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# Bismuth-Mediated Organic Reactions

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## Aims and Scope

The series *Topics in Current Chemistry* presents critical reviews of the present and future trends in modern chemical research. The scope includes all areas of chemical science, including the interfaces with related disciplines such as biology, medicine, and materials science.

The objective of each thematic volume is to give the non-specialist reader, whether at the university or in industry, a comprehensive overview of an area where new insights of interest to a larger scientific audience are emerging.

Thus each review within the volume critically surveys one aspect of that topic and places it within the context of the volume as a whole. The most significant developments of the last 5–10 years are presented, using selected examples to illustrate the principles discussed. A description of the laboratory procedures involved is often useful to the reader. The coverage is not exhaustive in data, but rather conceptual, concentrating on the methodological thinking that will allow the non-specialist reader to understand the information presented.

Discussion of possible future research directions in the area is welcome.

Review articles for the individual volumes are invited by the volume editors.

In references *Topics in Current Chemistry* is abbreviated *Top Curr Chem* and is cited as a journal.

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# Foreword

I have heard the following declaration made every 10 years or so: "Organic chemistry is all wrapped up. We are now able to prepare every possible molecule!". I believe this is far from true with respect to the actual status of organic synthesis. In fact, it is amazing to see how organic synthesis has changed and continues to evolve. Take, for instance, the total synthesis of a simple molecule of a natural product, which earlier required a period of 5–10 years, even with a number of postdocs devoting their time and expertise to the task. Nowadays, a single graduate student could synthesize the same complex natural molecule within a few years. I do think that this amazingly rapid growth far exceeds that which has occurred in other sciences. And I further believe that the study of organic synthesis should continue forever and that the number of future discoveries are limitless.

This book deals with only one element of the periodic table but still contains a large amount of new knowledge, all of which comes from a single element: bismuth! The history of bismuth in synthetic chemistry is relatively short. The most important features of this element, arising from its low toxicity and high reactivity, were first highlighted only recently. Each chapter describes a different aspect of the chemistry of bismuth, which I am confident will be rapidly recognized with increasing importance in future. Thus, I am already looking forward to reading the second volume of this book.

Science in its youth is always exciting to pursue. When I began my career forty years ago, aluminum chemistry was a newly emerging field. Thus, whatever I found was new and exciting. I am sure that every young researcher who is interested in bismuth chemistry will enjoy the still-unfolding era of this element prior to its full blooming – and I am also confident this book will provide a reliable compass for his or her journey of discovery.

Bon voyage!

The University of Chicago Hisashi Yamamoto

# Preface

## Bismuth in synthesis: an emerging area

These are exciting times for organic synthesis using green metals. During the last decade, the chemical community finally began considering the previously under-used chemistry of organobismuth derivatives and bismuth catalysts. Today, many academic groups around the world are entering the area.

The roots of this field date back to the early 1850's with Löwig's studies of the synthesis of organic derivatives of bismuth, followed by Michaelis' in the late 1880's. Further studies by Gilman in the late 1930's and early 1940's, involving the synthesis of triaryl derivatives of bismuth, were inspired by the seminal work of Michaelis. Wittig in the 1950's also worked on the synthesis of pentaaryl derivatives of bismuth. This line of research was subsequently continued by Sir Barton in the 1980–90's reporting efficient phenylation reactions using triarylbismuth [(III) and (V)] compounds. Further studies by Suzuki involved the synthesis of organobismuth(V) derivatives and bismuthonium salts. In 2006–2007, Mukaiyama demonstrated the utility of organobismuth(V) derivatives as very efficient reagents for various phenylations and oxidations.

The role of bismuth(III) salts as Lewis acids has only been studied since the late 1980's. Pioneering work by Dubac, Wada and others paved the way to wide and general methods using bismuth(III) catalysts. The versatile use of bismuth salts in synthesis has clearly been highlighted by the increasing number of publications in the field. The low toxicity of bismuth salts, associated with low cost, make them attractive and practical catalysts to use. Synergistic effects with other Lewis acids have also been recently highlighted.

The discovery that some bismuth salts could be used as Lewis acids in aqueous conditions finally opened the door to designing catalysts and to broadening the concept of hydrocompatible Lewis acids, which has since been applied to various reaction types.

Moreover, the use of bismuth catalysts has definitively contributed to the area of environmentally benign catalysts, known as green catalysts. These are fascinating

developments since such green catalysts are now widely appreciated and new reactions and catalysts are being designed and published on a regular basis.

The current developments allow us to demonstrate that bismuth chemistry truly is an emerging field. Efficient catalytic transformations using bismuth are definitively high potential processes, which encompass asymmetric catalysis using chiral bismuth(III) complexes as one of their most promising challenges to reach. The expanding activity in the field and the resulting constant need for knowledge developments make this volume an essential update in organic synthesis using bismuth.

Both areas of bismuth chemistry – organobismuth derivatives and the use of bismuth salts as catalysts – are covered in this volume, providing an overview of the field from experts in their respective areas. I would like to wholeheartedly thank all those who have contributed to making this volume such a wonderful and original source of knowledge. I hope it will inspire you to apply new methods using bismuth derivatives to solve some of your specific problems, but possibly also contribute to meeting some of the remaining challenges of synthetic organic chemistry.

Québec, Winter 2011 Thierry Ollevier

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# Bismuth Catalysts in Aqueous Media

**Shū Kobayashi, Masaharu Ueno, and Taku Kitanosono**

**Abstract** Several bismuth-catalyzed synthetic reactions, which proceed well in aqueous media, are discussed. Due to increasing demand of water as a solvent in organic synthesis, catalysts that can be used in aqueous media are becoming more and more important. Although bismuth Lewis acids are not very stable in water, it has been revealed that they can be stabilized by basic ligands. Chiral amine and related basic ligands combined with bismuth Lewis acids are particularly useful in asymmetric catalysis in aqueous media. On the other hand, bismuth hydroxide is stable and works as an efficient catalyst for carbon–carbon bond-forming reactions in water.

**Keywords** Aqueous media · Asymmetric catalyst · C–C bond-forming reaction · Lewis acid · Transmetalation

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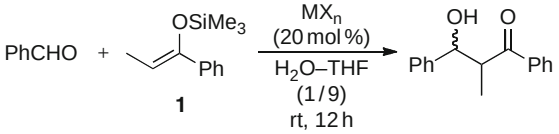
## 1 Introduction: Water-Compatible Lewis Acids

The use of water instead of organic solvents is key to attaining the goal of environmentally benign chemical synthesis. In this context, organic reactions in water are now of great interest and much research effort has been devoted to pursuing efficient reactions in water [1–5]. Unique reactivity and selectivity have been often observed in aqueous media, but one of the big issues is the stability of catalysts in water. Many active catalysts are not stable in water but decompose in the presence of even a small amount of water. To overcome this, we searched for efficient catalysts that are stable and can work well in aqueous media.

Lewis acids are quite often used as catalysts in organic synthesis. Although most Lewis acids decompose in water, it was found that rare earth triflates such as $Sc(OTf)_3$, $Yb(OTf)_3$, etc. can be used as Lewis acid catalysts in water or water-containing solvents (water-compatible Lewis acids) [6–9]. For example, the Mukaiyama aldol reactions of aldehydes with silyl enol ethers were catalyzed by $Yb(OTf)_3$ in water–THF (1:4) to give the corresponding aldol adducts in high yields [10, 11]. Interestingly, when the reactions were carried out in dry THF (without water), the yield of the aldol adducts was very low (ca. 10%). Thus, this catalyst is not only compatible with water but also is activated by water, probably due to dissociation of the counteranions from the Lewis acidic metal. Furthermore, the catalyst can be easily recovered and reused.

Metal salts other than those derived from rare earth elements were also found to be water-compatible Lewis acids. To find other Lewis acids that can be used in aqueous solvents and to find the criteria for water-compatible Lewis acids, the group 1–15 metal chlorides, perchlorates, and triflates were screened in the aldol reaction of benzaldehyde with silyl enol ether **1** in water–THF (1:9) (Scheme 1) [12]. This screening revealed that not only $Sc^{III}$, $Y^{III}$, and $Ln^{III}$ but also $Fe^{II}$, $Cu^{II}$, $Zn^{II}$, $Cd^{II}$, and $Pb^{II}$ worked as Lewis acids in this medium to afford the desired aldol adduct in high yields.

From these results, a correlation was revealed between the catalytic activity of the metal cations and two kinds of constants for the metal cations: hydrolysis constants ($K_h$) and exchange rate constants for substitution of inner-sphere water ligands (water exchange rate constants, WERC) [13–16]. Table 1 shows these constants for each metal cation. Metals that exhibited good catalytic activity in the screening (>50% yield) are indicated. These active metal compounds were found to have $pK_h$ values in the range from about 4 (4.3 for $Sc^{III}$) to 10 (10.08 for $Cd^{II}$) and WERC values greater than $3.2 \times 10^6\ M^{-1}s^{-1}$. Cations having large $pK_h$ values do not generally undergo efficient hydrolysis. In the case of $pK_h$ values being




**Scheme 1** Aldol reaction of benzaldehyde with silyl enol ether **1** in water–THF

**Table 1** Hydrolysis constants and exchange rate constants for substitution of inner-sphere water ligands

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $Li^{+1}$ 13.64 **$4.7\times10^{7}$** | Be — — | | | | | | | | | | | | $B^{+3}$ — — | C — — | N — — | | |
| $Na^{+1}$ 14.18 **$1.9\times10^{8}$** | $Mg^{+2}$ 11.44 $5.3\times10^{5}$ | | | | | | | | | | | | $Al^{+3}$ 4.97 $1.6\times10^{0}$ | $Si^{+4}$ — — | $P^{+5}$ — — | | |
| $K^{+1}$ 14.46 **$1.5\times10^{8}$** | $Ca^{+2}$ 12.85 **$5\times10^{7}$** | $Sc^{+3}$ **4.3** **$4.8\times10^{7}$** | $Ti^{+4}$ ≤ 2.3 — | $V^{+3}$ 2.26 $1\times10^{3}$ | $Cr^{+3}$ 4.0 $5.8\times10^{-7}$ | $Mn^{+2}$ **10.59** **$3.1\times10^{7}$** | $Fe^{+2}$ **9.5** **$3.2\times10^{6}$** | $Co^{+2}$ **9.65** $2\times10^{5}$ | $Ni^{+2}$ **9.86** $2.7\times10^{4}$ | $Cu^{+2}$ **7.53** **$2\times10^{8}$** | $Zn^{+2}$ **8.96** **$5\times10^{8}$** | $Ga^{+3}$ 2.6 $7.6\times10^{2}$ | $Ge^{+4}$ — — | As — — | | |
| Rb — — | Sr — — | $Y^{+3}$ **7.7** **$1.3\times10^{7}$** | $Zr^{+4}$ 0.22 — | $Nb^{+5}$ (0.6) — | $Mo^{+5}$ — — | Tc — — | $Ru^{+3}$ — — | $Rh^{+3}$ 3.4 $3\times10^{-8}$ | $Pd^{+2}$ 2.3 — | $Ag^{+1}$ 12 **$>5\times10^{6}$** | $Cd^{+2}$ **10.08** **$>1\times10^{8}$** | $In^{+3}$ 4.00 $4.0\times10^{4}$ | $Sn^{+4}$ — — | $Sb^{+5}$ — — | | |
| Cs — — | $Ba^{+2}$ 13.47 **$>6\times10^{7}$** | $Ln^{+3}$ **7.6–8.5** **$10^{6}$–$10^{8}$** | $Hf^{+4}$ 0.25 — | $Ta^{+5}$ (−1) — | $W^{+6}$ — — | $Re^{+5}$ — — | $Os^{+3}$ — — | $Ir^{+3}$ — — | $Pt^{+2}$ 4.8 — | $Au^{+1}$ — — | $Hg^{+2}$ 3.40 **$2\times10^{9}$** | $Tl^{+3}$ 0.62 $7\times10^{5}$ | $Pb^{+2}$ **7.71** **$7.5\times10^{9}$** | $Bi^{+3}$ 1.09 — | | | |
| $La^{+3}$ **8.5** **$2.1\times10^{8}$** | $Ce^{+3}$ **8.3** **$2.7\times10^{8}$** | $Pr^{+3}$ **8.1** **$3.1\times10^{8}$** | $Nd^{+3}$ **8.0** **$3.9\times10^{8}$** | Pm — — | $Sm^{+3}$ **7.9** **$5.9\times10^{8}$** | $Eu^{+3}$ **7.8** **$6.5\times10^{8}$** | $Gd^{+3}$ **8.0** **$6.3\times10^{7}$** | $Tb^{+3}$ **7.9** **$7.8\times10^{7}$** | $Dy^{+3}$ **8.0** **$6.3\times10^{7}$** | $Ho^{+3}$ **8.0** **$6.1\times10^{7}$** | $Er^{+3}$ **7.9** **$1.4\times10^{8}$** | $Tm^{+3}$ **7.7** **$6.4\times10^{6}$** | $Yb^{+3}$ **7.7** **$8\times10^{7}$** | $Lu^{+3}$ **7.6** **$6\times10^{7}$** | | | |

$M^{+n}$ — $pK_h$[a] — WERC[b]

Metals that exhibited good catalytic activity in the screening (>50% yield) are outlined in *bold*

[a]$pK_h = -\log K_h$ [13, 14]

[b]Exchange rate constants for substitution of inner-sphere water ligands [15]

less than 4, cations are readily hydrolyzed to produce protons in sufficient number to cause rapid decomposition of the silyl enol ether. On the other hand, in the case of $pK_h$ values higher than 10, the Lewis acidities of the cations concerned are too low to catalyze the aldol reaction. Large WERC values might be necessary to have sufficiently fast exchange between the water molecules coordinated to the metal and the aldehyde substrate, to act as an efficient catalyst. "Borderline" species such as $Mn^{II}$, $Ag^{I}$, and $In^{III}$, whose $pK_h$ and WERC values are close to the criteria limits, gave the aldol adduct in moderate yields. Whereas the precise activity of Lewis acids in aqueous media cannot be quantitatively predicted by $pK_h$ and WERC values, the use of this technique has led to the identification of promising metal compounds as water-compatible Lewis acid catalysts. As an example, Fringuelli and coworkers reported use of $Al^{III}$, $Ti^{IV}$, and $Sn^{IV}$ as Lewis acids for epoxide-opening reactions in acidic water whose pH was adjusted by adding $H_2SO_4$ [17], and also provided mechanistic insights into Lewis acid catalysis in aqueous media.

## 2 Chiral $Bi(OTf)_3$-Catalyzed Asymmetric Hydroxymethylation in Aqueous Media

Discovery of water-compatible Lewis acids has greatly expanded the use of Lewis acids in organic synthesis in aqueous media. However, conventional Lewis acids such as $Al^{III}$, $Ti^{IV}$, $Sn^{IV}$, etc. still cannot be used in aqueous media under standard conditions. Bismuth triflate, $Bi(OTf)_3$, is reported to exist in water as an equilibrium mixture of $Bi(OTf)_3$ with bismuth hydroxide and triflic acid [18].

Due to increasing demands for optically active compounds, many catalytic asymmetric reactions have been investigated in this decade. However, asymmetric catalysis in water or water/organic solvent systems is difficult because many chiral catalysts are not stable in the presence of water [19]. In particular, chiral Lewis acid catalysis in aqueous media is extremely difficult because most chiral Lewis acids decompose rapidly in the presence of water [20, 21]. To address this issue, catalytic asymmetric reactions using water-compatible Lewis acids with chiral ligands have been developed [22–29].

Formaldehyde is one of the most important C1 electrophiles in organic synthesis. Whereas hydroxymethylation of enolate components with formaldehyde provides an efficient method to introduce a C1 functional group at the α-position of carbonyl groups, few successful examples of catalytic asymmetric hydroxymethylation have been reported (for other examples of asymmetric hydroxymethylation, see [30–33]; for examples of catalytic asymmetric hydroxymethylation without using silicon enolates, see [32, 34, 35]).

Recently, highly enantioselective, catalytic hydroxymethylation reactions of silicon enolates with an aqueous formaldehyde solution have been developed using a novel scandium complex prepared from $Sc(OTf)_3$ and chiral bipyridine **2** [36]. Indeed, Lewis acid-catalyzed hydroxymethylation of silicon enolates is promising (for a review on silicon enolates, see [37]), and the reactions are expected to proceed regioselectively with excellent substrate generality and synthetic efficiency. As far as the formaldehyde source is concerned, use of a commercial aqueous solution of formaldehyde is the most convenient because it avoids tedious and harmful procedures for generating formaldehyde monomer from formaldehyde oligomers such as paraformaldehyde and trioxane (trioxane has been used as a formaldehyde surrogate [38]). It is noted that a novel chiral scandium complex has attained highly enantioselective, catalytic hydroxymethylation of silicon enolates with a formaldehyde aqueous solution.

As an extension of this work, other metal salts (10 mol%) and chiral bipyridine **2** [39, 40] (12 mol%) in the reaction of silicon enolate **1** with an aqueous formaldehyde solution were tested, and remarkably it was found that $Bi(OTf)_3$ [18, 41] gave promising results. In addition to the big difference in the ionic diameters of bismuth (2.34 Å for eight-coordination) and scandium (1.74 Å for eight-coordination), this result was unexpected because $Bi(OTf)_3$ is known to be hydrolyzed in the presence of water [41]. Indeed, only a trace amount of the hydroxymethylated adduct was obtained using $Bi(OTf)_3$ in the absence of the chiral bipyridine. $Sc(OTf)_3$ is a water-compatible Lewis acid, and it works well for hydroxymethylation even in the absence of a basic ligand [42]. It is known that silicon enolates such as **1** are rapidly decomposed by TfOH which was easily generated from $Bi(OTf)_3$ in water. On the other hand, decomposition of silicon enolate **1** was slow and the desired hydroxymethylation proceeded in the presence of $Bi(OTf)_3$ and **2**. These results indicate that $Bi(OTf)_3$ was stabilized by chiral bipyridine **2** in water. As a chiral bismuth catalyst, it was revealed that the desired product was obtained in 94% yield with 91% *ee* using 1 mol% $Bi(OTf)_3$ and 3 mol% **2** in the presence of 5 mol% of 2,2′-bipyridine. Several other substrates were applicable to this catalyst system

(Table 2) [43]. The hydroxymethylation proceeded smoothly using an aqueous formaldehyde solution to afford the desired adducts in high yields with high enantioselectivities. It is noteworthy that asymmetric quaternary carbons were constructed with high selectivities.

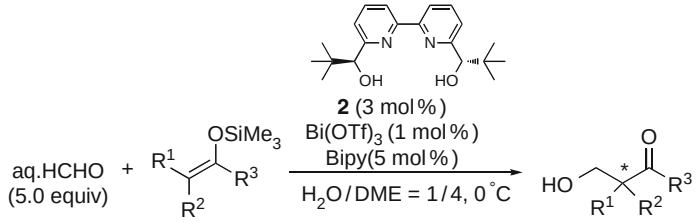
From several experiments, it was revealed that the active catalyst was formed from an equimolar mixture of $Bi(OTf)_3$ and **2**. The X-ray crystal structure of the $BiBr_3$–**2** complex is shown in Fig. 1. The complex adopts a pentagonal bipyramidal structure in which the tetradentate ligand occupies four of the equatorial sites. The structure of the $Bi^{III}Br_3$ complex of **2** is closely related to that of the corresponding $Sc^{III}Br_3$ complex. The angle of O-Bi-O is 165° and that of O-Sc-O is 151°. The torsional angle of two pyridines in the Bi complex is 27.0°, and that in the Sc complex is 19.4°. For the Sc complex, see [36].

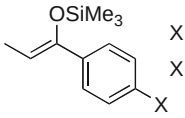
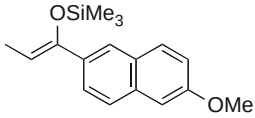
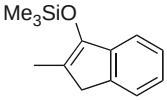
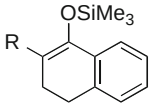
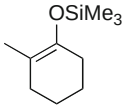
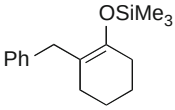
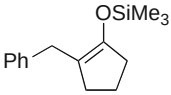
NMR analysis of formation of $Bi(OTf)_3$–**2** complexes with different ratios of $Bi(OTf)_3$ and **2** was conducted (Fig. 2). When $Bi(OTf)_3$ and **2** were combined in the ratio of 1:0.5, the signal at 5.49 ppm was dominant. Increasing the ligand to $Bi(OTf)_3$ ratio resulted in the appearance of another signal at 4.72 ppm and the concomitant decrease in intensity of the peak at 5.49 ppm until, at a ligand to $Bi(OTf)_3$ ratio of 3:1, it disappeared completely. These results indicate that two equivalents of $Bi(OTf)_3$ and one equivalent of **2** formed complex **3**, and that complex **4**, consisting of one equivalent of $Bi(OTf)_3$ and one equivalent of **2**, was generated when an excess amount of **2** was added (Scheme 2). The stability of complex **4** even in the presence of 2,2′-bipyridine was confirmed by the following experiments. When $Bi(OTf)_3$ (1 mol%) and **2** (3 mol%) were combined in DME at room temperature for 30 min and then 2,2′-bipyridine was added at 0 °C, the hydroxymethylation of **1** proceeded at 0 °C in 21 h to afford the desired adduct in 93% yield with 91% *ee*. On the other hand, the yield and the enantioselectivity decreased (73% yield, 85% *ee*) when $Bi(OTf)_3$ and 2,2′-bipyridine were combined at room temperature for 30 min and then **2** was added and the mixture stirred at room temperature for 30 min. However, when the mixture was stirred at room temperature for 1 h, the enantioselectivity was improved (81% yield, 91% *ee*). It is noted that complex **4** is stable even in the presence of 2,2′-bipyridine, and that **4** is readily formed from the $Bi(OTf)_3$–2,2′-bipyridine complex and **2**. The reaction rates using $Bi(OTf)_3$–**2**–2,2′-bipyridine complex and $Bi(OTf)_3$–2,2′-bipyridine complex are comparable: $Bi(OTf)_3$–**2**–2,2′-bipyridine complex gave 37% yield for 1.5 h and the $Bi(OTf)_3$–2,2′-bipyridine complex gave 20% yield for 1.5 h.

## 3 Chiral $Bi(OTf)_3$-Catalyzed Asymmetric Ring-Opening Reactions of *meso*-Epoxides

Chiral β-amino alcohols are important building blocks for the preparation of chiral auxiliaries, ligands, and natural products (for reviews on the asymmetric synthesis and use of vicinal amino alcohols, see [44–47]). Catalytic enantioselective

**Table 2** Bi-catalyzed asymmetric hydroxymethylation




| Entry | Silicon enolate | Time (h) | Yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|
| 1 | R = Me(**1**) | 21 | 93 | 91 |
| 2 | R = Et | 70 | 79 | 92 |
| 3 |  X = MeO | 30 | 80 | 88 |
| 4 | X = Cl | 34 | 87 | 89 |
| 5 |  | 22 | 59 | 92 |
| 6 |  | 9 | 89 | 88 |
| 7 |  R = Me | 22 | 81 | 95 |
| 8 | R = $C_4H_9$ | 22 | 68 | 93 |
| 9 |  | 20 | 66 | 77 |
| 10 |  | 48 | 79 | 92 |
| 11 |  | 20 | 82 | 79 |

[a]Isolated yield
[b]Determined by chiral HPLC analysis

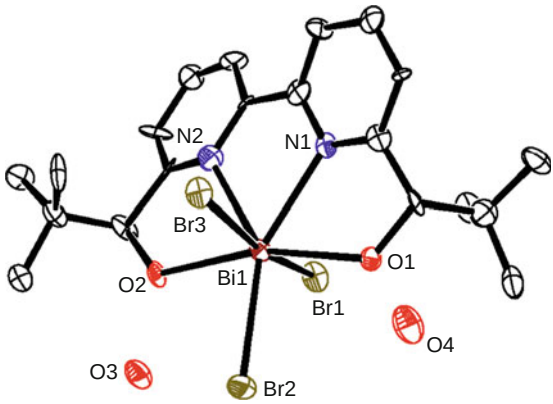



**Fig. 1** Ortep drawing of the X-ray crystal structure of $[BiBr_3 \bullet \mathbf{2}] \bullet (H_2O)_2 \bullet DME$. DME is omitted for clarity

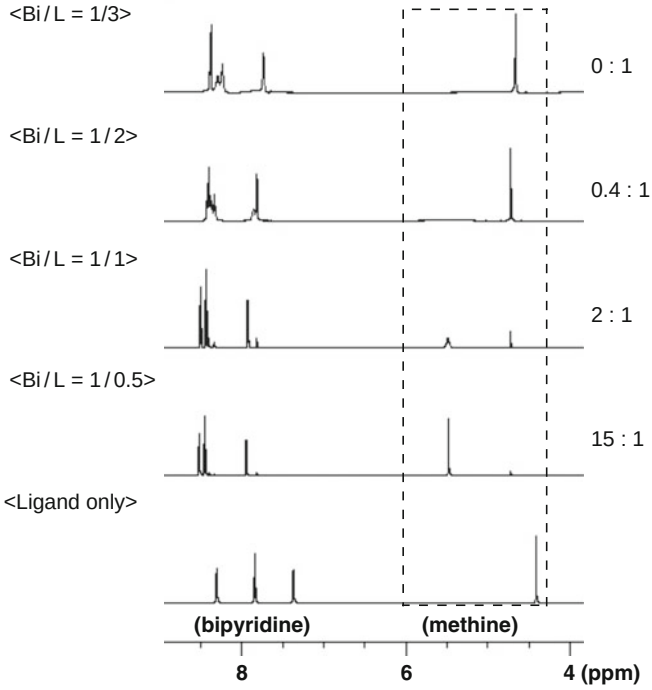
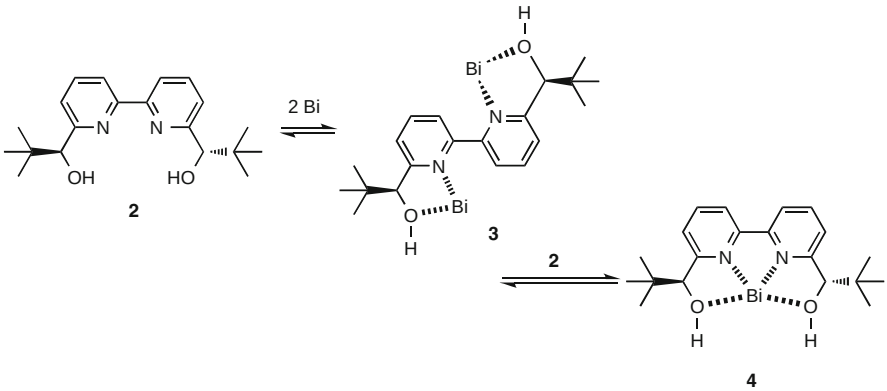



**Fig. 2** $^1$H NMR analysis of the bismuth catalyst structure

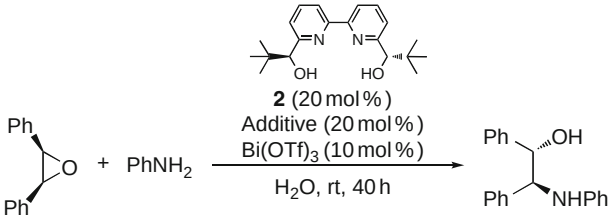
synthesis of these chiral building blocks mainly relies on asymmetric ring opening of *meso*-epoxides. Indeed, several examples using chiral catalysts (typically chiral Lewis acids) have been reported in the literature [48–52]. In the case of bismuth catalysts, however, all previous examples described nonenantioselective epoxide ring opening [53–55]. To address this issue, novel asymmetric bismuth-derived catalysts have been investigated.




**Scheme 2** Formation of chiral $Bi^{3+}$ catalysts

Initial results were not encouraging. In the first of the experiments *cis*-stilbene oxide was allowed to react with aniline in the presence of 10 mol% of $Bi(OTf)_3$ and 20 mol% of chiral ligand **2** in pure water (Table 3, entry 1). Under these conditions, however, no reaction took place and the starting materials were recovered. It was thought that the lack of reactivity might be due to poor solubility of the reactants, and a surfactant was used to overcome this problem. Although cetyl ammonium bromide (CTAB) and Triton X-100 did not lead to any improvement (Table 3, entries 2 and 3), use of sodium dodecyl sulfate (SDS) afforded the desired product with good enantioselectivity albeit in low yield (Table 3, entry 4). It was postulated that an anionic surfactant could interact with a bismuth cation to generate a Lewis acid–surfactant combined catalyst in situ [56]. Alternatively, it could stabilize a cationic species which might be generated on an epoxide ring by the interaction of an epoxide oxygen with $Bi(OTf)_3$. Among other anionic surfactants tested, sodium dodecylbenzene sulfonate (SDBS) was the most efficient in terms of yield and enantioselectivity (Table 3, entries 5 and 6). Reducing the catalyst loading to 5 mol % and the ratio of the metal to the ligand from 2 to 1.2 did not affect the enantioselectivity, although longer reaction times were needed to obtain complete conversion (Table 3, entry 7). In the case of hydromethylation using aqueous formaldehyde, three equivalents of **2** to $Bi(OTf)_3$ were required to obtain the best result. Here, we assumed that a 1:1 complex was formed [43]. It is noted that no diol formation was observed any of the cases. Interestingly, when the reaction was conducted in organic solvents, low yields and moderate enantioselectivities were observed (Table 3, entries 8–12). It has been reported that epoxides rearranged rapidly to form aldehydes or ketones in the presence of $Bi(OTf)_3$ in organic solvents; however, no rearranged products were formed under the those conditions in water [57]. Thus, the asymmetric ring-opening reaction of *cis*-stilbene oxide with aniline was carried out with 5 mol% of $Bi(OTf)_3$, 6 mol% of **2** and 20 mol% of SDBS in water as the sole solvent, affording the desired β-amino alcohol in 80% yield with 88% ee.

**Table 3** Bi-catalyzed asymmetric ring opening of *meso*-epoxide in water and organic solvents




| Entry | Solvent | Additive | Yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|
| 1 | $H_2O$ | – | no reaction | – |
| 2 | $H_2O$ | CTAB | no reaction | – |
| 3 | $H_2O$ | Triton X-100 | no reaction | – |
| 4 | $H_2O$ | SDS | 28 | 83 |
| 5 | $H_2O$ | AOT | 65 | 87 |
| 6 | $H_2O$ | SDBS | 70 | 89 |
| 7[c] | $H_2O$ | SDBS | 80 | 88 |
| 8 | DME | – | 3 | 50 |
| 9 | $CH_2Cl_2$ | – | 15 | 83 |
| 10 | THF | – | 18 | 63 |
| 11 | $CH_3CN$ | – | 10 | 60 |
| 12 | Dioxane | – | 17 | 64 |

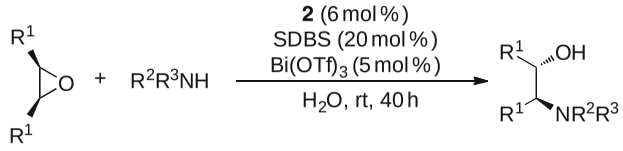
[a]Isolated yield
[b]Determined by chiral HPLC analysis
[c]5 mol% of $Bi(OTf)_3$ and 6 mol% of **2** were used. Reaction time was 30 h

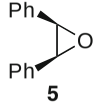
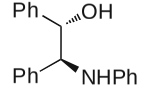
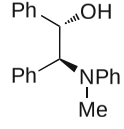
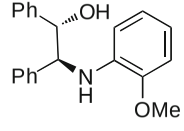
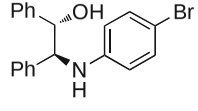
Under the optimized conditions, we next examined other substrates (Table 4) [58]. Sterically hindered anilines such as *N*-methylaniline maintained high yields and led to a further increase in enantioselectivity to 91% ee (Table 4, entry 2). The ring opening with an electron-rich amine such as *o*-anisidine also proceeded smoothly with slightly lower enantioselectivity. The product can easily be converted into the corresponding free 1,2-amino alcohol (Table 4, entry 3). Electron-deficient amines such as *p*-bromoaniline (Table 4, entry 4) and *m*-trifluoromethylaniline (Table 4, entry 5) gave the desired compounds in good yields with high enantioselectivities. The reactions between 1-naphthylamine and **5** (Table 4, entry 6), and aniline and *cis*-di-*p*-tolyloxirane (Table 4, entry 7) also proceeded efficiently.

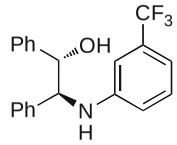
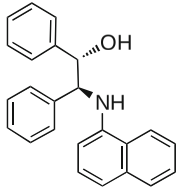
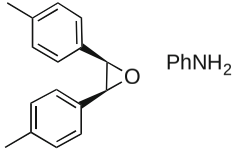
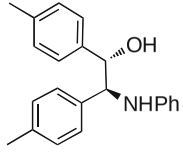
## 4 $Bi(OH)_3$-Catalyzed Allenylation

As demonstrated in previous sections, unique reactivity and selectivity have been often observed in aqueous media, but one of the big issues is the stability of catalysts in water. To overcome this, efficient catalysts that are stable and can work well in aqueous media were searched for, and metal hydroxides were found. With the exception of alkaline and alkaline earth metal hydroxides, these have not

**Table 4** Bi-catalyzed asymmetric ring opening of *meso*-epoxides




| Entry | Epoxide | Amine | Product | Yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|
| 1 |  **5** | $PhNH_2$ |  | 80 | 88 |
| 2 | 5 | PhNHMe |  | 85 | 91 |
| 3 | 5 | $o$-$MeOC_6H_4NH_2$ |  | 83 | 84 |
| 4 | 5 | $p$-$BrC_6H_4NH_2$ |  | 61 (78)[c] | 92 (91)[c] |

| | | | | | |
|---|---|---|---|---|---|
| 5 | 5 | *m*-$CF_3C_6H_4NH_2$ |  | 71 (90)[c] | 94 (93)[c] |
| 6 | 5 | 1-Naphthylamine |  | 73 | 83 |
| 7 |  | $PhNH_2$ |  | 68 | 89 |

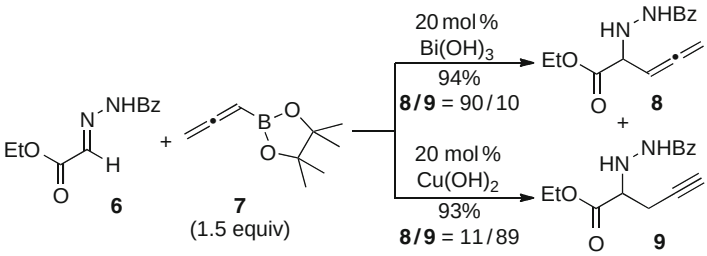
[a]Isolated yield
[b]Determined by chiral HPLC analysis
[c]10 mol% of **2** was used

been used as catalysts in organic synthesis until recently [59–64]. For reports on metal hydroxide or hydrous metal oxide catalyzed reactions, see [65–71], and for recent studies of supported metal hydroxide on metal oxide catalyzed reactions, see [72–74]. It has been reported that allylboronates react with hydrazonoesters in aqueous media in the presence of zinc hydroxide $Zn(OH)_2$–chiral diamine complex to afford allylglycine derivatives in high yields with high enantioselectivities [75]. $Zn(OH)_2$-catalyzed allylation reactions of aldehydes with allylboronates also proceeded in aqueous media [76]. Other metal hydroxides were further investigated, and it was found that several metal hydroxides worked well as catalysts in aqueous media.

Functionalized nitrogen-containing allenes and alkynes such as allenic and homopropargylic amines or hydrazines have proved to be versatile intermediates and building blocks [77–80]. Among the most efficient routes to these compounds are carbon–carbon bond-forming reactions such as the regiospecific addition of propargyl- and allenyl-metal compounds to C = N electrophiles. For examples, refer to the following publications: Lewis acid-catalyzed allenylation or propargylation [81–86]; synthesis of propargyl adducts [87–92]; synthesis of allenyl adducts [93–96]; and other examples [97–101]. Highly selective preparation of various types of allenic and homopropargylic hydrazines through regiospecific allenylation and propargylation of *N*-acylhydrazones with propargyl- or allenyltrichlorosilane have been reported [102, 103]. The reactions proceeded smoothly under anhydrous conditions using water-sensitive trichlorosilanes.

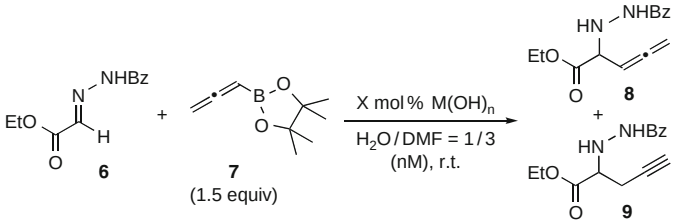
The reaction of hydrazonoester **6** with allenyl pinacol boronate **7** was set as a model, and several metal hydroxides (20 mol%) were screened as catalysts in $H_2O$–DMF (1:3) at room temperature [104]. It was found that allenyl adduct **8** was produced with high selectivity in the presence of bismuth(III) hydroxide, $Bi(OH)_3$ (Scheme 3). Interestingly, copper(II) hydroxide, $Cu(OH)_2$, preferentially gave propargyl adduct **9**. On the basis of these promising results, we further optimized the reaction conditions using $Bi(OH)_3$ and $Cu(OH)_2$ (Table 5).

$Cu(OH)_2$-catalyzed propargylation reaction was found to proceed rapidly and was completed within 5 min, even using 10 mol% of the catalyst to afford the desired product quantitatively (Table 5, entry 2). A lower loading (5 mol%) was also effective (Table 5, entry 3). On the other hand, the $Bi(OH)_3$-catalyzed allenylation reaction was completed within 1.5 h in the presence of 5 mol% of




**Scheme 3** Addition reactions of hydrazonoester with allenylboronate in aqueous media

**Table 5** Optimization of reaction conditions using $Bi(OH)_3$ and $Cu(OH)_2$



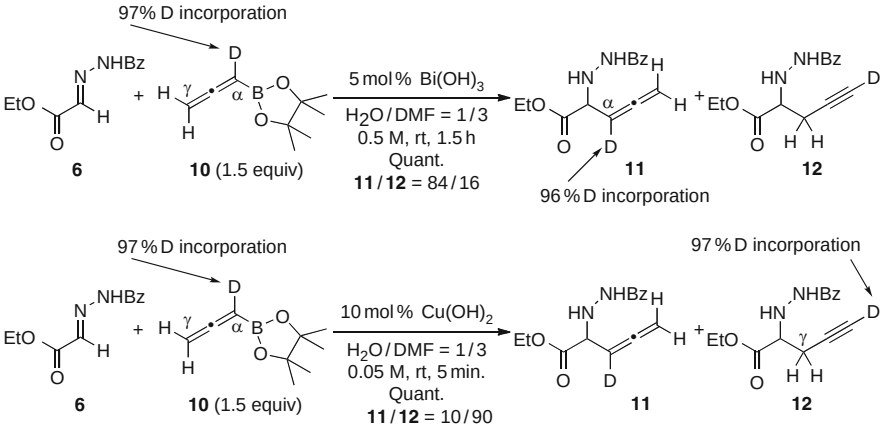

| Entry | Condition | Catalyst concentration ($X$) (mol%) | Concentration of **6** ($n$) (M) | Yield (%) | **8/9** |
|---|---|---|---|---|---|
| 1 | A | 20 | 0.05 | Quantitative | 11/89 |
| 2 | A | 10 | 0.05 | Quantitative | 9/91 |
| 3 | A | 5 | 0.05 | 83 | 5/95 |
| 4 | B | 20 | 0.05 | 94 | 81/19 |
| 5 | B | 10 | 0.05 | 95 | 83/17 |
| 6 | B | 5 | 0.05 | Quantitative | 85/15 |
| 7 | B | 5 | 0.1 | Quantitative | 86/14 |
| 8 | B | 5 | 0.2 | Quantitative | 90/10 |
| 9 | B | 5 | 0.5 | Quantitative | 94/6 |
| 10 | B | 5 | 1.0 | 90 | 80/20 |

Condition A: $Cu(OH)_2$, 5 min. Condition B: $Bi(OH)_3$, 1.5 h

the catalyst, and the desired product was obtained quantitatively (Table 5, entry 6). The propargyl to allenyl ratio was further improved when the reaction was conducted at higher concentration (Table 5, entry 9).

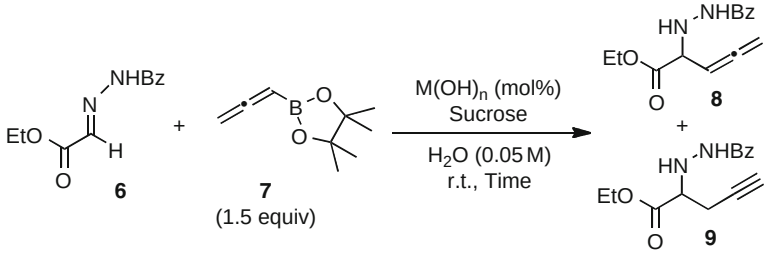
To elucidate the reaction pathway, deuterium-labeled allenyl pinacol boronate **10** was prepared, and the addition reaction with hydrazonoester **6** was conducted in the presence of $Bi(OH)_3$ and $Cu(OH)_2$ (Scheme 4). In both Bi- and Cu-catalyzed cases, the reactions proceeded smoothly (in quantitative yields in both cases). In the $Bi(OH)_3$-catalyzed reaction, a major product was allenyl compound **11**, in which the internal position was deuterized. It was assumed that a propargyl bismuth was formed via transmetalation from boron to bismuth, followed by addition to hydrazonoester via γ-addition to afford allenyl compound **11**. Thus, two γ-additions could selectively provide α-addition products [75, 76, 105, 106]. It was confirmed that isomerization of **10** did not occur. Recently, we reported $Ag_2O$-catalyzed *anti*-selective α-addition of α-substituted allyltributyltin with aldehydes in aqueous media [107]. On the other hand, in the $Cu(OH)_2$-catalyzed reaction, a major product was propargyl compound **12**, in which the terminal position was deuterized. A possible mechanism is that $Cu(OH)_2$ worked as a Lewis acid catalyst to activate hydrazonoester **6** and that allenyl boronate **10** [83–85] reacted with activated **6** via γ-addition to afford **12**.

Organic reactions in water without the use of any organic cosolvents are among the ideal reactions for green chemistry. However, successful examples are still




**Scheme 4** Deuterium-labeling experiments

**Table 6** Addition reaction of hydrazonoester with allenylboronate




| Entry | $M(OH)_n$ | $M(OH)_n$ concentration (mol%) | Sucrose concentration (mol%) | Time (h) | Yield (%) | **8/9** |
|---|---|---|---|---|---|---|
| 1 | – | – | – | 24 | 7 | 24/76 |
| 2 | – | – | 1.7 | 24 | 12 | 18/82 |
| 3 | $Cu(OH)_2$ | 20 | – | 0.5 | 75 | 26/74 |
| 4 | $Cu(OH)_2$ | 20 | 1.7 | 0.5 | 75 | 15/85 |
| 5 | $Bi(OH)_3$ | 10 | – | 24 | 12 | 52/48 |
| 6 | Bi(OH)3 | 10 | 1.7 | 24 | 93 | 77/23 |
| 7 | $Bi(OH)_3$ | 2.5 | 1.7 | 24 | 82 | 86/14 |

limited because most organic materials are hydrophobic, and thus are not soluble in water. To solve the problem, surfactants have often been used [59–64, 108–111]. It was found that addition of sucrose was effective in this system (Table 6). The propargylation reaction proceeded in water without the use of any organic solvents in the presence of 20 mol% of $Cu(OH)_2$ and 1.7 mol% of sucrose (Table 6, entry 4). On the other hand, in the $Bi(OH)_3$-catalyzed reaction, both the yield and the allenyl selectivity of the product were enhanced in the presence of sucrose (Table 6, entries 5 and 6). In this reaction, it is noted that as little as 2.5 mol% of $Bi(OH)_3$ catalyzed the reaction efficiently in water (Table 6, entry 7).

Thus, it was found that selective propargylation or allenylation reactions of hydrazonoester with allenyl pinacol boronate proceeded smoothly in the presence of a catalytic amount of bismuth(III) or copper(II) hydroxide in aqueous media. The use of metal hydroxide as a catalyst in organic synthesis is rare, and it is noteworthy that efficient catalysis occurred in aqueous media. In addition, the allenyl adduct was produced with high selectivity in the presence of $Bi(OH)_3$, whereas the propargyl adduct was obtained with high selectivity in the presence of $Cu(OH)_2$ as a catalyst.

## 5 Conclusion and Perspective

Several bismuth compounds that can be used in aqueous media have been introduced. Due to increasing demand of water as a solvent in organic synthesis, catalysts that can be used in aqueous media are becoming more and more important. Although bismuth Lewis acids are not very stable in water, it has been shown that they can be stabilized by basic ligands. Chiral amine and related basic ligands combined with bismuth Lewis acids are particularly useful in asymmetric catalysis in aqueous media. On the other hand, $Bi(OH)_3$ is stable in water and works as an efficient catalyst in water. Because of the unique characteristics of bismuth compounds, other chiral and achiral bismuth catalysts will be focused on and developed rapidly in the field of synthetic organic chemistry.

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# Pentavalent Organobismuth Reagents in Organic Synthesis: Alkylation, Alcohol Oxidation and Cationic Photopolymerization

**Yoshihiro Matano**

**Abstract** Organic transformations using organobismuth(V) reagents developed by my group are reviewed. The characteristic properties of bismuth, such as the inert pair effect, small bond dissociation energy, and polarized bonding are strongly related to the reactivity of pentavalent organobismuth compounds. The Bi(V) reagents discussed in this chapter include tetraorganylbismuthonium salts ($[Ar_3RBi^+][X^-]$), triarylbismuth ylides ($Ar_3Bi{=}CHCOR$), triarylbismuth imides ($Ar_3Bi{=}NCOR$), triarylbismuth oxides ($Ar_3Bi{=}O$), and triarylbismuth dichlorides ($Ar_3BiCl_2$). These organobismuth(V) compounds are readily accessible in a few steps from triarylbismuthanes ($Ar_3Bi$). New and efficient carbon–carbon bond forming reactions, carbon–heteroatom bond forming reactions, alcohol oxidation, and photoinduced cationic polymerization have been investigated using these reagents. In all these reactions, the good leaving ability as well as the high nucleofugality of the triarylbismuthonio group plays a crucial role in bond-forming and bond-breaking steps.

**Keywords** Bismuth · Bond formation · Oxidation · Polymerization

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## 1 Introduction

Bismuth is the heaviest member of the group 15 (pnictogen) elements with a ground state electronic configuration of $[Xe]4f^{14}5d^{10}6s^{2}6p^{3}$. By contrast to the surrounding heavy atoms such as mercury, thallium, lead, and antimony, bismuth is considered to be a nontoxic heavy metal. Consequently, it is important to develop efficient organic transformations by taking advantage of the characteristic properties of bismuth. In general, organobismuth compounds adopt trivalent Bi(III) or pentavalent Bi(V) states by utilizing the 6*s* and/or 6*p* orbitals. In most tertiary organobismuth(III) compounds, the bismuth center utilizes the three 6*p* orbitals in bond formation because of the low efficiency of hybridization between the diffuse 6*s* and 6*p* orbitals. In other words, the lone pair electrons in tertiary bismuthanes are inherently of *s* character. In pentacoordinate organobismuth(V) compounds, the bismuth center utilizes one of the 6*p* orbitals to form a three-center four-electron (3-c-4-e) bond. This type of hypervalent organobismuth(V) compound typically adopts a trigonal bipyramidal geometry wherein the 3-c-4-e bond is found between the bismuth center and the two apical atoms. In addition to these structural properties, bismuth–carbon bonds are known to be weak (143 kJ $mol^{-1}$ for triphenylbismuthane) and polarized ($Bi^{\delta+}$–$C^{\delta-}$) compared to the lighter pnictogen–carbon bonds [1]. The above-mentioned "inert pair effect," "small bond dissociation energy," and "polarized bonding" are deeply related to the reactivity of organobismuth compounds in the pentavalent oxidation state.

Organic synthesis based on organobismuth(V) reagents was extensively and systematically investigated by Barton and coworkers in the 1980s [2–7]. Of particular importance was the establishment of phenylation methods using the following types of polyphenylbismuth(V) compounds: $Ph_3BiX_2$, $Ph_4BiX$, and $Ph_5Bi$ (X = anionic groups). Barton's noncatalyzed and metal-catalyzed protocols proved to be effective for the phenylations of enols, phenols, alcohols, amines, and thiols, and have been extended by many groups [8–15]. Except for the phenylation reactions, however, organobismuth(V) reagents have received little attention compared to the lighter pnictogen(V) reagents. This chapter reviews organic transformations using organobismuth(V) compounds as developed by my group and includes tetraorganylbismuthonium salts ($[Ar_3RBi^{+}][X^{-}]$), triarylbismuth ylides ($Ar_3Bi{=}CHCOR$), triarylbismuth imides ($Ar_3Bi{=}NCOR$), triarylbismuth oxides ($Ar_3Bi{=}O$), and triarylbismuth dichlorides ($Ar_3BiCl_2$). The synthesis of organobismuth(V) reagents is summarized in Sect. 2. Representative reactions are discussed in Sects. 3–6 and are divided according to the reaction types: carbon–carbon bond forming reactions (Sect. 3), carbon–heteroatom bond forming reactions (Sect. 4), oxidation of alcohols to carbonyl compounds (Sect. 5), and the photoinduced cationic polymerization of epoxides (Sect. 6). Due to page

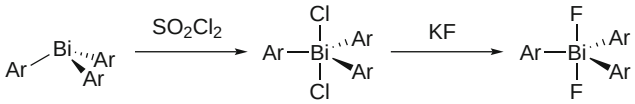
limitations, the reaction mechanisms are only briefly mentioned. Therefore, it is recommended that readers refer to the original references when the reactions described here need to be examined or studied in further detail. The literature contains several leading reviews, accounts, and books concerning organobismuth reagents in organic synthesis [16–26].

## 2 Synthesis of Organobismuth(V) Reagents

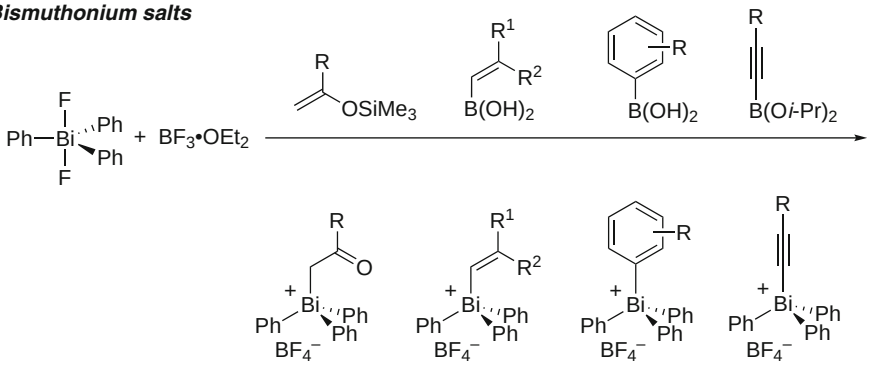
The organobismuth(V) reagents described in this chapter are accessible in a few steps from triarylbismuthanes ($Ar_3Bi$) (Scheme 1) (for the synthesis of organobismuth(V) compounds, see [27–30]). In general, triarylbismuthanes are easily oxidized by sulfuryl chloride, xenon difluoride, or peracids to afford the corresponding triarylbismuth(V) compounds of the type $Ar_3BiX_2$ (X = halides or acyloxy groups) in high yield. The difluorides ($Ar_3BiF_2$) may alternatively be prepared by metathesis of the dichlorides ($Ar_3BiCl_2$) with KF [31]. Alkyltriaryl- and tetraaryl-bismuthonium salts ($[Ar_3RBi^+][X^-]$; R = alkyl or aryl) may be conveniently synthesized by Lewis-acid-promoted metathesis reactions of $Ar_3BiF_2$ with organoboronic acids or organosilicon compounds. The Lewis acids, $BF_3$ and $Me_3SiOTf$, enhance the electrophilicity of the bismuth center through coordination to an apical fluorine atom and they are then transformed into the respective counter anions ($BF_4^-$ and $OTf^-$) by abstracting the fluoride atom as $F^-$. The counter anion of the bismuthonium salts can be replaced with other soft anions such as $PF_6^-$ and $SbF_6^-$ after bismuth–carbon bond formation. According to this methodology, a variety of organyl substituents such as methyl [32], 2-oxoalkyl [33, 34], 3-oxoalkyl [35], allyl [36], alkenyl [37, 38], alkynyl [39], and aryl [40–44] ligands can be introduced onto the bismuthonium center. The above two classes of organobismuth(V) compounds can be isolated by simple recrystallization from appropriate solvents with a few exceptions. Triphenylbismuth ylides of the type $Ph_3Bi{=}CHCOR$ are generated by α-proton abstraction of the 2-oxoalkylbismuthonium salts with strong bases such as KO*t*-Bu and $MN(SiMe_3)_2$ (M = Na, K) at low temperatures [45, 46]. Triarylbismuth oxides ($Ar_3Bi{=}O$ [47, 48]) and imides ($Ar_3Bi{=}NCOR$ [49, 50], $Ar_3Bi{=}NSO_2R$ [51]) are conveniently prepared by metathesis of the dichlorides with $H_2O$ and amides ($H_2COR$, $H_2NSO_2R$), respectively, in the presence of two equivalents of KO*t*-Bu. Alternative methods for the syntheses of triarylbismuth oxides and imides include oxo and nitrene transfer to $Ar_3Bi$ [52–55].

As mentioned in the Introduction, pentacoordinate triarylbismuth dihalides and related compounds have a trigonal bipyramidal geometry, in which the two anionic ligands (X) occupy the apical positions. Due to the hypervalency of the X–Bi–X linkage, the bismuth(V) center in $Ar_3BiX_2$ is essentially electrophilic. Tetraorganylbismuthonium salts bearing soft counter anions form a distorted tetrahedral geometry, wherein the cationic bismuth(V) center exhibits electrophilic character, as in $Ar_3BiX_2$. With counter anions of chloride, bromide, or iodide, the bismuthonium

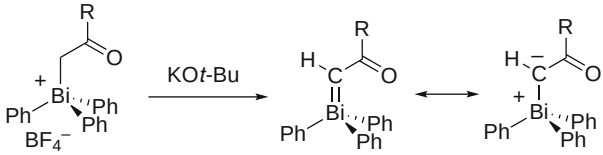
***Triarylbismuth dihalides***



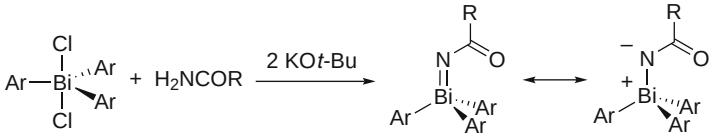

***Bismuthonium salts***



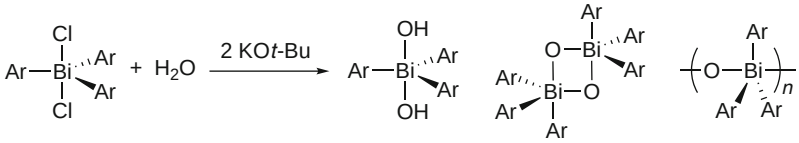

***Bismuth ylide***




***Bismuth imide***




***Bismuth oxide***




**Scheme 1** Synthesis of organobismuth(V) reagents

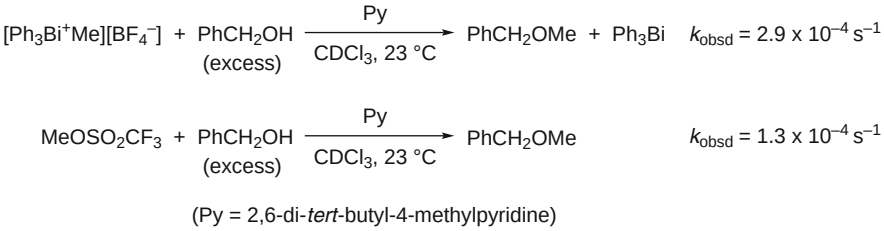
salts ($Ar_3RBiX$) thermally decompose to give $Ar_3Bi$ and organyl halides (RX). The bismuth ylides, imides, and oxides possess highly polarized bismuth(V)–carbon, bismuth(V)–nitrogen, and bismuth(V)–oxygen bonds, respectively.

The ylides and imides are present as monomers, and the bismuth center adopts a distorted tetrahedral geometry. In contrast, the structural properties of the bismuth oxides vary widely depending on the aryl ligands attached to the bismuth center; the oxides exist as hydrates, dimers, or polymers in solution and in the solid state. X-ray structural analysis of an oxide dimer revealed that the bismuth center has a distorted, trigonal bipyramidal geometry with the two oxygen atoms at the apical and equatorial positions [47, 48].

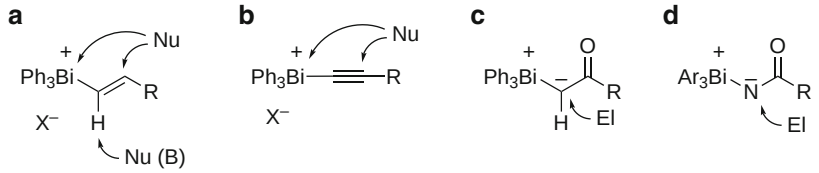
## 3 Carbon–Carbon Bond Forming Reactions

Sections 3 and 4 mainly focus on carbon–carbon and carbon–heteroatom bond-forming reactions using alkyltriarylbismuthonium salts and triarylbismuth ylides. As mentioned below, the bismuthonium salts undergo electrophilic alkylation, whereas the bismuth ylides undergo nucleophilic alkylation. In both cases, the observed reactivities are basically due to the good leaving ability as well as the high nucleofugality of the triarylbismuthonio groups. The leaving ability of the triphenylbismuthonio group was quantitatively evaluated using kinetic experiments in which the methylation of benzyl alcohol with methyltriphenylbismuthonium tetrafluoroborate was undertaken [32]. As shown in Scheme 2, the pseudo first-order rate constant obtained for the methylbismuthonium salt is twice as large as that for methyl triflate in $CDCl_3$. This result explicitly shows the extremely good leaving ability of the triphenylbismuthonio group as the bismuthane.

Scheme 3 shows the conceivable reaction sites of alkenylbismuthonium salts, alkynylbismuthonium salts, bismuth ylides, and bismuth imides in carbon–carbon and carbon–heteroatom bond forming reactions. In the initial step, nucleophiles (Nu) attack the positively charged bismuth(V) center, α-proton or β-carbon (Scheme 3a, b) whereas electrophiles (El) attack the negatively charged α-carbon or α-nitrogen (Scheme 3c, d). Usually, the resulting bismuth(V) intermediates




**Scheme 2** Methylation reactions of benzyl alcohol with methyltriphenylbismuthonium salt and methyl triflate [32]



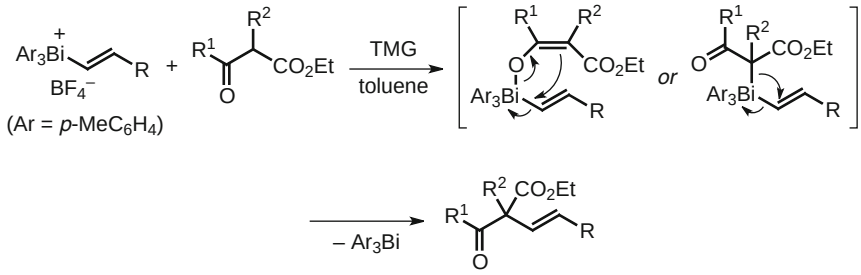

**Scheme 3** Reaction sites of organobismuth(V) reagents in C–C and C–X bond forming reactions: (**a**) alkenylbismuthonium salt; (**b**) alkynylbismuthonium salt; (**c**) bismuth ylide; (**d**) bismuth imide. *Nu* nucleophile, *B* base, *El* electrophile

quickly release the triarylbismuthonio group. Accordingly, in most of the bond-forming reactions, triarylbismuthanes are produced as side products.

## *3.1 C–C Bond Forming Reactions with Alkylbismuthonium Salts*

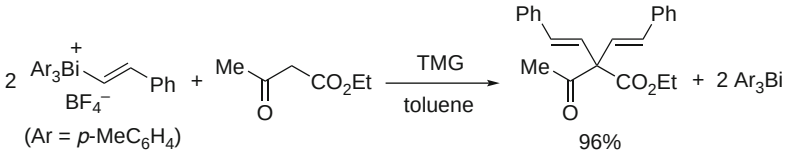
Alkyltriphenylbismuthonium salts behave as alkyl cation equivalents when reacting with carbon nucleophiles and undergo carbon–carbon bond forming reactions under mild conditions. Among the reactions studied by my group, the alkenylation of enolates and phenols, the cyclopropanation of olefins, and the Friedel–Crafts-type allylation of arenes are of interest from a synthetic point of view. Representative examples of these transformations are summarized in Schemes 4–6. The introduction of an alkenyl group to the α-positions of enolisable compounds is promising for the synthesis of β,γ-unsaturated (allylic) ketones and esters, which are versatile building blocks in organic synthesis. In basic organic chemistry, however, the nucleophilic substitution of vinyl halides is known to hardly occur under ambient conditions because of the low nucleofugality of the vinylic *ipso* halogen atom. In this regard, the attachment of a good leaving group at the vinylic $sp^2$ carbon is a promising strategy for enhancing its nucleofugality [56–61].

Scheme 4 illustrates some results for the alkenylation of α-substituted β-keto esters with alkenyltriarylbismuthonium salts [37, 38]. The reaction is promoted by adding a strong base, 1,1,3,3-tetramethylguanidine (TMG) or 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), and the resulting α-alkenylated carbonyl compounds are obtained in good yield with $Ar_3Bi$. No reaction proceeds in the absence of a base, indicating that enolates are the active nucleophiles during α-alkenylation. Careful NMR inspection of the reaction mixture produced during the reaction with ethyl 2-oxocyclohexanecarboxylate showed the presence of small amounts of α-arylated keto ester and alkenyldiarylbismuthane. This finding implies that the transfer of the 1-hexenyl group to the enolic carbon is much more preferable (>50/1 selectivity) than transfer of the 4-methylphenyl group. After removing the tertiary bismuthanes, the target allylic carbonyl compounds can be isolated by short silica-gel column chromatography. The selectivity of alkenyl versus aryl transfer was found to be dependent on the β-substituents of the vinyl moiety in the order: β-alkyl, β-phenyl

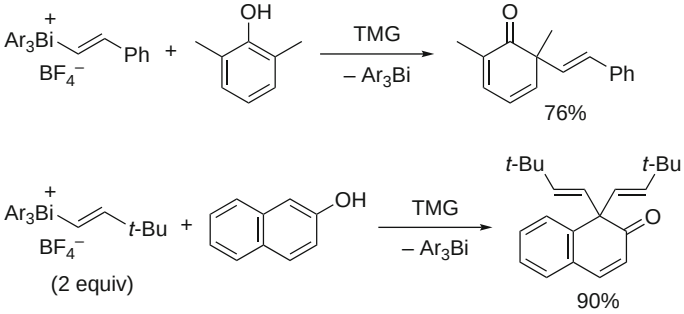



| entry | R | $R^1$, $R^2$ | yield/% |
|---|---|---|---|
| 1 | *n*-Bu | $(CH_2)_4$ | 89 |
| 2 | Ph | $(CH_2)_4$ | 88 |
| 3 | Ph | $(CH_2)_3$ | 90 |
| 4 | Ph | Me, Me | 90 |

**Scheme 4** Alkenylation of enolates with alkenylbismuthonium salts [38]




**Scheme 5** Alkenylation of a β-keto ester with an alkenylbismuthonium salt [38]




**Scheme 6** Alkenylation of phenols with alkenylbismuthonium salts [38]

> β-methyl > β,β-dimethyl. It should be noted that the stereochemistry of the alkenyl group is fully retained during carbon–carbon bond formation.

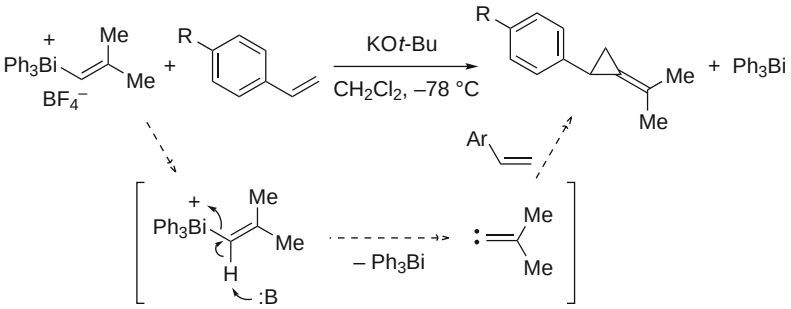
The above experimental results strongly support a ligand-coupling mechanism [62, 63] for bismuth(V)-assisted α-alkenylation. Thus, the enolate attacks the

bismuth center to generate a pentacoordinate bismuth(V) species, which is followed by ligand coupling. This explains the stereochemical outcome of the products and also how substituents affect the reactivity and selectivity. β-Dicarbonyl compounds without α-substituents undergo double alkenylation at the active methylene carbon (Scheme 5). When the α-proton of enolizable substrates is less acidic than the α-vinyl proton of the alkenylbismuthonium salts, however, α-proton abstraction from the vinyl function becomes a main pathway, to yield acetylenes presumably via alkylidene carbene intermediates.

The alkenylation of phenols also proceeds smoothly in the presence of TMG (Scheme 6). The major products are not aryl alkenyl ethers but α-alkenylated cyclohexa-2,4-dienones. That is, *C*-alkenylation occurs exclusively at the *ortho* position of phenols. When 2-naphthol reacts with two equivalents of the alkenylbismuthonium salt, α,α-dialkenyl ketone is obtained in good yield as the sole alkenylated product.

The treatment of the 2-methyl-1-propenylbismuthonium salt with KO*t*-Bu in the presence of excess styrene gives alkylidenecyclopropanes in good yield (Scheme 7). The *para* substituent effect on the relative reactivity is very small, indicating that a free alkylidene carbene is generated as the active species. In this case, the alkylidene carbene is trapped by the styrene in solution.

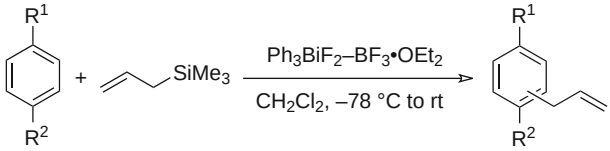
The addition of $BF_3$•$OEt_2$ to a solution containing $Ph_3BiF_2$, allyltrimethylsilane and excess arenes induces a Friedel–Crafts-type allylation at low temperatures to yield allylarenes [36]. Benzene, toluene, anisole, *p*-xylene, and *p*-dimethoxybenzene were all allylated with ease to give the corresponding allylation products, although diallylation could not be suppressed in the reaction with electron-rich




| entry | R | yield/%[a] | $k_{rel}$[b] |
|---|---|---|---|
| 1 | Me | 93 | 1.16 |
| 2 | H | 84 | 1.00 |
| 3 | Cl | 86 | 0.86 |

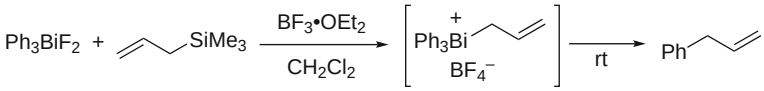
[a] Yield of cyclopropane.
[b] Relative reactivity vs $PhCH{=}CH_2$.

**Scheme 7** Cyclopropanation of styrenes with an alkenylbismuthonium salt [37]




| entry | $R^1$, $R^2$ | Yield/% | *o/m/p* |
|---|---|---|---|
| 1 | H, H | 61 | – |
| 2 | Me, H | 42[a] | 48/12/40 |
| 3 | MeO, H | 81[a] | 15/0/85 |
| 4 | Me, Me | 60[a] | – |
| 5 | MeO, MeO | 37[a] | – |

[a] Diallylated arenes were also formed.



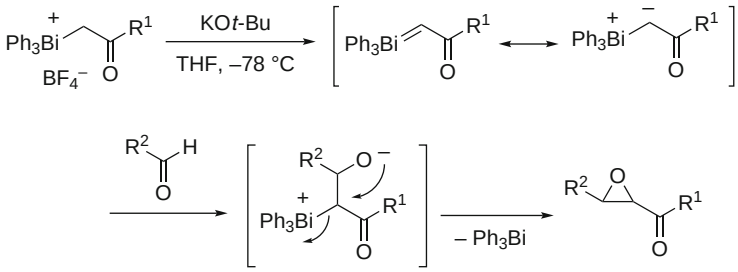

**Scheme 8** Friedel–Crafts allylation of arenes with an allylbismuthonium salt [36]

arenes (Scheme 8). In contrast, chlorobenzene was not allylated at all. The *ortho*/*meta*/*para* selectivity observed for the monosubstituted benzenes implies that an allyl cation or its equivalent is generated in situ via an allyltriphenylbismuthonium salt. When the reaction was conducted in the absence of arenes, allylbenzene was formed as the major product. This indicates that the allyltriphenylbismuthonium salt is thermally unstable and readily undergoes ligand coupling between the allyl and phenyl ligands.

## 3.2 C–C Bond Forming Reactions with Bismuth Ylides

Bismuth ylides of the type $Ph_3Bi{=}CHCOR$ are generated in solution from 2-oxoalkylbismuthonium salts ($[Ph_3Bi^+CH_2COR][BF_4^-]$) and a base at low temperatures [45, 46]. Typically, THF or toluene is used as the solvent and KO*t*-Bu, LDA, or $MN(SiMe_3)_2$ (M = Na, K) is used as the base. The generation of $Ph_3Bi{=}CHCO$*t*-Bu was confirmed by $^1H$ and $^{13}C$ NMR spectroscopy in THF-$d_8$ at low temperatures, where the ylidic carbon appeared at $\delta$ 86.4 ppm with a C–H coupling constant of 186 Hz. However, bismuth ylides of the type $Ph_3Bi{=}CHCOR$ are thermally unstable and decompose at room temperature, resulting in the formation of triphenylbismuthane as the major degradation product.

In a marked contrast to the lighter pnictogen (P, As, Sb) elements, this class of bismuth ylides readily undergoes Corey–Chaycovsky-type epoxidations with aromatic, aliphatic, and α,β-unsaturated aldehydes to afford the corresponding

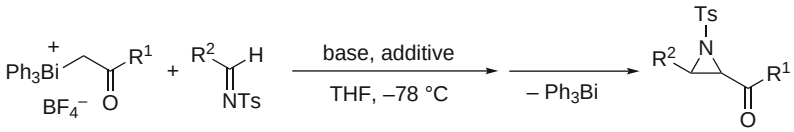



| entry | $R^1$ | $R^2$ | yield/% | *trans*/*cis* |
|---|---|---|---|---|
| 1 | *t*-Bu | Ph | 85 | 88/12 |
| 2 | *t*-Bu | *p*-$MeC_6H_4$ | 75 | 91/9 |
| 3 | *t*-Bu | *p*-$MeOC_6H_4$ | 70 | 100/0 |
| 4 | *t*-Bu | *p*-$ClC_6H_4$ | 70 | 91/9 |
| 5 | *t*-Bu | *o*-$MeC_6H_4$ | 66 | 100/0 |
| 6 | *t*-Bu | 1-naphthyl | 66 | 100/0 |
| 7 | Ph | Ph | 71 | 88/12 |
| 8 | Ph | *p*-$ClC_6H_4$ | 67 | 97/3 |
| 9 | *t*-Bu | PhCH=CH | 60 | 78/22 |
| 10 | Ph | *i*-Bu | 54 | 71/29 |
| 11 | OPh | Ph | 36 | 100/0 |
| 12 | OPh | *p*-$MeOC_6H_4$ | 43 | 100/0 |

**Scheme 9** Reaction of bismuth ylides with aldehydes [45, 46]

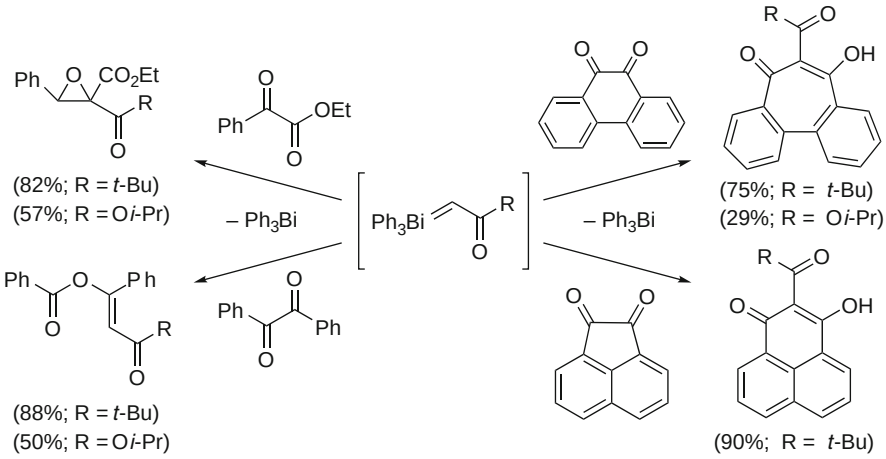
α,β-epoxy ketones with high *trans* selectivity [45, 46]. Selected results are summarized in Scheme 9. Intermolecular competition experiments between *para*-substituted benzaldehydes indicated that the nucleophilic attack of ylidic carbons on carbonyl carbons is involved in the rate-determining step. The exclusive formation of oxiranes may be reasonably explained by considering the good leaving ability of the triphenylbismuthonio group from betain-type intermediates (for a theoretical prediction, see [64]).

When *N*-tosylaldimines (tosyl = *p*-toluenesulfonyl) are used as substrates, α,β-aziridino ketones are obtained together with $Ph_3Bi$ [65]. Interestingly, the stereochemistry of the aziridines is controllable by changing the combination of bases and additives. As shown in Scheme 10, the use of KO*t*-Bu or $KN(SiMe_3)_2$ affords *trans*-rich aziridines whereas the combined use of $NaN(SiMe_3)_2$/HMPA or $NaN(SiMe_3)_2$/TMEDA gives *cis*-rich aziridines. The electrostatic interaction between the cationic bismuth center and the sulfonyl oxygen atom determines the conformation of the transition state at the C–C bond forming stage. Coordinative effects of *N*-sulfonyl groups on the stereoselectivity of aziridines have also been observed during carbene transfer reactions from iodonium ylides to *N*-sulfonylaldimines [66].




| entry | $R^1$ | $R^2$ | base | additive | yield/% | *trans*/*cis* |
|---|---|---|---|---|---|---|
| 1 | *t*-Bu | Ph | KO*t*-Bu | – | 91 | 95/5 |
| 2 | *t*-Bu | *p*-$MeC_6H_4$ | KO*t*-Bu | – | 80 | 100/0 |
| 3 | *t*-Bu | *p*-$ClC_6H_4$ | KO*t*-Bu | – | 86 | 100/0 |
| 4 | *t*-Bu | *p*-$ClC_6H_4$ | $KN(SiMe_3)_2$ | TMEDA | 74 | 100/0 |
| 5 | Ph | Ph | KO*t*-Bu | – | 66 | 82/18 |
| 6 | *t*-Bu | *p*-$ClC_6H_4$ | $NaN(SiMe_3)_2$ | – | 87 | 81/19 |
| 7 | *t*-Bu | *p*-$ClC_6H_4$ | $NaN(SiMe_3)_2$ | HMPA | 84 | 38/62 |
| 8 | *t*-Bu | *p*-$ClC_6H_4$ | $NaN(SiMe_3)_2$ | TMEDA | 87 | 14/86 |
| 9 | Ph | *p*-$ClC_6H_4$ | $NaN(SiMe_3)_2$ | – | 44 | 53/47 |
| 10 | Ph | *p*-$ClC_6H_4$ | $NaN(SiMe_3)_2$ | HMPA | 40 | 0/100 |

**Scheme 10** Reaction of bismuth ylides with *N*-tosylaldimines [65]




**Scheme 11** Reactions of bismuth ylides with α-dicarbonyl compounds [46, 67–70]

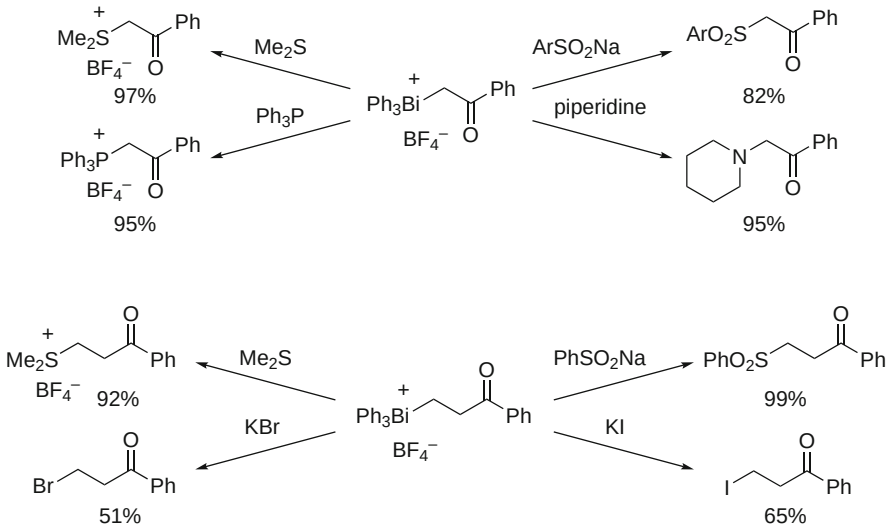
The bismuth ylides, $Ph_3Bi{=}CHCOR$, do not react with simple ketones and electron-rich olefins probably because of their relatively low electrophilic character. However, $Ph_3Bi{=}CHCOR$ reacts with α-keto esters [46, 67, 68], benzils [46, 67–69], *ortho*-quinones [46, 67, 68], and acenaphthenequinone [70] to give epoxides, *O*-aroyl enolates, 3-hydroxytropones, and 3-hydroxyphenalenones, respectively, accompanied by the formation of $Ph_3Bi$ (Scheme 11). In particular, transposition and ring expansion reactions are of interest from a mechanistic point of view, since these reaction modes are unprecedented in ylide chemistry.

## 4 Carbon–Heteroatom Bond Forming Reactions

Methyl-, 2-oxoalkyl-, 3-oxoalkyl-, and allyl-triphenylbismuthonium salts transfer their alkyl groups to various heteronucleophiles such as piperidine, triphenylphosphane, arylsulfinates, alcohols, arylthiolates, dimethyl sulfide, DMF, thioacetamide, and halides under mild conditions [33–36]. Selected examples are illustrated in Scheme 12. In all cases, triphenylbismuthane is recovered in good yield, indicating that the driving force of C–X bond formation is the good leaving ability of the triphenylbismuthonio group.

As mentioned in Sect. 3.1, nucleophilic substitution at the vinylic carbon is a promising method for obtaining functionalized olefins. (*E*)-1-styryl- and (*E*)-1-propenyl-triphenylbismuthonium salts transfer their alkenyl groups to sodium arylsulfinates to give vinyl aryl sulfones in good yield (Scheme 13). It should be noted that the carbon–sulfur bond is formed at the α-vinylic carbon with the retention of its stereochemistry. In this regard, carbon–sulfur bond formation probably takes place via a ligand-coupling mechanism from pentacoordinate bismuth(V) intermediates. The reaction of alkenylbismuthonium salts with sodium benzenethiolate affords vinyl phenyl sulfides as major products. In both cases, triphenylbismuthane is formed as a side product.

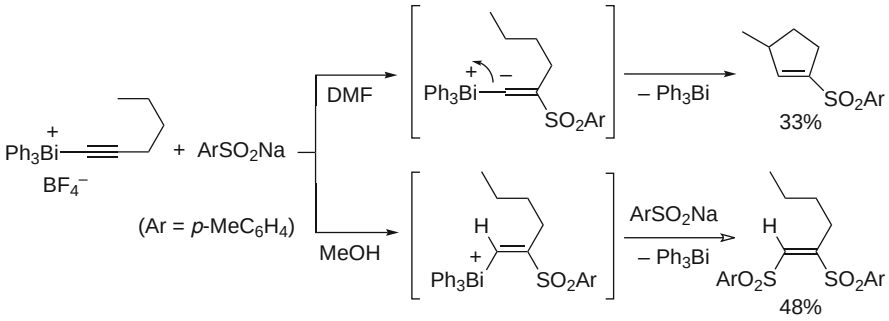
As shown in Scheme 14, 1-hexynyltriphenylbismuthonium tetrafluoroborate reacts with sodium *p*-toluenesulfinate in dual reaction modes, depending on the reaction media employed [39]. In DMF, 1-tosylcyclopentene is formed through the 1,5-C–H insertion of an alkylidene carbene intermediate, which was generated via the Michael addition of a sulfinate anion to the acetylenic β-carbon. In MeOH,




**Scheme 12** Reactions of 2-oxoalkyl- and 3-oxoalkyl-triphenylbismuthonium salts with hetero nucleophiles [33–35]

| entry | R | Ar | yield/% |
|---|---|---|---|
| 1 | Ph | *p*-$MeC_6H_4$ | 94 |
| 2 | *p*-$MeC_6H_4$ | Ph | 92 |
| 3 | PhCH=CH | Ph | 67 |
| 4 | Me | *p*-$MeC_6H_4$ | 66 |

**Scheme 13** Reaction of (*E*)-alkenylbismuthonium salts with sodium arylsulfinates [37]

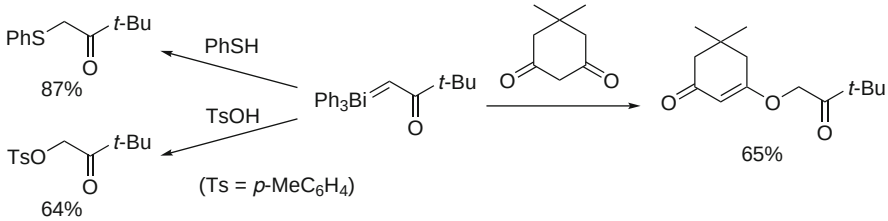



**Scheme 14** Reaction of 1-hexynylbismuthonium salt with sodium *p*-toluenesulfinate [39]

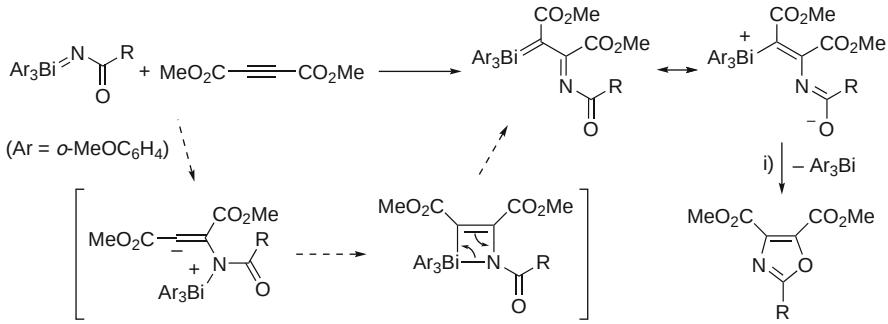
1,2-bis(sulfonyl)alkenes are produced via a sequential Michael addition onto the β-carbon and a nucleophilic substitution at the α-carbon. That is, two sulfinate ions are introduced into the acetylene function, yielding electron-deficient olefins in a one-pot procedure. Presumably, in MeOH, the α-carbon is protonated before the triphenylbismuthonio group is eliminated. The second sulfonylation might occur via a ligand coupling pathway through an alkenylbismuthonium salt.

Bismuth ylides $Ph_3Bi{=}CHCOR$ undergo carbon–heteroatom bond forming reactions with benzene thiol and *p*-toluenesulfonic acid via a selective acidolysis of the ylidic carbon–bismuth bond (Scheme 15). The coupling products were obtained in moderate to high yields together with $Ph_3Bi$. In the reaction with dimedone, an *O*-alkylation occurs to give an alkyl enol ether as the major product.

Both experimental and theoretical studies on the structure–reactivity relationship of a series of triarylpnictogen(V) imides have revealed that the bismuth(V)–nitrogen bonds in triarylbismuth *N*-acylimides and *N*-tosylimides essentially possess a highly polarized single-bond character [49, 50]. The bismuth *N*-acylimides, which are more reactive than the *N*-tosylimides, undergo Michael addition with dialkyl acetylenedicarboxylates under mild conditions to give highly conjugated acyclic bismuth ylides as thermally stable solids (Scheme 16). When heated at high temperatures or treated with a copper catalyst at room temperature, the resulting




**Scheme 15** Reaction of bismuth ylide with organic acids [45]




| entry | R | yield/%[a] |
|---|---|---|
| 1 | 3,5-$(CF_3)_2C_6H_3$ | 92 |
| 2 | $p$-$O_2NC_6H_4$ | 59 |
| 3 | $p$-$NCC_6H_4$ | 57 |
| 4 | $CF_3$ | 72 |

[a] Yield of bismuth ylide.

| entry | R | conditions for i) | yield/%[b] |
|---|---|---|---|
| 1 | 3,5-$(CF_3)_2C_6H_3$ | 200 °C, 5 min | 96 |
| 2 | 3,5-$(CF_3)_2C_6H_3$ | CuBr, rt, 12 h | 91 |
| 3 | $p$-$NCC_6H_4$ | 200 °C, 5 min | 92 |
| 4 | $p$-$NCC_6H_4$ | $Cu(OTf)_2$, rt, 12 h | 83 |

[b] Yield of oxazole.

**Scheme 16** Reaction of bismuth *N*-acylimides with an electron-deficient acetylene [71]

bismuth ylides eliminate triarylbismuthane to produce trisubstituted oxazoles via intramolecular cyclization [71]. Overall, the bismuth *N*-acylimides transfer their acylnitrene units as 1,3-dipoles onto activated carbon–carbon triple bonds in two steps.

## 5 Oxidation of Alcohols to Carbonyl Compounds

Organobismuth(V) compounds are potential oxidants because of their inherent oxidizing ability, which derives from the facile Bi(V)/Bi(III) redox process [72]. This characteristic property of bismuth has been utilized for alcohol oxidation

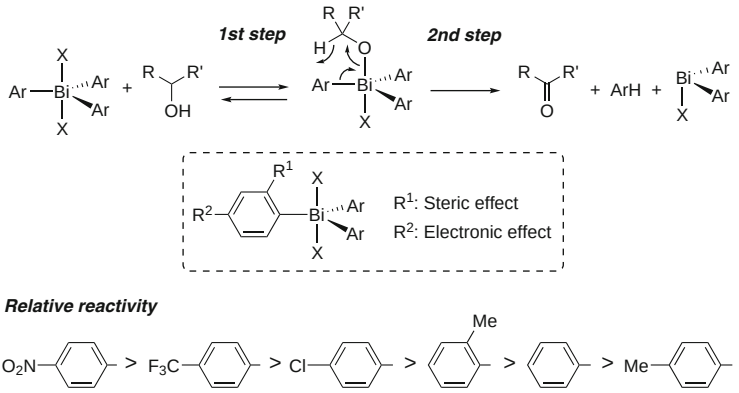
where several types of organobismuth(V) reagents oxidize primary and secondary alcohols to aldehydes and ketones, respectively [73–79]. In particular, Barton and coworkers extensively studied alcohol oxidation using triphenylbismuth(V) compounds of the $Ph_3BiX_2$ and $Ph_3Bi(X)OBi(X)Ph_3$ types. They found that these oxidants convert simple alcohols to carbonyl compounds through two main steps: the formation of alkoxytriphenylbismuth(V) intermediates (first step) and α-hydrogen abstraction by the phenyl ligand (second step) [77–79]. This mechanism implies that the oxidizing ability of organobismuth(V) compounds strongly depends on the intrinsic nature of the bismuth-bound organyl ligands. However, the effect of substituents on the oxidizing ability in alcohol oxidation has not been clarified until recently.

## 5.1 Oxidation with Triarylbismuth(V) Compounds

Scheme 17 illustrates the two-step mechanism for alcohol oxidation with $Ar_3BiX_2$-type oxidants, which was originally proposed by Barton and coworkers.

Recent comparative studies (intermolecular competition experiments using two different bismuth(V) oxidants and intramolecular competition experiments with unsymmetrically substituted bismuth(V) oxidants [80, 81]) revealed that the substituents affect the triarylbismuth(V) oxidants as follows:

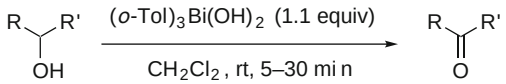
1. Aryl ligands bearing a methyl group at the *ortho* position and/or an electron-withdrawing group at the *para* position dramatically enhance the overall rate of oxidation.
2. The electron-deficient aryl ligands enhance the electrophilicity of the bismuth (V) center and, as a result, accelerate the first step.
3. The suitably bulky aryl ligands cause steric congestion at the bismuth center and dramatically accelerate the second step [81].

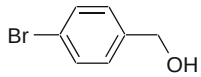
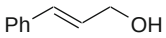
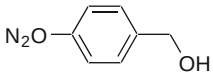
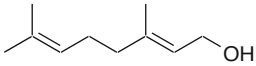
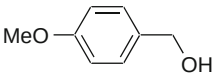
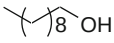
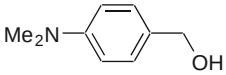
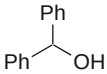
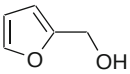
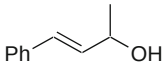
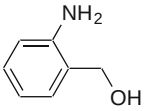
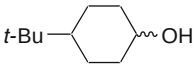



**Scheme 17** Oxidation of alcohols with triarylbismuth(V) oxidants [81]

For instance, the relative oxidizing ability of $Ar_3BiCl_2$ (in the $Ar_3BiCl_2$/DBU system) was found to be in the order: Ar = *p*-nitrophenyl > *p*-(trifluoromethyl) phenyl > *o*-methyl-*p*-chlorophenyl > *p*-chlorophenyl > *o*-methylphenyl > phenyl > *p*-methylphenyl. On the basis of these findings, new efficient triarylbismuth(V) oxidants have been prepared and some reagents are now commercially available.

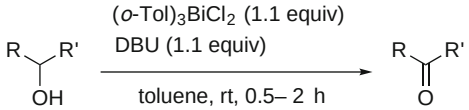
Triarylbismuth oxides can be readily prepared from the corresponding dichlorides, water and two equivalents of KO*t*-Bu, although their structures vary widely depending on the aryl ligands attached to the bismuth [47, 48]. Tris(*o*-tolyl)bismuth dihydroxide, a hydrate form of the oxide, shows remarkably high oxidizing ability toward a variety of primary and secondary alcohols without the addition of any promoters (Scheme 18). It should be noted that the over-oxidation of aldehydes to carboxylic acids does not proceed at all. It is also worth noting that allylic and benzylic alcohols as well as nonconjugative aliphatic alcohols are oxidized in good yield within short reaction times. In all cases, an equimolar amount of toluene was produced in addition to the expected carbonyl compounds.

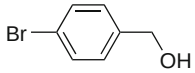
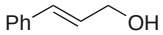
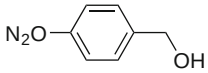
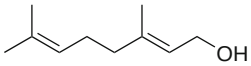
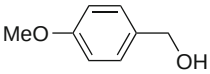
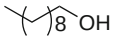
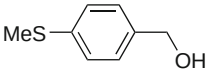
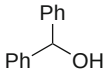
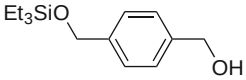
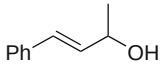
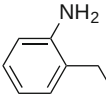
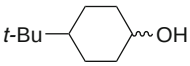



| entry | alcohol | yield/% | entry | alcohol | yield/% |
|---|---|---|---|---|---|
| 1 |  | 91 | 7 |  | 97 |
| 2 |  | 97 | 8 |  | 94 |
| 3 |  | 92 | 9 |  | 92 |
| 4 |  | 99 | 10 |  | 99 |
| 5 |  | 99 | 11 |  | 90 |
| 6 |  | 88 | 12 |  | 98 |

**Scheme 18** Oxidation of alcohols with tris(*o*-tolyl)bismuth dihydroxide [47, 48]

A practical drawback of triarylbismuth oxides is their thermal instability, causing bismuth oxides to slowly decompose in solution at room temperature. In contrast, triarylbismuth dichlorides, the precursors of the oxides, are thermally stable and can be stored for a long period of time in the solid state. Therefore, the combination of triarylbismuth dichloride and a base is more attractive as a practical system than the use of triarylbismuth oxides. After the screening of aryl ligands, bases, and solvents, a new efficient oxidation system, $Ar_3BiCl_2$/DBU/toluene, was successfully created. In this system, electron-deficient or suitably bulky aryl ligands such as *p*-trifluoromethylphenyl, *p*-nitrophenyl and *o*-tolyl were found to be effective (vide supra) [82]. Scheme 19 summarizes selected results on alcohol oxidation experiments using $(o\text{-Tol})_3BiCl_2$. As observed for triarylbismuth oxide oxidation, a variety of primary and secondary alcohols are converted to aldehydes and ketones, respectively, with high efficiency. In the system described in Scheme 19, $[(o\text{-Tol})_2BiCl_2^-][DBUH^+]$ and toluene are formed as side products. The former bismuth(III)ate complex precipitates out of the solution and can be easily recovered



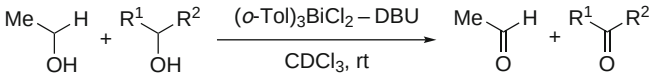

| entry | alcohol | yield/% | entry | alcohol | yield/% |
|---|---|---|---|---|---|
| 1 |  | 94 | 7 |  | >99 |
| 2 |  | 95 | 8 |  | 94 |
| 3 |  | 99 | 9 |  | 94 |
| 4 |  | 98 | 10 |  | 99 |
| 5 |  | 98 | 11 |  | >99 |
| 6 |  | >99 | 12 |  | 93 |

**Scheme 19** Oxidation of alcohols with $(o\text{-Tol})_3BiCl_2$–DBU in toluene [82]

from the reaction mixture. Hence, the carbonyl products can be isolated with ease using short column chromatography.

To estimate the relative reactivity of allylic, benzylic, and nonconjugative aliphatic alcohols toward the $Ar_3BiCl_2$/DBU system, intermolecular competitive oxidations were examined. As summarized in Scheme 20, cinnamyl and benzylic alcohols were preferentially oxidized in the presence of ethyl alcohol. The chemoselectivities observed for the $Ar_3BiCl_2$/DBU oxidant (Ar = *o*-tolyl) are considerably higher than those achieved by Dess–Martin periodinane [83, 84].

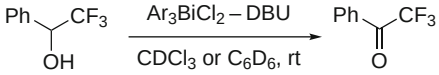
Interestingly, the newly developed $Ar_3BiCl_2$/DBU oxidants [Ar = *p*-nitrophenyl, *p*-(trifluoromethyl)phenyl] rapidly oxidize 2,2,2-trifluoro-1-phenylethanol [81], which is generally known to resist oxidation [85–87], to the corresponding trifluoromethyl ketone within 5–50 min at room temperature (Scheme 21). The difference in the reaction rates among the bismuth(V) oxidants is in good agreement with the results obtained for the intermolecular competition experiments.




| entry [a] | $R^1$ | $R^2$ | MeCHO/PhCOR | |
|---|---|---|---|---|
| | | | $Bi^V$/DBU | Dess-Martin[b] |
| 1 | PhCH=CH | H | 98/2 | 91/9 |
| 2 | Ph | H | 96/4 | 90/10 |
| 3 | Ph | Me | 95/5 | 75/25 |

[a] Three equivalents each of alcohols were used.
[b] Dess-Martin periodinane.

**Scheme 20** Chemoselective oxidation of alcohols with $(o\text{-Tol})_3BiCl_2$–DBU and Dess–Martin periodinane [82]

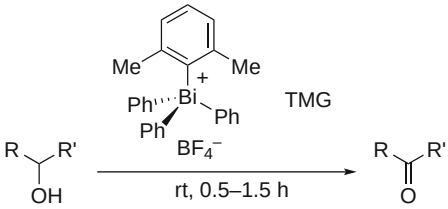


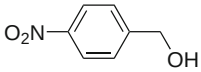
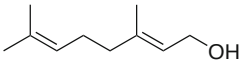
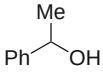
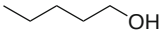

| entry | Ar | time | yield/% |
|---|---|---|---|
| 1 | $o\text{-MeC}_6H_4$ | 32 h | 98 |
| 2 | $p\text{-CF}_3C_6H_4$ | 50 min | >95 |
| 3 | $p\text{-NO}_2C_6H_4$ | 5 min | >95 |

**Scheme 21** Oxidation of 2,2,2-trifluoro-1-phenylethanol with $Ar_3BiCl_2$–DBU oxidants [81]

## 5.2 Oxidation with Tetraarylbismuth(V) Compounds

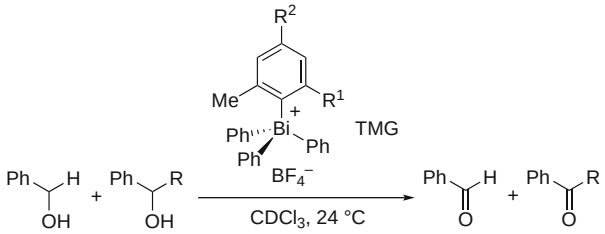
Tetraarylbismuth(V) oxidants have received little attention compared to triarylbismuth(V) oxidants [88]. This class of oxidants is also believed to oxidize alcohols in two steps: the nucleophilic attack of alcohol on the bismuth center (first step) and α-hydrogen abstraction from an alkoxytetraarylbismuth(V) intermediate (second step). This mechanism is based on the fact that triarylbismuthanes and arenes are formed as side products. Comparative intermolecular/intramolecular competition experiments to investigate substituent effects on the intrinsic oxidizing ability of tetraarylbismuthonium salts revealed that the electron-deficient aryl groups accelerate the first step and that the bulky aryl groups accelerate the second step [89, 90]. On the basis of these findings, new organobismuth(V) oxidants, mesityl- and 2,6-xylyl-triphenylbismuthonium tetrafluoroborates were designed. Scheme 22 shows representative results of the alcohol oxidation using the 2,6-xylylbismuthonium salt, which converts primary and secondary alcohols to the corresponding carbonyl compounds in the presence of TMG. It should be noted that cleavage of the bismuth–mesityl or bismuth–xylyl bond is preferred over that of the bismuth–phenyl bond (>300/1). Apparently, the bulky mesityl and 2,6-xylyl ligands accelerate α-hydrogen abstraction from the sterically crowded alkoxytetraarylbismuth (V) intermediates.



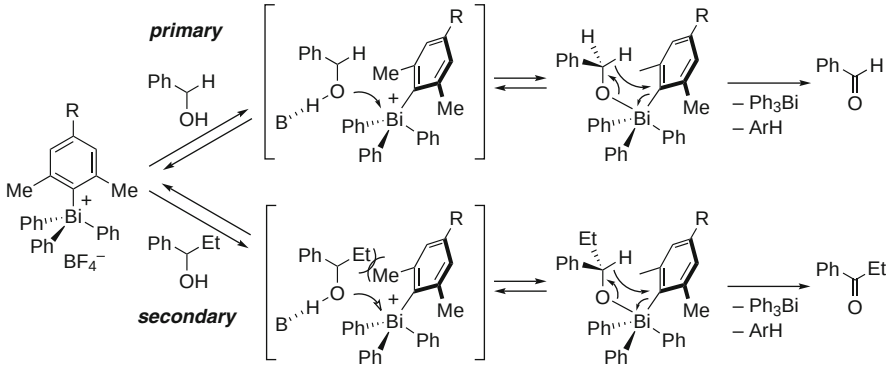

| entry | alcohol | solvent | yield/% |
|---|---|---|---|
| 1 |  | $CH_2Cl_2$ | 95 |
| 2 |  | $CH_2Cl_2$ | 99 |
| 3 |  | $CH_2Cl_2$ | 96 |
| 4 |  | toluene | 88 |
| 5 | | toluene | 88 |

**Scheme 22** Oxidation of alcohols with 2,6-xylyltriphenylbismuthonium salt [89, 90]

The bulky tetraarylbismuthonium salts were found to oxidize primary alcohols far more rapidly than secondary alcohols (Scheme 23). The primary/secondary selectivity achieved by the mesitylbismuthonium salt increases as the bulkiness of the α-substituents of the alcohols increases (Me < Et < *i*-Pr). This suggests that the α-substituents of the alcohol retard the nucleophilic attack on the bismuth center kinetically. The $PhCH_2OH$/PhCH(Et)OH selectivity observed for the mesityl- and 2,6-xylyl-bismuthonium salts (each 92/8) is considerably higher than the selectivities observed for the triphenyl(*o*-tolyl)bismuthonium salt (77/23), tris(*o*-tolyl)bismuth dichloride (63/37), and Dess–Martin periodinane (67/33). Obviously, the bulky bismuthonium salts discriminate between the steric bulkiness of the alcohol substrates efficiently.




| entry | R | $R^1$, $R^2$ | PhCHO/PhCOR |
|---|---|---|---|
| 1 | Me | Me, Me | 81/19 |
| 2 | Et | Me, Me | 92/8 |
| 3 | *i*-Pr | Me, Me | 94/6 |
| 4 | Et | Me, H | 92/8 |
| 5 | Et | H, H | 77/23 |




**Scheme 23** Competitive oxidations between primary and secondary benzyl alcohols by using the bulky bismuthonium salts [90]

## 6 Photoinduced Cationic Polymerization of Oxiranes

Photoinduced cationic polymerization (PICP) is a useful technique for curing with UV–visible light and has been the subject of numerous industrial and academic polymer chemistry studies [91–96]. Among the components of a typical PICP system, the photoinitiators play a crucial role in determining the efficiency of the polymerization processes because they are responsible for the generation of protic or Lewis acids via photodecomposition by UV–visible light. To date, several types of photoinitiators have been developed, among which triarylsulfonium and diaryliodonium salts are the most widely used cationic photoinitiators [91–96]. These onium salts undergo E–C bond homolysis [E = S(IV), I(III)] at their excited states and/or electron transfer from photoexcited sensitizers. Irrespective of the initial activation steps, plausible S(III) and I(II) intermediates abstract hydrogen atoms from the reaction media, followed by a reductive elimination of the S(II) and I(I) species. Overall, the abstracted hydrogen is formally oxidized to a proton, which initiates a cationic polymerization of the electron-rich monomers such as oxiranes and vinyl ethers.

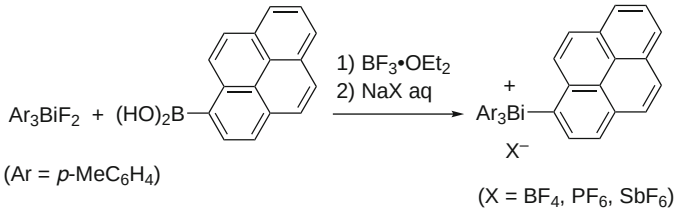
For efficient onium-based PICP systems, the initiators should satisfy the following prerequisites:

1. Low toxicity
2. Large absorption coefficients and high reduction potentials (highly absorbent and oxidizing)
3. Small E–C bond dissociation energy for cleavage under photoirradiation conditions
4. High quantum yields of proton generation
5. Reasonably high thermal stability

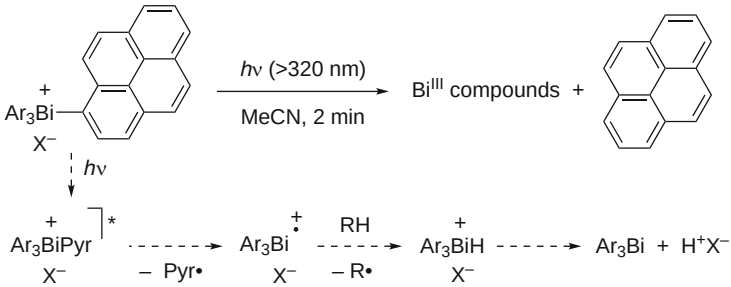
In this context, tetraarylbismuthonium salts are promising candidates because the characteristic properties of bismuth fulfill the above prerequisites. With this in mind, the first organobismuth(V)-based PICP system was recently investigated [97].

1-Pyrenyltriarylbismuthonium salts were designed to absorb intense light at 365 nm emitted from a high-pressure Hg arc lamp. Tetrafluoroborate, hexafluorophosphate, and hexafluoroantimonate were prepared in high yield by a $BF_3$-promoted metathesis reaction of triarylbismuth difluorides with 1-pyrenylboronic acid followed by anion exchange with the corresponding sodium salts (Scheme 24). X-ray crystallographic analysis of the hexafluoroantimonate revealed that the bismuth center adopts a distorted tetrahedral geometry with a spatially separated counter anion.

All the 1-pyrenylbismuthonium salts photochemically decompose ($\lambda_{ex} > 320$ nm; $I > 150$ mW cm$^{-2}$) to generate their respective protic acids, accompanied by the formation of bismuth(III) compounds and pyrene (Scheme 25). The quantum yields of the photodecomposition ($\Phi_{dec}$) in acetonitrile were determined by chemical actinometry to be 0.20–0.22. These values are comparable to the values reported for the triarylsulfonium and diaryliodonium salts ($\Phi_{dec} = 0.17$–$0.22$) [98, 99].



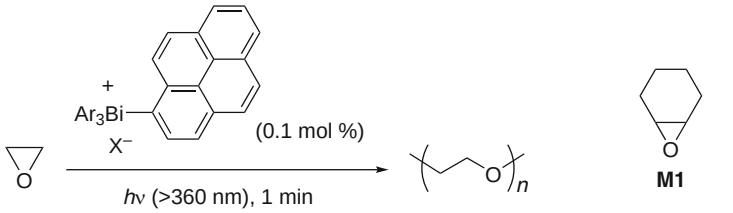

**Scheme 24** Synthesis of 1-pyrenyltriarylbismuthonium salts [97]




**Scheme 25** Photochemical decomposition of 1-pyrenylbismuthonium salts [97]

A plausible mechanism for the photodecomposition of the bismuthonium salts is shown in Scheme 25. A part of the excited bismuthonium salt undergoes Bi–C (pyrenyl) bond cleavage to generate a bismuth(IV) radical cation and a pyrenyl radical. It is probable that the π–π* transition of the pyrenyl moiety weakens the Bi–C(pyrenyl) bond selectively. The generated bismuth(IV) species should thus be highly reactive and it promptly generates a protic acid ($H^+X^-$) via hydrogen abstraction or proton-coupled electron transfer with the reaction media, accompanied by an elimination of triarylbismuthane. On the other hand, the pyrenyl radical probably abstracts a hydrogen atom from the media to afford pyrene. It must be emphasized that the pyrenylbismuthonium salts do not decompose in the dark.

Scheme 26 summarizes the results of the photoinduced cationic polymerization of some oxiranes using a series of 1-pyrenylbismuthonium salts as initiators [97]. In the absence of a bismuthonium salt, cyclohexene oxide (CHO) does not polymerize at all. In contrast, the polymerization of CHO takes place in the presence of 0.1 mol% hexafluoroantimonate or hexafluorophosphate under photoirradiation (365 nm) for 1 min, affording poly(cyclohexene oxide) (*poly*-CHO) (Scheme 26, entries 1,2). The number-average molecular weight ($M_n$) and polydispersity index (PDI) of *poly*-CHO were found to be 8,900–9,500 and 1.3–1.2, respectively. The yield of *poly*-CHO was found to decrease as follows: $SbF_6$ (88%) > $PF_6$ (41%) >> $BF_4$ (<1%), indicating that the efficiency of the cationic polymerization depends significantly on the counter anion (Scheme 26, entries 1–3). This is probably because less nucleophilic anions increase the stability of the carbenium ion intermediates generated in the chain-propagating step. The other oxiranes were also polymerized under similar irradiation




| entry | X | Monomer | Yield/% | $M_n$ (PDI) |
|---|---|---|---|---|
| 1 | $SbF_6$ | **M1** | 88 | 9500 (1.2) |
| 2 | $PF_6$ | **M1** | 41 | 8900 (1.3) |
| 3 | $BF_4$ | **M1** | <1 | – (–) |
| 4 | $SbF_6$ | **M2** | 48 | 7800 (1,2) |
| 5 | $SbF_6$ | **M3** | 90 | 15800 (1.4) |

**Scheme 26** Photoinduced cationic polymerization of oxiranes using 1-pyrenyltriarylbismuthonium salts [97]

conditions using 0.1–0.5 mol% hexafluoroantimonate to give the corresponding polymers in moderate to good yields within a minute (Scheme 26, entries 4,5).

## 7 Summary and Overview

Organobismuth(V) compounds possess at least three appealing features as potential reagents in organic synthesis. The first is their excellent oxidizing ability, a facile Bi(V)-to-Bi(III) redox process. This characteristic property of bismuth basically arises from the "inert pair effect." In terms of organic synthesis, the extremely high leaving ability of the triarylbismuthonio groups is exemplified throughout this chapter. The second feature is the high nucleofugality of the bismuth(V) center in the hypervalent and the onium-type compounds. This property allows for a feasible attack of the nucleophiles on the bismuth center or the adjacent positively charged carbons. The third feature is the weakness of the bismuth–carbon bonds. This fundamental property is evident in the thermal as well as photochemical reactions. In terms of atom efficiency, the use of a catalytic amount of organobismuth reagents is highly desirable. In this regard, the bismuth-based catalysts or initiators can be applied to radical, cationic, and anionic polymerizations. Recently, Yamago and coworkers developed several types of organobismuth(III) initiators for the living-radical polymerization of olefins [100–102], and my group has demonstrated the

potential utility of organobismuth(V) initiators for cationic photopolymerization, as shown in Sect. 6 [97]. Hopefully, the heavy-atom effects of pentavalent bismuth can be further utilized in organic synthesis and materials chemistry.

**Acknowledgements** I deeply thank my coworkers, whose names are listed in the references, for their significant contribution to the chemistry described herein. Most of the research projects were supported by the Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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# Environmentally Friendly Organic Synthesis Using Bismuth(III) Compounds

**Scott W. Krabbe and Ram S. Mohan**

**Abstract** With increasing environmental concerns, the need for environmentally friendly organic synthesis has gained increased importance. In this regard, bismuth (III) compounds are especially attractive as "green" reagents and catalysts for organic synthesis. Bismuth(III) compounds are remarkably nontoxic, relatively air and moisture stable, and easy to handle. The contributions from our laboratory in the last 5 years in the field of applications of bismuth(III) compounds as catalysts are presented.

**Keywords** Acetals, Acylals, Allylations, Bismuth(III), 3,4-Dihydro-2*H*-1-benzopyrans, Ene reactions, Epoxide-olefin cyclizations, Piperidines, Tetrahydroquinolines, THP ethers

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## 1 Introduction

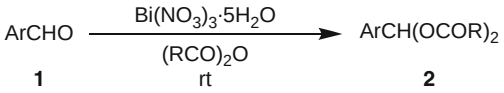
The last decade has seen a remarkable growth in the field of bismuth(III) chemistry [1–7]. This interest in bismuth and its compounds can be attributed to several attractive features that bismuth(III) compounds possess – they are remarkably nontoxic and hence attractive from a "green" chemistry perspective. In addition, many bismuth(III) compounds are reasonably tolerant of small amounts of air and moisture, are noncorrosive and relatively inexpensive. This chapter highlights our work with bismuth(III) compounds. Work that has already been published (Sects. 1–4) is summarized briefly while more recent (Sects. 5 and 6) is discussed in more detail.

## 2 Synthesis of Acylals

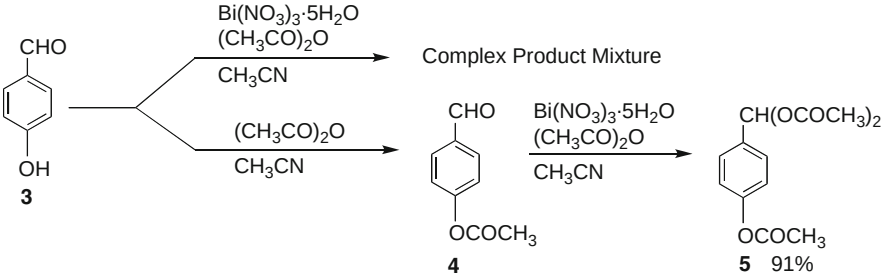
Acylals (geminal diacetates) are frequently used as protecting groups for aldehydes because of their stability to neutral and basic conditions [8]. In addition, the acylal functionality can be converted into other useful functional groups [9]. For example a novel synthesis of chiral allylic esters has been developed using palladium-catalyzed asymmetric allylic alkylation of *gem*-diesters [10]. The allylation of 1,1-diacetates to yield homoallyl esters has also been reported [11, 12]. We first reported the use of bismuth triflate [bismuth trifluoromethanesulfonate, $Bi(OTf)_3$] as a catalyst for acylal formation from aldehydes [13]. The search for a less corrosive and cheaper catalyst led to the discovery of bismuth(III) nitrate as a catalyst for acylal formation [14]. The reaction works well with a range of aromatic aldehydes in $CH_3CN$ as a solvent (Table 1).

A moderate yield of the corresponding acylal was obtained from 4-*tert*-butyldimethylsilyloxybenzaldehyde (Table 1, entry 7). Deprotection of the 4-*tert*-butyldimethylsilyl (TBDMS) group occurred to the extent of 15% while tetrahydropyranyl (THP) ethers proved unstable to the reaction conditions. The formation of acylals from activated aromatic aldehydes proved problematic. For example, the reaction of *p*-anisaldehyde with acetic anhydride in the presence of bismuth nitrate gave a complex product mixture. The less activated *m*-anisaldehyde gave a moderate yield of the corresponding acylal. Similarly, *p*-hydroxybenzaldehyde gave a complex product mixture but when it was first converted to *p*-acetoxybenzaldehyde, the corresponding acylal could be obtained in 91% yield (Scheme 1).

**Table 1** Formation of acylals using $Bi(NO_3)_3{\cdot}5H_2O$

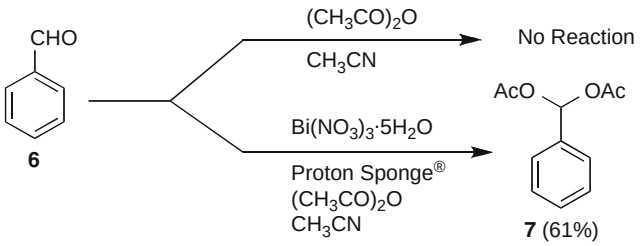



| Entry | Ar | R | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | Ph | $CH_3$ | 1.5 | 87 |
| 2 | $p$-$ClC_6H_4$ | $CH_3$ | 3 | 76 |
| | | $n$-Pr | 4 | 80 |
| | | $i$-Pr | 15 | 82 |
| 3 | $p$-$CH_3C_6H_4$ | $CH_3$ | 2.5 | 79 |
| 4 | $m$-$NO_2C_6H_4$ | $CH_3$ | 2.5 | 85 |
| 5 | $m$-$CH_3OC_6H_4$ | $CH_3$ | 15 | 57 |
| 6 | | $CH_3$ | 6 | 82 |
| 7 | $p$-$Me_2{}^tBuSiOC_6H_4$ | $CH_3$ | 14 | 59 |




**Scheme 1** Effect of a catalyst on acetylation of $p$-hydroxybenzaldehyde

Control studies suggested that with activated aldehydes ring nitration occurred to the extent of 10–20%. In contrast to aromatic aldehydes, aliphatic aldehydes reacted sluggishly even under solvent-free conditions. The reaction of a variety of aldehydes such as heptanal, hexanal, and phenylpropionaldehyde with acetic anhydride gave the expected acylal, unreacted aldehyde, and some unidentifiable products. The side products were not consistent with aldol condensation products of the aldehyde or the corresponding enol acetate that could arise from elimination of the expected acylal. Under the reaction conditions, ketones did not undergo any reaction and could be recovered unchanged. The reaction also worked with other anhydrides including butyric anhydride and isobutyric anhydride although most methods described in the literature for acylal formation employ only acetic anhydride. It was difficult to separate the unreacted butyric anhydride and isobutyric anhydride from the corresponding acylal product. The hydrolysis of higher anhydrides with aqueous $Na_2CO_3$ is also considerably slower than the hydrolysis of acetic anhydride due to solubility problems. A practical solution to this problem




**Scheme 2** Bismuth(III) nitrate-catalyzed synthesis of an acylal

was found by using methanol/aqueous $Na_2CO_3$ in the work-up. Pivalic anhydride and benzoic anhydride proved to be too unreactive at room temperature and significant reaction was not observed at higher temperatures. When bismuth nitrate is heated, it undergoes decomposition accompanied by the formation of a brown gas ($NO_2$). Therefore, all the reactions were carried out at room temperature.

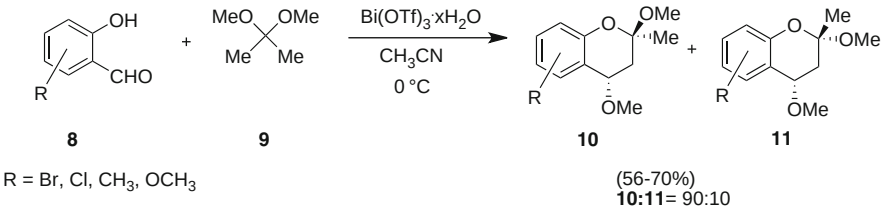
Although detailed mechanistic studies were not carried out, a few points merit comment and are summarized in Scheme 2.

The possibility that the reaction is catalyzed by nitric acid released from bismuth nitrate pentahydrate in $CH_3CN$ was considered. A suspension of bismuth nitrate in water as well as $CH_3CN$ is acidic (pH = 2). However, the reaction of benzaldehyde with acetic anhydride using 0.6 equivalents of $HNO_3$ did not afford the desired acylal in good yield. Even when the amount of $HNO_3$ was increased to 1.2 equivalents the starting aldehyde was recovered unchanged. The reaction of benzaldehyde with acetic anhydride catalyzed by bismuth nitrate in the presence of a proton-sponge® (*N*,*N*,*N*′,*N*′-tetramethyl-1,8-diaminonaphthalenediamine) was also carried out [15]. Although the reaction was slow, the desired product was formed in 61% yield after chromatographic purification. The lower yield was attributed to difficulty in separating the proton-sponge from the acylal product as well as the small scale of the reaction.

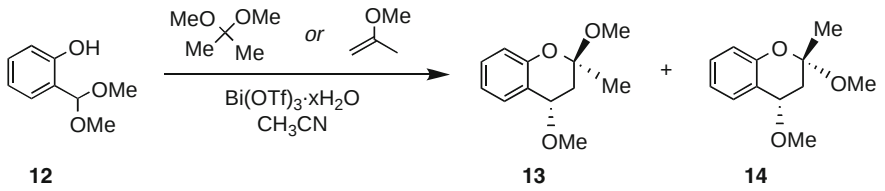
## 3 Synthesis of Heterocycles Using Bismuth(III) Compounds as Catalysts

### *3.1 Bismuth Triflate-Catalyzed Synthesis of Substituted 3,4-Dihydro-2*H*-1-Benzopyrans*

The dihydro-2*H*-1-benzopyran skeleton is found in many biologically active compounds. Such moieties have also been used in the synthesis of other biologically active molecules [16–18]. Hence their synthesis has received attention. Some catalysts used for formation of dihydro-2*H*-1-benzopyran include $(Ph_3P)_2PdCl_2$, [19] $I_2$ [20], and $Sc(OTf)_3$ [21]. Few of these methods are highly catalytic in nature or have been reported to use environmentally friendly reagents. For example,




**Scheme 3** Bismuth(III) triflate-catalyzed synthesis of substituted 3, 4-dihydro-2*H*-1-benzopyrans



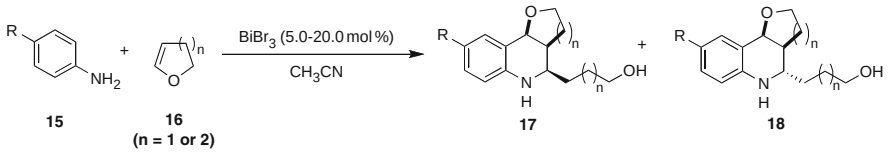

**Scheme 4** Bismuth(III) triflate-catalyzed synthesis of substituted 3, 4-dihydro-2*H*-1-benzopyrans using an acetal intermediate

$I_2$ vapor is extremely corrosive while scandium compounds are moisture-sensitive and very expensive. In addition, these reactions are carried out in an environmentally unfriendly solvent, $CH_2Cl_2$. We have reported the bismuth triflate-catalyzed synthesis of substituted dihydro-2*H*-1-benzopyrans by the condensation of substituted salicylaldehydes with 2,2-dimethoxypropane (Scheme 3) [22].

Although one diastereomer **10** was largely favored, the product was obtained as a mixture of diastereomers, and the previously unreported minor diastereomer **11** was also characterized. The stereochemistry of the products was established by nuclear Overhauser effect (NOE) studies. A plausible mechanism assumes the intermediacy of an acetal, and its reaction with 2-methoxypropene generated from 2,2-dimethoxypropane [20]. In order to test this mechanism, the dimethyl acetal of salicylaldehyde was synthesized and reacted independently with both 2,2-dimethoxypropane and 2-methoxypropene. Indeed, both reactions gave the same products as those from the reaction of salicylaldehyde with 2,2-dimethoxypropane (Scheme 4). The condensation of salicylaldehyde and 2,2-dimethoxypropane was also carried out in $CD_3CN$ and reaction progress was followed by $^1H$ NMR spectroscopy. This experiment also confirmed the formation of the acetal from salicylaldehyde (δ 5.52, singlet, C*H*$(OMe)_2$).

## *3.2 Bismuth(III) Bromide-Catalyzed Synthesis of Substituted Tetrahydroquinoline Derivatives*

Substituted tetrahydroquinoline derivatives are of considerable interest due to the range of their biological activities and presence in a variety of natural products




**Scheme 5** Bismuth(III) bromide-catalyzed synthesis of substituted tetrahydroquinoline derivatives

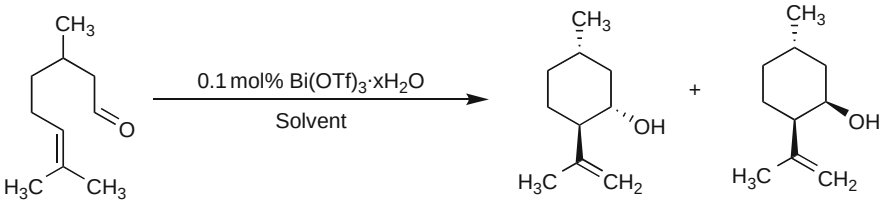
[23, 24]. The tetrahydroquinoline skeleton is also found in many compounds that have been tested as potential drugs [25, 26]. In addition to their biological properties, the tetrahydroquinolines have also generated interest because of their applications as pesticides [27], antioxidants [28], and in several dyes [29–31]. Their use as photosensitizers in photography has also been reported [32]. Hence, considerable efforts have been directed towards methods for their efficient synthesis [33]. One approach to their synthesis involves the Lewis acid-catalyzed cycloaddition reaction between an imine and an aldehyde. Often the imine is generated in situ from an aldehyde and an amine. Povarov and coworkers have described a synthesis of tetrahydroquinolines in which the imine, formed in situ from a substituted aniline and an enol ether, undergoes the Diels–Alder reaction with a second equivalent of the enol ether [34]. Several reagents have been utilized to catalyze such reactions. These include $Yb(OTf)_3$ [35], $Ln(OTf)_3$ [36], $Sc(OTf)_3$ [35], $Dy(OTf)_3$ [37], $InCl_3$ [38, 39], $AlCl_3$ [40], $FeCl_3$–NaI [41], $I_2$ [42], ceric ammonium nitrate [43–45], and trimethyl silyl (TMS)Cl–NaI [46]. Many of these catalysts are corrosive ($AlCl_3$, $I_2$), toxic ($InCl_3$), or very expensive (e.g., 5.0 g of scandium triflate costs US $169, and 5.0 g of dysprosium triflate costs US $60). An uncatalyzed synthesis of tetrahydroquinolines in hexafluoroisopropanol has also been reported [47]. However, the use of a toxic and corrosive solvent (hexafluoroisopropanol) detracts from the utility of this procedure. Our continued interest in bismuth compounds prompted us to investigate a bismuth(III) bromide-catalyzed synthesis of tetrahydroquinoline derivatives. Bismuth bromide was found to be an efficient catalyst for the synthesis of trisubstituted tetrahydroquinolines via a coupling reaction between substituted anilines and dihydrofuran or dihydropyran (Scheme 5) [48].

# 4 Cyclization Reactions Using Bismuth(III) Triflate as a Catalyst

## *4.1 Bismuth(III) Triflate-Catalyzed Carbonyl Ene Reactions*

The intramolecular carbonyl ene reaction is a useful way to generate a C–C bond and has been well studied [49–52]. Of particular interest is the cyclization of citronellal to yield isopulegol, an important intermediate in an industrial synthesis

**Table 2** Cyclization of citronellal catalyzed by $Bi(OTf)_3 \cdot xH_2O$ [22]




**19** **20** **21**

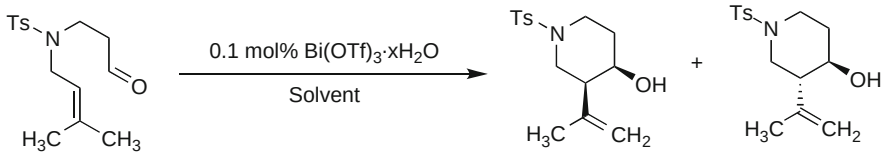
| Entry | Catalyst | Catalyst loading (mol%) | Solvent (temperature)[a] | Time[b] (min) | Ratio of yields **20:21** |
|---|---|---|---|---|---|
| 1 | $Bi(OTf)_3 \cdot xH_2O$ | 0.10 | $CH_2Cl_2$ | 5 | 78:22 |
| 2 | $Bi(OTf)_3 \cdot xH_2O$ | 1.0 | $CH_2Cl_2$ (−78 °C) | 60 | 79:21 |
| 3 | $Bi(OTf)_3 \cdot xH_2O$ | 1.0 | THF | 10 | 52:48 |
| 4 | $Bi(OTf)_3 \cdot xH_2O$ | 1.0 | DME | 50 | 61:39[d] |
| 5 | $Bi(OTf)_3 \cdot xH_2O$ | 1.0 | $CH_3CN$ | 300 | NR[e] |
| 6 | $Bi(OTf)_3 \cdot xH_2O$ | 1.0 | Toluene | 10 | 68:32 |
| 7 | $Yb(OTf)_3 \cdot xH_2O$ | 10.0 | $CH_2Cl_2$ | 60 | 78:22 |

[a]All reactions were carried out at room temperature using racemic citronellal unless stated otherwise. Citronellal was purified by distillation or flash chromatography prior to use
[b]Reaction progress was followed by GC and TLC
[c]Ratios were obtained by GC analysis of the crude reaction mixture. Products were separated and isolated by flash chromatography. Products were identified by comparison of their $^1H$ and $^{13}C$ NMR spectra with those reported in the literature. Typical isolated yields were 35–40% of **20** and 10–12% of **21**
[d]Crude product contained 39% unreacted citronellal
[e]No reaction; starting material was recovered unchanged

of menthol. The selectivity of this cyclization depends on the Lewis acid, solvent, and reaction temperature. Bismuth triflate (0.1 mol%) was found to be a highly efficient catalyst for the cyclization of citronellal **19**, a reaction that yields isopulegol **20** and neoisopulegol **21** in an 80:20 ratio, respectively (Table 2).

An attempt to see if complexation of the carbonyl group in citronellal to bismuth triflate induces a shift in the NMR signal was unsuccessful due to fast reaction times. The cyclization of citronellal in $CDCl_3$ catalyzed by 0.1 mol% $Bi(OTf)_3 \cdot xH_2O$ was complete in less than 5 min at room temperature (rt). The best selectivity was obtained in $CH_2Cl_2$ (Table 2, entries 1 and 2), while the use of tetrahydrofuran (THF) (Table 2, entry 3) gave a ca. 50:50 ratio of **20**:**21**. At −78 °C, the reaction in $CH_2Cl_2$ proceeded smoothly in the presence of 1.0 mol% $Bi(OTf)_3 \cdot xH_2O$ (Table 2, entry 2). However, no change in the ratio of isopulegol to neoisopulegol was observed even at this low temperature. The cyclization also worked in dimethylether (DME) and toluene but no reaction was observed in $CH_3CN$. In contrast to the high catalytic efficiency of $Bi(OTf)_3 \cdot xH_2O$, ytterbium triflate (Table 2, entry 7) proved less efficient, and required a catalytic loading of 10.0 mol% and a reaction time of 1 h. Other reported catalysts for this cyclization are

**Table 3** Synthesis of substituted piperidines catalyzed by $Bi(OTf)_3{\cdot}xH_2O$




**22** **23** **24**

| Entry | Catalyst | Catalyst loading (mol%) | Solvent (temperature) | Time[b] (min) | Ratio of yields **23**:**24**[c] |
|---|---|---|---|---|---|
| 1 | $Bi(OTf)_3{\cdot}xH_2O$ | 0.1 | $CH_2Cl_2$ | 10 | 70:30 |
| 2 | $Bi(OTf)_3{\cdot}xH_2O$ | 5.0 | $CH_2Cl_2$ (−70 °C) | 120[d] | 67:33 |
| 3 | $Bi(OTf)_3{\cdot}xH_2O$ | 1.0 | $CH_2Cl_2$ | 10 | 67:33 |
| 4 | $Bi(OTf)_3{\cdot}xH_2O$ | 1.0 | THF | 25 | 72:28 |
| 5 | $Yb(OTf)_3{\cdot}xH_2O$ | 20.0 | $CH_2Cl_2$ | 360[e] | 59:41 |
| 6 | TMSOTf | 1.0 | [bmim][OTf] (230 °C) | 5 | 40:60 |

[a]All reactions were carried out at room temperature unless stated otherwise
[b]Reaction progress was followed by TLC
[c]Ratios were obtained by NMR analysis of the crude reaction product as described in [21]. Products were separated and isolated by flash chromatography. Products were identified by comparison of their $^1H$ and $^{13}C$ NMR spectra with those reported in the literature [56]
[d]Crude product contained 35% unreacted starting material
[e]Crude product contained 43% unreacted starting material

also not nearly as efficient as bismuth triflate (e.g., equimolar amounts of $ZnBr_2$ [53], 5.0 mol% $Sc(OTf)_3$ [54], 10.0 mol% $NbCl_5$ [55]). Although $ZnBr_2$ gave the best stereoselectivity (94% isopulegol), $NbCl_5$ only afforded a 50:50 ratio of **20**:**21**. Scandium triflate afforded a ratio of **20**:**21** that was similar to that obtained with bismuth triflate at room temperature. However, in contrast to $Bi(OTf)_3{\cdot}xH_2O$, at −78 °C, Sc $(OTf)_3$ gave a 94:6 mixture of **20**:**21**.

We also extended this methodology to the intramolecular ene reaction of aldehyde **22** to synthesize substituted piperidines **23** and **24** (Table 3).

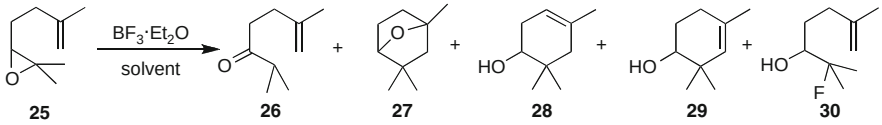
These cyclizations have been previously carried out with several catalysts, including $MeAlCl_2$, HCl, $AlCl_3$, $Sc(OTf)_3$, $SnCl_4$, and $CF_3SO_3H$ [56]. In addition to being highly corrosive, most of these reagents are not very catalytic (10–50 mol% was required) and some like HCl were used in excess [56]. We reported an efficient synthesis of 3,4-disubstituted piperidines catalyzed by as little as 0.1 mol% bismuth triflate. The intramolecular ene reaction of **22** afforded a 67:33 mixture of substituted piperidines **23** and **24**, respectively. It has been reported that the use of 30 mol% $MeAlCl_2$ [56] at −78 °C afforded a 70:30 ratio of **23**:**24**, while the use of 50 mol% $Sc(OTf)_3$ gave a 50:50 mixture of **23**:**24**. Thus, bismuth triflate (0.1 mol%) has proven to be remarkably efficient for this type of ene cyclization. Interestingly, the major product of cyclization of **22** with bismuth triflate is the *cis* isomer **23**, unlike the cyclization of citronellal, which afforded isopulegol, the *trans* isomer as the major product. Both **23** and **24** were separable by flash chromatography.

## 4.2 Bismuth(III) Triflate-Catalyzed Olefin-Epoxide Cyclizations

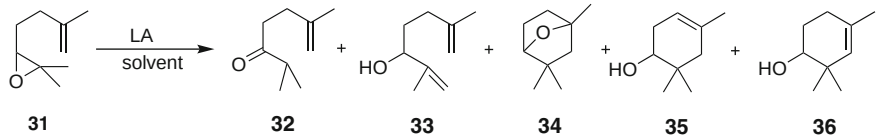
The cyclization of epoxyolefins has been the subject of intense study ever since the discovery that these reactions are involved in the biosynthesis of many terpenes, including cholesterol. An early example is the cyclization of geraniolene oxide **25** using $BF_3{\cdot}Et_2O$ to give a mixture of acyclic and cyclic products (Scheme 6) [57, 58].

A classic example of such a cyclization was first reported by van Tamelen who demonstrated that squalene 2,3-epoxide is an intermediate in the enzymatic cyclization of squalene to lanosterol and cholesterol [59–66]. Epoxyolefin cyclizations have been used to advantage in the synthesis of natural products such as *d,l*-malabaracanediol [67], (±)-martimol [68], (±)-karahana ether [69] and (+)-aphidicolin [70]. The cyclization of epoxy-silanes has been investigated using $TiCl_4$ [71, 72]. Epoxyolefin cyclizations have also been initiated by $MeAlCl_2$ [58] and bis(4-bromo-2,6-di-*tert*-butylphenoxide) [73]. However, most of the catalysts that have been used for epoxyolefin cyclizations are highly corrosive, toxic, and difficult to handle [74]. In addition, not many have been employed under highly catalytic conditions (ca. 0.1 mol% catalyst). An added problem with Lewis acids containing a nucleophilic anion is that products can arise from attack by the anion on the epoxide. For example, when geraniolene oxide **25** is treated with $BF_3{\cdot}Et_2O$, a significant amount of the fluorohydrin (Scheme 6, **30**) is obtained [57, 58]. In spite of their demonstrated versatility, metal triflates have not been used as catalysts for epoxyolefin cyclizations. We have shown that bismuth trifluoromethanesulfonate as well as several other metal triflates are highly effective (0.1 mol%) catalysts for the cyclization of geraniolene oxide (Scheme 7).

The reaction was also catalyzed by 0.10 mol% triflic acid and the ratio of products was essentially the same as that obtained with the metal triflates. This observation raised the possibility that the reactions in the presence of metal triflates are actually catalyzed by triflic acid, released in situ by hydrolysis of the metal triflates by any water present in the solvent, especially since anhydrous solvents were not used (Markó and coworkers have studied the role of triflic acid in metal




**Scheme 6** Cyclization of geraniolene oxide catalyzed by boron trifluoride etherate



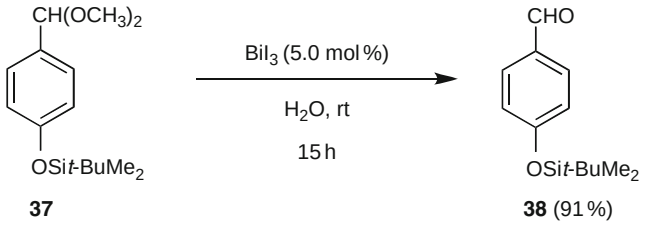

**Scheme 7** Cyclization of geraniolene oxide catalyzed by Lewis acids

catalyzed acylations [75]). In order to test this hypothesis, the $Bi(OTf)_3 \cdot xH_2O$ catalyzed reaction of geraniolene oxide was carried out in the presence of solid $K_2CO_3$ as well as a proton-sponge® (*N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine). It was found that no reaction occurred even after 24 h in the presence of the proton-sponge® and that the addition of $K_2CO_3$ had no effect on the reaction. In order to test the efficacy of $K_2CO_3$ in neutralizing any triflic acid generated in situ, geraniolene oxide **31** was treated with 0.1 mol% $CF_3SO_3H$ in the presence of $K_2CO_3$. In this case, no reaction was observed and the starting material was recovered. These observations suggest that bismuth triflate is indeed acting as a Lewis acid and presumably initiates the reaction by complexing with the epoxide oxygen[1] [76]. The inactivity of bismuth triflate in the presence of the proton sponge is probably due to the complexation of bismuth to the amine nitrogens. These results are in contrast to those obtained with bismuth nitrate-catalyzed synthesis of acylals where the proton-sponge did not affect the reaction. With $Bi(OTf)_3 \cdot xH_2O$ as the Lewis acid, it was found that the amount of cyclization product was dependent on concentration. When the reaction is carried out under high dilution conditions, greater percentages of cyclized products **34**, **35** and **36** are obtained. A lower reaction temperature, however, only marginally favors the cyclization products.

## 5 Bismuth(III) Iodide-Catalyzed Deprotection of Acetals

The deprotection of acetals is an important step in organic synthesis due to the wide application of acetals, especially in the course of a total synthesis [8]. Hence many reagents have been developed for this purpose (*p*-TsOH/acetone [77], 50% trifluoroacetic acid in $CHCl_3$-$H_2O$ [78], $LiBF_4$ [79], Amberlyst-15/aqueous acetone [80], aqueous DMSO [81], $Bi(NO_3)_3 \cdot 5H_2O$ [82, 83]). Considerable efforts have also been directed towards developing mild and selective methods for acetal deprotection ($TiCl_4$ [84], $FeCl_3 \cdot 6H_2O$ on silica gel [85], $Ph_3P/CBr_4$ [86], $CeCl_3$ [87], $FeCl_3 \cdot 6H_2O$ [88], $TMSN(SO_2F)_2$ [89], ceric ammonium nitrate [90], $Bi(OTf)_3 \cdot 4H_2O$ [91, 92], β-cyclodextrin [93], $HClO_4$/silica gel [94], $I_2$ [95], $CuSO_4$/NaI [96]). Bismuth iodide is a stable, commercially available solid that has been underutilized in organic synthesis [97–101]. Bismuth iodide was found to be an efficient catalyst for the deprotection of a wide range of acetals in water as the solvent. Under the reaction conditions, TBDMS ethers did not undergo deprotection (Scheme 8). Such chemoselectivity is especially useful in the course of a total

[1] We have previously reported that when the rearrangement of *trans*-stilbene oxide was carried out with $CF_3SO_3H$, the solution turned red and the product diphenylacetaldehyde was less pure than that obtained with bismuth triflate. This observation points to the role of bismuth(III) triflate as a Lewis acid in the rearrangement of epoxides and not to protic acid catalysis by triflic acid released by hydrolysis of bismuth triflate.




**Scheme 8** Bismuth(III) iodide-catalyzed chemoselective deprotection of an acetal

synthesis where selective deprotection of protecting groups is often necessary. Control studies using proton scavengers suggested that the active catalyst is HI.

## 6 Bismuth(III) Triflate-Catalyzed Synthesis of Dioxolanes, Dioxanes, and Dioxepines

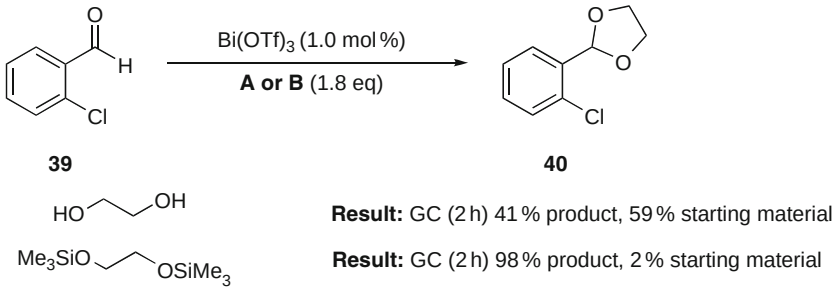
Cyclic acetals are useful and common protecting groups for aldehydes and ketones, especially during the course of a total synthesis [8]. The successful synthesis of acetals frequently relies on the removal of water, a by-product of the reaction between the carbonyl compound and the corresponding diol. A Dean–Stark trap is often used for the removal of water as an azeotrope with benzene, but this method is not suitable for small-scale reactions. In addition, the highly carcinogenic nature of benzene makes it an undesirable solvent. Many of the reported catalysts for acetal synthesis such as *p*-toluenesulfonic acid and boron trifluoride etherate are toxic and corrosive.

We developed a method for the synthesis of a variety of cyclic acetals that utilizes bismuth triflate as a catalyst and does not require the use of a Dean–Stark trap for removal of water [102]. In this method, an aldehyde or ketone is treated with 1, 2-bis (trimethylsiloxy)ethane in the presence of bismuth triflate. A comparison study using *o*-chlorobenzaldehyde showed that with ethylene glycol a low conversion to the dioxolane was observed after 2 h whereas the use of the 1,2-bis(trimethylsiloxy) ethane afforded the corresponding dioxolane in good yields. (Scheme 9).

The results of this study are summarized in Table 4. The product is isolated by filtration of the reaction mixture through a silica column, thus avoiding an aqueous waste stream.

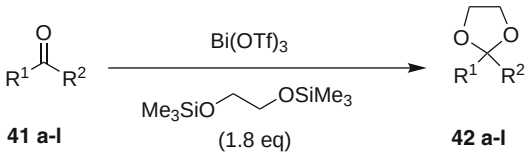
Extension of this methodology to the synthesis of 1,3-dioxanes was not facile because 1,3-bis(trimethylsiloxy)propane is not commercially available. Although 1,3-bis(trimethylsiloxy)propane was synthesized [103], its use in the synthesis of dioxanes required higher catalyst loadings in comparison to the use of 1,2-bis (trimethylsiloxy)ethane in dioxolane synthesis. Hence, 1,3-propanediol was used instead to generate the cyclic acetals, and the water by-product was removed using triethyl orthoformate (Table 5).

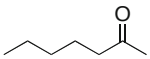
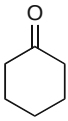
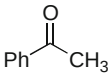
This methodology was also applicable to the synthesis of dioxepines from aldehydes and *cis*-2-butene-1, 4-diol (Table 6).




**Scheme 9** Bismuth(III) triflate-catalyzed synthesis of dioxolanes

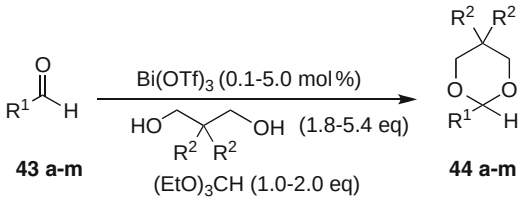
**Table 4** Synthesis of dioxolanes catalyzed by $Bi(OTf)_3$

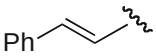
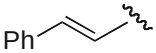



| Entry | $R^1$ | $R^2$ | $Bi(OTf)_3$ loading (mol%) | Time[a] | Yield[b,c] (%) |
|---|---|---|---|---|---|
| a | *o*-$ClC_6H_4$ | H | 1.0 | 4 h | 84[a,d] |
| b | *p*-$ClC_6H_4$ | H | 0.1 | 1 h 40 min | 95 |
| c | *o*-$BrC_6H_4$ | H | 0.1 | 1 h 30 min | 93 |
| d | *m*-$BrC_6H_4$ | H | 0.1 | 1 h 15 min | 97 |
| e | *p*-$NO_2C_6H_4$ | H | 0.1 | 1 h 20 min | 91[e] |
| f | *p*-$CH_3C_6H_4$ | H | 0.1 | 2 h 10 min | 86[d] |
| g | *p*-$CH_3OC_6H_4$ | H | 1.0 | 41 h | 85[f] |
| h | 2,4-$Cl_2C_6H_3$ | H | 1.0 | 2 h 5 min | 88 |
| i | $CH_3(CH_2)_8$ | H | 0.1 | 14 h | 94 |
| j |  | $R^2 = CH_3$ | 1.0 | 2 h | 85[d] |
| k |  | | 1.0 | 1 h 35 min | 84[d] |
| l |  | $R^2 = CH_3$ | 1.0 | 6 h 30 min | 89 |

[a]Reaction progress was followed by GC or TLC
[b]Refers to yield of pure, isolated product. All products were >98% pure unless stated otherwise
[c]New compounds were characterized by $^1H$ and $^{13}C$ NMR spectroscopy, and HRMS
[d]Product was isolated by direct filtration of the reaction mixture through a silica gel column
[e]Reaction was carried out in toluene at 100 °C (oil bath)
[f]Crude product was 94% pure by GC and $^1H$ NMR analysis. Remainder of the material was starting material

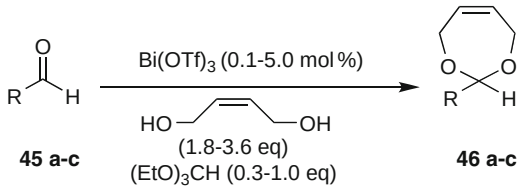
**Table 5** Synthesis of dioxanes catalyzed by $Bi(OTf)_3$

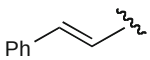



| Entry | $R^1$ | $R^2$ | Catalyst loading (mol%) | Diol concentration (equiv) | $(EtO)_3CH$ concentration (equiv) | Time[a] | Yield[b] (%) |
|---|---|---|---|---|---|---|---|
| a | *p*-$CH_3C_6H_4$ | H | 0.1 | 3.6 | 1.0 | 45 min | 93 |
| b | *p*-$ClC_6H_4$ | H | 1.0 | 1.8 | 1.0 | 1 h 30 min | 99 |
| c | *o*-$BrC_6H_4$ | H | 1.0 | 1.8 | 1.0 | 2 h 35 min | 78 |
| d | *m*-$CH_3OC_6H_4$ | H | 1.0 | 1.8 | 1.0 | 2 h | 81 |
| e | *p*-$OHC_6H_4$ | H | 1.0 | 3.6 | 2.0 | 1 h 20 min | 72 |
| f | *p*-$TBSOC_6H_4$ | H | 1.0 | 3.6 | 2.0 | 2 h 25 min | 83 |
| g | $CH_3(CH_2)_8$ | H | 5.0 | 1.8 | 1.0 | 1 h 15 min | 95 |
| h |  | H | 1.0 | 5.4 | 1.0 | 6 h | 71[c,d] |
| i | *p*-$CH_3OC_6H_4$ | $CH_3$ | 0.1 | 1.8 | 1.0 | 30 min | 82 |
| j | *p*-$CH_3C_6H_4$ | $CH_3$ | 0.1 | 1.8 | 1.0 | 1 h 30 min | 96 |
| k | *m*-$BrC_6H_4$ | $CH_3$ | 1.0 | 1.8 | 1.0 | 1 h 30 min | 80 |
| l | *p*-$ClC_6H_4$ | $CH_3$ | 1.0 | 1.8 | 0.3 | 4 h | 83 |
| m |  | $CH_3$ | 0.1 | 3.6 | 1.0 | 55 min | 99 |

[a]Reaction progress was followed by GC or TLC
[b]Refers to yield of pure, isolated product. All products were >98% pure unless stated otherwise
[c]The product was 96% pure (remaining material was starting material)
[d]Reaction was carried out on a 1-g scale in the presence of 0.50 g of anhydrous $MgSO_4$

**Table 6** Synthesis of dioxepines catalyzed by $Bi(OTf)_3$




| Entry | R | Catalyst loading (mol%) | Diol concentration (equiv) | $(EtO)_3CH$ concentration (equiv) | Time[a] | Yield[b] (%) |
|---|---|---|---|---|---|---|
| a | *o*-$BrC_6H_4$ | 1.0 | 3.6 | 0.3 | 1 h 35 min | 56[c] |
| b |  | 0.1 | 1.8 | 1.0 | 4 h 15 min | 60 |
| c | $CH_3(CH_2)_8$ | 5.0 | 3.6 | 0.3 | 1 h 45 min | 86 |

[a]Reaction progress was followed by GC or TLC
[b]Refers to yield of pure, isolated product. All products were >98% pure unless stated otherwise
[c]Product was found to be 97% pure (remainder was starting material) by GC analysis and $^1H$ NMR spectroscopy

# 7 Bismuth(III) Salt-Catalyzed Allylations

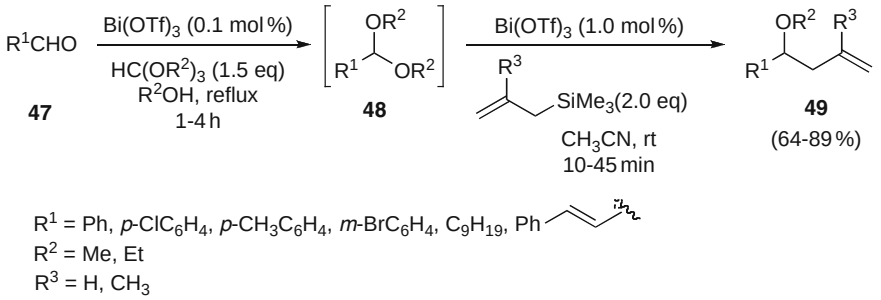
## *7.1 Synthesis and Allylation of Acyclic Acetals*

Acyclic acetals are simple protecting groups for aldehydes and ketones, and we have previously reported their synthesis catalyzed by $Bi(OTf)_3$ [104]. Acyclic acetals can also be converted to other useful functional groups. For example, allylation of acyclic acetals to give homoallyl ethers has been well investigated, and we have reported a $Bi(OTf)_3$-catalyzed method for the same [105]. The success of $Bi(OTf)_3$-catalyzed formation and allylation of acyclic acetals prompted us to develop a one-pot method for the synthesis of homoallyl ethers from aldehydes, catalyzed by bismuth triflate. A one-pot process saves steps by eliminating the need for isolation of the intermediate and thus minimizes waste. Three one-pot procedures for the synthesis of homoallyl ethers were developed [106].

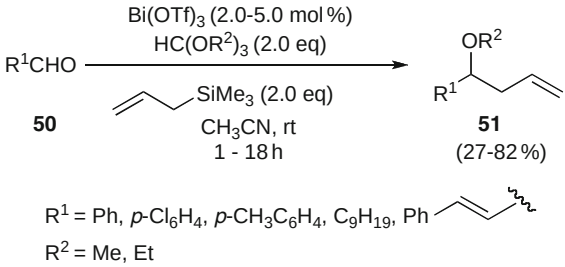
The first procedure is a one-pot sequential process in which the acetal is formed from the aldehyde in a $Bi(OTf)_3$-catalyzed reaction with trialkylorthoformate and the corresponding alcohol. After the aldehyde was consumed, the remaining alcohol was removed under reduced pressure. Acetonitrile, allyltrimethylsilane, and additional $Bi(OTf)_3$ were added and the desired homoallyl ethers were obtained in moderate to good yields (Scheme 10).

A three-component one-pot procedure was also developed. This method involves stirring the aldehyde, trialkylorthoformate, and allyltrimethylsilane in $CH_3CN$ in the presence of a catalytic amount of $Bi(OTf)_3$. The homoallyl ethers were again obtained in moderate to good yields with a more simple and straightforward procedure (Scheme 11).

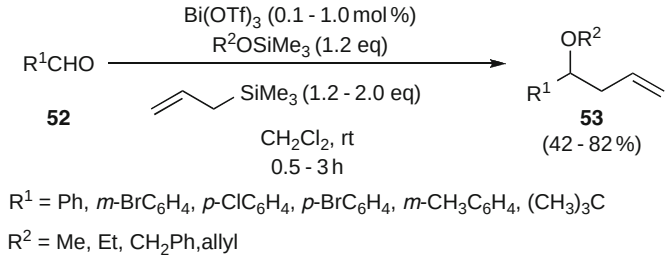
One drawback of both these methods is that only a few trialkylorthoformates are commercially available, and this limits the type of ether that can be formed. In addition, alkyl ethers are somewhat inert and not readily amenable to further synthetic manipulation. In contrast, a wide variety of alkoxytrimethylsilanes are commercially available and this fact prompted an investigation into their use [107].




**Scheme 10** Bismuth(III) triflate-catalyzed method for the conversion of aldehydes to homoallyl ethers via an acetal intermediate




**Scheme 11** Bismuth(III) triflate-catalyzed one-pot method for the conversion of aldehydes to homoallyl ethers

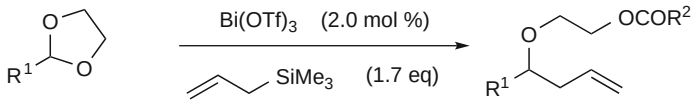



**Scheme 12** Bismuth(III) triflate-catalyzed one-pot method for the conversion of aldehydes to homoallyl ethers using alkoxysilanes

We found that the desired homoallyl ethers could be synthesized in good to moderate yields using alkoxytrimethylsilanes in place of the trialkylorthoformates (Scheme 12). In addition, a lower catalyst loading was required.

## *7.2 Allylation of Cyclic Acetals*

The use of cyclic acetals as protecting groups for aldehydes and ketones in synthesis is widely reported, but there are far fewer reports in the literature corresponding to the use of cyclic acetals as allylation substrates [108–116]. Most reagents (such as $TiCl_4$ and $AlCl_3$) used to date for these types of allylations are highly corrosive and are often used in stoichiometric amounts. The lack of a highly catalytic method for the allylation of cyclic acetals using nontoxic reagents inspired us to investigate a bismuth(III) triflate-catalyzed allylation of cyclic acetals. Initial attempts at the allylation of dioxolanes using allyltrimethylsilane resulted in low yields of the desired homoallyl ether product. Instead, a mixture of dioxolane, aldehyde, and homoallyl ether was isolated. In an attempt to capture the putative alkoxide resulting from dioxolane ring-opening, the allylation was carried out in the presence of acetic anhydride. Under these conditions, highly functionalized acetate esters were obtained in moderate to good yields (Scheme 13) [117]. Several acid anhydrides were subsequently used for in situ derivatization following dioxolane ring-opening.

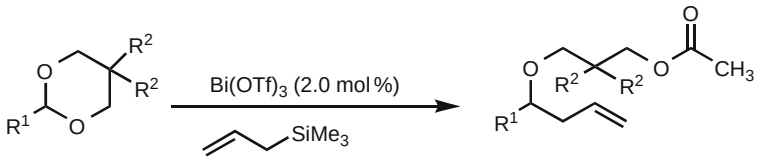



$R^1$ = *o*-$BrC_6H_4$, *m*-$BrC_6H_4$, *o*-$ClC_6H_4$, *p*-$ClC_6H_4$, *o*-$FC_6H_4$, *p*-$CH_3C_6H_4$, $PhCH_2$, $CH_3(CH_2)_8$

$R^2$ = $CH_3$, *i*-Pr, *t*-Bu

**Scheme 13** Bismuth(III) triflate-catalyzed allylation of dioxolanes followed by in situ derivatization to generate acetates

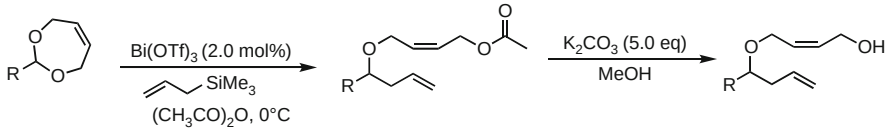
**Table 7** Allylation of dioxanes catalyzed by $Bi(OTf)_3$




| Entry | $R^1$ | $R^2$ | Time[a] (h) | Yield[b] (%) |
|---|---|---|---|---|
| a | *o*-$BrC_6H_4$ | H | 1.5 | 79 |
| b | *p*-$BrC_6H_4$ | H | 2 | 65 |
| c | *p*-$ClC_6H_4$ | H | 2 | 70 |
| d | *p*-$CH_3C_6H_4$ | H | 1.5 | 60 |
| e | *m*-$CH_3OC_6H_4$ | H | 1.5 | 70 |
| f | $CH_3(CH_2)_8$ | H | 4 | 75 |
| g | $BrCH_2CH_2$ | H | 2.5 | 70 |
| h | *p*-$ClC_6H_4$ | $CH_3$ | 10 min | 74[c] |
| i | *p*-$CH_3C_6H_4$ | $CH_3$ | 0.5 | 83 |
| j | $CH_3(CH_2)_8$ | $CH_3$ | 3.5 | 72 |

[a]Reaction progress was followed by GC or TLC
[b]Refers to yield of pure, isolated product. All products were >98% pure unless stated otherwise
[c]Product was found to be 97% pure (remainder was starting material) by GC analysis and $^1H$ NMR spectroscopy

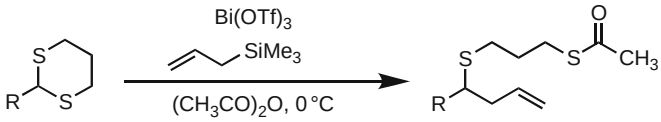
Initial success in the allylation of dioxolanes prompted us to investigate the allylation of other cyclic acetals including dioxanes (Table 7) and dioxepines (Scheme 14). To the best of our knowledge, this is the first example of the allylation of dioxanes and dioxepines [118]. Gratifyingly, following this protocol, highly functionalized ester products were obtained in good to moderate yields following purification by direct loading of the reaction mixture onto a silica gel column and elution with a mixture of ethyl acetate and heptane. The solvent-free procedure coupled with the easy work up that avoids an aqueous waste stream are advantages of this procedure.




**58a** R = *p*-$ClC_6H_4$ **59a** (67%) **60a** (90%)
**58b** R = $CH_3(CH_2)_8$ **59b** (59%) **60b** (93%)

**Scheme 14** Bismuth(III) triflate-catalyzed allylation of dioxepines followed by in situ derivatization to generate acetates

**Table 8** Allylation of dithianes catalyzed by $Bi(OTf)_3$




**61a-d** **62 a-d**

| Entry | R | $Bi(OTf)_3$ loading (mol%) | Time | Yield[a] (%) |
|---|---|---|---|---|
| a | $C_6H_5$ | 2.0[b] | 3 h 45 min | 78 |
| b | *p*-$ClC_6H_4$ | 2.0 | 2 h 45 min | 65 |
| c | *m*-$CH_3C_6H_4$ | 4.0 | 4 h 30 min | 74 |
| d | $CH_3(CH_2)_8$ | 10.0 | 3 h 30 min | 63 |

[a]Refers to yield of purified product obtained by filtration of reaction mixture through a silica gel column
[b]An additional 2.0 mol% $Bi(OTf)_3$ was added after 3 h

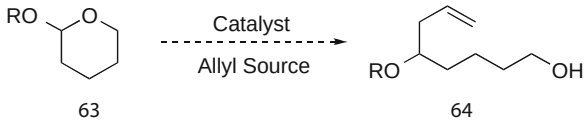
## 7.3 Allylation of Dithianes

To the best of our knowledge, the allylation of dithianes has not been previously reported in the literature. A range of dithianes underwent smooth allylation to give the desired thioester products in good yield; however, a slightly increased catalyst loading (2–10 mol%) was needed (Table 8).

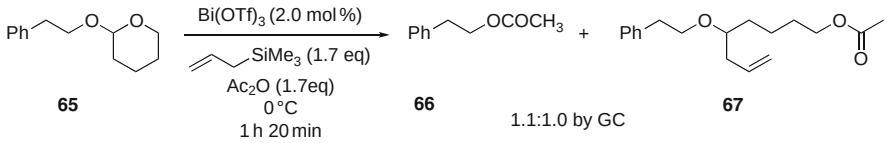
## 7.4 Allylation of Tetrahydropyranyl and Tetrahydrofuranyl Ethers

Tetrahydropyranyl (THP) and tetrahydrofuranyl ethers are important protecting groups for alcohols and phenols in organic synthesis, but they can also be converted to other useful functional groups [8, 118]. For example, allylation of a THP ether should yield a highly functionalized molecule (Scheme 15).

Despite the obvious synthetic utility of such a transformation, very few methods have been developed for the allylation of THP ethers. The reported methods suffer

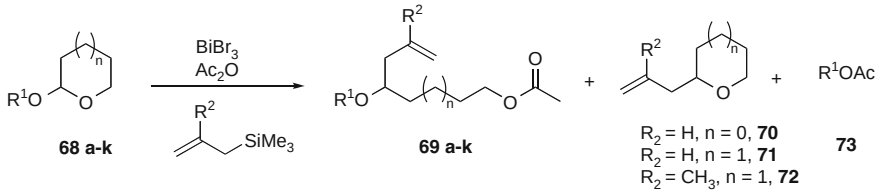



**Scheme 15** Allylation of a THP ether




**Scheme 16** Bismuth(III) triflate-catalyzed allylation of a THP ether followed by in situ derivatization to generate an acetate

**Table 9** Allylation of THP and THF ethers catalyzed by $BiBr_3$




| Entry | $R^1$ | $R^2$ | *n* | Time[a] | Yield[b] (%) of **69a–k** |
|---|---|---|---|---|---|
| a | $CH_3$ | H | 1 | 1 h | 58[c] |
| b | $CH_3(CH_2)_4$ | H | 1 | 1 h 45 min | 53 |
| c | $CH_3(CH_2)6$ | H | 1 | 2 h 35 min | 62 |
| d | Cyclohexyl | H | 1 | 1 h 30 min | 44 |
| e | $HC \equiv CCH_2CH_2$ | H | 1 | 1 h 15 min | 43[d] |
| f | $BrCH_2(CH_2)_2$ | H | 1 | 1 h 30 min | 45 |
| g | $PhCH_2(CH_2)_2$ | H | 1 | 2 h 15 min | 49[e] |
| h | $CH_3(CH_2)_4$ | $CH_3$ | 1 | 1 h 35 min | 35 |
| i | $CH_3$ | $CH_3$ | 1 | 1 h 30 min | 30[f] |
| j | $CH_3(CH_2)_6$ | H | 0 | 2 h 10 min | 21 |
| k | $PhCH_2(CH_2)_2$ | H | 0 | 1 h 30 min | 25 |

[a]Reaction progress was followed by GC or TLC

[b]Refers to yield of isolated, purified ester; reported yield is calculated assuming that the ester is the only product. In all cases the reaction mixture contained a significant amount (20–50%, by GC) of 2-allyltetrahydro-2*H*-furan or 2-allyltetrahydro-2*H*-pyran and much smaller amounts (ca. 10%) of the corresponding acetate (**73a–k**). Pure samples of the 2-allyltetrahydro-2*H*-furan or 2-allyltetrahydro-2*H*-pyran could not be isolated due to the fact that they had $R_f$ values very similar to the corresponding acetates

[c]2-Allyltetrahydro-2*H*-pyran was isolated in 24% yield (96% pure by GC)

[d]2-Allyltetrahydro-2*H*-pyran was isolated in 28% yield (99% pure by GC, $^1H$ and $^{13}C$ NMR analysis)[e]3-Phenylpropyl acetate (96% pure by GC and $^1H$ NMR) was isolated in 31% yield

[f]2-Methallyltetrahydro-2*H*-pyran was isolated in 55% yield (99% pure by GC, $^1H$ and $^{13}C$ NMR analysis)

from many drawbacks, including the use of stoichiometric amounts of toxic and corrosive reagents such as $TiCl_4$ and TMSOTf [119] or non-commercially available reagents such as allylborates [111]. Prompted by our successful use of $Bi(OTf)_3$ as a catalyst for the allylation of cyclic acetals, we initially tried the allylation of 2-phenethoxytetrahydro-*2H*-pyran with allyltrimethylsilane catalyzed by $Bi(OTf)_3$. Unfortunately, the desired allylation product was not observed, and instead phenethyl alcohol was isolated. As with the allylation of cyclic acetals, we postulated that the putative alkoxide intermediate could be captured with acetic anhydride. Such an attempt yielded a mixture of the desired ester product and phenethyl acetate. The direct conversion of THP ethers to acetates catalyzed by bismuth(III) salts has been previously reported [120, 121] (Scheme 16).

Initial attempts at the $BiBr_3$-catalyzed allylation of THP ethers gave consistently low to moderate yields of the desired ester product, suggesting the formation of side products not detectable under the gas chromatography conditions used. Careful chromatography and detailed NMR analysis of the product mixture revealed that a significant amount of 2-allyltetrahydropyran was also being formed (Table 9) [122]. An attempt to expand the scope of this methodology to THF ethers was less successful and the yields of the functionalized ester products were poor. Methallyltrimethylsilane was also substituted for allyltrimethylsilane in the allylation of THP ethers, but the yields were lower than those obtained with allyltrimethylsilane.

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# Bismuth-Catalyzed Addition of Silyl Nucleophiles to Carbonyl Compounds and Imines

**Thierry Ollevier**

**Abstract** Bismuth triflate was found to be an efficient catalyst both in the Mannich-type reaction of silyl enolates and in the Sakurai reaction of allyltrimethylsilane with *N*-alkoxycarbonylamino sulfones. The reactions proceeded smoothly with a low catalyst loading of $Bi(OTf)_3{\cdot}4H_2O$ (0.5–5.0 mol%) to afford the corresponding protected β-amino carbonyl compounds and homoallylic amines in very good yields (up to 96%). The latter compounds could also be obtained via a bismuth-mediated three-component reaction. We have also developed an efficient vinylogous Mukaiyama aldol reaction of 2-(trimethylsilyloxy)furan with various aromatic aldehydes mediated by bismuth triflate in a low catalyst loading (1 mol%). The reaction proceeds rapidly and affords the corresponding 5-[hydroxy(aryl)methyl]furan-2(5*H*)-ones in high yields with good to very good diastereoselectivities (diastereoisomeric ratios > 98:2). Such selectivities, although previously reported with other Lewis acids, could be achieved with a much lower catalyst loading. 5-[Hydroxy(alkyl)methyl]furan-2(5*H*)-ones derived from ketones could also be obtained with good diastereoselectivities. The vinylogous Mukaiyama aldol reaction has also been extended to 2,2-dimethyl-6-methylene-4-(trimethylsilyloxy)-1,3-diox-4-ene using 1 mol% of $Bi(OTf)_3{\cdot}4H_2O$.

**Keywords** Aza-Sakurai allylation reaction • Bismuth triflate • C–C bond formation • Mannich-type reaction • Mukaiyama aldol reaction • *N*-Alkoxycarbonylamino sulfones • Silyl nucleophiles

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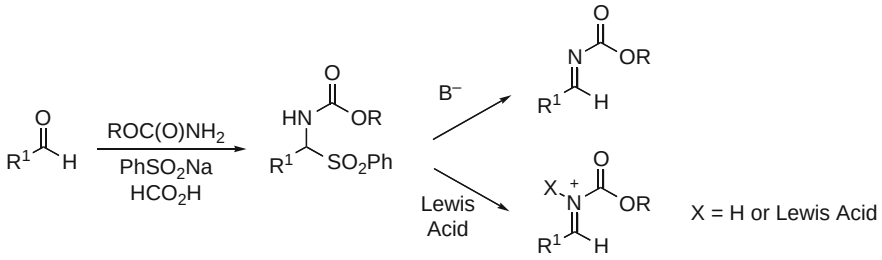
# 1 Bismuth-Catalyzed Addition to *N*-Alkoxycarbonylamino Sulfones

## *1.1 Introduction*

The development of new methods for the synthesis of β-amino carbonyl derivatives and homoallylic amines is an important area of synthetic efforts. β-Amino ketones and esters and homoallylic amines have attracted many synthetic efforts and enjoyed widespread use in natural product and bioactive molecule synthesis [1, 2]. Among the variety of synthetic methods so far reported, the Lewis acid-catalyzed reaction of imines with silyl nucleophiles provides an efficient route for the synthesis of such compounds. However, the instability of carbamate-protected alkyl imines has greatly hampered the development of catalytic reactions. Therefore, methods involving the in situ generation of imines are highly attractive, among which the one-pot allylation of imines and Mannich-type reactions have been proposed. Yet, most Lewis acids cannot be used in these reactions because they decompose or deactivate in the presence of the amine or water produced during imine formation. Very reactive *N*-acyliminiums, easily prepared from stable precursors, provide an attractive alternative [3–6]. Various reports are available on enantioselective syntheses [7–14] and *N*-alkoxycarbonylamino sulfones [15]. Scheme 1 illustrates the preparation of the *N*-acylimine precursor from the corresponding aldehydes [15]. *N*-Alkoxycarbonyl imines have been prepared from basic treatment of the *N*-alkoxycarbonylamino sulfones. The corresponding *N*-alkoxycarbonyl iminium derivatives have been prepared by the use of a Lewis acid (Scheme 1). Over the past years, some elegant syntheses have been described, using *N*-alkoxycarbonylamino sulfones as substrates, including Sakurai and Mannich-type reactions [3–15]. We wish to report herein $Bi(OTf)_3 \cdot 4H_2O$-catalyzed Sakurai and Mannich-type reactions of *N*-alkoxycarbonylamino sulfones. Alkoxycarbonyl-protected homoallylic amines and β-amino carbonyl compounds




**Scheme 1** Carbonylamino sulfones as acylimine/acyliminium precursors

were obtained efficiently in the presence of 0.5–5 mol% of $Bi(OTf)_3{\cdot}4H_2O$. Recently, synthetic methods involving Lewis acids such as $TiCl_4$, $SnCl_4$ or $InX_3$ (X = Cl, OTf) have been reported ([16–20], A related strategy has been disclosed in solid-phase synthesis [21]). However, the use of $Ti^{IV}$ and $Sn^{IV}$ salts in stoichiometric quantity or in large excess often restricts their utilization. Moisture sensitivity of these catalysts and the high cost of some of them also restrain their use.

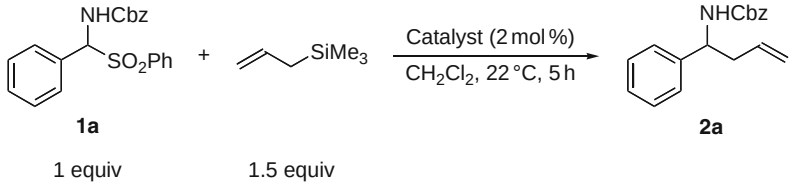
As a part of the increasing interest in bismuth(III)-catalyzed reactions involving silyl nucleophiles, we have reported a general $Bi(OTf)_3{\cdot}4H_2O$-catalyzed method for addition of silyl nucleophiles to *N*-alkoxycarbonylamino sulfones. Bismuth salts indeed provide a good alternative as they have recently attracted attention due to their low toxicity, low cost, and environmentally benign character. Bismuth salts have been reported as catalysts for opening of epoxides [22–25], Mukaiyama aldol reactions [26–29], Mannich-type and Sakurai reactions [30–39], formation and deprotection of acetals [40, 41], etherification reactions [42, 43], hydroamination reactions [44–46], Friedel–Crafts reactions, and Fries and Claisen rearrangements [47–49]. $Bi(OTf)_3{\cdot}4H_2O$ is particularly attractive because it is commercially available or can be easily prepared from commercially available compounds [50–56].

In this chapter, we wish to disclose our results on the nucleophilic addition of carbon nucleophiles to *N*-alkoxycarbonylamino sulfones. Both allyltrimethylsilane and silyl enolates will be considered as nucleophiles. The corresponding amines were obtained efficiently in the presence of 0.5–5 mol% of $Bi(OTf)_3{\cdot}4H_2O$ [57, 58].

## *1.2 Bismuth Triflate-Catalyzed Sakurai Allylation Reaction*

Initially, the allylation reaction was studied with the *N*-benzyloxycarbonylamino sulfone derived from benzaldehyde and benzoyloxycarbonyl (Cbz) carbamate (Scheme 1, $R^1$ = Ph, R = Bn). Various catalysts were screened for the allylation of benzyl phenyl(phenylsulfonyl)methylcarbamate **1a** with allyltrimethylsilane in dichloromethane (Table 1). Among the various Bi catalysts tested, $Bi(OTf)_3{\cdot}4H_2O$ was shown to be the most efficient (Table 1, entry 5). $BiCl_3$, $BiBr_3$, $Bi(OAc)_3$, or $Bi(OCOCF_3)_3$ did not allow the reaction to proceed and starting material was

**Table 1** Metal salt-catalyzed allylation of sulfone **1a** with allyltrimethylsilane



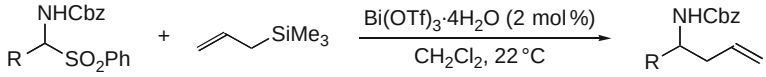

| Entry | Catalyst | Yield[a] **2a** (%) |
|---|---|---|
| 1 | $BiCl_3$ | –[b] |
| 2 | $BiBr_3$ | –[b] |
| 3 | $Bi(OAc)_3$ | –[b] |
| 4 | $Bi(OCOCF_3)_3$ | –[b] |
| 5 | $Bi(OTf)_3{\cdot}4H_2O$ | 94 |
| 6 | $Zn(OTf)_2$ | 35 |
| 7 | $Sc(OTf)_3$ | 57 |
| 8 | $Ga(OTf)_3$ | 71 |
| 9 | $Cu(OTf)_2$ | 60[c] |

Conditions: benzyl phenyl(phenylsulfonyl)methylcarbamate **1a** (1.0 equiv.), allyltrimethylsilane (1.5 equiv.), metal salt (2 mol%) in dry $CH_2Cl_2$ at 22 °C for 5 h
[a]Isolated yield
[b]No trace of product according to $^1$H NMR
[c]Reaction time was 6.5 h

recovered (Table 1, entries 1–4). Other metal triflates such as $Zn(OTf)_2$, $Sc(OTf)_3$, $Ga(OTf)_3$, or $Cu(OTf)_2$ also catalyzed this reaction but decreased yields were obtained (Table 1, entries 6–9). Interestingly, using allyltributylstannane as the nucleophile under the same conditions (2 mol% $Bi(OTf)_3{\cdot}4H_2O$, 22 °C) led only to traces of homoallylic amine **2a** (6%), although allyltrimethylgermane afforded **2a** in good yield (79%).

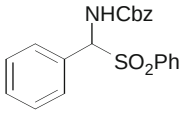
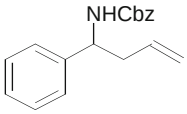
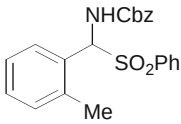
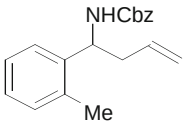
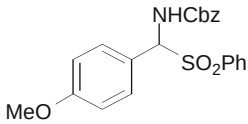
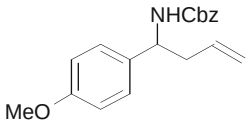
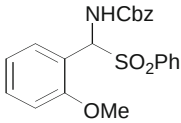
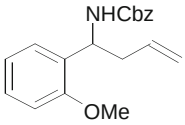
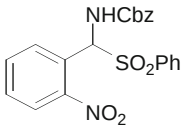
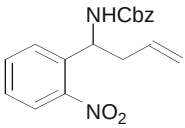
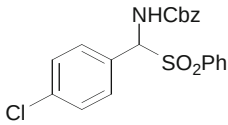
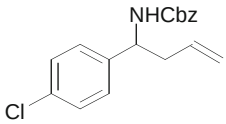
With regard to the success obtained with sulfone **1a** derived from benzaldehyde, we studied the scope and limitations of this reaction with respect to the sulfone employed in the process (Scheme 1; $R^1$ = Ar, Alk, 1 equiv. $BnOC(O)NH_2$, $H_2O$-MeOH/THF, 22 °C, 22–140 h). The results are summarized in Table 2. The addition of allyltrimethylsilane to various *N*-benzyloxycarbonylamino sulfones **1** proceeded readily employing $Bi(OTf)_3{\cdot}4H_2O$ as the Lewis acid (2–5 mol% $Bi(OTf)_3{\cdot}4H_2O$, $CH_2Cl_2$, 22 °C, 5–44 h). Generally, the corresponding homoallylic amines **2** were obtained in moderate to good yields (Table 2). Sulfones derived from electron-rich aromatic aldehydes, including *o*-substituted benzaldehydes, reacted smoothly to give the desired products in moderate to excellent yields (Table 2, entries 1–4). The reaction worked well with a variety of sulfones derived from electron-poor aromatic aldehydes, and the corresponding homoallylic amines **2** were obtained with moderate to good yields (Table 2, entries 5–10). Benzyloxycarbonylamino sulfone **1k** could be selectively prepared from *p*-acetyl benzaldehyde and subsequently allylated to give **2k** with complete chemoselectivity (Table 2, entry 11). In addition, heteroaromatic aldehyde-derived sulfones could also serve as substrates in

**Table 2** $Bi(OTf)_3{\cdot}4H_2O$-catalyzed allylation of Cbz-amino sulfones **1** with allyltrimethylsilane



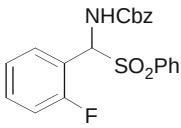
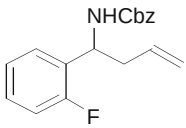
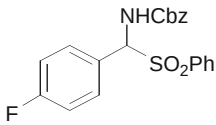
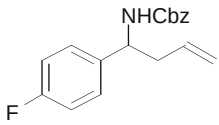
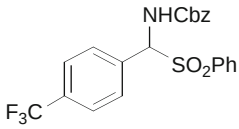
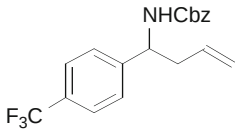
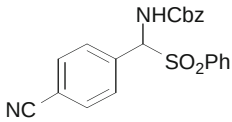
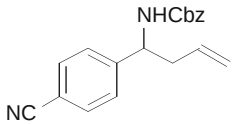
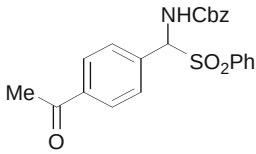
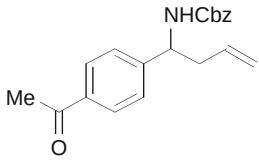
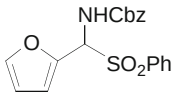
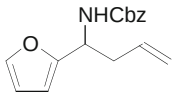
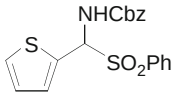
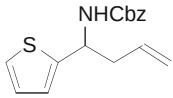

**1** **2**

1 equiv 1.5 equiv

| Entry | Sulfone **1** | Product **2** | | Time (h) | Yield[a] **2** (%) |
|---|---|---|---|---|---|
| 1 |  |  | **2a** | 5 | 94 |
| 2 |  |  | **2b** | 23 | 84 |
| 3 |  |  | **2c** | 12 | 86 |
| 4 |  |  | **2d** | 22 | 62[b] |
| 5 |  |  | **2e** | 24 | 74 |
| 6 |  |  | **2f** | 26 | 78 |

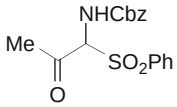
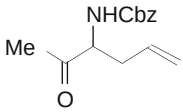
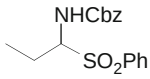
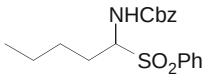
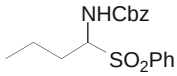
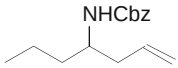
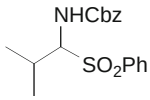
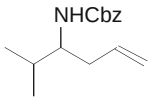
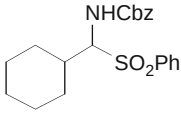
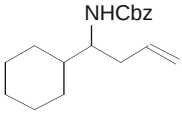
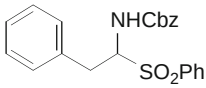
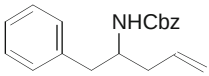
(continued)

**Table 2** (continued)

| Entry | Sulfone **1** | Product **2** | | Time (h) | Yield[a] **2** (%) |
|---|---|---|---|---|---|
| 7 |  |  | **2g** | 24 | 73 |
| 8 |  |  | **2h** | 24 | 78 |
| 9 |  |  | **2i** | 43 | 58 |
| 10 |  |  | **2j** | 40 | 74[b] |
| 11 |  |  | **2k** | 27 | 56 |
| 12 |  |  | **2l** | 24 | 45[b] |
| 13 |  |  | **2m** | 23 | 46 |

(continued)

**Table 2** (continued)

| Entry | Sulfone **1** | Product **2** | | Time (h) | Yield[a] **2** (%) |
|---|---|---|---|---|---|
| 14 |  |  | **2n** | 41 | 47[b] |
| 15 |  |  | **2o** | 24 | 73 |
| 16 |  |  | **2p** | 44 | 61 |
| 17 |  |  | **2q** | 28 | 74 |
| 18 |  |  | **2r** | 26 | 74 |
| 19 |  |  | **2s** | 22 | 76 |

Conditions: sulfone **1** (1.0 equiv.), allyltrimethylsilane (1.5 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (2 mol%) in $CH_2Cl_2$ at 22 °C

[a]Isolated yield

[b]The reaction was run with 5 mol% $Bi(OTf)_3{\cdot}4H_2O$ and 5.0 equiv. allyltrimethylsilane at reflux in $CH_2Cl_2$

this reaction, giving the corresponding homoallylic amines in moderate yields (Table 2, entries 12 and 13). Aliphatic aldehydes led to moderate to good yields of **2** (Table 2, entries 14–19). For selected substrates, higher yields could be obtained using a catalyst loading of 5 mol% with 5 equiv. of allyltrimethylsilane in dichloromethane at reflux (Table 2, entries 4, 10, 12, and 14).

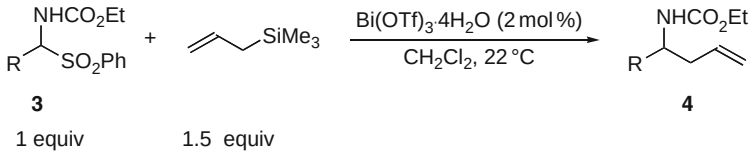
In order to get further insight into the allylation reaction, we decided to explore the mechanistic aspects of the $Bi(OTf)_3{\cdot}4H_2O$-catalyzed process in more detail. Given that the latter does not occur in the presence of $N^1,N^1,N^8,N^8$-tetramethylnaphthalene-1,8-diamine proton sponge (1 equiv. of **1a**, 1.5 equiv. of allyltrimethylsilane, 2 mol%

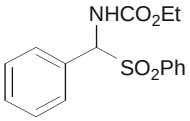
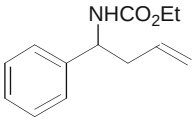
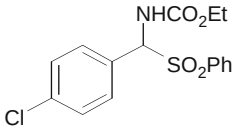
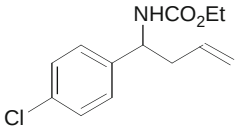
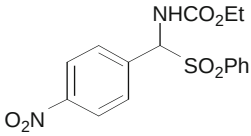
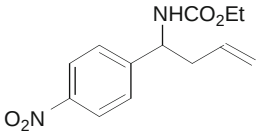
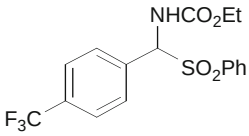
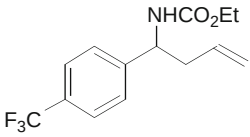
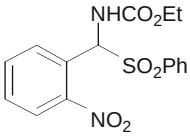
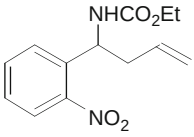
of $Bi(OTf)_3 \cdot 4H_2O$, 6 mol% of proton sponge, 22 °C, 28 h, 99% recovery of **1a**) or 2,6-di-*tert*-butylpyridine (1 equiv. of **1a**, 1.5 equiv. of allyltrimethylsilane, 2 mol% of $Bi(OTf)_3 \cdot 4H_2O$, 6 mol% of 2,6-di-*tert*-butylpyridine, 22 °C, 19 h, 100% recovery of **1a**), but still proceeds with $K_2CO_3$ as a proton scavenger (1 equiv. of **1a**, 1.5 equiv. of allyltrimethylsilane, 2 mol% of $Bi(OTf)_3 \cdot 4H_2O$, 6 mol% $K_2CO_3$, 22 °C, 19 h, 62% of **2a**) does not indicate unambiguously that triflic acid is involved in the mechanism. The pyridinium salt itself was also tested (1 equiv. of **1a**, 1.5 equiv. of allyltrimethylsilane, 6 mol% of 2,6-di-*tert*-butylpyridinium triflate, 22 °C, 92 h, no reaction, 100% of recovery of **1a**). Additionally, the allylation reaction does not occur using 2 mol% of HOTf or $Me_3SiOTf$. However, when HOTf (6 mol%) is used as the catalyst, the reaction proceeds to afford the expected product **2a**, indicating that HOTf is also an effective catalyst for the transformation (1 equiv. of **1a**, 1.5 equiv. of allyltrimethylsilane, 6 mol% of HOTf, 22 °C, 4 h, 67% of **2a**). In order to get further evidence on the role of HOTf as catalyst, the allylation of sulfones derived from both 3-pyridylcarboxaldehyde and 4-*N*,*N*-dimethylamino benzaldehyde was attempted, but no conversion in expected homoallylic amine was observed. Moreover, $Me_3SiOTf$ is an effective catalyst when used in 6 mol% (1 equiv. of **1a**, 1.5 equiv. of allyltrimethylsilane, 6 mol% of $Me_3SiOTf$, 22 °C, 5 h, 82% of **2a**). Since the allylation reaction does not occur using 2 mol% of HOTf or $Me_3SiOTf$ and since the chemical yields of the 6 mol% HOTf- and $Me_3SiOTf$-catalyzed reactions are lower than when using 2 mol% $Bi(OTf)_3 \cdot 4H_2O$ (compare with Table 1, entry 5), a dual mechanism, namely Lewis and Brønsted acid catalysis, cannot be ruled out. Despite the fact that $Bi(OTf)_3 \cdot 4H_2O$, HOTf, and TMSOTf could co-exist as catalysts, practical use of $Bi(OTf)_3 \cdot 4H_2O$ makes our method particularly valuable since $Bi(OTf)_3 \cdot 4H_2O$ is neither corrosive nor difficult to handle.

Next, the scope of this allylation reaction was evaluated with other *N*-alkoxycarbonylamino sulfones. Under the optimized reaction conditions, the allylation of ethyl carbamate-derived sulfones **3** was studied (Table 3). Generally, the allylation of such sulfones afforded good yields of the corresponding homoallylic amines **4**. Aromatic aldehyde-derived sulfones reacted smoothly to give **4** in moderate to good yields (Table 3, entries 1–5). With *N*-ethoxycarbonylamino sulfones derived from *p*-chloro and *p*-nitro benzaldehyde, the reaction did not proceed at room temperature. Upon reflux of dichloromethane and using 5 mol% $Bi(OTf)_3 \cdot 4H_2O$ and 5 equiv. allyltrimethylsilane, the expected homoallylic amines **4b** and **4c** could be obtained in good yields (Table 3, entries 2 and 3). The cyclohexylcarboxaldehyde-derived sulfone **3f** reacted smoothly to afford the expected product in good yield (Table 3, entry 6). Therefore, this Sakurai-type allylation could be extended to various carbamate-derived sulfones.

When the *tert*-butoxycarbonyl (Boc) carbamate-derived sulfone **5** was subjected to the $Bi(OTf)_3 \cdot 4H_2O$-catalyzed allylation conditions (Scheme 2), the cyclic carbamate **6** was obtained as the major product (36%, diastereoisomeric ratio (dr) = 82:18), along with the corresponding allylation product **7**, although in low yield (16%). Such cyclic carbamate resulting from the internal capture of an intermediate β-silyl cation with the Boc group and concomitant loss of isobutylene has already been reported in the literature [59].

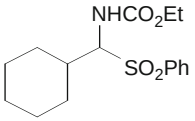
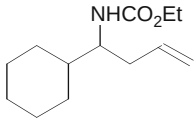
**Table 3** $Bi(OTf)_3$-catalyzed allylation of ethyl carbamate-derived sulfones **3** with allyltrimethylsilane



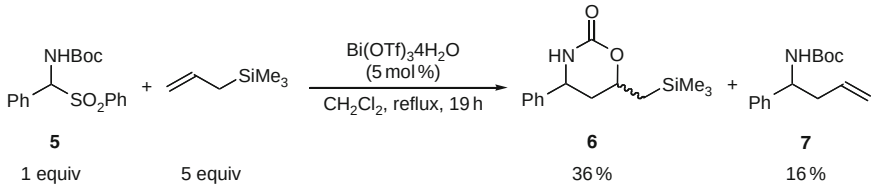

| Entry | Sulfone **3** | Product **4** | | Time (h) | Yield[a] **4** (%) |
|---|---|---|---|---|---|
| 1 |  |  | **4a** | 3.5 | 69 |
| 2 |  |  | **4b** | 19 | 80[b] |
| 3 |  |  | **4c** | 19 | 83[b] |
| 4 |  |  | **4d** | 22 | 68 |
| 5 |  |  | **4e** | 62 | 80 |

(continued)

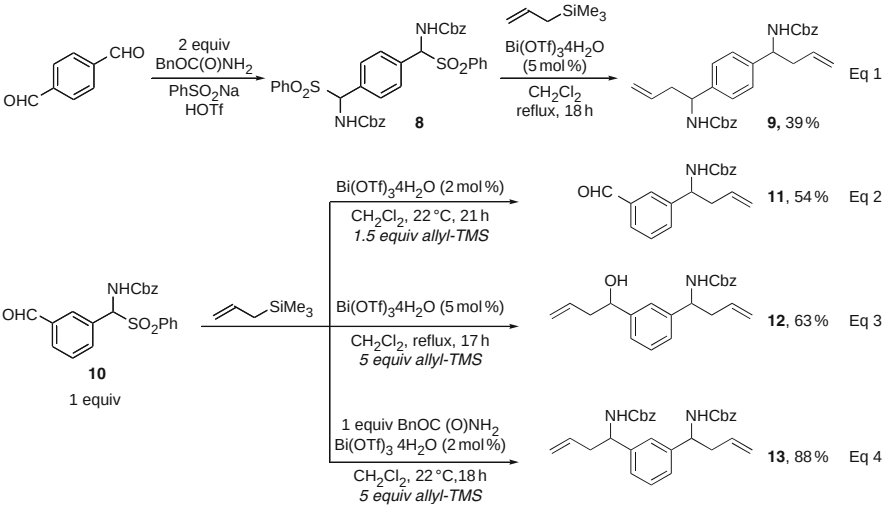
**Table 3** (continued)

| Entry | Sulfone **3** | Product **4** | | Time (h) | Yield[a] **4** (%) |
|---|---|---|---|---|---|
| 6 |  |  | **4f** | 62 | 76 |

Conditions: sulfone **3** (1.0 equiv.), allyltrimethylsilane (1.5 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (2 mol%) in $CH_2Cl_2$ at 22 °C
[a]Isolated yield
[b]Reaction was performed in $CH_2Cl_2$ at reflux in the presence of $Bi(OTf)_3{\cdot}4H_2O$ (5 mol%) with 5.0 equiv. allyltrimethylsilane




**Scheme 2** $Bi(OTf)_3{\cdot}4H_2O$-catalyzed allylation of Boc-amino sulfone **5** with allyltrimethylsilane




**Scheme 3** $Bi(OTf)_3{\cdot}4H_2O$-catalyzed allylation of bifunctional substrates

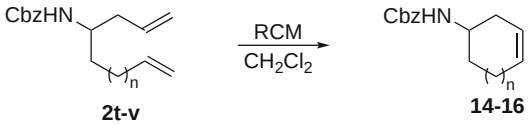
Encouraged by our previous results, we studied the allylation of bifunctional sulfones derived from dialdehydes such as terephthalaldehyde and isophthalaldehyde (Scheme 3). When the classical conditions for the preparation of sulfones

were used with terephthalaldehyde, an equimolar mixture of mono- and double sulfone (1:0.88) was formed. Unexpectedly, when triflic acid was used instead of formic acid, the double sulfone derived from terephthalaldehyde was obtained in high yield (5.0 equiv. $PhSO_2Na$, 5.0 equiv. $BnOC(O)NH_2$, THF/$H_2O$/HOTf, 70 °C, 72 h, 87% of **8**). Slight modification of the conditions applied to isophthalaldehyde led to the monosulfone **10** as the only product (2.0 equiv. $PhSO_2Na$, 2.0 equiv. $BnOC(O)NH_2$, THF/$H_2O$/$HCO_2H$, 70 °C, 72 h, 85% of **10**). Although the allylation of **8** afforded a poor yield of double homoallylic carbamate **9** (Scheme 3, Eq. 1), monosulfone **10** could be advantageously used as a key precursor. Chemoselective mono-allylation of **10** using 1.5 equiv. of allyltrimethylsilane smoothly afforded aldehyde **11** (Scheme 3, Eq. 2). Subsequent allylation of the carbonyl group could be obtained by using excess allyltrimethylsilane (Scheme 3, Eq. 3). Formation of the double homoallylic amine **13** could be possible via a $Bi(OTf)_3{\cdot}4H_2O$-catalyzed three-component reaction (Scheme 3, Eq. 4). However, the relative stereochemistry of products **8**, **9**, **12**, and **13** could not be determined.

Our allylation method allows the straightforward formation of high value precursors for ring-closing metathesis (RCM). Our initial investigations focused on the reaction of terminal dienes prepared by our methodology (**2t**, 59%; **2u**, 61%; **2v**, 64%) with various metathesis catalysts (Scheme 4). Grubbs I catalyst allowed the smooth formation of six- and seven-membered substituted Cbz carbamates. The corresponding cyclooctene derivative could be obtained using Grubbs II catalyst. The 3-Cbz protected cyclohexenylamine **14** has proven to be a valuable precursor of bicyclic urethanes after further cyclization involving electrophilic halogen atoms [60].

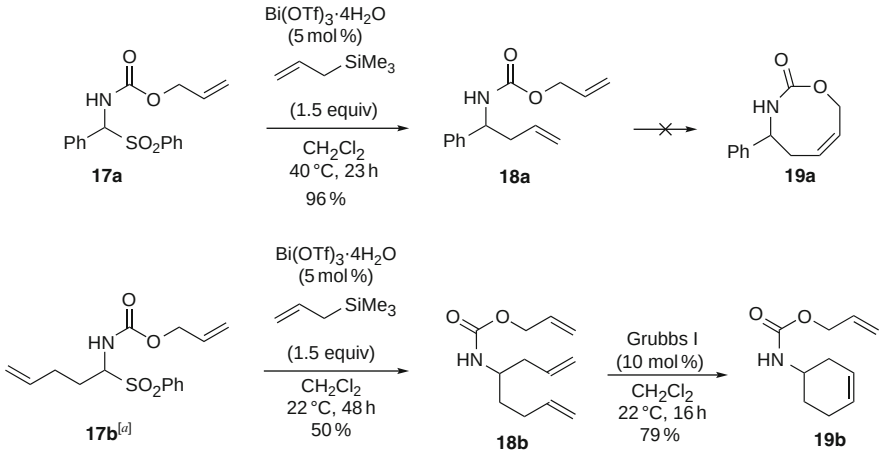
Other protecting groups could be used and allyloxycarbonyl (Alloc)-derived sulfones **17a** and **17b** could be allylated using our standard procedure (Scheme 5). At this point, use of Alloc instead of Cbz as the amine protecting group did not change the chemoselectivity of the RCM reaction since no RCM was observed with the Alloc group (Scheme 5). **18a** could not undergo RCM (Hoveyda–Grubbs II, $CH_2Cl_2$, reflux, 65 h, no conversion). On the other hand, Alloc-protected terminal diene **18b** afforded smoothly protected cyclohexenylamine **19b** (10 mol% Grubbs I, $CH_2Cl_2$, 22 °C, 16 h, 79%). The **19b** could then be easily deprotected using standard Pd(0)-catalyzed procedure [61].

In order to further extend the generality of our method, a functionalized allylsilane was also reacted with sulfone **1t**. Under the same optimized conditions, the corresponding homoallylic amine was obtained and subsequently subjected to



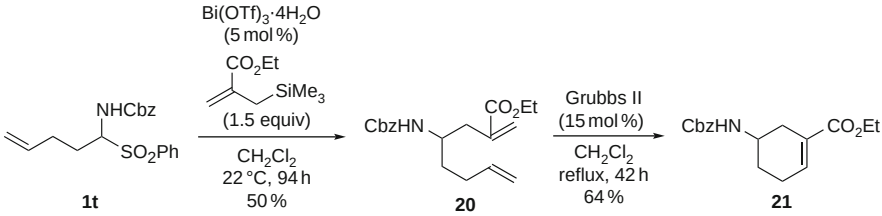

n = 1, **14** (93%) (5 mol% Grubbs I, 22 °C, 16 h)
n = 2, **15** (78%) (5 mol% Grubbs I, 22 °C, 45 h)
n = 3, **16** (35%, *Z*/*E* = 3.5: 1) (5 mol% Grubbs II, reflux, 20 h)

**Scheme 4** Ring-closing metathesis of terminal dienes




[a]Purity of starting material **17b** was estimated to be 95% by $^1$H NMR

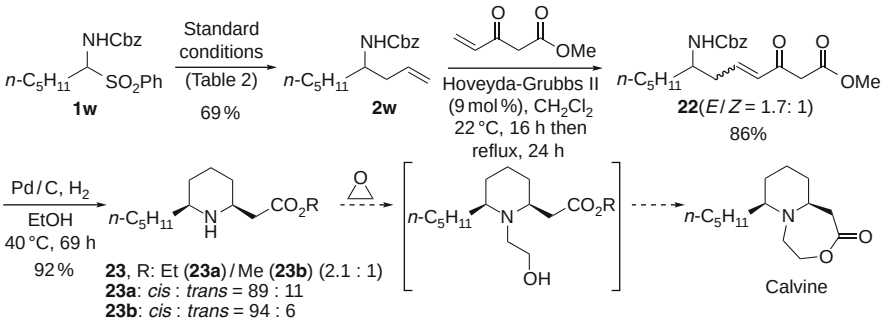
**Scheme 5** Allylation of Alloc-derived sulfones and ring-closing metathesis of an Alloc-protected homoallylic amine




**Scheme 6** $Bi(OTf)_3{\cdot}4H_2O$-catalyzed allylation using a functionalized allylsilane

RCM to afford compound **21** (Scheme 6). Although Grubbs II catalyst afforded compound in moderate yield (64%), only the dimerization product could be obtained using Grubbs I catalyst (10 mol% Grubbs I, PhMe, reflux, 16 h, 37% of dimerization product of **21′**, 6% of expected product **21**).

Our sequential allylation/RCM methodology was further applied to the preparation of a key intermediate in the synthesis of calvine (Scheme 7). Homoallylic amine **2w** was obtained in a moderate yield according to our standard conditions (Table 2, entry 12). Cross-metathesis of **2w** with methyl 3-oxopent-4-enoate, based on Blechert's work, afforded compound **22** in a good yield (86% of **22**, $E/Z = 1.7{:}1$) [6, 62]. The *cis*-disubstituted piperidine **23** was obtained with high yield and diastereoselectivity, with partial transesterification occurring during the transformation. Further transformation of **23** in calvine via ethylene oxide opening with **23b**, followed by ring-closing into the seven-membered lactone, has already been reported in the literature [63] (for a recent synthesis of calvine see [64]).




**Scheme 7** Synthesis of calvine

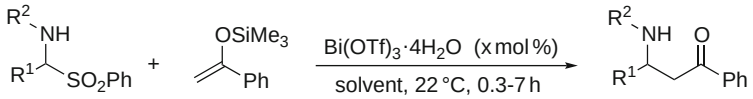
## *1.3 Bismuth Triflate-Catalyzed Mannich-Type Reaction*

Recently, Kobayashi has disclosed significant advances regarding rare-earth and lanthanide triflates as catalysts for Mannich-type reactions [65–68] and there are several reviews available on catalytic Mannich-type reactions [69–73]. High catalytic activity, low toxicity, and low tolerance to moisture and air make lanthanide triflates valuable catalysts. However, the high cost of these catalysts restricts their use. Bismuth compounds are of interest as lower toxicity and cheaper alternatives to such catalysts.

Initially, various solvents were screened for the Mannich-type reaction of *N*-alkoxycarbonylamino sulfones **1**, **3**, and **5** with trimethyl(1-phenylvinyloxy)silane in the presence of $Bi(OTf)_3{\cdot}4H_2O$. Interestingly, when **1** was treated with 0.5 mol% $Bi(OTf)_3{\cdot}4H_2O$ in THF for 7 h at 22 °C, the corresponding Cbz-protected β-amino ketone **24a** was isolated in moderate yield (51%, Table 4, entry 1). Among various polar solvents tested, acetonitrile and dichloromethane gave the best yields of the expected product (Table 4, entries 2 and 3). The same reaction in the presence of $Sc(OTf)_3$ led to recovery of starting material only (sulfone **1o**, trimethyl (1-phenylvinyloxy)silane, 0.5 mol% $Sc(OTf)_3$, $CH_2Cl_2$, 22 °C, 5 h). The catalyst loading had to be increased to 1 mol% for some substrates (Table 4, entries 4 and 5). Because of the poor solubility in acetonitrile of many of the *N*-alkoxycarbonylamino sulfones **1** presented here, dichloromethane was selected as the solvent of choice. Carbamate-derived sulfones **3a** and **5** led to very good yields of the desired products **24** (Table 4, entries 5 and 6). *N*-Benzyloxycarbonylamino sulfones were chosen as model substrates for subsequent studies.

Several examples of $Bi(OTf)_3{\cdot}4H_2O$-catalyzed Mannich-type reactions of various *N*-benzyloxycarbonylamino sulfones **1** with silyl enol ethers are summarized in Table 5. *N*-Benzyloxycarbonylamino sulfones **1** derived from differently substituted benzaldehydes were reacted with trimethyl(1-phenylvinyloxy)silane in dichloromethane at room temperature. The corresponding β-amino ketones **24** were smoothly obtained (Table 5, entries 1–6). The reaction was efficient using electron-deficient benzaldehyde-derived sulfones, and the corresponding β-amino ketones **24**

**Table 4** $Bi(OTf)_3{\cdot}4H_2O$-catalyzed Mannich-type reactions involving *N*-alkoxycarbonylamino sulfones and trimethyl(1-phenylvinyloxy)silane




**1**, **3**, **5** **2a** **24**

| Entry | $R^1$ | $R^2$ | Catalyst loading (*x*) (mol%) | Solvent | **24** | Yield[a] **24** (%) |
|---|---|---|---|---|---|---|
| 1 | Et | Cbz | 0.5 | THF | **24a** | 51 |
| 2 | Et | Cbz | 0.5 | MeCN | **24a** | 90 |
| 3 | Et | Cbz | 0.5 | $CH_2Cl_2$ | **24a** | 94 |
| 4 | Ph | Cbz | 1 | $CH_2Cl_2$ | **24b** | 85 |
| 5 | Ph | Boc | 1 | $CH_2Cl_2$ | **24c** | 80[b] |
| 6 | Ph | $CO_2Et$ | 0.5 | $CH_2Cl_2$ | **24d** | 85 |

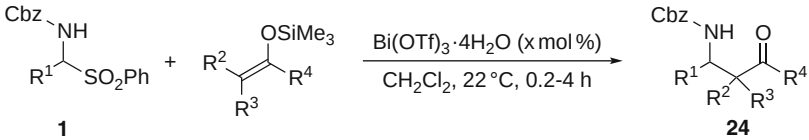
Conditions: *N*-alkoxycarbonylamino sulfone (1.0 equiv.), trimethyl(1-phenylvinyloxy)silane (1.3 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (0.5–1 mol%) at 22 °C
[a]Isolated yield
[b]Product **24c** slightly decomposed on silica gel chromatography and was contaminated by small quantities of deprotected β-aminoketone

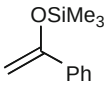
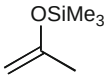
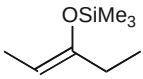
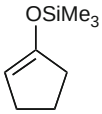
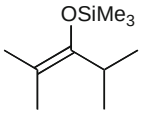
were obtained in very good yields (Table 5, entries 1 and 2). Sulfones derived from several electron-rich aromatic aldehydes led to the desired products in good yields (Table 5, entries 3–6). For selected substrates, a slightly better yield was obtained when using a catalyst loading of 1 mol% instead of 0.5 mol% (Table 5, compare entries 5 and 6). *N*-Benzyloxycarbonylamino sulfones derived from aliphatic aldehydes afforded products **24** in very good to excellent yields (Table 5, entries 7–9). Trimethyl(prop-1-en-2-yloxy)silane afforded β-amino ketone **24u** in good yield (Table 5, entry 10). Silyl enol ethers derived from 3-pentanone and cyclopentanone smoothly afforded β-amino ketones **24v** and **24w**, respectively (Table 5, entries 11 and 12). Tetrasubstituted silyl enol ethers readily produced the expected products **24x** and **24g** (Table 5, entries 13 and 14).

Further investigation with various silyl ketene acetals is summarized in Table 6. Silyl ketene acetals derived from various esters were reacted with *N*-benzyloxycarbonylamino sulfones **1** in the presence of 0.5–1 mol% $Bi(OTf)_3{\cdot}4H_2O$. The corresponding β-amino esters **24** were obtained in moderate to good yields (Table 6). Silyl enolates derived from esters as well as thioesters reacted smoothly to give the adducts. The *N*-benzyloxycarbonylamino sulfone derived from *n*-butyraldehyde **1p** led to moderate yields of β-amino esters when reacted with (thio)acetate-derived silyl ketene acetals (Table 6, entries 1 and 2). A very good yield was obtained when the same sulfone was subjected to a tetrasubstituted silyl ketene acetal (Table 6, entry 3). The latter afforded moderate to good yields of β-amino esters **24** with phenylacetaldehyde, *p*-tolualdehyde, and *o*-tolualdehyde-derived sulfones (Table 6, entries 4–6).

The potential of this catalytic approach is further demonstrated by the synthesis of a substituted 1,3-oxazinan-2-one via a reduction–cyclization strategy (Scheme 8).

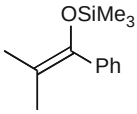
**Table 5** $Bi(OTf)_3{\cdot}4H_2O$-catalyzed Mannich-type reactions with various *N*-benzyloxycarbonylamino sulfones and silyl enol ethers




| Entry | $R^1$ | Silyl enol ether | Catalyst loading (*x*) (mol%) | **24** | Yield[a] **24** (%) |
|---|---|---|---|---|---|
| 1 | 4-$ClC_6H_4$ |  | 0.5 | **24f** | 84 |
| 2 | 4-$FC_6H_4$ | | 0.5 | **24h** | 92 |
| 3 | 4-$MeC_6H_4$ | | 0.5 | **24t** | 89 |
| 4 | 2-$MeC_6H_4$ | | 0.5 | **24b** | 88 |
| 5 | 4-$MeOC_6H_4$ | | 0.5 | **24c** | 83 |
| 6 | 4-$MeOC_6H_4$ | | 1 | **24c** | 87 |
| 7 | $CH_3(CH_2)_2$ | | 1 | **24p** | 87 |
| 8 | $(CH_3)_2CH$ | | 1 | **24o** | 96 |
| 9 | *c*-$C_6H_{11}$ | | 0.5 | **24r** | 85 |
| 10 | $CH_3(CH_2)_2$ |  | 0.5 | **24u** | 80 |
| 11 | $PhCH_2$ |  | 1 | **24v** | 77[b] |
| 12 | $CH_3(CH_2)_2$ |  | 0.5 | **24w** | 81[c] |
| 13 | 4-$MeC_6H_4$ |  | 0.5 | **24x** | 86 |

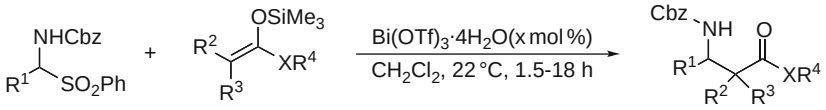
(continued)

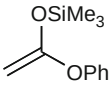
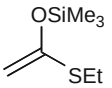
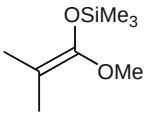
**Table 5** (continued)

| Entry | $R^1$ | Silyl enol ether | Catalyst loading ($x$) (mol%) | **24** | Yield[a] **24** (%) |
|---|---|---|---|---|---|
| 14 | $PhCH_2$ |  | 0.5 | **24g** | 59 |

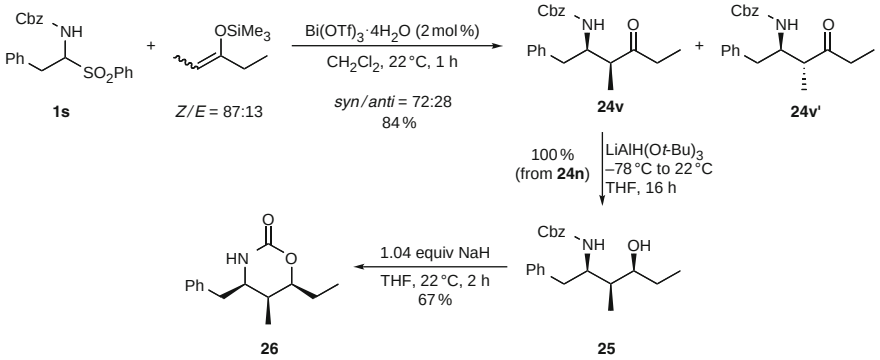
Conditions: *N*-benzyloxycarbonylamino sulfone (1.0 equiv.), silyl enol ether (1.3 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (0.5–1 mol%) in $CH_2Cl_2$ at 22 °C
[a]Isolated yield
[b]Silyl enol ether was used as a mixture of stereoisomers ($Z/E$ = 87:13). Product **24v** was isolated as a mixture of stereoisomers (*syn*/*anti* = 72:28) (ratio determined by $^1$H NMR)
[c]Product **24w** was isolated as a 57:43 mixture of diastereoisomers as determined by $^1$H NMR

**Table 6** $Bi(OTf)_3{\cdot}4H_2O$-catalyzed Mannich-type reactions with various *N*-benzyloxycarbonylamino sulfones and silyl ketene acetals




| Entry | $R^1$ | Silyl ketene acetal | Catalyst loading ($x$) (mol%) | Yield[a] **24** (%) |
|---|---|---|---|---|
| 1 | $CH_3(CH_2)_2$ |  | 0.5 | 66 |
| 2 | $CH_3(CH_2)_2$ |  | 0.5 | 61 |
| 3 | $CH_3(CH_2)_2$ |  | 1 | 86 |
| 4 | $PhCH_2$ | | 1 | 67 |
| 5 | 4-$MeC_6H_4$ | | 1 | 78 |
| 6 | 2-$MeC_6H_4$ | | 1 | 73 |

Conditions: *N*-benzyloxycarbonylamino sulfone (1.0 equiv.), silyl ketene acetal (1.3 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (0.5–1.0 mol%) in $CH_2Cl_2$ at 22 °C
[a]Isolated yield




**Scheme 8** Synthesis of 4-benzyl-6-ethyl-5-methyl-1,3-oxazinan-2-one **26** via the *N*-alkoxycarbonylamino sulfone pathway

Optimization of the previously reported Mannich-type reaction of trimethyl (pent-2-en-3-yloxy)silane with the sulfone **1s** derived from phenyl acetaldehyde (Table 5, entry 11) led to the corresponding β-amino ketone in a good yield with moderate diastereoselectivity (2 mol% $Bi(OTf)_3{\cdot}4H_2O$, yield = 84%, **24v**/**24v′** *syn*/*anti* = 72:28) (Scheme 8). Reduction of the major diastereoisomer **24v** with lithium tri-*tert*-butoxyaluminohydride afforded **25** as the only one diastereoisomer. Further cyclization of the latter with NaH afforded 4-benzyl-6-ethyl-5-methyl-1,3-oxazinan-2-one **26**. The relative configuration of the six-membered carbamate was established as *cis–cis* by NMR analysis.

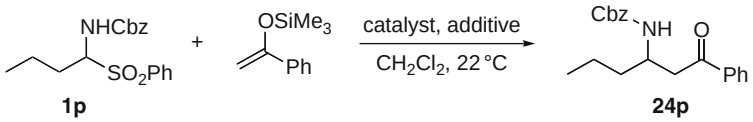
In order to obtain further insight into the mechanism of the Mannich-type reaction, sulfone **1p** and silyl enol ether derived from acetophenone were reacted in the presence HOTf or TMSOTf, which could be produced in the reaction medium when using $Bi(OTf)_3{\cdot}4H_2O$ as catalyst. It appeared that these two compounds efficiently catalyze the Mannich-type reaction (Table 7, entries 2 and 3). The reaction does not occur in the presence of 2,6-di-*tert*-butyl-4-methyl-pyridine [DTBMP] (1.0 equiv. of **1p**, 1.3 equiv. of silyl enol ether, 0.5 mol% of $Bi(OTf)_3{\cdot}4H_2O$, 1.5 mol% of 2,6-di-*tert*-butyl-4-methyl-pyridine, 22 °C, 20 h, 99% recovery of **1p**), which indicates that triflic acid is involved in the mechanism (Table 7, entry 4).

## 2 Bismuth-Mediated Three-Component Addition Reaction

### *2.1 Bismuth-Mediated Three-Component Aza-Sakurai Reaction*

The development of new methods for the synthesis of homoallylic amine derivatives is an important area of synthetic efforts. Homoallylic amines are extremely important compounds as biologically active molecules [1]. The Lewis acid-mediated reactions of imines with allyl silanes are among the most efficient for

**Table 7** Mechanistic studies for Mannich-type reactions of *N*-benzyloxycarbonylamino sulfone **1p**

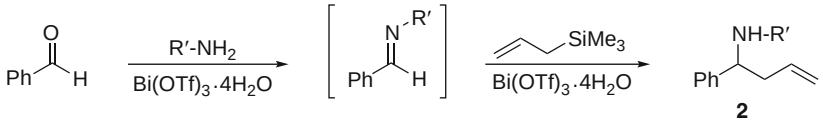



| Entry | Catalyst | Additive | Time (h) | Yield[a] **24p** (%) |
|---|---|---|---|---|
| 1 | $Bi(OTf)_3$ 1 mol% | – | 0.3 | 87 |
| 2 | TMSOTf 3.0 mol% | – | 0.5 | 100 |
| 3 | HOTf 1.5 mol% | – | 0.5 | 99 |
| 4 | $Bi(OTf)_3$ 0.5 mol% | DTBMP 1.5 mol% | 20 | 0 |

Conditions: sulfone (1.0 equiv.), silyl enol ether (1.3 equiv.), catalyst (0.5–3.0 mol%) in $CH_2Cl_2$ at 22 °C
[a]Isolated yield

the synthesis of homoallylic amines. Therefore, the development of new catalytic methods for their preparation is of first importance in organic synthesis. Catalytic allylation reactions have been reported by several groups as an efficient method to prepare the homoallylic amines [74–89]. However, many imines tend to be unstable during purification by chromatography, distillation, or prolonged storage. Thus, methods involving the in situ generation of the imine are highly valuable, among them the one-pot formation of imines formed in situ from aldehydes and amines has been proposed. Nevertheless, most Lewis acids cannot be used in this reaction because they decompose or deactivate in the presence of the amines and water produced during imine formation. Thus, it is desirable from a synthetic point of view that imines, formed in situ from carbonyl compounds and amines, immediately react with allyl silanes and provide homoallylic amines in a one-pot process. The direct three-component reaction has been reported for the preparation of homoallylic amines [90–105]. Recently, synthetic methods involving rare-earth and lanthanide triflates as catalysts for allylation reactions have been reported. High catalytic activity, low toxicity, and low tolerance to moisture and air make lanthanide triflates attractive catalysts. However, the high cost of these catalysts restricts their use. Lately, synthetic methodology involving bismuth has been reported. A Barbier–Grignard-type reaction involving $Sm/BiCl_3$ has been reported as an efficient synthesis of homoallylic amines in aqueous media [106]. A method involving bismuth triflate conjointly used with benzoic acid as catalyst for allylation of aldehydes or aldimines has been reported but has the major drawback of using stoichiometric quantities of allytributylstannane and benzoic acid [37, 107]. To overcome these limitations, we have reported a mild and efficient method for the allylation of a variety of imines with allyltrimethylsilane catalyzed by bismuth(III) without any additives [108]. The corresponding protected homoallylic amines are obtained in good yields using $Bi(OTf)_3{\cdot}4H_2O$ as a catalyst.

**Table 8** Bismuth-mediated three-component allylation reaction: synthesis of *N*-protected homoallylic amines



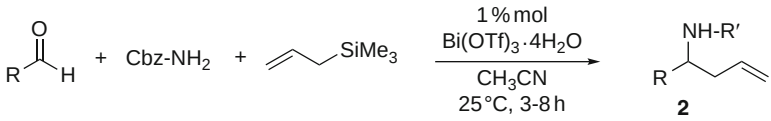

| Entry | R’ | Conditions | Yield[a] **2** (%) |
|---|---|---|---|
| 1 | Boc | 20 mol% $Bi(OTf)_3$, MeCN, 0.5 M, 25 °C, 6 h | 27 |
| 2 | Cbz | 10 mol% $Bi(OTf)_3$, $CH_2Cl_2$, 1 M, 25 °C, 24 h | 51 |
| 3 | Cbz | 10 mol% $Bi(OTf)_3$, MeCN, 1 M, 25 °C, 3 h | 59 |
| 4 | Cbz | 1 mol% $Bi(OTf)_3$, MeCN, 0.5 M, 25 °C, 3 h | 74 |

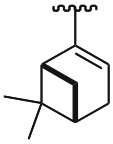
[a]Refers to yield of isolated product

The bismuth-catalyzed allylation reaction was first studied with isolated imines. Interestingly, when equimolar amounts of *N*-(benzyloxycarbonyl)benzaldimine and allyltrimethylsilane were treated with 1 mol% $Bi(OTf)_3{\cdot}4H_2O$ in acetonitrile for 14 h at 25 °C, the protected homoallylic amine **2** was isolated in low yield (18%). Consequently, a one-pot sequence involving the formation of the imine and its in situ allylation was investigated. We tried to generate the imine by the reaction of Cbz-$NH_2$ or Boc-$NH_2$ with benzaldehyde, catalyzed by $Bi(OTf)_3{\cdot}4H_2O$ (Table 8). The imine formed in situ was then subsequently allylated with allyltrimethylsilane to afford the desired homoallylic amine. Boc-protected homoallylic amine was obtained in poor yield using 20 mol% $Bi(OTf)_3{\cdot}4H_2O$ (Table 8, entry 1). When Cbz was used as the protecting group, the protected homoallylic amine **2** could be obtained in modest yield with 10 mol% of the catalyst. When acetonitrile was used instead of dichloromethane, a better yield was obtained (Table 8, entries 2 and 3). Moreover, a decreased quantity of $Bi(OTf)_3{\cdot}4H_2O$ (1 mol% versus 10 mol%) led to a good yield of the Cbz-protected homoallylic amine (Table 8, entry 4).

The scope and limitations of this reaction with respect to the aldehyde were studied. Cbz was chosen as protecting group. The results are summarized in Table 9. Allyltrimethylsilane was used as the allylation agent in all the reactions. Generally, excellent yields of homoallylic amines were obtained with 1 mol% $Bi(OTf)_3{\cdot}4H_2O$ at 25 °C in acetonitrile. No traces of the corresponding homoallylic alcohols resulting from direct addition of allyltrimethylsilane to the aldehyde were observed. All the aromatic and aliphatic aldehydes gave very good results using benzylcarbamate. The allylation was efficient using aliphatic aldehydes and the corresponding homoallylic amines were obtained with very good yields (Table 9, entries 1, 2, 4, and 5). Isobutyraldehyde led to the product **2q** with moderate yield (Table 9, entry 3). Steric hindrance in the aldehyde component does not seem to play a significant role (Table 9, entry 5). Conjugated aldehydes were also good substrates (Table 9, entries 5 and 6). Several aromatic aldehydes led to the desired products in good yields (Table 9, entries 8–10), except *p*-nitrobenzaldehyde, which led to **2t** in poor yield (Table 9, entry 11).

**Table 9** Synthesis of Cbz-protected homoallylic amines




| Entry | R | Time (h) | Yield[a] **2** (%) |
|---|---|---|---|
| 1 | Me | 5 | 78 |
| 2 | $CH_3(CH_2)_2$ | 6 | 82 |
| 3 | $(CH_3)_2CH$ | 7 | 58 |
| 4 | $c$-$C_6H_{11}$ | 4 | 86 |
| 5 |  | 8 | 77 |
| 6 | Ph–CH=CH | 8 | 73 |
| 7 | Ph | 3 | 74 |
| 8 | $p$-$ClC_6H_4$ | 4 | 75 |
| 9 | $p$-$MeOC_6H_4$ | 6 | 81 |
| 10 | $p$-$CF_3C_6H_4$ | 6 | 75 |
| 11 | $p$-$NO_2C_6H_4$ | 6 | 27 |

Conditions: substrates were mixed in 1:1 ratio with 1.1 equiv. of allyltrimethylsilane
[a]Yield refers to yield of isolated product

In summary, we have found that allylation of in situ prepared imines proceeds smoothly with allyltrimethylsilane and a catalytic amount of $Bi(OTf)_3{\cdot}4H_2O$. This method offers several advantages including mild reaction conditions, low quantity of the catalyst (1 mol%), and no formation of by-products. Moreover, our protocol does not require prior isolation of the imine. The homoallylic amine is directly obtained as a Cbz-protected group in a one-pot process.

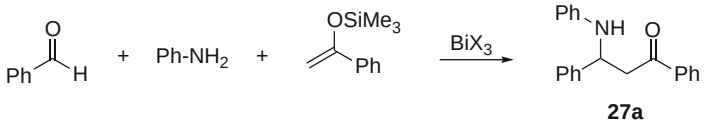
## 2.2 *Bismuth-Mediated Three-Component Mannich-Type Reaction*

In parallel to the bismuth(III)-catalyzed three-component allylation reaction, we have reported the corresponding three-component bismuth(III)-catalyzed Mannich-type reaction. A major merit of the three-component reaction is indeed that many unique structures can be afforded rapidly when three or more reactants are combined in a single step to afford new compounds. The development of an efficient bismuth-catalyzed Mannich-type three-component reaction that combines an aldehyde, an amine, and a silyl enolate to give compounds with a β-amino carbonyl core

structure was therefore attractive. β-Amino esters and ketones are obtained efficiently in the presence of 1–2 mol% of $Bi(OTf)_3{\cdot}4H_2O$ [109–111]. The scope and generality of the reaction are demonstrated in this section using a large selection of carbonyl compounds and silyl enolates. Recycling studies have also been included. In addition, further insight regarding the mechanism will be presented.

Initial investigations in the Mannich-type reaction of silyl enolates with benzaldehyde and aniline employed a series of bismuth(III) salts (Scheme 9, Table 10). These results were promising because the corresponding β-amino ketone could be obtained in moderate to good yield with bismuth halides, except bismuth fluoride (Table 10, entries 1–4). Bismuth nitrate smoothly afforded the expected product (Table 10, entry 5). While bismuth acetate gave no conversion, bismuth trifluoroacetate provided the product in only moderate yield (Table 10, entries 6 and 7). Phenyl bismuth ditriflate and diphenyl bismuth triflate appeared to be more efficient catalysts than all those previously tested (Table 10, entries 8 and 9). Bismuth(III) triflate led to the expected product in a good yield and in a short reaction time, without any difference between the anhydrous and the hydrated form (Table 10, entries 10 and 11).

With $Bi(OTf)_3{\cdot}4H_2O$ identified as an effective catalyst for the Mannich-type reaction, optimization of reaction conditions using various solvents was undertaken




**Scheme 9** $BiX_3$ salt-catalyzed Mannich-type reaction involving benzaldehyde, aniline, and (1-phenylvinyloxy)trimethylsilane

**Table 10** Mannich-type reaction of benzaldehyde, aniline, and (1-phenylvinyloxy)trimethylsilane using bismuth(III) salts as catalyst

| Entry | Catalyst | Time (h) | Yield[a] **27a** (%) |
|---|---|---|---|
| 1 | $BiF_3$ | 24 | 0 |
| 2 | $BiCl_3$ | 1.5 | 59 |
| 3 | $BiBr_3$ | 0.3 | 72 |
| 4 | $BiI_3$ | 7.5 | 62 |
| 5 | $Bi(NO_3)_3{\cdot}5H_2O$ | 0.2 | 67 |
| 6 | $Bi(OAc)_3$ | 23 | 0 |
| 7 | $Bi(OCOCF_3)_3$ | 0.8 | 36 |
| 8 | $Ph_2Bi(OTf)$ | 0.3 | 85[b] |
| 9 | $PhBi(OTf)_2$ | 0.1 | 89[b] |
| 10 | $Bi(OTf)_3{\cdot}4H_2O$ | 0.1 | 89[b] |
| 11 | $Bi(OTf)_3$ | 0.1 | 90[b] |

Conditions: benzaldehyde (1.0 equiv.), aniline (1.0 equiv.), (1-phenylvinyloxy)trimethylsilane (1.0 equiv.), $BiX_3$ (1 mol%), MeCN, 25 °C

[a]Isolated yield

[b]1.2 equiv. of (1-phenylvinyloxy)trimethylsilane was used

**Table 11** Mannich-type reaction of benzaldehyde, aniline, and (1-phenylvinyloxy)trimethylsilane in different solvents

| Entry | Solvent | Catalyst loading (*x*) (mol%) | Time (h) | Yield[a] **27a** (%) |
|---|---|---|---|---|
| 1 | PhMe | 1 | 3.5 | 54 |
| 2 | $Et_2O$ | 1 | 2.5 | 72 |
| 3 | $CH_2Cl_2$ | 1 | 1.5 | 60 |
| 4 | $MeNO_2$ | 1 | 0.1 | 71 |
| 5 | EtOH | 1 | 3 | 80 |
| 6 | MeCN | 1 | 0.5 | 82[b] |
| 7 | MeCN | 0.5 | 21 | 68 |
| 8 | MeCN | 2 | 0.5 | 84 |
| 9 | MeCN | 5 | 0.1 | 85 |

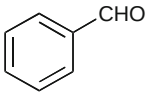
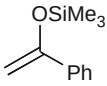
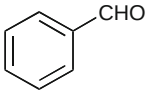
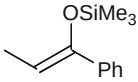
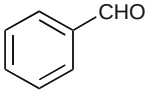
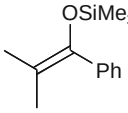
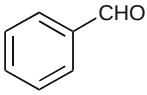
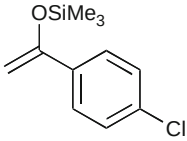
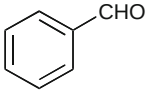
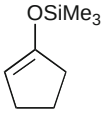
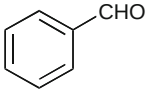
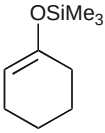
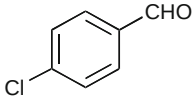
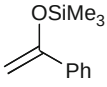
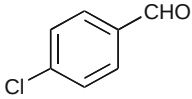
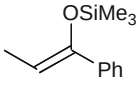
Conditions: benzaldehyde (1.0 equiv.), aniline (1.0 equiv.), (1-phenylvinyloxy)trimethylsilane (1.0 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (*x* mol%), 25 °C
[a]Isolated yield
[b]0.1 mol benzaldehyde scale, 85% yield

(Scheme 9, Table 11). Benzaldehyde, aniline, and (1-phenylvinyloxy)trimethylsilane were chosen as representative substrates. Among various solvents tested, toluene, diethyl ether, dichloromethane, and nitromethane gave moderate yields of the expected product (Table 11, entries 1–4). Ethanol afforded the product in good yield (Table 11, entry 5), although the best solvent was found to be acetonitrile. In acetonitrile, 1,3-diphenyl-3-(*N*-phenylamino)propan-1-one **27a** was obtained in the best yield (82%). Scaling up the reaction up to 0.1 mol afforded **27a** in 85% yield (Table 11, entry 6). Upon further optimization of the reaction conditions, we found that a lower catalyst loading gave decreased yields (Table 11, entry 7). Increasing the catalyst loading did not significantly affect the yield (Table 11, entries 8 and 9).

Several examples of $Bi(OTf)_3$-catalyzed Mannich-type reactions with various silyl enol ethers are summarized in Table 12. Silyl enol ethers derived from aromatic and aliphatic ketones were reacted with an equimolar mixture of aldehyde and aniline (Scheme 10). The corresponding β-amino ketones **27** were obtained in good yields (Table 12, entries 1–4) from aromatic-derived silyl enol ethers, except for the more hindered isobutyrophenone derivative. Silyl enol ethers derived from cyclopentanone or cyclohexanone afforded the β-amino ketones in good yields (Table 12, entries 5 and 6).

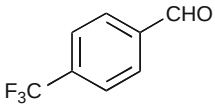
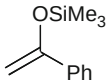
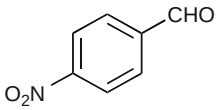
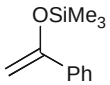
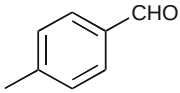
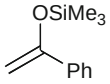
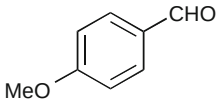
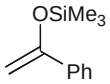
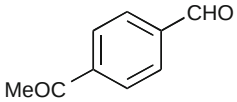
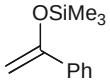
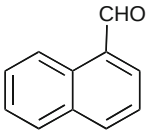
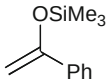
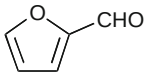
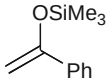
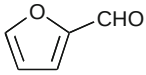
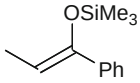
Other aldehydes were tested and, generally, moderate to excellent yields of β-amino ketone were obtained with silyl enol ethers and 1 mol% of $Bi(OTf)_3{\cdot}4H_2O$ at 25 °C in acetonitrile. Aromatic aldehydes reacted smoothly to give the corresponding β-amino ketone derivatives **27** in high yield (Table 12, entries 7–14). The reaction worked well with a variety of aldehydes including those bearing an electron withdrawing group, and the corresponding β-amino ketones **27** were obtained with very good yields. Several electron-rich aromatic aldehydes led to the desired products in good yields (Table 12, entries 11 and 12). 4-Acetylbenzaldehyde led to the expected product with complete chemoselectivity toward the aldehyde (Table 12, entry 13). Only a moderate yield was obtained with 1-naphthyl carboxaldehyde as the substrate (Table 12, entry 14). With an

**Table 12** Mannich-type reaction with silyl enol ethers derived from ketones

| Entry | Aldehyde | Silyl enol ether | Time (h) | Yield[a] **27** (%) | dr (*syn*/*anti*) |
|---|---|---|---|---|---|
| 1 |  |  | 0.1 | 89 | – |
| 2 |  |  | 2 | 94 | 50:50 |
| 3 |  |  | 37 | 45[b] | – |
| 4 |  |  | 0.5 | 82 | – |
| 5 |  |  | 1.5 | 80 | 68:32 |
| 6 |  |  | 0.5 | 81 | 61:39 |
| 7 |  |  | 0.8 | 82 | – |
| 8 |  |  | 1.5 | 83 | –[c] |

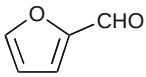
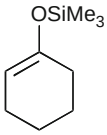
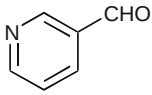
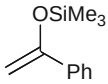
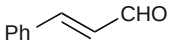
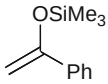
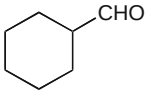
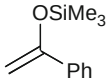
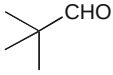
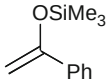
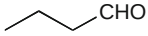
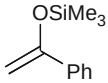
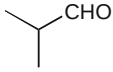
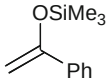
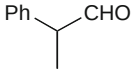
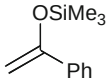
(continued)

**Table 12** (continued)

| Entry | Aldehyde | Silyl enol ether | Time (h) | Yield[a] **27** (%) | dr (*syn*/*anti*) |
|---|---|---|---|---|---|
| 9 |  |  | 0.5 | 88 | – |
| 10 |  |  | 0.5 | 87 | – |
| 11 |  |  | 1 | 81 | – |
| 12 |  |  | 0.7 | 86 | – |
| 13 |  |  | 0.1 | 92 | – |
| 14 |  |  | 1 | 44 | – |
| 15 |  |  | 1 | 76 | – |
| 16 |  |  | 3 | 80 | –[d] |

(continued)

**Table 12** (continued)

| Entry | Aldehyde | Silyl enol ether | Time (h) | Yield[a] **27** (%) | dr (*syn*/*anti*) |
|---|---|---|---|---|---|
| 17 |  |  | 1 | 78 | 58:42 |
| 18 |  |  | 4.5 | 49 | – |
| 19 |  |  | 1.5 | 72 | – |
| 20 |  |  | 0.8 | 77 | – |
| 21 |  |  | 1 | 54 | – |
| 22 |  |  | 17 | 61[e] | – |
| 23 |  |  | 18 | 51[e] | – |
| 24 |  |  | 3 | 70[e] | –[f] |

Conditions: aldehyde (1.0 equiv.), aniline (1.0 equiv.), silyl enol ether (1.0–1.2 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (1 mol%), 25 °C

[a]Isolated yield

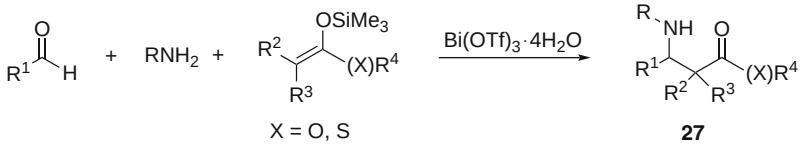
[b]$Bi(OTf)_3{\cdot}4H_2O$ (5 mol%)

[c]dr = 66:34

[d]dr = 61:39

[e]Reaction at 0 °C

[f]dr = 85:15



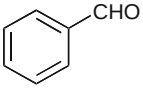
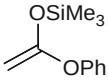
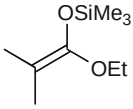
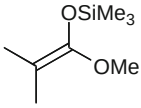
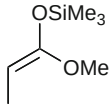
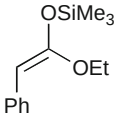
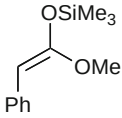
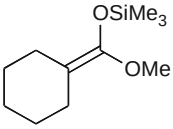

**Scheme 10** $Bi(OTf)_3{\cdot}4H_2O$-catalyzed Mannich-type reaction involving various aldehydes, amines, and silyl enolates

heterocyclic aldehyde, (e.g., furfural) the β-amino ketones were obtained in good yield (Table 12, entries 15–17). However, the reaction with 3-pyridylcarboxaldehyde gave a lower yield due to low conversion (Table 12, entry 18). A conjugated aldehyde was also shown to be a good substrate (Table 12, entry 19). Aliphatic aldehydes did not react under such conditions probably due to self condensation, except cyclohexane carboxaldehyde and pivaloyl aldehyde, which afforded product **27** in good yields (Table 12, entries 20 and 21). For enolizable aliphatic aldehydes, it was possible to obtain the corresponding β-amino ketones by a slight modification of the reaction conditions. Decreasing the reaction temperature to 0 °C and adding the aldehyde as the last reagent provided moderate to good yields of the expected products (Table 12, entries 22–24). Interestingly, we never observed side reaction products such as aldol and deamination products.

Several examples of $Bi(OTf)_3$-catalyzed Mannich-type reactions with various silyl ketene acetals are summarized in Table 13 (Scheme 10). Due to rapid hydrolysis of silyl ketene acetals under our standard conditions, it was necessary to optimize the reaction parameters. It was found that using 2 mol% of catalyst in THF at −78 °C gave the best yields. Thus, silyl ketene acetals derived from various esters were reacted with an equimolar mixture of benzaldehyde and aniline. The corresponding β-amino esters **27** were obtained in good yields (Table 13). Silyl enolates derived from esters as well as thioesters reacted smoothly to give the adducts. No adducts between aldehydes and the silyl enolates were observed in any reaction according to NMR analysis of the crude reaction mixture. As for the diastereoselectivity of the reaction, good results were obtained with the following substrates. [(*E*)-1-Methoxyprop-1-enyloxy]trimethylsilane afforded the expected product with *syn* stereoselectivity (Table 13, entry 4). Moderate *syn* selectivity was observed with [(*E*)-1-alkoxy-2-phenylvinyloxy]trimethylsilane (Table 13, entries 5 and 6). Geometry of the silyl ketene acetal did not influence the diastereoisomeric ratio because (*E*)- and (*Z*)-1-[(ethylthio)prop-1-enyloxy] trimethylsilane afforded the β-aminothioester with same *syn*/*anti* ratios (Table 13, entries 8 and 9). The relative stereochemistry was confirmed by base-cyclization to the corresponding β-lactam and comparison of the vicinal proton–proton coupling constants with those in the literature (Scheme 11) [112, 113].

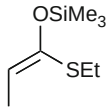
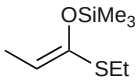
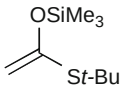
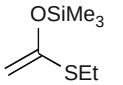
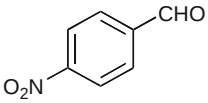
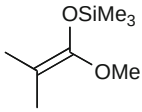
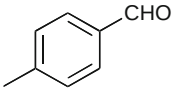
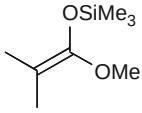
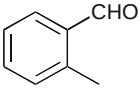
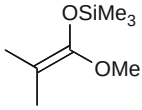
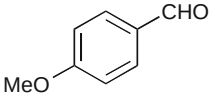
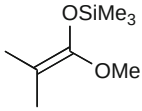
Generally, good yields of β-amino ester were obtained with aromatic aldehydes as well with an α,β-unsaturated aldehyde (Table 13, entries 12–16). Interestingly, we noted that the reaction was sterically sensitive because *ortho* substitution led to a decreased conversion (Table 13, compare entries 13 and 14). Aliphatic aldehydes

**Table 13** Mannich-type reaction with silyl ketene acetals derived from esters or thioesters

| Entry | Aldehyde | Silyl ketene acetal | Time (h) | Yield[a] **27** (%) | dr (*syn*/*anti*) |
|---|---|---|---|---|---|
| 1 |  |  | 3.5 | 84 | – |
| 2 | |  | 1.5 | 83 | – |
| 3 | |  | 0.8 | 85 | – |
| 4 | |  *E*/*Z* = 80:20 | 2.5 | 80 | 74:26 |
| | | *E*/*Z* = 80:20 | | | |
| 5 | |  *E*/*Z* = 78:22 | 2.5 | 81 | 78:22 |
| | | *E*/*Z* = 78:22 | | | |
| 6 | |  *E*/*Z* = 69:31 | 24 | 60 | 62:38 |
| | | *E*/*Z* = 69:31 | | | |
| 7 | |  | 1.7 | 59 | – |

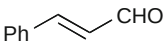
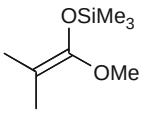
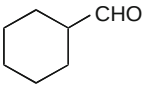
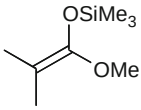
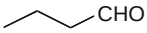
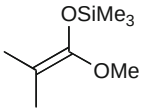
(continued)

**Table 13** (continued)

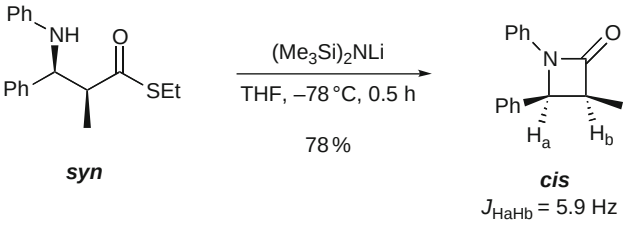
| Entry | Aldehyde | Silyl ketene acetal | Time (h) | Yield[a] **27** (%) | dr (*syn*/*anti*) |
|---|---|---|---|---|---|
| 8 | |   *E*/*Z* = 5:95 | 1 | 89 | 76:24 |
| 9 | | *E*/*Z* = 5:95   *E*/*Z* = 99:1 | 1.8 | 83 | 78:22 |
| 10 | | *E*/*Z* = 99:1   | 1 | 85 | – |
| 11 | |   | 1 | 90 | – |
| 12 |   |   | 2 | 82 | – |
| 13 |   |   | 1 | 76 | – |
| 14 |   |   | 3.5 | 34 | – |
| 15 |   |   | 2 | 70 | – |

(continued)

**Table 13** (continued)

| Entry | Aldehyde | Silyl ketene acetal | Time (h) | Yield[a] **27** (%) | dr (*syn*/*anti*) |
|---|---|---|---|---|---|
| 16 |  |  | 2.5 | 61 | – |
| 17 |  |  | 1 | 38 | – |
| 18 |  |  | 1.3 | 89 | – |

Conditions: aldehyde (1.0 equiv.), aniline (1.0 equiv.), silyl ketene acetal (1.2 equiv.), $Bi(OTf)_3 \cdot 4H_2O$ (2 mol%), THF, −78 °C
[a]Isolated yield

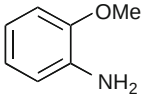
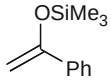
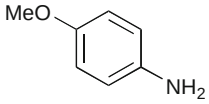
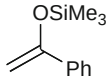
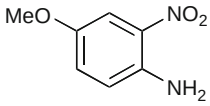
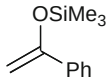
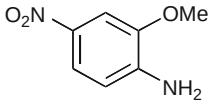
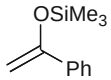
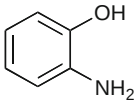
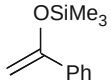
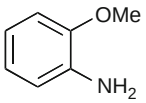
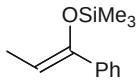
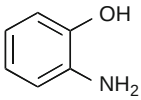
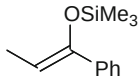
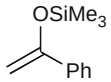



**Scheme 11** Determination of the relative stereochemistry of a β-amino thioester

also afforded the corresponding amino esters **27** in moderate to good yields. In all cases, the corresponding aldol derivative was never observed as a by-product.

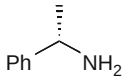
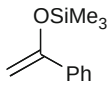
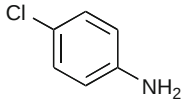
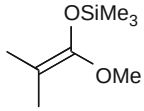
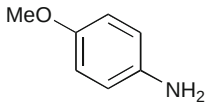
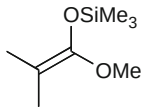
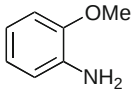
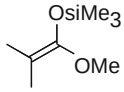
The scope of our method could be extended to other amines. Benzaldehyde was chosen in our model reaction (Scheme 10). The *ortho*- and *para*-anisidines gave good yields of the corresponding β-amino carbonyl compounds (Table 14, entries 1 and 2), which are known to be cleavable under oxidative conditions [114]. Other substituted anilines also afforded the β-amino carbonyl compounds in high yields (Table 14, entries 3–5). The reaction with *o*-anisidine or 2-amino phenol and silyl enol ether derived from propiophenone proceeded smoothly, although almost no diastereoselectivity was observed (Table 14, entries 6 and 7). Using benzyl carbamate instead of an aniline gave only a moderate yield of the Cbz-protected β-amino carbonyl compound (Table 14, entry 8). The reaction of the same silyl enol ether with benzaldehyde and α-methyl benzylamine did not afford the expected product

**Table 14** $Bi(OTf)_3 \cdot 4H_2O$-catalyzed Mannich-type reaction with amines

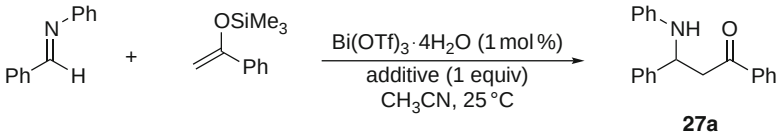
| Entry | Amine | Silyl enolate | Time (h) | Yield[a] **27** (%) |
|---|---|---|---|---|
| 1 |  |  | 2 | 78 |
| 2 |  |  | 1 | 79 |
| 3 |  |  | 0.5 | 88[b] |
| 4 |  |  | 0.5 | 85[b] |
| 5 |  |  | 2 | 78[b] |
| 6 |  |  | 1 | 92[c] |
| 7 |  |  | 4 | 88[d] |
| 8 | $CbzNH_2$ |  | 0.8 | 49[b] |

(continued)

**Table 14** (continued)

| Entry | Amine | Silyl enolate | Time (h) | Yield[a] **27** (%) |
|---|---|---|---|---|
| 9 |  |  | 21 | 0 |
| 10 |  |  | 0.8 | 90 |
| 11 |  |  | 2 | 70 |
| 12 |  |  | 22 | 55 |

Conditions: benzaldehyde (1.0 equiv.), amine (1.0 equiv.), silyl enolate (1.2 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (1 mol%), MeCN, 25 °C (entries 1–9) or $Bi(OTf)_3{\cdot}4H_2O$ (2 mol%), THF, −78 °C (entries 10–12)
[a]Isolated yield
[b]Reaction at 0 °C
[c]dr = 60:40
[d]dr = 50:50

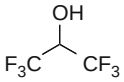



**Scheme 12** Use of additives in the $Bi(OTf)_3{\cdot}4H_2O$-catalyzed Mannich-type reaction

because of no conversion (Table 14, entry 9). For the reactions with a silyl ketene acetal, yields proved to be more dependent on aniline substitution. Excellent yield was obtained with an electron-poor aniline, but lower yields were observed with electron-rich anilines (Table 14, entries 10–12). Changing *p*-anisidine for a more sterically hindered *o*-anisidine also led to a decreased yield (Table 14, compare entries 11 and 12).

It is interesting to note that the two-pot version of this reaction, i.e. with prior formation and isolation of the imine, always occurred with very low conversions in our case (Scheme 12, Table 15). Knowing that the main difference between the

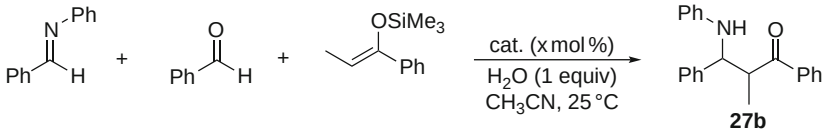
**Table 15** Mannich-type reaction of *N*-benzilideneaniline and (1-phenylvinyloxy)trimethylsilane

| Entry | Additive | Time (h) | Yield[a] **27a** (%) |
|---|---|---|---|
| **1** | – | 2 | 26 |
| **2** | $H_2O$ | 0.1 | 84 |
| **3** |  | 0.1 | 74 |

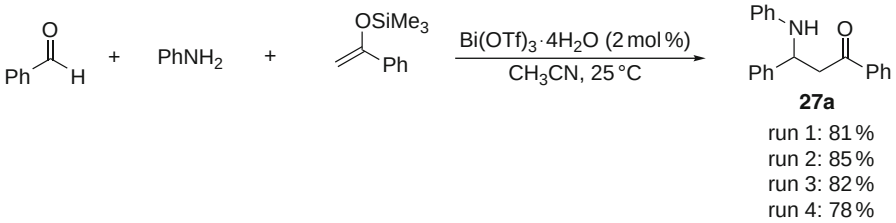
Conditions: benzilideneaniline **5** (1.0 equiv.), (1-phenylvinyloxy) trimethylsilane (1.0 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (1 mol%), additive (1 equiv.), MeCN, 25 °C
[a]Isolated yield

two-pot and the one-pot strategy is the in situ formation of water in the latter, the addition of a variety of acidic additives was examined. When the model reaction was studied with *N*-benzilideneaniline, β-aminoketone **27a** was obtained in low yield using 1 mol% of $Bi(OTf)_3{\cdot}4H_2O$ (Table 15, entry 1). However, addition of one equivalent of water or hexafluoroisopropanol provided the expected product (Scheme 12, Table 15, entries 2 and 3) in the usual high yields obtained in the three-component system.

As demonstrated, an aqueous solution of $Bi(OTf)_3$ is acidic [51], so the true catalyst is apparently HOTf released from the hydrolysis of $Bi(OTf)_3{\cdot}4H_2O$. The observation that the same reaction still occurs in the presence of hindered 2,6-di-*tert*-butylpyridine (1 equiv. of PhCHO, 1 equiv. of $PhNH_2$, 1 equiv. of (1-phenylvinyloxy)trimethylsilane, 1 mol% of $Bi(OTf)_3{\cdot}4H_2O$, 3 mol% of 2,6-di-*tert*-butylpyridine, 25 °C, 0.3 h, 80% of **27a**) does not indicate unambiguously that a Brønsted acid is not involved in the process, because the pyridinium salt itself also mediates the reaction (1 equiv. of PhCHO, 1 equiv. of $PhNH_2$, 1 equiv. of (1-phenylvinyloxy)trimethylsilane, 3 mol% of 2,6-di-*tert*-butylpyridinium triflate, 25 °C, 0.3 h, 80% of **27a**). However, replacing $Bi(OTf)_3{\cdot}4H_2O$ by HOTf as catalyst for the three-component model reaction showed that HOTf is indeed as effective as $Bi(OTf)_3{\cdot}4H_2O$ at catalyzing the Mannich-type reaction (1 equiv. of PhCHO, 1 equiv. of $PhNH_2$, 1 equiv. of (1-phenylvinyloxy)trimethylsilane, 3 mol% of HOTf, 25 °C, 0.3 h, 80% of **27a**). The HOTf-catalyzed Mannich-type reaction on the preformed imine affords the same product in good yield (1 equiv. of *N*-benzylideneaniline, 1 equiv. of (1-phenylvinyloxy)trimethylsilane, 1 equiv. $H_2O$, 3 mol% of HOTf, 25 °C, 0.1 h, 77% of **27a**) (compare with Table 6, entry 2). Moreover, the competition between the Mannich-type and the Mukaiyama aldol reaction was studied using $Bi(OTf)_3{\cdot}4H_2O$ and HOTf with (*Z*)-(1-phenylprop-1-enyloxy)trimethylsilane as the nucleophile (Scheme 13). In both cases, only the Mannich-type reaction occurred without formation of the corresponding aldol. The β-amino ketone **27b** was obtained in both cases with the same chemical yield, same diastereoselectivity, and same chemoselectivity (1 mol% $Bi(OTf)_3{\cdot}4H_2O$, 0.7 h, 82% of **27b**, dr = 51:49; 3 mol% HOTf, 0.6 h, 85% of **27b**, dr = 50:50). This result, in addition to the previous result, indicates that, most probably, $Bi(OTf)_3{\cdot}4H_2O$ is hydrolyzed under these conditions to afford triflic acid, which is expected to be the real catalytic species. Since HOTf is




**Scheme 13** Competition studies for diastereoselective Mannich-type reaction catalyzed by $Bi(OTf)_3{\cdot}4H_2O$ or HOTf




**Scheme 14** Recycling of the catalyst solution

very corrosive and difficult to handle, the practical use of $Bi(OTf)_3{\cdot}4H_2O$ makes our method particularly valuable.

From an environmental point of view, it is desirable to minimize the amount of waste for each organic transformation. We chose the reaction between benzaldehyde, aniline, and (1-phenylvinyloxy) trimethylsilane to study the effect of recycling the catalyst solution for subsequent runs. As the corresponding β-aminoketone was insoluble in acetonitrile, it could be easily recovered by simple filtration. The catalyst solution was recycled for subsequent cycles. Up to four runs could be achieved without noticeable decrease in yield (Scheme 14).

As an improvement over other catalyst systems, $Bi(OTf)_3{\cdot}4H_2O$ is a versatile catalyst for the Mannich-type reaction of a variety of silyl enolates with imines generated in situ. The reaction affords up to 94% yields in β-amino carbonyl compounds in short reaction times, and uses only 1–2 mol% of the catalyst. This method offers several advantages, including mild reaction conditions, highly catalytic process, and no formation of by-products. The conditions are suitable for a variety of aldehydes, aromatic amines, and silyl enolates. Also, the practical use of $Bi(OTf)_3{\cdot}4H_2O$ is highly valuable as a surrogate for HOTf because the latter is very corrosive and difficult to handle. Moreover, our protocol does not require prior isolation of the imine. The β-amino carbonyl compound is therefore directly obtained, usually as a crystalline product, in a one-pot process.

## 3 Bismuth-Catalyzed Mukaiyama Aldol Reaction

The aldol reaction is well-recognized as one of the most powerful synthetic tools for a fast carbon–carbon bond connection. This route provides a rapid access to β-hydroxy carbonyl compounds, which have attracted many synthetic efforts and

enjoyed widespread use in synthesis of natural products and bioactive molecules [115]. The Mukaiyama aldol reaction and its variants are probably the most notable achievements that have been made in the field by focusing on the addition of enolsilanes to aldehydes in the presence of catalytic amounts of Lewis acids [116, 117]. There are several reviews available on catalytic Mukaiyama aldol reactions [118, 119].

The vinylogous Mukaiyama aldol reaction rapidly provides 5-[hydroxy(aryl) methyl]furan-2(5*H*)-ones by addition of the γ carbon of a dienolate onto a carbonyl framework (for a review, see [120]). Over the past few years, some elegant enantioselective versions of this reaction using catalytic amounts of various chiral mediators have been described (for a review on enantioselective vinylogous Mukaiyama aldol, see [121]) [122–125], including a recent organocatalytic approach [126]. Recently, synthetic methods involving numerous lanthanide triflates have been reported [72, 127–129]. High catalytic activity and tolerance to moisture and air make lanthanide triflates attractive catalysts. However, their high cost often restricts their utilization.

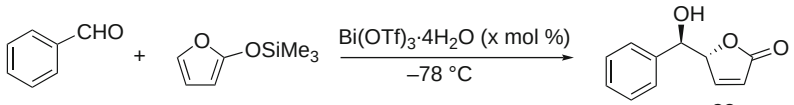
To our knowledge, all racemic examples up to now of vinylogous Mukaiyama aldol reactions with silyloxyfurans have employed Lewis acids such as $SnCl_4$, $ZnCl_2$, $TiCl_4$, $BF_3{\cdot}OEt_2$, $SiCl_4$, or silyl triflates. Yet, the moisture sensitivity of these catalysts and the high cost of some of them often restrain their use. In addition, all reported racemic reactions involve Lewis acid in large or even in stoichiometric amounts (for reviews on vinylogous aldol reaction with silyloxyfurans, see [130, 131]; for original reports [132–140]). A recent organocatalytic approach has also been reported [141]. In view of the versatile synthetic utility of 5-[hydroxy(aryl)methyl]furan-2(5*H*)-ones and 5-[hydroxy(alkyl)methyl]furan-2(5*H*)-ones, e.g. for the preparation of γ-alkylidene-butenolides [142–145], there is clearly a need for practical and efficient conditions that involve a bench-stable catalyst, used in very low loading. As a part of our ongoing interest in bismuth(III)-catalyzed aldol condensation reactions, we have reported a bismuth(III)-catalyzed vinylogous Mukaiyama aldol reaction. Using this method, aldols are obtained efficiently in the presence of 1 mol% of $Bi(OTf)_3{\cdot}4H_2O$.

Bismuth triflate has been reported by Dubac as an efficient catalyst for the Mukaiyama aldol reaction with silyl enol ethers [27] and was recently used with a chiral ligand, as reported by Kobayashi in an elegant hydroxymethylation reaction [26]. In regard to the importance of a diastereoselective synthesis of 5-[hydroxy(aryl) methyl]furan-2(5*H*)-ones, the $Bi(OTf)_3{\cdot}4H_2O$-catalyzed vinylogous Mukaiyama aldol has been investigated with 2-(trimethylsilyloxy)furans and various carbonyl compounds [146].

### *3.1 Bismuth-Catalyzed Mukaiyama Aldol Reaction of Silyloxyfurans*

Initially, various solvents were screened for the Mukaiyama aldol reaction of benzaldehyde with 2-(trimethylsilyloxy)furan in the presence of 1 mol% of $Bi(OTf)_3{\cdot}4H_2O$.

**Table 16** Vinylogous $Bi(OTf)_3$-catalyzed Mukaiyama aldol reactions involving benzaldehyde and 2-(trimethylsilyloxy)furan




**28a**

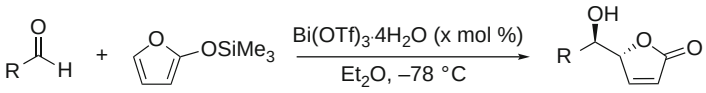
| Entry | Solvent | Catalyst loading (*x*) (mol%) | dr (*syn*/*anti*)[a] | Yield[b] **28a** (%) |
|---|---|---|---|---|
| 1 | MeCN | 1 | 60:40 | 75[c] |
| 2 | $CH_2Cl_2$ | 1 | 87:13 | 81 |
| 3 | THF | 1 | 89:11 | 87 |
| 4 | $Et_2O$ | 1 | 94:6 | 91 |
| 5 | $Et_2O$ | 0.5 | nd | – |
| 6 | $Et_2O$ | 5 | 93:7 | 80 |

Conditions: benzaldehyde (1.0 equiv.), 2-(trimethylsilyloxy)furan (1.2 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (*x* mol%)
*nd* not detectable
[a]Determined from $^1$H NMR of the crude reaction mixture
[b]Isolated yield
[c]The reaction was run at 0 °C

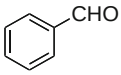
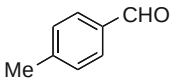
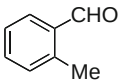
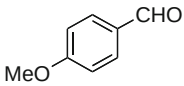
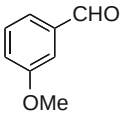
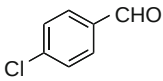
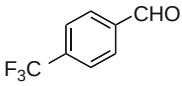
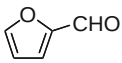
Among the various polar solvents tested, acetonitrile, dichloromethane, and THF afforded good yields of the expected product, although with moderate diastereoselectivity (Table 16, entries 1–3). The most suitable solvent was found to be diethyl ether. 5-[Hydroxy(phenyl)methyl]furan-2(5*H*)-one **28a** was obtained with the best yield and diastereoselectivity (Table 16, entry 4). With further optimization of the reaction conditions, we found that a lower catalyst loading (0.5 mol%) did not allow the reaction to proceed (Table 16, compare entries 5 and 4), although a higher catalyst loading (5 mol%) afforded the product with close diastereoselectivity but decreased yield (Table 16, compare entries 6 and 4).

Encouraged by our results in the reaction with benzaldehyde, we studied the scope and limitations of this reaction with respect to the aldehyde employed in the process. The results are summarized in Table 17. The addition of 2-(trimethylsilyloxy)furan to various aldehydes proceeded readily employing $Bi(OTf)_3{\cdot}4H_2O$ as the Lewis acid (Scheme 2, Table 17). Generally, excellent yields of 5-[hydroxy(aryl)methyl]furan-2(5*H*)-ones were obtained with 1.2 equivalents of 2-(trimethylsilyloxy)furan and 1 mol% of $Bi(OTf)_3{\cdot}4H_2O$ at −78 °C in $Et_2O$. Heteromatic aldehydes as well as an α,β-unsaturated aldehyde reacted smoothly to give the corresponding substituted furan-2(5*H*)-one **28** in high yield (Table 17, entries 8–10). Electron-rich *p*-, or *m*-methoxybenzaldehyde led to the desired product in good yield (Table 17, entries 4 and 5). The reaction worked well with a variety of aldehydes, including those bearing an electron-withdrawing group, and the expected product **28** was obtained with excellent yield (Table 17, entry 6), except that the *p*-trifluoromethyl derivative led to a moderate yield of product due to low conversion even at higher temperature (Table 17, entry 7). Such high diastereoselectivity (90:10 to > 98:2) had only been

**Table 17** Vinylogous $Bi(OTf)_3$-catalyzed Mukaiyama aldol reactions involving various aromatic or unsaturated aldehydes with 2-(trimethylsilyloxy)furan

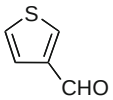
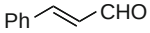



**28**

| Entry | Aldehyde | Time (h) | dr (*syn*/*anti*)[a] | Product | Yield[b] **28** (%) |
|---|---|---|---|---|---|
| 1 |  | 0.5 | 94:6 | **28a** | 91 |
| 2 |  | 1 | 94:6 | **28b** | 90 |
| 3 |  | 0.25 | 94:6 | **28c** | 90 |
| 4 |  | 0.5 | 90:10 | **28d** | 84 |
| 5 |  | 2 | 93:7 | **28e** | 81[c] |
| 6 |  | 0.5 | 93:7 | **28f** | 90 |
| 7 |  | 0.5 | >98:2 | **28g** | 65[c,d] |
| 8 |  | 0.7 | 72:28 | **28h** | 86[c] |

(continued)

**Table 17** (continued)

| Entry | Aldehyde | Time (h) | dr (*syn*/*anti*)[a] | Product | Yield[b] **28** (%) |
|---|---|---|---|---|---|
| 9 |  | 0.25 | 80:20 | **28i** | 85 |
| 10 |  | 0.15 | 70:30 | **28j** | 80 |

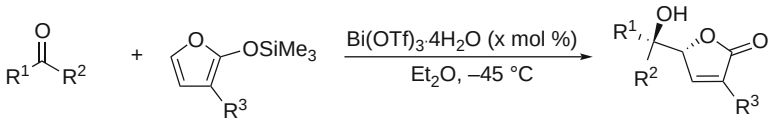
Conditions: aldehyde (1.0 equiv.), 2-(trimethylsilyloxy)furan (1.2 equiv.), $Bi(OTf)_3{\cdot}4H_2O$ (1 mol%), $Et_2O$, −78 °C
[a]Determined from $^1H$ NMR of the crude reaction mixture
[b]Isolated yield
[c]Warmed to −45 °C
[d]Using 2 mol% of $Bi(OTf)_3{\cdot}4H_2O$

previously reported with aromatic aldehydes and usually required high catalyst loadings or even stoichiometric amounts of a Lewis acid (1 equiv. $SiCl_4$, 2-(trimethylsilyloxy)furan, benzaldehyde, dr = 75:25 [133]; 0.5 equiv. TBSOTf, 3-benzyl-2-(*tert*-butyldimethylsilyloxy)-4-isopropylfuran, 4-(*tert*-butyldimethylsilyloxy)-3,5-dichlorobenzaldehyde, dr = 73:27 [136]; 1 equiv. $BF_3{\cdot}OEt_2$, 3-bromo-2-(trimethylsilyloxy) furan, benzaldehyde, 72%, dr > 99:1) [137]. In addition, heteroaromatic aldehydes such as furfural or thiophene 3-carboxaldehyde can also serve as a substrate in this reaction, giving the corresponding aldol in a very good yield (Table 17, entries 8 and 9). A conjugated aldehyde was also a good substrate (Table 17, entry 10).

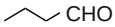
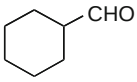
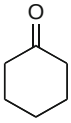
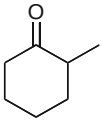
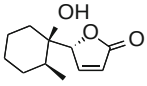
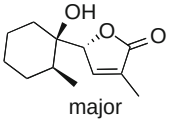
Our conditions were then applied to aliphatic aldehydes (Table 18). When *n*-butyraldehyde or cyclohexylcarboxaldehyde were reacted, the corresponding aldols **28k** and **28l** were obtained with moderate diastereoselectivity and poor yield due to low conversion (Table 18, entries 1 and 2).

At this point, we were curious to verify whether our methodology could be extended to ketones. It was surprising to find a very limited number of examples in the literature for the construction of tertiary alcohols by nucleophilic addition on unsymmetrical ketones [134, 147]. Clearly, this widely studied approach for aldehydes has not led to similar levels of success when employed with ketones. Apparently, low reactivity and low selectivity is the origin of this disparity [133, 148, 149]. A study by Romo showed that high diastereoselectivities could be obtained with ketones when choosing 3-methyl-2-(*tert*-butyldimethylsilyloxy) furan; however, high quantities of Lewis acids (0.4–3.0 equiv.) were necessary [134]. When our conditions using 5 mol% of $Bi(OTf)_3{\cdot}4H_2O$ were applied to ketones, such as cyclohexanone or the more hindered 2-methyl-cyclohexanone, we were delighted to isolate the aldol **28m** in good yield, and **28n** with good diastereoselectivity albeit moderate yield (Table 18, entries 3 and 4). The reaction of 3-methyl-2-(trimethylsilyloxy)furan [142] with 2-methyl-cyclohexanone afforded a very major diastereoisomer **28n′** in good yield (Table 18, entry 5).

**Table 18** Vinylogous $Bi(OTf)_3$-catalyzed Mukaiyama aldol reactions involving various aliphatic aldehydes and ketones with 2-(trimethylsilyloxy)furan




**28**

| Entry | Carbonyl compound | $R^3$ | Catalyst loading (*x*) (mol %) | dr (*syn*/*anti*) | Yield **28** (%) |
|---|---|---|---|---|---|
| 1 |  | H | 5 | 70:30[a] | 30 (**28k**)[b] |
| 2 |  | H | 2 | 75:25[a] | 25 (**28l**)[b] |
| 3 |  | H | 5 | na | 75 (**28m**) |
| 4 |  | H | 5 | 82:7:7:4 | 65 (**28n**)[c]  major diastereoisomer |
| 5 | | Me | 5 | 73:10:9:8 | 78 (**28n′**)[d]  major diastereoisomer |

Conditions: carbonyl compound (1.0 equiv.), 2-(trimethylsilyloxy)furan or 3-methyl-2-(trimethylsilyloxy)furan (1.5 equiv.), $Bi(OTf)_3 \cdot 4H_2O$ (*x* mol%), $Et_2O$, −45 °C, 0.5–3 h

*na* not applicable

[a]Determined from $^1H$ NMR of the crude reaction mixture

[b]Isolated yield

[c]Relative stereochemistry of **28n** was tentatively assigned by comparison of $^1H$ NMR with **28n′** of known relative stereochemistry

[d]The reaction was stirred for an additional hour at 0 °C

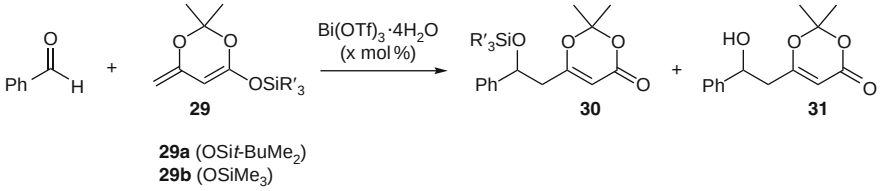
In summary, we have found that the vinylogous Mukaiyama aldol reaction proceeds smoothly with silyloxyfurans and a catalytic amount of $Bi(OTf)_3{\cdot}4H_2O$. This method offers several advantages, including mild reaction conditions, highly catalytic (1 mol%) process, no formation of by-products, and air-tolerance. Moreover, our methodology efficiently promotes the vinylogous Mukaiyama aldol reaction with ketones to provide one major diastereoisomer with good diastereoselectivity.

### *3.2 Bismuth-Catalyzed Mukaiyama Aldol Reaction of Dioxinone-Derived Silyl Dienol Ethers*

In view of the versatile synthetic utility of β-hydroxy-1,3-dioxin-4-ones (for enantioselective versions of the reaction (for a review, see [121]) [150–154]; for other applications [155–158]), e.g. for the synthesis of 4-hydroxy-2-pyrones via the oxidation of the hydroxyl group [157], there was clearly a need for practical and efficient conditions that involve a bench-stable catalyst, used in very low loading. As a part of our ongoing interest in bismuth(III)-catalyzed aldol reactions, we have reported a bismuth(III)-catalyzed vinylogous Mukaiyama aldol reaction with 2,2-dimethyl-6-methylene-4-(trimethyl-silyloxy)-1,3-diox-4-ene **29b** [159]. Aldols are obtained efficiently in the presence of 1 mol% of $Bi(OTf)_3{\cdot}4H_2O$. The $Bi(OTf)_3{\cdot}4H_2O$ (3 mol%)-catalyzed reaction of silyl ketene acetal **29a** with benzaldehyde led to the expected product as a mixture of silylated aldol **30** and aldol **31** in moderate to good yield (Table 19, entries 1–2). The need for a fluoride-mediated deprotection of silylated aldol **30** in aldol **31** motivated us to use trimethylsilyl (TMS) derivative **29b** instead of **29a** for easier work-up of the reaction mixture (aq. HCl, THF, 22 °C, 2 h). As shown in Table 19, the formation of the corresponding aldol **31** from readily available ketene acetal **29b** was achieved in good yield and complete γ-regioselectivity (Table 19, entries 3–9). Because of the better yield obtained for our model reaction, diethyl ether was selected as the solvent of choice with 1 mol% $Bi(OTf)_3{\cdot}4H_2O$ (Table 19, compare entries 7–8 with 4 and 5). Only 1.5 equivalents of the reagent were required to ensure complete conversion (Table 19, compare entries 5–8 with 3 and 4). More interestingly, from a preparative point of view, the drastic reduction of the catalyst loading (down to 0.5 mol%) did not cause any appreciable decrease of yield (Table 19, entry 9).

The addition of silyl ketene acetal **29b** to various aldehydes proceeded readily employing $Bi(OTf)_3{\cdot}4H_2O$ as the Lewis acid (Table 20). Generally, excellent yields of β-hydroxy-1,3-dioxin-4-ones were obtained with 1.5 equiv. of TMS-derived silyl ketene acetal **29b** and 0.01 equiv. of $Bi(OTf)_3{\cdot}4H_2O$ at −78 °C in $Et_2O$. Aromatic aldehydes as well as an α,β-unsaturated aldehyde reacted smoothly to give the corresponding β-hydroxy-1,3-dioxin-4-ones **31** in high yield (Table 20, entries 1–10). Electron-rich *p*-, *m*-, or *o*-methoxybenzaldehyde led to the desired product in excellent yield (Table 20, entries 3–5). The reaction worked well with a variety of aldehydes, including those bearing an electron-withdrawing group, and the expected product **31** was obtained with excellent yields (Table 20, entries 6–8).

**Table 19** $Bi(OTf)_3$-catalyzed vinylogous Mukaiyama aldol reaction of benzaldehyde




| Entry | **29** | Catalyst loading ($x$) (mol%) | Conditions | Yield[a] **30** (%) | Yield[a] **31** (%) |
|---|---|---|---|---|---|
| 1 | **29a** (1.2 equiv.) | 3 | $Et_2O$, −78 °C, 8 h | 43 | 21 |
| 2 | **29a** (1.5 equiv.) | 3 | $CH_2Cl_2$, −78 °C, 7.5 h | 75 | 6 |
| 3 | **29b** (1.2 equiv.) | 3 | $Et_2O$, −78 °C, 5.5 h | – | 75 |
| 4 | **29b** (1.2 equiv.) | 3 | $CH_2Cl_2$, −78 °C, 3 h | – | 82 |
| 5 | **29b** (1.5 equiv.) | 3 | $CH_2Cl_2$, −78 °C, 4 h | – | 98 |
| 6 | **29b** (1.5 equiv.) | 3 | THF, −78 °C, 4 h | – | 75 |
| 7 | **29b** (1.5 equiv.) | 3 | $Et_2O$, −78 °C, 4 h | – | 89 |
| 8 | **29b** (1.5 equiv.) | 1 | $Et_2O$, −78 °C, 4 h | – | 95 |
| 9 | **29b** (1.5 equiv.) | 0.5 | $Et_2O$, −78 °C, 4 h | – | 93 |

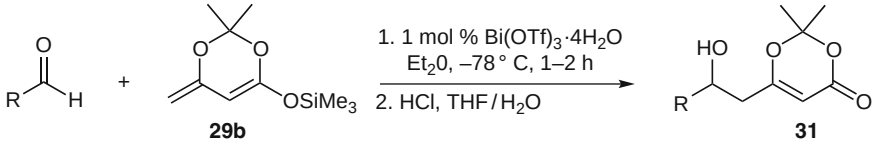
Conditions: $x$ mol% $Bi(OTf)_3{\cdot}4H_2O$, −78 °C, then 10% aq. HCl, THF, 22 °C, 2 h
[a]Isolated yield

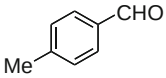
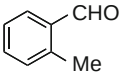
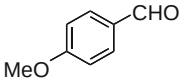
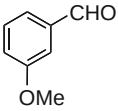
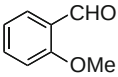
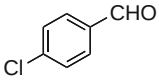
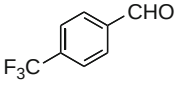
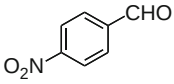
In addition, heteroaromatic aldehyde such as furfural can also serve as a substrate in this reaction, giving the corresponding aldol in a moderate yield (Table 20, entry 9). Conjugated aldehydes were also good substrates (Table 20, entry 10). Aliphatic aldehydes lead to a poor yield of the aldol due to incomplete conversion (Table 20, entries 11 and 12).

## 4 Conclusions

In summary, it has been found that both Sakurai and Mannich-type reactions of *N*-benzyloxycarbonylamino sulfones proceed smoothly in the presence of a catalytic amount of $Bi(OTf)_3{\cdot}4H_2O$. This method offers several advantages, including mild reaction conditions, low catalyst loading (0.5–5 mol%), and no formation of by-products. In addition, the process involves an environmentally benign, cheap, and easy to handle catalyst. The amines, already protected as carbamate derivatives, are smoothly obtained under mild conditions. Moreover, the vinylogous Mukaiyama aldol reaction proceeds smoothly with 2-(trimethylsilyloxy)furan or silyl dienol ether from dioxinone, and a catalytic amount of $Bi(OTf)_3{\cdot}4H_2O$. This method offers several advantages including mild reaction conditions, highly catalytic (1 mol%) process, no formation of by-products, and air-tolerance. High yields and good diastereoselectivities were obtained with silyloxyfurans and aromatic

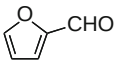
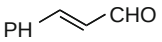
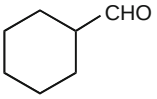
**Table 20** $Bi(OTf)_3$-catalyzed vinylogous Mukaiyama aldol reaction of various aldehydes




| Entry | Aldehyde | Compound | Yield[a] **31** (%) |
|---|---|---|---|
| 1 |  | **31b** | 86 |
| 2 |  | **31c** | 90 |
| 3 |  | **31d** | 91 |
| 4 |  | **31e** | 96 |
| 5 |  | **31f** | 93 |
| 6 |  | **31g** | 98 |
| 7 |  | **31h** | 97 |
| 8 |  | **31i** | 74[b] |

(continued)

**Table 20** (continued)

| Entry | Aldehyde | Compound | Yield[a] **31** (%) |
|---|---|---|---|
| 9 |  | **31j** | 73 |
| 10 |  | **31k** | 80 |
| 11 | | **31l** | 35[c] |
| 12 |  | **31m** | 28[c] |

Conditions: 1.5 equiv. silyl ketene acetal, 1 mol% $Bi(OTf)_3{\cdot}4H_2O$, $Et_2O$, −78 °C, then 10% aq. HCl, THF, 22 °C, 2 h
[a]Isolated yield
[b]2 h, −78 °C then 2 h, 22 °C
[c]Unoptimized conditions

aldehydes. Because of its numerous benefits for the Sakurai, the Mannich-type, and the Mukaiyama aldol reactions, $Bi(OTf)_3{\cdot}4H_2O$ catalysis should find utility in the synthesis of biologically active compounds. Asymmetric catalysis using bismuth salts will be an emerging area in a near future.

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# Bismuth Salts in Catalytic Alkylation Reactions

**Magnus Rueping and Boris J. Nachtsheim**

**Abstract** Alkylation reactions utilizing nontoxic Lewis acid catalysts and "green" alkylating reagents are of high interest due to the continuous need for environmentally benign C–C and C–X bond formation. This article shows recent advances in Bi(III)-catalyzed alkylations of arenes, 2,4-pentanediones and various oxygen- and nitrogen-containing nucleophiles. Instead of toxic alkyl halides, the electrophilic components for these transformations were benzyl and propargyl alcohols as well as substrates with activated double bonds such as styrenes. The fact that Bi(III) salts are capable of activating both σ- and π-donors highlights their unique character as versatile catalysts for catalytic alkylation reactions. In addition, Bi(III) salts are less toxic and cheaper than other Lewis acids that have been described for similar transformations.

**Keywords** Bismuth · Friedel–Crafts alkylation · Green chemistry · Hydroalkylation · Hydroarylation

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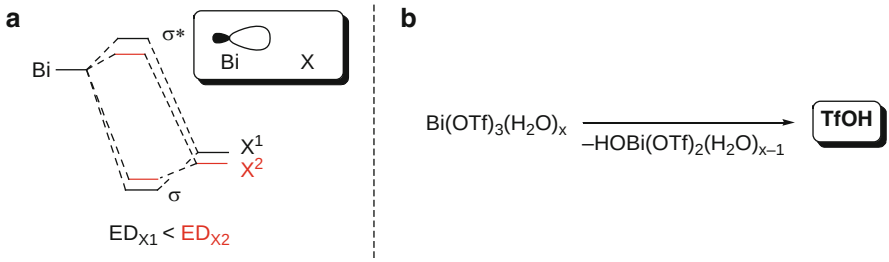
## 1 Introduction

An acid, by the general definition of Gilbert Newton Lewis from 1923, is a substance that "can employ a lone pair from another molecule in completing the stable group of one of its own atoms" [1]. Since then, numerous electron-deficient compounds or "Lewis acids" have been developed and applied in organic synthesis. According to the HSAB (hard and soft acids and bases) principle, they are divided into hard and soft Lewis acids [2–4]. In particular, main group metals in high oxidation states, such as Al(III), Ga(III) or In(III), are by definition "hard" Lewis acids, whereas transition metals in low oxidation states, such as Pd(II), Pt(II) or Cu(I), tend to be "soft" Lewis acids [3, 4].

First developments in the Friedel–Crafts alkylation were concentrated on the use of stoichiometric amounts of Lewis acids, such as $AlCl_3$, $BF_3$ or $TiCl_4$, to produce stoichiometric amounts of salt by-products [5–9]. However, in recent years more and more catalytic methods have been developed. In particular, rare earth metal triflates, including $Sc(OTf)_3$, $La(OTf)_3$ and $Yb(OTf)_3$, have been extensively used as Lewis acid catalysts in various C–C and C–X bond forming reactions [10–13]. Despite the benefit of their versatility for organic synthesis, these Lewis acids possess major drawbacks. They are expensive, rather toxic [14], and air- and moisture-sensitive.

As a suitable alternative, bismuth salts have emerged as cheap, nontoxic Lewis acids. Bismuth is the last element in the fifth main group of the periodic table and the heaviest nonradioactive element. It is primarily observed in two different oxidation states, Bi(III) and Bi(V). Bi(III) is the more stable form and has therefore been utilized in Lewis acid catalysis. In this context, various Bi(III)-catalyzed transformations have recently been developed, e.g. epoxide openings, oxidations, dihydroxylations, acetal cleavages, allylations, Diels–Alder reactions [15–17] and the SOHIO process [18]. Besides their great success in catalysis, Bi(III) derivatives are also used as therapeutic reagents. As such, ranitidine bismuth citrate (Tritec) is successfully used as a histamine receptor antagonist for the treatment of ulcer diseases and acts as a mild antibiotic. The only adverse reaction is a black tongue caused by the formation of $Bi_2S_3$.

Due to the continuous need for efficient and environmentally benign alkylation processes, the Rueping group decided to develop new C–C bond forming reactions using cheap, nontoxic and air-stable Bi(III) salts as Lewis acid catalysts. In this




**Scheme 1** (**a**) An antibonding σ* molecular orbital is thought to be the origin of the soft Lewis acidity of $BiX_3$. *ED* electron deficiency. (**b**) Alternative mode of action: in situ release of TfOH as the catalytic active species

context, Friedel–Crafts-type alkylations are of great interest due to their high importance in organic synthesis and the versatility of the resulting products.

The Lewis acidity of a group 15 element, such as Bi(III), is somewhat surprising since the remaining electron lone pair should, in principle, result in a weak Lewis basic behavior. This Lewis basic activity is described for the other group 15 elements, in particular nitrogen and phosphorous. The weak Lewis acidity of Bi(III) salts is thought to be the result of an antibonding $\sigma^*$ molecular orbital, which originates from an unoccupied *p*-orbital of the Bi(III) atom. Electron-deficient ligands or counterions such as $TfO^-$ can lower the energy of this antibonding orbital and subsequently increase its reactivity (Scheme 1a).

Recent results suggest that, for certain metal triflates $M(OTf)_x$, the counterion and its free acid TfOH are responsible for the observed catalytic activity [19, 20]. It is also likely that for many $Bi(OTf)_3$-catalyzed reactions, including those described in this review, the in situ generation of the strong Brønsted acid TfOH plays an important role in the catalytic cycle (Scheme 1b). By using $Bi(OTf)_3$ in combination with 2,6-di-*tert*-butylpyridine as proton scavenger, Salvador and coworkers recently showed that an in situ generated Brønsted acid might act as the catalytic active species in the $Bi(OTf)_3$-catalyzed Wagner–Meerwein rearrangement of terpenes [21]. Additionally, one could imagine the involvement of both species in the catalytic cycle and discuss a Brønsted-acid-assisted Lewis acid catalysis or a Lewis-acid-assisted Brønsted acid catalysis [22].

However, it is evident that Bi(III) salts have a unique activation mode and a strong Lewis acidic behavior. In this context, Bi(III) salts are well known for being capable of activating both σ-donors such as alcohols or amines and π-donors such as alkenes and alkynes. This fact makes Bi(III) a versatile Lewis acid for various alkylation reactions in which both alcohols and C–C multiple bonds can be utilized as an electrophilic component.

In this review, we will initially describe the role of Bi(III) salts as activators for σ-donors. In particular, benzyl and propargyl alcohols will be presented as mild electrophiles in alkylation reactions. In addition, we will show the versatility of Bi(III) salts and give a short overview of Bi(III)-catalyzed hydroarylation and hydroalkynylation reactions [23]. Besides our own results, which primarily focus

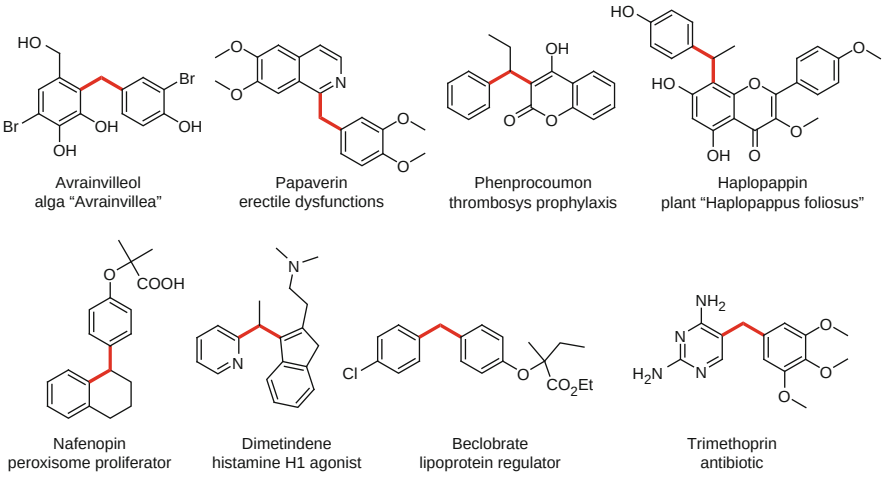
on Bi-catalyzed Friedel–Crafts alkylations, we will present related work from other research groups that have applied Bi(III) salts in the activation of various alcohols and C–C double and triple bonds.

## 2 Bismuth(III) Salts for $S_N1$-type Substitutions of Activated Alcohols

### *2.1 The Search for Environmentally Benign Friedel–Crafts Alkylations*

1,1-Diarylalkanes are important structural motifs that can be found in a variety of pharmaceuticals, agrochemicals and fine chemicals. Examples are papaverin, avrainvilleol and beclobrate (Scheme 2). Traditionally, 1,1-diarylalkanes can be prepared from benzyl halides and the corresponding arenes under Friedel–Crafts-type conditions.

Typically, stoichiometric amounts of a Lewis acid such as $AlCl_3$ are required and produce stoichiometric amounts of salts and mineral acids (HX) as side products. Furthermore, undesired side reactions such as multiple alkylations and a low functional group tolerance are observed. With the need for more environmentally and economically benign processes, the development of Friedel–Crafts-type reactions using catalytic amounts of a Lewis acid catalyst is desirable. In addition, the substitution of benzyl halides for other environmentally friendly alkylating reagents constitutes an attractive goal. In particular, benzyl alcohols are suitable



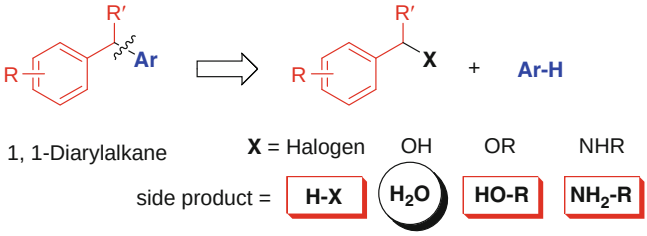

**Scheme 2** Diarylalkanes as desirable structural motif in many biologically active compounds and pharmaceuticals

alternatives to benzyl halides as they are readily available and the only by-product in a Friedel–Crafts-type reaction between benzyl alcohol and the arene would be water (Scheme 3).

The first systematic investigations of the catalytic Friedel–Crafts-type reaction with alcohols and olefines were performed by Yamamoto and colleagues. After reporting the development of a Pd-catalyzed method for the allylation of different naphthol derivatives [24], the authors used $Mo(CO)_6$ for the Friedel–Crafts-type alkylation of electron-rich arenes with allyl acetates [25]. The same molybdenum catalyst was additionally used for a Friedel–Crafts-type alkylation of arenes using 1-phenylethanol and styrene as alkylating reagents [26]. However, $Mo(CO)_6$ is toxic and must be handled under strictly inert conditions. Thus, more stable Lewis acids were necessary.

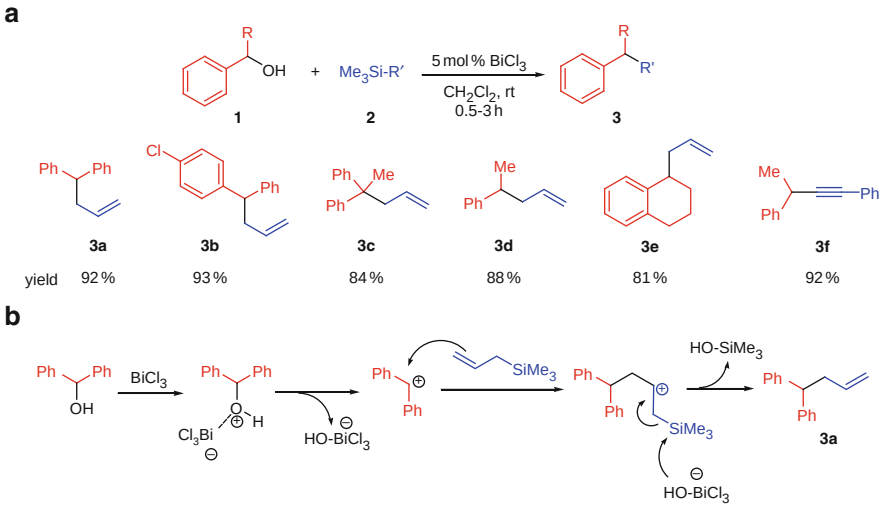
On the basis of these initial results, various rare earth metal triflates, including $Sc(OTf)_3$, $Hf(OTf)_4$ and $Yb(OTf)_3$ were applied as catalysts [27–29]. Recently Beller and coworkers developed efficient Friedel–Crafts alkylations with catalytic amounts of Rh, W, Pd, Pt and Ir complexes [30] or $FeCl_3$ [31–34] as Lewis acid catalysts. However, in the latter cases high catalyst loadings had to be applied. To overcome these major drawbacks, we decided to develop a Bi(III)-catalyzed Friedel–Crafts alkylation of arenes with benzyl alcohols. Although bismuth-catalyzed Friedel–Crafts acylations were well known at this time, Friedel–Crafts alkylations using benzyl alcohols had not been reported.

The principle of alcohol activation by Bi(III) salts was first described by Dubac and colleagues in 1994 [35]. They reported a $BiCl_3$-catalyzed transformation of various activated alcohols, including *tert*-butyl, allyl and benzyl alcohols, to the corresponding chlorides by employing chloromethylsilane as a chlorinating agent (Scheme 4) [35].




**Scheme 3** Retrosynthetic analysis of 1,1-diarylalkanes

**Scheme 4** First example of a Bi(III)-catalyzed substitution of activated alcohols

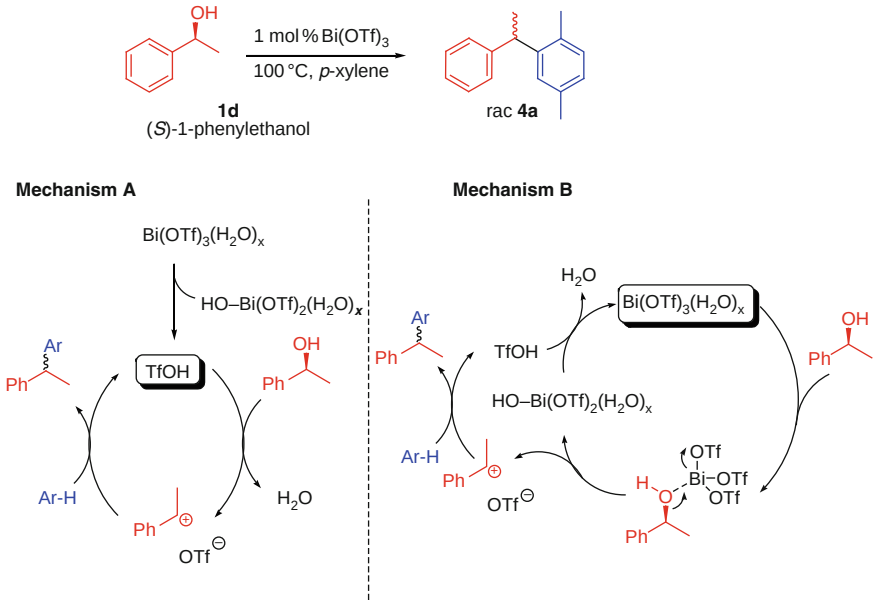



**Scheme 5** (**a**) Allylation of benzyl alcohols with a catalytic amount of $BiCl_3$. (**b**) Proposed reaction mechanism including a bifunctional role of Bi(III)

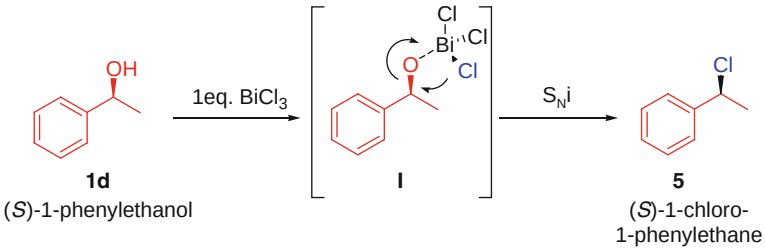
Besides chlorosilane, allyl and propargyl silane **2** were additionally found to be effective reagents (Scheme 5a). Different benzyl alcohols **1** such as benzhydrols (**1a** and **1b**), 1,1-diphenylethanol (**1c**), yielding even quaternary carbons in high yields, and 1-phenylethanol (**1d**) were applied [36]. With regard to the reaction mechanism it is proposed that bismuth acts as a Lewis acid activator of the σ-donating benzyl alcohol. The resulting carbocation is then attacked by the allyl silane. In its second role, in situ generated bismuth hydroxide acts as a nucleophilic activator. Binding of bismuth hydroxide to the alkylsilane results in Si–C-bond cleavage and release of the desired product **3a** (Scheme 5b).

As a result, the activation of unmodified benzyl alcohols with Bi(III) salts seemed to be feasible and the Rueping group began to develop a Bi(III)-catalyzed Friedel–Crafts alkylation of arenes with benzyl alcohols [37]. After initial optimizations, it was found that $Bi(OTf)_3$ was the most active Bi(III) salt and polar aprotic solvents such as nitromethane or dichloromethane were the solvents of choice. To elucidate the scope of this transformation, they tried to benzylate various arenes using benzyl alcohol and 1-phenylethanol as the alkylating reagents. With only 0.5 mol% of $Bi(OTf)_3$, the unmodified 1-phenylethanol yielded the desired 1,1-diarylalkanes in good yields (up to 95%) after short reaction times. Electron-rich arenes including phenol or anisole as well as heteroarenes such as 3-methylindole or thiophene were tolerated in this reaction.

When optically pure (*S*)-1-phenylethanol **1d** was treated with *p*-xylene only racemic 1,1-diarylalkane **4a** was isolated (Scheme 6). This strongly implies a carbocation as the reactive intermediate in the $Bi(OTf)_3$-catalyzed Friedel–Crafts alkylations. Mechanistically, it is not clear whether Bi(III), in situ generated TfOH, or both Lewis and Brønsted acids together are involved in the catalytic cycle



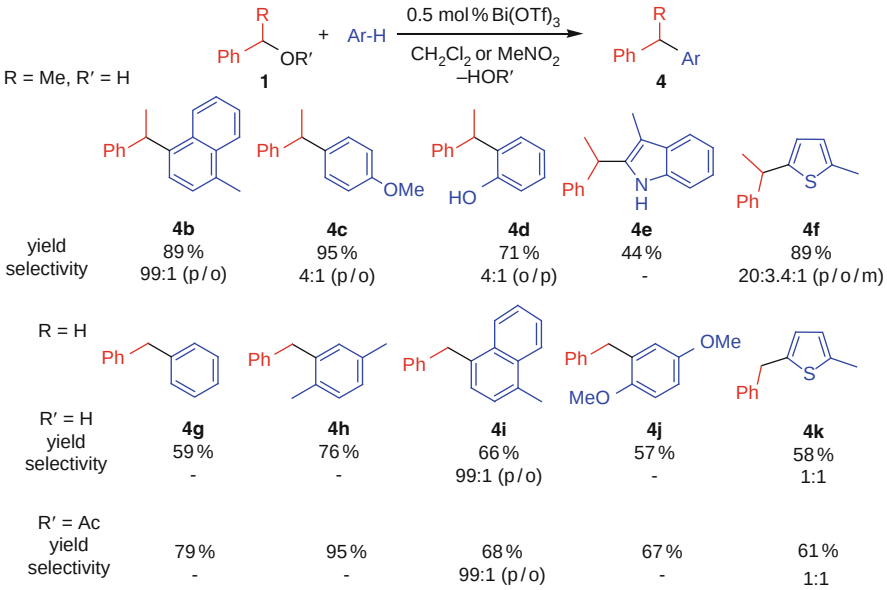

**Scheme 6** Loss of stereoinformation during the $Bi(OTf)_3$-catalyzed Friedel–Crafts-alkylation implies a carbocationic intermediate. *Mechanism A*: TfOH generated in situ from $Bi(OTf)_3$ is thought to be the catalytic active species. *Mechanism B*: Bismuth(III) acts as a Lewis acid. TfOH only regenerates $Bi(OTf)_3$ from its less reactive monohydroxide



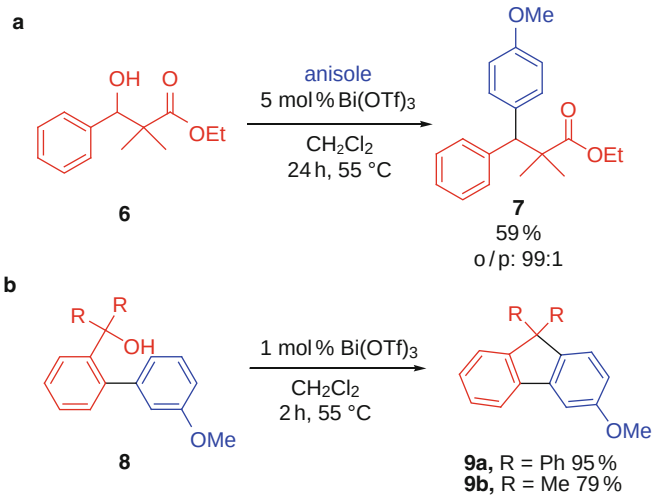

**Scheme 7** $BiCl_3$-mediated chlorination of (*S*)-1-phenylethanol with retention of the stereochemistry

(Scheme 6, mechanisms A and B). Interestingly, the observation regarding the loss of stereoinformation is in contrast to the previously described $BiCl_3$-mediated chlorination of 1-phenylethanol [38]. In this reaction, a complete retention of configuration was reported (Scheme 7). $BiCl_3$ is thought to act both as Lewis acid activator and chlorinating agent. Thus, the mode of action must be different.

Following their optimized protocol, the Rueping group prepared various 1,1-diarylalkanes (Scheme 8) employing either the free alcohols (R = Me, H; R′ = H) or, in case of benzyl alcohol, the corresponding acetate as well (R = H;



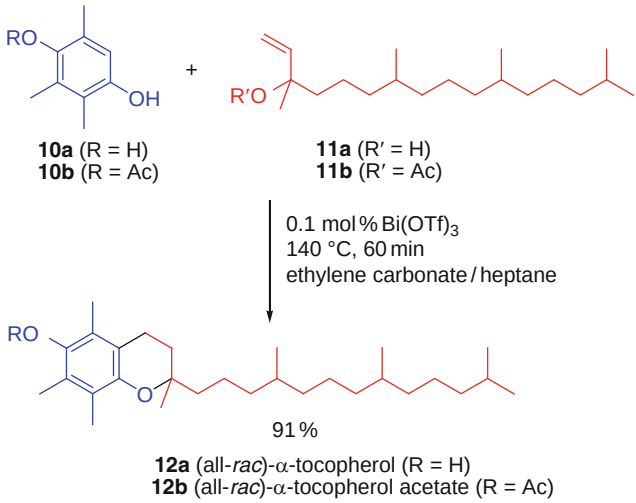

**Scheme 8** Bi(OTf)$_3$-catalyzed arylation of 1-phenylethanol, benzyl alcohol and benzyl acetate




**Scheme 9** (**a**) Friedel–Crafts-type alkylation of β-hydroxyesters. (**b**) Bi(OTf)$_3$-catalyzed synthesis of fluorenes

R′ = OAc). Besides benzene, electron-rich arenes as well as thiophenes were successfully benzylated.

This methodology has also been extended to the alkylation of β-hydroxyester **6** in order to obtain the β-carboxy-substituted diarylalkane **7** (Scheme 9a). The




**Scheme 10** $Bi(OTf)_3$-catalyzed synthesis of all-*rac* α-tocopherol

intramolecular reaction of tertiary alcohol **8** resulted in highly substituted fluorenes **9a** and **9b** (Scheme 9b).

This first example of a $Bi(OTf)_3$-catalyzed Friedel–Crafts alkylation originated in the following procedures, including benzylations of 2,4-pentanediones or hydroarylation and hydroalkylation reactions. A related procedure was simultaneously developed by Bonrath et al. [39]. The authors utilized $Bi(OTf)_3$ in the synthesis of (all-*rac*)-α-tocopherol (Vitamin E) [39]. Besides rare earth metal triflates, such as $Ga(OTf)_3$, $Hf(OTf)_3$, $Sc(OTf)_3$ and $Gd(OTf)_3$, $Bi(OTf)_3$ was shown to be the most efficient catalyst for the Friedel–Crafts-type reaction between trimethylhydroquinone acetate **10b** and isophytols **11a**, **b**. With only 0.02 mol% $Bi(OTf)_3$ (substrate to catalyst ratio 5,000:1) the desired α-tocopherols **12a** and **12b** were isolated in excellent yields (Scheme 10).

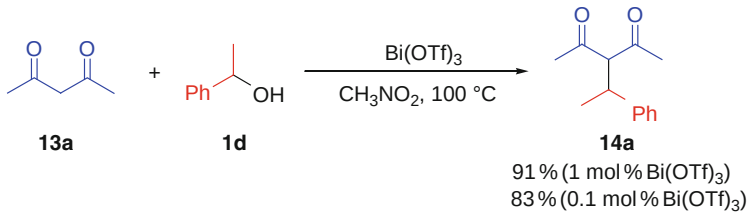
## 2.2 *$Bi(OTf)_3$-Catalyzed Alkylations of 1,3-Diketones*

Beside the Friedel–Crafts-type alkylation of arenes, the direct functionalization of 2,4-pentanediones is of great interest in Lewis acid catalysis. Although Pd-catalyzed Tsuji–Trost type allylations of 1,3-diketones are known, direct benzylation procedures catalyzed by Lewis acids are less explored [40–43]. Based on the previously described Friedel–Crafts alkylation of arenes and heteroarenes, the Rueping group developed a $Bi(OTf)_3$-catalyzed benzylation of 2,4-pentanediones. Alcohols such as benzyl, allyl or cinnamyl alcohols were used as the electrophilic component to yield important 2-alkylated 1,3-dicarbonyl compounds. Initially, different Bi(III) salts were screened. In contrast

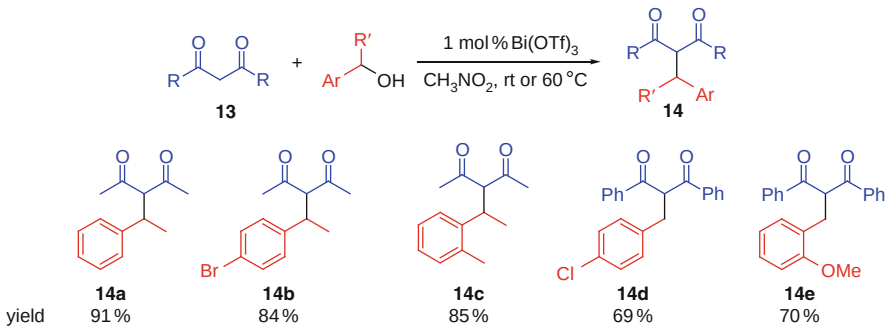
to the previously described Friedel–Crafts alkylation, the reaction could also be performed with various Bi(III) salts, including $BiCl_3$, $BiBr_3$ or $Bi(NO_3)_3$. However, $Bi(OTf)_3$ was still the most efficient catalyst and was thus used for further reaction development [44].

For instance, the reaction of acetylacetonate **13a** with 1-phenylethanol **1d** was performed with only 0.1 mol% $Bi(OTf)_3$ to give the corresponding product in 83% yield (Scheme 11). Subsequent investigations concentrated on the substitution patterns of the benzyl alcohols and 2,4-pentanediones. Besides acetylacetonate, its mono- and double-phenylated derivatives (1-phenylbutane-1,3-dione and dibenzoyl methane) were used and dibenzoyl methane was shown to be the most reactive nucleophile. Unfortunately, β-ketoesters, malonates and malonitriles could not be alkylated. With regard to the 1-phenylethanol scaffold, different electron-donating and electron-withdrawing functional groups in *ortho*, *meta* or *para* positions were tolerated, to provide the corresponding products **14a–e** in excellent isolated yields (Scheme 12). In addition to the 1-phenyl alkyl alcohols (R′ = alkyl), the less-reactive benzyl alcohols **1** (R′ = H) were shown to be good electrophiles. However, due to their decreased reactivity, the more reactive dibenzoylmethane had to be used instead of 2,4-pentanedione in order to observe sufficient reactivity.

In the reaction of the trimethoxy-substituted benzyl alcohol **15** and 2,4-pentanedione an unexpected side reaction was observed. Depending on the reaction temperature, either the desired benzylated 2,4-pentanedione **14f** or the



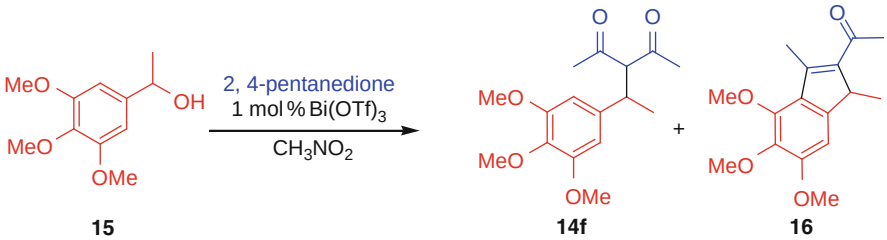

**Scheme 11** Low catalyst loadings used for the $Bi(OTf)_3$-catalyzed benzylation of 2,4-pentanedione




**Scheme 12** $Bi(OTf)_3$-catalyzed benzylation of 2,4-pentanediones

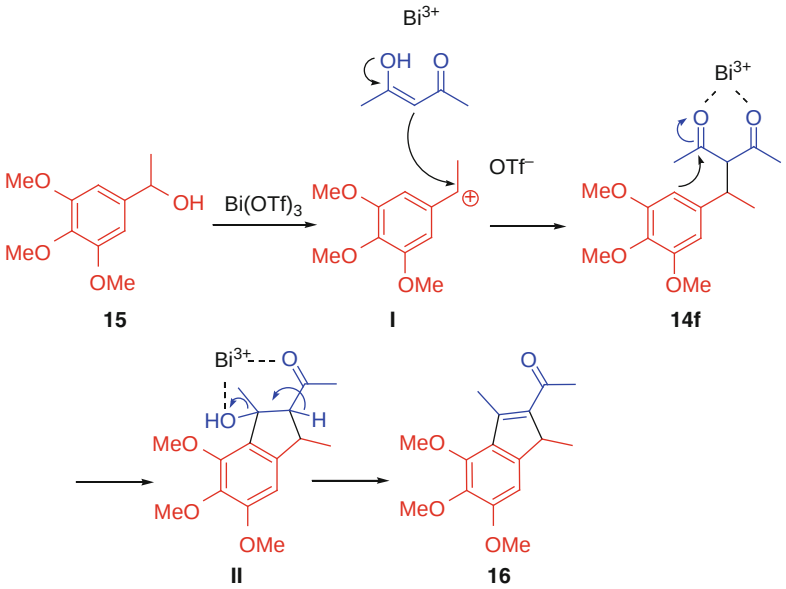
highly substituted indene **16** was isolated (Scheme 13). Interestingly, this type of indene synthesis had never been reported before.

From a mechanistic point of view, it can be envisaged that this reaction proceeds via the desired benzylated pentanedione intermediate **14f**. The subsequent intramolecular Friedel–Crafts alkylation of the electron-rich arene results in the quaternary benzyl alcohol **II**, which readily eliminates water to give the highly substituted indene **16** (Scheme 14).

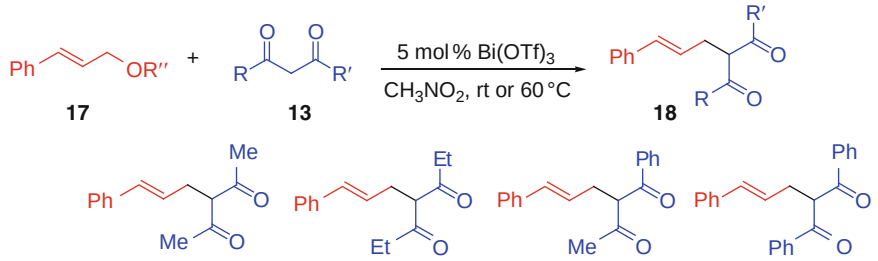



| | | |
|---|---|---|
| T = 25 °C | 76 % | 16 % |
| T = 60 °C | 46 % | 28 % |
| T = 100 °C | 0 % | 70 % |

**Scheme 13** $Bi(OTf)_3$-catalyzed route to substituted indenes




**Scheme 14** Mechanistic proposal for the $Bi(OTf)_3$-catalyzed synthesis of highly substituted indenes **16**




| yield | 18a | 18b | 18c | 18d |
|---|---|---|---|---|
| R″ = H | 62 %* | 62 % | 73 % | 62 % |
| R″ = Ac | 55 %* | 60 % | 70 % | 78 % |

*5:1 linear:branched

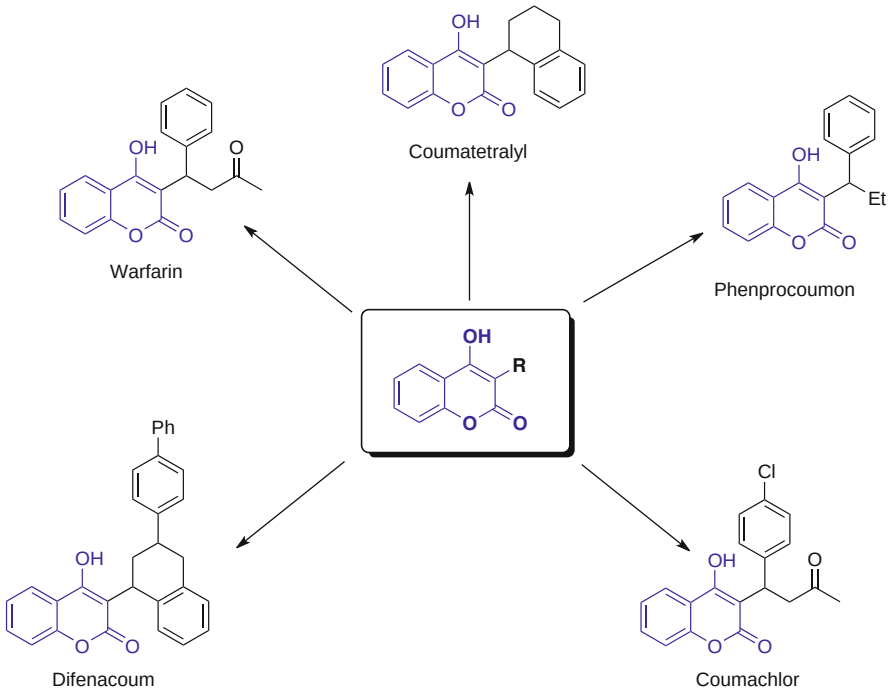
**Scheme 15** Scope of the $Bi(OTf)_3$-catalyzed alkylation of cinnamyl alcohols and acetates

In addition to 1-phenylethanol and benzyl alcohol, cinnamyl alcohol has also been utilized as alkylating reagent. In contrast to the $Bi(OTf)_3$-catalyzed Friedel–Crafts alkylation of benzyl alcohols, in which the corresponding acetate was shown to be more reactive than the free benzyl alcohol (Scheme 8), in this case the alkylation with cinnamyl alcohol or the corresponding acetate provided almost similar results. With 5 mol% $Bi(OTf)_3$, the desired allylated 2,4-pentanediones were isolated in good yields (Scheme 15).

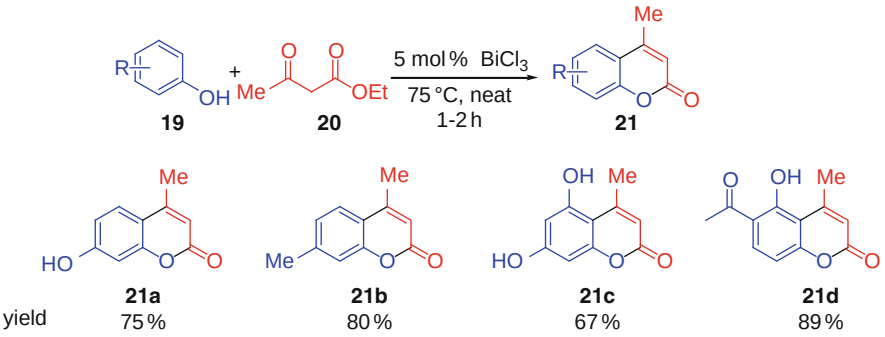
## 2.3 *$Bi(OTf)_3$-Catalyzed Synthesis of Warfarin Derivatives*

Warfarin and its derivatives, including phenprocoumon and coumatetralyl, are highly efficient Vitamin K antagonists and are widely used as anticoagulants for thrombosis prophylaxis and, in high doses, as rodenticides (Scheme 16). Despite their high benefit, catalytic methods describing the synthesis of warfarins are rare. In general, their synthesis starts from 4-hydroxycoumarin and alkylation reagents such as enones or benzyl halides. In the latter case, typically harsh reaction conditions involving concentrated sulfuric acid are necessary. In addition, asymmetric Michael additions have been reported in the enantioselective synthesis of warfarin [45–47]. Furthermore, Beller and coworkers developed an $FeCl_3$-catalyzed synthesis of warfarin and phenprocoumon starting from 4-hydroxycoumarin and 1-ethyl phenylalcohol [33, 34]. Yb-, Pd- and iodine-catalyzed procedures have also been described [48–50].

A bismuth-catalyzed alkylation of warfarins has not been described, although a bismuth-mediated synthesis of the coumarin core structure **21** starting from phenols **19** and ethyl acetoacetate **20** is known (Scheme 17) [51]. The synthesis of coumarins proceeds in the same way as the above-described indene synthesis. The initial reaction of phenol **19** and ethyl acetoacetate **20** leads to the ester.

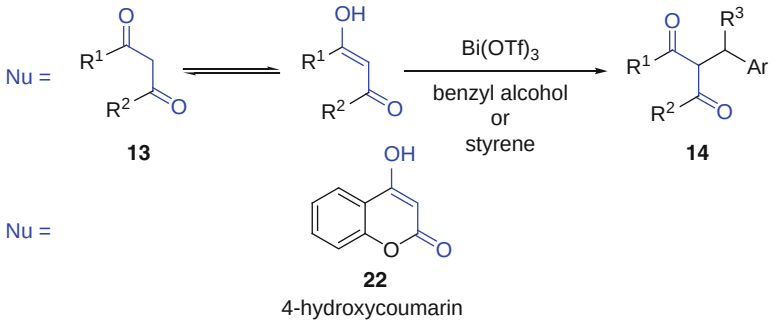



**Scheme 16** 3-Alkylated 4-hydroxycoumarins: the core structure for various warfarin derivatives

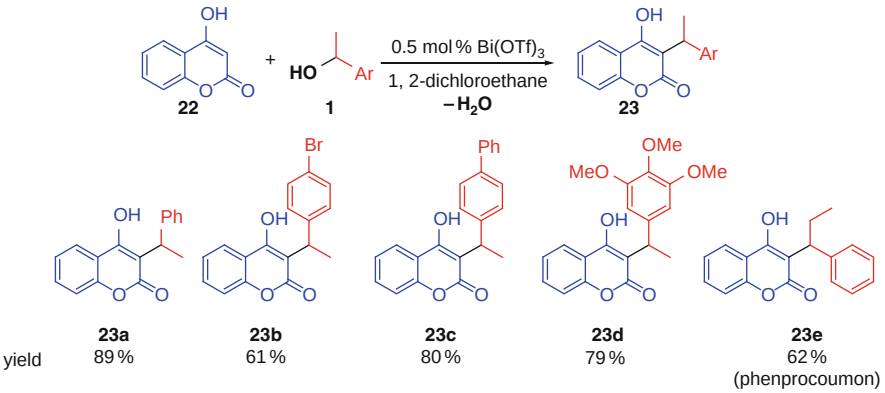



**Scheme 17** $BiCl_3$-catalyzed synthesis of coumarin core structures

Subsequent intramolecular Friedel–Crafts alkylation and elimination yields the coumarin derivatives (See Scheme 14, Sect. 2.2). With 5 mol% of $BiCl_3$, the desired products **21a–d** have been obtained in high yields after short reaction times (1–2 h) (Scheme 17).




**Scheme 18** Structural similarities between acetylacetonate and 4-hydroxycoumarin




**Scheme 19** $Bi(OTf)_3$-catalyzed synthesis of novel warfarin derivatives

The nucleophilic core of 4-hydroxycoumarin (Scheme 18) represents the enolic form of 1,3-dicarbonyl functionality, which was efficiently alkylated with a low amount of $Bi(OTf)_3$ (Schemes 11 and 12). Therefore, Rueping et al. investigated a $Bi(OTf)_3$-catalyzed benzylation of 4-hydroxycoumarins [52].

Among different Bi(III) salts, $Bi(OTf)_3$ again turned out to be the most effective catalyst for this transformation. With just 0.5 mol% $Bi(OTf)_3$, 4-hydroxycoumarin was efficiently alkylated employing several 1-phenyl ethyl alcohols. Again, aryl groups with electron-withdrawing as well as electron-donating functional groups were tolerated, resulting in the desired 3-benzylated 4-hydroxycoumarins **23a–e** in good yields after short reaction times (Scheme 19). With this new $Bi(OTf)_3$-catalyzed procedure, phenprocoumon (Marcoumar ), a widely used anticoagulant, was prepared in one step starting from 1-phenyl propanol. Compared to traditional methods this procedure needs only low amounts of nontoxic Bi(III) salts as the catalyst and, again, water is the only by-product that is produced in stoichiometric amounts. This is worth mentioning because potential pharmaceuticals can be directly isolated by this synthetic pathway starting from readily available substrates.

In addition to benzyl alcohols, styrenes have also been used as the electrophilic component in this procedure. This is described in more detail in Sect. 3.2.

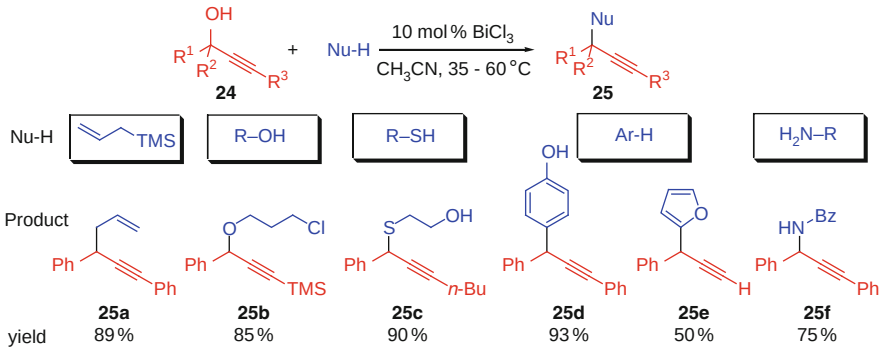
## 2.4 Bismuth(III)-Catalyzed Substitutions of Propargyl Alcohols

Alkynes are versatile building blocks and valuable intermediates for organic synthesis. They can readily be transformed into *E*- or *Z*-alkenes, hydrated, hydrometallated and hydroaminated, used as dienophiles in Diels–Alder reactions, used for indole synthesis, used in 3 + 2 cycloadditions with azides ("click chemistry") or used in metathesis [53–58]. Thus, substitution reactions involving propargyl alcohols are an important approach to introduce alkyne functional groups into nucleophilic molecules. One of the first attempts of a nucleophilic substitution of propargyl alcohols was the Nicholas reaction [54, 59]. In this reaction, stoichiometric amounts of $Co_2(CO)_8$ are necessary to stabilize the in situ generated propargyl cation. Furthermore, an oxidation step must follow the substitution reaction in order to achieve the cleavage of the Co-alkyne complex.

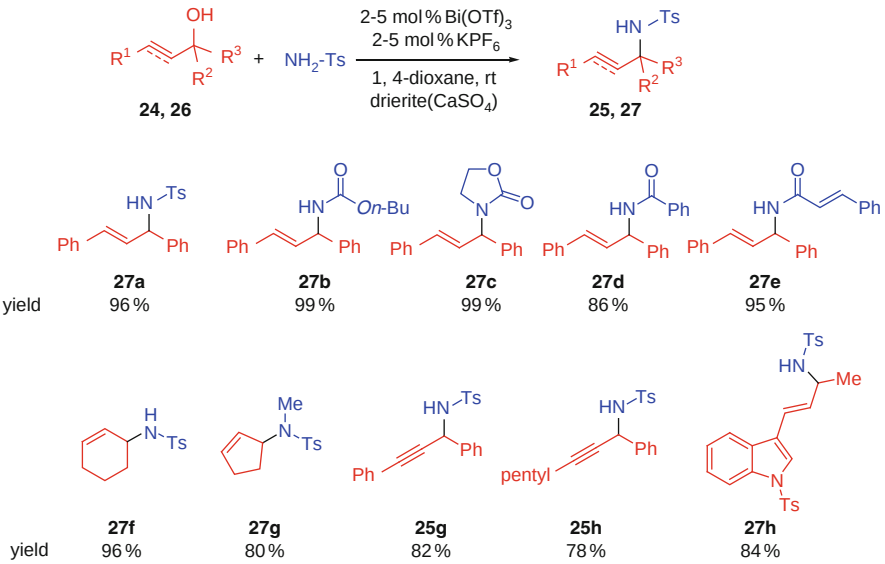
Recently, Lewis-acid-catalyzed nucleophilic substitution reactions of propargyl alcohols have been described. In general, costly transition metals such as Ru, Re, Pd or Au are used in these transformations. At this point Bi(III) salts are believed to be a cheap and environmentally benign alternative.

In 2006, Zhan et al. described the first $BiCl_3$-catalyzed substitution of propargyl alcohols [60]. Using 10 mol% of $BiCl_3$ the authors were able to allylate various propargyl alcohols **24** to yield highly desirable 1,5-enyne **25a** and analogs (Scheme 20). In addition, the authors were able to expand their method to other nucleophiles including different alcohols, thiols, electron-rich arenes and amides.

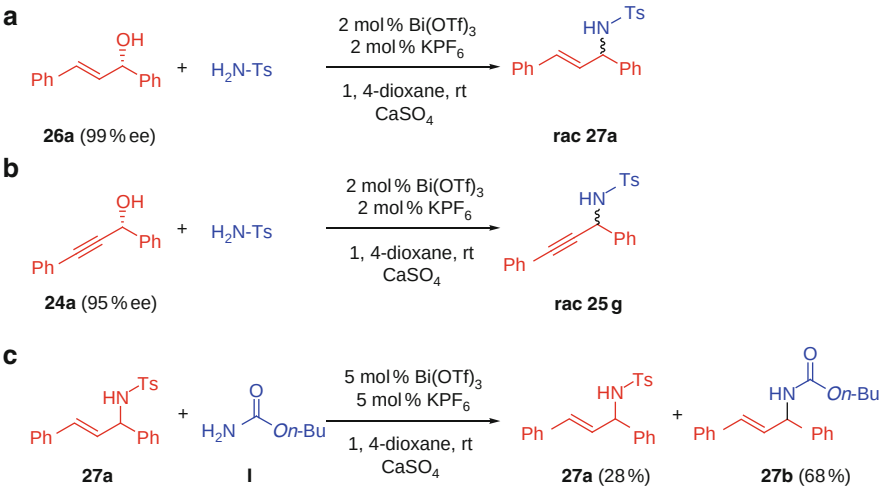
Shortly after this work, Shibasaki and coworkers developed a useful method for the substitution of allyl and propargyl alcohols using $Bi(OTf)_3$ [61]. Various amines such as tosylamine, carbamates, amides and cinnamylamide yielded allyl and propargyl amides **27a–h** and **25g–h** in excellent yields (Scheme 21). The addition of $KPF_6$ was




**Scheme 20** $BiCl_3$-catalyzed substitution of propargylic alcohols




**Scheme 21** $Bi(OTf)_3$-catalyzed allylation and propargylation of tosylamines




**Scheme 22** (**a**, **b**) Amination of the enantiopure alcohols **26a** and **24a** yields racemic cinnamyl and propargyl amides **27a** and **25g**. (**c**) Bismuth-catalyzed C–N bond cleavage makes this process reversible

found to considerably accelerate the reaction to provide the products in good yields. Furthermore, the addition of the dessicant Drierite improved the yields significantly.

In good agreement with previous results, both the enantio-enriched cinnamyl alcohol **26a** and propargyl alcohol **24a** resulted in racemic amides **27a** and **25g** (Scheme 22a, b). These results can be either explained by a carbocationic

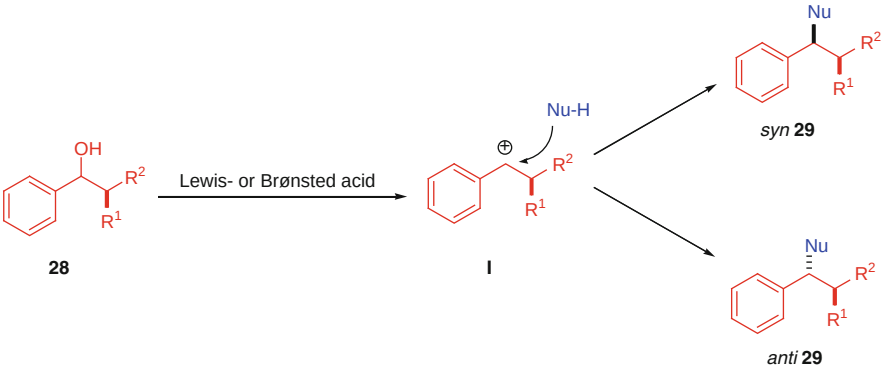
intermediate or as a result of a reversible addition reaction as suggested by the authors [61]. Indeed, when tosylamine **27a** is treated again with a carbamate **I** (Scheme 22c), a 2:1 mixture of the alkylated carbamate **27b** and **27a** is observed. This indicates that Bi(III) is able to cleave and reconstitute the newly formed C–N bond.

Both methodologies described in this chapter impressively illustrate the versatility of $Bi(OTf)_3$ as a mild Lewis acid catalyst. Most notably, in addition to arenes, other nucleophiles such as amines, amides, alcohols and thiols could as well be used in this transformation.

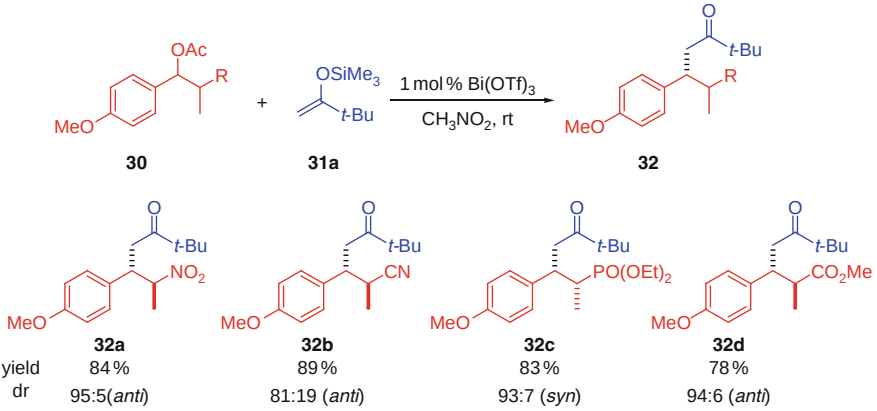
## 2.5 *Diastereoselective Substitutions of Activated Alcohols*

It has been demonstrated that in $Bi(OTf)_3$-catalyzed alkylation reactions the optical activity of enantiopure benzyl alcohols is lost and a racemic product is isolated. This can be explained by a $S_N1$-type reaction mechanism and the existence of a carbocationic intermediate. However, diastereoselective substitutions of benzyl alcohols with a chiral centre in close neighborhood to the electrophilic carbon should be feasible (Scheme 23).

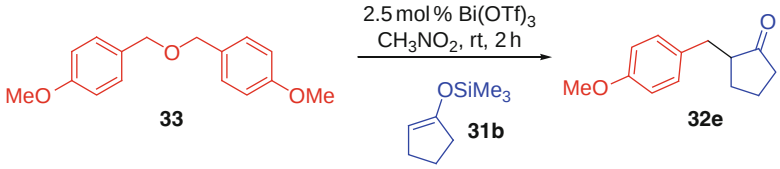
The concept of a diastereoselective Friedel–Crafts alkylation of α-chiral benzyl alcohols was first examined by Bach and coworkers [62, 63]. The initial protocol required stoichiometric amounts of strong Brønsted acids like $HBF_4$ and was followed by a more valuable methodology in which catalytic amounts of $AuCl_3$ were employed for the diastereoselective functionalization of chiral benzyl alcohols [64]. Beside arenes, allyl silanes, 2,4-pentanediones and silyl enol ethers have been used as nucleophiles. Depending on the diastereodiscriminating group and on the catalyst (Brønsted or Lewis acid), the authors observed either the *syn* or the *anti* diastereoisomer as the major product.




**Scheme 23** Diastereoselective Friedel–Crafts alkylations




**Scheme 24** $Bi(OTf)_3$-catalyzed diastereoselective benzylation of silyl enol ethers

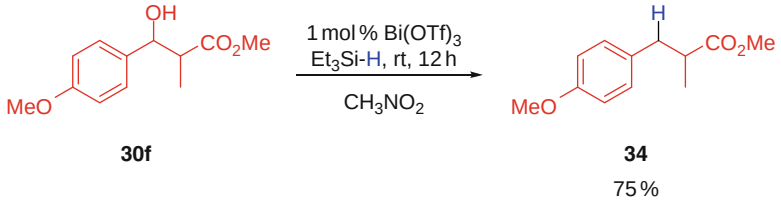



**Scheme 25** Dibenzyl ethers as the putative reactive precursors for the benzylation of silyl enol ethers

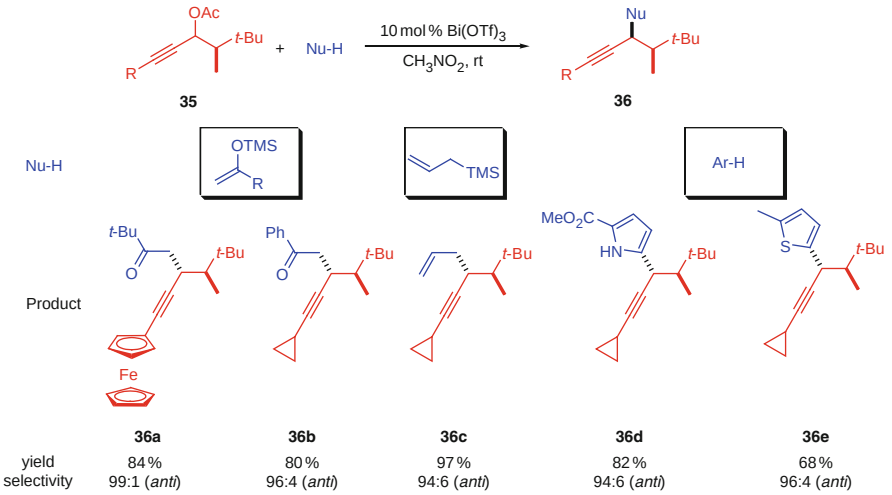
On the basis of this pioneering work, Rubenbauer and Bach developed a $Bi(OTf)_3$-catalyzed highly diastereoselective benzylation of silyl enol ethers [65]. Various cyclic and acyclic silyl enol ethers were amenable to this protocol (Scheme 24). Various α-substituted benzyl acetates were tested with *tert*-butyl-substituted silyl enol ether **31a**, and the use of only 1 mol% of $Bi(OTf)_3$ was enough to obtain the desired benzylated ketones **32** in high yields and with excellent diastereoselectivities (up to 95:5). Whereas α-nitro- (**30a**), α-cyano- (**30b**) and α-methylester-substituted (**30d**) benzyl acetates gave the *anti* diastereoisomer as the major product, the phosphonate-substituted benzyl acetate (**30c**) exclusively resulted in the *syn* isomer (Scheme 24).

During the reaction of *p*-methoxy benzyl alcohol with silyl enol ether **31b**, dibenzyl ether **33** was observed as a by-product, which disappeared after prolonged reaction time. In fact, if **33** was used as alkylating reagent, the silyl enol ether **31b** was benzylated and the desired cyclopentanone **32e** was obtained in a similar yield (Scheme 25).

In addition to the alkylation of benzyl alcohols with silyl enol ethers, the hydroxyl group could be removed in a reduction employing triethylsilane $Et_3SiH$ as the reductant. With 1 mol% of $Bi(OTf)_3$ as the catalyst, the desired β-arylester **34** could be isolated in 75% yield (Scheme 26).




**Scheme 26** $Bi(OTf)_3$-catalyzed reduction of benzyl alcohols with triethylsilane




**Scheme 27** Diastereoselective alkylation of propargyl alcohols with silyl enol ethers, allyl silanes and electron-rich arenes

The concept of a diastereoselective $S_N1$ reaction was subsequently expanded to chiral propargyl alcohols and their derivatives. Different Lewis acids, including $Cu(OTf)_2$, $FeCl_3$, $InCl_3$ and $AuCl_3$, have been explored for the propargylation of silyl enol ethers, but again $Bi(OTf)_3$ turned out to be the most effective catalyst [66]. However, in order to observe sufficient reactivity, the corresponding propargyl acetates had to be used as carbocation precursors. The scope of this reaction is displayed in Scheme 27. Various nucleophiles, including silyl enol ethers, allyl silanes and a variety of electron-rich arenes such as pyrroles, thiophenes and even furanes, reacted with propargyl acetate **35** very efficiently. On the other hand, different aryl-, alkene-, cyclopropene- and even ferrocene-substituted propargyl acetates have also been utilized. With 10 mol% $Bi(OTf)_3$ as catalyst, the desired alkylated alkynes **36** were isolated in high yields and almost perfect *anti* diastereoselectivities of up to 99:1.

# 3 Bismuth(III)-Mediated Activation of Alkenes and Alkynes

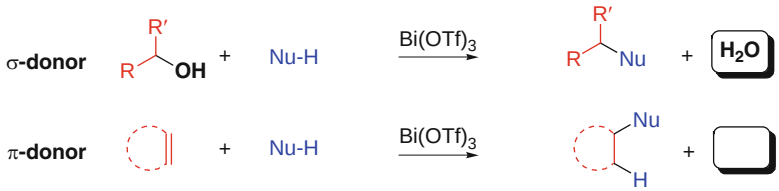
## *3.1 An Efficient Hydroarylation Approach to 1,1-Diarylalkanes*

Previously, benzyl alcohols have been shown to be environmentally benign alkylation reagents. However, in order to search for even more effective benzylation procedures a 100% atom economical procedure would be desirable. In this context, the only process that is more efficient than one having water as by-product is one having *no* by-product at all. This goal can only be achieved if double bonds are used as electrophiles. A hydroarylation approach to 1,1-diarylalkanes that used styrenes instead of benzyl alcohols would perfectly fulfill this task. Thus, ongoing efforts focused on the development of efficient $Bi(OTf)_3$-catalyzed alkylation reactions using substrates with activated double bonds (Scheme 28). Again, Bi(III) salts as borderline Lewis acids that activate both σ- and π-donors should be ideal catalysts.

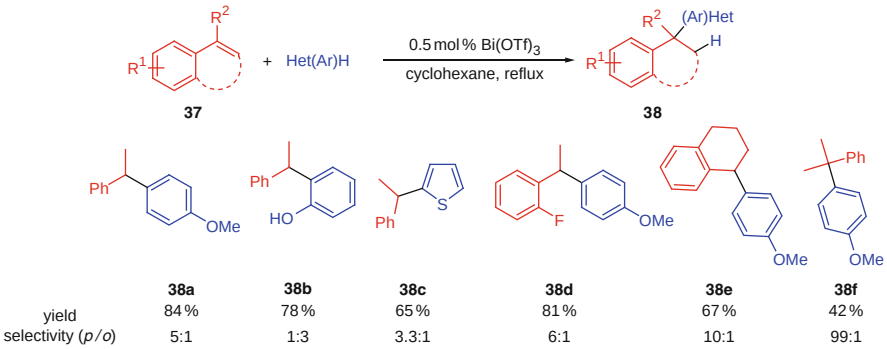
Besides the high efficiency of this route, many styrenes are readily available. This widens the product scope for 1,1-diarylalkanes and would additionally complement the previously described benzyl-alcohol-based Friedel–Crafts-type alkylations.

Initial investigation showed that catalytic amounts of $BiCl_3$, $BiBr_3$ and $Bi(NO_3)_3$ did not provide the desired 1,1-diarylalkanes in significant amounts. However, if 0.5 mol% of $Bi(OTf)_3$ was applied in the reaction between various styrene derivatives and anisole, the desired 1,1-diarylalkanes were isolated after short reaction times in good to excellent yields and with good *ortho*/*para* selectivities [67]. Although different arenes and heteroarenes such as thiophene could be efficiently alkylated, furanes were not compatible with such reaction conditions. In addition to styrene, dihydronaphtalene and α-methylstyrene have been demonstrated to be good electrophiles. In the latter case, the formation of a quaternary carbon atom was possible, albeit in lower yields (Scheme 29).

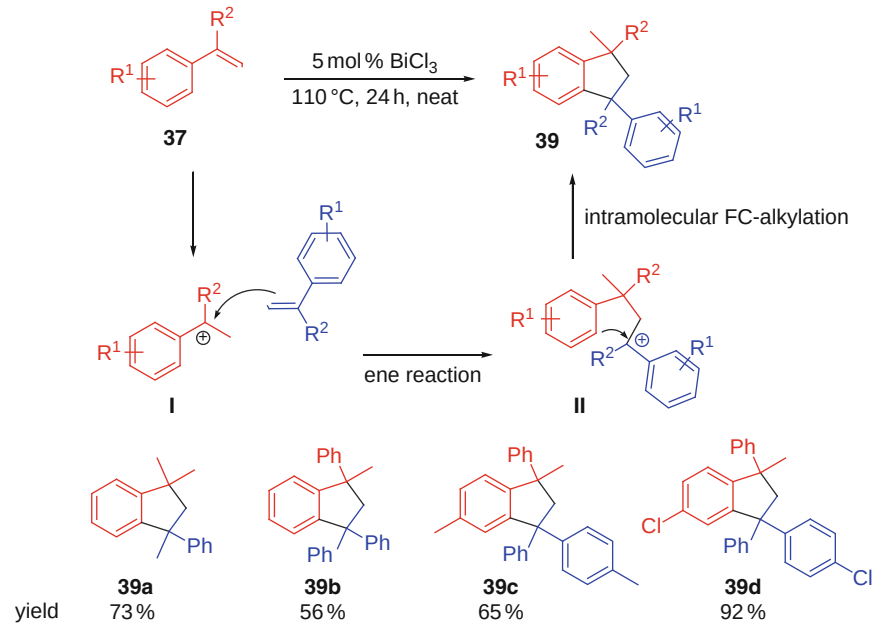
Similar to Rueping's procedure, Hua and coworkers developed a $BiCl_3$-catalyzed synthesis of 1,1-diarylalkanes also starting from electron-rich arenes and styrenes [68]. They found that styrenes **37** could be transformed to the substituted cyclopentanes **39** if catalytic amounts $BiCl_3$ were applied (Scheme 30). This reaction is believed to proceed via an intermolecular ene-reaction between styrene and the carbocationic intermediate **I**, followed by an intramolecular Friedel–Crafts alkylation of the resulting intermediate **II**.




**Scheme 28** Comparison of $Bi(OTf)_3$-catalyzed alkylations with σ-donors and π-donors



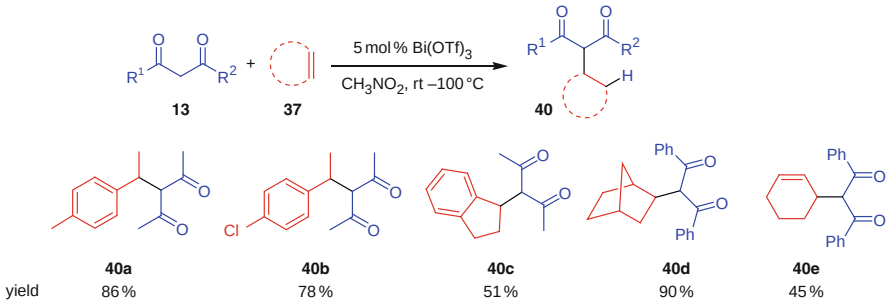

**Scheme 29** Scope of the $Bi(OTf)_3$-catalyzed hydroarylation of styrenes



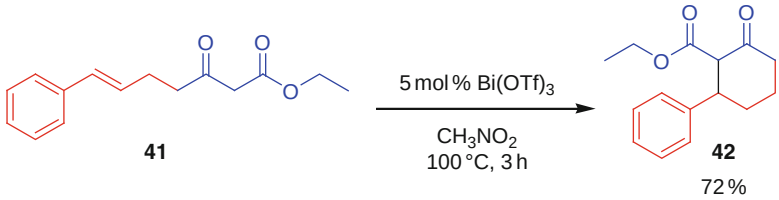

**Scheme 30** Dimerization of styrene mediated by $BiCl_3$ yields a highly substituted cyclopentane

## *3.2 Bi(OTf)$_3$-Catalyzed Alkylation of 2,4-Pentanediones with Activated Alkenes*

On the basis of previous results, the Rueping group started to study alkylations with activated alkenes and nucleophiles other than arenes. Recently, Lewis- and Brønsted-acid-catalyzed hydroalkylation procedures with 1,3-dicarbonyl compounds as nucleophiles have been developed [69, 70]. These reactions primarily utilized Pd




**Scheme 31** $Bi(OTf)_3$-catalyzed hydroalkylation of 2,4-pentanediones with activated double bonds



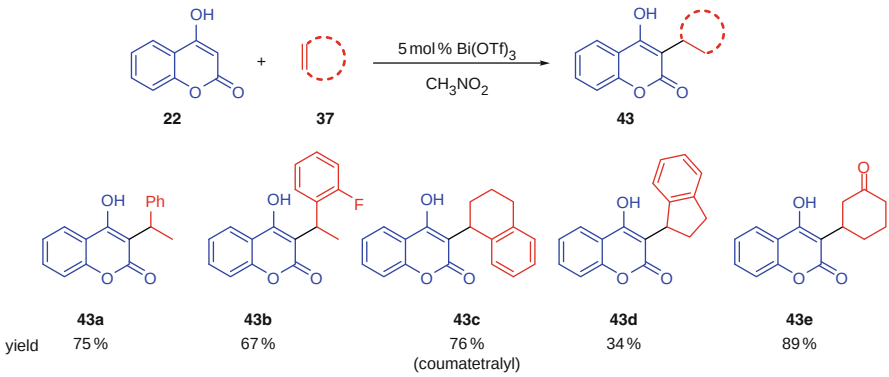

**Scheme 32** Intramolecular hydroalkylation of the substituted β-ketoester **41**

[71–81], Ag and Au [82] as Lewis acid catalysts or H-mont, a strong solid Brønsted acid catalyst [83]. Complementary to these existing methods it should be possible to develop a $Bi(OTf)_3$-catalyzed hydroalkylation of 1,3-dicarbonyls **13**. Indeed, with 5 mol% of $Bi(OTf)_3$ catalyst, various styrenes **37** and other substrates with activated double bonds, including indene, norbornene, and 1,4-cyclohexadiene, could be used as electrophiles in this procedure (Scheme 31) [84]. Styrenes bearing electron-donating as well as electron-withdrawing groups on the aryl residue were tolerated, making this method a 100% atom-efficient approach to 2-alkylated 1,3-diketones.

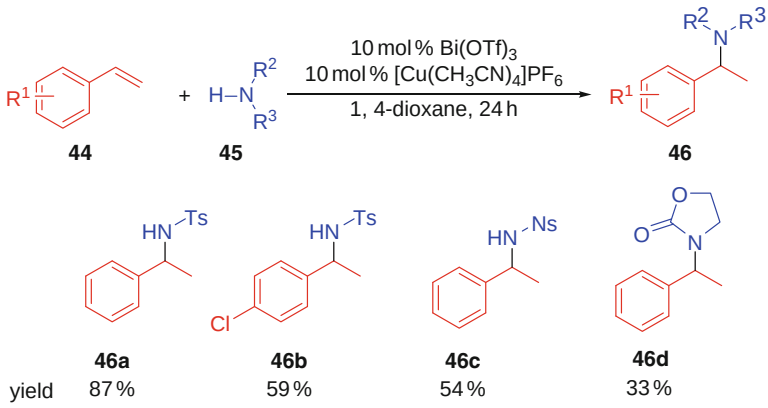
Furthermore, for the first time this procedure has been extended to β-ketoesters, although only an intramolecular reaction was feasible. However, with 5 mol% of $Bi(OTf)_3$, the styrene-substituted ketoester **41** was converted into the 2,3-disubstituted cyclohexanone **42** in 72% yield (Scheme 32).

In addition, this method has been extended to 4-hydroxycoumarin nucleophiles. This method represents a highly efficient synthetic route to new warfarin derivatives (Scheme 33). Again, 5 mol% of the Lewis acid was necessary to obtain the desired 3-alkylated 4-hydroxycoumarins in good isolated yields. Even dihydronaphtalene could be used as alkylating reagent and resulted in a one-step synthesis of coumatetralyl, a widely used rodenticide. Beside styrenes, enones could also be used as electrophiles in the $Bi(OTf)_3$-catalyzed alkylation reaction [52].

In addition to C-alkylation reactions, hydroaminations are of great interest in organic synthesis [85, 86]. Recently, Shibasaki and coworkers developed a $Bi(OTf)_3$-catalyzed intermolecular hydroamination using styrenes [87] and




**Scheme 33** Hydroalkylation of 4-hydroxycomarin yields highly desirable warfarin derivatives

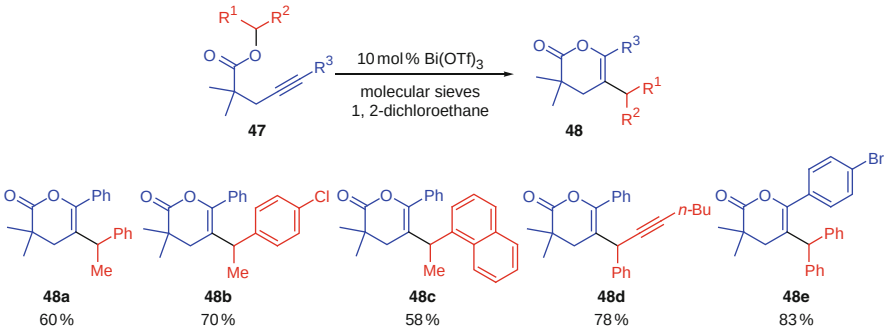



**Scheme 34** $Bi(OTf)_3$-catalyzed hydroamination of styrenes

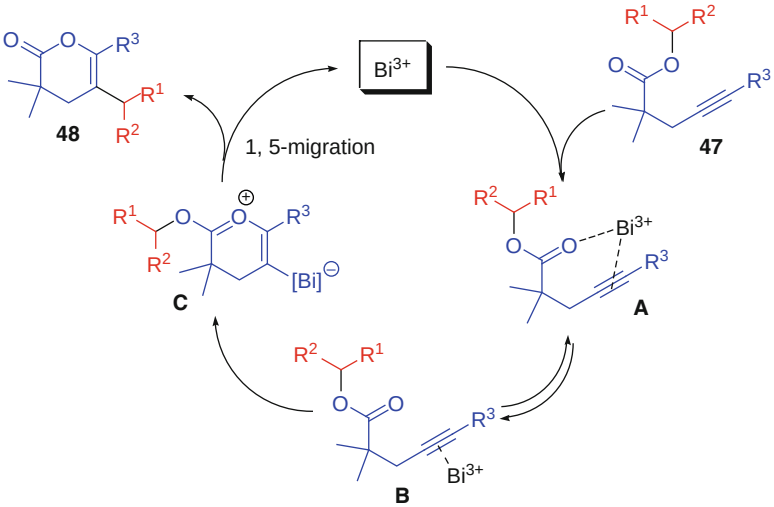
cyclohexadiene [88]. Various nitrogen-containing nucleophiles **45**, including tosyl amides and cyclic carbamates, were efficiently applied. Similar to the previously described amination of benzyl alcohols [61], a combination of $Bi(OTf)_3$ and a $M^+[PF_6]^-$ salt was essential for an efficient alkene activation [87] (Scheme 34).

## *3.3 From Alkenes to Alkynes: Bismuth-Catalyzed Carbo-oxycarbonylations*

It has been demonstrated that $Bi(OTf)_3$ is a versatile catalyst for the activation of both σ- and π-donors. Thus, in order to evaluate their potential in terms of a π-donor/π-acceptor interaction, Bi-catalyzed hydroalkynylations were investigated. As an example, Takaki and coworkers developed a $Bi(OTf)_3$-catalyzed intramolecular carbo-oxycarbonylation of alkynyl esters (Scheme 35) [89].




**Scheme 35** $Bi(OTf)_3$-catalyzed intramolecular oxycarbonylation




**Scheme 36** Possible reaction mechanism for the bismuth-catalyzed carbo-oxycarbonylation of alkynyl esters

Several Lewis acids, including $Cu(OTf)_2$, $Ni(OTf)_2$ and $Fe(OTf)_3$ were tested; however, the highest reactivity in terms of yields was achieved with $Bi(OTf)_3$. Interestingly, $Sc(OTf)_3$ as a hard Lewis acid, gave the corresponding carboxylic acid exclusively. With 10 mol% of $Bi(OTf)_3$, various alkynyl esters **47** were transformed into the desired lactones **48a–e**. Mechanistically, it is believed that Bi(III) activates the substrate through double coordination to the alkyne and the ester carbonyl groups and thus functions as a π- and σ-acceptor (**A**) (Scheme 36). This coordination should be in equilibrium with the transition state **B** where Bi(III) is coordinated to the alkyne alone. This bifunctional Lewis acid–Lewis base interaction allows a nucleophilic attack of the ester carbonyl group to yield the

metallated zwitterion **C**. This intermediate is not stable and is converted into the substituted lactone **48** via 1,5-migration of the benzyl group.

This reaction impressively demonstrates that even alkyne activation, to date an exclusive domain of late transition metals such as Pd or Pt, can be performed by the cheap and nontoxic Lewis acid $Bi(OTf)_3$ [90].

## 4 Conclusion

This overview impressively demonstrates that Bi(III) salts are not only versatile Lewis acid catalysts for the activation of σ-donors, including benzyl and propargyl alcohols, but also efficient catalysts for the activation of π-donors such as styrenes or alkynes. In recent years, various environmentally benign bismuth-catalyzed methods have been developed for the alkylation of arenes, heteroarenes, 2,4-pentanediones, silyl enol ethers, allyl silanes, alcohols and even thiols. Given the ongoing need for new economically and ecologically viable C–C and C–X bond forming reactions, the examples presented here are only the starting point for further developments in bismuth catalysis. Due to the inherent advantages of bismuth and its salts, it is highly likely that there will be many further developments and applications in the future.

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# New Applications for Bismuth(III) Salts in Organic Synthesis: From Bulk Chemicals to Steroid and Terpene Chemistry

**J.A.R. Salvador, S.M. Silvestre, R.M.A. Pinto, R.C. Santos, and C. LeRoux**

**Abstract** Bismuth(III) salts are currently considered efficient and "ecofriendly" reagents and catalysts for the development of new applications in organic synthesis. The preparation of bismuth(III) triflate and its analogues is reviewed as well as some of their applications to the synthesis of bulk chemicals via electrophilic addition and cyclization reactions. The use of bismuth(III) salts in the development of new chemical processes involving steroids and terpenes as substrates is also discussed.

**Keywords** Bismuth triflate · Bismuth(III) salts · Corticosteroids · Steroids · Triterpenoids

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## Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| Alk | Alkyl |
| Ar | Aryl |
| Bu | Butyl |
| CafEt | 1,3,7-Trimethyl-9-ethylxanthinium |
| DFT | Density-functional theory |
| DTBP | 2,6-Di-*t*-butylpyridine |
| eq. | Equivalent(s) |
| Et | Ethyl |
| FC | Friedel–Crafts |
| HSAB | Hard and soft acids and bases |
| Me | Methyl |
| MSA | Methanesulfonic acid |
| $NTf_2$ | *bis*(Trifluoromethanesulfonyl)amide |
| OAlk | Alkoxyl |
| OMe | Methoxyl |
| OTf | Triflate |
| Ph | Phenyl |
| RET | Rare earth triflate |
| *t* | *tert* |
| *t*-Bu | *tert*-Butyl |
| Tf | Triflyl |
| *vic* | Vicinal |
| XRD | X-ray diffraction |

## 1 Introduction

The growing relevance of green and sustainable chemistry and the application of its guiding principles to the development of new reactions and chemical processes are changing the face of chemistry [1–5]. Several strategies have been developed leading to more efficient, sustainable, and environmentally friendly chemical processes and products. Among those strategies, catalysis and the design of new

processes that avoid the use of toxic reagents have been the subject of intense research. In this context, bismuth(III) salts are suitable reagents for the design of "ecofriendly catalysts", and a large number of procedures involving the use of Bi(III) compounds in organic synthesis have been reported over the last decade [6–21]. Two review papers focusing on the recent advances in usage of Bi(III) salts in organic chemistry, with special emphasis on their application to the synthesis of compounds of pharmaceutical interest have been published recently [22, 23].

This current interest in the inexpensive and commercially available Bi(III) salts is mainly due to the relatively nontoxic character of this picnogen and heaviest stable element [24], making it suitable for the design of the ecofriendly catalysts required for green chemistry.

According to the theory of hard and soft acids and bases (HSAB), the Bi(III) cation is classified as a borderline element [25]. Bi(III) salts with electron-withdrawing groups act as soft Lewis acids leading to the formation of weak complexes with Lewis bases containing hard atoms (such as the carbonyl group). This property is responsible for the observed catalytic properties of Bi(III) salts, which act as soft Lewis acids and are compatible with acid sensitive substrates such as furan compounds (an oxo-heterocycle that is well known to polymerize in the presence of $AlCl_3$ or $TiCl_4$) [26]. Moreover, while on the one hand relativistic effects are responsible for the stabilization of the 6s orbital (inert pair) [27, 28], the Lewis acid behaviour of Bi(III) salts can, on the other hand, be attributed to the availability of unoccupied orbitals (d and/or Bi-X $\sigma^*$) [29–31], this latter property being accentuated by strong withdrawing groups such as trifluoromethanesulfonate (triflate). Despite the fact that several procedures to prepare Bi(III) triflate have been reported [32–34], none of these strictly give the anhydrous salt, and thus the hydrated $Bi(OTf)_3{\cdot}xH_2O$ (with $1 < x < 5$) is obtained in all cases. The majority of authors cite the procedure reported by Le Roux et al., and therefore Bi(III) triflate will be written as $Bi(OTf)_3{\cdot}xH_2O$ throughout this chapter. The progressive addition of water to anhydrous Bi(III) triflate is known to give tetrahydrated [35] and nonahydrated [36] forms before its complete and reversible hydrolysis [33], leading to hydrated Bi cationic species [37, 38] and triflic acid. Recent work with $Bi(OTf)_3{\cdot}xH_2O$ has clearly established that acidic protons are involved in its observed catalytic activity, as in the acylation of alcohols [39, 40], synthesis of porphyrins [41], and hetero-Michael addition reactions [42]) as a result of the hydrolysis of the Bi cation. Hydrated forms are known for other Bi(III) salts such as $Bi(NO_3)_3{\cdot}5H_2O$, $BiOClO_4{\cdot}xH_2O$, $BiCl_3{\cdot}2H_2O$, [43], and $BiBr_3{\cdot}2HBr{\cdot}4H_2O$ [44]. Keeping in mind the remarkable review on Brønsted and Lewis acid activations [45], it appears that the catalytic activity of Bi(III) salts and its hydrates cannot be attributed to single Lewis acid activation of the substrates by Bi cations. Therefore, a subtle mix between each Bi species of Brønsted and/or Lewis acidic activation (what could be called the hidden "Bi" behaviour of bismuth), depending on the substrates and the conditions used (such Lewis-assisted Brønsted acidity), has been proven in the case of rare earth triflate (RET where RE = Yb)-catalyzed preparation of calyx[4]resorcinarenes [46], a reaction also catalyzed by $Bi(OTf)_3{\cdot}xH_2O$) [47]. Moreover, from the amount of work already reported, it is evident that Bi(III) salts also exhibit a strong halophilic [48–50] and thiophilic

character [34, 51], and sometimes act as a shuttle for inorganic or organic ligands (ligand exchange). Such ligand exchanges have been reported with BiOCl [52], $BiBr_3$ [53], $Bi(NO_3)_3{\cdot}5H_2O$ [54], $Bi(OTf)_3{\cdot}xH_2O$ [55], and $ClBi(OTf)_2$ [34, 56]. The use of $Bi(NO_3)_3{\cdot}5H_2O$ to promote some oxidation reactions has also been reported, in which the Bi salt serves as a source of $NO_2$ [57].

This chapter is an update (2003 to present) of the main applications of Bi(III) Lewis acids in organic synthesis developed and, in some cases, co-developed, by French and Portuguese research groups. Thus, in this chapter, the preparation of Bi(III) catalysts and their application to chemical transformations ranging from electrophilic addition to cyclization reactions, will be reviewed. The development of new environmentally friendly chemical processes, using Bi(III) reagents and catalysts, with direct application to steroid chemistry and related compounds will also be considered.

## 2 Preparation of Bismuth(III) Triflate and Analogues

Although it was first prepared by Verma et al. in 1983 starting from Bi(III) trifluoroacetate [58], our group developed another strategy for the preparation of $Bi(OTf)_3$ [32]. The key point of our synthetic strategy is based on the acidic cleavage of the three carbon–bismuth bonds of triphenylbismuth by triflic acid in dichloromethane (Scheme 1). A study of the hydration of $Bi(OTf)_3{\cdot}xH_2O$ revealed that this compound can exist as three different hydrates, the nonahydrate, the tetrahydrate, and the dehydrate [35]. The structures of the nona- and tetrahydrate forms have been determined by ab-initio calculations [35] and XRD [36].

Our group has also discovered a "greener" procedure for the synthesis of $Bi(OTf)_3{\cdot}xH_2O$ starting from $Bi_2O_3$ and TfOH using an aqueous ethanol mixture as the solvent [33]. $Bi(OTf)_3{\cdot}xH_2O$ (with $1 < x < 4$) is obtained after freeze-drying of the solution (Scheme 2).

Recently, a new and inexpensive method has been published by our group [34]. It uses $Bi_2O_3$ and TfOH as starting materials and anhydrous chlorobenzene as solvent, which allows the recovery of $Bi(OTf)_3{\cdot}xH_2O$ (with $1 < x < 4$) simply by filtration (Scheme 3).

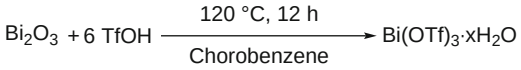
A survey of the available literature methods for the preparation of $Bi(OTf)_3{\cdot}xH_2O$ indicates that one of the most suitable is the procedure starting from

$$BiPh_3 + 3\ TfOH \xrightarrow[-3\ PhH]{CH_2Cl_2,\ -78\ °C} Bi(OTf)_3{\cdot}xH_2O$$

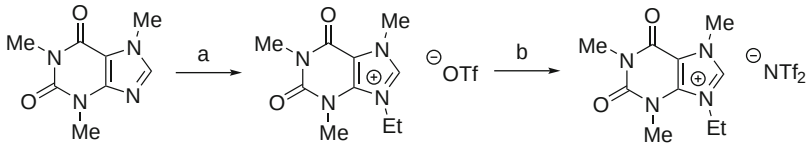
**Scheme 1** Preparation of $Bi(OTf)_3{\cdot}xH_2O$ starting from $BiPh_3$

$$Bi_2O_3 + 6\ TfOH \xrightarrow[EtOH/H_2O\ (75/25)]{65\ °C,\ 7\ h} Bi(OTf)_3{\cdot}xH_2O$$

**Scheme 2** Ecofriendly preparation of $Bi(OTf)_3{\cdot}xH_2O$ starting from $Bi_2O_3$




**Scheme 3** Industrial preparation of $Bi(OTf)_3{\cdot}xH_2O$ starting from $Bi_2O_3$




**Scheme 4** Preparation of 1,3,7-trimethyl-9-ethylxanthiniumbis(trifluoromethanesulfonyl) amide [CafEt][$NTf_2$]. Reagents and conditions: (*a*) EtOTf (1.2 eq.), $PhNO_2$, 100 °C, 16 h; (*b*) $LiNTf_2$ (1 eq.), acetone, room temperature

$Bi_2O_3$ and triflic acid in chlorobenzene [34]. This procedure allows the preparation of $Bi(OTf)_3{\cdot}xH_2O$ on an industrial scale (Scheme 3).

A supported version of $Bi(OTf)_3{\cdot}xH_2O$ has been developed using a caffeine-derived salt, (1,3,7-trimethyl-9-ethylxanthinium *bis*(trifluoromethanesulfonyl)-amide), as adsorbant. This compound has been prepared by direct alkylation of caffeine with ethyl triflate, followed by metathesis with $LiNTf_2$) (Scheme 4) [59].

Bi(III) *bis*(trifluoromethanesulfonyl)amide has also been prepared by our group [60]. This compound proved to be extremely moisture sensitive, and it has to be strictly manipulated (and stored) under argon.

## 3 Electrophilic Additions

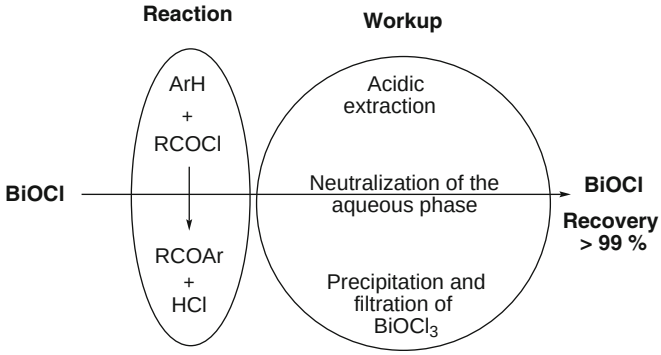
Friedel–Crafts (FC) alkylation, acylation, and sulfonylation reactions are important C–C or C–S bond forming reactions in organic chemistry [60–64]. Since the seminal works of Charles Friedel and James Mason Crafts published in 1877 in which they report the use of $AlCl_3$ for alkylation reactions [65], the search for more active catalysts, especially for acylation reactions, continues. Due to increasing environmental concerns, the need for green catalysts and processes for the FC reaction has gained significant importance. Bi(III) salts have shown to be efficient and recoverable catalysts with applicability in this area [13].

### *3.1 Acylation and Related Reactions*

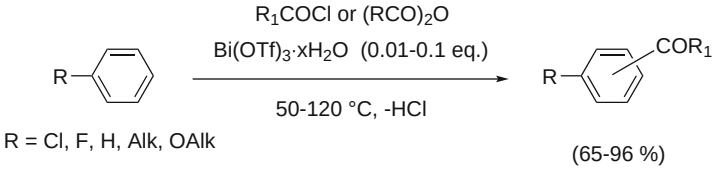
#### 3.1.1 Acylation Reactions

Bi salts proved to be as active as RET or other metallic triflates in the FC acylation of aromatic compounds using acyl chlorides or anhydrides [13, 66]. While

**Scheme 5** Reaction of BiOCl with acyl chlorides to afford $BiCl_3$ and the corresponding anhydride



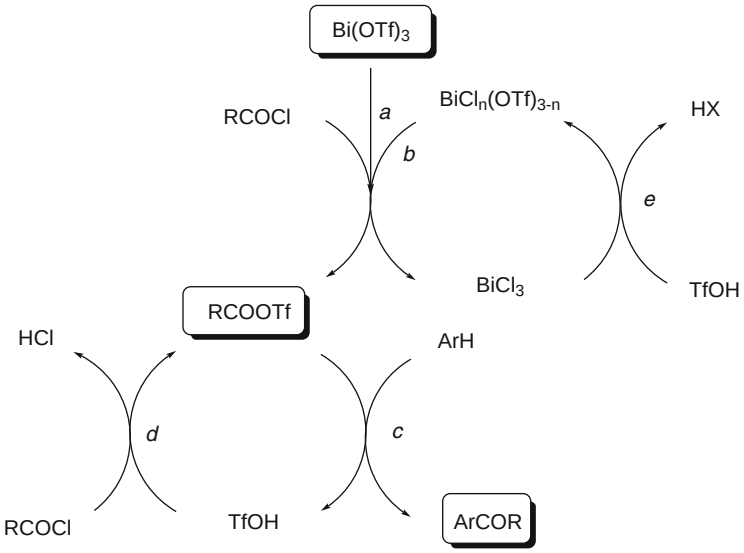

**Scheme 6** Bismuth-catalyzed acylation of arenes



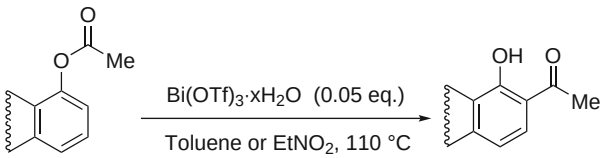

**Scheme 7** Acylation reactions catalyzed by $Bi(OTf)_3{\cdot}xH_2O$

restricted to the acylation of activated arenes (aromatic ethers, polyaromatic, and polyalkylated arenes), $BiCl_3$ which is less expensive than any RET, is recommended for these reactions. The thiophilicity of Bi precludes its use with sulphur-containing substrates such as thioanisole, in contrast to RET [67]. In contrast to $AlCl_3$, the interaction of $BiCl_3$ with acylating agents led to coordination complexes rather than ionic species [13]. Interestingly, BiOCl (a water-insensitive and nontoxic compound) proved to be a good procatalyst for FC reactions since its reaction with acyl chlorides through ligand exchange leads to $BiCl_3$ and the corresponding anhydride (Scheme 5) [66]. Thus, a green process in which BiOCl plays a key role is possible since this salt is almost completely recoverable from water (Scheme 6).

$Bi(OTf)_3{\cdot}xH_2O$ proved to be a superior catalyst than $BiCl_3$ for FC acylation (Schemes 7 and 8). Its activity as a Lewis acid is restricted to acid anhydrides since with acid chlorides $Bi(OTf)_3{\cdot}xH_2O$ leads to ligand exchange reactions in which mixed anhydrides (RCOOTf, see path *a* in Scheme 8) are the active acylating




**Scheme 8** Mechanism for the acylation reaction catalyzed by $Bi(OTf)_3{\cdot}xH_2O$




**Scheme 9** $Bi(OTf)_3{\cdot}xH_2O$ catalysis of the Fries rearrangement

species [55]. The acylation of alkylbenzenes has been reported to be the limit of this catalyst [13].

### 3.1.2 Fries Rearrangement

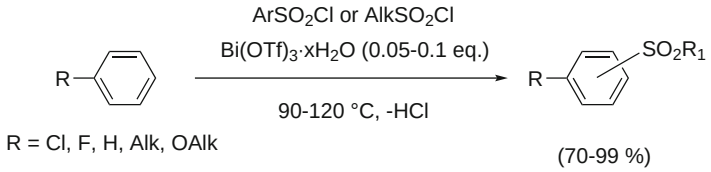
The rearrangement of aryl and naphthyl acetates has been reported to be catalyzed by $Bi(OTf)_3{\cdot}xH_2O$ (Scheme 9) [68, 69]. As previously reported, only *ortho*-Fries products (1-hydroxy-2-acylaromatics) were produced from substrates for which *ortho* acylation was possible. In the case of 2,6-dimethoxyphenyl acetate, only the 3,5-dimethoxy-2-hydroxy acetophenone was produced, indicating that in this case the mechanism involves an intermolecular acyl-group transfer. As in other reactions, the nature of the true catalyst is still unclear since triflic acid also catalyzes this reaction.

More recently, Mouhtady et al. demonstrated that $Bi(OTf)_3{\cdot}xH_2O$ and other metal triflates interact with methanesulfonic acid (MSA) to form an efficient synergic catalytic system for the Fries rearrangement of naphthyl acetate [70, 71].

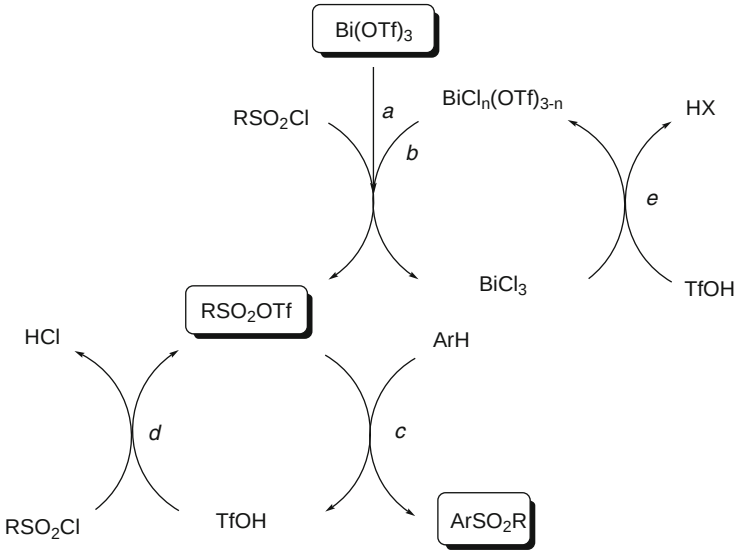
It has been suggested that the efficiency of these systems might result from the catalytic Lewis acid activation of the Brønsted acid.

## 3.2 Sulfonylation Reactions

In the case of sulfonylation (Scheme 10) [56] and sulfinylation reactions [34], Bi salts proved again to be efficient catalysts. In contrast to the arylsulfonylation, which is under partial control of triflic acid, depending on the substrates, a complete synergistic effect between triflic acid and Bi chloride has been found in the alkanesulfonylation of arenes. In this case, the formation of mixed triflic/alkanesulfonic anhydrides leads to the active electrophilic species. The formation of the latter exclusively requires the transient formation of a Bi chlorobistriflate species that acts as an intermediate shuttle for triflic acid, leading to the formation of the mixed anhydride precited (Scheme 11). Our experiments have shown that triflic




**Scheme 10** Sulfonylation reactions catalyzed by $Bi(OTf)_3{\cdot}xH_2O$




**Scheme 11** Mechanism for the sulfonylation reaction catalyzed by $Bi(OTf)_3{\cdot}xH_2O$

acid is not able to catalyze alkanesulfonylation reactions, as opposed to acylation reactions.

### 3.3 Chloro Sulfinylation Reaction

The catalytic activation of thionyl chloride by $Bi(OTf)_3{\cdot}xH_2O$ has been reported and applied to the preparation of the thermally unstable aryl sulfinyl chlorides [34]. It has been shown that this procedure is restricted to electron-rich aromatics (such as aromatic ethers and mesitylene). The mechanistic investigation seems to indicate that no ligand exchange occurs during the reaction.

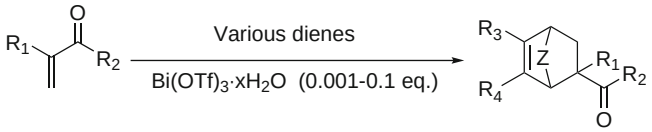
## 4 Cyclization Reactions

Since our group has discovered that $BiCl_3$ and $Bi(OTf)_3{\cdot}xH_2O$ are mild and efficient catalysts for Diels–Alder and related reactions [72–74], Bi salts have been largely used in different synthesis involving Diels–Alder reactions.

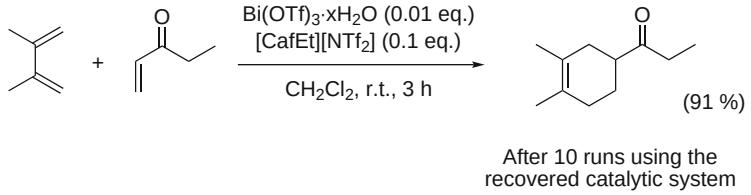
### 4.1 Diels–Alder Reactions

Among the various methods available for the activation of dienes in a Diels–Alder reaction, Lewis acid catalysis is certainly the most important. Our group has reported the first example of a Diels–Alder reaction catalyzed by $Bi(OTf)_3{\cdot}xH_2O$ (Scheme 12) [72], which showed high catalytic activity and regioselectivity in comparison to other Sc-, Ti-, Sm-, or Yb-metal-based Lewis acids, well-known for their efficient catalytic activity. $Bi(OTf)_3$ proved to be slightly more *endo*-selective than $Sc(OTf)_3$. Further, no polymerisation of dienes or dienophiles was observed. $Bi(OTf)_3$ was also found to be superior to $SnCl_4$ and $Cu(BF_4)_2$.

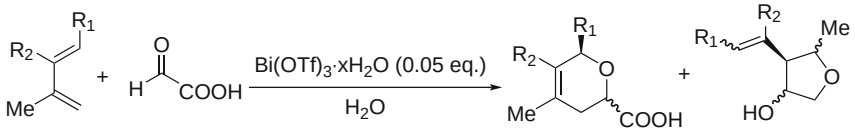
A new reusable catalytic system, consisting of a combination of $Bi(OTf)_3{\cdot}xH_2O$ and the novel ionic solid 1,3,7-trimethyl-9-ethylxanthinium *bis*(trifluoromethanesulfonyl)amide has been reported for the Diels–Alder reaction (Scheme 13) [59]. The hydrophobic nature of the $NTf_2$ counteranion simultaneously prevents the




**Scheme 12** Diels–Alder reactions catalyzed by $Bi(OTf)_3{\cdot}xH_2O$




**Scheme 13** Diels–Alder reaction of 2,3-dimethyl-1,3-butadiene and ethyl vinyl ketone catalyzed by the reusable $Bi(OTf)_3{\cdot}xH_2O$/[CafEt][$NTf_2$] catalytic system




**Scheme 14** Carbonyl Diels–Alder reactions catalyzed by $Bi(OTf)_3{\cdot}xH_2O$

hydration of $Bi(OTf)_3{\cdot}xH_2O$ and allows the recovery of the catalytic system for at least ten times without any loss of activity [59]. The reactivity has been further extended with success to the reaction of butadiene with maleic anhydride.

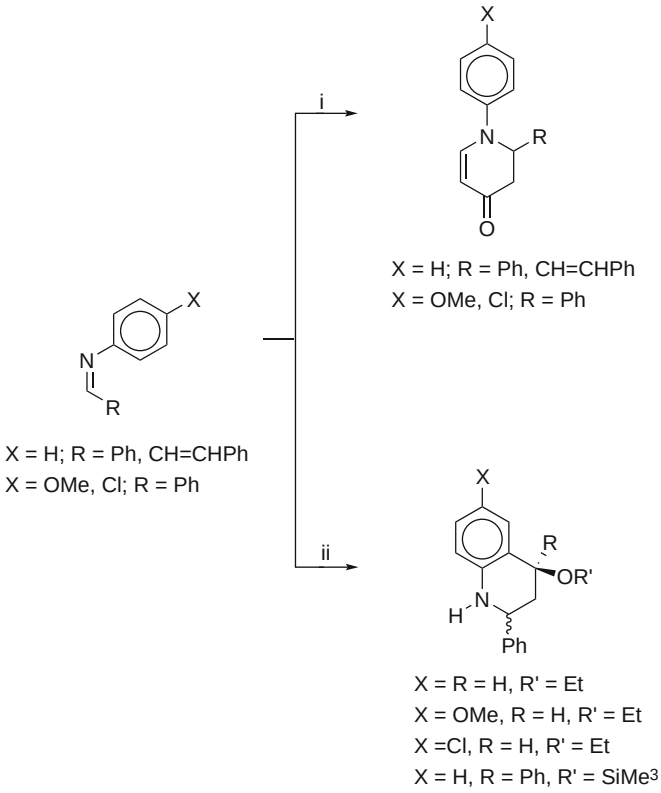
## *4.2 Hetero-Diels–Alder Reactions*

### 4.2.1 Carbonyl-Diels–Alder Reactions

$Bi(OTf)_3{\cdot}xH_2O$ has been found to catalyze carbonyl-Diels–Alder reactions in water involving glyoxylic acid as the dienophile (Scheme 14) [72]. In contrast to other Lewis acids (such as $Sn(OTf)_2$, $Yb(OTf)_3$, $Nd(OTf)_3$, $Ce(OTf)_3$ and $Sc(OTf)_3$), the strong catalytic power of $Bi(OTf)_3{\cdot}xH_2O$ made it necessary to reduce its amount as well as the reaction temperature. $Bi(OTf)_3{\cdot}xH_2O$ enhanced the reaction rate but with some dienes the reaction led to competitive formation of the ene reaction product.

### 4.2.2 Aza-Diels–Alder Reactions

Although several Lewis acids are known to catalyze the hetero-Diels–Alder reaction involving imino-dienes or imino-dienophiles (aza-Diels–Alder reaction), a large amount of the catalyst is often necessary. $Bi(OTf)_3{\cdot}xH_2O$ showed higher activity than lanthanide triflates in catalyzing the reactions of imines with Danishefsky's diene (Scheme 15) [72].




**Scheme 15** Aza Diels–Alder reactions catalyzed by $Bi(OTf)_3{\cdot}xH_2O$. Reaction conditions: (i) 1, $CH_3OCH = C(OSiMe_3)Me$, $Bi(OTf)_3{\cdot}xH_2O$ (0.05–0.1 eq.); 2, $H_2O$. (ii) 1, $HC(OEt) = CH_2$ or $PhC(OSiMe_3) = CH_2$, $Bi(OTf)_3{\cdot}xH_2O$ (0.05–0.1 eq.); 2, $H_2O$

Amounts as low as 0.02 eq. of $Bi(OTf)_3{\cdot}xH_2O$ led to the formation of the aza-Diels–Alder adducts in very high yield, in contrast to zinc chloride, which is required in stoichiometric amounts for the same effect. In addition, the $ZnCl_2$-promoted reaction is significantly slower (36 h instead of 0.5–1 h with $Bi(OTf)_3{\cdot}xH_2O$). Another advantage of using $Bi(OTf)_3{\cdot}xH_2O$ is that it is used in one-pot procedures. The imine can be generated in situ from the corresponding aldehyde and amine followed by an imino Diels–Alder reaction. Some tetrahydroquinolines were synthesized by both methods.

## 5 Bismuth(III) Reagents in Steroid and Terpene Chemistry

Steroid [75] and terpene [76] chemistry is undoubtedly a challenging topic of research that drives hundred of investigators all around the world. Terpenes are a large and structurally diverse family of natural products comprising C5 isoprene

units. Steroids belong to the terpenoid family due to their common biosynthesis starting from isoprene. A wide range of compounds from these groups have demonstrated an interesting pharmacological activity against several human pathologies such as cancer, AIDS, and malaria.

The use of Bi reagents in steroid and terpene chemistry is relatively limited. The first reports on their application to these natural products include the use of the Bi(V) reagent, $NaBiO_3$, for the cleavage of the pregnane side-chain of 17α-hydroxy compounds [77] and the oxidation of α-hydroxyketones to diketones with $Bi_2O_3$ combined with AcOH [22]. This last versatile process was applied to several steroidal substrates, including spirostane derivatives and to several diterpenes and triterpenes [22]. Later, the acylation [78–80] and tetrahydropyranylation [81] of hydroxyl groups of steroids and terpenes using several Bi-based processes were reported. Other interesting applications have been reported, such as the deprotection of oximes [82], the Ferrier rearrangement [83] and the aromatic nitration [84].

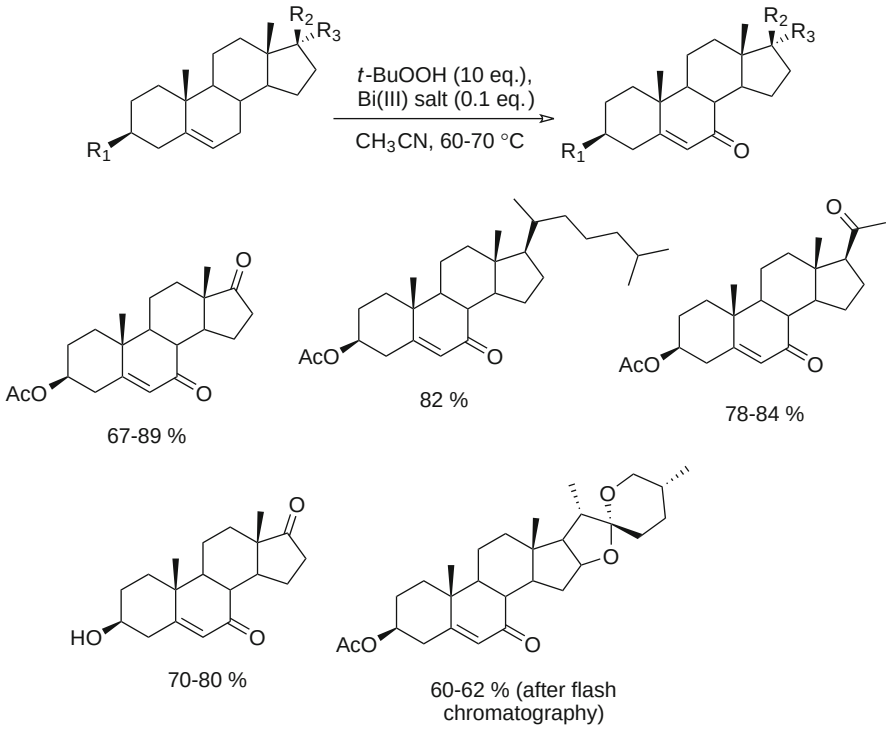
The new Bi(III)-based chemical processes that have been developed by our group, using steroids and terpenes as substrates, will be reviewed next.

## *5.1 Oxidation Reactions*

The preparation of steroids containing oxygenated functions in suitable positions of the steroid nucleus is of major importance and can be achieved by means of several oxidative processes [85, 86]. An example that has attracted interest over the years is the allylic oxidation of $\Delta^5$-steroids to their corresponding $\Delta^5$-7-ketones. These compounds have interesting bioactivities including anticancer action and are important intermediates for the synthesis of other derivatives with various biological activities, such as squalamine, a known antibiotic and anti-angiogenesis agent [85].

The classical method for performing the allylic oxidation of $\Delta^5$-steroids to $\Delta^5$-7-ketones involves the use of chromium reagents, but this metal has several known disadvantages. Of particular preparative interest has been the use of hydroperoxides, combined with different types of metal catalysts such as copper, cobalt, and vanadium in homogeneous and heterogeneous forms [85]. Compared to some transition metals, Bi has the advantage of being nontoxic and noncarcinogenic. Therefore, the combination of Bi(III) salts with *t*-butyl hydroperoxide in this reaction was studied and it was concluded that this system was useful for the efficient allylic oxidation of $\Delta^5$-steroids (Scheme 16) [87, 88]. In this study, the most efficient Bi(III) catalyst was $BiCl_3$, and $CH_3CN$ was generally used as solvent at 60–70 °C. Thus, using these reaction conditions, several $\Delta^5$-steroids were converted into the corresponding $\Delta^5$-7-keto-steroids, in good to high yields (Scheme 16).

While performing these reactions, the formation of a white solid that was recovered by filtration and identified by X-ray diffraction (XRD) analysis as BiOCl was observed. Thus, $BiCl_3$ can be recovered at the end of the reaction and reused as BiOCl, which is also active under these reaction conditions, or reconverted

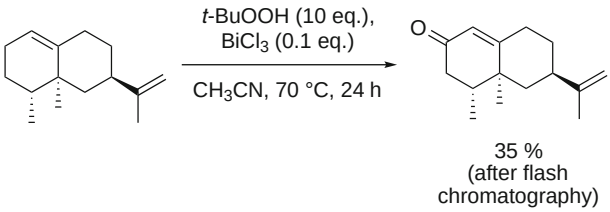



**Scheme 16** Allylic oxidation of $\Delta^5$-steroids catalyzed by Bi(III) salts, using *t*-BuOOH

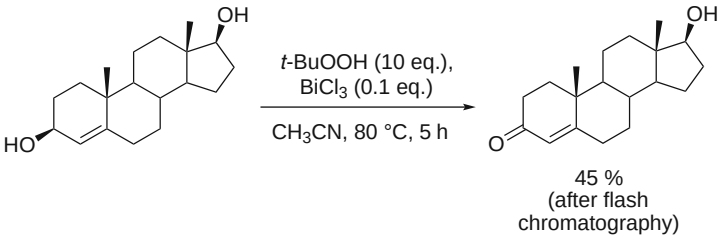
again into $BiCl_3$. The $BiCl_3$/*t*-BuOOH system proved to be very selective for this reaction, since no significant epoxidation of the double bond, secondary hydroxyl group oxidation, or cleavage of the diosgenin spiroketal side chain were observed (Scheme 16). The easier recovery of the catalyst in heterogeneous reactions led us to prepare and use $BiCl_3$/K-10 montmorillonite for this reaction. In fact, this heterogeneous catalyst not only allowed the selective obtention of $\Delta^5$-7-keto-steroids in high yields, but also led to an increase in the reaction rate.

The allylic oxidation of the sesquiterpenoid (+)-valencene has been performed using *t*-BuOOH as the oxidant and $BiCl_3$ as catalyst. Nootkatone was the major product, isolated in 35% yield by flash chromatography (ethyl acetate – light petroleum, boiling point 40–60 °C) (Scheme 17) [87, 88].

Considering the excellent chemoselectivity observed in the allylic oxidation of dehydroepiandrosterone (Scheme 16), it was interesting to evaluate the selective allylic alcohol oxidation in the presence of a secondary saturated hydroxyl group using the $BiCl_3$/*t*-BuOOH system. This study was performed using androst-4-ene-3β,17β-diol and it was observed that after complete consumption of this substrate, the important steroid hormone testosterone could be obtained, in 45% yield, after flash chromatography (Scheme 18) (Salvador JAR, Silvestre SM, unpublished results).




**Scheme 17** $BiCl_3$-catalyzed allylic oxidation of (+)-valencene using *t*-BuOOH




**Scheme 18** $BiCl_3$-catalyzed allylic alcohol oxidation of androst-4-ene-3β,17β-diol with *t*-BuOOH

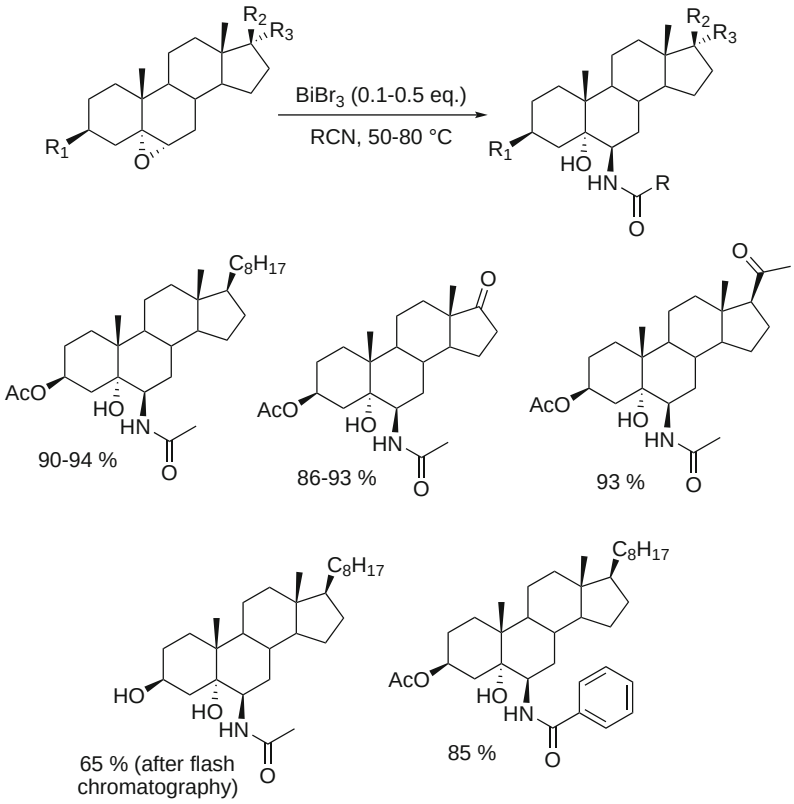
## *5.2 Nucleophilic Ring-Opening of Epoxides*

Epoxysteroids are important synthetic intermediates since their facile ring opening allows the introduction of various functionalities in a stereospecific manner [85, 86]. In fact, these compounds are often used in synthetic cascades towards several compounds with interesting biological and/or pharmacological activities.

### 5.2.1 Ritter Reaction of Epoxides

The Ritter reaction is a known synthetic strategy to obtain N-substituted amides and has been accomplished with nitriles and a variety of compounds capable of forming a carbonium ion as substrate, such as several alcohols and alkenes [89–91]. This reaction is usually promoted by Brønsted or Lewis acids, which generate the mentioned carbonium ions as reaction intermediates. Epoxides, including epoxysteroids, are also common substrates, affording *vic-N*-acylamino-hydroxy compounds as products [92]. Several processes for the Ritter reaction have been described over the years; however, despite the good reaction yields obtained, the large amounts of ecologically hazardous acids or metal reagents together with the difficult work-up [90, 91] led to the development of more environmentally friendly processes.

Several procedures have been reported using acetonitrile as solvent for Bi(III) salt-catalyzed transformations involving epoxides as substrates [54, 93–95]. However, no reference has been made about the occurrence of the Ritter reaction, even

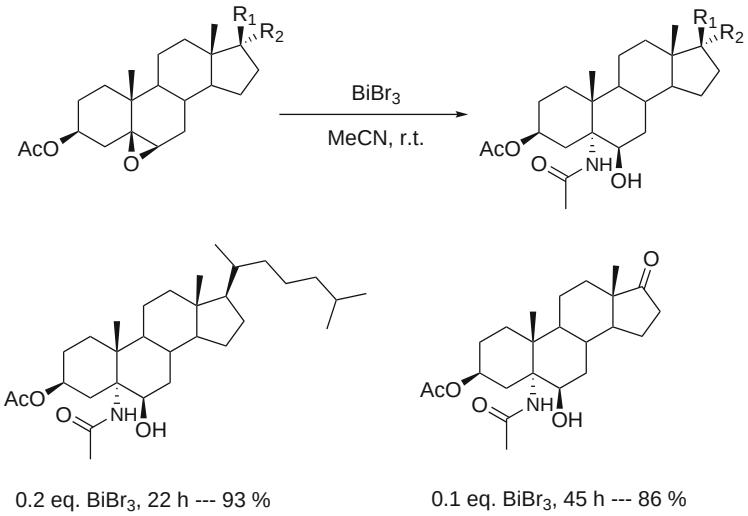



**Scheme 19** Ritter reaction of 5α,6α-epoxysteroids with nitriles, promoted by $BiBr_3$

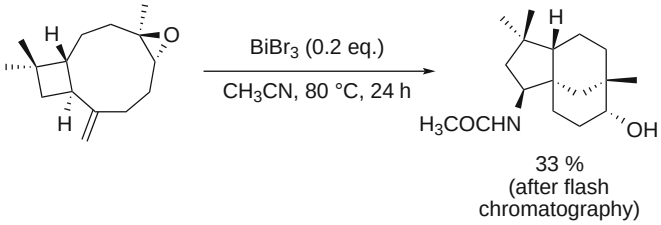
as a side-reaction and thus not even trace amounts of *vic-N*-acylamino-hydroxy compounds have been reported as by-products in those reactions.

In this context, a novel procedure for the Ritter reaction of epoxides using Bi(III) salts as catalysts was developed [92]. Among the Bi(III) compounds screened, $BiBr_3$ gave the best results. The reaction occurred under catalytic conditions (0.1 eq. of $BiBr_3$); however, an increase in the reaction rate was observed using larger amounts of this Bi(III) salt. This process was suitable for the high yielding regio-, chemo-, and stereoselective synthesis of several 6β-*N*-acylamino-5α-hydroxysteroids resulting from the ring opening of 5α,6α-epoxysteroids, in the presence of different nitriles (Scheme 19).

Interestingly, under these reaction conditions, 5α,6α-epoxycholestan-3β-ol, despite bearing a free hydroxyl group, originated the *vic-N*-acetylamino-hydroxy derivative in good yield, revealing the chemoselectivity of this reaction for the epoxide function [96]. In fact, the use of $Bi(OTf)_3{\cdot}xH_2O$ has been reported for the Ritter reaction of alcohols to afford the corresponding amides. Therefore $Bi(OTf)_3{\cdot}xH_2O$ (0.05 eq.) was screened as a catalyst for the Ritter reaction of 5α,6α-epoxycholestan-3β-yl acetate in acetonitrile, and the corresponding




**Scheme 20** Ritter reaction of 5β,6β-epoxysteroids with acetonitrile, catalyzed by $BiBr_3$




**Scheme 21** $BiBr_3$-catalyzed reaction of (−)-caryophyllene oxide under Ritter reaction conditions

6β-acetamido-5α-hydroxy product was obtained in 90%, after 2 h of reaction at 50 °C (Pinto RMA, Salvador JAR, Le Roux C, unpublished work).

When applied to 5β,6β-epoxysteroids, at room temperature, this process allowed the synthesis of the corresponding 5α-*N*-acylamino-6β-hydroxysteroids (Scheme 20). In fact, the nucleophilic attack invariably occurred at C6, in 5α,6α-epoxysteroids, or at C5, in 5β,6β-epoxides.

Under the Ritter reaction conditions above described, the sesquiterpene (−)-cariophyllene oxide undergoes an interesting rearrangement, originating an *N*-acylamino clovane-type compound, in 33% yield, after purification by flash chromatography (Scheme 21) [92].

### 5.2.2 Ring Opening of Epoxides with BI(III) Salts

The vicinal chlorohydrin group has been identified in several bioactive steroidal compounds, such as the withanolides [97]. In biological systems, hypochlorous

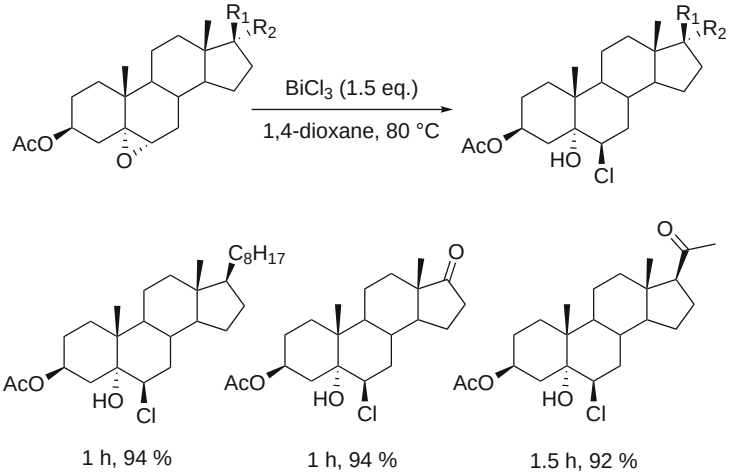
acid, which is generated from $H_2O_2$ and chlorine by myeloperoxidase, is known to form chlorohydrin addition products with unsaturated fatty acids and cholesterol [98]. The formation of cholesterol chlorohydrins has been a subject of intense research [99–102]. The role of these compounds is not yet fully understood, but in addition to cytotoxicity and a possible action on atherosclerosis [100], they have been suggested to be biomarkers of myeloperoxidase-derived HOCl [103]. Moreover, chlorohydrins and other halohydrins are useful intermediates for the synthesis of a vast range of biologically active natural and synthetic products [104, 105]. In fact, considering the importance of these compounds, their preparation is of major interest.

Halohydrins can be easily obtained from epoxide ring opening reactions, but the conventional reagents for this reaction have several disadvantages. In this context, our study started from the knowledge that under the Ritter reaction conditions described above, using $BiCl_3$ in stoichiometric amounts (1.5 eq.), 5α,6α-epoxycholestan-3β-yl acetate afforded a 1:1 ratio of the expected Ritter reaction product and 6β-chloro-5α-hydroxycholestan-3β-yl acetate. However, using 1,4-dioxane as solvent, instead of acetonitrile, Ritter reaction products could be avoided and high yields of several steroidal chlorohydrins were obtained from 5α,6α-epoxysteroids [106]. The reaction also occurred at room temperature, but was faster at 80 °C (Scheme 22).

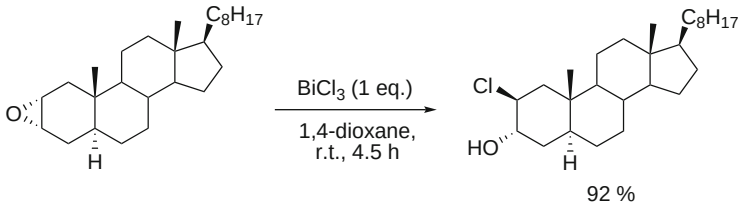
This system was also applied to a 2α,3α-epoxysteroid, and the corresponding 2β-chloro-3α-hydroxy derivative was prepared in high yield (Scheme 23).

The *trans*-diaxial ring opening of 5β,6β-epoxysteroids also gave the corresponding 5α-chloro-6β-hydroxy products (Scheme 24).

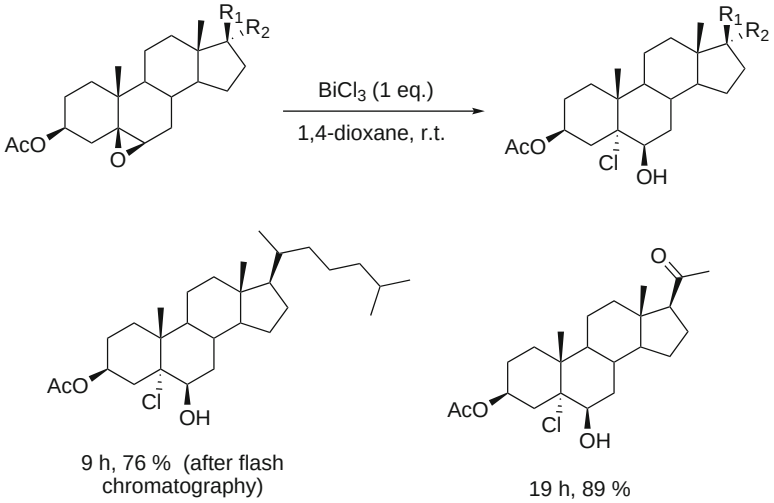
In similar conditions, using $BiBr_3$, a bromohydrin could also be efficiently prepared from the reaction of 5α,6α-epoxycholestan-3β-yl acetate (Scheme 25).



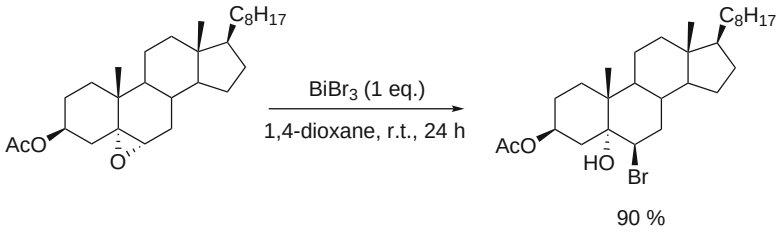

**Scheme 22** Ring opening of 5α,6α-epoxysteroids with $BiCl_3$




**Scheme 23** Ring opening of 2α,3α-epoxy-5α-cholestane with $BiCl_3$

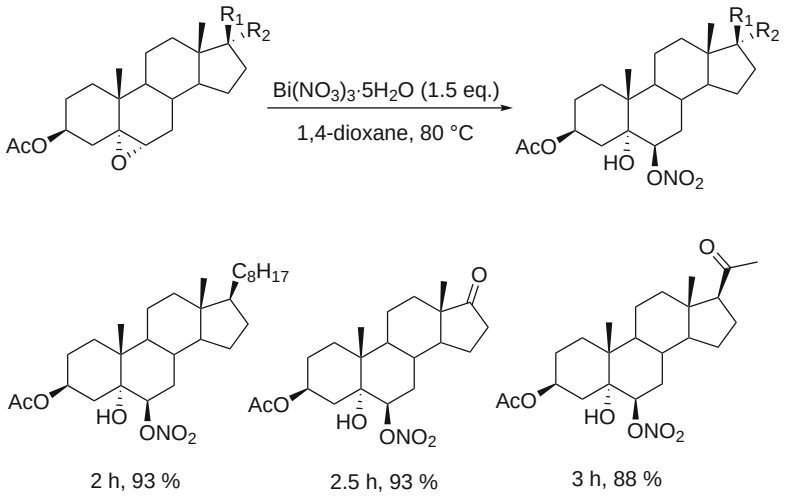



**Scheme 24** Ring opening of 5β,6β-epoxysteroids with $BiCl_3$

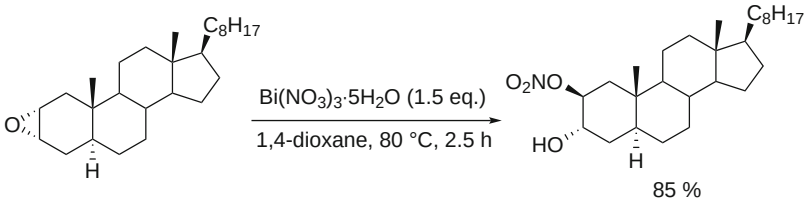



**Scheme 25** Ring opening of 5α,6α-epoxycholestan-3β-yl acetate with $BiBr_3$

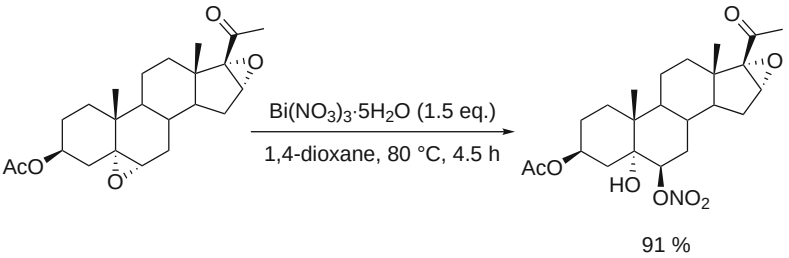
When this reaction was performed in the presence of $Bi(NO_3)_3{\cdot}5H_2O$, β-hydroxynitrate products were obtained instead of halohydrins. In fact, several 5α,6α-epoxysteroids and 2α,3α-epoxycholestan-3β-yl acetate originated the corresponding β-hydroxynitrate derivatives in high yields (Schemes 26–28).




**Scheme 26** Ring opening of 5α,6α-epoxysteroids with $Bi(NO_3)_3{\cdot}5H_2O$




**Scheme 27** Ring opening of 2α,3α-epoxy-5α-cholestane with $Bi(NO_3)_3{\cdot}5H_2O$




**Scheme 28** Ring opening of 5α,6α; 16α,17α-diepoxy-20-oxopregnan-3β-yl acetate with $Bi(NO_3)_3{\cdot}5H_2O$

Interestingly, the ring opening of the 5α,6α;16α,17α-diepoxy-20-oxopregnan-3β-yl acetate with $Bi(NO_3)_3{\cdot}5H_2O$ proved to be highly selective for the 5α,6α-epoxide group (Scheme 28), leaving the 16α,17α-epoxide group intact [107], allowing further important funtionalizations.

Cavdar and Saracoglu reported the ring opening of chemically equivalent diepoxides with $Bi(NO_3)_3{\cdot}5H_2O$ to give di-β-hydroxy nitrates [108]. However, we

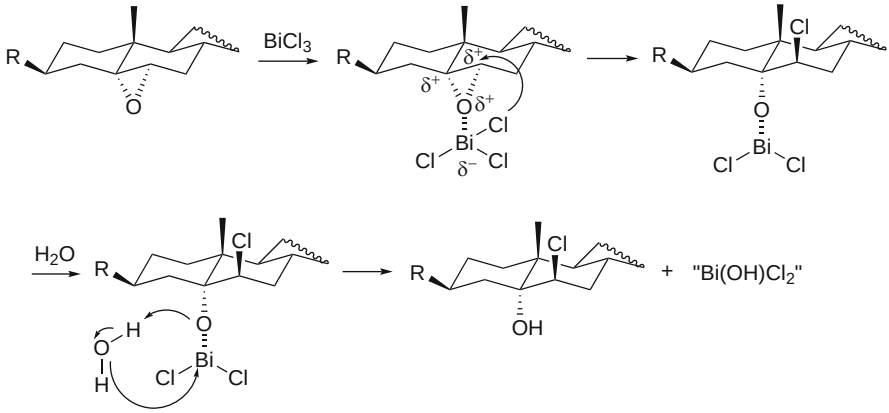
showed that our method is chemoselective for the 5α,6α-epoxide function in a 5α,6α;16α,17α-diepoxide steroid system. This is quite interesting taking the simplicity of $Bi(NO_3)_3{\cdot}5H_2O$ as a reagent into account. In fact, it is of great synthetic interest that such a reagent shows different chemical behaviour between nonequivalent epoxides.

In order to understand the nature of the nucleophilic species, the reaction was performed in the presence of 2,6-di-*t*-butylpyridine (DTBP), a known proton scavenger that only binds to protons and is unable to coordinate to metal ions due to the bulky *t*-butyl groups [42]. Thus, both $BiCl_3$ and $Bi(NO_3)_3{\cdot}5H_2O$ were able to afford the corresponding β-hydroxy-substituted products. These results suggest that the ring opening reaction is mediated by the Lewis acidity of Bi towards the epoxide, much like the Bi–O interaction suggested by Boyer and coworkers for the chlorination of alcohols with $BiCl_3$ [109].

Thus, whereas in the chlorination of alcohols, one of the chlorine atoms of the $ROH/BiCl_3$ complex attacks the carbon attached to the hydroxyl group [109], in the ring opening of epoxysteroids with $BiCl_3$, the chlorine attacks one of the carbons of the epoxide moiety, which are, of course, more susceptible to nucleophilic attack (Scheme 29). As suggested by Boyer et al., a new Bi species should be formed ("$BiCl_2OH$") [109]. In the ring opening of epoxides, one molecule of $H_2O$, participates by furnishing a $H^+$, present in the final hydroxyl group, whereas the $OH^-$ will act as the third ligand of the newly formed Bi species. The ring-opening reaction of epoxysteroids with $Bi(NO_3)_3{\cdot}5H_2O$ is expected to occur similarly.

In addition to the $H_2O$ of hydration present in the hygroscopic Bi(III) halides, the fact that the reactions were carried out in an open vessel, under non-inert atmosphere, explains the presence of $H_2O$, in these reaction conditions.

In another quite recent study, the Lewis acidity of $BiX_3$ (X = Cl, Br and I) towards alcohols has been investigated using density-functional theory (DFT) [110], and the results point to many of the conclusions experimentally found by Boyer et al. Interestingly, the DFT data suggested that the higher affinity of Bi for




**Scheme 29** Possible mechanism for the ring opening of epoxides with $BiCl_3$

Br prevents side reactions and makes $BiBr_3$ a better Lewis acid catalyst, which is in accordance with our work: $BiBr_3$ affords only Ritter reaction products in the high dielectric constant solvent $CH_3CN$, while $BiCl_3$ originates a mixture of both *vic-N*-acylamino-hydroxy compounds and chlorohydrins.

## 5.3 Rearrangement Reactions

Steroid and terpene rearrangements involving bond breaking at one point and re-formation at another position have been the subject of intense research. An explanation of this interest is that enthusiastic new skeletons derived from naturally occurring compounds can be easily prepared [111]. Moreover, rearrangement reactions are amongst the group of transformations for which atom economy is greater, which is especially interesting in the context of the actual paradigm of green chemistry [112].

Classically, rearrangement reactions have been performed using strong acidic reaction conditions. Several Brønsted and Lewis acids have been used over the years to promote a variety of chemical transformations that afforded several new structures that revealed potentially interesting bioactivities. Thus, considering the acid character of Bi(III) salts and their environmentally friendly nature when compared to other previously used Brønsted and Lewis acids, the study of their application in the referred rearrangements is an interesting subject.

### 5.3.1 Westphalen and "Backbone" Rearrangements

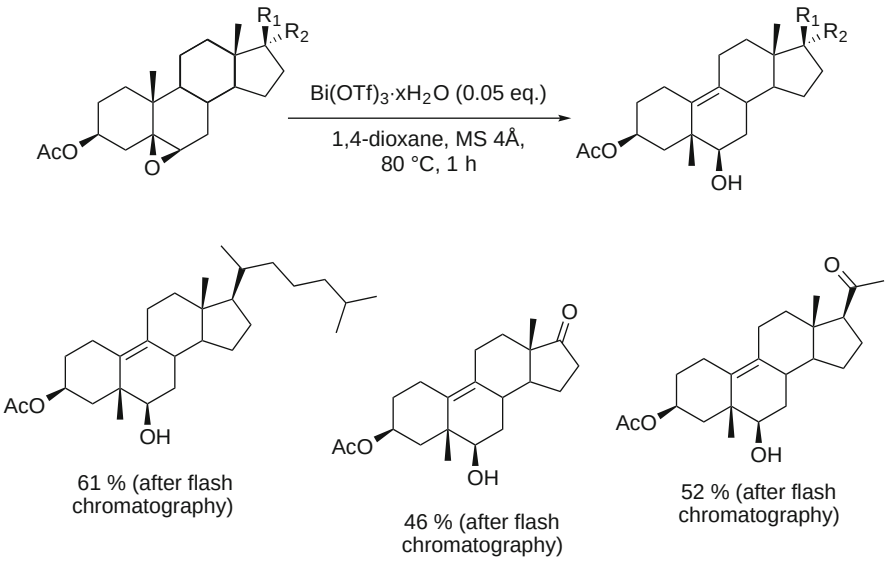
Westphalen and "backbone" rearrangements are classic examples of steroid transformations involving the acid-catalyzed migration of the C18- and C19-methyl groups, which allow the synthesis of olefinic 19-nor and 18,19-dinorsteroids [111, 113–115]. The Westphalen rearrangement is a well-known classic transformation in steroid chemistry and involves 10β-methyl group migration to the 5β-position, with the formation of the corresponding 5β-methyl-$\Delta^{9(10)}$-19-nor derivative [116]. "Backbone" rearranged products represent a further series of hydride and methyl shifts leading to compounds in which both the C18- and C19-methyl groups migrated from C10 and C13, to C5, and C14, respectively [113–115, 117]. Thus, the rearrangement is extended along the entire "backbone" of the steroid molecule, with inversion of configuration at every ring junction [117].

During the study of the Ritter reaction applied to 5β,6β-epoxysteroids [92], it was observed that at room temperature only *vic-N*-acylamino-hydroxy compounds were obtained. Under the same reaction conditions, with 5β,6β-epoxycholestan-3β-yl acetate as substrate, but using $Bi(OTf)_3{\cdot}xH_2O$ instead of $BiBr_3$, small amounts of a by-product, characterized as the backbone rearranged compound, were also found. However, at 50 °C, either using $BiBr_3$ or $Bi(OTf)_3{\cdot}xH_2O$, the major reaction product was not the *vic-N*-acylamino-hydroxy product, and two

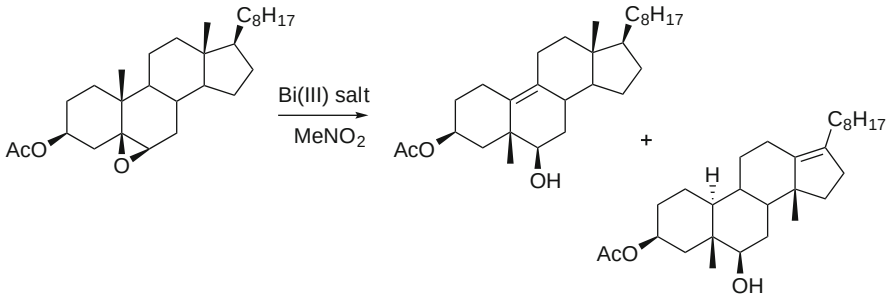
other additional compounds were isolated and identified as the result of Westphalen and backbone rearrangements. Thus, stronger Lewis acidity and higher temperatures changed the expected route from *vic-N*-acylamino-hydroxy compounds to complex rearrangement products [118]. Solvent screening evidenced that the solvent choice determines the path of rearrangement reactions. Using the same substrate and 0.05 eq. of $Bi(OTf)_3{\cdot}xH_2O$ in 1,4-dioxane, the formation of the Westphalen rearranged product, along with 5α,6β-dihydroxycholestan-3β-yl acetate was observed. In order to prevent the nucleophilic ring opening of the epoxide, this reaction was carried out in the presence of 4 Å molecular sieves and at 80 °C. In such reaction conditions, the corresponding 5β-methyl-$\Delta^{9(10)}$-norsteroid derivative could be isolated in 61% yield. When applied to other 5β,6β-epoxysteroids, these reaction conditions led to moderate yields of the Westphalen rearranged products (Scheme 30).

Using 5β,6β-epoxycholestan-3β-yl acetate as substrate, other solvents were also screened in this reaction and it was observed that using $MeNO_2$, a solvent with higher dielectric constant, the preferential formation of the backbone rearranged derivative occurred, but the Westphalen-type compound was also formed (Scheme 31).

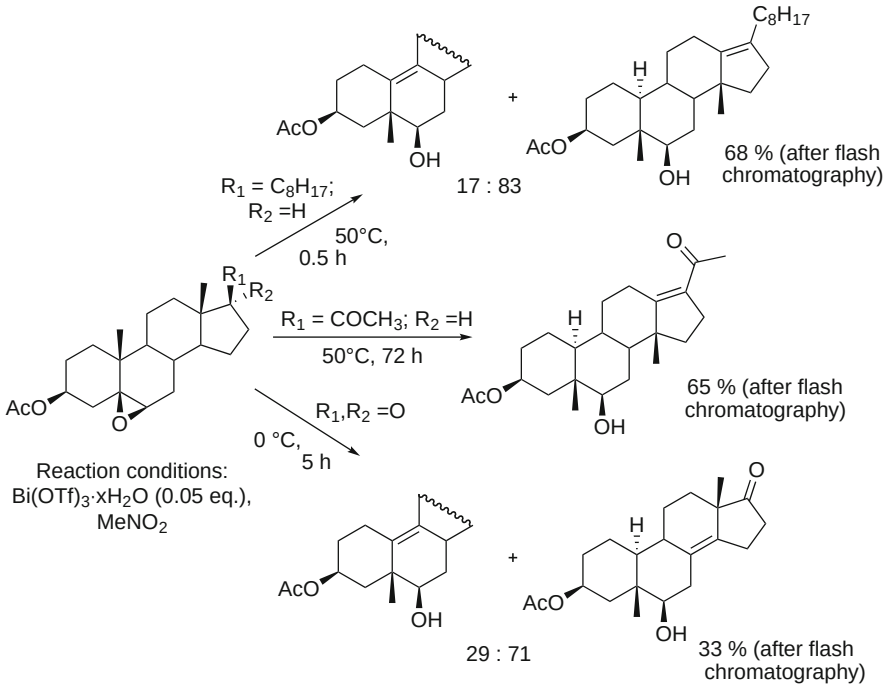
The study of the best reaction conditions revealed that among the Bi(III) salts screened, $Bi(OTf)_3{\cdot}xH_2O$ (0.05 eq.) gave the best results and 50 °C was found to be the best temperature. 5β,6β-Epoxy-20-oxopregnan-3β-yl acetate and 5β,6β-epoxy-17-oxoandrostan-3β-yl acetate [119] were also studied under similar reaction conditions and several interesting compounds could be obtained (Scheme 32). With the androstane derivative, due to the lack of a 17α-H, a full backbone




**Scheme 30** $Bi(OTf)_3{\cdot}xH_2O$-catalyzed Westphalen rearrangement of 5β,6β-epoxysteroids




**Scheme 31** Bismuth(III) salt-catalyzed rearrangement of 5β,6β-epoxycholestan-3β-yl acetate using $MeNO_2$ as solvent




**Scheme 32** $Bi(OTf)_3{\cdot}xH_2O$-catalyzed Westphalen and "backbone" rearrangement of 5β,6β-epoxysteroids

rearrangement was not expected and, in addition to the 5β-methyl-$\Delta^{9(10)}$-norsteroid derivative [120], the 5β-methyl-$\Delta^{8(14)}$-norsteroid was also formed (Scheme 32).

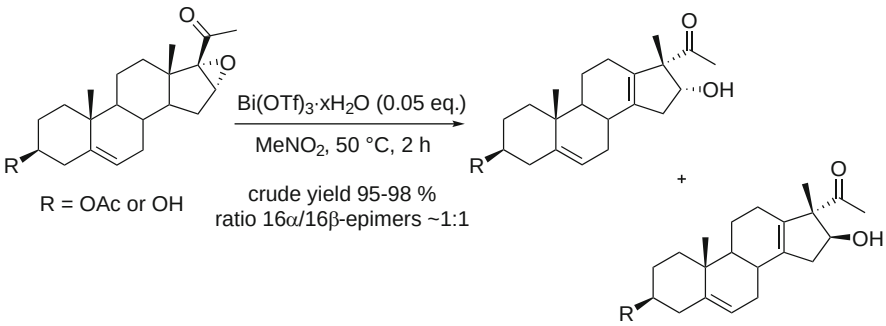
Despite the uncertainty surrounding the mechanism of the Westphalen rearrangement for which both the involvement of a carbocation intermediate [121] and a concerted mechanism [122] have been thought, it is evident from the available data that electronic (electron-withdrawing capability of a substituent

adjacent to C5) and steric (compression of the 10β-methyl group by a suitably β-oriented group, located at C2, C4 or C6, able to develop 1,3-*syn*-diaxial interactions) effects are responsible for the reactivity and product distribution of the rearrangement [123]. These rearrangements were found to occur specifically with 5β,6β-epoxides, and not with their corresponding 5α,6α-diastereomers. Thus, the 5β,6β-conformation is essential for the development of 1,3-*syn*-diaxial interactions with the angular 10β-methyl group, that are relieved during the rearrangement. Data obtained from X-ray crystallography and quantum chemical calculation on the equilibrium geometry of the free molecule revealed that important steric factors, such as the change in the torsion angle of the steroid nucleus, may contribute to the difference in reactivity observed between 5β,6β- and 5α,6α-epoxysteroids, which do not react under the same reaction conditions although similar electronic effects are present in the diastereomeric epoxides [120].

### 5.3.2 Wagner–Meerwein Rearrangements

The acid catalyzed migration of the angular C18-methyl group to afford olefinic 18-norsteroids is a particular type of Wagner–Meerwein rearrangement, occurring through the formation of a carbocation with 1,2-migration of the C18 methyl group to a neighbouring carbon, generally C17 [111, 115]. This reaction requires the use of Brønsted and Lewis acids, sometimes in the presence of an acylation agent and allows the formation of new bioactive structures and/or intermediates for a number of active compounds.

The application of Westphalen and backbone rearrangement reaction conditions ($MeNO_2$, $Bi(OTf)_3{\cdot}xH_2O$ catalyst) [118] to 16α,17α-epoxy-20-oxosteroids has also been studied [124]. At room temperature and 0.05 eq. of catalyst, low conversion of 16α,17α-epoxy-20-oxopregn-5-en-3β-yl acetate was observed. However, on increasing the temperature to 50 °C, 16α- and 16β-hydroxy-17β-methyl-$\Delta^{13}$-18-nor pregnane derivatives were formed in near similar amounts from 16α,17α-epoxy-20-oxosteroids (Scheme 33).



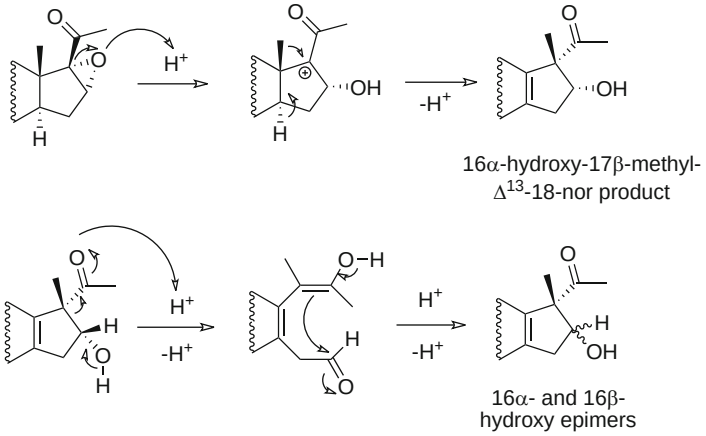

**Scheme 33** $Bi(OTf)_3{\cdot}xH_2O$-catalyzed rearrangement of 16α,17α-epoxy-20-oxosteroids

Several experiments using 16α,17α-epoxy-20-oxopregn-5-en-3β-yl acetate as substrate demonstrated that this rearrangement is mediated by Brønsted acid species generated in situ from the catalyst $Bi(OTf)_3 \cdot xH_2O$. It was also observed that the 16α-hydroxy-17β-methyl-$\Delta^{13}$-18-nor pregnane derivative undergoes epimerization under these reaction conditions. Thus, possibly, an in situ generated Brønsted acid species from $Bi(OTf)_3 \cdot xH_2O$ catalyzes the ring opening of the 16α,17α-epoxide, creating a tertiary carbocation at C17 followed by stereoselective 1,2-migration of the C18-methyl group to the 17β-position. In fact, as pointed out by Kočovský et al., Wagner–Merwein nonconcerted rearrangements with development of carbocation centres, result in 1,2-migration that occurs on the same plane ($sp^2$ alignment factor) [27]. Due to the 18-$CH_3$ → 17-$CH_3$ shift, a carbocation centered at C13 is formed, and further 14α-H elimination originates the $\Delta^{13}$-double bond. 16β-Epimers can be formed due to an acid-catalyzed retro-aldol equilibrium involving the 16-hydroxy-20-keto function of the rearranged steroid, under the reaction conditions employed, which is responsible for the epimerization at C16, as previously discussed by Herzog et al. [125, 126] and reviewed by Wendler (Scheme 34) [111].

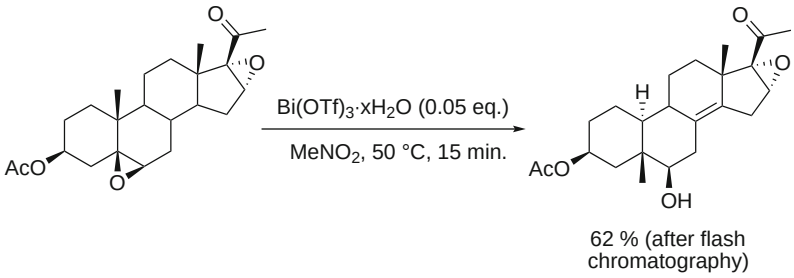
Interestingly, under these reaction conditions it was observed that the rearrangement of 5β,6β;16α,17α-diepoxy-20-oxopregnan-3β-yl acetate occurred preferentially at the 5β,6β-epoxide (Scheme 35).

In order to increase the stereoselectivity of the rearrangement, the reactions were studied in the presence of $Ac_2O$. In fact, it was observed that 16α-acetoxy rearranged derivatives were selectively prepared. To enlarge the scope of this $Bi(OTf)_3 \cdot xH_2O$-catalyzed rearrangement, other acylation agents were used, and several 17β-methyl-$\Delta^{13}$-18-norsteroids bearing different acyl groups at positions C3, C16 and C21 were selectively prepared (Scheme 36) [124].

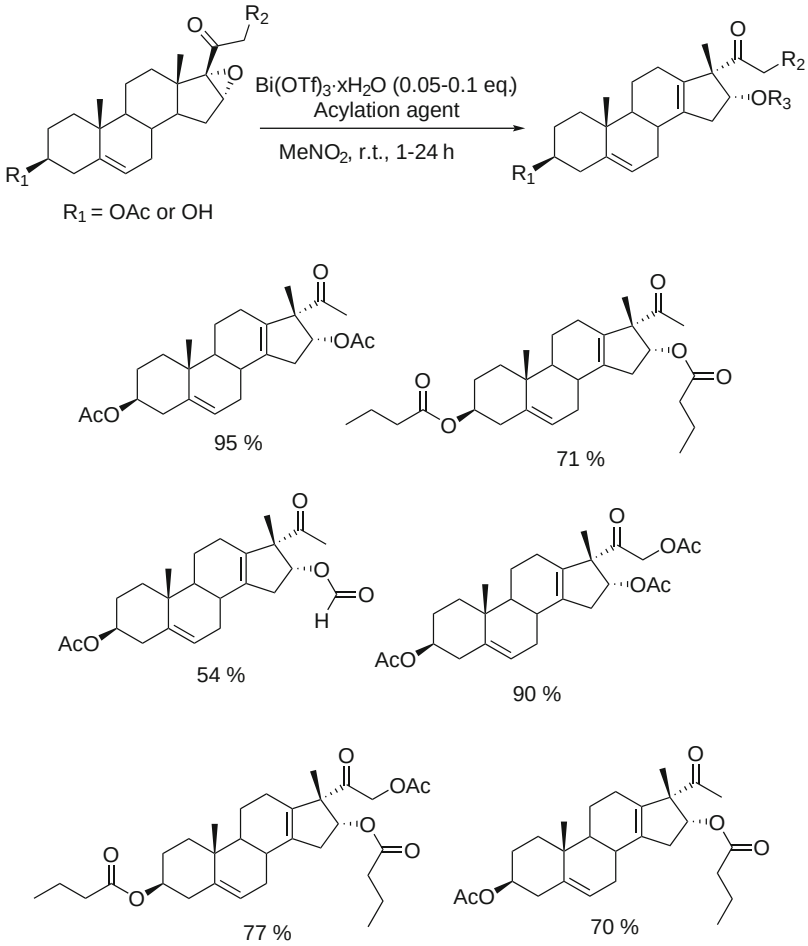
Wagner–Meerwein type rearrangements have also been widely reported in terpene chemistry [127, 128]. One well-known transformations involves the




**Scheme 34** Possible mechanism for the formation of 16α- and 16β-hydroxy-17β-methyl-$\Delta^{13}$-18-norsteroids




**Scheme 35** $Bi(OTf)_3 \cdot xH_2O$-catalyzed "backbone" rearrangement of 5β,6β;16α,17α-diepoxy-20-oxopregnan-3β-yl acetate

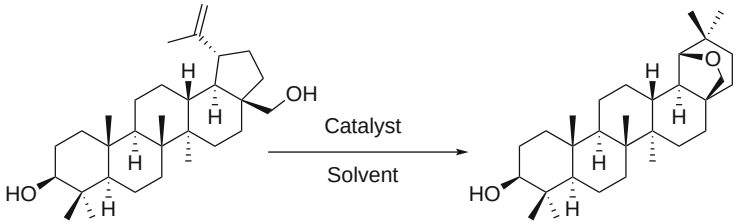



**Scheme 36** $Bi(OTf)_3 \cdot xH_2O$-catalyzed rearrangement of 16α,17α-epoxy-20-oxosteroids in the presence of an acylation agent

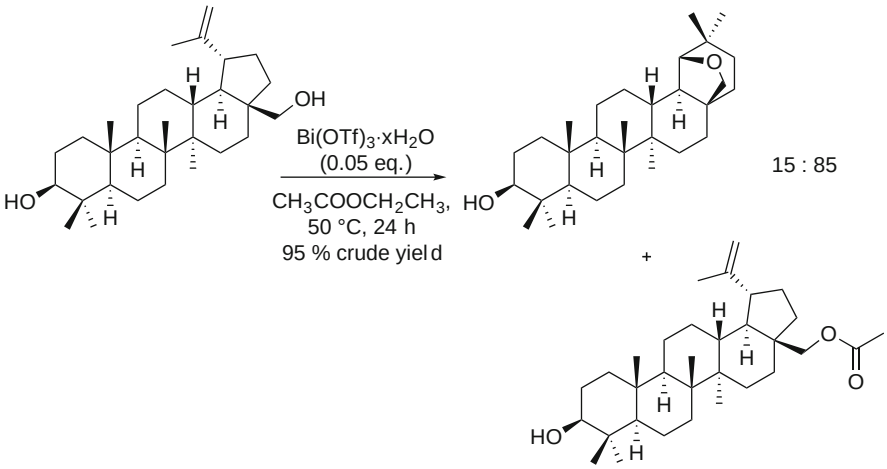
acid-catalyzed ring E rearrangement of betulin and important related triterpene derivatives [129–132], to 18α-oleanane compounds bearing a 19β,28-epoxide or 28,19β-lactone ring, and is commonly referred to as the "betulin–allobetulin rearrangement" [127]. Most of the described procedures have several disadvantages, such as the use of toxic, corrosive and/or expensive reagents, as well as the fact that most of them are non-catalytic. Following on the previous knowledge that Bi(III) salts are able to catalyze Wagner–Meerwein type rearrangements, their advantageous use as catalysts for the Wagner–Meerwein rearrangement of lupanes has recently been reported [133]. An example is betulin, which originated allobetulin (Scheme 37).

Among the Bi(III) salts screened, $Bi(OTf)_3{\cdot}xH_2O$ was the most efficient catalyst, and the best solvent was found to be $CH_2Cl_2$. When the reaction was performed using ethyl acetate as the solvent, betulin-28-yl acetate was obtained as the major reaction product, which demonstrated that $Bi(OTf)_3{\cdot}xH_2O$ is also an interesting transesterification catalyst (Scheme 38).

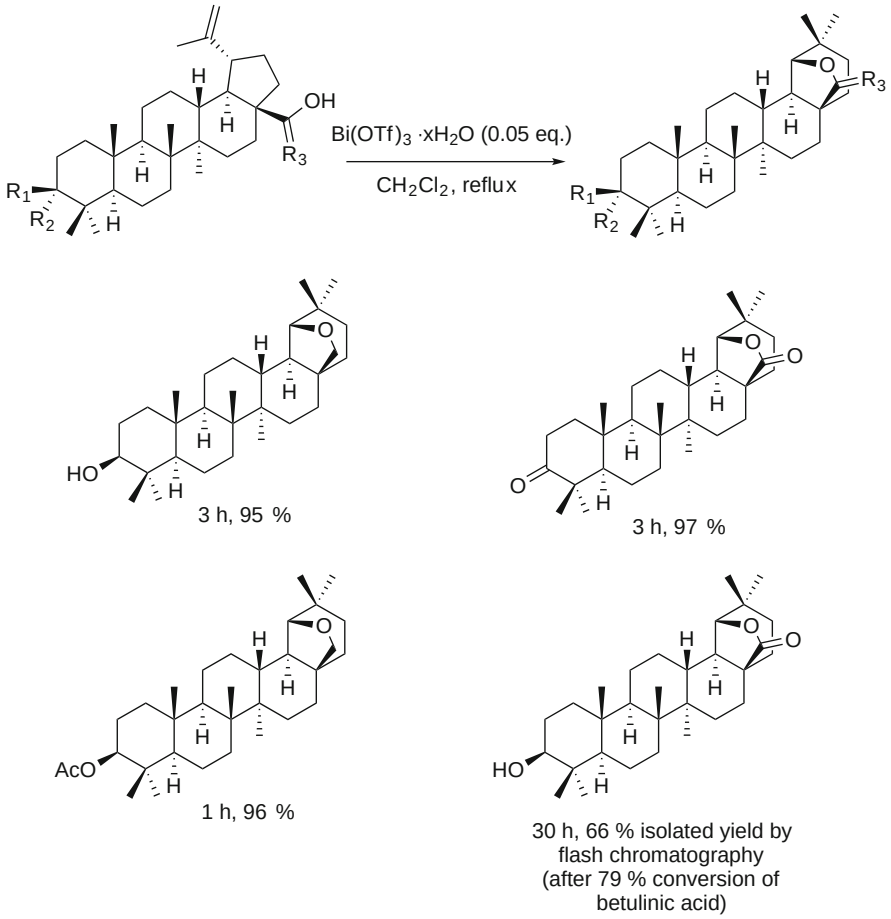
Thus, using $CH_2Cl_2$ as solvent and with $Bi(OTf)_3{\cdot}xH_2O$ catalysis (0.05–0.5 eq.), several lupane derivatives undergo a Wagner–Meerwein rearrangement with expansion of ring E and formation of an additional O-containing ring. By using




**Scheme 37** Wagner–Meerwein rearrangement of betulin to allobetulin




**Scheme 38** $Bi(OTf)_3{\cdot}xH_2O$-catalyzed reaction of betulin in ethyl acetate

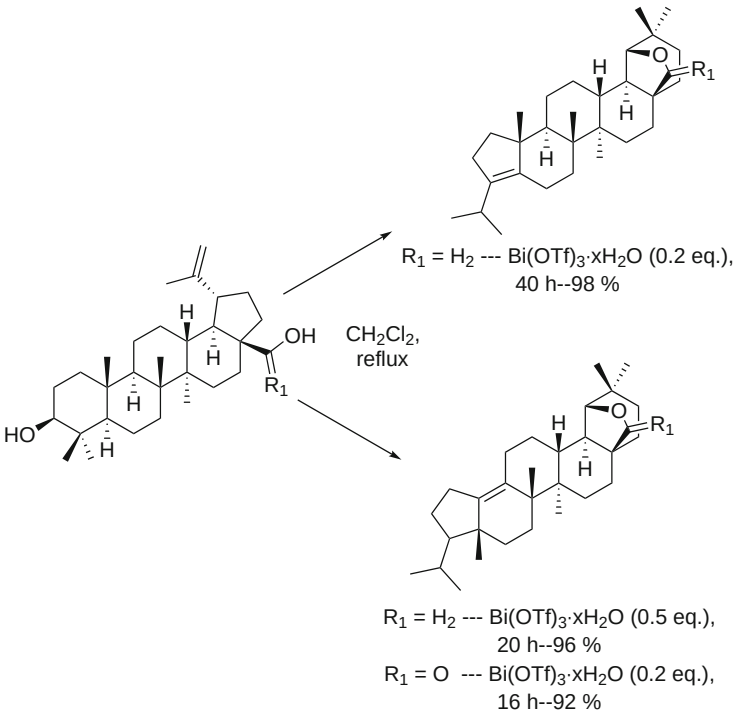



**Scheme 39** $Bi(OTf)_3{\cdot}xH_2O$-catalyzed Wagner–Meerwein rearrangement of lupanes

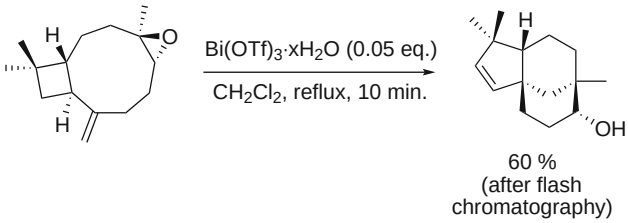
this process (with 0.05 eq. of $Bi(OTf)_3{\cdot}xH_2O$), several interesting 18α-oleananes could be efficiently obtained from lupanes by a single Wagner–Meerwein rearrangement (Scheme 39).

Under more vigorous conditions (0.2–0.5 eq. of the catalyst), the dehydration of the 3β-hydroxyl group occurred and the resulting compounds underwent a double Wagner–Meerwein rearrangement, originating A-neo-18α-oleanene compounds in high yields (Scheme 40).

By using betulin as substrate, some mechanistic studies were performed and it was demonstrated that these reactions are catalyzed by Brønsted acid species generated in situ from the hydrolysis of $Bi(OTf)_3{\cdot}xH_2O$. This process was also applied to other terpenic compounds. The sesquiterpene (−)-caryophyllene oxide originated clov-2-en-9α-ol by a "cariophyllene–clovane rearrangement" (Scheme 41) whereas 3-oxo-18α-olean-28-13β-olide was obtained from oleanonic acid (Scheme 42). With this triterpene derivative, only 28,13β-lactonization occurred, with inversion of the configuration of the stereocenter at C18 [133].



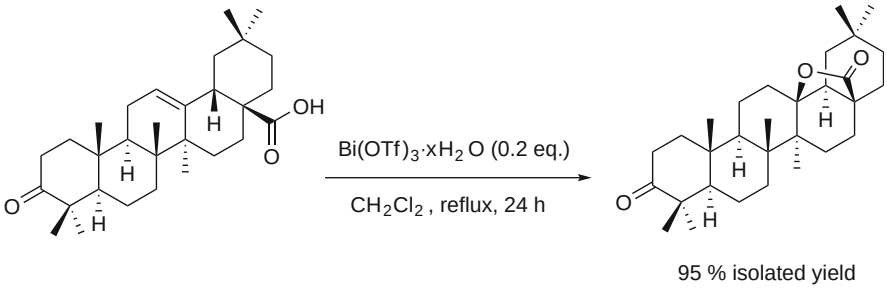

**Scheme 40** $Bi(OTf)_3{\cdot}xH_2O$-promoted dehydration and double Wagner–Meerwein rearrangement of betulin ($R_1 = H_2$) and betulinic acid ($R_1 = O$)



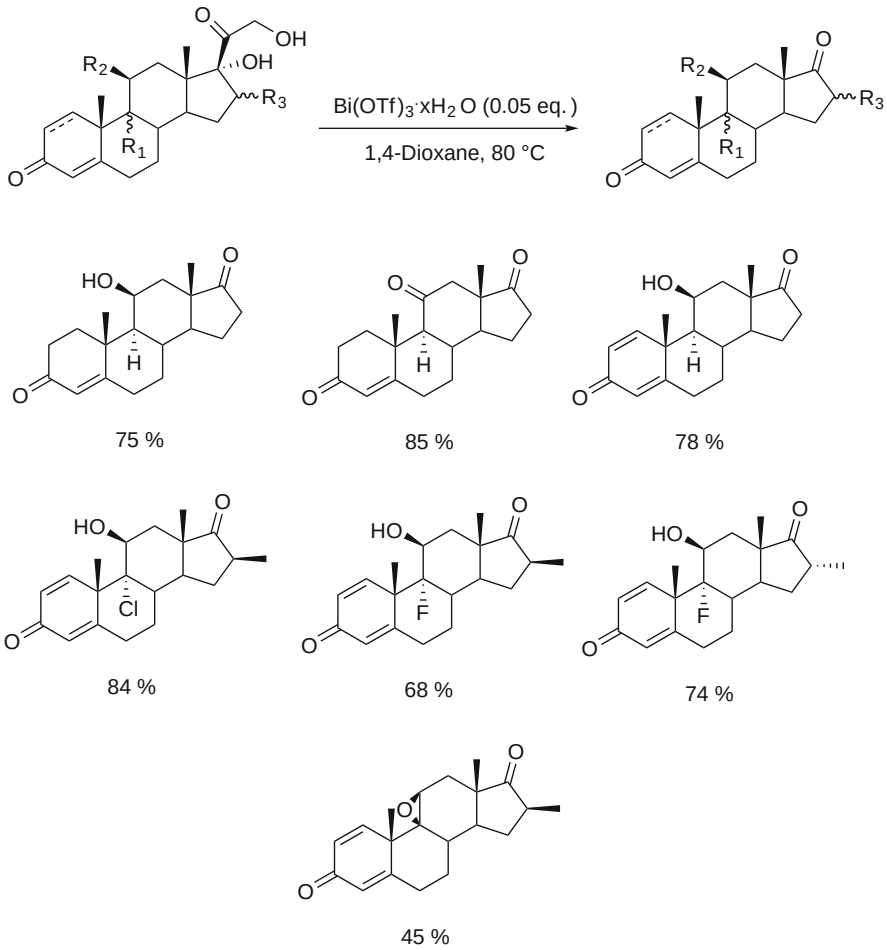

**Scheme 41** $Bi(OTf)_3{\cdot}xH_2O$-catalyzed Wagner–Meerwein rearrangement of (−)-caryophyllene oxide

## *5.4 Cleavage of the C17-Dihydroxyacetone Side Chain of Corticosteroids*

As an important drug class in the treatment of a variety of clinical situations [134], corticosteroids are readily available compounds. In fact, their industrial production reaches several tons per year [135], making them an useful source of substrates to obtain other steroids bearing a variety of chemical functions in rings A, B, C and D.




**Scheme 42** $Bi(OTf)_3{\cdot}xH_2O$-promoted lactonization of oleanonic acid




**Scheme 43** $Bi(OTf)_3{\cdot}xH_2O$-catalyzed cleavage of the C17-dihydroxyacetone side chain of corticosteroids

Starting from our previous findings of the reactivity of $Bi(OTf)_3 \cdot xH_2O$ towards secondary hydroxyl groups of lupane derivatives, promoting dehydration of the 3β-hydroxyl group and subsequent Wagner–Meerwein rearrangement, we decided to study the reactivity of Bi(III) salts towards several corticosteroids, which typically contain the tertiary 17α-hydroxyl group, the 21-hydroxy-20-keto moiety at C17-side chain and several other chemical functions, including, in most cases, additional hydroxyl groups at C11 [136].

Quite recent results showed that $Bi(OTf)_3 \cdot xH_2O$ is an efficient catalyst for the conversion of corticosteroids into highly functionalized 17-ketosteroids, by cleavage of the C17-dihydroxyacetone side chain. This reaction was typically performed using large amounts of oxidative or basic reactants [77, 137, 138]. The use of other Bi(III) salts and other solvents has been tested; however, the best results have been obtained with 0.05 eq. of $Bi(OTf)_3 \cdot xH_2O$, in 1,4-dioxane, at 80 °C. Under these reaction conditions, non-steroidal by-products have been observed. Their presence probably arises from the acid-catalyzed polymerization of the α-hydroxy ketone moiety derived from the cleavage of the corticosteroid side chain. Thus, purification by flash chromatography was needed to obtain pure 17-ketosteroids. Using this method several highly functionalized 17-ketosteroids have been prepared (Scheme 43).

The process proved to be very chemoselective, since functionalities of the starting corticosteroids, such as $\Delta^4$-3-keto, $\Delta^{1,4}$-3-keto, 11β-hydroxyl, and 9β,11β-epoxide, remained intact [136].

## 6 Conclusions

In the light of the increasing number of publications, it is clear that Bi(III) salts are emerging as efficient, nontoxic, inexpensive catalysts that can be easily recycled. From these important advantages, it is expected that the use of these catalysts will be enlarged to several other groups of natural products, namely in the context of drug discovery, development, and industrial production. Thus, in spite of the good reaction yields and selectivities observed, more reaction mechanism studies should still be developed in order to improve knowledge about the true catalytic species involved, aiming at a general improvement of the chemical processes of Bi catalysis. As a large number of organic and medicinal compounds are chiral, the development of Bi-mediated asymmetric reactions will continue to be an important research topic in the next few years. From this and other reviews, it is evident that some Bi-mediated/catalyzed asymmetric reactions have been developed; however, the stereoselectivity obtained is mainly due to the substrate and not to the catalyst itself. Thus, as observed with other metal and non-metal catalysts, the preparation of chiral Bi compounds/catalysts is another important challenge for the near future.

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# Cationic Bismuth-Catalyzed Hydroamination and Direct Substitution of the Hydroxy Group in Alcohols with Amides

**Shigeki Matsunaga and Masakatsu Shibasaki**

**Abstract** Bismuth-catalyzed hydroamination and direct substitution of the hydroxy group in alcohols are described in this chapter. Intermolecular 1:1 hydroamination of 1,3-dienes with carbamates, sulfonamides, and carboxamides was promoted by a combination of $Bi(OTf)_3$ and $Cu(CH_3CN)_4PF_6$. The mechanistic studies suggested that a cationic bismuth species would be an active species, which selectively promotes 1:1 hydroamination to give allylic amides in up to 96% yield. The cationic bismuth species was also applicable for hydroamination of vinyl arenes. The combination of $Bi(OTf)_3$ and $KPF_6$ was an excellent catalyst for direct substitution of the hydroxy group in allylic, propargylic, and benzylic alcohols with carbamates, sulfonamides, and carboxamides, giving allylic, propargylic, and benzylic amides, respectively, in up to 99% yield in one step.

**Keywords** Bismuth · Catalyst · C–N bond formation · Hydroamination · Substitution reaction

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## Abbreviations

| | |
|---|---|
| Dppe | 1,2-Bis(diphenylphosphino)ethane |
| EWG | Electron-withdrawing group |
| Ns | Nitrobenzenesulfonyl |
| Nu | Nucleophile |
| Ph | Phenyl |
| Tf | Trifluoromethanesulfonyl |
| Tol | Tolyl |
| Ts | Toluenesulfonyl |

## 1 Introduction

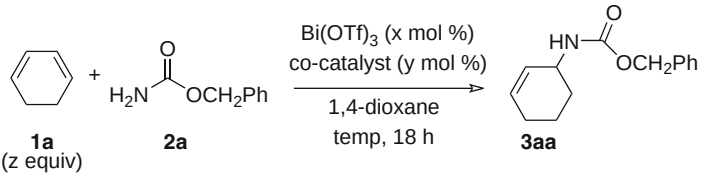
Amine derivatives are important building blocks for the synthesis of pharmaceuticals and fine chemicals. Therefore, studies on the development of new C–N bond forming reactions have attracted considerable interest. Among them, catalytic methods are potentially useful in order to minimize the waste and to realize high atom-economy [1] of the reactions. Intermolecular hydroamination of olefins is one of the most important topics in this area. Despite recent progress in intramolecular as well as intermolecular olefin hydroamination [2–5], mild and selective 1:1 intermolecular hydroaminations of electron-deficient nitrogen nucleophiles with alkenes are still limited [6–15], possibly due to competitive polymerization of alkenes. In this chapter, we will mainly describe our efforts on this issue using bismuth catalysis [16, 17]. Intermolecular 1:1 hydroamination of 1,3-dienes with amides was achieved with a cationic bismuth catalyst. For the highly chemoselective hydroamination reaction, the property of the bismuth metal center as a catalyst was successfully modified by using $Bi(OTf)_3$ together with a suitable co-catalyst, either $Cu(CH_3CN)_4PF_6$ or $KPF_6$ [18]. Mechanistic studies to clarify the role of co-catalysts as well as further applications of the bismuth catalyst to 1:1 intermolecular hydroamination of vinyl arenes with amides [19] and direct substitution of the hydroxy group in alcohols with amides [20] will also be discussed in detail.

## 2 Bismuth-Catalyzed Intermolecular Hydroamination

### *2.1 Intermolecular Hydroamination of 1,3-Dienes*

In order to find a suitable catalyst for intermolecular hydroaminations of 1,3-dienes, several metal sources were screened for the reaction of diene **1a** (4 equiv) with carbamate **2a**, and $Bi(OTf)_3$ gave promising results [21, 22]. The optimization studies using $Bi(OTf)_3$ are summarized in Table 1 and show that 10 mol% of

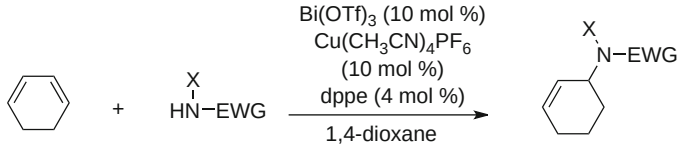
**Table 1** Optimization of reaction conditions



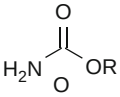
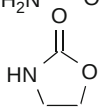
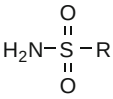
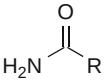

| entry | $Bi(OTf)_3$ (x mol %) | co-catalyst (y mol %) | temp (°C) | diene **1a** (z equiv) | yield (%) |
|---|---|---|---|---|---|
| 1 | 10 | 0 | 25 | 4 | 17 |
| 2 | 10 | $Cu(CH_3CN)_4PF_6$ (10) | 25 | 4 | 79 |
| 3 | 10 | $Cu(OTf)(C_6H_6)_{1/2}$ (10) | 25 | 4 | 24 |
| 4 | 10 | $KPF_6$(10) | 25 | 4 | 79 |
| 5 | 10 | $NH_4PF_6$(10) | 25 | 4 | 74 |
| 6 | 0 | $Cu(CH_3CN)_4PF_6$(10) | 25 | 4 | 0 |
| 7 | 10 | $Cu(CH_3CN)_4PF_6$(10) | 25 | 2 | 71 |
| 8 | 10 | $Cu(CH_3CN)_4PF_6$(10) | 50 | 2 | 66 |
| 9 | 10 | $Cu(CH_3CN)_4PF_6$(10) + dppe (4) | 50 | 2 | 80 |
| 10 | 10 | $KPF_6$(10) | 50 | 2 | 73 |
| 11 | 10 | $KPF_6$(10) + dppe (4) | 50 | 2 | 42 |

$Bi(OTf)_3$ gave a 1:1 product **3aa** in 17% yield together with polymerized byproducts (Table 1, entry 1). The addition of 10 mol% $Cu(CH_3CN)_4PF_6$ as a co-catalyst effectively suppressed the undesired polymerization, and the $Bi(OTf)_3$/Cu $(CH_3CN)_4PF_6$ system cleanly promoted the reaction at 25 °C in 1,4-dioxane to afford **3aa** in 79% yield (Table 1, entry 2). Other Cu sources such as Cu(OTf) $(C_6H_6)_{1/2}$ were not effective (Table 1, entry 3). On the other hand, $KPF_6$ and $NH_4PF_6$ co-catalysts gave comparably good results with $Cu(CH_3CN)_4PF_6$ (Table 1, entries 4 and 5). Control experiments using $Cu(CH_3CN)_4PF_6$ alone did not promote the desired hydroamination (Table 1, entry 6). With 2 equiv of diene **1a**, the yield of **3aa** decreased to 71% at 25 °C (Table 1, entry 7). By performing the reaction at 50 °C with 1,2-bis(diphenylphosphino)ethane (dppe), **3aa** was obtained in 80% yield after 18 h with 2 equiv of **1a** (Table 1, entry 9). We assume that dppe would coordinate to Cu (Table 1, entry 9) to suppress the undesired reaction at higher temperature. $KPF_6$ additive also worked well using 2 equiv of diene **1a** (Table 1, entry 10, 73%), although the yield of **3aa** was slightly lower than for Cu $(CH_3CN)_4PF_6$. In the case of $KPF_6$ additive, dppe did not have positive effects (Table 1, entry 11, 42% yield). Table 1, entry 11 shows that dppe coordinated to bismuth rather than potassium to decrease the Lewis acidity of the bismuth metal center, thereby resulting in low reactivity.

**Table 2** $Bi(OTf)_3/Cu(CH_3CN)_4PF_6$/dppe-catalyzed intermolecular hydroamination of **1a** with various carbamates, sulfonamides, and carboxamides

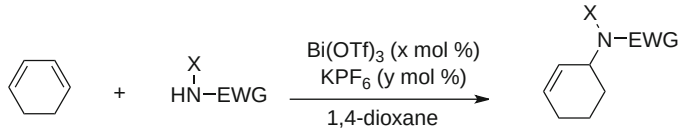



**1a** (x equiv) + **2** X = H, alkyl → **3**

| entry | | nucleophile | | temp (°C) | diene **1a** (x equiv) | time (h) | product | yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 |  | R = $CH_2Ph$ | **2a** | 50 | 2 | 18 | **3aa** | 80 |
| 2 | | R = $CH_3$ | **2b** | 50 | 2 | 18 | **3ab** | 96 |
| 3 | | R =*n*-Bu | **2c** | 50 | 2 | 18 | **3ac** | 85 |
| 4 |  | | **2d** | 50 | 2 | 18 | **3ad** | 92 |
| 5 | | R = Ph | **2e** | 50 | 2 | 3 | **3ae** | 80 |
| 6 |  | R = 4-Me-$C_6H_4$ | **2f** | 50 | 2 | 3 | **3af** | 84 |
| 7 | | R = 4-MeO-$C_6H_4$ | **2g** | 50 | 2 | 5 | **3ag** | 84 |
| 8 | | R = 4-$CF_3$-$C_6H_4$ | **2h** | 50 | 2 | 5 | **3ah** | 75 |
| 9 | | R = 2-$NO_2$-$C_6H_4$ | **2i** | 25 | 4 | 24 | **3ai** | 67 |
| 10 |  | R = Ph | **2j** | 100 | 4 | 12 | **3aj** | 75 |
| 11 | | R = 4-$CF_3$-$C_6H_4$ | **2k** | 90 | 4 | 17 | **3ak** | 77 |

The optimized reaction conditions in Table 1 (entries 9 and 10) were applicable to various carbamates, sulfonamides, and carboxamides. As summarized in Tables 2 and 3, all reactions completed within 3–24 h. Results using $Bi(OTf)_3/Cu(CH_3CN)_4PF_6$/dppe system are shown in Table 2. Both acyclic and cyclic carbamates **2a**–**2d** gave 1:1 adducts in 80–96% yield at 50 °C (Table 2, entries 1–4). Sulfonamides **2e**–**2i** also gave products in good yield, regardless of the presence of an electron-donating group (Table 2, entries 6 and 7) or electron-withdrawing group (Table 2, entry 8). *o*-$NsNH_2$ **2i** required a lower reaction temperature (25 °C) to avoid side reactions, and 4 equiv of **1a**, gave **3ai** in 67% yield (Table 2, entry 9). Carboxamides **2j** and **2k** were less reactive. Thus, the reactions were performed at higher reaction temperature (90–100 °C) to obtain desired 1:1 adducts in 75% and 77% yield, respectively (Table 2, entries 10 and 11). Results using the $Bi(OTf)_3/KPF_6$ system are shown in Table 3. With carbamates and carboxamides as nucleophiles (Table 3, entries 1–4, 10, and 11), the isolated yields of products were slightly lower than those obtained with $Cu(CH_3CN)_4PF_6$ as a co-catalyst in Table 2.

**Table 3** $Bi(OTf)_3/KPF_6$-catalyzed intermolecular hydroamination of **1a** with various carbamates, sulfonamides, and carboxamides




**1a** (y equiv) **2** X = H, alkyl **3**

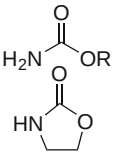
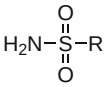
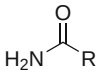
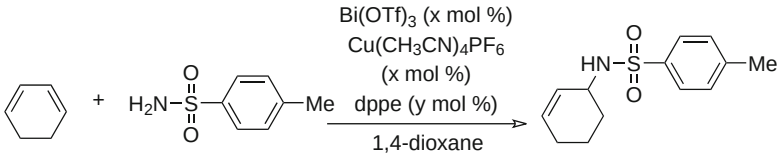
| entry | nucleophile | | $Bi(OTf)_3$ (x mol %) | $KPF_6$ (y mol %) | temp (°C) | diene **1a** (x equiv) | time (h) | product | yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  R = $CH_2Ph$ | **2a** | 10 | 10 | 50 | 2 | 18 | **3aa** | 72 |
| 2 | R = $CH_3$ | **2b** | 10 | 10 | 50 | 2 | 18 | **3ab** | 94 |
| 3 | R = *n*-Bu | **2c** | 10 | 10 | 50 | 2 | 18 | **3ac** | 72 |
| 4 | | **2d** | 10 | 10 | 50 | 2 | 18 | **3ad** | 88 |
| 5 | R = Ph | **2e** | 5 | 5 | 25 | 1.2 | 5 | **3ae** | 73 |
| 6 |  R = 4-Me-$C_6H_4$ | **2f** | 5 | 5 | 25 | 1.2 | 3 | **3af** | 83 |
| 7 | R = 4-MeO-$C_6H_4$ | **2g** | 5 | 5 | 25 | 1.2 | 5 | **3ag** | 84 |
| 8 | R = 4-$CF_3$-$C_6H_4$ | **2h** | 5 | 5 | 50 | 2 | 5 | **3ah** | 79 |
| 9 | R = 2-$NO_2$-$C_6H_4$ | **2i** | 10 | 10 | 25 | 4 | 24 | **3ai** | 62 |
| 10 |  R = Ph | **2j** | 10 | 10 | 100 | 4 | 12 | **3aj** | 69 |
| 11 | R = 4-$CF_3$-$C_6H_4$ | **2k** | 10 | 10 | 90 | 4 | 17 | **3ak** | 60 |

**Table 4** Trials to reduce catalyst loading



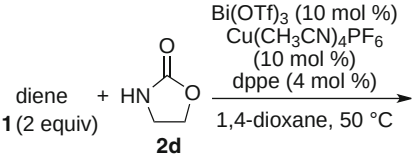

**1a** **2f** **3af**

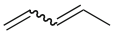
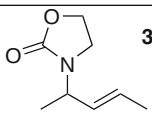
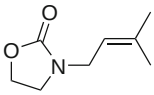
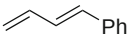
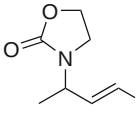
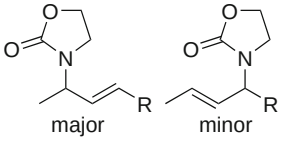
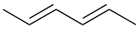
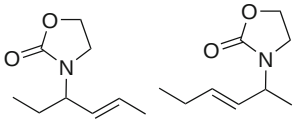
| entry | $Bi(OTf)_3$/ $Cu(CH_3CN)_4PF_6$ (x mol %) | dppe (y mol %) | **1a** (equiv) | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|---|
| 1 | 10 | 4 | 2 | 50 | 3 | 84 |
| 2 | 5 | 2 | 2 | 50 | 8 | 86 |
| 3 | 3 | 1.2 | 2 | 50 | 8 | 87 |
| 4 | 1 | 0.4 | 2 | 50 | 21 | 83 |
| 5 | 0.5 | 0.2 | 2 | 50 | 24 | 80 |

With sulfonamides, the $Bi(OTf)_3/KPF_6$ system promoted the reaction at 25–50 °C using 5–10 mol% of catalyst (Table 3, entries 5–9). Notably, the desired 1:1 adducts were obtained in good yield using only 1.2 equiv of diene **1a** with sulfonamides **2e**, **2f**, and **2g**. The results indicated that the chemoselectivity of the present system is very good (Table 3, entries 5–7).

The trials to reduce catalyst loading with sulfonamide **2f** as a nucleophile are shown in Table 4. The reaction completed within 8 h using 5 mol% and 3 mol% of $Bi(OTf)_3$ and $Cu(CH_3CN)_4PF_6$ (Table 4, entries 2 and 3). The reaction also proceeded without any problems using as little as 0.5 mol% of $Bi(OTf)_3$ and $Cu(CH_3CN)_4PF_6$ to afford **3af** in 80% yield (Table 4, entry 5), although longer reaction time was required. Table 5 shows the intermolecular hydroaminations of several acyclic 1,3-dienes **1b**–**1g** with carbamate **2d**. Acyclic 1,3-dienes were also applicable in the present system to afford products in 60–94% yield. The isomer ratio (1,2-adduct versus 1,4-adduct), however, depended on the structure of dienes. Diene **1c** exclusively gave 1,4-hydroamination adduct **3cd** (Table 5, entry 2), while

**Table 5** Intermolecular hydroamination of various 1,3-dienes with carbamate **2d**




| entry | diene | time (h) | product | yield (%) |
|---|---|---|---|---|
| 1 |  | **1b** 18 |  **3bd** | 94 |
| 2 | | **1c** 18 |  **3cd** | 60 |
| 3 |  | **1d** 18 |  **3dd** | 77 |
| 4<br>5 | <br>R = $(CH_2)_7CH_3$<br>R = $(CH_2)_2Ph$ | **1e** 18<br>**1f** 18 |  major minor | 73 (3:1)<br>74 (3:1) |
| 6 |  | **1g** 18 |  minor major | 76 (1:2) |

diene **1d** exclusively gave 1,2-hydroamination adduct **3dd** (Table 5, entry 3). Dienes **1e**–**1g** gave mixtures of isomers (Table 5, entries 4–6).

## 2.2 Mechanistic Studies

The present hydroamination gave unsatisfactory results with either $Bi(OTf)_3$ or $Cu(CH_3CN)_4PF_6$ alone (Table 1, entries 1 and 6). The results of entries 2–5 in Table 1 imply that $PF_6^-$ would be important rather than Cu metal. The results obtained by 1,3-dienes **1c** (1,4-adduct alone), **1d** (1,2-adduct alone), and **1e**–**1g** (mixture of isomers) suggested that both 1,2-attack and 1,4-attack are possible depending on the structure of dienes. To obtain insights into the reaction mechanism and the role of $PF_6^-$, the reaction profiles were monitored under several different reaction conditions: (a) **1a** and $Bi(OTf)_3$; (b) **1a** and $Cu(CH_3CN)_4PF_6$; (c) **1a**, $Bi(OTf)_3$, and $Cu(CH_3CN)_4PF_6$; (d) **1a**, $Bi(OTf)_3$, and amide **2f**; (e) **1a**, $Bi(OTf)_3$, $Cu(CH_3CN)_4PF_6$ and amide **2f**; and (f) **1a**, $Bi(OTf)_3$, $KPF_6$ and amide **2f**. Detailed reaction conditions and reaction profiles under each reaction condition are summarized in Figs. 1 and 2. In Fig. 1, in the absence of amide **2f**, the polymerization rate of

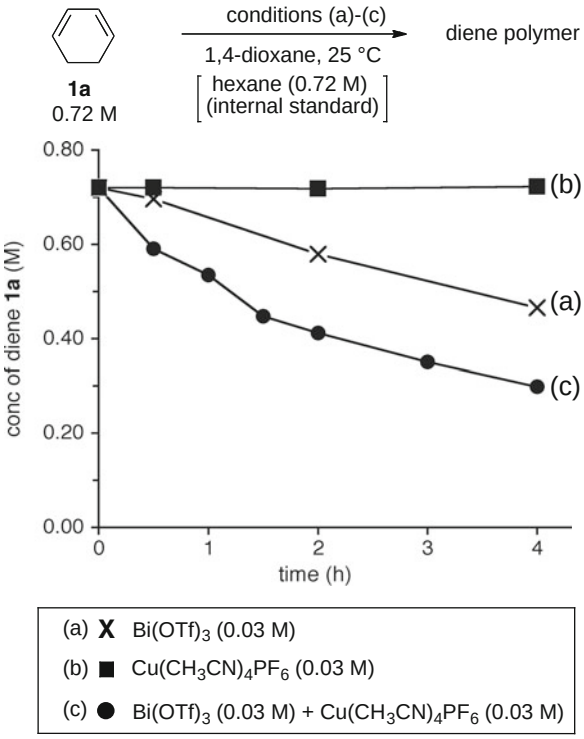



**Fig. 1** Reaction profile in the absence of amide **2f** using (*a*) $Bi(OTf)_3$; (*b*) $Cu(CH_3CN)_4PF_6$; and (*c*) $Bi(OTf)_3$ and $Cu(CH_3CN)_4PF_6$

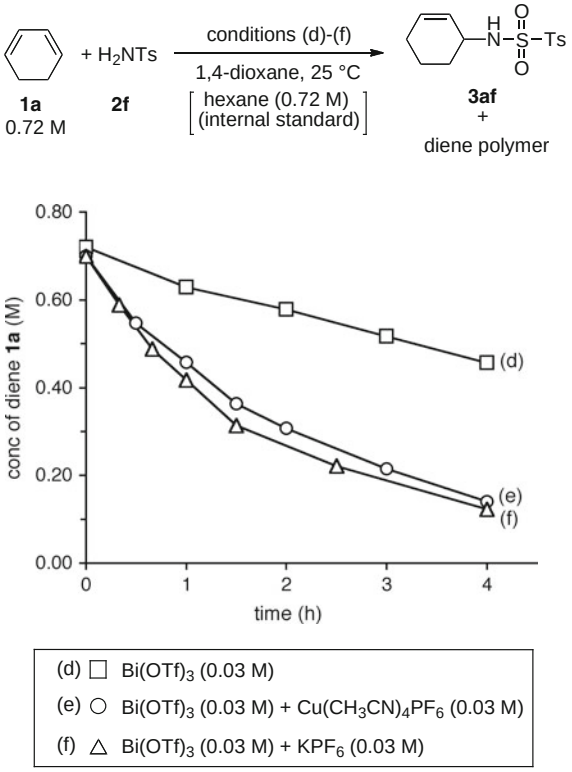



**Fig. 2** Reaction profile in the presence of amide **2f** using (*d*) $Bi(OTf)_3$; (*e*) $Bi(OTf)_3$ and $Cu(CH_3CN)_4PF_6$; and (*f*) $Bi(OTf)_3$ and $KPF_6$

diene **1a** was monitored by gas chromatography (GC) using hexane as an internal standard. GC analysis of diene **1a** indicated that $Bi(OTf)_3$ alone [Fig. 1, conditions (a)] promoted polymerization of the diene, while $Cu(CH_3CN)_4PF_6$ alone did not cause polymerization [Fig. 1, conditions (b)]. These results suggest that bismuth activates diene **1a** to generate allyl cationic species. The polymerization rate of the diene **1a** in the absence of amide **2f** increased under $Bi(OTf)_3$ with Cu $(CH_3CN)_4PF_6$ co-catalyst system [Fig. 1, conditions (a) versus (c)], suggesting the formation of more active bismuth species in the presence of $Cu(CH_3CN)_4PF_6$. Figure 2 shows the reaction profile in the presence of amide **2f**. Concentration of diene **1a** was monitored by GC in a similar way as for Fig. 1, and the desired product **3af** was isolated after 3 h to determine the ratio of polymerization to desired 1:1 hydroamination. Under conditions (d), the concentration profile of diene **1a** was similar to that observed under conditions (b). Under conditions (d), 0.20 mmol of **1a** was consumed after 3 h, while only 0.108 mmol of the desired 1:1 adduct **3af** was isolated at 3 h. Thus, the desired 1:1 addition and undesired polymerization competed in similar reaction rate under conditions (d). Under conditions (e) and (f), the best reaction rate was observed of those studied [conditions (a)–(f)]. Similar reaction rates in conditions (e) and (f) suggests the generation of similar active

species. Under conditions (e), 0.50 mmol of **1a** was consumed after 3 h. The amount of the desired 1:1 adduct **3af** isolated after 3 h was 0.438 mmol for conditions (e) and 0.498 mmol for conditions (f), suggesting that the desired reaction was the major pathway in conditions (e) and (f). Therefore, $PF_6^-$ clearly accelerated the desired 1:1 addition over undesired polymerization. In conditions (d), polymerization and the desired 1:1 addition competed with each other, while the desired reaction was the major pathway in conditions (e) and (f).

On the basis of results in Figs. 1 and 2, the proposed reaction mechanism of the bismuth-catalyzed hydroamination and the postulated role of co-catalyst is shown in Fig. 3. $Bi(OTf)_3$ activates 1,3-diene to generate an allyl cationic species, which is trapped with amides (desired reaction) or with 1,3-diene (undesired polymerization). Counter anion exchange with $PF_6^-$ would generate intermediate (A in Fig. 3). With $PF_6^-$ as the non-coordinating counter anion, the additional coordination site of the bismuth metal center would be available. Therefore, the amide can interact with the bismuth metal center and be positioned close to the reaction site (B in Fig. 3), accelerating the desired 1:1 addition. Protonation of the product (C in Fig. 3) regenerates catalyst (D in Fig. 3). The ability of bismuth metal to interact with the carbonyl group of benzamide **2j** was confirmed by IR and NMR analysis. In IR analysis, the peak corresponding to carbonyl of **2j** (1,733 $cm^{-1}$) shifted to 1,653 $cm^{-1}$ in the presence of $Bi(OTf)_3$ (without adding 1,3-diene), supporting the interaction of bismuth with carbonyl group of **2j**. $^{13}C$ NMR analysis also supported the interaction of bismuth with **2j**. Low field shift of the carbonyl peak of **2j** in the

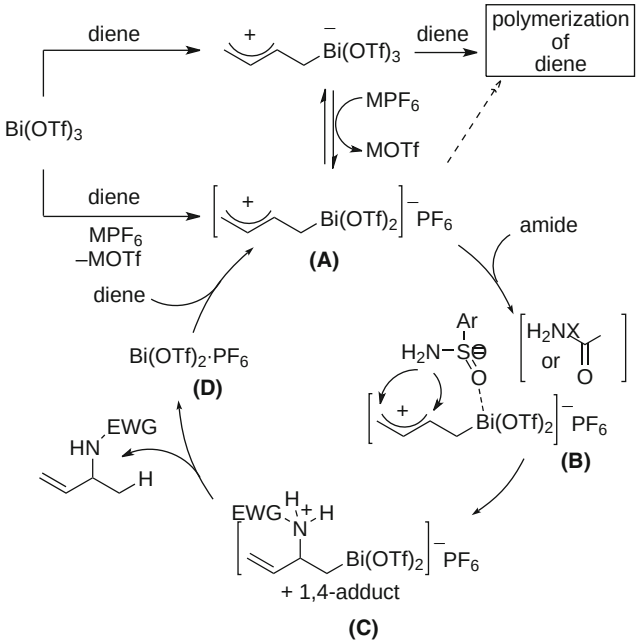


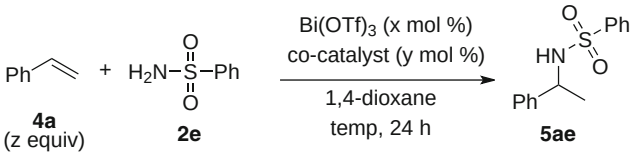

**Fig. 3** Postulated catalytic cycle

presence of $Bi(OTf)_3$ was observed in $^{13}C$ NMR (with $Bi(OTf)_3$, 173.5 ppm versus without $Bi(OTf)_3$, 167.9 ppm).

## 2.3 Intermolecular Hydroamination of Vinyl Arenes

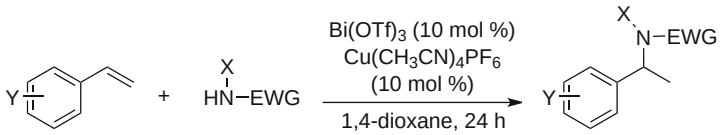
Mechanistic studies of the intermolecular hydroamination of 1,3-dienes suggested that an active species would be a cationic $Bi(OTf)_2$•$PF_6$, which functions as a π-acid to activate 1,3-dienes to generate a carbenium intermediate. Therefore, the similar bismuth catalyst is speculated to be suitable for intermolecular hydroamination of vinyl arenes [19]. Optimizations of the reaction conditions are summarized in Table 6. $Bi(OTf)_3/KPF_6$ promoted the reaction of styrenes **4a** (1.2 equiv) and sulfonamide **2e** at 25 °C (Table 6, entry 1, 54% yield). $Cu(CH_3CN)_4PF_6$ additive gave slightly better results (Table 6, entry 2, 62% yield). The results of a control experiment using either $Bi(OTf)_3$ (Table 6, entry 3) or $Cu(CH_3CN)_4PF_6$ (Table 6, entry 4) alone at 25 °C were not satisfactory. On the other hand, the addition of $NH_4PF_6$ slightly improved reactivity (Table 6, entry 5, 44% yield). The results in Table 6, entries 1–5, clearly indicated that both bismuth and $PF_6^-$ are important to achieve good reactivity at 25 °C. By increasing the amount of **4a** (2 equiv), the isolated yield of **5ae** increased to 78% (Table 6, entry 5). At 40 °C, **5ae** was obtained in 91% yield (Table 6, entry 6). The $Bi(OTf)_3/Cu(CH_3CN)_4PF_6$ system was applicable to hydroaminations of styrene **4a** with sulfonamides **2e**–**2i** and **2l**–**2m**, giving products in good yield (Table 7, entries 1–6, 80–97% yield). With *p*-$TsNH_2$ **2f**, the reaction proceeded smoothly at 25 °C (Table 7, entry 2, 87% yield). On the other hand, sulfonamide **2i** and carbamate **2d** gave less satisfactory results (Table 7, entry 7, 54% yield; entry 8, 33% yield). Unfortunately, the generality of vinyl arenes was

**Table 6** Optimization of reaction conditions for hydroamination of vinyl arene **4a**

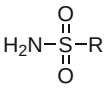
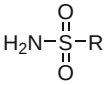



| entry | $Bi(OTf)_3$ (x mol %) | co-catalyst (y mol %) | temp (°C) | vinyl arene (z equiv) | yield (%) |
|---|---|---|---|---|---|
| 1 | 10 | $KPF_6$(10) | 25 | 1.2 | 54 |
| 2 | 10 | $Cu(CH_3CN)_4PF_6$ (10) | 25 | 1.2 | 62 |
| 3 | 10 | none | 25 | 1.2 | 21 |
| 4 | 0 | $Cu(CH_3CN)_4PF_6$ (10) | 25 | 1.2 | 0 |
| 5 | 10 | $NH_4PF_6$ (10) | 25 | 1.2 | 44 |
| 6 | 10 | $Cu(CH_3CN)_4PF_6$ (10) | 25 | 2.0 | 78 |
| 7 | 10 | $Cu(CH_3CN)_4PF_6$ (10) | 40 | 2.0 | 91 |

**Table 7** $Bi(OTf)_3/Cu(CH_3CN)_4PF_6$-catalyzed intermolecular hydroamination of vinyl arenes




**4** (2 equiv) **2** X = H, alkyl **5**

| entry | vinyl arene Y | **4** | nucleophile | | | temp (°C) | product | yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | H | **4a** | | R = Ph | **2e** | 40 | **5ae** | 91 |
| 2 | H | **4a** |  | R = 4-Me-$C_6H_4$ | **2f** | 25 | **5af** | 87 |
| 3 | H | **4a** | | R = 2-Me-$C_6H_4$ | **2l** | 40 | **5al** | 90 |
| 4 | H | **4a** | | R = 4-MeO-$C_6H_4$ | **2g** | 40 | **5ag** | 97 |
| 5 | H | **4a** | | R = 4-$CF_3$-$C_6H_4$ | **2h** | 40 | **5ah** | 80 |
| 6 | H | **4a** | | R = 4-Cl-$C_6H_4$ | **2m** | 40 | **5am** | 88 |
| 7 | H | **4a** | | R = 2-$NO_2$-$C_6H_4$ | **2i** | 40 | **5ai** | 54 |
| 8 | H | **4a** | | | **2d** | 40 | **5ad** | 33 |
| 9 | 4-Cl | **4b** |  | R = 4-Me-$C_6H_4$ | **2f** | 40 | **5bf** | 59 |
| 10 | 4-Me | **4c** | | R = 4-Me-$C_6H_4$ | **2f** | 25 | **5cf** | trace |

also rather limited with the $Bi(OTf)_3/Cu(CH_3CN)_4PF_6$ system, as shown in Table 7, entries 9 and 10. Vinyl arene **4c** with an electron-donating substituent gave only trace amounts of desired product due to competitive undesired polymerization of vinyl arene **4c**. We assume that the intermolecular hydroamination of vinyl arenes proceeds by a similar mechanism to that shown in Fig. 3 for 1,3-dienes: A cationic bismuth species, generated by anion exchange, would be the active species. Amide coordinates to the cationic bismuth metal center, and the catalyst activates vinyl arenes to generate a carbenium intermediate. Amide addition, followed by protonolysis, affords the product and regenerates the catalyst.

## 3 Direct Substitution of the Hydroxy Group in Alcohols with Amides

Readily available allylic and propargylic alcohols are desirable substrates for the synthesis of various allylic and propargylic amines. Substitution of the hydroxyl group in alcohols by amine nucleophiles generally requires pre-activation of the alcohols because of the poor leaving ability of the hydroxy group. Alcohols are usually transformed into the corresponding halides, carboxylates, carbonates, phosphonates, or related compounds with good leaving ability. The process inevitably produces

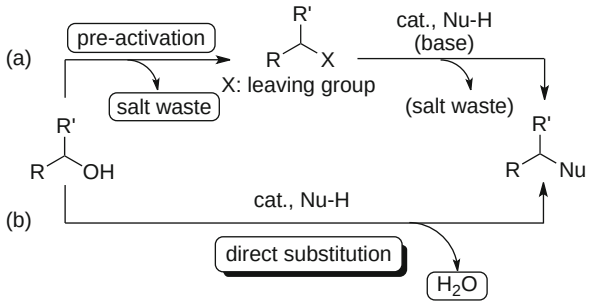
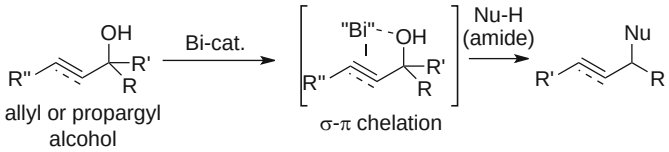



**Fig. 4** Substitution of the hydroxyl group in alcohols: (*a*) via pre-activation and (*b*) via direct catalytic substitution

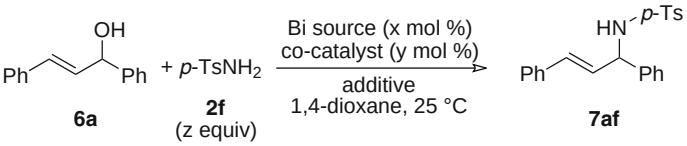



**Scheme 1** Working hypothesis to activate allylic and propargylic alcohols using a Bi catalyst via σ-π chelation

stoichiometric amounts of salt waste. Substitution of the halides and related compounds also produces salt waste and requires stoichiometric amounts of base [Fig. 4 path (a)]. In this context, well-established transition-metal-catalyzed allylic aminations of allylic acetates and their derivatives have intrinsic drawbacks in terms of atom economy [1]. Therefore, direct catalytic substitution of alcohols with amines is highly desirable to minimize the salt waste. The process, in which no additional stoichiometric hydroxyl group activator is utilized, produces products with water as the only waste [Fig. 4, path (b)].

A number of transition-metal-catalyzed direct allylic aminations have been reported [23–25]. However, efficient catalysts that promote the direct allylic aminations without any stoichiometric activators under mild reaction conditions are rather limited [26–32]. In addition, the use of less-reactive electron-deficient nitrogen nucleophiles for a broad range of alcohols is still rare [33–42]. We hypothesized that bismuth catalysis would be suitable for the direct activation of allylic and propargylic alcohols via σ-π chelation in a similar fashion to gold-catalysis (Scheme 1) [43, 44]. To test this hypothesis, the reaction of alcohol **6a** with sulfonamide **2f** was examined. The combined use of Bi $(OTf)_3$ and $KPF_6$ promoted the reaction smoothly, and **7af** was obtained in 94% yield after 0.2 h (Table 8, entry 1). $Cu(CH_3CN)_4PF_6$ as a co-catalyst gave comparable reactivity with $KPF_6$, but $KPF_6$ was used in this reaction because $KPF_6$ is much cheaper than $Cu(CH_3CN)_4PF_6$. To compare the efficiency of the $Bi(OTf)_3/KPF_6$ system, pairs of control experiments were investigated (Table 8, entries 2–4). $Bi(OTf)_3$ alone promoted the reaction, but only at a lower reaction rate (Table 8, entry 2, 2 h, 76% yield). $BiCl_3$ showed a much lower reaction rate, giving product in 70% yield after 12 h (Table 8, entry 3) [37]. $KPF_6$ alone did not promote the desired reaction at all (Table 8,

**Table 8** Optimization of reaction conditions for direct substitution of the hydroxyl group in alcohol

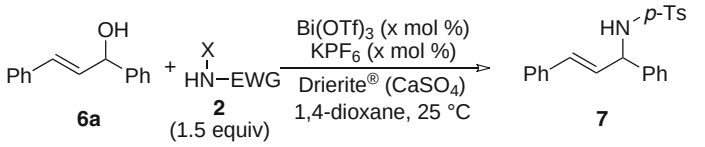


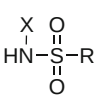
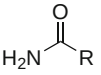
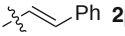

| entry | Bi source (x mol %) | co-catalyst (y mol %) | additive | amide **2f** (z equiv) | time (h) | yield (%) |
|---|---|---|---|---|---|---|
| 1 | $Bi(OTf)_3$ (10) | $KPF_6$ (10) | none | 2 | 0.2 | 94 |
| 2 | $Bi(OTf)_3$ (10) | none | none | 2 | 2 | 76 |
| 3 | $BiCl_3$ (10) | none | none | 2 | 12 | 70 |
| 4 | none | $KPF_6$ (10) | none | 2 | 12 | 0 |
| 5 | $Bi(OTf)_3$ (2) | $KPF_6$ (2) | none | 1.5 | 0.2 | 94 |
| 6 | $Bi(OTf)_3$ (2) | $KPF_6$ (2) | Drierite® | 1.5 | 0.2 | 96 |
| 7 | $Bi(OTf)_3$ (1) | $KPF_6$ (1) | Drierite® | 1.5 | 0.2 | 95 |

entry 4, 0% yield). Thus, it is clear that the combined use of $Bi(OTf)_3$ and $KPF_6$ was required to achieve high reactivity at 25 °C. The tendency is similar to that observed in the mechanistic studies on intramolecular hydroamination of 1,3-dienes. We speculate that $KPF_6$ has beneficial effects to generate a more reactive cationic $Bi(OTf)_2$•$PF_6$ species by anion exchange. With the $Bi(OTf)_3/KPF_6$ combined system, catalyst loading was successfully reduced to 2 mol% without any problems, giving product in 94% yield after 0.2 h (Table 8, entry 5). Product **7af** was obtained in 96% yield after 0.2 h in the presence of a desiccant, Drierite ($CaSO_4$) (Table 8, entry 6). Under the optimized conditions using Drierite, catalyst loading was further reduced to 1 mol% without problems (Table 8, entry 7, 95% yield, 0.2 h).

Amide substrate scope and limitations were investigated using allyl alcohol **6a** and 2–5 mol% of $Bi(OTf)_3$ and $KPF_6$ (Table 9). Using sulfonamides with electron-donating and electron-withdrawing substituents, the reaction completed within 0.2–1.5 h, and allyl amides were obtained in high yield (Table 9, entries 1–5, 85–99%). Carbamates **2a**–**2d** were also suitable for the present system, giving products in 97–99% yield within 0.2 h (Table 9, entries 6–9). With carboxamides **2j**, **2o**, and **2p**, the reaction rate decreased. Therefore, catalyst loading was increased to 5 mol% (Table 9, entries 10–12). With 5 mol% $Bi(OTf)_3/KPF_6$, carboxamide **2j** reacted smoothly, and product was obtained in 86% yield (Table 9, entry 10, 0.6 h). Carboxamides **2o** and **2p** were much less reactive. Products **7ao** and **7ap** were obtained in 88 and 95% yield, respectively, after 15–16 h at 25 °C (Table 9, entries 11 and 12). The reactions of selected substrates in the absence of Drierite are also shown (Table 9, entries 2, 4, 9, and 10) and the reactions proceeded without any difficulty. The addition of a desiccant is not essential for reactive allylic alcohols, such as **6a**. The use of Drierite is, however, recommended for good reproducibility with less reactive substrates (as shown in Tables 10–12).

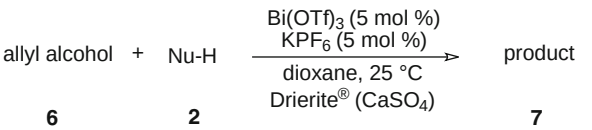
**Table 9** Direct catalytic allylic substitution of alcohol **6a** with various sulfonamides, carbamates, and carboxamides **2**




| entry | nucleophile | | | cat. (mol %) | time (h) | product | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | | X = H, R = Ph | **2e** | 2 | 0.2 | **7ae** | 99 |
| 2 |  | X = H, R = 4-$CH_3$-$C_6H_4$ | **2f** | 2 | 0.2 | **7af** | 96 (94)[a] |
| 3 | | X = H, R = 4-$CF_3$-$C_6H_4$ | **2h** | 2 | 0.2 | **7ah** | 97 |
| 4 | | X = H, R = 2-$NO_2$-$C_6H_4$ | **2i** | 2 | 0.2 | **7ai** | 93 (82)[a] |
| 5 | | X = Me, R = 4-$CH_3$-$C_6H_4$ | **2n** | 2 | 1.5 | **7an** | 85 |
| 6 | | | **2d** | 2 | 0.2 | **7ad** | 99 |
| 7 | | R = OBn | **2a** | 2 | 0.2 | **7aa** | 97 |
| 8 | | R = OMe | **2b** | 2 | 0.2 | **7ab** | 99 |
| 9 |  | R = O-*n*Bu | **2c** | 2 | 0.2 | **7ac** | 99 (91)[a] |
| 10 | | R = Ph | **2j** | 5 | 0.6 | **7aj** | 86 (89)[a] |
| 11 | | R = *n*Bu | **2o** | 5 | 15 | **7ao** | 88 |
| 12 | | R =  | **2p** | 5 | 16 | **7ap** | 95 |

[a]The number in parenthesis is the yield of the isolated product when the reaction was performed in the absence of Drierite

**Table 10** Direct catalytic substitution of cyclic allylic alcohols with amides



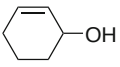
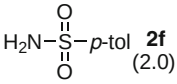
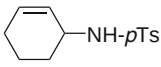
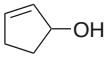
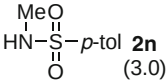
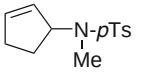
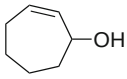
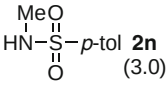
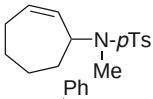
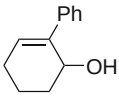
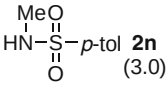
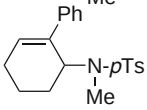
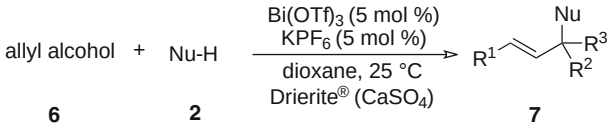

| entry | allyl alcohol | | nucleophile (equiv) | | product | | time (h) | yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 |  | **6h** |  | **2f** (2.0) |  | **7hf** | 2 | 96 |
| 2 |  | **6c** |  | **2n** (3.0) |  | **7cn** | 2 | 80 |
| 3 |  | **6d** |  | **2n** (3.0) |  | **7dn** | 2 | 66 |
| 4 |  | **6e** |  | **2n** (3.0) |  | **7en** | 17 | 74 |

**Table 11** Direct catalytic substitution of acyclic allylic alcohols with amides



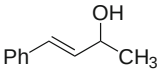
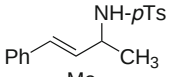
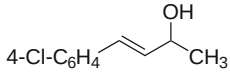
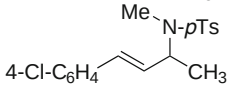
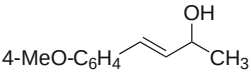
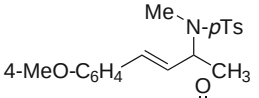
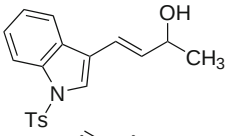
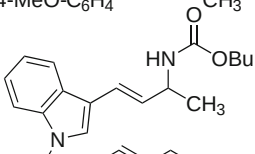
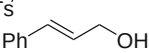
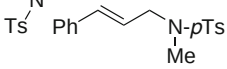
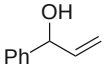
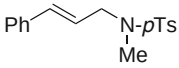
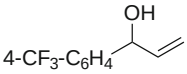
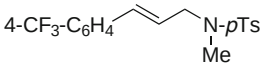
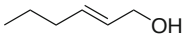
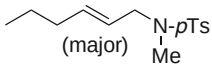
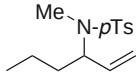
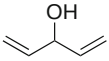
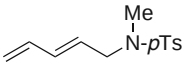
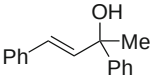
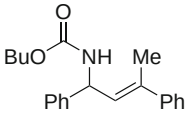
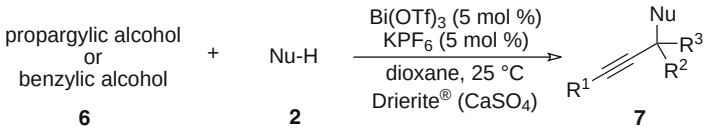
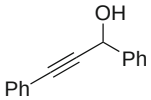
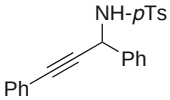
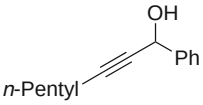
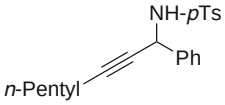
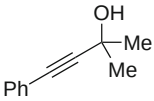
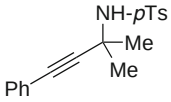
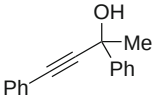
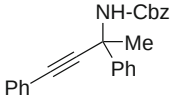
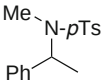

| entry | allyl alcohol | | nucleophile (equiv) | | product | | time (h) | yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 |  | **6f** | **2f** (1.5) | |  | **7ff** | 17 | 87 |
| 2 |  | **6g** | **2n** (3.0) | |  | **7gn** | 0.2 | 99 |
| 3 |  | **6h** | **2n** (3.0) | |  | **7hn** | 0.2 | 61 |
| 4 |  | **6i** | **2c** (1.0) | |  | **7ic** | 0.2 | 84 |
| 5 |  | **6j** | **2n** (3.0) | |  | **7jn** | 7 | 63 |
| 6 |  | **6k** | **2n** (3.0) | |  | **7kn** | 12 | 62 |
| 7 |  | **6l** | **2n** (3.0) | |  | **7ln** | 2 | 60 |
| 8 |  | **6m** | **2n** (3.0) | |  (major)  (minor) (major/minor = 6.7/1) | **7mn** | 1 | 55 |
| 9 |  | **6n** | **2n** (2.0) | |  | **7nn** | 1 | 69 |
| 10 |  | **6o** | **2c** (1.5) | |  | **7oc** | 0.1 | 60 |

**Table 12** Direct catalytic substitution of propargylic and benzylic alcohols with amides

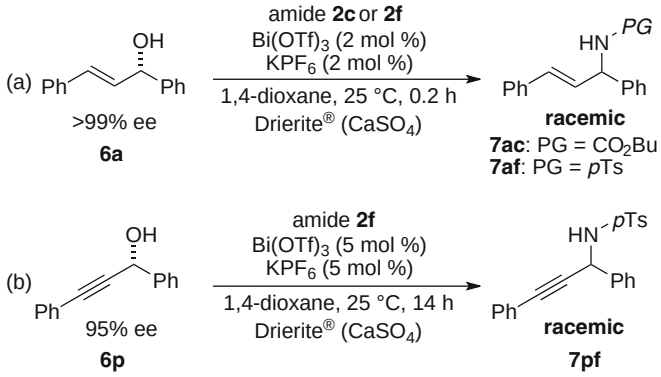



| entry | allyl alcohol | | nucleophile (equiv) | product | | time (h) | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | **6p** | **2f** (1.5) |  | **7pf** | 18 | 82 |
| 2 |  | **6q** | **2f** (1.5) |  | **7qf** | 8 | 78 |
| 3 |  | **6r** | **2f** (2.0) |  | **7rf** | 4 | 63 |
| 4 |  | **6s** | **2a** (2.0) |  | **7sa** | 5 | 65 |
| 5 | | **6t** | **2n** (2.0) |  | **7tn** | 7 | 60 |

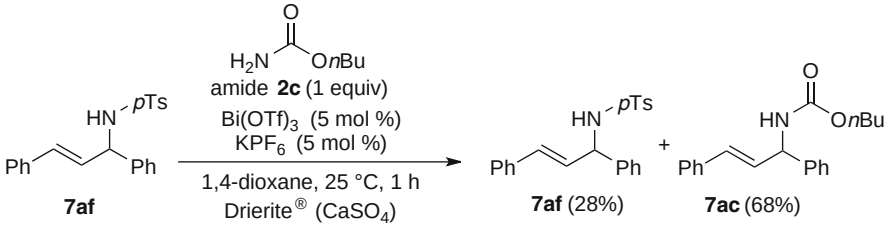
Alcohol substrate scopes are summarized in Table 10 (cyclic allylic alcohols), Table 11 (acyclic allylic alcohols), and Table 12 (propargylic and benzylic alcohols). The present catalyst was also applicable to non-benzylic allylic alcohols such as cyclic alcohols **6b**–**6e** (Table 10). Because the reactivity of cyclic alcohols **6b**–**6e** was lower than that of doubly activated benzylic allylic alcohol **6a**, 5 mol% of Bi $(OTf)_3$ and $KPF_6$ were required to give products in 66–96% yield. Cyclic alcohol **6e** with a phenyl substituent required a longer reaction time (17 h) (Table 10, entry 4) than other allyl alcohols, possibly due to steric hindrance. As shown in Table 11, acyclic allylic alcohols also reacted under the optimized reaction conditions. Non-benzylic allylic alcohol **6f** regioselectively reacted with sulfonamide **2f**, to give product **7ff** (Table 11, entry 1, 87%). Substrates with substituted aromatic rings **6g** and **6h**, and *N*-Ts indole **6i** also gave products regioselectively (Table 11, entries 2–4). It is noteworthy that the reaction of **6i** proceeded smoothly with just an equimolar amount of carbamate **2c** in 84% yield (Table 11, entry 4). With **6j**, the reaction proceeded regioselectively to afford **7jn** (Table 11, entry 5), which was

also obtained starting from benzylic allylic alcohol **6k** (Table 11, entry 6). Alcohol **6l** also reacted at sterically less hindered terminal carbon, giving **7ln** (Table 11, entry 7, 60%). Alcohol **6m** afforded **7mn** as a mixture of regioisomers in a ratio of 6.7:1 (Table 11, entry 8). From alcohol **6n**, diene **7nn** was obtained as a sole product (Table 11, entry 9). Tertiary alcohol **6o** selectively afforded regioisomer **7oc** in 60% yield after 0.1 h (Table 11, entry 10: *E* isomer). The observed regioselectivity in Table 11 suggested that amides **2** selectively attacked the sterically less hindered carbon. On the other hand, propargylic alcohols **6p**–**6s** reacted predominantly at the propargylic position (Table 12, entries 1–4). Regioisomeric allenic products were not observed for **6p**–**6s**. It is also noteworthy that the desired products were obtained using tertiary-propargyl alcohols **6r** and **6s**. Previously reported propargylic amination catalysts were not applied to tertiary-propargyl alcohols, possibly due to a competitive dehydration reaction to afford enynes [34, 35]. The addition of Drierite was essential to obtain products **7rf** and **7sa** in >60% yield (Table 12, entries 3 and 4). This bismuth catalysis was also applicable to benzylic alcohol **6t**, giving product **7tn** in 60% yield after 7 h at room temperature (Table 12, entry 5).

When optically active allylic alcohol **6a** and propargylic alcohol **6p** were reacted with amides **2c** and **2f**, only racemic products **7ac**, **7af**, and **7pf** were obtained (Scheme 2). The results suggested a mechanism through the formation of a carbenium intermediate. The observed racemization can also be ascribed to the reversibility of the present reaction. The result shown in Scheme 3 indicated that the reaction is reversible under the reaction conditions. When **7af** was treated with 5 mol% of $Bi(OTf)_3$ and $KPF_6$ and 1 equiv of carbamate **2c**, a mixture of **7af** (28%) and **7ac** (68%) was recovered after 1 h. The result suggested that $Bi(OTf)_3/KPF_6$ cleaved the C–N bond in **7af** derived from sulfonamide **2f**, and that **7ac** is thermodynamically more stable than **7af**. We assume that the desiccant (Drierite) had a beneficial effect on the reactions of substrates shown in Tables 10–12 because of the observed reversibility of the present reaction. In this reaction, the possibility




**Scheme 2** Allylic (**a**) and propargylic (**b**) aminations using optically active alcohols **6a** and **6p**




**Scheme 3** Experiment to check the reversibility of allylic amination

that either trifluoromethanesulfonic acid or $Bi(OTf)_3 \bullet 4H_2O$, generated from anhydrous $Bi(OTf)_3$ and $H_2O$, might promote the reaction cannot be excluded completely, even in the presence of desiccant. However, the result in Scheme 3, where no $H_2O$ is generated, supports the idea that $Bi(OTf)_3/KPF_6$ is working as a catalyst.

## 4 Conclusion

The utility of cationic bismuth species for C–N bond formation has been described in this chapter. The key for successful intermolecular 1:1 hydroamination of 1,3-dienes [18] and vinyl arenes [19] with carbamates, sulfonamides, and carboxamides was the combined use of $Bi(OTf)_3$ with either $Cu(CH_3CN)_4PF_6$ or $KPF_6$. Mechanistic studies suggested that cationic bismuth species, generated by counter anion exchange with $PF_6^-$, not only activated the carbon–carbon double bond, but also interacted with amides. The interaction of amides with the bismuth metal center was important to afford high chemoselectivity, even with poorly nucleophilic amides. Because the amides can be positioned close to the reaction site, the desired 1:1 addition was accelerated over undesired polymerization of 1,3-dienes and vinyl arenes. The $Bi(OTf)_3$ with $KPF_6$ system was also applicable for direct substitution of the hydroxy group in alcohols. A broad range of allylic, propargylic, and benzylic alcohols were smoothly reacted with carbamates, sulfonamides, and carboxamides in good yield, providing an atom-efficient method for the synthesis of allylic, propargylic, and benzylic amides in one step [20].

**Acknowledgements** The authors deeply thank Dr. Noriyuki Yamagiwa and Dr. Hongbo Qin for their contributions.

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# Transition-Metal Catalyzed C–C Bond Formation Using Organobismuth Compounds

**Shigeru Shimada and Maddali L. N. Rao**

**Abstract** Organobismuth(III) and organobismuth(V) compounds have been used in a variety of C–C bond forming reactions using transition-metal catalysis. Triarylbismuths are the most often used reagents among organobismuth reagents. All three aryl groups of triarylbismuths are potentially used in C–C bond formation, as shown in a number of reactions. Some heterocyclic organobismuth compounds have high potential as useful reagents for C–C bond forming reactions.

**Keywords** Carbon–carbon bond formation · Cross-coupling reaction · Organobismuth compounds · Transition-metal catalysis

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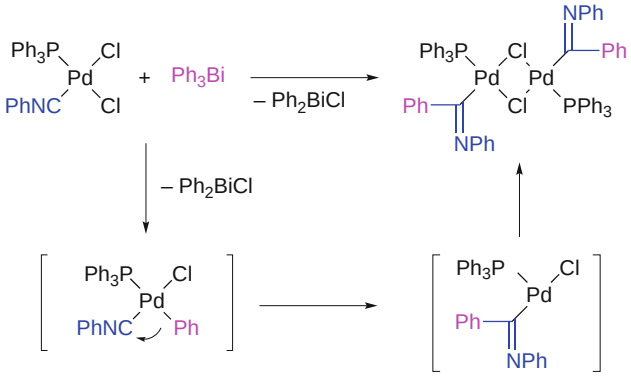
## Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| Acac | Acetylacetonate |
| Anis | Methoxyphenyl |
| Anth | Anthryl |
| Bn | Benzyl |
| c-Hex | Cyclohexyl |
| cod | 1,4-Cyclooctadiene |
| dba | Dibenzylideneacetone |
| de | Diastereomeric excess |
| DMA | *N*,*N*-Dimethylacetamide |
| DME | 1,2-Dimethoxyethane |
| DMF | *N*,*N*-Dimethylformamide |
| dipamp | Ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane] |
| dppf | 1,1′-Bis(diphenylphosphino)ferrocene |
| ee | Enantiomeric excess |
| HMPA | Hexamethylphosphoric triamide |
| Naph | Naphthyl |
| NMP | 1-Methyl-2-pyrrolidinone |
| Py | Pyridyl |
| RT | Room temperature |
| SPB | Spherical polyelectrolyte brushes |
| TBAB | Tetrabutylammonium bromide |
| Tf | Trifluoromethanesulfonyl |
| THF | Tetrahydrofuran |
| Tol | Tolyl |
| Ts | *p*-Toluenesulfonyl |

## 1 Introduction

Transition-metal catalysis is one of the most powerful tools for carbon–carbon bond forming reactions in organic synthesis. A variety of organometallic and organoheteroatom compounds such as organo-boron, -tin, -silicon, -magnesium, -zinc, etc. are used in carbon–carbon bond formation with transition-metal catalysis, providing indispensable tools for the synthesis of organic functional materials, pharmaceuticals, agrochemicals, natural products, etc. not only at laboratory scale, but also in industry [1].

Organobismuth compounds would have high potential as reagents for transition-metal catalyzed carbon–carbon bond forming reactions, because bismuth–carbon bonds are weak and can be easily cleaved by transition metals. The mean bond




**Scheme 1** Reaction of isocyanide Pd-complex with $Ph_3Bi$

dissociation energy of $Ph_3Bi$ (193.9 ± 10.8 kJ/mol) is the smallest among those of triphenyl compounds of group 15 elements and is about half of that of $Ph_3N$ (373.7 ± 4.2 kJ/mol) [2].

There have been several older reports describing carbon–carbon bond formation in stoichiometric reactions of organobismuth compounds with transition metal compounds. For example, in 1957, Solomakhina reported the reaction of $Ph_3Bi$ with $CuCl_2$, in which a small amount of biphenyl was formed as one of the many by-products [3]. In 1971, Crociani and coworkers reported the reaction of an isocyanide palladium (Pd) complex with $Ph_3Bi$, in which the isocyanide was converted to an imidoyl group by the addition of one Ph group of $Ph_3Bi$ (Scheme 1) [4]. However, the use of organobismuth compounds in transition-metal catalyzed carbon–carbon bond forming reactions was very limited until recently.

There are several review articles that include descriptions of transition metal-catalyzed carbon–carbon bond formation of organobismuth compounds [5–10]. During the last decade, considerable development has been achieved in this area. However, there is no comprehensive review of this topic. Therefore, this review intends to comprehensively summarize transition-metal catalyzed carbon–carbon bond formation using organobismuth compounds.

## 2 Transition-Metal Catalyzed C–C Bond Forming Reactions

### *2.1 Heck-Type Arylation Reaction*

Heck-type arylation reactions of organobismuth compounds were first reported by Asano et al. in 1973 [11]. This article described the stoichiometric reaction of styrene, $Ph_3E$ (E = group 15 elements) and $Pd(OAc)_2$ (Scheme 2). $Ph_3Bi$ afforded *trans*-stilbene only in 7% yield. The major product was biphenyl, which was

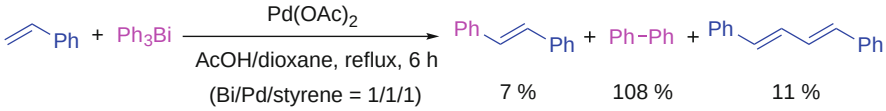
obtained in 108% yield based on $Pd(OAc)_2$. Formation of biaryls were often observed as a major or a minor product in a number of transition-metal catalyzed reactions of organobismuth compounds developed in later years.

A similar reaction using ethyl acrylate proceeded more efficiently. Ethyl cinnamate was obtained in 80% yield by using one equivalent of $Pd(OAc)_2$ (Scheme 3) [12]. With smaller amounts of $Pd(OAc)_2$, biphenyl was produced catalytically as the major product. The reaction of $Ph_3Bi$ with 1-octene under the same reaction conditions afforded a mixture of various phenylated octenes in moderate yields.

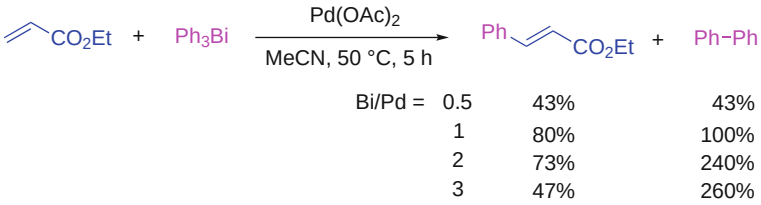
The reaction of alkenyltriphenylbismuthonium salt with ethyl acrylate in the presence of $Pd(OAc)_2$ (2 mol%) afforded both alkenylated and phenylated products in low yields (Scheme 4) [13]. In addition, ligand coupling products of the bismuthonium salt were also formed.

Heck-type phenylation of 1,2-diolcarbonate took place catalytically without ring opening of the cyclic carbonate moiety to give the phenylated product in moderate yields (Scheme 5) [14]. Both trivalent and pentavalent organobismuth compounds can be used. The corresponding 1,2-diolacetonide gave very similar results. The results are in contrast to those for allylic acetates and vinyl epoxides, in which elimination of an oxygen-leaving group took place (see Sect. 2.7).

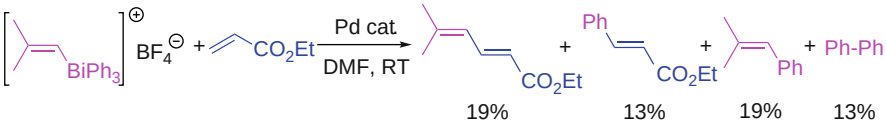
Recently, arylation of methyl acrylate was intensively studied [15–21]. Phenylation with $Ph_3BiX_2$ was largely affected by X, as shown in Scheme 6. $PdCl_2$ as well as $Pd_2(dba)_3$ (dba = dibenzylideneacetone) are efficient catalysts, whereas the addition of phosphine ligands retards the phenylation; e.g., $PdCl_2$/4 $PPh_3$ afforded no



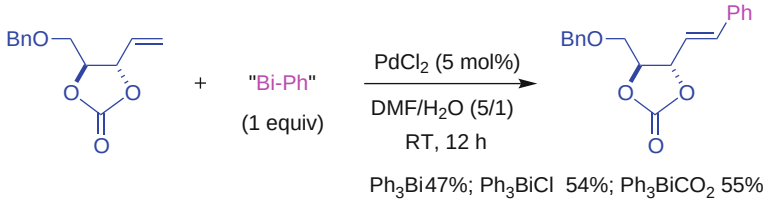

**Scheme 2** Heck-type phenylation reaction of styrene with $Ph_3Bi$



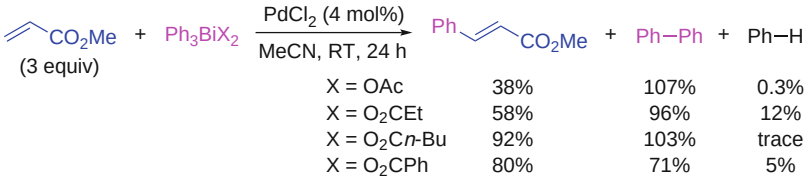

**Scheme 3** Heck-type phenylation reaction of ethyl acrylate with $Ph_3Bi$



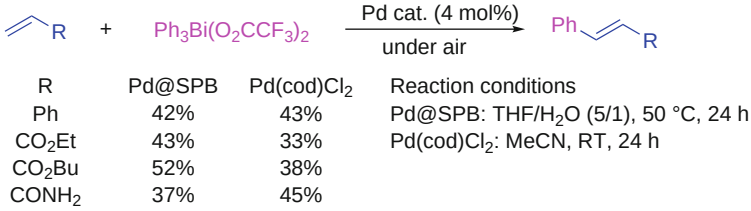

**Scheme 4** Reaction of alkenyltriphenylbismuthonium salt with ethyl acrylate




**Scheme 5** Heck-type phenylation reaction with organobismuth compounds




**Scheme 6** Heck-type phenylation reaction with $Ph_3BiX_2$

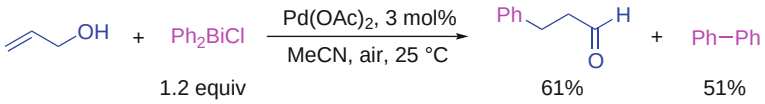



**Scheme 7** Heck-type phenylation reaction with $Ph_3Bi(O_2CCF_3)_2$

methyl cinnamete, but biphenyl was obtained in 138% yield based on bismuth. The same reaction with antimony compounds, $Ph_3Sb(O_2CR)$, selectively gave methyl cinnamate without biphenyl [22]. The difference in the selectivity between the bismuth and the antimony compounds probably comes from the difference in the C–Bi and C–Sb bond strengths, the former being much weaker than the latter [2]. The reaction of the intermediate phenyl–Pd species with methyl acrylate, giving methyl cinnamate, would compete with the biphenyl formation reaction of the intermediate with PhBi compounds.

The same reaction using tetraphenylbismuth compounds $Ph_4BiX$ (X = 4-$MeC_6H_4SO_3$, 2,4,6-$(NO_2)_3C_6H_2O$, 2,6-$Br_2$-4-$NO_2C_6H_2O$, etc.) was also examined [20]. In this case, not only methyl cinnamate, but also methyl hydrocinnamate were obtained (54% and 73%, respectively, for $Ph_4BiOSO_2C_6H_4Me$). Methyl hydrocinnamate was probably formed by acidolysis of the intermediate $PhCH_2CH{=}C(OMe)(OPd)$, with the acid HX being liberated during the formation of methyl cinnamate.

Phenylation of styrene, acrylic esters, and acrylamide with $Ph_3Bi(O_2CCF_3)_2$ was examined using palladium nanoparticles immobilized in spherical polyelectrolyte brushes (Pd@SPB) (Scheme 7) [21]. The reaction can be conducted under air, and




**Scheme 8** Heck-type phenylation reaction of allyl alcohol with $Ph_2BiCl$

the results obtained with Pd@SPB were comparable to those obtained using the homogeneous catalyst $Pd(cod)Cl_2$ (cod = 1,4-cyclooctadiene).

Heck-type phenylation of allyl alcohol with $Ph_2BiCl$ proceeded in the presence of $Pd(OAc)_2$ to afford an isomerized product, 3-phenylpropanal, in 61% yield together with biphenyl (Scheme 8) [23]. The reaction required air (or oxygen) for catalytic conversion. A similar reaction with $Ph_2SbCl$ was more efficient and afforded 3-phenylpropanal in 94% yield.

## 2.2 Copper-Catalyzed C–C Bond Forming Reactions

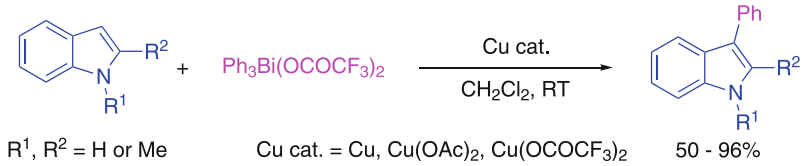
It is well established that metallic copper or copper salts efficiently catalyze N- and O-arylation reaction using pentavalent and trivalent organobismuth compounds [5–9, 24]. The C-arylation reaction of phenols and active methylene compounds using pentavalent organobismuth compounds are usually mediated by a base. However, in some cases, copper catalysts mediate C-arylation using pentavalent organobismuth compounds.

The C-phenylation reaction of 3-unsubstituted indoles by $Ph_3Bi(OCOCF_3)_2$ was catalyzed by metallic copper or copper(II) salts to give a 3-phenylated product in 50–96% yield (Scheme 9) [25]. The same reaction did not proceed with $Ph_3Bi(OCOCH_3)_2$. The reaction is believed to proceed through Cu(III) intermediates.

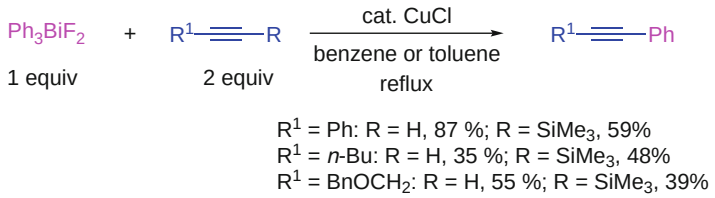
Phenylation of terminal alkynes took place with $Ph_3BiF_2$ in the presence of Cu(I) chloride (Scheme 10) [26]. Trimethylsilyl alkynes similarly worked as terminal alkynes. Other pentavalent organobismuth compounds such as $Ph_3BiCO_3$ and $Ph_3BiCl_2$ were much less efficient than $Ph_3BiF_2$. Biphenyl was also formed as a by-product. It was proposed that the products were formed through reductive elimination of the intermediate $Ph_3Bi(C{\equiv}CR^1)_2$.

Triphenylbismuthonium ylide reacted with terminal alkynes in the presence of a catalytic amount of copper(I) chloride to form furan derivatives (Scheme 11) [27]. Although the yields were low, the products were obtained regioselectively. The reaction was sensitive to steric factors, and internal alkynes did not provide the product. A carbenoid intermediate was probably involved in the reaction.

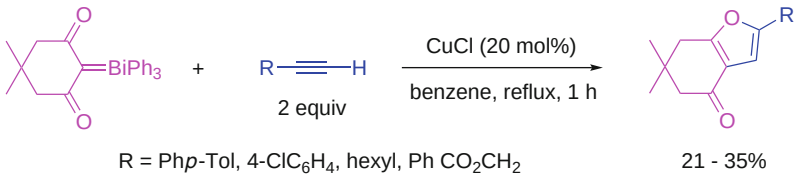
The reaction of the same bismuthonium ylide with isothiocyanates in the presence of a copper(II) catalyst afforded the sulfur-incorporated spiro-cyclic compound as the main product, in addition to a small amount of carbon–carbon bond formed products (Scheme 12) [28].



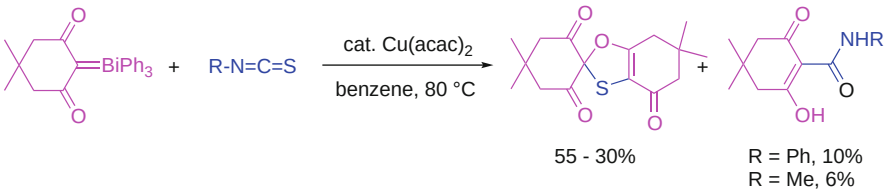

**Scheme 9** C-phenylation reaction of indoles with $Ph_3Bi(O_2CCF_3)_2$




**Scheme 10** Arylation reaction of alkynes with $Ph_3BiF_2$

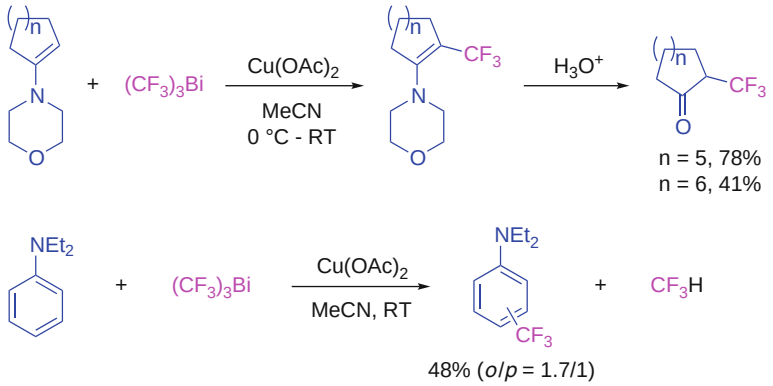



**Scheme 11** Reaction of bismuthonium ylide with alkynes

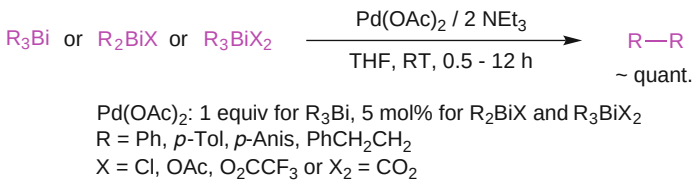



**Scheme 12** Reaction of bismuthonium ylide with isothiocyanates

Trifluoromethylation of 1-morpholinocycloalkene or *N*,*N*-diethylaniline with $(CF_3)_3Bi$ was mediated by $Cu(OAc)_2$ (Scheme 13) [29]. The reaction of 1-morpholinocycloalkene afforded 2-trifluoromethylcycloalkanones in moderate to good yields, after acid hydrolysis of the intermediate products. In the reaction of *N*,*N*-diethylaniline, equimolar amounts of trifluoromethylanilines and $CF_3H$ were produced. The reaction was believed to proceed through $CF_3$ radical, which was produced from intermediate $Cu(CF_3)(OAc)$.




**Scheme 13** Trifluoromethylation reaction using $(CF_3)_3Bi$

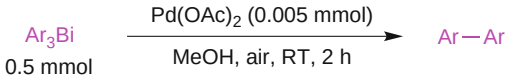



**Scheme 14** Ligand coupling reaction of organobismuth compounds

## *2.3 Ligand Coupling Reaction of Organobismuth(III) and (V) Compounds*

As already shown in the above sections, biaryls are often produced as by-products in the transition-metal catalyzed reaction of organobismuth compounds. Barton et al. were the first to focus their attention on this reaction [30]. Pd(0) species generated from $Pd(OAc)_2/2NEt_3$ combination efficiently catalyzed the ligand coupling reaction of trivalent compounds, $Ar_3Bi$ and $Ph_2BiX$, and pentavalent compounds $Ar_3BiX_2$ (Scheme 14). Not only the aryl–aryl coupling, but also the alkyl–alkyl coupling of $(PhCH_2CH_2)_3Bi$ took place in high yields, in which no styrene, a possible by-product, was formed. $Ar_3Bi$ required one equivalent of Pd $(OAc)_2$, whereas $Ph_2BiX$ and $Ar_3BiX_2$ needed only 5 mol% of the Pd catalyst. The reaction efficiently proceeded in tetrahydrofuran (THF) at room temperature, and the use of hexamethylphosphoric triamide (HMPA) shortened the reaction time to 10 min at 65 °C.

$Pd(PPh_3)_4$ is less efficient than the $Pd(OAc)_2/2Et_3N$ system for the ligand coupling reaction of $Ar_3BiCl_2$, and the effect of aryl substituents on the reaction rate was examined [31]. The remaining amounts of $Ar_3BiCl_2$, after heating at 40 °C for 1 h in $CDCl_3$ in the presence of $Pd(PPh_3)_4$, were 96% for $(4\text{-}MeOC_6H_4)_3BiCl_2$,




**Scheme 15** Ligand coupling reaction of $Ar_3Bi$

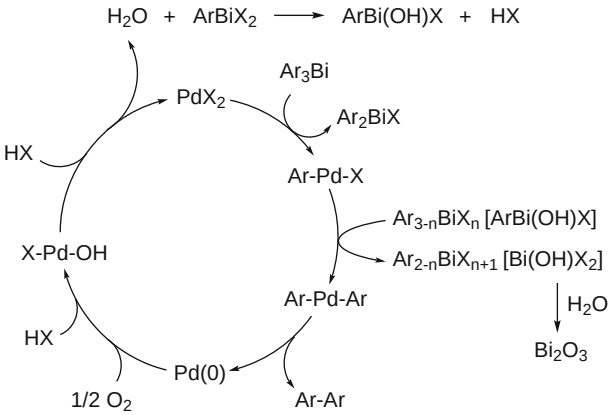


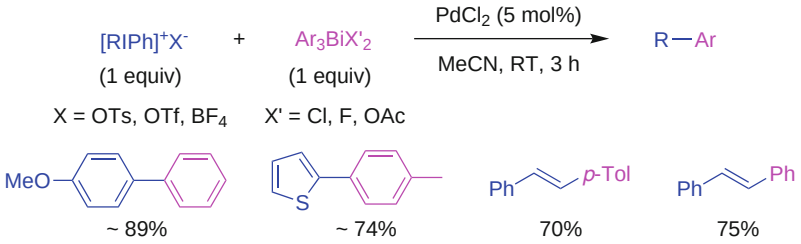

**Fig. 1** Plausible reaction mechanism for the ligand coupling reaction

82% for $Ph_3BiCl_2$, 39% for $(4\text{-}CF_3C_6H_4)_3BiCl_2$, and 27% for $(4\text{-}CNC_6H_4)_3BiCl_2$. The results are in good agreement with the reactivity of the bismuth–carbon bonds for oxidative addition reaction towards Pd(0).

Later, Uemura and coworkers found that the reaction of $Ar_3Bi$ can even be performed catalytically using only 1 mol% of $Pd(OAc)_2$, if the reaction was conducted under air (Scheme 15) [32]. The reaction proceeded in 80–99% yields, except for *ortho*-substituted substrates, which afforded products in poor yields, e.g., $(o\text{-Tol})_3Bi$ gave a yield of ~15%. The reaction using a mixture of two different triarylbismuths, $Ph_3Bi$ and $Tol_3Bi$, in a 1:1 ratio afforded Ph–Ph, Tol–Tol and Ph–Tol in 9:10:15 ratio, suggesting an intermolecular reaction. Fig. 1 shows a plausible reaction mechanism proposed by the authors. The mechanism involves two transmetalation steps to form $Ar_2Pd$ species from $Pd^{II}X_2$. No expected oxidative addition step of Ar–Bi to Pd(0) was involved.

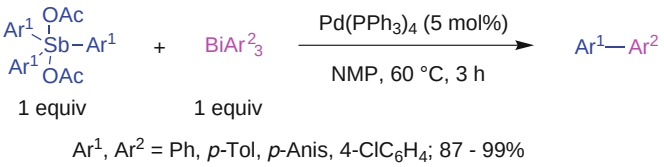
## 2.4 Reaction with Organoheteroatom Compounds

As mentioned in Sect. 2.3, the ligand coupling reaction of organobismuth compounds would be an intermolecular reaction. This fact suggests the possibility of a cross-ligand coupling reaction between organobismuth compounds and other organoheteroatom or organometallic compounds. Indeed, selective cross-ligand coupling




**Scheme 16** Cross-coupling reaction of $Ar_3BiX_2$ with iodonium salts

**Scheme 17** Cross-coupling reaction of $Ar_3BiX_2$ with organostannanes




**Scheme 18** Cross-coupling reaction of $Ar_3Bi$ with organoantimony compounds

reactions between organobismuth compounds and hypervalent organoiodonium salts, organotin, and organoantimony compounds have been reported.

The reaction of 4-methoxyphenyl-, 2-thienyl- and styryl-iodonium salts with triarylbismuth(V) compounds was efficiently catalyzed by $PdCl_2$ in MeCN at room temperature to afford cross-coupling products in good yields (Scheme 16) [33]. There is no mention about possible homo-coupling side-products.

A similar cross-coupling reaction between triarylbismuth(V) compounds and aryl-, heteroaryl-, or styryltributylstannanes smoothly proceeded under the same reaction conditions as those for the iodonium salts (Scheme 17) [34]. Homo-coupling side products were not mentioned.

Cross-coupling reactions of pentavalent antimony compounds, $Ar_3{}^1Sb(OAc)_2$, and trivalent bismuth compounds, $Ar_3{}^2Bi$, were catalyzed by $Pd(PPh_3)_4$ with high selectivity (Scheme 18) [35]. This reaction is highly solvent-dependent and 1-methyl-2-pyrrolidinone (NMP) is the solvent of choice. In this reaction, small amounts of homo-coupling by-products, $Ar^1$–$Ar^1$ and $Ar^2$–$Ar^2$, were also formed. Among the three aryl groups of $Ar_3Sb(OAc)_2$, only one can be used for the coupling reaction, while more than one aryl groups of $Ar_3Bi$ can be transferred.

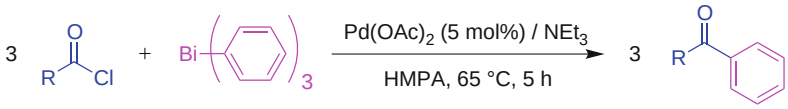
## 2.5 Reaction with Organic Halides and Triflates

### 2.5.1 Reaction with Acyl Chlorides

In 1988, Barton and coworkers found that the cross-coupling reaction of $Ph_3Bi$ and acyl chlorides to give aromatic ketones was efficiently catalyzed by Pd(0) generated in situ from $Pd(OAc)_2/2Et_3N$. The three phenyl groups from $Ph_3Bi$ can be effectively transferred in this coupling reaction (Scheme 19) [30]. Biphenyl was formed as a trace by-product.

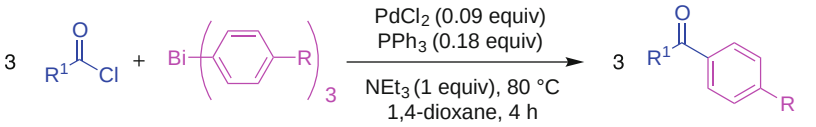
Subsequently, Rao and coworkers expanded the usefulness of triarylbismuth compounds as multicoupling reagents with a variety of acid chlorides under different catalytic conditions [36–38]. As summarized in Schemes 20–22, a variety of acid chlorides, including aromatic, hetero-aromatic, and aliphatic acid chlorides as well as bis-acid chlorides, can be coupled smoothly with $Ar_3Bi$ to give ketones in high yields. A bromine substituent did not affect the reaction, giving bromine-substituted ketones in good yields. The substituents on the aromatic ring of $Ar_3Bi$ showed an apparent effect on the reaction; i.e., *p*-$Anis_3Bi$ afforded the products in lower yields than $Ph_3Bi$ and *p*-$Tol_3Bi$ (Scheme 20).

Palladium/carbon (Pd/C) was also found to be effective in this cross-coupling reaction [38] (Scheme 23). The addition of $PPh_3$ was indispensable, whereas $Et_3N$ had a marginal effect in this catalytic system. The amount of Pd (less than 1 mol% of acid chlorides) is much smaller than for the former catalytic systems.




R = Ph, 96% ; R = Bn, 94% ; R = Me, 95% ;
R = Et, 92% ; R = *t*-Bu, 89% ; R = c-Hex, 91% .

**Scheme 19** Cross-coupling reaction of $Ph_3Bi$ with acid chlorides

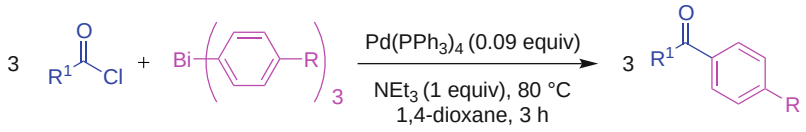



$R^1$ = Ph, R = H, 93%
R = Me, 92%
R = OMe, 76%

$R^1$ = 4-$BrC_6H_4$, R = H, 87%
R = Me, 86%
R = OMe, 63%

$R^1$ = c-Hex, R = H, 95%
R = Me, 90%
R = OMe, 76%

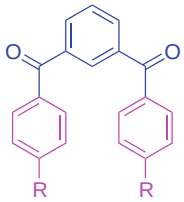
**Scheme 20** Cross-coupling reaction of $Ar_3Bi$ with aliphatic and aromatic acid chlorides



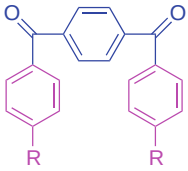

$R^1$ = 2-Furyl, R = H, 81%
R = Me, 92%
R = OMe, 84%
R = F, 86%

$R^1$ = 2-Thienyl, R = H, 77%
R = Me, 91%
R = OMe, 85%
R = F, 82%
R = Cl, 82%

**Scheme 21** Cross-coupling reaction of $Ar_3Bi$ with heteroaryl acid chlorides

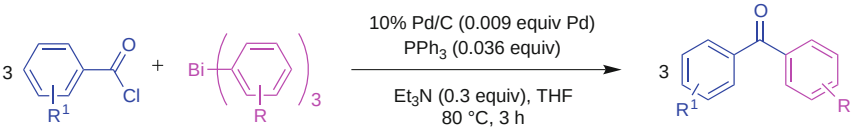


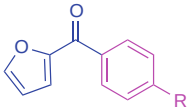

R = H, 85%
R = Me, 80%
R = OMe, 78%
R = F, 76%



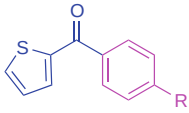

R = H, 82%
R = Me, 75%
R = F, 73%

**Scheme 22** Cross-coupling reaction of $Ar_3Bi$ with bis-acid chlorides




R = H, 84%
R = Me, 86%
R = OMe, 83%

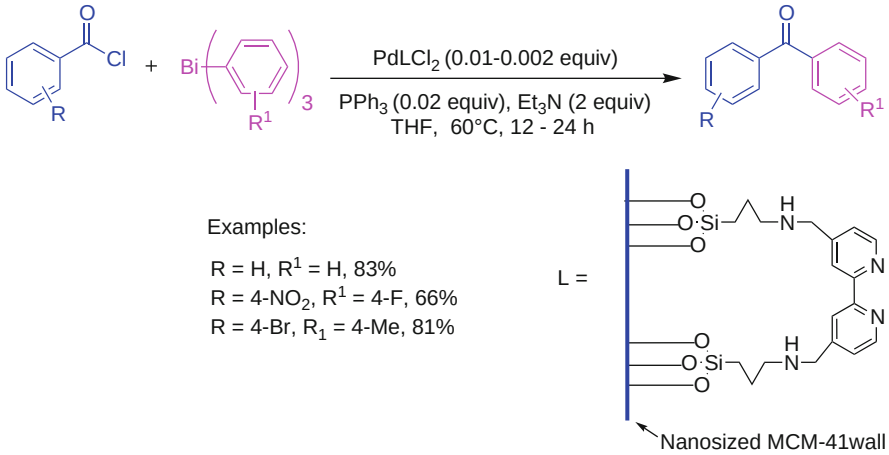



R = H, 80%
R = Me, 72%

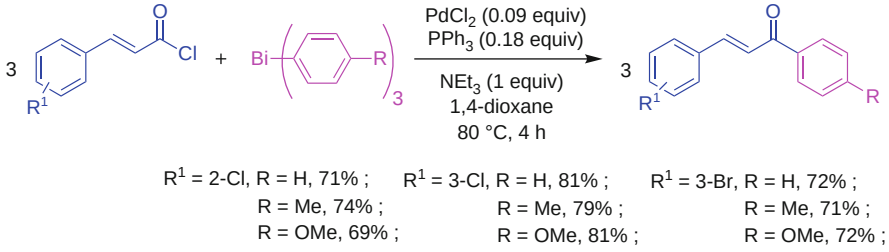
$R^1$ = 4-Me, R = H, 90%
$R^1$ = 4-$NO_2$, R = H, 52%
$R^1$ = 4-$NO_2$, R = 4-OMe, 58%
$R^1$ = 3-OMe, R = 4-OMe, 66%

**Scheme 23** Cross-coupling reaction of $Ar_3Bi$ with acid chlorides using Pd/C system

Another heterogeneous Pd catalyst, Pd bipyridyl complex anchored on nanosized mesoporous silica MCM-41, was also examined for the cross-coupling reaction of $Ar_3Bi$ with acid chlorides [39] (Scheme 24). In this catalyst system, $PPh_3$ was also indispensable. A variety of aromatic ketones were obtained in good to high yields, although higher amounts of $Ar_3Bi$ was required (acyl chlorides/ $Ar_3Bi$ = 1/0.5). The immobilized catalyst can be reused several times without considerable decrease in activity. The heterogeneous nature of the catalysis was




**Scheme 24** Cross-coupling reaction of $Ar_3Bi$ with acid chlorides using heterogeneous Pd-system

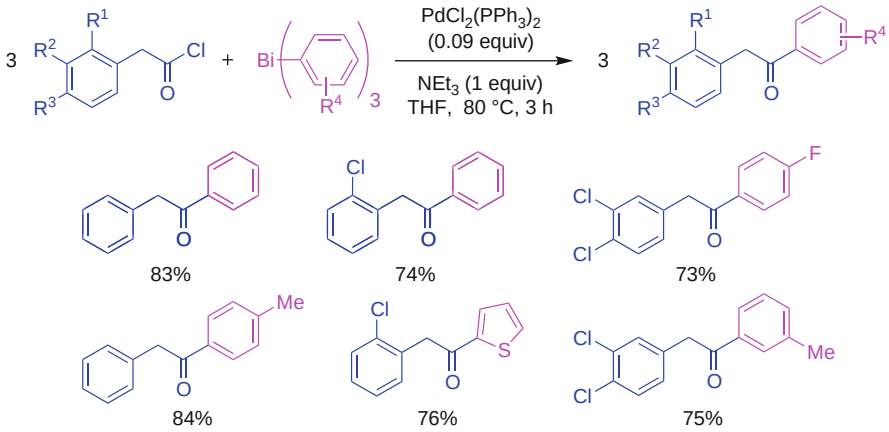



**Scheme 25** Cross-coupling reaction of $Ar_3Bi$ with unsaturated acid chlorides

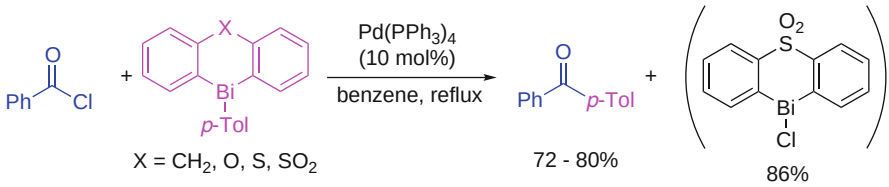
confirmed; when the catalyst was removed by filtration during the reaction, the progress of the reaction completely stopped.

Unsaturated acid chlorides also coupled with $Ar_3Bi$ under Pd catalysis to give a variety of conjugated ketones as given in Scheme 25 [40]. Additionally, cross-coupling reactions of α-arylacetyl chlorides with $Ar_3Bi$ gave α-arylacetophenones under Pd catalytic conditions (Scheme 26). This protocol was applied to the synthesis of a variety of regio-isomeric α-arylacetophenones [41].

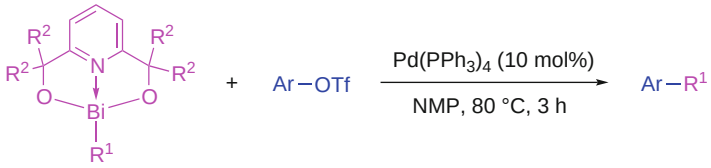
Cyclic triarylbismuth(III) compounds also undergo the Pd-catalyzed cross-coupling reaction with benzoyl chloride (Scheme 27) [42]. The exocyclic aryl group was selectively transferred to form 4-methylbenzophenone in good yield. Bismuth-containing products could not be isolated except for the cyclic bismuth compound possessing a $SO_2$ moiety, for which cyclic bismuth chloride was isolated in 86% yield.




**Scheme 26** Cross-coupling reaction of $Ar_3Bi$ with α-arylacetyl chlorides




**Scheme 27** Cross-coupling reaction of cyclic triarylbismuth compounds with benzoyl chloride




$R^1$ = Ph, $R^2$ = Et, Ar = 4-$AcC_6H_4$, 99%
Ar = 4-$CNC_6H_4$, 99%
Ar = 1-Naph, 80%
Ar = *p*-Anis, 0%
Ar = 2-Py, 78%

$R^1$ = $R^2$ = Me, Ar = 4-$AcC_6H_4$, 72%
Ar = 4-$PhCOC_6H_4$, 52%
Ar = 4-$CNC_6H_4$, 61%

**Scheme 28** Cross-coupling reaction of organobismuth alkoxides with aryl triflates

### 2.5.2 Reaction with Aryl Halides and Triflates

Hypervalent organobismuth compounds **1** bearing a 2,6-pyridinedialkoxide ligand [43] were used for the cross-coupling reaction with aryl triflates (Scheme 28) [44]. Phenylation using phenylbismuth compounds smoothly proceeded for the reactive

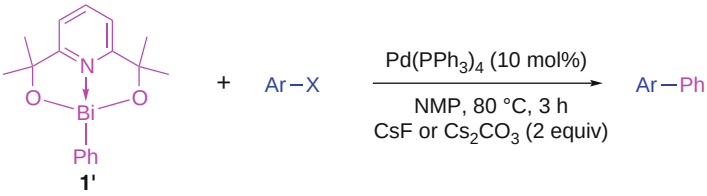
aryl triflates in the presence of 10 mol% of Pd catalyst. Methylation using methylbismuth compounds also proceeded, but less efficiently than the phenylation. This reaction is highly sensitive to the electronic nature of aryl triflate; i.e., no cross-coupling product was obtained for the less reactive aryl triflates possessing electron-donating substituents on the aromatic ring.

The similar cross-coupling reaction of compounds **1** with aryl iodides was less sensitive to the electronic nature of the substrates than that with aryl triflates; i.e., electron-deficient 4′-iodoacetophenone and electron-rich 4-iodoanisole afforded the cross-coupling products in 96% and 55% yields, respectively (Scheme 29) [45]. The addition of cesium salts improved the product yields considerably. Aryl bromides were less efficient than aryl iodides, and addition of cesium salts was necessary to improve the product yields.

$Ar_3Bi$ can be coupled efficiently with various aryl bromides, iodides, and triflates under Pd catalysis (Scheme 30) [46]. In this method, the coupling reaction of $Ar_3Bi$ with aryl iodides and triflates was carried out in NMP with $K_2CO_3$ as base. Instead, 1,2-dimethoxyethane (DME) as a solvent and CsF as a base were effective conditions for the coupling reaction of aryl bromides. It is worth noting that all of the three aryl groups from $Ar_3Bi$ are coupled effectively with aryl bromides, iodides, or triflates in these coupling reactions.

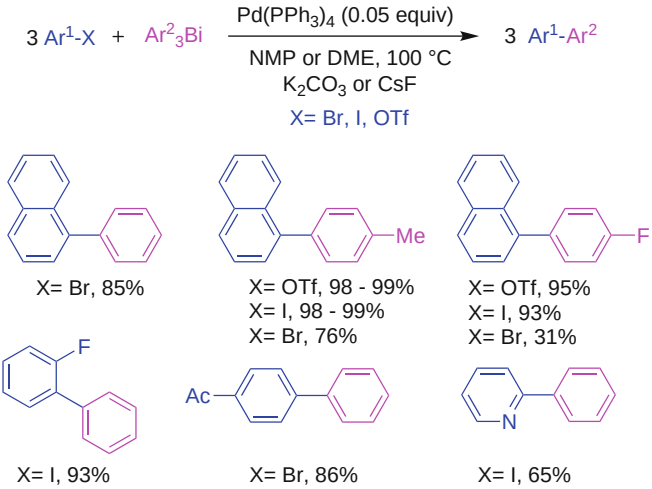
Further advancement in the cross-coupling reaction of $Ar_3Bi$ with aryl bromides, iodides, and triflates was achieved in subsequent studies [47, 48]. Thus, the combination of *N,N*-dimethylformamide (DMF) as a solvent and $K_3PO_4$ as a base was found to be effective for the cross-coupling reaction, giving the cross-coupling products in high yields in short reaction times (Scheme 31). Under these reaction conditions, the product yields for less-reactive electron-rich aryl halides and triflates were particularly improved. Homo-coupling biaryls from $Ar_3Bi$ were also formed invariably in minor amounts in these coupling reactions.

Furthermore, the couplings of aryl bromides, iodides, and triflates were found to be facile in *N,N*-dimethylacetamide (DMA) solvent with $Cs_2CO_3$ as a base [49].

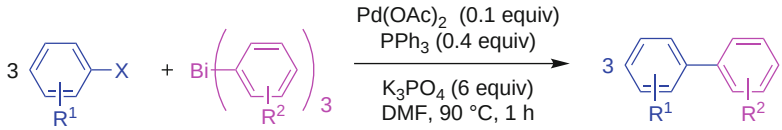



| Ar | Ar-I | | Ar-Br | |
|---|---|---|---|---|
| | no additive | Cs salt | no additive | Cs salt |
| 4-$AcC_6H_4$ | 96% | - | 63% | 99% |
| 1-Naph | 74% | 99% | 15% | 88% |
| *p*-Tol | 60% | 85% | - | 36% |
| *p*-Anis | 55% | 79% | - | - |
| 2-Py | 57% | 93% | - | 99% |

**Scheme 29** Cross-coupling reaction of organobismuth alkoxides with aryl iodides and bromides




**Scheme 30** Cross-coupling reaction of $Ar_3Bi$ with aryl halides and triflates

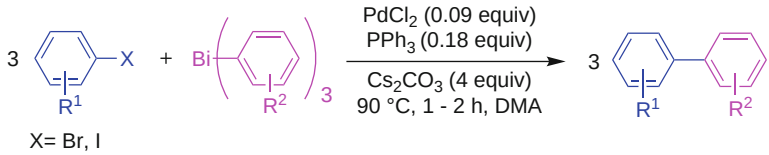



| | X=Br | X=I | X = OTf |
|---|---|---|---|
| $R^1$ = 4-Ac, $R^2$ = H, | 85% | 91% | $R^1$ = 4-Me, $R^2$ = 4-OMe, 61% |
| $R^2$ = 4-OMe, | 86% | 90% | $R^1$ = 4-$NO_2$, $R^2$ = H, 71% |
| $R^2$ = 4-Me, | 89% | 77% | $R^1$ = 4-Cl, $R^2$ = 4-Me, 73% |
| $R^2$ = 4-F, | 73% | 91% | $R^1$ = 4-Cl, $R^2$ = 4-OMe, 79% |
| $R^2$ = 4-Cl, | 65% | 82% | $R^1$ = 4-CN, $R^2$ = H, 56% |
| $R^2$ = 3-OMe, | 89% | 95% | $R^1$ = 4-$CH_3$, $R^2$ = H, 61% |

**Scheme 31** Generalized protocol for the cross-coupling reactions of $Ar_3Bi$ with aryl halides and triflates

Although aryl bromides and iodides reacted well without any additive (Scheme 32), tetrabutylammonium bromide (TBAB) was effective at improving the reactivity of aryl triflates under these conditions (Scheme 33).

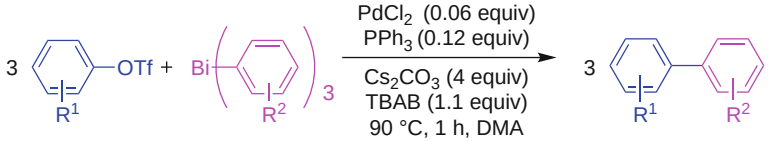
Hypervalent triarylbismuth compounds, 5,6,7,12-tetrahydrodibenz[c,f][1,5] azabismocines **2** [50–52], were found to be highly efficient reagents for the cross-coupling reaction with aryl bromides (Scheme 34) [53]. The coupling reaction smoothly proceeded without base activator in NMP, not only for highly reactive electron-deficient aryl bromides, but also for less-reactive electron-rich aryl bromides. Only the exocyclic organic groups were selectively transferred for the coupling reaction, and the bismuth–carbon bonds in the cyclic framework remained intact. After the reaction, cyclic bismuth bromide was formed quantitatively and could be easily separated.




X= Br, I

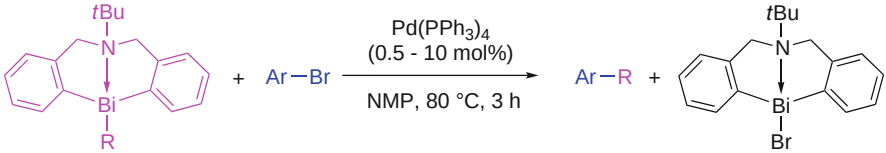
| X= Br | X= I |
|---|---|
| $R^1$ = 4-$NO_2$, $R^2$ = H, 85% | $R^1$ = 4-$CF_3$, $R^2$ = 4-OMe, 85% |
| $R^2$ = 4-OMe, 75% | $R^2$ = 4-Me, 92% |
| $R^2$ = 4-Me, 83% | $R^2$ = 4-OMe, 71% |
| $R^1$ = 3-$NO_2$, $R^2$ = 4-Me, 81% | $R^2$ = H, 87% |
| $R^1$ = 2-$NO_2$, $R^2$ = H, 72% | $R^1$ = 4-OMe, $R^2$ = H, 52% |
| $R^1$ = 2-$NO_2$, $R^2$ = 4-OMe, 63% | $R^2$ = 4-Me, 79% |

**Scheme 32** Cross-coupling reaction of $Ar_3Bi$ with aryl bromides and iodides




| | |
|---|---|
| $R^1$ = 3-Ac, $R^2$ = 4-OMe, 82% | $R^1$ = 4-CN, $R^2$ = H, 78% |
| $R^2$ = 4-Me, 87% | $R^2$ = H, 73% |
| $R^1$ = 3-CN, $R^2$ = H, 65% | $R^2$ = H, 80% |

**Scheme 33** Cross-coupling reaction of $Ar_3Bi$ with aryl triflates

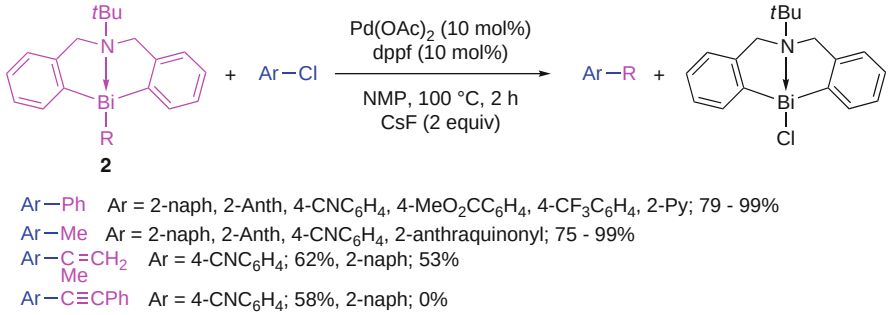



**2**

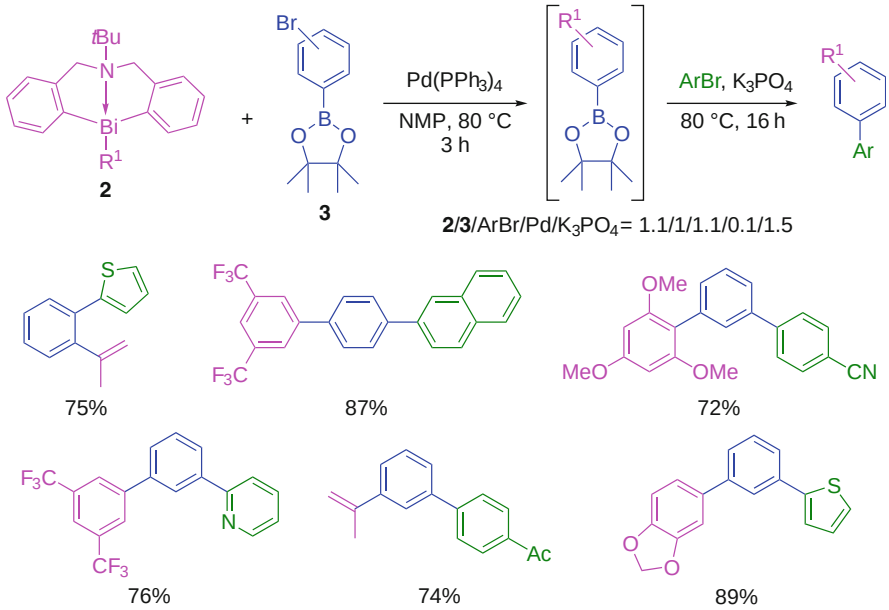
R = Ph, 3,5-$(CF_3)_2C_6H_3$, 3,4-$(CH_2O_2)_2C_6H_3$, 2,4,6-$(CH_3O)_3C_6H_2$, -CMe=$CH_2$
Ar = 1-Naph, 2-Anth, 4-$AcC_6H_4$, *p*-Tol, *p*-Anis, 4-$Me_2NC_6H_4$, 2-Py etc.
Isolated yield: 74 - 97%

**Scheme 34** Cross-coupling reaction of azabismocines with aryl bromides

Aryl chlorides can also be used as coupling partners for azabismocine reagents **2**. In the coupling reaction with aryl chlorides, $Pd(PPh_3)_4$ was not an efficient catalyst, and $Pd(OAc)_2$/1,1′-bis(diphenylphosphino)ferrocene (dppf) combination was found to be effective [54]. Not only the arylation, but also methylation, alkenylation and alkynylation reactions can be accomplished by using the corresponding bismuth compounds (Scheme 35). The addition of CsF improved the product yields. However, electron-rich aryl chlorides were unable to be coupled efficiently under these reaction conditions.

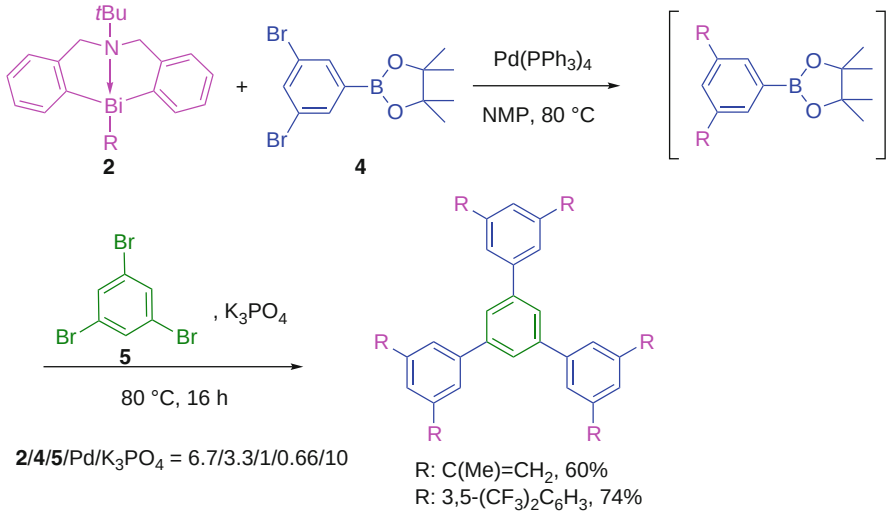



**Scheme 35** Cross-coupling reaction of azabismocines with aryl chlorides

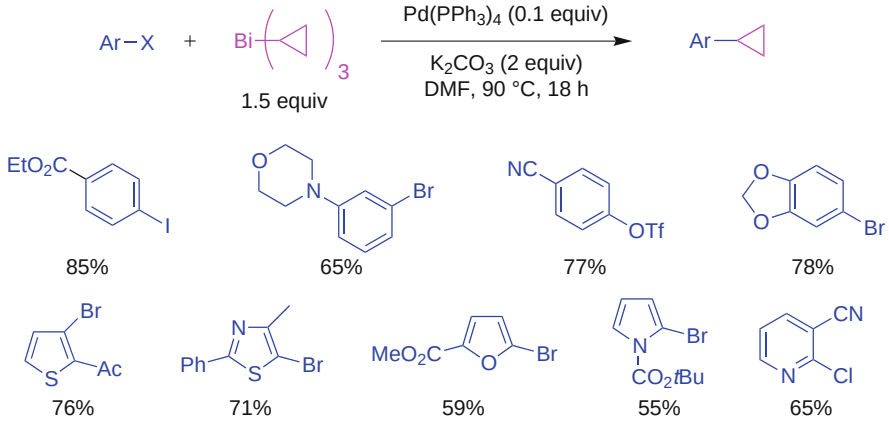



**Scheme 36** One-pot multicoupling reaction using azabismocines and bromophenylboronates

The cross-coupling reaction using organoboronic acids and esters usually requires base activators [55, 56]. On the other hand, the coupling reaction of azabismocine reagents **2** with aryl bromides does not require base activators. By using this reactivity difference, a one-pot multicoupling reaction can be accomplished as shown in Scheme 35 [53]. In the absence of a base activator, bromophenyl boronic esters can be selectively substituted at the bromine position by azabismocine **2** under Pd catalysis to provide a substituted phenylboronic ester intermediate, which subsequently reacts with another aryl bromide by the addition of a base activator in one pot to give the final product. As shown in Scheme 36, various double-coupling products were obtained in high yields.




**Scheme 37** One-pot multicoupling reaction using azabismocines and 3,5-dibormophenylboronate




**Scheme 38** Cross-coupling reaction of tricyclopropylbismuth with arylhalides and triflates

By using 3,5-dibromophenylboronic ester and 1,3,5-tribromobenzene in the same protocol, nine carbon–carbon bonds can be constructed in a one-pot manner to provide polyaromatic compounds in good yields (Scheme 37) [53].

A recent report has shown that tricyclopropylbismuth can be utilized in the cross-coupling reaction with aryl halides and triflates [57]. Representative examples are shown in Scheme 38. Addition of a base activator and excess of the bismuth reagents are necessary to obtain the coupling products in good yields, although more than one cyclopropyl group was transferred when 0.5 equivalents of

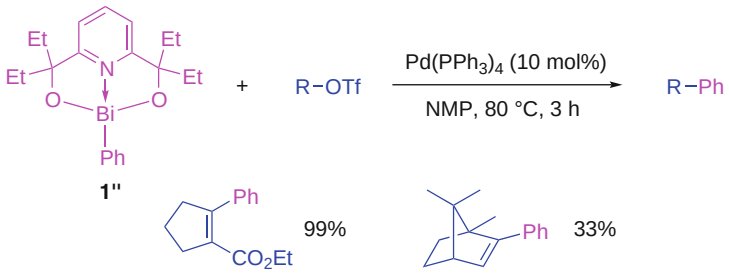
tricyclopropylbismuth was used. Trialkylbismuth compounds were also shown to be reactive in this cross-coupling reaction under similar reaction conditions [58].

### 2.5.3 Reaction with Alkenyl Halides and Triflates

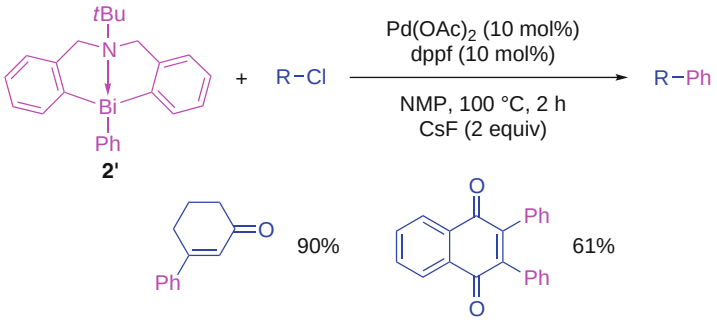
Organobismuth compound **1″** was also used for the cross-coupling reaction with alkenyl triflates. $CO_2Et$-substituted cyclopentenyl triflate afforded the coupling product quantitatively, while the sterically hindered triflate gave the product in poor yield (Scheme 39) [44]. Azabismocine **2′** reacted with activated alkenyl chlorides to give the coupling products in moderate to good yields (Scheme 40) [54].

Cross-coupling reaction of alkenyl iodides with $Ar_3Bi$ were efficient under Pd catalysis [59] (Schemes 41–43). Various alkenyl iodides furnished cross-coupling products in good yields in short reaction times under mild conditions. A bromine substituent did not affect the reaction and afforded the corresponding bromine-substituted products.

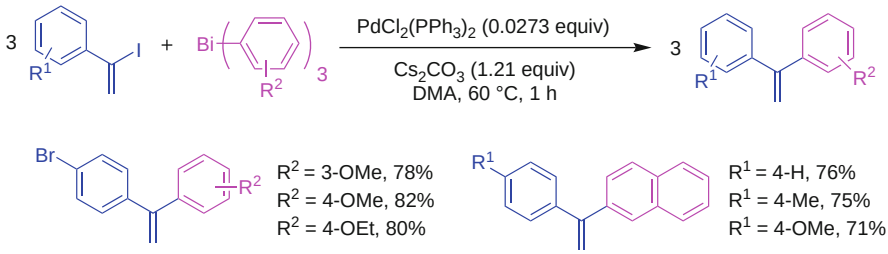
Functionalized isoflavones can be easily obtained from the cross-coupling reaction of 3-iodochromones with $Ar_3Bi$ under Pd catalysis (Scheme 44). The coupling reaction of a variety of substituted 3-iodochromones and $Ar_3Bi$ afforded substituted isoflavones in high yields [60].



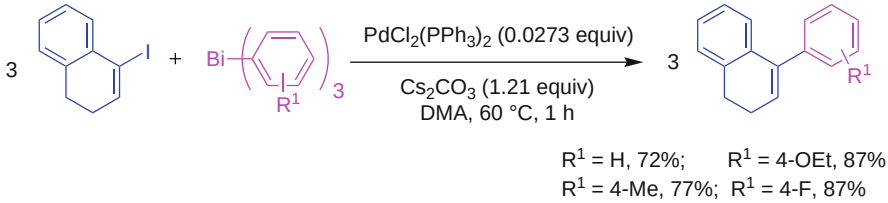

**Scheme 39** Cross-coupling reaction of phenylbismuth alkoxide with alkenyl triflates



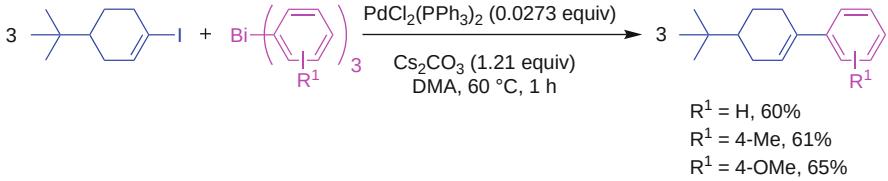

**Scheme 40** Cross-coupling reaction of phenylazabismocine with alkenyl chlorides



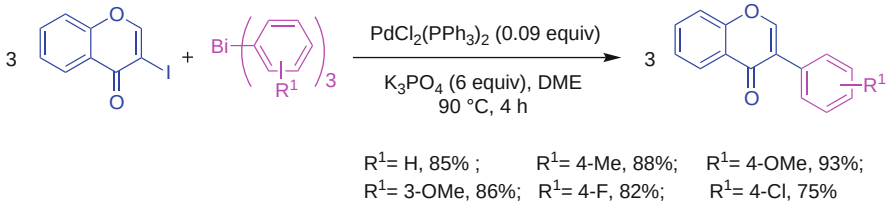

**Scheme 41** Cross-coupling reaction of $Ar_3Bi$ with 1-iodovinylbenzenes




**Scheme 42** Cross-coupling reaction of $Ar_3Bi$ with 4-iodo-1,2-dihydronaphthalene




**Scheme 43** Cross-coupling reaction of $Ar_3Bi$ with 4-*tert*-butyl-1-iodocyclohex-1-ene




**Scheme 44** Cross-coupling reaction of $Ar_3Bi$ with 3-iodochromone

### 2.5.4 Reaction Mechanism

Figure 2 shows a plausible reaction mechanism for the Pd-catalyzed cross-coupling reaction of organobismuth compounds with organic halides and triflates, which probably follows a typical reaction cycle of the similar cross-coupling reaction of organometallic and organoheteroatom compounds with organic halides and triflates [1]:

1. Oxidative addition of organic halides or triflates to Pd(0) to form an organopalladium(II) intermediate [step (i) in Fig. 2]
2. Transmetalation between the organopalladium(II) intermediate and organobismuth compounds to form diorganopalladium(II) intermediate [step (ii) in Fig. 2]
3. Reductive elimination of the cross-coupled product R–R′ from the intermediate to regenerate Pd(0) [step (iii) in Fig. 2]

Indeed, the reaction of a plausible intermediate $(Ph_3P)_2PdCl(C_6H_4CN)$ with phenylbismuth compounds [step (ii) in Fig. 2] afforded the cross-coupling product [54]. The reaction of $(Ph_3P)_2PdCl(C_6H_4CN)$ with $Ph_3Bi$, **1′**, or **2′** in DMF-$d_7$ at 100 °C for 1 h in the presence of two equivalents of $PPh_3$ gave 4-biphenylcarbonitrile in 44, 59, and >99% yields, respectively (Scheme 45).

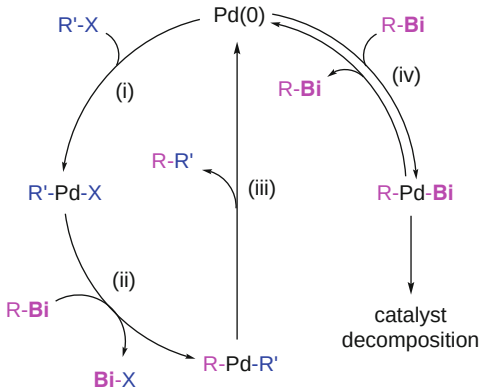
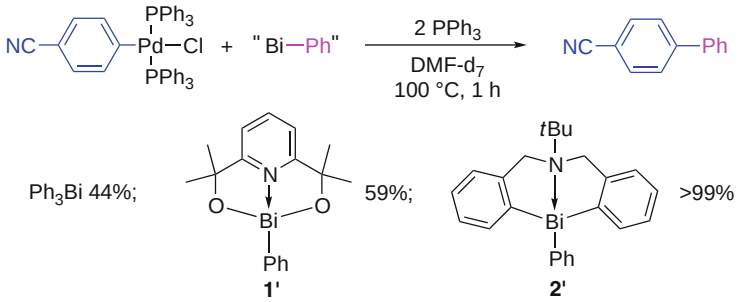



**Fig. 2** Plausible mechanism for the cross-coupling reaction of organobismuth compounds with organic halides and triflates

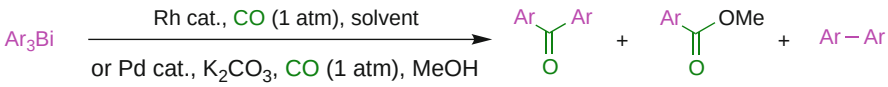



**Scheme 45** Cross-coupling reaction of organobismuth compounds with $(Ph_3P)_2PdCl(C_6H_4CN)$

As shown in Fig. 2, oxidative addition of Bi–C bonds to Pd(0) species is thought to lead to catalyst decomposition. This was confirmed by the following experiment: heating a 1:1 mixture of $Ph_3Bi$, **1′**, or **2′** and $Pd(PPh_3)_4$ in DMF-$d_7$ at 100 °C resulted in the decomposition of $Pd(PPh_3)_4$, and the decomposition rate was in the order $Ph_3Bi$ > **1′** >> **2′** [54]. Although the direct confirmation of Bi–C bond oxidative addition to Pd(0) has not been accomplished yet, a similar oxidative addition of Bi–C bonds of **1′** and **2′** toward a platinum(0) complex was confirmed, that of **1′** being much easier than that of **2′**. These results suggest that the decomposition of $Pd(PPh_3)_4$ is triggered by Bi–C oxidative addition to Pd(0), which is probably reversible and can be competitive with the desired oxidative addition of R′–X bonds [step (i) in Fig. 2]. As shown in Sect. 2.5.2, compounds **2** are more efficient reagents than compounds **1** and $Ar_3Bi$. The higher efficiency of **2** probably results from (1) the higher ability to transfer the organic group on the bismuth atom in the transmetalation step [step (ii) in Fig. 2], and (2) the lower ability of the Bi–C bond for oxidative addition to the Pd(0) species that leads to the catalyst decomposition [step (iv) in Fig. 2]. Although the effect of salt additives such as $K_2CO_3$, $Cs_2CO_3$, $K_3PO_4$, etc. was not clearly understood, coordination of the anion to the bismuth center may take place, which could facilitate the transfer of organic group in the transmetalation step and retard the direct oxidative addition of Bi–C bond to Pd(0) species.

## 2.6 Carbonylative Reaction

Carbonylative coupling reaction of $Ar_3Bi$ and carbon monoxide takes place under rhodium catalysis (Scheme 46) [61, 62]. $Ph_3Bi$ reacted with carbon monoxide in the presence of 5 mol% of $[RhCl(CO)_2]_2$ in MeCN at room temperature to give benzophenone in 71% yield together with a small amount of biphenyl. The same




Ar = Ph, *p*-Tol, *m*-Tol, *p*-Anis, 4-$ClC_6H_4$, 3-$ClC_6H_4$, 1-Naph

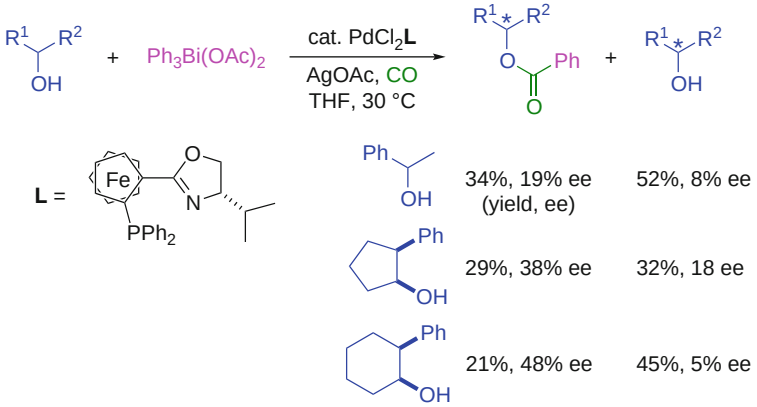
| Ar | Catalyst | Solvent | Products / % | | |
|---|---|---|---|---|---|
| | | | ArCOAr | ArCOOMe | $Ar_2$ |
| Ph | $[RhCl(CO)_2]_2$ | MeCN | 71 | - | 5 |
| Ph | $[RhCl(CO)_2]_2$ | MeOH | 73 | 26 | 0 |
| Ph | $Pd(OAc)_2$ | MeOH | 0 | 60 - 64 | 20 - 22 |
| 4-$ClC_6H_4$ | $[RhCl(CO)_2]_2$ | MeCN | 67 | - | trace |
| 4-$ClC_6H_4$ | $Pd(OAc)_2$ | MeOH | 0 | 60 | 33 |

**Scheme 46** Carbonylative coupling reaction of $Ar_3Bi$ with carbon monoxide

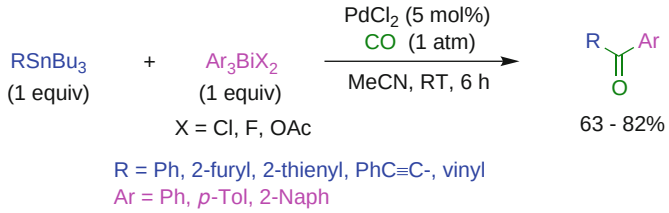
reaction in MeOH afforded 26% of methyl benzoate in addition to 73% of benzophenone. In this reaction, all three phenyl groups of $Ph_3Bi$ were transferred to the products. Interestingly, if the catalyst was changed to $Pd(OAc)_2$, the reaction in MeOH selectively produced methyl benzoate without benzophenone. When the rhodium-catalyzed reaction in MeCN was performed using a mixture of two different triarylbismuths, $Ar_3{}^1Bi$ and $Ar_3{}^2Bi$, not only the symmetric ketones $Ar^1COAr^1$ and $Ar^2COAr^2$, but also unsymmetric ketone $Ar^1COAr^2$ were obtained. This result suggests that the reaction involves intermolecular aryl-transfer steps.

A similar carbonylative coupling reaction was applied to the kinetic resolution of secondary alcohols [63]. In the presence of a Pd catalyst ligated by chiral oxazolinylferrocenylphosphine, the pentavalent $Ph_3Bi(OAc)_2$ and carbon monoxide effectively benzoylated secondary alcohols, and up to 48% enantiomeric excess (ee) was attained (Scheme 47). Although the enantioselectivity is not satisfactory, this is a unique new procedure for the kinetic resolution.

Carbonylative cross-coupling reaction between triarylbismuth(V) compounds and organostannanes is smoothly catalyzed by $PdCl_2$ under 1 atm CO at room temperature (Scheme 48) [34]. Not only arylstannanes, but also heteroaryl-, alkynyl-, and vinyltributylstannanes were employed efficiently.




**Scheme 47** Kinetic resolution of secondary alcohols by carbonylative coupling reaction of $Ph_3Bi(OAc)_2$




**Scheme 48** Carbonylative cross-coupling reaction of $Ar_3BiX_2$ with organostannanes

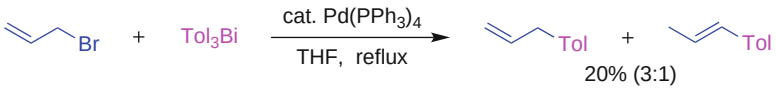
## 2.7 Allylic Coupling Reactions

Cross-coupling reaction of allyl bromide with $Ar_3Bi$ was first reported in 1989 by Wada and Ohki. In the presence of Pd(0) catalyst, the coupling products were obtained in low yield (Scheme 49) [64].

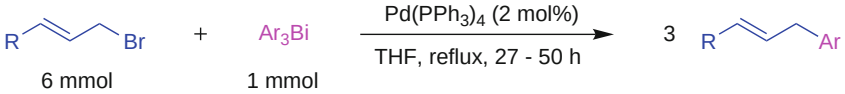
Later, a similar coupling reaction between allyl bromide or cinnamyl bromide with $Ar_3Bi$ was reported to provide the coupling products in good yields when the bromides were used in excess (Scheme 50) [65]. Under the same reaction conditions, arylation of propargyl bromide also proceeded to provide arylated allenes in moderate yields (Scheme 51) [65].

Allylic arylations of substituted cinnamyl acetates can be carried out with $Ar_3Bi$ under Pd catalysis. The couplings afforded 1,3-diarylpropenes in good yields in short reaction times (Scheme 52) [66].

The coupling reaction involving ring opening of vinyl epoxides with triarylbismuth(III) and (V) compounds readily proceeded to give the corresponding aryl substituted allylic alcohols under Pd catalysis [$PdCl_2$ or $PdCl_2$(dppf) or $Pd_2(dba)_3$] [14]. Both bismuth(III) and (V) compounds gave almost the same results, affording the arylation products at the terminal carbon atom. However, only in one case did arylation of the internal carbon atom take place to produce a homoallylic alcohol (Scheme 53).



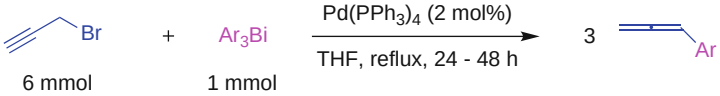

**Scheme 49** Cross-coupling reaction of $Tol_3Bi$ with allyl bromides




R = H, Ar = Ph, 87%
Ar = *p*-Tol, 83%
Ar = 4-$ClC_6H_4$, 51% (Ar-Ar, 32%)

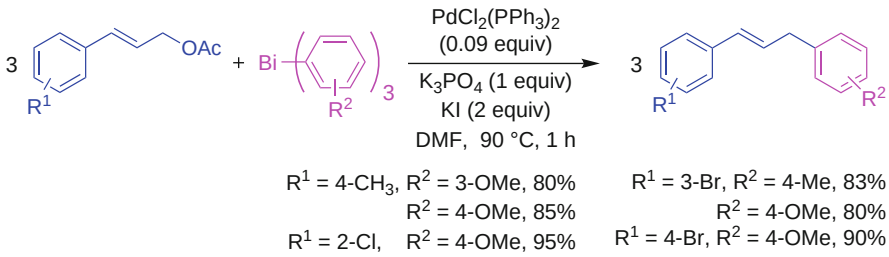
R = Ph, Ar = Ph, 77% (Ar-Ar, 10%)
Ar = *p*-Tol, 63% (Ar-Ar, 19%)
Ar = 4-$ClC_6H_4$, 32% (Ar-Ar, 37%)

**Scheme 50** Cross-coupling reaction of $Ar_3Bi$ with substituted allyl bromides

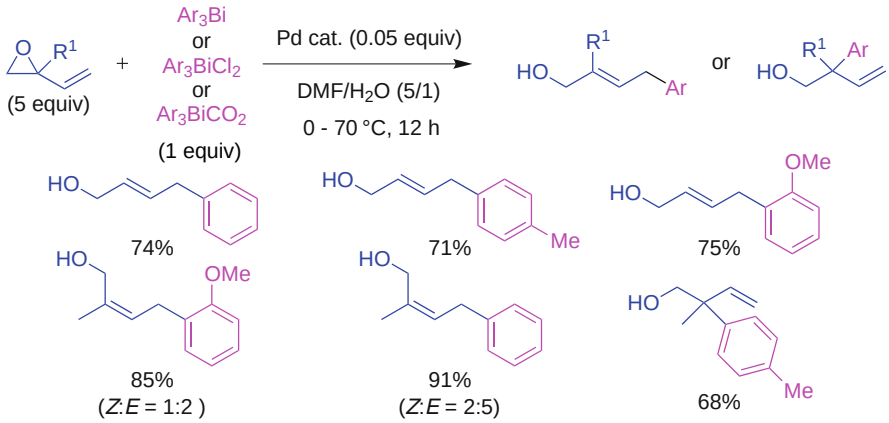



Ar = Ph, 60%; Ar = *p*-Tol, 67%; Ar = 4-$ClC_6H_4$, 49%

**Scheme 51** Cross-coupling reaction of $Ar_3Bi$ with propargyl bromide




**Scheme 52** Cross-coupling reaction of $Ar_3Bi$ with allylic acetates

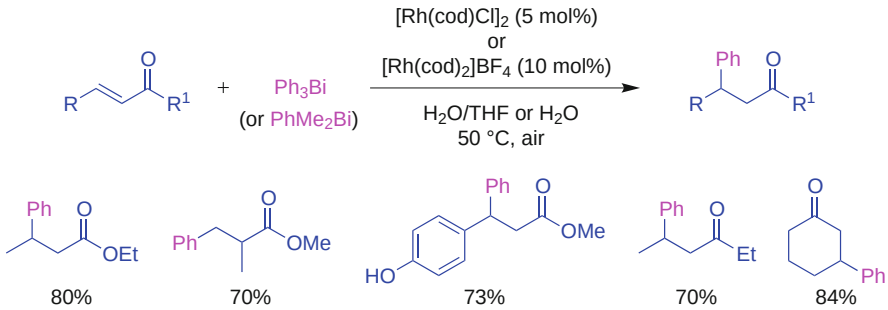



**Scheme 53** Reaction of organobismuth compounds with vinyl epoxides

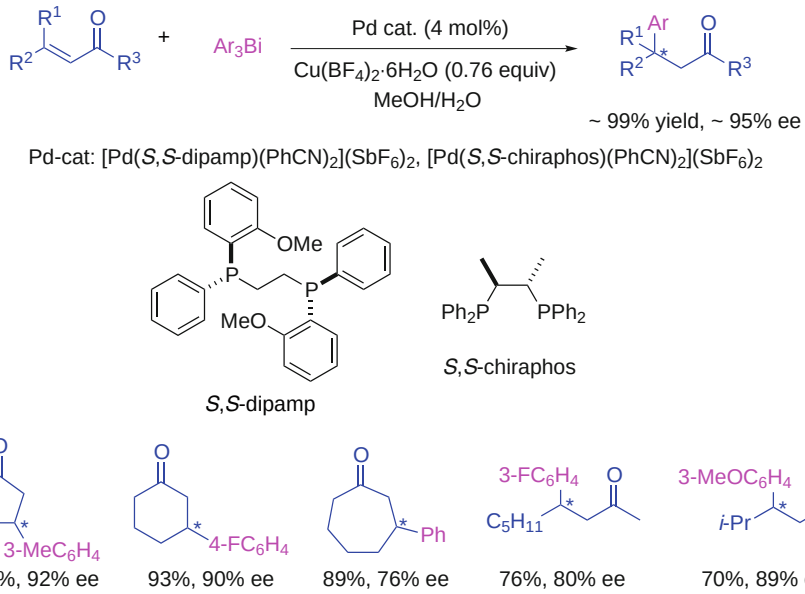
## 2.8 *1,4-Addition Reaction of α,β-Unsaturated Carbonyl Compounds*

The 1,4-addition reaction of unsaturated carbonyl compounds with $Ph_3Bi$ smoothly proceeded in the presence of rhodium catalysts (Scheme 54) [67, 68]. Interestingly, the reaction can be conducted in a $H_2O$/THF mixture under air. Methyl cinnamate, having an OH group on the aromatic ring, was efficiently phenylated without the protection of the OH group.

Enantioselective 1,4-additon to enones with $Ar_3Bi$ was catalyzed by Pd complexes possessing a chiral phosphine ligand (Scheme 55) [69, 70]. For 2-cyclohexanone and 2-cycloheptanone, the dipamp-ligated Pd complex gave good results, while chiraphos-ligated Pd complex was suitable for 2-cyclopentanone and acyclic enones. In this reaction, more than two aryl groups of $Ar_3Bi$ could be efficiently transferred to the enones. The reaction is believed to proceed through transmetalation of an aryl group to Pd to form $[ArPd]^+$ and subsequent insertion of an enone between the Pd–C bond.




**Scheme 54** 1,4-Addition reaction of unsaturated carbonyl compounds with $Ph_3Bi$

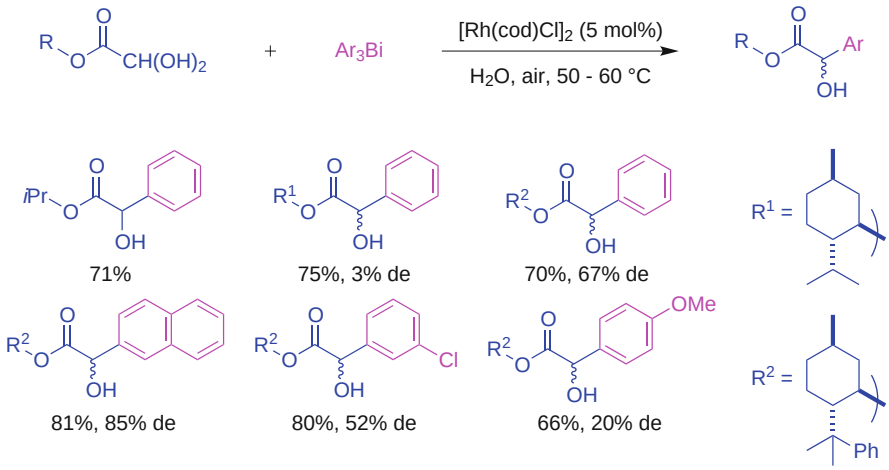



**Scheme 55** Enantioselective 1,4-additon reaction of enones with $Ar_3Bi$

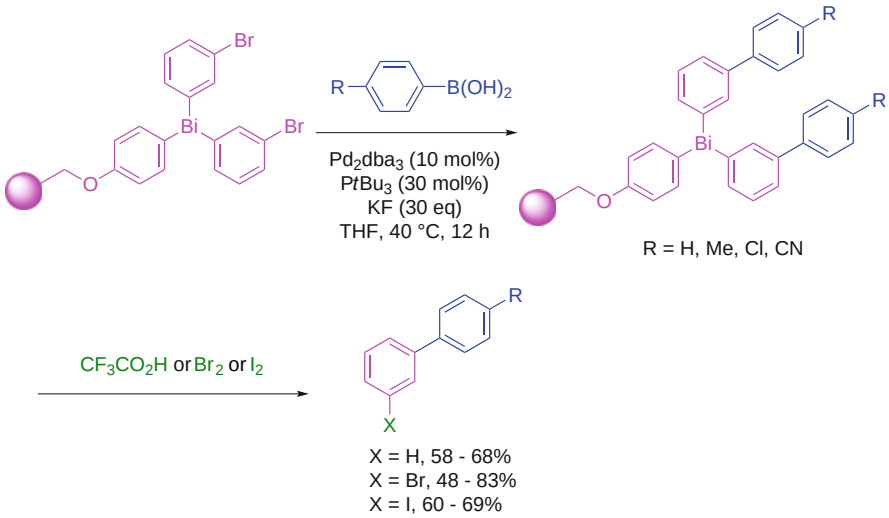
## 2.9 *Other C–C Bond Forming Reactions*

Glyoxylate hydrates reacted with $Ar_3Bi$ in the presence of a rhodium catalyst in water under air affording arylated products [71] (Scheme 56). Diastereoselective arylation was attained by using glyoxylates having chiral substituents. Solvents considerably influenced the diastereoselectivity, with water being superior to organic solvents such as THF and $CH_2Cl_2$.

Resin-bound triarylbismuth(III) reagents have been prepared for solid phase organic synthesis [72, 73]. As shown in Sect. 2.5, triarylbismuths are efficient




**Scheme 56** Arylation of glyoxylate hydrates with $Ar_3Bi$




**Scheme 57** Reaction of resin-bound triarylbismuth reagents

reagents for the Pd-catalyzed cross-coupling reaction with organic halides. However, selective Suzuki–Miyaura coupling between the resin-bound bromophenylbismuth reagent and arylboronic acids can take place under mild reaction conditions without the cleavage of the bismuth–carbon bonds (Scheme 57) [73]. Immobilization of triarylbismuth moiety on a resin successfully protected the bismuth–carbon bonds from the aryl transfer reaction. On the other hand, cleavage of the bismuth–carbon bonds in the resulting arylated triarylbismuths can be accomplished by the reaction with bromine, iodine, or trifluoroacetic acid to provide biaryls in moderate to good overall yields.

## 3 Conclusions

Organobismuth compounds are useful reagents for carbon–carbon bond forming reactions with transition-metal catalysis. The number of studies on this area have increased considerably during the last decade, as shown in this review, although they are still limited. The development of new synthetic procedures for a variety of organobismuth compounds would increase their usefulness as highly reactive reagents in organic synthesis.

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# Bismuth(III) Salts as Synthetic Tools in Organic Transformations

**J.S. Yadav, Aneesh Antony, and Basi V. Subba Reddy**

**Abstract** Bismuth is the heaviest stable element of the periodic table and even though it carries the status of heavy metal, it is rated as relatively nontoxic and noncarcinogenic unlike its neighboring elements. Additionally, the fact that it tolerates air and moisture makes the chemistry of bismuth attractive to synthetic chemists. The catalytic nature of this metal is attributed to the capability of its salts to acts as Lewis acids in reactions. The nontoxicity together with the ability to endure moisture makes bismuth compounds favorites of chemists and scientists who are concerned about environmental hazards, and such properties are highly desirable for scale-up of a method. The Lewis acidic nature of salts of this element have been thoroughly investigated in various types of reactions such as cycloaddition reactions, reactions of sugars, protection and deprotection reactions, synthesis of heterocyclic systems etc. Since the 1990s, various research groups have successfully utilized this catalytic nature for many organic transformations. Our group's contribution towards the development of methodologies that are useful in accomplishing various functional group manipulations by making use of the catalytic properties of bismuth salts is portrayed here. The mechanistic aspects and the catalytic efficiency of the bismuth(III) salts are accented together with the synthetic utility and the biological and pharmacological applications of the methodologies developed.

**Keywords** Bismuth(III) salts · Catalysis · Green chemistry · Lewis acidity · Moisture tolerance · Non-toxicity · Organic transformations

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# 1 Introduction

Bismuth, which has been known since ancient times, was often confused with lead and tin. Basilius Valentinus described some of its uses in 1450, but it was in 1753 that bismuth was shown by Claude François Geoffroy to be a distinct element. Bismuth occurs freely in nature and in such minerals as bismuthinite ($Bi_2S_3$), bismite ($Bi_2O_3$), and bismutite [$(BiO)_2CO_3$].

The word bismuth is derived from the German word *Weissmuth*, or white substance. It is the heaviest stable element of the periodic table. Even though it carries the status of heavy metal, this metal is rated as relatively nontoxic and noncarcinogenic, unlike its neighboring elements (in the periodic table) like arsenic, antimony, lead, and tin, which are highly toxic. This nontoxicity arises from the insolubility of its salts in neutral aqueous solutions such as biological fluids, which

confers to bismuth the enviable status of being an "ecofriendly" element likely to generate useful catalysts suitable for green chemistry. The wide scope of this peculiarity remained relatively unexplored until the early 1990s. Additionally, the fact that bismuth tolerates air and moisture makes the chemistry of bismuth one of the most evolving branches over the last two decades as far as its catalytic aspect is concerned. The catalytic nature of this metal is attributed to the capability of its salts to acts as Lewis acids in reactions. The nontoxicity together with the ability to endure moisture makes bismuth compounds favorites for most chemists and scientists who are concerned about environmental hazards.

Bismuth has an electron configuration of [Xe] $4f^{14}5d^{10}6s^{2}6p^{3}$, and it utilizes the three 6*p* electrons for bond formation (it exhibits an oxidation state of +5 in some of its organometal compounds). These bismuth(III) compounds show Lewis acidity due to the poor shielding by the 4*f* electrons. At first glance, its Lewis acid behavior might be somewhat surprising since compounds of some of the elements of group 15, such as phosphanes, are more commonly known for their Lewis base properties. In the case of bismuth, while relativistic effects are responsible for the stabilization of the 6*s* orbital (weak Lewis base), the Lewis acid behavior can be related to the tendency for the coordination around bismuth center to extend because of the availability of unoccupied orbitals. The Lewis acidity of these compounds increases with the presence of highly electronegative anions like chloride or triflate, and the catalytic aspects of these compounds becomes more influential when the expected product contains basic sites on which these Lewis acids can be trapped. Owing to this Lewis acidic nature and the capability of existing in two different oxidation states, bismuth one of the most interesting elements in the field of catalysis.

There have been many efforts made to highlight the synthetic value of this element and its compounds in the field of organic synthesis, and these have been published in reputed international journals [1–6]. In this chapter, we emphasize our group's work directed towards the development of newer methodologies utilizing the catalytic efficiency of bismuth(III) salts for functional group manipulations in organic synthesis. In this effort, the mechanistic aspects and the catalytic efficiency of the bismuth(III) salts are accented together with the synthetic utilities and the biological and pharmacological applications of the methodologies developed. The advantages of bismuth salts over the conventional methods are also discussed. The contents of this chapter are categorized into the following sections:

1. Reactions of aziridines and epoxides
2. Addition and condensation reactions
3. Cycloaddition reactions
4. Synthesis of heterocyclic systems
5. Reactions of sugars
6. Deprotection reactions
7. Reactions of quinones

## 2 Reactions of Aziridines and Epoxides

Epoxides and aziridines are two of the most versatile functional groups in organic chemistry due to their ready availability and ease of transformation into a wide variety of functional groups. These compounds are often used as starting materials and intermediates in organic synthesis due to the fact that they are well-known carbon electrophiles capable of reacting with various nucleophiles and of undergoing regioselective ring-opening reactions. They provide an easy access to 1,2-disubstituted organic moieties, most of which have medicinal or pharmaceutical value [7]. The nucleophilic opening of these epoxides has been studied extensively since it provides a suitable route to the formation of C–C, C–N, C–O, and C–S bonds, and there are several references for the opening of epoxides with alcohols, thiols, and amines [8–13].

### *2.1 Cross-Cyclization of Epoxides with Homoallylic Alcohols*

Cross-cyclization of epoxides with homoallylic amines is an easy way to access tetrahydropyran moieties, which form the core structure of many biologically important natural products such as avermectins, aplysiatoxin, oscillatoxins, latrunculins, talaromycins, acutiphycins, and apicularens. Even though many methods are available for the synthesis of this moiety [14–24], its importance and wide applicability demands further methods.

Styrene epoxide on reaction with 3-buten-1-ol in the presence of a catalytic amount of $BiCl_3$ gave two possible isomers, of which the *cis*-isomer was found to be the major one [25] (Fig. 1). The scope and versatility of the method is depicted in Table 1.

The formation of tetrahydropyrans with epoxides and homoallylic alcohols can be explained by the opening of epoxide ring with bismuth chloride followed by migration of hydrogen (in the case of, e.g., the first and second entries in Table 1) and aromatic group (in the case of, e.g., the third entry in Table 1) to generate the carbonium species, which after skeletal rearrangement to the cyclic tetrahydropyran carbonium species is attacked by the chloride nucleophile to give 4-chlorotetrahydropyran derivatives (Fig. 2).

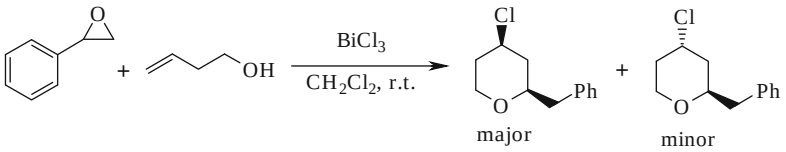
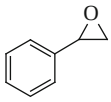
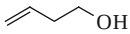
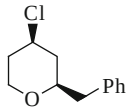
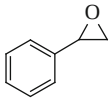
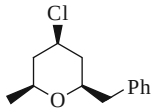
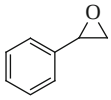
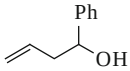
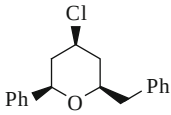
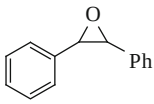
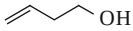
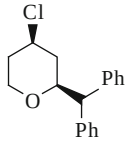
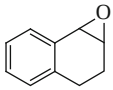
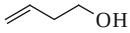
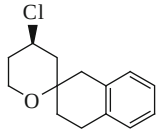



**Fig. 1** Reaction of styrene epoxide with 3-buten-1-ol

**Table 1** Cross-cyclization of epoxides with homoallylic alcohols

| Epoxide | Alcohol | Products | Yield (%) |
|---|---|---|---|
|  |  |  | 90 |
|  |  |  | 86 |
|  |  |  | 82 |
|  |  |  | 85 |
|  |  |  | 85 |

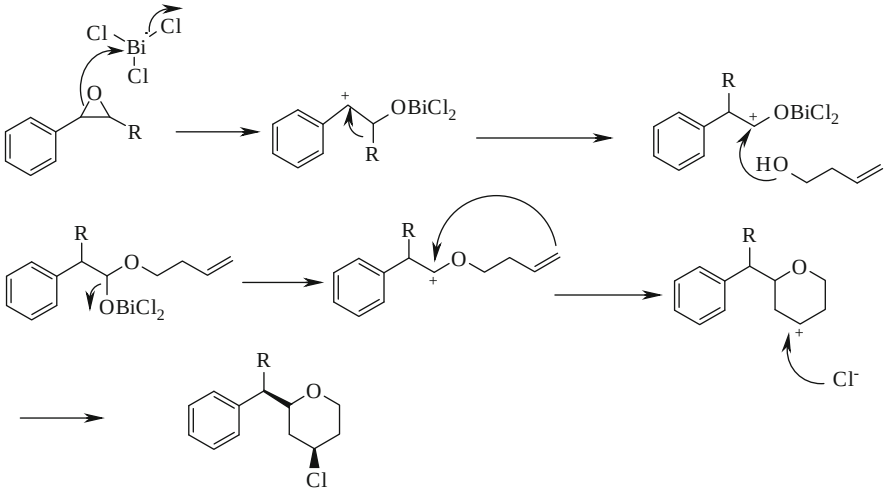



**Fig. 2** Mechanism for the formation of tetrahydropyran from epoxide and homoallylic alcohol

## 2.2 Aza-Prins Cyclization of Epoxides with Homoallylic Amines

Aza-Prins cyclization of epoxides with N-protected homoallylic amines furnishes substituted piperidines, making use of the catalytic efficiency of $BiCl_3$ [26]. Substituted piperidines are an important class of compounds and appear in many drugs and drug candidates. Compounds with the piperidine substructure exhibit antihypertensive, antibacterial, anticonvulsant, anti-inflammatory, and antiproliferative activities [27–29]. Many natural products having a piperidine moiety have been isolated and thus this moiety is an important building block for various biologically significant compounds [30, 31].

Stereoselective synthesis of *trans* 4-chloro-2-substituted piperidines can be achieved by the reaction of epoxides and N-protected homoallyllic amines using $BiCl_3$ as the Lewis acid catalyst (Fig. 3). This method furnishes very good generality with respect to various epoxides with a regioselectivity that favors the *trans*-2,4-diastereomer. Even though the N-protected homoallylic amines are very good substrates in this reaction, *N*-benzyl and *N*-allyl homoallyl amines fail to give this reaction. In this reaction, epoxides are always attacked on the less hindered carbon. The probable mechanism of this reaction is depicted in Fig. 4. The reaction is

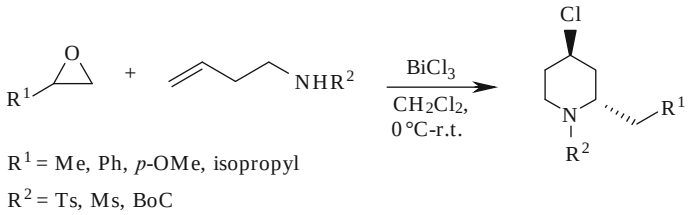



**Fig. 3** Aza-Prins cyclization of epoxides with N-protected homoallylic amines

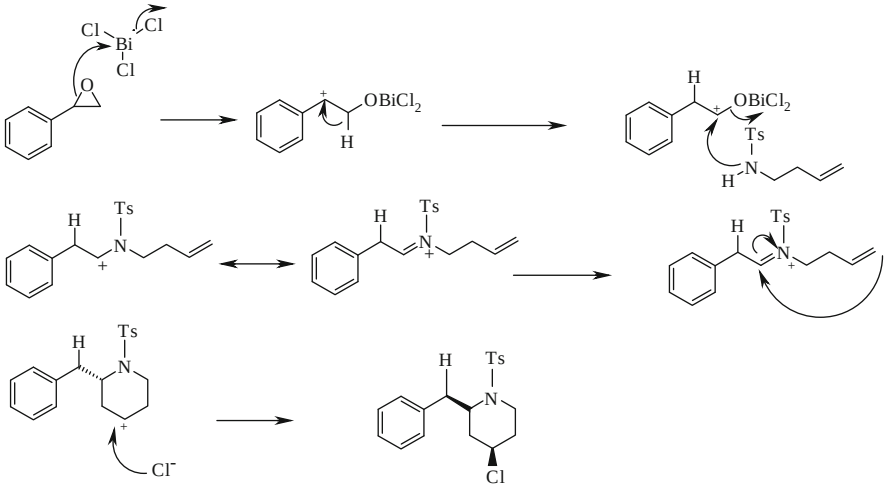



**Fig. 4** Mechanism of aza-Prins cyclization of epoxides with homoallylic amines

expected to proceed through iminium ion formation stabilized by adjacent sulfonyl or carbonyl functionalities.

## 2.3 Allylation of Epoxides and Aziridines

Stereoselective addition of allyl metal reagents to various functionalities is an important reaction in organic synthesis [32, 33]. The allylation of epoxides and aziridines with allyltin reagent is catalyzed by Lewis acids. Even though many Lewis acids have been reported to catalyze this reaction, $Bi(OTf)_3$ is distinct because it avoids the formation of byproducts and is also environmentally more compatible. It catalyzes the reaction of aryl epoxides with tetraallyltin to afford the corresponding homoallyllic alcohol [34].

Reaction of styrene oxide with tetraallyltin in the presence of $Bi(OTf)_3$ (2 mol%) affords the corresponding 1-phenyl-4-penten-2-ol (Fig. 5). In a similar fashion, various aryl substituted epoxides react smoothly with tetraallyltin to give the corresponding homoallylic alcohols. This method give generality as cycloalkyl oxiranes and sterically hindered ones give the corresponding homoallylic alcohols.

This method can successfully be extended to *N*-protected aziridines too. The reaction of aryl aziridines also proceeds smoothly with the allyl transfer occurring exclusively at the benzylic carbon to produce the corresponding γ-amino olefin (Fig. 6). The versatility of the method is illustrated by various examples in Table 2.

In all cases, the reactions proceeded with high selectivity. No regioisomers are detected and this clearly indicates that the oxiranes do not undergo cleavage with tetraallyltin under these reaction conditions. Initially, the epoxides undergo rearrangement in the presence of $Bi(OTf)_3$ to generate the corresponding aldehydes. This in situ-formed aldehyde reacts rapidly with tetraallyltin to afford the corresponding homoallylic alcohol.

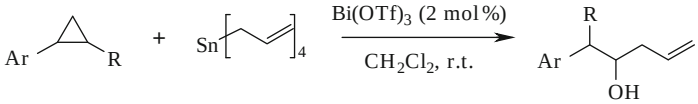



**Fig. 5** Allylation of epoxides with tetraallyltin

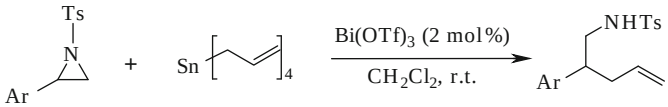
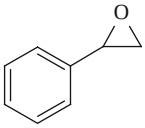
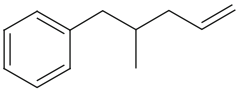
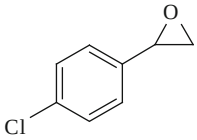
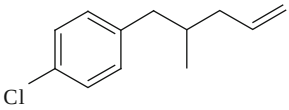
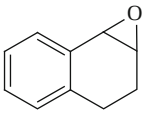
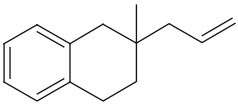
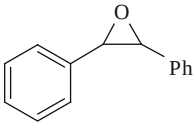
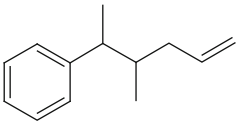
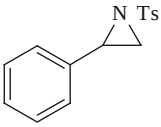
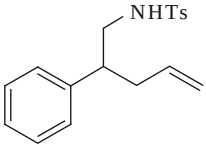
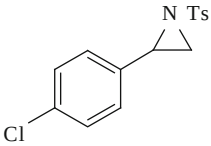
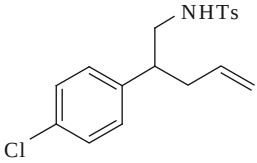



**Fig. 6** Allylation of N-protected aziridines with tetraallyltin

**Table 2** Allylation of epoxides and aziridines with tetrallyltin

| Epoxides/Aziridines | Product | Yield |
|---|---|---|
|  |  | 87 |
|  |  | 85 |
|  |  | 88 |
|  |  | 90 |
|  |  | 82 |
|  |  | 85 |

## 2.4 Hydrolysis of Epoxides and Aziridines

Various epoxides and aziridines undergo smooth ring opening with water in presence of bismuth triflate (10 mol%) to provide the corresponding *vic*-diols and β-amino alcohols with excellent regioselectivity [35]. Reaction of styrene oxide with water in the presence of $Bi(OTf)_3$ affords styrene 1,2-diols (Fig. 7). Similarly,

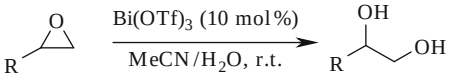



**Fig. 7** Hydrolysis of epoxides to furnish 1,2-diols

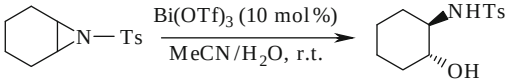



**Fig. 8** Hydrolysis of aziridines to produce 1,2-amino alcohols

various terminal as well as cyclic epoxides are good substrates under these conditions as in all cases the possible rearrangement of the epoxide does not happen.

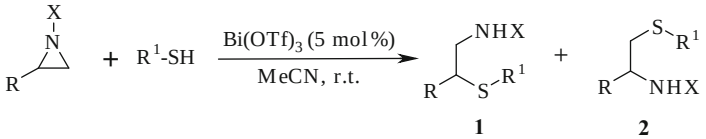
Likewise $Bi(OTf)_3$ catalyzes the reaction of aziridines to give the corresponding β-amino alcohols (Fig. 8). In the case of cycloalkyl aziridines, the stereochemistry of the ring-opened products was found to be *trans*. This method has some additional features of green aspects as it allows the recovery and re-usability of the catalyst.

## 2.5 *Thiolysis of Aziridines*

β-Aminosulfides, important building blocks for the synthesis of various bioactive molecules, can be prepared by the thiolysis of aziridines in the presence of $Bi(OTf)_3$ (5 mol%) [36]. Even though Lewis acids such as boron trifluoride etherate and zinc chloride, as well as Bronsted acids such as trifluoromethanesulfonic acid, have been employed as acid catalysts, these methods suffer from disadvantages like the use of stoichiometric amount of catalysts [37–40], harsh conditions, the use of large excess of thiols and necessitate anhydrous conditions to produce the desired products. Furthermore, these reagents cannot be recovered and recycled because they decompose or deactivate under quenching conditions.

The N-protected-2-aryl aziridines react smoothly with various thiols to afford the corresponding β-aminosulfides (Fig. 9). In the cleavage of *N*-benzyl- and *N*-tosyl-2-aryl aziridines, preferential cleavage is at the benzylic position of the aziridine ring, whereas *N*-tosyl-2-alkyl aziridines cleaves at the less hindered (terminal) aziridine-ring carbon.

Of course, the cleavage reactions of both 2-aryl- and 2-alkyl aziridines are stereoselective because only the *trans*-diastereomers of the corresponding regioisomers **1** and **2** are formed. In other words, 2-aryl substituted aziridines showed opposite regioselectivity to 2-alkyl aziridines. With bicyclic aziridines, exclusive formation of the *trans* diastereomer is observed in the case of symmetric bicyclic aziridines. Unsymmetrical aziridines such as styrene, octene, and undecene aziridines produce a minor amount of the other regioisomer.




R = phenyl, tolyl, hexyl, nonyl

$R^1$ = phenyl, tolyl *p*-anisyl, *n*-butyl, *p*-$ClC_6H_4$, *p*-$BrC_6H_4$

X = tosyl, benzyl

**Fig. 9** Reaction of N-protected 2-aryl or alkyl azides with thiols

## 3 Addition and Condensation Reactions

Lewis acid-catalyzed reactions can be observed anywhere in the field of organic chemistry. Most of these methodologies improved the available procedures for a particular transformation when it is reported. The quest for better methods for each and every transformation resulted in the evolution of many catalytic species. Likewise, the salts of bismuth also started to be exploited in this regard. In the perspective of addition and condensation reaction the contribution of this class of compounds has been very remarkable. There are a number of reports published showing that bismuth salts provide a useful alternative to many reactions like the Mannich reaction [41–43], Michael addition [44, 45], aldol reaction [46], Mukaiyama-aldol reactions [47, 48] etc. The advantage in using the catalytic aspects of bismuth lies in the fact that it poses comparatively lesser problems to the environment. Even though lanthanide triflates have comparable catalytic efficiency, their higher cost limits its usage in large scale preparations. Bismuth salts provide more attractive options owing to their lesser expense and higher reusability.

### *3.1 Conjugate Addition of Indole to* p-*Quinone*

The 3-indolylbenzoquinone fragment is a core structure in a number of biologically active natural products such as asterriquinones [49, 50]. The asterriquinones and demethylasterriquinones exhibit a wide spectrum of biological activities, including antitumor properties, and are inhibitors of HIV reverse transcriptase [51–53]. Asterriquinone A1 has been shown to stop the cell cycle in G1 and promote apoptotic cell death [54, 55]. Recently, asterriquinone has been reported to be an orally active non-peptidyl mimetic of insulin with antidiabetic activity [56]. The simplest and the most straightforward approach for the synthesis of indol-3-ylbenzoquinones involves the condensation of indoles with quinones under acidic conditions [57–59]. Being environmentally more compatible, the use of bismuth triflate, $Bi(OTf)_3$, is preferred and it efficiently furnishes the products at a highly catalytic quantity of 2 mol% [60] (Fig. 10). In the case of mono-substituted quinones, the indole regioselectively added to the quinones at the less hindered position.

The probable mechanism of the reaction is depicted in Fig. 11 and it seems to be the addition of the indole to the unsaturated position of the quinone that is activated

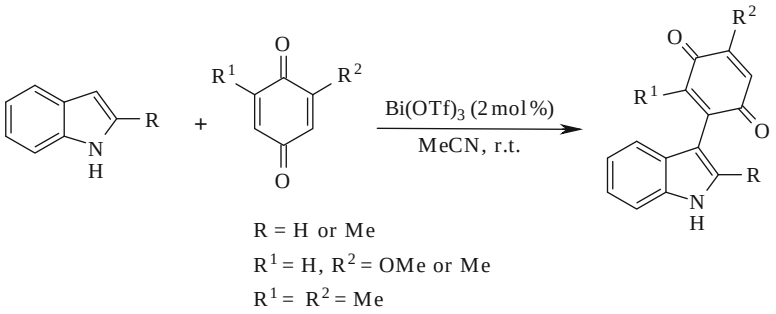



**Fig. 10** Conjugate addition of indoles to *p*-quinones

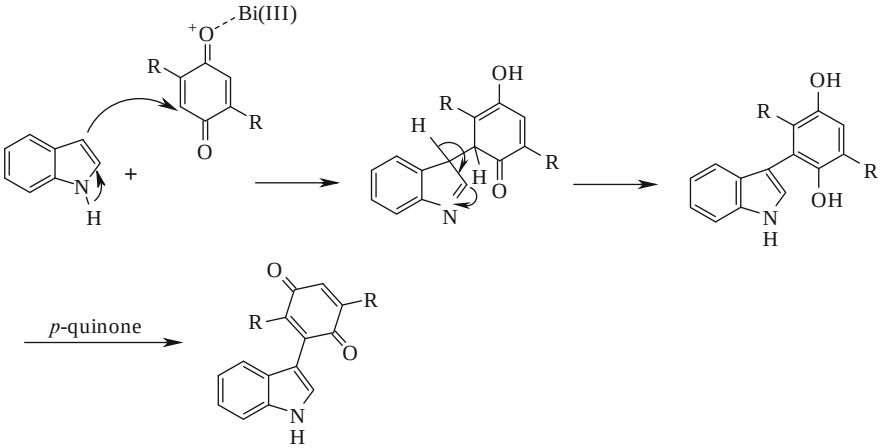



**Fig. 11** Mechanism of conjugate addition of indole to *p*-quinone

by bismuth triflate. The initial addition product tautomerizes to the hydroquinone, which subsequently undergoes rapid oxidation with another equivalent of *p*-quinone resulting in the formation of the indol-3-ylquinone.

## *3.2 Condensation of Isatin with Indole and Pyrrole*

3,3-Diaryl oxindoles are known to exhibit a wide range of biological activities such as antibacterial, antiprotozoal, and anti-inflammatory behavior [61–63]. Generally, 3,3-diaryl oxindoles are prepared by acid-catalyzed condensation of arenes with isatin [64–67]. $Bi(OTf)_3$ catalyzes the condensation of isatin with indoles and pyrroles to produce 3,3-diindolyl- and 3,3-dipyrrolyl oxindoles [68]. For example, reaction of indole with isatin in the presence of $Bi(OTf)_3$ (2 mol%) resulted in the formation of 3,3-di(3-indolyl)oxindole (Fig. 12). Substituted indoles such as

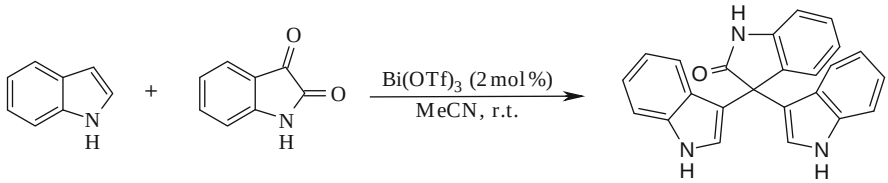



**Fig. 12** Reaction of indole with isatin to form 3,3-di(3-indolyl)oxindole

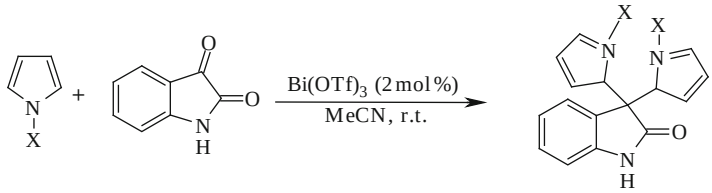



**Fig. 13** Reaction of pyrrole with isatin to form 3,3-di(2-pyrrolyl)oxindole

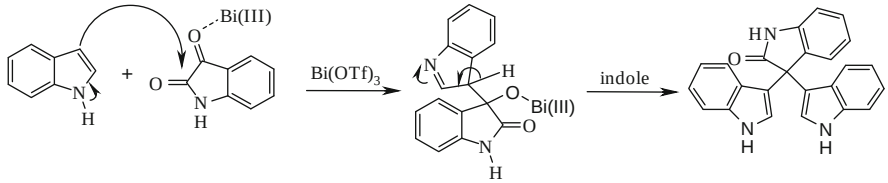



**Fig. 14** Mechanism of formation of 3,3-di(3-indolyl)oxindole

5-bromo, 5-methoxy, 7-ethyl, 2-methyl, and ethyl 2-carboxyindole afford the corresponding bisindolyl oxindoles.

This method was also effective for the preparation of *tert*-butyloxycarbonyl (Boc)-protected bis-indolyloxindole from the corresponding Boc-protected 2-methylindole without cleavage of the Boc group. Furthermore, pyrrole and *N*-methylpyrrole also react efficiently with isatin, under similar conditions, to afford 3,3-di(2-pyrrolyl) oxindole derivatives (Fig. 13).

The probable pathway of the reaction is shown in Fig. 14 and it seems to be an addition of the indole to the carbonyl group of isatin, followed by the condensation of a second indole moiety on the same carbon, resulting in the formation of 3,3-di (3-indolyl)oxindole.

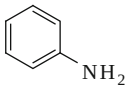
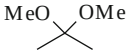
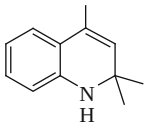
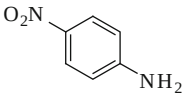
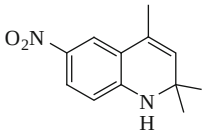
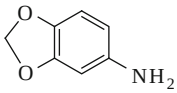
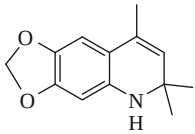
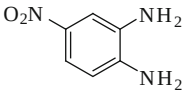
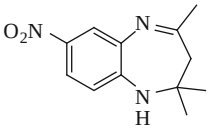
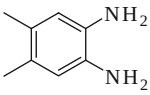
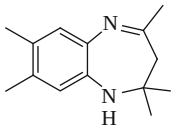
## *3.3 Condensation of 2,2-Dimethoxypropane with an Aromatic Amine*

1,2-Dihydroquinoline derivatives are known to exhibit a wide spectrum of biological activities such as antimalarial, antibacterial, and anti-inflammatory behavior [69–71]. In addition, substrates possessing the dihydroquinoline moiety

have been used as lipid peroxidation inhibitors, HMG-CoA reductase inhibitors, ileal bile acid transporter inhibitors, and progesterone agonists and antagonists [72]. Generally, 1,2-dihydroquinolines are prepared by the condensation of aromatic amines with ketones using a catalytic amount of $H_2SO_4$ via Skraup's procedure [73]. However, it requires high temperatures, high pressure, and long reaction times. Subsequently, various catalytic systems have been explored in search of improved efficiencies.

Bismuth triflate catalyzes the synthesis of 1,2-dihydroquinolines in an improved version of Skraup's procedure [74]. Accordingly, treatment of aniline with 2,2-dimethoxypropane (DMP) in the presence of $Bi(OTf)_3$ (5 mol%) in solvent-free conditions resulted in the formation of 2,2,4-trimethyl-1,2-dihydroquinoline. Various aromatic amines such as mono-, di- and tri-substituted anilines react efficiently with 2,2-DMP to give the corresponding 2,2,4-substituted dihydroquinolines. This method is equally effective for both electron-rich as well as electron-deficient aryl amines. Aromatic 1,2-diamines also condense smoothly under the same conditions with 2,2-DMP. The wide scope of this reaction is pointed out in Table 3 with respect to various aromatic amines.

**Table 3** Condensation of 2,2-dimethoxypropane with various aryl amines

| Aryl amine | DMP | Product | Yield |
|---|---|---|---|
|  |  |  | 90 |
|  | |  | 84 |
|  | |  | 83 |
|  | |  | 81 |
|  | |  | 87 |

# 4 Cycloaddition Reactions

Cycloaddition reactions are among the most important tools for synthesis in organic chemistry, since these reactions are vital to the synthesis of natural products and biologically imperative molecules. Cycloaddition reactions have been promoted by heat, light, Lewis acids, high pressure, or sonication. Metal Lewis acids play an increasingly important part in these reactions, often allowing several stereocenters to be selectively created and integrated in the target compounds. Of these metal catalysts, those of bismuth occupy a distinguished position, being more compatible with the environment.

## *4.1 Aza-Diels–Alder Reactions*

The aza-Diels–Alder reaction is one of the most powerful synthetic tools for constructing N-containing six-membered heterocycles [75, 76]. The aza-Diels–Alder reaction provides an easy access to quinoline derivatives, among which the pyrano/indeno quinolines attract much attention because they process a wide range of biological activities [77–79]. Bismuth(III) chloride catalyzes the aza-Diels–Alder reaction of *N*-aryl aldimines (generated in situ from aromatic aldehydes and anilines) with various olefins such as 3,4-dihydro-2*H*-pyran, cyclohexenone, ethylvinyl ether, and indene, to afford the corresponding quinoline derivatives [80]. Benzylideneanilines, on reaction with 3,4-dihydro-2*H*-pyran in the presence of a catalytic amount of $BiCl_3$ (10 mol%), afford the corresponding pyrano [3,2-c] quinolines as a mixture of *cis* and *trans* isomers whereas the reaction with indene furnishes only the *trans* isomer (Fig. 15).

## *4.2 Intramolecular Hetero-Diels–Alder Reactions*

Intramolecular cycloaddition reactions with high regio- and stereocontrol are important tools for the efficient assembly of complex molecular structures [76, 81, 82]. This strategy has been successfully applied to the synthesis of tetrahydroquinoline derivatives [83–89]. These compounds are an important class of natural products and are endowed with a wide spectrum of interesting biological activities [70, 90]. The high potential of these derivatives in a range of biological applications [77, 91] makes them inviting targets for synthesis. $BiCl_3$ catalyzes the highly efficient and stereoselective [4+2] cycloaddition reactions of anilines with the *O*-allyl derivative of the sugar-derived aldehyde from D-glucose [92] (Fig. 16). Of the two isomers of quinoline derivative thus formed, the *trans* isomer is found to be the major one. When a bulky group such as *tert*-butyl is present *ortho* to the amine the *trans* diastereomer is formed exclusively. The possible pathway of the

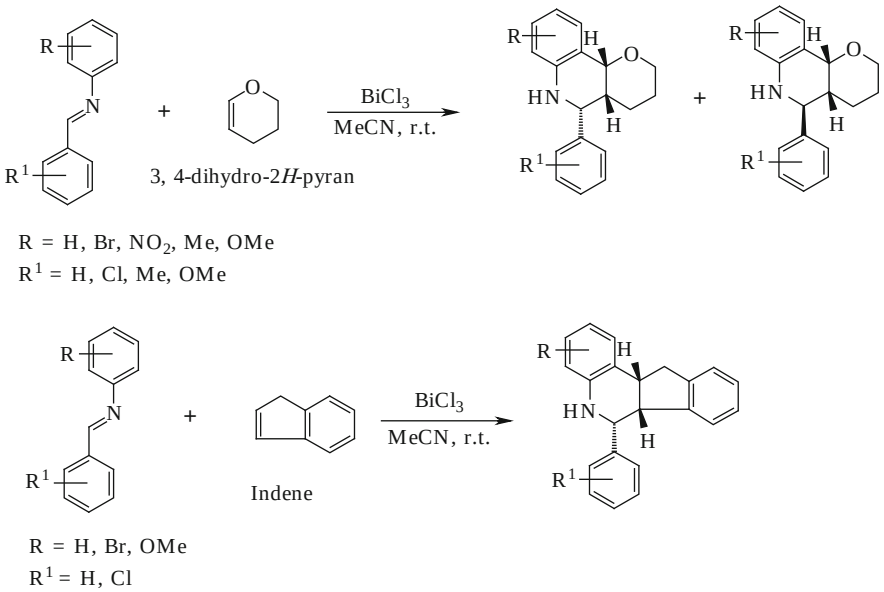



**Fig. 15** Aza-Diels–Alder reaction of benzylidine anilines with olefins

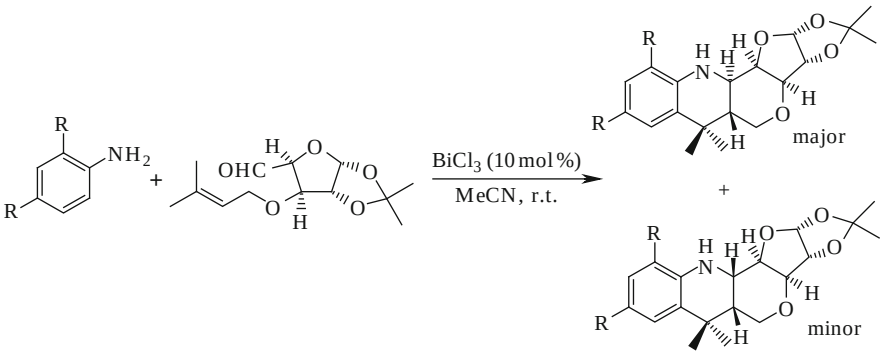



**Fig. 16** Cycloaddition reaction of *O*-allyl derivative of D-glucose derives aldehyde with aniline

reaction may proceed through an in situ generation of the imine followed by an intramolecular [4+2] cycloaddition reaction to afford the products. Although Lewis acids such as $ZnCl_2$, $FeCl_3$, $ZrCl_4$, $AlCl_3$, and $BF_3{\cdot}OEt_2$ have been found to promote the intramolecular hetero Diels–Alder reaction, more than stoichiometric amounts of acids are required and eventually result in some decomposition. The reaction takes a long time with only moderate yields. On the other hand, $BiCl_3$-catalyzed reactions overcome the aforementioned drawbacks and are therefore more effective.

A similar strategy can also be applied for the analogous synthesis of naphthyridine derivatives [93]. Here *N*-allyl derivatives of *o*-aminobenzaldehyde,

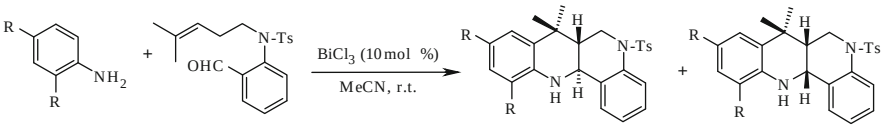



**Fig. 17** Cycloaddition reaction of *N*-allyl derivative of *o*-aminobenzaldehyde with aniline

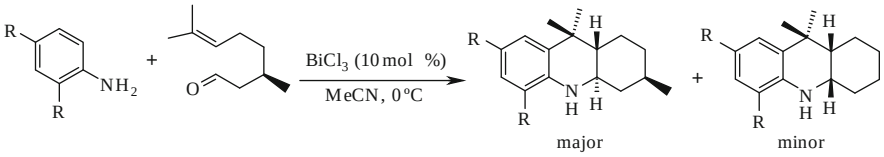



**Fig. 18** Cycloaddition reaction of citronellal with aniline

containing an electron-rich olefin substituent were used instead of *O*-allyl derivatives of the sugar-derived aldehydes (Fig. 17). But, the major difference of this method from the former one (reaction of *O*-allyl derivatives of sugar derived aldehydes) is that it lacks selectivity as the latter (reaction of *N*-allyl derivatives of *o*-aminobenzaldehyde)furnishes two possible isomers in a 1:1 ratio.

Octahydroacridine, an important pharmacophore, can be synthesized through $BiCl_3$-catalyzed cycloaddition reaction [94]. Owing to the importance of these compounds, many synthetic methods have been reported for the preparation of the octahydroacridine skeleton, such as catalytic hydrogenation of acridines, amino-Claisen rearrangement of geranyl aniline, Beckmann rearrangement of oxime sulfonates, and acid-catalyzed condensation of aniline with isophorone. The intramolecular hetero-Diels–Alder reaction of *N*-arylimines with non-activated olefins tethered to the diene system is the most powerful synthetic tool for constructing nitrogen heterocyclic compounds. For this transformation, a variety of strong Lewis or Brönsted acids can be used. However, these methods have drawbacks like the use of harsh conditions, longer reaction times, non-availability of raw materials, and the requirement of low temperatures (−78 °C), especially due to the lack of stereocontrol of the ring fusion. $BiCl_3$ catalyzes the reaction of citronellal with amines, providing a useful alternative to the available methods (Fig. 18). This method is highly diastereoselective as it favors the *trans* isomer.

## 5 Synthesis of Heterocyclic Systems

The synthesis of heterocyclic compounds is as important as the synthesis of natural products, because there exists hardly a single biologically active natural product without a heterocyclic ring in it. In this regard, bismuth salts, being catalytically highly efficient Lewis acids, contribute heavily to the synthesis of newer moieties and also to improving the existing methods.

## 5.1 Synthesis of Tetrahydropyran Derivatives

Tetrahydropyrans constitute key structural motifs of a large number of biologically active molecules. They are found in a number of natural products such as avermectins, aplysiatoxins, oscillatoxins, latrunculins, talaromycins, and acutiphycins [95–100]. Generally, tetrahydropyran derivatives are synthesized by Prins cyclization reactions using Lewis acid catalysis [18, 101–109]. The acid-catalyzed olefin–aldehyde condensation is known as the Prins reaction. Recently, $InCl_3$ and $Sc(OTf)_3$ have also been found to be effective for this transformation [19, 101, 102]. However, many of these procedures often involve stoichiometric amount of catalysts, long reaction times, expensive reagents and also produce a mixture of products while bismuth salts catalyze these reactions without most of these drawbacks.

### 5.1.1 Synthesis of 4-Amidotetrahydropyran Derivatives

The 4-aminotetrahydropyran ring system is found in many biologically active natural products, such as ambruticins, oligomers of glucoamino acids, sialic acid, and desyherbaine [110]. Bismuth(III) triflate is found to be an effective Lewis acid in catalyzing the three-component reaction of homoallylic alcohols, carbonyl compounds, and nitriles via the Prins–Ritter sequence to furnish 4-amidotetrahydropyrans with *cis* selectivity [111]. 3-Phenylpropanal, on reaction with but-3-en-1-ol in the presence of $Bi(OTf)_3$ (10 mol%), furnishes *cis*-4-acetamido tetrahydropyran (Fig. 19). This reaction proceeds well even with cyclic ketones such as cyclopentanone or cyclohexanone to give spirocyclic-4-acetamidotetrahydropyran. The versatility of the reaction is demonstrated in Table 4 with respect to various homoallylic alcohols, carbonyl compounds, and nitriles.

The formation of the products could be explained by hemiacetal formation followed by Prins cyclization and subsequent Ritter amidation. A tentative reaction mechanism to realize the *cis* selectivity is given in Fig. 20 and could be explained by assuming the formation of an (*E*)-oxocarbenium ion via a chair-like transition state, which has an increased stability relative to the open oxocarbenium ion owing to electron delocalization. The optimal geometry for this delocalization places the hydrogen atom at C4 in a pseudoaxial position, which favors equatorial attack of the nucleophiles.

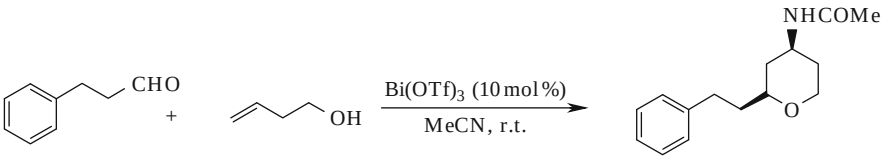
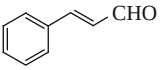
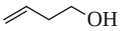
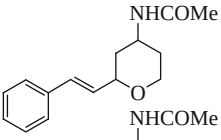
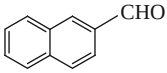
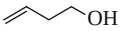
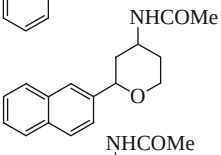
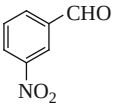
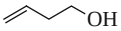
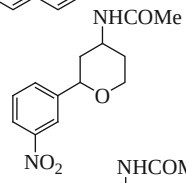
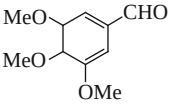
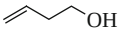
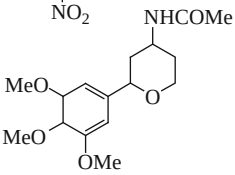
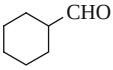
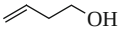
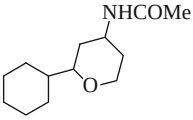
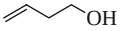
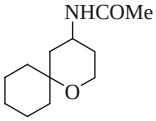
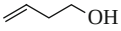
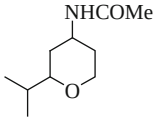
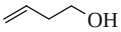
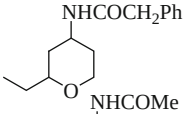
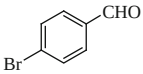
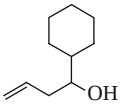
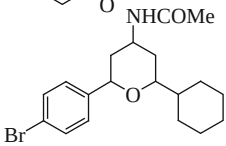



**Fig. 19** Reaction of 3-phenylpropanal with 3-buten-1-ol to form *cis*-4-acetamido tetrahydropyran

**Table 4** Synthesis of 4-acetamido tetrahydropyran

| Carbonyl Compound | Homoallyl alcohol | Nucleophile | Products | Yield (%) |
|---|---|---|---|---|
|  |  | $CH_3CN$ |  | 88 |
|  |  | " |  | 87 |
|  |  | " |  | 80 |
|  |  | " |  | 82 |
|  |  | " |  | 90 |
| |  | " |  | 88 |
| |  | " |  | 91 |
| |  | $PhCH_2CN$ |  | 86 |
|  |  | MeCN |  | 90 |

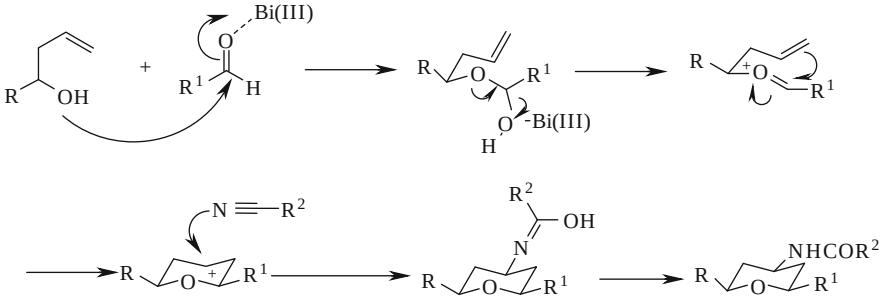



**Fig. 20** Mechanism of formation of 4-acetamido tetrahydropyran

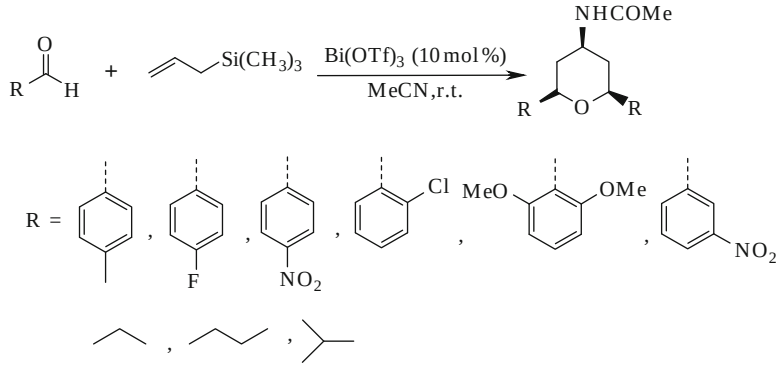



**Fig. 21** Synthesis of 4-acetamido tetrahydropyran by using allyltrimethyl silane

A diastereoselective synthesis of 4-amidotetrahydropyrans can also be achieved through a single-step Sakurai–Prins–Ritter reaction sequence in a domino fashion by the reaction of an aldehyde and allyltrimethylsilane in acetonitrile using Bi $(OTf)_3$ (10 mol%) as catalyst [112] (Fig. 21). The rate at which they react is better for aliphatic aldehydes, whereas aromatic aldehydes react sluggishly. Among these, aromatic aldehydes containing electron-withdrawing groups gave higher yields of products compared to those having electron-donating groups on the ring.

### 5.1.2 Synthesis of 4-Tetrahydropyranol Derivatives

Tetrahydropyrans hydroxylated at the 4-position have good synthetic value [113]. Although many synthetic methods have been reported [17–23, 114, 115], the search for potential alternate approaches and the development of eco-friendly and high-yielding reactions resulted in the development of a method that poses less problems for the environment. Synthesis of tetrahydropyranol derivatives can be achieved through the Prins-type cyclization reaction of homoallylic alcohols with aldehydes using bismuth triflate as catalyst in [bmim]$PF_6$ solvent system [108] (Fig. 22).

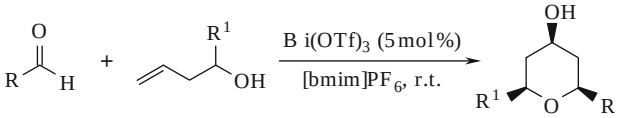



**Fig. 22** Synthesis of 4-tetrahydropyranol

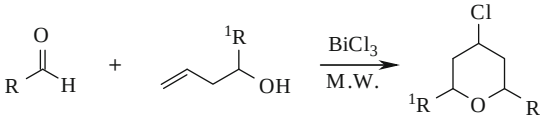



**Fig. 23** Synthesis of 4-chlorotetrahydropyran; *M.W.* microwave irradiation

The nature of the aldehydes shows some effect on the reaction. Aliphatic, aromatic, and moderately activated aldehydes such as chloro and methyl gave high yields of products when compared with deactivated aldehydes such as nitro-substituted ones.

### 5.1.3 Synthesis of 4-Chlorotetrahydropyran Derivatives

The cross-coupling reaction of homoallylic alcohols with aldehydes in the presence of bismuth trichloride in solvent-free conditions under microwave irradiation generated 4-chloro-2,6-disubstituted tetrahydropyrans with high *cis*-diastereoselectivity [15]. The reaction of benzaldehyde with 1-phenyl-3-buten-1-ol in the presence of bismuth trichloride under microwave irradiation gave the corresponding 2,6-diphenyl-4-chlorotetrahydropyran (Fig. 23).

The coupling reaction of aromatic aldehydes with their corresponding homoallylic alcohols in the presence of $BiCl_3$ gave symmetric 2,6-disubstituted-4-halotetrahydropyrans. The present method also avoids the use of anhydrous conditions or harmful organic solvents. Furthermore, the cross-coupling reaction between aromatic homoallylic alcohols and aliphatic aldehydes or the cross coupling between aliphatic homoallylic alcohols and aromatic aldehydes gave the corresponding unsymmetrical chloropyrans. Aliphatic, aromatic and moderately activated aldehydes like chloro, bromo, and *meta*-phenoxy benzaldehydes gave high yields of products compared to strongly deactivated nitro- or cyano-substituted aldehydes.

## *5.2 Synthesis of Benzopyran Derivatives*

The stereoselective synthesis of *cis*-fused pyrano and furanobenzopyran can be achieved through the one-pot three-component reaction of *o*-hydroxy benzaldehyde, aromatic amines, and cyclic enolethers in the presence of catalytic amounts of $Bi(OTf)_3$ (10 mol%) in air and the moisture-stable ionic liquid $[bmim]PF_6$ [116]. The reaction of salicilaldehyde, aniline and 2,3-dihydrofuran furnishes the *cis*-fused furanochroman. In a similar fashion, various substituted salicilaldehydes and

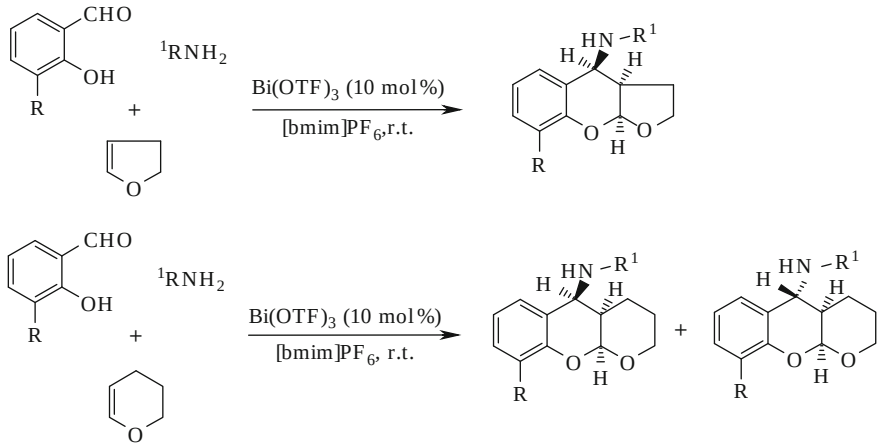



**Fig. 24** Synthesis of *cis*-fused pyano- and furanobenzopyran

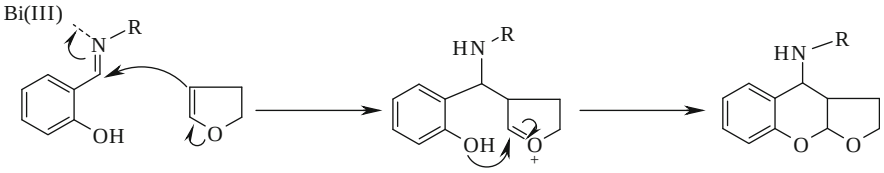



**Fig. 25** Mechanism of formation of furanobenzopyran

anilines undergo this reaction smoothly. Similar reaction with 3,4-dihydropyran furnishes both *cis* and *trans* isomers, of which *cis* is the major product. The biological importance of 4-aminobenzopyrans as modulators in potassium channels, and for their antihypertensive activity and anti-ischemic activity brings attraction to this method (Fig. 24).

The plausible mechanism of the reaction is shown in Fig. 25. The reaction probably proceeds through the activation of imine (formed in situ from the *o*-hydroxy benzaldehyde and the aromatic amine) by the catalyst followed by the addition and subsequent cyclization of the enol ether, resulting in the formation of the fused acetal. Ionic liquids are stable enough with amines and water and also effectively activate the imines to undergo cyclization. The recovered ionic liquid can be re-used with gradual decrease in the efficiency of the method. The hydrophobic nature of the ionic liquid also helps in recovery of the catalyst.

## 5.3 *Synthesis of* cis-*Aziridine Carboxylates*

Aziridines are well-known carbon electrophiles capable of reacting with various nucleophiles, and their ability to undergo regioselective ring-opening reactions

contributes largely to their synthetic value. The nucleophilic ring opening of aziridine carboxylates leads to many biologically active compounds such as α,β-unsaturated amino esters, β-lactam antibiotics, and alkaloids. As a result, a large number of methods have been reported for the preparation of aziridines. Among these methods, the nucleophilic addition of ethyl diazoacetate to imines is one of the most versatile synthetic approaches for their synthesis. Typically, copper salts are employed to promote the addition reactions of ethyl diazoacetate to imines to produce aziridine carboxylates. Although diazocarbonyl reactions are typically catalyzed by transition metal salts, new catalytic systems are being continuously explored in search of improved efficiencies and cost effectiveness. In this context, Lewis acids such as $CH_3ReO_3$, $BF_3{\cdot}OEt_2$, $InCl_3$, $Zn(OTf)_2$, and $Yb(OTf)_3$ are reported for the addition of ethyl diazoacetate to imines. In most cases, the products are obtained as a mixture of *cis*- and *trans*-aziridines, but the yields and selectivities reported are far from satisfactory. Furthermore, many of these reactions cannot be carried out in a one-pot operation with an aldehyde, amine, and ethyl diazoacetate because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids. In order to circumvent some of the problems associated with these methods, one-pot procedures have been developed for this conversion using lanthanide triflate as a novel catalyst. Being inexpensive, and owing to its unique catalytic efficiency, $Bi(OTf)_3$ can replace the former without any decrease in the efficiency of the method. Synthesis of *cis*-aziridine carboxylates can be achieved through the one-pot coupling of aldehydes, amines, and ethyl diazoacetate in ionic liquid in the presence of a catalytic amount of $Bi(OTf)_3$ [114] (Fig. 26).

Both aryl and alkyl imines react well to furnish the product. The scope of this reaction is depicted in Table 5. The reaction proceeds smoothly not only in ionic

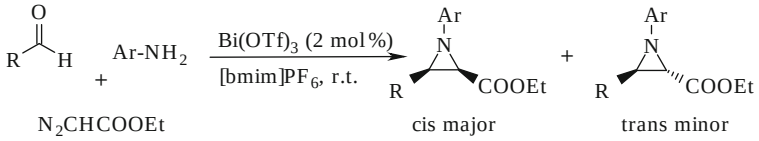
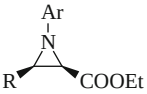



**Fig. 26** Synthesis of *cis*-aziridine carboxylates

**Table 5** Synthesis of *cis*-aziridine carboxylate through the three-component coupling of aldehyde and amine with ethyl diazoacetate

| RCHO | Ar-$NH_2$ |  | Yield (%) |
|---|---|---|---|
| PhCHO | $PhNH_2$ | R = Ph, Ar = Ph | 87 |
| *p*-ClPhCHO | *p*-ClPhCHO | R = *p*-ClPh, Ar = *p*-ClPh | 90 |
| *p*-MePhCHO | *p*-ClPhCHO | R = *p*-MePh, Ar = *p*-ClPh | 91 |
| *p*-MeOPhCHO | $PhNH_2$ | R = *p*-MeOPh, Ar = Ph | 82 |
| *t*-$C_4H_9$CHO | $PhNH_2$ | R = *t*-$C_4H_9$, Ar = Ph | 82 |
| $C_5H_{11}$CHO | *p*-ClPhCHO | R = Ph, Ar = *p*-ClPh | 75 |

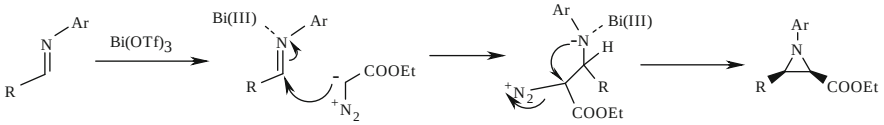



**Fig. 27** Mechanism of formation of *cis*-aziridine carboxylate

liquids but also in common organic solvents such as dichloromethane and acetonitrile. In most cases, the formation of the aziridines is accompanied by the corresponding enamine as side product when the reaction is performed in dichloromethane or acetonitrile using bismuth(III) triflate (2 mol%). This byproduct is due to 1,2-migration of either the R′ substituent or H to the incipient carbocation (Fig. 27).

However, the formation of enamine can be remarkably reduced by performing the reaction in ionic liquids at room temperature. Furthermore, ionic liquids give better *cis*-selectivity than organic solvents. The reaction probably proceeds through the activation of imine by complexation with bismuth(III) ion followed by nucleophilic addition of ethylenediamine (EDA) on the C=N double bond and subsequent ring closure with loss of $N_2$, resulting in the formation of aziridines. It is noteworthy that the product has survived under acidic environment and does not yield any side products arising from aziridine cleavage. Also, no carbene self-coupling product (diethyl maleate) was detected under the reaction conditions. The ionic liquid containing the catalyst can be recovered and recycled in subsequent reactions with gradual decrease in activity.

## *5.4 Friedländer Hetero-Annulation for the Synthesis of Quinoline Derivatives*

Quinolines possess a wide spectrum of biological activities such as antimalarial, antibacterial, anti-asthmatic, antihypertensive, and anti-inflammatory. Aryl-substituted quinolines are found to exhibit platelet-derived growth factor receptor tyrosine kinase (PDGF-RTK) inhibiting properties. In addition to medicinal applications, polyquinolines derived from quinolines undergo hierarchical self-assembly into a variety of nanostructures and mesostructures with enhanced electronic and photonic functions. Consequently, various approaches such as the Skraup, Doebner–von Miller, Friedländer, and Combes methods have been developed for the preparation of quinoline derivatives. Among them, the Friedländer annulation is one of the most simple and straightforward approaches for the synthesis of polysubstituted quinolines. Friedländer reactions are generally carried out either by refluxing an aqueous or alcoholic solution of reactants in the presence of base or by heating a mixture of the reactants at high temperatures ranging from 150–220 °C in the absence of catalyst. Under thermal or base catalysis conditions, *o*-aminobenzophenone fails to react with simple ketones such as cyclohexanone, deoxybenzoin,

and β-keto esters. Subsequent work showed that acid catalysts are more effective than base catalysts for the Friedländer annulation. Acid catalysts such as hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid (*p*-TSA), and phosphoric acids are widely used for this conversion. However, many of these traditional methods require high temperatures, prolonged reaction times, and drastic conditions and the yields reported are far from satisfactory due to the occurrence of several side reactions. Therefore, new catalytic systems are being continuously explored in search of improved efficiencies and cost effectiveness. As a result, Lewis acids such as $ZnCl_2$ and $AuCl_3{\cdot}3H_2O$ were found to be effective for this conversion. Owing to its unique catalytic properties, bismuth(III) triflate furnishes a better method in this context.

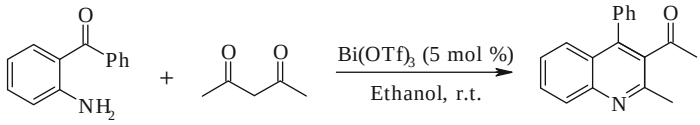
Reaction of 2-aminobenzophenone with acetyl acetone in the presence of $Bi(OTf)_3$ (5 mol%) results in the formation of 3-acetyl-2-methyl-4-phenylquinoline [117]. Various 1,3-diketones, acyclic ketones and cyclic ketone undergo the condensation with 2-aminoaryl ketones. The scope and generality of this process is illustrated with respect to various 2-aminoaryl ketones and a wide array of α-methylene ketones, and the results are summarized in Table 6. This method is free from side reactions such as the self-condensation of ketones, which is normally observed under basic conditions. Unlike reported methods, the present protocol does not require high temperature or drastic conditions to produce quinoline derivatives.

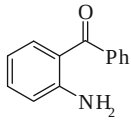
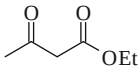
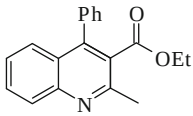
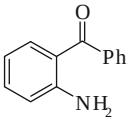
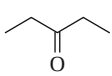
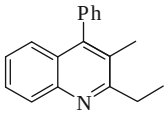
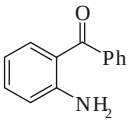
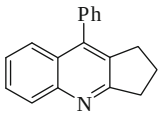
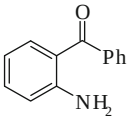
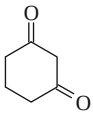
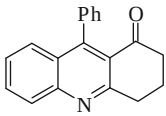
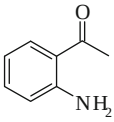
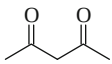
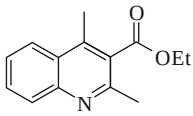
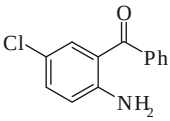
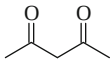
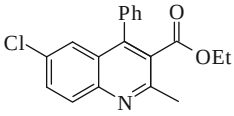
## *5.5 Synthesis of Furan, Pyrrole, and Thiophene Derivatives*

Heterocycles such as furan, pyrrole, and thiophene are versatile pharmacophores possessing a range of biological activities. In particular, pyrroles are found in many naturally occurring compounds such as heme, chlorophyll, and vitamin $B_{12}$. Therefore, many synthetic methods for the preparation of pyrrole derivatives have been reported in the literature. Among them, the Paal–Knorr reaction remains one of the most attractive methods for the synthesis of pyrroles. The furan moiety is a core structure of many alkaloids such as kallolides and cembranolides. The thiophene moiety also exists in many biologically active compounds. Thus, syntheses of these heterocycles are of great importance. Generally, furan, pyrrole, and thiophene derivatives are prepared from 1,4-dicarbonyl compounds using acid catalysts. Strong acids such as concentrated $H_2SO_4$, $P_2O_5$, *p*-TSA and montmorillonite KSF; basic reagents including TsCl/DBU, alumina, and zirconium phosphate/zirconium sulfophenyl phosphate; and microwave irradiation have all been employed for their synthesis. However, the synthesis of pyrroles and furans remains a challenge for synthetic chemists because of their sensitivity to acids. Bismuth triflate (5 mol%) immobilized in air and moisture-stable $[bmim]BF_4$ provide a useful and effective alternative for the synthesis of furan derivatives from 1,4-diketones [118] (Fig. 28).

1,4-Diketones can be used as the common precursor for the synthesis of furan, pyrrole, and thiophenes. The treatment of 1,4-diketones with aryl amines under similar conditions results in the formation of the corresponding pyrrole derivatives.

**Table 6** Friedländer annulation




| 2-aminoketone | Ketone | Quinoline | Yield (%) |
|---|---|---|---|
|  |  |  | 86 |
|  |  |  | 80 |
|  | |  | 90 |
|  |  |  | 81 |
|  |  |  | 82 |
|  |  |  | 80 |

In addition, 1,4-diketones react efficiently with Lawesson's reagent under similar reaction conditions to give trisubstituted thiophene derivatives. The scope of this reaction is depicted in Table 7.

The ionic liquid containing the catalyst can be recovered and recycled in subsequent reactions with only a gradual decrease in activity. The reactions proceed smoothly not only in ionic liquids but also in refluxing toluene in the presence of Bi

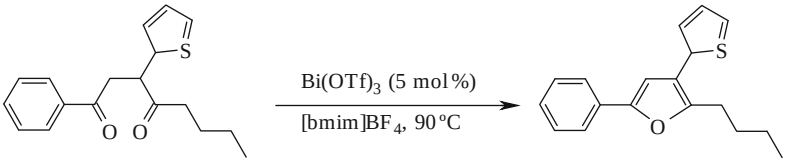
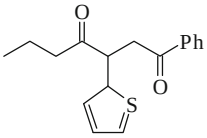
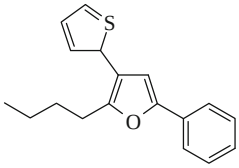
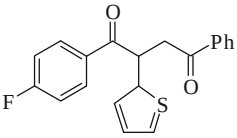
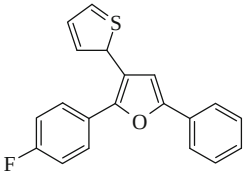
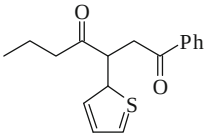
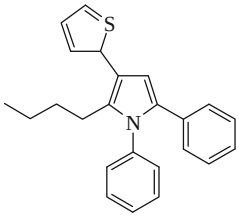
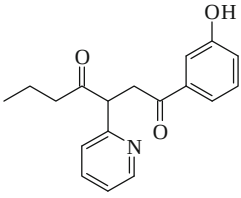
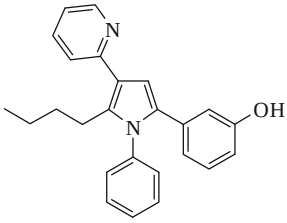
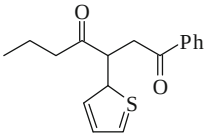
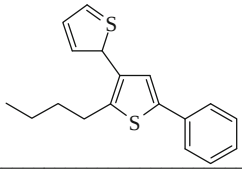



**Fig. 28** Synthesis of furan derivative from 1,4-diketones

**Table 7** Synthesis of furan, pyrrole, and thiophene derivatives

| 1,4-diketone | Product | Yield (%) |
|---|---|---|
|  |  | 85 |
|  |  | 80 |
|  |  | 83 |
|  |  | 85 |
|  |  | 80 |

$(OTf)_3$ (5 mol%). The use of bismuth triflate/[bmim]$BF_4$ is the ideal catalytic system for these condensations because the recovery and reuse of bismuth triflate is especially easy in ionic liquids compared to toluene.

### *5.6 Synthesis of Benzimidazole Derivatives*

Benzimidazoles are important biologically active heterocycles possessing selective neuropeptide YY1 receptor antagonists and 5-lipoxygenase inhibitors for use as novel anti-allergic agents, 5-HT3 antagonists in isolated guinea pig ileum, poly (ADP-ribose) polymerase (PARP) inhibitors, and factor Xa (Fxa) inhibitors. In addition, they exhibit significant activity against several viruses, such as HIV, herpes (HSV-1), RNA influenza, and human cytomegalovirus (HCMV). Benzimidazole derivatives have found commercial applications in veterinarian medicine as antihelmintic agents and in diverse human therapeutic areas, such as treatment of ulcers and as antihistamines. Medicinal chemists would certainly classify benzimidazoles as privileged substructures for drug design, as they display affinity towards a variety of enzymes and protein receptors.

A variety of methods have been developed for the preparation of substituted benzimidazoles. Of these, one of the most traditional methods involves the condensation of an *o*-phenylenediamine with carboxylic acid or its derivatives. Subsequently, several improved protocols have been developed for the synthesis of benzimidazoles via the condensation of *o*-phenylenediamines with aldehydes in the presence of acid catalysts under various reaction conditions. However, many of these methods suffer from certain drawbacks, including longer reaction times, unsatisfactory yields, harsh reaction conditions, expensive reagents, tedious work-up procedures, co-occurrence of several side reactions, and poor selectivity. Bismuth triflate provides a handy alternative to the conventional methods. It catalyzes the reaction of mono- and disubstituted aryl 1,2-diamines with aromatic aldehydes bearing either electron-rich or electron-deficient substituents on the aromatic ring in the presence of $Bi(OTf)_3$ (10 mol%) in water, resulting in the formation of benzimidazole [119] (Fig. 29). Furthermore, the reaction also works well with heteroaromatic aldehydes.

Since a water solution of $Bi(OTf)_3$ is acidic, it may be possible that the true catalyst is TfOH produced from the hydrolysis of $Bi(OTf)_3$. However, TfOH is not as effective as $Bi(OTf)_3$ in catalyzing this reaction (10% TfOH at 25 °C, 3 h, 65%), thus suggesting that a Lewis acid is probably involved in activating the aldehyde. Furthermore, the recovered aqueous solution of $Bi(OTf)_3$ could be reused in further reactions with gradual decrease in activity.

## 6 Reactions of Sugars

The chemistry of sugars is an important branch in the field of organic research as they are persuasive biological tools and potential therapeutics. The biological value of this class of compounds has made this field one of the favorites of researchers. In

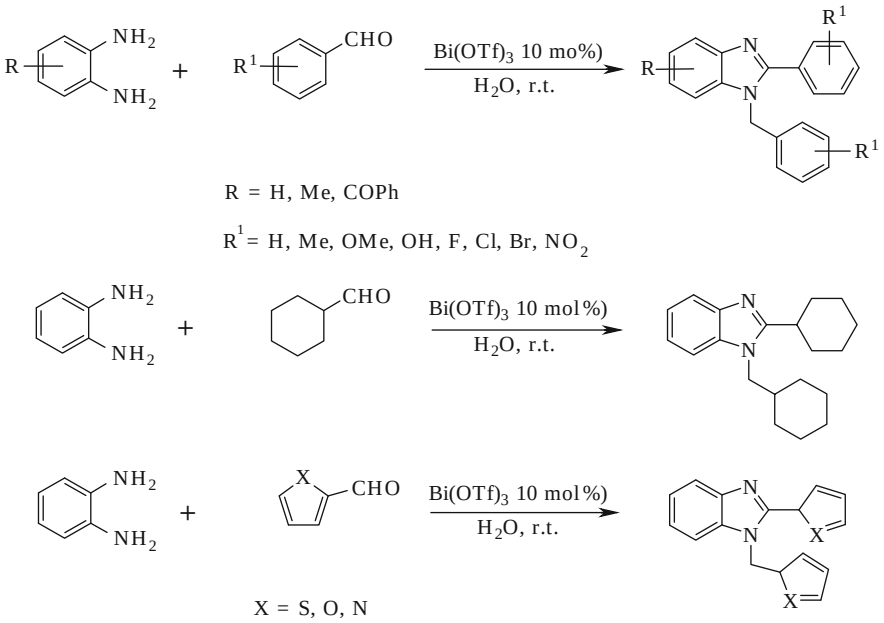



**Fig. 29** Synthesis of benzimidazole derivative from aromatic 1,2-diamines

most instances, the sugar parts of a drug molecule are essential for biological activity; however, the importance of the sugar moieties in them has not yet been evaluated.

## *6.1 Stereoselective Synthesis of C-Pseudoglycals*

C-Glycosides are versatile chiral intermediates for the synthesis of many biologically active macromolecules such as palytoxin, spongistatin, halichondrin, and many others [120–122]. In addition, C-glycosides are potential inhibitors of carbohydrate processing enzymes and they are stable analogs of glycals involved in important intra- and intercellular processes [123]. In particular, allyl glycosides and glycosyl cyanides are attractive because the former contains a terminal double bond that can be easily converted into other chiral molecules, carbohydrate derivatives, and glycosyl cyanides can be used as chiral intermediates for the synthesis of naturally occurring C-nucleoside antibiotics [124–128].

Protected D-glucal on reaction with allyltrimethylsilane or trimethylsilyl cyanide in the presence of $Bi(OTf)_3$ (2 mol%) gives the corresponding 2,3-unsaturated allyl glycoside or glycosyl cyanide with high α-selectivity [129] (Fig. 30). D-Galactal also undergoes allylic rearrangement with carbon nucleophiles under $Bi(OTf)_3$ catalysis to afford the corresponding pseudoglycal C-glycosides. This method is

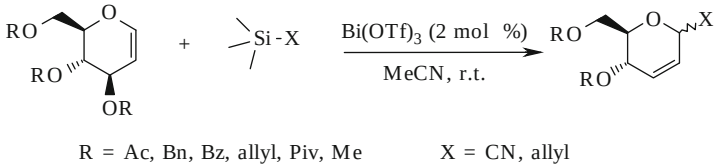



**Fig. 30** Synthesis of 2,3-unsaturated allyl glycosides or glycosyl cyanides

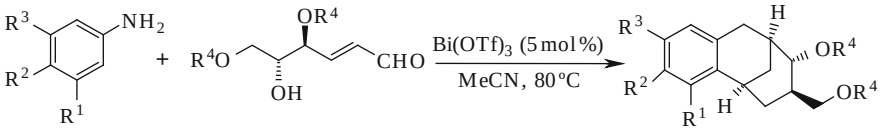



**Fig. 31** Synthesis of enantiopure sugar-derived tetrahydroquinoline derivatives

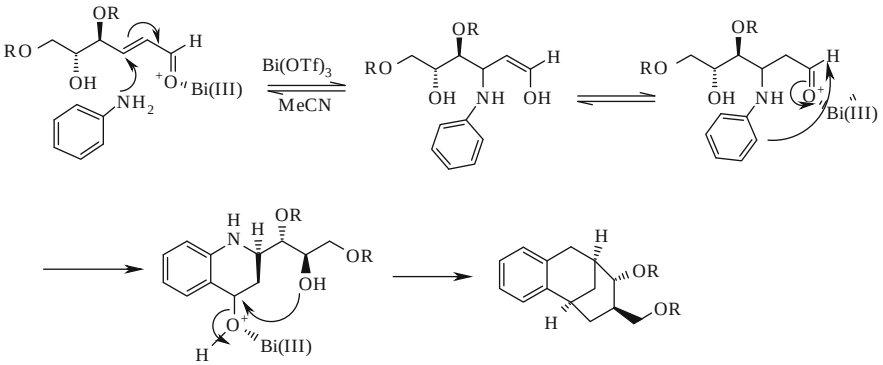



**Fig. 32** Mechanism of formation of enantiopure tetrahydroquinoline

also applicable for both ester and ether derivatives of D-glucal. There are several advantages in the use of $Bi(OTf)_3$ as catalyst for this transformation, which include high yields of products, cleaner reaction profiles, short reaction times, operational simplicity, and high α-selectivity.

## *6.2 Condensation of δ-Hydroxy-α,β-Unsaturated Aldehydes with an Aryl Amine*

Enantiopure sugar-derived tetrahydroquinolines can be synthesized through a $Bi(OTf)_3$-catalyzed reaction of δ-hydroxy-α,β-unsaturated aldehydes and aryl amines [130] (Fig. 31).

The δ-hydroxyl group has an inevitable role in this reaction as simple α,β-unsaturated aldehydes without a δ-hydroxyl group did not yield a bicyclic adduct. The probable mechanism is shown in Fig. 32 and seems to involve the

addition of the aniline to the unsaturated position of the conjugated aldehyde, which is activated by bismuth triflate. Thus, the initially formed Michael adduct may undergo a Friedel–Crafts-type intramolecular cyclization leading to the formation of the chiral tetrahydroquin line. Even though this reaction belongs to cycloaddition reactions, it is discussed separately because of the peculiar importance of sugar compounds. Similar reactions of *O*-allyl derivatives of sugar-derived aldehyde from D-glucose for the synthesis of tetrahydroquinoline derivative has already been discussed in Sect. 4.2).

## 7 Deprotection Reactions

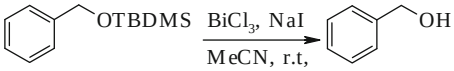
Protection and deprotection reactions of various functional groups are an integral part of organic synthesis, and its history is as old as that of the synthesis of natural products. In spite of its long history, important research is still going on in this particular field. The major reason is that these reactions when applied to a complex natural product might bring some unwanted reactions. Because of the same cause, these methods lack generality to some extent. However, many of these methods involve the use of strong acids, corrosive reagents, and elevated temperatures. Under such conditions, selectivity between the particular reaction of interest and the other possible competing reactions would be difficult. Hence, milder methods that use neutral conditions are still in demand for the protection and deprotection of various functional groups. Bismuth salts provide an excellent route for these kinds of reactions. They can be employed for the protection or deprotection of various functional groups such as hydroxyl [131–134], carbonyl [135–140], amino [141], acetals [142], and cyclic *N*,*O*-aminals [143].

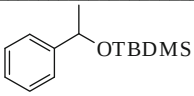
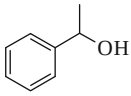
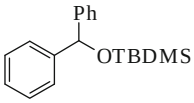
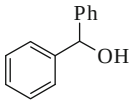
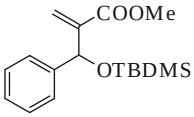
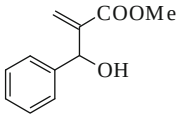
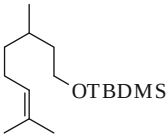
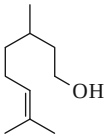
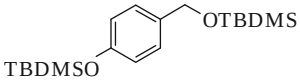
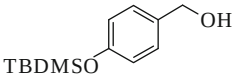
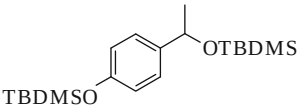
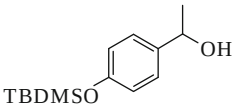
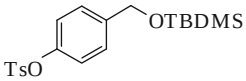
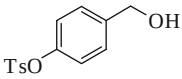
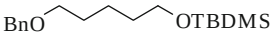
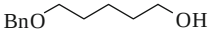
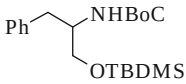
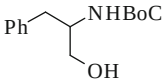
### *7.1 Cleavage of Alkyl* tert-*Butyl Trimethylsilyl Ether*

The protection of a hydroxyl group as a *tert*-butyl trimethylsilyl ether is one of the most important and useful reaction in organic synthesis because of its stability towards basic and mild acidic conditions [144]. The importance of any protecting group depends on how easily it can be installed and removed.

The most common deprotecting agent used is tetrabutyl ammonium fluoride [145]. Being strongly basic it may alter base-sensitive substrates. Even though various methods are available for deprotection, a selective deprotection of primary or secondary alkyl *tert*-butyl dimethylsilyl (TBDMS) ether over the aryl TBDMS ether was in need until $BiCl_3$ satisfied this demand [146]. Although $BiCl_3$ is a weak Lewis acid, its activity can be increased by the addition of NaI. The advantage of this method is that it avoids the use of highly acidic or basic conditions. This method also tolerates the presence of other protecting groups like OTs, OMe, OBn,

**Table 8** Deprotection of TDBMS ether




| TBDMS ether | Alcohol | Yield |
|---|---|---|
|   |   | 74 |
|   |   | 80 |
|   |   | 81 |
|   |   | 76 |
|   |   | 81 |
|   |   | 82 |
|   |   | 84 |
|   |   | 80 |
|   |   | 85 |

NHBoc etc. The versatility of this method is evident as it retains the configuration while deprotecting a secondary TBDMS group of methanol. The detailed picture of the versatility is presented in Table 8.

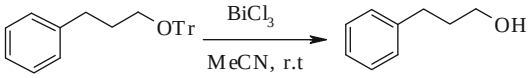
## 7.2 Cleavage of Trityl Ethers

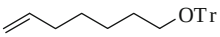
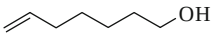
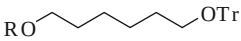
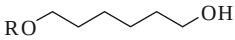
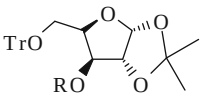
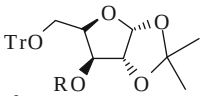
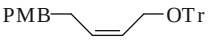
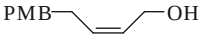
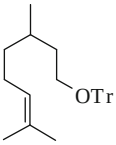
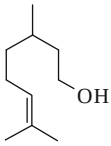
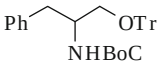
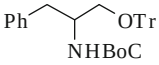
The triphenylmethyl (trityl) group is a commonly used protecting group for primary alcohols in carbohydrate and nucleoside chemistry due to its ease of installation and removal and its stability towards a variety of reagents [147–149]. In general, detritylation is accomplished under strong acidic conditions such as HCOOH, 80% $CH_3COOH$, mineral acids, $CF_3COOH$, or using Lewis acids such as $ZnBr_2$, $AlClEt_2$, $Yb(OTf)_3$, and $Ce(OTf)_4$. However, under protic acidic conditions, sensitive substrates frequently undergo acid-catalyzed deglycosylations, and Lewis acid detritylation procedures require anhydrous conditions, use of reagents in stoichiometric quantities, extended reaction times, and heating. $BiCl_3$-catalyzed trityl deprotection is a good alternative to these conventional methods as it avoids the use of protic acidic conditions [150]. The versatility of this method is obvious from the fact that it selectively cleaves the trityl group in presence of acid-sensitive tetrahydropyranyl (THP) and Boc groups; base-sensitive acetyl (Ac), benzoyl (Bz), tosyl (Ts), and pivaloyl (Piv) groups; and *tert*-butyldiphenylsilyl (TBDPS) or *p*-methoxybenzyl ether (PMB) groups. Furthermore, sugar substrates possessing glycosidic linkages and *O*-prenyl, *O*-allyl, and benzyl (Bn) groups also undergo selective cleavage of trityl groups to afford the corresponding alcohols. Trityl ethers having acetonides derived from secondary alcohols undergo selective deprotection of the trityl group leaving acetonides intact. In addition to the selectivity for cleavage of trityl ethers in the presence of a variety of acid- or base-sensitive groups in substrates such as carbohydrates, terpenes, and amino acids, the faster rate of detritylation also makes this procedure a valuable alternative. Various aspects of the method are exemplified in Table 9.

## 7.3 Cleavage of Acetals

Acetals are the most frequently used protecting group for carbonyl functionalities in organic synthesis. The deprotection of these groups into aldehydes or ketones is an important transformation and is usually accomplished with aqueous acid hydrolysis using acids like HCl, acetic acid, oxalic acid, *p*-TSA acid, trifluroacetic acid, etc. Other methods include using Lewis acids, oxidative conditions, or phosphorus- and silicon-based reagents. Many of these methods suffer from one or more drawbacks like lack of selectivity due to strongly acidic conditions, oxidizing nature, non-availability of the reagents, and unsatisfactory yields. For the effective cleavage of acetals selectively in the presence of the other ether-linked protecting groups, $BiCl_3$ can be used instead [151] (Fig. 33). This method can also be extended to doubly protected substrates. It selectively cleaves acetals in the presence of acid-sensitive substrates like THP ether, benzyl ether, or silyl ethers. The rate at which the reaction proceeds is lower for the 1,3-dioxalones of aliphatic compounds compared to the aromatic ones. It requires refluxing conditions for the aliphatic acetals.

**Table 9** Cleavage of trityl ether




| Trityl ether | Alcohol | Yield (%) |
|---|---|---|
|  |  | 90 |
|  |  | 86-90 |
| R = Ac, Bz, Ts, Piv, TBDPS, THP | | |
|  R = Bn, allyl, prenyl |  | 90-95 |
|  |  | 90 |
|  |  | 93 |
|  |  | 90 |

Selectivity of this method under mild Lewis acid conditions finds applications in organic synthesis.

## 8 Reactions of Quinones

Derivatives of quinones have always attracted attention because of their biological importance. As a consequence, a number of reactions have been investigated. After emerging as a fascinating alternative to most of the conventional stoichiometric

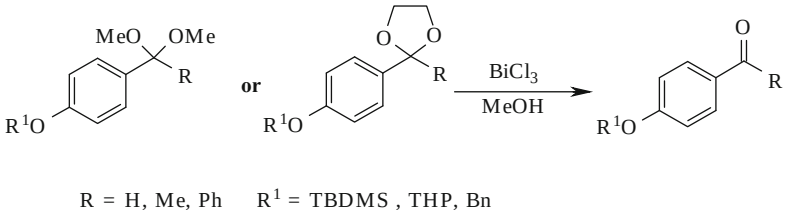



**Fig. 33** Deprotection of acetals

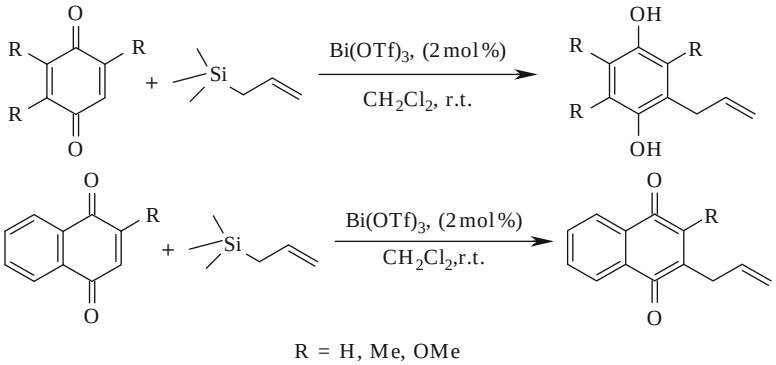



**Fig. 34** Allylation of quinone and benzoquinone

Lewis acids, $Bi(OTf)_3$ provides a simpler and convenient variant for the existing reactions.

## *8.1 Allylation of Quinones*

The allylation of quinones is an important reaction for the preparation of biologically active isoprenoid quinones such as vitamin E, vitamin K, coenzyme Q, and plastoquinones, which play a vital role in biological processes including electron transport, blood clotting, and oxidative phosphorylation [152–154]. Functionalized quinols are not only important in the biosynthesis and metabolism of natural phenols but are also useful as synthetic precursors to naturally occurring quinones and alkaloids [155, 156]. The allylation of quinones is generally carried out with allylsilanes using acid catalysts such as titanium tetrachloride and lithium perchlorate in diethyl ether (LPDE) [157, 158]. These methods involve the use of a stoichiometric amount of catalysts and prolonged reaction times, especially with LPDE, to produce allylated quinones. Other methods involve the addition of allyl indium, allyl magnesium, allyl nickel complexes, or allylstannane to the quinones [159–164]. A major side product in these procedures is the hydroquinone arising

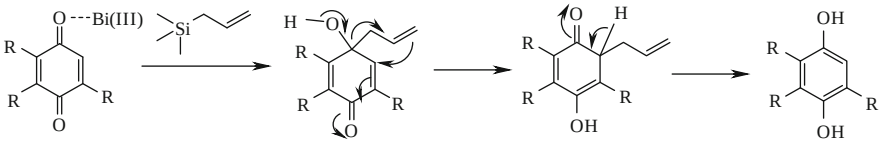



**Fig. 35** Mechanism of allylation of quinone

from simple reduction of *p*-benzoquinones. Furthermore, many of these procedures produce a mixture of products and also require a large excess of quinones to eliminate or at least minimize the formation of byproducts. Bismuth triflate catalyzes the reaction of allylsilane with substituted *p*-benzoquinone to produce the mono-allylhydroquinones [165] (Fig. 34). Other allylating agents such as allyltributylstannane and tetraallyltin also reacts smoothly with *p*-quinones in the presence of $Bi(OTf)_3$ (2 mol%). Unlike other reported methods, this method does not require the use of additives or ligands to suppress reduction of quinones, thereby increasing overall yields. This procedure avoids the disadvantages of polyalkylation, chromanol formation, or side-chain cyclization. This method is also effective for the allylation of hindered 1,4-benzoquinones such as duroquinone whereas most existing methods fail to produce *p*-allylquinols from duroquinone.

A plausible mechanism is shown in Fig. 35. It seems to involve addition of the allyl group at the less hindered carbonyl group followed by a [3,3] sigmatropic rearrangement, resulting in the formation of allyl-substituted hydroquinones or their oxidation products.

## *8.2 Acylation of* p-*Quinone*

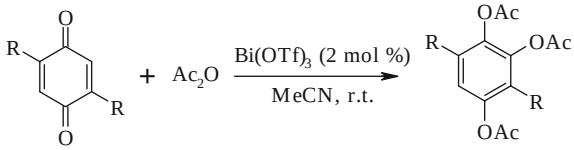
Many quinones derived from aromatic compounds are used as dienophiles in the Diels–Alder reaction, and functionalized hydroxyquinones are extensively used as anti-oxidants in the photo industry and as polymeric materials.

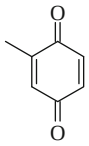
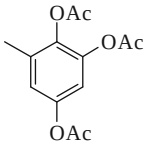
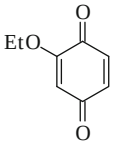
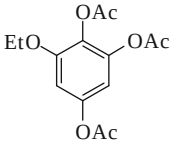
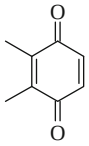
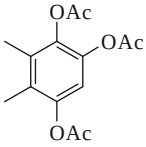
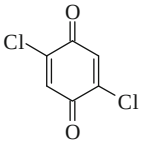
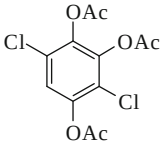
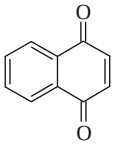
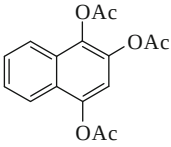
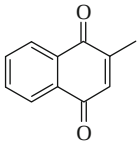
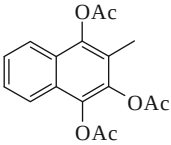
The Thiele–Winter acetoxylation is one of the simplest and most straightforward approaches for the synthesis of the triacetoxyaromatic precursors of hydroxyquinones. The method involves the reaction of quinones with acetic anhydride and is generally catalyzed by sulfuric acid. The use of sulfuric acid results in the formation of tars in some cases, due to its strong acidity and oxidizing character. Zinc chloride has been reported as a milder catalyst, but generally chloroquinones are formed as byproducts. Subsequently, boron trifluoride, perchloric acid, and triflic acid have been found to give higher yields than sulfuric acid. However, quinones bearing electron-donating groups failed to give the desired triacetates with boron trifluoride or sulfuric acid as the catalyst.

*p*-Quinones undergo smooth acylation with acetic anhydride in the presence of bismuth triflate (2 mol%) under mild conditions to afford the corresponding tri-acetoxybenzenes [166]. With monosubstituted quinones such as 2-methyl-

1,4-benzoquinone, 2-ethoxy- or 2-methoxy-1,4-benzoquinone, the addition occurred selectively at the 5-position. This method is clean and free from the chlorinated side products that are normally observed under zinc chloride catalysis. The method works well with both electron-donating as well as electron-deficient

**Table 10** Acylation of *p*-quinones




| Quinone | Product | Yield (%) |
|---|---|---|
|  |  | 79 |
|  |  | 65 |
|  |  | 85 |
|  |  | 70 |
|  |  | 84 |
|  |  | 75 |

benzoquinones to give the corresponding triacetates. However, most other methods that fail to produce a triacetate with 2-methylnaphthoquinone are also reported to give lower conversions with methoxy- or ethoxy-substituted quinines, as found here. The scope of this method is depicted in Table 10.

## 9 Conclusion

This chapter describes our group's contribution towards the development of methodologies that are useful in accomplishing various functional group manipulations by making use of the catalytic properties of bismuth salts. We hope this effort may enlighten the interest of many students and scientists in this field.

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