ACCOUNTS
of chemical research

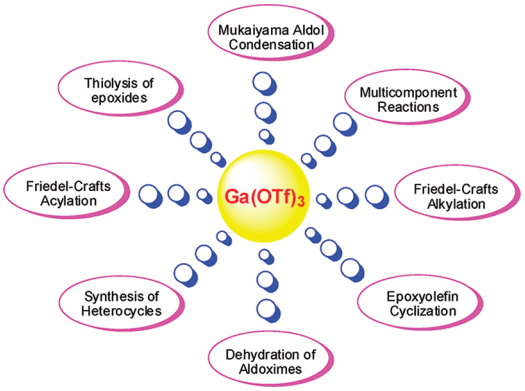
Gallium(III) Triflate: An Efficient and a Sustainable Lewis Acid Catalyst for Organic Synthetic Transformations

G. K. SURYA PRAKASH,* THOMAS MATHEW, AND GEORGE A. OLAH*

Donald P. and Katherine B. Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, 837 Bloom Walk, Los Angeles, California 90089-1661, United States

RECEIVED ON AUGUST 11, 2011

CONSPECTUS



Green chemical processes play a crucial role in sustainable development, and efficient recyclable catalysts that can be conveniently applied in various chemical reactions are the key elements for the development of sustainable synthetic processes. Many organic transformations rely on Lewis and Brønsted acid catalysts, and such molecules have been widely studied in organic synthesis. Over the years, researchers have looked for Lewis acid catalysts that provide high selectivity and high turnover frequency but are also stable in aqueous media and recoverable. Since the first preparation of trifluoromethanesulfonic acid by Hazeldine (triflic acid, HOTf), researchers have synthesized and used numerous metal triflates in a variety of organic reactions. Even though the rare earth metal triflates have played a major role in these studies, the majority of rare earth triflates lack one or more of the primary properties of sustainable catalysts: low cost and easy availability of the metals, easy preparation of triflates, aqueous/thermal stability, recyclability, and catalytic efficiency.

In this Account, we describe the synthetic applications of $Ga(OTf)_3$ and its advantages over similar catalysts. $Ga(OTf)_3$ can be conveniently prepared from gallium metal or gallium chloride in excess of trifluoromethanesulfonic acid (triflic acid) under reflux. Among many Lewis acid catalysts recently studied, $Ga(OTf)_3$ is water tolerant and soluble and requires very low catalyst loading to drive various acid-catalyzed reactions including Friedel–Crafts alkylation, hydroxyalkylation, and acylation selectively and efficiently. In many reactions $Ga(OTf)_3$ demonstrated high chemo- and regioselectivity, high yields, excellent stability, and recyclability. We successfully synthesized many biologically active heterocycles and their fluoroanalogs under mild conditions. Many challenging reactions such as the ketonic Strecker reactions proceed efficiently via $Ga(OTf)_3$ catalysis. Because it is stable in water, this catalyst provides the opportunity to study substrates and develop new synthetic protocols in aqueous media, significantly reducing the production of hazardous waste from organic solvents and toxic catalyst systems.

Introduction

Acid-catalyzed organic transformations require Lewis as well as Brønsted acid catalysts with enhanced efficacy, selectivity, stability, and recyclabilty. Lewis acid catalysis in organic synthesis has been well studied.[1,2] Over the years, there has been a wide search for an aqueous-stable and recoverable Lewis acid catalyst that provides high selectivity with high stability and high turnover frequency. Since the first preparation of trifluoromethanesulfonic acid by Hazeldine (triflic acid, HOTf),[3] numerous metal triflates

Published on the Web 12/09/2011 www.pubs.acs.org/accounts
10.1021/ar2002039 © 2011 American Chemical Society

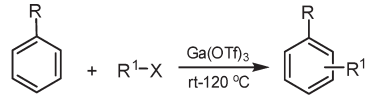
have been synthesized and applied in various organic reactions. Among these applications, the rare earth metal triflates have played a major role.[4] Considering many factors such as cost and availabilty of the metals, ease of preparation of triflates, aqueous/thermal stability, recyclability and catalytic efficiency, the majority of rare earth triflates including lanthanum triflate lack one or more of these properties critical to the sustainability of the catalysts.

During our continued effort to find a water-tolerant, nontoxic, nonhazardous, and reusable Lewis acid catalyst system, we prepared gallium(III) trifluoromethanesulfonate {$Ga(OTf)_3$, gallium triflate}, for the first time in a simple and efficient way and perceived its remarkable catalytic properties, identified from its thermal as well as aqueous stability and catalytic activity. In the intervening decade, advantages of $Ga(OTf)_3$ as a safe and stable water-tolerant Lewis acid have been extensively exploited in a significant number of organic reactions by us and others. In this Account, we discuss the development of $Ga(OTf)_3$ as an effective and nonhydrolyzable Lewis acid catalyst for many organic synthetic transformations.

Friedel–Crafts Alkylation and Acylation Reactions

Friedel–Crafts alkylation and acylation reactions are two powerful tools for C–C bond formation in organic synthesis for building molecular architectures.[2] However, in most cases strong Brønsted or Lewis acid catalysts are required in stoichiometric or excess amounts, and many of them are hydrolyzed and become inactive after the initial run. Therefore, stable, nontoxic, and reusable Lewis acid catalyst systems that are effective in significantly low amounts make the process highly efficient, economic, and eco-friendly. Even though the synthesis and characterization of the trifluoromethanesulfonates (triflates) of group IIIA metals (B, Al, Ga) were described,[5] they are much less studied. Our studies showed that, since $Ga(OTf)_3$ is stable in the presence of water, alcohols can also be used as good alkylating agents for Friedel–Crafts alkylation of arenes (Scheme 1).[5c]

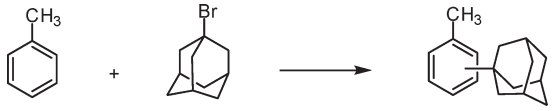
SCHEME 1. Alkylation of Aromatics Using $Ga(OTf)_3$ as Catalyst



R = CH_3, R^1 = Adamantyl, X= Br; Yield 100%
R = H, Me, Et, di-Me (*o, m, p*), OMe, F, Cl; R1 = $(CH_3)_2CH$, X = OH; Yield 16-97%

Theoretically, the Friedel–Crafts adamantylation of toluene can produce three isomeric products. However, it has been shown that during solid acid-catalyzed adamantylation reactions of toluene only *m*- and *p*-products were formed and the isomeric ratios of the tolyl adamantanes formed were highly dependent on the acid strength of the catalyst.[6] Kinetic measurements have revealed that the product ratio is the result of a secondary isomerization reaction: the *p*-product can rearrange to the *m*-isomer depending on the Brønsted acid strength. However, no

TABLE 1. Comparison of Catalytic Activity of $Ga(OTf)_3$ with Various Other Metal Triflates in the Adamantylation of Toluene with 1-Bromoadamantane



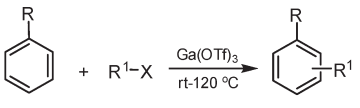
					selectivity (%)		
catalyst	temp. (°C)	time (min)	yield (%)	rate (mmol g^{-1} min^{-1})	meta	para	ditolyl adamantane (%)
$La(OTf)_3$	120	15	100	0.54	5	95	
	80	30					
$Sm(OTf)_3$	120	15	86	0.26	6	94	
	80	30					
$Sc(OTf)_3$	80	15	21	0.06	0	100	
$Yb(OTf)_3$	120	30	100	0.82	5	95	
	80	15	9	0.03	5	95	
	50	15	0.5	0.001	0	100	
$Y(OTf)_3$	120	30	100	0.43	42	50	8
	80	15					
$Ga(OTf)_3$	120	5	100		45	25	30
	80	5	100		47	32	21
	50	5	100		60	29	11
	35	5	100		53	41	6
	22	5	54	0.49	47	53	1

isomerization was observed below the Hammett values of $H_0 \approx -12$.[7] The kinetic and stereoselectivity features of the reaction make it a valuable fingerprint to test the strength of acid catalysts. Since Brønsted acid–base interaction always involves proton transfer, it allows a meaningful comparison of relative Brønsted acid strengths. Since the strengths or coordinating powers of different Lewis acids can vary widely against different Lewis bases, no such common relationship is observed in Lewis acid–base interaction leaving no room for a meaningful definition of acid strength for Lewis acids and hence no common acidity scale exists.[8] More recently, a quantitative scale for Lewis acidity based on fluoride ion affinities was calculated using *ab initio* calculations at the MP2/B2 level of theory.[9] However, when Lewis acids are exposed to protic solvents or substrates, the de facto catalysis can involve Brønsted conjugate acids.

While some metal triflates are effective catalysts at higher temperatures, the activity of $Ga(OTf)_3$ is quite significant even at room temperature.[5c] Similar effect is reflected in the regioselectivity of the products during adamantylation (Table 1). The least reactive triflates produced *p*-tolyladamantane selectively. However, formation of a high amount of *meta* substituted product resulting from the excessive isomerization of the *para* isomer shows that $Ga(OTf)_3$ is a strong Lewis acid catalyst with catalytic activity exceeding that of other well-known lanthanide triflates.[6]

Acylation of aromatics using acetyl chloride and benzoyl choride was also studied. During acylation (both benzoylation and acetylation) also, the *para* selectivity is very high, reaching 90–100% in most cases, *vide infra*. Benzoylation was found to be very efficient for activated aromatics resulting in high yields (Scheme 2). In the case of fluoro- or chlorobenzene, the yields are moderate with excellent regioselectivity (*para* selectivity). During acetylation, high chemo- and regioselectivity were observed though the yields are only moderate. In all alkylation and acylation studies, the loading of $Ga(OTf)_3$ is very low (<10 mol %) in contrast to other strong Lewis acids such as $AlCl_3$, which are required in stoichiometric amounts.

SCHEME 2. Acylation of Aromatics Using $Ga(OTf)_3$ as a Catalyst

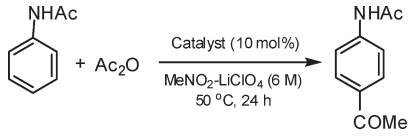


Acetylation: R = H, Me, Et, sec-butyl, *tert*-butyl,di-Me (*o*, *m*, *p*), tri-Me (1,3,5)
$R_1 = CH_3CO$, X = Cl; Yield 12-48%
Benzoylation: R = H, Me, Et, *sec*-butyl, *tert*-butyl,di-Me (*o*, *m*, *p*), tri-Me (1,3,5), F, Cl, CF_3
$R_1 = C_6H_5CO$, X = Cl; Yield 10-97%

Recent studies by Kobayashi[10a] have shown that catalytic acylation of aniline derivatives can be achieved in high yields using $Ga(OTf)_3$ as a catalyst and $LiClO_4$[10b] as a promoter. Since gallium tris(perfluoroalkanesulfonate) showed high catalytic activities in Friedel–Crafts acylations of benzene and deactivated benzenes, its application as highly selective and active catalyst was extended for the Friedel–Crafts acylation of anilides.[10,11] The reaction of acetanilide with acetic anhydride was systematically screened using various perfluoroalkanesulfonates of gallium and other rare earth metals and found that $Ga(OTf)_3$ (10 mol %) in 6 M $LiClO_4$ solution in nitromethane gave the product in 93% yield (Table 2).

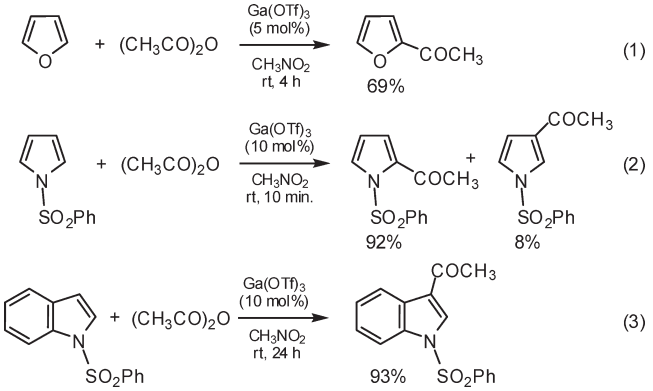
Since acylated heteroaromatics are key intermediates for the synthesis of various pharmaceuticals, catalytic acylation

TABLE 2. Effect of Lewis Acids in the Friedel–Crafts Acylation of Anilides



entry	catalyst	yield (%)
1	$Ga(OTf)_3$	93
2	$Ga(ONf)_3$	90
3	$Sc(OTf)_3$	10
4	$Sc(ONf)_3$	48
5	$Hf(OTf)_3$	44
6	$Bi(OTf)_3$	59
7	$Sb(OTf)_3$	59
8	$GaCl_3$	33
9	$AlCl_3$	<1

SCHEME 3. Acylation of Heteroaromatics Using $Ga(OTf)_3$ as a Catalyst



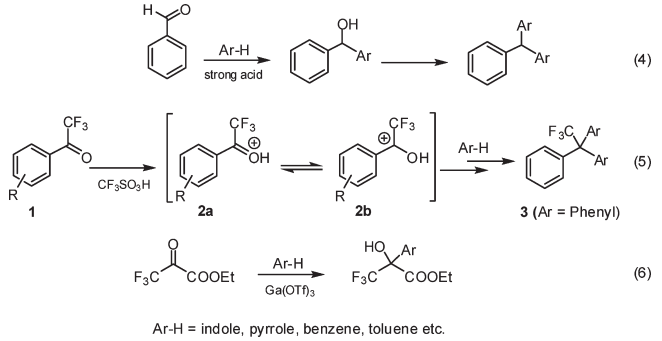
of heteroaromatics using safe and reusable catalysts is always important in the pharmaceutical industry. $Ga(OTf)_3$ can act as an efficient catalyst for Friedel–Crafts acylation of furan, pyrrole, and indole derivatives (Scheme 3, eqs 1–3).[12]

Although other metal triflates such as $Sn(OTf)_2$ and $Sc(OTf)_3$ were effective catalysts for acylation of furan/thiophene and benzofuran, respectively, acylation of 1-(phenylsulfonyl)pyrrole and 1-(phenylsulfonyl)indole was achieved in high yield and selectivity using $Ga(OTf)_3$ in catalytic amounts.

Hydroxyalkylation

Acid-catalyzed condensations of aldehydes and ketones with arenes is generally known as the hydroxyalkylation reaction (Scheme 4, eqs 4–6).[13] Though the reaction is often limited to activated, electron-rich arenes, aldehydes and ketones bearing electron-withdrawing groups also may react with benzene and even deactivated arenes under superacidic conditions (Scheme 4, eqs 5, 6).[14] Further protonation or protosolvation of the protonated aldehydes and ketones is possible under these conditions resulting in superelectrophilic or multi-ionic intermediates (superelectrophiles),[15] which can undergo successive condensation reactions with weaker nucleophiles such as deactivated aromatics. In Brønsted acid medium, when protonation occurs on the oxygen atom, the resulting cation is stabilized by both the oxygen and the neighboring phenyl group, thus making it a relatively weak electrophile. To decrease this neighboring group participation and increase the electrophilicity of the carbonyl carbon, further protonation of the system is required. This explains the ease of hydroxyalkylation protocol for aldehydes and ketones including trifluormethyl ketones[14a,16] with arenes in strongly acidic medium. The inductive effect of the trifluoromethyl group destabilizes the carboxonium ion intermediate **2** (eq 5) with significant enhancement in its electrophilicity. Superacid-catalyzed Friedel–Crafts hydroxyalkylation of aromatics using aldehydes and ketones is a very convenient method for the one-pot synthesis of diaryl and triarylmethane derivatives (Scheme 4, eqs 4, 5). Using a similar synthetic strategy, Mosher's esters were prepared in excellent yields by $Ga(OTf)_3$ catalyzed hydroxyalkylation of aromatics using ethyl trifluoropyruvate (Scheme 4, eq 6).[17]

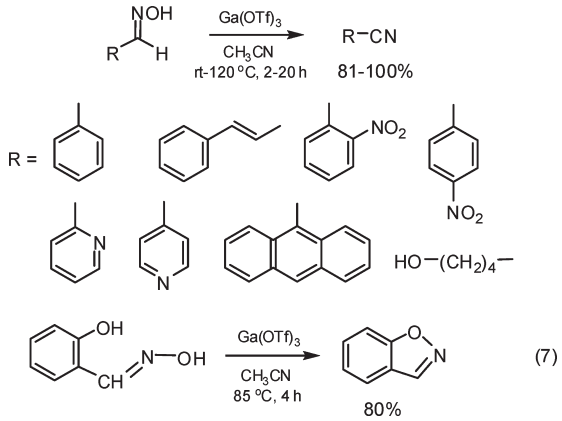
SCHEME 4. Hydroxyalkylation of Arenes with Carbonyl Systems



Dehydration of Aldoximes

Nitriles are precursors for the synthesis of various carbonyl compounds and carboxylic acids as well as versatile synthetic intermediates for pharmaceuticals, agricultural chemicals, dyes, and materials.[18] Dehydration of aldoximes is one of the direct, simple, and most useful methods for the synthesis of nitriles. Although numerous catalysts have been used for the dehydration of aldoximes, a mild and general efficient catalytic process is still in great demand. Due to the stability, water compatibility, and diverse functional group tolerance of $Ga(OTf)_3$, its use as a practical catalyst for the dehydration of aldoximes has been explored.[19] Aryl as well as aliphatic aldoximes can be dehydrated readily to nitriles keeping other functionalities such as C–C double bond and hydroxyl group intact. Interestingly, with salicylaldehyde oxime, dehydration results in intramolecular condensation–cyclization to form 1,2-benzisoxazole due to the presence of the proximal *o*-hydroxy group (Scheme 5, eq 7).

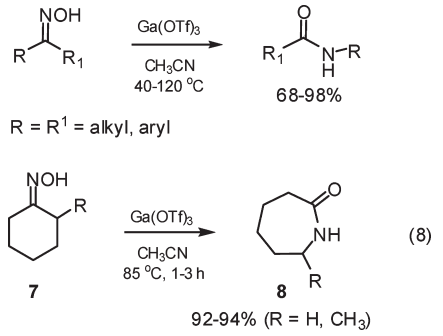
SCHEME 5. $Ga(OTf)_3$-Mediated Dehydration of Oximes



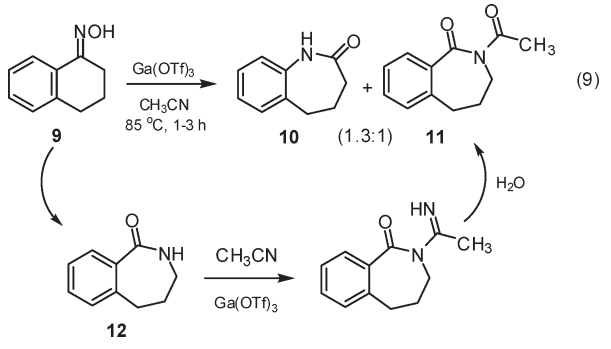
Beckmann Rearrangement of Ketoximes

Apart from its industrial importance in the manufacture of ε-caprolactam, a nylon-6 precursor derived from cyclohexanone oxime, Beckmann rearrangement provides a facile route for the incorporation of nitrogen into polycyclic structures for the synthesis of important pharmaceuticals or natural products, and many catalysts have been applied for this tranformation.[20] Though recent reports include the application of indium and ytterbium triflates,[4,21] $Ga(OTf)_3$ is found to be more advantageous and superior in its catalytic activity, air-stability, and other properties (Scheme 6).[22]

SCHEME 6. Beckman Rearrangement of Ketoximes Catalyzed by $Ga(OTf)_3$



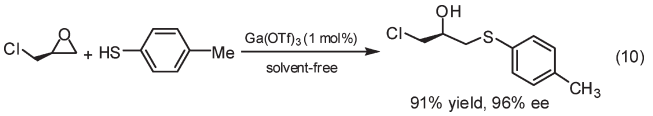
Beckmann rearrangement is stereospecific and generally the group *anti* to the hydroxyl group on the ketoxime will selectively migrate. This behavior is useful in assigning *syn* or *anti* configuration of the oximes. Even when the starting oximes are mixtures of *syn* and *anti* isomers,[22] single amide isomers were obtained as the products in most cases, based on their migratory aptitudes. This indicates that $Ga(OTf)_3$ is also capable of catalyzing the *syn*–*anti* isomerization (faster than the rearrangement) of oximes under the conditions of the Beckmann rearrangement. Larger amounts of catalysts are required for cyclic ketoximes such as cyclohexanone oxime **7** and tetralone oxime **9** due to the ring strain present in the seven-membered ring lactams. Specifically, α-tetralone oxime **9** requires also higher temperature (120 °C) and proceeds with 50 mol % catalyst. Both of the carbons

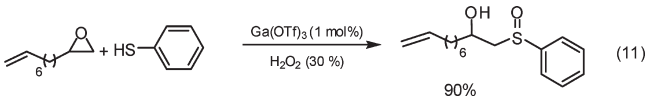


adjacent to the oxime carbon are prone to migration, and two corresponding products are obtained. At 120 °C, the solvent CH_3CN itself is activated to further react with the Beckmann rearrangement product to give the *N*-acetyl amide **11** (eq 9). Since access to the nitrogen atom in product **10** is sterically unfavorable, only product **12** undergoes acetylation by acetonitrile.

Thiolysis of Epoxides

Thiolysis reaction of epoxides is a widely used route for the synthesis of β-hydroxy sulfides and can be promoted by many Lewis acids including triflates.[23] β-Hydroxy sulfides and sulfoxides are important intermediates in organic synthesis.[24] $Ga(OTf)_3$ also catalyzes ring-opening of epoxides by thiols to β-hydroxy sulfides with high regio- and chemoselectivity.[25] The reaction is highly catalytic (only 1 mol % $Ga(OTf)_3$ is required) and occurs under solvent-free conditions (eqs 10 and 11). Using H_2O_2–$Ga(OTf)_3$ system, direct conversion of thiols to β-hydroxy sulfoxides is achieved in high yields (eq 11, 81–94%) without any detectable overoxidation to β-hydroxy sulfones.



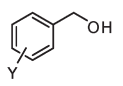
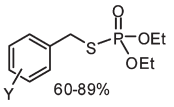
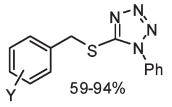
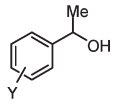
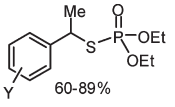
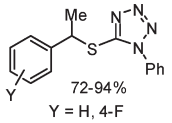
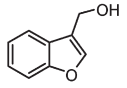
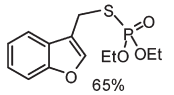
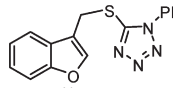
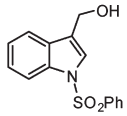
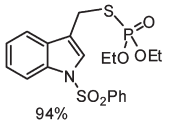
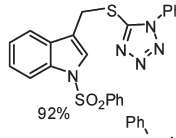
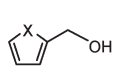
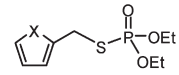
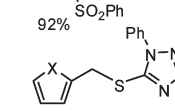


Direct Substitution of Alcohols with Sulfur Nucleophiles

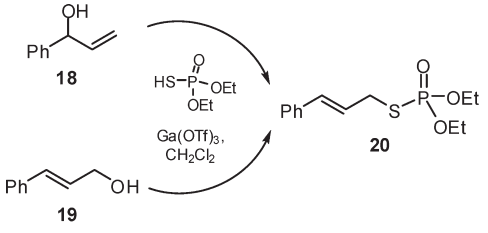
Sulfur-containing bioactive natural and pharmaceutical agents include H_2-receptor antagonists,[26] pyrimidine thionucleosides,[27] penicillamine, glutathione, and immunoconjugates.[28] Direct access to similar systems by simple nucleophilic substitution of the hydroxyl functional group with appropriate sulfur nucleophiles is highly desirable. Recently, Wu[29] has shown that $Ga(OTf)_3$ catalyzes the direct displacement of a wide range of alcohols with various sulfur nucleophiles very efficiently. The reaction is tolerant to oxygen, sulfur, and nitrogen heterocycles (Table 3, entries 2–4). Both> primary and secondary alcohols are compatible if at least one of the substituents is aromatic or allylic. This method is amenable to both electron-donating and electron-withdrawing substituents (entry 1, Y = H, 4-Cl, 4-F, 4-OMe, 2-NH_2, and 4-CO_2Me). Phosphorothioic esters **16** are useful intermediates in transition-metal-free allylic alkylations[30] and can be transformed to the corresponding alkenes or converted to thiols via hydrolysis or reduction. Sulfides **17** are valuable compounds since they can be oxidized to the corresponding sulfones, which can be used in Julia olefination reactions.

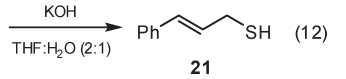
Thiols commonly utilized in sulfone olefination reactions were also found to be tolerant giving the products in good yields. It is interesting to note that both the regioisomeric alcohols **18** and **19** furnished the same product (eq 12). The corresponding phosphorothioate ester **20** can be efficiently

TABLE 3. $Ga(OT)_3$-Catalyzed Direct Substitution of Alcohols with Sulfur Nucleophiles

Entry	Alcohols (R-OH)	Products **16** from thiol **14**	Products **17** from thiol **15**
1		 60-89% Y = H, 4-Cl, 4-F, 4-OMe	 59-94% Y = H, 4-Cl, 4-F, 4-OMe, 2-NH_2, 4-CO_2Me
2		 60-89% Y = H	 72-94% Y = H, 4-F
3		 65%	 82%
4		 94%	 92%
5		 X = O, 63%; X = S, 89%	 X = O, 52%; X = S, 84%

hydrolyzed with KOH in aqueous THF to the corresponding thiol **21** in good yield (74%).

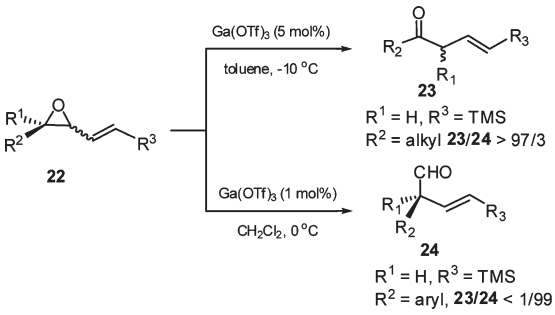




(12)

Rearrangement of Vinyl Epoxides

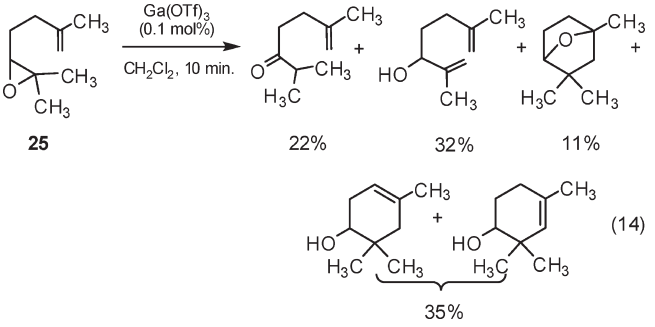
Vinyl epoxides are effective synthons in target oriented organic synthesis (TOS). They are also used in reversing the quenching of reactive radicals such as the glutathionyl radicals by their interaction forming reactive oxy-radical in the vicinity of DNA, enhancing the possibility of DNA damage in tumor cells.[31] They can be chemoselectively and regioselectively transformed into β,γ-unsaturated carbonyl compounds, another potentially useful synthon in organic synthesis.[32,33] Acid-catalyzed rearrangement of vinyl epoxides also required stoichiometric amounts of Lewis acids in most cases. However, it has been shown that in the presence of $Ga(OTf)_3$, 2-substituted vinyl epoxides **22** undergo rearrangement into β,γ-unsaturated carbonyl compounds with high regioselectivity (>97/3) with very low catalyst loading (1−5 mol %).[34] Products vary depending on the substitution; alkyl-substituted trimethylsilylvinyl epoxides give β,γ-unsaturated ketone **23**, whereas aryl substitution yields the aldehyde **24** (eq 13).



(13)

Epoxyolefin Cyclization

The cyclization of epoxyolefins is involved in the biosynthesis of many terpenes, including cholesterol. In the enzymatic cyclization of squalene to lanosterol and cholesterol, van Tamelen first reported such a cyclization involving squalene 2,3-epoxide as an intermediate.[35] Epoxyolefin cyclizations were also studied using BF_3-Et_2O[36] and $MeAlCl_2$[37] as catalysts. The reaction has been revisited using various Lewis acidic triflates, and it was found that $Ga(OTf)_3$ shows noticeably high conversions with substantially low catalyst loading (0.1 mol %).[38] For example, in the ring-opening reaction of geraniolene oxide **25** (eq 14), $Ga(OTf)_3$ initiates isomerization and cyclization to yield a mixture of synthetically important cyclized and rearranged products in high yields (85%)[38] mainly influenced by the nature of the solvent and substrate concentrations.



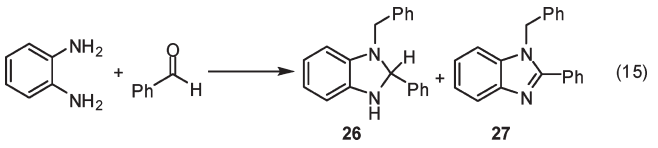
(14)

Synthesis of Heterocycles

Benzimidazolines, benzothiazolines, benzoxazolines, and dihydrobenzoxazinones are important classes of heteroaromatics

with wide applications. Benzimidazolines, often called organic hydrides, are good reducing agents as well as hydrogen storage materials.[39] Benzoxazolines and benzothiazolines have been widely used as plant growth regulants, herbicides, and anticonvulsants, in photochromic dyes, and for the treatment of ADD (attention defficiency disorder).[40] Dihydrobenzoxazinones are used as analgesics as well as efficient building blocks for therapeutics with antiviral, antifungal, antibacterial, and antiparasitic properties.[41] Since fluorine substitution in various drugs and pharmaceuticals often causes significant enhancement in their biological effects,[42] convenient methods for easy access to their fluorinated analogs have great synthetic value.

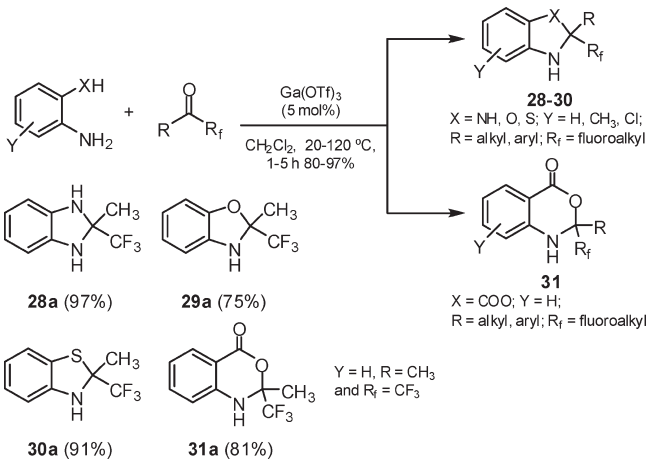
Preparation of benzimidazolines **26** from 1,2-phenylenediamines and benzaldehyde under ambient conditions (eq 15) usually results in the formation of benzimidazoles **27** due to further oxidation.[43] However, one pot synthesis of fluorinated benzimidazolines **28**, benzothiazolines **29**, benzoxazolines **30**, and dihydrobenzoxazinones **31** is easily achieved in high yields by the reaction of the corresponding ketones and *o*-aminoarene derivatives using $Ga(OTf)_3$.[44] 1,1,1-Trifluoroacetone undergoes smooth condensation−cyclization reaction with 1,2-phenylenediamine using gallium triflate (5 mol %) in CH_2Cl_2 at 50 °C to yield the trifluoromethylated benzimidazoline (Scheme 7). The reaction is very clean, and removal of solvent afforded the corresponding trifluoromethylated benzimidazoline derivatives in high yield and purity.



26 27 (15)

Quinoxaline nucleus is a part of several antibiotics such as echinomycin, levomycin, and actinomycin, which are known to inhibit the growth of Gram-positive bacteria and active against various transplantable tumors.[45] They are of high pharmaceutical interest because of their prominent therapeutic value such as antiviral, antibacterial, anti-inflammatory, and antiprotozoaval properties and also as kinase inhibitors.[46] The 1,5-benzodiazepine core has many pharmaceutical applications. They are reported to be muscle relaxants, anticonvulsants, sedatives, hypnotics, analgesics, anti-inflammatory, and antipyretics with low acute toxicity.[47] A convenient synthesis of quinoxalines and 1,5-diazepines was achieved in high purity by the condensation of aryl 1, 2-diamines (**32**) with 1,2- and 1,3-diketones (**33**, **34**),

SCHEME 7. Synthesis of Fluorinated Benzimidazolines, Benzothiazolines, Benzoxazolines, and Dihydrobenzoxazinones



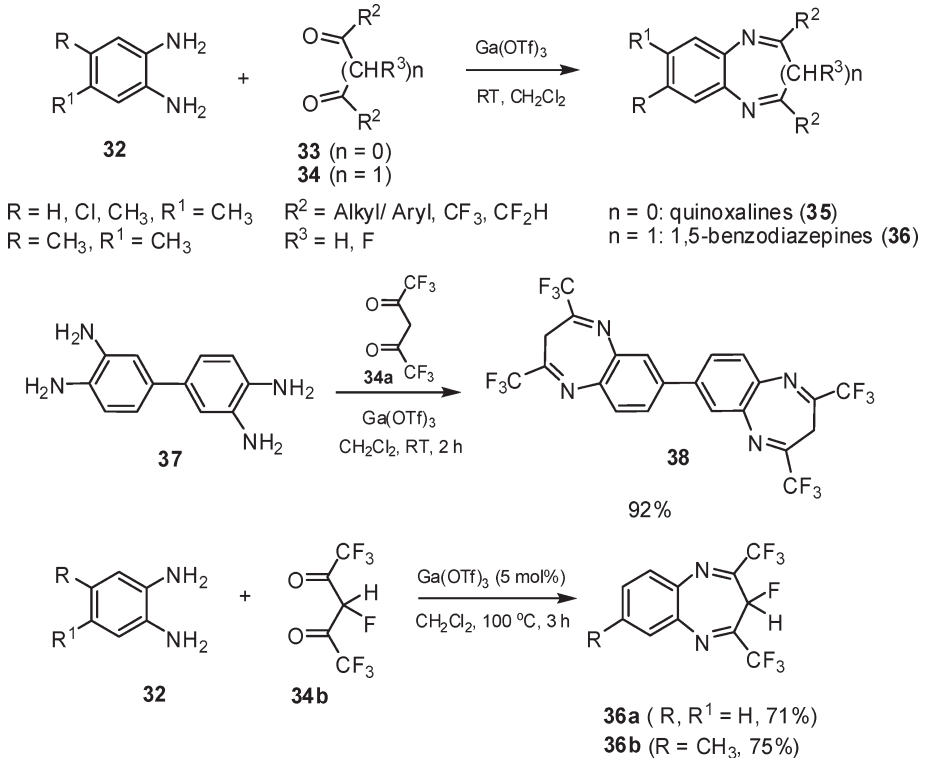
respectively, by using $Ga(OTf)_3$ as a Lewis acid catalyst (Scheme 8). $Ga(OTf)_3$-catalyzed reaction offers mild and facile access to both these frameworks at room temperature.[48] In certain reactions that can occur in the absence of catalyst, addition of 2−5 mol % $Ga(OTf)_3$ reduces the reaction time considerably resulting in clean and quantitative conversions.

Based on the fluorine effect on biological and therapeutic activities of various drug molecules,[42] fluoroanalogues of quinoxalines **35** and fluoromethylated 1,5-benzodiazepines **36** were also synthesized in high yields by condensing the appropriate 1,2-diamines **32** with fluorinated diketones **33** and **34**.

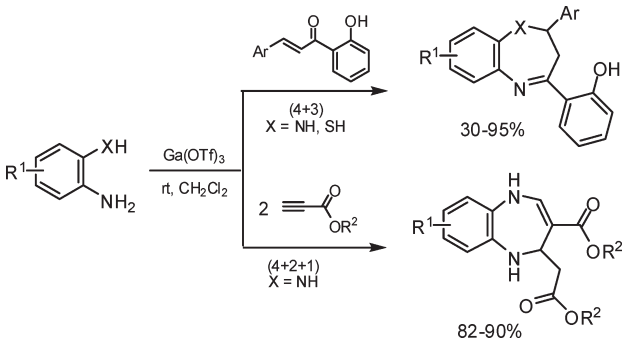
Synthesis of 1,5-benzodiazepines by cycloaddition approach involving (4 + 3) cycloadditions of *o*-phenylenediamine with α,β-unsaturated carbonyl systems or β-haloketones has been well studied. Recently, it has been shown that synthesis of diverse 2,4- and 3,4-disubstituted 1,5-benzodiazepines can be achieved in good yields by $Ga(OTf)_3$-catalyzed [4 + 3] and [4 + 2 + 1] cycloadditions of *o*-hydroxychalcones and alkynoates with phenylenediamines (Scheme 9).[49]

However, monoamines undergo $Ga(OTf)_3$-catalyzed condensation with 1,3-diketones and 1,4-diketones to give, respectively, β-enamino ketones (**39**) and pyrroles (**40**, the Paal−Knorr condensation product) under solvent-free conditions (eq 16).[50] This protocol is convenient and facile avoiding the use of hazardous organic solvents and excess of acid catalysts as well as tedious workup, thereby enhancing the yields significantly. Among various known methods, direct condensation of 1,3-dicarbonyl

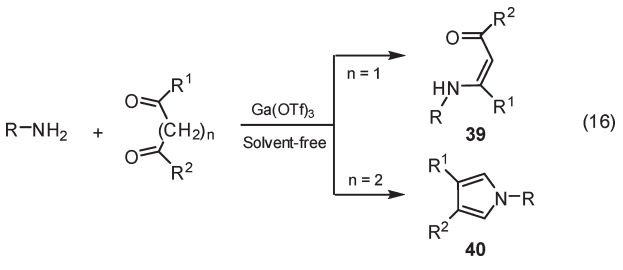
SCHEME 8. Gallium(III) Triflate Catalyzed Synthesis of Quinoxalines and 1,5-Benzodiazepines Using *o*-Phenylenediamines and 1,2/1,3-Diketones



SCHEME 9. Synthesis of 2,4- and 3,4-Disubstituted 1,5-Benzodiazepines from Phenylenediamines Using *o*-Hydroxychalcones and Alkynoates



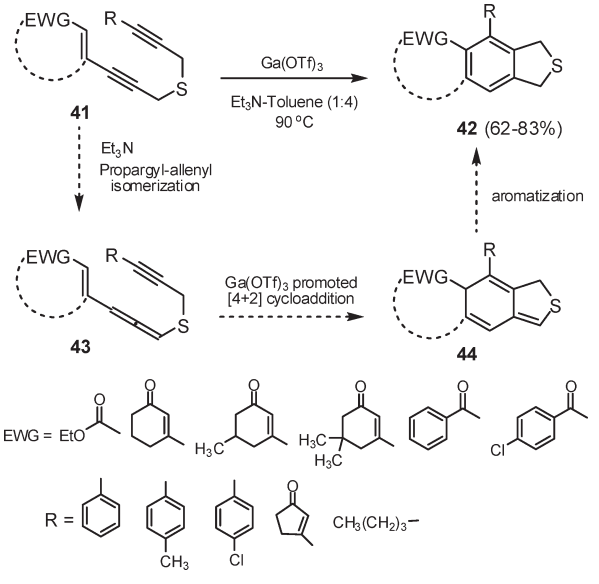
compounds with amines has been identified as an elegant approach for the synthesis of β-enamino ketones and pyrroles.



(16)

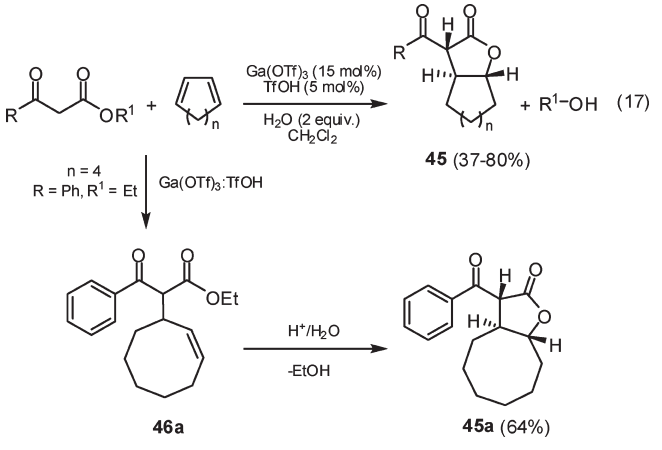
Recently, Zhou has reported the synthesis of 1,3-dihydrobenzo[*c*]thiophene derivatives (**42**) by a sequential reaction cascade via propargyl−allenyl isomerizations and intramolecular [4 + 2]-cycloaddition promoted by $Ga(OTf)_3$ in the presence of triethylamine (Scheme 10).[51] Sulfur-assisted propargyl-allenyl isomerization has been a useful protocol

SCHEME 10. Synthesis of 1,3-Dihydrobenzo[*c*]thiophene Derivatives by Gallium(III) Triflate Promoted Sequential Reactions



for direct access to thioallenes. The allene moiety could be considered as an "activated olefin", which generally enhances the diversity of reaction compared with a normal olefin. Thus, it is hypothesized that the intramolecular [4 + 2] cycloaddition of yne−allenes should provide a more convenient route than traditional intramolecular Diels−Alder reaction for the construction of complex ring systems. A plausible pathway for this reaction involves a base-catalyzed propargyl−allenyl isomerization to give the intermediate **43**, which sequentially undergoes an intramolecular [4 + 2] allene−yne cycloaddition promoted by $Ga(OTf)_3$ followed by aromatization of the cycloadduct **44** to give the 1,3-dihydrobenzo[*c*]thiophenes **42** in high yields. It is surmised that the vinylallene **43** serves as an effective diene to undergo cycloaddition with triple bonds to give cyclic precursors for aromatization.

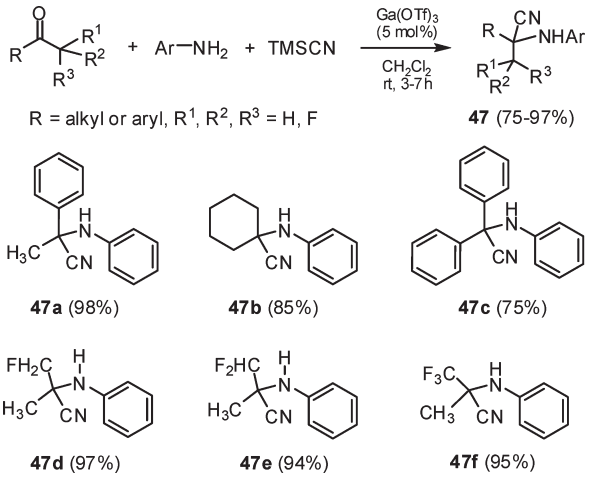
Li et al. noticed that $AuCl_3$−AgOTf combination catalyzed the addition of active methylenes to dienes, trienes, and cyclic enol ethers leading to the formation of functionalized carbocycles and heterocycles with high regioselectivity[52a] through a highly atom economical C−C bond formation process. However, addition of less activated methylene such as 2,4-pentanedione to cyclooctadiene failed to yield the expected product. This was successfully overcome by replacing the catalyst system with $Ga(OTf)_3$−TfOH, and extension of their studies using β-ketoesters led to the formation of fused bicyclolactones **45** (eq 17).[52b] Use of $Ga(OTf)_3$−TfOH resulted in the formation of lactone with both high conversion and selectivity. Though TfOH alone can also catalyze the reaction albeit in lower yield, addition of $Ga(OTf)_3$ increases the yield dramatically, manifesting the role of $Ga(OTf)_3$ as an important catalyst for this reaction. The intermediate **46a** from ethyl benzoyl acetate and cyclooctadiene can be isolated in the reaction, which undergoes subsequent lactonization to yield the bicyclic lactone **45a** in good yield.



Multicomponent Reactions (MCRs)

The Strecker reaction is one of the preeminent multicomponent reactions useful for the synthesis of α-amino acids via the intermediacy of α-amino nitriles. The Strecker reaction with aldehydes has been studied extensively with a variety of catalysts.[53] However, there are not many examples for efficient and clean three-component Strecker reaction using diverse ketones including fluorinated ketones. Quite often, these reactions had to be carried out in two steps (preparation of imines followed by cyanide addition) or under high pressure.[54] Our studies have revealed that $Ga(OTf)_3$ can act as an efficient catalyst for direct Strecker reaction of ketones with different types of amines and trimethylsilyl cyanide to afford the corresponding α-amino nitriles (precursors of α-amino acids) in high yields (Scheme 11).[55] Both aliphatic and aromatic ketones

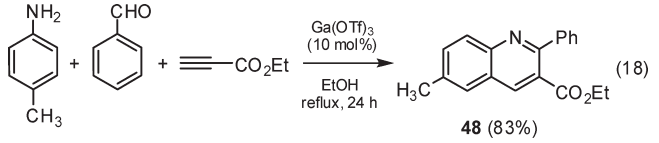
SCHEME 11. The Ketonic Strecker Reaction Catalyzed by $Ga(OTf)_3$



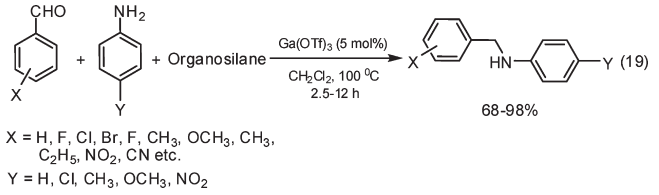
undergo ketonic Strecker reaction efficiently in the presence of $Ga(OTf)_3$ under mild conditions. Fluorinated ketones also undergo the one-pot three-component reaction smoothly with aromatic amines and trimethylsilyl cyanide to yield the corresponding fluorinated α-amino nitriles. Using this methodology monofluoro-, difluoro-, and trifluoromethyl moieties can be incorporated in to the α-amino nitrile product by simply varying the nature of the fluorinated ketones very efficiently.

Direct synthesis of Hantzsch pyridines (*N*-substituted 1,4-dihydropyridines) can be achieved in good yields by the three-component coupling reaction of aromatic amine, aldehyde, and ethyl propiolate supported on silica by microwave irradiation.[56] However, in an attempt to find milder conditions using a catalytic amount of Lewis acids and to avoid large amount of silica and microwave irradiation, such a reaction has been carried out using $Ga(OTf)_3$ as a catalyst. 2,3-Disubstituted quinoline **48** bearing an ester group at

the 3 position was obtained as the major product (83% yield), together with a small amount of the expected 1,4-dihydropyridines (<10%; eq 18). This would be a simple and convenient multicomponent approach for the synthesis of substituted quinolines directly from a mixture of aromatic amines, aromatic aldehydes, and ethyl propiolate.[57]

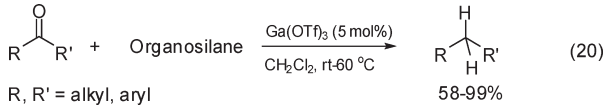


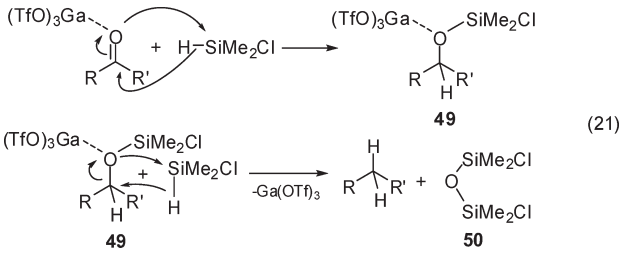
Direct hydroamination of aldehydes using amines in the presence of hydrosilanes in a three-component fashion is also catalyzed by $Ga(OTf)_3$ under mild conditions (eq 19).[58] Synthesis of diverse higher secondary amines with a high degree of functional group tolerance was achieved with reductive amination using stoichiometric amounts of triethylsilane, phenylsilane, and polymethylhydrosiloxane (PMHS). However, no reductive amination was observed with triethylsilane in the absence of $Ga(OTf)_3$.



Reduction of Ketones

Combination of organosilane and $Ga(OTf)_3$ has been further utilized as a convenient reducing system for carbonyls to methylenes (eq 20).[59] Among various organosilanes studied, dimethylchlorosilane was found to be the most efficient one for carbonyl reduction. This reaction is assumed to proceed by the pathway shown in eq 21, as suggested by Baba and co-workers.[60] The first step should involve the hydrosilylation of the carbonyl moiety by chlorodimethylsilane to give the corresponding silyl ether **49**. Activation of **49** by $Ga(OTf)_3$ followed by the reaction with another molecule of chlorodimethylsilane gives the desired methylene product and the disilylether **50**, with the regeneration of the catalyst.

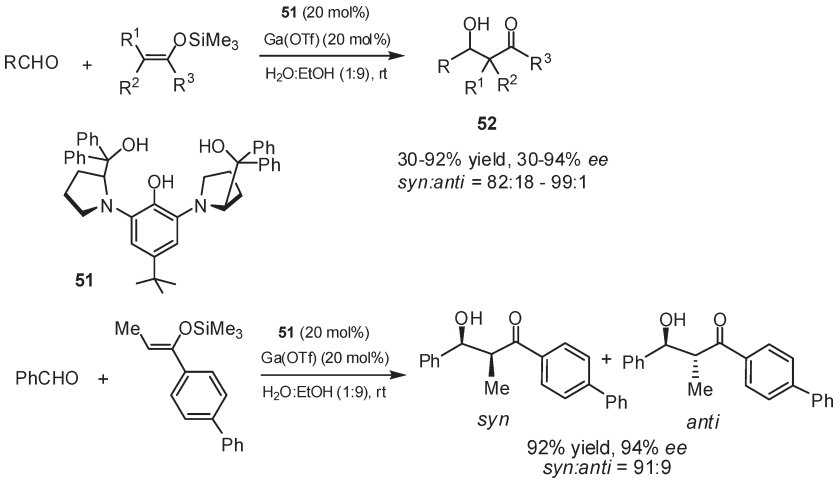




Mukaiyama Aldol Condensations in Aqueous Media

The Mukaiyama reaction[60] has been recognized as one of the most important Lewis acid catalyzed carbon–carbon bond forming reactions involving the aldol-type reaction of silyl enol ethers with carbonyl compounds. Since the first report of the asymmetric aldol reaction of silyl enol ethers catalyzed by the chiral diamine–$Sn(OTf)_2$ system,[61] several examples of asymmetric aldol reactions were developed.

SCHEME 12. Mukaiyama Asymmetric Aldol Condensation Reaction in Aqueous Medium Catayzed by $Ga(OTf)_3$–Chiral Ligand Combination



Mukaiyama aldol reactions of various aldehydes with silyl enol ethers in aqueous media using complexes of $Ga(OTf)_3$ with chiral basic ligands gave the corresponding aldol products in moderate to high yields (30−92%) with moderate to high enantioselectivities (30−94%).[62] For example, in the presence of a chiral gallium complex prepared from $Ga(OTf)_3$ and chiral ligand **51**, reactions of silicon enolates with aldehydes proceeded smoothly at room temperature in water−ethanol mixture to afford the desired aldol adducts **52** (Scheme 12). Though the combinations of silyl enolates derived from aliphatic ketones and aliphatic aldehydes resulted in lower yields and selectivities, silyl enolates derived from aromatic ketones and aromatic aldehydes gave high diastereo- and enantioselectivities.

Being a strong Lewis acid, the possibility of the formation of conjugate protic acid by $Ga(OTf)_3$ in aqueous medium cannot be completely ruled out. Studies by Hartwig[63a] on triflic acid catalyzed hydroamination and hydroalkoxylation by comparison with He's system involving metal trflates[63b,c] showed that the rates of reaction catalyzed by 1 mol % triflic acid were similar to the rates of reaction catalyzed by metal triflates in equal or greater amounts. It was mentioned that the decomposition of $Ga(OTf)_3$ by water has been prevented by the stabilization of $Ga(OTf)_3$ through complexation with chiral basic ligands.[62] However, it was shown that gallium triflate can be separated from its water solution by the removal of water and drying under vacuum[5c] showing that it is quite stable under aqueous conditions.

Conclusions

In conclusion, search for nontoxic, water-tolerant and reusable efficient catalyst systems revealed $Ga(OTf)_3$ as a catalyst superior to many Lewis acid catalysts with a significant degree of sustainability. It is effective in many organic synthetic transformations such as Friedel−Crafts reactions, rearrangements, nucleophilic substitutions, condensation cyclizations, tandem cycloaddition reactions, etc. Synthesis of many biologically active heterocycles and their fluoroanalogs were also achieved under mild conditions with very low catalyst loading. Many challenging reactions such as the ketonic Strecker reactions are successfully carried out under $Ga(OTf)_3$ catalysis. Due to its stability in water, it is possible to study various synthetic reactions with aqueous-amenable substrates resulting in the development of efficient synthetic protocols with significant reduction of hazardous wastes by avoiding the use of toxic organic solvents and catalyst systems.

Financial support of our work by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

BIOGRAPHICAL INFORMATION

G. K. Surya Prakash was born in Bangalore, India, in 1953. He received B.Sc. (Honors) in 1972 and M.Sc. in 1974 from the Bangalore University and IIT, Madras, respectively. He obtained his Ph.D. from the University of Southern California (USC) in 1978 under the tutelage of Professor George A. Olah. After his postdoctoral work at USC, he joined the faculty at USC. Currently he is a full professor in chemistry and Director of the Loker Hydrocarbon Research Institute holding the George A. and Judith A. Olah Nobel Laureate Chair in Hydrocarbon Chemistry. His research contributions and interests are in selective fluorination methods, new synthetic methods, mechanistic studies of organic reactions, electrochemistry, superacid chemistry, and hydrocarbon chemistry. He has received many honors and accolades including 2004 ACS Award for Creative Work in Fluorine Chemistry, the 2006 George A. Olah Award in Hydrocarbon or Petroleum Chemistry, and the 2006 Tolman Award.

Thomas Mathew is a senior scientist at the Loker Hydrocarbon Research Institute, University of Southern California. After receiving a Ph.D. (University of Kerala, India) in 1989 under the supervision of Professor C. P. Joshua, he did his initial postdoctoral studies with Professor M. V. George (Emeritus Scientist, CSIR) at the NIIST (formerly RRL), Trivandrum, India. Later, as a Humboldt Fellow, he spent two years (1994−1996) with Professor Horst Prinzbach at Albert-Ludwigs University, Freiburg, Germany. In 1996, he joined the Olah−Prakash research group at the Loker Hydrocarbon Research Institute. His main research interests are in superacid chemistry, hydrocarbon chemistry, development of new catalysts and organic synthetic methods, fluorine chemistry, and photochemistry.

George A. Olah is a distinguished professor of chemistry and the Founding Director of the Loker Hydrocarbon Research Institute at the University of Southern California. He received the Nobel Prize in Chemistry (1994) for his work on carbocations and hydrocarbon chemistry. His research interests are in synthetic and mechanistic chemistry with emphasis on energy and hydrocarbon chemistry.

FOOTNOTES

This Account is dedicated to Professor Horst Prinzbach with friendship and admiration on the occasion of his 80th birthday.

REFERENCES

1 *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vols. 1, 2.

2 Olah, G. A. *Friedel−Crafts Chemistry*; Wiley-Interscience: New York, 1973.

3 Hazeldine, R. N.; Kidd, J. M. Perfluoroalkyl derivatives of sulphur. Part I. Trifluoromethanesulphonic acid. *J. Chem. Soc.* **1954**, 4228–4232.

4 (a) Kobayashi, S.; Manabe, K. Stable Lewis acids in water. Development of novel Lewis acid catalysts for selective organic reactions in aqueous media. *Acc. Chem. Res.* **2002**, *35*, 209–217. (b) Kobayashi, S.; Sugimura, M.; Kitagawa, H.; Hidetoshi, L.; Lam, W. W.-L. Rare earth metal triflates in organic synthesis. *Chem. Rev.* **2002**, *102*, 2227–2302.

5 (a) Olah, G. A.; Farooq, O.; Farnia, S. M. F.; Olah, J. A. Boron, aluminum, and gallium tris(trifluoromethanesulfonate) (triflate): Effective new Friedel−Crafts catalysts. *J. Am. Chem. Soc.* **1988**, *110*, 2560–2565. (b) Baumizane, K.; Herzog-Cance, M. H.; Jones, D. J.; Pascal, J. L.; Potier, J.; Roziere, J. Synthesis, vibrational spectroscopy and EXAFS analysis of some divalent and trivalent trifluoromethanesulphonato complexes. *Polyhedron* **1991**, *10*, 2757–2769. (c) Prakash, G. K. S.; Yan, P.; Torok, B.; Bucsi, I.; Tanaka, M.; Olah, G. A. Gallium(III) trifluormethanesulfonate: A water-tolerant, reusable Lewis acid catalyst for Friedel−Crafts reactions. *Catal. Lett.* **2003**, *85* (1−2), 1–6.

6 (a) Olah, G. A.; Török, B.; Shamma, T.; Török, M.; Prakash, G. K. S. Solid acid (superacid) catalyzed regioselective adamantylation of substituted benzenes. *Catal. Lett.* **1996**, *42*, 5–13. (b) Laali, K. K.; Sarca, V. D.; Okazaki, T.; Brock, A.; Der, P. Triflic acid-catalyzed adamantylation of aromatics in [BMIM][OTf] ionic liquid; synthetic scope and mechanistic insight. *Org. Biomol. Chem.* **2005**, *3*, 1034–1042.

7 Beregszaszi, T.; Török, B.; Molnár, Á.; Olah, G. A.; Prakash, G. K. S. Friedel-Crafts reactions induced by heteropoly acids. Regioselective adamantyl substitution of aromatic compounds. *Catal. Lett.* **1997**, *48*, 83–87.

8 Olah, G. A.; Prakash, G. K. S.; Molnár, Á.; Sommer, J. *Superacid Chemistry*; Wiley Interscience: Hoboken, NJ, 2009; pp 23−27.

9 Christe, K. O.; Dixon, D. A.; McLemore, D.; Wilson, W. W.; Sheehy, J. A.; Boatz, J. A. On a quantitative scale for Lewis acidity and recent progress in polynitrogen chemistry. *J. Fluorine Chem.* **2000**, *101*, 151–153.

10 (a) Kobayashi, S.; Komoto, I.; Matsuo, J.-i. Catalytic Friedel-Crafts acylation of aniline derivatives. *Adv. Synth. Catal.* **2001**, *343*, 71–74. and references cited therein. (b) Kawada, A.; Mitamura, S.; Kobayashi, S. $Ln(OTf)_3$-$LiC1O_4$ as reusable catalyst system for Friedel-Crafts acylation. *J. Chem. Soc., Chem. Commun.* **1996**, 183–184.

11 Matsuo, J.; Odashima, K.; Kobayashi, S. Gallium nonafluorobutanesulfonate as an efficient catalyst in Friedel-Crafts acylation. *Synlett* **2000**, 403–405.

12 Komoto, I.; Matsuo, J.; Kobayashi, S. Catalytic Friedel-Crafts acylation of heteroaromatics. *Top. Catal.* **2002**, *19*, 43–47.

13 Fuson, R. C.; Weinstock, H. H.; Ullyot, G. E. A new synthesis of benzoins. 2′,4′,6′-Trimethylbenzoin. *J. Am. Chem. Soc.* **1935**, *57*, 1803–1804.

14 (a) Kray, W. D.; Rosser, R. W. Synthesis of multifunctional triarylfluoroethanes. 1. Condensation of fluoro ketones. *J. Org. Chem.* **1977**, *42*, 1186–1189. (b) Prakash, G. K. S.; Panja, C.; Shakhmin, A.; Shah, E.; Mathew, T.; Olah, G. A. BF_3-H_2O catalyzed hydroxyalkylation of aromatics with aromatic aldehydes and dicarboxaldehydes: efficient synthesis of triarylmethanes, diarylmethylbenzaldehydes, and anthracene derivatives. *J. Org. Chem.* **2009**, *74*, 8659–8668and references cited therein.

15 (a) Olah, G. A.; Prakash, G. K. S.; Lammertsma, K. Protonated (protosolvated) onium ions (onium dications). *Res. Chem. Intermed.* **1989**, *12*, 141–159. (b) Ohwada, T.; Yamagata, N.; Shudo, K. Friedel-Crafts-type reactions involving di- and tricationic species. Onium-allyl dications and O,O-diprotonated aci-nitro species bearing a protonated carbonyl group. *J. Am. Chem. Soc.* **1991**, *113*, 1364–1373. (c) Olah, G. A. Superelectrophiles. *Angew. Chem., Int. Ed.* **1993**, *32*, 767–788. (d) Olah, G. A.; Klumpp, D. A. *Superelectrophiles and Their Chemistry*; Wiley & Sons: New York, 2008.

16 O'Connor, M.; Boblak, K. N.; Spitzer, A. D.; Gucciardo, P. A.; Baumann, A. M.; Peter, J. W.; Chen, C. Y.; Peter, R.; Mitton, A. A.; Klumpp, D. A. Condensations of aryl trifluoromethyl ketones with arenes in acidic media. *Tetrahedron Lett.* **2010**, *51*, 4984–4987.

17 Prakash, G. K. S.; Yan, P.; Torok, B.; Olah, G. A. Superacid catalyzed hydroxyalkylation of aromatics with ethyl trifluoropyruvate: a new synthetic route to Mosher's acid analogues. *Synlett* **2003**, 527–531.

18 Fatiadi, A. J. In *Preparation and Synthetic Applications of Cyano Compounds*; Patai, S., Rappaport, Z., Eds.; Wiley: New York, 1983; p 1057.

19 Yan, P.; Batamack, P.; Prakash, G. K. S.; Olah, G. A. Gallium(III) triflate catalyzed dehydration of aldoximes. *Catal. Lett.* **2005**, *103*, 141–143.

20 (a) Gawley, R. E. The Beckmann reactions: Rearrangement, elimination-additions, fragmentations, and rearrangement-cyclizations. *Org. React.* **1988**, *35*, 14–24. and references therein. (b) Arisawa, M.; Yamaguchi, M. Rhodium-catalyzed Beckmann rearrangement. *Org. Lett.* **2001**, *3*, 311–312.

21 (a) Yadav, J. S.; Reddy, B. V. S.; Madhavi, A. V.; Ganesh, Y. S. S. $[Yb(OTf)_3]$ Catalysed facile conversion of ketoximes to amides and lactams. *J. Chem. Res. Syn.* **2002**, *5*, 236–238. (b) Barman, D. C.; Gohain, M.; Prajapati, D.; Sandhu, J. S. Indium trifluoromethanesulfonate ($In(OTf)_3$). A new catalyst for Beckmann rearrangement of ketoximes and facile dehydration of aldoximes. *Indian J. Chem. B* **2002**, *41B*, 154–156.

22 Yan, P.; Batamack, P.; Prakash, G. K. S.; Olah, G. A. Gallium(III) triflate catalyzed Beckmann rearrangement. *Catal. Lett.* **2005**, *103*, 165–168.

23 Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Zuccaccia, C.; Vaccaro, L. $In(OTf)_3$-catalyzed thiolysis of 1,2-epoxides by arylthiols under SFC. A new approach for the synthesis of thiazolopyridinium ionic liquids. *Green Chem.* **2006**, *2*, 191–196 and references cited therein.

24 Carrenño, M. C.; Pérez-González, M.; Ribagorda, M.; Somoza, Á.; Urbano, A. β-Hydroxysulfoxides as chiral cyclic ketone equivalents: Enantioselective synthesis of polysubstituted cyclohexanones, cyclohexenones and cyclohexenediones. *Chem. Commun.* **2002**, 3052–3053.

25 Su, W.; Chen, J.; Wu, H.; Jin, C. A general and efficient method for the selective synthesis of β-hydroxy sulfides and β-hydroxy sulfoxides catalyzed by gallium(III) triflate. *J. Org. Chem.* **2007**, *72*, 4524–4527.

26 Black, J.; Durant, G.; Emmett, J.; Ganellin, C. Sulphur-methylene isosterism in the development of metiamide, A new histamine H_2-receptor antagonist. *Nature* **1974**, *248*, 65–67.

27 Miura, S.; Yoshimura, Y.; Endo, M.; Machida, H.; Matsuda, A.; Tanaka, M.; Sasaki, T. Antitumor activity of a novel orally effective nucleoside, 1-(2-deoxy-2-fluoro-4-thio-beta-D-arabinofuranosyl)cytosine. *Cancer Lett.* **1998**, *129*, 103–110.

28 Trail, P.; Willner, D.; Lasch, S.; Henderson, A.; Hofstead, S.; Casazza, A.; Firestone, R.; Hellstrom, I.; Hellstrom, K. Cure of xenografted human carcinomas by BR96-doxorubicin immunoconjugates. *Science* **1993**, *261*, 212–215.

29 Han, X.; Wu, J. $Ga(OTf)_3$-catalyzed direct substitution of alcohols with sulfur nucleophiles. *Org. Lett.* **2010**, *12*, 5780–5782 and references cited therein.

30 (a) Maciagiewicz, I.; Dybowski, P.; Skowronska, A. A general and stereoselective method for synthesis of tri- and tetrasubstituted alkenes. *Tetrahedron* **2003**, *59*, 6057–6066.

31 Breen, A. P.; Murphy, J. A. Vinyl epoxides: Reagents for radical-induced DNA cleavage. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2979–2990.

32 Rosenberger, M.; Jackson, W.; Saucy, G. The synthesis of β,γ- and α,β-unsaturated aldehydes via polyene epoxides. *Helv. Chim. Acta* **1980**, *63*, 1665–1674.

33 Feng, X.; Shu, L.; Shi, Y. Chiral Lewis acid catalyzed resolution of racemic enol ester epoxides. Conversion of both enantiomers of an enol ester epoxide to the same enantiomer of acyloxy ketone. *J. Org. Chem.* **2002**, *67*, 2831–2836.

34 Deng, X.-M.; Tang, X.-L.; Sun, Y. Highly regioselective rearrangement of 2-substituted vinylepoxides catalyzed by gallium(III) triflate. *J. Org. Chem.* **2005**, *70*, 6537–6540 and references cited therein.

35 van Tamelen, E. E.; Leiden, T. M. Direct sterol synthesis by the nonenzymic cyclization of an acarbocyclic monosubstituted epoxide. *J. Am. Chem. Soc.* **1982**, *104*, 2061–2062 and references cited there in.

36 Goldsmith, D. J. The cyclization of epoxyolefins: The reaction of geraniolene monoepoxide with boron fluoride etherate. *J. Am. Chem. Soc.* **1962**, *84*, 3913–3918.

37 Corey, E. J.; Sodeoka, M. An effective system for epoxide-initiated cation-olefin cyclization. *Tetrahedron Lett.* **1991**, *32*, 7005–7008.

38 Lacey, J. R.; Anzalone, P. W.; Duncan, C. M.; hackert, M. J.; Mohan, R. S. A study of epoxyolefin cyclizations catalyzed by bismuth trifluoromethanesulfonate and other metal triflates. *Tetrahedron Lett.* **2005**, *46*, 8507–8511.

39 (a) Schwarz, D. E.; Cameron, T. M.; Hay, P. J.; Scott, B. L.; Tumas, W.; Thorn, D. L. Hydrogen evolution from organic "hydrides". *Chem. Commun.* **2005**, 5919–5921.

40 (a) D'Amico, J. J. N-Substituted benzothiazolines and benzoxazolines and their use as herbicides and plant growth regulants. U.S. Patent 4,336,060, 1982. (b) Robert, D. P.; Frank, A. H. Oxidation resistant composition containing a benzothiazoline compound. U.S. Patent 4,708,810, 1987

41 (a) Wright, W. B. Jr. Certain dihydrobenzoxazineones and dihydrobenzothiazineones and process. U.S. Patent. US 2776281, 1957. (b) Helsley, G. C; Lunsford, C. D.; Welstead, W. J., Jr.; Boswell, R. F., Jr.; Funderburk, W. H.; Johnson, D. N. Synthesis and analgetic activity of some 1-substituted 3-pyrrolidinylanilides and dihydrobenzoxazinones. *J. Med. Chem.* **1969**, *12*, 583–586.

42 *Bioorganic and Medicinal Chemistry of Fluorine*; Bégué, J.-P., Bonnet-Delpon, D., Eds.; Wiley: Hoboken, NJ, 2008.

43 Smith, J. G.; Ho, I. Organic redox reactions during the interaction of o-phenylenediamine with benzaldehyde. *Tetrahedron Lett.* **1971**, 3541–3544.

44 Prakash, G. K. S.; Mathew, T.; Panja, C.; Vaghoo, H.; Venkataraman, K.; Olah, G. A Efficient one-pot synthesis of fluorinated benzimidazolines, benzothiazolines, benzoxazolines, and dihydrobenzoxazinones using gallium(III) triflate as a catalyst. *Org. Lett.* **2007**, *9*, 179–182.

45 (a) Gilbert, D. E.; Van Der Marel, G. A.; Van Boom, J. H.; Feigon, J. Unstable Hoogsteen base pairs adjacent to echinomycin binding sites within a DNA duplex. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 3006–3010 and references cited therein. (b) Wakelin, L. P. G.; Waring, M. J. The Binding of echinomycin to deoxyribonucleic acid. *Biochem. J.* **1976**, *157*, 721–740.

46 (a) Lindsley, C. W.; Zhao, Z.; Leister, W. H.; Robinson, R. G.; Barnett, S. F.; Defeo-Jones, D.; Jones, R. E. Allosteric Akt (PKB) inhibitors: Discovery and SAR of isozyme selective inhibitors. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 761–764. (b) Hui, X.; Desrivot, J.; Bories, C.; Loiseau, P. M.; Franck, X.; Hocquemiller, R.; Figadère, B. Synthesis and antiprotozoal activity of some new synthetic substituted quinoxalines. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 815–820.

47 Grossi, G.; Di Braccio, M.; Roma, G.; Tognolini, M.; Calcina, F.; Barocelli, E. 1,5-Benzodiazepines. Part XIII. Substituted 4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepin-5-amines and 4H-imidazo[1,2-a][1,5]benzodiazepin-5-amines as analgesic, antiinflammatory and/or antipyretic agents with low acute toxicity. *Eur. J. Med. Chem.* **2002**, *37*, 933–944 and references cited therein.

48 (a) Prakash, G. K. S.; Vaghoo, H.; Venkat, A.; Panja, C.; Chacko, S.; Mathew, T.; Olah, G. A. Gallium(III) triflate catalyzed synthesis of heterocycles: Quinoxalines, 1, 5-benzodiazepines and their fluorinated derivatives. *Future Med. Chem.* **2009**, *1*, 909–920.

49 (a) Jiang, Y.-J.; Cai, J.-J.; Zou, J.-P.; Zhang, W. Gallium(III) triflate-catalyzed [4 + 2+1] cycloadditions for the synthesis of novel 3,4-disubstituted-1,5-benzodiazepines. *Tetrahedron Lett.* **2010**, *51*, 471–474.

50 Chen, J.; Yang, X.; Liu, M.; Wu, H.; Ding, J.; Su, W. Approach to synthesis of β-enamino ketones and pyrroles catalyzed by gallium(III) triflate under solvent-free conditions. *Synth. Commun.* **2009**, *39*, 4180–4198.

51 Zhou, H.; Zhu, D.; Xie, Y.; Huang, H.; Wang, K. $Ga(OTf)_3$-promoted sequential reactions via sulfur-assisted propargyl-allenyl isomerizations and intramolecular [4 + 2] cycloaddition for the synthesis of 1,3-dihydrobenzo[c]thiophenes. *J. Org. Chem.* **2010**, *75*, 2706–2709 and refernces cited therein.

52 (a) Nguyen, R.-V.; Yao, X.; Bohle, D. S.; Li, C.-J. Gold- and silver-catalyzed highly regioselective addition of active methylenes to dienes, triene, and cyclic enol ethers. *Org. Lett.* **2005**, *7*, 673–675. and the references therein. (b) Nguyen, R.-V.; Li, C.-J. An annulation toward fused bicyclolactones. *J. Am. Chem. Soc.* **2005**, *127*, 17184–17185.

53 (a) Olah, G. A.; Mathew, T.; Panja, C.; Smith, K.; Prakash, G. K. S. PVP-SO_2 complex as a solid mild acid catalyst for efficient one pot, three component, Strecker synthesis of α-aminonitriles. *Catal. Lett.* **2007**, *114*, 1–7 and references cited therein.

54 Matsumoto, K.; Kim, J. C.; Iida, H.; Hamana, H.; Kumamoto, K.; Kotsuki, H.; Jenner, G. Multicomponent Strecker reaction under high pressure. *Helv. Chim. Acta* **2005**, *88*, 1734–1753.

55 Prakash, G. K. S.; Mathew, T.; Panja, C.; Alconcel, S.; Vaghoo, H.; Do., C.; Olah, G. A. Gallium(III) triflate catalyzed efficient Strecker reaction of ketones and their fluorinated analogs. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 3703–3706.

56 Balalaie, S.; Kowsari, E. One-pot synthesis of N-substituted 4-aryl-1,4-dihydropyridines under solvent-free conditions and microwave irradiation. *Monatsh. Chem.* **2001**, *132*, 1551–1555.

57 Kikuchi, S.; Iwai, M.; Fukuzawa, S. A novel and facile method for the synthesis of 2,3-disubstituted quinolines by a three-component coupling reaction. *Synlett* **2007**, 2639–2642.

58 Prakash, G. K. S.; Do., C.; Mathew, T.; Olah, G. A. Gallium(III) triflate catalyzed direct reductive amination of aldehydes. *Catal. Lett.* **2010**, *137*, 111–117.

59 Prakash, G. K. S.; Do., C.; Mathew, T.; Olah, G. A. Reduction of carbonyl to methylene: Organosilane $Ga(OTf)_3$ as an efficient reductant system. *Catal. Lett.* **2011**, *141*, 507–511.

60 Mukaiyama, T. The directed aldol reaction. *Org. React.* **1982**, *28*, 203–331and references cited therein.

61 Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shina, I. Catalytic asymmetric aldol reaction of silyl enol ethers with aldehydes by the use of chiral diamine coordinated tin(II) triflate. *Chem. Lett.* **1990**, 129–132.

62 Kobayashi, S.; Ogawa, C. New entries to water-compatible Lewis acids. *Chem.—Eur. J.* **2006**, *12*, 5954–5960 and references cited therein.

63 (a) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. Hydroamination and hydroalkoxylation catalyzed by triflic acid. Parallels to reactions initiated with metal triflates. *Org. Lett.* **2006**, *8*, 4179–4182. (b) Yang, C. G.; Reich, N. W.; Shi, Z. J.; He, C. Intramolecular addition of alcohols and carboxylic acids to inert olefins catalyzed by silver (I) triflate. *Org. Lett.* **2005**, *7*, 4553–4556. (c) Zhang, J.; Yang, C.-G.; He, C. Gold(I)-catalyzed intra- and intermolecular hydroamination of unactivated olefins. *J. Am. Chem. Soc.* **2006**, *128*, 1798–1799.