

Synthetic Organometallic Radical Chemistry in Water

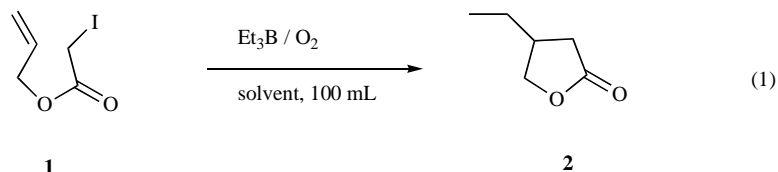
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Abstract: Several organic radical transformations in aqueous media using organometallic chemistry are presented. Group XIV-elements, such as Si and Ge, and Sn-centered radicals make use of novel methodologies in water which employ both hydrophilic and lipophilic substrates without the requirements of surfactants. Different radical initiation techniques that account for effective initiation of the radical chain reactions in aqueous media are also described, such as the thermal decomposition of azo compounds, the direct photolysis (in the absence of an organic peroxide or other photolytic radical promoter) of silanes, dioxygen initiation techniques, and radical initiation in the absence of solvent, and in the presence of adventitious oxygen. Hydrometallation of multiple bonds with $(\text{Me}_3\text{Si})_3\text{SiH}$ and germane analogs in water are also described with the above mentioned initiating techniques, under solvent-free conditions, and performed in continuous flow microreactors. The use of other metal-centered radicals that promote synthetically useful organic transformations in water, such as Mg, Mn, and Zn, is presented. These transformations encompass simple organohalide reductions, and several types of carbon-carbon bond forming reactions, demonstrating the wide scope of organometallic radical chemistry in water for accomplishing organic transformations. Group XIII- centered radicals are also shown to be excellent mediators for organic radical reactions in water, such as Barbier-type alkylations and allylations of carbonyl compounds.

1. INTRODUCTION

Water is the solvent of choice for reactions of radicals and carbenes since strong O-H bonds (enthalpy 436 KJ mol^{-1}) are not easily attacked. Recently, water has been examined as a solvent for these reactions. The realm of carbon-centered radical reactions involved in organic transformations in water is increasingly important. Significant solvent effects have been reported in atom-transfer radical cyclization reactions with carbon-centered radicals. For example, treatment of allyliodoacetate **1** in water with triethylborane (Et_3B), a radical initiator, provides the corresponding lactone product **2** in 78% yield. In organic solvents, however, the reaction is sluggish and yields no or little lactone product (eq 1).



solvent	yield%	solvent	yield%
hexane	0	acetonitrile	13
benzene	0	DMF	13
dichloromethane	0	DMSO	37
methanol	6	H₂O	78

As a matter of fact, the larger ring lactones are preferentially formed in water than in organic solvents. Eighteen-membered lactones can be formed by radical cyclization in water very efficiently (80% yield), where in benzene, the yield is quite low (14%) [1].

The use of phosphorous-centered radicals as reducing agents in water has been attempted for the reduction of various organic halides with phosphinic acid (hypophosphorous acid) in aqueous ethanol in the presence of radical initiator azobisisobutyronitrile (AIBN) and a base such as NaHCO_3 [2].

Next, the use of other organometallic reagents has been explored in water as radical-reducing agents, involved in

hydrometallation reactions, and as mediators in C-C bond formation reactions. This review is intended to survey the literature concerning the use of organometallic radicals in synthetically useful organic radical transformations in water.

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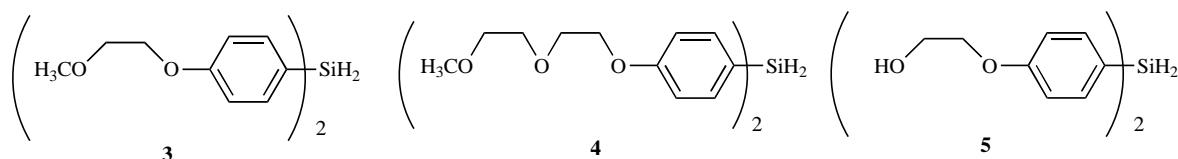
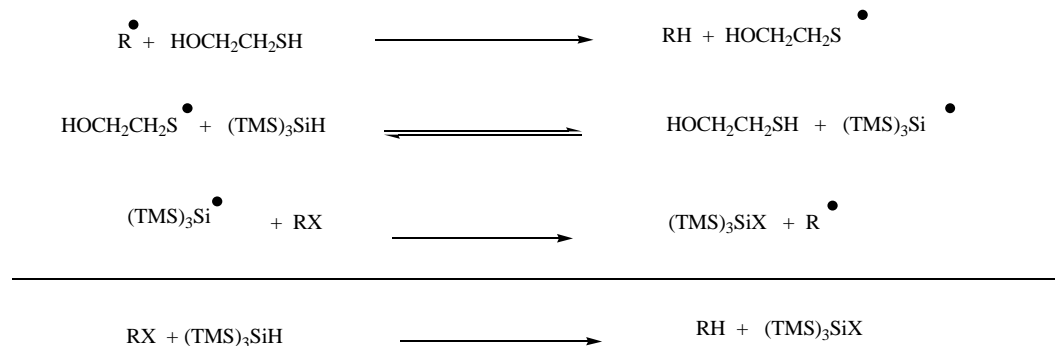


Fig. (1). Water-soluble arylsilanes utilized in radical reductions of hydrophilic organic halides.



Scheme 1. Polarity reversal catalysis of silanes with thiols.

2. GROUP XIV-CENTERED RADICALS IN WATER

In this section, we shall deal with organic radical reactions in water of synthetic utility employing radicals of group XIV elements, such as Si, Ge, and Sn.

Since the last decade, organic reactions in water and water-promoted organic reactions have attracted much attention because of the specific effects produced in water (*vide supra*, eq 1).

The majority of organic radical reactions employing Si-centered radicals take place in organic solvents, neat media, and on surface chemistry, and only recently has water been used as a convenient reaction medium for these radicals.

The development of novel water-soluble organosilane compounds and their applications to radical reactions in water is constantly being paid attention to, as a means to producing effective radical organic transformations in water, such as reductions of hydrophilic organic halides.

In the radical chain processes, the initial silyl radicals are generated by some initiation. The most popular initiator is 2',2'-azobisisobutyronitrile (AIBN), with a half life of 1 h at 81 °C, generating the incipient radicals that commence the radical chain reaction. Other azo-compounds are used from time to time [3] as well as the thermal decomposition of di-*tert*butyl peroxide [4] depending on the reaction conditions. Et₃B in the presence of very small amounts of oxygen is an excellent initiator for low temperature reactions (down to -78 °C). Also air-initiated reactions have recently been reported.

Togo and Yokohama [5] have dealt with the necessity of performing reduction reactions in water of water-soluble halides. They have shown that the reactivity of water-soluble arylsilanes, as reducing agents, is much higher than that of alkylsilanes, and that the reactivity of diarylsilanes was higher than that of monoarylsilanes and triarylsilanes. Thus, the solubilities of bis[4-(2-methoxyethoxy)phenyl]silane **3** and bis[4-(2-(2-methoxyethoxy)ethoxy)phenyl]silane **4** were about 1.0×10^{-2} M and 1.5×10^{-2} M, respectively.

The reduction of potassium *o*-bromobenzoate and potassium *o*-iodobenzoate, which form the sp² carbon radicals, showed that the bromine atom abstraction is somewhat difficult, whereas the iodine atom of potassium *o*-iodobenzoate is easily removed by the silyl radical. These results and others obtained by the same authors showed that organosilanes **3** and **4** (Fig. (1)) can promote radical reductions of alkyl bromides, alkyl iodides, and aryl iodides, initiated by Et₃B, in aqueous media under aerobic conditions.

Radical cyclizations in water using organosilanes **4** and **5** have also been studied. The radical cyclization of potassium 7-bromo-2-heptenoate with **4** and **5** was carried out to afford 48 and 82% yields of cyclopentyl acetic acid, respectively, while no direct reduction product, *i.e.* 2-heptenoic acid, was formed. This clearly demonstrated the radical nature of the process.

Water is also a choice of solvent for free-radical polymerization. The high heat capacity of water allows effective transfer of the heat from polymerization. Compared to organic solvents, the high polarity of water distinguishes remarkably the miscibility of many monomers from polymers. Today, aqueous free-radical polymerization is applied in industries [6].

Several interesting photoinitiators based on the silyl radical chemistry have been proposed as a means to effecting polymerization in aqueous suspensions [7]. Among these compounds, (4-tris(trimethylsilyl)silyloxy)benzophenone generates silyl radicals under light irradiation that produce high rates of polymerization. A water-soluble poly(methylphenylsilylene) derivative has been used as a photoinitiator of radical polymerization of hydrophilic vinyl monomers with great success [8].

It is known that in organic solvents, *tris*(trimethylsilyl)silane, (Me₃Si)₃SiH, is an efficient reducing agent for organic halides. Also, the reported methodology of polarity-reversal catalysis is well documented in organic solvents. The thiol/silane couple shows not only an efficient synergy of radical production and regeneration, but could also provide for the use of an amphiphilic thiol, in order to

enhance the radical reactivity at the interface. For the reduction of an organic halide (RX) by the couple $(\text{Me}_3\text{Si})_3\text{SiH} / \text{HOCH}_2\text{CH}_2\text{SH}$ under radical conditions, the propagation steps depicted in Scheme 1 are expected. That is, the alkyl radicals abstract hydrogen from the thiol and the resulting thiyl radicals abstract hydrogen from the silane, so that the thiol is regenerated along with the chain carrying silyl radical for a given RX [9,10].

The proposal of $(\text{Me}_3\text{Si})_3\text{SiH}$ in water can be attractive from the point of view of its commercial availability.

Recently, Postigo and Chatgililoglu [11] tested the reducing agent $(\text{Me}_3\text{Si})_3\text{SiH}$ in water and observed its high stability in deaerated aqueous media and high temperatures. They subjected a series of organic halides to reduction with $(\text{Me}_3\text{Si})_3\text{SiH}$ in water with different initiators, azo compounds and Et_3B .

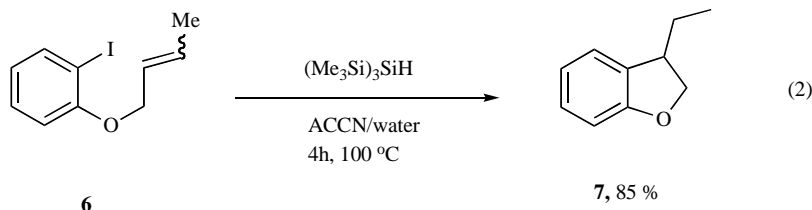
The initiators studied that afforded the best reduction yields with $(\text{Me}_3\text{Si})_3\text{SiH}$ were the water soluble 2,2'-azobis(2-amidinopropane) dihydrochloride (AAPH) and 1,1'-azobis(cyclohexanecarbonitrile) (ACCN, organic-solvent soluble). The half-life of ACCN at 100 °C is 2.33 h, while that of AAPH is *ca.* 1.1 h at 73 °C.

The reduction of hydrophilic 4-iodobutyric acid and hydrophobic 5-iodouracil, afforded the corresponding reduced products in yields >90 %, with both initiators.

The reduction of hydrophilic (1S)-bromocamphor-10-sulfonic acid and 5-bromouridine were also considered under

The reduction of water-insoluble organic substrates proceeded in a heterogeneous mixture of substrate, $(\text{Me}_3\text{Si})_3\text{SiH}$, and ACCN, in water which is previously de-oxygenated with Ar and heated at 100 °C for 4 h. Thus, the efficiency of a series of de-oxygenation reactions (Barton-McCombie reaction) is independent of the type of the thiocarbonyl derivative (e.g.: *O*-arylthiocarbonate, *O*-thiocarbamate, thiocarbonyl imidazole or xanthate) as previously reported for $(\text{Me}_3\text{Si})_3\text{SiH}$ in organic solvents. On the other hand, the water-soluble material does require the presence of the chain-carrier 2-mercaptoethanol. Thus, reduction of 5-bromo-nicotinic acid, 5'-iodo-5'-deoxyadenosine, and other hydrophilic halides do proceed by the couple $(\text{Me}_3\text{Si})_3\text{SiH} / \text{HOCH}_2\text{CH}_2\text{SH}$, where the alkyl or aryl radicals (R) abstract hydrogen from the thiol in the water phase, and the resulting thiyl radicals migrate into the lipophilic dispersion of the silane and abstract a hydrogen atom, thus regenerating the thiol along with the chain-carrying silyl radical for a given RX. The reaction of the silyl radical is expected to occur at the interface of the organic dispersion with the aqueous phase. It is worth mentioning that the reaction of thiyl radicals with silane is estimated to be exothermic by *ca.* $-3.5 \text{ Kcal mol}^{-1}$ [13].

The same reaction conditions were also applied to the radical cyclization of 1-allyloxy-2-iodobenzene derivative **6**, as shown in eq 2, but in this case, 2-mercaptoethanol was not needed. The reaction afforded 85 % yield of cyclized product **7**.



similar reaction conditions. Using the water-soluble AAPH initiator no reaction occurred for the camphor derivative, whereas 5-bromouridine afforded uridine in 82% yield (based on 17% converted substrate). However, when 3 mM ACCN is used as initiator, both substrates afforded 90% yields of the corresponding reduction products, although the conversion of the starting material was as low as 10%. By increasing the amount of ACCN, however, the disappearance of starting material increased in favor of reduction product [11].

In this work, the relevance of 2-mercaptoethanol in the reduction process was revealed. For the reduction of 5-bromouridine, the optimal ratio of substrate/2-mercaptoethanol was found to be 3-3.5.

Other substrates of biological relevance bearing halogen atoms such as 8-bromoadenosine and 8-bromoguanosine were also subjected to reduction with $(\text{Me}_3\text{Si})_3\text{SiH} / \text{HOCH}_2\text{CH}_2\text{SH}$ in water initiated by ACCN. Very high yields of reduced products were obtained under these reaction conditions (>80 %).

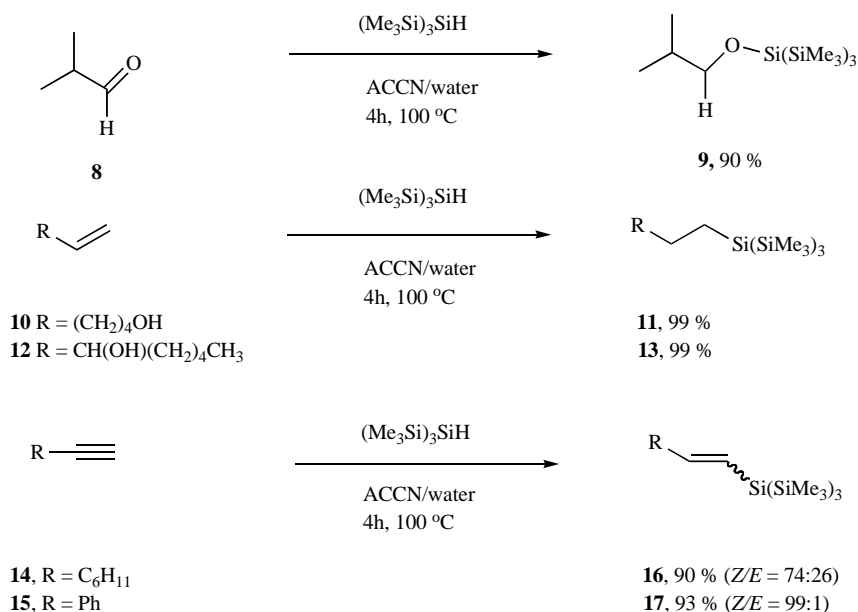
Later on, Postigo and Chatgililoglu [12] reported on two methods for the use of $(\text{Me}_3\text{Si})_3\text{SiH}$ in water, depending on the hydrophilic or hydrophobic character of the substrates.

The radical-base hydrosilylation reactions are generally performed in organic solvents, in water [12] or under solvent free conditions [14]. More recently, these reactions are also performed in continuous-flow microreactors [15].

Postigo *et al.* [12] effected the hydrosilylation reaction of unsaturated bonds in water, using different hydrophobic compounds, such as aldehydes (**8**), alkenes (**10,12**), and alkynes (**14,15**) under the same reaction conditions reported previously (Scheme 2).

Again, the efficiency of the reaction was very good, and in all cases, good to quantitative formation of the hydrosilylation products was achieved. It is worth mentioning the higher *cis* stereoselectivity observed in water *vs.* toluene (e.g.: *Z/E* = 51:49 for **16** and 84:16 for **17** in toluene at 90 °C).

These results showed that the nature of the reaction medium does not play an important role either in influencing the efficiency of the radical transformation or in the ability to dissolve the reagents. The authors attribute the success of the radical transformations of all water-insoluble material suspended in the aqueous medium to the vigorous stirring that creates an efficient vortex and dispersion. Probably, the



Scheme 2. Hydrosilylation reactions of multiple bonds using $(\text{Me}_3\text{Si})_3\text{SiH}$ in water.

Table 1. Reduction of Water-Soluble Azides

RN_3	CONVN (%)	RNH_2 , YIELD (%)
18	70	99
19	>99	90
20	>99	95
21	>99	99

radical initiation benefits from the enhanced contact surface of tiny drops containing $(\text{Me}_3\text{Si})_3\text{SiH}$ and ACCN [12].

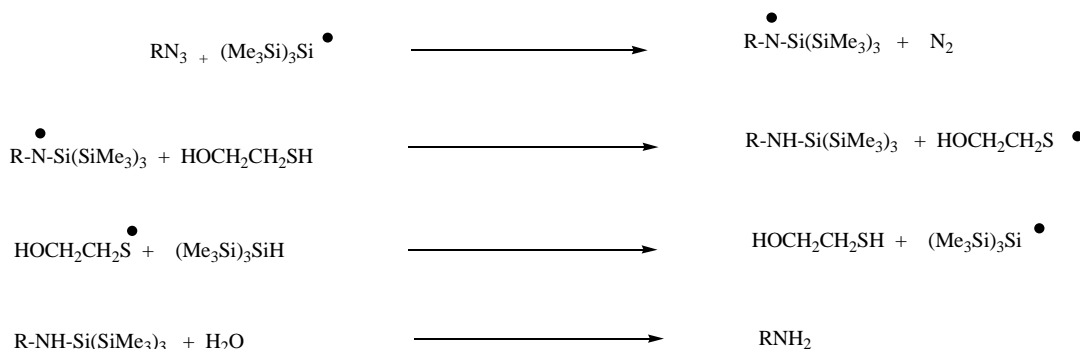
For water-soluble material, hydrosilylation of multiple bonds in water is reported by the same authors to vary slightly. In this case, as referred to before, the reducing system $(\text{Me}_3\text{Si})_3\text{SiH}$ / $\text{HOCH}_2\text{CH}_2\text{SH}$ in water is used. The amphiphilic thiol is successfully used for radical reactions in the heterogenous system of vesicle suspensions [16].

Excellent results of hydrosilylation of multiple bonds were achieved by adding this amphiphilic thiol to the system. A heterogenous mixture of water soluble starting material,

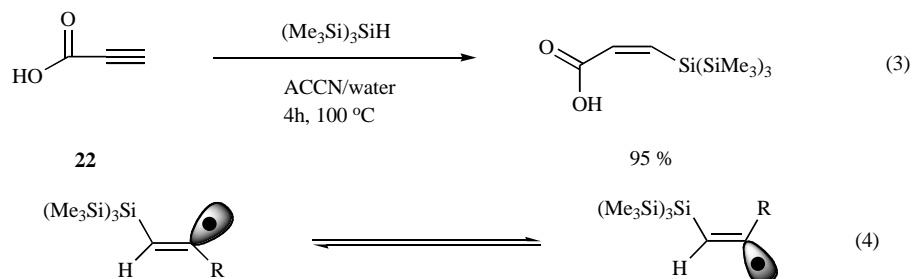
the system $(\text{Me}_3\text{Si})_3\text{SiH}$ / $\text{HOCH}_2\text{CH}_2\text{SH}$ and ACCN is flushed with Ar, and heated. The treatment of hydrophilic substrates in water has the additional advantage of an easy separation of the silane byproducts by partition between water and organic phases.

Another successful class of radical reductions in water has been obtained by the transformation of azides into primary amines under the same experimental conditions. The results are reported in Table 1.

Again, no reaction was observed in the absence of amphiphilic 2-mercaptoethanol. The mechanistic steps of



Scheme 3. Proposed reaction steps for the reduction of azides in water.



this reaction are shown in Scheme 3, in analogy with the pathways reported for the radical reduction of aromatic azides with triethylsilane in toluene [17].

The hydrosilylation of water-soluble propiolic acid **22** (eq 3) was also tested under the same conditions. The reaction proceeded efficiently giving the *Z*-alkene with optimal yield (eq 3). It is worth noting that the hydrosilylation has been recently reported to be efficient also under neat conditions, where the initiation was linked to the presence of adventitious oxygen [18].

More recently, Postigo *et al.* [19] undertook a comparative study of the radical initiation mechanism of the hydrosilylation of C-C multiple bonds, *e.g.*: hydrosilylation of alkenes and alkynes in water with $(\text{Me}_3\text{Si})_3\text{SiH}$. It was shown that hydrosilylation of alkenes in water by $(\text{Me}_3\text{Si})_3\text{SiH}$ can effectively be conducted both by a thermal and photochemical initiation (in the absence of a radical chemical precursor such as an organic peroxide), rendering the hydrosilylated end-products in high yields. Alkynes, are more effectively hydrosilylated in water by $(\text{Me}_3\text{Si})_3\text{SiH}$ through dioxygen initiation than alkenes are, where this condition affords only moderate to low yields of hydrosilylated alkanes. Remarkably, the hydrosilylation of alkynes in water by $(\text{Me}_3\text{Si})_3\text{SiH}$ proceeds with the highest *Z*-stereoselectivity when the reactions were initiated by dioxygen.

In this report [19] alkynes such as 1-octyne, 1-cyclohexylacetylene (**14**), 1-phenylacetylene (**15**) and propiolic acid (**22**) were treated with $(\text{Me}_3\text{Si})_3\text{SiH}$ in water under dioxygen initiation and yielded the respective alkenes stereoselectively in high yields. Normally *Z* alkenes (*Z:E* ratios >99:1, isolated alkene yields >95 %) are formed. In the case of propiolic acid, 2-mercaptoethanol is needed as chain carrier. Comparison of these data with the analogous reactions carried out in toluene at 80-90 °C and AIBN as

initiator [20], not only shows better product yields but also a higher stereoselectivity in favor of the *Z* isomer. Unconjugated vinyl radicals are known to be sp^2 hybridized and to invert with a very low barrier (eq 4)

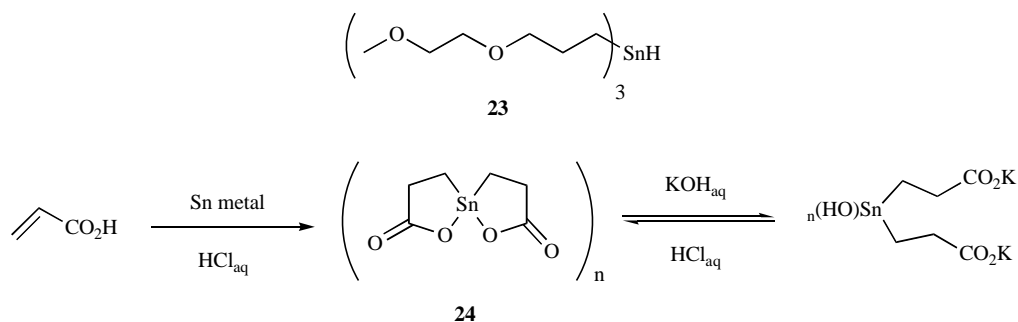
The authors [19] postulate that the higher stereoselectivity in favor of the *Z* isomer, under the experimental conditions, suggest that additional factors are playing a role in water. It could be hypothesized that the hindrance of approach of the bulky silane to the radicals may also be influenced by the organization of the organic material dispersed in water.

In this same report [19] the authors investigated the competition reaction between the *gem*-dichlorocyclopropane moiety reduction and hydrosilylation of double bonds in alkenyl-substituted *gem*-dichlorocyclopropane derivatives in water. The authors found that the hydrosilylation of the double bonds in alkenyl-substituted *gem*-dichlorocyclopropane derivatives precedes the chloro atom reduction in water.

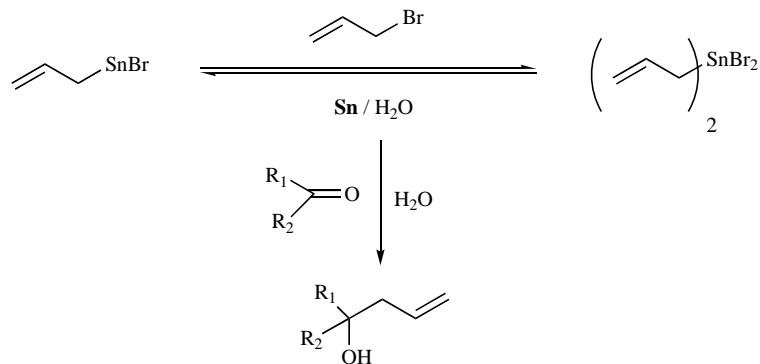
More recently, Russo *et al.* [21] undertook the hydrosilylation reaction of a series of alkenes in water with $(\text{Me}_3\text{Si})_3\text{SiH}$ (*e.g.*: 3-chloroprop-1-en, prop-2-en-1-ol, prop-2-en-1-amine, *tert*-butyl vinyl ether, and *n*-butyl vinyl ether) initiated by light and found very good yields of hydrosilylated alkanes. In the same manner, the authors studied the hydrosilylation of a series of alkynes (prop-2-yn-1-ol, chloroprop-1-yne, propiolic acid) in water, initiated by light, with the same silane, obtaining the respective hydrosilylated alkenes with high *Z* stereoselectivity.

Less environmental-friendly reducing agents, such as tin-derived compounds, have also been used in water. However, in designing these agents, much consideration is given to minimizing the disposal of tin garbage.

Maitra *et al.* reported [22] a simple methodology to accomplish dehalogenation reactions with tri-*n*-butyltin



Scheme 4. Some Water-soluble tin compounds used in radical reductions.



Scheme 5. Tin-promoted allylation of carbonyl compounds in water.

hydride (TBTH) in aqueous suspensions, as well as nucleophilic substitution on 2-iodobenzoates in water. For the dehalogenation of water soluble substrates, a water soluble tin hydride **23** (Scheme 4) was reported by Breslow [23]. The polarity of **23** facilitates product isolation. Although this reagent gave good yields in the dehalogenation of a number of water-soluble substrates, the synthesis of **23** (Scheme 4) takes several steps. There was another report on the reduction and free radical cyclizations of alkyl and aryl bromides carried out in aqueous base by NaBH_4 in the presence of a base-soluble dialkyltin (IV) reagent **24** and 4,4'-azobis(4-cyanovaleric) acid [24] (Scheme 4).

However, the method reported by Maitra *et al.* [22] using TBTH resulted in significant advantage, since not only water-soluble material could be reduced by TBTH, but also water-insoluble substrates could be reduced in high yields. Substrates such as 9-bromoanthracene, however, required the presence of a detergent. Cholesterol dibromide underwent smooth reduction to cholesterol (84 %) in the absence of detergent with 2 equiv. of TBTH. The same authors attempted the catalytic reduction of 4-iodobenzoic acid (through a catalytic cycle) by using 1 equivalent of TBTH in the presence of *ca.* 3 equivalents of NaBH_4 . No benzoic acid was obtained from tri-*n*-butyltin chloride- (TBTC) mediated reactions of 3-bromo and 4-iodobenzoic acids in the presence of a large excess of NaBH_4 . It seemed that the trialkyltin halide generated / added in the reaction medium was hydrolysing very rapidly, and that the regeneration of the hydride from the halide by NaBH_4 was slow under the reaction conditions.

Some C-C bond forming reactions have also been attempted in water with tin-centered radicals, either in homogeneous or heterogeneous systems. Chang *et al.* [25]

found that dialkyltin dibromide is an efficient allylating reagent of carbonyl compounds in aqueous media to give the corresponding homoallylic alcohols. Either aldehydes or ketones can be used, and the allylation products were usually obtained cleanly with high yields (Scheme 5).

The authors argued that the mechanism of this reaction could contemplate a surface metal-mediated radical or radical anion reaction.

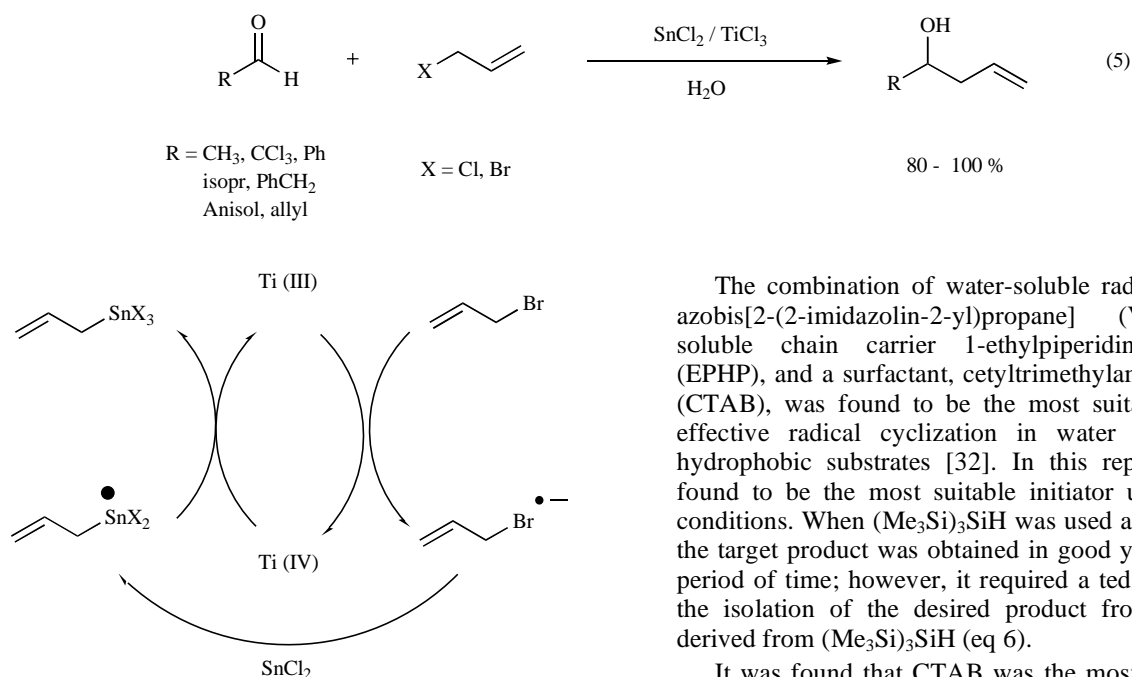
This Barbier coupling reaction between an allyl halide and a carbonyl compound in aqueous media has continued attracting considerable attention. Use of this elegant method allows homoallylic alcohols to be synthesized in a highly efficient and environmentally benign way.

Water-soluble reductive metal salts such as SnCl_2 in combination with TiCl_3 in fully aqueous media provide a high-yielding route to homoallylic alcohols (80- 100 % yields) [26]. In this procedure, there is no need to use any organic co-solvent or ultrasonic irradiation. In addition, since SnCl_2 and TiCl_3 are both soluble in water, it is fairly easy to stir the reaction mixture.

Allyl chloride and bromide provide similar yields in SnCl_2 - TiCl_3 -mediated allylation, although for allyl chloride a longer reaction time is needed. Both aromatic and aliphatic aldehydes can be allylated efficiently under those conditions (eq 5) [26].

Little allylation product was observed when only SnCl_2 was employed in the reaction. No allylation product was found when only TiCl_3 was employed; therefore, the mixture of both salts is required.

A possible mechanism for the TiCl_3 -catalyzed allylation is that Ti(III) transfers one electron to allyl halide in the first [27] step (Scheme 6). The allyl halide radical anion then reacts with SnCl_2 to form an allyltin radical, which is



Scheme 6. Reaction mechanism for the TiCl_3 -catalyzed allylation of carbonyl compounds.

oxidized by Ti(IV) yielding Ti(III) and a neutral allyltin compound. The allyltin compound, in turn, adds to the carbonyl group, yielding the homoallyl alcohol [28].

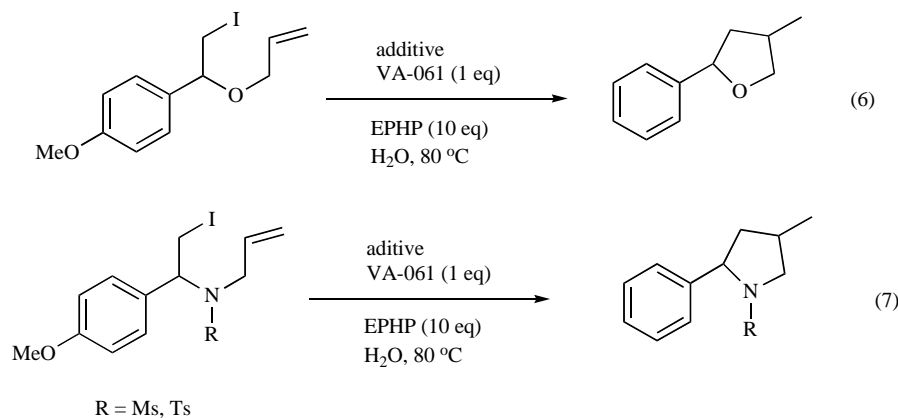
3. PHOSPHOROUS-CENTERED RADICALS IN WATER

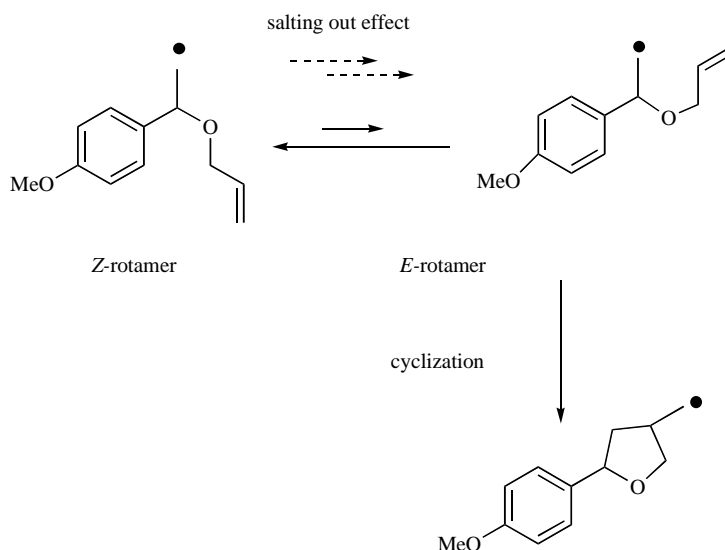
Tin-radical mediators in water, while extremely useful, result in environmentally unfriendly reagents for performing organic radical transformations in aqueous systems. One disadvantage stems from the difficulty in removing by-products from reaction mixtures. For these reasons, the quest for alternative mediators has been extremely active. Followed by the contributions from Barton and Jaszberenyi involving hypophosphorous acid in refluxing dioxane [29], Jang showed that the sodium salt of hypophosphorous acid could reduce water-soluble organohalides in water [30]. Dibutylphosphine and diphenylphosphine oxides were also introduced by Jang as new reducing agents in water (*vide infra*) [31].

The combination of water-soluble radical initiator 2,2'-azobis[2-(2-imidazolin-2-yl)propane] (VA-061), water soluble chain carrier 1-ethylpiperidine hypophosphite (EHPH), and a surfactant, cetyltrimethylammonium bromide (CTAB), was found to be the most suitable condition for effective radical cyclization in water for a variety of hydrophobic substrates [32]. In this report, VA-061 was found to be the most suitable initiator under the reaction conditions. When $(\text{Me}_3\text{Si})_3\text{SiH}$ was used as the chain carrier, the target product was obtained in good yield within a short period of time; however, it required a tedious procedure for the isolation of the desired product from the by-product derived from $(\text{Me}_3\text{Si})_3\text{SiH}$ (eq 6).

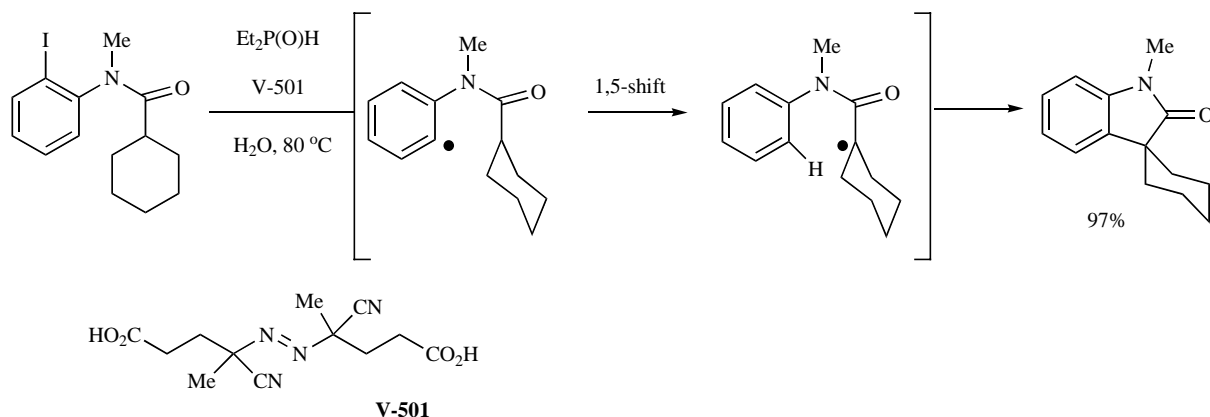
It was found that CTAB was the most efficient additive for the radical cyclization from the point of view of its rate of acceleration effect. In the absence of the additive, the reaction did not go to completion until 24 h. The synthesis of pyrrolidine nuclei was also accomplished successfully (eq 7) with the system VA-061, EPHP, and CTAB [32].

Later on, the same authors attempted to improve the yield of these radical reactions in water by the use of different additives [33]. Breslow et al. had already reported that Diels-Alder reactions in water were accelerated by addition of the salting out salt (*e.g.* LiCl) to the system, and that the rate of the reaction decreased by addition of the salting in salt (*e.g.* guanidine hydrochloride) [34]. A salting out salt is a material that increases the hydrophobic effect of water and thereby decreases the stability of the hydrocarbons, and a salting in salt is a material that decreases the association of hydrocarbon residues in water and thus increases the water stability of hydrocarbons. In other words, the addition of the salt to the water system helps to increase the internal pressure in water, thereby the cyclization substrate is transformed from the non-compact forming *Z*-rotamer into the compact forming *E*-rotamer, which is essential for the cyclization (Scheme 7).





Scheme 7. Effect of the salting out salt on the radical cyclization reaction in water.



Scheme 8. DEPO-mediated arylation of lactams in water.

In the case of the salting in salt, a large quantity of the salt was necessary to facilitate the cyclization reaction. To circumvent this problem, the use of different surfactants other than CTAB was studied, such as cetyl trimethylammonium chloride CTAC, sodium dodecyl sulfate, SDS, and triton X-100. All these surfactants gave excellent cyclization product yields.

Once this main family of P-centered mediators had been introduced (EHPH) Murphy [35] explored a water-soluble phosphine oxide which permitted higher isolated yields of reduced compounds than the corresponding reaction using EPHP. Upon using diphenylphosphine oxide (DEPO), sophisticated tin-free tandem radical reactions could be accomplished. Because DEPO is more lipophilic than hypophosphorous acid yet still water-soluble, the interaction between the water-soluble mediator and initiator and the lipophilic substrates could be accomplished without requiring a phase-transfer agent. Moreover, its pK_a of 6, ensured that this almost neutral excess reagent could be extracted into base during workup (Scheme 8).

One of the most impressive synthetic achievements of the P-based radical mediators is the deoxygenation of an erythromycin B derivative toward the industrial synthesis of

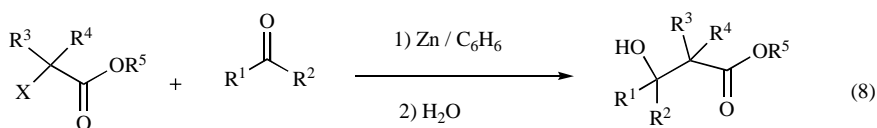
ABT-229, a potent motilin receptor agonist. Clean deoxygenation was achieved on a 15 Kg scale by using NaH_2PO_2 in an aqueous alcohol and a phase transfer agent [36].

Recently, Perchyonok reported on an interesting range of radical reductions, deoxygenation, and radical cyclization reactions utilizing quaternary ammonium salts of phosphinic acids as chiral and achiral hydrogen donors [37].

4. ZN, MG, MN, AND TI RADICALS IN WATER

The recent interest in aqueous medium metal-mediated carbon-carbon bond formation led to the continuing search for more reactive and selective metal species for such reactions.

The Reformatsky reaction (eq 8) between a 2-halo ester and a carbonyl compound in the presence of Zn was the first example of a large number of now commonly used C-C bond forming reactions: the addition of organometallic reagents to the carbonyl group. For nearly a century, these reactions were believed to require strictly anhydrous and oxygen-free conditions. Only during the past decade have chemists witnessed numerous examples of one-step reactions between organic halides, a reactive metal, and an electrophilic substrate commonly a carbonyl compound, which proceeded



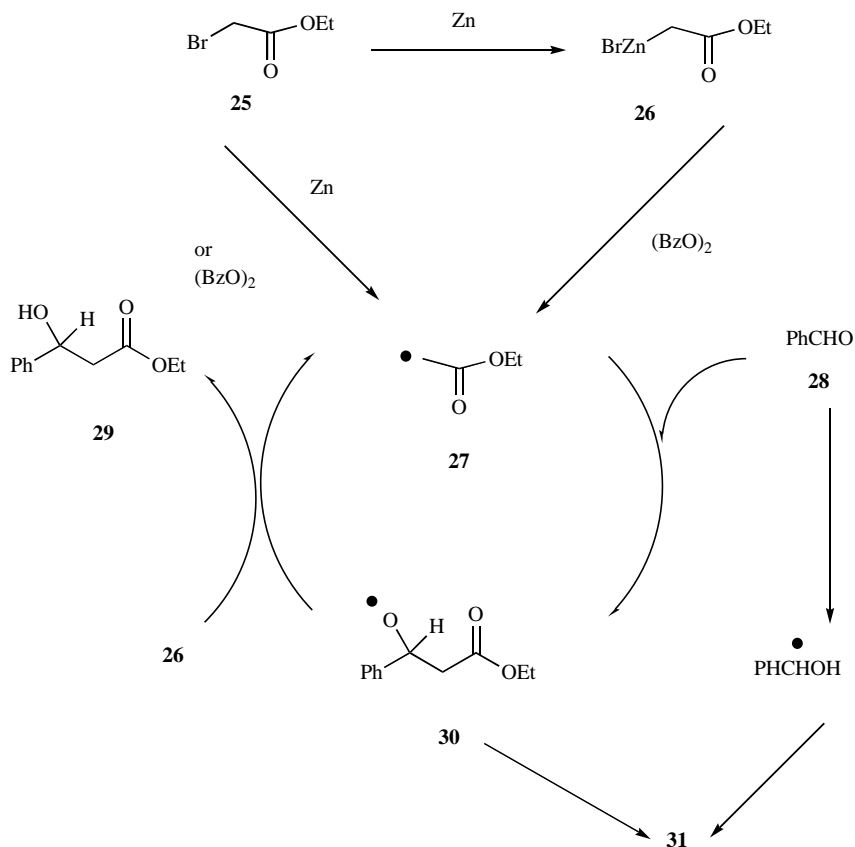
not only in wet solvents, but sometimes in water or salt solutions [38]. Many of these procedures gave addition products in preparative yields, comparable or superior to those obtained with preformed organometallic reagents under anhydrous conditions.

Bieber *et al.* [39] demonstrated that the Reformatsky reaction can be carried out in water with a wide range of carbonyl substrates including saturated and unsaturated aldehydes and ketones where the previously indium-promoted reaction in water was reported to be ineffective (*vide infra*) [40]. Preparatively interesting yields comparable to those of the classical procedure in anhydrous solvents, can be obtained from substituted benzaldehydes with ethyl bromoacetate and from aromatic and unsaturated aldehydes with ethyl 2-bromo*isobut*ylate. From the mechanistic point of view, the reaction was inhibited by galvinoxyl and hydroquinone, which is consistent with a radical mechanism of two Single Electron Transfer (SET) processes proposed by Chan [40]. In Scheme 9, an alternative radical chain mechanism was postulated by the authors, which does not involve hydrogen abstraction [39]. When Zn reacts with **25** (Scheme 9), it produces directly the Reformatsky reagent **26**. This will react with water to form ethyl acetate or with a benzoyl radical to form benzoate and radical **27** which adds to the aldehyde **28**, giving the oxyl radical **30**. Reduction of

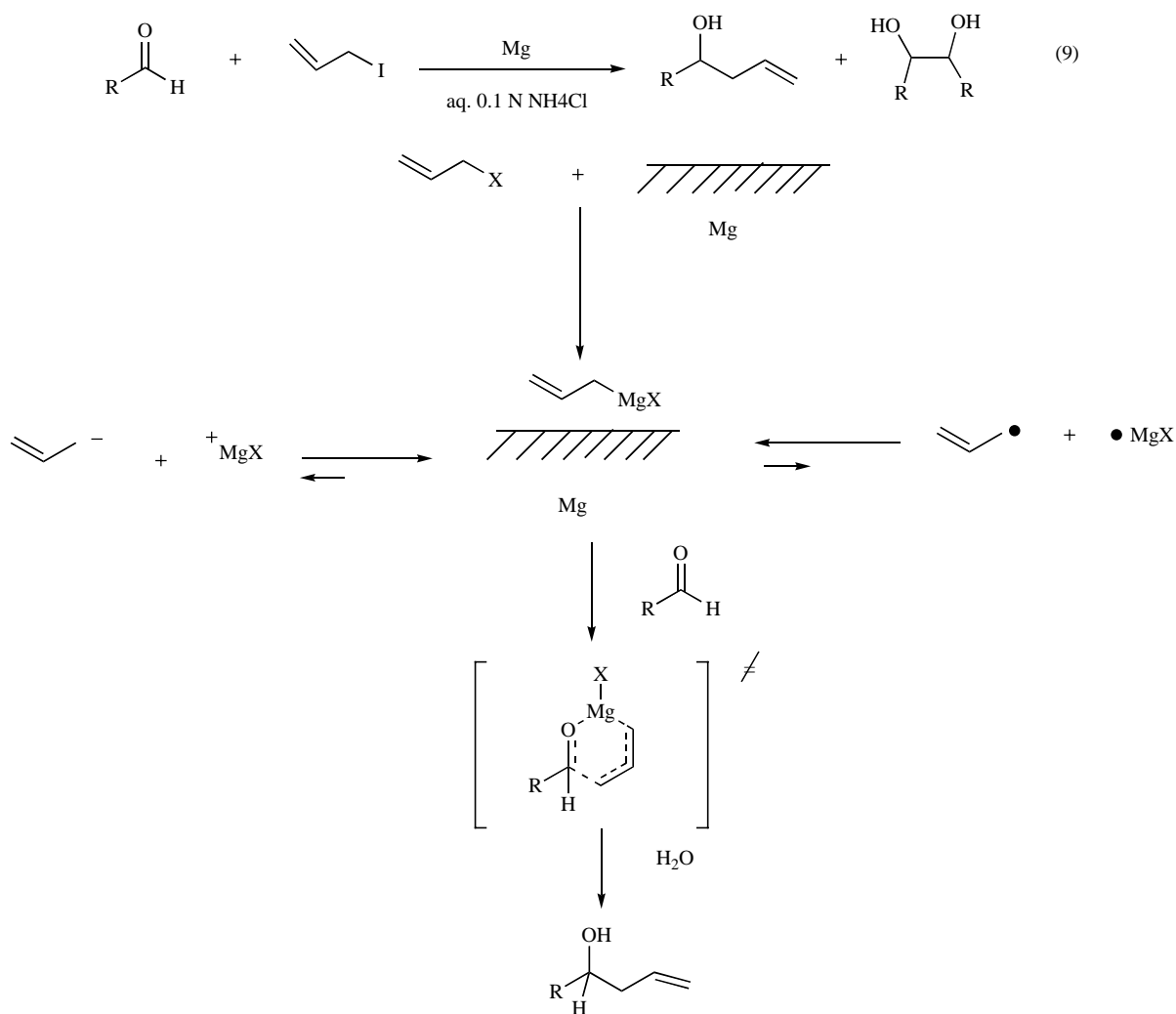
the intermediate **30** by another molecule of Reformatsky reagent **26** produces the final adduct **29** and a new radical **27** to continue the chain. Alternatively, the initial radical **27** may be produced by bromine abstraction from **25**, either by a phenyl radical or on the zinc surface.

In the past two decades, the one-pot Barbier procedure for coupling allylhalides with carbonyl compounds has gained renewed interest. Contrary to the Grignard reaction, the Barbier procedure does not require strictly anhydrous solvents but can be performed very efficiently in aqueous media. In fact, the allylation of aldehydes and ketones under the Barbier conditions usually occurs faster and gives rise to higher yields when water is used as a (co)solvent [41]. Furthermore, a number of metals are known to participate in the coupling reaction in aqueous media including zinc, indium, tin, manganese, antimony, bismuth, and magnesium.

Magnesium-mediated Barbier-Grignard-type alkylation of aldehydes with alkyl halides was investigated by Li *et al.* [42] It was found that the magnesium-mediated allylation of aldehydes with allyl bromide and iodide proceeded effectively in aqueous 0.1 M HCl or 0.1 M NH₄Cl. Aromatic aldehydes reacted chemoselectively in the presence of aliphatic aldehydes. A variety of aldehydes were tested with this alkylation method, according to eq 9.



Scheme 9. Proposed mechanism for the reformatsky reaction in water.



Scheme 10. Mg-Surface mediated electron transfer mechanism of allylation of carbonyl compounds.

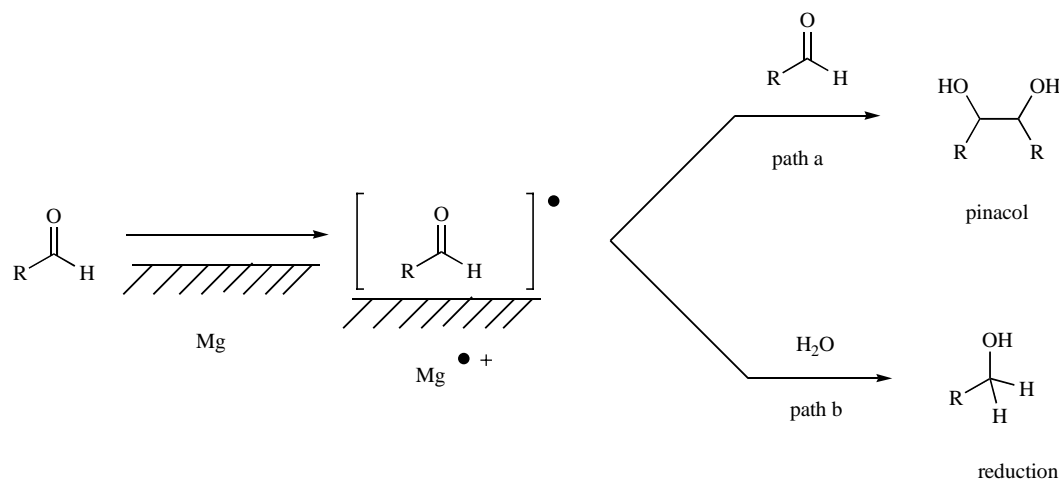
The allylation of aromatic aldehydes bearing halogen atoms proceeded without any problems. The allylation of hydroxylated aldehydes also afforded the allylation products in good yields. Reaction of 4-hydroxybenzaldehyde under the standard conditions led to the formation of the allylation product.

The mechanism of the classical magnesium-mediated Barbier and Grignard reactions have been studied intensively by several groups [43]. It is generally believed that the radicals on the metal surface are involved in the organo-magnesium reagent formation. For the Barbier allylation of carbonyl compounds with magnesium in anhydrous solvent, it is assumed that the reaction of allyl bromide on the metal surface generates an organometallic intermediate that is in equilibrium with the charge-separated form and the radical form, as proposed by Alexander [44], as shown in Scheme 10. The two forms will also lead to either the protonation of the carbanion (overall reduction of the halide) or Wurtz-type coupling, whereas the intermediate reacts with aldehydes through the usual six-membered ring mechanism. The radical intermediate could lead to the formation of 1,6-hexadiene, pinacol product and benzyl alcohol.

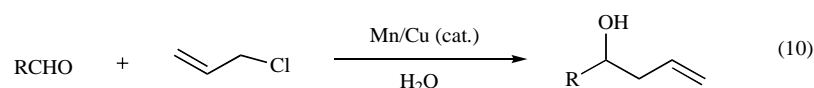
For the rationalization of the pinacol formation, the authors [42] postulate two potential pathways competing with each other generating either the pinacol-coupling product (path a, Scheme 11) or the benzyl alcohol product (path b, Scheme 11). The same authors observed that upon increasing the steric hindrance around the carbonyl group, a destabilization in the transition state responsible for the formation of the pinacol product (path a), would result in an increase in the formation of the benzyl product. Thus, they observed that no pinacol product was formed from the magnesium-mediated reaction with 2,6-dichlorobenzaldehyde, and a 74 % yield of the reduction product was encountered in this example (Scheme 10).

Madsen *et al.* [45] reported on a theoretical study of the Barbier-type allylation of aldehydes mediated by magnesium. They concluded that a radical anion was involved in the selectivity-determining event.

Other metals were used from time to time to mediate in the coupling reactions to construct new C-C bonds. Manganese was shown to be very effective for mediating aqueous medium carbonyl allylations and pinacol coupling reactions.



Scheme 11. Pinacol formation and reduction competing paths.



Li *et al.* [46] reported an unprecedented metal-mediated carbonyl addition between aromatic and aliphatic aldehydes. The allylation of aldehydes mediated by manganese in water in the presence of a catalytic amount of copper showed exclusive selectivity toward aromatic aldehydes. Manganese was found to be equally selective in promoting pinacol-coupling reactions of aryl aldehydes. When 3 equivalents of allyl chloride and manganese mediator were used, the isolated yield of the allylation product was 83 % (eq 10).

It was found that [46] various aromatic aldehydes were allylated efficiently by allyl chloride and manganese in water. It is noteworthy to mention that aromatic aldehydes bearing halogen atoms were allylated without any problems. The allylation of hydroxylated aldehydes was equally successful. On the other hand aliphatic aldehydes were inert under the reaction conditions. Such an unusual reactivity difference between an aromatic aldehyde and an aliphatic aldehyde suggested the authors [46] the possibility of an unprecedented chemoselectivity. When competitive studies were carried out involving both aromatic and aliphatic aldehydes (eq 11), a single allylation of benzaldehyde was generated when a mixture of heptaldehyde and benzaldehyde was reacted with allyl chloride. Such a selectivity appeared unique when aqueous methodologies mediated by other metals such as Zn, Sn and In all generated a 1:1 mixture of allylation products of both aldehydes.

The pinacol-coupling reaction (*vide supra*) is another fundamental reaction in organic chemistry. The pinacol coupling reaction in water mediated by Ti(III) (see eq 9 and Scheme 11) and other metals such as Zn-Cu have also been found to promote pinacol formation under ultrasonic

radiation conditions in aqueous acetone. When benzaldehyde was reacted with manganese in the presence of a catalytic amount of acetic acid in water, the corresponding pinacol coupling product was obtained smoothly. Other aryl aldehydes were coupled similarly. On the other hand, aryl and aliphatic ketones appeared to be inert under the same reaction conditions, and only the reduced product was obtained with aliphatic aldehydes [46].

Chang *et al.* [47] have recently reported that fluoride salts are equally effective in activating antimony in aqueous media to mediate in the coupling of allyl bromide with aldehydes to afford the corresponding homoallylic alcohols. 1 M Concentrations of NaF and KF were found to be equally effective as RbF and CsF or 2 M KF. The reaction proceeded well with either aromatic or aliphatic aldehydes. The allylation of α,β -unsaturated aldehydes as represented by *trans*-cinnamaldehyde occurred in a regiospecific manner and furnished solely the 1,2-addition product. Furthermore, electron donating or withdrawing groups on the aromatic ring did not seem to affect the reaction significantly either in the yield of the product or the rate of the reaction. With this metal, activated antimony, no alcohols or pinacols were detected as side products of the reactions, as has been shown previously for the Mn and Mg (*vide supra*) cases. Even the nitro substituent on the aromatic ring of the aldehyde was not reduced under the reaction conditions obtaining the corresponding allylated alcohol from *p*-nitrobenzaldehyde (usually the nitro group is sensitive to reduction by metals and cannot be allylated under Barbier conditions) [48]. In this sense, the authors argued [47] that the use of a fluoride salt as an activating agent is superior to the use of Al, Fe, or

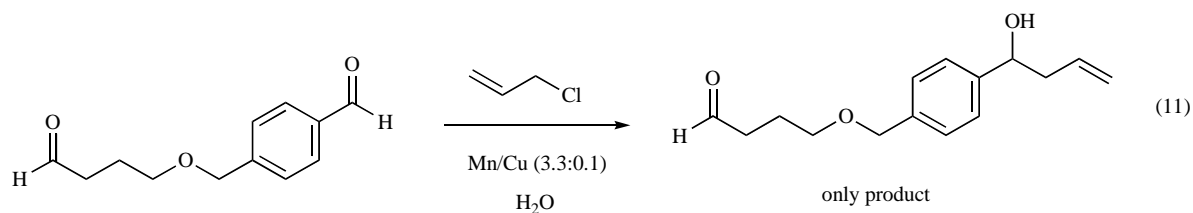
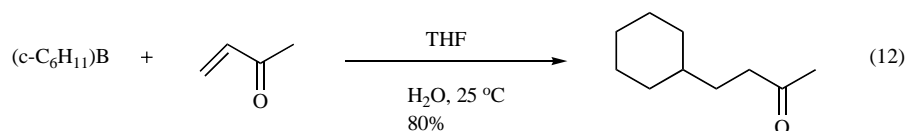
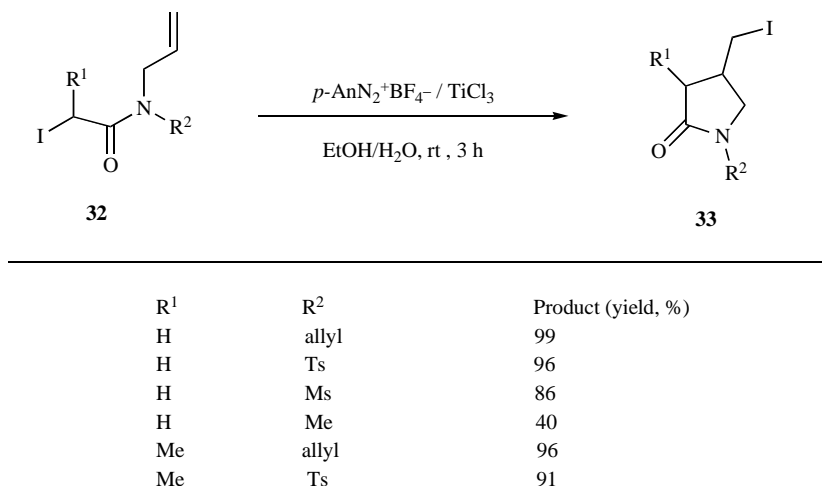


Table 2. *p*-Methoxybenzenediazonium Tetrafluoroborate/ TiCl₃ Mediated Iodine Atom-transfer Radical Cyclization

NaBH₄, reported previously. Efforts to allylate ketones failed by this Sb-mediated methodology. From the mechanistic point of view, the reaction proceeds between the allylmetal species and the aldehyde [49].

Recently, Li and Cao [50] demonstrated the efficiency of *p*-methoxybenzenediazonium tetrafluoroborate-TiCl₃ couple in promoting / initiating the halogen atom-transfer radical addition (ATRA) reaction and the iodine atom-transfer radical cyclization (ATRC) reaction as an entry to heterocycles such as lactones and lactams, as shown in Table 2.

The active species in the *p*-methoxybenzenediazonium tetrafluoroborate / TiCl₃ -chain process are the aryl radicals. Initiation relies on the fact that the aryl radical is generated selectively, and it abstracts an iodine atom from the substrate rather than adding to the C=C bond. This is because the rate constant for the iodine atom abstraction of a phenyl radical from an alkyl iodide is close to the diffusion-controlled limit ($>10^9 \text{ M}^{-1}\text{s}^{-1}$) which is about 100 times faster than the rate of phenyl radical addition to a monosubstituted alkene (*ca.* $3 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$). More importantly, the rate constant for the iodine atom-transfer from the substrate to the adduct radical is around $2.7 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, at least one order of magnitude higher than that for the trapping of the adduct radical by the diazonium ion *p*-methoxybenzenediazonium tetrafluoroborate. This allows the iodine atom-transfer chain process to evolve smoothly without the intervention of a termination step [50].

5. GROUP XIII CENTERED-RADICALS IN WATER

The reaction of trialkylboranes with 1,4-benzoquinones to give 2-alkylhydroquinones in quantitative yields was the first reaction of this type occurring without the assistance of a metal mediator [27].

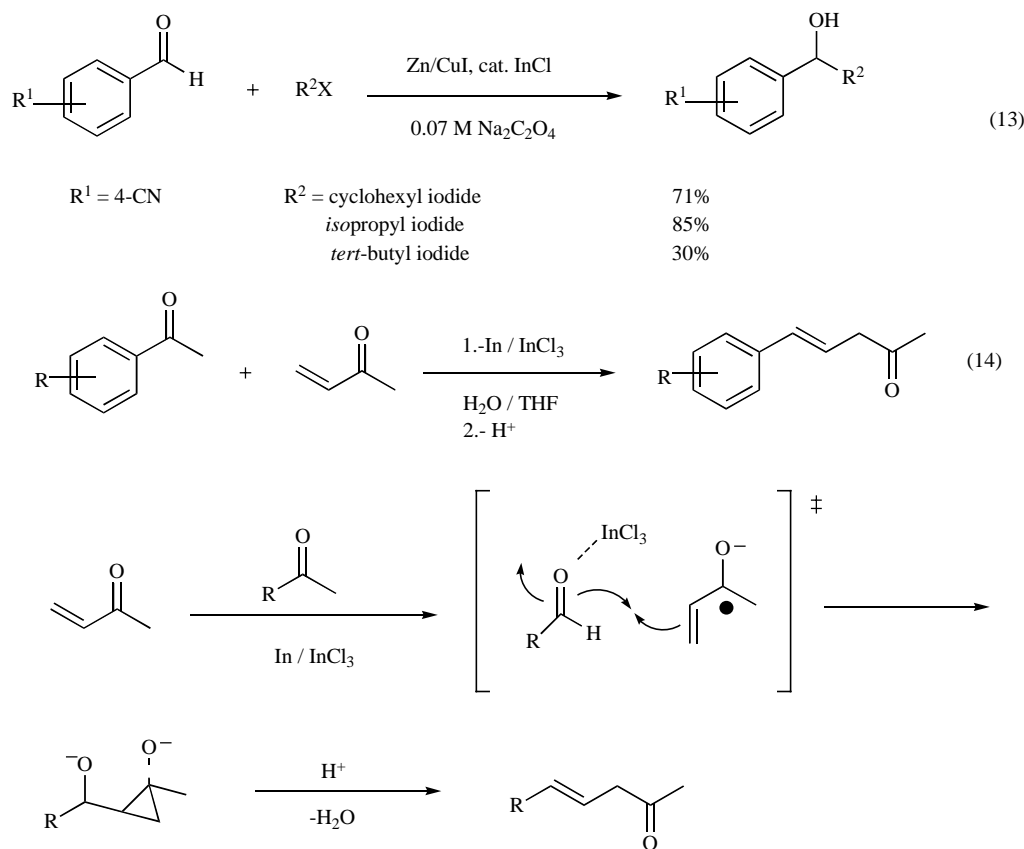
The reaction is inhibited by a radical scavenger such as galvinoxyl and iodine [51]. Then, it was demonstrated that

trialkylboranes are excellent reagents for conjugate addition to vinyl ketones (eq 12), acrolein, α -bromoacrolein and quinones.

Various attempts to extend this reaction to β -substituted- α,β -unsaturated carbonyl compounds such as *trans*-3-penten-2-one, mesityl oxide, 2-cyclohexen-1-one, and *trans*-crotonaldehyde were unsuccessful unless radical initiators were used.

Indium- and zinc-mediated carbon-carbon bond forming reactions in aqueous media have been of great importance from both economical and environmental points of view. Indium and zinc are stable under air, and it is much easier to run their reactions than those with SmI₂, and the toxicity is quite low. Moreover, the metal species can be easily removed from the reaction mixture by simple filtration and washing with water, unlike tributyltin hydride.

Electron-transfer reactions mediated by indium have attracted the attention of synthetic chemists due to its low first ionization potential at 5.79 eV, which is lower than many reducing metals such as aluminum (5.98 eV), tin (7.34 eV), magnesium (7.65 eV), zinc (9.39 eV), and close to that of alkali metals such as sodium (5.12 eV) and lithium (5.39 eV). The second ionization potential for indium is much higher (18.86 eV). Having such low first ionization potential makes indium attractive for conducting reduction reactions. This is particularly so because it is so much easier to handle than alkali metals, for example, the metal remains unaffected by air or oxygen at ordinary temperatures and is practically unaffected by water even at high temperatures, and very resistant to alkaline conditions. As indium has a low toxicity, has found considerable utility in dental alloys. It has also to be pointed out that a favorable experimental feature of indium-mediated radical reactions is that the reactions proceed in the absence of toxic tin hydride, providing the carbon-carbon bond forming method in aqueous media.



Scheme 12. Possible reaction mechanism for the indium-mediated synthesis of β,γ -unsaturated ketones.

Indium has shown great potential for a number of carbon-carbon bond forming reactions such as Reformatsky, Barbier type alkylation, allylation, and propargylation of carbonyl compounds. This is largely due to the fact that a highly reactive metal, such as indium, is required to break the non-activated carbon-halogen bond (as well as to react with the carbonyl once the organometallic intermediate is formed). However, even if the desired intermediate is successfully generated, various competing side reactions may occur when utilizing a highly reactive metal, for example, the reduction of water, the reduction of starting materials, the hydrolysis of the organometallic intermediate, and pinacol-coupling (*vide infra*) [52]. An efficient Barbier-Grignard-type alkylation of aldehydes in water in the presence of CuI, Zn, and catalytic InCl in dilute aqueous sodium oxalate affords alkylated alcohols in good yields [52]. According to eq 13, a series of alkyl halides can be used to afford alkylated alcohols in fairly good yields.

More recently, Loh and collaborators [53] have attempted the alkylation reaction of carbonyl compounds in water using unactivated alkyl halides and In/CuI/I₂ or In/AgI/I₂ system. From their results, it became apparent that the use of organic solvents inhibited the occurrence of the Barbier-Grignard-type alkylation reaction. In contrast to the work reported by Li and coworkers [52] it was noteworthy that even aliphatic aldehydes could also react efficiently with alkyl iodides to furnish the alkylated products in good yields.

The indium-mediated reaction of benzaldehydes and methyl vinyl ketones proceeded smoothly in the presence of InCl₃ in aqueous media to form β,γ -unsaturated ketones [54].

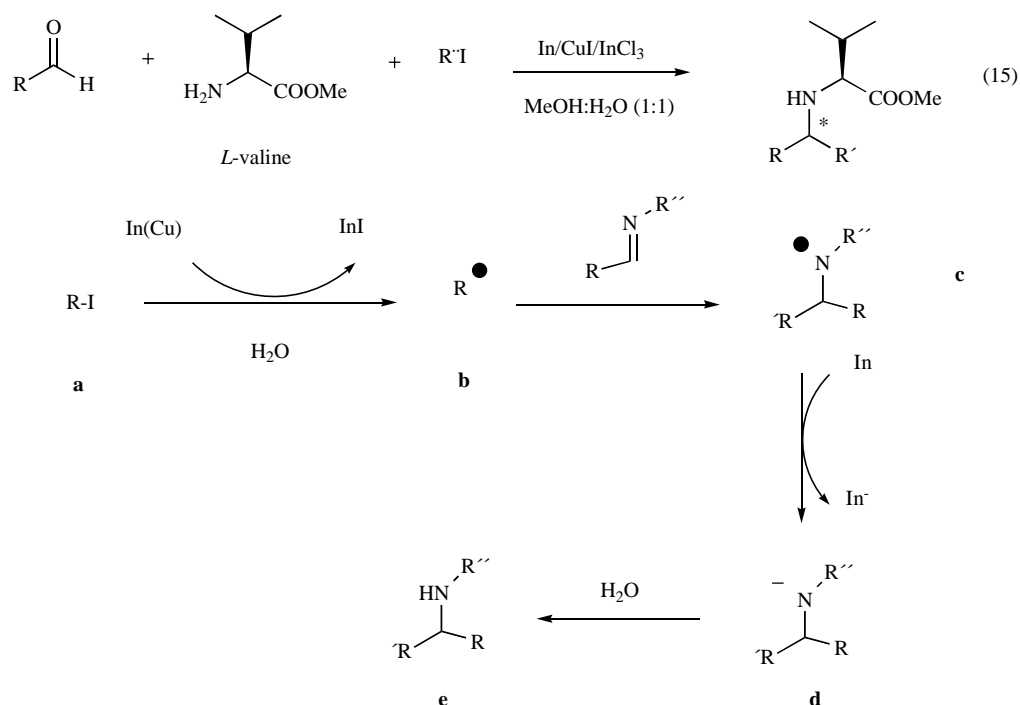
Thus benzaldehydes were reacted with methyl vinyl ketone in the presence of indium powder and InCl₃ in a solvent mixture of THF and H₂O at ambient temperature for 6-8 h. Addition of NH₄Cl to the reaction mixture afforded the desired β,γ -unsaturated ketones in good to moderate yields (eq 14).

Generally, the yields of products are not affected by the nature of the substituents on the phenyl ring. The reaction also proceeded with heteroaromatic aldehydes. With the absence of In, or InCl₃ the reaction did not occur. When other Lewis acids such as SnCl₄, FeCl₃, and CuCl₂ were used instead of InCl₃, low yields of β,γ -unsaturated ketones resulted (20-38%). When an aldehyde reacted with ethyl vinyl ketone instead of methyl vinyl ketone as a Michael acceptor, a coupling product was produced in 62 % yield. The reaction conditions were extended to other Michael acceptors such as acrolein, acrylonitrile, ethyl acrylate, and acrylic acid; however, the reactions did not proceed [54].

The reaction mechanism was postulated to be a radical mechanism involving the radical anion intermediate of methyl vinyl ketone formed from indium (Scheme 12).

The reaction intermediate undergoes radical cyclopropanation and addition to benzaldehyde. Upon addition of butylated hydroxytoluene (BHT) a rate retardation effect was observed [54].

Thus numerous and useful indium-mediated allylation reactions of carbonyl compounds have been reported [55]. However, the corresponding reaction of imine derivatives has not been widely studied because of the lower electrophilicity of carbon-nitrogen double bonds. Therefore, the



Scheme 13. Proposed reaction mechanism for the alkylation of imines in aqueous media.

development of indium-mediated reactions of imines in aqueous media has been a subject of recent interest. Chan *et al.* [56] reported on the first studies of indium-mediated allylation of N-sulfonylimines in aqueous media.

Among the many synthetic methods available for the synthesis of amines, the addition of organometallic reagents to imines provides one of the most straightforward methods to amines. Loh. *et al.* [57] reported on an efficient method for the alkylation of a wide variety of imines via a one-pot condensation of aldehyde, amine (including aliphatic and chiral amines), and alkyl iodides using indium-copper in aqueous media. These authors demonstrated that the combination of In/Cu/ InCl₃, was an efficient system for the activation of amine-alkylation in water, to generate the corresponding products in high yields (eq 15).

Among the several metals screened, indium proved to be the best for this reaction, following the order for activation of the imine alkylation reaction: In > Zn > Al > Sn [57].

It was worthwhile noting that the same reactions carried out in organic solvents such as MeOH, THF, CH₂Cl₂, DMF, DMSO, and hexane afforded the desired product in much lower yields. Even aliphatic amines, such as benzylamine could also react efficiently with different aldehydes and secondary alkyl iodides to furnish the desired products in fairly good yields. As shown in eq 15, enantiomerically-enriched amino compounds were also obtained. The one-pot reaction employing various aldehydes and alkyl iodides condensed efficiently with *L*-valine methyl ester to generate the desired products in good yields and good diastereoselectivities. It was also worthwhile noting that even aliphatic aldehydes (cinnamaldehydes and nonyl aldehyde) were also good substrates for these reactions. A proposed reaction mechanism is shown in Scheme 13.

The reaction was initiated by a single electron transfer from indium-copper to alkyl iodide **a** to generate an alkyl

radical **b** (Scheme 13). This radical attacked the imine to furnish a radical intermediate **c**. Subsequent indium-promoted reduction of intermediate **c** and the quenching of the generated amino anion **d** in the presence of water, afforded the desired product **e** (Scheme 13).

As depicted above, the carbon-nitrogen double bond could be considered a radical acceptor, and therefore several radical addition reactions have been reported in organic solvents [58]. On the other hand, it has been shown that imine derivatives such as oxime ethers, hydrazone, and nitrones are excellent water-resistant radical acceptors for the aqueous-medium reactions using Et₃B as a radical initiator [59].

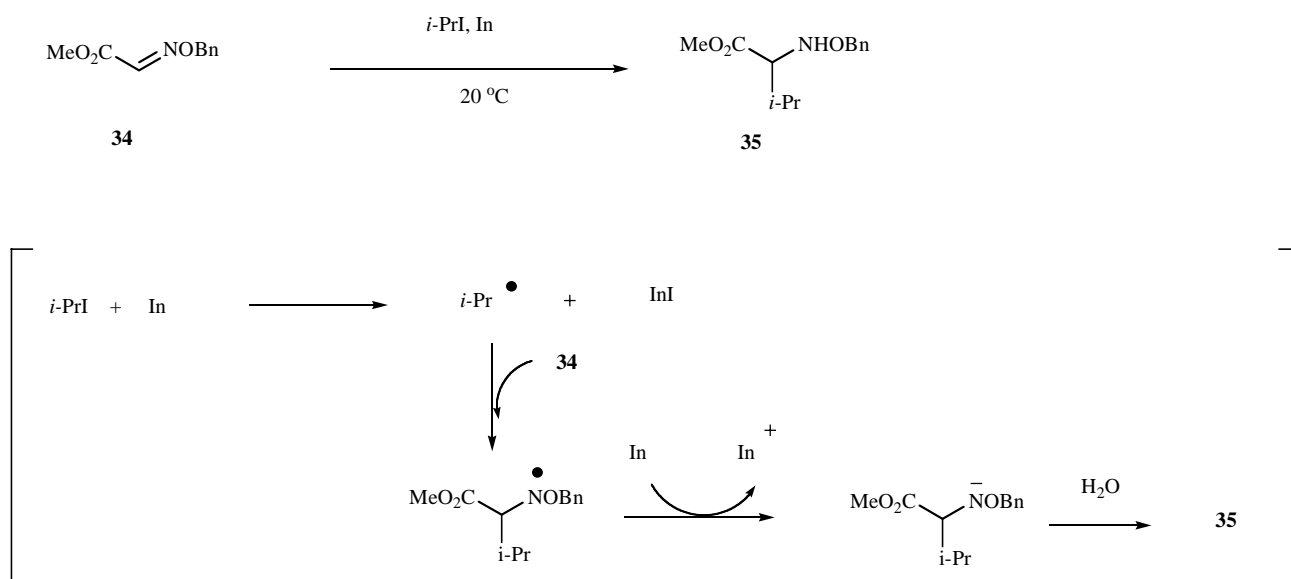
The reaction of glyoxylic oxime ether **34**, Scheme 14, with *i*-PrI (5 equiv) in H₂O-CH₂Cl₂ (4:1, v/v) and indium (7 equiv) afforded the *isopropylated* product **35** in 76% yield without formation of significant by-products [60].

It is noteworthy that no reaction of **34** occurred in the absence of water. This result suggests that water would be important for the activation of indium and for the proton-donor to the resulting amide anion. In the presence of galvinoxyl free radical (radical scavenger) the reaction did not proceed, purporting that a free radical mechanism based on the single electron transfer (SET) process from indium is operative.

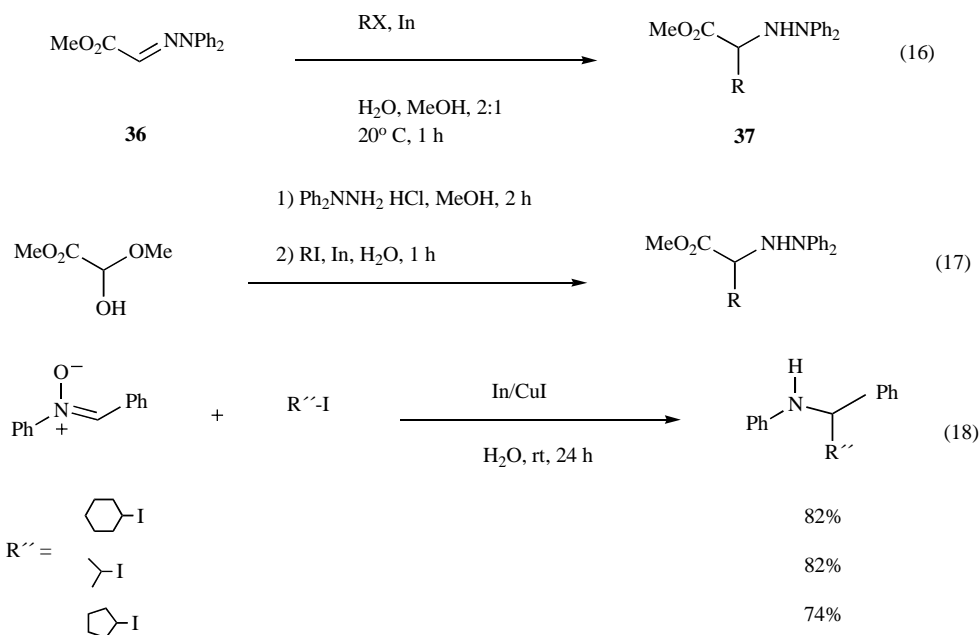
The indium-mediated alkyl radical addition to glyoxylic hydrazone **36** afforded α -aminoacids **37** (eq 16) [60].

Integration of multi-step chemical reactions into one-pot reactions is of great significance as an environmentally benign method. The indium-mediated reaction leading to the one-pot synthesis of α -aminoacid derivatives was therefore considered (eq 17).

More recently, Loh and coworkers [61] have attempted the indium-copper-mediated Barbier-type alkylation of nitrones in water to furnish amines and hydroxylamines.



Scheme 14. In-mediated reaction of oximes with alkyl halides in water.



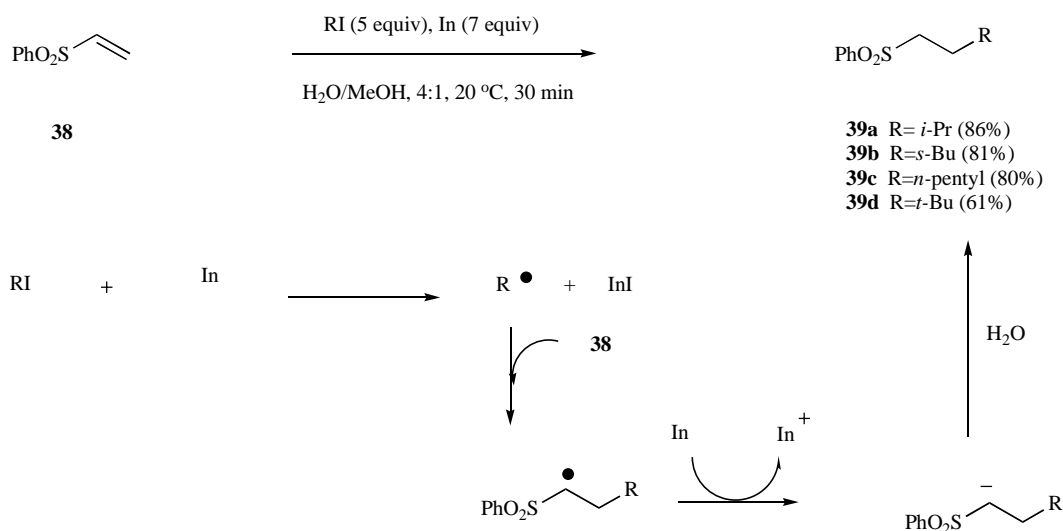
Among the different metals investigated, indium and zinc were observed to be effective metals for the activation of the alkylation reaction in water to obtain the corresponding amines (eq 18).

To test the utility of indium as a single-electron transfer radical initiator, the indium-mediated alkyl radical addition to electron-deficient C=C bonds (Scheme 15) was considered.

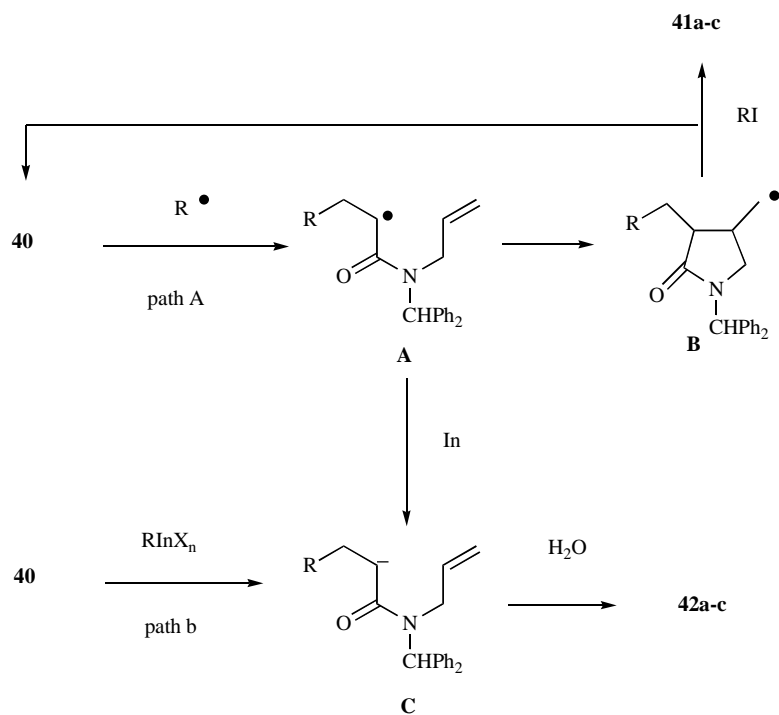
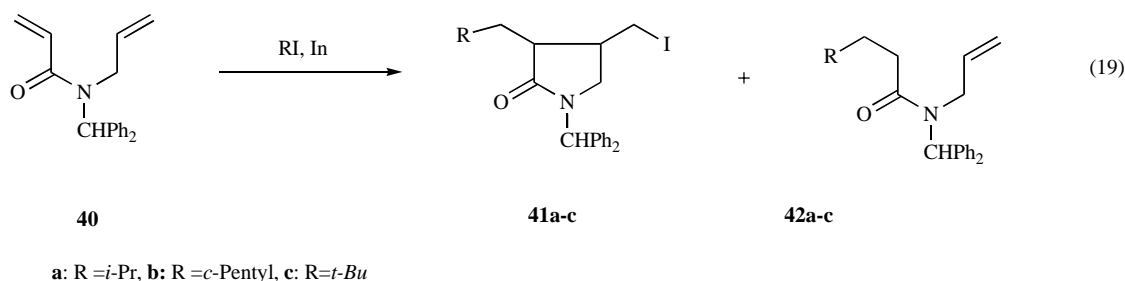
To a solution of phenylvinyl sulfone **38** and RI (5 equiv) in MeOH were added indium (7 equiv) and H₂O, and the reaction mixture was stirred at 20 °C for 30 min. As expected, **38** exhibits a good reactivity to render the desired alkylated products **39a-d** in good yields with no detection of by-products such as reduced products. The reaction proceeded by SET process from indium as shown in Scheme 15.

Strategies involving tandem radical reactions or radical annulations offer the advantage of multiple carbon-carbon bond formations in a single operation. Thus a number of extensive investigations to this effect were reported in recent years [62]. However, the aqueous-medium tandem construction of carbon-carbon bonds has not been widely explored, and therefore, tandem radical reactions in aqueous media have been a subject of recent interest [63].

Naito *et al.* [64] investigated the indium-mediated reaction of substrates having two different radical acceptors. At first, the tandem addition-cyclization-trap reaction (ACTR) of substrate **40** having acrylate and olefin moieties was examined (eq 19). To a suspension of **40** in water were added *i*-PrI (2 x 5 equiv) and indium (2 equiv), and then the reaction mixture was stirred at 20 °C for 2 h. The reaction proceeded smoothly affording the desired cyclic product **41a**



Scheme 15. Indium-mediated alkyl radical addition to electron-deficient C=C bond in water.

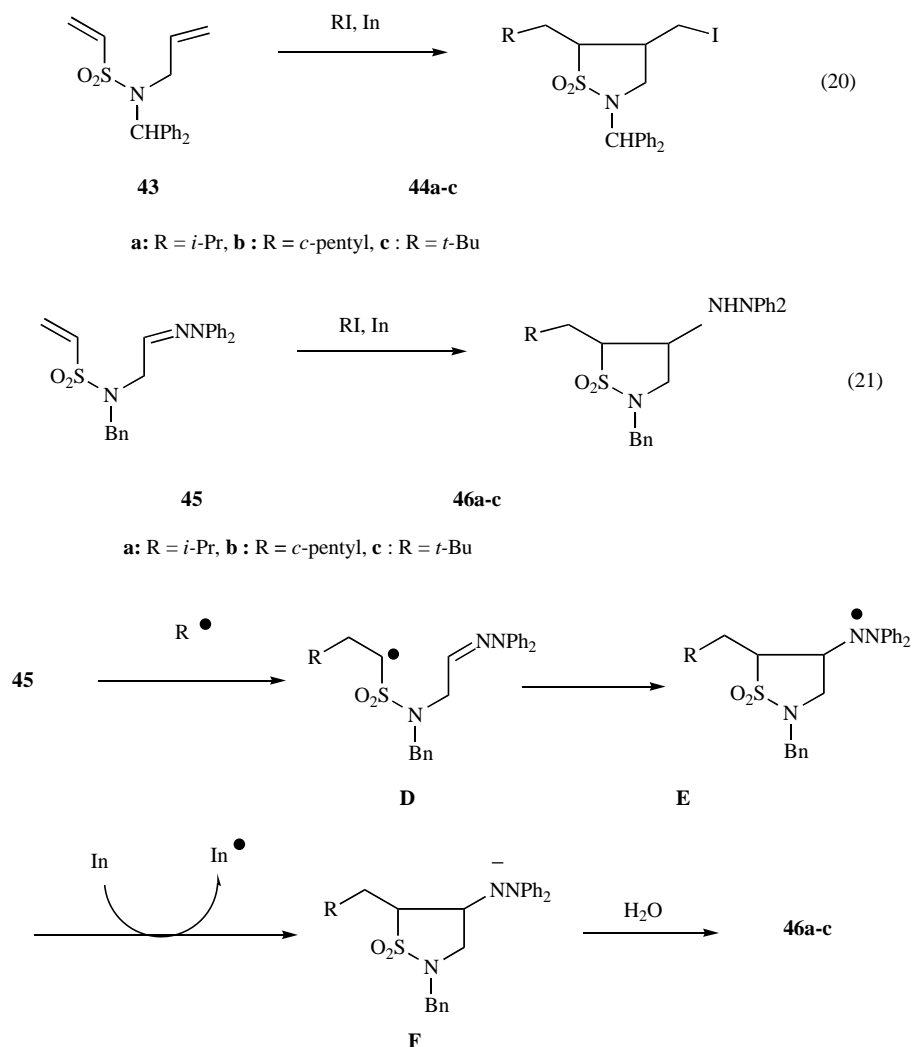


Scheme 16. Indium-mediated tandem addition-cyclization-trap reaction.

in 63% yield as a *trans/cis* mixture in 3:2:1 ratio, along with 13% yield of the addition product **42a**.

The preferential formation of cyclic products **41 a-c** could be explained by a radical mechanism (Scheme 16).

The indium-mediated reaction was initiated by SET to RI with generation of an alkyl radical which then attacked the electrophilic acrylate moiety of **40** to form the carbonyl-stabilized radical **A** (path A, Scheme 16). The cyclic



Scheme 17. Proposed reaction pathway for the indium-mediated radical-addition-cyclization of hydrazones in water.

products **41a-c** were obtained via intramolecular reaction of radical **A** with the olefin moiety followed by iodine atom-transfer reaction from RI to the intermediate primary radical **B**. Although there are many examples of anions adding to isolated double bonds, these reactions have been limited to lithium-mediated reactions [65].

Sulfonamides (electron-deficient alkenes) such as **43** (eq 20) have also been examined in indium-mediated tandem radical reactions [64]. As expected, sulfonamide **43** exhibited good reactivity to afford moderate and good yields of the desired cyclic products **44a-c** without the formation of other by-products.

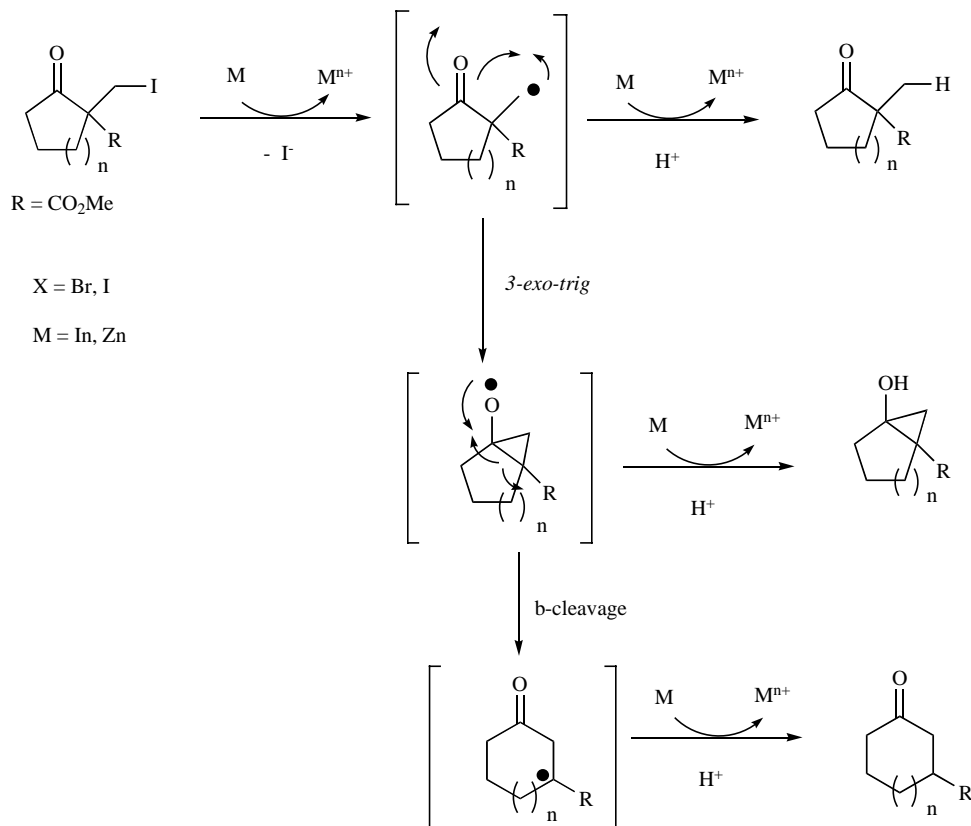
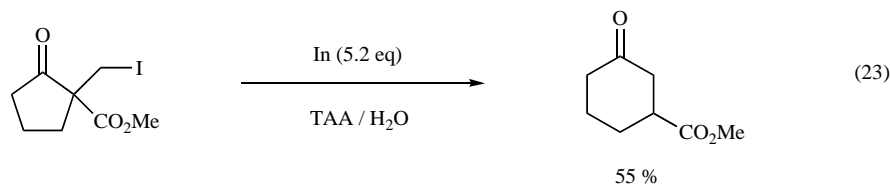
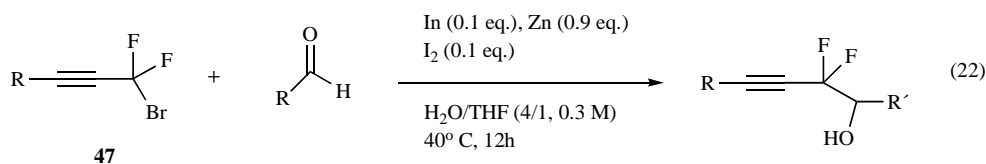
The indium-mediated tandem reaction of **43** with *i*-PrI in water afforded selectively the cyclic product **44 a** in 81% yield as a *trans/cis* mixture in 1:1.4 ratio, with no detection of simple addition products. Thus indium was found to be a highly promising radical initiator in aqueous media. Hydrazones connected with a vinyl sulfonamide group such as **45** have also been investigated in tandem-radical addition-cyclization reaction of imines (eq 21).

The radical reaction of **45** does not proceed via a catalytic radical cycle such as iodine atom-transfer; thus a

large amount of indium was required for a successful reaction to take place (Scheme 17).

The tandem reaction of hydrazone **45** with isopropyl radical was carried out in water-methanol for 5 h by using *i*-PrI (2 x 5 equiv) and indium (10 equiv). As expected, the reaction proceeded smoothly to render the *isopropylated* product **46 a** in 93% yield as a *trans/cis* mixture in a 1:1.2 ratio, without the formation of the simple addition product. The biphasic reaction of **45** in water-CH₂Cl₂ also proceeded effectively to afford 94% yield of **46a**. A cyclopentyl radical and a bulky *tert*-butyl radical worked well to give the cyclic product **46b** and **46c** in 86% and 42% yields, respectively. The stereochemical outcome for the cyclization of hydrazone **45** is almost the same as that in the case of olefin **43** (eq 20) in which *cis* products were the major products.

An intrinsic drawback of indium is the need for almost stoichiometric amounts of this relatively expensive metal, or as seen above, a large excess. In response to the cost factor, various combinations containing catalytic amounts of indium and a secondary cheaper metal (such as Al, Zn, Sn, or Mn) have been developed, but these protocols are limited to allylation of carbonyl compounds.



Scheme 18. Proposed reaction mechanism for the metal-mediated ring expansion of α -halomethyl cyclic β -keto esters.

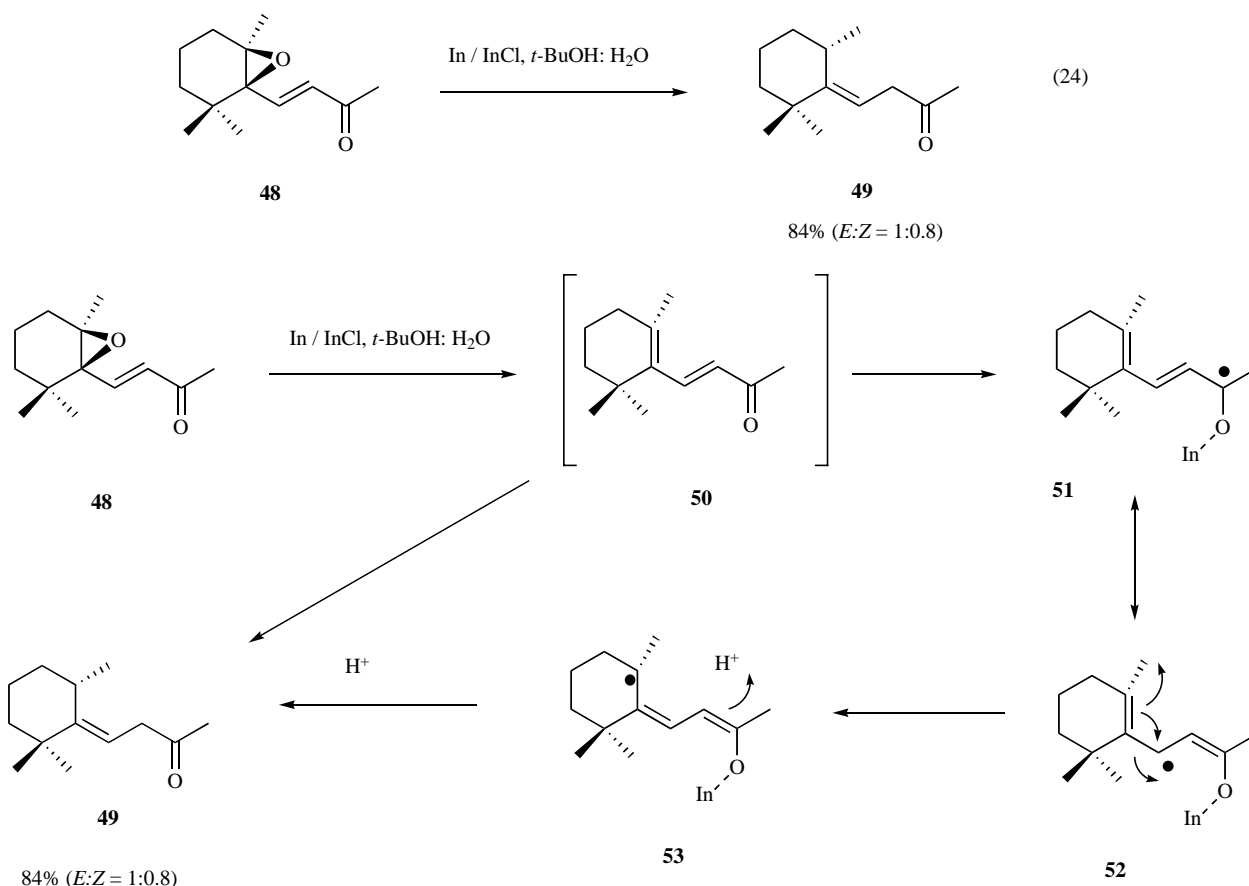
Hammond *et al.* [66] have recently synthesized *gem*-difluorohomopropargyl alcohols from *gem*-difluorohomopropargyl bromides **47** using indium and a catalytic amount of $\text{Eu}(\text{Otf})_3$ (5 mol%) as a water tolerant Lewis acid. Later on, the same authors employed a combination of Zn and catalytic amounts of indium and iodine (eq 22).

Only fluorinated propargyl alcohols were observed as products under the reaction conditions. The reaction is highly regioselective as the corresponding fluoroallenyl-alcohols were not detected [66].

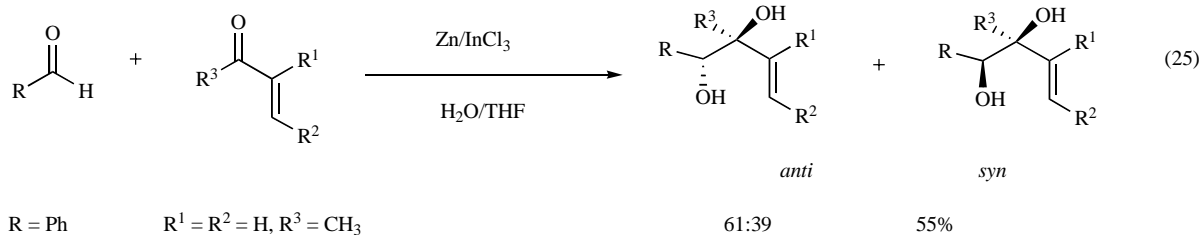
Among various types of radical reactions, radical cyclizations in the *5-exo-trig* and *6-exo-trig* manners are the most powerful and versatile methods for the construction of five- and six-membered ring systems. Recently, two-atom carbocyclic enlargement based on an indium-mediated Barbier-type reaction in water was reported [67]. A series of different ring-sized α -iodomethyl cyclic β -keto esters in a

mixture of *tert*-amyl alcohol (TAA) and water was examined (eq 23) [68].

The same ring expansions of α -iodomethyl cyclic β -keto esters with zinc powder, instead of indium powder were examined in a mixture of TAA (*tert*-amyl alcohol) and water (1:1). In these cases, the yields were surprisingly much increased. The presence of water in these reactions was found to be essential for an effective and high yielding of the ring-expanded products. Moreover, both bromomethyl and iodomethyl cyclic β -keto esters can be used for the ring-expansion reaction to provide 6-membered, 8-membered, 9-membered, 13-membered, and 16-membered products in yields ranging from 60 % upto 87% [68]. The reactions were extremely clean and operationally simple for isolation of products. A plausible reaction mechanism is depicted in Scheme 18.



Scheme 19. Plausible mechanism for the indium-mediated deoxygenation of epoxides in aqueous media.



The reaction is initiated by the first single electron transfer from metal (indium or zinc) to a α -halomethyl cyclic β -keto ester to form the corresponding methyl radical derivative, followed by 3-*exo-trig* cyclization and its β -cleavage. In this mechanism, only ring-expansion products are formed since there is no hydrogen donor such as a tin hydride or silicon hydride [68].

With a plethora of protective groups available for various types of functional groups, it is rather surprising that no practical protective groups have been developed for double bonds. Epoxidation can be used as a means of protecting double bonds, however, the successful implementation of this strategy would largely depend on the effective deoxygenation of epoxides back to alkenes.

Whereas indium metal has been used for so many reduction reactions and C-C bond forming reactions, it has not been exploited in the reduction of epoxides to form alkenes mediated by electron transfer from indium.

Murphy and collaborators [69], however, developed a facile and an environment-friendly protocol for the deoxy-

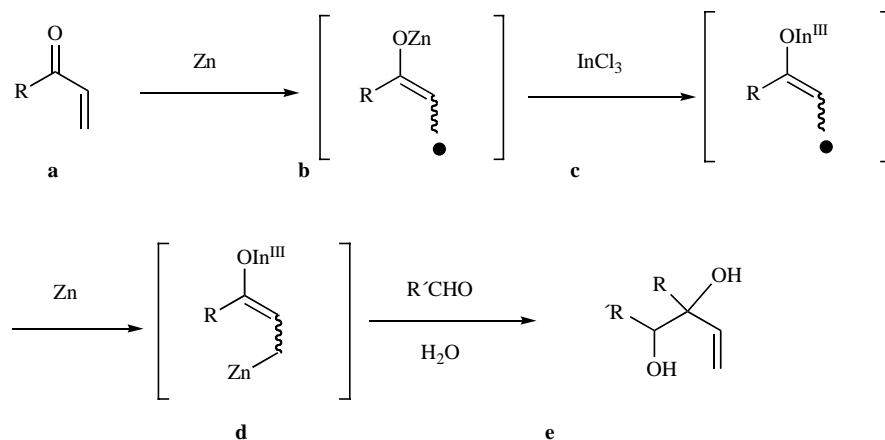
genation of epoxides with good radical-stabilizing groups adjacent to the oxirane ring, using indium metal and indium (I) chloride or ammonium chloride in alcohol / water mixtures (eq 24).

Oxirane **48** underwent smooth deoxygenation to afford the alkene **49** in an excellent 81% yield. The reaction sequence is depicted in Scheme 19.

The formation of alkene **49** can be explained via the reduction of the expected dienone intermediate **50** by indium metal (Scheme 19) [69].

Loh and collaborators [70] have very recently reported an efficient pinacol cross-coupling reaction of aldehydes and α,β -unsaturated ketones using Zn/InCl₃ in aqueous media. The 1,2-diols were thus obtained in moderate to good yields, with up to 93.7 % diastereoselectivity (eq 25).

A possible reaction mechanism is shown in Scheme 20. The reaction is initiated by a single electron transfer from zinc to the α,β -unsaturated ketone to form a radical enolate anion **b**. Fast trapping of the oxygen-metal bond in the radical enolate anion **b** by InCl₃ affords the γ -In(III)-substituted



Scheme 20. Proposed Mechanism for the Pinacol Formation.

allylic radical **c**. The radical **c** is further reduced by zinc to furnish the corresponding allylic zinc species **d**. Finally, coupling of the γ -In(III)-substituted allylic zinc species **d** with an aldehyde followed by quenching of the resulting 1,2-diolate with water generates the desired product **e**.

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