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Applications of bismuth(III) compounds in organic synthesis

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Contents

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1. Introduction

The word bismuth is derived from the German word Weissmuth or white substance. Bismuth is the 83rd element in the periodic table with an atomic mass of 208.980 and is the heaviest stable element on the periodic table. Although bismuth is a relatively rare element (ranking 64th in abundance in the Earth's crust), large quantities of bismuth are produced annually as a by-product of copper and tin refining. In spite of its heavy metal status, bismuth is considered to be safe, as it is *non-toxic* and *non-carcinogenic*.[1] This is in sharp contrast to closely located elements in the periodic table such as arsenic, antimony, lead and tin which are highly toxic and their use poses environmental hazards. Bismuth and its compounds have been used in medicinal preparations for over four hundred years. Several bismuth compounds have application as treatment for gastric disorders. Bismuth has an electron configuration of $[Xe]4f^{14}5d^{10}6s^{2}6p^{3}$, and due to the weak shielding of the 4f electrons (Lanthanide contraction), bismuth(III) compounds exhibit Lewis acidity. Bismuth also exhibits a +5 oxidation state and several organobismuth compounds with bismuth in the +5 are known. Most bismuth compounds are relatively non-toxic, easy to handle and can tolerate small amounts of moisture. With increasing environmental concerns and the need for 'green reagents', the interest in bismuth and its compounds has increased tremendously in the last decade. Several review articles and a monograph has focused on the applications of bismuth and its compounds in organic synthesis.[2–5] This report is limited to a review of the recent literature on applications of inorganic bismuth(III) compounds in organic synthesis. The report is organized by reaction type.

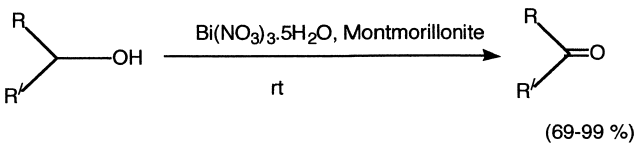
1.1. Availability of bismuth(III) compounds

Several bismuth(III) compounds are now commercially available at relatively low costs. These include bismuth(III) acetate $Bi(OAc)_3$ (CAS # *22306-37-2*), bismuth(III) bromide $BiBr_3$ (CAS # *7787-58-8*), bismuth chloride $BiCl_3$ (CAS # *7787-60-2*), bismuth(III) fluoride BiF_3 (CAS # *7787-61-3*), bismuth(III) iodide BiI_3 (CAS # *7787-64-6*), bismuth nitrate pentahydrate $Bi(NO_3)\cdot 5H_2O$ (CAS # *10035-06-0*), bismuth(III) oxide Bi_2O_3 (CAS # *1304-76-3*), bismuth oxide perchlorate $BiOClO_4$, bismuth(III) chloride oxide BiOCl (CAS # *7787-59-9*), bismuth(III) iodide oxide BiOI (CAS # *7787-63-5*), bismuth(III) phosphate $BiPO_4$ (CAS # *10049-01-1*), bismuth(III) selenide Bi_2Se_3 (CAS # *12068-69-8*), bismuth(III) subnitrate $BiONO_3$ (CAS # *10361-46-3*), bismuth(III) sulfide Bi_2S_3 (CAS # *1345-07-9*), bismuth(III) telluride Bi_2Te_3 (CAS # *1304-82-1*), bismuth(III) titanate $Bi_2O_3\cdot 2TiO_2$ (CAS # *12048-51-0*), and bismuth(III) tungstate $Bi_2(WO4)_3$ (CAS # *13595-86-3*). A versatile catalyst, bismuth triflate, $Bi(OSOCF_3)_3$ is not yet commercially available, but can be easily synthesized in lab following a literature procedure.[6–9] Most bismuth compounds are crystalline solids and are relatively stable in air.

2. Oxidations using bismuth(III) compounds

2.1. Oxidation of alcohols

The oxidation of 2° alcohols to ketones using bismuth nitrate, $Bi(NO_3)_3$, impregnated on montmorillonite has been reported (Scheme 1).[10] The oxidation is very rapid at room temperature and proceeds well with out the need for any



Scheme 1.

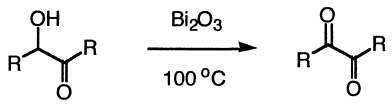
pre-treatment of the catalyst or microwave irradiation. All attempts to oxidize 1° alcohols using this reagent failed.

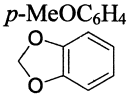
2.2. Oxidation of acyloins to diketones

One of the first examples of the use of bismuth compounds in organic synthesis was the use of bismuth(III) oxide, Bi_2O_3 for oxidation of acyloins to diketones.[11] The reaction can be carried out in acetic acid alone as the solvent or with 2-ethoxyethanol as a co-solvent (Scheme 2). For sensitive substrates such as pyridoin and furoin, this method was found to be superior to other oxidation methods such as copper catalyzed-ammonium nitrate oxidation. This reaction can also be used as a qualitative test for acyloins, since upon completion of the rapid oxidation at 100°C, a black precipitate of elemental bismuth is obtained. Since the oxidation works well with bismuth acetate also, it is proposed that bismuth triacetate formed under the reaction conditions is the actual oxidant.

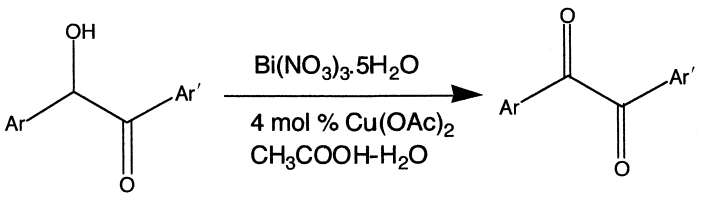
This methodology has been used in the synthesis of several natural products including the conversion of 2-hydroxypulegone to diophenolene. Several oxidative transformations of compounds containing a steroid ring are also known.

The oxidation of benzoins to benzils using bismuth nitrate in aqueous acetic acid has also been recently reported (Scheme 3).[12] While the bismuth oxide method requires the use of a slight excess of the oxidant, 0.40 equiv. of bismuth nitrate is sufficient for oxidation. The reaction is accelerated by the presence of 0.10 equiv. of copper(II) acetate. However, the oxidation of pyridoin and furoin (Scheme 3, entries 5 and 6) was not successful. When commercially available furil or pyridil were subjected to the reaction conditions, their disappearance could be followed by TLC and aqueous work-up did not yield any organic product. Hence, it is proposed that the expected products, pyridil and furil, are



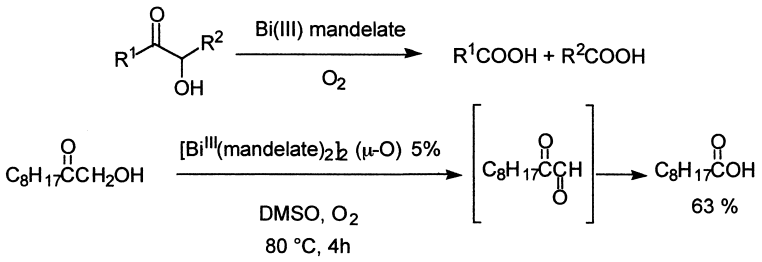
Entry	R	Time	Solvent	Yield (%)
1	Ph	1 h	AcOH-$HOCH_2CH_2OCH_2CH_3$	95
2	Ph	30 min	AcOH	93
3	*p*-$MeOC_6H_4$	1 h	AcOH-$HOCH_2CH_2O$ CH_2CH_3	95
4	*p*-$MeOC_6H_4$	20 min	AcOH	91
5		1.25 h	AcOH-$HOCH_2CH_2OCH_2CH_3$	97
6		45 min	AcOH-$HOCH_2CH_2OCH_2CH_3$	92
7		10 min	AcOH-H_2O	88
8	$CH_3CH_2CH_2$–	15 min	AcOH	64

Scheme 2.

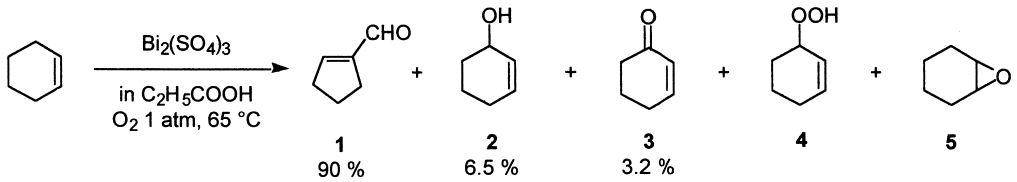


Entry	Ar	Ar'	Yield (%)
1	Ph	Ph	99
2	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	99
3	*p*-MeC_6H_4	*p*-MeC_6H_4	95
4	Ph	*p*-$MeOC_6H_4$	95
5			58
6			10

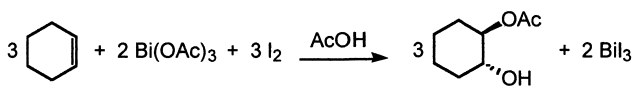
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

formed in good yields but they undergo subsequent C–C bond cleavage to give the corresponding water-soluble aldehydes.

The oxidation of α-ketols to carboxylic acids has been achieved with molecular oxygen as the oxidant and bismuth mandelate as a catalyst (Scheme 4).[13] This oxidation is accelerated in the presence of DMSO. The catalyst itself is prepared from Bi_2O_3 and mandelic acid. When the reaction was carried out under a nitrogen atmosphere, very little of the expected carboxylic acid was obtained suggesting that oxygen is essential in the oxidation.

There are many advantages to this system. The oxidant is cheap and clean. The reaction is catalytic in bismuth(III) in contrast to several other reagents known to achieve the same transformation such as sodium periodate. The functional group selectivity exhibited is also valuable since alcohols, geminal-diols and olefins are not affected under the reaction conditions.

2.3. Oxidative cleavage of olefins

The autoxidation of cyclohexene catalyzed by insoluble bismuth sulfate in acidic solvents has been reported (Scheme 5).[14]

The major product of this oxidation is 1-cyclopentene-1-carboxaldehyde. The product distribution was found to be dependent upon the solvent used. In benzene, the main products were cyclohexenol **2**, and cyclohexenone **3**. The oxidation of several other cycloolefins was also examined. 4-Methylcyclohexene was oxidized to the corresponding aldehyde in high selectivity while the presence of an alkyl group at 1, 2 or 3-positions retarded the reaction. A mechanism involving isomerization of peroxy radical catalyzed by the acidic sites of bismuth sulfate has been proposed. The observation that addition of small amounts of pyridine inhibited the reaction and changed the product distribution supports the role of acidic catalysis.

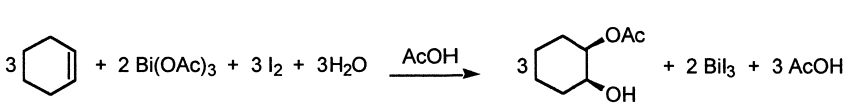
2.4. Conversion of alkenes to diols

The Prevost (dry) and the Woodward–Prevost (wet) reactions for the conversion of alkenes to diols are typically carried out with silver(I) salts.[15] Modifications of these reactions have also led to the use of mercury(II), copper(II), thallium(I) and lead(IV) salts. *cis*- and *trans*-diol derivatives can be prepared from alkenes by reaction with bismuth(III) acetate in 'wet' and 'dry' acetic acid, respectively (Schemes 6 and 7).[16] Bismuth acetate is commercially available but was also prepared in situ from the inexpensive and readily available bismuth oxycarbonate $(BiO)_2CO_3$. For preparation of *cis*-diols, it was found that maximum selectivity is obtained when equimolar amounts of alkene and water are used.

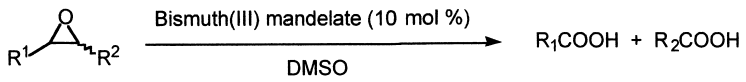
The advantages of using bismuth acetate include its low cost, favorable stoichiometry (all three acetate groups can be transferred) and above all, its low toxicity especially compared to lead, mercury and thallium salts.

2.5. Oxidation of epoxides

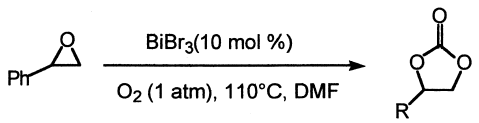
The oxidative cleavage of substituted styrene oxides to the



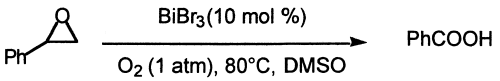
Scheme 7.



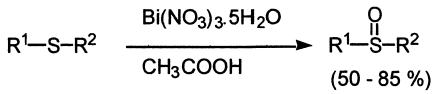
Scheme 8.



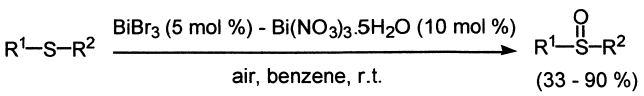
Scheme 9.



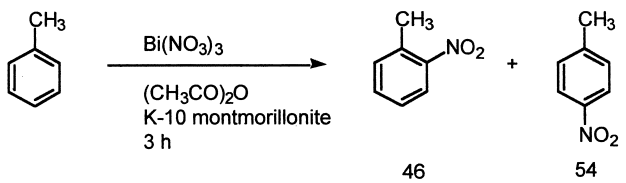
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

corresponding carboxylic acid in DMSO is catalyzed by bismuth(III) mandelate (Scheme 8).[17,18] The reaction is accelerated by the presence of electron-donating groups on the phenyl ring. This is consistent with a Hammet ρ value of -1.08.

The oxidation of epoxides to cyclic carbonates using molecular oxygen as the oxidant and $BiBr_3$ as the catalyst has been reported (Scheme 9).[19] This reaction is both catalyst and solvent specific. When the oxidation was carried out in DMSO, only the carboxylic acid was obtained (Scheme 10). When $BiCl_3$ was used in place of $BiBr_3$, no carbonate was obtained. Increasing the amount of $BiCl_3$ resulted in formation of the corresponding chlorohydrins as a mixture of isomers. However, no bromohydrin formation was noticed with $BiBr_3$ as the catalyst. It is proposed that the reaction involves the incorporation and oxidation of the carbonyl group of DMF.

2.6. Oxidation of sulfides to sulfoxides

The oxidation of sulfides to sulfoxides using $Bi(NO_3)\cdot 5H_2O$ in acetic acid as well as $BiBr_3-Bi(NO_3)_3\cdot 5H_2O$ in benzene has been described (Schemes 11 and 12).[20,21]

In benzene as the solvent, the use of bismuth nitrate alone did not result in complete oxidation. However, the addition of $BiBr_3$ enhanced the catalytic activity significantly. By carrying out the reaction under an oxygen atmosphere, it was demonstrated that the reaction consumed a stoichiometric amount of oxygen. The method is particularly attractive since several other functional groups such as aldehyde and alcohol did not suffer oxidation. The formation of NO_2 as evidenced by a brown gas suggests that $Bi(NO_3)_3$ and $BiBr_3$ serve as a source of NO_2 and a promoter of NO_2 release, respectively.

2.7. Nitration of aromatic hydrocarbons

Aromatic hydrocarbons are nitrated by $Bi(NO_3)_3\cdot 5H_2O$ impregnated on K10 montmorillonite in the presence of acetic anhydride (Scheme 13).[22] It was found that the choice of solvent significantly altered the product distribution. For example, the nitration of toluene gave the highest proportion (80%) of the *para* isomer in CCl_4 as the solvent. No nitration product was obtained in acetonitrile as the solvent. While nitration occurred in acetone, cyclohexane and 1,2-dichloroethane, none of these solvents gave *para* isomer (>50%) as the main product.

All these reactions display an induction period manifested by a color change that has been attributed to drying of the reaction centers by acetic anhydride at the solvent–clay interface. The best yields were obtained when the hydrocarbon was added at the end of this induction period.

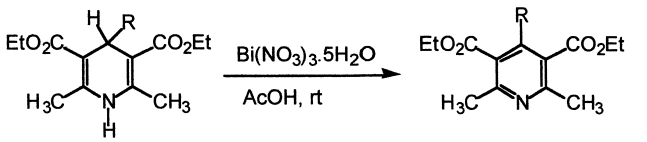
2.8. Oxidation of Hantzsch 1,4-dihydropyridines to pyridines

Hantzsch 1,4-dihydropyridines have been used as analogs of NAD(P)H coenzymes to study the mechanism and synthetic potential of various redox reactions. During the redox processes and in the course of drug metabolism, they are oxidized to the corresponding pyridine derivatives. Several of the existing methods for this oxidation require the use of corrosive and toxic reagents like CrO_3, PCC or ceric ammonium nitrate as well as harsh reaction conditions. A less harsh method that utilizes $Bi(NO_3)_3\cdot 5H_2O$ for the oxidation works well in acetic acid at room temperature has been reported (Scheme 14).[23]

3. Removal of common protecting groups

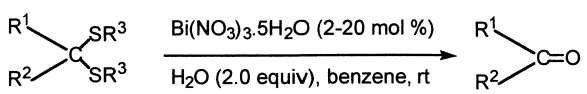
3.1. Deprotection of *S*,*S*-acetals to carbonyl compounds

The oxidative deprotection of *S*,*S*-acetals using $Bi(NO_3)_3\cdot 5H_2O$ as a catalyst proceeds smoothly at room temperature to give the corresponding carbonyl compounds in good yields (Scheme 15).[24]



R	Time (h)	Yield (%)
H	14	75
CH_3	5	68
C_6H_5	7	90
p-$(NO_2)C_6H_4$	2	84
p-$(OCH_3)C_6H_4$	8	82
CH_3CH=CH-	1	60
C_6H_5CH=CH-	1	50

Scheme 14.



R^1 = *p*-$MeOC_6H_4$, Ph, $Me(CH_2)_6$, $Me(CH_2)_5$, $Me(CH_2)_4$,

R^2 = H, Me, Et R^3 = $(CH_2)_2$, $(CH_2)_3$, Ph, Et, $(CH_2)_3$,

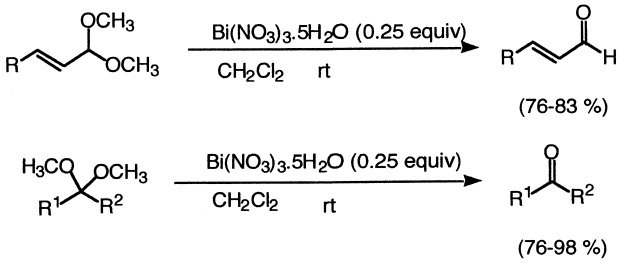
Scheme 15.

Most of the common methods for deprotection of *S*,*S*-acetals require the use of heavy metals such as copper(II), mercury(II), silver(I) and an oxidizing agent such as molecular halogen, *N*-halosuccinimdes or MCPBA. Thus, the use of air and a relatively non-toxic bismuth salt offers significant improvement over these existing methods. The addition of 5.0 mol% $BiCl_3$ accelerated the reaction rate in some cases. Benzene was found to be the best solvent though toluene and acetonitrile also worked well.

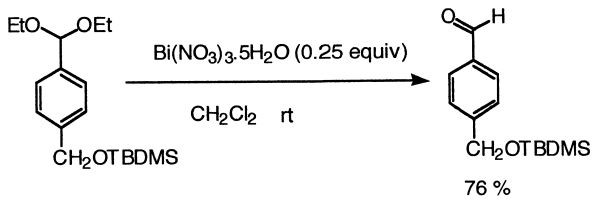
3.2. Deprotection of *O*,*O*-acetals

Several bismuth(III) compounds have been used to deprotect *O*,*O*-acetals. One chemoselective method for deprotection of acetals makes use of the catalytic activity of $BiCl_3$ in CH_3OH as the solvent (Scheme 16).[25] The method however requires the use of 0.5 equiv. of $BiCl_3$. Under these conditions, THP ethers, TBDMS groups and benzyl groups are not affected. The deprotection of 1,3-dioxolanes was slow at room temperatures but was accelerated under reflux conditions.

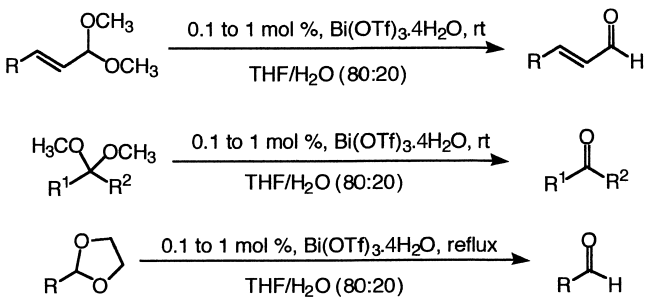
Another mild and chemoselective method utilizes $Bi(NO_3)_3{\cdot}5H_2O$ in CH_2Cl_2 for the deprotection of acetals



Scheme 17.



Scheme 18.

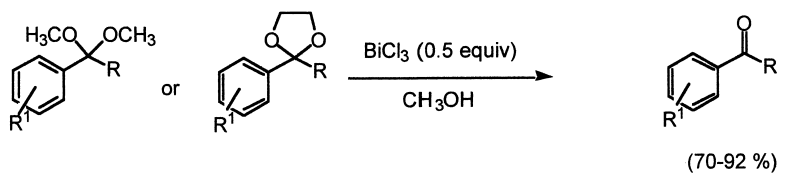


Scheme 19.

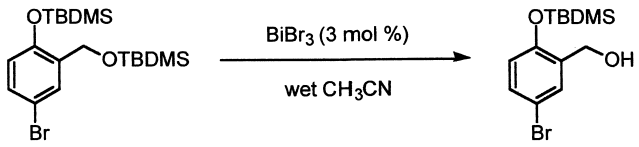
(Scheme 17).[26] Under these conditions, cyclic acetals are not deprotected. Acetals derived from non-conjugated aldehydes are also resistant to these reaction conditions.

The chemoselectivity of the method has been demonstrated by selective deprotection of a bi-functional compound (Scheme 18). The *tert*-butyldimethylsilyl group is not affected while the diethyl acetal group is removed at room temperature.

While the above methods for *O*,*O*-deprotection illustrate the versatility of bismuth(III) compounds as useful catalysts, these methods cannot be classified as highly catalytic. A highly catalytic, mild and efficient method for the deprotection of acetals, which takes advantage of the catalytic activity of bismuth(III) triflate has recently been reported (Scheme 19).[27] The added advantage of this method is that the solvent system (aqueous THF) is relatively non-toxic.



Scheme 16.



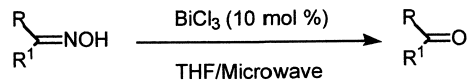
Scheme 20.

3.3. Deprotection of a *tert*-butyldimethylsilyl (TBDMS) group

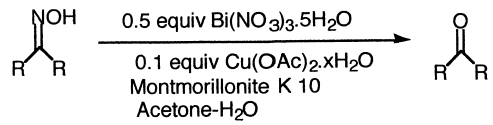
While several methods exist in the literature for the deprotection of a TBDMS group, few are selective in nature. A highly efficient procedure for the selective cleavage of alkyl TBDMS groups in the presence of aryl TBDMS groups using $BiBr_3$ in wet CH_3CN as a catalyst has been reported (Scheme 20).[28]

It is proposed that the hydrolysis is possibly catalyzed by HBr, that is generated in situ from the reaction of $BiBr_3$ with water. Since $BiBr_3$ is a stable solid, it is much easier to handle than other reagents such as I_2/TMSCl typically used to effect the same transformation. Another method that utilizes excess $BiCl_3$/NaI in CH_3CN has been developed (Scheme 21). However, it is not clear whether this method requires the use of wet CH_3CN or not.[29]

The selective removal of an alkyl TBDMS group using this method has also been achieved in the presence of other functional groups such as –OTs, NHBOC, –OMe, and –OBn. A variety of trimethylsilyl ethers of alcohols and phenols are easily removed in the presence of catalytic amounts of bismuth(III) salts such as $BiCl_3$, $Bi(CF_3COO)_3$, and $Bi(OTf)_3$ in methanol at room temperature (Scheme 22).[30] TBDMS groups are not affected by $BiCl_3$ or $Bi(CF_3COO)_3$ under these conditions but they are deprotected by $Bi(OTf)_3$. Thus it is clear that the solvent plays a crucial role in determining selectivity.



Scheme 23.

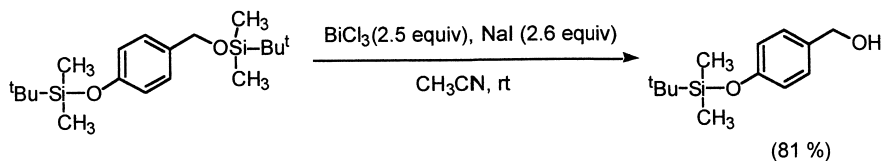


Scheme 24.

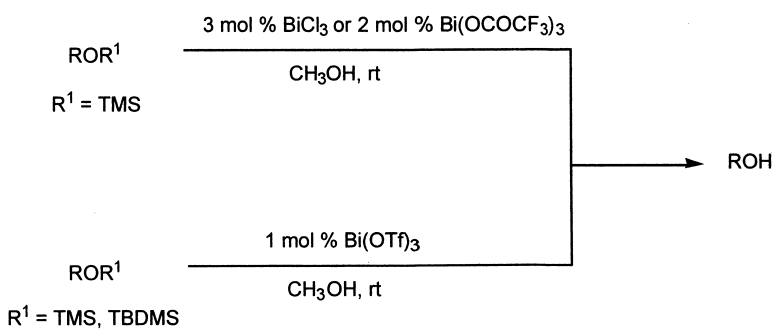
3.4. Deprotection of oximes to carbonyl compounds

The regeneration of carbonyl compounds from oximes is an important synthetic transformation, especially in light of the fact that oximes can be synthesized from non-carbonyl compounds. Several methods in the literature utilize chromium-based compounds for deprotection of oximes. However, the carcinogenic nature of chromium compounds makes their use less attractive. An efficient method that utilizes $BiCl_3$ and microwave irradiation has been used for oxime deprotection (Scheme 23).[31] This method works well with both aldoximes and ketoximes, though deprotection of oximes from α,β-unsaturated carbonyl compounds gave only modest yields.

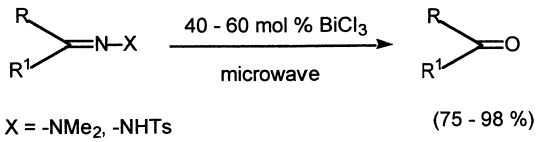
The selective deprotection of ketoximes has been achieved using $Bi(NO_3)_3{\cdot}5H_2O$ in a relatively non-toxic solvent system acetone–H_2O (Scheme 24).[32] Under these conditions, aldoximes are not affected. The use of montmorillonite K 10 served to accelerate the reaction rate. In the absence of copper(II) acetate, the product was found to contain a small amount of acetone oxime. The formation of acetone oxime is not surprising in light of the fact that oximes have been synthesized from aldehydes and ketones using acid catalyzed transoximations by acetone oxime.[33] Since a suspension of $Bi(NO_3)_3{\cdot}5H_2O$ in water is acidic, it is proposed that deprotection could be catalyzed by the nitric acid released under the reaction conditions. It is also



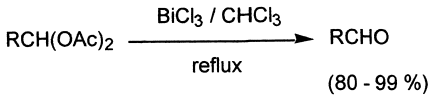
Scheme 21.



Scheme 22.



Scheme 25.



Scheme 26.

possible that owing to the Lewis acidity of bismuth(III) compounds, coordination of bismuth to the oxime nitrogen increases the susceptibility of the oxime carbon to nucleophilic attack by water.

3.5. Conversion of hydrazones and semicarbazones to carbonyl compounds

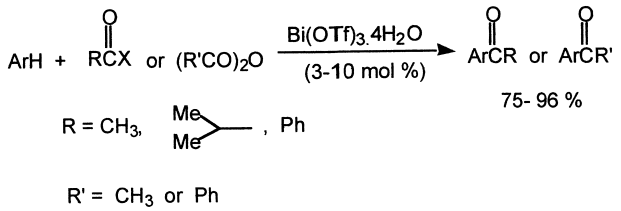
An efficient method for the hydrolytic cleavage of C=N bond of dimethyl and tosylhydrazones to yield the corresponding carbonyl compounds using $BiCl_3$ in wet THF under microwave irradiation has been reported (Scheme 25).[34] The method works well with hydrazones derived from both aldehydes and ketones. The mild nature of this method is illustrated by the fact that dimethylhydrazones from α,β-unsaturated ketone were hydrolyzed without rearrangement of the α,β-double bond. Under similar conditions, the deprotection of semicarbazones to the corresponding carbonyl compound has also been reported. Benzyltriphenylphosphonium peroxymonosulfate has been found to be an efficient reagent for the conversion of oximes, phenylhydrazones, 2,4-dinitrophenylhydrazones and semicarbazones to the corresponding carbonyl compounds.[35] This reaction is catalyzed by $BiCl_3$.

3.6. Deprotection of 1,1-diacetates (acylals)

1,1-Diacetates (acylals) have attracted recent attention since they are easily synthesized and can serve as selective protecting groups for aldehydes. Bismuth(III) chloride in $CHCl_3$ is a mild reagent for the deprotection of 1,1-diacetates (Scheme 26).[36] Acylals from aryl aldehydes are deprotected at a significantly faster rate than those from aliphatic aldehydes and hence the method can be used for selective deprotection of the former.

3.7. Cleavage of *tert*-butyl ethers

Bismuth(III) chloride, $BiCl_3$ and bismuth(III) triflate, $Bi(OTf)_3$ were found to be good catalysts for the cleavage



Scheme 28.

of 2-*tert*-butoxy derivatives of thiophenes and furans (Scheme 27).[37] Bismuth(III) chloride was found to be a superior catalyst to $ZnCl_2$ and $FeCl_3$.

In cleavage reactions catalyzed by bismuth(III) triflate, the intermediacy of a *tert*-butyl cation was demonstrated by the formation of *tert*-butyl methyl ether and isobutylene upon addition of methanol.

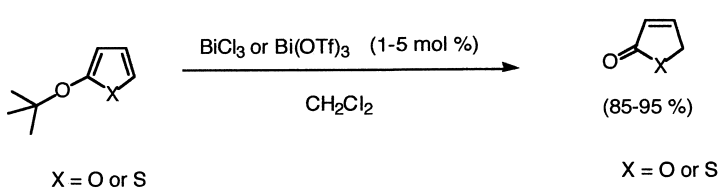
4. Carbon–carbon bond forming reactions

4.1. Friedel–Craft's acylation

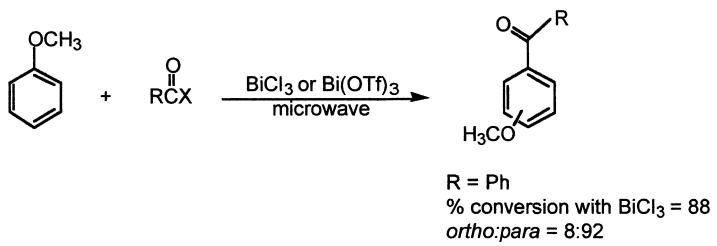
One of the most important reactions of aromatic compounds is the Friedel–Craft's acylation. Traditionally, this reaction is carried out in the presence of stoichiometric amounts of $AlCl_3$. The use of $AlCl_3$, however, leads to undesirable and corrosive gaseous effluents and mineral wastes and hence is not very attractive from an industrial viewpoint. Metal salts such as $FeCl_3$ and $ZnCl_2$ work in catalytic amounts, but their use is restricted to the acylation of activated aromatics. Triflic acid works well as a catalyst, however, its corrosive and hygroscopic nature makes handling and its subsequent recovery in anhydrous form rather difficult.

The use of bismuth(III) chloride and bismuth(III) trifluoromethanesulfonate (triflate), $Bi(CF_3SO_3)\cdot 4H_2O$ for the acylation of aromatics has been reported. (Scheme 28).[38] Bismuth(III) triflate has been reported to be an efficient catalyst for the Friedel–Craft's acylation of a variety of substituted benzenes.[39,40]

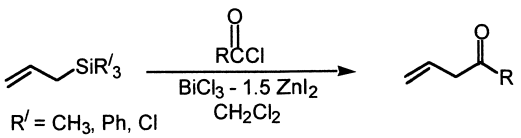
Preferential formation of the *para* isomer was observed in all cases. The Friedel–Craft's acylation of anisole catalyzed by $BiCl_3$ as well as Bi_2O_3 has been reported.[41] Bismuth(III) chloride is not a strong enough catalyst for the acylation of ketones. Detailed NMR studies suggest that the success of bismuth(III) salts in acting as catalysts for the Friedel–Craft's acylation lies in the fact that they preferentially complex to the acyl chloride relative to the ketones. Bismuth(III) compounds, in particular, $BiCl_3$ forms π complexes with aromatics and it has been suggested that this might facilitate solubility of $BiCl_3$ and hence lead to reaction in a homogeneous condition.



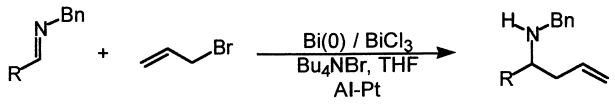
Scheme 27.



Scheme 29.



Scheme 30.



Scheme 31.

The acylation of aromatic ethers under microwave irradiation catalyzed by bismuth(III) salts has also been reported (Scheme 29).[42] The ease of handling of bismuth(III) salts and the preferential formation of *para* isomer makes them attractive catalysts for Friedel–Craft's acylation.

4.2. Allylation catalyzed by bismuth(III) salts

4.2.1. Allylation of acid chlorides (acylation of allyltrimethylsilane). In the presence of catalytic amounts of $BiCl_3$–3 NaI or $BiCl_3$–1.5 ZnI_2, the acylation of allyltrimethylsilane with a variety of acyl chlorides readily occurred at room temperature (Scheme 30).[43] This procedure is one of the first examples of a method that uses relatively non-toxic and inexpensive reagents for allylation of carbonyl compounds.

The acylation of allylsilanes catalyzed by $GaCl_3$ and $InCl_3$ has been studied. However, under these conditions, the isomerization of the product allylketones to 1-propenyl ketones could not be avoided. The advantage of the method shown in Scheme 30 is that compounds like 1-adamantanecarbonyl chloride, which undergo decarbonylation during Friedel–Craft's synthesis reacted readily to give 1-adamantylallyl ketone in 80% yield. Several control experiments suggest that $BiCl_3$ is indeed the active species in these reactions. In a few cases, a small amount of the conjugated ketone product was also obtained. Again, control studies ruled out isomerization of the allylsilane. Thus the conjugated ketone must be forming by isomerization of the allylketone.

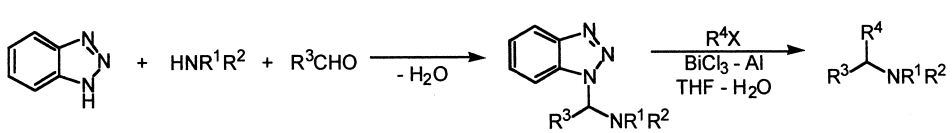
4.2.2. 'Barbier type' allylation of imines. The electroreductive Barbier type allylation of carbonyl compounds and imines has attracted much attention from both mechanistic and synthetic viewpoints. The electroreductive allylation of imines with allyl bromides had been carried out in a $Bi^0/BiCl_3/Bu_4NBr/THF$–(Al anode)–(Pt cathode) system (Scheme 31).[44] Lead(II) chloride also worked well in place of $BiCl_3$ but owing to the toxicity of lead salts, $BiCl_3$ is a better alternative. Zinc(II) chloride and tin(II) chloride were less effective catalysts. Ether solvents, such as THF and dimethoxyethane were found to be the most effective.

The alkylation of immonium cations to amines promoted by bismuth(III) chloride in aqueous media has been reported (Scheme 32).[45] A two step procedure for the alkylation of amines involving a Mannich reaction with benzotriazole and an aldehyde to yield the 1-(aminoalkyl)benzotriazole followed by alkylation with a Grignard reagent to give the N-alkylated amine on elimination of the benzotriazole has been developed. The alkylation described in Scheme 32 offers an advantage over the use of Grignard reagent. Substrates that are incompatible with a Grignard reagent, such as those containing an acidic hydrogen or soluble only in aqueous solutions can also be alkylated.

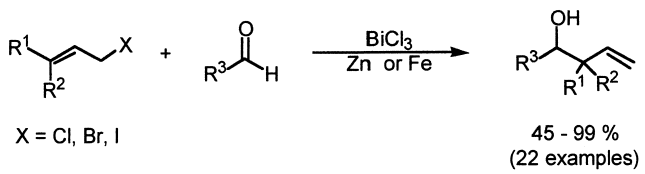
4.2.3. Addition of allyl groups to aldehydes. The addition of an allyl group to an aldehyde to give the corresponding homoallyl alcohol is a useful synthetic transformation. The allylation of aldehydes mediated by $BiCl_3$–metallic Zn or Fe proceeds under mild conditions to afford the corresponding homoallyl alcohol in good yield (Scheme 32).[46,47] The reaction is chemoselective and is specific for aldehydes. Carboxylic acids, nitriles and esters were recovered unchanged under the allylation conditions. The procedure suffers from the fact that $BiCl_3$ is required in stoichiometric amounts (Scheme 33).

A two-phase electroreductive system has also been developed for chemoselective allylation of aldehydes (Scheme 34).[48] The best results were obtained in acidic solutions.

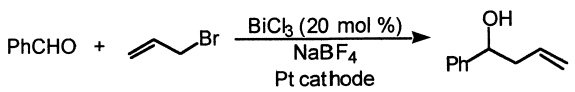
The bismuth(III) chloride mediated allyation of carbonyl compounds containing a carboxyl group has also been studied (Scheme 35).[49] With pyruvic acid, 2-oxobutyric



Scheme 32.



Scheme 33.



Scheme 34.

acid and acetoacetic acid lithium salts, the corresponding homoallyl alcohol was obtained in good yields. When 4-oxopentanoic acid, 5-oxohexanoic acid, 3-benzoylpropionic acid and phthaldehydic acid were used, the corresponding lactone derived from dehydration of the homoallyl alcohol was obtained in good yield.

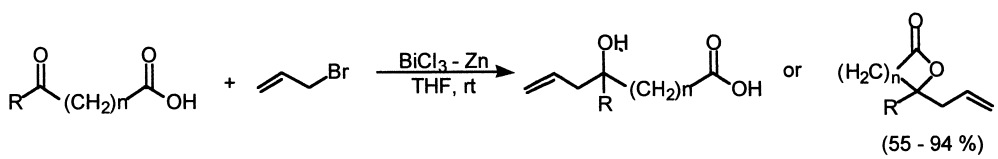
The intramolecular Sakurai cyclization of homoallylic alcohols to yield polysubstituted tetrahydropyrans is efficiently catalyzed by $Bi(OTf)_3{\cdot}H_2O$ (Scheme 36).[50] The products were obtained in good yields and none of the desilylated by-products were obtained.

4.3. Allylation of acetals

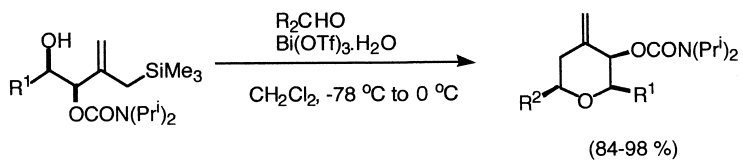
Since carbonyl groups are frequently protected as acetals, the direct allylation of acetals constitutes a useful synthesis of homoallyl ethers and hence this reaction has received much attention. In an early example, $BiBr_3$ (20 mol%) was shown to catalyze the allylation of dimethyl acetals derived from benzaldehyde and heptanal.[51] More recently, a highly catalytic procedure employing bismuth(III) triflate for the allylation of a variety of acetals has been developed (Scheme 37).[52] The corresponding homoallyl ethers are obtained in good yields under mild reaction conditions. It has been reported that with $TiCl_4$ as the activator, the reaction of cinnamaldehyde dimethyl acetal with allyltrimethylsilane gave only the diallylated product.[53] Even at low temperatures (−78°C) the monoallylated product was not formed. Similar results were obtained when allylation of cinnamaldehyde dimethylacetal was carried out using allyl bromide in the presence of $AlBr_3$.[54] In contrast, no diallylated product was observed using bismuth triflate as the catalyst.

4.4. Aldol condensations

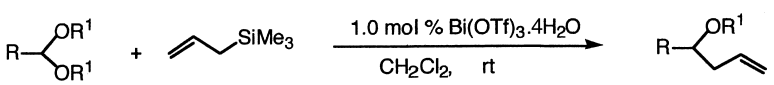
One of the most important carbon–carbon bond forming reactions in organic chemistry is the Mukaiyama-aldol condensation. Bismuth(III) chloride has been well studied as a catalyst for carbon–carbon forming reactions by Wada and co-workers as well as Dubac and co-workers and has proven to be an efficient and mild catalyst for such reactions. Bismuth(III) chloride (5 mol%) has been shown to be an efficient catalyst for the reaction of silyl enol ethers with aldehydes at room temperatures (Scheme 38).[55,56] Both aliphatic and aromatic aldehydes gave good yields. Not surprisingly, ketones gave lower yields than aldehydes especially with more hindered silyl enol ethers. With



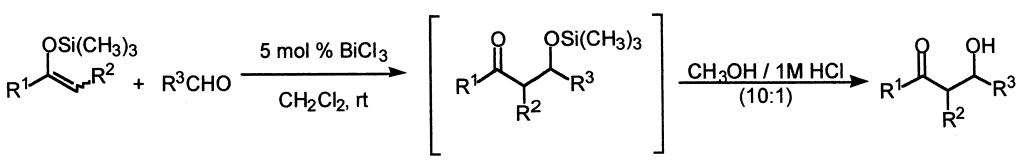
Scheme 35.



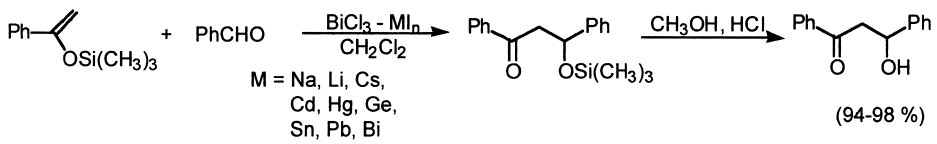
Scheme 36.



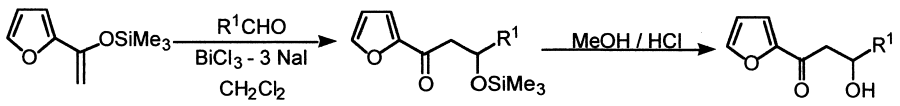
Scheme 37.



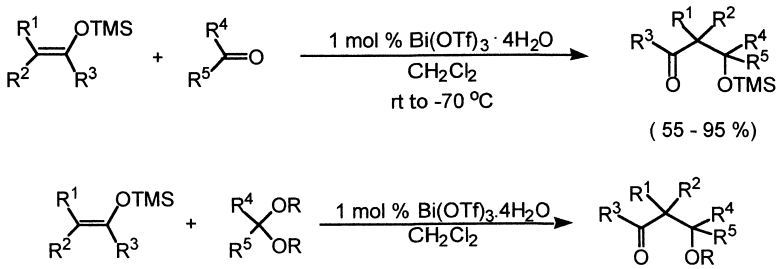
Scheme 38.



Scheme 39.



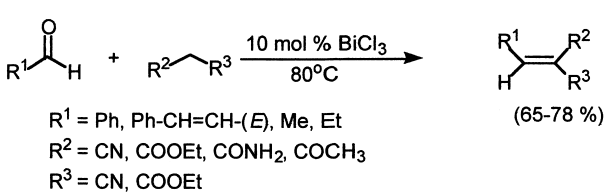
Scheme 40.



Scheme 41.

crotonaldehyde the 1,2 and 1,4 products were obtained in a 2.2:1 ratio while the reaction with chalcone gave the 1,4 product alone. The drawback of this method is the low diastereoselectivity observed.

Le Roux et al. have demonstrated that the catalytic power of $BiCl_3$ can be increased by the addition of several different metal iodides (Scheme 39).[57] Detailed optimization studies showed that with NaI, the optimal yields were obtained when the ratio of $BiCl_3$/NaI was 1:3. Interestingly, ultrasound had a remarkable accelerating effect on the rate of the reaction at room temperature but was ineffective at −30°C. The catalyst was typically prepared by mixing the two anhydrous halides $BiCl_3$ and MI_n in CH_2Cl_2 at room temperature. This resulted in an almost instantaneous formation of black crystals. Analysis of the crystals by X-ray powder pattern techniques indicated that BiI_3 was formed in all cases in addition to mixed halides. However, BiI_3 alone proved to be an ineffective catalyst for the reaction. Besides being relatively non-toxic, the use of bismuth salts for this reaction offers another advantage. The silylated intermediates can be isolated thus avoiding the hydrolysis in the presence of the catalyst, which can lead to undesirable side reactions. The mild reaction conditions allow a catalytic cross aldol reaction between aldehydes and silyl enol ethers derived from furfural, compounds normally prone to polymerization under strongly acidic conditions (Scheme 40).[58,59]



Scheme 42.

Pioneering work by Dubac and co-workers has led to the development of a very versatile bismuth(III) catalyst viz. bismuth trifluormethanesulfonate. Bismuth triflate, $Bi(CF_3SO_3)_3{\cdot}4H_2O$, is a very efficient catalyst for the Mukaiyama aldol-type reactions (Scheme 41).[60]

The reactions work well with both aliphatic and aromatic aldehydes. Bismuth triflate was found to be a superior catalyst in comparison to other metal triflates such as $Ce(OTf)_4$, $Sc(OTf)_3$ and $Yb(OTf)_3$. It is proposed that the mechanism of catalysis by bismuth triflate involves a transmetallation reaction between $Bi(OTf)_3{\cdot}4H_2O$ and the silyl enol ether resulting in the formation of trimethylsilyl triflate which could be the true catalyst for the reaction. Silicon NMR studies as well as the fact that the reaction of acetals is faster than that of aldehydes lends support to this mechanism. It has been previously shown that TMS triflate is a better activator of acetals than aldehydes. An advantage of $Bi(OTf)_3{\cdot}4H_2O$ over TMSOTf is that the former is easier to handle and is less moisture sensitive.

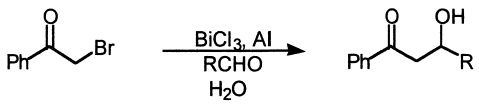
4.5. Knoevenagel condensation

The condensation of an aldehyde or ketone with an active methylene compound, the Knoevenagel reaction, is an important method to synthesize α,β-unsaturated carboxylic acids, and is typically catalyzed by organic amines. A solvent free procedure for the Knoevenagel reaction, catalyzed by $BiCl_3$ has been developed (Scheme 42).[61]

When the same reaction was carried out in benzene, longer reaction times were required and the isolated yields were also unacceptably low.

4.6. Reformatsky-type reactions

The Reformatsky reaction has traditionally been carried out



Scheme 43.

using zinc metal in an organic solvent. More recently, there have been reports of Reformatsky-type reactions in water using zinc powder or tin–aluminum couple. The reaction of α-halocarbonyl compounds with aldehydes in the presence of $BiCl_3$–Al occurs readily in water to yield the β-hydroxy compounds in good yields (Scheme 43).[62] The reaction, which can also be carried out with catalytic amounts of $BiCl_3$–Al, occurs readily with aliphatic and aromatic aldehydes. While detailed mechanistic studies were not carried out, based on the preferential formation of *erythro* products in case of reaction between 2-bromocyclohexanone and benzaldehyde, an acyclic transition state has been proposed. A cyclic transition state and single electron transfer (SET) mechanisms have been ruled out.

4.7. Asymmetric trimethylsilylcyanation of aldehydes using chiral bismuth compounds

Bismuth(III) chloride was found to be an efficient catalyst for the cyanation of aldehydes with TMSCN to afford the corresponding cyanohydrin in good yields (Scheme 44). While aldehydes reacted faster than ketones, both gave very high yields of the corresponding cyanohydrin.

The same authors have developed the first known asymmetric reaction with a chiral bismuth catalyst, opening new doors for bismuth chemistry. Moderate enantioselectivities were obtained by use of a chiral bismuth(III) catalyst prepared in situ from $BiCl_3$ and (2*R*,3*R*)-(+)-diethyl tartrate (Scheme 45). No asymmetric induction was observed when $BiCl_3$ was used along with a chiral co-catalyst. This is attributed to a lowering of the Lewis acidity of $BiCl_3$ up on complexation with the co-catalyst. The enantioselectivity was influenced considerably by the reaction temperature, with the best results obtained at −23°C. Interestingly, best results were obtained when the catalyst was prepared at 0°C for 3 h with a slight excess of $BiCl_3$. Asymmetric induction was observed in CH_2Cl_2 and $ClCH_2CH_2Cl$ but not in polar solvents although the reaction did proceed in reasonable yields in the latter solvents.

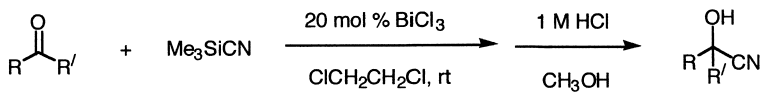
While the observed enantioselectivities are not sufficient to make this procedure practical, the future for chiral bismuth catalysts does hold promise. The catalyst structure, which has not yet been established, will need to be determined for further improvements in the observed enantioselectivities.

4.8. Diels–Alder and the aza-Diels–Alder reactions

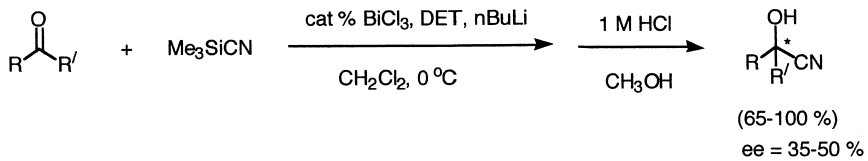
The Diels–Alder reaction still remains one of the best ways to construct a six-membered ring. Lewis acid catalysis of the Diels–Alder reaction has been a subject of rigorous study. Aluminum(III) chloride is one commonly employed Lewis acid catalyst for the Diels–Alder reaction but its use poses some disadvantages: it is rather corrosive and often leads to polymerization of the diene substrates. Dubac and co-workers discovered that $BiCl_3$ and $Bi(OTf)_3$ are mild and efficient catalysts for the Diels–Alder reaction (Scheme 46).[63] The catalytic activity exhibited by these bismuth(III) salts exceeds that of scandium, titanium, samarium and ytterbium based efficient catalysts.

One advantage of both bismuth chloride and bismuth triflate over scandium triflate is that they are much less expensive.

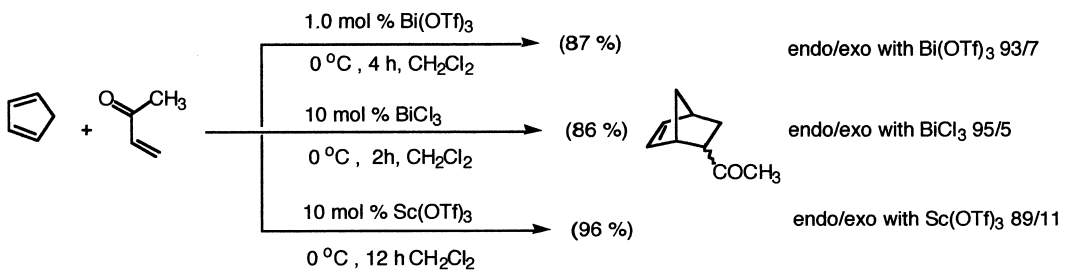
Dubac and co-workers also found that in the $BiCl_3$ catalyzed



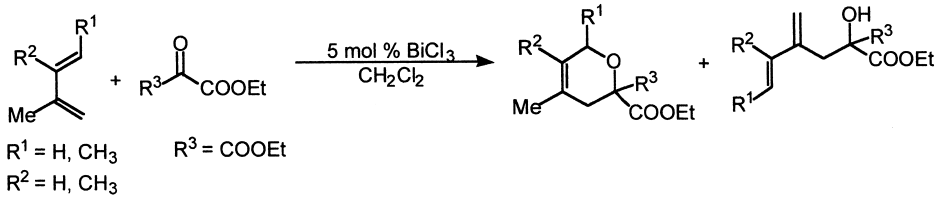
Scheme 44.



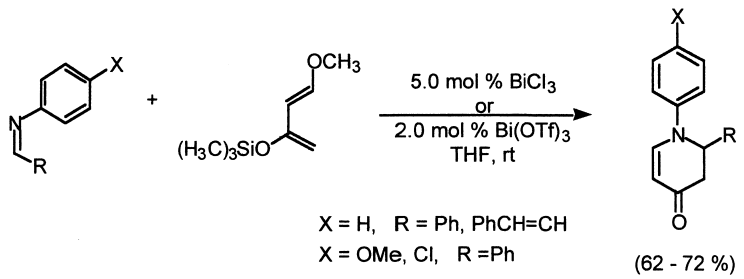
Scheme 45.



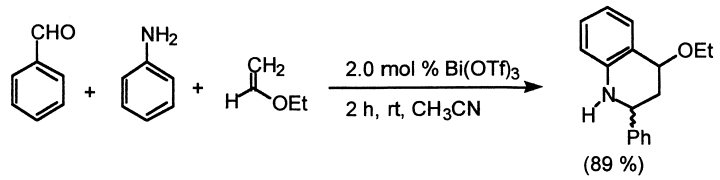
Scheme 46.



Scheme 47.



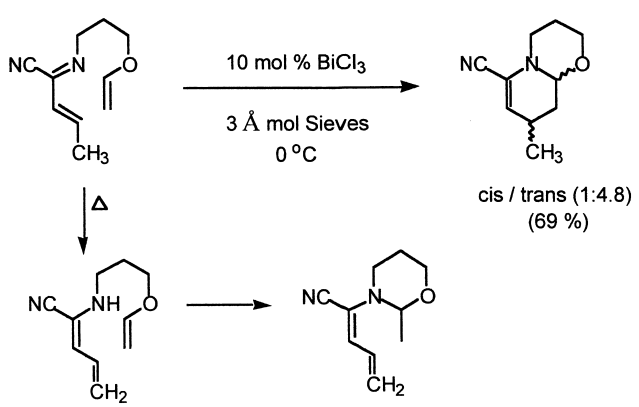
Scheme 48.



Scheme 49.

Diels–Alder reaction of dienes with electrophiles such as ethyl mesoxalate, in addition to the expected [4+2] product, the 2*H*-pyran, there was competitive (15–20%) formation of the ene reaction product (Scheme 47).[64] The two products, were however, easily separable by chromatography and thus this method allows relatively easy access to the 2*H*-pyrans.

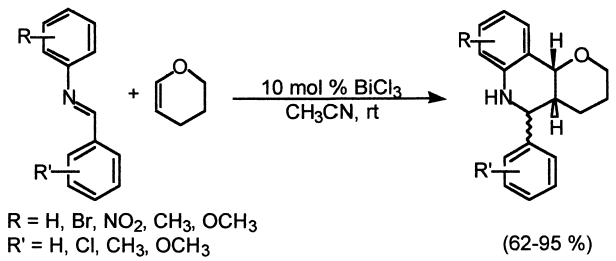
The hetero Diels–Alder reaction involving imino-dienes (the aza-Diels–Alder reaction) is a useful method for the synthesis of nitrogen containing heterocycles and has found application in the synthesis of several natural products. Both bismuth(III) chloride, $BiCl_3$ and bismuth triflate, $Bi(CF_3SO_3)_3$, are very efficient catalysts for the hetero Diels–Alder reactions of imines with Danishefsky's diene (Scheme 48).[65] In contrast, with zinc chloride as a promoter, a full equivalent of $ZnCl_2$ is required and the reaction times are considerably longer (36 h instead of 0.5–1 h). The advantage of using the relatively water stable catalyst bismuth(III) triflate is that the imine can be generated and subjected to the Diels–Alder reaction in a one pot procedure (Scheme 49).



Scheme 50.

A bismuth(III) catalyzed intramolecular hetero Diels–Alder reaction of 2-cyano-1-azadienes to yield oxazinopiperidines has been reported (Scheme 50).[66] Bismuth(III) chloride–copper(II) triflate was found to be one of the most effective catalysts for this reaction while silver salts such as AgOTf and $AbSbPF_6$ were found to be totally inactive. The use of $TiCl_4$ led to partial degradation of the product, presumably due to the presence of trace amounts of HCl. The reaction was found to be very sensitive to the solvent used. While the use of toluene and benzene gave good yields of the cycloaddition product, considerable decomposition of the azadiene occurred in more polar solvents such as CH_2Cl_2 and THF. No trace of the isomerized compound or the cyclic enamine, observed under thermal conditions, was detected using $BiCl_3$ as the catalyst. The slow reaction times led to some loss in catalyst activity due to hydrolysis but this was avoided by the addition of 3 Å sieves.

An efficient synthesis of pyrano quinolines derivatives also takes advantage of the ability of $BiCl_3$ to catalyze the aza-Diels–Alder reaction.[67] In this case, reaction of *N*-aryl aldimines with nucleophilic olefins affords the quinoline derivatives in high yields (Scheme 51).



Scheme 51.

The advantages of this method include mild reaction conditions, and recoverability of the catalyst.

A novel synthesis of hexahydrodibenzo[*b*,*h*] naphthapyridine derivatives using a $BiCl_3$ catalyzed intramolecular hetero Diels–Alder reaction has been reported by Sabitha and co-workers (Scheme 52).[68] The products are obtained as mixtures of *cis* and *trans*-diastereomers in a 1:1 ratio.

Another application of this method can be seen in the synthesis of tetrahydrochromano quinolines in good yields starting from aromatic amines and O-allylated derivatives of salicylaldehydes (Scheme 53).[69] By preparing the imine in situ, the problems associated with handling the moisture sensitive imines are avoided.

Due to their interesting biological properties, the synthesis of octahydroacridines has received much attention recently. A one-pot procedure for the stereocontrolled synthesis of octahydroacridines has been developed using an aza-Diels–Alder reaction catalyzed by $BiCl_3$ (Scheme 54).[70] The ratio of the *cis*/*trans* isomers is found to be highly temperature dependent. While the *trans*-isomer was obtained almost exclusively at 0°C, a 1:1 mixture of *cis* and *trans*-isomers resulted at room temperature.

5. Carbon–heteroatom bond forming reaction

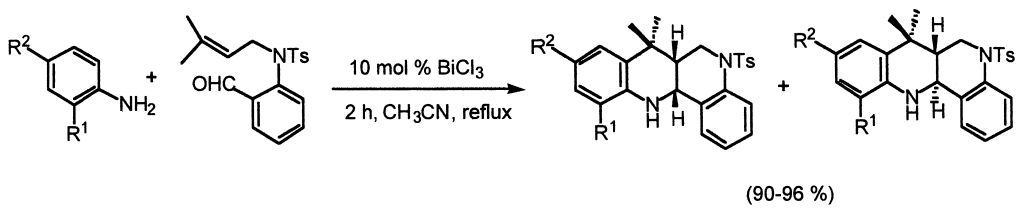
5.1. Carbon–nitrogen bond formation

5.1.1. N-Derivatization of L-proline esters. Katritzky and co-workers have developed an efficient $BiCl_3$ mediated method for the N-derivatization, in aqueous media, of L-proline and pipecolinic esters (Scheme 55).[71]

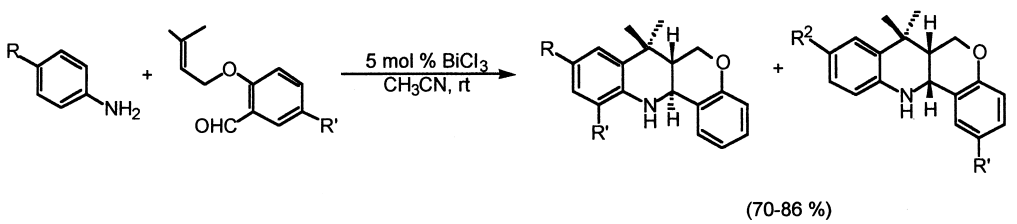
This method constitutes a useful synthesis of *N*-substituted α-amino acids, which are important due to their use in the preparation and conformation studies of peptide analogs as well as biological activity. The presence of multiple bonds in the newly introduced groups allows the potential for further synthetic manipulation. The methodology has also been extended to the N-derivatization of racemic *N*-pipecolinic acid ethyl ester.

5.1.2. Formation of azlactones. Bismuth(III) acetate has been used as a catalyst for the synthesis of azlactones from aromatic aldehydes (Scheme 56).[72]

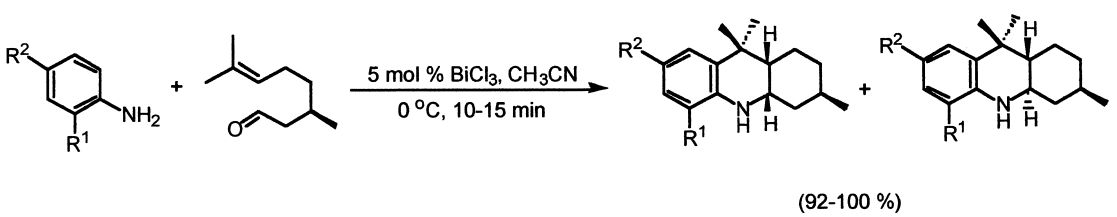
While the standard procedure for azlactone synthesis consists of using a stoichiometric amount of fused anhydrous sodium acetate, 10 mol% of $Bi(OAc)_3$ is sufficient to catalyze the reaction and the crude product is found to be >98% pure.



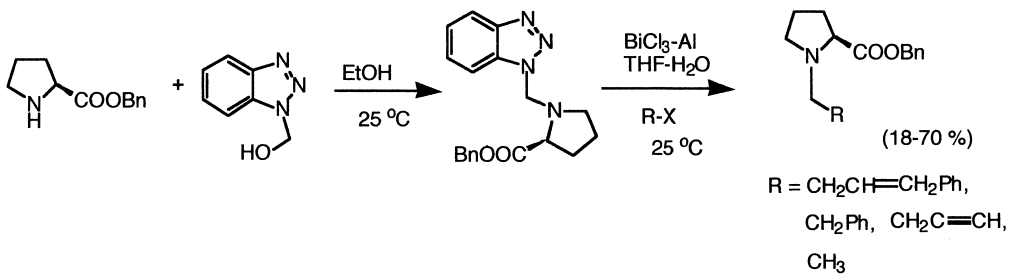
Scheme 52.



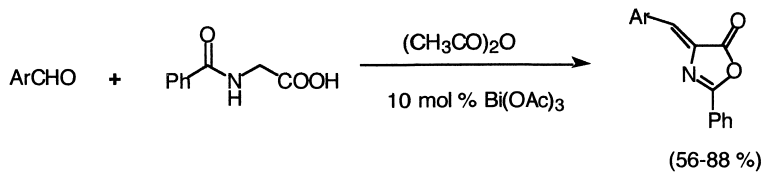
Scheme 53.



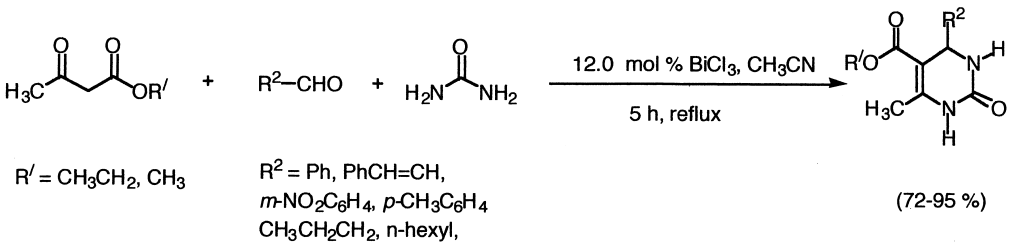
Scheme 54.



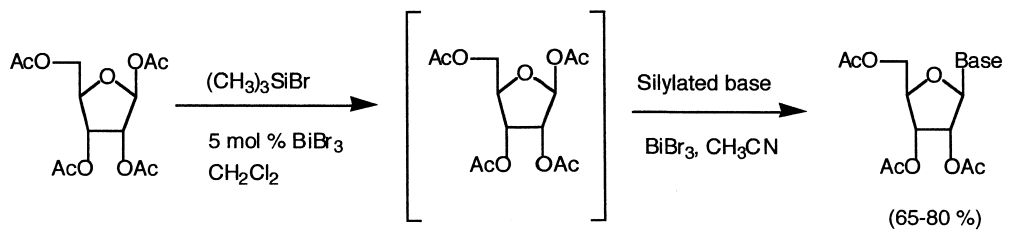
Scheme 55.



Scheme 56.



Scheme 57.



Scheme 58.

5.1.3. Formation of dihydropyrimidinones (the Biginelli reaction). Dihydropyrimidinones have attracted recent attention due to their interesting biological properties. They hold promise as calcium channel blockers and antihypertensive agents. The classical method for their synthesis, as developed by Biginelli involves one-pot condensation of ethyl acetoacetate, benzaldehyde and urea under strongly acidic conditions. This method however suffers from low yields. Bismuth(III) chloride has been found to be an attractive catalyst for the Biginelli reaction (Scheme 57).[73]

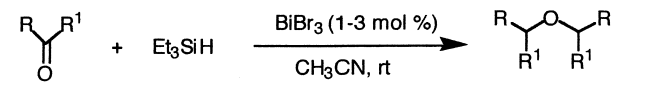
The method works even with aliphatic aldehydes which normally give poor yields in the Biginelli reaction.

5.1.4. One-pot synthesis of nucleosides using bismuth(III) bromide as a catalyst. One common method for synthesis of nucleosides is the condensation of a silylated base with a peracetylated ribofuranosyl halide in the presence of mercuric salts. Owing to the high toxicity of mercury, this method is not very environment friendly. Bismuth(III) chloride efficiently catalyzes the reaction of silylated heterocyclic bases with α-D-ribofuranosyl bromide to yield the corresponding β-D-glucoside in good yields (Scheme 58).[74] This method has the advantage of being a one-pot procedure and utilizes the relatively non-toxic salt $BiCl_3$.

5.2. Carbon–oxygen bond formation

5.2.1. Formation of ethers. The bismuth(III) catalyzed reductive homocoupling of carbonyl compounds and heterocoupling of a carbonyl compound with an alkoxysilane to afford the corresponding symmetrical and unsymmetrical ethers has been reported. This methodology has been utilized in the single-step preparation of novel crownophanes with olefinic and acetylenic linkages (Schemes 59 and 60).[75]

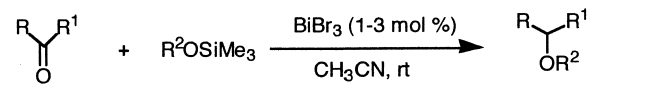
The reaction does not work with amino-substituted benzaldehydes, acetophenone or benzophenone. Similar results were observed in the homocoupling reactions.



R = Ph, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *o*-MeOC$_6$H$_4$ PhCH$_2$CH$_2$, Me(CH$_2$)$_6$-,

R^1 = H, CH$_3$, CH$_3$CH$_2$, Ph

Scheme 59.

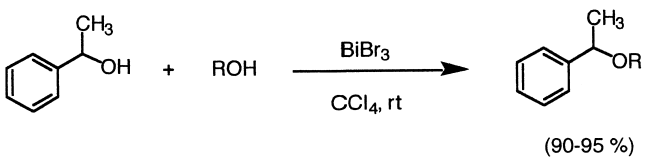


R = Ph, Me(CH$_2$)$_6$, HOCH$_2$, CH$_2$=CH

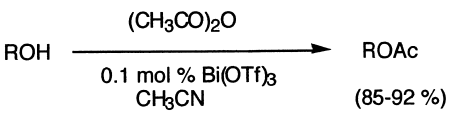
R^1 = H, CH$_3$, CH$_3$CH$_2$,

R^2 = PhCH$_2$, 2-octyl

Scheme 60.



Scheme 61.



Scheme 62.

5.2.2. Benzylation of alcohols promoted by $BiCl_3$. Arylation reactions with trivalent organobismuth compounds have limited scope. Triarylbismuthine reacts with metal halides to give arylation products. Arylation with pentavalent bismuth is better studied and such reactions have been extensively reviewed and are not considered here.[76–78] The benzylation of optically active aliphatic alcohols as well as *cis*-and *trans*-2-methylcyclohexanols catalyzed by bismuth(III) bromide in the presence of *sec*-phenethylalcohol has been studied (Scheme 61).[79–81] It is proposed that the reaction involves an intermediate with a hexa-coordinated bismuth atom. The use of a full equivalent of $BiBr_3$ and CCl_4 as the solvent detract from the synthetic utility of this procedure.

5.2.3. Acylation of alcohols catalyzed by bismuth(III) triflate. The acylation of alcohols has traditionally been carried out in the presence of tertiary amines. However, tertiary amines such as pyridine and 4-(dimethylamino)pyridine (DMAP) are highly toxic and unpleasant to handle. Hence, attention has focused on development of Lewis acid catalysts for acylation of alcohols. Among the most efficient is scandium triflate reported by Yamamoto and co-workers.[82] Recently, bismuth(III) triflate has been reported to be an efficient catalyst for the acylation of 1°, 2° and 3° alcohols.[83] The benzoylation and pivalation of 1° alcohols is also efficiently catalyzed by bismuth(III) triflate but 2° and 3° alcohols fail to react. The comparatively lower cost and ease of handling of bismuth triflate makes it an attractive alternative to scandium triflate for acylation of alcohols. A practical method suitable for large scale acetylation of alcohols has been developed using bismuth triflate (Scheme 62).[84]

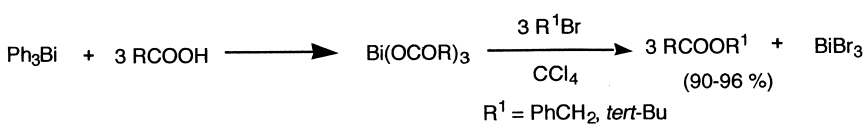
5.2.4. Selective esterification using bismuth(III) carboxylates. Bismuth(III) carboxylates, obtained by treatment of triphenylbismuth with various carboxylic acids, are efficient reagents for the selective esterification of acids, using benzylic and tertiary alkyl bromides (Scheme 63).[85]

The methodology has also been extended to formation of tosylates (Scheme 63). Since the bismuth carboxylates are almost colorless while $BiBr_3$ is a bright yellow solid, these reactions can be followed by a color change. The procedure does not work with primary bromides and hence esters of primary alcohols cannot be synthesized by this method. The authors have also carried out detailed investigations into the reactivity of bismuth(III) halides towards alcohols (Scheme 64).

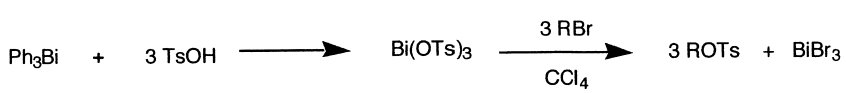
5.3. Formation of acetals catalyzed by bismuth(III) triflate

Acetals are obtained in good yields by treatment of aldehydes and ketones with trialkyl orthoformate and the corresponding alcohol in the presence of 0.1 mol% $Bi(OTf)_3{\cdot}4H_2O$ (Scheme 65).[86] The procedure works well for the synthesis of both dimethyl and diethyl acetals.

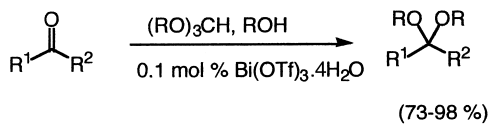
The synthesis of dialkyl acetals from diaryl ketones is more difficult, and the standard acetalization conditions generally do not work with diaryl ketones. Triflic acid (20 mol%) has been shown to be a catalyst for the synthesis of diaryl ketones.[87] Bismuth triflate (1.0 mol%) was found to be a very efficient catalyst for the acetalization of diaryl ketones as well (Scheme 66). The ease of handling of bismuth triflate compared to triflic acid coupled with its catalytic



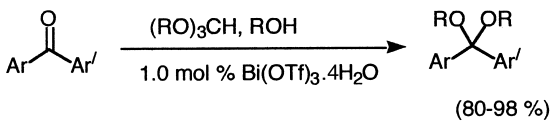
Scheme 63.



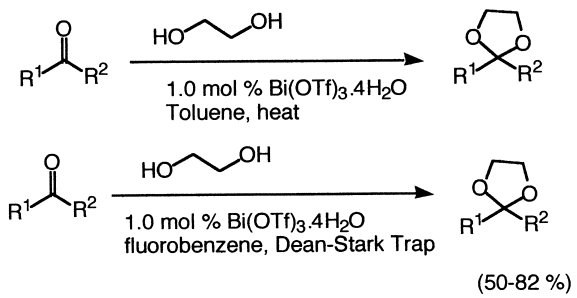
Scheme 64.



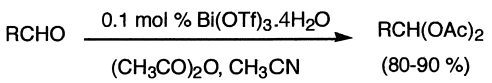
Scheme 65.



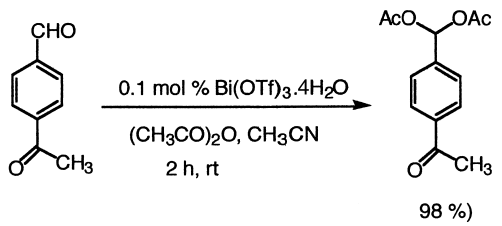
Scheme 66.



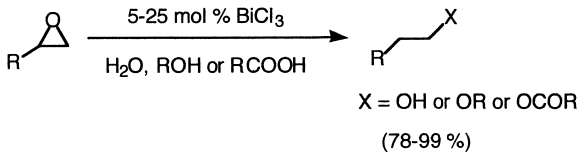
Scheme 67.



Scheme 68.



Scheme 69.



Scheme 70.

efficiency makes this procedure an attractive method for the synthesis of acetals of diaryl ketones.

1,3-dioxolanes or cyclic acetals are typically made from ethylene glycol and the equilibrium is shifted in favor of the product by azeotropic removal of water with benzene. Two methods for the synthesis of 1,3-dioxolanes catalyzed by bismuth triflate, both of which avoid the use of benzene, have been developed (Scheme 67). In refluxing toluene, not surprisingly while the reaction does not go to completion, high enough conversion is achieved to allow isolation of the pure dioxolane by chromatography in moderate to good yields.

5.4. Formation of 1,1-diacetates (acylals)

Acylals have often been used as protecting groups for carbonyl compounds because they are stable to neutral and basic conditions. Bismuth triflate, $Bi(OTf)_3{\cdot}4H_2O$, is a highly efficient catalyst (0.1 mol%) for the formation of acylals from aromatic aldehydes (Scheme 68).[88] Ketones are not affected under the reaction conditions and hence the chemoselective protection of aldehydes in the presence of ketones can be achieved (Scheme 69). The reaction can be carried out in solvent or under solvent-free conditions. Aliphatic aldehdyes reacted faster under solvent-free conditions.

5.5. Cleavage of epoxides catalyzed by bismuth(III) chloride

The cleavage of epoxides in a regio- and stereoselective manner to yield a variety of 1,2-difunctional compounds is a useful step in several synthetic schemes, and has received much attention. The synthesis of β-alkoxy and β-acetoxy alcohols and diols by catalytic ring opening of epoxides, is efficiently catalyzed by $BiCl_3$ (Scheme 70).[89]

This method works with both aliphatic and cyclic epoxides. With terminal epoxides, attack by the solvent occurs, as expected, on the less substituted carbon. The use of $BiCl_3$, which is relatively non-hygroscopic and inexpensive, offers some advantages over existing methods which make use of $FeCl_3$, $FeCl_3$–SiO_2, ceric ammonium nitrate and lanthanide triflates. Ferric chloride is very hygroscopic while ceric ammonium nitrate is not very catalytic in nature (80 mol%). Lanthanide triflates suffer from high cost.

5.6. Glycosylation promoted by bismuth(III) chloride

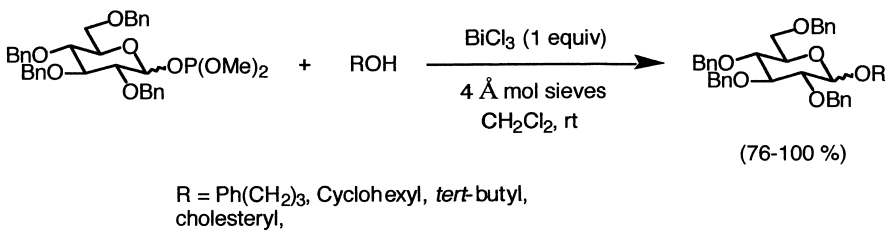
Glycosylations using 1-glycosyl dimethyl phosphite are promoted by bismuth(III) chloride to afford the corresponding glucoside as a mixture of anomers (Scheme 71).[90] Bismuth(III) chloride presumably acts as an activator by complexing to the soft base, phosphorous(III).

5.7. Selective hydrolysis of aryl esters using bismuth(III) mandelate

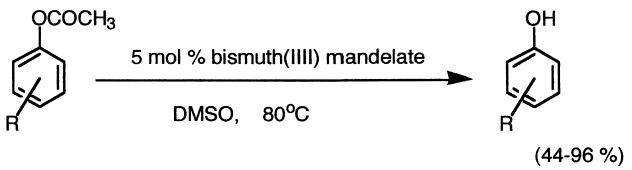
Bismuth(III) mandelate which is easily prepared from Bi_2O_3 and (L)-mandelic acid, is an efficient catalyst for the hydrolysis of aryl esters (Scheme 72).[91] The presence of molecular oxygen slightly increases the reaction rate, while the introduction of water decreases the catalytic activity.

5.8. Carbon–sulfur bond formation

5.8.1. Synthesis of thioacetals. Several bismuth(III) salts, such as $BiBr_3$, $BiCl_3$, BiI_3 and $Bi_2(SO_4)_3$ act as catalysts for the conversion of carbonyl compounds to the corresponding thioacetals (Scheme 73).[92] The reaction works well with a variety of aldehydes and ketones, with the best turnover value reaching 2300.



Scheme 71.



Scheme 72.

By adjusting the amount of the catalyst, preferential protection of one carbonyl compound over the other is possible. Thus, benzaldehyde is preferentially protected over acetophenone when reacted with 1,2-ethanethiol in the presence of 0.2 mol% $BiCl_3$ while cyclohexanone is preferentially protected over 2-heptanone in the presence of 0.5 mol% $BiCl_3$.

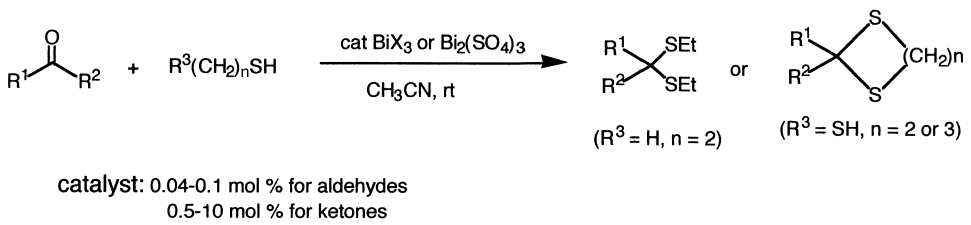
The conjugate addition of thiophenol to α,β-unsaturated carbonyl compounds is also catalyzed by $BiCl_3$ (Scheme 74).

5.8.2. Conversion of epoxides to thiiranes. A simple method for the conversion of epoxides to thiiranes using NH_4SCN and catalytic amounts of $BiCl_3$ has been developed (Scheme 75).[93] The short reaction times, high yields and the use of easy to handle reagents make this procedure an attractive way to synthesize thiiranes from epoxides.

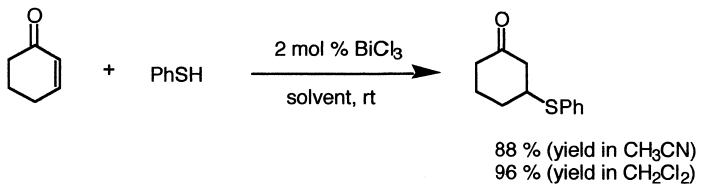
5.9. Sulfonylation of aromatics

The sulfonylation of aromatics is efficiently catalyzed by bismuth(III) chloride and bismuth(III) triflate (Scheme 76).[38,94] This work is the first report of the metal triflate catalyzed sulfonylation. Bismuth(III) chloride works well with activated substrates but not with deactivated aromatics such as chlorobenzene.

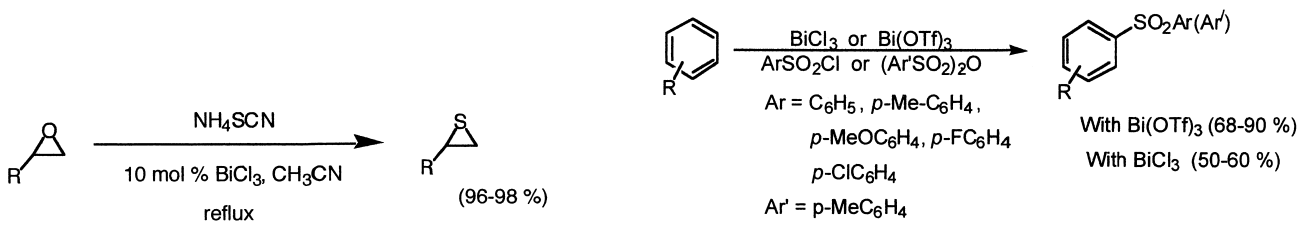
Detailed mechanistic studies have been conducted to elucidate the catalytic cycle with bismuth(III) triflate. These studies suggest a mechanism dependant on the electrophilic reagent used. With acid chlorides and sulfonyl chlorides, the proposed mechanism involves a TfO^-/Cl^- ligand exchange, leading to $BiCl_3$ and a mixed anhydride, RCOOTf or RSO_2OTf. The acylation or sulfonylation of the



Scheme 73.

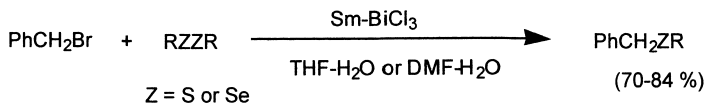


Scheme 74.

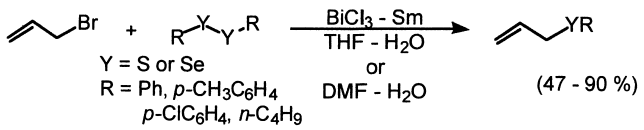


Scheme 75.

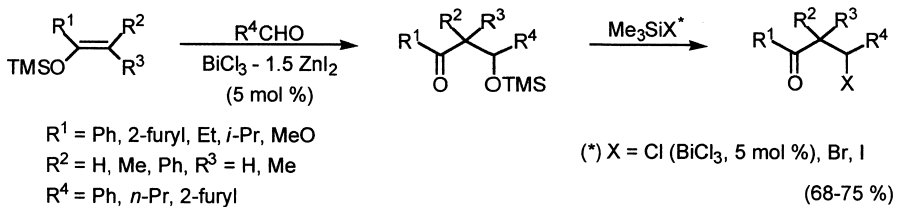
Scheme 76.



Scheme 77.



Scheme 78.



Scheme 79.

Scheme 80.

aromatic compound with these active electrophiles would also result in the formation of triflic acid, TfOH. Of the various other metal triflates, only $In(OTf)_3$ has shown catalytic activity comparable to $Bi(OTf)_3$. The mixed anhydride can then be regenerated by one of two possible pathways: reaction of TfOH with acid chloride, or with $BiCl_3$ leading to recovery of the triflate group on the bismuth atom. When the electrophile is an anhydride, it has been suggested that the mechanism involves a coordination complex. Triflic acid has also been used as a catalyst for the sulfonylation of arenes. Remarkably, the catalytic activity of triflic acid is remarkably enhanced by the addition of small amounts of bismuth(III) chloride.[95]

5.10. Synthesis of sulfides and selenides promoted by Sm–$BiCl_3$

The reaction of benzyl bromide with disulfides and diselenides to give benzyl sulfides and benzyl selenides is promoted by Sm–$BiCl_3$ in aqueous THF or aqueous DMF as the solvent (Scheme 77).[96]

5.11. Synthesis of allyl sulfides

A synthesis of allyl sulfides and allyl selenides via the reaction of allyl bromide with disulfides and diselenides promoted by the Sm–$BiCl_3$ system has been reported (Scheme 78).[97] An attractive feature of this method is that the reaction is carried out in relatively non-toxic solvent systems such as aqueous THF or aqueous DMF. The yields were significantly lowered when the reaction was carried out under air instead of a nitrogen atmosphere.

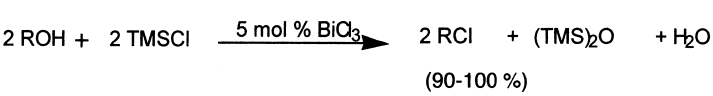
5.12. Formation of carbon–halogen bonds

5.12.1. Synthesis of β-haloketones and esters. β-Halocarbonyl compounds are useful intermediates in organic synthesis. However, in contrast to α-halocarbonyl compounds, which are easy to synthesize, there are fewer methods to obtain β-halocarbonyl compounds. β-Halocarbonyl compounds undergo dehydrohalogenation under drastic reaction conditions. A mild one-pot method for their synthesis couples the aldol condensation with halogenation (Scheme 79).[98] The method takes advantage of the activation of the silicon–chlorine bond of chlorotrimethylsilane by a Bi(III) salt.[99]

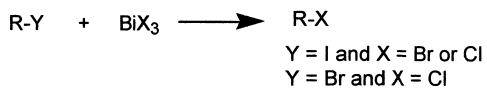
5.12.2. Chlorination of alcohols catalyzed by bismuth(III) salts. Bismuth(III) chloride has been shown to be an effective reagent for the chlorination of 2° and 3° alcohols (Scheme 80).[100] Benzyl alcohols gave only about a 30% yield of benzyl chloride while the main product was dibenzyl ether. Control experiments suggest that the ether is formed directly from the alcohol and not by way of the corresponding chloride.

The chlorination of a variety of 2°, 3°, allylic and benzylic alcohols by chlorosilanes is also catalyzed by $BiCl_3$ (Scheme 81).[101] Alkoxysilanes have been detected as intermediates in this reaction. With the exception of cinnamyl alcohol, the chlorination of allylic alcohols by this method was accompanied by rearrangement of the carbon skeleton to give a mixture of chlorides.

Efficient halogen exchange reactions catalyzed by $BiBr_3$ and $BiCl_3$ have also been developed (Scheme 82).[102] A

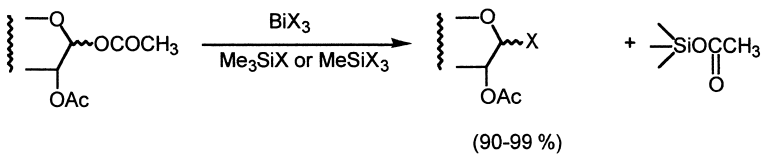


Scheme 81.

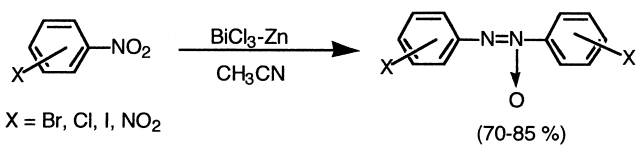


Scheme 82.

bismuth(III) halides as catalysts (Scheme 83).[103] Again, as in the chlorination of alcohols, advantage is taken of the fact that bismuth(III) halides are good activators of silicon–halide bond.



Scheme 83.

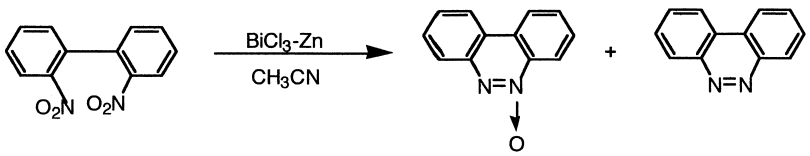


Scheme 84.

6. Reductions with bismuth compounds

6.1. Selective reduction of nitro compounds to azoxy compounds

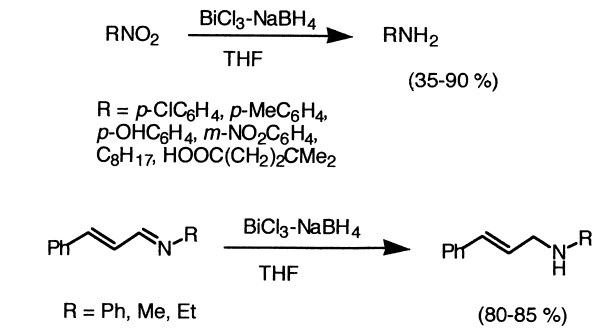
The selective reduction of nitro compounds to azoxy compounds has received considerable attention. However, many of these reactions suffer from accompanying side



Scheme 85.

reactions such as polymerization and dehalogenation of halogenated substrates. The selective reduction of nitro compounds to azoxy compounds using $BiCl_3$–metallic zinc has been reported (Scheme 84).[104]

When the reduction was applied to *o*,*o*′-dinitrobiphenyl, the corresponding benzo[*c*]cinnoline *N*-oxide was obtained in good yield (Scheme 85). Several other reagents such as Na_2S in aqueous ethanol, Ph_3P in alkaline ethanol, H_2 with Raney-Ni, Na/Hg in CH_3OH have been employed for the same reaction. However, in these cases, the product was a mixture of the *N*-oxide and the benzo[*c*]cinnoline.



Scheme 86.

variety of 2° and 3° alkyl iodides and bromides are quantitatively converted into the corresponding bromide and/or chloride by exposure to $BiBr_3$ or $BiCl_3$ in dichloroethane. A mechanism involving the formation of an ion-pair $R^+/YBiX_3$ has been proposed for this reaction.

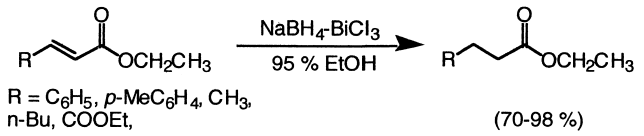
5.12.3. Synthesis of peracetylated glycosyl halides. Glycosyl halides are of interest in carbohydrate chemistry because they have been used for the formation of the glycosidic bond, as well as for generation of anomeric carbocations, radicals or carbanions. While the standard conditions for the preparation of peracetylated glycosyl chlorides involves the use of harsh reagents such as HCl gas or corrosive Lewis acids such as $AlCl_3$, $ZnCl_2$ or $TiCl_4$, a mild method has been developed using

6.2. Reduction of nitro compounds to amines

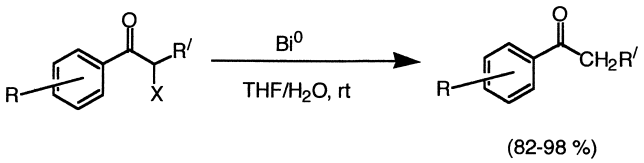
The bismuth(III) chloride promoted $NaBH_4$ reduction of a variety of substituted nitro compounds to amines has been reported (Scheme 86).[105] The procedure also works moderately well for aliphatic nitro compounds. However, benzonitrile, benzamide and nitrobenzene itself are not affected under these conditions. The reduction of azomethines to the corresponding amines has also been achieved using this method.

6.3. Chemoselective reduction of α,β-unsaturated ethyl esters using $BiCl_3$–$NaBH_4$

The chemoselective reduction of carbon–carbon double bonds in α,β-unsaturated esters using $BiCl_3$–$NaBH_4$ has been reported (Scheme 87).[106] The optimal conditions were found to be a combination of 4.0 mol of $NaBH_4$ and 0.5 mol



Scheme 87.



Scheme 88.

of $BiCl_3$ per mole of the ester. The reduction of the ester moiety was found to occur when a large excess of $NaBH_4$ over $BiCl_3$ was used. This method suffers from the limitation that only ethanol worked as a solvent, limiting the reduction to ethyl esters. Attempted reduction of methyl esters in ethanol gave a significant amount of the saturated ethyl ester, resulting from transesterification.

6.4. Reduction of aromatic α-haloketones

The reduction of aromatic α-bromo ketones and α-iodoketones in aqueous THF has been achieved using $BiCl_3$–$NaBH_4$ (Scheme 88).[107] The combination of $NaBH_4$ and $BiCl_3$ generates bismuth metal in a highly activated and divided state. α-Chloroketones can also be reduced using this method, but they must be first converted in situ to the iodo derivative by addition of NaI.

6.5. Miscellaneous reductions

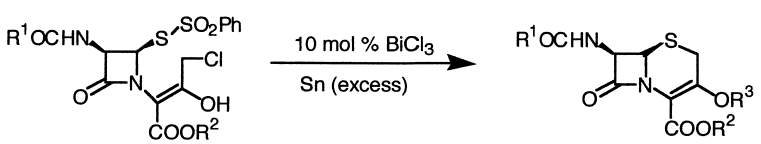
A key step in a novel synthesis of 3-hydroxycephems involves a reductive cyclization of chlorinated 4-(phenylsulfonylthio)-2-azetidinones using a $BiCl_3$/Sn redox couple in DMF containing pyridine (Scheme 89).[108] The reduction has also been carried out using the more corrosive Lewis acid, $TiCl_4$/Sn couple.

The yield was significantly lower without the addition of pyridine. While the role of the metal salt is not clear, it is speculated that the reduction of Bi(III) by Sn to lower valent bismuth works as a promoter of the reaction. Other mechanistic studies suggest that the cyclization occurs via the reduction of the terminal chloro group rather than the reduction of the thiosulfonate moiety.

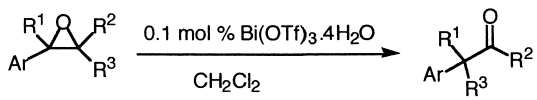
7. Rearrangements promoted by bismuth(III) salts

7.1. Rearrangement of epoxides

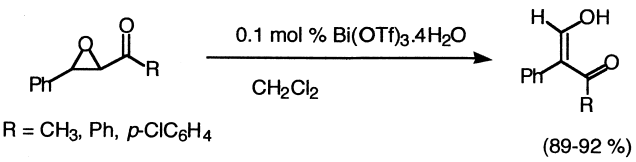
The rearrangement of epoxides to carbonyl compounds is an



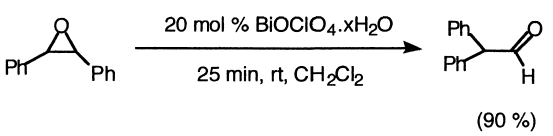
Scheme 89.



Scheme 90.



Scheme 91.

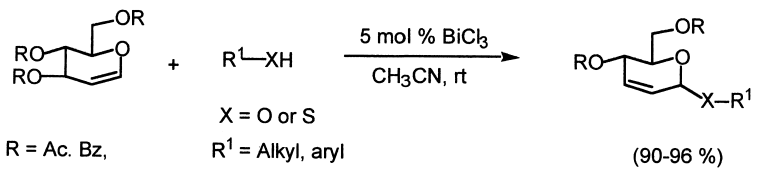


Scheme 92.

important synthetic transformation that has received much attention. Despite the number of methods that have been developed for epoxide rearrangement, only a few are both regioselective and catalytic in nature. Bismuth triflate is a highly efficient catalyst for rearrangement of aromatic epoxides to carbonyl compounds (Scheme 90).[109] One main advantage of this catalyst is that the use of an anhydrous solvent is not necessary since the catalyst is fairly insensitive to small amounts of moisture.

The catalyst is remarkably efficient and with *trans*-stilbene oxide, 0.01 mol% of $Bi(OTf)_3{\cdot}4H_2O$ was sufficient to cause rearrangement. When a solution of *trans*-stilbene oxide in dichloromethane was treated with 0.1 mol% of trifluoromethanesulfonic acid, the solution turned red and the resulting diphenylacetaldehyde was found to be considerably impure. This observation suggests that bismuth triflate is acting as a Lewis acid and not simply releasing triflic acid into the solution. Aliphatic epoxides bearing a tertiary epoxide carbon also underwent rearrangement readily. For example, 1-methylcyclohexene oxide underwent ready rearrangement to give an 89:11 mixture of 2-methylcyclohexanone (migration of methyl group) and 1-methyl-1-cyclopentanecarboxaldehyde (migration of C–C bond), respectively. Acyl-substituted epoxides underwent smooth rearrangement with exclusive migration of the acyl group (Scheme 91).

Thus, this method provides easy access to β-oxoaldehydes via rearrangement of epoxides. Epoxides bearing a cyano group and nitro group proved resistant to the reaction conditions and the starting epoxide was recovered in good yield in all cases. In contrast, when β-methylnitrostyrene oxide is treated with $BF_3{\cdot}Et_2O$, a mixture comprising of five different products is obtained.[110] In the presence of $InCl_3$,



Scheme 93.

rearrangement accompanied by loss of the nitro group to give 1-chloro-1-phenyl acetone is observed.[111]

The rearrangement of epoxides to carbonyl compounds is also efficiently promoted by bismuth(III) oxide perchlorate (Scheme 92).[112] While the authors do not report any problems with the use of this reagent, as with any perchlorate, due caution must be exercised while handling this reagent.

7.2. Allylic rearrangement of glycols (the Ferrier rearrangement)

The Lewis acid catalyzed allylic rearrangement of glycols is often used to synthesize 2,3-unsaturated glycosides (the Ferrier rearrangement). Several Lewis acid catalysts such as $BF_3{\cdot}Et_2O$, $SnCl_4$, *N*-iodosuccinimide, DDQ, and $Sc(OTf)_3$ have been employed for this purpose. While some of these Lewis acids such $BF_3{\cdot}Et_2O$, DDQ and $SnCl_4$ are corrosive in nature, some others such as $Sc(OTf)_3$ are rather expensive. Bismuth(III) chloride, a relatively inexpensive and easy to handle solid has been shown to be an efficient catalyst for the synthesis of 2,3-unsaturated glycopyranosides from alcohols and thiols (Scheme 93).[113] Several common functionalities, such as BOC, allyl and propargyl were stable under the reaction conditions.

8. Conclusions

With increasing environmental concerns, the development of relatively non-toxic reagents that are also catalytic in nature is in demand. Bismuth(III) compounds, by virtue of their low toxicity and high versatility, hold considerable promise as catalysts for various organic transformations. Bismuth compounds offer the added advantage of being relatively inexpensive and easy to handle. This is a research area which is still ripe for growth and no doubt, we will see new and novel applications of bismuth(III) compounds in organic synthesis.

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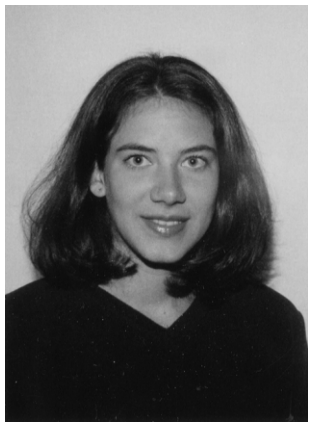

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