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# Boron trifluoride–tetrahydrofuran complex: a superior trigger for the Yamaguchi–Hirao alkylation of lithio-acetylides by epoxides

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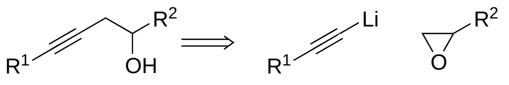
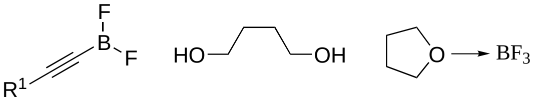
**Abstract**—Use of $BF_3{\cdot}THF$ complex in place of the usual $BF_3{\cdot}OEt_2$ analogue in the Yamaguchi–Hirao alkylation of lithio-acetylides **2** by monosubstituted epoxides **3** gives consistently superior isolated yields (ca. 90%) of homopropargylic alcohols **1**. © 2001 Elsevier Science Ltd. All rights reserved.

Our recent studies of various 5-*endo* cyclisation processes[1] have resulted in a continual requirement for various homopropargylic alcohols **1**. The perhaps most obvious and certainly the most popular way to prepare such intermediates is by alkylation of 1-lithio-acetylides **2** using monosubstituted epoxides **3**.



**1** **2** **3**

The relatively poor electrophilicity of the epoxide components **3** requires the addition of a Lewis acid to trigger successful reactions. The value of alkynylalanes in this respect was used during an early prostaglandin synthesis[2] and subsequently shown to be of some generality.[3] However, only relatively simple diethylalkynylalanes gave respectable yields under a variety of conditions which often feature lengthy reaction times but which are amenable to scale-up. By far the most popular form of this reaction, however, was developed by Yamaguchi and Hirao some ten years later and utilises boron trifluoride etherate [$BF_3{\cdot}OEt_2$] as the key Lewis acid, in place of the diethylaluminium chloride used to obtain the foregoing alanes.[4] The method involves rapid formation of an intermediate difluoroborane species **4** by treatment of a solution of a lithio-acetylide **2** in tetrahydrofuran at −78°C with $BF_3{\cdot}OEt_2$ which is followed by a similarly rapid coupling with an epoxide **3** at the same low temperature. A simple aqueous work-up then delivers the homopropargylic alcohol product **1**. In our experience,[1] and in general that of many others,[5] isolated yields of the desired alcohols are typically 70–75% using the original procedure which consists of adding 1 equiv. of an epoxide to a mixture of the lithio-acetylide (1.5 equiv.) and $BF_3{\cdot}OEt_2$ (1.6 equiv.). Yet another development is the use of catalytic amounts of trimethylgallium, as low as 0.08 equiv., to catalyse such alkylations.[6] This method, which offers the additional benefit of proceeding at ambient temperature, is usually at least as efficient as the Yamaguchi–Hirao method but has not become popular, probably because trimethylgallium, while commercially available, is both pyrophoric and expensive.



**4** **5** **6**

Returning to the Yamaguchi–Hirao method, we often encountered lower yields which seemed to be associated with the quality of the $BF_3{\cdot}OEt_2$ even, on occasions, when obtained from freshly opened bottles. A sure sign of this was the formation of varying amounts of 1,4-butanediol **5** as a second isolated product, formed by hydration of the tetrahydrofuran solvent. We therefore examined the use of the alternative ethereal solvents diethyl ether, dimethoxyethane (DME) and diethylene glycol dimethyl ether (diglyme) at a variety of temperatures. In all cases, yields of the desired homopropargylic alcohols **1** were lower, usually by a significant amount. At this stage, we noted that the boron trifluoride–tetrahydrofuran complex **6** had become commercially available[7] and elected to use this in place of $BF_3{\cdot}OEt_2$ on the basis that it might prove more com-

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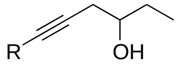
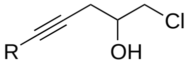
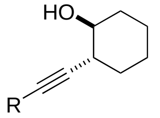
patible as a component of a reaction carried out in tetrahydrofuran. We were delighted to find that this seemingly simple change consistently delivered isolated yields of homopropargylic alcohols of around 90%. The reaction was successful with a range of both lithioacetylides as well as mono- and 1,2-disubstituted epoxides, including 1,2-epoxybutane, epichlorohydrin, epoxycyclohexane, 3-(4-methoxyphenyl)-1,2-epoxypropane and an example having a PMB function. The resulting products **7**–**11** are shown below, along with the isolated yields obtained in parenthesis.[8]



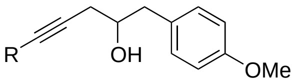
**7** R = Bu (93%)
R = Ph (92%)



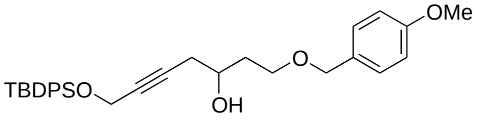
**8** R = Bu (88%)
R = Ph (94%)
R = TBDPSOCH$_2$ (91%)



**9** R = Bu (92%)
R = Ph (92%)



**10** R = Bu (84%)
R = Ph (89%)
R = TBDPSOCH$_2$ (88%)
R = Me$_3$Si (95%)



**11** (85%)

In the original Yamaguchi–Hirao procedure,[4] an excess (1.5 equiv.) of both the acetylide and $BF_3 \cdot OEt_2$ was used. A brief optimisation study using $BF_3 \cdot THF$ **6** revealed that a slight excess of the epoxide delivered the best yields. A typical procedure, which otherwise closely resembles the original is as follows:

*n*-Butyllithium (2.5 M solution in hexanes, 1.3 equiv.) was added dropwise to a stirred solution of the 1-alkyne (1.0 equiv.) in dry THF (~5 ml per mmol of *n*-BuLi) under a nitrogen atmosphere at −78°C. The resulting solution was stirred for 30 min, and then treated dropwise with boron trifluoride–THF complex (1.3 equiv.). After a further 15 min at −78°C, the epoxide (1.2 equiv.) in dry THF (~1:1 relative to the epoxide) was then added and the mixture stirred for approximately 2 h at −78°C. The reaction was quenched by the addition of saturated aqueous ammonium chloride (~5 ml per mmol of *n*-BuLi) and the organic layer separated. The aqueous layer was then extracted with ether (×3), and the combined organic solutions were washed with brine, then dried ($MgSO_4$) and evaporated. The crude material was purified by column chromatography on silica gel (20% ethyl acetate in petroleum ether).

As expected, it was essential that samples of $BF_3 \cdot THF$ complex **6** were carefully protected from moisture, in which case material which was over six months old (stored at 0°C) gave similarly high yields of alcohols **1**.

We have not made any attempts to determine the origins of these enhanced yields and can only speculate that these may be due to the presumed extra stability of complex **6** relative to $BF_3 \cdot OEt_2$. This could result in less epoxide polymerisation which we assume is the primary cause of loss of material.

## Acknowledgements

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7. Item 43, 428-0, Aldrich Chemical Co. Ltd.
8. Satisfactory spectroscopic and analytical data were obtained for all products **7**–**11**, along with literature comparisons.