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1-Bromo-1-lithioethene: A Practical Reagent for the Efficient Preparation of 2-Bromo-1-alken-3-ols

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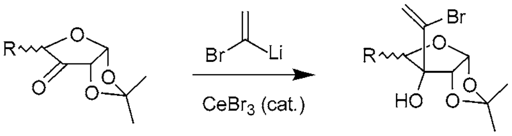
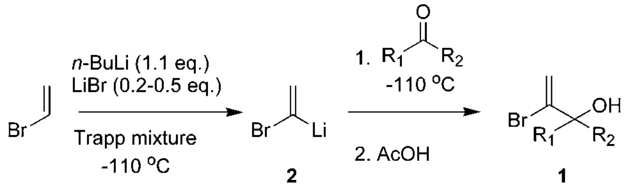
ABSTRACT



A reliable preparative-scale synthesis of 1-bromo-1-lithioethene is reported. This reagent undergoes clean 1,2-addition with a range of aldehydes and ketones at −105 °C to afford the corresponding 2-bromo-1-alken-3-ols in moderate to excellent yield. Efficient diastereoselective addition to α-siloxy and α-methylcyclohexanones, as well as protected 3-keto furanose sugars, is achieved in the presence of 10 mol % CeBr$_3$. The resulting bromoallylic alcohol adducts have considerable potential as synthetic building blocks.

Bromoalkenes are important substrates for the construction of C−C bonds in many modern organic reactions.[1] Recently, our attention was drawn to 2-bromo-1-alken-3-ols **1** (Scheme 1), which have considerable potential utility as synthetic building blocks. While some synthetic applications of **1** have already been demonstrated,[2−4] much remains to be learned about their synthetic utility. The preparation of **1** has previously been achieved by 1,2-addition of an alkynyllithium[2a] or an enolate[5] to 2-bromoacrolein,[6] or via HBr addition to a terminal alkyn-3-ol.[2b] In the latter case, a necessity to separate regiosomeric products was reported.[2b]

Scheme 1. Generation and Trapping of 1-Bromo-1-lithioethene



We were interested in exploring alternate synthetic routes to **1** that proceed via construction of the C(Br)−C(OH) bond through reaction between 1-bromo-1-lithioethene (**2**) and an

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[1] For example: (a) Pd(0)-catalyzed cross-coupling: *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. *Topics in Current Chemistry*; Miyaura, N., Ed. ; Springer-Verlag: Berlin, 2002; Vol. 219. (b) Organocuprate coupling: Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631. *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002. (c) Nozaki−Hiyama−Kishi coupling: Cintas, P. *Synthesis* **1992**, 248−257. Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1−36.

[2] For example: (a) Sonogashira coupling: Dai, W. M.; Wu, J.; Fong, K. C.; Lee, M. Y. H.; Lau, C. W. *J. Org. Chem.* **1999**, *64*, 5062−5082. (b) Marshall, J. A.; Sehon, C. A. *Org. Synth.* **1999**, *76*, 263−270.

[3] Bromohydroxylation/amination en route to α-methylene-γ-lactams: Mori, M.; Chiba, K.; Okita, M.; Kayo, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 375−385.

[4] Additional chemistry has been explored for the related 2-chloro- and 2-iodo analogues of **1**. For example: (a) 2-iodo-1-alken-3-ols undergo efficient Pd(0)-mediated carbonylative cross-coupling with intramolecular trapping by the alcohol moiety to afford α-methylene-γ-lactones: Adam, W.; Klug, P. *Synthesis* **1994**, 567−572. (b) Both 2-chloro- [Falck, J. R.; Barma, D. K.; Mioskowski, C.; Schlama, T. *Tetrahedron Lett.* **1999**, *40*, 2091−2094] and 2-iodo-1-alken-3-ols [Friesen, R. W.; Giroux, A. *Can. J. Chem.* **1994**, *72*, 1857−1865] undergo facile dehydrochlorination to the corresponding 1-alkyn-3-ol. (c) Ozonolysis of 2-chloro-1-alken-3-ols in methanol provides an attractive entry to α-hydroxy esters: Satoh, T.; Onda, K.; Yamakawa, K. *J. Org. Chem.* **1991**, *56*, 4129−4134. (d) Cr(VI) oxidation of 2-chloro-1-alken-3-ols affords 2-chloroalk-1-en-3-ones: Della, E. V.; Pigou, P. E. *Austr. J. Chem.* **1983**, *36*, 2261−2268.

[5] (a) Chen, C.; Crich, D. *Tetrahedron* **1993**, *49*, 7943−7954. (b) Nagasawa, K.; Ishihara, H.; Zako, Y.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 2523−2529.

[6] Smith, A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501−1513.

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aldehyde or ketone. Interestingly, however, very little is known about the use of 1-halo-1-lithioethenes (halo = Cl,[7] Br,[8] I[9]) as synthetic intermediates, presumably due to concerns over the rearrangement and/or decomposition of such metalated carbenoids.[9−11] Only a single report has appeared on the preparation and electrophilic trapping of 1-bromo-1-lithioethene **2**.[8] We now report a reliable preparative-scale synthesis of **2** and demonstrate its utility for the efficient trapping of aldehydes and ketones en route to the preparation of 2-bromo-1-alken-3-ols **1**.

n-BuLi had been previously used by Köbrich for the selective deprotonation of chloroethene at −110 °C to afford 1-chloro-1-lithioethene.[7a] However, Shimizu reported that attempted *n*-BuLi deprotonation of bromoethene was thwarted by several competing processes that led them to use LDA/Me_3SiCl for the α-deprotonation/silylation of bromoethene.[8] In stark contrast, we found that 1-bromo-1-lithioethene (**2**) could be generated cleanly via reaction of *n*-BuLi with commercially available bromoethene. The reproducible preparation of **2** required strict temperature control, which was achieved using a specially designed glass reactor.[12] Given its instability, **2** was immediately trapped with a suitable aldehyde or ketone (Scheme 1). After some optimization, it was found that the slow addition of *n*-BuLi to a solution of bromoethene in the Trapp mixture[13] at −110 °C followed by addition of acetone gave 57% isolated yield of the desired bromoallylic alcohol **1a** (Table 1, entry 1).

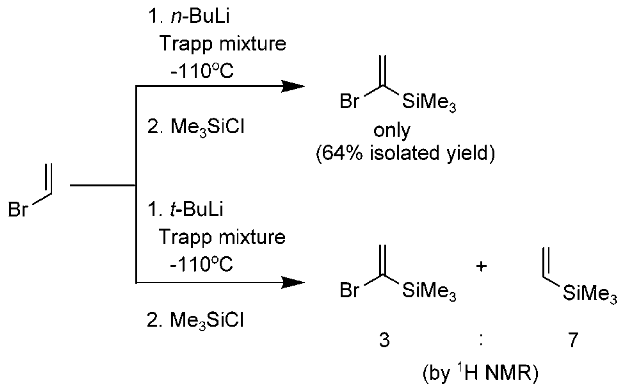
Table 1. Reaction of 1-Bromo-1-lithioethene with Aldehydes and Ketones $R_1C(O)R_2$

entry	R_1	R_2	product	% yield[a]
1	CH_3	CH_3	**1a**	57[b]
2	CH_3	CH_3	**1a**	77
3	CH_3	CH_3	**1a**	20[c]
4	CH_3	$CH_2{=}CH-$	**1b**	78
5	CH_3	$CH_2{=}CH-CH_2-CH_2-$	**1c**	84
6	$-CH_2CH_2CH_2CH_2CH_2-$		**1d**	85
7	$-CH{=}CH-C(Me)_2-CH_2CH_2-$		**1e**	80
8	CH_3CH_2	H	**1f**	46
9	*n*-C_6H_{13}	H	**1g**	50
10	Ph	H	**1h**	81
11	$CH_2{=}CH-$	H	**1i**	74

[a] Isolated yields of product obtained in 95-99% purity (by GC) after vacuum distillation. [b] No LiBr was present. [c] Bromoethene was added to *n*-BuLi solution (inverse addition).

The choice of alkyllithium base proved to be important. An attempt to deprotonate bromoethene with *tert*-butyllithium generated a mixture of lithioethene and 1-bromo-1-lithioethene (**2**), which was characterized by electrophilic trapping with chlorotrimethylsilane (Scheme 2). Clearly, competitive halogen−metal exchange had dominated during the attempted deprotonation step.

Scheme 2. Reaction of Bromoethene with Different Alkyllithium Bases



Carrying out the metalation step in the presence of 0.2−0.5 equiv of lithium bromide significantly increased the yield of acetone-trapped adduct **1a** (Table 1, entry 2). This product did not contain even traces of 2-methyl-3-buten-2-ol, indicating that deprotonation of bromoethene was not complicated by side reactions involving halogen−metal exchange under the reaction conditions employed.

When bromoethene was added to a low-temperature solution of *n*-butyllithium (i.e., inverse addition), the yield of **1a** dropped dramatically (entry 3) but again no 2-methyl-3-buten-2-ol was formed.

When the optimized conditions developed above for the trapping of acetone (entry 2) were employed with a range of other aldehydes and ketones, the desired bromoallylic alcohols **1** were obtained in moderate-to-excellent yield (entries 4−11). All ketones examined here afforded the desired adducts in high yield (entries 2, 4−7). α,*β*-Unsaturated ketones and aldehydes cleanly gave 1,2-adducts **1b**, **1e**, and **1i** (entries 4, 7, 11). While benzaldehyde and acrolein afforded high yields of adducts **1h** and **1i** (entries 10, 11), lower yields were obtained with simple aliphatic aldehydes (entries 8, 9). No products originating from vinyllithium addition were detected in any experiment. Throughout this study, it was apparent that the chemical behavior of 1-bromo-1-lithioethene at the reaction temperature was more similar to a simple organolithium reagent rather than to a carbenoid-type species.

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(7) 1-Chloro-1-lithioethene was prepared from chloroethene by Köbrich more than 35 years ago and was successfully trapped with a limited range of electrophiles that did not include aldehydes or ketones: (a) Köbrich, G.; Flory, K. *Chem. Ber*. **1966**, *99*, 1773−1781. (b) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 41−52. However, only one (moderate-to-poor-yielding) synthetic application of 1-chloro-1-lithioethene has subsequently appeared: (c) Kasatkin, A.; Whitby, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 7039−7049.

(8) 1-Bromo-1-lithioethene was generated from 1-bromoethene using LDA and trapped in 60% yield with Me_3SiCl (Shimizu, N.; Shibata, F.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 777−778), but no other applications of this reagent have appeared.

(9) 1-Iodo-1-lithioethene was prepared from 1-iodoethene and LDA: it was trapped by several electrophiles in very low yield (e.g., 10% for trapping with $Ph_2C{=}O$) due to its facile decomposition to ethyne even at −100 °C: Campos, P. J.; Sampedro, D.; Rodriguez, M. A. *Organometallics* **1998**, *17*, 5390−5396.

(10) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383−405.

(11) (a) Liu, F. *Jiegou Huaxue* **2002**, *21*, 210−213. (b) Schoeller, W. W. *Chem. Phys. Lett.* **1995**, 241, 21−25. (c) Lucchini, V.; Modena, G.; Pasquato, L. *J. Am. Chem. Soc.* **1995**, *117*, 2297−2300. (d) Wang, B. Z.; Deng, C. H.; Xu, L. X.; Tao, F. G. *Sci. China, Ser. B* **1990**, *33*, 421−429.

(12) Design for this glass reactor is provided in Supporting Information.

(13) THF/ether/pentane 4:1:1 by volume: see ref 7b.

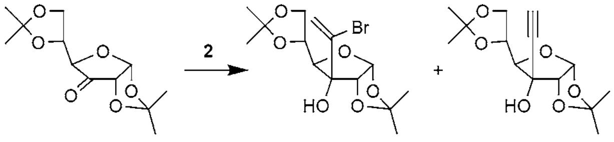
During these experiments, it was found that the deprotonation of bromoethene was quite slow. The optimal metalation time was found to be 1−2 h at −110 °C. Products derived from trapping unreacted *n*-BuLi were observed at shorter reaction times. During the metalation step, the reaction mixture appeared as a viscous white slurry in the temperature range −118 to −95 °C. Above −95 °C, a homogeneous solution formed but only products derived from trapping ethynyllithium (which is the product of the thermal decomposition of 1-halo-1-lithioethenes[10]) could be detected on workup.

Controlling the reaction time for the electrophilic trapping of **2** was critical, with times between 20 min and 1 h proving to be optimal. When trapping reactions with allylacetone and acrolein were allowed to proceed for more than 2 h, a significant drop in the corresponding yields of **1c** and **1i** were observed. A low-temperature (−105 °C) workup with a slight excess of a 2 M solution of acetic acid in the Trapp mixture[13] (this solution does not freeze at −105 °C) must be performed in order to avoid decreased yields of products **1**.

The mediocre yields obtained with simple aliphatic aldehydes (Table 1, entries 8 and 9) cannot be easily rationalized at present. The only products isolated here were the desired adducts **1f**,**g** and unreacted aldehyde. No evidence for the corresponding self-aldol adducts was observed. Indeed, it seems that aldehyde enolization was not a major problem during the reaction. A separate experiment in which the products derived from reaction of **2** with propanal were quenched by a slight excess of Me_3SiCl (instead of AcOH), followed by careful removal of solvent under anhydrous conditions, unexpectedly provided a 1:1 mixture (by ^1H NMR analysis) of 1-bromo-1-trimethylsilylethene (trapped unreacted **2**) and 2-bromo-3-trimethylsiloxy-1-pentene (trapped addition product). No traces of silyl enol ethers derived from trapping the propanal enolate could be observed.

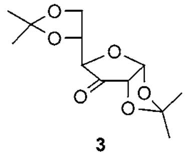
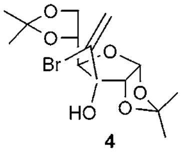
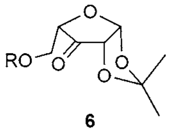
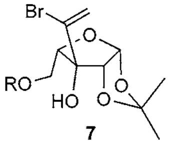
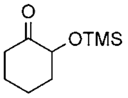
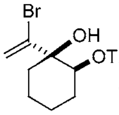
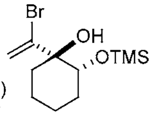
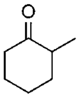
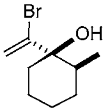
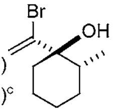
Given that the addition of 1-bromo-1-lithioethene (**2**) to simple ketones proceeded smoothly, we next explored its addition to more complex carbohydrate-derived ketone substrates. Using the optimized conditions described above, **2** was trapped using glucose-derived 3-keto furanose **3**. To our disappointment, only 9% (by ^1H NMR analysis) of the desired bromoethenyl adduct **4** was formed (albeit a single diastereomer), accompanied by 46% of the starting ketone **3** and 45% of the acetylenic adduct **5** (Scheme 3).[14] Common Lewis acid additives such as $CeCl_3$ and $Yb(OTf)_3$, as well as variations in the reaction conditions, only slightly improved the yield of **4**. The same trend was observed when L-arabinose-derived ketone **6** (Table 2, entry 2) was used as a substrate.

Scheme 3. Reaction of 1-Bromo-1-lithioethene with Glucose-Derived Ketone **3**



3 **4** **5**

Table 2. $CeBr_3$-Catalyzed Addition of 1-Bromo-1-lithioethene to α-Substituted Cyclohexanones and Protected 3-Ketofuranose Sugars

entry	reactant	products (diastereomeric ratio)	% yield
1	 **3**	 **4**	85[a, b] 9[b, c, d]
2	 **6**	 **7**	67[a, b, e]
3		 **8a** (88:12) (91:9)[f]  **8b**	70[a] 35[c, d, f]
4		 **9a** (88:12) (90:10)[c]  **9b**	47[d] 20[c, d]

[a] Isolated yield. [b] Single diastereomer. [c] No $CeBr_3$ additive was used. [d] ^1H NMR yield. [e] R = *t*-$BuPh_2Si$. [f] $CeCl_3$ (0.5 equiv) was added to **2** followed by 2-trimethylsiloxycyclohexanone.

We considered that the failure of the $CeCl_3$ additive to enhance the yield of **4** might be ascribed to its extremely low solubility in the Trapp mixture[13] at −110 °C.[15] Therefore, potentially more soluble $CeBr_3$ was examined as an additive.[16] After considerable experimentation, it was found that stirring a mixture of 3 equiv of preformed 1-bromo-1-lithioethene (**2**) with 0.1 equiv of $CeBr_3$ for 5−15 min at −110 °C followed by the addition of 1 equiv of carbohydrate-derived ketone **3** (or **6**) afforded the desired bromoallylic alcohol **4** (or **7**) as a single diastereomer in 67−85% yield

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(14) Acetylenic product **5** could originate from competitive dehydrobromination of the initially formed adduct **4** by unreacted 1-bromo-1-lithioethene (**2**).

(15) $CeCl_3$ does not form a true solution with THF and other ethereal solvents even at room temperature. The nonhomogeneous slurry is usually used "as is": Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787−6790.

(16) $CeBr_3$ was found to slowly dissolve in THF after prolonged stirring at room temperature and form a clear solution at a concentration of ca. 1−2%. There are very few reported examples of using $CeBr_3$ as a Lewis acid, and it seems that no significant difference in reactivity between $CeBr_3$ and $CeCl_3$ was previously observed. (For example: Fukuzawa, S.; Fujinami, T.; Yamaguchi, S.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1986**, *11*, 1929−1932.)

(Table 2, entries 1−2). In each case, attack of **2** from the less crowded convex face of the ketone is assumed. It was observed that the order of addition of reagents was critical. For example, when ketone **6** was premixed with $CeBr_3$ and the resulting clear homogeneous solution was added to 1-bromo-1-lithioethene, the yield of the bromoethenyl addition product **7** was less than 33%. Adding only small amounts of Lewis acid was also important: use of 0.5−0.6 equiv of $CeBr_3$ caused extensive decomposition of 1-bromo-1-lithioethene and formation of addition products derived from the resulting ethynyllithium.

When this $CeBr_3$-mediated variant was employed for the addition of **2** to 2-trimethylsiloxycyclohexanone and 2-methylcyclohexanone, we were delighted to find that significant improvements in the yields of the desired adducts **8** and **9** were observed (Table 2, entries 3 and 4). The stereochemistry of adducts **8a/8b** and **9a/9b** was assigned by analogy with published data.[17] It is interesting to note that the reactions conducted without the $CeBr_3$ additive furnished nearly the same diastereomeric ratios of products, albeit the conversion levels were much lower (by ^1H NMR analysis).

In summary, we have established the synthetic utility of 1-bromo-1-lithioethene (**2**) for addition to a variety of aldehydes and ketones. Experimental conditions favoring formation of the desired 2-bromo-1-alken-3-ol adducts were identified and carefully optimized. Use of $CeBr_3$ as a Lewis acid additive expanded the scope of applicable electrophiles to include sterically crowded, α-siloxy, and carbohydrate-derived ketones.

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Supporting Information Available: Detailed experimental procedures, design of the low-temperature reactor used in these studies, and spectral data for all compounds, including copies of ^1H and ^{13}C NMR spectra for **4**, **7**, **8a**, and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] (a) Pearson, W. H.; Walavalkar, R. *Tetrahedron* **2001**, *57*, 5081−5089. (b) Battoni, J. P.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1977**, 320−328.