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Efficient Hydroxymethylation Reactions of Iodoarenes Using CO and 1,3-Dimethylimidazol-2-ylidene Borane

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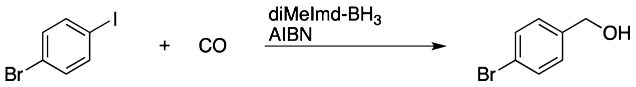
ABSTRACT



A hydroxymethylation reaction of a variety of iodoarenes proceeded effectively in the presence of CO, NHC-borane, diMeImd-BH$_3$ (2) as a radical mediator, and a catalytic amount of AIBN. 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 unsymmetrical ketones in good yields. Control experiments show that 2 would act as a hydrogen donor to acyl radicals and iodinated NHC-borane as a reducing agent of aldehydes.

Organo halides are among the most useful precursors to access carbon radical species, and they have consequently found numerous applications in chemical synthesis.[1] In the past two decades, the potential of CO as a radical C1 synthon has been established with examples yielding a wide range of carbonyl compounds.[2] Recently, we have reported radical hydroxymethylation[3] of alkyl iodides using CO and tetrabutylammonium borohydride (**1a**) (Figure 1). We also reported radical hydroxymethylation using HCHO and tetrabutylammonium cyanoborohydride (**1b**).[4] Due to a slower H donation ability of the borohydride reagents[5] 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.

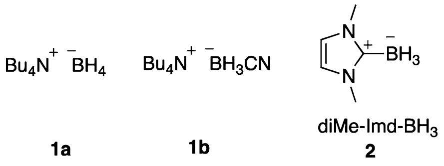


Figure 1. Borane reagents available for radical reactions.

Recently, Curran, Lacôte, and co-workers showed that *N*-heterocyclic carbene boranes (NHC-boranes) can be used for radical chain reactions as viable hydrogen transfer

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(1) For reviews on radicals in organic synthesis using organic halides, see: (a) Renaud, P.; Sibi, M. P., Ed. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001. (b) Togo, H., Ed. *Advanced Free Radical Reactions Organic Synthesis*; Elsevier: 2004. (c) Heinrich, M. R.; Gansäuer, A., Ed. *Topics Current Chemistry; Radicals in Synthesis III*; Springer: Berlin, 2012; Vols. 320. (d) Rowlands, G. J. *Tetrahedron* **2009**, *65*, 8603.

(2) For reviews on radical carbonylations, see: (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16. (d) Also see a review on acyl radicals: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(3) Kobayashi, S.; Kawamoto, T.; Uehara, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 1548.

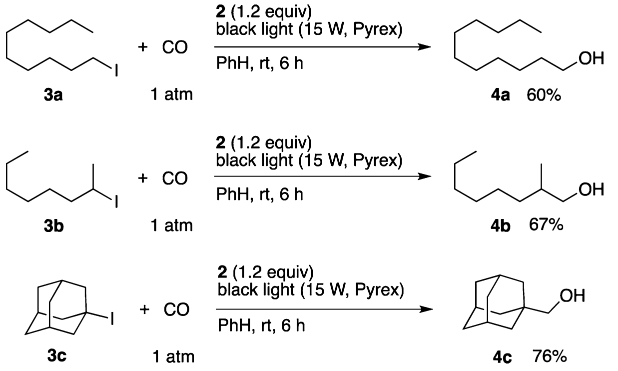
(4) (a) Kawamoto, T.; Fukuyama, T.; Ryu, I. *J. Am. Chem. Soc.* **2012**, *134*, 875. (b) Kawamoto, T.; Ryu, I. *Chimia* **2012**, *66*, 372.

(5) Ryu, I.; Uehara, S.; Hirao, H.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 1005.

10.1021/ol4006294

reagents.[6] In particular, the second-generation reagent 1,3-dimethylimidazol-2-ylidene borane (diMeImd-BH$_3$, **2**), a stable and easily handled solid, can smoothly reduce xanthates and related functional groups.[7] 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 a polarity reversal catalyst such as thiols when ordinary organohalides are employed as substrates.[8,9] Indeed, secondary alkyl radicals react with NHC-boranes with a rate constant on the order of 10^4 M^{-1} s^{-1}, which is 2 orders of magnitude slower than that of tributyltin hydride.[10] In the hope of expanding the substrate scope for hydroxymethylation reactions, we decided to examine the hydroxymethylation reaction of RX with CO using NHC-boranes as the reducing agent. Herein we report that NHC-borane **2** is an excellent reagent for radical hydroxymethylation of a wide variety of organoiodides including iodoarenes.

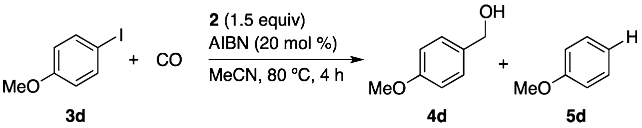
Scheme 1. Hydroxymethylation of Alkyl Iodides Using **2** and Atmospheric CO (balloon)



Initially we examined the potential of **2** as a mediator for radical hydroxymethylation of alkyl iodides using CO. Under an atmosphere of CO (balloon), a benzene solution of 1-iododecane (**3a**) and diMeImd-BH$_3$ (**2**) (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 **4a** in 60% isolated yield after flash chromatography on silica gel (Scheme 1). Secondary and tertiary alkyl iodides, such as 2-iodoocatane (**3b**) and 1-iodoadamantane (**3c**), were also converted to the corresponding alcohols **4b** and **4c** in good yields.

Having identified NHC-borane **2** as a suitable reagent for the hydroxymethylation of iodoalkanes, we then studied hydroxymethylation of iodoarenes.[11] We chose 4-iodoanisole (**3d**) as a model substrate for the initial study, and the results are summarized in Table 1. Disappointingly, photoirradiation of an acetonitrile solution containing **3d** (0.1 M) and **2** (1.5 equiv) with atmospheric pressure of CO for 4 h gave exclusively reduced anisole **5d** in 68% yield (entry 1). However, under 80 atm of CO, the reaction gave the desired 4-methoxybenzyl alcohol **4d** in 71% yield along with a 10% yield of anisole **5d** (entry 2). By decreasing the reaction concentration ([**3d**] = 0.05 M) **4d** was obtained as the sole product (entry 3).

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



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

We believe that, in the present hydroxymethylation reactions using **2**, similar to the borohydride reagents

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(6) For a review on NHC-borane, see: Curran, D. P.; Solovyev, A.; Makhlouf Brahmi, M.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 10294.

(7) For radical deoxygenation of xanthates, see: Ueng, S.-H.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *Org. Lett.* **2010**, *12*, 3002.

(8) For radical dehalogenation of alkyl halides bearing electron-withdrawing groups, see: Ueng, S.-H.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *Org. Biomol. Chem.* **2011**, *9*, 3415.

(9) For thiol catalyzed radical dehaloganation reaction, see: Pan, X.; Lacôte, E.; Lalevée, J.; Curran, D. P. *J. Am. Chem. Soc.* **2012**, *134*, 5669.

(10) For estimated rate constants for hydrogen abstraction from *N*-heterocyclic carbene borane complexes by an alkyl radical, see: Solovyev, A.; Ueng, S.-H.; Monot, J.; Fensterbank, L.; Malacria, M.; Lacôte, E.; Curran, D. P. *Org. Lett.* **2010**, *12*, 2998.

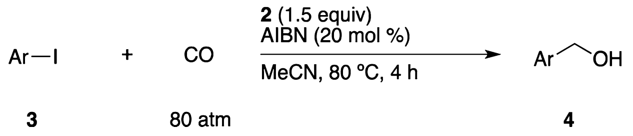
(11) For radical alkoxycarbonylation of aryl iodides, see: Zhang, H.; Shi, R.; Ding, A.; Lu, L.; Chen, B.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 12542.

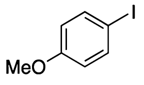
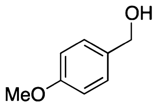
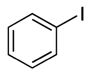
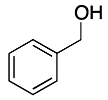
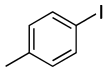
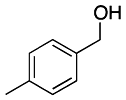
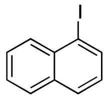
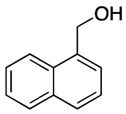
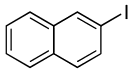
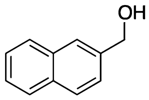
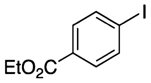
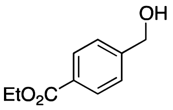
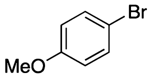
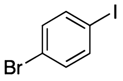
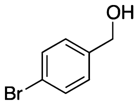
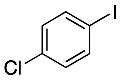
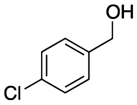
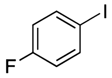
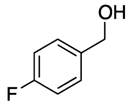
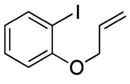
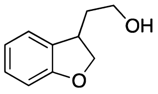
(12) (a) Horn, M.; Mayr, H.; Lacôte, E.; Merling, E.; Deaner, J.; Wells, S.; McFadden, T.; Curran, D. P. *Org. Lett.* **2012**, *14*, 82. (b) Taniguchi, T.; Curran, D. P. *Org. Lett.* **2012**, *14*, 4540.

(13) Lindsay, D. M.; McArthur, D. *Chem. Commun.* **2010**, *46*, 2474.

(14) Monot, J.; Solovyev, A.; Bonin-Dubarle, H.; Derat, É.; Curran, D. P.; Robert, M.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 9166.

Table 2. Hydroxymethylation of a Variety of Aryl Iodides[a]

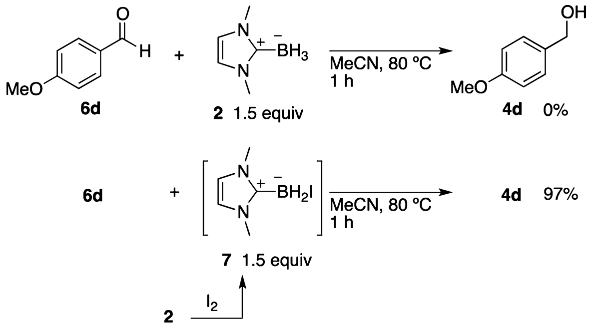


entry	3	4	yield[b]
1	 **3d**	 **4d**	78%
2	 **3e**	 **4e**	63%
3	 **3f**	 **4f**	66%
4	 **3g**	 **4g**	67%
5[c]	 **3h**	 **4h**	59%
6	 **3i**	 **4i**	66%
7[d]	**3i**	**4i**	73%
8	 **3d'**	**4d**	4%
9	 **3j**	 **4j**	62%
10	 **3k**	 **4k**	63%
11	 **3l**	 **4l**	54%
12	 **3m**	 **4m**	29%[e]

[a] Conditions: ArI (0.5 mmol), **2** (0.75 mmol), AIBN (0.1 mmol), CO (80 atm), 80 °C, 4 h. [b] Isolated yield after flash column chromatography on silica gel. [c] Reaction performed for 8 h. [d] CO (150 atm). [e] **3m** was recovered in 31% yield.

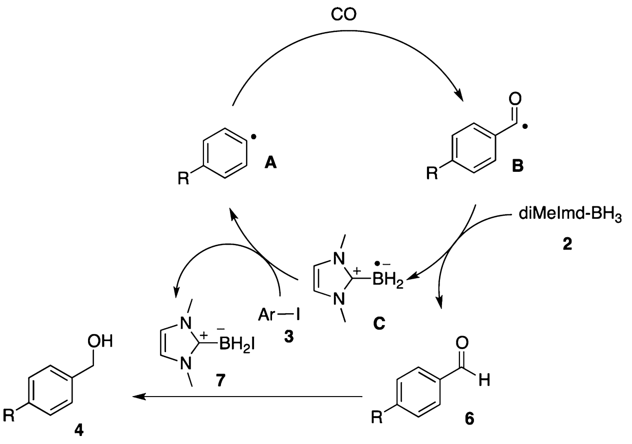
discussed earlier,[3] the precursors of **4** are the corresponding aldehydes formed by H-abstraction from **2** by acyl radicals. According to Curran's[12] and Lindsay's[13] work, however, NHC-boranes are able to reduce aldehydes and ketones in the presence of SiO_2 or Lewis acids. As a control reaction we took 4-anisaldehyde (**6d**) and reacted it with **2** at 80 °C. After 1 h, no reduction was observed (Scheme 2). In a separate experiment, an acetonitrile solution of 0.75 equiv of I_2 and 1.5 equiv of **2** was treated with **6d**. This caused the rapid disappearance of **6d** over 1 h, and **4d** was isolated in 97% yield after flash column chromatography on silica gel. This leads us to suggest that the iodinated NHC-borane **7**[14] may act as an effective aldehyde reducing agent, but not the NHC-borane itself.

Scheme 2. Reduction of 4-Anisaldehyde (**6d**)



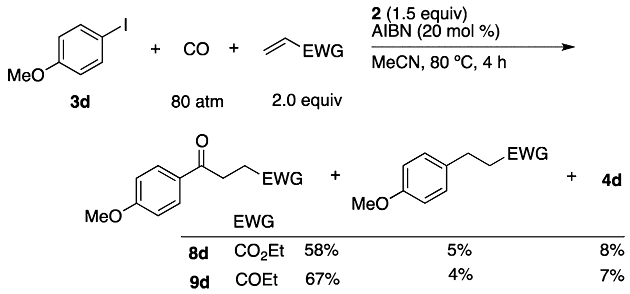
The proposed mechanism is shown in Scheme 3. Radical initiation of aryl iodide leads to generation of the aryl radical **A**. **A** could then add to CO to form the corresponding acyl radical **B**, which could further abstract hydrogen from diMeImd-BH_3 (**2**) to give an aldehyde **6** and the borane radical anion **C**. Subsequent iodine abstraction from **3** returns **A** and iodinated NHC **7**, thus completing the radical chain. Alcohol **4** is formed by hydride reduction of aldehyde **6** by **7**.

Scheme 3. Possible Reaction Mechanism



We then examined a three-component reaction leading to unsymmetrical ketones using **2**. When a mixture of

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



	EWG			
8d	CO_2Et	58%	5%	8%
9d	COEt	67%	4%	7%

4-iodoanisole (**3d**), CO, and ethyl acrylate (2 equiv) with diMeImd-BH_3 (**2**) was subjected to the radical reaction conditions, unsymmetrical ketone **8d** was obtained in 58% yield along with small amounts of the direct addition product and hydroxymethylation product **4d** (Scheme 4). Similarly, the reaction of **3d**, CO, and ethyl vinyl ketone gave 1,4-diketone **9d** in 67% yield.

In summary, we have demonstrated that hydroxymethylation reactions of alkyl and aryl iodides are successfully carried out using CO as a C1 source and diMeImd-BH_3 (**2**) as a radical mediator. Control experiments suggest that **2** serves as a hydrogen donor to acyl radicals and iodinated NHC **7**, formed by the radical generation process from iodoarene **3**, and serves as the in situ generated hydride donor to the aldehydes, giving the corresponding alcohol **4**. The NHC-borane mediated reaction system can also be applied to one-pot three-component coupling reactions leading to unsymmetrical ketones.

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Supporting Information Available. Detailed experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.