

## Some Applications of Zirconium(IV) Tetrachloride ( $ZrCl_4$ ) and Zirconium(IV) Oxydichloride Octahydrate ( $ZrOCl_2 \cdot 8H_2O$ ) as Catalysts or Reagents in Organic Synthesis

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Both  $ZrCl_4$  and  $ZrOCl_2 \cdot 8H_2O$  are commercially available solid chemicals. Due to their low toxicities ( $LD_{50}$  [ $ZrCl_4$  oral rate] = 1688 mg/kg), ( $LD_{50}$  [ $ZrOCl_2 \cdot 8H_2O$  oral rate] = 2950 mg/kg), low costs, ease of handling, high activity, the zirconium(IV) compounds are potential green catalysts or reagents which are of importance from different views. In this review we have paid attention to the applications of these compounds as reagents or catalysts in Friedel-Crafts reactions, Fries rearrangements, reduction and oxidation reactions, cycloaddition and hydrometalation reactions, protection and deprotection of functional groups, reactions of epoxides, iodination of alcohols, *S*-alkylation of thiols with alcohols, Michael addition, condensation of indoles with carbonyl compounds, Claisen ester condensation, Baylis-Hillman reaction, preparation of organozirconium compounds and some other miscellaneous reactions.

**Keywords:**  $ZrCl_4$  and  $ZrOCl_2 \cdot 8H_2O$ , Friedel-Crafts reaction, Fries rearrangement, Reduction, oxidation, cycloaddition, and hydrometalation, Michael addition, Claisen condensation, Baylis-Hillman reaction

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### INTRODUCTION

The ability of transition metals to mediate organic reactions either catalytically or stoichiometrically constitutes one of the most powerful strategies to achieve both selectivity and efficiency in synthetic organic chemistry [1]. Reports on the use of commercially available solid chemicals [2];  $ZrCl_4$  and  $ZrOCl_2 \cdot 8H_2O$ , as reagents or catalysts are limited to the given reactions discussed in the following sections. Due to their low toxicity [ $LD_{50}$  ( $ZrCl_4$  oral rate) = 1688 mg/kg] [3], [ $LD_{50}$  ( $ZrOCl_2 \cdot 8H_2O$ ) oral rate = 2950 mg/kg] [3], low costs, ease of handling, high activity, the zirconium(IV) compounds can be considered as safe potential catalysts or reagents in organic synthesis. In this review important reactions mediated

by  $ZrCl_4$  and  $ZrOCl_2 \cdot 8H_2O$  are presented. While the present article was under print, an excellent review appeared: "Application of Zirconium(IV) Chloride in Organic Synthesis" [4a].

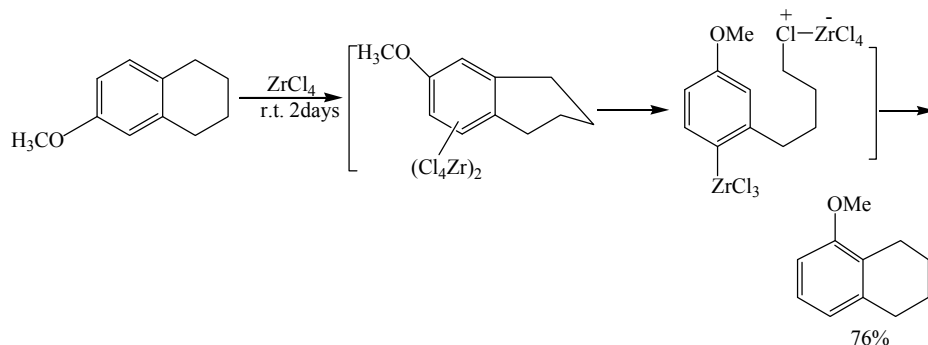
### FRIEDEL-CRAFTS REACTIONS AND FRIES REARRANGEMENTS

The catalytic activity of  $ZrCl_4$  in acylation [4] and alkylation reactions [5] has been studied over decades and has been compared with those obtained using traditional  $AlCl_3$  catalyst.

One interesting reaction related to Friedel-Crafts alkylation is the cyclohexane rearrangement mediated by  $ZrCl_4$  as shown in Scheme 1. In this reaction the rearrangement occurs at ambient temperature in chloroform and proceeds *via*

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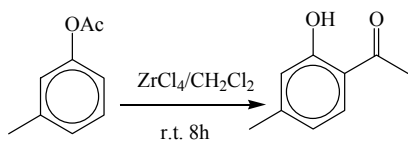
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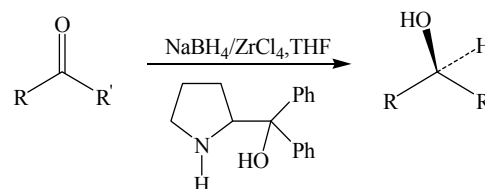
Scheme 1

fragmentation of the carbon-carbon bond para to the methoxy substituent followed by an intramolecular Friedel-Crafts alkylation [6].

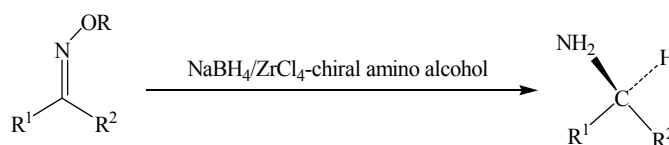
Fries rearrangement is a useful reaction for the synthesis of aryl ketones.  $ZrCl_4$  has been reported to be an effective catalyst for this purpose. A typical example is presented by Scheme 2 in which the rearrangement has occurred at ambient temperature with high selectivity giving the acetophenone derivative by acetyl group migration to the sterically least encumbered adjacent carbon [7].



Scheme 2



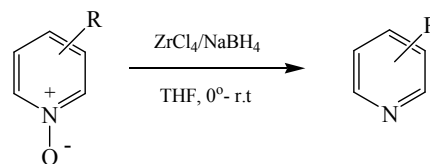
Scheme 3



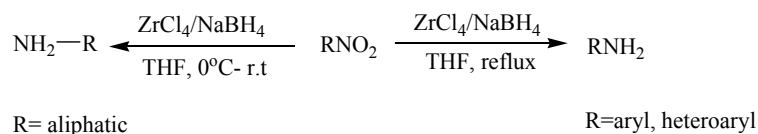
Scheme 4

## REDUCTION AND OXIDATION REACTIONS

A combination of sodium borohydride and  $ZrCl_4$  has been frequently used in the stereoselective reduction of various functional groups including carbonyls [8,9], oxime ethers [10], in the presence of chiral amino alcohols and olefins, imines, nitriles [9], N-oxides [11] and nitro [12] groups (Schemes 3-6).



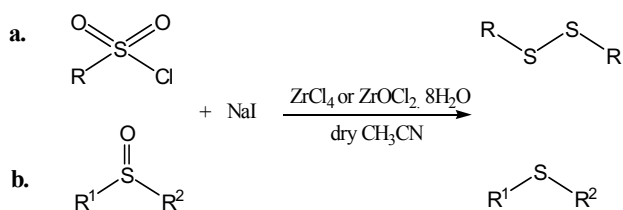
Scheme 6



Scheme 5

## Applications of ZrCl<sub>4</sub> and ZrOCl<sub>2</sub>·8H<sub>2</sub>O as Catalysts or Reagents

The use of zirconium tetrachloride/sodium iodide (ZrCl<sub>4</sub>/NaI) and ZrOCl<sub>2</sub>·8H<sub>2</sub>O/NaI for effective reductive coupling of sulfonyl chlorides to their corresponding disulfides and chemoselective reduction of sulfoxides to their thioethers in high yields have been also reported (Scheme 7) [13].



Scheme 7

Oxidation of sulfides is the most straightforward method for the synthesis of sulfoxides and sulfones [14], some examples of which are important as commodity chemicals and, in some cases, as pharmaceuticals [15]. This transformation has been accomplished in a variety of ways [16-28]. During recent years, very useful procedures involving aqueous hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) as the terminal oxidant, and a Lewis acid as an activator have been developed to promote this transformation [29]. Very recently, H<sub>2</sub>O<sub>2</sub>/ZrCl<sub>4</sub> system has been applied as a selective method to oxidize sulfides efficiently to their sulfoxides or sulfones even in the

presence of easily oxidized functional groups (Scheme 8) [30]. Reagents and conditions: (i) H<sub>2</sub>O<sub>2</sub> (14 equiv), ZrCl<sub>4</sub> (4 equiv), CH<sub>3</sub>OH, rt; (ii) H<sub>2</sub>O<sub>2</sub> (20 equiv), ZrCl<sub>4</sub> (5 equiv), CH<sub>3</sub>OH, rt.

## CYCLOADDITION REACTIONS

### Diels-Alder Reactions

The first successful asymmetric Diels-Alder reaction has been reported between cyclopentadiene and a chiral  $\alpha,\beta$ -unsaturated amide using different Lewis acids. The highest endo/exo selectivity has been observed in the presence of ZrCl<sub>4</sub> catalyst (Scheme 9) [31].

### [2+2] Cycloaddition Reactions

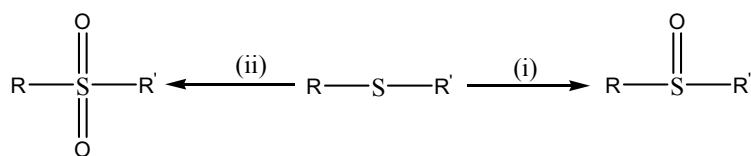
The [2+2] cycloaddition reaction of 1-(trimethylsilyloxy) cyclopentene and acetylene carboxylate in the presence of ZrCl<sub>4</sub>, was accompanied with desilylation to afford bicyclo [3.2.0] heptene carboxylate (Scheme 10) [32].

Allyltritylsilane reacted with aldehydes in different ways, depending on the nature of the Lewis acids employed. In Scheme 11 the catalytic effect upon the mode of reaction is presented between BF<sub>3</sub>·Et<sub>2</sub>O and ZrCl<sub>4</sub> [33].

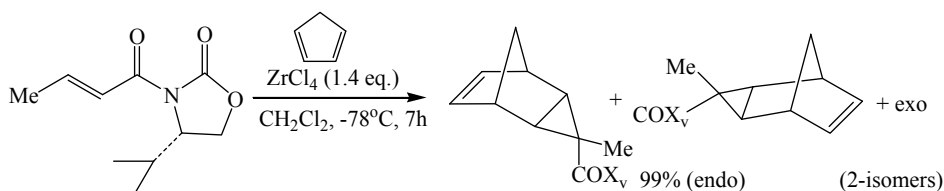
## HYDROMETALATION REACTIONS

Zirconium complexes are  $\pi$ -base accepting Lewis acids therefore, variety of reactions based on interaction of C-C  $\pi$ -bonds with zirconium have been investigated.

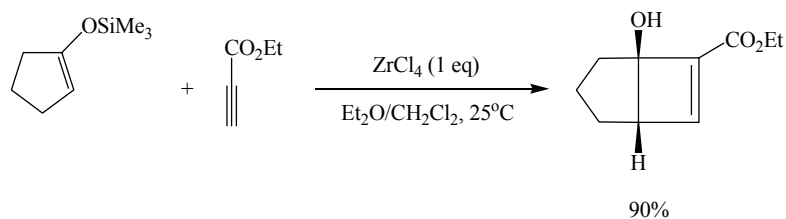
(a) Hydroalumination of olefins (Scheme 12) [34].



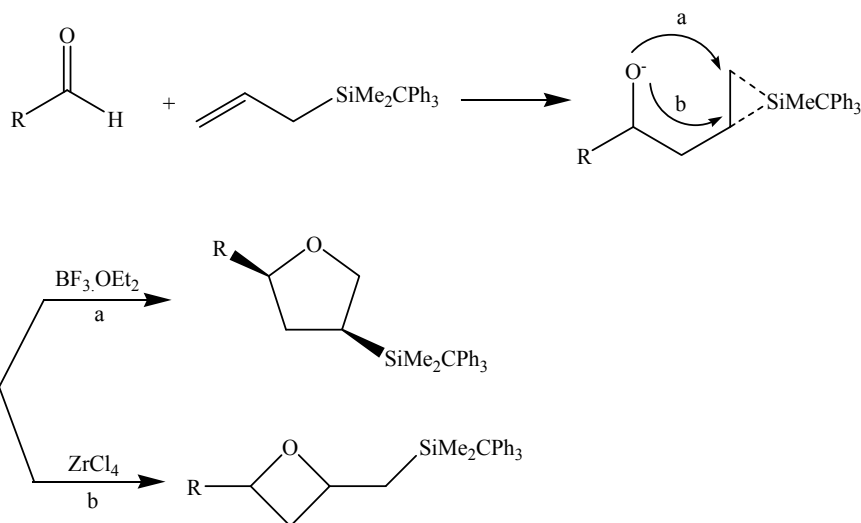
Scheme 8



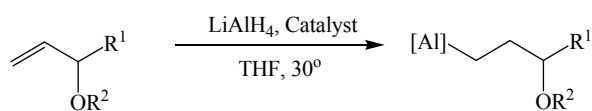
Scheme 9



Scheme 10



Scheme 11



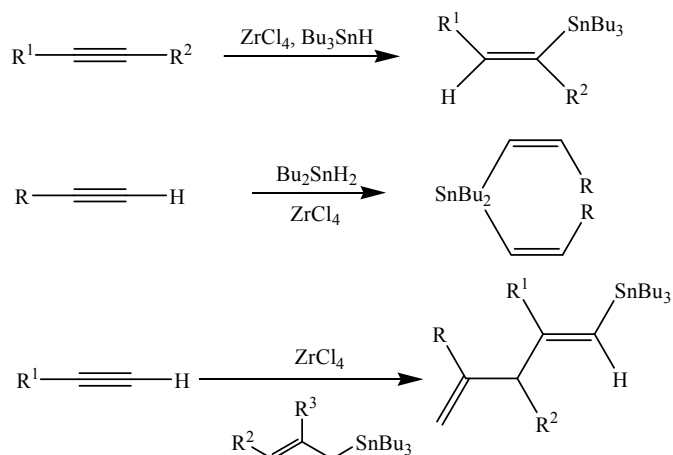
Catalysts:  $\text{ZrCl}_4$  (when  $\text{R}^2 = \text{H}$ )  
 $\text{CP}_2\text{ZrCl}_2$  (when  $\text{R}^2 = \text{alkyl}$  or phenyl)

Scheme 12

(b) Hydrostannation of alkynes (Scheme 13) [35].

## PROTECTION AND DEPROTECTION REACTIONS

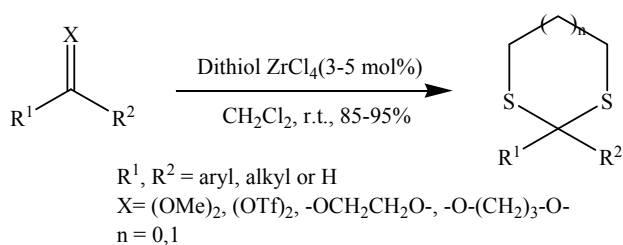
Carbonyl group is one of the most abundant functional group in organic molecules. Selective protection and deprotection of this functionality plays an important role in the multi-step synthesis of complex organic molecules such as natural products [36].



Scheme 13

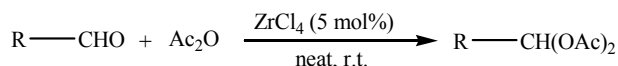
It has been found that  $\text{ZrCl}_4$  is an effective catalyst for highly chemoselective transthioacetalization of acetals with dithiols under mild reaction conditions (Scheme 14) [37].

## Applications of ZrCl<sub>4</sub> and ZrOCl<sub>2</sub>.8H<sub>2</sub>O as Catalysts or Reagents



Scheme 14

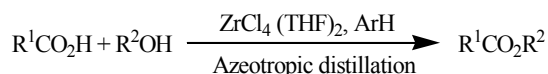
Also this catalyst has been used for chemoselective protection of aldehydes to geminal-diacetates (Scheme 15) and dipivalates [38]. The chemoselective deprotection of diacetates has been also achieved with ZrCl<sub>4</sub> under solvent free conditions at room temperature.



R = aryl, alkyl

Scheme 15

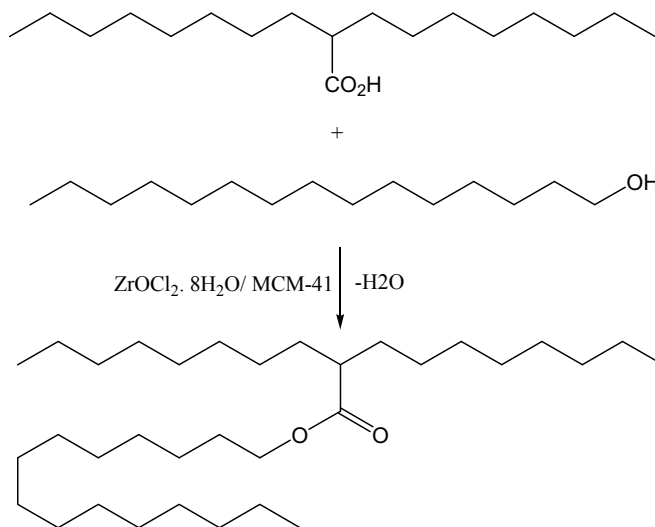
The THF complex of zirconium tetrachloride [ZrCl<sub>4</sub>(THF)<sub>2</sub>] is a highly effective catalyst for the selective esterification of primary alcohols with carboxylic acids in the presence of secondary or aromatic alcohols (Scheme 16) [39].



Scheme 16

ZrOCl<sub>2</sub>.8H<sub>2</sub>O supported on ordered mesoporous silica has been used as a catalyst for the esterification of long chain carboxylic acids with long chain primary and secondary alcohols successfully (Scheme 17) [40].

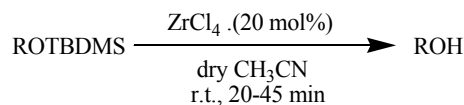
ZrCl<sub>4</sub> in the presence of Ac<sub>2</sub>O [41], and also ZrOCl<sub>2</sub>.8H<sub>2</sub>O in combination with acyl chloride [42], were used as highly



Scheme 17

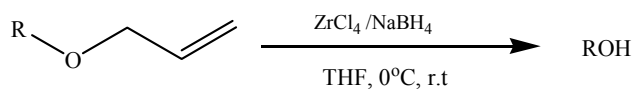
efficient and reusable catalysts for acetylation of structurally diverse phenols, thiols, amines, and alcohols under solvent-free conditions.

ZrCl<sub>4</sub> in CH<sub>3</sub>CN provided a mild and efficient catalytic system (20 mol%) for the highly selective deprotection of TBDMS ethers. The study demonstrated that both acid and base sensitive groups and also allylic and benzylic groups were unaffected (Scheme 18) [43].



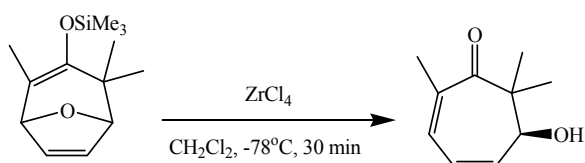
Scheme 18

ZrCl<sub>4</sub>/NaBH<sub>4</sub> reagent system in THF generated alcohols from their allyl ethers (Scheme 19). The reagent system can be considered as a general deallylating agent useful for aliphatic as well as aromatic allylic ethers. The important advantage of this reagent lies in its tolerance towards some of the reducible functionalities such as nitro, alkoxy, halo, benzyloxy, Boc, and Cbz [44].



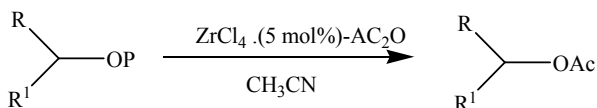
Scheme 19

In addition,  $\text{ZrCl}_4$  has been used for the cleavage of bis allylicly activated ether bridge (Scheme 20) [45].



Scheme 20

It was found that  $\text{ZrCl}_4$  (5 mol%) and acetic anhydride reagent system has been used for selective conversion of ethers to the corresponding acetates under mild reaction conditions (Scheme 21) [46].



P = TBS or THP  
 $\text{R}, \text{R}^1 = \text{Aryl}, \text{Alkyl}, \text{H}$

Scheme 21

## THE REACTION OF EPOXIDES MEDIATED BY $\text{ZrCl}_4$

It is well-known that epoxides are versatile intermediates in organic chemistry [47]. The deoxygenation of epoxides to olefins allows the use of the oxirane ring as a protective group for double bonds [48]. Thus, it is an important protocol to control olefin stereochemistry [49], for conversion of biomass-derived substrates to useful organic compounds [50], and also for structural analysis of natural products [51]. Relatively few

general methods exist for removing oxygen atoms from epoxides [52-65].

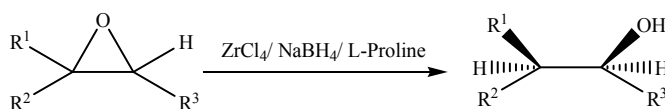
$\text{ZrCl}_4/\text{NaI}$  has been introduced as an expedient reagent for immediate and stereospecific deoxygenation of epoxides to olefins in excellent yields [66].

The results given in Table 1 illustrate the high efficiency of this protocol for the deoxygenation of structurally different epoxides in short reaction times.

$\beta$ -Amino alcohols are versatile intermediates in the synthesis of a vast range of biologically active natural and synthetic products [67], unnatural amino acids [68], and chiral auxiliaries for asymmetric synthesis [69]. The nucleophilic opening of epoxides with amines constitutes a well recognized route for the synthesis of amino alcohols [70]. The classical approach [71], involving heating epoxides with amines, works less well with poorly nucleophilic amines.

$\text{ZrCl}_4$  catalyzes the nucleophilic opening of epoxide rings by amines leading to the efficient synthesis of  $\beta$ -amino alcohols. The reaction works well with aromatic and aliphatic amines in short times at room temperature in the absence of solvent. Exclusive *trans* stereoselectivity is observed for cyclic epoxides. Aromatic amines exhibit excellent regioselectivity for preferential nucleophilic attack at the sterically less hindered position during the reaction with unsymmetrical epoxides. However, in the case of styrene oxide, selective formation of the benzylic amine has been observed during the reactions with aromatic amines [72].

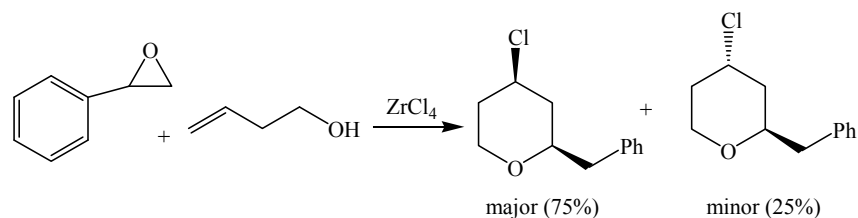
Also  $\text{ZrCl}_4$  in the presence of sodium borohydride and L-proline as a chiral auxiliary has been used for regioselective reduction of racemic epoxides to optically active alcohols [73].



Scheme 23

The formation of tetrahydropyran derivatives by mediation of  $\text{ZrCl}_4$  via cross-cyclization between aryl substituted epoxides and homoallylic alcohols has been reported (Scheme 24) [74].

Applications of  $\text{ZrCl}_4$  and  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  as Catalysts or Reagents



*Scheme 24*

**Table 1.** Deoxygenation of Epoxides Using  $\text{ZrCl}_4/\text{NaI}$  in Anhydrous  $\text{CH}_3\text{CN}$

Entry	Epoxide	Product	GC Yield (%)	Isolated yield (%)	Time (min)
1			100	93	immediately
2			96	90	immediately
3			97	87	immediately
4			100	92	immediately
5			95	87	immediately
6			100	88	immediately
7			100	87	immediately
8			100	90	immediately
9			100	90	immediately
10			95	88	immediately

Table 1. Continued

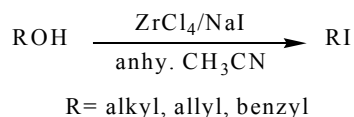
11			98	90	immediately
12			90	82	15
13			100	94	3

## FUNCTIONAL GROUP TRANSFORMATIONS

### Iodination of Alcohols

Among the halides, iodides are the most reactive and in some cases, they show unique reactivity [75]. Iodination of alcohols is the most general protocol for the preparation of alkyl iodides and therefore, this conversion is a frequently encountered transformation in organic synthesis. This transformation is very important in natural product synthesis, where such conversions are usually carried out by a two-step process consisting of transformation of the alcohol to mesylate followed by displacing the mesyloxy with iodide [76].

ZrCl<sub>4</sub>/NaI can be used as an efficient and selective system for one-pot conversion of structurally diverse alcohols to their iodides with high efficiency and selectivity and with a simple work-up procedure (Scheme 25, Table 2) [77].



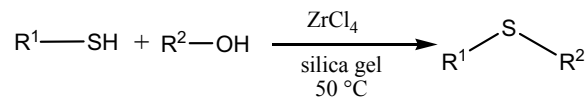
Scheme 25

### S-Alkylation of Thiols with Alcohols

Versatile synthetic uses of thioethers in both bioorganic

and organic chemistry have ensured many studies of their preparation by different methods. The thioether linkage has been used to prepare cyclic analogues of acyclic polypeptides to restrict their conformational mobility and thus to increase their biological activity and stability against biodegradation [78-81]. They are also useful heteroatom functional groups in organic synthesis. For example, by oxidation of thioethers, chiral sulfoxides can be generated which can be used as auxiliaries in asymmetric synthesis [82-85]. Moreover, sulfones have been employed for stabilizing  $\alpha$ -radicals [86],  $\alpha$ -anions [87], can act as cationic synthons [88], and also for the formation of C-C bonds [89].

Recently, it has been explored that ZrCl<sub>4</sub> dispersed on dry silica gel conducted the efficient preparation of thioethers by the reaction of thiols with alcohols under solvent-free conditions which is a useful addition to current methodologies. (Scheme 26) [90].



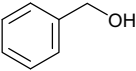
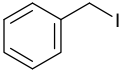
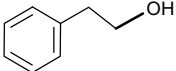
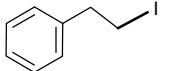
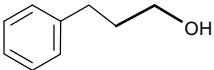
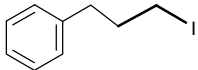
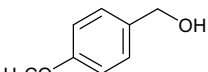
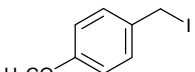
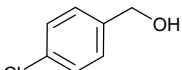
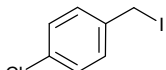
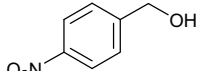
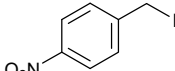
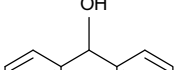
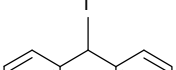
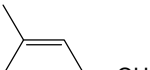
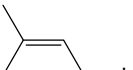
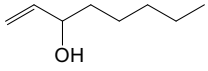
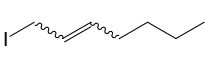
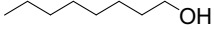





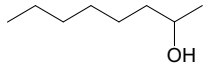
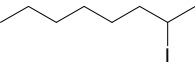
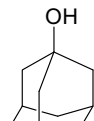
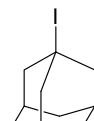
Scheme 26

This method is general and applicable for the preparation of thioethers from cinnamyl alcohol, adamantanol and structurally and electronically diverse benzyl alcohols with



Applications of  $ZrCl_4$  and  $ZrOCl_2 \cdot 8H_2O$  as Catalysts or Reagents

**Table 2.** Iodination of Alcohols Using  $ZrCl_4/NaI$  in Anhydrous  $CH_3CN$

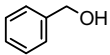
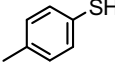
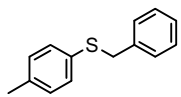

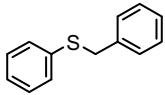
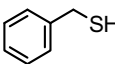
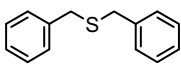
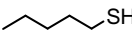
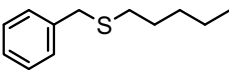

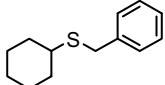
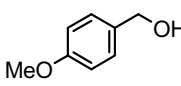
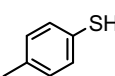
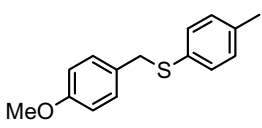
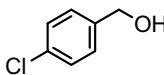
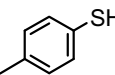
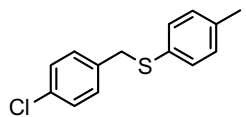
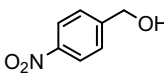
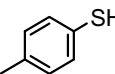
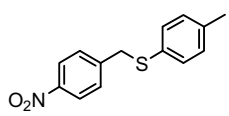
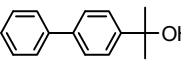
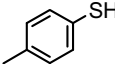
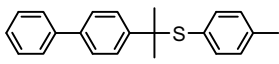
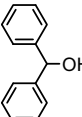
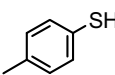
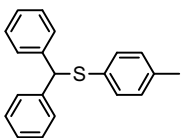
Entry	Alcohol	Time (min)	Product	Yield (%)
1		10		95
2		75		90
3		50		92
4		2		96
5		45		90
6		60		75
7		50		94
8		4		93
9		5		95
10		70		97
11		20		97
12		40		80
13		120		85
14		50		90

aromatic or aliphatic thiols. In addition, this method provides a high yielding preparation of dithioethers using dithiols (Table 3, Entries 23-25) which are valuable precursors for the preparation of macrocyclic or polymeric sulfur-containing

compounds.

Primary and secondary aliphatic alcohols do not react with thiols in the presence of this system and remain mostly intact after the appropriate reaction times (Table 3, Entries 15, 16).

**Table 3.** *S*-Alkylation of Thiols with Alcohols Using  $ZrCl_4$  Dispersed on Dry Silica Gel under Solvent-Free Conditions

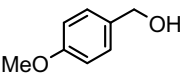
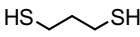
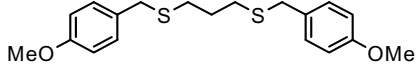
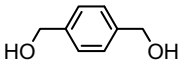
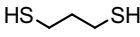
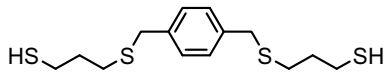
Entry	Alcohol	Thiol	Product	Time (min)	Isolated yield (%)
1				5	94
2	"			15	90
3	"			40	53
4	"			25	75
5	"			20	87
6				2	94
7				25	94
8				60	50
9				4	95
10				3	95

Applications of  $ZrCl_4$  and  $ZrOCl_2 \cdot 8H_2O$  as Catalysts or Reagents

Table 3. Continued

11				5	95
12	"			15	92
13	"			10	88
14	"			8	90
15				180	-
16				180	-
17				10	80
18				7	94
19	"			10	96
20	"			30	95
21	"			15	94
22	"			15	95
23	"			20	95

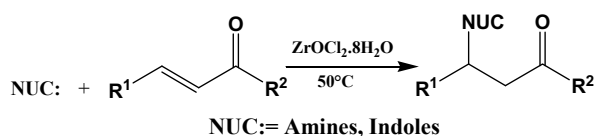
Table 3. Continued

24				10	96
25				20	94

## MICHAEL ADDITION REACTIONS

In recent years, considerable attention has been focused on the development of efficient and operationally simple protocols for carbon-carbon and carbon-hetero atom bond formation for the construction of valuable molecules. Michael reaction is one of the most important reactions in organic chemistry which is employed for C-C and C-X bond formation. For example, carbon-carbon bond formation through the addition of electrophiles to the C-3 position of the indoles leading to the bioactive indole alkaloids [91]. In addition, nitrogen-containing compounds are of significant importance in human life and also they are useful as biologically active substances, dyes, and fine chemicals [92]. For instance, the  $\beta$ -amino carbonyl group is a common moiety in a large variety of biologically active compounds such as alkaloids and polyketides [93,94b-94d]. They are also attractive precursors in preparation of  $\gamma$ -amino alcohols,  $\beta$ -lactams,  $\beta$ -amino acid derivatives and chiral auxiliaries [95-100], many of which serve as powerful antibiotics or other drugs [101,102]. There are some methods available for Michael addition of indoles and amines to  $\alpha,\beta$ -unsaturated carbonyl compounds catalyzed by Lewis acids [103].

It has been recently reported that  $ZrOCl_2 \cdot 8H_2O$  as a highly efficient and the moisture tolerant Lewis acid catalyzes Michael addition of amines and indoles to  $\alpha,\beta$ -unsaturated ketones under solvent-free conditions (Scheme 27) [104]. The reusability of the catalyst has been successfully examined without noticeable loss of its catalytic activity. The use of a safe catalyst and its insensitivity towards moisture combined with an easy work-up procedure are the strong points of the presented methodology for C-N and C-C bond formation *via* Michael addition reactions (Table 4).



Scheme 27

## CONDENSATION REACTIONS

### Condensation of Indoles with Carbonyl Compounds

Indole derivatives have attracted a plethora of research areas due to the vast applications in material sciences [105], agrochemicals [106], and pharmaceuticals [107]. Particularly, the substrates including bis(indolyl) motifs such as secondary metabolites [108], and marine sponge alkaloids [109], are of remarkable significance. Indoles can readily undergo electrophilic substitution reactions with the oxygen atom of carbonyl compounds in the presence of a suitable catalyst to form bis- and tris(1H-indol-3-yl) methanes. Different catalysts are known to catalyze this reaction [110-121].

$ZrOCl_2 \cdot 8H_2O$ /silica gel as a highly water-tolerant catalyst system has been applied for the preparation of bis(indolyl)methanes *via* electrophilic substitution reactions of indoles with carbonyl compounds under solvent-free conditions (Scheme 28) [122]. The yields of the isolated products are from good to excellent (Table 5).

### Claisen Ester Condensation

The Claisen ester condensation is recognized as a fundamental and useful C-C bond-forming reaction [123]. Traditional Claisen condensations using alkali-metal basic reagents such as NaOR, NaH, LDA and LiHMDS are widely applied to  $\alpha$ -monoalkylated esters giving the corresponding

Applications of  $ZrCl_4$  and  $ZrOCl_2 \cdot 8H_2O$  as Catalysts or Reagents

**Table 4.** Michael Addition of Amines and Indoles to  $\alpha,\beta$ -Unsaturated Ketones Catalyzed by  $ZrOCl_2 \cdot 8H_2O$  under Solvent-Free Conditions

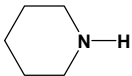
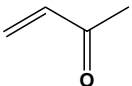
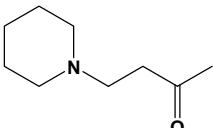
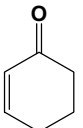
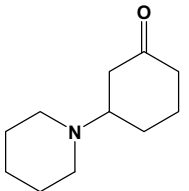
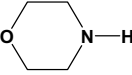
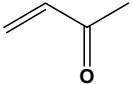
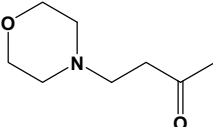
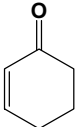
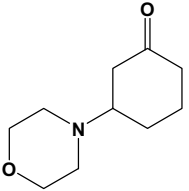
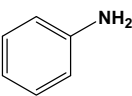
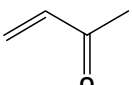
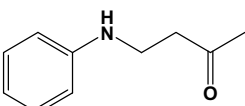
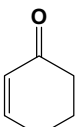
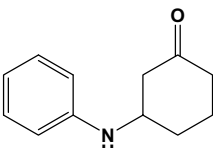
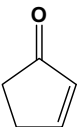
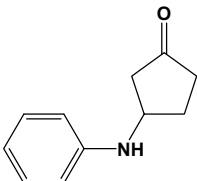
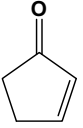
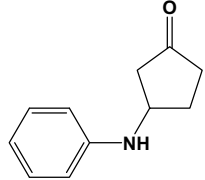
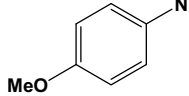
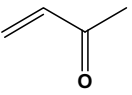
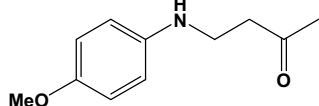
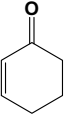
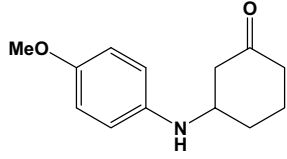
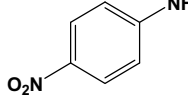
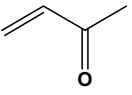
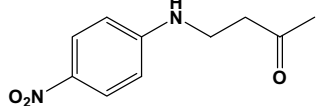
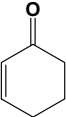
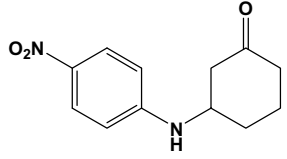
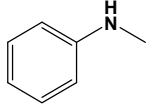
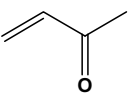
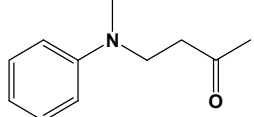
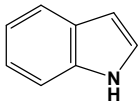
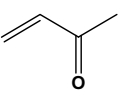
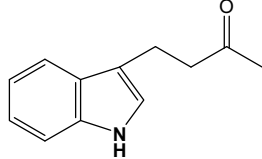
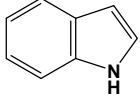
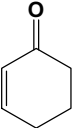
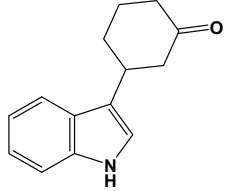
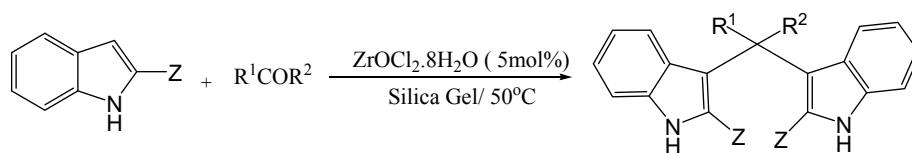
Entry	Substrate	$\alpha,\beta$ -Enone	Product	Time (min)	Isolated yield (%)
1				5	95
2	"			8	94
3				8	95
4	"			12	94
5				8	94
6	"			15	84
7	"			15	85

Table 4. Continued

7	"			15	85
8				2	95
9	"			8	94
10				12	95
11	"			20	94
12				20	75
13				120	77
14				120	65 + 20 of unidentified product

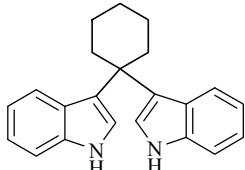
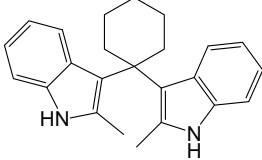
**Table 4.** Continued

15		30	95
16		50	94

*Scheme 28***Table 5.** Condensation of Indoles with Carbonyl Compounds Catalyzed by  $ZrOCl_2 \cdot 8H_2O$ /Silica Gel System under Solvent-Free Conditions

Entry	Indole	Carbonyl Compounds	Product	Time (min)	Isolated yield (%)
1	Z = H	R <sup>1</sup> = C <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	Z = H R <sup>1</sup> = C <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	40	84
2	Z = H	R <sup>1</sup> = <i>P</i> -MeC <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	Z = H R <sup>1</sup> = <i>P</i> -MeC <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	75	75
3	Z = H	R <sup>1</sup> = <i>P</i> -OHC <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	Z = H R <sup>1</sup> = <i>P</i> -OHC <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	120	76
4	Z = H	R <sup>1</sup> = <i>P</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	Z = H R <sup>1</sup> = <i>P</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	30	94
5	Z = Me	R <sup>1</sup> = C <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	Z = Me R <sup>1</sup> = C <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	20	85

Table 5. Continued

6	Z = Me	R <sup>1</sup> = <i>P</i> -OHC <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	Z = Me R <sup>1</sup> = <i>P</i> -OHC <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	120	75
7	Z = Me	R <sup>1</sup> = <i>P</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	Z = Me R <sup>1</sup> = <i>P</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>5</sub> R <sup>2</sup> = H	15	90
8	Z = H	R <sup>1</sup> = <i>n</i> -Buthyl R <sup>2</sup> = H	Z = H R <sup>1</sup> = <i>n</i> -Buthyl R <sup>2</sup> = H	60	90
9	Z = Me	R <sup>1</sup> = <i>n</i> -Buthyl R <sup>2</sup> = H	Z = Me R <sup>1</sup> = <i>n</i> -Buthyl R <sup>2</sup> = H	40	93
10	Z = H	Cyclohexanone		180	80
11	Z = Me	Cyclohexanone		150	85
12	Z = Me	Acetophenone	No reaction	180	-

dimeric  $\beta$ -ketoesters [123,124]. Powerful mediated Claisen ester condensations of  $\alpha,\alpha$ -dialkylated esters by ZrCl<sub>4</sub>-*i*Pr<sub>2</sub>NEt were performed to give the corresponding thermodynamically unfavorable  $\alpha,\alpha$ -dialkylated  $\beta$ -ketoesters, and Claisen-aldol tandem reactions between an intermediary Zr-enolate of a  $\alpha,\alpha$ -dialkylated  $\beta$ -ketoester and aldehydes also proceeded (Scheme 29) [125].

### BAYLIS-HILLMAN REACTION

Recently, the Baylis-Hillman reaction has become a very hot field for synthetic chemists. The combination of a Lewis base such as Me<sub>2</sub>S, Et<sub>3</sub>N or phosphine compounds with the Lewis acid such as TiCl<sub>4</sub>, ZrCl<sub>4</sub> can significantly speed up this reaction and give the corresponding chlorinated products. This reaction was initiated by chloride ion attacking at the  $\alpha,\beta$ -

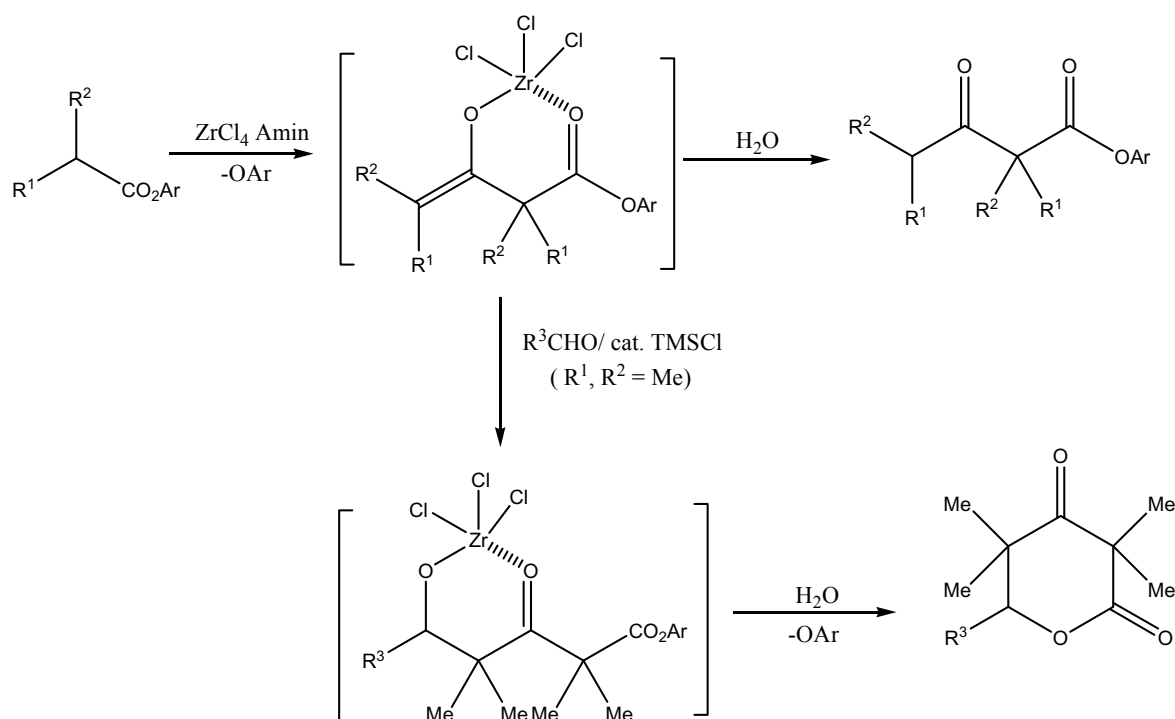
unsaturated ketone Michael acceptor. The chloride ion was produced by coordination of Lewis bases (SMe<sub>2</sub>, NEt<sub>3</sub>, PBu<sub>3</sub>) to Lewis acids such as TiCl<sub>4</sub>, ZrCl<sub>4</sub>. In this reaction system, it is very difficult to achieve high enantioselectivity just by using catalytic amounts of chiral Lewis bases (Scheme 30) [126].

### ORGANOZIRCONIUM COMPOUNDS AND THEIR USES IN ORGANIC REACTIONS

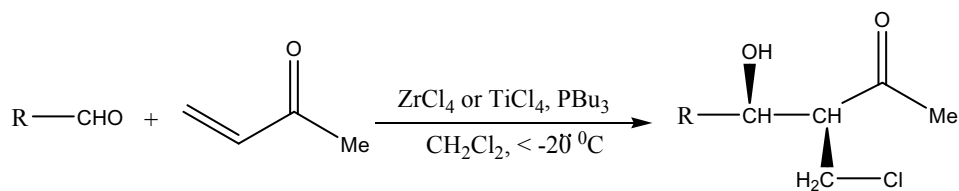
Roughly, 75-80% or possibly even more of the currently known organozirconium compounds are zirconocene and related derivatives. In reality, the great majority of synthetically useful organozirconium reactions known today involve Cp<sub>2</sub>Zr derivatives. Synthesis of Cp<sub>2</sub>Zr derivatives typically begins with the reaction of ZrCl<sub>4</sub> with CpLi, CpNa, or CpMgBr (or Cl) to produce Cp<sub>2</sub>ZrCl<sub>2</sub> [127].



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Scheme 29



a:  $R = p\text{-NO}_2\text{Ph}$ , b:  $R = m\text{-NO}_2\text{Ph}$ , c:  $R = p\text{-CF}_3\text{Ph}$ ,  
 d:  $R = p\text{-EtPh}$ , e:  $R = \text{Ph}$ , f:  $R = p\text{-ClPh}$ , g:  $R = \text{CH}_3(\text{CH}_2)_3$

Scheme 30

These organozirconium compounds have been used in a wide variety of organic reactions, for example, formation of carbon-heteroatom bonds, carbon-carbon bonds, carbonylation and other migratory insertion reactions, stoichiometric and catalytic carbometalation reactions *etc* [128].

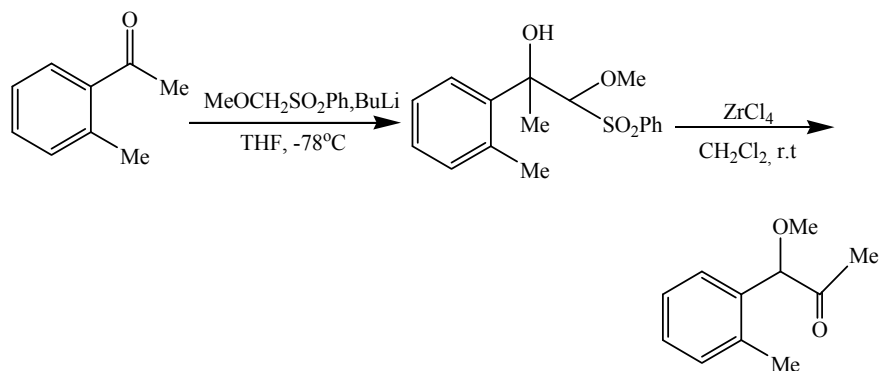
### MISCELLANEOUS REACTIONS

$ZrCl_4$  facilitates a high yielding homologation of ketones into  $\alpha$ -methoxy ketones [129], *via* intermediate sulfone

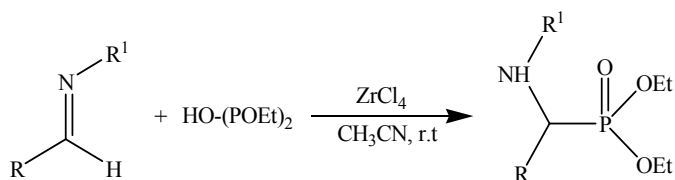
adducts (Scheme 31). This procedure allows the sulfone mediated homologation methodology to be applied to monocyclic and acyclic ketones.

$ZrCl_4$  has been also applied as an efficient catalyst for the synthesis of  $\alpha$ -aminophosphates (Scheme 32) [130]. The method is effective for aromatic, aliphatic, or  $\alpha,\beta$ -unsaturated aldehydes with excellent yields.

The imidazole ring is of therapeutic interest as it is widely recognized to be an important pharmacophore [131]. Its activity is often connected to its hydrogen bond donor-



Scheme 31



Scheme 32

acceptor capability [132] or with high affinity for the metals that are present in many protein-active sites [133]. These characteristics make imidazole derivatives attractive targets in organic synthesis. Imidazolin-2-ones represent an important part of the imidazole family that possess functional motifs found in biologically active molecules.

The  $ZrCl_4$ -mediated treatment of substituted aminocarbonyldiazene-carboxylates with 1,3-diketones or  $\beta$ -ketoesters leading to highly functionalized imidazolin-2-ones [134].

Halogen migration on aromatic substrates in the presence of a strong base, also known as the ‘halogen dance’ was discovered in the 1950s [135]; since then it has been thoroughly investigated [136-140]. In contrast, acid-promoted halogen migration occurs rarely on aromatic molecules [141], and is limited to iodine [142,143] and bromine [144-148] atoms. Recently, an electrophilic amination of aromatic substrates with various alkyl arylaminocarbonyldiazene-carboxylates in the presence of  $ZrCl_4$  [149]. It is reported that the  $ZrCl_4$ -promoted electrophilic amination of halogenated phenols was accompanied by the migration of a halogen atom. Thus, diisopropyl diazenedicarboxylate **2** and 2,4-dichloro-

phenol (**1**, X = Y = Cl) were reacted in the presence of  $ZrCl_4$  to produce a mixture of regioisomers **3a** and **4a** (Scheme 33). They also noticed that 2,4-dichlorophenol did not react with **2** if  $ZrF_4$  or  $ZrBr_4$  were used instead of  $ZrCl_4$  [150].

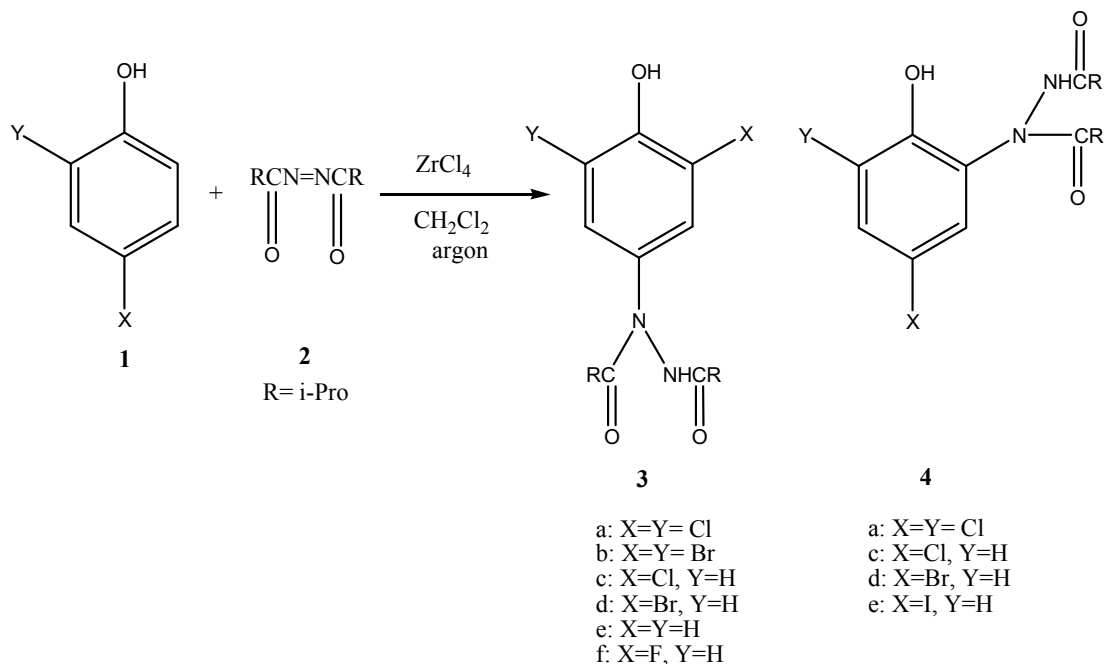
The reactions of aryl nitriles with  $\beta$ -aminoalcohols to prepare 2-aryloxazolines has been efficiently carried out in the presence of catalytic amounts of  $ZrOCl_2 \cdot 8H_2O$  using heat or microwave irradiation. Synthesis of mono- and bis-oxazolines from dicyanobenzenes was accomplished with high selectivity using this catalyst. Chemoselective conversion of aryl nitriles to their corresponding 2-oxazolines in the presence of alkyl nitriles was also achieved by this method [151].  $ZrOCl_2 \cdot 8H_2O$  has been also reported for efficiently catalyzed direct Mannich-type reaction of a variety of in situ generated aldimines using aldehydes and anilines with ketones in a three-component reaction under solvent-free conditions. The reaction proceeded rapidly and affords the corresponding  $\beta$ -amino ketones in good to high yields with good to excellent stereoselectivities [152].

Recently, preparation of 2-imidazolines and bis-imidazolines by reaction of ethylenediamine with nitriles in the presence of catalytic amounts of  $ZrOCl_2 \cdot 8H_2O$  as a reusable catalyst under reflux conditions is reported. Sonication of this system enhanced the catalytic activity which was led to higher yields and shorter reaction times. By this catalytic system under microwave irradiation, the reaction times were reduced and the yields were increased [153].

## CONCLUSIVE REMARKS

In this review we have paid attention to two zirconium(IV)

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Scheme 33

based compounds namely zirconium (IV) tetrachloride and zirconium(IV) oxydichloride octahydrate ( $ZrOCl_2 \cdot 8H_2O$ ) as remarkably effective catalysts or reagents in organic synthesis. Both  $ZrCl_4$  and  $ZrOCl_2 \cdot 8H_2O$  are commercially available solid chemicals [2]. Due to their low toxicities ( $LD_{50}$  [ $ZrCl_4$  oral rate] = 1688 mg/kg) [3], ( $LD_{50}$  [ $ZrOCl_2 \cdot 8H_2O$  oral rate] = 2950 mg/kg),<sup>3</sup> low costs, ease of handling, high activity, these zirconium(IV) compounds are potential catalysts or reagents which could be considered as important catalysts or reagents from different views such as environmental concerns and green chemistry. As it is evident from the results mentioned in this article, only a very few reports are available using  $ZrOCl_2 \cdot 8H_2O$  as catalyst or reagent in organic synthesis. Therefore, we expect studies upon basic transformations in organic synthesis will be appeared in the literature using  $ZrOCl_2 \cdot 8H_2O$  in near future. Reactions conducted in the presence of  $ZrCl_4$  are also rather limited and are at their very early stages of development.  $ZrCl_4$  should be applied to other catalytic reactions and also be used as a reagent for many other organic transformations which have not been reported in the literature yet. Supporting both  $ZrCl_4$  and  $ZrOCl_2 \cdot 8H_2O$  on solid supports and their use in organic

synthesis under heterogeneous conditions is of interest from academic and industrial point of views which should be explored in the future.

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