

Environmentally friendly organic synthesis using bismuth(III) and iron(III) compounds as catalysts

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This review is dedicated to Dr. Rajender Varma whose seminal contributions to green chemistry have inspired the principal author (RSM) and his undergraduate students to incorporate green chemistry principles into their synthetic efforts, and into the chemistry curriculum at Illinois Wesleyan University

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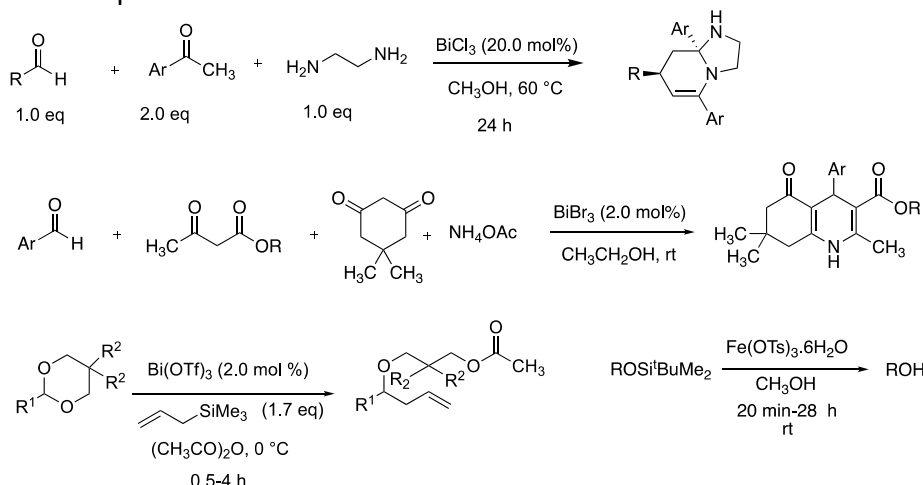
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Abstract

Bismuth(III) salts are remarkably nontoxic, inexpensive, and easy to handle. This makes them attractive as Lewis acid catalysts from a green chemistry perspective. This mini review summarizes modest contributions from my (RSM) research group to the applications of bismuth(III) salts as catalysts for a wide variety of reactions. These include synthesis of a variety of heterocycles, protection-deprotection chemistry, and C-C bond formations. A few examples of the first reported use of commercially available iron(III) tosylate as a non-corrosive catalyst are also reported.



Keywords: Bismuth, catalysis, green chemistry, Lewis acids, heterocycles

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1. Introduction

Bismuth, the 83rd element in the periodic table, is one of the least toxic elements despite its heavy metal status.¹ Bismuth(III) compounds are relatively nontoxic with many bismuth salts having LD₅₀ values comparable to NaCl.² Bismuth based compounds have increasingly found applications as pharmaceuticals, largely due to their nontoxic nature.³ Bismuth in the +3 oxidation state exhibits Lewis acid properties. Bismuth also exhibits a +5 oxidation state, however the chemistry of bismuth(V) compounds is less well explored.⁴ It is the nontoxic nature of bismuth(III) salts coupled with their Lewis acidic nature that has prompted us to explore the utility of bismuth(III) salts as Lewis acids for environmentally friendly organic synthesis.

Several bismuth salts are commercially available and these include bismuth(III) acetate, Bi(CH₃CO₂)₃ (CAS 22306-37-2), bismuth bromide, BiBr₃ (CAS 7787-58-8), bismuth chloride, BiCl₃ (CAS 7787-60-2), bismuth iodide, BiI₃ (CAS 7787-64-6), bismuth nitrate pentahydrate, Bi(NO₃)₃·5H₂O (CAS 10035-06-0), bismuth sulfate, Bi₂(SO₄)₃ (7787-68-0), and bismuth triflate, Bi(CF₃SO₃)₃ (CAS 88189-03-1). Bismuth(III) triflate can also be synthesized in the laboratory from trifluoromethanesulfonic acid and bismuth(III) oxide in aqueous alcohol solutions.⁵ Bismuth triflate is obtained or purchased as a hydrate (xH₂O, 0 < x < 4). Heating the hydrate to prepare the

anhydrous salt results in decomposition.⁶ Besides their nontoxic nature, bismuth(III) salts have other advantages too. They are reasonably stable in air and do not require inert atmosphere conditions. Bismuth salts undergo reversible hydrolysis in water to generate triflic acid which can often be the true catalyst in a reaction,⁷ unlike lanthanide triflates which do not undergo hydrolysis in water.⁸ Ollevier and Nadeau have shown that the three-component Mannich reaction between an aldehyde, aniline and a silyl enol ether is catalyzed by both $\text{Bi}(\text{OTf})_3$ and $\text{CF}_3\text{SO}_3\text{H}$. However, they also report that when the $\text{Bi}(\text{OTf})_3$ -catalyzed reaction is done in the presence of a proton scavenger such as 2,6-di-*tert*-butylpyridine, the reaction still occurred suggesting a Lewis acidic role for the Bi^{+3} salt.⁹ Hinkle and coworkers have done elegant work studying an intramolecular silyl-modified Sakurai reactions leading to dihydropyrans using $\text{Bi}(\text{OTf})_3$ to confirm that triflic acid is generated in reactions of $\text{Bi}(\text{OTf})_3$.¹⁰ The authors show that $\text{CF}_3\text{SO}_3\text{H}$ is not formed just from adventitious water, and they propose that the Bi^{+3} salt acts as a Lewis acid. It has been shown in many reactions that $\text{Bi}(\text{OTf})_3$ can be recovered from the aqueous layer by evaporation of the water.¹¹ Since we typically use very small amounts of bismuth triflate as a catalyst in our reactions, we have not attempted to recover the catalyst.

In an extensive study on Friedel-Crafts acylation using metal triflates, Dubac and coworkers showed that $\text{Bi}(\text{OTf})_3$ is more active than other metal triflates, and also more active than bismuth(III) halides.¹² Our general strategy has been to use bismuth(III) halides, especially BiBr_3 as we found BiCl_3 to be a bit more hygroscopic while BiI_3 was less active in most reactions. Only when these catalysts failed or when a nucleophilic anion was not desirable, such as in epoxide ring opening reactions, we attempted reactions with $\text{Bi}(\text{OTf})_3$.

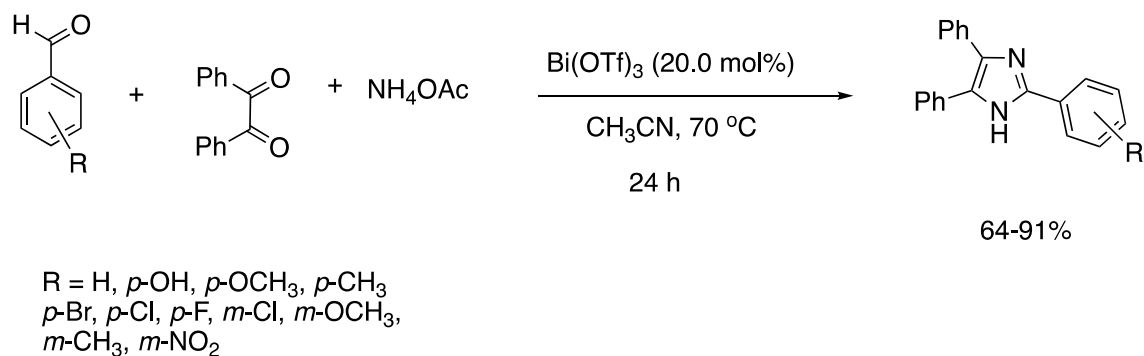
While attempting to prepare bismuth(III) tosylate, we discovered that iron(III) tosylate, $\text{Fe}(\text{OTs})_3 \cdot 6\text{H}_2\text{O}$ (CAS 312619-41-3) is commercially available but surprisingly, there were no reports of its use as a catalyst for organic transformations. We have reported a few examples of the utility of iron(III) tosylate which are summarized herein.

While a few reviews have appeared on the utility of bismuth(III) salts in organic synthesis,^{13, 14, 15, 16} this mini review summarizes some of the results from only our laboratory since 2002.

2. Results and Discussion

2.1. Synthesis of 2,4,5-trisubstituted imidazoles using bismuth(III) triflate.

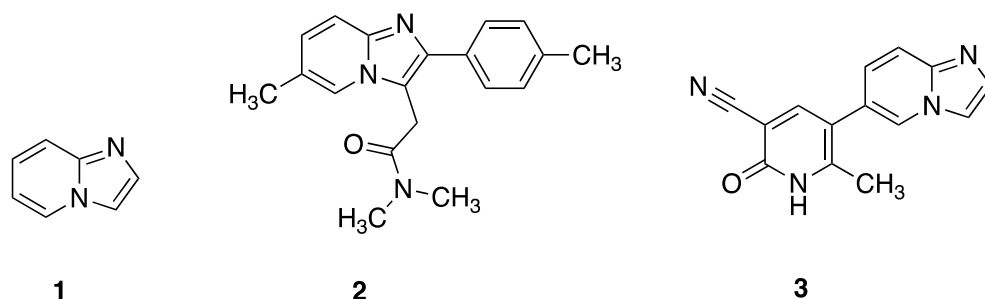
2,4,5-trisubstituted imidazoles have attracted attention due to the range of biological activities they exhibit. 2-substituted-4,5-diphenylimidazoles have been shown to exhibit antinociceptive and anti-inflammatory properties.¹⁷ As a result several methods have been developed for the synthesis of 2,4,5-trisubstituted imidazoles, the oldest being a multicomponent reaction between an aldehyde, benzil, and ammonium acetate.¹⁸ We have reported the multicomponent synthesis of 2,4,5-trisubstituted imidazoles using bismuth(III) triflate, $\text{Bi}(\text{OTf})_3$ as a catalyst (Scheme 1).¹⁹ Other bismuth salts such as $\text{BiO}(\text{NO}_3)$, BiBr_3 , $\text{Bi}(\text{OTf})_3$, FeCl_3 , and $\text{Fe}(\text{OTf})_3$ in several solvents such as CH_3OH , $\text{CH}_3\text{CH}_2\text{OH}$, CH_3COOH and CH_3CN were tried, but the best results were obtained with $\text{Bi}(\text{OTf})_3$ in CH_3CN .



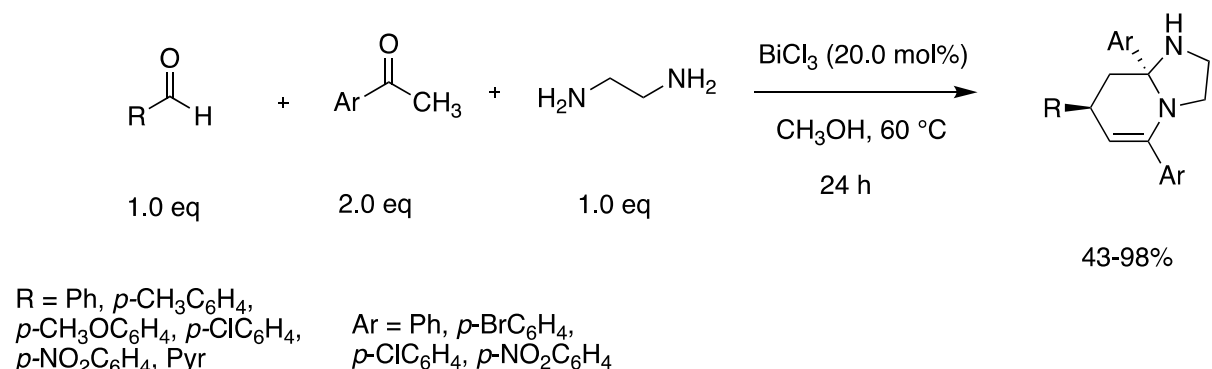
Scheme 1

2. 2. Multicomponent synthesis of substituted hexahydroimidazo[1,2-*a*]pyridines

Bridgehead nitrogen heterocycles, such as imidazo[1,2-*a*]pyridines **1**, are of considerable interest due to their biological activities. The imidazo[1,2-*a*]pyridine moiety is seen in drugs such as zolpidem **2** (sedative)²⁰ and olprinone **3** (cardiotonic agent).²¹



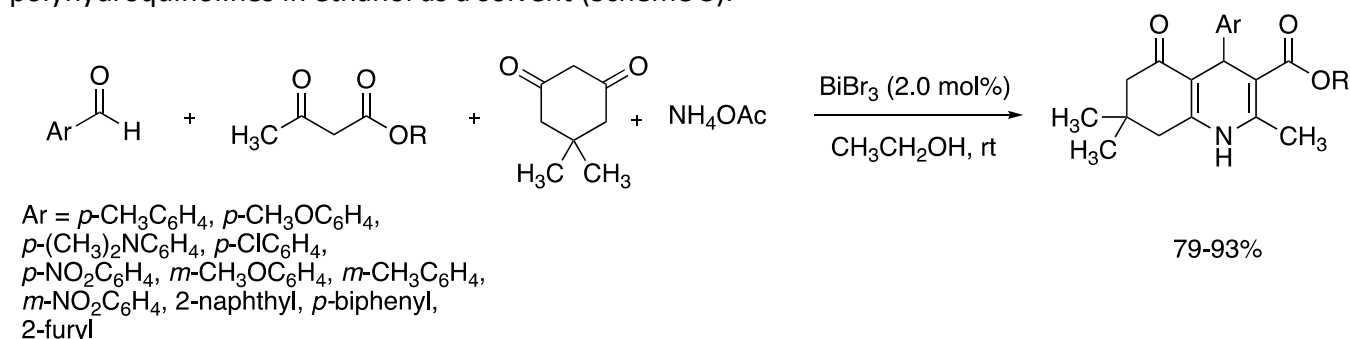
The first efficient synthesis of hexahydroimidazo[1,2-*a*]pyridines utilized a *p*-toluenesulfonic acid (*p*-TsOH) as catalyst for a multicomponent reaction between an aldehyde, a ketone, and 1,2-diaminoethane.²² Although a commonly used catalyst, *p*-toluenesulfonic acid (*p*-TsOH·H₂O) is somewhat toxic (LD₅₀ = 2.48 g/kg, rat oral) and highly irritating to the skin.²³ Li and co-workers report a similar synthesis using L-phenylalanine triflate as a catalyst, a compound that is not commercially available.²⁴ Other protocols that have been reported include a heteropolyacid containing ionic liquid-catalyzed multicomponent synthesis of hexahydroimidazo[1,2-*a*]pyridine derivatives.²⁵ The heteropoly acid-ionic liquid catalyst must be synthesized, which limits its utility. We have reported a bismuth(III) chloride BiCl₃-catalyzed synthesis of a series of hexahydroimidazo[1,2-*a*]pyridines using a multicomponent reaction between an aldehyde, a ketone, and 1,2-diaminoethane in CH₃OH (Scheme 2).²⁶ Although other catalysts such as BiBr₃ and Bi(OTf)₃ were also effective in a variety of solvents (CH₃OH, CH₃CH₂OH, *i*PrOH, CH₂Cl₂ and CH₃CN) at reflux temperatures, the best results were obtained with BiCl₃ in CH₃OH. No reaction was observed at room temperature.



Scheme 2

2.3. Bismuth(III) bromide catalyzed synthesis of polyhydroquinoline derivatives *via* The Hantzsch reaction

Polyhydroquinolines are derivatives of the 1,4-dihydropyridine skeleton. Their synthesis has attracted attention because they exhibit biological activities. Polyhydroquinolines hold promise in the search for therapies for Alzheimer's disease owing to their ability to reduce cellular tau levels.²⁷ A common route to polyhydroquinolines involves a modified Hantzsch reaction,²⁸ featuring the coupling of an aldehyde with a β -ketoester (such as ethyl acetoacetate), a diketone (such as dimedone), and ammonium acetate (Scheme 3). Several catalysts such as I₂,²⁹ metal triflates,³⁰ ceric ammonium nitrate,³¹ Baker's yeast,³² organocatalysts,³³ zeolites,³⁴ Ph₃P,³⁵ and GaCl₃³⁶ have been used for the synthesis of polyhydroquinolines via this approach. We have reported the utility of bismuth bromide, BiBr₃ as a catalyst for the multicomponent synthesis of polyhydroquinolines in ethanol as a solvent (Scheme 3).³⁷



R = Et, Me

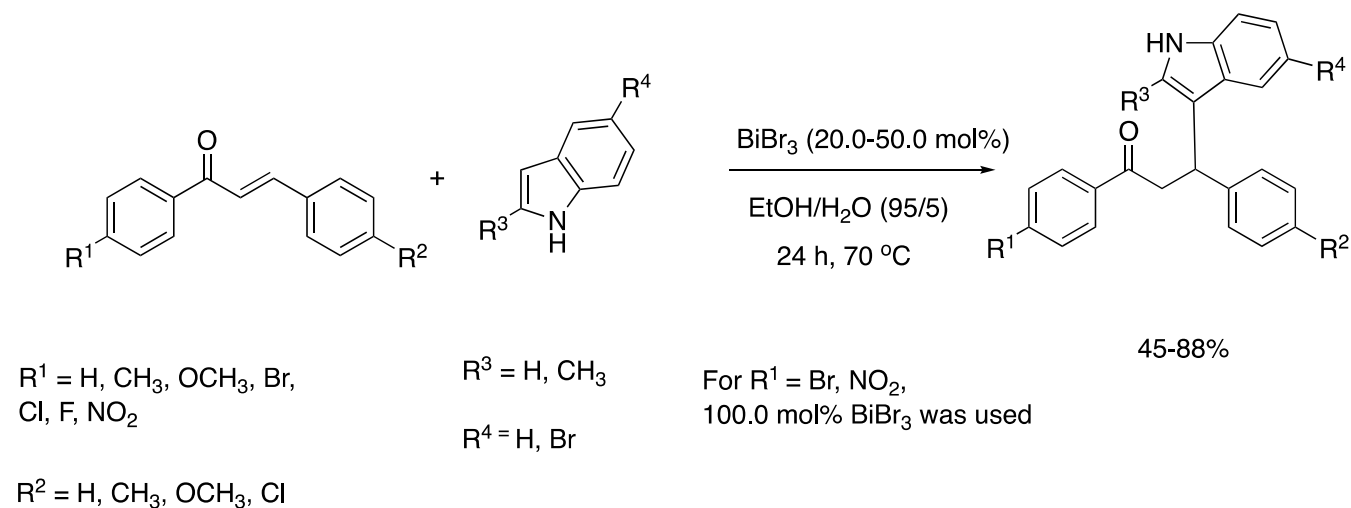
Scheme 3

The reactions were fast, and product was isolated by filtration of the reaction mixture, thus generating no aqueous waste stream. The reaction was also efficiently catalyzed by bismuth triflate (2.0 mol%). For example, *p*-tolualdehyde (R = *p*-CH₃C₆H₄) yielded 86% product (t = 2 h), but owing to the higher cost of bismuth(III) triflate (\$225/25 g from Acros Organics) relative to bismuth(III) bromide (\$25/25 g) and its increased moisture sensitivity, we chose bismuth(III) bromide. Ytterbium triflate, Yb(OTf)₃ (5.0 mol%) has also been reported as a catalyst for the formation of polyhydroquinolines, but a higher catalyst loading (5.0 mol%) and its high cost detract from its utility (\$395/25 g for the anhydrous salt, and \$136/25 g for the monohydrate).³³ Although we used anhydrous ethanol as the reaction solvent, one cannot rule out hydrolysis of BiBr₃ by adventitious water to generate HBr, which could act as a Brønsted acid catalyst. To get some insight into the role of BiBr₃ in the reaction, we carried out the reaction of *p*-chlorobenzaldehyde (Ar = *p*-ClC₆H₄) in the presence of BiBr₃ (2.0

mol%) and solid potassium carbonate (10.0 mol%). The pH of this reaction mixture was found to be $\sim 6-7$, and yet product was obtained in 86% yield, suggesting that BiBr_3 is acting as a Lewis acid and not just as a source of HBr . In addition, BiBr_3 is a lot easier to handle than HBr . In the absence of BiBr_3 , significant product formation did not occur.

2.4. Conjugate addition of indoles to α,β -unsaturated ketones using bismuth (III) bromide.

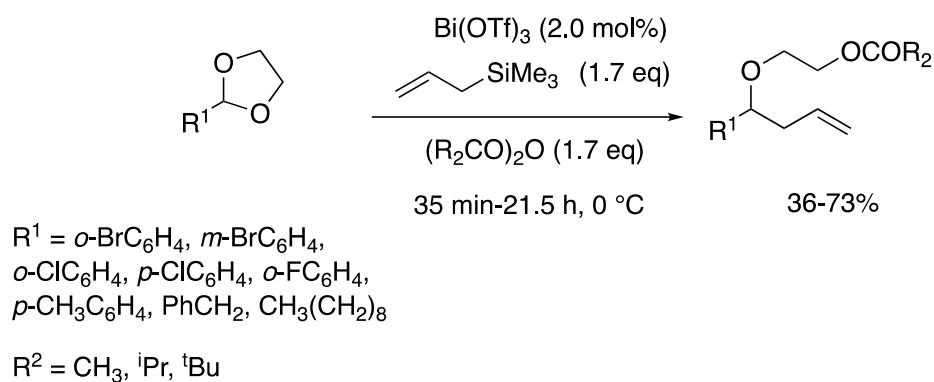
The synthesis of indoles and their derivatives has attracted considerable attention because they exhibit a wide range of biological activities.³⁸ Indoles undergo electrophilic substitution at the 3-position and hence a variety of methods have been developed for the synthesis of 3-substituted indoles.^{39, 40} The conjugate addition of indole to chalcone has also been reported with $\text{Bi}(\text{OTf})_3$ as a catalyst in CH_3CN .⁴¹ However, in this case products are isolated by column chromatography which results in considerable waste generation. We have reported the conjugate addition of indoles to a variety of chalcones using bismuth bromide, BiBr_3 , in a relatively green and inexpensive solvent, ethanol (190 proof) (Scheme 4).⁴² The product was isolated by evaporation of the solvent, filtration of the residue through a short plug of silica to remove the catalyst, and concentration of the filtrate followed by trituration of the residue with ethanol (190 proof). This method avoids the use of elaborate chromatography for product purification and also eliminates an aqueous waste stream. We chose ethanol (190 proof) over absolute ethanol or isopropanol as it is easier to remove than $i\text{PrOH}$, and is considerably cheaper and easier to obtain than absolute ethanol. When the reaction was carried out in the presence of Proton-Sponge[®],⁴³ 1,8-bis(dimethylamino)naphthalene, (0.60 equivalents) or solid K_2CO_3 , no product formed, and the starting materials were recovered. These results suggest that the primary role of BiBr_3 is to act as a source of HBr . Aqueous HBr is however very corrosive and difficult to handle unlike BiBr_3 , which is an air stable and easy to handle solid.



Scheme 4

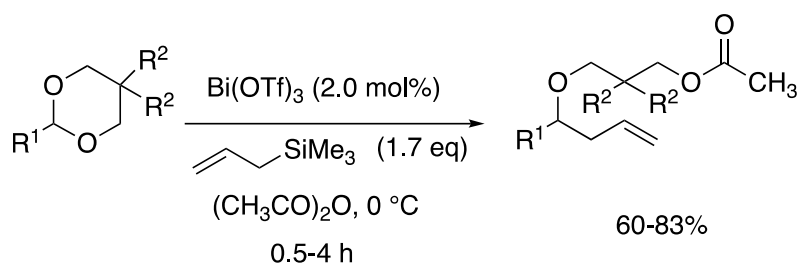
2. 5. Bismuth(III) triflate catalyzed allylation of cyclic acetals and dithianes followed by *in situ* derivatization to generate highly functionalized esters

The allylation of acyclic acetals to generate homoallyl ethers has been well documented in the literature.^{44, 45} Several catalysts have been developed for this purpose including TiCl_4 ,⁴⁶ AlCl_3 ,⁴⁷ $\text{BF}_3 \cdot \text{Et}_2\text{O}$,⁴⁸ BiBr_3 ,⁴⁹ $\text{Sc}(\text{OTf})_3$,⁵⁰ $\text{Bi}(\text{OTf})_3$,⁵¹ and CuBr .⁵² However, there are fewer reports in the literature describing the corresponding allylation of cyclic acetals. We have reported the bismuth(III) triflate catalyzed allylation of cyclic acetals and dithianes followed by *in situ* derivatization to generate highly functionalized esters (Scheme 5).⁵³

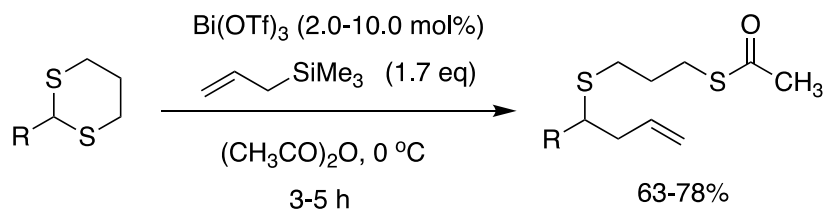


Scheme 5

The methodology was extended to dioxanes (Scheme 6) and dithianes (Scheme 7). One drawback of this method was the use of a slight excess of allyltrimethyl silane for optimal reaction times but isolation of product by filtration through a silica column eliminated an aqueous waste stream, minimizing waste generation.



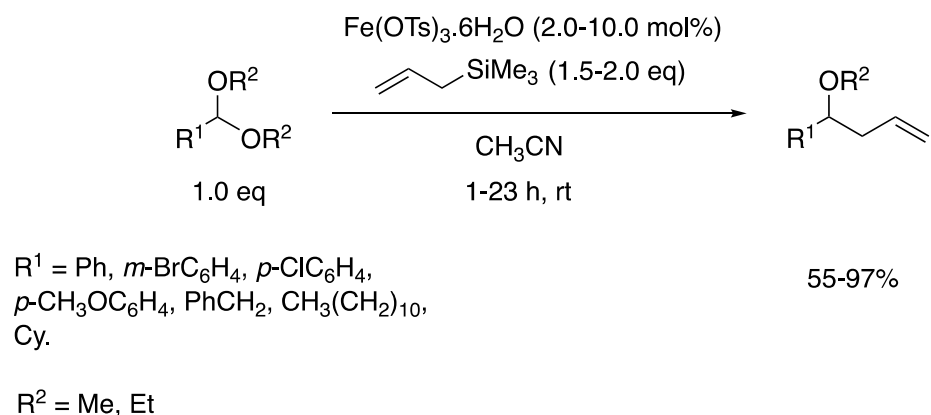
Scheme 6



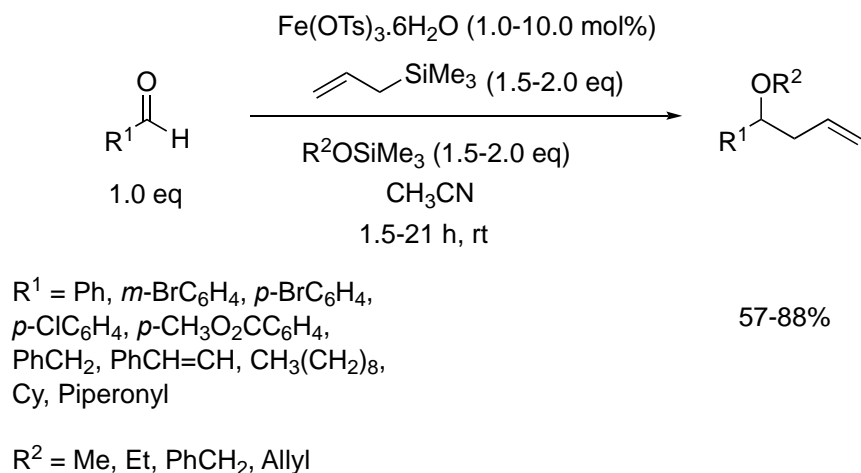
Scheme 7

2.6. Iron(III) *p*-toluenesulfonate catalyzed synthesis of homoallyl ethers from acetals and aldehydes

While attempting to prepare bismuth(III) tosylate, we did a search for commercially available metal tosylates and discovered that iron(III) tosylate is readily available, noncorrosive, and easy to handle. Surprisingly, there were no reports of its use as a catalyst for organic transformations. The synthesis of homoallyl ethers from acetals has attracted considerable attention. We have previously reported the utility of bismuth(III) triflate, $\text{Bi}(\text{OTf})_3$, as a catalyst for this transformation.⁵⁴ However many acetals have poor shelf lives and are often synthesized from the corresponding aldehyde. Hence a direct method for conversion of aldehydes to homoallyl ethers is desirable. Our interest in using iron(III) tosylate led us to develop a synthesis of homoallyl ethers from acetals (Scheme 8) and aldehydes (Scheme 9).⁵⁵



Scheme 8

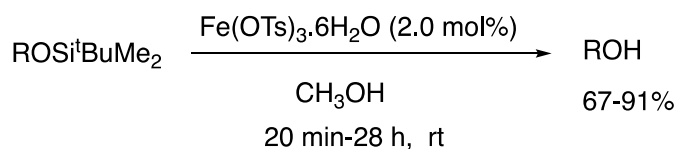


Scheme 9

2.7. Deprotection of *tert*-butyldimethylsilyl (TBDMS) ethers using iron(III) tosylate as a catalyst

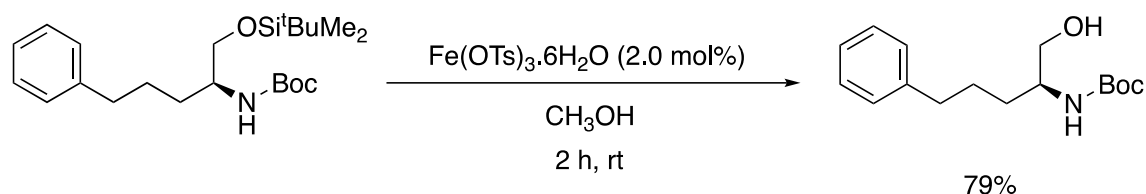
The *tert*-butyldimethylsilyl (TBDMS) protecting group, introduced by Corey and coworkers, is one of the most common silyl protecting groups for alcohols and phenols.⁵⁶ The most common methods for the deprotection of the TBDMS group utilize reagents containing a fluoride ion, with $n\text{-Bu}_4\text{N}^+\text{F}^-$ often being the reagent of choice. However, the highly basic nature of $n\text{-Bu}_4\text{N}^+\text{F}^-$ can lead to side reactions with base-sensitive substrates.⁵⁷ In addition, $n\text{-Bu}_4\text{N}^+\text{F}^-$ is extremely corrosive to the mucosa and the upper respiratory tract,⁵⁸ a

problem compounded by the fact that $n\text{-Bu}_4\text{N}^+\text{F}^-$ is required in stoichiometric amounts. We have reported a mild method for the deprotection of TBDMS ethers using iron(III) tosylate as a catalyst (Scheme 10).⁵⁹

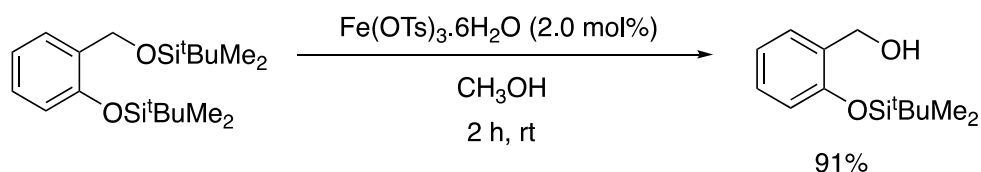


Scheme 10

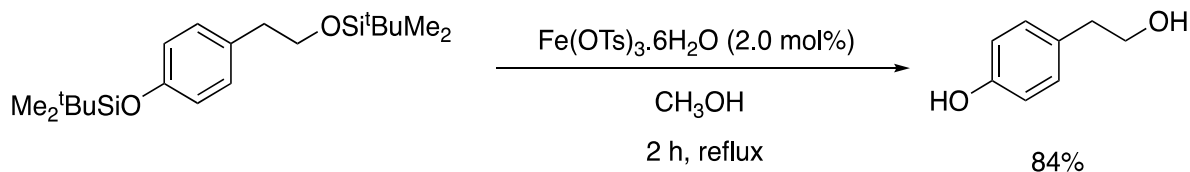
The experimental procedure was simple and consisted of stirring the silyl ether in methanol as the catalyst is added. The product was isolated by removal of methanol and filtration of the residue through a short silica column, thus avoiding an aqueous waste stream. A variety of chemoselective deprotections could be achieved under the reaction conditions. A TBDMS ether could be cleaved in the presence of a Boc (*tert*-butyloxycarbonyl) group (Scheme 11). Phenolic TBDMS ethers were unaffected while an alkyl TBDMS group was cleaved (Scheme 12). Both phenolic and alkyl TBDMS (*tert*-butyldimethylsilyl) groups were cleaved under reflux conditions (Scheme 13). We were also able to cleave a 1° TBDMS ether in the presence of a 1° TBDPS *tert*-butyldiphenylsilyl ether (Scheme 14).



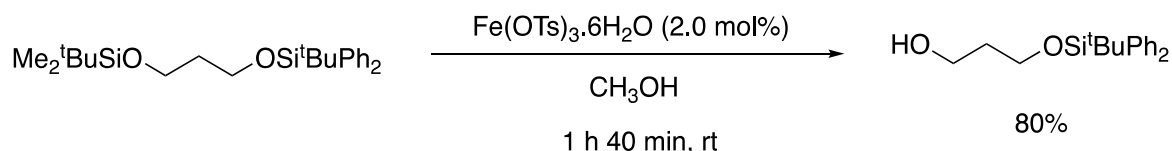
Scheme 11



Scheme 12



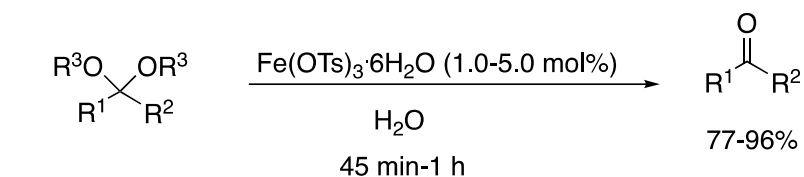
Scheme 13



Scheme 14

2.8. Iron(III) tosylate catalyzed deprotection of aromatic acetals in water

We have reported the iron(III) tosylate catalyzed deprotection of aromatic acetals in water as a solvent (Scheme 15).⁶⁰ Although we have previously demonstrated the iron(III) tosylate catalyzed deprotection of TBDMS ethers in methanol, no deprotection of a TBDMS group was observed when water is used as a solvent. Hence we could selectively cleave an acetal in the presence of a TBDMS ether ($R^1 = p\text{-}^t\text{BuMe}_2\text{SiOC}_6\text{H}_4$ in Scheme 15).

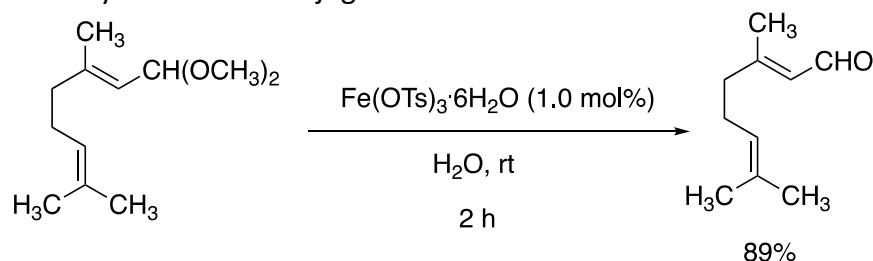


$R^1 = p\text{-ClC}_6\text{H}_4$, $m\text{-BrC}_6\text{H}_4$,
 $p\text{-BrC}_6\text{H}_4$, $p\text{-HOCC}_6\text{H}_4$, $p\text{-CH}_3\text{OC}_6\text{H}_4$,
 $p\text{-Me}_2\text{NC}_6\text{H}_4$, PhCH=CH ,
 $p\text{-}^t\text{BuMe}_2\text{SiOC}_6\text{H}_4$

$R^2 = \text{H}$, $R^3 = \text{Me}$ or Et

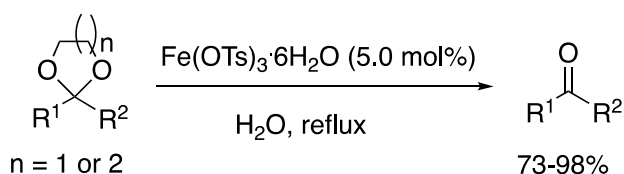
Scheme 15

Although the deprotection of aliphatic acetals was sluggish under the reaction conditions, the deprotection of dimethyl acetal of a conjugated acetal derived from citral was successful under the conditions (Scheme 16).



Scheme 16

The deprotection of cyclic acetals was also achieved in water under reflux conditions (Scheme 17).



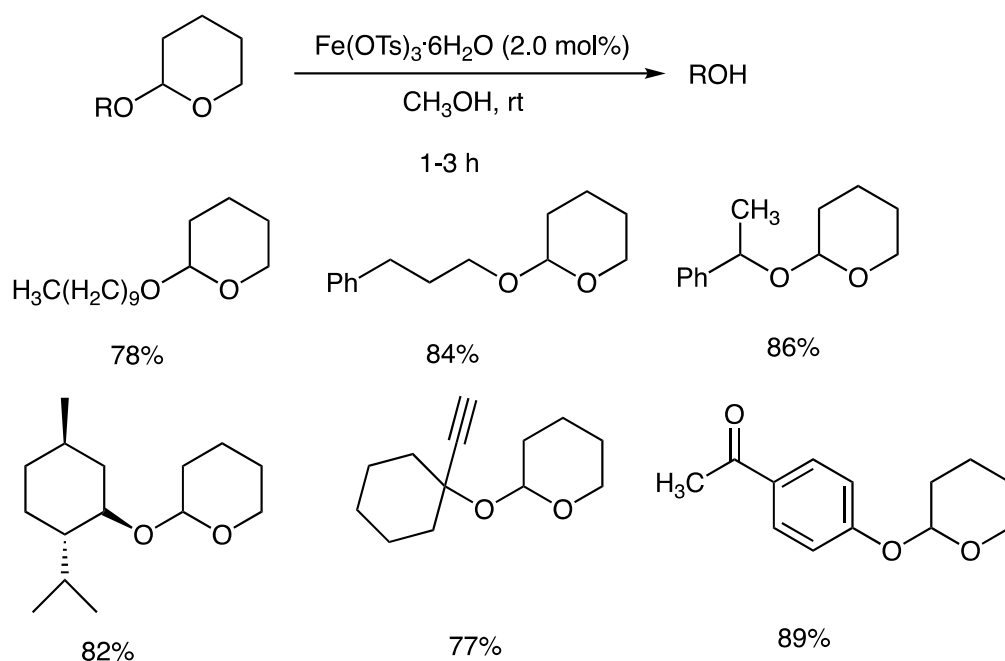
$R^1 = 2\text{-Ph}_3\text{CO-5-BrC}_6\text{H}_3$, $p\text{-NO}_2\text{C}_6\text{H}_4$, $p\text{-ClC}_6\text{H}_4$, $m\text{-BrC}_6\text{H}_4$,
 $m\text{-CH}_3\text{OC}_6\text{H}_4$, $p\text{-CH}_3\text{C}_6\text{H}_4$, $p\text{-CH}_3\text{OC}_6\text{H}_4$, PhCH=CH ,
 PhCCH_3

$R^2 = \text{H}$, CH_3

Scheme 17

2.9. Deprotection of tetrahydropyranyl ethers (THP) catalyzed by iron(III) tosylate

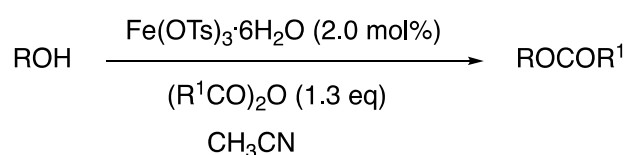
We have reported the deprotection of THP ethers using iron(III) tosylate as a catalyst (Scheme 18).⁶¹ A few representative substrates are shown in the scheme. Product could be isolated via an aqueous work up or by evaporation of methanol followed by filtration through a plug of silica, thus avoiding an aqueous waste stream. No deprotection was observed in water as the solvent. We have also reported the deprotection of THP ethers using bismuth triflate, Bi(OTf)₃, as a catalyst under non aqueous conditions (DMF-CH₃OH) at 110 °C.⁶² In contrast, the deprotection using iron(III) tosylate can be carried out in a more benign solvent, CH₃OH, and milder reaction conditions. This method also avoids DMF as a co-solvent.



Scheme 18

2.10. Iron(III) tosylate catalyzed acylation of alcohols, phenols, and aldehydes

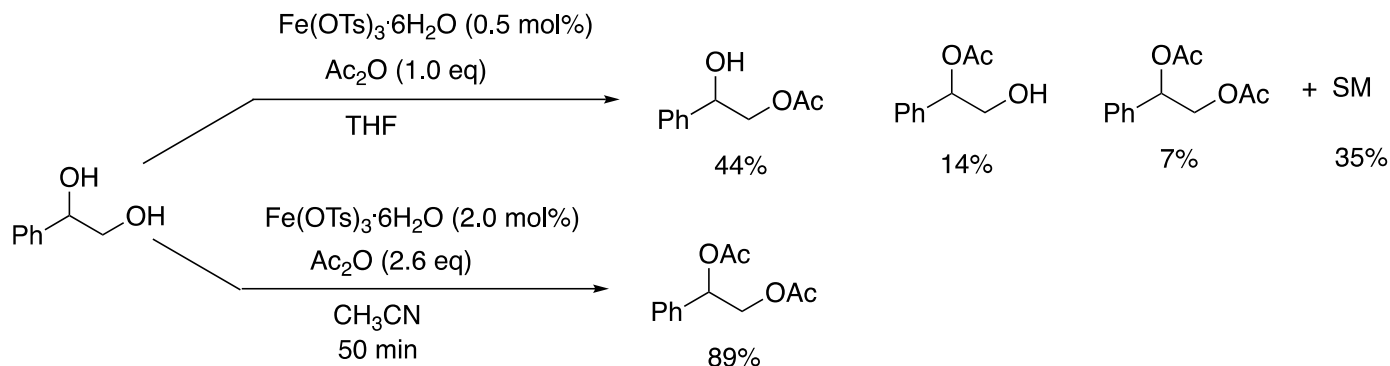
We have reported that iron(III) tosylate is a mild catalyst for the acylation of a variety of alcohols, phenols, and diols (Scheme 19).⁶³ Not surprisingly, 1° and 2° alcohols reacted fast (10 min to 1 h) while some 3° alcohols required longer reaction times (4-21 h). Highly hindered alcohols, such as triphenylmethanol, failed to give the corresponding acetate even under reflux conditions. The mild reaction conditions make this an attractive procedure for conversion of alcohols to the corresponding acetate.. We have previously reported the utility of bismuth triflate, Bi(OTf)₃, as a useful catalyst for the large scale acetylation of alcohols.⁶⁴



R¹ = CH₃, n-Pr, Ph

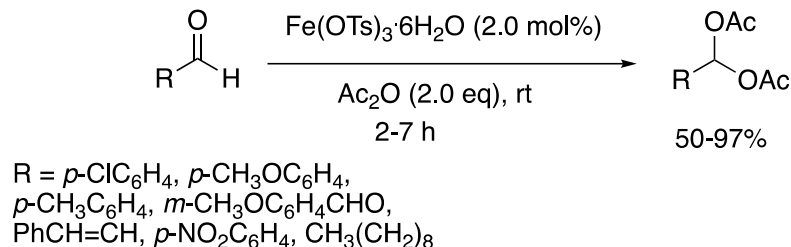
Scheme 19

We found a difference in rates of acetylation of a 1° vs 2° alcohol in THF as the solvent. Attempts to selectively acetylate a 1° alcohol in the presence of a 2° alcohol were not very successful. Use of excess acetic anhydride afforded the diacetate in good yields (Scheme 20).



Scheme 20

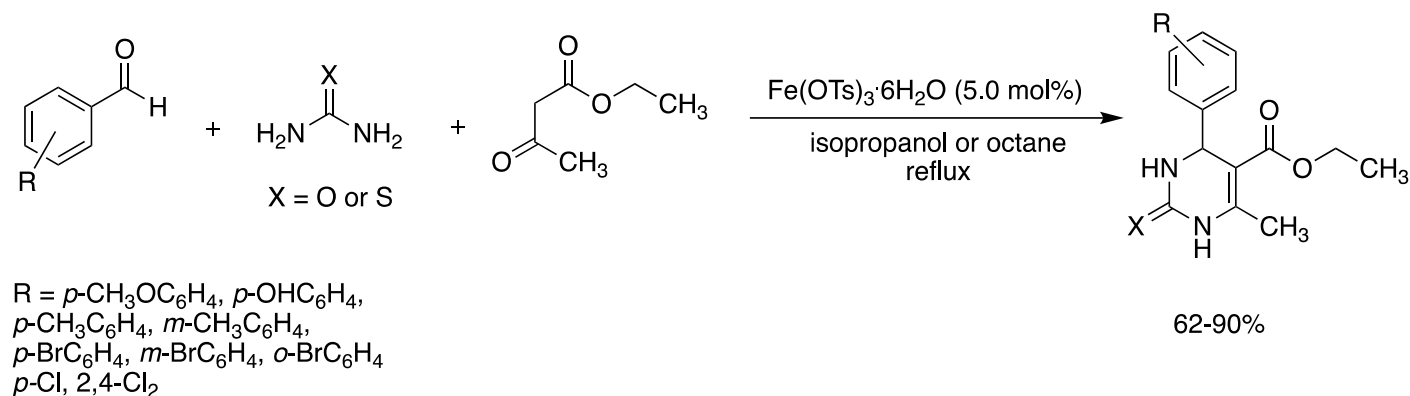
Aldehydes could also be converted to the corresponding 1,1-diesters (acylals) under the reaction conditions (Scheme 21). A similar reaction has also been reported by us using bismuth(III) triflate, Bi(OTf)₃, as a catalyst.⁶⁵



Scheme 21

2.11. Iron(III) tosylate catalyzed synthesis of 3, 4-dihydropyrimidin-2(1H)-ones/thiones via the Biginelli reaction

We have reported that iron(III) tosylate (5.0 mol%) is an efficient catalyst for the synthesis of dihydropyrimidinones and dihydropyrimidine thiones from a wide range of aldehydes via the Biginelli reaction (Scheme 22).⁶⁶ Dihydropyrimidinones are of interest due to the range of biological activity they exhibit.⁶⁷



Scheme 22

Both isopropanol and octane worked as solvents. Although octane is less environmentally friendly than isopropanol, it was easily recovered using a rotary evaporator or by decantation and recycled. Both procedures avoided an aqueous work-up, thus adding to the green aspect of the methodology.

Conclusions

Bismuth(III) compounds have shown promise as versatile Lewis acid catalysts for a range of organic transformations including protection-deprotection chemistry, C-C bond formations, and synthesis of a variety of heterocycles. The nontoxic nature of bismuth(III) salts makes them attractive from a green chemistry perspective. Additionally, we have demonstrated that iron(III) tosylate is also a versatile catalyst for a range of similar organic transformations.

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Sophie Thorp is a native of St. Louis, Missouri and graduated from IWU in 2023 with a BS degree in chemistry. As an undergraduate, Sophie worked in Professor Ram Mohan's lab and published two manuscripts. She was the recipient of the ACS Collegiate Scholar Award for the Heartland, IL section. Currently, she attends the

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Rem Quintin David is a native of the Philippines and is currently a junior biochemistry major at IWU. Rem is currently working in Professor Ram Mohan's lab and has published one manuscript as an undergraduate co-author. He works in the chemistry stockroom of IWU and helps set up the chemistry teaching labs at IWU. He plans to pursue a PhD in the future with an interest in natural product synthesis and the biochemical processes of plants. Rem likes to play volleyball, run, and listen to music in his free time.

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