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ARTICLE *in* TOPICS IN CURRENT CHEMISTRY · MARCH 2011

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Top Curr Chem (2012) 320: 93–120
DOI: 10.1007/128_2011_124

Published online: 31 March 2011

Hydrogen Atom Donors: Recent Developments

Andreas Gansäuer, Lei Shi, Matthias Otte, Inga Huth, Antonio Rosales, Iris Sancho-Sanz, Natalia M. Padial, and J. Enrique Oltra

Abstract This review highlights recent developments in the field of hydrogen atom transfer (HAT) reagents that circumvent the disadvantages of classical group 14 reagents, such as Bu_3SnH. Special emphasis is laid on the lowering of bond dissociation energies (BDEs) of molecules that could, as yet, not be used as HAT reagents and on the use of organometallic HAT reagents.

Keywords Bond dissociation energies · Catalysis · Chain reactions · Hydrogen atom transfer · Metal-hydrogen bonds · Radicals

Contents

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Abbreviations

AIBN	Azobisisobutyronitrile
BDE	Bond dissociation energy
CHAT	Catalytic hydrogen atom transfer
CHD	Cyclohexadiene
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppm	Bis(diphenylphosphino)methane
HAT	Hydrogen atom transfer
NHC	N-Heterocyclic carbene
TMP	2,2,6,6-Tetramethylpiperidine

1 Introduction

The reduction of radicals to the corresponding hydrocarbons through hydrogen atom transfer (HAT) is one of the most important radical reactions. This is highlighted by the use of HATs as essential parts of reductive radical chain reactions. To date, trialkylstannanes are the most popular reagents for carrying out this particular transformation due to their low Sn–H bond dissociation energies (BDE) and the accordingly fast HAT from tin to carbon-centered radicals [1–4]. However, rather serious drawbacks exist. The toxicity of these reagents and the necessity of a sometimes difficult removal of side-products preclude their use in pharmaceutical applications, especially on a large scale [5]. Moreover, the high efficiency of the HAT from tin-based reagents can also result in chemical disadvantages. If the desired radical chain reaction contains propagation steps that are noticeably slower than HAT from trialkylstannanes, the intermediate radicals will be prematurely reduced.

In the field of metal-mediated and metal-catalyzed reactions, similar issues can be critical. Radical reduction by a HAT must be slow enough to allow any desired reaction to occur, but the HAT must also be fast enough to prevent any undesired trapping of the radicals by metal centers with unpaired electrons.

Over the past few years significant progress has been made in replacing trialkylstannanes as radical generating reagents and hydrogen atom donors. Some aspects, such as the use of silanes and related compounds, and of cyclohexadienes have been reviewed recently and will not be covered here [1–5].

Instead, it is the goal of this chapter to highlight some conceptually novel developments in the field of HAT reactions. We will concentrate on complexes of borane with N-heterocyclic carbenes (NHCs), on organometallic hydrogen atom donors in stoichiometric and catalytic reactions, and on the activation of water and alcohols for HAT.

2 Complexes of Borane and N-Heterocyclic Carbenes as HAT Reagents

One of the novel exiting developments in the field of tin-free radical chain reactions is the development of complexes of borane with NHCs as HAT reagents [6]. Borane (BH_3) itself has a BDE of 106.6 kcal mol^{-1} which is much too high for its use in organic radical chain reactions. The group of Roberts and others have demonstrated that complexes of boranes with amines and phosphines have a reduced BDE and that they can be used in radical chain reactions [7]. However, the reduction is only moderate and too low to make these complexes generally applicable.

Computational studies by Rablen have suggested that ligands with π-donor abilities are much more efficient in the reduction of the B-H BDE [8]. On the basis of this finding, it has recently been demonstrated that complexes of NHCs and borane (NHC boranes) constitute a very interesting new class of radical hydrogen atom donors. Two of the first examples, **1** and **2**, together with their calculated BDEs, are shown in Scheme 1.

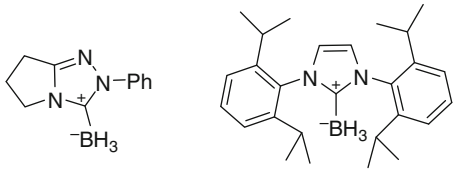
These NHC boranes can be employed as reducing agents for xanthates either with AIBN (Scheme 2) or Et_3B/O_2 as initiating system. The reaction is thought to proceed via a "normal" radical chain process. Chain initiation with Et_3B/O_2 resulted in higher yields of the desired product than the use of AIBN. Moreover, the amount of Et_3B could be reduced to 0.2 equiv. without significant reduction of the isolated yields.

The intermediacy of free radicals is further supported by the observation of 5-*exo* cyclizations and the ring opening of cyclopropyl carbinyl radicals.

A highly attractive feature of the NHC boranes is their straightforward synthesis and the availability of large numbers of NHCs. Thus, many NHC boranes have already been investigated in the short time since their discovery. It turned out that the performance of the reaction noticeably depends on the substitution pattern of the NHC. Gratifyingly, the "minimalist" low-weight NHC carbenes **3** and **4** are more efficient reagents than the initially developed **1** and **2** as shown in Scheme 3 [9].

Their reactions are faster and they do not have to be employed in overstoichiometric amounts to achieve complete conversion of the starting materials.

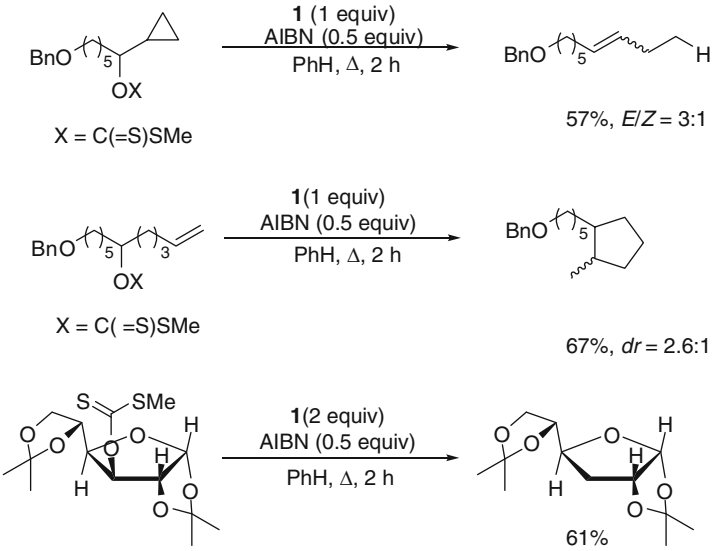
The reactions of NHC boranes have also been studied mechanistically in some detail [10]. It has been possible to isolate and characterize fully the (methylthiocarbonylthio)boranes arising from the reduction of xanthates.



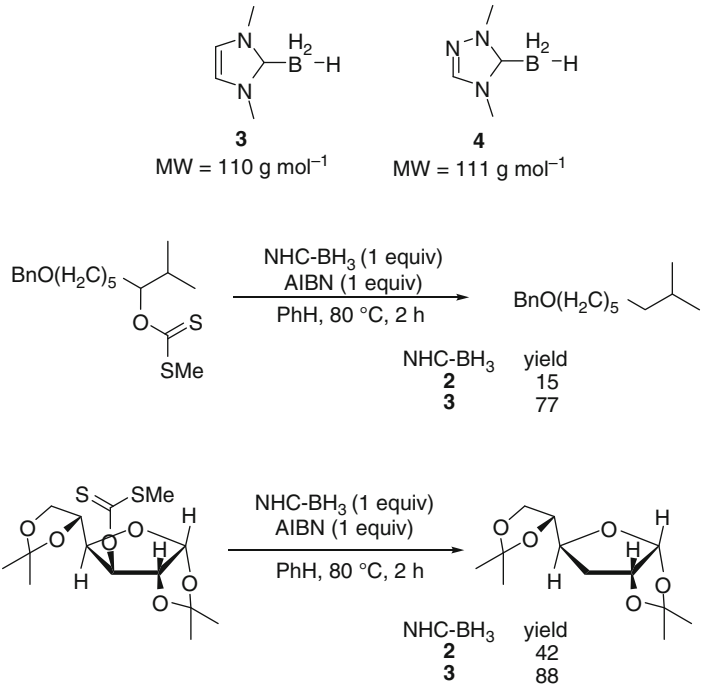
1
B-H = 74 kcal/mol

2
B-H = 80 kcal/mol

Scheme 1 First NHC boranes, their BDEs, and mechanism of the deoxygenation of xanthates



Scheme 2 Performance of NHC boranes in deoxygenation reactions



Scheme 3 Second generation "minimalist" NHC boranes and their reactions

The rate constant of HAT from **1** has been determined as $(3.4 \pm 1.0) \times 10^4$ M^{-1} s^{-1} at 28 °C by using a cyclobutyl carbinyl radical as clock. Also, the log A term of the Arrhenius equation is "normal" for a second-order HAT and thus the entropic demand of the NHC boranes is similar to that of group 14 metal hydrides. From the rate constant a BDE of about 88 kcal mol^{-1} for **2** was estimated by applying an Evans-Polanyi relationship. This value is somewhat higher than the calculated value of 80 kcal mol^{-1}.

For about 20 NHC boranes the HAT rate constants were estimated by competition experiments and found to be in the range of $10^4 - 8 \times 10^4$ M^{-1} s^{-1}. They are thus lower than for Bu_3SnH (3×10^6 M^{-1} s^{-1}), $(Me_3Si)_3SiH$ (4×10^5 M^{-1} s^{-1}), and Bu_3GeH (10^5 M^{-1} s^{-1}) but still above the threshold for successful radical chain reactions [11].

The EPR spectra of the NHC boryl radicals that were generated through HAT to the *tert*-butoxyl radical clearly show the delocalized π-type nature of these intermediates postulated to be essential by calculations [10, 12]. It was also demonstrated that the decay of the EPR signals could be fitted to a second-order decay having $2k_t = 9 \times 10^6$ M^{-1} s^{-1}. In agreement with this kinetic analysis, the NHC boryl radicals ultimately dimerize to give bis-NHC diborane derivatives. With the aid of EPR spectroscopy it was also established that the NHC boryl radicals readily abstract bromine atoms from primary, secondary, and tertiary alkyl bromides. However, chlorine atom abstraction is much slower and useful only for benzyl chloride.

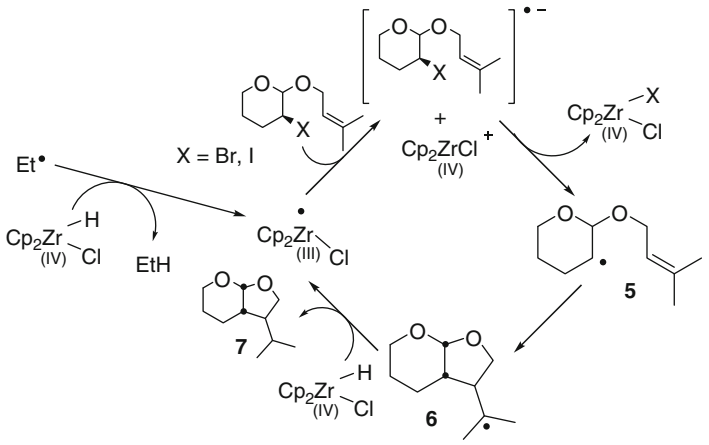
Very recently, the NHC boranes have been used as initiators for the photopolymerization of acrylates [13].

In conclusion, within a very short period of time NHC boranes have been developed into an attractive novel class of modular HAT reagents for conducting radical chain reactions through an impressive interplay of synthetic and mechanistic studies. The reagents should be especially attractive for reactions featuring slow propagation steps.

3 Organometallic Complexes as HAT Reagents

3.1 Organometallic Complexes as HAT Reagents in Radical Chain Reactions

In principle, organometallic complexes are also highly interesting candidates for efficient HAT reagents. This is because M–H bonds are usually much weaker than C–H bonds [14–16]. Also, it has been established for a number of cases that HAT from organometallic complexes can be very fast. Still, the rates of the processes can be modulated by the introduction of steric bulk around the metal center. Moreover, low valent hydrido metal complexes can also act as chain carrying reagents because



Scheme 4 Ueno-Stork cyclizations mediated by $Cp_2Zr(H)Cl$

the M–Hal bonds can be substantially stronger than C–Hal bonds. Thus, radical generation from organic halides is often possible.

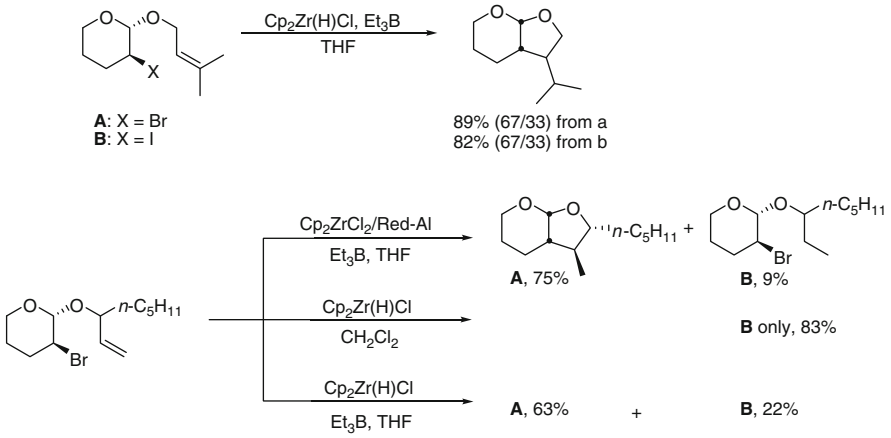
Oshima has demonstrated that the Schwartz reagent $Cp_2Zr(H)Cl$ can act as an excellent replacement for Bu_3SnH for Ueno-Stork cyclizations (Scheme 4) [17].

With an ethyl radical that is generated from the initiator BEt_3, $Cp_2Zr(H)Cl$ reacts via HAT to generate Cp_2ZrCl. This species constitutes a strong reductant and abstracts bromine or iodine from the organic substrate to generate free radical **5**. After cyclization, **6** is formed. HAT from $Cp_2Zr(H)Cl$ generates the desired product **7** and Cp_2ZrCl is regenerated. The overall reactions proceed efficiently with yields over 80%. Substrates containing chlorides are not sufficiently reactive, though. The process can also be used for other 5-*exo* cyclizations or the direct reduction of bromides and iodides.

A highly attractive feature of the process is that it can be conducted with catalytic amounts of the organometallic reagent. This is achieved by addition of Red-Al [$NaAlH_2(OCH_2CH_2OCH_3)_2$] as terminal reductant that is able to convert Cp_2ZrCl_2 and its mixed halide derivatives into the Schwartz reagent in situ. A minor drawback compared to the stoichiometric process is that Red-Al is reactive towards carbonyl groups. Thus, the functional group tolerance of the catalytic reaction is somewhat reduced. Examples are shown in Scheme 5.

Finally, it should be noted that enantiomerically pure derivatives of the Schwartz reagent are very appealing candidates for reagent controlled enantioselective and diastereoselective radical reductions. This is because a plethora of enantiomerically pure zirconocenes are available from other applications in enantioselective catalysis.

While this methodology is very useful, it is even more desirable to use milder and more readily available terminal reductants in these chain processes. Of special importance in this respect are H_2, H_2O, and simple alcohols as the ultimate hydrogen atom donors. We will start the discussion with the use of H_2, while the use of H_2O and alcohols will be treated separately at the end of this chapter.



Scheme 5 Radical reactions catalyzed by $Cp_2Zr(H)Cl$

In order to be able to use H_2 as the terminal reductant, a reagent must be available that activates H_2 to generate the desired HAT reagent. Many metal complexes are capable of doing so, of course, as hydrogen activation is essential for the extremely important field of hydrogenation methodology.

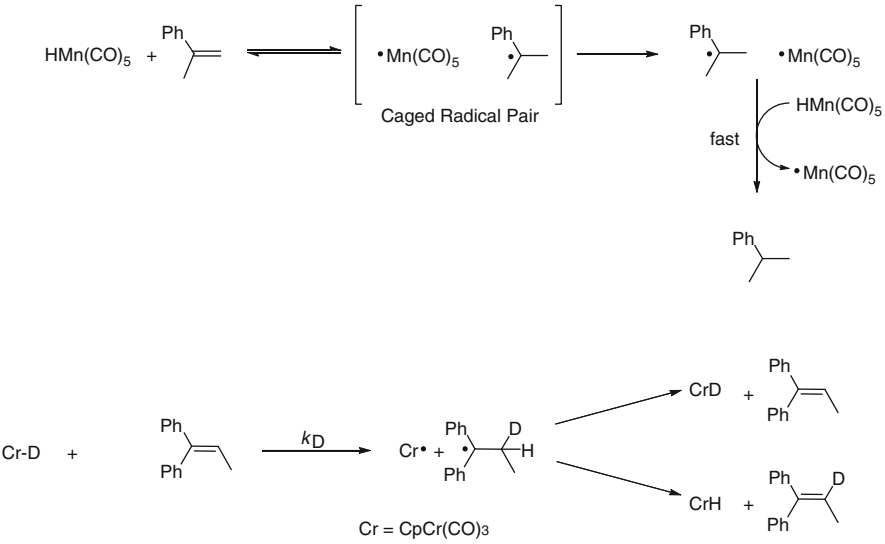
Before discussing catalytic hydrogen mediated radical reactions, processes based on preformed organometallic reagents will be discussed, because in this manner the elementary steps can be highlighted in a more accessible manner.

It has been demonstrated for some time that a number of metal monohydrides in stoichiometric amounts can reduce activated alkenes such as acrylates, styrenes, 1,3-dienes, and allenes by two consecutive HAT steps as shown in Scheme 6 [18–26].

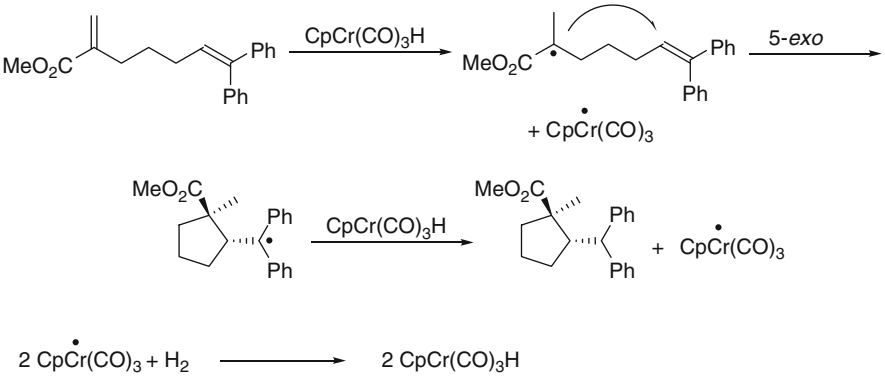
While these reactions are of limited use in the synthesis of complex molecules, they are very interesting from a mechanistic point of view. It has been firmly established that benzylic or allylic radicals and metal centered radicals are formed as intermediates through hydrogen atom transfer from the M–H bond to the C–C double bond. Interestingly, the addition of the hydrogen atom is reversible as demonstrated by isotope scrambling with deuterated olefins. If the radicals possess multiple sites for hydrogen atom abstraction, olefin isomerization can ultimately occur. HAT to unactivated olefins was not observed.

The radicals formed through HAT are then reduced by a second equivalent of the organometallic reagent to the corresponding hydrocarbon resulting in an overall "radical hydrogenation" of the olefin. In the cases investigated, the metal centered radicals dimerized and no attempts were made to regenerate the monohydrides by activation of H_2.

Polymerization reactions of suitably substituted acrylates can be initiated by radical generation through HAT [27]. It should be noted that hydrogen atom abstraction from the growing chain leads to interruption of chain growth. In such cases the organometallic complex possessing the pivotal M–H bond is reformed and



Scheme 6 Radical hydrogenations of activated olefins



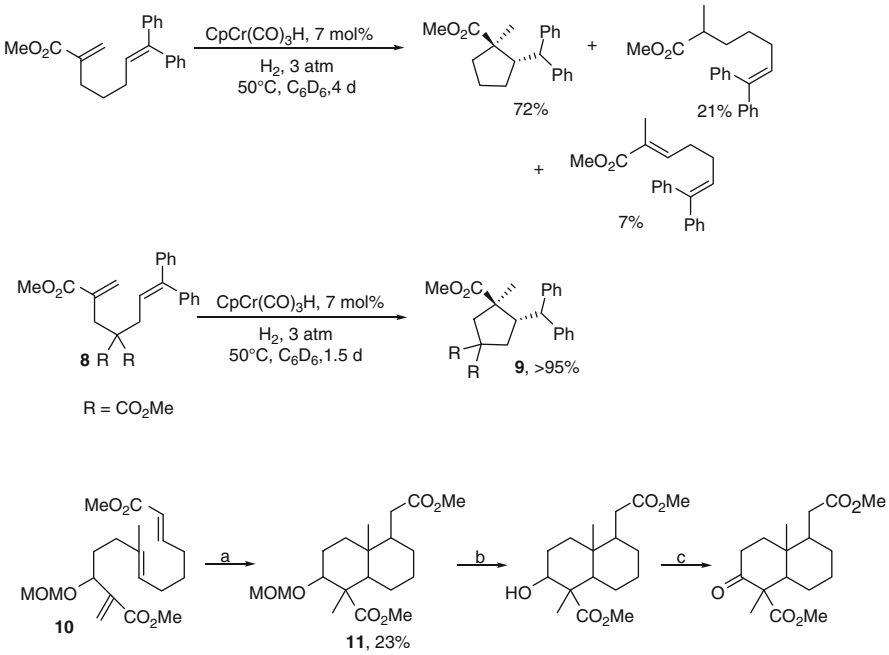
Scheme 7 $CpCr(CO)_3$ catalyzed, H_2 mediated radical cyclization

a novel chain can be initiated. Thus, complexes such as $CpCr(CO)_3H$ or $HMn(CO)_5$ can act as chain-transfer catalysts in the polymerization of olefins.

Thus, radical generation, the formation of C–C bonds, and radical reductions are possible in reactions with alkenes and organometallic complexes with M–H bonds.

Norton has recently combined these key-steps with the activation of H_2 by $CpCr(CO)_3$ to very elegant tin-free and catalytic radical cyclization mediated by H_2 that is highlighted in Scheme 7 [28, 29].

The $Cp(CO)_3Cr$ radical serves a threefold purpose in this process. First, it activates H_2 to give the pivotal $Cp(CO)_3CrH$. Second, $Cp(CO)_3CrH$ adds a hydrogen atom to the acrylates. Third, after the radical formed through a 5-*exo* cyclization, it is



(a) $CpCr(CO)_3H$, 7 mol%, C_6D_6, 50°C; (b) HCl, MeOH, 65°C; (c) CrO_3, aq H_2SO4, acetone.

Scheme 8 Examples of the catalytic radical cyclizations

reduced by a HAT from $Cp(CO)_3CrH$ and the H_2-activating $CpCr(CO)_3$ is regenerated. These conditions have been applied to a number of other substrates as summarized in Scheme 8.

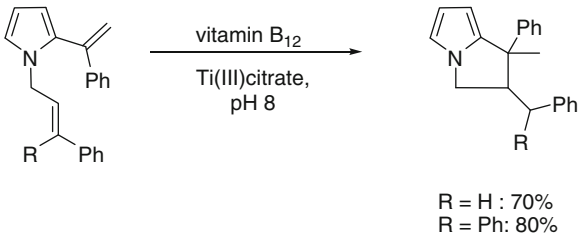
The substrate scope reveals the critical aspects of the process. The cyclization must be faster than the completing radical reduction though HAT. Thus, the olefin that serves as radical acceptor should be activated in order to achieve high yields. However, the HAT for radical generation must be chemoselective and thus the olefin that serves as radical acceptor should be at least trisubstituted to disfavor HAT kinetically to this functional group.

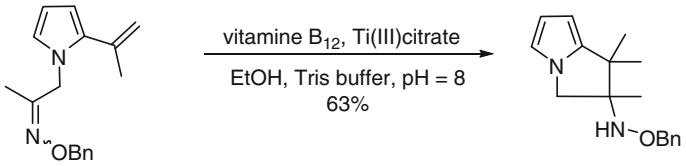
The introduction of the two ester groups in **8** results in an acceleration of the cyclization and hence in an almost quantitative yield of **9**. Unfortunately, alkyl substituted olefins as in **10** do not appear to be efficient radical acceptors in 6-*exo* cyclizations because the isolated yield of the desired product **11** is not high.

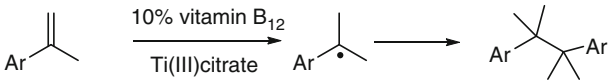
Despite these slight shortcomings, the development of the catalytic conditions constitutes a major conceptual advance in the field of radical cyclizations.

It should be noted that a related reaction has been developed by the Norton group, with $HV(CO)_4$dppe, a compound with an unusually weak M–H bond (about 57 kcal mol^{-1}), serving as a stoichiometric HAT reagent. The organometallic complex cannot be employed catalytically because $V(CO)_4$dppe that is formed after HAT is unable to activate H_2 [29, 30].

Scheme 9 Vitamin B_{12} catalyzed radical cyclizations







Ar	yield
Ph	85
4-Cl-C_6H_4	80
4-F-C_6H_4	70

Scheme 10 Unusual radical cyclizations and dimerizations of styrenes catalyzed by vitamin B_{12}

Another system for cyclizations based on HAT has been described by the group of van der Donk. It relies on vitamin B_{12} as the HAT-catalyst precursor [31]. The buffered Ti(III) citrate solution generates the active species containing the pivotal Co–H bond of vitamin B_{12}. Examples of cyclization reactions are shown in Scheme 9.

The reaction is broader in scope than the H_2 mediated cyclizations.

The Co-derived system constitutes a distinctly less efficient HAT reagent than $CpCr(CO)_3H$ and can also be used in kinetically less favored radical addition reactions, such as additions to oximes, and even dimerizations of benzylic radicals as shown in Scheme 10 [31, 32].

The mechanism of this unusual transformation has been studied very carefully and compelling evidence for the intermediacy of radicals has been presented. One of the arguments is the low diastereoselectivity of the dimerizations that is typical for a radical process. Moreover, it has been demonstrated that the persistent radical effect is “overcome” by reduction of the Co(II) metalloradicals to the catalytically

active Co(I) species by Ti(III)citrate. It remains to be seen whether further applications of this very efficient system for radical generation will be reported in the future.

3.2 *Organometallic HAT Reagents in Catalytic and Stoichiometric Metal Mediated Reactions*

Radical chain reactions are established as very powerful tools in the synthesis of complex molecules. The complementary approach to radical chemistry that relies on radical generation through electron transfer is also attractive, especially when radical generation is decoupled from the ensuing radical transformations and the final radical reduction. This is especially so for catalytic reactions.

Two major potential advantages of this approach are the possibility to use hydrogen atom donors that are not suitable for propagating a radical chain and a high functional group tolerance.

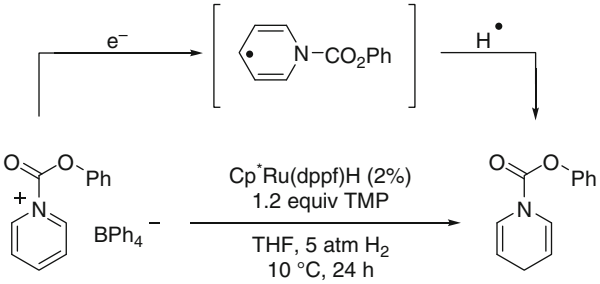
The Norton group has reported two examples of this type of transformation. In the first, a 1,4-reduction of pyridinium ions by Ru(II) hydrido complexes takes place in two steps, an SET followed by a HAT, as shown in Scheme 11 [33].

The presence of the Ru(III)-complex $[Ru–H]^+$ that is formed from **12** through electron transfer to the acyl pyridinium has been demonstrated by EPR spectroscopy. The reaction can be rendered catalytic in Ru by the addition of a base (Scheme 12).

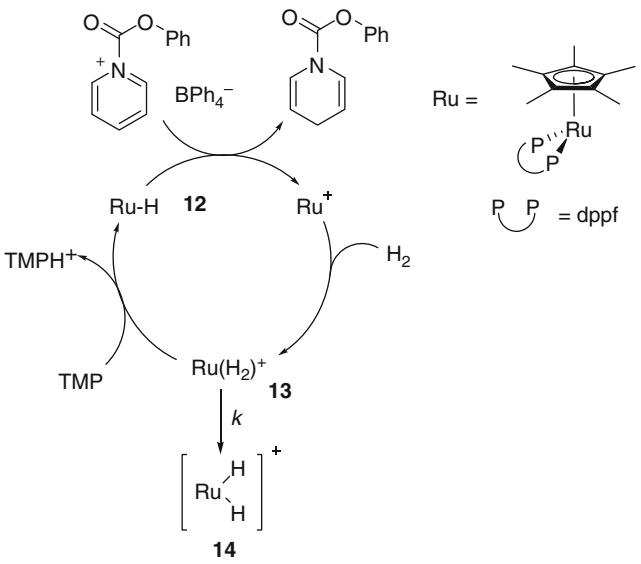
In this manner, the cationic dihydrogen complex **13** can be deprotonated to the catalytically active Ru(II) hydrido complexes. The undesired isomerization of **13** to the dihydride complex **14** can be avoided by lowering the reaction temperature and changing the solvent to THF.

In a second example, the Norton group has presented evidence that the reduction of phenyl substituted aziridinium cations to the corresponding amines by Cp*Ru (dppf)H proceeds via a similar mechanism [34] that is shown in Scheme 13.

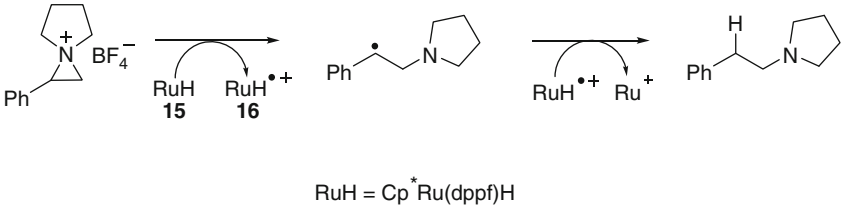
A key issue of this reaction is that aziridinium cations are electrochemically much more readily reduced (by 0.6–0.9 V) than their alkyl substituted analogs.



Scheme 11 Norton's radical hydrogenation of acyl pyridinium salts



Scheme 12 Mechanism of the catalytic radical hydrogenation of acyl pyridinium salts

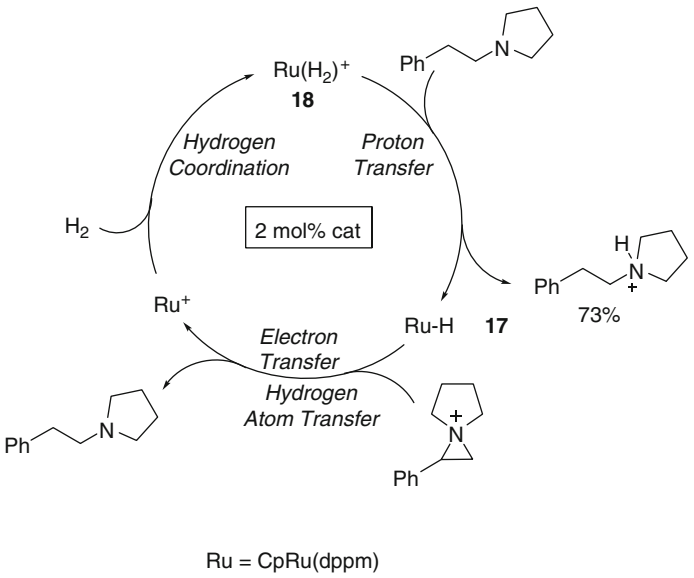


Scheme 13 Hydrogenation of aziridinium cations via Ru-mediated HAT

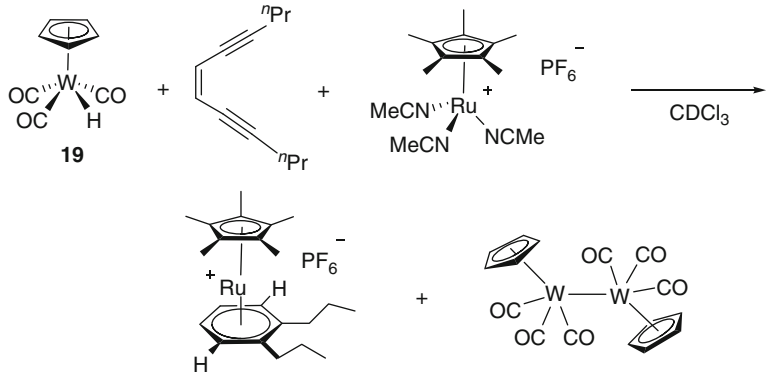
Moreover, the alternative pathway of an S_N1-type ring opening does not seem to operate as the necessary generation of the benzylic cation is too slow to be in agreement with the measured rate constants. Another strong piece of argument in favor of the ET mechanism is the significant line broadening of the Ru–H, the Cp*, and the ferrocenyl signals in the ^{1}H-NMR spectra that can be attributed to a self-exchange process of the catalyst **15** and its oxidized form **16**. The reaction can also be conducted with catalytic amounts of the Ru-complex as shown in Scheme 14.

The amine product plays a critical role, as it deprotonates the H_2 complex **18** to regenerate the catalytically active **17**. This also prevents side reactions based on nucleophilic ring opening of the aziridinium cations by the amine products. Alkyl substituted aziridinium cations react via a classical S_N2-mechanism.

The common feature of the radical hydrogenations and H_2-mediated cyclizations is that the metal complexes serve as both radical generating and reducing reagents. A complementary approach uses different reagents for both purposes. In this manner,



Scheme 14 Hydrogenation of aziridinium cations via Ru-catalyzed HAT



Scheme 15 Bergman cycloaromatization terminated by HAT from $CpW(CO)_3H$

the particular features of two reagents, such as chemo- and stereoselectivity, can be combined. This is especially attractive for catalytic processes.

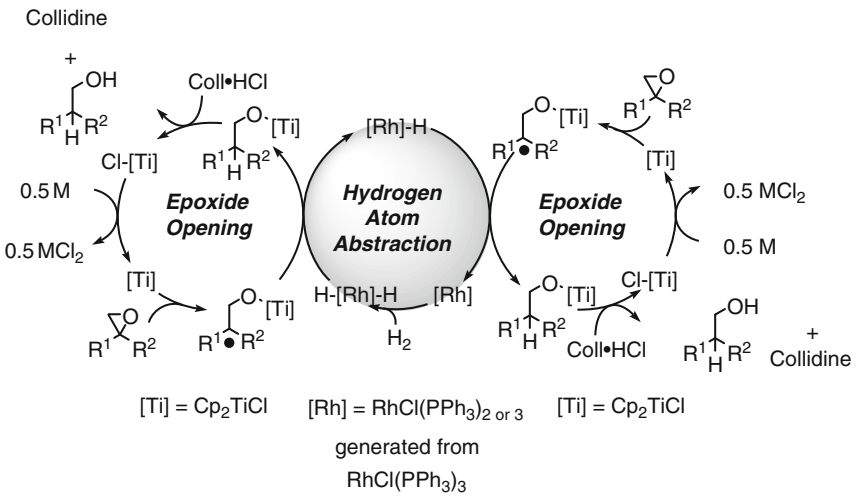
A stoichiometric example of the combination of two reagents has recently been reported by O'Connor in the context of the Bergman cycloaromatization. The generation of the aromatic diradical can be induced by $[Cp^*Ru(CH_3CN)_3]PF_6$. Radical reduction occurs through HAT from $CpW(CO)_3H$ to provide a cationic Ru-arene complex as shown in Scheme 15 [35].

It has been pointed out that the relatively high strength of the W–H bond is critical for the success of the cycloaromatization. The use of $CpCr(CO)_3H$, with a BDE of 10 kcal mol^{-1} less than **19**, does not result in the desired transformation, even though it is a better reducing agent for the diradical. This failure it due to a HAT of $CpCr(CO)_3H$ to the endiyne substrate that leads to extensive decomposition of the substrate. This very nicely highlights the importance of properly adjusting the reactivity of the reagents involved.

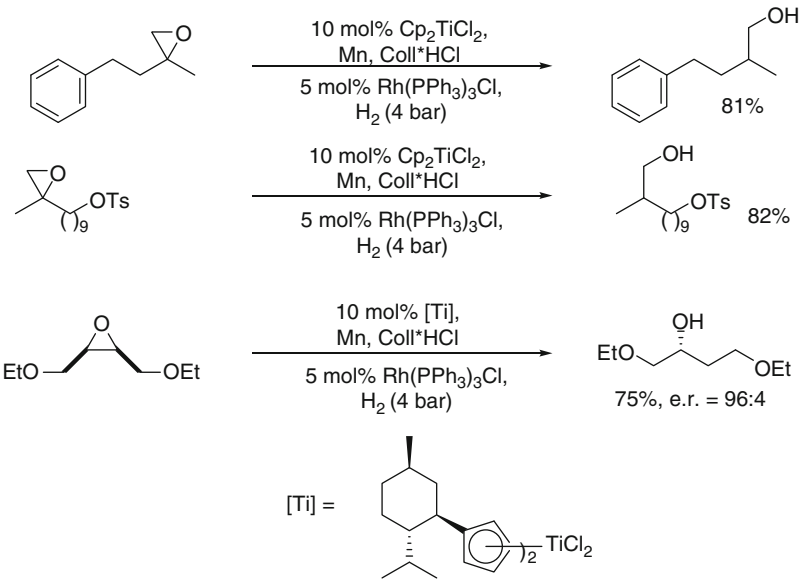
The coupling of independent catalytic cycles for both radical generation and reduction has been realized by the combination of the titanocene catalyzed reductive epoxide opening [36–40] via electron transfer and the catalytic reduction of radicals after H_2 activation by Wilkinson's complex $[Rh(PPh_3)_3Cl]$ as shown in Scheme 16 [41–43].

Two key issues are essential for the success of the catalytic HAT (CHAT) reaction. First, the two catalytic systems must be compatible. Because early and late transition metals usually bind ligands with opposing donor properties, they should remain mutually unaffected. Also, the Wilkinson catalyst should be stable under the slightly acidic conditions of the titanocene regeneration system (Zn, 2,4,6-collidine hydrochloride). Since it has been reported that $Rh(PPh_3)_3Cl$ is even stable towards BF_3*Et_2O, this was expected to be the case [44].

Second, it is essential that both $H_2Rh(PPh_3)_3Cl$ and $H_2Rh(PPh_3)_2Cl$ formed after the oxidative addition to H_2 react faster with the β-titanoxy radicals than Cp_2TiCl. Since the ring opening via ET is the rate determining step, this is critical. It is known that HAT from Rh-hydrides proceeds with rate constants as high as 10^9 M^{-1} s^{-1} and thus it seemed possible that the HAT may be faster than the reactions with titanocenes [45, 46]. Some of the results obtained with this system



Scheme 16 Coupled cycles for Rh-catalyzed HAT to β-titanoxy radicals



Scheme 17 Examples of catalytic HAT for the reduction of epoxides

are summarized in Scheme 17. The reaction is compatible with Kagan's complex [47, 48] in enantioselective and regiodivergent radical generations [49–54].

In general, the isolated yields are good and in the same range as those obtained with 5 equiv. of 1,4-CHD as hydrogen atom donor [55]. Thus, the concept of coupling catalytic cycles for enforcing a catalytic HAT (CHAT) has been successfully realized. In this manner, the use of expensive and toxic stoichiometric reagents can, in principle, be avoided. $CpCr(CO)_3H$ and Pd/C were also investigated for the CHAT. Both reagents gave substantially lower and varying yields of the desired products. It seems that the problem with these reagents is that they cannot activate H_2 swiftly enough to compete efficiently with radical trapping by the titanocenes.

The major problem with using Wilkinson's catalyst is that it also constitutes an excellent hydrogenation catalyst [56]. Thus, alkynes and terminal alkenes are not tolerated under the conditions of the coupled catalytic cycles. This implies that radical cyclizations terminated by a CHAT cannot be carried out under these conditions.

Therefore, CHAT reagents that activate H_2 efficiently without being hydrogenation catalysts were investigated. It turned out that Vaska's complex $Ir(CO)Cl(PPh_3)_2$ [57, 58] also gives satisfactory, albeit slightly lower, yields of the desired product as shown [42]. Since $H_2Ir(CO)Cl(PPh_3)_2$ does not possess a vacant coordination site, it is known not to be an active hydrogenation catalyst. Vaska's complex can also efficiently terminate radical cyclizations via CHAT [43]. Especially difficult but potentially rewarding reactions in this context are cyclizations leading to small rings and tandem cyclizations [59–69].

4 Generation of HAT Reagents from Water and Alcohols Through Coordination

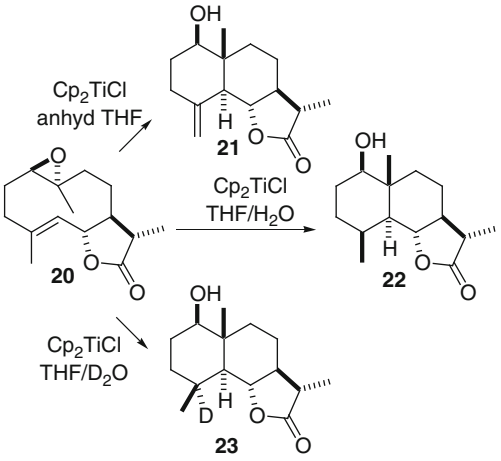
4.1 Activation of Water by Ti(III)

Since the discovery of free radicals, it has been believed that they are inert against water [70]. This lack of reactivity has been attributed to the strength of the H–OH bond (BDE = 117.6 kcal mol^{-1}) which in theory prevents any potential H-atom transfer from water to free radicals [71].

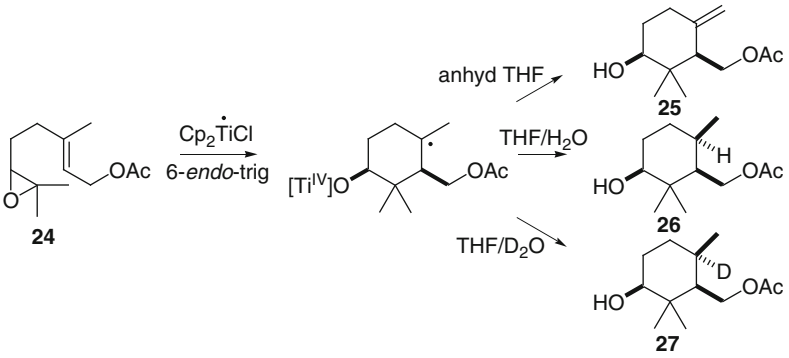
In 2002, however, it was observed that water did substantially affect radical cyclizations mediated by Ti(III) complexes. Thus, for example, when epoxide **20** was treated with Cp_2TiCl in dry THF, the exocyclic alkene **21** was obtained. When the same epoxide was treated with Cp_2TiCl in the presence of water, however, the corresponding reduction product **22** was formed. Moreover, with deuterium oxide instead of water, the deuterium labeled isotopomer **23** (Scheme 18) was isolated [72].

These and other preliminary results prompted Oltra and Rosales to publish the following comment: *Our results demonstrate that in Ti(III)-mediated free-radical chemistry water can act in a reductive way, working as a hydrogen atom donor. Therefore, we believe that the generally accepted passivity of water in free-radical chemistry should be carefully revised, especially in the presence of Ti(III) and other metal-centered free radicals* [72].

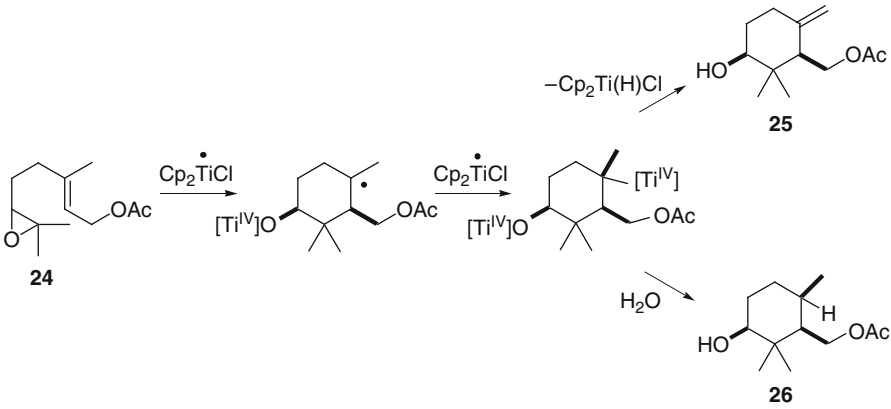
Subsequently, similar results were obtained with **24**. When treated with Cp_2TiCl in dry THF, **24** yielded the exocyclic alkene **25**. In contrast, in the presence of water, the corresponding reduction product **26**, and with D_2O, the deuterium labeled **27**, were isolated (Scheme 19) [73, 74].



Scheme 18 Dependence of the transannular cyclization of **20** on the presence of additives



Scheme 19 Dependence of the cyclization of epoxygeranyl acetate on the presence of additives

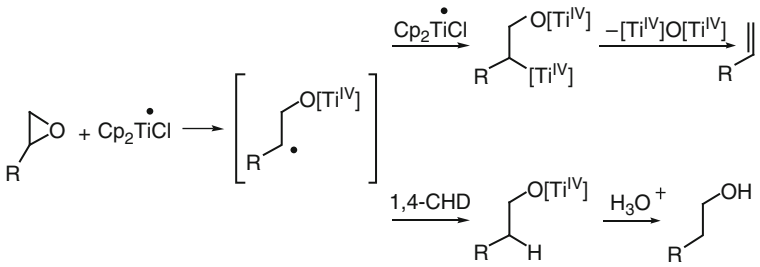


Scheme 20 Fate of the organometallic intermediate potentially formed during the cyclization of **24**

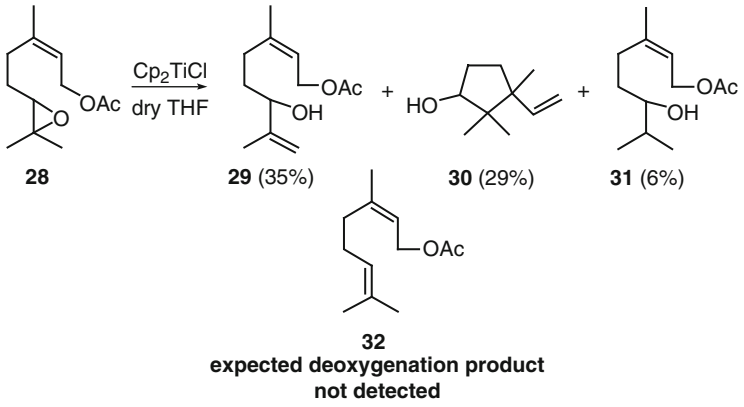
Nevertheless, the possibility of a more conventional mechanism involving the formation and subsequent hydrolysis of an organometallic alkyl-Ti(IV) intermediate (Scheme 20) was initially also considered.

However, since then, compelling evidence has been accumulated that this pathway is not relevant.

Under the deoxygenation conditions for epoxides introduced by Nugent and RajanBabu, the more stable β-titanoxy radical, which is generated through reductive epoxide opening, can be trapped by a second equivalent of Cp_2TiCl to produce an organometallic alkyl-titanium(IV) intermediate, which, after β-elimination, gives an alkene, the pivotal deoxygenation product. Nevertheless, in the presence of a hydrogen-atom donor such as 1,4-CHD, the β-titanoxy radical is reduced to give the less substituted alcohol (Scheme 21) [75].



Scheme 21 Cp_2TiCl mediated deoxygenation and reduction of monosubstituted epoxides



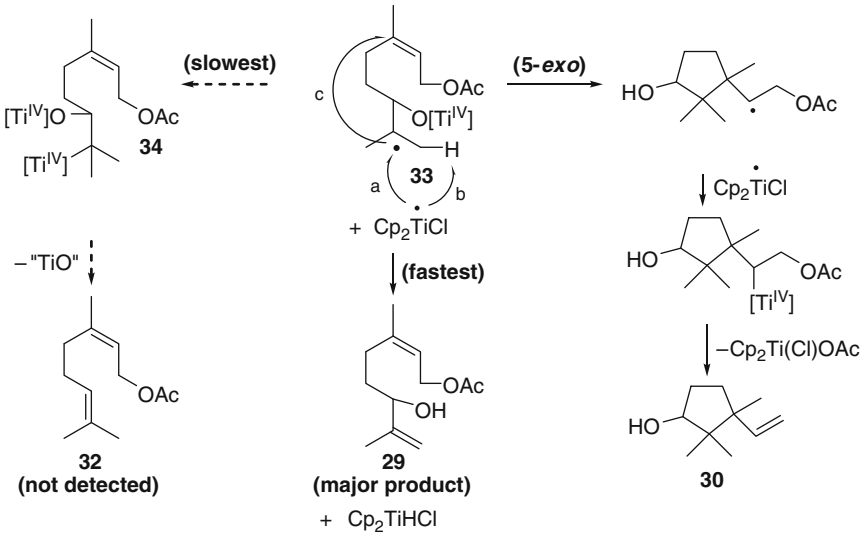
Scheme 22 Cp_2TiCl mediated opening of epoxyneryl acetate without water

When **28** was subjected to Cp_2TiCl in dry THF, the allylic alcohol **29**, together with the cyclization product **30** and a minor quantity of the reduction product **31**, was isolated. The expected deoxygenation product **32** was not formed at all (Scheme 22) [73, 74].

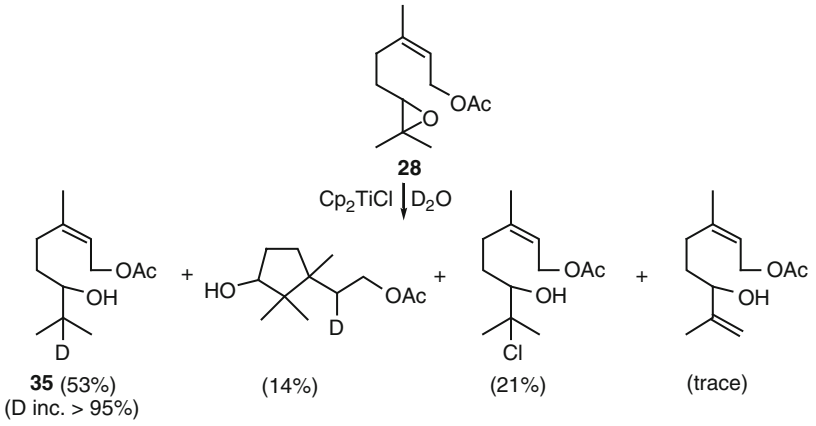
The formation of the major product suggested that a mixed disproportionation reaction between the radical intermediate **33** and a second equivalent of Cp_2TiCl had taken place [76]. This process was slightly faster than the cyclization reaction leading to **30** and much faster than the potential radical trapping by the second titanium species, which would have led to the elusive deoxygenation product **32** (Scheme 23).

Subsequently, **28** was treated with Cp_2TiCl in the presence of D_2O. Under these conditions, the deuterium-labeled alcohol **35** became the main product, at the expense of allylic alcohol **29** (Scheme 24) [73, 74].

Thus, deuterium transfer from D_2O was faster than the mixed disproportionation leading to the allylic alcohol **29**, which in turn had proved to be much faster than the potential radical trapping leading to the organometallic intermediate **34**. This strongly suggests that deuterium incorporation in **35** cannot occur via hydrolysis of **34** [73, 74].



Scheme 23 Potential pathways in the Cp_2TiCl mediated cyclization of epoxyneryl acetate



Scheme 24 Cp_2TiCl mediated opening of epoxyneryl acetate in the presence of D_2O

Oltra and Cuerva explored the fate of primary radicals in the presence of water next. However, since the titanium-promoted opening of epoxides generally gives the higher substituted radicals, the generation of primary radicals directly from epoxides seemed impossible. Nevertheless, primary radicals can be readily generated via cyclization to suitably substituted olefins. To this end, the transannular cyclization of caryophyllene oxide (**36**) that generates a *neopentyl*-type primary radical was employed. After treatment of **36** with Cp_2TiCl a mixture of stereoisomers **37** and **38** was formed via reduction of the intermediate primary radicals (Scheme 25) [73, 74].

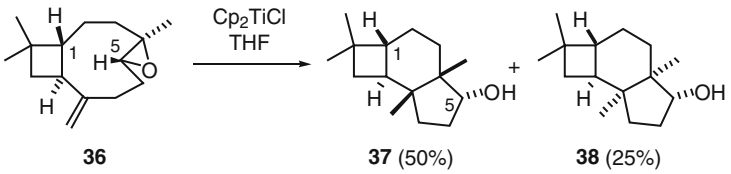
Subsequently, the following experiments were carried out to find out whether this radical reduction occurred through hydrolysis of an organometallic intermediate or from a hydrogen-atom transfer process.

First, **36** was treated with Cp_2TiCl in the presence of 1,4-CHD. After consumption of **36** (1 h), D_2O was added. From this reaction a mixture of **37** and **39** was obtained (Scheme 26).

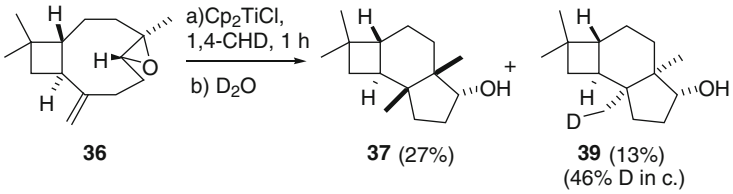
The lack of deuterium labeling in **37** indicated that the reduction of the primary radical took place by hydrogen-atom transfer from 1,4-CHD and not by hydrolysis of a potential organometallic intermediate. Then **36** was treated with Cp_2TiCl in the presence of 1,4-CHD and D_2O. A mixture of the "normal" products **37** and **38** as well as the deuterium-labeled **39** and **40** could be isolated (Scheme 27).

The 57% of deuterium incorporation in **40** demonstrates that deuterium transfer from D_2O was slightly faster than the hydrogen transfer from 1,4-CHD, which had been shown to be much faster than the radical trapping by a second equivalent of Cp_2TiCl. As before, deuterium incorporation in **40** can therefore not occur via protonation of an organometallic intermediate, such as **41** (Scheme 28).

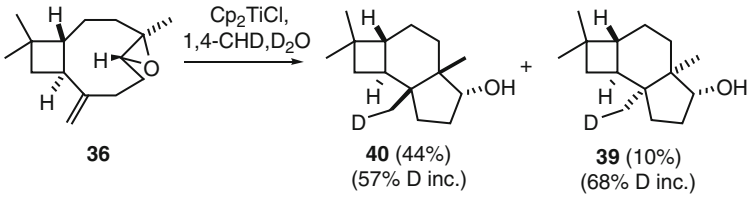
Finally, a kinetic isotope effect of 3.0 was determined for these HATs. This value is similar to that reported for a HAT from *tert*-butyl thiol to primary radicals [77].



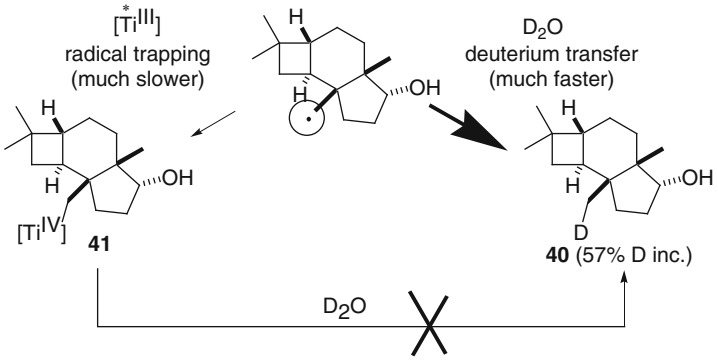
Scheme 25 Titanocene mediated cyclization of caryophyllene oxide



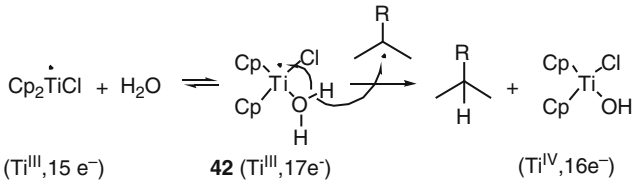
Scheme 26 Deuteration studies in the cyclization of caryophyllene oxide



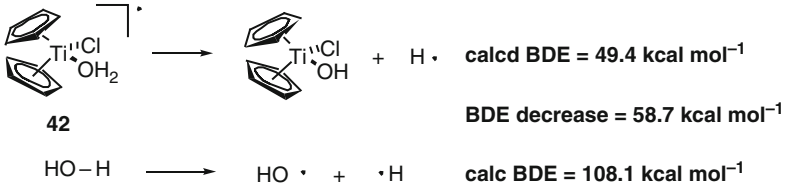
Scheme 27 Deuteration studies in the cyclization of caryophyllene oxide



Scheme 28 Deuteration studies in the cyclization of caryophyllene oxide



Scheme 29 HAT from water to free radicals mediated by **42**



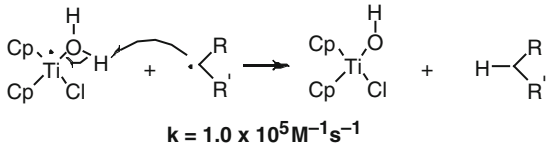
Scheme 30 BDE of water coordinated to Cp_2TiCl

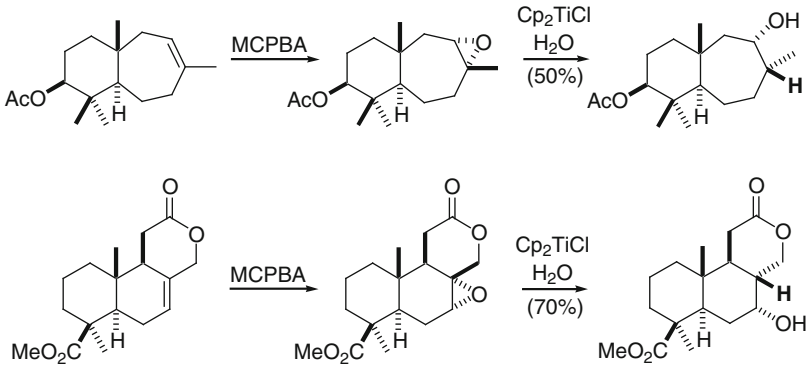
To explain the unprecedented HATs from water it was proposed that the co-ordination of water to Ti(III) might weaken the strength of the O–H bond. In this manner a single-electron transfer from titanium to oxygen might facilitate the HAT from the titanocene aqua-complex **42** to the free radicals (Scheme 29).

Theoretical calculations supported this hypothesis, indicating a bond-dissociation energy (BDE) for the titanocene aqua-complex **42** of only 49.4 kcal mol^{-1}, which represents a decrease of almost 60 kcal mol^{-1} compared to the calculated BDE of H_2O (Scheme 30) [73, 74].

In 2008, Jin and Newcomb confirmed the findings on the activation of water as hydrogen atom donor by Cp_2TiCl and, by using radical clocks, determined the rate constant for the H-atom transfer from the Ti(III) aqua-complex to secondary radicals (Scheme 31) [78].

Scheme 31 Rate constant of the reduction of secondary radicals by Cp_2TiCl/H_2O





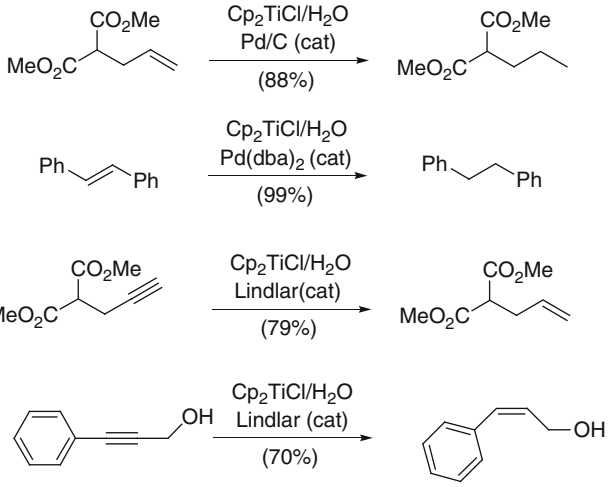
Scheme 32 *Anti*-selective reduction of epoxides by Cp_2TiCl/H_2O

Apart from these mechanistic considerations, the Cp_2TiCl/H_2O couple has emerged as an excellent reagent for the reductive opening of epoxides, avoiding the use of conventional hydrogen-atom donors such as 1,4-CHD, *tert*-butyl thiol, or Bu_3SnH, which are toxic, expensive, and/or foul-smelling.

The epoxidation-epoxide opening sequence with this reagent provides a convenient access to the products of an *anti*-Markovnikov addition of water to olefins. Interestingly, the Cp_2TiCl/H_2O couple combination shows *anti* stereoselectivity in the reduction step [73, 74], which is complementary to the hydroboration-oxidation method (Scheme 32).

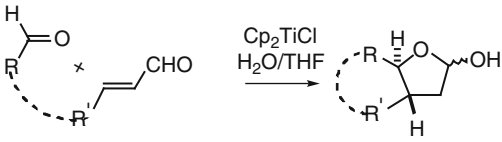
The reductive epoxide opening can also be carried out using substoichiometric quantities of Cp_2TiCl in the presence of collidine hydrochloride. Moreover, with D_2O deuterium-labeled alcohols can easily be obtained using relatively cheap D_2O as deuterium source [79].

The Cp_2TiCl/H_2O combination can also be used for the chemoselective reduction of aromatic ketones. The reaction discriminates between ketones and alkenes, between ketones and esters and, remarkably, between conjugated and non-conjugated ketones [80]. There is strong evidence that this reduction proceeds via ketyl-type radicals, which are finally reduced by H-atom transfer from **42** [81]. Under dry conditions, titanium-promoted ketyl radicals from aromatic ketones can be used for intermolecular and intramolecular cross-coupling of ketones [82]. Thus, depending on whether water is added or not, complementary and versatile synthetic procedure protocols are available.



Scheme 33 Hydrogenation of olefins and alkynes mediated by Cp_2TiCl/H_2O

Scheme 34 Radical additions of aldehydes to conjugated alkenals mediated by Cp_2TiCl/H_2O



Furthermore, in the presence of Pd or Rh catalysts, the Cp_2TiCl/H_2O couple can also be used for the hydrogenation of alkenes and alkynes by hydrogen transfer from water (Scheme 33) [83].

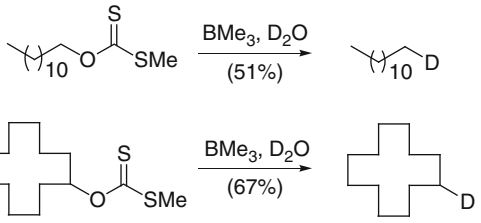
If D_2O is used instead of water, this method provides a straightforward access to doubly labeled products. The reaction mechanism seems to proceed via hydrogen transfer from **42** to the late-transition metal complex. This results in the formation of a hydrido metal complex that hydrogenates the alkene or alkyne substrate. Theoretical calculations strongly support this mechanistic proposal by suggesting an activation energy of only 17.3 kcal mol^{-1} for the HAT [83].

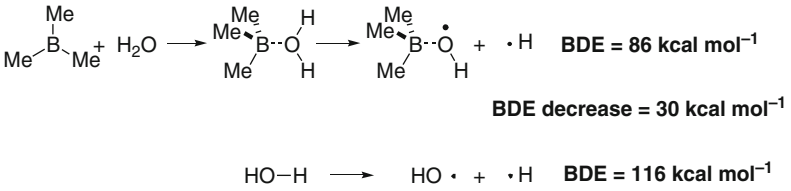
The Cp_2TiCl/H_2O couple can also be used to achieve inter- and intramolecular Michael-type additions of aldehydes to conjugated alkenals (Scheme 34) [84].

4.2 Activation of Water by Boron

In 2005, Wood and co-workers reported a conceptionally new version of the Barton-McCombie reaction by using water as hydrogen-atom source for the reduction of free radicals in the presence of trialkylboranes (Scheme 35) [85].

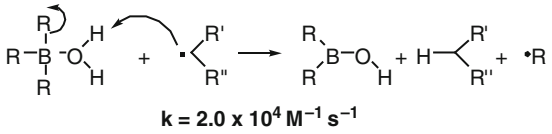
Scheme 35 Barton-McCombie reaction in the presence of trialkylboranes and water





Scheme 36 BDE of water coordinated to trimethylborane

Scheme 37 Rate constant of the reduction of secondary radicals by trialkylborane coordinated water



The authors proposed that the HAT from water was mediated by a boron aqua complex in which the strength of the O–H bond was weakened by 30 kcal mol^{-1} with respect to non-coordinated water (Scheme 36).

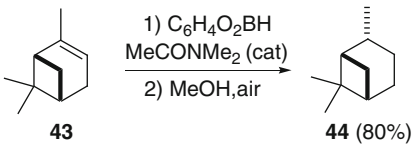
In 2007 the scope of the trialkylborane/water system was extended to the dehalogenation of alkyl iodides and the chemoselective deoxygenation of secondary alcohols in the presence of alkyl and aryl halides [86]. The rate constants for the hydrogen-atom transfer from this reagent to secondary radicals (Scheme 37) are substantially lower than those of the Ti(III) aqua-complex [78, 87].

4.3 Activation of Alcohols by Boron?

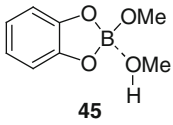
In 2005, Renaud and co-workers reported a novel procedure for the formal hydrogenation of alkenes via hydroboration with an excess of catecholborane, followed by treatment of the intermediate boronic acid esters with methanol in the presence of air as a radical initiator [88]. A typical example, the reduction of **43** to **44**, is shown in Scheme 38. Similar results were obtained for a wide range of primary, secondary, and tertiary alkylcatecholboranes.

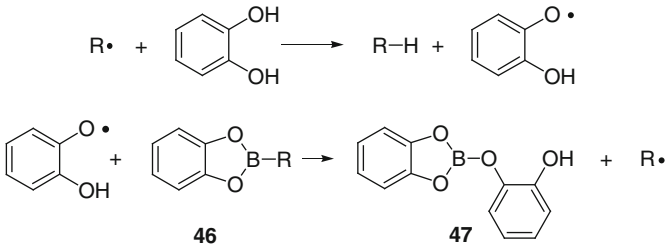
Kinetic and mechanistic investigations on this reaction were subsequently carried out by Jin and Newcomb [78, 89].

Scheme 38 "Radical hydrogenation" of olefins with catecholborane and methanol



Scheme 39 Postulated activation of MeOH by coordination with boron





Scheme 40 Mechanism of the radical reduction of boronates with free catechol

In the original paper, Renaud and co-workers hypothesized that complex **45**, resulting from the complexation of methoxycatecholborane, generated in situ from the excess of catecholborane and methanol, was the main source of H atoms. The authors proposed that the O–H bond of methanol was activated by complexation with the boron Lewis acid (Scheme 39).

More recently, experiments from the same group indicated that boronate complex **45** cannot be the source of hydrogen atoms [90]. Instead, it was suggested that "free" catechol was the actual source of hydrogen atoms.

Radical reduction is followed by a rapid reaction of the 2-hydroxyphenoxyl radical with the boronate **46**. In this manner, chain propagation is ensured by the regeneration of the initial alkyl radical and the formation of Meulenhoff's free acid **47** (Scheme 40).

5 Conclusion

Over the last few years, significant progress has been made in the development of novel hydrogen atom donor reagents that are attractive surrogates for the classical group 14 reagents. The issue of toxicity is addressed by using readily available, non-venomous terminal reductants, such as borane, water, methanol, or hydrogen.

Borane, methanol, and water, which have B–H and O–H bonds too strong to allow participation in radical reactions, are activated towards HAT by complexation with NHCs, boranes, or titanocene(III) complexes. This novel concept has resulted in exciting applications in both radical chain reactions and transition metal mediated and catalyzed transformations.

The use of hydrogen as terminal reductant has been accomplished by its activation with transition metal complexes. The resulting weak M–H bonds can be used in both radical generation and reduction through HAT. In this manner, conceptually novel radical chain reactions, such as hydrogen mediated cyclizations, or metal catalyzed processes with coupled catalytic cycles for radical generation and reduction, have been realized. The latter transformations are especially attractive for enantioselective synthesis.

It is expected that the use of boranes, methanol, water, and hydrogen as terminal HAT reagents will lead to the invention of exciting novel reactions in the near future.

Acknowledgements We are grateful for continued financial support by the Deutsche Forschungsgemeinschaft, the Alexander von Humboldt-Stiftung, and the Fonds der Chemischen Industrie. We also thank the Spanish Ministry of Science and Innovation and the Regional Government of Andalucía for projects CTQ2008-06790/BQU and P07-FQM-03213 and aids to the PAI group FQM-339.

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