CHEMICAL REVIEWS

REVIEW

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Synthetic Routes to N-Heterocyclic Carbene Precursors

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1. INTRODUCTION

N-Heterocyclic carbenes (NHCs) are defined as singlet carbenes, in which the divalent carbenic center is connected directly to at least one nitrogen atom within the heterocycle.[1,2] Wanzlick originally suggested their existence in the early 1960s[3] and proposed a practical way to generate them *in situ*. This early finding paved the way to their use as ligands in organometallic chemistry, as originally described in the seminal reports by Wanzlick[4] and Öfele[5] in 1968 and in the extensive work of Lappert in the 1970s and 1980s.[6] Nevertheless, the original chemists' perception of nucleophilic carbenes as elusive odd laboratory curiosities changed only in 1988 with the benchmark report by Bertrand and colleagues[7] of the first stable (phosphino)(silyl)carbene and in 1991 with the isolation and full characterization by Arduengo and co-workers of the stable, free NHC 1,3-di(adamantyl)imidazol-2-ylidene (IAd), obtained by deprotonation of its imidazolium precursor.[8]

Contrary to other carbenes, which are generally found to be electrophilic, N-heterocyclic carbenes are electron-rich nucleophilic species in which the carbene center benefits from the stabilization associated with both the σ-electron-withdrawing and π-electron-donating character of the nitrogen centers. Due to their strong σ-electron-donating properties, NHC ligands form stronger bonds with metal centers than most classical ligands, such as phosphines, thus giving transition metal complexes that are generally resistant to decomposition and can thus be used as precatalysts without an excess of ligand.[9] A further advantage for catalytic purposes rests on a better steric protection of the active site within the inner metal's coordination sphere, because the exocyclic nitrogen substituents of the NHC shield the metal center in a fence- or

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Chart 1. N-Heterocyclic Structures Taken into Account in This Review

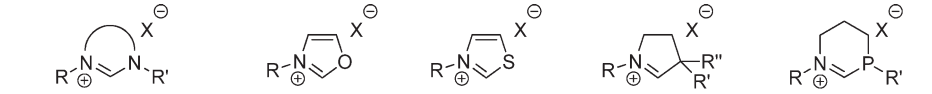
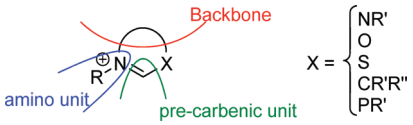
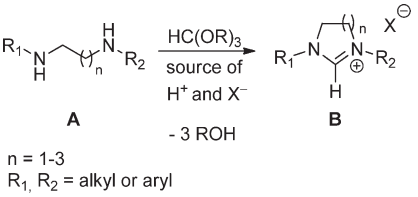


Chart 2. Schematic Differentiation and Classification of General Synthetic Pathways to NHC Precursors, Based on the Nature of the Unit Introduced in the Final Ring-Closing Step



Scheme 1. General Route to the Cyclic Formamidinium Salt B by Condensation of a Diamine with Trialkyl Orthoformate



fan-like fashion, more efficiently than a tertiary phosphine can do with its cone angle pointing away from the metal center.

These beneficial features have contributed to the recognition of NHCs, first as ubiquitous ligands in organometallic chemistry,[10] as evidenced by numerous applications ranging from homogeneous catalysis to material and medicinal sciences,[11] and second in their own right as excellent nucleophilic organocatalysts.[12]

These successes have motivated intense research efforts toward the design and development of a growing diversity of fascinating new NHC architectures, where it appears that *the real challenge in the design of a given N-heterocyclic carbene rests on the construction of its precursor, almost systematically implying a critical cyclization reaction.* Because the deprotonation of the heterocyclic ring precursors is by far the most commonly used method to access a free or ligated NHC, this review will only focus on the synthesis of such cationic heterocycles. Other methods for obtaining NHCs include (i) reduction of thiourea with molten potassium in boiling THF,[13] (ii) vacuum pyrolysis of an NHC−volatile compound adduct (like MeOH, $CHCl_3$, CHF_3, C_6F_5H),[14] (iii) *in situ* release of NHC from NHC−CO_2 or NHC−metal (Sn^{II}, Mg^{II}, Zn^{II}) adducts,[15] and (iv) reduction of a chloroformamidinium salt with $Hg(TMS)_2$[16] or with Pd(0) and Ni(0) complexes.[17] Nevertheless, the starting NHC−substrate adducts used in methods ii and iii are often derived from the corresponding azolium salts and will thus be treated in this review. The synthesis of the thioureas, substrates of methods i and iv will not be included due to the relative narrow applicability scope and limited examples of such methods.

Accordingly, the present review will cover the syntheses of cyclic formamidinium salts **A**, precursors of diaminocarbenes (whatever the nature of the backbone is), of oxazolium salts **B** and thiazolium salts **C**, of pyrrolidinium salts **D** (precursors of cyclic (alkyl)(amino)carbenes (CAAC)), and of phosphazinium salts **E** (precursors of cyclic (amino)(phosphino)carbenes) (Chart 1).[18]

An obvious and straightforward strategy to access these compounds consists in the quaternization of a nitrogen atom on a pre-existing neutral N-substituted imidazole, oxazole, or thiazole. However, because the syntheses of these heterocyclic compounds are well-documented in the literature,[19−21] the present review will focus on the direct formation of the cationic (or mesoionic) cycle through a cyclization step.

Considering that an NHC precursor is constructed by assembly of three distinct subunits, namely, (i) a precarbenic unit, (ii) an amino unit, and (iii) a backbone functionality (Chart 2), the myriad of synthetic protocols that have been reported so far can be classified in a simple and logical way upon consideration of the nature of the latest subunit being installed in the final cyclization step:

1. Ring closure by introduction of the precarbenic unit.
2. Ring closure by linkage of the backbone to the preassembled precarbenic and amino units.
3. Ring closure by introduction of the amino moiety.

2. CYCLIZATION BY INTRODUCTION OF THE PRECARBENIC ATOM MOIETY

Introduction of the C_1 precarbenic unit in the final ring-closing stage is still the most widely used strategy to NHC precursors, since it is generally high-yielding and easy to perform and tolerates various substituents.

Depending on the desired core of the N-heterocyclic carbene precursor, several reagents that allow introduction of the carbenic carbon-moiety have been identified. In this section, we will give an overview of the different possibilities, along with representative examples.

2.1. Trialkyl Orthoformate ($HC(OR)_3$) as the Precarbenic Unit

In 1991, Saba and Kaloustian reported that treatment of *N,N′*-disubstituted-α-to-ω-alkanediamines **A** with trialkyl orthoformate in the presence of a source of protons and anions leads to the corresponding cyclic formamidinium salt **B**, generally obtained in high yield (>90%) as shown in Scheme 1.[22] This method was also found to work efficiently for the synthesis of triazolium salts, a special case described at the end of this section.

Such a reaction constitutes the final step of a huge number of NHC-precursor syntheses since it is usually high-yielding and easy to perform. Indeed, the salts generally precipitate and can thus be recovered by simple filtration. Formally, any tethered secondary diamine may thus be converted into the corresponding cyclic formamidinium salt, the major issue being to find a suitable synthesis for the starting diamine **A** (Scheme 2). Depending on the characteristics of the target NHC precursor (nature of the linking backbone and of the nitrogen substituents, presence of a chirality or of annelated cycles, etc.), several synthetic pathways to substituted diamines have been developed, which could be sorted into six major strategies: (a) formation of a bisimine and reduction; (b) bisacylation of two amines and reduction; (c) monoalkylation and monoacylation of two amines

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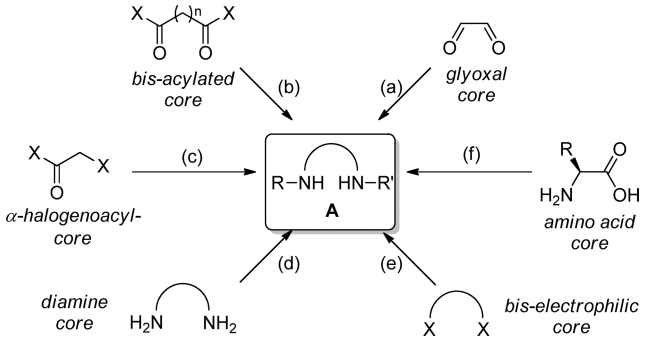
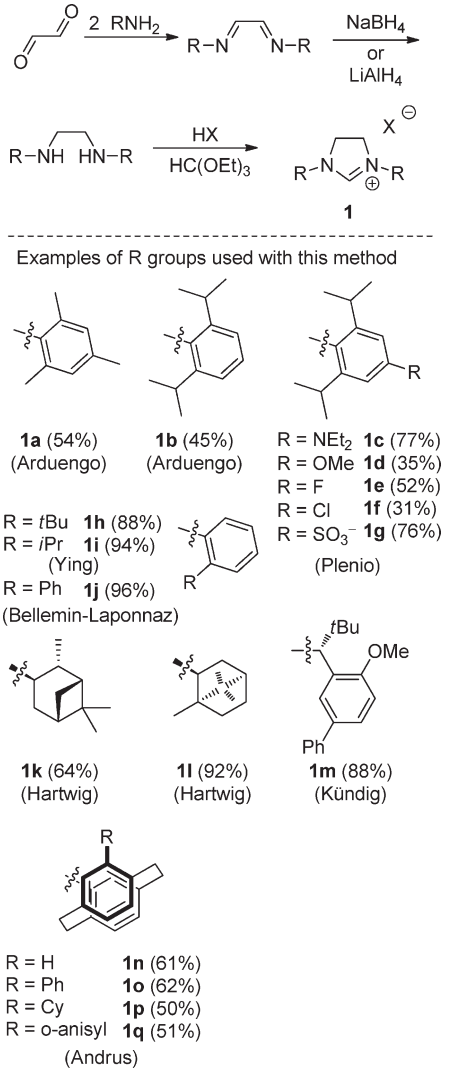
Scheme 2. Major Synthetic Strategies To Access the *N,N′*-Disubstituted Tethered Diamines

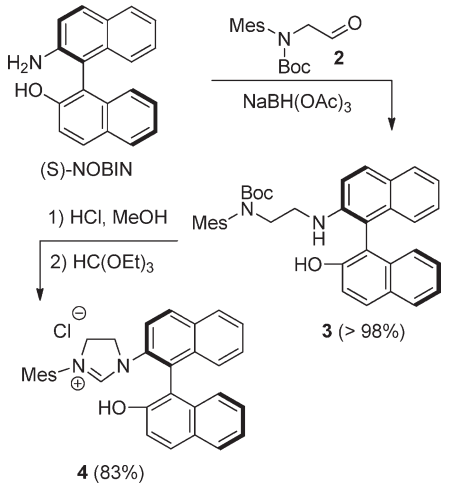


Scheme 3. Synthesis of the Symmetrical Imidazolinium Chlorides 1a−q in a Three-Step Sequence: Glyoxal Condensation with an Arylamine, Reduction of the Resulting Diimine, and Cyclization with Triethyl Orthoformate



followed by reduction; (d) substitution on an existing diamine core; (e) substitution of a bis-electrophilic core by amines; (f) use of an α-amino acid as building block.

Scheme 4. Synthesis of the Unsymmetrical, Chiral Imidazolinium Chloride 4 According to Hoveyda[a]



[a] Mes = 2,4,6-trimethylphenyl.

2.1.1. Condensation−Reduction Route. The synthesis of symmetrical imidazolinium salts in a three-step sequence following pathway a in Scheme 2 was originally described by Arduengo and co-workers in 1999.[23] In a general synthetic protocol, a diimine is first formed by condensation of an aryl- or alkylamine with glyoxal and subsequently reduced to the corresponding diamine, isolated as the free base or as the dihydrochloride salt at this stage. Cyclization occurs using triethyl orthoformate as the C_1-building block (and one equivalent of acid if starting from the free diamine) with formation of the corresponding imidazolinium salt **1** (Scheme 3).

This synthetic route now remains the most popular standard protocol to access common imidazolinium salts, since it is applicable to a wide variety of primary amines as illustrated by the selected examples provided in Scheme 3. For example, variation of the aryl group (e.g., 1-naphthyl, 3,5-dimethylphenyl, 4-biphenyl, 2-methylphenyl, 2,6-dimethylphenyl) was studied by several authors including Noels and co-workers,[24] Plenio and co-workers,[25] who generated a series of symmetrical diarylimidazolinium salts (**1c**−**g**) bearing various *para* substituents, Ying and co-workers,[26] and Bellemin-Laponnaz and co-workers[27] with mono, *ortho*-substituted aryl groups as nitrogen substituents (**1h**−**j**). A number of C_2-symmetric chiral imidazolinium salts bearing an asymmetric α-carbon atom on nitrogen were also prepared starting from the corresponding enantiopure alkylamine (**1k**−**m**),[28,29] and even bearing extremely bulky, chiral *para*-cyclophanic moieties as substituents (**1n**−**q**).[30] Finally, other imidazolinium salts were prepared by this method, which is not limited to the above representative examples.[31] Unfortunately, given that the first condensation step, an equilibrated reaction, is reversible, mixing glyoxal with two different amines always leads to a statistical distribution of the three expected diimine products, thereby restricting the scope of the method to the case of symmetrical imidazolinium salts. Nevertheless, Hoveyda and co-workers were able to apply the method to the synthesis of the unsymmetrical (and chiral) imidazolinium salt **4** from (*S*)-NOBIN in a two-step sequence with the Boc-protected amino aldehyde **2** as the key coupling partner (Scheme 4).[32] Deprotection of the Boc group occurred during the formation of

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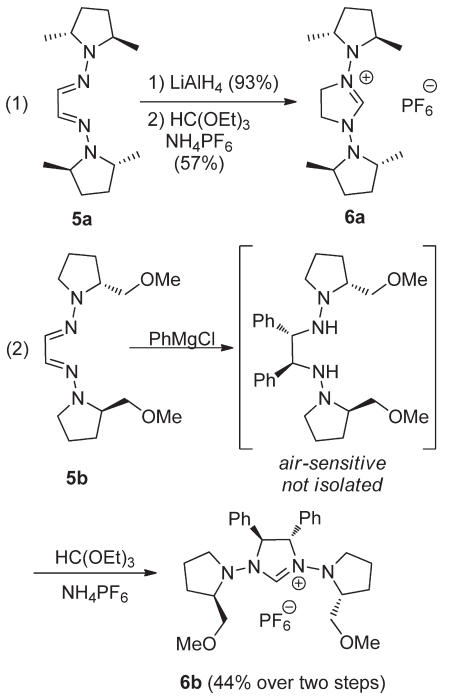
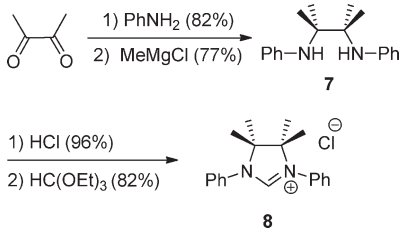
Scheme 5. Synthesis of the 1,3-Bis(*N*,*N*-dialkylamino)-imidazolinium Salts 6a and 6b Derived from Chiral *N*,*N*-Dialkylhydrazines



Scheme 6. Synthesis of the Imidazolinium Salt 8 Incorporating a Tetra-substituted Backbone

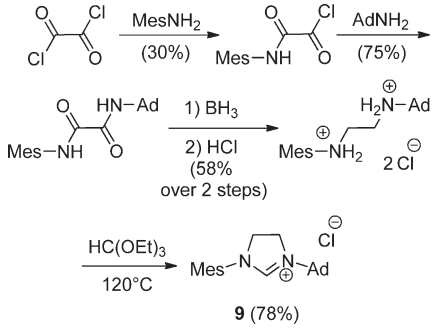


the dihydrochloride salt of the diamine. However, compound **2** had to be synthesized first from mesitylamine in a three-step route, which makes the overall synthetic procedure quite long.

Lassaletta and co-workers also applied this method to the cyclization of bis-hydrazine to yield 1,3-bis(*N*,*N*-dialkylamino)-imidazolinium salt **6a**, providing a new family of chiral N-heterocyclic carbene precursors (Scheme 5, eq 1).[33] Noticeably, the introduction of a chiral backbone into the target structure may also be accomplished using proline derivatives. For example, the stereoselective addition of PhMgCl to glyoxal RAMP bis-hydrazone **5b**,[34] followed by the direct treatment of the air-sensitive intermediate bis-hydrazine with $HC(OEt)_3$ and NH_4PF_6 afforded **6b** in 44% yield.

Following the same strategy, Grubbs and co-workers reported the introduction of a tetra-substituted backbone on the imidazolinium salt.[35] Condensation of 2,3-butanedione with aniline, followed by treatment of the resulting diimine with a methyl Grignard reagent, afforded the corresponding diamine **7**, which was subsequently converted into the imidazolinium salt **8** in the presence of an excess of triethyl orthoformate (Scheme 6). The same group also reported the introduction of an allyl group by reaction of the Grignard reagent with the diazabutadiene compound followed by reduction of the second imine function.[36]

Scheme 7. Synthesis of 1-Adamantyl-3-mesitylimidazolinium Chloride 9, According to Mol and Co-workers[a]



[a] Mes = 2,4,6-trimethylphenyl; Ad = 1-adamantyl.

2.1.2. Bisacylation/Reduction Route. The use of oxalyl chloride or derivatives such as monoethyl oxalyl chloride to synthesize *N*,*N*′-disubstituted-1,2-diamines retains the advantages of Arduengo's methodology in that it requires only inexpensive reagents and is practical for large-scale syntheses, while providing increased modularity and flexibility, allowing in particular the synthesis of unsymmetrical imidazoliniums. Mol and co-workers first reported the synthesis of the mixed adamantyl/mesityl N-heterocyclic precursor 1-(1-adamantyl)-3-mesityl-imidazolinium chloride **9** via reaction of an amine with oxalyl chloride followed by the reaction of a second amine with the intermediate acyl chloride (Scheme 7).[37] The oxalamide thus formed was subsequently reduced and cyclized using triethyl orthoformate. Since control of mono- vs bisamidation with oxalyl chloride could be sometimes problematic, ethyl oxalyl chloride was alternatively used to give access to unsymmetrical imidazolinium salts.[38]

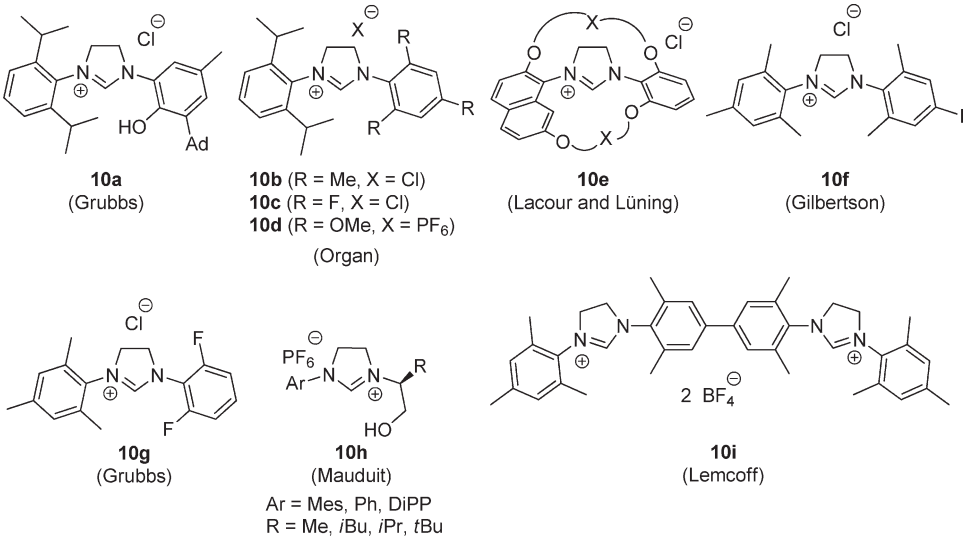
Due to its simplicity and its tolerance to functional groups, this approach is now the most widely used strategy for making unsymmetrical imidazolinium salts, and some representative examples are described in Chart 3. These include imidazoliniums bearing aryl groups with different steric or electronic properties (**10b**−**g**),[39] various functional groups (**10a**),[38a,40] or a chiral alkyl chain derived from amino alcohols (**10h**),[41] and even complex bis-imidazolinium structures (**10i**)[42] could be reached with this method.

Grubbs and co-workers reported an analogous synthesis of the six-membered, bulky 1,3-dimesityl-5,5-dimethyltetrahydropyrimidinium salt **11** in good yields starting from mesitylamine and dimethylmalonyl dichloride (Scheme 8).[43]

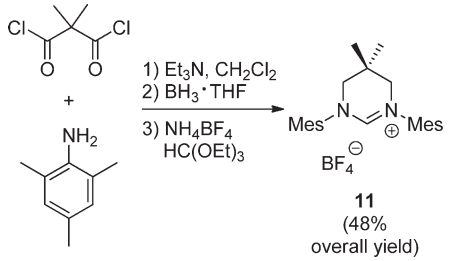
2.1.3. Acylation−Alkylation/Reduction Route. Kotschy and co-workers reported the modular synthesis of N-heterocyclic carbene precursors starting from chloroacetyl chloride (Scheme 9).[44] In a first step, nucleophilic addition of an amine to chloroacetyl chloride followed by nucleophilic substitution of the resulting α-chloroacetamide by a second amine furnished the corresponding α-amino acetamides **12**. After reduction with lithium aluminum hydride, treatment with trimethyl orthoformate in the presence of ammonium tetrafluoroborate afforded various imidazolinium salts **13** (Scheme 9). The yield of each step is good, and the method is applicable to a large variety of amines and anilines (R, R′ = aryl, alkyl, chiral alkyl groups).

The major advantage of this method compared with the earlier one resides in the possibility to differentiate the two carbon atoms in

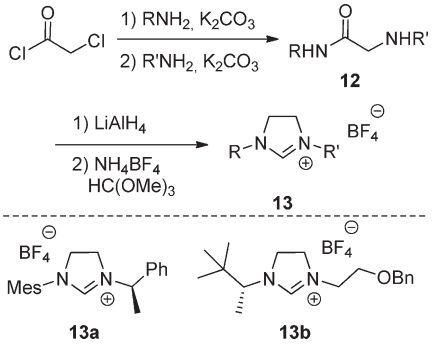
Chart 3. Unsymmetrical Imidazolinium Salts Obtained by the "Oxalic" Route



Scheme 8. Synthesis of Tetrahydropyrimidinium Salt 11



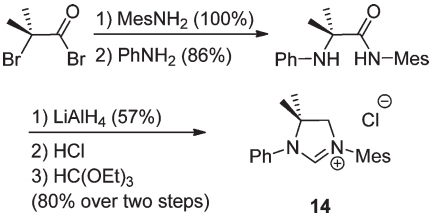
Scheme 9. Synthesis of the Imidazolinium Salts 13 Starting from Chloroacetyl Chloride According to Kotschy



positions 4 and 5 of the imidazolinium core. Grubbs and colleagues applied this strategy to the synthesis of the unsymmetrically substituted N-heterocyclic carbene precursor **14** bearing a *gem*-dimethyl group adjacent to the *N*-phenyl substituent (Scheme 10).[35] The desired imidazolinium salt was obtained in good yield from 2-bromo-2-methylpropionyl bromide.

2.1.4. Starting from a Preformed Diamine Core. Primary diamines may be used as readily available building blocks to access various N-containing heterocyclic salts (pathway d, Scheme 2), because many of these amines are commercially

Scheme 10. Synthesis of 14 Bearing a *gem*-Dimethyl Group Adjacent to the *N*-Phenyl Substituent



available or easily obtained by a straightforward procedure.[45] Depending on the nature of the substituents (alkyl or aryl group), two main distinct methods were used for the monofunctionalization of each amine as depicted in Scheme 11. The first one consists of an indirect reductive amination as illustrated by the synthesis of 1,3-dibenzylimidazolinium bromide **15**.[46] Compared with direct alkylation, it has the obvious advantage that it stops at the stage of mono-N-substitution. However, carbon atoms directly connected to the nitrogen atoms are necessarily primary (i.e., $-CH_3$) or secondary (i.e., $-CH_2R$) and this precludes any introduction of chirality in close proximity to the heterocyclic imidazolinium core. The second method for functionalization, the Buchwald−Hartwig amination[47] gives easy access to valuable *N*,*N*′-diarylimidazolinium salts, as illustrated by the synthesis of compound **17**, which was the first report based on this strategy.[48] Indeed, reaction of (1*R*,2*R*)-1,2-diaminocyclohexane with 2 equiv of 2-bromotoluene in the presence of NaO*t*Bu and a catalytic amount of $Pd(OAc)_2$ and *rac*-BINAP led to the corresponding secondary diamine **16** in 67% yield. Treatment with triethyl orthoformate and ammonium tetrafluoroborate thus gave the imidazolinium tetrafluoroborate salt **17** in 90% yield.

Hoveyda and co-workers showed that the latest method may be used to synthesize unsymmetrical chiral carbene precursors. Thus, treatment of (1*R*,2*R*)-diphenylethylenediamine with 1 equiv of aryl iodide in the presence of palladium catalyst followed by addition of an excess of mesityl bromide led to the formation of the corresponding diamine **18** in 65% overall yield. Deprotection of the methyl ether and treatment with HCl and triethyl

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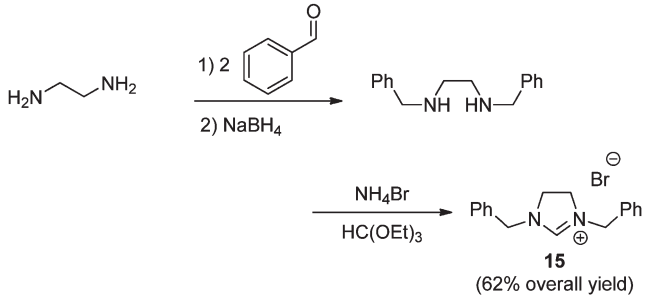
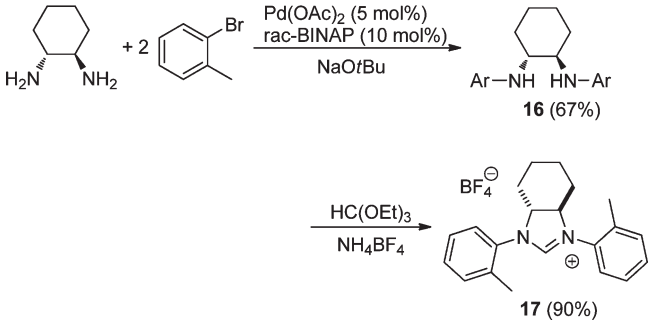
Scheme 11. The Two Major Pathways for the Monosubstitution of the Primary Diamines and Subsequent Cyclization

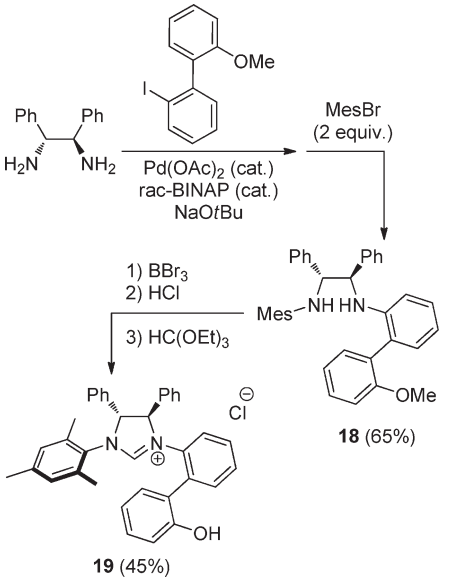
Pathway 1: indirect reductive amination



Pathway 2: Buchwald-Hartwig amination



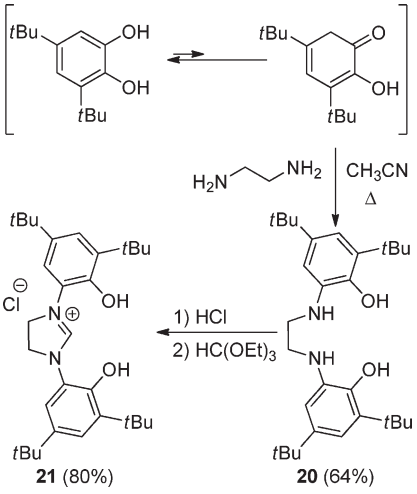
Scheme 12. Synthesis of the Unsymmetrical Imidazolinium Salt 19 via Successive Buchwald−Hartwig Arylations on (1*R*,2*R*)-Diphenylethylenediamine



orthoformate gave the desired chiral enantiopure imidazolinium **19** in 45% yield (Scheme 12).[49]

Based on a similar strategy following pathway 1, Bellemin-Laponnaz, Dagorne, and co-workers reported the synthesis of the potentially tridentate pincer-type NHC preligand **21**,[50] where the key step is the coupling between 3,5-di-*tert*-butylcatechol and ethylenediamine to form *N*,*N*-bis(3,5-di-*tert*-butyl-2-hydroxyphenyl)-ethylenediamine **20** (Scheme 13).[51] The originality of this approach is to take advantage of the keto−enol equilibrium in the starting catechol.

Scheme 13. Synthesis of the Symmetrical Bisaryloxide Imidazolinium Chloride 21 Starting from 3,5-Di-*tert*-butylcatechol and Ethylenediamine



This strategy is particularly efficient for the construction of chiral NHC precursors possessing a chiral backbone and has been applied to a huge number of chiral imidazolinium salts. Because the chiral information contained in the backbone has to be transmitted to the active space at the metal center of catalyst by means of the two nitrogen substituents, the latter are often a sterically hindered dissymmetric aryl group such as **22** or a bulky benzyl-type substituent such as **23** (Chart 4). By steric repulsion, the two N-substituents arrange in such a way that they reflect the C_2-symmetry of the backbone.[52] One of the nitrogen arms could also contain a second coordinating functionality in order to provide a bidentate ligand and to rigidify the chiral structure of the catalytically active center (compounds **24** and **25**, Chart 4 and compound **19**, Scheme 12).[53] All but a few of these imidazolinium salts derive from enantiopure 1,2-diphenylethylenediamine, but during the past few years, some other chiral skeletons have appeared, as illustrated by the camphor-derived chiral NHC precursor **26**.[54] It constitutes also one of the methods of choice for elaborating bigger cationic heterocyclic precursors or ones bearing a particular backbone. The application scope is illustrated by the selected examples depicted in Chart 4. First, cyclic formamidiniums with a fully saturated backbone (such as **27**) were synthesized by Cavell.[55] Richeson and colleagues reported in 2003 a novel family of carbenes based on the perimidine core.[56] The NHC precursors **28a**−**c** were derived from the same *N*-isopropyl-1,8-diaminonaphtalene intermediate, with the second N-substituent being attached either by reaction of the amine group with an electrophilic compound (acetone for **28a**, pivaloyl chloride for **28b**) followed by reduction with lithium aluminum hydride or with 3,5-dimethylphenyl iodide using Ullmann's coupling conditions for **28c**. Stahl and coworkers reported the synthesis of constrained 1,3-dialkyldiazepinium salts **29** and **30** from 2,2′-diaminobiphenyl (**29**) or from (*R*)-2,2′-diaminobinaphthyl (**30**).[57] The NHC ligands derived from such seven-membered amidinium exhibit a torsional twist that may be of interest for the development of efficient asymmetric catalysts. Interestingly, the authors noticed that the

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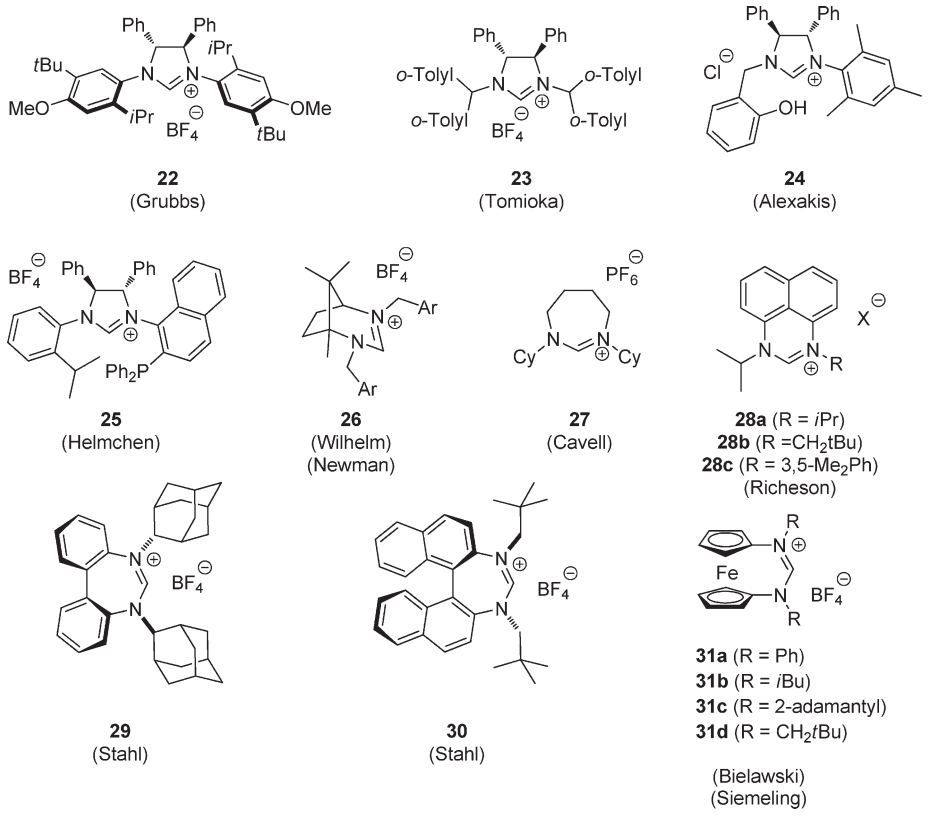
Chart 4. Scope of the Synthesis of NHC Precursors from Preformed Diamines

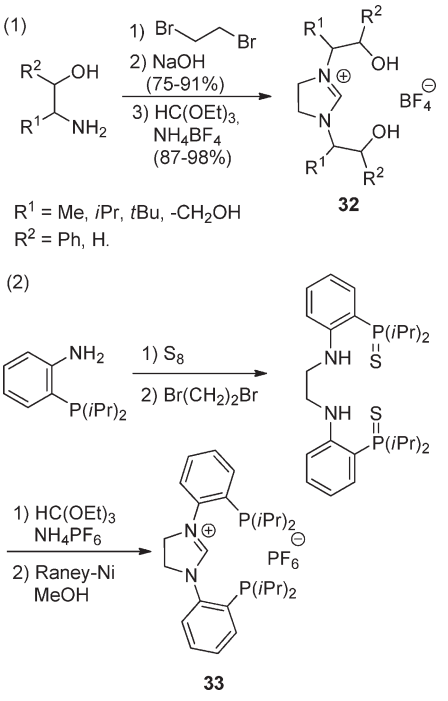


cyclization was unsuccessful for *N,N′*-diaryl amines. Such a lack of reactivity was assumed to be a consequence of the weak nucleophilicity of the diaryl-subtituted nitrogen atoms in this case. Finally, Bielawski and Siemeling independently developed the chemistry of diaminocarbene[3]ferrocenophanes derived from the formamidinium **31**.[58]

2.1.5. Reaction on a Bis-electrophilic Core. Primary amines react rapidly with alkyl halides to yield secondary ammonium salts, $R_2NH_2^+X^-$. Although it is known that these reactions do not stop cleanly after a single alkylation has occurred, direct alkylation of amines with 1,2-dibromoethane appears to be an efficient way to access the imidazolinium salts. Wilhelm and co-workers used this method to synthesize chiral imidazolinium salts bearing two hydroxy substituents (Scheme 14, eq 1).[59] The reaction of amino alcohols and 1,2-dibromoethane at 100 °C for 10 h (neat conditions) followed by a workup under basic conditions led to the corresponding bis(amino alcohol) in good yields. The imidazolinium salts **32** were then prepared by treatment with triethyl orthoformate in the presence of ammonium tetrafluoroborate. In the same manner, the saturated NHC-based PCP preligand **33** was obtained by alkylation of *o*-diisopropylphosphinoaniline, protected as a phosphine sulfide (Scheme 14, eq 2), under neat conditions. The classical trialkylorthoformate route followed by reduction of the sulfides led to the bis(phosphine) imidazolinium salt **33**.[60]

Gautier and co-workers recently showed that the "classical" SIMes imidazolinium salt could be obtained in 53% overall yield by using this alkylating route. Reaction of mesitylamine with 1,2-dibromoethane was efficiently conducted in methanol as solvent.[61]

Scheme 14. Synthesis of Tridendate Preligands 32 and 33 Starting from 1,2-Dibromoethane



Plenio and co-workers used an indirect approach to synthesize unsymmetrical imidazolinium salts. Starting from the

dx.doi.org/10.1021/cr100328e |*Chem. Rev.* 2011, 111, 2705–2733

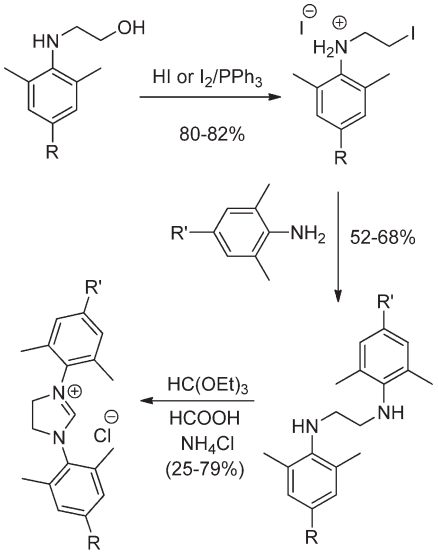
N-β-hydroxyethyl-substituted 2,6-dimethylanilines, treatment with HI or Ph_3P/I_2 generates the respective *N*-β-iodoethyl anilinium salt. Subsequent nucleophilic substitution of the iodide by 2,6-dimethylanilines (4-R = Br or NEt_2) affords the diamines, which then undergo cyclization to the corresponding imidazolinium salts **34a**−**c** using triethyl orthoformate (Scheme 15).[25b] The latest two steps were carried out in a one-pot reaction by Gilbertson and co-workers.[62] This approach is compatible with a number of potentially reactive groups (i.e., amino alcohols, amino phenols) and provides extremely easy access to unsymmetrical imidazolinium salts.

Benzimidazolium salts are also important precursors of NHCs. The first reported literature methods for the synthesis of such salts focused on N-alkylation reactions, which are inappropriate for the introduction of chirality directly at the carbon alpha to the nitrogen atom. Diver and collaborators reported a versatile synthesis of these compounds based on a successive Buchwald−Hartwig amination on 1,2-dibromobenzene and ring closure with triethyl orthoformate.[63] They particularly focused on the introduction of α-chiral primary amines onto the nitrogen substituents to form the chiral benzimidazolium salts **35a**−**e** as precursors of asymmetric NHC-based catalysts (Scheme 16).

Bielawski and co-workers extended this synthetic methodology to the benzobis(imidazolium) salts **37** as proligands for bimetallic carbene complexes via the formation of 1,2,4,5-tetrakis(alkyl- and arylamino)benzenes (Scheme 17).[64] The Buchwald−Hartwig amination reaction proved to be efficient with various amines including 1-adamantylamine, *tert*-butylamine, aniline, relatively bulky mesitylamine, and electron-rich *o*-anisidine. Ring closure was carried out by subjecting tetraamines **36** to acidified triethyl orthoformate solutions at high temperatures. It should be noted that the mesitylated derivative did not afford the corresponding benzobis(imidazolium) salt.

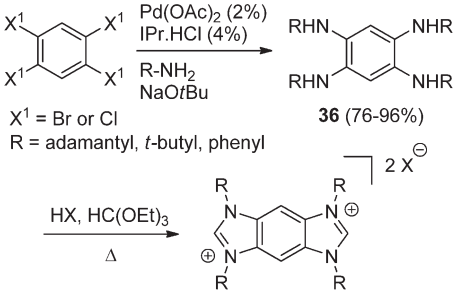
Finally, Heinicke and co-workers reported the synthesis of a quinoxaline-annelated diaminocarbene, which derived from the azolium **39** (Scheme 18).[65] Here, the intermediate diamine **38** was simply obtained by double nucleophilic aromatic substitu-

Scheme 15. Synthesis of Unsymmetrical Imidazolinium Salts 34 via Successive Nucleophilic Substitutions of Halides According to Plenio et al.



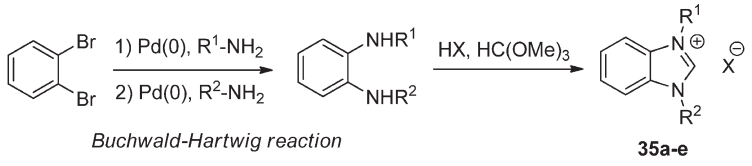
34a: R = H, R' = NEt_2
34b: R = H, R' = Br
34c: R = Br, R' = NEt_2

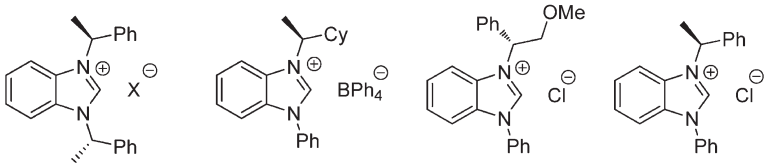
Scheme 17. Synthesis of the Benzo-bis(imidazolium) Salt 37 Using Successive Buchwald−Hartwig Amination/Triethyl Orthoformate Cyclization



37 (51-92%)
X = BF_4 or Cl

Scheme 16. Synthesis of Chiral Benzimidazolium Salts 35 Using the Tandem Buchwald−Hartwig Substitution−Triethyl Orthoformate Cyclization





35a: X = Cl, 58%
35b: X = ClO_4, 51%
35c: 50%
35d: 70%
35e: 75%

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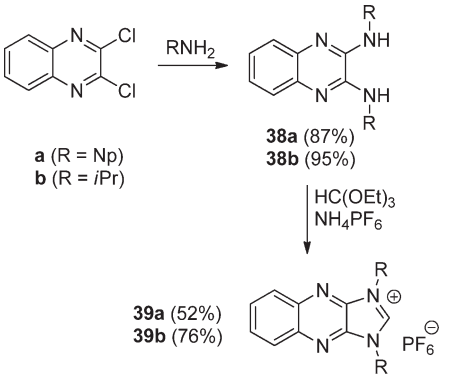
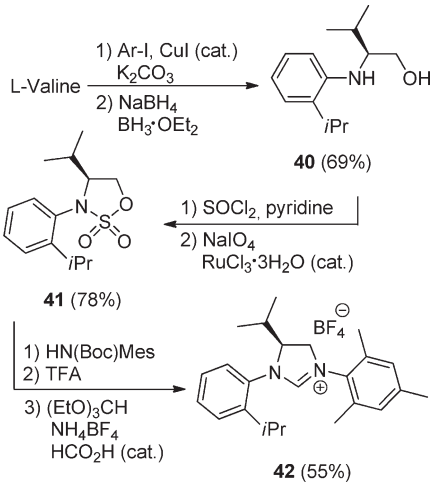
Scheme 18. Synthesis of Quinoxaline-Annelated Imidazolium Salt 39



Scheme 19. Synthesis of Unsymmetrically Substituted NHC Precursors 42

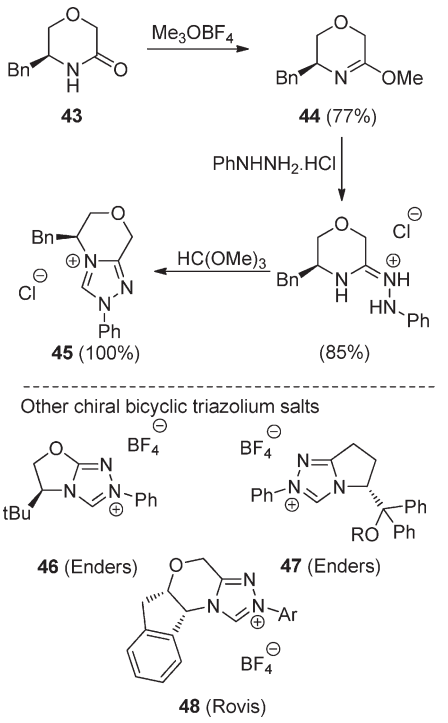


tion of 2,3-dichloroquinoxaline by alkylamines (neopentylamine or isopropylamine).

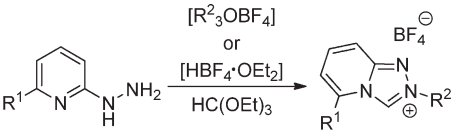
2.1.6. α-Amino Acids as Building Blocks. Blechert and co-workers recently described a practical method for the synthesis of chiral unsymmetrically substituted NHC systems (Scheme 19). The sulfamidate **41** was obtained in four steps and 54% overall yield starting from L-valine. Nucleophilic attack using Boc-mesidine followed by triethyl orthoformate cyclization gave the desired salt **42** in 55% (three steps).[66] Smith also reported the synthesis of imidazolinium salts from L-phenylalanine and L-valine, but this protocol suffers from a lack of generality.[52b]

The introduction of the "precarbenic" fragment using trialkyl orthoformate under acidic conditions is now a well-developed procedure, applicable to imidazolinium, benzimidazolium, tetrahydropyrimidinium, and diazepinium salts as well as to more complex structures. For a specific substrate, investigators have at their disposal a palette of methods, each having its own advantages and limitations. For example, it should be noted that no reduction is involved in pathways d and e (Scheme 2), rendering them suitable for substituents sensitive toward reduction. Thus, these methods are therefore complementary to the pathways a−c.

Scheme 20. Synthesis of Chiral Bicyclic Triazolium Chloride 45 by Leeper and Other Examples of Bicyclic Triazolium Structures



Scheme 21. Synthesis of Pyrido-annulated Triazolium Salts 49



49a: R^1 = H, R^2 = Me, 86%
49b: R^1 = H, R^2 = Et, 91% (86% with HBF_4·Et_2O)
49c: R^1 = Me, R^2 = Et, 65% (81% with HBF_4·Et_2O)

2.1.7. Triazolium Salts and Benzoxazolium Salts. Cyclization using trialkyl orthoformates also proved to be efficient for the synthesis of triazolium and benzoxazolium salts, and this section will deal with their synthesis.[67] In 1998, Leeper and colleagues reported the first synthesis of an enantiopure bicyclic triazolium in a three-step sequence starting from lactam **43**, derived from L-phenylalaninol (Scheme 20).[68] After activation of the amide function by methylation with Meerwein's reagent to form the methyl iminoester **44**, nucleophilic addition of phenylhydrazine hydrochloride followed by cyclization using trimethyl orthoformate yielded the triazolium salt **45**. For example, chiral enantiopure oxazolidinone- or pyroglutamic acid-based systems (respectively, **46**[69] and **47**[70]) or amino indanol-based triazolium salts **48**[71] were synthesized by this method.

Pyrido-annulated triazolium salts **49a−c** were prepared by You and co-workers, using a one-pot procedure. Reaction of the commercially available hydrazine with trialkyloxonium in the presence of trialkyl orthoformate gave directly the desired compound in high yield (Scheme 21). Alternatively, the alkylation

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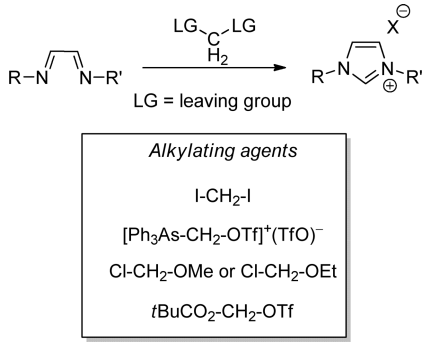
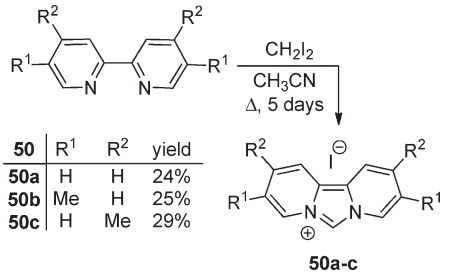
Scheme 22. Formation of Imidazolium Salts by Means of 1,1-Bis(electrophile) Compounds



Scheme 23. Synthesis of Dipyridoimidazolium Iodides 50a−c Using Methylene Iodide



50	R^1	R^2	yield
50a	H	H	24%
50b	Me	H	25%
50c	H	Me	29%

may be performed using HBF_4 in diethyl ether rather than a trialkyloxonium salt.[72]

2.2. 1,1-Bis(electrophile) Compounds as C_1 Providers

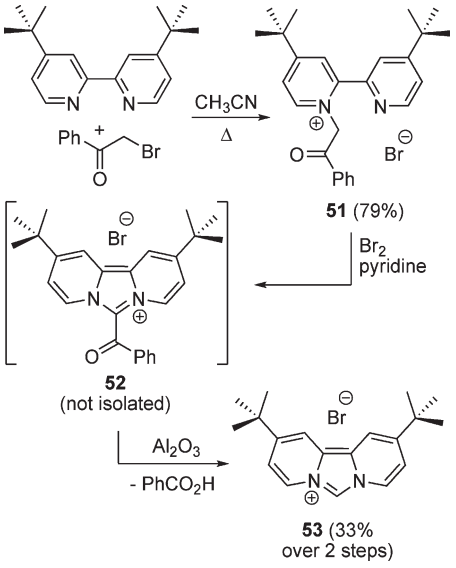
NHC precursors may also be obtained by double nucleophilic substitutions on 1,2-diimines by means of 1,1-bis(electrophile), that is, methylene compounds bearing two leaving groups. Scheme 22 displays several examples of dialkylating reagents that were used for that purpose. The present section will discuss these various possibilities.

2.2.1. *gem*-Dihalides as C_1 Building Blocks. The synthesis of dipyridoimidazolium salts **50a−c** was first described by Sasse and co-workers, who reported the double nucleophilic substitution of several 2,2′-bipyridyl derivatives with methylene iodide as early as 1963 (Scheme 23).[73]

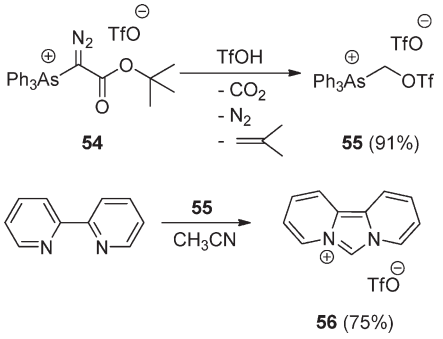
However, this reaction is inappropriate for bipyridyl compounds bearing electron-withdrawing groups like 4,4′-diphenyl-2,2′-bipyridyl, 5,5′-diethoxycarbonyl-2,2′-bipyridyl, or 2,2′-biquinolyl, which show a decrease of the nucleophilic character of the heteroatoms.

The same authors also reported another method for the synthesis of 6-carboxy-substituted-dipyridoimidazolium bromides of type **52** using α-haloketones in combination with bromine,[73b,74] and more recently, Kunz and co-workers used this approach to yield dipyridoimidazolium bromide **53** bearing *tert*-butyl groups at the 2- and 10-positions of the bipyrido moiety (26% overall yield) (Scheme 24).[75] Thus, 1-acylmethyl-2-(2-pyridyl)pyridinium bromide **51** was obtained by reaction of 2,2′-bipyridyls with 2-bromoacetophenone. Addition of bromine was accompanied by a bromoform reaction, followed by cyclization through a nucleophilic substitution of the α-position of the ketone by the second nitrogen to yield, after aromatization, the 6-carboxydipyridoimidazolium bromide **52**. Passing **52** over a column charged with activated neutral aluminum oxide led to a deacylation (Sasse and co-workers had already noted the possibility to induce this deacylation by acid or base catalysis) and finally to dipyridoimidazolium bromide **53**.

Scheme 24. Synthesis of 2,10-Di-*tert*-butyl-dipyridoimidazolium Salt 53



Scheme 25. Synthesis of Dipyridoimidazolium Salt 56 by Means of the Arsonium-Based Alkylating Agent 55



2.2.2. Using Weiss' Reagent. Weiss and co-workers described an alternative synthesis of dipyridoimidazolium salts using an arsonium salt as alkylating agent.[76] Starting from the elaborated diazo compound **54**,[77] reaction with trifluoromethanesulfonic acid afforded the arsonium salt **55**, a powerful bis-electrophile, which may be used to cyclize 2,2′-bipyridine into dipyridoimidazolium triflate **56** in 75% yield (Scheme 25). Although higher yields were obtained through this method, the potentially harmful use of an arsenic derivative obviously reduces the attractiveness of Weiss'pathway.

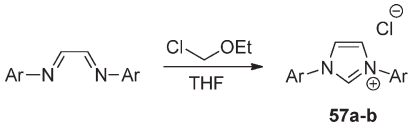
2.2.3. Using Chloromethyl Ethers. The synthesis of imidazolium salts using chloromethylalkyl ethers (alkyl = methyl or ethyl) was originally described by Arduengo and co-workers in 1999.[23] Starting from symmetrical 1,2-diimines, this route was applied to the synthesis of mesityl and 2,6-diisopropylphenyl

derivatives **57a,b** (Scheme 26). Although higher yields of the imidazolium **57a** were obtained via the one-pot synthesis previously described by the same group (see section 3.1), the chloromethylethyl ether synthetic pathway provides a direct and convenient access to hindered imidazolium salts and is easy to perform on a small scale (typically <1 g). Notably, as the imidazolium chlorides **57** precipitate during the course of the reaction, a simple filtration is required to isolate them, without the need of additional purification.

This procedure was particularly used for the synthesis of bulky or highly substituted imidazolium salts, such as, the tetrasubstituted imidazolium **58**,[78] the dendritic-type **59** (and its higher dendritic analogues),[79] the extremely bulky 2,6-terphenyl-substituted **60**,[80] or bis(imino)acenaphthene-based **61** (Chart 5).[81,82]

2.2.4. Using Chloromethyl Pivalate ("Glorius' Reagent"). Arduengo's procedure using chloromethylethyl ether is nevertheless inappropriate for the synthesis of bisoxazoline-derived imidazolium salts (IBiox·HX) since the halide anions generated *in situ* are seen to open the oxazoline ring, thereby preventing the formation of the expected imidazolium salt. Therefore, Glorius and colleagues developed an efficient alternative for the formation of rigid NHC architectures derived from bisoxazolines. The use of silver triflate in combination with chloromethyl pivalate led to the conversion of bisoxazoline to 4,5-dialkoxy-substituted tricyclic imidazolium salts **64** (Scheme 27) by means of the *in situ* generated and highly reactive (trifluoromethanesulfonato)methyl pivalate reagent **63**.[83] In order to avoid the formation of any bisoxazoline−silver complex, the silver chloride formed by reaction of AgOTf with chloromethyl pivalate needs to be filtered before being reacted with the bisoxazoline. Starting from achiral or enantiopure α-amino alcohols, the bisoxazoline **62** compounds were classically synthesized in a three-step sequence via amide formation from amino alcohols with diethyl oxalate, followed by chlorination of the remaining alcohol function with $SOCl_2$ and base-mediated cyclization.[84] This route allowed introduction of a variety of substituents R^1 and R^2 on the C4 position of the oxazoline rings.

Scheme 26. Cyclization of 1,2-Diimines into Imidazolium Salts 57a−b Using Chloromethylethyl Ether



57a-b

57a: Ar = 1-(2,4,6-trimethylphenyl); 40%
57b: Ar = 1-(2,6-diisopropylphenyl); 47%

Whereas the first publication dealt with the synthesis of the chiral IBiox-derived imidazolium triflate **64a−c**,[85] the authors subsequently applied this synthetic route to various sterically hindered bisoxazoline-derived imidazolium salts **64d−h** exhibiting restricted flexibility, brought by different carbocycle ring sizes ranging from two cyclopentyl rings to two cyclododecyl rings.[86,87] More recently, the (−)-menthyl-derived IBiox salt **64i** was obtained via the same route.[88] Imidazolium salts **64d−h** exhibit conformationally flexible cycloalkyl rings,[83] but in the particular case of (−)-menthyl-derived IBiox salt **64i**, the presence of the additional alkyl substituents on the cyclohexyl ring tends to shift the equilibrium toward the most sterically demanding conformation.

The same group also extended the application scope of this procedure to 2-imino-oxazolines and 2-iminopyridines to form, respectively, the unsymmetrical bicyclic imidazolium triflates **65a,b**[85] and 2*H*-imidazo[1,5-*a*]pyridin-4-ium bromides **66a−e** (isolated after an anion exchange),[89] as well as to thiazole-annelated imidazoliums **67a,b** (Chart 6).[90] It should be noted that attempts to apply this methodology to bisthiazoles failed to provide the corresponding imidazolium ring and stopped at the first alkylation stage.

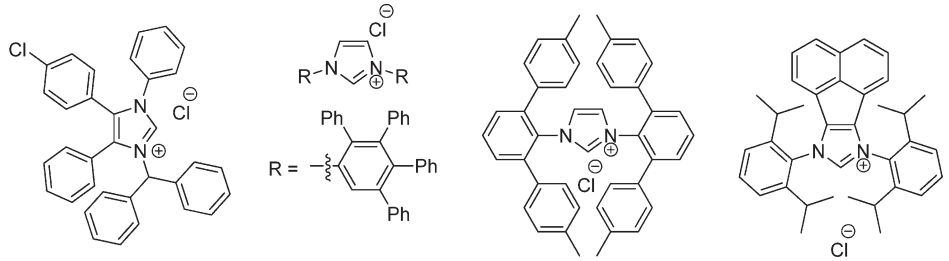
The utilization of Glorius' reagent was found to be quite versatile since, besides the examples discussed above, it was successfully applied to the synthesis of more classical imidazolium salts from the corresponding bisimines.[25c,65,82a,91] In some cases, silver triflate could even be omitted. However, the substrate scope of this route (and of all the alkylation methods actually) is limited to "non-enolizable" bisimines, since a competitive and preferential alkylation reaction may occur at the α-carbon due to an imine−enamine equilibrium.

2.3. Using Paraformaldehyde as the Precarbenic Unit

Paraformaldehyde can be employed as C_1-building block for the synthesis of both unsaturated and saturated NHC precursors. As shown in Scheme 28, treatment of 1,2-diimines with paraformaldehyde in the presence of 1 equiv of acid affords the corresponding imidazolium salts (eq 1), whereas the parallel treatment of diamines leads to cyclic aminals, which can be further converted into the corresponding cyclic formamidinium salts by oxidation (eq 2).

2.3.1. Imidazolium Salts. The condensation of a *N,N′*-diaryldiazabutadiene (DAD) with paraformaldehyde was first reported by Bildstein and co-workers and applied to the synthesis of redox-active ferrocenyl-substituted NHC precursors in 1999.[92] Starting from *N,N′*-diferrocenyl-1,4-diaza-1,3-butadiene **68**, which can be easily prepared in 95% yield by condensation of aminoferrocene with aqueous glyoxal, the *N,N′*-disubstituted

Chart 5. Examples of Imidazolium Chlorides Obtained via the Chloromethyl Ethyl Ether Route



58 (65%) **59** (69%) **60** (70%) **61** (84%)

dx.doi.org/10.1021/cr100328e |*Chem. Rev.* 2011, 111, 2705–2733

Scheme 27. Synthesis of IBiox·HOTf 64 Using Trifluoromethylsulfonyloxymethyl Pivalate 63 Formed by Addition of Silver Triflate to Chloromethyl Pivalate

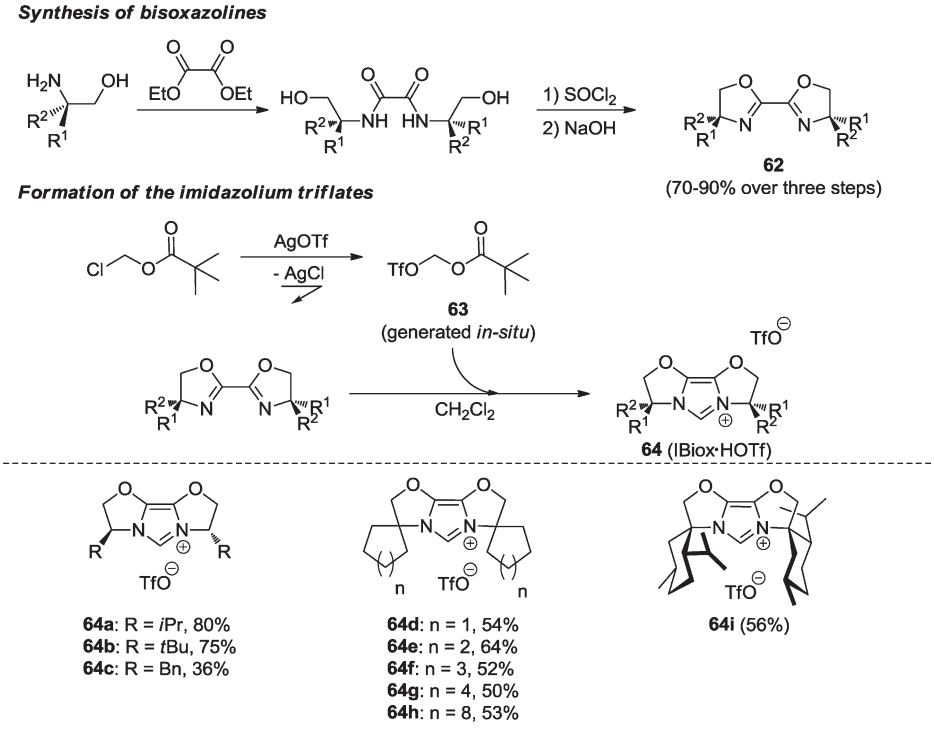
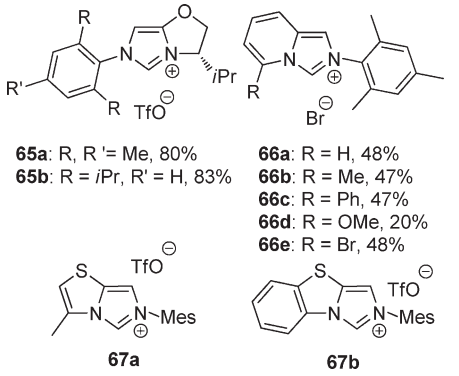


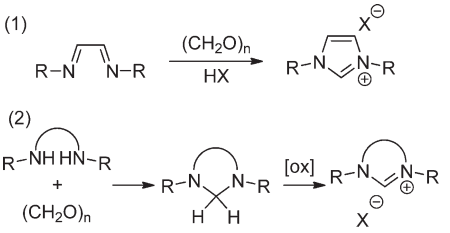
Chart 6. Unsymmetrical Imidazolium Salts Obtained via the Chloromethyl Pivalate/Silver Triflate Route



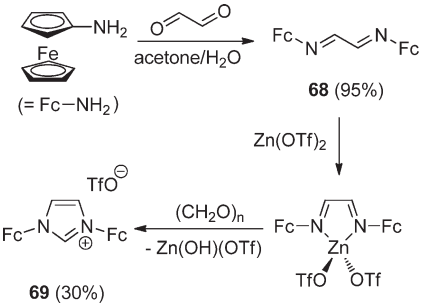
imidazolium salt **69** was then synthesized by activation of *N,N′*-diferrocenyl-1,4-diaza-1,3-butadiene with the strong Lewis acid $Zn(OTf)_2$ followed by ring closure with paraformaldehyde and elimination of zinc hydroxide triflate albeit in low yield (Scheme 29).

Soon after, Nolan and co-workers developed an efficient and scalable synthesis for the formation of the most studied and used imidazolium chlorides IMes·HCl (**71a**) and IPr·HCl (**71b**) (Scheme 30).[93] Typically, mixing the substituted aniline with aqueous glyoxal in methanol with a catalytic amount of acid leads to the rapid precipitation of the diazabutadienes **70a,b**. In a second step, the bisimines **70a,b** react with paraformaldehyde and hydrogen chloride (4 M in dioxane) under anhydrous conditions. The imidazolium chlorides **71a,b** precipitate along the course of the reaction and are collected as white to beige

Scheme 28. Synthesis of Unsaturated or Saturated NHC Precursors Using Paraformaldehyde as C_1 Building Block



Scheme 29. Synthesis of *N,N′*-Diferrocenylimidazolium Triflate 69



powders. This procedure works well for the title compounds **71**, but, as all the synthetic methods for imidazolium salts, it remains capricious and the conditions should be adapted to each substitution pattern of the imidazolium. Nevertheless, this route is

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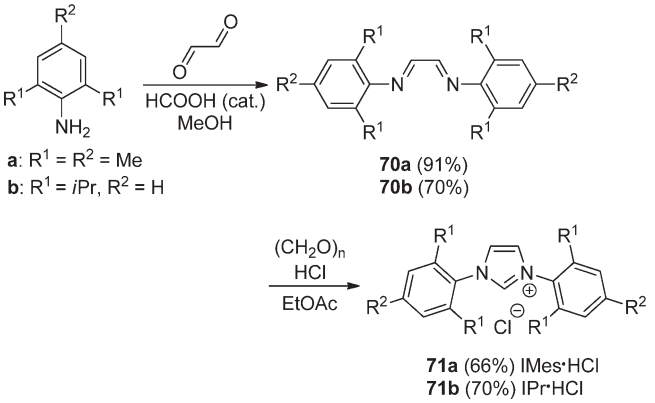
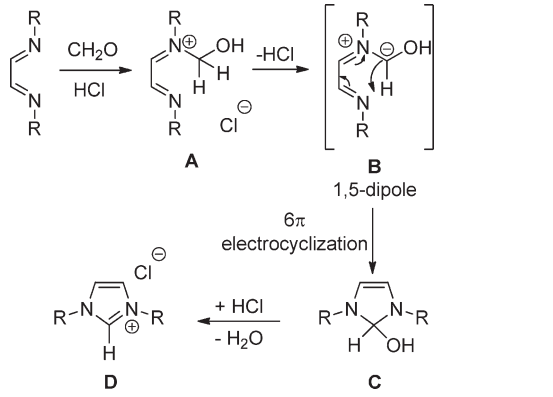
Scheme 30. Synthesis of Symmetrical *N,N′*-Diaryl-imidazolium Salts 71a,b



Scheme 31. Plausible Mechanism for the Condensation of Diazabutadiene with Formaldehyde in the Presence of Acid

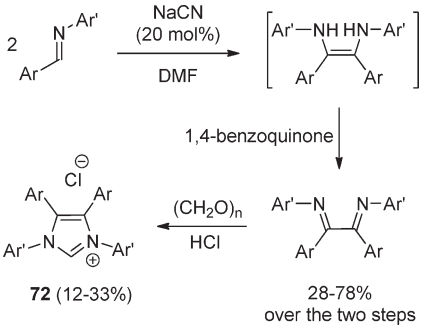


efficient for a large number of anilines with various substituents,[24,25] except those with strongly electron-withdrawing groups (i.e., $-CF_3$ or $-NO_2$), and even for alkylamines.[94] However, unsymmetrical imidazolium salts are not accessible since the condensation of amines with glyoxal is an equilibrium reaction and would lead to a mixture of diazabutadienes. As a special case, 2-iminopyridines are suitable substrates for this cyclization and lead to the formation of 2*H*-imidazo[1,5-*a*]-pyridin-4-ium salts.[95]

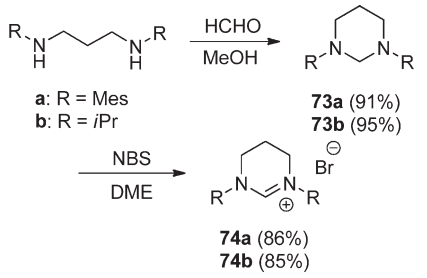
Hintermann reported an improved procedure for the synthesis of **71a,b**, consisting of using chlorotrimethylsilane instead of anhydrous hydrogen chloride as a cheaper and more readily available chloride source.[96] Under such optimized conditions, the yields were improved up to 69% and 81% for **71a** and **71b**, respectively. The same author also proposed a plausible mechanism based on an 1,5-dipolar cyclization (Scheme 31): Alkylation of the diazabutadiene by formaldehyde and HCl (or Me_3SiCl) leads to the iminium salt **A**. Loss of HCl from **A** gives an iminoazomethinylide 1,5-dipole **B**, which subsequently undergoes a 6π electrocyclization[97] to form the hydroxyimidazoline **C**. Elimination of water by reprotonation then generates the imidazolium salt **D**.

Miller and co-workers reported a new and interesting method for the synthesis of highly substituted NHC precursors such as 1,3,4,5-tetraarylimidazolium salts **72**. This involves a cyanide

Scheme 32. Synthesis of *C*-Aryl and *N*-Aryl-Substituted Imidazolium Salts 72



Scheme 33. Synthesis of 1,3-Dimesityl- and 1,3-Diisopropyl-3,4,5,6-tetrahydropyrimidinium Bromides 74a,b



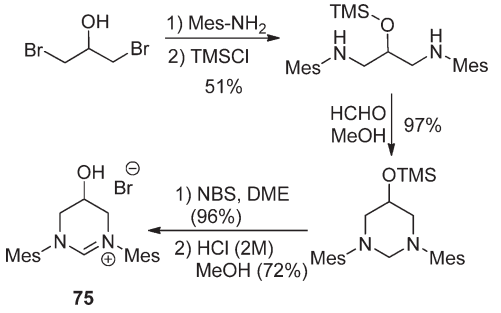
ion-catalyzed intermolecular coupling of aromatic aldimines followed by oxidation with 1,4-dibenzoquinone to give symmetrical diketimines, whereas the cyclization is achieved by using paraformaldehyde under acidic conditions (Scheme 32).[98] Notably, this catalysis proved to be efficient to access 1,2-diimines with sterically demanding substituents.[99]

2.3.2. Via Oxidation of a Cyclic Aminal. Perillo and coworkers first reported the synthesis of saturated six-membered NHC precursors using the paraformaldehyde route. 1-Aryl 3-substituted 3,4,5,6-tetrahydropyrimidinium salts were prepared by cyclization of the corresponding diamines into hexahydropyrimidines,[100] followed by dehydrogenation using *N*-halosuccinimide.[101] Buchmeiser and colleagues applied this method to the preparation of symmetrical 1,3-dimesityl- and 1,3-diisopropyl-3,4,5,6-tetrahydropyrimidinium bromides **74a,b**. The cyclization of *N,N′*-disubstituted propane-1,3-diamine by means of aqueous formaldehyde afforded the corresponding 1,3-disubstituted hexahydropyrimidine **73a,b**, which was then reacted with *N*-bromosuccinimide to yield **74a,b** (Scheme 33).[102]

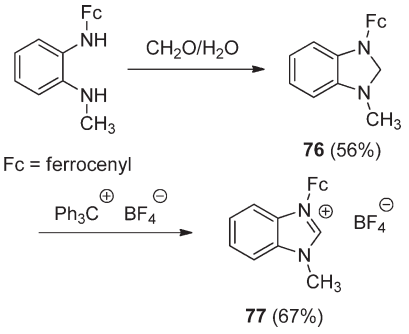
By the same approach, 5-hydroxy-1,3-dimesityl-3,4,5,6-tetrahydropyrimidinium bromide was synthesized from 1,3-bis(mesitylamino)-2-hydroxypropane, which was subject to O-protection with chlorotrimethylsilane prior to cyclization with paraformaldehyde and addition of *N*-bromosuccinimide to afford an O-protected tetrahydropyrimidinium salt (Scheme 34). Deprotection yielded the 5-hydroxy-1,3-dimesityl-3,4,5,6-tetrahydropyrimidinium bromide **75**, which may be further functionalized to be used as a supported catalyst precursor.[103] It should be noted that the cyclization step here requires only neutral conditions, contrary to the triethyl orthoformate route, and therefore is applicable to acid-sensitive substrates. Probably for the same reasons, Cavell and co-workers used this route for

dx.doi.org/10.1021/cr100328e |*Chem. Rev.* 2011, 111, 2705–2733

Scheme 34. Synthesis of 5-Hydroxy-1,3-dimesityl-3,4,5,6-tetrahydropyrimidinium Derivative 75



Scheme 35. Synthesis of the Ferrocenyl-Substituted Benzimidazolium Salt 77



the synthesis of a seven-membered NHC precursor containing a strained 5,6-dioxolane moiety.[55]

The paraformaldehyde route is applicable to benzimidazolium derivatives as well. The condensation of *N*-ferrocenyl-*N*′-methyl-1,2-diaminobenzene with aqueous formaldehyde was found to afford the 1-ferrocenyl-3-methyl-benzimidazoline **76**, which was then oxidized with trityl tetrafluoroborate into the benzimidazolium tetrafluoroborate **77** (Scheme 35).[104]

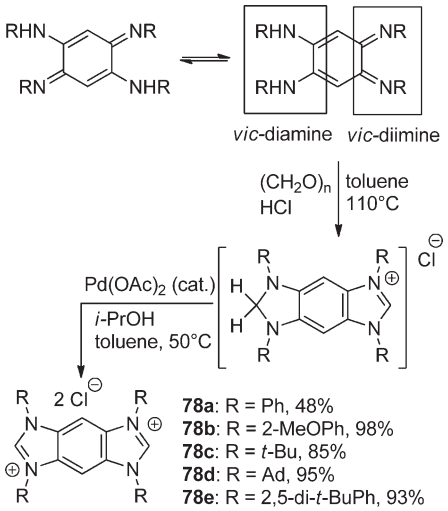
Finally, an analogous cyclization reaction was carried out on 2,5-diamino-1,4-benzoquinonediimines, which may exhibit an *ortho*- and *para*-quinoid equilibrium to yield annulated benzimidazolium/*N*,*N*′-aminal hybrids.[105] The Pd-mediated oxidation[106] of this intermediate afforded the respective benzobis(imidazolium) salts **78a**−**e** (Scheme 36).

2.4. Cyclization via a Preinstalled Formamide

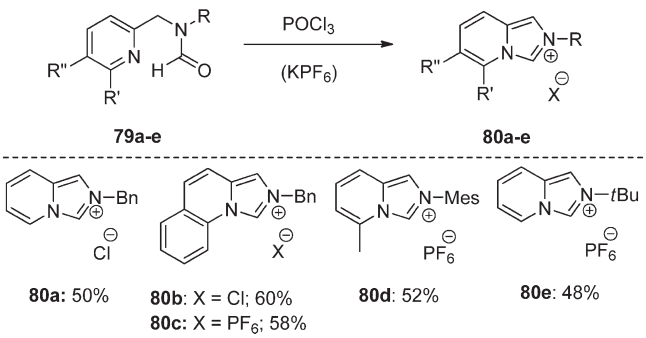
A less common method to access imidazolium salts is based on the formation a formamide followed by cyclization. For example, Lassaletta and colleagues used an intramolecular condensation reaction of formamide derivatives **79a**−**e** using phosphoryl chloride to yield imidazo[1,5-*a*]pyridinium salts **80a**−**e** (Scheme 37) in moderate yields (48−60%).[107]

Triazolium salts may also be formed by formamide cyclization.[108] Starting from *O*-benzyl-protected amino alcohols, the synthesis of triazolium salts **81a,b** was achieved in a one-pot procedure using phosphoryl chloride to yield isolable imidoyl chlorides, which were subsequently reacted with *N*-formyl-*N*-alkylhydrazine (obtained from alkyl hydrazine and methyl formate).[109] Cyclization with acetic anhydride followed by anion exchange afforded the desired triazolium perchlorates (Scheme 38). Benzyl deprotection gave hydroxy-

Scheme 36. One-Pot Cyclization/Oxidation Reaction Sequence to Yield Various Benzobis(imidazolium) Salts 78a−e



Scheme 37. Intramolecular Cyclization of Formamide Derivatives 79a−e into Imidazo[1,5-*a*]pyridinium Salts 80a−e



functionalized triazolium salts, which were then attached to a Merrifield resin.

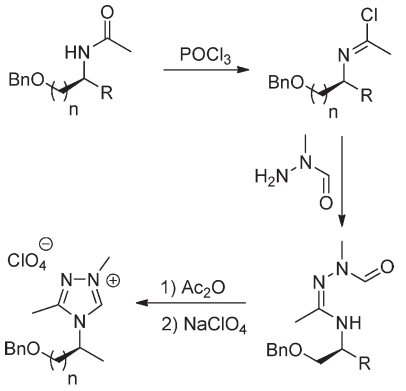
3. RING CLOSING BY THE FINAL INTRODUCTION OF THE BACKBONE

Whereas the previous section dealt with cyclization reactions involving the final introduction of the C_1 precarbenic unit, we will consider here the second general synthetic route consisting of a capping of the precarbenic unit with the desired heterocyclic backbone. We will show that this strategy not only produces "classical" heterocyclic precursors but also provides access to more unusual compounds and is thus complementary to the one presented above. This section will be organized around the nature of the precarbenic function, that is, (i) reaction onto an aminal moiety, (ii) functionalization of a formamidine, and cyclization onto (iii) an imine, (iv) a phosphaformamidinate, and (v) a thioformamide.

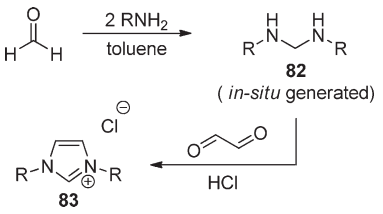
3.1. Condensation onto an Aminal Moiety

The synthesis of *N*,*N*′-disubstituted symmetric imidazolium salts by one-pot condensation between glyoxal, 2 equiv of aliphatic or aromatic amine, and an equivalent of paraformaldehyde in the presence of hydrochloric acid was actually the original

Scheme 38. One-Pot Synthesis of Trialkyl-Substituted Triazolium Salts 81a,b



Scheme 39. One-Pot, Four-Component Procedure for the Preparation of Imidazolium Chlorides 83 According to Arduengo



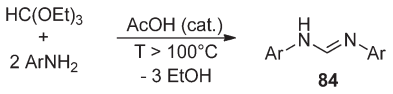
procedure patented by Arduengo in 1991.[110] In a typical experiment, this protocol starts with the dropwise addition of 2 equiv of the amine to a suspension of paraformaldehyde in toluene, leading to the *in situ* formation of the *N,N′*-disubstituted aminal **82** (Scheme 39). The imidazolium chloride **83** is then obtained through the condensation of this intermediate with 1 equiv of hydrochloric acid and 1 equiv of aqueous glyoxal.

Although this synthetic strategy is straightforward and is efficient for a number of alkyl and aryl amines (for example, *i*-propylamine,[110] *n*-propylamine,[110] *p*-toluidine,[110] cyclohexylamine,[111] chiral 1-(aryl)alkylamines,[112] mesitylamine,[113] 3,5-di-*tert*-butylaniline[114]), it suffers from a lack of generality since the majority of anilines or sterically congested amines fail to react or lead to low yields of product (in particular, IPr·HCl could not be synthesized) and from the characteristic generation of dark-brown to black impurities that render the imidazolium purification tedious, requiring numerous washings or column chromatographic workup. For these reasons, after having been the only one available for a while, the method has given way to cleaner and more efficient ones.

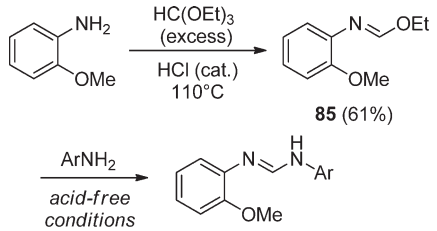
3.2. Cyclization Starting from a *N,N′*-Disubstituted Formamidine

This strategy emerged quite recently (6−7 years ago) and is now used more and more frequently because of the numerous possibilities afforded for making the "classical" NHC precursors but also more sophisticated structures only available by this route. In a first part, the synthesis of *N,N′*-disubstituted formamidines, the common starting platform, is detailed. Then, the different cyclizations are listed by the type of cyclization involved.

Scheme 40. General Scheme for the Preparation of Symmetric *N,N′*-Diarylformamidines 84



Scheme 41. Stepwise Synthesis of Unsymmetric Diarylformamidine 86a,b



3.2.1. Preparation of *N,N′*-Disubstituted Formamidines.

N,N′-Diarylformamidines have been known for more than a century,[115] and a simple, practical synthesis was first disclosed by Roberts in 1949, who evidenced in particular the key catalytic role of acids.[116] Formamidines **84** are indeed obtained in one-step through the condensation of 1 equiv of triethyl orthoformate with 2 equiv of a primary aniline in the presence of a catalytic amount of acetic acid (usually 5 mol %) at a temperature over 110−120 °C (Scheme 40). The ethanol is distilled out of the reaction mixture to shift the equilibrium to the formation of the symmetric *N,N′*-diarylformamidine **84**. The procedure is high yielding and easy to perform, can be carried out on large scale, and is efficient for a large palette of anilines.[117] Because the *N,N′*-diarylformamidines **84** are also air- and moisture-stable, all those advantages make them ideal starting materials for the construction of symmetric and cyclic formamidiniums, the precursors of the most common cyclic diaminocarbenes.

Unsymmetric *N,N′*-diarylformamidines could also be obtained by a slight modification of the procedure. As an illustrating example, the synthesis of *N*-(anisid-2-yl)-*N′*-arylformamidine **86a,b** is represented in Scheme 41.[118] In a first step, the ethyl formimidate **85** was obtained by the acid-catalyzed condensation of *o*-anisidine with an excess of triethyl orthoformate, according to the procedure described by DeWolfe.[119] Condensation of this iminoester with a second equivalent of aniline under acid-free conditions yielded formamidines **86a,b** in good yields. The absence of any trace of acid is necessary in order to render this second reaction irreversible and thus to exclude a thermodynamic distribution of the aryl groups on the two nitrogen atoms.[120]

In contrast to anilines, alkyl amines failed to react with triethyl orthoformate under the conditions stated in Scheme 40. Taylor et al. indeed demonstrated that a full equivalent of acetic acid (relative to triethyl orthoformate) is required for the formation of the *N,N′*-dialkylformamidinium acetates **87a,b** (Scheme 42).[121] These compounds were purified by crystallization (**87a**) or even by direct distillation (**87b**). The free *N,N′*-dialkylformamidines could then be generated by deprotonation with sodium carbonate. Nevertheless, some precautions have to be taken, since the

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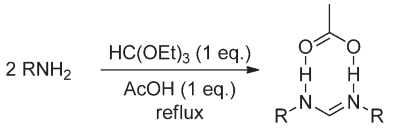
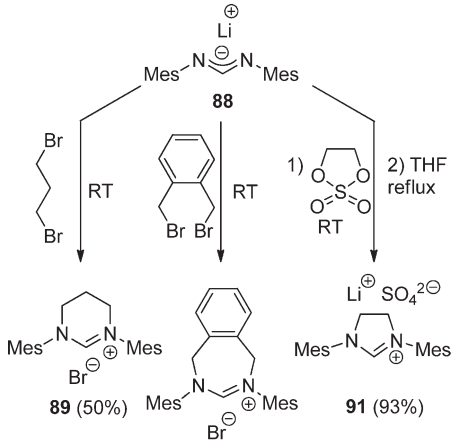
Scheme 42. Synthesis of *N,N′*-Dialkylformamidinium Acetates 87a,b



87a (R = Cy, 85%)
87b (R = *n*-Pr, 62%)

Scheme 43. Bisalkylation of Lithium Formamidinate 88 According to Bertrand and Co-workers

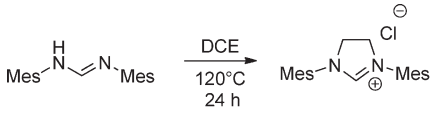


N,N′-dialkylformamidines are usually more sensitive toward hydrolysis than their aryl-substituted congeners.

3.2.2. Cyclization via a Bisalkylation Route. In 2006, Bertrand and co-workers reported the preparation of five-, six- and seven-membered carbene precursors **89**−**91** via reaction of the lithium formamidinate **88** (simply obtained by deprotonation of the corresponding formamidine with *n*BuLi in THF) with different alkyl bis-electrophiles (Scheme 43).[122] 1,3-Dibromopropane and α,α′-dibromo-*o*-xylene are suitable alkylating reagents for the preparation of **89** and **90** respectively. However, the imidazolinium **91** is not available by addition of 1,2-dibromoethane to **88**, since a preferred HBr-elimination reaction occurs due to the high basicity of the formamidinate anion. Fortunately, the 1,3,2-dioxathiolane-2,2-dioxide readily acts as the bis-electrophile, but because alkylsulfonates are less reactive than alkyl bromides, the quaternization of the second nitrogen needs to be performed at a higher temperature in this case.

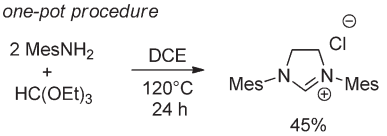
Though the latter protocol is straightforward, it necessitates inert, moisture-free conditions and is thus limited to substrates that tolerate a strong organolithium reagent. So, the alternate use of a neutral formamidine would be highly desirable for a more convenient synthesis. Grubbs and Kuhn thus developed in 2008 a very simple and straightforward preparation of imidazolinium chlorides involving the direct reaction of formamidines with an excess of dichloroethane (DCE) (Scheme 44).[123] The reactions were carried out in 10−20 equiv of neat dichloroethane in the presence of a slight excess of an external base (diisopropylethylamine, DIPEA) (method A) or without any base (method B). In the latter case, one-half of the starting formamidine serves as

Scheme 44. Synthesis of SIMes·HCl by Alkylation with Dichloroethane (DCE) According to Grubbs



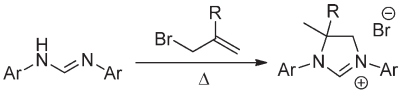
method A: with *i*Pr$_2$NEt, yield = 92%
method B: no base, yield = 49%
(98% based on a 50% theoretical yield)

one-pot procedure



45%
(90% based on a 50% theoretical yield)

Scheme 45. Synthesis of 92a,b Using a One-Pot, Alkylation−Hydroiminiumation Procedure



Ar = 2,6-diisopropylphenyl

92a: R =H, 66%
92b: R = Me, 70%

sacrificial base and can thus be recovered at the end of the reaction. Yields are generally good to excellent but are seen to decrease with the steric hindrance brought by the *ortho* substituents of the aryl groups. Unsymmetric formamidines were also found to be suitable substrates, except dialkylformamidines probably due to their high basicity. Finally, the symmetric *N,N′*-diarylformamidine, as intermediate and base, could even be formed *in situ* in a one-step, three-component synthesis starting from aniline, triethyl orthoformate, and DCE.

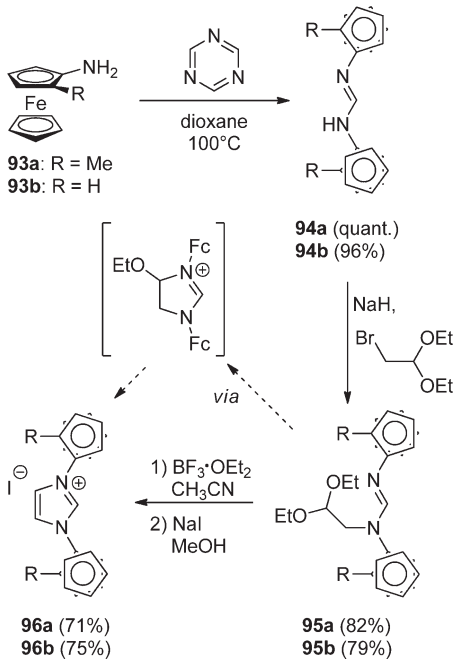
Around the same period, Cavell, Dervisi, Fallis, and co-workers reported a similar procedure based on the use of a bis-electrophile in the presence of half an equivalent of potassium carbonate in refluxing acetonitrile. This allowed the preparation of an extended range of cyclic carbene precursors exhibiting various ring sizes including imidazolinium, tetrahydropyrimidinium, and tetrahydrodiazepinium cores.[124] Both preparations can be carried out in air, without any special precaution, and are operative on large scale (20−30 g were reported). Inherent to the alkylation reaction, some undesirable side products are formed by alternative ring closure with a *N*-mesityl-*N′*-(pyridin-2-yl)-formamidine as substrate (due to the competition between pyridyl and formamidinyl nitrogens)[118] or with 1,4-dichlorobut-2-ene as bis-electrophile (S_N2 vs S_N2' reaction).[125] Fortunately, the formation of such side products can be avoided by simple optimization of the temperature conditions and by using bromoalkyl instead of iodoalkyl.

3.2.3. Cyclization by Alkylation−Hydroiminiumation Sequence. In 2007, Bertrand and colleagues reported the synthesis of cyclic iminium chlorides by a "hydroiminiumation" strategy (see section 3.3 for details). Despite the increased basicity of formamidines relative to imines, these authors successfully applied this methodology to the synthesis of imidazolinium salts (Scheme 45).[126] Starting with the reaction of the formamidine with allyl chloride, they first developed a two-step

sequence where the intermediate alkenylformamidine is isolated and subsequently reacts with hydrogen chloride to form the corresponding imidazolinium salt. However, since HX, needed for the second step, is generated *in situ* by the alkylation reaction, the synthesis of imidazolinium salts **92a,b** can be performed in a one-pot procedure (Scheme 45), which constitutes a valuable practical advantage.

3.2.4. Cyclization by Alkylation−Condensation Reactions. In 2005, Togni and co-workers reported a new synthetic strategy for the preparation of chiral and achiral *N,N′*-diferrocenylimidazolium salts **96a,b**,[127] starting from the electron-rich, strongly nucleophilic, and air-sensitive aminoferrocenes **93a,b** (Scheme 46).[128] In this special case, the formation of formamidines **94a,b** was accomplished by the introduction of the methinyl group from *s*-triazine,[129] whereas the C_2-fragment was introduced by treating **94a,b** with sodium hydride and bromoacetaldehyde−diethylacetal to give the acetal intermediates **95a,b**. Addition of an excess of $BF_3 \cdot OEt_2$ led to cyclization into 4-ethoxyimidazolinium cations and under prolonged heating allowed the aromatization of the imidazolium core by ethanol elimination. The imidazolium iodides **96a,b** were finally isolated after a counteranion exchange with an excess of NaI in methanol.

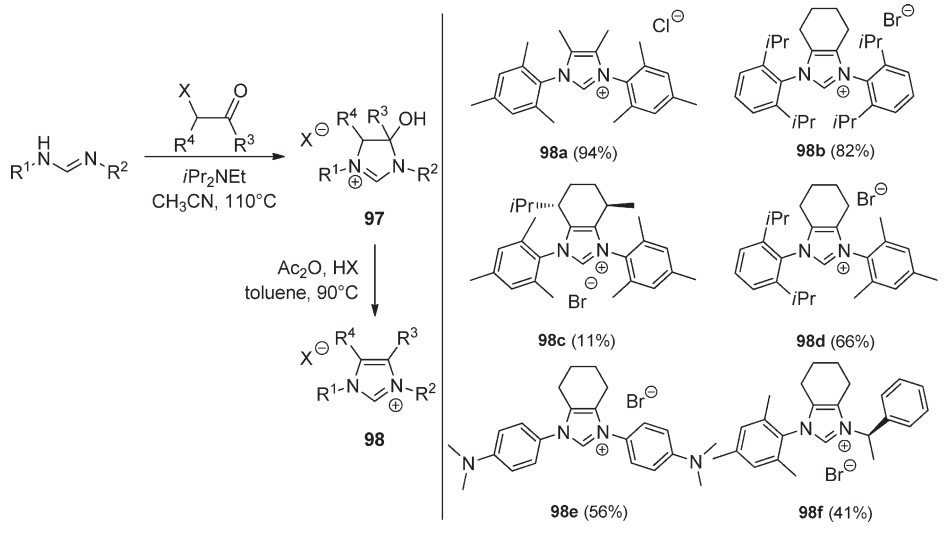
Scheme 46. Formation of Imidazolium Iodides 96a,b by Use of Bromoacetaldehyde Diethylacetal



Glorius and co-workers recently reported a versatile and modular one-pot method for the preparation of 4,5-dialkylimidazolium salts **98**.[130] The procedure involves the use of α-halo ketones, which are commercially available or easily prepared, for example, by bromination of ketones. In the key step, formamidines and the α-halo ketones are coupled at 110 °C in presence of diisopropylethylamine (iPr_2NEt) in acetonitrile to yield the 4-hydroxyimidazolinium salts **97**, which are the same intermediates as in the heterocyclic interconversion strategy developed by Fürstner et al. (see section 4.1). The aromatic imidazolium salts were obtained by an acylation-induced dehydration using acetic anhydride at 90 °C. Nineteen examples were given with various 4,5-substitution patterns ranging from simple alkyl substituents (**98a**) to 4,5-annelated achiral (**98b**) or even chiral (**98c**) cycle with sterically (**98d**) or electronically (**98e**) different aryl groups on the nitrogens and even with a chiral alkyl arm (**98f**) (Scheme 47). Noticeably, the procedure was recently used by Bertrand and co-workers for the synthesis of C2-substituted imidazolium salts, namely, the *N,N′*-bis(1,3-bis(2,6-diisopropylphenyl)-2,4-diphenylimidazolium salts.[131] By deprotonation of these precursors, the generation and the isolation of the first *free* "abnormal" NHCs were possible.[132]

3.2.5. Cyclization via an Amination Reaction. In 2006, Bielawski and co-workers reported the first synthesis of quinone-annulated imidazol-2-ylidene, whose imidazolium precursor **100** was obtained by a condensation reaction between *N,N′*-dimesitylformamidine **99** and 2,3-dichloro-1,4-naphthoquinone in acetonitrile under mildly basic conditions (Na_2SO_4, Scheme 48).[133] Although the yield was already statisfactory (73%), they recently found that the use of an additional equivalent of formamidine as sacrificial base in place of sodium sulfate yields quantitatively a 1:1 mixture of **100** and formamidinium chloride **99**·HCl, from

Scheme 47. Modular One-Pot Preparation of Various 4,5-Dialkylimidazolium Salts According to Glorius' Method



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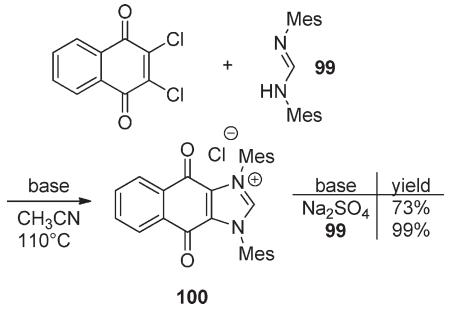
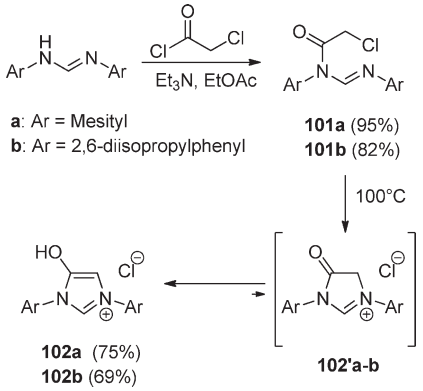
Scheme 48. Synthesis of the Quinone-Annulated Imidazolium Chloride 100



Scheme 49. Synthesis of 4-Hydroxyimidazolium Chlorides 102 According to César and Lavigne

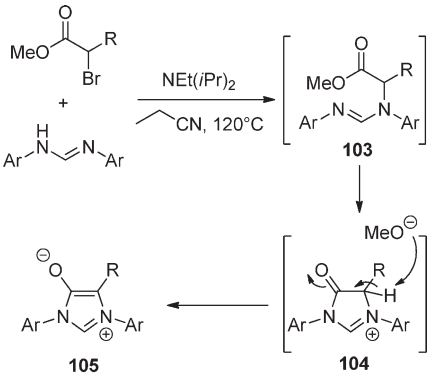


which the product can be easily isolated after a selective regeneration of **99** with $NaHCO_3$.[134]

3.2.6. Cyclization via an Alkylation−Acylation Sequence. In 2009, César, Lavigne, and co-workers reported the synthesis of a new anionic five-membered N-heterocyclic carbene, namely, a lithium imidazol-2-ylidene-4-olate bearing an enolate unit as the C_2 heterocyclic backbone.[135] Based on the keto/enol equilibrium of hydroxyaromatics, the 4-hydroxyimidazolium chloride **102**, precursor of this carbene, was prepared in two steps by acylation of the *N*,*N*′-diarylformamidines with chloroacetyl chloride, giving compound **101**, which was readily cyclized by quaternization of the second nitrogen. The intermediate 4-oxoimidazolinium **102′** was not detected due to its fast conversion into the more stable 4-hydroxyimidazolium **102** (Scheme 49). Clearly, here, the aromaticity of the imidazolium ring appears as the driving force favoring an equilibrium shift toward the enol form.

Soon after, Glorius and co-workers, in analogy to their synthetic procedure for imidazolium salts based on α-halo ketones (see section 3.2.4), developed a straight-forward preparation of 5-substituted imidazolium-4-olate **103** (Scheme 50).[136] This one-pot procedure starts with the alkylation of the formamidine with an α-bromo methylester in presence of Hünig's base (iPr_2NEt) to form the intermediate **103**, which readily cyclizes by quaternization of the second nitrogen to yield the 4-oxoimidazolinium salt **104** and finally the mesomeric betaine[137] **105** with concomitant formation of methanol. This reaction was found to be specific for the methyl α-bromo esters, since reactions with ethyl esters stop after the substitution step. Several

Scheme 50. Synthesis of the Zwitterionic Imidazolium-4-olate 105 by Glorius and co-workers



substitution patterns of the zwitterion were synthesized but as in the previous example, the method was found to be limited to *N*,*N*′-diarylformamidines. Noticeably, the 5-unsubstituted mesoionic heterocycle analogous to **105** was also generated and isolated by deprotonation of compound **102** with triethylamine.

3.2.7. Cyclization by Bisacylation of the Formamidine. Whereas pyrimidinium betaines of type **106** have been repeatedly reported in literature,[138] they were only recently found to be suitable precursors for the preparation of a series of anionic six-membered NHCs bearing a malonate backbone (Scheme 51).[139] Mesoionic heterocycles **106a**,**b** were obtained by a high-yielding peptide-type coupling between *N*,*N*′-dimesitylformamidine and a monosubstituted malonic acid with dicyclohexylcarbodiimide (DCC) as the activator. Alternatively, such compounds could be generated by reacting a formamidine directly with a monosubstituted malonyl dichloride derivative in presence of a base as exemplified by the synthesis of compounds **106c**−**e**.[140] These compounds are neutral and stable against air and moisture and can be easily purified by column chromatography. Concerning their electronic structure, they are best described as constituted by two separate π-electron subunits: a six-π-electron malonate unit and a 4-π-electron formamidinium unit; but in order to have a more classical view of the distribution of double bonds and charges within the betaine, the mesomeric structure represented in Scheme 51 is also used.

In a transposition of the latter procedure, compound **107** was prepared by coupling *N*,*N*′-dimesitylformamidine with dimethylmalonyl dichloride in dichloromethane in the presence of an excess of triethylamine as a base.[141] Surprisingly, it did not display any salt-like character, being in particular soluble in aromatic solvents. The compound is in fact a masked formamidinium formulated as **107**, in which the incipient chloride anion has attacked the C(2) carbon center of the diamidomethyne nucleus, rendered sufficiently electrophilic by the attachment of the two electron-withdrawing carbonyl functionalities onto the nitrogen atoms.[142] Nevertheless, **107** can be deprotonated to yield the corresponding diamidocarbene. The intermediate formamidinium **108** was even prepared and isolated (the synthesis of **108** was actually anterior to that of **107**).[143] For this purpose,

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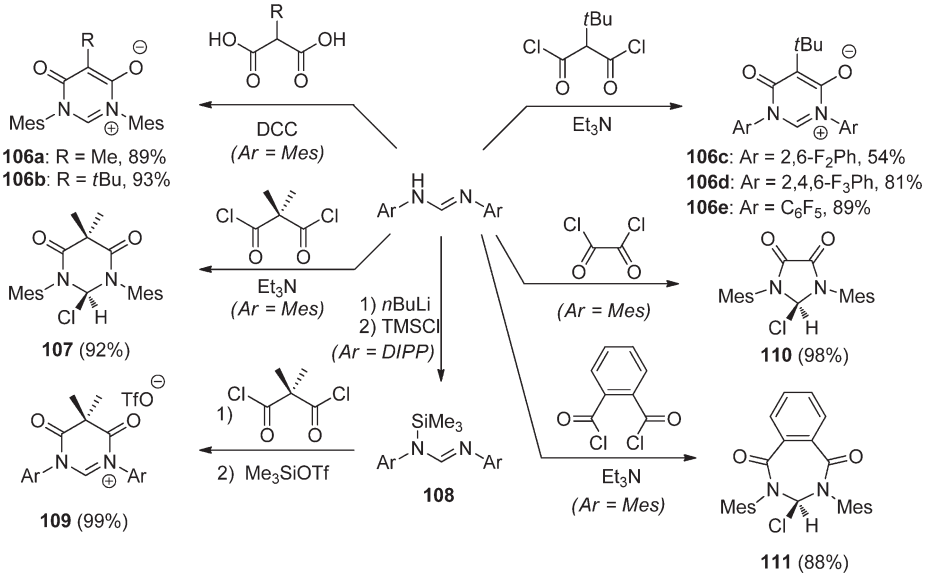
Scheme 51. Bisacylations of Formamidines Leading to Five-, Six-, and Seven-Membered Heterocyclic Compounds



weakly nucleophilic chloride atoms were trapped as chlorotrimethylsilane by means of trimethylsilylformamidine **108** and trimethylsilyl triflate. Compound **109** was found to rapidly decompose in presence of water and other coordinating solvents, including THF. This high reactivity is a testament to the highly electrophilic nature of the cation. In that sense, the "chloride-stabilized" compound **107** was thought to be a more convenient NHC precursor. More recently, the five-membered analogue of **107**, namely, the 2-chloro-4,5-dioxoimidazolidine **110**, was synthesized in 98% yield by direct treatment of the formamidine with oxalyl chloride.[144] In that case, no base is required since oxalyl chloride is much more reactive than dimethyl malonyl dichloride. Whereas the 4,5-dioxoimidazolin-2-ylidene derived from **110** is not stable in the free form, it could be generated at low temperature and immediately trapped by sulfur, isocyanide, or a metallic precursor. Finally, this family was extended to seven-membered heterocycles with the synthesis of the 2-chloro-1,3-diazepin-4,7-dione **111** through condensation of *N*,*N*′-dimesitylformamidine with phthaloyl chloride.[145]

3.2.8. Introduction of an Inorganic Backbone. The term "NHC with an inorganic backbone" refers here to a cyclic diaminocarbene whose skeleton contains main-group elements such as phosphorus and boron. Actually, all the precursors for such NHCs were obtained by grafting the inorganic moiety to a *N*-silyl-*N*,*N*′-disubstituted formamidine **112** (Scheme 52).

In 2004, Grubbs and Despagnet-Ayoub successfully prepared the four-membered, phosphorus-containing cation **113** by coupling **112** with an aminodichlorophosphine in presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf).[146] The latter reagent allowed the cyclization by abstraction of the chloride atom from the phosphorus center, which additionally facilitates the workup since the only byproduct is then the easily removable chlorotrimethylsilane. Soon after, Roesler and co-workers reported the first example of an NHC incorporating a boron-containing backbone, consisting of a five-membered B_2N_2C ring and generated from the imidazolium triflate **114**.[147] The diboron moiety was introduced using Grubbs' strategy with TMSOTf as the chloride scavenger. However, this strategy had to be adapted in the case of the four-π-electron, four-membered BN_2C cation reported by Bertrand and colleagues.[148] Treatment of **112** with dibromodi(isopropylamino)borane indeed afforded the acyclic derivative **115a** in excellent yield. But the halogen-exchange with TMSOTf only gave the opened form **115** with trifluoromethanesulfonate instead of bromide. Fortunately, the use of tetra(pentafluorophenyl)borate, $[B(C_6F_5)_4]^-$, an even weaker coordinating anion, led to the desired cyclization product **116a**. It was then shown that compounds **116** were not antiaromatic despite the presence of 4π-intracyclic electrons. The antiaromatic energy is released by a weak π-interaction between the endocyclic nitrogens and the boron center and an extensive delocalization over the NCN unit. The empty p orbital of boron is stabilized either by the lone pair of the exocyclic nitrogen in **116a** or by the phenyl ring in **116b**, albeit to a smaller extent.

Six-membered boron-containing cations were also reported, first by the group of Bertrand with the cationic carbon-containing heterocyclic equivalent of borazine **119**.[149] The symmetric, diisopropylamino-substituted derivative **119a** was obtained in one-step by condensation of **112** with compound **117**. Noticeably, the use of TMSOTf was not found necessary in this case to shift the reaction toward cyclization. The modulation of boron substituents necessitates another synthetic approach since 1,3-dibromo-1,3-diboranes are only readily available with amino substituents. Thus, reaction of formamidine **112** with *B*-bromo aminoborane **118** yields the acyclic formamidine **120**, which cyclizes after deprotonation with *n*-butyllithium and reaction with a substituted dibromoborane into dissymmetric **119b** and symmetric **119c** in 74% and 71% yields, respectively. Here again, the six π-electrons of the heterocycle are divided into two separate allyl moieties: a cationic four π-electron NCN and a neutral two π-electron BNB fragment. Finally, Roesler and co-workers reported the anionic equivalent **123** of **119** by formally replacing the (NR) fragment at the heterocyclic position 5 by an isolobal $(CR)^-$ fragment.[150] The synthesis starts with the coupling of **112** with 1,1-bis(methylchloroboryl)ethane **121** in presence of TMSOTf to form the zwitterionic heterocycle **122**, in which the triflate group is coordinated to one of the boron atoms in the solid state. The ^1H, ^{13}C, and ^{11}B NMR spectra indicate a dissociation of the triflate in solution and the formation

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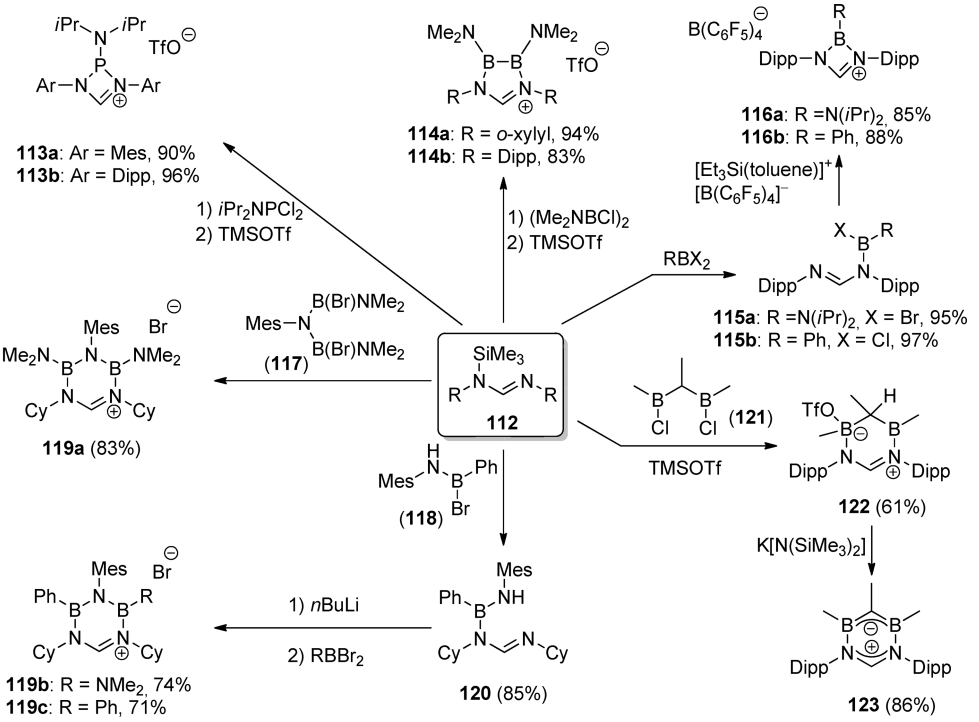
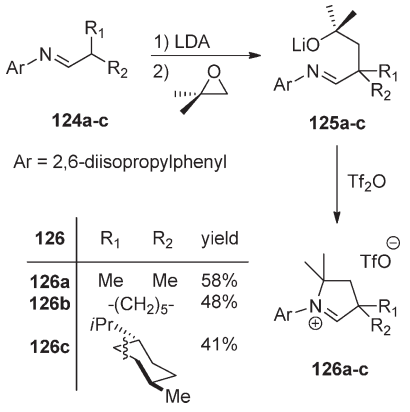
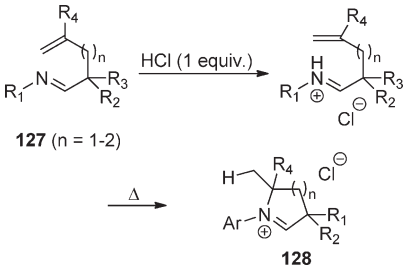
Scheme 52. Synthesis of NHC Precursors Featuring an Inorganic Backbone



Scheme 53. Original Synthesis of the Cyclic Iminium Compound 126



Scheme 54. Formation of the Cyclic Aldiminium 128 by an Intramolecular "Hydroiminiumation" Methodology



of an ion pair with a C_s-symmetry. Deprotonation of **122** with potassium hexamethyldisilazide (KHMDS) cleanly yields the 1,5-diaza-2,4-diborine **123** exhibiting a planar $N_2B_2C_2$ heterocycle. As in the case of compound **119**, the six π-electrons appear to be distributed over two allyl-like fragments, a 4π-electron N_2C^+ and a 2π-electron B_2C^- system, to form a zwitterionic structure, rather than being delocalized over the entire ring framework. It should be also noted that despite being formally an anionic N-heterocyclic carbene, the compound generated by deprotonation of **123** with *n*BuLi or $PhCH_2K$ behaves better as a phenylide than as a "real" N-heterocyclic carbene.[151]

3.3. Cyclization by Quaternization of an Imine

In 2005, Bertrand and co-workers published the synthesis of a new series of stable cyclic (alkyl)(amino)carbenes (CAAC) bearing one nitrogen atom and a quaternary carbon atom connected to the carbene center.[152] Their pyrrolidinium precursors **126** were originally obtained through a three-step reaction (Scheme 53), where the imine **124** (simply obtained by condensation between the corresponding aniline and aldehyde) was deprotonated by lithium diisopropylamide (LDA) and alkylated with 1,2-epoxy-2-methylpropane to form the lithium alkoxide **125**, which was directly converted into the iminium **126** via a highly reactive tertiary alkyl triflate intermediate.

Although the above method can be carried out in one pot without isolation of intermediates, it requires the use of highly reactive reagents and produces only moderate yields (41−58%) of the final product. This led the same group to develop an alternate strategy starting from alkenylaldimines and involving an intramolecular "hydroiminiumation" as the key cyclization step (Scheme 54).[126,153] They were encouraged in this way by previous studies reporting that hydroamination of weakly basic amines can be catalyzed by Brönstedt acids.[154] Considering that imines are less basic than amines, the "hydroiminiumation"

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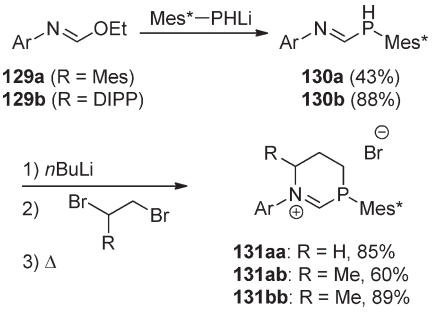
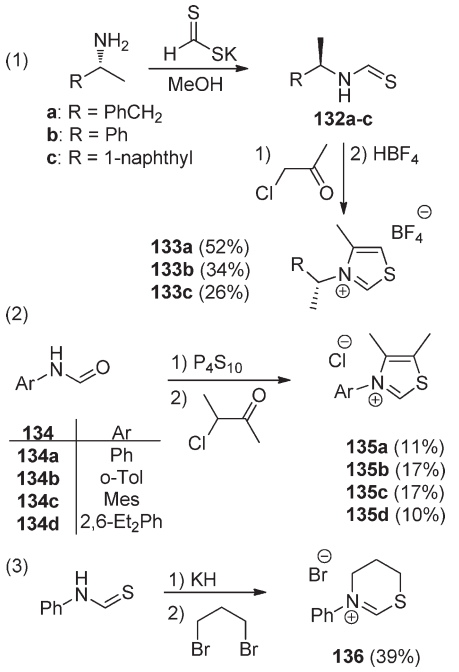
Scheme 55. Synthesis of Phosphazinium Bromides 131 According to Bertrand and Co-Workers[a]



[a] Mes* = 2,4,6-$tBu_3C_6H_2$.

Scheme 56. Preparation of N,S-Containing Cationic Heterocycles from Thioformamides

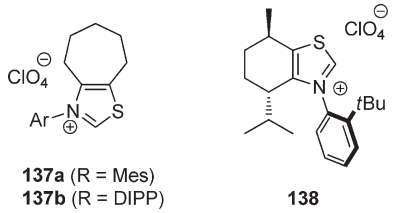


reaction was found to be a powerful cyclization strategy in this case. The addition of a stoichiometric amount of HCl to the alkenylaldimine **127** results in a protonation of the sp^2-nitrogen atom, whereas subsequent heating induces a clean and regioselective ring closure via formal addition of the N−H bond to the pendant C=C double bond (Scheme 54). This methodology was applied to the formation of both five-membered rings and six-membered rings in good yields and could be scaled up quite easily.[155]

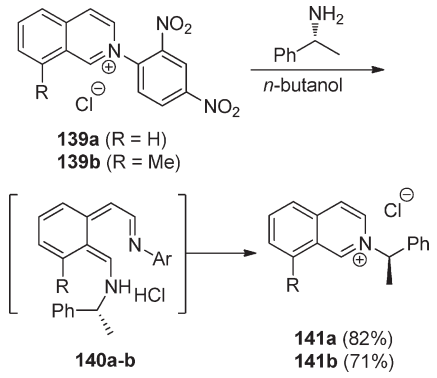
3.4. Cyclization Starting from a N,P-Disubstituted Phosphaformamidinate

Since N,P-disubstituted phosphazinium salts **131** appeared to be potentially suitable precursors for the generation of the corresponding free (amino)(phosphino)carbenes (P-NHCs), they were synthesized by Bertrand and co-workers in 2008.[156] It was then shown that P-NHC can be generated only from compound **131bb** due to a competitive deprotonation between

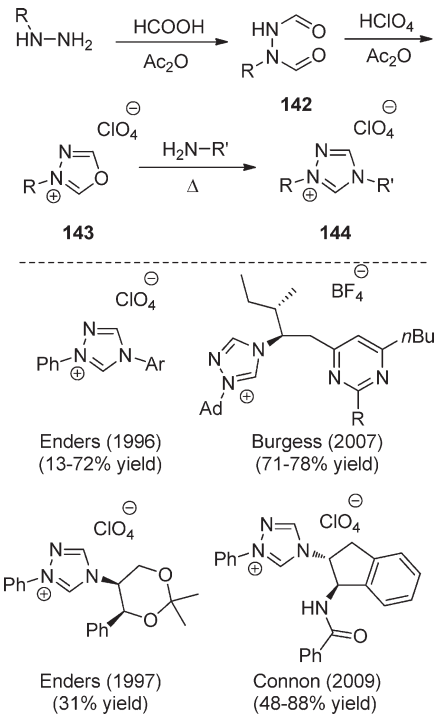
Chart 7. Thiazolium Salts Obtained by Oxidation of Their Corresponding Thiazoline-2-thiones



Scheme 57. Zincke Reaction Leading to Chiral Isoquinolinium Chlorides 141a,b



Scheme 58. General Scheme for the Synthesis of 1,2,4-Triazolium Perchlorates 144 via the Intermediacy of 1,3,4-Oxadiazolium 143 and Some Representative Examples of Triazolium Salts Obtained by This Strategy[a]



[a] Yields refer to the last step **143** → **144**) (Ad = 1-adamantyl.

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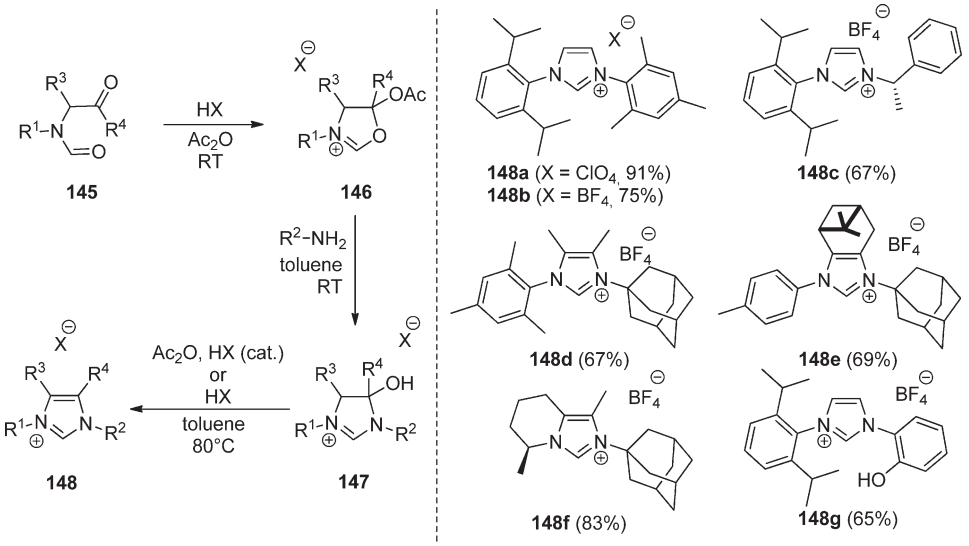
Scheme 59. General Scheme for Preparation of Unsymmetrical Imidazoliums According to Fürstner et al. and Representative Examples of the Application Scope



positions 2 and 4 of the cationic heterocycle. Compounds **131** were synthesized from phosphaformamidines **130** by a bisalkylation procedure (Scheme 55), by analogy with the authors' previous report on formamidines.[122] Few examples of phosphamidines and phosphamidinates had been reported,[157] but none of their synthetic procedures is applicable to the preparation of phosphaformamidines, since they would involve the use of unstable formimide chlorides [RN=C(H)Cl] or of acidic hydrogen cyanide, which would protonate the second phosphide reagent. Fortunately, the reaction of primary lithium phosphide Mes*PHLi (Mes* = 2,4,6-tBu$_3$C$_6$H$_2$) with ethyl *N*-arylformimidates **129** leads to the clean formation of the phosphaformamidines **130**.[158] Addition of 1,3-dibromopropane or 1,3-dibromobutane to a solution of the lithium salt of **130** (obtained by deprotonation with nBuLi), followed by heating, then furnishes phosphazinium bromides **131** in moderate to good yields.

3.5. Cyclization Starting from a Thioformamide

The preparation of N,S-containing cationic cycles from an N-substituted thioformamide has been described only in few cases. Nevertheless, several thiazolium salts have been prepared by condensation of the latter compounds with an α-chloroketone, according to a procedure first reported by Götze.[159] As an example, chiral thiazolium tetrafluoroborates **133a−c** were obtained in two steps from the corresponding commercial enantiopure amines (Scheme 56, eq 1).[160] In a first step, the amines react with potassium dithioformate to give the thioformamides **132a−c**. Condensation with chloroacetone, followed by an ion-exchange from chloride to tetrafluoroborate for purification reasons, lead to the thiazolium salts **133a−c** in moderate yields.[161] Noticeably, this last step is regioselective because only the 4-methylthiazolium ring is obtained. Following a similar procedure, Grubbs and Vougioukalakis developed more recently the series of thiazolium chlorides **135** for evaluation of the corresponding thiazol-2-ylidenes as supporting ligands in Grubbs(II)- and Hoveyda-type metathesis catalysts.[162] The sequence starts with the *in situ* generation of *N*-thioformyl anilines from the formanilidines **134** (simply obtained by reacting the aniline with the mixed formyl−acetyl anhydride) and phosphorus pentasulfide (Scheme 56, eq 2). Condensation with 3-chlorobutanone gives the desired 4,5-dimethylthiazolium chlorides **135** in low yields (10−17%). Finally, Bertrand and co-workers reported the synthesis of the 1,3-thiazinium bromide **136** by reacting *N*-phenyl thioformamide with 1,3-dibromopropane, albeit in moderate yield (39%) (Scheme 56, eq 3).[122]

An alternative strategy is based on the formation of a cyclic thiazoline-2-thione from a thiocarbamate and its subsequent oxidation to the cationic thiazolium. This synthetic route was successfully employed to access bicyclic thiazolium perchlorates **137a,b**,[163] or chiral, atropoisomeric thiazolium perchlorate **138** (Chart 7).[164]

4. FINAL INTRODUCTION OF THE AMINO MOIETY

4.1. Via a Heterocyclic Interconversion

Lassaletta and co-workers reported the preparation of isoquinolinium salts **141a,b** by a Zincke reaction between salts **139a,b**, easily prepared by aromatic nucleophilic substitution of 1-chloro-2,4-dinitrobenzene with isoquinoline and (*R*)-phenylethylamine (Scheme 57).[165,166] This heterocyclic interconversion is thought to proceed through a ring-opening/ring-closing sequence via intermediates such as **140a,b**.[167]

A versatile and convenient preparation of 1,4-disubstituted-1,2,4-triazolium salts is based on a procedure first described by Boyd et al.[168] Starting from an alkyl or an aryl hydrazine, the bisformyl hydrazines **142** can be obtained using the mixed anhydride of formic acid and acetic acid. Dehydration of the latter in the presence of acetic anhydride and perchloric acid affords the corresponding 1,3,4-oxadiazolium perchlorates **143**. Reaction of the latter with a primary alkyl- or arylamine R′−NH$_2$ results in a ring-opening/ring-closing sequence leading to the desired 1,2,4-triazolium perchlorates **144** (Scheme 58).[169] This strategy has been applied by several groups for the construction of simple to complex triazolium architectures, as exemplified in Scheme 58.[170] It is noteworthy that chiral amines are suitable substrates and that tetrafluoroboric acid can advantageously replace the hazardous perchloric acid. However, the reaction of oxadiazolium **143** with *N,N*-dialkyl hydrazines to yield the

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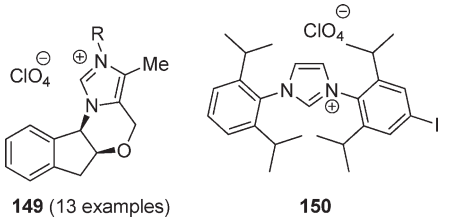
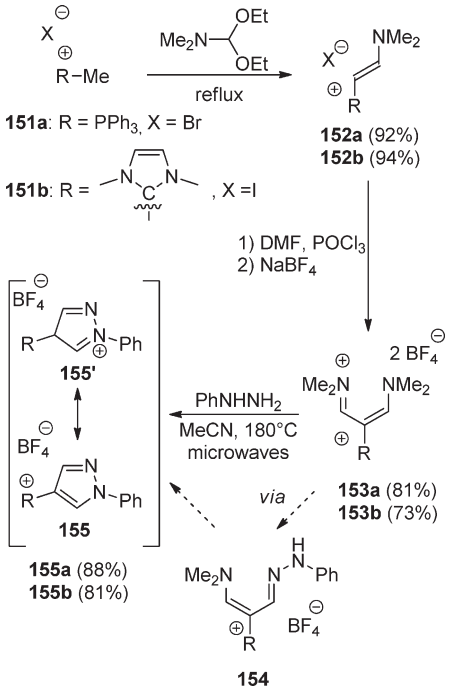
Chart 8. Imidazolium Salts Synthesized According to Fürstner's Method



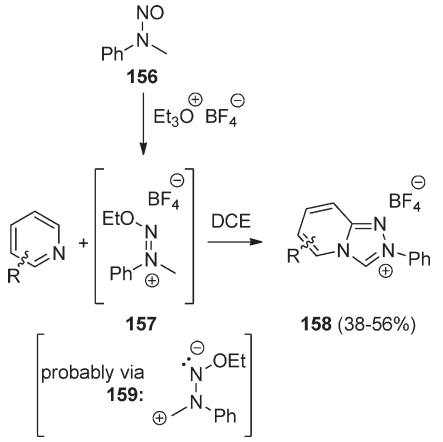
Scheme 60. Synthesis of Cationic 1,2-Diazolium Salts 155a,b According to Fürstner and Colleagues



corresponding compound **144** does not work even under forcing conditions.[171] An obvious limitation of this strategy is the impossibility to annelate the triazolium core with another cycle to build a rigid chiral bicyclic structure, which would normally give better stereoselective induction (see section 2.1.7).

Following a similar strategy, Fürstner and co-workers developed in 2006 a new, convenient, and flexible method for the preparation of unsymmetrical imidazolium salts.[172] The procedure starts from compound **145**, where the carbenic carbon atom and the backbone are already installed on the first amine as formyl and β-ketoalkyl groups, respectively (Scheme 59). Surprisingly, reaction of **145** with 1 equiv of $HClO_4$ or HBF_4 in acetic anhydride does not lead to the aromatic oxazolium analogous to **143** but stops at the intermediate acetal stage **146**. Condensation of this oxazolinium moiety with a second amine of choice proceeds smoothly to yield the 4-hydroxyimidazolinium salt **147**, which aromatizes by dehydration to finally afford the desired imidazolium salt **148**. As shown by selected examples, this methodology is quite general and versatile, since it accommodates alkyl and aryl amines, acyclic and cyclic backbones, chirality onto the amine

Scheme 61. Synthesis of Triazolium Salts 158 According to Lassaletta and Co-workers



and the backbone (no racemization occurs), tertiary alkyl substituents and functional groups on the nitrogen atoms, and bicyclic structures.

Soon after, Bode and co-workers used this methodology to synthesize a series of chiral aminoindanol-derived imidazolium salts of type **149**,[173] analogues of their well-known chiral triazolium, and Azumaya and Saito used it for unsymmetrical *N,N′*-diarylimidazolium **150** (Chart 8).[174]

4.2. Through Condensation with a Hydrazine Derivative

In 2008, the groups of Kawashima and Fürstner independently introduced a new N-heterocyclic carbene, namely, an (amino)(ylidic)carbene (AYC), in which the carbene center is directly connected to an amino atom and to an sp^2-hybridized anionic carbon atom.[175] Although their cationic precursors were first prepared by a simple quaternization of the N atom of an indol-derived ylide, Fürstner et al. developed a more elaborated and flexible synthesis of these compounds (Scheme 60). Key intermediates of the procedure were the 2-phosphoniovinamidinium **153a** and 2-(imidazolium)vinamidinium **153b**, which derived from methyltriphenylphosphonium bromide **151a** and 1,2,3-trimethylimidazolium iodide **151b**, respectively, through a two-step sequence.[176] Noticeably, the reactivity of the 2-methylimidazolium **151b** is comparable to that of methylphosphonium **151a**. It could be explained by the analogy between phosphonium ylides and ene-1,1-diamines, deprotonation products of **151a** and **151b**.[177] Condensation of **153** with phenylhydrazine gave first the acyclic intermediate **154**, which under higher heating in a microwave oven cyclized with elimination of dimethylamine to give the desired cationic heterocycles **155**. Whereas two resonance forms **155** and **155′** are conceivable, the X-ray diffraction structures of **155a,b** suggest that the mesomeric extreme **155** gains importance, wherein the positive charge largely resides on the lateral R group (a phosphonium for **155a**, an imidazolium for **155b**).

Finally, Lassaletta and collaborators synthesized the series of heterocycle-annelated triazolium salts **158** (Scheme 61).[178] For this purpose, they used a slight modification of an original procedure by Eicher and co-workers,[179] based on alkoxydiazenium cation **157**, easily accessible by the alkylation of nitrosamine **156** with triethyloxonium tetrafluoroborate. Albeit not fully confirmed, the formation of **158** is thought to proceed via the dipole **159** obtained by deprotonation of **157**.[180]

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5. CONCLUSION

N-heterocyclic carbenes have become an essential tool in the field of organometallic chemistry with many diversified applications. Their attractiveness as ligands in catalysis is a result of several beneficial features: (i) the stability of their complexes, resulting in high robustness of the system against air, moisture, or heat; (ii) the importance of steric effects, which may be modulated by playing either with the nature of R substituents on the nitrogen atom or with the size of the ring; (iii) their modulable electronic character having, for example, an impact on diverse elementary steps of a catalytic cycle (oxidative addition, reductive elimination, etc.); and finally (iv) as shown in the present account, the rich diversity and efficiency of synthetic methods giving access to their precursors.

The aim of this review was to lay out a general user's guide for the synthesis of azolium salts that have been used as carbene precursors. The need to obtain an increasing variety of N-heterocyclic carbene architectures has motivated the search for better methods to access their precursors. To date and apart from the classical quaternization of the nitrogen atom of a neutral imidazole (or parent), the chemist has the option to form the expected cationic cycle through a final cyclization step, which can be achieved through three different strategies (according to the unit introduced during the last cyclization step), each having its own advantages and limitations. Ultimately, it is possible to modulate the size and the number of heteroatoms of the heterocycle and to introduce independently various substituents.

Finally, as revealed by the present overview, progress in the organic synthesis of NHC precursors in recent years has been so rapid that it is no doubt that with ongoing creative investigations in this area, many exciting new archetypes of N-heterocyclic carbenes are still to be discovered in the near future.

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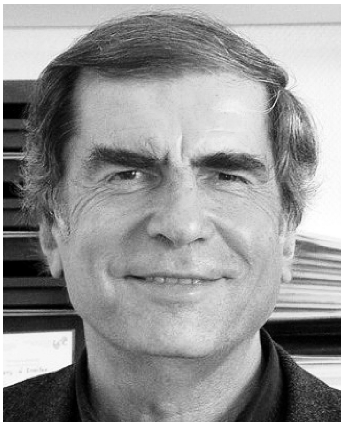
BIOGRAPHIES

Laure Benhamou was born in 1983 in Châtenay Malabry, France. She studied chemistry at the Université Paul Sabatier in Toulouse. In 2009, she obtained her Ph.D. degree under the supervision of Dr. G. Lavigne and Dr. V. César at the "Laboratoire de Chimie de Coordination du CNRS" working on functionalized N-heterocyclic carbene ligands. She is currently a postdoctoral associate in the group of Prof. D. Zargarian at the "Université de Montréal" working on the chemistry of nickel(III) complexes. In 2011, she will join Prof. E. P. Kündig at the University of Geneva (Switzerland) as a postdoctoral fellow.

Edith Chardon was born in 1985 in Orléans, France. In 2008, she received her M.Sc. from the University of Rennes I as well as her engineering degree from the Ecole Nationale Supérieure de Chimie de Rennes (France). She is currently Ph.D. student in the group of Dr. Stéphane Bellemin-Laponnaz in Strasbourg and the group of Dr. Gilles Guichard in Bordeaux (France) investigating the chemistry of N-heterocyclic carbenes and their biomedical applications.



Guy Lavigne earned his degrees in chemistry at the *University Paul Sabatier*, in Toulouse. He was appointed as CNRS research scientist in 1973 and graduated from the *University Pierre & Marie Curie* (Paris VI) where he received the "*Doctorat d'Etat es Sciences*" in 1979 under the guidance of Professor Yves Jeannin. He joined the *Laboratoire de Chimie de Coordination* (LCC) in Toulouse in 1980. After postdoctoral studies at UCLA with Herbert D. Kaesz (1983−1984), he was promoted CNRS senior research scientist (Directeur de recherches) at the LCC in 1988, originally working in the field of base-promoted reactions of ruthenium carbonyls, a work highlighted in *Angewandte Chemie* (2000). He is presently head of the group "Molecular design of transition metal pre-catalysts" at LCC−CNRS. His present research projects are focusing on the conceptual and experimental design of ruthenium-based precatalysts including Ru(0) carbonyl complexes (for C−H/olefin coupling) and Ru(II) complexes for olefin metathesis and transfer hydrogenation. In addition, the group is now focusing on a conceptually new family

of anionic N-heterocyclic carbenes paving the way to zwitterionic catalysts and their readily modulable functionalized derivatives. Among diverse professional activities, Guy Lavigne has been president of the coordination chemistry division of the "Société Chimique de France" (2006−2009) and is presently member of the European board of the Division of Inorganic Chemistry of EuCheMS.

Stéphane Bellemin-Laponnaz studied chemistry at Université Joseph Fourier (Grenoble) and Université Louis Pasteur (Strasbourg). In 1994, he joined the group of Professor John A. Osborn at Université Louis Pasteur to obtain his doctorate in 1998 studying the chemistry of oxo compounds. In 1999, he became a member of the group of Professor Gregory C. Fu at Massachusetts Institute of Technology (Cambridge, MA) as a postdoctoral fellow working on kinetic resolution and phosphametallocene chemistry. In late 2000, he joined the group of Professor Lutz H. Gade at Université Louis Pasteur (currently at University of Heidelberg) as a CNRS researcher and recently moved to the Institut de Physique et Chimie des Matériaux de Strasbourg as a CNRS Director of Research. His research is mainly focused on organometallic chemistry, coordination chemistry, and homogeneous catalysis. He was awarded a Bronze Medal by the CNRS in 2005 and Coordination Chemistry Section Prize of the Société Chimique de France in 2009.

Vincent César was born in 1977 in Nancy, France. He studied chemistry at the Ecole Normale Supérieure in Lyon, where he obtained an "Agrégation" in Physical Sciences (major in chemistry) in 2000. He completed his thesis in 2004 under the supervision of Prof. L. H. Gade and Dr. S. Bellemin-Laponnaz at the "Université Louis Pasteur" in Strasbourg working on chiral oxazolinyl/N-heterocyclic carbene ligands. He then joined Prof. A. Fürstner at the Max Planck Institut für Kohlenforschung in Mülheim (Germany) as an Alexander-von-Humboldt fellow. In 2006, he was appointed CNRS researcher at the "Laboratoire de Chimie de Coordination du CNRS" in Toulouse, where he is working with Dr. G. Lavigne. His research is mainly focused on the design and development of new N-heterocyclic carbenes for organometallic chemistry and homogeneous catalysis.

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NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on 1/14/2011, with errors in Scheme 24. These were corrected in the version that was published to the Web on 1/26/2011.