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P. Veeraraghavan Ramachandran, Michael P. Drolet

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Direct, high-yielding, one-step synthesis of vic-diols from aryl alkynes

P. Veeraraghavan Ramachandran^a* and Michael P. Drolet^a

^a Herbert C. Brown Center for Borane Research, Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907-2084, USA. * E-mail address: <u>chandran@purdue.edu</u> Telephone: 765-494-5303

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ABSTRACT

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Keywords: Ammonia borane Hydroboration Alkyne 1,2-diols Open-flask An unprecedented, high yielding, direct, one-step synthesis of vic-diols from alkynes has been developed *via* metal-free, open-to-air dihydroboration with ammonia borane. The electronics of the alkyne and the reaction stoichiometry are critical for obtaining optimal yields of the 1,2-diol.

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Hydroboration, discovered six decades ago, has become a mainstay in organic syntheses.¹ Despite involving pyrophoric reagents requiring strictly anhydrous conditions, some with short shelf lives, it has found myriad industrial-scale applications for the preparation of valuable intermediates and target molecules. In addition to the common borane reagents, borane-dimethyl sulfide (BMS, 1) and borane-tetrahydrofuran (BTHF, 2), several monoand di-substituted alkyl-, alkoxy-, and haloboranes have been developed for hydroboration.¹ While the uncatalyzed addition of B-H bonds to alkenes is common, the corresponding reaction of alkynes has been restricted,² mostly to those involving terminal alkynes with hindered dialkylboranes.^{1,3}

Ideally, the two unsaturations in alkynes can result in as many hydroborations providing bi-functionalized molecules. On this basis, the laboratories of Brown,⁴ Hassner,⁵ and Pasto⁶ independently examined the hydroboration of alkynes with gaseous diborane or 2. With hex-1-yne and -3-yne as substrates, Brown and Zweifel concluded that the hydroboration/oxidation of internal aliphatic alkynes resulted in ketones, whereas those of terminal alkynes formed hexan-1-ol via geminal diboro intermediates. Altering the oxidation conditions, they achieved 54% yield of the corresponding aldehyde and small amounts (10-12%) of the 1,2-diol.^{4,7} Subsequently, Brown developed the hydroboration of terminal alkynes with dialkylboranes for aldehyde synthesis, which has become a classic textbook reaction. Hassner, on the other hand, examined the hydroboration/oxidation of only an aromatic internal alkyne, diphenylacetylene (4a), with a large excess of diborane bubbled through tetrahydrofuran (THF), and reported the formation of mixtures of hydrobenzoin (6a) and 1,2-diphenylethanol (7a) in low yields.^{5,8} Pasto carried out deuterium labelling studies and confirmed that terminal alkynes predominantly produce 1°-ols and internal aromatic alkynes give roughly equal amounts of ketone and 1,2-diols, in low yields.⁶ All of these studies were limited in the scope of substrates and conditions, providing low amounts of vicinal diols.

Since these initial reports, there has been little effort^{9,10} to examine the dihydroboration of alkynes in detail to provide broad conclusions. As part of our program on amine-borane chemistry,¹¹ we recently reported the first open-flask, non-dissociative hydroboration of alkenes with ammonia borane (AB, **3**).¹² To expand the utility of air and moisture stable **3** as a hydroborating agent, alkynes were included as substrates to possibly achieve the direct synthesis of valuable vicinal diols in high yields.¹³ The fruitful results of this study follow (Scheme 1).

Brown and Zeife	l, 1961 ⁴	
H ₉ C ₄ ———————————————————————————————————	1) 2 equiv. BTHF (2), <u>1 M THF, 0 °C, 2 h</u> 2) [O]	$HO \qquad OH \\ H_9C_4 \qquad H$
Hassner and Bra	un, 1963 ⁵	19%
Ph-=-Ph	1) 7 equiv. B_2H_6 THF, 4 °C, 14 h	но он
	2) [O]	Ph Ph
Pasto, 1964⁶ Ph 	1) 0.67 equiv. BTHF (2) 0.25 M THF, RT, 12 h	37% HOOH
	2)[O]	Ph Ph 31%
<u>This Wor</u> k RR'	1) 2 equiv. H ₃ NBH ₃ (3) 2 M THF, reflux, 1-2 h	но он
к <u>—</u> К	2)[O]	
		$\Box n to X0\%$

Scheme 1. Hydroboration/oxidation of alkynes

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The project was initiated with the hydroboration of a representative internal alkyne, diphenylacetylene (4a) with 0.33 equiv 3, in THF at room temperature. ¹¹B NMR spectroscopic analysis of an aliquot of the reaction mixture revealed no progress after 1 h. Gradual increase of the temperature, followed by analysis showed that reaction occurred only at reflux, when after 1 h, the ¹¹B NMR spectrum revealed the consumption of 3 and the presence of several overlapping peaks centered at δ -5 ppm. This suggested the formation of polymeric⁴ alkylborane-ammonia complexes, attempted separation of which failed. Nevertheless, purification of an identical reaction after alkaline H2O2 oxidation afforded 57% deoxybenzoin (5a) and 11% (±)-hydrobenzoin (6a), along with 19% of recovered 4a. The recovery of a large amount of 4a prompted the examination of the effect of stoichiometry on the reaction outcome (Table 1).

Table 1. Stoichiometry-controlled product distribution^a

4a	,	5a	^{rn} 6a ^{rn}	
Ph-=	-Ph $\frac{1 \text{ M THF, reflux}}{2 \text{ NaOH, H}_2 \text{ O}_2}$	^x O Ph Ph	+ Dh	±)
	1) 3 (equiv.)	_		

Entry	3 (equiv.)	Time ^b (h)	Recovery 4a (%) ^c	Yield 5a (%) ^c	Yield 6a (%) ^c
1	0.33	1	19	57	11
2	0.5	3	3	70	15
3	1	5	4	18	62
4	1	22	3	22	64
5	2	22	3	7	76
6	3	28	3	6	83
7	2	1	3	6	78

^aConcentration with respect to **3**. ^bTime required for complete consumption of **3** by hydroboration or thermal decomposition as determined by ¹¹B NMR spectroscopy. ^cIsolated yield.

Increasing the equivalents of **3** to 0.5 resulted in an increased yield of the ketone 5a (70%) and diol 6a (15%), with very little recovery of 4a. Hydroboration-oxidation with one equivalent of 3 for 5 h yielded a drastically different product distribution of 18% 5a and 62% 6a, with negligible recovery of 4a. Prolonging the reaction had no effect on the outcome. Isolation of significantly larger quantity of the vicinal diol than previously reported encouraged further increases in 3 to achieve maximum yield. We hypothesized that an excess of 3 may be required for full saturation of the triple bond since the vinylborane-ammonia complex from the first hydroboration might be a slower hydroborating reagent than 3 due to steric hindrance. Utilizing 2 equivalents of 3, gratifyingly, resulted in an improved yield of 6a (76%, Table 1, Entry 5), supporting our assumption. Further increase of 3 to 3 equivalents improved the yield, modestly, to 83% (Entry 6), while incurring an unacceptable loss to atom economy. In all cases, only minimal (3-4% of the isolated diol) meso-hydrobenzoin was detected. Thus, 2 equivalents of 3 was chosen as optimal for further standardization.

Reactions were also performed in several other etheric solvents, such as 1,2-dimethoxyethane, 2-methyltetrahydrofuran, diisopropyl ether, and dioxane, with no improvement in yield.¹⁴ The effect of the reagent concentration in THF was gauged and 2 M was deemed best, providing **6a** in 79% yield. The presence of excess reagent made it difficult to determine the time required for completion by ¹¹B NMR spectroscopy. Accordingly, **3** and **4a** were heated at reflux in THF for 1 h and worked up. Gratifyingly, the product distributions remained the same (Table 1, Entry 7) as with the reaction performed for 22 h (Entry 5). This optimal condition, 2 equivalents **3** in refluxing THF at 2 M

for 1 h, was then applied to other alkynes, focusing initially on aryl alkynes (Table 2).

The steric and electronic environment on either side of the alkyne was varied, proceeding from doubly aromatic-substituted alkyne 4a to singly substituted phenylacetylene (4b) to a mixed aryl alkyl substituted 1-phenylprop-1-yne (**4**c). The corresponding products **6b** and **6c** were isolated in 75% and 76% yields, respectively (Table 2, entries 2-3), with the racemic anti-diol 6c.14 only detected for Electron-deficient 4-fluorophenylacetylene (**4d**) and 4-(trifluoromethyl)phenylacetylene (**4e**) were subjected to hydroboration with 3 and diols 6d and 6e were isolated in 78% yield each (Table 2, entries 4-5).

Table 2. 1,2-Dihydroboration and oxidation of alkynes^a

Entry	Alkyne (4)	Diol (6)	Time (h)	Yield (%) ^b
1		6a	1	78
2		6b	1	75
3		6c	1	76
4	F-	6d	2	78
5	$F_3C - 4e$	6e	1	78
6	4f	6f	1	71
7	کے	6g	1	70
8		6h	1	68
9	o-(6i	2	54
10	C ₈ H ₁₇ ────────────────────────────────────	6j	1	36
11	$C_{4}H_{9} - C_{4}H_{9}$	6k	1	53

^a Reagents and conditions: **3** (4 mmol), alkyne (2 mmol), THF (2 M) under open-flask conditions. ^bIsolated yield.

Adding a methyl substituent at the *ortho-* (**4f**), *meta-* (**4g**), and *para-* (**4h**) positions of phenylacetylene provided the diols **6f-h** in 71%, 70%, and 68% yields, respectively (Table 2, entries 6-8). This effect of the electron-donating group was even more apparent for 4-methoxyphenylacetylene (**4i**), with the isolation of only 54% of **6i** (Table 2, Entry 9). We expected that even electron-rich aliphatic alkynes would behave in a similar manner to **4i**.¹⁵ Indeed, when a terminal aliphatic alkyne dec-1-yne (**4j**) was submitted to these conditions (Table 2, Entry 10), only 36%

of diol **6j** was isolated with 48% of decan-1-ol (**7j**) as the major product. This points to preferential geminal dihydroboration for electron-rich alkynes as reported previously.^{4,6} Similarly, dec-5-yne (**4k**) resulted in low yields (53%) of the racemic, *anti*-(\pm)-5,6-decanediol (**6k**).

The generality of the preference for vicinal dihydroboration, as seen with 3, was explored by treating 4a with other common hydroborating reagents (Table 3).

Table 3. Hydroboration with common hydroborating reagents^a

1) Borane (2 equiv.), 2 M THF Ph———Ph $\xrightarrow{\text{reflux, 2 h}}$ HO OH 2) NaOH/H ₂ O ₂			
	4a	^{Ph} 6a ^{Ph}	
Entry	Borane	Yield 6a (%) ^b	
1	$H_3B \cdot NH_3$ (3)	78	
2	$H_3B \cdot SMe_2(1)^c$	71	
3	$H_3B\bullet THF(2)^c$	71	
	N. D.L. (1.6		
4	$NaBH_4/I_2$	57	
4 5	$NaBH_4/l_2$ $NaBH_4/(NH_4)_2SO_4^d$	57 83	
4 5 6	$\begin{array}{c} \text{NaBH}_4/l_2^{\circ} \\ \text{NaBH}_4/(\text{NH}_4)_2\text{SO}_4^{\text{d}} \\ \text{Chx}_2\text{BH} \left(8 \right)^{\circ} \end{array}$	57 83 42 ^e	
4 5 6 7	$\begin{array}{c} \text{NaB}\text{H}_{4}/\text{I}_{2}^{c}\\ \text{NaB}\text{H}_{4}/(\text{NH}_{4})_{2}\text{SO}_{4}^{d}\\ \text{Chx}_{2}\text{BH}\left(\boldsymbol{8}\right)^{c}\\ \text{Chx}_{2}\text{BH}\left(\boldsymbol{8}\right)^{c,f}\end{array}$	57 83 42 ^e 62 ^g	

^aReagents and conditions: borane reagent (4 mmol), diphenylacetylene (2 mmol),THF (2 M), unless noted otherwise. ^bIsolated yields. ^cReaction performed under nitrogen. ^dReaction performed at 1 M. ^e56% **7a** isolated. ¹6 equiv reagent used. ^g32% **7a** isolated. ^h65% **7a** isolated.

Reagents 1 and 2 gave yields lower than 3, with the isolation of **6a** in 71% each (Table 3, entries 2 and 3).¹⁶ The increased yields of diol from using 2, as compared to those reported in the literature,^{4,5,6} might be due to the effect of temperature and stoichiometry on the product distribution. Generation of B_2H_6 *in situ* from sodium borohydride and iodine¹⁷ in THF gave only 57% yield of **6a** after isolation (Table 3, Entry 4), possibly due to the loss of gaseous B_2H_6 at elevated temperatures. This prompted us to consider the *in situ* generation of **3** from sodium borohydride and ammonium sulfate in THF.^{11a} To our delight, the reaction proceeded akin to pre-synthesized **3**, with the isolation of **6a** in 83% yield (Table 3, Entry 5) (Scheme 2).

$$Ph = Ph = Ph = \frac{1) \text{ NaBH}_{4} (2 \text{ equiv.})}{(\text{NH}_{4})_{2}\text{SO}_{4} (2 \text{ equiv.})} + HO = OH = \frac{OH}{20 \text{ NaOH/H}_{2}\text{O}_{2}} + HO = \frac{OH}{Ph} = \frac{OH}{6a} = \frac{OH}{83\%}$$

Scheme 2. One-flask hydroboration of diphenylacetylene with $NaBH_4/(NH_4)_2SO_4$.

Dicyclohexylborane (8), which has been used extensively to prepare ketones from internal alkynes,¹ was examined next. When 2 equivalents of this sterically hindered reagent were heated at reflux in THF with 4a for 2 h, surprisingly, 42% of 6a was isolated along with 56% yield of monoalcohol 7a (Table 3, Entry 6). Utilizing an equivalency of available hydride analogous to 1 (6 equiv 8) increased the yield of 6a to 62%, although at great loss to atom economy. A representative alkylamine-borane, *tert*-butylamine-borane (9) was subjected to these conditions to examine the effect of substituted amine-boranes on alkyne hydroboration. While only 12% yield of 6a was isolated, we were surprised to discover that the bulky amine-borane reacted to form monoalcohol 7a in 65% isolated yield. Future investigation will include the reaction between alkylamine-boranes and alkynes, particularly chiral amine-boranes. In conclusion, we have demonstrated that ammonia borane can be utilized for the dihydroboration of alkynes in THF at reflux to provide vicinal diols in good yields. The formation of the vicinal diols seems to rely on the stoichiometry and electronics of the alkyne. Examination of other common hydroborating agents, such as BTHF and BMS, established the superiority of ammonia borane for the direct synthesis of diols from alkynes. Considering the reported low yields of diols using conventional hydroborating agents, we believe that the higher temperature of the reaction also plays a major role in achieving better yields. A one-pot reaction involving the *in situ* synthesis of ammonia borane, was also very successful. The air and moisture stability and ready availability¹⁸ of ammonia borane, as well as the scope of diols in organic synthesis make this transformation a valuable addition to the synthetic chemists' arsenal.

Acknowledgments

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1,2-Dihydroboration of aromatic alkynes • with ammonia borane is described

Hydroborations was performed under ٠

completely open-flask conditions

Accepter Direct, uncatalyzed, synthesis of racemic •