Catalytic Radical Reactions

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Metal-Catalyzed β-Functionalization of Michael Acceptors through Reductive Radical Addition Reactions

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conjugate addition · homogeneous catalysis · Michael acceptors · radical reactions · umpolung

Transition-metal-catalyzed radical reactions are becoming increasingly important in modern organic chemistry. They offer fascinating and unconventional ways for connecting molecular fragments that are often complementary to traditional methods. In particular, reductive radical additions to α,β-unsaturated compounds have recently gained substantial attention as a result of their broad applicability in organic synthesis. This Minireview critically discusses the recent landmark achievements in this field in context with earlier reports that laid the foundation for today's developments.

1. Introduction

1.1. Aim and Scope of this Minireview

The field of organic radical chemistry has experienced a rapid growth over the past years. The recent developments in oxidative, reductive, and photoinitiated radical coupling reactions as well as reactions initiated by hydrogen atom transfer (HAT) are important milestones.[1] These reactions address some of the shortcomings of classical radical chemistry, such as the use of toxic reagents, the limited number of radical precursors, the low atom economy of many transformations, and the lack of reagent- or catalyst-controlled processes.[2] Enantioselective transformations were even realized and, thus, the myth of the difficulty of controlling the selectivity of radical processes has been refuted.[3] These reactions display remarkable mildness and selectivity and, hence, provide unique and unprecedented possibilities to form C–C bonds, including overall umpolung reactions.[4]

Since radicals are generated in situ, it is clear that one of the major disadvantages of classical polar additions, the preformation of organometallic reagents, is not encountered in radical chemistry.

Recently, several significant reports have appeared on reductive radical additions to Michael acceptors that are of high synthetic value. To fully appreciate the significance of these advances, it is indispensable to discuss them in the context of earlier studies, which provided the basis for their development. Therefore, this Minireview will not only provide a summary of the different coupling types and recent developments, it will also point out conceptual similarities with the preceding literature.

Photoredox catalysis is a highly topical approach to the catalyzed generation of radicals, but will be discussed only briefly.[5] Although the photoredox catalysts employed for radical additions to Michael acceptors may contain metal centers (for example, $[Ru(bpy)_3]^{2+}$; bpy = 2,2'-bipyridine), these complexes act usually as redox dyes, which undergo diffusion-controlled electron-transfer processes. They usually do not actively interact with a substrate through coordination. The resulting reactions are often similar to classical free-radical additions and are, therefore, complementary to most of the transition-metal-catalyzed radical additions discussed here.[6]

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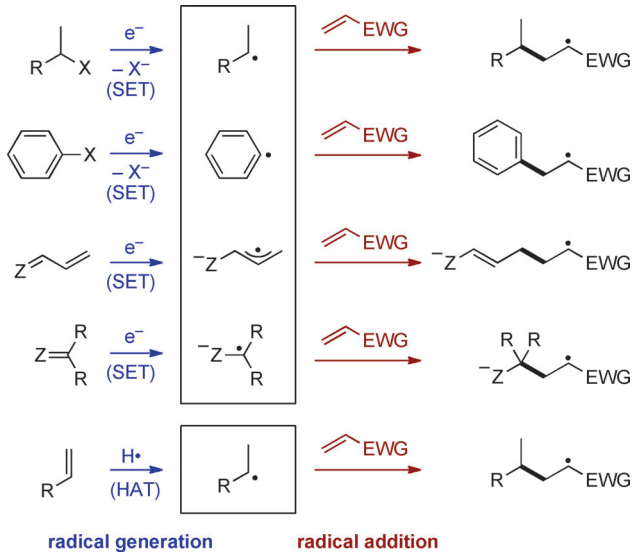
1.2. Free-Radical Reactions versus Reagent-Controlled Additions

In principle, the conjugate radical additions in this Minireview consist of two essential steps: reductive radical generation (blue) and a subsequent radical addition (red, Scheme 1). The first step represents either a single-electron-transfer (SET) event that results in reductive cleavage of the C–X bond and the generation of allylic or ketylic radical anions, or alternatively a HAT to an alkene. As will be shown

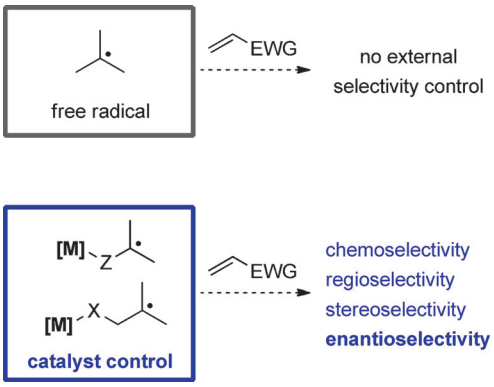


Scheme 1. The two essential steps: Reductive radical generation by SET or HAT and subsequent radical addition. EWG = electron-withdrawing group.

in the following, a variety of catalytic approaches have been developed for this initiation event.

The selectivity-determining step, however, is the subsequent addition to the α,β-unsaturated system. Traditional free-radical additions proceed under substrate control, which often results in low selectivity (Scheme 2). This problem has been overcome to some extent by the installation of auxiliary groups on the Michael acceptor for coordination to a (chiral) Lewis acid co-catalyst. Radical addition processes under direct control of the HAT or SET catalyst, however, are more attractive. Here, the catalyst remains coordinated to the attacking radical throughout the addition step and, thus, allows highly chemo-, regio-, stereo-, and even enantioselective addition reactions.

In the following, we will discuss catalyzed radical reactions by grouping them by the type of initiation to allow an easy comparison of the different approaches. The advantages of such catalyst-controlled processes will be highlighted if applicable.



Scheme 2. In contrast to free-radical additions, high stereo-, regio-, and chemoselectivity can be achieved by coordination of a metal catalyst to the substrate during the radical addition step (catalyst control).

2. Reductive C–X Homolysis

2.1. Functionalized and Unfunctionalized Alkyl Halides

Inter- and intramolecular additions of alkyl halides to alkenes, alkynes, and in particular Michael acceptors—the so called Kharasch reactions or atom-transfer radical additions—can be efficiently catalyzed by transition metals.[7] The generation of the radical occurs by abstraction of a halogen atom. Termination of the overall addition takes place by transfer of a halogen atom from the M–X bond formed during radical generation to the radical (Scheme 3). Although the overall reactions are redox neutral, they serve as excellent examples of metal-catalyzed radical addition processes under substrate control. Certainly the most important achievement in the field of radical chemistry is the development of the Cu-catalyzed polymerization reactions of acrylates.[8] In these cases, the catalyst influences the efficiency of the halide transfer and hence controls the concentration and the life time of the propagating radical with high precision.

In contrast, very few catalytic examples are known for the corresponding reductive radical addition processes that are initiated by cleavage of the C–X bonds of alkyl halides and terminated by a hydrogen atom transfer. For example, an In^{III}-catalyzed radical addition was reported, which allowed the coupling of primary or secondary alkyl iodides, as well as selected bromides, with acrylates or acrylonitrile.[9] Interest-

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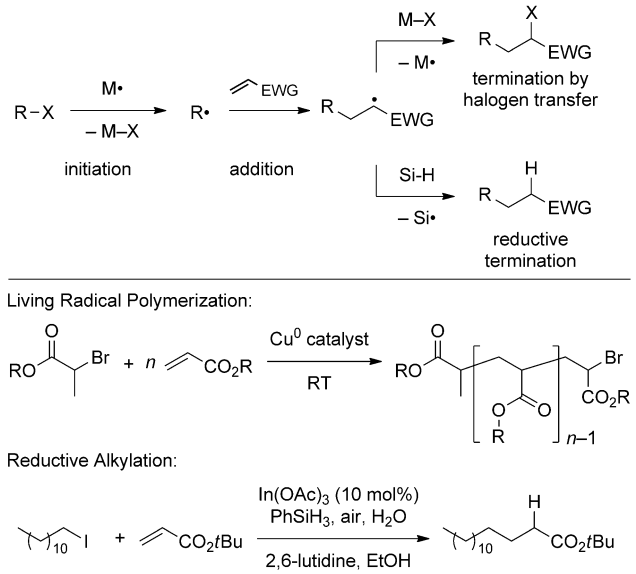
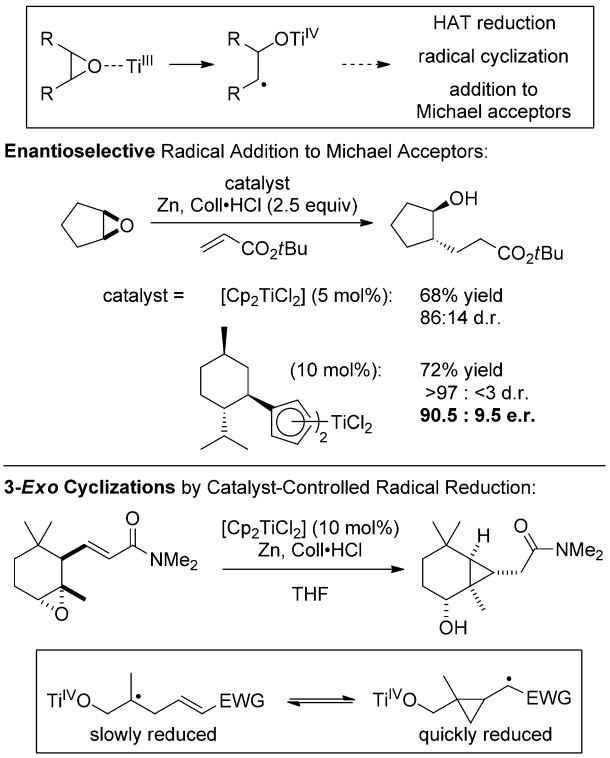


Scheme 3. Redox-neutral copper-catalyzed living radical chain polymerization and indium-catalyzed reductive addition.



Scheme 4. Reagent control in titanocene-catalyzed addition reactions of epoxides to Michael acceptors. Cp = C_5H_5.

ingly, the process required oxygen and water in addition to phenylsilane, which was employed as the terminal reductant.

In addition to this example, there have been reports on Co- and Ni-catalyzed reductive conjugate addition reactions of alkyl halides.[10] Nonradical mechanisms following either Co^{I}/Co^{III} or Ni^{0}/Ni^{II} pathways were proposed. However, a radical pathway could not be fully excluded.

2.2. Epoxide Precursors for Catalyst-Controlled Additions

As an alternative approach to the cleavage of C–X bonds, radical additions can be efficiently initiated by homolysis C–O bonds. In this regard, epoxides are a highly attractive class of precursors for the reductive generation of functionalized alkyl radicals for two main reasons: First, the release of ring strain and the formation of a strong metal–oxygen bond provides a driving force for the generation of the radical. Second, epoxides are available from a number of functional groups, such as olefins, ketones, and diols, and therefore a large number of functionalized radicals can be predictably prepared by reductive ring opening provided that the regioselectivity can be controlled.[11]

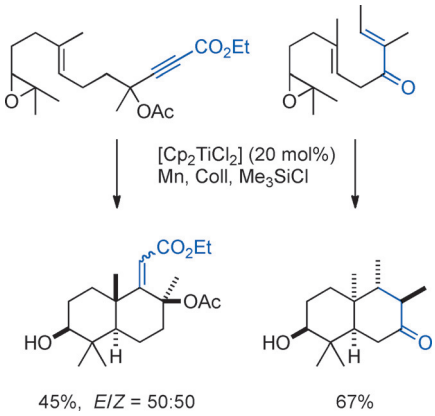
The introduction of "Cp_2TiCl"-catalyzed radical epoxide opening constituted a major breakthrough because radicals can be generated from epoxides with often excellent regioselectivity to yield a more stable radical. "Cp_2TiCl", which exists in THF as a mixture of [Cp_2TiCl] and its dimer ([Cp_2TiCl] hereafter),[12] exhibits a remarkably low Lewis acidity and a high chemoselectivity for electron transfer to epoxides.[13] Moreover, [Cp_2TiCl] reduces the radicals formed only slowly. Epoxide-derived radicals behave like typical nucleophilic alkyl radicals and can be employed in reductions by HAT,[13c] in 5-*exo* cyclizations,[13a] and in addition reactions to Michael acceptors (Scheme 4).[13b,14] Importantly, the titanium reagent remains coordinated throughout the whole process, which allows high reagent control of the selectivity.

In principle, catalytic turnover can be mediated by protonation[15] of the Ti^{IV}–O bond with Coll·HCl or by its silylation[16] with Coll·Me_3SiCl followed by in situ reduction of the liberated [Cp_2TiCl_2] to regenerate [Cp_2TiCl]. The protic conditions have proven to be especially valuable in intermolecular addition reactions to Michael acceptors, in particular acrylates, acrylamides, and acrylonitriles.[17]

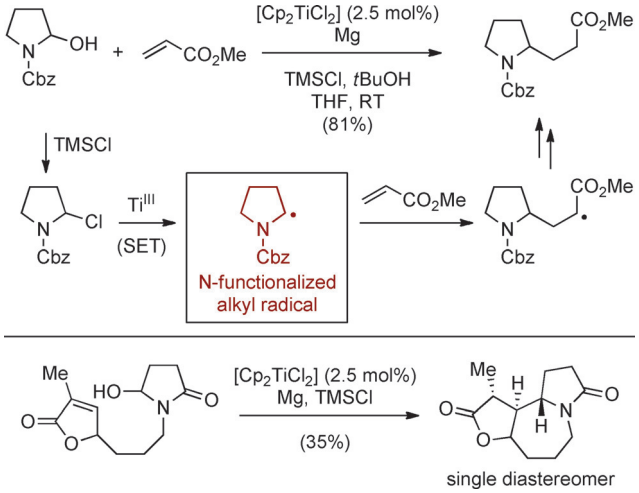
The use of Kagan's titanocene complex results in an enantioselective reaction that exhibits a higher diastereoselectivity than [Cp_2TiCl]. Reagent control is, thus, exerted both at the stage of radical generation (control of regioselectivity of ring opening) and at the stage of the ensuing radical reaction (addition to the Michael acceptor). For the planning of tandem sequences, it is important to note that typical 5-*exo* cyclizations are faster than the intermolecular Michael additions.[18]

Ti^{III}-catalyzed regioselective epoxide opening was later successfully applied to radical cyclizations for the synthesis of small rings, namely cyclopropanes and cyclobutanes,[19] as well as trisubstituted cyclopentanols.[20] Here, radical reduction is reagent controlled, since the cyclized carbonyl-substituted electrophilic radicals are reduced much faster than the epoxide-derived nucleophilic alkyl-substituted radicals (Scheme 4, bottom). The persistence of the radicals generated can be increased through the use of alkyl-substituted titanocenes.[19c]

The use of Coll·Me_3SiCl to achieve a turnover-enabling Ti–O silylation[16] has been most successful in the field of bio-



Scheme 5. Catalytic, bio-inspired terpene synthesis through radical addition to Michael acceptors.



Scheme 6. Titanium-catalyzed reductive coupling with amino-functionalized alkyl radicals generated from hemiaminals. TMS = trimethylsilyl, Cbz = benzyloxycarbonyl.

inspired terpene synthesis via radicals.[21] Michael acceptors can be employed to terminate the process to allow synthesis of ketone- and ester-substituted terpenes (Scheme 5).[22] Equally fascinating is a report on the use of ketoepoxypolyprenes containing enones for terpene synthesis. In these reactions, products of "interrupted" polyene cyclizations and *cis*-fused ring systems can be obtained, both of which are highly valuable for further manipulations.[23] Neither reaction is possible with cationic intermediates.

The conceptual similarity between titanocene catalysis proceeding in single electron steps and classic organometallic catalysis is becoming increasingly clear. The performance of the catalyst can be tailored by fine-tuning ligand properties,[24] and catalysis by [Cp_2TiCl] is compatible with catalysis by late-transition metals.[25] The initial systems employed the activation of H_2 with Rh and Ir complexes for radical reduction. As recent reports show (see also Section 2.4), reactions combining [Cp_2TiCl] with Ni or Pd catalysis can also be realized.[26]

Finally, epoxides of chalcones and related aryl ketones have been reductively opened through photoredox catalysis.[27] The use of Hantzsch esters and Michael acceptors resulted in the addition products being obtained. Without the Michael acceptors, only the reduction product was obtained. However, reagent control of the ring opening and the addition reaction is not possible.

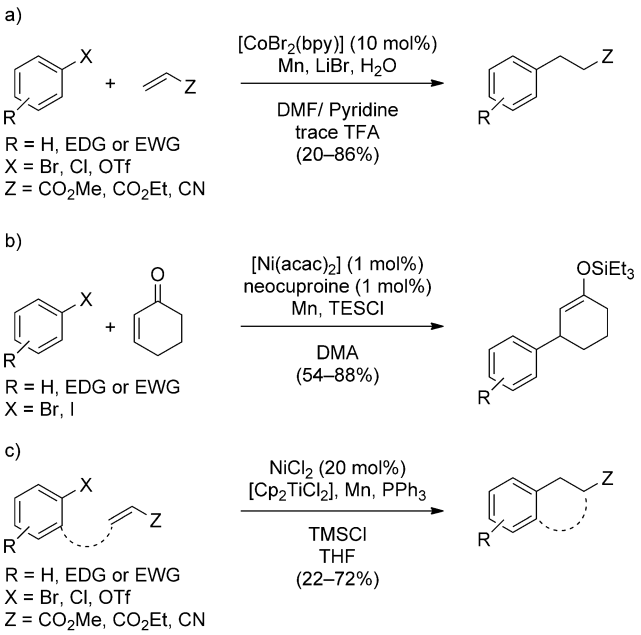
2.3. Formal Cleavage of C–OH Bonds

Ti^{III} catalysis was also found to be suitable for achieving radical addition reactions of α-aminoalkyl radicals, which were generated by a formal cleavage of C–OH bonds as the initiation step (Scheme 6).[28] Hemiaminals were employed, which acted as masked aminoalkyl halides, and were formed in situ with Me_3SiCl. Furthermore, catalytic amounts of [Cp_2TiCl_2] were used in combination with Me_3SiCl, *tert*-butanol, and Mg. The authors proposed that the hemiaminal was first transformed into the aminoalkyl chloride. Single-electron reduction would then afford the aminoalkyl radical, which would subsequently attack the Michael acceptor. Ti^{III} catalysis gave superior results compared to the earlier SmI_2-mediated procedure.[29] The scope regarding the Michael acceptor was exceptionally broad, since acrylates, acrylamides, acrylonitrile, vinylketones, α,β-unsaturated lactones, propionates, and even allene- and butadiene carboxylic esters were suitable coupling partners. The corresponding cyclization reaction was applied in the synthesis of 9,10-di-*epi*-stemoamide and gave a single diastereomer together with the dehydroxylated substrate as by-product.

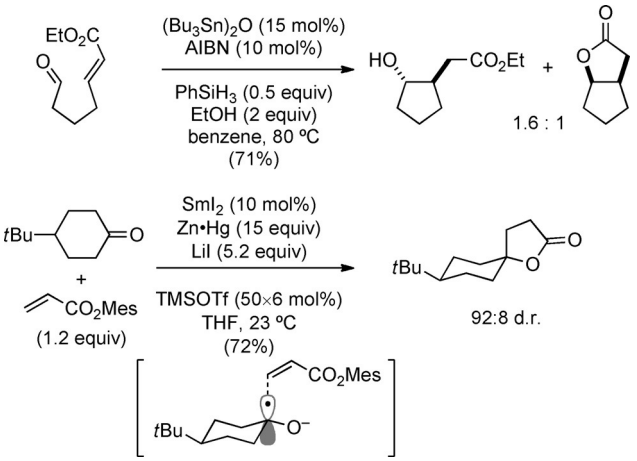
2.4. Reductive Radical Arylations

Reductive additions of aryl radicals to Michael acceptors have been realized using aryl diazonium salts and Ti^{III} reagents as the reductant. This reductive version of the Meerwein arylation was applied to the synthesis of β-arylated ketones, esters, and nitriles.[30,31] Catalytic radical coupling reactions involving aryl radicals have been known for a long time. Nickel-catalyzed Ullmann-type dimerizations of aryl halides were discussed to proceed through radical mechanisms.[32,33] Reductive cross-coupling reactions with Michael acceptors were first reported as reductive Heck reactions in the presence of palladium or nickel catalysts.[34] Recently, more broadly applicable cobalt-catalyzed variants were reported, which allowed the effective cross-coupling between aryl halides and acrylates (Scheme 7a).[35]

Although the palladium-catalyzed processes emerged from alternative pathways to the traditional Heck reaction, the mechanisms for the nickel- and cobalt-catalyzed reactions were not fully clarified. Although M^n/M^{n+2} mechanisms were discussed, the alternative generation of radical intermediates by these metals could not be ruled out. Recently, the nickel-catalyzed cross-coupling between aryl halides and Michael acceptors was revisited (Scheme 7b). The use of silyl chloride additives allowed additions to cyclic enones at low catalyst loadings. On the basis of stoichiometric studies, a reaction mechanism was proposed, which started with the formation of an allylnickel species from the catalyst and the enone.[36]



Scheme 7. Examples of reductive Heck or Meerwein-type coupling reactions to Michael acceptors by a) cobalt catalysis, b) nickel catalysis, and c) a titanium(III)-mediated nickel catalysis. TFA = trifluoroacetic acid, TES = triethylsilyl, EDG = electron-donating group, DMA = *N*,*N*-dimethylacetamide.



Scheme 8. Reductive addition reactions of carbonyl precursors to Michael acceptors via free radicals in the presence of tin or samarium catalysts. AIBN = 2,2'-azobisisobutyronitrile, Tf = trifluoromethanesulfonyl.

However, a radical mechanism could also not be fully excluded in this case.

A combination of a Ti^{III} reagent and a nickel catalyst enabled versatile intra- and intermolecular coupling reactions to Michael acceptors and allowed the use of various aryl halides or triflates (Scheme 7c).[26d,f] Here again, a Ni^0/Ni^{II} mechanism was proposed, and the titanium(III) reagent was suggested to further activate the carbonyl group and to facilitate the reduction of the Ni^{II} catalyst after the coupling process.

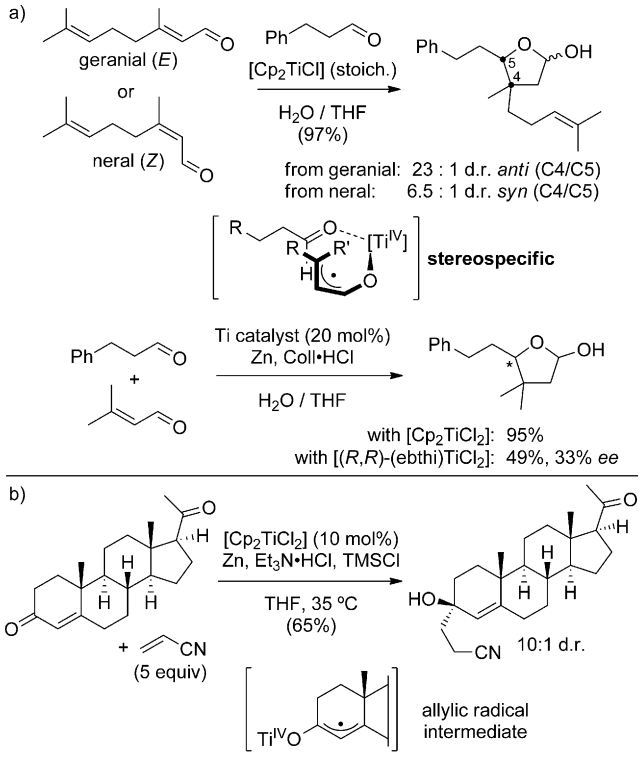
3. Single-Electron Transfer to Carbonyl Compounds

3.1. Coupling of Carbonyl Compounds to Michael Acceptors

Under classical conditions, the reductive radical addition of carbonyl compounds to Michael acceptors is achieved in the presence of tributyltin hydride and an initiator[37] or single-electron-transfer agents such as SmI_2.[38] Alternatively, Zn in combination with Me_3SiCl[39] or ammonia was established as a reductant for such carbonyl addition reactions to electron-deficient alkenes.[40] Following earlier reports on Sn-catalyzed radical reactions,[41] a Sn-catalyzed variant was developed by Hays and Fu in which $PhSiH_3$ was employed as a stoichiometric reductant. The reductive coupling of aldehydes or ketones to α,β-unsaturated esters in the presence of 15 mol% $(Bu_3Sn)_2O$ resulted in the formation of γ-hydroxy esters and γ-lactones (Scheme 8).[42] The addition occurred through a free-radical process and, therefore, proceeded with low diastereoselectivity in favor of the *trans* product. The corresponding intermolecular coupling reactions were reported shortly afterwards in the form of a Sm^{II}-catalyzed procedure.[43] Here, the reactions proceeded at room temperature, but were limited to mesityl acrylate as the Michael acceptor. The experimental procedure required the slow addition of the coupling partners to a mixture of SmI_2 and Zn·Hg followed by portionwise addition of Me_3SiOTf and was, therefore, not very practical. A 92:8 diastereoselectivity was obtained with 4-*tert*-butylcyclohexanone, which matched the expected outcome of a radical attack after single-electron reduction of the ketone.

In 2006, Cuerva, Oltra, and co-workers reported a titanocene-mediated and -catalyzed procedure that allowed the diastereoselective and stereospecific cross-coupling of carbonyl compounds with enals (Scheme 9a).[44] It was proposed that the Ti^{III} reagent formed in situ reduced the enal to an allylic radical anion and then coordinated both substrates to form a compact, selectivity-determining transition state. The stereospecifity of this transformation was exemplified by employing geranial and its *Z* isomer neral as precursors. The catalytic reaction was demonstrated by the coupling of hydrocinnamaldehyde with prenal and a first asymmetric reaction was even achieved by employing a chiral ansa-titanocene catalyst. The Ti-catalyzed approach also allowed the selective cross-coupling reaction between enones and Michael acceptors.[45] Here, sterically demanding enones added selectively through the carbonyl carbon atom to acrylonitrile as the coupling partner (Scheme 9b). In this way, a tertiary allylic alcohol was introduced at the β-position of the nitrile. Complex precursors such as the Hajos–Parrish ketone or progesterone could also be employed. The latter resulted in a 65% yield and an excellent 10:1 diastereoselectivity.

It should be noted that related transformations were reported by means of Ni catalysis.[46] In the presence of $[NiBr_2(phen)]$ (5 mol%, phen = 1,10-phenanthroline), for example, a number of aryl aldimines were successfully coupled with acrylates, acrylonitrile, or a vinyl sulfone, and



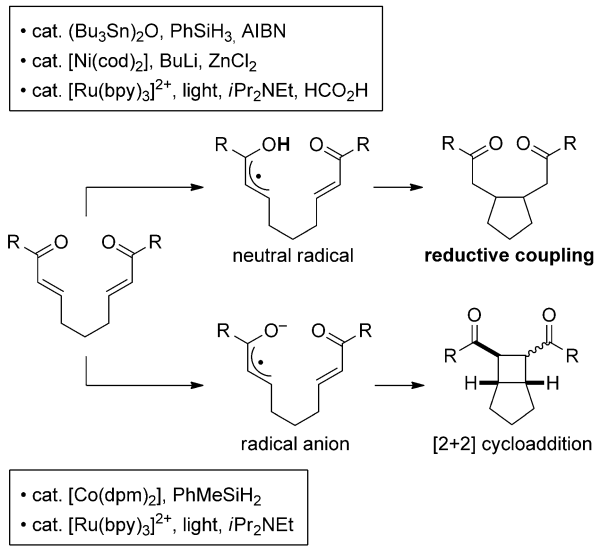
Scheme 9. Titanium-mediated and catalyzed stereospecific cross-coupling of carbonyl compounds with Michael acceptors. ebthi = 1,2-ethylene-1,1′-bis(η^5-tetrahydroindenyl).

the corresponding γ-aminated products were obtained. As for the Ni-catalyzed examples in Section 2, a Ni^0/Ni^{II} mechanism was proposed instead of a radical process.

3.2. Coupling Reactions between Two Michael Acceptors

Reductive conjugate radical additions have been thoroughly investigated in the form of cyclizations between tethered Michael acceptors, and bisenones were frequently employed as substrates.[47] The Sn-catalyzed procedure discussed above (Section 3.1) was also suitable for these radical cyclizations (Scheme 10).[42] Furthermore, this type of intramolecular reductive coupling was also achieved by Ni catalysis.[48] Interestingly, the Sn-catalyzed conditions gave the *trans* product with moderate selectivity, while the nickel-catalyzed reaction favored the *cis* diastereomer. This indicates a reagent-controlled reaction pathway in the latter case. In contrast to the other Ni-catalyzed examples discussed herein, a radical pathway was discussed as a possible alternative to a Ni^0/Ni^{II} mechanism.

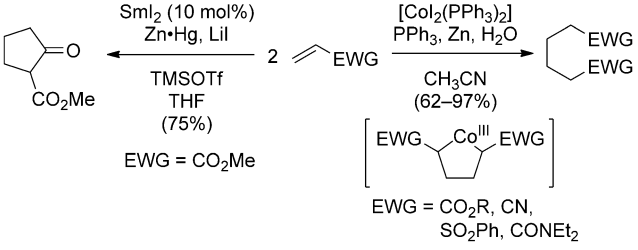
Importantly, a different reaction outcome was observed in the presence of a cobalt catalyst and a silane reductant. An overall redox-neutral [2+2] addition took place, which was also observed under electrochemical reducing conditions or by reduction with sodium chrysenide.[49] The Co catalysis gave the all-*syn* product preferentially, while the purely substrate-controlled electroreductive [2+2] addition resulted in a mixture of α-*syn*/*anti* diastereomers with a β-*syn* configuration.



Scheme 10. Divergent reaction outcome from bisenone substrates. A neutral radical pathway leads to reductive coupling, while radical anions lead to a formal [2+2] addition. The preferred diastereomer depends on the catalyst. dpm = dipivaloylmethyl.

It was reasoned that the reductive coupling to the cyclopentanedione products emerged from a neutral radical pathway, while the [2+2] cycloaddition products were the result of the addition of a radical anion. These conclusions were further supported several years later by photoreductive free-radical [2+2] additions and cyclizations with $[Ru(bpy)_3]^{2+}$ as a photocatalyst: The reaction could be steered from a [2+2] addition to a reductive coupling by addition of a Brønsted acid.[50,51] Although the reaction initiation was different (photoredox catalysis), the underlying C–C coupling events were classical free-radical addition reactions. Thus, with this system, external stereocontrol can probably be achieved only by additional co-catalysis, as was demonstrated recently for related pinacol-type cyclization reactions.[52] To date, no explanation has been put forward to illustrate the different behavior of neutral radical and radical anion intermediates

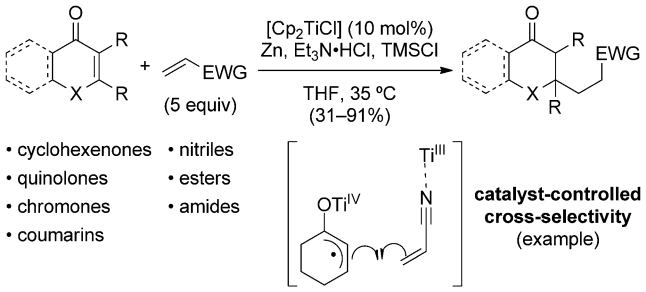
Catalytic intermolecular coupling reactions were realized with acrylates by using the SmI_2-catalyzed conditions discussed above (Section 3.1), which led to a subsequent Dieckmann cyclization forming the corresponding β-ketoesters (Scheme 11).[43] A more general cobalt catalysis was reported afterwards, which led to the same linear dimerization



Scheme 11. Catalytic reductive tail-to-tail dimerization of Michael acceptors.

products as obtained from the classical Baizer-type electroreductive coupling reactions.[53] In contrast to the intramolecular Co-catalyzed reactions shown in Scheme 10, a Co^{I}/Co^{III} pathway via a cyclometalated intermediate was proposed.

The cross-selective reductive radical addition of activated alkenes to Michael acceptors was realized by titanium(III) catalysis (Scheme 12).[45] Several enones were successfully



Scheme 12. Titanium-catalyzed reductive radical coupling of Michael acceptors to directly afford 1,6-difunctionalized, β-alkylated ketones.

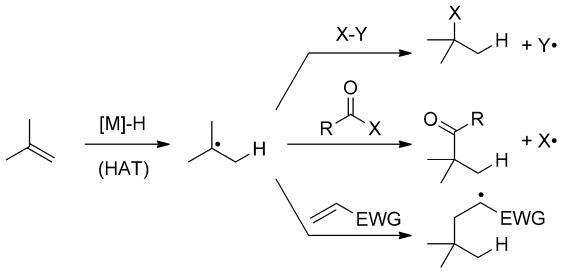
cross-coupled with acrylonitriles and certain acrylic amides in excellent yields. Furthermore, this reaction was suitable for the construction of quaternary carbon centers. In the absence of the titanium catalyst, only homocoupling of the enone was observed, thus showing the importance of the catalyst to achieve controlled cross-selectivity. This study represented the first example of a cross-selective conjugate addition reaction with simple alkene precursors and was also the first example to provide direct access to such β-alkylated addition products without the need for preformed organometallic reagents. Furthermore, this method appeared to be complementary to the reactions discussed above, in which a radical anion pathway resulted not in a reductive coupling, but a [2+2] addition reaction. The method was further applied to the synthesis of functionalized quinolone and chromone derivatives, for which acrylates could also be employed as coupling partners.[54]

4. Hydrogen Atom Transfer

For the reductive coupling of unfunctionalized alkenes, it is important to achieve a good control of the radical coupling to avoid competing radical chain polymerization events. Industrial styrene/acrylonitrile copolymers are produced by such radical copolymerization processes, for example.[55] Confirmed reductive radical addition reactions between unfunctionalized alkenes and Michael acceptors have been reported in the form of Sn-mediated cyclizations of mono-, bi-, and trisubstituted alkenes to tethered α,β-unsaturated ketones.[56] The drawback of this method was the reaction procedure, which required the slow addition of the tin hydride species to the refluxing reaction mixture, and the free-radical nature of the coupling, which did not allow the development of the corresponding enantioselective reactions.

As an alternative, a series of transition-metal-catalyzed reductive coupling reactions of alkynes and allenes with Michael acceptors has been reported, a great number of which were Ni or Co catalyzed. They worked very well for regioselective intermolecular and intramolecular reductive coupling reactions,[48b,57,58] and even a cobalt-catalyzed enantioselective reductive coupling between alkynes and α,β-unsaturated ketones was reported.[59] However, these reactions were mostly proposed to proceed through cyclometalation pathways.

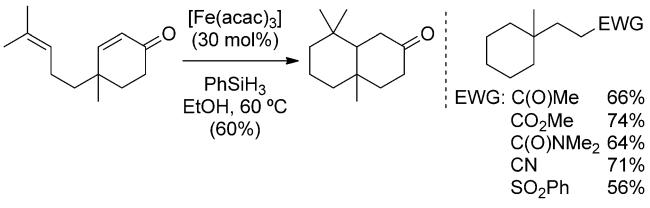
A complementary approach is initiation of the reaction by hydrogen atom transfer (HAT) to an alkene functionality (Scheme 13).[60] The use of Co or Mn catalysts in combination



Scheme 13. Exemplary alkene functionalizations initiated by transition-metal-catalyzed HAT.

with a silane or other hydride sources such as 2-propanol for HAT-initiated alkene functionalizations is well documented.[61,62] In addition, iron hydride complexes that are generated in the presence of $NaBH_4$ or a silane, for example, can also be employed in HAT reactions, which was demonstrated for the first time more than 30 years ago.[63,64] In these reactions, a hydrogen atom transfer to an alkene generates the more-stabilized carbon-centered radical, which is then available for interception by a (pseudo-)halogen, a carbonyl compound, or a Michael acceptor.

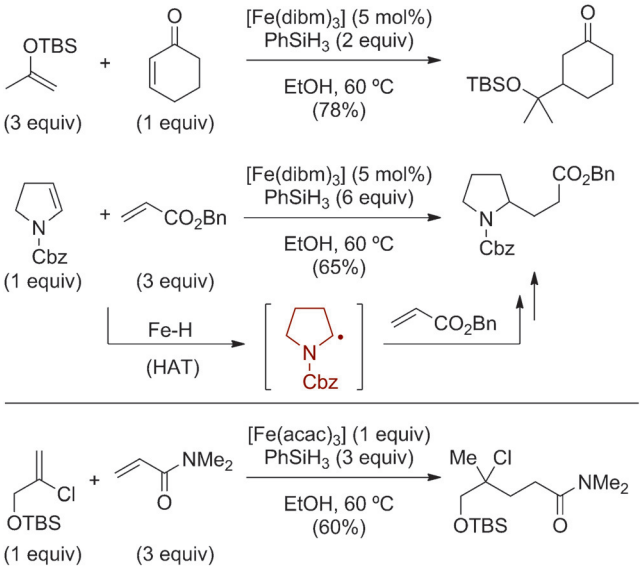
Recently, a method for the reductive radical addition of unfunctionalized alkenes to Michael acceptors was reported that combined the concepts of Fe-catalyzed HAT and HAT-initiated radical additions to Michael acceptors.[65] A number of unfunctionalized alkene precursors underwent the reported radical addition in an intra- and intermolecular fashion in the presence of $[Fe(acac)_3]$ and $PhSiH_3$, (Scheme 14). The iron complex could be employed in substoichiometric amounts (20–30 mol%). The reactions proceeded under mild conditions (≤ 60 °C) in protic solvents and tolerated a number



Scheme 14. Iron-catalyzed HAT-initiated intra- and intermolecular radical addition to α,β-unsaturated compounds.

of common functional groups. One of the limitations of this and other HAT-initiated processes, however, is the requirement for alkene precursors that lead to the generation of a stabilized carbon-centered radical intermediate after the HAT, otherwise, the yields are reduced. Therefore, one likely application of this approach could be the synthesis of building blocks with quaternary carbon centers.

This reaction was then advanced further to the addition of ketyl-, aminomethyl, and other heteroatom-functionalized radicals to Michael acceptors (Scheme 15).[66] These could be

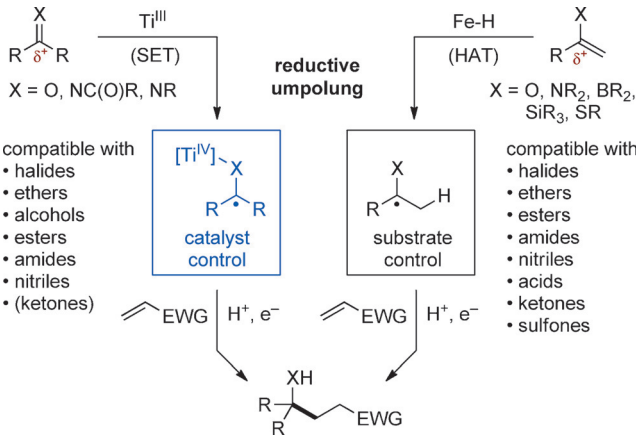


Scheme 15. Iron-catalyzed and -mediated reductive addition of functionalized alkenes to Michael acceptors. dibm = diisobutyrylmethane.

generated from the corresponding enol ethers and enamines in a similar fashion. The ketyl-type radical intermediates obtained after the HAT would then attack the desired Michael acceptor. Importantly, this ketyl or aminomethyl radical addition step was identical to the previously reported Ti^{III}-catalyzed reactions (Sections 2 and 3). This was also true for the overall umpolung reactions, which connected two similarly polarized carbon atoms. This is illustrated by the addition of the identical pyrrolidinyl radical to acrylates (see Schemes 6 and 15).[67] In addition, the radical addition step was a substrate-controlled process similar to the classical HAT-mediated coupling reactions. Such conceptual similarities should be kept in mind for the assessment of new developments in the field.

The method could be applied to vinylboranes, vinylsilanes, and vinyl thioethers. Vinyl chlorides could also be employed.

Overall, the scope of the titanium(III) catalysis by SET and the iron(II) catalysis by HAT in terms of the Michael acceptor was comparable, but the iron-catalyzed reaction offered more versatility with regard to the radical precursor (Scheme 16). On the other hand, the titanium catalysis allowed control of the stereoselective carbon–carbon bond-forming step, which was an advantage over the HAT-initiated radical reactions.



Scheme 16. Titanium-catalyzed and iron-catalyzed generation of hetero-functionalized carbon radicals from carbonyl derivatives and alkenes, respectively. TBS = *tert*-butyldimethylsilyl.

5. Summary and Conclusions

It has been demonstrated that reductive radical additions to Michael acceptors allow the realization of a number of challenging carbon–carbon bond-forming reactions. They often exhibit a remarkable functional group tolerance, can be used for the installation of quaternary carbon centers, and the coupling of similarly polarized components in so-called umpolung reactions. The current state of the art offers a variety of approaches to initiate such catalytic radical additions. These are mostly homolysis of C–X bonds, SET, and HAT events.

The reductive radical additions can be divided into free-radical reactions in which the selectivity of the addition process is solely governed by the substrate, and reactions in which the catalyst remains coordinated throughout the carbon–carbon bond-forming event. These so-called catalyst-controlled additions can proceed with impressive chemo-, regio-, and stereoselectivity. First-row transition metals, such as titanium or iron, as well as metals such as Sn, Sm, or In can be employed in catalytic amounts. For other metals, such as nickel or cobalt, similar reductive additions have been reported and radical mechanisms could not be fully excluded. Hence, there has been substantial literature precedence for the catalytic generation of radicals and subsequent conjugate additions of radicals using these metals, which should be given the credit they deserve in future studies.

Finally, even in 2013 it was still stated that the fundamental weakness of the conjugate addition reaction approach—the need for preformed organometallic reagents—remains.[36] Indeed, the opposite appears to be the case for radical reactions. As this Minireview clearly demonstrates, transition-metal-catalyzed radical reactions achieve exactly this goal: avoiding the preformation of organometallic species.

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