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REVIEW

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Nitrilium ions – synthesis and applications

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Nitrilium ions have been well-established in organic chemistry for many decades, but recent developments show them to be far more versatile than hitherto recognized. They are known as stable salts, can be generated *in situ*, or are present as transient intermediates. We provide a succinct, but comprehensive review on the synthesis, stability, and reactivity of nitrilium ions as synthons for imines, their use in the synthesis of a large spectrum of heterocycles, and their reactions with transition metal complexes. By offering this overview, we aim for a renewed focus on readily accessible and simple to use nitrilium ions as valuable reagents for the synthesis of organic compounds.

1. Introduction

Nitrilium ions **1** (Scheme 1) have been known for a long time as *reactive intermediates* in valuable organic transformations like the Beckmann rearrangement and the Ritter, von Braun, and Bischler–Napieralski reactions, while Meerwein and others reported on *stable nitrilium salts* half a century ago. This duality of *reactivity versus stability* is ideal to fully exploit the synthetic potential of such a simple synthon, but this is not quite what has happened in the past few decades. Although much has been accomplished, as illustrated by two earlier reviews,[1] nitrilium ions are now being rediscovered because of their versatile reactivity, which is addressed in this review. By first sketching the historical perspective of nitrilium ions it becomes abundantly clear that this important synthon has tremendous synthetic value beyond its current boundaries.

2. Nitrilium ions

2.1. Reactive intermediates

The best-known reaction in which the nitrilium ion plays a prominent role is the Beckmann rearrangement that converts

[a]*Department of Chemistry and Pharmaceutical Sciences, Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands. E-mail: K.Lammertsma@vu.nl*

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Dr Tom van Dijk received his B.Sc. and M.Sc. degrees in chemistry from the Vrije Universiteit Amsterdam where he worked under the guidance of Koop Lammertsma. In 2017 he obtained his PhD degree from the Vrije Universiteit Amsterdam. During that time his research focused on the application of nitrilium ions in the synthesis of anionic phosphaamidinates and neutr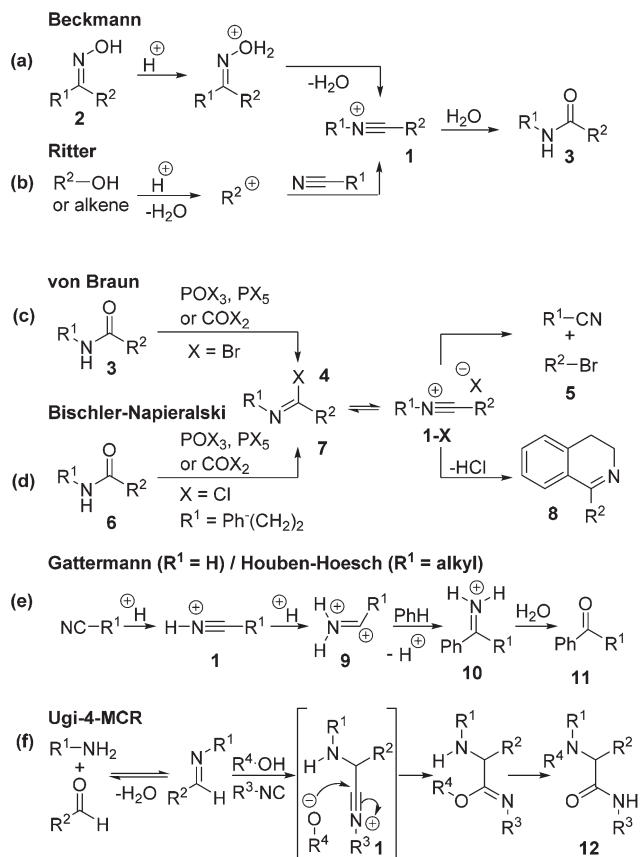al 1,3-P,N-ligands and the application of these ligands in coordination chemistry. He currently holds a teaching position in organic chemistry at the Department of Engineering and Applied Sciences at the Hogeschool Rotterdam.

Tom van Dijk

Dr J. Chris Slootweg obtained his PhD degree from the Vrije Universiteit Amsterdam in 2005. As a post-doctoral researcher, he studied C–H activation at the ETH Zürich, for which he received a TALENT stipend from the NWO. In 2006, he returned as an Assistant Professor to the VU, where he coordinated the Marie Curie Initial Training Network SusPhos on sustainable phosphorus chemistry. In 2013, he received a NWO VIDI grant on main-group chemistry and catalysis. He was promoted to Associate Professor in May 2014, and moved to the University of Amsterdam in November 2016 to continue exploring his interests in sustainable chemistry.

J. Chris Slootweg

10134 | *Org. Biomol. Chem.*, 2017, **15**, 10134–10144

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Scheme 1 Reactions involving nitrilium ion intermediates.

oximes **2** into amides **3** (Scheme 1a). In this reaction, first reported in 1886,[2] the protonated oxime eliminates water to give a nitrilium ion that hydrolyses to an amide. In some cases the nitrilium ion intermediate has been observed spectroscopi-

cally[3] and even been isolated.[4] Amides are also formed by hydrolysis of nitrilium ions in the closely related Ritter reaction,[5] irrespective of whether they are obtained from a nitrile or a carbenium ion that is acid-generated from an alcohol or alkene (Scheme 1b).[6] Nitrilium ions act also as intermediates in the von Braun reaction,[7] which instead concerns the degradation of an amide on treatment with a bromide source to give an alkyl bromide (Scheme 1c). The degradation starts by converting a secondary N-alkyl amide **3** into imidoyl bromide **4**, which is in equilibrium with nitrilium bromide **1-Br**. The latter dissociates into a nitrile and a carbenium ion that reacts with the liberated bromide ion to give alkyl bromide **5**.[6c,8] Another transformation involving the nitrilium ion is the Bischler–Napieralski reaction[9] that converts β-phenethylamides **6** into 3,4-dihydroisoquinolines **8** (Scheme 1d). In this reaction the amide is treated with a chloride to give an equilibrium mixture of imidoyl chloride **7** and nitrilium chloride **1-Cl** that undergoes a phenyl-induced ring closure,[6c,10] but if the phenyl group is not nucleophilic enough, the nitrilium ion can expel a nitrile to give either β-phenethylchloride by the von Braun amide degradation or styrene by the retro-Ritter reaction.[6c,10] Nitrilium ions have been implicated in the Gattermann[11] and Houben–Hoesch[12] reactions (Scheme 1e) in which aromatic compounds are formylated or acylated under acidic conditions with hydrogen cyanide or a nitrile, respectively;[13] even protonated nitrilium ion **9** (i.e., a dication) may be involved as the reaction with benzene occurs only in superacids.[14] Nitrilium ions are also known to be intermediates in the hydrolysis of imidoyl chlorides[15] and the acid catalyzed hydrolysis of isocyanides[16] and ketenimines.[17] Also the widely applied Ugi 4-component reaction[18] for the synthesis of α-amino acrylamides **12**, but not the related Passerini reaction,[19] is considered to proceed through a nitrilium ion intermediate (Scheme 1f).[20]

These examples amply illustrate the relevance of nitrilium ion intermediates in organic synthesis. This review goes beyond these established reactions to expand the scope of nitrilium ions as imine synthons for the synthesis of N-heterocycles and N,P-ligands that have their merits in coordination chemistry.
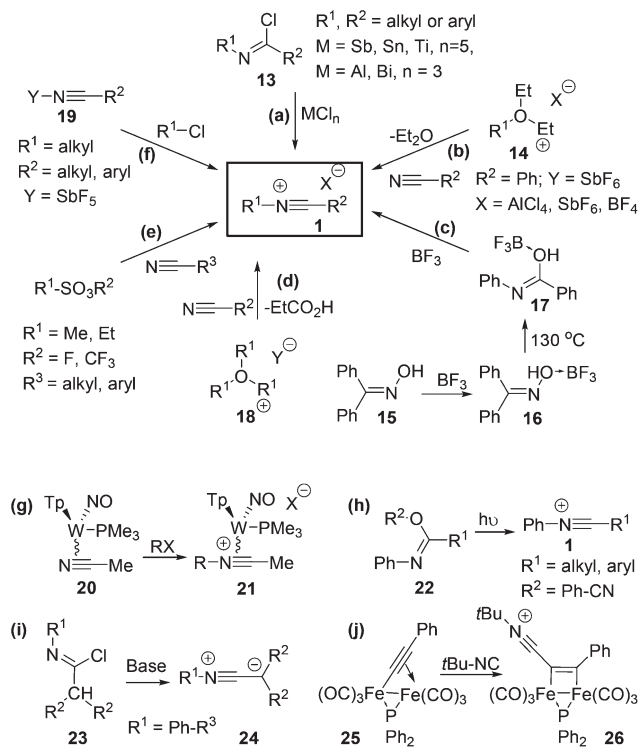
2.2. Stable nitrilium salts

Stable nitrilium salts are equally well established as reactive intermediates that hydrolyze,[4a,21] expel a nitrile, or undergo cyclization and are commonly generated from imidoyl halides or nitriles. Already in the 1950s, both Klages[22] and Meerwein[23] reported stable nitrilium salts by abstracting a Cl⁻ ion from imidoyl chlorides **13** with Lewis acids like $SbCl_6$, $SnCl_5$, $TiCl_5$, $AlCl_3$, $BiCl_3$, and BCl_3 (Scheme 2a);[21c] recently we have applied TMSOTf successfully.[24] Imidoyl chlorides undergo first order dissociation in aqueous organic solvents to nitrilium ions, which, of course, hydrolyze instantly to amides.[15] Meerwein was the first to show that nitriles can be N-alkylated with triethyloxonium-BF_4 (**14**), known as Meerwein's reagent, or its $SbCl_6^-$ and $AlCl_4^-$ derivatives (Scheme 2b).[23] He also showed that the nitrilium ions are involved in the Beckmann

Prof. Koop Lammertsma (born in 1949 in Makkum, the Netherlands) was educated at the Universities of Groningen (1974) and Amsterdam (Ph.D., 1979). After postdoctoral work with F. Sondheimer (London), P. v. R. Schleyer (Erlangen-Nürnberg), and Nobel laureate G. A. Olah (USC), in 1983 he moved to the University of Alabama at Birmingham, USA, and became Full Professor in 1992. In 1996 he moved to the Vrije Universiteit Amsterdam, The Netherlands. Since 2015, he holds a Distinguished Visiting Professor position at the University of Johannesburg, South Africa. His interest in physical organic chemistry has increasingly focused on computationally supported phosphorus chemistry.
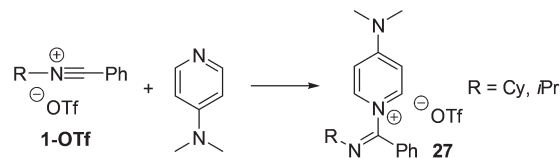
Koop Lammertsma

Scheme 2 Syntheses of stable nitrilium salt.

Scheme 3 Base stabilized nitrilium triflates.

the attack of *t*-butylisocyanide on (Cp(CO)Fe)$_2$(μ-CO)(μ-CH)$^+$PF$_6^-$.[37]

Recently we have shown that treating thermally labile *N*-alkyl nitrilium triflates with DMAP renders moderately air-stable adducts **27** (Scheme 3), which much improves the handling of the nitrilium ion while retaining their reactivity.[38] For instance, solid DMAP adduct **27** (R = iPr) gave only 9% of the hydrolyzed product upon exposure to air for one month.

2.3. Structural properties

Nitrilium ions have a linear conformation with an N≡C triple bond, implying a formally positively charged nitrogen atom. Illustrative are the three X-ray crystal structures shown in Fig. 1.[24,39] The average N≡C bond length of 1.135 Å for the nine nitrilium ions found in the Cambridge Structural Database[24,31,35–37,39,40] compares well with the 1.131 Å of a nitrilium ylide,[41] the 1.138 Å of aryl nitriles,[42] and the 1.136 Å of alkyl nitriles.[42] The average C–N≡C and N≡C–C bond angles of 174.5° and 177.1°, respectively, reflect the near linearity of the ions. The IR stretching vibrations observed for 21 nitrilium salts, carrying aryl and alkyl groups, range from 2300 to 2420 cm^{-1} and are fully in line with the N≡C triple bond character.[4a,21c,24,27a,43] The observed ^{13}C NMR chemical shifts of the –N≡C– carbon of 14 nitrilium ions[24,28d,30b,44] range from 102.6 to 125.2 ppm and compare with the 116.4 ppm

rearrangement by obtaining nitrilium-BF$_4$ salt **1** by heating the BF$_3$ adduct (**16**) of benzophenone oxime **15** and treating product **17** with additional BF$_3$ (Scheme 2c).[4c]

Subsequently, stable nitrilium salts have been shown to result from *N*-alkylating acetonitrile and benzonitrile with reagents such as HC(OEt)$_2$$^+$SbCl$_6^-$ (**18**, Scheme 2d),[25] the *O*-methyldibenzofuranium-BF$_4$ salt,[26] methyl triflate,[27] MeSO$_3$F,[28] and EtSO$_3$F (Scheme 2e).[28b] Protonation of nitriles with HF/AsF$_5$ or HF/SbF$_5$ in anhydrous HF has been recently accomplished.[29] *N*-Alkylnitrilium salts are also formed on reacting alkyl halides with FeCl$_3$ or SbCl$_5$-coordinated nitriles **19**[23,30] (Scheme 2f) and even by treating a CN-containing phosphaylide with Meerwein's salt,[31] while a μ^2-TpW(NO)(PMe$_3$) stabilized nitrilium ion (**21**) results from the corresponding coordinated acetonitrile **20** (Scheme 2g), obtained *in situ* from the μ^2-benzene complex.[32]

Light-induced fragmentation is another method as illustrated in the formation of the *N*-phenylnitrilium ion **1** by photocleavage of benzimidate ester **22** (Scheme 2h).[21a,b] Even nitrilium ylides, such as **24**, can be obtained by aqueous deprotonation of imidoyl chlorides **23** (Scheme 2i) and trapped by dipolarophiles like methyl acrylate.[33] There are a few cases of transition metal mediated syntheses of stable nitrilium ions, such as the nucleophilic attack of *t*-butylisocyanide on μ$_2$-η^2-acetylide diiron complex **25** to give ion **26** (Scheme 2j).[34] Similar reactions have been reported for the allenyl [Fe$_2$(CO)$_6$(μ-PPh$_2$)] complex[35] and Os$_3$- and Ru$_3$-complexes;[36] a related Fe$_2$-complexed nitrilium ion results from

Fig. 1 Molecular structures of the (*N*-2,6-dimethylphenyl)(methyl)carbonitrilium ion[39] (top left), (*N*-phenyl)(*tert*-butyl)carbonitrilium ion[24] (top right) and (*N*-2,4,6-trimethylphenyl)(phenyl)carbonitrilium ion[24] (bottom). Reported selected bond lengths (Å) and angles (°) for the top left structure: N1–C7 1.132, C1–N1–C7 177.4, N1–C7–C8 179.2, for the top right structure: N1–C1 1.125(3), C1–N1–C6 179.3(2), N1–C1–C2 177.7(2), for the bottom structure (second crystallographically independent structure between brackets): N1–C1 1.140(4) [1.142(4)], C1–N1–C8 176.1(3) [176.0(3)], N1–C1–C2 177.6(4) [174.8(3)].

(CDCl$_3$) for acetonitrile;[45] *C*-alkyl nitrilium ions (108.6–125.2 ppm) are generally deshielded from the *C*-aryl substituted ones (102.6–107.7 ppm). The ions typically have ^1J(C,N) coupling constants of 42.1 to 50.0 Hz. It is worth noting that the ^{14}N NMR resonance for [Me–N≡C–Me]$^+$ is 110 ppm deshielded from that of acetonitrile,[4a] reflecting the difference in N-coordination.

3. Imine synthons

One of the early examples of using nitrilium salts to generate imines comes from Turrell *et al.*, who synthesized aminoester **28** from (*N*-phenyl)(phenyl)-**1-SbF$_5$** and phenol (Scheme 4a).[43a] Treating *in situ* generated **1-BF$_4$** with alcohols also gives **28**, which on reduction (NaBH$_4$) converts readily into secondary amines.[46] Similarly, *N*-methyl-**1-OTf** reacts with alcohols to give **28** and forms thioamino-esters on using thiols.[27b] Recently, based on ^{1}H NMR ^5J(H,H) coupling constants,[47] it has been concluded that the addition of methanol and ethanol to (*N*-methyl)(methyl)-**1-O$_3$SF** forms the expected *Z*-iminium ions, which on deprotonation isomerize to the *E*-imines.[28d] Such behavior was also reported for the nucleophilic attack of acetate on nitrilium ions, which showed the selective formation of *Z-N*-acyl-acetamides with subsequent slow isomerization to the *E*-isomer.[48] Likewise, the reaction of an azide anion with nitrilium ions resulted selectively in *Z*-imidoylazides, which upon slow isomerization cyclized to the corresponding tetrazoles.[48] Other *O*-nucleophiles can also be used, such as olefin-bound η²-acrolein osmium(II) complexes in which the carbonyl oxygen attacks the nitrilium ion, resulting in a η³-vinyl osmium complex.[49]

The reaction of *N*-aryl-**1-SbCl$_6$**,[43a] *N*-alkyl-**1-FeCl$_4$**,[50] and **1-OTf**,[27b] with primary or secondary amines gives amidines **29** upon deprotonation of the amidinium intermediate (Scheme 4b). The power of this method was demonstrated by Gordon *et al.* for the high-yield synthesis of otherwise inaccessible *N-tert*-butylamidines as precursors for bulky amidinate
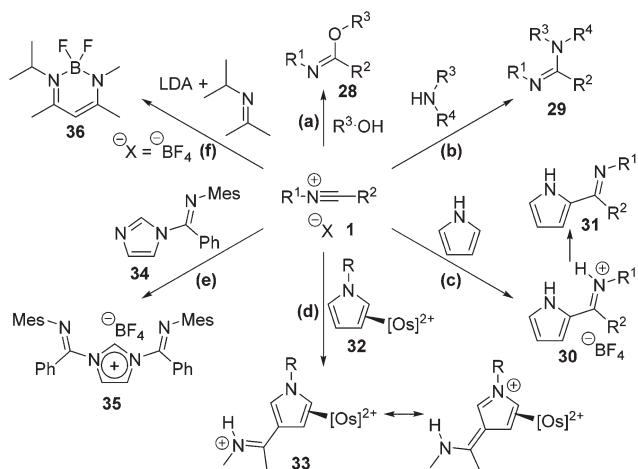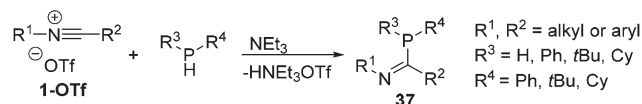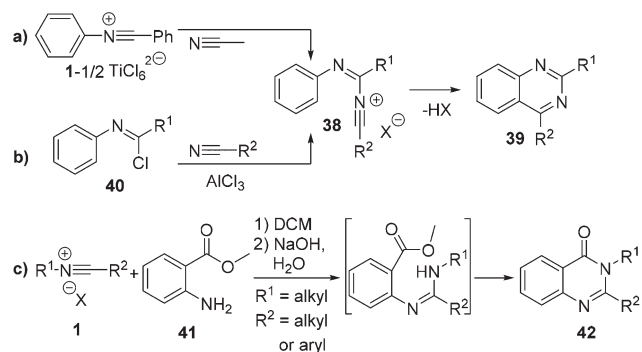

Scheme 5 Synthesis of imino-phosphanes.

ligands.[51] Also carbon-based nucleophiles can be used as illustrated by the reaction of (*N*-methyl)(methyl)-**1-BF$_4$** with pyrrole (Scheme 4c) that gives a mixture of the iminium ion **30** and imine **31**; full conversion to **31** results in NaOH quenching. A study on the reactivity of pentaamineosmium(II)-η²-pyrrole complex **32** revealed that the pyrrole group changes from the α to the β-position on addition of a nitrilium ion to give **33** (Scheme 4d).[52] A similar β-addition to nitrilium ions was shown for the analogue η²-furan complexes.[53]

C-Phenyl nitrilium salts **1-BF$_4$** reportedly react in high yield with imino-imidazoles **34** to bis-imino-imidazolium salt **35** (Scheme 4e) that are precursors for bis-imino N-heterocyclic carbenes, but the parent imidoyl chloride shows no reactivity.[54] (*N*-Methyl)(methyl)-**1-BF$_4$** has been shown to react in THF with a lithiated *C*-methyl imine to generate the BF$_2$-adduct of asymmetrically substituted β-diimine **36** in poor yield (Scheme 4f).[55] Recently, we have shown that **1-OTf** can be used as an imine synthon for the high-yield synthesis of iminophosphanes **37**, which can function as either anionic phosphaamidinate ligands (for R^3 = H)[24] or as neutral 1,3-P,N-ligands (R^3, R^4 = Ph, *t*Bu or Cy)[56] for transition metal coordination (Scheme 5).

4. Heterocycles

4.1 From stable nitrilium ions

Various heterocyclic compounds have been synthesized by the nucleophilic attack on a nitrilium ion followed by intramolecular cyclization. For instance, when nitriles were reacted with (*N*-phenyl)(phenyl)-**1-(TiCl$_6$)$_{0.5}$** (Scheme 6a) or *N*-phenyl-imidoylchloride **40**, using AlCl$_3$ for Cl-abstraction, the resulting intermediate **38** cyclized immediately to chinazoline **39** (Scheme 6b)[57] except when the *N*-phenyl group carried *ortho*-

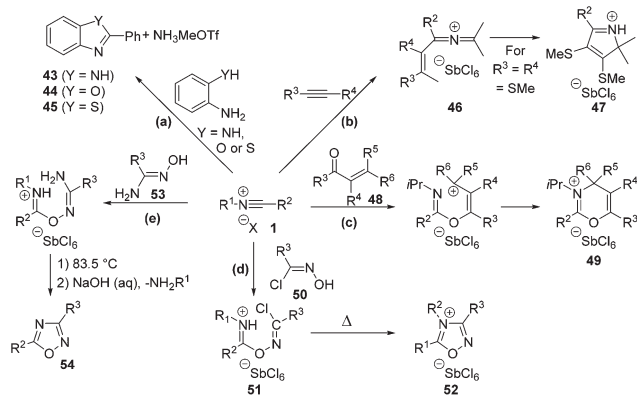**Scheme 4** Nitrilium salts as imine synthons.

Scheme 6 Synthesis of chinazolines and 3,4-dihydro-4-oxo-quinazolines from nitrilium ions.

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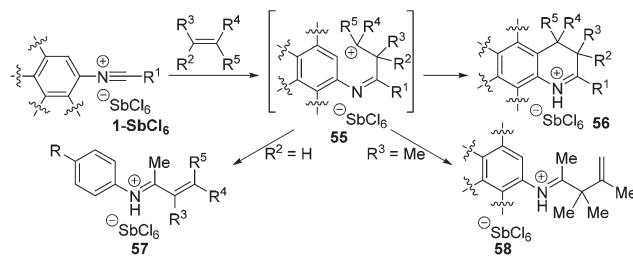
Org. Biomol. Chem., 2017, **15**, 10134–10144 | **10137**

methyl substituents. The method has been used for the synthesis of 2-aminochinazolines (*i.e.*, R^1 = NR^3R^4; R^3, R^4 = aryl or alkyl) by using SnCl$_4$ as a Lewis acid.[58] A similar methodology is reportedly also suited for the synthesis of 3,4-dihydro-4-oxo-quinazoline **42** by the *N*-nucleophilic attack of methyl-anthranilate **41** at *N*-alkyl-**1-FeCl$_4$**[59] or its triflate[27b] (Scheme 6c) as well as for imidazoles when propargylamine or α-aminoesters are used.[59]

*C*1-Phenyl-substituted benzamidazole **43** was obtained from (*N*-methyl)(phenyl)-**1-OTf** and 2-aminoaniline with benzoxazole **44** and benzothiazole **45** resulting likewise from 2-aminophenol and 2-aminothiophenol, respectively (Scheme 7a);[13b] in the reaction affording **43**, the amine groups of 2-aminoaniline attack the nitrilium carbon atom sequentially with expulsion of methylammonium triflate. Reacting diaminomaleonitrile with (*N*-methyl)(methyl)-**1-OTf** afforded likewise 2-dimethyl-5-amino-4-(*C*-cyanoformimidoyl)imidazole and 6-carbamoyl-purines on subsequent treatment with ketones.[60]

Reacting *N*-isopropyl-**1-SbCl$_6$** with acetylenes yielded 2-azoniaallenes **46** after a 1,5-H shift (Scheme 7b). When instead 1,2-bis(methylthio)acetylene was used a subsequent slow cyclization occurred to give the 2*H*-pyrrolium salt **47**.[30b] A variety of 4*H*-1,3-oxazinium salts **49** were obtained from the reaction of *N*-alkyl-**1-SbCl$_6$** with chalcone **48a** (R^3, R^5 = Ph; R^4, R^6 = H), presumably by the attack of the carbonyl oxygen at the nitrilium salt followed by the *N*-nucleophilic attack at the resulting carbocation (Scheme 7c).[61] 6*H*-1,3-Oxazinium salts resulted instead with α,β-unsaturated aldehydes (**48b**, R^3 = H), presumably *via* an initial [2 + 2]-cycloaddition of the aldehyde and the nitrilium ion followed by ring opening and cyclization by *O*-nucleophilic attack. 3,4,5-Trisubstituted 1,2,4-oxadiazolium salts **52** resulted from the *O*-nucleophilic attack of *N*-hydroxycarboximidoyl chloride **50** at *N*-alkyl-**1-SbCl$_6$** and heat induced cyclization of intermediate **51** (Scheme 7d);[62] **52** resulted in a single step at room temperature on using nitrile oxides instead of **50**. Similarly, amide oximes **53** were shown to react with both *N*-alkyl- and *N*-aryl-**1-SbCl$_4$** to give 3,5-disubstituted 1,2,4-oxadiazoles **54** upon basic work-up and expulsion of an amine (Scheme 7e).[63]

Scheme 8 3,4-Dihydroquinolinium salts synthesis from *N*-aryl nitrilium ions and alkenes.

N-Aryl-**1-SbCl$_6$** reportedly reacts with alkenes to yield 3,4-dihydroquinolinium salts **56** (Scheme 8).[64] The reaction was postulated to proceed by the electrophilic attack of the nitrilium ion on the alkene to give intermediate **55**, followed by intramolecular electrophilic aromatic substitution. Support for **55** came from the isolation of Houben–Hoesch product **57** and formation of the ene-reaction product **58**. Similarly, electron rich acetylenes were shown to provide quinolones.[65]

1,4,5-Tetrazolium salts **60** were stereoselectively formed on reacting azides with **1-SO$_3$F** (Scheme 9).[66] The *N*-nucleophilic attack of azides on the nitrilium ion gives intermediate **59**, which cyclizes to 1,4,5-tetrazolium salt **60**. This salt can be converted to tetrazoline **61** by reduction with LiBH$_4$ or reaction with organolithium reagents.
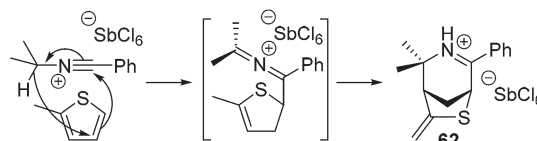
The reaction between *N*-iso-propyl-**1-SbCl$_6$** and 2-methyl-thiophene affording hetero-bicyclic **62** (Scheme 10) was postulated to proceed by an intermolecular ene-reaction followed by cyclization through the electrophilic attack on the heterocyclic double bond and subsequent tautomerization, albeit that the last step may also proceed by means of a concerted 6-(3,5)-ene cyclization.[30a]

4.2. From *in situ* generated nitrilium ions

Heterocyclic compounds are equally well accessible by means of *in situ* generated nitrilium ions that undergo an intramolecular cyclization. Exemplary is the synthesis of pyrazolo[3,4-*d*]pyrimidines **65** by treating *C*5-substituted *N*-pyrazolyl imidoyl chlorides **63** with SnCl$_4$ in the presence of nitriles

Scheme 7 Heterocycle synthesis from nitrilium ions.
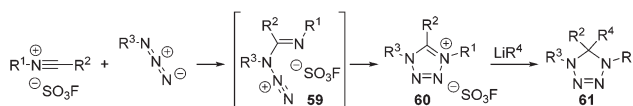
Scheme 9 The reaction of nitrilium ions with azides.

Scheme 10 Ene reactions with nitrilium ions.

10138 | *Org. Biomol. Chem.*, 2017, **15**, 10134–10144

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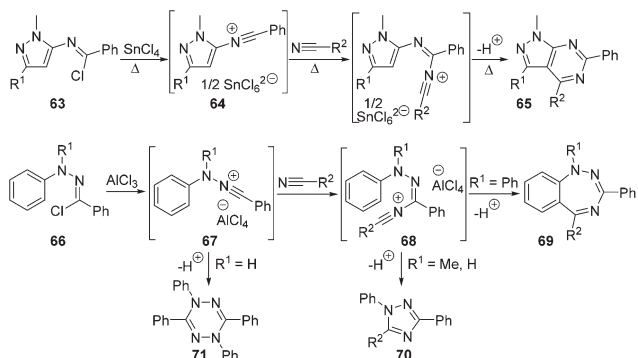
Scheme 11 Synthesis of pyrazolo[3,4-*d*]pyrimidines (top) and 1*H*-1,2,4-benzotriazepines and 1,2,4-triazoles (bottom).

Scheme 13 Synthesis of cyclobutapyrimidines.

(Scheme 11, top), which proceeds analogous to the discussed synthesis of chinazolines (Scheme 6; top). Nitrilium ion **64**, generated by Lewis a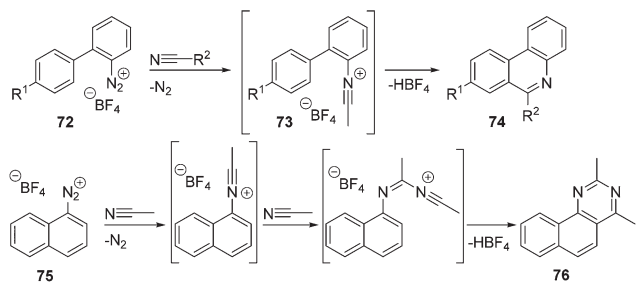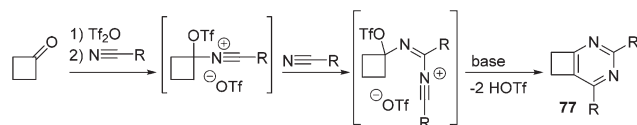cid induced Cl-abstraction, reacts with the nitrile to subsequently undergo cyclization by intramolecular electrophilic aromatic substitution.[67] Likewise, hydrazine based imidoylchlorides **66** have been converted to 1*H*-1,2,4-benzotriazepines **69**, but the reaction is sensitive to the hydrazine *N*-substituent (Scheme 11, bottom).[68] Although **69** was formed when this substituent is a *N*-phenyl group, this is not the case with the *N*-methyl derivatives that gave instead 1,2,4-triazoles **70**, apparently by the preferred electrophilic attack at the amine of intermediate **68**. In the absence of an *N*-substituent, **66** also reacted to give triazole **70** besides the deprotonated dimer **71** of nitrilium ion **67**.[69]

The biaryldiazonium-BF$_4$ salts **72** react with nitriles under expulsion of N$_2$ to give **73** as intermediates, which undergo an intermolecular electrophilic aromatic substitution to phenanthridines **74** (Scheme 12, top) that are tedious to isolate and often convert to picrates.[70]

Interestingly, the nitrilium ion resulting from the reaction of 1-naphthalenediazonium-BF$_4$ (**75**) with acetonitrile didn't cyclize to 2-methylbenzo[*c*,*d*]indole, but reacted instead with another acetonitrile molecule to cyclize to 2,4-dimethylbenzo[*h*]quinazoline (**76**; Scheme 12, bottom);[70] the reaction resembles Meerwein's chinazoline synthesis shown in Scheme 6. Similar reactivity with the double uptake of a nitrile was found in the reaction with cyclobutanone when treated

with triflic anhydride giving cyclobutapyrimidines **77** as the product (Scheme 13).[71]

Heterocycles can also be generated in a Ritter-like reaction in which the nitrilium ion, generated *in situ* from a carbocation and a nitrile, undergoes intramolecular cyclization. Illustrative is the synthesis of dihydro-1,3-oxazine **80** from diol **78**, which proceeds by generating an incipient carbocation that reacts with a nitrile to generate the transient nitrilium ion intermediate **79** (Scheme 14).[72] A similar reaction occurred with dinitrile succinonitrile as only one nitrile reacted with the dihydro-1,3-oxazine with a pendant nitrile group.[73] Ritter-like reactions can also be used for the synthesis of 2-thiazolines,[74] 5,6-dihydro-1,3-thiazines,[74] and non-nitrile functionalized dihydro-1,3-oxazines.[75]

Diazocarbonyls **81** have been reacted with nitriles in the presence of AlCl$_3$ to give oxazoles **83**,[76] which was postulated to be formed *via* nitrilium intermediate **82** that undergoes intramolecular cyclization by the *O*-nucleophilic attack (Scheme 15). However, executing the reaction with less than 2 equivalents of AlCl$_3$ generated α-chlorocarbonyl as a by-product, which could be prevented by using BF$_3$ instead.[77]

In situ generation of nitrilium ion **85** from amide **84** and POCl$_3$ was shown to lead to a cascade reaction resulting in 6*H*-[1]benzopyrano[4,3-*b*]quinolone **86** (Scheme 16; top).[78] Similarly, generating ion **88** from amide **87** and trimethylsilylpolyphosphate (PPSE) led directly to pyrroline ester **89** by the electrophilic attack of the nitrilium carbon on the olefin.[79] Reduction of **89** with NaBH$_4$ initiates a second cyclization to give benzylidinepyrrolizidone **90** (Scheme 16; bottom).

Although the extensively reviewed Ugi reaction[18c,20a,b,80] (Scheme 1f) is beyond the scope of the present review, there are Ugi-like reactions involving a nitrilium ion intermediate with subsequent cyclization to a heterocycle, *i.e.*, by the intra-

Scheme 12 Phenanthridine synthesis from diaryldiazonium salts and nitriles.
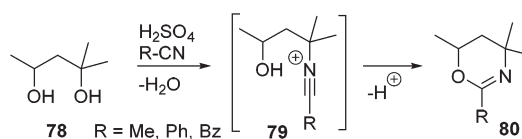
Scheme 14 Ritter like synthesis of dihydro-1,3-oxazines.
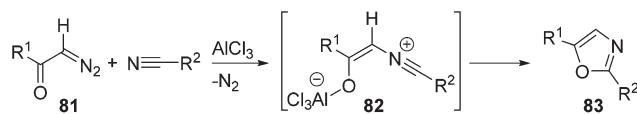
Scheme 15 Lewis acid promoted reaction of diazocarbonyls and nitriles.
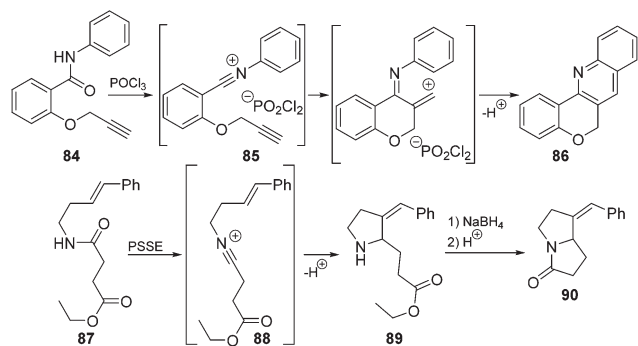
Scheme 16   Direct nitrilium ion generation from amides.

Scheme 18   Synthesis of aminooxazoles **100** from imine **99** and isocyanides.

Scheme 19   Synthesis of 4-imino-4*H*-3,1-benzoxazines **103**.

molecular nucleophilic attack of the isocyanide at the ion center (Scheme 17). Typically, the nucleophile is part of the amine reactant (H$_2$N^Nu), as is the case for the reactions of 2-aminopyridine, 2-aminopyrimidine, and other heterocyclic amidines that render bicyclic 3-aminoimidazoles **91** (Scheme 17a).[81] Also pyrazole amidines have been shown to react in a 3-component reaction with benzaldehydes and isocyanides to give 3-aminoimidazoles **92** (Scheme 17b).[82] Asymmetric pyrazole tetrazo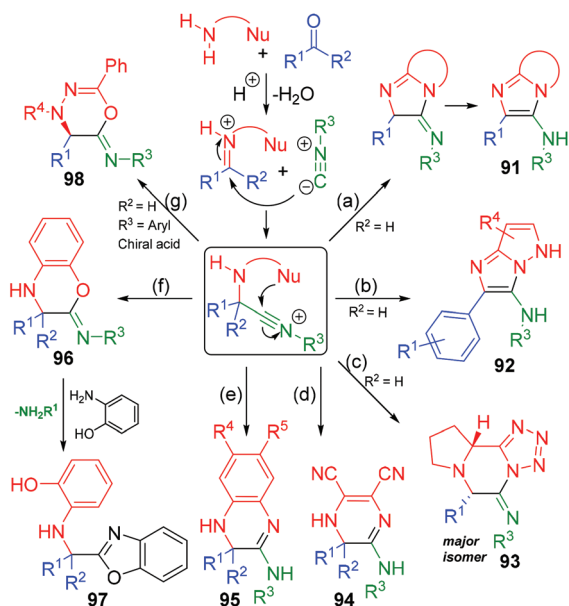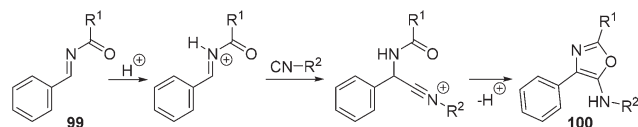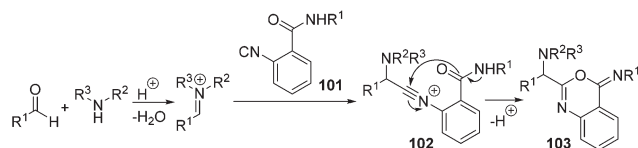le derivatives have been employed to synthesize heterocycles **93** (Scheme 17c).[83] The intramolecular nucleophile can also be another amine group, as was shown for the reaction of 2,3-diaminomaleonitrile with ketones and isocyanides to afford heterocycle **94** (Scheme 17d);[84] the reaction of ethylenediamine[85] with aldehydes and isocyanides yields similar results. Reaction of *o*-phenyldiamine with ketones (R^1, R^2 = alkyl) and isocyanides gave 3,4-dihydroquinoxalin-2-amines **95** (Scheme 17e);[86] on using

aldehydes (R^2 = H), **95** could be converted to quinoxalines on oxidation with DDQ.[87]
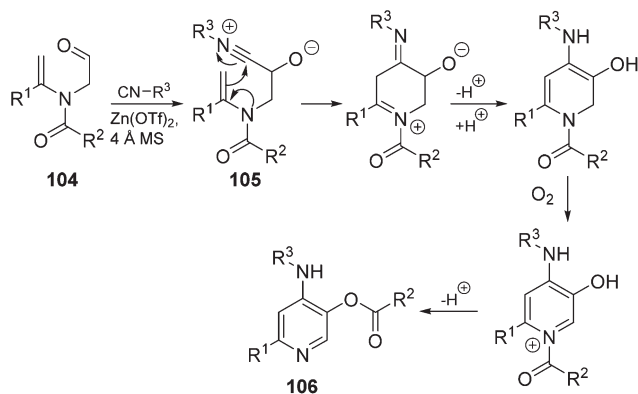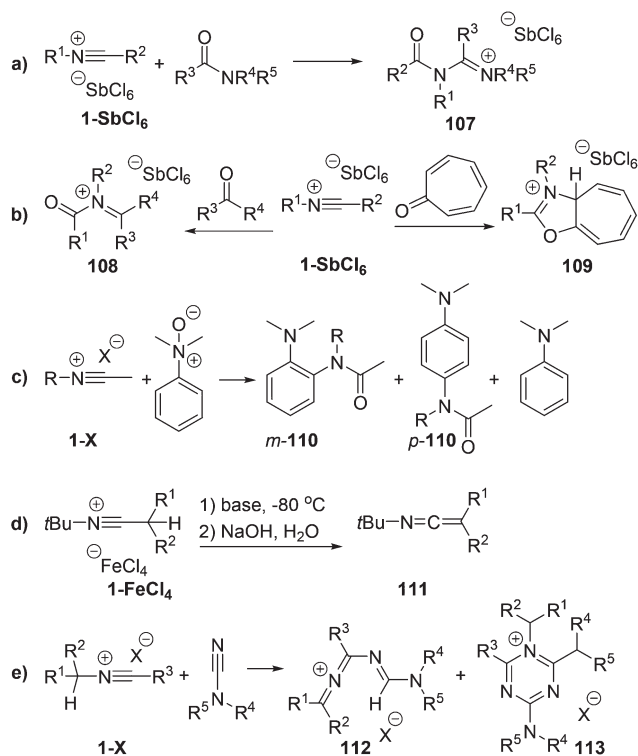
Oxygen nucleophiles can also be used, as has been shown for the reaction of 2-aminophenol, the cyclic ketone *N*-methyl-4-piperidone, and isocyanides that afforded bicyclic **96** (Scheme 17f).[88] A subsequent reaction with another molecule of 2-aminophenol led to double addition at the imine carbon of **96** to give benzoxazoles **97** on expulsion of R^3-NH$_2$. With aldehydes (R^2 = H) instead of ketones, tautomerization of **96** occurred to give 4*H*-benzo[1,4]oxazin-2-amines;[89] oxidation with DDQ gave 2*H*-benzo[1,4]oxazin-2-imines.[90] *N'*-Benzylbenzohydrazide reportedly gives heterocycle **98** (Scheme 17g) in high ee in the presence of a catalytic amount of a chiral acid, such as 3,3′-substituted (*R*)-binaphthalenyl-2,2′-dicarboxylic acid derivatives, which transfers its chiral information as the counter ion.[91] An alternative route to C,N-cyclic heterocycles **98** is the synthesis directly from C,N-cyclic *N'*-acyl azomethine imines and isonitriles.[92] Similarly, imine **99** was shown to react with isocyanides under acidic conditions to give aminooxazoles **100** (Scheme 18).[93]

The nucleophile in the intramolecular reaction does not need to be part of the amine component, as was demonstrated for 2-isocyanobenzamide (**101**) with its amide oxygen attacking the nitrilium carbon of intermediate **102** to give 4-imino-4*H*-3,1-benzoxazines **103** (Scheme 19).[94]

The nucleophilic attack of isocyanides on *N*-formyl,methyl-substituted enamides **104** gave nitrilium ylide **105**, which after tautomerization and oxidation with molecular oxygen, underwent an intermolecular acyl transfer from nitrogen to oxygen, to afford the pyridine derivatives **106** (Scheme 20).[95]

5.   Miscellaneous reactions

The reaction of nitrilium salts with a range of amides has been studied. Although tertiary amides gave *N*-acylamidinium salts **107** as the sole product (Scheme 21a),[44a] isomeric mixtures were obtained with secondary amides.[96] Reacting **1-SbCl$_6$** with a range of ketones resulted in the insertion of the nitrilium

Scheme 17   Isocyanide based heterocycle syntheses through nitrilium ion trapping.

10140 | *Org. Biomol. Chem.*, 2017, **15**, 10134–10144

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Scheme 20 Synthesis of pyridines **106**.

Scheme 21 Miscellaneous reactions with nitrilium ions.

Non-interconverting azoniaallenes, $R_2C{=}N^+{=}CR{-}N{=}CH{-}NR_2$ (**112**), and triazinium salts **113** have reportedly been formed on reacting aminonitriles with nitrilium ions that carry an N-α-hydrogen (Scheme 21e).[99] The azoniaallenes were postulated to be formed by an ene reaction, while the triazinium salts were considered to be the product of a concerted or stepwise [2 + 2 + 2] cycloaddition.

Nitriles can be converted to aldehydes by means of a nitrilium ion strategy. The nitriles are first converted to N-isopropyl-**1**-$FeCl_4$ by treatment with $FeCl_3$ and isopropylchloride, followed by reduction with triethylsilane to imines and subsequent hydrolysis to aldehydes.[100] The method is suited for a wide range of alkyl and aryl nitriles and gives aldehydes in nearly quantitative yields.

6. Reactions with transition metal complexes

Nitrilium ions coordinate to transition metals in a manner similar to the isoelectronic and isostructural acetylenes. Exemplary is the η^2-coordination of (N-methyl)(phenyl)-**1**-BF_4 to vanadocene (**114**; Scheme 22a).[101] Similar η^2-nitrilium complexes have been reported for $TpW(NO)(PMe_3)$, which were synthesized by alkylating the nitrile complexes (Scheme 2g).[32] Nitrilium Ir–carbene complexes **116** can be accessed by reacting iridium(III) hydride complex **115** with various N-methyl-**1**-**OTf** (Scheme 22b).[102]

Nitrilium ions can react by means of a formal [2 + 2] cycloaddition with a $W{\equiv}C$ triple bond as in tungsten complex **117** to form imino–carbene complex **118**; the molecular structure showed the imino–carbene unit to be η^3-coordinated to the transition metal (Scheme 22c).[103]

Scheme 22 Reactions of nitrilium ions with transition metal complexes.

ion to give **108** (Scheme 21b, left),[44b] except for tropone that gave instead cycloaddition product **109** (Scheme 21b; right),[97] presumably by the attack of the oxygen on the nitrilium carbon followed by cyclization.

When N,N-dimethylaniline oxide was reacted with C-methyl-**1-X** a mixture of *ortho*- and *para*-N,N-dimethylaniline acetamides **110** and N,N-dimethylaniline was obtained (Scheme 21c), likely by the O-nucleophilic attack on the nitrilium ion followed by the dissociation and recombination of the AcN-R fragment.[28c] Nitrilium ions **1**-$FeCl_4$ with an α-hydrogen on the C-substituent can be deprotonated at −80 °C to ketene imines **111** (Scheme 21d),[98] but di- or trimerization occurs at higher reaction temperatures.
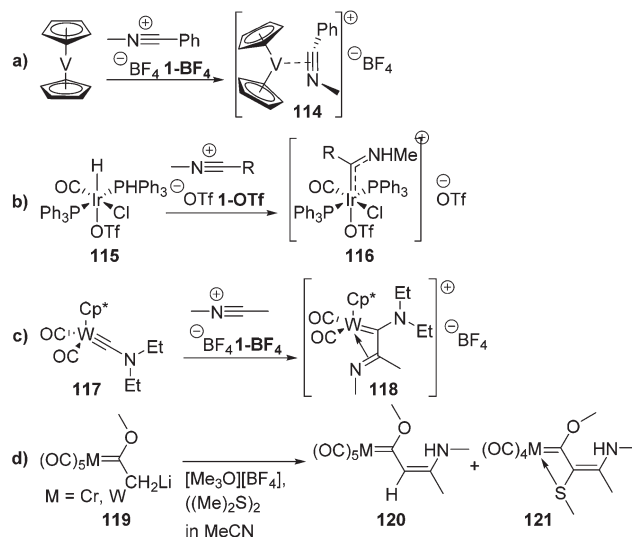
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Org. Biomol. Chem., 2017, **15**, 10134–10144 | **10141**

Treatment of deprotonated complex **119** (M = Cr, W) with the MeS$^+$-reagent $[(CH_3)_2(CH_3S)S][BF_4]$, generated *in situ* in acetonitrile from dimethyl disulfide and Meerwein's reagent, showed the formation of both **120** and **121** (Scheme 22d) and evidently involves the incorporation of an iminium ion.[104] This ion likely results from *in situ* formation of a nitrilium ion by methylation with Meerwein's reagent of acetonitrile. Thioalkylation of the tautomer of **120** is assumed to give **121**, which showed coordination of the thiol group to the metal center.

7. Conclusion and perspectives

Stable, isolable nitrilium ions can be readily synthesized by alkylating nitriles or by Lewis acid-induced chloride abstraction from imidoyl chlorides with typically $SbCl_6^-$, BF_4^-, a metal halide, fluorosulfate or triflate as a counter anion. Not only are the nitrilium ions convenient synthons to generate diverse nitriles, they also provide access to otherwise cumbersome to synthesize anionic phosphaamidinates and neutral 1,3-P,N-ligands applicable in transition metal complexes used for homogeneous catalysis. Moreover, a broad spectrum of heterocyclic compounds can be comfortably generated from both stable and *in situ* generated (transient) nitrilium ions by the intramolecular electrophilic attack of the nitrilium nitrogen atom or its neighboring iminium carbon on (heterocyclic) olefinic or (hetero) aromatic groups as exemplified by, *e.g.*, the Beckmann rearrangement and the Ritter, von Braun, Bischler–Napieralski, and Ugi-like reactions. Although less explored, nitrilium ions also react with ketones, amides, aniline oxides, and aminonitriles, and coordinate with transition metal complexes.

We hope that the recent advances to access nitrilium ions by very simple synthetic protocols as well as the ability to improve the handling of thermally unstable ones by DMAP-complexation will stimulate the advancement of these remarkably useful synthons in organic synthesis.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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