



Review Article

The Advances and Applications of Arynes and Their Precursors to Synthesize the Heterocyclic Compounds: A Review

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Abstract: The aryne and its intermediates or their precursors are the most important compounds in organic synthesis for the purpose of aryne or benzyne insertion in many reactions. Arynes are among the first reactive intermediates known to organic chemists. Since their discovery, they have fascinated chemists from both theoretical and synthetic perspectives. These remarkable intermediates possess a wide reactivity profile, engaging in the different types of reactions especially in organic chemistry fields like nucleophilic addition reactions, pericyclic reactions, [4+2] and [3+2] cycloaddition reactions and transition metal-mediated/catalyzed reactions. This methodology would also be applicable for the synthesis of biologically and pharmaceutically active products such as isocoumarins, benzodiazepines and other important compounds in one pot reactions.

Keywords: Arynes, Benzyne, Cycloaddition Reactions, Heterocycles, Isocoumarins, Nucleophilic Reactions, Pericyclic Reactions

1. Introduction

Arynes or benzyne are the highly reactive species derived from an aromatic ring by removal of two ortho substituents [1, 2]. The uses and applications of aryne precursors as the efficient reactivity in the organic synthesis reactions have attracted the significant attention since the 1950s. The necessities of the using of aryne are increasing day by day even in the advance level of synthetic organic chemistry. The insertion of the aryne derivatives successfully developed in the [4+2], [3+2]cycloaddition reactions as well as [2+2]cycloaddition-type adducts formation [3-5].

Arynes have received considerable attention, as readily generated reactive intermediates over the past few years and many valuable transformations comprising aryne have been reported [6-8]. Notably, meanwhile over 75 natural products have been successfully synthesized by using aryne as key intermediates [9]. Aryne are ubiquitous active intermediates with numerous synthetic applications, primarily attributed to their versatility in the concomitant incorporation of various functional groups on the vicinal positions of an arene ring [5, 10]. For the synthesis of different amines by the help of some rearrangement procedures, the aryne compounds are also very much effectively used [11].

The 2,3-Dihydrobenzofurans and benzofurans are also

useful building blocks as well as core structures in biologically active natural products [12]. Most of the reported synthetic approaches have involved the use of the oxygen-atom containing arenes such as *ortho*-functionalized phenols or other phenol derivatives [13]. Few methods are based on the aromatic C-O-bond formation [14]. Thus, the researchers felt attracted to the possibility of a new aromatic C-O-bond-forming route starting from the arynes.

2. Ways of Existence and Generation of Benzyne/Arynes

Arynes are usually best described as having a strained triple bond; however, they possess some biradical character as well (Figure 1). The term aryne is most closely associated with *ortho*-aryne (1,2-didehydrobenzene), however 1,3- and 1,4-didehydrobenzene intermediates have been described.

After the Kobayashi's successful discovery of a very mild

way of generating highly reactive aryne intermediates [15], chemistry of arynes has become a subject of contemporary interest [3]. Since then, plenty of meticulous new applications of aryne reactions have been continuously reported by synthetic chemists [16]. That's why, the generation of these arynes and its derivatives are also growing interest to the chemists very fast way. The arynes like benzyne can be generated in many synthetic pathways. The following methods were already reported to generate the benzyne in different conditions by the researchers (Figure 2).

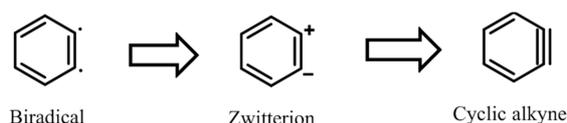


Figure 1. Different ways of the existence of benzyne/aryne molecules.

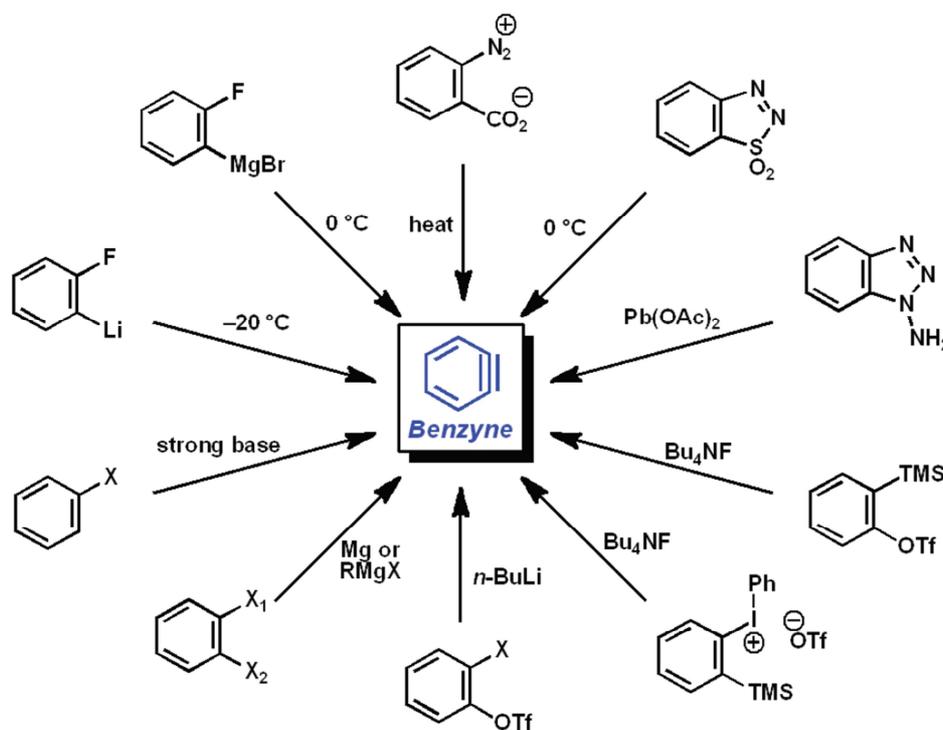


Figure 2. Different methods for the generation of Benzyne/Arynes.

[T. Kitamura, *et al.*, *J. Chem. Soc., Chem. Commun.* 1995, 983. C. D. Campbell, *et al.*, *J. Chem. Soc., C* 1969, 742. T. Matsumoto, *et al.*, *Tetrahedron Lett.* 1991, 32, 6735. L. Friedman, *et al.*, *J. Am. Chem. Soc.* 1963, 85, 1792. L. Friedman, *et al.*, *Org. Synth.* 1968, 48, 12. G. Wittig *et al.*, *Org. Synth.* 1967, 47, 4. R. W. Hoffmann, *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. T. Kitamura, *Aust. J. Chem.* 2010, 63, 987. A. M. Dyke, *et al.*, *Synthesis* 2006, 4093. H. Kobayashi, *et al.*, *Chem. Lett.* 1983, 1211.]

3. Reactions and Applications

The reactions involving the arynes or arynes precursors are

carried out numerous by the chemist throughout the world. 2-(trimethylsilyl)phenyl triflate is used as one of the most important aryne precursor to synthesize the heterocyclic compounds. The usage of arynes is also developed in the fields of multicomponent reactions. The two-component and three-component coupling reactions with arynes have been efficiently done catalytically specially by copper catalyst [17]. The synthesis of natural products has been developed by three component aryne coupling process [18]. Some symmetric and unsymmetric alkynes compounds were also synthesized with the help of aryne like benzyne catalytically under the microwave conditions where conventional heating takes long time for the reaction completion [19]. Along with the

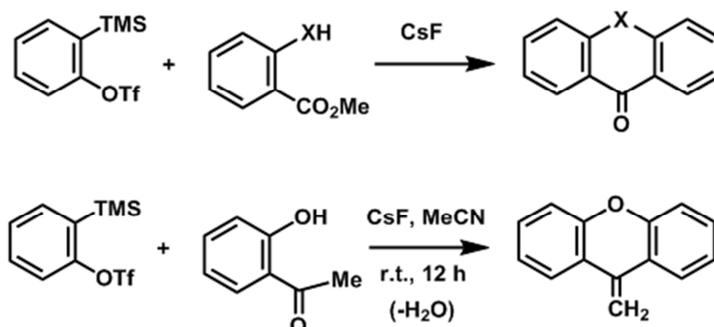
development of mild aryne generation conditions by Kobayashi and Hoye, aryne chemistry has commenced a renaissance in recent years [20, 21]. Certain limitations, however, remain to be solved in aryne chemistry. For instance, the existence of a formal triple bond of a standard aryne intermediate could only allow functionalization on the 1,2-positions of an arene ring. Whereas, three or more substituted arenes are widespread in natural products and medicines [3, 22, 23]. Breaking this two site bonding restriction of an aryne intermediate could provide synthetic

chemists a broader spectrum of means in terms of constructing multi-substituted arenes for the purpose of quick [24, 25].

Some of the recent advances in the reactions and the applications of arynes/benzyne for the development of different synthetic compounds especially the heterocycles are described below.

Reaction of benzyne with *ortho*-substituted benzoate esters [26] and with *ortho*-hydroxyacetophenone [27] for the synthesis of heterocyclic compounds (Scheme 1).

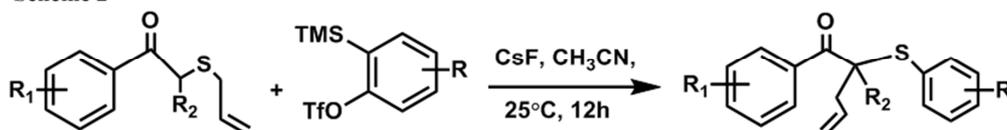
Scheme 1



A mild and transition-metal-free synthesis of β -keto arylthioethers has been developed by the aryne triggered [2, 3] Stevens rearrangement of allylthioethers [28]. At the time of completing this reaction, the sulfur ylide intermediate for the

rearrangement was formed by the S-arylation of allylthioethers with arynes generated from 2-(trimethylsilyl)aryl triflates using CsF (Scheme 2).

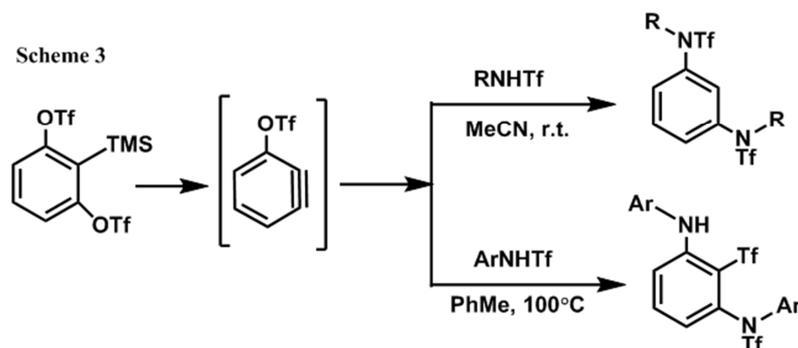
Scheme 2



The arynes and its intermediates can be utilized in the transition-metal catalyzed reactions also. In the synthetic pathway, the most commonly utilized diamination approaches involve transition-metal catalyzed amination of halobenzenes for example Buchwald–Hartwig reaction [29] or Ullman reactions reaction [30]. The restricted usage of transition metals in the late stage of drug synthesis prompts people to seek transition-metal-free as well as environmentally friendly manipulation conditions. To overcome the

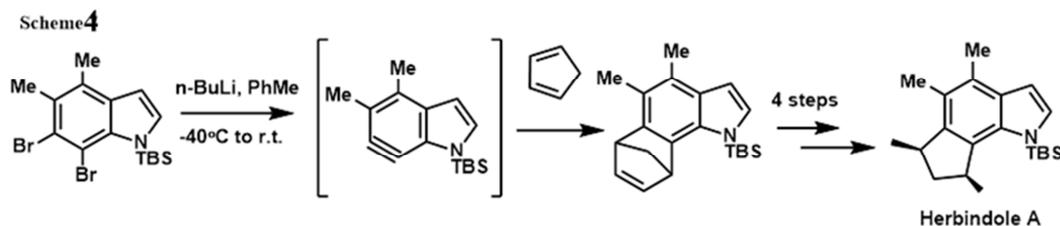
1,2-difunctionalization limitation by a standard aryne intermediate, the researchers recently developed a domino aryne precursor, which can feature a sequential formation of two aryne intermediates during the reaction [31]. Finally they developed the reaction of a domino aryne precursor with sulfonamides efficiently afforded both the 1,3-diaminobenzenes and trisubstituted 1,3-diaminobenzenes by simply varying the reaction conditions (Scheme 3) [32].

Scheme 3



The [4+2] cycloadditions of arynes have been commonly applied to natural product in total synthesis. The main limitation of such approach, however, is the need to use constrained dienes, such as furan and cyclopentadiene [33]. In

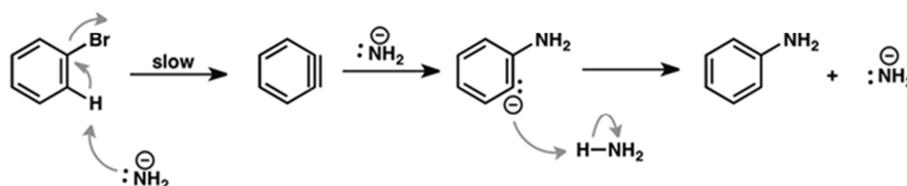
2009 Buszek and his co-workers synthesized Herbindole A (Scheme 4) using aryne [4+2]cycloaddition [34]. 6,7-indolyne also undergoes [4+2] cycloaddition with cyclopentadiene to afford the complex tetracyclic product.



In the case of nucleophilic addition of arynes or benzyne, upon treatment with basic nucleophiles, aryl halides deprotonate alpha to the leaving group, resulting in dehydrohalogenation. The resulting benzyne forms addition

products, usually by initial protonation [35]. It is mentioned that, the generation of the benzyne intermediate is the slow step in this reaction (Scheme 5).

Scheme 5

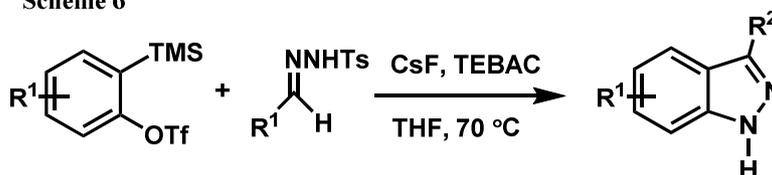


Recently, the new and effective routes for the synthesis of indazoles utilizing aryne [3 + 2] dipolar cycloaddition reactions have been developed. The chemists [36-38] reported the dipolar cycloaddition of arynes with diazo compounds to be an effective route to indazoles, and Moses disclosed the [3 + 2] dipolar cycloaddition of arynes with in situ generated nitrile imides [38].

Also the readily available, stable, and inexpensive N-tosylhydrazones react with arynes under mild reaction conditions to afford 3-substituted indazoles in moderate to

good yields [39]. The reaction appears to involve a dipolar cycloaddition of in situ generated diazo compounds and arynes. Here, the researchers have developed a method for the preparation of 3-arylindazoles (Scheme 6) starting material from arynes and readily available, bench stable, inexpensive N-tosylhydrazones. The reaction appears to involve in situ formation of a diazo compound and eliminates the problem of preparing and isolating such unstable and hazardous intermediates.

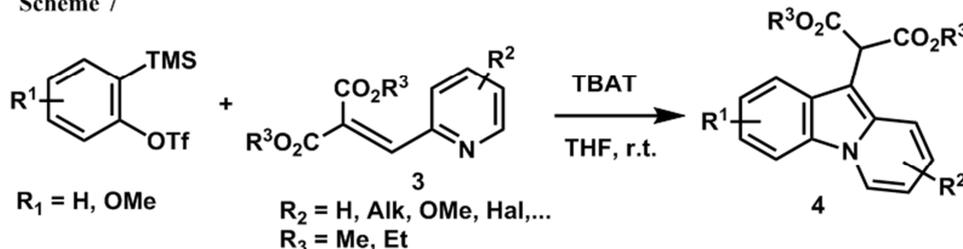
Scheme 6



Arynes or benzyne also show the [3 + 2] Annulation reactions to synthesize the following heterocyclic compounds with the help of TBAT. In an attempt to increase the electrophilicity of the Michael acceptor, diethyl 2-(pyridin-2-ylmethylene)malonate (3) was synthesized by

condensing diethyl malonate with 2-pyridinecarboxaldehyde. This substrate reacted cleanly with benzyne to form diethyl 2-(pyrido[1,2-a]indol-10-yl)malonate (4) in a good yield (Scheme 7). However, a significant portion of the starting material was remained in this procedure [40].

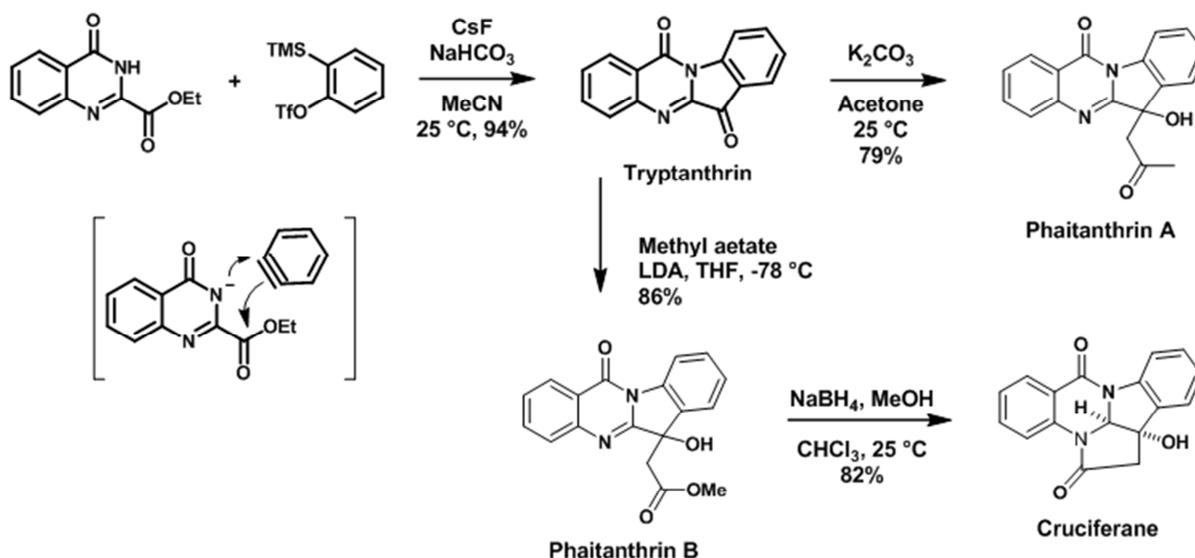
Scheme 7



Aryne precursors are also used to synthesize different kinds of natural products. More specifically, to synthesize the fused quinazolinones such as asperlicins, benzomalvins, circumdatins, phaitanthrins, and their synthetic congeners have been imperative targets due to their structural

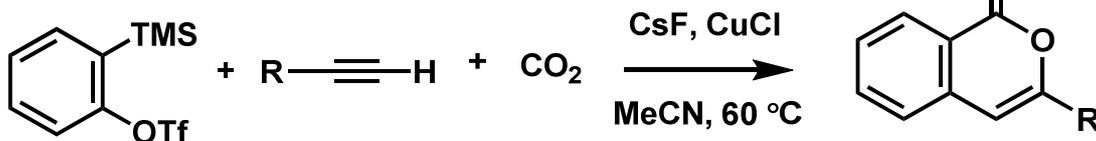
architectures and promising bioactivities (Scheme 8) [41, 42]. Several well-designed synthetic routes involving intramolecular cyclization strategies have been known for these significant targets [41, 43].

Scheme 8

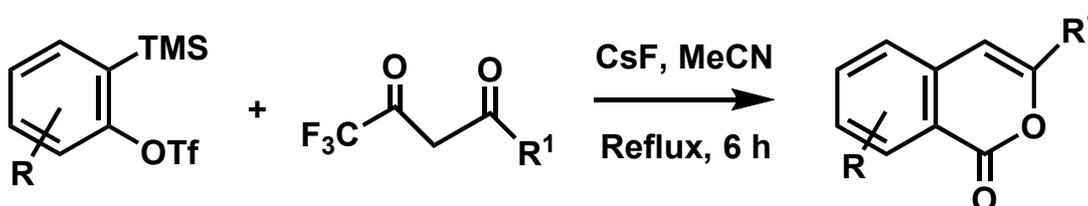


Benzyne or arynes are also used for the synthesis of heterocyclic compounds like isocoumarins [44] with the help of acetylenes and CO₂ (Scheme 9a) as well as with the help of trifluoroacetylated 1,3-diketones (Scheme 9b).

Scheme 9a

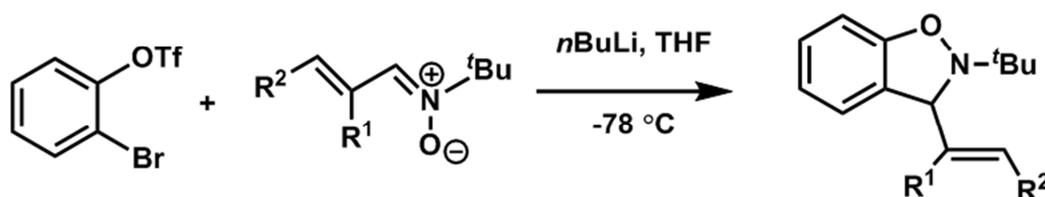


Scheme 9b



A novel α , β -unsaturated nitron-aryne [3+2] cycloaddition was reported recently [45]. To get this, a general method for the 1,3-dipolar cyclization between α , β -unsaturated nitrones and arynes has been developed (Scheme 10). In addition, a highly efficient N-O bond reduction-elimination-electrocyclization

Scheme 10

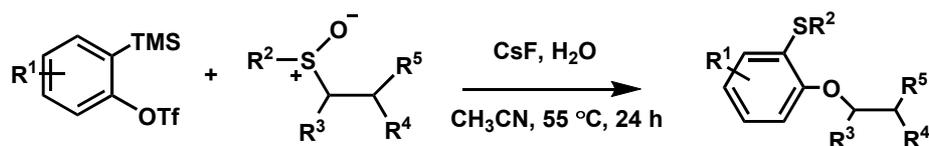


aryne insertion with sulfur oxygen vinyl migration and excellent stereospecificity: The reaction of in situ generated arynes with aryl vinyl sulfoxides provides ortho-arylsulfinylaryl vinyl ethers via aryne bonded insertion into the S-O-bond and concomitant stereospecific S-O-vinyl

sequence furnishes polysubstituted 2H or 2-alkylated-1-benzopyrans. The application of this methodology was further demonstrated in the synthesis of the oxa [3. 2. 1] octene moiety of cortistatin A.

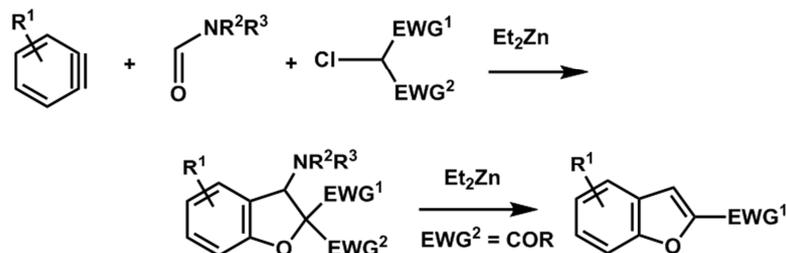
migration (Scheme 11) [46]. The cascade allows preparing di- or trisubstituted vinyl ethers with excellent stereospecificity. The chemistry presented here was valuable for the stereoselective preparation of highly substituted vinyl ethers.

Scheme 11



Synthesis of dihydrobenzofurans and benzofurans from Arynes: Synthesis of dihydrobenzofurans (Scheme 12) was achieved by a route involving the insertion of arynes into formamides followed by trapping with zinc enolates of

Scheme 12



α -chlorinated methines. Benzofurans were generated from dihydrobenzofurans having a ketone group via the addition of an ethyl anion, the retro-aldol type reaction, and the elimination of an amino group [47].

4. Conclusions

In this study, it was shortly reported that, the research and development of the arynes and their precursors are increasing very fast to the scientists. Many researchers are engaging to their study with these reagents as like as hot cake especially in the heterocyclic chemistry arena. There are many new and mild generation methods have increased the aryne-based methodologies. The arynes react as electrophiles and also in some pericyclic reactions because of their low-lying LUMO result. Their utility in total synthesis has also been proved to date. In spite of benzyne are innately unstable and highly reactive, organic synthesis exploits these qualities. From the different published works it was predicted that the TMS-aryl-triflates is one of the most preferred precursors for preparing arynes or benzyne *in situ*. The advancement of arynes, its intermediates and their precursors can be assumed from their rapid applications in the synthetic area of various heterocyclic compounds.

Conflict of Interest

The authors have no conflict of interest to publish this article.

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