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Review

Synthetically useful metal-mediated radical transformations in water and aqueous media

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ABSTRACT

In this review non-carbon-centered radicals are used in water and aqueous mixtures to induce and accomplish several synthetically useful organic transformations such as Reformatsky reactions, alkylation and allylation reactions of carbonyl compounds, electron deficient alkenes and imine derivatives, radical conjugate additions, metal-mediated radical cyclizations, reductive cross coupling reactions and other coupling reactions, oxidation and reduction reactions in water. In doing so, the array of metal radicals used encompass elements from the main groups (IIIB, IVB, VB and VIB groups),

Abbreviations: ABCVA, 4,4′-azobis(4-cyanovaleric acid); ACCN, 1,1′-azobis(cyanocyclohexane); AcOH, acetic acid; ACTR, addition–cyclization–trap reaction; aq, aqueous; ATRA, atom transfer radical cyclization; BDE, bond dissociation energy; BHT, butylated hydroxytoluene; BNP, 2-bromo-2-nitropropane; $(BzO)_2$, dibenzoylperoxide; CAN, cerium ammonium nitrate; *cp*, cyclopentadienyl; CTBA, cetyl trimethylammonium hypophosphite; *de*, diastereomeric excess; DMF, dimethylformamide; dr, diastereoselectivity; *ee*, enantiomeric excess; EPHP, *N*-ethylpiperidine hypophosphite; ESI-MS, electrospray ionization mass spectrometry; Et, ethyl; Et_3B, triethylborane; EtOH, ethanol; HAT, hydrogen atom transfer; HMPA, hexamethylphosphoramide; $In(OAc)_3$, indium triacetate; *i*-PrI, *iso*propylodide; *i*-$PrNH_2$, *iso*propylamine; *i*-PrOH, *iso*propanol; Me, methyl; MeCN, acetonitrile; MeOH, methanol; MW, microwave; *n*-Bu_3SnH, tributyl tin hydride; OBz, benzyloxy; OEt, ethoxyl; OTBDMS, *tert*-butyldimethylsiloxy; $Pd(PPh_3)_4$, tetrakis(triphenylphosphine)palladium; Ph, phenyl; PhCOH, benzaldehyde; $PhSiH_3$, phenylsilane; PMP, *p*-methoxyphenyl; RCA, radical conjugate addition; r.t., room temperature; SDS, sodium dodecylsulfate; SET, single electron transfer; TAA, *tert*-amyl alcohol; *t*-BuOH, *tert*-butanol; TBHP, *tert*-butylhydroperoxide; THF, tetrahydrofuran; *vic*, vicinal.

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Metal-mediated radical reductions and oxidations in water

as well as transition metals. However, the important class of radical hydrometallation reactions of carbon–carbon multiple bonds in water is not the subject of this work.

1. Introduction

Nowadays, a vast array of organic synthetic transformations are realized by the use of main-group and transition metals, which assist in anchoring molecular reactive sites, such high-electron density groups or coordinate lone electron pairs of heteroatoms present in the molecules, thus filling or expanding the vacant metal orbitals and ensuing transformations. Thus transition metal-catalyzed reactions have contributed with enormous improvements to organic synthetic strategies. These metal-catalyzed reactions fall out the scope of this review.

Redox properties of transition metals also facilitate spontaneous or induced electron transfer processes. These latter give rise to discrete reaction intermediates such as radicals and radical ions, which control reactivity, regioselectivity and/or stereoselectivity of the reactions. To this effect, there have been comprehensive and interesting review articles on carbon–carbon bond formation reactions mediated by metal radical species in organic solvents [1a–d].

More recently, chemists have successfully started to explore the use of water in radical reactions, and the intervention of metal-centered radicals to accomplish organic synthetic transformations in this medium. Butler and Coyne have recently reviewed metal-mediated catalyzed organic transformations in water, including pericyclic reactions, olefin metasthesis, Mizoroki-Heck, Suzuki, and Snogashira reactions [2a]. Radical hydrometallation reactions of carbon–carbon multiple bonds (through silicon, germanium, and tin hydrides) in water have also been the subject of recent review articles [2b], and fall out the scope of the present work.

Most metal-mediated radical reactions in water are often presented in the literature under a certain metal-centered radical chemistry or category. However, as a vast group of metal-centered radicals show similar reactivity in water facilitating a common group of organic transformations such as carbon–carbon bond formation and carbon–heteroatom bond formation reactions, these will be presented under "types of reactions in water" rather than under a single metal-centered radical heading or subtitle.

Solvent polarity can have tremendous effects on the kinetics of reactions involving charged species in solution. On the other hand, reactions of neutral radicals are less sensitive to solvent polarity effects, mainly because charged species are not involved, and there is not a significant change in dipole moment in the progression from reactants to transition state. Consequently, instances where solvent *dramatically* affects the rate or selectivity of reactions involving neutral radicals are rare and noteworthy.

A recent example of a significant solvent effect has been reported by Ingold and co-workers, who found that rate constants for hydrogen atom abstractions from phenols are reduced in solvents where the phenol is stabilized by hydrogen bonding [1e,2c]. In this case, it is the reactivity of the substrate, not the radical, that is diminished as a result of a solute/solvent interaction. They concluded that there are large solvent effects on the rates of hydrogen atom abstraction from O–H bonds (and to a lesser extend from N–H bonds) [3–6].

However large or small solvents effects may be on the rates of radical reactions, radical reactivity in water has proved a source of facile and unexpected organic transformations.

Of the principal methods developed for the generation of radicals, redox processes based on electron-transfer deserve special mention. Chemical methods for electron-transfer oxidation involve the use of salts of high-valence metals such as Mn(III), Ce(IV), Cu(II), Ag(I), Co(III), V(V), and Fe(III). Among these, Mn(III) has received the most attention. In spite of the well-established and frequent use of this reagent for the generation of electrophilic carbon-centered radicals from enolic substrates, particularly in intramolecular processes, procedural problems associated with it have prompted the development of other oxidants of choice.

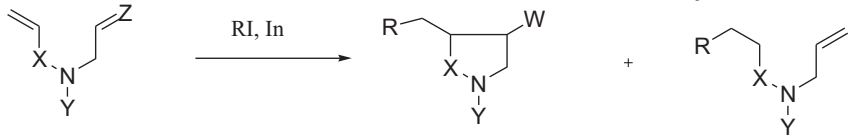
Undoubtedly, metal-mediated radical reactions have become an active area of research, which has seen a rebirth with the use of water and other aqueous systems, lowering the environmental impact of transition metal chemistry.

2. Metal radical-mediated carbon–carbon and carbon–sulfur bond formation reactions in water

2.1. Metal-mediated intramolecular radical cyclizations and ring-expansion reactions in water

Radical cyclization reactions in water involving non-metallic radical species have been reviewed by Li [7a]. On the other hand, Larry Yet has presented a thorough review on metal-mediated cyclization and ring-expansion reactions, some of them of radical nature and taking place mostly in organic solvents [7b].

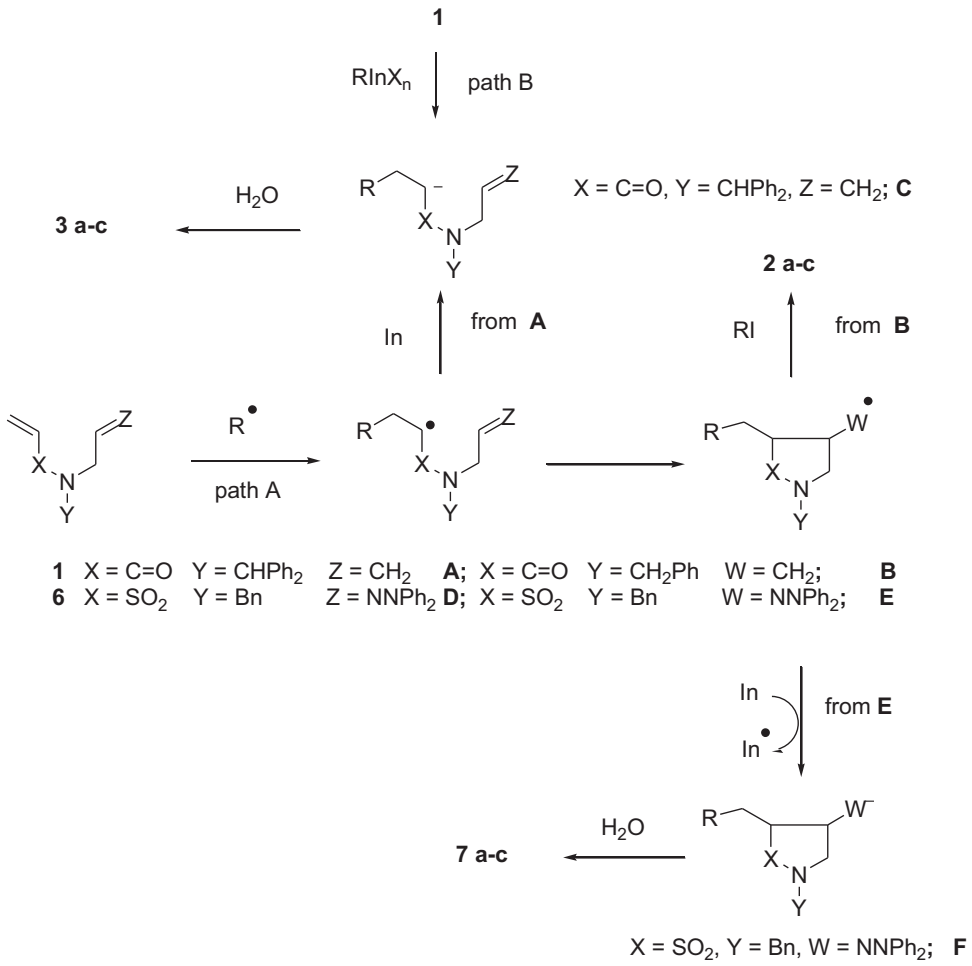
Strategies involving tandem radical reactions or radical annulations offer the advantage of multiple carbon–carbon bond formations in a single operation, therefore contributing to atom minimization and low environmental impact. Thus a number of extensive investigations to this effect have been reported in recent years [7c]. However, the aqueous-medium tandem construction of carbon–carbon bonds through metal radicals has not been widely explored, and therefore, tandem radical reactions in aqueous media have been a subject of recent interest [8].



1 X = C=O Y = $CHPh_2$ Z = CH_2 W = CH_2I **2a-c**
4 X = SO_2 Y = $CHPh_2$ Z = CH_2 W = CH_2I **5 a-c**
6 X = SO_2 Y = Bn Z = $NNPh_2$ W = $NHNPh_2$ **7 a-c**

3 a-c

(1)



Scheme 1. Indium-mediated tandem addition–cyclization–trap reaction mechanism (Ref. [10]).

Naito et al. [9a] investigated the indium-mediated reaction of substrates having two different radical acceptors. At first, the tandem addition–cyclization–trap reaction (ACTR) of substrate *1* having acrylate and olefin moieties was examined (Eq. (1)). To a suspension of *1* in water are added *i*-PrI and indium, and then the reaction mixture is stirred at 20 °C for 2 h. The reaction proceeds smoothly affording the desired cyclic product *2a* in 63% yield as a *trans*/*cis* mixture in 3:2.1 ratio, along with 13% yield of the addition product *3a*. Some of these reactions have been later reviewed by Majumdar and collaborators, and Perchyonok et al. [9b,c].

The preferential formation of cyclic products *2a–c* could be explained by a radical mechanism (Scheme 1).

The indium-mediated reaction is initiated by single electron transfer (SET) to RI with generation of an alkyl radical which then attacks the electrophilic acrylate moiety of *1* to form the carbonyl-stabilized radical A (path A, Scheme 1). The cyclic products *2a–c* are 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 [10]. The radical mechanisms for the formation of products *3a–c* and *7a–c* are also depicted in Scheme 1.

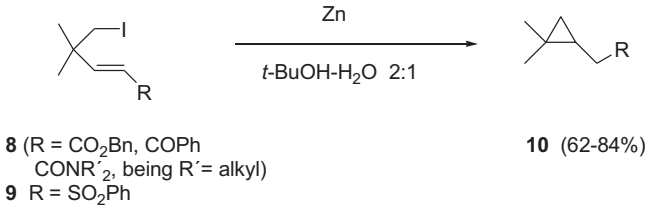
Sulfonamides (electron-deficient alkenes) such as *4* (Eq. (1)) have also been examined in indium-mediated tandem radical reactions in aqueous medium [10a]. As expected, sulfonamide *4* exhibits good reactivity to afford moderate and good yields of the desired cyclic products *5a–c* without the formation of other by-products.

The indium-mediated tandem reaction of *4* with *i*-PrI in water affords selectively the cyclic product *5a* in 81% yield as a *trans*/*cis* mixture in 1:1.4 ratio, with no detection of simple addition products (Eq. (1)). Thus indium is a highly promising radical initiator in aqueous media. Addition reactions to imines and hydrazones have recently been reviewed by Kobayashi and collaborators [10b] and by Friestad et al. [10c] Hydrazones connected with a vinyl sulfonamide group such as *6* (Eq. (1)) have also been investigated in tandem-radical addition–cyclization reaction of imines (Eq. (1), Scheme 1).

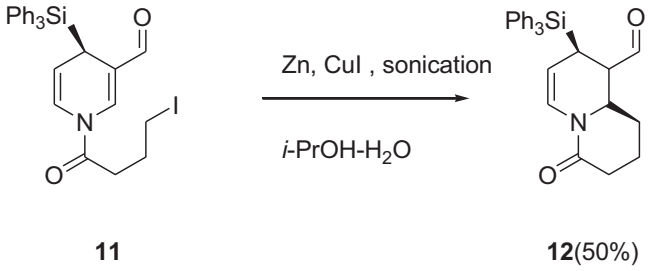
The radical reaction of *6* (Eq. (1)) does not proceed via a catalytic radical cycle such as iodine atom-transfer (*vide infra*); thus a large amount of indium is required for a successful reaction to take place (Scheme 1).

The tandem reaction of hydrazone *6* with *iso*propyl radical is carried out in water–methanol by using *i*-PrI and indium. As expected, the reaction proceeded smoothly to render the *iso*propylated product *7a* 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 *6* in water–CH_2Cl_2 also proceeds effectively to afford 94% yield of *7a*. A cyclopentyl radical and a bulky *tert*-butyl radical work well to give the cyclic product *7b*, and *7c* in 86% and 42% yields, respectively. The stereochemical outcome for the cyclization of hydrazone *6* is almost the same as that in the case of olefin *4* (Eq. (1)) in which *cis* products are the major products.

An intrinsic drawback of indium is the need for almost stoichiometric amounts of this relatively expensive metal, or as seen



Scheme 2. Formation of cyclopropanes via rare *3-exo-trig* cyclizations of β-iodoalkenyl substrates using Zn in *t*-BuOH/water (Ref. [11]).



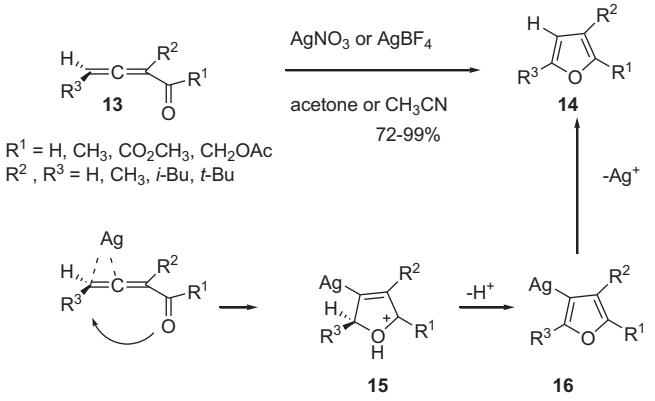
Scheme 3. 6-*exo intramolecular* RCA of 1,4-dihydropyridine derivatives under Luche conditions in *i*-PrOH/water (Refs. [17,18]).

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 (*vide infra*).

Togo reported the Zn-mediated formation of cyclopropanes *10* via rare 3-*exo-trig* cyclizations of substrates *8*, *9* (Scheme 2) [11]. Geminal dialkyl substitution is required. The zinc presumably functions as a single-electron reductant both in forming the initial alkyl radical and in reducing the incipient α-carbonyl or sulfonyl radical faster than the potential fragmentation can occur. This method compares well to similar reactions promoted by SmI_2, as the latter reagent is air-sensitive and mostly employed in organic solvents.

Mangeney performed a regio- and stereoselective 6-*exo* intramolecular radical conjugate addition (*intramolecular* RCA) of 1,4-dihydropyridine *11* under Luche conditions [12–16] (Scheme 3) [17,18]. The product is transformed into both (*K*)-lupinine and (*C*)-*epi*-lupinine *12*. This also constitutes an example of *exo-trig* radical cyclization described earlier for the formation of cyclopropane rings (Scheme 2). For *intermolecular* RCA reactions see Section 2.7.

In 1990, Marshall and co-workers published that, upon treatment with $AgNO_3$ or $AgBF_4$, allenals (*13*, R^1 = H) and allenones (*13*, R^1 = CH_3, alkyl) afford furans (*14*) (Scheme 4) [19]. These authors



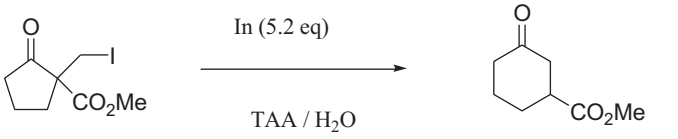
Scheme 4. Proposed reaction mechanism for the Ag-mediated synthesis of furans (Ref. [19]).

have developed this methodology and published many applications, always trying to improve the experimental conditions. The best set of conditions can be $AgNO_3/CaCO_3$/acetone/water [20] or 10% $AgNO_3$ on silica gel and hexane [21]. The following reaction pathway has been proposed: the process is initiated by coordination of Ag(I) with the allenyl π-system. Attack by the carbonyl oxygen would lead to the oxo-cation *15*. Ensuing proton loss from cation *15* would result in the Ag(I)–furan intermediate *16*. This could undergo direct protonolysis with loss of Ag(I) to afford furan product *14*. Deuterium incorporation experiments support this mechanism, though the involvement of radical ions could not be excluded [22]. It is important to point out that the choice of the transition-metal catalyst is crucial to form this kind of substituted furans, because, under similar conditions, allenic ketones deliver different products when catalyzed by Pd(II) or Hg(II) [23]. Presumably, some electron transfer pathways are also in operation in these reaction sequences as well.

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 has been reported [24]. A series of different ring-sized α-iodomethyl cyclic β-keto esters in a mixture of *tert*-amyl alcohol (TAA) and water has been examined (Eq. (2)) [25a].

The same ring expansions of α-iodomethyl cyclic β-keto esters with zinc powder, instead of indium powder have been examined in a mixture of TAA and water (1:1) (Eq. (2)). In these cases, the yields are surprisingly much increased. The presence of water in these reactions is 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 ring products in yields ranging from 60% up to 87% [25a]. The reactions are extremely clean and operationally simple for isolation of products. A plausible reaction mechanism is depicted in Scheme 5.

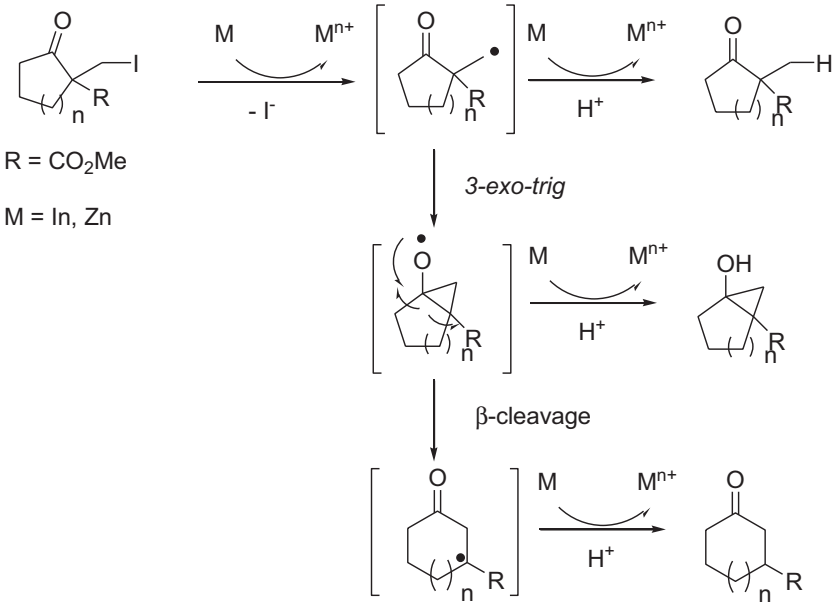
The reaction is initiated by the first single electron transfer from metal (indium or zinc) to a α-halomethyl cyclic β-keto ester to form the corresponding methyl radical derivative, followed by *3-exo-trig* cyclization and its β-cleavage. In this mechanism, only ring-expansion products are formed since there is no hydrogen donor such as a tin hydride or silicon hydride [25a].



(2)

Metal-mediated atom-transfer radical cyclization reactions (ATRC) in organic solvents have been discussed by several authors [25b–e]. Recently, Li and Cao [26a] have demonstrated the efficiency of *p*-methoxybenzenediazonium tetrafluoroborate–$TiCl_3$ 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 1. The reactions are carried out in EtOH–water mixtures.

The active species in the *p*-methoxybenzenediazonium tetrafluoroborate/$TiCl_3$-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



Scheme 5. Proposed reaction mechanism for the metal-mediated ring expansion of α-halomethyl cyclic β-keto esters (Ref. [25a]).

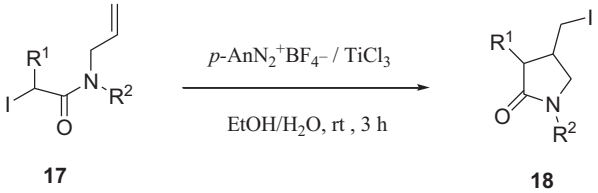
is close to the diffusion-controlled limit (>10^9 M^{-1} s^{-1}) which is about 100 times faster than the rate of phenyl radical addition to a monosubstituted alkene (*ca.* 3×10^7 M^{-1} s^{-1}). More importantly, the rate constant for the iodine atom-transfer from the substrate to the adduct radical is around 2.7×10^7 M^{-1} 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 [26a].

Majumdar and collaborators have recently reviewed some ATRC reactions mediated by thiyl radicals [26b]. One such atom transfer cyclization mediated by Mn(III) as one-electron oxidant afforded 2-arylbenzothiazoles in high yields from arylthioamides, according to Scheme 6 [26c].

Togo et al. [29] have undertaken the In-mediated cyclopropanation of 2,2-disubstituted 1,3-diiodopropanes and 1,3-dibromopropanes in dioxane solution of 20% water and THF solution of 20% water. However, the cyclopropanation of 2,2-disubstituted-1,3-dichloropropanes with indium powder can only be accomplished in ionic liquids.

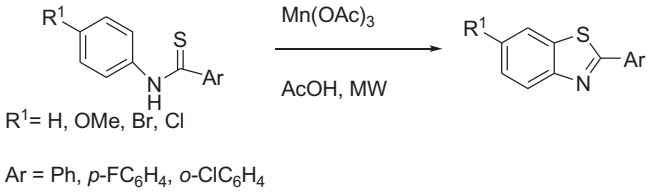
As regards the reaction mechanism, when 2,2-disubstituted-1,3-diiodopropanes are treated with In powder in THF solution of

Table 1
p-Methoxybenzenediazonium tetrafluoroborate/$TiCl_3$ mediated iodine atom-transfer radical cyclization in EtOH/H_2O at room temperature (3 h) (Ref. [26a]).



17 18

R^1	R^2	Product (yield, %)
H	Allyl	99
H	Ts	96
H	Ms	86
H	Me	40
Me	Allyl	96
Me	Ts	91



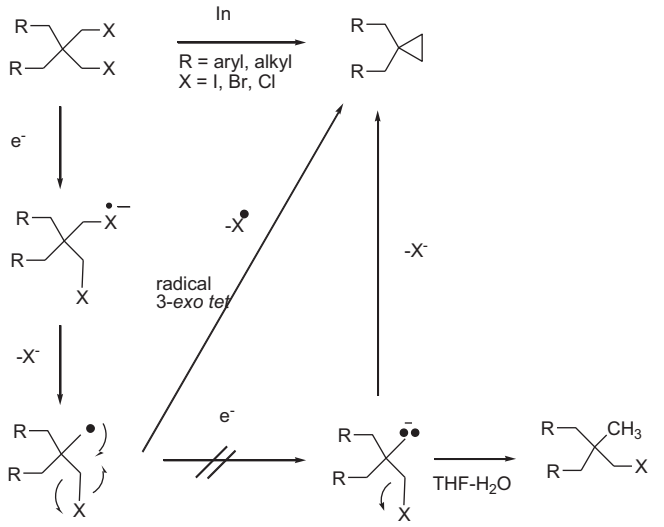
Scheme 6. Mn(III)-mediated thiyl radical cyclization of arylthioamides in AcOH under microwave irradiation (Refs. [26c–28]).

20% H_2O and dioxane solution of 20% H_2O, only 1,1-disubstituted cyclopropanes are obtained in high yields without the formation of 2,2-disubstituted 1-iodopropanes and 2,2-disubstituted propanes, which could be formed through the reactions of the corresponding carbanions with H_2O. This result suggests that the present cyclization reaction of 2,2-disubstituted-1,3-dihalopropane with In powder may proceed in the radical 3-*exo*-*tet* manner, as shown in Scheme 7.

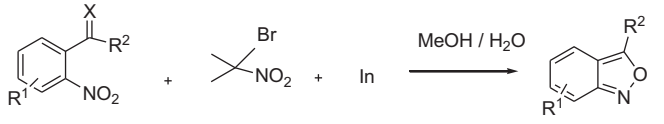
A rapid stereoselective route to the *trans* hydrindane ring system has been achieved by Khan et al. using tin-, indium-, and ruthenium-based reagents starting from tetrabromonorbornyl derivatives [30].

Kim and collaborators [31] have reported on the syntheses of 2,1-benzisoxazol derivatives in aqueous media employing indium and 2-nitrobenzaldehydes, in the presence of 2-bromo-2-nitropropane (BNP) in a methanol/water (v/v: 1:2) mixture (Scheme 8).

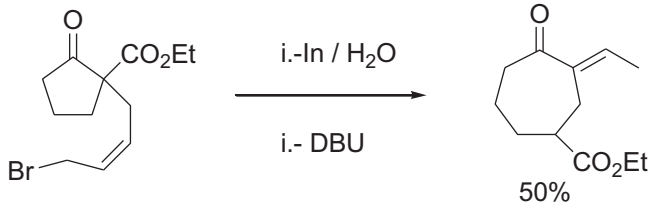
Usually, the reaction in an aqueous solution completes much faster than in methanol. The optimum condition is obtained when 2 equiv of BNP and 5 equiv of indium are applied in methanol/water (v/v = 1:2) with 2-nitrobenzaldehyde at 50 °C and the reaction time is diminished dramatically compared to the previous zinc-mediated reaction. It produces almost a quantitative yield of desired 2,1-benzisoxazole within 10 min. The role of BNP is to be an electron acceptor due to its low-lying antibonding π-orbital and the utility of BNP has been described by Russell et al. [32]. Furthermore, addition of di-*tert*-butyl nitroxide or *m*-dinitrobenzene has shown strong inhibitory effects. Di-*tert*-butyl nitroxide is a known radical scavenger and *m*-dinitrobenzene is known to quench radical anion intermediates [33,34a]. The reactions of nitrobenzaldehyde/BNP/indium in MeOH in the presence of di-*tert*-butyl



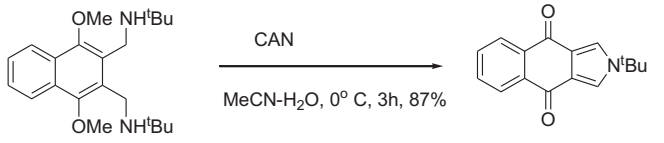
Scheme 7. Proposed reaction mechanism for the cyclopropanation of 2,2-disubstituted-1,3-dihalopropanes (Ref. [29]).



Scheme 8. Reactions of 2-bromo-2-nitropropane with nitrobenzaldehydes (X = O, R^2 = H) in water/methanol mixtures promoted by In (Ref. [31]).



Scheme 9. Indium-mediated intramolecular allylation-ring expansion reaction in water (Ref. [34b,c]).



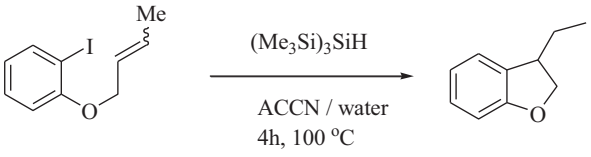
Scheme 10. CAN-mediated synthesis of benzo[*f*]*iso*indole-4,9-diones from 2,3-bis(aminomethyl)-1,4-dimethoxy naphthalenes in acetonitrile/water at 0 °C (Refs. [34d,35]).

nitroxide or *m*-dinitrobenzene have shown about 1 h initial retardation for each.

An interesting indium-mediated (Barbier-type) intramolecular allylation-ring expansion reaction in water has been reported by Haberman and collaborators, according to Scheme 9 (see also Section 2.6 – for allylation reactions) [34b,c].

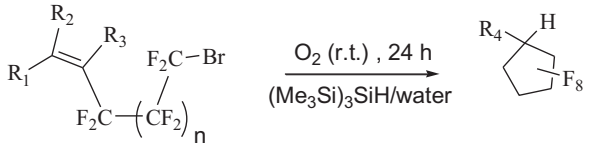
Oxidation of aminomethyl moieties to the corresponding aldehydes by cerium ammonium nitrate (CAN) has recently been used in the targeted synthesis of benzo[*f*]*iso*indole-4,9-diones from 2,3-bis(aminomethyl)-1,4-dimethoxy naphthalenes, according to Scheme 10 [34d,35].

The radical cyclization in water of 1-((*E*)-but-2-enyloxy)-2-iodobenzene (*19*) to afford 3-ethyl-2,3-dihydrobenzofuran (*20*) in 85% yield (Eq. (3)) has been reported, when $(Me_3Si)_3SiH$ and an azo initiator ACCN (1,1′-azobis(cyanocyclohexane)) are employed [36]. In this account, no atom transfer is observed in the presence of the hydrogen donor $(Me_3Si)_3SiH$.



19 **20,** 85% (3)

In another account, 6-bromo-3,3,4,4,5,5,6,6-octafluoro-1-hexene *21* [2b] is subjected to reaction with $(Me_3Si)_3SiH$ and dioxygen in water, and obtained the *exo-trig* cyclization product 1,1,2,2,3,3,4,4-octafluoro-5-methylcyclopentane *22* (Eq. (4)) in 76% yield (isolated) [37,38].



21 R_1=R_2=R_3= H, n = 2
23 R_1=R_2=R_3= F, n = 1
22 R_4 = CH_3
24 R_4 = F (4)

Though the measurement of the rate constant for cyclization in the heterogeneous water system is difficult to be obtained, the cyclohexane cyclized product has not been observed in water under the reaction conditions reported. No uncyclized-reduced product is either observed [2b,38a].

Analogously, cyclization of 5-bromo-1,1,2,3,3,4,4,5,5-nonafluoro-pent-1-ene *23* in water triggered by $(Me_3Si)_3SiH$/dioxygen leads to nonafluorocyclopentane, the *endo-trig* cyclization product *24* in 68% yield (isolated). No reduced product could be isolated from the reaction mixture. The reaction carried out in benzene-d_6 does not lead to cyclization product (Eq. (4)) [2b,38a].

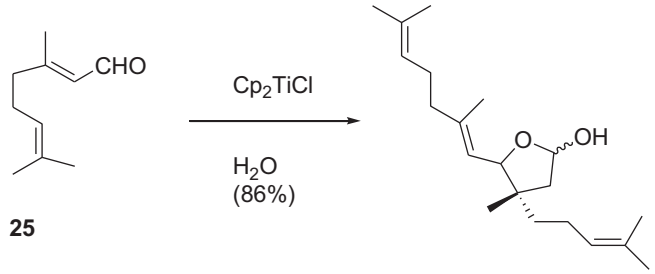
Notably, the radical hydrosilylation product derived from allylic alcohol [39] in water, only affords an open chain product (99% isolated yield), as opposed to allylamine where a cyclic product (2,2-bis(trimethylsilyl)-1,2-azasilolidine) is observed (Scheme 11). This notorious difference could be related to the difference in the nucleophilicity of oxygen- and nitrogen-centered radicals in water, as opposed to organic solvents [39].

2.2. Metal-mediated homocoupling and intermolecular radical cyclizations in water

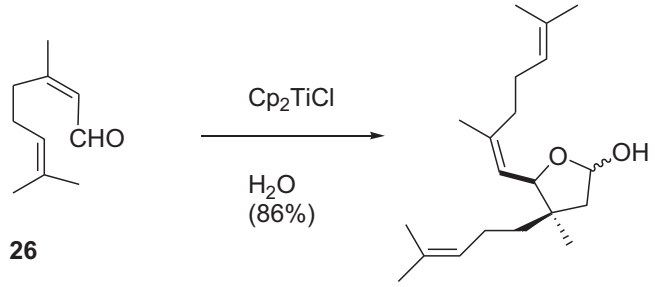
In the presence of water, titanocene(III) complexes are reported [35a,b] to promote a stereoselective carbon–carbon bond-forming reaction that provides γ-lactols by radical coupling between aldehydes and conjugated alkenals. The method is useful for both intermolecular reactions and cyclizations. The relative stereochemistry of the products can be predicted with confidence with the aid of model Ti-coordinated intermediates. The procedure can be carried out enantioselectively using chiral titanocene catalysts. Thus, the Ti(III) homocoupling of geranial *25* is achieved (Scheme 12), and that of neral *26* is obtained according to these techniques (Scheme 13).

When 3,3,4,4-tetrafluoro-1,5-hexadiene *27* is allowed to react in water with $(Me_3Si)_3SiH$/dioxygen and C_2F_5I, product *28* is obtained

Scheme 11. Proposed mechanism for formation of cyclic product 2,2-bis(trimethylsilyl)-1,2-azasilolidine from the hydrosilylation reaction of allyl amine in water (Ref. [40]).

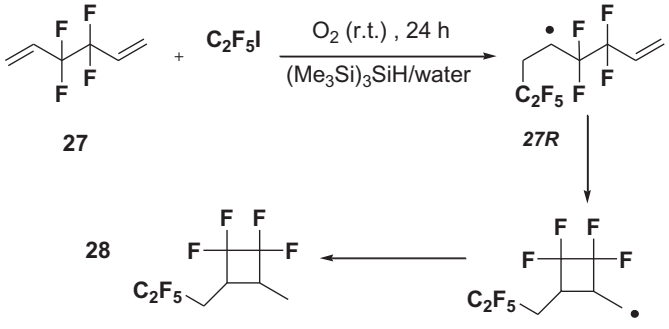


Scheme 12. Ti(III)/H_2O-promoted homocoupling of geranial *25* (Ref. [35a,b]).



Scheme 13. Ti(III)/H_2O-promoted homocoupling of neral *26* (Ref. [35a,b]).

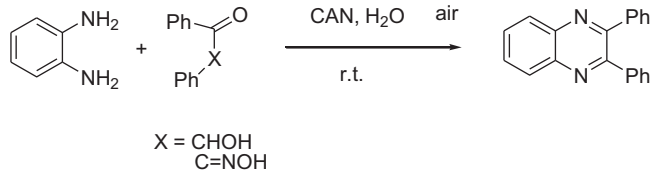
in 61% yield (the 4-*exo* cyclization product), based on C_2F_5I (Eq. (5)).



(5)

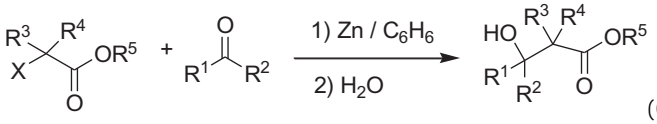
Though cyclobutanation is an uphill process due to considerable strain in ring formation, Dolbier found that fluorinated cyclobutanes appear to be less strained than their hydrocarbon counterparts and that fluorinated 4-pentenyl radicals *27R* (Eq. (5)) cyclize both in a favored kinetic and thermodynamic manner [38].

The question why 4-pentenyl radical *27R* (Eq. (5)) prefers to cyclize in an *exo* fashion to render the four-membered ring compound *28* in water is not yet clear. Fluorinated 4-pentenyl radical derived from *23* (Eq. (4)) cyclizes in an *endo* fashion to yield the five-membered ring nonafluorocyclopentane (Eq. (4)).



Scheme 14. Synthesis of quinoxaline derivatives by CAN in water at room temperature (Ref. [37]).

The direct conversion of α-hydroxy ketones and α-keto oximes into quinoxaline derivatives in the presence of a catalytic amount of CAN, via metal-catalysis followed by *in situ* trapping with aromatic 1,2-diamines in water was reported by Shaabani and Maleki, and illustrated in Scheme 14 [37].

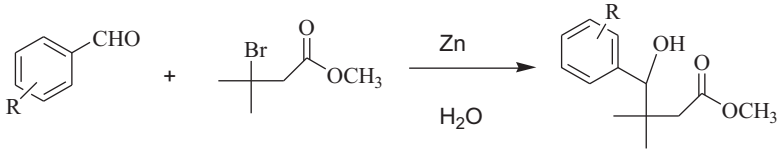


(6)

2.3. Reformatsky reactions in water

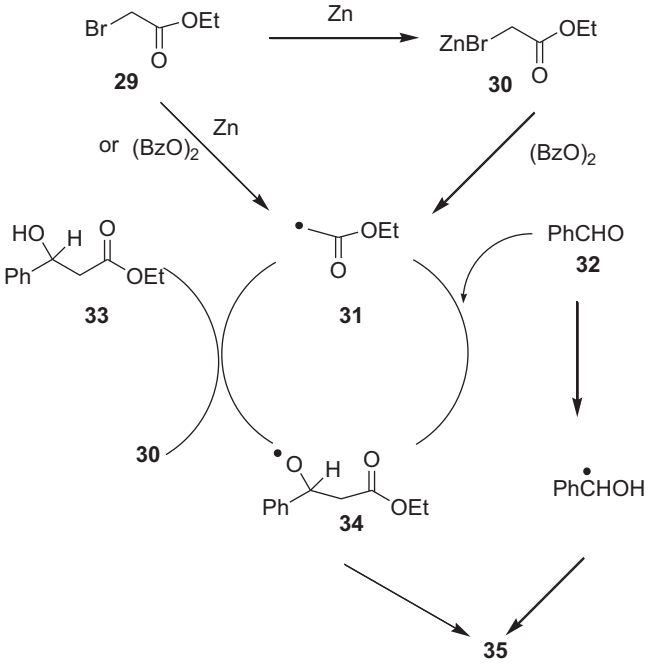
The Reformatsky reaction (Eq. (6)) between a 2-halo ester and a carbonyl compound in the presence of Zn was the first example of a large number of now commonly used carbon–carbon bond forming reactions: the addition of organometallic reagents to the carbonyl group. For nearly a century, these reactions were believed to require strictly anhydrous and oxygen-free conditions. Dolbier and collaborators have reviewed Reformatsky reactions in organic solvents, using a variety of metals such as Zn, Cr, and In in organic solvents [41a]. Only during the past decade chemists have witnessed numerous examples of one-step reactions between organic halides, a reactive metal, and an electrophilic substrate commonly a carbonyl compound, which proceed not only in wet solvents, but sometimes in water or salt solutions [41b,c]. Many of these procedures give addition products in preparative yields, comparable or superior to those obtained with preformed organometallic reagents under anhydrous conditions.

Bieber et al. [42] have 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 ineffective (*vide infra*) [43a]. 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 methyl 3-bromo-3-methylbutanoate (Eq. (7)).



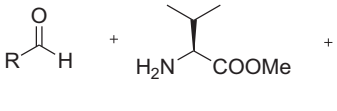
(7)

From the mechanistic point of view, the reaction is inhibited by galvinoxyl and hydroquinone, which is consistent with a radical mechanism of two Single Electron Transfer (SET) processes proposed by Chan [43a].



Scheme 15. Proposed mechanism for the Reformatsky reaction in water (Ref. [42]).

Li reviewed some Zn-mediated Reformatsky reactions in water in 2005 [7a]. In Scheme 15, an alternative radical chain mechanism is postulated by the authors, which does not involve hydrogen abstraction [42]. When Zn reacts with *29* (Scheme 15), it produces directly the Reformatsky reagent *30*. This will react with water to form ethyl acetate or with a benzoyl radical to form benzoate and radical *31* which adds to the aldehyde *32*, giving the oxyl radical*34*. Reduction of the intermediate *34* by another molecule of Reformatsky reagent *30* produces the final adduct *33* and a new radical *31* to continue the chain. Alternatively, the initial radical *31* may be produced by bromine abstraction from *29*, either by a phenyl radical or on the zinc surface. Formation of compounds *35* provides a termination step.

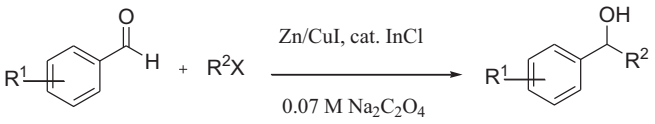


L-valine

Reformatsky reactions in THF mediated by Sm have been thoroughly reviewed by Kagan, and some examples with SmI_2-mediation have been documented in water [43b].

2.4. Radical alkylation reactions of carbonyl compounds, imine derivatives and electron-deficient alkenes in water

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 [44,45]. According to Eq. (8), a series of alkyl halides can be used to afford alkylated alcohols in fairly good yields.



R^1 = 4-CN	R^2 = cyclohexyl iodide	71%
	*iso*propyl iodide	85%
	tert-butyl iodide	30%

(8)

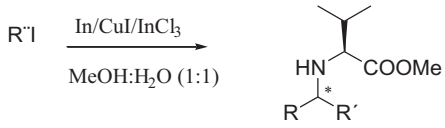
An interesting alkylative amination of aldehydes has been reported by Porta and collaborators [46]. The strategy consists of an aqueous acidic $TiCl_3$ solution that promotes alkylative amination of aldehydes in a one-pot reaction involving up to four components, according to the stoichiometry of Scheme 16.

The reactions are carried out by adding the phenyldiazonium salt, as the fluoroborate (method I) or as the chloride (method II), portion wise over 2 h at 20 °C to a solution containing *36*, *37*, *38*, and $TiCl_3$ under N_2 atmosphere (Scheme 16).

The mechanism proposed (Scheme 17) involves generation of phenyl radicals by a redox process (i), which abstract an iodine atom from RI to generate the alkyl radical which adds to the benzaldehyde–amine adduct, protonated imine derivative, to generate an aminyl radical cation (iv) which upon further reduction by Ti(III) generates the alkylative amination products *39*.

Bieber and collaborators [47] have treated benzylic chlorides in aqueous dibasic potassium phosphate under silver catalysis with aromatic aldehydes in the presence of zinc dust to give 1,2-diaryl alcohols in moderate to good yields (Scheme 18). Dimerization to bibenzyls and reduction of the halide are important side reactions. A wide range of substituted aromatic and heteroaromatic aldehydes and of substituted benzylic chlorides can be used. Aliphatic aldehydes and ketones are unreactive. A mechanism of two SET on the metal surface is proposed.

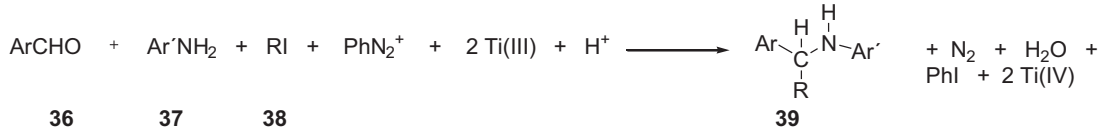
Among the many synthetic methods available for the synthesis of amines, the addition of organometallic reagents to imines provides one of the most straightforward methods to amines. Loh et al. [48] have reported on an efficient method for the alkylation of a wide variety of imines via a one-pot condensation of aldehyde, amine (including aliphatic and chiral amines), and alkyl iodides using indium–copper in aqueous media. These authors have demonstrated that the combination of In/CuI/$InCl_3$, is an efficient system for the activation of amine-alkylation in water, to generate the corresponding products in high yields (Eq. (9)).



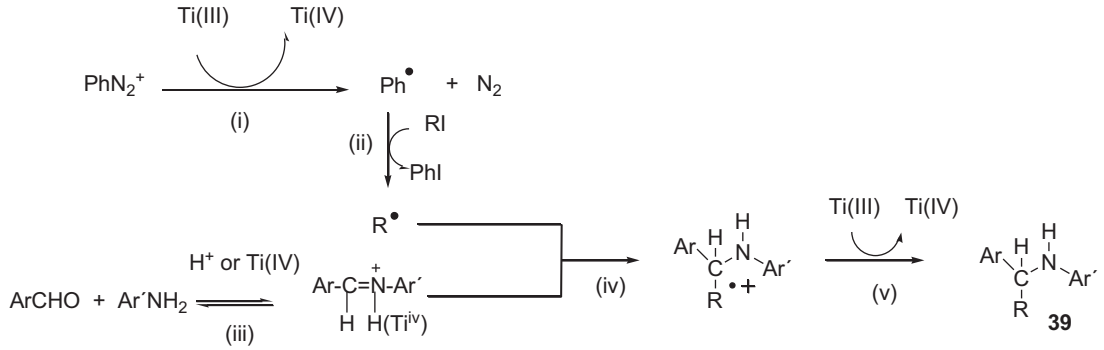
(9)

Among the several metals screened, indium is the best for this reaction, following the order for activation of the imine alkylation reaction: In > Zn > Al > Sn [48]. Li and co-workers have reported the conjugate addition of the alkyl group to enamides mediated by zinc in aqueous NH_4Cl to generate α-amino acid derivatives [7a].

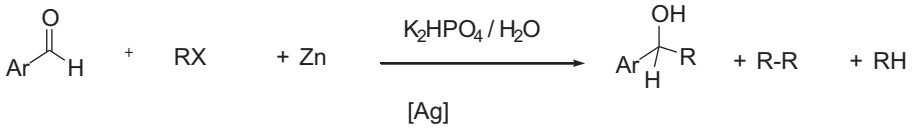
The same reactions carried out in organic solvents such as MeOH, THF, CH_2Cl_2, DMF, DMSO, and hexane afford the desired product in much lower yields. Even aliphatic amines, such as benzylamine could also react efficiently with different aldehydes and secondary alkyl iodides to furnish the desired products in fairly good yields. As shown in Eq. (9), enantiomerically enriched amino compounds are also obtained. The one-pot reaction employing various aldehydes and alkyl iodides condensed efficiently with



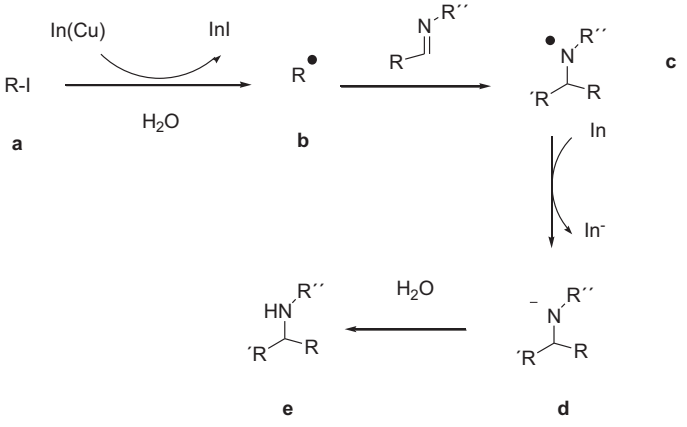
Scheme 16. Alkylative amination of aldehydes with Ti(III) using alkyl iodides, phenyldiazonium salts in acididc water (Ref. [46]).



Scheme 17. Proposed mechanism for the alkylative amination of aldehydes (Ref. [46]).



Scheme 18. Alkylation of aldehydes with aqueous dibasic potassium phosphate under silver catalysis (Ref. [47]).



Scheme 19. Proposed reaction mechanism for the alkylation of imines in aqueous media.

L-valinemethyl ester to generate the desired products in good yields and good diastereoselectivities. It is also worthwhile noting that even aliphatic aldehydes (cinnamaldehydes and nonyl aldehyde) are also good substrates for these reactions. A proposed reaction mechanism is shown in Scheme 19.

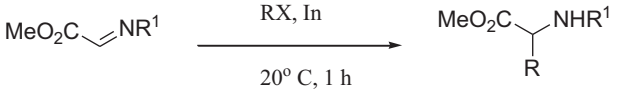
The reaction is initiated by a single electron transfer from indium–copper to alkyl iodide to generate an alkyl radical b (Scheme 19). This radical attacks the imine to furnish a radical intermediate c. Subsequent indium-promoted reduction of intermediate c and the quenching of the generated amino anion d in the presence of water, affords the desired product e (Scheme 19).

As depicted above, the carbon–nitrogen double bond can be considered a radical acceptor, and therefore several radical addition reactions have been reported in organic solvents [10b,49]. On the other hand, it has been shown that imine derivatives such as oxime ethers, hydrazones, and nitrones are excellent water-resistant radical acceptors for the aqueous-medium reactions using Et_3B as a radical initiator [50].

The reaction of glyoxylic oxime ether *40*, Eq. (10), with *i*-PrI in H_2O–CH_2Cl_2 (4:1, v/v) and indium affords the *iso*propylated product *41* in 76% yield without formation of significant by-products [51].

It is noteworthy that no reaction of *40* occurs 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 does not proceed, purporting that a free radical mechanism based on the single electron transfer (SET) process from indium is operative.

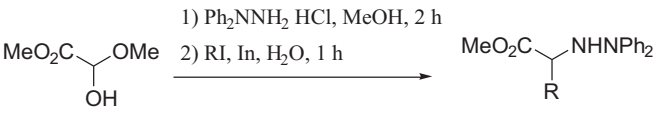
The indium-mediated alkyl radical addition to glyoxylic hydrazone *42* affords α-aminoacids *43* (Eq. (10)) [52].



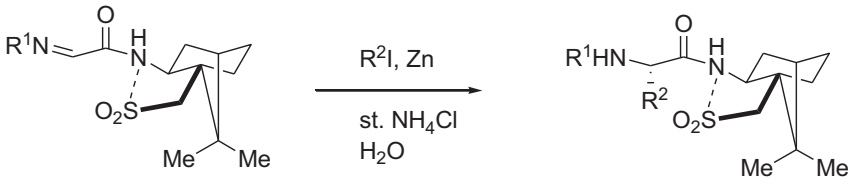
40 R^1 = OBn H_2O, CH_2Cl_2, 4:1 **41** R^1 = OBn, R = *i*Pr
42 R^1 = NPh_2 H_2O, MeOH, 2:1 **43** R^1 = NPh_2, R = alkyl

(10)

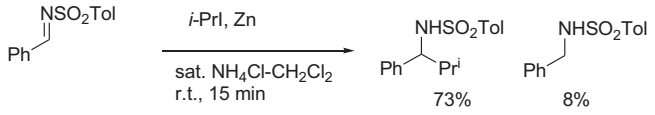
Integration of multi-step chemical reactions into one-pot reactions is of great significance as an environmentally benign method. The indium-mediated reaction leading to the one-pot synthesis of α-aminoacid derivatives has therefore been considered (Eq. (11)).



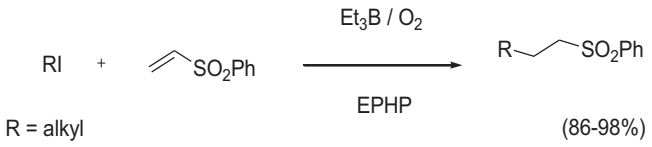
(11)



Scheme 20. Zn-mediated alkylation of imine derivatives using alkyl iodides in water (Ref. [53a]).

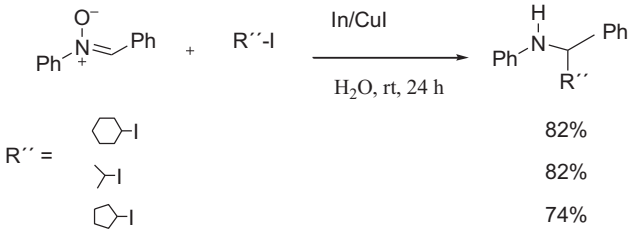


Scheme 21. Zn-mediated *iso*propyl radical addition to *N*-sulfonylimines in saturated NH_4Cl (aq)–CH_2Cl_2 mixtures at room temperature (Ref. [53b]).



Scheme 23. Alkylation reactions of sulfones using *N*-ethylpiperidine hypophosphite initiated by Et_3B/O_2 in water (Ref. [54b]).

More recently, Loh and coworkers [52] have attempted the indium–copper-mediated Barbier-type alkylation of nitrones in water to furnish amines and hydroxylamines. Among the different metals investigated, indium and zinc are observed to be effective metals for the activation of the alkylation reaction in water to obtain the corresponding amines (Eq. (12)).



(12)

Ueda has proposed a zinc-mediated diastereoselective addition of alkyl iodides to imines in water [53a] (Scheme 20).

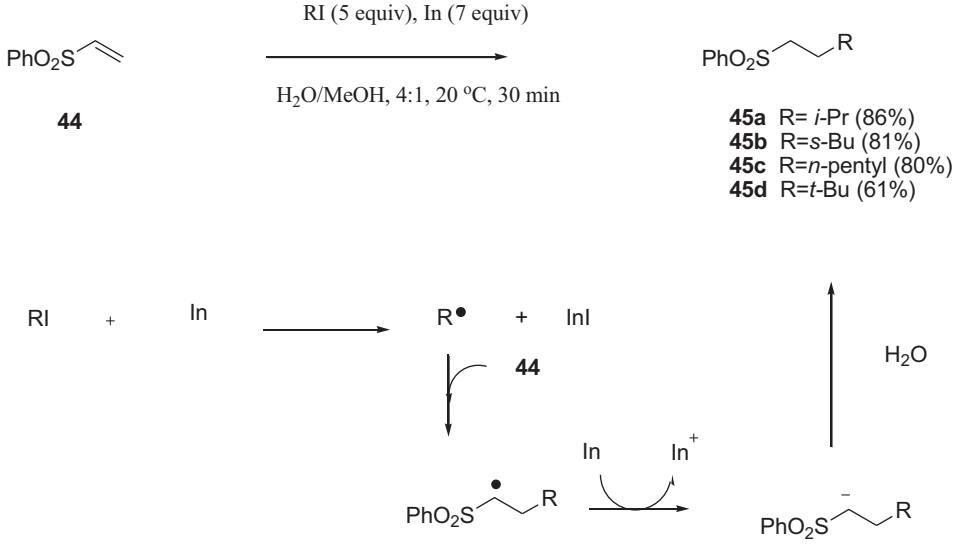
The addition of alkyl radicals to *N*-sulfonylimines has been attempted by Naito and collaborators using Zn, in a NH_4Cl–H_2O and CH_2Cl_2 as a cosolvent, according to Scheme 21. The mechanism proposedis a SET reaction from Zn metal [53b]. Mechanistic proofs include quenching of the reaction in the presence of radical scavenger galvinoxyl free radical.

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 22) has been considered. To a solution of phenylvinyl sulfone *44* and RI in MeOH are added indium and H_2O, and the reaction mixture is stirred at 20 °C for 30 min. As expected, *44* exhibits a good reactivity to render the desired alkylated products *45a–d* in good yields with no detection of by-products such as reduced products (Scheme 22). The reaction proceeds by SET process from indium as shown in Scheme 22.

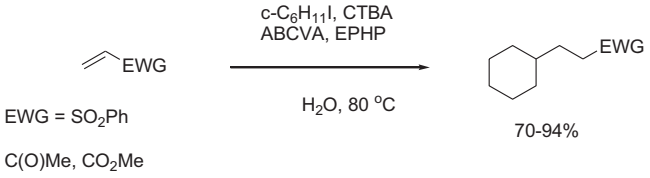
In addition, the alkylation of sulfones can also be carried out in the absence of metals and in water. Jang reported the use of *N*-ethylpiperidine hypophosphite (EPHP) as a substitute for *n*-Bu_3SnH in radical conjugate additions (RCAs, see Section 2.7) to phenyl vinyl sulfone (Scheme 23) [54b].

α,β-Unsaturated esters and ketones can also be used as alkyl radical acceptors with reduced yields (for radical conjugate additions, RCA, see Section 2.7). Some of these reactions have been reviewed in 2005 by Li [7a]. Significantly, use of the initiator 4,4-azobis(4-cyanovaleric acid) (ABCVA) in conjunction with cetyltrimethylammonium bromide (CTAB) allows performance of the reaction in water (Scheme 24) [55]. The surfactant can be omitted if tetraalkylammonium hypophosphites are employed instead of EPHP [56] (see Section 2.7 – for intermolecular RCA reactions [57–66]).

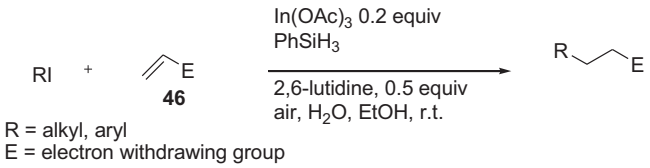
Miura, Hosomi et al. have recently developed a convenient In(III)-catalyzed intermolecular radical addition of organic iodides



Scheme 22. Indium-mediated alkyl radical addition toelectron-deficient C=C bond in water.



Scheme 24. Alkylation of sulfone derivatives using *N*-ethylpiperidine hypophosphite and an azo radical initiator (ABCVA) in water (Ref. [55]).



Scheme 25. In-silane-mediated addition of organic iodides to electron deficient alkenes in EtOH:H_2O (Ref. [67]).

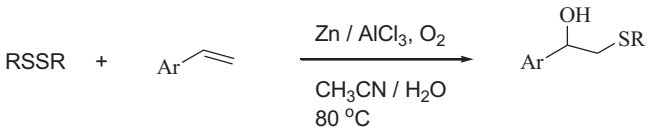
to electron-deficient alkenes [67]. In the presence of phenylsilane and catalytic amounts of indium(III) acetate, organic iodides add to electron deficient alkenes, according to Scheme 25.

The mechanism for this useful catalytic reaction is illustrated in Scheme 26.

The first step is the formation of $(AcO)_2InH$ by hydride transfer from $PhSiH_3$ to $In(OAc)_3$. The indium hydride undergoes H-abstraction by dioxygen from air to give *47* $(AcO)_2$–In•. The active species abstracts halogen from a halide *48* (R–X) to generate the corresponding carbon radical R• and $(AcO)_2InX$. The addition of R• to an alkene *46* followed by H-abstraction from indium hydrides (In–H) gives the corresponding adduct $RCH_2CH(•)E$ with regeneration of indium radicals (In•). The indium salt formed$(AcO)_2InX$ is converted into In–H by the reaction with $PhSiH_3$ in ethanol/water. The formation of *49*, RH, is the result of direct H-abstraction of R• from InH. The successive addition of R• to two molecules of alkene *46* forms the adduct *50*. The present system enables proper control of the concentration of InH to avoid these side reactions.

2.5. Radical thioalkylation of olefins in aqueous systems

Movassagh and collaborators [68] have sought novel applications of zinc thiolates and zinc selenolates in chemical reactions. They have investigated a convenient, catalyst-free method for the anti-Markovnikov addition of thiols to styrenes at room temperature in water. Theyhave examined a new methodology for the synthesis of β-hydroxysulfides via the anti-Markovnikov addition of thiolate anions, generated *in situ* by reductive cleavage of diaryl disulfides in the presence of $Zn/AlCl_3$, to styrenes in aqueous acetonitrile and in the presence of oxygen (Scheme 27).



Scheme 27. Radical thioalkylation of styrene derivatives in aqueous media mediated by $Zn/AlCl_3$ initiated by dioxygen (Ref. [68]).

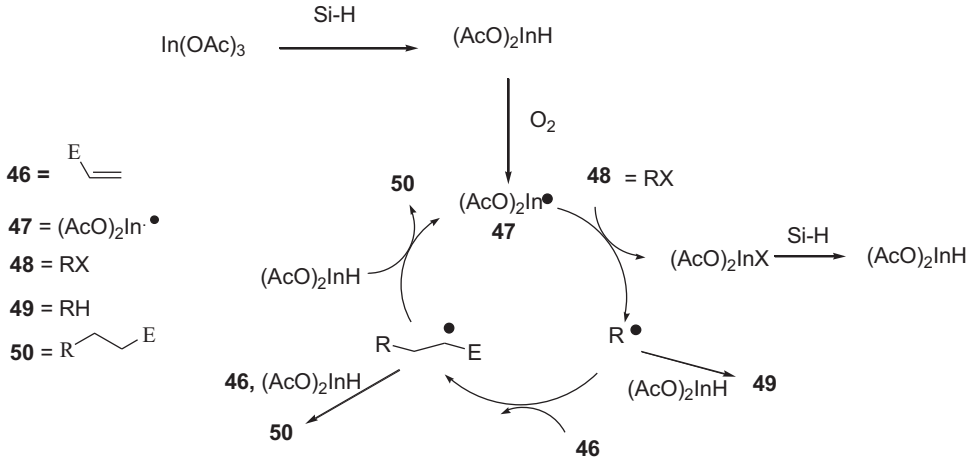
The experiments are initially conducted with styrene and diphenyl disulfide, as a model reaction by varying the molar ratios, solvents, and temperatures under ambient atmosphere. The authors found that the reactants are converted readily to the corresponding β-hydroxysulfide using the $Zn/AlCl_3$ system with a molar ratio of disulfide/$AlCl_3$/Zn/styrene = 0.5:1:3.5:1.2 in acetonitrile/water (4:1) at 80 °C. The formation of β-hydroxysulfides may be explained as follows: the oxygen may complex with the styrene assisted by hydrogen bonding with the water hydroxyls, and this would be followed by nucleophilic attack by zinc thiolate, $(RS)_2Zn$, prepared via reductive cleavage of the disulfide with $Zn/AlCl_3$ [68].

2.6. Radical allylation and propargylation of carbonyl compounds and imine-derivatives in water

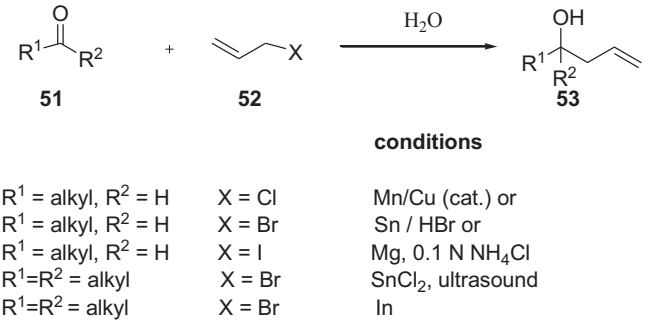
Indium and gallium-mediated allylation reactions of miscellaneous compounds in organic solvents such as THF, DMF, and NMP have been reviewed by Nair and collaborators [1a].

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 yieldswhen water is used as a (co)solvent [69]. Allylation reactions of carbonyl compounds using Zn [70], Bi [71], Sn [72], Mg [73], Mn [69], Sb [74], Pb [75], Hg [76], and In [77] in aqueous media have been reported (Scheme 28).

Magnesium-mediated Barbier–Grignard-type alkylation of aldehydes with allyl halides has been investigated by Li et al. [78] The magnesium-mediated allylation of aldehydes with allyl bromide and iodide proceeds effectively in aqueous 0.1 M HCl or 0.1 M NH_4Cl. Aromatic aldehydes react chemoselectively in the



Scheme 26. Proposed mechanism for the In-silane-mediated alkylation of alkenes (Ref. [67]).



Scheme 28. General metal-mediated allylation of carbonyl compounds in aqueous systems (Refs. [78–90]).

presence of aliphatic aldehydes. A variety of aldehydes have been tested with this allylation method, according to Scheme 28.

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

The mechanism of the classical magnesium-mediated Barbier and Grignard reactions has been studied intensively by several groups [79]. It is generally believed that the radicals on the metal surface are involved in the organomagnesium 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 [80], as shown in Scheme 29. 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.

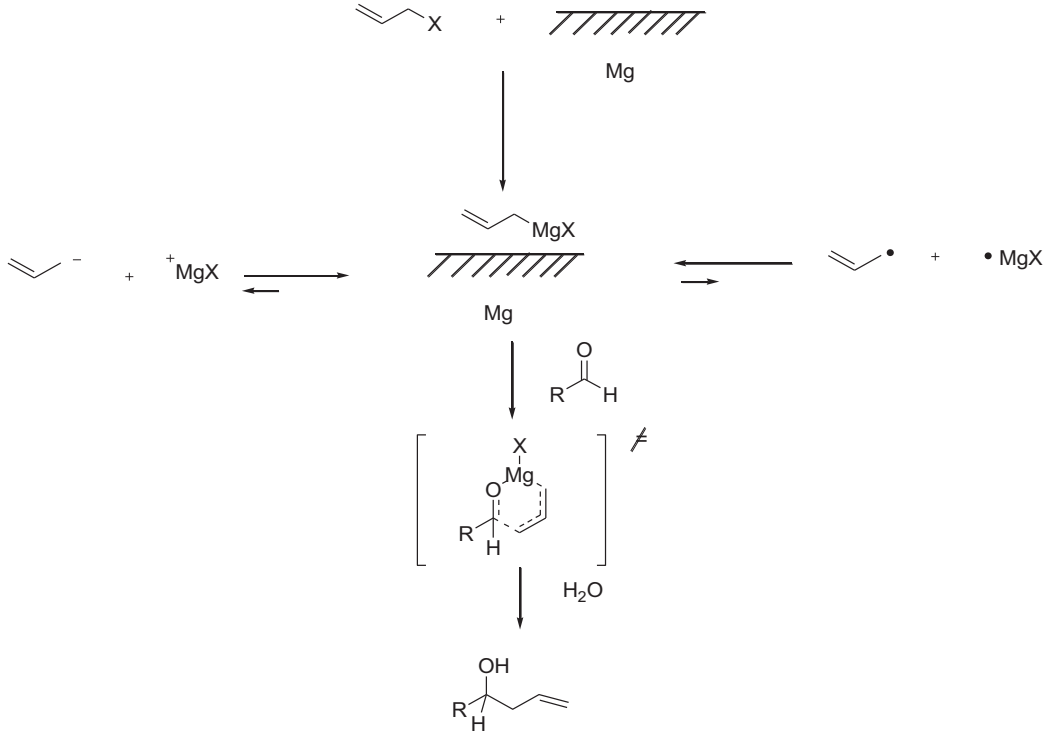
For the rationalization of the pinacol formation (Section 2.9), the authors [78] postulate two potential pathways competing with each other generating either the pinacol-coupling product (path a, Scheme 30, see also Section 2.9) or the benzyl alcohol product (path b, Scheme 30). The same authors observed 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 is formed from the magnesium-mediated reaction with 2,6-dichlorobenzaldehyde, and a 74% yield of the reduction product is encountered in this example (Scheme 30).

Madsen et al. [81] have reported on a theoretical study of the Barbier-type allylation of aldehydes mediated by magnesium. They have concluded that a radical anion is involved in the selectivity-determining event.

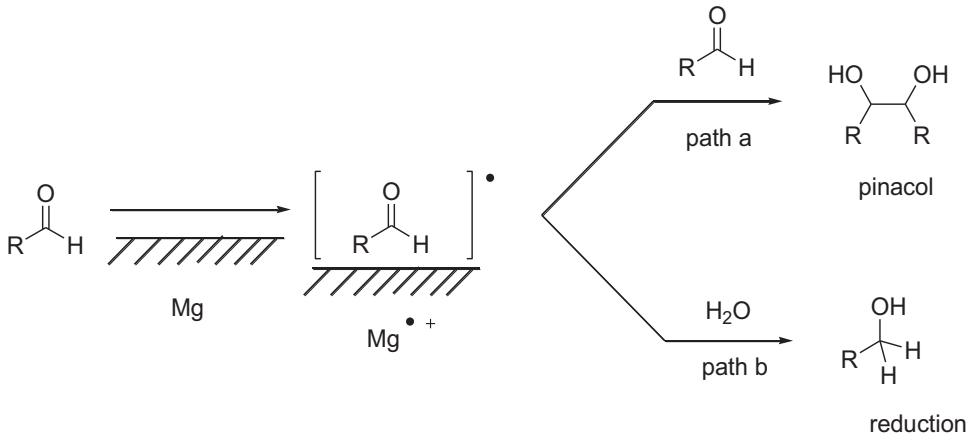
Other metals are used from time to time to mediate in the coupling reactions to construct new carbon–carbon bonds. Manganese is very effective for mediating aqueous medium carbonyl allylations and pinacol coupling reactions [69].

Li et al. [82] have reported an unprecedented metal-mediated carbonyl addition between aromatic and aliphatic aldehydes. When allyl chloride, benzaldehyde, and a manganese mediator are used, the isolated yield of the allylation product (R = Ph) is 83% with Mn/Cu catalyst (Scheme 28).

A series of aromatic aldehydes [82] has been allylated efficiently by allyl chloride and manganese in water. Aromatic aldehydes bearing halogen atoms are allylated without any problems. The allylation of hydroxylated aldehydes is equally successful. On the other hand aliphatic aldehydes are inert under the reaction conditions. Such an unusual reactivity difference between an aromatic aldehyde and an aliphatic aldehyde suggested the authors [82] the possibility of an unprecedented chemoselectivity. When competitive studies are carried out involving both aromatic and aliphatic

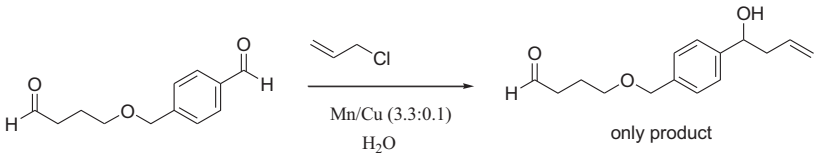


Scheme 29. Mg-surface mediated electron transfer mechanism of allylation of carbonyl compounds showing ion and radical pathways (Ref. [80]).



Scheme 30. Pinacol formation and reduction competing paths (Ref. [78]).

aldehydes (Eq. (13)), a single allylation of benzaldehyde is generated when a mixture of heptaldehyde and benzaldehyde reacts with allyl chloride. Such a selectivity appears unique when aqueous methodologies mediated by other metals such as Zn, Sn and In all generate a 1:1 mixture of allylation productsof both aldehydes (*vide infra*).



(13)

Chan et al. [74] 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 are equally effective as RbF and CsF or 2 M KF. The reaction proceeds well with either aromatic or aliphatic aldehydes. The allylation of α,β-unsaturated aldehydes as represented by *trans*-cinnamaldehyde occurs in a regiospecific manner and furnishes solely the 1,2-addition product. Furthermore, electron donating or withdrawing groups on the aromatic ring do 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 are 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 is 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, see Section 3 for reduction of nitro-compounds to amines) [83]. In this sense, the authors argue [74] that the use of a fluoride salt as an activating agent is superior to the use of Al, Fe, or $NaBH_4$, 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 [81].

In 1983, Nokami et al. have first reported on the successful coupling of a carbonyl compound (*51*) with allyl bromide (*52*) mediated by tin to give the homoallylic alcohol (*53*) in water (Scheme 28, with Sn/HBr) [84]. However, the reaction requires a catalytic amount of hydrobromic acid.

Later on, the addition of metallic aluminum powder or foil was found to improve the yield of the product dramatically [85]. On the other hand higher temperature can be used to replace aluminum [86]. Alternatively, Luche has found that the reaction can be performed in the absence of aluminum or hydrobromic acid by the use of ultrasonic irradiation together with saturated aqueous NH_4Cl/THF solution [87]. Various mechanisms have been proposed for the aqueous Barbier reactions, including the intermediacy of a radical [88], radical anion [89], and an allylmetal species [90]. In the latter case, it has been presumed that diallyltin dibromide is the organometallic intermediate in the tin-mediated allylation reactions; however, no experimental proof has been offered [91,92].

Allylation of carbonyl compounds can easily be accomplished in water using diallyl tin dibromide to obtain homoallyl alcohols in good yields [93]. Table 2 summarizes some examples of carbonyl substrates that can be allylated through this latter reagent.

Although an allyl tin bromide and diallyl tin bromide species have been postulated as intermediates in these reactions, these results however do not eliminate the possibility of a parallel process of metal surface-mediated radical or radical anion reactions. Nevertheless, the understanding that the reaction can proceed through an organotin intermediate has useful synthetic applications.

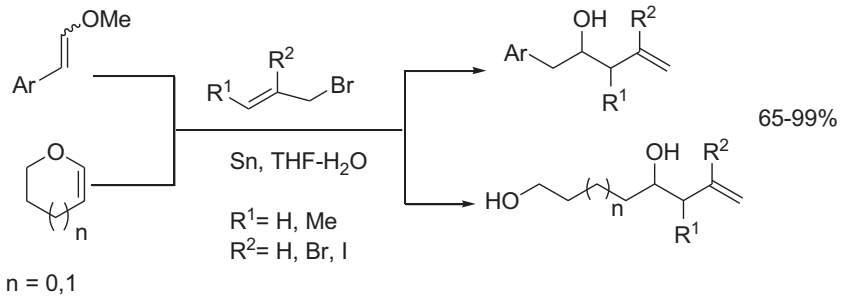
However, allylation reactions based on allylstannanes have serious drawbacks in the synthesis of biologically active compounds, because the inherent toxicity of organotin derivatives and the difficulty of removal of residual tin compounds often proves fatal.

Bian and collaborators [94a] have accomplished the allylation reaction of aromatic aldehydes and ketones with tin dichloride in water. The allylation reactions of aromatic aldehydes and ketones are carried out in 31–86% yield using $SnCl_2$–H_2O system under ultrasound irradiation at r.t. for 5 h. The reactions in the same system afford homoallyl alcohols in 21–84%yield with stirring at r.t. for 24 h (Scheme 28). Compared with traditional stirring methods, ultrasonic irradiation is more convenient and efficient.

In Table 3, the aromatic aldehydes and ketones studied are summarized. The allylation products are obtained in yields ranging from 73 to 86% by ultrasound irradiation, except for acetophenone, wich renders a low yield of the respective allylation product.

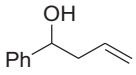
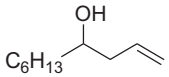
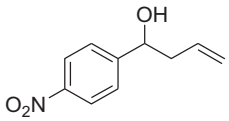
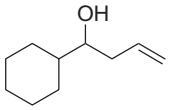
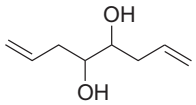
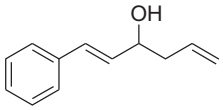
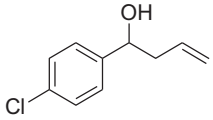
A very recent Sn-mediated allylation reaction in water has been accomplished by Lin and collaborators [94b]. They have achieved allylation reactions of enol ethers, both cyclic and acyclic ones in fairly good yields, according to Scheme 31.

Some of the indium-mediated allylation reactions of carbonyl compounds in some aqueous mixtures have been discussed by



Scheme 31. Tin-mediated allylation reactions of enol ethers in water:THF (Ref. [94b]).

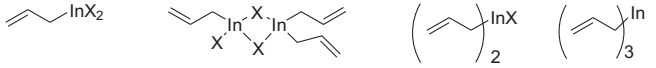
Table 2
Allylation reactions of carbonyl compounds with diallyltin dibromide in water at room temperature (Ref. [93]).

Entry	Carbonyl compound	Product	Yield, %
1	Benzaldehyde		95
2	Heptaldehyde		99
3	4-Nitrobenzaldehyde		97
4	Cyclohexylaldehyde		95
5	OHCCHO		95
6	Cinamaldehyde		99
7	4-Chlorobenzaldehyde		99

Nair et al. [1a]. Chan et al. [95] haveinvestigated the nature of the allylation reaction of carbonyl compounds with indium in water (Scheme 28). The authors postulate a series of intermediates, among which those in Scheme 32a re considered.

Table 3
Allylation reactions of aldehydes with $SnCl_2/H_2O$ under ultrasound and stirring conditions (Ref. [94a]).

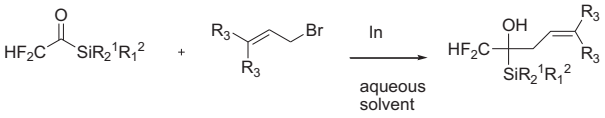
Entry	Substrate	Yield, % (stirring)	Yield, % (ultrasound)
1	Benzaldehyde	84	86
2	4-Chlorobenzaldehyde	77	76
3	Furfural	58	59
4	Cinnamaldehyde	71	73
5	3,4-$(CH_3O)C_6H_3CHO$	84	79
6	4-$CH_3OC_6H_4CHO$	–	–
7	$C_6H_5COCH_3$	21	31



X = Cl, Br

Scheme 32. Intermediates proposed in the indium-mediated allylation of carbonyl compounds (Ref. [95]).

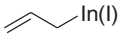
Table 4
Indium-mediated allylation reaction of difluoroacetyltrialkylsilane in aqueous mixtures at room temperature (Ref. [96]).



54

Entry	R^1	R^2	R^3	Solvent	% *54*
1	Phenyl	t-Butyl	H	THF–water	97
2	Ethyl	Ethyl	H	THF–water	83
3	Isopropyl	Isopropyl	H	THF–water	85
4	Ethyl	Ethyl	CH_3	THF–water	–
5	Ethyl	Ethyl	CH_3	THF–water NH_4Cl	–

However, through a series of experiments [95], it was concluded that indeed the allyl indium intermediate contained indium(I), and the structure of the intermediate supported by experiments is that shown in equation 14:



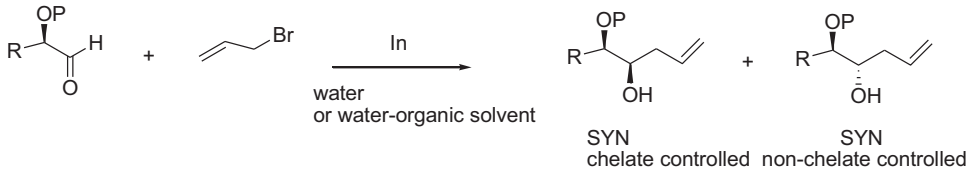
(14)

Welch and collaborators [96] have explored the generality of the indium-mediated allylation reaction with various difluoroacetyltrialkylsilanes in water and THF mixture.

Desired homoallylic alcohols 54 (Table 4) are synthesized in good yields without enol silyl ether formation. Substituents on silicon have no effect on the product formation. However, in reaction with a substituted allyl bromide such as 4-bromo-2-methyl-2-butene, the desired homoallylic alcohol is not formed, rather, the acylsilane is recovered (Table 4).

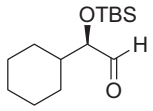
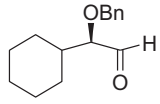
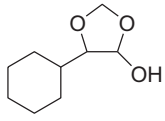
The regio- and stereoselectivity of metal-mediated allylation reactions in aqueous media is well understood [97]. In general, regioselectivity is governed by the substituent on the allyl halide. The formation of γ-adducts is exclusively observed under some conditions, however, allyl halides bearing bulky γ-substituents such as 1-bromo-4,4-dimethyl-2-pentene and (3-bromopropenyl)trimethylsilane resulted in the formation of α-adducts. In contrast, diastereoselectivity is affected by the steric and chelating effect of substituents. These reactions have also been attempted with zinc.

Paquette et al. [98b] have investigated the stereochemical course of indium-promoted allylations to α- and β-oxy aldehydes in solvents ranging from anhydrous THF to pure H_2O. The free hydroxyl derivatives react with excellent diastereofacial control



Scheme 33. In-mediated allylation of α-oxygenated aldehydes in water (Ref. [98b]).

Table 5
Indium-mediated allylations of α-oxygenated aldehydes in water (Ref. [98b]).

Entry	Aldehyde	Reaction time (h)	*Syn ratio*	*Anti*	Yield, %
1	 *55*	3.5	1	3.9	90
2	 *56*	3	1	1.2	92
3	 *57*	24–30	2.3	1	90–95

to render preferentially*syn*-1,2-diols and *anti*-1,3-diols, respectively (Scheme 33, for *syn*-1,2-diols from α-oxy aldehydes). Relative reactivities were determined in the α-series, and the hydroxyl aldehydes are the most reactive substrates. This reactivity ordering suggests that the selectivity stems from chelated intermediates.

The results obtained with *55* (entry 1, Table 5) and *56* (entry 2, Table 5) provide important calibration points for non-chelate-controlled behavior (Scheme 33). In both instances, the *anti*-product is favored. Presumably because the basicity of the *tert*-butyldimethylsiloxy substituent falls below that of the benzyloxy, the *anti*-percentages reach a maximum for *55*. The pH considerations have been dealt with by Araki and collaborators [99].

β-*Oxy-substituted aldehydes*: A free hydroxyl substituent β- to a carbonyl group has been considered to be exploitable for 1,3-asymmetric induction during condensation with allylindium reagents in water. Aldehydes *58* (Scheme 34) were selected because of their structural simplicity, similarity to *55*–*57*, and varied basicity at the β-oxygen. If chelation were to gain importance and nucleophilic attack were to occur from the less hindered diastereotopic π-face of the aldehyde carbonyl, then *anti*-adduct *59* (Scheme 34) would result.

The unprotected hydroxyl derivative *58* exhibits the most pronounced face selectivity as anticipated. Clearly the free β-OH group is capable of chelation control in water, finding it possible to coordinate to the indium ion despite its preexisting solvation by water molecules [97b,98b].

2.6.1. *Mechanistic considerations [97b,98b]*

The sense of asymmetric induction in the α-series, *viz.* a strong kinetic preference for formation of the *syn* diol, is consistent with operation of the classic Cram model as in A (Fig. 1). Once complexation occurs, the allyl group is transferred to the carbonyl carbon from the less hindered π-surface opposite to that occupied from the R group. In B (Fig. 1), the chelation pathway is seen to be capable of adoption of a chair conformation which concisely accommodates favored formation of the *syn* diol (*61-syn*). For the β-chelate reactions, the factors which influence product formation appear to be the same. When C forms (Fig. 1), intramolecular attack is guided to occur *syn* to the preexisting hydroxyl. This reaction trajectory leads preferentially to the *anti* diol (*anti-61*), provided that a chair like transition state approximating D (Fig. 1) is followed. Importantly, it is one single allylindium that chelates and reacts. Although similar working models have been advanced in explanation of the mode of addition of titanium [100] or borane reagents [101], this behavior is distinct from other chelation-controlled reactions where the reacting reagent is different from the chelating agent. This may well be an argument that the indium-mediated reaction takes place on the metal surface.

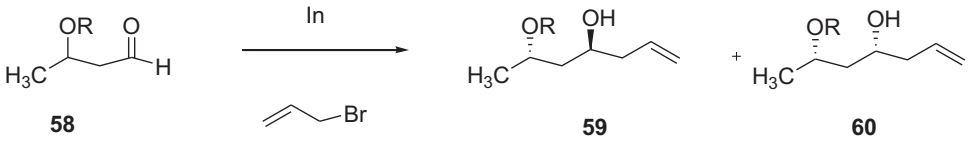
The present studies elegantly conducted by Paquette and collaborators [97b,98b] have demonstrated a direct kinetic link between stereoselectivity and the presence of a neighboring hydroxyl group. While this relationship has been extensively discussed [102,103], the support of this concept is not universal. Several experimental and theoretical reports have appeared supporting the notion that π-complexation is not a kinetically important event [104,105]. Clearly, additional studies on this entire question would be welcomed.

The precise mechanism of indium-promoted reactions remains therefore unclear. In the mid-1980s, the involvement of radical pairs is advanced in explanation of tin-promoted allylations (*vide supra*) [106]. Subsequent recourse to radical clock experiments demonstrated unambiguously that free radicals could not be involved, however, the involvement of radical ions is not ruled out [107]. Single electron transfer process similar to that advanced by Chan have been proposed [108]. According to this reaction profile, the allyl bromide approaches the surface of the indium metal where the SET process generates the reactive radical anion/indium radical cation pairE (Fig. 1) (similar to that proposed for Mg in Schemes 29 and 30, *vide supra*). These conditions operate, of course, only when indium metal is present as a reactant. Acyclic diastereofacial control is presently recognized to occur in a wide range of reactions [106,109]. Suffice it to indicate at this point that the preformation of allylindium reagents may well bypass the involvement of E (Fig. 1), suggesting an alternative pathway involving the more conventional species F (Fig. 1) can also operate [111,112a]. Proper selection of reaction conditions could alter the precise pathway at work [97b,98b].

Loh and collaborators have reported the indium-mediated allylation of steroidal compounds in water leading to a wide variety of 22-hydroxysteroids with reasonable diastereoselctivity [112b].

When benzaldehyde is treated with 3-bromo-2-chloro-l-propene *62* and indium in water, it gave the corresponding allylation product *63* (Scheme 35) in 78% yield. Upon ozonolysis, compound *63* is converted to the corresponding β-hydroxyl methyl ester *64* in 82% yield (Scheme 35) [112,113].

Other aldehydes reacted similarly, and the results are summarized in Table 6. Attachment of various functionalities on the aromatic ring provides an equivalent or better overall yields of the product (entries 2, 4, 5 and 7, Table 6). Aliphatic aldehydes are similarly transformed to the corresponding γ-hydroxyl esters (entries



Scheme 34. In-mediated allylation of β-oxygenated aldehydes in water (Ref. [98b]).

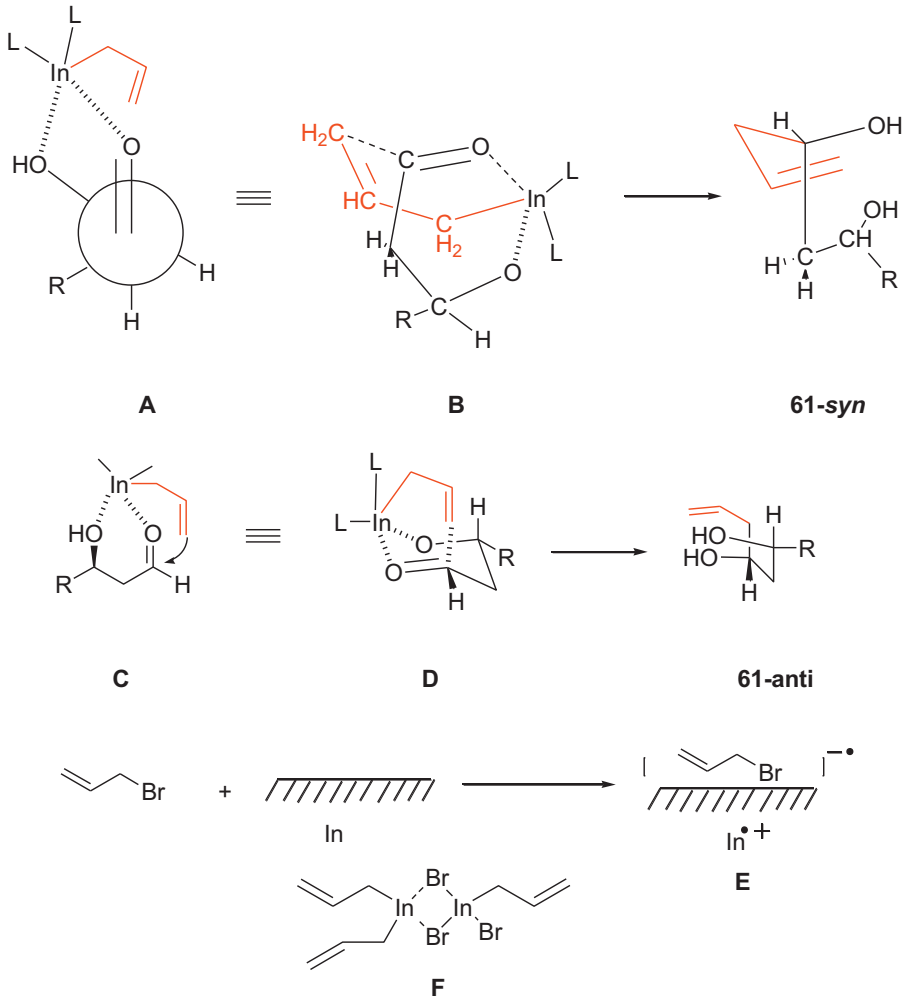
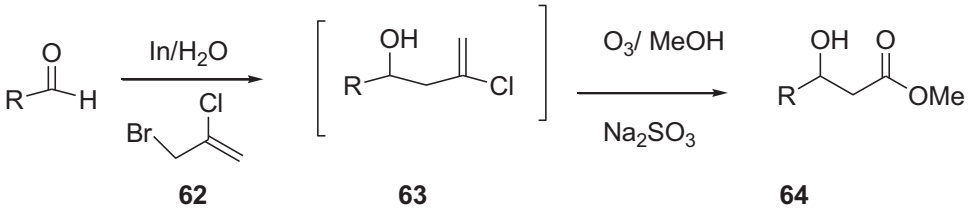


Fig. 1. (A) Cram's model for the formation of product *61-syn*. (B) Conformation adopted for product *61-syn*. (C) and (D) Conformations for the formation of the *anti* product *61*. (E) Radical ion intermediates proposed. (F) Allyl indium intermediate proposed.

3 and 6, Table 6). The use of a mixture of water and THF as solvent for the indium mediated allylation did not affect the reaction result (entry 4, Table 6). Compounds with a free hydroxyl group (entry 8, Table 6) can be converted directly to the corresponding γ-hydroxyl ester. In entry 9, Table 6, even though the aldehyde existed in its cyclized hemiacetal form, the compound is transformed to the desired compound without any difficulty.

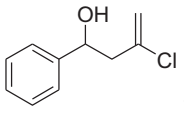
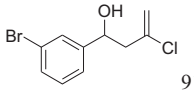
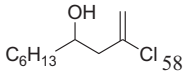
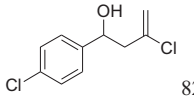
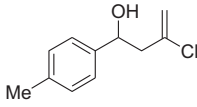
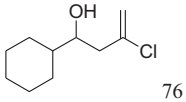
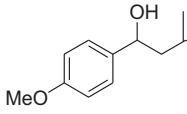
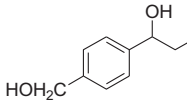
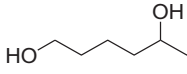
Oshima and collaborators [114] have performed the radical allylation of α-halo carbonyl compounds with allylgallium in water (Scheme 36). The use of other non-conventional metals such as Co, Sc, and Ge-mediated allylation reactions of carbonyl compounds have been reviewed by Li in 2005 [7a].

The origin of the favorable solvent effect is not clear at this stage. Similar phenomena have been reported on atom-transfer radical

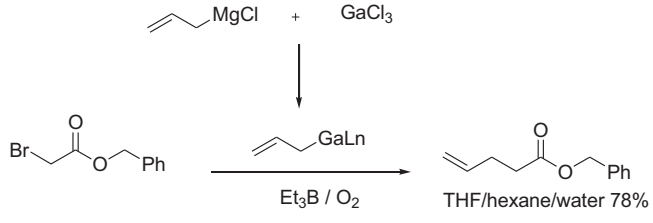


Scheme 35. In-mediated allylation of aldehydes with 3-bromo-2-chloro-l-propene *62* in water (Refs. [112,113]).

Table 6
In-mediated allylation of aldehydes with 3-bromo-2-chloro-l-propene *62* in water (Refs. [112,113]).

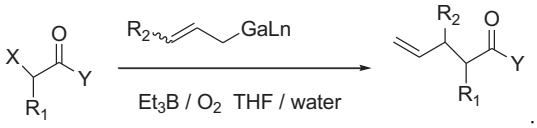
Entry	Substrate	Product, %
1	Benzaldehyde	 78
2	3-Bromobenzaldehyde	 91
3	Heptaldehyde	 58
4	4-Chlorobenzaldehyde	 82
5	4-Methylbenzaldehyde	 91
6	Cyclohexylaldehyde	 76
7	4-Methoxybenzaldehyde	 77
8	4-Benzylic carbaldehyde	 60
9	2-Hydroxy-tetrahydropyrene	 84

reaction of α-iodo carbonyl compounds in aqueous media, where the high cohesive energy density of water causes reduction of the volume of an organic molecule (see Section 2.1). In the present case, the addition step could be accelerated because the addition necessarily accompanies the decrease of the total volume of the reactants. It is also probable that the structure of the allylgallium species would change and that the addition of water could increase the reactivity of allylgallium. Allylgallium dichloride is likely to be transformed into allylgallium hydroxide that is possibly more reactive for radical allylation.



Scheme 36. Radical allylation of α-halo carbonyl compounds with allygallium in water (Ref. [114]).

Table 7
Radical allylation of α-halocarbonyl compounds with allyl gallium in water initiated by Et_3B/O_2 in THF/water mixtures (Ref. [114]).



Entry	X	Y	R^1	R^2	Time (h)	Yield, %
1	Br	OCH_2Ph	H	H	2	78
2	Br	OCH_2Ph	Me	H	2	63
3	Br	NMe_2	Me	H	2	64
4	I	OCH_2Ph	H	H	0.5	89
5	I	OCH_2Ph	Me	H	0.5	81
6	I	$NHCH_2CHCHC_{10}H_{21}$	H	H	1	87
7	I	$OCH_2CHCHC_3H_7$	H	H	0.5	95
8	I	$O(CH_2)_6Cl$	H	H	1	85
9	I	$O(CH_2)_2\ OCH_2CHCH_2$	H	H	0.5	64
10	I	$OCHPhCH_2CHCH_2$	H	H	2	71
11	I	$OCH(C_3H_7)COC_3H_7$	H	H	1	84
12	I	OCH_2Ph	H	Me	0.5	60
13	I	$NHCH_2CHCHC_{10}H_{21}$	H	Me	2	85
14	I	$O(CH_2)_6Cl$	H	Me	2	46
15	I	OCH_2Ph	H	Me	1	50
16	Br	NMe_2	Me	Me	7	65

Various combinations of α-carbonyl compounds and allylic gallium reagents have been examined (Table 7). More reactive α-iodo carbonyl compounds give better results compared with their bromo analogues. 2-Halopropanoate or 2-halopropanamide also reacts with the allylgallium reagent to give 2-methyl-4-pentenoate or 2-methyl-4-pentenamide (entries 2, 3, and 5, Table 7). In contrast, 2-bromo-2-methylpropanoate does not give the anticipated product, and the starting material is recovered unchanged, probably due to the steric hindrance around the carbon-centered radical. Interestingly, allylation is effective for the substrates having a terminal carbon–carbon double bond (entries 9 and 10, Table 7).

An electron-deficient (alkoxycarbonyl)methyl radical reacts faster with the highly electron-rich alkene moiety of the allylgallium species than with the olefinic parts of the substrate and of the product. Allylation of the ketone moiety is not observed.

Chan and collaborators [116,117b,c] have reported on a simple synthesis of 1,3-butadienes from carbonyl compounds in aqueous medium according to Fig. 2. Atypical experimental procedure consists of a mixture of the carbonyl compound *65*, 1,3-dichloropropene (*66*, X = C1), and zinc powder in water to give the corresponding 1,3-butadiene *70*. The reaction has a number of interesting features. First, it is important to note that, in the reaction of benzaldehyde, the yield of 1-phenylbutadiene is quite satisfactory under these conditions in aqueous medium but fails to proceed at all in diethyl ether or other organic solvents normally used for

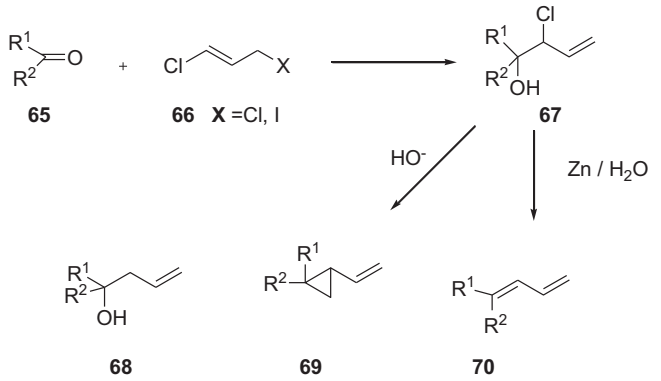
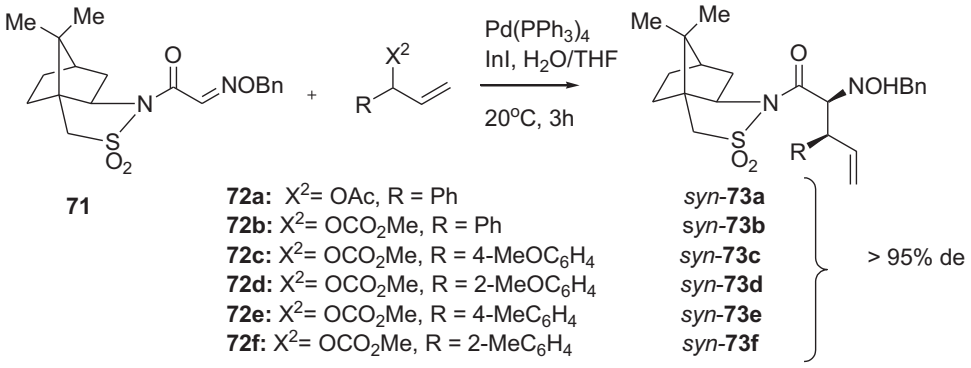


Fig. 2. Formation of product *67–70* (Refs. [116,117b,c]).



Scheme 37. The reaction of imine derivatives with allylic acetates in the presence of $Pd(PPh_3)_4$ and indium(I) iodide in water, to afford the γ-adduct *syn-73a* (Ref. [117]).

organometallic reactions. Second, the reaction seems to proceed with both aldehydes and ketones. With cinnamaldehyde, the corresponding triene is obtained. Third, the butadienes are formed stereoselectively and, in the case of aldehydes, exclusively as the *E* isomers. Furthermore, unprotected hydroxyl compounds such as glyceraldehyde and 5-hydroxypentanal undergo the diene conversion without difficulty. On the other hand, the yield of *70* is modest at best in all cases, in spite of efforts to vary the reaction temperature, time, amount of metal, etc. The poor yield was traced to the formation of the homoallylic alcohol *68*, which must have been formed by the zinc-mediated reduction of the intermediate chlorohydrin *67*.

The reaction of allylmetals with electrophiles has been developed as an important carbon–carbon bond forming method. In general, γ-adducts (branched products, Fig. 3) are obtained in the allylation of aldehydes and imines using allylmetals. The selective synthesis of α-adducts (linear products) has been a subject of current interest (Fig. 3).

Recently, the preparation of allylindium reagents via transient organopalladium intermediates has been studied by Araki et al. [117a].

Numerous and useful indium-mediated allylation reactions of carbonyl compounds have been reported [117b]. However, the corresponding reaction of imine derivatives has not been widely studied because of the lower electrophilicity of carbon–nitrogen double bonds. Therefore, the development of indium-mediated reactions of imines in aqueous media has been a subject of recent interest. Chan et al. [117c] have reported on the first studies of indium-mediated allylation of *N*-sulfonylimines in aqueous media. This is likely an area for further development and new discoveries.

Allylation reactions of electron-deficient imines with allylic alcohol derivatives in the presence of a catalytic amount of palladium(0) complex and indium(I) iodide has been studied by Takemoto et al. [118a]. The reversibility of allylation is observed in the reaction of glyoxylic oxime ether having camphorsultam. γ-Adducts are observed with high regioselectivity in water. However, in general, allylation of an aldehyde (in organic solvents) with allylic indium reagent occurs regioselectively at the γ-position to afford γ-homoallylic alcohols in the absence of sterically bulky substituents at the carbonyl group, however, solvent polarity plays an important role in determining the regioselectivity of this reactions, and in water, α-adducts prevail (see Fig. 3) [118b].

The reaction of *71* with allylic acetate *72a* in the presence of $Pd(PPh_3)_4$ and indium(I) iodide in water/THF, affords the γ-adduct *syn-73a* in 90% yield as a single diastereomer (Scheme 37 and Table 8). In comparison with the reaction of glyoxylic oxime ether, the authors have investigated the allylation of *N*-sulfonylimine under similar reaction conditions (Scheme 38) [117].

Although the reaction of *74* proceeds smoothly (Scheme 38), the formation of α-adducts is obtained even under anhydrous THF. These observations indicate that the allylation of *N*-sulfonylimine *74* is not a reversible process due to extra stabilization of indium-bonding adduct by electron withdrawing *N*-sulfonyl group. The bulky γ,γ-dimethylallyl acetate *78c* and carbonate *78d are* less effective for the allylation reaction of *N*-sulfonylimine. The reaction of *74* with α,α,-dimethylallyl acetate *77c* give the γ-adduct *75d* in 36% yield (Scheme 38).

In another account, Takemoto et al. have successfully attempted the propargylation reaction of hydrazones and glyoxylic oxime ethers in water mediated by Pd–indium iodide, demonstrating the role of water in directing the diastereoselectivity [119a].

Bieber and collaborators have accomplished the allylation of iminium ions, generated *in situ*, promoted by zinc (CuI) in aqueous medium, according to Scheme 39 [119b]. The authors postulate a SET mechanism to account for the reaction mechanism.

Chan et al. have reported [113a] that indium can effectively mediate the coupling between 1,4-dibromobut-2-yne (*79*) and carbonyl compounds in aqueous media to give regioselective 1,3-butadien-2-ylmethanols *80* in good yields (Scheme 40).

The reaction is likely to proceed via an organoindium intermediate *81* which reacts with the aldehyde to give adduct *82* (Scheme 41). Further reaction of the bromide with indium can lead to another organoindium intermediate, *83*, which is quenched by water to give 1,3-butadienyl-2-methanol *80*. Reaction of *83* with another molecule of aldehyde to give di-adduct *84* is not observed, presumably because of steric hindrance. However, the authors were able to show that with glutaric dialdehyde intramolecular

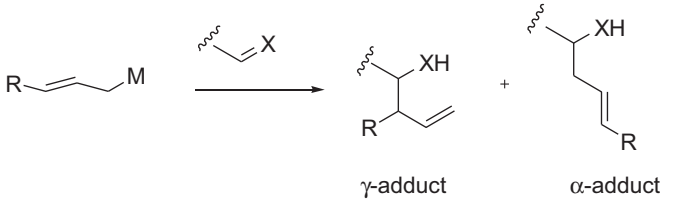
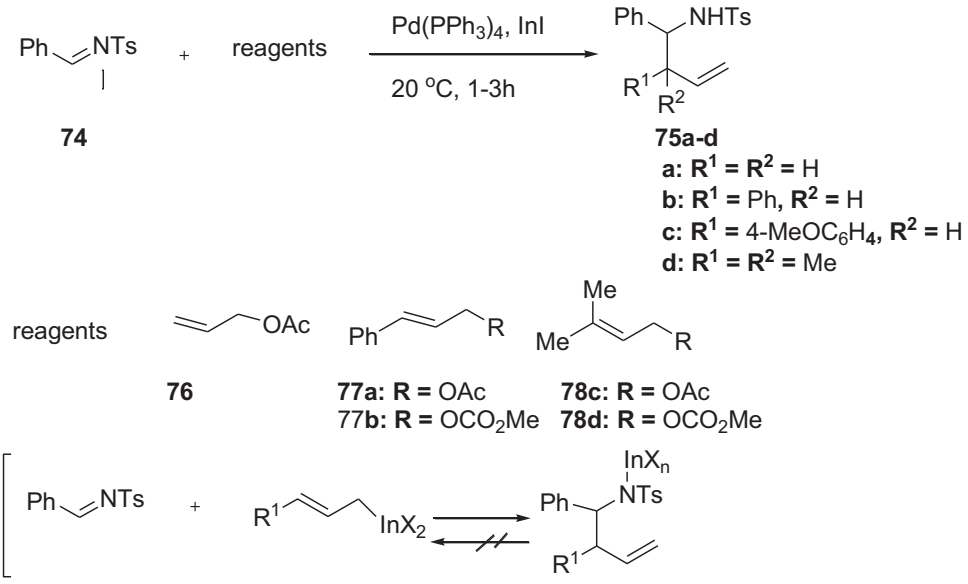


Fig. 3. Regioselectivity in allylation reactions (Ref. [118b]).

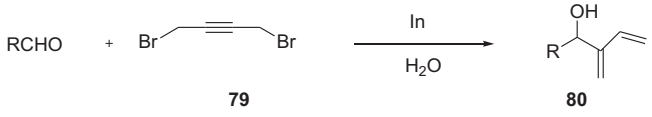
Table 8
Reaction (3-h) of *71* with allyl alcohol derivatives *72c–f* (see Scheme 41 for conditions) (Ref. [118b]).

Entry	Reagent	Solvent	Product	Yield (%)
1	*72c*	H_2O–THF	*syn-73c*	90
2	*72d*	H_2O–THF	*syn-73d*	81
3	*72e*	H_2O–THF	*syn-73e*	71
4	*72f*	H_2O–THF	*syn-73f*	72

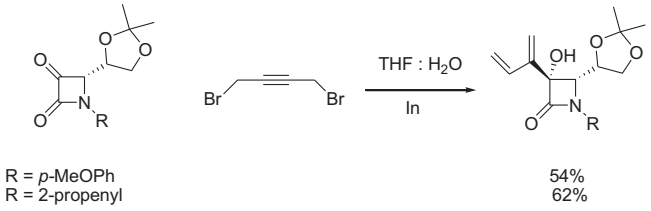


Scheme 38. Allylation of *N*-sulfonylimine with allylic acetate derivatives in the presence of $Pd(PPh_3)_4$ and indium(I) iodide in water.

Scheme 39. Allylation of iminium ions generated *in situ* by Zn (CuI) in aqueous acetic acid (Ref. [119b]).



Scheme 40. In-mediated 1,3-butadien-2-ylation of carbonyl compounds in water (Ref. [113a]).



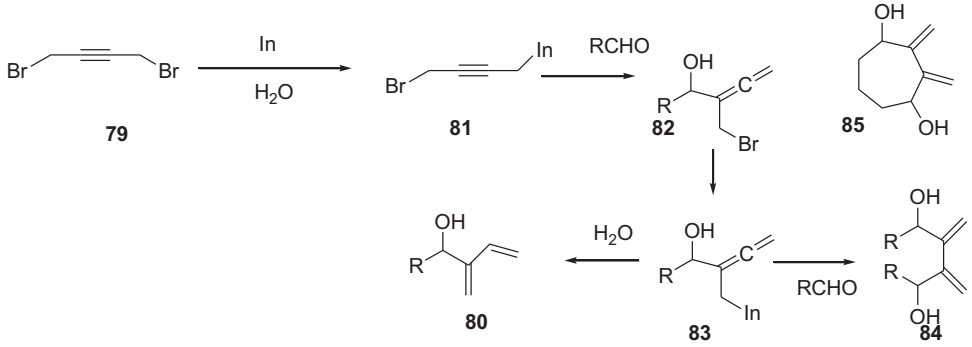
Scheme 42. 1,3-Butadien-2-ylation of azetidine-2,3-diones in THF:water/In (Ref. [113b]).

trapping of intermediate *83* is possible and the cyclic di-adduct *85* was obtained in 40% isolated yield [113a]. With this methodology, a series of dienes is synthesized, and the yields are reported in Table 9.

Alcaide, Almendros and collaborators [113b] have also carried out the regio- and stereoselective 1,3-butadien-2-ylation of azetidine-2,3-diones in aqueous media, according to Scheme 42.

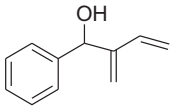
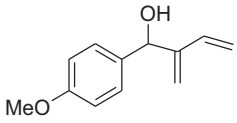
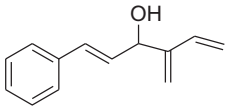
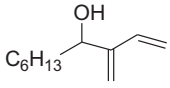
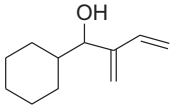
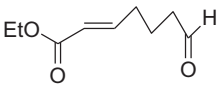
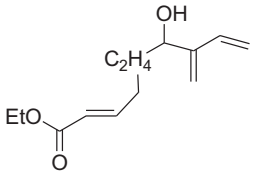
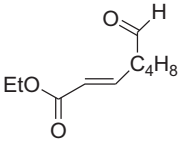
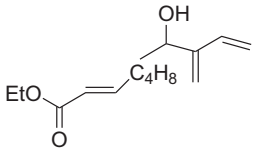
This synthesis provides a route to potentially bioactive 3-substituted-3-hydroxyl-β-lactam moiety.

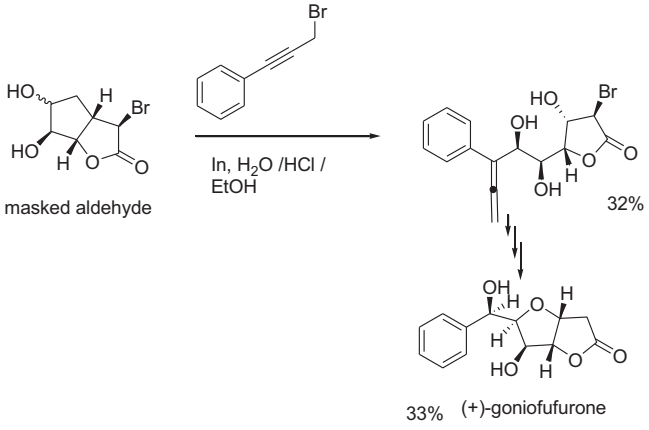
The regio- and diastereoselective allenylation of an aldehyde toward the total synthesis of (+)-goniofufurone is achieved in water through the use of In metal, according to Scheme 43 [119c].



Scheme 41. Proposed mechanism for the In-mediated 1,3-butadien-2-ylation of carbonyl compounds in water (Ref. [113a]).

Table 9
Indium-mediated 1,3-butadien-2-ylation of carbonyl compounds in water (Ref. [113a]).

Entry	Aldehyde	Product	Yield, %
1	Benzaldehyde		53
2	4-Methoxybenzaldehyde		55
3	Cinalmaldehyde		60
4	Heptaldehyde		
5	Cyclohexylaldehyde		64
6			67
7			68



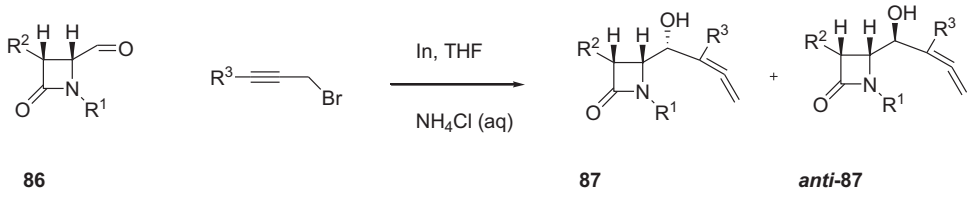
Scheme 43. Synthesis of (+)-goniofufurone promoted by In, in H_2O/HCl/EtOH (Ref. [119c]).

Alcaides, Almendros and collaborators have performed the synthesis of 2-azetidinone allenol derivatives in high yields through the indium-mediated reaction in water (Scheme 44 and Table 10) [120a,b].

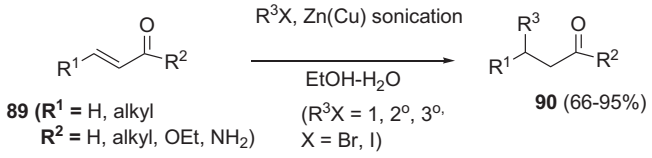
2-Azetidinone-tethered allenols *87a–k* (Table 10) are obtained by a metal-mediated Barbier-type carbonylallenylation reaction of β-lactam aldehydes *86a–f* in aqueous media by using previously described methodologies (Scheme 44 and Table 10) [120a,b].

The yields of lactam *87* range from 50 to 89% yields, with the prevalence of the *syn* isomer. In several cases, the *syn* isomer is obtained exclusively.

Hammond and others [45,120] have recently synthesized *gem*-difluorohomopropargyl alcohols from *gem*-difluorohomopropargyl bromides *88* using indium and a catalytic amount of $Eu(OTf)_3$ as a water tolerant Lewis acid. Later on, the same authors employed a combination of Zn and catalytic amounts of indium and iodine (Eq. (15)).

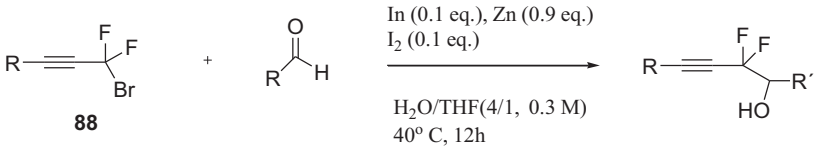


Scheme 44. Synthesis of 2-azetidinone-tethered intermediates promoted by In, in THF/NH_4Cl (Ref. [120a]).



Scheme 45. Intermolecular addition of alkyl halides to α,β-unsaturated aldehydes, ketones, esters, and amides in EtOH–H_2O mediated by Zn(Cu) under ultrasound conditions (Ref. [12k–14]).

Only fluorinated propargyl alcohols are observed as products under the reaction conditions. The reaction is highly regioselective as the corresponding fluoroallenylalcohols are not detected [45].



(15)

2.7. Radical conjugate additions (RCA) to α,β-unsaturated carbonyl compounds in water

Conjugate addition [54a] of alkyl groups to α,β-unsaturated carbonyl compounds is a versatile synthetic method for the construction of C–C bonds. Among the various methods available, the most commonly employed strategies involve the use of organometallic species such as Grignard reagents (RMgX) or organolithium (RLi) reagents. However, the use of these highly reactive organometallic reagents can lead to undesired side reactions such as hydrolysis, Wurtz coupling, β-elimination of the organometallic reagent, and the reduction of carbonyl compounds. Also, 1,2-addition of the alkyl group to the carbonyl group can compete with the 1,4-conjugate addition reaction. If this reaction could be developed to take place in water without the above-mentioned side reactions, it would greatly aid organic chemists.

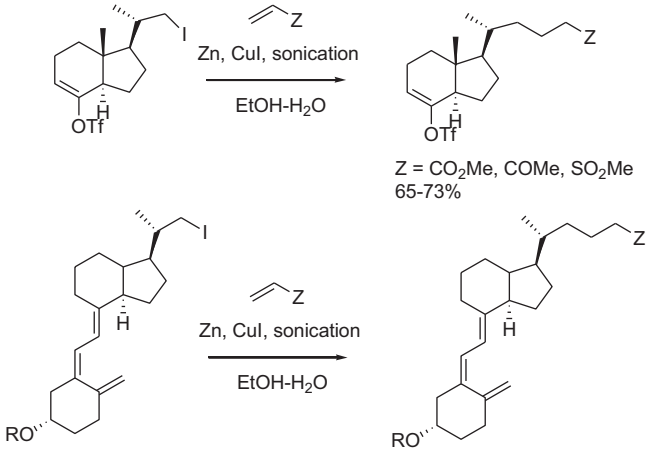
Thus, alkylation by organometallic species such as Mg [12a], Cd [12b], Li [12c], Mn [12d] and Zr [12e] derivatives afford good yields of the 1,4 adducts only in some cases and under copper catalysis [12f], and an improvement in the regioselectivity is possible only by complexation of the carbonyl group [12g] or through a derivatization/protection procedure (*e.g.* via imines or acetals).

As for radical alkylation in organic solvents, application to α,β-unsaturated aldehydes is limited to a few examples including early work on borane radical induced alkylations [12h] as well as radical generation via decomposition of α-hydroxydiazenes [12i] and via photolysis of alkylmercury halides [12j].

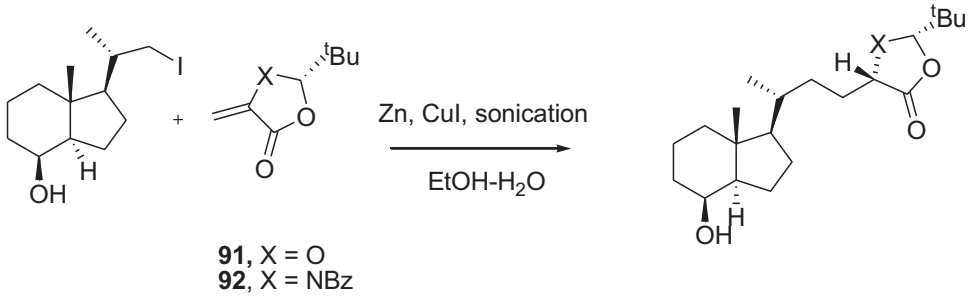
Luche has found that the combination of Zn–Cu couple and sonication mediates in the intermolecular addition of alkyl radicals to α,β-unsaturated aldehydes, ketones, esters, and amides in aqueous EtOH (Scheme 45) [12k–14].

These reactions are typically most efficient with tertiary and secondary radicals. Mechanistic studies suggest that the intermediate α-carbonyl radical is reduced to an enolate and subsequently protonated [15].

Mouriño has used the Luche conditions with acrylate, enolate, and vinyl sulfone acceptors to synthesize vitamin D_3 analogues (Scheme 46) [57–59].



Scheme 46. Synthesis of vitamin D_3 analogues mediated by Zn/CuI under ultrasound conditions in EtOH/H_2O (Refs. [57–59]).



Scheme 47. Zn-mediated RCA on methylene lactones in EtOH–water (Refs. [63–65]).

Table 10
Regio and stereoselective allenylation of 4-oxaazetidine-2-carbaldehydes 86 (Scheme 44) in water/NH_4Cl (Ref. [120a]).

Aldehyde	R^1	R^2	R^3	Product	*Syn*/*anti*	Yield(%)
(+)-*86a*	Allyl	MeO	Me	(+)-*87a*	95:5	75
(+)-*86a*	Allyl	MeO	Ph	(+)-*87b*	100:0	64
(+)-*86b*	3-Methyl-but-2-enyl	MeO	Me	(+)-*87c*	85:15	68
(+)-*86b*	3-Methyl-but-2-enyl	MeO	Ph	(+)-*87d*	100:0	61
(+)-*86c*	3-Methyl-but-2-enyl	MeO	Ph	(+)-*87e*	100:0	51
(+)-*86d*	Methallyl	PhO	Me	(+)-*87f*	90:10	79
(+)-*86d*	Methallyl	PhO	Ph	(+)-*87g*	100:0	58
(+)-*86e*	Methallyl	Vinyl	Me	(+)-*87h*	10:90	60
(+)-*86e*	PMP	Vinyl	Ph	(+)-*87i*	70:30	89
(+)-*86f*	PMP	Isopropyl	Me	(+)-*87j*	10:90	73
(+)-*86f*	PMP	Isopropyl	Ph	(+)-*87k*	65:35	63

PMP: *p*-MeOPh.

In conjunction with studies of stereoselective Luche-type intermolecular RCAs [60–62], Sarandeses and Perez Sestelo have later employed chiral acceptors *91*, *92*, allowing introduction of a stereocenter at C-24 (Scheme 47) [63–65]. In a synthesis of C-18-modified vitamin D_3 analogues, Sarandeses has performed an intermolecular RCA of hindered neopentylic iodide *93* to methyl acrylate (Scheme 48) [66]. Similar alkyl radical addition reactions occur in chiral vinyl phosphine oxides [7a].

Sarandeses and Perez Sestelo have employed the Luche protocol in diastereoselective radical conjugate addition (RCA) reactions. Methylene–dioxolanone *95* and γ,δ-dioxolanyl-α,β-unsaturated ester *97* serve as effective chiral acceptors for the stereoselective synthesis of α- and γ-hydroxy acid derivatives *96* and *98*, respectively (Scheme 49) [60,61].

Similar RCAs conducted with *N*-Cbz methyleneoxazolidinone *99* provide α-amino acid derivatives *100* with very good yields and diastereoselectivities (dr's) (Scheme 49) [62].

In the course of a synthesis of sinefungin analogues, Fourrey has discovered that sonication is not required to promote RCA of ribose derivative *101* to dehydroalanine *103* under modified Luche conditions (Scheme 50) [16,120,121]. Rather, vigorous stirring is sufficient. Similar reactions can also be induced by a Zn–Fe couple [122].

Crich has demonstrated that alkyl radicals generated via the reductive mercury method undergo intermolecular conjugate addition to dehydroalanine *104* to render α-aminoacids *105* in CH_2Cl_2–water mixtures (Scheme 51) [123]. Primary, secondary, and tertiary alkylmercury bromides and chlorides can all be used in this reaction.

Crich has extended this process to the intermolecular RCA of alkyl radicals to dehydroalanine-containing dipeptides *106* (Table 11) [124].

The stereocenter present in each substrate has exerted little influence over the hydrogen atom abstraction step, as the products *107* (Table 11) are obtained in low *de*. Tripeptides are also viable substrates in this reaction, producing RCA adducts in good yields (87–88%) but poor *de* (3–15%).

Yim and Vidal have shown that the Crich method could be employed in the solid-phase synthesis of α-amino acids by anchoring the dehydroalanine radical acceptor to a Wang resin (Scheme 52) [125]. Cleavage of the *N*-acetyl amino acid from the resin is accomplished by acid treatment.

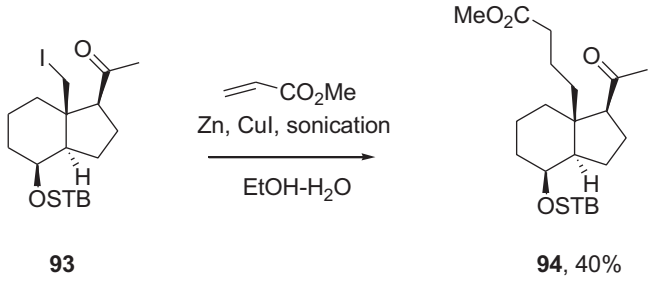
The pioneering works by Luche, Li, Naito and others have shown that it is possible to carry out alkyl additions to conjugated systems in water. Unfortunately, in most cases, the use of harsh reaction conditions such as ultrasonication, inert atmospheres, cosolvent systems, and the narrow substrate scope limit their applicability to complex molecule synthesis. Therefore, the development of more general and practical methods for alkyl addition to α,β-unsaturated carbonyl compounds under mild conditions is highly desirable.

More recently, Loh and collaborators [126] have attempted the alkylation reaction of α,β-unsaturated carbonyl compounds in water using activated alkyl halides and In/CuI/I_2 or In/AgI/I_2 system. From their results, it becomes apparent that the use of organic solvents inhibits the occurrence of the Barbier–Grignard-type alkylation reaction. In contrast to the work reported by Li and coworkers [82] it is noteworthy that even aliphatic aldehydes can also react efficiently with alkyl iodides to furnish the alkylated products in good yields.

Lately, Loh and coworkers have developed alkylation reactions of unactivated alkyl iodides to α,β-unsaturated carbonyl compounds in water (including a chiral version) using indium/copper in water [98]. In addition, the formation of symmetrical *vic*-diarylalkanes is observed when aryl-substituted alkenes are used as the substrates.

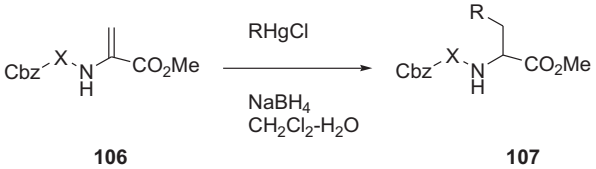
Initial studies have focused on the reaction of α,β-unsaturated ester and cyclohexyl iodide under different reaction conditions.

As shown in Table 12, the combination of In/CuI/$InCl_3$ (6:3:0.1) is an efficient system for activation of the conjugate addition reaction of *110* in water (see Table 12). The reaction proceeds

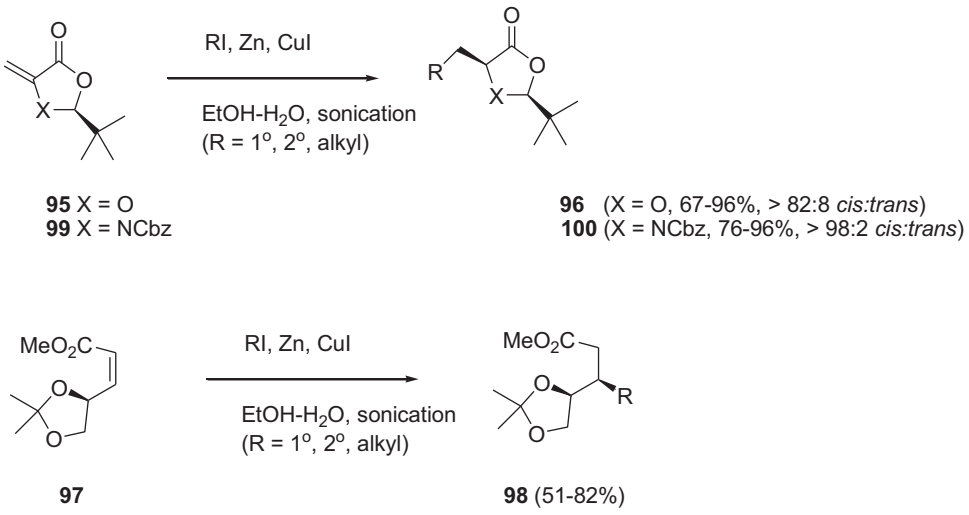


Scheme 48. Zn-induced intermolecular RCA of hindered neopentylic iodide *93* to methyl acrylate (Ref. [66]).

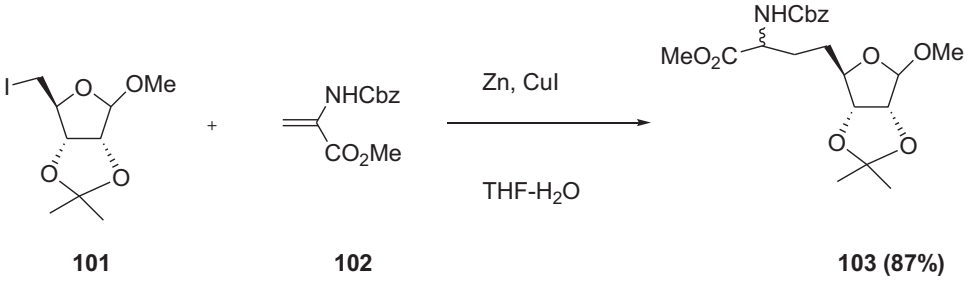
Table 11
Alkylation of peptides in aqueous mixtures using RHgCl/$NaBH_4$ (Ref. [123]).



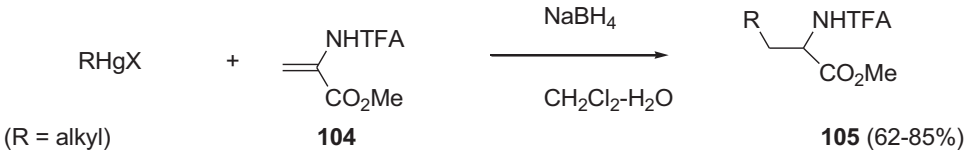
Entry	X	R	Yield (%)	*de* (%)
1	L-Val	*c*-C_6H_{11}	71	11
2	L-Phe	*c*-C_6H_{11}	64	5
3	L-Cys(Z)	*c*-C_6H_{11}	70	6
4	L-Ser	*c*-C_6H_{11}	42	1
5	L-Pro	*i*-Pr	98	1



Scheme 49. Zn-mediated diastereoselective radical conjugate addition in EtOH–H_2O (Refs. [60–62]).

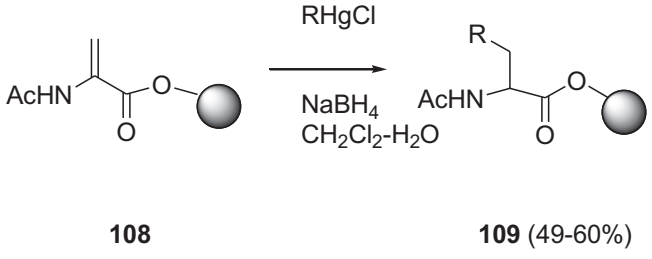


Scheme 50. Zn-induced radical conjugate addition with a ribose derivative in THF–water (Refs. [16,120,121]).



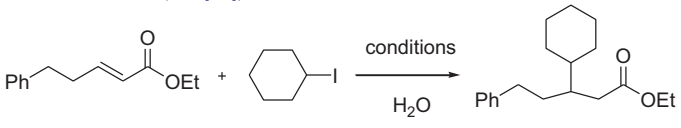
Scheme 51. Synthesis of dehydroalanine derivatives via RCA in CH_2Cl_2–H_2O (Ref. [123]).

smoothly at room temperature to generate the corresponding adduct *111* in 80% yield (entry 1). It is important to note that, without the use of CuI, the reaction proceeds sluggishly to give the desired product in poor yield (entry 2). Without the addition of $InCl_3$, the yield of the product decreases to 54% (entry 3). In addition, the use of the metal (*i.e.* indium) is also indispensable (entry 4). Among the several metals screened, indium proves to be the best for this reaction. The following order is apparent for activation of the conjugate alkylation: In > Zn > Al > Sn. Other copper and silver compounds such as CuBr, CuCl, and AgI were also investigated, but all gave the products in lower yields in comparison to CuI (entries 5–7). The reactions proceed more efficiently in water than in organic solvents such as MeOH, THF, CH_2Cl_2, DMF, DMSO, and hexane. Furthermore, the reactions are



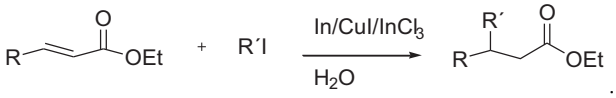
Scheme 52. Solid state synthesis of α-amino acids in CH_2Cl_2–H_2O (Ref. [125]).

Table 12
Reactions of a α,β-unsaturated ester with cyclohexyliodide under different conditionsin water (Ref. [98]).



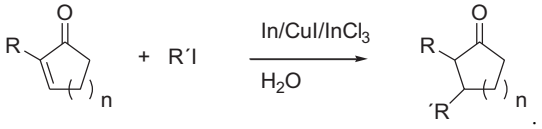
Entry	Conditions	Yield *111* (%)
1	In/CuI/$InCl_3$	80
2	In/$InCl_3$	<20
3	In/CuI	54
4	CuI/$InCl_3$	0
5	In/CuBr/$InCl_3$	68
6	In/CuCl/$InCl_3$	<50
7	In/AgI/$InCl_3$	48

Table 13
Radical conjugate additions of alkyl iodides to different α,β-unsaturated esters in water, employing In/CuI/$InCl_3$ in water at room temperature (Ref. [98]).



Entry	α,β-Unsaturated ester R	Alkyl iodide R′	Yield (%)
1	$PhCH_2CH_2$	Cyclohexyl iodide	80
2	$PhCH_2CH_2$	Cyclopentyl iodide	84
3	$PhCH_2CH_2$	Isopropyl iodide	70
4	$PhCH_2CH_2$	2-Iodobutane	73
5	$PhCH_2CH_2$	Cyclohexyl iodide	70
7	$PhCH_2CH_2$	Cyclohexyl iodide	61
8	C_5H_{13}	Cyclohexyl iodide	84
9	CH_3	Cyclohexyl iodide	76
10	$PhCH_2OCH_2$	Cyclohexyl iodide	46

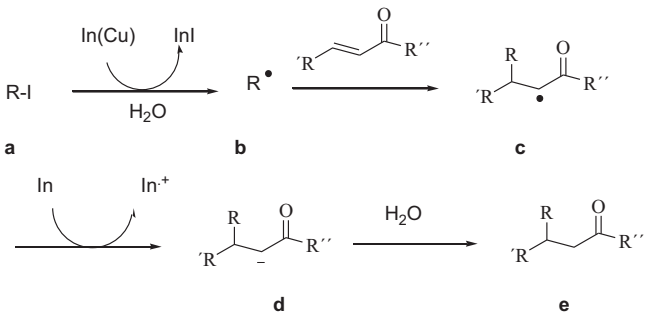
Table 14
Radical conjugate additions of alkyl iodides to different α,β-unsaturated enones in water, employing In/CuI/$InCl_3$ at room temperature (Ref. [98]).



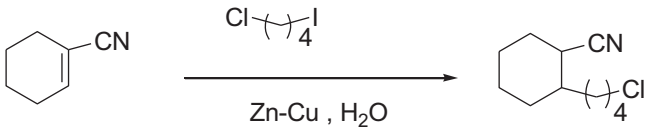
Entry	Enone	Alkyl iodide, R′I	Yield (%)
1	R = H, *n* = 2	Cyclohexyl iodide	85
2	R = H, *n* = 2	Cyclopentyl iodide	78
3	R = H, *n* = 2	Isopropyl iodide	73
4	R = H, *n* = 2	Hexyl iodide	45
5	R = H, *n* = 1	Cyclohexyl iodide	53
6	R = Me, *n* = 1	Cyclohexyl iodide	81
7	$R = C_6H_{13}$, *n* = 1	Cyclohexyl iodide	83
8	R = H, *n* = 3	Cyclohexyl iodide	74

carried out without an inert atmosphere and ultra-sonication is unnecessary.

The reaction is extended to various α,β-unsaturated esters and enones, as shown in Tables 13 and 14. A plausible reaction mechanism is proposed (Scheme 53). The reaction is possibly initiated by a single-electron transfer from indium/copper to alkyl iodide *a* (Scheme 53) to generate an alkyl radical *b* (Scheme 53). This radical can attack the α,β-unsaturated carbonyl compound via 1,4-conjugate addition to furnish a radical intermediate *c* (Scheme 53). Subsequent indium-promoted reduction of intermediate *c* and quenching of the generated anion *d* in the presence of water affords the expected product *e*. This method works with a wide variety of α,β-unsaturated carbonyl compounds. The mild reaction conditions, moderate to good yields, and the simplicity of the reaction procedure make this method an attractive alternative to



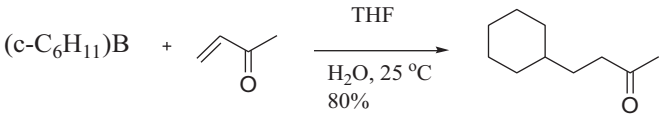
Scheme 53. Proposed mechanism for the RCA of α,β-unsaturated compounds with alkyl iodides employing In/CuI/$InCl_3$.



Scheme 54. Zn–Cu-induced conjugate additions of alkyl halides to alkenenitriles in water (Ref. [128]).

conventional methods using highly reactive organometallic reagents in anhydrous conditions.

Later on, it was demonstrated that trialkylboranes are excellent reagents for conjugate addition to vinyl ketones (Eq. (16)), acrolein, α-bromoacrolein and quinones.



(16)

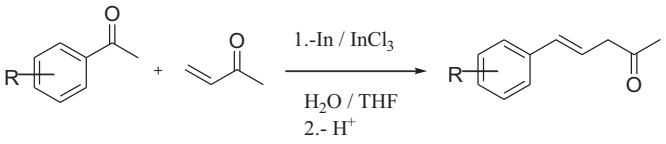
Various attempts to extend this reaction to β-substituted-α,β-unsaturatedcarbonyl compounds such as *trans*-3-penten-2-one, mesityl oxide, 2-cyclohen-1-one, and *trans*-crotonaldehyde were unsuccessful unless radical initiators were used.

Fleming and collaborators [128] have utilized a silica-supported zinc–copper matrix for promoting conjugate additions of alkyl iodides to alkenenitriles in water. Acyclic and cyclic nitriles react with functionalized alkyl iodides, overcoming the previous difficulty of performing conjugate additions to disubstituted alkenenitriles with nonstabilized carbon nucleophiles. Conjugate additions with ω-chloroalkyl iodides generate cyclic nitriles primed for cyclization, collectively providing one of the few annulation methods for cyclic alkenenitriles (Scheme 54).

2.8. Synthesis of β,γ-unsaturated ketones

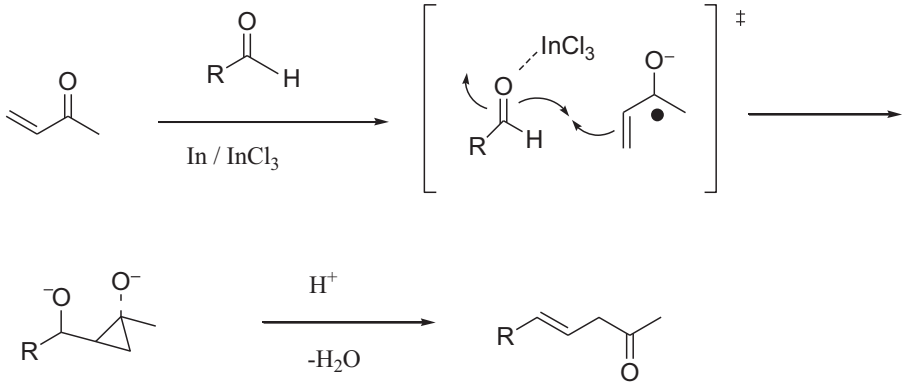
Through this review, it has been shown that indium has a great potential for a number of carbon–carbon bond forming reactions such as Reformatsky, Barbier type alkylation, allylation, and propargylation of carbonyl compounds. This is largely due to the fact that a highly reactive metal, such as indium, 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*) [127].

The indium-mediated reaction of benzaldehydes and methyl vinyl ketones proceeded smoothly in the presence of $InCl_3$ in aqueous media to form β,γ-unsaturated ketones [129]. Addition of NH_4Cl to the reaction mixture affords the desired β,γ-unsaturated ketones in good to moderate yields (Eq. (17)).



(17)

Generally, the yields of products are not affected by the nature of the substituents on the phenyl ring. The reaction also proceeds with heteroaromatic aldehydes. With the absence of In, or $InCl_3$ the reaction does not occur. When other Lewis acids such as $SnCl_4$, $FeCl_3$,



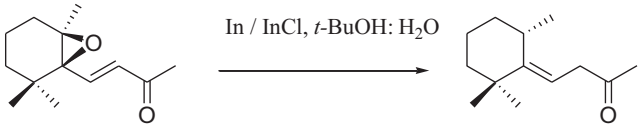
Scheme 55. Possible reaction mechanism for the In-mediated synthesis of β,γ-unsaturated ketones (Ref. [129]).

and $CuCl_2$ are used instead of $InCl_3$, low yields of β,γ-unsaturated ketones result (20–38%). When an aldehyde reacts with ethyl vinyl ketone instead of methyl vinyl ketone as a Michael acceptor, a coupling product is produced in 62% yield. The reaction conditions have been extended to other Michael acceptors such as acrolein, acrylonitrile, ethyl acrylate, and acrylic acid; however, the reactions didnot proceed [129].

The reaction mechanism is postulated to be a radical mechanism involving the radical anion intermediate of methyl vinyl ketone formed from indium (Scheme 55).

The reaction intermediate undergoes radical cyclopropanation and addition to benzaldehyde. Upon addition of butylated hydroxytoluene (BHT) a rate retardation effect is observed [129]. When the reaction is followed by ^{1}H NMR in a 1:1 mixture of THF-d_8 and D_2O, the cyclopropanyl proton signals are observed at δ 1.2–0.5 as multiplet. Quenching the reaction mixture with DCl in D_2O after an appropriate reaction time and examination of the $CDCl_3$-extracted products by ^{1}H NMR show the signal of the 5-phenyl-4-penten-2-onetogether with peaks of some MVK decomposed compounds.

Murphy and collaborators [130], however, have developed a facile and an environment-friendly protocol for the deoxygenation of epoxides with good radical-stabilizing groups adjacent to the oxirane ring, using indium metal and indium (I) chlorideor ammonium chloride in alcohol/water mixtures (Eq. (18)). This reaction affords β,γ-unsaturated ketone compounds.



112 **113**

84% (*E*:*Z* = 1:0.8)

(18)

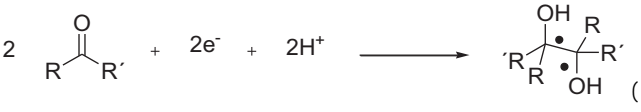
Oxirane *112* undergoes smooth deoxygenation to afford the alkene *113* in an excellent 84% yield. The reaction sequence is depicted in Scheme 55.

The formation of alkene *113* can be explained via the reduction of the expected dienone intermediate *114* by indium metal (Scheme 56) [130]. Epoxides can also be converted to the corresponding vicinal diols through reaction with cerium ammonium nitrate (CAN) in water [130].

2.9. Metal radical-mediated pinacol and other reductive cross coupling reactions in water

Since the first report of the reaction of acetone with sodium in 1858 [131], various low-valent metals such as Al [132], Sm [133], V [134], Mg [135], Zn [136], Mn [137], Sn [138], Ti [139], Ce [140], Te [141], U [142], Cr [143], Ga [144], and In [145] have been used to promote this reductive coupling reaction. Among these methods, some require absolutely anhydrous system under inert atmosphere, and some reagents and solvents are costly, moisture-sensitive, and toxic. In order to find environmental friendly conditions, it is very attractive to develop a new convenient method for the pinacol coupling by utilizing less toxic reagents and solvents. During past decades, great efforts have been devoted by chemists to explore environmentally benign systems for pinacol reaction. Different catalysts/co-catalysts in aqueous media including $TiCl_3$, VCl_3/Al, Mn/HOAc, Al/MF, etc. have been reported with promising results.

As is well known the reductive (pinacol) coupling of carbonyl compounds is a useful method for the creation of carbon–carbon bonds with 1,2-difunctionality (Eq. (19)). Although detailed mechanistic studies of pinacol coupling are lacking, the reactions are generally considered to involve the generation and reaction of the substrate ketyl (radical anion) with either the neutral substrate or another ketyl species.

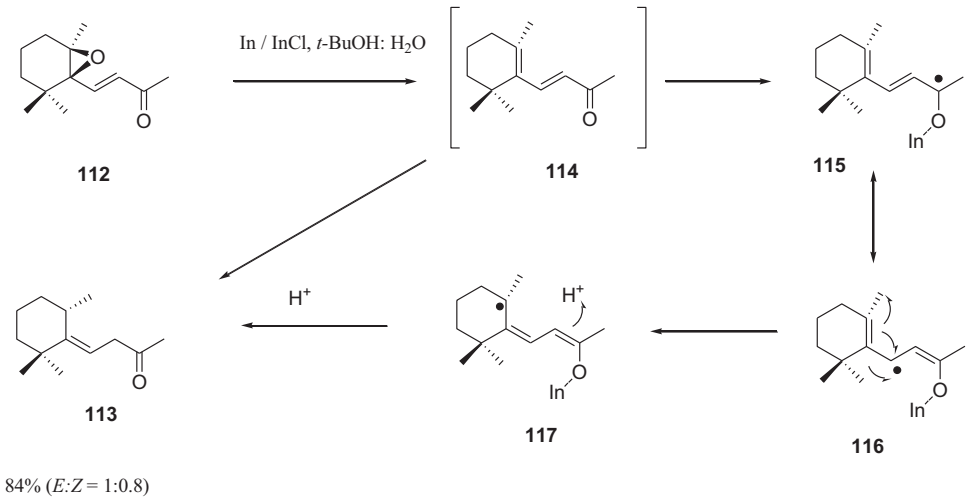


(19)

The pinacol-coupling reaction (*vide supra*) is a fundamental reaction in organic chemistry. The pinacol coupling reaction in water mediated by Ti(III) and other metals such as Zn–Cu also promote pinacol formation under ultrasonic radiation conditions in aqueous acetone [139]. When benzaldehyde reacts with manganese in the presence of a catalytic amount of acetic acid in water, the corresponding pinacol coupling product is obtained smoothly. Other aryl aldehydes are coupled similarly. On the other hand, aryl and aliphatic ketones appear to be inert under the same reaction conditions, and only the reduced product is obtained with aliphatic aldehydes [82].

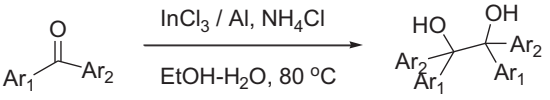
Aromatic aldehydes react with Mn in an aqueous solution in the presence of a catalytic amount of acetic acid or in aqueous ammonium chloride to yield diols. The yields are good but the selectivity is poor [69,147b].

Pan, Wu, and collaborators have reported on the pinacol coupling of aromatic aldehydes and ketones using $InCl_3$/Al in aqueous media [147a]. Under the optimized conditions (Table 15, entry 1),



Scheme 56. Plausible mechanism for the indium-mediated deoxygenation of epoxides in aqueous media (Ref. [130]).

Table 15
Pinacol coupling of substituted benzophenones by using $InCl_3$/Al in EtOH/H_2O under various reaction times (Ref. [147a]).



118a-h **119a-g**

Entry	Ar_1	Ar_2	Time (h)	Yield of *119* (%)
1	Ph	Ph	5	*119a*, 92
2	4-$CH_3C_6H_4$	Ph	5	*119b*, 90
3	4-F C_6H_4	4-F C_6H_4	5	*119c*, 98
4	4-MeO C_6H_4	4-F C_6H_4	11	*119d*, 48
5	4-MeO C_6H_4	Ph	11	*119e*, 72
6	4-Cl C_6H_4	Ph	3	Mixture
7	4-C_6H_5 C_6H_4	Ph	3	Mixture
8	4-Cl C_6H_4	Ph	5	*119f*, 64
9	4-C_6H_5 C_6H_4	Ph	5	*119g*, 65
10	2-Cl C_6H_4	Ph	5	–

various substituted benzophenones have been investigated to give a series of 1,1,2,2-tetraaryl substituted -diols (*119a–h*) (Table 15).

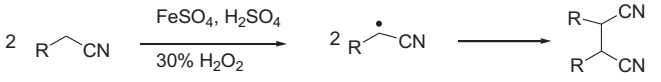
From these results, the authors find that *119a–h* are obtained in excellent yields without formation of by-product due to reduction of the carbonyls to the corresponding alcohols (Table 15, entries 1–3). Benzophenones bearing electron-donating groups (*118d,e*) *para* to ketones are reduced to the corresponding pinacols in the moderate yields even after 11 h (Table 15, entries 4 and 5). Unfortunately, the reactions of benzophenones bearing electron-withdrawing groups (*118f,g*) *para* to ketones with $InCl_3$/Al reagent at 80 °C for 3 h afford miscellaneous products, in which most starting materials have been consumed (Table 15, entries 6 and 7). On the other hand, lower temperature give pinacols in moderate yields (Table 15, entries 8 and 9) along with a small quantity of the corresponding alcohols. Unexpectedly, benzophenone bearing a chlorine group (*118h*) *ortho* to ketone only give the corresponding alcohol as the main product.

Coupling of water-soluble acetonitrile derivatives has been developed by Holtz, Pinhas, and coworkers using a Fenton's reagent (Scheme 57) [147].

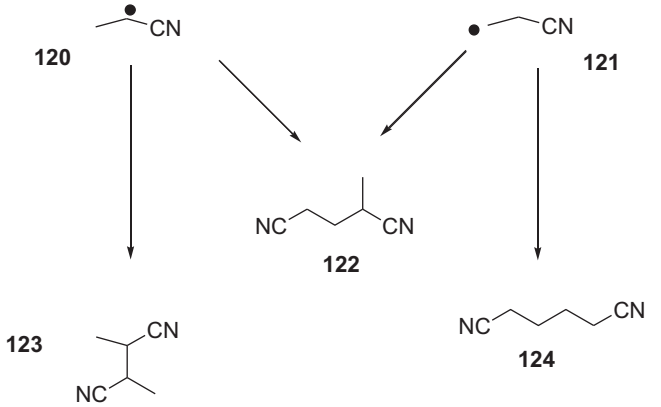
For this reaction, it does not matter if a free radical or an iron oxo complex is formed. What matters is that the Fenton chemistry generates a radical [148,149] or radical-equivalent [150] that can remove a hydrogen atom from the alkyl chain of the alkyl nitrile, and then two of these "alkyl radicals" can couple. This type of coupling reaction was first mentioned about 50 years ago [151], but unfortunately, the yields were low and the regiochemistry was not investigated in detail. In another report, the coupling of acetonitrile and other water-soluble alkyl nitrilesis discussed [152]. Reaction yields are improved, and in addition, the authors have investigated the regiochemistry of the coupling reaction. This regiochemistry not only is important from a synthetic perspective, but also it tells the energetics of hydrogen-atom removal from various positions on the alkyl chain.

Since the cyanomethyl radical is the only radical that can be obtained from acetonitrile, succinonitrile is the only dinitrile product. However, propionitrile can form two radicals: a resonance-stabilized secondary radical (*120*) formed by abstraction of an α-hydrogen atom or a primary radical (*121*) by abstraction of α-hydrogen atom. The products formed by all possible combinations of these two radicals are illustrated in Scheme 58.

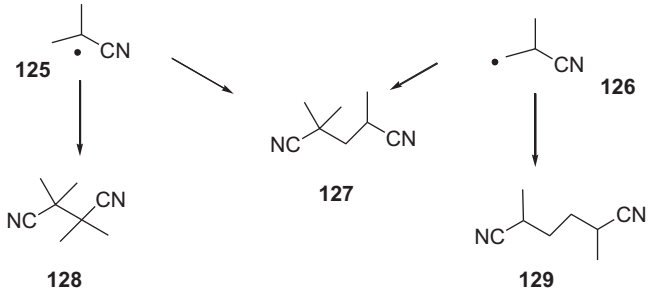
Stereoisomers of 2,3-dimethylsuccinonitrile (*123*) (D,L-pair and a *meso* compound) are formed by the coupling of two molecules of the secondary radical (*120*), while two primary radicals (*121*)



Scheme 57. Pinacol coupling of nitriles by Fenton reagent in aqueous media (Ref. [147]).



Scheme 58. Possible combination products from pinacol coupling of propionitrile (Ref. [152]).



Scheme 59. Possible combination products from pinacol coupling of *iso*butyronitrile (Ref. [152]).

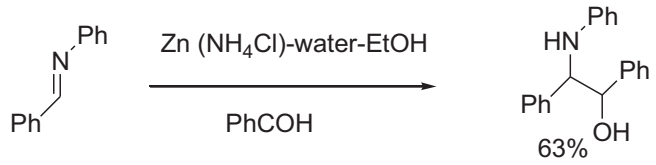
combine to form adiponitrile (*124*). Cross-coupling of these two radicals produces 2-methylglutamonitrile (*122*). The observed ratio for dinitrile isomers *122:123:124* is 50:45:5. After correcting for the number of abstractable hydrogen atoms at each position, it has been determined that the resonance-stabilized secondary radical (*120*) and the primary radical (*121*) form in a 1.5:1 ratio rather than the statistical ratio of 2:3.

*Iso*butyronitrile can also form two radicals: a resonance-stabilized tertiary radical (*125*) formed by abstraction of an α-hydrogen atom or a primary radical (*126*) by abstraction of β-hydrogen atom. The products formed by all possible combinations of these two radicals are illustrated in Scheme 59.

Stereoisomers of 2,5-dimethyladiponitrile (*129*) (D,L-pair and a *meso* compound) are formed by the coupling of two molecules of the primary radical (*126*), while two tertiary radicals (*125*) combine to form 2,2,3,3-tetramethysuccinonitrile (*128*). Cross-coupling of these two radicals produces 2,2,4-trimethylglutamonitrile (*127*).

The observed ratio for dinitrile isomers *127:128:129* is 26:29:45. After correcting for the number of abstractable hydrogen atoms at each position, it has been determined that the resonance-stabilized tertiary radical (*126*) and the primary radical (*125*) form in a 4.3:1 ratio rather than the statistical ratio of 1:6.

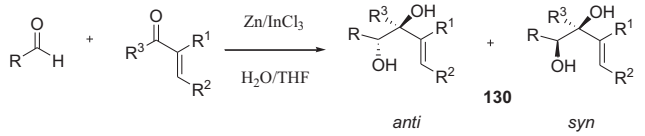
Since the cyanomethyl radical is easily reduced to the cyanomethyl anion by iron(II), with a stoichiometric amount of iron, the lower yield is not surprising. To improve the yield, the concentration of iron(II) should be kept low. Thus for large scale preparation of succinonitrile via Fenton's reagent, the reaction should be catalytic in iron(II), keeping its concentration as low as possible. Iron(0) is an attractive candidate as a reducing agent because iron(II) is the only product of the oxidation–reduction reaction.



Scheme 61. Zn-induced cross coupling of benzaldehyde and *N*-benzylidine aniline in EtOH–water (Refs. [154b,155b]).

Although the use of iron(0) creates a heterogeneous reaction which leads to greater variability in the product yield, the increased production of succinonitrile indicates that iron(0) has an effect on the coupling reaction by reducing iron(III) to iron(II).

Loh and collaborators [154a] have very recently reported an efficient pinacol cross-coupling reaction of aldehydes and α,β-unsaturated ketones using Zn/$InCl_3$ in aqueous media. The 1,2-diols*130* are thus obtained in moderate to good yields, with up to 93.7% diastereoselectivity (Eq. (20)).



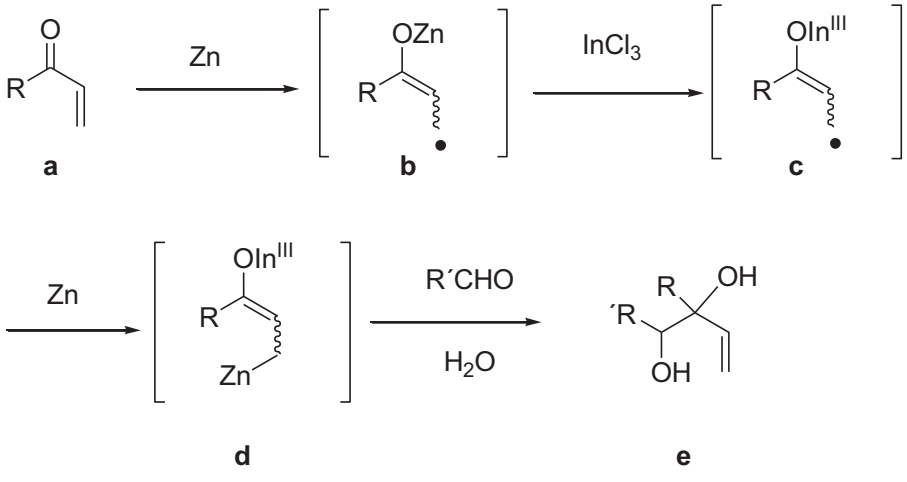
R = Ph $R^1 = R^2 = H$, $R^3 = CH_3$ 61:39 55%

(20)

A possible reaction mechanism is shown in Scheme 60. 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 $InCl_3$ affords the γ-In(III)-substituted allylic radical *c* (Scheme 60). 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* (Scheme 60).

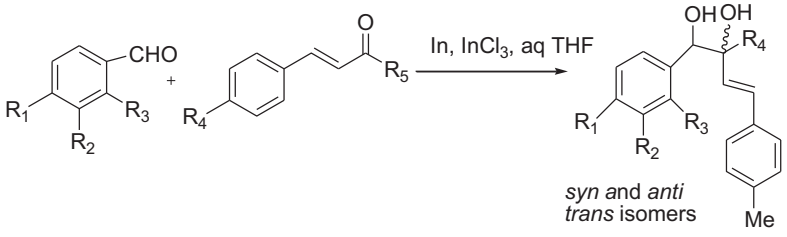
More recently, an intermolecular reductive cross coupling of *N*-benzylidene aniline and benzaldehyde is achieved in an aqueous medium, by using zinc powder and NH_4Cl as an additive (Scheme 61) [154b,155b].

Kalyanaman and Rao [155a] have reported a novel reductive coupling of aldimines*131* brought about by indium to vicinal diamines as described in Eq. (21) [155b]. The reaction occurs in



Scheme 60. Proposed mechanism for the pinacol cross coupling of enones and aldehydes (Ref. [154a]).

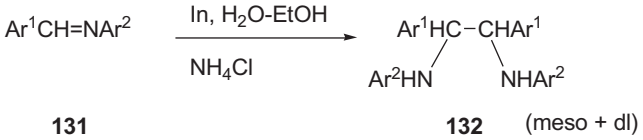
Table 16
Synthesis of substituted but-3-ene-1,2-diols using In, $InCl_3$ in aqueous THF (Ref. [155]).



134-141

Entry	Substituents	Products	Yield (%)	Ratio
1	$R^1 = R^2 = Cl$, $R^3 = R^4 = H$, $R^5 = Ph$	134	56	1:2
2	$R^1 = R^2 = Cl$, $R^3 = R^4 = H$, $R^5 = Me$	135	42	0:1
3	$R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = Me$, $R^5 = Ph$	136	60	1:2
4	$R^1 = Cl$, $R^2 = R^3 = R^4 = H$, $R^5 = Ph$	137	61	0:6.2
5	$R^1 = Cl$, $R^2 = R^3 = R^4 = H$, $R^5 = Me$	138	46	0:1
6	$R^1 = R^2 = H$, $R^3 = Cl$, $R^4 = Me$, $R^5 = Ph$	139	56	0:6.1
7	$R^1 = R^2 = R^4 = H$, $R^3 = Cl$, $R^5 = Ph$	140	42	0:4.1
8	$R^1 = R^2 = R^4 = H$, $R^3 = Cl$, $R^5 = Me$	141	56	0:1

aqueous ethanol. While NH_4Cl is not essential for the reaction, the reaction is accelerated by its presence. The reaction fails completely in CH_3CN, DMF and DMF containing small quantities of water. Indium used in the reaction is in the form of small rods made from a sheet of indium of about 1 mm thickness. It may be mentioned that optically pure derivatives of *132* have considerable potential in asymmetric synthesis (Eq. (21)).



131 **132** (meso + dl)

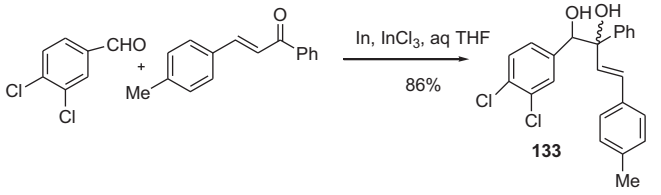
(21)

Some important aspects of the reaction are to be noted. The reaction occurs in aqueous medium and does not require exclusion of oxygen or anhydrous conditions as needed by other reagents mentioned in the literature for effecting the same transformation as in Eq. (21). The complete absence of the side product in the crude reaction mixture, $Ar'CH_2–NHAr$ (Eq. (21)) (a resultant of unimolecular reduction as happens in some of the methods employed for this transformation) is noteworthy. Further, the reaction is brought about by indium rods and does not require fine indium powder. The product *132* is invariably a 1:l mixture of *dl* and *meso* isomers indicating fast coupling of any putative radical intermediates. The reaction fails in the case of substrates, $Ph(CH_3)C{=}NPh$ and $PhCH{=}NCH_2Ph$, showing selectivity for the coupling of aldimines obtained from aromatic aldehydes and aromatic amines.

Nair et al. have reported on the indium/indium trichloride-mediated pinacol cross coupling of reaction of aldehydes and chalcones in aqueous media to obtain substituted but-3-ene-1,2-diols [155]. In an initial experiment, 3,4-dichlorobenzaldehyde is treated with 4-methylbenzylidene acetophenone in the presence of indium and indium trichloride in aqueous THF at room temperature to yield an isomeric mixture of 1-(3,4-dichlorophenyl)-2-phenyl-4-*p*-tolylbut-3-ene-1,2-diols*133* in 66% yield (Scheme 62).

Similar results are obtained with other chalcones and aldehydes (Table 16). With benzylidene acetone and aldehydes, only one *trans*-isomer is formed whereas with other α,β-unsaturated ketones and aldehydes a mixture of *syn* and *anti trans* isomers is obtained.

Halterman and collaborators have achieved the pinacol coupling of benzaldehydes in water mediated by $CrCl_2$ [156]. The pinacol



Scheme 62. Indium/indium trichloride-mediated pinacol cross coupling reaction of aldehydes and enones in aqueous media (Ref. [155]).

coupling of benzaldehyde in water is catalyzed by $CrCl_2$ in the presence of Zn-dust or Al-dust at 20 °C. In all cases at most 50% of the pinacol coupling product, 1,2-diphenyl-1,2-ethanediol, is obtained with the major product, benzyl alcohol, being formed by a competitive two-electron reduction of the carbonyl moiety. The DL- to *meso*-diastereoselectivity of the pinacol products ranged from 0.6:1 to nearly 1:1 (Fig. 4).

According to the catalytic scheme depicted in Fig. 5, Cr(II) can initially reduce the aldehyde (step a) to form radical intermediate B. The reactive carbon site in B can combine with a second aldehyde unit (either before or after its reduction) as in step b to form a coupled product C. Hydrolysis to release the 1,2-diol and reduction of the chromium species back to a lower valent metal as in step c completes the desired catalytic cycle. However, intermediate B can be further reduced by a second electron from coordinated chromium or by an electron from an external metal as in step d. This competitive side reaction can lead to the formation of the undesired reduced benzyl alkoxide D that can hydrolyze to form benzyl alcohol. In terms of the chemical selectivity for the pinacol coupling versus reduction to form benzyl alcohol, the benzyl alcohol is always the major product under all conditions studied. Under most conditions, the ratio of pinacol to benzyl alcohol varied from 1:1 to 1:2 [156]. The authorshave noted that at higher temperature with a higher ratio of starting chromium catalyst, a lower selectivity for the pinacol coupling is obtained.

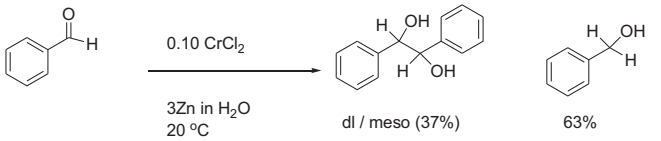


Fig. 4. Pinacol coupling of benzaldehyde by $CrCl_2$/Zn catalyst in water (Ref. [156]).

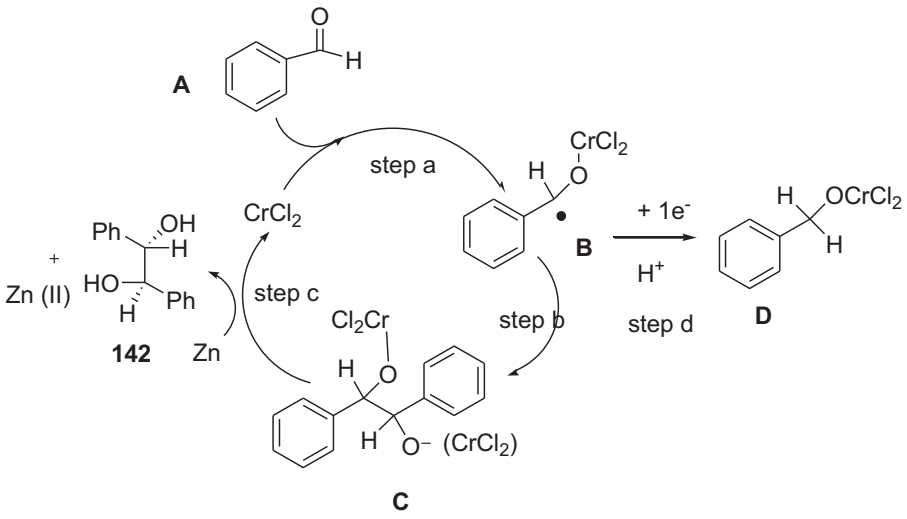
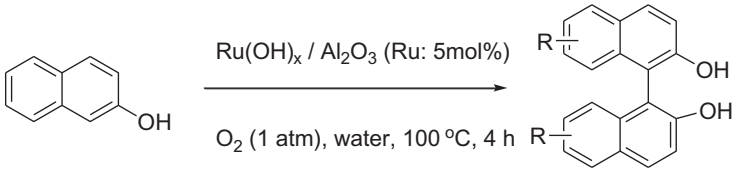


Fig. 5. Catalytic cycle for Cr(II)–Zn-catalyzed pinacol reaction with competitive benzaldehyde reduction (Ref. [156]).

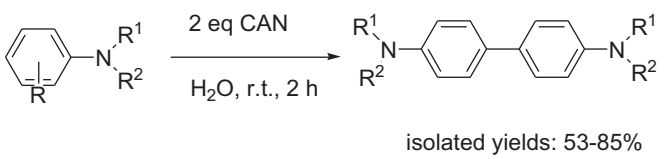
The catalytic reactions produce both diastereomeric pinacol products DL-*142* and *meso-142 with* the *meso*-product favored in ratios from 0.6:1 to nearly 1:1. The stereoselectivity in the presence of aluminum as the stoichiometric reductant is similar to that when zinc-dust is used.

Biaryl coupling of 2-naphthols and substituted phenols is efficiently promoted by a supported Ru catalyst using O_2 as an oxidant in water (Eq. (22)) [151]. The supported catalyst can be reused seven times without losing catalytic activity. The big advantages of this method are that an environmentally friendly oxidant (O_2) and solvent (H_2O) can be used. The studies on the mechanism behind the reaction showed that the Ru-catalyzed biaryl coupling reaction proceeds through the radical coupling mechanism.



(22)

Benzidine derivatives are obtained via oxidative coupling of *N,N*-dialkylarylamines using CuBr as a catalyst and H_2O_2 as an oxidant in water [157]. When cerium ammonium nitrate (CAN) is used as oxidant, homocoupling of *N,N*-dialkylarylamines is also effectively promoted using water as solvent (Eq. (23)) [158]. A rationale for the mechanism of this coupling reaction is proposed via dimerization of diradical cations. Unlike homocoupling of 2-naphthols and substituted phenols which give *ortho* products to the OH group, *para*-substituted products are selectively formed from *N,N*-dialkylarylamines substrates.



(23)

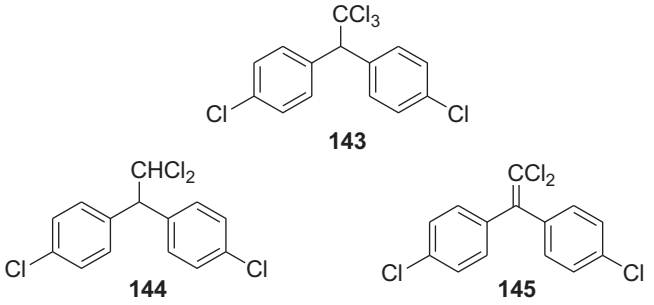
3. Metal-mediated reduction reactions in water

Reduction of organohalides in water by the non-metallic silicon-containing radical species such as silanes, have been thoroughly reviewed by Postigo and collaborators [36,37,160a,b]. Organotin water-soluble reducing agents have also been used successfully in the reduction of organohalides [160b].

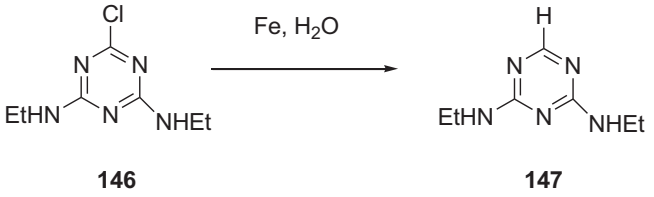
The capability of powdered zerovalent iron to dechlorinate DDT and related compounds at room temperature has been investigated by Sayles et al. [160]. Specifically, DDT (*143*), DDD [1,1-dichloro-2,2-bis-(*p*-chlorophenyl)ethane] (*144*), and DDE [1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene] (*145*) are successfully dechlorinated by powdered zerovalent iron in buffered anaerobic aqueous solution at 20 °C, with or without the presence of nonionic surfactant Triton X-114 (Scheme 63).

Granular iron metal causes the reductive dechlorination of two important chloracetanilide herbicides, alachlor and metolachlor [161], used for broadleaf weeds and annual grasses in domestic soybean and corn crops. The products of the reaction are chloride ion (84% mass balance for alachlor and 68% for metholachlor) and the corresponding dechlorinated acetanilides. The *N*-dealkylated acetanilide is a minor byproduct (9%) in the case of alachlor.

Atrazine (2-chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine) (*146*) is a herbicide used extensively in corn, sorghum, and sugarcane fields for the last 30 years [162], with a long half-life in the environment (up to one year) [163]. The possible water contamination, combined with the uncertainty of atrazine's carcinogenic and toxicological effects, has spurred interest in techniques that might more rapidly degrade atrazine and its metabolites. Batch aqueous experiments using fine-grained (100 mesh) zerovalent iron as an electron donor resulted in reductive dechlorination of atrazine to give 2-ethylamino-4-isopropylamino-1,3,5-triazine (*147*) (Scheme 64) [164].



Scheme 63. Reductive dechlorination of DDT (*143*), DDD (*144*), and DDE (*145*) by powdered Fe in aqueous solution (Ref. [160]).



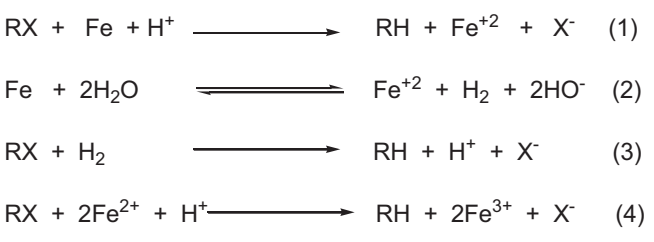
Scheme 64. Dechlorination of atrazine*146* by Fe in water (Ref. [165]).

The dechlorination of atrazine (*146*) with metallic iron under low-oxygen conditions was studied at different reaction mixture pH values (2.0, 3.0, and 3.8) (Scheme 64) [165]. The observed products of the degradation reaction are dechlorinated atrazine (*147*) and possibly hydroxyatrazine (2-ethylamino-4-isopropylamino-6-hydroxy-1,3,5-triazine). Triazine ring protonation is proposed to account, at least in part, for the observed effect of pH on atrazine by metallic iron.

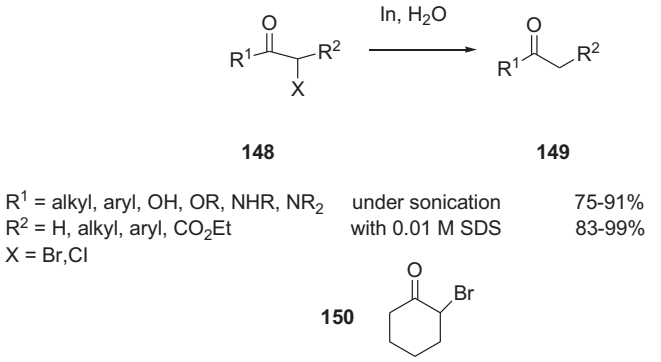
Although the mechanisms of these reductions with zerovalent iron are not well elucidated, it appears that, generally, a two-electron transfer process occurs either directly at the iron surface (by absorption of the organic halide) or through some intermediary (Scheme 65) [166]. In a different mechanistic context, numerous studies have shown that dissociative adsorption of water takes place at clean iron metal surfaces, resulting in surface-bound hydroxyl, atomic oxygen, and atomic hydrogen ("nascent hydrogen") [167]. The latter species can combine with itself, accounting for the formation of molecular hydrogen, or react with other compounds in the system, resulting in their hydrogenation (Scheme 65). A third possibility would be the reduction by iron(II), resulting from corrosion of the metal (Scheme 65). A debate over the relative importance of these mechanisms [168] has gone on for many years, but the electron-transfer model is generally preferred.

Indium is currently used as a reducing agent in water for organic halides.

The first systematic study on the dehalogenating power of indium was carried out by Ranu et al. [169]. This group provided an efficient and general methodology for the chemoselective reduction of α-halocarbonyl compounds and benzyl halides by indium



Scheme 65. Proposed reaction mechanism for the reduction of alkylhalides by Fe/H^+ in water (Ref. [168]).



Scheme 66. In-promoted dehalogenation of α-halo carbonyl compounds in water by ultrasound and with SDS (Refs. [170,171]).

metal in water under sonication. A wide range of structurally different α-iodo- and α-bromoketones and esters *148* underwent reduction, leading to the corresponding dehalogenated carbonyl compounds *149* (Scheme 66) [170].

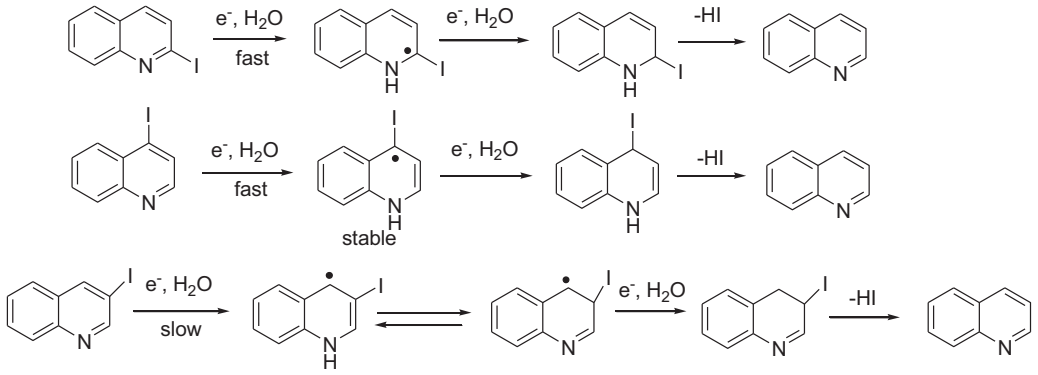
Brominated substrates are reduced slower than iodinated substrates. In fact, alkyl and aryl iodides remain inert although benzyl iodides and α-iodo-ketones are reduced. Selective deiodination is observed at the benzylic position *vs.* the aromatic carbon–iodine bond in the same substrate. The use of indium metal in aqueous medium has been extended to the stereoselective reduction of aryl-substituted *gem*-dibromides to vinyl bromides. The compatibility with several sensitive functional groups (OMe, OBz, Cl, OTBDMS, and *o*-allyl) and the absence of over reduction processes are the main advantages of this methodology. However, thiophene- and furan-substituted *gem*-dibromides do not show any stereoselectivity, whereas low effectiveness is observed for alkyl-substituted *gem*-dibromides. The use of micellar solutions as reaction media has shown an enhancement in the reactivity of certain processes [170]. Such is the case of the indium-mediated dehalogenation of α-halocarbonyl compounds *150* in water and in the presence of a catalytic amount of the surfactant sodium dodecyl sulfate (SDS) [171]. These conditions have been applied by Kim et al. to α-haloketones, esters, carboxylic acids, amides, and nitriles (Scheme 66).

For α-chlorocarbonyl compounds, the reaction is rather slow in comparison with that of the bromo derivatives, and a slightly higher temperature is required. In the absence of SDS, the reaction proceeds slowly and most of the starting materials are recovered unaltered after prolonged reaction times. The same group has reported the efficient reductive conversion of 3-iodomethylcephalosporin into the corresponding 3-methylcephems by indium in an aqueous system [172].

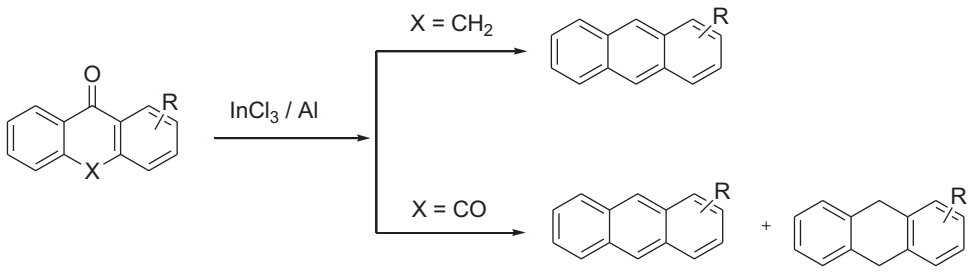
Sugimoto, Tanji, et al. have investigated the indium-mediated reduction of haloheteroaromatics in water [173]. The authors found that the deiodination of iodoheteroaromatics using indium in water is very effective. The proposed mechanism for the deiodination of iodoquinolines is depicted in Scheme 67.

When α or γ iodoquinoline is used as substrate, the dihydroquinoline radical generates smoothly since the radical is stabilized by iodine atom. On the other hand, β-iodoquinoline reacts with indium in water more slowly than α or γ iodo-quinoline because the dihydroquinoline radical is not stabilized by iodine atom. Several haloheteroaromatics are successfully dehalogenated by indium metal in water, such as iodopyridines, and iodoquinoline derivatives [173].

Kim and collaborators [174] have undertaken the reduction of nitroarene derivatives to anilines in the presence of indium and $InCl_3$ in THF/water (v/v = 5/1) at 50 °C (Table 17). Pan and collaborators [175] have developed an $InCl_3$-catalyzed reduction of



Scheme 67. Proposed deiodination mechanism of iodoquinolines in water mediated by indium metal (Ref. [173]).



Scheme 68. Reduction of anthrone and anthraquinone derivatives in water by $InCl_3$/Al (Ref. [175]).

anthrones and anthraquinones by using aluminum powder in aqueous media (Scheme 68). As R groups, alkyl and halide substituents can be present in the substrates. The yields of anthracene derivatives range from 72 to 92%.

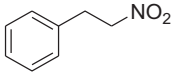
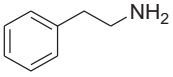
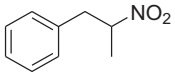
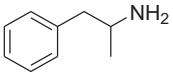
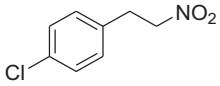
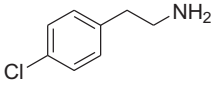
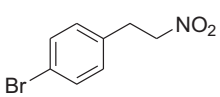
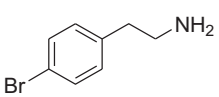
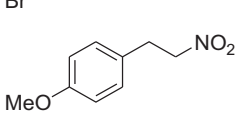
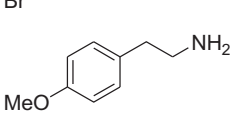
The reaction of 1,4-disubstituted anthraquinones, in which R is H or C_2H_5, with $InCl_3$/Al give different products. When the substituted anthraquinone, indium chloride, Al powder, and AcOH are mixed in 50% aqueous alcohol and stirred at reflux for 11 h, it affords compound *152* in good yields (Scheme 69).

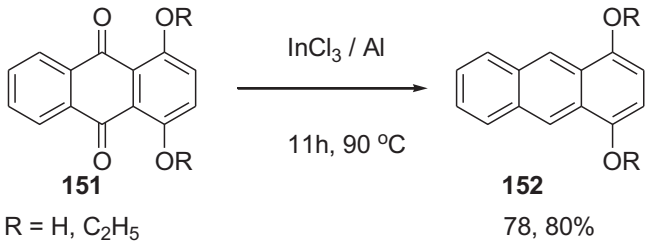
Based on the results from experiments, proposed mechanisms are provided. It is thought that the mechanism of reduction of anthrones is similar to the reduction at metal surfaces involving ketyl radical anions (Scheme 70). Protonated anthrone accepts an electron to form the intermediate *156*. Intermediate *156* can react in two directions: anthracene *154* and 9,10-dihydroanthracene *155* are obtained, respectively. In these experiments, the intermediate *156* is easy to react along route *154*, which just requires room temperature. Higher temperature is required *en route* to *155*. Therefore, when the temperature is reduced from 90 °C to r.t., anthracene *154* is obtained as single product in $InCl_3$-catalyzed reduction of anthrone *153*.

For the reduction of 9,10-anthraquinone *157*, another possible mechanism is also proposed (Scheme 71). 9,10-Anthraquinone *157* is reduced to anthrone *158* firstly. Then anthrone formed from 9,10-anthraquinone reacts in the way described in Scheme 70. Higher temperature is required during reduction of compound *158* to compound *154*, which is in agreement with experimental findings. At higher temperature, anthracene together with dihydroanthracene is obtained from anthrone. So anthracene cannot be obtained as single product in $InCl_3$-catalyzed reduction of 9,10-anthraquinone *157*. In order to further verify the proposed mechanism, $InCl_3$-catalyzed reduction process of 9,10-anthraquinone *157* is monitored by ESI-MS. Finally, the mechanism of $InCl_3$-catalyzed reduction of 1,4-disubstituted anthraquinones (R ¼ H, C_2 H_5) (Scheme 69) is proposed (Scheme 70).

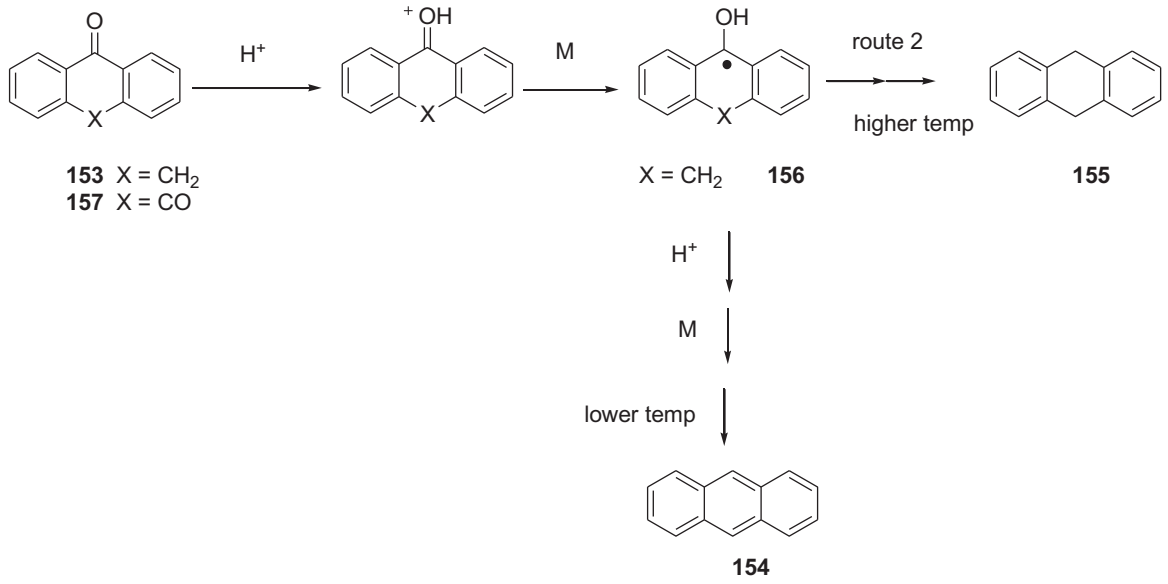
Samarium (as SmI_2) has been used profusely in a plethora of reduction reactions in organic solvents (THF), such as organic halide

Table 17
Reduction of nitroalkanes in water/THF by SmI_2/*iso*propylamine (Refs. [175,177a]).

Entry	Starting material	Product	Yield, %
1			99
2			92
3			95
4			60
5			96



Scheme 69. Reduction of anthraquinone derivatives in water by $InCl_3$/Al.



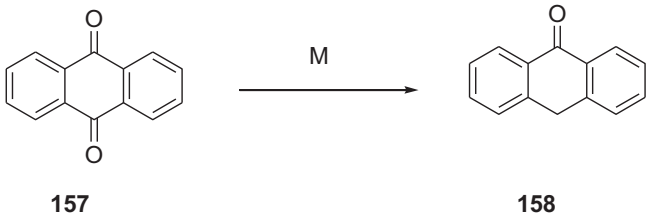
Scheme 70. Proposed reaction mechanism for the reduction of anthrone and anthraquinone in water.

reductions, reductions of carbonyl compounds, epoxides, sulfoxides, imine derivatives, lactones, deoxygenation of alcohols, and also in carbon–carbon bond forming reactions [43b].

Hilmersson and collaborators have accomplished the reduction of nitroalkanes and α,β-unsaturated nitroalkenes in water mediated by SmI_2/water/amine [177a]. Initial experiments have revealed that addition of a dilute solution of the nitro compound to a premixed THF solution of SmI_2, isopropylamine and water gave a clean and almost quantitative conversion of aliphatic nitro compounds to the respective amines, Table 17. All the reactions are instantaneous.

As a result of the successful reduction of the nitro group, the possibility to reduce α,β-unsaturated nitroalkenes directly to amines using the SmI_2/H_2O/amine reagent has been investigated. GC analysis indicates clean and instantaneous conversion to saturated amines. However, the isolated yields after workup are only 22–75%, see Table 18. The dimethoxy derivative (entry 6) is isolated in fairly high chemical yields (75%). Again, the competing reduction of the aryl bromide is observed with the aryl bromide substrate (entry 4).

An indium-promoted reduction–rearrangement reaction of nitro-substituted *β*-lactams has been used for a convenient synthesis of oxazines in aqueous ethanol. Treatment of the nitro-*β*-lactams *159* with indium–ammonium chloride in aqueous ethanol under reflux produces oxazines *160* with an excellent yield (Scheme 72). The reaction does not proceed in the absence of water. Other metals, such as zinc and tin, fail to promote the ring-cleavage reaction effectively. Reduction of the aromatic nitro group to the amino group and its nucleophilic attack to the *β*-lactam carbonyl presumably are the steps involved in the rearrangement toward oxazines (Scheme 72) [177b,c].



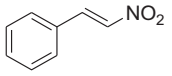
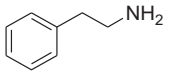
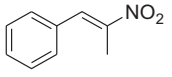
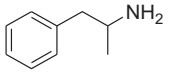
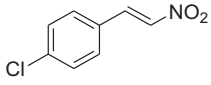
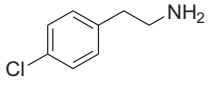
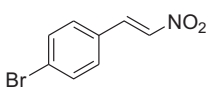
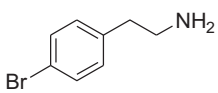
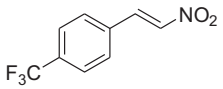
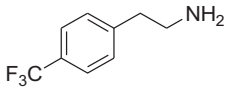
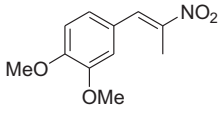
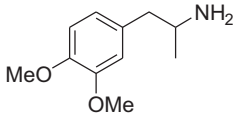
Scheme 71. Metal-induced reduction of anthraquinone in water.

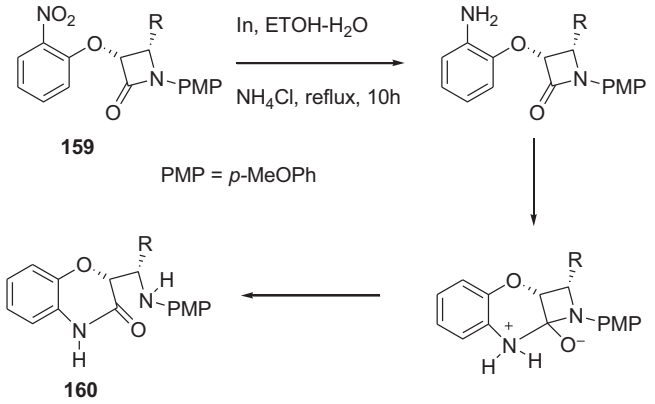
Manabe, Ito and collaborators have attempted the reductive deprotection of aryl and alkyl propargyl ethers with the couple SmI_2/amine in water, according to Scheme 73 [177d]. This protocol is very convenient for the propargyl ether deprotection of propargyl termini of protected oligosaccharadides.

The reduction of sodium alkyl thiosulfates is accomplished by the use of Sm in THF-aq NH_4Cl solution, according to Scheme 74 [177e].

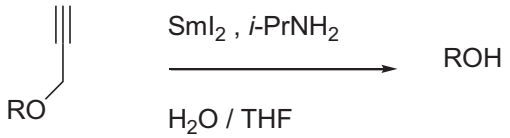
Procter and collaborators have accomplished the reduction of lactones and cyclic 1,3-diesters in water mediated by SmI_2 [177]. The authors have reported on the first reduction of lactones to diols using SmI_2/H_2O. The reagent system is selective for the reduction of lactones over esters, furthermore, it displays complete ring size-selectivity in that only 6-membered lactones are converted to the

Table 18
Reduction of nitroalkenes in water/THF by SmI_2/*iso*propylamine (Ref. [177a]).

Entry	Starting material	Product	% Yield
1			60
2			52
3			47
4			22
5			45
6			75



Scheme 72. In-promoted synthesis of oxazine *160* from nitro-β-lactams *159* in EtOH–H_2O under reflux (Ref. [177b,c]).



Scheme 73. Deprotection of propargyl ethers with SmI_2–amine in water–THF (Ref. [177d]).

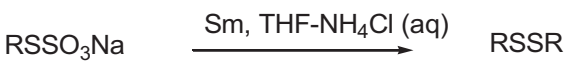
corresponding diols. Experimental and computational studies suggest the selectivity originates from the initial electron-transfer to the lactone carbonyl and that anomeric stabilization of the radical-anion formed is an important factor in determining reactivity.

Mixtures of lactones are prepared and treated with SmI_2/H_2O. In all cases, no reduction products arising from 5, 7 and 8-membered lactones are observed while 6-membered lactones are reduced smoothly (Scheme 75).

Modified SmI_2 reagent systems employing additives (HMPA, DMPU, LiBr) are also ineffective for the reduction of other lactones. A possible mechanism for the transformation is given in Scheme 76.

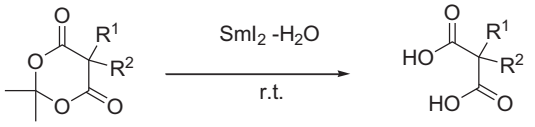
Activation of the lactone by coordination to Sm(II) and electron-transfer generates radical anion *163* that is then protonated. A second electron transfer generates carbanion *165* which is quenched by the H_2O cosolvent. Lactol *166* is in equilibrium with hydroxy aldehyde *167* and is reduced by a third electron-transfer from Sm(II) to give a ketyl radical anion *168*. A final electron-transfer from Sm(II) gives an organosamarium that is protonated by H_2O. The amount of SmI_2 (approximately 7 equiv) required experimentally is consistent with the amount predicted by the proposed mechanism (4 equiv).

For 6-membered lactones, the authors [177] believe that reduction generates a radical anion intermediate *163* (Scheme 76) that is stabilized by interaction with the lone-pairs on both the endocyclic and exocyclic oxygen atoms. Such interactions are known to be more pronounced in 6-membered rings than in other, conformationally more labile, ring systems. It appears that the greater stability of the radical anion *163*, compared to analogous radicals formed from the reduction of 5-, 7- and 8-membered lactones, promotes the initial reduction step. This hypothesis is supported by the observation that 2-oxabicyclo[2,2,2]octan-3-one *169* (Scheme 77), from which an intermediate radical-anion would be unable to



Scheme 74. Reduction of sodium alkylsulfates (Ref. [177e]).

Table 19
Reduction of lactones using SmI_2 in water at room temperature (Ref. [177]).



R^1	R^2	R^1	R^2	Yield *171* (%)
Bn	Bn	Bn	Bn	88
	$-(CH_2)_4-$		$-(CH_2)_4-$	81
H	Bn	H	Bn	68
H	4-$MeOC_6H_4$	H	4-$MeOC_6H_4$	78
H	4-BrC_6H_4	H	4-BrC_6H_4	77
H	*i*-Bu	H	*i*-Bu	94
Me	Bn	Me	Bn	98
H	Ph	H	Ph	72
	=CH*i*Pr	H	*i*-Bu	87
	$-(CH_2CH_2)-$	H	Et	75

adopt the chair conformation necessary for optimal stabilization, is not reduced by SmI_2/H_2O (Scheme 77).

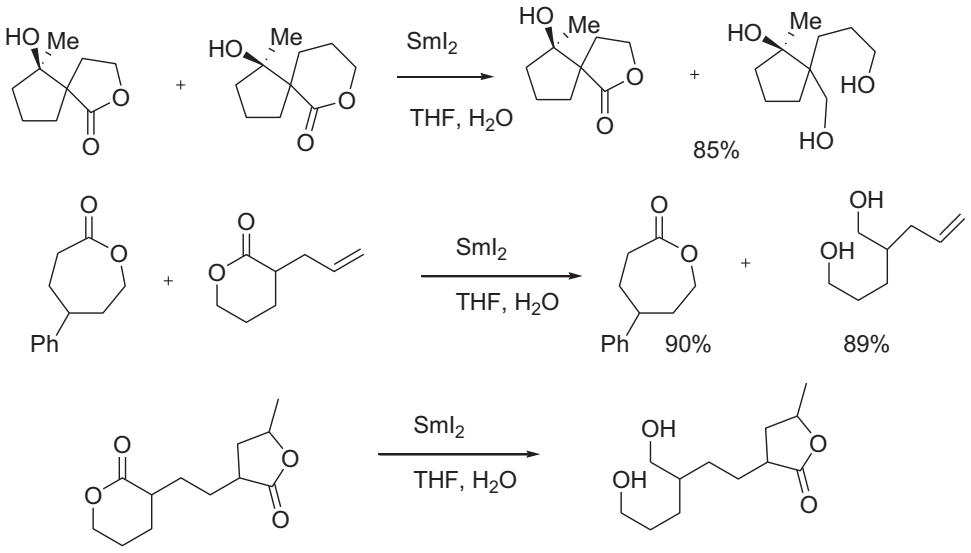
Calculations suggest that the first electron-transfer to the lactone carbonyl is endothermic (100 kJ mol^{-1}) in all cases. The relative reaction energy of this step for 6-membered lactones, however, is calculated to be 116 kJ mol^{-1}, about 25–26 kJ mol^{-1} lower than those involving 5- and 7-membered rings. The relative reaction energy for the first electron-transfer to bicyclic lactone *169* is calculated to be 147.4 kJ mol^{-1}. The second electron transfer is lower in energy and similar for all systems, agreeing with kinetic studies showing that the first electron-transfer is the rate-determining step. The calculated lowest energy conformation of the radical anion derived from a 6-membered anion suggests that the radical does indeed adopt a *pseudoaxial* orientation apparently enjoying stabilization by an anomeric effect. Activation of the lactone by coordination to Sm(II) and electrostatic stabilization of the product radical-anion by coordination to Sm(III) is likely to render these reductions more favorable than the calculated relative reaction energies suggest (Scheme 77). The same authors [177] have also accomplished the reduction of cyclic 1,3-diesters employing SmI_2/H_2O, as shown in Table 19 below.

The activation of the lactone by coordination to Sm(II) and electrostatic stabilization of the product radical-anion by coordination to Sm(III) is depicted in Scheme 78.

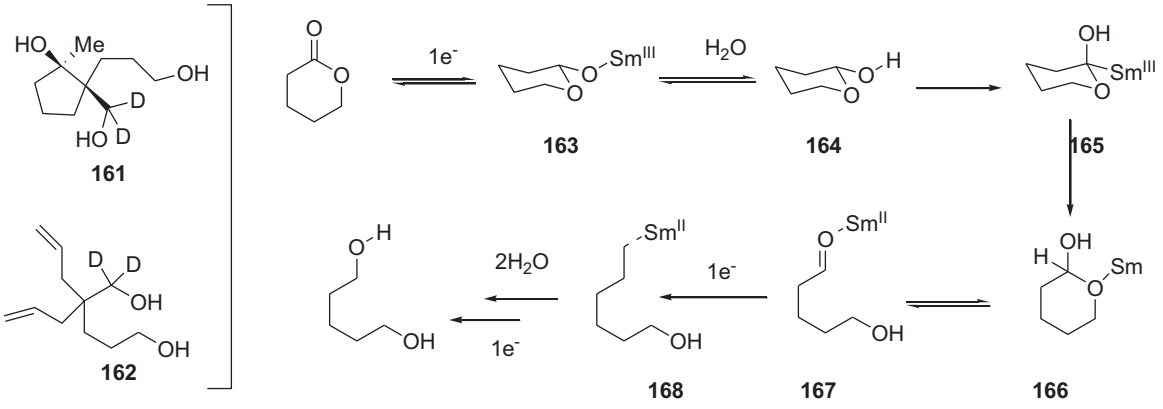
The mechanism proposed also involves radical-ion intermediates as shown in Scheme 79. The reduction of *172* with SmI_2/D_2O gives *173* (see Scheme 79) suggesting that anions are generated and protonated by H_2O during a series of electron transfer steps. A possible mechanism for the transformation is given in Scheme 79. Activation of the ester carbonyl by coordination to Sm(II) and electron transfer generates radical anion*174* that is then protonated (*175*). A second electron transfer generates carbanion *176* which is quenched by H_2O. Hemiacetal *177* is in equilibrium with aldehyde *178*, which is reduced by a third electron transfer from Sm(II) to give a ketyl-radical anion *179*. A final electron transfer from Sm(II) gives an organosamarium that is protonated. The amount of SmI_2 (approximately 7 equiv) required experimentally is consistent with the amount predicted by the proposed mechanism (4 equiv) (Scheme 79).

Hilmersson and collaborators [179a] have also investigated the mechanistic details of reduction of organic halides mediated by SmI_2/H_2O/amine system.

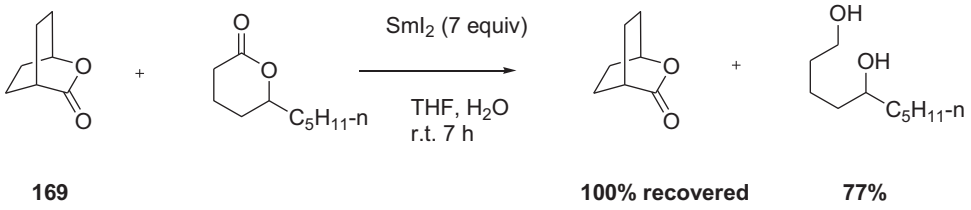
Aromatic aldehydes and ketones, such as benzaldehyde and acetophenone, have been reduced enantioselectively by Ir complexes in aqueous media [179d].



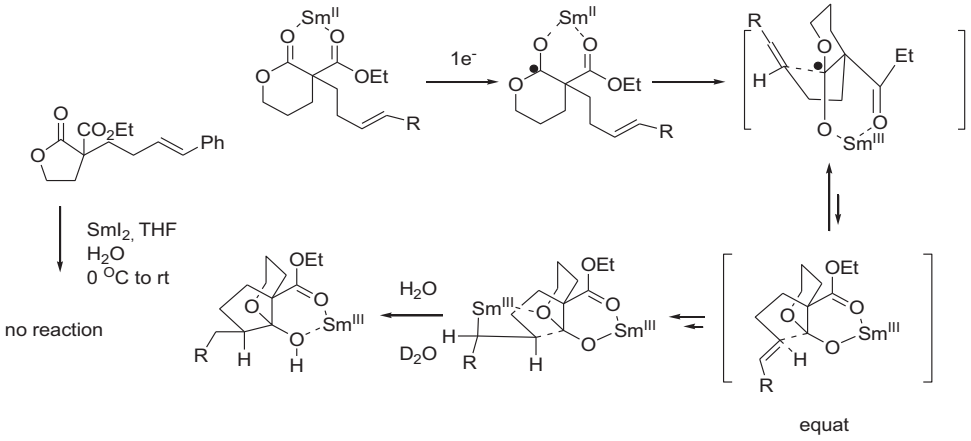
Scheme 75. Reduction of 6-membered lactones promoted by SmI_2 in THF–water (Ref. [177]).



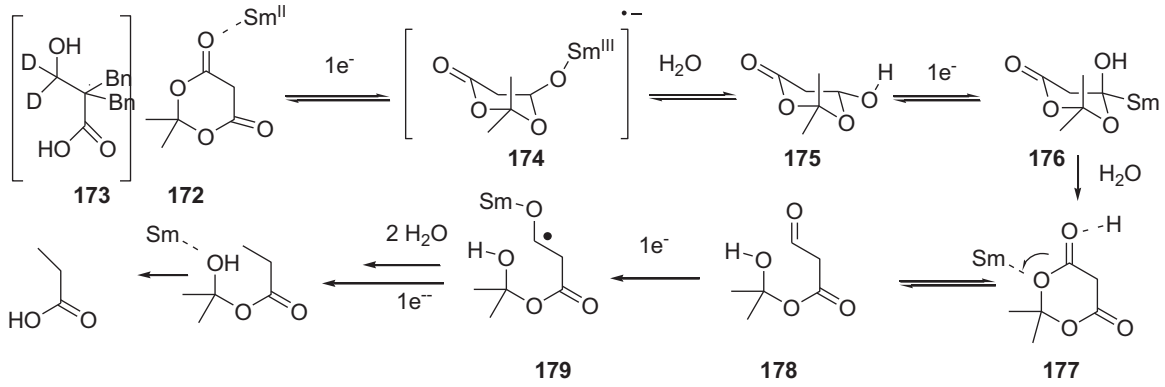
Scheme 76. Reduction mechanism of lactones.



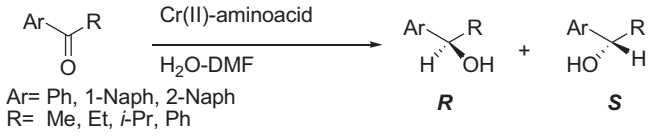
Scheme 77. Reduction of lactones by SmI_2 in water.



Scheme 78. Activation of the lactone by coordination to Sm(II) and electrostatic stabilization of the product radical-anion by coordination to Sm(III)..



Scheme 79. Mechanism proposed for the reduction of lactones.



Scheme 80. Reduction of carbonyl compounds by Cr(II)–aminoacid complexes (Ref. [180a]).

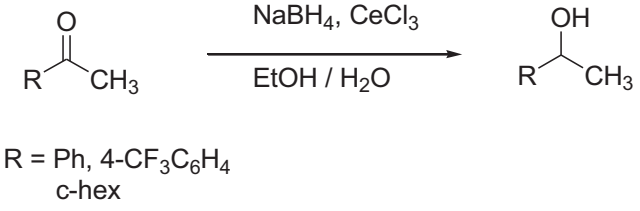
Cr(II)–aminoacid complexes have been used for the enantioselective reduction of carbonyl compounds in water–DMF mixtures, according to Scheme 80 [180a].

The aminoacids employed are L-*aminoacids*. High chemical yields could be achieved especially with Ala and Asp ligands but Leu produces poorer values. The highest *ee* values are obtained when His is used as the ligand (7–55%) while Ala and Val result in lower induction (5–38% and 5–40%, respectively). Leu which exerts only moderate activating effect and, hence, poorer conversions and chemical yields, also proves to be the least effective inductor (1–18% *ee*). Asp and L-glutamic acid (Glu) ligands result in similar chiral induction in accordance with their similar coordination behavior [180a]. A SET process is proposed as a likely mechanism for these reactions.

Higashiyama and collaborators have accomplished the chemoselective reduction of methyl ketone derivatives in the presence of other trifluoromethyl ketone compounds and obtained the α-methyl acohols, using a mixture of $NaBH_4$ and $CeCl_3$ in ethanol:water, according to Scheme 81 [181a].

There has been an increasing emphasis on the development of alternative hydrogen transfer agents due in large part to concerns about the toxicity of tin-containing compounds.

As mentioned above, silanes have emerged as important reducing agents in water [160,180b]. Some of the more exciting advances in this direction involve the use of water and alcohols as safe "green" hydrogen atom transfer agents. The high O–H bond dissociation energies (BDEs) of alcohols (*ca.* 105 kcal/mol) and water (118 kcal/mol) suggest that hydrogen atom transfers from these sources to carbon-centered radicals will be too slow to be useful,



Scheme 81. Chemoselective reduction of methyl ketones with $NaBH_4/CeCl_3$ in ethanol/water mixture (Ref. [181a]).

but Lewis acid complexed alcohols and water have much reduced O–H BDEs and can react with alkyl radicals rapidly [181b].

Several water–boron complexes have been used as hydrogen source donor to carbon-centered radicals in water and alcohols systems [181,182].

Titanium and several organic complexes containing it have emerged as interesting metal sources for complexing water efficiently and allowing it to operate as a convenient hydrogen atom source toward carbon-centered radicals.

More recently, Oltra and collaborators have carried out the Cp_2TiCl-mediated epoxide ring opening and observed that the reduced product is obtained when water is added to the reaction mixture [183]. The mechanism of this reaction is postulated to involve the water complex, which may act as a hydrogen atom donor by single electron transfer to the oxygen atom resulting in a Ti(iv) complex. Calculations have shown again a marked decrease of the O–H homolytic bond dissociation energy when water is coordinated to the $Cp_2Ti(III)Cl$ complex (49 kcal/mol).

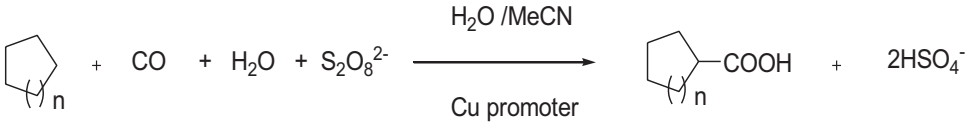
Newcomb and collaborators [184] have determined the rate constants for reactions of $Cp_2Ti^{III}Cl$-complexed water and methanol with a secondary alkyl radicals. The titanium(III) reagent apparently activates water and methanol more strongly than Et_3B with the result that the H-atom transfer reaction of the $Cp_2Ti^{III}Cl–H_2O$ complex is 5 times as fast as the H-atom transfer reaction of $Et_3B–H_2O$ at room temperature [184].

Radical reductions by H-atom transfer from water or alcohol complexes of $Cp_2Ti^{III}Cl$ will be useful when radicals are generated by reduction of epoxides or α,β-unsaturated ketones [184].

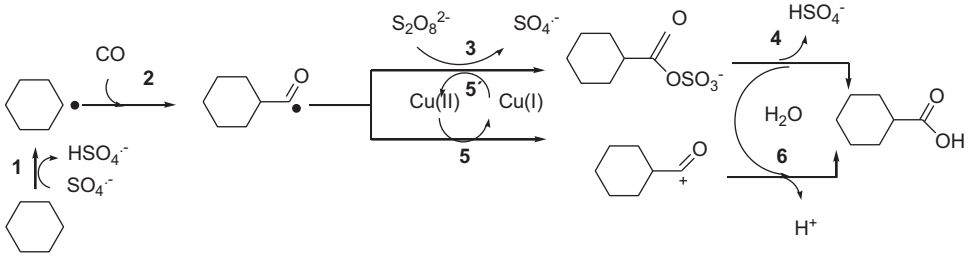
More recently, Cuerva and Cárdenas [185] have demonstrated the initial assumption that titanocene(III)–water complexes are a unique class of hydrogen atom transfer (HAT) reagents. They are able to reduce efficiently carbon-centered radicals of diverse nature. The success of this transformation is based on two key features: (a) an excellent binding capabilities of water toward titanocene(III) complexes and (b) a low activation energy for the HAT step. Therefore, the observed reactivity can be explained in the framework of an unprecedented HAT reaction involving water [185].

4. Metal-mediated oxidation reactions in water

In an aqueous micelle system using *tert*-butyl hydroperoxide (TBHP)-Fe as oxidant in the presence of O_2 (Eq. (24)) it is possible to obtain oxygenated cycloalkanes from their hydrocarbon precursors [186]. Use of a surfactant is necessary to create the micelles, and no reaction occurred in its absence. The reaction gives a mixture of cyclohexanol, cyclohexanone, and *tert*-butylperoxycyclohexane in the case of cyclohexane and 2-cyclohexen-1-ol, 2-cyclohexen-1-one and 3-(*tert*-butylperoxy)

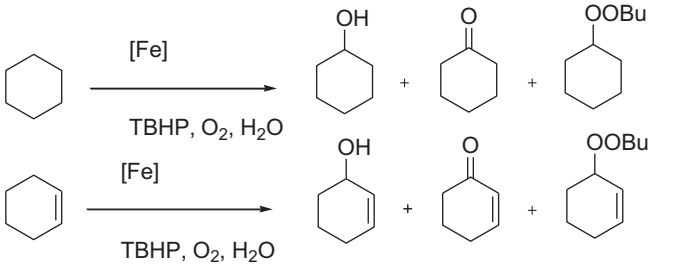


Scheme 82. Cu-promoted hydrocarboxylation of cycloalkanes to the corresponding cycloalkanecarboxylic acids in water/acetonitrile (Ref. [187]).



Scheme 83. Proposed simplified mechanism for the hydrocarboxylation of cyclohexane in water/acetonitrle (Ref. [187]).

cyclohexene in the case of cyclohexene. The product ratio is dependent upon the amount of TBHP and starting material used. A radical mechanism, in which the favorable redox chemistry of the iron complexes in the aqueous micelle system provides *t*-BuO• and *t*-BuOO• radicals as initiators (Harber–Weiss process), is proposed (Scheme 83).



(24)

A simple and effective method for the transformation, under mild conditions and in aqueous medium, of various cycloalkanes (cyclopentane, cyclohexane, methylcyclohexane, *cis*- and *trans*-1,2-dimethylcyclohexane, cycloheptane, cyclooctane and adamantane) into the corresponding cycloalkanecarboxylic acids bearing one more carbon atom, has been achieved by Pombeiro et al. [187]. This method is characterized by a single-pot, low-temperature hydrocarboxylation reaction of the cycloalkane with carbon monoxide, water and potassium peroxodisulfate in water/acetonitrile medium, proceeding either in the absence or in the presence of a metal promoter (Scheme 82). The influence of various reaction parameters, such as type and amount of metal promoter, solvent composition, temperature, time, carbon monoxide pressure, oxidant and cycloalkane, has been investigated, leading to an optimization of the cyclohexane and cyclopentane carboxylations. The highest efficiency is observed in the systems promoted by a tetracopper(II)triethanolaminate-derived complex, which also shows different bond and stereoselectivity parameters (compared to the metal-free systems) in the carboxylations of methylcyclohexane and stereoisomeric 1,2-dimethylcyclohexanes.

A free radical mechanism is proposed for the carboxylation of cyclohexane as a model substrate, involving the formation of an acyl radical, its oxidation and consequent hydroxylation by water (Scheme 83). Relevant features of the present hydrocarboxylation method, besides the operation in aqueous medium, include the exceptional acid-free reaction conditions, a rare hydroxylating role of water, substrate versatility, low temperatures (*ca.* 50 °C) and a rather high efficiency (up to 72% carboxylic acid yields based on cycloalkane).

For both metal-free and copper-promoted carboxylations of cyclohexane, it involves the formation of a free cyclohexyl radical, which is generated by H atom abstraction from C_6H_{12} (reaction 1, Scheme 83) by the sulfate radical $SO_4^{\bullet -}$. The latter is derived from the thermolytic and copper-promoted decomposition of $K_2S_2O_8$. This involvement of cyclohexyl radical is confirmed by performing the carboxylations (both metal-free and copper-promoted) in the presence of the carbon-centered radical trap $CBrCl_3$, what results in the full suppression of cylcohexanecarboxylic acid formation and the appearance of cyclohexyl bromide as the main product. The radical pathway is also supported by the inhibiting effect of O_2, acting as a cyclohexyl trap to give the $C_6H_{11}COO^{\bullet}$ peroxyl radical.

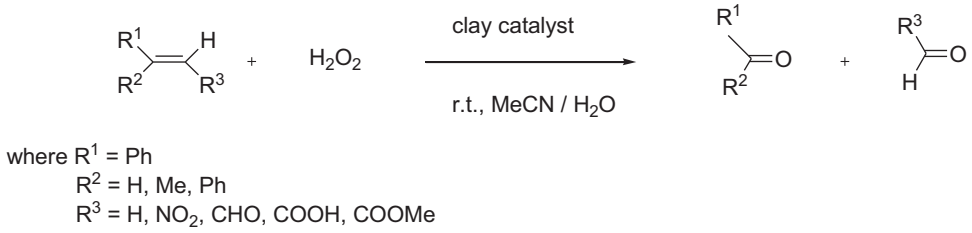
Subsequent carbonylation of the cyclohexyl radical by carbon monoxide results in the acyl radical $C_6H_{11}CO^{\bullet}$ (reaction 2, Scheme 83) that upon oxidation by $S_2O_8^{2-}$ generates the acyl sulfate $C_6H_{11}C(O)OSO_3^-$ (reaction 3, Scheme 83). This is hydrolyzed by water (reaction 4, Scheme 83) furnishing the cyclohexanecarboxylic acid. In the copper-promoted process, an alternative route (reaction 5) can occur, where the tetracopper(II)complex can behave as an oxidant of the acyl radical (reaction 5, Scheme 83).

This route involves the Cu(II)/Cu(I)redox couple and requires $K_2S_2O_8$ for regeneration (reaction 5) of the Cu(II) form. The highest activity of copper(II) in comparison with the other tested metal compounds can be accounted for by its particular effectiveness in the oxidation of carbon-centered radicals. Hydrolysis of the thus formed acylation $C_6H_{11}CO^+$ ultimately leads to the $C_6H_{11}COOH$ product (reaction 6, Scheme 83), via protonated cyclohexanecarboxylic acid $C_6H_{11}C(OH)_2^+$ which is deprotonated by water.

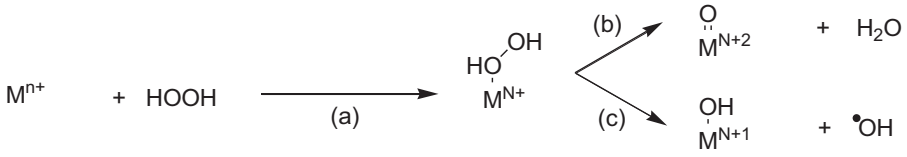
The hydroxylating role of water is played in both metal-free ($3 \rightarrow 4$) and copper-promoted ($5 \rightarrow 6$) pathways, as confirmed by experiments with $H_2{}^{18}O$ leading to $C_6H_{11}CO^{18}OH$ as the main product. Less favorable routes include the formation of unlabeled C_6 $H_{11}COOH$, proceeding through the mixed anhydride $C_6H_{11}C(O)OSO_3H$ that is obtained by protonation of the acyl sulfate by HSO_4^-, or by coupling of $C_6H_{11}CO^+$ with HSO_4^-. This anhydride would undergo intramolecular H-transfer with elimination of SO_3, thus furnishing the C_6H_{11} COOH product.

Oxidation of styrene and styryl derivatives can be accomplished by Fe-catalyzed oxidative cleavage in aqueous mixtures [188]. Oxidative cleavage of styrene yields benzaldehyde, as shown in Scheme 84.

Complete mechanistic interpretation of these results requires consideration of two main pathways in which the O–O bond of hydrogen peroxide can be cleaved upon reaction with the catalyst



Scheme 84. Oxidative cleavage of styrene in aqueous systems (Ref. [188]).

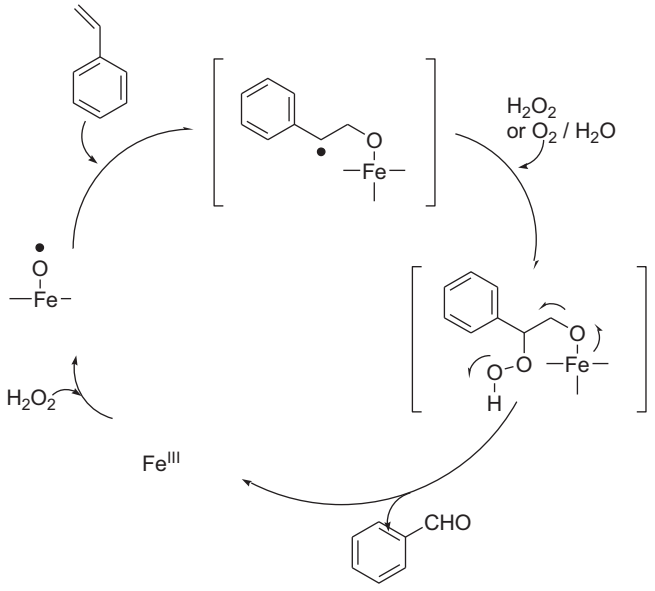


Scheme 85. Proposed reaction mechanism for the oxidation process (Ref. [189]).

(Scheme 84). Hydrogen peroxide typically reacts with a metal complex to form an initial metal–allylperoxo intermediate (a). The O–O bond of the coordinated peroxide can then cleave heterolytically to form high-valent metal oxo complex and water (b) or homolytically to form OH radicals and a metal hydroxide complex (c) (Scheme 85).

In the proposed mechanism (Scheme 86), the active oxidizing species (formed upon reaction of hydrogen peroxide with the catalyst) is described as high-valent Fe(V)]O [189]. It can add onto the double bond leading to a carbon radical intermediate (proposed by Tuynman et al.) [190]. This carbon radical intermediate is trapped by molecular oxygen followed by the abstraction of hydrogen or by the reaction between the carbon radical and activated hydrogen peroxide, which finally rearranges to give benzaldehyde as the sole product.

When $FeCl_3$ is used as a stoichiometric oxidation reagent and catalyst, homocoupling of 2-naphthols and substituted phenols successfully occurred in water [191,192].



Scheme 86. Proposed mechanism for the oxidation of styrene derivatives to benzaldehyde derivatives.

5. Summary and concluding remarks

Radical atom transfers reactions (such as those studied in Sections 2.1 and 2.4) are classical examples of atom efficiency in organic synthesis devoted to waste minimization. For radical rearrangement reactions (intramolecular cyclization reactions, Section 2.1), a single reactant leads to a single product with nearly the same mass and an almost identical structure. All these factors support the notion for the good prospects that hold Radical Chemistry in water as have been exposed in this account.

Among the synthetic advantages (chemoselective and stereoselective advantages) encountered in performing metal-mediated radical reactions in water, the following became apparent alongside our discussion:

i. The alkylation reaction of carbonyl compounds in water using unactivated alkyl halides and In/CuI/I_2 or In/AgI/I_2 system proved that the use of organic solvents inhibited the occurrence of the Barbier–Grignard-type alkylation reaction.
ii. Indium-mediated radical alkylation reactions of imine derivatives proceed in much higher yields when the reactions are performed in water.
iii. Imine derivatives such as oxime ethers, hydrazones, and nitrones are excellent water-resistant radical acceptors for the aqueous-medium reactions using Et_3B as a radical initiator.
iv. 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. In every example, allylations performed in either H_2O or H_2O–THF (1:1) proceeded at appreciably more rapid rates than in THF alone.
v. Manganese in water can accomplish the radical allylation reaction of aldehydes chemoselectively, thus allowing the reactions of aromatic aldehydes to proceed effectively to completion, whereas aliphatic aldehydes are unreactive under the same reaction conditions.
vi. Pd(0) allylation reactions of carbonyl compounds lead to γ-adducts with high regioselectivity in water. On the other hand, allylation of an aldehyde with allylic indium reagent occurs regioselectively at the γ-position in organic solvents to afford γ-homoallylic alcohols. However, in water, α-adducts prevail with allylindium reagents.
vii. The Zn-mediated allylation of carbonyl compounds (both aldehydes and ketones) with 1,3-dihalopropene derivatives yields 1,3-butadienes. These reactions are quite satisfactory in aqueous medium but fail to proceed at all in diethyl ether or

other organic solvents normally used for organometallic reactions.

viii. The origin of the favorable solvent effect on atom-transfer radical reaction of α-iodo carbonyl compounds in aqueous media can be rationalized in terms of a high cohesive energy density of water that causes reduction of the volume of an organic molecule, and promotes transfer reactions.

ix. Preparatively superior yields in water of Reformatsky reactions (a reaction between a 2-halo ester and a carbonyl compound) comparable to those of the classical procedure in anhydrous solvents can be obtained with a large series of metal species.

x. The novel reductive coupling of aldimines brought about by indium to vicinal diamines occurs in aqueous ethanol. The reaction fails completely in CH_3CN, DMF and DMF containing small quantities of water.

xi. Reduction of lactones to diols using SmI_2/H_2O is chemoselective in the sense that only lactones and no esters are reduced, and furthermore, it displays complete ring size-selectivity in that only 6-membered lactones are converted to the corresponding diols in water.

xii. Using a mixture of water and ethanol, it is possible to accomplish a chemoselective reduction of methyl ketone derivatives in the presence of other trifluoromethyl ketone compounds to obtain only the α-methyl acohols, using a mixture of $NaBH_4$ and $CeCl_3$ in ethanol:water,

Acknowledgments

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