Organoboranes as a Source of Radicals

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1. Introduction

Since the historical report of Frankland in 1860,[1,2] organoboron chemistry has received a great deal of interest from chemists. This research culminated with H. C. Brown's Nobel Prize in 1979 for the development of boron-containing compounds into important reagents in organic synthesis.[3] Many efforts have been made in developing convenient, efficient, and useful transformations taking advantage of the electron deficiency caused by the vacant p-orbital on the boron atom of organoboranes and the metallic properties of boron derivatives. A rich chemistry was developed around these properties. For instance, hydroboration of alkenes and alkynes; allylation and propargylation of aldehydes with allylic and allenic boronic esters, respectively; alkylation of boron enolates; 1,2-migration of α-haloalkylborates as well as asymmetric reduction; Diels−Alder reactions; and Suzuki coupling were thoroughly investigated.[4−8] Since 1967, organoboranes were recognized to participate in free-radical processes. This reactivity was initially demonstrated by Davies and Roberts and was applied to synthesis by Brown and Suzuki.[9,10] Following the spectacular development of radical chemistry in organic synthesis,[11−14] the use of organoboranes has recently led to many novel and useful synthetic applications.[15] In this review, we will describe the basic radical reactivity of organoboranes leading to the generation of carbon-centered radicals by cleavage of carbon−boron bonds. The utility of organoboranes as radical initiators and radical precursors will be presented. Reactions involving generation of alkyl radicals from amine−boryl radicals via hydrogen atom abstraction will not be covered by this review since this work has recently been compiled[16−18] and does not involve the homolytic cleavage of carbon−boron bonds.

2. Radical Reactivity of Organoboranes: Homolytic Substitution at the Boron Atom

Trialkylboranes easily undergo bimolecular homolytic substitutions at the boron atom. An alkyl residue is readily displaced by a peroxyl, an alkoxyl, a ketone triplet, an aminyl, and a thiyl radical. Such reactions are thermodynamically favored by the high strengths of the B−X bond formed {BDE (B−C) for Et_3B = 344 kJ/mol; BDE (B−O) for $(EtO)_3B$ = 519 kJ/mol; BDE (B−N) for $[(CH_3)_2N]_3B$ = 422 kJ/mol; BDE (B−S) for $(EtS)_3B$ = 377 kJ/mol}.[19−21] Numerous reviews and book chapters written by Davies and Roberts summarize the information in this field.[22−26]

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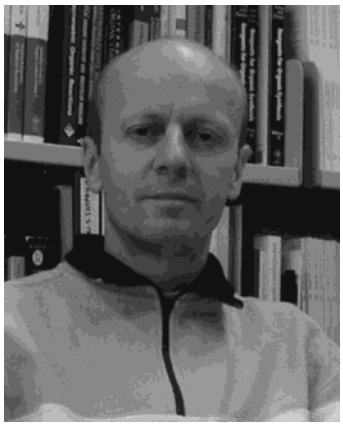
Cyril Ollivier was born in Neuilly, France, in 1971. He received his Diplôme d'Etudes Approfondies in Organic and Bioorganic Chemistry from the Université Pierre et Marie Curie (Paris) under the guidance of Prof. Jean-François Normant in 1995, working on the reactivity of carbenoids in 1,2-metalate rearrangement. After 1 year of national service at the Ecole Nationale Supérieure de Techniques Avancées (Paris) as scientist associate in the laboratory of Dr. Laurent El Kaim, he joined Prof. Philippe Renaud's group at the Université de Fribourg in 1996 for a Ph.D. program in collaboration with the laboratory of Prof. Max Malacria, Université Pierre et Marie Curie (Paris). He worked on the utilization of organoboranes as source of radicals, on the developments of novel radical hydroxylation and azidation processes, and gained his doctorate in cotutelle in 2000. He was awarded a Swiss National Foundation Fellowship to pursue research studies at the University of Texas at Austin (Austin, TX) in Professor Philip Magnus' group where he is involving in the total synthesis of diterpenes.



Philippe Renaud was born in Neuchâtel in 1959. After undergraduate study at the University of Neuchâtel, he continued his education at the ETH Zürich obtaining his Ph.D. in 1986 under the supervision of Prof. Dieter Seebach. From October 1986 to December 1987, he was a postdoctoral associate of Prof. Marye Anne Fox at the Unviersity of Texas at Austin. He started in 1988 an independent research program at the University of Lausanne. In 1992, he obtained the Alfred Werner Fellowship, which allowed him to continue his research work in Lausanne. In October 1993, he moved to the University of Fribourg as an associate professor. Since March 2001, he has been a professor of organic chemistry at the University of Bern. His research interests include the development of novel synthetic methods based on radical reactions, the use of Lewis acids for asymmetric synthesis, and the preparation of biologically active compounds.

Herein, we simply highlight the different homolytic substitutions that occur at the boron atom. Interestingly, a common feature of all these homolytic reactions is the Lewis basic character of the radicals. This basicity leads to the formation of complexes with trialkylboranes that fragment to give carbon-centered radicals.[27]

2.1. Peroxyl Radicals: The Autoxidation of Organoboranes

The vigorous reactivity of organoboranes with oxygen was demonstrated in 1860 by Frankland with the beautiful green flame of burning triethylborane.[1,2] Several mechanistic investigations of the autoxidation of organoboranes were performed leading to the opinion that a radical mechanism was not operating.[28−33] However, the complete racemization of optically active 1-phenylethylboronic acid during the autoxidation process and the inhibition of this reaction in the presence of radical scavengers such as galvinoxyl suggest a radical process.[34−38] The widely accepted mechanism of the autoxidation, confirmed by ESR[39−42] and NMR,[43,44] is depicted in Scheme 1.

Scheme 1. Mechanism of Autoxidation of Organoboranes

Initiation

$$R_3B + O_2 \xrightarrow{S_H2} R_2BOO\bullet + R\bullet$$

Propagation

$$R\bullet + O_2 \longrightarrow ROO\bullet$$

$$ROO\bullet + R_3B \xrightarrow{S_H2} (ROO)BR_2 + R\bullet$$

Further reactions

$$(ROO)BR_2 + O_2 \longrightarrow (ROO)_2BR \quad (1)$$

$$(ROO)BR_2 + R_3B \longrightarrow 2\,(RO)BR_2 \quad (2)$$

$$(RO)BR_2 + O_2 \longrightarrow [(RO)(ROO)BR] \longrightarrow (RO)_3B \quad (3)$$

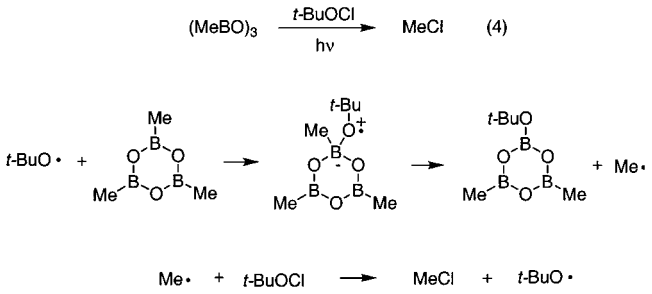
A homolytic substitution (S_H2) reaction between triplet oxygen and trialkylborane initiates the reaction and liberates an alkyl radical. The reaction of this radical with oxygen furnishes a peroxyl radical that propagates the chain by further S_H2 reaction. The rate constant for the homolytic substitution at the boron center of tributylborane by a butylperoxyl radical has been measured to be $2.0 \times 10^6\ M^{-1}\ s^{-1}$ at 30 °C.[38,45,46] The monoperoxyborane will react further either with oxygen to give a diperoxyborane that is inert toward oxygen (eq 1) or with the starting trialkylborane (eq 2). In the latter case, a dialkyl borinate [$(RO)BR_2$] is produced that can further react with oxygen to give finally a trialkyl borate [$B(OR)_3$] (eq 3).[47−52] Hydrolysis as well as oxidative and reductive treatments of the autoxidation products lead either to hydroperoxides or alcohols.

2.2. Alkoxyl Radicals

The reaction of trimethylboroxine with *tert*-butyl hypochlorite under irradiation affords chloromethane (eq 4).[53] This indicates that *tert*-butoxyl radicals can displace a methyl group at boron. A radical mechanism involving an addition−elimination process through a tetracoordinate "ate" complex was suggested (Scheme 2).[53,54]

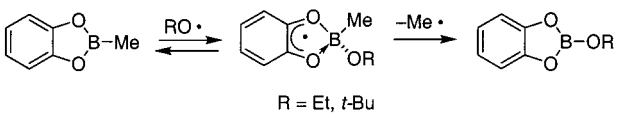
Following this work, various speculations on the mechanism were reported. A concerted bimolecular

Scheme 2. Reaction of Trimethylboroxine with *tert*-Butyl Hypochlorite under Irradiation



homolytic substitution was preferred since no tetracoordinate intermediate was detected by ESR experiments.[39,40,42,55] Further kinetic studies on trialkyl- and triphenylboranes with di-*tert*-butyl peroxide or *tert*-butylhypochlorite[25,41,55−57] as well as with ketone triplets [58,59] corroborate the previous results. However, the combination of kinetic measurements and ESR experiments for the reaction of triphenylborane with di-*tert*-butyl peroxide support the formation of a tetracoordinate boranyl radical followed by rapid fragmentation.[57] Interestingly, alkoxyl radicals have been shown to be more reactive than alkylperoxyl radicals. The following reactivity order has been established: $R_3B > R_2BOR > RB(OR)_2$ (R = alkyl).[25,60] The rate constants for homolytic substitutions at boron centers have been measured for several different systems.[38,45,46,55,57] Typical values for the reaction of *tert*-butoxyl radicals with different trialkylboranes are as follow: Bu_3B, 1.5×10^8 M^{-1} s^{-1}; *i*-Bu_3B, 5.1×10^6 M^{-1} s^{-1}; Ph_3B, 1.0×10^8 M^{-1} s^{-1}.[57] Electronic and steric effects considerably influence the reactivity of organoboranes toward peroxyl radicals.[25] Due to π-bonding between boron and oxygen, boronic esters are less reactive than trialkylboranes toward alkoxyl radicals. On the basis of this simple consideration, *B*-alkylcatecholboranes should be more reactive than the corresponding dialkyl boronates since the lone pair at oxygen is partially delocalized into the aromatic ring. More importantly, it was clearly demonstrated by ESR that a delocalized perboryl radical intermediate (a radical "ate" complex) is involved in the substitution reaction at boron (Scheme 3).[60] The stabilization of this intermediate certainly accounts for the high reactivity of *B*-alkylcatecholboranes in radical reactions (see sections 4.1.1.2 and 4.1.2 for synthetic applications).

Scheme 3. Reaction of *B*-Methylcatecholborane with Alkoxyl Radicals

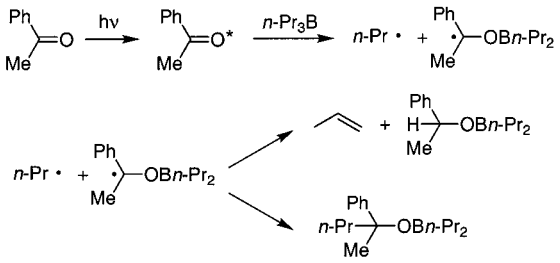


R = Et, *t*-Bu

2.3. Ketone Triplets

Davies has reported the reaction of ketone triplets with organoboranes.[59] The measured rate constants for homolytic substitutions with trialkylboranes were found to be very similar to the reaction of the *tert*-butoxyl radical.[61] This reaction has however not yet been applied to synthetic purposes, presumably due to recombinations and dismutations that remove radicals from the reaction mixture as shown in Scheme 4.

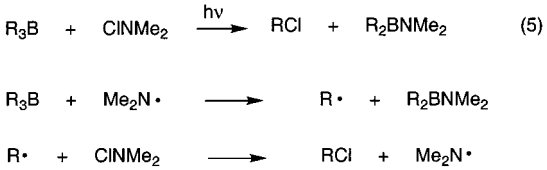
Scheme 4. Reaction of Tripropylborane with Triplet Acetophenone



2.4. Dialkylaminyl Radicals

Brown et al. have reported an interesting amination procedure of trialkylboranes with chloramine under basic conditions that takes place via a polar mechanism.[62] Surprisingly, similar experiments carried out with dimethylchloramine lead to the formation of the aminoborane and alkyl chloride (Scheme 5, eq 5).[63] A chain radical pathway involving di-

Scheme 5. Reaction of Trialkylboranes with Dimethylchloramine



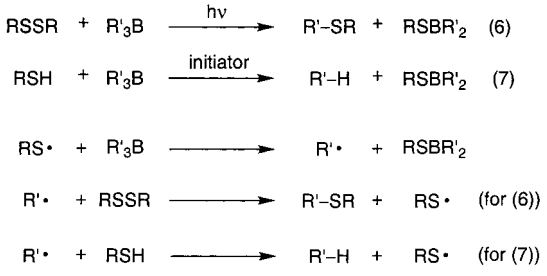
methylaminyl and alkyl radicals was proposed and confirmed by their complete inhibition in the presence of a free-radical scavenger such as galvinoxyl.[64] In addition, ESR investigations have clearly demonstrated the formation of alkyl radicals, resulting from the displacement of alkyl groups at boron by dimethylaminyl radicals (Scheme 5).[65]

Because of the Lewis acidity of organoboranes, a precomplexation between trialkylboranes and chloramine is possible. After chlorine abstraction, the resulting aminyl−borane complex may evolve readily via fragmentation and release of an alkyl radical. ESR experiments by Roberts strongly support that the reactions between dimethylaminyl radicals and trialkylboranes proceed in a stepwise manner via a short-lived aminyl−trialkylborane radical $Me_2N(^{\bullet})\rightarrow BR_3$.[66,67]

2.5. Alkylthiyl Radicals

The reaction between organoboranes and thiols leading to alkane compounds[68] was initially assumed to involve a four-center polar mechanism.[69] Later, the involvement of free radicals was proven.[70,71] On the basis of kinetic and ESR experiments, Davies and Roberts have established that alkylthiyl radicals, generated from disulfides or thiols, react with trialkylboranes to form either a thioether or an alkane, respectively (Scheme 6, eqs 6 and 7). The following reactivity sequence toward thiyl radicals was established: Bu_3B > *i*-Bu_3B > *s*-Bu_3B > $Bu_2B(SBu)$.[72] Rate

Scheme 6. Reaction of Trialkylboranes with Thiyl Radicals

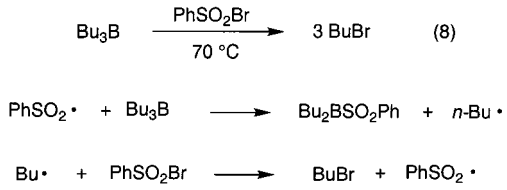


constants of $0.8-1.3 \times 10^8$ M^{-1} s^{-1} were measured for the reaction of *tert*-butylthiyl radicals with trialkylboranes.[73] The reaction between thiocyanyl radicals (NCS•) and triphenylborane leading to PhSCN has also been reported.[74]

2.6. Arenesulfonyl Radicals

The reaction of tributylborane with benzenesulfonyl bromide at 70 °C affords bromobutane via the chain process (Scheme 7, eq 8).[24] The key step is a homolytic substitution at boron by a phenylsulfonyl radical.

Scheme 7. Reaction of Tributylborane with a Phenylsulfonyl Radical

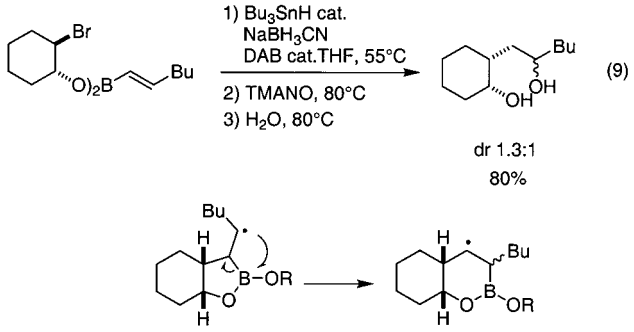


2.7. Carbon-Centered Radicals

Homolytic displacements by carbon-centered radicals at boron center are not common. A low substitution rate constant ($k = 5.9 \times 10^3$ M^{-1} s^{-1}) was measured in the gas phase for the reaction of methyl radicals with triethylborane.[75,76] The reaction of organoboranes with trifluoromethyl radicals has also been reported.[77,78]

More recently, Batey observed a novel rearrangement during boron tethered free-radical cyclizations (Scheme 8). Treatment of a 2-bromocyclohexyl alkenylboronate with Bu_3SnH gives a 1,4-diol rather than the expected 1,3-diol (eq 9). The 1,4-diol results from a ring expansion of the five-membered ring occurring via intramolecular homolytic substitution at boron before tin hydride reduction (eq 9).[79]

Scheme 8. Intramolecular Reaction of a Carbon-Centered Radical with an Alkenylboronate



3. Triethylborane as a Radical Initiator

As previously shown (section 2.1), trialkylboranes give free alkyl radicals upon treatment with oxygen. Utimoto and Oshima were the first to apply the reaction of triethylborane with oxygen to initiate radical reactions.[80] Over classical initiators, the system Et_3B/O_2 offers the great advantage of being efficient even at low temperature (−78 °C). This aspect proved to be particularly important for the development of stereoselective radical reactions and for radical reactions involving thermally unstable adducts or products. The use of triethylborane as radical initiator recently became very popular; however, the experimental procedure may cause reproducibility problems. Our experience in this field has shown that reproducible results are obtained with freshly prepared triethylborane solutions, the use of commercial solutions gives less satisfactory results. After preparation of the reaction mixture under the strict absence of oxygen, air (up to 1 equiv of oxygen relative to Et_3B) is added via a syringe (slow addition technique). Best results are obtained when the needle is below the surface of the reaction mixture.

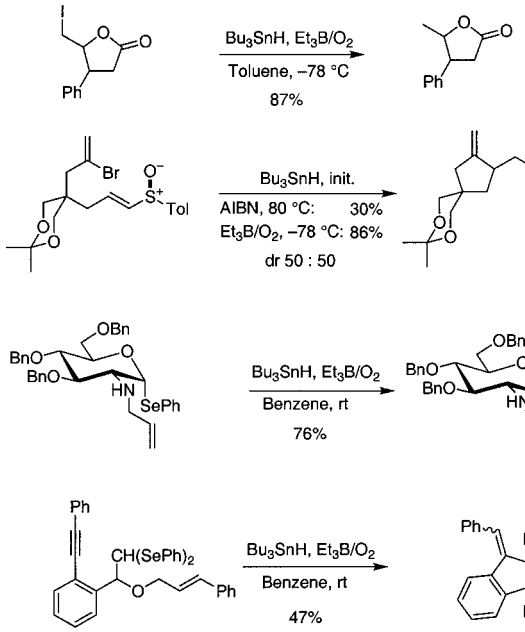
Diethylzinc has also been used as a radical initiator[81] and chain transfer reagent.[82−85] This reagent behaves like triethylborane and may represent an interesting alternative. However, the stronger Lewis acidity and nucleophilicity of zinc reagents are a potential drawback when mild reaction conditions are required.

3.1. Tin-Mediated and Related Processes

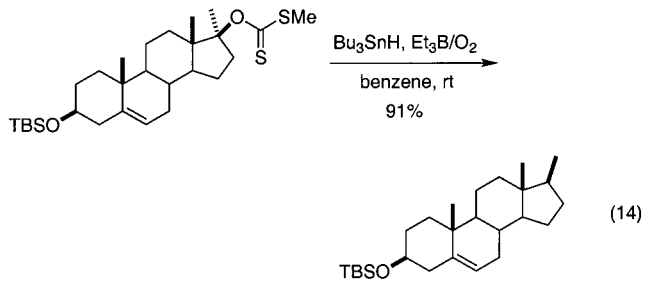
3.1.1. Halogen Atom Abstraction

Triethylborane proved to be an efficient initiator for the generation of tin radicals from tin hydrides. A wide range of alkyl iodides and bromides were readily reduced (∼30 min) by treatment with Bu_3SnH in the presence of a catalytic amount of triethylborane (10 mol %) at −78 °C (eq 10). Also the reduction of alkenyl iodides and bromides as well as aryl iodides proceeds in high yield.[80] Radical cyclization initiated by Et_3B/O_2 has become a standard procedure. Lacôte and Malacria used this procedure to cyclize an alkenyl sulfoxide at low temperature in order to avoid the formation of a conjugated diene by thermal elimination of sulfinic acid (eq 11).[86] Czernecki et al. have shown that the synthesis of 2-amino-2-deoxy-α-D-*C*-glucopyranoside by radical cyclization of an anomeric selenide occurs only under the mild conditions offered by the Et_3B/O_2 procedure (eq 12).[87] Finally, a better yield for the double radical cyclization of a bis(phenylseleno)ketal is obtained with Et_3B/O_2 rather than under thermal conditions (eq 13).[88]

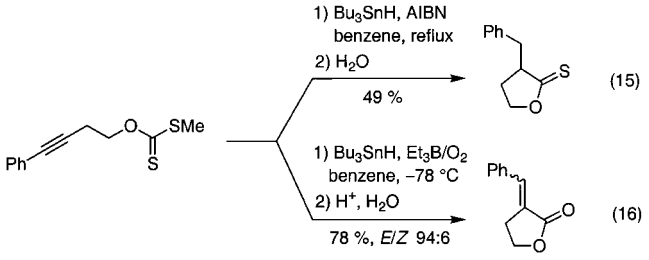
Radical initiation with Et_3B/O_2 at room temperature has been applied to the deoxygenation of secondary[89,90] and tertiary alcohols[91] via the corresponding dithio- or thiocarbonates. This alternative to the classical thermal initiation of the Barton−McCombie



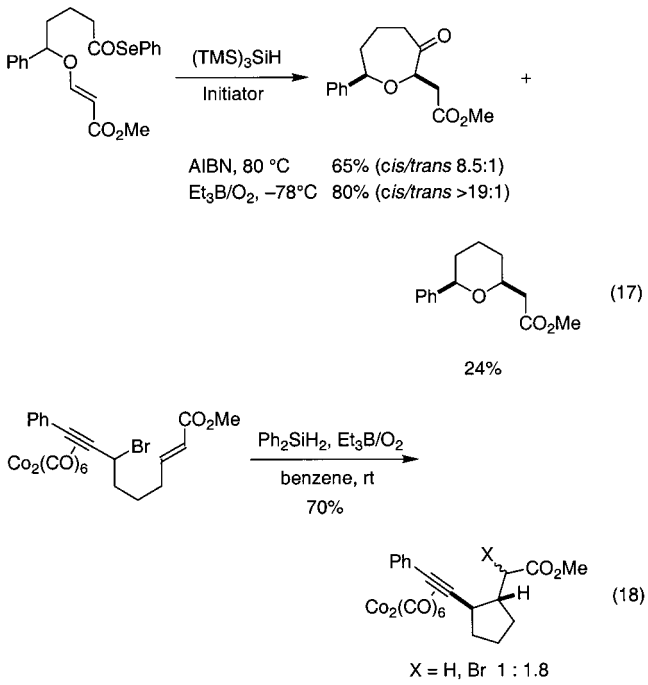
deoxygenation[92−95] is particularly useful with tertiary dithiocarbonates in order to prevent a possible Chugaev fragmentation reaction (eq 14).



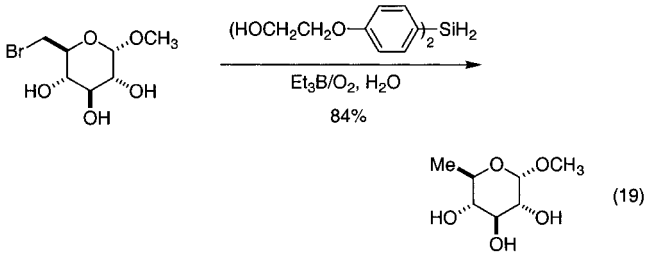
Switching from traditional AIBN initiation to Et_3B/O_2 occasionally changes the course of the reaction. For example, under AIBN initiation, a homopropargylic xanthate gives a saturated γ-thionolactone (eq 15)[96] while initiation with Et_3B/O_2 affords the α,β-unsaturated lactone (eq 16).[97,98]



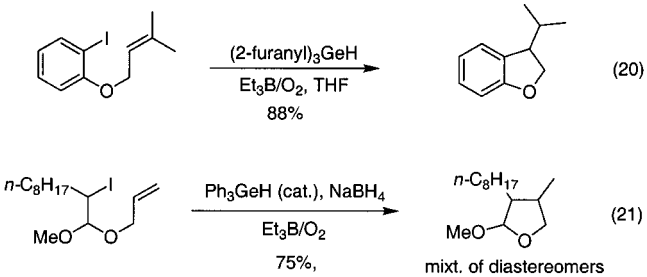
Triethylborane can also initiate the formation of silyl or germanyl radicals from the related hydrides. For example, Evans and Roseman reported the cyclization of acyl radicals to vinylogous carbonates in the presence of $(TMS)_3SiH$. By using Et_3B/O_2 initiation rather than AIBN, the *cis*-oxepanones are obtained in higher stereoselectivity and yield since the decarbonylation of the intermediate acyl radical is suppressed (eq 17).[99] In another striking example, a thermally unstable propargyl bromide cobalt complex cyclizes in the presence of Ph_2SiH_2 under Et_3B/O_2 initiation at 20 °C. A mixture of reduced and bromine atom-transfer products are isolated (eq 18).[100]



Interestingly, Et_3B/O_2 initiation can be performed in aqueous solution. For instance, a wide range of aryl and alkyl halides are reduced in water by water-soluble organosilanes using Et_3B/O_2 initiation (eq 19).[101]

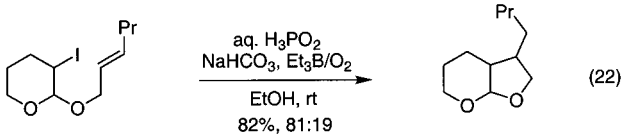


Germanes are also used for the reduction of various organic halides at ambient temperature under Et_3B/O_2 initiation. For example, tri-2-furanylgermane mediated radical cyclizations of aryl iodides proceed in good yields (eq 20) and are also possible with $NaBH_4$ in the presence of a catalytic amount of triphenylgermane (eq 21).[102]



Tin free-radical reduction by an organophosphite[91] and phosphinic acid can also be initiated by Et_3B/O_2. Radical cyclizations using phosphinic acid, a base,

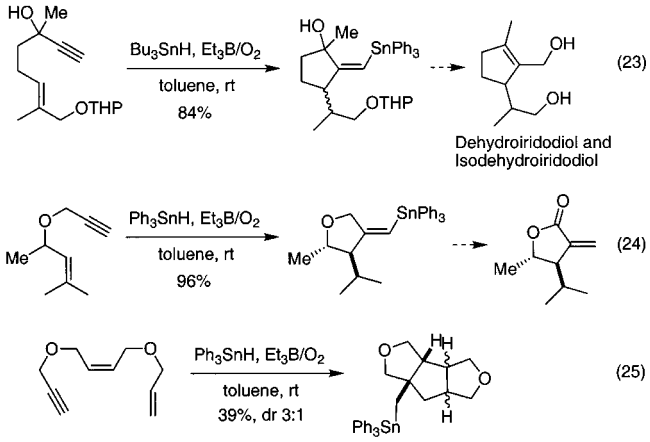
and Et_3B/O_2 as a radical initiator in aqueous ethanol were recently reported (eq 22).[103]



(22)

3.1.2. Addition to Alkynes and Alkenes

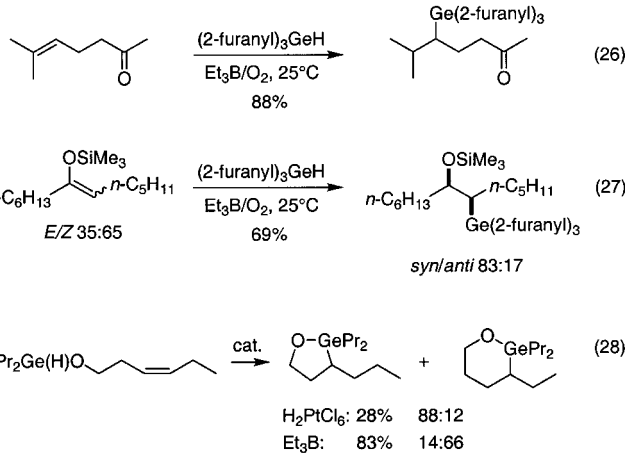
The hydrostannylation of acetylenic compounds is usually run under thermal initiation with AIBN, but high dilutions are required to achieve radical cyclizations.[104,105] This problem was partially overcome by use of the Et_3B/O_2 initiator system. Under these conditions, the triphenylstannyl radical adds selectively at the terminal alkynes to give a mixture of (*E*)- and (*Z*)-vinylstannanes. The reaction was successfully applied to enyne radical cyclizations as shown for the synthesis of dehydroiridodiol/isodehydroiridodiol (eq 23) and α-methylene-γ-butyrolactones (eq 24). The tandem radical addition−cyclization provides (*Z*)-vinylstannanes selectively.[106−108] A triphenyltin-mediated radical cascade cyclization of a 1,4-dioxadienyne is shown in eq 25.[109]



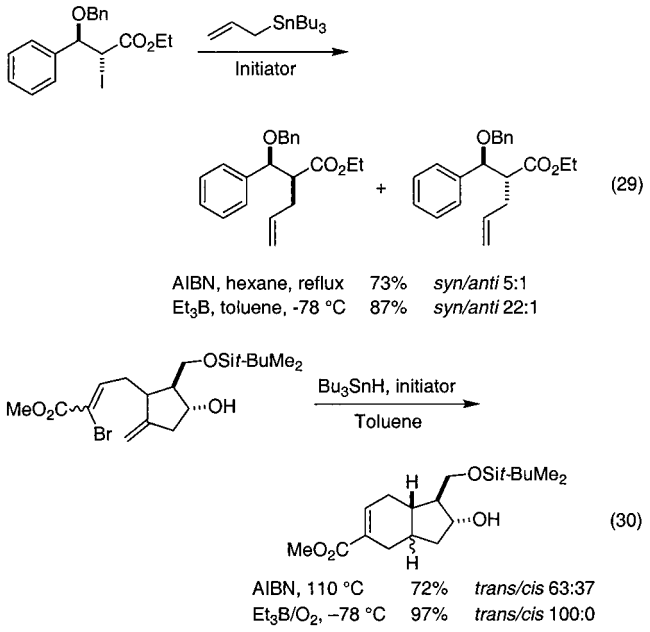
Similarly, tris(trimethylsilyl)silane,[110,111] thiols,[112] and germanes[113] add easily to terminal alkynes in the presence of Et_3B/O_2. This process was extended to internal alkenes (eq 26) as well as silyl enol ethers (eq 27) by using tri-2-furanylgermane. In this last case, basic or acidic treatment of the main syn β-siloxygermane furnishes the corresponding *E*- or *Z*-alkene, respectively.[114] An interesting reversal of the regioselectivity is observed during the intramolecular hydrogermylation of homoallylic and homopropargylic alcohols when switching from Pt to Et_3B/O_2 catalysis (eq 28).[115]

3.1.3. Stereoselectivity Control

The control of the stereochemical outcome of radical processes has been intensively studied during the last 20 years.[116] Many efforts have been made to find suitable conditions for optimal control. As expected, temperature is a critical factor: high stereoselectivities are often reached by running the reactions at low temperature with Et_3B/O_2 as a radical initiator. Selected examples illustrating the crucial role of temperature on the stereocontrol of radical processes will be presented here.

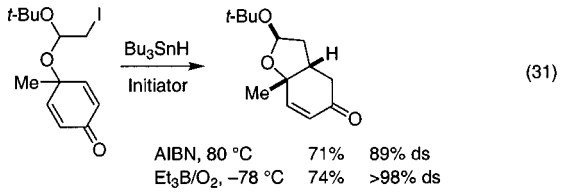


Control of Diastereoselectivity. Stereoselective radical-mediated reduction and allylation of acyclic α-halo-β-alkoxy esters are well-documented reactions. A transition state model based on the minimization of $A^{1,3}$-strain and dipole−dipole repulsion was proposed.[116,117] The temperature has a strong influence on the stereochemical outcome. For example, the allylation depicted in eq 29 furnishes the syn allylated product with moderate stereocontrol (syn/anti 5:1) under thermal AIBN initiation. A higher stereoselectivity (syn/anti 22:1) is obtained at −78 °C with Et_3B/O_2 as initiator.[118] Stereocontrolled *trans*-hydrindane ring formation was carried out by radical cyclization according to eq 30. The total stereochemical control observed at low temperature is rationalized by steric repulsions between the (*tert*-butyldimethylsilyl)oxy group and Bu_3SnH.[119]



Ueno−Stork radical cyclization can be efficiently controlled by the stereogenic acetal center.[120,121] The control of the temperature is critical to attain high diastereoselectivity. In eq 31, a very high diastereoselectivity (>98% ds) is obtained at −78 °C under

Et_3B/O_2 initiation. Under thermal AIBN initiation, the diastereoselectivity is significantly lower (89% ds).[122] Synthesis of a benzo[*a*]quinolizide skeleton by an efficient diastereoselective cascade radical cyclization has been recently reported. The best diastereoselectivity (dr 37:1) is obtained with Et_3B/O_2 as an initiator at −78 °C in toluene (eq 32).[123]



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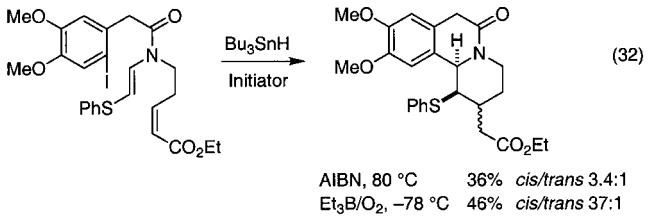
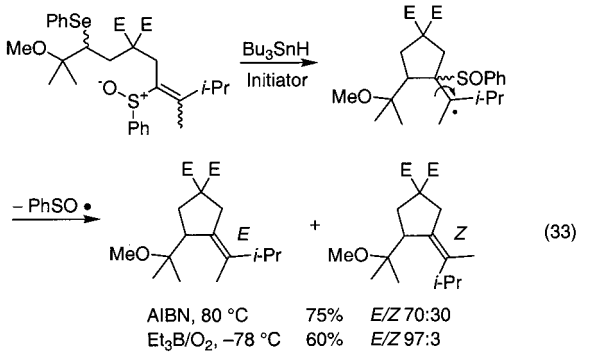


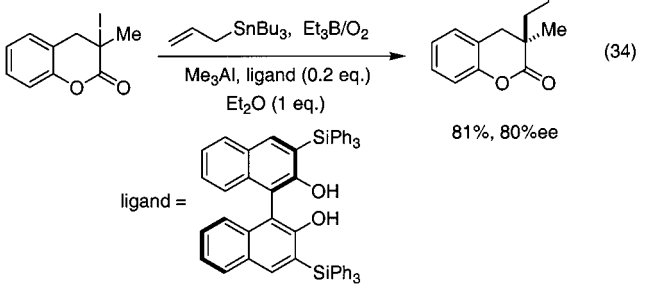
(32)

A diastereoselective intramolecular alkenylation of an alkyl radical was reported by Malacria and collaborators. The configuration of the alkene moiety, fixed during the β-elimination process, is temperature dependent. A significant improvement of the diastereocontrol in favor of the *E* isomer is observed at low temperature (eq 33).[124]



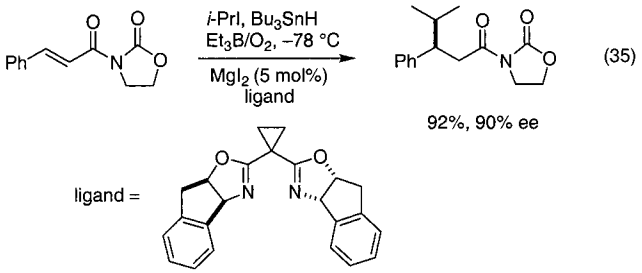
(33)

Control of Enantioselectivity. Hoshino has reported an efficient asymmetric construction of chiral quaternary carbon centers at low temperature by enantioselective allylation of α-iodolactones with allyltributyltin in the presence of a substoichiometric amount of a chiral Lewis acid (20 mol %) initiated by Et_3B/O_2 (eq 34).[125]



(34)

Sibi and Porter have reported the first example of β-enantioselectivity in an acyclic system.[126] Highly enantioselective radical additions using catalytic amounts of a chiral Lewis acid at −78 °C are described. A typical example is depicted in eq 35.[127,128]

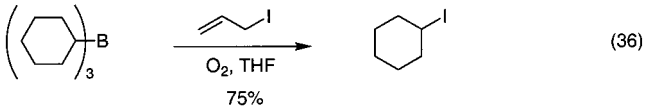


(35)

3.2. Atom-Transfer Reactions

3.2.1. Iodine Atom Transfer

Autoxidation of trialkylboranes is inhibited in the presence of molecular iodine. It was suggested that alkyl radicals, generated by reaction with molecular oxygen, may react with iodine prior to their oxygenation. The reaction produces iodine atoms that cannot propagate the chain.[129] A similar inhibition of the autoxidation is observed with alkyl iodides. However, in the presence of a stoichiometric amount of oxygen, trialkylboranes react with allyl iodide to afford the corresponding alkyl iodides (eq 36). Moreover, allylic and benzylic iodides couple in high yields upon treatment with an excess of organoborane (eq 37).[130]



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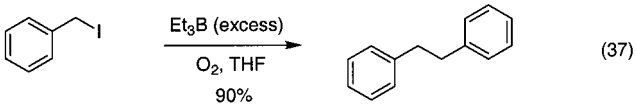
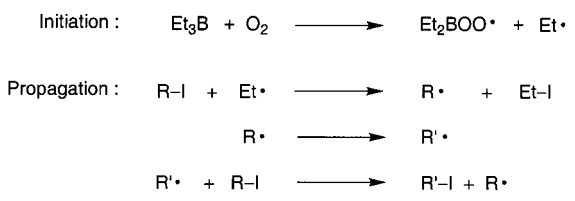


(37)

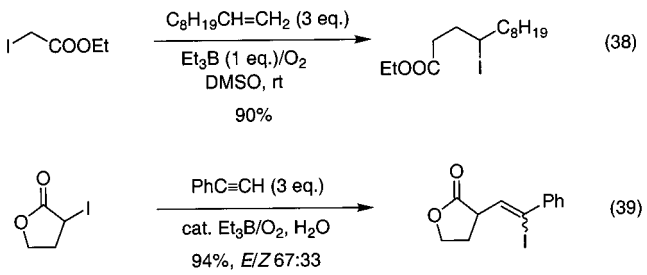
Triethylborane in combination with oxygen provides an efficient and useful system for iodine atom abstraction from alkyl iodide and thus is a good initiator for radical iodine atom-transfer reactions.[131,132] Indeed, the ethyl radical, issued from the reaction of triethylborane with molecular oxygen, can abstract an iodine atom from the radical precursor to produce a radical R• that enters into the chain process (Scheme 9). The iodine exchange is fast and efficient when R• is more stable than the ethyl radical.

Scheme 9. Mechanism of the Et_3B-Mediated Iodine Atom-Transfer Reaction

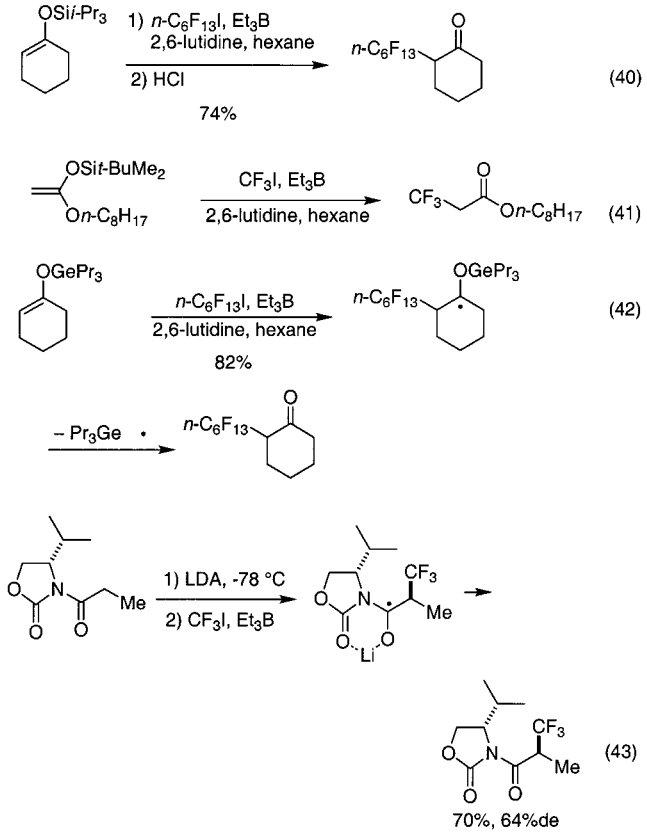


Et_3B-induced addition of perfluoro alkyliodides,[133] α-iodoesters (eq 38),[134] α-iodonitriles,[134] and simple

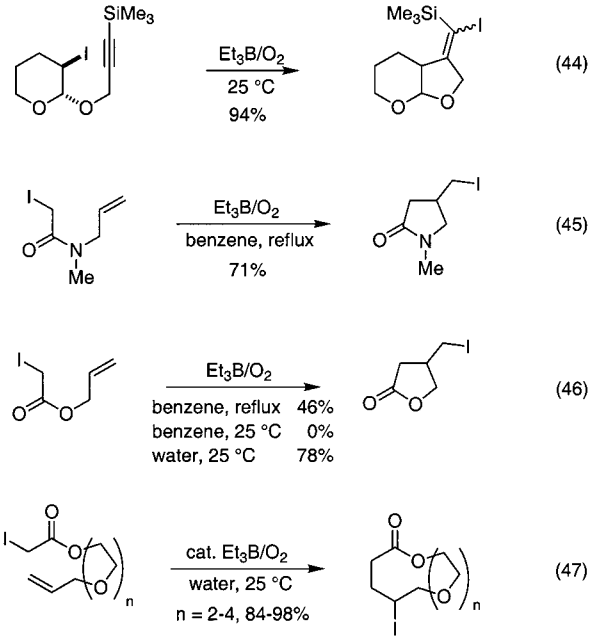
alkyl iodides[135] to alkenes and alkynes has been reported. Interestingly, these reactions were also performed with success in aqueous media demonstrating the ability of Et_3B to act as initiator in water (eq 39).[136]



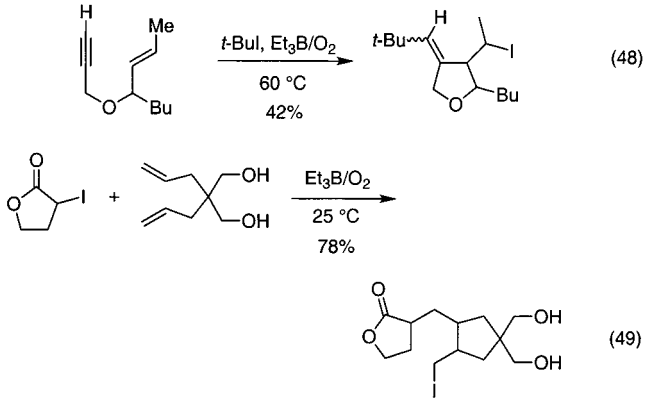
Silyl enol ethers have also been used as a trap for electrophilic radicals derived from α-haloesters[134] or perfluoroalkyl iodides.[137] They afford the α-alkylated ketones after acidic treatment of the intermediate silyl enol ethers (eq 40). Similarly, silyl ketene acetals are converted into α-perfluoroalkyl esters upon treatment with perfluoroalkyl iodides (eq 41).[137,138] With germyl enol ethers, the radical adduct decomposes readily via *β*-elimination and provides the α-perfluoroalkyl ketone and a trialkylgermanyl radical as a chain carrier (eq 42).[137] The Et_3B/O_2-mediated diastereoselective trifluoromethylation[139,140] (eq 43) and (ethoxycarbonyl)difluoromethylation[141,142] of lithium enolates derived from *N*-acyloxazolidinones have also been achieved.



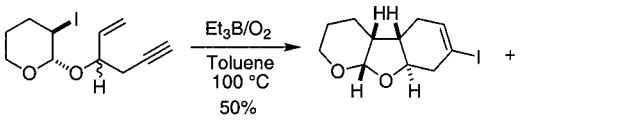
Triethylborane is also an excellent initiator for intramolecular iodine atom-transfer reactions. For example, cyclization of the propargyl α-iodoacetal depicted in eq 44 gives the corresponding bicylic vinyliodide in high yield.[135] Allyl iodoacetamides (eq 45) and allyl iodoacetates (eq 46) cyclize cleanly under Et_3B/O_2 initiation. In the case of the ester, the reaction has to be run in refluxing benzene in order to allow *Z*/*E*-ester isomerization prior to cyclization.[143,144] No trace of cyclized product was detected when the reaction was carried out at room temperature. Interestingly, by running the same reaction in water, Oshima and collaborators obtained the desired lactone in 78% yield. It was suggested that water facilitates the *Z*/*E* isomerization. Efficient preparation of medium and large ring lactones in water have also been reported (eq 47).[145,146]

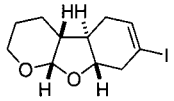


Examples of tandem intermolecular addition−cyclization under iodine atom-transfer conditions are depicted in eqs 48 and 49.[135,136]



Finally, Et_3B-induced radical cascade reactions with 1,5-enynes and 1,5-diynes have been applied to the synthesis of dioxatriquinanes and tricyclic glucoconjugates (eqs 50 and 51).[147,148] Some of these elegant cascade cyclizations were also performed under mild conditions at −50 °C.





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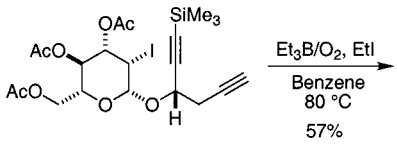
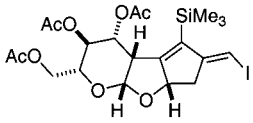
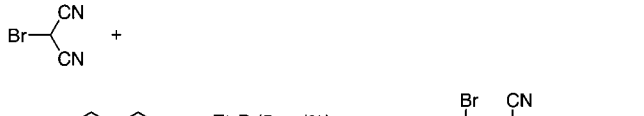




(51)

3.2.2. Bromine Atom Transfer

Bromides are less reactive than the corresponding iodides in atom-transfer processes. However, activated bromides such as diethyl bromomalonate[134] and bromomalonitrile[149] (eq 52) react with olefins under Et_3B/O_2 initiation. Kharasch-type reactions of bromotrichloromethane with alkenes are also initiated by Et_3B/O_2; a typical example is shown in eq 53.[136] On the other hand, a remarkable Lewis acid effect was reported by Mero and Porter. Atom-transfer reactions of an α-bromooxazolidinone amide with alkenes are strongly favored in the presence of Lewis acids such as $Sc(OTf)_3$ or $Yb(OTf)_3$. This reaction was successively applied to the diastereoselective alkylation of chiral oxazolidinone derivatives (eq 54).[150]



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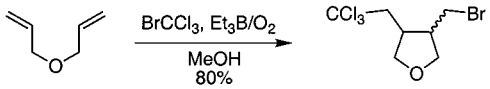

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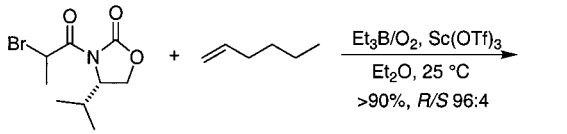
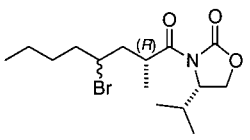
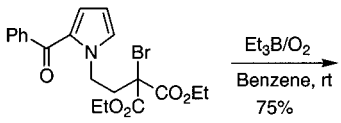




(54)

3.3. Aromatic Substitutions

Regioselective inter- and intramolecular aromatic substitution of 2-benzoylpyrrole derivatives by malonyl radicals is efficiently achieved under Et_3B/O_2 initiation. Since the reaction is not a chain process, a stoichiometric amount of Et_3B is necessary. This reaction has been applied as a key step in the synthesis of ketorolac, a non-narcotic analgesic (eq 55).[151] Further applications to intermolecular homolytic aromatic substitutions of pyrrole, furan and thiophene by electrophilic carbon-centered radicals ($PCH(^{\bullet})CO_2R$ or $F_9C_4^{\bullet}$) were reported by Baciocchi and Muraglia.[152] With furan and thiophene, the rearomatization step is achieved by iron(III) (eq 56). 1,4-Aryl migration from tin to carbon under Et_3B/O_2 initiation was recently reported by Oshima and coworkers (eq 57).[153]



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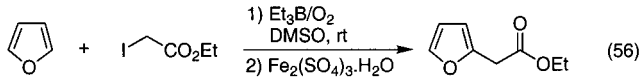

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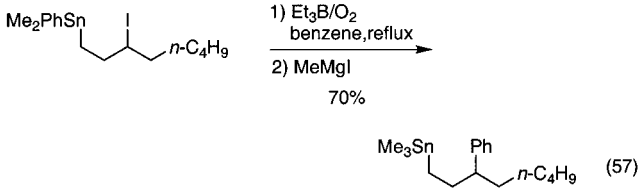
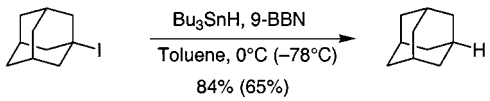


(57)

3.4. 9-BBN as a Radical Initiator

Recently, 9-BBN was applied as an initiator for tin hydride free-radical reduction at low temperature and in the absence of oxygen. Several classes of radical precursors were tested with success, and this procedure proved to be superior to triethylborane under anaerobic conditions (eq 58).[154] No mechanism for this intriguing initiation procedure has been proposed.



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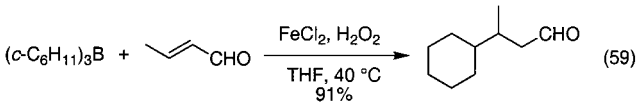
4. Organoboranes as Reagents

4.1. Conjugate Addition

4.1.1. Unsaturated Ketones and Aldehydes

4.1.1.1. From Trialkylboranes. Organoboranes exhibit a high tendency to undergo fast conjugate addition to various types of α,β-unsaturated ketones and aldehydes. For instance, the addition of triphenylborane to α,β-unsaturated carbonyl compounds in the presence of copper salts was reported in 1963.[155] An extension of this approach was reported by Suzuki and co-workers, who adds trialkylboranes to α,β-unsaturated ketones in the presence of Fenton's reagent ($H_2O_2/FeCl_2$) as a source of

hydroxyl radicals to initiate the reaction. Addition of cyclohexylborane to crotonaldehyde furnished the corresponding conjugate addition product in 91% yield (eq 59).[156]



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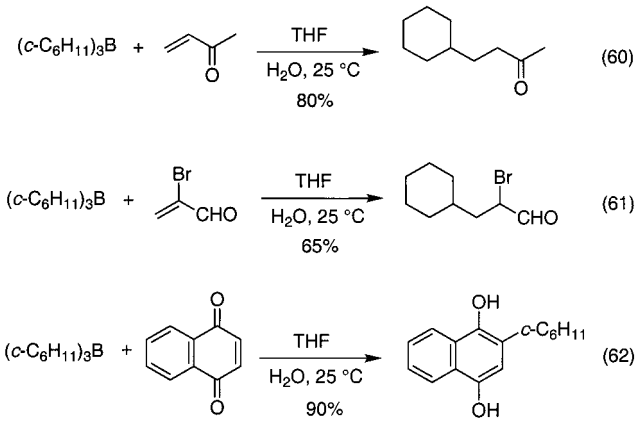
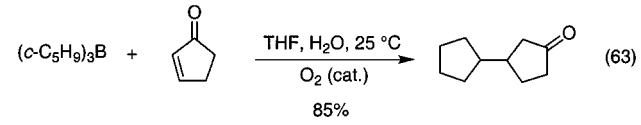
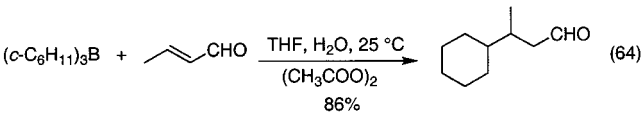
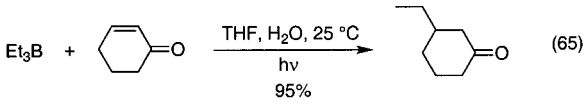
The reaction of trialkylboranes with 1,4-benzoquinones to give in quantitative yield 2-alkylhydroquinones was the first reaction of this type occurring without the assistance of a metal mediator.[157,158] An ionic mechanism was originally proposed but rapidly refuted since the reaction is inhibited by radical scavengers such as galvinoxyl and iodine.[159] Then, it was demonstrated that trialkylboranes, readily available via hydroboration, are excellent reagents for conjugate addition to vinyl ketones (eq 60),[160] acrolein,[161] α-methylacrolein,[162] α-bromoacrolein[162] (eq 61), 2-methylenecyclohexanone,[163] and quinones[157,159,164] (eq 62). Traces of oxygen present in the reaction mixture are sufficient to initiate these reactions. Their free-radical nature was demonstrated by their complete inhibition in the presence of free-radical scavangers such as galvinoxyl (5 mol %)[165] or iodine.[129]



Various attempts to extend this reaction to β-substituted α,β-unsaturated carbonyl compounds such as *trans*-3-penten-2-one, mesityl oxide, 2-cyclohexen-1-one, and *trans*-crotonaldehyde[166] were unsuccessful[165,167] unless radical initiators were used.[168] For instance, in the presence of oxygen,[167] diacetyl peroxide[168] or, under irradiation,[168] trialkylboranes produce alkyl radicals that add to β-substituted α,β-unsaturated carbonyl compounds (eqs 63−65).

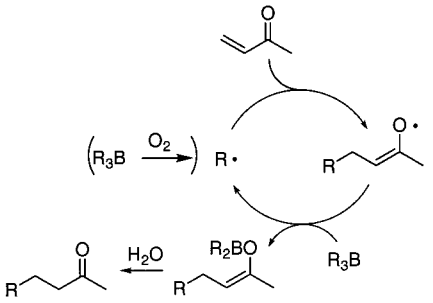




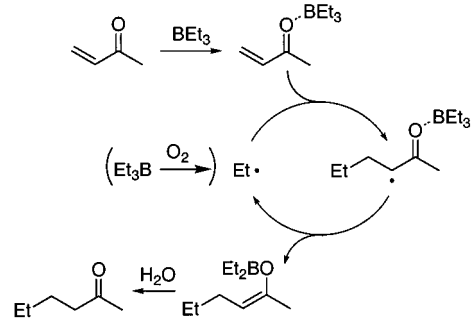


Brown proposed a mechanism where the enolate radical resulting from the radical addition reacts with the trialkylborane to give a boron enolate and a new alkyl radical that can propagate the chain (Scheme 10).[165] The formation of the intermediate boron enolate was confirmed by ^{1}H NMR spectroscopy.[169,170] The role of water present in the system is to hydrolyze the boron enolate and to prevent its degradation by undesired free-radical processes. This hydrolysis step is essential when alkynones[171] and acrylonitrile[9] are used as radical traps since the resulting allenes or keteneimines, respectively, react readily with radical species. Recently, Maillard and Walton have shown by ^{11}B NMR, ^{1}H NMR, and IR spectroscopy that triethylborane does complex methyl vinyl ketone, acrolein, and 3-methylbut-3-en-2-one. They proposed that the reaction of triethylborane with these traps involves complexation of the trap by the Lewis acidic borane prior to conjugate addition (Scheme 11).[172]

Scheme 10. Brown Mechanism for the Conjugate Addition of Organoboranes to Methyl Vinyl Ketone

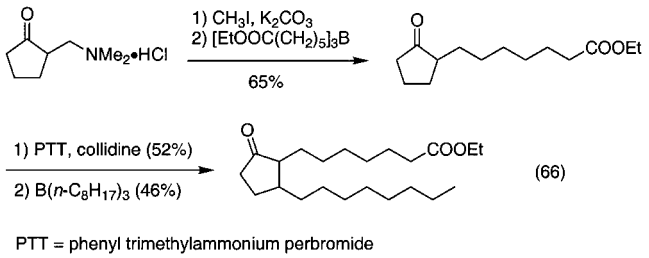


Scheme 11. Maillard−Walton Mechanism for the Conjugate Addition of Et$_3$B to Methyl Vinyl Ketone

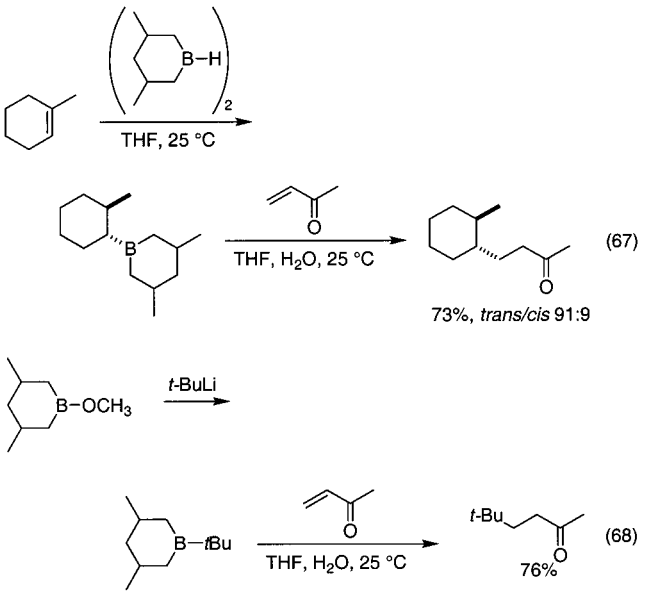


The reaction between trialkylboranes and enones has not found many synthetic applications. An exception is the preparation of prostaglandin precursors from *exo*-methylene cyclopentanone, generated in situ from a Mannich base. After dehydrogenation, a second conjugate addition of trioctylborane was used to introduce the ω-chain (eq 66).[173]

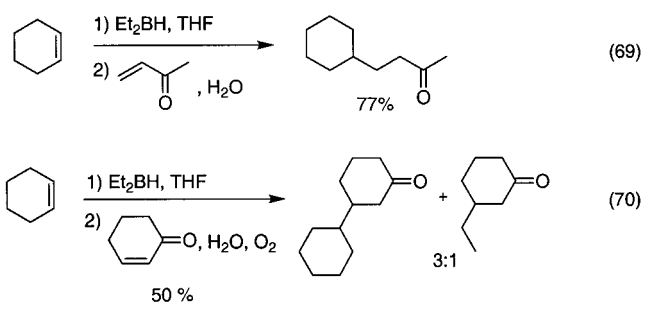
Synthetically, a serious drawback of the trialkylborane approach is that it requires a 1:1 trialkylborane/radical trap ratio to obtain good yields. Therefore, the method is restricted to trialkylboranes obtained by hydroboration of easily available and



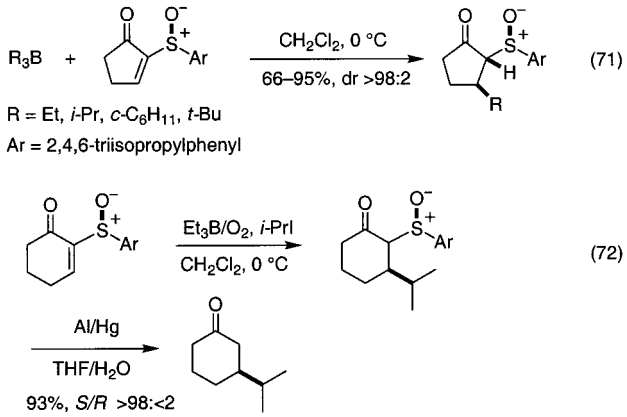
cheap alkenes. To overcome this limitation *B*-alkylboracyclanes have been used.[174,175] According to Brown and Negishi and co-workers, 3,3-dimethylborinane, prepared from BH_3 and 2,4-dimethyl-1,4-pentadiene, is the most efficient reagent. With this system, a selective cleavage of the boron−alkyl bond is possible for secondary and tertiary alkyl groups (eqs 67 and 68). This method, referred to later as the Brown−Negishi reaction, is not suitable for primary alkyl radicals (yield <35%) and for radical traps substituted at the β-position. With these traps, the addition of extra oxygen is necessary to run the chain reaction, and under these conditions the cleavage of the carbon−boron bond is no longer selective.



Recently, we have shown that similar results are obtained with cyclohexyldiethylborane, (easily prepared from Et_2BH and cyclohexene). The efficient addition to methyl vinyl ketone is possible (eq 69). However, when cyclohexenone is used as radical trap, addition of oxygen is necessary and a 3:1 mixture of products resulting from the addition of cyclohexyl and ethyl radicals is obtained (eq 70).[176]



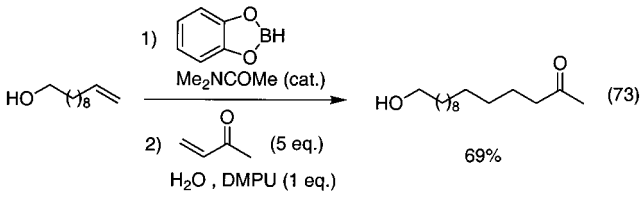
Toru and co-workers have investigated the stereoselectivity of the conjugate addition of trialkylboranes to 2-arylsulfinylcyclopentenones. Excellent stereocontrol is achieved with different alkyl radicals (eq 71). Related reactions in six-membered rings are also reported. Interestingly, the use of Et_3B together with an excess of secondary and tertiary alkyl iodides allows the transfer of different alkyl groups due to an initial iodine atom-transfer process (eq 72).[177−180] In the acyclic series, the lack of diastereoselectivity in the addition step and a competitive Pummerer rearrangement has limited the synthetic potential of this reaction.[181]



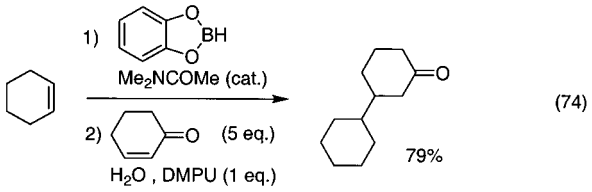
4.1.1.2. From *B*-Alkylcatecholboranes. To circumvent the lack of selectivity in the cleavage of trialkylboranes, *B*-alkylcatecholboranes can be used as precursors of alkyl radicals. As previously discussed (Scheme 3), *B*-alkylcatecholboranes are very reactive toward alkoxyl radicals and also triplet oxygen. A modified version of the Brown−Negishi reaction using *B*-alkylcatecholboranes was recently reported by us. This novel method is based on a simple one-pot procedure involving the hydroboration of various substituted alkenes with catecholborane, followed by treatment with catalytic amount of oxygen/DMPU/water and a radical trap. Efficient radical additions to α,β-unsaturated ketones and aldehydes have been reported. Primary alkyl radicals are efficiently generated by this procedure, and the reaction has been applied to a 300 mmol scale synthesis of the γ-side chain of (−)-perturasinic acid (eq 73).[182] The reaction was also applied to the radical addition to cyclohexenone (eq 74) and to other β-substituted enones and enals as well as to cyclization (eq 75) and annulation reactions.[176]

4.1.2. Other Activated Alkenes

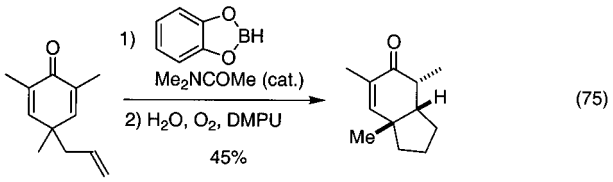
The above-described modification of the Brown−Negishi reaction is efficient with any type of mono-β-substituted enol or enal. However, other classical radical traps such as unsaturated esters, amides, and sulfones failed to react.[183] This failure is a consequence of an inefficient propagation step between the radical adducts and the *B*-alkylcatecholboranes, presumably due to the low-spin density at the oxygen atom. By using a chain-transfer reagent, which is able to convert a carbon-centered radical into an oxygen-centered radical, it is possible to extend the



(73)

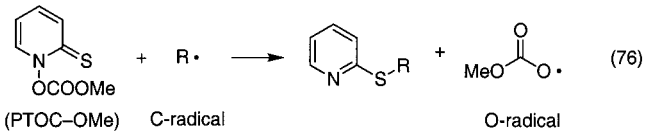


(74)



(75)

reaction to any type of radical trap. The Barton carbonate PTOC−OMe (PTOC = pyridine-2-thione-*N*-oxycarbonyl) proved to be a very efficient chain carrier (eq 76) as well as a good initiator for this type of radical reaction by irradiation with a standard 150-W tungsten lamp.[184]

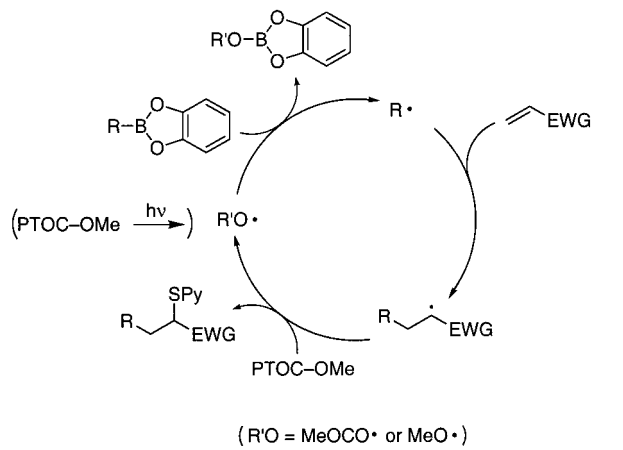


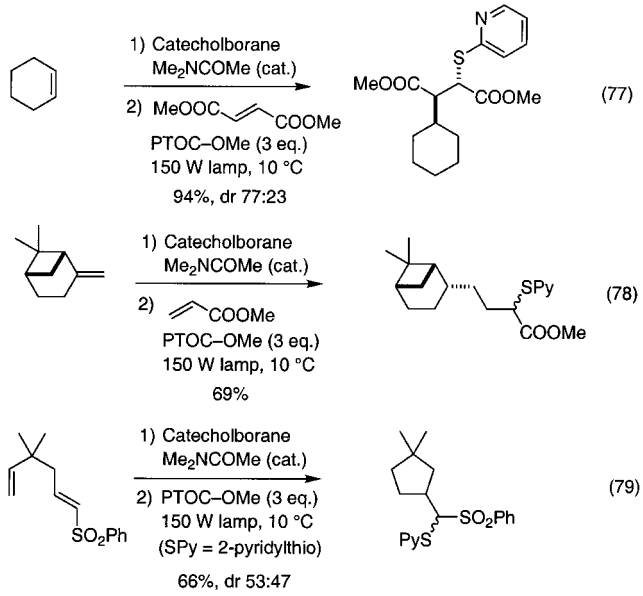
(76)

With this system, intermolecular radical additions can be performed in good yields in a one-pot procedure (eqs 77 and 78). In contrast to tin hydride-mediated reactions, no slow addition of the chain carrier (PTOC−OMe) is necessary. Moreover, the nonreductive nature of this method is the advantage of allowing further elaboration of the addition products. Cyclization reactions involving the regioselective hydroboration of dienes are also possible (eq 79).[184]

The mechanism of this reaction is depicted in Scheme 12 and nicely parallels the classical tin

Scheme 12. Modified Brown−Negishi Reaction[184]





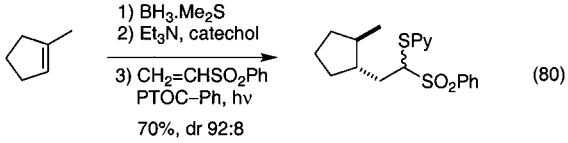
(77)

(78)

(79)

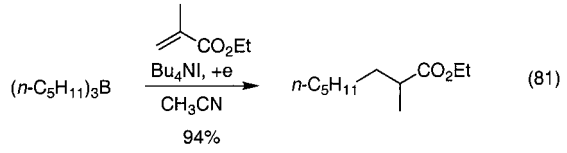
hydride-mediated conjugate addition (Giese reaction[11,185]): the abstraction of a halide by the stannyl radical is replaced by the homolytic substitution of an alkylborane by an alkoxyl radical. The three radicals involved in this chain reaction possess very different reactivities that allow an efficient fulfillment of the selectivity criteria formulated by Giese.

A related reaction using the Barton ester (PTOC−Ph) as a chain carrier has been developed independently by Dalko and co-workers (eq 80).[186]



(80)

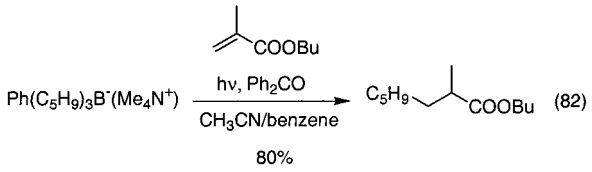
A different strategy to add radicals generated from organoboranes to unsaturated esters is based on the electrolysis of trialkylboranes. Indeed, it is known that electrooxidation of tricylohexylmethoxyborate gives radicals that can react with alkenes such as butadiene.[187] Dimerization of alkyl radicals generated from trialkylboranes/sodium methanolate is also described but is of limited synthetic utility.[188,189] The electrochemical alkylation of compounds containing an acidic hydrogen such as acetonitrile,[190] nitromethane,[191] and 1-alkynes[192] by trialkylboranes has also been reported and may involve radical intermediates. Interestingly, the electrochemical reduction of trialkylboranes in the presence of α,β-unsaturated esters produces the corresponding alkylated esters in good yields (eq 81).[193]



(81)

Alkyl radicals are also generated from trialkylarylborates upon irradiation in the presence of benzophenone and add to activated alkenes such as butyl

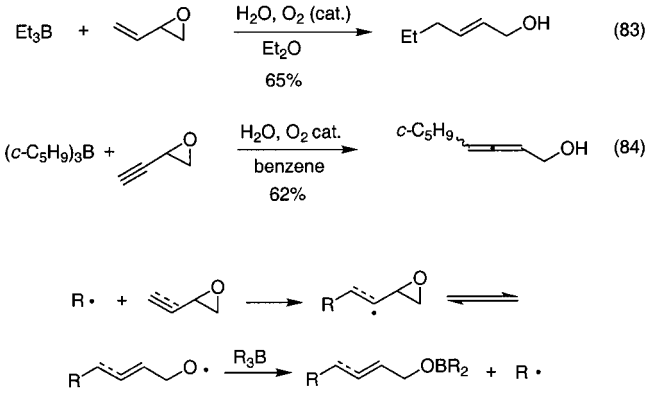
methacrylate. In this particular process, the three alkyl groups can be transferred to the radical trap (eq 82).[194]



4.2. Addition to Ethenyl- and Ethynyloxiranes

Brown and Suzuki and co-workers have shown that treatment of trialkylboranes with ethenyl- (eq 83) and ethynyloxiranes (eq 84) in the presence of a catalytic amount of oxygen affords the corresponding allylic or allenic alcohols. The mechanism may involve the addition of alkyl radicals to the unsaturated system leading to 1-(oxiranyl)alkyl and 1-(oxiranyl)-alkenyl radicals followed by rapid fragmentation to give alkoxyl radicals that finally complete the chain process by reacting with the trialkylborane (Scheme 13).[195−197]

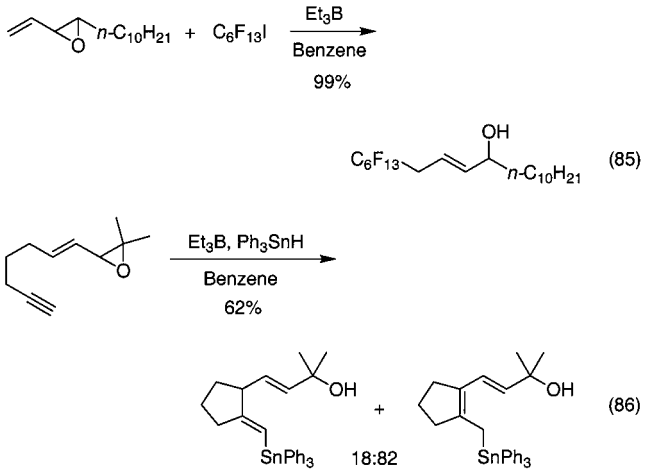
Scheme 13. Reaction of Trialkylboranes with Ethenyl- and Ethynyloxiranes



Addition of activated bromides such as CBr_4 and $BrCCl_3$ and iodides to alkenyl- and alkynyloxiranes in the presence of stoichiometric amounts of Et_3B and tin hydride are reported.[198] Since ethyl radicals are sufficiently reactive to abstract iodine atoms, perfluoroalkyl iodides react with ethenyloxiranes under tin-free conditions (eq 85). An example of cyclization fragmentation of a (hept-1-en-6-ynyl)oxirane is shown in eq 86.[198]

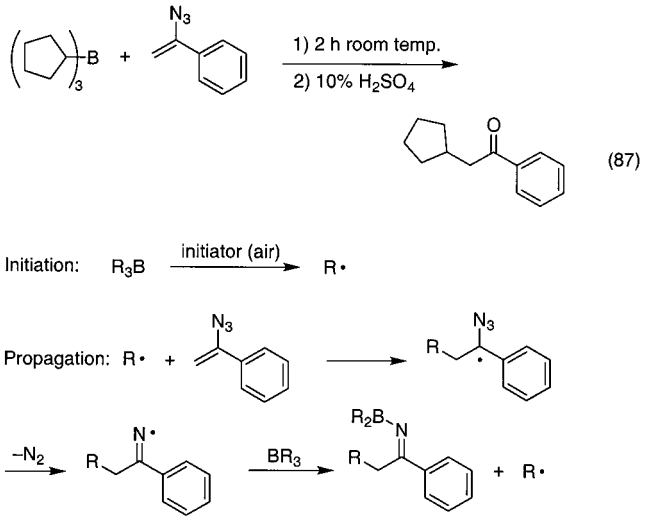
4.3. Addition to Azidoalkenes

In 1975, Suzuki et al. reported the reaction of trialkylboranes with α-azidostyrene to prepare alkyl aryl ketones (eq 87).[199] The reaction outcome was rationalized by formation of a Lewis acid−base complex followed by a concerted 1,4-alkyl group migration and elimination of a nitrogen molecule leading to an iminoborane. A few years later, this mechanism was corrected by Roberts and co-workers, who showed, based on experimental data and ESR spectroscopy, that radicals were involved.[200] The formation of the iminoborane results from radical addition to the alkenyl azide followed by nitrogen



elimination and reaction of the iminyl radical with the trialkylborane (Scheme 14).

Scheme 14. Radical Addition to α-Azidostyrene

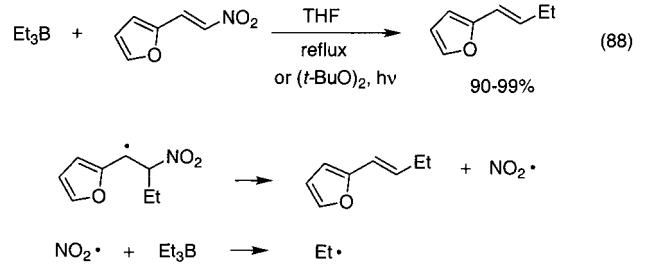


4.4. Alkenylation and Arylation Reactions

4.4.1. Addition–Elimination to Nitroalkenes and Nitroarenes

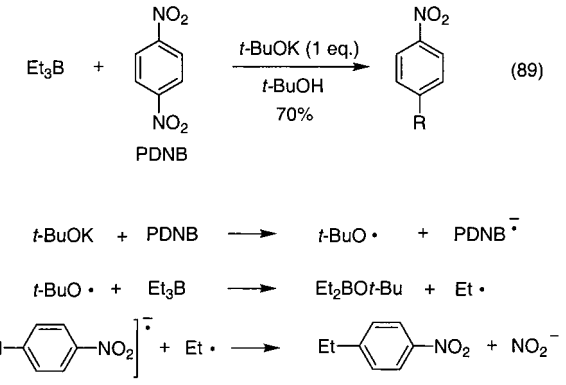
The free-radical substitution of β-nitrostyrene (2-nitroethenylbenzene) by trialkylboranes has been reported to involve a radical addition to the β-position (α- to the nitro group) followed by fragmentation of NO_2• that can react with Et_3B in a chain process (Scheme 15). The reaction is *E* selective and works with a broad range of trialkylboranes allowing the introduction of tertiary, secondary, and allylic carbon moieties (eq 88).[201]

Scheme 15. Radical Substitution of (2-Nitrovinyl)arenes with Et_3B



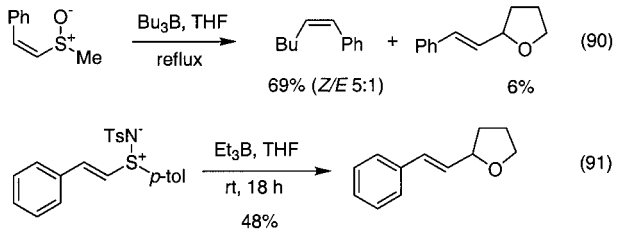
Recently, the aromatic ipso-substitution of one nitro group of *p*-dinitrobenzene (PDNB) with Et_3B in the presence of potassium *tert*-butyl alcoholate was reported (eq 89). The reaction proceeds by the $S_{RN}1$ mechanism shown in Scheme 16. A *tert*-butoxyl radical is generated via an electron transfer between PDNB and *t*-BuOK; this radical reacts with Et_3B to deliver an ethyl radical suitable for the substitution reaction.[202]

Scheme 16. Aromatic *ipso*-Substitution of a Nitro Group



4.4.2. Addition–Elimination to Styryl Sulfones, Sulfoxides, and Sulfinimides

Nozaki and co-workers reported the reaction of trialkylboranes with styryl sulfoxides and sulfones. Alkyl radicals generated from trialkylboranes add at the β-position of β-styryl sulfoxides and sulfones (α-to the sulfur atom). The resulting radicals fragment and deliver the β-styryl adducts.[203] Interestingly, the sulfoxides eliminate very rapidly leading to partially stereospecific substitution (eq 90). The radical nature of the process is demonstrated by the presence of a side product derived from the solvent (THF) by hydrogen atom abstraction. Unsaturated sulfinimides react similarly, and the THF adduct is the major product of the reaction (eq 91).[204]



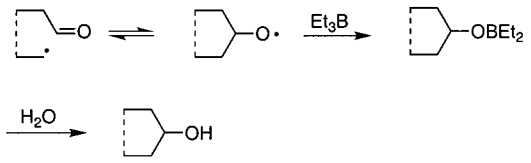
4.5. Et_3B-Mediated Addition to Aldehydes and Ketones

4.5.1. Direct Addition

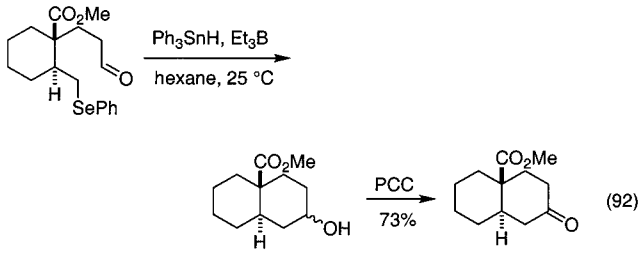
Addition of alkyl radicals to carbonyl functions are reversible and usually endothermic or nearly thermoneutral; therefore, they are difficult to achieve under classical conditions.[11] However, trapping the intermediate alkoxyl radical in an irreversible manner with Et_3B allows the equilibrium to be displaced toward the addition product (Scheme 17).

The concept was first reported by Clive, who prepared a trans ring-fused bicyclic system from a

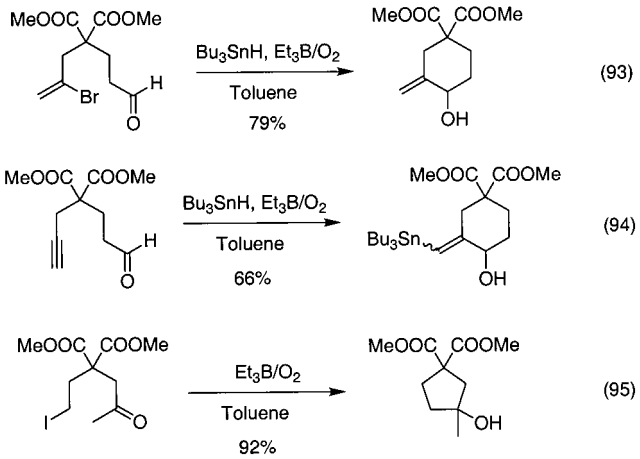
Scheme 17. Equilibrium Displacement during the Radical Addition to Ketones and Aldehydes in the Presence of Et_3B



6-phenylselenoaldehyde upon treatment with Ph_3SnH in the presence of an excess of Et_3B (eq 92). Under Ph_3SnH/AIBN conditions, the alcohol is isolated in low yield together with monocyclic side-products resulting from β-scission of the cyclohexyloxyl radical intermediate.[205]

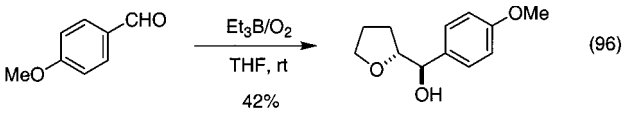


Recently, Malacria and co-workers have reported an efficient method for the preparation of versatile α-methylenecycloakanols units based on the intramolecular addition of vinyl radicals to carbonyl compounds. Treatment of vinyl bromides[206] or terminal alkynes[207] with tin hydride and excess Et_3B provide vinyl radical intermediates that undergo addition to the aldehyde moiety and furnish the α-methylenecycloalkanols (eqs 93−95). When iodides are used as radical precursors, the liberated ethyl radical is able to carry on the chain, and the use of tin hydride is not necessary (eq 95).[208]



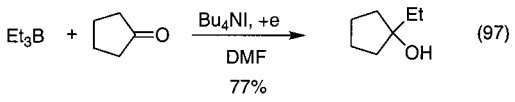
The intermolecular reaction of trialkylboranes with formaldehyde initiated by molecular oxygen has been known for a long time.[209] More recently, it was shown that the reaction of Et_3B with aromatic aldehydes in THF leads to (aryl)(tetrahydrofuran-2-yl)methanol in good diastereomeric excess (eq 96). Such units are present in biologically active acetogenins polyketides. The key tetrahydrofuran-2-yl radical is generated

from the initial ethyl radical by a hydrogen atom abstraction.[210]



(96)

The electrochemical addition of trialkylboranes to carbonyl compounds under similar conditions with platinum cathode and copper anode was recently reported (eq 97).[211] The corresponding alcohols are produced in good yields, but the involvement of radicals in the mechanism has not been proven.

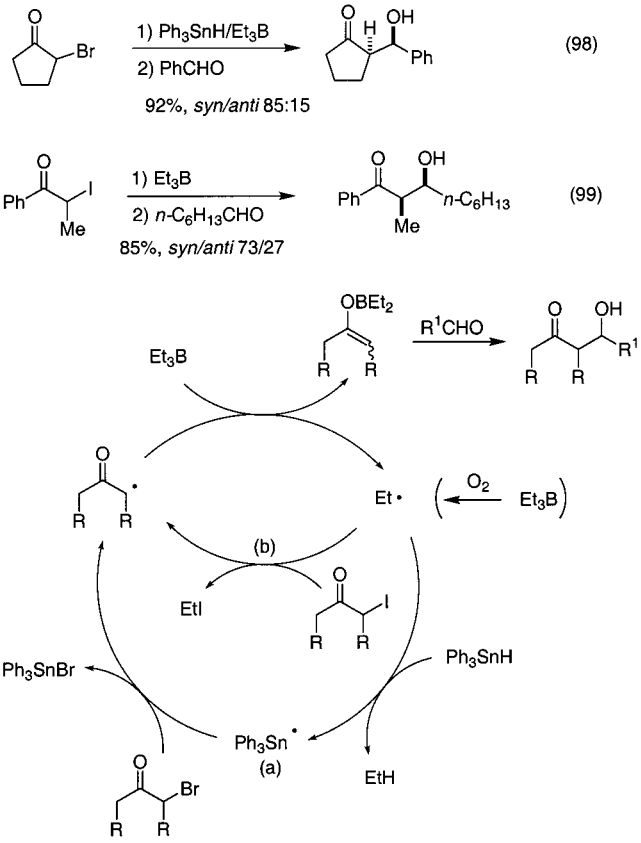


(97)

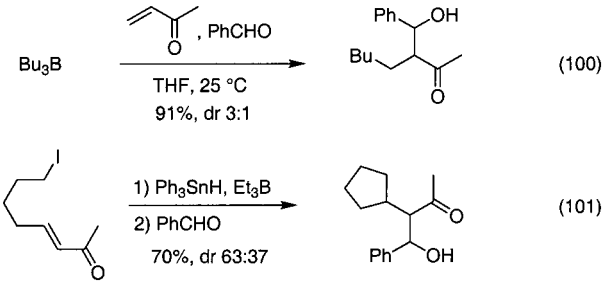
4.5.2. Via Boron Enolates (Aldol Reactions)

Boron enolates prepared from α-carbonyl radicals and triethylborane can be used for aldol-type chemistry.[212,213] For instance, the Et_3B/Ph_3SnH-mediated Reformatsky-type reaction of α-bromoketones with aldehydes and ketones affords β-hydroxyketones in good yields (eq 98). α-Iodoketones react similarly, but the use of tin hydride is not necessary (eq 99). In both reactions, Et_3B works as a radical initiator as well as a chain-transfer reagent by reacting with the enolate radical (Scheme 18). The bromine atom abstraction requires a stannyl radical (pathway a) while iodine abstraction is efficiently achieved by the ethyl radical (pathway b).[212−215]

Scheme 18. Radical Generation of Enolates from 2-Bromoketones (a) and 2-Iodoketones (b)



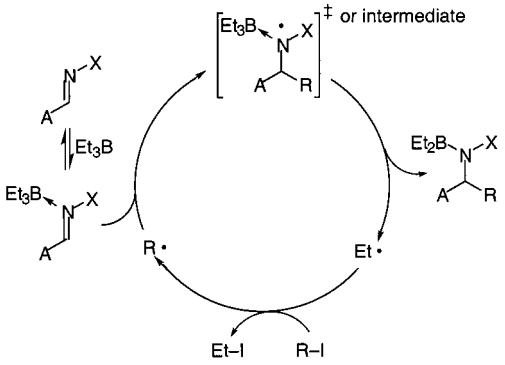
As previously shown (section 4.1.1.1, Schemes 10 and 11), boron enolates are generated during the conjugate addition to enones. The boron enolate prepared by addition of tri-*n*-butylborane to methyl vinyl ketone reacts with benzaldehyde to give the β-hydroxyketone (eq 100).[170] The addition of alkyl radicals, generated from Et_3B and secondary or tertiary alkyl iodides as well as diiodides or perfluoroalkyl iodides, to enones provides another route to boron enolates suitable for subsequent aldol reactions. Even primary alkyl iodides can give such reactions when triphenyltin hydride is added to the reaction mixture (eq 101).[212,213]



4.6. Addition to Imines and Related Compounds

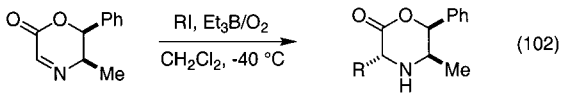
Intramolecular radical addition to imines, hydrazones, and oxime ethers can be run under classical tin hydride/AIBN conditions.[216] More recently, it has been demonstrated that intermolecular reactions are efficiently carried out with triethylborane under tin-free conditions according to the mechanism depicted in Scheme 19. Complexation of the nitrogen atom to

Scheme 19. Mechanism of the Et_3B-Mediated Radical Addition to Imines and Related Compounds (R = *sec*- or *tert*-alkyl; A = Aryl, COOR, $CONR_2$; X = Alkyl, NR_2, OR)



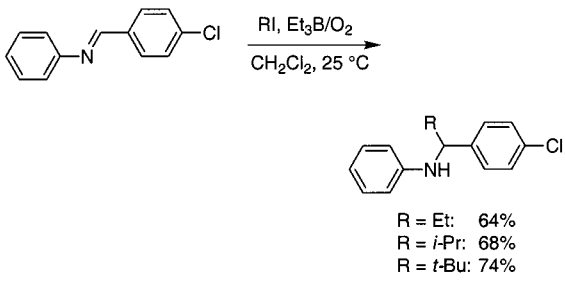
Et_3B favors the radical addition and facilitates the chain-transfer process.[217]

Bertrand has applied this reaction to the alkylation of chiral glyoxylate imines. Excellent stereoselectivities are obtained in cyclic systems under Et_3B/O_2 initiation (eq 102).[217,218]



(102)

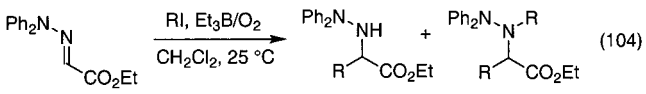
The crucial role of Et_3B has been demonstrated by the reaction with imines derived from aniline and *p*-chlorobenzaldehyde. Under standard tin hydride/AIBN conditions, no reaction takes place. When Et_3B is used, satisfactory yields are obtained at room temperature (eq 103).[83]



(103)

R = Et: 64%
R = *i*-Pr: 68%
R = *t*-Bu: 74%

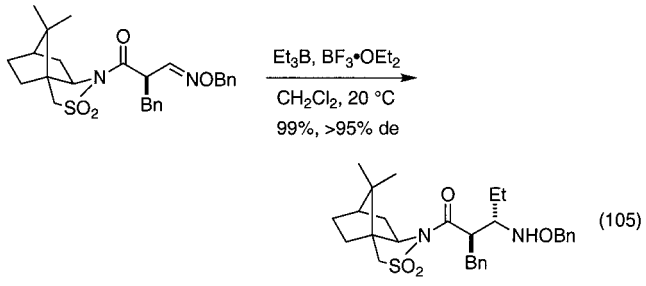
Naito and co-workers have shown that unactivated hydrazones do not react with alkyl iodides in the presence of Et_3B. However, addition of ethyl iodide to hydrazones derived from glyoxylic acid furnish the expected hydrazines in moderate yield accompanied with the N-ethylation product (eq 104).[219] As expected, no N-alkylation is observed when Et_3B is used as unique source of ethyl radicals and when secondary or tertiary alkyl iodides are added.[83]



(104)

EtI, Et_3B/O_2	41%	43%	[219]
Et_3B/O_2	89%	-	[83]
i-PrI, Et_3B/O_2	68%	-	[83]
t-BuI, Et_3B/O_2	82%	-	[83]

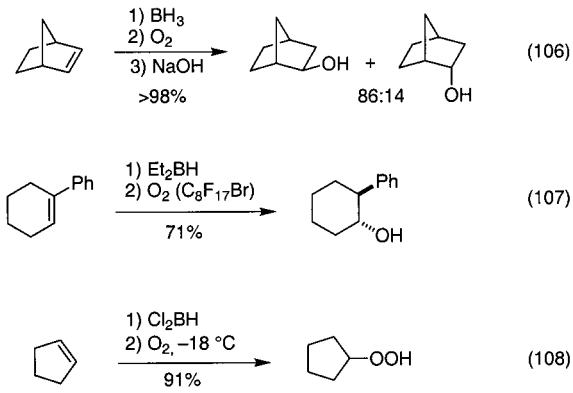
Intra- or intermolecular radical additions to oxime ethers have been reported by Naito and co-workers under tin and tin-free conditions.[219−224] Interestingly, Et_3B-mediated radical additions to polymer-supported oxime ethers are described and offer novel perspectives in parallel synthesis.[84,225,226] Reactions with the camphor sultam derived from glyoxylic acid are highly stereoselective.[227] Unactivated oxime ethers are also good substrates for stereoselective reactions. An elegant application for the preparation of enantiomerically pure α,*β*-dialkyl-*β*-amino acids is depicted in eq 105. The stereochemical outcome is best explained by a model based on minimization of allylic 1,3-strain.[228] Tandem radical addition−cyclization reactions were recently performed for the asymmetric synthesis of *γ*-butyrolactones and *β*-amino acids.[229]



(105)

4.7. Hydroxylation and Related Reactions

The mechanistic aspects of the oxidation of trialkylboranes with oxygen have been discussed under section 2.1. Trialkylboranes, easily prepared via hydroboration of alkenes, are efficiently converted into alcohols in nearly quantitative yields (eq 106).[49,50] More recently, Klement and Knochel have reported that the direct oxidation of organoboranes with oxygen in perfluoroalkanes affords the corresponding alcohols with retention of configuration.[230] This stereochemical outcome is rationalized by an oxygen insertion mechanism rather than by a radical chain mechanism (eq 107). Dalko and Cossy and co-workers have reported the hydroxylation of alkylboronic esters in the presence of Et_3N and molecular oxygen. The parallel polar and radical mechanisms were probed by a radical clock experiment.[231] Reactions of trialkylboranes with oxygen have also been used for the preparation of alkylhydroperoxides. Their formation is favored at low temperature in the presence of a controlled quantity of oxygen (2 mol of O_2/R_3B).[51,232,233] However, only two of the three alkyl groups are converted into hydroperoxides. This limitation can be overcome by using alkyldichloroborane etherates, which undergo clean autoxidation at −18 °C to give primary and secondary hydroperoxides in high yields (eq 108).[52]



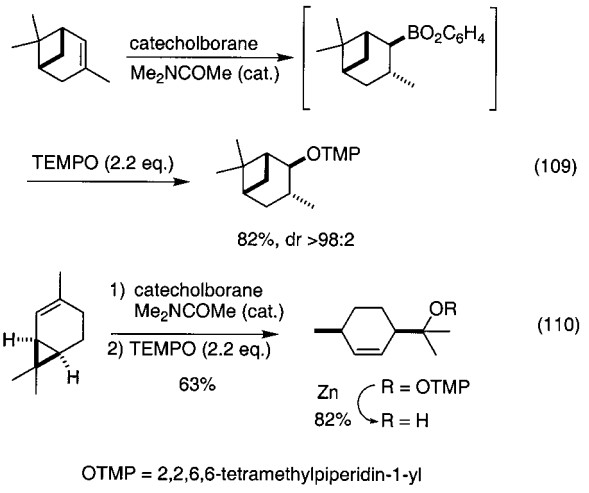
(106)

(107)

(108)

Recently, we have shown that *B*-alkylcatecholboranes react efficiently with TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) to afford the corresponding alkoxyamines that can easily be reduced to alcohols.[234] For instance, hydroboration of α-pinene with catecholborane followed by reaction with TEMPO gives the alkoxyamine in excellent yield and stereoselectivity (eq 109). Two equivalents of TEMPO are necessary to carry out the reaction: the first equivalent is consumed for the generation of alkyl radicals by homolytic substitution with the catecholborane, and the second equivalent traps the intermediate alkyl radical. The process is not a chain reaction. In another example, the hydroboration of (+)-2-carene followed by treatment with TEMPO afforded the ring-opening product (eq 110).

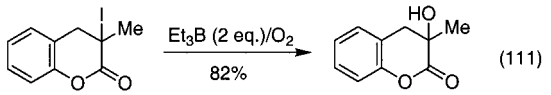
Indirect radical generation from alkyl iodides is also possible. For instance, treatment of α-iodocarboxylic acid derivatives with 2 equiv of triethylborane under an atmosphere of oxygen gives the corresponding α-hydroxyacid derivatives.[235] This method is based on an iodine atom transfer from the ethyl radical, generated by the reaction of triethylborane and oxygen, with the α-iodocarbonyl compound. This oxygenation procedure offers several



(109)

(110)

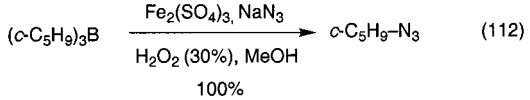
advantages over classical ionic substitution reactions: no elimination product is observed, tertiary iodides are efficiently converted to alcohols (see eq 111), and finally, this one step procedure works with substrates sensitive to nucleophiles.



(111)

4.8. Azidation

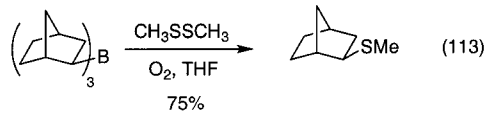
A unique azidation process of organoboranes species with iron(III) azide in the presence of hydrogen peroxide was reported by Suzuki et al. In a one-pot procedure, alkenes are converted into anti-Markovnikov azides via hydroboration and treatment with NaN_3, iron(III) sulfate, and hydrogen peroxide (eq 112).[236] The main drawback of this approach is that only one out of the three alkyl groups at boron is converted into the corresponding azide.[237] The mechanism proposed by the authors involves the very hypothetical reaction of azido radicals at sp^3 carbon in the trialkylborane. Other mechanisms are more plausible. For instance, the reaction of trialkylboranes with hydroxyl radicals can generate alkyl radicals. Subsequent oxidation of these transient species to carbocations that react with azide anions could close the reaction sequence. This could explain why primary azides are formed in much lower yields than secondary azides.



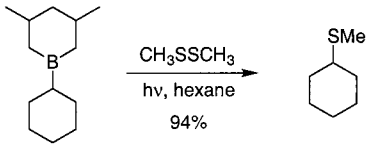
(112)

4.9. Sulfurization

Homolytic substitution at boron by thiyl radicals was discovered by Davies and Roberts[72] and used by Brown and Midland to convert trialkylboranes into thioethers.[238] Phenyl and methyl disulfides react slowly with trialkylboranes at room temperature. The reaction is much faster under sun lamp irradiation or in the presence of oxygen and is a convenient method for converting alkenes into thioethers (eq 113). The nonsymmetrical *B*-alkyl-3,5-dimethylboranes react with dimethyl disulfide under irradiation with excellent chemoselectivity since only cleavage of the boron−*sec*-carbon bond is observed (eq 114).

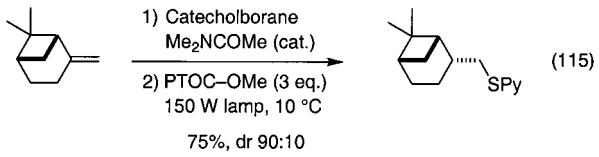


(113)



(114)

On the other hand, *B*-alkylcatecholboranes can be easily converted into the corresponding thiopyridyl adducts in high yield by treatment with the Barton carbonate PTOC−OMe[184] (eq 115) or PTOC−Ph[186] under irradiation. A mechanism similar to the one discussed under section 4.1.2 is operating.



(115)

4.10. Halogenation

Nonstabilized alkyl radicals generated from organoboranes, such as the ethyl radical, are efficiently iodinated by reactive iodides. This is the key step of the iodine atom-transfer reaction described in section 3.2.1 (see the mechanism in Scheme 9) but is only rarely used for the preparative iodination of organoboranes (see eq 36 for an exception).

The reaction of copper(II) salts with organoboranes is well-documented. Treatment of benzeneboronic acid in refluxing water with cupric chloride or bromide gives chlorobenzene and bromobenzene, respectively. [239] Similar results are obtained with 2-furanboronic acid,[240] ferroceneboronic acid,[241] and triphenylboroxine.[242] This reaction is also suitable for the preparation of alkyl halides from trialkylboranes and copper(II) salts (2 equiv per alkyl group).[243] The formation of alkyl radicals by electron-transfer oxidation of trialkylboranes is the key step of this process. The radicals then react with a second equivalent of copper(II) halide to give the corresponding alkyl halides. Two possible mechanisms involving an "inner-sphere" or an "outer-sphere" activated complex with participation of water are suggested.[244]

Related examples of reactions between trialkylboranes and iron(III) chloride have been reported. Good yields of alkyl chlorides are obtained. In contrast to the above-mentioned copper(II) method, the three alkyl groups of trialkylboranes are converted to the chloride.[156]

5. Conclusions

The tremendous development of the use of radicals in organic synthesis has led to a revival of radical organoborane chemistry. The basic principles of this

chemistry, mainly discovered during the 1960s and the 1970s, have allowed the development of novel and innovative processes. Some of these applications, such as the use of triethylborane as initiator for radical chain reactions, are now part of the classical arsenal of organic chemists. Very attractive tin-free processes for the formation of carbon−carbon and carbon−heteroatom bonds take advantage of the particular reactivity of organoboranes. Further developments in asymmetric radical reactions based on the well-documented diastereo- and enantioselective hydroboration are expected as well as applications of these novel radical reactions to more complex processes such as cascade reactions.

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