Recent Advances of Bismuth(III) Salts in Organic Chemistry: Application to the Synthesis of Aliphatics, Alicyclics, Aromatics, Amino Acids and Peptides, Terpenes and Steroids of Pharmaceutical Interest

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Abstract: In this review recent uses of the inexpensive and commercially available bismuth(III) salts in organic chemistry will be highlighted. Their application to the development of new processes or synthetic routes that lead to compounds of pharmaceutical interest will be matter of discussion. It will focus on bismuth(III) salt-mediated reactions involving the preparation of non-heterocyclic compounds such as aliphatics and alicyclics, monocyclic and polycyclic aromatics, amino acids and peptides, terpenes and steroids.

Keywords: Bismuth(III) salts, aliphatics, alicyclics, aromatics, amino acids, peptides, terpenes, steroids, pharmaceutical interest.

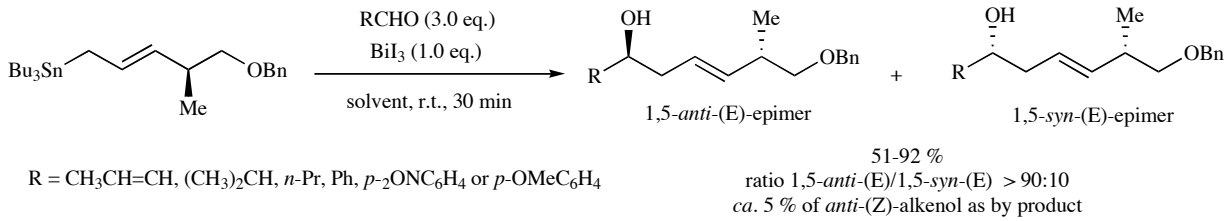
1. INTRODUCTION

The increasing concern about the environment and the need for "green reagents" has placed bismuth and its compounds into focus over the last decade. Despite the fact that bismuth is a heavy metal, bismuth and bismuth(III) salts are considered safe, non-toxic and appropriate "ecofriendly" reagents for green chemistry purposes [1]. Moreover, bismuth has an electron configuration of $[Xe]4f^{14}5d^{10}6s^{2}6p^{3}$, and due to the weak shielding of the 4*f* electrons (Lanthanide contraction), bismuth(III) compounds exhibit Lewis acidity, which may be accentuated by strong withdrawing groups such as triflate. Concerning the discrepancy related to the presentation of an uniform designation for the hydration number of bismuth(III) triflate, this salt will be written as $Bi(OTf)_3{\cdot}xH_2O$, following the discussion previously made by Gaspard-Iloughmane and Le Roux [2a]. If many bismuth-promoted reactions can be explained at the light of its Lewis acid character, recent works established a role for the acid protons derived from the hydrolysis of bismuth(III) salts, designated by "the hidden «Bi» behavior of bismuth" [2a].

The use of the inexpensive and commercially available bismuth(III) salts in organic chemistry [2] as well as in biological and medicinal chemistry [3] has been the subject of several reviews. In this review recent applications of these reagents to organic synthesis will be discussed. Special emphasis will be placed on the development of new processes or synthetic routes using bismuth(III) salt-mediated reactions that lead to compounds of pharmaceutical interest. Our intention has been to highlight the potential of bismuth-promoted reactions for the construction and/or functionalization of important molecular structures valuable from the medicinal chemistry point of view [4]. This review focuses on the use of bismuth(III) salts for the synthesis of the following groups of non-heterocyclic compounds: aliphatics and alicyclics, monocyclic and polycyclic aromatics, amino acids and peptides, terpenes and steroids, and has been organized according to the nature of the reaction products. When appropriate, examples of biological relevance will be presented as well as the final products of pharmaceutical interest in the course of synthetic routes.

2. ALIPHATIC AND ALICYCLIC COMPOUNDS

Allyl-bismuth(III) dihalides, generated by transmetallation of allylstannanes with bismuth(III) halides, were found to be useful intermediates for reactions with aldehydes. High levels of 1,5-stereocontrol were observed from the reaction with 5-benzyloxy-4-methylpent-2-enyl(tributyl)stannane (up to a ratio of 93:3 in favor of 1,5-*anti*-(E)-epimers), however in moderate to good yields. Several examples using aromatic and non-aromatic aldehydes were reported [5] (Scheme **1**). Similar results can be achieved starting from allylbromine derivatives using the BiI_3/Zn system as an *in situ* generator of Bi(0) [6]. The reaction products of these reactions can be seen as adequate intermediates for the synthesis of naturally occurring compounds bearing a 1,5-*syn*-dimethyl moiety (see discussion in [6, 7]).



Scheme 1.

Due to their importance both as bioactive lead compounds [8] and as versatile building blocks [9], the synthesis of β-enaminone and β-enamino esters has been an active field of research in organic chemistry. These compounds can be obtained by the direct condensation of β-dicarbonyl compounds with amines. The reaction can be performed in water [10] or tetrabutylammonium bromide (TBAB) [11] using bismuth(III) trifluoroacetate, $Bi(TFA)_3$, as catalyst. The advantage of the $Bi(TFA)_3$/TBAB system is the fact that it can be recovered and reused. Both methods have been applied to the synthesis of aliphatic (Scheme **2**) and aromatic enaminones.

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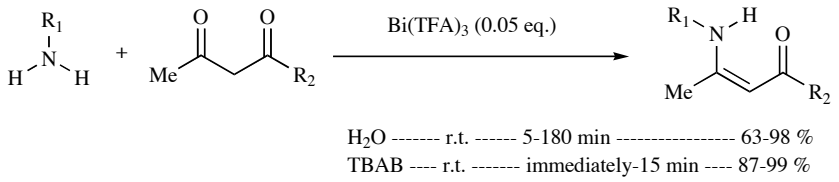
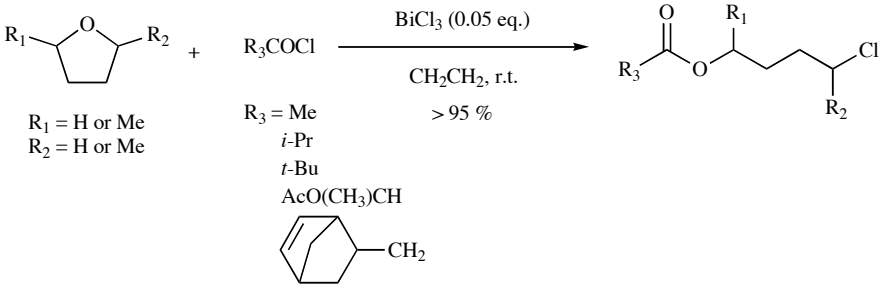
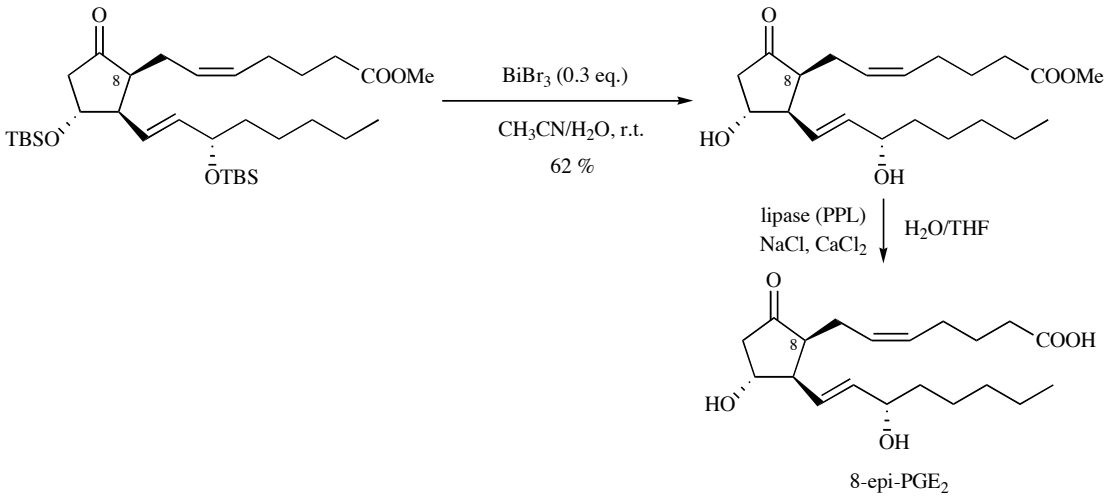


R_1 = *n*-Bu, $H_2NCH_2CH_2$, $HOCH_2CH_2$ or $CH_3CH_2CHCH_3$
R_2 = OEt or Me

Scheme 2.



Scheme 3.



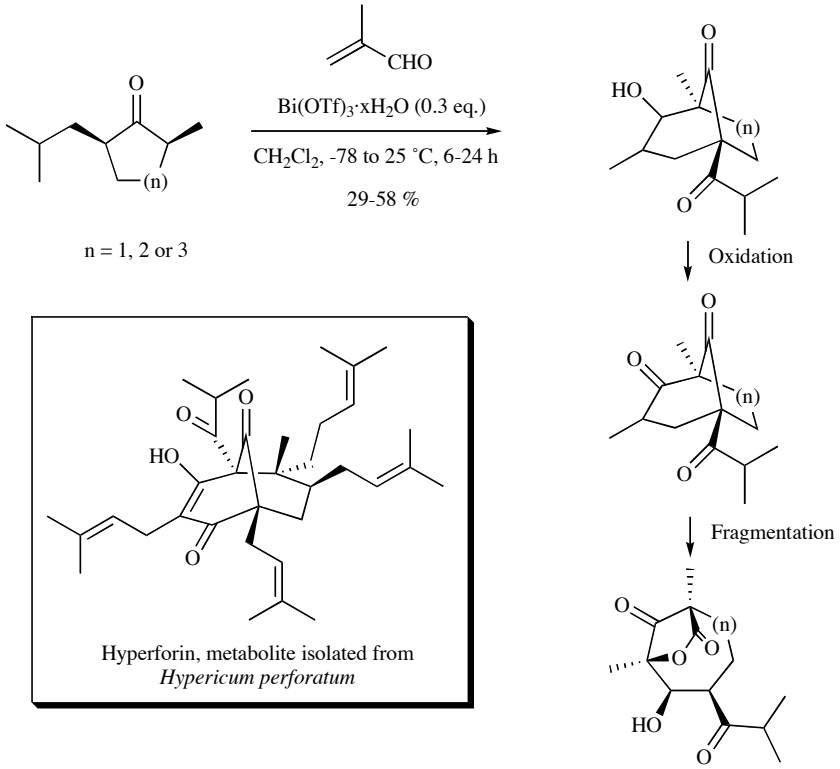
Scheme 4.

The *O*-acylative cleavage of cyclic ethers has been reported in the presence of bismuth(III) salts. The cleavage of tetrahydrofuran and its 2-methyl and 2,5-dimethyl derivatives with aliphatic and alicyclic acyl halides, catalyzed by Bi(III) halides, in CH_2Cl_2 at 20 ºC, resulted in the formation of aliphatic and alicyclic haloacyloxyester derivatives, respectively, in very high yields (Scheme **3**) [12, 13]. More recently, Bi(III) salts, including $Bi(NO_3)_3{\cdot}5H_2O$, $Bi(OTf)_3{\cdot}xH_2O$ and $BiCl_3$ were reported as catalyst (5-10 mol %) for the cleavage of cyclic and acyclic ethers using aromatic and aliphatic acyl chlorides, under solvent-free conditions [14].

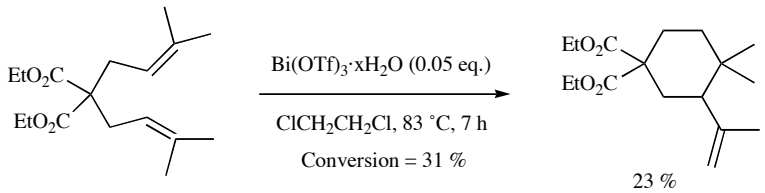
The use of $BiBr_3$ has been reported for the mild cleavage of silyl protective groups during the total synthesis of E_1 and E_2 isoprostanes [15]. This modification of Bajwa *et al*. procedure [16], which uses a slightly higher amount of $BiBr_3$ (30 mol %) in CH_3CN/H_2O at room temperature, allowed the selective cleavage of the TBS protecting group avoiding epimerization to the thermodynamically more stable *trans*-isomer (Scheme **4**). E_1 and E_2 isoprostanes have been identified *in vivo*, and recent studies established their role in important biological processes [17].

Nicolaou and co-workers reported the use of $Bi(OTf)_3{\cdot}xH_2O$, among other catalysts, in the annulation reaction between simple cyclic ketones and α,β-unsaturated aldehydes to afford polyfunctional molecules with bridged medium rings (Scheme **5**). These bicyclic hydroxy diketones constitute the core of important naturally occurring compounds, such as hyperforin a metabolite isolated from *Hypericum perforatum* (St. John's wort), famous for its antidepressant properties. Moreover, these bicyclic hydroxy diketones can be further functionalized by oxidation and subsequent ring fragmentation to large-size ring containing derivatives, which are also of considerable interest (*e.g*. perforatumone, also found in *Hypericum perforatum*) [18].

The use of $Bi(OTf)_3{\cdot}xH_2O$ has been reported for the preparation of polysubstituted six-membered carbocycles. Although better results were accomplished by the use of Sn(IV) salts, the cycloisomeration of 1,6-diene diethyl diprenylmalonate afforded the corresponding *gem*-dimethyl cyclohexene product in 23 % yield, after 7 h, at 83 ºC using 5 mol % of the bismuth(III) catalyst (Scheme **6**) [19].



Scheme 5.



Scheme 6.

3. MONOCYCLIC AND POLYCYCLIC AROMATIC COMPOUNDS

Aromatic rings constitute quite rigid, flat, relatively lipophilic moieties with considerable electron density. This electron density can be modulated by substituents attached to the aromatic ring with electron donating or withdrawing character. The spatial position of aromatic compounds is markedly influenced by the bond angles formed with their substituents. These properties of the aromatic ring enhance uniqueness and fit to receptor sites for endogenous mediators. The aromatic ring thus forms the nucleus for a number of pharmacophores [20].

3.1. 1,1-Diaryl Compounds

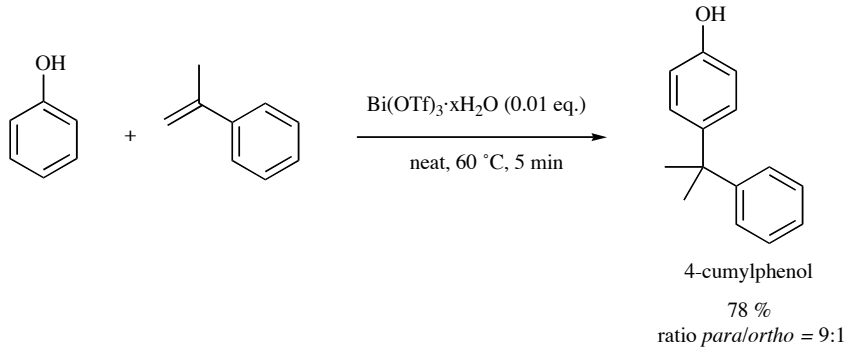
In the group of diaryl compounds we include the ones in which two aromatic rings are linked by one carbon atom, which may belong to an alkyl, alkenyl, alkynyl chain that may be or not further substituted. For instance, many biologically active compounds and pharmaceuticals contain the 1,1-diarylmethane motif, such as methadone and diphenhydramine [21]. Tamoxifen, a drug widely used for breast cancer therapy, contains a 1,1-diarylalkene moiety [22] as well as compounds from a new class of HIV-1 non nucleoside reverse transcriptase inhibitors known as alkenyldiarylmethanes (ADAM) [23], among others.

From the above considerations, the potentiality of developing new efficient procedures for the preparation of these compounds becomes evident. In the past few years bismuth-catalyzed processes have been reported for the synthesis of both 1,1-diaryalkanes and 1,1-diarylalkenes.

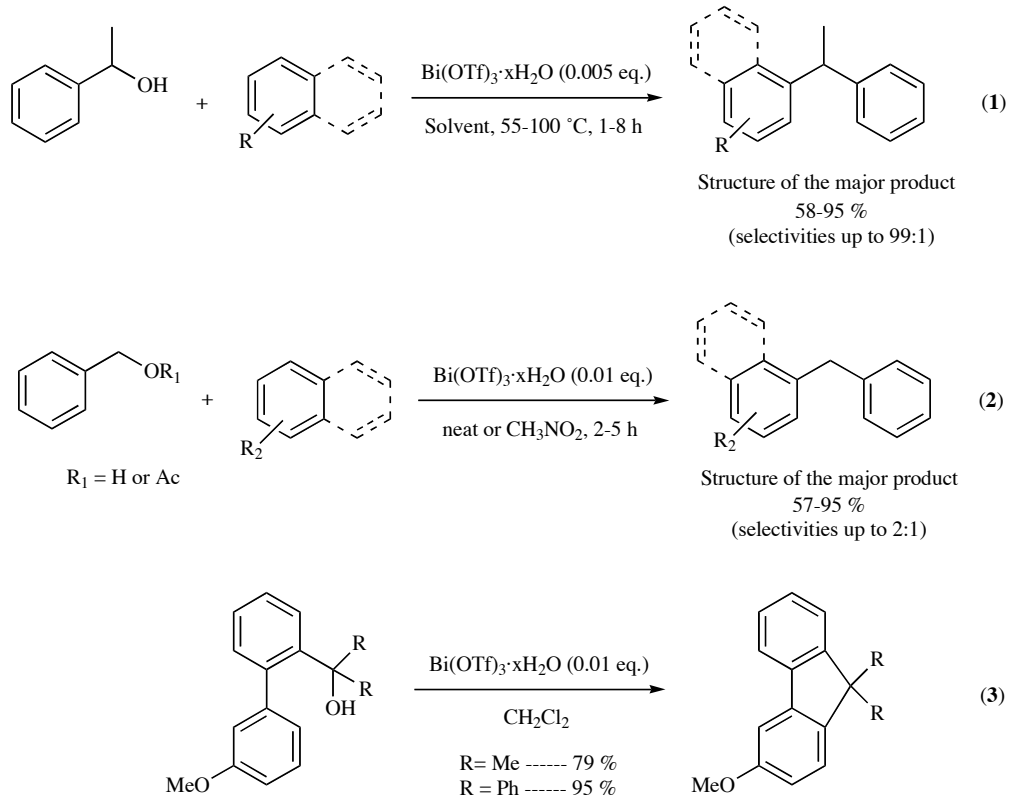
Le Rouzo *et al*. reported the highly *para*-regioselective synthesis of 4-cumylphenol in 78 % yield from the Friedel-Crafts alkylation of phenol with α-methylstyrene in the presence of $Bi(OTf)_3 \cdot xH_2O$ (1 mol %) (Scheme **7**) [24].

Rueping *et al*. reported the benzylation of arenes and heteroarenes in the presence of catalytic amounts of $Bi(OTf)_3 \cdot xH_2O$. Using 1-phenylethanol as the benzylation agent, a great variety of arenes were efficiently converted into the corresponding 1,1-diarylalkanes in good to very high yields (58-95 %), with selectivities up to 99:1 (Scheme **8**, reaction 1) [25]. Other benzylation agents were screened in the reaction with anisole. Both benzyl halides and benzylamine failed to react under these reaction conditions while a 3-hydroxy-3-phenylpropanoate derivative gave only moderate yield. On other hand benzyl alcohol and benzyl acetate were found to be suitable benzylation agents for this reaction affording the desired products in very high yields (91 % and 92 %, respectively). Further examples were investigated from the reaction of benzyl alcohol and benzyl acetate with other arenes, but despite the good yields the selectivities were generally lower (Scheme **8**, reaction 2) [25]. The extension to an intramolecular variant of this procedure provided a valuable route to substituted fluorenes [25] (Scheme **8**, reaction 3).

Later, Rueping *et al*. reported the same reaction using the readily available styrene derivatives, instead of benzylic alcohols [26]. Among the Bi(III) salts screened and the temperatures and solvents



Scheme 7.



Scheme 8.

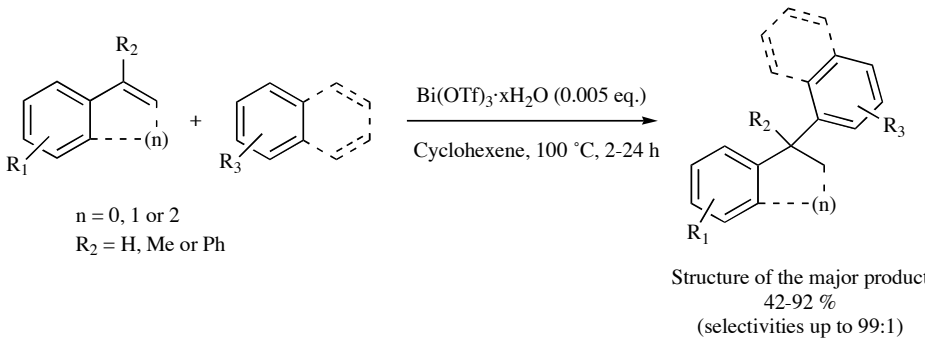
tested, the optimal reaction conditions for such procedure were found to be $Bi(OTf)_3 \cdot xH_2O$ (0.5 mol %) in cyclohexene or CH_3NO_2 at 100 ºC. Thus a large number of 1,1-diarylalkanes were prepared in good to high yields (42-92 %), with selectivities up to 99:1 (Scheme **9**) [26].

Similar results have been reported by Sun *et al*., by the use of $BiCl_3$ (10 mol %) [27]. The authors also studied the reaction of α-substituted styrenes in the absence of arenes. This reaction occurred with 5 mol % of $BiCl_3$ at 110 ºC during 24 h, and intermolecular hydroarylation of α-substituted styrenes followed by subsequent intramolecular hydroarylation produced the cyclic dimers of α-substituted styrenes in good yields (56-92 %) (Scheme **10**) [27].

The use of $BiCl_3$ in the direct deoxygenative allylation of benzhydrols with allyltrimethylsilane has been published. Other allyl sources failed to react. The best solvent proved to be CH_2Cl_2 and $BiCl_3$ (1-5 mol %) was better catalyst when compared to the other Lewis acids tested, that included $Bi(OTf)_3 \cdot xH_2O$ (5 mol %). Thus several benzhydrol derivatives with electron-donating or withdrawing groups on the aryl ring reacted with silyl nucleophiles, in the presence of 5 mol % of $BiCl_3$, at room temperature, and the desired alkenes were obtained smoothly as the only reaction products in 84-95 % yields (Scheme **11**) [28].

An unusual reactivity was found in the reaction between acyl chlorides and arenes in the presence of catalytic amounts of $BiCl_3$ (10 mol %) or $BiBr_3$. Instead of the normal Friedel-Crafts acylation products, 1,1-diarylalkene derivatives were obtained in 25-63 % yields (Scheme **12**, reaction 1) [29]. It was suggested that the initially formed Friedel-Crafts acylation product was converted to a vinyl chloride derivative by HCl or acyl chloride, followed by the final Friedel-Crafts-type vinylation reaction with another arene molecule. The reaction between several arenes and vinyl chlorides was also investigated, and the corresponding 1,1-diarylalkene products were formed in moderate to high yields (29-80%), with very high selectivities in most cases (Scheme **12**, reaction 2) [29].

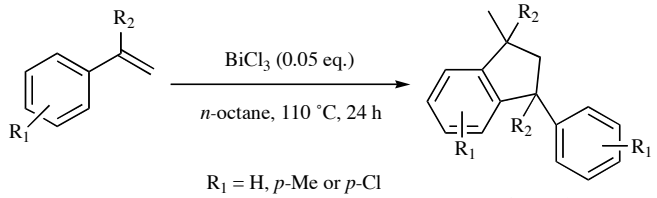
Some reports on the synthesis of miscellaneous 1,1-diaryl compounds substituted on the alkane chain have been published. In this context, $BiCl_3$, Bi_2O_3 and $Bi(NO_3)_3 \cdot 5H_2O$ have been used in the palladium(II)-catalyzed Michael-type hydroarylation of nitroalke-



n = 0, 1 or 2
R_2 = H, Me or Ph

Structure of the major product
42-92 %
(selectivities up to 99:1)

Scheme 9.



R_1 = H, *p*-Me or *p*-Cl
R_2 = Me or Ph

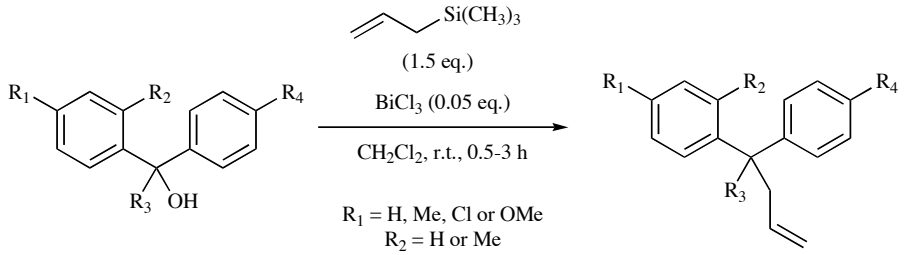
56-92 %

Scheme 10.

nes with aryltin compounds. The addition of Bi(III) salts clearly improved the reaction yields of the corresponding 2-nitro-1,1-diphenylethane derivatives, however the formation of biphenyl by-products was also observed (Scheme **13**) [30].

The rearrangement of stilbene oxides to afford diphenylacetaldehydes in the presence of $BiOClO_4 \cdot xH_2O$ (10 mol %) [31] and $Bi(OTf)_3 \cdot xH_2O$ (0.1 mol %) [32] has been reported. The $BiOClO_4 \cdot xH_2O$-catalyzed reaction was found to be regioselective giving only the corresponding diphenylacetaldehydes, in 68-90 % yields, after 25-45 min at r.t. in CH_2Cl_2, as the result of preferential migration of the phenyl group. Kozik and co-workers applied the above mentioned method to one of the synthetic steps towards a 1-amino-4-arylnaphthalene-2-carbonitrile derivative, for which biological activity against some phytopathogenic fungi was observed (Scheme **14**) [33].

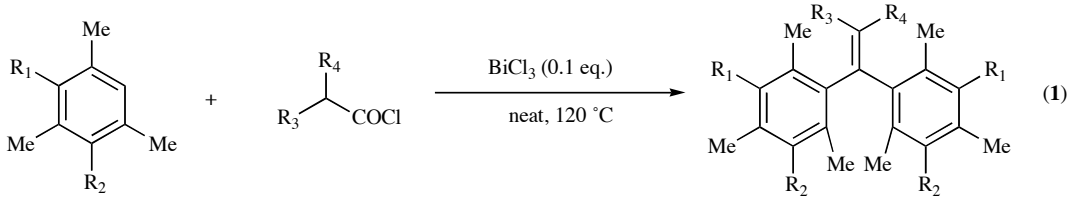
The reaction of 2,3-dichloroanisole (performed on 40-100 g scale) or *m*-chloroanisole with ethyl glyoxylate polymer using $Bi(OTf)_3 \cdot xH_2O$ as catalyst afforded the corresponding *p,p*-dimer in good yield. For the reaction of *m*-chloroanisole, the reaction pro-



R_1 = H, Me, Cl or OMe
R_2 = H or Me
R_3 = H, Me or Ph
R_4 = H or OMe

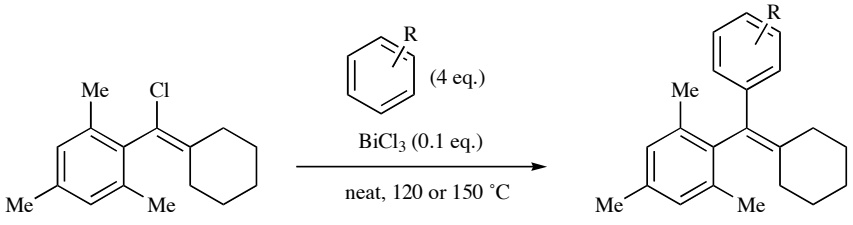
84-95 %

Scheme 11.



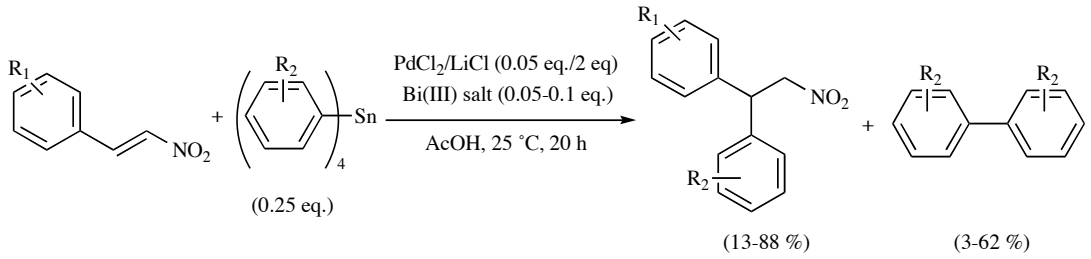
$R_1 = R_2$ = H; R_3 = H or Me; R_4 = Me or *n*-Pr or R_3,R_4 = cyclohexanyl: 25-63 %

$R_1 = R_2$ = Me; R_3 = H; R_4 = Me: 27 % ($BiBr_3$ 0.2 eq)

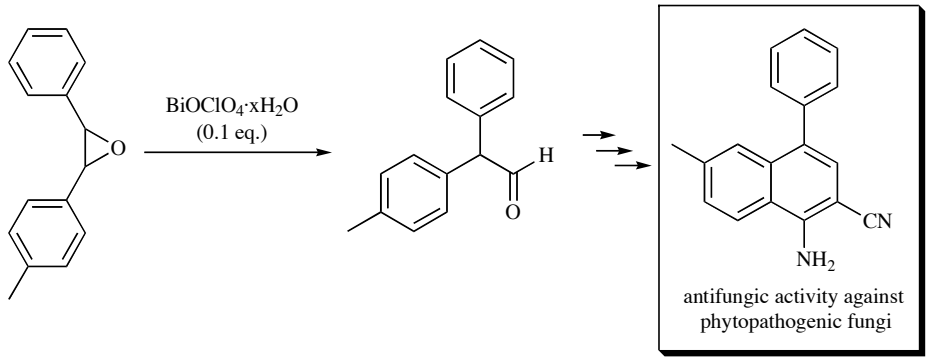


29-80 %
selectivity ranging
from 55 to 100 %

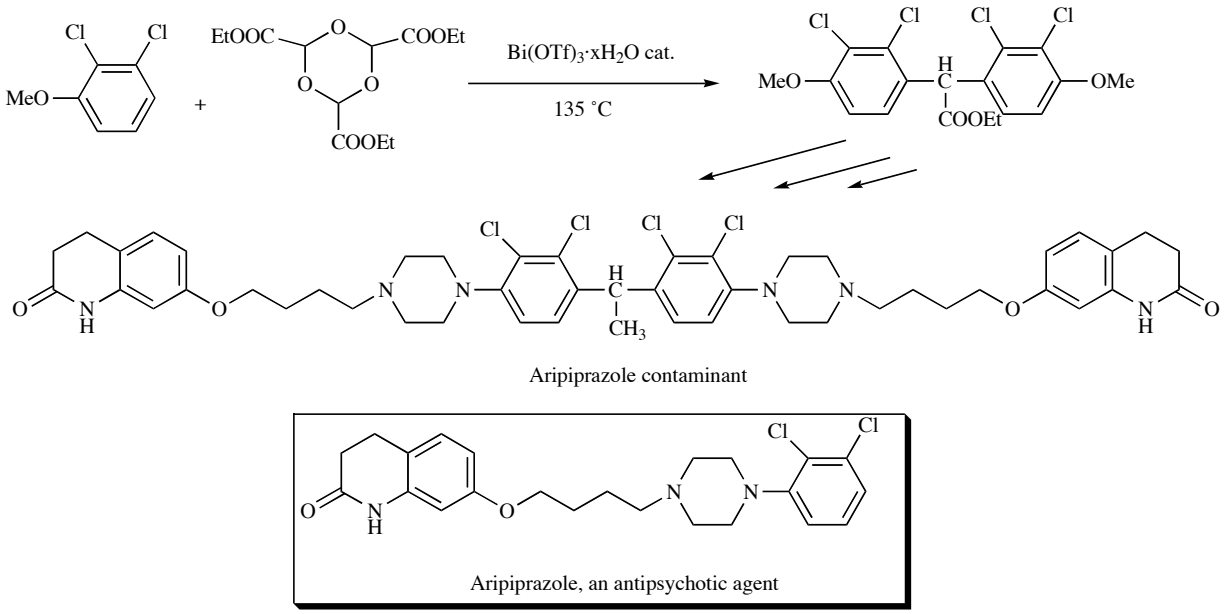
Scheme 12.



Scheme 13.



Scheme 14.



Scheme 15.

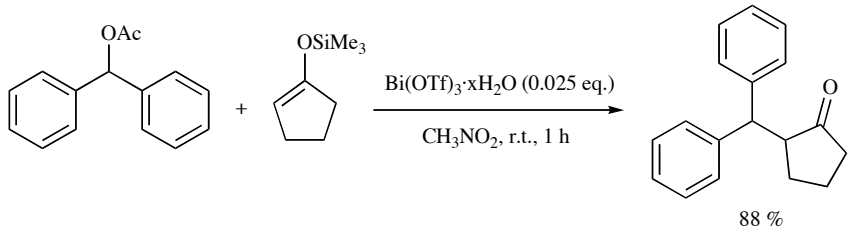
ceeded better in a $M^n(OTf)_n/MgSO_4/SiO_2$ system, which prevented hydrolysis side reaction [34]. The reaction with 2,3-dichloroanisole was used as initial step for the synthesis of a minor contaminant of aripiprazole, an antipsychotic agent (Scheme **15**) [35, 36]. This contaminant is a dimeric derivative of aripiprazol in which two molecules of the drug are connected by a 1,1-diarylethane bridge.

Quite recently, the reaction between benzhydryl acetate and a cyclic silyl enol ether has been reported in CH_3NO_2 at r.t. in the presence of 2.5 mol % of $Bi(OTf)_3 \cdot xH_2O$. The resulting product contained a 2-oxocyclopentyl group attached to the 1,1-diphenylmethane moiety (Scheme **16**) [37].

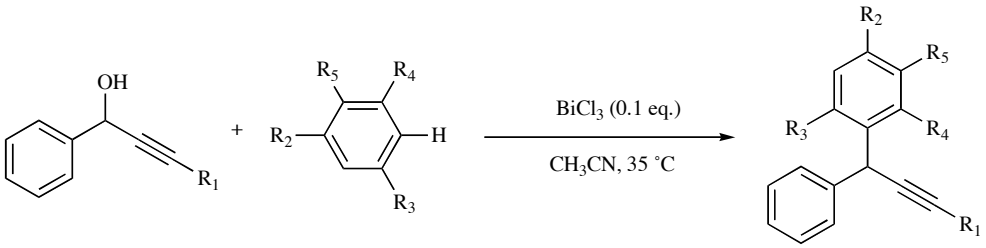
The synthesis of alkynyl derivatives of 1,1-diphenylmethane can be successfully achieved by the reaction of benzylic propargylic alcohols and aromatic nucleophiles. The corresponding Friedel-Crafts arylated products are obtained in high yields (62-94 %) in the presence of $BiCl_3$ (10 mol %) (Scheme **17**, reaction 1) [38]. Another efficient approach has been reported by De and Gibbs, in which the diaryl alkynyl derivative was prepared from the direct deoxygenative allylation of benzhydrol with $PhC{\equiv}CSiMe_3$, in the presence of $BiCl_3$ (5 mol %) (Scheme **17**, reaction 2) [28].

3.2. Diaryl Carbonyl Derivatives

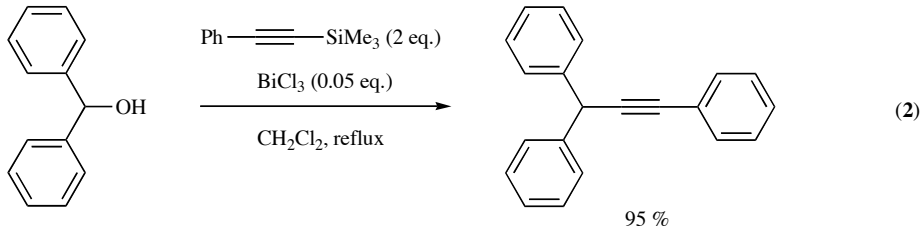
In the group of diaryl carbonyl compounds we include the ones in which a carbon atom containing a carbonyl group is linking two aromatic rings. The diaryl carbonyl core is present in several marketed molecules, including the known ketoprofen, fenofibrate and



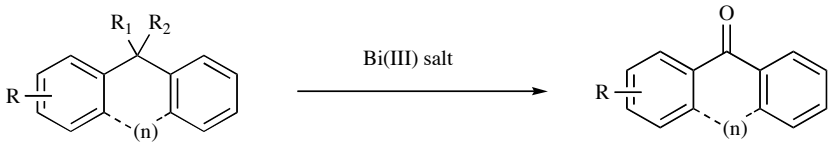
Scheme 16.



R_1 = TMS ---------- $R_2 = R_4$ = OMe; $R_3 = R_5$ = H---------- 3 h ---------- 75 %
R_1 = Ph ---------- R_2 = OH; $R_3 = R_4 = R_5$ = H---------- 0.5 h ---------- 93 %
R_1 = Ph ---------- R_2 = H; R_3 = OH; R_4,R_5 = fused benzene ring----- 0.5 h ---------- 94 %
R_1 = Ph ---------- R_2 = H; R_3 = OMe; R_4,R_5 = fused benzene ring--- 0.5 h ---------- 90 %
R_1 = H ---------- R_2 = H; R_3 = OH; R_4,R_5 = fused benzene ring----- 24 h, 60 °C --- 62 %



Scheme 17.



R_1,R_2 = NMe_2, NHTs, NOH, $NHCONH_2$, S or
R_1 = OMe and R_2 = OMe or
R_1 = OH, Br, OTMS or OTHP and R_2 = H

Scheme 18.

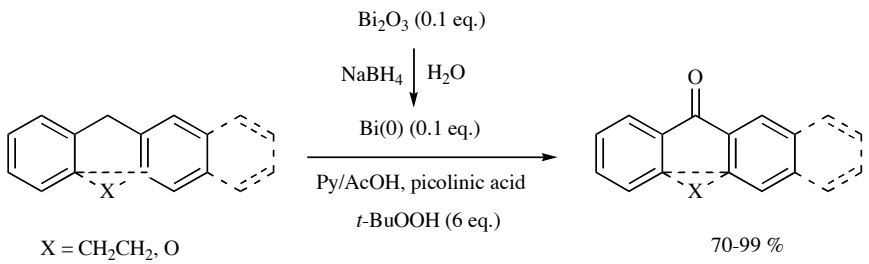
mebendazol [21]. Important diaryl carbonyl compounds also include simple molecules such as fluorenone [39] and benzophenone [40], which have an important role in medicinal chemistry.

A large variety of reactions is known to afford diaryl carbonyl compounds. This class of compounds can be prepared from diaryl derivatives, in which a parent function is converted into a carbonyl group. Several bismuth-based processes have been reported, including conversion of hydrazones [41], alcohols [42], TMS and THP ethers [43], ketoximes [41b, 44], semicarbazones [41b, 44e], thiocarbonyls [45], halides [46] and acetals [47] to the corresponding diaryl carbonyl derivatives (Scheme **18**).

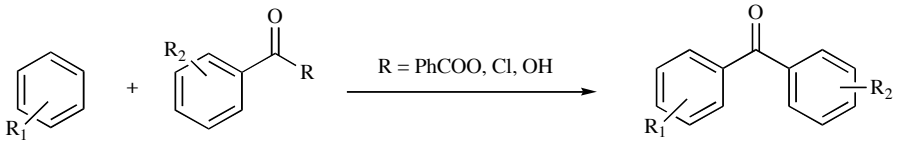
A bismuth-catalyzed process using *tert*-butyl hydroperoxide (*t*-BuOOH) as oxidant has also been reported for the benzylic oxidation of 1,1-diaryl methane substrates affording diaryl carbonyl derivatives. Elemental bismuth, Bi(0) (20 mol %), prepared *in situ* from a Bi(III) salt, proved to be the best catalyst for this reaction when compared to $(BiO)_2CO_3$, $BiCl_3$, Bi_2O_3 and $Bi(NO_3)_3{\cdot}5H_2O$ [48a]. Recent studies have furnished some insight on the bismuth species involved in the benzylic oxidations and seems that the reactions proceed via a radical mechanism with the intermediacy of a bismuth(III) picolinate complex intermediate [48b]. Under these reaction conditions, benzophenone and 9*H*-fluoren-9-one were prepared in 95 % and 91 % yield, respectively, among other examples (Scheme **19**) [48a].

Other strategies available for the synthesis of these compounds are based on aromatic electrophilic substitution reactions, namely the classical Friedel-Crafts acylation with benzoylation agents. In these cases, new diaryl carbonyl derivatives are obtained from the reaction between other two molecules, an aromatic compound, more or less activated, and a benzoylation reagent, such as derivatives of benzoic anhydride, benzoic chloride or benzoic acid (Scheme **20**).

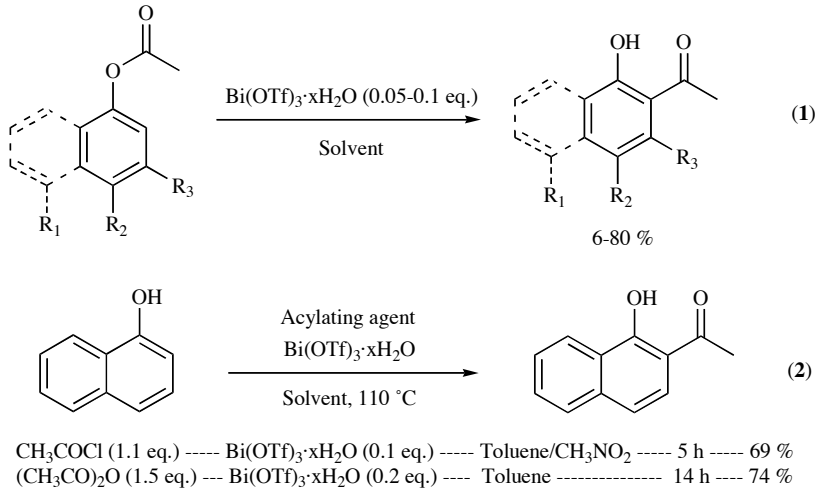
If there is an area of fruitful developments on the use of bismuth(III) salts in organic chemistry, is undoubtedly their applications to Friedel-Crafts reactions. Several research original works and patents and one review devoted to this theme have been published [2f]. Mechanistic studies on bismuth(III)-catalyzed Friedel-Crafts transformations have been carried out [2f], including the establishment of the key role of bismuth(III) chlorotriflate,



Scheme 19.



Scheme 20.



Scheme 21.

$ClBi(OTf)_3$, as intermediate in the reactions that use $Bi(OTf)_3 \cdot xH_2O$ or $BiCl_3$/TfOH system as catalysts [49].

Thus, the reaction of aromatic ethers, benzene, toluene and halobenzenes with PhCOCl or $(PhCO)_2O$, in the presence of bismuth(III) salts, allows the preparation of several benzophenone derivatives, in which the best results achieved occurred with $Bi(OTf)_3 \cdot xH_2O$ as catalyst [50, 51].

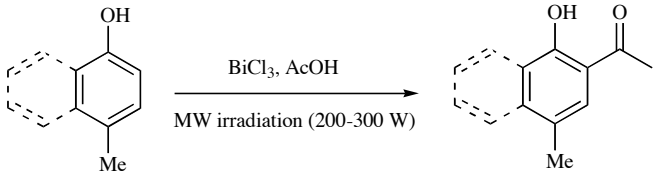
An interesting approach for the Friedel-Crafts benzoylation of aromatics uses $BiCl_3$ generated *in situ* from BiOCl and PhCOCl [52]. When performed in ionic liquids, the catalytic activity of Bi(III) salts, such as $Bi(OTf)_3 \cdot xH_2O$, Bi_2O_3, BiOCl and $BiCl_3$, for the Friedel-Crafts benzoylation reaction was found to increase dramatically. Loadings as low as 1 mol % of $Bi(OTf)_3 \cdot xH_2O$ or Bi_2O_3 in $[emim][NTf_2]$ or $[bmim][NTf_2]$ were enough to achieve clean, high-yielding, benzoylation of a diversity of aromatic compounds [53]. More recently, the use of benzoic acid in the presence of trifluoroacetic anhydride (1.5 equiv) and $Bi(OTf)_3 \cdot xH_2O$ (3.3-10 mol %), at 30 ºC, has been reported for this transformation. For the benzoylation of strongly deactivated substrates, such as chlorobenzene, benzoic acid was combined with $Bi(OTf)_3 \cdot xH_2O$ (3.3-10 mol %) and heptafluorobutyric anhydride (1.5 equiv), at 75-100 ºC [54].

3.3. *ortho*-Hydroxyaryl ketones

ortho-Hydroxyaryl ketones are considered important synthetic intermediates in the synthesis of biologically active compounds such as chalcones, flavanones, naphthoquinones and pesticides [55, 56]. Straightforward approaches to the synthesis of *ortho*-hydroxyaryl ketones include Friedel-Crafts reactions by direct 2-acylation of phenols or 1-naphthols and the Fries Rearrangement of phenyl or 1-naphthyl acyl derivatives.

This latter reaction has been performed in the presence of $Bi(OTf)_3 \cdot xH_2O$. The Fries rearrangement of phenyl and 1-naphthyl acetates proceeded smoothly with 5-10 mol % of $Bi(OTf)_3 \cdot xH_2O$ to afford the corresponding *ortho*-hydroxyaryl ketones, in good yields (Scheme **21**, reaction 1) [55, 56]. Ollevier's group also investigated the catalytic activity of $Bi(OTf)_3 \cdot xH_2O$ in the direct 2-acylation of 1-naphthol using acetyl chloride or acetic anhydride as acylating agents. The reaction was selective, with only C-acylation being observed. Using the best reaction conditions [20 mol % of $Bi(OTf)_3 \cdot xH_2O$, Ac_2O (1.5 equiv), toluene, 110 ºC], the *ortho*-hydroxyaryl ketone was formed in 74 % yield (Scheme **21**, reaction 2) (Note: optimized yield of $Bi(OTf)_3 \cdot xH_2O$-catalyzed Fries rearrangement of 1-naphthyl acetate: 80 %) [56].

The most desirable acylation agents in Lewis acid-assisted Friedel-Crafts transformations are probably carboxylic acids, because the reaction produces a Lewis acid/water complex as the only by-product [57]. Recently, several Lewis acids were screened for the conversion of 1-naphthol and *p*-cresol into the corresponding 2-acyl products in the presence of acetic acid under solvent-free conditions, microwave irradiation and atmospheric pressure. Using



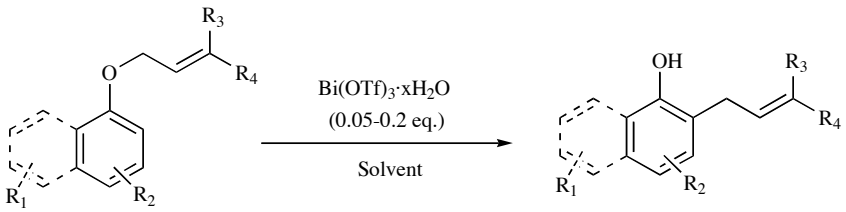
p-cresol ------- AcOH (1.26 eq.) ---$BiCl_3$ (0.66 eq.) --- 2 min ------ 90 %
1-naphthol ---- AcOH (1.74 eq.) -- $BiCl_3$ (0.46 eq.) --- 0.66 min -- 10 %

Scheme 22.

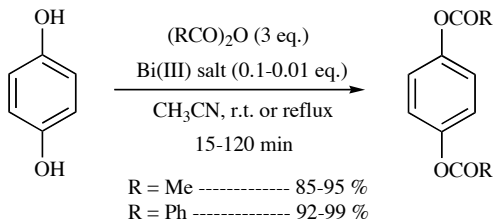
0.46 equivalents of $BiCl_3$, only 10 % of 2-acetyl naphthol derivative was formed, but 90 % of 2-acetyl derivative of *p*-cresol was obtained in the presence of 0.66 equivalents of this Bi(III) salt (Scheme **22**) [58].

3.4. *ortho*-Allyl Phenols and Naphthols

The [3,3] sigmatropic shift (Claisen rearrangement) of allyl aryl ethers is an accessible reaction for the preparation of *ortho*-allyl phenols and naphthols. These are versatile intermediates in the synthesis of biologically active compounds, such as 1,4-naphthoquinones and anthracyclinones [59]. The Claisen rearrangement of allyl phenyl ethers catalyzed by $Bi(OTf)_3{\cdot}xH_2O$ has been described initially by Sreedhar *et al.* [55]. In the presence of 5 mol % of this catalyst several *ortho*-allyl phenols were obtained in moderate to high yields (45-90 %), after a relatively short reaction time (< 2 h) (Scheme **23**). When the reaction was performed with 2,6-dimethoxy allyl phenyl ether, the allyl group selectively rearranged to afford the *para*-allyl product in 95 % yield [55]. More recently, Ollevier's group reported the use of $Bi(OTf)_3{\cdot}xH_2O$ as an efficient catalyst for the Claisen rearrangement of allyl naphtyl ethers. The reaction was performed in acetonitrile, using 20 mol % of $Bi(OTf)_3{\cdot}xH_2O$, and the corresponding *ortho*-allyl naphthols were obtained in moderate to good yields (57-85 %) (Scheme **23**) [59]. Interestingly, rearrangement of 2-substituted allyl 1-naphthyl ethers resulted in the formation of *para*-allyl naphthol derivatives in good yields, through a sequential *ortho*-Claisen rearrangement followed by a second [3,3] rearrangement. These reaction conditions were also found to be suitable for the double Claisen rearrangement of 1,4-, 1,5- and 2,6-di(allyloxy)naphthalenes, although not always with good selectivities [59].



Scheme 23.



R = Me ---------- 85-95 %
R = Ph ---------- 92-99 %

Scheme 24.

The same authors investigated the [1,3] rearrangement of aryl 3-methylbut-2-enyl ethers in the presence of 5 mol % of $Bi(OTf)_3{\cdot}xH_2O$ (Scheme **23**, $R_3 = R_4 = CH_3$). The reaction occured rapidly in an apolar solvent such as toluene and, depending on the substitution pattern of the aromatic ring, the corresponding *ortho*- and *para*-prenyl phenol and naphthol derivatives were isolated in moderate to good yields [60].

3.5. Hydroquinones

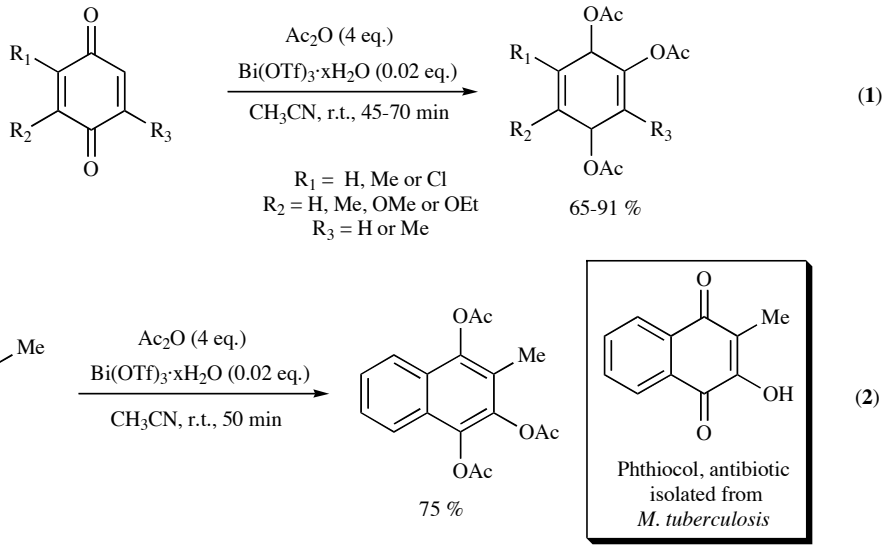
Molecules with the quinoid structure constitute one of the most interesting classes of compounds in organic chemistry. Many naturally occurring hydroxylated quinones exhibit important biological activities, as is the case of the complex natural trimeric hydroxynaphthoquinone conocurvone, a potential anti-HIV agent [61]. Some marketed drugs include the hydroquinone core on their structure, such as doxorubicin, an anthracycline antibiotic used in the treatment of a wide range of cancers [21].

The acetylation and benzoylation of hydroquinone with acetic and benzoic anhydride in the presence of $BiCl_3$ (10 mol %), $Bi(TFA)_3$ (5 mol %) or $Bi(OTf)_3{\cdot}xH_2O$ (1 mol %) has been reported. The corresponding diacyloxy products were obtained in 85-99 % yields (Scheme **24**) [62].

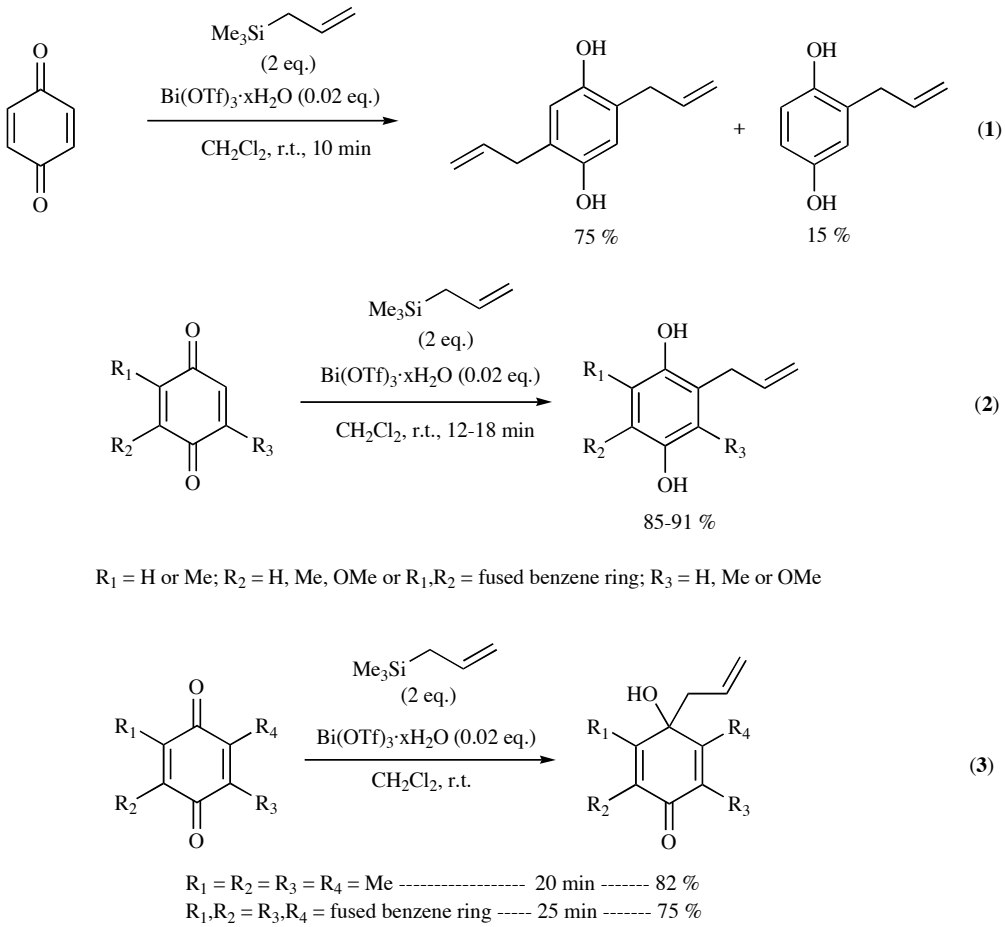
A milder and bismuth-catalyzed method has been reported for the classical Thiele-Winter acetoxylation of quinones. Thus, the reaction of *p*-quinones with acetic anhydride in the presence of $Bi(OTf)_3{\cdot}xH_2O$ (2 mol %) afforded the corresponding 1,2,4-triacetoxyhydroquinones, in high yields (Scheme **25**, reaction 1). These reaction conditions were also suitable for the conversion of 1,4-naphthoquinone and 2-methylnaphthoquinone (menadione) into their triacetoxy derivatives [63]. Of special importance is the synthesis of the triacetate derived from menadione, which is a precursor of phthiocol, an antibiotic isolated from *Mycobacterium tuberculosis* (Scheme **25**, reaction 2) [63].

The allylation of quinones is an important reaction for the preparation of isoprenoid quinones such as vitamins E and K, and coenzyme Q which play a crucial role in biological processes [64]. Functionalized quinols are not only important in the biosynthesis and metabolism of natural phenols but are also useful as synthetic precursors of naturally occurring quinones and alkaloids [64]. Yadav *et al.* described the use of $Bi(OTf)_3{\cdot}xH_2O$ (2 mol %) as catalyst in the allylation reaction of several *p*-quinones with allyltrimethylsilane, which afforded the corresponding allyl substituted benzene derivatives, *p*-allylquinols and allyl substituted 1,4-naphthoquinones, in very high yields (75-91 %) and high regioselectivity (Scheme **26**, reactions 1-3) [64].

A bismuth-catalyzed conjugate addition of indoles to α,β-enones, including naphthoquinone derivatives, has been reported to give the corresponding Michael adducts in high yields [65]. This reaction was further developed, and a wide range of indoles were found to undergo conjugate nucleophilic addition to *p*-benzoquinones or 1,4-naphthoquinones in the presence of only 2 mol % of $Bi(OTf)_3{\cdot}xH_2O$, and afford the corresponding indol-3-yl quinones in 75-93 % yield, with high selectivity (Scheme **27**, reaction 1) [66]. Indol-3-yl benzoquinones are particularly relevant because this moiety is the core structure of asterriquinones. This group of natural compounds exhibits a wide spectrum of biological



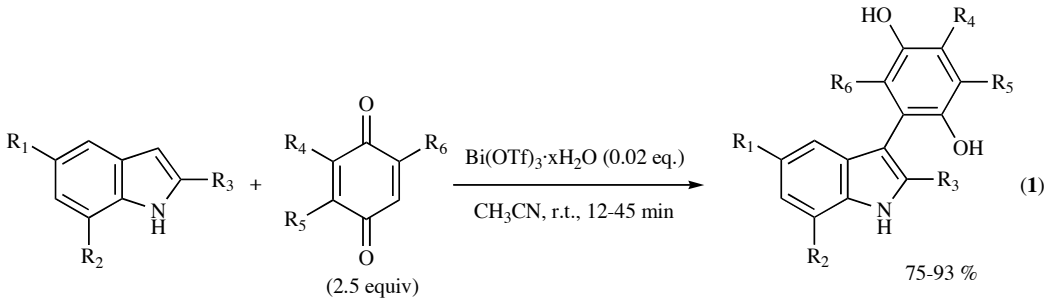
Scheme 25.



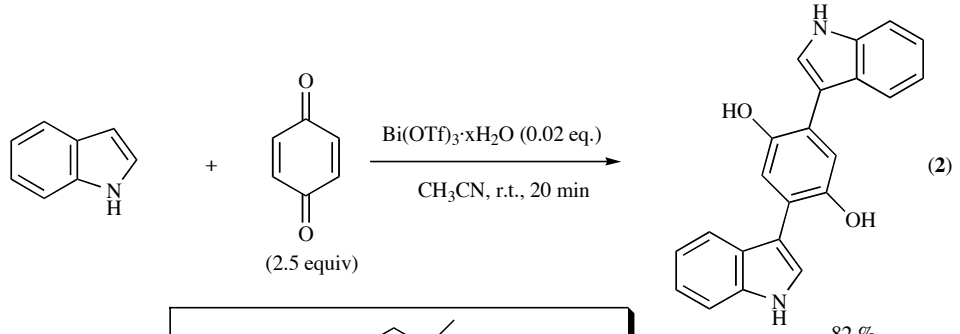
Scheme 26.

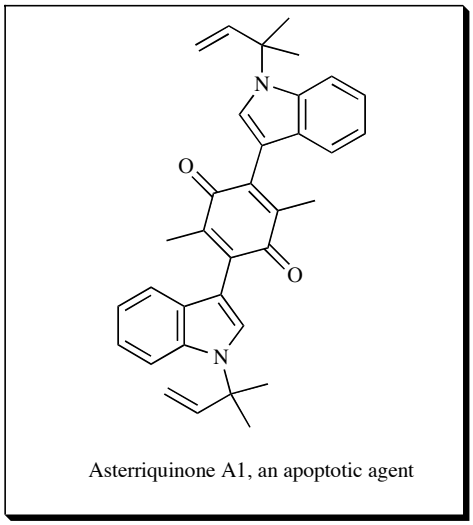
activities that include inhibition of the HIV reverse transcriptase and antitumoral properties and can also act as insulin mimetics thus acting as antidiabetics [67]. Interestingly, Yadav's procedure seems to be suitable for the construction of the asterriquinone nucleus, since the reaction of indole with *p*-benzoquinone gives the corresponding bis(3-indolyl)-hydroquinone derivative in 82 % isolated yield (Scheme **27**, reaction 2) [66].

During the study of the nitration of aromatic compounds under solvent-free conditions, using supported $Bi(NO_3)_3{\cdot}5H_2O$ on silica sulfuric acid, hydroquinone was converted to nitrohydroquinone in



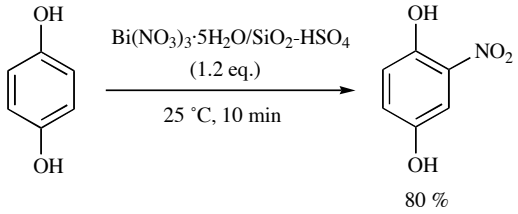
R_1 = H, OMe or Br; R_2 = H or OEt; R_3 = H, Me or COOEt
R_4 = H or Me; R_6 = H, Cl, OMe; R_5 = H or Cl or R_4 = R_5 = fused benzene ring





Scheme 27.

80 % yield, after 10 min of reaction at room temperature (Scheme **28**) [68].



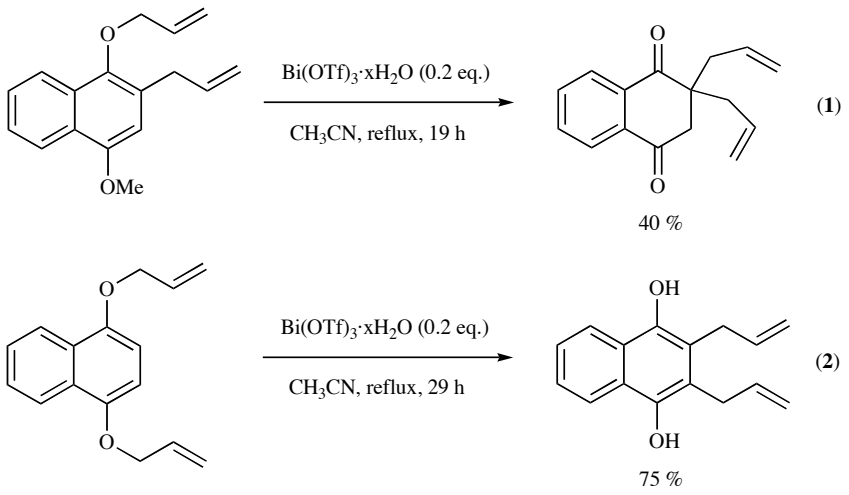
Scheme 28.

The $Bi(OTf)_3 \cdot xH_2O$-catalyzed rearrangement of a 2,4-disubstituted allyl naphthyl ether in CH_3CN at reflux, has been reported to yield 2,2-diallyl-2,3-dihydronaphthalene-1,4-dione in 40 % yield, presumably after acid hydrolysis of the enol ether function (Scheme **29**, reaction 1) [59]. Under the same reaction conditions, 1,4-di(allyloxy)naphthalene afforded the corresponding doubly rearranged product in 75 % yield (Scheme **29**, reaction 2).

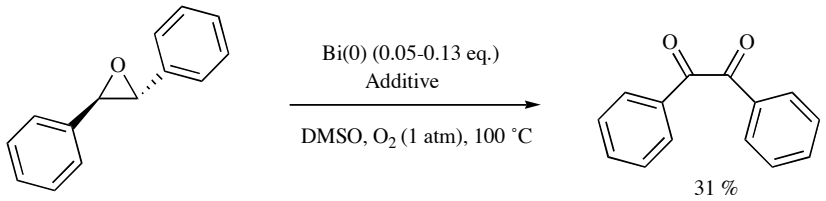
3.6. Miscellaneous Monocyclic and Polycyclic Aromatic Compounds

Bismuth-mediated oxidation reactions involving terminal aryl epoxides have been extensively studied [69]. Recently, Antoniotti and Duñach reported the catalytic oxidation of epoxides to α-diketones by bismuth derivatives under atmosphere of O_2, in DMSO [70]. Mechanistic studies were carried out and the role of bismuth catalyst both as a Lewis acid and an active redox agent has been elucidated [71]. The best catalytic systems for this conversion were Bi(0), in the presence of an additive [TfOH or $Cu(OTf)_2$], and $Bi(OTf)_3 \cdot xH_2O$. Using this method, aromatic epoxides afforded only 31 % of the diketone product in a non-selective fashion (Scheme **30**) [71].

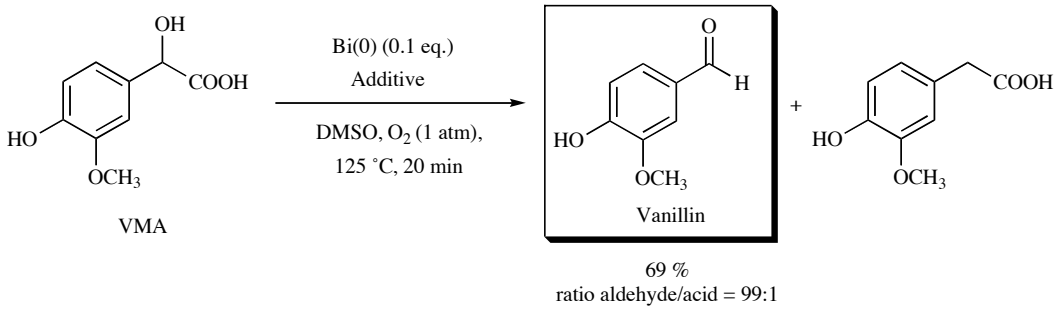
The similar catalytic oxidative system, Bi(0) in DMSO under O_2 atmosphere, has been applied to the oxidation of mandelic acid derivatives. The nature of the substituents on the aromatic ring



Scheme 29.



Scheme 30.



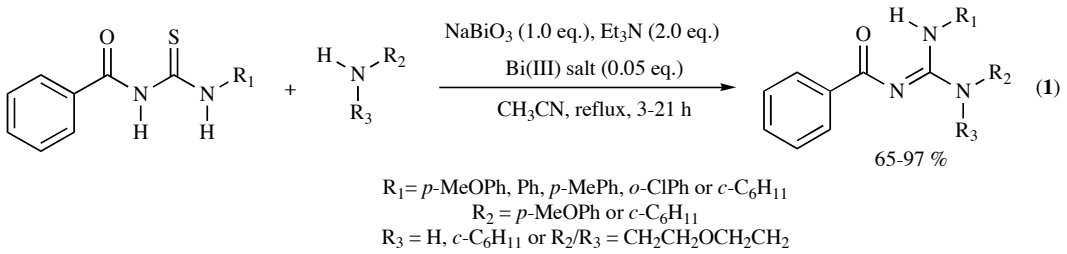
Scheme 31.

strongly influenced the reaction chemoselectivity leading to the benzaldehyde or benzoic acid derivatives as the major product [72, 73]. Of special interest is the oxidation of vanillylmandelic acid (VMA or 4-hydroxy-3-methoxymandelic acid) to give vanillin (Scheme **31**), which is a flavor agent and an intermediate in drug synthesis produced industrially at ton-scale.

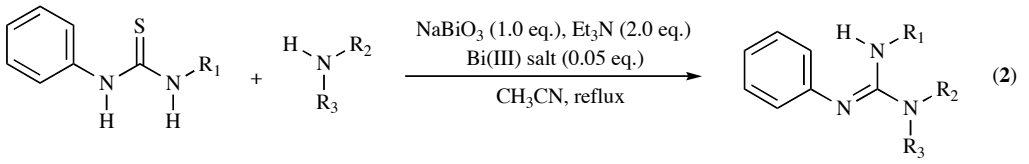
The guanidine moiety is known to elicit a variety of pharmacological responses, often associated with its strong cationic nature, and is present in several marketed drugs or drug candidates [74], as well as in many natural compounds [75]. The preparation of *N*-benzoylguanidines has been reported from the reaction of *N*-benzoylthioureas with 2 equivalents of amine in the presence of 1 equivalent of $Bi(NO_3)_3{\cdot}5H_2O$ and Et_3N [76]. Cunha and Rodrigues rationalized the need of stoichiometric amounts of $Bi(NO_3)_3{\cdot}5H_2O$ as result of the formation of the poorly soluble Bi_2S_3, which is unable to activate the thiourea derivatives. Thus, in the presence of an oxidant as a co-reagent, Bi_2S_3 would be converted to the more soluble $(SO_x)^{y-}$-derivatives of Bi(III), capable of promoting the guanylation reaction. Both $Bi(NO_3)_3{\cdot}5H_2O$ and BiI_3 were active at only 5 mol % in the presence of 1 equivalent of $NaBiO_3$ as oxidant, and 2 equivalents of Et_3N [77]. This new bismuth-catalyzed process allowed the synthesis of polysubstituted guanidines, in good yields, through the guanylation reaction of *N*-benzoyl or *N*-phenylthioureas, with primary and secondary amines (Scheme **32**, reactions 1 and 2).

The bismuth-catalyzed Friedel-Crafts benzoylation reactions have been previously discussed when synthetic strategies leading to diaryl carbonyl derivatives were reviewed. The Friedel-Crafts transformations have a much larger broad of application in the preparation of functionalized aromatic compounds, but an exhaustive review of these bismuth-catalyzed reactions is out of the scope of this section.

To illustrate the potential of Friedel-Crafts acylation reactions, the synthesis of 2-acetyl-6-methoxynaphthalene, a well-known intermediate for the synthesis of naproxen, has been reported from the reaction of 2-methoxynaphthalene and Ac_2O in the presence of Lewis acids. The addition of 6 equivalents of $LiClO_4$ proved to be essential, seeing that in the absence of this salt the major reaction product was the 1-acyl adduct. Thus, although better results have been achieved with $Sb(OTf)_3$, when the reaction was performed with $Bi(OTf)_3{\cdot}xH_2O/LiClO_4$ in CH_3NO_2, at 50 ºC during 4 hours,

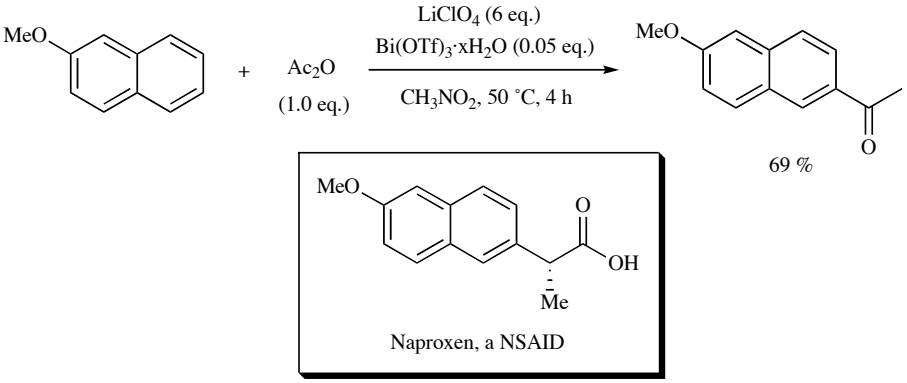


R_1= *p*-MeOPh, Ph, *p*-MePh, *o*-ClPh or *c*-C_6H_{11}
R_2 = *p*-MeOPh or *c*-C_6H_{11}
R_3 = H, *c*-C_6H_{11} or R_2/R_3 = $CH_2CH_2OCH_2CH_2$



R_1 = *p*-MeOPh; R_2/R_3 = $CH_2CH_2OCH_2CH_2$ ------ 3 h ------ 95 %
R_1= R_2 = *c*-C_6H_{11}; R_3 = H ---------- ---- 7 h ------ 95 %

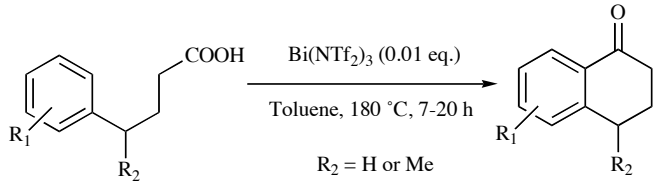
Scheme 32.



Scheme 33.

the desired 2-acetyl-6-methoxynaphthalene was obtained in 69 % yield (Scheme **33**) [78].

The synthesis of 1-tetralones which are important intermediates for the preparation of pharmaceuticals such as sertraline [79], has been reported with the intramolecular Friedel-Crafts acylation of 4-arylbutyric acids in the presence of Lewis acids. The best results were observed with $Bi(NTf_2)_3$ (1 mol %) in toluene, at 180 ºC, and thus several 1-tetralones were prepared in very high yields under these reactions conditions (Scheme **34**) [80].



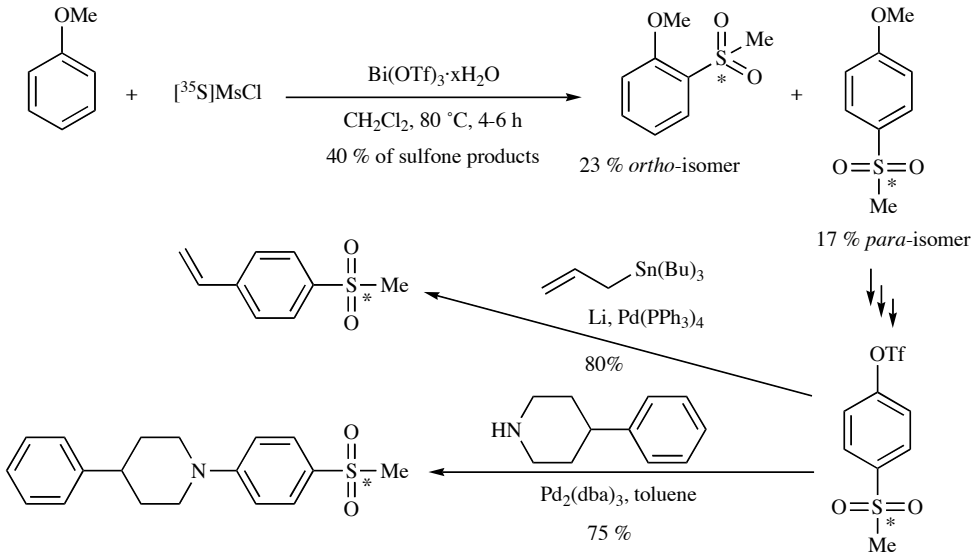
Scheme 34.

Le Roux and co-workers have paved the way for bismuth(III)-catalyzed Friedel-Crafts sulfonylation of arenes and provided outstanding results for the aryl- and alkyl-sulfonylation of arenes [2f, 81]. Wallace *et al*. reported the Lewis acid-assisted sulfonylation of anisole with [^{35}S]methanesulfonyl chloride to afford high specific activity (> 900 Ci/mmol) aryl [^{35}S]sulfones. Both $In(OTf)_3$ and $Bi(OTf)_3{\cdot}xH_2O$ were used but higher yields of sulfone products (as a mixture of *ortho*- and *para*-isomers) were achieved with the Bi(III) salt as catalyst (Scheme **35**) [82]. The resulting *para*-isomer was subsequently converted into the corresponding aryl [^{35}S]sulfone triflate. This compound proved to be a very versatile synthetic intermediate in several standard triflate reactions, including amination and Stille-type coupling reactions. The resulting products provided [^{35}S]-radioligands applicable in biological assays, such as receptor occupancy and binding studies [82].

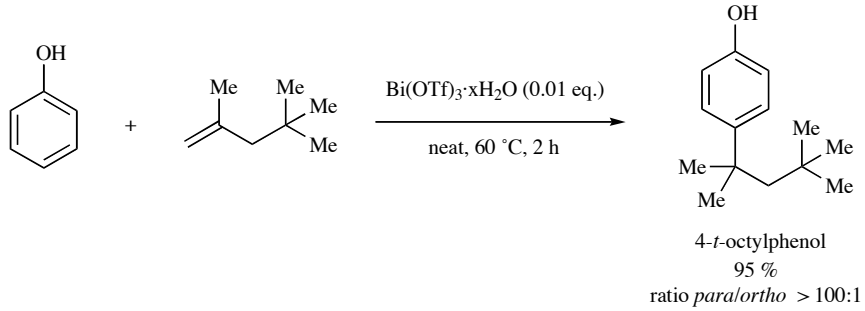
Alike Friedel-Crafts acylations and sulfonylations, FC-alkylation reactions also play an important role in fine chemistry, especially when good regioselectivities, such as selective *para*-orientation, are obtained. The alkylation of phenol with 2,4,4-trimethylpent-1-ene was studied in the presence of several metal triflates and triflimidates and the best results were achieved with $Bi(OTf)_3{\cdot}xH_2O$ (1 mol %). Thus, *t*-octylphenol was obtained in 95 % yield (ratio *para*/*ortho* > 100:1) under solvent-free conditions and in an inert atmosphere, at 60 ºC after 2 hours of reaction (Scheme **36**) [24].

An efficient and straightforward approach for the synthesis of tetralins by intramolecular Friedel-Crafts alkylation starting from tetrahydrofurans has been reported by Coles *et al*. Thus, using $BiCl_3$ as catalyst, the *O*-acylative cleavage of 2-(3-phenylprop-1-yl)-tetrahydrofuran with acetyl chloride resulted in a smooth acylation/cyclisation sequential reaction to afford an acyl tetralin core-containing compound, in 87 % yield, after 3 hours at room temperature. (Scheme **37**) [12].

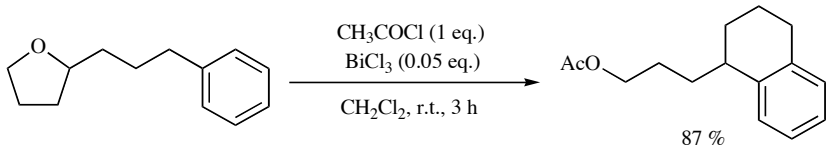
Iodination of activated arenes with molecular iodide and stoichiometric amounts of $Bi(NO_3)_3{\cdot}5H_2O$ supported on silica as oxidant has been reported for the preparation of iodoarenes [83].



Scheme 35.



Scheme 36.



Scheme 37.

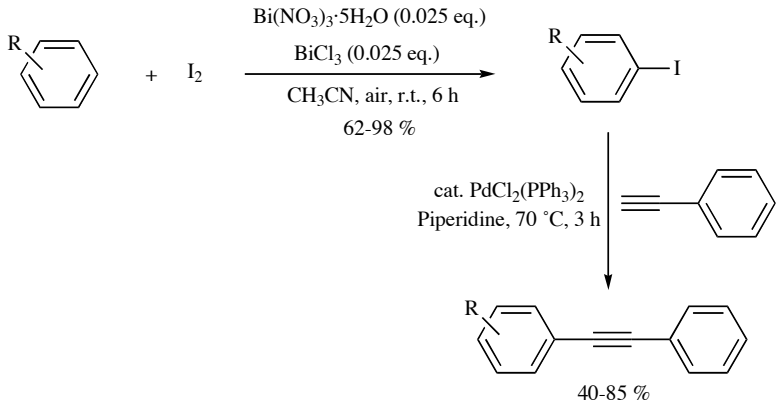
More recently, this reaction was performed using air as the oxidant in the presence of the $Bi(NO_3)_3{\cdot}5H_2O/BiCl_3$ catalytic system, which proved to be better than other catalysts such as $BiCl_3$, Bi_2O_3, $Cu(OAc)_2$, $CuCl_2$, $Cu(NO_3)_2$, $Fe(NO_3)_3$, $K_2S_2O_8$, and $KMnO_4$, both used alone or in combination. The reactions proceeded at room temperature in CH_3CN and 2.5 mol % of $Bi(NO_3)_3{\cdot}5H_2O/BiCl_3$ system were used to efficiently promoted the iodination of arenes to afford the desired products in 62-98 % yield (Scheme **38**) [84]. The resulting iodoarenes were converted to arylalkynes by a selected palladium-catalyzed coupling reaction with terminal alkynes in the same reaction-pot. Arylalkynes are useful intermediates for the preparation of important compounds including natural products and pharmaceuticals [84].

The reaction of *sec*-benzyl alcohols with allytrimethylsilane, at 80 ºC, catalyzed by $BiCl_3$ afforded the corresponding deoxygenated allylation products in very high yields (Scheme **39**) [28]. However, when the reaction was performed at room temperature, intermolecular nucleophilic etherification was observed [28].

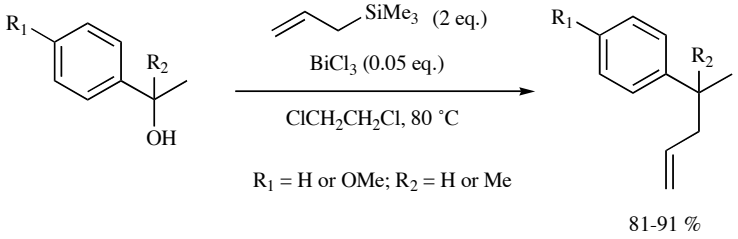
The direct benzylation of 2,4-pentanediones using benzyl alcohols and its derivatives has been reported in the presence of Bi(III) salts. The reaction was performed in CH_3NO_2 at 100 ºC and $Bi(OTf)_3{\cdot}xH_2O$ (1 mol %) was chosen as the best catalyst. It was noteworthy that no reaction was observed with Brønsted acids, such as TfOH and HCl. Different 1,3-dicarbonyl compounds were screened in the reaction with both primary and secondary benzyl alcohols (Scheme **40**). Generally, the reactions performed with the secondary alcohol 1-phenyl ethanol gave a higher yield which is in agreement with a more stabilized carbocation intermediate [85].

Rueping and co-workers, replaced benzyl alcohols by styrene derivatives in the inter- and intramolecular hydroalkylation reactions using 1,3-dicarbonyl compounds as nucleophiles. In this case, among the Bi(III) salts tested, only $Bi(OTf)_3{\cdot}xH_2O$ (1-5 mol %) was effective in the hydroalkylation of styrene with 2,4-pentanedione, in CH_3NO_2, at 100 ºC. Various styrenes as well as non-aromatic alkenes such as norbornene reacted, under optimized conditions, with alkyl and aryl 1,3-dicarbonyl compounds to afford the desired hydroalkylation products in 41-90 % yield. (Scheme **41**, reactions 1 and 2) [86].

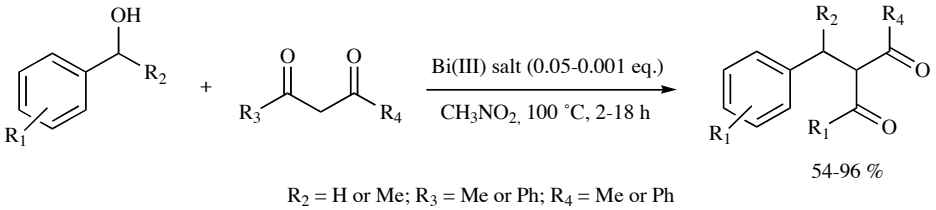
Using the bismuth-catalyzed procedure for the direct benzylation of 2,4-pentanediones with benzyl alcohols [85], Rueping *et al.*



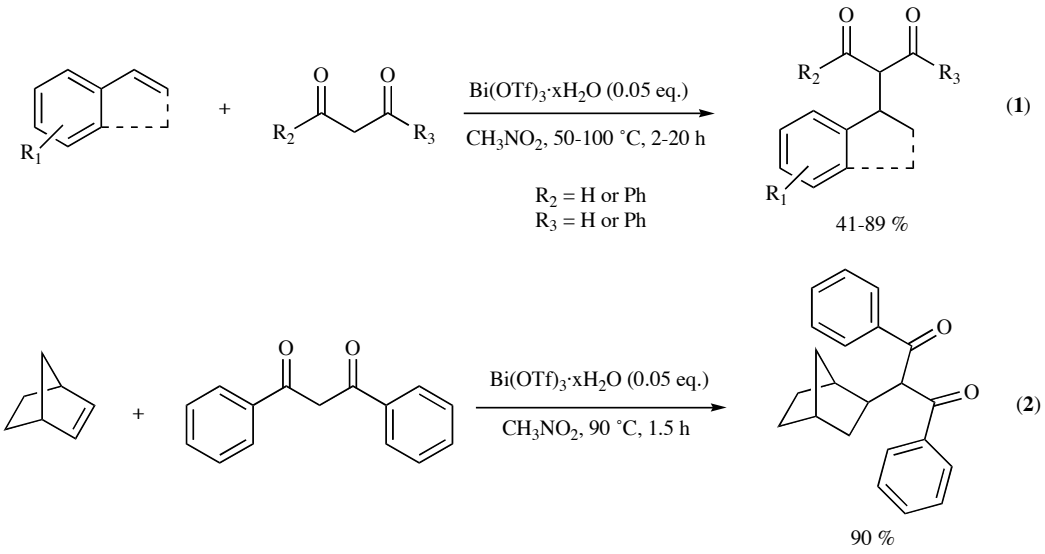
Scheme 38.



Scheme 39.



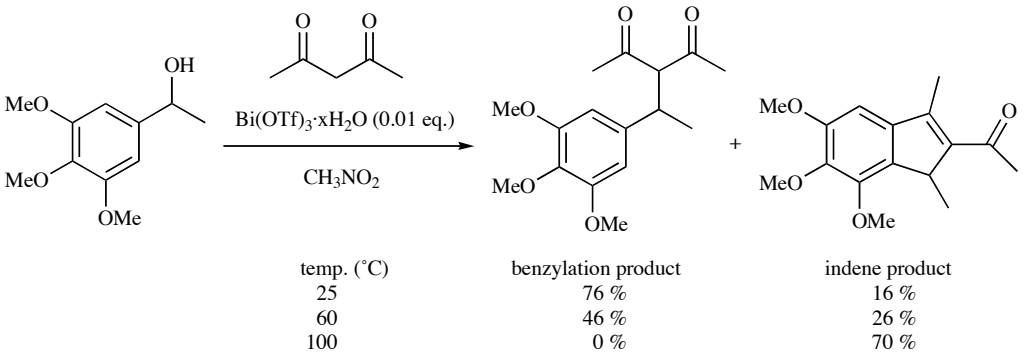
Scheme 40.



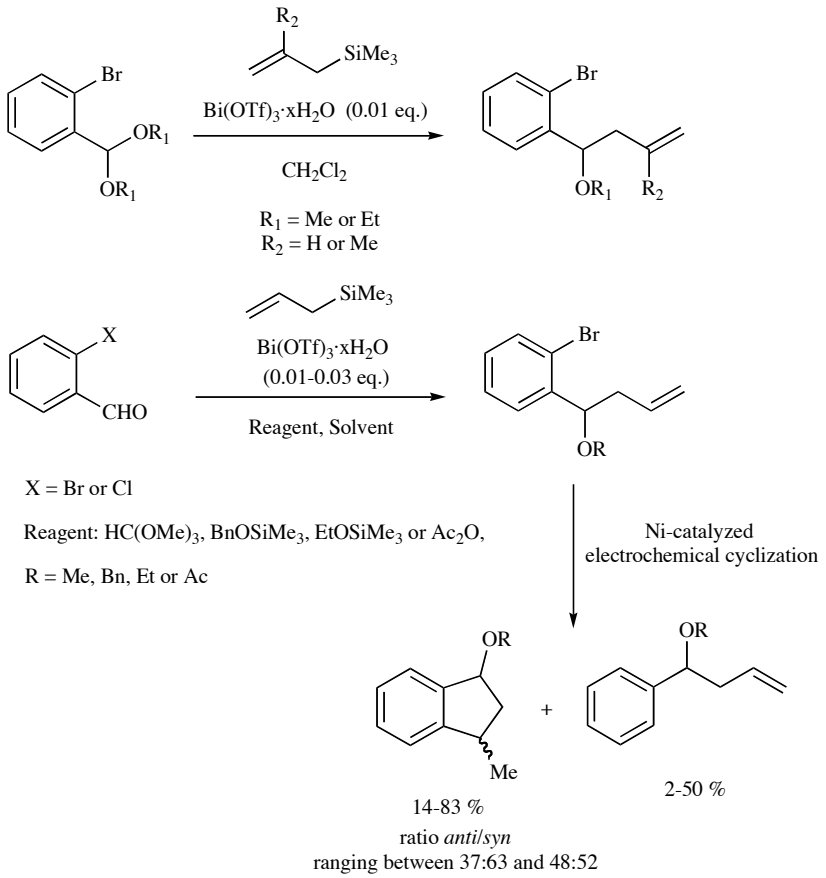
Scheme 41.

described the reaction of 1-trimethoxyphenylethanol with pentane-2,4-dione. At 25 ºC, in addition to the expected benzylation product, an indene derivative that resulted from an intramolecular arylation reaction was also formed. At 100 ºC, it became the major reaction product being isolated in 70 % yield (Scheme **42**) [85].

From the collaboration between Duñach and Mohan research groups, an interesting approach for the synthesis of functionalized indanes has been reported via a sequential synthetic route involving the Ni-catalyzed electrochemical cyclization of *ortho*-halo-substituted homoallyl ethers and esters [87]. These intermediates



Scheme 42.



Scheme 43.

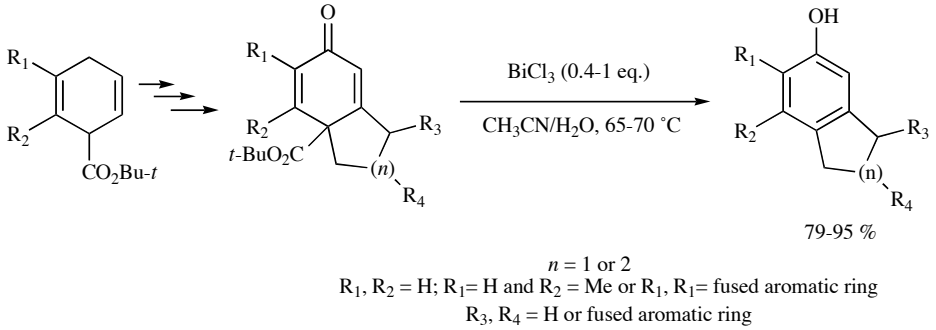
were prepared according to previously developed strategies using $Bi(OTf)_3{\cdot}xH_2O$ as catalyst (Scheme **43**) [88, 89]. Thus, homoallyl ethers were prepared from allylation of acetal derivatives with organosilicon reagents in the presence of $Bi(OTf)_3{\cdot}xH_2O$ [88], or directly from the corresponding aldehydes, either by *in situ* generation of the acetal followed by its reaction with allyltrialkylsilane, or by a three-component synthesis in which the aldehyde, trimethylorthoformate or an alkoxytrimethylsilane and allyltrimethylsilane are mixed together in the presence of catalytic amounts of $Bi(OTf)_3{\cdot}xH_2O$ [89]. In addition, when acetic anhydride was mixed with the aldehydes and allyltrimethylsilane in an appropriate solvent, in the presence of $Bi(OTf)_3{\cdot}xH_2O$, the corresponding homoallyl acetates were obtained [89].

Recently, Clive and Sunasee described a new indirect method for the synthesis of benzo-fused carbocycles starting from *tert*-butyl benzoate derivatives. One of the key steps involved the rearomatization of the cyclization intermediate products, in a $BiCl_3$-promoted reaction, in CH_3CN/H_2O. Using 0.4-1.0 equivalents of $BiCl_3$, efficient cleavage of *tert*-butyl esters followed by decarboxylation afforded the desired benzo-fused carbocycles (Scheme **44**) [90].

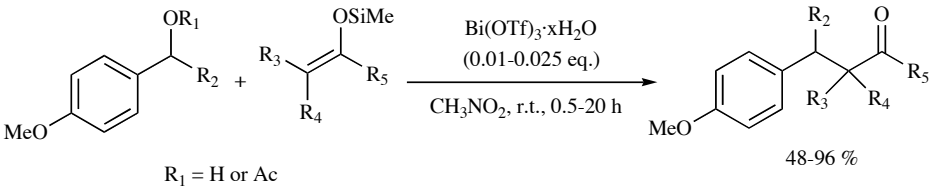
The direct alkylation of silyl enol ethers with *para*-methoxybenzylic alcohols or their corresponding acetates was efficiently catalyzed by $Bi(OTf)_3{\cdot}xH_2O$ in CH_3NO_2. The reaction provided the α-benzyl carbonyl compounds, in high yields, after short reaction times, using 1-2.5 mol % of the catalyst. Benzylic acetates other than *para*-methoxybenzylic acetates were reactive, contrary to what was found for their corresponding alcohols (Scheme **45**) [37].

4. AMINO ACIDS AND PEPTIDES

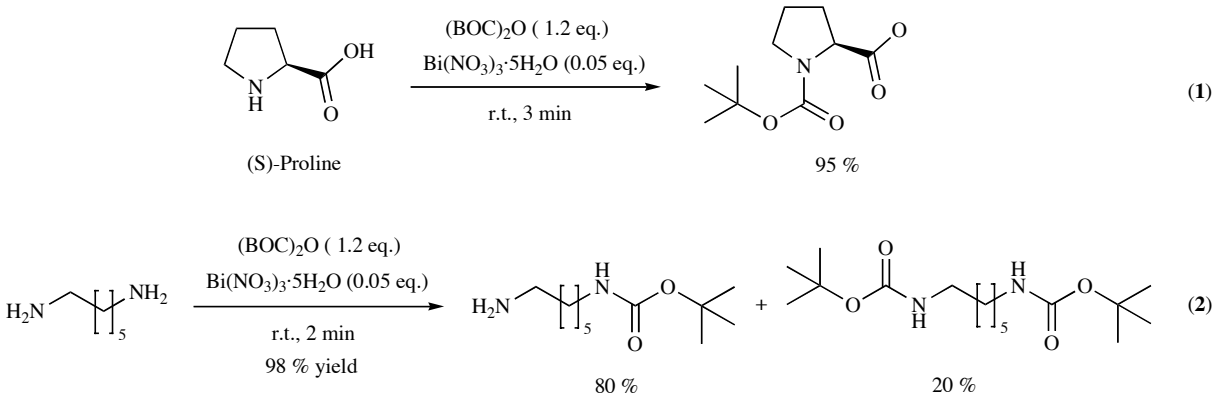
Amino acids and peptides are of unquestionable value in the field of medicinal chemistry. Of great interest are the reactions



Scheme 44.



Scheme 45.



Scheme 46.

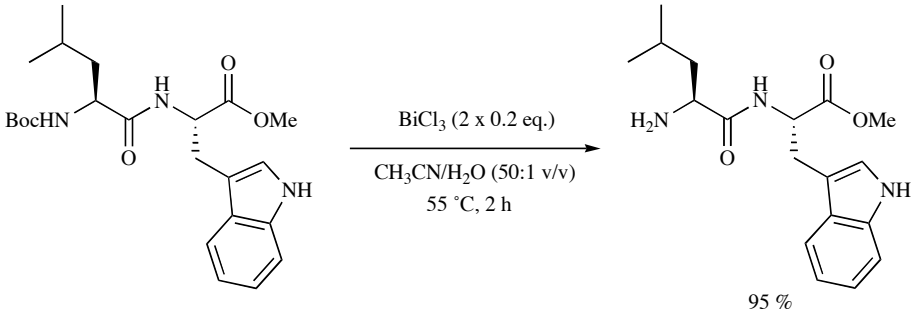
related to the protection/deprotection of their amine groups. In this context bismuth(III) salts have been used with considerable success. The *N-tert*-butoxycarbonylation reaction is on the most common strategies to protect peptidic amines. Various primary, secondary and aryl amines were efficiently converted into their corresponding *N*-Boc protected derivatives by reaction with di-*tert*-butyl dicarbonate, in the presence of 5 mol % of $Bi(NO_3)_3{\cdot}5H_2O$, under solvent-free conditions, including the α-amino acid proline (Scheme **46**, reaction 1) [91]. A diversity of functional groups, including acetyl, benzyl and some isopropylidenes were stable under these reaction conditions. This method seems to be also appropriate for the preparation of mono *N*-Boc derivatives of diamines (Scheme **46**, reaction 2) [91].

The use of $BiCl_3$ for the chemoselective deprotection of *N*-Boc groups in amino acids and peptides has been reported. The dipeptide Boc-Leu-Trp-OMe was deprotected using 0.4 equivalents of this bismuth(III) salt in CH_3CN/H_2O, at 55 ºC (Scheme **47**). Under these reaction conditions no alkylation of the indolyl side chain of the tryptophan residue by the *tert*-butyl cation was observed. Methyl esters, hydrazines, hydroxamic acids and other protecting groups, including Pmc (2,2,5,7,8-pentamethylchroman-6-sulphonyl) and *tert*-butyl esters were found to be stable under these reaction conditions [92].

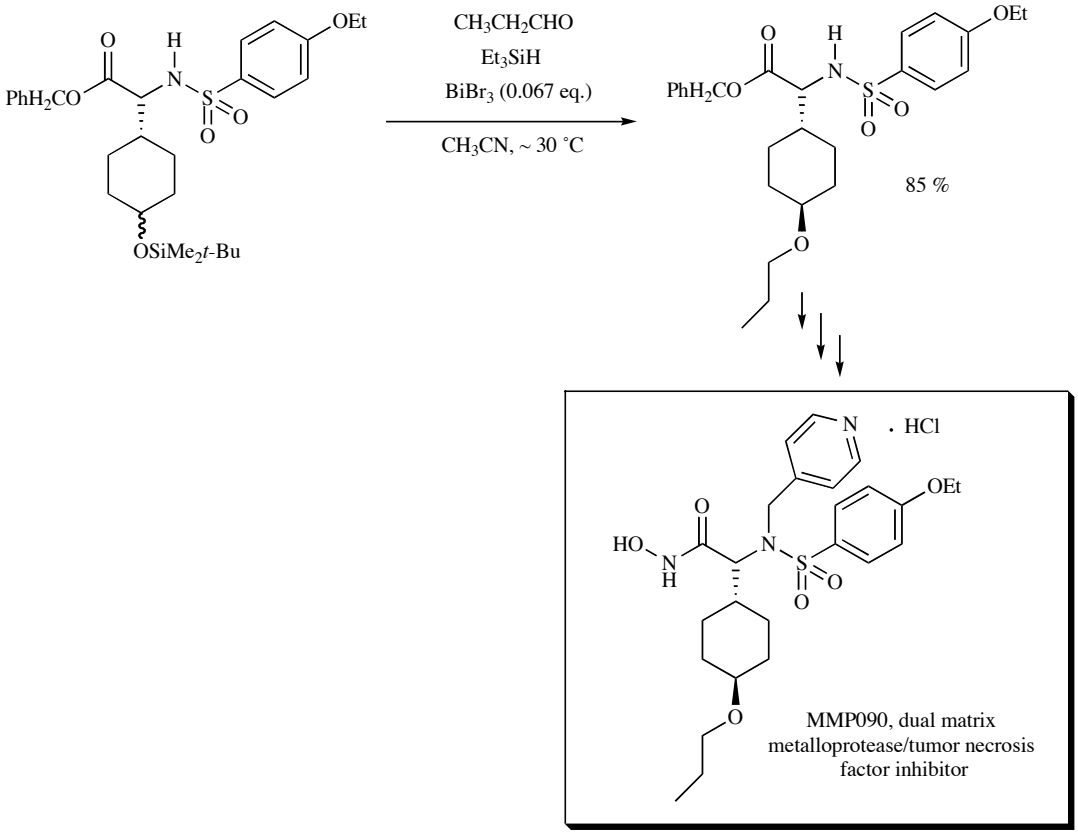
The dual matrix metalloprotease/tumor necrosis factor inhibitor MMP090 is a highly functionalized, reduced hydroxyphenylglycine derivative in which the cyclohexyl oxygen is alkylated with an *n*-propyl group and the nitrogen is alkylated and sulfonylated. A 9-step synthesis of this compound starting from *D*-4-hydroxyphenylglycine was recently reported in 12 % overall yield [93]. One of the most critical steps involved the direct conversion of the protecting TBDMS ether of the 4-hydroxycyclohexyl side chain into the corresponding *n*-propyl ether in the presence of a catalytic amount of $BiBr_3$. This reaction was based on the previous report by Komatsu *et al*. [94], but detailed mechanistic study was carried out by Bajwa and co-workers [95]. Thus, the TBDMS ether derivative was converted into the desired product in 85 % yield with great enantioselectivity (> 99 %, determined by HPLC) by reaction with propionaldehyde, triethylsilane and $BiBr_3$ (6.7 mol %) in dry acetonitrile (Scheme **48**) [93].

5. TERPENES

Commonly considered as the largest group of natural products, terpenes are widely distributed in nature. For many years their role in nature remained obscure, but recent studies clearly show a great diversity of biological activities [96].



Scheme 47.



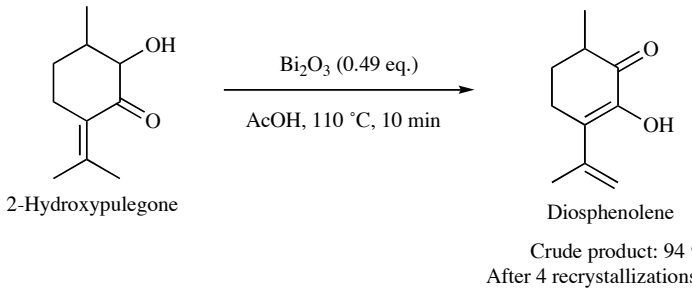
Scheme 48.

Despite its simple structure, monoterpenes such as menthol, geraniol, linalool, borneol or citronellal are important compounds of pharmaceutical interest. In addition to their well established value as synthetic intermediates [97], several biological activities have been reported for this group of compounds [96, 98, 99]. A quite recent review focused on the mechanism of action of menthol (agonist of thermally sensitive receptor TRPM8, formally CMR1 or Trpp8) and its dermatologic applications [99]. Anticancer activity has been found for (R)-(–)-carvone and geraniol, whereas antiviral and antifungic activities have been observed for borneol and β-pinene, respectively. The acetate derivative of linalool, linalyl acetate, has shown analgesic and edema-reducing activities [96b].

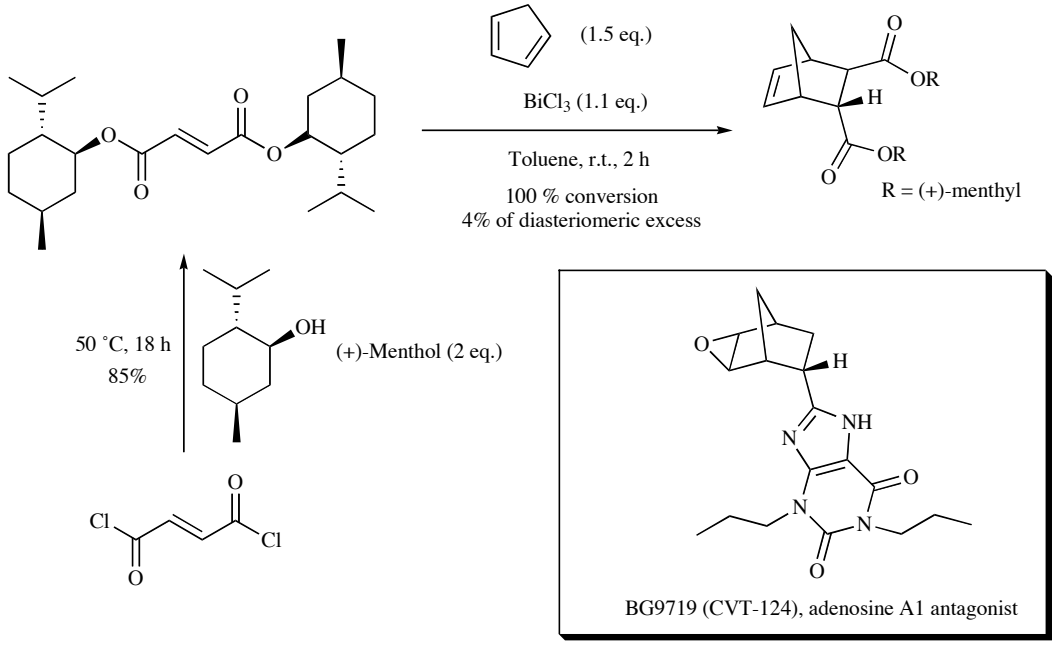
Diosphenolene is a readily available compound which can be easily prepared from piperitone oxide, the major constituent of the essential oil of *Mentha rotundifolia*. The synthesis of diosphenolene was described starting from pulegone. The final step involved the oxidation of 2-hydroxypulegone with Bi_2O_3 in acetic acid and the final product was obtained in 34% yield after four recrystalizations (Scheme **49**) [100].

The asymmetric Diels-Alder reaction of (+)-dimenthyl fumarate and cyclopentadiene has been extensively investigated in order to determine which conditions lead to the best yield and diastereomeric excess. (+)-Menthol was used as an inexpensive chiral auxiliary in the course of the development of a large-scale production process for the preparation of the enantiomerically pure (2R,3R)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid, an intermediate in the synthesis of the adenosine A1 antagonist BG9719 (CVT-124). Among the Lewis acids tested, $BiCl_3$ promoted reaction rendered 100% conversion, but poor diastereomeric excess (Scheme **50**) [101].

By the use of bismuth(III) salts as catalysts for acylation reactions, several monooxygenated monoterpenes have been converted into the corresponding acyloxy products [62, 102-105] (Scheme **51**, reactions 1-9). Although different in terms of the Bi(III) salt, amount of catalyst, equivalents and nature of acylation agent, solvent and temperature used, very high yields were obtained with all the reported processes. The $Ac_2O/Bi(OTf)_3 \cdot xH_2O$ system has been applied to the acetylation of geraniol (Scheme **51**, reaction 1) [102],



Scheme 49.



Scheme 50.

borneol (Scheme **51**, reaction 2) [102], linalool (Scheme **51**, reaction 4) [102] and menthol (Scheme **51**, reaction 6) [62, 102b, 103, 104]. $BiCl_3$ and $Bi(TFA)_3$ were also described as efficient catalysts for the acetylation of menthol [62, 103], despite the fact that higher temperatures and/or reaction times were needed to achieve identical yields (Scheme **51**, reactions 6 and 7). The acetylation of menthol was also carried out using $BiCl_3$ generated *in situ* from the procatalyst BiOCl and acetyl chloride, which also acted as the acetylation agent (Scheme **51**, reaction 8) [105]. Retention of configuration was achieved in the conversion of both (+)-menthol [105] or (–)-menthol [62, 103] to the corresponding acetate derivatives (Scheme **51**, reactions 6-8). $Bi(OTf)_3{\cdot}xH_2O$ is also an effective catalyst for the pivalation of borneol and menthol with pivaloyl anhydride or pivaloyl chloride (Scheme **51**, reactions 3 and 9) [102]. (–)-Menthol was quantitatively converted into the corresponding formate and benzoate derivatives after reaction with ethyl formate [103] and benzoic anhydride [62], respectively, in the presence of $BiCl_3$, $Bi(TFA)_3$ or $Bi(OTf)_3{\cdot}xH_2O$ (Scheme **51**, reactions 5 and 10).

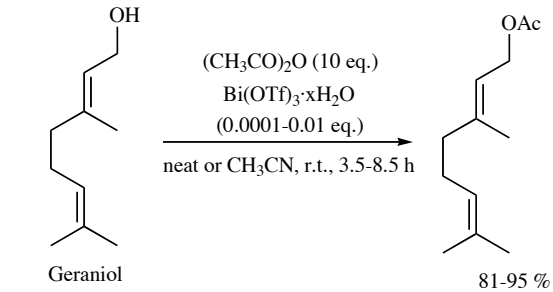
Keramane and co-workers reported the benzylation of (S)-(–)-menthol with racemic 1-phenylethanol in the presence of catalytic amounts of $BiBr_3$ [106]. The corresponding ether was obtained as an equimolar mixture of diastereomers in 90 % yield (Scheme **52**), and thus the reaction was shown to occur specifically with retention of configuration.

The tetrahydropyranylation of the secondary hydroxyl groups of geraniol and menthol (Scheme **53**, reaction 1) and the tertiary alcohol of linalool has been accomplished by reaction with 3,4-dihydro-2*H*-pyran (DHP) in the presence of 0.1 mol % of $Bi(OTf)_3{\cdot}xH_2O$ [107]. More recently, $Bi(NO_3)_3{\cdot}5H_2O$ was reported to be a more efficient catalyst, affording the tetrahydropyranyl (THP) ethers of menthol (Scheme **53**, reaction 1) and geraniol in 90 % and 88 % yield, respectively, after a shorter reaction time [108]. The high yield depyranylation reaction of these monoterpene THP ethers derivatives was reported using 1 mol % $Bi(OTf)_3{\cdot}xH_2O$ in DMF-MeOH (9:1 v/v) [107] or $BiCl_3$ (3 mol %), $Bi(TFA)_3$ (5 mol %) and $Bi(OTf)_3{\cdot}xH_2O$ (1 mol %) in MeOH (Scheme **53**, reaction 2) [109].

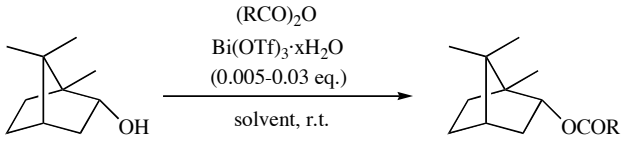
Bismuth(III) salts catalyzed the direct conversion of the THP ether of menthol to the corresponding formate, acetate and benzoate derivatives by reaction with appropriate acylation reagents (Scheme **53**, reactions 3-6). The reactions proceeded at reflux with ethyl formate or acetic acid (Scheme **53**, reactions 3 and 4) [110] whereas the use of acetic or benzoic anhydrides, at room temperature, was enough to achieve high yields with short reaction times (Scheme **53**, reactions 5 and 6) [111].

The deprotection of the *tert*-butyldimethylsilyl ether of (–)-menthol was accomplished using the $BiCl_3$/NaI system in acetonitrile, at room temperature, in 80 % yield, without loss of the original configuration (Scheme **54**) [112].

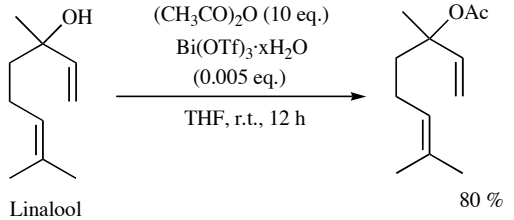
The deprotection of citral dimethylacetal has been performed in the presence of 0.1 mol % of $Bi(OTf)_3{\cdot}xH_2O$ using THF/H_2O (4:1 v/v) as solvent (Scheme **55**, reaction 1) [113]. More recently, the



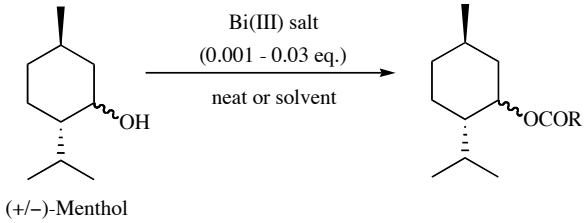
(**1**)



R = Me (10 eq.) ------ THF ------- 7 h ----- 99 % (**2**)
R = *t*-Bu (1.5 eq.) ---- CH_2Cl_2 ---- 4 h ---- 97 % (**3**)

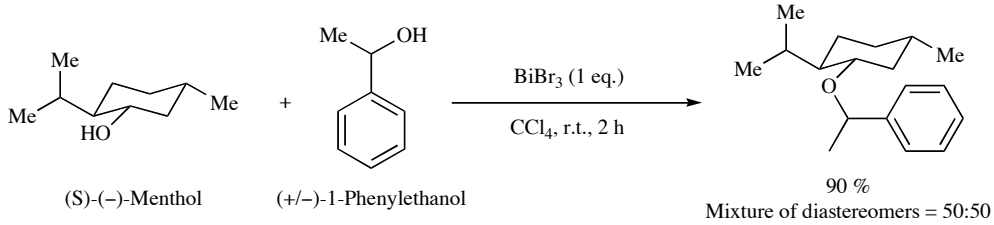


(**4**)



HCO_2Et ---------- reflux ---------- 60-75 min --------- R = H (75-95 %) (**5**)
Ac_2O (1.5-10 eq.) --- r.t.-reflux ----- 20 min-1.5 h ------ R = CH_3 (87-97 %) (**6**)
AcOH ---------- r.t ---------- 30-65 min ---------- R = CH_3 (90-98 %) (**7**)
$BiOCl/CH_3COCl$ ---- r.t. ---------- 5 min ---------- R = CH_3 (93 %) (**8**)
$(t\text{-BuCO})_2O$ ---------- r.t. ---------- 4 h ---------- R = *t*-Bu (93 %) (**9**)
$(PhCO)_2$ ---------- r.t. ---------- 45-60 min ---------- R = Ph (90-95 %) (**10**)

Scheme 51.



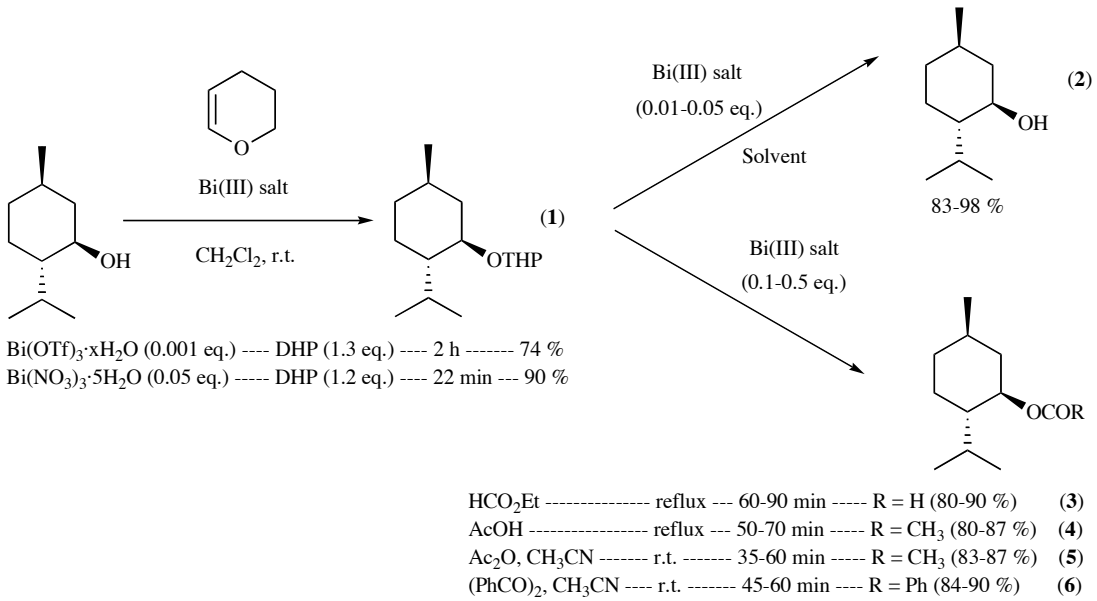
Scheme 52.

same reaction has also been reported with BiI_3 (1 mol %) in H_2O (Scheme **55**, reaction 2) [47].

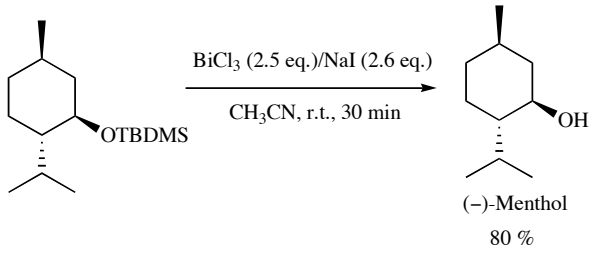
The oxidation of the allylic alcohol moiety of carveol has been reported with montmorillonite impregnated with $Bi(NO_3)_3 \cdot 5H_2O$ to afford carvone, a naturally occurring monoterpene relevant in food and flavor industries (Scheme **56**) [42].

The $BiCl_3$-catalyzed reaction of (–)-β-pinene with an equimolar amount of chloral in CH_2Cl_2/Et_2O gave the corresponding H-ene adduct, in 49% yield [ratio (11R)/(11S)-diastereomers = 64:36] (Scheme **57**) [114].

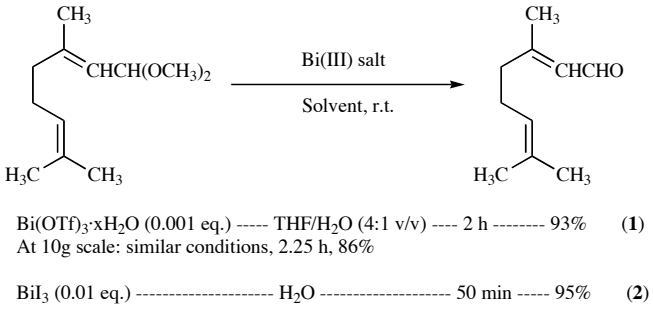
The role of citronellal in organic chemistry is well established [97b]. Its cyclization to (–)-isopulegol, an important intermediate in



Scheme 53.

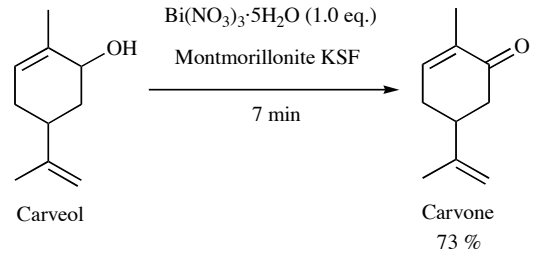


Scheme 54.



Scheme 55.

the industrial production of (–)-menthol (Takasago process) is an example of such. This reaction has been reported to be catalyzed by $BiCl_3$ (2-5 mol %) [114] and $Bi(OTf)_3{\cdot}xH_2O$ (0.1 mol %) [115] (Scheme **58**). Along with the desired product, neoisopulegol was also formed in low amounts (< 30%) in both processes.

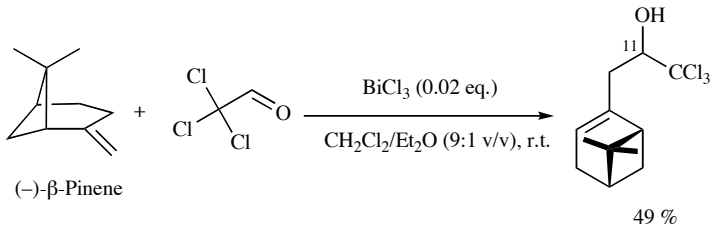


Scheme 56.

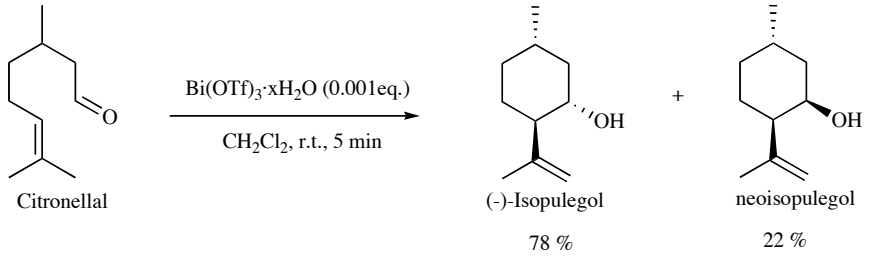
Epoxyolefin cyclizations are an important field of research since the discovery that these reactions are involved in biosynthetic pathways of terpenes. The cyclisation of geraniolene oxide has been investigated in the presence of several metal triflates, including $Bi(OTf)_3{\cdot}xH_2O$. The reaction product ratio was found to be mainly influenced by the choice of the solvent and substrate concentration rather than by the choice of the metal triflate. Cyclization products were preferentially formed in CH_2Cl_2 and under high dilution conditions whereas acyclic compounds were mostly obtained in ethereal solvents (Scheme **59**) [116].

Later Smith and co-workers, in the course of the study of Lewis acid mediated cyclization reactions of 6,7-epoxygeranyl pivalate ester, reported the use of stoichiometric amounts of $BiCl_3$ and $BiO{\cdot}ClO_4{\cdot}xH_2O$. Despite the fact that good activity was observed, poor selectivity for the desired bicyclic ether was found (Scheme **60**) [117].

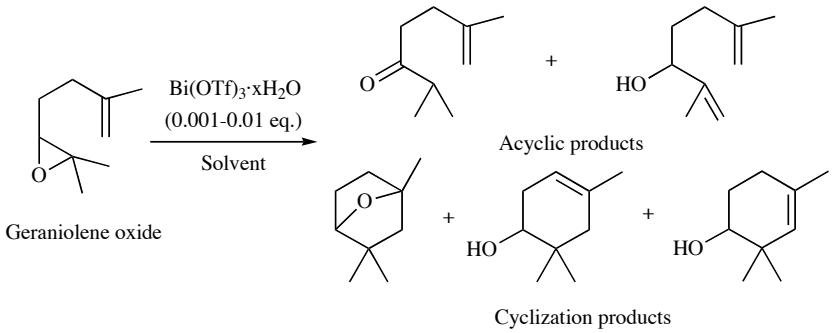
Bismuth(III) salts-promoted reactions using sesquiterpenes, diterpenes and triterpenes as substrates have also been reported.



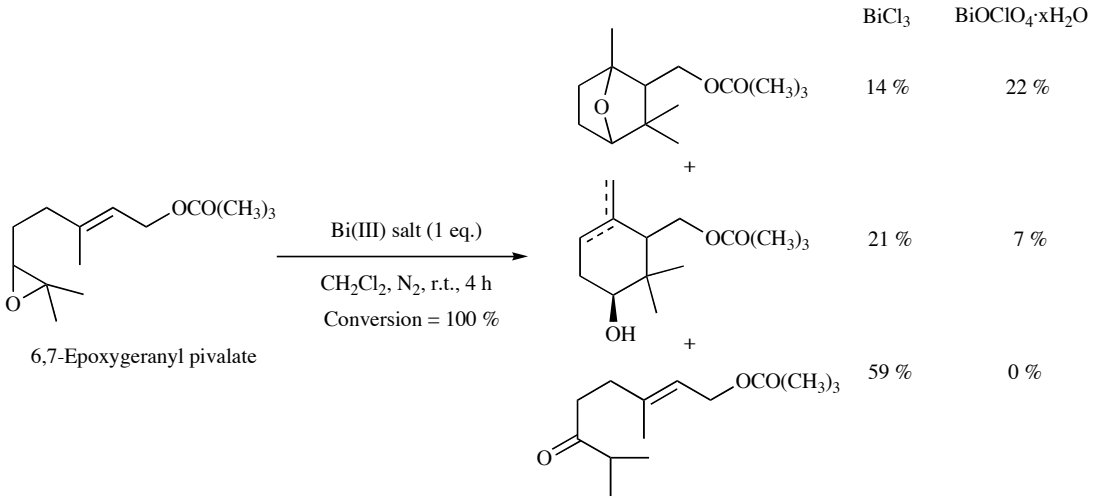
Scheme 57.



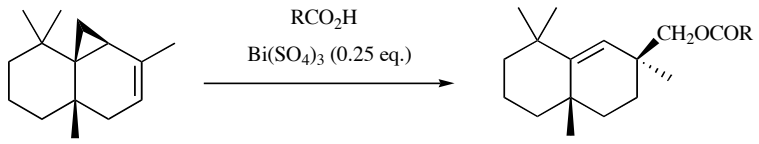
Scheme 58.



Scheme 59.



Scheme 60.

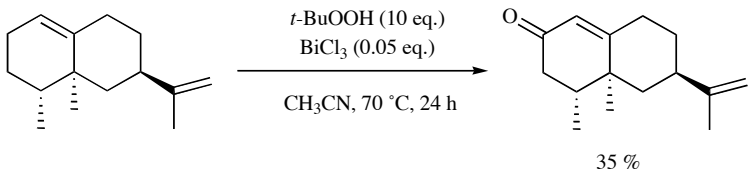


Scheme 61.

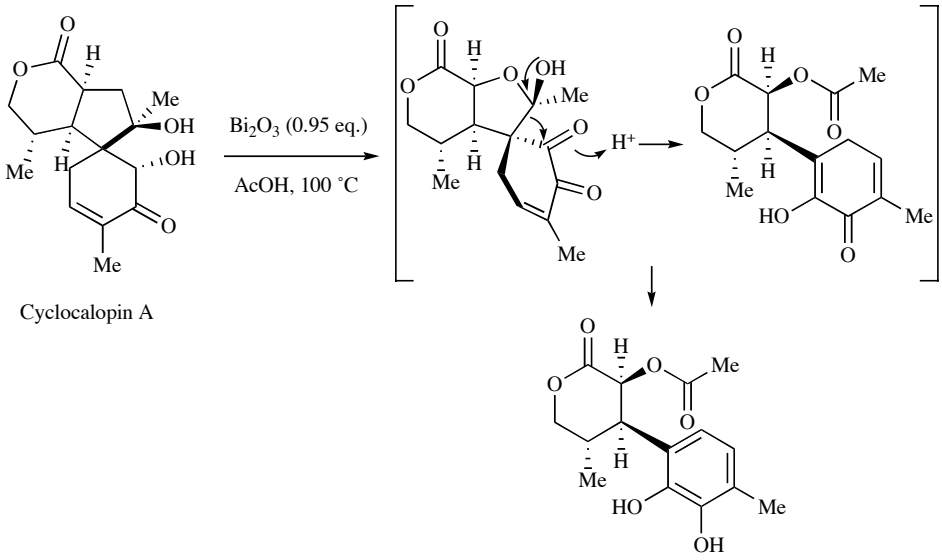
Thujopsene is a tricyclic sesquiterpene, which was originally isolated from the wood neutral oil of the Japanese Hiba tree. This compound has been found in several other plant essential oils, with pharmacological properties [118]. Abe and Ito reported the use of catalytic amounts of bismuth(III) sulphate for the esterification of *cis*-(–)-thujopsene with a series of organic acids ranging from acetic to octanoic acid. The reactions were carried out using excess of organic acid in the presence of 25 mol % of $Bi(SO_4)_3$, and afforded the corresponding esters, after a skeletal rearrangement, in 20-34 % yield only (Scheme **61**) [119].

The allylic oxidation of valencene was reported using $BiCl_3$ in combination with *tert*-butyl hydroperoxide (*t*-BuOOH), and the corresponding α,β-unsaturated ketone, nootkatone, was obtained in 35 % yield (Scheme **62**) [120]. This sesquiterpene compound is a well-known potent insect repellent [121a] and the most important and expensive aromatic of grapefruit with applications in the cosmetic industry due to its decreasing the somatic fat ratio properties [121b].

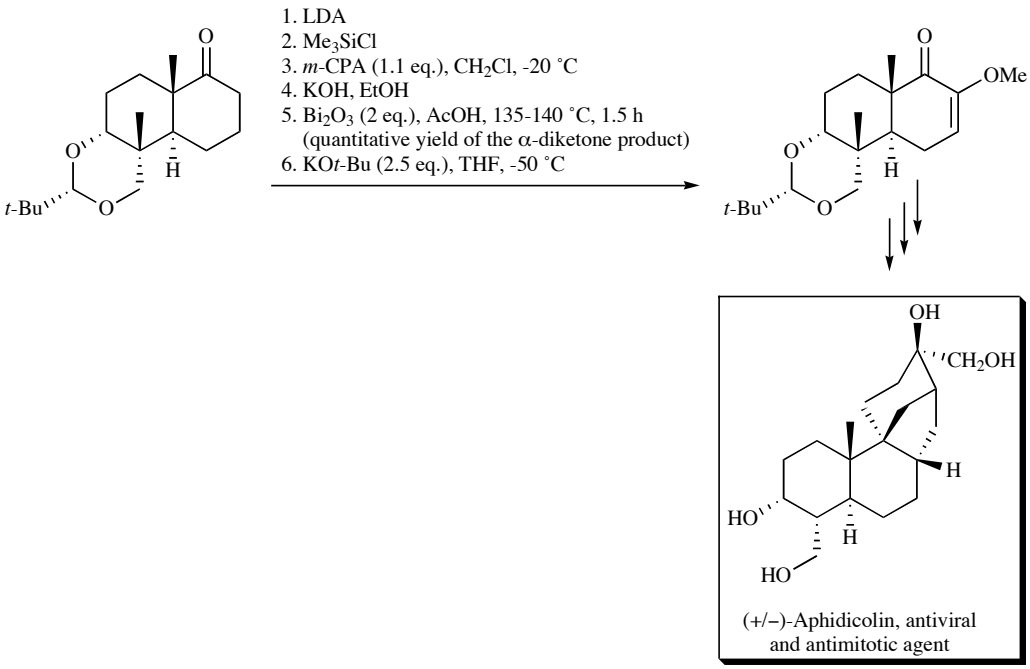
During the study of bismuth(III)-promoted Ritter reaction of epoxides, the conversion of caryophyllene oxide into a clovan-9-ol derivative bearing a 2β-acetamide group at ring A was reported [122]. Despite the low yield (33 %), this reaction is an alternative approach for the synthesis of clovane-type compounds with nitrogen atoms directly attached to C-2. Similar 2-alkoxyclovane-9α-ol derivatives have shown to inhibit the growth of the fungus *Botrytis cinerea* [123].



Scheme 62.



Scheme 63.

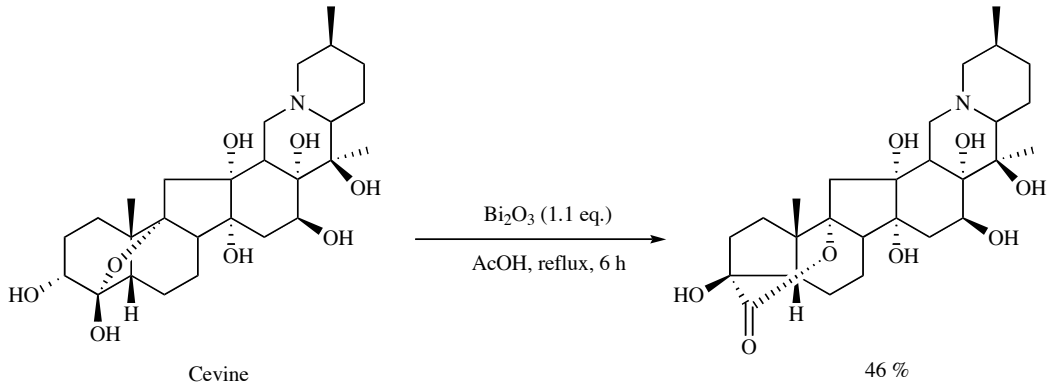


Scheme 64.

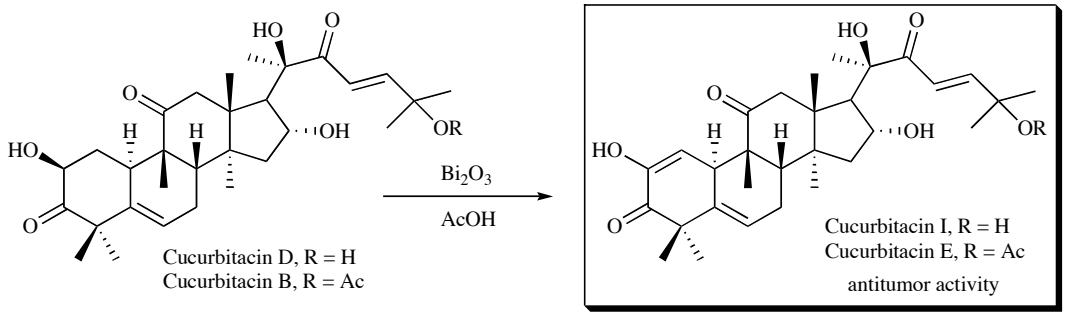
Cyclocalopins and calopins are C_{15}-compounds isolated from *Boletus calopus* and related species responsible for the bitter taste of these mushrooms. Hellwig *et al*. reported the oxidation of cyclocalopin A with Bi_2O_3 in acetic acid at 100 ºC to give O-acetylcalopin (Scheme **63**). This chemical conversion, which involved a retroaldol cleavage of the 1,2-diketone intermediate followed by aromatization, established the same stereochemistry for both cyclocalopins and calopin type of metabolites, for which a terpenoid origin was proposed [124].

During the total synthesis of the racemate of aphidicolin, a tetracyclic diterpene compound with potent antiviral and antimitotic properties, Bi_2O_3 in acetic acid was used in one of the intermediate steps to give a α-diketo compound, which was further modified in order to obtain the desired product (Scheme **64**) [125].

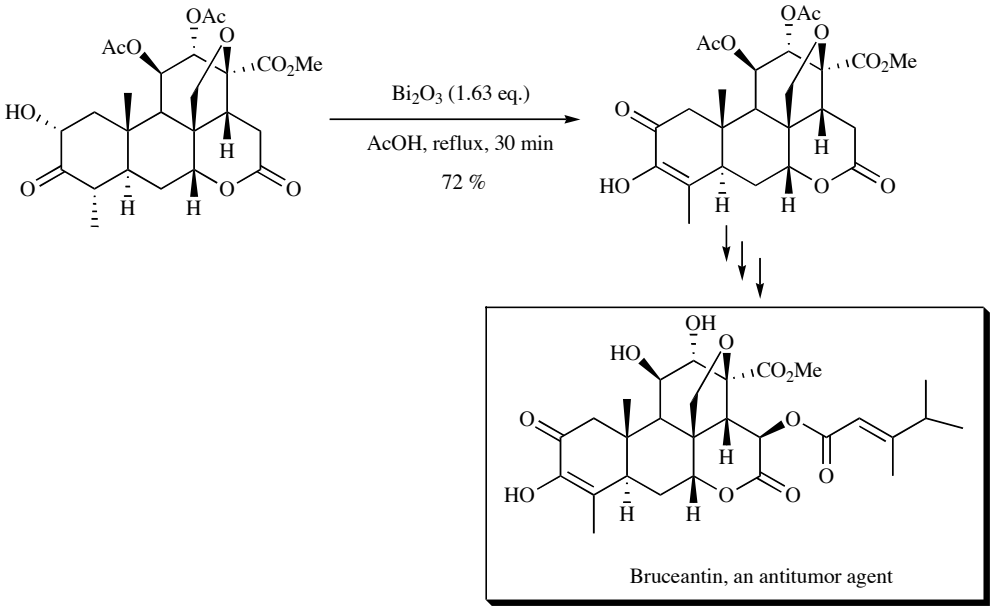
The use of Bi_2O_3 in acetic acid has also been successfully applied to the oxidation of some triterpene structures. The triterpene alkaloid cevine, bearing a hemiacetal function, was converted into a



Scheme 65.



Scheme 66.



Scheme 67.

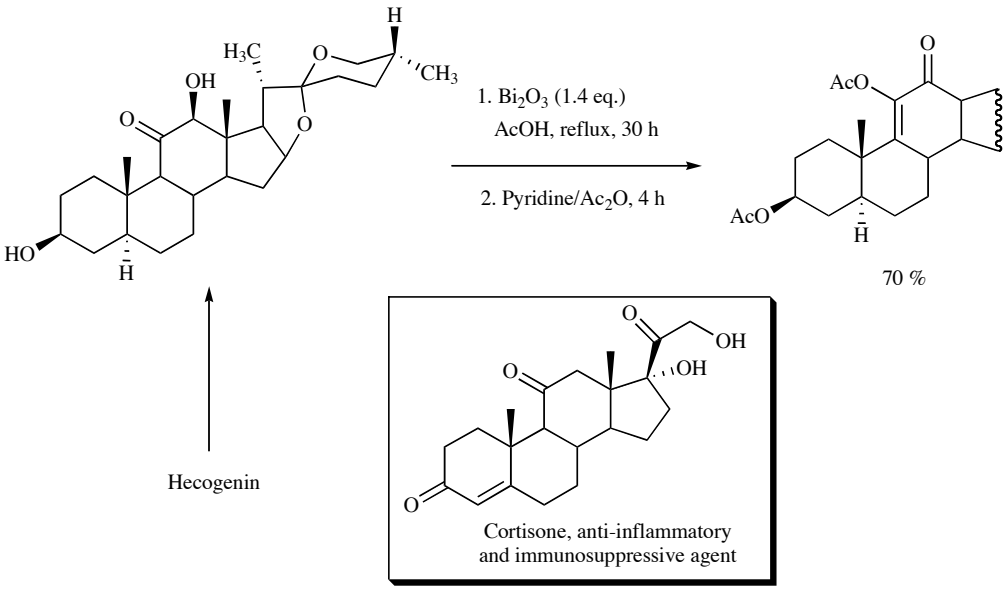
hydroxy-δ-lactone product by treatment with the Bi_2O_3/AcOH system (Scheme **65**) [126]. Similarly, the conversion of the related triterpenes veracevine and cevagenine into the same hydroxy-δ-lactone derivative was also reported by Kupchan and Lavie [126].

Lavie's group used the Bi_2O_3/AcOH system for the selective oxidation of the α-hydroxyketone functionality present in ring A of the highly oxygenated tetracyclic triterpenes, cucurbitacin D [127] and cucurbitacin B [128] (Scheme **66**). Cucurbitacin I, the product that resulted from the oxidation of cucurbitacin D was found to be a potent antitumor agent against human cancer cells [129].

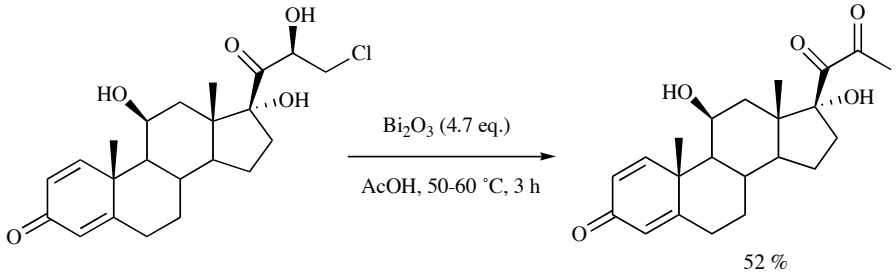
More recently, during the total synthesis of bruceantin, a potent antitumoral agent, the Bi_2O_3/AcOH system was applied to the oxidation of a α-hydroxy ketone intermediate to afford the corresponding diosphenol, in 72 % yield (Scheme **67**) [130].

6. STEROIDS

Over the last decades, hundreds of steroid compounds have been isolated from natural sources and many thousands of them have been obtained synthetically [131]. These include the sex hormones, corticosteroids hormones (cortisol, aldosterone and their



Scheme 68.



Scheme 69.

synthetic analogues), bile acids, vitamin D derivatives, cardiotonic steroids (e.g. digoxin), among several other examples. This group is of considerable medicinal interest and there are several steroid molecules present in a wide diversity of marketed medicines (e.g. dexamethasone, nandrolone, finasteride, levonorgestrel) [21].

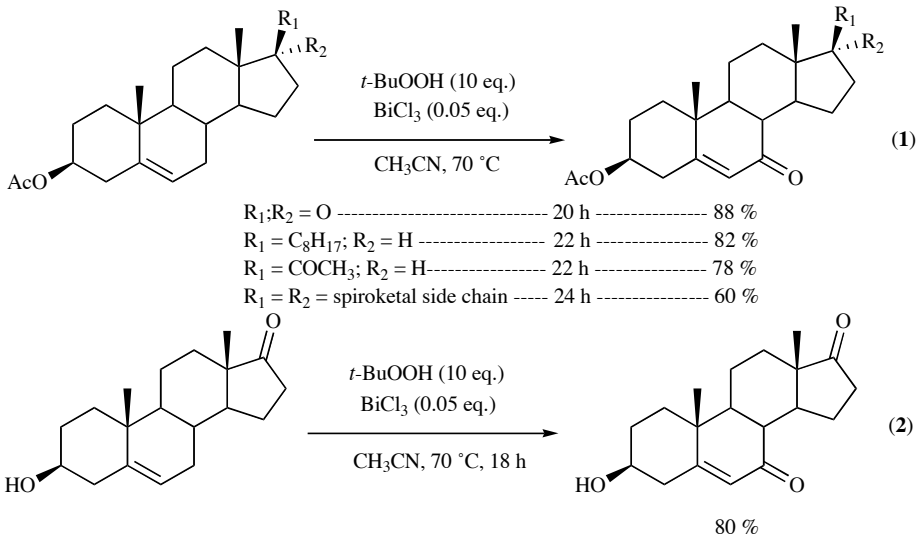
The use of Bi_2O_3, in refluxing acetic acid was found to be an efficient and selective oxidant agent for the conversion of α-hydroxyketones into the corresponding diones, which were generally obtained as a mixture with its enol from. The (25R)-5α-spirostan-3β-ol side chain was kept intact and thus the method could be applied to the preparation of an intermediate in the synthesis of cortisone starting from hecogenin (Scheme **68**) [132].

This versatile process has also been used for the synthesis of $\Delta^{9(11)}$-11-hydroxy-12-keto-steroids with a cholane [132], pregnane [133] and androstane [134] backbone. Oxidation of ring A α-hydroxyketone moiety by Bi_2O_3/AcOH was reported by several authors as an efficient way to obtain Δ^1-2-hydroxy-3-keto-steroids [135]. The Bi_2O_3/AcOH oxidation of the 20,21-ketol group of a 21-chloromethyl-pregnane derivative resulted in the formation of a dehydrohalogenated 20,21-diketo product in 52 % yield (Scheme **69**) [136].

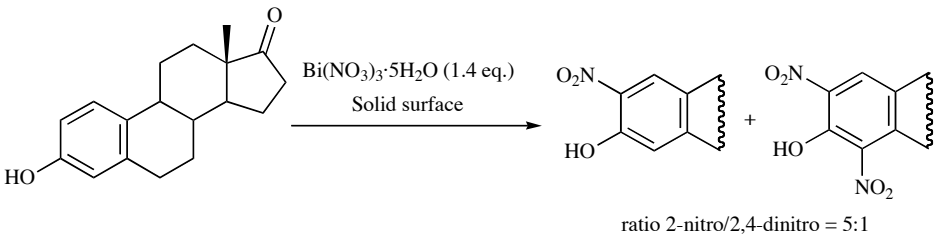
The allylic oxidation of Δ^5-steroids [137] using several homogenous or heterogeneous bismuth catalyts in combination with *t*-BuOOH has been reported [120]. $BiCl_3$ was found to be the best catalyst and several Δ^5-steroids were converted into the corresponding Δ^5-7-keto-steroids, in good to high yields (Scheme **70**, reactions 1 and 2). This catalyst could be recovered at the end of reaction as BiOCl, which can be used as catalyst in subsequent reactions or reconverted into $BiCl_3$. The $BiCl_3$/*t*-BuOOH system proved to be very selective for this reaction, since no significative epoxidation of the double bond, secondary hydroxyl group oxidation or cleavage of the diosgenin side chain was observed (Scheme **70**, reactions 1 and 2). Thus, this method is a suitable alternative for the synthesis of Δ^5-7-keto-steroids, which are very important molecules, both from the synthetic [138] and the biological point of view [139].

Estrogen derivatives bearing nitro groups on the phenolic ring A are important biologically active molecules, among other useful applications [140]. In particular, 2-nitro and 4-nitro derivatives of estradiol were studied as molecular probes for binding to the estrogen receptor and promoting gene induction [141]. 2-Nitro-17β-estradiol was found to be a moderate competitive inhibitor of aromatase [142]. Montmorillonite impregnated with bismuth nitrate was found to be an efficient reagent for the nitration of estrone affording the 2-nitro and 4-nitro derivatives as a 1:1 mixture, in 94 % yield [143]. More recently, the same group reported further developments of the initial methodology using various metal nitrates, including $Bi(NO_3)_3{\cdot}5H_2O$, and screening several solid supports and reaction conditions. The best results with $Bi(NO_3)_3{\cdot}5H_2O$ were accomplished using florisil or molecular sieves at refluxing benzene in a Dean Stark apparatus or alumina under dry conditions. With these reaction conditions, a 5:1 ratio of the 2-nitro and the 2,4-dinitro derivatives was obtained (Scheme **71**) [144].

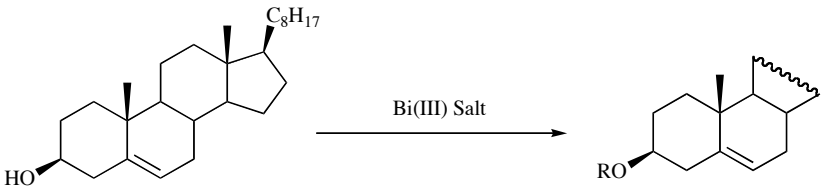
The acylation of alcohols is an important reaction in organic chemistry, especially in fine chemistry, where acyl groups play an important role as protecting groups of hydroxyls. Reese and co-



Scheme 70.



Scheme 71.



R = Ac: $Bi(OAc)_3$ (1.1. eq.), neat, 160 °C, 25 h, 48 % (**1**)
$Bi(OTf)_3 \cdot xH_2O$ (0.01 eq.), Ac_2O (10 eq.), THF, 25 °C, 1 h, 97 % (**2**)
BiOCl (0.005 eq.), CH_3COCl (2 eq.), CH_2Cl_2, r.t., 30 min, 96 % (**3**)

R = Piv: $Bi(OTf)_3 \cdot xH_2O$ (0.03 eq.), $(t\text{-BuCO})_2O$ (1.5 eq.), CH_2Cl_2, 25 °C, 5 h, 97 % (**4**)

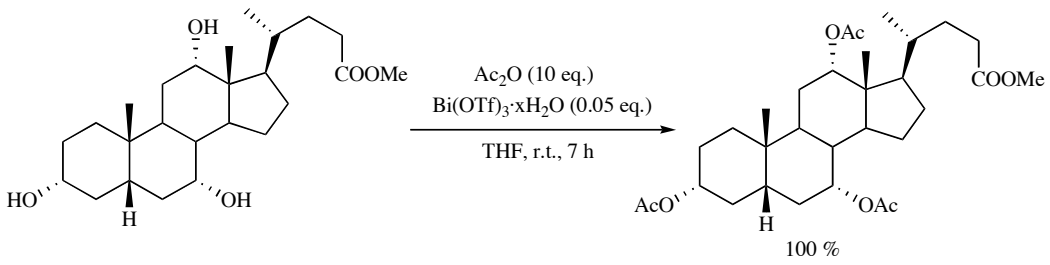
R = THP: $Bi(NO_3)_3 \cdot 5H_2O$ (0.05 eq.), DHP (1.2 eq.), CH_2Cl_2, r.t., 45 min, 82 % (**5**)

Scheme 72.

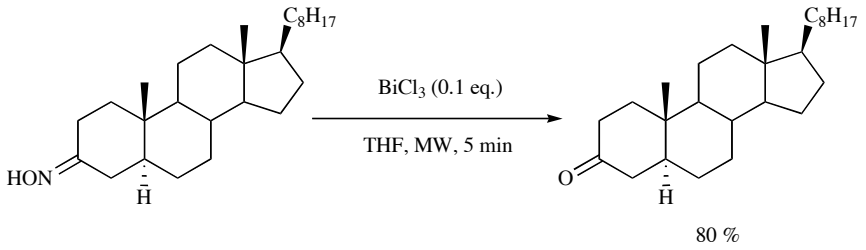
workers described the use of stoichiometric amounts of $Bi(OAc)_3$ for the conversion of cholesterol and cholesterol formate into the corresponding 3β-acetoxy derivative in 48 % (Scheme **72**, reaction 1) and 87 % yield, respectively [145]. (Scheme **72**, reaction 1). More recently, acylation processes using bismuth(III) salts as catalysts were reported [62, 102-105, 146]. The acetylation of cholesterol using $Bi(OTf)_3 \cdot xH_2O$ in the presence of acetic anhydride was described (Scheme **72**, reaction 2) [102]. Remarkably, all the three hydroxyl groups of the 3α,7α,12α-triol derivative of cholic acid were converted to the corresponding acetoxy groups in excellent yield regardless of the sterically hindered 12α-hydroxy group (Scheme **73**) [102]. A very efficient process using $BiCl_3$ generated *in situ* from the procatalyst BiOCl and acetyl chloride was described for the acetylation of cholesterol (Scheme **72**, reaction 3) [105]. The pivalation of cholesterol was described by Orita and coworkers using $Bi(OTf)_3 \cdot xH_2O$ (3 mol %) in the presence of pivaloic anhydride, in very good yield (Scheme **72**, reaction 4) [102b].

The protection of hydroxyl groups as THP ether is common when necessary a more stable protecting group. The tetrahydropyranylation of cholesterol occurred in 82 % yield, by reaction with DHP in the presence of 5 mol % of $Bi(NO_3)_3 \cdot 5H_2O$ (Scheme **72**, reaction 5) [108].

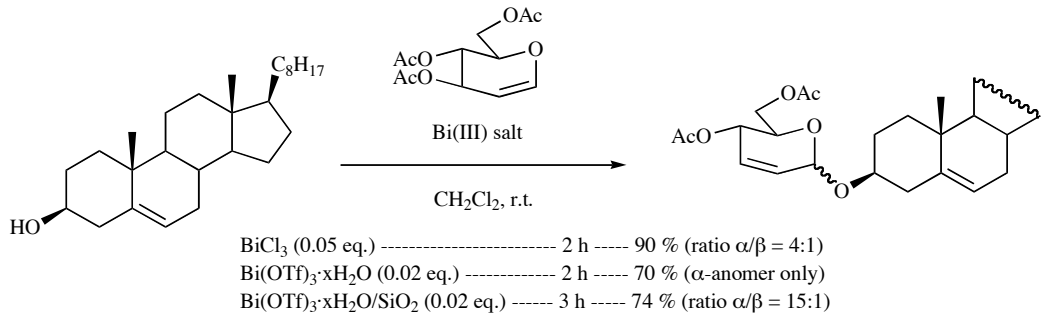
The cleavage of oximes to carbonyl compounds is a useful reaction in synthetic chemistry. A catalytic procedure using 10 mol % of $BiCl_3$, in THF, under microwave irradiation, was reported for the regeneration of carbonyl groups from their oximes. The methodology was applied to cholestan-3-one oxime and the corresponding 3-keto-steroid was obtained in 80 % yield (Scheme **74**) [44a].



Scheme 73.



Scheme 74.



Scheme 75.

Glycosilation of steroids is a reaction of special interest due to the biological importance of some glycosilated steroids (for a review see [147]). The Ferrier rearrangement is a well known methodology for the preparation of alkyl and aryl 2,3-unsaturated-*O*-glycosides by reaction of glycals with alcohols catalyzed by Lewis acids. By reaction of cholesterol with 3,4,5-tri-*O*-acetyl-D-glucal in the presence of $BiCl_3$ (5 mol %) or $Bi(OTf)_3{\cdot}xH_2O$ (2 mol %), the corresponding 2,3-unsaturated-*O*-glycoside was obtained in good yield [148, 149]. The use of $Bi(OTf)_3{\cdot}xH_2O$ or its heterogenous form, $Bi(OTf)_3{\cdot}xH_2O/SiO_2$, proved to be more stereoselelective, affording the α-anomer almost exclusively (Scheme **75**) [149].

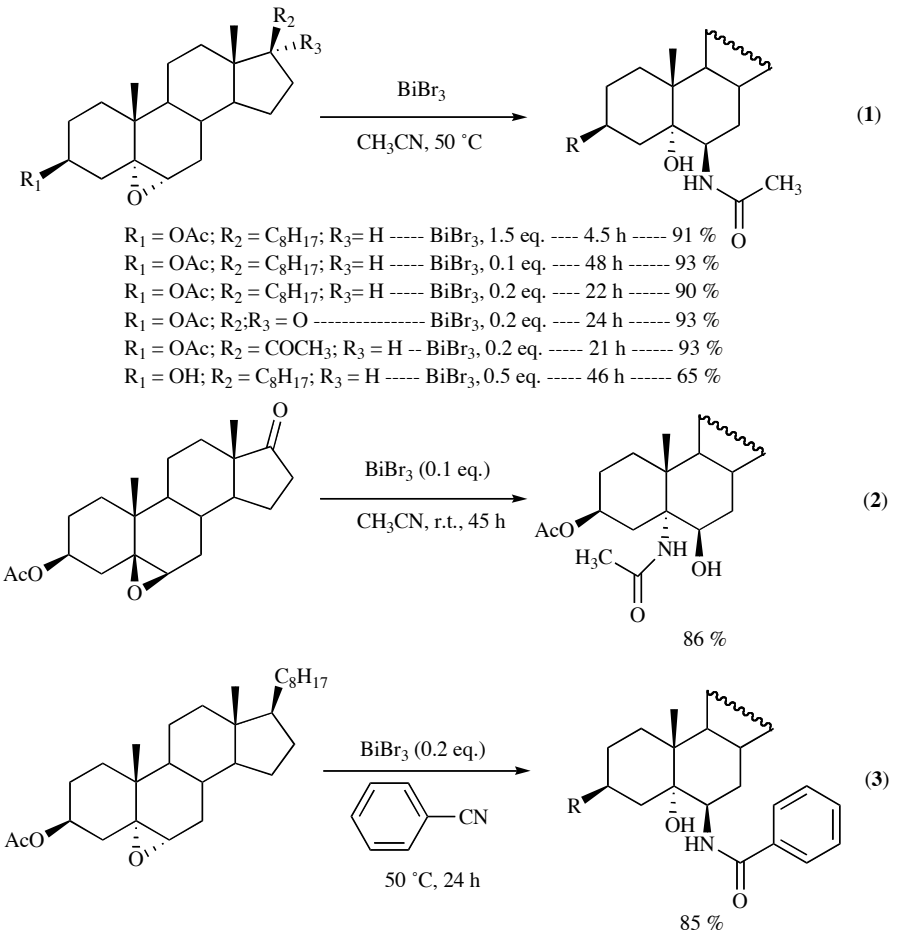
Epoxysteroids are versatile and reactive intermediates that lead to a diversity of products [137, 150]. The Ritter reaction of 5α,6α- and 5β,6β-epoxysteroids with nitriles in the presence of bismuth(III) salts was reported to give the corresponding *vic*-acylamino-hydroxy products, in high yields (Scheme **76**, reactions 1-3) [122, 151]. This process was stereo- and regioselective as the result of the *trans*-diaxial ring-opening of the epoxysteroids. In the presence of several other functional groups, such as hydroxyl, ketone or ester, the reaction occurred selectively at the epoxide group.

The Ritter reaction of epoxysteroids was found to occur under catalytic and stoichiometric conditions with $BiBr_3$ [122]. However, when stoichiometric amounts of $BiCl_3$ or $Bi(NO_3)_3{\cdot}5H_2O$ were used to promote the Ritter reaction in acetonitrile, a competitive side product was detected, in each case. These products were found to be the result of the epoxide ring-opening by $BiCl_3$ and $Bi(NO_3)_3{\cdot}5H_2O$, respectively (Scheme **77**) [152].

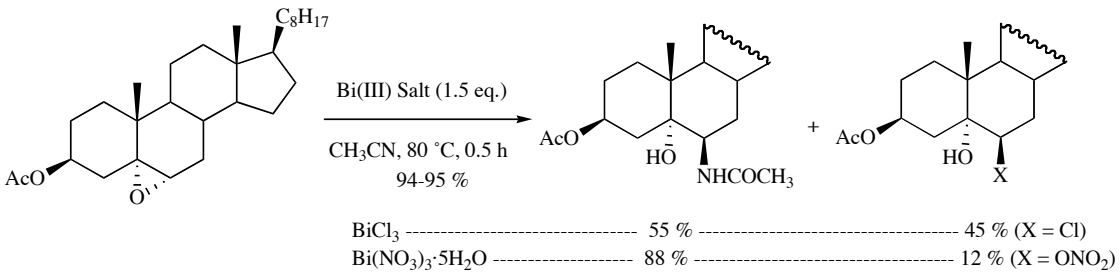
Thus, simply by changing the solvent to 1,4-dioxane, halohydrins and β-hydroxy-nitrates could be obtained in high yields by ring-opening of 5α,6α-, 5β,6β- and 2α,3α-epoxysteroids (Scheme **78**, reactions 1-4). The reactions were also stereo-, regio- and chemoselective. Notably, ring opening of a 5α,6α;16α,17α-diepoxysteroid proved to be highly specific for the 5α,6α-epoxide group (Scheme **78**, reaction 4) [152].

These new procedures are an efficient alternative to the classical methods that use mineral acids. Of special interest is the synthesis of cholesterol chlorohydrins due to their presence in biological systems as the result of the formation of $HClO_4$ in inflammatory tissues [153]. The vicinal chlorohydrin moiety is also present in various steroidal natural compounds [152]. The introduction of nitrate groups in steroid compounds have recently been employed in the synthesis of NO-releasing drugs, such as the 4'-(nitrooxymethyl)benzoate derivative of prednisolone (NCX 1015) [154].

Quite recently, bismuth(III) salts were described as catalysts for the Westphalen and "backbone" rearrangements of 5β,6β-epoxysteroids [155]. The reactions were found to be particularly sensitive to changes on the solvent, temperature, stereochemistry of the starting epoxysteroids and their substituents at C-17. Thus, in 1,4-dioxane, Westphalen-type products were preferentially obtained, whereas in CH_3NO_2, a high dielectric constant solvent, the "backbone" rearranged compounds were found to be the major reaction products [155]. The $Bi(OTf)_3{\cdot}xH_2O$-catalyzed reaction of 5β,6β-epoxycholestan-3β-yl acetate in 1,4-dioxane at 80 ºC afforded the 5β-methyl-$\Delta^{9(10)}$-19-norsteroid in 61% yield (Scheme **79**,



Scheme 76.



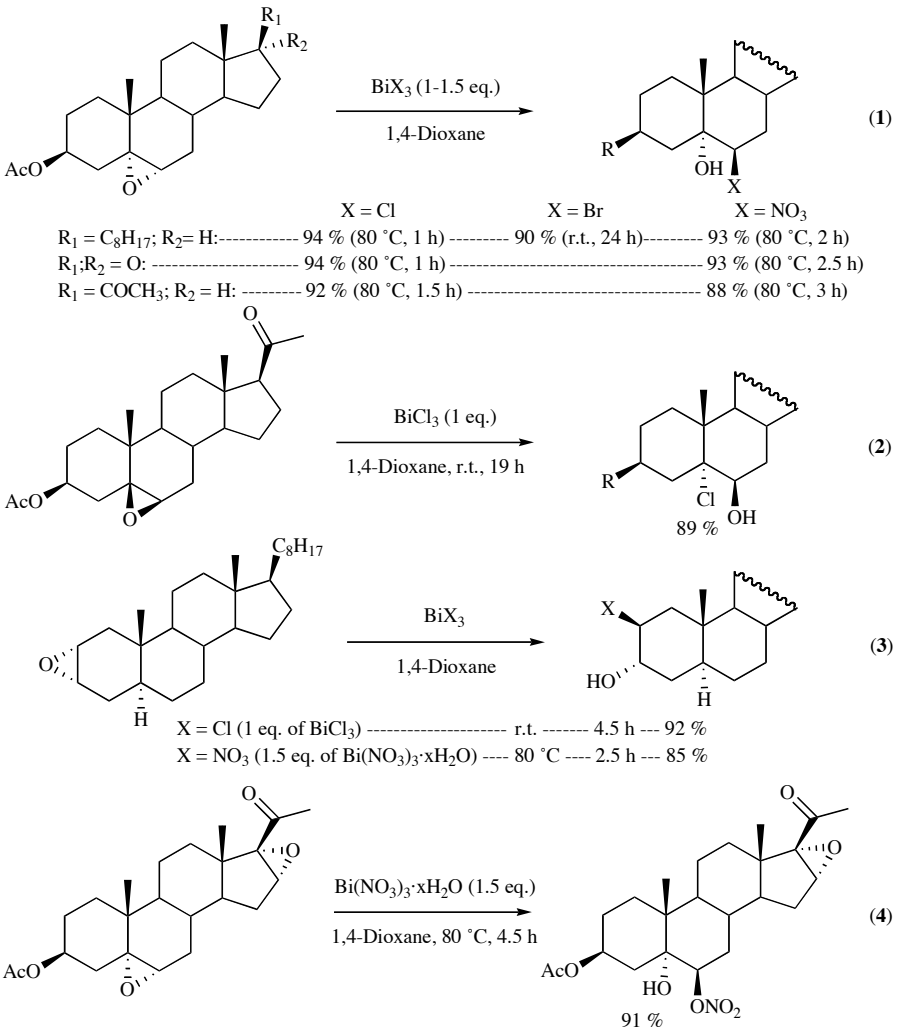
Scheme 77.

reaction 1). On the other hand, the 5β,14β-dimethyl-$\Delta^{13(17)}$-18,19-dinorsteroid was the major product obtained from the reaction of 5β,6β-epoxycholestan-3β-yl acetate in $Bi(OTf)_3 \cdot xH_2O/CH_3NO_2$, at 50 ºC, isolated in 68 % yield (Scheme **79**, reaction 2).

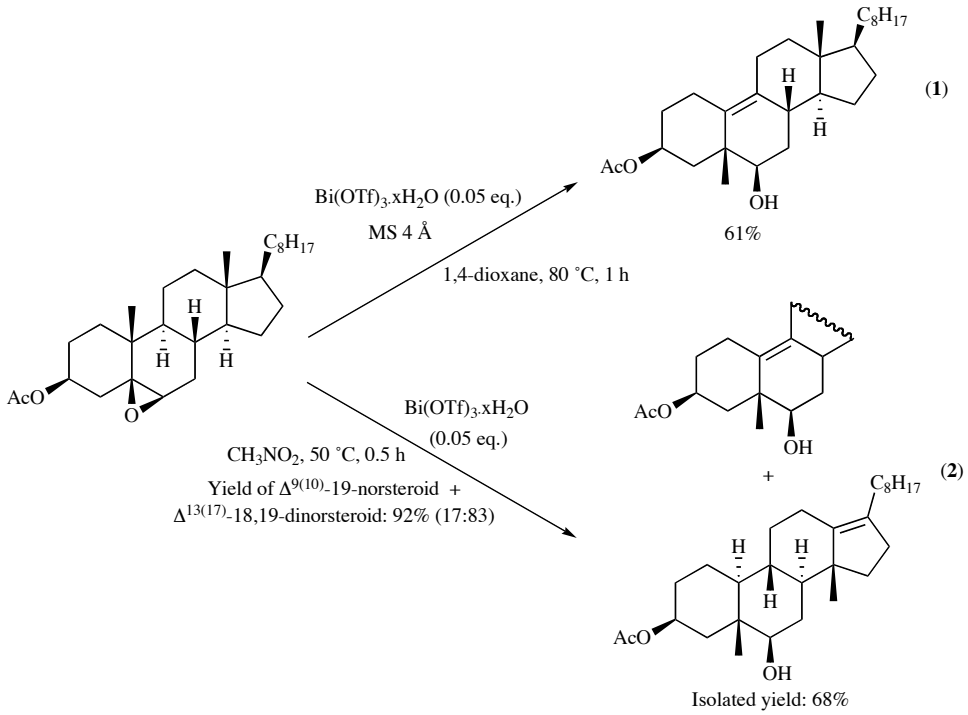
Westphalen and "backbone" rearrangements of other 5β,6β-epoxysteroids with androstane and pregnane backbone were also reported. Interestingly, for the "backbone" rearranged 5β,14β-dimethyl-$\Delta^{13(17)}$-18,19-dinorsteroids and 6β-hydroxy-5β-methyl-17-oxo-19-norandrost-8(14)-en-3β-yl acetate an abnormal A/B rings *trans*-fused (5β,10α) steroid structure was found. These reactions constitute a new approach for the synthesis of biological important olefinic 18-nor- and 18,19-dinorsteroids [155].

7. CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The development of new synthetic strategies in organic chemistry using "ecofriendly" conditions is an issue of increasing interest. In this field, bismuth(III) salts have emerged as suitable reagents/catalysts for this purpose. Due to their very low toxicity these compounds have an enormous potential for large-scale synthesis, which become more obvious when dealing with products that must meet strictly specifications concerning the residual levels of toxic metals, such as active pharmaceutical ingredients (API) or its synthetic intermediates. This review focused on applicability of bismuth(III) salts to the preparation of compounds of pharmaceutical interest including the preparation of useful synthetic intermediates or its use in the course of synthetic routes of important molecules. The advances observed on the pursuit of new applications of bismuth lead to a great diversity of reactions, many of them constitute alternative processes for classical reactions that use stoichiometric, corrosive and/or toxic reagents. Therefore in the next few years more applications of these bismuth-based procedures, both at laboratory bench during the synthesis of new chemical entities (NCE) and at industrial level in the large-scale fine and pharmaceutical



Scheme 78.



Scheme 79.

chemistry should be expected. Strategies leading to the recovery and reuse of bismuth(III) salts are likely to be developed.

8. ACKNOWLEDGEMENTS

J.A.R. Salvador thanks Universidade de Coimbra for financial support. R.M.A. Pinto (SFRH/BD/18013/2004) and S.M. Silvestre (SFRH/BPD/41612/2007) acknowledge Fundação para a Ciência e Tecnologia for a grant. Dr. Christophe Le Roux is also acknowledged for his very kind contribution to the correction of the manuscript.

ABBREVIATIONS

Ac	=	acetyl
AcO	=	acetoxy
ADAM	=	alkenyldiarylmethanes
API	=	active pharmaceutical ingredients
bmim	=	1-butyl-3-methylimidazolium
Bn	=	benzyl
BnO	=	benzyloxy
Boc	=	*tert*-butoxycarbonyl
n-Bu	=	*n*-butyl group
t-Bu	=	*tert*-butyl
t-BuO	=	*tert*-butoxy
c-C_6H_{11}	=	cyclohexyl
dba	=	dibenzylideneacetone
DHP	=	3,4-dihydro-2*H*-pyran
DMF	=	dimethylformamide
DMSO	=	dimethylsulfoxide
emim	=	1-ethyl-3-methylimidazolium
eq.	=	equivalent(s)
Et	=	ethyl
EtO	=	ethoxy
FC	=	Friedel-Crafts
gem	=	geminal
HIV	=	human immunodeficiency virus
HPLC	=	high pressure liquid chromatography
LDA	=	lithium diisopropylamide
Leu	=	leucine
m	=	*meta*
m-CPBA	=	*meta*-chloroperbenzoic acid
Me	=	methyl
MeO	=	methoxy
min	=	minute(s)
$M^n(OTf)_n$	=	metal triflate
Ms	=	mesylate
MS	=	molecular sieves
MW	=	microwaves
NCE	=	new chemical entities
NSAID	=	non-steroidal anti-inflammatory drug
NTf_2	=	bis-trifluoromethanesulfonyl amide
o	=	*ortho*
p	=	*para*
PGE_2	=	prostaglandin E_2
Ph	=	phenyl
Piv	=	pivaloyl
Pmc	=	2,2,5,7,8-pentamethylchroman-6-sulphonyl
PPL	=	porcine pancreatic lipase
n-Pr	=	*n*-propyl
Py	=	pyridine
r.t.	=	room temperature
TBAB	=	tetrabutylammonium bromide
TBDMS	=	*tert*-butyldimethylsilyl
TBS	=	tributylsilyl
Tf	=	trifluoromethanosulfonyl (or triflyl)
TFA	=	trifluoroacetate
TfO	=	trifluoromethanesulfonate (or triflate)
THF	=	tetrahydrofuran
THP	=	tetrahydropyranyl
THPO	=	tetrahydropyranyloxy
TMS	=	trimethylsilyl
TMSO	=	trimethylsilyloxy
Trp	=	tryptophan
Ts	=	tosyl
vic	=	vicinal
VMA	=	vanillylmandelic acid (or 4-hydroxy-3-methoxymandelic acid)

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