Recent Advances in Free Radical Chemistry of C-C Bond Formation in Aqueous Media: From Mechanistic Origins to Applications

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Abstract: Recent advances in free radical chemistry have expanded the versatility and flexibility of carbon-carbon bond formation in water or aqueous media. This review highlights the substantial progress, which has been made in the last decade to "tame" the reactive free radical species in aqueous phase reactions. This review focused on recent advances in several classes of widely useful free radical reactions in water leading to the formation of C-C bonds. The review will also explore the recent advances in performing stereo-selective free radical reactions in an aqueous medium and its application in synthesis of natural and unnatural amino acids, preparation of novel materials and solid support chemistry. Some practical hints for help design high yielding free radical reactions in aqueous medium are also presented.

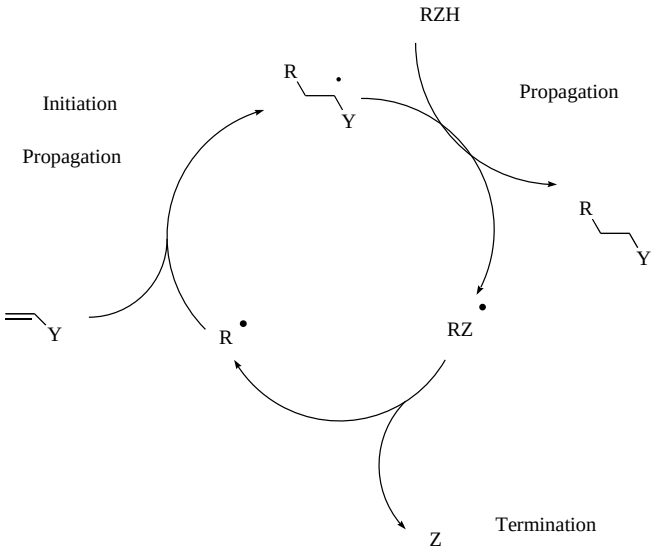
1. INTRODUCTION

Life, the most complex form of organic compounds on Earth, requires the construction of chemical bonds in an aqueous environment [1]. Following the natures lead, the challenge for today's chemist is to move away from highly volatile and environmentally harmful organic solvents and towards friendly and biologically compatible media [2]. The obvious solvent choice of solvent is water due to its abundance, cost effectiveness and biological compatibility. The potential usefulness of free radical reactions in water is demonstrated by ever-increasing studies over the last 5 years [3].

Free radicals are ubiquitous, reactive chemical entities. Free radical reactions are an important class of synthetic reactions that have been traditionally performed in organic solvents. In recent years, the number of reports of free radical reactions that use water has increased [1-9]. Water is an ideal solvent for free radical reactions as it possesses no reactive functional groups and strong O-H bonds that make hydrogen abstraction unlikely [4,7,9].

Radical reaction is one of the most useful methods for organic reactions in water, because most of the organic radical species are stable in water, and they do not react with water [6-12]. In addition, by harnessing free radical reactivity within the laboratory, biological processes can be studied and controlled, leading in turn to the prevention of disease and the development of new treatments for disease states mediated by free radicals [13,14].

Whilst there have been several excellent reviews on carbon-carbon (C-C) bond formation and reactions of carbon hydrogen (C-H) bonds in water [4,6-9], this review addresses C-C bond formations in aqueous media *via* radical reactions (alkylation, radical cyclization and tandem radical reactions) within the past decade. There is a specific focus on C-C bond forming reactions as they represent one of the major classes of the most useful and utilized class of reactions. In these reactions a C-C bond is formed through a chain mechanism involving radical initiation, radical propagation and radical termination steps (Scheme **1**). This reaction is important in biology, in the chemical industry and in the chemical laboratory [1,2,10-15].



Scheme 1. General diagram radical addition to C=C in the presence of the H-donor.

The review can be classified broadly into six main sections; the generation of carbon-centred free radicals, radical initiators, solubility of substrate and radical addition reactions with the particular focus on a formation of C-C bonds, including stereochemical aspects of the transformation and applications.

2. GENERATION OF CARBON-CENTERED FREE RADICALS IN AQUEOUS MEDIA

In aqueous media carbon centred free radicals are typically generated by either chemical, photolysis or radiolysis methods. These methods are briefly discussed below and the criteria for the selection of a radical initiator and hydrogen donor are discussed in section 3 and 5 respectively.

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Chemical methods used to generate carbon-centred radicals include so called "building block" reactions of free radical chemistry, such as hydrogen atom transfer reactions [2,3], Barton-McCombie deoxygenation reactions [3,4], free radical additions to double bonds [2,4], Fenton type reactions [3] and thermal homolysis of organometallic compounds such as certain chromium species [16]. Application of this method for generation of free radicals will be discussed further in section 3.

Photochemical methods for the formation of alkyl and other carbon centred radicals have been applied to the following "building block" reactions in the arsenal available to free radical chemists [17,18]. Well suited for use in biological systems has also being used in synthetic applications in aqueous and organic solvents [3,4,5,6].

Radiolysis methods for the generation of carbon centred radicals in aqueous solution include irradiation of the reaction mixture to produce e_{aq}^-, H• or •OH radicals with various organic compounds. Although, this method is not currently used in synthesis, it is a very accurate and reliable probe for exploring mechanistic and kinetic properties of free radicals generated *in vivo* [19,20-25].

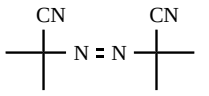
3. RADICAL INITIATORS FOR AQUEOUS FREE RADICAL REACTIONS

There are three major classes of radical initiators; azo-based initiators, peroxides and boranes. In a free radical reaction ttypically 5-10 mol% of the initiator is added, either in one portion or by slow addition to the reaction over a period of time. Water soluble azo initiators have a number of advantages over organic peroxides. They are relatively inexpensive, do not produce undesirable decomposition products and/or toxic by-products and have a greater thermal stability. There are several commercially available azo radical initiators, see Fig. (**1**) for structures, that can be used for free radical reactions in aqueous media.

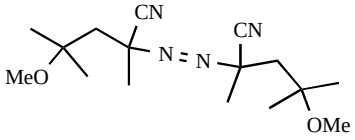
The most popular thermal radical initiator is 2',2'-azobisisobutyronitrile (AIBN) which has a half-life ($t_{1/2}$) in toluene of 1 h at 81 ºC and 10 h at 65 ºC [26-29]. Whilst AIBN is a popular choice, other azo compounds can give superior results due to their varying half-life. The half-life of the radical is dependent on its substitution, consequently 2,2'-azobis-(4-methoxy)-3,4-dimethyl-valeronitrile (AMVN) has a half-life in toluene of 1 h at 56 ºC and 10 h at 33 ºC, 2,2'-azobis-(2-methylpropionamidine) dihydrochloride (APPH), a hydrophilic azo compound, has a $t_{1/2}$ of 10 h at 56 ºC in organic solvents. The radical initiators AIBN, AMVN, V-501 and AAPH have been used in aqueous reactions [2-4]. Peroxides are used when the reaction requires a more reactive initiating species [27,30]. Initially an acyloxyl radical is formed, followed by decarboxylation and a subsequent bimolecular reaction that affords the reactive carbon centred radical. Common peroxides that are used in organic media are *tert*-butyl perbenzoate (PhC(O)OOBu-*t*) and di-*tert*-butyl peroxide (*t*-BuOOBu-*t*), whose $t_{1/2}$ are 1 h at 125 ºC and 147 ºC respectively [24,27].

Photochemically generated radical chain reactions are less familiar to the synthetic chemist than those described above [3]. The above mentioned peroxides, *tert*-butyl perbenzoate and di-*tert*-butyl peroxide, have been used in the presence of light to initiate radical chain reactions at room temperature or lower. Azo compounds decompose under photochemical conditions and therefore are rarely used [30].

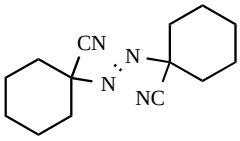
Triethyl borane (Et_3B), in the presence of a very small amount of oxygen, is an excellent initiator for radical chain



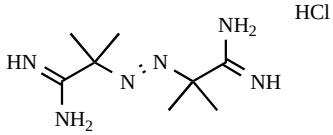
AIBN



AMVN

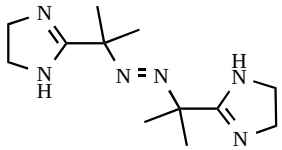


ACCN



HCl

AAPH



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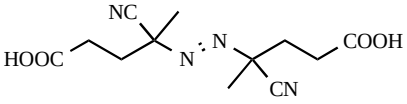
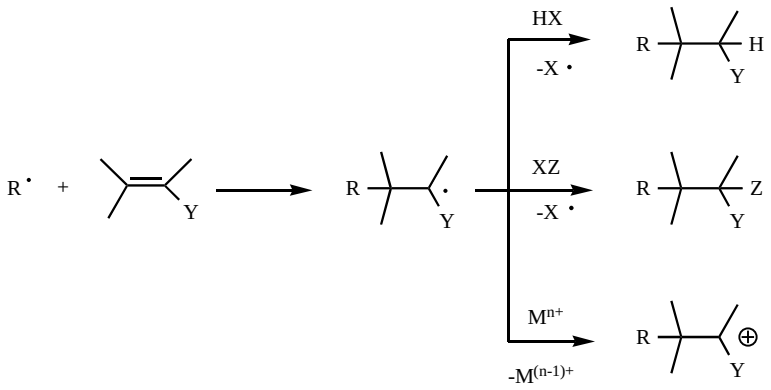


V-501

Fig. (1). Commercially available free radical azo-initiators.



Scheme 2. General mechanistic considerations for radical additions to C=C bonds.

reactions. For a long time it has been known that trialkylboranes (R_3B) will react spontaneously with molecular oxygen to give the corresponding alkyl radical (R•), but only in the last 10 years has this approach being successfully applied to the initiation of free radical reactions [30]. These reactions can be run at temperatures as low as -78 ºC, which allows for a high degree of stereo, regio and enantioselectivity required in the synthesis of complex molecules [19,26,27,31-33].

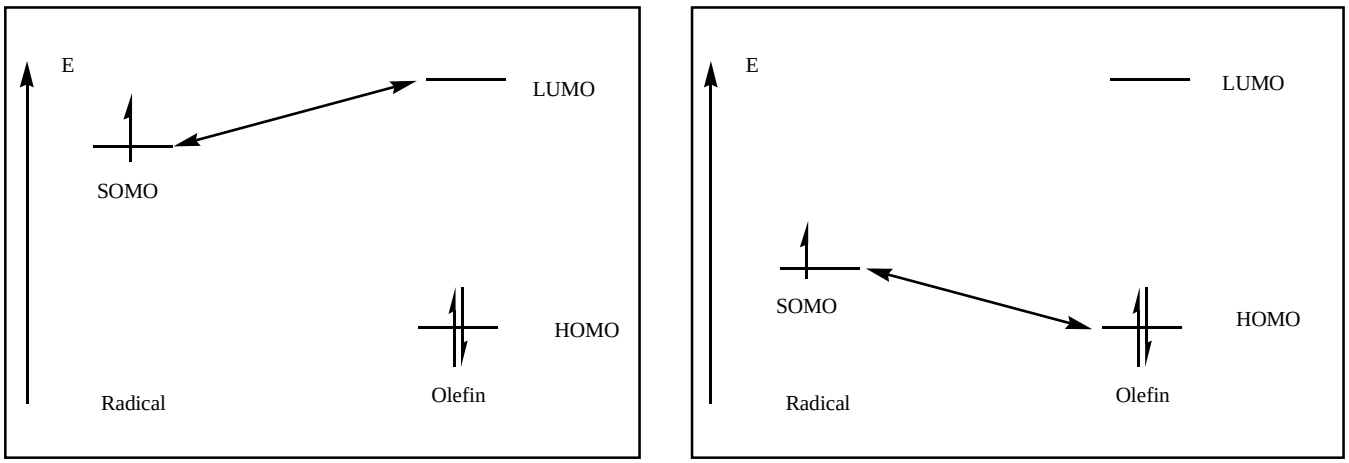
It is advisable to add the initiators slowly during the course of the reaction with particular attention being paid to the half life of the decomposition of the initiator at the operating temperature of the reaction. The direct addition of the thermal initiator with a reaction temperature much higher than that of the 1 h half life generally does not lead to the optimal outcome of the free radical reactions. At low temperatures, when the thermal initiation is not viable, Et_3B/O_2 is the best initiator to use initially.

4. ALKYL RADICAL ADDITION TO OLEFINS

4.1. General Principles and Considerations

The most important methodology for the aliphatic C-C bond formation *via* radical reactions is the addition of the radical to alkene double bond, by both inter- and intramolecularly (with the 5-exo-ring cyclization mode preferred in the later case). This reaction leads to adduct radicals that must be converted to non-radical products before polymerisations will take place. For this reason, polymerization is avoided either by intermolecular trapping of adduct radicals or by intramolecular, homolytic bond cleavage. Hydrogen atom donors X-H, heteroatom donors X-Z or electron donors M^{n+} are used as trapping agents (Scheme **2**).

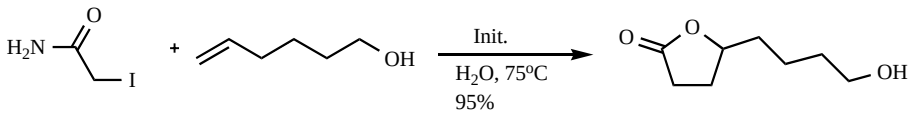
Relatively straight forward but extremely useful Hydrogen Atom Transfer (HAT) reactions involve the replacement of various X groups with hydrogen without alterations of the carbon skeleton. If the intermediate carbon radical could be intercepted by a carbon –carbon bond forming process before the HAT reaction takes place, then the architecture of the substrate could be profoundly modified and its complexity rapidly increased. The factors that play an important role in the outcomes of the radical additions to olefins can be broadly classed as polar and steric effects (Scheme **3**) [34]. Often the interaction between two molecules can be expressed as a combination of attractive and repulsive terms reflecting polar (electrostatic and orbital interactions) and steric effects (usually repulsive). However in case of the radicals, which are not charged species, the relative differ-



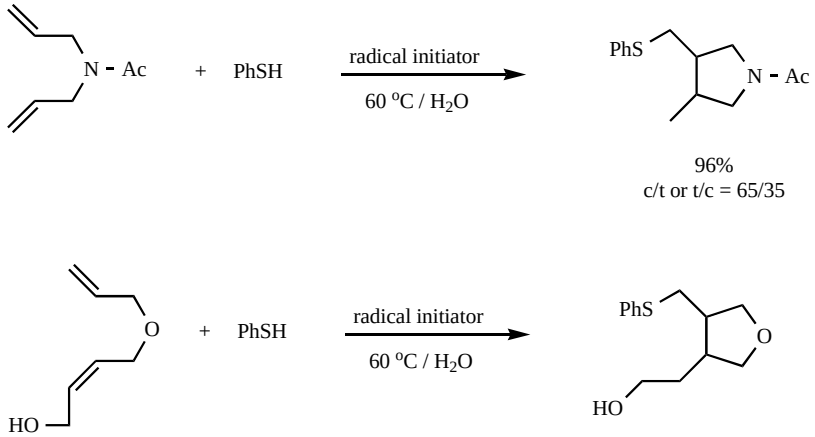
Radical addition to electron-poor olefins

Radical addition to electron-rich olefins

Scheme 3. Radical additions to electron-poor and electron-rich olefins.



Scheme 4. Addition of 2-iodoacetarnide to alkenol 12 afforded γ-lactone.



Scheme 5. Atom transfer radical cyclization of 2-iodoamides [36].

ence in the electrostatic (or coulombic) term is small or negligible, and polar effects become dominated by orbital interactions [34]. Frontier orbitals, thus play a prominent role, and the reactivity can indeed be often understood, at a qualitative level, by simply looking at the energy gap between the SOMO of the radical and the LUMO or the HOMO of the olefin (Scheme **3**) [35].

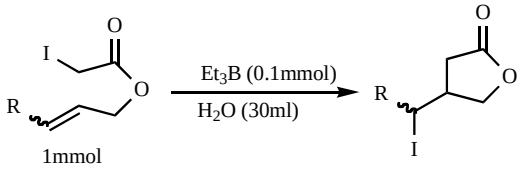
4.2. "Metal Free" radical addition to C=C double bond in water or aqueous media

The addition of carbon-based radicals has been shown to be successful in water [36,37]. Thus, radical additions of 2-iodo alkanamide or 2-iodoalkanoic acid to alkenols using water soluble radical initiator 4,4'-azobis(4-cyanopentanoic acid) or 2,2'-azobis(2-methylpropanamidine) dihydrochloride carried out in water generated γ–lactones (Scheme **4**).

The addition of perfluoroalkyl iodides to simple olefins has been quite successful under aqueous conditions to synthesize fluorinated hydrocarbons [36,37].

In addition to carbon based radicals, other radicals such as sulfur-based radicals, generated from the RSH-type precursor (R=alkyl, acyl) with AIBN also smoothly added to α-allyl glycine [36]. Optimal results were obtained when both the unsaturated amino acids and RSH dissolved completely in the reaction medium (dioxane:water or methanol:water where found to be superior solvents) [36,37]. Radical additions of thiophenol to carbon-carbon multiple bonds and radical cyclization of *N*-allyl-2-iodoalkanamide in aqueous media proceeded smoothly to *N*-acetylpyrrolidine derivative in 96% yield. Under similar experimental conditions, atom transfer radical cyclization of 2-iodo amides in water gave corresponding lactams in 96% and 85% yield (Scheme **5**) [36].

Table 1. Cyclization of Allyliodoacetates with Triethylborane in Water

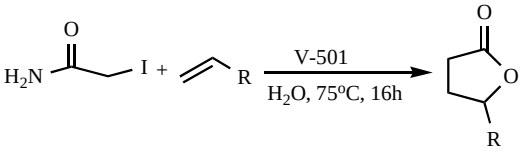


Entry	R	Solubility in Water	Yield (%)
1	H	10mM	67
2	CH_3	4.4mM	77
3	C_2H_5	1.4mM	72
4	n-C_3H_7	0.4mM	18
5	n-$C_{10}H_{21}$	0	0
6	CH_2OH	170mM	89

Although a media effect in radical reactions was believed to be almost negligible, Oshima and co-workers reported recently that water increases the rate of radical reactions [38-40]. They have found that the atom transfer radical cyclization of allyl iodoacetate, promoted by triethylborane, is accelerated in water [38]. Moreover, they found that the yields of the cyclized products correspond to the solubility of the starting allyl iodoacetate derivative in water (Table **1**).

A similar solubility effect was observed in the radical addition of iodoacetamide to alkenes in water (Table **2**) [38]. Whereas, alkenes with hydrophilic groups produced the lactone in high yields, water insoluble 1-octene did not yield the desired lactone under the identical reaction conditions. The addition of organic co-solvent ($EtOH/H_2O$=9/1) was required for the addition of iodoacetamide to 1-octene.

Table 2. Radical Addition of Various Acetamides to Alkenes in Water [38]



Entry	R	Yield (%)
1	CH_2OH	88
2	$(CH_2)_2OH$	91
3	$(CH_2)_3OH$	85
4	$(CH_2)_4OH$	95
5	$(CH_2)_2CO_2H$	94
6	n-C_6H_{13}	0

Water as a reaction solvent also markedly promotes the cyclization of large-membered rings. Stirring a solution of 3,6-dioxa-8-nonenyl iodoacetate in water in the presence of triethyl borane at 25 °C for 10 hours provided the 12 membered ring product, 4-iodo-6,9-dioxa-11-undecanolide, in 84% yield whereas the cyclization in benzene afforded the lactone in only 22% yield [39]. *Ab initio* calculations on the cyclization indicated that the large dielectric constant of water lowers the barrier not only of the rotation from the Z-rotamer to the E-rotamer that can cyclize but also of the cyclization constructing the γ–lactone framework. Moreover, the high cohesive energy of water also effects acceleration of the cyclization because water forces a decrease in the volume of the reactant (Scheme **6**) [39]. This observation is suggestive of a fact that water is not an inert solvent as previously anticipated.

In parallel, the oxime ethers are well known to be excellent radical acceptors [41].

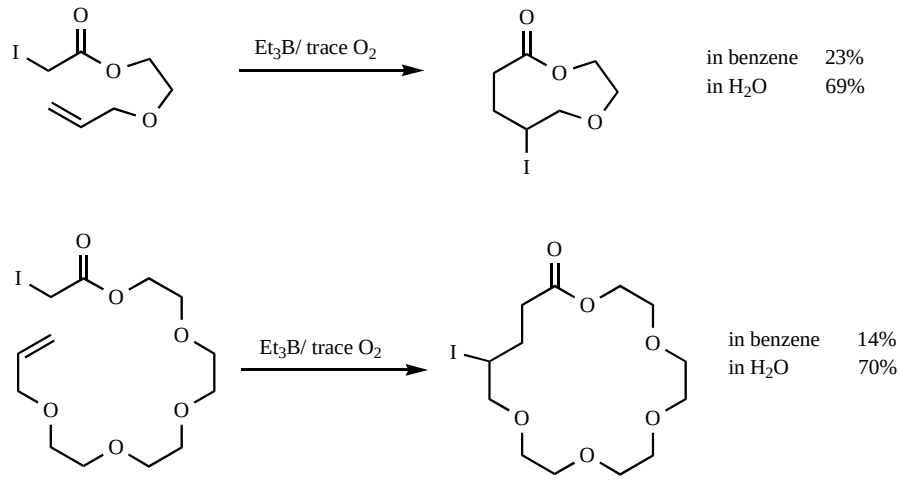
Naito and co-workers investigated the aqueous-medium radical addition to glyoxylic oxime ether due to its good reactivity in organic solvents [42]. It is noteworthy that triethylborane acts as a radical initiator and terminator to trap the intermediate alkyl radical (Scheme **7**).

Recently they have shown new free-radical-mediated tandem reactions of oxime ethers for the synthesis of heterocycles *via* two C-C bond-forming processes. In addition to radical cyclization of oxime ethers, the tandem radical reactions disclosed a broader aspect of the utility of oxime ethers as a radical acceptor in the synthesis of various types of amino compounds, as shown in Scheme **8** [43].

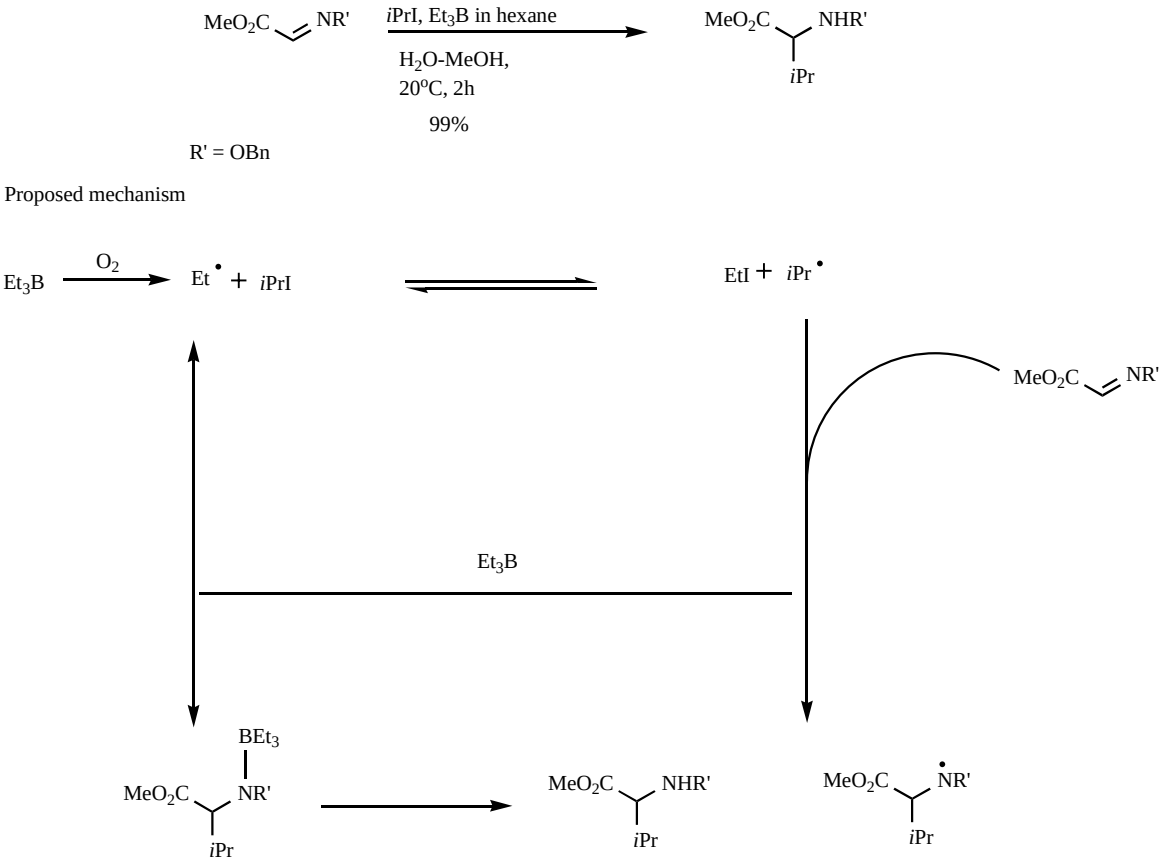
4.3. Indium Mediated Radical Reactions in Aqueous Medium

The utility of indium as a free radical initiator in aqueous media can be directly linked with the first ionisation potential (5.8ev) and is as low as that of lithium and sodium [44]. Therefore, it is well accepted that indium has the potential to induce radical reactions as a radical initiator *via* a single – electron transfer process (Scheme **9**) [44].

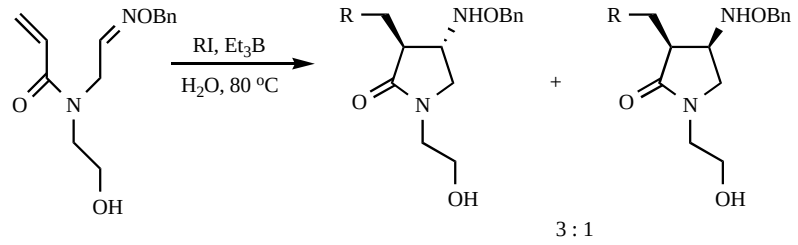
In 1991, Li and Chan reported the use of indium to mediate Barbier- Grignard-type reactions in water [45]. The work was designed on the basis of the first ionization potentials of different elements, in which indium has the lowest first ionization potential relative to the other metal elements near it in the periodic table. On the other hand, indium metal is not sensitive to boiling water or alkali and does not form oxides readily in air. Such special properties of indium indicate that



Scheme 6. Medium- and Large-ring formation by radical cyclization in water [39].

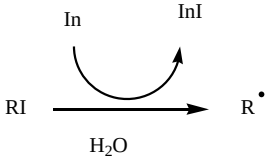


Scheme 7. Alkyl radical addition to glyoxylic oxime initiated by Et_3B.

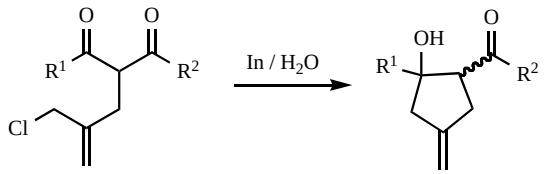


Scheme 8. Oxime ethers as radical acceptors in synthethis [43].

it is perhaps a promising metal for aqueous Barbier-Grignard-type reactions. Indeed, it appears that indium is the most reactive and effective metal for such reactions. When the allylation was mediated by indium in water, the reaction went smoothly at room temperature without any promoter, whereas the use of zinc and tin usually requires acid catalysis, heat, or sonication. A variety of 1,3-dicarbonyl compounds have been alkylated successfully using allyl bromide or allyl chloride in conjunction with either tin or indium (Scheme **10**). The reaction can be used readily for the synthesis cyclopentane derivatives [46].

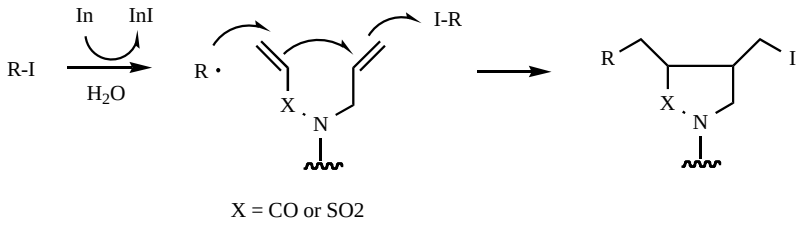


Scheme 9. Indium as a radical initiator in H_2O.

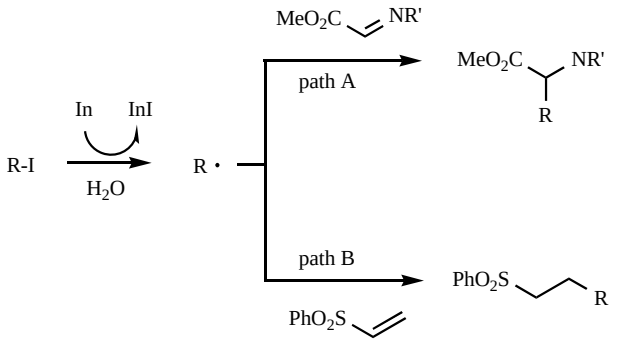


Scheme 10. Alkylation of 1,3-dicarbonyl compounds using allyl bromide or allyl chloride using indium in water.

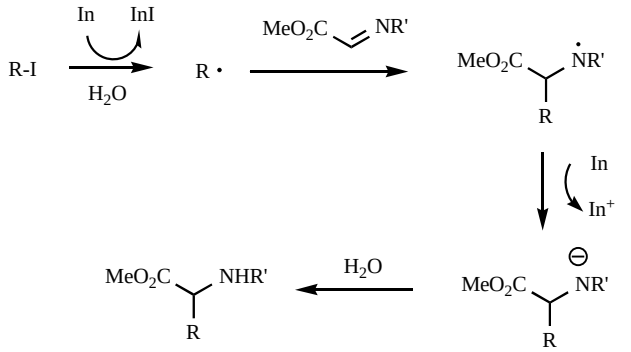
Recently Naito and co-workers were studied the addition-cylcization-trap reaction in aqueous media mediated by indium [47]. Tandem C-C bond forming reactions were studied by using indium as a single-electron-transfer radical initiator. The radical addition-cyclization-trap reaction of a substrate having a vinyl sulphonamide group and an olefin moiety preceded smoothly in aqueous media. The radical addition-cyclization reaction of hydrazone gave the functionalized cyclic products, as shown in Scheme **11**.



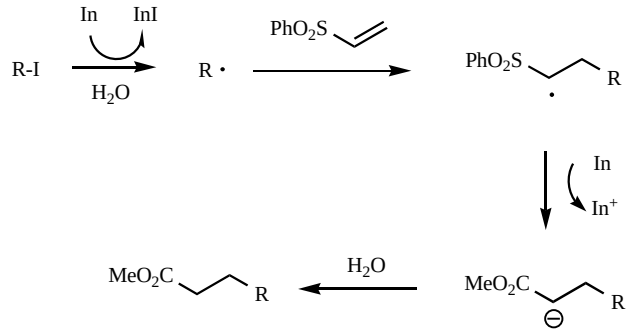
Scheme 11. Indium mediated tandem radical addition-cyclization-trap reactions in aqueous media.



Proposed mechanism for path A



Proposed mechanism for path B



Scheme 12. Proposed mechanisms for indium mediated C-C bond formation [48].

The intermolecular alkyl radical addition to imine derivative was studied in aqueous media using indium as a single electron transfer radical initiator. The one pot reaction based on radical addition to glyoxylic hydrazone provided a convenient method for preparing the α-amino acids. The indium mediated radical additions to an electron deficient C=C bond also proceeded effectively to provide the new carbon-carbon bond forming method in aqueous media (Scheme **12**) [48].The carbon-nitrogen double bond has emerged as a radical acceptor, and thus several intermolecular radical additions reactions have been recently investigated in organic solvents [27,49].

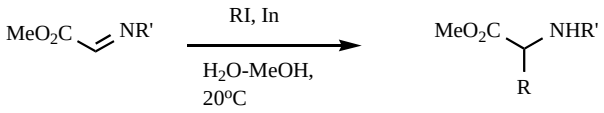
However, recent investigations of Naito and co-workers have shown that imines derivatives such as oxime ethers, hydrozones and nitrones are excellent water resistant radical acceptors for aqueous-medium reactions using triethylborane as radical initiator. The one pot reaction based on radical addition to glyoxylic hydrazone was examined under several reaction conditions (Table **3**) [47,50]

The monophasic reaction of imine in H_2O-MeOH gave isopropylated product after stirring for only 30 minutes, without formation of significant by products such as reduced product [50]. It is also important to note that practically no reaction have occurred in the absence of water. This observation suggests that water would be important for the activation of indium and for proton donation to the resulting amide anion. In the presence of a galvinoxyl free radical as radical scavenger, the reaction did not proceed effectively; and suggests that this reaction would proceed *via* free radical mechanism [47,48].

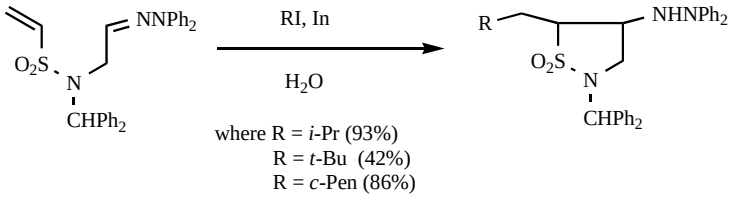
Another strategy involving tandem radical reaction offer an advantage of multiple carbon-carbon bond formation in a single operation in the aqueous-medium tandem construction of carbon-carbon bonds have been widely being studied by Naito and co-worker and there for the tandem reaction in aqueous medium. The investigation of indium-mediated tandem carbon-carbon bond forming reaction of substrate shown in Scheme **13** having two different radical acceptors [43]. The tandem radical addition-cyclization-trap reactions in the presence of RI in water gave the cyclic products in the good yields without the formation of other by-products [43].

Recently, the related indium-mediated radical reactions have been widely studied (Scheme **14**) [44]. Indium iodide-mediated radical cyclization was first reported by Cook and co-workers [51]. The indium-mediated 1,4-addition of alkyl radicals to *(/E/)*-but-2-enenitrile was investigated by using 1-ethylpiperidinum hypophosphite (EPHP) as a hydrogen source in aqueous media (Scheme **14**) [52]. The atom transfer radical cyclization and reductive radical cyclization were studied by using indium and iodine [53]. Indium mediated alkyl radical addition to dehydroamino acid derivatives was also reported [54]. The indium-mediated radical ring expansion of α-halomethyl cyclic β-ketoesters, shown in Scheme **14**, was achieved in aqueous alcohols [55].

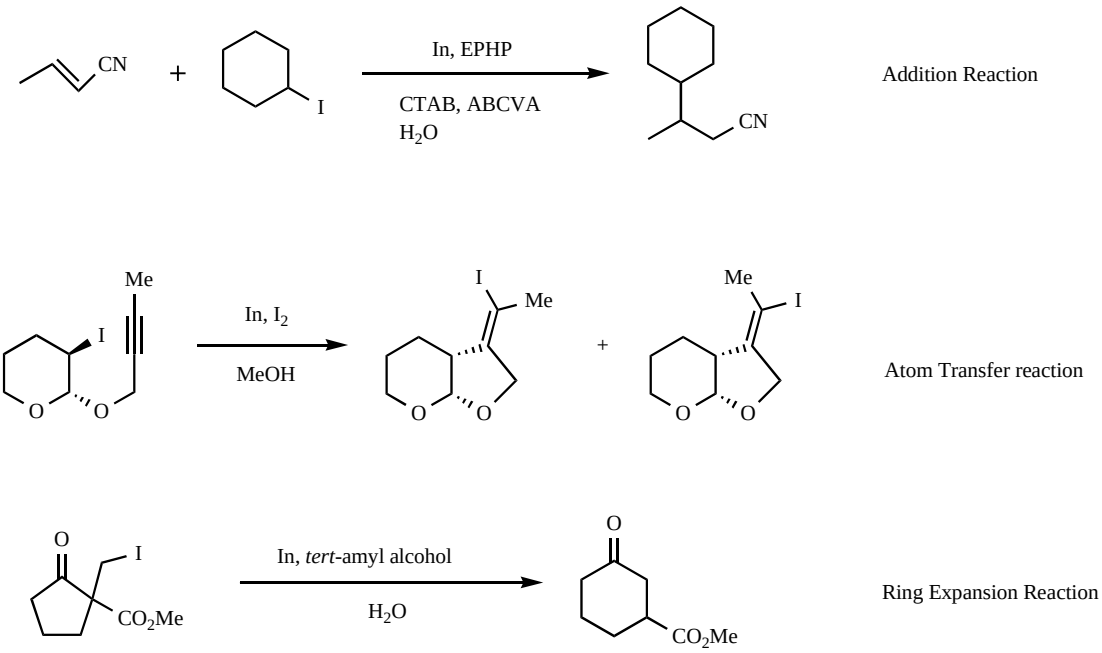
Table 3. Alkylation Reactions of Various Amines [47]



Entry	R'	R	Yield (%)
1	OBn	*i*-Pr	74
2	NPh_2	*i*-Pr	98
3	NPh_2	*cyclo*-Pentyl	90



Scheme 13. Tandem radical addition-cyclization reaction mediated by indium [43].

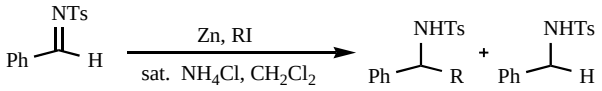


Scheme 14. Various radical reactions mediated by Indium.

4.4. Zinc Meditated Alkylations of C=N Bond

Zinc-mediated carbon-carbon bond forming reactions have attracted considerable interest in recent years [9,56]. Among the various types of known zinc-mediated reactions, radical reactions have captured much recent attention because of their exceptional tolerance to functional groups [57].

The carbon-nitrogen double bond of imine derivatives has been shown to act as a radical acceptor. For example, in recent studies showed that *N*-sulfonylimines are excellent radical acceptors for the aqueous-medium reaction using zinc as a single-electron transfer radical initiator (Scheme **15**) [58].



Where R is *i*-Pr, *c*-Pentyl, *s*-Bu, *t*-Bu, Me

Scheme 15. Zinc mediated alkyl radical addition to N-Sulfonylimine.

The mechanism of the zinc mediated addition to N-sulfonylimine is proposed to be as illustrated in Fig. (**2**).

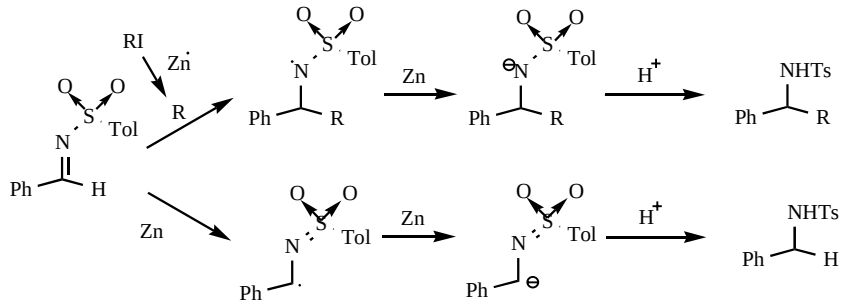


Fig. (2). Possible reaction pathway for the Zinc mediated alkyl radical addition to N-Sulfonylimine

As part of environmentally benign synthetic reaction in aqueous media [48,50,59,60] employing imines as a substrate, the zinc-mediated radical addition to the glyoxylic oxime ethers and hydrazones for asymmetric synthesis of a-amino acids, have been reported. The zinc-mediated isopropyl radical addition to achiral glyoxylic oxime ether (shown in Scheme **16**), in aqueous media (sat. NH_4Cl aq/ MeOH) was examined. In that reaction isopropylated product was formed in 96% yield. It was suggested that this reaction proceeds through the radical pathway based on a single-electron transfer from zinc [42,58,61,62].

5. STEREO-SELECTIVE RADICAL ADDITION TO C=N BOND

5.1. General Aspects of Stereoselectivity and Enantioselectivity in Water or Aqueous Media

With a few notable exceptions, the majority of asymmetric reactions are performed in apolar and aprotic media, which precludes the use of water-soluble compounds. It's imperative that water, too, is fully explored as a reaction medium for asymmetric synthesis. Provided that substrates and reagents can be used that do not react with water, how will the selectivity of reactions in inert solvents be affected by the progression to a participating solvent such as water? Learning how to take advantage of the uniquely complex solvating properties of water may lead to new concepts and possibilities in asymmetric synthesis. Initial work in this area has indeed lead to some interesting and surprising results.

In general, the diastereoselectivity and enantioselectivity in the free radical transformation can be achieved by using the following modes of stereoselectivity controls:

a. A chiral Lewis acid [63] can be used to bind to substrate or radical species and determine the approach of the other reacting component while accelerating the chiral pathway relative to the background reaction.

b. A chiral catalyst can be coordinated temporarily to the substrate and/or the reacting radical and bring about the reaction in an intramolecular sense [64].

c. A chiral chain-transfer agent can be used: this will determine the approach in an atom-transfer step [65].

d. A chiral environment can be provided, as in the photolysis of chiral crystals [66].

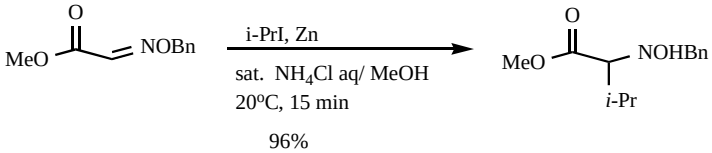
e. A chiral inductor along with the substrate can be trapped in an organized medium [67].

f. The chirality inherent in the molecule can be converted to molecular chirality (memory of chirality) [68].

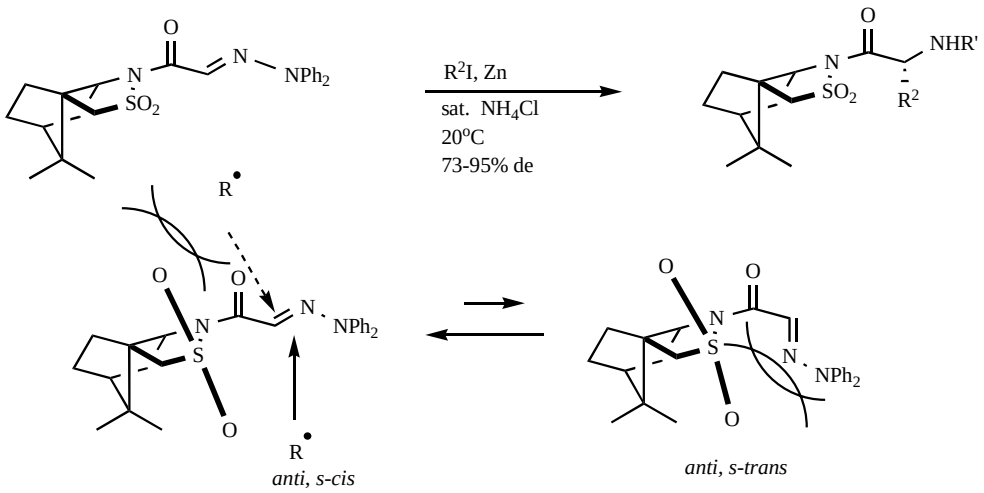
Although reasonable well utilized in stereo-specific free radical chemistry in conventional organic solvents the following principles are at the infancy of being applied and utilized in aqueous media. The examples discussed in details will focus on the two most common ways of stereo-control: reactant control and reagents control diastereo- and enantioselective examples in free radical alkylation reactions in aqueous media.

5.2. Stereoselectivity in Free Radical Alkylation of C=N Bond

In conclusion, we have established the diastereoselective zinc-mediated alkyl radical addition to imine derivatives such as oxime ether and hydrazone in aqueous media. The reactions proceeded with good diastereoselectivities, providing access to a range of α-amino acid. The zinc-mediated radical reaction of the hydrazone bearing a chiral camphorsultam provided the corresponding alkylated products with good diastereoselectivities, which could be converted into enantiomerically pure α-amino acids The diastereoselective radical addition to hydrazone was examined under several reaction conditions. The biphasic reaction of hydrazone with isopropyl radical in aqueous NH_4Cl-CH_2Cl_2 (4:1, v/v) proceeded slowly to give the corresponding alkyl substituted derivative in the 73% yield and 95% d.e. after being stirred for 22 h (Scheme **17**) [67]. As expected, the diastereoselectivity observed can be explained due to the rotamer having the carbonyl group *anti* to the sulfonyl group would be favoured in order to minimize dipole-dipole interactions be-



Scheme 16. Zinc mediated addition to C=N bond in aqueous media.



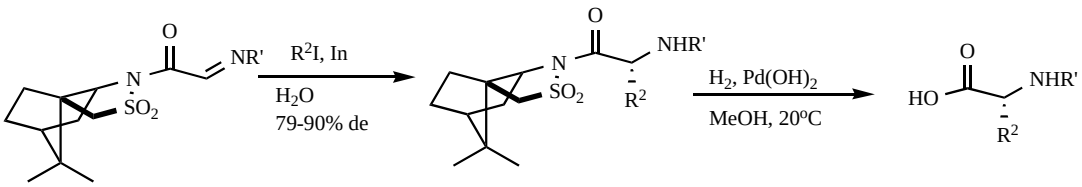
Scheme 17. Stereoselective radical addition to the C=N bond mediated by Zn [67-71].

tween these groups (Scheme **17**). As suggested by the studies on the camphosultam derivatives of glyoxylic acid [67-71].

Furthermore, the isopropylated product has been converted into α-amino acid (Scheme **18**), through cleavage of the N-N bond of diastereomerically pure product by hydrogenolysis in the presence of Pearlman's [67]. In earlier work on triethylborane-induced radical reactions in organic solvents, oxime ether has shown an excellent reactivity. Thus we expect that the direct comparison of indium-mediated reactions with triethylborane-induced reactions would lead to informative and instructive suggestions regarding reactivity and stereochemical course of the transformation in question.

5.3. Enantioselective Radical Addition Reactions to the C=N Bond Utilizing Chiral Quaternary Ammonium Salts of Hypophosphorous Acids in Aqueous Media

Recently, D. O. Jang and co-workers, have reported on the development of an enantioselective radical addition reaction to glyoxilate oxime ether for the preparation of α-amino acids under mild reaction conditions with chiral quaternary ammonium salts of hypophosphorous acid in aqueous media [72]. The newly prepared chiral quaternary ammonium hypophosphites are inexpensive, less toxic then metal containing compounds and reaction conditions and work up are mild and simple (Table **4**). It's also important to note that chiral quaternary hypophospahates are recyclable without altering the performance. The enantioselectivities afforded high yields of the addition products with a high enantioselectivity that can be attained without using metals (Scheme **19**). The absolute configuration of the addition adducts allowed authors to propose the plausible rationalization for the observed si-face attack of the alkyl radical on the substrate shown in Fig. (**3**) involving π-stacking and hydrogen bonding. The substrate is bound to QP by hydrogen bonds between N-H and C=O/C=N with a CO/CN s-*cis* planar conformation and also through π-stacking. In this arrangement, the re-face of C=N bond is blocked by the quinoline ring of

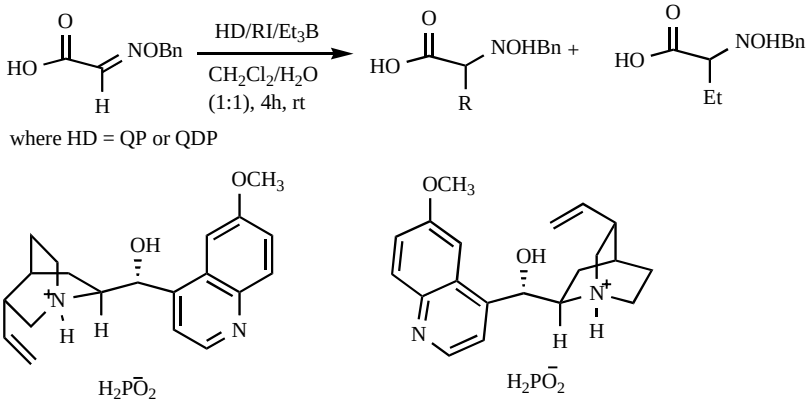


Scheme 18. Stereoselective radical addition to the C=N bond mediated by Indium towards synthesis of amino acids.

Table 4. Radical Addition Reactions to Glyoxylic Oxime Ether Under Various Reaction Conditions [72]

Entry	RI	HD	Yield[a](%)	Selectivity[b] (*R*:*S*)
1	*i*Pr-I	QP	83(7)	21:79
2	*i*Pr-I	QDP	82(10)	62:38
3	1-Ad-I	QP	45(35)	>1:99
4	1-Ad-I	QDP	47(37)	>99:1
5	*n*Oct-I	QP	50(25)	40:60
6	*n*Oct-I	QDP	48(30)	58:42

[a]The yield in parenthesis is for side product 2b. [b]Enantiomeric ratio was determined by HPLC analysis using chiral column (Daicel Chiralpack AD-H) with hexane-isopropanol as the solvent.



Scheme 19. Radical addition reaction to the C=N bond utilizing chiral quaternary ammonium salts [72].

QP. An alkyl radical then attacks the C=N bond from the *si*-face to afford the addition products (Fig. **3**).

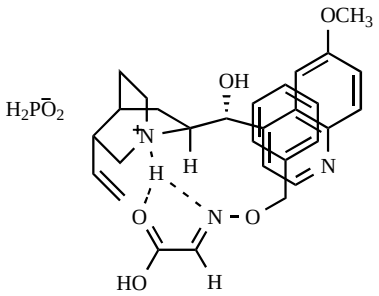
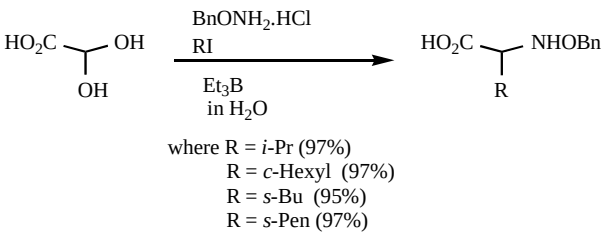


Fig. (3). Plausible model to explain the observed enantioselectivity.

6. APPLICATIONS

6.1. Synthesis of Natural and Unnatural Amino Acids in Aqueous Medium

The further survey of the scope and limitations of the reaction provided a convenient method for preparing the a-amino acids and assessed the feasibility of using several imine derivatives in the radical alkylation reaction (Scheme **20**) [38,48,73,74,75]. The remarkable feature of this reaction by employing a water-resistant radical species and integrating a multi step reaction into one pot three components convenient method for preparing α-amino acids (Scheme **20**).



Scheme 20. Synthesis of amino acids in water.

6.2. Radical Polymerisation of Alkenes

One of the most distinguishable features of radical polymerisation is its tolerance to water, relative to the ionic counterparts, which should be done under stringent conditions without moisture and protonic or basic impurity. Because of unique features, suspension, dispersion and emulsion processes in aqueous or alcoholic media are widely employed in radical polymerisation [76]. Sawamoto *and* coworkers, have developed living radical polymerisation of methyl methacrylate (MMA) and related acrylic and styrenic monomers mediated by a ruthenium complex $[RuCl_2(PPh_3)_3]$ in water and alcohols (suspension process). The living polymerisation of interest utilized MMA in water and alcohol by using $[RuCl_2(PPh_3)_3]$ in conjunction within organic halide initiator like $PhCOCHCl_2$ or CCl_3Br (Scheme **21**).

Coelho and co-workers have recently reported another use of water in the living polymerisation in the synthesis of a block copolymer (poly(vinyl) chloride-β-poly(n-butyl acrylate)-β-poly(vinyl cloride). The new material was synthesized by single-electron-transfer/degenerative-chain-transfer-mediated living radical polymerisation (SET-DTLRP) in two steps [77].

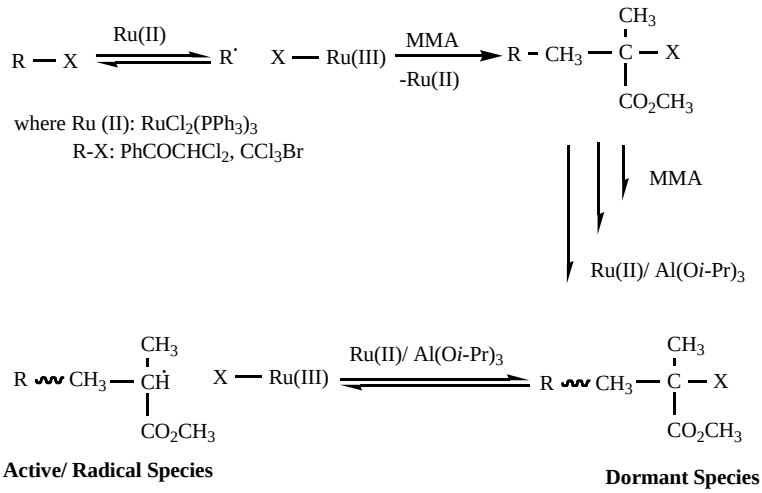
6.3. Free Radical C-C Bond Formation on Solid Support Towards Green Combinatorial Chemistry and Drug Discovery

Combinatorial chemistry has become a core technology for the rapid development of novel lead compounds in the pharmaceutical industry and for optimisation of the therapeutic efficacy [78]. In recent years, a variety of reactions have been performed on solid support. However, the carbon-carbon bond-forming solid phase reactions are less common than the carbon-heteroatom bond-forming solid phase reactions [78].

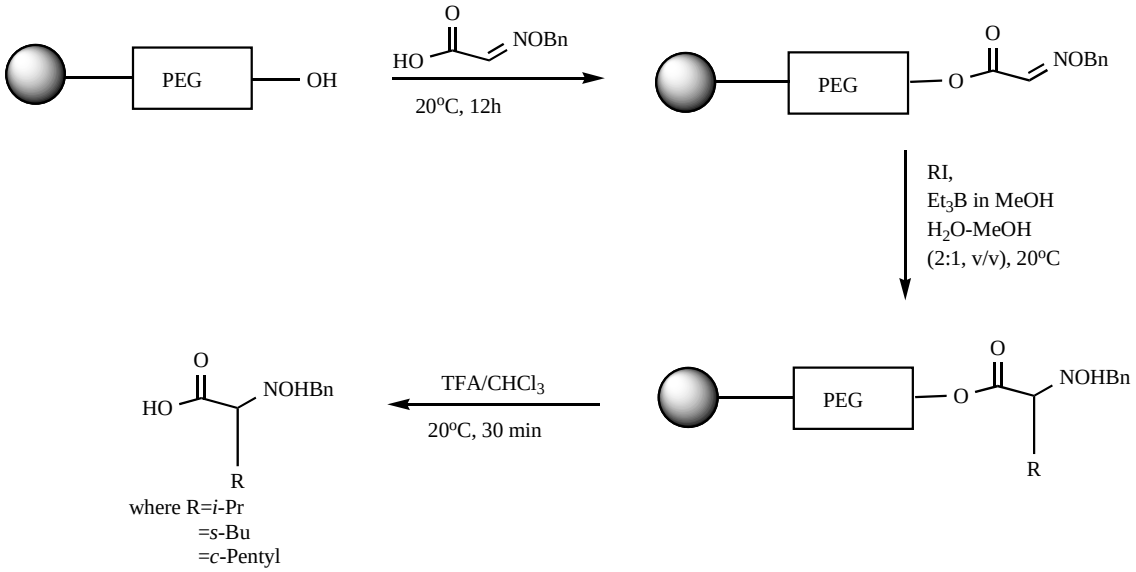
Naito and co-workers have developed the triethylborane-induced solid-phase radical reactions of oxime ethers anchored to the TentaGel OH to produce various natural and unnatural amino acid derivatives in aqueous media (Scheme **22**, Table **5**) [79].

7. CONCLUSION

This review highlights several methods for carbon-carbon in aqueous media under various experimental conditions. The simplicity of water, its abundance and wide availability, will undoubtedly lead the development of novel and exciting methodologies. The development of environmentally benign applications based on radical carbon-carbon bond formations is just around the corner.



Scheme 21. Living Polymerization in aqueous media [76].



Scheme 22. Solid phase radical synthesis of amino acid derivatives [79].

Table 5. Alkyl Addition to the TentaGel OH Resin-Bound Glyoxylic Oxime Ether in Aqueous Media [79]

Entry	Solvent	Et_3B	Yield (%)[a]
1[b]	H_2O:MeOH(2:1,v/v)	in hexane	No reaction
2[b]	H_2O:MeOH(2:1,v/v)	in THF	66
3[b]	H_2O:MeOH(2:1,v/v)	in MeOH	79
4[c]	CH_2Cl_2	In hexane	57

[a]Isolated yields.
[b]Reactions were carried out with Et_3B (10equiv.) at 20°C for 15min.
[c]Reaction was carried out with Et_3B (3.6equiv.) at 20°C for 1h.

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