C-C Bond Forming Reactions Using Borohydride Reagents as Radical Mediators

ボロヒドリドをラジカルメディエーターとした

炭素–炭素結合形成反応

C–C Bond Forming Reactions Using Borohydride Reagents

as Radical Mediators

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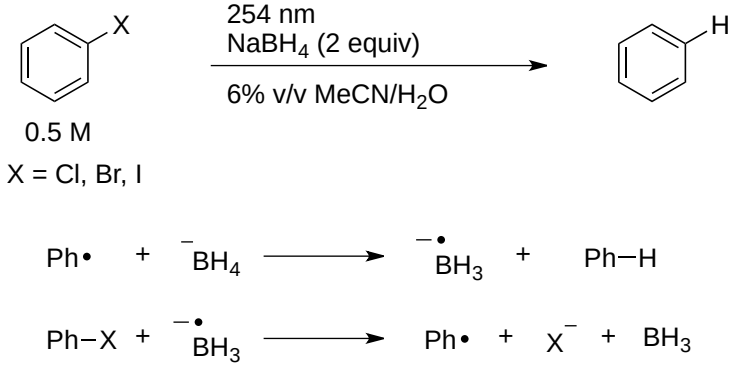
1 Introduction and General Summary

Since the discovery of the triphenylmethyl radical by Gomberg a century ago,[1] radical chemistry has become a very useful tool in preparative organic synthesis.[2] In the early years of free radical chemistry, radical intermediates were considered too reactive to be used in synthetic chemistry. However, important contributions by physical organic chemists in the mid 1970's led to an understanding of kinetics of various radical processes. Furthermore, structural data on a variety of radicals became available. An understanding of kinetic and the structural information of these reactive intermediates paved the way for the development of the modern synthetic radical chemistry. The very rapid development of these reactions could be attributed to the emergence of highly efficient ways to conduct them. Among these methods, tin hydride mediated addition of carbon radicals to activated alkenes has played major role. Tin radical can abstract halogens, such as I, Br, and Cl, from organo halides to generate carbon radicals. Then radical reaction takes place. In the end radicals can abstract hydrogen from tin hydride to give the product. Though excellent as a radical mediator, one of the major problems in tin-based radical chemistry is toxicity of triorganyltin compounds. It is quite difficult to remove toxic tin byproducts completely. These drawbacks strongly limit the use of tin mediated radical reactions in pharmaceutical industry. It is therefore not surprising that many groups have started research programs directed towards tin free radical chemistry.[3] This study focuses on the use of borohydride reagents as hydrogen source in radical reactions, which can create a tin-free radical reaction system.

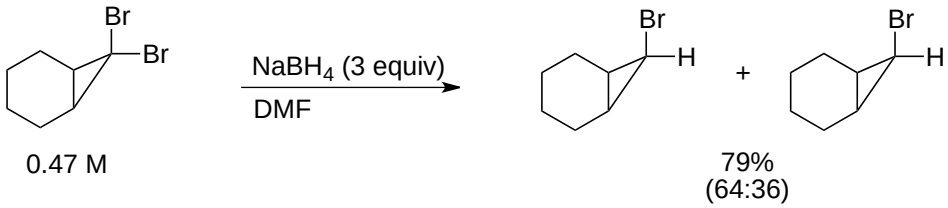
1.1 Early Work on the use of Borohydrides and Borane-Lewis Base Complexes as Radical Mediator (1967-2007)

1.1.1 Radical Reduction and Reductive Cyclization

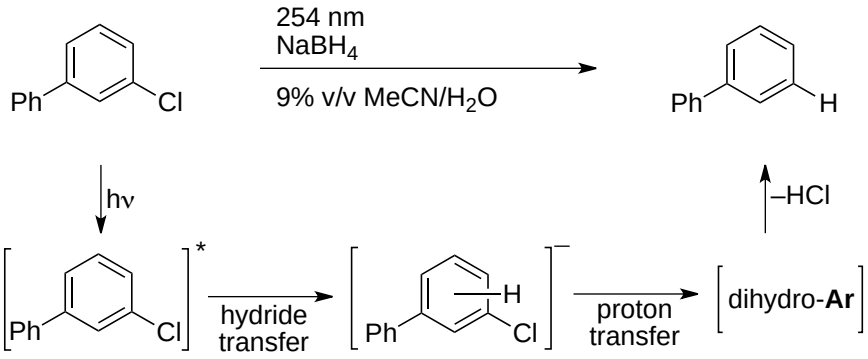
The reduction of alkyl and aryl halides with borohydride is well-known and is usually considered to proceed via hydride transfer. However, in 1973, Barltrop and Bradbury reported that photoredctuion of aromatic chlorides, bromides, and iodides by sodium borohydride in aqueous acetonitrile solution proceeds via a radical chain mechanism to give the aromatic hydrocarbon.[4]



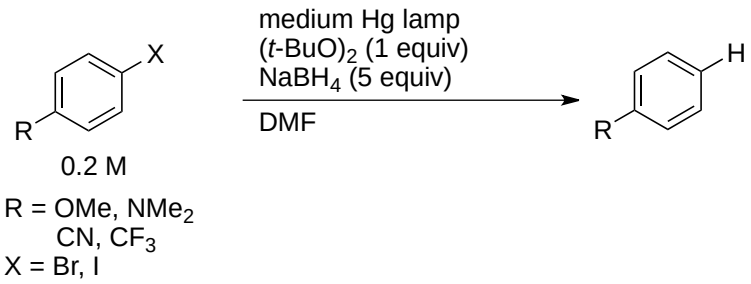
In 1994, the reduction of the *gem*-dibromide, 7,7-dibromonorcarane, was carried out by using sodium borohydride in DMF.[5] Since the reaction was inhibited by molecular oxygen, the radical chain mechanism was proposed.



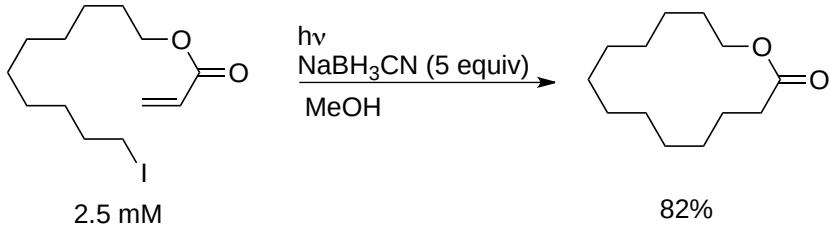
Ohashi *et al.* reported photo-reduction of biphenyl chloride by sodium borohydride, in which they proposed a consecutive hydride-proton-transfer mechanism.[6]



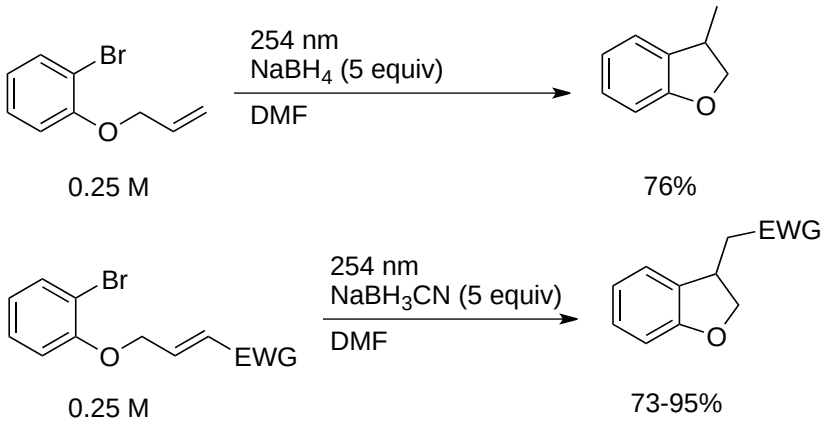
About one decade later, Beckwith *et al.* reported photo-stimulated reduction of aryl bromides and iodides with sodium borohydride in the presence of radical initiator in dimethylformamide.[7]



In 1994, Kurata *et al.* reported interesting photo-induced macrocyclization of ω-iodo-acrylates using several borohydride reagents.[8] The precise role of borohydride reagents was not clear, but they advocated radical mechanism involving the cyanoborate radical anions.

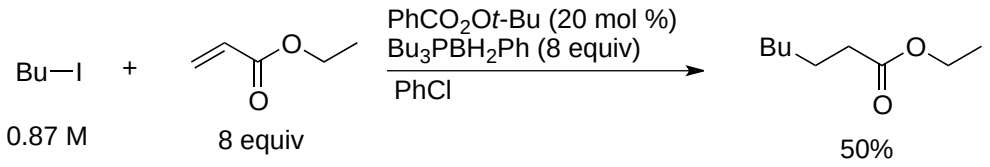


In 2005, Liu and Yu *et al.* accomplished the simple photochemical approach for reductive radical cyclization using sodium borohydride.[9] In the case of substrates having electron deficient double bonds, they used $NaBH_3CN$ instead of $NaBH_4$.



1.1.2 Intermolecular Radical Reactions

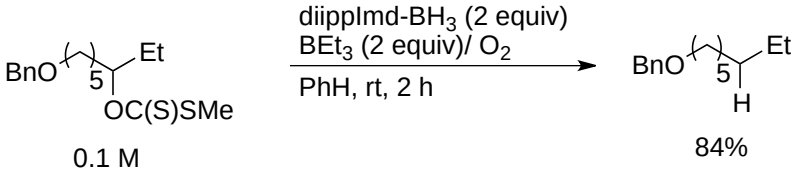
The reaction of butyl iodide with ethyl acrylate in the presence of Bu_3PBH_2Ph and tert-butyl perbenzoate in chlorobenzene at 110 ºC afforded the reductive addition product ethyl heptanoate in moderate yield (50%). Other examples of reductive addition reactions are provided, however, yields are low.



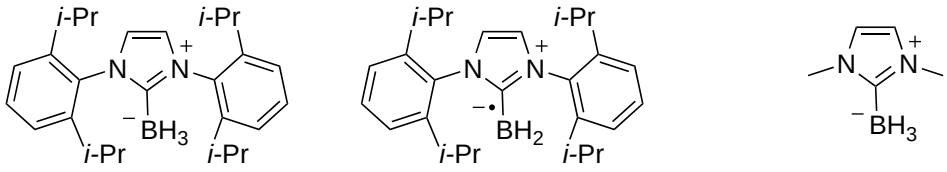
1.2 Recent Work on Borohydrides and Borane-Lewis Base Complexes as Radical Mediator

1.2.1 Radical Reduction and Reductive Cyclization

In 2008, Curran and Lacôte *et al.* reported that radical chain reduction of xanthates and related functional groups using *N*-heterocyclic carbene borane (NHC-boranes)[10], such as dippImd-BH_3, as radical mediator.[11]



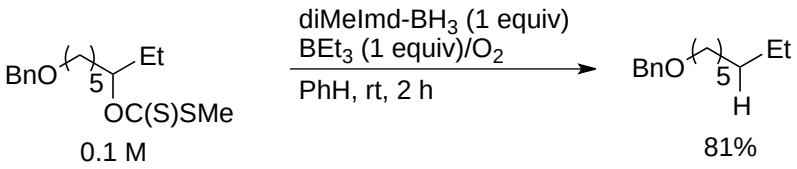
They measured the rate constant for hydrogen transfer (k_H) from dippImd-BH_3 to a secondary alkyl radical and they detected the intermediate radical (dippImd-$BH_2^{\bullet}$**)** by EPR spectroscopy.[12] DippImd-BH_3 turned out to be a modest hydrogen donor (k_H = 2–4 x 10^4 $M^{-1}s^{-1}$).[13] They surveyed rate constants for hydrogen transfer of about two dozen NHC-boranes, and identified 1,3-dimethylimidazol-2-ylidene borane (diMeImd-BH_3) as significantly improved "second-generation" reagent.



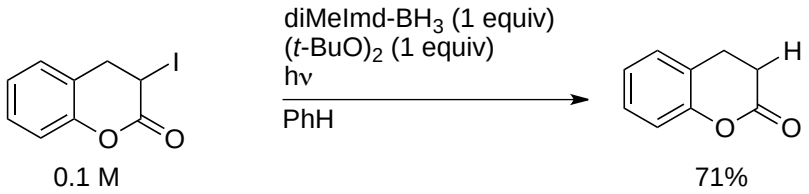
dippImd-BH_3 dippImd-$BH_2^{\bullet}$ diMeImd-BH_3

2nd generation NHC-borane

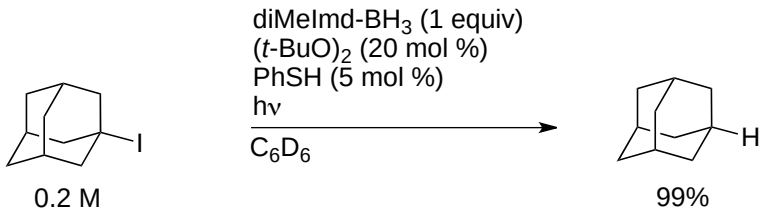
DiMeImd-BH_3, a stable and easily handled solid, can smoothly reduce xanthates and the related functional groups.[14]



On the other hand, radical reduction of organo halides have been limited to compounds possessing electron withdrawing groups near the halide.[15] Simple alkyl halides such as 1-iodoadamantane have not been reduced efficiently.

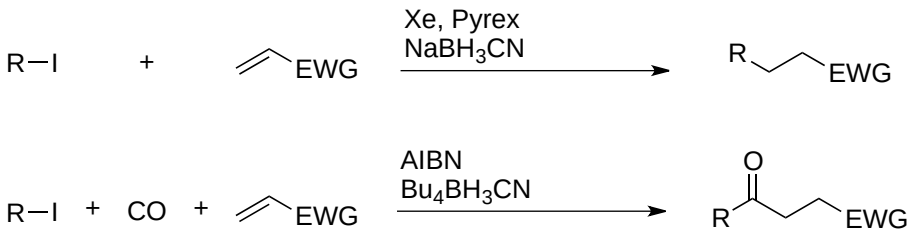


The problem in alkyl halide reduction by radical mechanism lies in slow hydrogen atom transfer. The use of thiols as polarity reversible catalyst considerably expands the scope of reductions of alkyl halides using NHC boranes.[16]



1.2.2 Intermolecular Radical Reactions

In 2008, Ryu *et al.* reported Giese reaction and the related radical carbonylation process proceeded efficiently in the presence of sodium cyanoborohydride and tetrabutylammonium cyanoborohydride.[17]



1.3 General Summary

This thesis focuses on borohydride mediated carbon-carbon bond forming reactions. From chapter 2 to 4 the author has investigated the hydroxymethylation of alkyl and aryl halides. Hydroxymethylation has two types of reaction courses, Type 1 and Type 2. Type 1 reaction employs radical addition to CO to give acyl radicals as key intermediates. On the other hands, Type 2 reaction employed radical addition to formaldehyde to give alkoxy radicals as key intermediates.

Chapter 2 describes the development of hydroxymethylation of alkyl iodides under atmospheric pressure of CO in the presence of tetrabutylammonium borohydride in conjunction with photoirradiation using black light.[18] A hybrid radical/ionic mechanism is proposed.

Chapter 3 describes hydroxymethylation of alkyl and aryl iodides with CO in the presence of diMeImd-BH_3 as radical mediator.[19] The reaction took place chemoselectively at the aryl-iodine bond but not at the aryl-bromine and aryl-chlorine bonds. A three-component coupling reaction comprising aryl iodides, CO, and electron-deficient alkenes also proceeded well to give unsymmestrical ketones in good yields. DiMeImd-BH_3 would act as a hydrogen donor to acyl radicals and iodinated NHC-borane as a reducing agent of aldehyde.

Chapter 4 describes that hydroxymethylation of alkyl halides was achieved using paraformaldehyde as a radical C1 synthon in the presence of tetrabutylammonium cyanoborohydride as a hydrogen source.[20] The reaction proceeds via a radical chain mechanism involving an alkyl radical addition to formaldehyde to form an alkoxy radical, which abstracts hydrogen from a hydroborate anion.

Chapter 5 describes the determination of rate constants for primary alkyl radical from tetrabutylammonium cyanoborohydride by the pyridine-2-thioneoxycarbonyl (PTOC) competition kinetic method at a single concentration point.

Chapter 6 describes that cyanoborohydride promoted radical arylation reaction of benzene. The reaction took place chemoselectively at the aryl-iodine bond but not at the aryl-bromine and chlorine bonds.

1.4 References

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2 Radical/Ionic Hydroxymethylatyion of Alkyl Iodides

2.1 Introduction

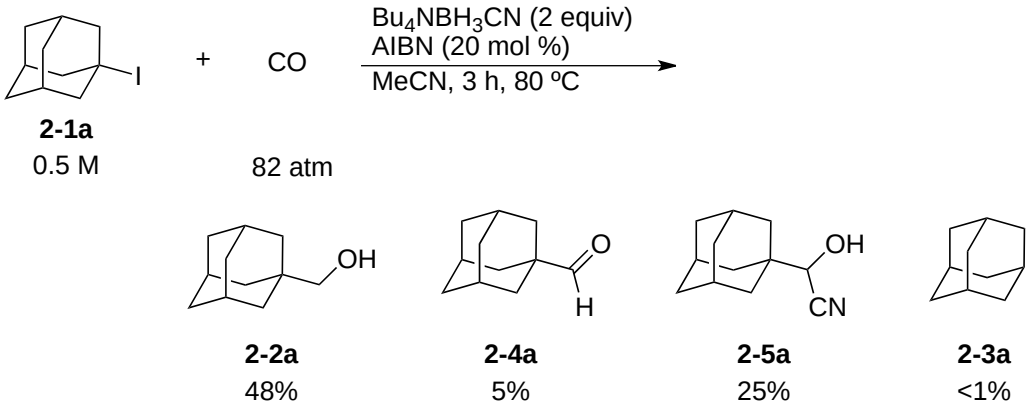
In the last two decades, the potential of CO as a radical C1 synthon has been well established with applications yielding variety of carbonyl compounds.[1] One-carbon homologation generating alcohol derivatives is an important class of synthetic transformations, and the use of CO for such processes is highly desirable.[2] Gupta and Kahne reported hydroxymethylation of alkyl halides using the combination of a catalytic amount of triphenylgermanium hydride and excess $NaBH_3CN$.[3] The reaction comprises i) radical carbonylation followed by ii) *in situ* hydride reduction of the resulting aldehyde. Ryu *et al.* reported a similar hydroxymethylation of organic halides employing catalytic amounts of fluorous tin hydride.[4] All these studies contribute to creating greener reaction systems with a minimum use of tin reagents, however, the author decided to investigate the possibility of conducting hydroxymethylation of haloalkanes without using any tin reagents at all.

Recently, Ryu *et al.* reported that tin-free Giese reaction and the related radical carbonylation reaction proceeded in the presence of cyanoborohydrides.[5] This chapter describes that the hydroxymethylation of alkyl iodides proceeded under atmospheric pressure of CO in the presence of tetrabutylammonium borohydride. This method is simple and less toxic compared to the traditional conditions.

2.2 Results and Discussion

Bu_4NBH_3CN proved to be optimal in the tin-free Giese reactions; therefore, the author initially examined the reaction of 1-iodoadamantane (**2-1a**) and CO (82 atm) in the presence of Bu_4NBH_3CN (3 equiv) under thermal initiation conditions using AIBN as the radical initiator (Scheme 2-1). The excepted hydroxymethylation product **2-2a** was obtained in 48% yield along with 1-adamantane carboxaldehyde (**2-4a**) (5%) and, unexpectedly, its cyanohydrin **2-5a** (25%). It is noteworthy that the direct reduction product, adamantane (**2-3a**), was obtained in less than 1% yield and that the expected course of the reaction progressed even with a high concentration of the substrate (0.5 M). Another advantage is that this reaction does not require a very efficient hydrogen source, such as tin hydride. Hydrogen abstraction by alkyl radicals commonly competes with CO trapping, and high dilution conditions are typically required to make

the relative concentrations of CO to tin hydride high.[6] It is reasonable to assume that **2-2a** forms by reduction of the initially formed 1-adamantane carboxaldehyde. On the other hand, the unexpected cyanohydrin was thought to form as a result of transfer of the cyano group from the borohydride reagent.



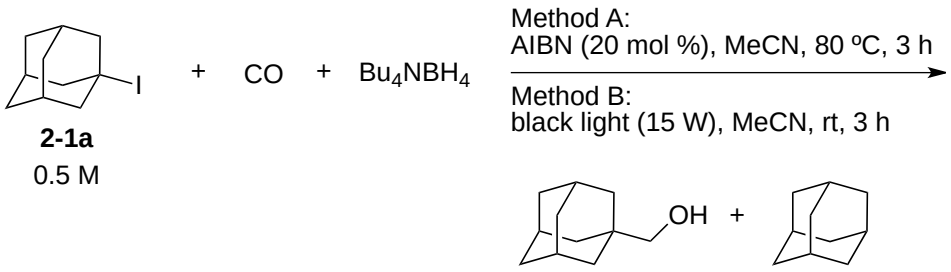
Scheme 2-1. Radical Hydroxymethylation of 1-Iodoadamantane (**2-1a**) in the Presence of Tetrabutylammonium Cyanoborohydride

In an effort to improve the yield of the hydroxymethylation product, screening of borohydride reagents was undertaken. Reductants such as $NaBH_4$, $NaBH(OAc)_3$, or $BH_3 \cdot NMe_3$ gave poor results, whereas application of Bu_4NBH_4 provided the hydroxymethylation product **2-2a** in 88% yield (Table 2-1, entry 1). It should be noted that less than 2% yield of the reduction product, adamantane (**2-3a**), was detected by GC. This suggests that the carbonylation step by adamantyl radical was not hampered by the presence of Bu_4NBH_4. Neither aldehyde nor cyanohydrin was detected under the reaction conditions. Acetonitrile was found to be superior to hexane (50% yield), benzene (83% yield), toluene (72% yield), THF (78% yield), tetrahydropyran (73% yield), and EtOH (21% yield).

The author next sought to determine whether the present hydroxymethylation would proceed under very low CO pressures. This may be possible because for this reaction an efficient hydrogen source (such as Bu_3SnH) is not present to quench alkyl radicals. In order to investigate this, 1-iodoadamantane (**2-1a**) was exposed to tin-free thermal radical conditions with Bu_4NBH_4 under low CO pressures (entries 2-5). Results indicated that hydroxymethylation product **2-2a** was obtained in 73% yield even under 5 atm of CO (entry 4). Interestingly, when the reaction was performed using a CO

balloon (1 atm), **2-2a** was still formed, albeit in low yield (entry 5). In this case, the yield of the reduction product **2-3a** increased up to 33% yield. This insufficient yield of **2-2a** was not improved by decreasing the concentration of the substrate or by lowering the reaction temperature to 40 °C with V-70 as the radical initiator.[7] At 1 atm of CO, a simple reduction course plagued the carbonylation. However, notable improvement was achieved by using photoirradiation conditions in place of thermal radical initiation. When a solution of **2-1a** and Bu_4NBH_4 in MeCN was irradiated with a 500 W xenon lamp through a Pyrex filter (>280 nm) for 3 h under a CO atmosphere, **2-2a** was obtained in 78% yield (entry 6). A similar result was obtained when a more energy-saving 15 W black light (peak wavelength 352 nm) was used (entry 7). The reaction was also effected in DMF (entry 8).

Table 2-1. Hydroxymethylation of 1-Iodoadamantane (**2-1a**) with Bu_4NBH_4



2-1a
0.5 M

2-2a **2-3a**

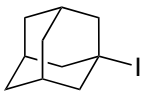
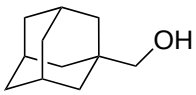
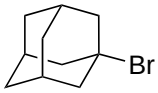
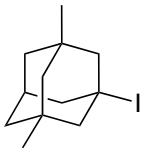
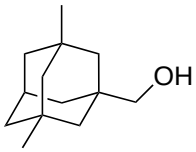
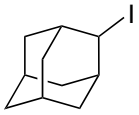
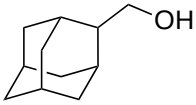
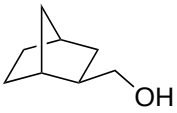
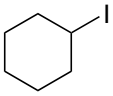
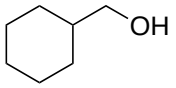
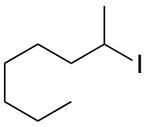
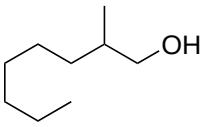
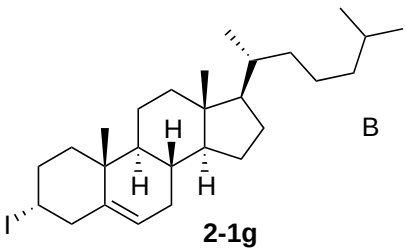
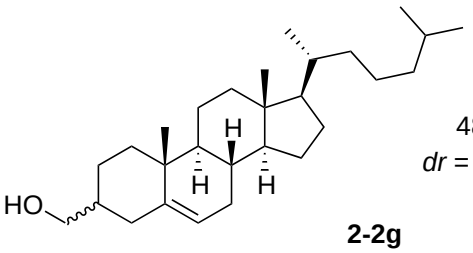
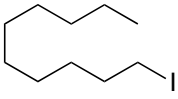
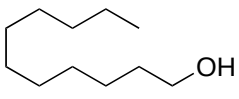
entry	CO [atm]	Method	**2-2a**[a]	**2-3a**[b]
1[c]	85	A	88%	1%
2	20	A	79%	2%
3	10	A	76%	4%
4	5	A	73%	8%
5	1	A	27%	33%
6[d,e]	1	B	78%	8%
7	1	B	74%	16%
8[e,f]	1	B	64%	12%

a Isolated yield after column chromatography on SiO_2. *b* GC yield. *c* 3 equiv of Bu_4NBH_4 was used. *d* 500 W xenon lamp was used for irradiation. *e* The reaction was performed at a concentration of 0.25 M **2-1a**. *f* $NaBH_4$ (1.1 equiv) was used instead of Bu_4NBH_4.

After identifying the optimal conditions, the authors next explored the generality of the tin-free radical hydroxymethylation by varying the alkyl iodides (Table 2-2). Among the substrates tested, tertiary iodides gave the best results (entries 1, 2, 4, and 5). This may be due to the facility of the iodine atom transfer step to cause the generation of the stable tertiary radical. In contrast, alkyl bromide was insusceptible to these conditions (entry 3). When the reactions were carried out with secondary iodides, yields were varied according to the structure of the substrate (entries 6-12). Photoirradiated hydroxymethylation of 2-iodoadamantane (**2-1c**) and 2-iodonorbornane (**2-1d**) at atmospheric CO afforded alcohols **2-2c** and **2-2d** in 64% and 70% yield, respectively (entries 7 and 8). On the other hand, simpler secondary iodides such as 1-iodocyclohexane (**2-1e**) and 2-iodooctane (**2-1f**) resulted in a lower yield, in which the reduction course preceded (entries 9 and 10).

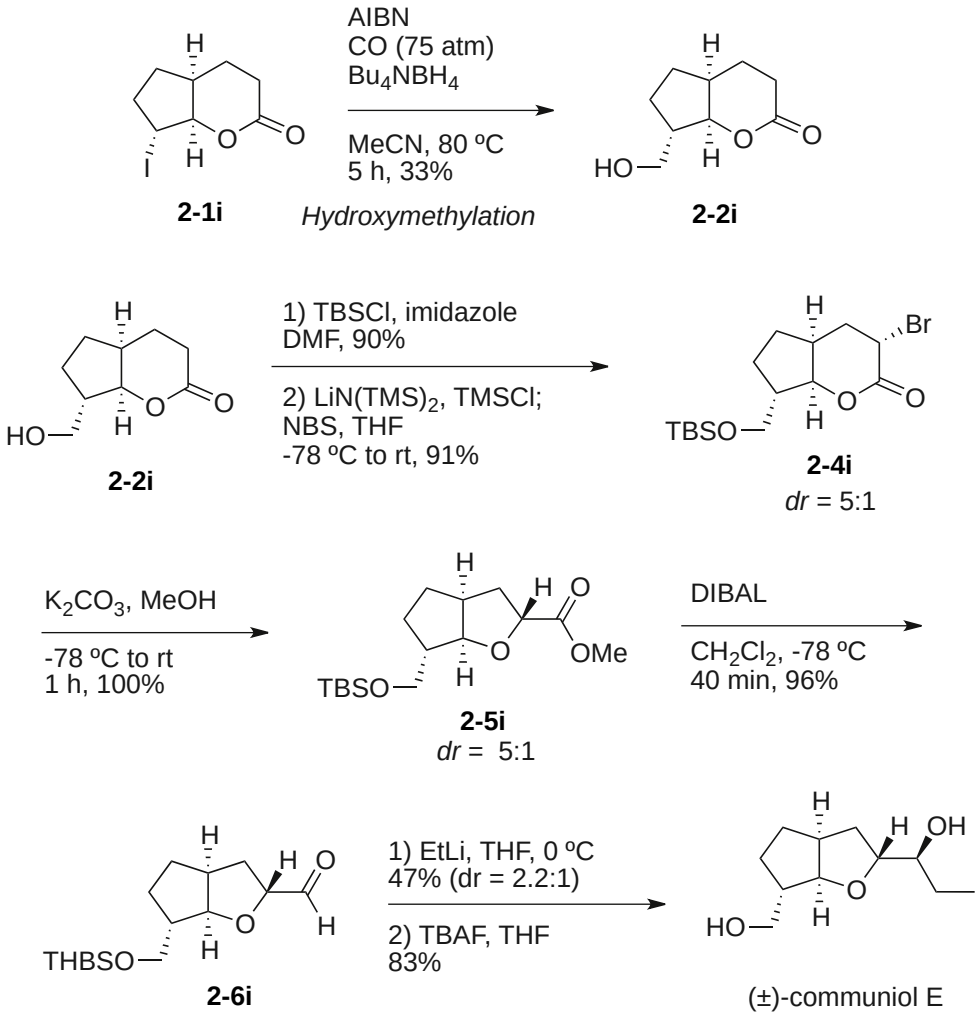
These results suggested that the steric factor played a crucial role in efficient hydroxymethylation; the major side reaction was an S_N2-type hydride reduction by Bu_4NBH_4, which was suppressed by increasing the bulkiness around the reaction center. It is important to note that functionalized iodides such as cholesteryl iodide **2-1g** underwent hydroxymethylation to give alcohols **2-2g** (entry 11). The author found that primary iodides were not suited for hydroxymethylation, due to competition by hydride reduction (entry 12).

Table 2-2. Radical/Ionic Hydroxymethylation of a Variety of Alkyl Iodides

entry	**2-1**		conditions	**2-2**		yield[a]
1		**2-1a**	A		**2-2a**	88%
2			B			74%
3		**2-1a'**	A			<3%
4		**2-1b**	A		**2-2b**	91%
5			B			70%
6[b]		**2-1c**	A		**2-2c**	82%
7			B			64%
8	 *exo/endo* = 96/4	**2-1d**	B		**2-2d**	70% *exo/endo* = 93/7
9		**2-1e**	B		**2-2e**	36%
10		**2-1f**	B		**2-2f**	42%[c]
11[d]		**2-1g**	B		**2-2g**	48% *dr* = 50/50
12		**2-1h**	B		**2-2h**	11%[e]

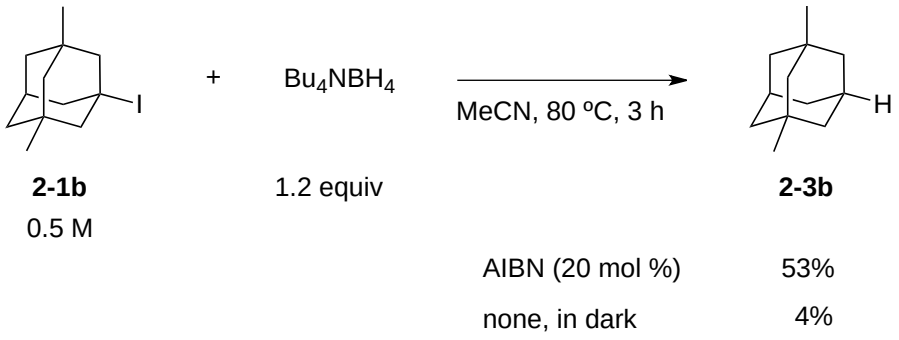
Conditions A: [**2-1**] = 0.5 M, CO (80-85 atm), AIBN (20 mol %), Bu_4NBH_4 (3 equiv), 80 ºC, 3 h. Conditions B: [**2-1**] = 0.5 M, CO (1 atm), Bu_4NBH_4 (1.2 equiv), black light, 25 ºC, 3 h. [a] Isolated yield after column chromatography on SiO_2. [b] Reaction time was 6 h. [c] 44% of *n*-octane was detected by GC. [d] Performed in benzene/CH_3CN (2:1) for 17 h with 0.17 M **2-1g**. [e] 75% of *n*-decane was detected by GC.

With the scope and limitation of the reaction established, the author then examined its application in the synthesis of (±)-communiol E, which is obtained from the culture broth of the horse dung-inhabiting fungus Podospora communis (Scheme 2-2).[8] Thus treatment of iodolactone with carbon monoxide in the presence of tetrabutylammonium borohydride and AIBN provided hydroxymethylation product. It should be noted that the highly susceptible lactone moiety survived under these reduction conditions, albeit in modest yield. After protection of the hydroxyl group as a TBS ether, bromination was effected to provide an inseparable mixture of bromolactones in favor of the desired diastereomer. The crucial rearrangement was realized in a stereospecific manner and afforded ester **2-5i** quantitatively. DIBAL reduction of **2-5i** at –78 ºC gave aldehyde **2-6i** without forming the alcohol, which was followed by ethylation and deprotection to furnish (±)-communiol E.



Scheme 2-2. Total Synthesis of (±)-Communiol E

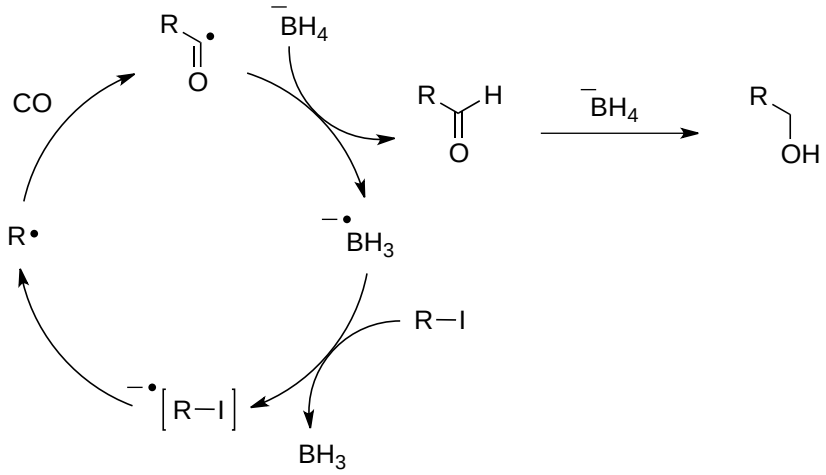
Thus, the author has succeeded in efficient hydroxymethylation of tertiary and secondary iodides without the use of group 14 radical mediators. It seems unusual that a significant amount of reduction product was formed in the reaction of a bulky tertiary iodide, such as **2-1a**, in the absence of a powerful hydrogen donor such as Bu_3SnH (see Table 2-1). **2-1a** can not undergo direct reduction through an ionic S_N2 process; therefore, the adamantyl radical arising from **2-1a** directly abstracted a hydrogen from borohydride and certain electron transfer processes were thought to propagate the radical chain. In an effort to gain further insight, the author performed some control experiments without CO. When a mixture of 3,5-dimethyl-1-iodoadamantane (**2-1b**), AIBN, and Bu_4NBH_4 in MeCN was refluxed for 3 h without shading, the corresponding reduction product **2-3b** was obtained in 53% yield along with 25% recovery of **2-1b** (Scheme 2-3). On the other hand, the reaction in the absence of AIBN under dark conditions afforded a trace amount of **2-3b** (4%) and the starting iodide **2-3b** was recovered (85%). Similarly, **2-3b** was obtained in 35% yield together with 51% recovery of **2-1b** upon exposure of **2-1b** to black light in the presence of Bu_4NBH_4 for 3 h at room temperature. These results indicated that radical processes were involved in the reduction of **2-1b** and Bu_4NBH_4 served as the hydrogen source.



Scheme 2-3. Reduction of 3,5-dimethyl-1-iodoadamantane (**2-1b**)

Taking the above results into consideration, two possible reaction mechanisms are conceivable for the present tin-free hydroxymethylation reaction. The first mechanism involves iodine atom transfer from alkyl iodides to acyl radicals followed by hydride reduction of the resulting acyl iodide (Scheme 2).[9, 10, 11]

The second mechanism shown in Scheme 2-4 involves an electron transfer mediated by borohydride reagent[12] ($S_{RN}1$ mechanism[13]). Thermal initiation or photoirradiation of alkyl iodides generates the initiating alkyl radicals ($R^{\bullet}$), which react with CO to form acyl radicals ($RCO^{\bullet}$). The acyl radicals abstract hydrogens from borohydride (BH_4^-) to form aldehydes and generates the borane radical anions ($BH_3^{\bullet -}$). While aldehydes undergo hydride reduction by borohydride anions to give alcohols, the generated borane radical anions ($BH_3^{\bullet -}$) react with alkyl iodides (R-I) through electron transfer to give radical anions ($[R\text{-}I]^{\bullet -}$) that fragment to alkyl radicals ($R^{\bullet}$) and iodide ions (I^-), thus completing a radical chain. The reduction product formed at low CO pressure gives strong indication that this mechanism is feasible.



Scheme 2-4. Possible Mechanism

2.3 Conclusion

In conclusion, the author has developed a novel hydroxymethylation reaction using CO and borohydride reagents without the use of toxic radical mediators such as trialkyltin hydrides or its precursors. The reaction can be applied to tertiary and secondary iodides. Furthermore, a combined system involving atmospheric pressure of CO and black light irradiation was successfully employed. The author has proposed a mechanism in which the borohydride reagents work both as a hydrogen source and a hydride source, and therefore act as a radical mediator. The reaction conditions are simple and mild. Therefore, this reaction represents a useful method for introducing the hydroxymethyl unit into organic molecules.

2.4 Experimental

General information. ^{1}H -NMR spectra were recorded with a JEOL JMN-500 (500 MHz) spectrometer, a JEOL ECS-400 (400 MHz) spectrometer, or a Varian MR400 (400 MHz) spectrometer in $CDCl_3$ and referenced to the solvent peak at 7.26 ppm. ^{13}C NMR spectra were recorded with a JEOL JMN-ECP500 (125 MHz) spectrometer, a JEOL ECS-400 (400 MHz) spectrometer, or a Varian MR400 (100 MHz) spectrometer and referenced to the solvent peak at 77.00 ppm. Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer and are reported as wavenumber (cm^{-1}). High resolution mass spectra were recorded with a JEOL MS700 spectrometer.

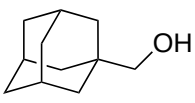
General Procedure for hydroxymethylation by thermal irradiation.

3,5-dimethyl-1-iodoadamantane **2-1b** (144 mg, 0.498 mmol), Bu_4NBH_4 (387 mg, 1.50 mmol), AIBN (18.4 mg, 0.112 mmol), and MeCN (1 mL) were placed in a 30 mL stainless steel autoclave. The autoclave was closed, purged three times with CO, pressured with 75 atm of CO, and then heated at 80 °C for 3 h. Excess CO was discharged at room temperature. The reaction mixture was concentrated and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5) to give 3,5-dimethyladamantene-1-methanol **2-2b** (88.8 mg, 0.457 mmol, 91%).

General Procedure for hydroxymethylation by photoirradiation.

3,5-dimethyl-1-iodoadamantane **2-1b** (151 mg, 0.520 mmol), Bu_4NBH_4 (162 mg, 0.632 mmol), and MeCN (1 mL) were placed in a Pyrex 30 mL two-necked round-bottomed flask and the mixture was irradiated by blacklight (15 W) with stirring for 3 h under atmosphere of CO balloon. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (hexane/EtOAc = 5) to give 3,5-dimethyladamantane-1-methanol **2-2b** (70.8 mg, 0.365, 70%).

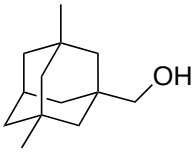
1-Adamantanmethanol (**2-2a**).



colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43-1.58 (m, 6H), 1.60-1.70 (m, 3H), 1.70-1.80 (m, 3H), 1.96-2.04 (m, 3H), 3.20 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ

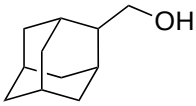
28.17, 34.47, 37.16, 39.02, 73.86. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

3,5-Dimethyladamantane-1-methanol (**2-2b**).



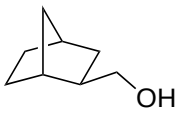
colorless solid; mp. 58-59 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.82 (s, 6H), 1.07-1.13 (m, 3H), 1.13-1.20 (m, 3H), 1.30-1.36 (m, 7H), 2.06-2.11 (m, ^{1}H), 3.24 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.30, 30.58, 30.91, 36.33, 37.65, 43.38, 45.32, 51.40, 73.30.

2-Adamantanemethanol (**2-2c**).



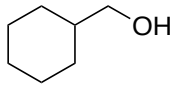
colorless solid; mp. 82-84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (bs, 1H), 1.52-1.59 (m, 2H), 1.71-1.95 (m, 13H), 3.73 (d, *J* = 8Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.93, 28.37, 29.19, 31.91, 38.16, 38.86, 47.10, 65.08.

2-Norbornanemethanol (exo / endo = 93 / 7) (2-2d).



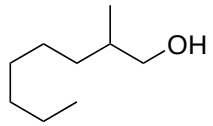
colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91-1.20 (m, 1H), 1.06-1.12 (m, 1H), 1.12-1.23 (m, 2H), 1.23-1.28 (m, 1H), 1.32-1.42 (m, 2H), 1.43-1.58 (m, 2H), 1.61-1.70 (m, 1H), 2.14 (m, 1H), 2.18-2.24 (m, 1H), 3.28-3.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): d 28.91, 29.82, 33.99, 35.13, 36.09, 38.09, 44.89, 66.92.

Cyclohexanemethanol (**2-2e**).



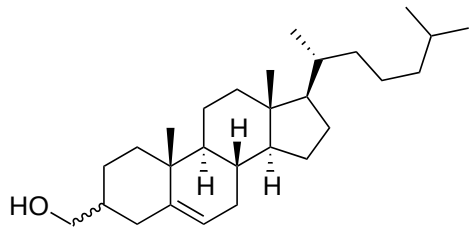
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87-0.96 (m, 2H), 1.13-1.28 (m, 2H), 1.42-1.73 (m, 1H), 1.72-1.75 (m, 6H), 2.63-2.90 (m, 1H), 3.42 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.81. 26.57, 29.52, 40.45, 68.78. This product is commercially available and the ^{1}H - and ^{13}C -NMR spectra are consistent with those of the authentic sample.

2-Methyloctanol[14] (**2-2f**).



^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86-0.92 (m, 6H), 1.06-1.13 (m, 1H) 1.19-1.49 (m, 10H), 1.53-1.65 (m, 1H), 3.42 (dd, *J* = 6.4, 10.6 Hz, 1H), 3.51 (dd, *J* = 6.0, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.24, 16.71, 22.80, 27.07, 29.74, 31.99, 33.27, 35.87, 68.53.

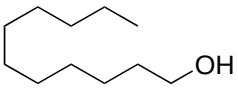
3-Hydroxymethylcholest-3-ene (dr = 50/50) (**2-2g**).



colorless solid; mp. 108-109 °C; Rf = 0.27 (hexane/AcOEt = 5); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.67 (d, *J* = 2.4 Hz, 3H), 0.83-2.10 (m, 41H), 2.42-2.53 (m, OH), 3.46-3.57 (m, 2H), 5.27-5.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.0, 140.2, 121.3, 119.9, 68.4, 63.8, 56.7, 56.1, 50.4, 50.3, 42.2, 42.0, 39.8, 39.7, 39.4, 38.9, 37..4, 37.3, 36.7, 36.1, 35.7, 34.3, 33.7, 31.8, 28.2, 27.9, 25.3, 24.2, 24.2, 23.8, 23.1, 22.8, 22.5, 20.9, 20.7, 19.4, 19.3, 18.6, 11.8, 11.8; FT-IR (KBr): 3323, 2932, 1459, 1380, 1333, 1142, 1024, 997, 961, 834, 798, 628, 420 cm^{-1}; HRMS calcd for $C_{28}H_{48}O$ $[M]^{+}$ 400.3705,

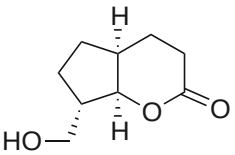
found 400.3682. The diastereomeric ratio was determined by ^{1}H and ^{13}C NMR. The olefinic carbons of one of the diastereomer gave absorptions at δ 142.0 and δ 121.3, and for another diastereomer at δ 140.2 and 119.9.

1-Undecanol (**2-2h**).



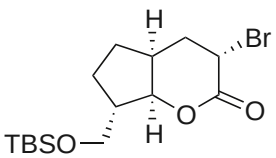
colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 6 Hz, 3H), 1.18-1.50 (m, 16H), 1.53-1.58 (m, 2H), 3.64 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.10, 22.67, 25.71, 29.32, 29.42, 29.60, 31.90, 32.77, 63.07. This product is commercially available and the ^{1}H - and ^{13}C NMR spectra are consistent with those of the authentic sample.

(±)-7-Hydroxymethyl-hexahydro-cyclopentapyran-2-one (**2-2i**).



colorless oil; Rf = 0.10, hexane/AcOEt = 1/2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.32-1.42 (m, 1H), 1.42-1.64 (m, 2H), 1.90-2.01 (m, 2H), 2.11-2.18 (m, 1H), 2.28-2.39 (m, 3H), 2.50 (dt, *J* = 16.5, 4.4 Hz, 1H), 3.65 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.74 (dd, *J* = 10.4, 5.6 Hz, 1H), 4.59 (dd, *J* = 7.3, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.47, 26.17, 29.06, 30.65, 36.37, 49.12, 63.66, 84.62, 173.37; FT-IR (neat): 3414, 2945, 2872, 1727 cm^{-1}; HRMS calcd for $C_9H_{14}O_3$ $[M]^+$ 170.0943, found 170.0944.

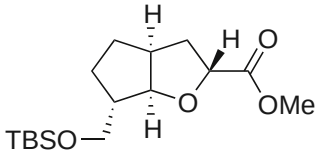
(±)-(3*S*,4*aS*,7*S*,7*aR*)-3-Bromo-7-((tert-butyldimethylsilyloxy)methyl)hexahydrocyclopenta[b]pyran-2(3H)-one (2-4i).



To a solution of alcohol **2-2i** (410 mg, 2.41 mmol) and imidazole (820 mg, 12.0 mmol) in DMF (12 mL) was added TBSCl (904 mg, 6.00 mmol). The mixture was stirred at room temperature for 2 h before addition of hexane and saturated NH_4Cl solution. The resulting mixture was extracted with hexane 3 times, and the combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10) to give a corresponding TBS ether (618 mg, 2.17 mmol, 90%). Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.38-1.63 (m, 3H), 1.82-1.98 (m, 2H), 2.08-2.17 (m, 1H), 2.21-2.39 (m, 3H), 2.48 (dt, *J* = 5.2, 16 Hz, 1H), 3.60 (dd, *J* = 4.8, 10 Hz, 1H), 3.69 (dd, *J* = 4.8, 10 Hz, 1H), 4.57 (dd, *J* = 4.4, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –5.4, –5.5, 18.2, 23.4, 25.8, 26.0, 29.0, 30.8, 36.6, 49.0, 63.2, 84.3, 173.3; FT-IR (film) 1107, 1067, 1177, 1251, 1321, 1361, 1388, 1434, 1463, 1471, 1746, 2710, 2858, 2930, 2952 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{28}O_3Si$ $[M - tBu]^+$ 227.1103, found 227.1123.

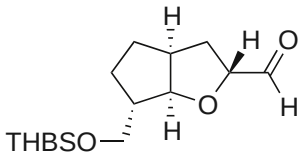
To a solution of TBS ether (204 mg, 0.717 mmol) in THF (3 mL) was added $LiN(TMS)_2$ (1.0 M solution in THF, 803 μL, 0.803 mmol) at –78 ºC. The mixture was stirred at –78 ºC for 5 min followed by the addition of TMSCl (114 μL, 0.896 mmol). The reaction mixture was warmed to 0 ºC and stirred for 30 min. The mixture was again cooled to –78 ºC followed by the addition of NBS (1.06 g, 5.96 mmol) in THF (9 mL). The resulting mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with water and extracted with Et_2O twice. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10) to give a 5:1 inseparable diastereomeric mixture of bromolactone **2-4i** (246 mg, 0.652 mmol, 91%). **2-4i** (dr = 5:1): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, for major isomer): δ 0.05 (s, 6H), 0.89 (s, 9H), 1.40-1.56 (m, 2H), 1.82-1.94 (m, 1H), 1.99-2.08 (m, 2H), 2.26-2.36 (m, 1H), 2.43-2.54 (m, 2H), 3.66 (dd, *J* = 4.4, 10 Hz, 1H), 3.74 (dd, 1H, *J* = 5.2, 10 Hz, 1H), 4.46 (t, *J* = 3.2 Hz, 1H), 4.97 (dd, *J* = 4.8, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, for major isomer): δ –5.30, –5.32, 18.4, 26.0, 26.6, 32.1, 33.0, 33.9, 39.3, 49.8, 63.0, 84.4, 167.9; FT-IR (film) 1078, 1103, 1146, 1201, 1254, 1299, 1361, 1388, 1440, 1463, 1471, 1743, 2710, 2738, 2857, 2928, 2952 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{27}BrO_3Si$ $[M - tBu]^+$ 307.0189, found 307.0157.

(±)-(2*R*,3*aS*,6*S*,6*aR*)-Methyl 6-((tert-Butyldimethylsilyloxy)methyl)hexahydro-2H-cyclopenta[*b*]furan-2-carboxylate (2-5i).



To a solution of bromolactone **2-4i** (227 mg, 0.601 mmol) in MeOH (12 mL) was added K_2CO_3 (83.1 mg, 0.601 mmol) at –78 ºC. The mixture was allowed to warm to room temperature with stirring for 5 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc twice. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10) to give a 5:1 inseparable diastereomeric mixture of ester **2-5i** (189 mg, 0.601 mmol, 100%). **2-5i** (dr = 5:1): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$, for major isomer): δ 0.03 (s, 6H), 0.88 (s, 9H), 1.34-1.55 (m, 2H), 1.74-2.02 (m, 3H), 2.13-2.20 (m, 2H), 2.62-2.74 (m, 1H), 3.52 (dd, *J* = 6.4, 10 Hz, 1H), 3.60 (dd, *J* = 5.2, 10 Hz, 1H), 3.74 (s, 3H), 4.49 (dd, *J* = 2.8, 7.2 Hz, 1H), 4.53 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, for major isomer): δ –5.3, 18.5, 26.1, 28.0, 31.5, 37.5, 42.7, 49.0, 52.2, 64.2, 77.3, 88.9, 173.7; FT-IR (film) 1006, 1094, 1154, 1205, 1255, 1362, 1388, 1437, 1463, 1471, 1740, 1757, 2361, 2858, 2882, 2931, 2952 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{30}O_4Si$ $[M - tBu]^+$ 257.1209, found 257.1194.

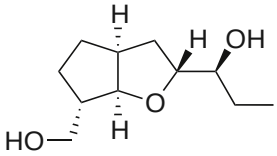
(±)-(2R,3aS,6S,6aR)-6-((*tert*-Butyldimethylsilyloxy)methyl)hexahydro-2H-cyclopenta[*b*]furan-2-carbaldehyde (2-6i).



To a solution of ester **2-5i** (81.9 mg, 0.260 mmol) in CH_2Cl_2 (2.6 mL) was added DIBAL (1.04 M solution in hexane, 275 μL, 0.286 mmol) at –78 ºC. After stirring for 40 min at –78 ºC, the reaction mixture was treated with hexane and saturated Rochelle salt solution. The resulting mixture was stirred at room temperature for 3 h and

extracted with Et_2O twice. The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10 to 3) to give a 5:1 inseparable diastereomeric mixture of aldehyde **2-6i** (70.7 mg, 0.249 mmol, 96%). **2-6i**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, for major isomer): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.35-1.52 (m, 2H), 1.77-1.99 (m, 3H), 2.08 (dt, *J* = 8.1, 12.6 Hz, 1H), 2.16-2.21 (m, 1H), 2.61-2.72 (m, 1H), 3.56 (d, *J* = 6.3 Hz, 2H), 4.33 (td, *J* = 1.8, 7.5 Hz, 1H), 4.43 (dd, *J* = 2.7, 6.6 Hz, 1H), 9.64 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, for major isomer): δ –4.97, –4.95, 18.8, 26.4, 28.6, 31.9, 34.7, 43.2, 49.6, 64.6, 83.4, 89.6, 203.0; FT-IR (film): 1007, 1074, 1101, 1255, 1361, 1388, 1463, 1471, 1541, 1558, 1736, 2711, 2738, 2802, 2858, 2885, 2930, 2952, 3410 cm^{-1}; HRMS (EI): m/z calcd for $C_{15}H_{28}O_3Si$ [M – *t*Bu]$^+$ 227.1103, found 227.1132.

(±)-Communiol E.



To a solution of aldehyde **2-6i** (21.9 mg, 0.0770 mmol) in THF (2 mL) was added EtLi (0.5 M solution in benzene and cyclohexane, 422 μL, 0.211 mmol) at 0 ºC. The reaction mixture was stirred at 0 ºC for 1 h and quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with Et_2O twice, and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was again dissolved in THF (2 mL) and treated with EtLi (0.5 M solution in benzene and cyclohexane, 703 μL, 0.352 mmol) at 0 ºC for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O three times. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 20) to give the desired alcohol (11.3 mg, 0.0363 mmol, 47%) and a mixture of other stereoisomers (5.3 mg, 0.017 mmol, 22%). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.88 (s, 9H), 0.99 (t, *J* = 7.2 Hz, 3H), 1.25-1.57 (m, 4H),

1.74-1.83 (m, 1H), 1.89-1.98 (m, 2H), 2.01-2.10 (m, 2H), 2.64 (quint, *J* = 7.6 Hz, 1H), 3.54 (dd, *J* = 6.4, 10 Hz, 1H), 3.61 (dd,, *J* = 5.6, 10 Hz, 1H), 3.72-3.78 (m, 1H), 3.90 (ddd, *J* = 3.2, 5.2, 10.4 Hz), 4.31 (dd, *J* = 3.6, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ –5.2, 10.6, 18.5, 25.9, 26.1, 28.7, 31.6, 32.0, 43.1, 50.0, 64.6, 72.9, 80.8, 87.4; FT-IR (film): 1005, 1032, 1070, 1101, 1254, 1361, 1388, 1463, 1471, 2738, 2859, 2930, 2955, 3451 cm^{-1}; HRMS (FAB) m/z calcd for $C_{17}H_{35}O_3Si$ $[M + H]^+$ 315.2355, found 315.2310.

To a solution of alcohol (5.1 mg, 16 μmol) in THF (162 μL) was added TBAF (1.0 M solution in THF, 24 μL, 24 μmol). The mixture was stirred at room temperature for 17 h and quenched with saturated $NaHCO_3$ solution. The resulting mixture was extracted with Et_2O twice and EtOAc three times, and the combined organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (EtOAc only) to give communiol E (2.7 mg, 14 μmol, 83%). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, *J* = 7.6 Hz, 3H), 1.29-1.39 (m, 2H), 1.42 (quint, *J* = 7.6 Hz, 2H), 1.52 (br dd, *J* = 5.6, 12.4 Hz, 1H), 1.79-1.86 (m, 1H), 1.91-2.00 (m, 2H), 2.02-2.11 (m, 1H), 2.68 (quint, *J* = 8.0 Hz, 1H), 3.60 (dd, *J* = 7.6, 10.4 Hz, 1H), 3.65 (dd, *J* = 6.8, 10.8 Hz, 1H), 3.76 (td, *J* = 3.2, 6.4 Hz, 1H), 3.93 (ddd, *J* = 3.6, 5.6, 10.4 Hz, 1H), 4.34 (dd, *J* = 4.4, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.6, 25.9, 28.6, 31.3, 31.8, 43.1, 50.0, 65.2, 72.8, 80.9, 88.1; FT-IR (film): 1019, 1044, 1074, 1146, 1234, 1304, 1374, 1448, 1465, 2872, 2939, 2957, 3367 cm^{-1}; HRMS (FAB): m/z calcd for $C_{11}H_{21}O_3$ $[M + H]^+$ 201.1491, found 201.1523.

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3 Radical/Ionic Hydroxymethylation of Alkyl and Aryl Iodides using NHC-BH_3

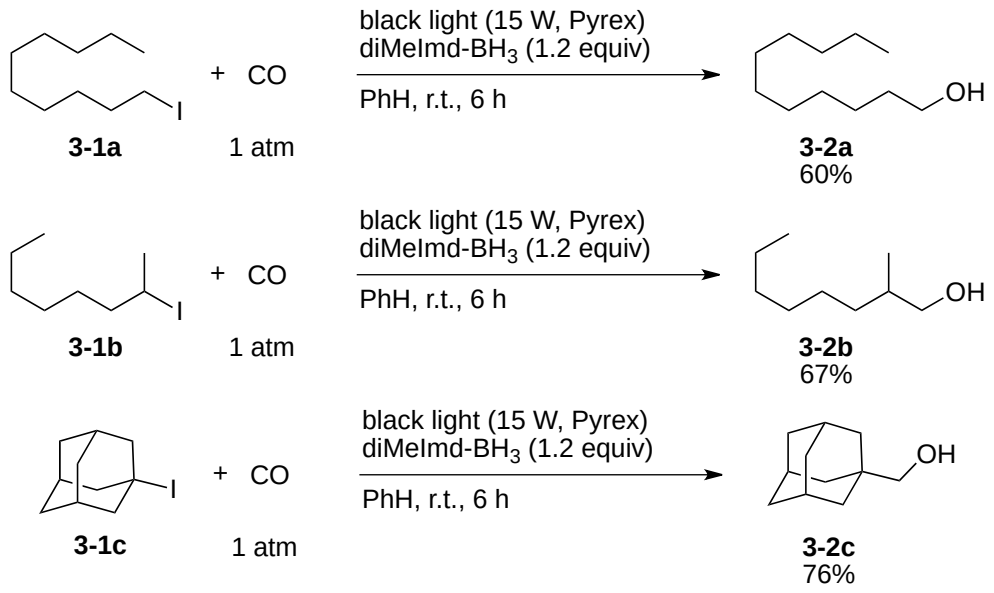
3.1 Introduction

Organo halides are among the most useful precursors to access carbon radical species and they have consequently found numerous applications in chemical synthesis. In the last two decades, the potential of CO[1] as a radical C1 synthon has been established with examples yielding a wide range of carbonyl compounds. In chapter 4, the author described radical hydroxymethylation of alkyl iodides using CO and tetrabutylammonium borohydride.[2] Due to a slower H donation ability of the borohydride reagents[3] compared with that of tributyltin hydride, the carbonylation could proceed efficiently, even under an atmospheric pressure of CO, without premature quenching of the key radicals by the borohydride reagents. While secondary and tertiary alkyl iodides worked well in these reactions, primary alkyl iodides faced competing hydride reduction to the corresponding alkanes. The other drawback of borohydride-mediated hydroxymethylation is that it is not compatible with iodoarenes, as the major product is the directly reduced arene.

Recently, Curran, Lacôte, and coworkers showed that *N*-heterocyclic carbene boranes (NHC-boranes) can be used for radical chain reactions as viable hydrogen transfer reagents.[4] In particular, the second-generation reagent 1,3-dimethylimidazol-2-ylidene borane (diMeImd-BH_3), a stable and easily handled solid, can smoothly reduce xanthates and related functional groups.[5] On the other hand, radical reduction of organo halides have been limited to compounds possessing electron withdrawing groups at the α position and this necessitates the use of polarity reversal catalyst such as thiols when ordinary organo halides are employed as substrates.[6, 7] Indeed, primary alkyl radicals react with NHC-boranes with a rate constant in the order of 10^4 M^{-1} s^{-1}, which is two orders of magnitude slower than that of tributyltin hydride.[8] In the hope of expanding the substrate scope for hydroxymethylation reactions, the author decided to examine the hydroxymethylation reaction of RX with CO using NHC-boranes as the reducing agent. Herein the author report that NHC-borane (diMeImd-BH_3) is an excellent reagent for radical hydroxymethylation of a wide variety of organo iodides including iodoarenes.

3.2 Results and Discussion

Initially the author examined the potential of diMeImd-BH_3 as a mediator for radical hydroxymethylation of alkyl iodides using CO. Under an atmosphere of CO (balloon), a benzene solution of 1-iododecane (**3-1a**) and diMeImd-BH_3 (1.2 equiv) was irradiated with a 15 W black light through a Pyrex flask for 6 h at rt, which gave the desired homologated alcohol **3-2a** in 60% isolated yield after flash chromatography on silica gel. Secondary and tertiary alkyl iodides, such as 2-iodoocatane (**3-1b**) and 1-iodoadamantane (**3-1c**), were also converted to the corresponding alcohols **3-2b** and **3-2c** in good yields.

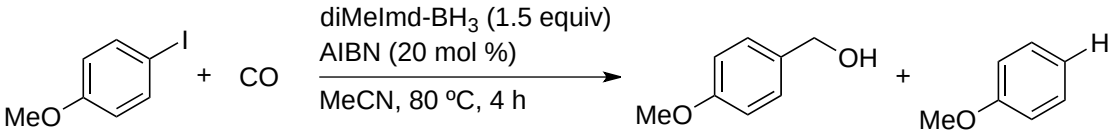


Scheme 3-1. Radical Hydroxymethylation of Alkyl Iodides

Having identified diMeImd-BH_3 as a suitable reagent for the hydroxymethylation of iodoalkanes, the author then studied hydroxymethylation of iodoarenes.[9] The author chose 4-iodoanisole (**3-1d**) as a model substrate for the initial study, and the results are summarized in Table 3-1. Disappointingly, photo-irradiation of an acetonitrile solution containing **3-1d** (0.1 M) and diMeImd-BH_3 (1.5 equiv) with atmospheric pressure of CO for 4 h gave exclusively reduced anisole **3-3d** in 68% yield (entry 1). However, under 80 atm of CO, the reaction gave the desired 4-methoxybenzyl alcohol **3-2d** in 71% yield along with 10% yield of anisole **3-3d** (entry 2). By decreasing the reaction concentration ([**3-1d**] = 0.05 M) **3-3d** was obtained as the sole product (entry

3).

Table 3-1. Hydroxymethylation of 4-Iodoanisole (**3-1d**)



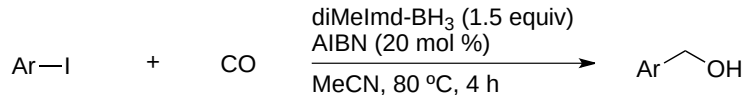
3-1d **3-2d** **3-3d**

entry	**3-1d** [M]	CO [atm]	conv.[a]	**3-2d**[b]	**3-3d**[c]
1[d]	0.1	1	100%	0%	68%
2	0.1	80	100%	71%	10%
3	0.05	80	100%	78%	trace

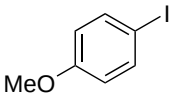
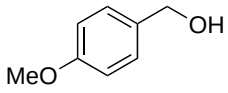
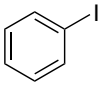
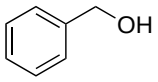
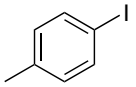
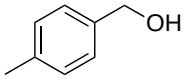
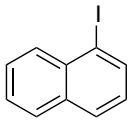
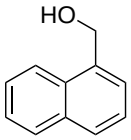
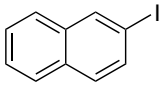
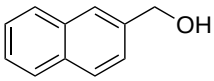
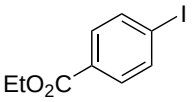
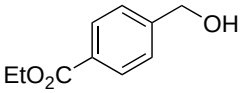
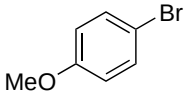
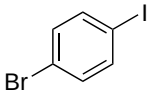
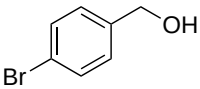
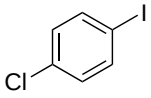
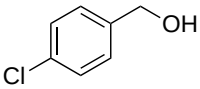
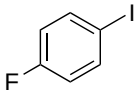
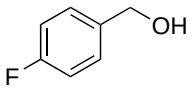
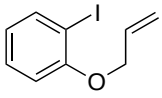
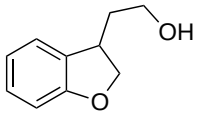
[a] Detemined by 1H NMR. [b] Isolated yield after flash column chromatography on silica gel. [c] GC yield. [d] Black light (15 W, Pyrex) was used instead of AIBN at rt.

Table 3-2 shows the results of hydroxymethylation of a variety of aryl iodides, which was conducted at 80 atm of CO using diMeImd-BH_3 as a radical mediator and AIBN as a radical initiator. Iodobenzene (**3-1e**), 4-iodotoluene (**3-1f**), 1-iodonaphthalene (**3-1g**), and 4-iodonaphtalene (**3-1h**) gave the corresponding alcohols **3-2e**, **3-2f**, **3-2g**, and **3-2h** in 63, 66, 67, and 59% yields, respectively (entries 2-5). The reaction of ethyl-4-iodobenzoate (**3-1i**) was also successful, giving **3-2i** in 66% yield (entry 6). Given the poor result of 4-bromoanisole (**3-1d'**) (entry 8), the author expected that the reaction was chemoselective with respect to iodoarenes. To confirm this the author found that the reaction of 1-bromo-4-iodobenzene (**3-1j**), 1-chloro-4-iodobenzene (**3-1k**), and 1-fluoro-4-iodobenzene (**3-1l**) proceeded chemoselectively at the aryl-iodine bond to give the corresponding bromine-, chlorine-, and fluorine-containing products **3-2j**, **3-2k**, and **3-2l**, respectively (entries 9-11). The tandem intramolecular cyclization-hydroxymethylation sequence of substrate **3-1m** also proceeded, albeit in 29% yield.

Table 3-2. Hydroxymethylation of a Variety of Aryl Iodides

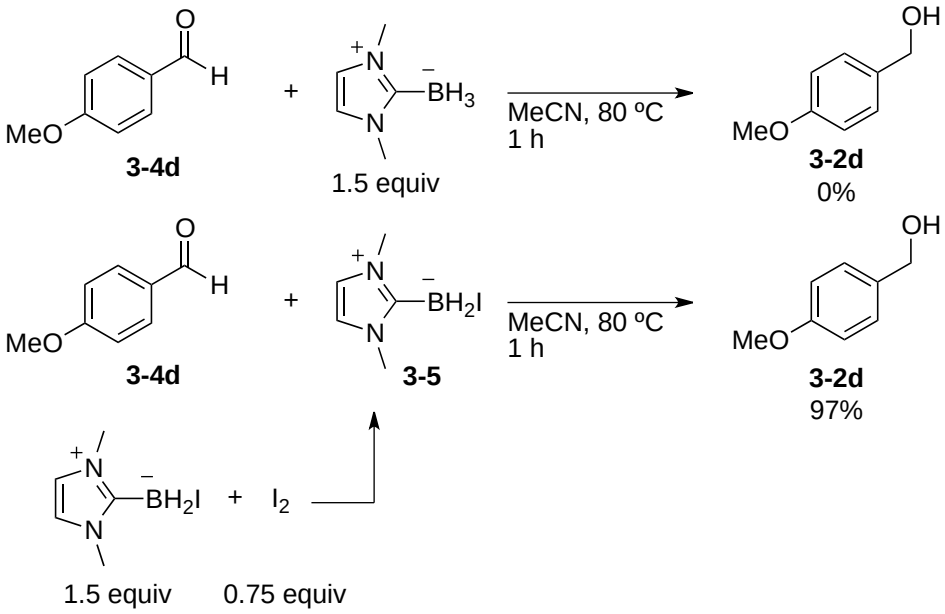


3-1 80 atm **3-2**

Entry	**3-1**		**3-2**		Yield[b]
1		**3-1d**		**3-2d**	78%
2		**3-1e**		**3-2e**	63%
3		**3-1f**		**3-2f**	66%
4		**3-1g**		**3-2g**	67%
5[c]		**3-1h**		**3-2h**	59%
6					66%
7[d]		**3-1i**		**3-2i**	73%
8		**3-1d'**	**5-2d**		4%
9		**3-1j**		**3-2j**	62%
10		**3-1k**		**3-2k**	63%
11		**3-1l**		**3-2l**	54%
12		**3-1m**		**3-2m**	29%[e]

[a] Conditions: ArI (0.5 mmol), **3-1** (0.75 mmol), AIBN (0.1 mmol), CO (80 atm), 80 ºC, 4 h. [b] Isolated yield after flash column chromatography on silica gel. [c] Reaction performed for 8 h. [d]CO (150 atm) [e] **3-1m** was recovered in 31% yield.

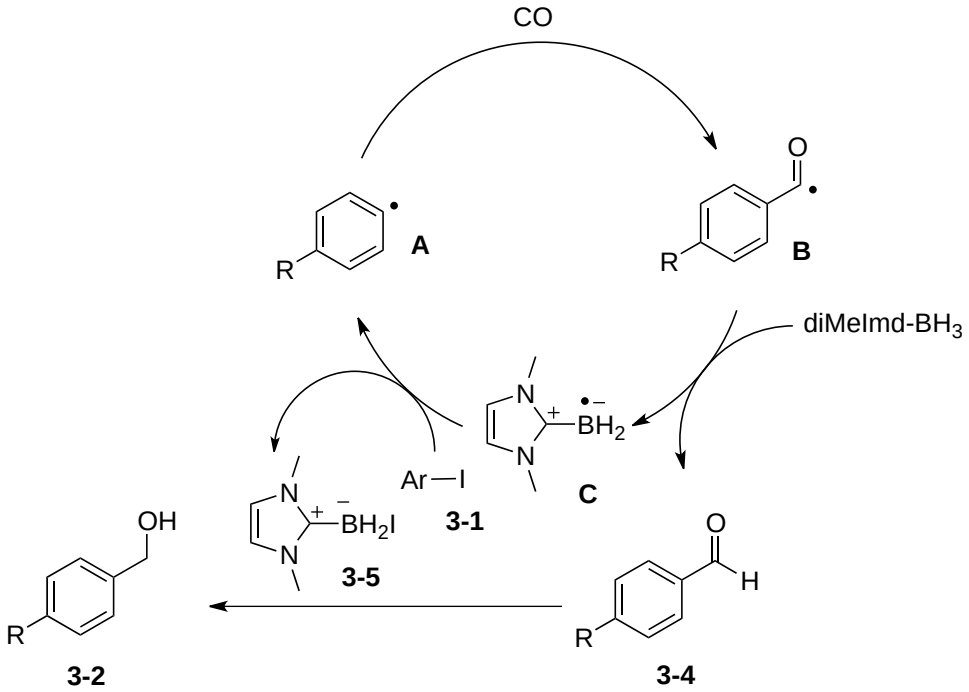
In the present hydroxymethylation reactions using diMeImd-BH, similar to the borohydride reagents discussed in Chapter 2, the precursors of **3-2** are thought to be the corresponding aldehydes formed by H-abstraction from NHC-borane by acyl radicals. According to Curran's[10] and Lindsay's[11] work, however, NHC-boranes are able to reduce aldehydes and ketones in the presence of SiO_2 or Lewis acids. As a control reaction the author took 4-anisaldehyde (**3-4d**) and reacted it with diMeImd-BH_3 at 80 ^oC. After 1 h, no reduction was observed (Scheme 3-2). In a separate experiment, an acetonitrile solution of 0.75 equiv of I_2 and 1.5 equiv of NHC-borane was treated with **3-4d**. This caused rapid disappearance of **3-4d** over 1 h and **5-2d** was isolated in 97% yield after flash column chromatography on silica gel. This result suggests that the iodinated NHC-borane **3-5**[12] may act as an effective aldehyde reducing agent, but not the NHC-borane itself.



Scheme 3-2. Reduction of 4-Anisaldehyde (**3-4d**)

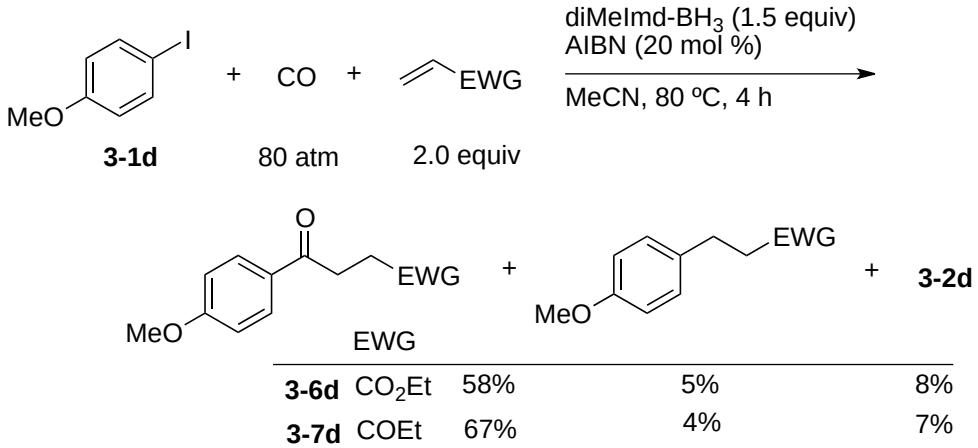
The proposed mechanism is shown in Scheme 3-3. Radical initiation of aryl iodide leads to generation of the aryl radical **A**. **A** could then add to CO to form the corresponding acyl radical **B**, which could further abstract hydrogen from diMeImd-BH_3 to give an aldehyde **3-4** and the borane radical anion **C**. Subsequent iodine abstraction from **3-1** returns **A** and iodinated NHC **3-5**, thus completing the

radical chain. Alcohol **3-2** is formed by hydride reduction of aldehyde **3-4** by **3-5**.



Scheme 3-3. Possible Mechanism

The author then examined a three-component reaction leading to unsymmetrical ketones using diMeImd-BH_3 (Scheme 3-4). When a mixture of 4-iodoanisole (**3-1d**), CO, and ethyl acrylate (2 equiv) with diMeImd-BH_3 was subjected to the radical reaction conditions, unsymmetrical ketone **3-6d** was obtained in 58% yield along with small amounts of direct addition product and hydroxymethylation product **3-2d**. Similarly, the reaction of **3-1d**, CO, and ethyl vinyl ketone gave 1,3-diketone **3-7d** in 67% yield.



Scheme 3-4. DiMeImd-BH_3 Mediated Three Component Reaction of 4-Iodoanisole (**3-1d**), CO, and Ethyl Acrylate or Ethyl Vinyl Ketone

3.3 Conslusion

In summary, the author has demonstrated that the hydroxymethylation reactions of alkyl and aryl iodides are successfully carried out using CO as a C1 source and diMeImd-BH_3 as a radical mediator. Control experiments suggest that NHC-borane serves as hydrogen-donor to acyl radicals and iodinated NHC **3-5**, formed by the radical generation process from iodoarene **3-1**, and serves as the in situ generated hydride-donor to the aldehydes, giving the corresponding alcohol **3-2**. The NHC-borane mediated reaction system can also be applied to one-pot three-component coupling reactions leading to unsymmetrical ketones.

3.4 Experimental

General information. ^{1}H -NMR spectra were recorded with a JEOL JMN-500 (500 MHz) spectrometer, a JEOL ECS-400 (400 MHz) spectrometer, or a Varian MR400 (400 MHz) spectrometer in $CDCl_3$ and referenced to the solvent peak at 7.26 ppm. ^{13}C NMR spectra were recorded with a JEOL JMN-ECP500 (125 MHz) spectrometer, a JEOL ECS-400 (400 MHz) spectrometer, or a Varian MR400 (100 MHz) spectrometer and referenced to the solvent peak at 77.00 ppm.

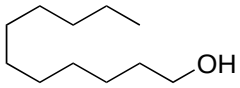
General Procedure for the Hydroxymethylation of alkyl iodides

1-Iodoadamantane (131 mg, 0.50 mmol), diMeImd-BH_3 (63 mg, 0.58 mmol), and benzene (1 mL) were placed in a Pyrex 20 mL two-necked round-bottomed flask and the mixture was irradiated by black light (15 W) with stirring for 6 h under atmosphere of CO balloon. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (hexane/ether = 5, 2) to give **3-2c** (63.5 mg, 0.38 mmol, 76%).

General Procedure for the Hydroxymethylation of aryl iodides

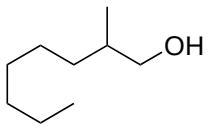
4-iodoanisole (116 mg, 0.50 mmol), diMeImd-BH_3 (84 mg, 0.76 mmol), AIBN (16 mg, 0.097 mmol), and MeCN (10 mL) were placed in a 30 mL stainless steel autoclave. The autoclave was closed, purged three times with CO, pressured with 80 atm of CO, and then heated at 80 °C for 4 h. Excess CO was discharged at room temperature. The reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (hexane/ether =10, 5, 2) to give **3-2d** (53 mg, 0.39 mmol, 78%).

1-Undecanol (**3-2a**).



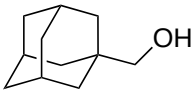
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 5.6 Hz, 3H), 1.18-1.50 (m, 16H), 1.53-1.58 (m, 2H), 3.64 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.27, 22.83, 25.87, 29.48, 29.58, 29.76, 32.05, 32.93, 63.23. This product is commercially available and the ^{1}H - and ^{13}C -NMR spectra are consistent with those of the authentic sample.

2-Methyloctanol[13] (**3-2b**).



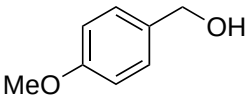
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86-0.92 (m, 6H), 1.06-1.13 (m, 1H) 1.19-1.49 (m, 10H), 1.53-1.65 (m, 1H), 3.42 (dd, *J* = 6.4, 10.6 Hz, 1H), 3.51 (dd, *J* = 6.0, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.24, 16.71, 22.80, 27.07, 29.74, 31.99, 33.27, 35.87, 68.53.

1-Adamantanemethanol (**3-2c**).



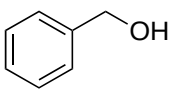
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (m, 1H), 1.46-1.54 (m, 6H), 1.60-1.67 (m, 3H), 1.69-1.76 (m, 3H), 1.93-2.01 (m, 3H), 3.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.27, 34.57, 37.26, 39.13, 73.91. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

(4-Methoxyphenyl)methanol (**3-2d**).



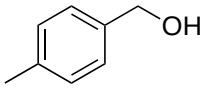
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.53 (t, *J* = 6.0 Hz, 1H), 3.81 (s, 3H), 4.62 (d, *J* = 6.0 Hz, 2H), 6.88-6.92 (m, 2H), 7.29-7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.42, 65.16, 114.07, 128.79, 133.22, 159.32. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

Benzyl alcohol (**3-2e**).



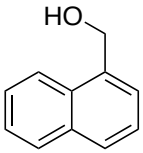
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.60-1.66 (m, 1H), 4.71 (d, *J* = 6.0 Hz, 2H), 7.26-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 65.16, 127.05, 127.64, 128.58, 140.91. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

(4-Methylphenyl)methyl alcohol (**3-2f**).



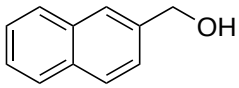
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.54 (t, *J* = 6.0 Hz, 1H), 2.36 (s, 3H), 4.66 (d, *J* = 6.0 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.25, 65.27, 127.21, 129.32, 137.44, 137.99. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

1-Naphthylenemethanol (**3-2g**).



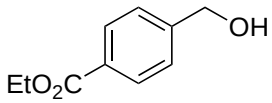
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.71 (t, *J* = 6.0 Hz, 1H), 5.17 (d, *J* = 6.0 Hz, 2H), 7.42-7.58 (m, 4H), 7.82-7.90 (m, 2 H), 8.14 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 63.64, 123.72, 125.38, 125.48, 125.95, 126.41, 128.62, 128.74, 131.27, 133.84, 136.32. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

2-Naphthylenemethanol (**3-2h**).



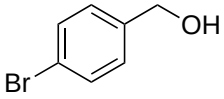
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.87 (s, 2 H), 7.4**3**-7.52 (m, 3H), 7.81-7.87 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 65.58, 125.29, 125.55, 126.02, 126.31, 127.84, 128.01, 128.46, 133.04, 133.46, 138.40. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

4-Hydroxymethylbenzoic acid ethyl ester[14] (**3-2i**).



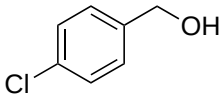
^{1}H NMR ($CDCl_3$, 400MHz): δ1.40 (t, *J* = 6.9 Hz, 3H), 1.76-1.82 (br, 1H), 4.35 (q, *J* = 6.9 Hz, 2H), 4.78 (d, *J* = 6.0 Hz, 2H), 7.43, (d, *J* = 8.3 Hz, 2H), 8.04 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.33, 61.09, 64.45, 126.44, 129.39, 129.75, 146.20, 166.76.

4-Bromophenylmethanol (**3-2j**).



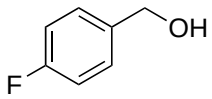
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.64 (t, *J* = 6.0 Hz, 1H), 4.66 (d, *J* = 5.9 Hz, 2H), 7.20-7.25 (m, 2H), 7.48-7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 64.52, 121.49, 128.67, 131.67, 139.80. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

4-Chlorophenyl methanol (**3-2k**).



^{1}H NMR ($CDCl_3$, 400MHz): δ 1.64 (t, *J* = 6.0 Hz, 1H), 4.68 (d, *J* = 6.0 Hz, 2H), 7.29-7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 64.57, 128.38, 128.76, 133.42, 139.33. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

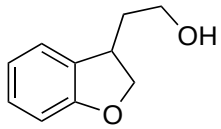
1-Fluoro-4-hydroxymethylbenzene (**3-2l**).



^{1}H NMR ($CDCl_3$, 400MHz): δ 1.67 (t, *J* = 5.5 Hz, 1H), 4.67 (d, *J* = 5.2 Hz, 2H), 7.02-7.08 (m, 2H), 7.31-7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 64.71, 115.49 (d, J_{C-F} = 21.0 Hz), 128.88 (d, J_{C-F} = 7.7 Hz), 136.66 (d, J_{C-F} = 2.8 Hz), 162.40 (d, J_{C-F} =

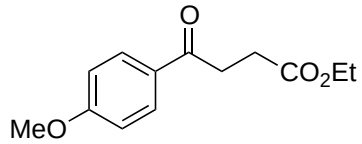
243.5 Hz). This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

2-(2,3-Dihydrobenzofuran-3-yl)ethanol[15] (**3-2m**).



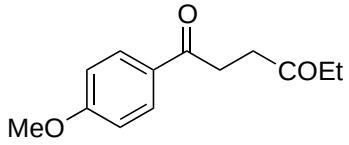
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.33 (t, *J* = 5.2 Hz, 1H), 1.80-1.90 (m, 1H), 2.02-2.10 (m, 1H), 3.56-3.65 (m, 1H), 3.78 (q, *J* = 6.4 Hz, 2H), 4.28 (dd, *J* = 9.2, 6.8 Hz, 1H), 4.68 (t, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.88 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.54, 39.15, 60.90, 77.08, 109.72, 120.57, 124.44, 128.38, 130.58, 159.87.

2-(4-Methoxyphenyl)-2-oxo-butyric acid ethyl ester[16] (**3-6d**).



^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.27 (t, *J* = 6.8 Hz, 3H), 2.74 (t, *J* = 6.4 Hz, 2H), 3.27 (t, *J* = 6.8 Hz, 2H), 3.87 (s, 3H), 4.16 (q, *J* = 8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.24, 28.40, 33.03, 55.49, 60.63, 113.75, 129.71, 130.32, 163.57, 173.09, 196.68.

1-(4-Methoxyphenyl)hexane-1,2-dione[17] (**3-7d**).



^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10 (t, *J* = 7.2 Hz, 3H), 2.57 (q, *J* = 7.6 Hz, 2H), 2.85 (t, *J* = 6.0 Hz, 2H), 3.25 (t, *J* = 6.4 Hz, 2H), 3.87 (s, 3H), 6.92-6.95 (m, 2H), 7.96-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.91, 32.14, 35.93, 36.16, 55.52, 113.74,

129.80, 130.37, 163.55, 197.29, 210.42.

3.5 References

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4 Hydroxymethylation of Alkyl Halides with HCHO

4.1 Introduction

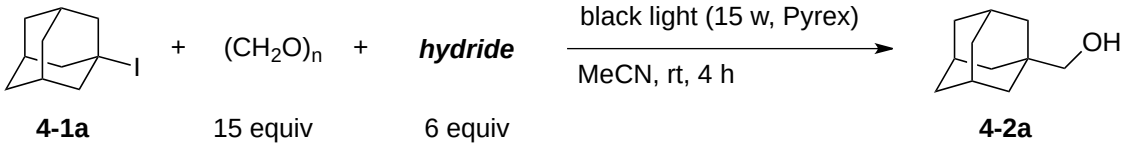
Whereas the use of formaldehyde as a C1 synthon is quite common in carbanion reactions, the synthetic use of formaldehyde in radical reactions is rarely reported.[1] In 1958, Fuller and Rust reported di-*tert*-butylperoxide (DTBPO) mediated reaction of cyclohexane with formaldehyde leading to cyclohexanemethanol in 38% yield.[2] In 1965, a similar type of reaction with ethanol and formaldehyde to give ethylene glycol was reported by Oyama.[3] Later on, the work was followed independently by Kollar[4] and Sanderson.[5] In 1972, Suzuki, Miyaura, Brown, and co-workers reported the reaction of trialkylborane with formaldehyde under air to give one-carbon homologated alcohols, which is thought to involve alkyl radical addition to formaldehyde to form alkyl borate as the precursor to alcohols.[6] While these reactions were noteworthy as a pioneering effort to use formaldehyde in radical reactions, to establish the usefulness of formaldehyde as a radical C1 acceptor,[7,8] a novel efficient reaction system had to be explored.

In chapter 2, the author described that the radical hydroxymethylation of alkyl iodides can be carried out under atmospheric pressure of CO in the presence of borohydride reagents.[9] The author became interested in whether a system in which CO is simply replaced by formaldehyde would work or not for the hydroxymethylation of alkyl halides. This chapter described that alkyl iodides and bromides undergo radical mediated hydroxymethylation with paraformaldehyde in the presence of tetrabutylammonium cyanoborohydride (Bu_4NBH_3CN) as a radical mediator.[10]

4.2 Results and Discussion

1-Iodoadamantane (**4-1a**) was chosen as a model substrate for the initial study (Table 4-1). When a mixture of **4-1a**, paraformaldehyde, and Bu_4NBH_3CN in acetonitrile was irradiated with a 15 W black light (peak wave length at 352 nm) using a Pyrex flask for 4 h under nitrogen, the desired 1-hydroxymethyladamantane (**4-2a**) was obtained in 91% yield. The reaction using $NaBH_3CN$ gave 70% yield of **4-2a**, whereas Bu_4NBH_4, $NaBH_4$, BH_3•NMe_3, BH_3•NH_2*t*-Bu, and Bu_3SnH did not work.

Table 4-1. Screening of Radical Mediator

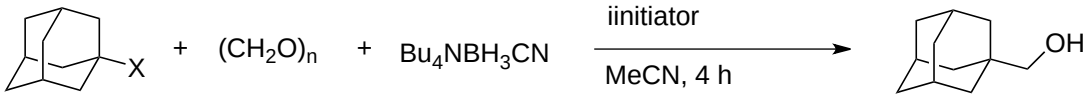


4-1a 15 equiv 6 equiv **4-2a**

Bu_4NBH_3CN	Bu_4NBH_4	$NaBH_3CN$	$BH_3•NMe_3$	$BH_3•NH_2t$-Bu	Bu_3SnH
91%	0%	70%	0%	0%	0%

The reaction using thermal conditions with 2,2'-azobisisobutyronitrile (AIBN) as a radical initiator also worked well (Table 4-1, entry 2), whereas the reaction with heating without AIBN did not proceed (entry 3). This suggests that the present reaction would proceed via a radical chain process. When 1-bromoadamantane (**4-1a'**) was irradiated with a 15 W black light, no hydroxymethylation product was obtained. However, irradiation using a 6 W low-pressure Hg lamp (peak wave length at 254 nm) through a quartz tube affected smooth hydroxymethylation reaction, which gave 85% yield of **4-2a** (entry 5).

Table 4-2. Screening of Radical Initiator



4-1a 15 equiv 6 equiv **4-2a**

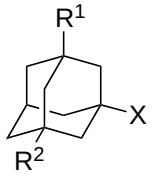
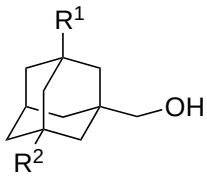
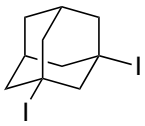
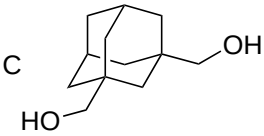
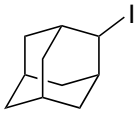
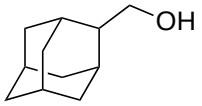
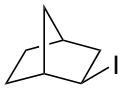
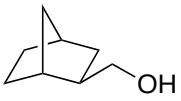
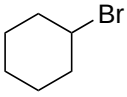
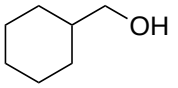
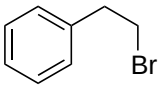
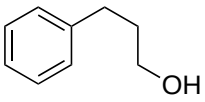
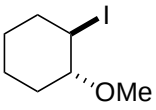
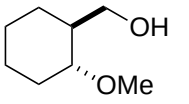
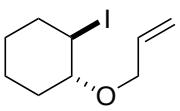
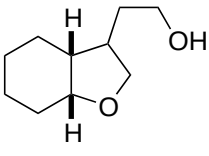
entry	X (**4-1**)	initiator	temp, °C	**4-2**[a]
1	I (**4-1a**)	black light (15 W, Pyrex)	25	85%
2[b]	I (**4-1a**)	AIBN (20 mol %)	90	87%
3	I (**4-1a**)	none	90	0%
4[c]	Br (**4-1a'**)	black light (15 W, Pyrex)	25	0%
5[c]	Br (**4-1a'**)	low-pressure Hg lamp (6 W, quartz)	25	85%

[a] Isolated yield by flash column chromatography on SiO_2. [b] $(CH_2O)_n$: 7.5 equiv; Bu_4NBH_3CN: 2.0 equiv. [c] Reaction time, 12 h.

Encouraged by the results shown in Table 1, the author then applied these reaction

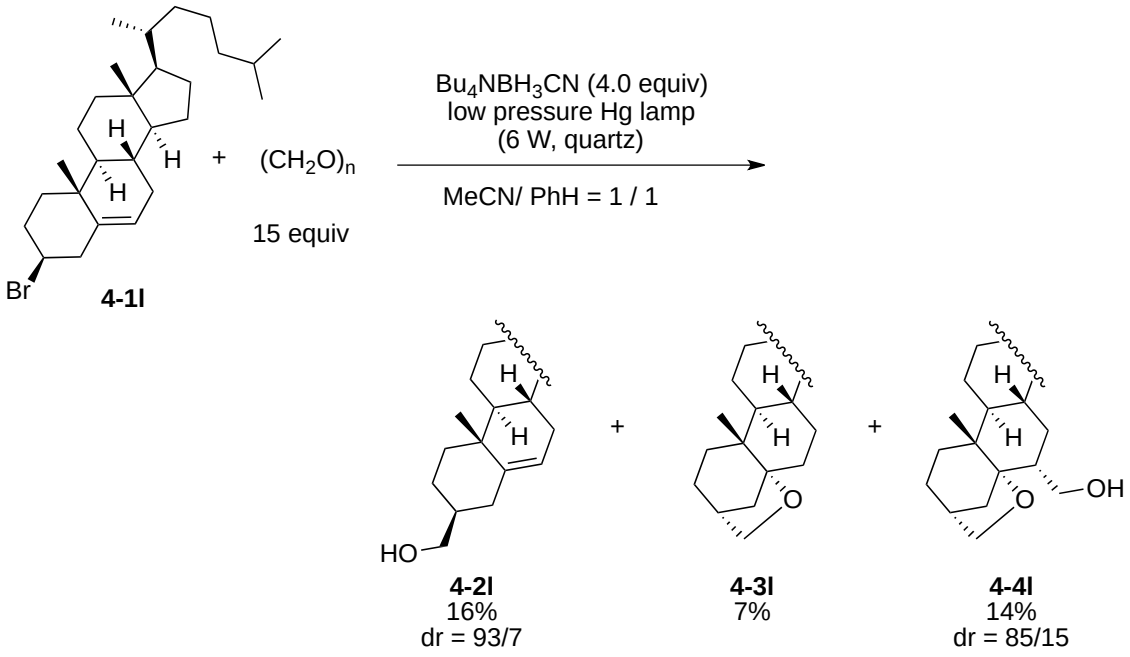
conditions to the hydroxymethylation of various alkyl halides (Table 4-3). Substituted 1-iodoadamantanes **4-1b** and **4-1c** gave the corresponding alcohols **4-2b** and **4-2c** in good yields (entries 3 and 4). Similarly, 1,3-diiodoadamantane (**4-1d**) underwent dihydroxymethylation to give diol **4-2d** in 77% yield (entry 5). Secondary alkyl halides **4-1e**, **4-1f** and **4-1g** also reacted smoothly with formaldehyde to form the corresponding alcohols **4-2e**, **4-2f** and **4-2g** in good yields (entries 6–8). However, in the reaction of primary alkyl halides such as 1-bromodecane (**4-1h**) and (2-bromoethyl)benzene (**4-1i**), the yields of the hydroxymethylated products were low (entries 9 and 10). This is due to the competitive direct S_N2 reduction of the alkyl halides by the hydride anion. 2-Methoxy-iodocyclohexane (**4-1j**) underwent hydroxymethylation to give alcohol **4-2j** in 50% yield (entry 11). In the case of 2-allyloxy-iodocyclohexane (**4-1k**), a bicyclic alcohol (**4-2k**) was formed in 39% yield via sequential 5-exo radical cyclization and addition to formaldehyde (entry 12).

Table 4-3. Hydroxymethylation of Haloalkane with $(HCHO)_n$ and Bu_4NBH_3CN

Entry	**4-1**	Method[a]	**4-2**	Yield (%)[b]
				
1	$R^1 = R^2 = H$, X = I	**4-1a** A	**4-2a**	85
2	$R^1 = R^2 = H$, X = Br	**4-1a'** B	**4-2a**	86
3	$R^1 = R^2 = Me$, X = I	**4-1b** A	**4-2b**	85
4	$R^1 = H$, $R^2 = OH$, X = I	**4-1c** C	**4-2c**	77
5[c]		**4-1d** C		**4-2d** 77
6		**4-1e** A		**4-2e** 60
7	 *exo/endo* = 96/4	**4-1f** A		**4-2f** 62 *exo/endo* = 99/1
8		**4-1g** B		**4-2g** 57
9	$C_{10}H_{21}I$	**4-1h** B	$C_{10}H_{21}$OH	**4-2h** 25
10		**4-1i** B		**4-2i** 41
11		**4-1j** C		**4-2j** 50 trans/cis = 78/22
12		**4-1k** C		**4-2k** 39 dr = 75/25

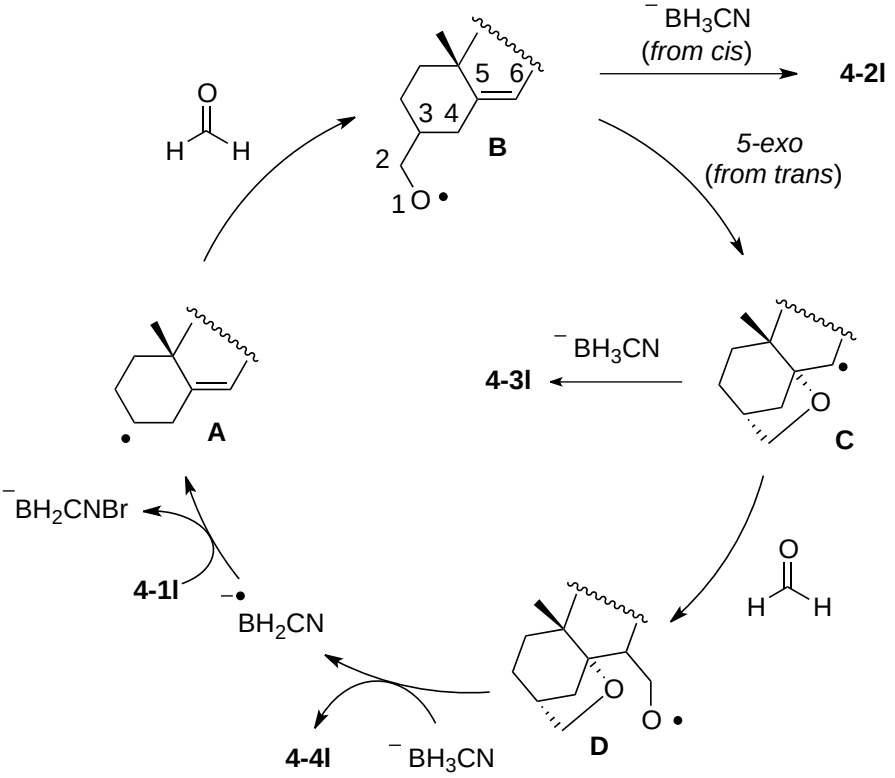
[a]Method A: black light (15 W, Pyrex), rt. For entries 1, 3, and 6, 4 h. For entry 7, 18 h. Method B: low-pressure Hg lamp (6 W, quartz), rt, 12 h. Method C: AIBN (20 mol %), 90 °C. For entries 4 and 12, 6 h. For entry 5, 8 h. For entry 11, 22 h. [b]Isolated yield by flash chromatography on SiO_2. [c]Bu_4NBH_3CN, 8.0 equiv.

The reaction of cholesteryl bromide (**4-1l**) was intriguing in terms of a radical cascade and the stereochemistry. Hydroxymethylation product **4-2l** was obtained stereoselectively along with cyclized products **4-3l** and **4-4l**, the latter of which incorporated two molecules of formaldehyde. This is in contrast to hydroxymethylation system using CO in chapter 2, which gave inherently a cis/trans mixture of a hydroxymethylation product.



Scheme 4-1. Hydroxymethylation of Cholesteryl Bromide (**4-1l**)

The mechanistic rationale for the reaction of **4-1l** with formaldehyde and Bu_4NBH_3CN is summarized in Scheme 4-2. Radical initiation generates the alkyl radical **A** from **4-1l**, which adds to formaldehyde to give a *cis* and *trans* mixture of alkoxy radical **B**. Whereas 3α-alkoxy radical **B** (*trans*) undergoes 5-exo cyclization to give **C**, which would add to a second molecule of formaldehyde to give **D**, 3β-alkoxy radical **B** (*cis*) encounters steric difficulties in undergoing 5-exo cyclization. Thus formed alkoxy radicals abstract hydrogen from (BH_3CN^-) to form an alcohols **4-2l** and **4-4l**.[11,12,13] The resulting borane radical anion ($BH_2CN^{\bullet -}$), would abstract bromine atom from **4-1l** to form **A**. Alternative mechanism would involved single electron transfer leading to ($[R\text{-}Br]^{\bullet -}$) followed by elimination of (Br^-) to give **A**, thus sustaining the radical chain.[14]



Scheme 4-2. Possible Mechanims

4.3 Conclusion

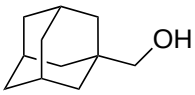
To date formaldehyde has seldom been utilized in radical chain reactions. However, as the present results demonstrate when coupled with a judicious choice of radical mediator, such as a borohydride reagent, formaldehyde can serve as a useful C1 radical synthon. Applications of formaldehyde in radical cascade reactions as well as further mechanistic studies are currently underway in our laboratory.

4.4 Experimental

General information. ^{1}H -NMR spectra were recorded with a JEOL JMN-500 (500 MHz) spectrometer, a JEOL ECS-400 (400 MHz) spectrometer, or a Varian MR400 (400 MHz) spectrometer in CDCl3 and referenced to the solvent peak at 7.26 ppm. ^{13}C NMR spectra were recorded with a JEOL JMN-ECP500 (125 MHz) spectrometer, a JEOL ECS-400 (400 MHz) spectrometer, or a Varian MR400 (100 MHz) spectrometer and referenced to the solvent peak at 77.00 ppm. Infrared spectra were recorded on a JASCO FT/IR-4100 spectrometer and are reported as wavenumber (cm-1). High

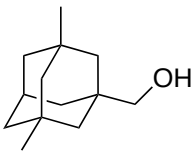
resolution mass spectra were recorded with a JEOL MS700 spectrometer.

1-Adamantanmethanol (4-2a).



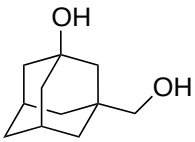
colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43-1.58 (m, 6H), 1.60-1.70 (m, 3H), 1.70-1.80 (m, 3H), 1.96-2.04 (m, 3H), 3.20 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.17, 34.47, 37.16, 39.02, 73.86. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

3,5-Dimethyladamantane-1-methanol (4-2b).



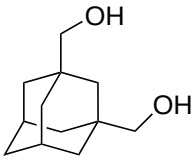
colorless solid; mp. 58-59 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.82 (s, 6H), 1.07-1.13 (m, 3H), 1.12-1.20 (m, 3H), 1.30-1.36 (m, 7H), 2.06-2.11 (m, 1H), 3.24 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.30, 30.58, 30.91, 36.33, 37.65, 43.38, 45.32, 51.40, 73.30.

3-Hydroxy-1-adamantanemethanol (4-2c).



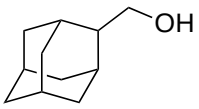
colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42-1.57 (m, 10H), 1.62-1.73 (m, 4H), 2.22-2.25 (m, 2H), 3.29 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.35, 35.59, 37.71, 38.44, 44.85, 46.66, 68.84, 68.84, 72.66; FT-IR (KBr): 3374, 3307 cm^{-1}; MS (EI) *m/z* (rel intensity) 182 (M^+, 32), 151 (100), 107 (12), 95 (33), 91 (11), 77 (11) ; HRMS calcd for $C_1{}^{1}H_{18}O_2$ $[M]^+$ 182.1307, found 182.1307.

1,3-Adamantanedimethanol (4-2d).



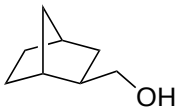
colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (bs, 2H), 1.43-1.64 (m, 12H), 2.11 (brs, 2H), 3.26 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.12, 34.97, 36.66, 38.62, 40.44, 73.48. FT-IR (KBr): 3314 cm^{-1}; MS (EI) *m/z* (rel intensity) 196 (M^+, 17), 165 (100), 147 (28), 104 (31), 90 (20) 81 (11), 79 (18); HRMS calcd for $C_{12}H_{20}O_2$ $[M]^+$ 196.1463, found 196.1470.

2-Adamantanemethanol (4-2e).



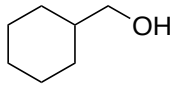
colorless solid; mp. 82-84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (bs, ^{1}H), 1.52-1.59 (m, 2H), 1.71-1.95 (m, 13H), 3.73 (d, *J* = 8Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.93, 28.37, 29.19, 31.91, 38.16, 38.86, 47.10, 65.08.

2-Norbornanemethanol (exo / endo = 99 / 1) (4-2f).



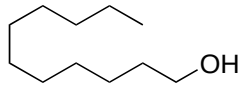
colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92-1.20 (m, 1H), 1.06-1.12 (m, 1H), 1.12-1.23 (m, 2H), 1.23-1.28 (m, 1H), 1.32-1.42 (m, 2H), 1.43-1.58 (m, 2H), 1.61-1.70 (m, 1H), 2.14 (m, 1H), 2.18-2.24 (m, 1H), 3.28-3.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): d 28.91, 29.82, 33.99, 35.13, 36.09, 38.09, 44.89, 66.92.

Cyclohexanemethanol (4-2g).



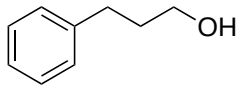
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87-0.96 (m, 2H), 1.13-1.28 (m, 2H), 1.42-1.73 (m, ^{1}H), 1.72-1.75 (m, 6H), 2.63-2.90 (m, 1H), 3.42 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.81. 26.57, 29.52, 40.45, 68.78. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

1-Undecanol (4-2h).



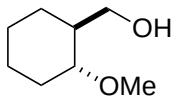
colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (t, *J* = 6 Hz, 3H), 1.18-1.50 (m, 16H), 1.53-1.58 (m, 2H), 3.64 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.10, 22.67, 25.71, 29.32, 29.42, 29.60, 31.90, 32.77, 63.07. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

3-Phenyl-propane-1-ol (4-2i).



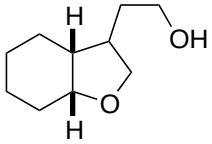
colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.90 (q, *J* = 6.8 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 3.69 (t, *J* = 6.4 Hz, 2H), 7.17-7.31 (m, 5H).; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 32.06, 34.22, 62.31, 125.86, 128.40, 128.42, 141.79. This product is commercially available and the ^{1}H and ^{13}C NMR spectra are consistent with those of the authentic sample.

2-Methoxycyclohexyl methanol[15] (4-2j).



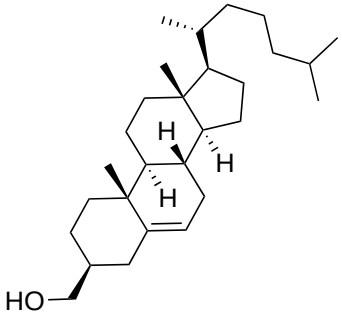
colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92 (dq, *J* = 3.2, 12.6 Hz, ^{1}H), 1.03-1.28 (m, 3H), 1.52-1.85 (m, 4H), 2.12-2.20 (m, 1H), 3.06 (dt, *J* = 3.6, 9.8 Hz, 1H), 3.37 (s, 3H), 3.47-3.56 (m, 1H), 3.61 (t, *J* = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.27, 25.13, 27.70, 30.01, 45.07, 55.60, 68.71, 86.06.

2-Octahydrobenzofuran-3-yl)ethanol (**4-2k**) (dr = 75/25).



colorless oil; (major isomer)^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.02-1.19 (m, 2H), 1.22-1.79 (m, 7H), 1.83-1.90 (m, 1H), 1.92-2.00 (m, 1H), 2.39-2.50 (m, 1H), 3.55 (dd, *J* = 2.4, 7.2 Hz, 1H), 3.59-3.69 (m, 2H), 3.97 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.43, 22.03, 24.46, 28.48, 30.57, 39.97, 40.61, 62.10, 70.92, 78.16; FT-IR (neat) : 3398, 2930, 2860, 1446, 1433, 1157 cm^{-1}; MS (EI) *m/z* (rel intensity) 170 (M^{+}, 23), 125 (100), 98 (15), 83 (20), 81 (24) ; HRMS calcd for $C_{10}H_{18}O_2$ $[M]^{+}$ 170.1307, found 170.1299.

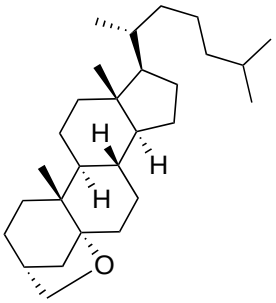
3-Hydroxymethylcholest-3-ene (dr = 93/7) (4-2l).



colorless solid; mp. 108-109 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.67 (s, 3H), 0.83-2.10 (m, 41H), 3.48 (t, *J* = 5.6 Hz, 2H), 5.31-5.33 (m, 1H); ^{13}C NMR($CDCl_3$, 100 MHz): δ 11.85, 18.70, 19.45, 22.55, 22.82, 23.82, 24.27, 25.34, 28.00, 28.23, 30.94, 31.87, 35.79, 36.18, 37.34, 39.00, 39.50, 39.80, 42.11, 42.29, 50.38, 56.14, 56.80, 68.50, 119.95, 142.30 ; FT-IR (KBr): 3338, 2931, 1458, 1376, 1332, 1141, 1066, 999, 960, 834 cm^{-1}; MS (EI) *m/z* (rel intensity) 400 (M^{+}, 100), 385 (88), 301 (45), 245 (45), 95 (45), 81 (36);

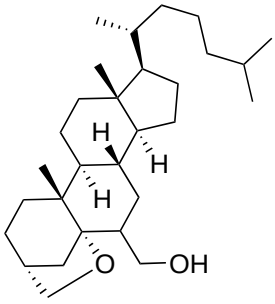
HRMS calcd for $C_{28}H_{48}O$ $[M]^+$ 400.3705, found 400.3714.

(**4-3l**)



colorless solid; mp. 90-91 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.63 (s, 3H), 0.85 (d, *J* = 2 Hz, 3H), 0.87 (d, *J* = 2 Hz, 3H), 0.89 (d, *J* = 6 Hz, 3H), 0.90 (s, 3H), 0.93-1.62 (m, 27H), 1.73-1.85 (m, 1H), 1.89 (d, *J* = 11.6 Hz, 1H), 1.96 (dt, *J* = 2.8, 12.0 Hz, 1H), 2.31 (brs, 1H), 3.73-3.81 (m, 2H); ^{13}C NMR($CDCl_3$, 100 MHz): δ 11.89, 16.53, 18.65, 20.60, 22.55, 22.83, 23.92, 24.21, 27.44, 28.00, 28.25, 28.44, 32.51, 32.81, 34.85, 35.84, 36.16, 36.22, 39.49, 39.90, 41.09, 42.46, 47.86, 55.95, 56.23, 71.67, 85.4; FT-IR (KBr): 2920, 2857, 1459, 1382, 1116, 1037, 970, 945, 860, 791, 760 cm^{-1}; MS (EI) *m/z* (rel intensity) 400 (M^+, 100), 385 (22), 260 (12), 244 (15), 245 (20), 95 (11); HRMS calcd for $C_{28}H_{48}O$ $[M]^+$ 400.3705, found 400.3711.

(4-4l)



colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.64 (s, 3H), 0.82-0.91 (m ,12H), 0.96-1.37 (m, 17H), 1.48-1.67 (m, 7H), 1.70-1.88 (m, 3H), 1.93-2.02 (m, 2H), 2.39 (brs, 1H), 3.47 (dt, *J* = 2.4, 9.6 Hz, 1H), 3.69-3.82 (m, 2H), 4.08 (dd, *J* = 2.4, 11 Hz, ^{1}H); ^{13}C NMR($CDCl_3$, 100 MHz): δ 11.88, 16.38, 18.64, 20.59, 22.53, 22.81, 23.90, 24.14, 27.06, 27.98, 28.25, 31.91, 32.72, 34.07, 34.25, 35.76, 35.82, 36.14, 37.29, 39.46, 39.86,

41,77, 42.34, 47.84, 55.99, 56.19, 64.58, 71.40, 89.96; FT-IR ($CHCl_3$): 3019, 2399, 1521, 1424, 1212, 1046, 929 cm^{-1}; MS (EI) *m/z* (rel intensity) 430 (M^+, 100), 412 (18), 400 (21), 399 (25), 275 (13), 95 (17), 81 (15); HRMS (FAB) calcd for $C_{28}H_{48}O$ $[M-H]^+$ 431.3811, found 431.3871.

4.5 References

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5 Approximate Rate Constants for Hydrogen Abstraction from Tetrabutylammonium Cyanoborohydride by a Primary Alkyl Radical

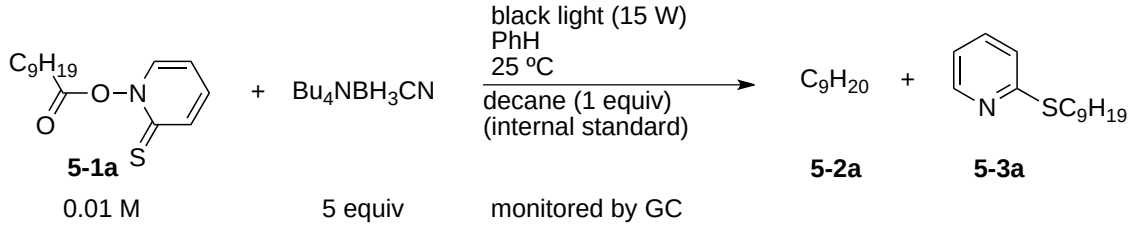
5.1 Introduction

The aim of the work in this chapter is to determine the rate constant for hydrogen transfer from borohydrides by the pyridine-2-thioneoxycarbonyl (PTOC) competition kinetic method at a single concentration point.

5.2 Results and Discussion

Scheme 5-1 shows the results of a typical kinetic experiment. A solution of the pyridine-2-thioneoxycarbonyl (PTOC), Bu_4NBH_3CN, and decane (internal standard) in benzene was irradiated with a 15W black light for 30 min. Then the yields of the nonane (**5-2a**) (5.7–6.6%) and 2-nonylthiopyridine (**5-3b**) (71.2–75.1%) were determined by GC analysis of the crude product against the internal standard.

Scheme 5-1. Results of a Typical Single-Point Kinetic Experiment with PTOC Ester **5-1a** and Hydrogen Donor Bu_4NBH_3CN

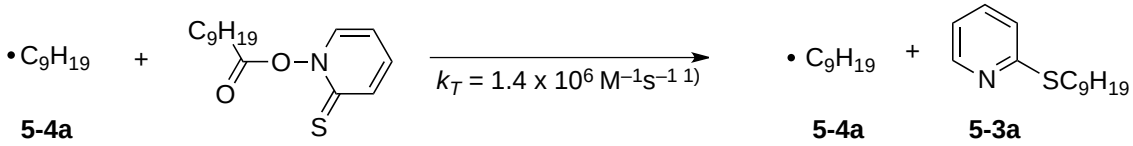


run	**5-2a** (%)	**5-3a** (%)	k_H ($M^{-1}s^{-1}$)
1	6.6	72.9	5.01×10^3
2	5.9	71.2	3.73×10^3
3	5.7	71.6	3.35×10^3
4	6.3	75.1	4.27×10^3

Figure 5-1 shows the mechanistic framework for analysis of the results. Nonyl radical generated from PTOC ester has two competing options. It can react with the starting PTOC ester to provide **5-3a** and another nonyl radical, or it can react with cyanoborohydride to provide nonane (**5-4a**) and borane radical anion **5-5a**. The rate constant for H-transfer (k_H) is then calculated in the usual way from the known rate constant for self-trapping (k_T) and the experimentally determined product ratio.

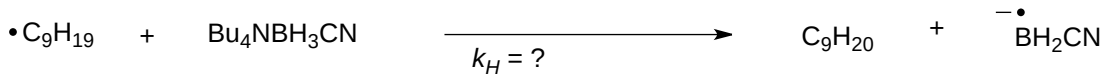
Figure 5-1. Competing options for the nonyl radical **5-4a** with known (option 1) and unknown (option 2) rate constants.

option 1, reaction with PTOC ester, known k_T



5-4a **5-4a** **5-3a**

option 2, reaction with Bu_4NBH_3CN, unknown k_H



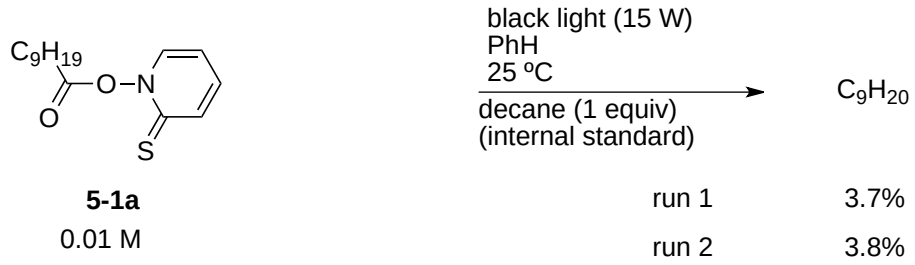
5-4a **5-2a** **5-5a**

The following equation was used to calculate k_H:

$$k_H = \frac{k_T\,[\textbf{5-2a}][\textbf{5-1a}]}{[\textbf{5-3a}][Bu_4NBH_3CN]}$$

$$k_H = \frac{k_T\,[\text{yield\% (}\textbf{5-2a}\text{)–blank (\%)}] \times C_0(\textbf{5-1a})/2}{\text{yield \% (}\textbf{5-3a}\text{)}\times\{C_0(Bu_4NBH_3CN)–[(\text{yield\% (}\textbf{5-2a}\text{)–blank \%}) \times C_0(\textbf{5-1a})]/2\}}$$

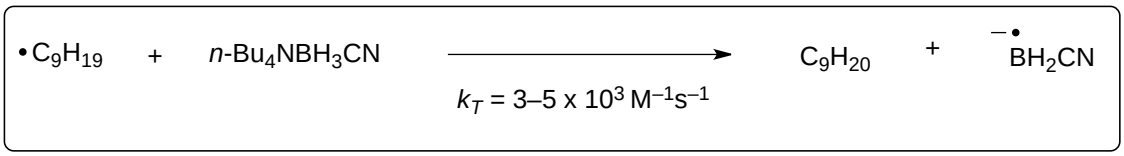
The yield of nonane **5-2a** was corrected by subtraction of 3.75% because this amount of nonane formed in the control experiment without a hydrogen donor (Scheme 5-2) (“background” reduction).



Scheme 5-2. Background Reduction

The average concentration of PTOC ester **5-1a** during the reaction is approximated by half of starting concentration C_0(**5-1a**). The average concentration of a hydrogen donor during the reaction, [Bu_4NBH_3CN], is approximated as the average between the starting and final concentrations C(Bu_4NBH_3CN) assuming that the hydrogen donor is consumed only for formation of nonane **5-2a**.

In this way, the rate constant k_H for the reaction of primary alkyl radical with Bu_4NBH_3CN was deterimined to be 3–5 x 10^3 $M^{-1}s^{-1}$.



5.3 Conclusion

The author has implemented a simple kinetic competition experiment with PTOC ester to measure rate constants for radical hydrogen abstraction from Bu_4NBH_3CN. The rate constants are summarized in Figure 5-2. This is lower than thouse of tin hydride,[1] tris(trimethylsilyl)silicon hydride,[2] germanium hydride,[3] and NHC-borane.[4]

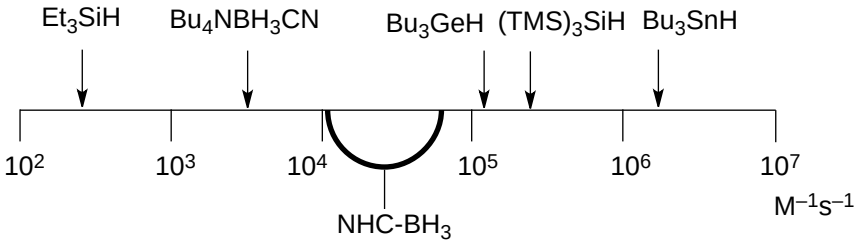
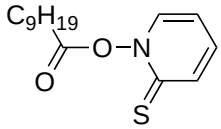


Figure 5-2. Scale of rate constants for donations of hydrogen atoms to alkyl radicals

5.4 Experimental

Determination of k_H for Bu_4NBH_3CN by the PTOC Method: Stock solutions of PTOC ester **5-1a** (0.10 M in PhH) and decane (0.02 M in PhH) were prepared. A yellow solution of Bu_4NBH_3CN (70.9 mg, 0.25 mmol, 5 equiv), PTOC ester **5-1a** (0.1 M solution in PhH, 0.10 mL, 0.010 mmol), decane (0.02 M solution in PhH, 0.50 mL, 0.010 mmol) in PhH (0.40 mL) (total volume is about 1 mL) was irradiated with a black light (15 W) for 30 min. During irradiation, temperature maintained at 25 °C. The colorless reaction mixture was analyzed by GC. Products were identified by comparing their retention times (tR) with those of authentic samples: **5-2a**– 4.3 min; decane – 6.8 min, **5-3a** – 14.1 min. The yields were calculated from areas of peaks using previously determined response factors: dodecane – 1.00; **5-2a** – 1.00; **5-3a** – 1.82. Such GC analysis of the reaction mixture showed the formation of nonane **5-2a** (6.6 %) and 2-(nonylthio)pyridine 7 (72.9 %).

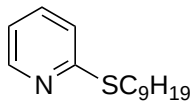
2-Thioxopyridin-1(2H)-yl decanoate (**5-1a**).



^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.9 Hz, 3H), 1.26 (m, 10H), 1.35-1.50 (m, 2H), 2.70 (quintet, *J* = 7.5 Hz, 2H), 2.70 (t, *J* = 2H), 6.63 (ddt, *J* = 1.0, 6.9, 6.9 Hz, ^{1}H), 7.19 (ddd *J* = 1.0, 6.9, 8.7 Hz, ^{1}H), 7.57 (dd, *J* = 1.2 Hz, 6.9 Hz, ^{1}H), 7.66 (dd, *J* = 1.5, 8.7 Hz, ^{1}H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 24.3, 29.0, 29.1, 29.2, 29.3, 31.6, 31.8, 112.6, 133.6, 137.3, 137.7, 169.1, 175.8. The product was stored in the

refrigerator in the flask wrapped into the aluminum foil.

2-(Nonylthio)pyridine (5-3a).



^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.27 (m, 10H), 1.40-1.48 (m, 2H), 1.66-1.76 (m, 2H), 3.16 (t, *J* = 7.4 Hz, 2H), 6.96 (ddt, *J* = 0.9, 0.9, 8.1 Hz, ^{1}H), 7.47 (ddd, *J* = 2.1, 7.2, 8.1 Hz, ^{1}H), 8.43 (ddd, *J* = 0.9, 1.8, 5.1 Hz, ^{1}H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 29.0, 29.2, 29.3, 29.3, 29.5, 30.1, 31.9, 119.1, 122.1, 135.8, 149.4, 159.6.

5.5 References

[1] Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.

[2] Chatgilialoglu, C.; Guerrini, A. *J. Org. Chem*. **1992**, *57*, 3405.

[3] Wilt, J. W.; Lusztyk, J.; Peeran, M.; Ingold, K. U. *J. Am. Chem. Soc*. **1988**, *110*, 281.

[4] Solovyev, A.; Ueng, S.; Monot, J.; Fensterbank, L.; Malacria, M.; Lacôte, E.; Curran, D. P. *Org. Lett.* **2010**, *12*, 2998.

6 Cyanoborohydride Promoted Arylation of Benzene

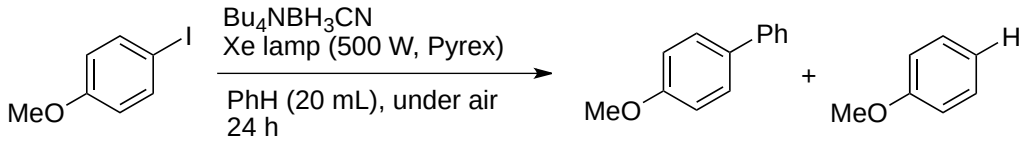
6.1 Introduction

Biaryl compounds are important materials in manufacturing of fine chemicals and pharmaceuticals.[1] In the past decades, some efficient transition metal catalyzed arylation of aryl halides with unactivated arenes has been developed.[2] On the other hands, homolytic aromatic substituions (HAS) can be used for synthesis of biaryl products.[3,4,5] Recent research in this area includes base-promoted HAS (BHAS) reactions, for example in 2008, Itami reported that biaryl coupling of electron-deficient nitrogen heterocycles and haloarenes was promoted by KO*t*-Bu.[6] Kwong/Lei,[7] Shi,[8] and Shirakawa/Hayashi,[9] all independently expanded this benzene-arylation chemistry by using a strong base and a bidentate ligand.[10] More recently, Curran and Studer have reported BHAS reactions using $PhNHNH_2$ as an initiator with KO*t*-Bu.[11] Rossi and Zheng/Guo independently demonstrated that BHAS reactions could proceed under photoirradiation conditions at ambient temperature.[12,13] Despite rapid progress in this field, substrates are limited to those resistant to strong bases[14] and chemoselective reaction with regard to substrates bearing both iodine and bromine in the haloarenes is rarely attained. Recently, ryu *et al.* reported radical C-C bond forming reaction using borohydride reagents as chain mediators.[15, 16] The author reports that cyanoborohydride promotes the synthesis of biaryl compounds from iodoarenes and benzene under aerobic photoirradiation conditions. This reaction proceeds in chemoselective fashion for bromo- and iodo- substituted arenes.

6.2 Results and Discussion

Treatment of 4-iodoanisole (**6-1a**) was chosen as a model substrate for the initial study (Table 6-1). When a benzene solution of **6-1a** was irradiated with a 500 W Xe lamp using Pyrex tube for 24 h under air, the desired 4-methoxy-1-phenylbenzene (**6-2a**) was obtained in 55% yield (entry 1). The addition of Bu_4NBH_3CN as radical mediator increased the yield of **6-2a**. A more amount of Bu_4NBH_3CN decreased the yield (entries 3 and 4).

Table 6-1. Optimization of Reaction Conditions



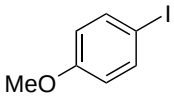
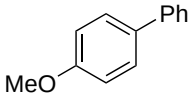
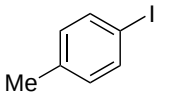
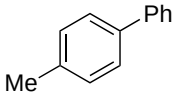
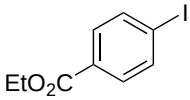
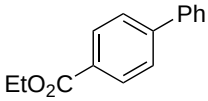
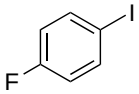
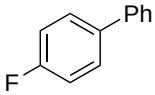
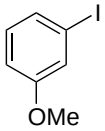
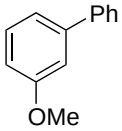
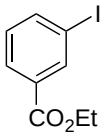
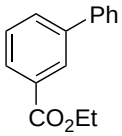
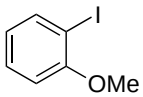
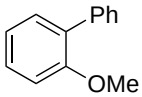
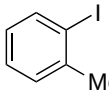
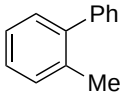
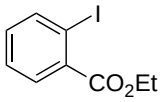
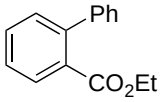
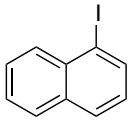
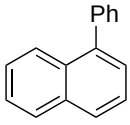
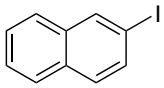
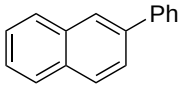
6-1a
0.5 mmol

6-2a **6-3a**

entry	Bu_4NBH_3CN		
1	0	52%	0%
2	1	77%	8%
3	2	38%	41%
4	4	30%	57%

With the optimized conditions in hand, the author next examined the substrate scope for this transformation, and the results are shown in Table 6-2. 4-Iodotoluene (**6-1b**), 1-ethyl-4-iodobenzoate (**6-1c**), and 1-fluoro-4-iodobenzene (**6-1d)** gave the corresponding biaryls **6-2b**, **6-2c**, and **6-2d** in 70, 68%, and 67% yields, respectively (entries 2 and 3). The reaction took place chemoselectively at aryl iodine bond but not at the aryl-fluorine and aryl-chlorine bonds (entries 4 and 5). The reaction of 3-iodoanisole (**6-1e**), ethyl-3-iodobenzoate (**6-1f**), 2-iodoanisole (**6-1g**), 2-iodotoluene (**6-1h**), and ethyl-2-iodobenzoate (**6-1i**) was also successful. The author also examined 1-iodonaphthalene (**6-1j**) and 2-iodonaphthalene (**6-1k**). The reaction proceeded to give 1-phenylnaphthalene (**6-2j**) and 2-phenylnaphthalene (**6-2k**) in 57 and 82% yields, respectively (entries 11 and 12).

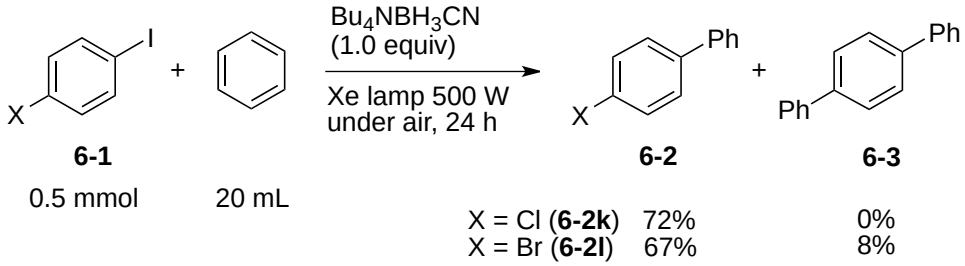
Table 6-2. Radical Arylation Reaction

entry	**6-1**		**6-2**		yield[a]
1		**6-1a**		**6-2a**	78%
2		**6-1b**		**6-2b**	70%
3		**6-1c**		**6-2c**	68%
4		**6-1d**		**6-2d**	67%
5		**6-1e**		**6-2e**	79%
6		**6-1f**		**6-2f**	62%
7		**6-1g**		**6-2g**	50%
8		**6-1h**		**6-2h**	47%
9		**6-1i**		**6-2i**	70%
10		**6-1j**		**6-2j**	57%
11		**6-1k**		**6-2k**	82%

[**6-1**] = 0.025 M, Bu_4NBH_3CN (1 equiv), Xe lamp (500 W, Pyrex), rt, 24 h [a] Isolated yield by flash chromatography on SiO_2

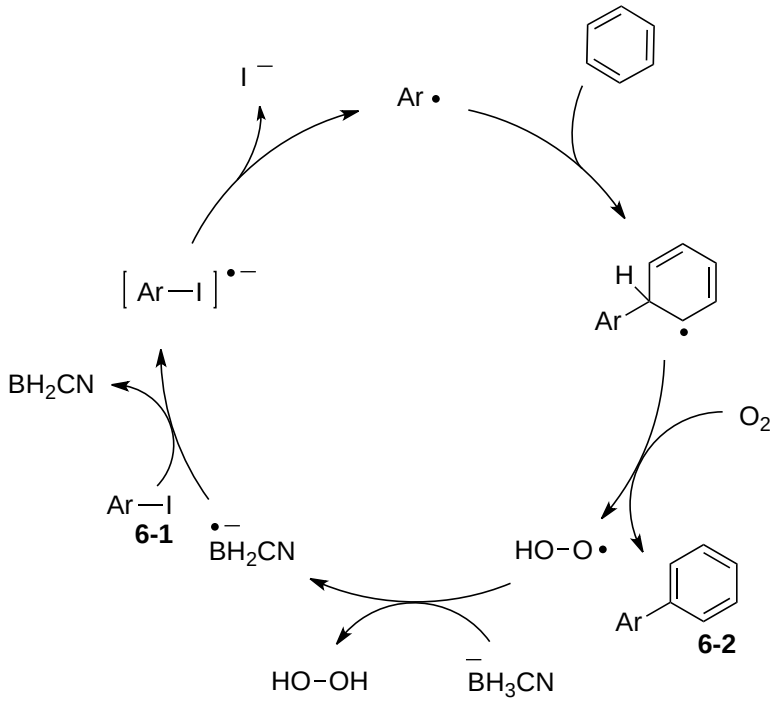
Shirakawa and Hayashi have reported that under controlled conditions the HAS reaction of 1-bromo-4-iodobenzene (**1o**) with NaO*t*-Bu and catalytic amount of Ph-phen

(4,7-diphenyl-1,10-phenanthroline) takes place chemoselectively at the aryl-iodine bond to give 4-bromobiphenyl (**6-2l**).[9] In contrast, KO*t*-Bu promoted HAS reaction of benzene with either 1-chloro- (**6-1l)** or 1-bromo-4-iodobenzene (**6-2l)** afforded only 1,4-diphenylbenzene (**6-3**).[7,8,11,12,14b,14f,14g] To gain insight into the chemoselectivity of the present method, we tested the arylation of benzene with the bihaloarenes **6-1k** and **6-1l** using cyanoborohydride (Scheme 6-1). Under our standard reaction conditions, a chemoselective reaction took place at the aryl-iodine bond, but at neither the aryl-bromine nor aryl-chlorine bond. The carbon–bromine bonds present in the biaryl products can be subsequently converted to carbon-carbon bonds by cross-coupling reactions.



Scheme 6-1. Arylation of 1-Halo-4-iodobenzene

A potential mechanism, mediated by oxygen and cyanoborohydride, is shown in Scheme 6-2. Photoirradiation of aryl iodide leads to generation of an aryl radical.[4] The aryl radical adds to benzene to form cyclohexadienyl radical, which reacts with oxygen to give biaryl product and hydroperoxy radical.[4a,17] The resulting hydroperoxy radical could abstract hydrogen from cyanoborohydride to give cyanoborane radical anion. Subsequent reaction with aryl iodide through single electron transfer would give the corresponding radical anion that fragments to aryl radical and iodide ion, thus completing the radical chain reaction.



Scheme 6-2. Possible Mechanism

6.3 Conclusion

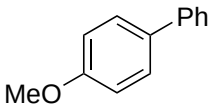
In summary, the author has found that cyanoborohydride can promote arylation of benzene under aerobic conditions. Using this protocol, both aryl iodides bearing an electron donating or withdrawing group can be accommodated. The reaction takes place chemoselectively at the aryl-iodine bond in preference to either an aryl-bromine or aryl-chlorine bond. These mild reaction conditions are unusual for base promoted HAS reactions and provide considerable synthetic flexibility.

6.4 Experimental

General information. ^{1}H -NMR spectra were recorded with a JEOL ECS-400 (400 MHz) spectrometer or a Varian MR400 (400 MHz) spectrometer in CDCl3 and referenced to the solvent peak at 7.26 ppm. ^{13}C NMR spectra were recorded with a JEOL ECS-400 (100 MHz) spectrometer or a Varian MR400 (100 MHz) spectrometer and referenced to the solvent peak at 77.00 ppm.

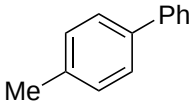
General information. ^{1}H -NMR spectra were recorded with a JEOL ECS-400 (400 MHz) spectrometer or a Varian MR400 (400 MHz) spectrometer in $CDCl_3$ and referenced to the solvent peak at 7.26 ppm. ^{13}C NMR spectra were recorded with a JEOL ECS-400 (100 MHz) spectrometer or a Varian MR400 (100 MHz) spectrometer in $CDCl_3$ and referenced to the solvent peak at 77.00 ppm.

4-Methoxybiphenyl (6-2a).



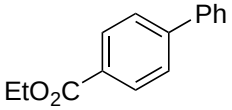
^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.86 (s, 3H), 6.98 (d, J = 7.6 Hz, 2H), 7.27-7.32 (m, 1H). 7.38-7.44 (m, 2H), 7.51-7.57b (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.24, 114.14, 126.60, 126.66, 128.08, 128.66, 133.67, 140.74, 159.07.

4-Methylbiphenyl (6-2b).



^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40 (s, 3H), 7.23-7.35 (m, 3H), 7.40-7.45 (m, 2H), 7.48-7.51 (m, 2H), 7.56-7.60 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.07, 126.94, 128.68, 129.45, 136.96, 138.31, 141.11.

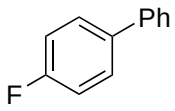
Ethyl-4-phenylbenzoate (6-2c).



^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.42 (t, *J* = 6.8 Hz, 3H) 4.41 (q, *J* = 6.8 Hz, 2H), 7.38-7.41 (m, 1H), 7.43-7.48 (m, 2H), 7.60-7.69 (m, 4H), 8.10-8.13 (m, 2H); ^{13}C NMR

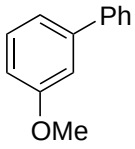
($CDCl_3$, 100 MHz): δ 14.31, 60.92, 126.94, 127.21, 128.05, 128.85, 129.16, 130.00, 139.97, 145.45, 166.45.

4-Fluorobiphenyl (6-2d).



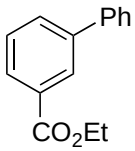
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10-7.16 (m, 2H), 7.32-7.37 (m, 1H), 7.41-7.46 (m, 2H), 7.52-7.57 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 115.56 (d, *J* = 21.0 Hz), 127.00, 127.24, 128.66 (d, J = 7.7 Hz), 128.80, 137.32, 140.22, 162.43 (d, J = 243.5 Hz).

3-Methoxybiphenyl (6-2e).



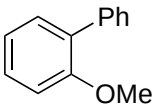
^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.89 (s, 3H), 6.90-6.93 (m, 1H), 7.12-7.22 (m, 2H), 7.32-7.50 (m, 4H), 7.59-7.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.26, 112.63, 112.86, 119.65, 127.17, 127.38, 128.71, 129.72, 141.06, 142.73, 159.89.

Ethyl-3-phenylbenzoate (6-2f)



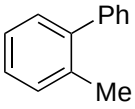
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.43 (t, *J* = 7.2 Hz, 3H), 4.43 (q, *J* = 7.2 Hz, 3H), 7.37-7.42 (m, 1H), 7.44-7.54 (m, 3H), 7.60-7.68 (m, 2H), 7.76-7.82 (m, 1H), 8.03-8.09 (m, 1H), 8.28-8.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.31, 61.00, 127.11, 127.64, 128.16, 128.25, 128.74, 128.81, 130.96, 131.37, 140.11, 141.35, 166.50.

2-Methoxybiphenyl (6-2g).



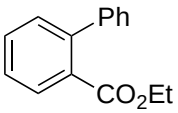
^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.81 (s, 3H), 6.97-7.04 (m, 2H), 7.25-7.44 (m, 5H), 7.51-7.55 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 55.5, 111.1, 120.8, 126.9, 128.0, 128.6, 129.5, 130.9, 138.5, 148.2, 156.4.

2-Methylbiphenyl (6-2h).



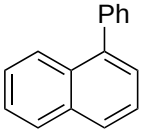
^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.28 (s, 3H), 7.24-7.43 (m, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.5, 125.7, 126.7, 127.1, 127.2, 128.0, 129.2, 129.8, 130.3, 135.3, 141.9.

Ethyl-2-phenylbenzoate (6-2i).



^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (d, J = 7.2 Hz, 1H), 7.43-7.40 (m, 1H), 7.34-7.22 (m, 7H), 4.00 (q, J =13.9 Hz, 2H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.6, 142.1, 141.2, 130.8, 130.3, 129.4, 128.1, 127.7, 126.9, 60.6, 13.4.

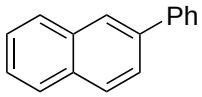
1-Phenylnaphthalene (6-2j).



^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.56 (m, 9H), 7.84-7.92 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 125.3, 125.7, 126.0, 126.89, 126.91, 127.1, 127.2, 127.6, 128.2, 130.0,

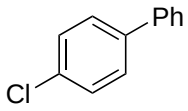
131.5, 133.7, 140.2, 140.7.

2-Phenylnaphthalene (6-j).



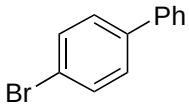
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03 (s, 1 H), 7.91-7.83 (m, 3 H), 7.75-7.70 (m, 3 H), 7.49-7.44 (m, 4 H), 7.39-7.36 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.06, 138.50, 133.62, 132.56, 128.83, 128.38, 128.16, 127.61, 127.39, 127.32, 126.25, 125.90, 125.76, 125.55.

4-Chlorobiphenyl (6-k).



^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.48 (m, 5H), 7.49-7.57 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 126.96, 127.56, 128.35, 128.86, 133.34, 139.62, 139.96.

4-bromobiphenyl (6-k).



^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.39 (m, 1H), 7.42-7.48 (m, 4H), 7.53-7.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 121.50, 126.91, 127.60, 128.71, 128.87, 131.82, 139.95, 140.08.

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7 Conclusion

In this thesis, the development of new methodology based on borohydride reagents was studied.

From chapter 2 to 4 the author has focused on the hydroxymethylation of alkyl and aryl halides. Hydroxymethylation has two types of reaction courses, Type 1 and Type 2. Type 1 reaction employs radical addition to CO to give acyl radicals as key intermediates. On the other hands, Type 2 reaction employed radical addition to formaldehyde to give alkoxy radicals as key intermediates.

Chapter 2 describes the development of hydroxymethylation of alkyl iodides under atmospheric pressure of CO in the presence of tetrabutylammonium borohydride in conjunction with photoirradiation using black light. A hybrid radical/ionic mechanism is proposed. The author achieved total synthesis of (±)-communiol E using this methodology.

In chapter 3, hydroxymethylation with CO were further expanded. The reaction took place chemoselectively at the aryl-iodine bond but not at the aryl-bromine and aryl-chlorine bonds using *N*-heterocyclic carbene borane. A three-component coupling reaction comprising aryl iodides, CO, and electron-deficient alkenes also proceeded well to give unsymmestrical ketones in good yields.

Chapter 4 demonstrates when coupled with a judicious choice of radical mediator, such as a borohydride reagent, formaldehyde can serve as a useful C1 radical synthon.

Chapter 5 describes the determination of rate constants for primary alkyl radical from tetrabutylammonium cyanoborohydride. The rate constant of Bu_4NBH_3CN is lower than thouse of tin hydride, tris(trimethylsilyl)silicon hydride, germanium hydride, and NHC-borane.

Chapter 6 describes that cyanoborohydride promoted radical arylation reaction of benzene. The reaction took place chemoselectively at the aryl-iodine bond but not at the aryl-bromine and chlorine bonds.

Present studies on these borohydride mediated carbon-carbon bond forming reaction may offer a new efficient method for induction of C1 synthon, and will contribute to the development of organic synthesis via radical intermediate.

8 Pubilication List

(1) “Black-Light-Induced Radical/Ionic Hydroxymethylation of Alkyl Iodides with Atmospheric CO in the Presence of Tetrabutylammonium Borohydride” Kobayashi, S.; Kawamoto, T.; Uehara, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 1548.

(2) ”Thermal Retro-Aldol Reaction Using a Fluorous Ether F-626 as a Reaction Medium” Fukuyama, T.; Kawamoto, T.; Okamura, T.; Denichoux, A.; Ryu, I. *Synlett* **2010**, 2193.

(3) ”Stereocontrolled Synthesis of Substituted Bicyclic Ethers through Oxy-Favorskii Rearrangement. Total Synthesis of (±)-Communiol E” Kobayashi, S.; Kinoshita, T.; Kawamoto, T.; Wada, M.; Kuroda, H.; Masuyama, A.; Ryu, I. *J. Org. Chem.* **2011**, *76*, 7096.

Highlighted in Synfacts, 2011, 11.

(4) ”Radical Addition of Alkyl Halides to Formaldehyde in the Presence of Cyanoborohydride as a Radical Mediator. A New Protocol for Hydroxymethylation Reaction” Kawamoto, T.; Fukuyama, T.; Ryu, I. *J. Am. Chem. Soc.* **2012**, *134*, 875.

Highlighted in Synform, 2012, 5.

Highlighted in Nachrichten aus der Chemie, 2012, 60, 210.

Highlighted in J. Synth. Org. Chem. 2012, Oct.

(5) “Free Radical-mediated Hydroxymethylation Using CO and HCHO” Kawamoto, T.; Ryu, I. *Chimia* **2012**, *66*, 372.

(6) ”Efficient Hydroxymethylation Reactions of Iodoarenes Using CO and 1,3-Dimethylimidazol-2-ylidene Borane” Kawamoto, T.; Okada, T.; Curran, D. P.; Ryu, I. *Org. Lett.* **2013**, *15*, 2144.

(7) ”Flow Giese reaction using cyanoborohydride as a radical mediator” Fukuyama, T.; Kawamoto, T.; Kobayashi, M,; Ryu, I. *Beilstein J. Org. Chem.* **2013**, *9*, 1791.

(8) “Cyanoborohydride Promote the Biaryl Coupling of Iodoarenes and Benzene” Kawamoto, T.; Sato, A.; Ryu, I. in preparation.

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