Free Radical-mediated Hydroxymethylation Using CO and HCHO

Takuji Kawamoto and Ilhyong Ryu*

Abstract: Tin-free radical hydroxymethylations of haloalkanes using CO and HCHO as a C1 unit proceed efficiently in the presence of borohydrides as radical mediators. In the approach using CO, the formation of aldehydes by radical carbonylation and their subsequent reduction by hydrides lead to alcohols. On the other hand, the use of formaldehyde is more straightforward, in which the key reaction is alkyl radical addition to formaldehyde to give alkoxy radical, which abstracts hydrogen from borohydride reagents. The cascade sequences were observed in the reaction of cholesteryl bromide with HCHO, which displays the diverse applications of HCHO in radical chemistry.

Keywords: Borohydrides · Carbon monoxide · Formaldehyde · Hydroxymethylation · One-carbon Homologation · Radical reaction

1. Introduction

Radical cascade reactions are powerful tools in organic synthesis.[1] In the last two decades, the potential of CO as a radical C1 synthon has been well established with applications yielding a significant variety of carbonyl compounds.[2,3] In contrast formaldehyde (HCHO) has rarely been utilized in radical chemistry after initial pioneering studies.[4–9] In this short review, we focus on two types of hydroxymethylation reaction of organohalides, in which CO and HCHO were utilized as radical C1 synthons. The reactions are coupled with borohydride reagents which act as a radical mediator thus enabling these reactions to be run in the absence of toxic tin hydride reagents.

2. Radical Hydroxymethylation of Alkyl Halides: Earlier Work

In 1990, one of us demonstrated that CO can be used for formylation of alkyl halides, when coupled with the use of tri-butyltin hydride and 2,2'-azobisisobutyronitrile (AIBN, Scheme 1).[10] This work served as a breakthrough of radical carbonylation reactions, which has since emerged as a standard method for the synthesis of a variety of carbonyl compounds.
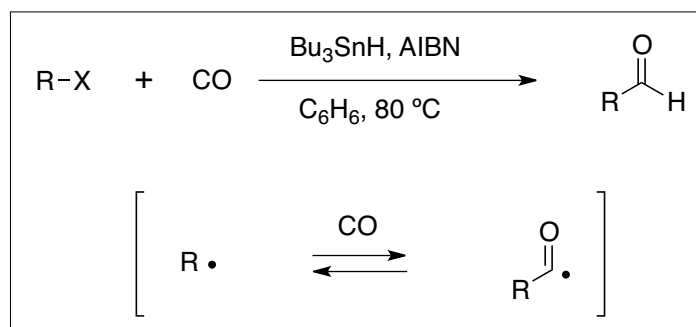
In 1993, the application of the radical formylation for hydroxymethylation of a sugar iodide was reported by Gupta and Kahne.[11] They used the combination of a catalytic amount of triphenylgermanium hydride (Ph₃GeH) and excess NaBH₃CN (Scheme 2). The reaction comprises of i) radical carbonylation followed by ii) *in situ* hydride reduction of the resulting aldehydes. Although sugar iodide gave a rather low yield of the desired one-carbon homologated alcohol, a simple alkyl iodide like 1-iodoadamantane gave the corresponding alcohol in 75% yield. In spite of the lower hydrogen-donating ability of triphenylgerman compared to tributyltin hydride, it still required pressurized CO conditions to compete with premature quenching of the key alkyl radicals by triphenylgerman.

In collaboration with the Curran group, we carried out a similar hydroxymethylation of organic halides employing catalytic amounts of fluorous tin hydride.[12,13] Combining fluorous tin hydride with NaBH₃CN as a reducing agent allowed us to carry out the triphasic workup (H₂O/CH₂Cl₂/perfluoro hexane) to separate inorganic byproducts, hydroxymethylated products, and fluorous tin hydride. Later we noticed that an organic/fluorous hybrid ether, F-626: (2-perfluorohexyl)ethyl 1,3-dimethylbutyl ether) is a good solvent for hydroxymethylation using fluorous tin hydride. The separated F-626 solution containing fluorous tin hydride was successfully used for the second iteration of experiments.[14] The recovered fluorous tin hydride can be used over and over again. All these studies contribute to creating greener reaction systems with a minimum use of tin reagents, however, we decided to investigate the possibility of conducting hydroxymethylation of haloalkanes without using any tin reagents at all.
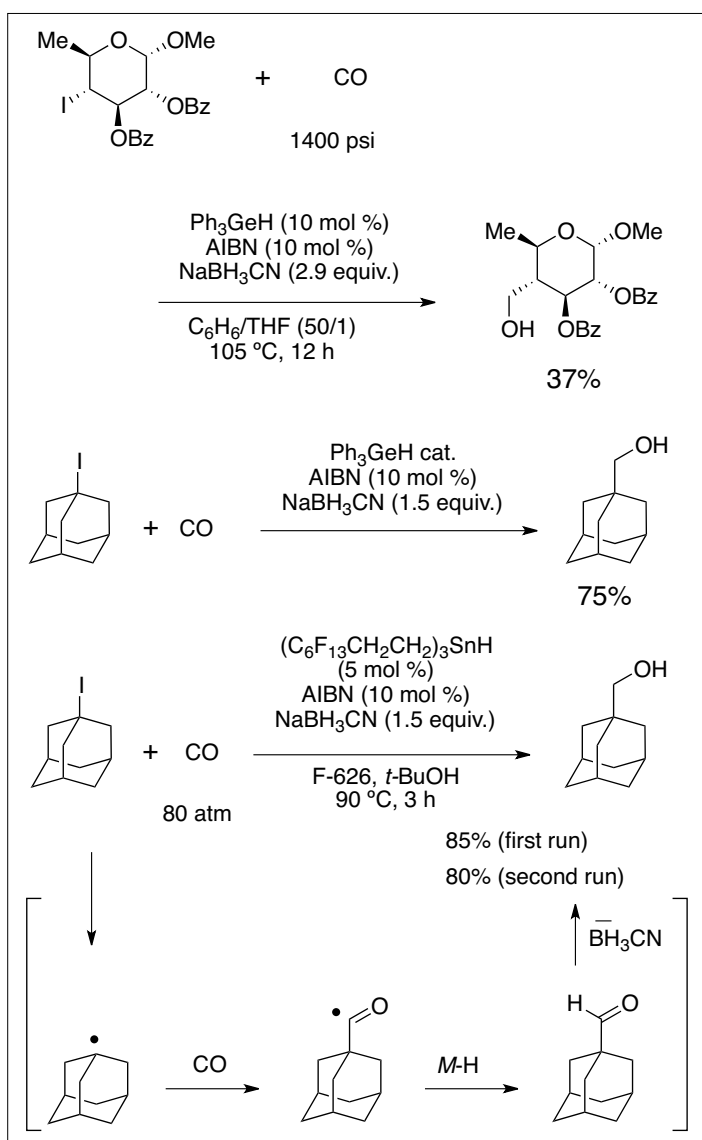
3. Tin-free Radical Hydroxymethylation of Alkyl Iodides Using CO

An opportunity arose from our discovery that the Giese reaction and the related carbonylation reaction can be carried out using tetrabutylammonium cyanoboro-

Correspondence: Prof. I. Ryu
Department of Chemistry, Osaka Prefecture University
Sakai, 599-8531, Osaka, Japan
Tel. +81-72-254-9695
E-mail: ryu@c.s.osakafu-u.ac.jp

Scheme 1. Free-radical formylation.

Scheme 2. Radical hydroxymethylation with catalytic amount of metal hydrides.

Scheme 3. Tin-free Giese reaction and relative carbonylation.

Scheme 4. Tin-free hydroxymethylation using CO.

Scheme 5. Hydroxymethylation of various alkyl iodides.
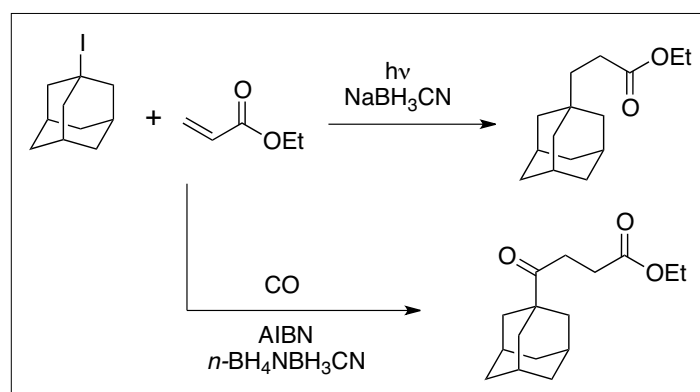
hydride as a substitute for tin hydride (Scheme 3).[15]

The development of this borohydride-based tin-free approach led us to reexamine that hydroxymethylation reaction. Indeed hydroxymethylation of alkyl iodides using tetrabutylammonium borohydride gave the expected hydroxymethylation product in good yield (Scheme 4).[16]

Interestingly, less than 2% yield of the reduction product, adamantane, was detected, suggesting that the H-abstraction of adamantyl radical from borohydride anion is sluggish and therefore does not compete with the carbonylation step. Consequently, we found that by employing photo-irradiation conditions, hydroxymethylation could proceed under *atmospheric* pressure of CO.
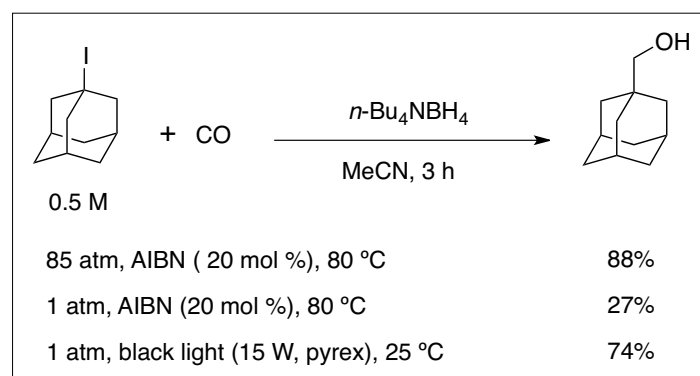
Having optimized conditions for hydroxymethylation of alkyl iodides in hand, we applied the method to a variety of iodoalkanes (Scheme 5). The reaction of

cholesteryl radical gave a 50:50 *cis/trans* mixture of hydroxymethylation product. The hydroxymethylation reaction was also applied to prepare a key intermediate in the synthesis of (±)-communiol E.[17]
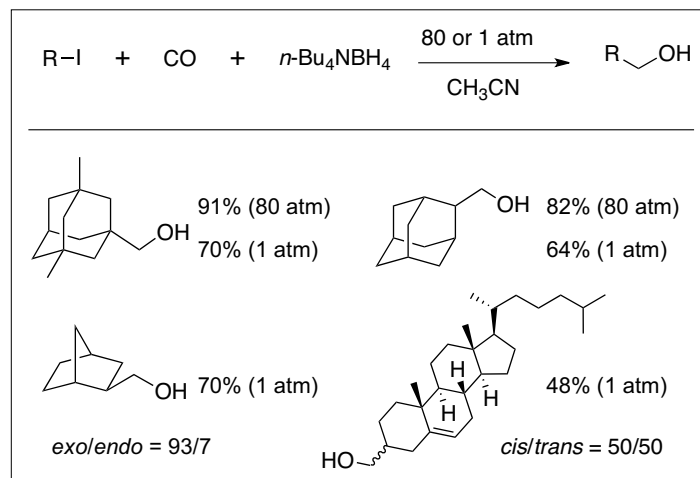
We propose a mechanism involving radical carbonylation and the subsequent trapping of the resulting acyl radical by H abstraction from hydroborate anion. The borate anion radical may undergo one-electron donation to the alkyl iodide to generate radical and iodo borate anion,[18] thus sustaining the radical chain (Scheme 6).

## 4. HCHO in Radical Chemistry: Earlier Work

Successful hydroxymethylation of haloalkanes, through the use of HCHO in radical addition chemistry is straightforward and highly desirable (Scheme 7).

Trapping formaldehyde by alkyl radical was first reported in 1958 by Fuller and Rust.[4] They observed that the reaction of cyclohexyl radical with formaldehyde resulted in the production of cyclohexane methanol (Scheme 8).
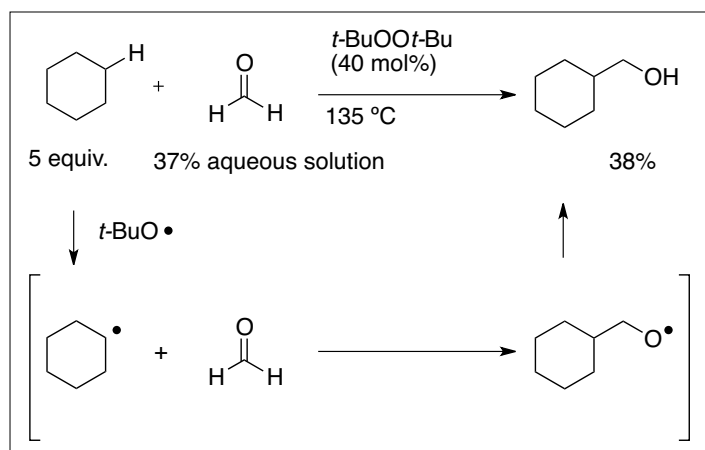
In 1965, Oyama reported that reaction of methanol with formaldehyde in the presence of di-tertiary butyl peroxide gave ethylene glycol.[5] Later, this work was re-
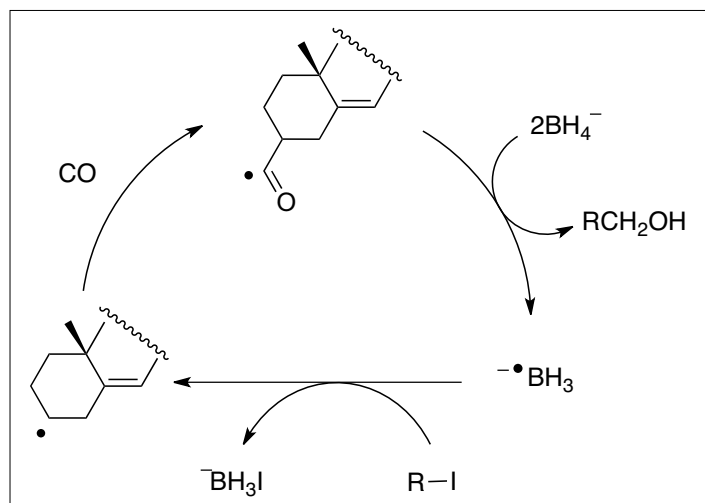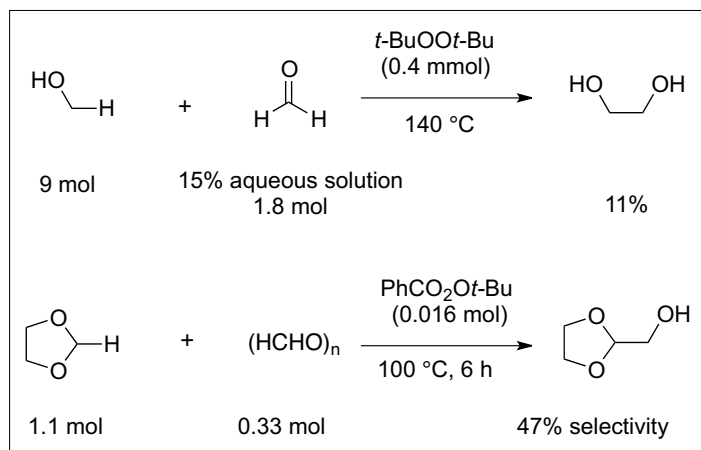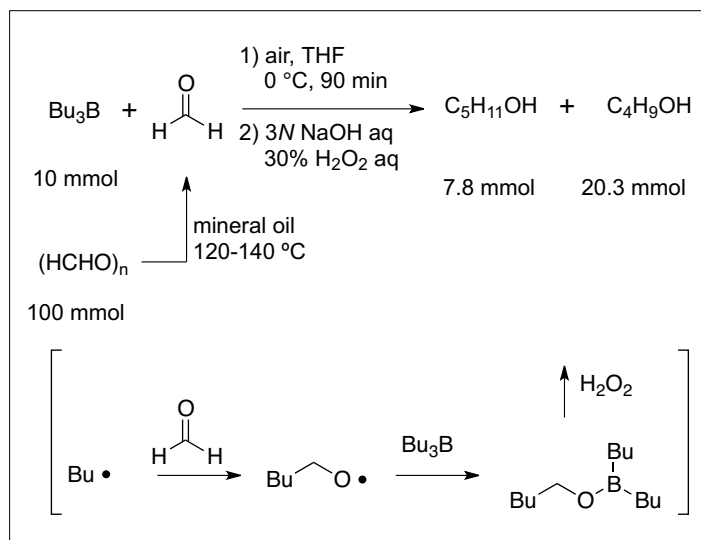
Scheme 6. Proposed mechanism.
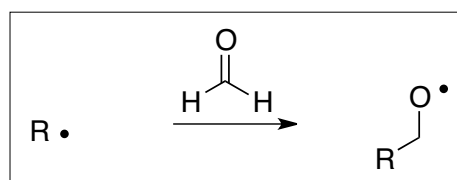
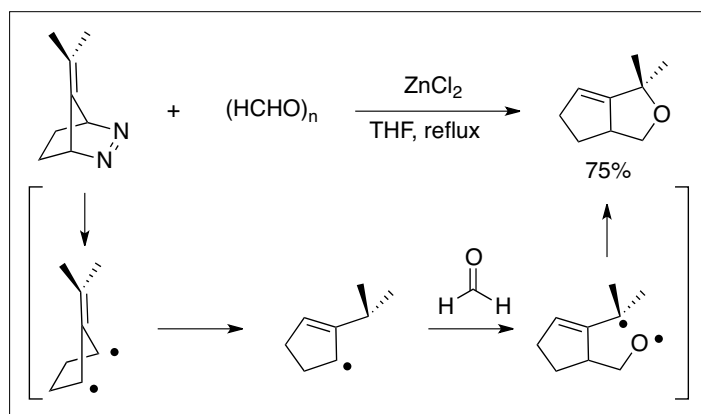Scheme 7. Key radical species of hydroxy-methylation using HCHO.

Scheme 8. First report using HCHO as a radical acceptor.

Scheme 9. α-Hydroxymethylation of methanol and 1,3-dioxolane.

Scheme 10. Oxygen-promoted hydroxymethylation of tributylborane.

Scheme 11. Intermolecular cycloaddition of formaldehyde.

investigated by Kollar from the industrial point of view.[6] Sanderson and coworkers examined the regiochemistry of hydroxymethylation of 1,3-dioxolanes and reported that hydrogen abstraction from the methylene attached to two oxygen atoms showed higher reactivity than that of a methylene with a single oxygen bond (Scheme 9).[7]

In 1972, Brown and coworkers reported the reaction of tributylborane with formaldehyde under air to give a mixture of 1-pentanol and 1-butanol after hydrolytic oxidation (Scheme 10).[8] This reaction is thought to involve butyl radical addition to formaldehyde to give 1-pentyloxy radical, which then reacts with tributylborane to form borate ester as the precursor to the alcohols.

A rather peculiar but interesting example of cycloaddition reaction was reported in 1985 by Little and coworkers, in which they used HCHO as a trap of 2-methylene 1,3-diyl (Scheme 11).[9] Zinc chloride was essential in obtaining the high level of regioselectivity.

After these earlier efforts, the radical chemistry of formaldehyde has been only rarely utilized for a quarter century. With our knowledge that borohydride reagents could act as radical mediators, we decided to explore hydroxymethylation using HCHO.

5. Radical Hydroxymethylation of Alkyl Halides using HCHO

Initially we attempted the hydroxymethylation of 1-iodoadamantane using paraformaldehyde in the presence
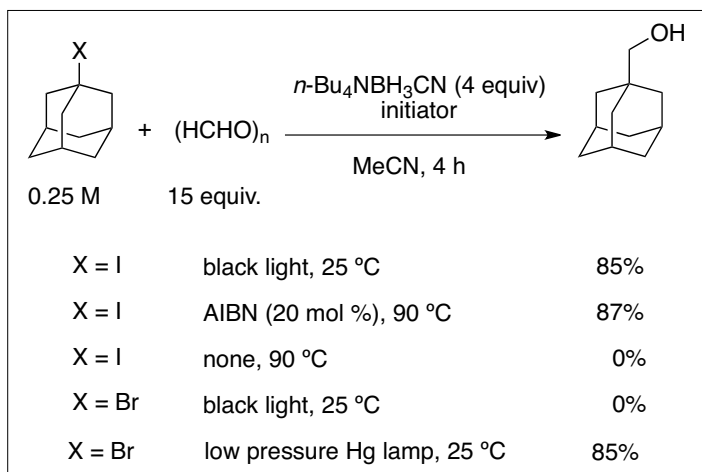
Scheme 12. Radical hydroxymethylation using HCHO.
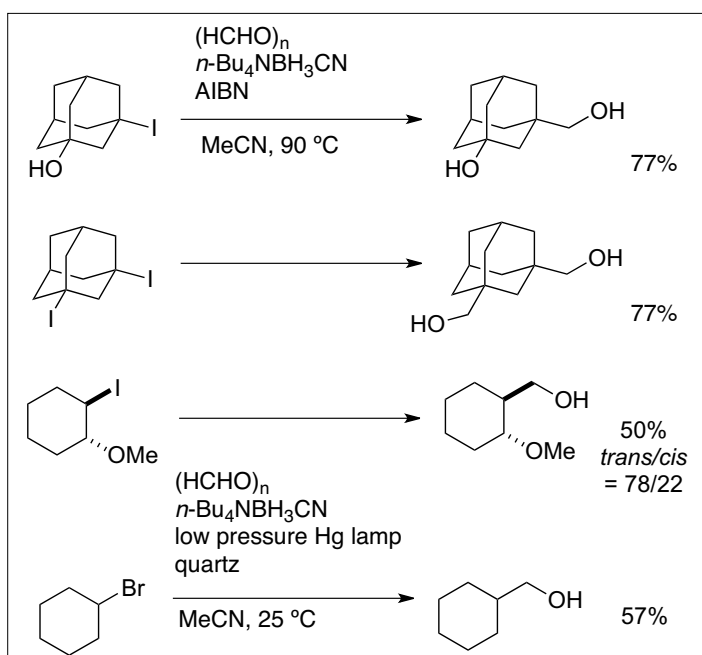
Scheme 13. Hydroxymethylation of various alkyl halides.

Scheme 14. Hydroxymethylation of cholesteryl bromide.

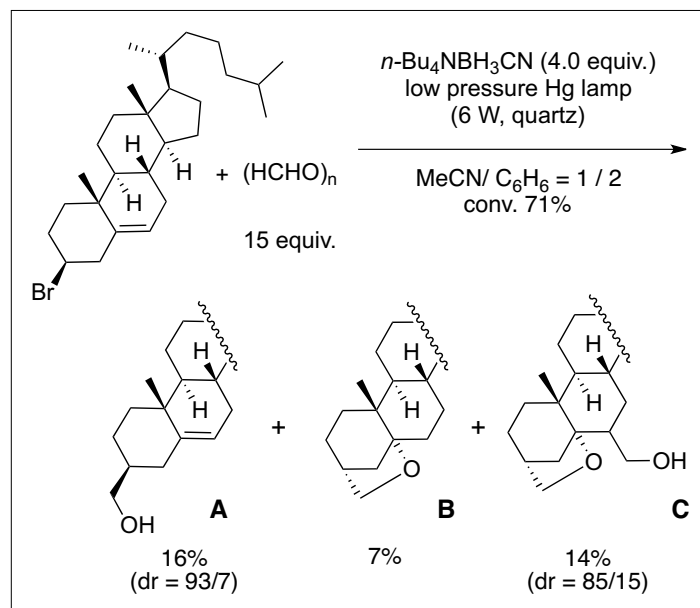Scheme 15. Proposed mechanism.

of tetrabutylammonium borohydride. Unfortunately, the reaction was unsuccessful due to rapid reduction of formaldehyde by the borohydride anion. As the cyanoborohydride is known to be a more mild reducing agent, we again tested the reaction using n-Bu$_4$NBH$_3$CN and found that it worked beautifully (Scheme 12).

Irrespective of whether the radical reaction was initiated by black-light irradiation or thermal initiation using AIBN, the reaction gave good yield of the desired 1-adamantanemethanol.[19] The reaction of bromoalkanes was more difficult, however, UV light irradiation resulted in the smooth conversion and good yields of the desired product (Scheme 13).
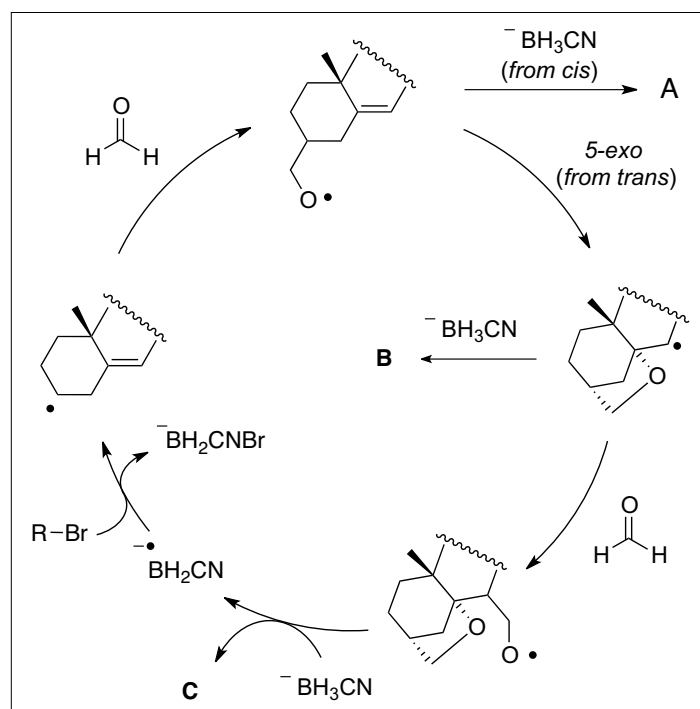
As discussed above, the reaction of cholesteryl iodide using CO and tetrabutylammonium borohydride gave a 50:50 *cis/trans* mixture of hydroxymethylation product. Both α/β-stereoisomers of the acyl radical abstract hydrogen from tetrabutylammonium borohydride. In this case the 5-exo cyclization of the acyl radicals is unfavorable due to steric congestion, and the product resulting from cyclization is not observed. On the other hand, the reaction of cholesteryl bromide with HCHO and tetrabutylammonium cyanoborohydride gave not only hydroxymethylated product but also cyclized product (Scheme 14).

The hydroxymethylation product A was formed with high *cis* stereoselectivity to the angular Me group. The alkoxy radical with the *trans* geometry undergoes 5-exo radical cyclization onto the C–C double bond (Scheme 15).[20] The subsequently formed THF radical can then undergo two alternative reactions: i) abstraction of hydrogen from cyanoborohydride to give B or ii) addition to a second molecule of HCHO to give C.[21–23]

6. Conclusion and Future Directions

We have shown that radical mediated hydroxymethylation of alkyl halides can be achieved by the use of CO and tetrabutylammonium borohydride under tin-free reaction conditions. Due to a slower H donation ability of the borohydride reagent compared to tributyltin hydride, the

reaction can be conducted even under an atmospheric pressure of CO without suffering from premature quenching of key alkyl radicals. We also found that HCHO, when coupled with cyanoborohydride as radical mediator, can serve as a useful reagent for hydroxymethylation of alkyl halides. The results with cholesteryl bromide hold promise that HCHO could become a promising C1 synthon in radical cascade chemistry and we are now engaged in the development of multicomponent reactions using HCHO.

Acknowledgement

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