REVIEW

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Catalytic Synthesis of 1,2,4,5-Tetrasubstituted-1*H*-imidazole Derivatives: State of the Art

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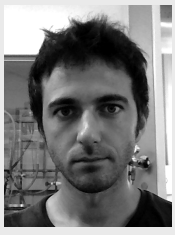
Abstract. 1,2,4,5-Tetrasubstituted-1*H*-imidazoles are a large family of heteroarene derivatives that are known to include natural products isolated from marine sponges and synthetic compounds possessing a broad range of biological and pharmacological properties. Consequently, a great deal of attention has been given to the synthesis of these heteroarenes and reviews covering some synthetic aspects of this topic have been published in recent years. However, none of these reviews provides a comprehensive overview of the several catalytic methods developed in the literature for the preparation of this important class of heteroarenes. This article review with 469 references, 63% of them being related to the period 2010–2017, aims to provide an updated critical picture of the catalytic processes reported in the literature up to the end of 2017 for the synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles illustrating these protocols and their characteristic features such as scope, efficiency, versatility, and limitations. The review also summarizes the mechanisms of the catalytic processes proposed for many of the reported processes.

Keywords: imidazoles; catalysis; regioselectivity; cyclo-condensation; C–H functionalization; annulation; cross-coupling.

Renzo Rossi was born in Pisa (Italy) and graduated in Organic Chemistry with first-class honours at the University of Pisa defending a thesis performed under the guidance of Professor Piero Pino. In 1969 he became Assistant Professor and in 1971 he earned the *libera docenza* in Organic Chemistry. After holding other intermediate positions at the University of Pisa and the Scuola Normale Superiore of Pisa, in 1980 he became Full Professor of Organic Chemistry at the University of Calabria. In 1982, he again joined the University of Pisa where he has held the Chair of Chemistry of Naturally Occurring Compounds. In 1999, the University of Pisa awarded him the *Ordine del Cherubino*. His current research interests include: i) new catalytic methods for the synthesis of oxygen-containing heterocycles; *ii)* the preparation of substances which exhibit significant cytotoxicity against human tumor cell lines and antivascular properties; *iii)* the study of new methodologies for carbon–carbon bond formation that involve the use of organometallic reagents; *iv)* palladium-catalyzed cross-coupling reactions; *v)* transition metal-catalyzed direct arylation reactions of substrates with activated sp^3-hybridized C–H bonds with aryl halides and pseudohalides; *vi)* the design, development and applications of new, highly chemo- and regioselective methods for the transition metal-catalyzed direct *C*- and *N*-arylation reactions of electron-rich heteroaromatic systems, including free (NH)-azoles, with aryl halides and pseudohalides, and their application in the synthesis of bioactive natural and unnatural compounds. In recent years, several successful studies have also been performed by his research group in the field of the synthesis and evaluation of the biological properties of insect sex pheromone components, insecticidal carboxyamides, natural phototoxins, and naturally-occurring compounds of marine origin and their structural analogues which are characterized by the 2(5*H*)-furanone ring. Professor Rossi, who has coauthored over 235 research publications and a number of highly cited review articles and patents, is a fellow of the Royal Society of Chemistry and the American Chemical Society. For many years he has been a reviewer for international journals dealing with synthetic organic chemistry and organometallics.

Gaetano Angelici was born in Porto San Giorgio (Italy) in 1979. He studied pure and applied chemistry at the Department of Chemistry "G. Ciamician" at the University of Bologna, where he graduated in 2009 with a PhD thesis on the De Novo Design of secondary structures, in the group of Prof. Claudia Tomasini. He then moved for a post-doctoral period in the group of Prof. Helma Wennemers at the University of Basel (Switzerland), where he worked on the identification of N-heterocyclic carbene-peptide conjugates organocatalysts, using a combinatorial screening approach. He then obtained a fellowship "Novartis Stiftung zur Förderung der Forschung" to work on the synthesis and evaluation of substrates and potential inhibitors of N-succinyl-L,Ldiaminopimelic acid desuccinylase (DapE), at the Laboratory of Molecular Evolution of Dr. Marc Creus. In 2014 he moved in France, to study the weak backbone London interactions which help to promote helix folding of more flexible peptoids, in the group of Prof. Claude Taillefumier, at the University Blaise Pascal in Clermont-Fd. In 2015 he won a Marie Curie Individual European Fellowship to study new amphiphilic molecules for the stabilization and crystallization of membrane protein. Since 2017 he is researcher at the Department of Chemistry and Industrial Chemistry of the University of Pisa (Italy), where he works on the synthesis and conformational analysis of pseudopeptides, and in the development of new sustainable methods in organic synthesis.



Gianluca Casotti was born in Lucca (Italy) in 1987 and graduated in chemistry with first-class honours at the University of Pisa in 2017 defending a thesis performed under the guidance of Professor Adriano Carpita. Currently, he holds a position as PhD student at the Department of Chemistry and Industrial Chemistry of the University of Pisa under the guidance of Professor Anna Iuliano. He is currently working on the development of new protocols for the chemo-, regio- and stereoselective formation of C-C bonds via organozinc halides and to their application to the synthesis of natural and bioactive compounds.

Chiara Manzini was born in Lucca (Italy) in 1986 and graduated in chemistry with first-class honours at the University of Pisa in 2011. In January 2012, she began her PhD fellowship in the labora- tory of Professor Bellina and received her PhD degree in 2015, submitting a thesis on the development and application of new protocols for the selective arylation of *N*-containing heteroaromatics. In the same year she hold a post-doctoral position at the University of Pisa and she

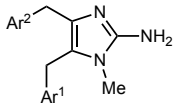
worked on the synthesis of new chromophores for Luminescent Solar Concentrators.

Marco Lessi was born in Livorno (Italy) in 1979. He studied chemistry at the University of Pisa and received his Laurea Degree with first-class honours in June 2004 defending a thesis per- formed under the guidance of Professor Dario Pini. In January 2005, he began his PhD fellowship in the laboratory of Professor Pini and received his PhD degree in 2008, submitting a thesis on the preparation and applications of new insoluble polymer-bound (IPB) enantioselective catalytic systems. The studies were focused on the synthesis of transition-metal complexes obtained from bisoxazoline and BINOL ligands. In the period of January 2008 through March 2009, Dr. Lessi worked for Solvay Solexis S.p.A. on the development of new routes for the preparation of high- fluorinated low-molecular-weight molecules and oligomers. In March 2009, he re-joined the University of Pisa, and at present he is an organic chemistry re-searcher, working in the group of Professor Bellina. The research interests of Dr. Lessi involve the development of novel and efficient protocols for highly selective transition-metal-catalyzed C(sp^3)–H and C(sp^2)–H bond activation, and the discovery of novel organic dyes for energetic applications.

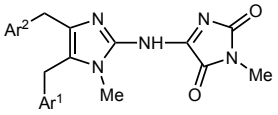
1. Introduction

Over the past four decades, the synthesis and evaluation of the biological properties of 1,2,4,5-tetrasubstituted-1*H*-imidazoles have received much attention. In fact, members of this large family of heteroarene derivatives include antinociceptive compounds,[1] Tie 2 receptor kinase inhibitors,[2] P2X7 receptor antagonists,[3] inhibitors of the p53-MDM2 interaction,[4] anti-inflammatory derivatives,[5] serotonin antagonist receptor inhibitors that block both 5-HT_{2A} receptors and the serotonin transporter,[6] antibacterial derivatives,[7] non-nucleoside inhibitors of HIV-1 release transcriptase,[8] selective cannabinoid CB_2 receptor antagonists,[9] CB_1 receptor inverse agonists,[10] dual inhibitors of p38α mitogen-activated protein kinase and c-Jun *N*-terminal kinase 3,[11] inhibitors of p38 mitogen-activated protein kinase,[12] angiotensin II receptor antagonists,[13] derivatives with trypanocidal activity,[14] an apoptosis-inducing compound that binds to heat shock protein 70,[15] and a small molecule that blocks the ATPase activity of cellular protein $H_{SC}70$ by binding to its ATPase domain.[16]

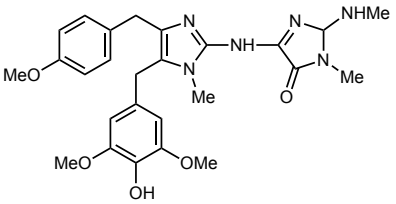
Furthermore, many 2-amino-4,5-dibenzyl-1-methyl-1*H*-imidazole derivatives have been isolated from marine sponges. The structures of these compounds, **1a–e**, **2a–e**, **3** and **4a-e**, are shown in Figure 1. Leucettamine A (**1a**) that was first isolated from the Palauan sponge *Leucetta micrographus*[17] was found to show potent leukotriene B_4 receptor binding activity.[17a] Naamine G (**1b**) that was isolated from the Indonesian sponge *Leucetta chagosensis*[18] proved capable to exhibit strong antifungal activity against the fungus *Cladosporium herbarium* and mild cytotoxic activity against mouse lymphoma (L5178Y) and human cervix carcinoma (HeLa) cell lines.[18] Naamine A (**1c**) and Naamine F (**1e**) were isolated from the Indonesian sponge *L. chagosensis.*[18] Naamine C (**1d**) and pyronaamidine (**2d**) were isolated from the sponge *L. chagosensis* collected in Chuuk State (Micronesia).[19] Naamidine J (**2a**) was isolated from the South China Sea sponge *Pericharax heteroraphis.*[20] and was found to exhibit cytotoxicity against the K562 cell line with and IC_{50} value of 11.3 μM.[20] Naamidine H (**2b)** and Naamidine I (**3**) were isolated from the Indonesian sponge *L. chagosensis.*[21] Naamidine G (**2d**) was isolated from a calcareous sponge *Leucetta* sp. of the Coral Sea.[22] Naamidine B (**2e**) was isolated from the Egyptian Red Sea sponge *L. chagosensis.*[23] 4-Hydroxynaamidine A (**4a**), 14-hydroxynaamidine G (**4b**), 14-methoxynaamidine A (**4c**), 14-methoxynaamidine G (**4d**), and 14-oxonaamidine G (**4e**) were isolated from a calcareous sponge *Leucetta* sp. of the Coral Sea. [22]



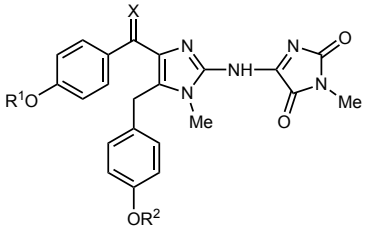
1a : $Ar^1 = Ar^2$ 3,4-OCH_2O (Leucettamine A)
1b : Ar^1 = 3,5-$(MeO)_2$, 4-HOC_6H_3; Ar^2 = 4-$MeOC_6H_4$ (Naamine G)
1c : Ar^1 = 4-HOC_6H_4 ; Ar^2 = 4-$MeOC_6H_4$ (Naamine A)
1d : Ar^1 = 2-HO, 3,4 $(MeO)_2C_6H_2$; Ar^2 = 4-$MeOC_6H_4$ (Naamine C)
1e : Ar^1 = 3-MeO, 4-HOC_6H_3 ; Ar^2 = 4-$MeOC_6H_4$ (Naamine F)



2a : Ar^1 = 3,4-$(MeO)_2$ C_6H_3 ; Ar^2 = 4-$MeOC_6H_4$ (Naamidine J)
2b : Ar^1 = 3,5-$(MeO)_2$, 4-HOC_6H_2; Ar^2 = 4-$MeOC_6H_4$ (Naamidine H)
2c : Ar^1 = 2-HO, 3,4-$(MeO)_2C_6H_2$; Ar^2 = 4-$MeOC_6H_4$ (Pyronaamidine)
2d : $Ar^1 = Ar^2$ = 4-$MeOC_6H_4$ (Naamidine G)
2e : Ar^1 = 3-HO, 4-$MeOC_6H_3$; Ar^2 = 4-$MeOC_6H_4$ (Naamidine B)



3 (Naamidine I)



4a : R^1 = Me; R^2 = H; X = H, OH (14-Hydroxynaamidine A)
4b : $R^1 = R^2$ = Me; X = H, OH (14-Hydroxynaamidine G)
4c : R^1 = Me; R^2 = H; X = H, OH (14-Methoxynaamidine A)
4d : $R^1 = R^2$ = Me; X = H, OMe (14-Methoxynaamidine G)
4e : $R^1 = R^2$ = Me; X = O (14-Oxonaamidine G)

Figure 1. Structures of 2-amino-4,5-dibenzyl-1-methyl-1*H*-imidazoles **1a-e**, **2a–e**, **3**, and **4a-e** isolated from marine sponges

In the light of the importance of 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives a great deal of attention has been given to their preparation and several reviews on the synthesis and biological properties of these compounds, which also include active components of optoelectronic devices,[24a] have been published.[24b–i] However, none of these reviews provides a comprehensive overview of the catalytic methods developed in the scientific literature for the synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles. In fact, in some of these reviews, the attention was mainly directed to summarize the syntheses of this class of heteroarenes *i)* via one-pot four component reactions of symmetrical 1,2-diketones with appropriate aldehydes, primary amines and $AcONH_4$ in the presence of homogeneous or heterogeneous catalysts[24c,g,h] and *ii)* by treatment of an α-keto-monoxime with an aryl aldehyde and $AcONH_4$ under acidic conditions.[24c,f,g,h] Only in the review published in 2007 by our research group[24c] and in those published in 2015 by Heravi and coworkers[24g] and by Gupta and coworkers[24f] a short description of a few other catalytic methods for the multistep synthesis of tetrasubstituted-1*H*-imidazoles was reported.

This article review with 469 references presents an updated picture of the methods that have been described in the scientific literature until the end of 2017 for the synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazole derivatives and involve a catalytic reaction as a key step. Particular attention has been paid to summarize and critically comment synthetic protocols that have not been mentioned in previous reviews and, among these, the processes that are different from those involving one-pot three- or four-component cyclo-condensation reactions. The review also includes a short description of the reaction mechanisms that have been proposed for some catalytic reactions developed for the preparation of the target compounds.

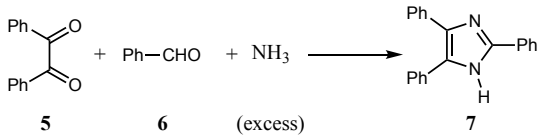
The synthetic processes that have been described and commented in this review have been categorized into the following types: *i)* syntheses via one-pot four-component cyclocondensation reactions involving the use of homogeneous, catalysts, heterogeneous catalysts and ionic liquids as catalysts or dual catalysts-solvents; *ii)* one-pot three-component syntheses; *iii)* syntheses via [3 + 2] or [2 + 2 + 1] annulations; *iv)* syntheses via cyclization of propargyl guanidines; *v)* synthetic protocols involving a thiazolinium-catalyzed reaction of aldehydes with α-amidosulfones; *vi)* syntheses via oxidative/dehydrogenative coupling reactions; *vii)* syntheses via Pd-catalyzed direct arylation reaction of imidazole substrates; *viii)* syntheses via Pd-catalyzed cross-coupling reactions involving the use of stoichiometric amounts of organometallic reagents; *ix)* syntheses via Pd/Cu-catalyzed Sonogashira type reactions; *x)* syntheses via aza-Wittig reactions; *xi)* syntheses from 2*H*-aziridines; and *xii)* other synthetic methods.

However, data from the patent literature have not been reviewed.

2. Syntheses by One-Pot Four-Component Condensation Reactions

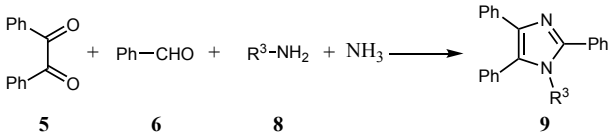
In 1882, Radziszewski synthesized 2,4,5-triphenyl-1*H*-imidazole (**7**) by the one-pot reaction of commercially available benzil (**5**)

and benzaldehyde (**6**) with excess of ammonia (Scheme 1).[25]



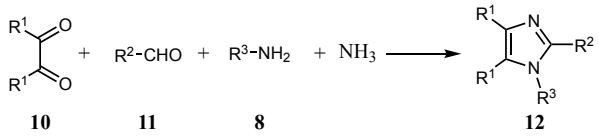
Scheme 1. Radziszewski's reaction

In 1960, Drefahl and Herma found that the synthetic potential of the Radziszewski three-component reaction could be significantly increased by using a primary amine **8** instead of an equivalent of NH_3 and that this four-component reaction provided 1-substituted-2,4,5-triphenyl-1*H*-imidazoles **9** (Scheme 2).[26]



Scheme 2. Four-component synthesis of 1-substituted-2,4,5-triphenyl-1*H*-imidazoles **9**

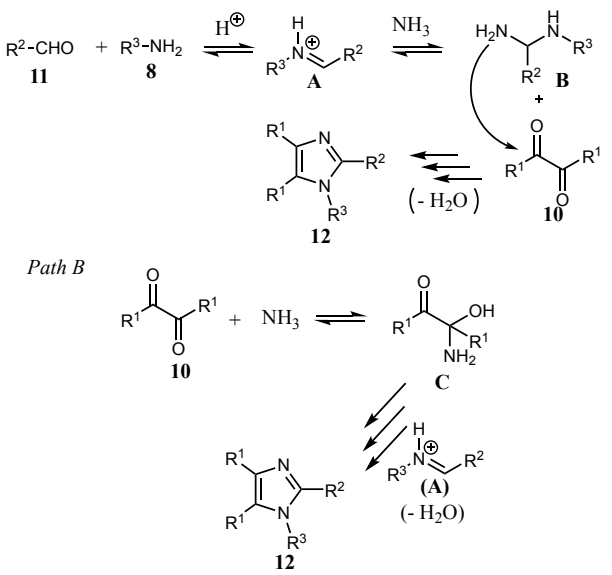
However, the synthetic utility of this modified protocol resulted significantly limited by the fact that the four-component condensation allowed only the synthesis of tetrasubstituted-1*H*- imidazoles of general formula **12** bearing identical groups at the 4 and 5 positions. In fact, regioselectivity issues only allowed the use of symmetrically disubstituted α-diketones **10** and the preparation of tetrasubstituted-1*H*-imidazoles **12** through catalytic reactions in which diketones **10** are reacted with aldehydes **11**, primary amines **8** and NH_3 (Scheme 3).



Scheme 3. Synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles **12** by one-pot cyclo-condensation reaction

It is also interesting to note that $AcONH_4$ has been generally used as a source of ammonia in the four-component cyclo-condensation reaction shown in Scheme 3, which, as will be reported in section 2.1, has been frequently carried out using AcOH as a catalyst and solvent.

Two pathways (*A* and *B*) were proposed for the mechanism of the AcOH-catalyzed four component cyclo-condensation reaction (Scheme 4).[27]



Scheme 4. The two pathways (*A* and *B*) proposed for the synthesis of imidazoles **12**

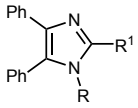
In pathway *A*, aldehydes **11** react with amines **8** in the presence of AcOH to give the protonated aldimines **A**. The subsequent reaction between **A** and ammonia gives the diamino intermediates **B** that react with diketones **10** and in the following steps form compounds **12** and water.

In pathway *B*, ammonia reacts with α-diketones **10** providing aminoalcohols **C**. Subsequently, these intermediates react with **A**, whereupon the imidazoles derivatives are formed and water is eliminated.[27]

Much attention has also been directed in the literature to improve the reaction conditions and yields of the synthetic process shown in Scheme 3. Thus, a large variety of protocols have been developed in which the one-pot four-component cyclo-condensation reaction takes place thermally or under microwave irradiation by using homogeneous or heterogeneous catalysts or ionic liquids as dual catalysts-solvents. These protocols, in which α-diketones generally correspond to benzil (**5**), are described in the following three subsections of this section. Notably, two of these subsections also include the description of protocols in which substrates different from **5** have been used for the catalytic synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles.

2.1. One-Pot Four-Component Syntheses carried Out Using Homogeneous Catalysts

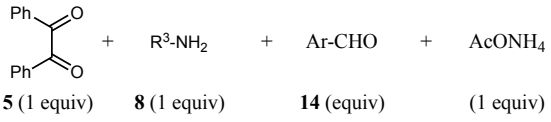
Solution phase syntheses of tetrasubstituted-1*H*-imidazoles of general formula **13** (Figure 2) have been carried out *i)* in refluxing AcOH which is used as dual solvent-catalyst;[28] *ii)* in a mixture of AcOH and $CHCl_3$ at 160 °C employing a microwave-assisted protocol;[27] and *iii)* in a mixture of AcOH and *N*-methyl-2-pyrrolidinone (NMP).[29] Unfortunately, the yields were generally modest.



13

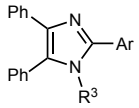
Figure 2. Chemical structure of tetrasubstituted imidazoles **13**

Nevertheless, improvements in the yields and/or reaction times were obtained by using catalysts such as *p*-toluenesulfonic acid,[30] boric acid,[31] 2-ethylhexanoic acid,[32] molecular iodine,[33] $FeCl_3·6H_2O$,[34] $ZrCl_4$,[35] $InCl_3·3H_2O$,[36], cyclic phosphonic acid,[37] $BiBr_3$,[38] citric acid,[39] 1,4-diaza[2.2.2]bicyclooctane (DABCO),[40] trityl chloride,[41] L-proline,[42] and L-proline triflate.[43] Furthermore, in 2009, 1-substituted-2-aryl-4,5-diphenyl-1*H*-imidazoles **15a–n** were synthesized in good to excellent yields through trifluoroacetic acid (TFA)-catalyzed condensation of benzil (**5**), primary amines **8**, aryl aldehydes **14** and $AcONH_4$ under microwave-assisted solvent-free conditions (Scheme 5).[44]



5 (1 equiv) **8** (1 equiv) **14** (equiv) (1 equiv)

TFA (20 mol%)
solvent-free
MW, 150 W, 4 min

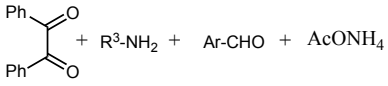


15

15	R^3	Ar	yield%
a	Bn	Ph	92
b	Ph	Ph	88
c	Bn	4-MeC_6H_4	94
d	Bn	4-ClC_6H_4	89
e	Ph	4-MeC_6H_4	85
f	$BnCH_2$	4-MeC_6H_4	88
g	Bn	3-ClC_6H_4	80
h	*i*-Bu	Ph	85
i	*i*-Bu	4-MeC_6H_4	85
j	Et	4-MeC_6H_4	79
k	Ph	2-MeC_6H_4	88
l	4-ClC_6H_4	2-MeC_6H_4	91
m	4-BrC_6H_4	2-MeC_6H_4	90
n	Ph	4-ClC_6H_4	83

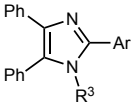
Scheme 5. TFA-catalyzed synthesis of imidazoles **15a-n** under microwave-irradiated solvent free conditions

In 2012, six tetrasubstituted-1*H*-imidazoles of general formula **15** were synthesized in good yields by *n*-Bu_4NBr-catalyzed reaction of equimolar amounts of benzil (**5**), amines **8**, aryl aldehydes **14** and $AcONH_4$ in *t*-BuOH at 80 °C for 8 h (Scheme 6).[45]



5 **8** **14**

n-Bu_4NBr (10 mol%)
t-BuOH, 80 °C, 8 h

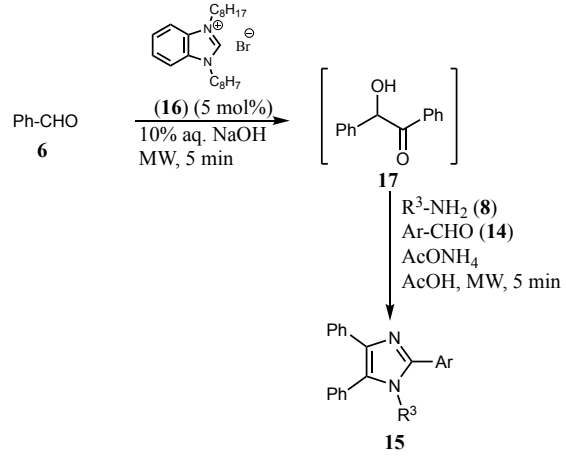


15

15	R^3	Ar	yield %
a	Bn	Ph	80
b	Ph	Ph	87
n	Ph	4-ClC_6H_4	80
o	Ph	4-FC_6H_4	81
p	Ph	4-$MeOC_6H_4$	75
q	3-Cl,4-FC_6H_3	Ph	78

Scheme 6. *n*-Bu_4NBr-catalyzed synthesis of imidazoles **15a,b** and **15n–q**

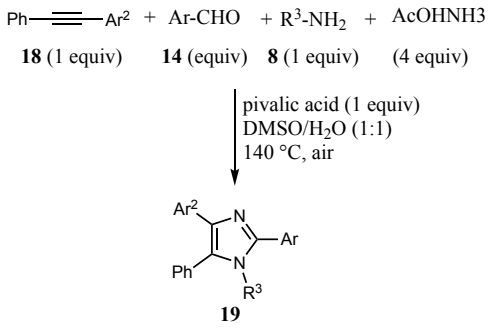
Again in 2012, a starting material different from benzil (**5**) was employed in a catalytic synthesis of seven tetrasubstituted-1*H*-imidazoles of general formula **15**. Specifically, the synthesis of compounds **15b**, **15e** and **15r-v** was achieved in high yields by AcOH-promoted microwave-irradiated reaction of equimolar amounts of the required aldehydes **14** and primary amines **8** with $AcONH_4$ and benzoin (**17**). The latter compound was in turn synthesized *in situ* by microwave-promoted reaction of benzaldehyde (**6**) with a catalytic amount of the *N*-heterocyclic carbene obtained by treatment of the benzimidazolium salt **16** with aqueous NaOH (Scheme 7).[47]



15	R^3	Ar	Yield%
b	Ph	Ph	91
e	Ph	4-MeC_6H_4	88
r	4-ClC_6H_4	Ph	87
s	4-MeC_6H_4	4-$MeOC_6H_4$	89
t	4-MeC_6H_4	Ph	88
u	4-ClC_6H_4	4-MeC_6H_4	86
v	3-ClC_6H_4	Ph	84

Scheme 7. AcOH-mediated synthesis of imidazoles **15b**, **15e** and **15r–v**

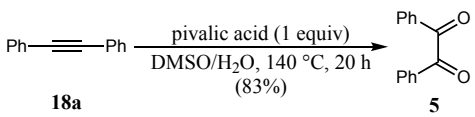
A year later, Wang and coworkers described a new, simple and eco-friendly method for the synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles of general formula **19** (Scheme 8).[47] It involved the pivalic acid-promoted reaction of acetylenes **18** with 1 equiv of aldehydes **14**, primary amines **8** and 4 equiv of $AcONH_4$ in a 1 : 1 mixture of DMSO and water at 140 °C for 24–48 h that provided imidazoles **19** in yields ranging from 65 to 88%.[47]



19	Ar	Ar^2	R^3	yield%
a	Ph	Ph	Ph	88
b	4-BrC_6H_4	Ph	Ph	75
c	4-ClC_6H_4	Ph	Ph	71
d	4-$(NO_2)C_6H_4$	Ph	Ph	65
e	4-$MeOC_6H_4$	Ph	Ph	87
f	*i*-Pr	Ph	Ph	78
g	2-furyl	Ph	Ph	80
h	Ph	3-$MeOC_6H_4$	Ph	84
i	4-$MeOC_6H_4$	2-$MeOC_6H_4$	Ph	85
j	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Ph	88
k	4-$MeOC_6H_4$	2-MeC_6H_4	Ph	82
l	4-$MeOC_6H_4$	3-MeC_6H_4	Ph	83
m	4-$MeOC_6H_4$	4-MeC_6H_4	Ph	80
n	Ph	2-thienyl	Ph	82
o	Ph	Ph	4-BrC_6H_4	79

Scheme 8. Pivalic acid-promoted synthesis of imidazoles **19** via a four-component reaction involving the use of diarylacetylenes **18** as starting materials

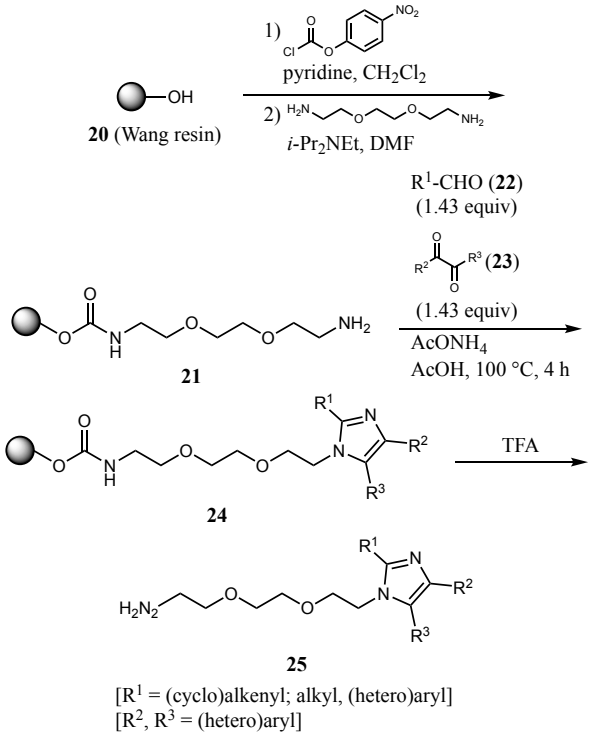
It is interesting to note that the reactions turned out to be regioselective also when unsymmetrical diarylacetylenes were used as starting materials, but unfortunately no explanation of this result was given. Nevertheless, the authors supposed that the reactions involve the formation of α-diketones from diarylacetylenes. In fact, in confirmation of this hypothesis, they found that the reaction of diphenylacetylene (**18a**) with 1 equiv of pivalic acid in DMSO/H_2O at 140 °C for 20 h gave benzil (**5**) in 83% yield (Scheme 9).[47]



Scheme 9. Synthesis of benzyl (**5**) from diphenylacetylene (**18a**)

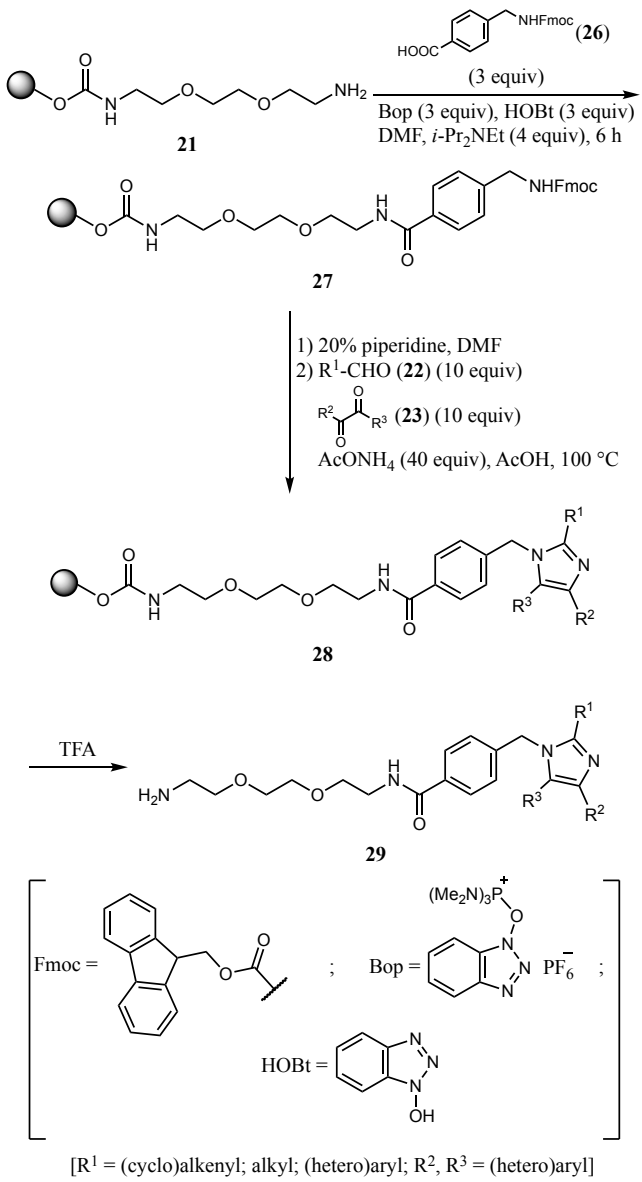
It is also worth mentioning that AcOH has been used as catalyst/solvent in syntheses of tetrasubstituted-1*H*-imidazoles involving the use of solid supported reagents. In fact, in 2007, in order to identify small molecules that induce neurogenesis in skeletal muscle, Shin and coworkers[49] synthesized

a library of tetrasubstituted imidazoles of general formula **25** according to the reaction sequence shown in Scheme 10 in which Wang resin (**20**) was used as a starting material. [50] A key step of this sequence was the AcOH-mediated reaction between resin **21**, aldehydes **22**, α-diketones **23** and $AcONH_4$ at 100 °C, which provided resins **24**. Finally, cleavage of the solid support from **24** by treatment with trifluoroacetic acid (TFA) gave compounds **25**.[49]



Scheme 10. Synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles **25** starting from Wang resin

Resin **21** was also used by Shin and coworkers in the synthesis of imidazoles of general formula **29** via the reaction sequence shown in Scheme 11.[49]

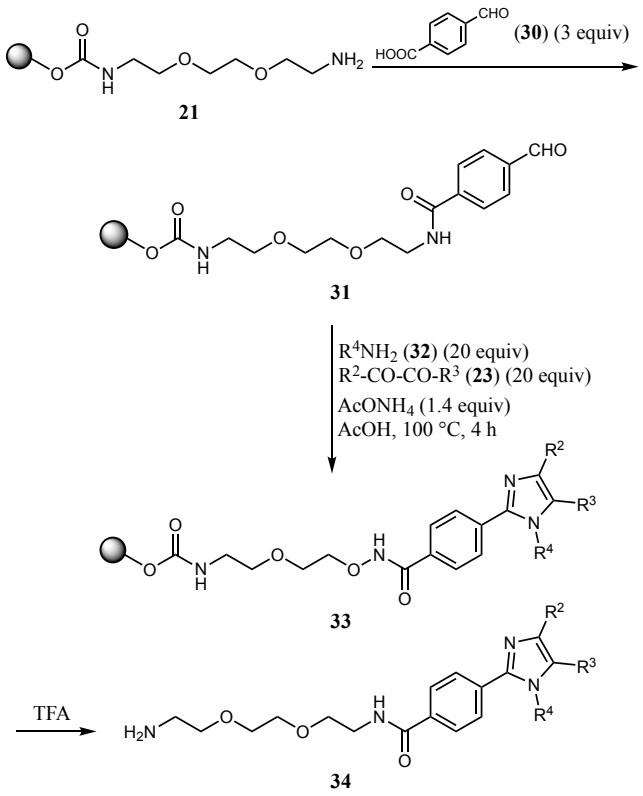


Scheme 11. Synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles **29** from resin **21**

Specifically, resin **21** was treated with a solution of fluorenylmethoxycarbonyl- (Fmoc)-protected 4-(aminomethyl)benzoic acid (**26**), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (Bop), hydroxybenzotriazole (HOBt) and *i*-Pr_2NEt in DMF yielding resin **27**. After removal of the Fmoc protecting group by treatment with 20% piperidine in DMF, the resulting aminoresin was reacted with aldehydes **22**, α-diketones **23** and $AcONH_4$ at 100 °C to give resins **28**. Finally, treatment of **28** with TFA provided imidazoles **29**.[49]

Interestingly, resin **21** proved to be a good starting material also for the synthesis of tetrasubstituted imidazoles of general formula **34**

through the reaction sequence shown in Scheme 12.[49] The reaction of **21** with 3 equiv of *p*-formylbenzoic acid (**30**), 3 equiv of Bop, 3 equiv of HOBt and 4 equiv of *i*-Pr_2NEt in DMF for 6 h gave resin **31**, which was then reacted with 20 equiv of primary amines **32**, 20 equiv of α-diketones **23** and 1.4 equiv of $AcONH_4$ at 100 °C for 4 h resulting in resin **33**. Finally, removal of resin from **33** with TFA gave imidazoles **34**.[49]



[R^2, R^3 = (hetero)aryl; R^4 = (hetero)aryl; (heteroarylmethyl; cycloalkyl; (cyclo)alkylmethyl]

Scheme 12. Synthesis of tetrasubstituted imidazoles **34** from resin **21**

However, Shin and coworkers did not mention regioselectivity issues in the construction of the imidazole ring of compounds **25**, **29** and **34** by using unsymmetrical α-diketones.

2.2. One-Pot Four-Component Syntheses carried Out Using Heterogeneous Catalysts

The homogeneous catalysts used in the synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles are generally less advantageous than heterogeneous catalysts because they are hardly recoverable and recyclable. Thus, economic reasons have promoted the development of a vast array of protocols for the one-pot four-component synthesis of tetrasubstituted-1*H*-imidazoles involving the use of solid-supported catalysts. In fact, these processes can result in easy of handling, simple work-up, recoverability of the catalysts and their recycle. However, to our knowledge, the leaching behaviour of these catalysts has never been thoroughlu investigated.

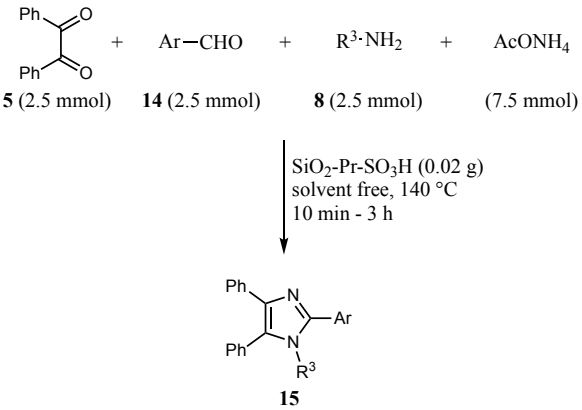
In recent years, the use of silica-supported catalysts has received considerable attention and it has been shown that the synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles from benzil (**5**), aldehydes, primary amines and $AcONH_4$ can be catalyzed by perchloric acid adsorbed on silica gel,[52] silica-supported BF_3,[53] silica-supported polyphosphoric acid,[54.55] 12-phosphotungstic acid (PWA)-supported on silica gel,[56] P_2O_5 supported on silica gel,[57] nano-$TiCl_4$-SiO_2,[58] silica supported SnO_2,[59] $HBF_4{\cdot}SiO_2$,[60] carboxylic acid functionalized porous silica nanoparticles,[61] silica coated magnetic $NiFe_2O_4$ nanoparticle supported phosphomolybdic acid,[62] silica supported Preyssler nanoparticles heteropolyacid,[63] $SbCl_3$ adsorbed on silica gel,[64] concentrated HNO_3 supported on nanosilica,[65] $Bi(NO_3)_3{\cdot}SiO_2$,[66] $NaHSO_4$ supported on silica gel,[67] $SbCl_3$ immobilized on silica gel (SiO_2-$OSbCl_2$),[68a] and $K_5CoW_{12}O_{40}{\cdot}4H_2O$.[68b] Interestingly, some of the above mentioned catalysts were used in solvent-free reactions[54–56,59,62,65,67] and some of thecyclo-condensation reactions were carried out under microwave irradiation rather than under classical heating conditions.[55,58] Notably, some of these catalysts could be easily separated from the reaction mixtures and reused several times without significant loss of their catalytic activity.[57,59,60,62,64]

High yields of 1,2,4,5-tetrasubstituted-1*H*-imidazoles were also obtained via condensation of benzoin (**17**) or benzil (**5**) with aromatic aldehydes, primary amines and $AcONH_4$ in the presence of silica gel under microwave irradiation.[69,70]

Furthermore, in 2009, some 1,2,4,5-tetrasubstituted-1*H*-imidazoles were synthesized in high yields using high surface area SiO_2 as the catalyst, benzil (**5**) as the α-diketone and exposing the four component mixture of reagents to direct sunlight for 2–2.5 h in CH_2Cl_2.[71]

In recent years, even silica functionalized with sulfonic acids have been used as efficient catalysts

for four-component one-pot reactions of α-diketones with aryl aldehydes, primary amines and $AcONH_4$. In 2015, mesoporous silica SiO_2-Pr-SO_3H was used by Ziarani and coworkers as a heterogeneous solid acid catalyst for the synthesis of tetrasubstituted imidazoles **15** in excellent yields under solvent-free conditions at 140 °C (Scheme 13).[72,73]



15	R^3	Ar	Yield (%)	Reach time (min)
n	Ph	4-ClC_6H_4	95	25
w	Ph	3-$(NO_2)C_6H_4$	98	10
x	Ph	4-$MeOC_6H_4$	96	150
e	Ph	4-MeC_6H_4	89	150
d	Bn	4-ClC_6H_4	94	100
y	Bn	4-$(HO)C_6H_4$	94	180
z	Bn	4-$Me_2NC_6H_4$	85	120
c	Bn	4-MeC_6H_4	92	120
aa	Bn	3-$MeOC_6H_4$	88	180
ab	Bn	3,4-$(MeO)_2C_6H_3$	95	180

Scheme 13. SiO_2-Pr-SO_3H-catalyzed synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles **15**

SiO_2-Pr-SO_3H was prepared in the following way: the surface of silica was grafted with (3-mercaptopropyl)trimethoxysilane and the thiol functionalities of the resulting solid were oxidized to sulfonic acid groups by treatment with H_2O_2 to give the solid heterogeneous catalyst.[72,73]

A large variety of tetrasubstituted imidazoles of general formula **15** was also synthesized in 2016 using sulfonic acid functionalized SBA-15 nanoporous material (SBA-Pr-SO_3H) with a pore size of 6 nm as a green, recyclable solid catalyst that could be reused several times without significant loss of activity.[74]

,… One year earlier, Davoodnia and coworkers had reported that nano-Fe_3O_4 encapsulated silica particles bearing sulfonic acid groups (Fe_3O_4@SiO_2-OSO_3H) could be used as an efficient and magnetically separable heterogeneous catalyst for the high yielding one-pot synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles **15** at 130 °C for 15–60 min under neat conditions.[75] Importantly, the catalyst was easily separated from the reaction mixture by a permanent magnet and could be reused several times without significant loss of activity.[75]

In 2012, MCM-41-SO_3H was prepared by reacting chlorosulfonic acid with ordered mesoporous silica MCM-41[76] and was then employed as a highly efficient, reusable nanocatalyst for the rapid and green one-pot synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles in excellent yields under solvent-free conditions. [76]

Two years later, mesoporous MCM-41-*n*-Pr-$NHSO_3H$ (Figure 3) was synthesized from MCM-41 by treatment with 3-aminopropyltriethoxysilane followed by the reaction of the resulting amino-functionalized-MCM-41 [MCM-41-$(CH_2)_3NH_2$] with chlorosulfonic acid in the presence of Et_3N.

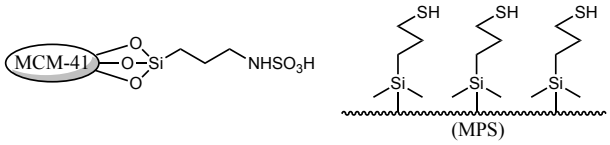
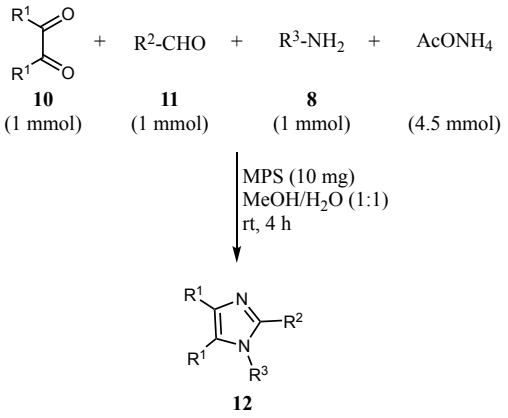


Figure 3. Schematic structures of MCM-41-*n*-Pr-$NHSO_3H$ and MPS

MCM-41-*n*-Pr-$NHSO_3H$ was characterized by X-ray diffraction (XRD), FT-IR, transmission electron microscopy (TEM), thermogravimetric analysis (TGA), scanning electron microscopy (SEM), and nitrogen physisorption measurements and was used as a novel and effective nanoreactor for the one-pot, high yielding synthesis of tetrasubstituted-1*H*-imidazoles at 130 °C under solvent-free conditions. [77]

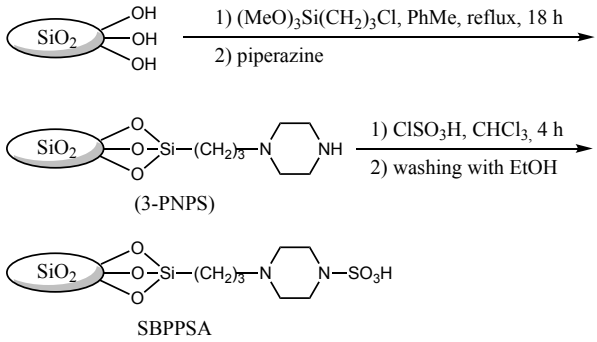
In the past years, other silica modifications have been used as catalysts for the synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles. In 2010, the known heterogeneous solid acid catalyst mercaptopropyl-modified mesoporous silica (MPS) (Figure 3)[78] was efficiently prepared in water by a modified literature procedure and was employed for the efficient synthesis of a variety of tetrasubstituted imidazoles **12** (Scheme 14).[79] The synthetic protocol, which involved the reaction of 1 mmol of α-diketones **10** with 1 mmol of aldehydes **11**, 1 mmol of amines **8**, 4.5 mmol of $AcONH_4$ and 10 mg of MPS in a 1: 1 mixture of MeOH and water at room temperature, provided compounds **12** in yields ranging from 65 to 92%.[79]



12	R^1	R^2	R^3	Yield (%)
a	Me	4-BrC_6H_4	4-ClC_6H_4	65
b	Me	4-BrC_6H_4	4-MeC_6H_4	68
c	Ph	4-BrC_6H_4	4-ClC_6H_4	87
d	Ph	2-ClC_6H_4	4-ClC_6H_4	90
e	Ph	3-$(NO_2)C_6H_4$	4-ClC_6H_4	84
f	Ph	4-$(NO_2)C_6H_4$	4-ClC_6H_4	85
g	Ph	4-$Me_2NC_6H_4$	4-ClC_6H_4	92
h	Ph	3-(CHO)C_6H_4	4-ClC_6H_4	89

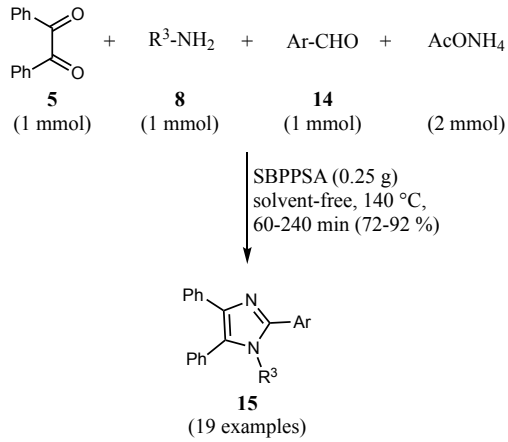
Scheme 14. MPS-catalyzed synthesis of tetrasubstituted imidazoles **12a–h**

In recent years, certain silica modifications have also been used for one-pot four component syntheses of tetrasubstituted-1*H*-imidazoles under solvent-free conditions. Thus, in 2011, silica-bonded propylpiperazine *N*-sulfonic acid (SBPPSA) was prepared by the reaction of 3-piperazine-*N*-propylsilica (3-PNPS) with chlorosulfonic acid in $CHCl_3$ (Scheme 15). [80]



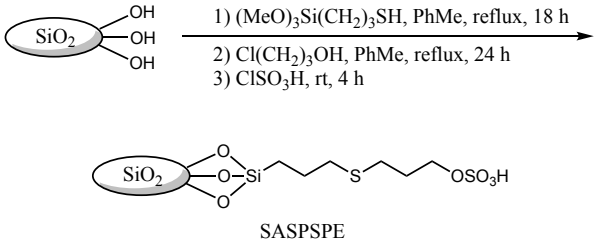
Scheme 15. Synthesis of SBPPSA

SBPPSA was then employed as catalyst for the synthesis of tetrasubstituted-1*H*-imidazoles by the reaction of benzil (**5**) (1 mmol), aldehydes **14** (1 mmol), amines **8** (1 mmol) and $AcONH_4$ (2 mmol) at 140 °C under solvent-free conditions, providing compounds **15** in yields ranging from 70 to 92% (Scheme 16).[80] Interestingly, the catalyst could be easily recovered and reused for subsequent cyclo-condensation reactions.[80]



Scheme 16. SBPPSA-catalyzed synthesis of tetrasubstituted-1H-imidazoles **15**

In 2012, sulphuric acid ([3-(3-silicapropyl)sulfanyl]propyl]ester (SASPSPE) was synthesized as outlined in Scheme 17.[81]

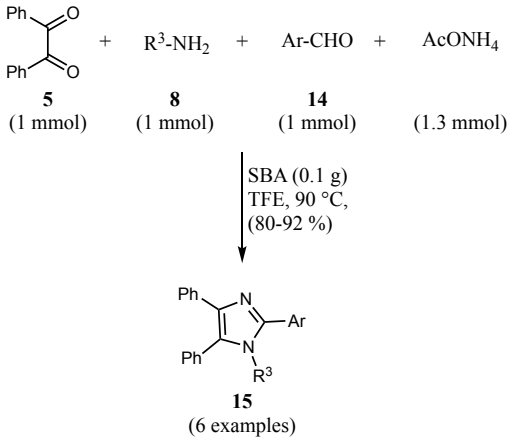


Scheme 17. Synthesis of the heterogeneous catalyst SASPSPE

This recyclable heterogeneous catalyst was used for a four-component one-pot synthesis of imidazoles **15** under solvent-free conditions at 140 °C for 10–210 min providing the required heteroarenes in yields ranging from 71 to 92%. [81]

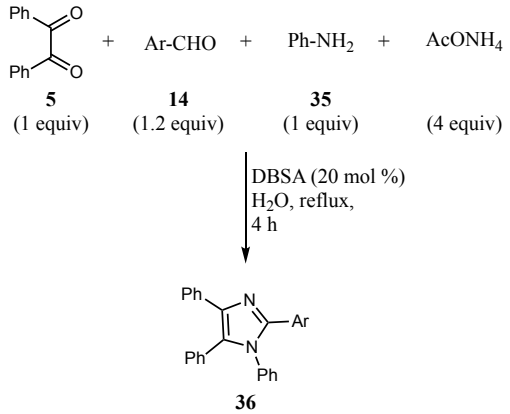
In 2014, another heterogeneous catalyst consisting of solid silica chloride (SiO_2-Cl) was used for the one-pot four-component synthesis of five 1,2,4,5-tetraaryl-1*H*-imidazoles of general formula **15**. [82] In this case the cyclo-condensation reactions were carried out at 80 °C for 30-40 min under solvent-free conditions providing the required heteroarene derivatives in yields ranging from 78 to 87%. [82]

Rostamnia and Zabardasti had previously reported that the adduct of unfunctionalized silica SBA-15 and 2,2,2-trifluoroethanol (SBA-15/TFE) acts as a recyclable catalyst for the reaction between aldehydes, primary amines and $AcONH_4$ with benzil (**5**) at 90 °C to give imidazoles of general formula **15** in yields ranging from 80 to 92% (Scheme 18). [82b]



Scheme 18. SBA-15/TFE-mediated synthesis of imidazoles **15**

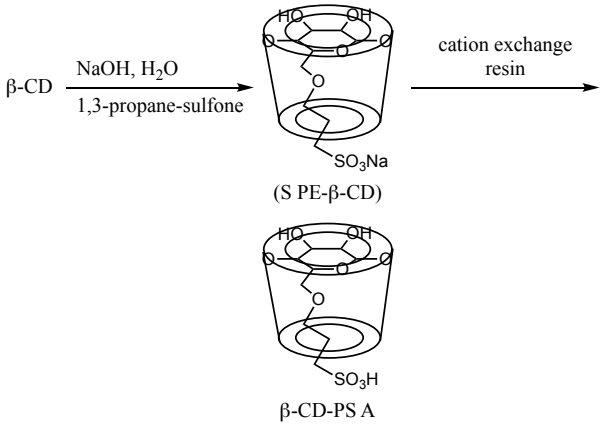
Interestingly, numerous other types of heterogeneous catalysts, different from those based on modified silica, have been used for the one-pot four-component synthesis of tetrasubstituted imidazoles in water, organic solvents or under solvent-free conditions. In 2013, *p*-dodecylbenzenesulfonic acid (DBSA) was found to catalyze the synthesis of 2-aryl-1,4,5-triphenyl-1*H*-imidazoles **36a–h** in good yields from benzil (**5**), aldehydes **14**, aniline (**35**) and $AcONH_4$ in water under reflux for 4 h (Scheme 19).[83]



36	Ar	Yield (%)
a	4-MeC_6H_4	73
b	4-BrC_6H_4	76
c	4-ClC_6H_4	73
d	4-$MeOC_6H_4$	86
e	3-HOC_6H_4	74
f	4-$(NO_2)C_6H_4$	81
g	3-$(NO_2)C_6H_4$	76
h	Ph	81

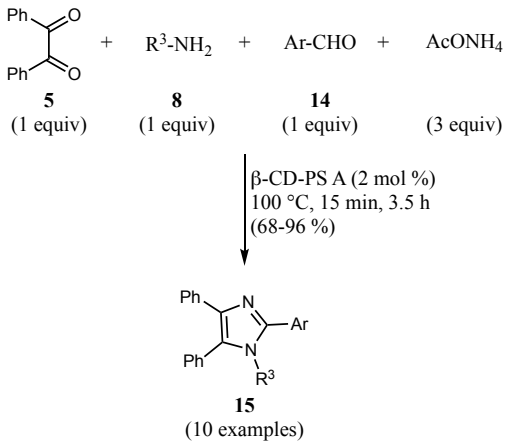
Scheme 19. DBSA-catalyzed synthesis of imidazoles **36a–h**

In 2015, Zhang and coworkers synthesized β-cyclodextrin-propylsulfonic acid (β-CD-PSA) from commercially available β-CD as shown in Scheme 20. [84]



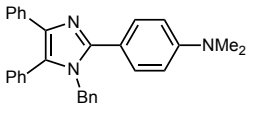
Scheme 20. Synthesis of β-CD-PSA

Specifically, β-CD was reacted with 1,3-propanesultone in NaOH solution to give sulfopropyl ether β-CD (SPE-β-CD). This was further treated with an acidic resin to give β-CD-PSA, which was then used as catalyst for the one-pot four-component synthesis of imidazoles **15** at 100 °C under solvent free-conditions in good to excellent yields (Scheme 21).[84]

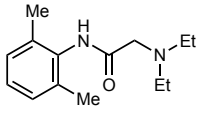


Scheme 21. β-CD-PSA-catalyzed synthesis of tetrasubstituted-1*H*-imidazoles **15**

Notably, compound **15z** (Figure 4), which was synthesized in 73% yield according to this protocol, proved to exhibit local anesthetic activity higher than that of lidocaine (Figure 4), which was used as standard agent for comparison. [84]



15z



lidocaine

Figure 4. Chemical structures of compound **15z** and lidocaine

Still in 2015, chitosan-supported sulphuric acid (CTSA) (Figure 5) was identified as an effective biodegradable solid acid catalyst for the one-pot four-component synthesis of tetrasubstituted-1*H*-imidazoles **38a–h**.[85]

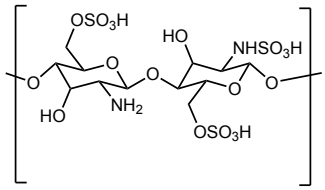
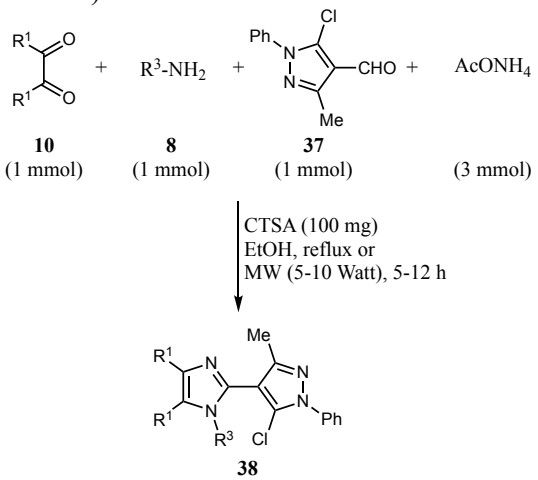


Figure 5. Chemical structure of chitosan-supported sulphuric acid (CTSA)

Compounds **38** were obtained in high yields by reaction of α-diketones **10** (1 mmol), primary amines **8** (1 mmol), 5-chloro-4-formyl-3-methyl-1-phenylpyrazole (**37**) (1 mmol), $AcONH_4$ (3 mmol) and CTSA (100 mg) in EtOH under reflux or in a microwave reactor cavity at 5-10 Watt for 12 h (Scheme 22).



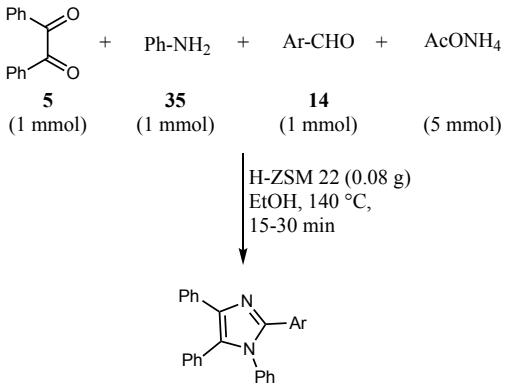
			Microwave irradiation	
10	R^1	R^3	Yield (%)	Time (h)
a	Ph	Ph	91	7
b	Ph	4-$MeOC_6H_4$	89	6
c	Ph	4-ClC_6H_4	87	8
d	Ph	4-MeC_6H_4	90	5
e	Ph	4-HOC_6H_4	91	10
f	Ph	Bn	90	6
g	4-MeC_6H_4	4-MeC_6H_4	88	8
h	4-MeC_6H_4	4-ClC_6H_4	90	10

Scheme 22. CTSA-catalyzed synthesis of tetrasubstituted imidazoles **38a–h**

Notably, high yields of the required tetrasubstituted imidazoles were also obtained when 3-formylindole was used instead of aldehyde **37** in the one-pot reaction. [85]

Recently, also zeolites, which are microporous aluminasilicates, have been used as catalysts for solvent-free syntheses of tetrasubstituted imidazoles. In 2015, zeolite ZSM-5-SO_3H, which was available as a white powder by reacting ZSM-5 with chlorosulfonic acid, [86] was employed as catalyst for the one-pot four-component synthesis of seventeen imidazoles **15** through the reaction of benzil (**5**) (1 mmol) with amines **8** (1 mmol), aldehydes **14** (1 mmol) and $AcONH_4$ (6 mmol) at 110 °C for 30–100 min under solvent-free conditions. Compounds **15** were obtained in yields ranging from 51 to 94% without side-products. [87]

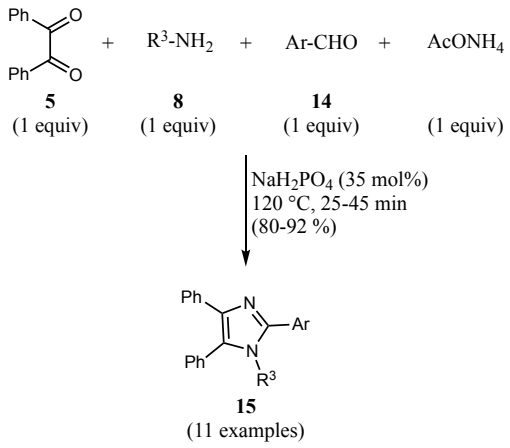
In 2016, imidazoles **36c**, **36f**, **36h** and **36i** were prepared in good yields using zeolite H-ZSM-22 as catalyst. [88] These compounds were obtained by reacting 1 mmol of benzil (**5**), 1 mmol of aniline (**35**) and 1 mmol of aldehydes **14** with 5 mmol of $AcONH_4$ and 0.008 g of H-ZSM-22 in EtOH at 140 °C (Scheme 23).[88]



36	Ar	Yield (%)
h	Ph	81
c	4-ClC_6H_4	86
f	4-$(NO_2)C_6H_4$	81
i	4-HOC_6H_4	76

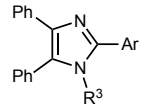
Scheme 23. H-ZSM 22-catalyzed synthesis of imidazoles **36c**, **36f**, **36h** and **36i**

Even other solid acid catalysts, different from those mentioned above, have been used for the one-pot synthesis of tetrasubstituted imidazoles. In 2010, sodium dihydrogen phosphate (NaH_2PO_4) was found to efficiently catalyze the condensation of equimolar amounts of benzil (**5**), aldehydes **14**, primary amines **8** and $AcONH_4$ at 120 °C for 25–45 min under solvent-free conditions. The resulting imidazoles **15** were obtained in yields ranging from 80 to 92% (Scheme 24).[89]



Scheme 24. NaH_2PO_4-catalyzed synthesis of tetrasubstituted imidazoles **15**

In 2011, imidazoles **15a**, **15b** (**36h**), **15c**, **15d** (**36c**), **15e**, **15n**, and **15ac** (Figure 6) were prepared in yields ranging from 78 to 89% by one-pot four-component cyclo-condensation of **5** with aldehydes, primary amines and $AcONH_4$ under microwave irradiation using Amberlyst A-15, a water-tolerant, recoverable and reusable ion exchange resin, as catalyst. [90]



15a: R^3 = Bn; Ar = Ph
15b = **36h**: R^3 = Ar = Ph
15c: R^3 = Bn; Ar = 4-MeC_6H_4
15d = **36c**: R^3 = Bn; Ar = 4-ClC_6H_4
15e: R^3 = Ph; Ar = 4-MeC_6H_4
15n: R^3 = Ph; Ar = 4-ClC_6H_4
15ac: R^3 = Ph; Ar = 4-$(NO_2)C_6H_4$

Figure 6. Chemical structures of imidazoles **15a**, **15b** (**36h**), **15c**, **15d** (**36c**), **15e**, **15n**, and **15ac.**

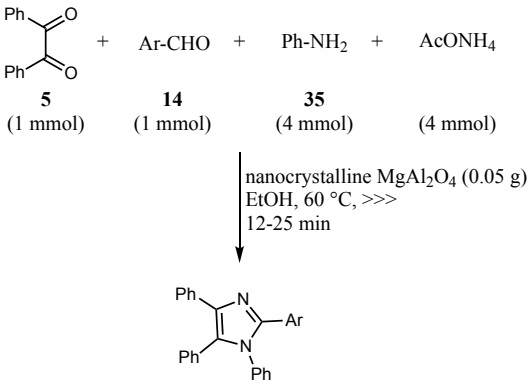
Still in 2011, the carbon-based solid acid, which was obtained by heating an aromatic compound such as naphthalene in sulphuric acid at 473–573 K, [91] proved to be a highly efficient, recyclable catalyst for the one-pot four-component synthesis of imidazoles **15** at 130 °C under solvent-free conditions.[92]

Even several metal-based heterogeneous catalysts have recently found application in the one-pot synthesis of tetrasubstituted-1*H*- imidazoles. In 2010, it was reported that $AlPO_4$ exhibits remarkable and reusable activity in the high yielding, solvent-free synthesis of imidazoles **15** at 140 °C or under microwave irradiation. [93]

In 2011, alumina supported ammonium dihydrogen phosphate ($NH_4H_2PO_4/Al_2O_3$) was found to be an efficient, recyclable catalyst for the preparation of a variety of compounds **15** at 130 °C under solvent-free conditions in yields ranging from 80 to 91%.[94a]

Still in 2011, a series of imidazoles **15** were synthesized by Bahrani and coworkers in yields ranging from 94 to 99% by cyclo-condensation reactions in which ZnO was employed as an efficient reusable catalyst. [94b]

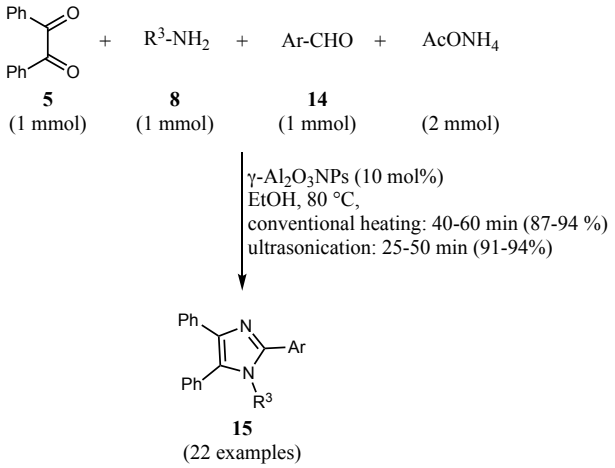
In 2013, Safari and coworkers demonstrated that nanocrystalline $MgAl_2O_4$ was an efficient catalyst for the four-component synthesis of imidazoles **36** in EtOH at 60 °C under ultrasonic irradiation (Scheme 25). [95]



36	Ar	Yield (%)
h	Ph	91
a	4-MeC_6H_4	95
d	4-$MeOC_6H_4$	93
f	3,4-$(MeO)_2C_6H_3$	90
c	4-ClC_6H_4	96
b	4-BrC_6H_4	94
k	2-FC_6H_4	93
l	2-HOC_6H_4	90
m	3,5-$(MeO)_2C_6H_3$	97
i	4-HOC_6H_4	89

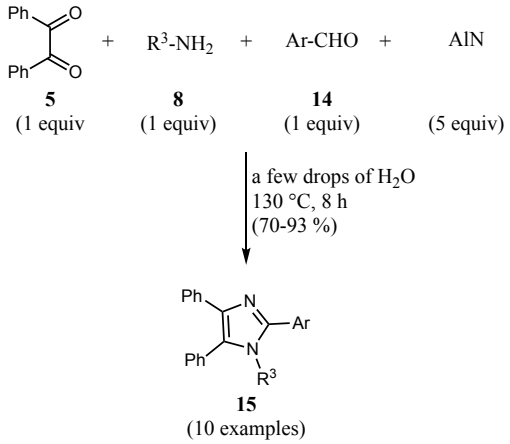
Scheme 25. Nanocrystalline $MgAl_2O_4$-catalyzed synthesis of tetrasubstituted imidazoles **36**

In 2015, γ-alumina nanoparticles (NPs) were used by Vijayakumar and coworkers for catalyzing the synthesis of imidazoles **15** via a one-pot four component reaction.[96] The cyclo-condensation reaction (Scheme 26) was carried out in EtOH under conventional heating at 80 °C or ultrasonication providing compounds **15** in good to excellent yields. Generally, the yields of compounds **15** prepared under ultrasonication were higher than those obtained by conventional heating.[96]



Scheme 26. γ-Al_2O_3 NPs–catalyzed one-pot synthesis of imidazoles **15**

Still in 2015, nano-aluminum nitride (AlN) was used in the synthesis of imidazoles **15** at 130 °C under solvent-free conditions.[97] The reactions were carried out using a large molar excess of nano-AlN in the presence of a few drops of water, which reacted with AlN generating a solution of ammonia and $Al(OH)_3$ which acted as catalyst (Scheme 27).[97]

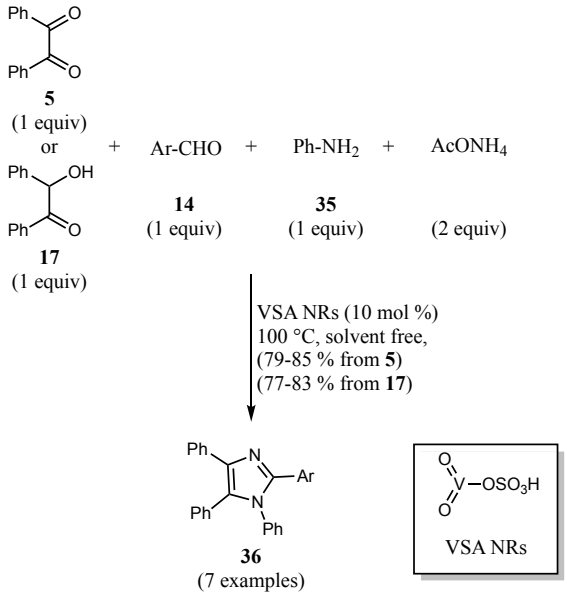


Scheme 27. Synthesis of tetrasubstituted imidazoles **15** using nano-AlN as a solid source of ammonia and the catalyst $Al(OH)_3$

Kannan and Sreekumar had previously described that even the clay supported titanium catalyst K10Ti, which could be prepared from commercially available clay montmoillonite K10 and titanocene dichloride, was a highly active catalyst for the one-pot synthesis of tetrasubstituted imidazoles **15** at 80–120 °C under solvent-free conditions.[98] The catalyst, which very likely contained a mixture of $(SiO_2)TiCl_2$, $(SiO)TiCl_3$ and $(SiO_3)TiCl$ titanium sites, appeared to be stable over three catalytic cycles without appreciable loss of activity.[98]

In 2014, Pourshamsian found that, under optimized conditions, imidazoles **15** could be synthesized in yields ranging from 75 to 93% by one-pot four-component cyclo-condensation reactions in which 20 mol% nano–TiO_2 were used as catalyst at 110 °C for 30-60 min under solvent-free conditions.[99] In that same year, even $ZrO(NO_3)_2{\cdot}xH_2O$ was used by Babu as catalyst for the one-pot synthesis of several imidazoles **15** at 110–120 °C under solvent-free conditions with yields ranging from 65 to 90%.[100]

In 2015, Nasr-Esfahani and coworkers [101] prepared in high yields some imidazoles of general formula **36** by the reaction of benzil (**5**) or benzoin (**17**) with aldehydes **14**, aniline (**35**) and $AcONH_4$ at 100 °C under solvent-free conditions using nanorod vanadatesulfuric acid (VSA NRs)[102] as a recyclable and eco-benign catalyst (Scheme 28).



Scheme 28. Nanorod vanadatesulfuric acid-catalyzed synthesis of imidazoles **36**

In 2016, Olyaei and coworkers reported that nano aluminium-containg mesoporous silica MCM-41 (Al-MCM-41) was an effective catalyst for the one-pot synthesis of imidazoles 36 at 120 °C under solvent-free conditions. [103] The reactions, which were carried out in 30–50 min using benzil (**5**) as a starting material, produced compounds **36** in yields ranging from 85 to 92%. Nano Al-MCM-41 was prepared according to a procedure described in the literature. [104]

In the last decade. also iron-based heterogeneous catalysts have been used in one-pot four-component syntheses of tetrasubstituted imidazoles.

In 2010, Fe^{3+}-montmorillonite K10 was shown to exhibit high catalytic activity in the microwave-assisted high yielding synthesis of imidazoles **15** under solvent-free conditions. [105]

In 2012, the four-component condensation of benzil (**5**) (or benzoin (**17**)) with aldehydes **14**, primary amines **8** and $AcONH_4$ was carried out in high yields using anhydrous $FePO_4$ as catalyst in refluxing EtOH. [106]

Still in 2012, tetrasubstituted imidazoles **15** were also synthesized at 80 °C under solvent-free conditions using magnetic Fe_3O_4 nanoparticles as a high efficient, eco-friendly catalyst, which could be easily recovered and reused.[107] Two years later, Cu nanoparticles supported on Fe_3O_4-polyethyleneglycol nanocomposites were synthesized, characterized and used as an efficient catalyst for the synthesis of imidazoles **15** in excellent yields at 110 °C under solvent-free conditions.[108] The magnetic properties displayed by the catalyst allowed its fast separation from the reaction mixtures using a simple magnet.[108]

In 2016 copper ferrite ($CuFe_2O_4$) nanoparticles were used as a magnetically separable catalyst for the one-pot four-component condensation leading to imidazoles **15** under ultrasonic irradiation at 40 °C in EtOH.[109a] The catalyst, which was prepared according to a literature procedure,[109b] was characterized using Fourier Transform Infrared Spectroscopy (FTIR), Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), X-ray Powder Diffraction (XRD,) and particle size analyser.[109b]

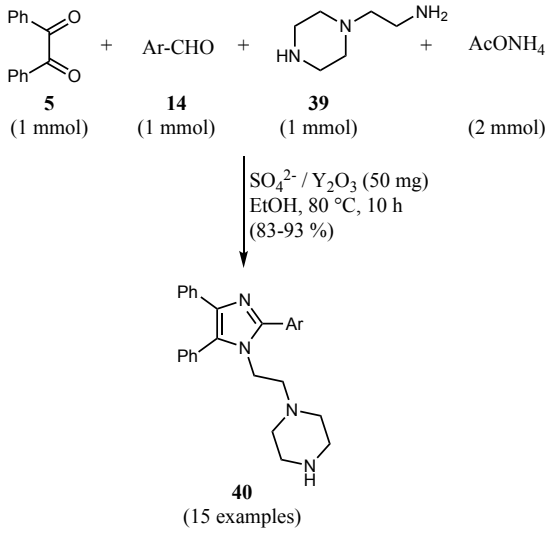
Subsequently, Nemati and coworkers synthesized six tetrasubstituted imidazoles of general formula **15** in 70–90% yield by condensation of 1 mmol of benzyl (**15**), 1 mmol of aryl aldehydes **14**, 1 mmol of $AcONH_4$ and 1 mmol of arylamines R^3-NH_2, **8**, at 90 °C under solvent-free conditions, in the presence of 0.05 g of magnetically separable nano-copper ferrite.[109c]

In 2016, Khazaei, Moosavi-Zare and coworkers synthesized magnetic core-shell titanium dioxide nanoparticles (Fe_3O_4@SiO_2@TiO_2) and studied these catalyst using several techniques including XRD, TEM, field-emission scanning electron microscopy and energy-dispersive X-ray spectroscopy. [110] These nanoparticles were then applied for the efficient preparation of imidazoles **15** from benzyl, aldehydes, primary amines and $AcONH_4$ at 110 °C for 8–20 min under solvent-free conditions.[110]

In 2015, Safa and coworkers reported that several imidazoles **15** could be prepared in high yields via one-pot cyclo-condensation reactions carried out under ultrasonic irradiation in which Cu(II) nitrate impregnated H-SAPO-34 zeolite was used as catalyst.[111]

Karami and coworkers had previously reported that a large variety of tetrasubstituted-1*H*-imidazoles **15** could be obtained in high yields by one-pot four component cyclo-condensation reactions in which, under optimized conditions, 15 mol% $Y(NO_3)_3{\cdot}6H_2O$ were used as a reusable catalyst. [112]

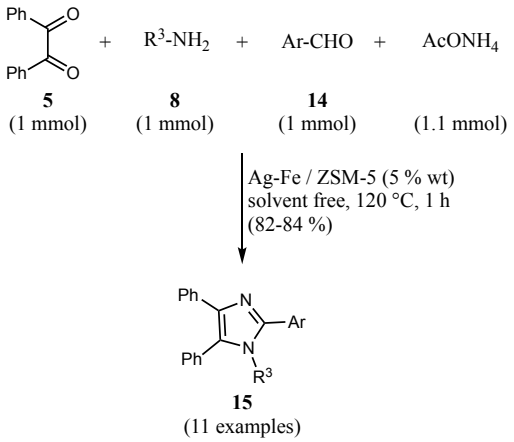
In 2015, sulphated yttria (SO_4^{2-}/Y_2O_3) was used by Krishnasamy and coworkers as a recyclable catalyst for the synthesis of 1-[2-(2,4,5-triphenyl-1*H*-imidazol-1-yl)ethyl]piperazine derivatives **40** in 83–93% yield by cyclo-condensation of benzil (**5**), aryl aldehydes **14**, 1-*N*-(2-aminoethyl)piperazine (**39**) and $AcONH_4$ in EtOH at 80 °C for 10 h (Scheme 29).[113]



Scheme 29. Sulfated yttria-catalyzed synthesis of imidazoles **40**

Teimuri and Chermahini[114] had previously reported that nano-crystalline sulphated zirconia[115] is an efficient superacidic catalyst for the synthesis of 2-aryl-1,4,5-triphenyl-1*H*-imidazoles **36** in high yields and short reaction times by the reaction of benzil (**5**), aryl aldehydes **14**, aniline (**35**) and $AcONH_4$ in EtOH under reflux. Notably, nano-crystalline sulphated zirconia could be recovered from the reaction mixtures and reused without any appreciable loss of activity.[114]

In 2016, the Ag-Fe/ZSM-5 bimetallic nanorodes[116] were used by Safa and coworkers as catalyst for the four-component synthesis of imidazoles **15** at 120 °C for 1 h under solvent-free conditions.[117] The developed protocol (Scheme 30) allowed the synthesis of eleven compounds **15** in yields ranging from 82 to 84%.[117] Notably, the cyclo-condensation reactions occurred without formation of by-products such as 2,4,5-triaryl-1*H*-imidazoles and oxidized products of amines and aldehydes, which are generally observed in strongly acidic media.[117]

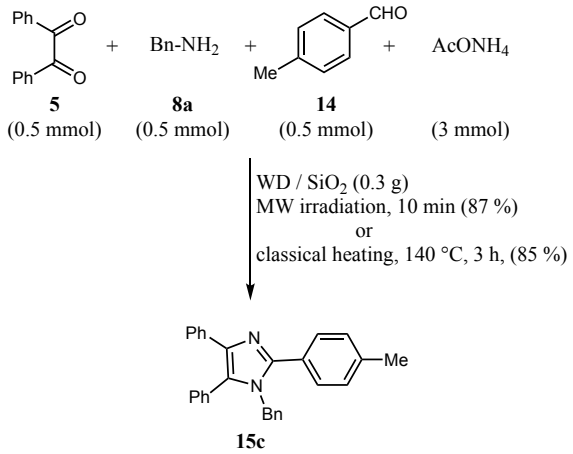


Scheme 30. Ag-Fe/ZSM-5–catalyzed synthesis of tetrasubstituted imidazoles **15**

Even heteropolyacids, which are strong Brønsted acids composed of heteropolyanions and protons as the counter cations, have found application as catalysts for the one-pot four-component synthesis of tetrasubstituted imidazoles.

In 2007, Keggin-type heteropolyacids, represented by the formula $H_{n-8}[XM_{12}O_{40}]$ where X is the heteroatom, n its oxidation state, and M is usually Mo^{6+} or W^{6+}, were used by Heravi and coworkers as green and reusable catalysts for the high yielding synthesis of imidazoles **15** in EtOH under reflux.[118]

In 2010, several tetrasubstituted imidazoles **15** were synthesized in good to excellent yields by using heteropolyacid $H_6P_2W_{18}O_{62}{\cdot}24H_2O$ (Well-Dawson heteropolyacid)-supported on silica (WD/SiO_2) as an effective catalytic system for the condensation of benzil (**5**), aldehydes **14**, amines **8** and $AcONH_4$ by conventional heating or microwave irradiation under solvent-free conditions.[119] A representative example of this type of cyclo-condensation reactions is shown in Scheme 31.[119] Interestingly, benzoin (**17**) instead of benzil (**5**) could be used for the synthesis of compounds **15**, but in this case the yields were found to be quite low.[119]



Scheme 31. WD/SiO_2-catalyzed synthesis of imidazole **15c**

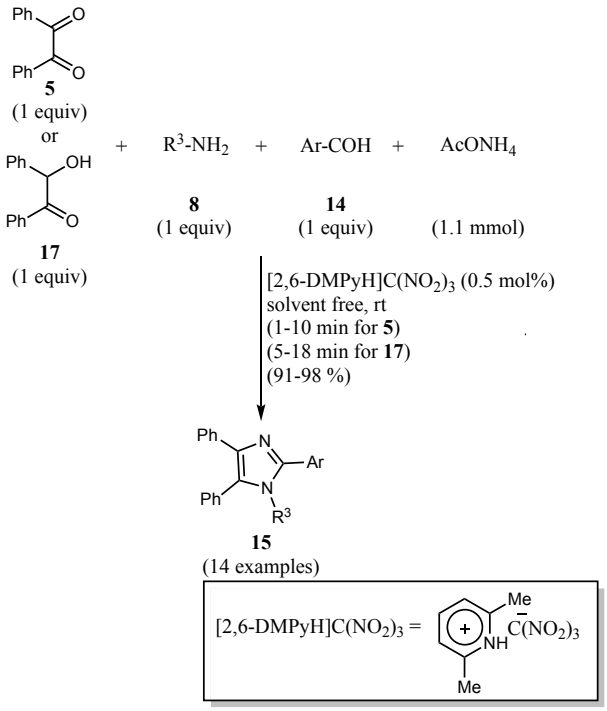
In 2011, it was observed that high yields of compounds **15** were obtained by performing the cyclo-condensation of benzil with aromatic aldehydes, primary amines and $AcONH_4$ using Preyssler heteropolyacid $H_{14}[NaP_5W_{30}O_{110}]$ (1 mol%) as a reusable catalyst in EtOH under reflux for 10–30 min.[120]

In 2016, a series of imidazoles **15** was prepared in excellent yields and short reaction times by cyclo-condensation reactions in which heteropolyacid $H_3PW_{12}O_{40}$ nanoparticles immobilized onto a dendrimer polymer functionalized nanosilica was the catalyst system.[121] The reaction were carried out at 90 °C under solvent-free conditions or in EtOH at room temperature under ultrasonic irradiation.[121]
(4 mmol)

Nagarapu and coworkers had previously reported that tetrasubstituted imidazoles **15** are also available in high yields using potassium dodecatungstocobaltate trihydrate [K5CoW12O40•3H2O] (0.1 mol%) as catalyst for cyclo-condensation reactions carried out under microwave irradiation or classical heating conditions in which benzil (**5**) was a starting material.[122] However, compounds **15** were obtained in low yields when benzoin (**17**) was used in place of benzil.[122]

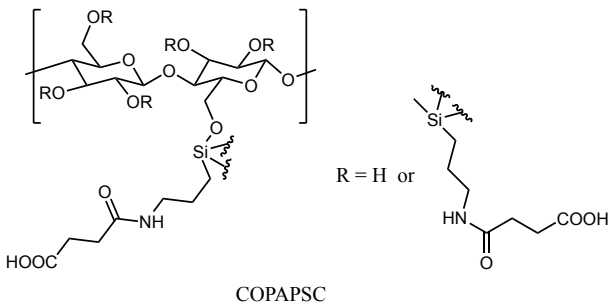
In 2013, Kalkhorani and Heravi described that four-component one-pot cyclo-condensation reactions carried out at 140 °C under solvent-free conditions using $K_7Na_3P_2W_{18}Cu_4O_{68}$ (0.2 mol%) as catalyst provided imidazoles **15** in high yields. [123]

In 2015, Zolfigol, Moosavi-Zare and coworkers designed a novel nano-structured molten salt, namely 2,6-dimethylpyridinium trinitromethanide {[2,6-DMPyH]C(NO_2)$_3$} and used this salt as catalyst in the one-pot four-component synthesis of fourteen imidazoles of general formula **15** at room temperature under solvent-free conditions (Scheme 3).[124]



Scheme 32. 2,6-Dimethylpyridinium trinitromethanide-catalyzed synthesis of tetrasubstituted imidazoles **15**

In 2015, Salimi and coworkers synthesized (carboxy-3-oxopropylamino)-3-propylsilylcellulose (COPAPSC) (Figure 7), which then they used as catalyst (5 mol%) for the one-pot synthesis of twelve imidazoles of general formula **15** in yields ranging from 75 to 87%.[125] The cyclo-condensation reactions were carried out at 110 °C for 3.5–5.5 h under solvent-free conditions.[125]



COPAPSC

Figure 7. Chemical structure of carboxy-3-oxopropylamino)-3-propylsilylcellulose (COPAPSC).

More recently, Majumdar and coworkers reported the synthesis of nine *N*-substituted 2-aryl-4,5-diphenyl-1*H*-imidazoles in 60–81% yield via reaction of benzyl (**5**)/benzoin (**17**) (2 mmol) with aryl aldehydes (2 mmol), $AcONH_4$ (2.5 mmol) and primary amines (phenylamine, benzylamine or methylamine) in EtOH under reflux in the presence of Amberlite IR 120H$^+$ (20 mg, 5% w/w).[126a] Notably, the insoluble catalyst could be recovered and recycled without any noticeable decrease in its activity.[126]

Concluding this section, it is worth mentioning that, still recently, Sreekumar and co-workers found that the copper complex of amidoamine dendronized polymer having ethylene glycol initiated polyepichlorohydrin as core was a highly efficient heterogeneous catalyst for the synthesis of a series of tetrasubtituted imidazole derivatives by reaction of benzyl (**5**) (1 mmol), aryl aldehydes (1 mmol), $AcONH_4$ (4 mmol), and primary amines (1 mmol) in EtOH at room temperature for 1–2 h.[126b] The catalyst (0.012 mol%) that could be reused five times without a significant loss of activity allowed the synthesis of the required tetrasubstituted imidazoles in 75–95% yield.[126b]

2.3. One-Pot Four-Component Syntheses carried Out Using Ionic Liquids as Catalysts or Dual Catalysts-Solvents

In recent years, ionic liquids, which are recognized as environmentally benign compounds that can be used as green solvents, ligands, stabilizing agents and co-catalysts,[127] have been applied in the one-pot four component synthesis of tetrasubstituted-1*H*-imidazoles as catalysts or dual catalysts-solvents.

In 2010, 3-methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulphate (Figure 8), a Brønsted acidic ionic liquid, was used as an efficient and reusable green catalyst for the synthesis of imidazoles **15** at 140 °C for 2-2.5 h under solvent-free conditions.[128] Good yields (85–94%), relatively short times (2–2.5 h) and easy of work-up were some advantages of this protocol. Furthermore, the catalyst could be reused after a simple work-up, but unfortunately its activity gradually declined. [128]

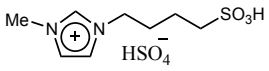
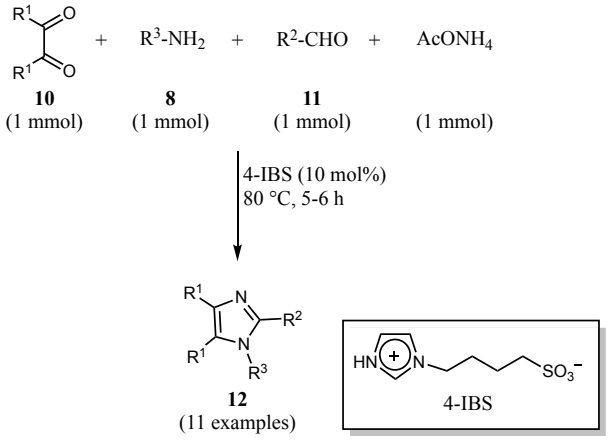


Figure 8. Chemical structure of 3-methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulphate

In 2012, 4-(1-imidazolium)butane-1-sulfonate (4-IBS) was shown to be an excellent catalyst for the synthesis of tetrasubstituted imidazoles of general formula **12** by reaction of 1,2-diketones **10** with aldehydes **11**, primary amines **8** and $AcONH_4$ at 80 °C under solvent-free conditions (Scheme 33).[129]



12	R^1	R^2	R^3	Yield (%)
b	Me	4-BrC_6H_4	4-MeC_6H_4	63
c	Ph	4-ClC_6H_4	4-ClC_6H_4	75
i	Ph	Ph	Bn	82
j	Ph	Ph	*c*-C_6H_{11}	75
k	Ph	4-MeC_6H_4	Ph	78
l	Ph	4-ClC_6H_4	4-FC_6H_4	72
m	Ph	4-MeC_6H_4	Bn	80
n	Ph	4-ClC_6H_4	Bn	78
o	Ph	4-ClC_6H_4	Ph	80
p	Ph	4-ClC_6H_4	4-ClC_6H_4	75
q	Ph	2-ClC_6H_4	Bn	75
r	Ph	4-HOC_6H_4	Bn	78
s	Ph	2-HOC_6H_4	4-MeC_6H_4	72
t	Ph	4-$MeOC_6H_4$	Bn	76
u	Ph	3-$(NO_2)C_6H_4$	4-MeC_6H_4	75
v	Ph	*n*-Pr	Bn	78

Scheme 33. Synthesis of imidazoles **12** via 4-IBS-catalyzed cyclo-condensation reaction

A year before, Shaterian and coworkers demonstrated that triphenyl(propyl-3-sulfonyl)phosphonium *p*-toluenesulfonate (TPSPT) (Figure 9), a Brønsted acidic ionic liquid, efficiently catalyzes the four-component reaction of benzil or benzoin with aldehydes, primary amines and $AcONH_4$ at 100 °C under solvent-free conditions providing a series of forty tetrasubstituted-1*H*-imidazoles **15** in good to excellent yields.[130] Notably, the catalyst could be easily recovered and reused for seven cycles without loss of its activity.

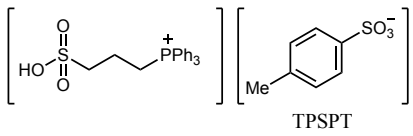


Figure 9. Chemical structure of triphenyl(propyl-3-sulfonyl)phosphonium *p*-toluenesulfonate (TPSPT)

Various other ionic liquids, which include *N*-methyl-2-pyrrolidonium hydrogen sulphate ($NMP^+HSO_4^-$),[131] diethylammonium hydrogen sulphate (DEAHS),[132a,b] *N*-butylpyridinium tetrafluoroborate {[BPy][BF_4]},[133] 1-butyl-3-methyl-1-imidazolium tetrafluoroborate [BMIM][BF_4],[134] poly/4-vinylpyridinium butanesulfonic acid) hydrogen sulphate [P(4-VBSA)],[135] 1-methyl-3-(3-trimethoxysilylpropyl)imidazolium chloride immobilized on super-magnetic Fe_3O_4 nanoparticles (IL-MNPs),[136] di-*n*-propylammonium hydrogen sulphate [*n*-Pr_2NH_2][HSO_4],[137] 1,3-disulfonic acid imidazolium hydrogen sulphate [DS_{im}]HSO_4,[138a] and tri(1-butyl-3-methylimidazolium) gadolinium hexachloride {[bmim]$_3$[$GdCl_6$],[139] (Figure 10) have been used as catalysts for the one-pot four-component synthesis of tetrasubstituted-1*H*-imidazoles **15**.

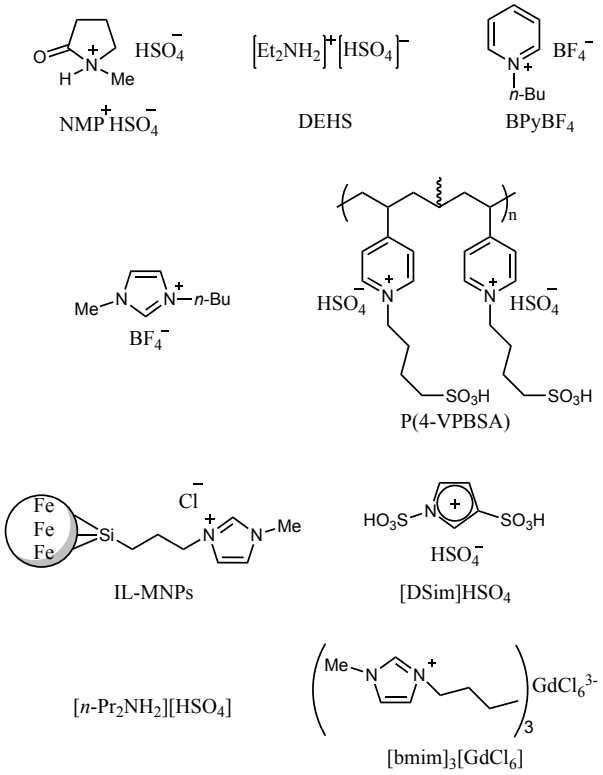
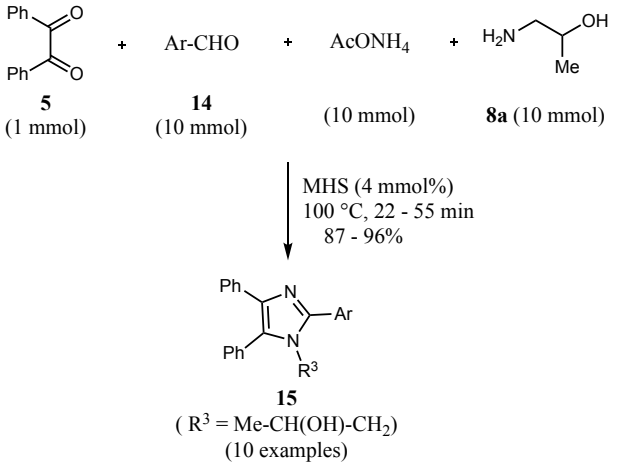


Figure 10. Chemical structures of some ionic liquids used as catalysts for the synthesis of tetrasubstituted-1*H*-imidazoles

It should be noted that DEAHS and P(4-VPBSA) appeared to be reusable catalysts capable of providing the required imidazoles **15** in short reaction times with good to excellent yields. It deserves also to be mentioned that *i)* the reactions catalysed by the ionic liquids listed in Figure 10 were carried out using solvent-free conditions, and that *ii)* the cyclo-condensations that were carried carried out using [BMIM][BF_4],[134] and (IL-MNPs)[136] as reaction media occurred under microwave irradiation. On the other hand, the syntheses of 1,2,4,5-tetrasubstituted imidazoles that were performed in neutral ionic liquid 1-butyl-3-methylimidazolium bromide were achieved under microwave irradiation and/or conventional heating. [138b]

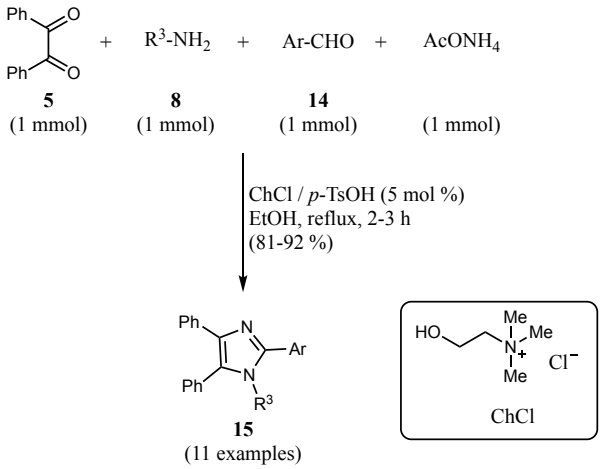
In 2017, Mohamed and coworkers synthesized ten tetrasusbtituted imidazoles **15** (R^3 = Me-CH(OH)-CH_2) characterized by anti-inflammatory activity via the reaction of aromatic aldehydes **14** (10 mmol) with benzyl (**5**) (10 mmol), $AcONH_4$ (10 mmol), 1-amino-2-propanol (**8a**) (10 mmol) and morpholinium hydrogen sulphate (MHS) (4 mmol) at 100 °C for 22–55 min (Scheme 35).[140] Under these solvent-free conditions the required imidazole derivatives were obtained in yields ranging from 87 to 96%.[140]



Scheme 34. Morpholinium hydrogen sulphate-catalyzed synthesis of tetrasubstituted imidazoles

In concluding this subsection we also want to mention that high yielding syntheses of tetrasubstituted-1*H*-imidazoles of general formula **15** were also achieved using deep eutectic salts as ionic liquid catalysts. On the other hand, deep eutectic solvents, which are formed from an eutectic mixture of Brønsted and Lewis acids and bases, are similar to conventional ionic liquids in terms of low flammability, low vapour pressure, biodegradability and eco-sustainability.

In 2013, He and coworkers prepared a Brønsted acid deep eutectic solvent based on choline chloride (ChCl) and *p*-toluenesulfonic acid and used it as an effective catalyst for the one-pot synthesis of several imidazoles **15** in refluxing EtOH for 2-3 h with high yields (Scheme 34).[141]



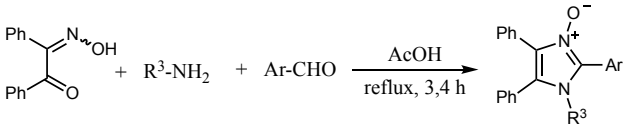
Scheme 35. ChCl/*p*-TsOH-catalyzed synthesis of imidazoles **15** in EtOH under reflux

Still in 2013, Mobinikhaledi and Amiri demonstrated that imidazoles **15** were available in 56–83% by condensation of benzil, aldehydes, primary amines and $AcONH_4$ at 100 °C under solvent-free conditions using ChCl·2$ZnCl_2$ (15 mol) as catalyst. [142]

3. One-Pot Three-Component Reactions

For several decades, the synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles via one-pot three component reactions is another active area of research. Compared with the routes involving one-pot four-component cyclo-condensation reactions, this synthetic approach offers several advantages that include the possibility to access 1,2,4,5-tetrasubstituted-1*H*-imidazoles featuring four different substituents with atom economy and conciseness.

In 1979, Woolhouse demonstrated that 1,2,4,5-tetraaryl-1*H*-imidazole 3-oxides **42** could be synthesized in satisfactory yields by AcOH-mediated cyclo-condensation of a stereoisomeric mixture of α-benzil monoxime (**41**) with aryl aldehydes **14** and primary amines **8** under reflux for 3-4 h (Scheme 36). [143]

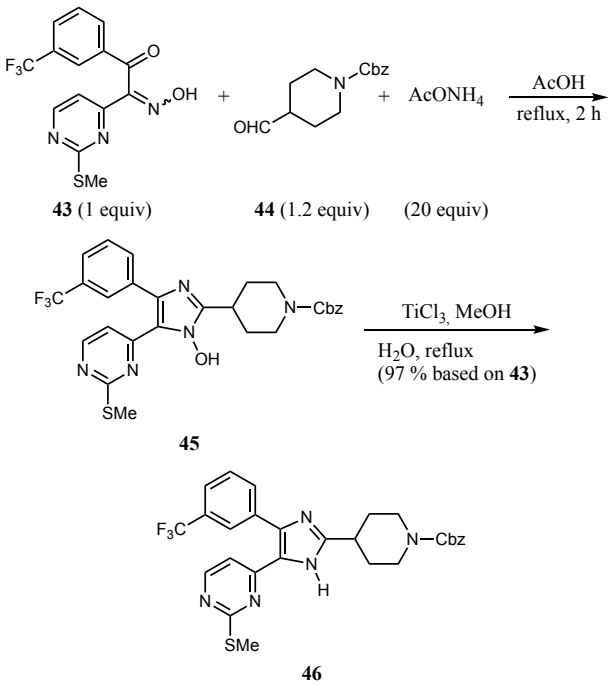


41 **8** **14** **42**

42	R^3	Ar	Yield (%)
a	Ph	Ph	73
b	4-MeC_6H_4	Ph	70
c	Ph	2-MeC_6H_4	65
d	4-$MeOC_6H_4$	Ph	65
e	Ph	4-$MeOC_6H_4$	78
f	4-ClC_6H_4	Ph	80
g	4-BrC_6H_4	Ph	68

Scheme 36. One-pot three-component synthesis of 1,2,4,5-tetraaryl-1*H*-imidazole 3-oxides **42**

In 1999, as part of a study on the design and synthesis of potent, selective and orally bioavailable tetrasubstituted imidazole inhibitors of p38 mitogen-activated protein kinase, Liverton and coworkers synthesized crude 1-hydroxy-5-[2-(methylthio)pyrimidin-4-yl]-4-[3-(trifluoromethyl)phenyl]-2-[4-(*N*-benzyloxycarbonyl)piperidinyl]imidazole (**45**) by AcOH-mediated condensation reaction of a stereoisomeric mixture of 1-[2-(methylthio)pyrimidin-4-yl]-2-[3-(trifluoromethyl)phenyl]ethane-1,2-dione-1-oxime (**43**) with aldehyde **44** and $AcONH_4$ in AcOH under reflux (Scheme 36).[144] A MeOH solution of crude **45** was subsequently reacted with an aqueous HCl solution of $TiCl_3$ to give 1*H*-imidazole **46** in 97% yield based on **43** (Scheme 37).[144]



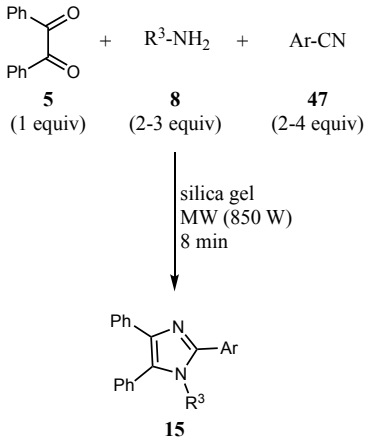
43 (1 equiv) **44** (1.2 equiv) (20 equiv)

45

46

Scheme 37. Synthesis of 1-hydroxy-1*H*-imidazole **45** and trisubstituted imidazole **46**

In 2003, Ballalaie and coworkers described an efficient approach to tetrasubstituted imidazoles **15** that involved the one-pot silica gel-mediated three-component reaction of benzil (**5**) with benzonitrile derivatives **47** and primary amines **8** under solvent-free conditions and microwave irradiation.[145] In this way compounds **15** were obtained in satisfactory to good yields (Scheme 38).[145] It was observed that the use of silica gel in this protocol was important. In fact, the cyclo-condensation reaction leading to compound **15a** occurred in only 10% yield when it was carried out without the use of silica gel. [145]



5 (1 equiv) **8** (2-3 equiv) **47** (2-4 equiv)

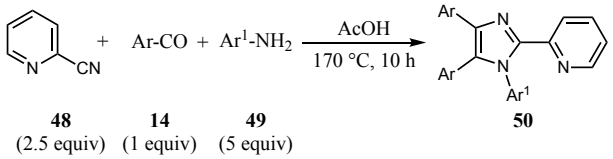
15

15	R^3	Ar	Yield (%)
a	Bn	Ph	87
c	Bn	4-MeC_6H_4	90
j	Et	4-MeC_6H_4	87
ac	PhCH(Me)	Ph	92
ad	Me	4-MeC_6H_4	78
ae	*t*-Bu	4-MeC_6H_4	90
af	Bn	3-BrC_6H_4	65
ag	Bn	3-$(NH_2)C_6H_4$	58

Scheme 38. One-pot three component synthesis of imidazoles **15**

In 2010, Ren and Cai demonstrated that imidazoles of general formula **15** could be alternatively synthesized in good yields by three-component condensation of benzil (**5**), benzonitrile derivatives and primary amines **8** under solvent-free conditions using molecular iodine (10 mol%) as a catalyst.[146] Unfortunately, the reaction failed to proceed when the primary amines were aniline derivatives, probably to the difficulty of forming Schiff bases from **5** and the aniline derivatives.

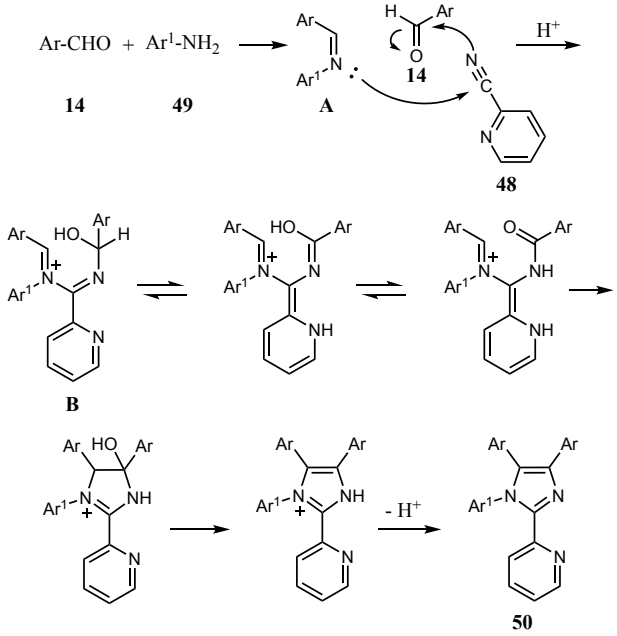
In that same year, Ji and coworkers reported that the reaction of 2.5 equiv of 2-cyanopyridine (**48**) with 1 equiv of aryl aldehydes **14** and 5 equiv of arylamines **49** in AcOH at 170 °C for 10 h led to 2-(pyridine-2-yl)-1,4,5-triaryl-1*H*-imidazoles **50** in good to excellent yields (Scheme 39).[147]



50	Ar	Ar^1	Yield (%)
a	4-$MeOC_6H_4$	4-$MeOC_6H_4$	92
b	4-$MeOC_6H_4$	4-MeC_6H_4	89
c	4-$MeOC_6H_4$	Ph	83
d	4-$MeOC_6H_4$	4-ClC_6H_4	87
e	4-$MeOC_6H_4$	3-ClC_6H_4	82
f	4-ClC_6H_4	4-$MeOC_6H_4$	97
g	4-ClC_6H_4	4-MeC_6H_4	95
h	4-ClC_6H_4	Ph	85
i	4-ClC_6H_4	4-ClC_6H_4	92
j	4-ClC_6H_4	4-BrC_6H_4	90
k	4-ClC_6H_4	3-ClC_6H_4	90

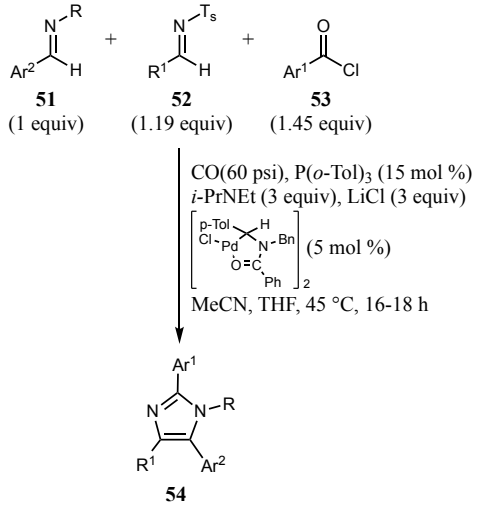
Scheme 39. AcOH-mediated synthesis of 2-(pyridine-2-yl)-1,4,5-triaryl-1*H*-imidazoles **50**

Ji and coworkers also proposed a possible mechanism for the formation of compounds **50** in which imines **A**, formed by **14** and **49**, react with 2-cyanopyridine (**48**) and another molecule of aldehydes **14** in acidic conditions producing intermediates **B**. These intermediates would be involved in the intramolecular nucleophilic attack that would give rise to intermediates **C**. The latter would finally undergo elimination of water and a proton to give rise to compounds **50** (Scheme 40).[147]



Scheme 40. Plausible mechanism for the formation of 2-(pyridine-2-yl)-1,4,5-triaryl-1*H*-imidazoles **50**

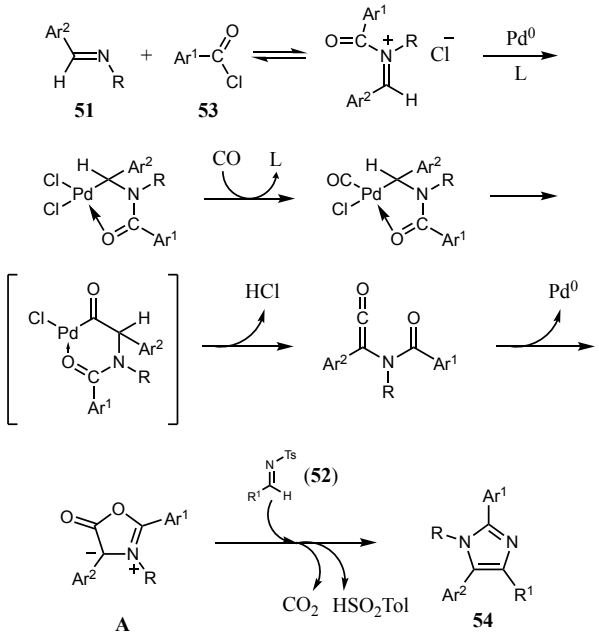
In 2006, Siamaki and Arndtsen[148] developed an elegant one-step regioselective synthesis of tetrasubstituted-1*H*-imidazoles of general formula **54** which consisted in the reaction of 1 equiv of imines **51** with 1.19 equiv of *N*-tosylimines **52** and 1.45 equiv of acyl chlorides **53** in MeCN at 45 °C for 16–18 h in the presence of carbon monoxide (60 psi), 15 mol% P(*o*-Tol)$_3$, 3 equiv of *i*-Pr_2NEt in THF, 3 equiv of LiCl, and 5 mol% [PdCl(η^2-*p*-Tol)-*N*-benzyl(COPh)]$_2$[148] (Scheme 41).



54	R	Ar^2	R^1	Ar^1	Yield (%)
a	Et	4-MeC_6H_4	Ph	Ph	76
b	4-$MeOC_6H_4$	4-MeC_6H_4	2-furyl	4-MeC_6H_4	71
c	Bn	*t*-Bu	Ph	4-MeC_6H_4	67
d	$Me(CH_2)_5$	4-MeC_6H_4	2-thienyl	Ph	70
e	Et	4-MeC_6H_4	Ph	*i*-C_3H_7	60
f	Et	4-$MeSC_6H_4$	3-pyridyl	2-furyl	70
g	Et	4-MeC_6H_4	CEI-steryl	Ph	74
h	Et	4-MeC_6H_4	*c*-C_6H_{11}	4-MeC_6H_4	68
i	Et	4-MeC_6H_4	*n*-Bu	4-$MeOC_6H_4$	69

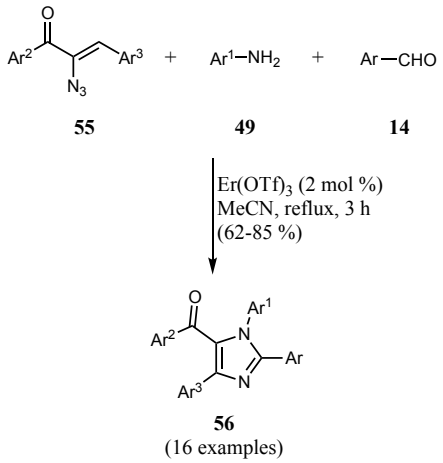
Scheme 41. One-pot Pd-catalyzed three-component synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles **54**

The selectivity of this process that involved the simultaneous coupling of two different imines was believed to result from the catalytic mechanism shown in Scheme 42 in which 1,3-oxazolium-5-olates (münchnones) **A**[149] would be generated from the Pd-catalyzed reaction of imines **51** with acyl chlorides **53** and carbon monoxide.[148]



Scheme 42. Postulated mechanism for the synthesis of imidazoles **54**

In 2014, Muthusubramanian and coworkers [150] synthesized aryl(1,2,4-triaryl-1*H*-imidazol-5-yl)methanones **56** by reaction of equimolar amounts of α-azidochalcones **55**,[151] arylamines **49** and aryl aldehydes **14** in MeCN under reflux for 3 h, in the presence of 2 mol% $Er(OTf)_3$ (Scheme 41).



Scheme 43. Erbium triflate-catalyzed three component synthesis of imidazoles **56**

This protocol allowed for instance to prepare compounds **56a**, **56b** and **56c** (Figure 10) in 62, 71 and 83% yield respectively.[150]

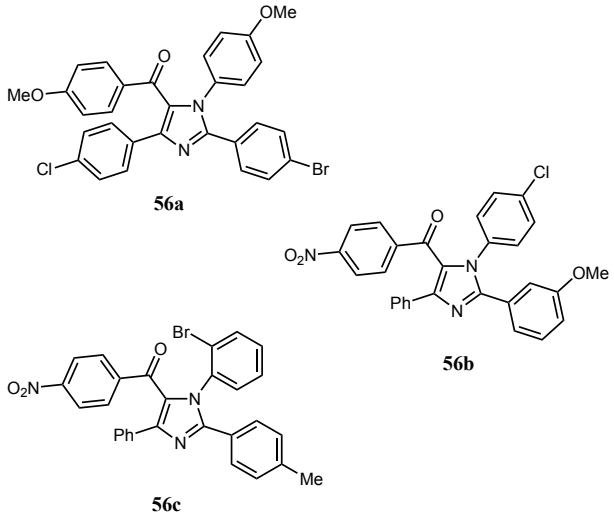
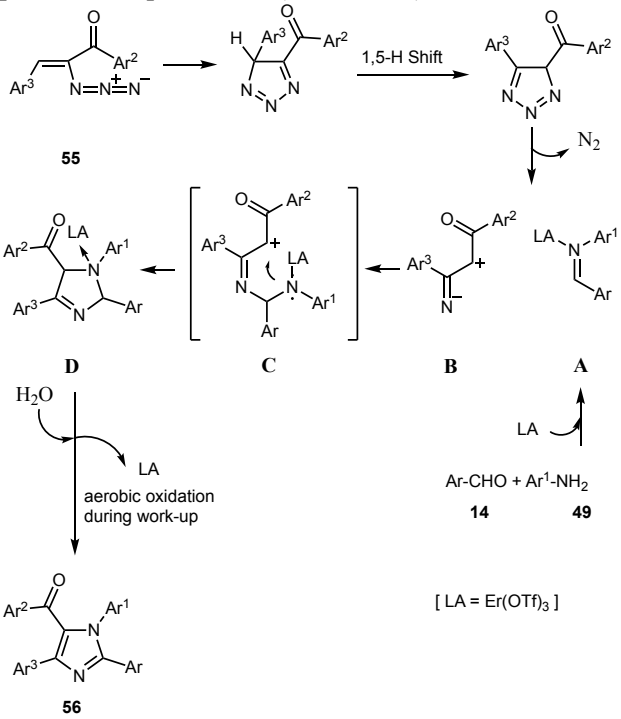


Figure 10. Chemical structures of tetrasubstituted imidazoles **56a–c**

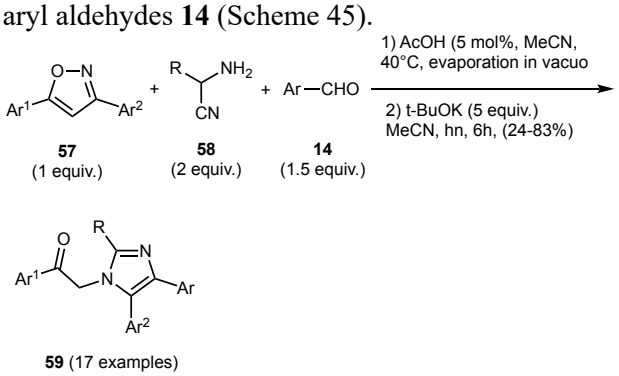
The one-pot reaction was proposed to occur via the mechanism illustrated in Scheme 44, in which Lewis acid $Er(OTf)_3$ could coordinate the imines generated from **14** and **49** giving rise to intermediates **A**. The

lone pair electrons of the nitrogen atom of intermediates **B** generated from α-azidochalcones **55** could then attack the electrophilic centre of **A** forming intermediates **C**. A subsequent attack of the electron pair of **C** on the α-position of the carbonyl group would result in the dihydroimidazoles **D**, which by air-oxidation during work-up would provide compounds **56** (Scheme 44).[150]



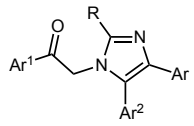
Scheme 44. Proposed mechanism for the formation of imidazoles **5**

Still in 2014, Pusch and Opatz[152] described a one-pot three-component catalytic synthesis of regioisomerically pure 2-[2-substituted-4,5-diaryl-1*H*-imidazol-1-yl]-1-arylethanones **59** from 3,5-diarylisoxazoles **57**,[153] α-aminonitriles **58**[154] and aryl aldehydes **14** (Scheme 45).



Scheme 45. One-pot two-step synthesis of imidazoles **59**

Specifically, a mixture of isoxazoles **57** (1 equiv), α-aminonitriles **58 (**2 equiv) and aldehydes **14** (1.5 equiv) was dissolved in MeCN in the presence of 5 mol% AcOH. The solvent was then evaporated *in vacuo* at 40 °C and the residue was dissolved in MeCN, degassed and reacted with 5 equiv of *t*-BuOK under irradiation at 700 nm for 6 h providing compounds **59** in yields ranging from 24 to 88%.[152] For example, compounds **59a**, **59b** and **59c** (Figure 11) were obtained in 24, 66 and 88% yield, respectively.



59a : Ar^1 = Ph, Ar^2 = Me; Ar = 4-(NO$_2$)C$_6$H$_4$; R = 4-FC$_6$H$_4$
59b : Ar^1 = Ar^2= Ph; Ar = 4-(CN)C$_6$H$_4$; R = Ph
59c : Ar^1 = Ar^2= Ph; Ar = 4-(CN)C$_6$H$_4$; R = *c*-C$_6$H$_{11}$

Figure 11. Chemical structures of compounds **59a–c**

It was also determined that compounds **59** that derived from the *t*-BuOK-mediated reaction of isoxazoles **57** with α-(alkylideneamino)nitriles **60** (Figure 12) were obtained by condensation of aldehydes **14** with α-aminonitriles **58**.[152]

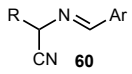
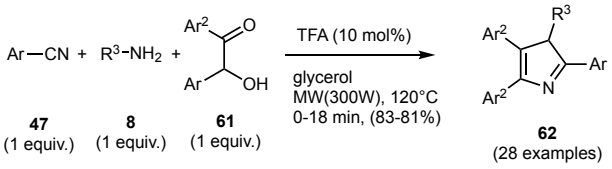


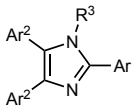
Figure 12. Chemical structure of α-(alkylideneamino)nitriles **60**

In 2016, Khalafi-Nezhad and coworkers carried out the synthesis of a series of 1,2,4,5-tetrasubstituted-1*H*-imidazoles of general formula **62** by microwave-promoted reaction of aromatic nitriles **47** with primary amines **8** and α-hydroxyketones **61** in glycerol at 120 °C for 6-8 min in the presence of trifluoroacetic acid (TFA) (10 mol%) (Scheme 46).[155]



Scheme 46. Microwave-promoted TFA-catalyzed one-pot three-component synthesis of imidazoles **62**

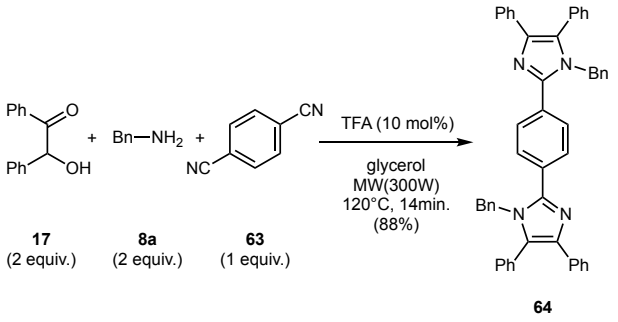
This protocol enabled the synthesis of twenty-eight compounds **62** in good to excellent yields, but failed in the attempted preparation of compounds **62a-d** (Figure 13).



62a: Ar = Ph; R^3 = 4-$(NO_2)C_6H_4$; Ar^2 = Ph
62b: Ar = Ph; R^3 = 2-$(NO_2)C_6H_4$; Ar^2 = Ph
62c: Ar = Ph; R^3 = Ph; Ar^2 = 4-$MeOC_6H_4$
62d: Ar = 4-$(NO_2)C_6H_4$; R^3 = Bn ; Ar^2 = 4-$MeOC_6H_4$

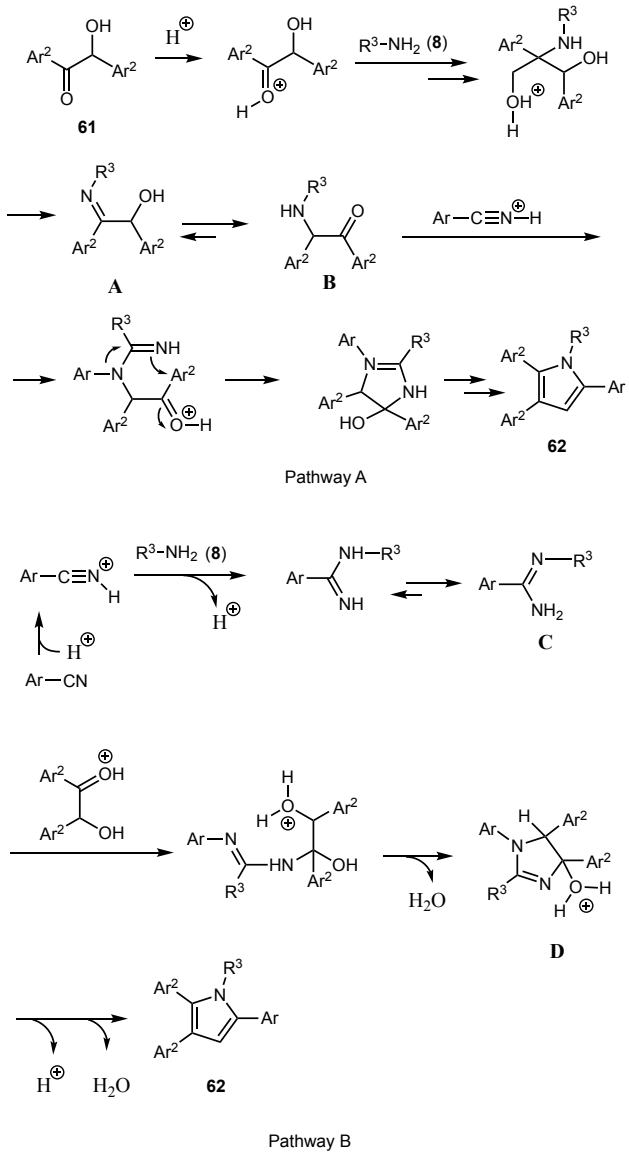
Figure 13. Chemical structures of imidazoles **62a–d**

Nonetheless, the method proved suitable for the condensation of benzoin (**17**) (2 equiv) and benzylamine (**8a**) (2 equiv) with terephthalonitrile (**63**) (1 equiv) that gave rise to bis-imidazole **64** in 88% yield after 14 min (Scheme 47).[155]



Scheme 47. Synthesis of bis-imidazole **64**

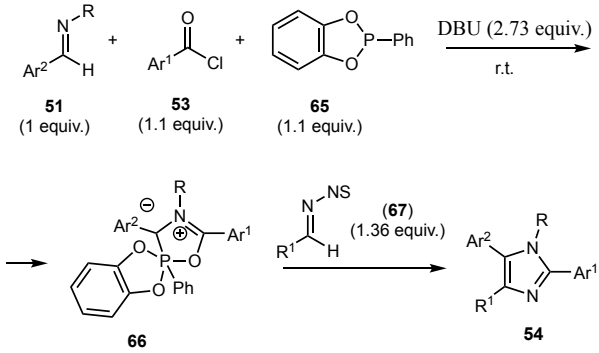
Finally, two different mechanistic pathways (*A* and *B*) were postulated to rationalize the synthesis of imidazoles **62**. Pathway *A* (Scheme 48) begins with the condensation of benzoins **61** with amines **8** that produces the α-aminocarbonyl compounds **B** via tautomerization of the imino intermediates **A**. The subsequent nucleophilic attack of **B** on the protonated form of nitriles **47** followed by a cyclization reaction would provide imidazoles **62**.



Scheme 48. Plausible mechanisms for the formation of imidazoles **62**

In pathway *B*, amidines *C* that are formed by the reaction of amines **8** with the protonated form of nitriles **47** would undergo reaction with the protonated form of benzoins **61** to produce imidazoles **62** via intermediates **D**.[154]

In 2015, Arndtsen and coworkers developed an efficient and elegant regioselective synthesis of tetrasubstituted imidazoles **54** that involved the 2-phenylbenzo[*d*][1.3.2]dioxaphosphole [PPh(catechyl)] (**65**)-mediated reaction of imines **51** with acyl chlorides **53** (Scheme 49).[156] The reaction of imines **51** with aroyl chlorides **53** and [PPh(catechyl)] (**65**) was proposed to generate phospha-münchnones **66**, which would undergo regioselective cycloaddition with *N*-nosylimines **67** to give imidazoles **54** in moderate to good yields.[156]

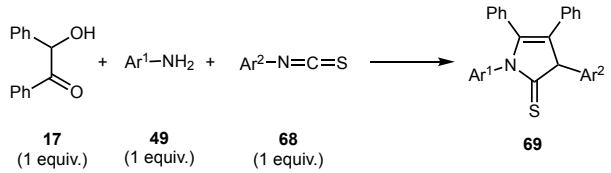


51 (1 equiv.) 53 (1.1 equiv.) 65 (1.1 equiv.) 66 54

54	Ar^2	R^1	Ar^1	R	Yield (%)
a	4-$MeSC_6H_4$	4-FC_6H_4	4-MeC_6H_4	Bn	63
b	2-thienyl	Ph	Ph	Et	77
c	Ph	$4MeC_6H_4$	2-thienyl	Bn	62
d	3-BrC_6H_4	Ph	4-MeC_6H_4	Me	50
e	4-MeC_6H_4	Ph	$4FC_6H_4$	Bn	41
f	4-MeC_6H_4	Ph	2-furyl	Bn	36
g	4-ClC_6H_4	2-furyl	*i*-Pr	Bn	45
h	Ph	2-furyl	4-MeC_6H_4	4-$MeOC_6H_4$	68
i	3,4-$(OCH_2O)C_6H_3$	4-MeC_6H_4	Ph	Bn	35

Scheme 49. One-pot synthesis of imidazoles **54** via phospha-münchnone cycloaddition

In 2017, Shaker and coworkers described a simple and efficient synthesis of 1,3,4,5-tetrasubstituted-1*H*-imidazole-2(3*H*)-thiones **69** via a one-pot three-component AcOH-mediated reaction of benzoin (**17**) with aromatic primary amines **49** and aryl isothiocyanates **68** (Scheme 50).[157] The reaction was carried out under reflux for 5–6 h producing compounds **69** in yields ranging from 58 to 70%. Higher yields, however, were obtained when the reaction was carried out at room temperature for 0.5 h in AcOH in the presence of a small amount of Keggin heteropolyacid $H_3[PMo_{12}O_{40}]$ (Scheme 50).[157]

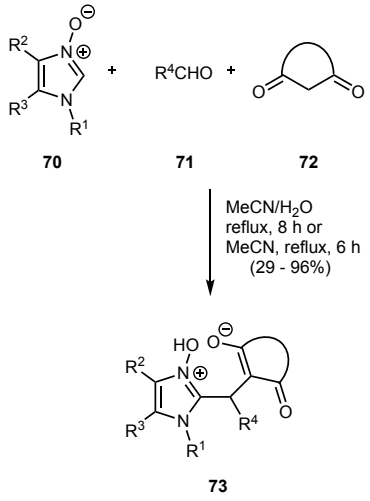


17 (1 equiv.) 49 (1 equiv.) 68 (1 equiv.) 69

69	Ar^1	Ar^2	AcOH	heteropolyacid
			Yield%	yield%
a	4-MeC_6H_4	4-MeC_6H_4	65	80
b	3-ClC_6H_4	4-ClC_6H_4	58	92
c	4-MeC_6H_4	4-ClC_6H_4	68	82
d	3-ClC_6H_4	4-MeC_6H_4	62	86
e	3-$(NO_2)C_6H_4$	4-ClC_6H_4	70	86
f	3-MeC_6H_4	4-ClC_6H_4	62	85

Scheme 50. One-pot synthesis of 1,3,4,5-tetrasubstituted-1*H*-imidazole-2(3*H*)thiones **69**

Still in 2017, Mityanov and coworkers developed a method for the synthesis of tetrasubstituted 1*H*-imidazoles of general formula **73** which consisted in the condensation of 2-unsubstituted imidazole-*N*-oxides **70** (2 mmol) with (hetero)aryl or alkyl aldehydes **71** (2 mmol) and CH-acids **72** (2 mmol) in a mixture of MeCN (5 mL) and water (2 mL) under reflux for 8 h (Scheme 51).[158] This simple method for the C-2 fuctionalization of 2-unsubstituted imidazole-*N*-oxides allowed access to a variety of compounds **73** in yields ranging from 29 to 96%. The CH-acids used in this method were barbiturtic acid, 1,3-dimethylbarbituric acid, dimedone, 1,3-indandione, 4-hydroxycoumarin and 4-hydroxy-6-methyl-2*H*-pyran-2-one.[158]



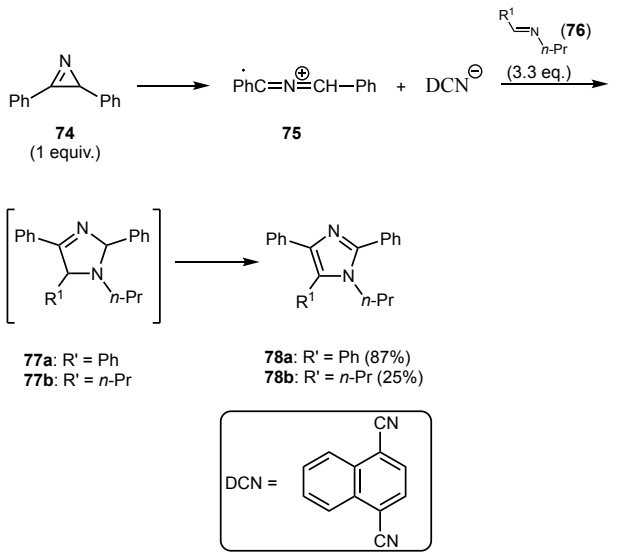
70 71 72 73

Scheme 51. Condensation of 2-unsubstituted imidazole-*N*-oxides **70** with (hetero)aryl or alkyl aldehydes **71** and CH-acids **72**

4. Syntheses via [3 + 2] or [2 + 2 + 1] Annulation Reactions

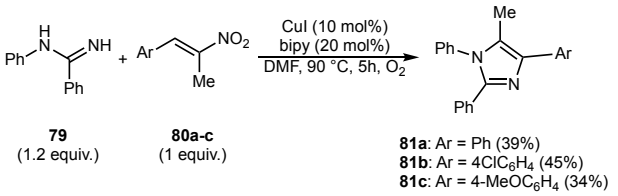
In 1991, Müller and Mattay found that the synthesis of 1-propyl-2,4,5-triphenyl-1*H*-imidazole (**78a**) could be achieved in 87% yield by direct irradiation of a mixture 2,3-diphenylazirine (**74**) and a molar excess of imine **76a** (R^1 = Ph) in MeCN at 359 nm in the presence of a catalytic amount of 1,4-naphthalenedicarbonitrile (DCN) (Scheme 52).[159] These authors also reported that an analogous reaction between **74** and imine **76b** (R^1 = *n*-Pr) produced 1,5-dipropyl-2,4-diphenyl-1*H*-imidazole (**78b**) in 25% yield (Scheme 52).

The reaction leading to imidazoles **78a,b** was proposed to involve the [3 + 2] cycloaddition reaction of radical cation **75** with imines **76a,b**, followed by ring closure and aromatization of the resulting dihydroimidazoles **77a,b** (Scheme 52).[159]



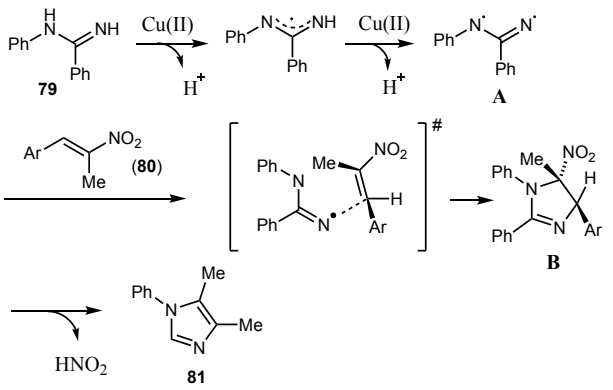
Scheme 52. Synthesis of imidazoles **78a,b** via [3 + 2] cycloaddition reactions involving radical cation **75**

In 2013, B.-H. Chen and coworkers synthesized 4-aryl-1,2-diphenyl-5-methyl-1*H*-imidazoles **81a–c** regioselectively and in moderate yields by CuI/2,2'-bipyridine (bipy)-catalyzed [3 + 2] cycloaddition of commercially available *N*-phenylbenzamidine (**79**) with nitroalkenes **80a–c**[160] in DMF at 90 °C for 5 h under an O_2 atmosphere (Scheme 53).[161]



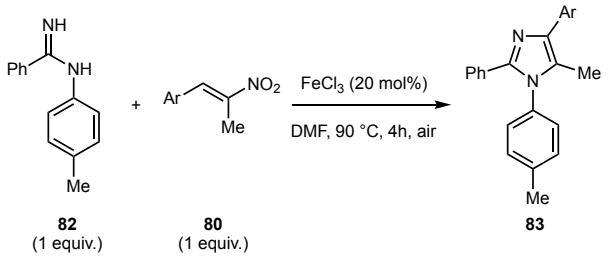
Scheme 53. Synthesis of imidazoles **81a–c** via Cu-catalyzed [3 + 2] cycloaddition reactions

The synthesis of compounds **81** was proposed to occur via the mechanism depicted in Scheme 54 in which Cu(I) would be initially oxidized to Cu(II) under O_2 atmosphere. The subsequent reaction of Cu(II) with amidine **79** would give rise to the diradical intermediate **A**, which would react with nitroolefins **80** via [3 + 2] cycloaddition providing intermediates **B**. Finally, elimination of HNO_2 from **B** would afford compounds **81**.[161]



Scheme 54. Proposed mechanism for the Cu-catalyzed synthesis of imidazoles **81**

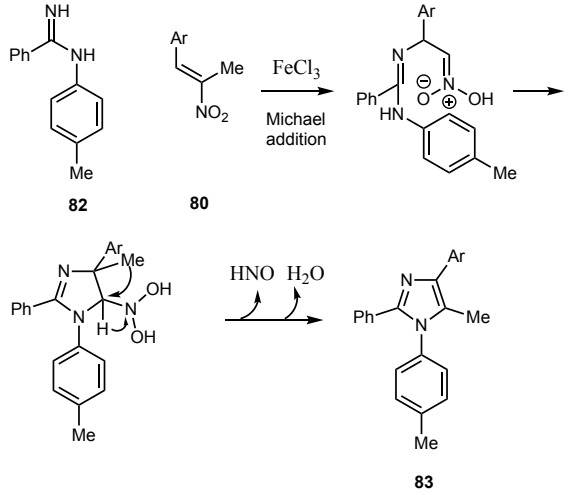
Still in 2013, B. Chen and coworkers synthesized 4-aryl-5-methyl-2-phenyl-1-*p*-tolyl-1*H*-imidazoles **83a-e** in moderate yields by $FeCl_3$-catalyzed [3 + 2] cyclo-addition of appropriate nitroolefins **80** with *N*-*p*-tolylbenzamidine (**82**) in DMF at 90 °C under air atmosphere (Scheme 55).[162]



81	Ar	Yield (%)
a	Ph	47
b	4-$MeOC_6H_4$	35
c	4-BrC_6H_4	41
d	4-ClC_6H_4	45
e	4-$(CN)C_6H_4$	56

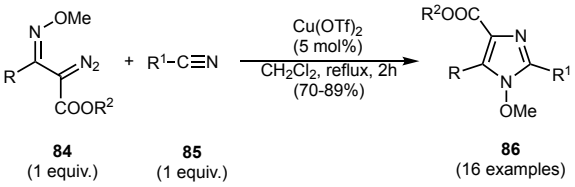
Scheme 55. $FeCl_3$-catalyzed synthesis of imidazoles **83a-e**

Notably, the proposed mechanism for this reaction was significantly different from that of the analogous Cu-catalyzed [3 + 2] cyclo-addition in the presence of O_2 leading to compounds **81**.[160] In fact, it was speculated that the NO_2 group was the terminal oxidant of the process leading to imidazoles **83**.[162] It was also hypothesized that the $FeCl_3$-catalyzed reaction involves a Michael addition of amidine **82** to nitroolefins **80** and that nitroxyl (HNO) and water are eliminated in the final step (Scheme 56).[162]



Scheme 56. Proposed mechanism for the $FeCl_3$-catalyzed synthesis of imidazoles **83**

In 2016, Emmanuvel and coworkers synthesized regioselectively and in high yields a wide variety of 2,5-disubstituted-4-alkoxycarbonyl-1-methoxy-1*H*-imidazoles **86** via a $Cu(OTf)_2$-catalyzed [3 + 2] cyclo-addition of nitriles **85** with the oximino carbenoids derived from the α-diazo oximino esters **84** (Scheme 57).[163]



Scheme 57. $Cu(OTf)_2$-catalyzed synthesis of 1-methoxy-1*H*-imidazoles **86**

For instance, compounds **86a**, **86b**, **86c**, **86d** and **86e** (Figure 14) were in this way synthesized in 89, 75, 80, 75 and 76% yield, respectively.

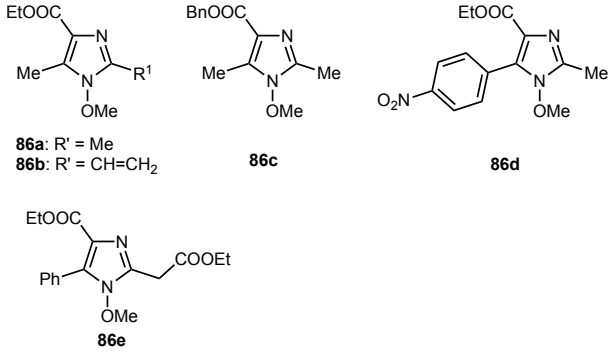
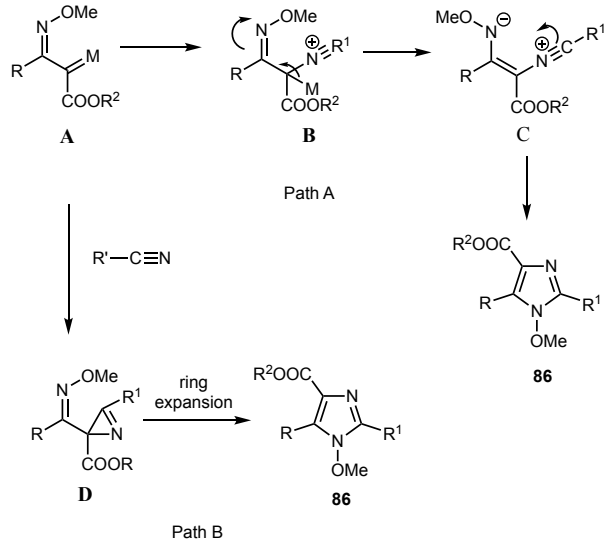


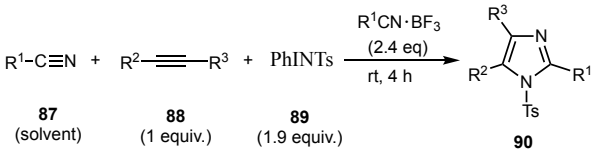
Figure 14. Chemical structures of compounds **86a-e**

This versatile reaction was proposed to occur via formation of metal carbenoids **A** from the diazocompounds **84** followed by attack of nitriles **85** to give intermediates **B** and **C**. These intermediates then would undergo cyclization to produce imidazoles **86** (path *A*, Scheme 58). However, the reaction could also proceed through formation of aziridines **D** from **A** and subsequent ring expansion (path *B*, Scheme 58).[163]



Scheme 58. Plausible mechanisms for the $Cu(OTf)_2$-catalyzed synthesis of imidazoles **86**

In 2015, the synthesis of 1-tosyl-2,4,5-trisubstituted-1*H*-imidazoles **90a-f** was elegantly and concisely achieved by Saito and coworkers[164] via $BF_3{\cdot}R^1CN$ complex-promoted oxidative [2 + 2 + 1] annulation of nitriles **87**, internal alkynes **88** and *N*-tosyliminophenyliodinane (PhINTs).[165] The annulation reaction was carried out in the presence of 2.4 equiv of complex $BF_3{\cdot}$**87** at room temperature for 4 h using nitriles **87** as solvent (Scheme 59).

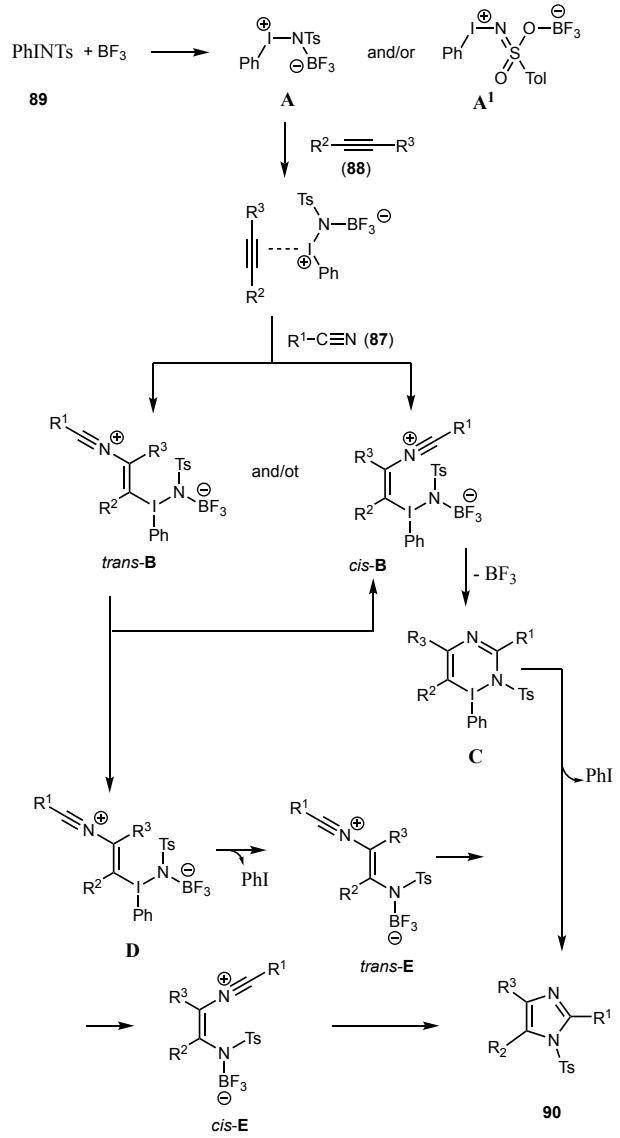


90	R^1	R^2	R^3	Yield (%)
a	Me	Ph	Me	54
b	Me	*i*-Pr	Me	43
c	Me	*n*-Pr	*n*-Pr	72
d	Et	*n*-Pr	*n*-Pr	63
e	*t*-Bu	*n*-Pr	*n*-Pr	50
f	Ph	*n*-Pr	*n*-Pr	49

Scheme 59. $BF_3{\cdot}R^1CN$-mediated synthesis of 1-tosyl-1*H*-imidazoles **90a-f**

The process enabled the synthesis of compounds **90a-f** in yields ranging from 49 to 72%, but unfortunately no information was given on the regioselectivity of the reactions that gave rise to

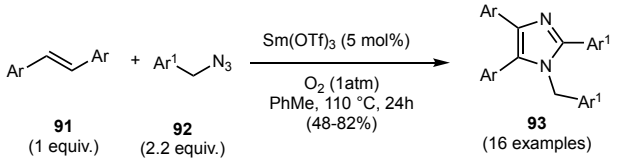
compounds **90a** and **90b** having different substituents at the 4 and 5 positions. Nevertheless, it was proposed that the synthesis of compounds **90** occurs via the reaction pathway shown in Scheme 60 in which intermediates *trans*-**B** and/or *cis*-**B** would be obtained through activation of alkynes **88** by the iodonium species **A** (and/or $\mathbf{A^1}$) and the subsequent addition of nitriles **87**. *Trans*-**B** would then be converted to *cis*-**B** by the addition and elimination of **87**.



Scheme 60. Proposed mechanism for the BF_3-R^1CN-mediated synthesis of imidazoles **90**

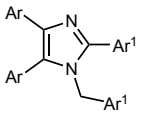
Finally, the cyclization reaction of *cis*-**B** followed by reductive elimination of Ph-I in intermediates **C** would give imidazoles **90**. In an alternative route, *trans*-**B** would give intermediates *trans*-**E** via the transition state **D**. The subsequent isomerization of *trans*-**E** to *cis*-**E** via enamine-imine tautomerization, followed by cyclization would provide imidazoles **90** (Scheme 60).[164]

Still in 2015, Wang, Pan and coworkers achieved the synthesis of 1-arylmethyl-2,4,5-triaryl-1*H*-imidazoles **93** in high yields via samarium triflate-catalyzed [2 + 2 + 1] annulation of symmetric stilbenes **91** with arylmethyl azides **92** in toluene at 110 °C under O_2 atmosphere (Scheme 61).[166]



Scheme 61. $Sm(OTf)_3$-catalyzed synthesis of imidazoles **93**

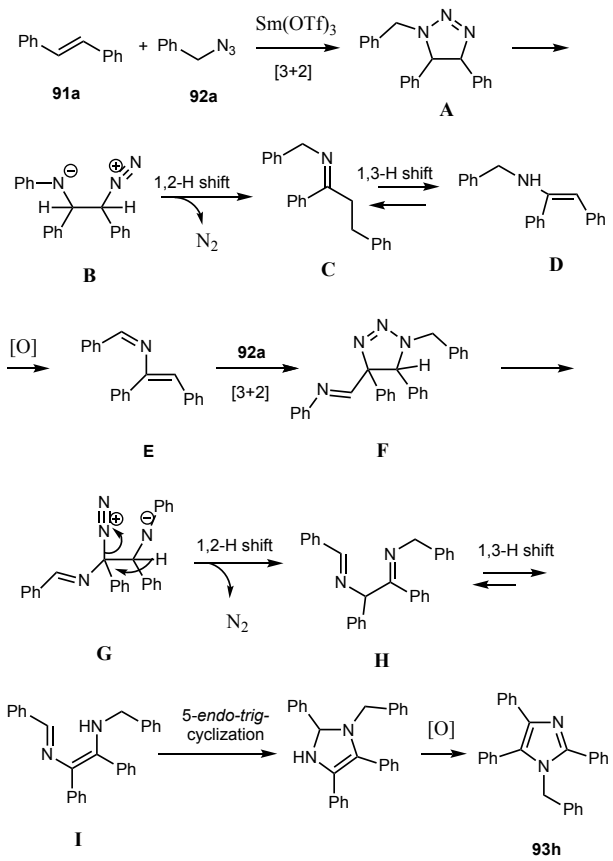
In general, azides **92** possessing electron-donating groups on the phenyl ring provided compounds **93** in higher yields than those obtained from azides bearing electron-withdrawing groups. In fact, compounds **93a–c** (Figure 15) were obtained in 78, 79 and 82% yield, respectively, whereas compounds **93d–g** (Figure 15) were obtained in 62, 65, 60 and 61% yield, respectively.[166]



93	Ar	Ar^1	Yields (%)
a	Ph	4-MeC_6H_4	78
b	Ph	4-*t*-BuC_6H_4	79
c	Ph	4-$MeOC_6H_4$	82
d	Ph	2-FC_6H_4	62
e	Ph	4-BrC_6H_4	65
f	Ph	3-$CF_3C_6H_4$	60
g	Ph	4-$(CN)C_6H_4$	61

Figure 15. Chemical structures of compounds **93a-g**

On the basis of literature data[167] a plausible mechanism for the formation of 1-benzyl-2,4,5-triphenyl-1*H*-imidazole (**93h**) from stilbene (**91a**) and benzylazide (**92a**) was proposed (Scheme 62).[166]

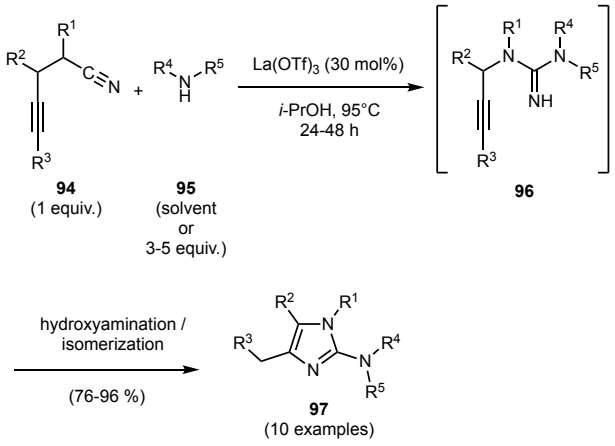


Scheme 62. Plausible mechanism for the $Sm(OTf)_3$-catalyzed synthesis of imidazole **93a**

In this mechanistic pathway, the $Sm(OTf)_3$-catalyzed 1,3-dipolar cycloaddition of **91a** to **92a** would give rise to the unstable triazoline intermediate **A**. The subsequent decomposition of **A** to **B**, followed by 1,2-H shift with loss of N_2 would give **C**, which would undergo 1,3-H shift providing intermediate **D**. Oxidation of enamine **D** would deliver imine **E**, which would undergo 1,3-dipolar cyclo-addition to give intermediate **F**. The subsequent loss of N_2 and 1,2-H shift from **G**, derived from a ring-opening reaction of **F**, would give intermediate **H**, which by 1,3-H shift would form intermediate **I**. Finally, 5-*endo-trig* cyclization of **I** followed by oxidation would generate imidazole **93h**.[166]

5. Syntheses via Cyclization of Propargyl Guanidines

In 2009, Looper and coworkers developed an interesting protocol for the rapid access to 2-aminoimidazoles of general formula **97** from propargyl cyanamides **94** and amines **95** (Scheme 63).[168] The protocol involved the reaction of compounds **94** with a large molar excess of amines **95** in the presence of 30 mol% $La(OTf)_3$ at 95 °C, gaving rise to propargyl guanidines **96**. A subsequent hydroamination/isomerization process of these intermediates gave imidazoles **97** in 76–96% yield (Scheme 63).



Scheme 63. Synthesis of 2-aminoimidazoles **97**

For instance, compounds **97a**, **97b** and **97c** (Figure 16) were so prepared in 85, 76 and 90% yield, respectively.

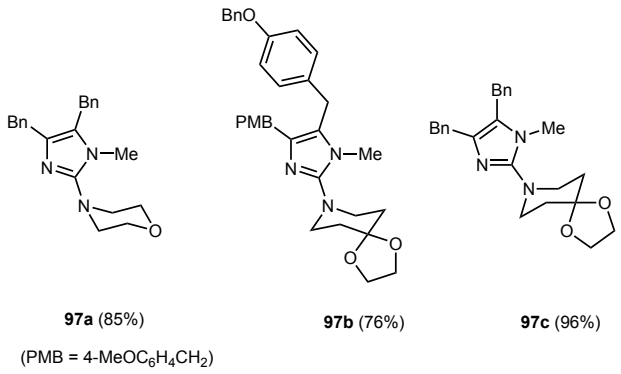
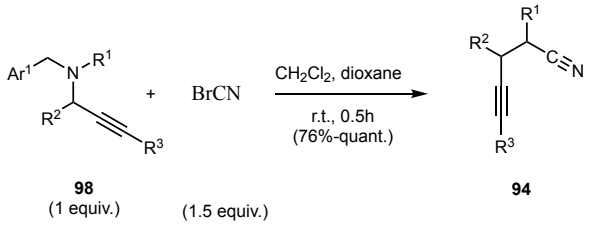


Figure 16. Chemical structures of 2-aminoimidazoles **97a-c**

Compounds **94** were in turn obtained by the von Braun reaction[169] of aminoacetylenes **98** with BrCN in a mixture of CH_2Cl_2 and dioxane in the presence of K_2CO_3 (Scheme 64).[168]

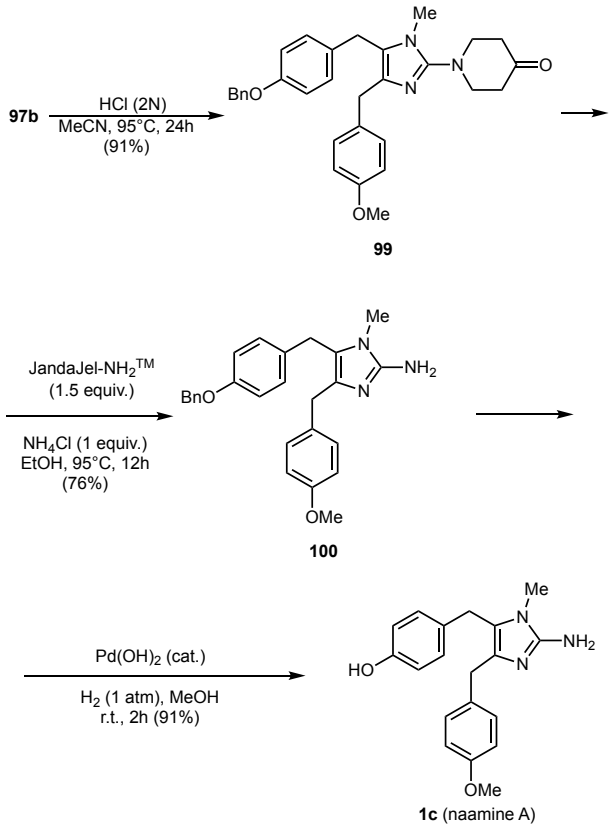


Scheme 64. Synthesis of cyanamides **94**

Commenting on the process developed for the synthesis of 2-aminoimidazoles **97** it must be noted

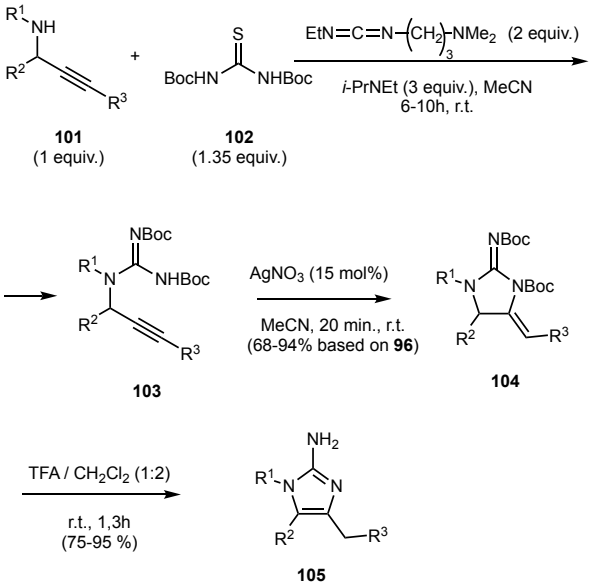
that, unfortunately, it required a high catalyst loading and a large molar excess of amines. Nevertheless, its synthetic utility was demonstrated by using one of its derivatives, i.e. compound **97b**, as precursor to naamine A (**1c**), a natural 2-amino imidazole first isolated from the marine sponge *Leucetta chagosensis* collected in the Red Sea.[18]

The synthesis of **1c** from **97b** was carried out as shown in Scheme 65. [168] Ketal **97b** was treated with 2N HCl and MeCN at 95 °C for 24 h to give piperidinone **99** in 91% yield. Compound **99** was then treated with 1.5 equiv of pre-washed JandaJel^{TM}-NH_2 and 1 equiv of NH_4Cl in EtOH at 95 °C for 12 h providing 5-[4-(benzyloxy)benzyl]-4-(4-methoxybenzyl)-1-methyl-1*H*-imidazol-2-amine (**100**) in 76% yield. Finally, debenzylation of **100** by treatment with hydrogen (1 atm) in MeOH at room temperature for 2 h in the presence of a catalytic amount of $Pd(OH)_2$ gave compound **1c** in 91% yield (Scheme 65).[168]



Scheme 65. Synthesis of naamine A (**1c**) from ketal **97b**

In 2010, Van der Eycken and coworkers described a novel, and efficient three-step synthesis of 2-aminoimidazoles of general formula **105** in which propargyl guanidines **103** were key intermediates (Scheme 66).[170]

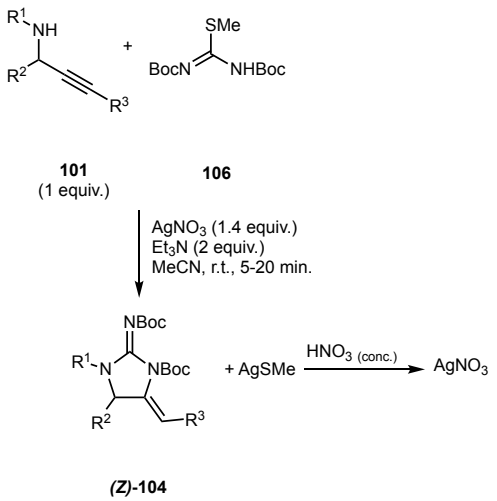


105	R^1	R^2	R^3	Yield %
a	*t*-Bu	*i*-Bu	Ph	85
b	*c*-C_7H_{13}	*i*-Bu	Ph	95
c	*c*-$C_{12}H_{23}$	*i*-Bu	Ph	78
d	3-$MeOC_6H_{14}CH_2$	*i*-Bu	Ph	80
e	Bn	Ph	Bn	75
f	Bn	*p*-Tol	*p*-$AmOC_6H_4$	92

Scheme 66. Three-step synthesis of 2-aminoimidazoles **105**

Specifically, guanylation of compounds **101** with *N,N'*-bisprotected thiourea **102** in the presence of 1-ethyl-3-(dimethylaminopropyl)carbodiimide and *i*-Pr_2NEt led to propargylguanidines, which underwent cyclization by treatment with 15 mol% $AgNO_3$ in MeCN at room temperature providing Boc-protected 2-iminoimidazolines (*Z*)-**104** in 68–94% yield based on compounds **101**. Finally, removal of the Boc protecting groups from (*Z*)-**104** by treatment with 1: 2 mixture of TFA and CH_2Cl_2 gave 2-aminoimidazoles **105** in high yields (Scheme 66).[170]

It was also discovered that the hitherto unknown compounds (*Z*)-**104** were available in high yields and in a single step by reaction of propargylamines **101** with 1.25 equiv of protected *S*-methylisothiourea **106** in MeCN at room temperature for 15 min in the presence of 1.4 equiv of $AgNO_3$ and 2 equiv of Et_3N. As shown in Scheme 67, the reaction also produced AgSMe which could be converted readily into $AgNO_3$ by treatment with conc. HNO_3 at 150 °C and reused. [170]



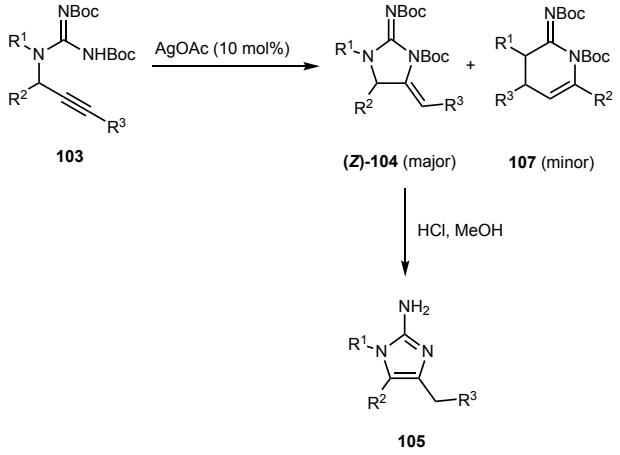
Scheme 67. One-step synthesis of compounds (*Z*)-**104**

Next, Van der Eycken and coworkers applied the protocol involving the one-step synthesis of compounds (*Z*)-**104** to the total synthesis of all naturally-occurring trisubstituted 2-aminoimidazole naamine alkaloids.[171,172]

In 2011. Looper and coworkers described that 2-aminoimidazoles **105** could also be obtained through AgOAc-catalyzed cyclization of propargyl guanidines **103** in CH_2Cl_2 at room temperature in the presence of AcOH and subsequent removal of the Boc protecting groups (Scheme 68).[172] However, the AgOAc-catalyzed reaction led to mixtures of **Scheme 68.** Synthesis of 2-aminoimidazoles **105** via AgOAc-catalyzed via cyclization of propargyl guanidines **103**

compounds (*Z*)-**104** and **107** in which compounds (*Z*)-**104** derived from a Ag-catalyzed 5-*exo-dig* hydroamination reaction were the major components and compounds **107** derived from a Ag-catalyzed 6-*endo-dig* hydroamination reaction were the minor components.[172] The required 2-aminoimidazoles **105** were subsequently obtained by treatment of compounds (*Z*)-**104** with HCl in MeOH.

It was also found that when $[Rh_2(oct)_4]$ was used instead of AgOAc as a catalyst for the cyclization reaction of compounds **103**, the 6-*endo-dig* hydroamination reaction of **103** leading to compounds **107** was significantly favoured.[173]



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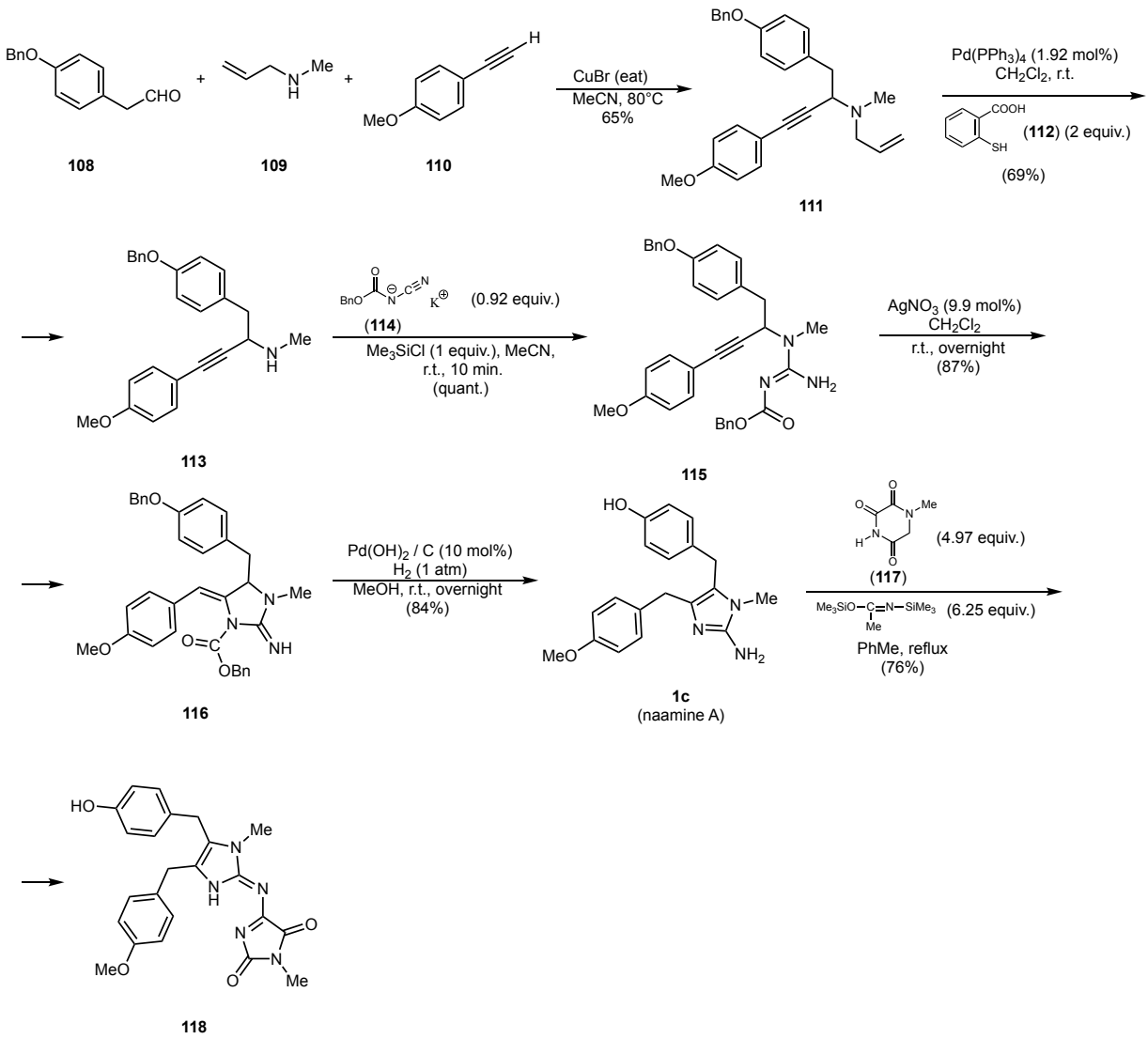
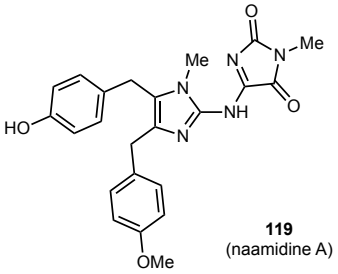


Scheme 69. Total synthesis of naamine A (**1c**) and compound **118** via Ag-catalyzed hydroamination reaction of compound **11**

In 2015, Looper and coworkers employed the $AgNO_3$-catalyzed N^3-5-*exo-dig* cyclization of *N*-carboxybenzyloxy-1-[1-(4-benzyloxy)phenyl-4-(4-methoxyphenyl)but-3-yn]-1-methylguanidine (**115**) as a key step of a novel total synthesis of naamine A (**1c**).[174] As shown in Scheme 69, the total synthesis began with the CuBr-catalyzed reaction of aldehyde **108** with amine **109** and 1-alkyne **110**

The resulting *tert*-propargylamine **111** was then converted into the corresponding *sec*-amine **113** by treatment with 2 equiv of thiosalicylic acid (**112**) in CH_2Cl_2 at room temperature in the presence of a catalytic quantity of $Pd(PPh_3)_4$. The subsequent reaction of **113** with benzyloxycarbonylcyanamide potassium salt (**114**) and Me_3SiCl in MeCN at room temperature gave the monoacylguanidine **115** in quantitative yield. Compound **115** was then treated with a catalytic amount of $AgNO_3$ in CH_2Cl_2 at room temperature yielding compound **116** in 87% yield. Finally, cleavage of the benzyloxycarbonyl group of **116** under standard hydrogenolysis conditions gave naamine A (**1c**) in 84% yield.

Looper and corkers also found that treatment of **1c** with 1-methylparabanic acid (**117**) and bis(trimethylsilyl)acetamide in toluene under reflux provided compound **118** in 76% yield (Scheme 69). Unfortunately, these authors assumed that **118** had the structure of naamidine A,[174] a natural product isolated from a Fijan *Leucetta* sp. sponge[175] and a Red Sea *Leucetta* sp. sponge.[175] It should however be borne in mind that it had previously reported that naamidine A has the structure **119** (Figure 18)[175,176] and is an antagonist of the epidermal growth factor and an in vivo antitumor agent.[175]

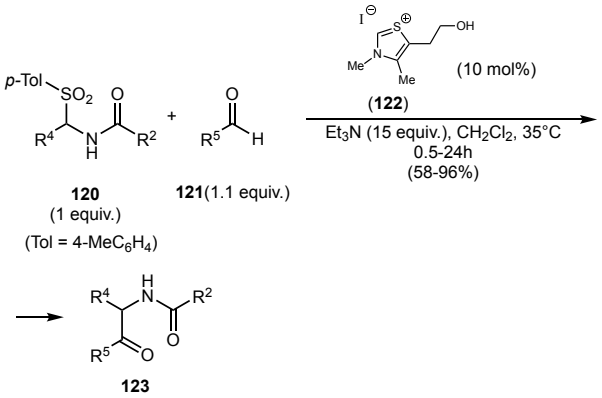


119
(naamidine A)

Figure 17. Chemical structure of naamidine A

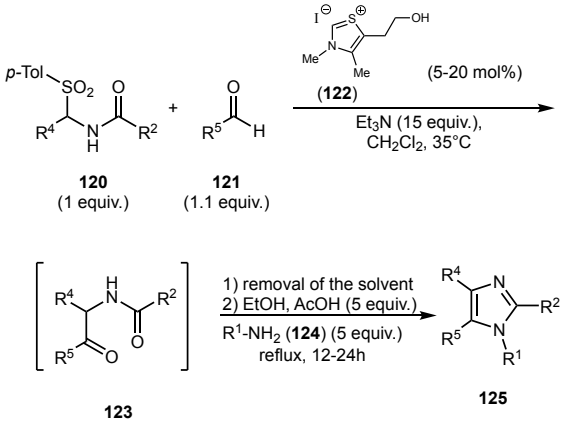
6. Syntheses via Protocols Involving a Thiazolium-catalyzed Reaction of Aldehydes with α-Amidosulfones

In 2011, Murry, Frantz and coworkers described that structurally diverse *N*-acyl-β-aminoketones **123** were available in good to excellent yields by reaction of *N*-tosylamides **120** with aldehydes **121** in CH_2Cl_2 at 35 °C in the presence of 10 mol% commercially available 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide (**122**) and 15 equiv of Et_3N (Scheme 70).[177]



Scheme 70. Thiazolium salt-catalyzed synthesis of *N*-tosylamides **123**

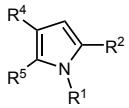
Three years later, Frantz and coworkers employed the reaction shown in Scheme 70 as a key step of the one-pot synthesis of tetrasubstituted imidazoles of general formula **125** (Scheme 71). [178] Specifically, they removed the solvent from the solution of crude compounds **123**, which were obtained by thiazolium-catalyzed reaction of α-amido sulfones **120** with aldehydes **121**. EtOH, AcOH and primary amines **124** were then added and the resulting mixture was heated to reflux for 12–24 h. In this way compounds **125a**, **125b**, **125c** and **125d** were synthesized in 22, 76, 80 and 75% yield, respectively (Scheme 71). [178]



125	R^1	R^2	R^4	R^5	Yield (%)
a	3-pyridylCH_2	*c*-C_6H_{11}	Ph	BnO	22
b	$Ph(CH_2)_3$	Ph	2-furyl	4-pyridyl	76
c	$(MeO)_2CH$-CH_2	Ph	Ph	4-pyridyl	80
d	HO-$(CH_2)_2$	Ph	Ph	4-pyridyl	75

Scheme 71. One-pot synthesis of imidazoles **125** via AcOH-mediated reaction of *N*-acyl-β-aminoketones **123** with primary amines

In 2005, Li and Lam used a similar protocol for the synthesis of 1,2,4,5-tetrasubstituted imidazoles **125e–l** (Figure 19).[179]

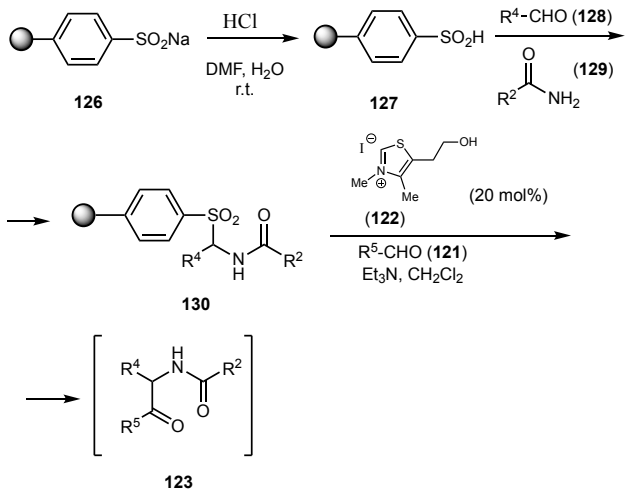


125

125	R^1	R^2	R^4	R^5	Yield %
e	HO$(CH_2)_2$	Ph	Ph	4-pyridyl	35
f	*n*-Bu	Ph	Ph	4-pyridyl	34
g	*n*-Bu	Me	Ph	4-pyridyl	31
h	*n*-Bu	Me	Ph	Ph-CH=CH	24
i	*n*-Bu	Ph	4-FC_6H_4	4-pyridyl	27
j	EtCH(Me)	Me	Ph	4-pyridyl	30
k	*n*-Bu	Ph	Me_2CHCH_2	4-pyridyl	27
l	HO$(CH_2)_2$	Ph	Et	4-pyridyl	24

Figure 18. Chemical structures of imidazoles **125e–l**

However, in this case, crude precursors **123** were synthesized via a three-step process starting from polystyrene/1% divinylbenzene sodium sulfinate (**126**) (Scheme 72).[179]



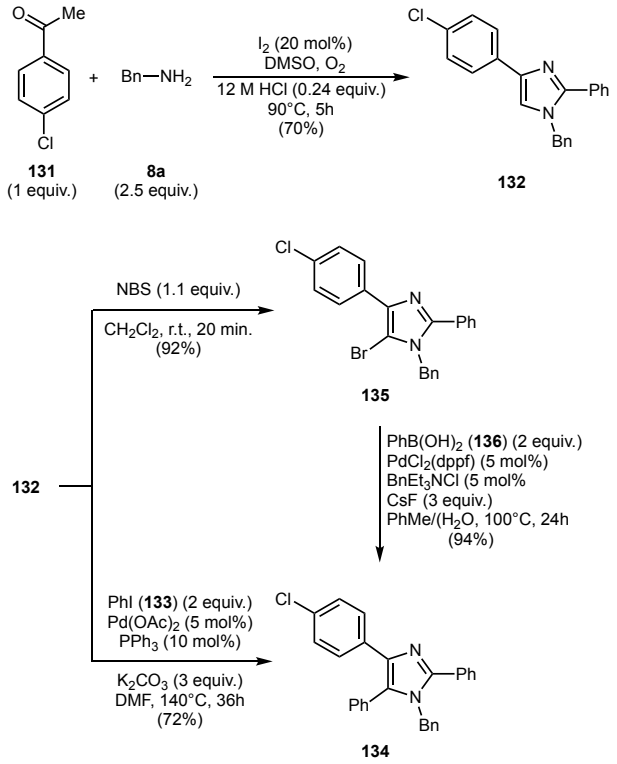
Scheme 72. Synthesis of crude α-amidosulfones **123** starting from polystyrene/1% divinylbenzene sodium sulfinate (**126**)

In particular, **126** reacted with HCl at room temperature providing polymer-supported phenylsulfinic acid **127**. Condensation of **127** with aldehydes **128** and amides **129** gave polymer-supported arylsulfonamides **130**, which generated α-amidosulfones **123** *in situ* by treatment with excess of Et_3N and aldehydes **121** in CH_2Cl_2 at 35 °C in the presence of 20 mol% thiazolium salt **122** (Scheme 72). Finally, concentration of the reaction mixtures followed by the addition of 8 equiv of amines **124** in EtOH and 8 equiv of AcOH and refluxing under nitrogen atmosphere gave compounds **125 e–f** in 24–34% yield.[179]

7. Syntheses via Oxidative/Dehydrogenative Coupling Reactions

Oxidative coupling reactions have recently emerged as powerful and attractive tools for the synthesis of various kinds of functionalized molecules[180] that include polysubstituted imidazoles and a lot of efforts have been directed to develop catalytic oxidative methods involving the use of air or oxygen as terminal oxidant.

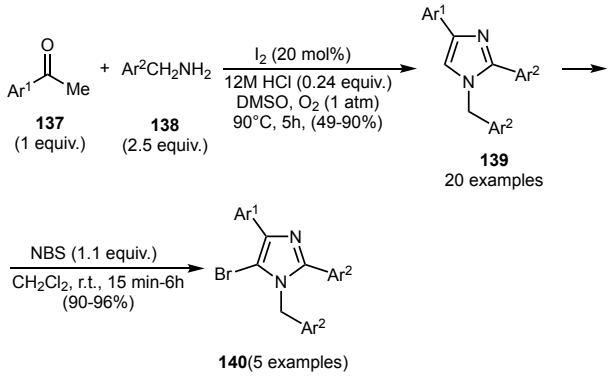
In 2013, Jiang and coworkers[181] described that 1-benzyl-4-(4-chlorophenyl)-2,5-diphenyl-1*H*-imidazole (**134**) could be prepared in 50% overall yield via a two-step protocol in which the first step was the iodine-catalyzed aerobic oxidative cyclization of 4-chloroacetophenone (**131**) with benzylamine (**8a**) and the second step consisted in the $Pd(OAc)_2/PPh_3$-catalyzed direct C-5 arylation of the resulting compound **132** with iodobenzene (**133**) in DMF at 140 °C in the presence of K_2CO_3 as base[182] (Scheme 73).



Scheme 73. Syntheses of imidazole **134** using 1-benzyl-4-(4-chlorophenyl)-2,5-diphenyl-1*H*-imidazole (**132**) as a common intermediate

Compound **134** was also synthesized in a high yield by C-5 bromination of **132** with NBS in CH_2Cl_2 at room temperature followed by a $PdCl_2$(dppf)-catalyzed Suzuki-type cross-coupling reaction of the resulting bromide **135** with phenylboronic acid (**136**) in a mixture of toluene and water at 100 °C in the presence of 5 mol% $BnEt_3NCl$ and 3 equiv of CsF (Scheme 73).[181]

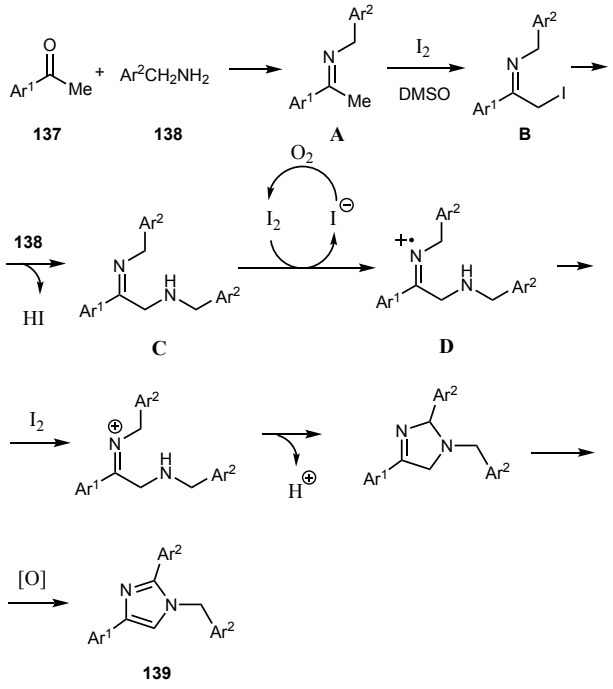
It deserves to be noted that the high yielding protocol used to prepare compound **135** from **131** and **8a** was also employed for the synthesis of 1-substituted-5-bromo-2,4-diaryl-1*H*-imidazoles **140**.[181] As shown in Scheme 74, the latter compounds were obtained in good to excellent yields by C-5 bromination of trisubstituted imidazoles **139**, which in turn were obtained in good yields by aerobic iodine-mediated cyclization of aryl ketones **137** with benzylamines **138**. Notably, compounds **140** proved capable to undergo $PdCl_2$(dppf)-catalyzed Suzuki cross-coupling reactions.



140	Ar^1	Ar^2	Yield %
a	Ph	Ph	93
b	4-MeC_6H_4	Ph	94
c	4-FC_6H_4	4-FC_6H_4	90
d	4-FC_6H_4	4-MOC_6H_4	94
e	4-BrC_6H_4	4-MeC_6H_4	96

Scheme 74. Two-step synthesis of 1-arylmethyl-5-bromo-2,4-diaryl-1*H*-imidazoles **140**

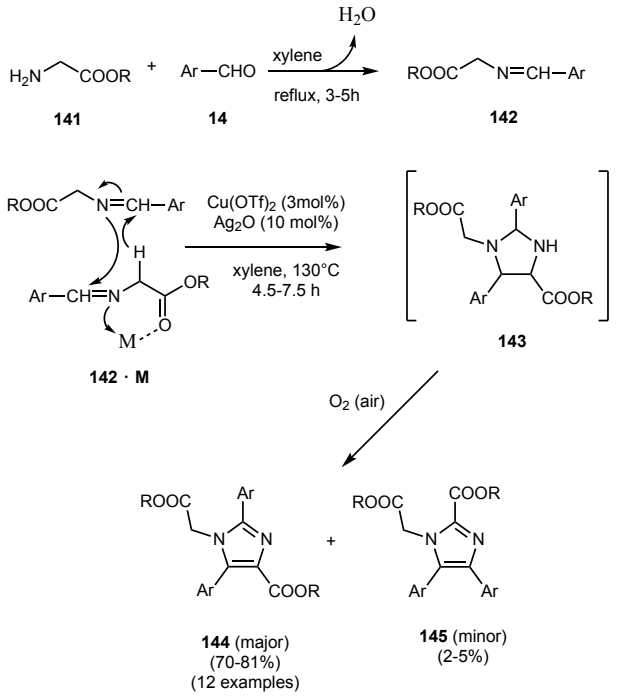
Jiang and coworkers then suggested that the formation of compounds **139** from ketones **137** and benzylamines **138** could occur through the mechanism shown in Scheme 75 in which imines **A,** which would be *in situ* formed from **137** and **138**, would undergo α-iodination to give iodides **B**.



Scheme 75. Plausible mechanism for the iodine-catalyzed aerobic oxidative cyclization of ketones **137** with amines **138**

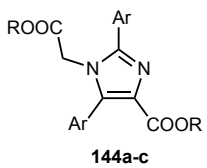
Subsequent coupling of **B** with amines **138** would provide intermediates **C**, which through subsequent oxidation would give rise to intermediates **D** via sp^3 C–H functionalization under iodine-mediated reaction conditions. Finally, the nucleophilic cyclization of **D** followed by oxidation would provide imidazoles **139**.[181]

In 2012, Maiti and coworkers described a catalytic process for the synthesis of 1,4-difunctionalized-2,5-diaryl-1*H*-imidazoles **144** that involved the $Cu(OTf)_2$ (3 mol%)–Ag_2O (10 mol%) combo-catalyzed bimolecular cyclization of imines **142** in refluxing toluene and the subsequent dehydrogenation with molecular oxygen (air) of the resulting tetrahydroimidazoles **143** (Scheme 76).[183] Imines **142** were in turn obtained by reaction of aminoacid esters **141** with aldehydes **14** in xylene under reflux with continuous removal of water using a Dean-Stark apparatus.



Scheme 76. $Cu(OTf)_2$–Ag_2O combo-catalyzed aerobic dehydrogenative cyclization of imines **142**

In all cases examined, imidazoles **144** were obtained in good isolated yields. For instance, compounds **144a**, **144b** and **144c** (Figure 19) were obtained in 76, 71 and 74% yield, respectively. However, traces of regioisomers **145** were also found in the reaction mixtures.

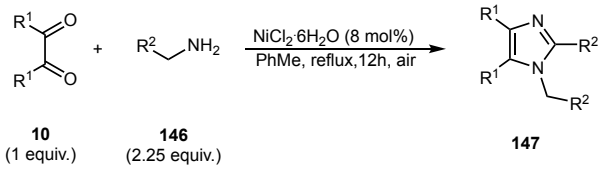


144	R	Ar	Yield %
a	Et	2-$MeOC_6H_4$	76
b	Et	4-BrC_6H_4	71
c	Et	Ph	74

Figure 19. Chemical structures of imidazoles **144a–c**

Notably, aldimines **142** with electron-withdrawing or electron-donating substituents were well tolerated in the reaction, but the dehydrogenative coupling was unsuccessful with 4-cyanophenyl aldimines.[183]

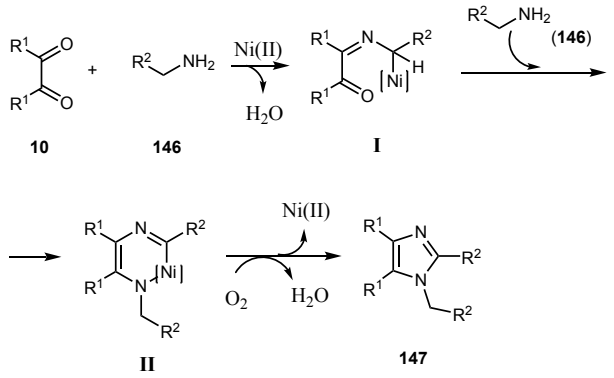
Later, the Maiti research group demonstrated that Ni(II) salts such as $NiCl_2{\cdot}6H_2O$ or $Ni(OAc)_2{\cdot}4H_2O$ are efficient catalysts for the synthesis of tetrasubstituted imidazoles of general formula **147** through oxidative cyclization of symmetrical α-diketones **10** with benzyl or aliphatic amines **146** in refluxing toluene under air (Scheme 77).[184] Interestingly, excellent yields of imidazoles **147** were obtained when benzylamine and its derivatives bearing electron-rich groups were used as reagents.



147	R^1	R^2	Yield %
a	Ph	Ph	90
b	Ph	4-MeC_6H_4	92
c	Ph	4-$MeOC_6H_4$	94
d	4-BrC_6H_4	Ph	89
e	Ph	4-FC_6H_4	87
f	Ph	4-pyridyl	85
g	Me	Ph	75
	Et	Ph	78

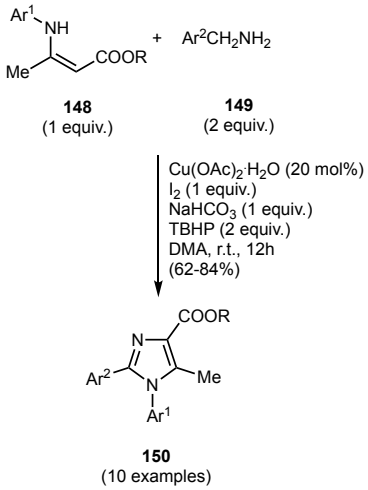
Scheme 77. Ni(II)-catalyzed oxidative cyclization of α-diketones **10** with primary amines **146**

The formation of compounds **147** was explained to occur via the mechanism shown in Scheme 78 in which the Ni(II) salt performs the selective activation of Cα–H bonds of the primary amines **146** leading to the formation of intermediates **I** with diketones **10**. The subsequent reaction of **I** with amines **146** would give intermediates **II**, which would undergo the cyclization process affording imidazoles **147** via an O_2-mediated C–N coupling also involving the elimination of the Ni(II) catalyst.[184]



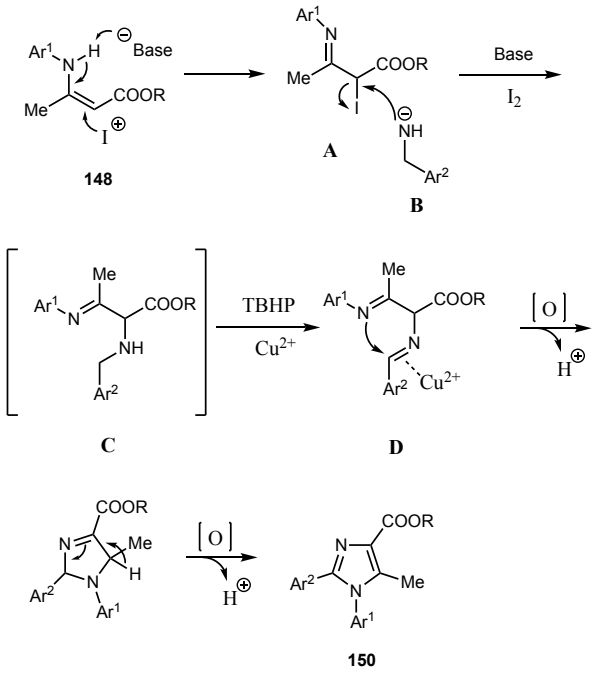
Scheme 78. Proposed mechanism for the Ni(II)-catalyzed synthesis of imidazoles **147**

Concurrently, Pandya and Agrawal reported a concise synthesis of 4-alkoxycarbonyl-1,2-diaryl-5-methyl-1*H*-imidazoles **150**, which involved a copper-mediated oxidative cyclization of alkyl (*Z*)-3-arylamino-2-butenoates **148**[185] and benzylamines **149**.[186] In particular, β-aminoesters **148** were reacted with 2 equiv of amines **149**, 1 equiv of $NaHCO_3$, 20 mol% $Cu(OAc)_2{\cdot}H_2O$, 2 equiv of *t*-BuOOH (TBHP) and 1 equiv of molecular iodine in DMA at room temperature for 12 h providing compounds **150** in yields ranging from 62 to 84% (Scheme 79).[186]



Scheme 79. Synthesis of imidazoles **150** via copper-mediated oxidative C–H functionalization

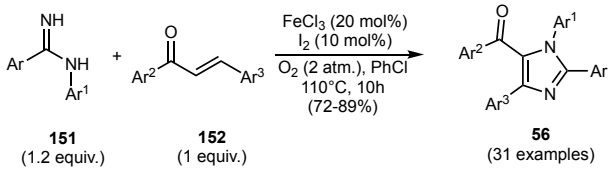
The reaction, which presumably was carried out under air, was proposed to take place through the mechanism shown in Scheme 80 in which intermediates **A** would be obtained by base-catalyzed iodination of β-enamino esters **148**. Intermediates **A** would undergo a nucleophilic attack by anions **B** resulting from amines **149** to give intermediates **C**.



Scheme 80. Proposed mechanism for the Cu-mediated oxidative reaction of compounds **148** with amines **149**

Oxidative dehydrogenation of these intermediates and coordination of Cu^{2+} ion would then provide intermediates **D**, which eventually would be converted into the required imidazoles **150** by cyclization and oxidation (Scheme 80).[186]

In 2015, Li and coworkers[187] successfully carried out the regioselective synthesis of 5-aroyl-1,2,4-triaryl-1*H*-imidazoles **56** by $FeCl_3/I_2$-catalyzed aerobic oxidative coupling reaction of amidines **151** [188] with chalcones **152**. The reaction that involved treatment of 1.2 equiv of amidines **152** with 1 equiv of chalcones **152**, 10 mol% $FeCl_3$ and 10 mol% I_2 in chlorobenzene at 110 °C under an atmosphere of oxygen provided imidazoles **56** in 72–89% yield (Scheme 81).

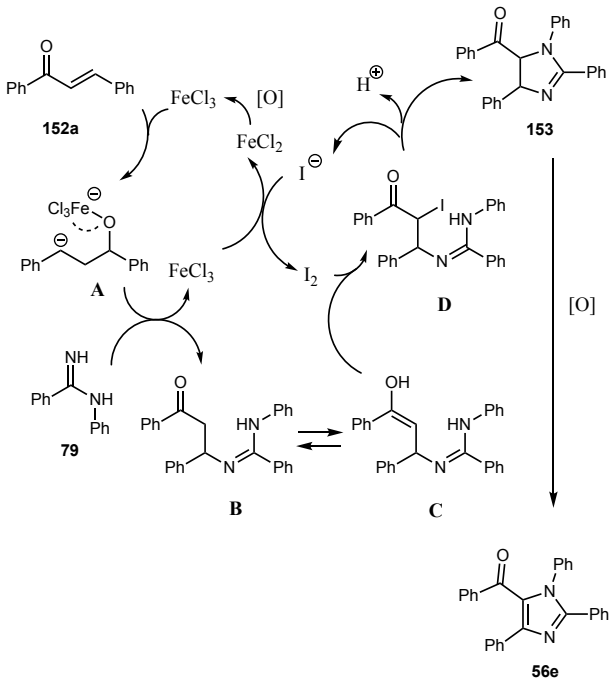


Scheme 81. $FeCl_3/I_2$-catalyzed aerobic oxidative coupling reaction of amidines **151** with chalcones **152**

Higher yields were obtained using arylamidines bearing electron-withdrawing substituents. Furthermore, high yields of imidazoles **56** were obtained using chalcones **152** with electron-withdrawing substituents on the phenyl rings whatever connected to the C–C double bond or adjacent to the carbonyl group.

It was also found that the addition of the radical scavenger TEMPO (1.5 equiv) to the $FeCl_3/I_2$-catalyzed reaction of *N*-phenylbenzamidine (**79**) with benzalacetophenone (**152a**: Ar^2= Ar^3= Ph) did not significantly decrease the yield of the required tetrasubstituted imidazole. On the other hand, when the $FeCl_3/I_2$-catalyzed reaction of **79** with **152a** was carried out under argon rather than oxygen atmosphere, imidazoline **153** [phenyl(81,2,4-triphenyl)-4,5-dihydro-1*H*-imidazol-5-yl)methanone] was obtained in 14 % yield thus demonstrating that dioxygen is critical to the formation of imidazoles **56** via the process shown in Scheme 81.[187]

On the basis of these results and literature data[189] the authors proposed a plausible mechanism for the $FeCl_3/I_2$-catalyzed aerobic oxidative reaction of *N*-phenylbenzamidine (**79**) with benzalacetophenone (**152a**) (Scheme 82).

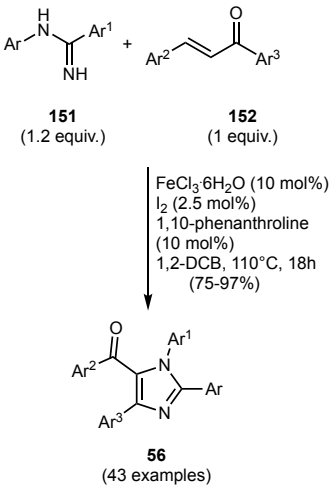


Scheme 82. Postulated mechanism for the $FeCl_3/I_2$-catalyzed synthesis of imidazole **56e** under aerobic conditions

First, activation of **152a** by means of $FeCl_3$ followed by addition of **79** to the resulting intermediate **A** would give the Michael adduct **B**. The subsequent tautomerization of **B** would provide **C** that would react with I_2 producing intermediate **D**. Cyclization of **D** would yield imidazoline **153**, which by oxidation under aerobic conditions would lead to

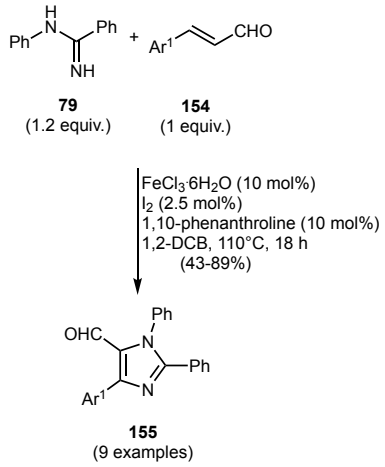
imidazole **56e**. Furthermore, iodide anion would be oxidized to I_2 by $FeCl_3$ and the resulting Fe(II) would be oxidized to Fe(III) in the dioxygen atmosphere, thus completing the catalytic cycle.[187]

Still in 2015, Chen and coworkers described efficient regioselective syntheses of 5-aroyl-1,2,4-triaryl-1*H*-imidazoles **56** via iron(III)/iodine-catalyzed Csp^2–H activation of α,β-unsaturated ketones/aldehydes with amidines.[190]. Compounds **56** were generally obtained in good to excellent yields by treatment of 1 equiv of α,β-unsaturated ketones **152** with 1.2 equiv of amidines **151** in 1,2-dichlorobenzene (1,2-DCB) in the presence of 10 mol% $FeCl_3$..·$6H_2O$, 2.5 mol% I_2 and 10 mol% 1,10-phenanthroline (1,10-phen) (Scheme 83). However, the reactions involving 1-phenylpent-1-en-3-one and 1-phenylhexa-2,4-dien-1-one did not produce the required imidazoles.



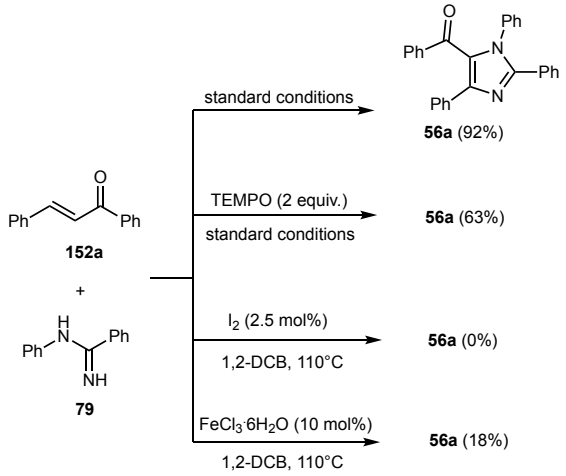
Scheme 83. Fe(III)/I_2/1,10-phenanthroline-catalyzed synthesis of imidazoles **56**

Interestingly, the reaction conditions used to prepare compounds **56** proved also suitable for the synthesis of compounds **155** in moderate to good yields from *N*-phenylbenzamidine (**79**) and α,β-unsaturated aldehydes **154** (Scheme 84).[190]



Scheme 84. Fe(III)/I_2/1,10-phenanthroline-catalyzed synthesis of 5-formyl-1,2,4-triaryl-1*H*-imidazoles **155**

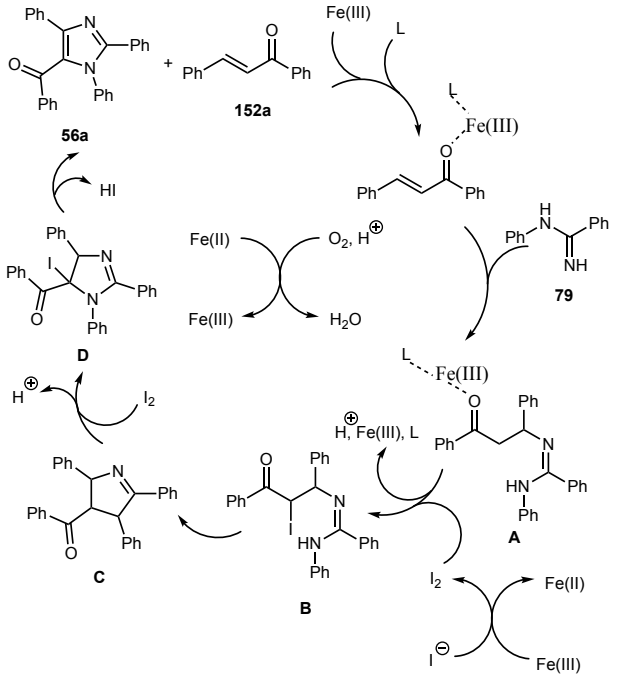
In order to elucidate the mechanism of the reaction the authors carried out the experiments shown in Scheme 85 involving the reaction between **79** and benzalacetophenone (**152a**).



Scheme 85. Control experiments involving the synthesis of imidazole **56a**

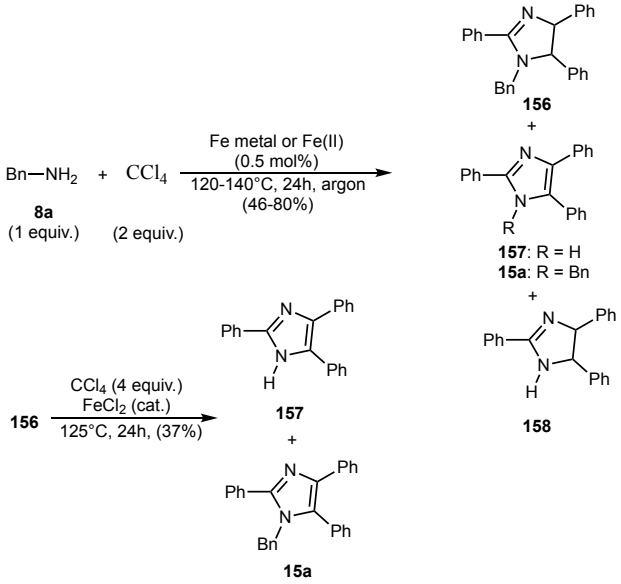
The obtained results showed that the reaction might not proceed via radical pathway since treatment of **152a** with **79** in the presence of 2 equiv of the radical scavenger TEMPO under standard conditions reduced the yield of the reaction from 92 to 63%. It was also found that molecular iodine alone was not sufficient to catalyze the reaction and that the use of $FeCl_3·6H_2O$ alone gave **56a** in 18% yield. On the basis of these results and literature data[191] the plausible reaction mechanism shown in Scheme 86 was proposed.[190] A Michael addition of amidine **79** to chalcone **152a** in the presence of $FeCl_3·6H_2O$ would give intermediate **A**. The subsequent reaction of **A** with molecular iodine would provide

intermediate **B**, which would undergo cyclization to form intermediate **C**. Iodination of **C** followed by elimination of HI would eventually give the desired product **56a**. In this process iodide anion would be oxidized by Fe(III) and the resulting Fe(II) would be converted to Fe(III) in the presence of dioxygen and H^*.[190]



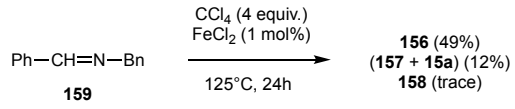
Scheme 86. Proposed mechanism for the formation of compound **56a** from **79** and **152a**

It deserves also to be mentioned that, in 1983, Tsuji and coworkers reported the first example of a synthesis of a tetrasubstituted-1*H*-imidazole via a transition metal-catalyzed cross dehydrogenative coupling reaction in the absence of air or dioxygen as terminal oxidant.[192] These authors described that the reaction of 1 equiv of benzylamine (**8a**) with 2 equiv of CCl_4 at 120–140 °C for 24 under argon in the presence of 0.5 mol% Fe metal or a Fe(II) compound such as $FeCl_2$ or $FeCl_2(PPh_3)_2$ produced a mixture of 1-benzyl-2,4,5-triphenyl-1*H*-imidazole (**156**), 2,4,5-triphenyl-2-imidazole (**157**), 1-benzyl-2,4,5-triphenyl-1*H*-imidazole (**15a**) and 2,4,5-triphenyl-2-imidazoline (**158**) in which compound **156** was the major component (Scheme 84). It was also found that compound **156** was converted to a mixture of imidazoles **156** and **15a** when **8a** was reacted with 4 equiv of CCl_4 in the presence of a catalytic quantity of $FeCl_2$ (Scheme 87).



Scheme 87. Iron-catalyzed reaction of benzylamine (**8a**) with CCl_4

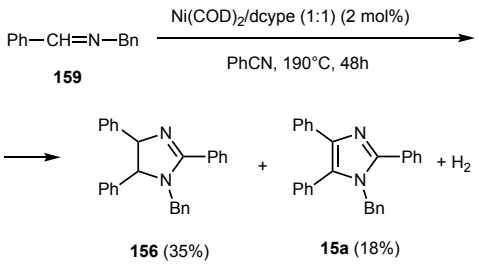
Furthermore, it was shown that, with $FeCl_2$ catalysis, *N*-benzylidene benzylamine (**159**) react with CCl_4 to form compounds **15a** and **156–158** (Scheme 88).



Scheme 88. $FeCl_2$-catalyzed reaction of *N*-benzylidene benzylamine (**159**) with CCl_4

On the basis of these results, Tsuji and coworkers proposed a reaction mechanism involving the formation of *N*-benzylidene benzylamine (**159**) from benzylamine (**8a**), the dehydrogenative dimerization of **159** to form imidazoline **156**, and the subsequent benzylation and debenzylation of this compound to give **157**, **158** and **15a**.[192]

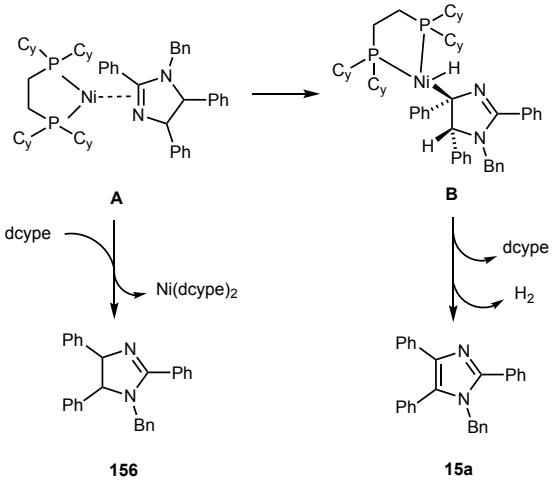
In 2014, Garcia and coworkers showed that imidazoline **156** and imidazole **15a** could be synthesized in 37 and 18% yield, respectively, by reaction of *N*-benzylidene benzylamine (**159**) at 190 °C in benzonitrile with 1 equiv of 1,2-bis(dicyclohexylphosphino)ethane (dcype) and a catalytic amount (2 mol%) of the complex obtained from $Ni(COD)_2$ (COD = 1,5-cyclooctadiene) and 1 equiv of 1,2-bis(dicyclohexylphosphino)ethanie (dcype) (Scheme 89).[193]



Scheme 89. Ni(0)-catalyzed synthesis of imidazoline **156** and imidazole **15a**

However, the $Ni(COD)_2$/dcype (1:2)-catalyzed reaction of fluoro-, trifluoromethyl-, methoxy- and methyl-substituted *N*-benzylidene benzylamines produced the sole formation of imidazolines.

Garcia and coworkers also proposed the mechanism depicted in Scheme 90 to explain the formation of imidazole **15a** from imidazoline **156**. They assumed that intermediate **A**, precursor to imidazoline **156**, undergoes C–H bond activation at the imidazoline framework to give rise to intermediate **B**. The latter Ni(II) derivative would then release **15a** through β-elimination, concomitant reductive elimination of H_2 and recoordination of dcype to the Ni(0) center.[193]

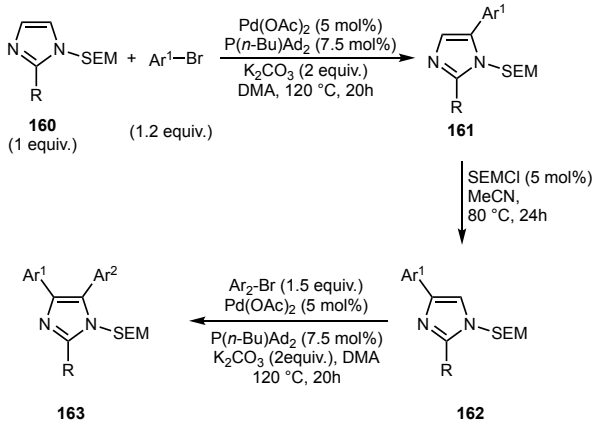


Scheme 90. Proposed mechanism for the formation of imidazole **15a**

8. Syntheses via Pd-Catalyzed Direct Arylation Reactions of Imidazole Substrates

The past three decades have witnessed significant progress in the transition metal-catalyzed direct arylation reactions of heteroarenes with (hetero)aryl halides [194] and several studies have focused on regioselective direct *C*-arylation reactions of imidazole and its derivatives. [195]

Palladium-catalyzed direct arylation reactions have been recently used for the regioselective synthesis of tetrasubstituted-1*H*-imidazoles. In 2010, Sames and coworkers synthesized 2-substituted-4,5-diaryl-1-SEM-1*H*-imidazoles **163** (SEM = [2-(trimethylsilyl)ethoxy]methyl acetal]) via the three-step route shown in Scheme 91 involving the sequential double arylation of 2-substituted 1-SEM-1*H*-imidazoles **160** [195i] which was enabled by the SEM group transposition (SEM switch) from the N-1 to N-3 nitrogen of the imidazole ring.[196] Specifically, the $Pd(OAc)_2$/P(*n*-Bu)Ad_2-catalyzed reaction of compounds **160** with aryl bromides in DMA at 120 °C in the presence of K_2CO_3 gave regioselectively imidazoles **161**. The SEM group of these compounds was then transposed from one nitrogen to the other nitrogen of the imidazole ring by treatment with a catalytic amount of SEM-Cl in MeCN at 80 °C providing compounds **162** in high yields. In this process the unreactive C-4 position of compounds **161** for direct arylation was transformed to the reactive C-5 position of compounds **162**. In fact, these imidazole derivatives underwent $Pd(OAc)_2$/P(*n*-Bu)Ad_2-catalyzed reaction with aryl bromides in DMA at 120 °C in the presence of K_2CO_3 resulting in the required compounds **163** in high yields.

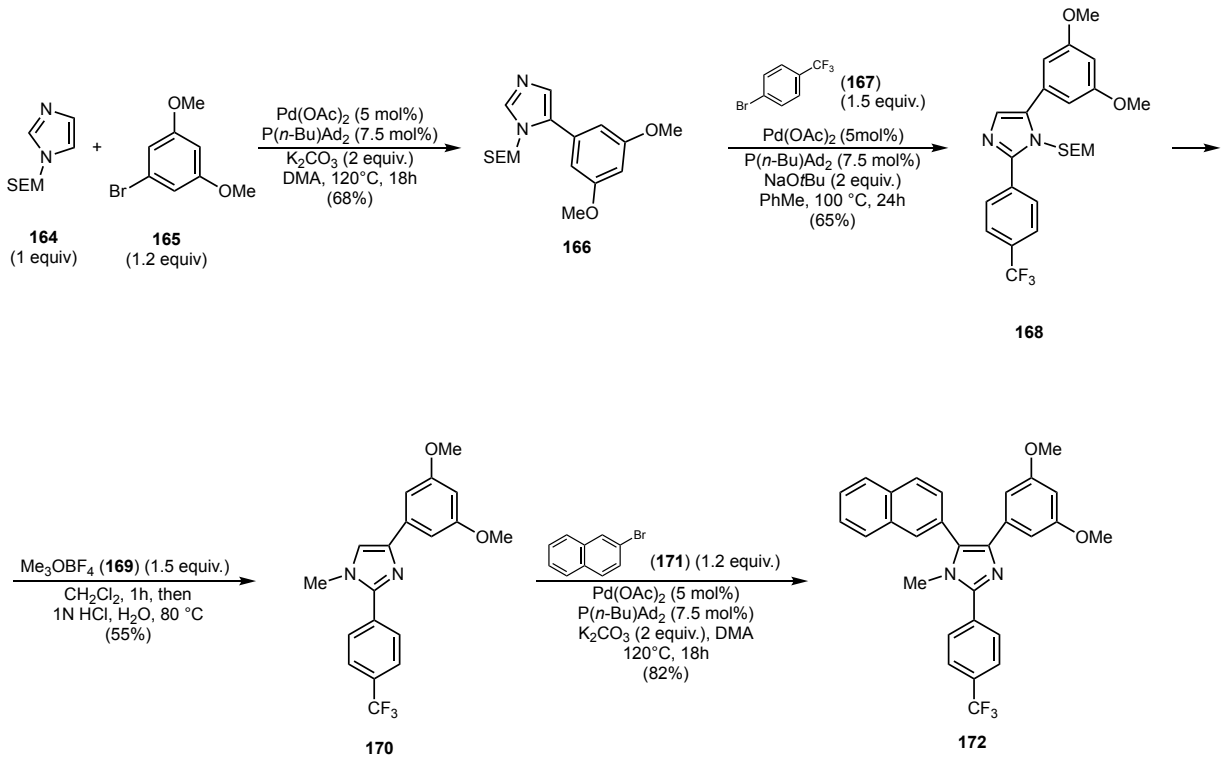


163	R	Ar^1	Ar^2	Overall yield %
a	Ph	3-$MeOC_6H_4$	3-pyridyl	52.2
b	Ph	3-$CF_3C_6H_4$	3,6-Me_2-2-pyperinyl	57.5
c	Ph	3-$EtOOCC_6H_4$	4-$Me_2NC_6H_4$	48.8
d	*n*-Bu	4-FC_6H_4	3-pyridyl	72.8
e	*N*-piperidinyl	Ph	3-$Me_2NC_6H_4$	47.2

Scheme 91. Synthesis of imidazoles **163** via sequential double arylation enabled by the SEM-group switch

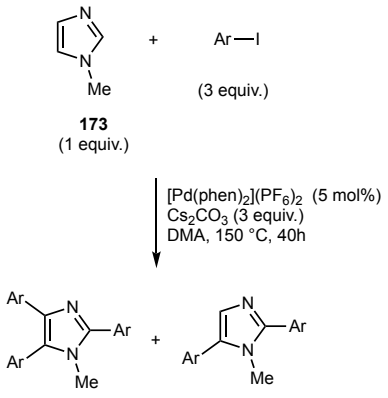
Notably, the sequential C-arylation that was enabled by the SEM switch also allowed the four

step synthesis of 1-methyl-2,4,5-triaryl-1*H*-imidazole **172** starting from 1-SEM-1*H*-imidazole (**164**) (Scheme 92). [195i]

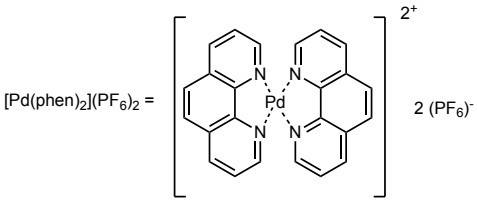


Scheme 92. Synthesis of 4-(3,5-dimethoxyphenyl)-1-methyl-5-(naphthalene-2-yl)-2-[4-(trifluoromethyl)phenyl]-1*H*-imidazole (**172**)

In detail, the $Pd(OAc)_2$/P(*n*-Bu)Ad_2-catalyzed C-5 arylation of **164** [182] with bromide **165** gave rise to compound **166** from which compound **168** was obtained by $Pd(OAc)_2$/P(*n*-Bu)Ad_2-catalyzed C-2 direct arylation with 4-bromobenzotrifluoride (**167**) in toluene at 100 °C in the presence of NaO*t*-Bu.[196] *N*-Methylation of **168** with trimethyloxonium tetrafluoroborate (**169**) followed by SEM deprotection gave compound **170** which was eventually C-5 arylated with 2-bromonaphthalene (**171**) in DMA at 120 °C using a combination of $Pd(OAc)_2$ and P(*n*-Bu)Ad_2 as catalyst to furnish compound **172** in 19.9% overall yield based on **164**.[195i]

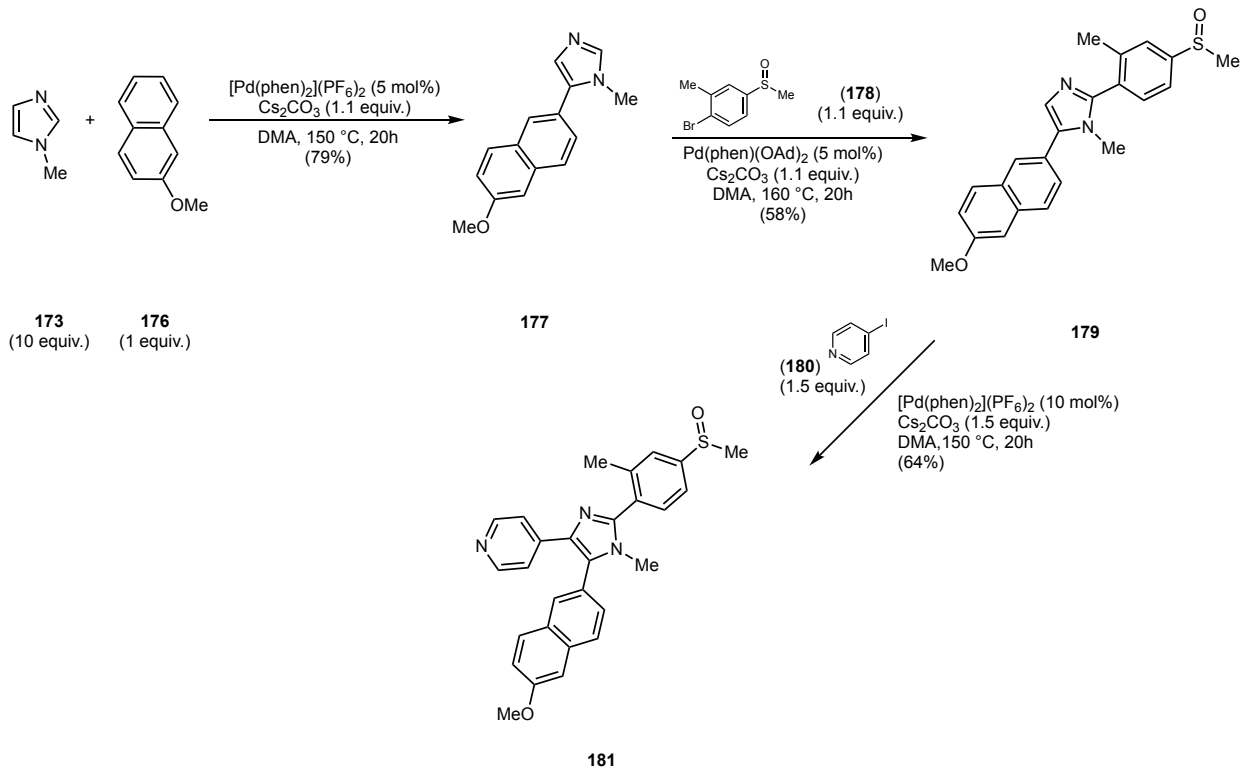


174	Ar	Yield %
a	4-$CF_3C_6H_4$	59
b	Ph	61
c	4-$MeOC_6H_4$	44



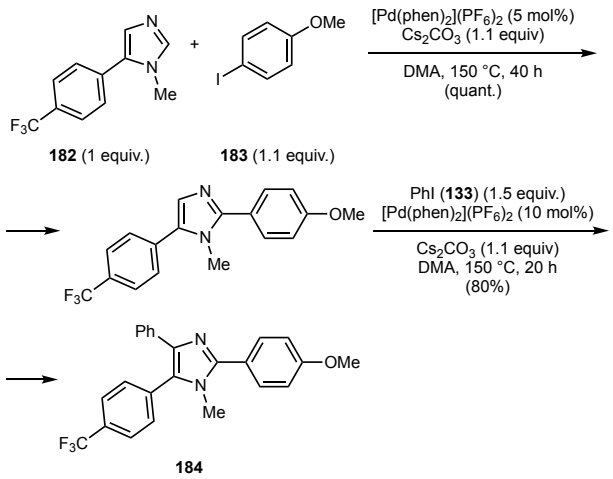
Scheme 93. $[Pd(phen)_2](PF_6)_2$-catalyzed triarylation of *N*-methylimidazole (**173**)

In 2011, Shibahara and Murai discovered that the reaction of *N*-methylimidazole (**173**) with 3 equiv of aryl iodides in DMA at 150 °C for 40 h in the presence of 3 equiv of Cs_2CO_3 and 5 mol% $[Pd(phen)_2](PF_6)_2$ gave 1-methyl-2,4,5-triaryl-1*H*-imidazoles **174** in moderate yields along with minor amounts of 2,5-diaryl-1-methyl-1*H*-imidazoles **175** (Scheme 93).[195k] It was thus demonstrated that, by using the $[Pd(phen)_2](PF_6)_2$ catalyst, compound **173** could undergo efficient C-4 arylation thus overcoming the problem associated with the low reactivity of the imidazole derivatives at this position. It was also found that, by using a large molar excess of **173**, selective C-5 monoarylation could be achieved. In a typical example, 1-methoxy-5-(6-methoxy-2-naphthyl)-1*H*-imidazole (**177**) was synthesized in 79% yield by reaction of 10 equiv of **173** with 1 equiv of 6-methoxy-2-naphthyl iodide (**176**) in DMA at 150 °C for 20 h in the presence of 1.1 equiv of Cs_2CO_3 and 5 mol% $[Pd(phen)_2](PF_6)_2$ (Scheme 94).[195k] Compound **177** was then used in the regioselective two-step synthesis of 1-methyl-2-(methanesulfonyl-2-methylphenyl)-4-(4-pyridyl)-5-(6-methoxynaphthalen-2-yl)-1*H*-imidazole (**181**) (Scheme 94),[195k] a Tie-2 tyrosine kinase inhibitor.[2] In detail, the reaction of **177** with 1.1 equiv of bromide **178** [195f] in DMA at 160 °C in the presence of 1.1 equiv of Cs_2CO_3 and 5 mol% $[Pd(phen)_2](PF_6)_2$ gave 1-methyl-2,5-diaryl-1*H*-imidazole **179** in 58% yield. Finally, C-4 arylation of **179** (1 equiv) with 4-iodopyridine (**180**) (1.5 equiv) in DMA at 150 °C in the presence of Cs_2CO_3 (1.5 equiv) and a catalytic amount (10 mol%) $Pd(phen)_2](PF_6)_2$ provided the target compound **181** in 64% yield (Scheme 94).[195k]



Scheme 94. Three-step synthesis of the Tie-2 tyrosine kinase inhibitor **181**

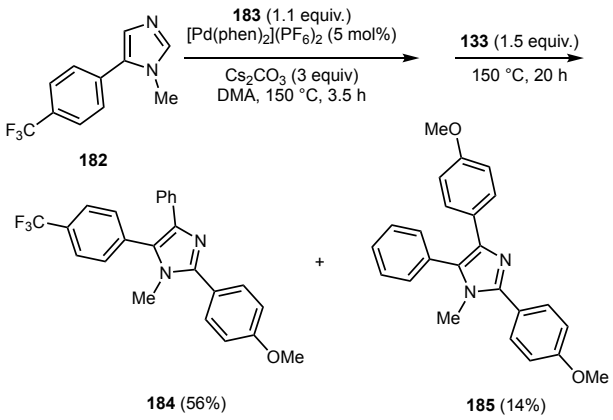
In 2012, Shibahara, Murai and coworkers, in continuation of their studies on multiple arylation reactions of azoles with aryl halides catalysed by Pd-phenanthroline complexes such as $[Pd(phen)_2](PF_6)_2$,[195k,198] performed the synthesis of 2-(4-methoxyphenyl)-1-methyl-4-phenyl-5-(4-trifluoromethylphenyl)-1*H*-imidazole (**184**) using two different protocols.[197e]



Scheme 95. Stepwise synthesis of imidazole **184**

The first synthetic approach (Scheme 95) involved the stepwise sequential arylation of 5-(4-trifluoromethylphenyl)-1-methyl-1*H*-imidazole (**182**) with 4-methoxyphenyl iodide (**183**) and phenyl iodide (**133**) in DMA at 150 °C in the presence of catalytic amounts of $[Pd(phen)_2](PF_6)_2$ which produced compound **184** in 80% overall yield.

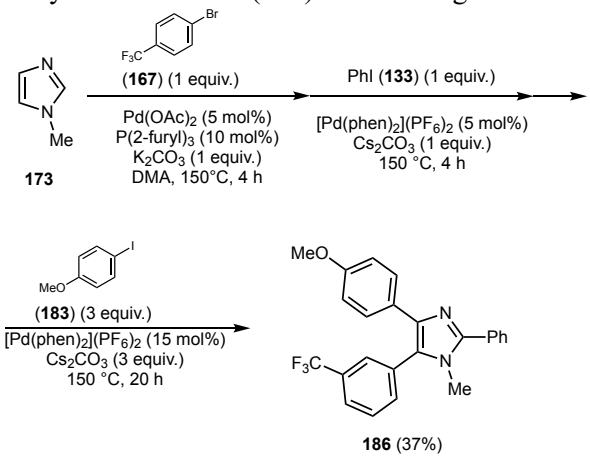
The second approach (Scheme 96) involved the one-pot sequential $[Pd(phen)_2](PF_6)_2$-catalyzed arylation of compound **182** with aryl iodides **183** and **133**.



Scheme 96. One-pot sequential C-2, C-4 diarylation of imidazole **182**

Specifically, under optimized condition, **182** was reacted with 1.1 equiv of **183** in DMA at 150 °C in the presence of 5 mol% $[Pd(phen)_2](PF_6)_2$. After this arylation reaction was complete (3.5 h), iodobenzene (**133**) (1.5 equiv) was added and the mixture was stirred at 150 °C for a further 20 h to give imidazole **184** in 56% yield along with bis(4-methoxyphenylated)imidazole **185** in 14% yield [197e]

Finally, the synthesis of 4-(4-methoxyphenyl)-1-methyl-4-phenyl-5-(4-trifluoromethylphenyl)-1*H*-imidazole (**186**) via the one-pot triarylation of 1-methyl-1*H*-imidazole (**173**) was investigated.



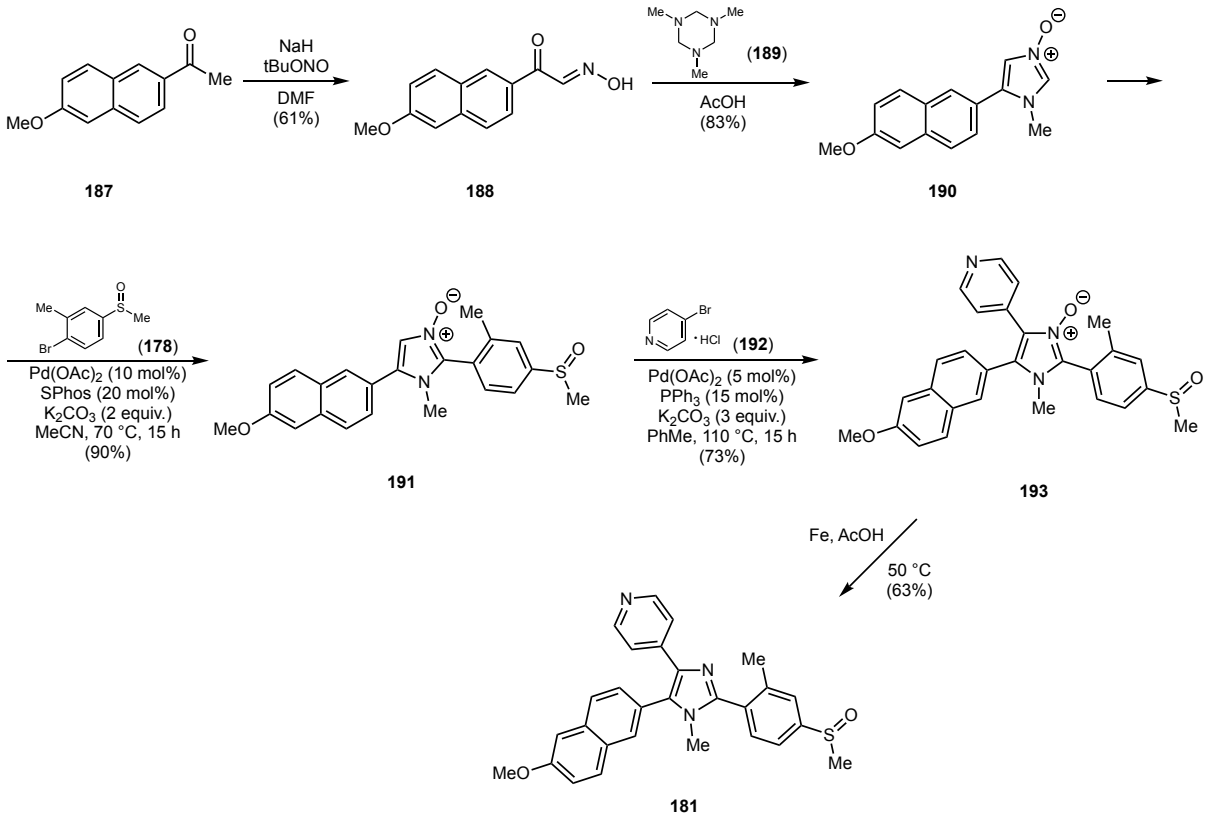
Scheme 97. Synthesis of compound **186** via one-pot sequential triarylation of 1-methyl-1*H*-imidazole (**173**)

Thus, compound **173** was reacted with 1 equiv of 4-bromobenzotrifluoride (**167**), 1 equiv of K_2CO_3, 5 mol% $Pd(OAc)_2$ and 10 mol% P(2-furyl)$_3$ at 150 °C for 4 h under argon. After cooling the reaction mixture at room temperature, 1 equiv of iodobenzene (**133**), 1 equiv of Cs_2CO_3 and 5 mol% $[Pd(phen)_2](PF_6)_2$ were added and the resulting mixture was stirred at 150 °C for 4 h. Subsequently, 3 equiv of 4-iodoanisole (**183**), 3 equiv of Cs_2CO_3 and 15 mol% $[Pd(phen)_2](PF_6)_2$ were added portionwise to the reaction mixture every 0.5 h at 150 °C and the resulting mixture was stirred for 20 h at 150 °C. Chromatographic purification of the crude reaction product enabled the isolation of compound **186** in 37% yield (Scheme 97).[197e]

As mentioned in Section 7 of this review, in 2013, Jiang and coworkers synthesized 1-benzyl-4-(4-chlorophenyl)-2,5-diphenyl-1*H*-imidazole (**134**) in 72 % yield by $Pd(OAc)_2/PPh_3$-catalyzed direct C-5 arylation of 1-benzyl-4-chlorophenyl-2-phenyl-1*H*-imidazole (**132**) with iodobenzene in DMF at 140 °C for 36 h (Scheme 73).[181]

Finally, in 2009, Fagnou and coworkers[195f] synthesized the Tie tyrosine kinase inhibitor **181** using a synthetic strategy completely different from those hitherto mentioned in this section. They began the synthesis of **187** (Scheme 98) with the preparation of α-ketooxime **188** by treatment of ketone **187** with NaH and *t*-butyl nitrite. Compound **188** was then reacted with 1,3,5-triazinane **189** providing imidazole-*N*-oxide **190** in 83% yield. The subsequent regioselective direct C-2 arylation of **190** was carried out in 90% yield by treatment with aryl bromide **178** in MeCN at 70 °C for 15 h in the

presence of 10 mol% $Pd(OAc)_2$, 20 mol% 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) and 2 equiv of K_2CO_3. A second direct arylation at C-4 of the resulting *N*-oxide **191** was achieved by treatment with 4-bromopyridine hydrochloride (**192**) in toluene at 110 °C for 15 h in the presence of 5 mol% $Pd(OAc)_2$, 15 mol% PPh_3 and 3 equiv of K_2CO_3. The reaction produced compound **193** in 73% yield. Finally, treatment of **193** with Fe metal and AcOH at 50 °C allowed the selective reduction of the *N*-oxide moiety of **193** leaving the sulfoxide group intact and yielded compound **181** in 63% yield (Scheme 98).[195f]

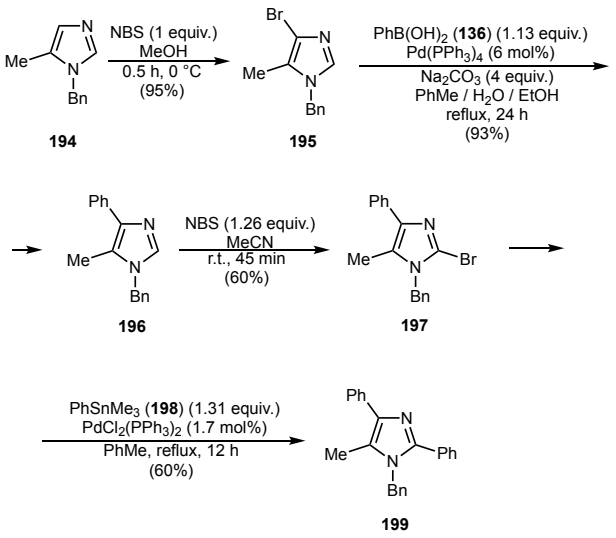


Scheme 98. Synthesis of the Tie tyrosine kinase inhibitor **181** via Pd-catalyzed sequential direct C–H arylation reaction of imidazole-*N*-oxides **190** and **191**

9. Syntheses via Pd-Catalyzed Cross-Coupling Reactions Involving the Use of Organometallic Reagents

Over the last two decades, even classical methods for the C–C bond formation by means of transition metal-catalyzed cross-couplings such as the Stille, Suzuki-Miyaura and Negishi reactions and the Pd-catalyzed cross-coupling reactions with triorganoindium reagents have been used for the synthesis of tetrasubstituted-1*H*-imidazoles.

In 1994, a combination of Pd-catalyzed Suzuki and Stille reactions were used by Wang and Haseltine in a four-step synthesis of 1-benzyl-2,4-diphenyl-5-methyl-1*H*-imidazole (**199**) in which 1-benzyl-5-methyl-1*H*-imidazole (**194**) was employed as the starting material (Scheme 99).[199] In detail, compound **194** was reacted with 1.1 equiv of NBS in MeCN to give regioisomerically pure bromide **195** in 95% yield. The subsequent $Pd(PPh_3)_4$-catalyzed Suzuki-Miyaura reaction of **195** with 1.1 equiv of phenylboronic acid (**136**) in a mixture of toluene, water and EtOH under reflux, in the presence of Na_2CO_3 as base provided trisubstituted imidazole **196** in 93% yield.

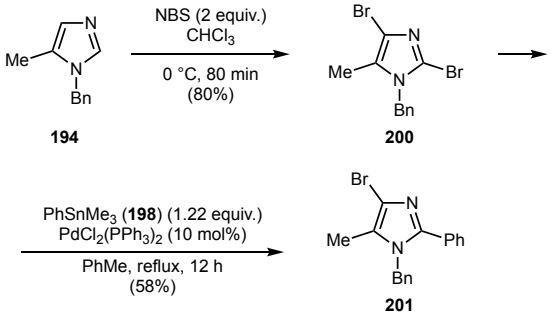


Scheme 99. Four-step synthesis of 1-benzyl-2,4-diphenyl-5-methyl-1*H*-imidazole (**199**)

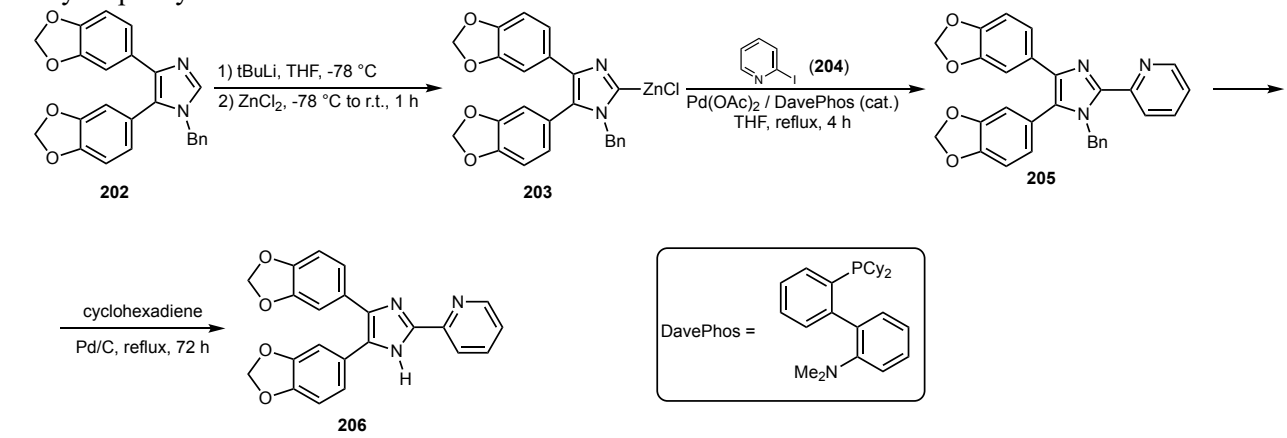
This compound was brominated at C-2 in 60% yield by treatment with 1.26 equiv of NBS in MeCN at room temperature and the resulting compound **197** was reacted with 1.3 equiv of phenyltrimethyltin (**198**) in toluene under reflux in the presence of 1.7 mol% $PdCl_2(PPh_3)_2$ producing the required tetrasubstituted imidazole **199** in 60% yield.

Wang and Haseltine also reported that treatment of **194** with 2 equiv of NBS in $CHCl_3$ at 0 °C gave 1-benzyl-2,4-dibromo-5-methyl-1*H*-imidazole (**200**) in 80% yield and that the reaction of this compound with 1.22 equiv of phenyltrimethyltin (**198**) in toluene under reflux in the presence of 10 mol% $PdCl_2(PPh_3)_2$ gave **Scheme 100.** Synthesis of 1-benzyl-4-bromo-5-methyl-2-phenyl-1*H*-imidazole **201**

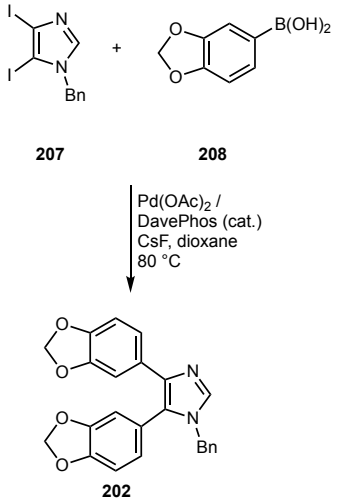
regioselectively 1-benzyl-4-bromo-5-methyl-2-phenyl-1*H*-imidazole (**201**) in 58% yield (Scheme 100).[199]



In 2003, Dobler synthesized 1-benzyl-4,5-bis(3,4-methylenedioxyphenyl)-2-(2-pyridyl)-1*H*-imidazole (**205**) via C-2 lithiation of 1-benzyl-4,5-bis(3,4-methylenedioxyphenyl)-1*H*-imidazole (**202**) with *t*-BuLi in THF at – 78 °C followed by addition of $ZnCl_2$ and $Pd(OAc)_2$/DavePhos-catalyzed Negishi-type reaction of the resulting organozinc derivative **203** with 2-iodopyridine (**204**) in THF under reflux (Scheme 101).[12b] Unfortunately, the yield of compound **205** was not reported, but it was described that the *N*-debenzylation reaction of **205** by treatment with cyclohexadiene under reflux in the presence of Pd/C gave the 2,4,5-triarylated-1*H*-imidazole **206** (Scheme 101).[12b] Compound **202** was in turn obtained by Suzuki-type reaction of 1-benzyl-4,5-diiodo-1*H*-imidazole (**207**)[200] with 4 equiv of 3,4-methylenedioxyphenylboronic acid (**208**) in dioxane at 80 °C in the presence of CsF as base and a $Pd(OAc)_2$/DavePhos catalyst system (Scheme 102).[12b]

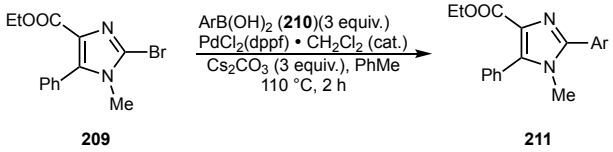


Scheme 101. Synthesis of imidazole **200** involving the *N*-debenzylation reaction of tetrasubstituted-1*H*-imidazole 2**05**



Scheme 102. Synthesis of 1-benzyl-4,5-bis(3,4-methylenedioxyphenyl)-1*H*-imidazole (**202**)

In 2004, Janda and coworkers reported that 2-aryl-4-ethoxycarbonyl-1-methyl-5-phenyl-1*H*-imidazoles **211a–h** were available in excellent yields by $PdCl_2(dppf)\cdot CH_2Cl_2$-catalyzed Suzuki-Miyaura reaction of 2-bromo-4-ethoxycarbonyl-1-methyl-5-phenyl-1*H*-imidazole (**209**) with 3 equiv of the required arylboronic acids **210** and 3 equiv of Cs_2CO_3 in toluene at 110 °C for 2 h (Scheme 103).[201] Compound **209** was in turn prepared via the three-step reaction sequence shown in Scheme 104 in which the first step was the $Rh_2(oct)_4$-catalyzed N–H insertion reaction of *N*-methylurea (**212**) with α-diazo-β-ketoester **213**.[202]

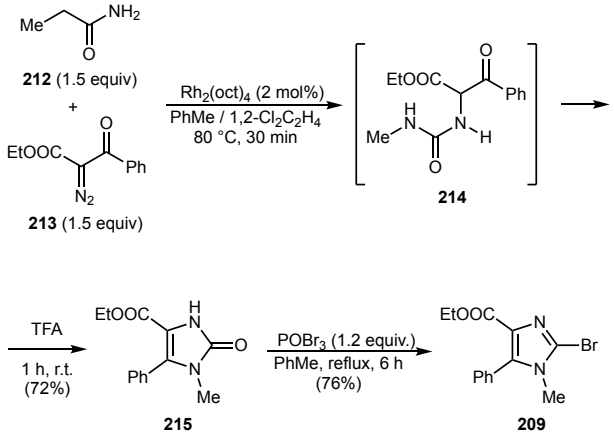


209 **211**

211	Ar	yield %
a	Ph	99
b	4-$CF_3C_6H_4$	99
c	4-PhC_6H_4	97
d	1-naphthyl	97
e	styryl	95
f	4-$MeOC_5H_4$	90
g	4-$EtOOCC_6H_4$	97
h	4-$TBDMSOC_6H_4$	93

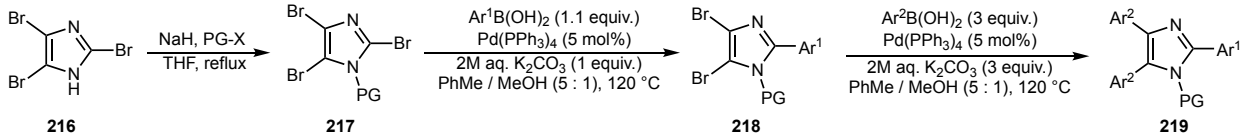
Scheme 103. Synthesis of 2-aryl-4-ethoxycarbonyl-1-methyl-5-phenyl-1*H*-imidazoles **211a–h**

The crude product **214** resulting from this reaction was treated with TFA at room temperature producing imidazolone **215** in 72% yield. Finally, treatment of **215** with $POBr_3$ in refluxing toluene gave the required compound **209** in 76% yield (Scheme 104).[201]



Scheme 104. Synthesis of 2-bromo-4-ethoxycarbonyl-1-methyl-5-phenyl-1*H*-imidazole (**209**)

In 2013, 1-protected-2-aryl-4,5-dibromo-1*H*-imidazoles **218** and 1-protected-2,4,5-triaryl-1*H*-imidazoles **219** were synthesized by Schnürch, Mihovilovic and coworkers using a novel strategy based on Pd-catalyzed Suzuki-type reactions of brominated imidazoles, in which commercially available 2,4,5-tribromo-1*H*-imidazole (**216**) was the starting material (Scheme 105).[203] Specifically, **216** was converted to 1-protected-2,4,5-tribromo-1*H*-imidazoles **217** bearing different protecting group (Bn, SEM or PMB) with orthogonal properties. Compounds **217** were then regioselectively converted to 1-protected-2-aryl-4,5-dibromo-1*H*-imidazoles **218** by treatment with 1.1 equiv of arylboronic acids $Ar^1B(OH)_2$ in a 5 :1 mixture of toluene and MeOH at 120 °C in the presence of 1 equiv of 2 M aq K_2CO_3 and 5 mol% $Pd(PPh_3)_4$. Notably, the nature of the protecting groups had no major influence on the yields of the cross-coupling reactions. Compounds **218** were then reacted with 3 equiv of arylboronic acids $Ar^2B(OH)_2$, 3 equiv of 2 M aq K_2CO_3 and 5 mol% $Pd(PPh_3)_4$ in a 5 :1 mixture of toluene and MeOH at 120 °C providing compounds **219** bearing identical aryl groups at positions 4 and 5 (Scheme 105).
However, Schnürch, Mihovilovic and coworkers observed that, unfortunately, it was impossible the synthesis of 1-protected triarylated imidazoles bearing three different aryl groups since selective cross-couplings at position 5 of dibromoimidazoles **218** could not be achieved.[203] They also found that when the arylation reactions leading to compounds **218** and **219** were not complete after a few hours, more equivalents of arylboronic acids had to be added. Nevertheless, the arylation reactions involving 2-tolylboronic acid in the second c
ross-coupling reactions resulted in low yields likely due to the steric hindrance of this arylating reagent.
[203]



216 **217** **218** **219**

218	PG	Ar^1	yield %
a	Bn	Ph	81[a]
b	Bn	4-$MeOC_6H_4$	78
c	Bn	3-$(NO_2)C_6H_4$	55
d	Bn	4-$(NO_2)C_6H_4$	64
e	Bn	2-MeC_6H_4	75[b]
f	Bn	2-furyl	43[c]
g	SEM	Ph	82
h	SEM	4-$MeOC_6H_4$	74
i	SEM	3-$(NO_2)C_6H_4$	65
j	SEM	4-$(NO_2)C_6H_4$	68
k	SEM	2-MeC_6H_4	74
l	SEM	2-furyl	31[d]
m	PMB	Ph	74
n	PMB	4-$MeOC_6H_4$	77
o	PMB	3-$(NO_2)C_6H_4$	63
p	PMB	2-MeC_6H_4	59
q	PMB	2-furyl	35

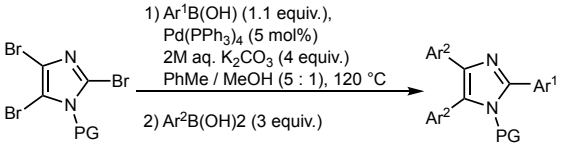
[a] Boronic acid used: 1.2 equiv.
[b] Boronic acid used: 1.3 equiv.
[c] Boronic acid used: 4.1 equiv.
[d] Boronic acid used: 3.6 equiv.

219	PG	Ar^1	Ar^2	yield %
a	Bn	Ph	Ph	79
b	Bn	Ph	4-$MeOC_6H_4$	85
c	Bn	Ph	3-$(NO_2)C_6H_4$	55
d	Bn	Ph	2-MeC_6H_4	37
e	Bn	4-$MeOC_6H_4$	3-$(NO_2)C_6H_4$	60
f	Bn	4-$MeOC_6H_4$	2-MeC_6H_4	32
g	Bn	3-$(NO_2)C_6H_4$	Ph	85
h	Bn	4-$(NO_2)C_6H_4$	Ph	79
i	Bn	2-MeC_6H_4	4-$MeOC_6H_4$	68
j	Bn	2-MeC_6H_4	3-$(NO_2)C_6H_4$	39[a]
k	Bn	2-furyl	4-$MeOC_6H_4$	81
l	SEM	Ph	Ph	91
m	SEM	4-$MeOC_6H_4$	Ph	80
n	SEM	4-$MeOC_6H_4$	2-MeC_6H_4	11[b]
o	SEM	3-$(NO_2)C_6H_4$	4-$MeOC_6H_4$	53
p	SEM	4-$(NO_2)C_6H_4$	4-$MeOC_6H_4$	21
q	SEM	2-MeC_6H_4	3-$(NO_2)C_6H_4$	74[c]
r	SEM	2-furyl	4-$MeOC_6H_4$	96
s	PMB	3-$(NO_2)C_6H_4$	4-$MeOC_6H_4$	92
t	PMB	2-MeC_6H_4	3-$(NO_2)C_6H_4$	42
u	PMB	2-furyl	4-$MeOC_6H_4$	53

[a] Boronic acid used: 3.5 equiv.
[b] Boronic acid used: 5 equiv.
[c] Boronic acid used: 6 equiv.

Scheme 105. Synthesis of 1-protected-2-aryl-4,5-dibromo-1*H*-imidazoles **218** and 1-protected-2,4,5-triaryl-1*H*-imidazoles **219**

Interestingly, compounds **219** were also available using a one-pot protocol in which 1-protected-2,4,5-tribromo-1*H*-imidazoles **217** were first reacted with 1.1 equiv of arylboronic acids $Ar^1B(OH)_2$, 5 mol% $Pd(PPh_3)_4$ and 4 equiv of 2 M aq K_2CO_3 in a mixture of toluene and MeOH. When the consumption of the substrate was complete, the reaction mixture was treated with 3 equiv of arylboronic acids $Ar^2B(OH)_2$ producing compounds **219** (Scheme 106).



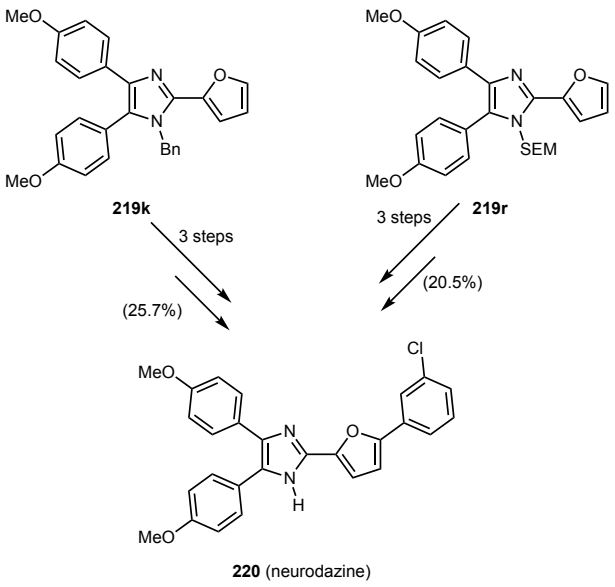
216 **219**

219	PG	Ar^1	Ar^2	yield %
b	Bn	Ph	4-$MeOC_6H_4$	85
e	Bn	4-MeC_6H_4	3-$(NO_2)C_6H_4$	73
r	SEM	2-furyl	4-$MeOC_6H_4$	25
o	SEM	3-$(NO_2)C_6H_4$	4-$MeOC_6H_4$	58

Scheme 106. One-pot synthesis of imidazoles **219**

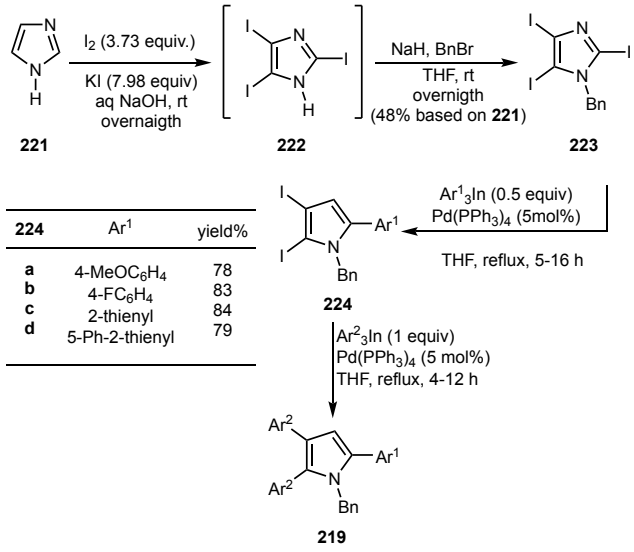
Notably, using this one-pot protocol, compounds **219b**, **219e** and **219o** were obtained in yields higher than those obtained in the stepwise protocol.[203]

Next, Schnürch, Mihovilovic and coworkers demonstrated the utility of the developed approaches to imidazoles **219** using compounds **219k** and **219r** as key intermediates in the synthesis of neurodazine (**220**) (Scheme 107), a trisubstituted imidazole that promotes neurogenesis in pluripotent cells[204] and induces neuronal differentiation in neuroblastoma and fibroplast cells.[205]



Scheme 107. Retrosynthesis of neurodazine (**220**)

In 2014, imidazoles of general formula **219** were also elegantly and efficiently synthesized by Martínez, Sarandeses and coworkers[206] using Pd-catalyzed cross-coupling reactions with triorganoindium compounds, a class of reagents capable of transferring efficiently the three groups attached to the metal in transition metal-catalyzed reactions.[207] In detail, *N*-benzyl-2,4,5-triiodo-1*H*-imidazole (**223**) was prepared in 48 % yield by reacting imidazole (**221**) with 3.73 equiv of molecular iodine and 7.98 equiv of KI in aq NaOH at room temperature, treatment of the resulting crude 2,4,6-triiodo-1*H*-imidazole (**222**) with NaH in THF and benzyl bromide (Scheme 108).



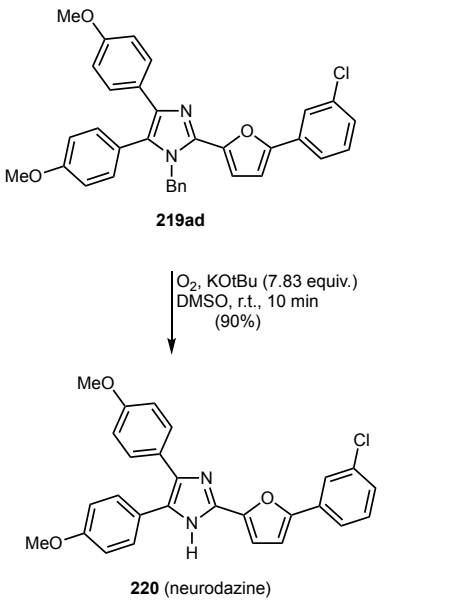
224	Ar^1	yield%
a	4-$MeOC_6H_4$	78
b	4-FC_6H_4	83
c	2-thienyl	84
d	5-Ph-2-thienyl	79

219	Ar^1	Ar^2	yield%
v	4-FC_6H_4	4-$MeOC_6H_4$	87
k	2-furyl	4-$MeOC_6H_4$	90
w	5-Ph-2-thienyl	4-$MeOC_6H_4$	80
y	5-Ph-2-thienyl	2-benzo[*b*]thiophenyl	89
z	4-FC_6H_4	2-benzo[*b*]thiophenyl	98
aa	2-furyl	2-benzo[*b*]thiophenyl	87
ab	4-$MeOC_6H_4$	5-Ph-2-thienyl	68
ac	4-$MeOC_6H_4$	5-(3-ClC_6H_4)furan-2-yl	92
ad	5-(3-ClC_6H_4)furan-2-yl	4-$MeOC_6H_4$	91

Scheme 108. Synthesis of imidazoles **224** and **219** via Pd-catalyzed reactions with triarylindium reagents

Compound **223** was then reacted with 0.5 equiv of triarylindium reagents $Ar^1{}_3In$[208] in THF under reflux in the presence of 5 mol% $Pd(PPh_3)_4$ to give regioselectively 2-aryl-1-benzyl-4,5-diiodo-1*H*-imidazoles **224** in 78–84% yields. The subsequent reaction of compounds **224** with 1 equiv of triarylindium reagents $Ar^2{}_3In$ in THF under reflux in the presence of 5 mol% $Pd(PPh_3)_4$ produced compounds **219** in yields ranging from 68 to 98% (Scheme 108).

The synthetic utility of this atom efficient protocol was then established by converting compound **219ad** into neurodazine (**220**) (Scheme 109).[208]



Scheme 109. Synthesis of neurodazine (**220**) by *N*-debenzylation of compound **219ad**

10. Syntheses via Pd/Cu-catalyzed Sonogashira Reactions

The Pd/Cu-catalyzed Sonogashira cross-coupling reaction [209] of (hetero)aryl halides with 1-alkynes has found wide application in the areas of synthetic heterocyclic and medicinal chemistry.[210]

In 2009, the reaction was used by Kerwin and coworkers in a key step of the synthesis of 1,2-dialkynyl-1*H*-imidazole **225** (Figure 20), a potent (IC_{50} = 200 nM) and selective inhibitor of p38α that exhibits minimal cytochrome P450 2D6 inhibition.[211]

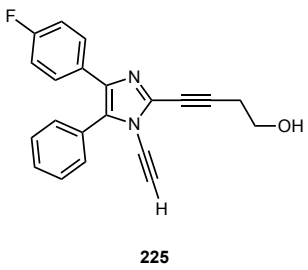
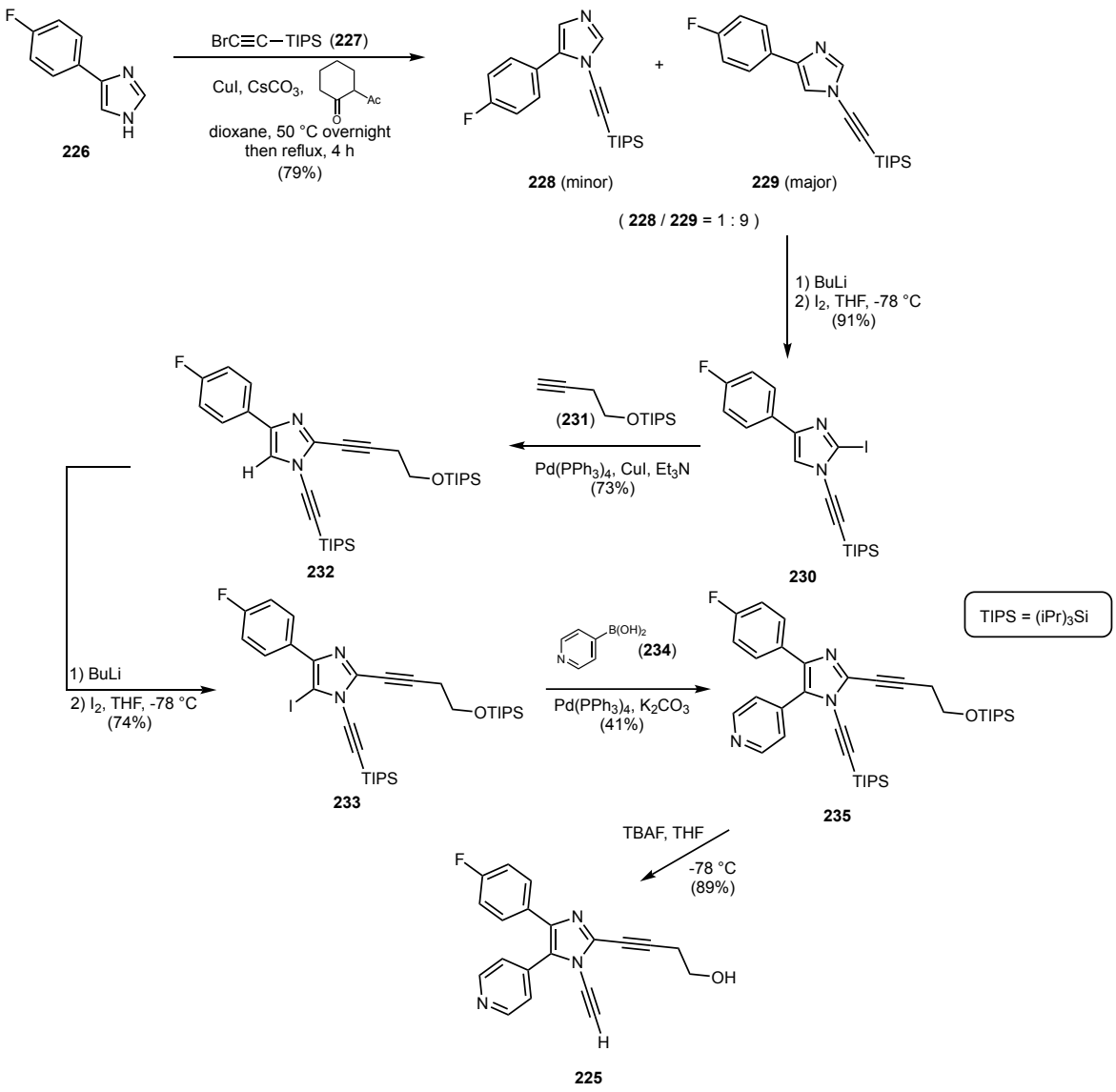


Figure 20. Chemical structure of 1,2-dialkyl-1*H*-imidazole **225**

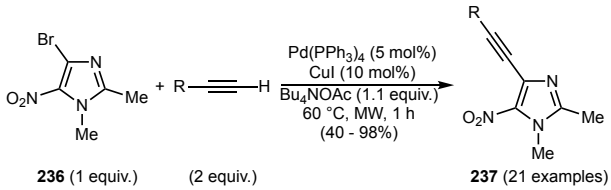
Scheme 110 shows the synthetic route followed for the synthesis of **225**. In detail, commercially available 4-fluorophenyl-1*H*-imidazole (**226**) was reacted according to a literature protocol[212] with 1-bromo-1-alkyne **227**, catalytic amounts of CuI and 2-acetylcyclohexanone and 2 equiv of Cs_2CO_3 in dioxane providing a 9 : 1 mixture of regioisomeric compounds **228** and **229** in 79% yield. Iodination of **228** at the 2-position produced 2-iodoimidazole **230**, which underwent $Pd(PPh_3)_4$/CuI-catalyzed Sonogashira coupling with 1-alkyne **231** in Et_3N to give 1,2-dialkynylimidazole **232** in 73% yield. Finally, a three-step reaction sequence involving the conversion of **232** to 5-iodoimidazole **233** and the Suzuki-type cross-coupling reaction of this compound with pyridine-4-boronic acid (**234**), followed by deprotection of the resulting compound **235** by treatment with TBAF in THF gave the required 1,2-dialkynyl-1*H*-imidazole **225** in 27% yield based on compound **232** (Scheme 110).[211] Interestingly, compound **225** was found capable of covalently modify p38α and to exhibit minimal CYP450.206 inhibition.[211]

In 2013, various 4-(1-alkynyl)-1,2-dimethyl-5-nitro-1*H*-imidazoles **237** were synthesized by Vanelle and coworkers via $Pd(PPh_3)_4$/CuI-catalyzed cross-coupling reaction of 4-bromo-1,2-dimethyl-5-nitro-1*H*-imidazole (**236**) with 2 equiv of 1-alkynes in MeCN at 60 °C under microwave irradiation using Bu_4NOAc as base (Scheme 111).[213]



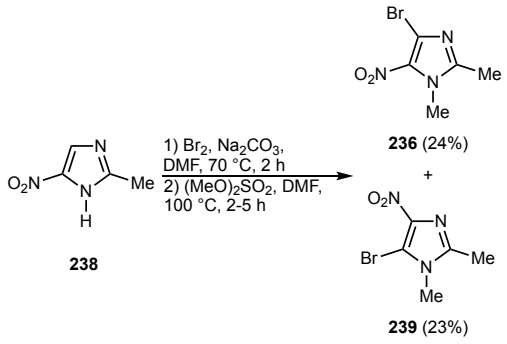
Scheme 110. Synthesis of 1,2-dialkynyl-1*H*-imidazole **225**

A wide range of 1-alkynes also containing functional groups such as OH, F, OMe and NH_2 was shown to undergo this microwave-assisted Sonogashira cross-coupling reaction that provided compounds **237** in moderate to good yields.



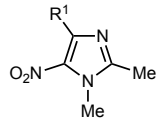
Scheme 111. Microwave-assisted Sonogashira-type reaction of bromoimidazole **236** with 1-alkynes

Compound **236** was in turn prepared in 24% yield by sequential bromination of 2-methyl-5-nitro-1*H*-imidazole (**238**) with elemental bromine and methylation of the resulting 4-bromo derivative with dimethyl sulphate in DMF at 100 °C.[213, 214] Unfortunately, the latter reaction was not regioselective and also produced 5-bromo-1,2-dimethyl-4-nitro-1*H*-imidazole (**239**) in 23% yield (Scheme 112).[214]



Scheme 112. Synthesis of 4-bromo-1*H*-imidazole **236**

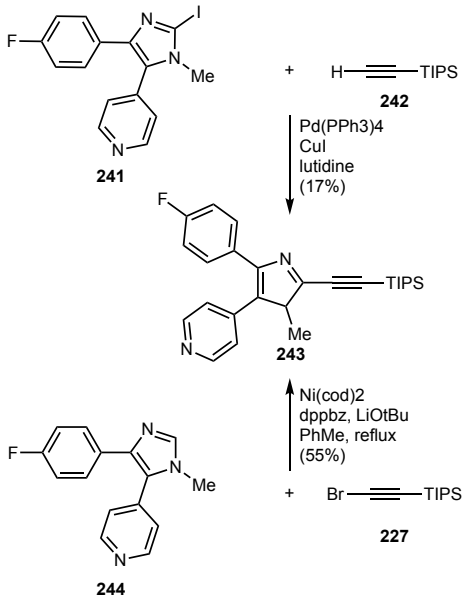
Interestingly, bromide **236** also appeared able to undergo microwave-assisted $Pd(PPh_3)_4$-catalyzed Suzuki-Miyaura cross-coupling reaction with aryl, heteroaryl and styrylboronic acids providing 4-aryl-. 4-heteroaryl- and 4-styryl-1,2-dimethyl-5-nitro-1*H*-imidazoles **240** (Figure 21) in good to excellent yields.[214]



240 (R^1 = aryl, heteroaryl, styryl)

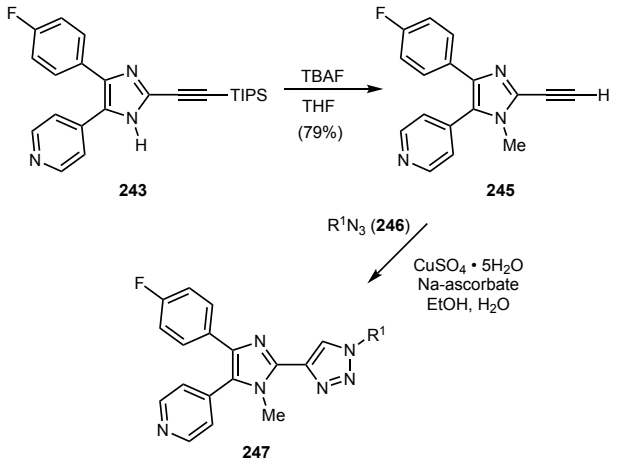
Figure 21. Chemical structure of compounds **240**

In 2014, as part of a study on the design, synthesis and biological evaluation of novel triazolyl p38α MAPK inhibitors with improved water solubility, Seerden and coworkers synthesized in only 17% yield 4-(4-fluorophenyl)-1-methyl-5-(4-pyridyl)-2-(triisopropylsilylethynyl)-1*H*-imidazole (**243**) by $Pd(PPh_3)_4$/CuI-catalyzed Sonogashira reaction of 2-iodoimidazole **241** with 1-triisopropylsilylacetylene (**242**) using lutidine as solvent and base (Scheme 113).[215]



Scheme 113. Synthesis of 4-fluorophenyl-1-methyl-5-(4-pyridyl)-2-(triisopropylsilylethynyl)-1*H*-imidazole (**243**)

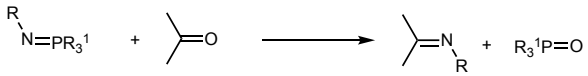
In addition, they found that compound **243** could be alternatively prepared in 55% yield by $Ni(cod)_2$/dppbz- [1,2-bis(diphenylphosphino)benzene]-catalyzed direct C-2 alkynylation of 4-(4-fluorophenyl)-1-methyl-5-(4-pyridyl)-1*H*-imidazole (**244**) with 2-bromo-1-triisopropylsilylacetylene (**227**) in toluene under reflux using LiO*t*-Bu as base (Scheme 113)[215] according to the protocol previously described by Miura and coworkers for the Ni-catalyzed direct alkynylation of azoles with alkynyl bromides.[216] The subsequent reaction of **243** with TBAF in THF gave alkyne **245** in 79% yield, which when subjected to Cu(I)-catalyzed 1,3-cycloaddition with azides **246** provided novel triazolyl p38α MAPK inhibitors **247** (Scheme 114).[215]



Scheme 114. Synthesis of triazolyl p38α MAPK inhibitors **247**

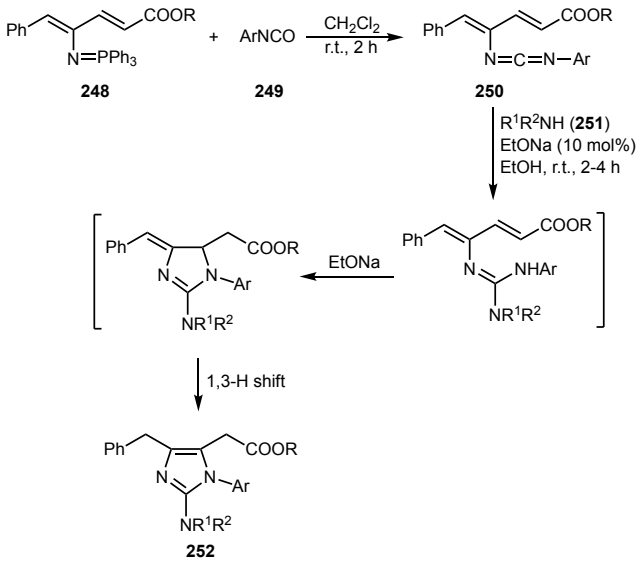
11. Syntheses via Aza-Wittig Reaction

In recent years, the aza-Wittig reaction of phosphazene compounds with carbonyl derivatives (Scheme 115) such as aldehydes, ketones, esters, amides, anhydrides, thioesters and sulfimides was found to be an efficient tool for the construction of carbon–nitrogen double bonds also applicable to the preparation of heterocyclic compounds.[217]



Scheme 115. The aza-Wittig reaction

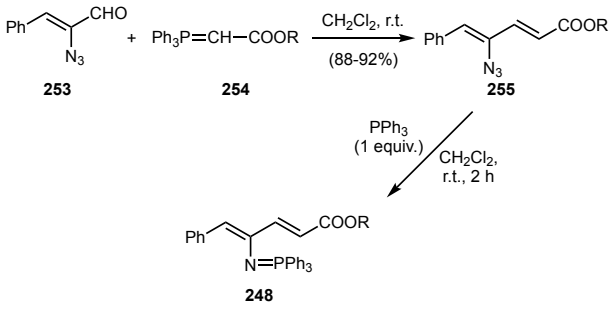
In 2012, Ding and coworkers reported a high yielding regioselective synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles **252** through the reaction of alkyl 5-phenyl-[4-(triphenylphosphoranylidene)amino]penta-2,4-dienoates **248** with arylisocyanates **249** in CH_2Cl_2 at room temperature, followed by treatment of the resulting carbodiimides **250** with secondary amines **251** in EtOH at room temperature in the presence of a catalytic amount of EtONa (Scheme 116).[218]



252	Ar	NR^1R^2	R	yield%
a	4-ClC_6H_4	morpholin-4-yl	Et	86
b	4-FC_6H_4	morpholin-4-yl	Et	82
c	3-MeC_6H_4	morpholin-4-yl	Et	84
d	4-MeC_6H_4	morpholin-4-yl	Et	83
e	4-ClC_6H_4	morpholin-4-yl	Me	87
f	4-ClC_6H_4	NEt_2	Et	84
g	4-ClC_6H_4	NBu_2	Et	79
h	4-ClC_6H_4	piperidin-1-yl	Et	80
i	4-ClC_6H_4	piperidin-1-yl	Me	81
j	4-ClC_6H_4	piperidin-1-yl	Et	82
k	4-ClC_6H_4	piperidin-1-yl	Me	83

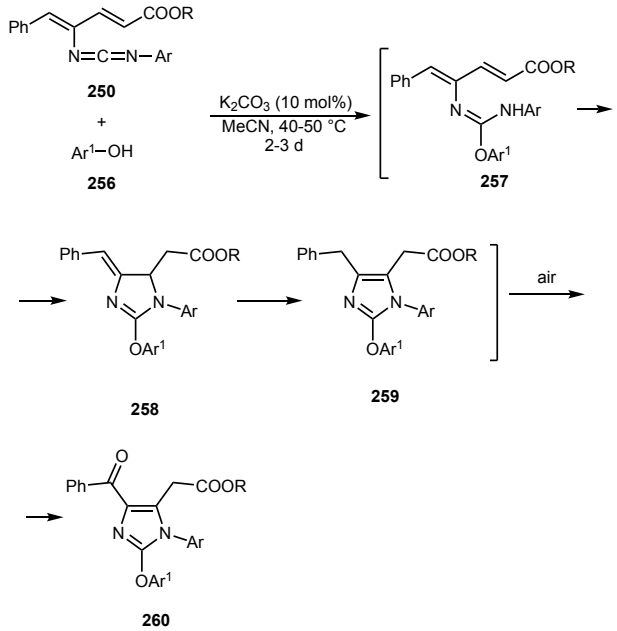
Scheme 116. Synthesis of 1,2,4,5-tetrasubstituted -1*H*-imidazoles **252**

Iminophosphoranes **248** were in turn prepared by treatment of α-azidocinnamaldehyde (**253**)[218] with ylidenetriphenylphosphoranes **254** followed by Staudinger reaction[219] of the resulting azides **255** with PPh_3 in CH_2Cl_2 at room temperature (Scheme 117).[218]



Scheme 117. Synthesis of iminophosphoranes **248**

Deng and coworkers also accomplished an efficient synthesis of 2-aryloxy-4-phenacylimidazoles **260** via K_2CO_3-catalyzed reaction of carbodiimides **250** with phenols **256** (Scheme 118).[218] These authors discovered that the K_2CO_3-catalyzed reaction of carbodiimides **240** with phenols **256** in MeCN at 40–50 °C for 2-3 days produced compounds **260** instead of imidazoles **259** and rationalized this result hypothesizing that arylphenoxides would undergo reaction with carbodiimides **250** to give intermediates **257**.



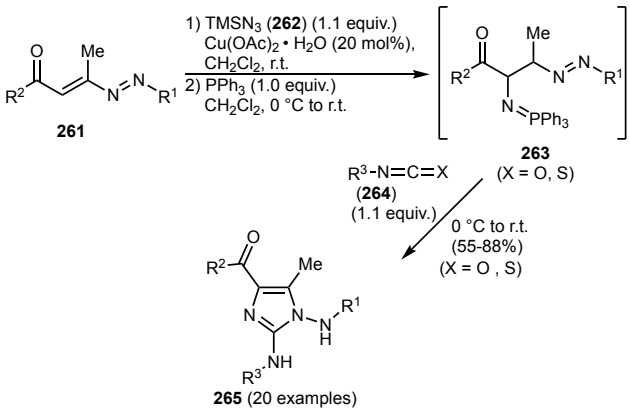
260	Ar^1O	Ar	R	yield%
a	4-ClC_6H_4O	Ph	Et	67
b	PhO	4-ClC_6H_4	Et	73
c	4-MeC_6H_4O	4-ClC_6H_4	Et	75
d	2,4-$Cl_2C_6H_3O$	4-ClC_6H_4	Et	69
e	4-ClC_6H_4O	4-MeC_6H_4	Et	73
f	4-ClC_6H_4O	4-ClC_6H_4	Et	72
g	4-ClC_6H_4O	4-MeC_6H_4	Me	62

Scheme 118. Synthesis of 2-aryloxy-4-phenacyl-1*H*-imidazoles **260**

The latter compounds would undergo intramolecular Michael addition providing dihydroimidazoles **258**. Subsequent isomerization of **258** through 1,3-H shift would produce imidazoles **259**, which would be oxidized by air to give 2-aryloxy-4-phenacyl-1*H*-imidazoles **260**.[218]

Still in 2012, Santeusanio and coworkers carried out a one-pot efficient synthesis of several 1,2-diamino-1*H*-imidazoles of general formula **265** via sequential aza-Michael, Staudinger and aza-Wittig reactions[219,220] on 1,2-diaza-1,2-dienes **261** (Scheme 119).[221] The synthesis was specifically carried out as follows. Trimethylsilylazide (**262**) was added to 1,2-diaza-1,2-dienes **261**[222] in CH_2Cl_2 at room temperature in the presence of a catalytic amount of $Cu(OAc)_2{\cdot}H_2O$ and the crude α-azidohydrazone derivatives resulting from the aza-Michael 1,4-addition reaction[223] were treated with PPh_3 for the Staudinger reaction[220] delivering crude

iminophosphoranes **263**. Finally, the aza-Wittig reaction[217] of compounds **263** with aryl isocyanates **264** gave 1,2-diamino-1*H*-imidazoles **265** in yields ranging from 55 to 88%.



Scheme 119. One-pot synthesis of 1,2-diamino-1*H*-imidazoles **265**

For example, 2-anilino-1-[(anilinocarbonyl)amino]-*N,N*-diethyl-5-methyl-1*H*-imidazole-4-carboxamide (**265a**) and *tert*-butyl {2-anilino-4-[(dimethylaminobenzyl]-5-methyl-1*H*-imidazol-1-yl]carbamate (**265b**) (Figure 22) were synthesized in 61 and 71% yield respectively.

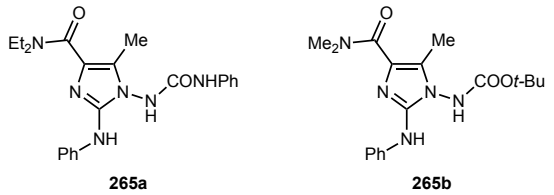
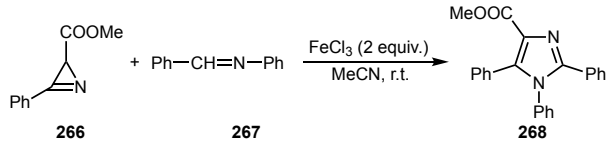


Figure 22. Chemical structures of 1,2-diamino-1*H*-imidazoles **265a** and **265b**

12. Syntheses from 2*H*-Azirines

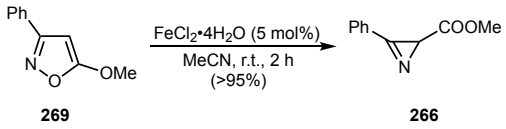
Since 1978, it has been shown that the Lewis acid-mediated ring-opening reaction of 2*H*-azirines [224] gives rise to intermediates capable of generating imidazole derivatives.[225]

In 2012, Auricchio and coworkers synthesized methyl 1,2,5-triphenyl-1*H*-imidazole-4-carboxylate (**268**) in 65% yield by $FeCl_3$-mediated reaction of 3-phenyl-2*H*-azirine-2-carboxylic acid methyl ester (**266**) with *N*-benzylideneaniline (**267**) (Scheme 120). [226]



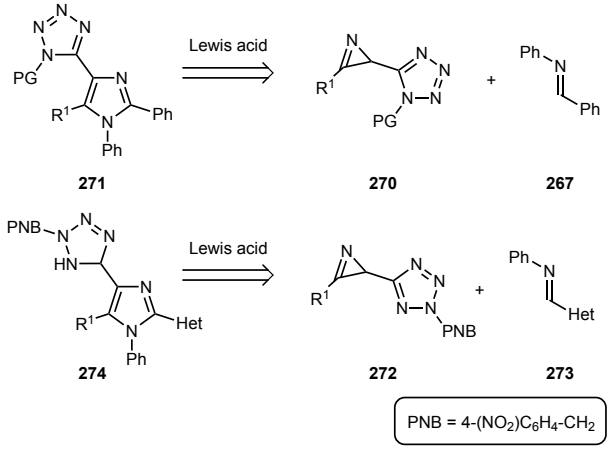
Scheme 120. Synthesis of methyl 1,2,5-triphenyl-1*H*-imidazole-4-carboxylate (**268**)

Compound **266** was in turn prepared by $FeCl_2{\cdot}4H_2O$-catalyzed isomerization of 5-methoxy-3-phenylisoxazole (**269**)[227] in MeCN at room temperature (Scheme 121).[228] In this regard, it deserves to be noted that the reaction between an azirine and aldimines had previously been employed by Müller and Mattay for the synthesis of tetrasubstituted imidazoles **78a** and **78b**[159] (see: section 4)



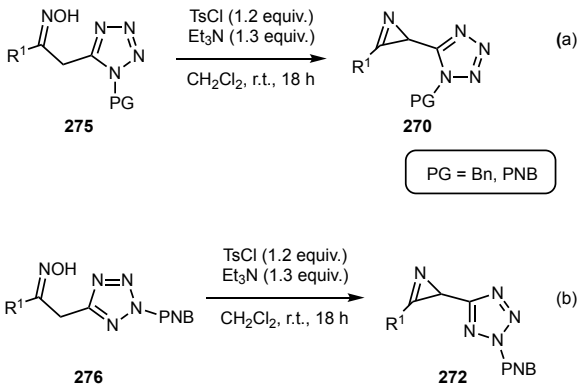
Scheme 121. Fe(II)-catalyzed isomerization of 5-methoxy-3-phenylisoxazole (**269**)

In 2014, 2-(tetrazol-5-yl)-2*H*-azirines of general formula **270** and **272**, which are isosteres of the corresponding 2*H*-azirine-2-carboxylates,[229] were used by Pinho e Melo and coworkers as precursors to 4-(1*H*-tetrazol-5-yl)-1*H*-imidazoles **271** and 4-(2*H*-tetrazol-5-yl)-1*H*-imidazoles **274**, respectively.[230] As shown in Scheme 122 in which the retrosynthesis of imidazoles **271** and **274** is outlined, imidazoles **271** were synthesized by the reaction of azirines **270** with *N*-benzylideneaniline (**267**) in the presence of a Lewis acid. Imidazoles **274** were analogously synthesized by Lewis acid-catalyzed reaction of azirines **272** with imines **273**.



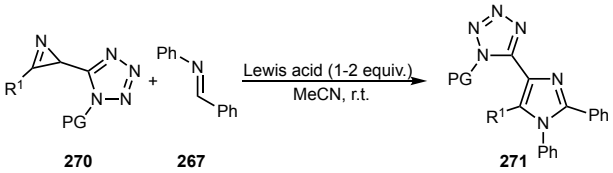
Scheme 122. Retrosynthesis of imidazoles **271** and **274**

Azirines **270** were prepared according to the Neber approach[231] that involved the treatment of β-ketoxime tetrazoles **275** with 1.2 equiv of TsCl and 1.3 equiv of Et_3N in CH_2Cl_2 at room temperature for 18 h (Scheme 123, eq. a).[219] Azirines **272** were similarly prepared in satisfactory yields from β-ketoxime tetrazoles **276** (Scheme 123, eq. b).[219]



Scheme 123. Synthesis of azirines **270** and **272**

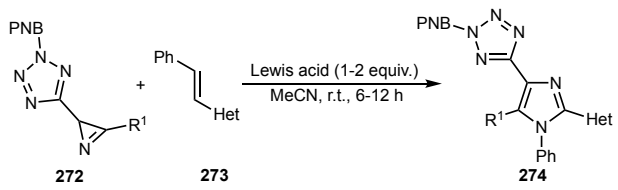
As shown in Scheme 124, 4-(1*H*-tetrazol-5-yl)-1*H*-imidazoles **271** were synthesized in high yields by $FeCl_3$- or $Zn(OTf)_2$-mediated reaction of azirines **270** with equimolar amounts of *N*-benzylideneaniline (**267**) in MeCN at room temperature.



271	PG	R^1	Lewis acid (equiv.)	yield%
a	PNB	Ph	$FeCl_3$ (2)	72
b	Bn	Ph	$FeCl_3$ (2)	68
a	PNB	Ph	$Zn(OTf)_2$ (1)	81
c	PNB	2-furyl	$Zn(OTf)_2$ (1)	80
d	PNB	2-thienyl	$Zn(OTf)_2$ (1)	67

Scheme 124. Synthesis of 4-(1*H*-tetrazol-5-yl)-1*H*-imidazoles **271**

On the other hand, 4-(2*H*-tetrazol-5-yl)-1*H*-imidazoles **274** were synthesized in moderate to good yields via $Zn(OTf)_2$- or $FeCl_3$-mediated reaction of azirines **272** with imines **273** in MeCN at room temperature for 6–12 h (Scheme 125).[230]

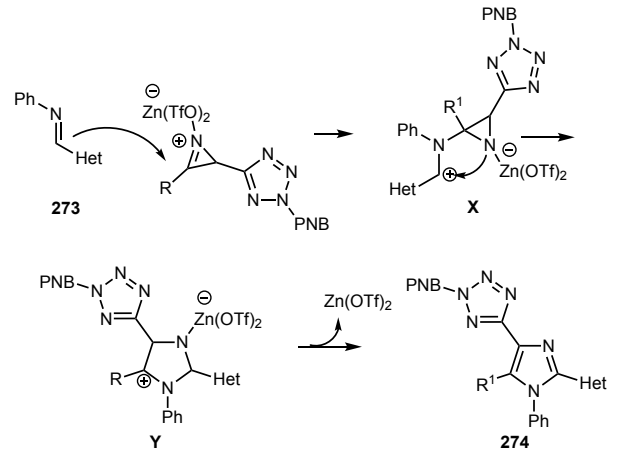


274	R^1	Het	Lewis acid (equiv.)	yield%
a	Ph	2-furyl	$Zn(OTf)_2$ (1)	75
a	Ph	2-furyl	$FeCl_3$ (1)	39
b	2-furyl	2-furyl	$Zn(OTf)_2$ (1)	69
c	2-thienyl	2-furyl	$Zn(OTf)_2$ (1)	56
d	Ph	2-pyridyl	$Zn(OTf)_2$ (1)	53[a]
d	Ph	2-pyridyl	$Zn(OTf)_2$ (1)	49[b]
d	Ph	2-pyridyl	$FeCl_3$ (2)	35[a]

[a] Reaction time : 12 h ; [b] Reaction time : 24 h

Scheme 125. Synthesis of 4-(2*H*-tetrazol-5-yl)-1*H*-imidazoles **274**

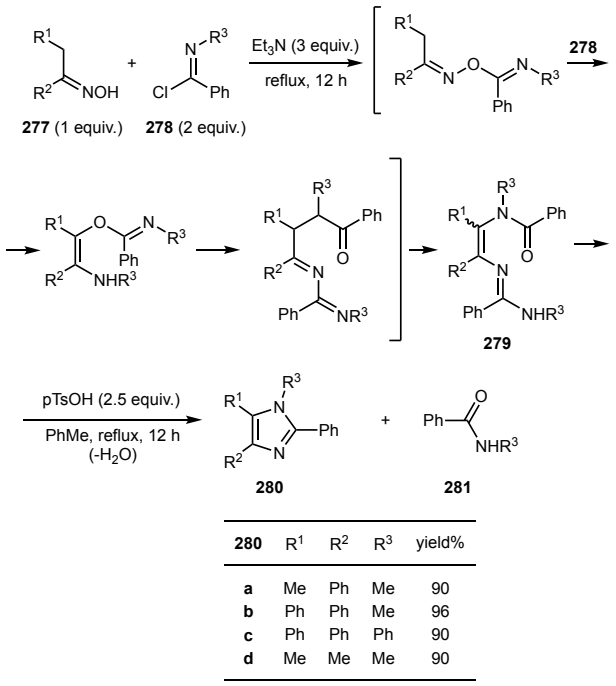
The formation of compounds **274** was proposed to occur through intermediates **X** which would be obtained by nucleophilic addition of imines **273** to the $Zn(OTf)_2$-activated C=N bond of azirines **272**. Subsequent ring expansion of the azirine ring of **X** would give intermediates **Y**, which would undergo aromatization giving rise to the target imidazoles **274** (Scheme 126).[230]



Scheme 126. Proposed mechanism for the formation of imidazoles **274**

13. Other Synthetic Methods

In 1993, Lantos, Eggleston and coworkers [232] developed a two-step route to 1,2,4,5-tetrasubstituted-1*H*-imidazoles **280** that involved the *p*-TsOH-mediated cyclization of amidines **279** resulting from the hetero-Cope rearrangement[233] of the compounds which were obtained by treatment of oximes **277** with benzene carboximidoyl chlorides **278**[234] and Et_3N in THF (Scheme 128).

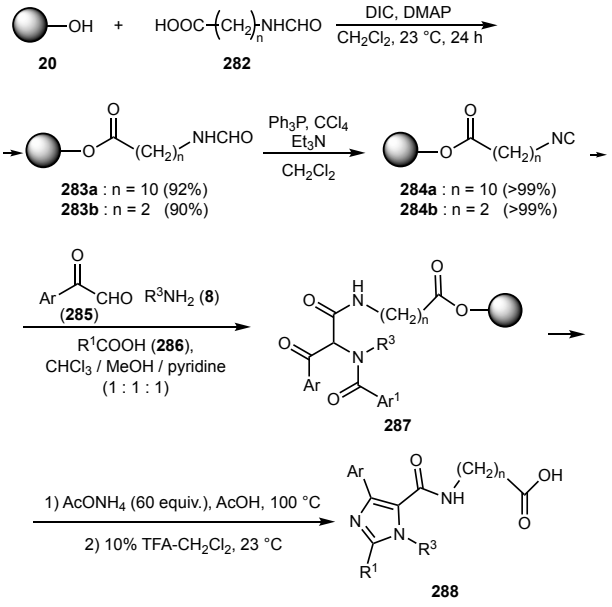


280	R^1	R^2	R^3	yield%
a	Me	Ph	Me	90
b	Ph	Ph	Me	96
c	Ph	Ph	Ph	90
d	Me	Me	Me	90

Scheme 127. Synthesis of imidazoles **280** via hetero-Cope rearrangement of amidines **279**

The method provided the required imidazoles **280** in high yields, but it lacked atom economy. In fact, in all experiments *N*-substituted benzamides **281** were obtained together with almost equivalent amounts of imidazoles **280**.[232]

In 1996, Mjalli and coworkers reported that Wang resin-supported α-(*N*-acyl-*N*-alkylamino)-β-ketoamides **287** were converted to tetrasubstituted imidazoles **288** in moderate yields by AcOH-mediated reaction with a large molar excess of $AcONH_4$ at 100 °C, followed by treatment with 10% TFA-CH_2Cl_2 at 23 °C (Scheme 128).[235] Compound **287** were in turn prepared via a three-step route in which the first step, leading to resins **283a,b**, consisted in the treatment of the Wang resin with formamido carboxylic acids **282a,b** in CH_2Cl_2 at 23 °C in the presence of *N,N'*-diisopropylcarbodiimide (DIC) and 4-dimethylaminopyridine (DMAP).[236]



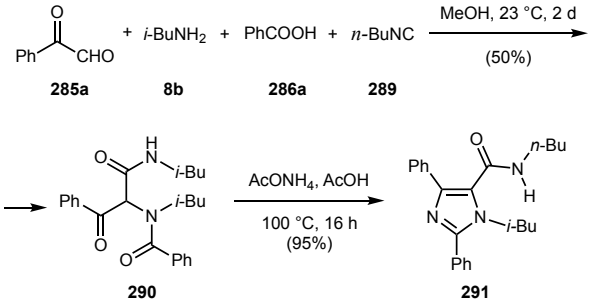
288	n	Ar	R^3	R^1	yield%
a	10	Ph	iBu	Ph	45
b	2	Ph	iBu	Ph	44[a]
c	10	Ph	iBu	4-FC_6H_4	35
d	10	Ph	iBu	nBu	36
e	10	Ph	iBu	Bn	47
f	10	Ph	Ph	Ph	16
g	10	Ph	4-$MeOC_6H_4$	Ph	43
h	10	Ph	Bn	Ph	36[a]
i	10	4-$MeOC_6H_4$	iBu	Ph	51[a]
j	10	4-FC_6H_4	iBu	Ph	49[a]

[a] This compound was converted to the corresponding methyl ester prior to purification

Scheme 128. Synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles **288**

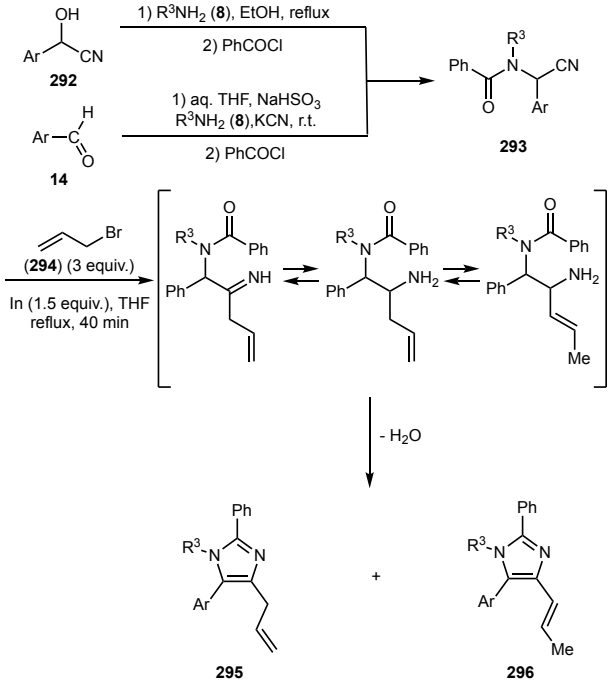
Dehydration of **283a** and **283b** with equimolar amounts of PPh_3, CCl_4 and Et_3N gave resins **284a** and **284b** in almost quantitative yields. The subsequent reaction with arylglyoxals **285**, primary amines **8** and carboxylic acids **286** in a 1 : 1 : 1 mixture of $CHCl_3$, MeOH and pyridine at 60 °C yielded compounds **287**.[235]

Mjalli and coworkers also synthesized 1-isobutyl-2,4-diphenyl-(*N*-butylcarboxamido)-1*H*-imidazole (**291**) in solution via the two-step route shown in Scheme 129 which involved the reaction of phenylglyoxal (**285a**), isobutylamine (**8b**), benzoic acid (**286a**) and *n*-butyl isocyanide (**289**) in MeOH at 23 °C for 2 d and treatment of the resulting compound **290** with $AcONH_4$ in AcOH at 100 °C for 16 h. In this way, compound **291** was obtained in 47.5% yield.[235]



Scheme 129. Two-step synthesis of tetrasubstituted imidazole **291**

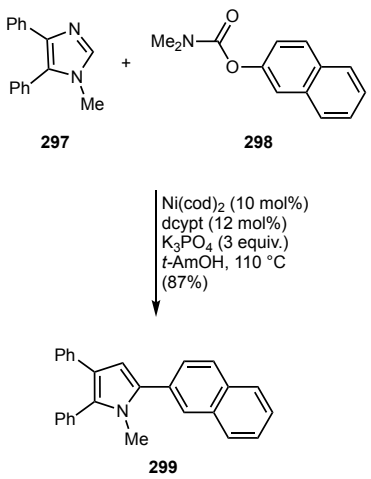
In 2010, J. N. Kim and coworkers reported that mixtures of 1-substituted-4-allyl-5-aryl-2-phenyl-1*H*-imidazoles **295** and 1-substituted 5-aryl-2-phenyl-4-[(*E*)-1-propenyl]-1*H*-imidazoles **286** were available via In-mediated Barbier-type reaction of *N*-benzoyl-α-aminonitriles **293** with allyl bromide (**294**) in THF under followed by a dehydrative cyclization cascade (Scheme 130).[237] The yields of the reaction and the **295**/**296** ratio were found to be dependent on several parameters including the reaction time, the reaction temperature and the amount of indium. The highest combined yields of imidazoles **295** and **296** were obtained using 3.0 equiv of allyl bromide, 1.5 equiv of indium and a reaction time of 40 min. Typical results of this protocol are shown in Scheme 130 in which it is also shown that *N*-benzoyl-α-aminonitriles **293** could be alternatively prepared from α-hydroxynitriles **292** and primary amines **8** in refluxing EtOH and treatment of the resulting compounds with benzoyl chloride[238] or by addition of KCN to the imines generated *in situ* from the corresponding aldehydes **14** and amines **8** in the presence of $NaHSO_3$ and treatment of the resulting compounds with benzoyl chloride.[239]



295	296	R^3	Ar	yield% 295	yield% 296
a	**a**	4-ClC_6H_4	Ph	62	17
b	**b**	Ph	Ph	40	23
c	**c**	4-MeC_6H_4	Ph	30	25
d	**d**	Bn	Ph	36	30
e	**e**	*c*-C_6H_{11}	Ph	40	21
f	**f**	4-FC_6H_4	2-BrC_6H_4	41	27

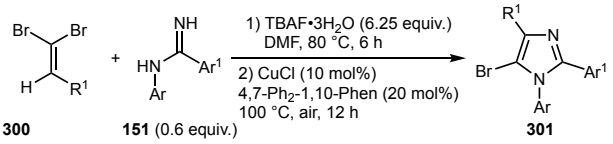
Scheme 130. Synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles **295** and **296**

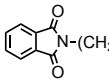
In 2015, Yamaguchi, Itami and coworkers discovered that imidazoles undergo regioselective C-2 arylation with arylcarbamates in *tert*-amyl alcohol at 110 °C in the presence of K_3PO_4 and catalytic amounts of $Ni(OTf)_2$ or $Ni(cod)_2$ and 1,2-bis(dicyclohexylphosphino)ethane (dcype) or 3,4-bis(dicyclohexylphosphino)thiophene (dcypt).[240] These newly developed conditions, which allowed the Ni-catalyzed C–H arylation of 1,3-azoles with phenol derivatives,[241] enabled the synthesis of 4,5-diphenyl-1-methyl-2-(2-naphthyl)-1*H*-imidazole (**299**) in 87% yield by treatment of 4,5-diphenyl-1-methyl-1*H*-imidazole (**296**) with 1.5 equiv of carbamate **298**, 3.0 equiv of K_3PO_4, 10 mol% $Ni(cod)_2$ and 12 mol% dcypt in *tert*-amyl alcohol at 110 °C (Scheme 131).[240] The reaction was thought to involve the oxidative addition of the C–O bond of **298** to a Ni(0) species affording a Ni(II) intermediate. The subsequent base-promoted C–H nickelation of imidazole **297** followed by reductive elimination would furnish the coupling product **299** with regeneration of the reactive Ni(0) species.[240]



Scheme 131. Synthesis of 4,5-diphenyl-1-methyl-2-(2-naphthyl)-1*H*-imidazole (**299**) by Ni(0)-catalyzed direct C-2 arylation of imidazole **297**

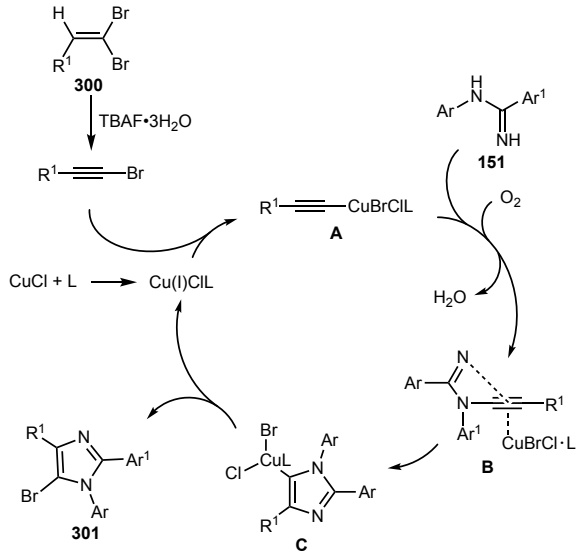
In the same year, Li and coworkers performed a facile regioselective synthesis of a diverse array of 5-bromo-1,2,4-trisubstituted-1*H*-imidazoles **301** in moderate to good yields through a functional group tolerant one-pot process in which 1,1-dibromo-1-alkenes **300** were reacted with 6.25 equiv of TBAF·3H$_2$O in DMF at 80 °C for 6 h and the resulting products were treated with 0.62 equiv of amidines **151**, 10 mol% CuCl and 20 mol% 4,7-diphenyl-1,10-phenanthroline (4,7-Ph$_2$-1,10-Phen) at 100 °C for 12 h under air (Scheme 132).[242]



301	R^1	Ar	Ar^1	yield%
a	4-EtOC$_6$H$_4$	Ph	Ph	51
b	Me$_2$CH-(CH$_2$)$_2$	Ph	Ph	73
c	*n*-C$_6$H$_{13}$	Ph	Ph	75
d	*n*-C$_7$H$_{15}$	Ph	Ph	76
e	c-C$_6$H$_{11}$-CH$_2$	Ph	Ph	71
f	Cl-(CH$_2$)$_3$	Ph	Ph	81
g		Ph	Ph	52
h	*n*-C$_4$H$_9$-C≡C-(CH$_2$)$_2$	Ph	Ph	48
i	*n*-C$_6$H$_{13}$	4-FC$_6$H$_4$	*c*-Pr	82
j	Me$_2$CH-(CH$_2$)$_2$	4-FC$_6$H$_4$	Ph	70
k	*n*-C$_6$H$_{13}$	1-naphthyl	*c*-Pr	68
l	Ph	Ph	Ph	57

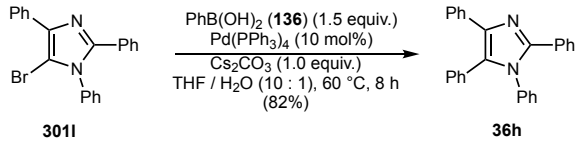
Scheme 132. Synthesis of 5-bromo-1,2,4-trisubstituted-1*H*-imidazoles **301**

The tentative mechanism suggested for this efficient cycloamination reaction commenced with the TBAF·3H$_2$O-mediated dehydrobromination of compounds **300** (Scheme 133).[243] The subsequent oxidative addition of the resulting 1-bromo-1-alkynes to CuCl produced intermediates **A**, which reacted with amidines **151** in the presence of air delivering intermediates **B**. The latter Cu-complexes were proposed to undergo intramolecular 5-*endo-dig* cyclization producing intermediates **C**, which finally could afford compounds **301** by reductive elimination with concomitant formation of Cu(I) (Scheme 133).[242]



Scheme 133. Proposed mechanism for the cycloamination reaction leading to imidazoles **301**

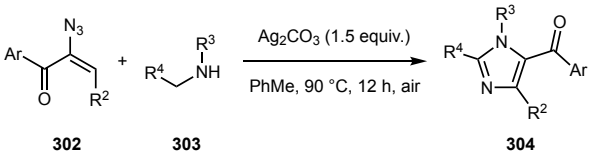
Li and coworkers also described that imidazole **301l** was able to undergo Pd(PPh$_3$)$_4$-catalyzed Suzuki-Miyaura reaction with phenylboronic acid (**136**) in a 10 : 1 mixture of THF and water at 60 °C in the presence of Cs$_2$CO$_3$ to give 1,2,4,5-tetraphenyl-1*H*-imidazole (**36h**) in 82% yield (Scheme 134).[242]



Scheme 134. Synthesis of imidazole **36h** by Suzuki-Miyaura reaction of 5-bromoimidazole **301l**

In 2016, Maurya and coworkers synthesized (1,2,4-triaryl-1*H*-imidazol-5-yl)arylmethanones **304** in high yields and with high atom economy utilizing

the operationally simple Ag_2CO_3-mediated reaction of α-ketovinylazides **302** with secondary amines **303** in toluene at 90 °C (Scheme 135).[244]



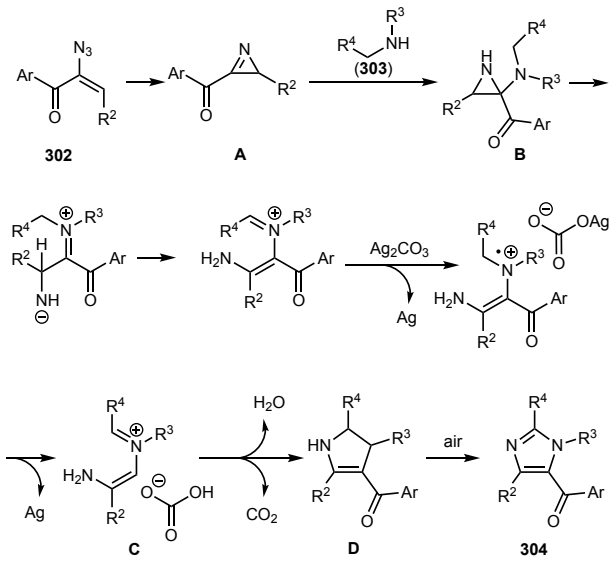
302 303 304

304	R^3	R^4	R^2	Ar	yield%
a	Ph	Ph	4-ClC_6H_4	4-$MeOC_6H_4$	79
b	Ph	Ph	4-$(NO_2)C_6H_4$	Ph	80
c	4-$MeOC_6H_4$	Ph	4-$(NO_2)C_6H_4$	Ph	81
d	Bn	Ph	4-$(NO_2)C_6H_4$	Ph	65

Scheme 135. Synthesis of (1,2,4-triaryl-1*H*-imidazol-5-yl)arylmethanones **304**

Compounds **302**, which unfortunately are potentially shock sensitive and explosive reagents, were prepared according to a previously reported procedure.[245] It deserves also to be noted that after the completion of the Ag_2CO_3-mediated reaction of α-ketovinylazides **302** with amines **303** most of the silver was found to be deposited as silver mirror on the reaction flask.[246] Nevertheless, it could be converted to $AgNO_3$ according to a literature procedure.[246]

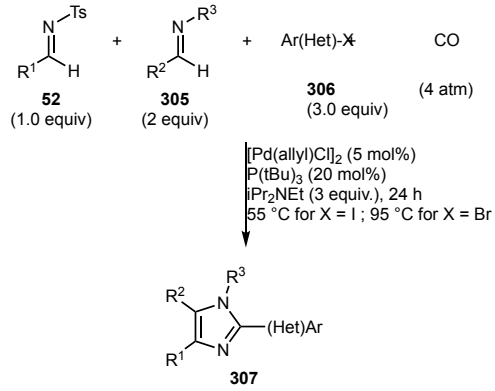
The formation of compounds **304** was rationalized by a mechanism involving the formation of 2*H*-azirines **A** by thermal decomposition of compounds **302** and the subsequent attack of amines **303** to **A** leading to intermediates **B** (Scheme 136). These intermediates were proposed to undergo ring-opening and cyclization via iminium ions **C** providing intermediates **D**. Finally, oxidation by air of intermediates **D** would furnish imidazoles **304**.[244]



302 A B C D 304

Scheme 136. Proposed mechanism for the formation of imidazoles **304**

More recently, Tjutrins and Arndtsen described an efficient one-pot $[Pd(allyl)Cl]_2/P(t\text{-}Bu)_3$-catalyzed synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles of general formula **307** from *N*-tosylimines **52**, aldimines **305**, (hetero)aryl halides **306** and carbon monoxide (Scheme 137).[247]



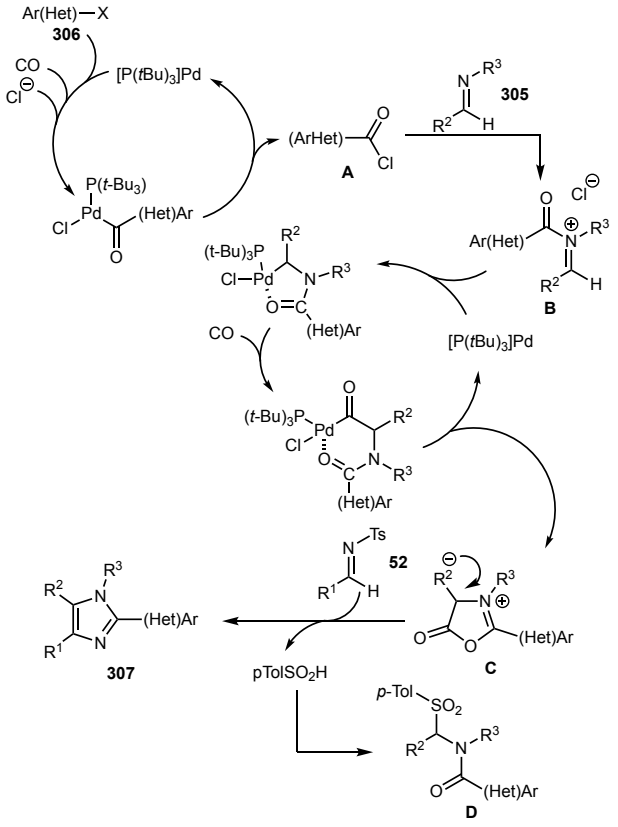
307	R^1	R^2	R^3	(Het)Ar	yield%
a	Ph	4-FC_6H_4	Bn	4-MeC_6H_4	78[a]
b	Ph	3-BrC_6H_4	Et	4-MeC_6H_4	76[a]
c	2-thienyl	4-MeC_6H_4	Et	4-MeC_6H_4	82[a]
d	4-pyridyl	4-MeC_6H_4	Bn	4-MeC_6H_4	46[a]
e	*(E)*-Ph-CH=CH	4-MeC_6H_4	Et	4-MeC_6H_4	74[a]
f	3-BrC_6H_4	4-MeC_6H_4	Et	4-MeC_6H_4	75[a]
g	Ph	4-MeC_6H_4	Et	4-MeC_6H_4	72[b]
h	Ph	4-MeC_6H_4	Et	3-thienyl	56[b]
i	Ph	4-MeC_6H_4	Et	4-$MeSC_6H_4$	78[a]
j	2-furyl	4-MeC_6H_4	Et	4-MeC_6H_4	80[a]
k	*n*-Pr	4-MeC_6H_4	Bn	4-MeC_6H_4	81[a]

[a] Obtained from (hetero)aryl iodide
[b] Obtained from (hetero)aryl bromide

Scheme 137. Synthesis of tetrasubstituted 1*H*-imidazoles **307** from (hetero)aryl halides **306**

Notably, compounds **52**, **305** and **306** could be modulated in this reaction, which was carried out in MeCN in the presence of *i*-Pr_2NEt at 55 °C or at 95 °C for 24 h in the case of (hetero)aryl iodides or bromides, respectively, using reaction vessels pressurized with 4 atm of CO. Representative examples of this novel process to prepare imidazoles with four orthogonal diversification groups are shown in Scheme 137.[247]

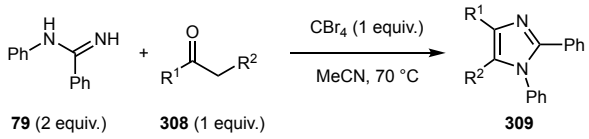
Tjutrins and Arndtsen also proposed that the reaction proceeds via the catalytic cascade illustrated in Scheme 138.



Scheme 138. Proposed mechanism for the formation of imidazoles **307**

The first step of this mechanism would involve the formation of acyl chlorides **A** from (hetero)aryl halides **306**, CO and anions chloride. The subsequent reaction between **A** and imines **305** would form *N*-acyliminium salts **B**, which would react first with [P(*t*-Bu)$_3$]Pd(0) and subsequently would subject to cyclocarbonylation resulting in münchnones **C**. Finally, cycloaddition of *N*-tosylimines **52** would lead to imidazoles **307** and the concomitant liberation of *p*-tolylsulfinic acid. The latter compound would be trapped with iminium salts **B** forming compounds **D**.[247]

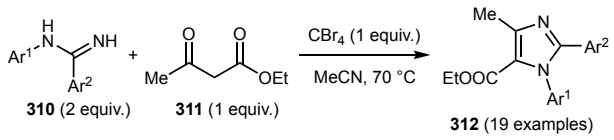
In concluding this section we also consider it appropriate to reporte that, very recently, Huang and coworkers described a facile metal-free synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles **309** through a CBr_4-mediated tandem cyclization of amidines **79** with carbonyl compounds (ketones, β-ketoesters and 1,3-diones) **308** in MeCN at 70 °C. Compounds **309** were so obtained in moderate to good yields (Scheme 139).[248]



309	R^1	R^2	yield%
a	Me	COOEt	81
b	Me	COO*i*Pr	79
c	Me	COO*t*Bu	78
d	Ph	COOEt	77
e	Me	COPh	61
f	Ph	COPh	60
g	Me	Ac	51
h	Ph	Me	40

Scheme 139. Synthesis of imidazoles **309** from amidines **79** and carbonyl compounds **308**

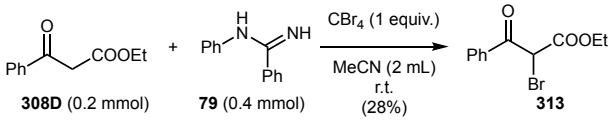
Huang and coworkers also found that high yields of imidazoles of general formula **312** could be generally obtained by CBr_4-mediated reaction of amidines **310** with ethyl 3-oxobutanoate (**311**) (Scheme 140).



Scheme 140. Synthesis of tetrasubstituted-1H-imidazoles **312**

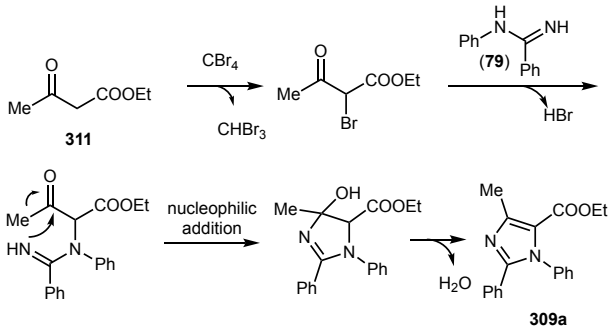
Specifically, amidines **310** derived from anilines with electron-withdrawing or electron-donating groups gave imidazoles **312** in yields ranging from 67 to 84%, but imidazole **312a** with Ar^1= Ph and Ar^2 = 4-$MeOC_6H_4$ was obtained in only 34% yield.[248] Huang and coworkers also discovered that when the reaction of amidine **79** with ethyl acetoacetate (**29**) was conducted in the presence of 2.0 equiv of the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) no inhibition was observed and compound **311a** was obtained in 79% yield. Furthermore, the α-brominated intermediate **313**

was isolated in 28% yield from the CBr_4-mediated reaction between **308d** and **79** in MeCN at room temperature (Scheme 139).



Scheme 141. CBr_4-mediated synthesis of compound **313** from **308d** and **79** in MeCN at room temperature

On the basis of these results and previous literature data,[249] Huang and coworkers proposed the mechanism shown in Scheme 140 for the CBr_4-mediated reaction of ethyl acetoacetate (**311**) and amidine **79**.[248]



Scheme 142. Proposed mechanism for the CBr_4-mediated reaction of ethyl acetoacetate (**311**) and amidine **79** leading to imidazole **309a**

14. Conclusions

In the present review we have described the evolution of the state of the art in the catalytic synthesis of 1,2,4,5-tetrasubstituted-1*H*-imidazoles illustrating the vast array of synthetic methods developed over the past sixty years for the chemo- and regioselective synthesis of this important class of heteroarenes. Particular attention has been paid to summarize and comment the efficient, innovative and sometimes environmentally benign protocols and methods developed in the last decade. also highlighting the practicality and versatility of all these catalytic processes with respect to substrate scope. Besides, the mechanisms proposed for many of the recently developed methods have been summarized.

However, we wish to point out that although the newly developed processes have reached a remarkable level of efficiency and versatility and some of then feature exceptionally mild reaction conditions, several challenges still need to be addressed in the field of the catalytic processes of tetrasubstituted imidazoles. For example, strategies that allow the synthesis of *C*- and *N*-alkenyl heteroarenes by transition metal- or Brønsted /Lewis acid-catalyzed reactions[250] have never been applied to the synthesis of the unexplored classes of *C*- and *N*-alkenyl tetrasubstituted-1*H*-imidazole derivatives. In particular, regioselective oxidative *C*-alkenylation reactions of trisubstituted-1*H*-imidazoles through transition metal-catalyzed twofold C–H bond functionalization have not been developed so far.[251] Other unexplored research fields include i*)* the synthesis of tetrasubstituted *C*-aryl and *C*-alkenyl-1*H*-imidazoles via direct *C*-arylation and *C*-alkenylation reactions mediated by recoverable and recyclable heterogeneous catalysts;[252] and *ii)* the synthesis of fully substituted bis-imidazole derivatives via transition metal-catalyzed oxidative C–H/C–H cross-coupling between two trisubstituted-1*H*-imidazoles.[253] Nevertheless, we hope that the data of this review will stimulate the interest of organic and medicinal chemists in paving the way for innovative realization in this rapidly expanding field of research. The substantial and continuing interest in this area of research is on the other hand witnessed by numerous studies published after we had finished writing of this review. Some of these literature data have been listed in reference 254.

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