lineages which are resistant to pro-apoptotic stimuli. The large panel of synthesized compounds allowed drawing some conclusions concerning the structure-activity relationship.



We also investigated the chiral properties of macrocycles **1** and showed that due to their cyclophane-type structure, depending on the ring size, some of these compounds are planar chiral molecules.

Abstract

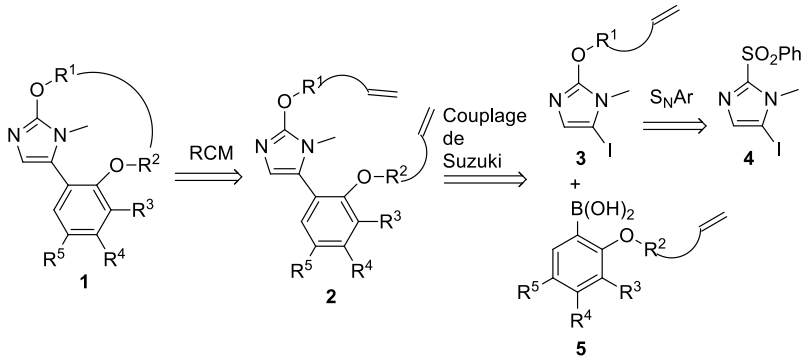
In a second part, we have developed a regioselective *N*-alkylation of azoles providing the more sterically hindered isomer. Our methodology consists in a three-step one-pot process: protection of the parent azole, regioselective *N*-alkylation and finally deprotection.



Les imidazoles sont des structures clé en chimie médicinale. De nombreux dérivés d'imidazole sont utilisés pour le traitement de parasites, des maladies infectieuses, cardiovasculaires, du cancer, du métabolisme ainsi que pour les désordres du SNC mais aussi comme analgésique et anti-inflammatoire.

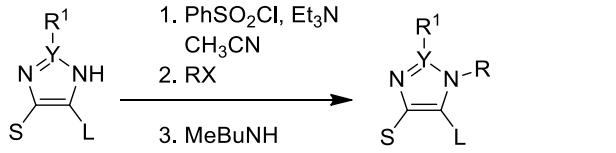
Un des objectifs de cette thèse est la synthèse et l'évaluation biologique d'une nouvelle famille de macrocycles possédant un motif 5-aryl-1*H*-imidazole. Les stuctures envisagées **1** consistent en l'insertion d'un grand cycle incorporant ce motif par la connection C2 de l'imidazole avec l'*ortho*-aryl. Notre stratégie pour la synthèse de ces macrocycles débute par la formation régiosélective de l'intermédiaire clé **4** utilisant une méthodologie développée au sein de notre laboratoire. Ensuite la formation du macrocycle est basée sur trois étapes: la S_NAr, un couplage de Suzuki et une fermeture de cycle par métathèse. Les variations structurales ont été introduites via les groupements R^1-R^5. Nous avons aussi étudié la possibilité de former le dérivé 2-aminoimidazole correpondant (à la place du 2-alcoxyimidazole).

Nous avons trouvé que nos composés possédaient des effets cytostatiques envers des cellules cancéreuses incluant les cellules résistantes aux stimuli pro-apoptotiques. Le large panel de composés synthétisés nous a permis de tirer quelques conclusions concernant l'étude de la relation structure-activité.



Nous avons aussi investigué les propriétés chirales de nos macrocycles **1** et montré que par leur structure de type cyclophane, dépendant de la taille du cycle, quelques-uns de ces composés sont des molécules avec une chiralité planaire.

Dans la seconde partie, nous avons développé une *N*-alkylation régiosélective d'azoles fournissant l'isomère le plus encombré. Notre méthode consiste en un procédé en trois étapes one-pot: la protection de l'azole, l'alkylation régiosélective et finalement la déprotection.



Y = C, N
S = petit groupement
L = groupement volumineux

Abbreviations

Ac	acetate
acac	acetylacetone
AcOEt	ethyl acetate
Alk.	alkyl
APCI	atmospheric pressure chemical ionisation
ATP	adenosine triphosphate
ADP	adenosine diphosphate
BINAP	2,2'-bis(diphénylphosphino)-1,1'-binaphthyl
Boc	N-*tert*-butoxycarbonyle
Bn	benzyl
bs	broad signal
BuLi	butyllithium
CAN	ceric ammonium nitrate
CCC	compare correlation coefficients
cod	1,5-cyclooctadiene
CuAAC	copper-catalyzed azide-alkyne cycloaddition
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBBA	5,5-dibromobarbituric acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCPB	2-(dicyclohexylphosphanyl)bipheny
DIPEA	*N*,*N*-diisopropylethylamine
DMAS	*N*,*N*-dimethylsulfamoyl

Abbreviations

DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DME	1,2-dimethoxyethane
DMGs	directed metalation groups
DMPM	3,4-dimethoxybenzyl
dmso	dimethyl sulfoxide
DoM	directed *ortho* metalation reaction
dppf	1,1'-Bis-diphenylphosphino-ferrocene
EA	ethyl acetate
EOM	ethoxymethyl
equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
GI	first generation of Grubbs' catalyst
GII	second generation of Grubbs' catalyst
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IC_{50}	half maximal inhibitory concentration
ILs	ionic liquids
IR	infrared
LDA	lithium di*iso*propylamide
m	multiplet
MCRs	multi component reactions
Me	methyl

Mes	mesyl
MIDA	*N*-methyliminodiacetic acid
MOM	methoxymethylether
MS	mass spectrometry
M.S.	molecular sieve
MTT test	colorimetric assay using (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
MW	micro-wave
NBS	*N*-bromosuccinimide
NCI	national cancer institute
n.d.	not determined
NBP	*N*-butylpyrrolidinone
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOE_{diff}	nuclear overhauser enhancements difference
OAc	acetate
Oct	octanoate
OTf	trifluoromethane sulfonate
PEG	polyethylene glycol
PG	protecting group
Pi	inorganic phosphate
piv	pivalate
PMB	*para*-methoxybenzyl
ppm	part per million
Pr	propyl
PTSA	*para*-toluenesulfonic acid
Py	pyridine
RCM	ring closure metathesis

Abbreviations

Regio.	regioselectivity
rt	room temperature
SAR	structure activity relationship
S_NAr	aromatic nucleophilic substitution
$S_{RN}Ar$	aromatic radicalar nucleophilic substitution
t	triplet
t	ter
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*N*-butylammonium fluoride
TBDMS	*tert*butylsimethylsilyl
TBS	*tert*butylsimethylsilyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TIPS	triisopropylsilyl ether
TLC	thin layer chromatography
TMEDA	*tetra*-methylethylenediamine
TMS	trimethylsilyl
Tos, Ts	tosyl
TosMIC	tosylmethyl isocyanide
Tr	trityl
XPhos	2-Dicyclohexylphosphino-2′,4’,6′-triisopropylbiphenyl
))))	ultrasound

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Chapter 1 - Introduction: The beginning of the imidazole story…

1. IMIDAZOLES

1.1. Definition

Imidazole (1,3-diaza-2,4-cyclopentadiene or 1,3-diazole) is an aromatic five-membered ring system with 3 carbon atoms and 2 nitrogen atoms in position 1 and 3. It contains one pyrrole type and one pyridine type N-atom. The former contributes to two electrons to the π-system while the nonbonding electron pair of the pyridine N-atom is perpendicular to, and thus not involved in, the aromatic system (Figure 1).

This amphoteric structure offers contradictory reactivities. Imidazole is a moderate Lewis base, the pK_a value of its conjugated acid is 6.95. It also contains a weak acidic N-H, its pK_a value is 14.52, that can be deprotonated by moderately strong bases.

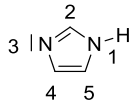


Figure 1. Imidazole nucleus.

Electrophilic substitution is possible in position 4 and 5 while position 2 is much less nucleophilic. Nucleophilic substitution can occur in position 2 but is confined largely to displacements of an electro-withdrawing group. The lone pair of N3 has a nucleophilic character and can react with an electophile (see chapter 5).

1.2. Imidazoles in chemistry

Due to their nucleophilic and basic properties as well as their coordination ability, imidazole derivatives have found various applications. Numerous imidazole compounds are known to be good organocatalysts (see chapter 3), act as ligands[1] or be precursors of ionic liquids.

Concerning the use of imidazole as a ligand, the N3 atom is easily coordinated to Lewis acids or metallic ions, whereas the substitution of C–H or N–H protons allows the synthesis of complex derivatives.

One example is the coordination of silver metal by nitroimidazole. Rowan et al.[2] have developed new metal-based antimicrobial complexes with silver-containing agents. Reaction of $MeNO_2$imidazole with $AgClO_4$ in a 2:1 molar ratio gives $[Ag(MeNO_2imH)_2]ClO_4.3H_2O$ in good yield (Figure 2). This Ag(I) monohydrate complex was crystallographically characterized. The metal ion lies on a centre of

symmetry and the perchlorate anion rests on a mirror plane. The metal ion is bonded to the imine N atoms (adjacent to the nitro group) of two diagonally opposed $MeNO_2$imidazole ligands. There are also long intramolecular contacts between one nitro O atom on each $MeNO_2$imidazole ligand and the metal. The $[Ag(MeNO_2imH)_2]^+$ cations are linked into two-dimensional sheets via shorter ONO–Ag–ONO axial interactions.

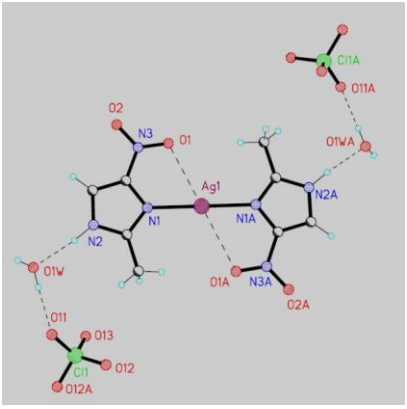


Figure 2. Structure of $[Ag(MeNO_2imH)_2]ClO_4.H_2O$.

Ionic liquids (ILs), currently defined as salts with melting points below 100°C, have been known for almost a century. The synthesis of low melting point imidazolium-based salts ionic liquids was reported by Wilkes et al.[3] (Figure 3).

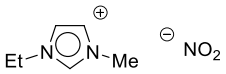


Figure 3. Ionic liquid based on EtMe[imidazole].

These new ionic liquids have unique and useful properties including high thermal stabilities and very low volatilities, which improve their reusability. When used as solvents, ionic liquids were found to produce unique selectivities and reactivities, so become promising alternatives to volatile organic solvents. Moreover, the imidazolium cation is frequently used because it is known to produce salts with low melting points, favorable viscosities, and high thermal stabilities as compared to other ILs. Also chiral ionic liquids (CILs) have been developed due to their potential chiral discrimination capabilities.[4]

1.3. Imidazoles in medicinal chemistry

Imidazole nucleus can be found in numerous biologically active compounds naturally occurring or synthetic ones. Imidazole plays a critical role in many

structures within the human body such as the essential amino acid histidine, histamine, purine derivatives present in DNA (adenine, guanine and xanthine) and in several other biomolecules (Figure 4).[5]

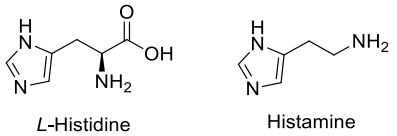


Figure 4. Examples of biomolecules including an imidazole ring.

In nature, this heterocycle is included in alkaloids from marine sponges such as *Stylotella aurantium* (sponge-derived palau'amine) and *Leucetta chagosensis* (sponge-derived naamine) (Figure 5). Several of these alkaloids were reported to exhibit pharmacologically interesting activities, including antibiotic activity, cytotoxicity, antifungal, antitumor, and immunosuppressive activities,…[6] These natural occurring molecules are attractive targets for total synthesis and development of new methods.[7]

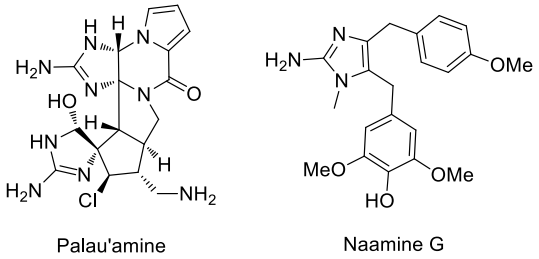


Figure 5. Imidazole alkaloids.

Imidazole's insertion is an important synthetic strategy in drug discovery and has broad applications in clinical medicine. Imidazole is present in the antifungal derivative, Ketoconazole (Figure 6).[8] This antifungal imidazole was synthesized and developed by Janssen Pharmaceutica in 1977. It is considered to be the "gold standard" among the azole derivative antifungal drugs. Ketoconazole is indicated as a drug of choice for different systemic fungal infections. It interferes with the fungal synthesis of ergosterol, a constituent of fungal cell membranes.

Another imidazole-based compound is involved in the treatment of cancer. *Ras* plays a major role in the intracellular signaling pathways that control cancer proliferation. Activation of Ras proteins requires post-translational farnesylation, a process that attaches a 15-carbon (farnesyl moiety), to cysteine residues and enables the protein to be membrane-associated (important for the cellular signaling function). As a result, there has been recently a considerable interest in searching for

inhibitors of farnesyltransferase (FTase). A series of macrocyclic 3-aminopyrrolidinone farnesyltransferase inhibitors (FTIs) have been synthesized (Figure 6).[9]

The imidazole motif was also found in razaxaban which is a Factor Xa inhibitor. The factor Xa is a key serine protease in the coagulation cascade and is a promising target enzyme for the design of new therapeutic agents for the treatment and prevention of arterial and venous thrombosis (Figure 6).[10]

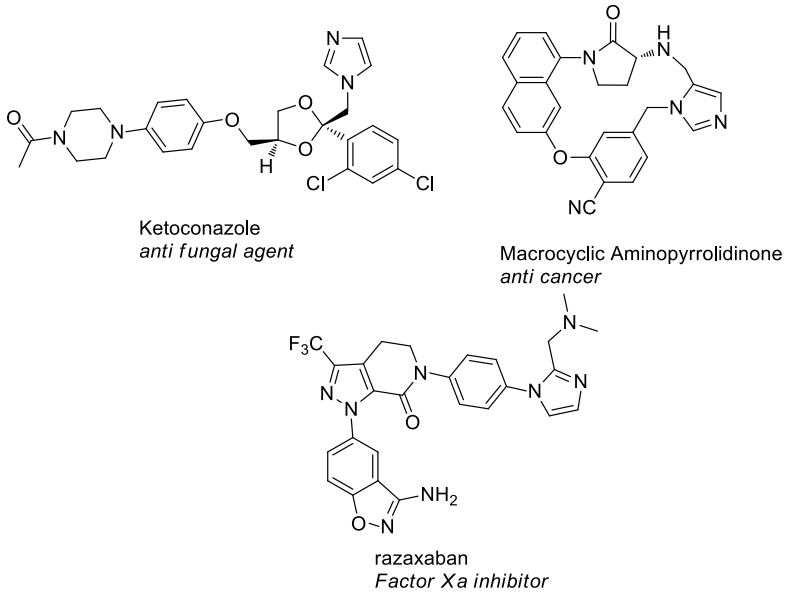


Figure 6. Imidazoles in medicinal chemistry.

Imidazole derivatives are also used to treat inflammatory disorders. A therapeutic target for the treatment of this defense reaction is the mitogen-activated protein kinase p38 (MAPK). This serine/threonine kinase is responsible for the cytokines'production. And elevated levels of proinflammatory cytokines are associated with several autoimmune diseases such as rheumatoid arthritis, osteoarthritis,… Pyridinylimidazoles (SB203580) are potent inhibitors of p38-MAPK by competing with ATP for binding to the ATP pocket (Figure 7).[11]

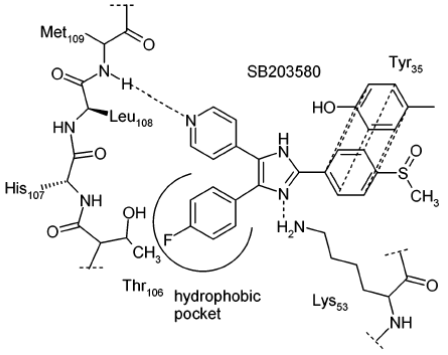
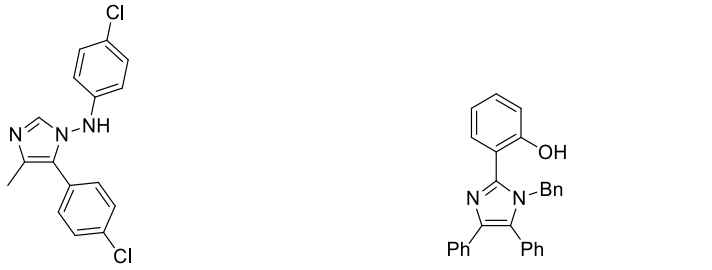


Figure 7. Active site interactions between SB203580 and p38-MAPK. (‘‘‘‘= interactions, single dotted line: Hydrogen bond; multiple doted lines: π-π interactions between the 2 cycles)

5-aryl-1*H*-imidazole motif is also present in anti HIV drugs or in compounds possessing analgesic activities. Indeed, acquired immunodeficiency syndrome (AIDS) is the most fatal disorder for which no complete and successful chemotherapy has been developed so far. So an effort has been made to develop new drug’s family such as the 5-phenyl-1-phenylamino-1*H*-imidazole derivatives (Figure 8).[12] While 1-benzyl-2-substituted-4,5–diphenyl-1*H*-imidazoles showed moderate to good analgesic activities ranged not far from morphine. Moreover they are also found to have a low lethal toxicity.[13]



5-phenyl-1-phenylamino-1*H*-imidazole
anti HIV

1-benzyl-2-substituted-4,5-diphenyl-1*H*-imidazole
analgesic activity

Figure 8. Biological activities of 5-aryl-1*H*-imidazoles.

Imidazole derivatives are also present in many other areas of pharmaceutical chemistry; carbonic anhydrase activators, anti-coagulants, carboxypeptidase A inhibitors, heme oxygenase inhibitors, NOs inhibitors, modulators of calcium-activated potassium channel, 5-LOX inhibitors, TRPV-1 antagonists, COX-2 inhibitors, anti-bacterial agents, anti-viral agents, anti-tubercular agents, anti-

malarial agents, anti-diabetic agents, anti-obesity agents, neurogenerative disorders, anti-aging agents,…[5,14]

In conclusion, the imidazole core is a heterocycle with high potential for developing new drugs for the treatment of infectious diseases, cancer, metabolic, cardiovascular, and CNS disorders as well as analgesic and inflammatory conditions. Knowing this high medicinal potential of the imidazole core, numbers of strategies have been developed to synthesize compounds including this heterocyclic motif.

1.4. Synthesis

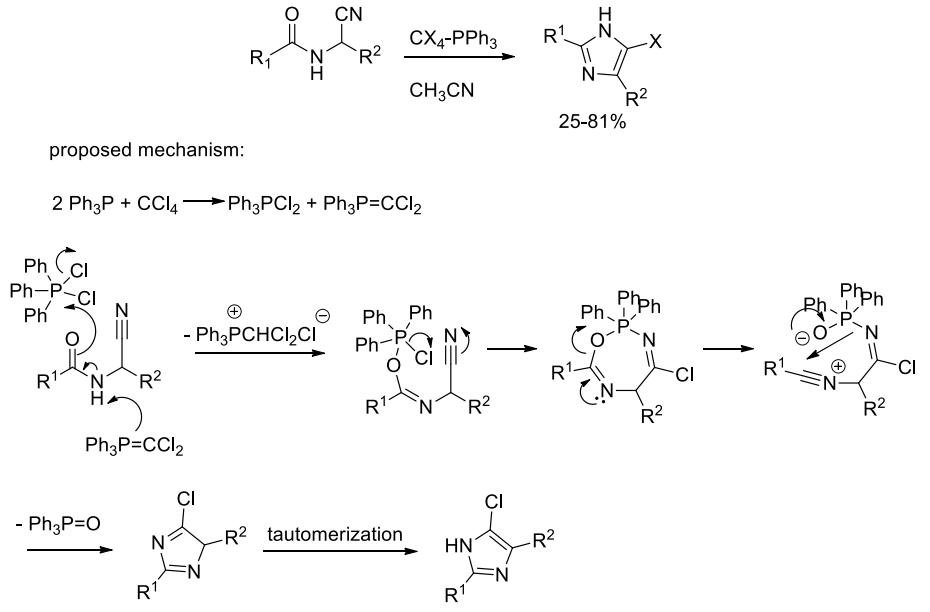
There are different strategies to synthesize substituted imidazole. One of these methods consists in the formation of the imidazole ring. This methodology is widely reviewed in the literature and will not been discussed in details in this manuscript.[15] Another method is the formation of the imidazole ring by the transformation of other heterocycles. A third method is the functionalization of the imidazole core. In the context of this thesis, we have focused our attention on this later strategy. Accordingly, this approach will be largely developed in the next sections.[16,17]

1.4.1. Formation of the imidazole ring

There are numerous methods to synthesize the imidazole ring via cyclo-condensation. Here are some examples of methods used sorted according to the number of fragments involved to form the imidazole nucleus.

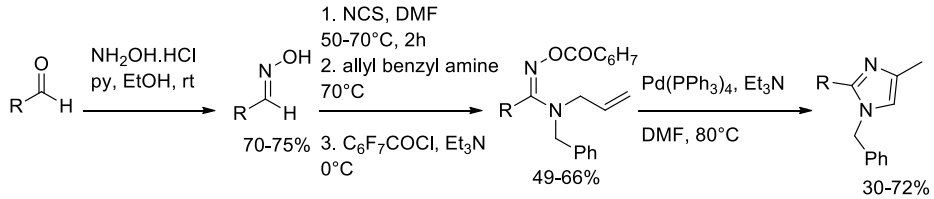
1.4.1.1. Intramolecular cyclization

Acylated α-aminonitriles can be used to form the imidazole ring by cyclization in the presence of triphenylphosphine and carbon tetrahalide (Scheme 1).[18] PPh_3-CCl_4 mediates the chlorination of the acylated α-aminonitrile and leads to a seven-membered ring intermediate which undergoes ring opening, intramolecular addition and tautomerization. 2,4,5-Trisubstituted imidazoles were synthesized by this method with different substituents with good to moderate yield. A possible mechanism has been postulated on the basis of PPh_3-CCl_4 mediating chlorination of alcohol and some intermediates observed through NMR experiments.[19]



Scheme 1. Synthesis of functionalized imidazoles from *N*-acylated α-aminonitriles. R^1 = aryl, alkyl; R^2 = aryl, alkyl; X = Cl, Br.

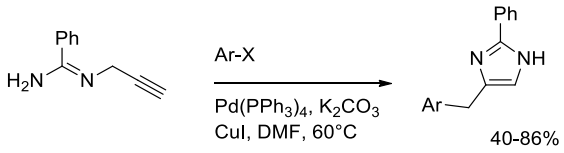
Secondly, a synthesis of 2-substituted 1-benzyl-4-methylimidazoles was developed based on a palladium(0)-catalyzed amino Heck reaction (an electrophilic amination sequence) of amidoximes (Scheme 2).[20] The amidoxine was obtained by reaction of the corresponding aldehyde with hydroxylamine in the presence of pyridine. After, it was converted to the corresponding hydroxamoyl chloride by NCS which was not isolated and coupled *in situ* with allyl benzyl amine. Then the substrate was converted to the pentafluorobenzoyl amidoxine and finally the amino Heck cyclization was done. This method was also extended to the preparation of amino acid mimetics.



Scheme 2. Amino Heck cyclization. R = $PhCH_2$, $Ph(CH_2)_2$, CO_2Me.

Moreover, another palladium catalyzed synthesis has been developed to prepare 4-substituted-2-phenyl imidazoles starting from *N*-propargyl-benzamidine and aryl halides (Scheme 3).[21] This reaction worked well with halides bearing an

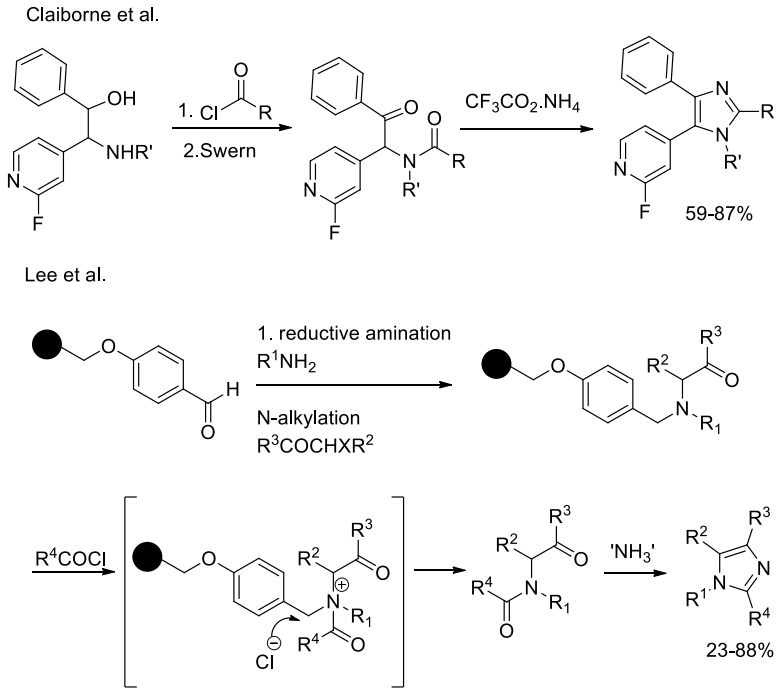
electron-withdrawing group on the ring and with heteroaryl such as pyridine whereas a moderate yield was obtained with an electron-rich group.



Scheme 3. Tandem palladium catalyzed synthesis. Ar-X = substituted halogenated aryl and heteroaryl.

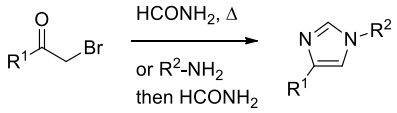
1.4.1.2. Two fragments

Imidazole ring has been formed from ketoamide. This later can be obtained from the corresponding amino alcohol that is coupled with acid chloride and subsequent oxidation (Scheme 4).[22] Cyclization occurs upon heating with a source of ammonia. A solid phase synthesis has been also developed.[23] It is based on benzylic acylammonium cholide reactivity. This approach involves the formation of *N*-benzyl tertiary amine on resin followed by *N*-acylation to release *in situ* a tertiary amide. Then this amide is cyclized with ammonium acetate to form the imidazole ring. Tetra-substituted imidazoles are obtained with moderate to good yields.



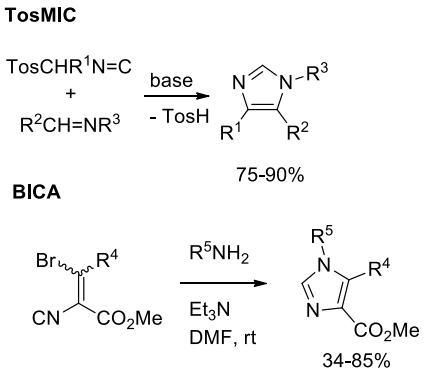
Scheme 4. Synthesis of imidazoles from ketoamides. R = alkyl; R' = H, Me, alkyl; R^1= alkyl, aryl, R^2 = H, Me, Ph, Ac; R^3 = alkyl, aryl; R^4 = alkyl, aryl.

Futhermore, the Bredereck formamide, i.e. cyclization of an α-acetoxy or α-halogenomethyl ketone with formamide, is also used to form imidazole rings. Numbers of biologically active imidazole derivatives were synthesized by this reaction (Scheme 5).[24]



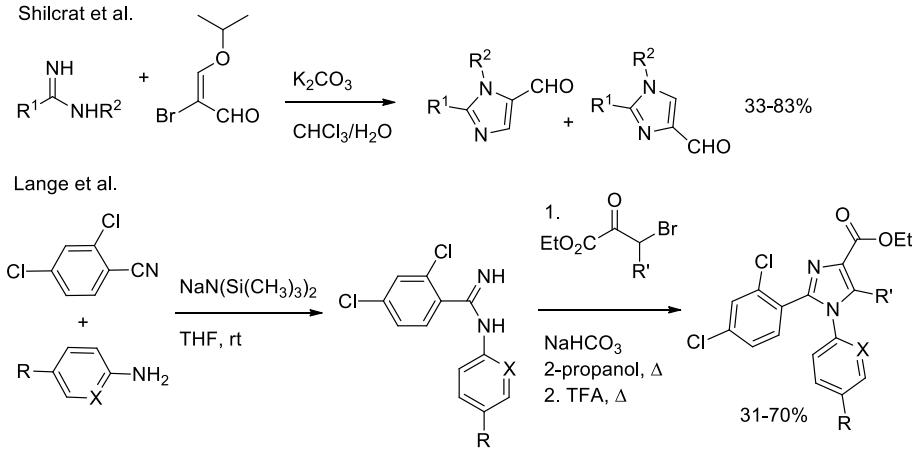
Scheme 5. Bredereck reaction.

The van Leusen synthesis uses the TosMIC (tosylmethyl isocyanide) intermediate for the synthesis of imidazoles from aldimines (Scheme 6).[25] Another variation of the isocyanate is the use of BICA (methyl 3-substituted 3-bromo-2-isocyanoacrylate).[26] In this strategy a Michael reaction of primary amines with α,β-unsaturated esters and successive β-elimination of hydrogen bromide occurs. And finally removal of the acidic proton of the enamine leads to intramolecular cyclization affording imidazoles.



Scheme 6. Imidazole from isocyanates. R^1 = Me, Ph; R^2 = Me, Ph; R^3, R^4, R^5 = aryl, alkyl.

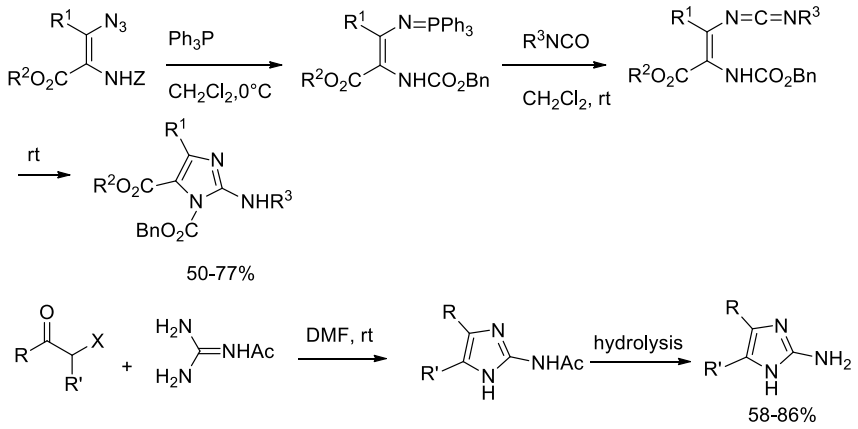
Amidines derivatives can also be used to form the imidazole ring by reaction with a bromo enol ether or a bromoester (Scheme 7).[27] In the reaction of an amidine and a bromo enol ether two isomers are formed (1,2,5 and 1,2,4). Bulky substituents at the 1-position ensured high regioselectivities (1,2,5) while R^1 substituent did not seem to affect the yield. Condensation of amidine and bromoester has been used to synthesize an intermediate of a bioactive tetrasubstituted imidazole which proved to be a selective CB1 Cannabinoid Receptor antagonists.



Scheme 7. Imidazole synthesis from amidines. R^1 = Bu, Ph; R^2 = aryl, alkyl; R = Cl, Br, F, OMe, CF_3; R'= H, C_2H_5; X = CH, N.

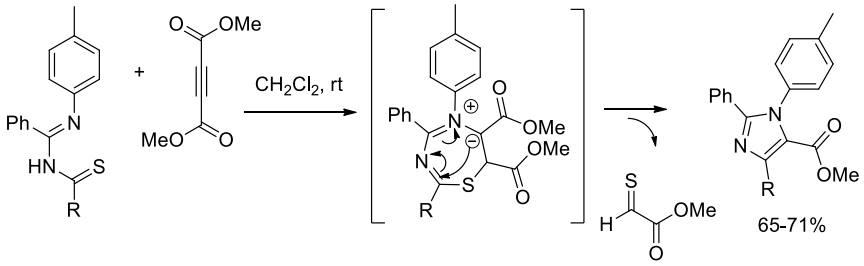
On the other hand, iminophosphoranes have been used to synthesize 2-aminoimidazole derivatives.[28] The strategy consists in a tandem aza-Wittig/carbodiimide-mediated annulation (Scheme 8). This methodology was applied to the preparation of naturally occurring isonaamine A and dorimidazole A.

Another 2-aminoimidazole synthesis utilized acetylguanidine and α-bromoketone.[29] The guanidine was acetylated because when the free base of guanidine is used a mixture of non-identifiable compounds is obtained. So one more step was needed to deacetylate the 2-amino group by hydrolysis.



Scheme 8. Iminophosphorane-mediated synthesis of 2-aminoimidazoles with acetylguanidine. R^1 = H, aryl; R^2 = Et, Bn; R^3 = Bn, Pr, aryl with different substituents; R = aryl, alkyl; R' = H, Me, Ph; X = Br, Cl.

Marwaha et al.[30] have described a single-pot synthesis of functionalized imidazole derivatives by the reaction of thioamides with dimethyl acetylenedicarboxylate. A plausible mechanism involves the formation of a cyclic azomethine ylide after intramolecular cyclisation (Scheme 9).

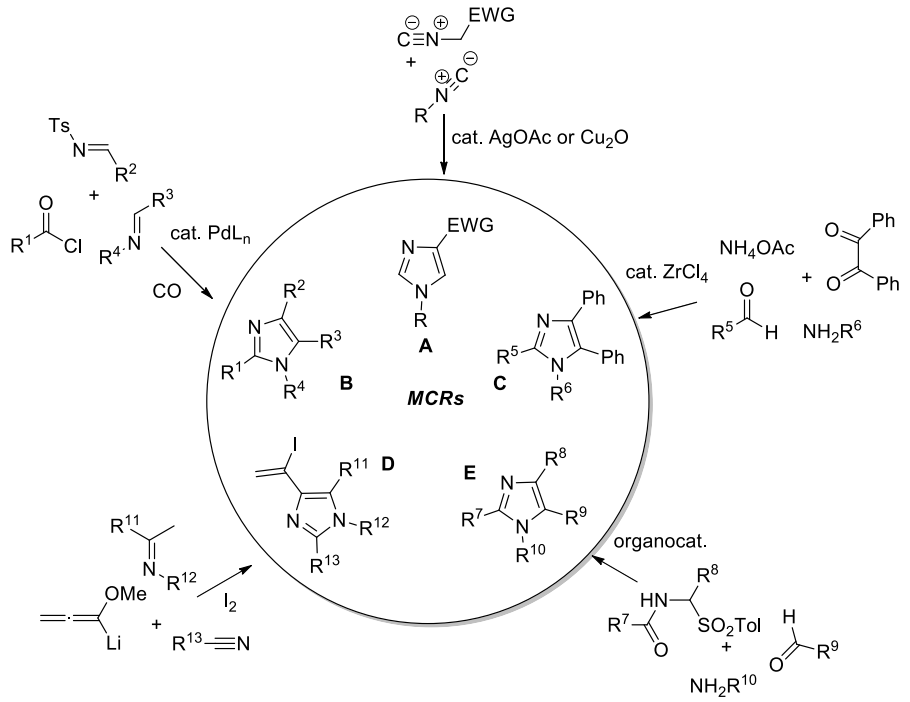


Scheme 9. Imidazole formation from thioamides and acetylenedicarboxylate. R = dimethylamine, pyrrolidine, piperidine, morpholine.

1.4.1.3. Multi components reactions

Finally, imidazole core can be obtained by multi components reactions (MCRs) utilizing a variety of catalysts (Scheme 10). Imidazole **A** can be prepared by homodimerization of isocyanoacetates catalyzed with silver.[31] But only two

examples have been reported. It can also be formed by copper-catalyzed (with phenanthroline as ligand) cross-cycloaddition of two different isocyanides; a isocyanobenzene and an isocyanide with an electron-withdrawing group (EWG).[32] Different isocyanobenzene (*ortho*-, *meta*-, *para*-substitutions, conjugation), can be used indicating that the transformation proceeds irrespectively of the nature of the aryl isocyanides. However, when alkyl isocyanides were used, only low yields were obtained.



Scheme 10. Multi-components reactions. Reaction conditions : A : homodimerization : R = CO_2Me, $CO_2CH_2CH{=}CH_2$ with 88-90%, with 2 isocyanide: R = substituted aryl, EWG = CO_2Et, CO_2NEt_2, CO_2t-Bu, $PO(OEt)_2$ with 62-98%; B: R^1 = aryl, heteroaryl, alkyl, R^3 = aryl, alkyl, R^4 = aryl, heteroaryl, alkyl, α,β-unsaturated substituents with 60-76%; C: $R^{5,6}$ = aryl, heteroaryl, alkyl with 84-95%; D: $R^{11,13}$ = aryl, alkyl, R^{12} = Ph, Ts with 35-80%; E: R^7 = H, aryl, $R^{8,9}$ = aryl, heteroaryl, R^{10} = H, aryl, heteroaryl, alkyl with 22-83%.

Compound **B** can be synthesized from imines and acid chlorides with a palladium catalysis under CO atmosphere.[33] This method allows obtaining tetrasubstituted imidazoles with a range of building blocks. The mechanism is based on the 1,3-dipolar cycloaddition of 1,3-oxazolium-5-olates, formed with the previous reagents, with tosyl-imine.

Another MCR is the Lewis acid catalyzed reaction to form imidazole **C**.[34] Using $ZrCl_4$ at room temperature the condensation of dibenzyl with aldehyde in the presence of an excess of NH_4OAc with or without a primary amine affords tri- or tetra-substituted imidazoles. Different aldehydes and amines were used and gave good yields.

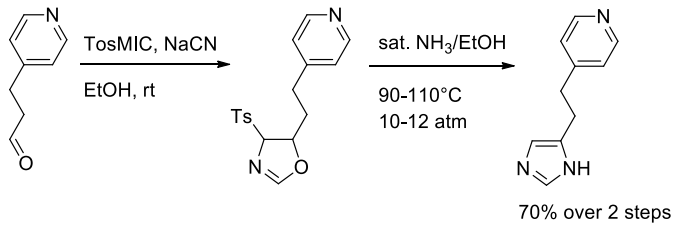
A four components synthesis was obtained with lithiated methoxyallene.[35] Addition of this compound to imines provided allenyl amines which upon reaction with iodine in different nitriles as solvent furnished dihydroimidazole derivatives and finally elimination of methanol afforded tetrasubstituted imidazole **D**. Good to moderate yields were obtained with this three-step sequence with different substituents but the nitrile should be used in excess.

MCRs have been also catalyzed by organomolecules such as thiazolium anion.[36] A one pot synthesis through the use of α-ketoamide was developed. The formation of the α-ketoamide was performed with the thiazolium-catalysed addition of aldehydes to acylamines generated from α-sulfonylamides. Finally treatment of the α-ketoamide with an amine gave the tetrasubstituted imidazole **E**.

Although these traditional approaches for the formation of the imidazole ring have been greatly improved, each method has its scope and efficiency limitations. Often, these methods are inefficient for the preparation of an assembly of compounds; for example the synthesis of different isomers (2,5-substitution or 4,5) or focus analogs (one position substituted). Moreover, the synthesis of analogs from a library will require the entire synthetic sequence which involves parallel repetition of linear synthetic sequences.

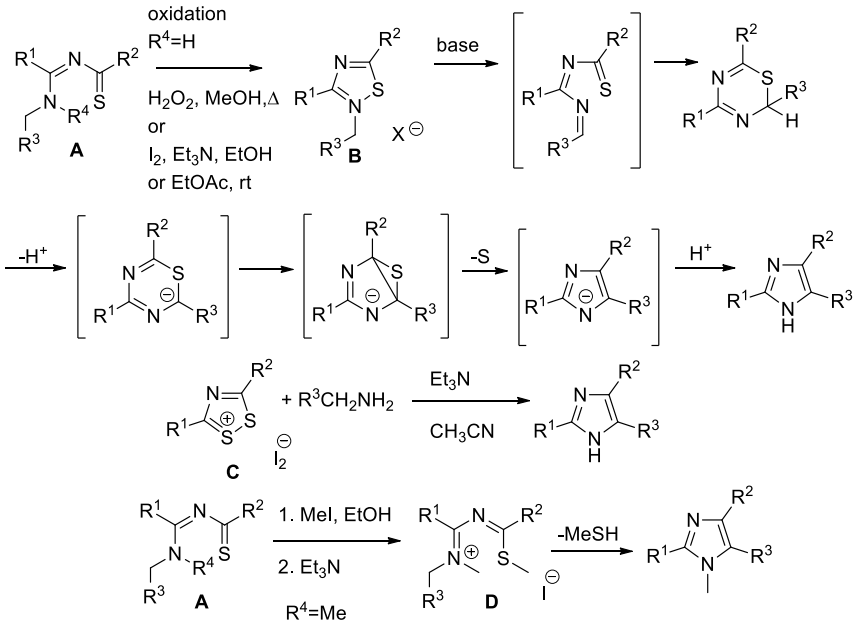
1.4.2. Transformation of other rings

The imidazole core can be obtained by transformation of other rings. For instance, tosyl-substituted oxazoline can be converted into imidazole with ammonia at elevated temperature (Scheme 11). This oxazoline can be prepared from an aldehyde and TosMIC *via* a (3+2) anionic cycloaddition (van Leusen imidazole synthesis).[37]



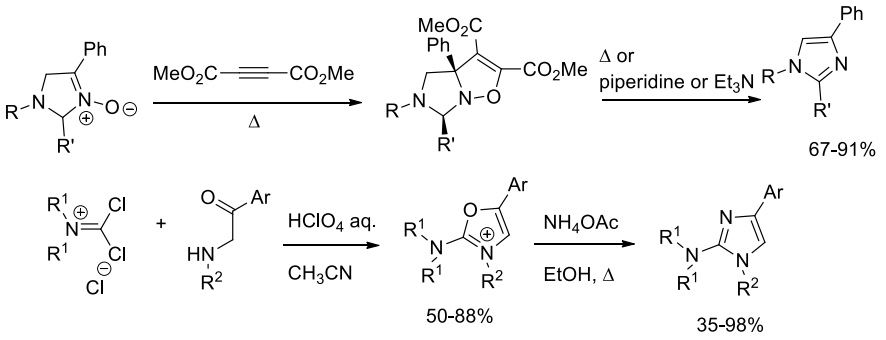
Scheme 11. Imidazole ring from oxazoline.

Secondly, a ring transformation/desulfurization of substituted 2-methyl-1,2,4-thiadiazolium salts **B** can also provide imidazole ring (Scheme 12).[38] This last species can be obtained by *in situ* oxidative cyclization of substituted *N*-methyl-*N*'-(thiocarbonyl)amidines **A** using hydrogen peroxide in methanol or iodine in the presence of triethylamine. The expected 1,2,4-thiadiazolium salts then undergo smooth desulfurization/ring transformation to corresponding imidazoles. A variety of substituents can be introduced. An extremely short synthesis of imidazoles (R^1, R^2 = aryl) was discovered by reaction of 3,5-diaryl-1,2,4-dithiazolium triiodides **C** with glycinates or aminoacetonitrile. This ring transformation of 1,2,4-dithiazolium salts to imidazoles comprises nucleophilic ring opening to give (thiocarbonyl)amidines **A** (R^4 = H), oxidation of the (thiocarbonyl)amidines to 1,2,4-thiadiazolium salts **B** (X^- = I) by the triiodide anion, and conversion of salt **B** to the imidazoles. *N*,*N*-disubstituted *N*'-(thiocarbonyl)amidines **A** (R^4 = methyl) cannot be oxidized to 1,2,4-thiadiazolium salts **B**. In order to get access to 1-substituted imidazoles, these amidines **A** were *S*-methylated with methyl iodide in the presence of triethylamine. Intermediate *N*-imidoylisothioimidates **D** would be expected, but loss of methylthiol afforded *N*-methylimidazoles in the reaction mixture. The application of this method to *N*-monosubstituted (thiocarbonyl)amidines **A** (R^4 = H) gives the same imidazoles similarly to the oxidative routes but in somewhat lower yields.



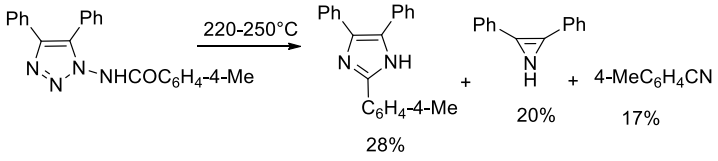
Scheme 12. Imidazole from thiadiazolium salts.

Thirdly, cyclic nitrones can be used to form imidazole (Scheme 13). The cycloaddition of imidazoline *N*-oxides with the dipolarophile dimethyl acetylenedicarboxylate in benzene at reflux gave the corresponding imidazoisoxazolines in almost quantitative yields. Then, thermal or base-induced ring opening can take place to form imidazole core.[39] 1,3-Oxazolium salts has also been used. This 5-membered ring was formed from 2-amino-1-arylethanones with *N*,*N*-dialkyl-dichloromethaniminium chlorides to give 2-(dialkylamino)-1,3-oxazole salts derivatives under mild conditions in good yields. These 2-(dialkylamino)-1,3-oxazolium salts can also be preparated from the corresponding 2-(dialkylamino)-1,3-oxazoles by alkyation with $(MeO)_2SO_2$. Then treatment of these salts with NH_4OAc gave 1-substituted-4-aryl-2-(dialkylamino)-1*H*-imidazoles.[40]



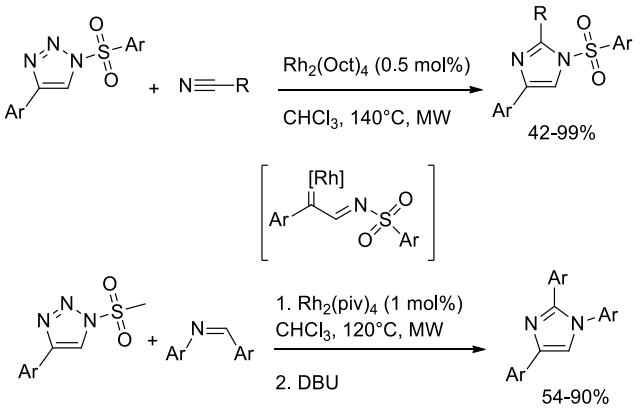
Scheme 13. Imidazole from imidazoline *N*-oxides and oxazolium salts. R = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4 ; R' = H, Ph ; NR_2^1 = Me_2N, Et_2N, morpholino, pyrrolidin-1-yl; R^2 = 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4Ph$; Ar = 4-MeC_6H_4, 4-ClC_6H_4, Ph.

Furthermore, 2,4,5-triarylimidazoles have been obtained from pyrolysis of 1,2,3-triazoles.[41] The pyrolysis of the protected-triazole generates homolytic cleavage of the triazole-protecting group and subsequent abstraction of N_2. Imidazole was formed as the major product (28%) but also aziridine (20%) and deshydrated protecting group (17%).



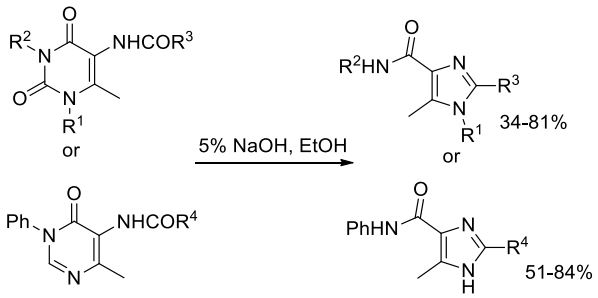
Scheme 14. Imidazoles from pyrolysis of triazole.

A last example of ring transformations is the *N*-tosyl triazoles that can be transformed into *N*-tosyl imidazoles by rhodium catalysis. Triazoles derivatives and rhodium complex form Rh-iminocarbenoids which, upon reaction with nitriles, produce imidazoles in moderate to excellent yields (Scheme 15). Later, 1,2,5-trisubstituted imidazoles were formed from *N*-mesylimidazoles and aldimines under Rh-catalysis. [42]



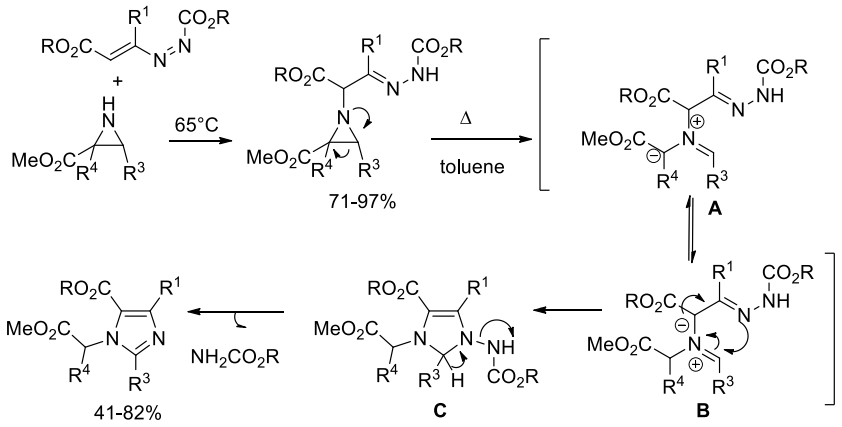
Scheme 15. Imidazoles from 1,2,3-triazole. R = alkyl, aryl.

On the other hand, imidazole can also been obtained by ring reduction of 5-acylaminouracils and pyrimidin-4(3H)-ones. This transformation was done at reflux in ethanol and an aqueous solution of NaOH (Scheme 16). [43]



Scheme 16. Imidazoles from ring contraction. R^{1-3} = Me, Ph; R^4 = Me, Et, Pr, Ph.

Now, concerning the ring expansion, thermal ring opening of α-aziridinohydrazones has been achieved. 1,4-Conjugate addition of aziridines to the azo-ene system of 1,2-diaza-1,3-butadienes under solvent free conditions at 65 °C afforded the corresponding α-aziridinohydrazones in excellent yields (Scheme 17). Thermolytic cleavage of the aziridine C-C bond affords azomethine ylide **A**, whose formation is favored by the stabilizing effect of the adjacent electron-withdrawing methoxycarbonyl group(s). The latter would also assist tautomeric equilibration of ylide **A** to azavinyl azomethine ylide **B**, which is also stabilized by the adjacent carbonyl group. Subsequently, 1,5-electrocyclic ring closure of conjugated ylide **B** results in the formation of 2,3-dihydroimidazole **C**. In turn, aromatization with concomitant loss of a carbamate residue by cleavage of the N-N bond affords imidazoles.[44]



Scheme 17. Imidazole formation by ring expansion. R = Me, Et, *t*-Bu; R^1 = Me, Et; R^2 = OMe, OEt, NEt_2; R^3 = H, Ph; R^4 = H, Ph, CO_2Me.

1.4.3. Functionalization of the imidazole

1.4.3.1. (NH)-substitution

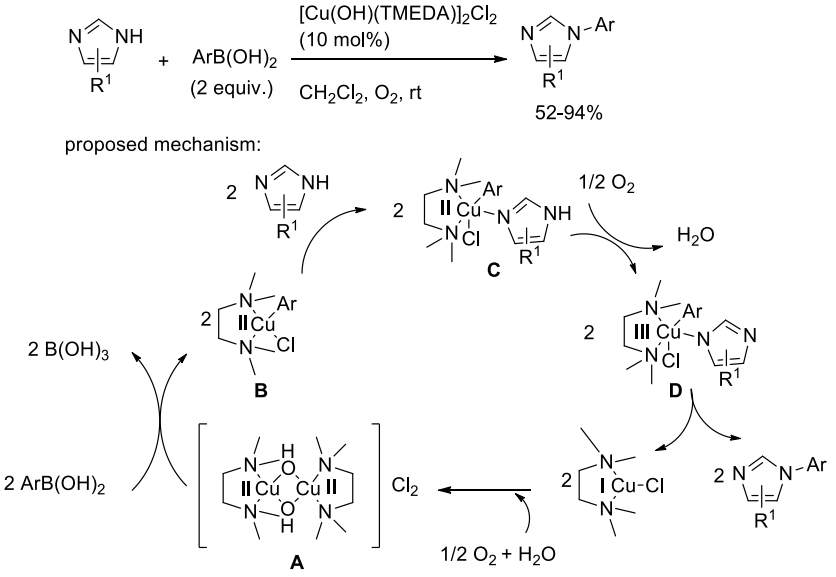
The N-H of imidazole can be substituted by alkyl, aryl, alkenyl, alkynyl or allyl groups using different methodologies.

In the first place, the *N*-alkylation of imidazole can be done by addition of an electrophile in the presence of a moderate or strong base. This methodology will be discussed in details in Chapter 5 which deals with the development of a regioselective *N*-alkylation of imidazole strategy.

In the second place, the imidazole can be *N*-arylated by S_NAr with aryl halides.[45] However this approach requires aryl halides with electron-withdrawing substituents that limits its scope. Another commonly used method for the construction of *N*-arylamine is the Ullmann-type coupling.[46] This traditional coupling can be used with a range of aryl halides but requires high temperatures and gives varying yields.

Recently, different groups have developed Cu catalyzed *N*-arylation reactions.[47] These latter required however high temperature or equimolar amount of Cu. Efforts thus turned to other Cu-catalyzed coupling reactions. Collman et al.[48] reported an efficient diamine copper complex-catalyzed *N*-arylation of imidazole using arylboronic acids. Arylboronic acids were coupled with imidazoles in the presence of a catalytic amount of $[Cu(OH).TMEDA]_2Cl_2$ at room temperature under an atmosphere of dioxygen (Scheme 18). Good to excellent yields were obtained, but with 4(5)-substituted imidazoles, a mixture of 5- and 4-substituted imidazoles were

obtained even after optimization of the reaction conditions (ratio reactants). The 4-isomer was always the major component obtained. The postulated mechanism is first the coordination of the arylboronic acid with catalyst **A** to generate complex **B**. Next, the imidazole coordinates copper to generate species **C**. In the presence of oxygen the Cu(II) is oxidized to Cu(III) to form intermediate **D** which then undergoes reductive elimination to give the *N*-arylimidazole along with the Cu(I) complex. The latter should regenerate catalyst **A**.



Scheme 18. Cu-catalysed *N*-arylation of (NH)imidazoles. R^1 = H, Me, Ph; Ar = *o*-, *p*-substituted aryl.

They also reported that this catalytic *N*-arylation can be done in water although lower yields are obtained. The use of a phase-transfer catalyst or basic/acidic pH decreases the yield.[49] They also tried different Cu-ligand and found that TMEDA was the ligand of choice.[50] Another group developed a similar catalytic system to synthesize *N*-arylated hindered imidazoles (1,2,5-substituted) from (bis)-*o*-substituted arylboronic acids and 2,5-substituted-(NH)imidazole.[51] Cu-base heterogeneous catalyst have been also employed for *N*-arylation of (NH)-imidazole with arylboronic acids such as Cu-exchanged fluoroapatite, cellulose supported Cu(0), silica-tethered Cu catalysts,...[52] The use of these catalysts allows their easy separation and recyclability. Instead of using arylboronic acids cyclic aryltriolborates can also be used (Figure 9).[53] These novel cyclic triolborates are exceptionally stable in air and water. These species has been employed as arylating reagents in Cu-catalyzed reactions with imidazoles in DMF.[54] They were found to be

better reagents than arylboronic acids or potassium aryltrifluoroborates. Arylboronic acids are air and moisture sensitive. Potassium trifluoroborates are not sensitive but their metal-catalyzed bond-forming reactions are very slow in the absence of a base because of the low nucleophilicity of the organic group owing to the high electronegativity of the fluorine atoms. Moreover they are less soluble in organic solvents than aryltriolborates.

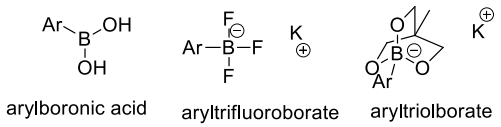
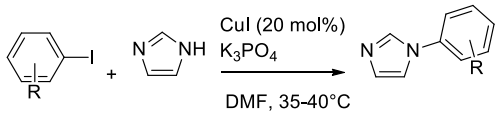


Figure 9. Organoboronic species.

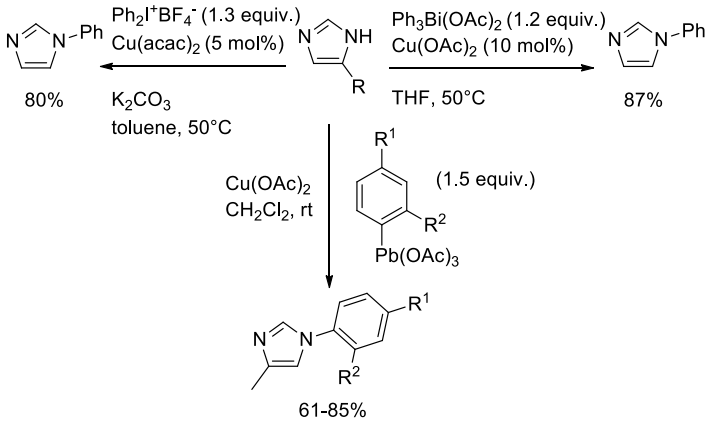
N-arylation can also be done with aryl halides under Cu-catalyzed reaction under ligand-free conditions. Numerous examples have been reported but some protocols required high temperatures and gave low yields. Nevertheless, some groups found appropriate conditions. *N*-arylimidazoles can be obtained in modest to excellent yields by microwave-assisted reaction of (NH)-imidazoles with aryl bromides in tetraethyl orthosilicate in the presence of K_2CO_3 and catalytic CuI.[55] Zhu et al.[56] have also developed a mild CuI-catalysed procedure for the *N*-arylation of imidazole with a variety of aryl iodides (Table 1). This procedure employs K_3PO_4 as a base and DMF as a solvent at a temperature of 35-40°C. This method tolerates a wide range of functional groups such as alkynyl, hydroxy, amino, amido, aldehyde, ester, haloid, nitro, and methoxy substituents. So this method is highly chemoselective avoiding other parasite Cu-catalyzed reaction (with high temperature) such as *N*-arylation of amine (with amine substituents), *O*-arylation (with hydroxy substituents), Sonogashira reaction (with alkynyl substituents), aryl amidation (with amido substituents). Even hindered 2-iodoanisole gives good yield.

Table 1. Mild CuI-catalysed *N*-arylation.



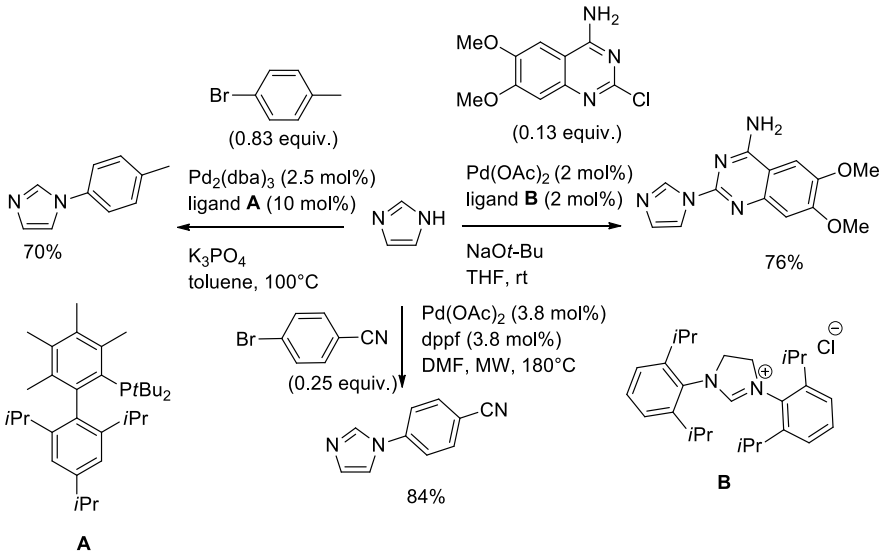
R	Yields (%)	R	Yields (%)
H	93	*m*-CH_2OH	54
p-$CCC(OH)(CH_3)_2$	93	*m*-NH_2	66
p-CO_2Et	91	*p*-CH_3	80
p-OCH_3	95	*p*-CCH	82
p $NHCOCH_3$	98	*p*-OH	63
p-Br	87	o-OCH_3	78
o-CH_3	62	*p* CH_2OH	60
p-NH_2	73	*p*-COH	98
p-NO_2	94		

Futhermore, *N*-arylation can be done from diaryliodonium salts or triarylbismuth diacetates and aryllead triacetates. Commercially hypervalent iodonium salts were used as electophiles in Cu-catalysed *N*-arylation. Kang et al.[57] have demonstrated that treatment of imidazole with diphenyliodonium tetrafluoroborate in the presence of copper and a base gave *N*-phenylimidazole with 80% yield (Scheme 19). Moreover, it has been showed that triphenylbismuth diacetate can also be used in Cu-catalysed *N*-arylation.[58] With aryllead triacetates, different examples have been made. Lopez-Alvarado et al.[59] found that treatment of imidazole with 4-tolyllead triacetate in CH_2Cl_2 with $Cu(OAc)_2$ gives *N*-(4-tolyl)imidazole with 82% yield. Another group reported complete regioselectivity in the arylation of 4(5)-substituted imidazoles with aryllead triacetates. This method was also applied on histidine derivatives.[60]



Scheme 19. Cu-catalysed *N*-arylation with diaryliodonium salts, triaryl bismuth diacetates and aryllead triacetates. R= H or Me; R^1= H, OMe; R^2= H, OMe.

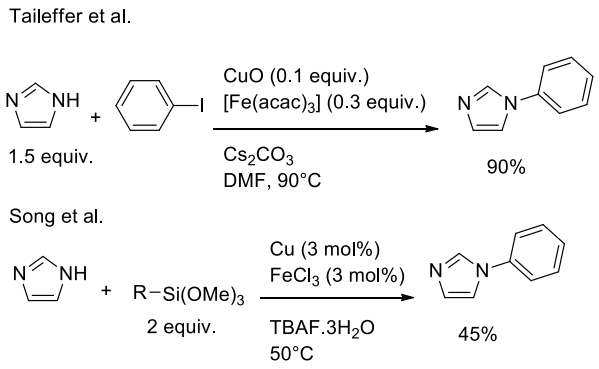
Coupling between imidazole derivatives and aryl halides can also be catalyzed by Pd.[61] Anderson et al. showed an example with an unactivated aryl bromide with the catalytic system $Pd_2(dba)_3$ and specially hindered ligand *tert*-Butyl XPhos (ligand A) (Scheme 20). Wan et al. performed a microwave heating version of Pd-catalyzed *N*-arylation with 4-bromobenzonitrile. And Andrus et al. carried out this reaction between imidazole and quinazoline chloride with $Pd(OAc)_2$, imidazolium derivatives as ligand and NaO*t*-Bu.



Scheme 20. Pd-catalyzed *N*-arylation of imidazoles.

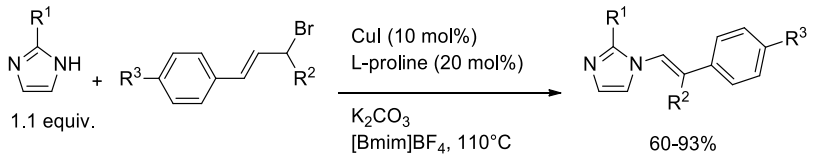
Ligands based Cu catalyzed reactions are another way to synthesize *N*-arylimidazole with aryl halides. Numbers of studies on Cu-catalyzed *N*-arylation with a large variety of ligands have been performed.[62] The first example was reported by Buchwald and coworkers with the use of phenanthrolines as ligand.

Futhermore, *N*-arylation can be catalyzed by Fe/Cu-catalysis with aryl iodides or aryltrimethoxysilanes (Scheme 21). Phenyl-imidazole can be obtained in 91% yield from imidazole and iodobenzene in the presence of the bimetallic system CuO and $Fe(acac)_3$ and Cs_2CO_3 as a base.[63] Song et al.[64] also reported *N*-arylation of imidazole with aryltrimethoxysilanes with the system Cu-$FeCl_3$ with TBAF.$3H_2O$ as a base under solvent-free conditions with 45 and 58% yield for respectively *N*-phenyl and *N*-tolyl-imidazole.



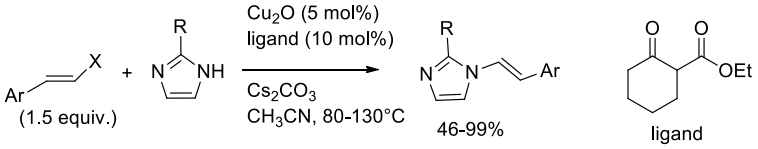
Scheme 21. Cu-Fe catalyzed arylation. R = phenyl or tolyl.

Thirdly, different methods exist for the *N*-alkenylation of imidazole. Classical protocols without catalyst includes direct addition of free (NH)-imidazoles to alkynes[65],... Morever, Cu-catalyzed *N*-alkenylations of imidazoles with alkenyl halides have been developed. Bao and coworkers have described few different procoles.[66] 1-styrylimidazoles can be formed from (NH)-imidazoles and β-styryl bromides in $[Bmim]BF_4$ (ILs; 1-butyl-3-methylimidazolium tetrafluoroborate) in the presence of catalyst system CuI and L-proline and K_2CO_3 as a base at 110°C (Scheme 22).



Scheme 22. L-proline promoted *N*-alkenylation of imidazole. R^1 = H, Me; R^2 = H, Me; R^3 = H, Me, Cl.

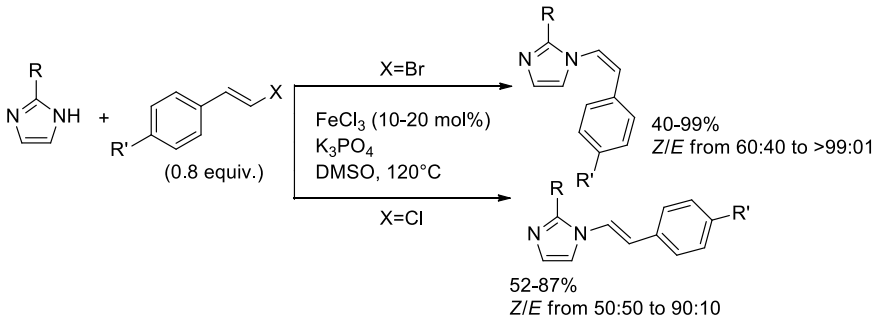
Later, they also found that the system Cu_2O-ethyl 2-oxocyclohexanecarboxylate worked in CH_3CN at 80-90°C (milder system). Interestingly, if the reaction was carried out without ligand, 80% yield was obtained. So they have found that the imidazole was a ligand in the Cu(I)-catalyzed couplings, though it was inferior to ethyl 2-oxocyclohexanecarboxylate. β-bromostyrenes bearing both electron-donating and electron-withdrawing groups were suitable for this reaction and the desired *N*-vinylimidazoles were obtained in excellent yields and it worked also with an hetero-aryl vinyl bromide. The reaction seems however sensitive to the steric effects: when 2-methylimidazole was employed as a nucleophilic substrate, it only gave a moderate yield. Vinyl chloride was also successfully coupled under reaction conditions, whereas higher reaction temperature and longer reaction time were required. The reaction was also stereoselective for the (*E*)-vinyl halide involved coupling. The double bond geometry of the *N*-vinylimidazoles from the (*E*)-vinyl halide was retained (Scheme 23).



Scheme 23. Coupling of imidazoles and vinyl halides. R = H, Me; X = Br, Cl; Ar = *p*-MePh, *p*-OMePh, *m*,*p*-diOMePh, *p*-ClPh, *p*-F-Ph, naphthyl, furane, CH=CHPh.

Other groups used different ligands for this Cu-catalyzed *N*-alkenylation such as ethylene diamine.[67]

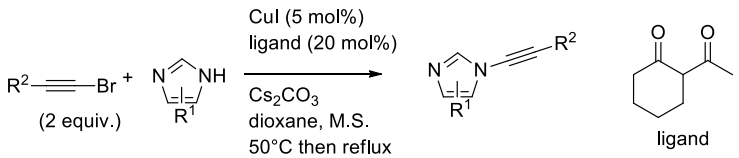
Another *N*-alkenylation has been done with iron catalysts without ligand. Interestingly, Mao et al.[68] found that the coupling of (*E*)-vinyl bromides led to (*Z*)-products predominantly, while the reactions of (*E*)-vinyl chlorides afforded (*E*)-isomers as the major product. Thus, this could provide a facile means to satisfy the demand for different isomers of *N*-(1-alkenyl)imidazoles (Scheme 24).



Scheme 24. $FeCl_3$-catalyzed synthesis of *N*-(*Z*)- and *N*-(*E*)-styrylimidazoles. R = H, Me; R' = H, OMe, Me, Cl.

The synthesis of *N*-(1-alkynyl)imidazoles is not well documented. Nadipuram et al.[69] synthesized 2-iodo-1-(phenylethynyl)imidazole with only 29% yield by treatment of the 2-iodoimidazole sodium salt with phenyl(phenylethynyl)iodonium tosylate. More recently, Laroche et al.[70] synthesized with good to moderate yields *N*-(1-alkynyl)imidazoles by coupling imidazoles and bromoalkynes with the system CuI-2-acetylcyclohexane in dioxane in the presence of Cs_2CO_3 at 50°C (Table 2). Unfortunately, poor regioselectivities were observed with 4(5)-substituted imidazoles.

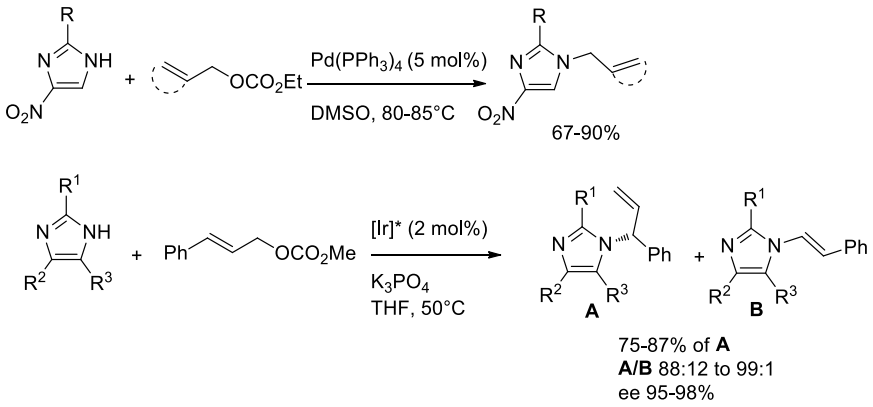
Table 2. Preparation of *N*-alkynylimidazoles.



R^1	R^2	Yields (1,4-1,5)	R^1	R^2	Yields (1,4-1,5)
H	Ph	52	4(5)-Ph	TIPS	90
H	TIPS	53	4(5)-Ph	*n*-C_6H_{13}	44
H	*n*-C_6H_{13}	53	2-Me	Ph	28
H	CH_2OTBS	22	4(5)-Me	Ph	29 (1:1)
4(5)-Ph	Ph	71 (9:1)	4(5)-(4-FPh)	TIPS	79 (9:1)
			4(5)-(4-FPh), 4(5)-(4-pyridyl)	TIPS	15 (4:1)

Concerning the last (NH)-substitution, the *N*-allylation, Pd(0)-catalysts and iridium-phosphoramidite complex are used to couple imidazole and allylic

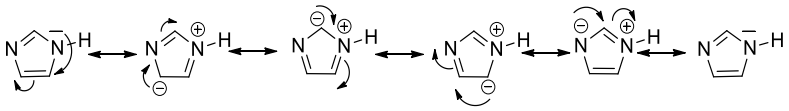
electrophiles. For examples, Arnau et al[71] found that (NH)-4(5)-nitroimidazoles can be *N*-allylated with allyl carbonates in the presence of catalytic $Pd(PPh_3)_4$ in good yields (Scheme 25). Hartwig and coworkers[72] reported also regioselective and enantioselective branched *N*-allyl imidazoles from reactions of imidazole with achiral linear allylic carbonates in the presence of single-component iridium catalysts.



Scheme 25. *N*-allylation with Pd and Ir catalyst. R = H, Me; substituted alkene = H, Ph or cyclohexene; R^1, R^2, R^3 = H, Ph.

1.4.3.2. Direct lithiation

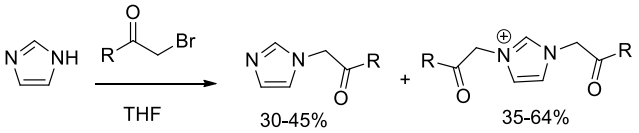
Imidazole has different proton acidity. The more acidic proton is obviously the N-H proton. Then the C2-position is the more acidic allowing deprotonation with common organolithium bases. Indeed, the C2-H bond is located between two electronegative atoms, the N1 and N3 nitrogen atoms. There is a little difference in acidity between protons in position 4 and 5; this latter being a little bit more acidic than proton H4. One can see this difference by drawing the resonance forms (Scheme 26). Indeed, if the lone pair of the nitrogen N1 is delocalize in the C5-N1 bond, the electronic density increases at C4. We will see methods to distinguish them.



Scheme 26. Resonance form of imidazole.

As described above, the first species to be deprotonated is the NH of imidazole. The imidazolyl anion formed by addition of alkyllithium base is a convenient intermediate for the formation of *N*-protected imidazoles. Indeed, it has

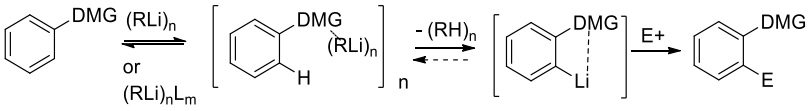
been demonstrated that if no base is employed to do the imidazolyl, one can have a mixture of 1- and 1,3-*N*-substituted imidazole. Wong et al.[73] have showed that addition of α-bromoketones on imidazole (in excess) gives the undesired imidazolium salt as the major product (Scheme 27).



Scheme 27. *N*-alkylation of imidazole without base. R = alkyl, aryl, OEt.

The (NH)-protection is obligatory to do lithiation at the carbon positions. Ideally, the (NH)-protecting group should be available from cheap reagents and capable of being removed in a one pot reaction under reaction conditions which do not affect other functional groups. Two types of protecting groups exist. They can be viewed as "directing agent" or as "blocking group"[74]. "The directing agents" are employed in some cases and can guide the direct metalation in ortho position; they are called directing metalation groups (DMGs).[75] The DMG group must be a good coordinating site for alkyl lithium and a poor electrophilic site in order to avoid the attack by the lithiated base. A heteroatom is therefore a good component of the DMGs.

The directed ortho metalation reaction (DoM) can be decomposed into three steps: coordination of the $(RLi)_n$ aggregate to heteroatom DMG, deprotonation to give the coordinated ortho-lithiated specie and reaction with an electrophile (Scheme 28).



Scheme 28. Directed ortho metalation reaction.

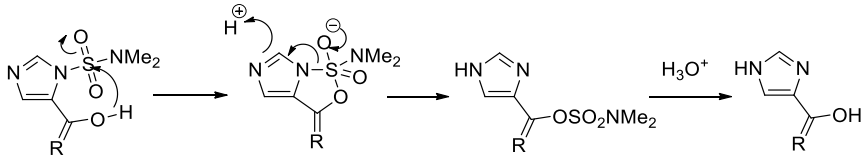
Here is a list of some imidazole NH-protection groups and their conditions of deprotection (Table 3).

Table 3. (NH)-protecting groups and their deprotection conditions.

NH Protecting groups	Deprotection conditions
alkyl ether: MOM, EOM	Acidic hydrolysis
arylsulfonyl	Nucleophilic attack
	carboxylic anhydre + pyridine
DMAS	Acidic hydrolysis (Δ)
	Nucleophilic attack
silyl: SEM, TMS, TBS	Fluorine or acidic
Tr	acidic
Bn	H_2
THP	Acidic hydrolysis

One must find a good compromise between stability of the protecting group under the reaction conditions, its compatibility with functionnal groups present and the ease of its removal.

So, every protecting group has its advantages and its drawbacks.[76] For example, under lithiation conditions benzyl protecting groups can be lithiated on their methylene group. Trialkylsilyl group have a tendency for N to C silyl group rearrangement. Sulfonyl groups are easily introduced but they can undergo nucleophilic attack by an organilithium species. Trityl group are easily removed but position C5 cannot be lithiated due to steric hindrance.[77] For the dimethylsulfamoyl group (DMAS), if there is a neighbouring group with a hydroxyl, this can lead to anchimeric assistance and help the removal of the DMAS (Scheme 29)[78],…



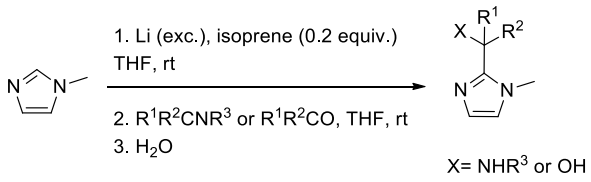
Scheme 29. Anchimeric assistance of DMAS group's deprotection. R = Ph_2, O.

Now that the annular nitrogen is blocked, carbon lithiation can take place in the order C2 >> C5 > C4.

Alkyllithium and lithium azides, such as *n*-BuLi and LDA, were widely used for lithiation of imidazole. They allow introduction of different electrophiles at the C2 position such as alkyl, alkenyl, hydroxyalkyl, halogen, acyl, carboxyl, silyl, sulfanyl and azido.[79] However, they cannot produce good results with enolysable

carbonyl and imine compounds. Katrizky et al. have explained the variety of yields obtained with different electrophiles in terms of hard-soft acid-base theory. It suggests that the reaction with imidazole salt with hard electrophiles produces higher yields than with soft electrophiles.

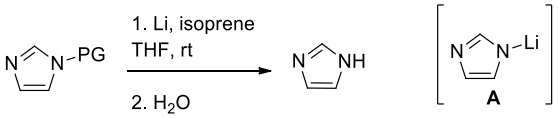
In order to improve the functional group tolerance, Torrega et al. have developed an isoprene-promoted lithiation using mild reaction conditions at room temperature. They succeeded in synthesizing 2-(hydroxyalkyl)imidazole derivatives in excellent yields (Scheme 30). The reaction of the organolithium intermediate with imine electrophiles allowed the isolation of new interesting 2-[(*N*-arylamino)benzyl]imidazoles in good yield. Primary amino functionalized imidazoles were obtained by using N-silylimines[80]. In this methodology lithium metal (low reactivity) is activated by isoprene which acts as an electron carrier. The use of this additive (or other electron carriers) was a determining factor to improve the yield of the final product.



Scheme 30. Isoprene-promoted lithiation.

They also found that their method can be useful for the removal of some commonly employed NH-protecting group. The lithium/isoprene methodology is applicable to cleave sulfonyl, carbonyl, alkoxycarbonyl, trialkylsilyl and carbon substitutents such as vinyl, trityl, benzyl and allyl (Table 4)[81].

Table 4. Deprotection of *N*-protected-imidazoles via isoprene-catalyzed lithiation process.



PG	Isoprene (%)	Yield (%)	PG	Isoprene (%)	Yield (%)
Tr	0	45	Ts	0	49
Tr	50	74	Ts	100	88
Tr	100	95	Boc	0	22
allyl	0	54	Boc	100	90
Allyl	100	85	Acetyl	0	74
Bn	0	55	Acetyl	100	99
Bn	100	74	TMS	0	88
Vinyl	0	24	TMS	100	94
Vinyl	100	43	TBS	0	82
DMAS	0	<5	TBS	100	85
DMAS	100	49			

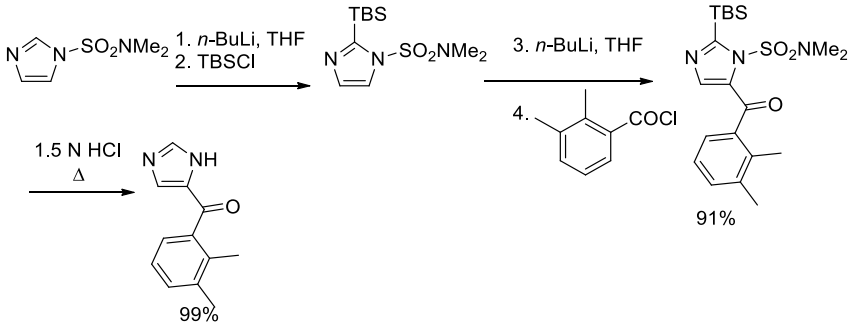
The yield of the deprotection (which occurs via intermediate **A**) is lower in the absence of isoprene. Low yields are obtained for the DMAS and vinyl groups. The treatment of 1-(diethoxymethyl)-imidazole gave no scission of the protecting group under these conditions and conduct to corresponding organolithium. So they need to take this protectiong group (or methyl as showed above) to do lithiation at C2 position with their methodology. After acidic conditions the corresponding 2-substituted-1*H*-imidazole is obtained.

The C5 position is the second most acidic carbon center. The second lithiation occurs preferentially at this carbon and this selectivity is enhanced with the introduction of a DMGs group on the N1 atom. Using several equivalents of base, it is possible to lithiate both positions C2 and C5 on a NH-protected imidazole.

There are different methods to block temporary position C2 by introducing labile groups to obtain 5-substituted-imidazoles. Four functional groups have been employed for that purpose: TMS[7882], phenylsulfonyl[83] carboxylate[84], and chlorine. TMS group is removed under acidic conditions but 2- to 5-position migration of 2-(trialkylsilyl)-substituted 5-lithio-*N*-methylimidazole has been observed rendering the silyl group less attractive as a blocking group. The phenylsulfonyl group is removed with aluminium amalgam while decarboxylation of carboxylate derivatives

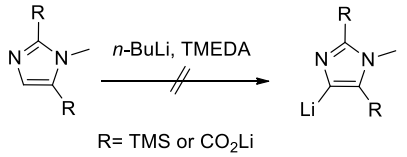
is performed under acidic conditions. Chlorine group can be removed by hydrogen[85] or simply by halogen-metal exchange and subsequent hydrolysis.

One can block position N1 and C2 and perform their deprotection in one step. Kudzma et al. have done it in his synthesis of the biomolecule metetomidine that is a α_2-adrenergic agonist with an excellent yield (Scheme 31)[86].



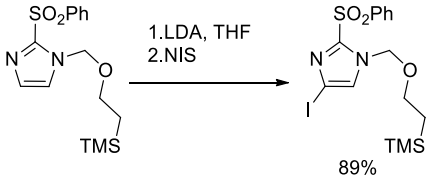
Scheme 31. Application of N1, C2 blocked positions in the synthesis of metetomidine.

Finally, the less reactive position is the C4. When positions C2 and C5 are substituted by a TMS group, lithiation does not produce C4 lithiation but after work-up the 2-desilylated product is obtained. Even if position C2 and C5 are blocked with a carboxylate, lithiation conduct to decarboxylation at C2 (Scheme 32)[77].



Scheme 32. Attempted direct lithiation at C4.

There are however exceptions of the direct lithiation of C4. Phillips at al.[87] have, for instance, reported direct lithiation on 1-[2'-(trimetylsilyl)ethoxymethyl]-2-phenylsulfonylimidazole using LDA (Scheme 33).



Scheme 33. Substitution at C4.

Another way to access to 4-lithioimidazoles is the rearrangement of the protecting group to the less hindered isomer. We will see one example of this rearrangemenr in the chapter on regioselective alkylation (chapter 5).

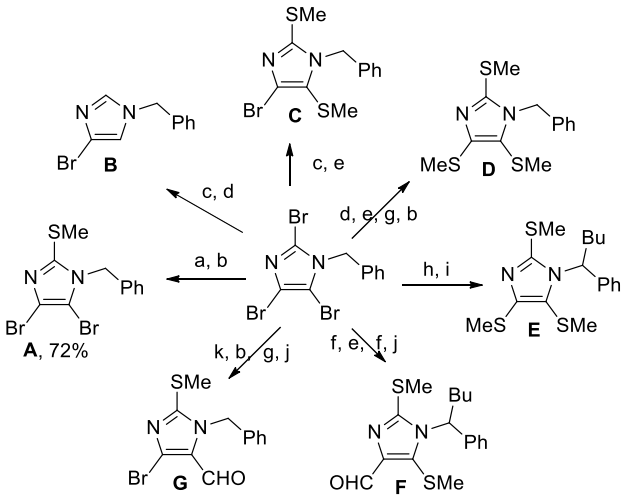
1.4.3.3. Halogen-metal exchange

The halogen-metal exchange reaction involves an extra step, namely halogenation of the parent imidazole to produce 2,4,5-trihalogenated imidazole. The 2,4,5-tribromo imidazole and the corresponding 1-protected need to be manipulated carefully because it can be deprotected *in vivo* to give 2,4,5-trihalogenated imidazole which are neurotoxic.

Polyhalogenated imidazoles are useful substrates and the halogen-exchange proceeds via the same order of reactivity than lithiation: C2 >> C5 > C4. And the relative rate of halogens exchange is: I > Br >> Cl.

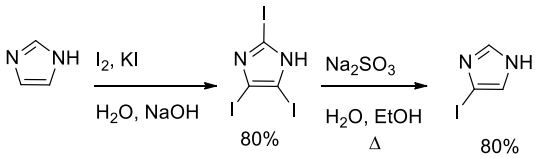
Iddon et al.[88] have showed convenient synthesis of polysubstituted imidazoles from 1-protected-2,4,5-tribromoimidazole. These compounds are formed by elemental bromination of imidazole and protection of nitrogen by standard procedure. 1-Protected-2,4,5-tribromoimidazole in the presence of one equivalent of *n*-BuLi does not react regioselectively and gives both 2- and 5-lithiated products. However, with other organolithium reagents such as PhLi, a regioselective attack at the 2-bromine can be achieved. Thus 1-protected-2,4,5-tribromoimidazole reacts successively with one equivalent of PhLi and dimethylsulfide to give 72% of compound **A** (Scheme 34). Compound **B** (71%) and **C** (72%) were formed using 2 equivalents of BuLi followed by either water or dimethyl sulfide. Trilithiated 1-protected imidazole was formed using 3 equivalents of BuLi followed by addition of dimethylsulfide to give the attempted compound **D** but only in 5% yield. The major product of this latter reaction is compound **C** in 71% yield. When this reaction was repeated with 5 equivalents of BuLi and an excess of dimethyl sulfide the imidazole **E** was isolated in 33% yield. The explanation could be that the tetralithiated intermediate reacts with the butyl bromide generated in the initial halogen-metal exchange. This difficulty of exchanging the 4-bromine atom for lithium has been explained by the destabilization of any carbanionic character at C4 both by adjacent N3 lone pair as well as by carbanionic character of C5, called the ALP effect (Adjacent Lone Pair). The basis of the adjacent lone pair effect is that a ring-nitrogen atom bearing an sp^2 lone pair provides a sizable electrostatic effect obstacle to the generation of an sp^2 carbanion at an adjacent ring-carbon atom.[89] To prevent this reaction to occur, imidazole **C** was formed and then directly treated in a one pot manner with one equivalent of BuLi and dimethyl sulfide which gave imidazoles **D** (67%) and **C** (12%). So tetrasubstituted compound **F** was similarly synthesized with

46% yield, namely formation of imidazole **C** and then addition of 2 equivalents of BuLi and one equivalent of DMF. Here, they took advantage of the introduction of an alkyl group into the protecting group. Indeed, this resulting *N*-protecting group is now sensitive to acidic conditions whereas benzyl group needed reductive conditions. And finally, imidazole **G** was formed in 60% yield by successive addition of one equivalent of MeLi and one equivalent of electrophiles.



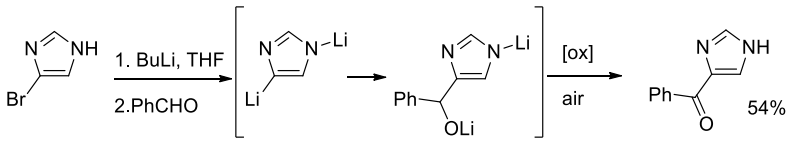
Scheme 34. Reactions from 1-benzyl-2,4,5-tribromoimidazole. Conditions: a. 1 equiv. PhLi, THF, -78°C; b. 1 equiv $(MeS)_2$; c. 2 equiv. BuLi, Et_2O, -78°C; d. H_2O; e. 2 equiv $(MeS)_2$; f. 2 equiv. BuLi, THF, -78°C; g. 1 equiv. BuLi, THF, -78°C; h. 5 equiv. BuLi, THF, -78°C; h. 3 equiv $(MeS)_2$; i. DMF; j. 1 equiv. MeLi, THF, -78°C.

With halogen-lithium exchange, one can also lithiate position C4 and/or C5 directly without the use of a protecting group in C2 position. 4-Iodoimidazole can be formed by reduction of the 2,4,5-triiodoimidazole which itself can be formed from imidazole (same methodology that for the polybromation) (Scheme 35).



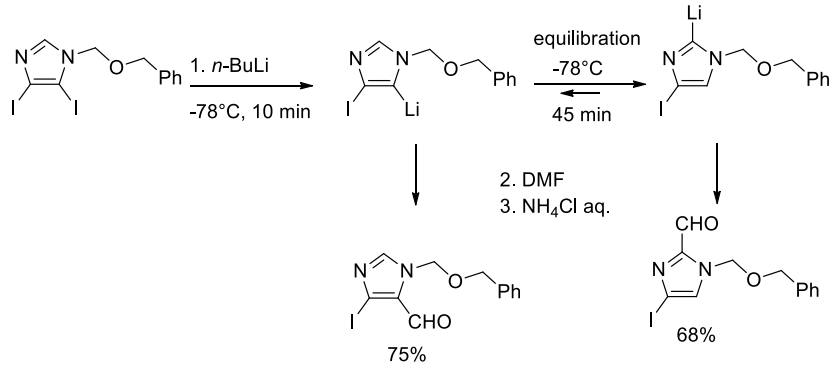
Scheme 35. Formation of 4-iodoimidazole.

Furthermore, halogen-metal exchange allows generation of imidazolyl anion from unprotected (NH)-imidazoles (Scheme 36).[77]



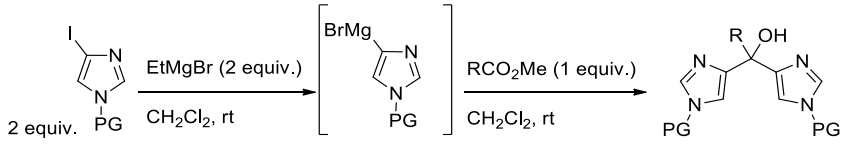
Scheme 36. C4 lithium-halogen exchange.

Sometimes when halogen-metal exchange takes place and produces an anion, this anion can rearrange into the more stable one. An example has been showed by Groziak et al.[90] When the halogen-metal exchange reaction of a 1-protected-4,5-diiodoimidazole and BuLi was allowed to equilibrate at -78°C for 45 minutes before quenching with DMF, the isomeric 1-protected-4-iodoimidazole-2-carboxaldehyde was obtained in 68% yield with only traces of the desired product (Scheme 37).



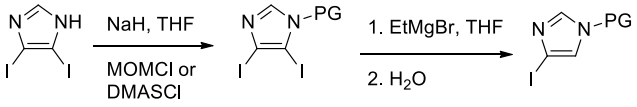
Scheme 37. Isomerization of lithiated imidazole.

As an alternative to overcome this problem, Jacobi et al. used halogen-magnesium exchange to form 4-metalated Grignard intermediates which do not rearrange to the isomeric 2-metalated specie[91]. With that method they have synthesized bis(imidazolyl)methylenes wich is a motif found in natural product (Scheme 38). Tr and DMAS protecting groups can be used and good yields are obtained with different R substituents.



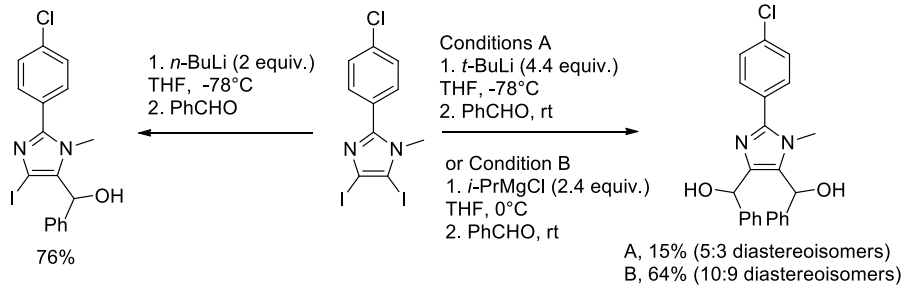
Scheme 38. Synthesis of bis(imidazolyl) carbinols by double Grignard reaction. R = H, alkyl chain.

One can also use this halogen-magnesium exchange to form regioselectively the 4-halogenoimidazole from the 4,5-halogenoimidazole. This method can be used for reductive removal of 5-substituent (Scheme 39).[92]



Scheme 39. Reductive removal of 5-iodo substituent.

Besides, imidazolyl dianions can also be formed by dimagnesio species. Halogen-magnesium exchange allows the production of imidazolyl dianions with vicinal dianions. In this context, Butz et al.[93] showed that organomagnesium species have greater stability than organolithium species. Indeed, they tried to do vicinal lithiation by treatment of the diiodoimidazole with *n*-Buli at -78°C followed by addition of benzaldehyde but it did not yield any dianion-derived products (Scheme 40). Instead, an iodo compound arising from 5-monoanion formation was isolated in 76% yield. A reaction performed with *t*-Buli at -78°C, followed by addition of benzaldehyde, did yield the desired 4,5-disubstituted product but only in 15% yield (5:3 ratio of diastereoisomers). These conditions were experimentally less convenient than those using *i*-PrMgCl. However, it was found that 4,5-dimagnesioimidazoles appear to be more readily formed than the corresponding dilithio compounds. An explanation can be the existence of destabilizing electrostatic interactions in the transition state leading from the presumed 5-monomagnesio intermediate to the vicinal diamagnesio compound is reduced (in comparison to the dilithio species) due to the greater covalency of the C-Mg bond.

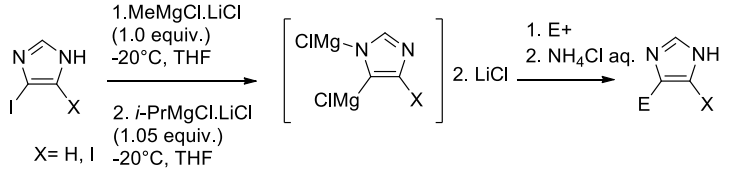


Scheme 40. Reaction of 4,5-iodoimidazole with an electrophile.

Moreover, different electrophiles were also introduced on other N1, C2-protected imidazoles with varying yields. To know if the C4- and C5-anions might react with electrophiles at different rates in a regioselective manner, one experiment has been done. Benzaldehyde (1 equiv.) was added to a solution of the dianion derived from diiodide 1-methyl-2-phenylimidazole at -78°C. The reaction was then

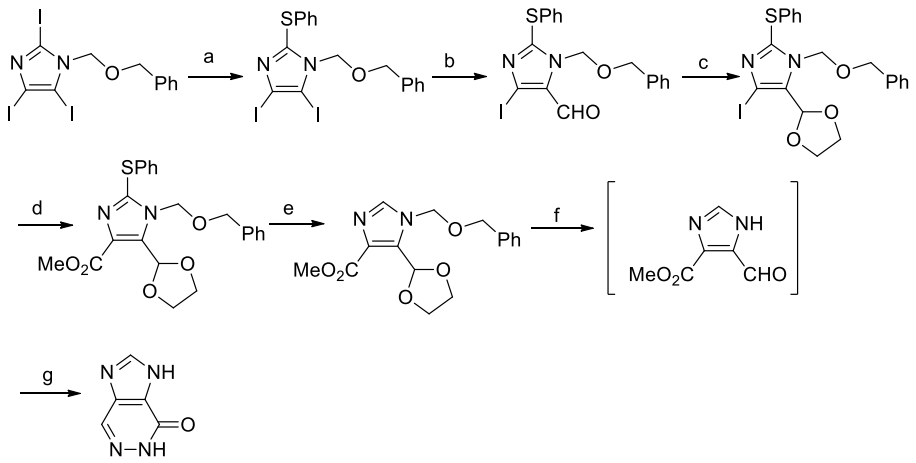
allowed to warm to ambient temperature and fully quenched with water to give (1-methyl-2-phenyl-1*H*-imidazole-4,5-diyl)bis(phenylmethanol) (34%; 10:9 ratio of diastereoisomers), (1-methyl-2-phenyl-1*H*-imidazol-5-yl)(phenyl)methanol (24%), (1-methyl-2-phenyl-1*H*-imidazol-4-yl)(phenyl)methanol (10%), and 1-methyl-2-phenyl-1*H*-imidazole (17%). In summary, the results do not indicate any synthetically useful differences in reactivity between the two carbanions.

Futhermore, Kopp et al.[94] reported iodine-magnesium exchange on unprotected imidazole. 1,4-Dimagnesioimidazoles were formed and then different electrophiles were added allowing substitution at C4 position without using protecting groups. This reaction was carried out in the presence of LiCl which improved the solubility of organometallic reagents and at the same time, enhance dramatically their reactivity (Scheme 41).



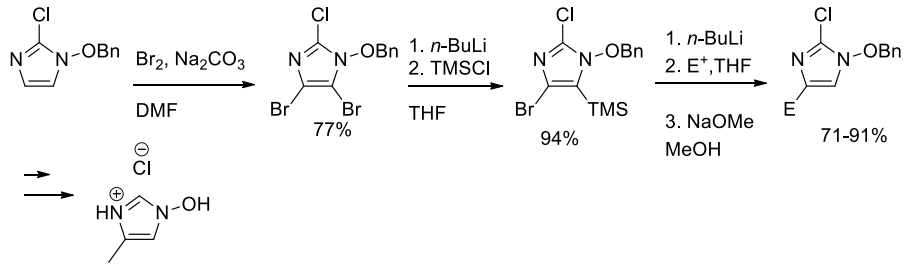
Scheme 41. C4-substitution by I-Mg exchange on unprotected imidazole.

2,4,5-Polyhaloganated imidazoles can undergo sequential metal-substitution reaction in the order 2 > 5 > 4. These versatile substrates are employed in synthesis such as the synthesis of imidazopyridazinone (purine-ring analog, Scheme 42).[95] The synthesis of this 4,5-non-symmetrically-disubstituted imidazole was carried out in 7 steps from the 1-[(benzyloxy)methyl]-2,4,5-triiodoimidazole. The halogen-metal exchange allows sequential functionalization, first at C2 (SPh, blocking agent), then C5 (CHO, and subsequently protected) and finally C4 (ester) position. And lasts steps are the deprotection of C2 and *N*-protecting group followed by cyclization to obtain a purine-ring analog which is a potential inhibitor of cellular purine nucleoside-specific facilitated diffusion.



Scheme 42. Synthesis of 2-aza-3-deazahypoxanthine. Reactions conditions: a. BuLi, -78°C, PhSSPh, -78 to 25°C, 94%; b. BuLi, -78°C, DMF, 99%; c. $OH(CH_2)_2OH$, py/TsOH, benzene, 58%; d. BuLi, -78°C, $ClCO_2Me$, 80%; e. Al(Hg), 25°C, 6h, 59%; f. 3M HCl, 74%; g. NH_2NH_2, EtOH, reflux, 24h, 59% over two last steps.

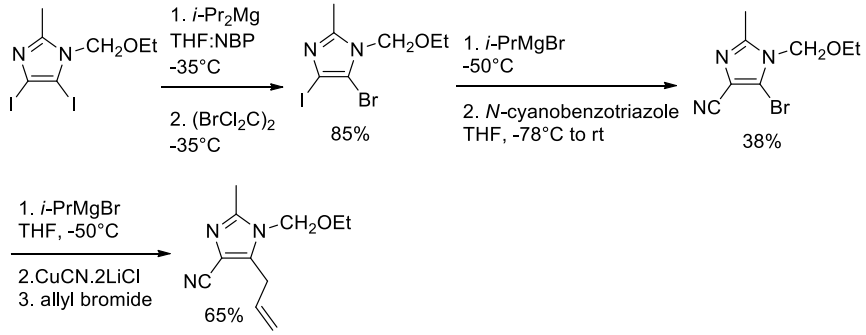
Even better, one can also uses the difference in reactivity between chlorine, bromine, iodine, allowing another order of control. Eriksen et al.[96] have reported the synthesis of 4- and 5-substituted 1-hydroxyimidazole using this strategy (Scheme 43). Here, *n*-BuLi has selectively exchange with bromine in preference over chlorine even if this latter was located at the more reactive C2 position.



Scheme 43. Synthesis of 1-hydroxyimidazole. E^+= H, Me, CHO, I.

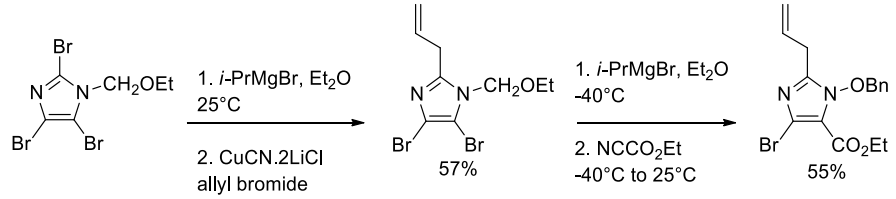
Knockel and coworkers[97] have also performed chemoselective double functionalization from *N*-protected-4,5-diiodoimidazole. The 5-iodine substituent is the most reactive position toward I/Mg-exchange due to the formation of a chelate stabilized magnesium reagent (complexation with the protecting group: CH_2OEt). They did a contra-thermodynamic I/Mg-exchange of the iodine at position 4 (Scheme 44). Thus treatment of the diiodoimidazoles with *i*-PrMgBr and reaction with $(BrCCl_2)_2$ gave the bromoiodoimidazole in 85% yield. Its reaction with *i*-

PrMgBr led to a fast I/Mg-exchange. Then reaction with an electrophile, *N*-cyanobenzotriazole, provided the C4-substitution which after bromine-magnesium exchange and allylation furnished the disubstituted imidazole.



Scheme 44. Chemoselective functionnalization on dihalogeno-imidazole.

Concerning the sequential metalation, halogen-magnesium exchange can also be used. Abarbri et al.[98] have observed that Br-Mg exchange reactions on heterocycles are significantly more selective than the corresponding Br-Li exchange reaction. This Br-Mg exchange has been aplied to tribromoimidazoles (Scheme 45). First, the bromide in position 2 undergoes a Br-Mg exchange and after allylation the dibromoimidazole is obtained with 57% yield. This excellent selectivity is only obtained by performing the reaction in ether. Next the bromide in position 5 undergoes the Br-Mg exchange in THF at -40°C affording after reaction with ethyl cyanoformate the expected 2,5-functionnalizated-4-bromo-imidazole wich is an excellent substrate for futher Br-Mg exchange.

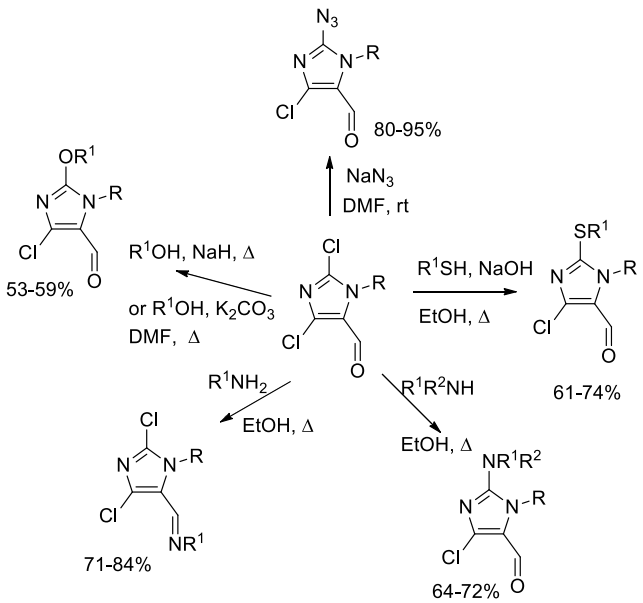


Scheme 45. Sequential Br-Mg exchange reactions.

1.4.3.4. C2-substitution by S_NAr

C2-substitution can be done by aromatic nucleophilic substitution reaction. This reaction requires three typical conditions; a good nucleophile, a good leaving group on the aromatic species and electron-withdrawing groups in *ortho* or *para*-position from the leaving group (however the most important factor is the electrophilicity of the carbon). The nucleophile can be an alcohol, an amine, a thiol, a cyano or a fluoro

group while the leaving group is a halogen atom, a sulfonic or a nitro group. The S_NAr involves two steps: the addition of a nucleophile on the aromatic ring, on the carbon which bears a leaving group, and the expulsion of this leaving group to reform the aromaticity. The addition is the rate limiting step. In the case of imidazole, the attack takes place at the C2-position. Different methodological studies have been done. Chornous et al.[99] estimated the reactivity and selectivity of reactions of imidazoles with versatile nucleophiles by a quantum chemical investigation of the molecule of *N*-protected-2,4-dichloro-5-formylimidazole in the processes of the chlorine substitution (Scheme 46). They found that in each cases substitution occuered in C2 position and not C4. They have introduced different functions at C2; azido, alcool, thiol, secondary amine with moderate yields. But for the primary amine, no incorporation at C2 was observed but formation of an imine by addition to aldehyde occurred.



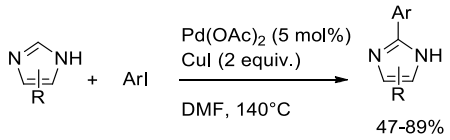
Scheme 46. S_NAr . R= Me, Ph, 4-FC_6H_4, 4-ClC_6H_4, 2-$MelC_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$; $R^{1,2}$= alkyl, aryl.

Sulfonyl group are also used has leaving group at C2 position to give sulfur and oxygen substitutents at C2 position.[100]

1.4.3.5. C-functionalization using transition metal-catalysis

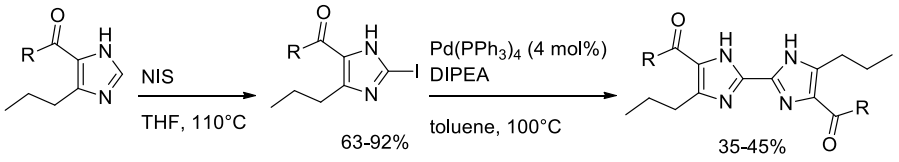
1.4.3.5.1. C2 functionalization

Bellina et al.[101] have described a base- and ligand-free Pd- and Cu-mediated C2-arylation of (NH)-imidazoles. Electron-deficient, electron-rich and electron-neutral 2-arylimidazoles were obtained in good yields in the presence of a catalytic amount of $Pd(OAc)_2$ and two equivalents of CuI in DMF at 140°C. This protocol enabled high regioselectivities (Scheme 47).



Scheme 47. Pd-catalysed Cu-mediated C2-arylation of (NH)-imidazoles. R = H, Ph; Ar = Ph, *p*-MeOPh, *p*-CF_3Ph, *o*-MePh.

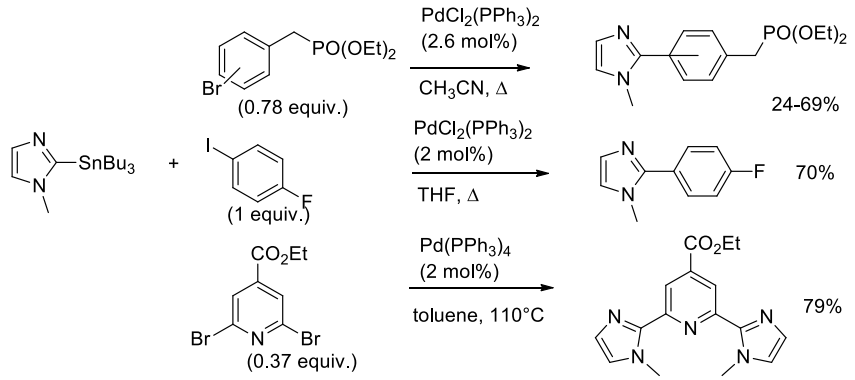
Causey et al.[102] have formed bisimidazole by Pd-catalysed homocoupling of 2-iodoimidazoles in toluene in the presence of DIPEA. The installation of the 2-iodine was made with NIS (Scheme 48).



Scheme 48. Synthesis of (NH)-2,2'diimidazoles. R = NHMe, NHAr, NHAlk., pyrrolidine.

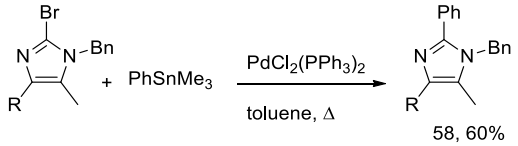
Concerning the C2 functionnalization of 1-substituted imidazoles, different Pd-catalysed reactions were used such as the Stille, Suzuki, Negishi and Sonogashira coupling reactions.

The Stille type reactions use a 2-stannylimidazole and an aryl halide. Methyl-2-tributylstannylimidazole can be prepared from C2 lithiation of *N*-methylimidazole followed by treatment with tributyltin chloride. Different research groups have employed this Stille reaction. For instance, Kennedy et al.[103] and Brauer et al.[104] used catalytic $PdCl_2(PPh_3)_2$ in reflux of CH_3CN and THF respectively with different aryl halides while Vermonden et al.[105] used $Pd(PPh_3)_4$ as catalyst for a double cross-coupling (Scheme 49).



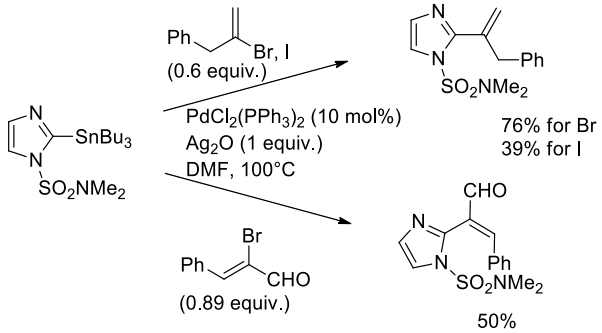
Scheme 49. Stille-type reaction for the synthesis of C2-substituted imidazoles. Br and $CH_2PO(OEt)_2$ in *o,m,p*-positions.

One can also inverse the reactants by using a 2-bromoimidazole and an aryltrimethyltin. Wang et al.[106] have done so with the system $PdCl_2(PPh_3)_2$ at reflux of toluene with moderate yields (Scheme 50).



Scheme 50. Stille coupling with 2-bromoimidazoles and aryltrimethyltin. R= Br, Ph.

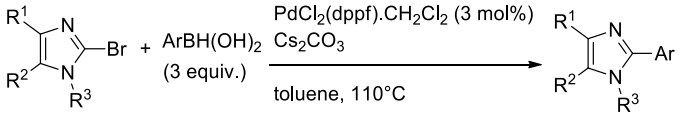
Another Stille reaction was developed with 1-(*N*,*N*-dimethylsulfamoyl)-2-tributylstannylimidazole and alkenyl halides (Scheme 51).[107] This coupling was catalyzed by $PdCl_2(PPh_3)_2$ with stoechiometric amount of Ag_2O which seems to be important for the acceleration of the reaction. Best yields were obtained with bromoderivatives.



Scheme 51. Stille cross-coupling with alkenyl halides.

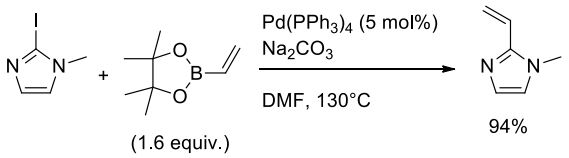
For the Suzuki coupling, halogenated species, boronic acids (or esters) and a base are needed. Lee et al.[108] have synthesized a variety of 1-substituted-2-arylimidazole by reaction of arylboronic acids and 1-substituted-2-bromoimidazoles with the system $PdCl_2$(dppf), Cs_2CO_3 (Table 5).

Table 5. Suzuki coupling with 2-bromoimidazoles.



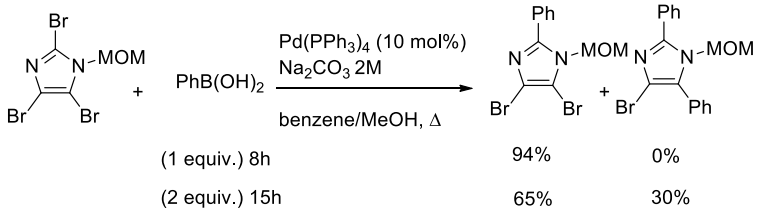
R^1	R^2	R^3	Ar	Yield (%)
CO_2Et	Ph	Me	Ph	99
CO_2Et	Ph	Me	4-CF_3Ph	99
CO_2Et	Ph	Me	4-Ph-Ph	97
CO_2Et	Me	Ph	4-(OTBS)Ph	93
H	Ph	Ph	Ph	41
CO_2Et	Ph	Me	1-naphthyl	97
CO_2Et	Ph	Me	styryl	95
CO_2Et	Me	Ph	4-OMePh	90
CO_2Et	Me	Ph	4-(CO_2Et)Ph	97

Moreover, boronic esters have been used. 1-Methyl-2-iodoimidazole has been coupled with commercially available pinacol vinyl boronate to give in excellent yield 1-methyl-2-vinylimidazole (Scheme 52).[109]



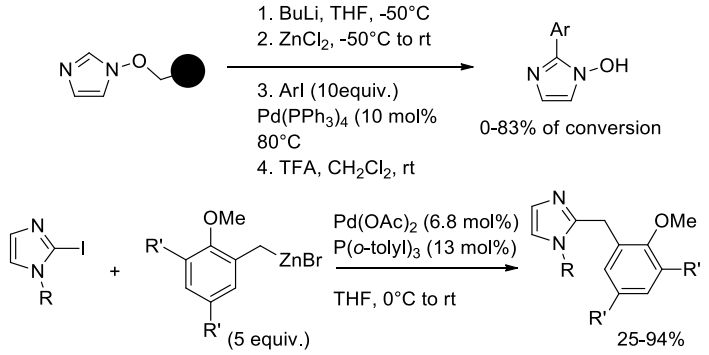
Scheme 52. Suzuki coupling with boronic esters.

Trihalogenated imidazoles have been also used for selective Pd-catalyzed at C2 position. 1-Protected-2,4,5-tribromoimidazole has been used for selective C2-substitution with boronic acids. The use of an equimolar amount of arylboronic acids gave the corresponding aryldibromides but when two equivalents of phenylboronic acid and prolonged reaction time were used, the 2,5-diphenylimidazole was produced (Scheme 53).[110]



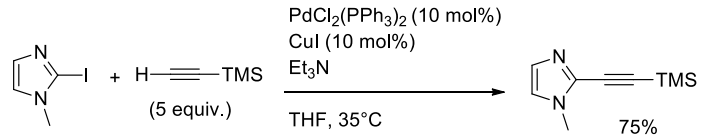
Scheme 53. Suzuki coupling with trihalogenated imidazoles.

Neigishi coupling can also be achieved. Havez et al.[111] have reported that 1-hydroxyimidazole bound to a resin can be lithiated (with *n*-BuLi) at C2 position and then transmetallated to give 2-imidazolylzinc chloride (Scheme 54). This latter species can cross-couple with aryl iodides in the presence of catalytic $Pd(PPh_3)_4$. Good conversion was obtained with *meta*- and *para*- aryl iodides (electron-donating and -withdrawing group) but not with *ortho*-substituted likely due to steric hindrance. Finally, treatment with TFA afforded 2-aryl-1-hydroxyimidazole. One can also use the inverse reactivity namely; haloganeted imidazoles and benzylzinc halides. Utas et al.[112] have reported such coupling reactions with $Pd(OAc)_2$-P(*o*-tolyl)$_3$-catalyst in THF with good yields.



Scheme 54. Neigishi coupling for the synthesis of 2-substituted imidazoles. Ar = *p*-Me, OMe, NH_2, NO_2, *m*-OCOMe, *o*-NO_2, OCOMe, F; R = Me, Bn; R' = H, *t*-Bu.

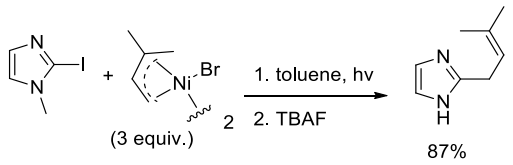
Furthermore, Sonogashira coupling reactions are used for C2-functionalization but limited examples exist. For instance, Nakamura et al.[113] synthesized 1-methyl-2-TMSethynylimidazole in 75% yield with $PdCl_2(PPh_3)_2$/CuI-catalyzed of 1-methy-2-iodoimidazole and an excess of TMSacetylene (Scheme 55).



Scheme 55. Synthesis of 2-alkenylimidazole by Sonogashira coupling.

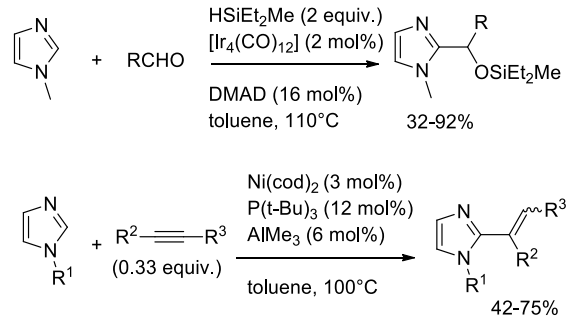
Moreover, other catalyzed systems have been developed for the introduction of alkyl, alkenyl, aryl groups at position C2 of the imidazole.

Allylation of imidazole has also been done with (π-allyl)nickel reagents. 2-Iodo-1-SEMimidazole in the presence of an excess of η^3-prenylnickel bromide dimer in toluene gave resulting C2-allylated imidazole after deprotection with TBAF (Scheme 56).[114]



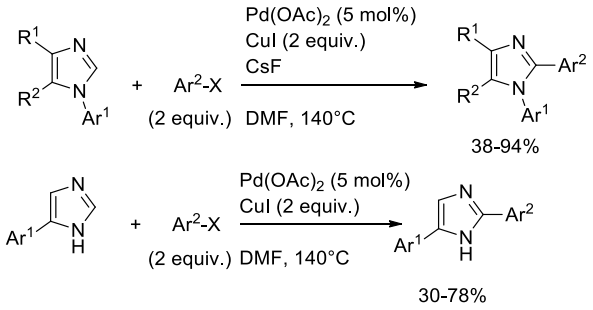
Scheme 56. Synthesis of 2-prenylimidazoles.

In addition, an Irridium complex has been developed by Fukumoto et al.[115] This system employs 1-methyl-imidazole with aldehyde and dimethylsilane in the presence of $[Ir_4(CO)_{12}]$ and acetylenedicarboxylate (DMAD) as a ligand (Scheme 57). No reaction occurred in the absence of diethylmethylsilane. Different aldehydes with alkyl, aryl, alkylester substituents were used with moderate to good yields. Kanyiva et al.[116] used a Ni-Lewis acid catalyst for direct C2-alkenylation of imidazoles thanks to C-H bond activation and insertion of internal alkynes. The system used was a $Ni(cod)_2/P(t\text{-}Bu)_3/AlMe_3$ catalyst in toluene. Interestingly, when symmetric acetylenes substituted with dialkyl or 1-alkyl-2-trimethylsilylacetylenes were used, the reaction products was enriched in their (*E*)-stereoisomers. And when symmetric acetylenes with diaryl substituents were employed prevalent (*Z*)-isomers were obtained (isomerization under reactions conditions).



Scheme 57. Ir- and Ni-catalysed synthesis of 2-substituted imidazoles. R = alkyl, aryl, alkylester, R^1 = Bn, Me, Ph; $R^2 = R^3$ = n-Pr (*E*/*Z*) = 93:7, Ph (*E*/*Z*) < 1:99 or $R^2 \neq R^3$: TMS and Ph (*E*/*Z*) = 20:80, TMS and n-C_6H_{13}(*E*/*Z*) > 99:1.

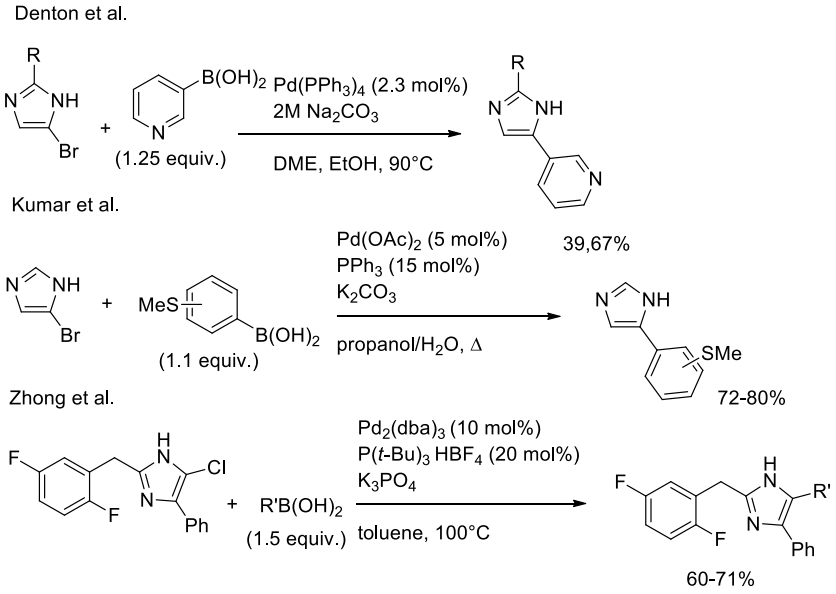
Few protocols of transition-catalyzed direct C2 arylation of 1-substituted imidazoles with aryl halides have been reported. Kondo et al.[117] showed that the addition of CuI in a Pd-catalyst ($Pd(OAc)_2$, PPh_3, Cs_2CO_3) arylation gives selective C2-arylation. Without CuI, the C5-arylation was obtained. Other protocols with ligand-free conditions (from 1-protected imidazole) have been also developed. For example, Bellina et al.[118] synthesized 1,2-arylimidazoles containing electron-withdrawing and electron-donating group with moderate to good yields by coupling 1-arylimidazoles with aryl halides in the presence of catalytic $Pd(OAc)_2$, CuI and CsF (Scheme 58). But (NH)-4(5)-Imidazoles can also be used as reactant. Bellina et al. have showed that 2,4(5)-diarylimidazoles could be synthesized in modest to good yields by direct arylation of 4(5)-arylimidazoles with activated or unactivated aryl bromides and iodides in the presence of catalytic $Pd(OAc)_2$, CuI under base- and ligand-free conditions.



Scheme 58. Synthesis of 2-arylimidazoles by direct C2-arylation. X = Br, I; R= H, Cl, Me.

1.4.3.5.2. C4 functionalization

(NH)-imidazoles can be functionalized in their C4 position by Suzuki cross-coupling. In the literature, one can find that the Suzuki coupling involves reaction of (NH)-4(5)-haloimidazoles with boronic acids. 3-((2-Methyl)imidazol-4yl)pyridine were prepared from 4-bromoimidazole and pyridine-3-ylboronic acid with $Pd(PPh_3)_4$ as a catalyst in the presence of Na_2CO_3 as a base in DME/EtOH (Scheme 59).[119] Another group performed arylation with methylthienylboronic acids with the system $Pd(OAc)_2/PPh_3$ and obtained good yields of the desired C4-arylated imidazoles.[120] 4(5)-Chloroimidazole were also used as a reactant. Zhong et al.[18] reported the coupling of 4(5)-chloroimidazole with aryl- and alkenylboronic acids with a catalyst specially developed for chloroaryl species.[121]

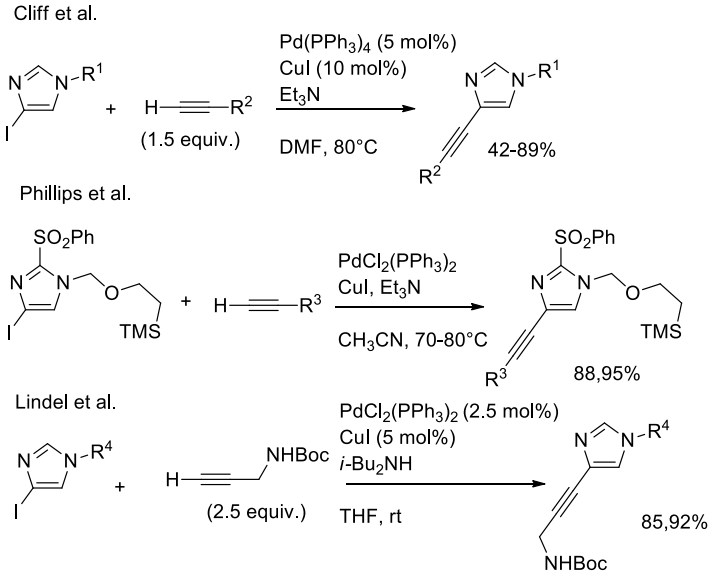


Scheme 59. C4-functionalization of (NH)-imidazoles with Suzuki coupling. R = H, Me; -SMe in *o*,*m*,*p*-positions; R' = CH=CH, *n*-Bu, *o*-MePh, Ph.

Concerning the C4-functionalization of *N*-substituted imidazoles, as for the functionalization of C2, Pd-catalyzed reactions are used: Sonogashira reaction, Stille, Heck, Neigishi and Suzuki coupling.

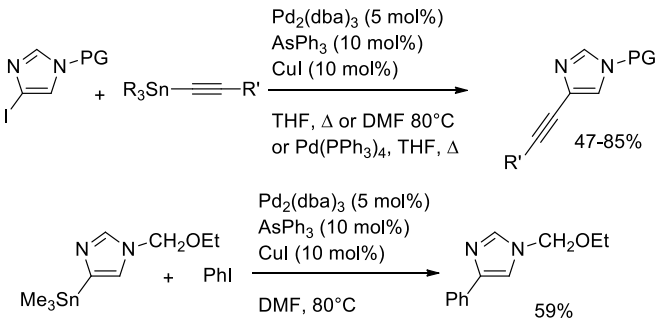
So, 1-alkynyl groups have been introduced on 1-protected-4-iodoimidazoles by Sonogashira-type reactions. Cliff et al.[122] synthetized a variety of 4-(1-alkynyl)imidazoles with the system $Pd(PPh_3)_4$ and CuI-catalyzed with different 1-protected-4-iodoimidazoles with 1-alkynes (Scheme 60). Phillips et al.[123] also

utilized similar conditions with SEM-protected imidazoles and terminal alkynes. Boc-protected propargylic amine can also be coupled with iodoimidazoles under the reaction conditions: $PdCl_2(PPh_3)_2$/CuI-catalysed, in the presence of $(i\text{-Bu})_2NH$ as a base.[124]



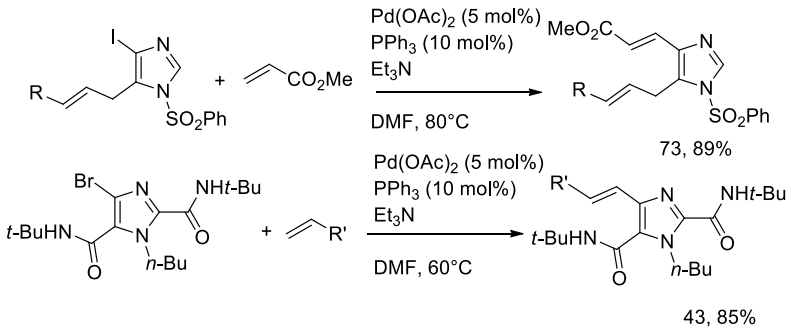
Scheme 60. Synthesis of 4-alkynylimidazole by Sonogashira reaction. R^1 = Ts, SO_2Ph, CH_2OEt, Tr: R^2 = Ph, CH_2OTBS, $(CH_2)_2OTBS$; R^3 = $(CH_2)_2OTHP$, TMS; R^4 = Tr, SO_2Ph.

For the Stille coupling, Cliff et al. have also performed it.[122] A larged variety of 1-protected-4-(1-alkynyl)imidazoles have been synthesized with Pd-CuI-catalyzed reactions, 1-protected-4-iodoimidazoles and 1-alkynyltrialkylstannanes (Scheme 61). 4-Alkenylimidazoles have also been formed by this Stille reaction. One can also use the inverse reactivity by using 1-substituted-4-trialkylstannylimidazoles and iodobenzene.



Scheme 61. Stille reaction for C4-functionnalization of imidazoles. PG = Ts, SO_2Ph, CH_2OEt; R = Bu, Me; R' = Ph, CH_2OTBS, $(CH_2)_2OTBS$, $(CH_2)_4CH_3$.

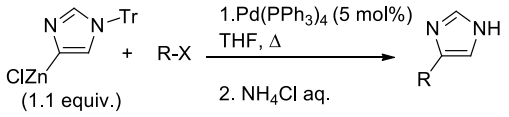
Only a few examples of Heck coupling have been reported. Moreover, in several cases, reaction of 4-iodoimidazole with substituted butenes do not give the desired product but the product of homocoupling.[125] Nevertheless, some groups succeeded in performing Heck reaction. Dobler et al.[126] performed reaction between 4-iodoimidazole and methyl acrylate with the system $Pd(OAc)_2/PPh_3$ with Et_3N (Scheme 62). Chittiboyina et al.[127] have also used similar conditions but with 4-bromoimidazole derivatives.

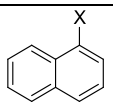
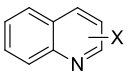
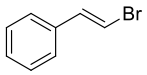
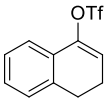


Scheme 62. Heck-coupling for C4-functionalization of imidazoles. R = H, Me; R' = CO_2Me, *p*-OMePh.

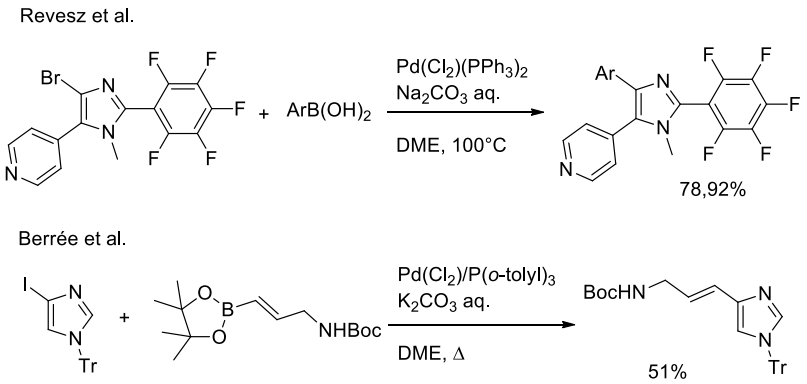
Neigishi-type reaction has been used. The imidazolylzinc chloride was coupled with different halides or triflates compounds (Table 6). Good yields were obtained with the different electrophiles. The N1-protected group of imidazole, the trityl group, was directly deprotected after the coupling reaction.[128]

Table 6. C4-functionalization of imidazole by Neigishi coupling.



RX	Yields (%)	RX	Yields (%)
	X= I, 80 X= OTf, 76		X= 4-OTf, 72 X= 3-Br, 74
	71		76

Even the Suzuki coupling has found widespread applications for the C4-functionalization of *N*-substituted imidazoles. For examples, Revesz et al.[129] reported the synthesis of 1-SEM-2,4,5-triarylimidazole by $PdCl_2(PPh_3)_2$-catalyzed reaction of 1-SEM protected 4-bromoimidazole with arylboronic acids (Scheme 63). While Berrée et al.[130] used boronic esters and 4-iodoimidazole for the synthesis of 4-alkenylimidazole. The *E* regioselectivity from the boronic ester was retained in the Suzuki product without detection of the *Z*-form.

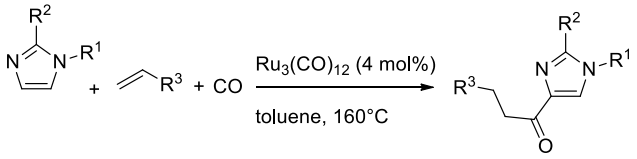


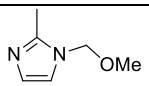
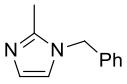
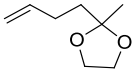
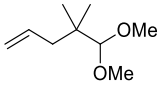
Scheme 63. Suzuki coupling for C4-functionalization of imidazoles. Ar = benzo[b]furan, 3-(CF_3)phenylboronic acid.

In addition of Pd-catalyzed reaction, other metal-catalysed reaction has been used like ruthenium-catalyzed reaction. Regioselective acylation at C4 of 1,2-disubstituted imidazoles has been described with 1-alkenes and CO in the presence of a catalytic amount of $Ru_3(CO)_{12}$ (Table 7).[131] The reaction is both highly efficient

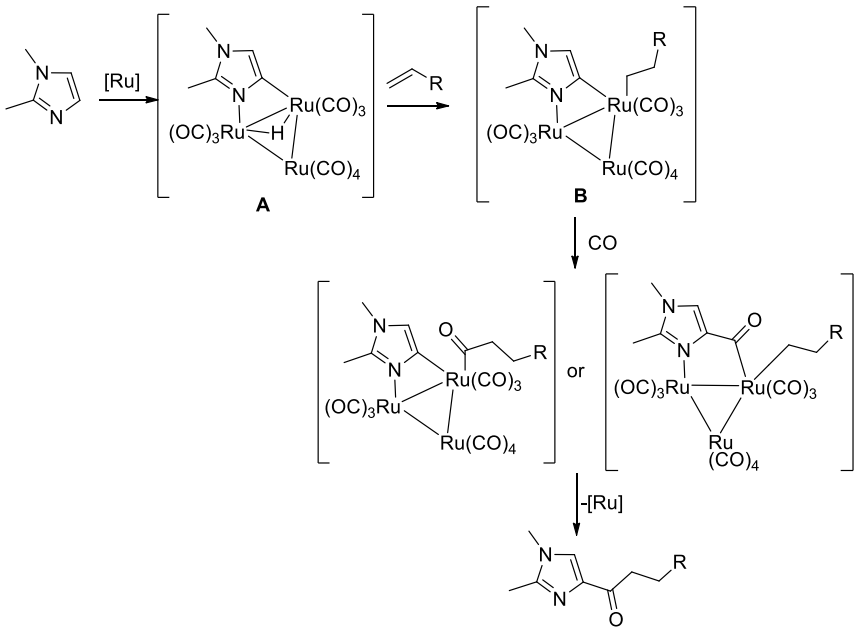
and selective. A cyclic olefin was applicable to the present reaction. The reaction of *R*-methylstyrene gave a somewhat lower yield but led to a single isomer. The present reaction was also compatible with *N*-protecting groups such as methoxymethyl and benzyl. Unsaturated ketals underwent coupling reactions to produce the monoprotected 1,6-diketones and 1,2-fused bicyclic imidazoles also underwent coupling regioselectively.

Table 7. [Ru]-catalyzed coupling of imidazoles/CO/olefins.



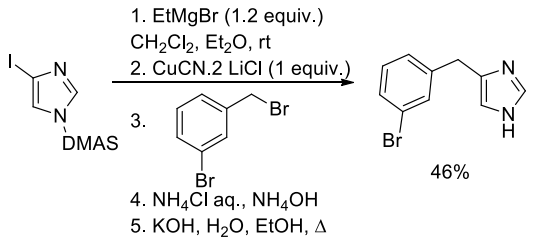
Imidazole	Olefin	Yields ,% (Regio.)	Imidazole	Olefin	Yields ,% (Regio.)
		50			95 (>99:1)
		42 (>99:1)			72 (97:3)
		79 (>99:1)			90 (>99:1)

A mechanism has been postulated for this reaction (Scheme 64). The coordination of the sp^2 nitrogen to ruthenium leads to the oxidative addition of a C-H bond at the 4-position to give the hydride-ruthenium complex **A**. This latter reacts with an olefin to give the alkyl-ruthenium complex **B**. Then the alkyl-ruthenium complex **B** undergoes CO insertion, followed by reductive elimination to give the final product. The issue of whether the insertion of CO occurs into the alkyl-ruthenium bond or imidazolyl-ruthenium bond is not known.



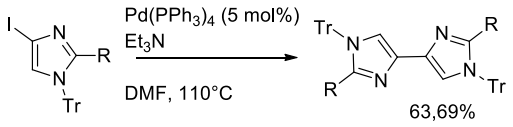
Scheme 64. Plausible mechanism for carbonylation of imidazoles.

Futhermore, an example of the use of a cuprate for the C4-functionalization of 1-substituted-4-halideimidazole has been described. Wijtmans et al.[132] generated a Grignard intermediate from DMAS-protected 4-iodoimidazole (Scheme 65). After a magnesium-copper exchange, the resulting cuprate was reacted with 4-bromo-benzylbromide to install the benzylic moity. Following basic deprotection, they obtained a moderate yield (46%) of the C4-imidazole derivatives.



Scheme 65. Synthesis of 4(5)-(3-bromobenzyl)imidazole.

Finally, Pd-catalyzed homocoupling was used by Cliff et al.[133] to synthesize 4,4'-biimidazole derivatives. The homocoupling was performed with 4-iodo-1-tritylimidazoles, catalytic $Pd(PPh_3)_4$, Et_3N in DMF with good yields (Scheme 66).

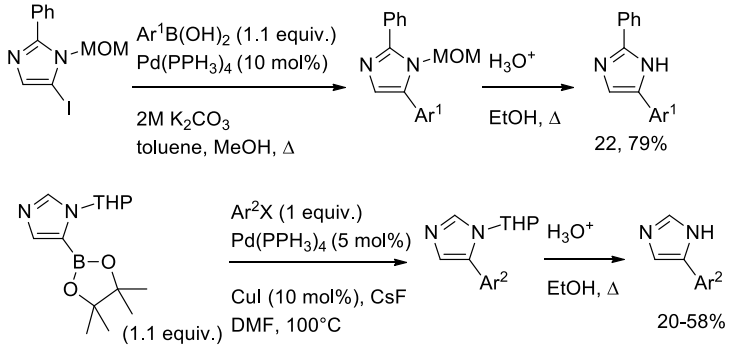


Scheme 66. Synthesis of 4,4'-diimidazoles. R = Me, H.

1.4.3.5.3. C5 functionalization

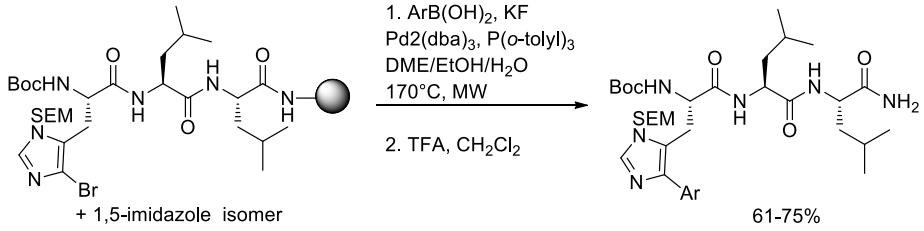
Similary to other carbon functionnalization, C5-functionalization uses transition metal-catalyzed C-C bond forming reactions which include Suzuki and Stille cross-coupling reactions, direct arylation with (hetero)aryl halides and insertion of alkynes into C-H bond of imidazoles.

Concerning the Suzuki coupling, 5-iodo-*N*-protected imidazole can react with phenylboronic acid in the presence of a catalytic amount of Pd(0). For example, 5-aryl-1-methoxymethyl-2-phenylimidazoles were obtained from the corresponding 5-iodoimidazole and arylboronic acids in the presence of $Pd(PPh_3)_4$ and K_2CO_3 as a base (Scheme 67).[134] Boronic esters on imidazole have also been used. Even in the presence of fragile groups (CN, CO_2Et, CHO), the coupling either with (het)aryl iodides or bromides takes place. The results are, nevertheless, better with iodo derivatives.[135]



Scheme 67. C5-functionnalization of imidazoles by Suzuki coupling. Ar^1 = *o*-AcPh, *p*-MeSPh; Ar^2 = aryl with *o,m,p*-substituents, heteroaryl.

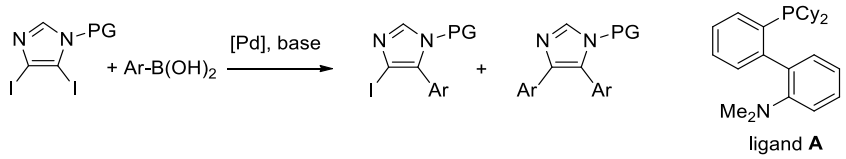
Microwave irradiation was also used to promote efficiently the Suzuki coupling. Cerezo et al. [136] coupled SEM-protected-5-bromohistidine tripeptidyl (on resin) with other arylboronic acids possessing substituted benzene, pyridine, and thiophene rings (4 equiv.) derivatives in a mixture of MeOH, DME, water in the presence of KF as a base and $Pd_2(dba)_3$ (20 mol%), P(*o*-tolyl)$_3$ (0.4 equiv.) as a catalyst. The reaction was done at 170°C with microwave irradiation during 15 minutes with moderated to good yields (Scheme 68).



Scheme 68. C5 functionnalization via Suzuki coupling under microwave heating. Ar = aryl with *o*, *m*, *p*-substituents, pyridine, thiophene.

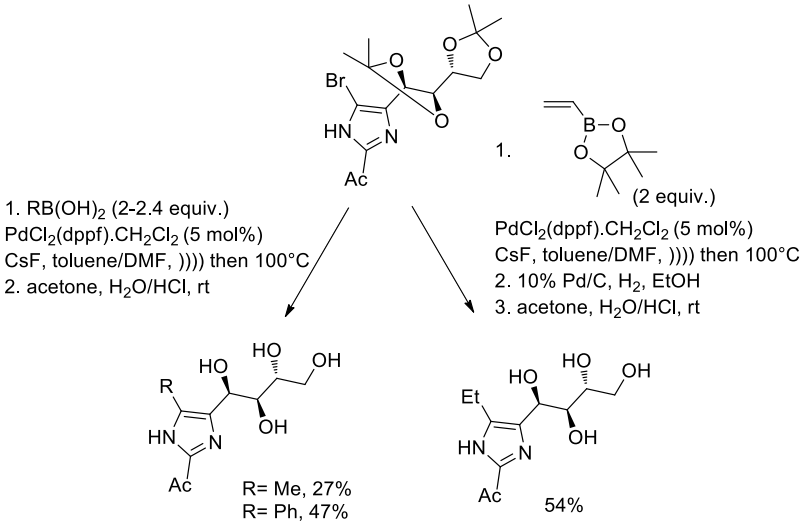
When 4,5-diiodoimidazoles was used in the Suzuki coupling with different equivalent of arylboronic acids, C5 selectivity was observed but subsequent bis-coupling was also observed (Table 8). However, a balance between the base and the stability of the *N*-protecting group was found to be crucial for high overall yields. Especially the use of the sulfamoyl group led to certain limitations of the reaction conditions and often resulted in moderate to low reaction yields. Both electron deficient and electron rich boronic acids were found to react with the diiodoimidazole under the highlighted conditions.[126]

Table 8. Suzuki reaction of 1-protected-4,5-diiodoimidazoles.



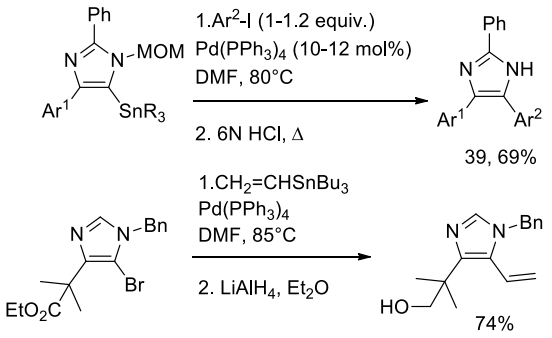
PG	$ArB(OH)_2$		Conditions	Yields (%)	
	Ar	Equiv.		5-aryl	4,5-aryl
Bn	4-FC_6H_4	2	$Pd(PPh_3)_4$, Na_2CO_3, EtOH/DME, 95°C, 8h	27	53
Bn	4-FC_6H_4	4	$Pd(PPh_3)_4$, Na_2CO_3, EtOH/DME, 95°C, 16h	_	91
Bn	3,3-$(MeO)_2C_6H_3$	4	$Pd(OAc)_2$, **A**, CsF, dioxane/DMF, 80°C, 12h	_	95
DMAS	Ph	2	$Pd(PPh_3)_4$, K_2CO_3, DMF, 60°C, 12h	16	24
Me	Ph	2	$Pd(OAc)_2$, **A**, CsF, dioxane/DMF, 80°C, 12h	24	48

Even free (NH)-5-bromoimidazole undergoes ultrasound-promoted Suzuki cross-coupling with methyl- and phenyl-boronic acids (Scheme 69). After ketal deprotection were obtained in moderate yield. An analogous reaction was done with vinylboronic pinacol ester. This 5-vinyl was subsequently hydrogenated to give the corresponding 5-ethylimidazole.[137]



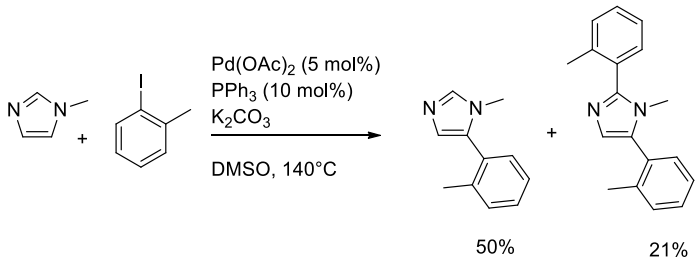
Scheme 69. Suzuki coupling with free (NH)-imidazole.

Secondly, the Stille reaction, despite its drawbacks due to the presence of toxic, hard to remove tin by-products and low atom economy, has been frequently used for C5-functionnnalization of 1-protected imidazoles. 5-Trialkylstannylimidazoles and aryl iodides were used for the Stille reaction in the presence of $Pd(PPH_3)_4$ (Scheme 70). (NH)-2,4,5-Triarylimidazoles was formed after deprotection of the MOM group.[138] C5-vinyl substituent was also introduced by Stille coupling between 5-bromoimidazole and vinyltributylstannane.[139]



Scheme 70. Stille reaction with 1-protected imidazoles. Ar^1 =Ph, Py; Ar^2 = m-$CF_3C_6H_4$, MeSpyrimidine.

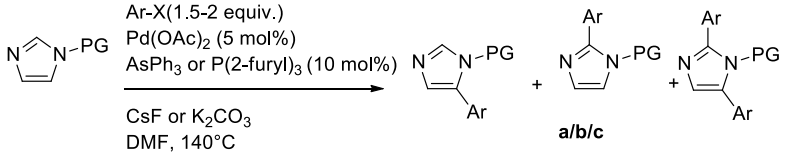
Direct Pd-catalyzed C5 arylation of *N*-substituted imidazoles with (hetero)aryl halides has been developed. This methodology offers advantages such as simplicity and the use of readily available reactants. But it suffers from low regioselectivities. One early example was done by Arai et al.[140] The Pd-catalyzed reaction of 1-methylimidazole with 2-iodotolunene resulted in a mixture of 5- and 2,5-(di)arylated products (Scheme 71).



Scheme 71. C5 and C2-C5 products from direct Pd-arylation.

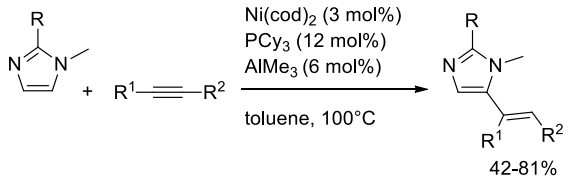
Bellina and coworkers[141] conducted many assays on Pd-catalyzed selective C5-arylation. They have used 1-arylimidazoles and found that this could be achieved without C2 and C2/C5 (bis)arylation when it was done with aryl bromides or iodides. The reaction was done in DMF with CsF and $Pd(OAc)_2/AsPh_3$ as a catalytic system (Table 9). However, no arylation was observed when strongly deactivated 2,4,5-trimethoxyphenyl iodide was used as an electrophile or with an imidazole bearing a strong electron-withdrawing group (4-$MeSO_2C_6H_4$) on the nitrogen atom. This methodology was also applied to *N*-methyl and benzylimidazole. Yields ranged from 24 to 80% with the catalytic system $Pd(OAc)_2/As(2\text{-furyl})_3$ and K_2CO_3 as a base.

Table 9. Pd-catalyzed C5 direct arylation with 1-protected imidazoles. [a] reagent quantitatively recovered.



PG	X	Ar	Yields in %, (a/b/c).
Ph	I	4-$MeOC_6H_4$	49, (95:5:0)
Ph	Br	4-MeC_6H_4	43, (100:0:0)
Ph	I	Ph	41, (86:3:11)
4-$MeOC_6H_4$	I	4-MeOPh	63, (88:3:9)
3,4,5-$(MeO)_3C_6H_2$	Br	4-$MeOC_6H_4$	61, (100:0:0)
4-ClC_6H_4	I	4-$MeOC_6H_4$	36, (100:0:0)
4-$MeOC_6H_4$	I	3,4,5-$(MeO)_3C_6H_2$	[a]
4-$MeSO_2C_6H_4$	Br	4-$MeOC_6H_4$	[a]
Me	Br	4-$MeOC_6H_4$	49, (100:0:0)
Me	Br	naphthyl	67, (100:0:0)
Me	Br	4-$CF_3C_6H_4$	74, (93:7:0)
Me	Br	pyridyl	66, (100:0:0)
Bn	Br	Ph	73, (100:0:0)
Bn	Br	4-$MeOC_6H_4$	58, (100:0:0)
Bn	Br	4-$CF_3C_6H_4$	45, (99:1:0)
Bn	Br	naphtyl	72, (100:0:0)
Bn	Br	pyrimidyl	57, (94:6:0)
MOM	Br	4-$MeOC_6H_4$	65, (100:0:0)

Finally, catalytic system composed of $Ni(cod)_2$, PCy_3, $AlMe_3$ was used for C5 alkenylation of 2-substituted-1-methylimidazoles (Scheme 72).[116] The hydroheteroarylation with unsymmetric alkynes proceeded smoothly in excellent regio- and stereoselectivities to give the corresponding adducts with a bulkier substituent located *trans* to the imidazolyl ring.



Scheme 72. [Ni]-catalysed C5 alkenylation. R= Ph, Me, TBS ; R^1= *n*-Pr, *n*-C_6H_{13}, Me; R^2= *n*-Pr, TMS, *t*-Bu.

2. DESIGN AND SYNTHESIS OF NEW IMIDAZOLE DERIVATIVES ACTING AGAINST THE Na^+/K^+ ATPASE

2.1. Context and design

The sodium pump or Na^+/K^+ ATPase (J.C. Skou received a Nobel Price for its first identification, 1997) is a ubiquitous membrane-bound enzyme which plays a role in the active transport of sodium and potassium ions and the maintenance of a concentration gradient of these ions through the plasma membrane, utilizing ATP as driving force.[142] Studies suggest that it might have an effect in the regulation of tight junction, induction of polarity, regulation of actin dynamics, control of cell movement, and cell signaling.[143] The sodium pump is an integral membrane protein composed of catalytic α and regulatory β-subunits. The α-subunits are multipass transmembrane proteins containing the binding site for Na^+, K^+, ATP and cardiotonic steroid (CS) while β-subunits control α, β heterodimer assembly and insertion into the plasma membrane.[144] To date, there are four α and three β isoforms which have been identified. Due to its ubiquitous distribution, this sodium pump suggests a central role in the cell regulation and a number of diseases have been correlated with alterations in Na^+/K^+ enzyme activity.[145]

Few years ago, in the context of a collaboration with the Unibioscreen s.a. firm, our lab became interested in the design and synthesis of a new drug acting against the Na^+/K^+ ATPase. This compagny wanted to discover a new class of compounds that act against this pump to open a new avenue to combat cancer.[146] Indeed, variations in the expression of Na, K isoforms occur in human cancers and contrasts with corresponding normal tissues.[147] Besides, some other criteria were given:

- they were searching for a sodium pump reversible inhibitors with a structure different from cardiac glycosides.
- not to be dependent on hemisynthesis

- possibility of numerous chemical modulations
- have an original mode of action, different comparing to cardiotonic steroids such as ouabain

After a comprehensive survey of the literature on compounds reported to be active against the Na^+/K^+ pump, our group focused his attention on the structure of BIIA, an imidazoisoquinoline which is a nonsteriodal inotrope (Figure 10). It has been reported that BIIA does not bind the ouabain biding site of the sodium pump, but binds at a Na^+ site, blocking ion transport. The guanidine of BIIA appears to be sodium mimetic.[148]

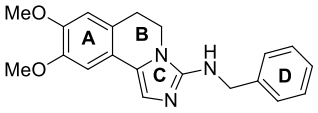
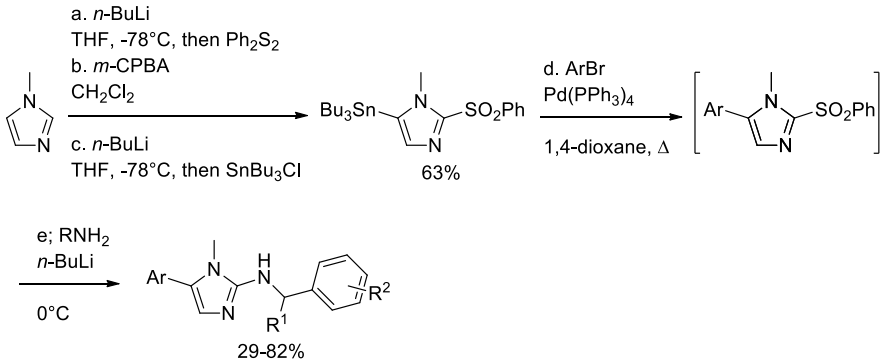


Figure 10. Structure of the BIIA

Blass et al.[149] have studied a series of aminoimidazoles based on the structure of the BIIA. They believed that the removal of the **B** ring would permit a greater conformational mobility, enhance the interaction on the binding site and thereby increase their potency. They took *N*-methylimidazole as their central building block to synthesize their analogues. Then functional groups were successively introduced by depronation of the imidazole with *n*-BuLi. The intermediate was engaged in a Stille reaction with a phenylboronic acid. And the last step is the introduction of an amine in position 2 via an aromatic nucleophilic substitution (Scheme 73).



Scheme 73. Synthesis of BIIA analogues. When Ar = Ph the Suzuki coupling was used instead of Stille reaction.

The library of analogues synthesized, the biological evaluation on the Na^+/K^+ ATPase were done (Table 10).

Table 10. Examples of analogues of the BIIA and enzyme activities.

entry	Ar	R^1	R^2	IC_{50} (µM)
1	Ph	Me	H	38
2	Ph	(*R*)-Me	H	10
3	Ph	(*S*)-Me	H	61
4	Ph	Me	4-Cl	1,3
5	Ph	Me	4-F	10
6	Ph	*sec*-Butyl	H	77
7	Ph	Et	4-Cl	0,8
8	2-Naphthyl	Me	H	2,1
9	3-Biphenyl	Me	H	14
10	4-CF_3O-Ph	Me	H	33
11	3,5-di-F-Ph	Me	H	52
12	3,5-di-CF_3-Ph	Me	H	88
13	3,4-di-CH_3O-Ph	Me	H	99

One can notice that cycle **B** is not necessary for the biological activity. Secondly, the activity seems to be sensitive to the chirality of the amine (entries 1-3). Thirdly, cycle **A** is probably associated to a hydrophobic pocket of the biding site of Na^+/K^+ ATPase. Indeed, when Ar = naphthyl the activity is 50 times higher than when Ar = 3,4-di-CH_3O-Ph (entries 8-13, overall trend).

In conclusion, cycle **B** is not essential for the activity while cycles **A** and **C** are important. Accordingly, in order to develop new imidazole compounds acting against Na^+/K^+ ATPase, our group decided to synthesize 5-aryl-*N*-methylimidazole, i.e. maintain cycles **A** and **C**. And to guarantee their originality (the company wishing to patent these compounds), our lab planned to introduce a macrocycle connecting C2 position with the *ortho*-aryl one. With this large ring the pharmacophore 5-aryl-1*H*-imidazoles will have more flexibility than with a small ring (Figure 11).

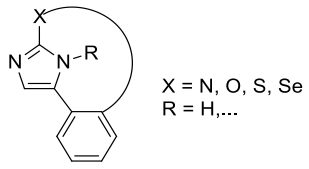
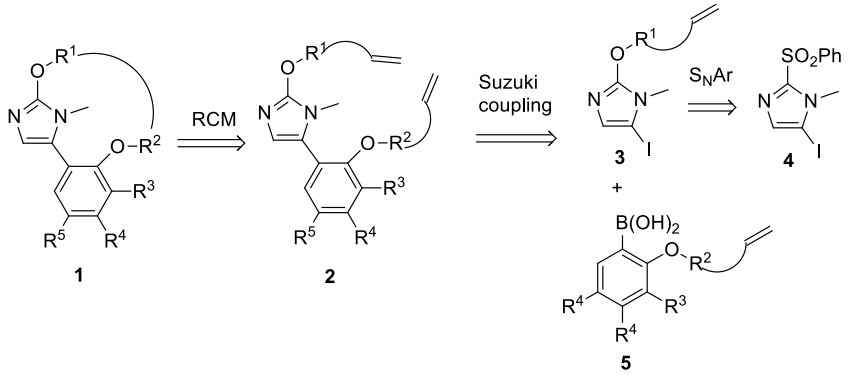


Figure 11. Scaffold of our original molecule.

Macrocycles have been used on most classes of pharmaceutical targets. Originating from natural products (vancomycin, cyclosporine,…), synthetic macrocycles have already made significant contributions to drug discovery.[150]

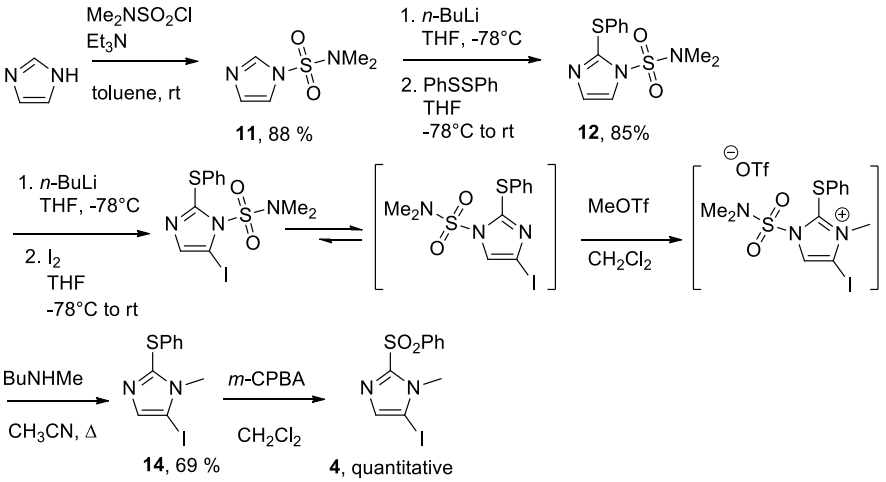
2.2. Synthesis of original macrocycles

The planned strategy for the synthesis of this new family of 5-aryl-1*H*-imidazole derivatives is depicted in Scheme 74. The formation of macrocycle **1** is based on three keys steps: a ring closure metathesis, a Suzuki coupling and an aromatic nucleophilic substitution.



Scheme 74. Retro-synthetic pathway.

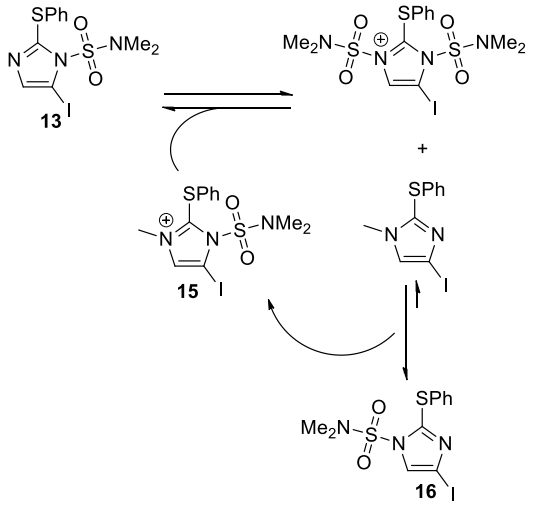
The first challenge of this synthesis was the preparation of the 1,2,5-trisubstituted imidazole **4**, the common intermediate. Our lab has developed a regioselective synthesis to obtain compound **4** from the (NH)-imidazole (Scheme 75).[151]



Scheme 75. Synthesis of key intermediate **4**.

The first step is the protection of the (NH)-imidazole with the *N*,*N*-dimethylsulfamoyl (DMAS) group. This latter is a protecting group but also an ortho-directing group, it allows directing ortho-metallation in the two next steps. Indeed, the first deprotonation with *n*-Buli takes place at position 2 (more acidic proton). The acidity of proton 4 and 5 are nearly the same so that is why an ortho-directing group is used. The DMAS group stabilizes lithium carbanions formed in ortho position (position 5) by chelation of lithium with the doublets of the oxygen atom.[152]

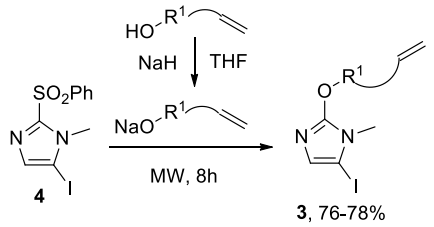
After that, a regioselective alkylation-deprotection takes place. It was found that when compound **13** is engaged in reaction with methyl triflate an *in situ* rapid isomerization occurs leading to the less sterically hindered 1,2,4-isomer. Experiments have revealed that this isomerization can be catalyzed either by the triflate anion or the salt **15** (Scheme 76). Methylation of 1,2,4-isomer followed by deprotection (with BuNHMe) leads then to 1,2,5-trisubstituted imidazole **16**.



Scheme 76. Isomerisation of **13** catalyzed by compound **15**.

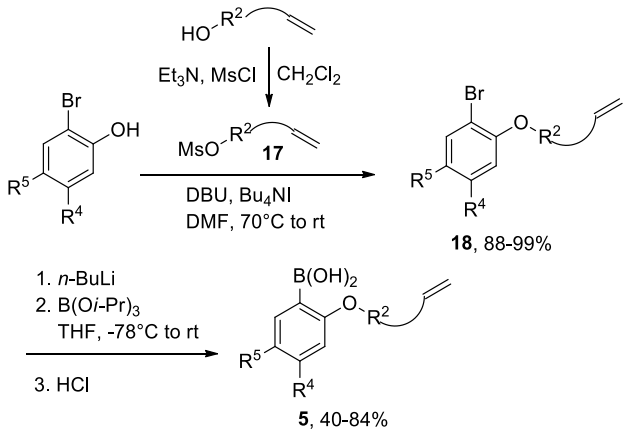
The last step is the oxidation of the sulfure **14** into sulfone **4** to activate the carbon 2 toward the aromatic nucleophilic substitution.

The key intermediate in hands, one can introduce the first variation: the arm R^1. This substitution was done under micro-wave heating (Scheme 77).



Scheme 77. S_NAr.

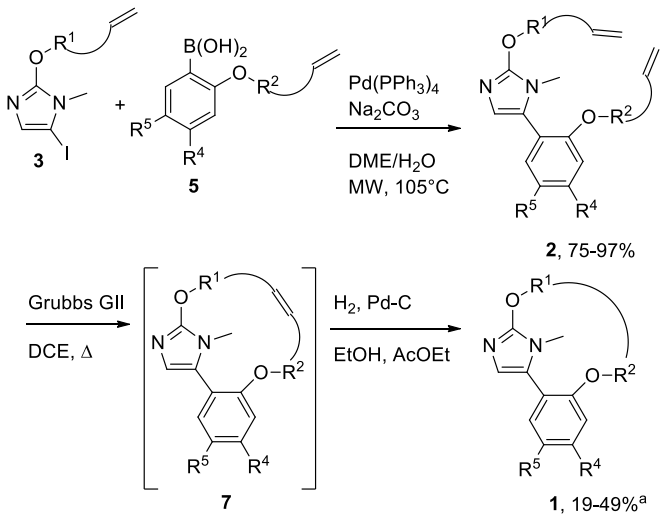
In parallel, some boronic acids were synthesized following the procedure depicted in Scheme 78. With these acids three variations have been introduced; the arm R^2 and substituents R^4 and R^5.



Scheme 78. Synthesis of boronic acids (**5**).

Commercially available bromophenols were alkylated using mesylated alcohols (**17**) to form ethers **18**. In the next step, a halogen-metal exchange was performed with *n*-butyllithium, then a complex "ate" is formed with the addition of the tri*iso*-propyl ether. Finally, the boronic acid **5** is obtained after an acidic work up.

The next step is the Suzuki coupling between imidazole **3** and boronic acids **5** to form the "open compounds" **2** (Scheme 79). Finally, macrocycle **1** was obtained by a ring closure metathesis and hydrogenation of the resulting double bound.

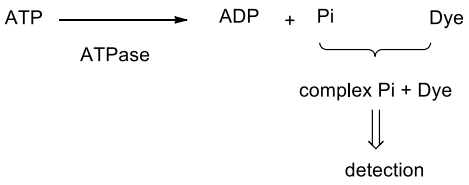


Scheme 79. Synthesis of macrocycles **1**. [a] over two steps.

A dozen macrocycles (**1**) and "open compounds" (**2**) were synthesized by Dr. Bruno Delest, Dr. Prosper Nshimyumukiza and Emilie Van Den Berge (master's thesis) using this strategy. They were all biologically evaluated for their activity against Na^+/K^+ ATPase.

2.3. Biological evaluation of macrocycles

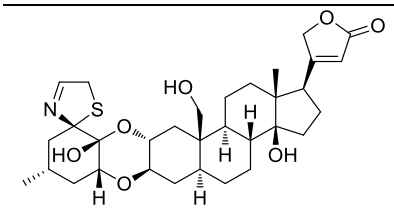
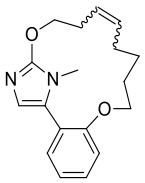
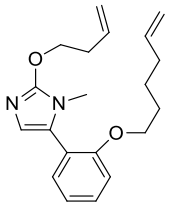
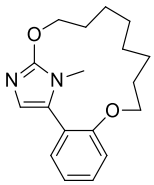
The evaluation of Na^+/K^+ ATPase activity was done by a colorimetric assay using Biomol green (molybdate/malachite green = dye) which allows a colorimetric phosphate quantification. The intensity of color is proportional to free phosphate ions, so is an indicator of the hydrolysis of ATP reflexting the sodium pump activity (Scheme 80).



Scheme 80. Colorimetric assays.

The test was done on Na^+/K^+ ATPase from the pig cerebral cortex and as positive control with a new cardenolide, developed at Unibioscreen and in clinical tests Phase I (2008). Some results of activities of a macrocycle and its intermediate are reported in Table 11.

Table 11. Effect of imidazole derivatives on Na^+/K^+ ATPase.

compound	IC_{50}	compound	IC_{50}
	100 nM		47 µM
	16 µM		53 µM

This analysis showed that the tested imidazoles are weaker inhibitors of the Na^+/K^+-ATPase than the cardenolide (> 100 times less actives). In view of that, Unibioscreen decided to stop investigating this new family of compounds for their use as anticancer agents.

To valorize this new family, our group decided to send some of these imidazoles to Cerep Company (France) for testing.[153] The diversity profile of macrocycle (n = 1, $R^{4,5}$ = H) has been evaluated by performing test binding against a panel of 71 receptors and 16 enzymes. And they found four hits; our molecules are active against the dopamine D_1 receptor, Adenosine A_3 receptor, chlorine channel (GABA-gated) and choline transporter. These targets play an important role in the central nervous system and for inflammatory affection.

Adenosine receptors (ARs) are major targets of caffeine and theophylline. Adenosine has potent effects on both the cardiovascular and immune systems. Thus, A(3)AR agonists may be a new family of drugs to be developed as potent inhibitors of autoimmune inflammatory diseases.[154]

Dopamine is thought to play a role in such a diverse array of processes as motor control, neuroendocrine and cardiovascular regulation as well as in regulation of cognition, emotion and reward.[155] Although the first Dopamine D_1 receptor selective ligand was introduced more than two decades ago, clinically useful D_1 receptor selective ligands are rare.

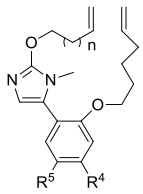
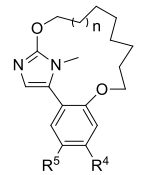
$GABA_A$ receptors are chloride ion channels that mediate fast synaptic transmission. $GABA_A$ receptors are the major inhibitory neurotransmitter receptors in the brain and the site of action of many clinically important drugs.[156] Drugs that

enhance synaptic gamma-aminobutyric acid (GABA)ergic neurotransmission are widely utilized in the clinical setting.

Choline plays an important role in the synthesis of the membrane phospholipid components of the cell membranes. Abnormal choline transport and metabolism have been implicated in a number of neurodegenerative disorders such as Alzheimer's and Parkinson's disease.[157]

Thus, all the synthesized compounds were tested on these four targets. The specific ligand binding to the receptors is defined as the difference between the total binding and the nonspecific binding determined in the presence of an excess of unlabelled ligand. The results are expressed as a percent of control specific binding ((measured specific binding/control specific binding) x 100) and as a percent inhibition of control specific binding (100-((measured specific binding/control specific binding) x 100)) obtained in the presence of the test compounds. The tests were made twice at different concentrations (Table 12).

Table 12. Biological evaluation of the new compounds.

Compound	**n**	**R^4**	**R^5**	**% of inhibition**			
				Adenosine A_3 receptor	Dopamine D_1 receptor	Chlorine channel	Choline transporter
	3	H	H	96	87	74	81
	1	H	H	93	84	86	16
	1	OMe	H	96	54	79	63
	1	Me	H	96	93	63	75
	1	F	H	94	51	58	65
	1	H	F	96	88	72	73
	3	H	H	99	99	73	98
	1	H	H	84	69	52	52
	1	OMe	H	73	56	50	46
	1	Me	H	94	97	67	87
	1	F	H	95	90	49	47
	1	H	F	88	80	54	43

An analysis of these results shows the low influence of aryl substitution ($R^{4,5}$) on the binding properties of the macrocycles toward adenosine A_3 receptor and chlorine channel while for dopamine D_1 receptor and choline transporter significant variations occurred with methyl substituted macrocycle.

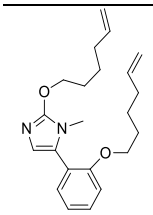
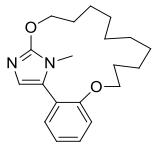
The influence of macrocyclization can also be investigated. The formation of the 15-membered ring has no, or negative, effect on the binding activity on

adenosine A_3 receptor, dopamine D_1 receptor and chlorine channel. This decrease can probably be due to the lower flexibility of macrocycle compounds. However, for choline transporter, one observes an increase in binding activity with macrocyclization for the non-substituted and 4-methylated derivatives. For the other substituents the activity also decreases on this target.

The influence of the conformational flexibility can be put on evidence with the enlargement of the size of macrocycle. The 17-membered macrocycle is more active than the corresponding 15-membered ring. The enlargement is beneficial for the activity toward the four biological targets.

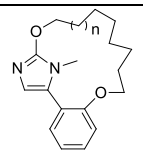
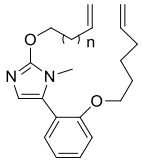
Finally, the IC_{50} for the more potent macrocycle (n = 3, $R^{4,5}$ = H) and its corresponding non-cyclized product was also determined (Table 13). The IC_{50} values for these two compounds confirm their high binding activities and highlight the interest of this novel family of compounds. One can also notice the beneficial character of the macrocyclization.

Table 13. IC_{50} values.

Compound	**IC_{50} (µM)**			
	Adenosine A_3 receptor	Dopamine D_1 receptor	Chlorine channel	Choline transporter
	1.2	6.5	7.3	3.3
	0.85	1.1	7.2	3.2

In parallel, other biological tests were done at the ULB (Pr. V. Mathieu and Dr. R. Kiss). MTT tests were done with a few molecules and interesting activities against cancer cell lines which are apopto-sensitives (APO S) and apopto-resistants (APO R) were observed. These preliminary results are showed in Table 14.

Table 14. preliminary MTT tests. APO S, R: cancer cells which are sensitive or resistant to pro-apoptotic stimuli.

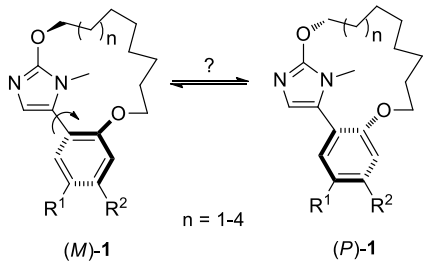
Compound	n	IC_{50} (µM)	
		APO S	APO R
	1	50±1	68±7
	3	29±3	38±4
	1	13±3	22±6
	3	6±1	7±1

Chapter 2 - Objectives and strategies

This project is incorporated within the continuity of the work of our lab on the synthesis and biological evaluation of 5-aryl-1*H*-imidazole derivatives as described in the Introduction. First, we have asked ourself "are our macrocycles chirals?" and we will carry out some studies to answer this question. Second, we will investigate further the anti-cancer activity of these 5-aryl-1*H*-imidazole derivatives. And third, we are planning to generalize the regioselective *N*-methylation of *N*,*N*-dimethylsulfamoyl imidazole to (NH)-azoles and other alkylating reagents.

1. CHIRALITY STUDIES OF MACROCYCLES

We reasoned that macrocycles **1** can potentially be chiral. Indeed, two motifs could induce chiraly: the steric effects could prevent rapid rotation around the aryl imidazole C-C bond (atropisomerism) and the cyclophane type structure of the macrocycle may prevent the alicyclic ring from flipping from one side of the plane of the imidazole ring to the other (Scheme 81).



Scheme 81. Possible stereoisomers of macrocycles.

We are planning to prepare macrocycles **1** with different alicyclic chain lengths (n = 1-4) in order to investigate the influence of the ring size on the conformational equilibrium and chirality. We would also like to synthesize the corresponding 1,2,4-trisubstituted imidazole macrocycle to investigate the influence of the *N*-methyl group on chirality. Theses macrocycles will be analyzed by NMR and Chiral HPLC.

Due to their unique properties of basicity, nucleophilicity and coordination ability, imidazole derivatives are found in various applications. And one interest of optically pure imidazoles is to provide useful chiral materials such as catalyst. So our chiral macrocycles will be tested as chiral organocatalysts in different reactions.

In this context, we are planning to synthesize chiral macrocycles with an ether function in the alicyclic chain in order to find applications in the field of complexation of cations.[158]

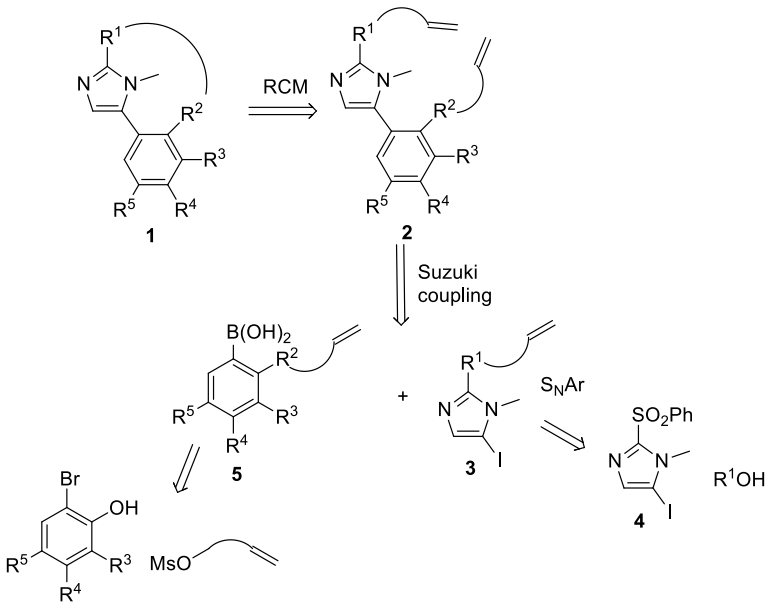
Finally, the synthesis of chiral macrocycles with a thiourea function in the cyclophane chain will be envisaged. Indeed, novel bifunctional organocatalysts bearing both a thiourea moiety and an imidazole group on a chiral scaffold have already been synthesized and applied in different reactions.[159]

2. SYNTHESIS AND BIOLOGICAL EVALUATION OF A SERIES OF 5-ARYL-1*H*-IMIDAZOLES AS ANTICANCER AGENTS

As described in the Introduction, preliminary MTT tests on some imidazole-containing macrocycles **1** have revealed that they display interesting activities against cancer cell lines which are apopto-sensitives (APO S) and apopto-resistants (APO R).

The objective of this section is to perform a structure activity relationship (SAR) with the 5-aryl-1*H*-imidazole derivatives in order to refine their activity as anti-cancer drugs. We would also like to decipher their mechanism of action.

Accordingly, a family of 5-aryl-1*H*-imidazoles will be synthesized following the strategy previously developed in our lab (Scheme 82). Stuctural variations will be done by changing substituents R^3, R^4 and R^5 as well as the R^1 and R^2 arms.

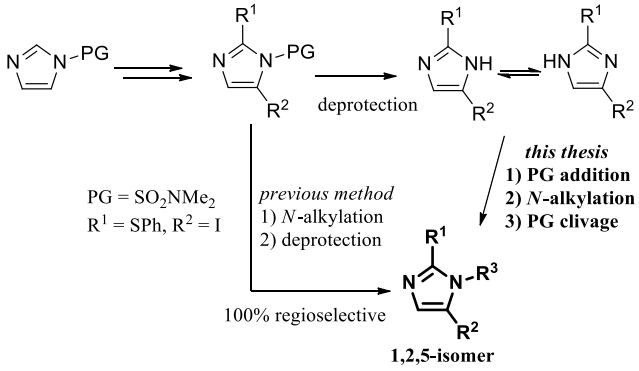


Scheme 82. Retrosynthetic strategy.

These compounds will be tested at the Faculty of Pharmacy at the ULB (Prof. V. Mathieu and Dr. R. Kiss).

3. DEVELOPMENT OF A GENERAL AND REGIOSELECTIVE N-ALKYLATION STRATEGY OF AZOLES

Our lab had developed a regioselective strategy toward *N*-methyl-2,5-disubstituted imidazoles from 1-(*N*,*N*-dimethylsulfamoyl)imidazole (Scheme 83). The purpose of this part of our work will be the development of a similar strategy but starting from any (NH)-imidazoles The imidazole will be protected with an appropriated protecting group, then alkylated and finally deprotected to obtain the desired isomer.



Scheme 83. Regioselective alkylation.

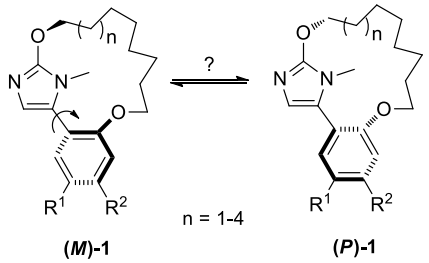
Finally, this methodology will be extended with other alkylating agent ($R^3 \neq$ Me) and other (NH)-azoles such as benzimidazoles, (benzo)triazoles and purines.

Chapter 3 - Chirality studies of macrocycles

1. INDRODUCTION

Axial and planar chiralities are special cases of asymmetry in which the chiraly does not come from a stereogenic center, the most commun form in organic compounds, but from a chiral axis or plane. A famous example of axial chiraly is found in atropoisomeric biaryl compounds such as BINAP, where the rotation around the aryl-aryl bond is restricted. The planar chirality is attributed to stereoisomerism resulting from the arrangement of out-of-plane groups with respect to a plane. One of the most common examples is the ferrocene family.

Our macrocycles could potentially be chiral due to the presence of a macrocycle and a 5-aryl-1*H*-imidazole motif. These two motifs could restrict the conformational equilibrium between **P** and **M** isomers (Scheme 84). Indeed, steric effects could prevent rapid rotation around the aryl imidazole C–C single bond (atropisomerism as seen in biaryl compounds). The cyclophane-type structure of the macrocycle may also prevent the alicyclic ring from flipping from one side of the plane of the imidazole ring to the other (rope skipping motion).



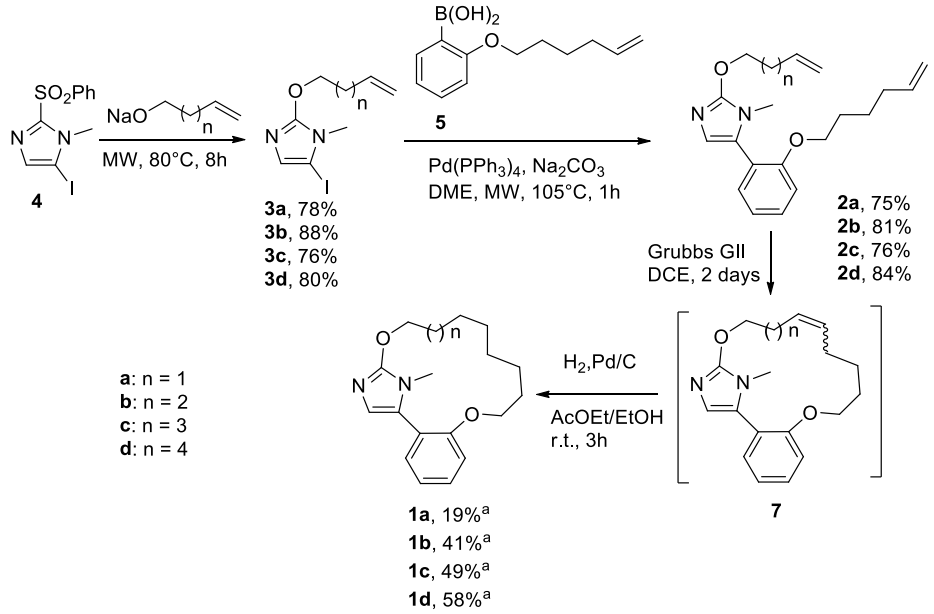
Scheme 84. Equilibrium between **M** and **P**-isomers.

Here, we would like to investigate if these macrocycles are indeed chiral as well as the influence of the alicyclic chain length, the chain flexibility and the *N*-methyl group on the rate of the conformational equilibrium. Secondly, if our macocycles are chiral, we would like to utilize them as chiral catalysts. Indeed, imidazole derivatives are reported to be good catalysts in some reactions.

2. SYNTHESIS OF MACROCYCLES OF DIFFERENT SIZE

In order to investigate the influence of the size of the macrocycle on the chirality, we have synthesized four compounds with four different sizes of cycle: from 15- to 18-membered ring (n = 1-4, Scheme 85). To do so, we have used the

strategy previously developed in our lab (see chapter 1, 2.2. Synthesis of original macrocycles). The key intermediate **4**, which was obtained by a highly regioselective method (see chapter 1, 2.2.), was substituted using an aromatic nucleophilic substitution under microwave heating allowing to place the first alkene chain (Scheme 85). Next, the Suzuki coupling between imidazoles **3** and boronic acid **5** leads to compounds **2** in good yields (see Chapter 1 for the synthesis of **5**). The last steps, the ring closure metathesis and the hydrogenation of the resulting double bond provide macrocycles **1** in moderate yields. The stereoselectivity of the double bond of the intermediate **7** was 45:55 (determined by ^{1}H NMR).

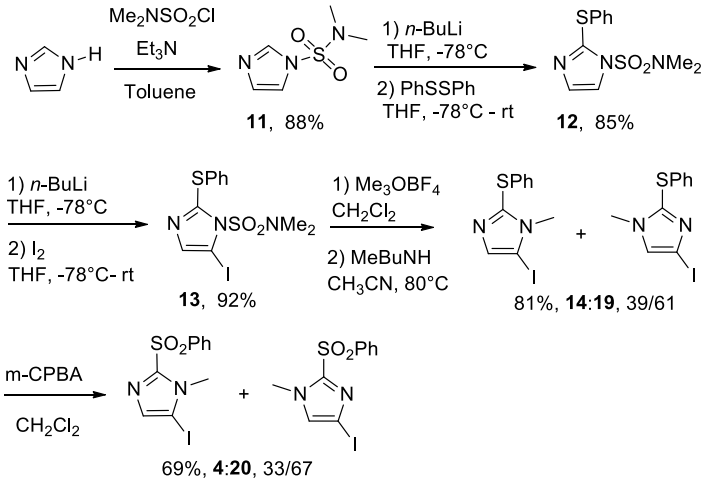


Scheme 85. Synthesis of macrocycles **1a-d.** [a] yield over two steps.

3. SYNTHESIS OF A MACROCYCLE CONTAINING A 1,2,4-IMIDAZOLE

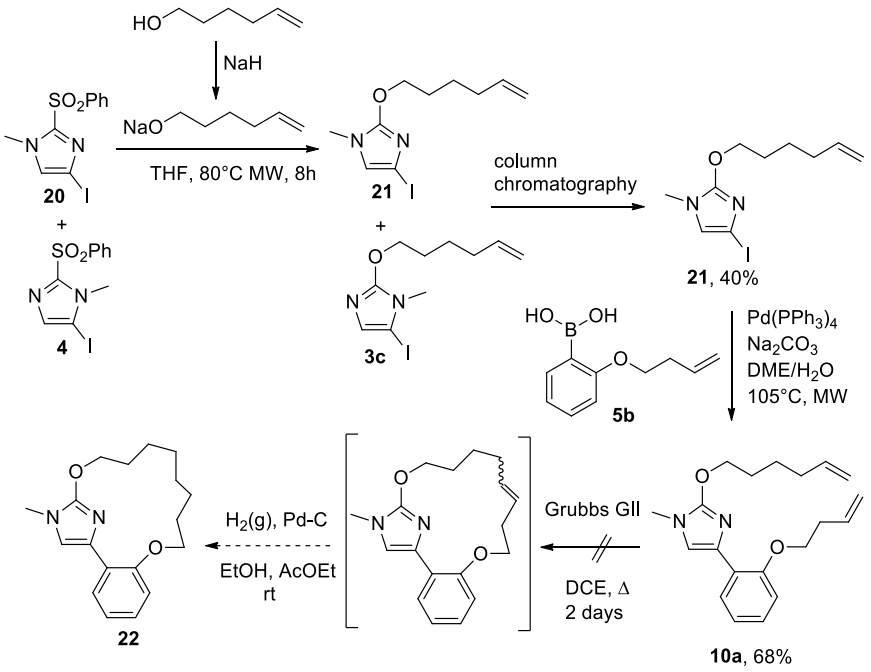
In order to investigate the importance of the *N*-methyl group on chirality, we also synthesized the other isomer, the macrocycle containing the 1,2,4-imidazole. This macrocycle could be prepared from the other isomer of the common intermediate **4** (Scheme 86). As described by our group,[151] this latter can also be obtained from **13** but using a different methylation agent, which promotes less *in situ* isomerization of **13**. Using Meerwein's reagent, **14/19** is obtained with a 39/61 regioselectivity in favour ot the 1,2,4-isomer. Another possibility is the methylation

of the (NH)-imidazole by MeI in the presence of NaH (selectivity 57:43) or *i*-Pr_2NEt (selectivity 64:36) as a base.[160] At this stage, the two isomers were difficult to separate by column chromatography. Subsequent oxidation by *m*CPBA provides a 33/67 mixture of **4**/**20** in 69% yield. Again, no conditions allowing the separation of isomers could be found and the mixture of isomers was engaged in the next step: the S_NAr.



Scheme 86. Synthesis of compounds **4**, **20**.

Sulfones **4** and **20** were substituted by an alcoolate to form compounds **3c** and **21** (Scheme 87). At this stage, a flash column chromatography allowed to successfully separate the two isomers. Only the 1,2,4-isomer was engaged in the Suzuki coupling to form compound **10** in good yield. Finally, the last steps are the RCM and the hydrogenation. As previously, the RCM was performed with the second generation Grubbs catalyst at reflux of DCE. However, no cyclized product (**22**) could be observed and after purification we found unexcepted compound **23** (about 40% yield) (Figure 12).



Scheme 87. Synthesis of the open compound **22**.

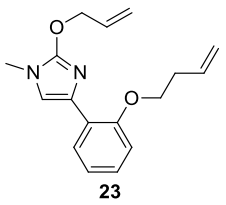


Figure 12. Product obtained by isomerization during olefin methathesis.

This compound is the result of an undesired isomerization of the double bond. If such side reactions have been extensively reported, the exact mechanism(s) responsible for this isomerization is/are not yet understood. One explanation can be the formation of ruthenium hydride species such as **24** (Figure 13) formed from de decomposition of the ruthenium metathesis catalysts which can catalyse the migration of olefins. It was found that a solution to prevent this isomerization is to add 1,4-benzoquinone in the reaction mixture.[161] So the RCM was carried out with 10% mol of benzoquinone. After hydrogenation, no desired macrocycle could be observed (^{1}H NMR and MS spectra). So we decided to test other catalysts: Grubbs GI and benzoquinone this time in dichloromethane at 40°C. Here a compound was isolated after the hydrogenation: a mixture of 1,2,4-dimers and RCM product in a 70:30 ratio.

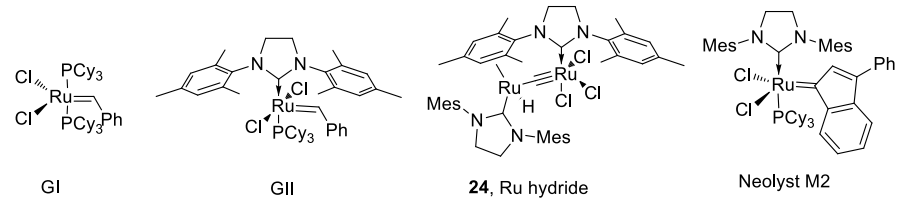


Figure 13. Ruthenium catalysts.

Two possible 1,2,4-dimers can be formed: the head to head or head to tail dimers (Figure 14).

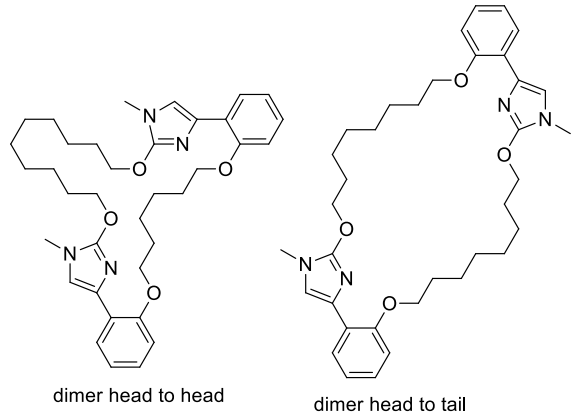


Figure 14. Possible dimers formed.

The presence of dimers was proved by MS. Also, in chiral HPLC a longer retention time was observed than expected. The last test was done with the Neolyst M2 catalyst at reflux of DCE and again a dimeric structure was isolated in 26% yield.

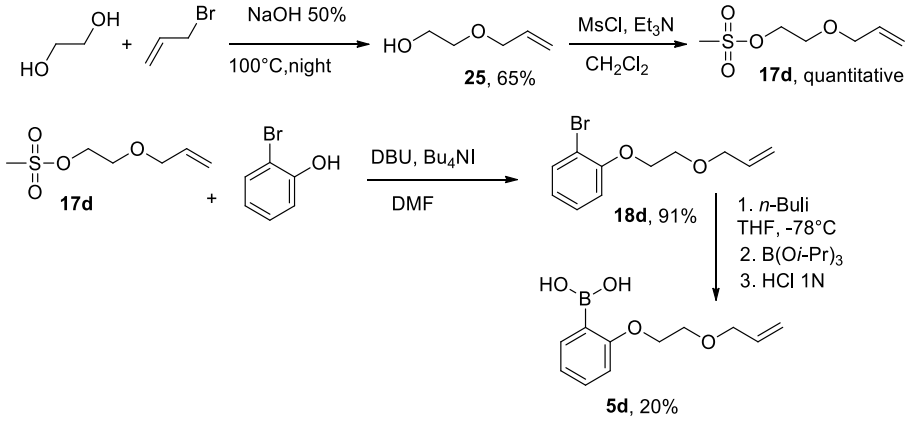
In conclusion, besides different conditions were used to performed the RCM reaction, we did not succeed in synthesizing the macrocycle with a 1,2,4-imidazole.

4. SYNTHESIS OF MACROCYCLES CONTAINING A HETEROATOM IN THE ALICYCLIC CHAIN

4.1. Introduction of an oxygen

We decided to introduce an oxygen atom in the alicyclic chain, i.e. replace one of the CH_2 of the alicyclic chain by an ether function. This variation will allow

investigating the influence of the flexibility of the alicyclic chain on the rate of equilibrium but also introduces a hereroatom for testing this macrocycle as chiral complexation agent. Our first idea was to introduce this variation on the aryl part; thus during the synthesis of the boronic acid (Scheme 88). The first step is the synthesis of the mesylate alcohol **17d**. Ethylene glycol and allyl bromide were stirred overnight in the presence of sodium hydroxide to give the corresponding alcohol (**25**) in 65 % yield. Then, the alcohol was activated by formation of a mesylate in quantitative yield. The rest of synthesis of boronic acid **5d** follows the same steps as previously described in Chapter 1 (see 2.2. Synthesis of original compounds). First, the substitution of bromophenol with the mesylate alcohol in the presence of iodine and DBU gives compound **18d** in excellent yield. Second, formation of boronic acid **5d** was performed using *n*-BuLi (halogen-metal exchange) followed by addition of *iso*-propylboronate an acidic work up. For this last step, we have utilized only one equivalent of *n*-BuLi to avoid secondary reactions. But still the yield was low and we observed by NMR and MS the formation of the (2-hydroxyphenyl)boronic acid (same quantity as **5d**). This product can be formed by deprotonation in alpha position of the dialkylether function, and elimination of phenolate which decomposed during the acidic work up leads to the corresponding phenol.

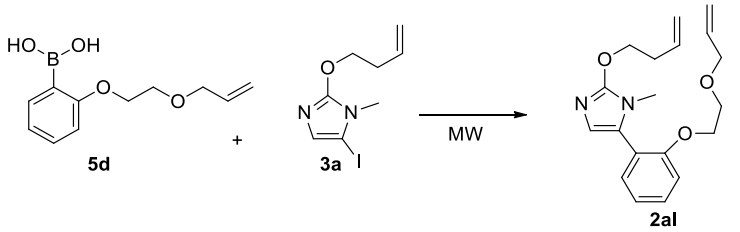


Scheme 88. Synthesis of boronic acid **5d**.

The boronic acid in hand, Suzuki coupling was investigated. Classical reaction conditions for this coupling gave no results (Table 15, entry 1). We thus tried other conditions by changing the solvent, the base and the reaction time but we never obtained the desired product. An explanation for this failure could be the complexation of the palladium by the dialkylether oxygen atom which would

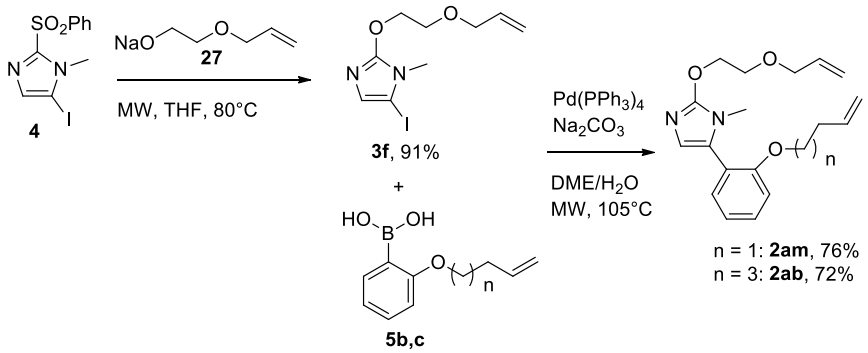
inhibits the Suzuki coupling. It is also possible that the palladium complex reacts with the allylether function to form a π-allyl complex.

Table 15. Assays for the Suzuki coupling.



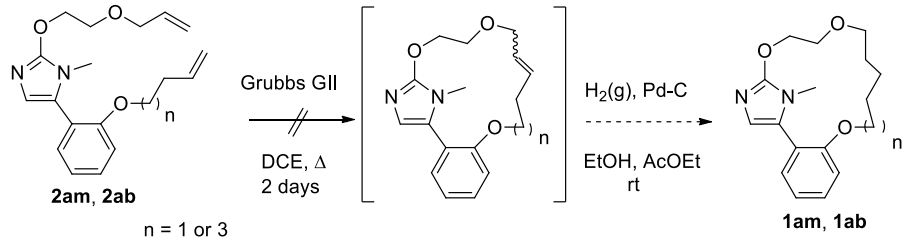
Entry	Conditions					Results
	catalyst	base	solvent	t	time	
1	3 % $Pd(PPh_3)_4$	Na_2CO_3	DME/H_2O	105°C	2h	Imidazole **3a** and aromatic compounds
2	3 % $Pd(PPh_3)_4$	Na_2CO_3	DME/H_2O	105°C	1h	″
3	6 % $Pd(PPh_3)_4$	Na_2CO_3	DME/H_2O	105°C	3h	″
4	3 % $Pd(PPh_3)_4$	Na_2CO_3	THF	105°C	1h	″
5	3 % $Pd(PPh_3)_4$	Cs_2CO_3	DME/H_2O	105°C	1h	″
6	3 % $Pd(PPh_3)_4$	Na_2CO_3	DMF	105°C	1h	″

After these assays, we decided to introduce the oxygen atom via the other arm, the one on C2 position of the imidazole. This imidazole was synthesized in excellent yield via the aromatic nucleophilic substitution using alcolate **27** (Scheme 89). Then the Suzuki coupling was carried out successfully to obtain the "open" compound **2am** and **2ab** in 76 (not totally pure) and 72% yield respectively.



Scheme 89. Synthesis of compounds **2am** and **2ab**.

Finally, the ring closure metathesis and the hydrogenation were attempted (Scheme 90). However, none of the tested conditions allowed observing formation of the RCM product, even with a larger cycle (n = 3). In ^{1}H NMR, a complex mixture was observed with more aromatic protons than aliphatic one. By question of time, this synthesis was not repeated.

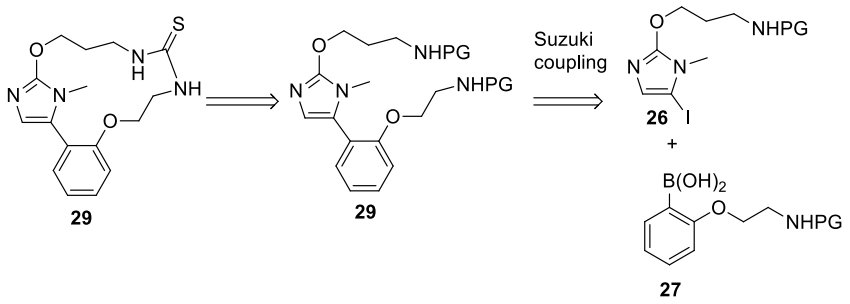


Scheme 90. Synthesis of macrocycles **28**.

In conclusion, we did not succeed in formation of the macrocycle with an ether function in the alicyclic chain. When this ether function was introduced in the R^2 chain, the Suzuki reaction did not work and when it was introduced in the R^1 chain, the "open compound" **2** was obtained but the RCM failed.

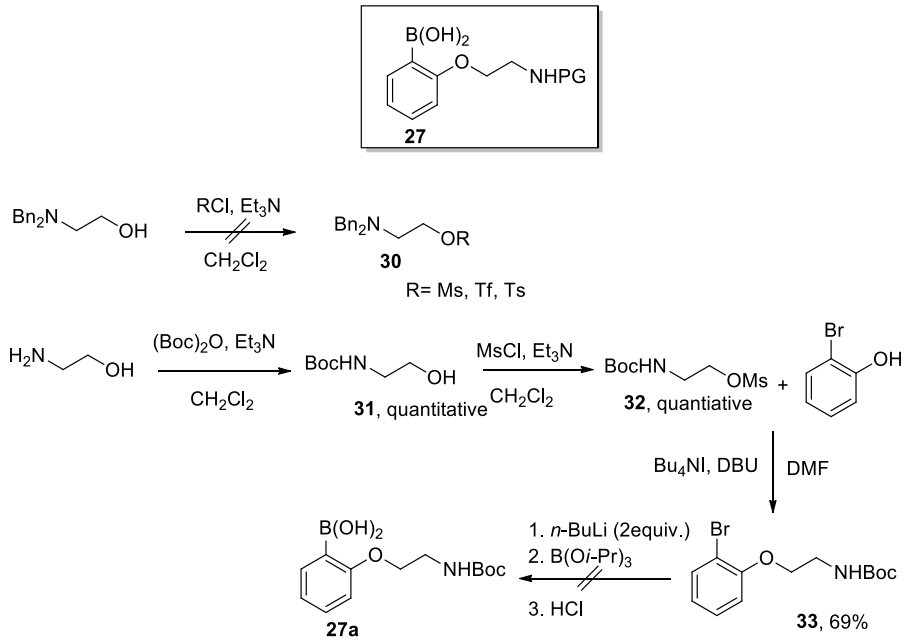
4.2. Introduction of a thiourea

In the aim of developing new chiral bifunctionnal organocatalysts, we decided to introduce a thiourea function in the alicyclic chain. Thioureas are useful organocatalysts through their double hydrogen-bonding interactions. Our stategy was to synthesize the two fragments with a protected amine at the end of the chain (Scheme 91). So we need to use a protecting group that cannot interfer with the different reaction conditions of our methodology. We chose the benzyl protecting group.



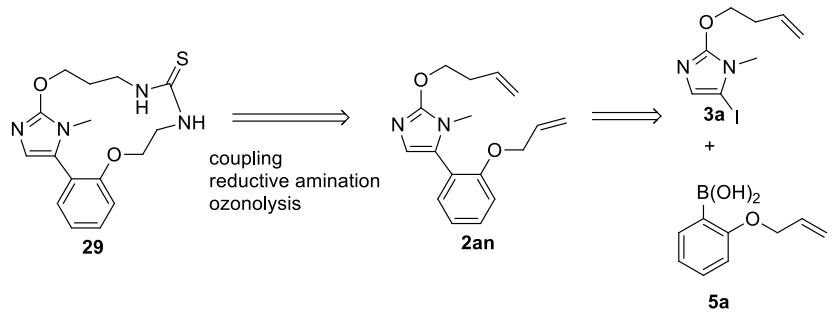
Scheme 91. Strategy for the synthesis of thiourea.

So we have begun with the synthesis of boronic acid **27** (Scheme 92). The commercially available 2-(dibenzylamino)ethanol was engaged in the first step, the activation of the alcohol function toward substitution. Unfortunately, this step did not work. We have tried different activating group; mesyl, triflate and tosyl, but we never succeeded, no reaction was observed. We thus changed the protecting group of the amine to *tert*-butyloxycarbonyl group (Boc). The 2-aminoethanol was first protected with Boc group for the amino part and secondly activated with mesyl for the alcohol part with quantitative yield without purification. Next, bromophenol was alkylated with this mesylate (**32**) in 69 % yield. Finally, we tried different conditions for the synthesis of boronic acid **27a** but we did not succeed in obtaining it. We tried work up at different pH or tried to synthesize the boronic ester but degradation was systematically observed and the molecular mass was not found by MS.



Scheme 92. Synthesis of boronic acid **27a**.

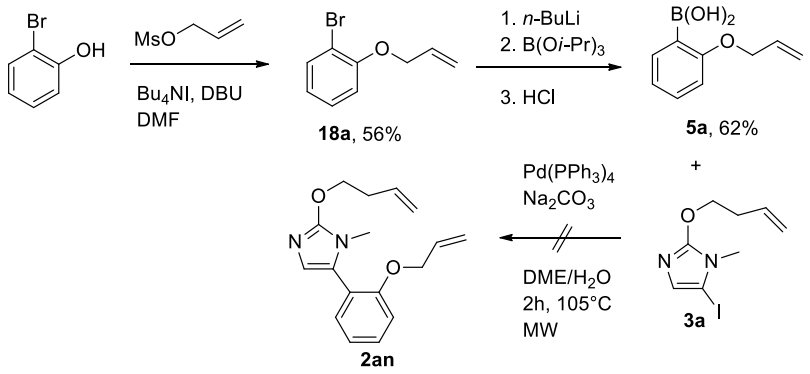
After this failure, we have changed our strategy and decided to apply the classical strategy to form the "open" compound **2an** with two arms ended by a double bond, and at this stage introduce the amine by ozonolysis followed by a reductive amination and a coupling to form the thiourea (Scheme 93).



Scheme 93. Second strategy for the synthesis of thiourea.

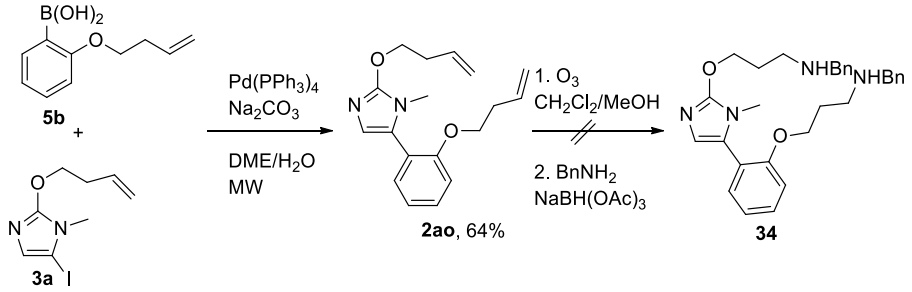
We thus focused our attention on the synthesis of boronic acid **5a** using the previously developed procedure (Scheme 94). Alkylation of bromophenol and formation of boronic acid worked well in moderate yields. But for the Suzuki coupling, we did not observe the desired product. In ^{1}H NMR, there was a lot of

noise; maybe was it still a problem with the π-allyl formation between the palladium complex and the boronic acid.



Scheme 94. Synthesis of compound **2an**.

We have solved the problem by adding one more carbon in the alkyl chain of the boronic acid and compound **5b** was obtained in moderate yield. Then we tried a one pot conversion of alkene to amine following a reported procedure (Scheme 95).[162] After a few unsuccessful attempts (different reaction time,…), we decomposed these steps and performed just the ozonolysis step. The reaction was followed by TLC until the disappearance of the starting material and the ozonolides were quenched with dimethylsulfur. But again we did not succeed; a complex mixture of unidentified products was obtained. Maybe there was degradation of compound **2ao**. However, we can find in the literature ozonolysis of similar function; -O-C_4H_7.[163]



Scheme 95. Synthesis of compound **34**.

For a question of time, the synthesis of **34** was abandoned at this stage.

Having in hand a series of macrocycles (**1a-d)** with different ring size (15- to 18-membered ring), we investigated their chiral properties by different means.

5. CHIRALITY STUDIES

5.1. Chiral HPLC analyses

The first thing to do was to find the right chiral column and the suitable elution conditions. We have obtained good results with the CHIRALPAK® IB which is a cellulose carbamate chiral stationary phase. HPLC analyses were performed at a flowrate of 1 mL/min with a mixture of 95% hexane and 5% ethanol (%v/v) as the mobile phase, using a UV detector (282 nm) at room temperature (Figure 15).

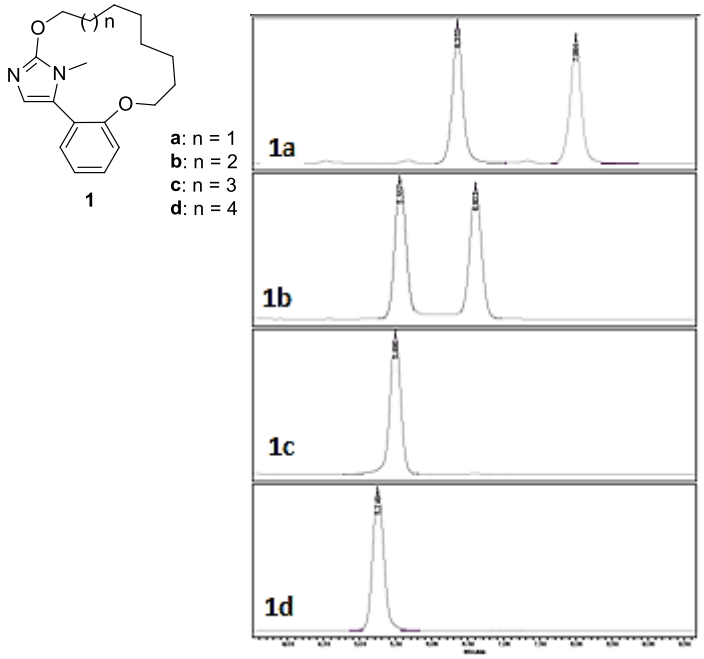


Figure 15. Chiral HPLC chromatograms of macrocycles **1a-d**.

Two peaks were observed in the case of macrocycles **1a** and **b** (n = 1 and 2, respectively). Their UV spectra indicated that they correspond to the two enantiomers. This shows that there is no rapid equilibration between the two atropisomeric *P* and *M* forms at the timescale of the HPLC. A careful analysis of the chromatogram for **1b** reveals the occurrence of a plateau-shape, indicative of an enantiomer interconversion on the column at a rate similar to that of the separation process. This plateau-shape has been confirmed by performing HPLC analyses at different temperatures (Figure 16). Determination of the kinetic constant for interconversion from the height of this plateau gives an estimated activation free energy of 22.9 kcal/mol (see Appendix for details). For compounds **1c** and **1d** only

one peak was observed on the chromatogram (even with lower temperature) meaning that there must be a rapid equilibration between the two atropisomeric *P* and *M* forms at the timescale of the HPLC.

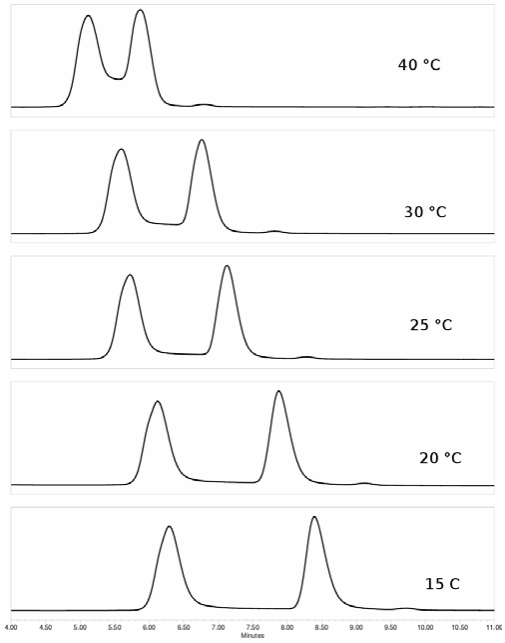


Figure 16. Chiral HPLC chromatograms of **1b** at different temperatures.

The corresponding non-cyclic "open" compounds **2a** and **2b** were also analyzed by HPLC. Whatever the column and the conditions, we found only one signal. This indicated that the macrocyclic nature of **1a** and **1b** plays an important role in the determining the rate of the conformational equilibrium between the two atropisomeric forms.

Next, we investigated the kinetics of enantiomerisation by ^{1}H NMR spectroscopy.

5.2. NMR Studies

Recorded ^{1}H NMR spectrum of the macrocycles **1a-d**, revealed a non equivalence of the two germinal protons of methylene groups adjacent to the oxygens atoms for **1a-c** while there was no splitting for the OCH_2 signals for **1d** (Figure 17). This observation could be accounted for the chiral nature of **1a-c** which would render these methylene protons diastereotopic.

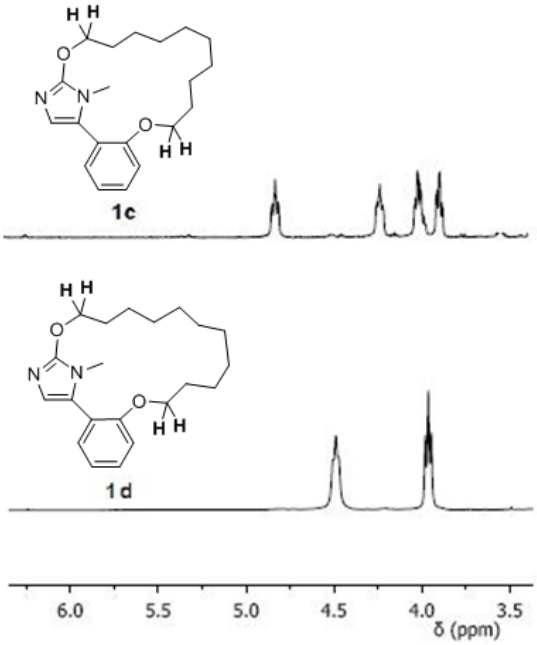


Figure 17. ^{1}H NMR spectra showing the diastereotopic nature of the two germinal OCH_2 for **1c** and their equivalence for **1d.**

To confirm these observations, we tried to find a convenient chiral shift agent allowing to observe the formation of two diastereomeric complexes. In this aim, different chiral agents were tested in a ratio one to one with macrocycle **1a-d**: europium complex (Eu(III) tris [3-heptafluoropropyl-hydroxymethylene)-*d*-camphorate]), *R*-(-)alpha-methoxyphenylacetic acid, S-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol. With the *S*-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, we found some splitting of signals of **1a-c** which indicates the formation of diastereomeric complexes (Figure 18). This observation confirms that isomerization does not occur rapidly on ^{1}H NMR timescale at 25°C. For imidazole **1d**, no splitting could be observed what suggests a rapid enantiomerization.

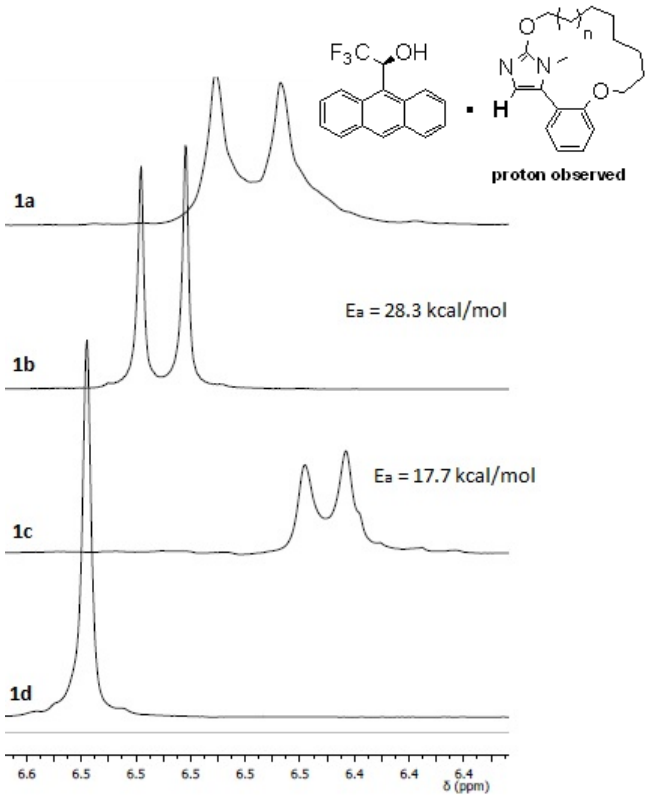


Figure 18. ^{1}H NMR studies of macrocycles **1a-d** in the presence of a chiral derivatizing agent.

^{1}H NMR studies of the diastereomeric solvation complexes of **1b** and **1c** at different temperature (from -30 to 50°C in TCE) have been made in order to determine the coalescence temperature and the exchange rate constant of isomerisation. The activation energy of isomerisation calculated from these rate constants, using Arrhenius equation, is 28.3 and 17.7 kcal/mol at 25°C for **1b** and **1c**, respectively (see Appendix for details).

5.3. Calculations

We investigated further the origin of chirality in the case of **1a-b** and the factors influencing the kinetic of enantiomerisation by computational methods. These calculations were done by Pr. R. Robiette.

There are two conceivable pathways for isomerisation (Figure 19): rope-skipping motion can either involves crossing of the *N*-methyl group and alicyclic

chain (**A**) or occur in the opposite direction with this latter going through the imidazole plane on the C^4-H side (**B**). We have obtained transition structure for both pathways with our calculations indicating that the mechanism involving a steric clash between *N*-methyl group and the alicyclic chain (**A**) is thoroughly less favoured (see Appendix for full results).

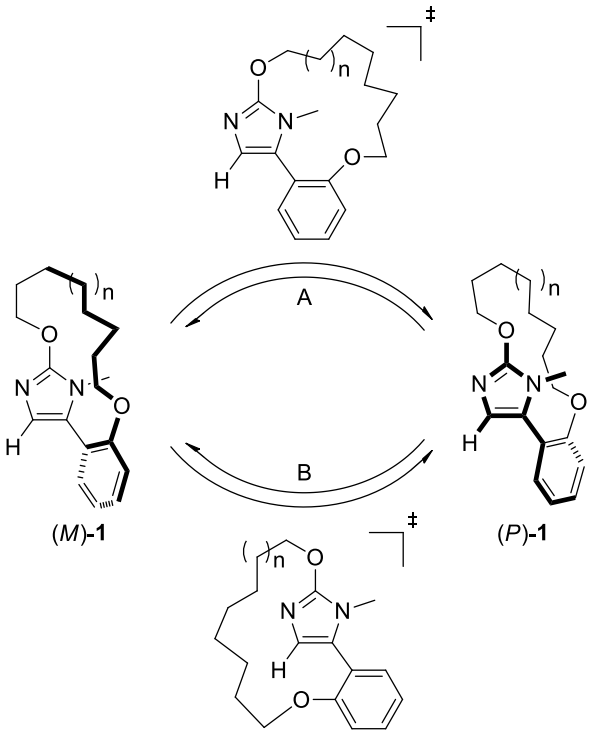


Figure 19. Possible pathways for isomerization.

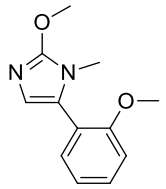
Obtained energy barriers corroborate the chiral nature of imidazoles **1a** and **1b** at room temperature (Table 16). Indeed, computed activation free energies ($\Delta G^{\ddagger}$ = 40.9 and 26.2 kcal/mol, respectively) predict a half live of racemisation, at 25°C, of *ca.* 40 days for **1b** and several trillions of years for **1a**. For imidazoles **1c** and **1d** with a larger macrocycle our calculations predict a rapid isomerisation ($t_{1/2\ enantio}$ < 3 min) as observed by chiral HPLC and ^{1}H NMR.

Our computational results are thus in good agreement with our experimental observations and activation energies estimated by NMR for imidazoles **1b** and **1c**. They confirm also the significant decrease of the energy barrier to isomerisation with the size of the macrocycle, and show that solvation and entropic effects have only a low influence.

Table 16. Computed energy barrier (kcal/mol^{-1}) for enantiomerisation of **1a-d** and **2o** at the SCS-MP2/cc-pVTZ//B3LYP/6-31G* level.

compound	$\Delta E^{\ddagger}$	$\Delta E^{\ddagger}(CHCl_3)$	$\Delta G^{\ddagger}(CHCl_3)$
1a	37.8	38.5	40.9
1b	24.8	25.7	26.2
1c	17.1	17.9	20.2
1d	14.5	15.4	16.3
2o	5.2	5.0	6.8

The importance of the alicyclic ring was further confirmed by the low barrier to rotation computed for compound **2o** (Figure 20), revealing the absence of atropisomerism in the non-macrocyclic derivatives (Table 16), as suggested by the HPLC analysis of imidazoles **2**. This result indicates thus that the steric clash induced by rotation around the aryl-imidazole C-C single bond cannot account for the chiral nature of imidazoles **1a-b** at room temperature, and confirms further the decisive role of the alicyclic moiety on the rate of isomerisation of imidazoles **1a-d**.



2o

Figure 20. Model of non-macrocyclic compound.

Analysis of transition states structure indicates in fact that the barrier to atropisomerism is mainly due to the steric interactions between the imidazole C^4-H and the alicyclic chain in the TS region (Figure 21). The influence of the ring size is thus explained as follow: the shorter the alicyclic chain is, the less possibility the chain has to accommodate for decreasing the steric clash with the C^4-H in the transition state.

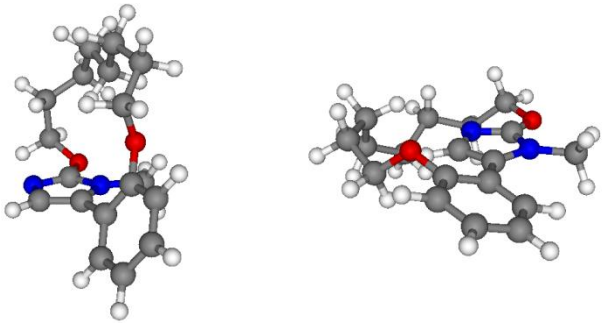
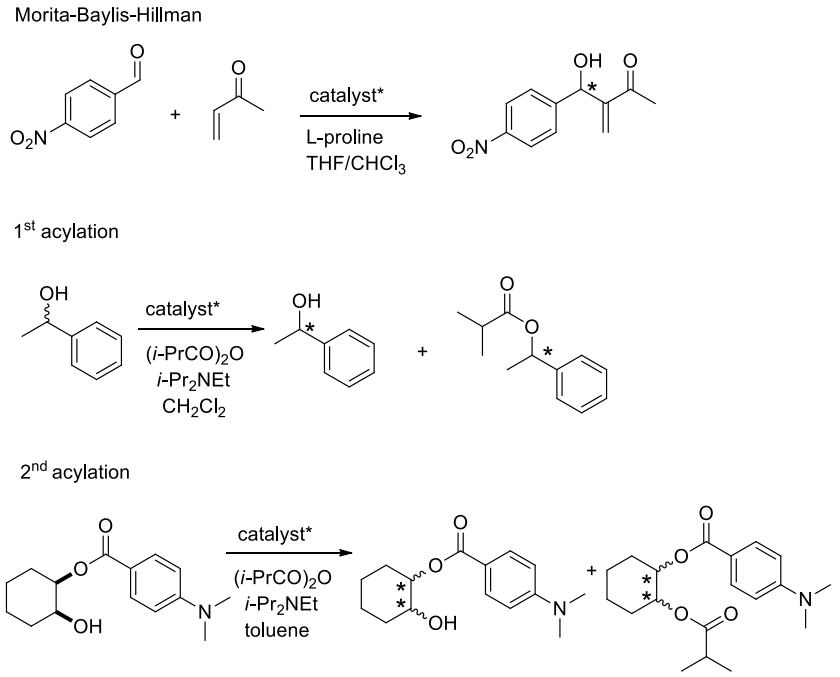


Figure 21. Optimised ground state (left) and isomerisation TS (right) structures for **1a**.

According to the computed free energy barrier, the two enantiomers of **1a** should be stable enough to be isolated and stored separately. We thus performed the separation of the two enantiomers of **1a** by HPLC on a semipreparative scale in order to investigate the influence of chirality on its biological activity (see Chapter 4) as well as explore the possibility of application of this macrocycle as chiral organocatalyst. Transposition of the analytical chiral HPLC conditions allowed us to obtain the two enantiomers of **1a** in milligram amounts with an enantiomeric excess > 99%. As predicted by our calculations these two isolated enantiomers were found to be configurationally stable for months at room temperature.

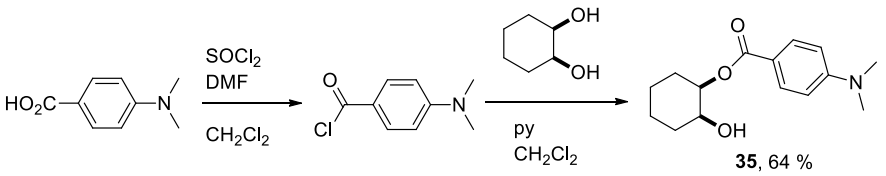
6. CATALYTIC ASSAYS WITH A CHIRAL MACROCYCLE

In the literature, one can find diverse examples of chiral organocatalysts based on imidazole for asymmetric reaction such as asymmetric acyl transfer, conjugate addition, Morita-Baylis-Hillman reaction, phosphorylation reaction, enantioselective silylations of achiral diols,…[164]. We thus tried to apply our chiral macrocycle **1a** for chirality-induction and began with two acylation reactions[165,166] and a Morita-Baylis-Hillman[167] reaction (Scheme 96).



Scheme 96. Reactions tested with macrocycle **1a** as catalyst.

For the second acylation we have synthesized the reactant in two steps. 4-(dimethylamino)benzoic acid was transformed into the corresponding acid chloride. Then this acid was coupled with the diol to form the desired product **36** in 64 % yield over the two steps (Scheme 97).



Scheme 97. Synthesis of compound **35**.

We first performed the three catalyzed reactions using *N*-methylimidazole as catalyst as control reactions. They also allowed us to find HPLC conditions allowing to separate the two enantiomeric products. Secondly, these reactions were carried out using racemic macrocycle **1a** in order to see the ability of this macrocycle to catalyse these reactions. For the Morita-Baylis-Hillman reaction, **1a** seemed to be a poor catalyst, only trace of product was observed after three days. We thus have abandoned this reaction. Concerning the kinetic resolutions, we have performed the reaction with one chiral macrocycle. However, macrocycle **1a** was found to be a moderate catalyst (conversion below 30 %) for the two acylations and unfortunately

no useful chirality-induction was observed (48 and 47 % ee). With these poor results, we did not persevered and did not try to catalyse other reactions with our chiral macrocycle.

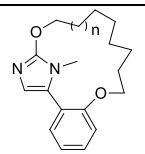
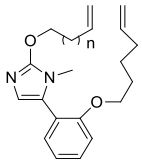
In conclusion, valorization of chiral macrocycles failed as organocatalysts. But in the field of drug design, we can test them to investigate the importance of chirality on their biological activity (see Chapter 4).

Chapter 4 – Synthesis and phamacological evaluation of a series of 5-aryl-1*H*-imidazoles as anticancer agents

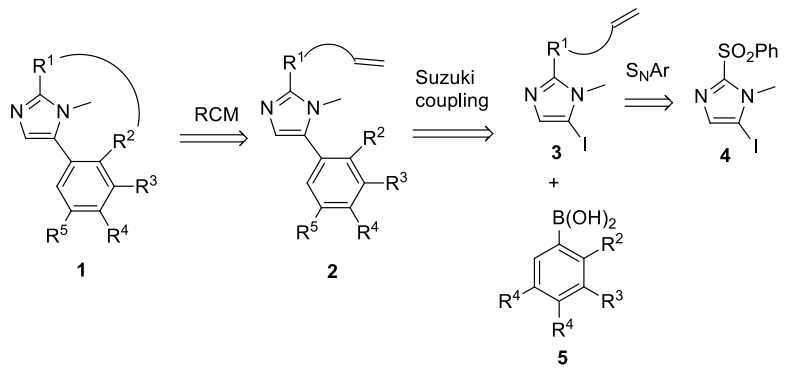
1. INTRODUCTION

This Chapter is dedicated to the study of 5-aryl-1*H*-imidazole derivatives developed in our lab as anticancer agents. The preliminary results showed that our compounds have interesting activities against cancer cell lines which are apopto-sensitives (APO S) and apopto-resistants (APO R) (Table 17). The IC_{50} *in vitro* growth inhibitory concentration of macrocycles (**1**) and "open" compounds (**2**) were below 100 µM.

Table 17. Preliminary MTT tests. APO S, R: cancer cells which are sensitive or resistant to pro-apoptotic stimuli.

Compound	n	IC_{50} (µM)	
		APO S	APO R
	1	50±1	68±7
	3	29±3	38±4
	1	13±3	22±6
	3	6±1	7±1

Therefore, we will synthesize and test a large varity of new compounds in order to be able to perform a SAR study and identify promising lead compounds. Different structural modifications will be introduced; variations on the two arms (R^1, R^2), substitution of the aryl part (R^3, R^4, R^5) and synthesis of 2-aminoimidazole derivatives (Scheme 98).



Scheme 98. Retro-synthetic pathway.

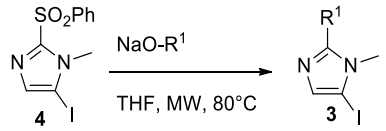
2. SYNTHESIS

2.1. Variations on the 2 arms

First, we decided to modify the R^1 arm by adding fluorine atoms, a phenyl group, a triple bond or simply a saturated chain with different chain lengths. This variation was introduced during the S_NAr.

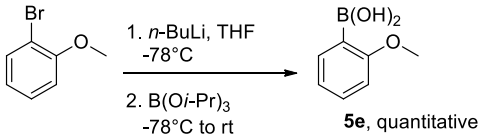
The reaction of intermediate **4** with corresponding alkoxides allowed obtaining seven new compounds (**3**) (Table 18). Low yields are obtained for several compounds but the yields were not improved and compounds **3** were directly engaged in the next step. For the fluorinated chain, conversion was not complete; after purification 68% of the sulfone was recovered. For the alkoxide with a conjugated alkene, the (2*E*,4*E*)-hexa-2,4,dien-1-oxide, reactants were found after reaction. We tried with another base, LiHMDS, but again no conversion was observed.

Table 18. S_NAr with different alkoxides.



Compound	R^1	Yields (%)
3e	OCH_3	79
3f	OC_4H_9	60
3g	OC_6H_{13}	71
3h	$O(CH_2)_4CCH$	16
3i	$OCH_2(CF_2)_4CF_3$	20
3j	$O(CH_2)_3Ph$	77
3k	$O(CH_2)_4Ph$	79
3l	$OCH_2CH=CHCH=CHCH_3$	0

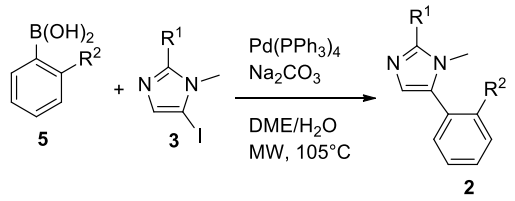
We have also varied the R^2 chain. Variations are introduced during the synthesis of boronic acids. The biological tests were done in parallel of the synthesis of this new family. And after a few tests, we observed that the R^2 chain has no significant influence on the biological activity. So after knowing this information we synthesized compounds with a small R^2 chain: OMe, OH, Me, F or H. The *o*-methoxyphenyl boronic acid was prepared in one step from corresponding bromide using usual conditions (Scheme 99) while the other boronic acids (R^2 = OH, Me, F, H) were commercially available.



Scheme 99. Synthesis of *o*-metoxyphenyl boronic acid (**5e**).

Finally, Suzuki coupling took place in good yields and 16 new compounds were synthesized (Table 19).

Table 19. Results of Suzuki coupling with different R^1 and R^2 arms.

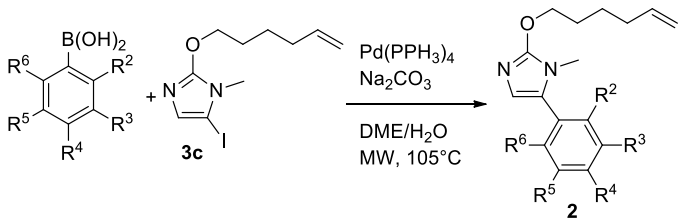


compound	R^1	R^2	Yield (%)
2o	OCH_3	OCH_3	72
2p	$O(CH_2)_2CH=CH_2$	OCH_3	72
2q	$O(CH_2)_4CH=CH_2$	OCH_3	56
2r	OCH_3	$O(CH_2)_4CH=CH_2$	57
2s	OC_4H_9	OCH_3	29
2t	OC_6H_{13}	OCH_3	63
2w	$O(CH_2)_4CH=CH_2$	H	81
2ad	$O(CH_2)_4CH=CH_2$	F	80
2u	$O(CH_2)_4CCH$	OCH_3	32
2v	$OCH_2(CF_2)_4CF_3$	OCH_3	40
2x	$O(CH_2)_3Ph$	OCH_3	91
2y	$O(CH_2)_4Ph$	OCH_3	85
2z	$O(CH_2)_3Ph$	H	68
2aa	$O(CH_2)_4Ph$	H	72
2ac	$O(CH_2)_4CH=CH_2$	Me	71
2ae	$O(CH_2)_4CH=CH_2$	OH	60

2.2. Variations on the aryl part

Firstly, we have carried on with the indroduction of different substituents on the aryl part. For that purpose we have performed the Suzuki coupling with imidazole **3c** and commercially available boronic acids (Table 20).

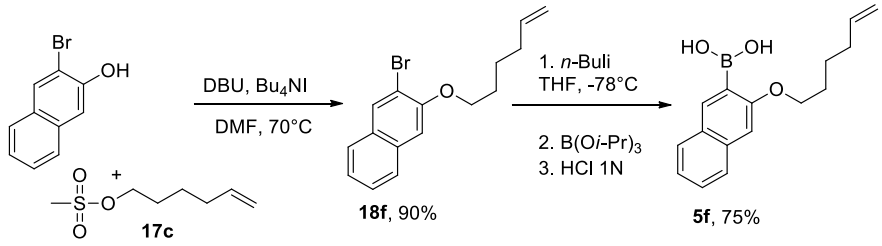
Table 20. Suzuki coupling of **3c** with different arylboronic acids.



Compound	R^2	R^3	R^4	R^5	R^6	Yield (%)
2af	OCH_3	H	H	*i*-propyl	H	93
2ag	OCH_3	H	H	Cl	H	79
2ah	OCH_3	H	Cl	H	H	82
2ai	OCH_3	OCH_3	H	H	H	81
2aj	OCH_3	H	H	CF_3	H	74
2a	OCH_3	H	F	F	H	75
2ap	F	H	H	H	F	0

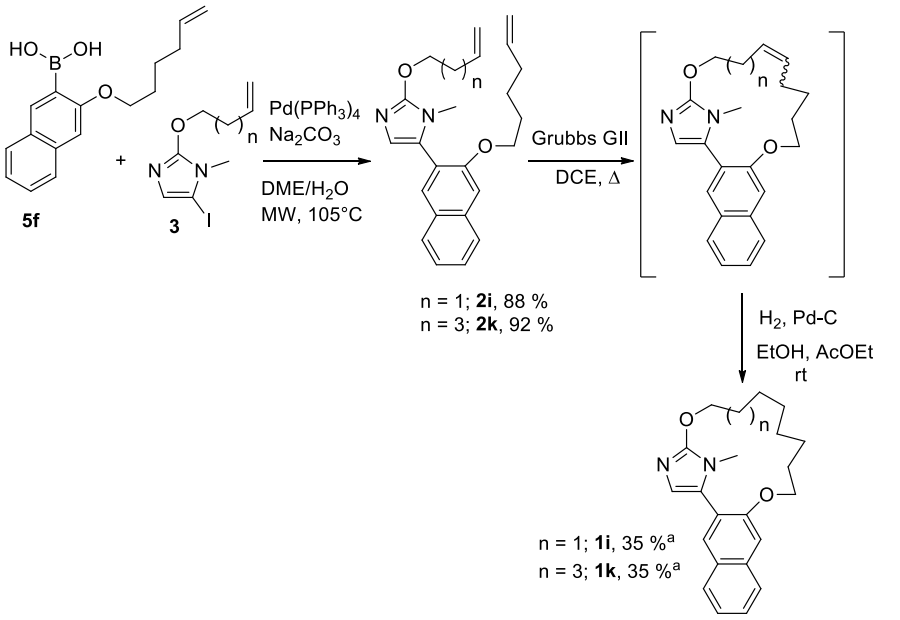
Good yields were obtained with the different arylboronic acids excepted for the *o*-difluoro derivatives for which no conversion was observed. The reaction has not been attemped with longer time reaction.

Secondly, the aryl part was replaced by a naphthyl group. A new bronoric acid (**5f**) containing the naphthyl was synthesized from the bromonaphtol using classical conditions (Scheme 100).



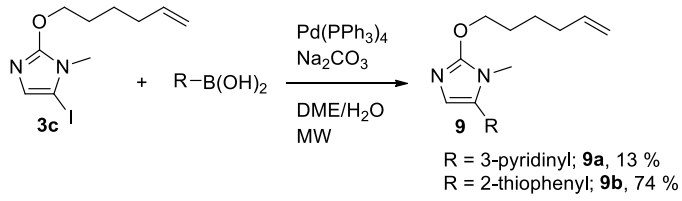
Scheme 100. Preparation of naphthyl boronic acid (**5f**).

Then Suzuki coupling gave compounds **1i** and **1k** in excellent yields. And finally RCM and hydrogenation occurred with a moderate yield; about 35 % for the two compounds (Scheme 101).



Scheme 101. Synthesis of macrocycles **1i,k**. [a] yield over 2 steps.

We have also replaced the aryl part by a heteroaromatic cycle. For that synthesis, Suzuki coupling was carried out with commercially available heteroaromatic boronic acids (Scheme 102). Good yield were obtained with the thiophene derivatives. For the pyridine derivatives, the product was difficult to purify on column chromatography (even with Et_3N) what explains the low isolated yield.

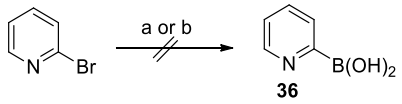


Scheme 102. Suzuki coupling of heterocycles.

We tried to do this reaction with the 2-furan boronic acid but even with longer reaction time we could not obtain the desired product.

We also attempted the synthesis of 2-pyridylboronic acid (**36**) to obtain the corresponding "open" compound (Scheme 103). So we have used the classical method from the commercially available 2-bromopyridine namely, addition of *n*-Buli, followed by the borate and acidic work up. But we failed even when the reaction was quenched at milder pH.

It is known that haloazine gives side-reactions such as deprotonation, addition to the substrate, elimination or migration of the halogen under these conditions. So we tried milder reaction conditions using transmetalation between Grignard azine and *tris*-trimethylsilylborate to access to boronic acid.[168] But yet with this milder method, the desired product was not obtained.



36

Scheme 103. Synthesis of 2-pyridinylboronic acid (**36**). a) 1. *n*-Buli, 2. $B(O\textit{i}\text{-}Pr)_3$, HCl 1N, b) 1. *i*-PrMgCl, rt 2. $((CH_3)SiO)_3B$, 0°C to rt, 3. HCl/H_2O (6 < pH < 7), 0°C to rt.

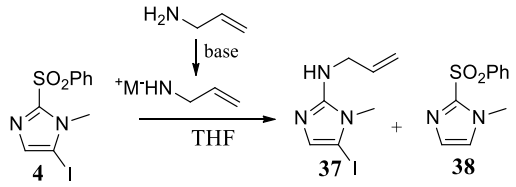
2.3. Synthesis of a 2-aminoimidazole derivatives

We envisaged the synthesis of a 2-aminoimidazole analogue of our macrocycles. Indeed, in the literature we have found more examples of biologically active 2-amino than 2-alkoxyimidazole. Moreover, the introduction of an amine instead of an oxygen atom will increase the basicity of imidazole core and so may well have an impact on the biological activity. Preliminary works had already been carried out in our group when started this thesis.

2.3.1. Previous work

Few attempts of amination were already done by Dr. P. Nshimyumukiza (Table 21). Key intermediate **4** was subjected to a S_NAr with an allyl amine under different reaction conditions.

Table 21. Amination of **4**.

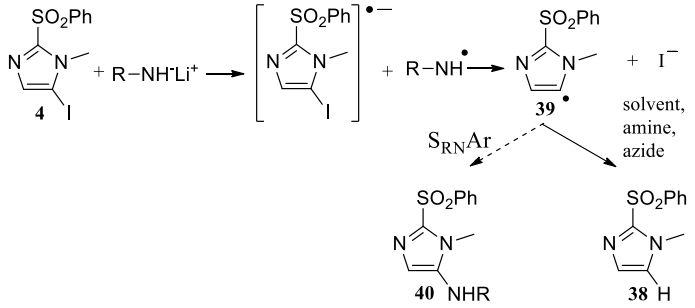


Entry	Conditions	Results (%)		
		4	**37**	**38**
1	1) allylamine (4 equiv.), *n*-BuLi (3,8 equiv.), rt, 30 min 2) **4** (50 mg), rt, 15 h	0	0	100
2	1) allylamine (1,5 equiv.), NaH (1 equiv.), rt, 1 h 2) **4** (50 mg), rt, 15 h	0	0	100
3	1) allylamine (1,5 equiv.), NaH (1 equiv.), rt, 1 h 2) **4** (50 mg), reflux, 24 h	95	0	5
4	1) allylamine (2 equiv.), NaH (1,5 equiv.), rt, 1 h 2) **4** (200 mg), MW, 80°C, 15 h	74	0	26
5	1) allylamine (2 equiv.), NaH (1,5 equiv.), rt, 1 h 2) **4** (200 mg), 18-crown-6 ether, MW, 80°C, 15 h	26	0	74
6	1) allylamine (4 equiv.), KH (3,8 equiv.), rt, 2 h 2) **4** (100 mg), rt, 20 h	0	0	100
7	1) allylamine (500 equiv.) 2) **4** (5 mg), rt, 15 h	100	0	0
8	1) **4** (20 mg) 2) NaH (5 equiv.)	89	0	11

The desired product was never observed. Instead, reactant or/and deiodinated product (**38**) was obtained. Even if one changes the base, utilizes microwave heating, varies the proportion of reactants, it did not work. Dr. P. Nshimyumukiza has also tested if the base or the amine were responsible of the reduction of compound **4** to **38** (entries 7-8 in Table 21). But it was not the case.

In order to prevent formation of **38**, we tried, during our Master thesis, to understand the mechanism of its formation. In the literature, a radical mechanism was brought out in aromatic nucleophilic substitution as well as in reaction of halogenated alkyls with lithium dialkylazide.[169,170] We thus speculated that compound **38** could be formed by a radical mechanism (Scheme 104). The azide

could be the initiator by giving an electron to compound **4** that would then breakdown rapidly to give radical **39** and an iodine ion. After, there are two possible reactions: addition of a second equivalent of azide followed by monoelectronic transfert to conduct to the radical nucleophilic substitution ($S_{RN}Ar$) or the abstraction of a hydrogen atom (from solvent, amine, azide...) to form compound **38**.



Scheme 104. Possible radical mechanism.

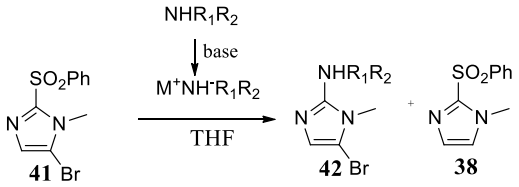
Experiments were carried out (Master's thesis E. Van Den Berge) with a radical sensor; the 1,4-dinitrobenzene. We have also changed the solvent, heating or not and do the reaction in the dark. But unfortunately, when the reaction worked compound **38** was obtained without the desired product.

With these results, we wondered if the problem was due to a very high reactivity of the C-I bond toward radical reactions or to a particularly low reactivity of the imidazole toward amination. So we engaged the product **38** in reaction with alkylazide. We observed the apparition of a new product: the desired 2-aminoimidazole. It was confirmed by MS and NMR but there was too low quantity to isolate it.

Accordingly, we decided to synthesize the imidazole with a bromide in position 5 instead of iodine. Indeed, C-Br bond should be more resistant than C-I bond toward electron transfer reactions.[171]

Key intermediate **42** with a bromide was synthesized using the same methodology for sulfone **4** but here the imidazole was brominated with NBS. Then amination was attempted with different azides and reactions conditions (Table 22). Always the same results was obtained; reactant **42** and/or compound **38**. Moreover, one can notice that the proportion of dehalogenated product **38** was higher with bromide than with iodine which is the inverse of what is demonstrated in the literature.[171]

Table 22. Amination attempts with 4-bromoimidazole **41**.



Entry	Conditions	Results (%)		
		41	**42**	**38**
1a	1) *n*-amylamine (4 equiv.), *n*-BuLi (3,8 equiv.), -78°C then rt 2) **41** (50 mg), rt, 21 h, THF	31	0	69
1b	1) *n*-amylamine (4 equiv.), *n*-BuLi (4 equiv.), -78°C then rt 2) **41** (50 mg), 21 h at rt then 7 h MW at 80°C, THF	29	0	71
2a	1) MeBuNH (4 equiv.), *n*-BuLi (3,8 equiv.), -78°C then rt 2) **41** (50 mg), rt, 21 h, THF	100	0	0
2b	1) MeBuNH (4 equiv.), *n*-BuLi (3,8 equiv.), -78°C then rt 2) **41** (50 mg), 21 h at rt then 7 h MW at 80°C, THF	100	0	0

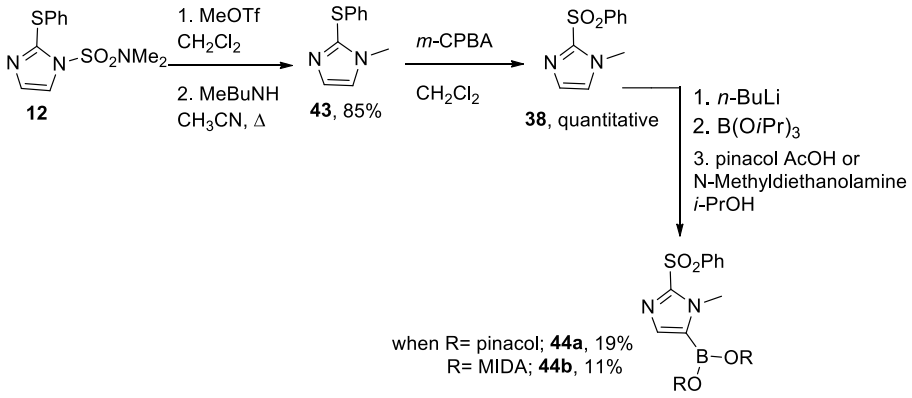
Finally, we tried to carry out the amination on the "open" compound **2** to have a blocked position 5 with an aryl (inverse the sequence amination-Suzuki coupling). However, the reaction did not work probably due to steric interactions with the R^2 arm already present in the molecule.

This ended the different attempts which were done before our thesis concerning the preparation of a 2-aminoimidazole derivatives.

2.3.2. Our works

The first attempt consisted in forming a carbon-boron bond instead of the carbon-iodine bond and see if this C-B$(OR)_2$ bond resist under the amination conditions. The beginning of the synthesis starts with the methylation of imidazole **12** (from the general method of formation of the key intermediate, see Chapter 1, 2.2.2.) with 85 % yield. Secondly, the sulfur atom is oxidized quantitatively to give

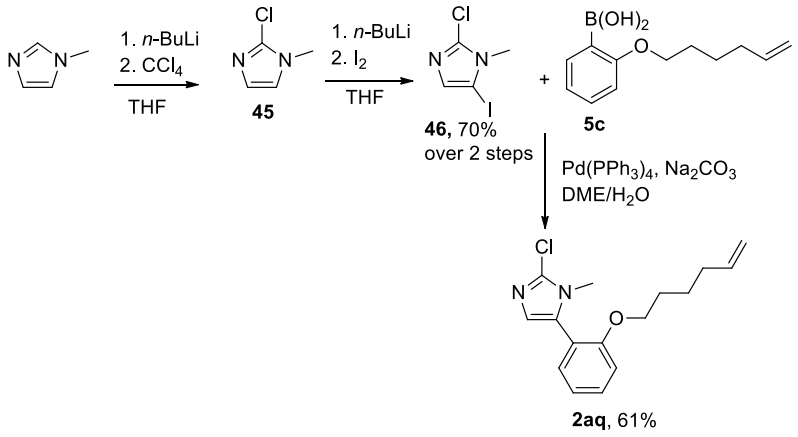
sulfone **38**. The last steps are deprotonation in position 5 followed by addition of triisopropylborate to give the boronic ester. And finally, we have prepared two different esters with a pinacol and a MIDA type ligands[172] (Scheme 105). The yields were not improved and we tested them directly in amination conditions.



Scheme 105. Formation of boronic esters **44**.

We have used the standard conditions of amination, *n*-amylamine, *n*-BuLi room temperature, and after 15h we have observed for the two boronic esters formation, once again, of the compound **38**. C-B(OR)$_2$ bond was not strong enough under amination conditions.

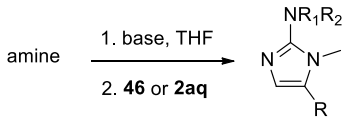
The second attempt was to synthesize the 2-chloroimidazole. Indeed, for the S_NAr we need an electon withdrawing group in position 2. We have seen that with the sulfone it did not work so we decided to put a chlorine atom which is sterically less hindering. For this purpose commercially available *N*-methylimidazole was successively substituted by chlorine and iodine to form compound **46** in 70 % yield. Then Suzuki coupling was carried out under usual conditions to conduct to imidazole **2aq** in 61 % yield (Scheme 106).



Scheme 106. Synthesis of 2-chloroimidazoles (**2aq**).

Afterwards, different amination conditions were attempted with these two chlorinated compound (**46** and **2aq**) (Table 23). Unfortunately, after this set of experiments, it still did not work. We tried primary, secondary and protected amine, different bases strong and weak, different reactions conditions (heating, HMPA,..).

Table 23. Amination conditions of compounds **46** and **2aq**.

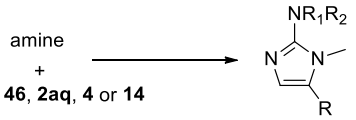


Conditions				Results
amine	**base**	**imidazole**	**Heating, additive**	
amylamine	*n*-BuLi	**2aq**	rt and Δ	Reactant found
amylamine	*n*-BuLi	**46**	MW	″
amylamine	NaH	**2aq**	MW	″
amylamine	DBU	**46**	rt and Δ	″
amylamine	DBU	**2aq**	rt and Δ	″
MeBuNH	*n*-BuLi	**2aq**	MW	″
MeBuNH	NaH	**2aq**	MW	″
$TsNH(CH_2)_2CH=CH_2$	*n*-BuLi	**46**	rt + or not HMPA	″
$TsNH(CH_2)_2CH=CH_2$	*n*-BuLi	**46**	MW + HMPA	″

Finally, we tried others methods with primary or protected amine in different solvents and temperature or in pure phase. And only for the reaction done

in ethanol, we found traces of the desired product but we could not improve the yield. We tried also the conditions of Thomae et al.[173] which succeded in S_NAr with 2-methylsulfur thiazole and a secondary amine (10 equiv.) at reflux (here engaged with sulfure **14**, Table 24)

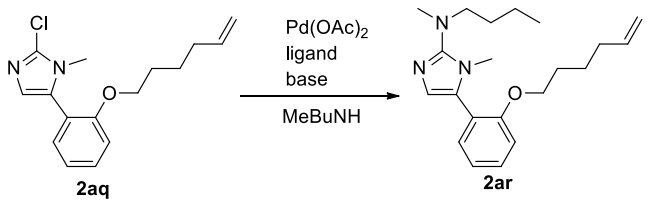
Table 24. Others aminations conditions.



	Conditions			Results
amine	**imidazole**	**additive**	**heating**	
$TsNH(CH_2)_2CH=CH_2$	**46**	HCl, THF	rt or MW	Reactant found
amylamine	**46**	TMSBr, THF	rt or MW	″
amylamine	**46**	EtOH	70°C	Trace after 5 days
amylamine	**2aq**	EtOH	70°C	Reactant found
amylamine	**46**	/	120°C	″
amylamine	**2aq**	Et_3N, DMF	rt or MW	″
amylamine	**46**	Et_3N, DMF	rt or MW	″
amylamine	**4**	Et_3N, DMF	rt or MW	″
morpholine	**14**	/	130°C	″

We tried also the reaction conditions of the palladium catalyzed amination of Buchwald-Hartwig; [174] We have used the *rac*-BINAP as catalyst but also the ligand of Buchwald the 2-(dicyclohexylphosphanyl)biphenyl[175](DCPB). And again, no desired product was obtained and traces of dehalogenated (imidazolone) reactant were obtained (Table 25).

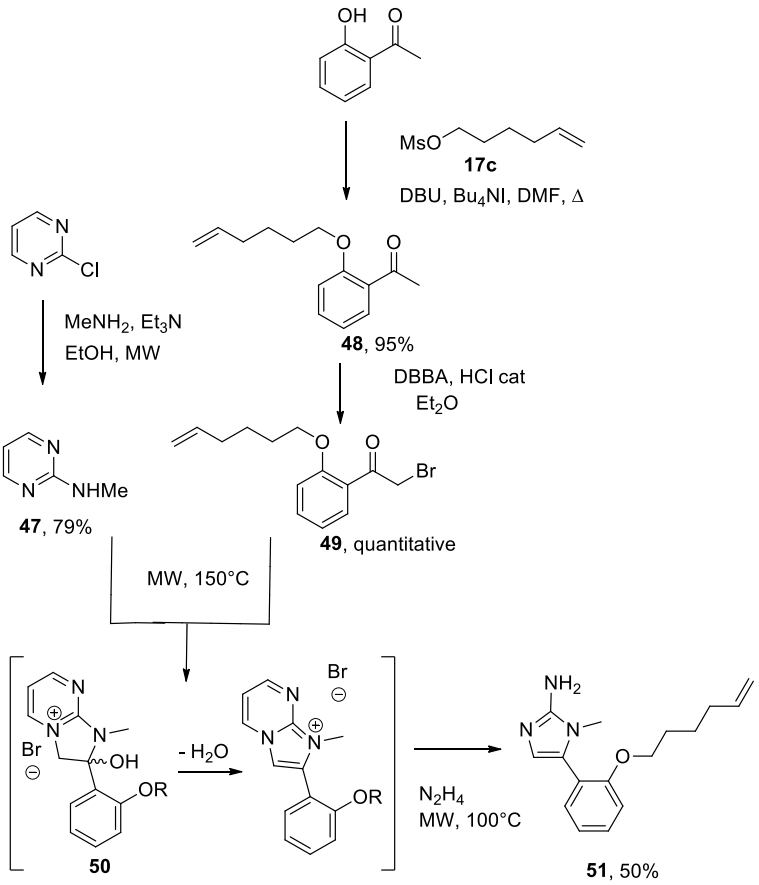
Table 25. Buchwal-Hartwig conditions.



2aq **2ar**

Conditions				Results
ligand	**base**	**T (°C)**	**Solvent, time**	
rac-BINAP	Cs_2CO_3	80	1,4-dioxane, 18h	Reactant found
rac-BINAP	NaO*t*-Bu	120	Toluene, 24h	Reactant found + traces of imidazolone
DCPB	NaO*t*-Bu	120	Toluene, 24h	″

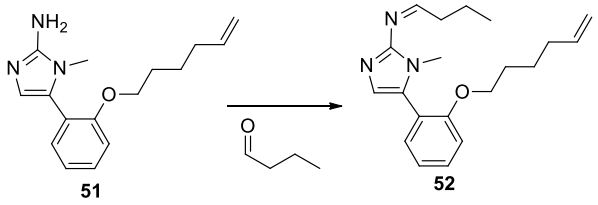
After many attempts, we have changed strategy. And we succeeded in obtaining the desired 2-aminoimidazole **51** using an adaptation of the Van der Eycken method.[176] This methodology involves the condensation of an α-bromoketone with a 2-aminopyridine to form an imidazo[1,2-*a*]pyridine (Scheme 107). Then this pyridine is cleaved upon treatment with hydrazine. 2-Aminopyridine (**47**) was synthesized from the corresponding 2-chloropyridine by a S_NAr under microwave heating with 79 % yield. In parallel, α-bromoketone (**49**) was formed in two steps. Commercially available α-hydroxyacetophenone was alkylated under usual conditions; with a mesylated alcohol (**17c**) in the presence of iodine and DBU. The next step is the the bromination reaction. We have tried different methods. Firstly, bromination with Br_2[177], but this reagent seemed to be too reactive (smoke formation) and the double bond of the molecule also reacted under these conditions. Secondly, we tried NBS with or without PTSA[178] and we found by spectrometry analysis the formation of a secondary product: NBS reacted also with the double bond (introduction of 2 bromine atoms). Finally, we have used DBBA[176], a mild bromination agent, and we have formed the desired product **49** in quantitative yield. We have developed for the last step a microwave heating reaction. Compound **47** and **49** were heated at 150°C under microwave heating to form salt **50**. After aqueous hydrazine addition the mixture was again heated at 100°C under microwave to form compound **51** in 50 % yield.



Scheme 107. Synthesis of 51 using the method of E. Van der Eycken.

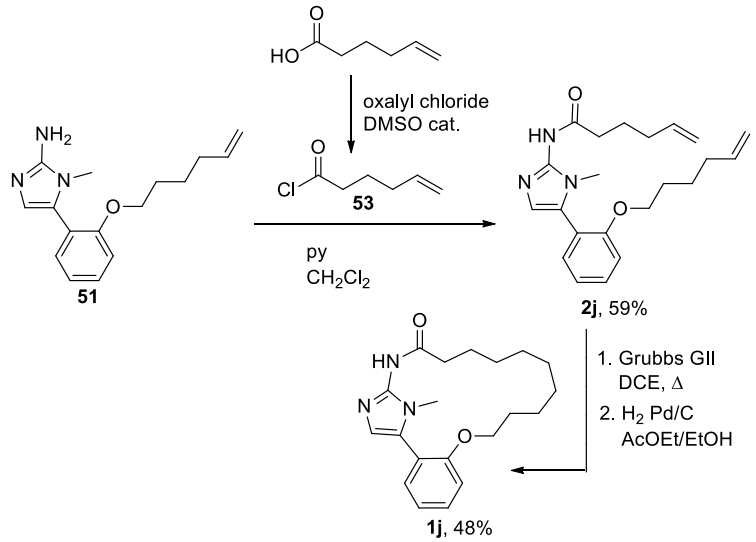
Formation of the 2-aminoimidazole done, it remained the alkylation of this latter. So we tried usual alkylation conditions with a mesylated alcohol, iodine and DBU but we did not succeed in. There was degradation. Secondly, we tried reductive amination. For the first step of this reaction, different conditions were tried (Table 26). Only, addition of an aldehyde did not give the desired product (reactions were carried out without work up). So we added a drying agent: molecular sieves, magnesium sulfate with or without Et_3N[179]and it did not work yet. Even when potassium carbonate or alumina[180] were used.

Table 26. Imine formation conditions.



conditions		Results
additives	**heating**	
toluene	rt or 110°C	degradation
M.S., toluene	rt	″
$MgSO_4$, toluene	rt	″
$MgSO_4$, Et_3N, CH_2Cl_2	rt	″
K_2CO_3, toluene	rt	″
Al_2O_3 neutral, CH_2Cl_2	rt	″

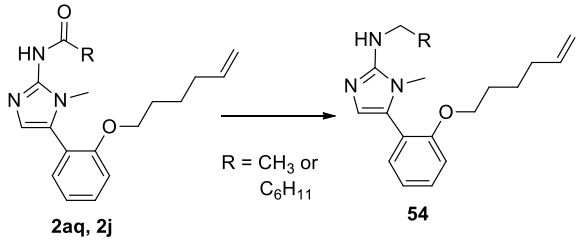
Finally, we decided to go one oxidation stage ahead and form an amide[181]. Acid chloride was synthesized just prior to be engaged in the amide formation (Scheme 108). Corresponding acid was stirred with oxalyl chloride in the presence of a catalytic amount of DMSO and acid chloride (**53**) was obtained in quantitative yield. After, the amide formation was performed in dichloromethane with pyridine to form compound **2j** in a moderate yield. We also synthesized the corresponding macrocycle **1j** without any problems.



Scheme 108. Synthesis of macrocycle **1j**.

The last step is the reduction of the amide group into an amine function. In order to investigate this reaction, we synthesized compound **2ak** (economy of atom) in 49 % yield. We tried different conditions starting with $LiAlH_4$ with or without a Lewis acid ($AlCl_3$), but also with borane dimethyl sulfide[182]. We tried also a transition-metal-catalyzed transformation of amides to the corresponding amines using monohydrosilanes as a reducing agent as reported by Igarashi at al.[183] But again it did not work (even with the corresponding macrocycles **1j**) (Table 27).

Table 27. Conditions for the reduction of amide.



2aq, 2j **54**

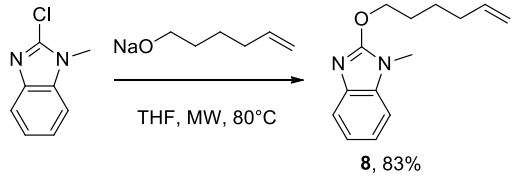
Imidazole	Conditions additives	Results
2aq	$LiAlH_4$, THF rt or 70°C	Reactant or degradation
2aq	$LiAlH_4$, $AlCl_3$, Et_2O, rt	″
2j	$LiAlH_4$, THF rt or 70°C	″
1j	$LiAlH_4$, THF rt or 70°C	″
2j	$(Me)_2SBH_3$, Na_2CO_3, Toluene, 110°C	″
2j	$HSiEt_3$, $RuCl_2(CO)_2(PPh_3)_2$, EtI, toluene, 110°C	″
1j	$HSiEt_3$, $RuCl_2(CO)_2(PPh_3)_2$, EtI, toluene, 110°C	″

This ends the synthesis of the 2-aminoimidazole. For a question of time, we could not carry on. We thus did not succeed in synthesizing the 2-aminoderivatives but we however managed the synthesis of the corresponding 2-amidoimidazoles **2j** and **1j**. All these new compounds have been tested to confirm their biological activities.

2.4. Other products for biological testing

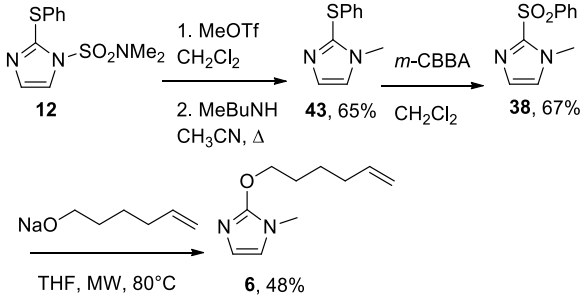
Other products were synthesized to refine our SAR study.

Firstly, we have synthesized benzimidazole derivatives (**8**). We tried a palladium catalyzed arylation[184] using $Pd_2(dba)_3$ as catalyst, BINAP as ligand, *t*-BuONa as a base in THF at reflux. But even after 6 hours at reflux or under microwave heating, no conversion was observed. Thus we tried our classical S_NAr reaction conditions and **8** could be obtained in 83% yield (Scheme 109).



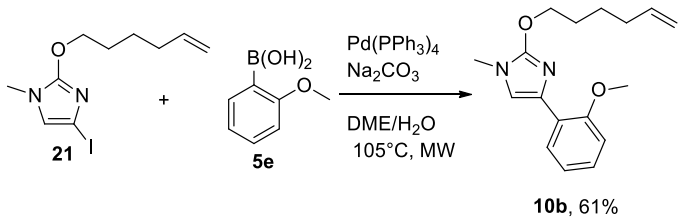
Scheme 109. Synthesis of benzimidazole **8**.

Secondly, we wanted to investigate the importance of the imidazole substitution on biological activities by preparing a derivative without any substituent in position 4 and 5. So we began with compound **12** (from the synthesis of the key intermediate, see Chapter 1, 2.2.2.), did the methylation and then the oxidation of sulfide into sulfone to obtain imidazole **38** (Scheme 110). The last step was the S_NAr to form the final product in 48% yield.



Scheme 110. Synthesis of imidazole **6**.

We have also synthesized the "open" compound with the 1,2,4-imidazole with R^2 arm = OMe using the same methodology as explain in section Chapter 3, 2. (Scheme 111). Indeed, biological tests revealed that the R^2 chain did not have a significant effect on the biological activity.



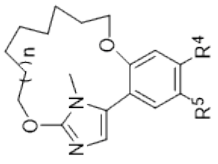
Scheme 111. Formation of compound **10**.

3. BIOLOGICAL RESULTS AND SAR STUDIES

3.1. Inhibition activity toward A_3 and D_1 receptors, chlorine channel and choline transporter

We first have completed the biological study of our compounds as inhibitors of A_3 and D_1 receptors, chlorine channel and choline transporter by testing our last macrocycles including the chiral ones as racemate and enantiomererically pure forms (Table 28).

Table 28. Specific binding tests (concentration = 10 µM).

Compound	n	R^4	R^5	% Inhibition			
				Adenosine A^3 receptor	Dopamine D_1 receptor	Chlorine channel	choline transporter
	(+/-)-1	H	H	84	69	52	52
	(+)-1	H	H	65	8	36	3
	(-)-1	H	H	42	59	23	0
	(+/-)-2	H	H	86	73	56	23
	3	H	H	99	99	73	98
	4	H	H	92	83	61	46
	1	naphthyl		91	57	-11	41
	3	naphthyl		95	53	2	59

The results revealed that the size of the ring has little influence on the inhibition activity. For the four targets, an increase in the ring size seems to be beneficial.

The influence of chirality was examined. For adenosine A_3 receptor and chloride channel binding, the enantiomer (+)-**1a** is found to be slightly more active

than (–)-**1a**. For dopamine D_1 receptor, the absolute configuration of **1a** has a significant impact on the binding inhibition activity: (–)-**1a** is found to be active, whereas (+)-**1a** is inactive. And for choline transporter, there was no activity for the racemic one nor the enantiomerically pures.

Concerning the naphthyl derivatives, there was no more activity against the chlorine channel. While for the other targets an activity is observed but not as good as for the corresponding non-substituted macrocycle.

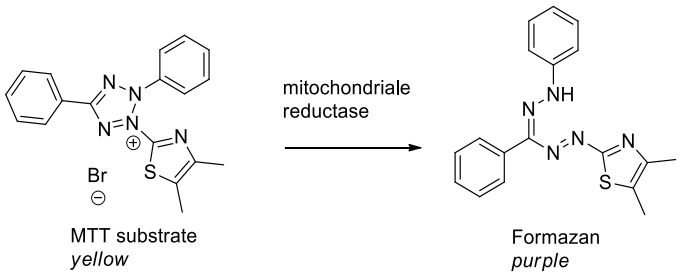
3.2. Anticancer activity

Preliminary MTT colorimetric assays revealed that compounds **1** and **2** show interesting activities against cancer cell lines which are apopto-sensitive (APO S) and apopto-resistances (APO R) (see Chapter 1, 2.3.). This is of particular interest since survival of several cancer types has been markedly improved despite enrichment of the chemical libraries used in oncology with natural as well as synthetic compounds due to resistance phenomena (inter alia resistant to pro-apoptotic stimuli). It is thus important to discover new compounds which are active against APO R in order to avoid this resistance.

In this section, we will (1) subject the large panel of compounds we have synthesized (macrocycles and intermediates; about 60 compounds) to biological (MTT) testing on various cancer cell lines in order to perform a structure-activity relationship (SAR) study to improve the activity and (2) investigate the mechanism of action of these imidazole derivatives.

Four cancer cell lines displaying actual sensitivity to pro-apoptotic stimuli were analyzed, i.e. the mouse B16F10 melanoma, and the human prostate (PC-3), breast (MCF-7) and colon (LoVo) carcinoma cell lines. In the same manner, four human cancer cell lines that displayed various levels of resistance to pro-apoptotic stimuli were also analyzed and included: the human U373 and T98G gliomas, the SKMEL-28 melanoma and the A549 non-small cell lung carcinoma (NSCLC).

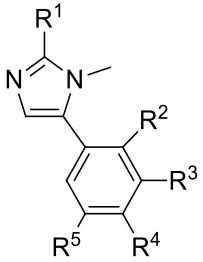
MTT test is a colorimetric assay which is a rapid, sensitive quantification of proliferation and viability of cells. This assay measurement is based on the activity of cellular enzymes (deshydrogenase succinate) that reduce the tetrazolium dye, MTT ((3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide), to insoluble formazan, giving a purple color. This is the quantities of formazan formed that are detected by spectrometry (Scheme 112).

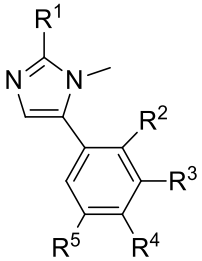


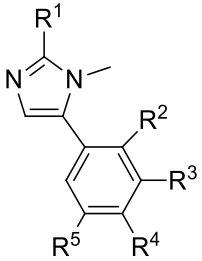
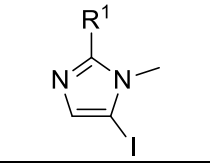
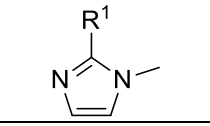
Scheme 112. Reaction of MTT tests.

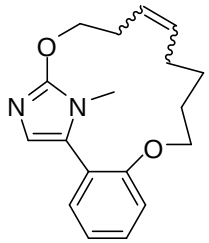
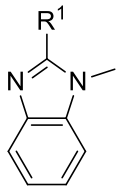
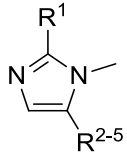
These *in vitro* growth inhibitory effects were determined in each cancer cell line by calculating the concentration that decreased by 50% the growth of this cancer cell line after having cultured it for 72 h in the presence of the drug of interest. Obtained results are reported in Table 29.

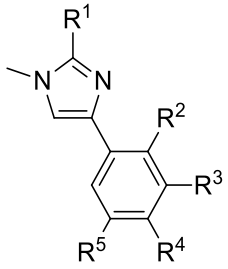
Table 29. Mean IC_{50} growth inhibitory concentrations (μM) of synthesized compounds determined by colorimetric MTT assay after 72h incubation (APO S, APO R mean, respectively, senstivive and resistant to apoptotic stimuli). § B16F10 cells were not assayed. * U373 cells were not assayed..

Compound	Structure	R^1	R^2	R^3	R^4	R^5	IC_{50} (APO S)	IC_{50} (APO R)
(+/-)-1a§		$O(CH_2)_8O$		H	H	H	50 ± 1	68 ± 7
(+)-1a§		$O(CH_2)_8O$		H	H	H	43 ± 3	67 ± 3
(-)-1a§		$O(CH_2)_8O$		H	H	H	54 ± 6	71 ± 8
1b§		$O(CH_2)_9O$		H	H	H	55 ± 11	73 ± 2
1c§		$O(CH_2)_{10}O$		H	H	H	29 ± 3	38 ± 4
1d§		$O(CH_2)_{11}O$		H	H	H	36 ± 3	47 ± 4
1e§		$O(CH_2)_8O$		H	CH_3	H	35 ± 1	54 ± 5
1f§		$O(CH_2)_8O$		H	OCH_3	H	35 ± 2	57 ± 6
1g§		$O(CH_2)_8O$		H	F	H	38 ± 4	60 ± 6
1h§		$O(CH_2)_8O$		H	H	F	49 ± 3	70 ± 4
1i§		$O(CH_2)_8O$		H	naphthyl		20 ± 3	26 ± 2
1j§		$NHCO(CH_2)_9O$		H	H	H	52 ± 9	51 ± 6
1k§		$O(CH_2)_{10}O$		H	naphthyl		26 ± 1	26 ± 3
2a§		$O(CH_2)_2CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	H	H	13 ± 3	22 ± 6
2b§		$O(CH_2)_3CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	H	H	13 ± 8	8 ± 4
2c		$O(CH_2)_4CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	H	H	6 ± 1	7 ± 1
2d§		$O(CH_2)_5CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	H	H	55 ± 12	70 ± 4
2e§		$O(CH_2)_2CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	CH_3	H	51 ± 5	67 ± 14
2f§		$O(CH_2)_2CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	OCH_3	H	38 ± 3	62 ± 7

Compound	Structure	R^1	R^2	R^3	R^4	R^5	IC_{50} (APO S)	IC_{50} (APO R)
2g§		$O(CH_2)_2CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	F	H	56 ± 6	> 89 ± 6
2h§		$O(CH_2)_2CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	H	F	44 ± 4	76 ± 6
2i§		$O(CH_2)_2CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	naphthyl		21 ± 4	26 ± 2
2j§		$NHCO(CH_2)_3CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	H	H	14 ± 4	11 ± 4
2k§		$O(CH_2)_4CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	naphthyl		33 ± 4	37 ± 9
2l§		SO_2Ph	OH	H	H	H	> 85 ± 15	> 100
2m§		SO_2Ph	$O(CH_2)_2CH=CH_2$	H	H	H	47 ± 10	> 83 ± 10
2n§		SO_2Ph	$O(CH_2)_4CH=CH_2$	H	H	H	28 ± 2	53 ± 9
2o§		OCH_3	OCH_3	H	H	H	> 91 ± 9	>100
2p§		$O(CH_2)_2CH=CH_2$	OCH_3	H	H	H	25 ± 1	25 ± 5
2q§		$O(CH_2)_4CH=CH_2$	OCH_3	H	H	H	11 ± 7	8 ± 2
2r§		OCH_3	$O(CH_2)_4CH=CH_2$	H	H	H	77 ± 15	> 91 ± 5
2s*		OC_4H_9	OCH_3	H	H	H	59 ± 8	88 ± 4
2t*		OC_6H_{13}	OCH_3	H	H	H	31 ± 3	44 ± 6
2u*		$O(CH_2)_4CCH$	OCH_3	H	H	H	19 ± 6	30 ± 5
2v*		$OCH_2(CF_2)_4CF_3$	OCH_3	H	H	H	56 ± 7	77 ± 5
2w		$O(CH_2)_4CH=CH_2$	H	H	H	H	29 ± 7	30 ± 3
2x		$O(CH_2)_3Ph$	OCH_3	H	H	H	10 ± 6	3 ± 1
2y		$O(CH_2)_4Ph$	OCH_3	H	H	H	33 ± 4	42 ± 1
2z		$O(CH_2)_3Ph$	H	H	H	H	28 ± 7	32 ± 1
2aa		$O(CH_2)_4Ph$	H	H	H	H	38 ± 6	53 ± 6
2ab§		$O(CH_2)_2OCH_2CH=CH_2$	$O(CH_2)_4CH=CH_2$	H	H	H	31 ± 3	55 ± 7
2ac		$O(CH_2)_4CH=CH_2$	CH_3	H	H	H	38 ± 7	36 ± 3
2ad		$O(CH_2)_4CH=CH_2$	F	H	H	H	39 ± 5	40 ± 3

Compound	Structure	R^1	R^2	R^3	R^4	R^5	IC_{50} (APO S)	IC_{50} (APO R)
2ae*		$O(CH_2)_4CH=CH_2$	OH	H	H	H	70 ± 2	59 ± 3
2af*		$O(CH_2)_4CH=CH_2$	OCH_3	H	H	*i*-Pr	4 ± 1	9 ± 3
2ag*		$O(CH_2)_4CH=CH_2$	OCH_3	H	H	Cl	37 ± 6	29 ± 1
2ah*		$O(CH_2)_4CH=CH_2$	OCH_3	H	Cl	H	55 ± 6	38 ± 2
2ai*		$O(CH_2)_4CH=CH_2$	OCH_3	OCH_3	H	H	35 ± 5	26 ± 5
2aj*		$O(CH_2)_4CH=CH_2$	OCH_3	H	H	CF_3	69 ± 10	57 ± 2
2ak*		$O(CH_2)_4CH=CH_2$	OCH_3	H	F	F	45 ± 4	38 ± 2
3a		$O(CH_2)_2CH=CH_2$	/	/	/	/	89 ± 12	>100
3b		$O(CH_2)_3CH=CH_2$	/	/	/	/	87 ± 11	>100
3c		$O(CH_2)_4CH=CH_2$	/	/	/	/	84 ± 12	>100
3d		$O(CH_2)_5CH=CH_2$	/	/	/	/	80 ± 10	99 ± 1
4		SO_2Ph	/	/	/	/	>100	>100
6		$O(CH_2)_4CH=CH_2$	/	/	/	/	88 ± 12	>100

Compound	Structure	R^1	R^2	R^3	R^4	R^5	IC_{50} (APO S)	IC_{50} (APO R)
7a		$O(CH_2)_2CH=CH(CH_2)_4O$		H	H	H	59 ± 6	85 ± 5
8		$O(CH_2)_4CH=CH_2$	/	/	/	/	89 ± 5	>100
9a		$O(CH_2)_4CH=CH_2$	3-pyridinyl				>100	>100
9b			2-thiophenyl				35 ± 13	63 ± 2

Compound	Structure	R^1	R^2	R^3	R^4	R^5	IC_{50} (APO S)	IC_{50} (APO R)
10		$O(CH_2)_4CH=CH_2$	OCH_3	H	H	H	78±4	98 ± 2

The panel of compounds synthesized and tested allows some conclusions to be drawn concerning structure-activity relationships (Figure 22).

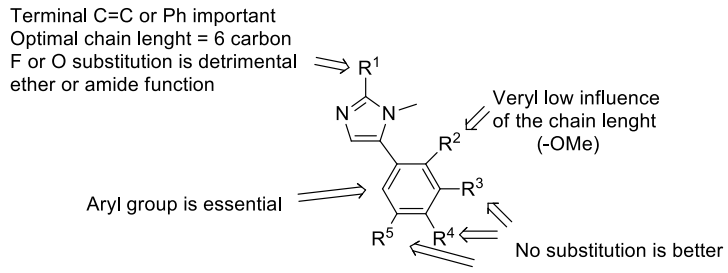


Figure 22. Structure-activity relationship analysis.

First, the non-cyclized compounds (**2**) are systematically more active than their respective macrocyclic structure (**1, 7a**).

The chirality has no significant impact on the biological activity. Each enantiomers (**(+)-1a, (-)-1a**) has nearly the same activity compare to the mixture of the two enantiomers (**(+/-)-1a**).

Concerning the substitution pattern ($R^{3,4,5}$), the obtained IC_{50} for compounds **1e-i,k** and **2e-i,k,af-ak** indicate that substitution of the aryl group at the *ortho*, *meta* or *para* positions (R^3, R^4, $R^5 \neq H$) leads to a decrease of inhibition activity. Excepted for compound **2af** (R^5 = *i*-Pr) which has an IC_{50} similar to the non-substituted coumpound **2c**.

The nature of the R^2 chain does not significantly influence the biological activity, as compounds with a OCH_3 group in that position shows similar activities to those possessing a longer chain (compare for instance **2c** and **2q**). However, when this chain is replaced by a hydrogen (**2w**), a methyl (**2ac**), a fluorine atom (**2ad**) or a hydroxyl group (**2ae**), the activity decreases.

In contrast, the nature of the substituent in position 2 of the imidazole (R^1) appears to have marked impact on the growth inhibition activity in cancer cell line models. Indeed, variations in the chain length (see **2a-d**) induce large difference in IC_{50}, with an optimal chain length of six carbon atoms ($R^1 = O(CH_2)_4CH=CH_2$, **2c**). The inclusion of fluorine (**2v**) or oxygen (**2ab**) atoms, a terminal alkyne (**2u**) in this chain (R^1) is detrimental to its activity. Moreover, the terminal unsaturation is important for the activity (see for instance **2s-t** with a saturated chain) with the best results being obtained with a terminal double bond (with 6 carbon atoms) or a phenyl group (with 3 carbon atoms) (**2c** and **2x**).

The synthesis and biological evaluation of amide derivatives **1j** and **2j** indicated that 2-alkoxy and 2- amido imidazole derivatives possess very similar inhibition activities (compare **2c** with **2j**).

Intermediates in the synthesis of our 5-aryl-1*H*-imidazole derivatives (**3a-d** and **4**) were also tested but show low activities. Futhermore, when the aryl part was removed (**6**) or replaced by formation of a benzimidazole (**8**), 5-pyridinylimidazole (**9a**) or 5-thiophenylimidazole (**9b**), the activity also decreases.

Finally, we point out that the regiochemistry on the imidazole part was crucial. Indeed, the 1,2,4-substituted imidazole (**10**) has lower activity than the correspondind 1,2,5-isomer (**2q**).

Interestingly, the most active compounds, i.e., **2b-c**,**a**,**x**,**af** displayed similar *in vitro* growth inhibitory activity in the various cancer cell lines analyzed regardless of the cell line level of resistance to pro-apoptotic stimuli. Thus, it is unlikely that the *in vitro* growth inhibitory effects of these compounds are related to pro-apoptotic effects.

In order to study the effects of our compounds, a computer-assisted phase-contrast microscopy (quantitative videomicroscopy) analysis was carried out with compound **2c** (the most active compound) on two cancer cell lines, NSCLC A549 and glioblastome U373 which are resistant to proapoptotic stimuli. A picture of the developing cell cultures, one control test versus in the presence of 7 µM of **2c**, was taken every 4 minutes during 72 hours (Figure 23). This experiment was done in triplicate.

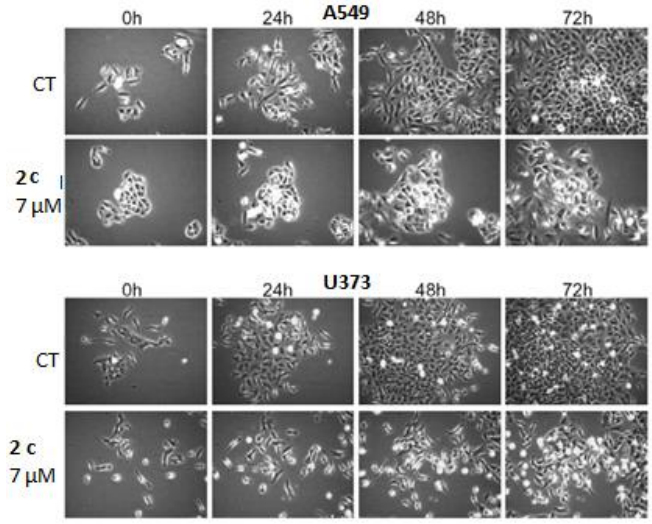
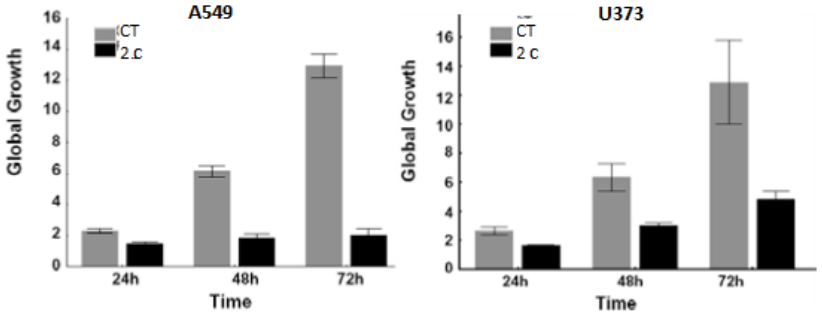


Figure 23. Quantitative videomicroscopy. CT = control test.

One can see that the proliferation of cells decrease in the presence of compound **2c** (as compared to the control test) and the cells tend to be bigger. This

approach can also determine the ratio of cell death and so establish with accuracy the cytostatic versus cytotoxic nature of the effect of compound of interest (Figure 24).



A549			U373		
time	% cell death		time	% cell death	
	CT	2c		CT	2c
24h	0 ± 0	0 ± 0	24h	0.3 ± 0.3	1.1 ± 0.6
48h	0 ± 0	2 ± 1	48h	0.4 ± 0.2	2.4 ± 0.4
72h	0.1 ± 0.1	2 ± 1	72h	0.3 ± 0.2	2.2 ± 0.2

Figure 24. Global growths and percentage of cells death for the A549 and U373 cell lineages. CT = test control.

One can notice that compound **2c** does not induce cell death at 7 µM. This means that our compound has cytostatic effect and not cytotoxic.

Compound **2c** was also analyzed by the *National Cancer Institute* (NCI) on a panel of 60 cancer cell lines at 10 µM. We then compared the **2c** *in vitro* growth inhibitory response profiles to the full NCI database compound profiles using the COMPARE algorithm developed by the NCI in order to try to obtain "Compare Correlation Coefficients" (the CCC index) with respect to the more than 763,000 compounds already present in the NCI database.[185] The best CCC index we obtained did not reach a threshold > 0.7, meaning that the mechanisms of action of **2c** as a potential anticancer agent should be distinct from those mechanisms of action, at least in terms of *in vitro* cancer cell growth inhibition, of the > 763,000 compounds already present in the NCI database.

The transcriptomic characterization of highly versus less sensitive melanoma models were compared to compound **2c,** and this approach enabled us to highlight the mitochondria as a potential target candidate for **2c**. Indeed, the gene set

enrichment analysis revealed 43 genes coding for proteins related to mitochondrial location (27/43 proteins, 10/27 mitochondrial membrane-related proteins) and/or energetic and redox balance (31/43 proteins), two biological processes in which mitochondria play key roles. Such mitochondria targeting is of clinical interest.

The mean IC_{50} concentration on cancer cells lines of **2c** (6 µM) was further compared to its IC_{50} concentrations determined on immortal and primary non-cancerous cell lines. While immortal cells were as sensitive to **2c** as cancer cells (data not shown), NHDF and NHLF normal fibroblasts revealed to be 6 and 4 times less sensitive to **2c** respectively (NHDF: IC_{50} = 36 µM; NHLF: IC_{50} = 22 µM). This result indicates that **2c** could display some bioselectivity towards highly proliferative and metabolically active cells.

Moreover, we discovered that these compounds could induce perturbations of mitochondrial energetic metabolism, leading to increased O_2 consumption and reactive oxygen species production (collaboration with Pr. D. Serteyn, ULg). Since this metabolism is known to be reprogrammed in cancer cells, these compounds could represent a new way to combat apoptosis-resistant cancer types.

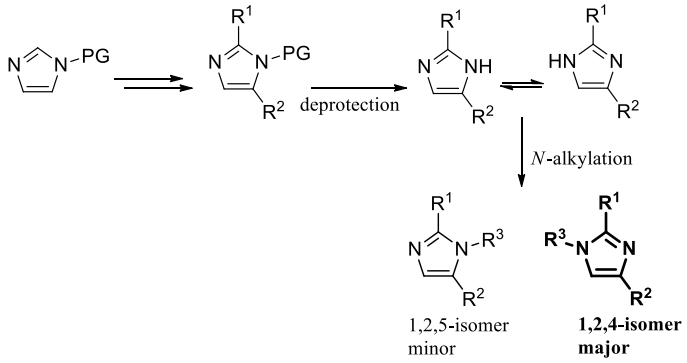
In conclusion, we have synthesized a panel of *ca*. 60 5-aryl-1*H*-imidazoles, among which several compounds displayed single digit µM 50% growth inhibitory concentration against various cancer models, including apoptosis-resistant. Interestingly, the mechanism by which these compounds (at least **2c**) exert their anti-cancer cytostatic activities does not correlate with any compound from the NCI database. In contrast, we discovered that these compounds could induce perturbations of mitochondrial energetic metabolism.

Chapter 5 - Development of a general and regioselective *N*-alkylation strategy of azoles

1. INTRODUCTION

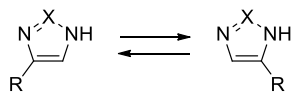
Azoles such as (benz)imidazoles, (benzo)triazoles and purines are the central structures of numerous medicinally important compounds.[186] They are also versatile precursors in the preparation of synthetically useful compounds such as catalysts, ligands or ionic solvents (see Chapter 1: Introduction). As a result, a number of strategies have been explored for the synthesis of these nitrogen heterocyclic motifs. One common challenge in the synthesis of azoles is the control of the regioselectivity.

As discussed in the Introduction of this manuscript, one of the most common strategies for substituting imidazole involves the use of a *N*-protecting and *ortho*-directing group which allows placing regioselectively substituents in position 2 and 5, R^1 and R^2, respectively (Scheme 113).



Scheme 113. Classical *N*-alkylation.

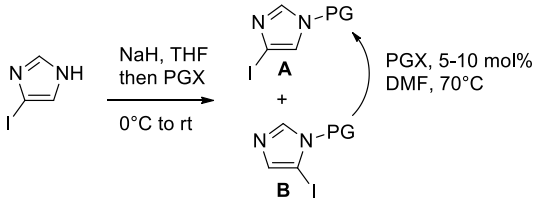
However, when this protecting group needs to be changed to another substituent, by a deprotection-alkylation process, a mixture of isomers is obtained. Indeed, a consequence of the amphoteric character of imidazole is the isomerization of 4-substituted isomer to the corresponding 5-substituted (NH)-imidazole and *vice versa*, because the hydrogen atom can be located on N1 and N3 nitrogen atoms (Scheme 114). This process is called the annular tautomerism.[187] As a result, alkylation of (NH)-imidazoles leads to mixtures of 1,2,4- and 1,2,5-isomers in which the former, which is less sterically hindered, is the major product.



Scheme 114. Annular tautomerism. X = N or CH.

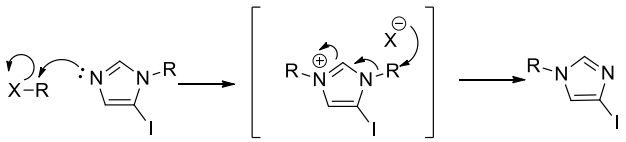
Similar tautomeric equilibria have also been reported for *N*-protected imidazole (i.e. with PG instead of H) in the presence of a catalytic amount of protecting group. Indeed, a mixture of 1,4- and 1,5-isomers resulting from electrophilic substitution of N1 can converged to the 1,4-isomer upon heating and treatment with an additional electrophilic species used to protect the N1 atom (Table 30)[188].

Table 30. Protection and isomerization of 4(5)-iodoimidazoles. [a] Yields and ratios are based on the crude products from alkylation step.[b] Yields and ratios are after the isomerization step.



PG-X	Yield, % (A/B)[a]	Yield, % (A/B)[b]
BnBr	93 (1:0.3)	93 (1:0)
SEMCl	96 (1:0.3)	95 (1:0)
MOMCl	86 (1:0.5)	80 (1:0)
MeI	93 (1:0.7)	86 (1:0.3)

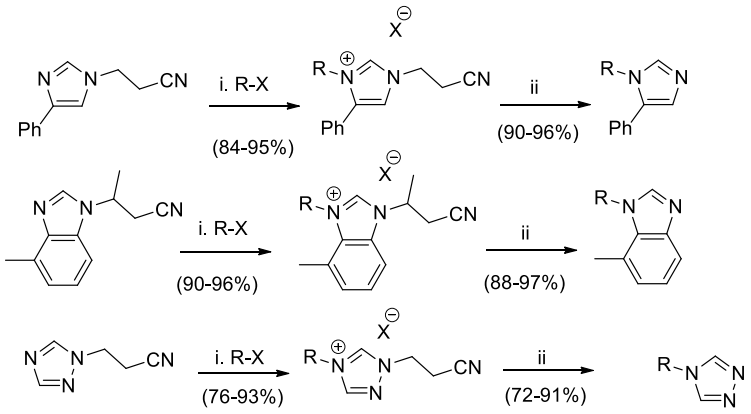
One can see that if the size of the protecting group decreases more of the 5-isomer is formed. This can be interpreted by the steric hindrance between the iodo moeity and the protecting group PG. A mechanism has been proposed for this isomerization: the N3 nitrogen attacks the alkyl halide to generate an imidazolium salt which then undergoes a nucleophilic displacement at the N1-substituent to provide the 4-isomer (Scheme 115). Overall, this strategy thus allows obtaining the 1,4-isomer in excellent regioselectivity.



Scheme 115. Proposed mechanism for the isomerization step.

There are also some occasional examples of regioselective *N*-alkylation of imidazole leading to 1,5-isomer. Horvath[189] has reported a route to sterically more crowded azoles from the parent (NH)-azoles via Michael addition. It utilizes a three-step process in which the parent azoles are first converted into their Michael adducts, then quaternized and finally deprotected with an Hoffman-type elimination

(Scheme 116). Since quaternization of azoles takes place exclusively on the unsubstituted nitrogen, the overall regioselectivity of this process depends on the regioselectivity of the first species; the *N*-protected azoles. (NH)-azoles were protected with an α,β-unsaturated nitrile. From isolated disubstituted (less hindered) azoles, alkyl halides were added to form the quaternary azolium salts and then these salts were deprotected by Hoffman elimination (by strong bases).

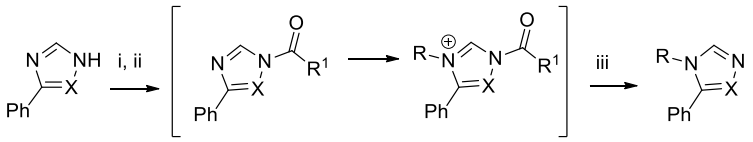


Scheme 116. Regioselective alkylation of azoles. Reaction conditions: i: CH_3CN or CH_3CN/NaI Δ, R-X = $Br(CH_2)_3CN$, $C_6H_5CH_2Br$, $CH_2=CHCH_2Br$, $BrCH_2CONHC_6H_4CO_2CH_3$; ii: NaOHaq. or MeONa/MeOH, rt.

Good yields were obtained with 4-phenylimidazole but this protocol leaded to a mixture of isomers for 4-methylimidazole. Moreover, with the weakly nucleophilic Michael adduct of 4-nitroimidazole, it did not work due to the equilibrium quaternization-alkylation shifted towards the starting material.

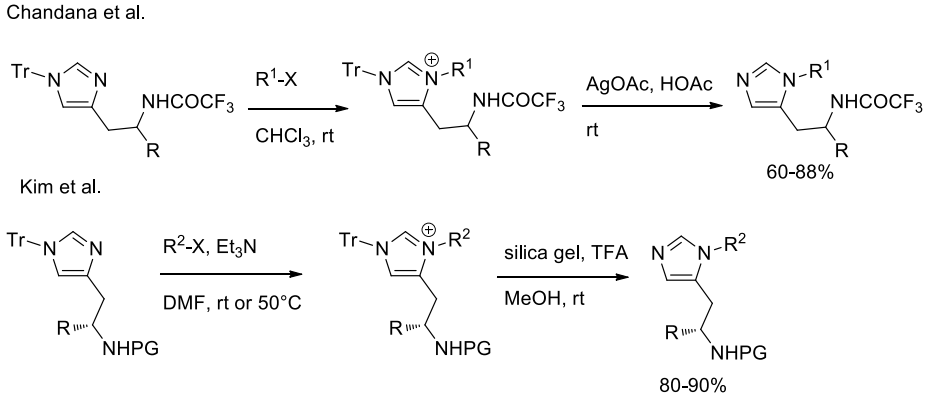
A similar strategy has also been reported using *N*-acyl heterocycles. Kashimi et al.[190] have used acetic anhydride followed by *N*-alkylation with alkyl halides to prepare sterically more hindered 1,5-disubstituted imidazoles (Table 31). Unfortunately they obtained good regioselectivities only when butyl bromide was used as alkylating agent. Moreover the reaction must be done in a sealed vessel. Olofson et al.[191] have also shown that using *N*-acyl imidazole can lead to selective *N*-alkylation of imidazole in good yields and softer reaction conditions (temperature, pressure) than Kashima et al. (Table 31). They also applied their methodology to 1,2,4-triazole and formed exclusively the 4-methyl-1,2,4-triazole in 77% yield. Indeed, in classical *N*-alkylation this is the 1-methyl-1,2,4-triazole that is the major product (non symmetric one).

Table 31. Regioselective alkylation of imidazoles using acetyl protecting group. R^1 = acetyl, benzoyl; R = Et, Me, Bu; X = CH or N. Regio.: 1,5-imidazole and 3,4-triazole exclusively.



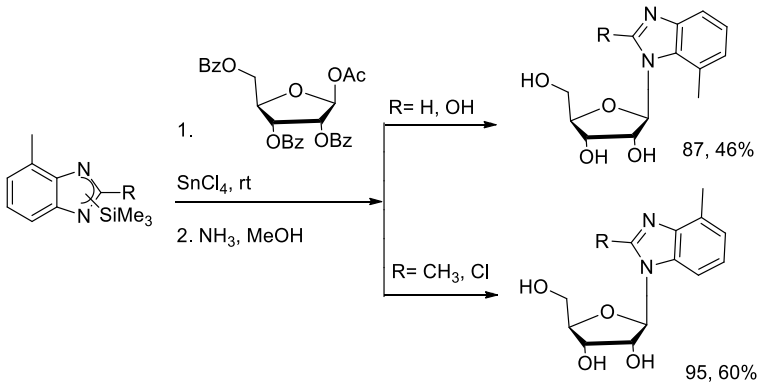
Conditions	Kashima et al.	Olofson et al.
i	Ac_2O, benzene, 80°C	PhCOCl (imidazole) or AcOCl (triazole), NaH, acetone/H_2O, rt, 95%
ii	BuBr, benzene, 140°C, seal tube	Et_3OBF_4 (imidazole) or Me_3OBF_4 (triazole), CH_2Cl_2, rt
iii	H_2O, 52% over three steps	H_2O, Na_2CO_3, 86 and 77% over two steps

Another protecting groups used in the synthesis of imidazole derivatives is the trityl group (Scheme 117). Chandana et al.[192] have synthesized 3-alkylhistidine and 3-alkylhistamine using the trityl protecting group. The imidazolium salts were not isolated and directly deprotected in good yield to form the more sterically hindered 1,5-disubstituted imidazoles. Moreover, Kim et al.[193] have shown selective deprotection of trityl group of histidine and histamine intermediate salt with Boc or Trityl group at the primary amine. They have introduced alkyl and aryl N1-substituents.



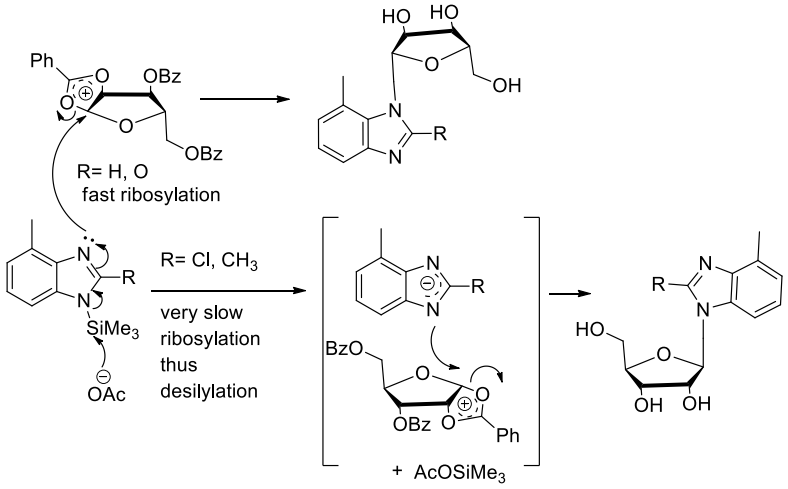
Scheme 117. Regioselective alkylation of bioimidazoles. R = H, CO_2Me; R^1 = Bn, Me, Et, R^2 = allyl, substituted aryl, Bn, PG = Boc or Tr.

With the benzimidazole nucleosides, under appropriate reaction conditions, both N1 and N3-isomers could be obtained by glycosidation of silylated 4-methyl-1*H*-benzimidazole and protected ribofurane (only N1 substitution with (NH)-derivatives). The regioselectivity was however shown to depend on the nature of C2 substituents (Scheme 118).



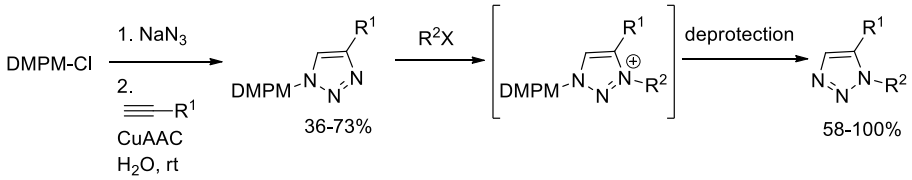
Scheme 118. Regioselective synthesis of benzimidazole nucleotides.

Ji et al.[194] have proposed a mechanism for theses transformations (Scheme 119). Silylation takes place preferably on position N1 due to the blockage of position N3 by the 4-silyl group. When R does not result in steric hindrance at the C2 position, the ribosylation at the N3 position is faster than cleavage of the N1-TMS bond whereas when R is bulkier, ribosylation at the N3 position significaly slowed down and occurred at the N1 position after cleavage of the N-TMS bond.



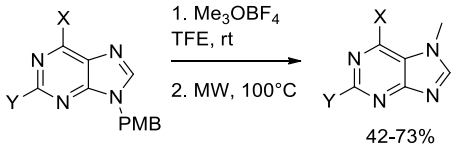
Scheme 119. Proposed mechanism for regioselective ribosylation.

A methodology was developed by Kogushi et al.[195] to obtain 1,5-disubstituted 1,2,3-triazoles via 1-protected-3,4-disubstituted 1,2,3-triazolium salt. The triazole was formed by copper-catalyzed regioselective Huisgen cycloaddition of an alkyne and an azide. The alkylation and deprotection allow obtaining 1,5-disubstituted 1,2,3-triazoles in 58% to quantitative yield (Scheme 120).



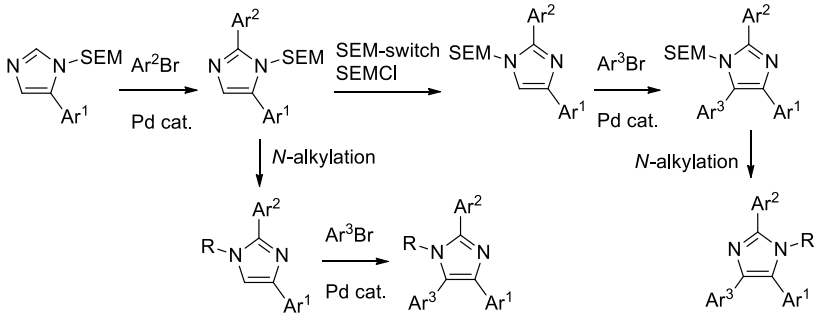
Scheme 120. Synthesis of 1,5-disubstituted 1,2,3-triazoles. R^1 = Ph, *n*-Bu, c-Pr, R^2X = MeI, BnBr, EtI, *n*-BuI, $OH(CH_2)Br$, deprotection: NH_4NO_3, DMF, 120°C or CAN, DMF.

Concerning the purine, different protecting group have been utilized for the regioselective *N*-alkylation of the N7 nitrogen. A mild and general method was developed by Lebraud et al.[196] using PMB as protecting group. The alkylation step was carried out with Meerwein reagent and trifluoroethanol as solvent. This solvent slightly acidic may assist the PMB deprotection under microwave irradiation. This method offers moderate to good yields even with sterically hindered groups **X** and **Y** in 2 and 6 positions (Scheme 121). Few examples with trimethyloxonium tetrafluoroborate to enable N7-ethylation have also been reported.



Scheme 121. Selective N7 methylation of *N*-methoxybenzyl purines. X = CN, Cl, OEt, TIPS, cyclohexymethanol; Y = NH_2, I, CN, F, amino chain.

There are also examples of regioselective *N*-alkylation of imidazole with palladium catalysis. Joo et al.[197] described a regioselective and sequential arylation of the three C-H bonds using SEM group transposition. They elaborated a sequential method from SEM-imidazole to furnish 1-alkyl-2,4-triarylimidazoles and 1-alkyl-2,4,5-triarylimidazoles. With the SEM-switch, they transposed unreactive C4 position to reactive C5 position (Scheme 122).

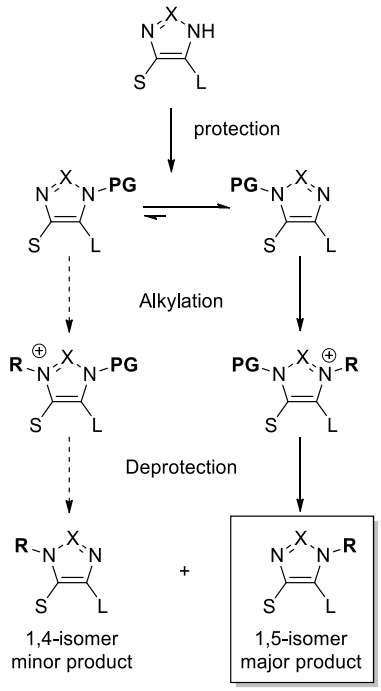


Scheme 122. Regioselective Pd-catalyzed alkylation.

In summary, few punctual examples for obtaining the more hindered isomer of azoles through of regioselective *N*-alkylation reaction were reported. Efforts have however still to be done to develop a convenient and general strategy that can be applied on different azoles.

2. DEVELOPMENT OF THE METHODOLOGY

We reasoned that a similar strategy to the one developed previously in our lab could be used to develop a general method for the *N*-alkylation of (NH)-azoles providing selectively the more hindered isomer. Indeed, in the synthesis of intermediate **4**, our lab has shown that a rapid equilibrium between the two isomeric forms of **14** could be observed and that it resulted that alkylation and then deprotection let to the exclusive formation of the 1,2,5-isomer (see Chapter 1, 2.2. Synthesis of original macrocycles). This indicates thus (1) that replacing N-H by N-PG should allow displacing the tautomeric equilibrium (see Scheme 114) toward the sterically less hindered isomer (2) and that an alkylation/deprotection process (instead of classical deprotection/alkylation) should then lead selectively to the more hindered *N*-alkylated derivatives (Scheme 123). Protection of the less hindered nitrogen prevents indeed alkylation in this position and therefore directs it on the other nitrogen, the most hindered one.



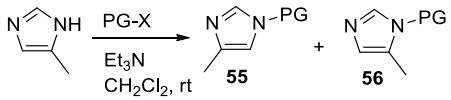
Scheme 123. Designed strategy for regioselective *N*-alkylation of azoles. S = small group; L = large group.

First, we have investigated each step of our strategy separately on a model compound, 4-methyl-1*H*-imidazole, in order to find the most appropriate protecting group and the best reaction conditions for the alkylation and deprotection steps. We then have developed a one pot procedure of our methodology before applying it to a series of azoles.

2.1. Step 1: protection

The ideal protecting group must allow high conversion and provide *N*-protected imidazole with a high regioselectivity. We thus investigated the reaction of our model compound, 4-methyl-1*H*-imidazole, with a series of protecting group, observing the evolution of the regioselectivity over time. Obtained results are summarized in Table 32.

Table 32. Investigation of the protection reaction. [a] Reaction conditions: 1.1 equiv. PGX, 1.2 equiv. Et_3N.



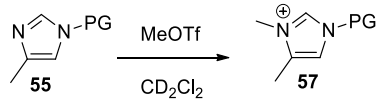
PG-X	Conversion (%) (55/56)	
	After 1h	After 15h
Me_2NSO_2Cl	70 (71/29)	98 (85/15)
SEMCl	81 (65/35)	91 (63/37)
BnBr	40 (67/33)	45 (68/32)
$PhSO_2Cl$	97 (93/7)	100 (>98/2)
TMSCl	< 5 (n.d.)	< 5 (n.d.)
$(Boc_2)O$	88 (77/23)	100 (75/25)
$O(COCF_3)_2$	< 5 (n.d.)	< 5 (n.d.)
TBSCl	53 (55/45)	83 (40/60)

Differents protecting groups were used: groups with an amide, a sulfone, silylated compounds,… The attribution of isomers was proven by HMBC (^1H-^{13}C) experiments for a few protecting groups and the experiments worked with the SEM group. For the TMS group, we tried other counterion such as triflate or bromide but no change was observed. One can see that the best results in term of conversion and ratio of the two isomers are obtained with the dimethylsulfamoyl and phenylsulfonyl groups (for the dimethylsulfamoyl group, isomer **7** was obtained exclusively after a few days in pure phase). It is interesting to note that it is the two cases where an increase in regioselectivity was observed over time, suggesting the presence of an equilibrium between the two regioisomers under the reaction conditions. So we decided to continue our studies with these two protecting groups.

2.2. Step 2: methylation

This step was carried out directly in a deuterated solvent (CD_2Cl_2) to analyze the evolution of the reaction at different times (1h, 6h, 22h) by ^1H NMR. The results are reported in Table 33.

Table 33. Conversion and regioselectivity for the methylation step.



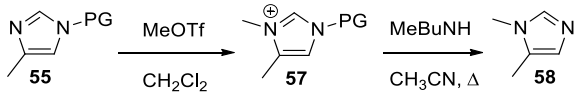
PG	conv. (%)	Regio.
Me_2NSO_2	> 95%	83/17
SO_2Ph	> 95%	> 98/2

Observed conversion in salt **57** was high for the two considered protecting groups. No change in regioisomeric ratio was observed; salts **57** being obtained in a similar regioisomeric distribution to starting **55**. In the case of the DMAS protecting group, two imidazole species were present. For the phenylsulfonyl group, after one hour there was no more reactant.

2.3. Step 3: methylation-deprotection

The sequence alkylation-deprotection was then investigated. Protected 4-methylimidazoles **55** were reacted with methyltriflate at room temperature for one day and then *in situ* deprotected by addition of a nucleophile, MeBuNH (Table 34)

Table 34. Alkylation-deprotection steps.

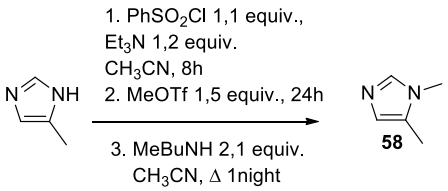


PG	conv.(%)	Regio.
Me_2NSO_2	40%	n.d.
SO_2Ph	> 95%	> 98/2

When the two step procedure was carried out for the reaction with DMAS protecting group, reactant was also obtained (conversion 40%). However, for the phenylsulfonyl protecting group, the alkylation-deprotection process allowed obtaining **58** in excellent yield and regioselectivity. This last protecting group was thus considered for further developments of our methodology.

2.4. One-pot methodology

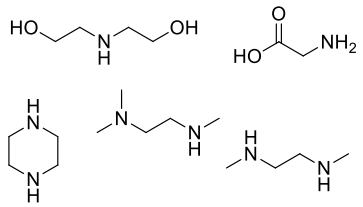
In order to develop a one-pot procedure of our methodology, we first have to find a convenient solvent for the three steps. The solvent must solubilize all the reactants and must have a boiling point allowing the heating needed for the deprotection step. We decided to try CH_3CN, DCE and THF. For THF, the mixture turned solid when it was heated with the amine. For DCE we did not observed **58** and obtain another unknown species (unexpected displacement in ^1H NMR). In CH_3CN, all the reactants were solubilized and imidazole **58** was formed. So CH_3CN was the solvent of choice for our one-pot methodology (Scheme 124).



Scheme 124. One pot regioselective methylation.

We thus performed the reaction in a one-pot manner by adding successively Et_3N and $PhSO_2Cl$ into a solution of 4-methyl-1*H*-imidazole in CH_3CN. After 8 hours at room temperature, MeOTf was added and the mixture was stirred for 24 hours. Finally, deprotection with the amine was performed at 80°C overnight. After a basic work up, the ^1H NMR of the mixture was pretty clear: two compounds were present; the desired product 1,5-dimethyl-1*H*-imidazole and *N*-butyl-*N*-methylbenzenesulfonamide. We had however some difficulties to isolate 1,5-dimethyl-1*H*-imidazole by column chromatography. When silica gel was used, with or without Et_3N, the compound remained attached on the column and no conditions were found to do the purification on basic alumina or reverse phase. So we tried to find another nucleophile which would produce a side product which could be separate from the obtained imidazole by simple aquous washing. First, we tried with an old bottle of sodium ethoxide and surprisingly no secondary product was obtained and the desired imidazole was obtained in excellent purity after work up (experiment reproducible). However, when we tried to reproduce this reaction with a new bottle of sodium ethoxide it did not work. Addition of water or ethanol (to reproduce the hydrolyzed old bottle), did not give the desired result. We also tried to do directly a basic workup without adding a nucleophile but it did not work: few species were obtained. Finally, we tried different amines (Scheme 125) as nucleophiles to change the solubility of the secondary product and favour its passing into the aqueous phase. But even by changing the pH of the aqueous phase or the

nature of the organic solvent for the workup we did not succeed in obtaining the pure imidazole.



Scheme 125. Amines tested for the deprotection reaction.

In conclusion, 1,5-dimethyl-1*H*-imidazole was obtained in 80% conversion with the one-pot methodology and the regiochemistry was confirmed by ^{1}H-^{15}N HMBC (see Appendix). This NMR experiment is convenient to determine the regiochemistry of small molecules. Next, we would like to apply our methodology to others azoles and also to use other alkylating agents.

3. SCOPE OF THE METHODOLOGY

3.1. Alkylation

Different alkylating agents were tested in the one-pot methodology (Table 35).

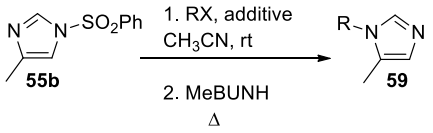
Table 35. Alkylating agents used in the regioselective one-pot reaction.

Alkylating agents	Results
$MsO(CH_2)_4CH=CH_2$	no *N*-alkyl incorporation
$BrCH_2CH=CH_2$	″
$TfOCH_2CH=CH_2$	″
BrBn	″
$BrCH_2CO_2Me$	″
	″

For every alkylating agent, no desired product was obtained. We have changed the leaving group of the alkylating agent but it had no effect on the reaction. We also tried a benzyl group, an α-bromoester and an epoxyde but it did not work either: no *N*-alkyl incorporation was observed. For the allyl group, we tested the reaction without an amine but we have obtained the reactant.

For some of them, we have decomposed the one-pot reaction into two parts: the protection and the alkylation-deprotection. The protection step was performed without any problem (see 2.1. Step1: Protection). Then, we studied the alkylation-deprotection (Table 36).

Table 36. Alkylation-deprotection with different RX.



RX	additive	Results
$BrCH_2CO_2Me$	Bu_4NI	no *N*-alkyl product
$BrCH_2CO_2Me$	$AgNO_3$	″
	TMSBr	″
Et_2OCCO_2Et	Δ	″

We added some additives to see if there will be a difference in reactivity. But with the α-bromoester and the epoxyde it did not work. We also have tried an oxalic ester. Indeed in the literature one can see that oxalic esters have been utilized as reagents in N-, O- and S-alkylation reactions.[198] But again it did not work.

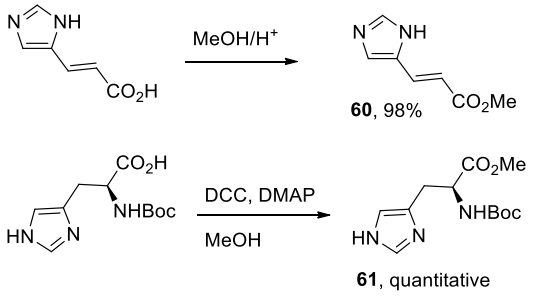
Finally, we tried the alkylation reaction in d_2-dichloromethane for the α-bromoester and the allyl triflate and we have noticed that the salt was formed in very low quantities. Accordingly, we reasoned that the phenylsulfonyl imidazole derivatives (**55b**) must not be reactive enough toward *N*-alkylation. This could be explained by the electron-withdrawing character of the protecting group which deactivates the imidazole toward N-alkylation. One solution to this problem could thus be the use of a neutral or electron-donating group as protecting group. This will be envisaged in section 3.5.

3.2. Methylation of (benz)imidazoles

Concerning the imidazole ring, we planned to apply our regioselective *N*-methylation methodology to a variety of 5- and 2,5-substituted (NH)-imidazoles. So the first thing to do was the synthesis of non-commercially available NH-imidazoles.

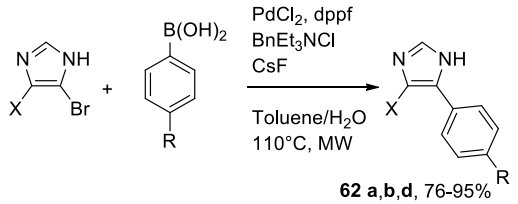
3.2.1 Synthesis of starting materials

For the 5-substituted (NH)-imidazoles we have synthesized the protected uraconic acid and a protected histidine (Scheme 126). For the uraconic acid, we have protected the acid into an ester following procedure of Pirrung et al.[199] and the acid of Boc-histidine was also protected using the reaction conditions developed by Lopez-Larrubia et al.[200] (DMAP was used in catalytic amount because it was hard to eliminate it).



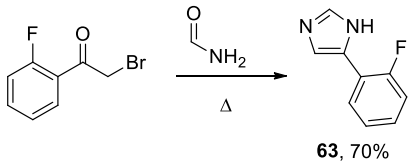
Scheme 126. Synthesis of protected uraconic acid (**60**) and histidine (**61**).

Then we have formed different (4),5-arylimidazoles by Suzuki cross-coupling.[201] Good yields were obtained for monosubstituted imidazole **62a** (X = H, R = OMe) and **62b** (X = H, R = CO_2Et) and also the disubstituted imidazole **62d** (X = Me, R = Ph). But for the monosubstituted imidazole **62c** (X = H, R = NHCOMe) it did not produce the desired product even with longer reaction time (Scheme 127).



Scheme 127. Suzuki coupling. X = H or Me, R = H, OMe, CO_2Et, NHCOMe.

We also tried these conditions to form 5-*o*-fluorophenyl-1*H*-imidazole but we never succeeded in obtaining it (even with longer reaction time). So we have changed the strategy and decided to form the imidazole ring by reaction of an α-bromoketone and formamide (Scheme 128). The desired imidazole could be obtained in 70% yield.[202]

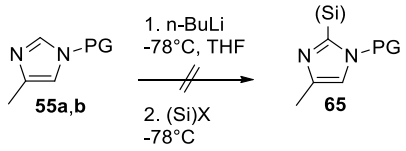


Scheme 128. Synthesis of 5-(2-fluorophenyl)-1*H*-imidazole.

Next, we planned to synthesize imidazole derivatives disubstituted in position C2 and C5. For that point we needed to block position N1 of a 4-substituted imidazole, do the C2 substitution and then deprotect N1 position. Accordingly, we have taken an intermediate of the synthesis of the key intermediate **4**, namely compound **13** and performed the *N*-deprotection. The deprotection of the DMAS group was carried out under acidic conditions to obtained compound **64** in 87% yield (Scheme 129).

Scheme 129. Deprotection of the DMAS group.

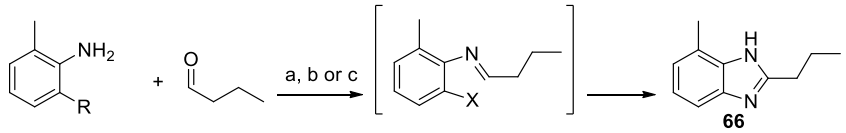
Then, we have used 4-methyl-1-(phenylsulfonyl)-1*H*-imidazole (already synthesized) to form another 2,5-disubtituted NH-imidazole. This imidazole was deprotonated with *n*-BuLi and then TBDMSCl was added (Scheme 130).[203] Unfortunately, the starting material was recovered with only traces of the desired product (even if we change reaction time and temperature). We tried also to introduce a TMS group or use the *N*,*N*,4-trimethyl-1*H*-imidazole-1-sulfonamide as reactant but it did not give better results.



Scheme 130. C2 silylation of imidazole. PG = SO_2Ph, DMAS; (Si)X = TBDMSCl, TMSBr.

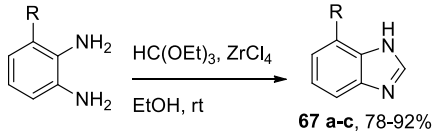
In order to see the aptitude of the *n*-BuLi to deprotonate the imidazole we have quenched the reaction with deuterium oxide and we have noticed that about one half of the imidazole was deuterated.

Now for benzimidazole synthesis we have used a reductive cyclization of o-nitroaniline in the presence of an aldehyde (Scheme 131).[204] This method was not reproductible (one time 42% of yield) but when the solvent was changed to methanol we obtained the desired product in 45% yield. This methodology was however not reproductible either; after few assays the reactant was recovered. We tried another method using solvent-free conditions with PEG-mediated synthesis of 2-substituted benzimidazole. PEG helps maintening a neutral reaction medium during the condensation of the diaminobenzene with the aldehyde.[205] But with these conditions the imine intermediate was formed and we never succeeded in obtaining the imidazole ring. Next, we tried the cyclization with an oxidizing agent, the iodobenzene diacetate.[206] And here, no condensation was observed.



Scheme 131. Formation of benzimidazoles. Conditions : a : R = NO_2, $Na_2S_2O_4$, MeOH or EtOH, 80°C ; b : R = NH_2, PEG-400, 110°C; c: R = NH_2, $PhI(OAc)_2$, dioxane.

Finally, we succeeded in forming the benzimidazole ring in the presence of a Lewis acid catalyst and an ortho-ester instead of an aldehyde.[207] Three different benzimidazoles were synthesized by this method (Scheme 132).

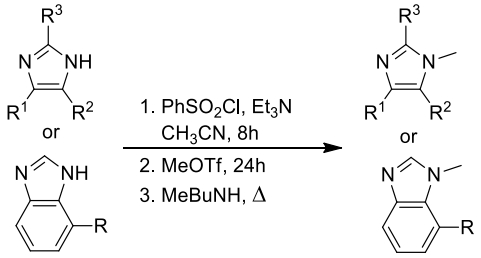


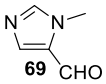
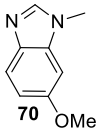
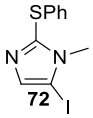
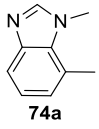
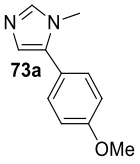
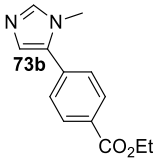
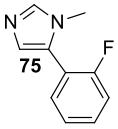
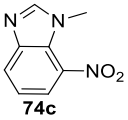
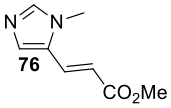
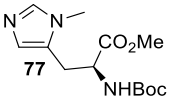
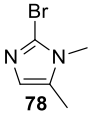
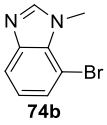
Scheme 132. Synthesis of benzimidazoles catalysed by Lewis acid. R = Me (**67a**), Br (**67b**), NO_2 (**67c**).

3.2.2. Regioselective N-methylation

After the synthesis of (NH)-(benz)imidazoles, we have engaged them, as well as commercially available ones, in the one-pot regioselective *N*-methylation (Table 37). We always obtained good regioselectivities and the identification of the more hindered imidazole was done by ^{1}H-^{15}N HMBC (see Appendix). Unfortunately, not all the product could be purified by column chromatography (even with Et_3N) or gave poor isolated yields. For three of them, compounds **58**, **68**, **69** (which could not been purified column chromatography), a purification on a C18 solid phase extraction was done (eluent: H_2O + 1% TFA/CH_3CN 90:10).

Table 37. Yields and regioselectivities for the regioselective *N*-methylation. It was assumed that only the desired product and the secondary product were present in the ^{1}H NMR. [a] yield for isolated compound; [b] no detectable signal for the other isomer was found in ^{1}H NMR; [c] Δ during methylation, conversion done with internal standard.



 **58**	 **68** I	 **69** CHO	 **70** OMe
80(31[a])% yield > 98/2[b] regio.	66(55)% yield > 98/2 regio.	90(37)% yield > 98/2 regio.	70(67)% yield 55/45 regio.
 **71** Ph	 SPh **72** I	 **73d** Ph	 **74a**
96(70)% yield >98/2 regio.	49(53)% yield > 98/2 regio.	47(47)%[c] yield > 84/16 regio.	100(90)% yield > 98/2 regio.
 **73a** OMe	 **73b** CO_2Et	 **75** F	 **74c** NO_2
100(70)% yield > 98/2 regio.	82(40)% yield > 98/2 regio.	80(32)% yield > 98/2 regio.	55(52)% yield > 98/2 regio.
 **76** CO_2Me	 **77** CO_2Me NHBoc	 Br **78**	 Br **74b**
50(50)% yield 90/10 regio.	45(42)% yield > 98/2 regio.	70(38)% yield > 98/2 regio.	40(24)% yield > 98/2 regio.

For 4,5-disubtituted imidazole **73d** the conversion is not total. So we heated during the methylation to have more conversion but with these conditions the other

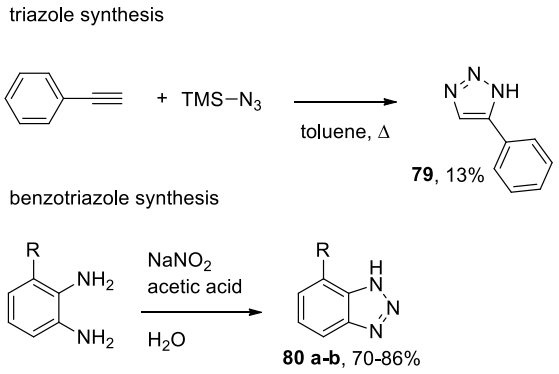
isomer appeared (regio. 84/16). The regioselective methylation was also done with a 5-substituted benzimidazole (**70**). We would like to known if one could have a difference in the isomers ratio even with this benzimidazole. And one noticed that no difference of regioisomers was induced (regio.:45/55). We have also tried this strategy with 2-substituted 7-methyl-2-propyl-1*H*-benzo[d]imidazole (**66**) (formation of the starting material not reproductible, see section 3.2.1.) and the conversion was not complete (67% of conversion) even with longer time reaction.

We have showed that this methodology gives good results with the regioselective *N*-methylation of (benz)imidazoles. Now, we will try to apply this strategy to other (NH)-azoles.

3.3. Methylation of (benzo)triazoles

3.3.1. Synthesis of (NH)-(benzo)triazoles

One (NH)-1,2,3-triazole and two (NH)-1,2,3-benzotriazoles were synthesized (Scheme 133). The triazole was prepared by cycloaddition between phenylacetylene and trimethylsilyl azide to form the desired triazole derivatives after aqueous hydrolysis of the trimethylsilyl group.[208] Benzotriazoles were synthesized from the corresponding diaminobenzene by addition of sodium nitrite and acetic acid.[209]

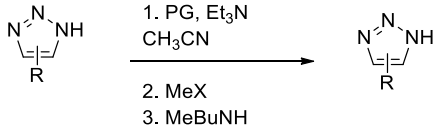


Scheme 133. Synthesis of (benzo)triazoles. R = Me (**80a**), NO_2 (**80b**).

3.3.2. N-Methylation

The regioselective *N*-methylation was applied to the synthesized (NH)-triazole and (NH)-benzotriazoles. Unfortunately, very low yields were obtained (Table 38).

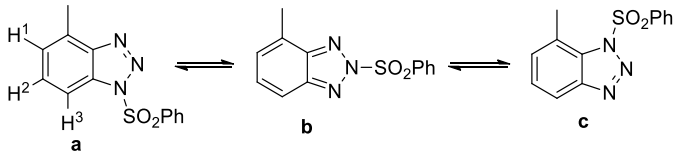
Table 38. Regioselective *N*-methylation of (benzo)triazoles. [a] classical: 1. 1.1 equiv. $PhSO_2Cl$, 1.2 equiv. Et_3N, 8h, rt; 2. 1.5 equiv. MeX, 24h, rt; 3. 2.1 equiv. MeBuNH, 1 nigth, 80°C. [b] step 1 then steps 2-3.



Reactant	Conditions		Yield
	mode	MeX	(%)
79	classical [a] one pot	MeOTf	7
79	one pot: methylation 2 days rt	MeOTf	13
79	2 steps [b]:	MeOTf	25
80a	one pot 60°C during 2-3	MeOTf	18
80a	2 steps	MeI	/
80a	2 steps	Me_3OBF_4	38
80a	one pot	Me_3OBF_4 1-1.5 equiv.	/
80a	one pot	Me_2SO_4	/
80a	one pot: DMASCl as PG	MeOTf	37, (77:23)
80a	classical one pot	MeOTf	11

In order to identify the origin of the low yield and try to improve the method, we investigated the two steps procedure, namely, protection and then alkylation-deprotection. There was no problem with the protection step, a quantitative yield was obtained for the triazole **79** and 86% yield for the benzotriazole **80a**. After the alkylation-deprotection was performed with MeOTf and a slightly better yield was obtained (25%), as compared to the one-pot procedure, even if we heated during the methylation step. We then tried other (more reactive) alkylation reagents. Using Meerwein salt, a similar yield was obtained (38 %) in the two steps procedure but when it was engaged in the one-pot reaction no product was found. The Meerwein salt seems to be too reactive for employing it in the one-pot strategy. With MeI or Me_2SO_4, the desired product was not obtained. We also have changed the protection group for the DMAS group and this time we obtained the two isomers in a 77:23 ratio (37% yield). This reaction proved that we have made a good choice for the protecting group. Concerning the deprotection, we have noticed that it proceeds with similar yield without heating. And finally, we tried the simple benzotriazole to see if we had the same results and again only 11% of yield was obtained.

So we wondered if there is an equilibrium between the different isomers of N-protected (benzo)triazole (Scheme 134). This equilibrium can influence the methylation and be the origin of observed low yields. Indeed, Katritzky et al.[210] has showed the spontaneous interconversion of benzotriazole. This equilibrium is influenced by substituents (electronic and steric effects) present in the benzene part (on position 4-7), the *N*-alkylating agent and also by the polarity of the solvent. One can expect that isomer **b** coul be not reactive toward *N*-alkylation.

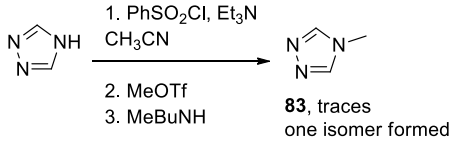


Scheme 134. Equilibrium between the different forms of *N*-protected benzotriazole.

In our case, isomer **c** is strongly disfavored due to destabilizing steric interactions between the protecting group and the methyl group at the C7 position (Scheme 134). By different NMR analyses (2D ^{1}H-^{13}C NMR were made to identify proton H1-3 and then ^{1}H-^{15}N HMBC gave a ^{4}J between H2 and substituted nitrogen), we have observed that isomer **a** was the major isomer in a ratio 83 to 17 (**a**/**b**). So this equilibrium cannot account for the obtained low yields.

Another explanation could be the lower nucleophilicity of the azole as compared to imidazole. Accordingly, this problem maybe could be resolve by the use of a neutral or electron-donating group as protecting group. This will be envisaged in section 3.5.

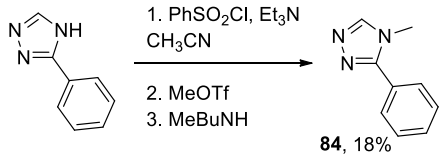
Finally, we tried to extend our regioselective *N*-methylation methodology to 1,2,4-triazoles. Application of the methodology to (NH)-1,2,4-triazole led to 4-methyl-4*H*-1,2,4-triazole but in very low quantities (Scheme 135, regio. > 98:2).



Scheme 135. Regioselective *N*-methylation of (NH)-1,2,4-triazole.

Indeed, this product is volatile and water soluble. So we solved the problem by using 3-phenyl-4*H*-1,2,4-triazole as a starting material. And again, only one *N*-methylated product was observed (**84**) but with a low yield, 18% (Scheme 136). Heating during the methylation did not allow increasing the yield. Then, the non regioselective methylation (conditions: NaH, MeI) was carried out and compound

84 was obtained as the minor product with the two others isomers (1.9:4.0:3.0). This proved that our regioselective methodolody gives selectively the minor triazole obtained with the non regioselective manner.

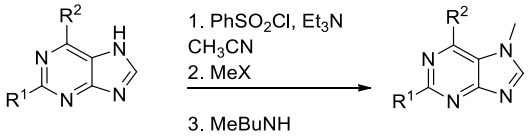


Scheme 136. Regioselective *N*-methylation of 3-phenyl-4*H*-1,2,4-triazole.

3.4. Methylation of purines

A series of commercially available purines were engaged in the regioselective *N*-methylation (Table 39).

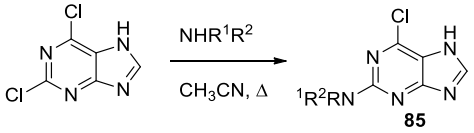
Table 39. Regioselective *N*-methylation of with (NH)-purines. [a] classical: 1. *i*. equiv. $PhSO_2Cl$, 1.2 equiv. Et_3N, 8h, rt; *ii*. 1.5 equiv. MeX, 24h, rt; *iii*. 2.1 equiv. MeBuNH, 1 night, 80°C. [b] step 1 then steps 2-3.



	Conditions		Results
R^1, R^2	**mode**	**MeX**	
Cl, H	classical [a] one pot	MeOTf	traces
Cl, H	one pot: methylation 80°C	MeOTf	traces
Cl, H	2 steps[b]	MeOTf	product + others purines
Cl, H	2 steps	Me_2SO_4	product + others purines
Cl, H	one pot	Me_3OBF_4	no *N*-methyl product
Cl, H	2 steps	Me_3OBF_4	20%
Cl, H	one pot	MeI	no *N*-methyl product
H, H	classical on pot	MeOTf	no *N*-methyl product
Cl, Cl	classical one pot	MeOTf	S_NAr product
Cl, MeBuNH	classical one pot	MeOTf	no *N*-methyl product
Cl, Ph	classical one pot	MeOTf	34%

6-chloro-7*H*-purine was first engaged in the classical one-pot *N*-methylation and only traces of the desired product were obtained. When we heated

during the methylation it did not worked better. So we tested the two steps procedure. The protection was carried out with 91% yield. For the alkylation-deprotection using MeOTf different purine derivatives (*N*-methylated and not) were obtained even if we used Me_2SO_4. As seen before, the one pot methodology with Meerwein salt did not work but in the two steps procedure we have isolated the desired product in 22% yield. Another difficulty was the isolation the purine. After many attempts, normal silica gel was used with a mixture of AcOEt/MeOH as eluent. We tried the one-pot *N*-methylation with MeI but we failed: no *N*-methyl incorporation was observed. Secondly, we tried the one-pot procedure with the 7*H*-purine and again no *N*-methyl incorporation was observed. So we decided to block position 2, this may account for the obtaining of different purines. 2,6-Dichloro-7*H*-purine was used and this time another product was isolated: the *N*-methylated purine but with a methylbutylamine substituent in position 2. Formation of this adduct can be explained by a S_NAr of the amine during the deprotection step. So we tried to synthesize a purine with an amino substituent in position 2 by S_NAr of an amine with the 2,6-dichloro-7*H*-purine in the same conditions as for the deprotection step (Scheme 137).

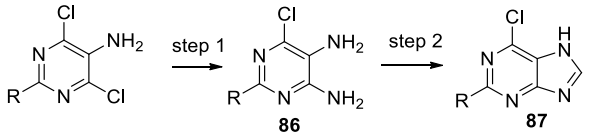


Scheme 137. S_NAr on purines. $NR^1R^2 = Me_2NH$, MeBuNH.

We never succeeded in forming the dimethylamine derivatives (**85a**). And for the methybutylamine derivatives, we thought that the product was formed. The MS was good but the interpretation of ^1H and ^{13}C NMR was difficult due to the conformational equilibrium around the N-$C_{arom.}$ bond (broad signal in ^1H and duplication in ^{13}C). Finally, this reagent was engaged in the one-pot reaction and again no *N*-methyl was incorporated.

Finally, we decided to synthesize a purine with another substituent than chlorine or an amine in position 2 to eliminate parasite S_NAr. For that purpose a two steps synthesis was developed (Table 40).

Table 40. Synthesis of 6-chloro-2-phenyl-7*H*-purine. [a] % of yield.



R	Step 1 Conditions	Results	R	Step 2 Conditions	Results
Me	NH_4OH, MW, 110°C, 30 min	78%[a]	Me	$CH(OEt)_3$, 100°C, 75 min	/
Ph	NH_4OH, MW, 110°C, 30 or 90 min	reactant	Me	$CH(OEt)_3$, 120°C, 75 min	/
Ph	NH_4OH, EtOH, MW, 90°C, 2h	reactant	Me	$CH(OEt)_3$, acetic anhydride, 140°C, 90 min	trace
Ph	NH_3 in MeOH, MW, 75°C, 5h	traces	Ph	$CH(OEt)_3$, acetic anhydride, 140°C, 90 min	70%
Ph	NH_4OH, CH_3CN, MW, 90°C, 60h	91%			

The commercially available 4,6-dichloro-2-substituted pyrimidin-5-amines must be aminated by S_NAr. This first step was performed with the methyl derivatives following a previously reported procedure[211] and 78% yield was obtained. The second step is the cyclization of the imidazole ring by addition of an orthoester to the intermediate.[212] But this step was difficult; we found that the orthoester had reacted with the diamine but no deshydratation occured even if we heated more. Then acetic anhydride was added and traces of the product were observed (by MS) but we did not succeed in increasing the yield. So we turned our attention to the phenyl derivatives. Here, it was the first step that caused problems. We tried amination with different source of amine, solvent under microwave heating and the conversion was low. But after 60 hours in the microwave, it worked, the conversion was total. The second step was performed with orthoester and acetic anhydride in 70% yield.

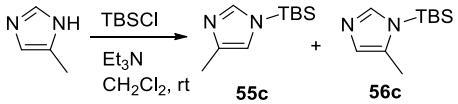
Last of all, the new purine was test in the one-pot *N*-methylation and the yield (not isolated) was 23% and the mixture was not so clean as usual (more than two species).

3.5. Assays with TBS protecting group

Given the low yields obtained with our general methodology for azoles other than (benz)imidazoles as well as with other alkylating agents, we were wondering if the SO_2Ph protection group was not too much deactivating the alkylation step (by its electron-withdrawing character). So we tested others protecting group to see if there could be a difference with azoles and with others alkylating agents. After few tests we choose the TBS protecting group.

As seen in point 3.1., the protection of 4-methyl-1*H*-imidazole gave a mixture of isomers. However, we found that the use of an excess of silylating reagent allows obtaining regioselectovely the 1,4-isomer after 1h (Table 41).

Table 41. Protection of 4-methyl-1*H*-imidazole with TBSCl.



equiv. TBS	Conversion (%) (55c/56c)	
	After 1h	After 15h
1.1	53 (55/45)	83 (60/40)
1.7	35 (96/4)	100 (53/47)

After we tried the *N*-methylation step on the mixture **55c**/**56c** (experience with 1.7 equiv. of TBSCl) and we obtained a mixture of isomers in a 48:52 ratio (after 22h of methylation).

The first thing to do was to find appropriate deprotection conditions. TBAF was used but the cation tetrabutylammonium was found after the work up and even after a flash chromatography. So we tried KF with and without water. And a better result was obtained without water. We also tried TASF as deprotecting reagent. Good results were obtained but again the cation tris(dimethylamino)sulfonium necessitates several steps of washing to be removed. Moreover the molecule was heavy and so big quantities were necessary. According to these results, KF was employed as deprotection agent and some tests have been made.

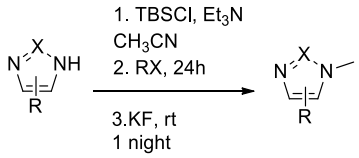
Table 42 lists assays of the one-pot reaction with TBS group. First, we have tested the method with 4-methyl-1*H*-imidazole: 48% yield was obtained and when we increased the quantities of TBS, the yield reached 62% (1 hour of protection). But when we increased this reagent the desired product was found after work up and

contaminant TBSF and also the corresponding silanol (TBS hydrolyzed during workup) that were difficult to evaporate. When the protection was performed over two days the non-desired regioisomer appeared. The same result was observed when we heated during the protection step. We also found that one hour of protection was enough. But if we increased the percentage of triethylamine it decreases the yield to 30%.

Second, we tried other alkylating agents. With an α-bromoester and an allyl bromide no desired product was obtained. With benzyl bromide, the desired product was found in MS but we did not succeed in isolating it (major specie in the mixture).

Third, we have applied our regioselective *N*-alkylation strategy to other azoles (Table 42). With 2-bromo-4-methyl-1*H*-imidazole only 14% yield was obtained. With 4-phenyl-1*H*-imidazole, no selectivity was observed with MeOTf and with BnBr, no *N*-alkyl group was incorporated. For methylbenzotriazole (**80a**), 40% of the 1,7-dimethylbenzotriazole were obtained with 1.1 equivalent of TBSCl. When we increased the quantity of this latter the yield decreased. Finally, with the 4-phenyltriazole (**79**) different secondary products were obtained and for the purine (**87**) no *N*-methylation was observed.

Table 42. One-pot *N*-alkylation with TBS group. [a] no signal was found in ^{1}H NMR except silane species. 4-Meimid.: 4-methyl-1*H*-imidazole, 4-Phimid.: 4-methyl-1*H*-imidazole, 2-br-4-Meimid.: 2-bromo-4-methyl-1*H*-imidazole



compound	Conditions		Results
	Step 1	Step 2	
4-Meimid.	1.1 equiv. TBSCl, 1.2 equiv. Et_3N, 8h, rt	1.5 equiv. MeOTf, 24h, rt	48%
4-Meimid.	1.7 equiv. TBSCl, 1.2 equiv. Et_3N, 1h, rt	1.5 equiv. MeOTf, 24h, rt	62%
4-Meimid.	1.7 equiv. TBSCl, 1.2 equiv. Et_3N, 2 days	1.5 equiv. MeOTf, 24h, rt	70% (88:12)
4-Meimid.	1.1 equiv. TBSCl, 1.2 equiv. Et_3N, 8h, 80°C	1.5 equiv. MeOTf, 24h, rt	52% (92:8)

Compound	Conditions		Results
	Step 1	Step 2	
4-Meimid.	1.1 equiv. TBSCl, 1.2 equiv. Et_3N, 1h, rt	1.5 equiv. MeOTf, 24h, rt	53%
4-Meimid.	1.7 equiv. TBSCl, 1.8 equiv. Et_3N, 1h, rt	1.5 equiv. MeOTf, 24h, rt	30%
4-Meimid.	1.1 equiv. TBSCl, 1.2 equiv. Et_3N, 8h, rt	1.5 equiv. $BrCH_2CO_2CH_3$, 24h, rt	_[a]
4-Meimid.	1.1 equiv. TBSCl, 1.2 equiv. Et_3N, 8h, rt	1.5 equiv. allyl bromide, 24h, rt	_[a]
4-Meimid.	1.1 equiv. TBSCl, 1.2 equiv. Et_3N, 1h, rt	1.5 equiv. BnBr, 24h, rt	MS found
2-br-4-Meimid.	1.7 equiv. TBSCl, 1.2 equiv. Et_3N, 1h, rt	1.5 equiv. MeOTf, 24h, rt	14%
4-Phimid.	1.7 equiv. TBSCl, 1.2 equiv. Et_3N, 1h, rt	1.5 equiv. MeOTf, 24, rt	no selectivity
4-Phimid.	1.1 equiv. TBSCl, 1.2 equiv. Et_3N, 1h, rt	1.5 equiv. BnBr, 24h, rt	no *N*-alkyl incorporation
80a	1.1 equiv. TBSCl, 1.2 equiv. Et_3N, 8h, rt	1.5 equiv. MeOTf, 24h, rt	40%
80a	1.7 equiv. TBSCl, 1.2 equiv. Et_3N, 1h, rt	1.5 equiv. MeOTf, 24h, rt	24%
79	1.1 equiv. TBSCl, 1.2 equiv. Et_3N, 1h, rt	1.5 equiv. MeOTf, 24h, rt	secondary products
87b	1.1 equiv. TBSCl, 1.2 equiv. Et_3N, 1h, rt	1.5 equiv. MeOTf, 24h, rt	no *N*-methyl products

In conclusion, the TBS method did not give satisfactory results with the different azoles and alkylating agents. The only advantage is that no purification step is necessary.

Chapter 6 - Conclusions and perspectives

1. CHIRALITY STUDIES OF MACROCYCLES

We have synthesized four 5-aryl-1*H*-imidazole-containing macrocycles (**1a-d**) with varying alicyclic chain lengths. HPLC and ^{1}H NMR studies of these imidazoles have shown that **1a-b** are planar chiral molecules whereas their larger-ringed homologues **1c-d** isomerise rapidly at room temperature. It is thus possible to tune the rate of racemization (chirality) of these imidazoles simply by changing the size of the alicyclic chain.

The conformational equilibrium between the two atropisomers has been investigated by computational means. The energy barriers obtained are in good agreement with rate constants estimated by ^{1}H NMR analysis at different temperatures in the presence of a chiral shift reagent.

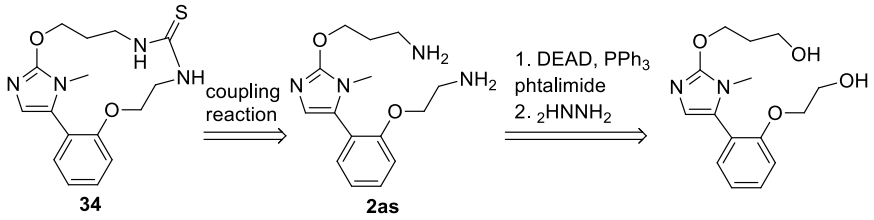
Calculations also gave insights into the origin of the chirality, which is that the cyclophane-type structure of **1a-b** is responsible for their chirality (and not their biaryl-type nature). Moreover, our computational results show that the mechanism of isomerisation involves a rope skipping motion of the alicyclic chain going through the imidazole plane on the C4-H side and not on the *N*-Me side. Transposition of the analytical chiral HPLC conditions to a semipreparative scale allowed us to obtain the two enantiomers of **1a** in milligram amounts with an enantiomeric excess of 99%.

Biological evaluation of the two optically pure enantiomers of **1a** enabled us to investigate the influence of chirality on its biological activities and show that there is no significant influence.

We also examined the possibility of using chiral imidazole-containing macrocycle **1a** in organocatalysis. However, no significant conversion and/or enantiomeric excess could be observed in the considered reactions.

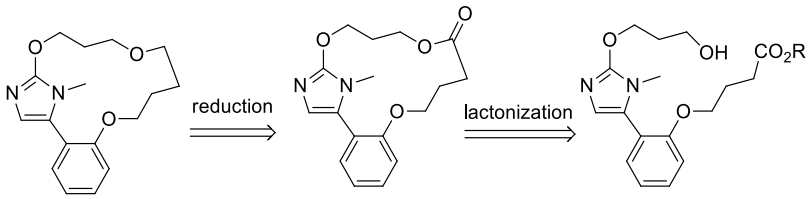
We then tried to synthesize macrocycles with a thiourea or ether function in the alicyclic chain. Concerning the thiourea function, two different strategies have been explored. The first, the introduction of the protected amine, did not work because the boronic acid partern could not be formed. And for the second, that was the ozonolysis of the terminal double that did not work. For the ether function, first this function was introduced in the R^2 chain but the Suzuki reaction did not work. And second, when it was introduced in the R^1 chain, the "open compound" **2** was obtained but the RCM failed. Additional efforts must therefore be done to find another strategy to obtain them.

For the introduction of a thiourea function, other strategies can be considered. Instead of using the reaction sequence ozonolysis-reductive amination with the terminal alkene of compound **2an**, one could test a hydroboration-amination strategy.[213] One could also use the classical method to form the "open compound" **2as** but with a terminal alcohol instead of a double bond (Scheme 138). Then a Mitsunobu reaction with phtalimide and subsequent addition of hydrazine would place the terminal primary amine. Finally the last step would be the coupling of the two amines with a thiocarbonyl reagent to form the macrocycle.



Scheme 138. New strategies for the introduction of a thiourea.

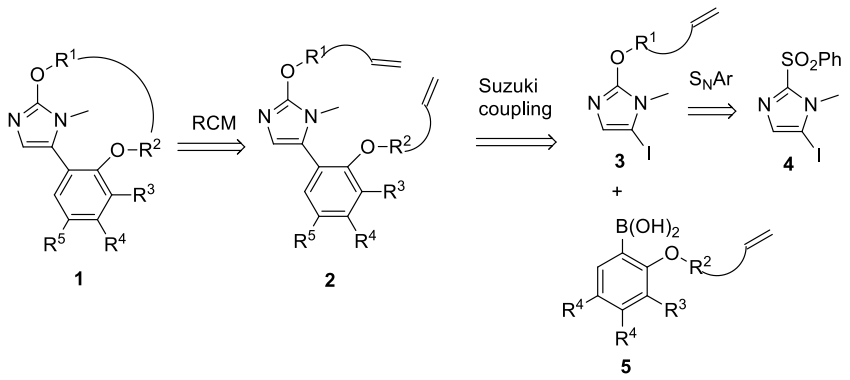
Concerning the indroduction of an ether function in the alicyclic chain, the ring could be closed by a lactonization reaction and then reduction would give a cyclic ether (Scheme 139). A terminal alcohol and ester must be introduced in the "open compound" **2**.



Scheme 139. New strategies for the introduction of an ether.

2. SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF A SERIES OF 5-ARYL-1*H*-IMIDAZOLES AS ANTICANCER AGENTS

About 60 imidazole compounds have been synthesized and tested for their anticancer activity during this thesis. The synthesis was carried out using the convergent methodology developed in our lab (Scheme 140), except for the 2-amido derivatives for which another strategy has been developed through the method of Pr. E. Van der Eycken.



Scheme 140. General strategy.

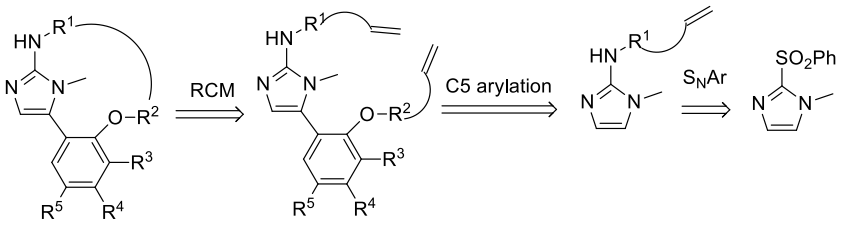
For the biological part, MTT tests were done with the library of compounds on cancer cell lineages which are sensitive or resistant to proapoptotic stimuli. During the SAR study, we have found that the motif 5-aryl-1*H*-imidazole is important for the biological activity. The arm R^1 is also crucial for the activity while the R^2 arm is not. Substituents on aryl part (R^3, R^4, R^5) have no effect or decrease the activity.

Moreover, with one of our lead compound **2c**, quantitative videomycroscopy was done and prove that compound **2c** has a cytostatic and not cytotoxic effect. Interestingly, the mechanism by which these compounds exert their anti-cancer cytostatic activities does not correlate with any compound from the NCI database. Futhermore, we discovered that these compounds could induce perturbations of mitochondrial energetic metabolism, leading to increased O_2 consumption and reactive oxygen species production. Because this metabolism is known to be reprogrammed in cancer cells, these compounds could represent a new way to combat apoptosis-resistant cancer types.

As perspectives, concerning the synthetic part, efforts have to been made to synthesize the 2-aminoimidazole derivatives which could not be obtained thus far. Indeed, reduction of the 2-amidoimidazole did not work. Perhaps, the formation of a thioamide instead of an amide will be a solution. Indeed, thioamide shoud be easier reduced compare to amide.

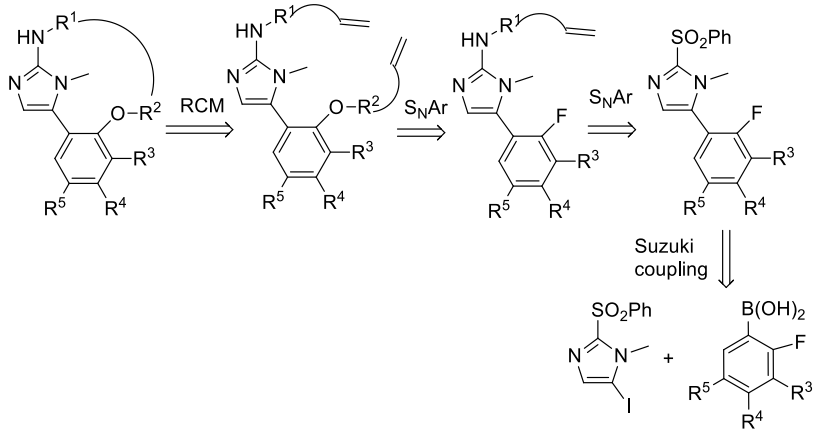
We have seen that if one conducts the S_NAr with an azide on compounds **4**, it does not give the desired product but instead the reduced compound **38**. However, when this compound was used as reactant for the S_NAr, we have found the molecular pic of the desired product in MS. Now, efforts must be done to increase the conversion of this reaction. Indeed, the desired 2-amino-5-aryl-1*H*-imidazole

could be obtained by a direct C5 arylation (for methods see Chapter 1, section 1.4.3.5.3.) (Scheme 141).



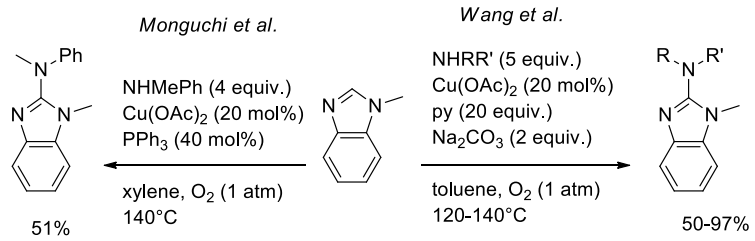
Scheme 141. New strategy fot the formation of the 2-amino-1*H*-imidazole derivative.

Secondly, we have seen that if the Suzuki coupling was done before the S_NAr (see the general strategy, Chapter 1, section 2.2.), this last reaction does not work. The reason is probably that there is too much steric hindrance (OR^2 arm) on the molecule for the addition of the alcoxide. One solution could be to reduce the steric hindrance by replacing the OR^2 arm by a fluorine atom and do the S_NAr with an azide (Scheme 142). After, the OR^2 arm would be placed by a second S_NAr.



Scheme 142. Other strategy for the formation of the 2-amino-1*H*-imidazole derivative.

Another stategy to access 2-amino-1*H*-imidazole derivatives could be the direct oxidative C-H amination. Indeed, different groups reported direct amination of *N*-methylbenzimidazole (Scheme 143).[214] The reaction is catalyzed by copper under oxygen atmosphere. The use of a large excess of amine nucleophile is necessary to prevent a competing side reaction which was identified by Wang et al. as the dimerization of benzimidazole. Application of this methodology on 5-aryl-1*H*-imidazole could be tested.

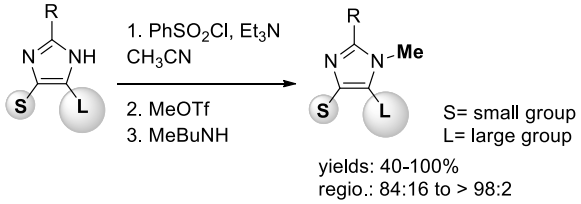


Scheme 143. Direct oxidative C-H functionalization of benzimidazoles. NHRR' = NHMeTs, amides, ureas, carbamates, sulfonamides. With primary amides and sulfonamides 2 equiv. of $Cu(OAc)_2$ was used.

Concerning the biological part, studies are currently underway in the group of Prof. V. Mathieu (ULB) to decipher further the mechanism of action of our compounds.

3. DEVELOPMENT OF A GENERAL AND REGIOSELECTIVE N-ALKYLATION OF AZOLES

A practical and highly regioselective *N*-methylation of NH-(benz)imidazoles was developed (Scheme 144). The interest of our methodology does not only reside in the excellent observed regioselectivity but first and foremost in the nature of the regioisomer formed: the sterically more hindered, less stable, and usually minor regioisomer. Another interest of our methodology is that it involves very mild reaction conditions and tolerates a wide range of functional groups which should make it very practical in the context of total synthesis.



Scheme 144. Regioselective methylation of (benz)imidazoles.

In the scope of our methodoly, we tried to use others alkylating agents but we did not succeed in. This methodology was also extended to other azoles: (benzo)triazoles and purines. Unfortunately, although regioselectivities were excellent, poor yields were obtained. Another convenient protecting group must be found.

In perspective, we could repeat our screening of protecting groups on (NH)-(benzo)triazole derivatives. Indeed, some protecting groups may have given poor results for imidazoles but lead to better ones in the case of (benzo)triazoles.

Then, for the imidazole serie, one could also use additives during the protection step to see if there is a difference in the regioisomeric ratio. For example, add KI for the Bn protecting group in order to favor equilibration.

One could also imagine a more sterically hindered benzyl protecting group (less de-activating than phenylsulfone) by adding substituent on the *ortho* position of the aryl. Maybe it will displace the equilibrium toward the less sterically hindered isomer.

Finally, our methodology could be applied to sugar substrate. Few tests were already done with *N*-SO_2Ph-purine, *N*-SO_2Ph-imidazole derivatives with a protected β-D-ribofuranose but were not concluding and efforts to find a good procedure must be continued (changing the protecting group). Indeed, nucleosides are involved in the regulation of a myriad of cellular metabolic pathways and have been the subject of intense areas of research seeking to identify therapeutic agents for a variety of diseases including viral infections, cancer, cardiovascular diseases, CNS diseases, etc.[215] It would be interesting to synthesize selectivly the more hindered isomer of these monomeric units of DNA and see the effect on their biological activities.

Chapter 7 - Experimental Section

1. GENERALITIES

Flash chromatography was performed on silica gel (230-400 mesh). TLC was performed on aluminum backed silica plates which were developed using standard visualizing agents: UV fluorescence (254 and 366 nm), $KMnO_4$.

NMR spectra were recorded on a Bruker at 300 or 500 MHz for ^{1}H NMR, at 75 or 125 MHz for ^{13}C NMR and 282 MHz for ^{19}F NMR. Chemical shifts (δ) are given in part per million downfield from the residual peak of deuterium solvent (7.26 for $CDCl_3$, 2.5 for d_6-DMSO). For ^{1}H-^{15}N HMBC, the reference used is CH_3NO_2 at 381.7 ppm. When it was needed for the attribution, HMBC and HMQC were done.

Reactions under microwave heating were conducted in a sealed tube using a *MicroSYNTH* equipment (Milestone Srl). Temperature of the reaction mixture was monitored via an infrared sensor.

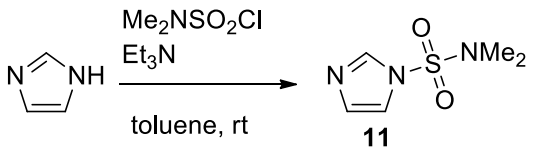
Mass spectra (MS) were recorded on a *Finnigan MAT LCQ* mass spectrometer. HRMS were recorded by the MAPS laboratory at the University College of London and also at UCL on a *thermo orbitrap exactive*. Mass are given in Dalton. Ionization mode of HRMS was the same that MS.

Infrared spectra (IR) were recorded in transmittance on a *Shimadzu FTIR-8400S*. The samples were analysed as films deposited on a ZnSe crystal. Data of IR spectra are reported in terms of frequency of absorption in cm^{-1}.

Purity of intermediates was measured by ^{1}H and ^{13}C NMR and for final compounds sended for biological tests, it was determined by analytical reverse-HPLC (Xbridge C18), conditions: H_2O + 1% TFA/acetonitrile. Measured purity is >95%. The chirality studies were performed on a HPLC Water 600 with a PDA 996 detector.

2. SYNTHESIS OF SULFONES

2.1 Synthesis of 1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazole (11)



11

Chemical formula: $C_5H_{10}N_3O_2S$
Molecular weight: 175.21 $g.mol^{-1}$

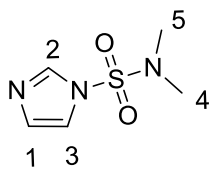
CAS Registry Number: 78162-58-0

Procedure

Imidazole (177.0 mmol, 1 equiv., 12.05 g) was dissolved in toluene (120 mL). Triethylamine (212.2 mmol, 1.2 equiv., 29.5 mL) was then added dropwise followed by dimethylsufamoyle chloride (193.9 mmol, 1.1 equiv., 20.8 mL). After 24 hours of stirring, the mixture was filtrated on celite and the precipitate was washed twice with toluene (20 mL). The filtrate was concentrated under reduced pressure. The oil was dissolved in CH_2Cl_2/MeOH (200 mL) and washed twice with an aqueous solution of 10 % of K_2CO_3 (50 mL). The combined aqueous phases were extracted twice with CH_2Cl_2/MeOH (50 mL). The organic phases were collected and washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude mixture was purified by recrystallization in diisopropyl ether.

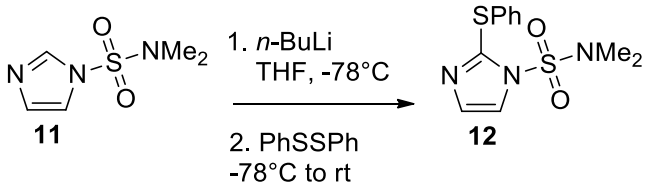
Yield: 91%.

Aspect: yellow-white crystals.



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (s, 1H, 2), 7.26 (d, 1H, *J* = 1.0 Hz, 3), 7.15 (d, 1H, *J* = 1.0 Hz, 1), 2.86 (s, 6H, 4-5).

2.2 Synthesis of 1-(*N*,*N*-dimethylsulfamoyl)-2-thiophenyl-1*H*-imidazole (12)



Chemical formula: $C_{11}H_{13}N_3O_2S_2$
Molecular weight: 283.04 g.mol^{-1}
CAS Registry Number: 123914-19-2

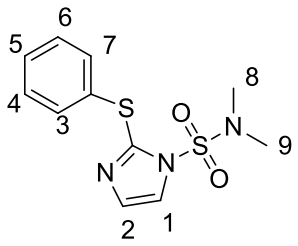
Procedure

A 2.5 M solution of *n*-butyllithium in hexanes (20.63 mmol, 1.2 equiv., 8.25 mL) was added dropwise to a solution of 1-(*N*,*N*-dimethylsulfamoyl)-2-phenylthio-1*H*-imidazole (**11**, 17.12 mmol, 1 equiv., 3 g) in dry THF (35 mL), at -78 °C. The

cooled bath was removed and the reaction mixture was stirred until temperature raised to room temperature (about 1h30). At -78 °C, a solution of PhSSPh (25.68 mmol, 1.5 equiv., 5.61 g) in THF (15 mL) was added slowly. The reaction mixture was then allowed to warm to room temperature and stirred overnight. A saturated solution of ammonium chloride (40 mL) and water (20 mL) were added. The phases were separated, and the aqueous phase was extracted twice with ethyl acetate (10 mL). The organic phases were collected and washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude mixture was purified by flash chromatography over silica with cyclohexane/ethyl acetate 80/20 to 50:50 as eluent.

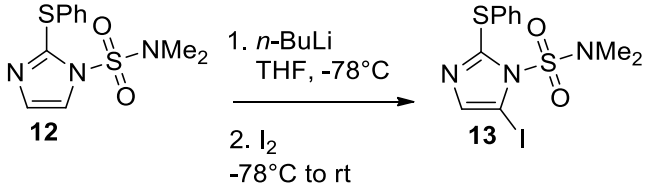
Yield: 83%.

Aspect: brown-yellow solid.



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.55 (m, 2H, 3,7), 7.39-7.36 (m, 3H, 4-6 and 1 or 2), 7.02 (d, 1H, *J* = 1.6 Hz, 1 or 2), 2.98 (s, 6H, 8-9).

2.3. Synthesis of 1-(*N*,*N*-dimethylsulfamoyl)-5-iodo-2-phenylthio-1*H*-imidazole (13)



Chemical formula: $C_{11}H_{12}IN_3O_2S_2$
Molecular weight: 409.27 g.mol^{-1}
CAS Registry Number: 1051373-76-2

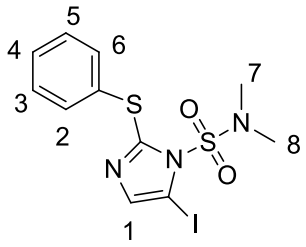
Procedure

A 2.5 M solution of *n*-butyllithium in hexanes (9.27 mmol, 1.3 equiv., 3.7 mL) was added dropwise to a solution of 1-(*N*,*N*-dimethylsulfamoyl)-2-phenylthio-1*H*-imidazole (**12**, 7.06 mmol, 1 equiv., 2 g) in dry THF (52 mL), at -78 °C. The reaction mixture was stirred for 3 h at -78 °C, and a solution of iodine (9.18 mmol, 1.3 equiv., 2.33 g) in THF (12 mL) was added slowly. The reaction mixture was then allowed to warm to room temperature and stirred overnight. Ethyl acetate (200

mL), a saturated solution of ammonium chloride (80 mL), and sodium bisulfite (0.3 g) were added. The phases were separated, and the organic phase was washed twice with a saturated aqueous solution of ammonium chloride (50 mL). The combined aqueous phases were extracted twice with ethyl acetate (50 mL). The organic phases were collected and washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude mixture was purified by flash chromatography over silica with cyclohexane/ethyl acetate 70/30 as eluent.

Yield: 92%

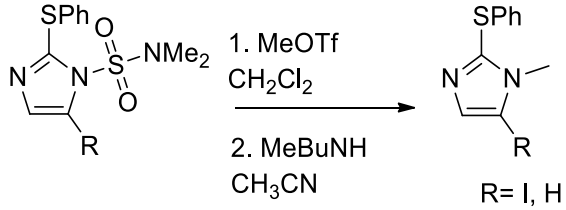
Aspect: yellow solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.54 (m, 2H, 2, 6), 7.42-7.40 (m, 3H, 3-5), 7.03 (s, 1H, 1), 3.10 (s, 6H, 7-8).

2.4. Regioselective methylation/deprotection

2.4.1. General protocol



Methyltrifluoromethanesulfonate (9.53 mmol, 1.3 equiv., 1.12 mL) was added dropwise to a solution of imidazole (7.33 mmol, 1 equiv.) in dichloromethane (15 mL), at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 24 hours. Then another portion of methylating agent was added (5.13 mmol, 0.7 equiv., 0.6 mL) and the mixture was stirring for 8h. The solvent was evaporated under reduced pressure. The crude solid was dissolved in acetonitrile (20 mL), and butylmethylamine (15.40 mmol, 2.1 equiv., 1.82 mL) was added at room temperature. The solution was heated at reflux for 15 h and then evaporated under to reduced pressure.

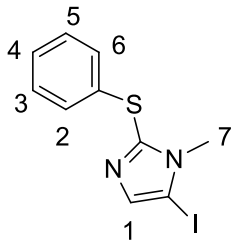
2.4.2. Characterization of 5-iodo-1-methyl-2-(phenylthio)-1H-imidazole (14)

Chemical formula: $C_{10}H_9IN_2S$
Molecular weight: 316.16 $g.mol^{-1}$
CAS Registry Number: 220480-63-7

Purification conditions: The suspension was filtered and washed with acetonitrile.

Yield: 73%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.17 (m, 6H, 1-6), 3.65 (s, 3H, 7).

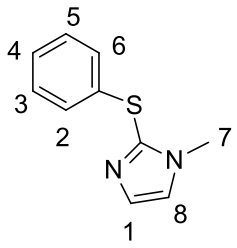
2.4.3. Charactrization of 1-methyl-2-(phenylthio)-1H-imidazole (43)

Chemical formula: $C_{10}H_{10}N_2S$
Molecular weight: 190.26 $g.mol^{-1}$
CAS Registry Number: 79487-95-9

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

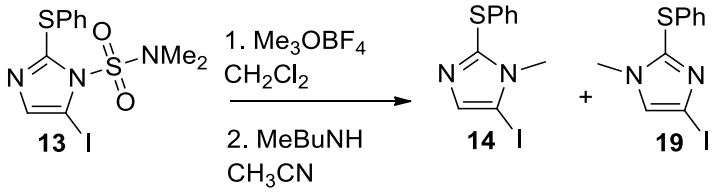
Yield: 65%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.00 (m, 7H, 1-6 and 8), 3.63 (s, 3H, 7).

2.5. Non-regioselective methylation/deprotection



Chemical formula: $C_{10}H_9IN_2S$
Molecular weight: 316.16 $g.mol^{-1}$

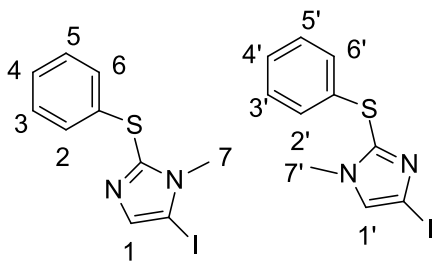
Procedure

Trimethyloxonium tetrafluoroborate (10.13 mmol, 1.5 equiv., 1.58 g) was added dropwise to a solution of imidazole **13** (6.75 mmol, 1 equiv., 2.76 g) in acetonitrile (15 mL), at room temperature. The mixture was stirring for 24 hours. Then, butylmethylamine (14.18 mmol, 2.1 equiv., 1.73 mL) was added and the solution was heated at 80°C overnight. CH_2Cl_2 (10 mL) was added and the solution was washed twice with an aqueous solution of NaOH 1M (10 mL). The aqueous phases were extracted with CH_2Cl_2 (10 mL). The organic phases were dried ($MgSO_4$), and concentrated under reduced pressure. The mixture was purified by flash chromatography with EA/cyclohexane 20:80 as eluent.

Yield: 81%

Selectivity: 42:58 (**14**/**19**)

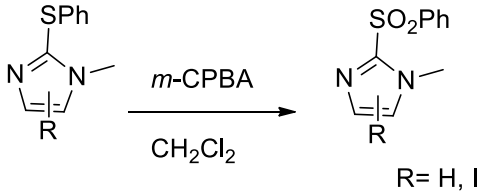
Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.16 (m, 12H, 1-6 and 1'-6'), 3.67 (s, 3H, 7), 3.62 (s, 3H, 7').

2.6. Oxydation

2.6.1. General procedure



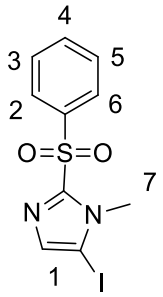
m-CPBA 70% (8.66 mmol, 2.2 equiv.) was added to a solution of methylated product (3.94 mmol, 1 equiv.) in dichloromethane (75 mL), in a flask surrounded by aluminum foil to protect the solution from light. After 8 h at room temperature, sodium bisulfite (8.66 mmol, 2.2 equiv.), water (30 mL), and a saturated sodium bicarbonate solution (40 mL) were successively added. The phases were separated, and the organic phase was washed twice with a saturated solution of sodium bicarbonate (30 mL). The aqueous phases were extracted twice with dichloromethane (40 mL). The combined organic phases were washed with brine (40 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

2.6.2. Characterization of 5-iodo-1-methyl-2-phenylsulfonyl-1H-imidazole (4)

Chemical formula: $C_{10}H_9IN_2O_2S$
Molecular weight: 348.16 $g.mol^{-1}$
CAS Registry Number: 345349-05-5

Yield: quantitative

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07-8.04 (m, 2H, 2,6), 7.73-7.67 (m, 2H, 3,5), 7.62-7.57 (m, 1H, 4), 3.97 (s, 3H, 7).

2.6.3. Characterization of 1-methyl-2-(phenylsulfonyl)-1H-imidazole (38)

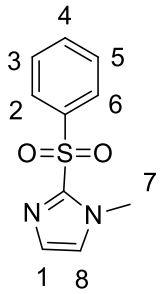
Chemical formula: $C_{10}H_{10}N_2O_2S$
Molecular weight: 222.26 $g.mol^{-1}$

CAS Registry Number: 465617-04-3

Purification conditions: flash chromatography CH_2Cl_2/*i*-propanol 97:3

Yield: 67%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05-8.03 (m, 2H, 2,6), 7.65-7.54 (m, 3H, 3-5), 7.13 (s, 1H, 1 or 8), 6.97 (s, 1H, 1 or 8), 3.98 (s, 3H, 7).

2.6.4. Characterization of a mixture of isomers

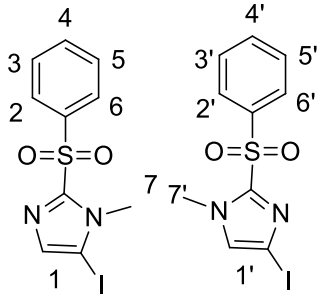
Chemical formula: $C_{10}H_9IN_2O_2S$
Molecular weight: 348.16 g.mol^{-1}

Purification conditions: flash chromatography EA/hexane 40:60

Yield: 64%

Selectivity: 60:40 (**4**/**20**)

Aspect: white solid

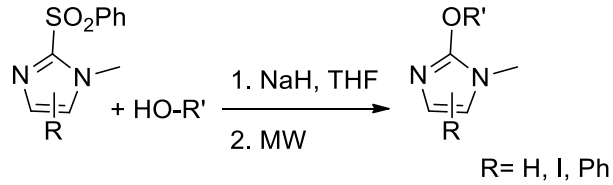


^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05-8.01 (m, 4H, 2,6 and 2',6'), 7.66-7.56 (m, 6H, 3-5 and 3'-5'), 7.24 (s, 1H, 1), 7.04 (s, 1H, 1), 3.95 (s, 3H, 7), 3.94 (s, 3H, 7).

3. SYNTHESIS OF THE NON-CYCLIC COMPOUNDS

3.1. Aromatic nucleophilic substitution

3.1.1. General procedure



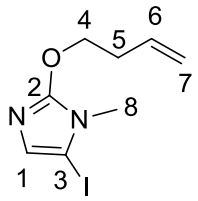
Alcohol (10.40 mmol, 5 equiv.) was added to a solution of sodium hydride (60 wt% suspensions in mineral oil, 9.58 mmol, 4.6 equiv.) in dry THF (7 mL), under argon atmosphere. The solution was stirred until no more gas evolution was observed and then added to a solution of 2-sulfonylimidazole (2.08 mmol, 1 equiv.) in dry THF (35 mL). The reaction mixture was transferred into a sealed tube and heated under microwave for 8 h at 80 °C. Ethyl acetate (50 mL) and saturated sodium chloride solution (30 mL) were successively added. The organic phase was further washed twice with brine (30 mL). Combined aqueous phases were extracted with ethyl acetate (20 mL). The combined organic phases were dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica using a mixture of hexane/ethyl acetate as eluent.

3.1.2. Characterization of 5-iodo-1-methyl-2-(but-3-enyloxy)-1H-imidazole (3a)

Chemical formula: $C_8H_{11}IN_2O$
Molecular weight: 278.09 $g.mol^{-1}$
CAS Registry Number: 1051373-88-6

Yield: 60%.

Aspect: yellow oil.



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72 (s, 1H, 1), 5.90-5.77 (m, 1H, 6), 5.17-5.07 (m, 2H, 7), 4.34 (t, 2H, *J* = 6.6 Hz, 4), 3.32 (s, 3H, 8), 2.55-2.48 (m, 2H, 5),

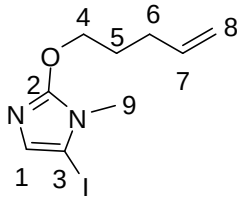
3.1.3. Characterization of 5-iodo-1-methyl-2-(pent-4-enyloxy)-1H-imidazole (3b)

Chemical formula: $C_9H_{13}IN_2O$
Molecular weight: 292.12 g.mol^{-1}

Purification conditions: flash chromatography EA/hexane 20:80

Yield: 88%.

Aspect: yellow oil.



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H, 1), 5.88-5.79 (m, 1H, 7), 5.09-4.98 (m, 2H, 8), 4.34 (t, 2H, *J* = 6.5 Hz, 4), 3.34 (s, 3H, 9), 2.21-2.16 (m, 2H, 5 or 6), 1.90-1.85 (m, 2H, 6 or 5).
^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6 (2), 137.5 (1 or 7), 130.1 (7 or 1), 115.3 (8), 69.1 (4), 31.1 (9), 30.0 (5 or 6), 28.2 (6 or 5), 3 not observed.

IR (cm^{-1}): 2947, 1641, 1541, 1497, 1377, 1254, 1142, 1018, 912, 797, 708.

APCI-MS m/z (%): 292 (10) $[M]^{\cdot +}$, 225 (100), 98 (28).

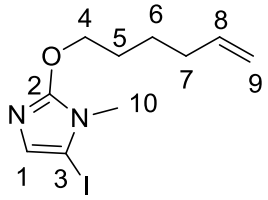
HRMS calcd for $C_9H_{13}IN_2O$: 292.00671, found 292.00703.

3.1.4. Characterization of 2-(hex-5-enyloxy)-5-iodo-1-methyl-1H-imidazole (3c)

Chemical formula: $C_{10}H_{15}IN_2O$
Molecular weight: 306.02 g.mol^{-1}
CAS Registry Number: 1236073-91-8

Yield: 76%.

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1H, 1), 5.84-5.75 (m, 1H, 8), 5.04-4.94 (m, 2H, 9), 4.31 (t, 2H, *J* = 6.6 Hz, 4), 3.32 (s, 3H, 10), 2.11-2.09 (m, 2H, 7), 1.80-1.75 (m, 2H, 5), 1.54-1.49 (m, 4H, 6).

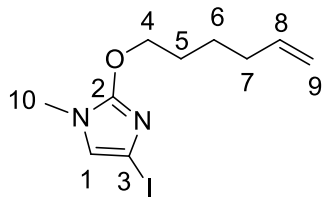
3.1.5. Characterization of 2-(hex-5-en-1-yloxy)-4-iodo-1-methyl-1H-imidazole (21)

Chemical formula: $C_{10}H_{15}IN_2O$
Molecular weight: 306.02 g.mol^{-1}

Purification conditions: flash chromatography EA/cyclohexane 10:90

Yield: 40% (from the mix of isomers)

Aspect: yellow oil



^{1}H NMR (500 MHz, $CDCl_3$): δ 6.60 (s, 1H, 1), 5.87-5.74 (m, 1H, 8), 5.05-4.95 (m, 2H, 9), 4.33 (t, 2H, *J* = 6.6 Hz, 4), 3.37 (s, 3H, 10), 2.14-2.07 (m, 2H, 7), 1.81-1.72 (m, 2H, 5), 1.56-1.46 (m, 4H, 6).
^{13}C NMR (125 MHz, $CDCl_3$): δ 153.3 (2), 138.5 (8), 121.7 (1), 115.0 (9), 74.2 (3), 70.2 (4), 33.4 (7), 30.7 (10), 28.5 (5), 25.2 (6).

IR (cm^{-1}): 2929, 1541, 1475, 1379, 1254, 1142, 1018, 910, 797, 708.

APCI-MS m/z (%): 307 (100) $[M+H]^+$, 224 (22).

HRMS calcd for $C_{10}H_{16}IN_2O$: 307.03018, found 307.03023.

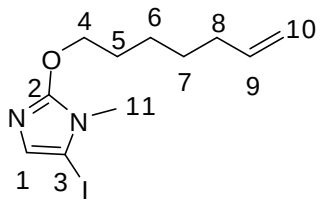
3.1.6. Characterization of 2-(hept-6-enyloxy)-5-iodo-1-methyl-1H-imidazole (3d)

Chemical formula: $C_{11}H_{17}IN_2O$
Molecular weight: 320.17 g.mol^{-1}

Purification conditions: flash chromatography EA/hexane 20:80

Yield: 80%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H, 1), 5.85-5.76 (m, 1H, 9), 5.03-4.93 (m, 2H, 10), 4.31 (t, 2H, *J* = 6.6 Hz, 4), 3.33 (s, 3H, 11), 2.08-2.05 (m, 2H, 5-8), 1.80-1.75 (m, 2H, 5-8), 1.46-1.43 (m, 4H, 5-8).
^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9 (2), 138.8 (9), 130.2 (1), 114.6 (10), 69.8 (4), 33.7 (5-8), 31.2 (11), 28.9 (5-8), 28.6 (5-8), 25.4 (5-8), 3 not observed.

IR (cm^{-1}): 2929, 1541, 1475, 1379, 1254, 1142, 1018, 910, 797, 708.

APCI-MS m/z (%): 320 (12) $[M]^{\cdot+}$, 225 (100), 98 (22).

HRMS calcd for $C_{11}H_{18}IN_2O$: 321.04638, found 321.04619.

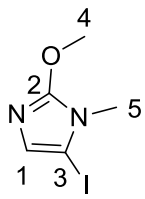
3.1.7. Characterization of 5-iodo-2-methoxy-1-methyl-1H-imidazole (3e)

Chemical formula: $C_5H_7IN_2O$
Molecular weight: 238.03 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 50:50

Yield: 79 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 1H, 1), 4.00 (s, 3H, 4), 3.32 (s, 3H, 5).
^{13}C NMR (75 MHz, $CDCl_3$): δ 153.2 (2), 130.2 (1), 56.6 (4), 31.2 (5), 3 not observed.

IR (cm^{-1}): 1780, 1548, 1400, 1253, 1136, 1028.

APCI-MS m/z (%): 239 (100) $[M+H]^+$.

HRMS calcd for $C_5H_7IN_2O$: 238.96813, found 238.96848.

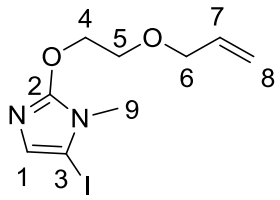
3.1.8. Characterization of 2-(2-(allyloxy)ethoxy)-5-iodo-1-methyl-1H-imidazole (3f)

Chemical formula: $C_9H_{13}IN_2O_2$
Molecular weight: 308.12 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 50:50

Yield: 91%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.72 (s, 1H, 1), 5.83-5.96 (m, 1H, 7), 5.16-5.30 (m, 2H, 8), 4.48 (t, 2H, *J* = 4.6 Hz, 4 or 5), 4.04 (t, 2H, *J* = 5.6 Hz, 6), 3.76 (t, 2H, *J* = 4.6 Hz, 4 or 5), 3.34 (s, 3H, 9).
^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5 (2), 134.5 (7), 130.2 (1), 117.4 (8), 72.2 (4-6), 69.0 (4-6), 68.2 (4-6),

31.3 (9), 3 not observed.

IR (cm^{-1}): 1750, 1431, 1371, 12223, 891, 198.

APCI-MS m/z (%): 309 (100) $[M+H]^+$,

HRMS calcd for $C_9H_{14}IN_2O$: 309.01000, found 309.00962.

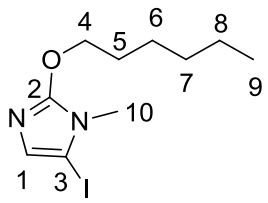
3.1.9. Characterization of 2-(hexyloxy)-5-iodo-1-methyl-1H-imidazole (3g)

Chemical formula: $C_{10}H_{17}IN_2O$
Molecular weight: 308.16 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 15:85

Yield: 71%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1H, 1), 4.29 (t, 2H, *J* = 6.6 Hz, 4), 3.31 (s, 3H, 10), 1.79-1.69 (m, 2H, 5-8), 1.42-1.37 (m, 2H, 5-8), 1.19-1.35 (m, 4H, 5-8), 0.87 (t, *J* = 6.8 Hz, 3H, 9).
^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9 (2), 130.2 (1), 69.9 (4), 63.5 (3), 31.5 (10), 31.6 (5-8), 29.0 (5-8), 25.5 (5-8), 22.6 (5-8), 14.1 (9).

IR (cm^{-1}): 2928, 2359, 1541, 1468, 1377, 1016, 665.

APCI-MS m/z (%): 309 (100) $[M+H]^+$, 225 (15).

HRMS calcd for $C_{10}H_{17}IN_2O$: 309.0458, found 309.0464.

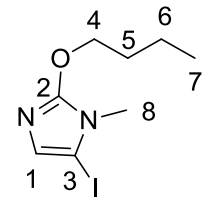
3.1.10. Characterization of 2-(butoxy)-5-iodo-1-methyl-1H-imidazole (3f)

Chemical formula: $C_8H_{13}IN_2O$
Molecular weight: 280.11 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 15:85

Yield: 66%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1H, 1), 4.30 (t, 2H, *J* = 6.6 Hz, 4), 3.31 (s, 3H, 8), 1.76-1.69 (m, 2H, 5-6), 1.47-1.40 (m, 2H, 5-6), 0.94 (t, *J* = 7.4 Hz, 3H, 7).
^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9 (2), 130.2 (1), 69.9 (4), 63.5 (3), 31.5 (8), 31.1 (5-6), 19.1 (5-6), 13.8 (7).

IR (cm^{-1}): 2955, 1543, 1474, 1379, 1142, 1040.

APCI-MS m/z (%): 281 (100) $[M+H]^+$, 225 (26).

HRMS calcd for $C_8H_{14}IN_2O$: 281.0145, found 281.0150.

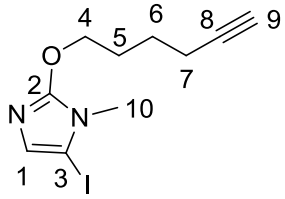
3.1.11. Characterization of 2-(hex-5-yn-1-yloxy)-5-iodo-1-methyl-1H-imidazole (3h)

Chemical formula: $C_{10}H_{13}IN_2O$
Molecular weight: 304.13 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 40:60

Yield: 21%.

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H, 1), 4.32 (t, 2H, *J* = 6.4 Hz, 4), 3.31 (s, 3H, 10), 2.24 (td, $J_{6,7}$ =7,0; $J_{7,8}$ = 2,7, 2H, 7), 1.94 (t, $J_{9,7}$=2.7, 1H, 9), 1.92-1.83 (m, 2H, 5-6), 1.70-1.60 (m, 2H, 5-6).
^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0 (2), 130.4 (1), 84.1 (9), 69.2 (4), 68.9 (8), 63.9 (3), 31.4 (10), 28.1 (5-7), 25.0 (5-7), 18.2 (5-7).

IR (cm^{-1}): 2949, 2359, 1758, 1541, 1474, 1254, 1026.

APCI-MS m/z (%): 305 (100) $[M+H]^+$.

HRMS calcd for $C_{10}H_{14}IN_2O$: 305.0145, found 305.0151.

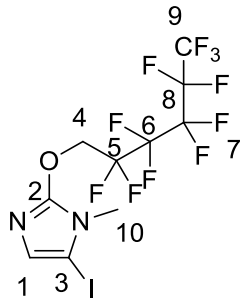
3.1.12. Characterization of 5-iodo-1-methyl-2-((2,2,3,3,4,4,5,5,6,6-undecafluorohexyl) oxy)-1H-imidazole (3i)

Chemical formula: $C_{10}H_6F_{11}IN_2O$
Molecular weight: 506.05 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 15:85 → 50:50

Yield: 20%

Aspect: yellow solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H, 1), 4.83 (t, 2H, $J_{4,5F}$ = 13.1 Hz, 4), 3.36 (s, 3H, 10).
^{13}C NMR (75 MHz, $CDCl_3$): δ 151.9 (2), 130.4 (1), 65.2 (t, $J_{4,5F}$= 27,54 Hz, 4), 31.5 (10), 3, 5, 6, 8, 9 not observed but present in the noise due to fluorine coupling.
^{19}F NMR (282 MHz, $CDCl_3$): δ -82.5 (9), -121.6 (5 or 8), -124.4 (6 or 7), -124.9 (6 or 7), -127.7 (5 or 8).

IR (cm^{-1}): 2957, 1541, 1506, 1238, 1142, 1072, 741, 652.

APCI-MS m/z (%): 507 (100) $[M+H]^+$.

HRMS calcd for $C_{10}H_6F_{11}IN_2O$: 506.9422, found 506.9419.

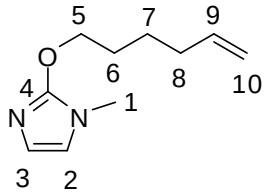
3.1.13. Characterization of 2-(hex-5-enyloxy)-1-methyl-1H-imidazole (6)

Chemical formula: $C_{10}H_{16}N_2O$
Molecular weight: 180.25 $g.mol^{-1}$

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 48%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60 (d, 1H, *J* = 1.5 Hz, 2), 6.49 (d, 1H, *J* = 1.5 Hz, 3), 5.87-5.74 (m, 1H, 9), 5.04-4.94 (m, 2H, 10), 4.33 (t, *J* = 6.5 Hz, 5), 3.38 (s, 3H, 1), 2.14-2.03 (m, 2H, 7), 1.83-1.73 (m, 2H, 6), 1.58-1.48 (m, 2H, 8).
^{13}C NMR (75 MHz, $CDCl_3$): δ 152.9 (4), 138.5 (9), 122.6 (2 or 3), 116.0 (3 or 2), 114.8 (10), 69.5 (5), 33.6 (8), 32.3 (1), 28.6 (6), 25.2 (7).

IR (cm^{-1}): 3383, 2937, 2860, 1641, 1541, 1499, 1381, 1281, 1223, 1140, 1018, 910, 689.

APCI-MS m/z (%): 181 (100) $[M+H]^+$.

HRMS calcd for $C_{10}H_{17}N_2O$: 181.13354, found 181.13354.

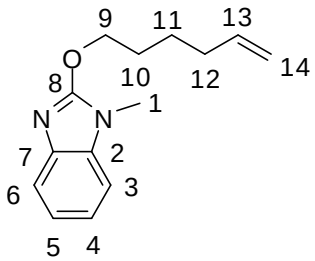
3.1.14. Synthesis of 2-(hex-5-enyloxy)-1-methyl-1H-benzo[d]imidazole (8)

Chemical formula: $C_{14}H_{18}N_2O$
Molecular weight: 230.31 g.mol^{-1}

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 98:02

Yield: 83%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56-7.52 (m, 1H,), 7.19-7.11 (m, 3H,), 5.89-5.76 (m, 1H, 13), 5.08-4.96 (m, 2H, 14), 4.54 (t, 2H, *J* = 6.6 Hz, 9), 3.53 (s, 3H, 1), 2.18-2.11 (m, 2H, 11), 1.93-1.83 (m, 2H, 10), 1.63-1.53 (m, 2H, 12).
^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7 (8), 140.1 (7 or 2), 138.4 (12), 134.3 (2 or 7), 121.5 (3-6), 120.8 (3-6), 117.6 (3-6), 115.0 (13), 107.9 (3-6), 70.2 (8), 33.4 (12), 28.5 (10), 28.0 (1), 25.2 (11).

IR (cm^{-1}): 3407, 2935, 1736, 1624, 1541, 1454, 1285, 1007, 910, 739, 652.

APCI-MS m/z (%): 231(100) $[M+H]^+$.

HRMS calcd for $C_{14}H_{19}N_2O$: 231.14919, found 231.14919.

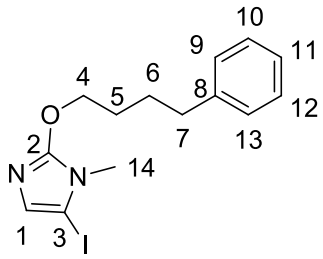
3.1.15. Characterization of 5-iodo-1-methyl-2-(4-phenylbutoxy)-1H-imidazole (3k)

Chemical formula: $C_{14}H_{17}IN_2O$
Molecular weight: 356.20 g.mol^{-1}

Purification conditions: flash chromatography EA/hexane 20:80

Yield: 79%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.17 (m, 5H, 9-13), 6.72 (s, 1H, 1), 4.34 (t, *J* = 6.2 Hz, 4), 3.31 (s, 3H, 14), 2.67-2.62 (m, 2H, 7), 1.80-1.77 (m, 4H, 6-7).
^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0 (2), 142.1 (8), 130.3 (1), 128.5 (3C, 10-12), 126.0 (2C, 9, 13), 69.6 (4), 63.6 (3), 35.6 (7), 31.2 (14), 28.7 (6 or 7), 27.7

(6 or 7).

IR (cm^{-1}): 2924, 1736, 1541, 1473, 1253, 1020, 665.

ESI-MS m/z (%): 357 (92) $[M+H]^+$, 225 (100).

HRMS calcd for $C_{14}H_{18}N_2O$: 357.04583, found 357.04568.

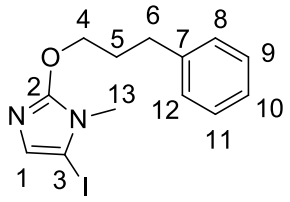
3.1.16. Characterization of 5-iodo-1-methyl-2-(3-phenylpropoxy)-1H-imidazole (3j)

Chemical formula: $C_{13}H_{15}IN_2O$
Molecular weight: 342.18 $g.mol^{-1}$

Purification conditions: flash chromatography EA/hexane 20:80

Yield: 77%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.17 (m, 5H, 8-12), 6.72 (s, 1H, 1), 4.35 (t, *J* = 6.5 Hz, 4), 3.31 (s, 3H, 14), 2.79-2.74 (m, 2H, 6), 2.13-2.08 (m, 2H, 5).
^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0 (2), 141.3 (7), 130.3 (1), 128.5 (3C, 9-11), 126.1 (2C, 8, 12), 69.1 (4), 63.6 (3), 32.2 (6), 31.2 (13), 30.7 (5).

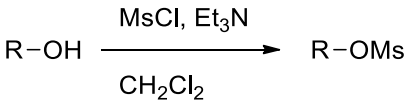
IR (cm^{-1}): 2924, 1736, 1541, 1473, 1253, 1020, 665.

ESI-MS m/z (%): 343 (100) $[M+H]^+$, 225 (50).

HRMS calcd for $C_{13}H_{16}N_2O$: 343.03018, found 343.03007.

3.2. Synthesis of mesylates

3.2.1. General procedure



The alcohol (14.98 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (15 mL). At 0°C, Et_3N (16.47 mmol, 1.1 equiv.) and MsCl (16.47 mmol, 1.1 equiv.) were added dropwise. After one night of stirring at room temperature, CH_2Cl_2 (45 mL) and a saturated $NaHCO_3$ solution (45 mL) were successively added. The organic phase was further washed twice with a saturated $NaHCO_3$ solution (15 mL). Combined

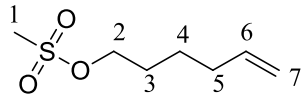
aqueous phases were extracted twice with CH_2Cl_2 (45 mL). The combined organic phases were washed with a brine (45 mL) and dried over $MgSO_4$, and concentrated under reduced pressure.

3.2.2. Characterization of hex-5-en-1-yl methanesulfonate (17c)

Chemical formula: $C_7H_{14}O_3S$
Molecular weight: 178.25 $g.mol^{-1}$
CAS Registry Number: 64818-36-6

Yield: quantitative

Aspect: yellow oil



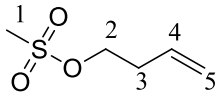
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85-5.70 (m, 1H, 6), 5.07-4.94 (m, 2H, 7), 4.22 (t, 2H, *J* = 6.5 Hz, 2), 2.99 (s, 3H, 1), 2.14-2.06 (m, 2H, 5), 1.80-1.46 (m, 4H, 3-4).

3.2.3. Characterization of but-3-en-1-yl methanesulfonate (17b)

Chemical formula: $C_5H_{10}O_3S$
Molecular weight: 150.20 $g.mol^{-1}$
CAS Registry Number: 40671-34-9

Yield: quantitative

Aspect: yellow oil



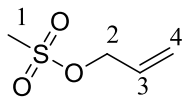
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85-5.71 (m, 1H, 4), 5.30-5.14 (m, 2H, 5), 4.27 (t, 2H, *J* = 6.7 Hz, 2), 3.00 (s, 3H, 1), 2.54-2.48 (m, 2H, 3).

3.2.4. Characterization of allyl methanesulfonate (17a)

Chemical formula: $C_4H_8O_3S$
Molecular weight: 136.17 $g.mol^{-1}$
CAS Registry Number: 6728-21-8

Yield: 49%

Aspect: yellow oil



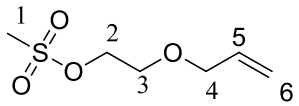
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.01-5.89 (m, 1H, 3), 5.48-5.35 (m, 2H, 4), 4.71-4.69 (m, 2H, 2), 3.00 (s, 3H, 1).

3.2.5. Characterization of 2-(allyloxy)ethyl methanesulfonate (17d)

Chemical formula: $C_6H_{12}O_4S$
Molecular weight: 180.22 g.mol^{-1}
CAS Registry Number: 153901-22-5

Yield: quantitative

Aspect: yellow oil



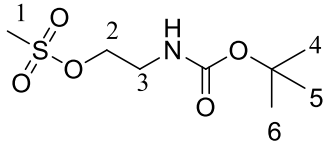
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.95-5.82 (m, 1H, 5), 5.32-5.20 (m, 2H, 6), 4.42-4.34 (m, 2H, 2-4), 4.05-4.03 (m, 2H, 2-4), 3.72-3.69 (m, 2H, 2-4), 3.06 (s, 3H, 1).

3.2.6. Characterization of 2-((tert-butoxycarbonyl)amino)ethyl methanesulfonate (32)

Chemical formula: $C_8H_{17}O_5S$
Molecular weight: 239.29 g.mol^{-1}
CAS Registry Number: 96628-67-0

Yield: 97%

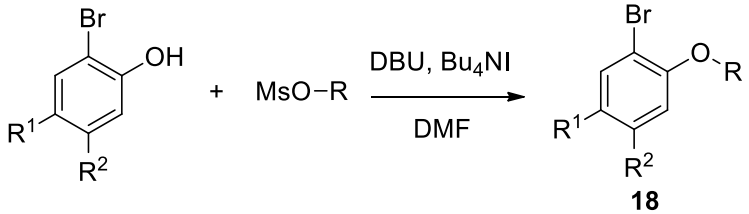
Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 4.90 (bs, NH), 4.28 (t, 2H, *J* = 5.1 Hz, 2), 3.50-3.44 (m, 2H, 3), 3.03 (s, 3H, 1), 1.44 (s, 9H, 4-6).

3.3. Synthesis of bromophenols

3.3.1. General procedure



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To a solution of 2-bromophenol (10.56 mmol, 1 equiv.) in anhydrous DMF (15 mL) were successively added, 1,8-diazabicyclo[5.4.0]undec-7-ene (15.85 mmol, 1.5

equiv.), mesylated alcohol (13.73 mmol, 1.3 equiv.) and tetra-*n*-butylammonium iodide (0.32 mmol, 0.03 equiv.). The mixture was heated at 70°C for 7h and then stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was taken up in ether (160 mL). Water (25 mL) and HCl 1M (8.3 mL) were successively added. The phases were separated and the organic phase was washed with water (2 × 35 mL). The combined aqueous phases were extracted with ether (2 x 50 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated under vacuo. The crude product was purified by flash chromatography using a mixture of cyclohexane/ethyl acetate as eluent.

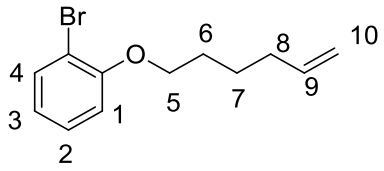
3.3.2. Characterization of 1-bromo-2-(hex-3-en-1-yloxy)benzene (18c)

Chemical formula: $C_{12}H_{15}BrO$
Molecular weight: 255.15 g.mol^{-1}
CAS Registry Number: 1236073-88-3

Purification conditions: flash chromatography with EA/cyclohexane 05:95

Yield: 91%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (dd, 1H, *J* =1.6, 7.9 Hz, 1 or 4), 7.24 (ddd, 1H, *J* = 1.6, 7.4, 8.3 Hz, 2 or 3), 6.88 (dd, 1H, *J* = 1.3, 8.3 Hz, 1 or 4), 6.82 (dt, 1H, *J* = 1.4, 7.6 Hz, 2 or 3), 5.89-5.78 (m, 1H, 9), 5.01-4.99 (m, 2H, 10), 4.03 (t, 2H, *J* = 6.4 Hz, 5), 2.20-2.10 (m, 2H, 8), 1.90-1.80 (m, 2H, 6), 1.70-1.60 (m, 2H, 7).

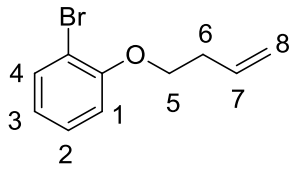
3.3.3. Characterization of 1-bromo-2-(but-3-en-1-yloxy)benzene (18b)

Chemical formula: $C_{10}H_{11}BrO$
Molecular weight: 227.10 g.mol^{-1}
CAS Registry Number: 87280-00-0

Purification conditions: flash chromatography with EA/cyclohexane 05:95

Yield: 76%

Aspect: whire solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.52 (m, 1H, 1-4), 7.26-7.22 (m, 1H, 1-4), 6.91-6.80 (m, 2H, 1-4), 6.03-5.89 (m, 1H, 7), 5.23-5.11 (m, 2H, 8), 4.07 (t, *J* = 6.8 Hz, 5), 2.64-2.57 (m, 2H, 6).

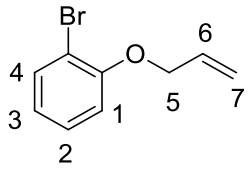
3.3.4. Characterization of 1-(allyloxy)-2-bromobenzene (18a)

Chemical formula: C_9H_9BrO
Molecular weight: 213.07 $g.mol^{-1}$
CAS Registry Number: 60333-75-7

Purification conditions: flash chromatography with EA/cyclohexane 05:95

Yield: 56%

Aspect: white solid

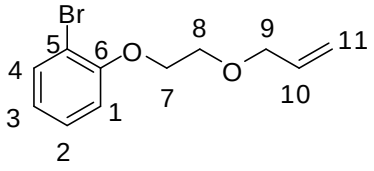


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (dd, 1H, *J* = 4.8 and 0.9 Hz, 1-4), 7.25-7.23 (m, 1H, 1-4), 6.89 (dd, 1H, *J* = 4.9 and 0.9 Hz, 1-4), 6.86-6.84 (m, 1H, 1-4), 6.08-6.03 (m, 1H, 6), 5.51-5.47 (m, 1H, 7a or b), 5.33-5.30 (m, 1H, 7a or b), 4.63-4.62 (m, 2H, 5).

3.3.5. Characterization of 1-[2-(allyloxy)ethoxy]-2-bromobenzene (18d)

Chemical formula: $C_{11}H_{13}BrO_2$
Molecular weight: 257.12 $g.mol^{-1}$
Yield: 91%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (dd, 1H, $J_{4,3}$ = 7.8 Hz and $J_{4,2}$ = 1.5 Hz, 4), 7.21-7.24 (m, 1H, 2), 6.93 (dd, 1H, $J_{1,2}$ = 8.1 Hz and $J_{1,3}$ = 1.2 Hz, 1), 6.80-6.85 (m, 1H, 3), 5.87-5.96 (m, 1H, 10), 5.32 (dd, 1H, $J_{11a,10}$ = 17.1 Hz and $J_{11a,11a'}$ = 1.5 Hz, 11a), 5.20 (dd, 1H, $J_{11a',10}$ = 10.5 Hz and $J_{11a',11a}$ = 1.5 Hz, 11a'), 4.14-4.20 (m, 4H, 7 or 8 and 9), 3.86 (t, 2H, $J_{7,8}$ = 4.8 Hz, 8 or 7).
^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4 (6), 134.7 (10), 133.5 (1-4), 128.5 (1-4), 122.2 (1-4), 117.3 (11), 113.7 (1-4), 112.4 (5), 72.6 (9), 69.1 (7 or 8), 68.4 (8 or 7).

IR (cm^{-1}): 3055, 2953, 2872 (C-H), 703, 725, 733 (C-Br).

ESI-MS m/z (%): 280 (98, ^{81}Br) $[M+Na]^+$, 278 (100, ^{79}Br) $[M+Na]^+$.

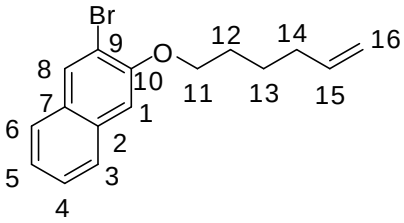
HRMS calcd for $C_{11}H_{13}BrO_2$: 256.00934, found 256.00834.

3.3.6. Characterization of 2-bromo-3-(hex-5-en-1-yloxy)naphtalene (18f)

Chemical formula: $C_{16}H_{17}BrO$
Molecular weight: 305.21 g.mol^{-1}

Yield: 90 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H, 8), 7.70 (d, 1H, *J* = 4.8 Hz, 3 or 6), 7.68 (d, 1H, *J* = 4.5 Hz, 6 or 3), 7.53-7.43 (m, 1H, 4 or 5), 7.40-7.34 (m, 1H, 5 or 4), 7.13 (s, 1H, 1), 5.95-5.92 (m, 1H, 15), 5.12-5.00 (m, 2H, 16), 4.14 (t, 2H, *J* = 6.5 Hz, 11), 2.29-2.17 (m, 2H, 14), 2.00-1.91 (m, 2H, 12), 1.75-1.65 (m, 2H, 13).

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.2 (10), 138.7 (15), 133.7 (2 or 7), 132.3 (8), 129.5 (7 or 2), 126.7 (2C, 3 and 6), 126.8 (4), 124.5 (5), 115.0 (16), 114.1 (9), 107.6 (1), 69.0 (11), 33.5 (14), 28.6 (12), 25.5 (13).

IR (cm^{-1}): 3053, 2988, (C-H), 736, 725, 702 (C-Br).

APCI-MS m/z (%): 305 (98, ^{81}Br) $[M]^{\cdot+}$, 307 (100, ^{79}Br) $[M]^{\cdot+}$.

HRMS calcd for $C_{16}H_{17}BrO$: 304.04573, found 304.04539.

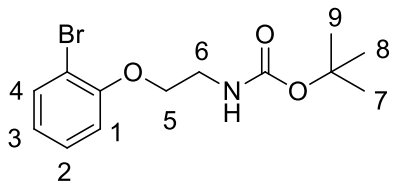
3.3.7. Characterization of tert-butyl (2-(2-bromophenoxy)ethyl)carbamate (33)

Chemical formula: $C_{13}H_{18}BrO_3$
Molecular weight: 316.19 g.mol^{-1}
CAS Registry Number: 1204333-53-8

Purification conditions: flash chromatography with EA/cyclohexane 20:80

Yield: 69%

Aspect: white solid

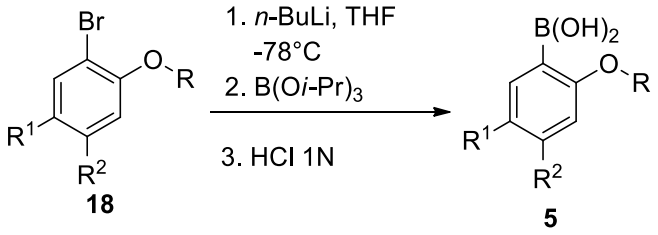


^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (dd, 1H, *J*= 7.9 and 1.6 Hz, 1-4), 7.29-7.23 (m, 1H, 1-4), 6.91-7.83 (m, 2H, 1-4), 5.09 (bs, NH),

4.08 (t, 2H, *J*= 5.1 Hz, 5), 3.59-3.56 (m, 2H, 6), 1.45 (s, 9H, 7-9).

3.4. Synthesis of boronic acids

3.4.1. General procedure



Bromophenol (7.93 mmol, 1 equiv.) was dissolved in THF (25 mL). The solution was then cooled to -78°C and *n*-BuLi 2.5M in hexanes (10.30 mmol, 1.3 equiv.) was added dropwise. The resulting solution was stirred for 1h at –78°C and triisopropylborate (15.85 mmol, 2.0 equiv.) was then added dropwise at -78°C. The mixture was allowed to warm up slowly to room temperature without removing the cooling bath and stirred overnight. Ethyl acetate (12 mL) was added to the suspension and HCl 1N was added until pH =1 (about 11 mL). The two phases were separated and the aqueous phase was extracted with ethyl acetate (3x15 mL). The organic phases were combined and washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure.

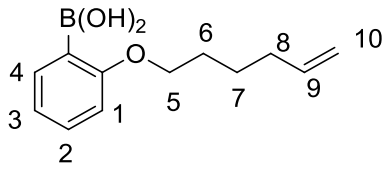
3.4.2. Characterization of (2-(hex-3-en-1-yloxy)phenyl)boronic acid (5c)

Chemical formula: $C_{12}H_{17}BO_3$
Molecular weight: 220.07 $g.mol^{-1}$
CAS Registry Number: 1236073-85-0

Purification conditions: flash chromatography with EA/cyclohexane 30:70

Yield: 84%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (dd, 1H, *J* = 7.3, 1.7 Hz, 1-4), 7.45-7.40 (m, 1H, 1-4), 7.03 (t, 1H, *J* = 7.3 Hz, 1-4), 6.90 (d, 1H, *J* = 8.3 Hz, 1-4), 6.04 (bs, 2H, OH), 5.89-5.75 (m, 1H, 9), 5.08-4.98 (m, 2H, 10), 4.09 (t, 2H, *J* =

6.6 Hz, 5), 2.19-211 (m, 2H, 8), 1.90-1.80 (m, 2H, 6), 1.65-1.55 (m, 2H, 7).

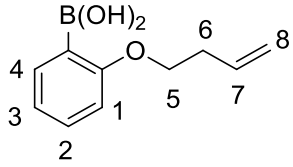
3.4.3. Characterization of (2-(but-3-en-1-yloxy)phenyl)boronic acid (5b)

Chemical formula: $C_{10}H_{13}BO_3$
Molecular weight: 192.02 g.mol^{-1}
CAS Registry Number: 1334402-83-3

Purification conditions: flash chromatography with EA/cyclohexane 30:70

Yield: 55%

Aspect: whire solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (dd, 1H, 7.54-7.52 (m, 1H, *J* = 7.2 and 1.5 Hz, 4), 7.43 (dd, 1H, *J* = 8.4 and 1.5 Hz, 2), 7.02 (t, 1H, *J* = 7.2 Hz, 3), 6.90 (d, 1H, *J* = 8.4 Hz, 1), 5.96-5.69 (m, 1H, 7), 5.28-5.18 (m, 2H, 8), 4.14 (t, *J* = 6.2 Hz, 5), 2.65-2.59 (m, 2H, 6).

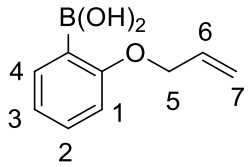
3.3.8. Characterization of (2-(allyloxy)phenyl)boronic acid (5a)

Chemical formula: $C_8H_{11}BO_3$
Molecular weight: 178.00 g.mol^{-1}
CAS Registry Number: 151414-76-52

Purification conditions: flash chromatography with EA/cyclohexane 20:80

Yield: 62%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86-7.78 (m, 1H, 1-4), 7.44-7.37 (m, 1H, 1-4), 7.05-6.99 (m, 1H, 1-4), 6.91-6.87 (m, 1H, 1-4), 6.13-6.05 (m, 1H, 6), 5.81 (bs, OH), 5.45-5.34 (m, 2H, 7), 4.65-4.62 (m, 2H, 5).

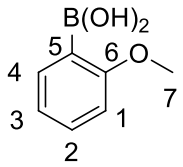
3.4.4. Characterization of (2-methoxy)phenyboronic acid (5e)

Chemical formula: $C_7H_9BO_3$
Molecular weight: 151.96 g.mol^{-1}
CAS Registry Number: 5720-06-9

Purification conditions: flash chromatography with EA/cyclohexane 15:85

Yield: quantitative

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, 1H, *J* = 7.3 Hz, 4), 7.48-7.43 (m, 1H, 2 or 3), 7.06-7.02 (m, 1H, 3 or 2), 6.92 (d, 1H, *J* = 8.3 Hz, 1), 3.92 (s, 3H, 7).

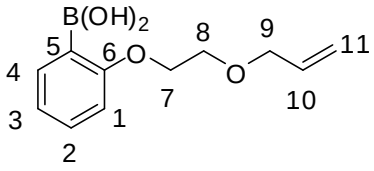
3.4.5. Characterization of 2-(2-(allyloxy)ethoxy)phenylboronic acid (5d)

Chemical formula: $C_{11}H_{15}BO_4$
Molecular weight: 222.05 g.mol^{-1}

Purification conditions: flash chromatography with AE/cyclohexane 15:85

Yield: 20%

Aspect: oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.28 (m, 2H,1 and 4), 7.00-6.94 (m, 2H, 2 and 3), 6.02-5.91 (m, 1H, 10), 5.34 (dd, 1H, $J_{11a,10}$ = 17.4 Hz and $J_{11a,11a'}$= 1.5 Hz, 11a), 5.26 (dd, 1H, $J_{11a',10}$= 10.5 Hz and $J_{11a',11a}$= 1.5 Hz, 11a'), 4.18-4.11 (m, 4H, 7 or 8 and 9), 3.83 (t, 2H, $J_{7,8}$ = 4.8 Hz, 8 or 7).
^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9 (6), 134.7 (10), 129.5 (2C, 1-4), 121.0 (1-4), 117.5 (11), 114.7 (2C, 1-4), 72.5 (9), 68.6 (7 or 8), 67.4 (8 or 7), 5 not observed.

IR (cm^{-1}): 3445, 3053, 3016, 3005, 2988, 2970, 2949, 2920 (C-H).

MS not found

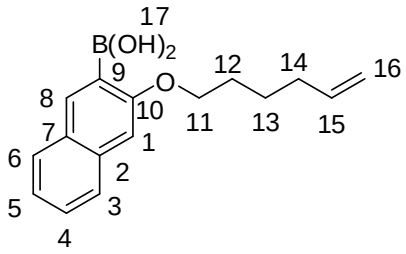
3.4.6. Characterization of 3-(hex-5-enyloxy)naphtalen-2-ylboronic acid (5f)

Chemical formula: $C_{16}H_{19}BO_3$
Molecular weight: 270.13 g.mol^{-1}

Purification conditions: flash chromatography with EA/cyclohexane 15:85

Yield: 75 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90-7.83 (m, 3H, 3,6,8), 7.55-7.53 (m, 1H, 4 or 5), 7.47-7.45 (m, 1H, 5 or 4), 7.28 (s, 1H, 1), 6.06-5.92 (m, 1H, 15), 5.22-5.10 (m, 2H, 16), 4.21 (t, 2H, *J* = 6.5 Hz, 11), 2.30-2.25 (m, 2H, 14), 2.02-1.95 (m, 2H, 12), 1.80-1.72 (m, 2H, 13).

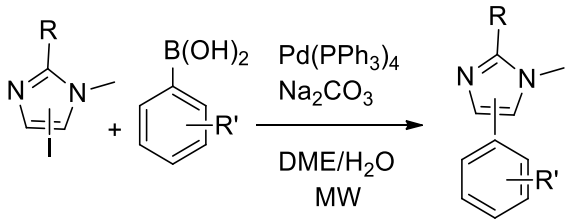
^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2 (10), 138.7 (15), 134.7 (2), 129.4 (8), 129.0 (7), 127.8 (6), 126.8 (3 or 4), 126.4 (4 or 3), 123.6 (5), 114.9 (16), 106.6 (1), 67.9 (11), 33.6 (14), 28.8 (12), 25.4 (13).

IR (cm^{-1}): 2980, 1709, 1626, 1240, 1153.

APCI-MS m/z (%): 83 (100), $[M]^{\cdot+}$ not found.

3.5. Suzuki coupling

3.5.1. General procedure



Tetrakis(triphenylphosphino)palladium (0.03 equiv.) with imidazole derivatives (R = alcoholate: 1 equiv. R = Cl: 1.1 equiv., 0.82 mmol) in dimethoxyethane (8 mL) were introduced in a microwave tube. Boronic acid (R = alcoholate: 1.1 equiv. R = Cl: 1 equiv.) in dimethoxyethane (8 mL) was then added. Finally, water (8 mL) and an aqueous solution of sodium carbonate (20%, 2.5 mmol, 3 equiv.) were added. The reaction was carried out under microwave heating: 200 W, 105°C, 1-2 hours. Ethyl acetate (100 mL) and water (50 mL) were added. The phases were separated and the aqueous phases were extracted with ethyl acetate (50 mL). The organic phases were collected, washed with brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography.

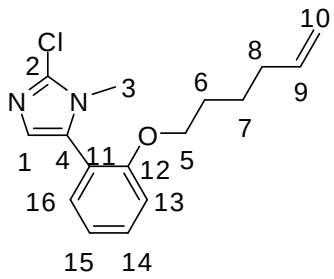
3.5.2. Characterization of 2-chloro-5-(2-(hex-5-enyloxy)phenyl)-1-methyl-1H-imidazole (2ap)

Chemical formula: $C_{16}H_{19}ClN_2O_2$
Molecular weight: 290.79 g.mol^{-1}

Purification conditions: flash chromatography with EA/cyclohexane 30:70

Yield: 54%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.36 (m, 1H, 12), 7.26-7.22 (m, 2H, 14 and 15), 7.02-6.95 (m, 1H, 16), 6.91 (s, 1H, 1), 5.81-5.70 (m, 1H, 9), 5.02-4.95 (m, 2H, 10), 3.97 (t, 2H, *J* = 6.5 Hz, 5), 3.42 (s, 3H, 3), 2.09-2.02 (m, 2H, 7), 1.75-1.67 (m, 2H, 6), 1.49-1.39 (m, 2H, 8).
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9 (2), 138.4 (9), 132.6 (12 or 11, 4), 132.4 (11 or 4, 12), 132.3 (13-16), 130.8 (13-16), 126.7 (1), 120.9 (13-16), 118.8 (4 or 11), 115.0 (10), 112.2 (13-16), 68.4 (5), 33.3 (8), 32.1 (3), 28.6 (6), 25.3 (7).

IR (cm^{-1}): 2930, 1736, 1470, 1373, 1240, 1124, 929, 912, 754, 336.

APCI-MS m/z (%): 291(100, ^{35}Cl) $[M+1]^+$, 293(35, ^{37}Cl) $[M+1]^+$, 209 (21), 149 (43).

HRMS calcd for $C_{16}H_{19}N_2OCl$: 290.11804, found 290.11931.

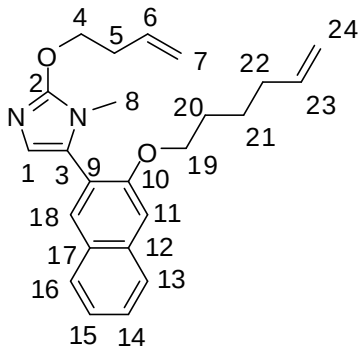
3.5.3. Characterization of 2-(but-3-enyloxy)-5-(3-(hex-5-enyloxy)naphtalen-2-yl)-1-methyl-1H-imidazole (2i)

Chemical formula: $C_{24}H_{28}N_2O_2$
Molecular weight: 376.49 g.mol^{-1}

Purification conditions: flash chromatography CH_2Cl_2/*i*-propanol 97:3

Yield: 88 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.72 (m, 3H, 13, 16, 18), 7.45 (dd, 1H, $J_{15,14\ et\ 15,16}$ = 7.9 Hz, $J_{15,13}$= 1.4 Hz, 15), 7.35 (dd, 1H, $J_{14,15\ et\ 14,13}$ = 7.9 Hz, $J_{14,16}$ = 1.4 Hz, 14), 7.18 (s, 1H, 11), 6.72 (s, 1H, 1), 5.96-5.75 (m, 2H, 6, 23), 5.30-4.96 (m, 4H, 7, 24), 4.47 (t, 2H, *J* = 6.7 Hz, 19), 4.09 (t, 2H, *J* = 6.6 Hz, 4), 3.28 (s, 3H, 8), 2.63-2.56 (m, 2H, 5), 2.13-2.06 (m, 2H, 22), 1.87-1.78 (m, 2H, 20), 1.57-1.47 (m, 2H, 21).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.5 (6 or 23), 134.4 (23 or 6), 131.3 (13-16 or 18), 127.8 (13-16 or 18), 126.8 (13-16 or 18), 126.5 (13-16 or 18), 124.2 (13-16 or 18), 122.3 (1), 117.3 (7 or 24), 115.0 (24 or 7), 106.6 (11), 68.6 (4 or 19), 68.3 (19 or 4), 33.7 (5 or 22), 33.4 (22 or 5), 29.6 (8), 28.6 (20), 25.4 (21).

IR (cm^{-1}): 2941, 1632, 1537, 1369, 1250, 1178, 1033, 709.

APCI-MS m/z (%): 377 (100) $[M+H]^+$.

HRMS calcd for $C_{24}H_{28}N_2O_2$: 376.21453, found 376.21461.

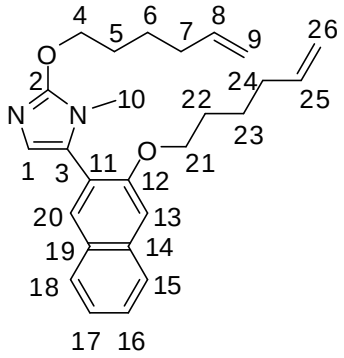
3.5.4. Characterization of 2-(hex-5-enyloxy)-5-(3-(hex-5-enyloxy)naphtalen-2-yl)-1-methyl-1H-imidazole (2k)

Chemical formula: $C_{26}H_{32}N_2O_2$
Molecular weight: 404.54 $g.mol^{-1}$

Purification conditions: flash chromatography CH_2Cl_2/*i*-propanol 97:3

Yield: 92 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77-7.72 (m, 3H, 15, 18, 20), 7.45 (ddd, 1H, $J_{17,16\ et\ 17,18}$ = 7.9 Hz, $J_{17,15}$ = 1.3 Hz, 17), 7.37 (ddd, 1H, $J_{16,17\ et\ 16,15}$ = 7.9 Hz, $J_{16,18}$ = 1.3 Hz, 16), 7.18 (s, 1H, 13), 6.72 (s, 1H, 1), 5.89-5.75 (m, 2H, 8, 25), 5.07-4.96 (m, 4H, 9, 26), 4.42 (t, 2H, *J* = 6.6 Hz, 21), 4.09 (t, 2H, *J* = 6.6 Hz, 4), 3.28 (s, 3H, 10), 2.16-2.08 (m, 4H, 7, 24), 1.88-1.80 (m, 4H, 5, 22), 1.61-1.50 (m, 4H, 6, 23).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2 (12), 153.8

(2), 138.6 (8 or 25), 138.5 (25 or 8), 134.6 (14), 131.2 (15-18 or 20), 128.7 (19), 127.8 (15-18 or 20), 126.8 (15-18 or 20), 126.5 (15-18 or 20, 3), 124.2 (15-18 or 20), 122.3 (1), 121.5 (11), 115.0 (9 or 26), 114.9 (26 or 9), 106.6 (13), 69.4 (4 or 21), 68.3 (21 or 4), 33.5 (7 or 24), 33.4 (24 or 7), 29.6 (10), 28.8 (5 or 22), 28.6 (22 or 5), 25.4 (6 or 23), 25.3 (23 or 6).

IR (cm^{-1}): 2939, 1537, 1458, 1250, 1178, 1032, 910, 862.

APCI-MS m/z (%): 405 (100) $[M+H]^+$, 323 (15).

HRMS calcd for $C_{26}H_{33}N_2O_2$: 405.2542, found 405.2536.

3.5.5. Characterization of 2-(but-3-en-yloxy)-5-[2-(hex-5-en-1-yloxy)phenyl]-1-methyl-1H-imidazole (2a)

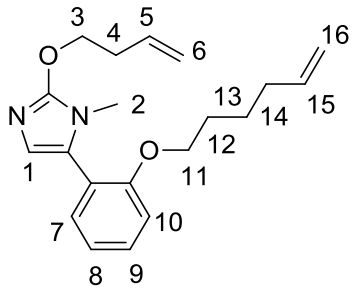
Chemical formula: $C_{20}H_{26}N_2O_2$
Molecular weight: 326.43 $g.mol^{-1}$

CAS Registry Number: 1236073-83-8

Purification conditions: flash chromatography EA/cyclohexane 15:85

Yield: 82%

Aspect: orange oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (td, 1H, *J* = 8.2 and 1.5 Hz, 7-10), 7.26-7.23 (m, 1H, 7-10), 7.00-6.93 (m, 2H, 7-10), 6.63 (s, 1H, 1), 5.95-5.73 (m, 2H, 5 and 15); 5.21-4.94 (m, 4H, 6 and 16); 4.48 (t, 2H, *J* = 6.7 Hz, 3 or 11), 3.97 (t, 2H, *J* = 6.6 Hz, 3 or 11), 3.25 (s, 3H, 2), 2.61-2.57 (m, 2H, 4), 2.10-2.03 (m, 2H, 14), 1.78-1.72 (m, 2H, 12), 1.49-1.42 (m, 2H, 13).

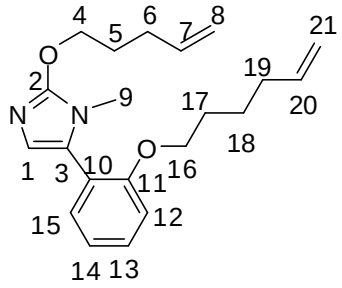
3.5.6. Characterization of 5-(2-(hex-5-enyloxy)phenyl)-1-methyl-2-(pent-4-enyloxy)-1H-imidazole (2b)

Chemical formula: $C_{21}H_{28}N_2O_2$
Molecular weight: 340.46 $g.mol^{-1}$

Purification conditions: flash chromatography CH_2Cl_2/*i*-propanol 97:3

Yield: 81%

Aspect: orange oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.23 (m, 2H, 12-14), 7.00-6.92 (m, 2H, 12-14), 6.61 (s, 1H, 1), 5.89-5.72 (m, 2H, 7, 20), 5.10-4.94 (m, 4H, 8, 21), 4.40 (t, 2H, *J* = 6.5 Hz, 4 or 16), 3.96 (t, 2H, *J* = 6.5 Hz, 16 or 4), 3.25 (s, 3H, 9), 2.28-2.20 (m, 2H, 5 or 6 or 17-19), 2.10-2.02 (m, 2H, 5 or 6 or 17-19), 1.97-1.87 (m, 2H, 5 or 6 or 17-19), 1.80-1.70 (m, 2H, 5 or 6 or 17-19), 1.52-1.42 (m, 2H, 5 or 6 or 17-19).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8 (2), 153.4 (11), 138.5 (7 or 20), 137.8 (20 or 7), 132.0 (12-15), 129.6 (12-15), 126.5 (3 or 10), 121.6 (1), 120.7 (12-15), 119.9 (10 or 3), 115.3 (8 or 21), 114.9 (21 or 8), 112.2 (12-15), 68.8 (4 or 16), 68.3 (16 or 4), 33.4 (5 or 6 or 17-19), 30.2 (5 or 6 or 17-19), 29.5 (9), 28.7 (5 or 6 or 17-19), 28.5 (5 or 6 or 17-19), 25.3 (5 or 6 or 17-19).

IR (cm^{-1}): 2941, 1537, 1496, 1244, 1009, 910, 752, 680.

APCI-MS m/z (%): 341 (56) $[M+H]^+$, 273 (100), 191 (26).

HRMS calcd for $C_{21}H_{29}N_2O_2$: 341.2229, found 341.2231.

3.5.7. Characterization of of 2-(hex-3-en-yloxy)-5-[2-(hex-5-en-1-yloxy)phenyl]-1-methyl-1H-imidazole (2c)

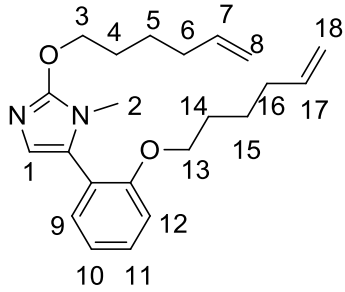
Chemical formula: $C_{20}H_{30}N_2O_2$
Molecular weight: 354.49 $g.mol^{-1}$

CAS Registry Number: 1236074-00-2

Purification conditions: flash chromatography EA/cyclohexane 15:85

Yield: 76%

Aspect: orange oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (td, 1H, *J* = 8.1 and 1.8 Hz, 9-12), 7.25 (dd, 1H, *J* = 8.1 and 1.8 Hz, 9-12), 6.97 (dt, 1H, *J* = 7.4 and 0.9 Hz, 9-12), 6.94 (d, 1H, *J* = 8.1 Hz, 9-12), 6.61 (s, 1H, 1), 5.90-5.71 (m, 2H, 7 and 17); 5.07-4.94 (m, 4H, 8 and 18); 4.38 (t, 2H, *J* = 6.7 Hz, 3 or 13), 3.97 (t, 2H, *J* = 6.6 Hz, 3or 13), 3.25 (s, 3H, 2), 2.18-2.02 (m, 4H, 4-6 and 14-16), 1.88-1.70 (m, 4H, 4-6 and 14-16), 1.62-1.42 (m, 4H, 4-6 and

14-16).

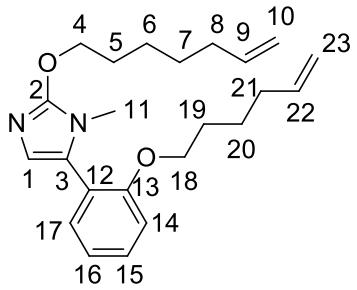
3.5.8. Characterization of 2-(hept-6-enyloxy)-5-(2-(hex-5-enyloxy)phenyl)-1-methyl-1H-imidazole (2d)

Chemical formula: $C_{23}H_{32}N_2O_2$
Molecular weight: 368.51 g.mol^{-1}

Purification conditions: flash chromatography CH_2Cl_2/*i*-propanol 97:3

Yield: 84%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.23 (m, 2H, 14-17), 7.00-6.92 (m, 2H, 14-17), 6.61 (s, 1H, 1), 5.86-5.73 (m, 2H, 9, 22), 5.04-4.93 (m, 4H, 10, 23), 4.38 (t, 2H, *J* = 6.6 Hz, 4 or 18), 3.96 (t, 2H, *J* = 6.6 Hz, 18 or 4), 3.25 (s, 3H, 11), 2.09-2.03 (m, 4H, 5-8 or 19-21), 1.85-1.70 (m, 4H, 5-8 or 19-21), 1.52-1.42 (m, 6H, 5-8 or 19-21).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8 (2), 153.5 (13), 138.9 (9 or 22), 138.5 (22 or 9), 132.0 (14-17), 129.6 (14-17), 126.4 (3 or 12), 121.6 (1), 120.7 (14-17), 120.0 (12 or 3), 114.9 (10 or 23), 114.5 (23 or 10), 112.2 (14-17), 69.4 (4 or 18), 68.4 (18 or 4), 33.7 (5-8 or 19-21), 33.4 (5-8 or 19-21), 29.4 (11), 29.1 (5-8 or 19-21), 2×28.7 (5-8 or 19-21), 25.5 (5-8 or 19-21), 25.3 (5-8 or 19-21).

IR (cm^{-1}): 2927, 1535, 1497, 1448, 1380, 1244, 1144, 995, 910, 752.

APCI-MS m/z (%): 369 (100) $[M+H]^+$, 273 (72), 191 (15).

HRMS calcd for $C_{23}H_{33}N_2O_2$: 369.2542, found 369.2536.

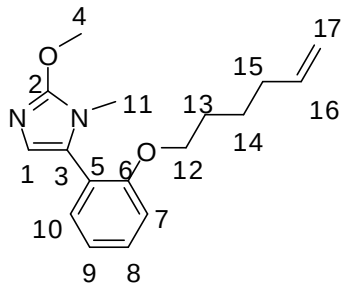
3.5.9. Characterization of 5-(2-(hex-5-enyloxy)phenyl)-2-methoxy-1-methyl-1H-imidazole (2r)

Chemical formula: $C_{17}H_{22}N_2O_2$
Molecular weight: 286.37 g.mol^{-1}

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 57 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.23 (m, 2H, 7-10), 7.00-6.93 (m, 2H, 7-10), 6.62 (s, 1H, 1), 5.84-5.71 (m, 1H, 16), 5.03-4.94 (m, 2H, 17), 4.07 (s, 3H, 4), 3.96 (t, 2H, *J* = 6.6 Hz, 12), 3.25 (s, 3H, 11), 2.10-2.03 (m, 2H, 15), 1.79-1.70 (m, 2H, 13), 1.52-1.42 (m, 2H, 14).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8 (2 or 6), 153.9 (6 or 2), 138.5 (16), 132.0 (7-10), 129.7 (7-10), 126.8 (3 or 5), 121.5 (7-10), 120.7 (7-10), 119.8 (5 or 3), 114.8 (17), 112.2 (7-10), 68.3 (12), 56.4 (4), 33.3 (15), 29.5 (11), 28.6 (13), 25.3 (14).

IR (cm^{-1}): 2937, 2361, 1545, 1244, 1013, 754, 652.

ESI-MS m/z (%): 287 (100) $[M+H]^+$.

HRMS calcd for $C_{17}H_{23}N_2O_2$: 287.1760, found 287.1767.

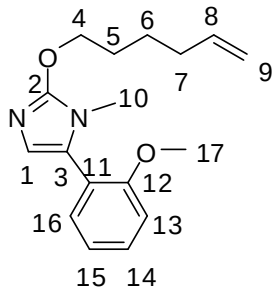
3.5.10. Characterization of 2-(hex-5-enyloxy)-5-(2-methoxyphenyl)-1-methyl-1H-imidazole (2q)

Chemical formula: $C_{17}H_{22}N_2O_2$
Molecular weight: 286.37 $g.mol^{-1}$

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 56 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.32 (m, 2H, 13-16), 7.00-6.93 (m, 2H, 13-16), 6.62 (s, 1H, 1), 5.88-5.79 (m, 1H, 8), 5.07-4.96 (m, 2H, 9), 4.39 (t, 2H, *J* = 6.6 Hz, 12), 3.81 (s, 3H, 17), 3.23 (s, 3H, 10), 2.18-2.11 (m, 2H, 7), 1.88-1.79 (m, 2H, 5), 1.62-1.55 (m, 2H, 6).

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2 (2 or 12), 153.5 (12 or 2), 138.6 (8), 132.0 (13-16), 129.7 (13-16), 126.3 (3 or 11), 121.5 (1), 120.8 (13-16), 119.6 (11 or 3), 114.8 (9), 110.8 (13-16), 69.3 (4), 55.4 (17), 33.5 (7), 29.3 (10), 28.7 (5), 25.3 (6).

IR (cm^{-1}): 2939, 2361, 1481, 1246, 1028, 754, 652.

ESI-MS m/z (%): 287 (100) $[M+H]^+$.

HRMS calcd for $C_{17}H_{23}N_2O_2$: 287.1760, found 287.1765.

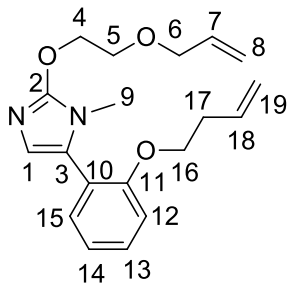
3.5.11. Characterization of 2-(2-(allyloxy)ethoxy)-5-(2-(but-3-en-1-yloxy)phenyl)-1-methyl-1H-imidazole (2am)

Chemical formula: $C_{19}H_{24}N_2O_3$
Molecular weight: 328.41 g.mol^{-1}

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 76 % not totally purified

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.24 (m, 2H, 12-15), 6.93-7.00 (m, 2H, 12-15), 6.61 (s, 1H, 1), 6.00-5.73 (m, 2H, 7 and 18), 5.34-5.05 (m, 4H, 8 and 19), 4.57-4.54 (m, 2H, 4-6 or 16), 4.09-3.99 (m, 4H, 4-6 or 16), 3.85-3.82 (m, 2H, 4-6 or 16), 3.28 (s, 3H, 9), 2.51-2.45 (m, 2H, 17).
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.6 (2 or 11), 153.1 (11 or 2), 134.6 (7 or 18), 134.3 (18 or 7), 132.1 (12-15), 129.6 (12-15), 126.6 (3 or 10), 121.4 (1), 120.8 (12-15), 119.8 (10 or 3), 117.3 (2C, 8,19), 112.2 (12-15), 72.2 (4), 68.7 (5 or 6,16) , 68.5 (5 or 6,16), 67.7 (5 or 6,16), 33.7 (17), 29.6 (9).

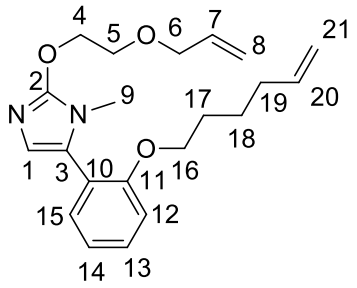
3.5.12. Characterization of 2-(2-(allyloxy)ethoxy)-5-(2-(hex-5-enyloxy)phenyl)-1-methyl-1H-imidazole (2ab)

Chemical formula: $C_{21}H_{28}N_2O_3$
Molecular weight: 356.46 g.mol^{-1}

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 72 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.22 (m, 2H, 12-15), 6.97-6.92 (m, 2H, 12-15), 6.61 (s, 1H, 1), 5.99-5.73 (m, 2H, 7 and 20), 5.35-5.19 (m, 2H, 8 or 21), 5.03-4.94 (m, 2H, 21 or 8), 4.56 (t, 2H, *J* = 4.6 Hz, 4-6 or 16), 4.09-4.08 (m, 2H, 4-6 or 16), 3.96 (t, 2H, *J* = 6.6 Hz, 4-6 or 16), 3.85-3.82 (m, 2H, 4-6 or 16), 3.28 (s, 3H, 9), 2.10-2.03 (m, 2H, 19), 1.80-1.70 (m, 2H, 17),

1.52-1.42 (m, 2H, 18).
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.9 (2 or 11), 153.2 (11 or 2), 138.5 (7 or 20), 134.7 (20 or 7), 132.1 (12-15), 129.7 (12-15), 126.7 (3 or 10), 121.6 (1), 120.7 (12-15), 119.8 (10 or 3), 117.4 (8 or 21), 114.9 (21 or 8), 112.2 (12-15), 72.2 (4), 68.8 (5 or 6,16) , 68.5 (5 or 6,16), 68.4 (5 or 6,16), 33.3 (19), 29.6 (9), 28.7 (17), 25.3 (18).

IR (cm^{-1}): 663, 754, 1146, 1244, 1450, 1537, 2939 cm^{-1};

APCI-MS m/z (%): 357 (100) $[M+H]^+$.

HRMS calcd for $C_{21}H_{29}N_2O_3$: 357.2178, found 357.2167.

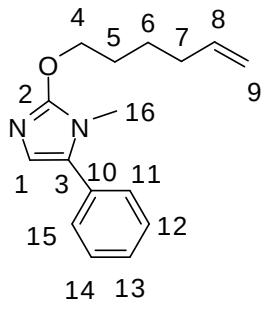
3.5.13. Characterization of 2-(hex-5-enyloxy)-1-methyl-5-phenyl-1H-imidazole (2w)

Chemical formula: $C_{16}H_{20}N_2O$
Molecular weight: 256.34 $g.mol^{-1}$

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 81 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.30 (m, 5H, 11-15), 6.68 (s, 1H, 1), 5.88-5.79 (m, 1H, 8), 5.07-4.96 (m, 2H, 9), 4.39 (t, 2H, *J* = 6.6 Hz, 4), 3.41 (s, 3H, 16), 2.18-2.11 (m, 2H, 7), 1.86-1.81 (m, 2H, 5), 1.60-1.55 (m, 2H, 6).
^{13}C NMR (75 MHz, $CDCl_3$): δ 154 (2), 138.6 (8), 130.6 (3 or 10), 129.6 (3 or 10), 128.8 (2C, 11,15 or 12,14), 128.0 (2C, 11,15 or 12,14), 127.4 (13), 121.1 (1), 115.0 (9), 69.6 (4), 33.5 (7), 29.7 (16), 28.7 (5), 25.3 (6).

IR (cm^{-1}): 2941, 1537, 1495, 1379, 1148, 760, 700, 652.

APCI-MS m/z (%): 257 (100) $[M+H]^+$.

HRMS calcd for $C_{16}H_{21}N_2O$: 257.16484, found 257.16500.

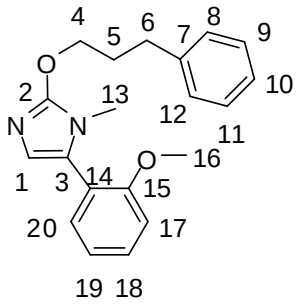
3.5.14. Characterization of 5-(2-methoxyphenyl)-1-methyl-2-(3-phenylpropoxy)-1H-imidazole (2x)

Chemical formula: $C_{20}H_{22}N_2O_2$
Molecular weight: 322.40 $g.mol^{-1}$

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 91 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.19 (m, 8H, 8-12 and 17-20), 7.00-6.93 (m, 2H, 8-12 and 17-20), 6.61 (s, 1H, 1), 4.43 (t, 2H, *J* = 6.5 Hz, 4), 3.81 (s, 3H, 16), 3.22 (s, 3H, 13), 2.80 (t, 2H, *J* = 7.7 Hz, 6), 2.20-2.10 (m, 4H, 5).

^{13}C NMR (75 MHz, $CDCl_3$): δ157.3 (16), 153.4 (2), 141.6 (7), 132.1 (10 or 18-20), 129.8 (10 or 18-20), 128.5 (4C, 8-9 and 11-12), 126.3 (14 or 3), 126.0 (10 or 18-20), 121.5 (1), 120.8 (10 or 18-20), 119.6 (3 or 14), 110.9 (17), 68.8 (4), 55.5 (16), 32.3 (5-6), 30.9 (5-6), 29.3 (13).

IR (cm^{-1}): 2949, 1531, 1497, 1493, 1379, 1300, 1142, 1055, 754, 700.

APCI-MS m/z (%): 323 (100) $[M+H]^+$, 205 (27).

HRMS calcd for $C_{20}H_{23}N_2O_2$: 323.1754, found: 323.17544.

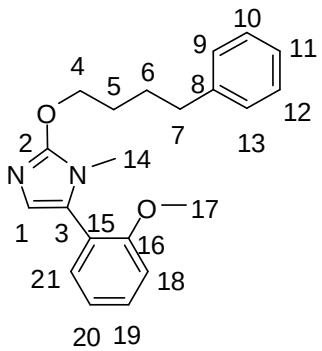
3.5.15. Characterization of 5-(2-methoxyphenyl)-1-methyl-2-(4-phenylbutoxy)-1H-imidazole (2y)

Chemical formula: $C_{21}H_{24}N_2O_2$
Molecular weight: 336.43 $g.mol^{-1}$

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 85 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.19 (m, 8H, 9-13 and 18-21), 7.02-6.94 (m, 2H, 9-13 and 18-21), 6.61 (s, 1H, 1), 4.41 (t, 2H, *J* = 6.2 Hz, 4), 3.81 (s, 3H, 17), 3.22 (s, 3H, 14), 2.70 (t, 2H, *J* = 7.3 Hz, 7), 1.88-1.79 (m, 4H, 5,6).

^{13}C NMR (75 MHz, $CDCl_3$): δ157.3 (16), 153.3 (2), 142.3 (8), 132.2 (11 or 19-21), 130.0 (11 or 19-21), 128.6 (2C, 10,12 or 9,13), 128.5 (2C, 10,12 or 9,13), 126.5 (15 or 3), 125.9 (11 or 19-21), 121.0 (1), 120.9 (11 or 19-21), 119.4 (3 or 15), 110.9 (18),

69.7 (4), 55.5 (17), 35.6 (5-7), 29.3 (14), 28.9 (5-7), 27.8 (5-7).

IR (cm^{-1}): 2941, 1582, 1537, 1495, 1379, 1246, 1142, 1028, 754, 700.

APCI-MS m/z (%): 337 (100) $[M+H]^+$, 205 (7), 79 (79).

HRMS calcd for $C_{21}H_{25}N_2O_2$: 337.19105, found 337.19105.

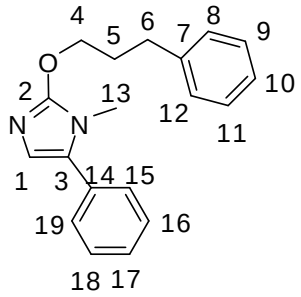
3.5.16. Characterization of 1-methyl-5-phenyl-2-(3-phenylpropoxy)-1H-imidazole (2z)

Chemical formula: $C_{19}H_{20}N_2O$
Molecular weight: 292.37 $g.mol^{-1}$

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 68 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.23 (m, 10H, 8-12 and 15-19), 6.68 (s, 1H, 1), 4.43 (t, 2H, *J* = 6.5 Hz, 4), 3.38 (s, 3H, 13), 2.80 (t, 2H, *J* = 7.7 Hz, 6), 2.20-2.10 (m, 2H, 5).

^{13}C NMR (75 MHz, $CDCl_3$): δ153.9 (2), 141.5 (7), 130.7 (3 or 14), 129.6 (14 or 3), 128.8 (2C, 8,12 or 9,11; 15,19; 16,18), 128.5(4c, 8,12 or 9,11; 15,19; 16,18), 127.9 (2C, 8,12 or 9,11; 15,19; 16,18), 127.3 (10 or 17), 126.1 (10 or 17), 121.2 (1), 69.0 (4), 32.3 (6 or 5), 30.8 (5 or 6), 29.6 (13).

IR (cm^{-1}): 2950, 1537, 1497, 1379, 1148, 1013, 762, 700, 652.

APCI-MS m/z (%): 293 (100) $[M+H]^+$, 79 (23).

HRMS calcd for $C_{19}H_{21}N_2O$: 293.16484, found 293.16539.

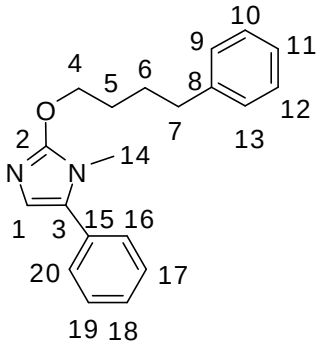
3.5.17. Characterization of 1-methyl-5-phenyl-2-(4-phenylbutoxy)-1H-imidazole (2aa)

Chemical formula: $C_{20}H_{22}N_2O$
Molecular weight: 306.40 $g.mol^{-1}$

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 72 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.22 (m, 10H, 9-13 and 16-20), 6.73 (s, 1H, 1), 4.46 (t, 2H, *J* = 6.2 Hz, 4), 3.43 (s, 3H, 14), 2.74 (t, 2H, *J* = 7.2 Hz, 7), 1.91-1.84 (m, 4H, 5-6).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0 (2), 142.2 (8), 130.7 (3 or 15), 129.5 (15 or 3), 128.8 (2C, 9,13 or 10,12 or 16,20, 17,19), 128.5 (2C, 9,13 or 10,12 or 16,20, 17,19), 128.4 (2C, 9,13 or 10,12 or 16,20, 17,19), 127.9 (2C, 9,13 or 10,12 or 16,20, 17,19), 127.3 (11 or 18), 125.9 (11 or 18), 121.2 (1), 69.4 (4), 35.6 (5-7), 29.6 (14), 28.8 (5-7), 27.8 (5-7).

IR (cm^{-1}): 2943, 1537, 1494, 1379, 1145, 759, 698, 651.

APCI-MS m/z (%): 307 (100) $[M+H]^+$, 175 (61).

HRMS calcd for $C_{20}H_{23}N_2O$: 307.18049, found 307.18066.

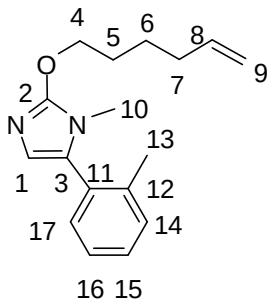
3.5.18. Characterization of 2-(hex-5-en-1-yloxy)-1-methyl-5-(o-tolyl)-1H-imidazole (2ac)

Chemical formula: $C_{17}H_{22}N_2O$
Molecular weight: 270.37 $g.mol^{-1}$

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 71%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.19 (m, 4H, 14-17), 6.52 (s, 1H, 1), 5.90-5.76 (m, 1H, 8), 5.07-4.96 (m, 2H, 9), 4.38 (t, 2H, *J* = 6.5 Hz, 4), 3.15 (s, 3H, 10), 2.23 (s, 3H, 13), 2.18-2.10 (m, 2H, 7), 1.88-1.78 (m, 2H, 5), 1.62-1.52 (m, 2H, 6).

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.2 (2), 138.6 (8), 138.3 (12), 131.4 (14-17), 130.3 (14-17), 129.8 (10 or 11), 128.6 (14-17), 127.9 (10 or 11), 125.8 (14-17), 121.2 (3), 114.9 (9), 69.5 (4), 33.5 (7), 28.8 (10), 28.7 (5), 25.3 (6), 20.2 (13).

IR (cm^{-1}):.2945, 1541, 1494, 1379, 1142, 1008, 762.

APCI-MS m/z (%): 271 (100) $[M+H]^+$, 189 (15).

HRMS calcd for $C_{17}H_{23}N_2O$: 271.18049, found 271.18060.

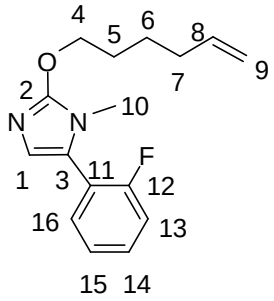
3.5.19. Characterization of 5-(2-fluorophenyl)-2-(hex-5-en-1-yloxy)-1-methyl-1H-imidazole (2ad)

Chemical formula: $C_{16}H_{19}FN_2O$
Molecular weight: 274.33 g.mol^{-1}

Purification conditions: flash chromatography with CH_2Cl_2/*i*-propanol 97:03

Yield: 80%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.28 (m, 2H, 13-16), 7.20-7.10 (m, 2H, 13-16), 6.70 (s, 1H, 1), 5.90-5.76 (m, 1H, 8), 5.07-4.96 (m, 2H, 9), 4.40 (t, 2H, J = 5.9 Hz, 4), 3.31 (s, 3H, 10), 2.18-2.10 (m, 2H, 7), 1.89-1.78 (m, 2H, 5), 1.63-1.53 (m, 2H, 6).
^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0 (12, $J_{C\text{-}F}$ = 247.5 Hz), 154.0 (2), 138.5 (8), 131.6 (16, $J_{C\text{-}F}$ = 2.7 Hz), 129.8 (14, $J_{C\text{-}F}$ = 8.1 Hz), 124.4 (15, $J_{C\text{-}F}$ = 3.5 Hz), 123.5 (3), 122.6 (1), 118.4 (11, $J_{C\text{-}F}$ = 15.2 Hz), 115.9 (13, $J_{C\text{-}F}$ = 22.1 Hz), 114.9 (9), 33.4 (7), 29.4 (10), 29.6 (5), 25.2 (6).
^{19}F NMR (282 MHz, $CDCl_3$): δ -114.8.

IR (cm^{-1}): 2945, 1537, 1494, 1379, 1236, 1218, 1148, 1010, 912, 760.

APCI-MS m/z (%): 275 (100) $[M+H]^+$, 193 (19).

HRMS calcd for $C_{16}H_{20}FN_2O$: 275.15542, found 275.15584.

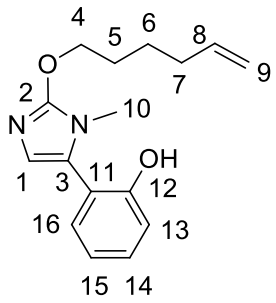
3.5.20. Characterization of 2-(2-(hex-5-en-1-yloxy)-1-methyl-1H-imidazol-5-yl)phenol (2ae)

Chemical formula: $C_{16}H_{20}N_2O_2$
Molecular weight: 272.34 g.mol^{-1}

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 60%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.24 (m, 1H, 13-16), 7.17-7.15 (m, 1H, 13-16), 7.04-7.01 (m, 1H, 13-16), 6.94-6.88 (m, 1H, 13-16), 6.59 (s, 1H, 1), 5.84-5.76 (m, 1H, 8), 5.04-4.92 (m, 2H, 9), 4.36-4.29 (m, 2H, 4), 3.28 (s, 3H, 10), 2.11-2.05 (m, 2H, 7), 1.81-1.72 (m, 2H, 5), 1.55-1.49 (m, 2H, 6).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4 (12) 153.7 (2), 138.5 (8), 131.6 (13-16), 130.2 (13-16), 125.0 (3 or 11), 121.4 (1), 117.1 (3 or 11), 116.1 (13-16), 114.9 (9), 69.7 (4), 33.2 (7), 29.2 (10), 28.6 (5), 25.2 (6).

IR (cm^{-1}): 2933, 1740, 1589, 1529, 1452, 1380, 1248, 1144, 997, 912, 756.

APCI-MS m/z (%): 273 (100) $[M+H]^+$, 181 (20), 99 (21).

HRMS calcd for $C_{16}H_{21}N_2O_2$: 273.15975, found 273.15957.

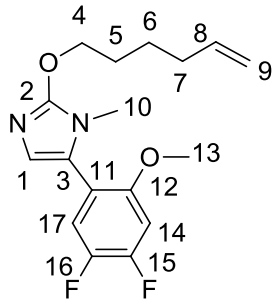
3.5.21. Characterization of 5-(4,5-difluoro-2-methoxyphenyl)-2-(hex-5-en-1-yloxy)-1-methyl-1H-imidazole (2ak)

Chemical formula: $C_{17}H_{20}F_2N_2O_2$
Molecular weight: 322.35 $g.mol^{-1}$

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 75%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11-7.05 (m, 1H, 14 or 17), 6.80-6.74 (m, 1H, 14 or 17), 6.60 (s, 1H, 1), 5.90-5.76 (m, 1H, 8), 5.07-4.96 (m, 2H, 9), 4.38 (t, 2H, J = 6.6 Hz, 4), 3.79 (s, 3H, 13), 3.22 (s, 3H, 10), 2.18-2.11 (m, 2H, 7), 1.88-1.79 (m, 2H, 5), 1.62-1.52 (m, 2H, 6).

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7 (2 or 12), 153.6 (2 or 12), 150.5 ($J_{C\text{-}F}$ = 248.0 and 13.6 Hz, 15 or 16), 144.1 ($J_{C\text{-}F}$ = 240.0 and 12.6 Hz, 15 or 16), 138.5 (8), 124.0 (3 or 11), 122.2 (1), 120.2 ($J_{C\text{-}F}$ = 18.6 Hz, 17 or 14), 115.5 (3 or 11), 114.9 (9), 101.2 ($J_{C\text{-}F}$ = 21.2 Hz, 17,14), 69.4 (4), 33.4 (7), 29.2 (10), 28.6 (5), 25.2 (6).

^{19}F NMR (282 MHz, $CDCl_3$): δ -134.8 (d, J = 22.5 Hz), -148.6 (d, J = 22.5 Hz).

IR (cm^{-1}): 2939, 1535, 1492, 1414, 1321, 1205, 1144, 1034, 815.

APCI-MS m/z (%): 323 (100) $[M+H]^+$, 241 (13).

HRMS calcd for $C_{17}H_{21}F_2N_2O_2$: 323.15656, found 323.15651.

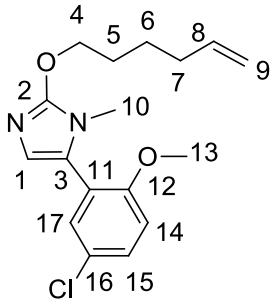
3.5.22. Characterization of 5-(5-chloro-2-methoxyphenyl)-2-(hex-5-en-1-yloxy)-1-methyl-1H-imidazole (2ag)

Chemical formula: $C_{17}H_{21}ClN_2O_2$
Molecular weight: 320.81 $g.mol^{-1}$

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 79%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.22 (m, 2H, 14-15), 6.88-6.85 (m, 1H, 17), 6.63 (s, 1H, 1), 5.90-5.76 (m, 1H, 8), 5.07-4.96 (m, 2H, 9), 4.39 (t, 2H, *J* = 6.6 Hz, 4), 3.80 (s, 3H, 13), 3.23 (s, 3H, 10), 2.18-2.10 (m, 2H, 7), 1.88-1.79 (m, 2H, 5), 1.62-1.52 (m, 2H, 6).
^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9 (2 or 12) 153.7 (2 or 12), 138.5 (8), 131.5 (17 or 14,15), 129.1 (17 or 14,15), 125.6 (3 or 11, 16), 125.0 (3 or 11, 16), 122.2 (1), 121.2 (3 or 11, 16), 114.9 (9), 112.0 (17 or 14,15), 69.4 (4), 55.8 (13), 33.4 (7), 29.4 (10), 28.6 (5), 25.3 (6).

IR (cm^{-1}): 2939, 1575, 1494, 1379, 1246, 1142, 1028, 912, 810, 712.

APCI-MS m/z (%): 321 (100, ^{35}Cl) $[M+H]^+$., 323 (32, ^{37}Cl) $[M+H]^+$, 239 (13).

HRMS calcd for $C_{17}H_{22}ClN_2O_2$: 321.13643, found 321.13656.

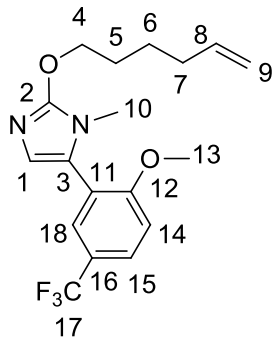
3.5.23. Characterization of 2-(hex-5-en-1-yloxy)-5-(2-methoxy-5-(trifluoromethyl)phenyl)-1-methyl-1H-imidazole (2aj)

Chemical formula: $C_{18}H_{21}F_3N_2O_2$
Molecular weight: 354.37 $g.mol^{-1}$

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 74%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, 2H, *J* = 6.0 Hz, 14-15), 7.26 (d, 2H, *J* = 6.0 Hz, 14-15), 6.68 (s, 1H, 1), 5.90-5.77 (m, 1H, 8), 5.08-5.00 (m, 2H, 9), 4.40 (t, 2H, *J* = 6.6 Hz, 4), 3.88 (s, 3H, 13), 3.26 (s, 3H, 10), 2.18-2.11 (m, 2H, 7), 1.89-1.80 (m, 2H, 5), 1.63-1.53 (m, 2H, 6).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.2 (2 or 12) 154.1 (2 or 12), 138.5 (8), 132.0 (14), 131.5 (J_{C-F} = 32.3 Hz, 16), 125.0 (3 or 11), 124.0 (J_{C-F} = 270.9 Hz, 17), 122.8 (3 or 11), 117.7 (J_{C-F} = 3.8 Hz, 15 or 18), 114.9 (9), 107.7 (J_{C-F} = 3.7 Hz, 15 or 18), 69.5 (4), 55.7 (13), 33.5 (7), 29.8 (10), 28.6 (5), 25.3 (6).

^{19}F NMR (282 MHz, $CDCl_3$): δ -63.1 (3F).

IR (cm^{-1}): 2914, 1537, 1413, 1329, 1242, 1126, 1032, 885, 741.

APCI-MS m/z (%): 355 (100) $[M+H]^+$.

HRMS calcd for $C_{17}H_{22}ClN_2O_2$: 355.16279, found 355.16267.

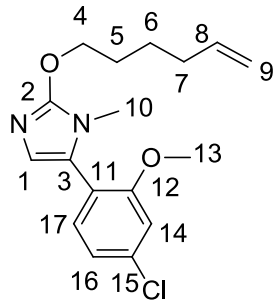
3.5.24. Characterization of 5-(4-chloro-2-methoxyphenyl)-2-(hex-5-en-1-yloxy)-1-methyl-1H-imidazole (2ah)

Chemical formula: $C_{17}H_{21}ClN_2O_2$
Molecular weight: 320.81 $g.mol^{-1}$

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 82%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-7.15 (m, 1H, 14), 7.00-6.93 (m, 2H, 16-17), 6.60 (s, 1H, 1), 5.90-5.76 (m, 1H, 8), 5.07-4.95 (m, 2H, 9), 4.39 (t, 2H, *J* = 6.6 Hz, 4), 3.81 (s, 3H, 13), 3.22 (s, 3H, 10), 2.17-2.10 (m, 2H, 7), 1.88-1.78 (m, 2H, 5), 1.62-1.52 (m, 2H, 6).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.8 (2 or 12) 153.7 (2 or 12), 138.5 (8), 135.1 (15), 132.6 (14, 16 or 17), 125.2 (3 or 11), 121.9 (1), 120.9 (14, 16 or 17), 118.2 (3 or 11), 114.8 (9), 111.7 (14, 16 or 17), 69.3 (4), 55.7 (13), 33.4 (7), 29.3 (10), 28.6 (5), 25.2 (6).

IR (cm^{-1}): 2939, 1531, 1494, 1402, 1379, 1248, 1145, 1029, 870.

APCI-MS m/z (%): 321 (100, ^{35}Cl) $[M+H]^+$, 323 (32, ^{37}Cl) $[M+H]^+$.

HRMS calcd for $C_{17}H_{22}ClN_2O_2$: 321.13643, found 321.13641.

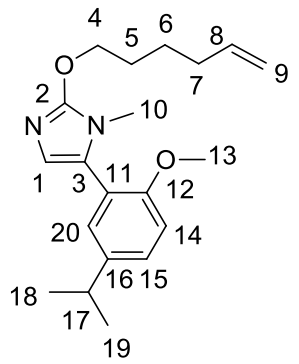
3.5.25. Characterization of 2-(hex-5-en-1-yloxy)-5-(5-isopropyl-2-methoxyphenyl)-1-methyl-1H-imidazole (2af)

Chemical formula: $C_{20}H_{28}N_2O_2$
Molecular weight: 328.45 $g.mol^{-1}$

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 93%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (dd, 1H, $J_{15\text{-}14}$ = 9.0 Hz and $J_{15\text{-}20}$= 3.0 Hz, 15), 7.12 (d, 1H, $J_{20\text{-}15}$ = 3.0 Hz, 20), 6.88 (d, 1H, $J_{14\text{-}15}$= 9.0 Hz, 14), 6.63 (s, 1H, 1), 5.90-5.76 (m, 1H, 8), 5.07-4.95 (m, 2H, 9), 4.40 (t, 2H, J = 6.6 Hz, 4), 3.79 (s, 3H, 13), 3.24 (s, 3H, 10), 2.92-2.83 (m, 1H, 17), 2.18-2.10 (m, 2H, 7), 1.88-1.79 (m, 2H, 5), 1.62-1.52 (m, 2H, 6), 1.25-1.22 (m, 6H, 18-19).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3 (2 or 12) 153.4 (2 or 12), 141.3 (16), 138.6 (8), 130.2 (20,14 or 15), 127.4 (20, 14 or 15), 126.7 (3 or 11), 121.3 (1), 119.3 (3 or 11), 114.8 (9), 110.7 (20, 14 or 15), 69.3 (4), 55.5 (13), 33.5 (7), 33.4 (17), 29.3 (10), 28.6 (5), 25.2 (6), 24.2 (2C, 18-19).

IR (cm^{-1}): 2957, 1537, 1489, 1246, 1028, 910, 814.

APCI-MS m/z (%): 329 (100) $[M+H]^+$.

HRMS calcd for $C_{20}H_{29}N_2O_2$: 329.22235, found 329.22235.

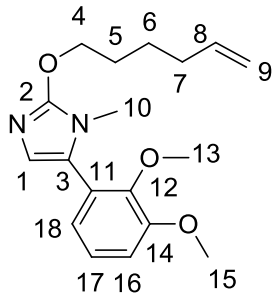
3.5.26. Characterization of 5-(2,3-dimethoxyphenyl)-2-(hex-5-en-1-yloxy)-1-methyl-1H-imidazole (2ai)

Chemical formula: $C_{18}H_{24}N_2O_3$
Molecular weight: 316.39 $g.mol^{-1}$

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 81%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08-7.03 (m, 1H, 16-18), 6.94-6.83 (m, 2H, 16-18), 6.62 (s, 1H, 1), 5.97-5.74 (m, 1H, 8), 5.05-4.93 (m, 2H, 9), 4.37 (t, 2H, *J* = 6.6 Hz, 4), 3.88 (s, 3H, 13 or 15), 3.58 (s, 3H, 13 or 15), 3.26 (s, 3H, 10), 2.16-2.08 (m, 2H, 7), 1.86-1.77 (m, 2H, 5), 1.60-1.50 (m, 2H, 6).

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7 (2 or 13,14) 153.0 (2 or 13,14), 145.0 (2 or 13,14), 138.5 (8), , 125.9 (3 or 11), 125.0 (3 or 11), 124.3 (16-18), 123.7 (16-18), 121.5 (1), 114.9 (9), 112.4 (16-18), 69.4 (4), 60.4 (13 or 15), 55.9 (13 or 15), 33.4 (7), 29.5 (10), 28.7 (5), 25.3 (6).

IR (cm^{-1}): 2931, 2382, 1535, 1263, 1028, 1005, 791.

APCI-MS m/z (%): 317 (100) $[M+H]^+$.

HRMS calcd for $C_{18}H_{25}N_2O_3$: 317.18597, found 317.18594.

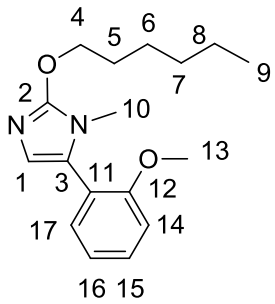
3.5.27. Characterization of 2-(hexyloxy)-5-(2-methoxyphenyl)-1-methyl-1H-imidazole (2t)

Chemical formula: $C_{16}H_{21}N_2O_2$
Molecular weight: 288.38 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 30:70

Yield: 63%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.32 (m, 1H, 17), 7.26-7.25 (m, 1H, 14-16), 7.00-6.93 (m, 2H, 14-16), 6.62 (s, 1H, 1), 4.41-4.38 (m, 2H, 4), 3.91 (s, 3H, 13), 3.23 (s, 3H, 10), 1.85-1.75 (m, 2H, 5), 1.47-1.41 (m, 2H, 6), 1.38-1.24 (m, 4H, 7-8), 0.91-0.87 (m, 3H, 9).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.5 (12), 153.8 (2), 126.4 (3 or 11), 121.5 (1), 119.6 (11 or 3), 132.2 (14-17), 129.8 (14-17), 120.8 (14-17), 110.9 (14-17), 69.8 (4), 55.6 (13), 29.3 (5-8), 31.9 (5-8), 29.2 (10), 25.7 (5-8), 22.7 (5-8), 14.2 (9).

IR (cm^{-1}): 2930, 1537, 1497, 1466, 1379, 1246, 1144, 1028, 754.

APCI-MS m/z (%): 289 (100) $[M+H]^+$, 205 (6).

HRMS calcd for $C_{17}H_{25}N_2O_2$: 289.1910, found 289.1913.

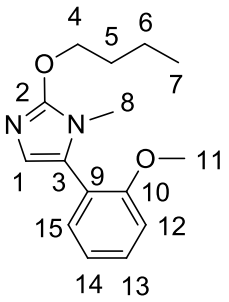
3.5.28. Characterization of 2(butoxy)-5-(2-methoxyphenyl)-1-methyl-1H-imidazole (2s)

Chemical formula: $C_{15}H_{20}N_2O_2$
Molecular weight: 260.33 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 40:60

Yield: 29%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.32 (m, 1H, 15), 7.33-7.24 (m, 1H, 12-14), 7.01-6.93 (m, 2H, 12-14), 6.62 (s, 1H, 1), 4.39 (t, 2H, *J* = 6.6 Hz, 4), 3.82 (s, 3H, 11), 3.23 (s, 3H, 8), 1.84-1.75 (m, 2H, 5), 1.56-1.43 (m, 2H, 6), 0.98 (t, 3H, *J* = 7.4 Hz, 7).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3 (10), 153.6 (2), 126.4 (3 or 9), 121.4 (1), 119.6 (9 or 3), 132.2 (12-15), 129.8 (12-15), 120.9 (12-15), 110.9 (12-15), 69.5 (4), 55.5 (11), 31.4 (), 29.9 (5-8), 19.3 (5-8), 14.0 (7).

IR (cm^{-1}): 2957, 1537, 1497, 1466, 1377, 1246, 1028, 754.

APCI-MS m/z (%): 261 (100) $[M+H]^+$.

HRMS calcd for $C_{15}H_{21}N_2O_2$: 261.1597, found 261.1599.

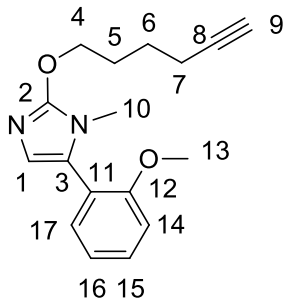
3.5.29. Characterization of 2-(hex-5-yn-yloxy)-5-(2-methoxyphenyl)-1-methyl-1H-imidazole (2u)

Chemical formula: $C_{17}H_{20}N_2O_2$
Molecular weight: 284.35 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 30:70

Yield: 32%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.32 (m, 1H, 17), 7.24-7.23 (m, 1H, 14-16), 7.01-6.93 (m, 2H, 14-16), 6.61 (s, 1H, 1), 4.41 (t, 2H, *J* = 6.3 Hz, 4), 3.82 (s, 3H, 13), 3.23 (s, 3H, 10), 2.28 (td, 2H, *J* = 7.0 and 2.6 Hz, 7), 1.98-1.91 (m, 3H, 9 and 5or 6), 1.74-1.69 (m, 2H, 5 or 6).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.4 (12), 153.2 (2), 126.6 (3 or 11), 121.3 (1), 119.7 (11 or 3), 132.4 (14-17), 130.0 (14-17), 120.9 (14-17), 110.9 (14-17), 84.1 (17), 69.1 (4), 68.8 (8), 55.4 (13), 29.5 (10), 28.3 (5-7), 25.3 (5-7), 18.3 (5-7).

IR (cm^{-1}): 2949, 1539, 1497, 1481, 1435, 1246, 1142, 1028, 754.

APCI-MS m/z (%): 285 (100) $[M+H]^+$, 101 (39).

HRMS calcd for $C_{17}H_{21}N_2O_2$: 285.1597, found 298.1593.

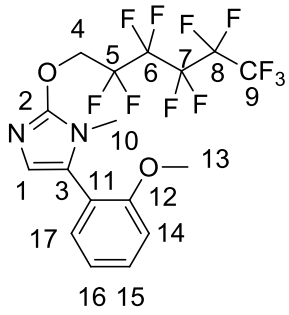
3.5.30. 5-(2-methoxyphenyl)-1-methyl-2-((2,2,3,3,4,4,5,5,6,6,6-undecafluorohexyl)oxy)-1H-imidazole (2v)

Chemical formula: $C_{17}H_{13}F_{11}N_2O_2$
Molecular weight: 486.28 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 30:70

Yield: 40%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.36 (m, 1H, 17), 7.27-7.24 (m, 1H, 14-16), 7.03-6.95 (m, 2H, 14-16), 6.62 (s, 1H, 1), 4.92 (t, 2H, *J* = 13.2 Hz, 4), 3.83 (s, 3H, 13), 3.27 (s, 3H, 10).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.5 (12), 151.4 (2), 127.8 (3 or 11), 121.4 (1), 118.9 (11 or 3), 132.4 (14-17), 130.3 (14-17), 121.9 (14-17), 110.9 (14-17), 65.2 (t, J_{C-F} = 26.8 Hz, 4), 55.5 (13), 29.5 (10).

^{19}F NMR (282 MHz, CDF_3): *δ* -81.3 (9), -120.5 (5 or 8), -123.4 (6 or 7), -123.9 (6 or 7), -126.7 (5 or 8).

IR (cm^{-1}): 2972, 1533, 1398, 1194, 1142, 1016, 808, 754.

APCI-MS m/z (%): 487 (100) $[M+H]^+$.

HRMS calcd for $C_{17}H_{21}N_2O_2$: 487.0874, found 487.0870.

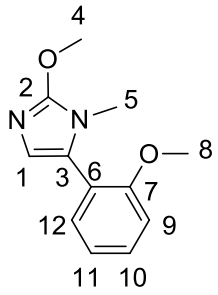
3.5.31. Characterization of 2-methoxy-5-(2-methoxyphenyl)-1-methyl-1H-imidazole (2o)

Chemical formula: $C_{12}H_{14}N_2O_2$
Molecular weight: 218.10 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 30:70

Yield: 72%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.33 (m, 1H, 12), 7.26-7.24 (m, 1H, 9-11), 7.02-6.92 (m, 2H, 9-11), 6.63 (s, 1H, 1), 4.08 (s, 3H, 4), 3.82 (s, 3H, 8), 3.23 (s, 3H, 5).

^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3 (7), 153.8 (2), 127.8 (3 or 11), 132.3 (1), 129.7 (3 or 6), 126.6 (9-12), 121.4 (9-12), 120.7 (9-12), 119.4 (9-12), 110.7 (3 or 6), 56.6 (4), 55.4 (8), 29.2 (5).

IR (cm^{-1}): 1531, 1246, 1013, 754, 663.

APCI-MS m/z (%): 219 (100) $[M+H]^+$, 204 (19).

HRMS calcd for $C_{15}H_{18}N_2O_2$: 219.1134, found 219.1129.

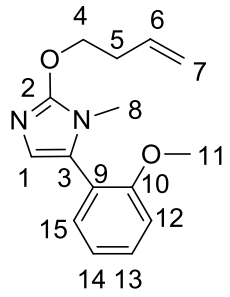
3.5.32. Characterization of 2-(but-3-en-1-yloxy)-5-(2-methoxyphenyl)-1-methyl-1H-imidazole (2p)

Chemical formula: $C_{15}H_{18}N_2O_2$
Molecular weight: 258.32 $g.mol^{-1}$

Purification conditions: flash chromatography EA/cyclohexane 30:70

Yield: 72%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.32 (m, 2H, 13-14), 7.00-6.92 (m, 2H, 12,15), 6.62 (s, 1H, 1), 5.93-5.82 (m, 1H, 6), 5.19-5.08 (m, 2H, 7), 4.45 (t, 2H, *J* = 6.6 Hz, 4), 3.81 (s, 3H, 11), 3.22 (s, 3H, 8), 2.60-2.53 (m, 2H, 5).
^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3 (2 or 10), 153.3 (2 or 10), 134.4 (6), 132.0 (12-15), 129.3 (12-15), 126.4 (3 or 9), 121.5 (1), 120.8 (12-15), 119.6 (3 or 9), 117.2 (7), 110.9 (12-15), 68.5 (4), 55.5 (11), 33.7 (5), 29.3 (8).

IR (cm^{-1}): 1548, 1498, 1254, 1030, 708.

APCI-MS m/z (%): 259 (100) $[M+H]^+$.

HRMS calcd for $C_{15}H_{18}N_2O_2$: 258.13628, found 258.13614.

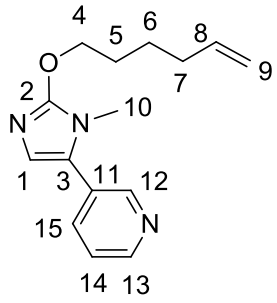
3.5.33. Characterization of 3-(2-(hex-5-en-1-yloxy)-1-methyl-1H-imidazol-5-yl)pyridine (9a)

Chemical formula: $C_{15}H_{19}N_3S$
Molecular weight: 257.33 $g.mol^{-1}$

Purification conditions: flash chromatography CH_2Cl_2/*i*-propanol 97:03 + 3% Et_3N

Yield: 13% (fraction very pure)

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (s, 1H, 11), 8.57-8.55 (m, 1H, 13), 7.70-7.55 (m, 1H, 14-15), 7.37-7.33 (m, 1H, 14-15), 6.78 (s, 1H, 1), 5.89-5.76 (m, 1H, 8), 5.07-4.95 (m, 2H, 9), 4.44 (t, 2H, *J* = 6.6 Hz, 4), 3.43 (s, 3H, 10), 2.17-2.10 (m, 2H, 7), 1.89-1.80 (m, 2H, 5), 1.62-1.54 (m, 2H, 6).
^{13}C NMR (125 MHz, $CDCl_3$): δ 154.5 (2), 148.6 (12 or 13), 148.4 (12 or 13), 138.5 (8), 134.9 (14 or 15), 126.7 (3 or 11), 126.1 (3 or 11), 123.6 (14 or 15), 122.4 (1), 115.0 (9), 69.8 (4), 33.4 (7), 29.7 (10), 28.6 (5), 25.2 (6).

IR (cm^{-1}): 1739, 1529, 1495, 1365, 1221, 1150, 997, 912, 802, 713.

ESI-MS m/z (%): 536 (64), 258 (100) $[M+H]^+$, 176 (71), 150 (95).

HRMS calcd for $C_{15}H_{20}N_3O$: 258.16009, found 258.15989.

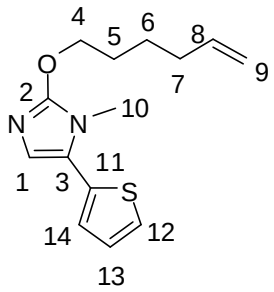
3.5.34. Characterization of 2-(hex-5-en-1-yloxy)-1-methyl-5-(thiophen-2-yl)-1H-imidazole (9b)

Chemical formula: $C_{14}H_{18}N_2OS$
Molecular weight: 262.37 g.mol^{-1}

Purification conditions: flash chromatography CH_2Cl_2/*i*-propanol 97:03

Yield: 74%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.27 (m, 1H, 12), 7.07-7.10 (m, 2H, 13-14), 6.70 (s, 1H, 1), 5.90-5.76 (m, 1H, 8), 5.07-4.96 (m, 2H, 9), 4.38 (t, 2H, *J* = 6.6 Hz, 4), 3.44 (s, 3H, 10), 2.17-2.10 (m, 2H, 7), 1.87-1.78 (m, 2H, 5), 1.61-1.51 (m, 2H, 6).

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9 (2), 138.5 (8), 131.8 (3 or 11), 127.3 (12), 125.3 (14 or 13), 125.2(13 or 14), 122.5 (1), 114.9 (9), 69.6 (4), 33.4 (7), 29.3(10), 28.6 (5), 25.2 (6). 1C not found 3 or 11.

IR (cm^{-1}): 2945, 1537, 1491, 1379, 1267, 1148, 1031, 912, 696.

APCI-MS m/z (%): 263 (100) $[M+H]^+$, 181 (20).

HRMS calcd for $C_{14}H_{19}N_2OS$: 263.12126, found 263.12143.

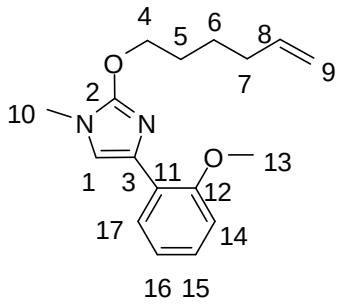
3.5.35. Characterization of 2-(hex-5-enyloxy)-4-(2-methoxyphenyl)-1-methyl-1H-imidazole (10b)

Chemical formula: $C_{17}H_{22}N_2O_2$
Molecular weight: 286.37 g.mol^{-1}

Purification conditions: flash chromatography with EA/cyclohexane 15:85

Yield: 61%

Aspect: white solid



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (dd, 1H, $J_{17\text{-}16}$= 4.7 Hz and $J_{17\text{-}15}$= 1.1 Hz, 17), 7.17-7.14 (m, 1H, 15), 7.11 (s, 1H, 1), 7.00 (dt, 1H, J = 4.5 Hz and $J_{16\text{-}14}$= 0.6 Hz, 16), 6.91 (dd, 1H, $J_{14\text{-}15}$= 4.8 Hz and $J_{14\text{-}16}$= 0.6 Hz, 14), 5.87-5.79 (m, 1H, 8), 5.06-4.96 (m, 2H, 9), 4.43 (t, 2H, J = 6.6 Hz, 4), 3.92 (s, 3H, 13), 3.43 (s, 3H, 10), 2.16-2.12 (m, 2H, 7), 1.85-1.79 (m, 2H, 5), 1.58-1.53 (m, 2H, 6).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0 (2), 152.3 (12), 138.7 (8), 130.9 (3), 127.0 (14-17), 126.5 (14-17), 123.3 (11), 120.9 (1), 116.3 (14-17), 114.8 (9), 110.5 (14-17), 69.6 (4), 55.3 (13), 33.5 (7), 30.6 (10), 28.7 (5), 25.3 (6).

IR (cm^{-1}): 1717, 1568, 1543, 1489, 1242, 1026, 752.

M.P.: 51-52°C

APCI-MS m/z (%): 287 (100) $[M+H]^+$, 205 (7).

HRMS calcd for $C_{17}H_{23}N_2O_2$: 287.17540, found 287.17588.

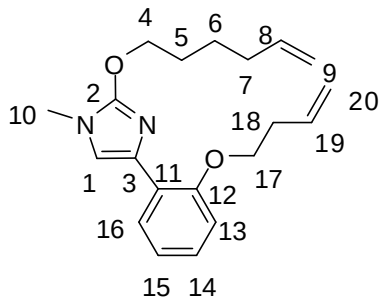
3.5.36. Characterization of 4-(2-(but-3-enyloxy)phenyl)-2-(hex-5-enyloxy)-1-methyl-1H-imidazole (10a)

Chemical formula: $C_{20}H_{26}N_2O_2$
Molecular weight: 326.43 $g.mol^{-1}$

Purification conditions: flash chromatography with EA/cyclohexane 10:90

Yield: 68%

Aspect: white solid



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, 1H, $J_{16\text{-}15}$ = 7.5 Hz and $J_{16\text{-}14}$ = 1.8 Hz, 16), 7.20 (s, 1H, 1), 7.15-7.12 (m, 1H, 14), 7.00 (dt, 1H, J = 7.5 Hz and $J_{15\text{-}13}$ = 1 Hz, 15), 6.89 (dd, 1H, $J_{13\text{-}14}$ = 8.0 Hz and $J_{13\text{-}15}$ = 0.8 Hz, 13), 5.95-5.80 (m, 2H, 8,19), 5.28-5.23 (m, 2H, 9 or 20), 5.07-4.97 (m, 2H, 20 or 9), 4.44 (t, 2H, J = 6.5 Hz, 4 or 17), 4.15 (t, 2H, J = 6.5 Hz, 17 or 4), 3.41 (s, 3H, 10), 2.70-2.65 (m, 2H, 18), 2.17-2.12 (m, 2H, 7), 1.86-1.80 (m, 2H, 5), 1.60-1.54 (m, 2H, 6).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.1 (2), 152.2 (3), 138.7 (8 or 19), 135.5 (19 or 8), 130.9 (10), 127.0 (13-16), 126.4 (13-16), 123.3 (11), 117.1 (13-16), 116.7 (13-16), 114.8 (9 or 20), 111.1 (20 or 9), 69.6 (4 or 17), 67.3 (17 or 4), 34.2 (7 or 18), 33.5 (18 or 7), 30.6 (10), 28.7 (5), 25.3 (6).

IR (cm^{-1}): 1568, 1543, 1491, 1240, 1225, 1030, 912, 750.

M.P.: 67-68°C

APCI-MS m/z (%): 327 (100) $[M+H]^+$.

HRMS calcd for $C_{20}H_{27}N_2O_2$: 327.20670, found 327.20657.

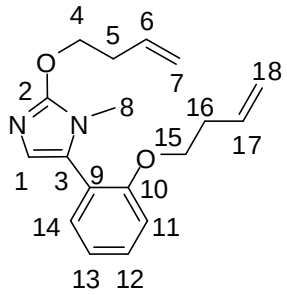
3.5.37. Characterization of 2-(but-3-enyloxy)-5-(2-(but-3-enyloxy)phenyl)-1-methyl-1H-imidazole (2ao)

Chemical formula: $C_{18}H_{22}N_2O_2$
Molecular weight: 298.38 $g.mol^{-1}$

Purification conditions: flash chromatography with EA/cyclohexane 30:70

Yield: 68%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.31 (m, 1H, 14), 7.26-7.22 (m, 1H, 11-13), 7.01-6.93 (m, 2H, 11-13), 6.64 (s, 1H, 1), 5.96-5.72 (m, 2H, 6,17), 5.20-5.04 (m, 4H, 7,18), 4.51 (t, 2H, *J* = 6.5 Hz, 4 or 15), 4.01 (t, 2H, *J* = 6.7 Hz, 15 or 4), 3.24 (s, 3H, 8), 2.61-2.44 (m, 4H, 5,16).

^{13}C NMR (125 Hz, $CDCl_3$): δ 156.6 (10), 153.2 (2), 134.4 (6 or 17), 134.3 (17 or 6), 132.0 (11-14), 129.7 (11-14), 126.5 (3), 121.4 (1), 121.0 (11-14), 119.9 (9), 117.3 (7 or 18), 117.2 (18 or 7), 112.2 (11-14), 68.5 (5 or 16), 67.7 (16 or 5), 33.8 (4 or 15), 33.6 (15 or 4), 29.5 (8).

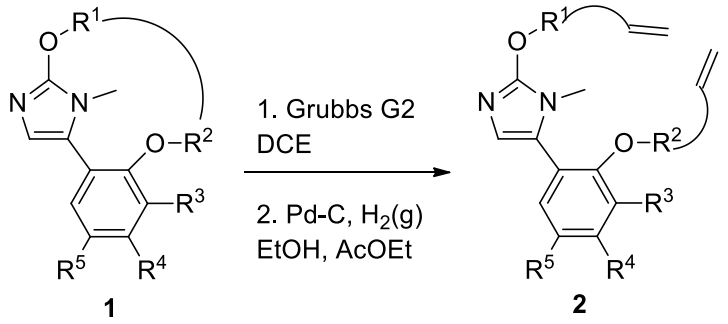
IR (cm^{-1}): 1732, 1250, 1537, 1053, 989, 754.

ESI-MS m/z (%): 299 (100) $[M+H]^+$.

HRMS calcd for $C_{18}H_{23}N_2O_2$: 299.17540, found 299.17563.

4. SYNTHESIS OF MACROCYCLES

4.1. General procedure for RCM and hydrogenation



Imidazole **2** (0.266 mmol, 1 equiv.) and 1,2-dichloroethane (70 mL) were introduced in a flask under argon. The mixture was heated at 95°C (reflux). Grubbs catalyst (second generation) (0.013 mmol, 0.05 equiv.) was added. After 24 hours, a second fraction of Grubbs catalyst (0.007 mmol, 0.025 equiv.) was added and the solution was stirred at reflux for 24 hours. The mixture was cooled down until room temperature and potassium isocyanate (20 mg) was added. After one hour of stirring, the solvent was evaporated. The crude product was filtrated over silica with a mixture of cyclohexane/ethyl acetate as eluent and directly engaged into the next step. Then in the second step the resulting product (1 equiv., 0.44 mmol), ethanol (10mL) and ethyl acetate (10 mL) were added in a flask. The catalyst Pd/C 10% (0.05 equiv., 0.02 mmol) was added and the mixture was placed under H_2(g) atmosphere. After 2h30, the mixture was filtrated and concentrated under vacuum. The crude product was purified by flash chromatography over silica with a mixture of cyclohexane/ethyl acetate as eluent.

4.2. Note for RCM products

The ratio cis-trans obtained for every mixture was about 55:45 (when it was possible to see it on ^{1}H NMR).

4.3. Characterization of hydrogenated products

4.3.1. Characterization of 21-methyl-8,17-dioxa-19,21-diazatricyclo [16.2.1.0^{2,7}] henicosa-1(20),2,4,6,18-pentane (1a)

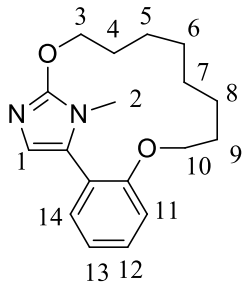
Chemical formula: $C_{18}H_{24}N_2O_2$

Molecular weight: 300.40 g.mol^{-1}
CAS Registry Number: 1236073-81-6

Purification conditions: flash chromatography CH_2Cl_2/EA 75:25

Yield: 19% over 2 steps

Aspect: colorless oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.26 (m, 2H, 14, 12 or 13), 7.00 (td, 1H, *J* = 7.5 and 1.2 Hz, 12 or 13), 6.91-6.89 (m, 1H, 11), 6.58 (s, 1H, 1), 4.98-4.91 (m, 1H, 3a-b or 10a-b), 4.19-4.12 (m, 1H, 3a-b or 10a-b), 3.98-3.91 (m, 1H, 3a-b or 10a-b), 3.87-3.81 (m, 1H, 3a-b or 10a-b), 3.22 (s, 3H, 2), 1.80-1.20 (m, 12H, 4-9).

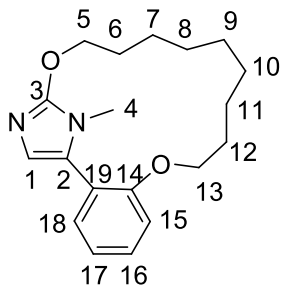
4.3.2. Characterization of 20-methyl-3,4,5,6,7,8,9,10-octahydro-2H-12,15-epimino-1,11,13-benzodioxazacycloheptadecine (1b)

Chemical formula: $C_{19}H_{26}N_2O_2$
Molecular weight: 314.42 g.mol^{-1}

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 41% over 2 steps

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.27 (m, 2H, 15-18), 7.00-6.90 (m, 2H, 15-18), 6.54 (s, 1H, 1), 4.90-4.82 (m, 1H, 5a-b or 13a-b), 4.29-4.22 (m, 1H, 5a-b or 13a-b), 4.17-4.11 (m, 1H, 5a-b or 13a-b), 3.78-3.71 (m, 1H, 5a-b or 13a-b), 3.25 (s, 3H, 4), 1.86-1.26 (m, 14H, 6-12).

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1 (3), 153.3 (14), 131.8 (15-18), 129.9 (15-18), 126.5 (2 or 19), 121.2 (1), 120.8 (15-18), 120.2 (19 or 2), 111.9 (15-18), 69.4 (5 or 13), 68.4 (5 or 13), 30.0 (6-12), 29.5 (4), 28.1 (6-12), 28.0 (6-12), 27.7 (6-12), 26.7 (6-12), 24.7 (6-12), 24.5 (6-12).

IR (cm^{-1}): 2931, 1580, 1537, 1450, 1278, 1246, 1049, 1015, 752.

ESI-MS m/z (%): 315 (100) $[M+H]^+$, 191 (5).

HRMS calcd for $C_{19}H_{27}N_2O_2$: 315.2073, found 315.2083.

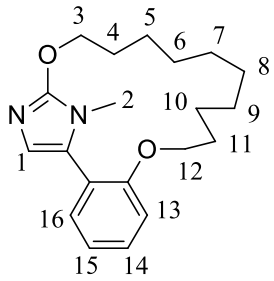
3.5.38. Characterization of 23-methyl-8,19-dioxa-21,23-diazatricyclo[18.2.1.02,7] tricosa-1(22),2,4,6,20-pentane (1c)

Chemical formula: $C_{20}H_{28}N_2O_2$
Molecular weight: 328.45 g.mol^{-1}
CAS Registry Number: 1236074-05-7

Purification conditions: flash chromatography CH_2Cl_2/EA 75:25

Yield: 49% over 2 steps

Aspect: colorless oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (td, 1H, *J* = 7.7 and 1.8 Hz, 14 or 15), 7.27 (dd, 1H, *J* = 7.4 and 1.8 Hz, 13 or 16), 6.98 (dt, 1H, *J* = 7.4 and 1.0 Hz, 14 or 15), 6.92 (d, 1H, *J* = 8.2 Hz, 13or 16), 6.56 (s, 1H, 1), 4.81 (dt, 1H, *J* = 10.5 and 2.9 Hz, 3a-b or 12a-b); 4.20 (dt, 1H, *J* = 7.1 and 2.9 Hz, 3a-b or 12a-b), 4.00-3.96 (m, 1H, 3a-b or 12a-b); 3.88 (dt, 1H, *J* = 7.7 and 3.0 Hz, 3a-b or 12a-b,), 3.23 (s, 3H, 2), 1.98-1.20 (m, 16h, 4-11).

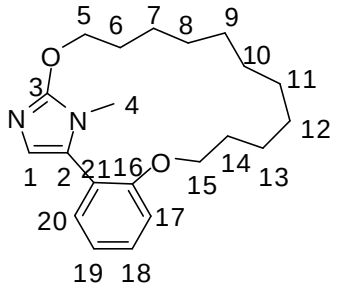
4.3.3. Characterization of 22-methyl-3,4,5,6,7,8,9,10,11,12-decahydro-2H-14,17-epimino-1,13,15-benzodioxazacyclononadecine (1d)

Chemical formula: $C_{21}H_{30}N_2O_2$
Molecular weight: 342.48 g.mol^{-1}

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 58% over two steps

Aspect: incolore oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.25 (m, 2H, 17-20), 6.99-6.91 (m, 2H, 17-20), 6.55 (s, 1H, 1), 4.50-4.47 (m, 2H, 5b or 15b), 3.97-3.94 (m, 2H, 5a or 15a), 3.25 (s, 3H, 4), 1.82-1.28 (m, 18H, 6-14).
^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1 (3), 153.4 (16), 132.3 (17-20), 129.8 (17-20), 126.8 (2 or 21), 121.1 (1), 120.7 (17-20), 120.1 (21 or 2), 111.9 (17-20), 68.5 (5 or 15), 68.4 (5 or 15), 29.7 (6-14),

29.3 (4), 28.7 (6-14), 28.1 (6-14), 27.9 (6-14), 27.5 (6-14), 26.8 (6-14), 26.0 (6-14), 25.7 (6-14), 24.6 (6-14).

IR (cm^{-1}): 2927, 1580, 1537, 1494, 1448, 1244, 1142, 1053, 1009, 752.

ESI-MS m/z (%): 343 (100) $[M+H]^+$, 191 (6).

HRMS calcd for $C_{21}H_{31}N_2O_2$: 343.2386, found 343.2393.

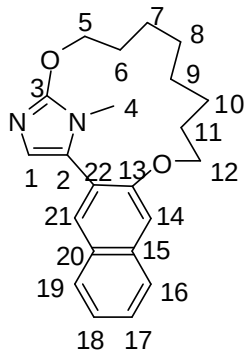
4.3.4. Characterization of 2-(but-3-enyloxy)-5-(3-(hex-5-enyloxy)naphthalen-2-yl)-1-methyl-1H-imidazole (1i)

Chemical formula: $C_{22}H_{26}N_2O_2$
Molecular weight: 350.45 $g.mol^{-1}$

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 35% over two steps

Aspect: light brown oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79-7.73 (m, 3H, 16, 19, 21), 7.45 (ddd, 1H, $J_{18,19 \text{ and } 18,17}$ = 6.9 Hz, $J_{18,16}$ = 1.5 Hz, 18), 7.35 (ddd, 1H, $J_{17,16 \text{ and } 17,18}$ = 6.9 Hz, $J_{17,19}$ = 1.5 Hz, 17), 7.16 (s, 1H, 14), 6.68 (s, 1H, 1), 4.99-4.96 (m, 1H, 5a or 12a), 4.20-3.98 (m, 3H, 5b and 12 or 12a and 5), 3.23 (s, 3H, 4), 1.49-1.26 (m, 12H, 6-11).
^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8 (13), 152.7 (3), 135.0 (15), 131.2 (16-19 or 21), 128.6 (20), 128.0 (16-19 or 21), 127.0 (16-19 or 21), 126.5 (16-19 or 21), 125.8 (2 or 22), 124.1 (16-19 or 21), 121.7 (1), 106.3 (14), 71.6 (12 or 5), 68.1 (5 or 12), 29.8 (6-11), 29.1 (6-11), 28.8 (4), 27.9 (6-11), 26.5 (6-11), 26.4 (6-11), 23.2 (6-11).

IR (cm^{-1}): 2933, 1531, 1454, 1251, 1180, 1042, 680.

ESI-MS m/z (%): 351 (100) $[M+H]^+$, 241 (5).

HRMS calcd for $C_{22}H_{26}N_2O_2$: 351.2073, found 351.2089.

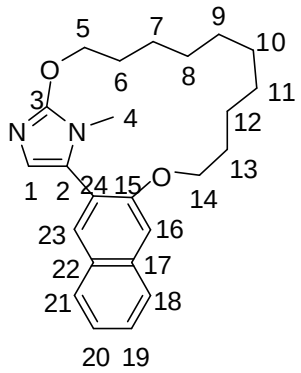
4.3.5. Characterization of 2-(hex-5-enyloxy)-5-(3-(hex-5-enyloxy)naphtalen-2-yl)-1-methyl-1H-imidazole (1j)

Chemical formula: $C_{24}H_{30}N_2O_2$
Molecular weight: 378.51 $g.mol^{-1}$

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 35% over two steps

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.72 (m, 3H, 18, 21, 23), 7.45 (ddd, 1H, $J_{20,19 \text{ and } 20,21}$ = 6.9 Hz, $J_{20,18}$ = 1.3 Hz, 20), 7.35 (ddd, 1H, $J_{19,20 \text{ and } 19,18}$ = 7.8 Hz, $J_{19,21}$ = 1.3 Hz, 19), 7.16 (s, 1H, 16), 6.66 (s, 1H, 1), 4.85-4.79 (m, 1H, 5a or 14a), 4.26-4.01 (m, 3H, 5b and 14 or 14a and 5), 3.25 (s, 3H, 4), 2.04-1.26 (m, 16H, 6-13).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.6 (15), 153.2 (3), 134.9 (17), 131.6 (18-21 or 23), 128.7 (22), 127.9 (18-21 or 23), 126.9 (18-21 or 23), 126.5 (18-21 or 23), 124.1 (18-21 or 23), 121.6 (2 or 24), 121.4 (1), 106.4 (16), 69.8 (14 or 5), 68.7 (5 or 14), 29.5 (6-13),29.4 (4), 28.4 (6-13), 28.1 (6-13), 28.0 (6-13), 27.5 (6-13), 27.2 (6-13), 26.4 (6-13), 25.9 (6-13).

IR (cm^{-1}): 2925, 1602, 1529, 1446, 1377, 1250, 1047, 713.

ESI-MS m/z (%): 379 (100) $[M+H]^+$, 241 (5).

HRMS calcd for $C_{22}H_{26}N_2O_2$: 379.2386, found 379.2394.

4.3.6. Characterization of the mixture of monomer and dimer of the 1,2,4-imidazole

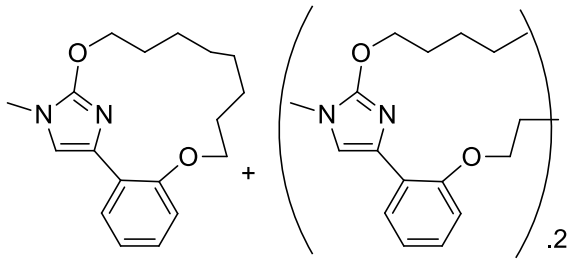
Chemical formula: $C_{18}H_{24}N_2O_2$ and $C_{36}H_{50}N_4O_4$
Molecular weight: 300.40 and 600.72 $g.mol^{-1}$

Purification conditions: flash chromatography EA/hexane 30:70

Yield: 34%

Selectivity: 70:30 (dimer/mononer)

Aspect: white solid



^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11-8.10 (m, H_{arom}), 8.07-8.06 (m, H_{arom}), 7.13-7.11 (m, H_{arom}), 7.07 (s, H_{arom}), 7.00-6.98 (m, H_{arom}), 6.97-6.87 (m, H_{arom}), 4.43 (t, *J* = 3.3 Hz, OCH_2), 4.11 (t, *J* = 3.3 Hz, OCH_2), 3.22 (s, 3H, NCH_3), 3.21 (s, NCH_3), 1.93-1.25 (m, CH_2).
^{13}C NMR (125 MHz, $CDCl_3$) : δ 155.4, 155.3, 152.1, 131.2, 127.1, 127.0, 126.5, 132.1, 120.8, 120.6, 116.3, 111.3, 111.0, 70.0, 67.9, 67.8, 30.4-22.8 (13 signals).

IR (cm^{-1}): 2927, 1568, 1543, 1490, 1240, 750, 707, 665.

APCI-MS m/z (%): 601 (100) $[M_{dimer}+H]^+$, 301 (40) $[M_{monomer}+H]^+$, 79 (36).

HRMS calcd for $C_{36}H_{51}N_4O_4$: 601.37483, found 601.37454.

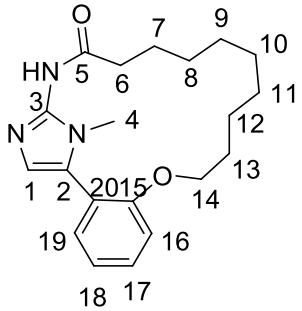
4.3.7. Characterization of 21-methyl-3,4,5,6,7,8,9,10-octahydro-2H-13,16-epimino-1,12,14-benzoxadiazacyclooctadecin-11(12H)-one (1j)

Chemical formula: $C_{20}H_{27}N_3O_2$
Molecular weight: 341.45 $g.mol^{-1}$

Purification conditions: flash chromatography with CH_2Cl_2 with 3% Et_3N

Yield: 46% over two steps

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21(d, 1H, *J* = 7.2 Hz, 19), 7.53(s, 1H, 1), 7.22-7.19 (m, 1H, 16-18), 7.05-7.00 (m, 1H, 16-18), 6.93-6.87 (m, 1H, 16-18), 4.18-4.09 (m, 2H, 14), 3.15 (s, 1H, 4), 2.75-2.70 (m, 2H, 6), 1.85-1.26 (m, 14H, 7-13).
^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2 (5), 156.3 (15), 135.8 (3 or 20), 128.6 (1 or 16-19), 128.0 (1 or 16-19), 121.8 (3 or 20), 111.1 (1 or 16-19), 110.0 (1 or 16-19), 68.1 (14), 36.4 (6), 29.4 (7-13), 29.3 (4), 26.9 (7-13), 26.7 (7-13), 26.2 (7-13), 26.0 (7-13), 25.9 (7-13), 24.2 (7-13).

IR (cm^{-1}): 2937, 1736, 1688, 1614, 1366, 1229, 1217, 748.

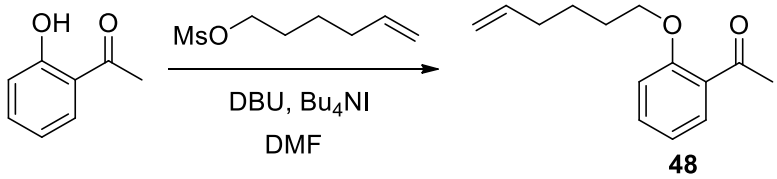
M.P.: 177-178°C.

ESI-MS m/z (%): 342 (100) $[M+H]^+$.

HRMS calcd for $C_{20}H_{28}N_3O_2$: 342.2182, found 342.2169.

5. SYNTHESIS OF MACROCYCLES WITH THE 2-AMIDOIMIDAZOLE

5.1. Synthesis of 1-(2-(hex-5-enyloxy)phenyl)ethanone (48)



48

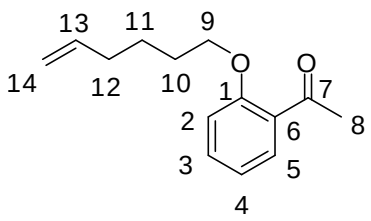
Chemical formula: $C_{14}H_{18}O_2$
Molecular weight: 218.29 $g.mol^{-1}$

Procedure

2-Hydroxyacetophenone (2.92 mol, 1 equiv., 0.35 mL) was dissolved in DMF (5 mL). DBU (6.41 mmol, 2.2 equiv., 0.96 mL) and hex-5-enyl methanesulfonate (5.83 mmol, 2 equiv., 1.04 g) were added drop wise. Finally, Bu_4NI (0.15 mol, 0.05 equiv., 53.8 mg) was added. The reaction mixture was heated for 7 hours at 70°C and then stirred at room temperature overnight. The solvent was evaporated. Diethyl ether (50 mL), water (10 mL) and an aqueous solution of HCl 1N (4 mL) were added. The phases were separated and the organic phase was washed with water (20 mL). The aqueous phases were extracted with diethyl ether (20 mL). The collected organic phases were dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica with cyclohexane/ethyl acetate 90/10 as eluent.

Yield: 99 %

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (dd, 1H, *J* = 7.8 and 1.5 Hz, 3), 7.46-7.41 (m, 1H, 5), 4.09-4.04 (m, 2H, 2, 4), 5.89-5.75 (m, 1H, 13), 5.07-4.97 (m, 2H, 14), 4.07 (t, 2H, *J* = 6.3 Hz, 9), 2.63 (s, 1H, 8), 2.15-2.11 (m, 2H, 11), 1.90-1.85 (m, 2H, 10), 1.63-1.57 (m, 2H, 12).

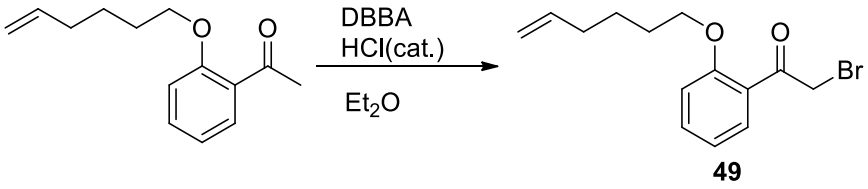
^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0 (7), 158.5 (1), 138.3 (13), 133.7 (2,3,4 or 5), 130.5 (2,3,4 or 5), 128.4 (6), 120.5 (2,3,4 or 5), 115.1 (14), 112.3 (2,3,4 or 5), 68.4 (9), 33.42 (12), 32.2 (8), 28.7 (10), 25.6 (11).

IR (cm^{-1}) : 2941, 1672, 1595, 1450, 1292, 1236, 910, 754.

APCI-MS m/z (%): 218 (50) $[M+H]^+$, 137 (100), 83 (9).

HRMS calcd for $C_{14}H_{18}O_2$: 219.13850, found 219.13841.

5.2. Synthesis of 2-bromo-1-(2-(hex-5-enyloxy)phenyl)ethanone (49)



49

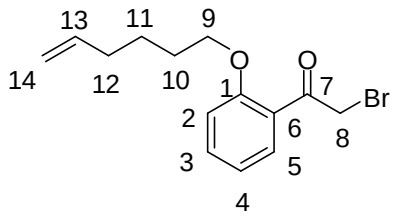
Chemical formula: $C_{14}H_{17}BrO_2$
Molecular weight: 297.19 $g.mol^{-1}$

Procedure

DBBA (3.71 mol, 0.7 equiv., 1.09 g) was dissolved in Et_2O (30 mL) and 1-(2-(hex-5-enyloxy)phenyl) ethanone (5.30 mol, 1 equiv., 1.16 g) in Et_2O (10 mL) was added. HCl 4N in dioxane (0.53 mol, 0.1 equiv., 0.13 mL) was added as a catalyst. The mixture was stirred at room temperature for 24h. Et_2O (100 mL) and a saturated aqueous solution of $NaHCO_3$ (100 mL) were added. The phases were separated and the organic phase was washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure.

Yield: quantitative.

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (dd, 1H, *J* = 7.8, 1.8 Hz, 3), 7.53-7.47 (m, 1H, 5), 7.11-6.55 (m, 2H, 2, 4), 5.88-5.76 (m,1H, 13), 5.09-5.00 (m, 2H, 14), 4.61 (s, 2H, 8), 4.13-4.09 (m, 2H, 9), 2.18-2.14 (m, 2H, 11), 1.91-1.88 (m, 2H, 10), 1.63-1.57 (m, 2H, 12).

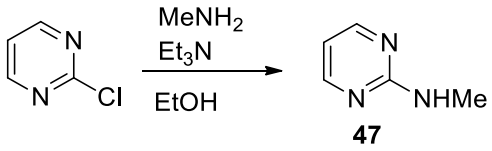
^{13}C NMR (75 MHz, $CDCl_3$): δ 192.7 (7), 158.4 (1), 138.2 (13), 134.8 (2,3,4 or 5), 132.8 (2,3,4 or 5), 125.1 (6), 121.1 (2,3,4 or 5), 115.3 (14), 112.4 (2,3,4 or 5), 68.8 (9), 37.6 (8), 33.42 (12), 28.6 (10), 25.6 (11).

IR (cm^{-1}): 2914, 1681, 1599, 1450, 1296, 993, 754.

APCI-MS m/z (%): 298 (11, ^{81}Br) $[M]^{\cdot+}$, 296 (10, ^{79}Br) $[M]^{\cdot+}$, 219 (100), 137 (79).

HRMS calcd for $C_{14}H_{17}BrO_2$: 296.04064, found 296.03962.

5.3. Synthesis of *N*-methylpyrimidin-2-amine (47)



47

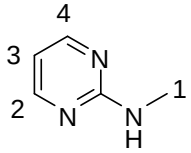
Chemical formula: $C_5H_7N_3$
Molecular weight: 109.13 $g.mol^{-1}$
CAS Registry Number: 931-61-3

Procedure

In a microwave vial, 2-chloropyrimidine (52.40 mol, 1 equiv., 6 g) methylamine (68.12 mol, 8.03 M in EtOH, 1.3 equiv., 8.5 mL) and triethylamine (78.60 mol, 1.5 equiv., 11.0 mL) were successively dissolved in EtOH (34 mL). The reaction tube was irradiated at 120°C during 25 minutes. After the mixture was diluted in water (180 mL), extracted with CH_2Cl_2 (2 × 180 mL) and the combined organic phases were dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica with cyclohexane/ethyl acetate 30/70 as eluent.

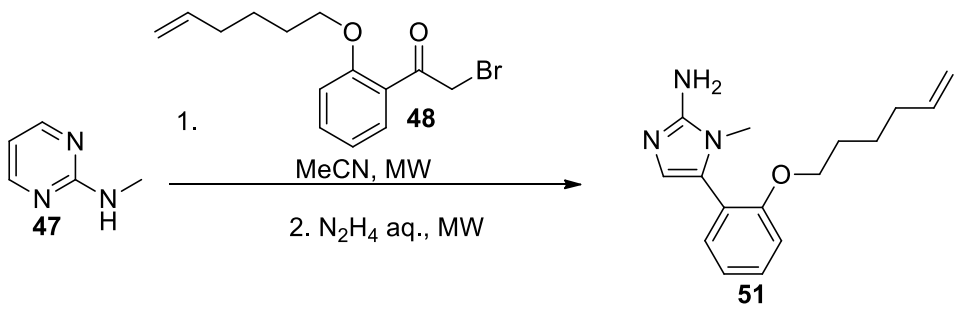
Yield: 83 %

Aspect: colorless solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, 2H, *J* = 4.8 Hz, 2, 4), 6.53 (d, 1H, *J* = 4.8 Hz, 3), 2.99 (d, 3H, *J* = 5.1 Hz, 1).

5.4. Synthesis of 5-(2-(hex-5-enyloxy)phenyl)-1-methyl-1H-imidazol-2-amine (51)



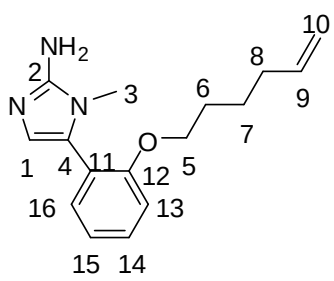
Chemical formula: $C_{16}H_{21}N_3O$
Molecular weight: 271.36 $g.mol^{-1}$

Procedure

In a microwave vial, *N*-methylpyrimidin-2-amine (0.46 mmol, 1 equiv., 50 mg) and 2-bromo-1-(2-(hex-5-enyloxy)phenyl)ethanone (0.62 mmol, 1.35 equiv., 184 mg) were successively dissolved in MeCN (5 mL). The reaction tube was irradiated at 150°C during 35 minutes. Then aqueous hydrazine (2.29 mmol, 5 equiv., 0.18 mL) was added and the mixture was irradiated at 100°C for another 10 minutes. The mixture was diluted in water (10 mL), extracted with CH_2Cl_2 (2×10 mL) and the combined organic phases were again washed with water (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica with CH_2Cl_2/MeOH 95/05 + 3% Et_3N as eluent. And finally, the residue was washed twice with water to take off Et_3N.

Yield: 50 %

Aspect: orange oil



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, 1H, *J* = 7.5 Hz, 16), 7.17-7.10 (m, 3H,1, 14), 6.98-6.90 (m, 2H, 13, 15), 5.89-5.71 (m, 1H, 9), 5.07-4.98 (m, 2H, 10), 4.08 (t, 2H, *J* = 6.6 Hz, 5), 2.93 (s, 3H, 3), 2.18-2.11 (m, 2H, 8), 1.97-1.86 (m, 2H, 6), 1.67-1.57 (m, 2H, 7).

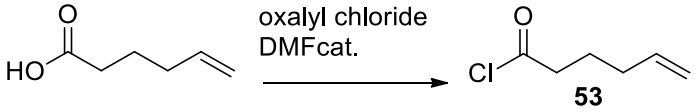
^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9 (2 or 12), 151.2 (12 or 2), 138.3 (9), 126.7 (13-16), 125.8 (13-16), 121.3 (1), 115.2 (10), 112.2 (13-16), 68.4 (5), 33.5 (8), 30.6 (3), 29.0 (6), 25.7 (7). 4 and 11 not found.

IR (cm^{-1}): 3398, 3161, 3238, 3182, 3074, 2974, 2937, 2872, 2802, 1581, 1595 (NH_2).

APCI-MS m/z (%): 272 (100) $[M+H]^+$.

HRMS calcd for $C_{16}H_{22}N_3O$: 272.1763, found 272.1766.

5.5. Synthesis of hex-5-enoyl chloride (53)



53

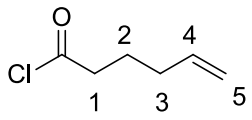
Chemical formula: C_6H_9ClO
Molecular weight: 132.59 $g.mol^{-1}$
CAS Registry Number: 36394-07-7

Procedure

5-Heptenoic acid (2.31 mmol, 1 equiv., 0.28 mL) was stirred with one drop of DMF. Oxalyl chloride (2.77 mmol, 1.2 equiv., 0.25 mL) was added dropwise. The mixture was stirred until no release of gaz was observed. Then another portion of oxalyl chloride was added (2.77 mmol, 1.2 equiv., 0.25 mL) and stirred for one hour. The mixture was concentrated under vacuo.

Yield: quantitative

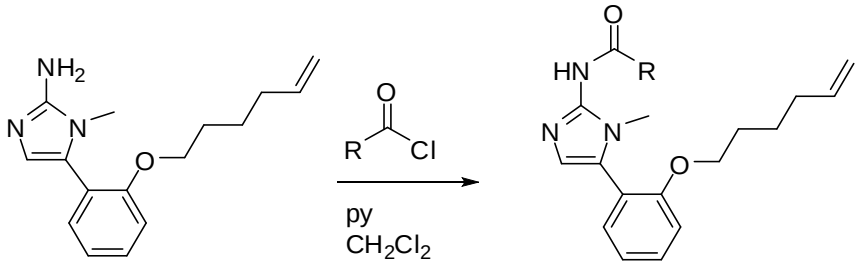
Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 5.79-5.66 (m, 1H, 4), 5.06-5.01 (m, 2H, 5), 2.9-2.85 (m, 2H, 1), 2.13-2.07 (m, 2H, 2-3), 1.84-1.74 (m, 2H, 2-3).

5.6. Amide formation

5.6.1. General procedure



The amine (0.55 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (2 mL). Pyridine (0.69 mmol, 1.25 equiv.) and acetyl chloride (0.66 mmol, 1.2 equiv.) were added dropwise at -10°C. The mixture was stirred overnight at room temperature. AcOEt (10 mL), water (5 mL) and a saturated aqueous solution of NH_4Cl (5 mL) were added. The phases were separated and the aqueous phase was extracted twice with AcOEt (5 mL). The organic phases were washed with water (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica with CH_2Cl_2 + 3% Et_3N as eluent.

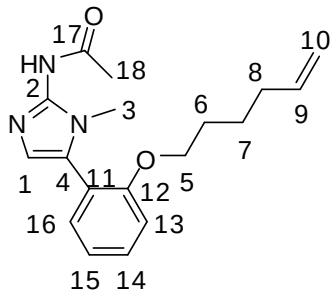
5.6.2. Characterization of N-(5-(2-(hex-5-enyloxy)phenyl)-1-methyl-1H-imidazol-2-yl)acetamide (2aq)

Chemical formula: $C_{18}H_{23}N_3O_2$
Molecular weight: 313.39 g.mol^{-1}

Purification conditions: flash chromatography with CH_2Cl_2 + 3% Et_3N

Yield: 37%

Aspect: yellow solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (dd, 1H, $J_{16,15}$ = 4.8 Hz and $J_{16,14}$ = 0.9 Hz, 16), 7.43 (s, 1H, 1), 7.24-7.21 (m, 1H, $J_{14,16}$ = 0.9 Hz, 14), 7.05-7.02 (m, 1H + NH, $J_{15,16}$ = 4.8 Hz, 15), 6.91 (d, 1H, $J_{13,14}$ = 4.8 Hz, 13), 5.85-5.78 (m, 1H, 9), 5.05-4.98 (m, 2H, 10), 4.12 (t, 2H, J = 3.6 Hz, 5), 3.15 (s, 3H, 3), 2.47 (s, 3H, 18), 2.18-2.14 (m, 2H, 8), 1.95-1.90 (m, 2H, 6), 1.70-1.67 (m, 2H, 7).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (17), 156.1 (2), 151.6 (12), 138.3 (9), 128.5 (1 or 13-16), 128.2 (1 or 13-16), 120.9 (1 or 13-16), 115.2 (10), 111.2 (1 or 13-16), 109.7 (1 or 13-16), 68.0 (5), 33.7 (8), 29.5 (3 or 18), 29.2 (6), 25.9 (7), 24.1 (3 or 18).

IR (cm^{-1}) : 1685, 1382, 1346, 1161, 750, 694.

M.P.: 114-115°C

ESI-MS m/z (%): 314 (100) $[M+H]^+$, 272 (19).

HRMS calcd for $C_{18}H_{24}N_3O_2$: 314.1869, found 314.1857.

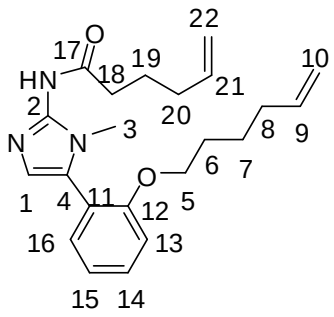
5.6.3. Characterization of N-(5-(2-(hex-5-enyloxy)phenyl)-1-methyl-1H-imidazol-2-yl)hex-5-enamide (2j)

Chemical formula: $C_{22}H_{29}N_3O_2$
Molecular weight: 367.48 $g.mol^{-1}$

Purification conditions: recrystallization in Et_2O

Yield: 46%

Aspect: yellow solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, 1H, *J* = 7.5 Hz, 16), 7.46 (s, 1H, 1), 7.24-7.19 (m, 1H, 14), 7.06-7.01 (m, 1H, 15 or 13), 6.92 (d, 1H, *J* = 8.1 Hz, 13 or 15), 5.90-5.74 (m, 2H, 9 and 21), 5.10-4.98 (m, 4H, 10 and 22), 4.12 (t, 2H, *J* = 6.3 Hz, 5), 3.15 (s, 3H, 3), 2.74 (t, 2H, *J* = 7.4 Hz, 18), 2.20-2.13 (m, 4H, 8 and 19 or 20), 1.96-1.86 (m, 4H, 6 and 19 or 20), 1.70-1.62 (m, 2H, 7).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9 (17), 156.1 (2), 151.7 (12), 138.3 (9 or 21), 137.4 (21 or 9), 128.6 (13-16), 128.2 (13-16), 120.9 (1), 116.0 (10 or 22), 115.2 (22 or 10), 111.2 (13-16), 109.1 (13-16), 68.0 (5), 35.2 (6-8 or 18-20), 33.6 (6-8 or 18-20), 33.0 (6-8 or 18-20), 29.6 (3), 29.1 (6-8 or 18-20), 25.8 (6-8 or 18-20), 23.1 (6-8 or 18-20).

IR (cm^{-1}) : 2952, 1696, 1610, 1390, 1190, 910, 752, 696.

M.P.: 94-95°C

APCI-MS m/z (%): 368 (32) $[M+H]^+$, 272 (100).

HRMS calcd for $C_{20}H_{30}N_3O_2$: 368.2338, found 368.2329.

6. FORMATION OF THE FUMARATE SALTS FOR BIOLOGICAL TESTS

General procedure

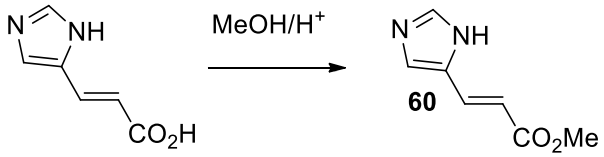
The final compound for biological test (1 equiv.) was dissolved in MeOH. In parallel, fumaric acid (1 equiv.) was also dissolved in MeOH. Then the two fractions were combined and stirred overnight. Finally, the solvent was evaporated under reduced pressure. The 1 to 1 ratio was confirmed by ^{1}H NMR.

The fumarate salt of compound **1**, **2** was heated at 37°C in a mixture of H_2O/dmso (95:5) during one week. This test was monitoring by HPLC and we found no significant degradation of the compound

7. REGIOSELECTIVE *N*-ALKYLATION OF AZOLES

7.1. Synthesis of reactants

7.1.1. Synthesis of (E)-methyl 3-(1H-imidazol-5-yl)acrylate (60)



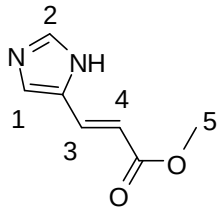
Chemical formula: $C_7H_8N_2O_2$
Molecular weight: 152.15 g.mol^{-1}
CAS Registry Number: 70346-51-9

Procedure

Urocanic acid (3.62 mmol, 1 equiv., 0.5 g) and anhydrous Na_2SO_4 (71 mg) were added to anhydrous methanol (5.5 mL). Concentrated sulfuric acid (0.28 mL) was added to the reaction, which was heated at reflux for 30 h. The solid Na_2SO_4 was filtered off, and the solvent was removed under reduced pressure. The remaining white solid was dissolved in a small amount of water and neutralized with saturated $NaHCO_3$/H_2O until no gas was evolved. The cloudy aqueous solution was extracted with ethyl acetate (3×15 mL). The organic layer was dried over Na_2SO_4, and the solvent was concentrated under reduced pressure.

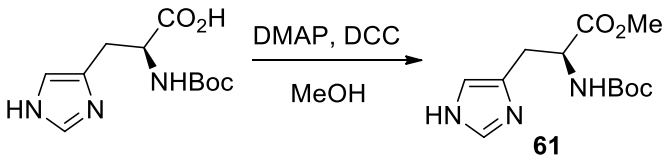
Yield: 98%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (s, 1H, 2), 7.64 (d, 1H, *J* = 15.6 Hz, 4), 7.27 (s, 1H, 1), 6.53 (d, 1H, *J* = 15.6 Hz, 3), 3.79 (s, 3H, 5)

7.1.2. Synthesis of (S)-methyl 2-(tert-butoxycarbonylamino)-3-(1H-imidazol-4-yl)propanoate (61)



61

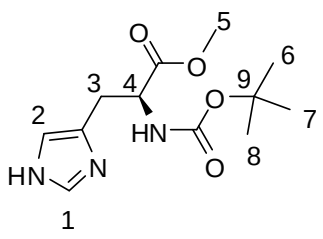
Chemical formula: $C_{12}H_{19}N_3O_4$
Molecular weight: 269.30 g.mol^{-1}
CAS Registry Number: 2488-14-4

Procedure

To a solution of DMAP (0.078 mmol, 0.1 equiv., 9.6 mg) in CH_2Cl_2 (2 mL) under argon atmosphere, a solution of (+)-*Nα-tert*-butoxycarbonyl-*L*histidine (0.78 mmol, 1 equiv., 200 mg) in CH_3OH (2 mL) was added. The reaction mixture was cooled to 0°C followed by a slow addition of a solution of DCC (0.78 mmol, 1 equiv., 162 mg) in CH_2Cl_2 (1 mL). The reaction was stirred for 5 min at 0°C, and left at room temperature for two days. Afterwards, the solvent was evaporated under reduced pressure and the residue was treated with CH_2Cl_2 to precipitate DCU that was filtered off under reduced pressure.

Yield: quantitative

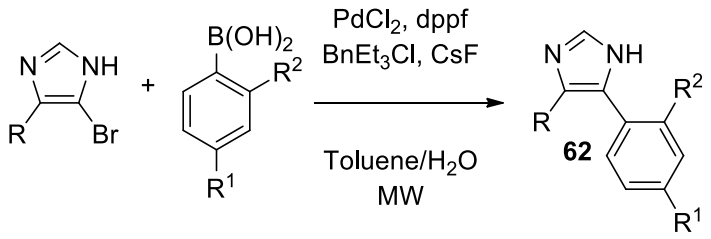
Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (s, 1H, 1), 6.82 (s, 1H, 2), 5.73 (bm, 1H, 9), 4.54 (bm, 1H, 4), 3.71 (s, 3H, 5), 3.09 (m, 2H, 3), 1.42 (s, 9H, 6-8).

7.1.3. Directed arylation

7.1.3.1 General procedure



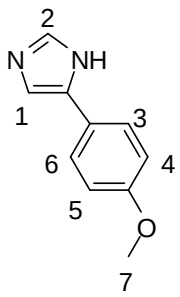
A mixture of 4(5)-bromo-1*H*-imidazole (0.670 mmol, 1 equiv.), an arylboronic acid (2 equiv.), CsF (1.98 mmo, 3 equiv.,l), $PdCl_2$ (0.033 mmol, 0.05 equiv.,), dppf (0.033 mmol, 0.05 equiv.,), and $BnEt_3NCl$ (0.033 mmol, 0.05 equiv.,), in toluene (3.5 mL) and water (3.5 mL) was degased under argon during 30 minutes in a microwave tube. The reaction was carried out under microwave irradiation: 500 W, 110°C, 10-15 hours. The mixture was cooled to room temperature and partitioned between water and AcOEt, and the organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography using a mixture of CH_2Cl_2/MeOH 95:05 as eluent.

*7.1.3.2. Characterization of 5-(4-methoxyphenyl)-1H-imidazole (**62a**)*

Chemical formula: $C_{10}H_{10}N_2O$
Molecular weight: 174.20 g.mol^{-1}
CAS Registry number: 35512-31-3

Yield: 76%

Aspect: solid



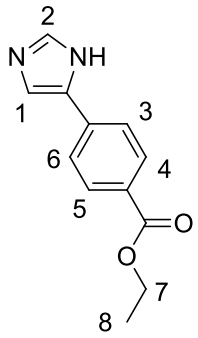
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70-7.34 (m, 3H, 2 and 4-5), 7.25 (s, 1H, 1), 6.94 (d, 2H, *J* = 8.5 Hz, 3,6), 3.85 (s, 3H, 7).

*7.1.3.2 Characterization of 4-(1H-imidazol-5-yl)phenyl propionate (**62b**)*

Chemical formula: $C_{12}H_{12}N_2O_2$
Molecular weight: 216.24 g.mol^{-1}
CAS Registry Number: 1260539-44-3

Yield: 95%

Aspect: oil



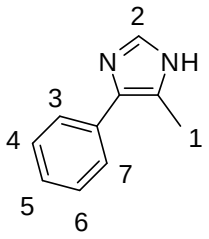
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, 3H, *J* = 8.1 Hz, 4-5), 7.81-7.78 (m, 3H, 2, 3, 6), 7.45 (s, 1H, 1), 4.37 (q, 2H, *J* = 14.23 Hz, 7), 1.39 (t, 3H, *J* = 6.9 Hz, 8).

*7.1.3.3. Characterization of 5-methyl-4-phenyl-1H-imidazole (**62d**)*

Chemical formula: $C_{10}H_{10}N_2$
Molecular weight: 158.20 g.mol^{-1}
CAS Registry Number: 156671-43-1.

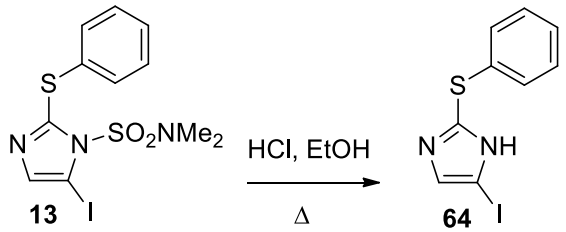
Yield: 73%

Aspect: solid



^{1}H NMR(300 MHz, $CDCl_3$): δ 7.63-7.57 (m, 2H, 3,7), 7.45-7.39 (m, 2H, 4,6), 7.31-7.26 (m, 2H, 2,5), 2.47 (s, 3H, 1).

7.1.4. Synthesis of 5-iodo-2-(phenylthio)-1H-imidazole (64)



Chemical formula: $C_9H_7IN_2S$
Molecular weight: 302.13 g.mol^{-1}

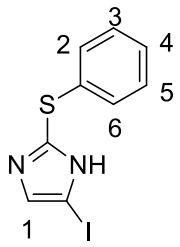
CAS Registry Number: 1051373-75-1

Procedure

Imidazole **13** (1 mmol,) was dissolved in EtOH (12 mL) and concentrated HCl (1 mL) was added. The mixture was heated at reflux for 3 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ (10 mL) was added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extract was dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product which was purified by flash chromatography using a mixture of CH_2Cl_2/MeOH 97:03 as eluent.

Yield: 87%

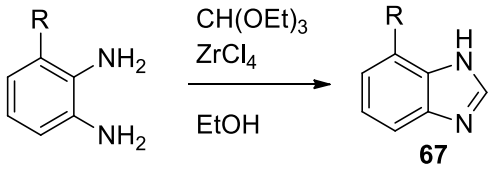
Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.23 (m, 5H, 2-6), 7.17 (s, 1H, 1).

7.1.5. Synthesis of 7-substituted benzimidazole derivatives (67)

7.1.5.1. General procedure



67

A mixture of o-phenylenediamine (1 mmol, 1 equiv.), triethyl orthoformate (1.2 equiv.) and $ZrCl_4$ (0.1 mmol, 0.1 equiv.) in 2 mL EtOH was stirred at room temperature for 2 hours. After completion of the reaction, as indicated by TLC, the solvent was evaporated under reduced pressure and the resulting product was directly purified by flash chromatography using a mixture of CH_2Cl_2/MeOH as eluent.

*7.1.5.2. Characterization of 7-methyl-1*H*-benzo[d]imidazole **(67a)***

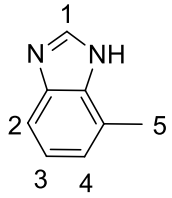
Chemical formula: $C_8H_8N_2$

Molecular weight: 132.17 g.mol^{-1}
CAS Registry Number: 4887-83-6

Purification conditions: flash chromatography CH_2Cl_2/MeOH 93:07

Yield: 92%

Aspect: brown solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (s, 1H, 1), 7.51 (d, 1H, *J* = 8.04 Hz, 2), 7.26-7.21 (m, 1H, 3), 7.13 (d, 1H, *J* = 7.29 Hz, 4), 2.65 (s, 3H, 5).

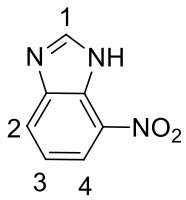
*7.1.5.3. Characterization of 7-nitro-1H-benzo[d]imidazole (**67c**)*

Chemical formula: $C_7H_5N_3O_2$
Molecular weight: 163.16 g.mol^{-1}
CAS Registry Number: 10597-52-1

Purification conditions: flash chromatography CH_2Cl_2/MeOH 92:08

Yield: 78%

Aspect: orange solid



^{1}H NMR (300 MHz, d_6-dmso): δ 13.3 (bs, NH), 8.46 (s, 1H, 1), 8.19-8.16 (m, 2H, 2 and 4), 7.46-7.40 (m, 1H, 3).

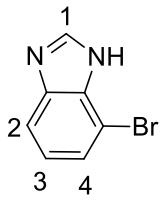
*7.1.5.4. Characterization of 7-bromo-1H-benzo[d]imidazole (**67b**)*

Chemical formula: $C_7H_5B_rN_2$
Molecular weight: 197.03 g.mol^{-1}
CAS Registry Number: 83741-35-9

Purification conditions: flash chromatography CH_2Cl_2/MeOH 92:08

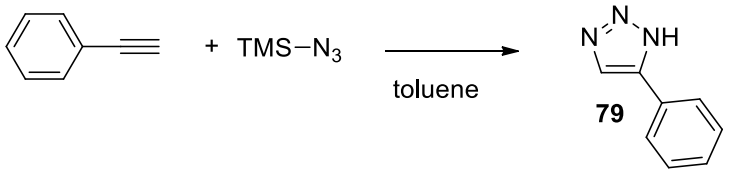
Yield: 89%

Aspect: brown solid



^{1}H NMR (300 MHz, d_6-dmso): δ 12.7 (bs, NH), 8.31 (s, 1H, 1), 7.55-7.53 (m, 1H, 4), 7.41 (d, 1H, *J* = 7.74 Hz, 2), 7.14 (t, 1H, *J* = 7.88 Hz, 3).

7.1.6. Synthesis of 5-phenyl-1H-1,2,3-triazole (79)



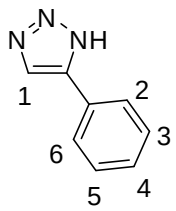
Chemical formula: $C_8H_7N_3$
Molecular weight: 145.16 g.mol^{-1}
CAS Registry Number: 1680-44-0.

Procedure

To a stirring solution of phenylacetylene (1.9 mmol, 1 equiv., 0.22 mL) in toluene (4 mL) was added trimethylsilylazide (3.84 mmol, 2 equiv., 0.52 mL). The resulting solution was heated at reflux for 2 days. To this mixture was added water (0.5 mL) and after evaporation, the residue was purified by flash chromatography using a mixture of AcOEt/cyclohexane 50:50 as eluent.

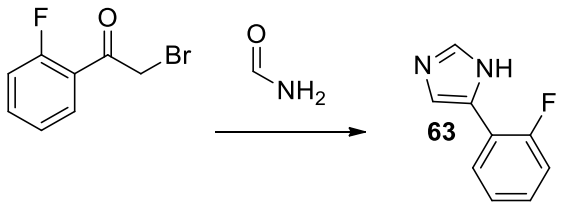
Yield: 13%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (s, 1H, 1), 7.84-7.82 (m, 2H, 2,6), 7.49-7.37 (m, 3H, 3-5).

7.1.7. Synthesis of 5-(2-fluorophenyl)-1H-imidazole (63)



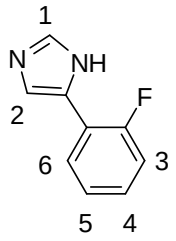
Chemical formula: $C_9H_7FN_2$
Molecular weight: 162.16 $g.mol^{-1}$
CAS Registry number: 912763-52-1

Procedure

A solution of 2-bromo-(2-fluorophenyl)ethanone (0.92 mmol) was heated (170-180 °C) in formamide (15 mL) for 7 h. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extract was dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product which was purified by flash chromatography using a mixture of CH_2Cl_2/MeOH 93:07 as eluent.

Yield: 70%

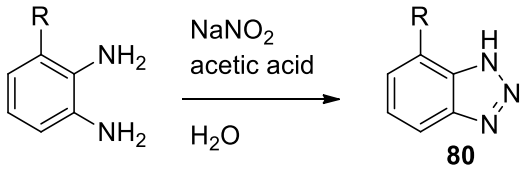
Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06-8.00 (m, 1H, 1), 7.74 (s, 1H, 2), 7.54-7.52 (m, 1H, 6), 7.24-7.07 (m, 3H, 3-5).

7.1.8. Synthesis of 7-substituted benzotriazoles (80)

7.1.8.1. General procedure



80

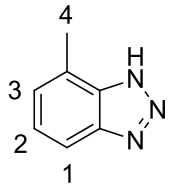
A solution of the diamine (1.6 mmol, 1 equiv.,) in acetic acid (1 mL) and water (2 mL) was treated dropwise with a solution of sodium nitrite (1.1 equiv.) in water (2 mL). The reaction mixture was stirred at room temperature for 18 hours. The brown solid formed was filtered off, washed with water and died under reduced pressure.

*7.1.8.2. Characterization of 7-methyl-1*H*-benzo[d][1,2,3]triazole (**80a**)*

Chemical formula: $C_7H_7N_3$
Molecular weight: 133.15 g.mol^{-1}
CAS Registry Number: 29878-31-7

Yield: 70%

Aspect: brown solid



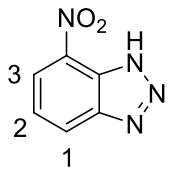
^{1}H NMR (300 MHz, $CDCl_3$): δ7.65 (d, 1H, J = 8.25 Hz, 1 or 3), 7.39-7.34 (m, 1H, 2), 7.21 (d, 1H, J = 7.08 Hz, 1 or 3), 2.76 (s, 3H, 4).

*7.1.8.3. Characterization of 7-nitro-1*H*-benzo[d][1,2,3]triazole (**80b**)*

Chemical formula: $C_6H_4N_4O_2$
Molecular weight: 164.12 g.mol^{-1}
CAS Registry Number: 6299-39-4

Yield: 86%

Aspect: brown solid

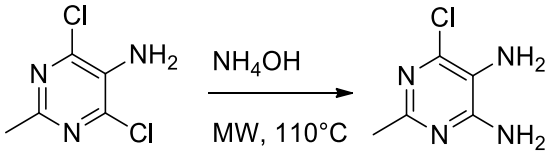


^{1}H NMR (300 MHz, d_6-dmso): δ 13.03 (bs, NH), 8.53-8.44 (m, 2H, 3.1), 7.59 (t, 1H, J = 8.00 Hz, 2)

.

7.1.9. Synthesis of purines (87)

*7.1.9.1. Synthesis of 6-chloro-2-methylpyrimidine-4,5-diamine (**86a**)*



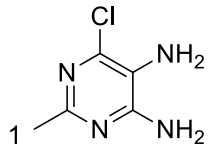
Chemical formula: $C_5H_7ClN_4$
Molecular weight: 158.59 $g.mol^{-1}$
CAS Registry Number: 933-80-2

Procedure

4,6-Dichloro-2-methylpyrimidin-5-amine (1.12 mmol, 1 equiv., 200 mg) was dissolved in aqueous NH_4OH (33%, 3 mL) in a seal tube. The mixture was heated under microwave heating at 110°C for 30 min. The residue was concentrated under reduced pressure. The solid obtained was purified by flash chromatography using a mixture of CH_2Cl_2/MeOH 93:07 as eluent.

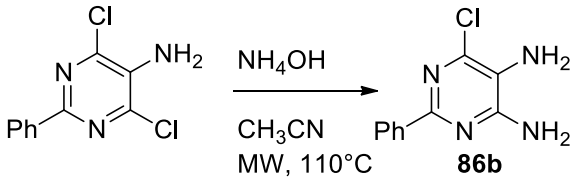
Yield: 78%

Aspect: white solid



^{1}H NMR (300 MHz, d_6-dmso): δ 6.65 (bs, 2H, NH_2), 4.70 (bs, 2H, NH_2), 2.19 (s, 3H, 1).

*7.1.9.2. Synthesis of 6-chloro-2-phenylpyrimidine-4,5-diamine (**86b**)*



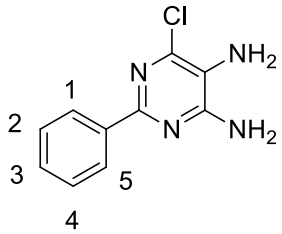
Chemical formula: $C_{10}H_9ClN_4$
Molecular weight: 220.66 g.mol^{-1}
CAS Registry Number: 424830-76-2

Procedure

4,6-dichloro-2-phenylpyrimidin-5-amine (0.83 mmol, 1 equiv., 200 mg) was dissolved in aqueous NH_4OH (33%, 3 mL) and CH_3CN (4 mL) in a sealed tube. The mixture was heated under microwave irradiation at 90°C for 60h. The residue was concentrated under reduced pressure.

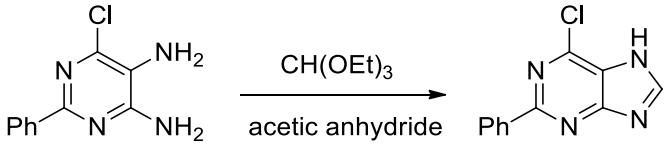
Yield: 91%

Aspect: white solid



^{1}H NMR (300 MHz, d_6-dmso): δ 8.13-8.10 (m, 2H, 1,5), 7.40-7.37 (m, 3H, 2-4), 6.82 (bs, 2H, NH_2), 5.10 (bs, 2H, NH_2).

*7.1.9.3. Synthesis of 6-chloro-2-phenyl-7*H*-purine (**87b**)*



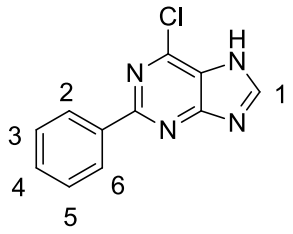
Chemical formula: $C_{11}H_7ClN_4$
Molecular weight: 230.65 g.mol^{-1}
CAS Registry Number: 106823-67-0

Procedure

6-Chloro-2-phenylpyrimidine-4,5-diamine (6.80 mmol, 1 equiv., 150 mg) was refluxed for 90 min in triethyl orthoformate (47.98 mmol, 7.06 equiv., 0.81 mL) and acetic anhydride (47.49 mmol, 6.99 equiv., 0.45 mL). After evaporation under reduced pressure the mixture was diluted with hexane and the solid obtained was crystallized in EtOH/Et_2O.

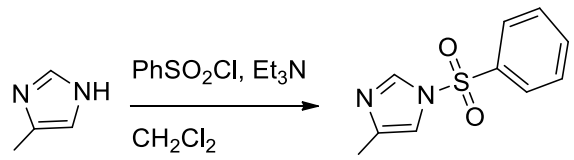
Yield: 70%

Aspect: yellow solid



^{1}H NMR (300 MHz, d_6-dmso): δ 9.12 (s, 1H, 1), 8.46-8.43 (m, 2H, 2,6), 7.60-7.58 (m, 3H, 3-5).

7.2. Synthesis of the intermediate 55b used in the development of the general method



Name: 4-methyl-1-(phenylsulfonyl)-1*H*-imidazole
Chemical formula: $C_{10}H_{10}N_2O_2S$
Molecular weight: 222.26 g.mol^{-1}

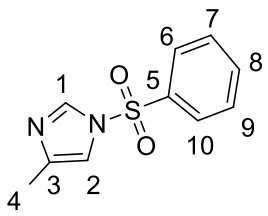
Procedure

4-Methylimidazole (1.83 mmol, 1 equiv., 150 mg) was dissolved in CH_2Cl_2 (4.5 mL) in a flask under argon. Successively, Et_3N (2.20 mmol, 1.2 equiv., 0.31 mL) and $PhSO_2Cl$ (2.01 mmol, 1.1 equiv., 0.22 mL) were added dropwise. The mixture was stirred overnight. CH_2Cl_2/MeOH (30 mL) were added and washed twice with an aqueous solution of 10 % of K_2CO_3 (15 mL). The combined aqueous phases were extracted twice with CH_2Cl_2/MeOH (15 mL). The organic phases were collected and washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure.

Purification conditions: flash chromatography CH_2Cl_2/MeOH 98:02

Yield: 75 %

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97-7.92 (m, 3H, 1, 6, 10), 7.71-7.55 (m, 3H, 7-9), 7.00 (s, 1H, 2), 2.20 (s, 3H, 4).

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4 (5), 138.3 (3), 136.3 (1 or 8), 134.8 (1 or 8), 129.9 (2C, 6,10), 127.3 (2C, 7,9), 113.5 (2), 13.7 (4).

IR (cm^{-1}) : 3107, 1448, 1375, 1174, 1091, 1080, 997, 729, 685.

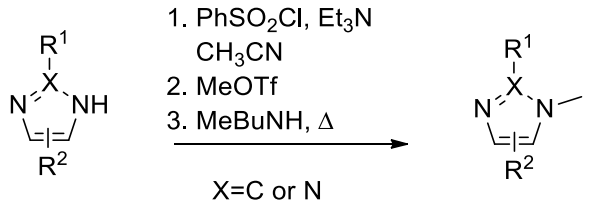
M.P.: 70-71°C

ESI-MS m/z: **M+1** 223.

HRMS calcd for $C_{10}H_{11}N_2O_2S$: 223.0541, found 223.0551.

7.3. Protocole and analyses of products

7.3.1. General protocole

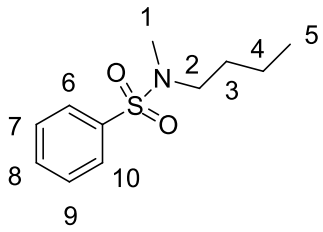


Imidazole (1 equiv., 100mg) was dissolved in CH_3CN in a flask under argon atmosphere. Successively, Et_3N (1.2 equiv.) and $PhSO_2Cl$ (1.1 equiv.) were added dropwise. The mixture was stirred for 8 hours and then MeOTf (1.5 equiv.) was added. After 24 hours, MeBuNH (2.1 equiv.) was added and the solution was heated at 80°C overnight**.** CH_2Cl_2 (10 mL) was added and the solution was washed twice with an aqueous solution of NaOH 1M (10 mL). The aqueous phases were extracted with CH_2Cl_2 (10 mL). The organic phases were dried ($MgSO_4$), and concentrated under reduced pressure.

When the final product could be purified, conditions of purification were noted. Otherwise, the final product was obtained with the secondary product and conversion was noted. For compounds **58**, **68**, **69**, a C18 solid phase extraction (SPE) was done.

7.3.2. Characterization of the secondary product: N-butyl-N-methylbenzenesulfonamide

Chemical formula: $C_{11}H_{17}NO_2S$
Molecular weight: 227.32 g.mol^{-1}
CAS Registry Number: 119059-69-7



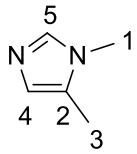
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79-7.76 (m, 2H, 6,10), 7.61-7.49 (m, 3H, 7-9), 3.00 (t, 2H, *J* = 7.5 Hz, 2), 2.72 (s, 3H, 1), 1.56-1.44 (m, 2H, 3-4), 1.41-1.29 (m, 2H, 3-4), 0.92 (t, 3H, *J* = 7.5 Hz, 5).

7.3.3. Characterization of 1,5-dimethyl-1H-imidazole (58)

Chemical formula: $C_5H_8N_2$
Molecular weight: 96.13 g.mol^{-1}
CAS Registry Number: 10447-93-5

Conversion: 80%

Yield: 39% (SPE, H_2O +1% TFA/CH_3CN 90:10)



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 1H, 5), 6.77 (s, 1H, 4), 3.54 (s, 3H, 1), 2.19 (s, 3H, 3).
^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2 (5), 127.8 (2), 126.1 (4), 31.3 (1), 9.1 (3).

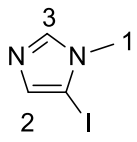
Regioselectivity determined by ^{1}H-^{15}N HMBC: N1 162.8 ppm and N3 250.7 ppm.

7.3.4. Characterization of 5-iodo-1-methyl-1H-imidazole (68)

Chemical formula: $C_4H_5IN_2$
Molecular weight: 208.00 g.mol^{-1}
CAS Registry Number: 71759-88-1

Conversion: 66%

Yield: 51% (SPE, H_2O +1% TFA/CH_3CN 90:10)



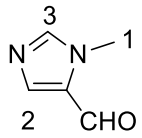
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (s, 1H, 3), 7.16 (s, 1H, 2), 3.64 (s, 3H, 1).

7.3.5. Characterization of 1-methyl-1H-imidazole-5-carbaldehyde (69)

Chemical formula: $C_5H_6N_2$
Molecular weight: 110.11 $g.mol^{-1}$
CAS Registry Number: 39021-62-0

Conversion: 90%

Yield: 37% (SPE, H_2O +1% TFA/CH_3CN 90:10)



^{1}H NMR (300 MHz, $CDCl_3$): δ 9.77 (s, 1H, CHO), 7.77 (s, 1H, 2), 7.61 (s, 1H, 3), 3.95 (s, 3H, 1).

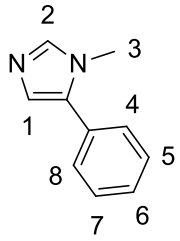
7.3.6. Characterization of 1-methyl-5-phenyl-1H-imidazole (71)

Chemical formula: $C_{10}H_{10}N_2$
Molecular weight: 158.20 $g.mol^{-1}$
CAS Registry Number: 2154-38-3

Purification conditions: flash chromatography CH_2Cl_2/MeOH 97:03+ 3% Et_3N

Yield: 70%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ7.61 (s, 1H, 2), 7.45-7.38 (m, 5H, 4-8), 7.12 (s, 1H, 1), 3.69 (s, 3H, 3).

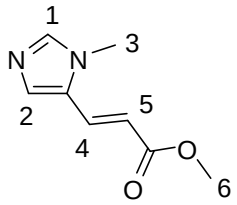
7.3.7. Characterization of (E)-methyl 3-(1-methyl-1H-imidazol-5-yl)acrylate (76)

Chemical formula: $C_8H_{10}N_2O_2$
Molecular weight: 166.18 $g.mol^{-1}$
CAS Registry Number: 79960-24-0

Purification conditions: flash chromatography CH_2Cl_2/MeOH 92:08 + 3% Et_3N

Yield: 50%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.47 (m, 3H, 1,2,4), 6.27 (d, 2H, *J* = 16.2 Hz, 5), 3.80 (s, 3H, 6), 3.73 (s, 3H, 3).

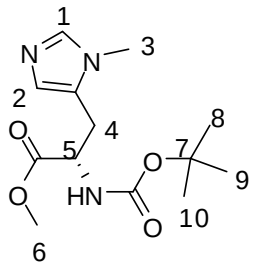
7.3.8. Characterization of (S)-methyl 2-(tert-butoxycarbonylamino)-3-(1-methyl-1H-imidazol-5-yl)propanoate (77)

Chemical formula: $C_{13}H_{21}N_3O_4$
Molecular weight: 283.32 g.mol^{-1}
CAS Registry Number: 72212-51-2

Purification conditions: flash chromatography CH_2Cl_2/MeOH 92:08 + 3% Et_3N

Yield: 42%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (s, 1H, 1), 6.77 (s, 1H, 2), 5.15 (m, 1H, 7), 4.52 (m, 1H, 5), 3.72 (s, 3H, 6), 3.55 (s, 3H, 3), 3.07-3.08 (m, 2H, 4), 1.40 (s, 9H, 8-10).

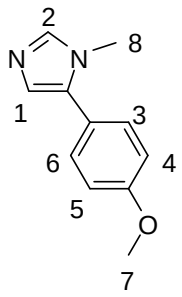
7.3.9. Characterization of 5-(4-methoxyphenyl)-1-methyl-1H-imidazole (73a)

Chemical formula: $C_{11}H_{12}N_2O$
Molecular weight: 188.23 g.mol^{-1}
CAS Registry Number: 190377-29-8

Purification conditions: flash chromatography CH_2Cl_2 + 3% Et_3N

Yield: 70%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ7.54 (s, 1H, 2), 7.31 (d, 2H, *J* = 8.73 Hz, 4-5), 7.04 (s, 1H, 1), 6.97 (d, 2H, *J* = 8.73 Hz, 3,6), 3.85 (s, 3H, 7), 3.64 (s, 3H, 8).

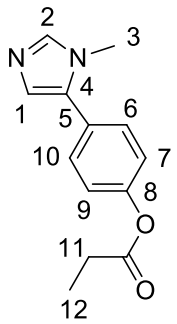
7.3.10. Characterization of 4-(1-methyl-1H-imidazol-5-yl)phenyl propionate (73b)

Chemical formula: $C_{13}H_{14}N_2O_2$
Molecular weight: 230.26 g.mol^{-1}

Purification conditions: flash chromatography CH_2Cl_2 + 3% Et_3N

Yield: 40%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, 2H, *J* = 8.4 Hz, 7,9), 7.62 (s, 1H, 2), 7.47 (d, 2H, *J* = 8.4 Hz, 6, 10), 7.20 (S, 1H, 1), 4.40 (q, 2H, *J* = 7.1 Hz, 11), 3.72 (s, 3H, 3), 1.41 (t, 3H, *J* = 7.1 Hz, 12).
^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2 (11), 140.0 (2), 134.2 (8), 132.6 (4), 130.0 (8-9), 129.6 (5), 129.2 (1), 127.8 (6, 10), 61.2 (11), 32.9 (3), 14.4 (12).

IR (cm^{-1}) : 1709, 1610, 1489, 1275, 1180, 1103, 1013, 922, 825, 773, 706.

ESI-MS m/z (%): 231 (100) $[M+H]^+$, 203 (15).

HRMS calcd for $C_{13}H_{15}N_2O_2$: 231.1134, found 231.1126.

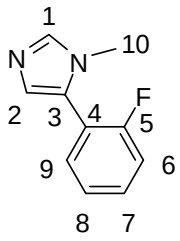
7.3.11. Characterization of 5-(2-fluorophenyl)-1-methyl-1H-imidazole (75)

Chemical formula: $C_{10}H_9FN_2$
Molecular weight: 176.19 g.mol^{-1}

Purification conditions: flash chromatography CH_2Cl_2 + 3% Et_3N

Yield: 32%

Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (s, 1H, 1), 7.43-7.13 (m, 4H, 6-9), 7.10 (s, 1H, 2), 3.59 (s, 3H, 10).
^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0 (5, *J* = 246.4 Hz), 139.2 (1), 131.9 (9 or 8), 130.5 (7, *J* = 8.1 Hz), 129.5 (8 or 9), 127.7 (3), 124.5 (2), 117.7 (4, *J* = 15.4 Hz), 116.0 (6, *J* = 21.9 Hz), 32.2 (10).
^{19}F NMR (282 MHz, CDF_3): δ -113.1.

IR (cm^{-1}) : 1556, 1477, 1229, 1203, 1111, 916, 760.

APCI-MS m/z (%): 177 (100) $[M+H]^+$.

HRMS calcd for $C_{10}H_9N_2F$: 176.07443, found 176.07414.

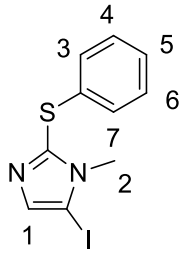
7.3.12. Characterization of 5-iodo-1-methyl-2-(phenylthio)-1H-imidazole (72)

Chemical formula: $C_{10}H_9IN_2S$
Molecular weight: 316.16 $g.mol^{-1}$
CAS Registry Number: 220480-63-7

Purification conditions: flash chromatography CH_2Cl_2/MeOH 95:05

Yield: 53%

Aspect: white solid



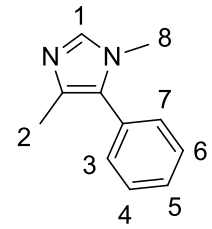
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.19 (m, 6H, 1,3-7), 3.64 (s, 3H, 2).

7.3.13. Characterization of 1,4-dimethyl-5-phenyl-1H-imidazole (73d)

Chemical formula: $C_{11}H_{12}N_2$
Molecular weight: 172.23 $g.mol^{-1}$
CAS Registry Number: 62576-11-8

Purification conditions: flash chromatography CH_2Cl_2/MeOH 93:07 + 3% Et_3N

Yield: 47%



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.28 (m, 6H, 1,3-7), 3.55 (s, 3H, 8), 2.23 (s, 3H, 2).

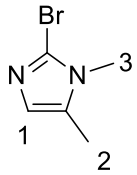
Regioselectivity determined by ^{1}H-^{15}N HMBC: N1 159.4 ppm and N3 257.6 ppm.

7.3.14. *Characterization of 2-bromo-1,5-dimethyl-1H-imidazole (78)*

Chemical formula: $C_5H_7BrN_2$
Molecular weight: 175.03 g.mol^{-1}
CAS Registry Number: 235426-31-0

Purification conditions: flash chromatography CH_2Cl_2 + 3% Et_3N

Yield: 38%



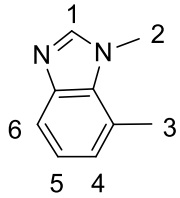
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 1H, 1), 3.47 (s, 3H, 3), 2.20 (s, 3H, 2).

7.3.15. *Characterization of 1,7-dimethyl-1H-benzo[d]imidazole (74a)*

Chemical formula: $C_9H_{10}N_2$
Molecular weight: 146.19 g.mol^{-1}
CAS Registry Number: 17583-45-8

Purification conditions: flash chromatography CH_2Cl_2/MeOH 98:02

Yield: 90%



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 1H, 1), 7.63 (d, 1H, *J* = 8.1 Hz, 4), 7.15 (t, 1H, *J* = 7.7 Hz, 5), 7.03 (d, 1H, *J* = 7.2 Hz, 6), 4.08 (s, 3H, 2), 2.74 (s, 3H, 3).

Regioselectivity determined by ^{1}H-^{15}N HMBC: N1 144.0 ppm and N3 240.4 ppm.

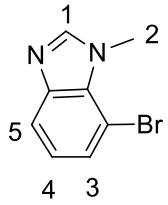
7.3.16. *Characterization of 7-bromo-1-methyl-1H-benzo[d]imidazole (74b)*

Chemical formula: $C_8H_7BrN_2$
Molecular weight: 211.06 g.mol^{-1}

CAS Registry Number: 1233542-00-1

Purification conditions: flash chromatography CH_2Cl_2/MeOH 95:05

Yield: 24%



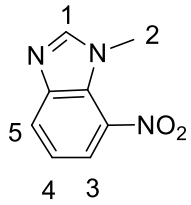
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (s, 1H, 1), 7.80 (d, 1H, *J* = 8.2 Hz, 3), 7.49 (d, 1H, *J* = 7.7 Hz, 5), 7.19 (t, 1H, *J* = 7.9 Hz, 4), 4.23 (s, 3H, 2).

7.3.17. Characterization of 7-nitro-1-methyl-1H-benzo[d]imidazole (74c)

Chemical formula: $C_8H_7N_3O_2$
Molecular weight: 177.16 g.mol^{-1}
CAS Registry Number: 57155-23-4

Purification conditions: flash chromatography CH_2Cl_2/MeOH 95:05

Yield: 52%



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 1H, 1), 8.16-8.07 (m, 2H, 3,5), 7.41 (t, 1H, *J* = 8.1 Hz, 4), 4.11 (s, 3H, 2).

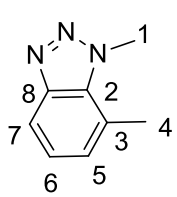
7.3.18. Characterization of 1,7-dimethyl-1H-benzo[d][1,2,3]triazole (82a)

Chemical formula: $C_8H_9N_3$
Molecular weight: 147.18 g.mol^{-1}

Purification conditions: flash chromatography EA/cyclohexane 50:50

Yield: 18%

Aspect: sticky brown solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, 1H, *J* = 7.9 Hz, 7 or 5), 7.28-7.18 (m, 2H, 6 and 5 or 7), 4.51 (s, 3H, 1), 2.78 (s, 3H, 4).
^{13}C NMR (75 MHz, $CDCl_3$): δ 146.6 (2), 133.0 (8), 128.5 (5-7), 124.3 (5-7), 121.0 (3), 117.8 (5-7), 37.0 (1), 18.3 (4).

Regioselectivity determined by ^{1}H-^{15}N HMBC: 217.5, 334.4, 378.5 ppm

IR (cm^{-1}) : 1734, 1452, 1373, 1211, 1061, 1011, 870, 791, 756, 735.

APCI-MS m/z (%): 148 (100) $[M+H]^{+}$.

HRMS calcd for $C_{10}H_9N_2F$:148.0869, found 148.0870.

7.3.19. Characterization of 1-methyl-5-phenyl-1H-1,2,3-triazole (81)

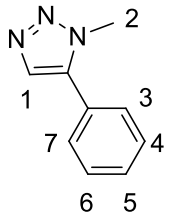
Chemical formula: $C_9H_9N_3$
Molecular weight: 159.19 $g.mol^{-1}$

CAS Registry Number: 15966-55-9

Purification conditions: flash chromatography EA/cyclohexane 40:60

Yield: 7%

Aspect: solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (s, 1H, 1), 7.51-7.40 (m, 5H, 3-7), 4.07 (s, 3H, 2).

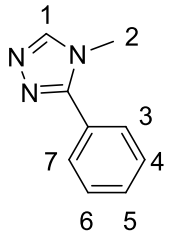
7.3.20. Characterization of 4-methyl-3-phenyl-4H-1,2,4-triazole (84)

Chemical formula: $C_9H_9N_3$
Molecular weight: 159.19 $g.mol^{-1}$
CAS Registry Number: 3357-31-1

Purification conditions: flash chromatography AE/cyclohexane 40:60

Yield: 18%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.64 (s, 1H, 1), 7.72-7.70 (m, 2H, 3,7), 7.56-7.54 (m, 3H, 4-6), 3.86 (s, 3H, 2).

7.4. Synthesis of a mix of isomer of disubstituted azole

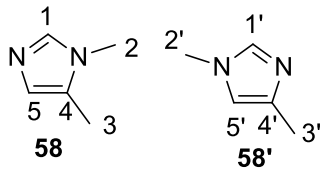
7.4.1. General procedure

Monosubstituted azole (1 equiv., 100 mg) was dissolved in THF (3 mL). At 0°C, NaH was added (1.05 equiv.) slowly. Then the cooling bath was removed and the mixture stirred until no degagement of gaz was observed. MeI (1.05 equiv.) was added and the solution stirred for 48 hours. CH_2Cl_2 (10 mL) was added and the solution was washed twice with an aqueous solution of NaOH 1M (10 mL). The aqueous phases were extracted with CH_2Cl_2 (10 mL). The organic phases were dried ($MgSO_4$), and concentrated under reduced pressure.

7.4.2. Characterization of 1,4- and 1,5-dimethylimidazole

Chemical formula: $C_5H_8N_2$
Molecular weight: 96.13 g.mol^{-1}

CAS Registry Number: 10447-93-5 and 6338-45-0



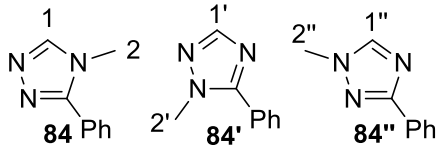
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (s, 1H, 1'), 7.33 (s, 1H, 1), 6.77 (s, 1H, 5'), 6.58 (s, 1H, 5), 3.62 (s, 3H, 2), 3.54 (s, 3H, 2'), 2.21 (s, 3H, 3), 2.19 (s, 3H, 3').

Selectivity: 38:62 (**58**;**58'**), attribution determined by ^{1}H-^{15}N HMBC.

7.4.3. Characterization of 1,5-, 2,5-, 4,5-methylphenyl-1,2,4-triazole

Chemical formula: $C_9H_9N_3$
Molecular weight: 159.19 g.mol^{-1}

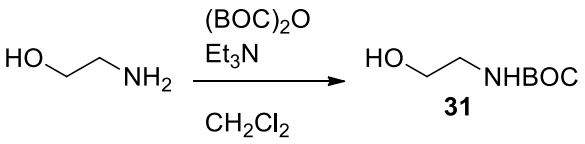
CAS Registry Number: 10447-93-5, 29945-53-7 and 39696-58-7



^{1}H NMR (300 MHz, $CDCl_3$): δ 8.25 (s, 1H, 1), 8.10-8.06 (m, H_{arom}), 7.94 (s, 1H, 1'), 7.69-7.66 (m, H_{arom}), 7.53-7.50 (m, H_{arom}), 7.44-7.40 (m, H_{arom}), 4.00 (s, 3H, 2' or 2''), 3.97 (s, 3H, 2' or 2''), 3.77 (s, 3H, 2).

Selectivity: 3.00:4.01:1.90

8. SYNTHESIS OF TERT-BUTYL (2-HYDROXYETHYL)CARBAMATE (31)



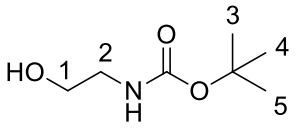
Chemical formula: $C_5H_{17}NO_3$
Molecular weight: 161.20 $g.mol^{-1}$
CAS Registry Number: 26690-80-2

Procedure

Ethanolamine (8.19 mmol, 1 equiv., 0.5 mL) was dissolved in CH_2Cl_2 (15 mL). Then, Et_3N (9 mmol, 1.1 equiv., 1.26 mL) and $(BOC)_2$ (9 mmol, 1.1 equiv., 2.11 mL) were added slowly and stirred at room temperature overnight. The mixture was washed twice with a saturated aqeous solution of NaCl (15 mL) and the combined aqeous phases were extractes with CH_2Cl_2 (15 mL). The organic phases were dried ($MgSO_4$), and concentrated under reduced pressure.

Yield: quantitative (without purification)

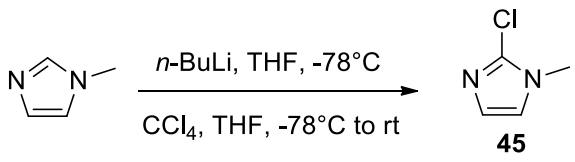
Aspect: yellow oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72-3.68 (m, 2H, 1), 3.31-3.26 (m, 2H, 2), 1.44 (m, 9H, 3-5).

9. SYNTHESIS OF 2-CHLORO-5-IODO-1-METHYL-1*H*-IMIDAZOLE (46) FROM *N*-METHYLIMIDAZOLE

9.1. Synthesis of 2-chloro-1-methyl-1H-imidazole (45)



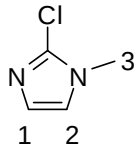
Chemical formula: $C_4H_5ClN_2$
Molecular weight: 116.55 g.mol^{-1}
CAS Registry Number: 253453-91-7

Procedure

N-Methylimidazole (2.5 mmol, 1 equiv., 0.20 mL) was dissolved in THF (5 mL). At -78°C, *n*-BuLi (3 mmol, 1.2 equiv., 1.2 mL) was added dropwise. Then the mixture was stirred at -45°C for one hour. After, at -78°C carbon tetrachloride (2.5 mmol, 1 equiv., 0.24 mL) dissolved in THF (5 mL) was added dropwise. The mixture was maintained at this temperature for one hour and then quenched with an aqueous solution saturated of ammonium chloride (2 mL). The mixture was diluted with diethyl ether and dried over $MgSO_4$, the solvent was evaporated under reduced pressure. The crude product was not purified and directly engaged in the following reaction.

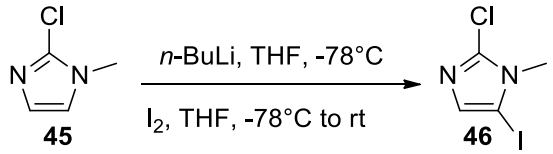
Yield: calculated over the two step (see compound **46**)

Aspect: dark oil



^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (d, 1H, *J* = 1.4 Hz, 1), 6.88 (d, 1H, *J* = 1.4 Hz, 2), 3.61 (s, 3H, 3).

9.2. Synthesis of 2-chloro-5-iodo-1-methyl-1H-imidazole (46)



Chemical formula: $C_4H_4ClIN_2$
Molecular weight: 242.45 g.mol^{-1}

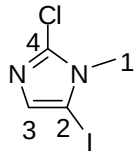
Procedure

Imidazole **45** (1.09 mmol, 1 equiv., 127 mg) was dissolved in THF (4 mL). The mixture was stirred for 15 min at -78°C and *n*-BuLi (1.09 mmol, 1 equiv., 0.44 mL) was added dropwise. Then the mixture was stirred at this temperature for 30 min. After, iodine (1.09 mmol, 1 equiv., 277 mg) dissolved in THF (2 mL) was added dropwise. The mixture was maintained at this temperature for one hour and

then quenched with a saturated aqueous solution of NH_4Cl (2 mL). The mixture was diluted with diethyl ether (15 mL) and dried over $MgSO_4$, the solvent was evaporated under reduced pressure. The crude product was not purified and directly engaged in the following reaction (Suzuki coupling).

Yield: 70%

Aspect: dark oil



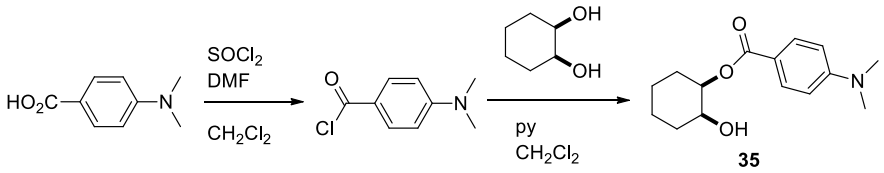
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07 (s, 1H, 3), 3.61 (s, 3H, 1).
^{13}C NMR (75 Hz, $CDCl_3$): δ 135.5 (3), 133.1 (2), 34.7 (1), (4) not observed.

IR (cm^{-1}): 2918, 2849 (C-H), 810, 926 (C-Cl and C-I).

ESI-MS m/z (%): 387 (100), 243 (23) $[M+H]^+$.

HRMS calcd for $C_4H_4ClIN_2$: 241.91022, found 241.91121.

10. SYNTHESIS OF (1R,2S)-2-HYDROXYCYCLOHEXYL 4-(DIMETHYLAMINO)BENZOATE (35)



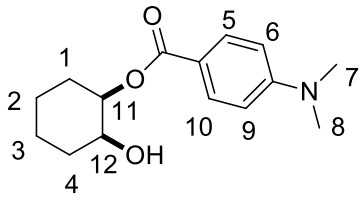
Chemical formula: $C_{15}H_{21}NO_3$
Molecular weight: 263.33 $g.mol^{-1}$
CAS Registry Number: 187985-69-9

Procedure

4-(Dimethylamino)benzoic acid (1 mmol, 1 equiv., 169 mg) was dissolved in CH_2Cl_2 (10 mL). Sulfurous dichloride (2.6 mmol, 2.6 equiv., 0.19 mL) and a few drops of DMF was added and stirred for 20 hours. The solvent was evaporated under reduced pressure. At 0°C, the acyl chloride formed in CH_2Cl_2 (5 mL) was added to a solution of (1R,2S)-cyclohexane-1,2-diol (1 mmol, 1 equiv., 117 mg) and pyridine (1.1 mmol, 1.1 equiv., 89 µL) in CH_2Cl_2 (5 mL). The mixture was stirred for 3 hours and the solvent was evaporated under reduced pressure. A flash chromatography was done as purification with AcOEt/cyclohexane 40:60 as eluent.

Yield: 64%

Aspect: white solid



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92-7.90 (m, 2H, 5,10), 6.66-6.62 (m, 2H, 6,9), 5.17-5.14 (m, 1H, (m, 1H, 11 or 12), 3.94-3.92 (m, 1H, 11 or 12), 3.03 (s, 6H, 7-8), 2.03-1.42 (bs, 8H, 1-4).

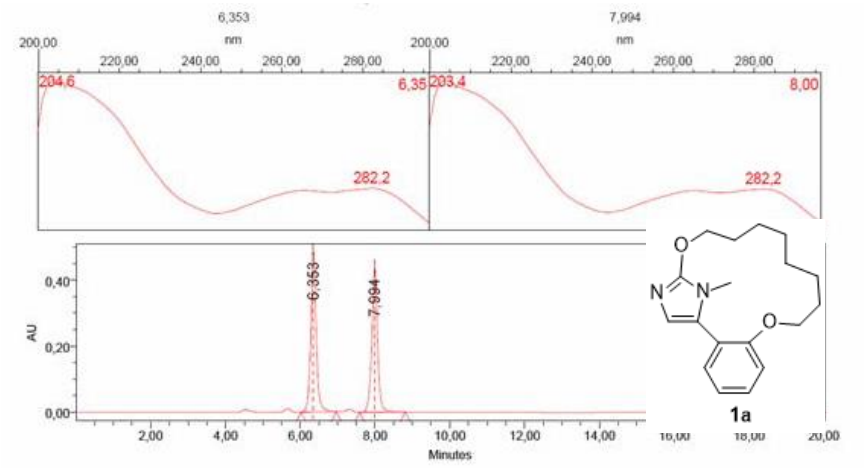
Chapter 8 - Appendix

1. CHIRALITY STUDIES

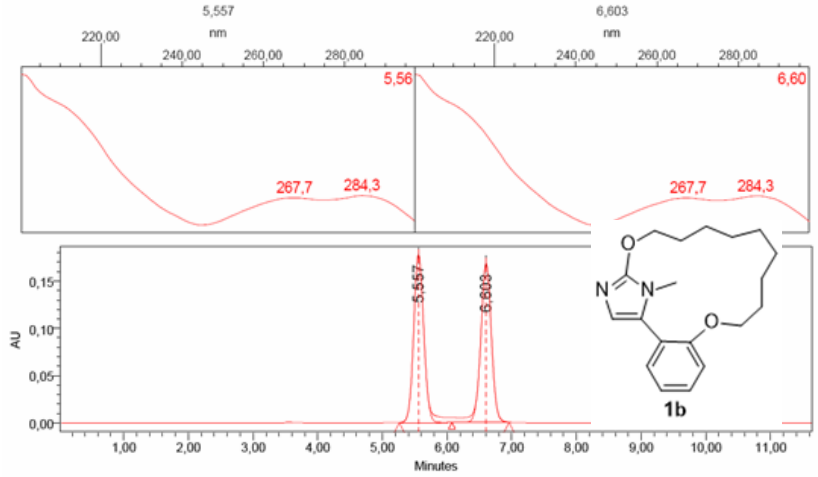
1.1. Chiral HPLC analysis of macrocycles 1a-d

HPLC analyses were performed at a flowrate of 1 mL/min on a Daicel Chiralpak® IB 4 6x250 mm 5 µm column with a mixture of 95% hexane and 5% ethanol (%v/v) as the mobile phase, using a UV detector. Unless mentionned otherwise, these analyses were performed at room temperature.

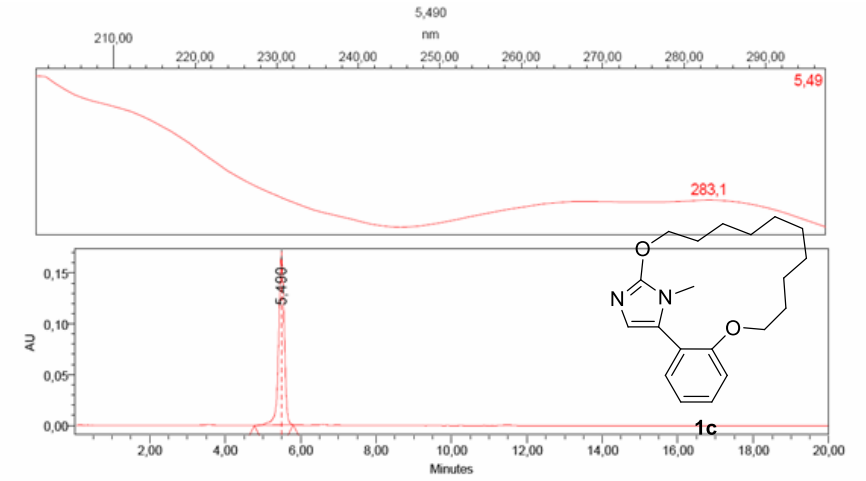
Compound **1a**



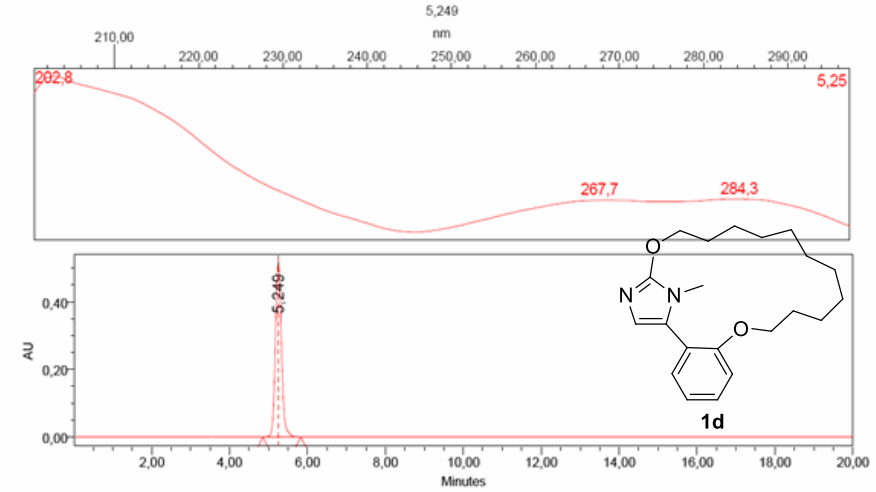
Compound **1b**



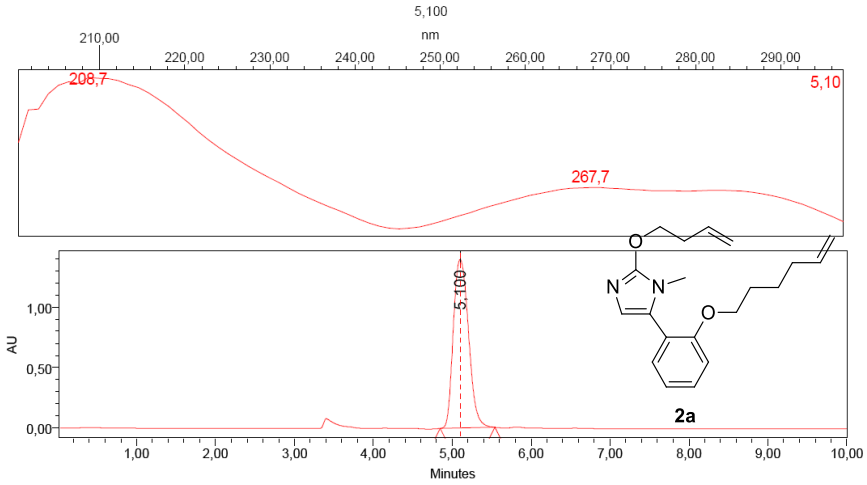
Compound **1c**



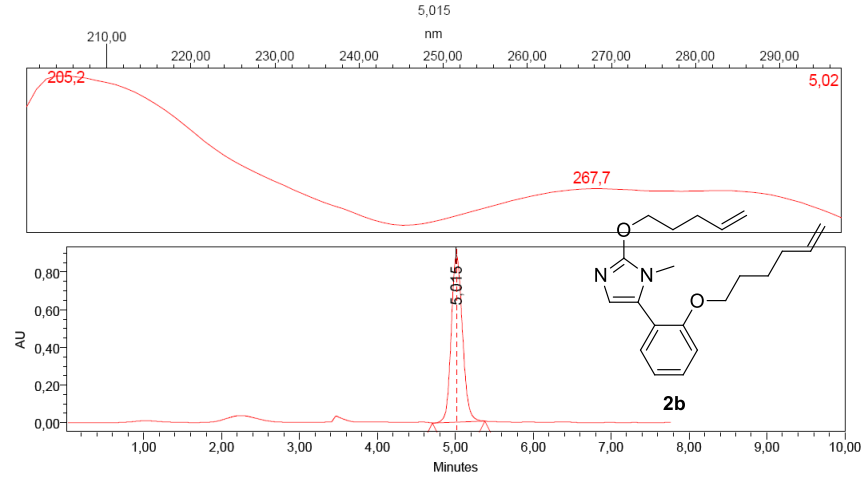
Compound **1d**



Compound **2a**

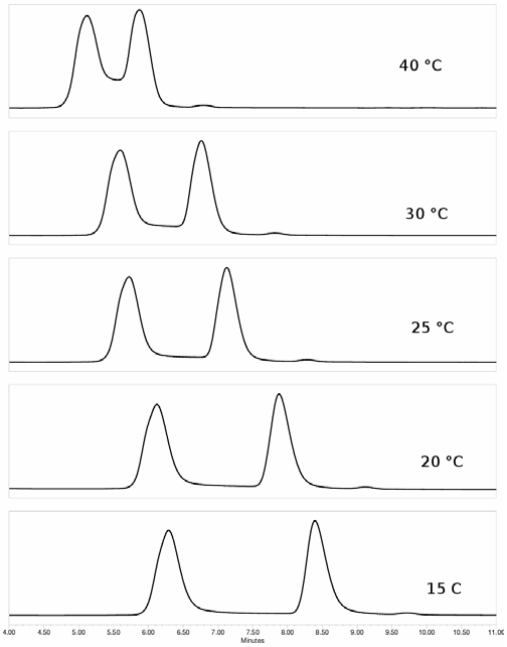


Compound **2b**



1.2. Investigation of the plateau-shape and dynamic HPLC study for 1b

HPLC analyses were performed at a flowrate of 1 mL/min on a Daicel Chiralpak® IB 4 6x250 mm 5 µm column with a mixture of 95% hexane and 5% ethanol (%v/v) as the mobile phase, using a UV detector. Temperature was controled using a Waters 2695 HPLC oven.



The kinetic constant for interconversion has been estimated at 30°C and 40°C using the method described by V. Schurig[216] .Measured experimental data and estimated kinetic constants and free energy barriers have been calculated with this formula:

$$k_1^{approx} = -\left[\frac{1}{t_R^A}\ln\left[\frac{1}{\Delta t_R}\left(1-\frac{h_{plateau}}{100}\left(0.5-\frac{1}{\sqrt{2\pi N}}\right)\right)\right]\right]$$

$$-\frac{1}{t_R^A}\ln\left[\begin{array}{l}\dfrac{1}{\Delta t_R}\left(1-\dfrac{h_{plateau}}{100}\left(0.5-\dfrac{1}{\sqrt{2\pi N}}\right)\right)\\ +\dfrac{0.01h_{plateau}e^{-\frac{\Delta t_R^2}{2\sigma_A^2}}-e^{-\frac{\Delta t_R^2}{8\sigma_A^2}}}{2\sigma_A\sqrt{2\pi}}\\ +\dfrac{0.01h_{plateau}-e^{-\frac{\Delta t_R^2}{8\sigma_B^2}}}{2\sigma_B\sqrt{2\pi}}\end{array}\right]$$

Where t_R = retention time; $h_{plateau}$ = height of plateau; N = number of theoretical plateau; σ = peak width at the base.

At 303.15 K → $\Delta G^{\neq}$ = 22.4 kcal/mol and at 313.15 K → $\Delta G^{\neq}$ = 22.9 kcal/mol.

1.3. Kinetic of isomerisation for 1b and 1c

The energy of activation (E_a) of the isomerization for **1b** and **1c** can be extracted from raw ^{1}H-NMR data using various methods.[217] The simplest method relies on the determination of the coalescence temperature (T_c) from which ΔG of the isomerization can be calculated. Disappointingly, this method cannot be used in our case because, eventhough we were able to determine the coalescence temperature of the isomerization, under our experimental conditions we were not able to reach sufficiently low temperature where the exchange rate between the isomers $k << \Delta\nu$. As a consequence we were not able to determine the maximum peak separation of the two isomers. Therefore we decided to determine the E_a of the isomerization by determining the exchange rates of the isomerization (k)[i] in the intermediate exchange range (rate constants between the coalescence temperature and slow exchange) using the following equation:

$$k = \frac{\pi}{\sqrt{2}}[(\Delta\theta_A)^e_{1/2} - (\Delta\theta_A)^0_{1/2}]$$

Where

$(\Delta\nu_A)^e_{1/2}$ is the linewidth at half height of exchanging peaks

$(\Delta\nu_A)^0_{1/2}$ is the linewidth at half height at temperature where the rate of exchange is very low.

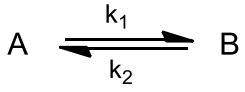
Since the spin-spin relaxation time is very long (≈ 5 sec.), $(\Delta\nu_A)^0_{1/2}$ is negligible and may be dropped out. It results that the equation can be simplified to

$$k = \frac{\pi}{\sqrt{2}}[(\Delta\theta_A)^e_{1/2}]$$

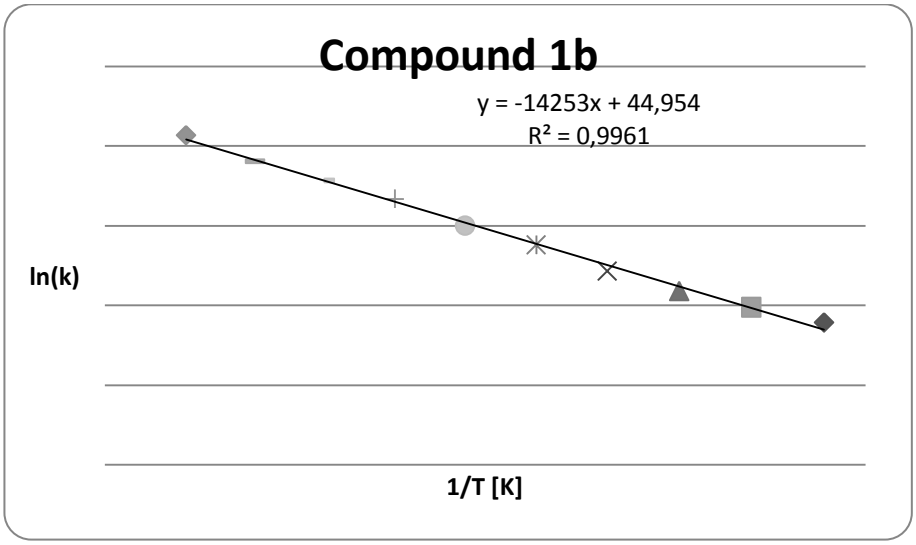
The energy of activation (E_a) was determined using an Arrhenius plot (ln(k) vs. 1/T) based on the knowledge of the isomerisation rate constant (k) at different temperatures.

Using this equation for compound **1b**, an Arrhenius plot of ln(k) vs.1/T gave a very linear fit with r^2 = 0.9961. The slope of the linear fit was -14253 and

[i] The exchange rate constant (k) in nearly all NMR exchange situations is actually k_1+k_2 in a system for **A** exchanging with **B**, where



therefore we could determine E_a of compound **1b** isomerization as E_a = 28.3 kcal/mol with and error of at least ± 2.8 kcal/mol.



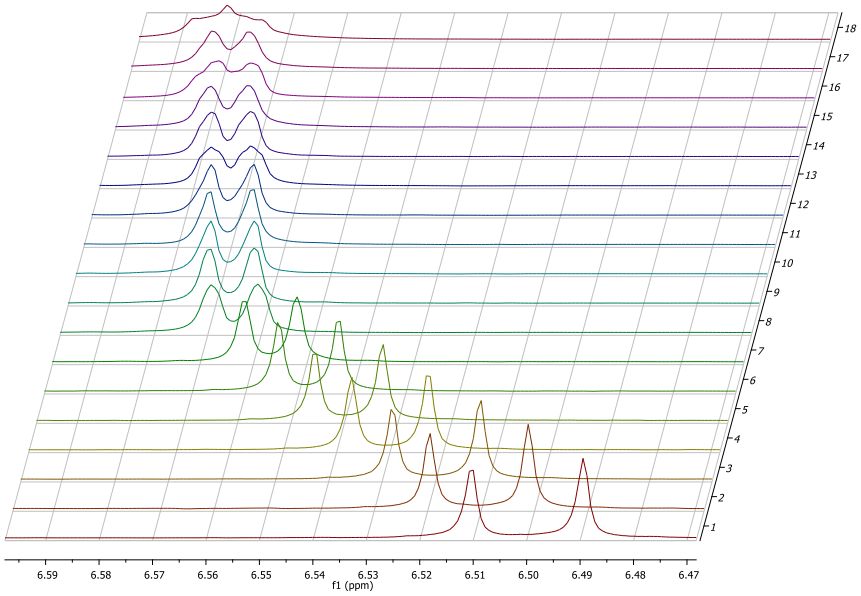
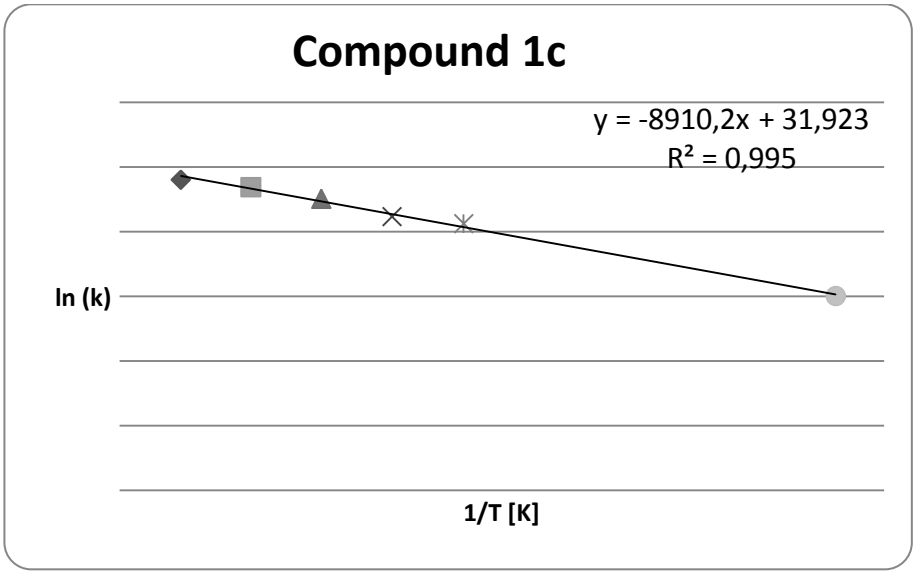


Figure 25 : ^{1}H-NMR spectra of imidazole hydrogen of **1b**.

For compound **1c**, using this equation, an Arrhenius plot of ln(*k*) vs.1/T gave a very linear fit with r^2 = 0.9950. The slope of the linear fit was -8910.2 and

therefore we could determine E_a of compound **1c** isomerization as E_a = 17.7 kcal/mol with and error of at least ± 1.8 kcal/mol.



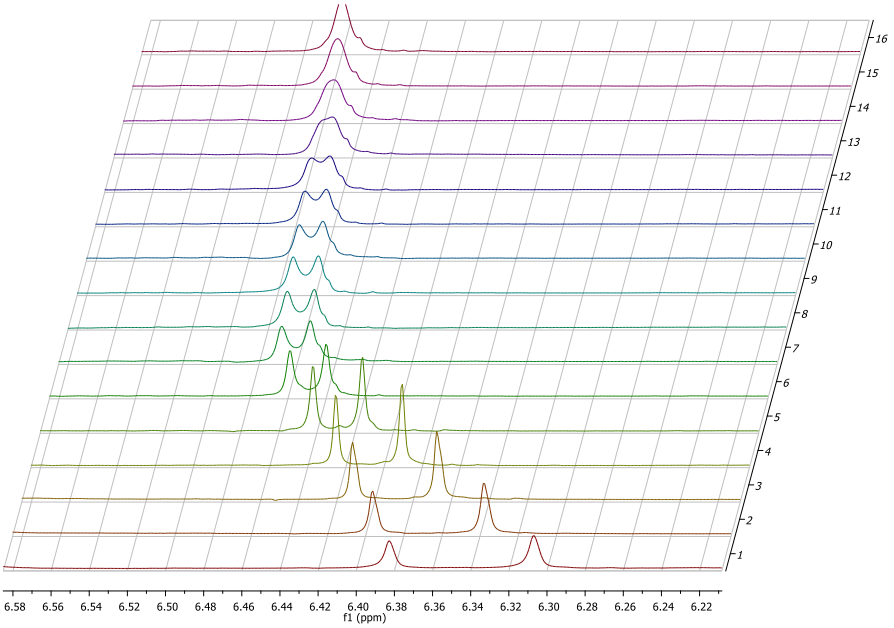


Figure 26 : ^{1}H-NMR spectra of imidazole hydrogen of **1c**.

2. COMPUTATIONAL DETAILS

All structures were obtained from geometry optimization in vacuum using the Jaguar 7.5 pseudospectral program package[218] These calculations used the well established B3LYP hybrid functional[219], as implemented in Jaguar 7.5, and the standard 6-31G* basis set[220] on all atoms (default grid and geometry convergence criteria were used). For the large systems considered here, there are several local minima or saddle points corresponding associated with multiple conformations of substituents (in particular the alicyclic chain). Each minimum was subjected to conformational searching at the B3LYP/6-31G* level, using Spartan, to identify the lowest-energy conformer.

Single point energy calculations were carried out at the SCS-MP2 level of theory with the cc-pVTZ basis[221], using the ORCA package.[222] Solvation effects were estimated at this level of theory using the conductor-like screening model (COSMO) as implemented in ORCA, using the parameters appropriate for chloroform.

Vibrational frequencies were computed for all stationary points at the B3LYP/6-31G* level of theory and were used to include corrections for zero-point energy as well as thermal and entropic corrections to compute free energies. The correct nature of stationary points was checked: transition states have only one imaginary frequency whereas minima have no imaginary frequency.

There are two conceivable pathways for isomerisation (Figure 27): rope-skipping motion can either involves crossing of the *N*-methyl group and alicyclic chain (**A**) or occur in the opposite direction with this latter going through the imidazole plane on the C^4-H side (**B**). We have obtained transition structure for both pathways with the results reported in table below.

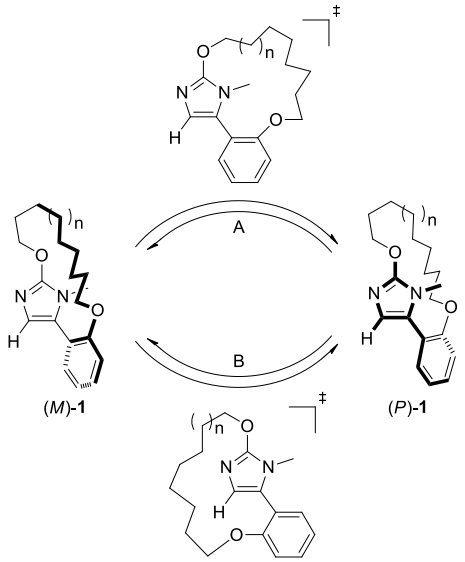


Figure 27 : Isomerization pathways.

Table 43 : Computed energy barrier (kcal/mol) for enantiomerisation of **1a-d** and **7** at the SCS-MP2/cc-pVTZ//B3LYP/6-31G* level.

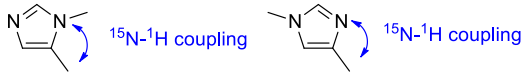
compound	TS-A	TS-B
1a	46.6	37.8
1b	27.0	24.8
1c	23.5	17.1
1d	18.5	14.5
7	9.1	5.2

3. DETERMINATION OF REGIOCHEMISTRY OF *N*-METHYLAZOLES

Regiochemistry was determined by ^{1}H-^{15}N HMBC for compounds **58**, **71**, **74a** and **82a** whereas for other *N*-methylazoles compounds data were compared to the literature (see manuscript for references). 2D NOE experiments were also attempted but no prove of regiochemistry was observed.

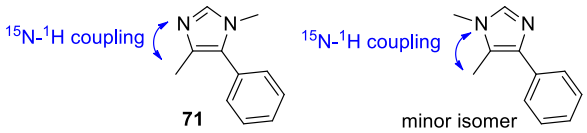
In the case of **58**, observation of a coupling between N(1) (162.8 ppm) and the ^{1}H of the methyl group at 2.19 ppm indicates that this latter is in position 5 (and not 4). In the minor isomer (obtained by classical alkylation methods), that is N(3)

(at 250.7 ppm) which shows a coupling with the C-CH_3. These attributions are in perfect agreement with reported ^{1}H NMR data (see Kashima, I.; Harada, Y.; Hosomi, A, *Heterocycles*, **1993**, *35*, 433-440).



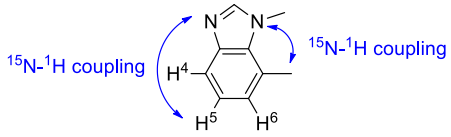
58 **58'**, other isomer

For **71**, the ^{1}H-^{15}N HMBC analysis of the major isomer shows a coupling between N(3) (257.6 ppm) and the C-CH_3 (2.23 ppm) allowing to identify it as 1,4-dimethyl-5-phenyl-1*H*-imidazole. In the minor isomer, that is the N(1) which shows a coupling with C-CH_3 in agreement with the 1,5-dimethyl-4-phenyl-1*H*-imidazole structure.



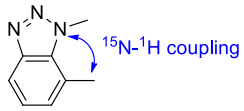
71 minor isomer

The ^{1}H-^{15}N HMBC analysis of **74a** reveals a coupling between H(5) (at 7.15 ppm) and N(3) (at 240.4 ppm) what allows attributing the 1,7-dimethyl-1*H*-benzo[d]imidazole regiochemistry to **74a**. A coupling between C-CH_3 (2.74 ppm) and N(1) (144.0 ppm) is also observed.



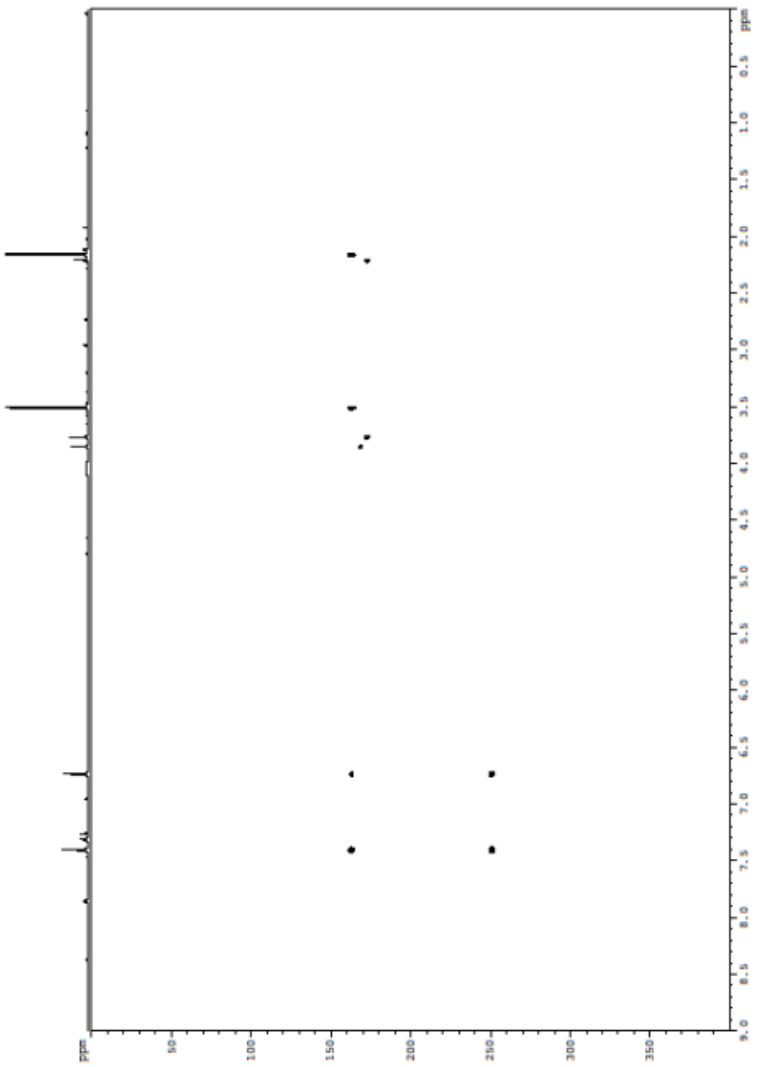
74a

Finally, the regiochemistry of **82a** was proved by the coupling between N(1) (217.5 ppm) and C-CH_3 (2.78 ppm).

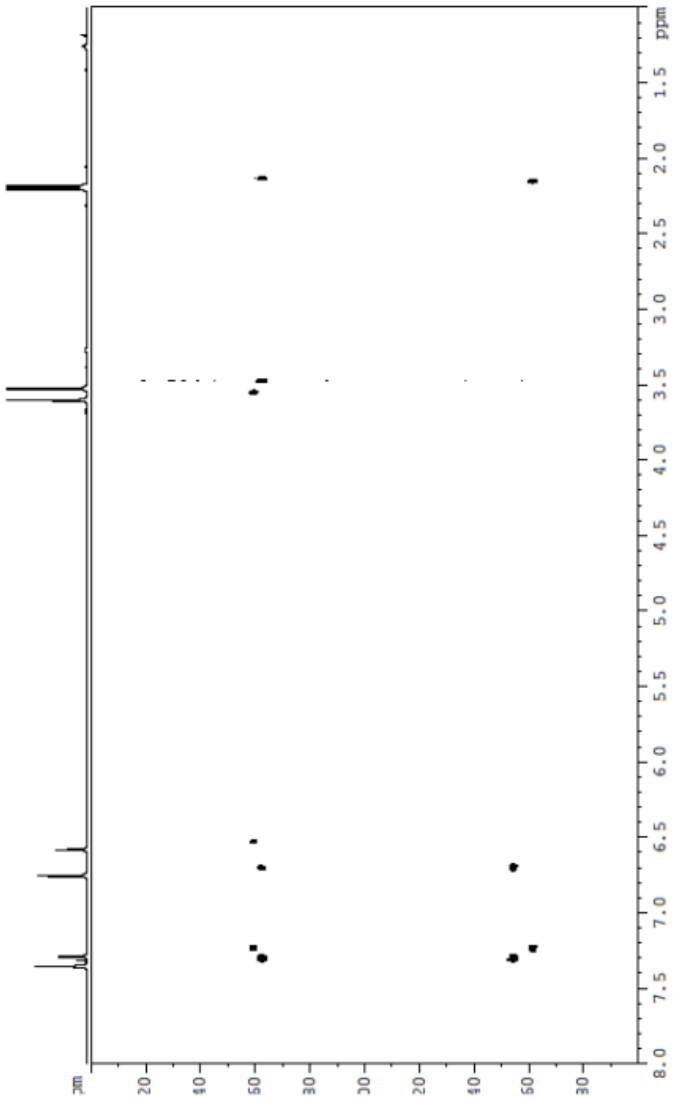


82a

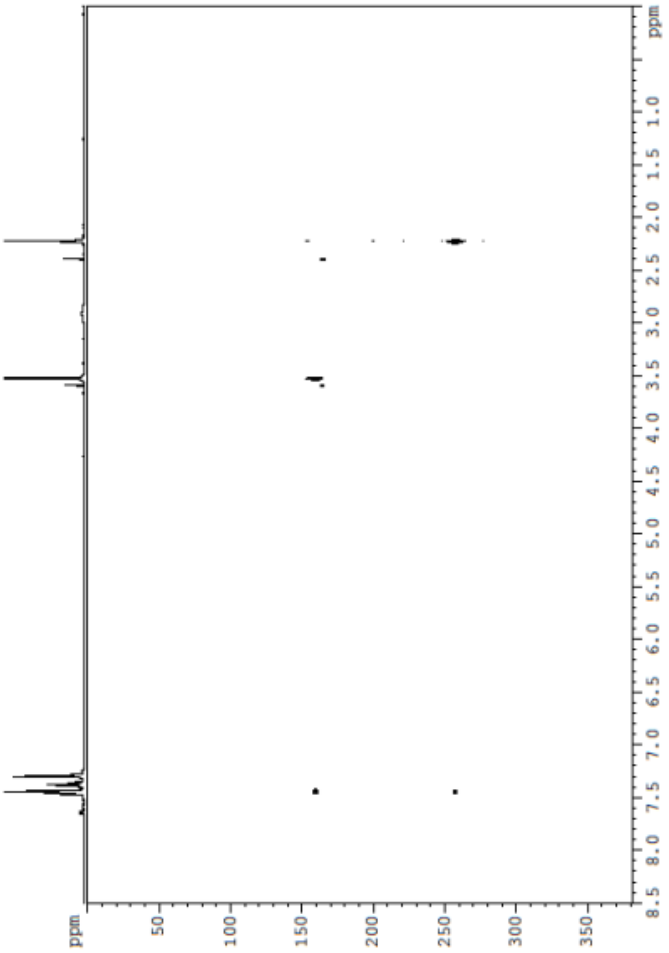
Compound **58** ($CDCl_3$, 500 MHz)



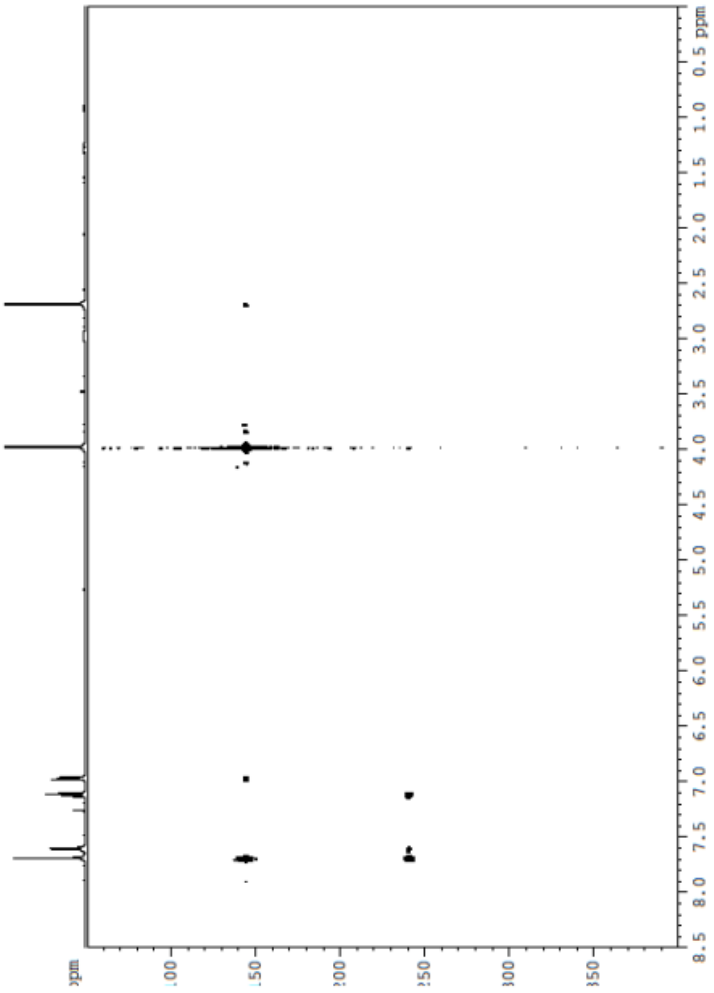
Compound **58** and the other regioisomer (**58'**) ($CDCl_3$, 500 MHz)



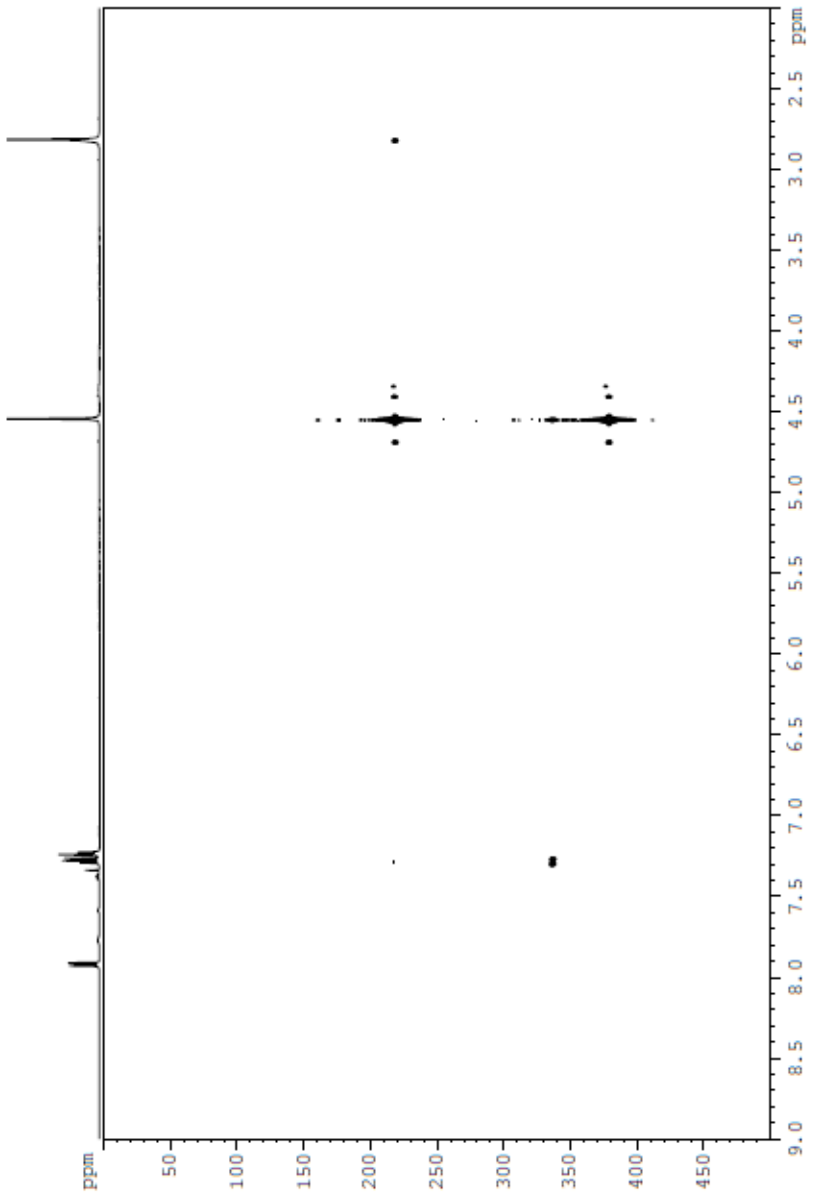
Compound **71** + traces of the other regioisomer ($CDCl_3$, 500 MHz)



Compound **74a** ($CDCl_3$, 500 MHz)



Compound **80a** ($CDCl_3$, 500 MHz)



4. BIOLOGICAL TESTING DETAILS

4.1. Cell lines and compounds

Seven human and one mouse cancer cell lines were obtained from either the European Collection of Cell Cultures (ECACC; Salisbury, UK) or the American Type Culture Collection (ATCC; Manassas, VA). The two glioma cell lines were the U373 (ECACC code 89081403) and T98G (ATCC code CRL-1690) astroglioma cell lines. The carcinoma cell lines were the A549 non small cell carcinoma cell line (ATCC code CCL185), the MCF-7 mammary breast carcinoma cell line (ATCC code HTB-22), the Lovo colon cancer cell line (ATCC code CCL-229) and the PC-3 prostate cancer cell line (ATCC code CRL-1435). The melanoma cell lines were the mouse B16F10 cells (ATCC code CRL-6475) and the human SKMEL-28 cells (ATCC code HTB-72). The two immortal noncancerous cell lines were the HBL100 human breast epithelial cells (330178) and the HaCat human keratinocyte cells (300493) that were purchased from Cell Lines Service (Eppelheim, Germany). The two human normal primary cell lines were from fibroblast origin (NHDF and NHLF: normal human dermal fibroblasts and normal human lung fibroblasts respectively; codes CC-2509 and CC-2512) and were purchase from Lonza (Braine L'Alleud, Belgium). The human melanoma primary cultures were obtained as previously described with full genomic and transcriptomic characterization.[223] All biological assays were performed on fumaric salts.

4.2. Determination of the IC_{50} growth inhibitory concentration.

We made use of a colorimetric MTT assay to determine the concentration that reduced the whole cell population by 50% after 72h of exposure to the compound as described previously.[224] This test is based on the ability of living cells to reduce 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) salt in purple formazan crystals via mitochondrial succinate dehydrogenase enzymatic activity. Each experimental condition was run in six replicates.

The following table contents the detailed IC_{50} concentrations obtained for each compound on each cell line.

compounds	IC_{50} (μM) in vitro inhibitory concentrations							
	apoptosis-stimuli resistant				apoptosis-stimuli sensitive			
	U373	T98G	A549	SKMEL-28	LoVo	MCF7	PC3	B16F10
(+/-)-1a	69	84	52	68	53	50	48	ND
(+)-1a	69	75	59	64	37	44	49	ND
(-)-1a	71	92	54	66	63	43	57	ND
1b	78	74	69	72	34	71	61	ND
1c	31	41	48	31	33	24	31	ND
1d	48	56	36	47	32	41	36	ND
1e	57	63	41	55	34	34	36	ND
1f	63	68	40	57	34	32	40	ND
1g	73	77	58	72	43	52	52	ND
1h	70	69	43	58	32	35	46	ND
1i	24	32	26	23	16	19	25	ND
1j	38	64	43	59	33	61	61	ND
1k	29	22	20	33	28	24	25	ND
2a	33	29	9	17	12	8	19	ND
2b	5.1	3.3	3.3	19	3.8	7	28	ND
2c	6	8	4	4	3	4	14	8
2d	76	63	62	79	32	63	70	ND
2e	33	94	59	83	41	53	59	ND
2f	67	74	43	62	33	37	43	ND
2g	73	87	61	82	38	43	52	ND
2h	>100	>100	74	83	45	59	64	ND
2i	27	32	21	7	25	25	11	ND
2j	7	22	8	7	10	22	11	ND
2k	33	40	16	59	25	37	38	ND
2l	>100	>100	100	>100	56	>100	>100	ND
2m	>100	>100	73	60	32	67	42	ND
2n	36	71	38	38	27	25	33	ND
2o	>100	>100	>100	>100	73	>100	>100	ND
2p	16	39	22	21	24	27	25	ND
2q	9	5	5	13	4	5	24	ND
2r	>100	>100	80	85	47	98	86	ND

compounds	IC_{50} (μM) in vitro inhibitory concentrations							
	apoptosis-stimuli resistant				apoptosis-stimuli sensitive			
	U373	T98G	A549	SKMEL-28	LoVo	MCF7	PC3	B16F10
2s	90	96	87	71	39	55	82	71
2t	38	58	37	33	27	27	43	38
2u	26	35	22	21	11	10	38	34
2v	79	78	83	72	51	63	66	38
2w	32	33	20	33	18	27	48	22
2x	8	3	3	4	3	3	27	7
2y	40	44	40	42	27	28	43	34
2z	33	30	32	31	14	23	45	28
2aa	47	69	46	49	26	37	56	34
2ab	60	65	34	59	26	32	36	ND
2ac	42	29	38	34	35	24	56	36
2ad	43	34	46	35	36	30	54	35
2ae	ND	74	66	69	63	64	61	49
2af	ND	6	4	3	3	18	9	7
2ag	ND	48	34	28	28	25	32	29
2ah	ND	67	47	50	35	37	36	43
2ai	ND	35	43	27	11	28	36	27
2aj	ND	88	62	56	51	61	57	59
2ak	ND	53	43	40	36	32	40	43
3a	>100	>100	>100	>100	>100	>100	>100	54
3b	>100	>100	>100	>100	91	>100	>100	55
3c	>100	>100	>100	>100	84	>100	>100	51
3d	>100	>100	97	>100	75	91	>100	55
4	>100	>100	>100	>100	>100	>100	>100	>100
6	>100	>100	>100	>100	>100	>100	>100	51
7a	82	100	74	85	40	63	62	70
8	>100	>100	>100	>100	78	81	>100	95
9a	>100	>100	>100	>100	>100	>100	>100	92
9b	62	67	59	62	52	50	63	3
10	>100	>100	91	>100	81	77	86	69

4.3. Quantitative videomicroscopy.

The effects of tested compounds on cell morphology, cell proliferation and cell death were assessed with the global view system developed in our lab and described previously.[224,225] Briefly, each cell culture field was photographed every 4 minutes over a 72-h period to be compressed in a short 1-minute movie. Global growth (GG) is the ratio between the number of cell present on the picture at one time point and the number of cell present at time 0. Each condition was tested in three replicates. The global growth ratio (GGR) is calculated by dividing the treated global growth value by the global growth value of the control condition. In that case, the control GGR is 1.

References

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