Superelectrophiles in heterocyclic ring-forming reactions

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Abstract
Superelectrophiles are multiply charged cationic species which may exhibit remarkable reactivities towards weak nucleophiles. Since their discovery in the 1970s, many novel synthetic methodologies have been developed using superelectrophiles. In the following Account, superelectrophilic ring-forming reaction will be examined, specifically those reaction which produce heterocyclic systems.

**Keywords:** Superelectrophiles, dications, superacids, heterocycles

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1. Introduction

During the 1960s and 1970s, there were a number of reports describing electrophilic reactions in which the cationic electrophiles were notably more reactive in solutions of increasing acidities.[1] These electrophiles were often capable of reacting with even the weakest nucleophiles, such as alkanes or deactivated arenes. This pattern of chemistry was first recognized by Olah with the proposed concept of superelectrophilic activation. As described in the early papers by the Olah group,[1] superelectrophilic activation may occur when a cationic electrophile interacts with a

Brønsted or Lewis acid, generating a species with an increasing amount of positive charge.[2] In the limiting cases, this may involve formation of a fully formed dicationic species. Because cationic electrophiles are typically very weak bases, the formation of superelectrophiles is most common in strong or superacidic solutions.[3]

   Two important and typical superelectrophilic systems are the nitronium and acetyl cations. In aprotic solvents, nitronium tetrafluoroborate ($NO_2^+BF_4^-$) reacts readily with activated, electron rich arenes (i.e., good nucleophiles), but it does not react with strongly deactivated arenes, such as *m*-dinitrobenzene.[4] In superacidic media however, *m*-dinitrobenzene reacts with nitronium tetrafluoroborate to give 1,3,5-trinitrobenzene in 70% yield. This increasing electrophilic reactivity can be explained by partial or complete protonation at the oxygen lone pair electrons to give superelectrophiles **2** or **3** (Scheme 1). In a similar respect, acetyl cation salts (i.e. $CH_3CO^+SbF_5^-$) are unreactive to *iso*-alkanes in SO_2, SO_2ClF, AsF_3, or CH_2Cl_2.[5] Reaction in superacidic $HF-BF_3$ leads to efficient hydride abstraction from the *iso*-alkanes,[6] and consequently, the superelectrophilic acetyl dication (**5** or **6**) is thought to be involved. In both the nitronium and acetyl ion superelectrophiles, the enhanced reactivities stem from the increasing dipositive charge on the electrophiles. This is the key element of superelectrophilic activation, as proposed by Olah and coworkers.[2] Over the past several decades, the term "superelectrophile" has at times been used rather loosely, describing everything from metals in high oxidation states to compounds with multiple nitro groups. While these systems may exhibit novel reactivities and chemistry, they generally cannot be considered superelectrophiles according to Olah's original concept.
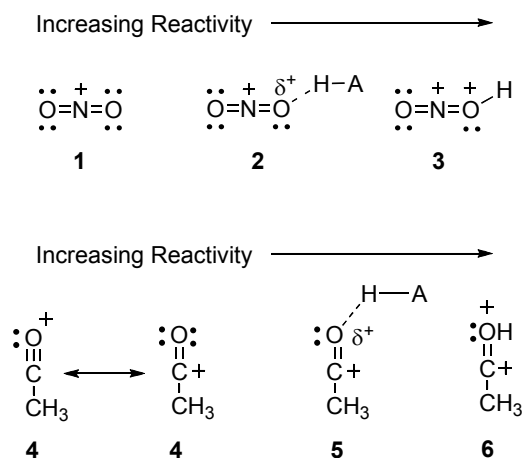

**Scheme 1.** Nitronium and acetyl ion superelectrophiles.

   Superelectrophiles are organized into two categories, depending on the distance between the charge centers: *gitionic* (close) and *distonic* (distant) superelectrophiles. Gitionic superelectrophiles are defined as those in which the two positive charges are separated by no more than one carbon atom or heteroatom. The gitionic superelectrophiles are further broken

down into geminal, vicinal, and 1,3-dicationic systems. Examples of the geminal systems are diprotonated H_2S (H_4S^{2+}, **7**) and the analogous heterocyclic system (**8**, Figure 1).[7,8] With these systems, the two positive charges are centered at one atom. In polyatomic ions such as **7-8**, it is understood that atomic charges are an approximation and that the charges are delocalized by resonance, induction, and other effects. The vicinal systems are characterized by cationic charge centers being located on adjacent atoms, such as in the bicyclic hydrazinium ion system (**9**).[9] Finally, the 1,3-dicationic systems are considered those systems in which the positive charges are separated by a single atom. The piperidine derivative **10** is an example of a 1,3-dicationic system.[10]

The distonic superelectrophiles have cationic charge centers that are separated by two or more carbon (or hetero) atoms. There are many examples of heterocyclic distonic superelectrophiles, some of which (**11-13**) are shown in Figure 1.[11] With increasing separation of charge centers, the dicationic species are no longer considered superelectrophiles. Several types of experimental studies have shown that such dicationic species (those with widely separated charge centers) exhibit electrophilic chemistry that is similar to monocationic electrophiles.[2e] For example, protonated acetophenone (**14**) is unreactive to benzene in the condensation chemistry (eq 1).[12] However, 4-acetylpyridine (**15**) forms a reactive superelectrophile (**16**) that reacts readily with benzene and other arenes (eq 2).[12] In the case of **16**, the pyridinium ring enhances the electrophilic reactivity of the adjacent carboxonium ion, and consequently it is capable of reacting with the weak nucleophile benzene. When the pyridyl ring and ketone group are separated by several carbon atoms however, the carboxonium group does not show superelectrophilic reactivity despite forming a dicationic system (**17**, eq 3). Thus, superelectrophilic activation is directly related to the proximity of the charge centers.
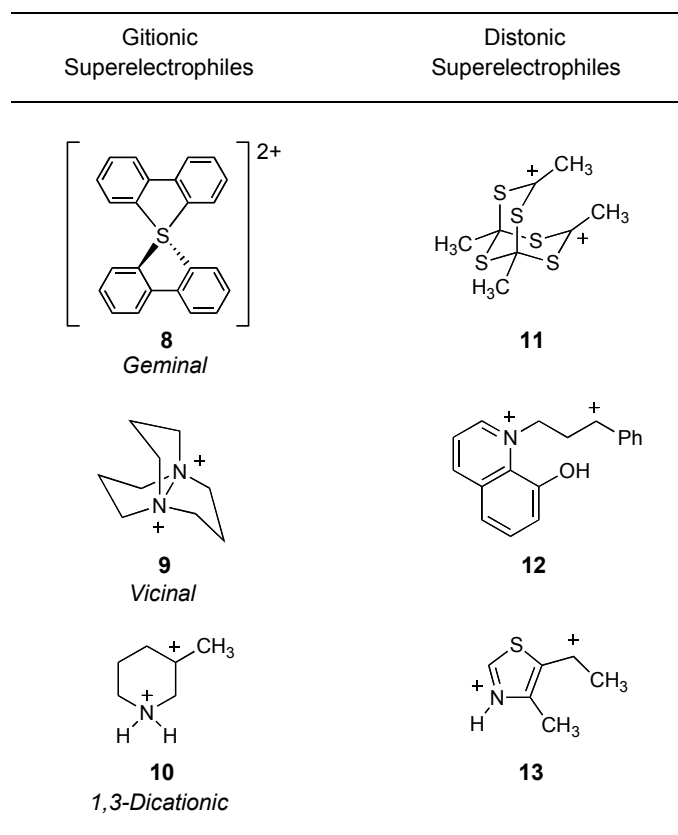
**Figure 1.** Types of superelectrophilic systems.
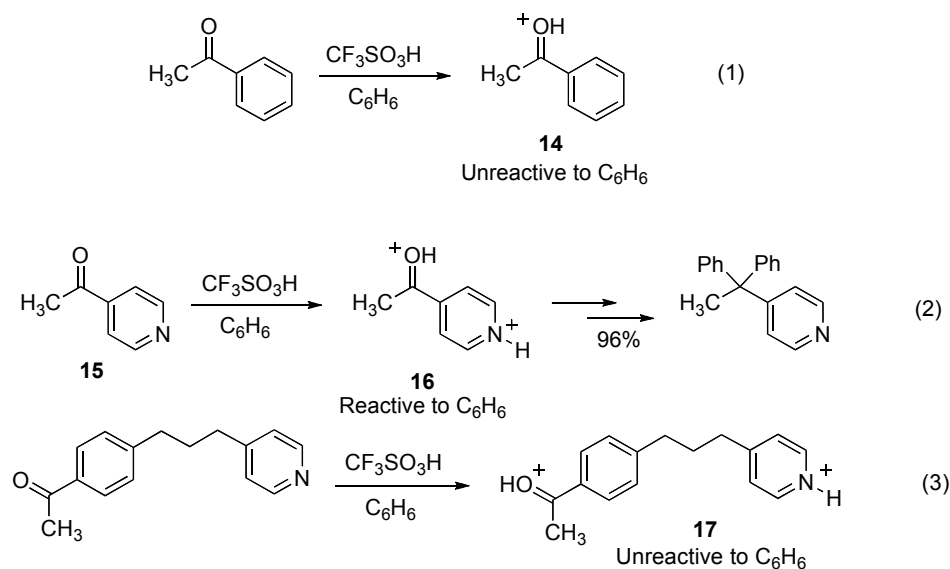
Superelectrophilic chemistry has been studied extensively since Olah's early publications in this area.[2] Superelectrophiles are the basis for many useful synthetic transformations and they have been the subject of numerous mechanistic and theoretical studies. Moreover, a number of

gas-phase superelectrophiles have been generated in mass spectrometry studies, including both the nitronium and acetyl ion superelectrophiles (**3** and **6**).[13] The chemistry of superelectrophiles has been reviewed several times, including most recently in a comprehensive monograph.[2e] In the following account, superelectrophilic heterocylic chemistry will be reviewed, with an emphasis on the synthetic aspects of this chemistry. This Account will specifically examine heterocylic ring-forming reactions involving superelectrophiles. Although a number of mechanistic studies have involved heterocyclic superelectrophiles, these reports will not be discussed.

2. Ring-forming Reactions

2.1.1 Gitionic superelectrophiles: geminal systems

Although *geminal*-superelectrophiles are the least common type of superelectrophile, there have been a couple heterocycles prepared from this variety of superelectrophile. Ionization of the *N*-oxide (**18**) in CF_3SO_3H leads to the superelectrophile **19**, which may be considered a type of nitrogen-centered *geminal*-superelectrophile on the basis of one of its resonance forms (eq 4).[14] Cyclization then gives the natural product alkaloid (**20**). An oxygen-center *geminal*-superelectrophile may be involved in the cyclization of 2,5-hexanediol in FSO_3H-SbF_5 at −60°C.[15] Upon warming the solution to −30°C, the diprotonated substrate gives the protonated tetrahydrofuran derivative (eq 5). It has been shown that water may be diprotonated in very strong superacid, forming H_4O^{2+}.[16] Since a free hydroxy group is unlikely under these conditions, the *geminal*-superelectrophile **21** (or a partially protonated species) is proposed.
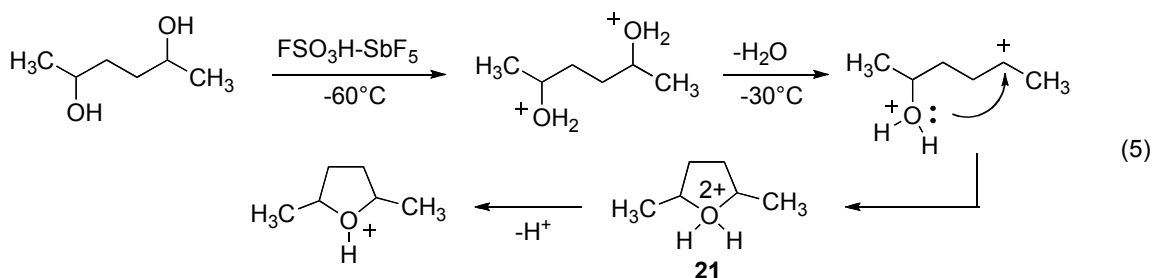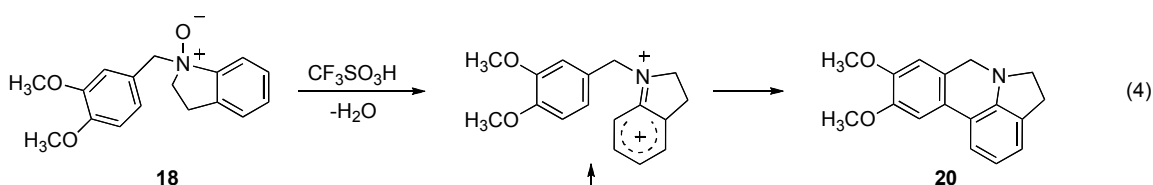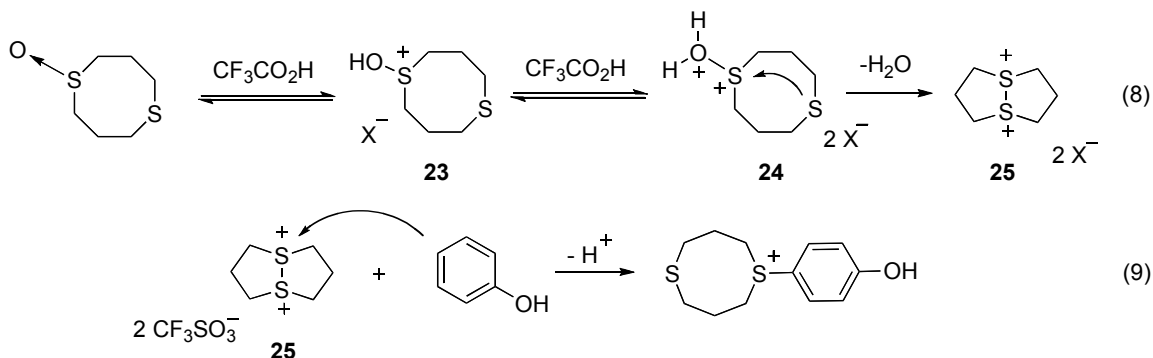
2.1.2 Gitionic superelectrophiles: vicinal systems

A number of *vicinal*-superelectrophiles have participated in ring-forming reactions. The Pictet-Spengler and Bischler-Napieralski reactions are useful synthetic methods to give the important isoquinoline ring system.[17] With monocationic iminium ions, the cyclization is most effective with activated aryl nucleophiles. However in studies of the Pictet-Spengler reaction using superacidic conditions, Shudo and Ohwada found kinetic evidence for the involvement of *vicinal*-superelectrophiles.[18] Moreover, they demonstrated that superelectrophilic activation enabled the cyclization to be done with less nucleophilic aryl groups (eq 6-7). In these reactions, an equilibrium is established between the iminium ion and the superelectrophile (i.e. **22**) which cyclizes rapidly.
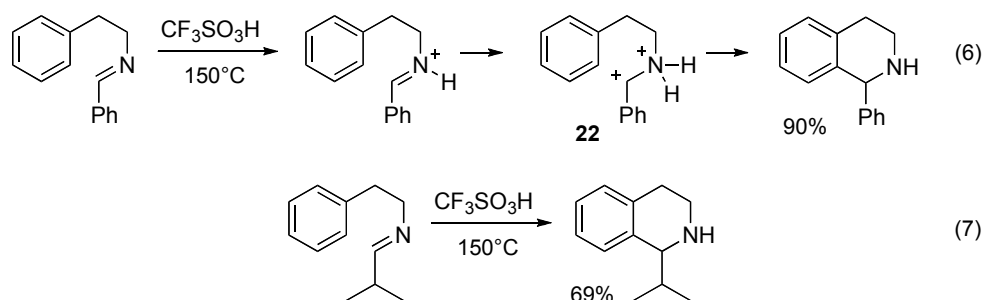

Bis-sulfonium dications are well known species that may be considered *vicinal*-superelectrophiles. The disulfonium-dication **25** can be prepared by reaction of the mono-S-oxide with acid (eq 8).[19] Dimethylsulfoxide has been shown to form the *O,S*-diprotonated species in superacid.[20] By analogy, this suggests a mechanism in which protonation of monocation **23** leads to the *vicinal*-superelectrophile **24** and ring formation give the disulfonium-dication **25**. However as noted by Nenajdenko and Alabugin, alternative mechanisms have been proposed for the conversion leading to **25**.[21] This species (**25**, X = $CF_3SO_3^-$) has been shown to react with electron-rich arenes to provide arylated products (eq 9).[22]


A diprotonated carbonyl group will also generate a *vicinal*-type of gitionic superelectrophile. Among the diprotonated carbonyl groups found in superelectrophilic chemistry, one example

involves heterocyclic ring formation. When ninhydrin is reacted with arenes in acidic media, product formation depends on acidity (eq 10).[23] Condensation in H_2SO_4 gives high yields of the 2,2-diaryl-1,3-indandione (**26**), while reaction in superacidic CF_3SO_3H leads to formation of 3-(diarylmethylene)-isobenzofuranones (**27**). If the 1,3-indandione is isolated and reacted with superacid, then the isobenzofuranone is obtained in quantitative yield. When the acid strengths are considered, it suggests a rearrangement mechanism involving the *gitionic*-superelectrophile **28** (eq 11).


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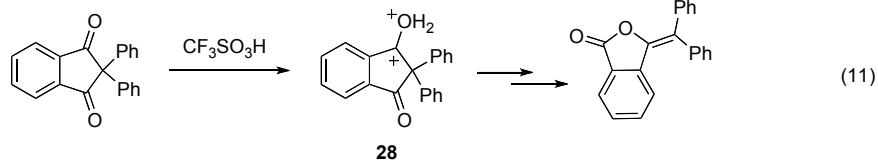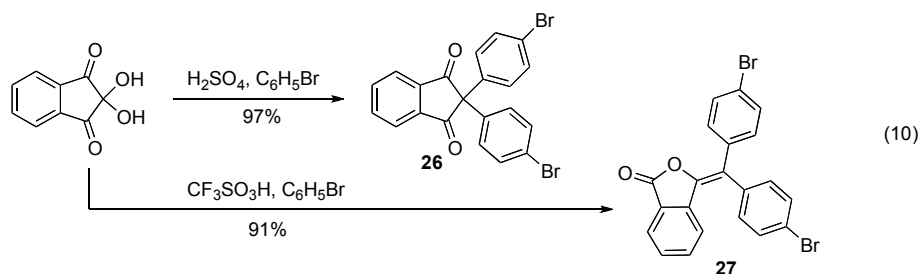
2.1.3 Gitionic superelectrophiles: 1,3-dicationic systems
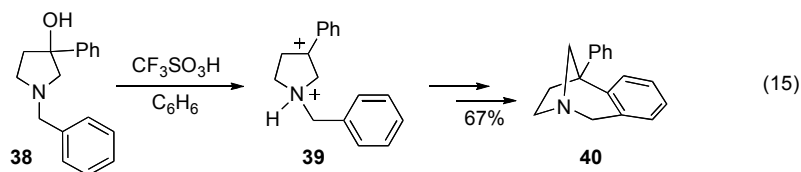
Several 1,3-dicationic superelectrophiles have been shown to form new heterocyclic ring systems. Recently, a number of aza-Nazarov reactions have been described and one variety is thought to proceed by 1,3-dicationic superelectrophiles.[24,25] For example, reaction of the *N*-acyliminium ion **29** with CF_3SO_3H gives the cyclized product **32** (eq 12). In CF_3SO_3H (H_o -14.1), the yield of the conversion is 50%, but in CF_3CO_2H (H_o -2.7) there is no cyclization product.[25] This suggests the formation of either the superelectrophile **30** or the protosolvated species (**31**). Theoretical calculations have shown that formation of the superelectrophilic *N*-acyliminium ion leads to a decreased energy barrier (by more than 10 kcal/mol) for the cyclization. Over the years, the cyclizations of *N*-acyliminium ions have been an effective tool for alkaloid syntheses.[26]
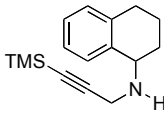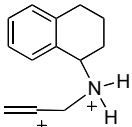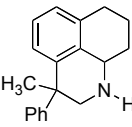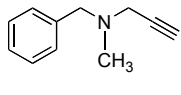

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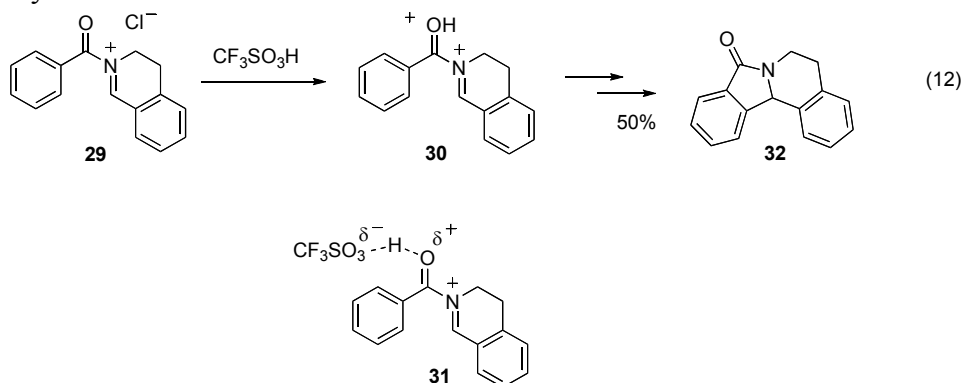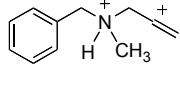
The superacid promoted synthesis of isoquinolinones was described recently and based on the increasing yields and reaction rates, a superelectrophilic species (**34**) was proposed (eq 13).[27] A modest degree of diastereoselectivity (90% d.r.) was obtained with cyclization of a chiral *N*-acyliminium ion **36** in superacid (eq 14).[27]
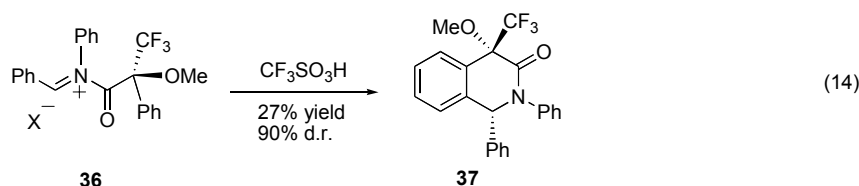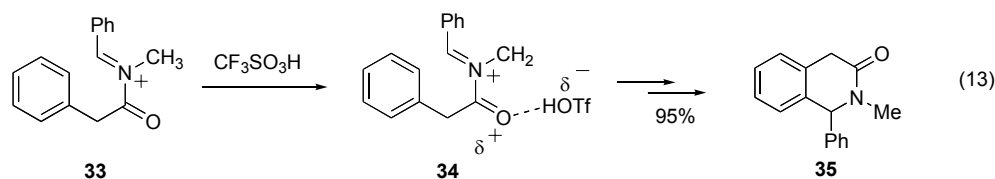
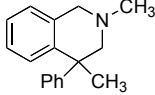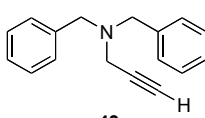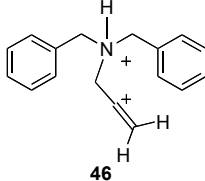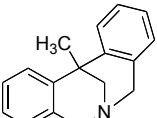Several other types of heterocyclic systems have been prepared from cyclizations with adjacent benzyl groups. The pyrrolidinol **38** ionizes in CF_3SO_3H to give the 1,3-dication **39**, and intramolecular reaction with the benzyl group occurs exclusively, despite the presence of a large amount of benzene (eq 15).[28] Superelectrophiles similar to **39** were directly observed by low temperature NMR. Compounds **41-43** also react with the superacid to generate the vinyl-ammonium dications (**44-46**; Figure 2).[29] In the case of **41**, the silyl group is cleaved rapidly in superacid and the superelectrophile **44** is formed. Cyclization of **44** with the benzyl group leads to formation of an exocyclic methylene group, and further protonation give another 1,3-dicationic superelectrophile (not shown). This reacts with benzene to give **47**. Similar mechanisms are proposed for compounds **42-43** and their cyclizations to the heterocyclic products.

Substrate	1,3-Dication	Product	Yield
41	**44**	**47**	93%[a]
42	**45**	**48**	69%[a]
43	**46**	**49**	95%[b]

[a]Conditions: Excess CF_3SO_3H with C_6H_6. [b]Conditions: Excess CF_3SO_3H.

Figure 2. Cyclizations of benzyl groups with 1,3-dicationic superelectrophiles.

An interesting cyclization was reported from the reactions of some nitroolefins in superacid. When 1-nitrocyclohexene is reacted with CF_3SO_3H and benzene at 40°C, formation of an initial 1,3-dicationic superelectrophile (**50**) leads to subsequent reaction with benzene and cyclization (eq 16).[30] In this case, the *4H*-1,2-benzoxazine (**51**) is formed in good yield. Thermolysis of the product *4H*-1,2-benzoxazines has been shown to provide good conversions to *o*-benzoquinone methides by retro-cycloaddition.[31]

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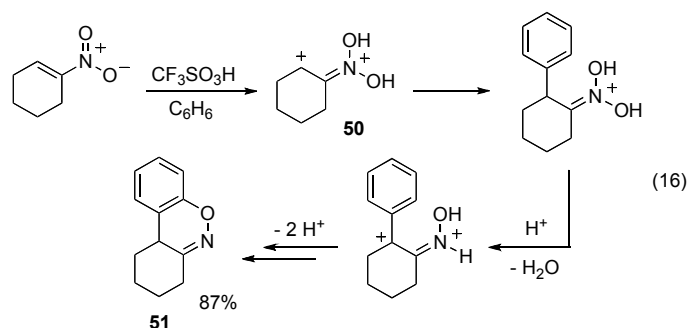
2.2 Distonic superelectrophiles

A fairly significant number of heterocyclic synthetic methods have been developed based on the reactions of distonic superelectrophiles. For example, the Grewe cyclization is a well-known synthetic methodology used in the preparation of morphine analogs (i.e. **55**) and it involves the

formation of a distonic superelectrophile (**54**, eq 17).[32] Protonation of the olefinic group and nitrogen atom gives the 1,4-dication **54**, which cyclizes to form the desired heterocyclic ring system (**55**). There are two important aspects in the success of this chemistry. Because of electrostatic repulsive effects, protonation at the double bond regioselectively forms the 1,4-dication (as opposed to the 1,3-dication from protonation at the 4-carbon). This insures formation of the proper ring system. Moreover, strong acids are known to promote polymerizations of olefins, however the Grewe cyclizations are typically clean conversions. Based on the mechanism for cationic polymerization of olefins, an oligomerization of **52** would require attack of dication **54** on the monocation **53**, an unlikely process due to electrostatic repulsive effects. Thus, the protonated nitrogen is a key element in the success of this reaction.
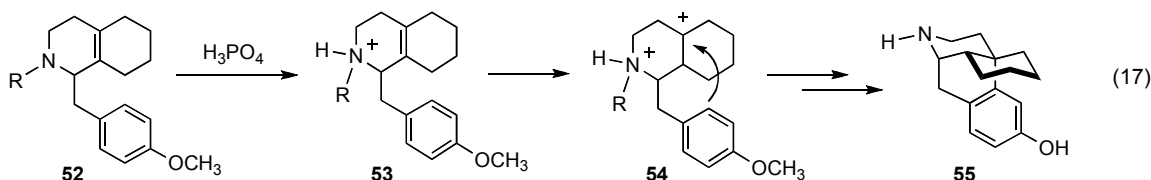

The Knorr cyclization is another classical heterocyclic synthetic method involving distonic superelectrophiles.[33] In 1964, Staskun reported that the Knorr cyclization is best conducted with excess Brønsted or Lewis acid, and remarkably, he proposed a mechanism involving dicationic intermediates.[34] Recent experimental and theoretical evidence confirms the main idea in Staskun's proposed mechanism (i.e., that dications are involved).[35] The Knorr cyclization is accomplished by the reaction of β-ketoamides under conditions of high acidity to give quinolin-2-one products (eq 18). As expected with a reaction involving a superelectrophilic intermediate, the conversions are best done in superacidic media (CF_3SO_3H), providing higher yields than with mineral acids (at lower temperature with shorter reaction times, too). The superelectrophile **57** is formed by protonation of the two carbonyl oxygen atoms which triggers cyclization. Superelectrophiles like **57** can be directly observed using low temperature ^{15}N and ^{13}C NMR and stable ion conditions.[35] Experimental NMR data for the superelectrophile compared favorably with the NMR data from DFT calculations.
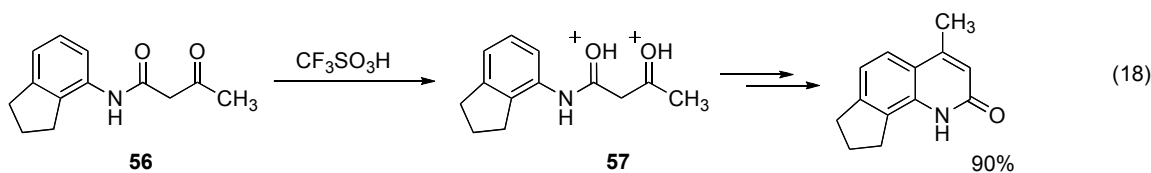
In somewhat related conversions, α-ketoamides will cyclize in the presence of superacid and an arene nucleophile to give aryl-substituted oxyindoles (i.e. **60**) and related products (eqs 19-20).[36] The mechanism is thought to involve the *O,O*-diprotonated superelectrophile (**59**), which cyclizes to form the oxyindole ring system. Subsequent steps involve dehydration and reaction

with the arene nucleophile. The *O,O*-diprotonated superelectrophile (i.e., **59**) was also characterized by spectroscopic experiments and theoretical calculations.
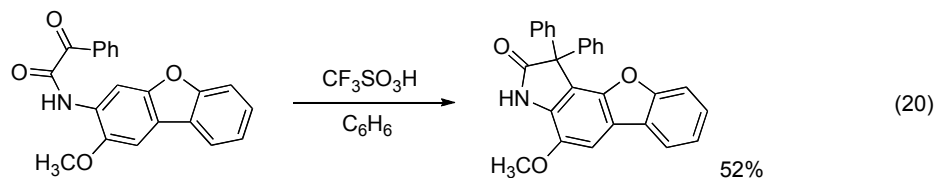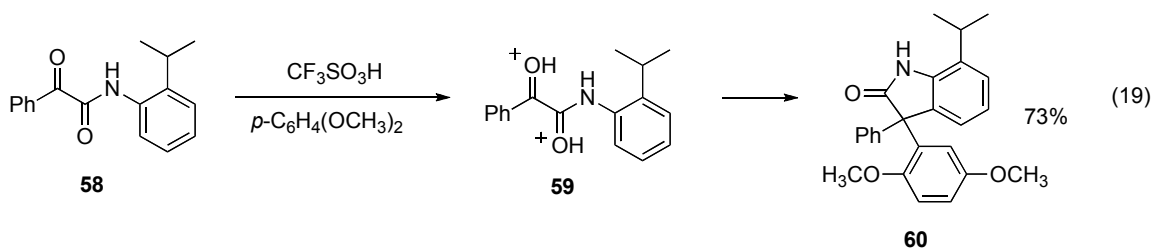
Other cyclizations of carbocations with aryl groups have given heterocyclic systems. Olefinic and alkynyl systems readily generate the distonic superelectrophiles and may give heterocyclic systems (eqs 21-23).[37-39] Although there is a general tendency to form dications with the greatest possible distance between the charges (*vide infra*), formation of the more highly-substituted carbocation generally outweighs the charge separation factors, as seen in the formation of superelectrophile **66**. Formation of benzylic cations can facilitate the formation of the superelectrophilic intermediates, as seen in **71** an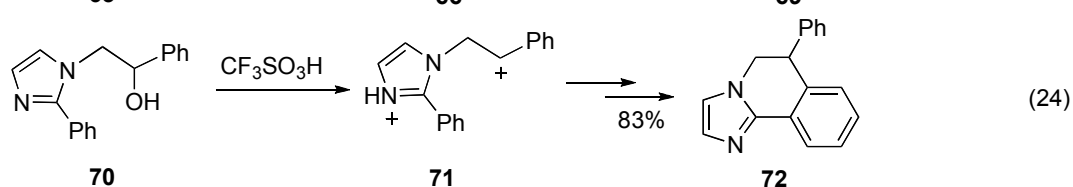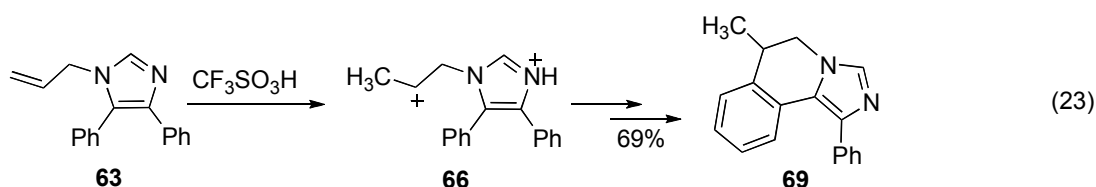d **75-76** (eqs 24-26).[39,40] Ionization of alcohol or olefin substrates may lead to these reactive superelectrophiles. In the case of compounds **73** and **74**, the superelectrophiles (**75-76**) are formed regioselectively due to the preference for maintaining the maximum distance between the two positive charges.

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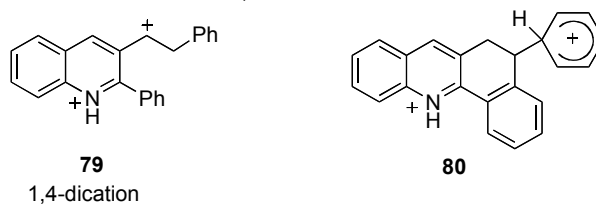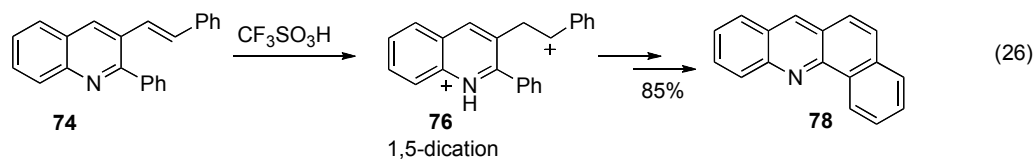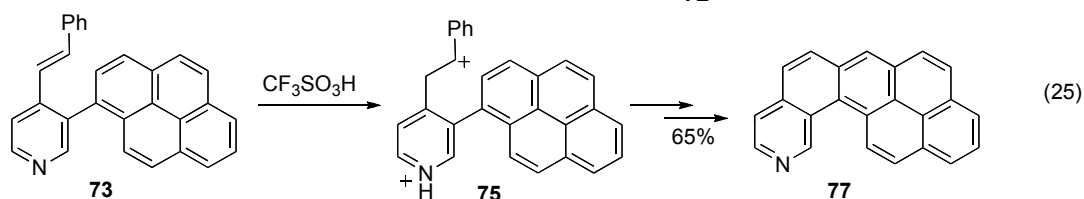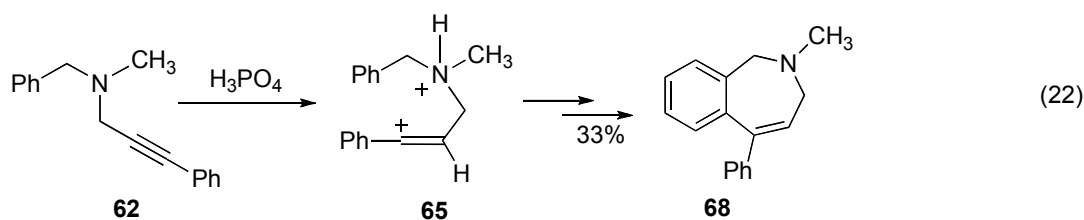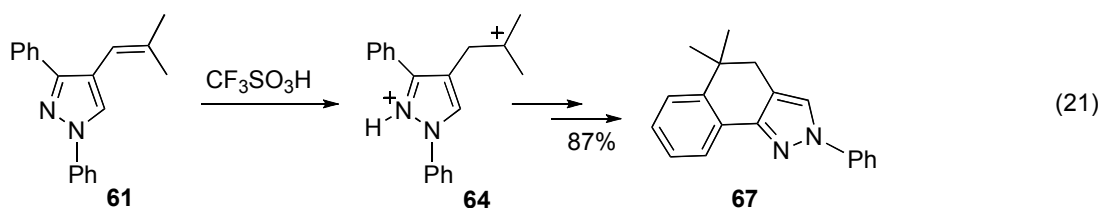
Thus, dication **79** is not formed from protonation of the olefin. Theoretical calculations estimate the energy difference between **76** and **79** to be about 10 kcal/mol (MP2/6-311G (d) level).[40] Under superacidic conditions, the phenyl group may be considered a type of leaving group and *ipso* protonation (**80**) of a phenyl group may lead to the formal elimination of benzene. This can occur in good yield, especially if an extended aromatic system is produced, as in products **77-78** (eqs 25-26). In the case of product **72** (eq 24), benzene elimination is

suppressed by use of mild reaction conditions. The preference for charge-separated dications may also be seen in the reaction of alcohol **81** (eq 27).[41] Initial ionization of the alcohol (**81**) leads to formation of the 1,4-dication **82**. Charge migration gives the 1,5-dication **83**, which undergoes cyclization and benzene elimination to provide the final condensation product **84**. Deuterium labeling experiments indicated that such charge migrations are the result of deprotonation-reprotonation steps rather than via 1,2-hydride shift.[41]

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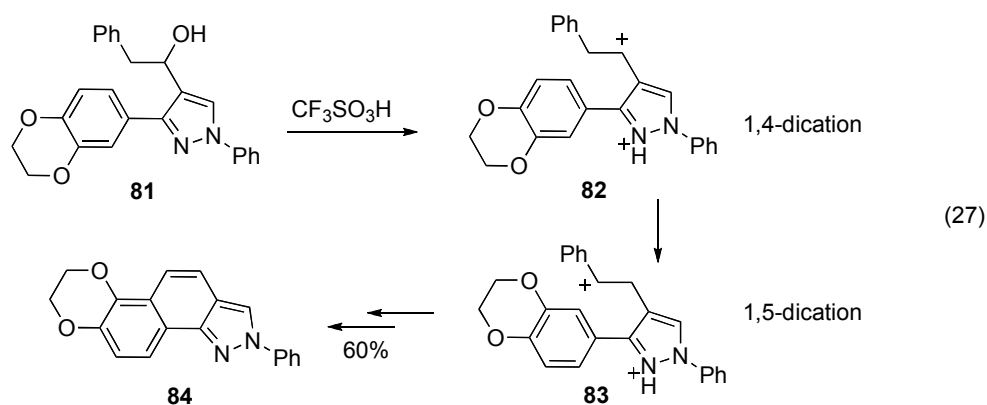
Sommer has described several types of cyclizations involving amide-derived distonic superelectrophiles.[42] For example, both the alkene and alkyne derivatives cyclize in strong and superacid media (eqs 28-29).

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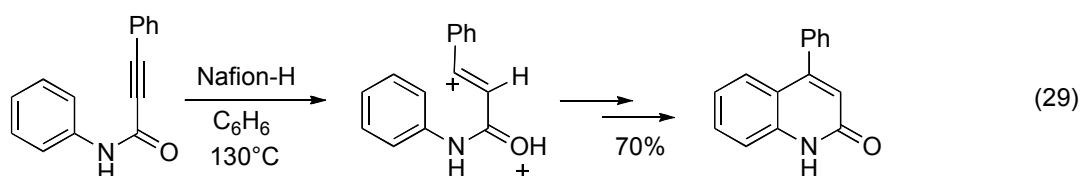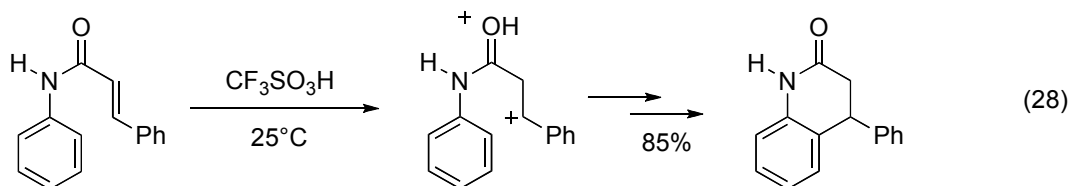
An interesting cyclization was reported by Koltunov et al. involving the reaction of 8-hydroxyquinoline with benzene in excess $AlCl_3$ or $AlBr_3$.[43] Initial reaction with acid leads to formation of **85** and the addition of benzene. Formation of another distonic superelectrophile **86** then leads to cyclization with the phenyl group and the heterocyclic alcohol **87** is produced (eq 30). It is notable that monocation **88** is unreactive to benzene.

(30)

88
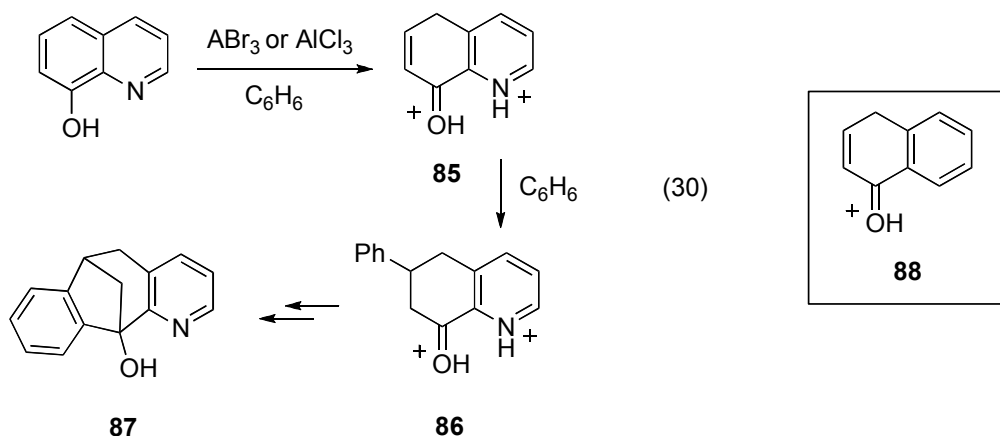
The reductive phenylation of nitroarenes in superacid has been shown to be an effective means for making biaryl bonds. An application of this chemistry yields the aporphine alkaloid ring system (eq 31).[44] In this reaction, it is likely that the nitro group is *at least* monoprotonated in superacid, forming superelectrophile **90**. This leads to positive charge formation in the aryl-ring and subsequent carbon-carbon bond formation.

(31)
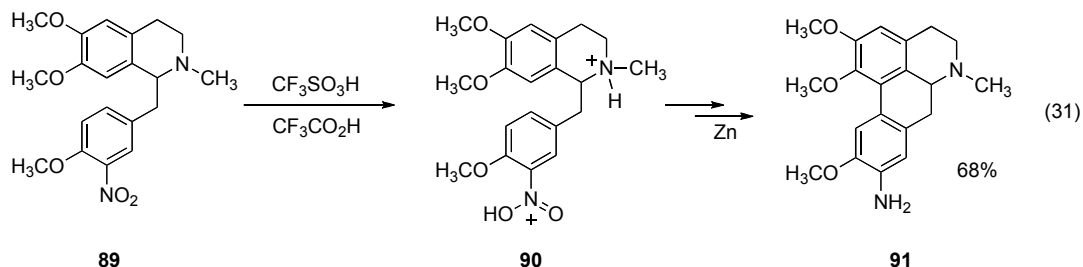
In a conversion related to the Grewe cyclization, seven-member heterocyclic rings were prepared by reactions of cyclohexene derivative in mineral acids (eq 32).[45] Although no mechanism is proposed for the conversion, it is likely that ring closure involves formation of the distonic superelectrophile **92**. As noted by the authors of this study, this is one of the only examples of a Grewe-type cyclization leading to a seven-member heterocycle (**93**).

(32)
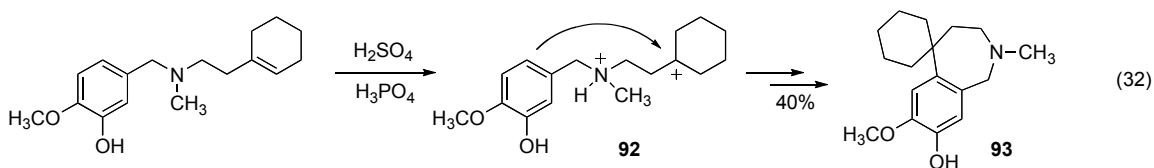
Among the heterocycles prepared from superelectrophiles, the vast majority are nitrogen-containing heterocycles. Nevertheless, some oxygen-containing heterocycles have been formed from superelectrophiles. One unusual example came from the superacid protonation of lactic acid.[46] In studies by Olah and Ku, reaction of lactic acid with $FSO_3H\text{-}SbF_5\text{-}SO_2$ led to the formation of superelectrophile **94** which could be observed by low temperature NMR (eq 33).

Upon warming to −30°C, the lactic acid dimerizes to give the oxygen-containing heterocycle, diprotonated lactide (**95**).

(33)
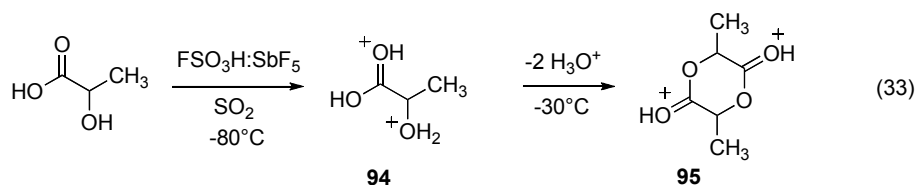
3. Summary

Electrophile-nucleophile reactions constitute perhaps the most important type of chemical reaction in organic synthesis. By virtue of their high reactivities, superelectrophiles are often capable of reacting with very weak nucleophiles. This aspect allows superelectrophilic chemistry to further expand the scope of electrophile-nucleophile reactions. These properties have been exploited in the development of a variety of new methods for preparing heterocyclic products. Although this Account has been confined to discussing heterocyclic ring-forming reactions, there are also many superelectrophilic reactions that provide heterocycle functionalization, group transfer reactions, and side-chain modification.[2e] Thus, it is expected that superelectrophilic chemistry will continue to be a useful tool in the synthesis of heterocyclic products.

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