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Review Article

Bioactive Phytochemicals: Bioactivity, Sources, Preparations, and/or Modifications *via* Silver Tetrafluoroborate Mediation

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This review provides an overview of the biological activities, natural occurrences, and the silver tetrafluoroborate- (AgBF4-) mediated synthesis of proanthocyanidins, glycosides, N-heterocyclic alkaloid analogues (of pyrrole, morphine, quinoline, isoquinoline, and indole), furan analogues, and halocompounds. $AgBF_4$ has been reviewed as an effective reaction promoter, used extensively in the synthesis of relevant biologically active compounds *via* carbon-carbon and carbon-heteroatom bonds formation. The literatures from 1979 to April 2014 were reviewed.

1. Introduction

Naturally occurring bioactive compounds are ubiquitous in most dietary higher plants available to humans and livestock. The natural products such as plant extracts provide unlimited opportunities for new drug discoveries, mostly because of plethora of varieties of chemicals [1, 2]. Literally, relative to available synthetic medicines, thousands of accessible medicinal and agricultural phytochemicals are safer and largely more effective alternatives with less adverse effects. For this reason, coupled with advancing microbial resistance to the synthetic drugs, ethnopharmacognosy is rapidly gaining world recognition [2]. The strong growing value and interest in the crucial role that nutrition plays in maintaining human health, animal health, productivity, and reproductive performance of livestock and poultry are greatly recognised [3]. Sasidharan et al. (2011) and other authors have sturdily expressed useful biological activities of phytochemicals. They observed that plant chemicals exhibit anticancer, antimicrobial, antioxidant, antidiarrheal, analgesic, and wound healing actions on animals [2].

The most popular phytochemicals are the polyphenolics which consist of flavonoids and phenolic acids that form the building blocks for polymeric tannins (hydrolysable and condensed tannins or proanthocyanidins) [4]. Flavonoids are large collection of plant secondary metabolites whose chemical structures are based on a C_6-C_3-C_6 carbon ring system **1** and consist of five major subgroups: flavones **2**, flavonols **3**, flavanones **4**, flavanols **5,** and anthocyanidins **6** (Figure 1). Being universally distributed in green plant kingdom, flavonoids therefore form an integral part of human and animal diets. It is well known that flavonoids display a potpourri of biological activities in plants that biosynthesize them and in humans and livestock that feed on those plants and allied products. The bulk of animal feed, which is of plant origin, is known to contain a range of different biologically active compounds such as flavonoids, tocopherols, tocotrienols, and carotenoids [3]. Reports show that, in a particular animal feed portion, the bioactivity of flavonoids is about twice more than other bioactive source compounds [3]. Flavonoids play such important roles [5] *in situ* as signal 37 molecules [6], phytoalexins [7, 8], detoxifying agents [9–11] and stimulants for germination of spores [12–15]. Additionally, they also act as UV-filters [16, 17], in temperature acclimation [18], drought resistance [19], pollinator attractants [20] and allelochemical agents [21, 22]. For the scope of this review paper, our focus was limited to proanthocyanidins: polymers of flavanols (catechin) and the analogues (Figure 1) [23].

Glycoside compounds are another important group of bioactive phytochemicals. They essentially constitute hormones, sweeteners, alkaloids, flavonoids, antibiotics, and so

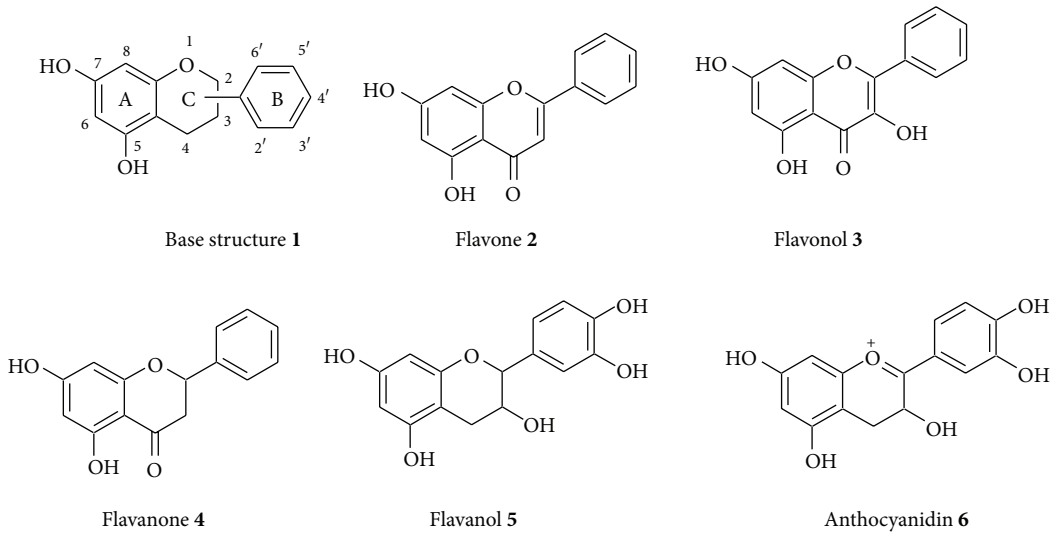


Figure 1: Base structure and subgroups of flavonoids.

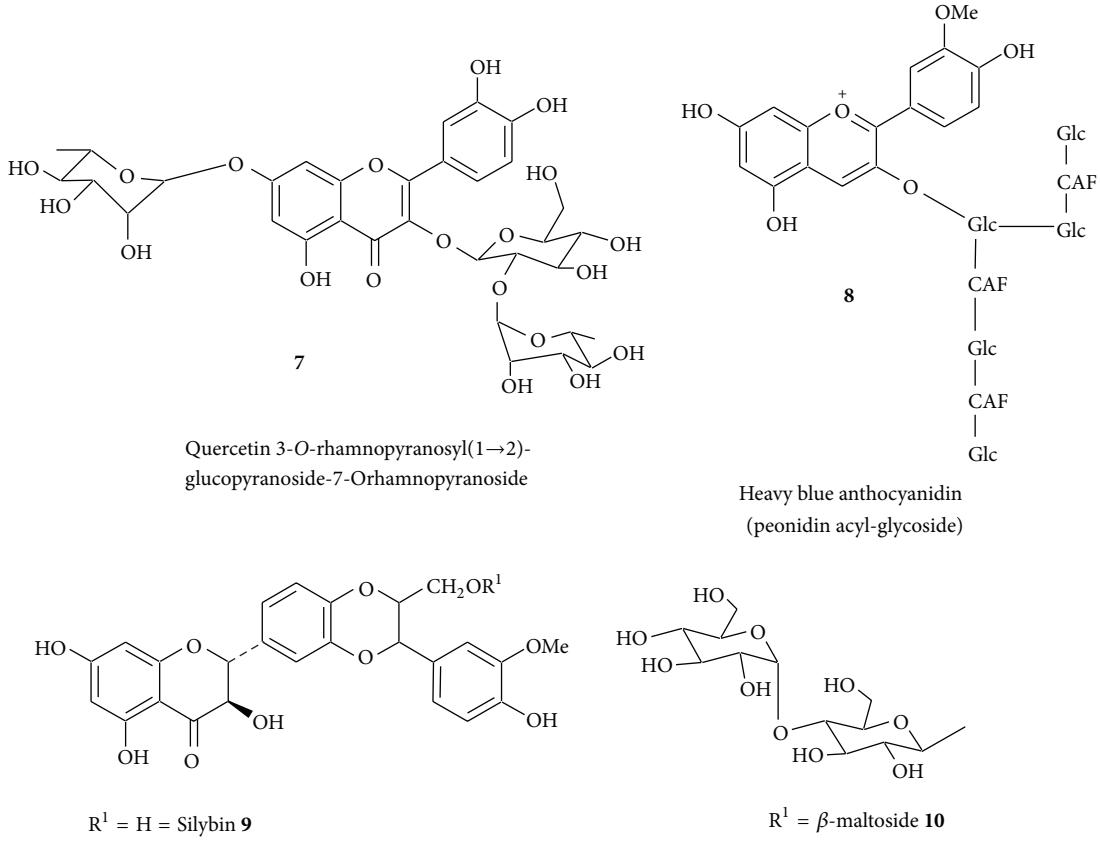
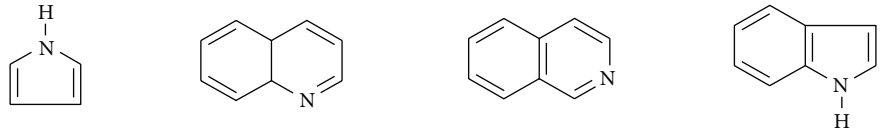


Figure 2: Natural polyphenolic flavonoid glycosides.

forth [24]. Literature revealed that amongst these glycosides are a range of natural polyphenolic flavonoid glycosides, richly found in legume plants (Figure 2) [25–28].

Typical alkaloids, mainly derived from plant sources, are a large group of secondary metabolites containing usually basic nitrogen in a heterocycle, which are broadly varied in chemical structure and in pharmacological action (Figure 3) [29]. The toxicity of some alkaloids is widely recognized; however they are a source of many biologically active phytochemicals with great potential for medicinal and agricultural uses. Many alkaloids have attractive pharmacological effects and are used as medications, such as recreational drugs, or in entheogenic rituals [30, 31].

Furans, particularly 2,3-dihydrofurans, are one of the abundant structural motifs found in plants that possess impressive biological activities and, as a result, are extensively



Pyrrole **11** Quinoline **12** Isoquinoline **13** Indole **14**

Figure 3: Typical basic structure of alkaloids.

used in the pharmaceutical, flavour, insecticidal, and fish antifeedant industries [32–37].

Another group of phytochemical derivatives that are increasingly gaining attention in recent times in the agrochemical and pharmaceutical industries is the halocompounds. Though they are usually isolated from nature in low yields, the halogenated phytochemicals are known for their high bioactivity [38, 39].

Owing to the significance of these rare and sparsely available natural compounds to human health and biota, scientists have made desperate efforts to mimic nature and make these compounds more accessible through chemical synthetic methods. In that pursuit, silver tetrafluoroborate proved to be an efficient tool to achieve this purpose. $AgBF_4$ was found to promote a variety of reactions through its ability to complex with and activate electron rich atoms and bonds under mild conditions.

Our literature search for $AgBF_4$-promoted reactions thus revealed two reviewed papers published in 2008, covering silver-mediated reactions, including the $AgBF_4$-mediated reactions [40–43]. Abbiati and Rossi in their review [44] referred to the use of $AgBF_4$ by Liu (2011) to facilitate their 3-component cascade synthesis of bioactive Pyrrole-2-carboxaldehyde [44, 45]. These reports were concurrently summarized and therefore are excluded from the present review. A study of the available reports revealed that most of the compounds synthesized *via* $AgBF_4$ mediation are biologically active phytochemicals. With this revelation in mind, we summarized the publications with the aim of pursuing two objectives: firstly, to provide a brief overview of the bioactivity and natural occurrences of the main groups of the compounds within the scope of this paper; and, secondly, to review the $AgBF_4$-promoted synthesis of the compounds and/or analogues. Herein, we reviewed bioactivity and natural sources of some phytochemicals and formation of such compounds and/or analogues *via* $AgBF_4$-mediated reactions based on published information on $AgBF_4$-promoted carbon-carbon and carbon-heteroatom bond formation since 1979, when Fry and Migron record of its use in this regard appeared, until April 2014.

2. Proanthocyanidins

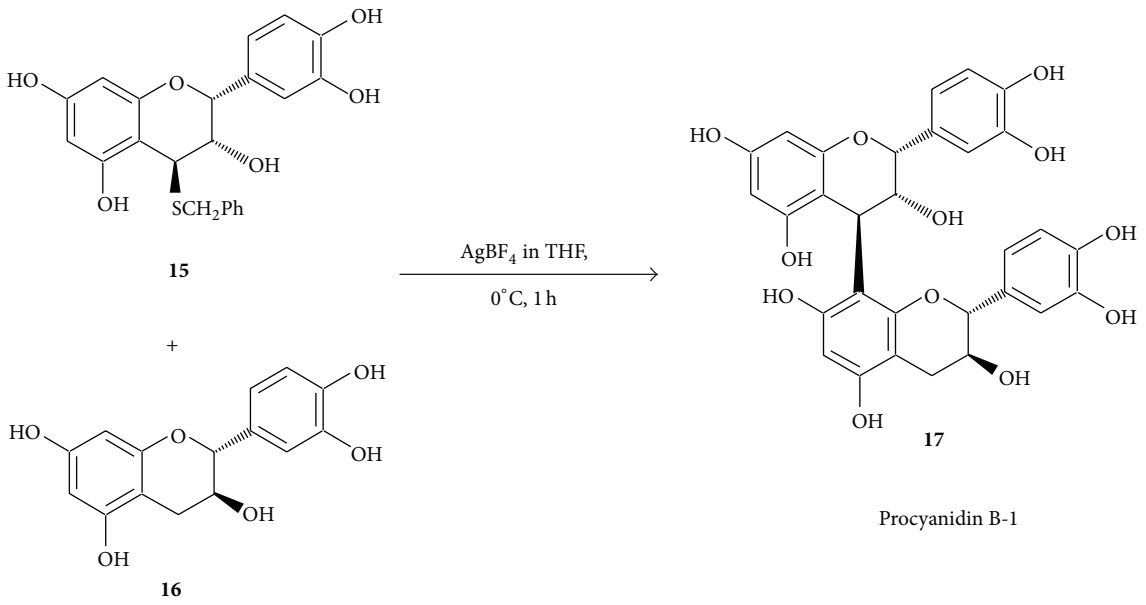
Proanthocyanidins, oligomers and/or polymers of flavan-3-ols, are among the most abundant naturally occurring polyphenolic plant metabolites. They are commonly available in different parts of plants (e.g., legumes, cocoa) and crops such as fruits (grapes, apples, and pears), nuts, seeds, flowers, and bark [46]. Proanthocyanidins display a wide range of biological activities, such as antioxidant, antibacterial, antiviral, antimutagenic, anti-inflammatory, hypertensive, and other heart related diseases [47, 48]. Their high significance in the general well-being of animals warranted intensive studies by researchers on their sources and accessibility. Hence, Steynberg and co-workers [49] (1998) and other research groups [50, 51] have widely exploited different ways of synthesizing the largely varied proanthocyanidin compounds.

A popular methodology in this regard involved using a substrate bearing a leaving group that contains oxygen or sulphur heteroatom. The affinity of $AgBF_4$ towards oxygen and sulfur is exploited to enhance capabilities of the leaving group [49–51]. This property has been explored to create good routes to obtain procyanidins **17** under neutral reaction conditions. The protocol involves treating a mixture of 4β-benzylsulfanylepicatechin **15** and catechin **16** in THF with $AgBF_4$ (2.5 equiv.) for 1 h at 0°C to obtain procyanidin B-1 in 38% yield (Scheme 1) [49].

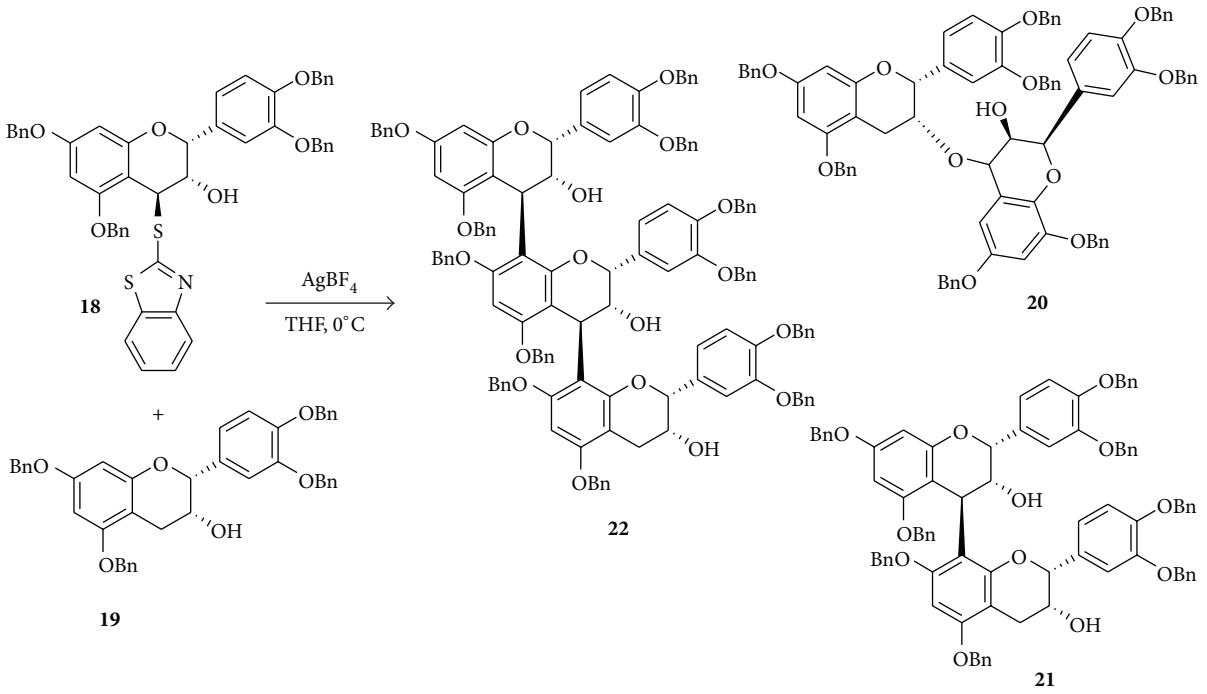
A 2-mercaptobenzothiazole is used to obviate the offensive odour associated with 4-thioderivatives. Then, condensation of **18** and **19** in dry THF in the presence of anhydrous $AgBF_4$ at 0°C yielded the procyanidin oligomers (**20**, **21**, and **22**), as presented in Scheme 2 [50].

The ability of $AgBF_4$ to activate OH groups to synthesize ether-linked proanthocyanidins (proteracacinidin and promelacacinidin) was further explored. The protocol involved treating a mixture of the epioritin-4β **23** and 4α-ols **24** in dry THF at 0°C with $AgBF_4$ for 90 min under nitrogen before the reaction was quenched with water. After workup and purification processes including acetylation, the expected products epioritin-(4β → 4)-epioritin-4α-ol **25** (9.1%) and epioritin-(4β → 3)-epioritin-4α-ol **26** (7.8%) were obtained as the octa-*O*-acetyl derivatives, accompanied by a C-C-linked compound, epioritin-(4β → 6)-epioritin-4α-ol **27** (Scheme 3) [51].

The $AgBF_4$ activating C-H group between carbonyl and aryl functional groups affords a novel synthesis of proanthocyanidins from 3-oxo-flavans, accessible from readily available flavan-3-ols *via* Dess-Martin periodinane oxidation, thus circumventing the need for C-4 functionalization. In contrast with flavan-3-ol based syntheses, where the C-3 stereochemistry determines the C-4 stereochemistry, the 3-oxo-flavans have no stereochemistry on C-3 and the C-2 determines absolute configuration on C-4, giving access in hitherto synthetically unavailable 3,4-*cis* procyanidins (Scheme 4) [52].



Scheme 1: Interflavanyl bond formation in procyanidins under neutral conditions.



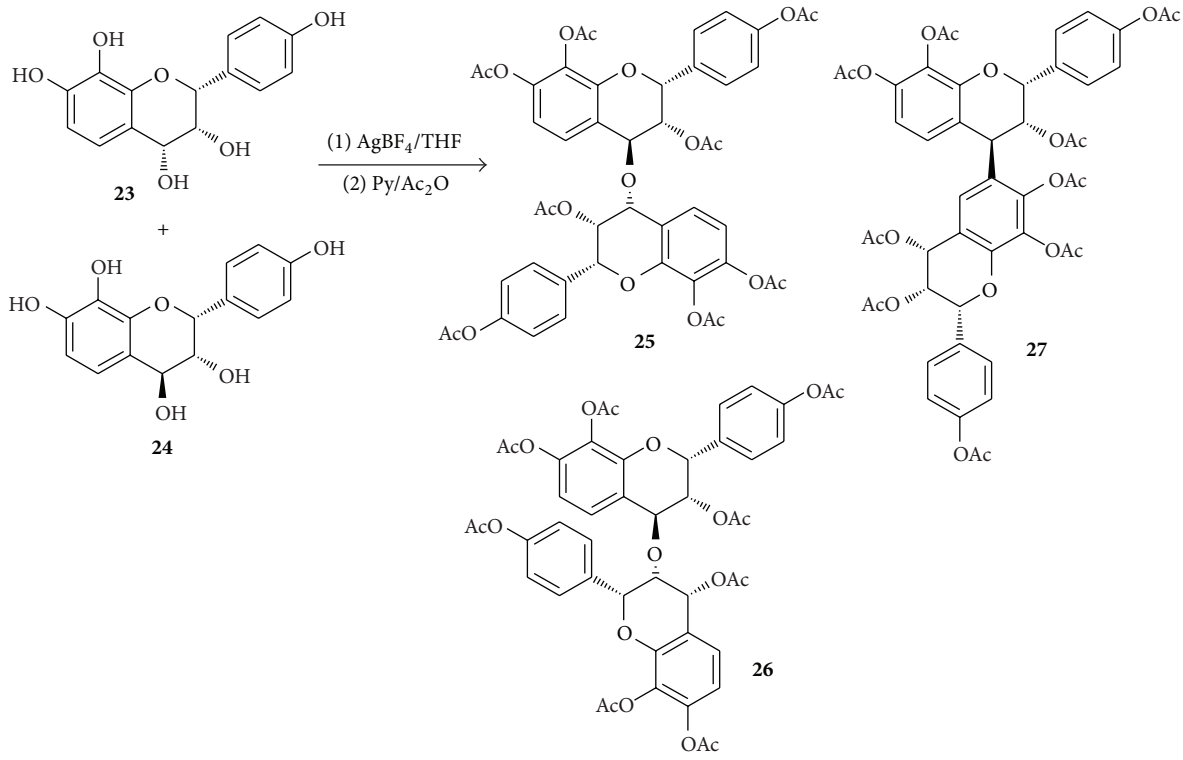
Scheme 2: Synthesis of procyanidin oligomers using 4-[(2-benzothiazolyl)thio] derivative.

The requirement of an excess of $AgBF_4$ and the observation of a silver mirror (reduction of Ag^1 to Ag^0) may indicate an oxidative mechanism (Scheme 5) [53].

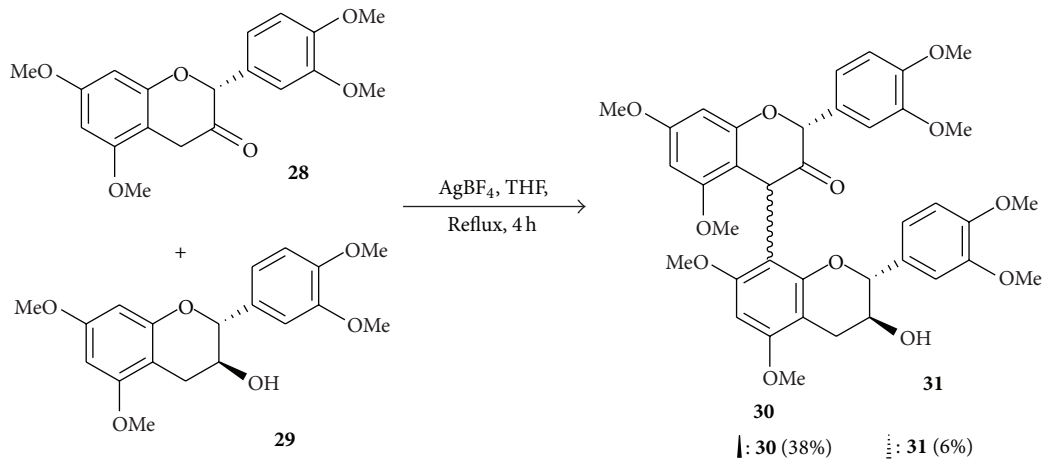
The BF_4^- counter ion probably assists in stabilizing the 4-carbocation **34** *via* the quinone methide tautomer **36**. Another major advantage of this synthesis is that no self-condensation was observed as was the case with the conventional syntheses based on a flavan-3-ol with a C-4 leaving group.

3. Glycosides

Natural occurring bioactive glycosides are many and are mainly essential class of compounds such as hormones, sweeteners, alkaloids, flavonoids, and antibiotics [24]. It is widely attested that the glycosidic moiety can be crucial for the compound's activity or in certain cases it only improves its pharmacokinetic properties such as circulation, elimination, and concentration in the body fluid [24].

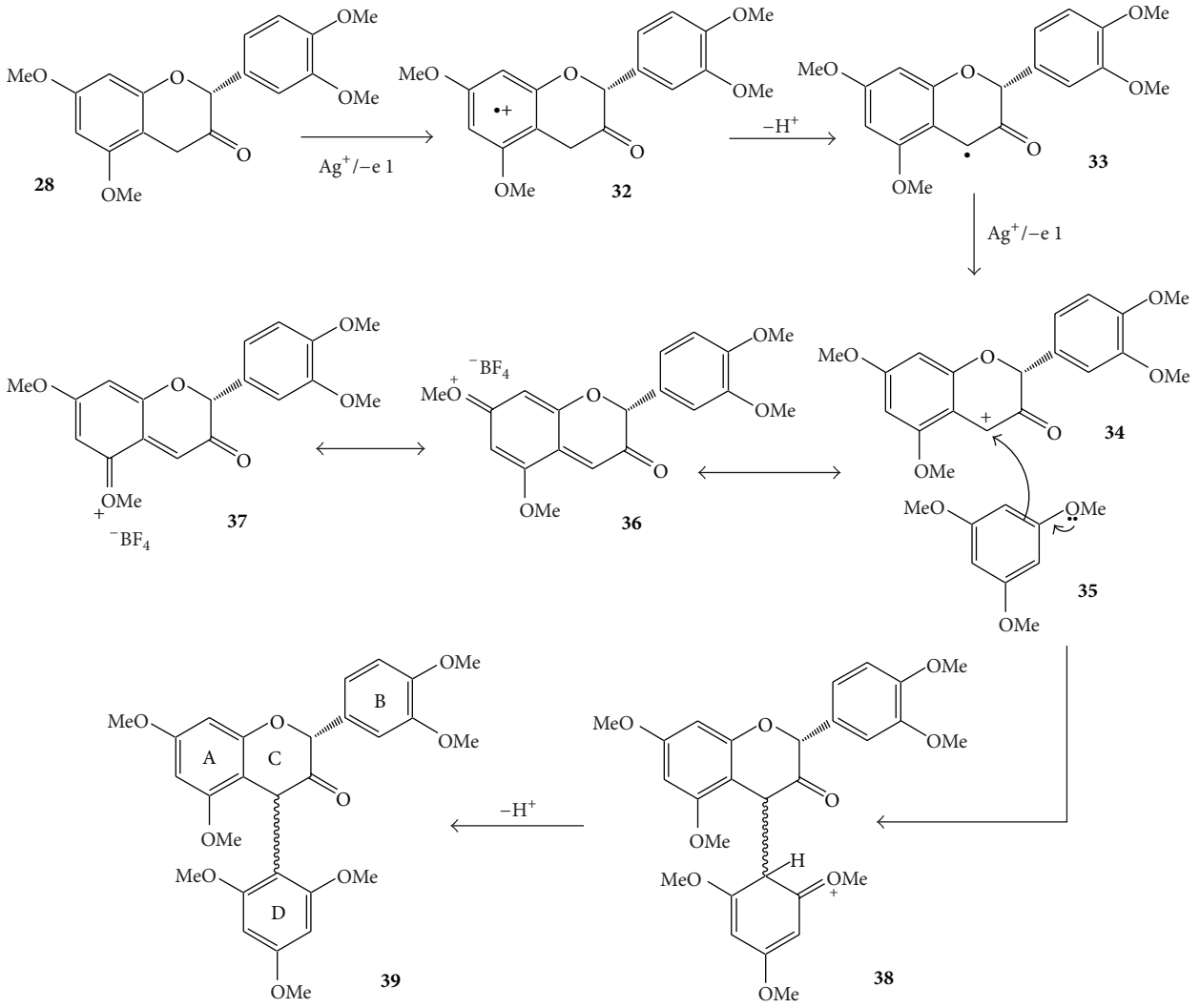


Scheme 3: Synthesis of ether-linked proteracacinidins **25** and **26** and the C-C coupled analogue **27**.



Scheme 4: Condensation reaction between **28** and **29**.

Glycosides are more water soluble than aglycons; therefore attaching glycosidic residue into the molecule will increase the compound's hydrophilicity. Consequently, the effect will be seen in the compound's pharmacokinetic activities such as inhibiting cell uptake of the glycoside by building placenta barrier, thus preventing foetal intoxication by metabolites of xenobiotics [24]. Varieties of natural polyphenolic flavonoid glycosides (Figure 2) are found in abundance in legume plants [28]. Glycoflavonoids, mainly isoflavonoids (e.g., quercetin 3-*O*-rhamnopyranosyl(1 → 2)-glucopyranoside-7-*O*-rhamnopyranoside **7**) present in legumes such as *Vicia faba* and *Lotus edulis* (Leguminosae), are purported to exert chemopreventive actions [25] on certain cancer types (colon, breast, and prostate) [26] and cardiovascular diseases [27]. Flavonoid glycosides are prepared synthetically, usually for pharmaceutical purposes [24]. Anthocyanin glycosides improve the antioxidant and "deepening" colour stabilization controlled by the glycosyl residue. A typical molecule is the "heavy blue anthocyanidin," peonidin acyl-glycoside **8**. Another example is Silybin **9**, a flavonolignan extracted from seeds of milk thistle (*Silybum marianum*) used as potent hepatoprotectant and an antidote in mushroom poisoning.



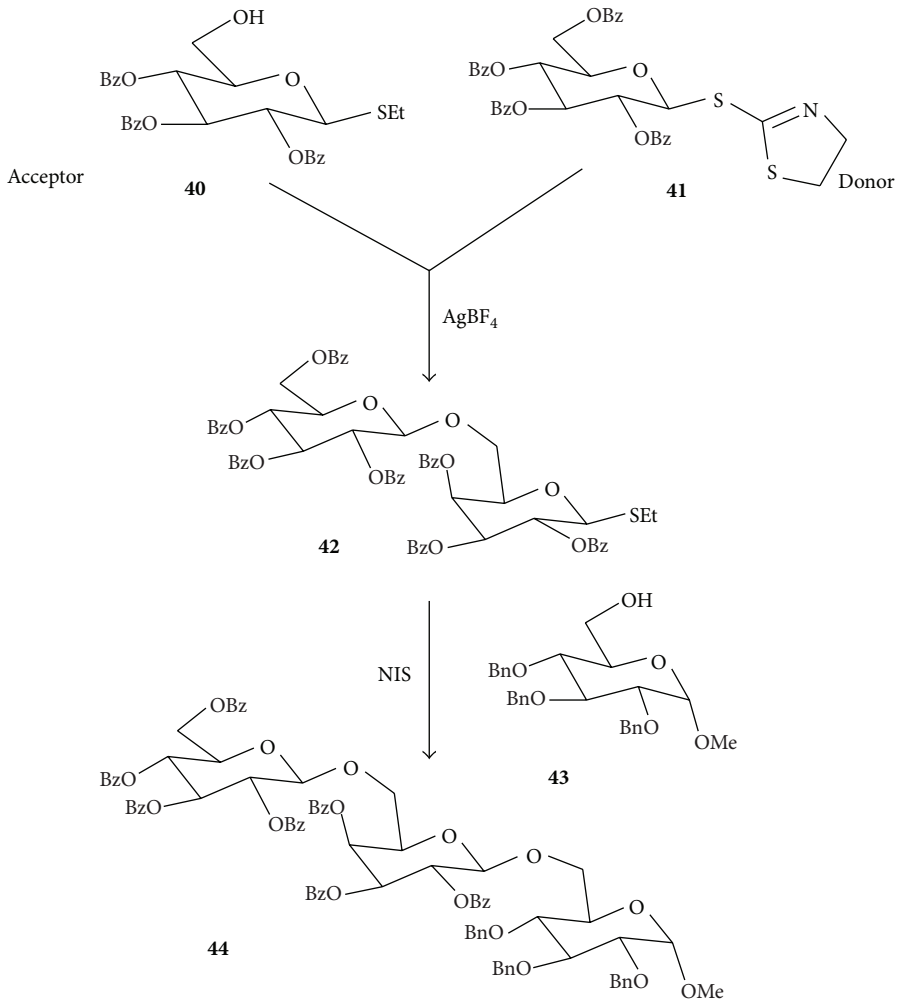
Scheme 5: Proposed mechanism for oxidative synthesis of **30** and **31** based on the model reaction.

However, the major drawback of water solubility of this phytochemical compound was dealt with by chemical glycosylation to afford compound **10** [24, 28]. The demand for biologically relevant and therapeutically active oligosaccharides is on the increase in recent times. This has spurred synthetic biologists and chemists to increase efforts in developing effective glycosylation methods for oligosaccharides.

A typical work is that of Kaeothip et al. (2008) who used silver tetrafluoroborate to activate glycosyl donors such as glycosyl halides, trichloroacetimidates, and thioimidates [53, 54]. Glycosyl thioimidates **40** and **41** could be selectively activated in the presence of thioglycosides to afford a simple one-pot synthesis of trisaccharides (Scheme 6). The glycosyl acceptor (S-ethyl glycoside) is expected to withstand $AgBF_4$ activation but later readily activated when N-iodosuccinimide (NIS) was added, followed by addition of new acceptor, methoxy glycoside **43**.

4. Alkaloids

Alkaloids, typically derived from plant sources, are a large group of secondary metabolites containing usually basic nitrogen in a heterocycle. The types and occurrences of alkaloids [29] within the scope of this paper are as follows (Figure 3): pyrrole *Coca* spp. (Erythroxylaceae); quinolone *Cinchona* spp. (Rubiaceae), *Remijia* spp. (Rubiaceae), *Angostura or cusparia bark, Galipea officinalis* (Rutaceae); isoquinoline *Papaver somniferum* (Papaveraceae), *Corydalis* and *Dicentra* spp. (Fumariaceae), numerous genera of the Berberidaceae, Ranunculaceae and Papaveraceae, *Cephaelis* spp. (Rubiaceae), Curare obtained from plants of Menispermaceae, *Papaver somniferum* (Papaveraceae), *Erythrina* spp. (Leguminosae), *Leucojum aestivum* (Amaryllidaceae); and indole (benzopyrrole), *Claviceps* spp. (Hypocreaceae), *Rivea corymbosa, Ipomoea violacea* (Convolvulaceae), *Physostigma*



Scheme 6: $AgBF_4$ as a potent promoter for chemical glycosylation.

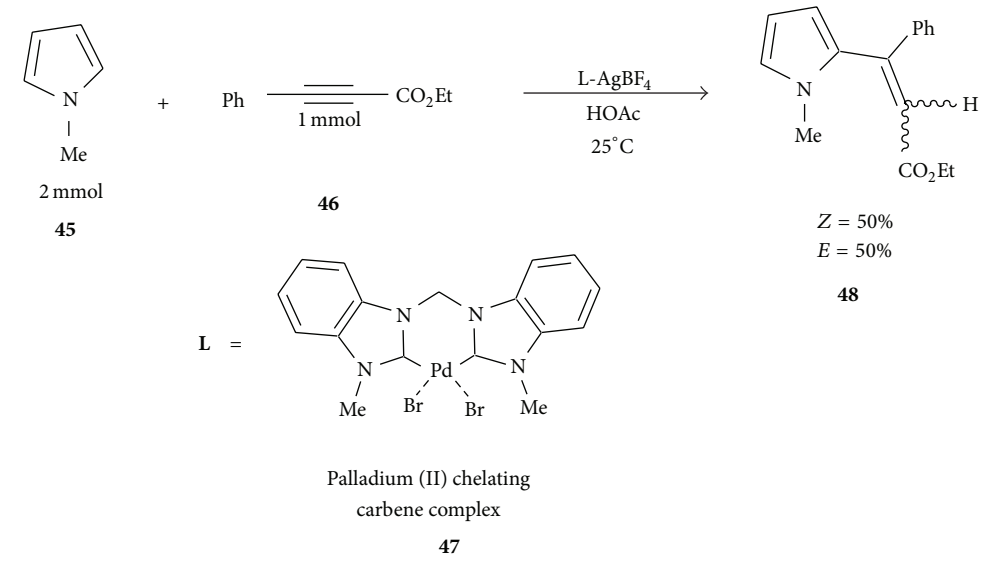
venenosum (Leguminosae), *Rauwolfia* spp. (Apocynaceae), *Aspidosperma* spp. (Apocynaceae), *Catharanthus roseus* (Apocynaceae), and *Strychnos* spp. (Loganiaceae). Though many alkaloids are toxic, some have pharmacological effects and are used as medications, recreational drugs, or in religious rites [30, 31]. Only N-heterocyclic alkaloids synthesized *via* $AgBF_4$ mediation are summarized here.

4.1. Pyrroles. Pyrroles are a very important class of heterocyclic compounds serving as key structural characteristic of many bioactive natural products and pharmaceutical resources [55]. Many classical reaction methods requiring the use of prefunctionalized substrates to obtain bioactive pyrrole analogues have been developed [56].

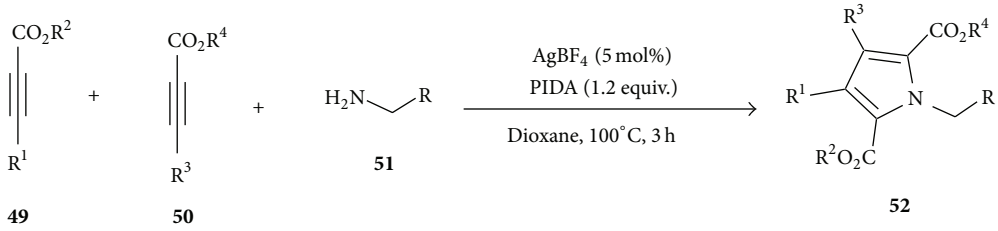
In 2010, Buscemi et al. reported the use of ligand-$AgBF_4$ complex to synthesis substituted pyrrole not involving prefunctionalized substrate. This reaction allows hydroarylations of ethyl 3-phenylpropanoate **46** with 1-methylpyrrole **45** to obtain the ethyl 3-(1-methyl-1*H*-pyrrol-2-yl)-3-phenylacrylate **48** in 70% yield. The C-H bond functionalization of an aromatic heterocycles requires the chelating dicarbene Pd (II) ligand **47** to be activated by extraction of the halides with silver additives ($AgBF_4$) possessing a noncoordinating anion (Scheme 7) [56].

Reports on an efficient one-pot $AgBF_4$-catalyzed and phenyliodine diacetate- (PIDA-) mediated synthesis of polysubstituted pyrroles, in which dimethyl but-2-ynedioate was treated with various amines (*via* tandem reactions), afforded corresponding pyrroles in moderate to excellent isolated yields of 53–88% [55]. By the protocol, a facile and highly efficient C-N and C-C bond formation method to construct a direct pyrrole framework (Scheme 8) as described by the proposed reaction mechanism (Scheme 9) was established.

4.2. Morphine. Morphine, the major alkaloid in opium, a dried sap of the unripe seed capsule of poppy (*Papaver somniferum*), is an analgesic. However, it has serious side effects such as being additive and causing nausea, decrease in



Scheme 7: Pd carbene complex $AgBF_4$-mediated synthesis of compound **48**.



Scheme 8: Synthesis of polysubstituted pyrroles from various alkynoates and amines.

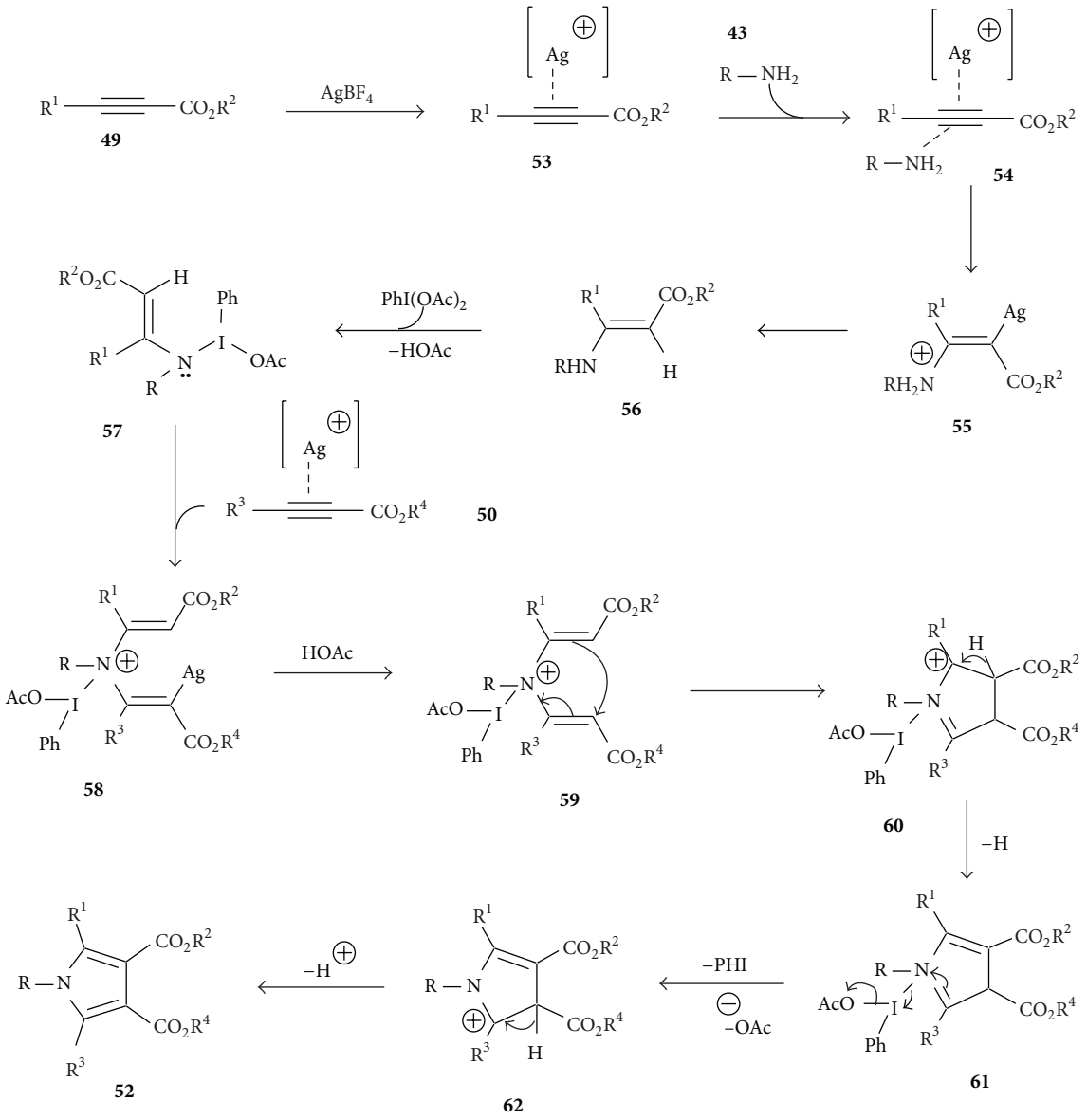
blood pressure, and depressed breathing [57]. Morphine was first isolated in 1805 and its first synthesis in the laboratory was in 1952.

After three decades, a concise methodology to morphinan ring system **64** was described [58]. The reaction mechanism relies upon intramolecular trapping of an aziridinium cation generated *in situ* by the treatment of pyrrolidine **63** with $AgBF_4$. The protocol involves treatment of a solution of **63** (54 mg, 0.13 mmol) in 3 mL of toluene with $AgBF_4$ (56 mg, 0.29 mmol) in 2 mL of toluene, and an immediate formation of AgCl precipitate was purported to drive the reaction forward, affording the desired compound **64** (19 mg, 56%), following purification on silica gel preparative TLC (eluting with 12% $MeOH/CH_2Cl_2$) (Scheme 10).

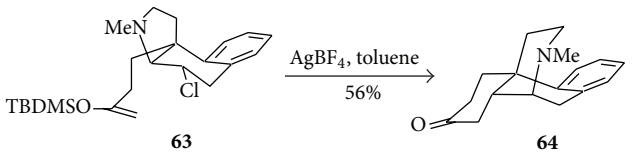
4.3. Quinolines. Quinolines are made up of compounds that exhibit extensive bioactivities. According to the record of South and Liebeskind 1984, benzoquinones (methylbenzoquinone, ethylbenzoquinone) are defensive agents against predators in arthropods [59], while menaquinones play important role in blood clotting process [60], and many derivatives of natural products such as benzoquinone, naphthoquinone, and anthraquinone show significant antibiotic and/or antitumor properties [61]. It is widely recorded that polysubstituted dihydroquinolines are important building blocks in natural products, exhibiting a broad range of bioactivities (psychotropy, antiallergy, anti-inflammatory, and estrogen) and potential pharmaceutical applications [62–67].

The first example of a silver-catalyzed regioselective domino reaction between anilines and alkynes was reported to obtain partially hydrogenated quinoline moiety bearing different functional groups (polysubstituted 1,2-dihydroquinolines) [68]. The work involved treating Phenylethyne **65** (1.0 mmol) and phenylamine **66** (4.0 mmol) with $AgBF_4$ (9.7 mg, 0.05 mmol), HBF_4 (11.2 mg, 0.07 mmol), and $BF_3{\cdot}Et_2O$ (11.3 mg, 0.08 mmol) as cocatalysts, for 12 h at 160–190°C to yield **67** (77%) (Scheme 11). A proposed mechanism is given in Scheme 12.

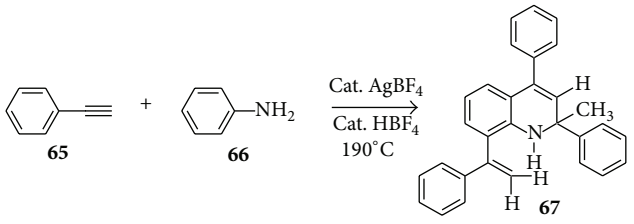
The works of Tang et al. (2010) demonstrated further ability of $AgBF_4$ in heteroatoms activation as well as alkyne group reactions. In the presence of $AgBF_4$, 2-alkynylbenzenamines and tetraalkylthiuram disulfides reacted *via* ammonolysis-cyclization tandem to produce quinoline thiaz-analogue 4-methylene-4*H*-benzo[*d*][1,3]thiazin-2-amines (Scheme 13) [69].



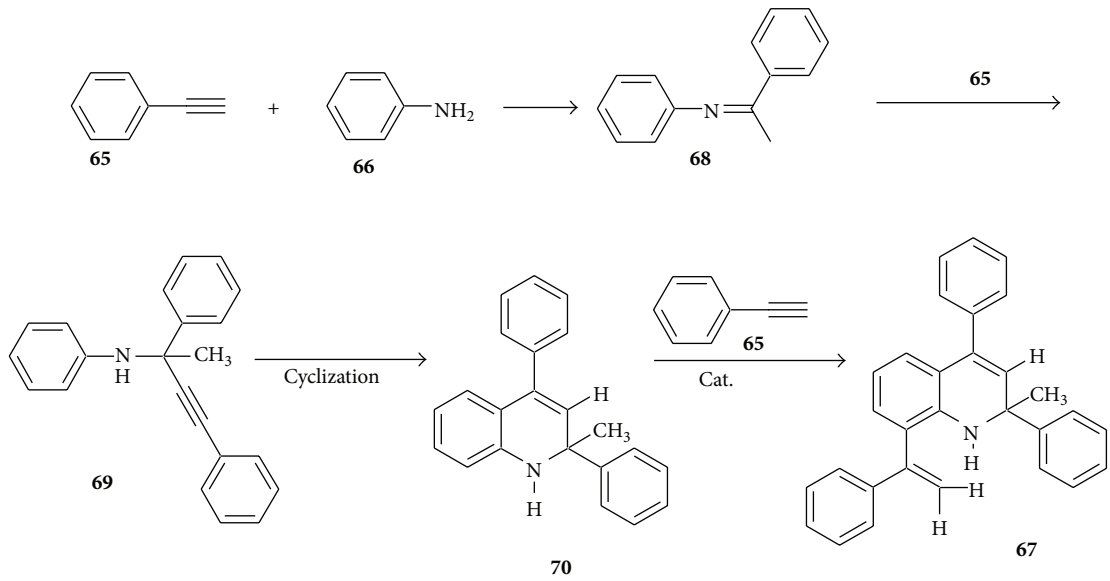
Scheme 9: A plausible mechanism for the addition/oxidative cyclization reaction in the formation of **52**.



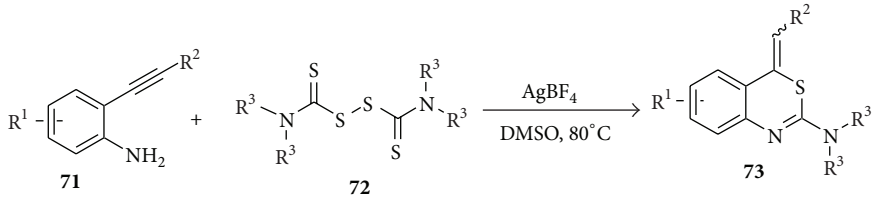
Scheme 10: $AgBF_4$-mediated synthesis of morphinan.



Scheme 11: A silver-catalyzed efficient synthesis of 1,2-dihydroquinoline derivatives.



Scheme 12: Proposed mechanism for the synthesis of **67**.



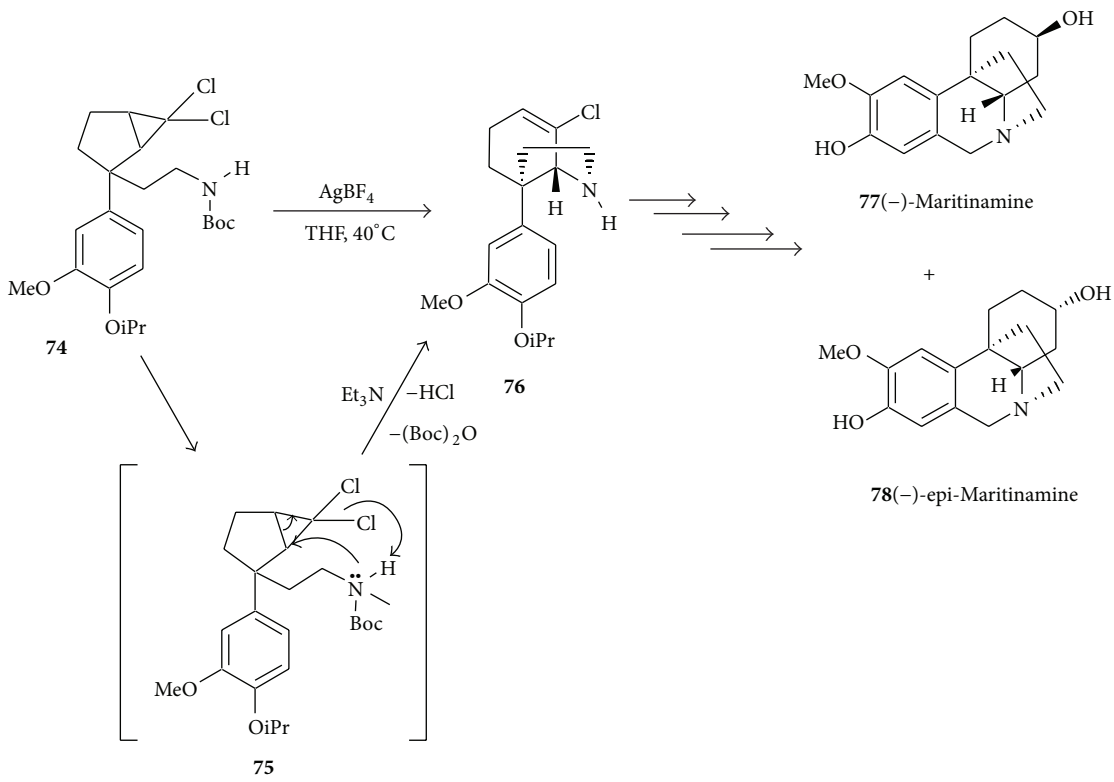
Scheme 13: Synthesis of 4-methylene-4*H*-benzo[*d*][1,3]thiazin-2-amines.

4.4. Isoquinoline. Crinine alkaloids are our focus here. They represent an important subclass (Galantamine) within the large family of *Leucojum aestivum* (Amaryllidaceae) alkaloids. Members of this subclass exhibit attractive biological properties including immune-stimulatory, cytotoxic, and antimalaria activities [70]. Accordingly, these natural products (e.g., maritinamine, erythramine, etc.) interests and synthetic studies have proved this since 1966 when it was first synthesised [70–83]. Cyclopropanes are ubiquitously basic structural moiety in a variety of the naturally occurring alkaloid compounds [84]. Banwell (2008) has demonstrated the use of $AgBF_4$ to open the strained cyclopropanes and trapped the resulting allylic cation by the carbamate nitrogen [70, 85] to synthesize maritinamine *via* an arylated hexahydroindole from 6,6-dichlorobicyclo[3.1.0]hexane (Scheme 14).

It was purported that deprotonation of *gem*-dihalopropane **79** with LiHMDS and subsequent reaction of the conjugate base with $AgBF_4$ affords a diastereoisomeric mixture of products **80** (26%) and its C-3 epimer **81** (30%) [85]; and the completion of the synthesis of erythramine **82** took three further steps as shown in Scheme 15.

4.5. Indole. Indole ring system is a prevalent structural motif extensively present in naturally occurring compounds; and its derivatives display a broad variety of powerful and therapeutically fascinating biological activities [86]. For example, serotonin alkaloid is a bioactive alkaloid known as a neurotransmitter in the cardiovascular system, blood cells and the peripheral, and central nervous system. Psilocin and psilocybin are the main alkaloids in hallucinogenic mushrooms belonging to the genus *Psilocybe* [87]. In 1977, the first isolation of hallucinogenic bisindolylalkane was obtained and, subsequently, several bioactive bisindolylalkanes have been isolated from nature and this pulled a lot of scientific attention. Typically, some indole derivatives (3 substituted indoles) are known to exhibit various biological activities including antibacterial, cytotoxic, antioxidative, and insecticidal activities [88]. Following this line of thought, synthetic chemists in their pursuit for more efficient routes to synthesize the richly endowed indole molecules shifted from the common methods of preparing indole scaffold (Fischer, Bischler, Reissert, Madelung, and Smith methodologies) to organometallic reagents of which coinage metals (silver and gold) were the first choice [86].

Reports by Ko et al. (2013) established that stable bis-cyclometalated gold(III) catalysts **85** can exhibit high catalytic activity in organic synthesis *via* gold–silver dual catalysis for substrate activation [89]. They also supposed that silver salts can react synergistically with bis-cyclometalated gold(III) complexes in the indole alkylation. Thus, using



Scheme 14: Synthesis of epi-Maritinamine **78**.

85 (2.5 mol%) with $AgBF_4$ (5.0 mol%), alkynyl alcohol **83** reacted with N-methylindole **84** to obtain the naturally occurring alkylated indole analogue (3-(tetrahydro-2-methylfuran-2-yl)-1-methyl-1*H*-indole) **86** in 80% isolated yield at room temperature in 2 h (Scheme 16). Poor yields (10–13%) or no product formation was found when only a single metal catalyst was used.

Shaikh and Chen (2011) showed that carbonyl compounds **88** can be activated towards nucleophilic attack by indoles **87** with $AgBF_4$ to synthesise bisindolylmethanes **89** in excellent yields [88]. Thus, reaction of *p*-nitrobenzaldehyde and indole in the presence of $AgBF_4$ (10%) in methylene chloride gave a 96% yield at room temperature within 2 h (Scheme 17). The proposed mechanism is presented in Scheme 18.

In the work of Grierson et al. (1992), it was discovered that condensation of allylic aminonitrile **93** and diacid **96** led to the production of 4-[bis(methoxycarbonyl)methyl]-3-(3-indolylmethyl)-1-methyl-1,4,5,6-tetrahydropyridine **97** [90]. The C-7 indole-substituted aminonitriles **93** or **95a,b**, when treated with $AgBF_4$, yielded the desired reactive intermediate (5,6-dihydropyridinium salt **94**), which on reaction with sodium dimethyl malonate **96** was converted to the **97** (76%) (Scheme 19).

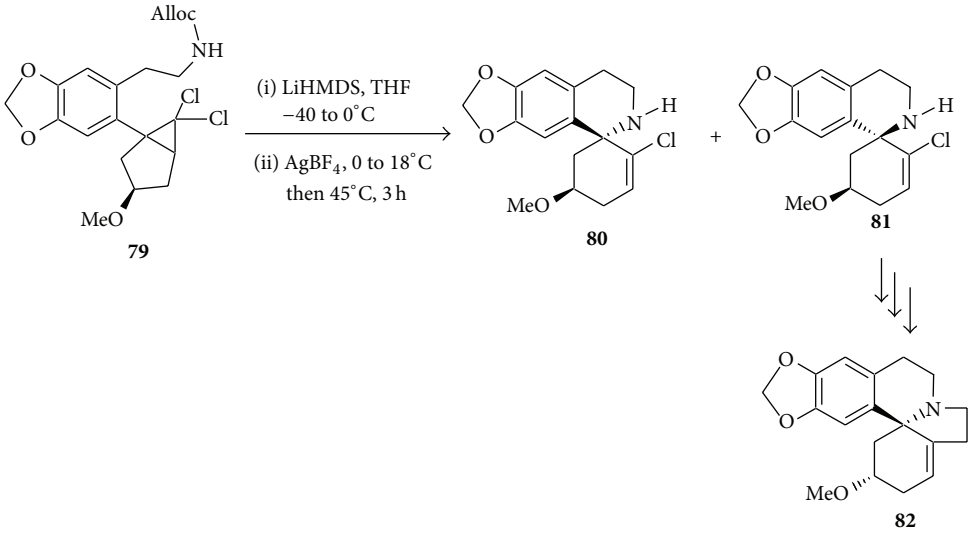
Another example is $AgBF_4$-mediated cyclopropane ring opening and trapping of the intermediate cation in the synthesis of a diastereoisomeric mixture of Hapalindole C **100** (Scheme 20) [85].

Kuehne et al. (1991) recorded successful enantioselective synthesis of vinblastine [66], a natural occurring bioactive binary indole-indoline alkaloid. The compound generally has a long history of investigation and thus has been extensively reviewed since it was first synthesized in 1967 [91–94]. Here, we therefore summarize accessing the compound via the synthesis of the intermediate promoted by $AgBF_4$. The authors established that the reaction of the chloro-imine **101** with silver tetrafluoroborate and a natural compound, vindoline hydrofluoroborate, provided the tetracyclic C16′-C14′ parf indolenine **102** as white foam (Scheme 21) [95].

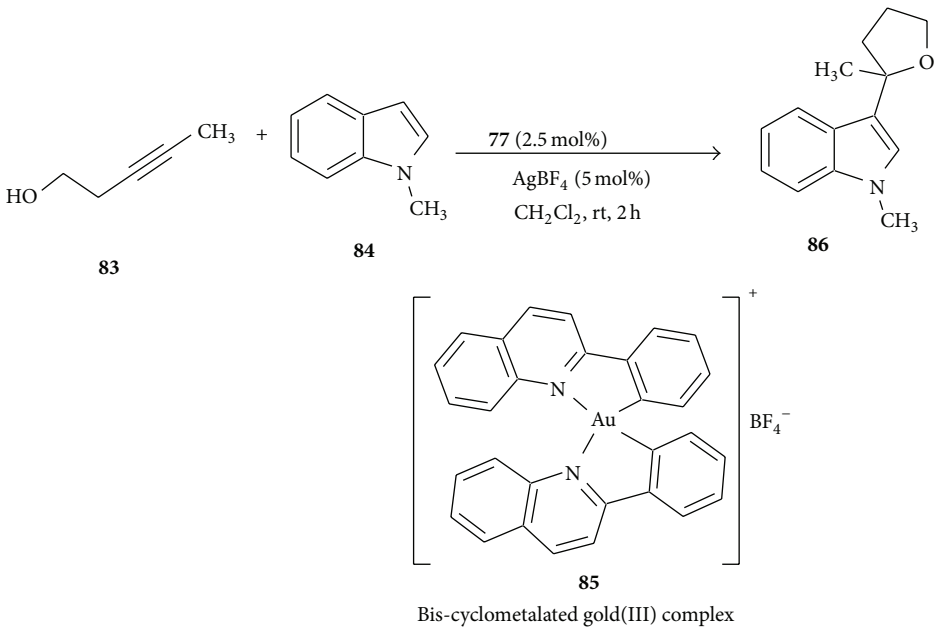
5. Furans

Furan structural motif occurs in a variety of natural products, and the 2,3- and 3,4-substitutions are the most abundant in nature [96, 97]. Typically, 2,3-dihydrofurans are amongst the structural units ubiquitously found in natural products and they exhibit impressive biological activities. Accordingly, they are extensively used in the pharmaceuticals, as flavourant, insecticidal, and fish antifeedant industries [32]. Thus, researchers are prompted to search for better methods to synthesize or modify the natural products.

Hence, Xia et al. (2011) reported their investigation in the use of $AgBF_4$ to generate carbenes from diazo compounds [32]; namely, (1) several Ag(I) containing catalysts were used for the synthesis of 2,3-dihydrofurans starting from 2-diazo-5,5-dimethyl cyclohexanedione **103** and styrene **104**; (2) Ag_2O, Ag_2CO_3, $AgNO_3$, $AgClO_4$, and $AgOSO_2CF_3$ at 70°C for 10 h gave no cycloadducts, while, with $AgBF_4$ (10 mol%) in toluene at room temperature for 48 h, the expected



Scheme 15: Synthesis of (-)-erythramine **82**.



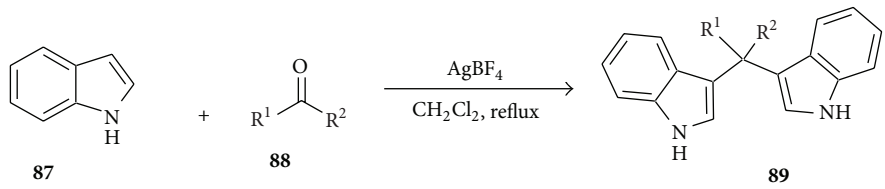
Scheme 16: Gold(III) complex silver-catalyzed cyclization-addition reactions of alkynyl alcohols **83** and substituted indoles **84**.

product **105** was produced in 22% yield (Scheme 22); and (3) raising the temperature to 70°C increased the yield to 47%, but, by using the ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4), as a cocatalyst, the yield was increased to 71%. The general procedure for the synthesis involves addition of silver tetrafluoroborate (0.10 mmol) and (Bmim) BF_4 (0.1 mL) to a solution of cyclic diazodicarbonyl compound **103** (1.0 mmol) and the corresponding olefin **104** (5.0 mmol) in toluene (2.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 24 h or at 70°C for 5 h, and the mechanism is given in Scheme 23.

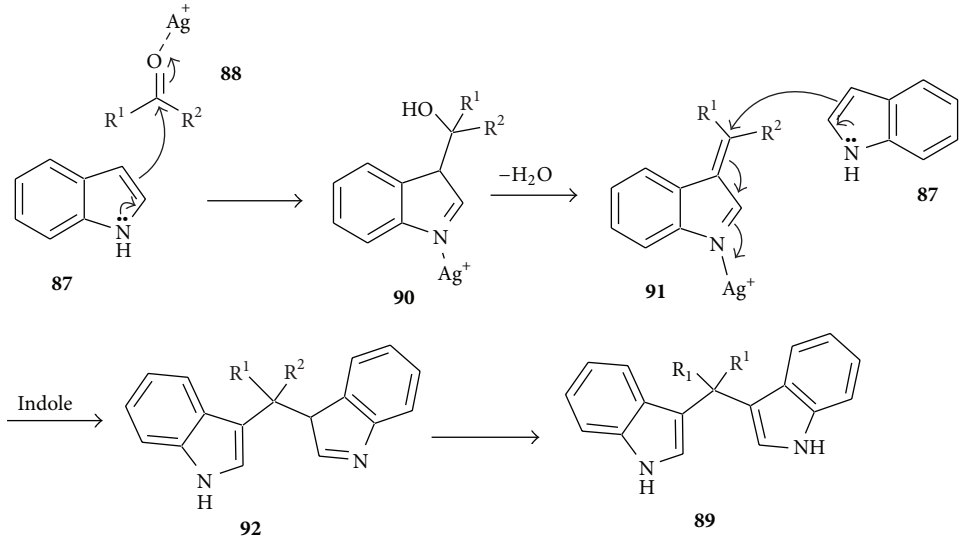
$AgBF_4$ has also been used to activate trimethylsilyl enols as nucleophiles in substitution reactions. In a study [96], 2,3-diiodo-1-(phenylsulfonyl)-1-propene (DIP) **109** and (cyclohex-1-enyloxy)trimethylsilane (CH-TMS) **110** were treated at 25°C in methylene chloride (0.05 M), with 2.0 equivalents of $AgBF_4$ to obtain iodo-(phenylsulfonyl) ketone **111**. Addition of triethylamine in THF at 25°C cyclized the ketone compound to form the 2-phenylsulfonylmethyl substituted furan **112** (Scheme 24).

6. Organohalogen Compounds

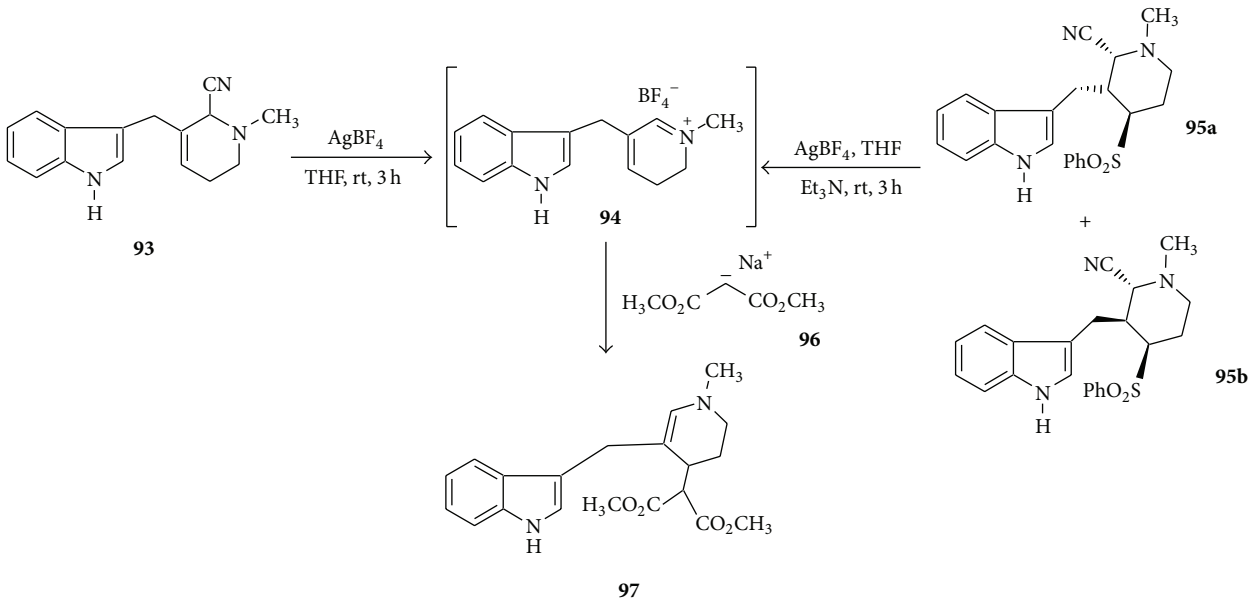
According to Gribble (2012), the number of naturally occurring organohalogen compounds (particularly, halogenated alkaloids) has grown from a dozen in 1954 to >5000 at



Scheme 17: Synthesis of 3-substituted indole derivatives.

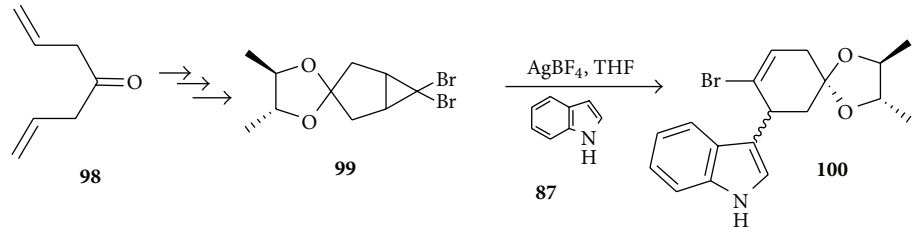


Scheme 18: $AgBF_4$-mediated synthesis of C-7 indole-substituted aminonitriles.

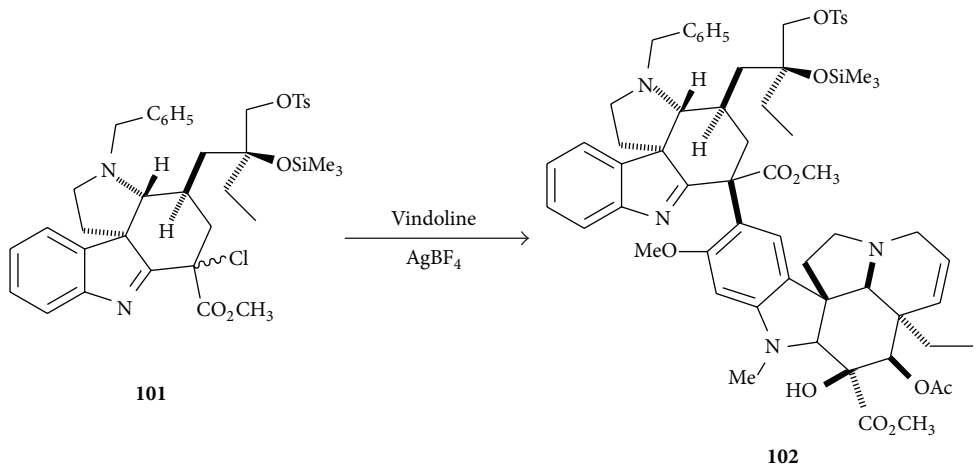


Scheme 19: $AgBF_4$-mediated synthesis of C-7 indole-substituted aminonitriles.

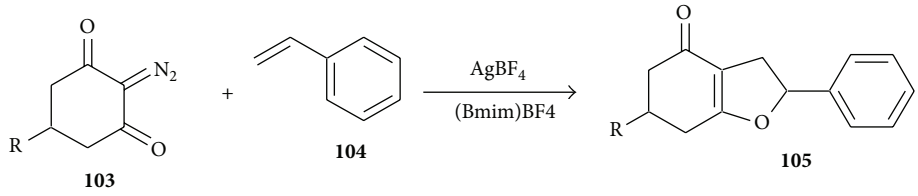
the time [98]. However, not many compounds containing fluorine atom(s) have been found in nature [39–100]. Nevertheless, it is widely recognised that these compounds exhibit interesting biological activities [101–106]. A typical example is kinamycin D [101], produced by *Streptomyces murayamaensis* (5-diazobenzo[*b*]fluorine), which is a naturally occurring diazo compound that possesses modest antitumor properties and antibiotic activity against Gram-positive organisms [101–105]. Again, record shows that introducing fluorine into organic molecules, more often than not, significantly



Scheme 20: Synthesis of Hapalindole C.



Scheme 21: Synthesis of indolenine **102**.



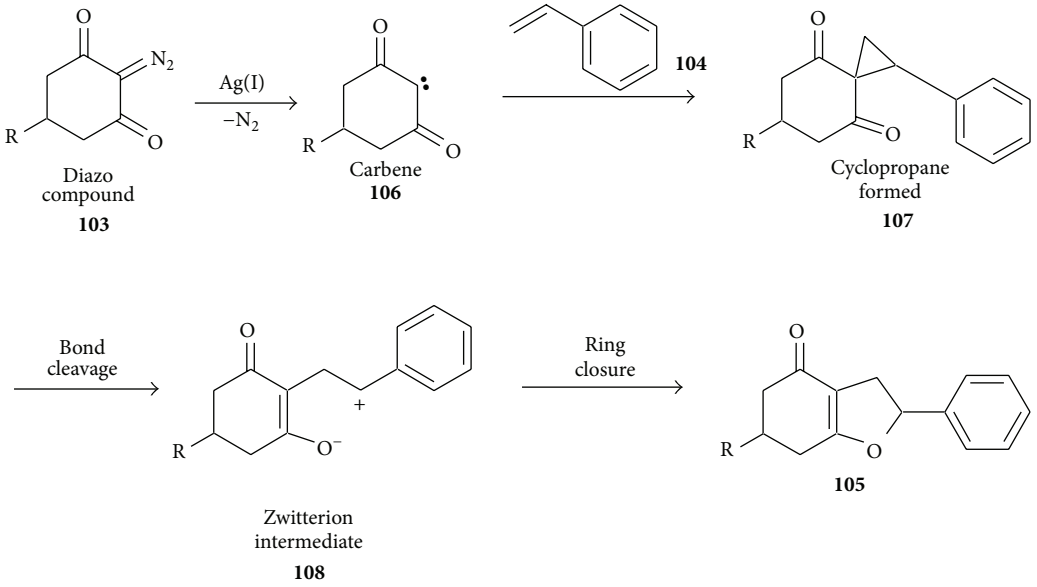
R = alkyl, aryl

Scheme 22: Synthesis of 2,3-dihydrofurans **105**.

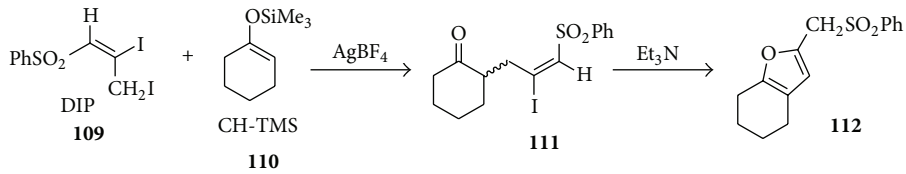
improves their physical, chemical, and biological properties [106]. These reactions have been demonstrated in some compounds such as steroids. Steroids are important naturally occurring bioactive compounds. Unfortunately most of these compounds lack methods for their synthesis; and fluorination has been a gateway to access these rare compounds [107]. The report of Wang et al. (2013) and other authors expressed that arene compounds with fluorine or a trifluoromethyl substituent display unique pharmaceutical properties such as improved metabolic stability and lipophilicity. For this reason, a large number of drug candidates containing ArF and $ArCF_3$ are routinely evaluated in modern drug discovery [108–111]. Given that fluorinated compounds are notably sparsely available from nature, their chemical synthesis are highly challenging [112, 113]. Accordingly, fluorination of molecules has gained a prestigious position in the design and synthesis of biologically active compounds [39].

Studies by Wang et al. (2013) [108] revealed that $AgBF_4$ in a nonpolar solvent (such as toluene) was most effective in promoting the substrate cyclization and subsequent fluorination to afford 96% product yield. The general procedure for the stoichiometric fluorination reaction involves dissolving **113** (0.1 mmol) and $AgBF_4$ (0.15 mmol) in 5.0 mL of toluene under inert atmosphere, and the resulting mixture was stirred at 90°C for 2 h. Thereafter, the crude reaction mixture was filtered through a small column packed with silica gel and the required product **114** was isolated by column chromatography on silica gel (Scheme 25). A proposed reaction mechanism is shown in Scheme 26.

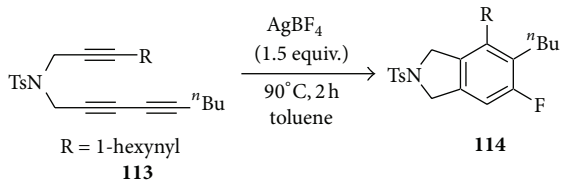
It was recently illustrated [107] that P_2Pt-dicationic catalysts can mediate enantioselective cation-olefin **120** cyclization/fluorination reactions of the polyenes to yield C3-fluorinated carbocycles. Their catalyst formulation is comprised of 10 mol% (S)-(xylyl-phanephos)PtI_2, 25 mol%



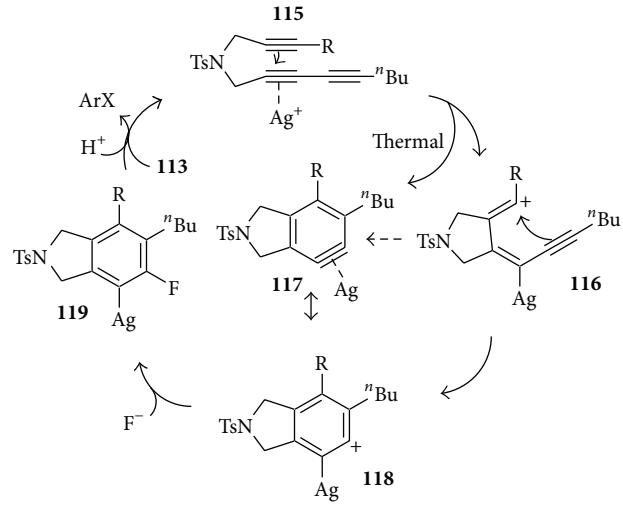
Scheme 23: Proposed reaction mechanism to afford the 2,3-dihydrofuran.



Scheme 24: Synthesis of substituted furans **112**.



Scheme 25: Synthesis of compound **114**.



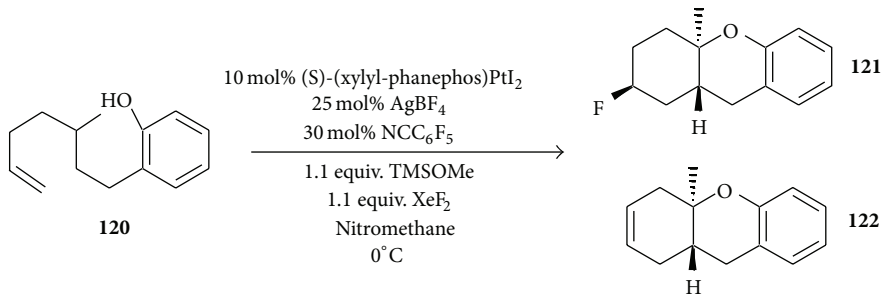
Scheme 26: A proposed reaction mechanism for compound **108**.

$AgBF_4$, 30 mol% NCC_6F_5, and stoichiometric quantities of XeF_2 and TMSOMe, which at 0°C provided moderate to quantitative yields of **121** (49–80%) with enantiomeric excess (10–81%) and low to trace yields of **122** (22%-trace) (Scheme 27).

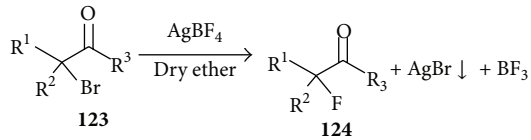
The fluoride in the BF_4^- can be liberated as an F^- nucleophile. Following this line of thought, α-fluorocarbonyl molecules **124** can be prepared *via* the substitution of carbonyl α-bromo substituents (Scheme 28), presumably *via* neighbouring group participation by the carbonyl oxygen (Scheme 29) to obtain α-fluorocarbonyl compounds [114].

Another example of BF_4^- participation in fluorination reaction *via* halogen-exchange is in the synthesis of trifluoromethyl sulfides [115], *gem*-difluorides, and trifluorides [116]. For the sulfides, the general procedure involved treatment of aprotic solution of mercaptan **126** with a base (NaH) and thereafter with CF_2Br_2 or CF_2BrCl. The resulting bromodifluoromethyl sulfide **127** was subsequently treated with $AgBF_4$ to obtain desired trifluoromethyl sulfide **128** in moderate yield (41%) (Scheme 30) [115].

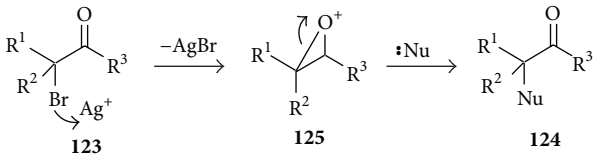
The reaction conditions for the formation of the *gem*-difluorides and trifluorides involved treating respective substrate **129** or **131** with $AgBF_4$ (1.1 molar equiv. per halide)



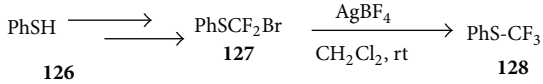
Scheme 27: Catalytic cyclization and C3-fluorination of polyene.



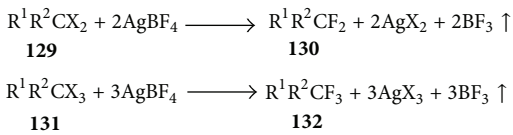
Scheme 28: Synthesis of α-fluorocarbonyl compounds **124**.



Scheme 29: Proposed reaction mechanism for α-fluorocarbonyl compounds.



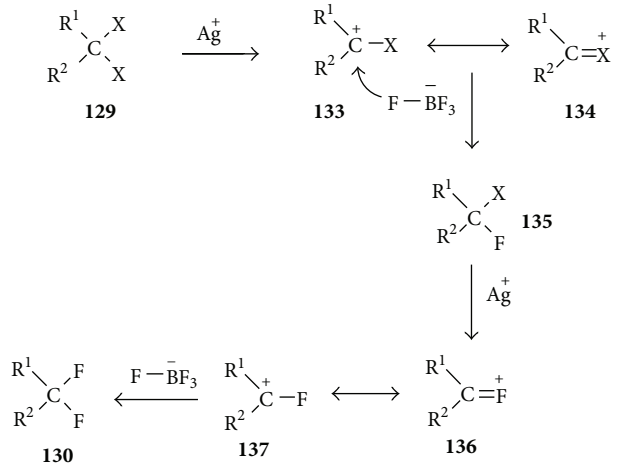
Scheme 30: $AgBF_4$-mediated synthesis of trifluoromethyl sulfide.



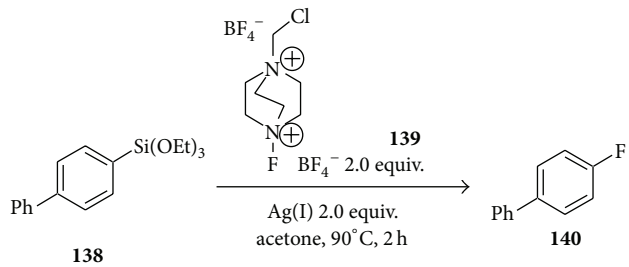
Scheme 31: Exchange-fluorination by reaction with $AgBF_4$.

in CH_2Cl_2 for 1 hour at room temperature followed by workup to obtain 35–84% yields (Scheme 31). Bloodworth et al. suggested that the reactions proceeded *via* cationic intermediates as demonstrated by the proposed mechanism in Scheme 32 [116].

In another study [117], direct electrophilic fluorination reaction of aryl silanes **138** with F-TEDA-BF_4 **139** catalyst afforded less than 4% yield. Not only did addition of $AgBF_4$ to the reaction system improve the yield to 11% but also regiospecific fluorination was observed. Intriguingly, Ag(I) oxide was identified as the silver salt that resulted in the highest yield of aryl fluoride (60–90%) (Scheme 33).

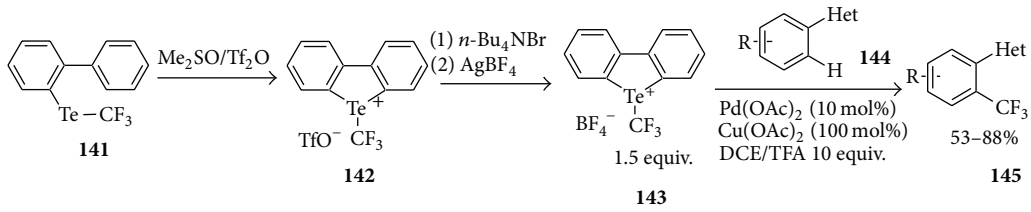


Scheme 32: Mechanism of exchange-fluorination by reaction with $AgBF_4$.

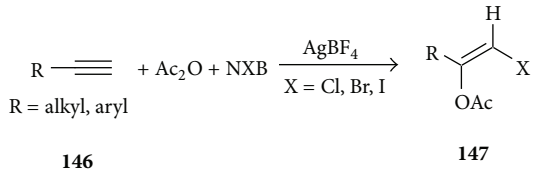


Scheme 33: Silver-mediated synthesis of 4-fluorobiphenyl.

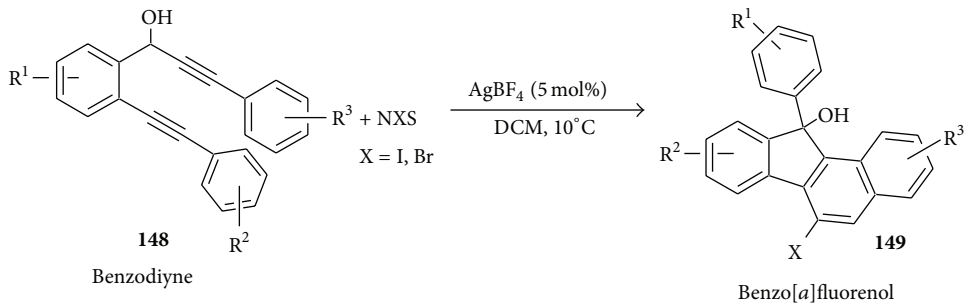
In addition to the reactivities of $AgBF_4$ described above, an effective electrophilic trifluoromethylating reagent, being (trifluoromethyl)dibenzotellurophenium salt, was developed [39, 108]. The experimental protocol aimed to afford the salt



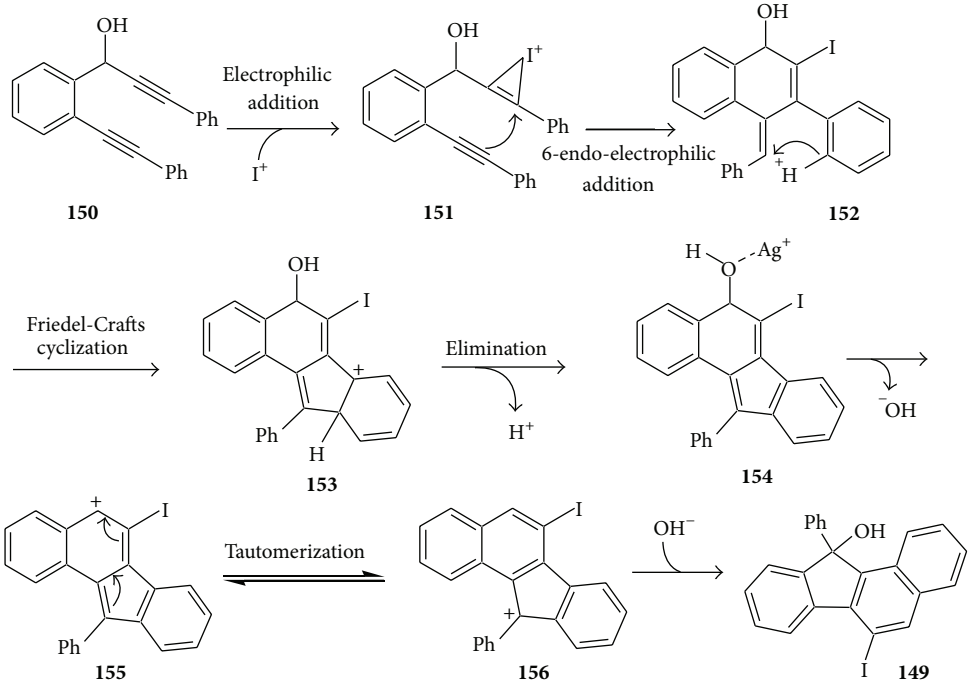
Scheme 34: Synthesis of Umemoto reagent and *ortho*-trifluoromethylation of heterocycle-substituted arenes.



Scheme 35: Highly regio- and stereoselective synthesis of (*Z*)-*β*-haloenol acetates.



Scheme 36: Synthesis of halo-substituted benzo[*a*]fluorenols.



Scheme 37: Mechanism for $AgBF_4$-catalyzed sequential electrophilic cyclization reaction.

consisting of treatment of telluride **141** with an equimolar mixture of triflic anhydride and DMSO at 0°C, followed by anion exchange with $AgBF_4$ [118]. Synthesized trifluoromethylated arenes **145** (53–88% yields) were obtained by reacting substituted arenes **144** with Umemoto reagents **143**, $Pd(OAc)_2$, and $Cu(OAc)_2$ at 110°C in a mixture of dichloroethane (DCE) and 10 equiv. of trifluoroacetic acid (TFA) (Scheme 34) [39].

The $AgBF_4$ activates alkyne moieties *via* π-complexes as exemplified in the regio- and stereoselective difunctional synthesis of (*Z*)-β-haloenol acetates from terminal alkynes (Scheme 35) [119]. Interestingly, reaction of phenylacetylene **146** and *N*-halosuccinimide in acetic anhydride in the presence of $AgBF_4$ at 120°C affords 60–90% yield of (*Z*)-β-haloenol acetate compounds **147**. These vinyl halides are thus important starting materials for transition-metal-catalyzed cross coupling reactions and halogen-metal exchange reactions [120].

Reports indicate that $AgBF_4$ and NXS catalysed electrophilic cascade cyclization of halo-substituted benzo[*a*]fluorenols **149** under mild conditions (Scheme 36) [38]. Into a CH_2Cl_2 (0.5 mL) mixture of *N*-iodosuccinimide (0.24 mmol) and $AgBF_4$ (0.01 mmol) at 10°C, was added a CH_2Cl_2 (1.0 mL) solution of benzodiyne **148** (0.20 mmol) under nitrogen. After 12 h, the reaction mixture was quenched with saturated ammonium chloride solution (3 mL) and flash column chromatography (ethyl acetate/*n*-hexane, 1 : 50) purification afforded **149** (76%) as a light yellow solid. A plausible mechanism is depicted in Scheme 37. The fused fluorenol derivatives **149** are well known to be widely applied in optoelectronic materials because of their highly conjugated rigid systems. They are extensively found as structural moieties in numerous natural products such as kinamycin D, recognised as 5-diazobenzo[*b*]fluorine, a naturally occurring diazo compound that possesses antitumor properties and antibiotic activity against Gram-positive organisms [38].

7. Conclusions

Phytochemicals have generally been noted to exhibit important health effects such as anticancer, antimicrobial, antioxidant, antidiarrheal, analgesic, and wound healing actions to humans and animals. Accordingly, a number of $AgBF_4$-mediated syntheses of biologically active phytochemicals have been described over the past six years; in addition to these there are those not reviewed in the previous reviews [40–43]. Hence, herein we reviewed the bioactivity and natural occurrences of some phytochemicals synthesized through $AgBF_4$-promoted reactions from 1979, when Fry and Migron published its use in this regard, until April 2014.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgment

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