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Radical Chain Reduction of Alkylboron Compounds with Catechols

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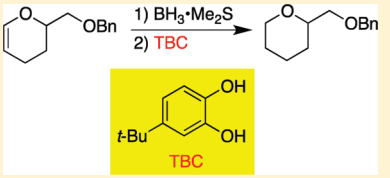
Supporting Information

ABSTRACT: The conversion of alkylboranes to the corresponding alkanes is classically performed via protonolysis of alkylboranes. This simple reaction requires the use of severe reaction conditions, that is, treatment with a carboxylic acid at high temperature (>150 °C). We report here a mild radical procedure for the transformation of organoboranes to alkanes. 4-*tert*-Butylcatechol, a well-established radical inhibitor and antioxidant, is acting as a source of hydrogen atoms. An efficient chain reaction is observed due to the exceptional reactivity of phenoxyl radicals toward alkylboranes. The reaction has been applied to a wide range of organoboron derivatives such as *B*-alkylcatecholboranes, trialkylboranes, pinacolboronates, and alkylboronic acids. Furthermore, the so far elusive rate constants for the hydrogen transfer between secondary alkyl radical and catechol derivatives have been experimentally determined. Interestingly, they are less than 1 order of magnitude slower than that of tin hydride at 80 °C, making catechols particularly attractive for a wide range of transformations involving C−C bond formation.



INTRODUCTION

The reduction of alkenes to alkanes has attracted the interest of synthetic chemists for decades, and many efficient methods have been developed. However, in the field of natural product synthesis, the issue of functional group tolerance, stereochemical control, and chemoselectivity may render this simple process problematic. In some cases, double bonds have to be reduced via a hydroboration-reduction process. The usual sequence to achieve this transformation is the conversion of the intermediate organoboron species to an alcohol followed by a multistep deoxygenation process.[1] Despite the rich panel of transformations available from organoboron compounds, their simple reduction remains challenging. Except for two reports where two alkyl−boron bonds of a trialkylborane are protonolyzed in refluxing water,[2,3] the transformation of a C(sp^3)−B bond into a C−H bond generally requires assistance. The best-studied protonolysis of trialkylboranes by carboxylic acids[2] is efficient at room temperature for the first alkyl group, but, due to the lower acidity of the newly formed borinic ester, further reactivity requires prolonged stirring or heating. The protonolysis of the third group occurs only with propionic acid in refluxing diglyme.[4] Mineral acids can also form a complex with a trialkylborane and subsequently transfer a proton to the carbon atom. Nevertheless, except with anhydrous HF (in a bomb), the reaction stops after the first alkyl displacement.[5] Basic protonolysis is even less efficient, and forcing conditions or stabilization of the negative charge are required.[6] The hydrogenation of a B−C bond takes place at high temperatures (≥150 °C) and high pressures of hydrogen (≥200 bar) and delivers mixtures of products.[7] First reported by Gilman and Nelson in 1937, the reduction of trialkylboranes by thiols involves radicals and occurs under particularly mild conditions.[8] Extensive studies by Mikhailov and Bubnov have demonstrated that a long chain radical process initiated by traces of oxygen takes place.[9] The mechanism relies on a fast homolytic substitution (S_H2) of an alkyl group of the trialkylborane by the thiyl radical.[10] However, this process is limited to the reduction of one out of the three alkyl groups of trialkylboranes. Herein, we report an extensive study of the radical reaction of organoboranes with 4-*tert*-butylcatechol (TBC). The reduction of different classes of organoboron compounds has been investigated. The unexpected reactivity of aryloxyl radical toward organoboranes is the key factor for the large scope of this reaction.

Trialkylboranes are known to undergo bimolecular homolytic substitutions (S_H2) where the attack of a heteroatom centered radical onto the boron liberates an alkyl radical. This behavior has led to many applications, and organoboranes are commonly found as initiators, chain transfer reagents, or substrates.[11] Due to the delocalization of the lone pair of the heteroatom into the empty orbital of boron, the lower Lewis acidity of borinic and boronic esters drastically lowers their tendency to undergo S_H2; thus, generally only one out of the three alkyl groups of a trialkylborane can be used for synthetic purposes. Recently, we have shown that reactive *B*-alkylcatecholboranes are very efficient for a wide range of radical reactions.[12] Since these organoboron derivatives are sensitive to oxygen and moisture, they are best prepared *in situ* by hydroboration with an excess of catecholborane. Intriguingly, we observed that when this excess was solvolyzed with methanol, reduction of the radical intermediate was observed as a side-reaction in allylation processes.[13,14] Taking advantage of this observation, we reported a protocol for the reduction of alkenes to alkanes via hydroboration with catecholborane followed by treatment of the intermediate alkylboronate with methanol in the presence of a radical initiator.[15] Based on preliminary mechanistic observations, the Lewis acid/base complex **A** (Scheme 1) formed between

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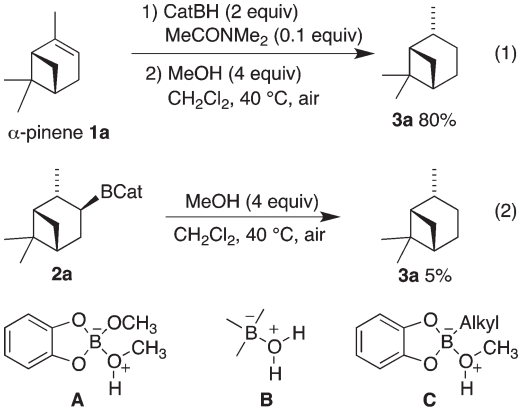
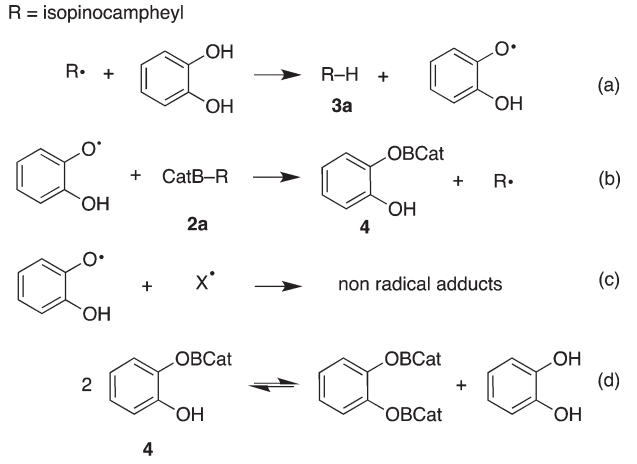
Scheme 1. Methanol Mediated Reduction of α-Pinene,[15] Postulated Complexes

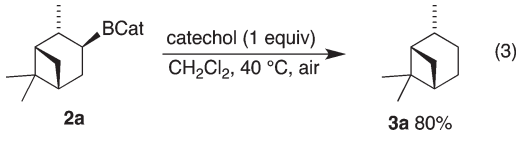


Scheme 2. Mechanism for the Reduction of *B*-Isopinocampheylcatecholborane 2a[17]



2-methoxybenzo[*d*][1,3,2]dioxaborole (MeOBCat, generated in situ from methanol and the excess of catecholborane) and methanol was proposed as the reducing species. This hypothesis was also supported by the work of Wood et al. showing that a related trimethylborane/water complex (Scheme 1, complex **B**) was acting as a reducing species in a Barton−McCombie deoxygenation process.[16]

Since the oxygen lone pair donating effect makes boric ester derivatives less Lewis acidic than their boronic ester counterparts, the methanol complex of MeOBCat (Scheme 1, complex **A**) is expected to be weaker than that of *B*-2-alkylbenzo[*d*][1,3,2]dioxaborole (RBCat, Scheme 1, complex **C**), thus forecasting for the latter a better hydrogen atom donor ability. Although the reduction of a series of olefins was successful (e.g., α-pinene in Scheme 1, eq 1), almost no reduced product was formed when treating distilled *B*-isopinocampheylcatecholborane with methanol (Scheme 1, eq 2). This and unexpected kinetic results, where PrBCat/MeOH was shown to be a slower reducing environment than MeOBCat/MeOH, urged us to study the degree of complexation by methanol. ^{11}B NMR studies failed to bring any evidence for the formation of a complex for both PrBCat and MeOBCat. Instead, transesterification was shown to take place to a large extent for MeOBCat, leading to a significant amount of free catechol in solution, when PrBCat was relatively stable to methanolysis.[17] Moreover, when a solution of pure *B*-isopinocampheylcatecholborane was exposed to catechol and air, *cis*-pinane was now obtained in good yield (eq 3).



This result is particularly interesting, since it invalidates the initially proposed mechanism involving complex **A**, and it demonstrates that the chain process was propagated by what is generally seen as an antioxidant. Indeed, phenols have a low O−H bond dissociation energy (75−90 kcal/mol depending on the substitution of the ring) allowing facile hydrogen atom abstraction.[18] The stabilized aryloxyl radical generally disrupts the chain via recombination and disproportionation reactions.[19] As *B*-alkylcatecholboranes **2** are known to react even with persistent radicals such as TEMPO,[20] the S_H2 of the alkyl radical by the resulting aryloxyl/semiquinone radical was proposed to propagate the radical chain (Scheme 2, eq b). The efficiency of that reaction minimizes recombination and disproportionation reactions and allows a good chain process (Scheme 2, eq c). Meulenhoff's free acid (**4**) is also a potential reducing agent (vide infra). Due to its low solubility and tendency to equilibrate with catechol and boric ester derivatives (Scheme 2, eq d), its exact role was found difficult to study.

RESULTS AND DISCUSSION

Reduction of Organoboron Species. The reaction of *B*-isopinocampheylcatecholborane **2a** with catechol (eq 3) was run for mechanistic purpose.[17] This new protocol shows some very promising features that could lead to the development of a useful preparative process. The reaction involving the *B*-alkylcatecholborane **2b** obtained by hydroboration of 4-phenylmethylenecyclohexane **1b** was used for the optimization process (eq , Table 1). 4-*tert*-Butylcatechol (TBC) was preferred to catechol due to its better solubility, lower toxicity, and better reactivity (compare also entries 3 and 6).[21] The effects of the solvent and of the initiator were examined first. Dichloromethane, *tert*-butyl methyl ether, 1,2-dichloroethane, toluene, and benzene (entries 1−5) were tested. Best results were obtained with 1,2-dichloroethane (entry 3) and benzene (entry 5). Concerning the initiator, both di-*tert*-butyl hyponitrite (entry 3),[22] that thermally decomposed to *tert*-butoxyl radicals, and air (entry 7) gave nearly quantitative yields. Dibenzoyl peroxide was less efficient (entry 8). Reactions with di-*tert*-butyl hyponitrite allow a better control of the reaction parameters, and it was therefore used for the optimization process. Interestingly, when air was used to initiate the reaction, no autoxidation of the *B*-alkylcatecholboranes was observed and this mode of initiation was employed for the scope and limitation study (vide infra).[23]

The effect of concentration of the reaction mixture was examined next. Due to the competition between the S_H2 at boron and the recombination/disproportionation process, an optimum concentration was expected. The best concentration was found to be 0.3 M (Table 2, entries 1−4). The reaction with substoichiometric amounts of 4-*tert*-butylcatechol (entries 5−6)

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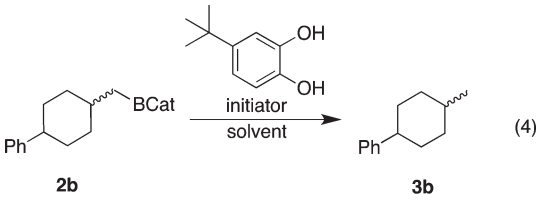
Table 1. Optimization of the Reaction Conditions for the Reduction of 2b with 4-*tert*-Butylcatechol According to Equation[a]



entry	solvent	temperature	initiator	yield (GC)
1	CH_2Cl_2	40 °C	*t*-BuON=NO*t*-Bu	74
2	*t*-BuOMe	55 °C	*t*-BuON=NO*t*-Bu	69
3[c]	$ClCH_2CH_2Cl$	83 °C	*t*-BuON=NO*t*-Bu	99 (87)[d]
4	toluene	80 °C	*t*-BuON=NO*t*-Bu	93
5	benzene	80 °C	*t*-BuON=NO*t*-Bu	89[d]
6[b]	$ClCH_2CH_2Cl$	83 °C	*t*-BuON=NO*t*-Bu	93
7	$ClCH_2CH_2Cl$	83 °C	air	99
8	$ClCH_2CH_2Cl$	83 °C	dibenzoyl peroxide	79

[a] General procedures: 1 equiv of *B*-alkylcatecholborane, 0.3 M, 1 equiv of 4-*tert*-butylcatechol. [b] 4-*tert*-butylcatechol replaced by 1 equiv of catechol. [c] 3 mol % initiator gave 70% GC-yield after 1 h, additional 3 mol % 95% after 2 h, and further 3 mol % quantitative GC-yield after 3 h. [d] Isolated yield.

Table 2. Optimization of the Concentration for the Reduction of 2b to 3b According to equation in 1,2-Dichloroethane and Di-*tert*-butyl Hyponitrite as an Initiator

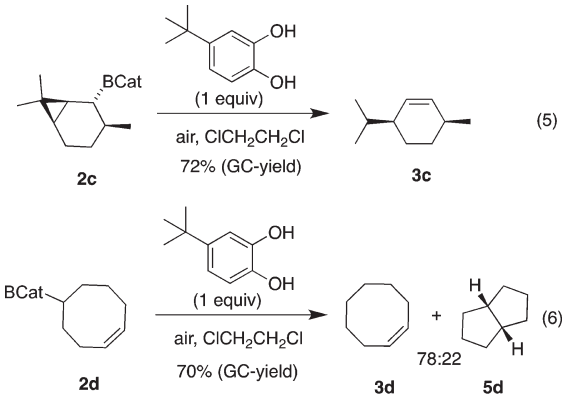
entry	TBC [equiv]	[**2b**]	temperature	GC-yield
1	1	0.1 M	80 °C	71
2	1	0.3 M	80 °C	>99
3	1	0.5 M	80 °C	90
4	1	1 M	80 °C	90
5	0.5	0.3 M	80 °C	80
6	0.8	0.3 M	80 °C	84
7[a]	1	0.3 M	23 °C	traces (3 h)

[a] Initiation with 50 mL of air for 1 mmol **2b**.

afforded good yields, indicating either that Meulenhoff's free acid is a source of hydrogen atoms in a chain process or that two molecules of Meulenhoff's free acid can equilibrate to give 4-*tert*-butylcatechol according to Scheme 2 (eq c). Finally, an attempt to run the reaction at room temperature (initiation with air) gave only 20% of the alkane **3b** after 48 h. Concerning the purification, a filtration through a short pad of neutral alumina was found to be enough to remove impurities derived from 4-*tert*-butylcatechol and boron derivatives yielding in most cases analytically pure products. For instance, under the optimized reaction conditions of entry 3, the reduced product **3b** was isolated in 87% yield.

The reduction of *B*-alkylcatecholboranes under our optimized conditions was examined next for two more systems that should illustrate the radical nature of the process (Scheme 3). In the first reaction (Scheme 3, eq 5), the boronate **2c** obtained by hydroboration of 2-carene afforded **3c** resulting from cyclopropane ring-opening, confirming the radical mechanism. When *B*-cyclooct-4-enylcatecholborane **1d** (eq 6) was subjected to the

Scheme 3. Reductive Radical Rearrangements of *B*-Alkylcatecholboranes



reaction conditions, a 78:22 mixture of cyclooctene **3d** and bicyclo[3.3.0]octane **5d** was formed in 70% yield (vide infra).

Based on the results obtained with the *B*-alkylcatecholborane **2b**, a one-pot sequence starting from alkenes involving hydroboration and reduction has been developed (Scheme 4). The reaction of cholesteryl benzoate **1e** was attempted first (eq 7). Hydroboration at room temperature using two equivalents of catecholborane and *N*,*N*-dimethylacetamide as a catalyst[24] afforded an intermediate organoborane that was directly treated with 4-*tert*-butylcatechol in the presence of air. This reaction afforded the reduced product **3e** in 93% isolated yield as a 5α/5β (9:1) mixture of diastereomers. The nonprotected cholesterol **1f** could also be reduced under similar conditions (eq 8). In this case, however, the hydroboration was performed with 3 equiv of catecholborane under neat conditions at 100 °C. The reaction afforded the alcohol *trans*-**3f** in 72% yield as a single diastereomer. Several attempts to perform a transition metal catalyzed hydroboration with Wilkinson's catalyst[25] led to poor recovery after filtration over aluminum oxide.[26] Indeed, Wilkinson catalyst/quinone complex have been reported to activate molecular oxygen.[27] The rapid change of color from clear to dark red after addition of 4-*tert*-butylcatechol may be a sign for the oxidation of the catechol derivative to the corresponding *o*-quinone. The latter would then act as an excellent radical trap leading to new catechol derivatives.[28] Screening some additives to poison the catalyst, 1,4-dithiane proved to efficiently prevent this side reaction. Nevertheless, on our model alkene **1b**, the new rhodium species drastically slows down the reaction and 46 h was required to obtain the reduced product **2b** in 73% GC-yield (eq 9). The reduction of alkene **1g** (eq 10) and **1h** (eq 11) demonstrates that the method is suitable for the reduction of double bonds in the presence of an aryl iodide and a nitroarene, respectively, two groups that are reduced with most methods used to hydrogenate double bonds.

Encouraged by the positive results obtained for the reduction of *B*-alkylcatecholboranes, the reduction of trialkylboranes was investigated next. So far, no mild method allows the conversion of the three alkyl groups into the corresponding alkane(s). However, based on mechanistic considerations, the complete reduction of trialkylboranes by catechol was anticipated. Indeed, when exposed to oxygen, trialkylboranes **6** generate alkyl radicals that are readily reduced by catechol (Scheme 5, eq a,b). The

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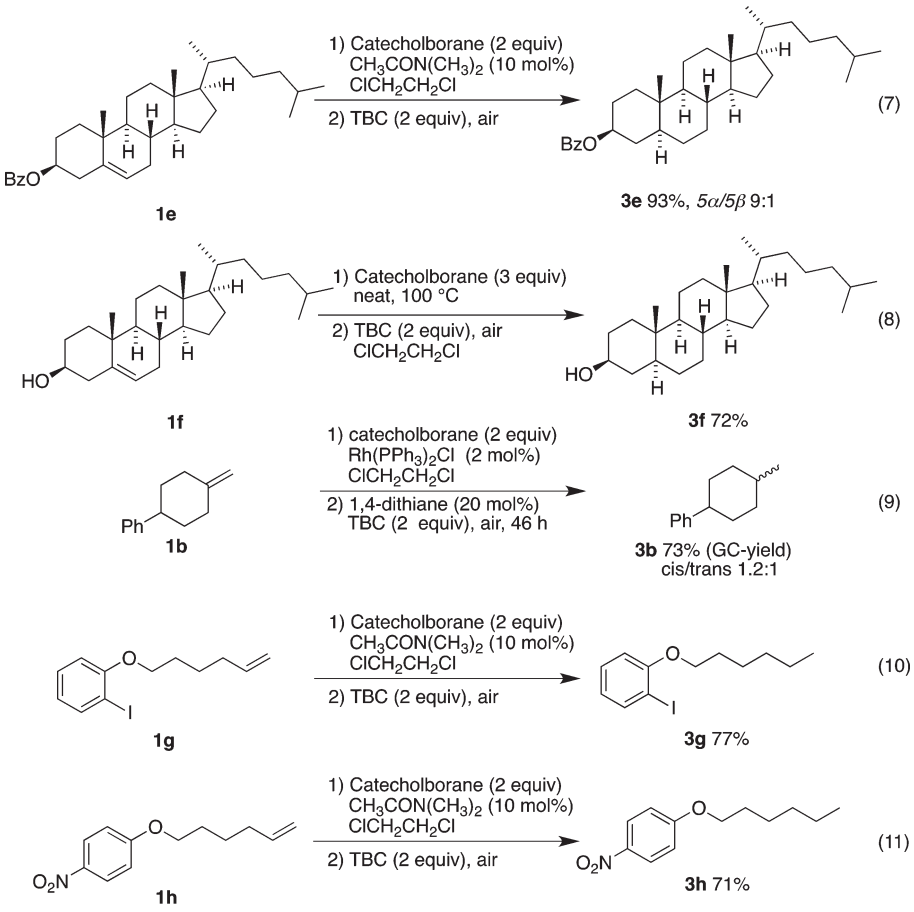
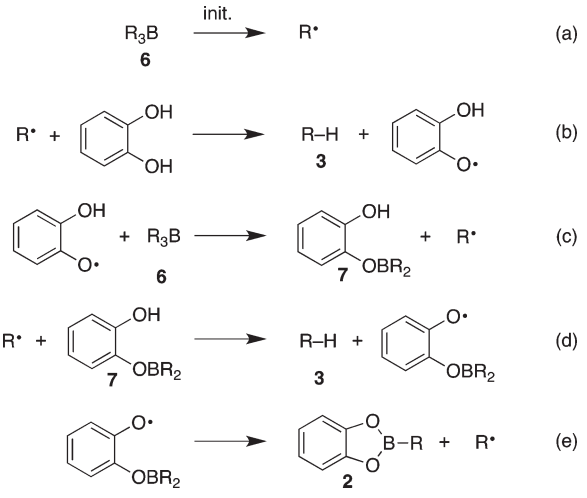
Scheme 4. One-Pot Reduction of Alkenes Using Catecholborane Mediated Hydroboration



homolytic substitution at the boron of an alkyl residue by the aryloxy radical should take place as previously proposed and afford borinic esters **7** (Scheme 5, eq c). These esters are also thought to be capable of hydrogen atom transfer to alkyl radicals or to the semiquinone radical (Scheme 5, eq d).[29] The resultant aryloxyl radicals could undergo intramolecular homolytic substitution to liberate a second alkyl radical and the *B*-alkylcatecholboranes **2** (Scheme 5, eq e) which are efficiently reduced as previously demonstrated (vide supra).[30] Following this mechanism, the three alkyl groups should be efficiently reduced. The deactivation due to the formation of less acidic borinic and boronic acid derivatives that is usually observed when trialkylboranes are used as radical precursors does not take place. Indeed, the second alkyl group is generated from borinic acid **7** via a favorable intramolecular homolytic substitution, and the third alkyl group is produced from the reactive *B*-alkylcatecholborane **2**.

A first trial with the isolated trialkylborane **6i** derived from β-pinene **1i** was run. Treatment of **6i** with three equivalents of 4-*tert*-butylcatechol afforded *cis*-pinane **3a** in 83% GC-yield (Scheme 6, eq 12). A one-pot process starting directly from the alkene was examined next. The reaction of **1b** with $BH_3 \cdot Me_2S$ followed by treatment with 4-*tert*-butylcatechol gave the reduced product **3b** in good isolated yield as a 1:1 mixture of diastereomers (eq 13). The use of a substoichiometric amount of initiator (3 × 3 mol %) demonstrates the effectiveness of the

Scheme 5. Hypothetic Mechanism for the Complete Conversion of Trialkylborane 5 to Alkane 3



chain process. Generally, the limitations of this two-step protocol were found to be similar to those of the classical hydroboration−oxidation sequence, with the main drawback being the difficulties to follow the formation and the disappearance of the reactive

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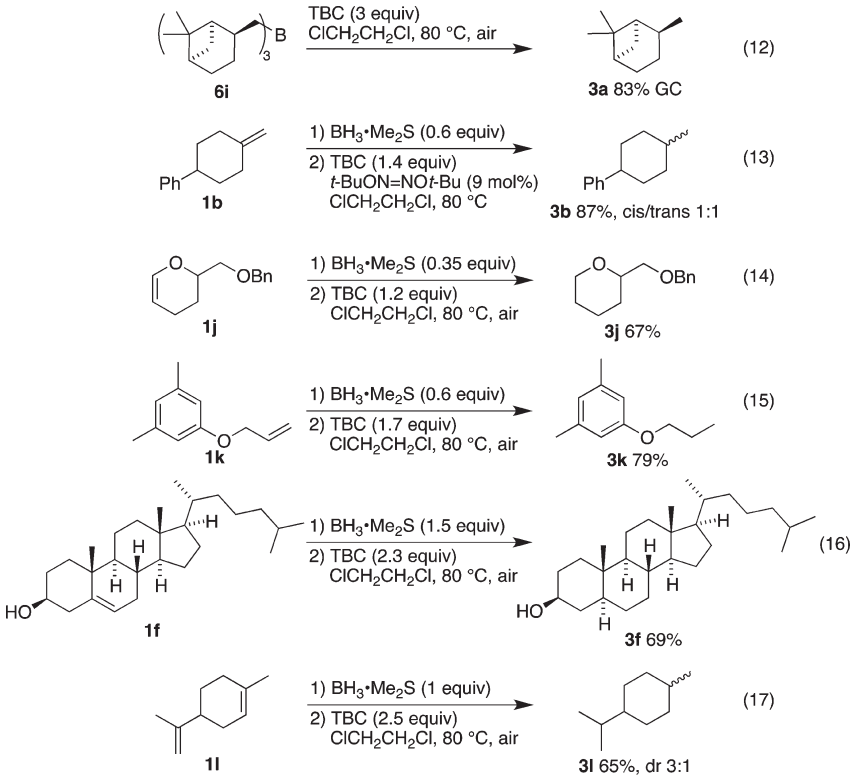
Scheme 6. Reduction of Trialkylboranes



organoboron species.[31] Thus, hydroboration of dihydropyrane **1j** had to be optimized in order to obtain an acceptable yield (eq 14).[32] Similarly, hydroboration of allyl ether **3k** had to be performed in 30 min (eq 15), and a longer reaction time led to lower yields.[33] Cholesterol **1f** was reduced to **3f** in 69% yield by running the hydroboration with 1.5 equiv of $BH_3 \cdot Me_2S$ (eq 16). The reaction of limonene **1l** with $BH_3 \cdot Me_2S$ followed by treatment with 4-*tert*-butylcatechol produced 4-methyl-1-isopropyl cyclohexane **3l** as a 3:1 mixture of diastereomers in 65% isolated yield (eq 17). This reduction was performed on 40 mmol of limonene, showing the scalability of the reaction. Interestingly, by decreasing the amount of hydroborating agent, it was not possible to isolate a monohydrogenated product. This result can be explained by the fact that the hydroboration with BH_3 of the terminal double bond is followed by a rapid intramolecular hydroboration of the internal double bond.[34]

The use of nonsymmetrical trialkylborane was also examined (Scheme 7). For instance, hydroboration of **1b** with 9-BBN followed by treatment with 4-*tert*-butylcatechol afforded **3b** in 82% yield as a 3:7 mixture of diastereomers (eq 18). The use of diethylborane, easily produced by mixing Et_3B (2 equivalents) and $BH_3 \cdot Me_2S$, provided **3b** in 76% yield (eq 19).[35] The hydroboration is generally highly selective for the less hindered olefin. A competitive experiment with a 1:1 mixture of **1b** and **1e** afford the reduced product **3b** in 76% yield and let the more substituted olefin **1e** unchanged (98% recovery, eq 20). Similarly, the single reduction of the methylene group of limonene **1l** was selectively achieved in 65% yield, using 9-BBN as hydroborating agent (Scheme 7, eq 21).

Finally, an ethanol-mediated reduction using a substoichiometric amount of 4-*tert*-butylcatechol was tested (Scheme 8, eq 22). Ethanol can regenerate 4-*tert*-butylcatechol from Meulenhoff's free acid 4′. Thus, the olefin **1b** was treated first with $BH_3 \cdot Me_2S$ and then with 0.1 equiv of 4-*tert*-butylcatechol, ethanol (5 equiv), and air. Under these conditions, the reduced product **3b** was formed in good yield as a 1:1 mixture of diastereomers. In a blank experiment without 4-*tert*-butylcatechol, the formation of 16% product was observed after 12 h of reaction. No increase was obtained upon prolonging the reaction time (5 days).

Whereas *B*-alkylcatecholboranes and trialkylboranes both readily react with oxygen, pinacolboranes and boronic acids are bench-stable. In the literature, no report can be found of either of them being used as a radical precursor in a chain process. Furthermore, no mild protocol for their protonolysis is reported. However, in situ generation of *B*-alkylcatecholboranes by esterification of the corresponding boronic acids should allow their reduction via a radical process. In the presence of alcohols such as methanol and catechol, their boronic ester counterparts equilibrate in transesterification reactions.[17] The cleavage of the B−C bond would displace the equilibrium and may allow the complete reduction of an organoboron species. Indeed, when dodecyl boronic acid **9** was heated in the presence of 4-*tert*-butylcatechol, dodecane **10** was obtained in good yield (Scheme 9, eq 23). Pinacolboranes, unlike unhindered boronic esters, do not transesterify under mild conditions. However, when a substoichiometric amount of sulfuric acid is added to induce pinacol rearrangement, transesterification and reduction could take place. For instance, the pinacolboronate **11** was converted to dodecane **10** in 61% yield (eq 24).

Kinetics of the Reduction with Catechol Derivatives. Among the comprehensive literature concerning the kinetics of hydrogen atom transfer from phenol derivatives, some values toward alkyl radicals are available. Scaiano and Ingold first

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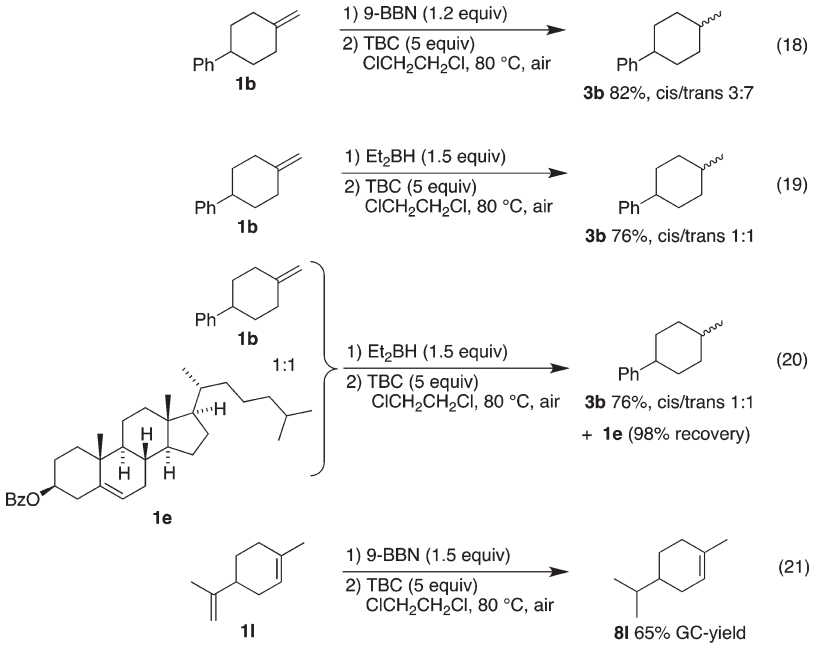
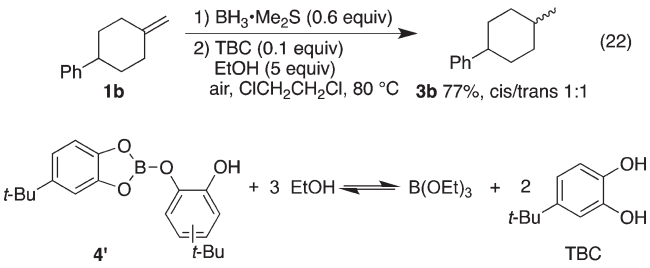
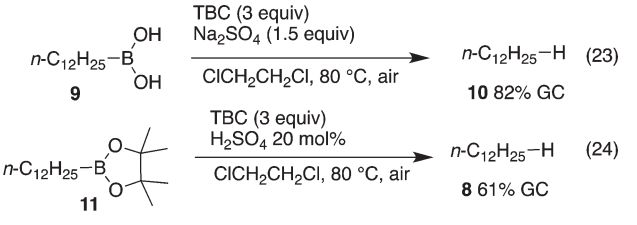
Scheme 7. Reduction of Mixed Trialkylboranes



Scheme 8. Reduction with a Catalytic Amount of 4-*tert*-Butylcatechol

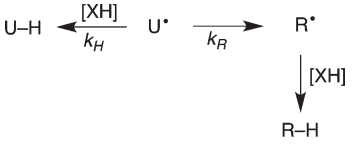


Scheme 9. Reduction of *n*-Dodecyl Boronic Acid and *n*-Dodecyl Boronic Pinacol Ester



measured a value of 1.7×10^6 M^{-1} s^{-1} (343 K) for the reaction of α-tocopherol with primary alkyl radicals using the 5-hexenyl radical clock. More recently, Pedulli and Lucarini studied the reactivity of a wide range of phenols with primary alkyl radical reporting hydrogen atom transfer rate constants from 2×10^3 to 7×10^5 M^{-1} s^{-1} (298 K).[36] The effect of substituent on the O–H BDE of phenols is now well established: while both electron donating (EDG) and withdrawing (EWG) groups stabilize the

Scheme 10. Radical Clock Experiment



aryloxyl radical, EDG destabilize the parent phenol resulting in a reduced BDE.[37] For catechols, in addition to the electronic effect of the second hydroxyl group, an intramolecular hydrogen bond activates the free hydrogen toward hydrogen atom transfer.[38,39] Many experimental and theoretical studies have treated this reactivity enhancement; nevertheless, no values for the reduction of alkyl radicals by catechol can be found most probably due to experimental difficulties associated with the radical chain inhibition properties of catechol derivatives.[40−42]

Competing unimolecular radical rearrangements (radical clocks) have been widely used to determine the rate of bimolecular reaction of radicals with radical traps such as hydrogen donors.[43,44] Ideally, the reaction of the unrearranged radical U• with the trap XH leading to the reduced product UH (second-order rate constant k_H) is considered to compete only with the irreversible unimolecular reaction leading to the rearranged radical R• (first-order rate constant k_R) (Scheme 10).

If the variation of the concentration in trapping agent is negligible (i.e., [XH] is considered to be constant), the kinetic model can be simplified to pseudo first order and then integrated to give eq 25. The rate constant of interest (k_H in our case) can be easily obtained by conducting a series of experiments by varying the concentration of the reducing agent XH. A plot of [UH]/[RH] versus [XH] has a slope of k_H/k_R. If unknown, the rate constant of rearrangement can be calibrated using a radical trap for which the rate constant is already known. The use

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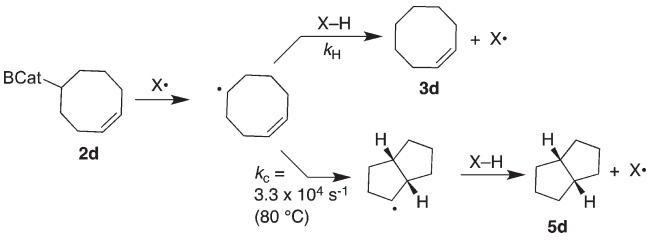
Scheme 11. Cyclooct-4-enyl Radical Clock



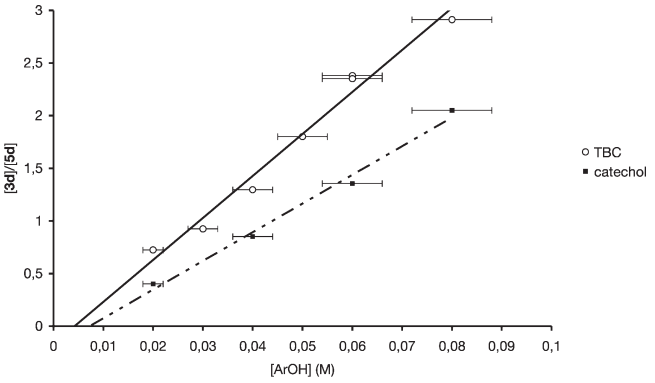


Figure 1. Product ratios from reactions of cyclooct-4-enyl radical in presence of catechol and 4-*tert*-butylcatechol.

of Bu_3SnH to calibrate radical clocks is a well-established procedure.[44]

$$\frac{[UH]}{[RH]} = \frac{k_H}{k_R}[XH] \qquad (25)$$

Our first attempts to measure the rate of hydrogen atom transfer from catechol using well established radical clocks[45] such as the 5-hexen-1-yl radical generated from the corresponding iodide in the presence of different initiators[46] only led to a scattered distribution of points. Indeed, when treated under these conditions, the semiquinone radical breaks the chain process, preventing any accurate measurement. As the reaction already proved to proceed cleanly, we decided to use *B*-cyclooct-4-enylcatecholborane **2d** as the substrate for the radical clock (Scheme 3, eq 6). The reduction with 4-*tert*-butylcatechol is efficient and affords a measurable mixture of products resulting from 5-*exo*-*trig* cyclization (**5d**) and of direct reduction (**3d**). The experiment was conducted in benzene at 80 °C using a large excess of hydrogen atom donor (ca. 7−30 equiv) in order to satisfy the pseudo first order conditions (Scheme 11).

Using the rate constant for the reduction with tributyltin hydride from the Arrhenius equation for the trapping of the cyclohexyl radical,[47] the cyclization rate was approximated to 3.3 ± 0.3 × 10^4 s^{-1} (353 K) using 4-iodocyclooctene as a radical precursor (see the Supporting Information). The plots of [**3d**]/[**5d**] versus [catechol] or [TBC] are shown in Figure 1. The error limits are two standard deviations and take in account the experimental error on the dilutions. Relative and absolute rates are reported in Table 3. In benzene at 80 °C, the rate constants for the reduction of cyclooctenyl radicals with catechol and 4-*tert*-butylcatechol were found to be about 7 and 4 times slower than tributyltin hydride, respectively, in accordance with

Table 3. Relative and Absolute Rate Constants for the Reduction with Catechol and 4-*tert*-Butylcatechol at 353 K

reducing agent	concentration (M)	k_H/k_c	k_H (M^{-1} s^{-1})
n-Bu_3SnH	0.05−0.2	185 ± 19	6.02 × 10^6 (ref 47)
catechol	0.02−0.08	27 ± 7	0.9 ± 0.3 × 10^6
4-*tert*-butylcatechol	0.02−0.08	40 ± 9	1.3 ± 0.4 × 10^6

the expected substituent effect. The absolute values for catechol and 4-*tert*-butylcatechol (secondary alkyl radicals) are found just slightly below the one previously mentioned for α-tocopherol (primary alkyl radical) in similar reaction conditions (1.7 × 10^6 M^{-1} s^{-1}, 70 °C, benzene). These results corroborate recent conclusions on the importance of the intramolecular hydrogen bond on the BDE of catechol.[39,40] Indeed, the authors determined the BDE for 3,5-di-*tert*-butylcatechol and α-tocopherol to be almost identical using the EPR equilibration method (79.3 and 78.2 kcal/mol, respectively) in contradiction to some computational studies.[41]

CONCLUSIONS

The present study demonstrates that catechol derivatives, an important class of natural and non-natural antioxidants, are powerful and synthetically useful reducing agents in radical chain reactions involving organoboranes. The reaction described herein constitutes not only a valid and attractive alternative to the use of toxic and expensive tin hydride reagents for the reduction of alkyl radicals, but also represents the first report of a catechol-mediated reduction able to sustain an efficient radical chain. 4-*tert*-Butylcatechol, unlike tin hydride, has low toxicity, is cheap, and is easily removed from reaction products. Furthermore, the so far elusive rate constants for the reduction of alkyl radicals by catechol and 4-*tert*-butylcatechol could be determined. Interestingly, they are less than 1 order of magnitude slower than tin hydride at 80 °C, making them particularly attractive for a wide range of transformations. The rate constants measurements were made possible by an unprecedented radical clock based on an organoborane precursor. A protocol allowing the reduction of all three alkyl groups of a trialkylborane has been developed. This represents a formal one-pot reduction of nonactivated olefins, showing complementary functional group tolerance to that of the catalytic hydrogenation. Selective reduction in a system bearing multiple insaturations is made possible by the selective hydroboration of the desired double bond. In situ esterification also allows the reduction of bench-stable boronic acids and esters.

ASSOCIATED CONTENT

Supporting Information. Experimental details; ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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