Recent Developments in Nucleophilic Radical Addition to Imines: the Key Role of Transition Metals and the New Porta Radical-Type Version of the Mannich and Strecker Reactions

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Abstract: This review summarizes the interesting results obtained during the last decade in the radical aminoalkylation of a wide range of nucleophilic radicals (deriving from hydrocarbons, ethers, alcohols, halogenated derivatives and amides) promoted by transition metals. We focus on the two main procedures which recently yielded the most relevant results in this field: the dimethylzinc-air process and the new Porta reaction, based on the Ti(III)/hydroperoxide system. These protocols often provide competitive alternatives to classical landmark transformations, like the Mannich reaction and the Strecker synthesis. Moreover, a brief overview of other significant examples is given in the last section of the review.

Keywords: Imine, nucleophilic radical addition, dimethylzinc, titanium trichloride, transition metal, hydroperoxide.

1. INTRODUCTION

For several years, imines and iminium salts have represented suitable electrophilic substrates in C-C ionic bond formation and in the synthesis of a wide range of polyfunctional derivatives. Nevertheless, nowadays, environmental and economical standards require more efficient, mild and cheap procedures for the synthesis of derivatives with high added value. This makes the radical addition to imines more attractive as compared with the classical and widely developed ionic ones, which often require multi-step procedures, expensive reagents, long reaction times and highly controlled operating conditions.

In addition, whereas electron-withdrawing groups are suitable for the ionic nucleophilic addition, electron donor groups directly bonded to the radical center favor the nucleophilic radical addition. As a consequence, the products deriving from the radical version are often complementary to those obtained following the ionic routes.

Nevertheless, studies involving the reductive radical addition to aldimines and ketimines are scant in comparison to those dealing with C=N derivatives containing functional groups (such as oxime ethers, hydrazones, etc.). The reason of this lack in the literature can be ascribed to the intrinsic nature of these substrates: simple aldimines, like unprotonated heteroaromatic bases, have slower radical addition rates because the electrophilicity of the C=N bond is not adequate for the fast addition of nucleophilic radicals; furthermore they easily undergo hydrolysis, thus requiring anhydrous conditions and, in contrast to oximes and hydrazones, do not have the potential of stabilizing a three-electron π-bond in the intermediate aminyl radical.

However, in the last decade many intriguing results have been reported for the addition of a wide range of nucleophilic radical species to imines [1]. These new protocols seem to overcome the above-mentioned limits through the mediation of different transition metal derivatives, which play a key role in both the initiation and propagation steps of the radical chains. In many cases they also represent an environmentally suitable alternative to trialkyltin hydrides, which, in spite of their versatile role in promoting radical processes, show detrimental aspects, especially from an industrial point of view, due to incomplete removal and toxicity of tin derivatives [2].

2. DIMETHYLZINC-INITIATED RADICAL PROCESSES

Dialkylzinc reagents have been widely employed in organic synthesis as advantageous alkyl group donors when suitably activated by transmetallation or complexation with a variety of transition metal salts [3]. Nevertheless, for a long time it was impossible to achieve efficient alkylation of imines because of the poor electrophilicity of the C=N bond.

Only in the last decade it was found that metals bearing chiral ligand complexes, like copper [4], zirconium [5], hafnium [6] and titanium [7], were able to accelerate the alkylation of imines by dialkylzinc [8]. A few examples are shown in Scheme **1**.

In 2000 Tomioka and coworkers found an unexpected behavior of dimethylzinc in the presence of air [9]. When operating in an ethereal solvent, they obtained the first example of an α-alkoxy radical generation through hydrogen abstraction from the ether by Me_2Zn (Scheme **2**, *path i*), instead of the usually observed alkyl addition. Thus, the final product in the presence of an imine resulted in the direct α-alkoxy radical addition to the C=N bond.

Since then, several examples have been reported, mainly by the same research group, for the selective radical functionalization of imines by applying the dimethylzinc-air system in the presence of different nucleophilic radical sources (Scheme **2**) [10]. Besides further development of the α-alkoxy radical addition protocol, through a three-component reaction involving the *in situ* formation of an imine [10a], advances have also made possible the direct aminoalkylation of cycloalkanes (Scheme **2**, *path ii*) [10b] and the introduction of C1, C2 and C3 units to imines (Scheme **2**, *path iii*) [10c,e] *via* dimethylzinc-initiated radical processes.

The iodine atom-transfer reaction of primary alkyl (Scheme **2**, *path iv*) [10d] and, very recently, of alkoxy methyl iodides (Scheme **2**, *path v*) [10f] resulted to be a suitable source of alkyl and acyloxymethyl radicals, respectively. The addition of these radicals to imines, in the presence of dimethylzinc, afforded the corresponding adducts from good to excellent yields.

These results are important as the analogous halogen atom-transfer reactions, conducted in the presence of diethylzinc, were efficient only for the radical functionalization of C=N bonds bearing functional groups, such as oxime ethers [11]. In addition, with Et_2Zn, only secondary or tertiary alkyl iodides leading to exothermic halogen atom-transfer to the ethyl radical were appropriate substrates, whereas with Me_2Zn, the formation of the more reactive methyl radical allows the use of primary alkyl iodides.

Bertrand and coworkers [12] reported that phenylorganotellurium compounds could represent a good alternative to alkyl iodides

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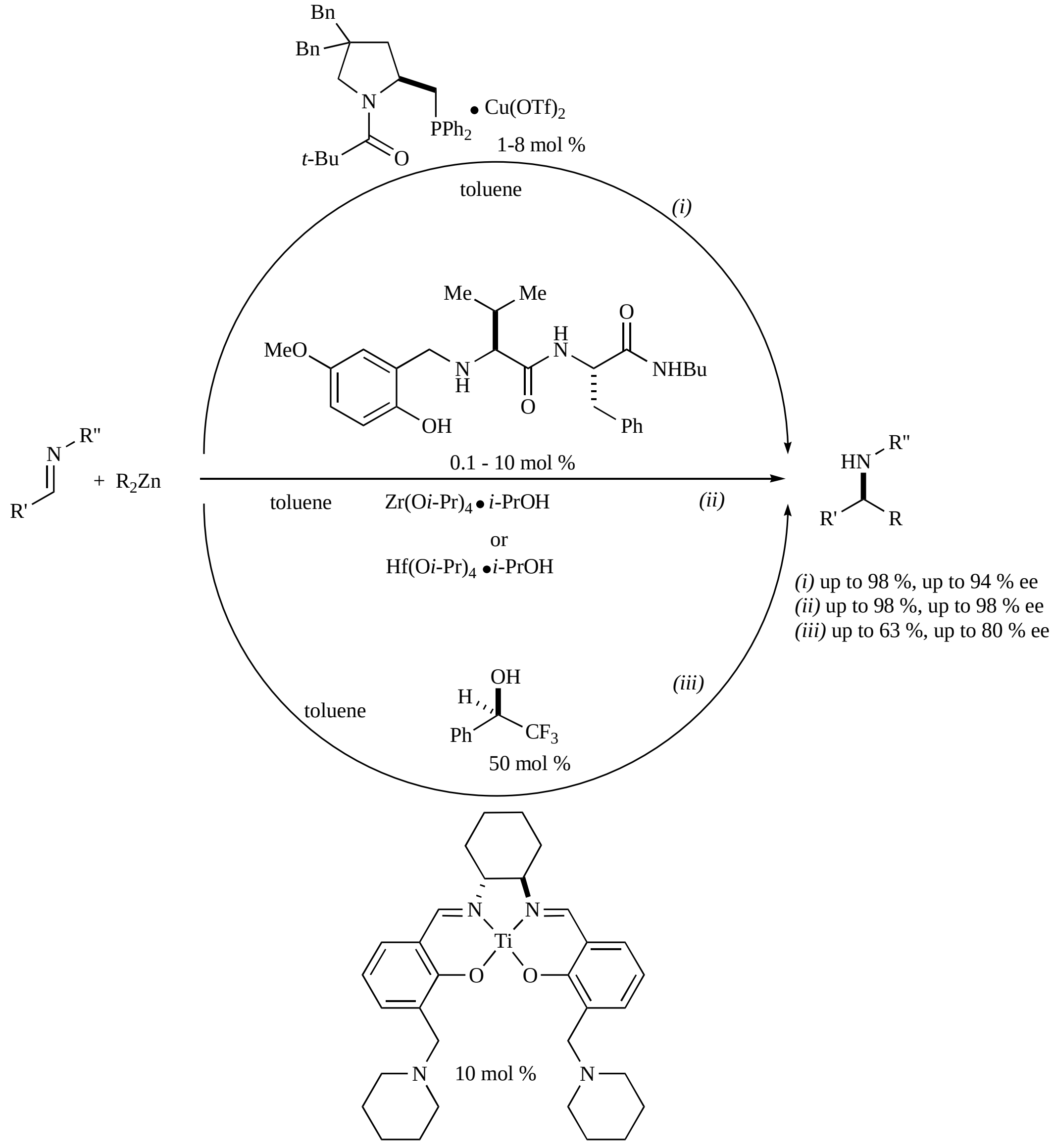
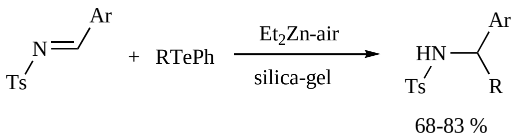


Scheme 1.

as radical precursors in dialkylzinc-mediated radical additions to C=N double bonds (Eq. 1).



(Eq. 1)

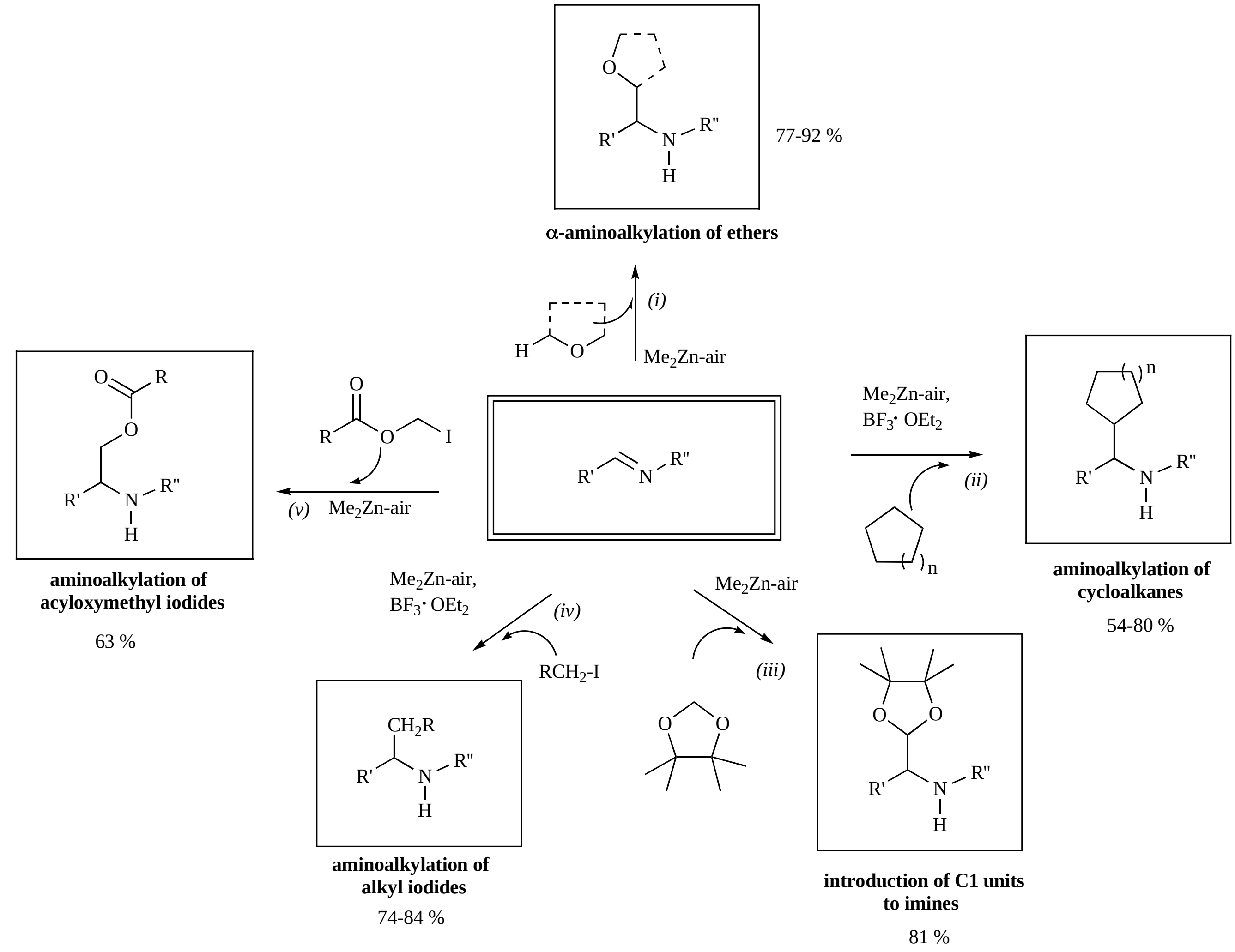
The general proposed mechanism for the dimethylzinc/air mediated process is presented in Scheme **3**. Dimethylzinc and oxygen would initiate the reaction by releasing a methyl radical. Due to its enhanced instability, as compared with that of other alkyl radicals, the methyl radical would be able to undergo hydrogen or iodine atom-transfer with a generic radical source R-X, affording the radical R·. The generated R· would add to the C=N bond leading to an aminyl radical, which would undergo homolytic substitution with another Me_2Zn complex affording the desired products and the chain propagating methyl radical.

Although the high reactivity of zinc alkyls towards oxygen is known since the middle of the nineteenth century, the reaction mechanism related to their aerobic activation is still controversial. In the last years, Lewiński and coworkers have been able to isolate and characterize zinc alkyl peroxides and alkoxides by oxygenation of R_2Zn compounds [13]. These results seem to exclude the commonly assumed free-radical chain mechanism for dialkylzinc activation.

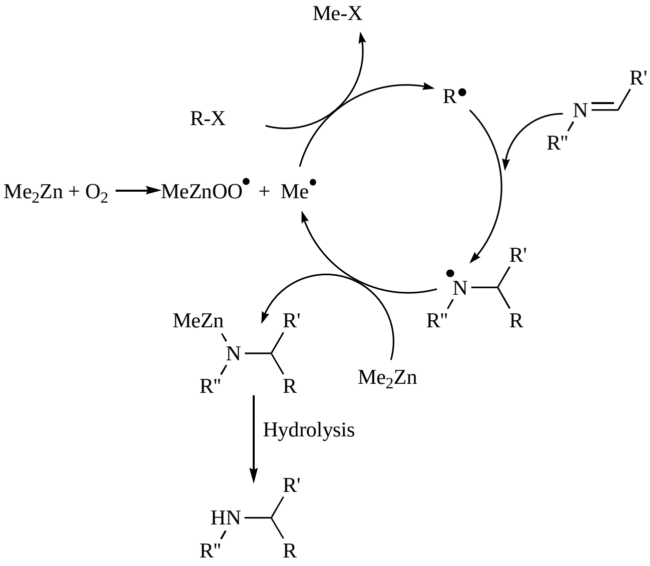
3. PORTA REACTION: TITANIUM SALTS PROMOTED RADICAL ADDITION

In 1990 Porta and coworkers reported the first example of a one-pot methodology for the selective radical functionalization of imines, mediated by titanium salts [14]. The Porta group has subsequently extended the role of titanium salts in developing new routes for the synthesis of a wide range of polyfunctional derivatives.

Titanium salts are highly specific reagents for these multicomponent reactions, acting as radical initiators and radical terminators in the lower-(III) oxidation state (Eq. 4) and contributing, as Lewis acids in the higher-(IV) oxidation state, to the imine formation and



Scheme 2.



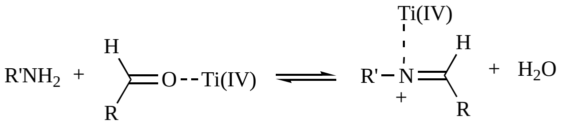
Scheme 3.

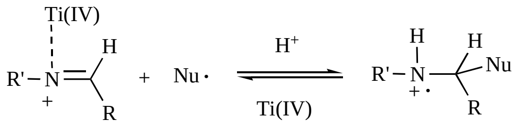
its subsequent activation towards a radical addition, due to their coordinative power (Eqs. 2 and 3).

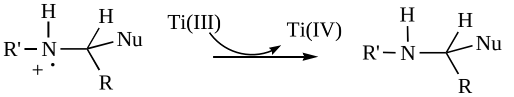
The synthetic potential of this radical approach arises from the facile and versatile functionalization of imines generated *in situ* from ready available aldehydes and amines (Scheme **4**).

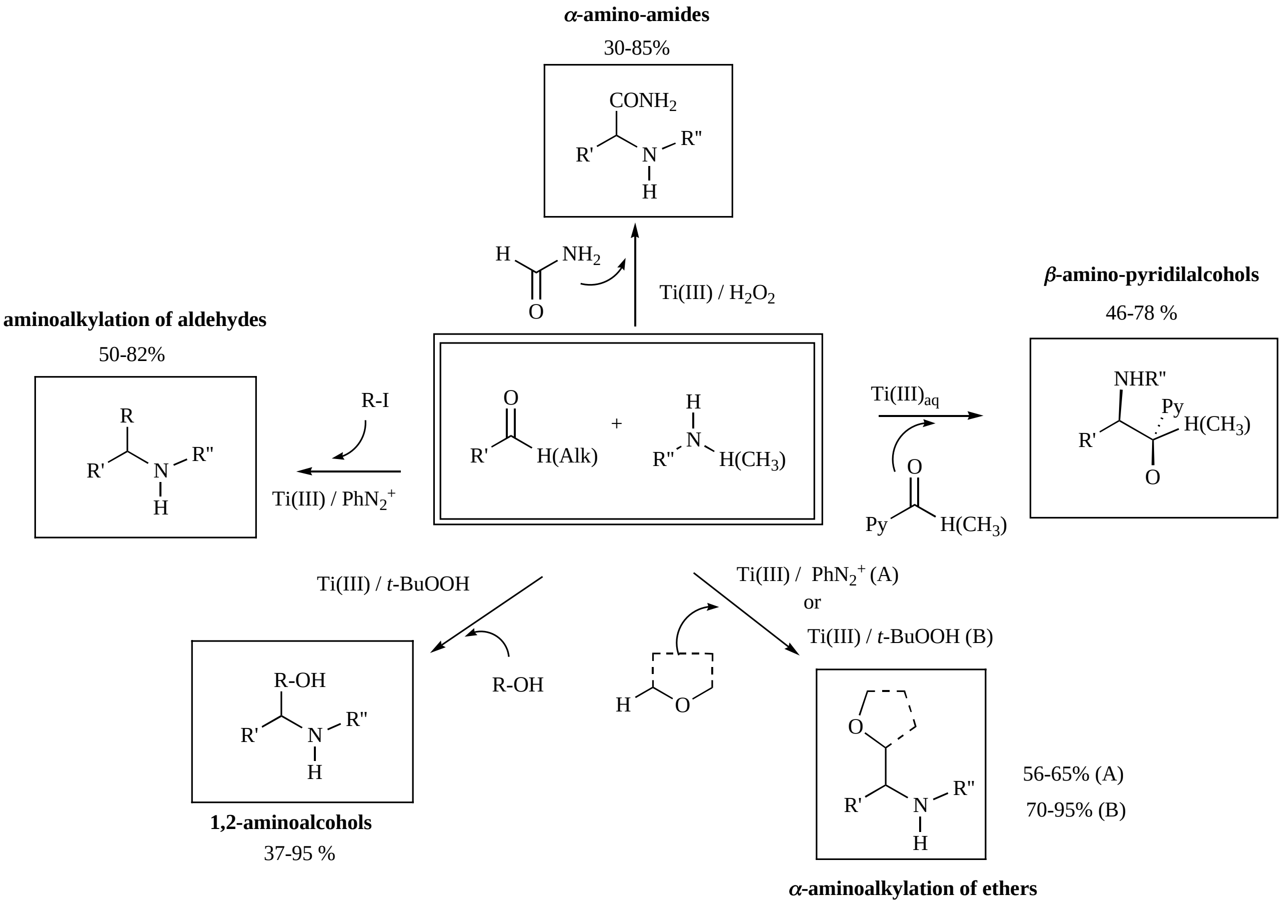
By operating under mild conditions, these "one-pot" domino reactions allow of the formation of several bonds in one sequence without isolating the intermediates and, thus, minimizing the waste.

Synthetic applications of reductive alkyl radical addition to various C=N bonds containing functional groups began to emerge since 1980 [1]. However, as previously discussed, simple imines could not be employed in these reactions, as they easily undergo


(Eq. 2)


(Eq. 3)

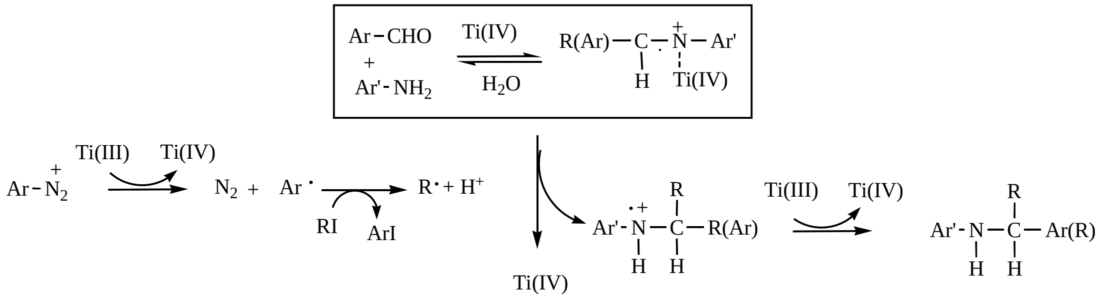

(Eq. 4)



Scheme 4.

hydrolysis and have a slower radical addition rate due to their lower electrophilic character [15].

Notwithstanding these drawbacks, the Porta group has recently reported that a simple one-pot selective amino alkylation of aryl aldehydes occurs in the presence of an aqueous acidic $TiCl_3$ solution, by using the diazonium salt/alkyl iodide system through the sequence indicated in Scheme **5** [16].



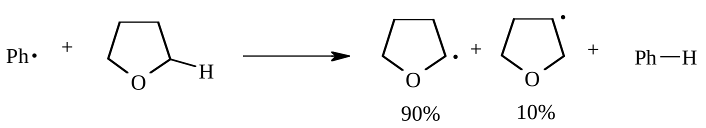
Scheme 5.

The phenyl radical, arising from the Ti(III)-induced decomposition of the diazonium salt, generates an alkyl radical by selective iodine-atom transfer. The alkyl radical adds to the C-atom of the imine formed *in situ* and activated towards nucleophilic radical addition by either nitrogen protonation or Ti(IV)-nitrogen complexation. The resulting electrophilic aminium radical is then readily reduced by a second equivalent of Ti(III), affording the final product.

The fact that the alkyl radicals considered are more nucleophilic than a phenyl radical [17] and that the iodine-atom abstraction by a phenyl radical is faster than its addition to the C=N bond, further contributes to practically eliminate the competitive phenylation reaction.

The addition reaction is relatively insensitive to the electronic effect of the *para*-substituent on the aldehyde ring, because the polarization of the C=N bond, induced by protonation or Ti(IV) complexation, overcomes the substituent effect. Furthermore, Ti(IV) coordination enhances the stability of the imine in the aqueous medium, making simple imines also suitable substrates for this process.

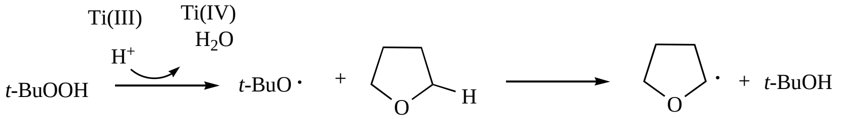
When the $TiCl_3/PhN_2^+$ system was employed in tetrahydrofuran as a co-solvent, the resulting phenyl radical was able to abstract a α-H atom from THF (Eq. 5), leading to the addition of nucleophilic α-alkoxyalkyl radicals to the C-atom of aldimines [18].



(Eq. 5)

The basic nitrogen of the C=N bond offers a site for Lewis acid-complexation that enhances the imine reactivity towards nucleophilic radicals; as seen before, the phenyl radical indeed promotes the radical addition of ethers (THF, 1,4-dioxane and Et$_2$O) to imines formed *in situ* and, notwithstanding the aqueous medium, the reaction is applicable even to formaldimine and imines of enolisable aliphatic aldehydes. The competitive phenylation of the imine [14] was less than 5 % and, also in this case, the C-substituent of the imines had no influence on the imine reactivity.

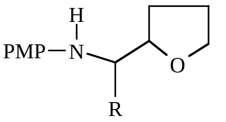
More recently, [19] the Porta group found that the aqueous acid TiCl$_3$/*t*-BuOOH system (Eq. 6) was even more practical, efficient and selective as a radical precursor of α-alkoxyalkyl radicals from ethers than the previously reported TiCl$_3$/PhN$_2^+$ system and that even methylene iminium salts or formaldehyde-imines might be successfully used as radical acceptors (Table **1**).



(Eq. 6)

It should be underlined that the product arising from the addition of the β-THF radical to the C-atom of the imine was never observed, showing that TiCl$_3$/*t*-BuOOH is a more selective system than the TiCl$_3$/PhN$_2^+$ in the hydrogen abstraction from THF.

Table 1. Porta Radical Mannich Type Reaction (Scheme 6) in the Presence of p-CH$_3$O-phenyl aniline and THF

Entry	R	Product 1, yield %^{a} 
1	H	72
2	CH$_3$	80
3	*p*-Br-C$_6$H$_4$	63
4	*p*-CH$_3$-C$_6$H$_4$	74
5	*p*-OCH$_3$-C$_6$H$_4$	80
6	C$_6$H$_5$	70
7	cyclohexyl	80

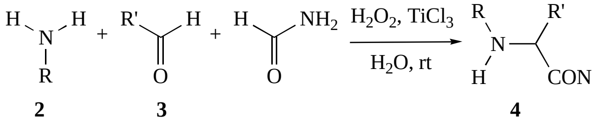
^{a}Isolated yields based on the starting amine.

In contrast with the substituent effect found in acid-catalyzed condensation of aromatic amines and aldehydes [20], an electron-donating group on the aromatic ring of the aldehyde would increase the equilibrium concentration of the Ti(IV) complexed aldehyde and would favour the Ti(IV)-assisted loss of water from the intermediated hemiaminal (Scheme **6**).

Besides, the increased basic strength of the imine would also increase the equilibrium concentration of the Ti(IV)-complexed imine, which is the reactive counterpart of the incoming nucleophilic radical.

This reaction can be regarded as the radical version of the classical Mannich reaction with the substantial difference that the functional group directly bonded to the reactive carbon atom is electron-withdrawing for the ionic and must be electron-donor for the radical addition.

Further investigation of the synthetic potential of the TiCl$_3$/hydroperoxide system allowed the same group to disclose a new free radical protocol (Eq. 7) leading to α-aminoamides (precursors of aminoacids) in high yields, operating in formamide as a co-solvent [21].

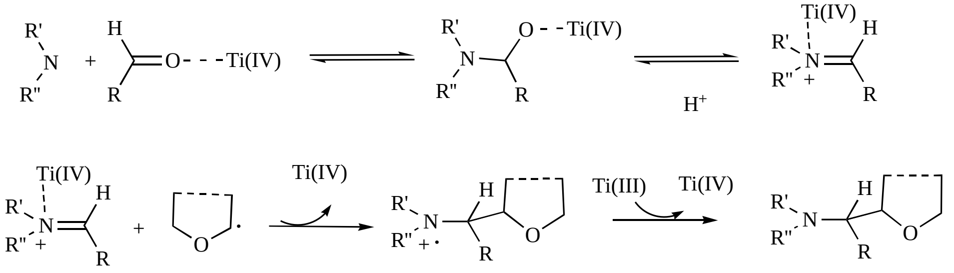


(Eq. 7)

According to the proposed mechanism, the hydroxyl radical, generated by the Ti(III) one-electron reduction of H$_2$O$_2$, abstracts a hydrogen atom from formamide, leading to the corresponding carbamoyl radical which then adds to imines generated *in situ*.

This approach, in which a carbamoyl radical acts as a nucleophilic carboxylate synthon in place of the nucleophilic ionic cyanide, may be regarded as an efficient radical version of the Strecker Synthesis (Table **2**).

Only bulky substituents at the C-atom of the intermediate imine depress the yields, pointing out that, in this case also, the reaction is insensitive to the polar nature of the substituents on aldehydes and aniline. In fact, the polarization of the C=N bond, induced by N-Ti(IV) complexation, overcomes the substituent effect and the last



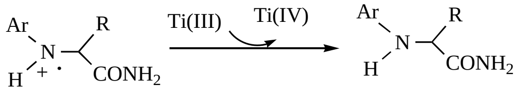
Scheme 6.

Table 2. Porta Radical Strecker Type Reaction (Eq. 7) in the Presence of p-CH$_3$O-phenyl Aniline

Entry	3 R'-	4 %[a]
1	CH_3-	60
2	$(CH_3)_2CHCH_2$-	75
3	$(CH_3)_2CH$-	62
4	$(C_2H_5)(CH_3)CH$-	65
5	$Ph(CH_3)CH$-	40
6	cyclohexyl-	50
7	$(CH_3)_3C$-	45
8	$PhCH=CH_2$-	55
9	Ph-	79
10	*p*-HO-C_6H_4-	66
11	piperonyl-	70
12	*o*-HO-C_6H_4-	30
13	*o*-CH_3O-C_6H_4-	60
14	*m*-CH_3O-C_6H_4-	59
15	*p*-CH_3O-C_6H_4-	66
16	*p*-Br-C_6H_4-	64
17	*p*-F-C_6H_4-	60
18	1-naphthyl-	37
19	2-naphthyl-	60
20	2-furyl-	85

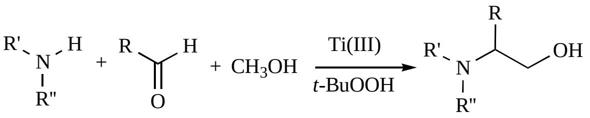
[a] Isolated yields based on the starting aldehyde R'CHO.

irreversible step (Eq. 8) becomes the driving force of the whole reaction.



(Eq. 8)

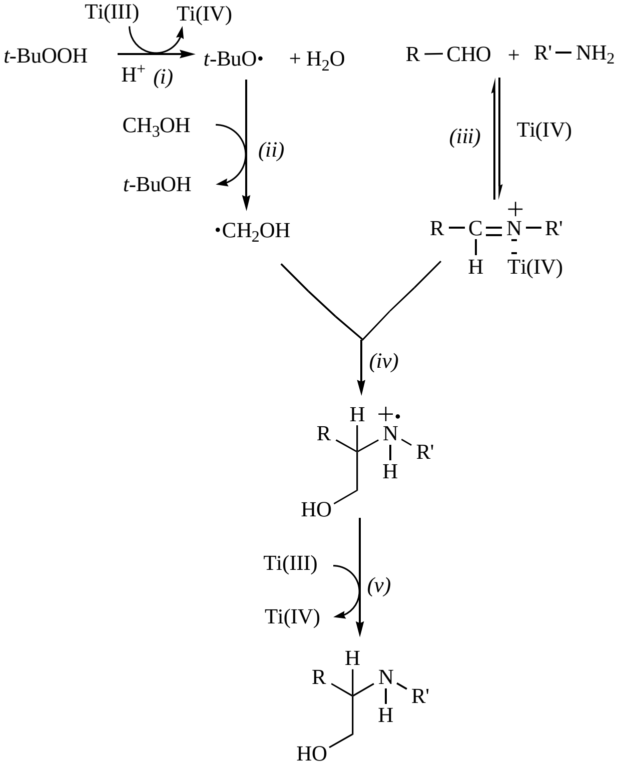
Very recently [22] the $TiCl_3$/*t*-BuOOH system was employed, in methanol as a co-solvent, to promote a radical domino multicomponent reaction with a wide range of amines and aldehydes for the preparation of α,β-amino alcohols (Eq. 9), which are suitable intermediates in the synthesis of unnatural amino acids, β-blockers, insecticidal agents and antibiotics. Furthermore, they are successfully employed in asymmetric synthesis as chiral auxiliaries or chiral catalysts.



(Eq. 9)

Both aliphatic and aromatic amines and aldehydes were suitable for these protocols, thus confirming the general applicability of the reported procedure.

The simple one-pot selective hydroxymethylation would proceed by the sequence (*i*-*v*) reported in Scheme **7**, where titanium species play a multiple key role.



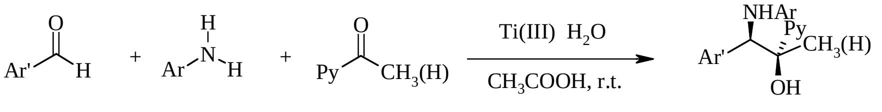
Scheme 7.

Finally, the Porta group found [23] that an aqueous $TiCl_3$ solution was able to assemble β-aminopyridyl alcohols in good yield from a one- pot reaction utilizing an acetylpyridine or a pyridine aldehyde, an aromatic aldehyde and aniline (Eq. 10).

According to the proposed mechanism (Scheme **8**), the ketyl radical **A,** formed by chemo-selective Ti(III) one-electron reduction of **3**, adds to the C-atom of the imine formed *in situ* and activated by Ti(IV)-N complexation towards addition of nucleophilic radical. The resulting electrophilic aminium radical **B** is then easily reduced to the final *syn*-aminoalcohol **4** by a second equivalent of Ti(III).

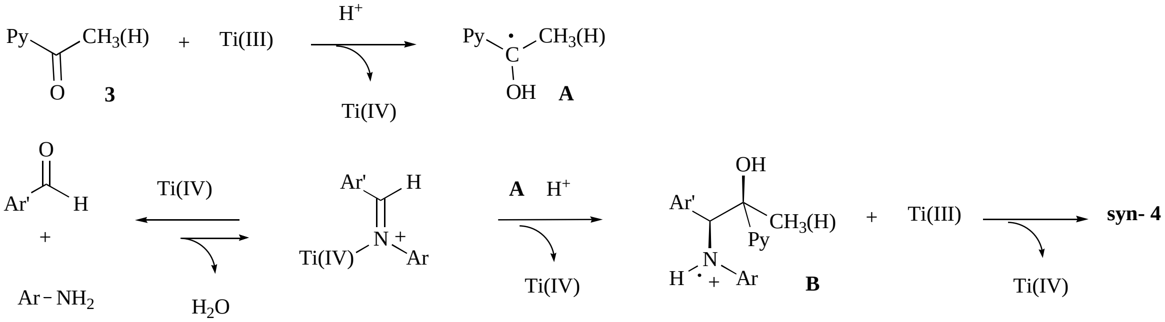
The large body of work presented in this section show that the Porta-type intermolecular addition of carbon radicals is indeed synthetically useful for a variety of compounds where the C=N bond is activated by titanium salts. Furthermore, the use of cheap and benign alcohols or ethers or formamide in aqueous solution both as the co-solvent and the primary source of radicals, as well as the ultimately nontoxic titanium oxide residue, are also of relevance and render these reactions significant from an ecological point of view.

Nevertheless, this methodology still presents some limitations. Whyle it is particularly effective with aldimines, poor results were achieved in the presence of ketimines, because of their lower stabil-



(Eq. 10)

1 **2** **3** **syn-4**



Scheme 8.

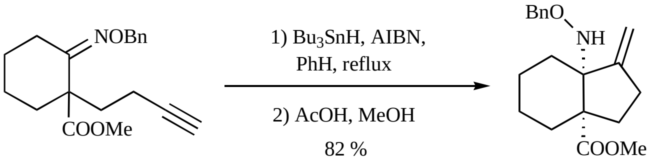
ity in the aqueous medium. However, preliminary results suggest a possible solution for increasing the ketimine reactivity and further studies are now in progress.

Moreover, it was impossible to achieve a high enantioselectivity of products, due to the formation of the iminium intermediate, but the choice of appropriate Ti(IV) ligands might open new avenues to achieve enanctioselective transformations.

In conclusion, the seminal studies of the Porta group have demonstrated that the direct reductive amination can be accomplished simply *via* a radical approach and that may well complement the existing ionic methods, so to provide a fascinating radical version of two classical landmark transformations, like the “Mannich reaction” and the “Strecker synthesis”.

4. ACTIVATION BY OTHER TRANSITION METALS

The free-radical reductive cyclization of imine-type substrates mediated by transition metal species has aroused great interest, especially because of their application in the synthesis of products with pharmacological activities [1]. In this context, Enholm *et al.* reported the first example of a radical addition to a C=N bond mediated by stannyl radical attack to a terminal alkyne, thus promoting the radical cyclization to the corresponding oxime (Scheme **9**) [24].



Scheme 9.

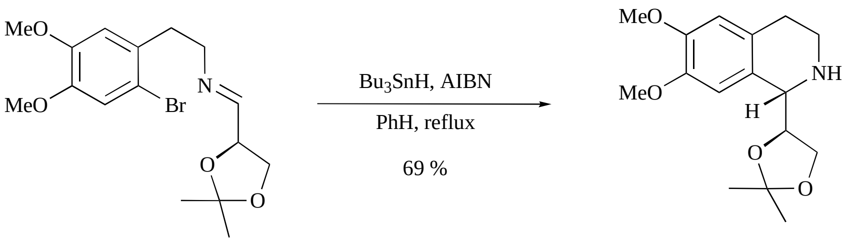
In the same year Takano *et al.* reported the first example of an imine as a radical acceptor in the synthesis of cryptostylline alkaloids mediated by Bu_3SnH (Scheme **10**) [25].

Because of the presence of cyclic amino alcohols in a variety of natural products, extensive studies have been devoted to the C-C bond construction *via* pinacol-type reductive coupling of aldehydes and/or ketones with C=N radical acceptors.

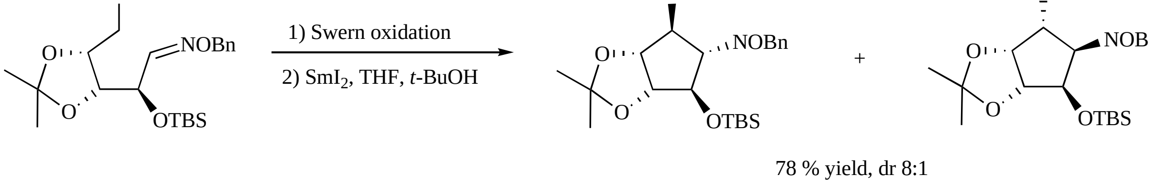
In the recent years, samarium(II) iodide has aroused great attention as a convenient one electron reductant in organic synthesis, especially in the preparation of aminoalcohols by intramolecular cyclization of ketyl-type radicals. Shono and Fallis, independently, established that the C=N bond was not reduced under coupling conditions, but the reaction was initiated by a one-electron reduction of the C=O bond [26]. These cyclizations mediated by samarium salts are not easily explained by the Beckwith-Houk model: this could be ascribed to both the coordination chemistry of Sm(III) and the Lewis basic character of the intermediates. Similarly, *O*-stannyl ketyl radicals, generated by reversible stannyl radical addition to the oxygen of the C=O, lead to reductive cyclization with C=N acceptors. Thus, the two methods involving the generation of ketyl radicals, by SmI_2 and Bu_3SnH, respectively, offer various applications.

Marco-Contelles *et al.* have developed a protocol for the reductive cyclization of carbohydrate-derived oxime ethers containing δ- or ε- carbonyl groups, in which Swern oxidation of the alcohol, followed by treatment with SmI_2, gives a good stereocontrol of the reaction (Scheme **11**) [27].

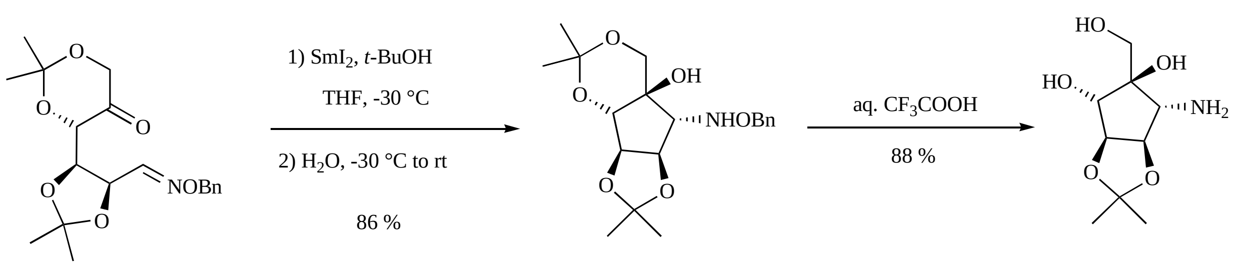
Samarium-mediated ketyl cyclizations were independently used by Giese and Chiara in the synthesis of aminocyclitols of interest into glycosidase inhibition (Scheme **12**) [28].



Scheme 10.



Scheme 11.

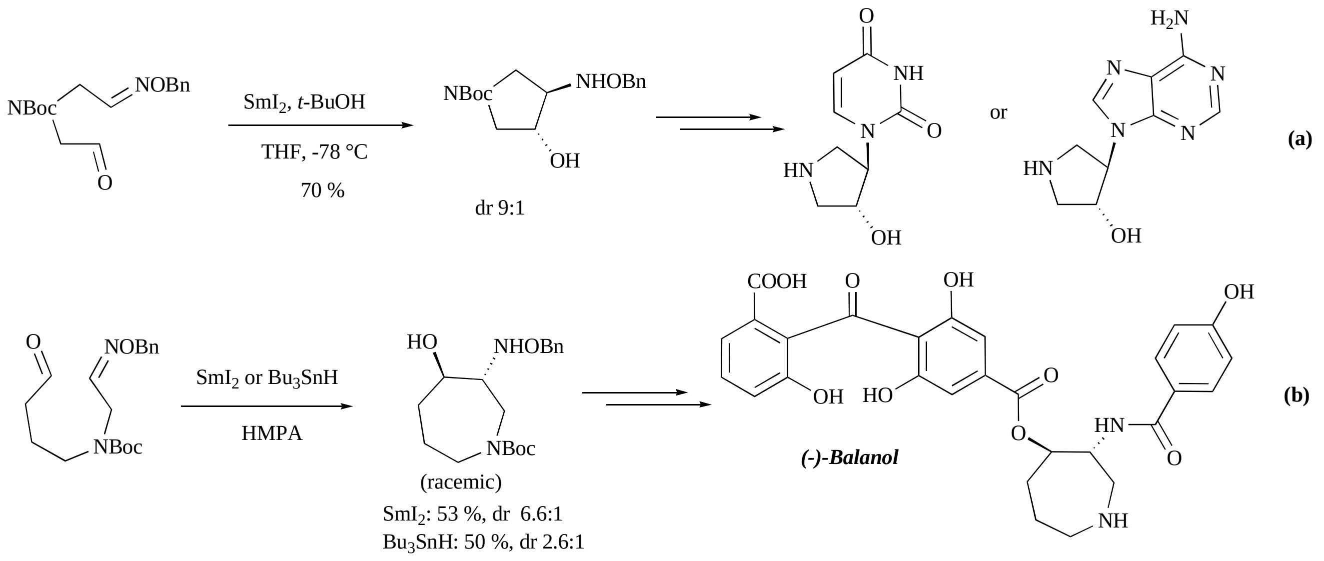


Scheme 12.

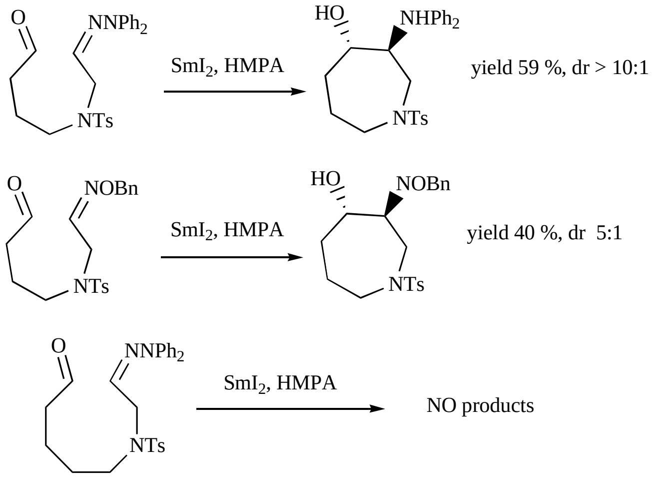
SmI_2-induced cyclizations were also used by the Naito group in the synthesis of pyrrolidine nucleoside (Scheme **13a**) [29]. In this synthetic approach, hexamethylphosphoramide (HMPA) was found to be important in the cyclization to 7-membered ring products, whereas good yields and stereoselectivity to *trans* amino-alcohols were observed in the synthesis of pyrrolidine framework in the absence of HMPA. The same 7-membered ring closure carried out in the presence of Bu_3SnH, instead of SmI_2, gave similar yields but lower selectivity (Scheme **13b**).

Skrydstrup *et al.* studied a *(-)-Balanol* synthetic route with the SmI_2/HMPA system focusing attention on the stereoselectivity of the ring closure [30]. In their studies, different reducing agents such as SmI_2, $SmBr_2$, $SmCl_2$, $CpTiCl_2$ and $Cp_2TiPhCl$ were discussed. Carbonyl hydrazones gave higher *trans* diastereoselectivity and yields than the oxime ethers and no products were recovered with a 8-membered ring precursor (Scheme **14**).

In 1998 Uemura and co-workers obtained enantiomerically pure cyclic *trans*-1,2-diamines and aminoalcohols by intramolecular cyclization of optically pure complexes of biaryls with $Cr(CO)_3$ [31]. In all the reported examples the predominant diastereoisomer was the *trans* one (Scheme **15**).



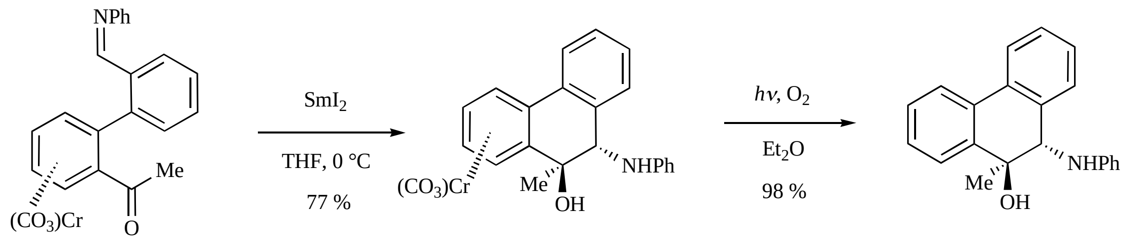
Scheme 13.



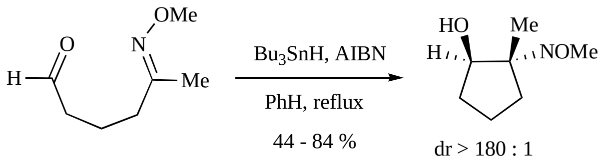
Scheme 14.

Bu_3SnH has been largely used as the reagent of choice by Naito *et al.* in a series of papers leading to the cyclization of oxime ethers to 5-, 6- and 7-membered heterocyclic *trans*-1,2-aminoalcohols because of their importance in the synthesis of biologically active molecules (Scheme **16**) [32].

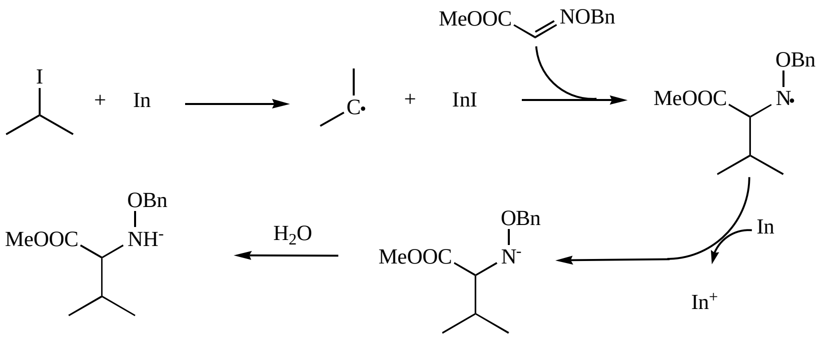
In more recent works, the Naito group introduced a new protocol for the synthesis of α-amino acids in aqueous solution mediated by indium [33]. These one-pot reactions are based on the radical addition to glyoxylic hydrazones and proceed *via* a radical mechanism, which involves a single electron transfer process from indium (Scheme **17**). The first investigation was focused on glyoxylic oxime ethers under several reaction conditions. It is important to note that no reaction was observed in the absence of water, denoting her importance in the activation of indium.



Scheme 15.

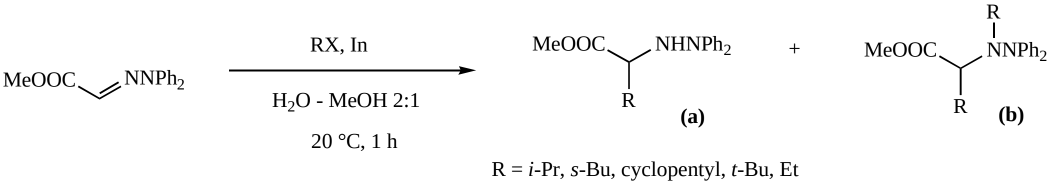


Scheme 16.



Scheme 17.

Similar protocols were applied to glyoxylic hydrazones giving a new selective method for the synthesis of α-aminoacids (Scheme **18**). In fact, when the reactions were performed in aqueous media in the presence of indium, the selective *C*- monoalkylation **(a)** took place whereas, in the presence of triethylborane, the *C*- and *N*-dialkylated products **(b)** were recovered [34].



R = *i*-Pr, *s*-Bu, cyclopentyl, *t*-Bu, Et

Scheme 18.

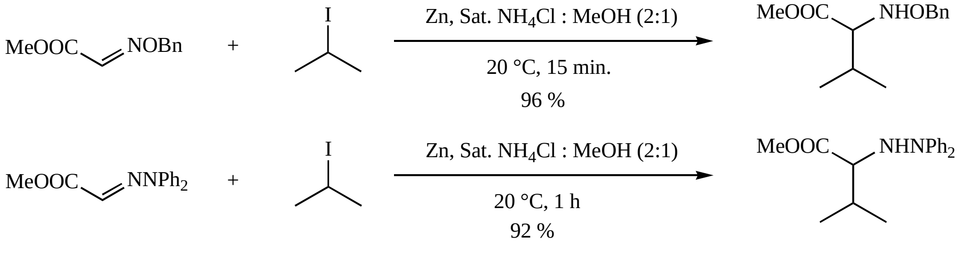
Zinc powder has been used as a radical initiator by the Naito group for the synthesis of α-amino acids in aqueous media (Scheme **19**) [35]. Both oxime ethers and hydrazones were used as substrates in the presence of alkyl iodides as radical sources.

Ammonium chloride plays a key role in the activation of Zn, as testified by the fact that no reaction occurs in the absence of it; moreover, no conversion is obtained when alkyl bromides are used as a radical source because of the higher BDE value of the C-Br bond with respect to the C-I one.

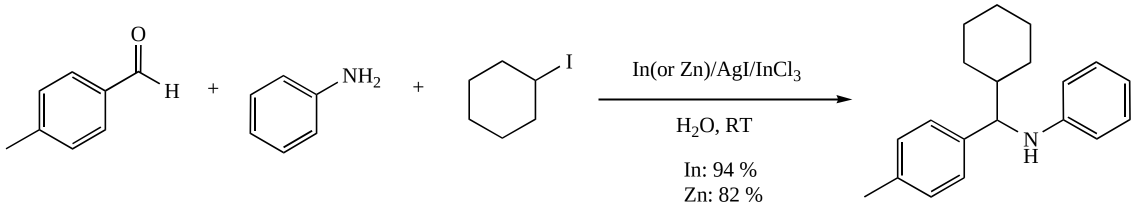
In 2008 Loh and co-workers have reported indium-silver- and zinc-silver-mediated Barbier-Grignard-type one-pot condensation of various aldehydes, amines and secondary alkyl iodides in aqueous media [36]. After a screening of different metals, they found that the In/AgI/$InCl_3$ system was the most efficient in the one-pot alkylation of imines in aqueous media (Scheme **20**).

At the beginning of 2000, the Friestad group reported an intermolecular addition of primary alkyl iodides to *N*-acylhydrazones mediated by manganese carbonyl photolysis and $InCl_3$ as a Lewis acid (Scheme **21**) [37].

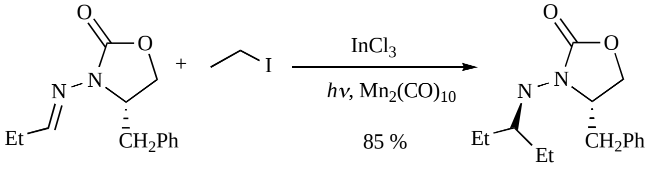
The great advantage of using $Mn_2(CO)_{10}$ is that the photolytic Mn-Mn homolysis, which does not requires a sensitizer, can be successfully applied to the intermolecular addition of primary alkyl



Scheme 19.



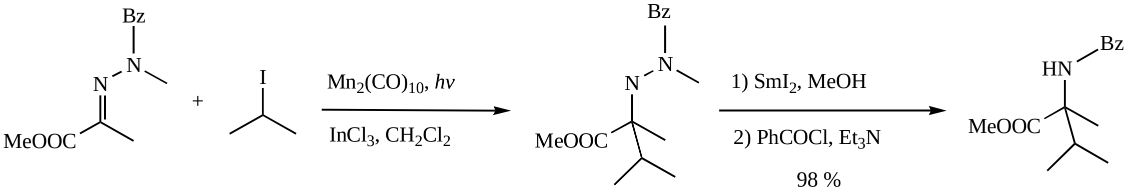
Scheme 20.



Scheme 21.

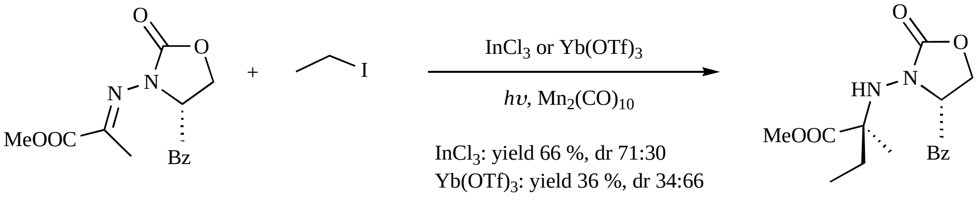
radicals to C=N bonds avoiding the formation of toxic tin by-products obtained in previous protocols.

While, at first, these Mn-mediated coupling reactions were limited only to imines deriving from aldehydes, very recently the addition to imines derived from ketones also aroused attention because it could provide an easy route to α,α-disubstituted α-amino esters (Scheme **22**) [38].

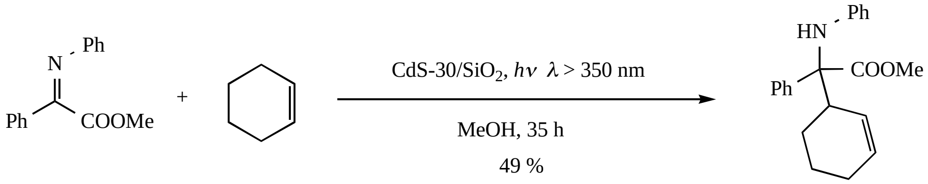


Scheme 22.

It is interesting to note that the stereoselectivity depends upon the Lewis acid used. A screening of different acids showed that $InCl_3$, $Zn(OTf)_2$, $La(OTf)_3$ and $Mg(ClO_4)_2$ led to similar results, whereas $La(OTf)_3$ and $Yb(OTf)_3$ gave inverted diastereoselection (Scheme **23**).



Scheme 23.



Scheme 24.

Finally, photocatalysed C-C bond formation reactions in which imines are the radical acceptors have been disclosed by Kisch and co-workers [39]. In these processes, CdS and both silica or zinc sulfide-supported CdS, upon irradiation with visible light (λ > 350 nm), promoted the formation of carbon-centered radicals on hydrocarbons, leading to the formation of the corresponding addition products (Scheme **24**).

5. CONCLUSIONS

Transition metals play a fundamental key role in the functionalization of a wide range of imines *via* nucleophilic radical addition. Besides, operating under very mild conditions, they also allow for the use of simple aldimines and ketimines, which are usually unstable in the classical ionic-system media. In particular, the Porta reaction is of general applicability and, thanks to the multiple role played by titanium salts, require neither *N*-protection of the imines nor anhydrous conditions, making this approach particularly fascinating from the synthetic point of view.

The authors believe that this area has the potential to prefigure not only clean and environmentally benign radical reactions but also the development of efficient enantioselective variants, and possibly thoroughly new avenues of research.

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