

Generation of Cations from Alkoxides: Allylation of Propargyl Alcohols

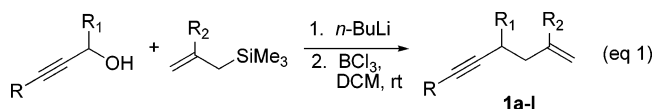
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The relative stabilities of benzylic, allylic, and propargylic carbocations are well-documented and have been the subject of numerous theoretical and experimental studies.¹ However, the availability of these cations has not resulted in their general use as synthetic intermediates due to the strong acidic conditions required to generate them.² In recent years, our group has developed a series of reactions involving the coupling of benzylic, allylic, and propargylic alkoxides with alkenylboron dihalides and alkynylboron dihalides.³ These novel transformations provide for direct substitution of hydroxyl groups with stereodefined alkenyl and alkynyl groups under very mild reaction conditions (room temperature and transition-metal free). Our initial mechanistic studies indicated that these reactions proceed through cationic intermediates.⁴ The generation of cations from alkoxides using organoboron dihalides under such mild reaction conditions was unprecedented. However, the subsequent reaction between the newly formed cation and the organic moiety on the boron limited the utilization of the cation in other organic transformations.

We have discovered that boron trichloride can also be used to generate cations from alkoxides even though it is generally assumed that alkoxides (RO⁻) react with Lewis acids (MCl_x) to yield the corresponding complexes M(OR)_nCl_{x-n}.⁵ In contrast to the direct generation of cations from alcohols, no Brønsted acids are produced while generating cations from alkoxides using this methodology. The absence of a Brønsted acid can make a significant difference in organic syntheses. In this communication, we describe the application of this new methodology to the allylation of propargyl alcohols (eq 1).



Compared to the allylation of benzylic and allylic alcohols,⁶ allylation reactions of propargyl alcohols using allyltrimethylsilane have been relatively unexplored despite the synthetic utility of the resultant 1,5-enynes. Lewis acid mediated allylations of propargyl alcohols generally yield mixtures of propargylated and allenylated compounds.^{7,8} Therefore, allylations of propargylic alcohols have traditionally been carried out using the Nicholas reaction⁹ (a multistep reaction involving transition metal stabilized propargylic cations). Recently, Toste et al.¹⁰ and Nishibayashi et al.¹¹ have reported several efficient rhenium- and diruthenium-catalyzed substitutions of propargyl alcohols, including allylation reactions.^{10b} Because the Ru-catalyzed reactions proceed through an allenylidene intermediate (Ru=C=C=CR₂), only propargyl alcohols bearing terminal alkynes undergo the reaction. In 2005, Campagne reported gold-catalyzed propargylic allylations.¹² In these reactions, NaAuCl₄ acts as both a Lewis acid and a transition metal catalyst. However,

the syntheses and costs of these catalysts affects the utility of these reactions. Thus, development of an efficient allylation method using inexpensive reagents would be highly desirable.

The results of a study involving the boron trichloride mediated reaction of allyltrimethylsilane with *in situ* generated lithium propargyloxide are shown in Table 1.¹³ It is interesting to note that

Table 1. Boron Trichloride Mediated Allylation of Lithium Propargyloxides (eq 1)^a

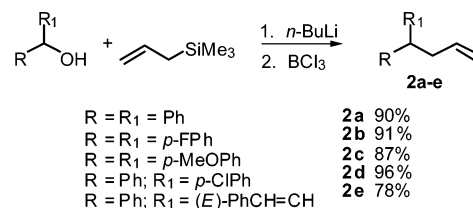
entry	R	R ₁	R ₂	yield ^b (%)
1	Ph	Ph	H	1a , 76
2	Ph	<i>p</i> -ClPh	H	1b , 73
3	<i>p</i> -MePh	<i>p</i> -ClPh	H	1c , 67
4	Ph	<i>o</i> -MePh	H	1d , 71
5	<i>p</i> -MePh	<i>o</i> -MePh	H	1e , 57
6	<i>p</i> -OMePh	<i>o</i> -MePh	H	1f , 63
7	Ph	3,4,5-(MeO) ₃ Ph	H	1g , 41
8	<i>m</i> -FPh	3,4,5-(MeO) ₃ Ph	H	1h , 53
9	Ph	<i>p</i> -FPh	H	1i , 64
10	<i>n</i> -C ₄ H ₉	<i>p</i> -ClPh	H	1j , 74
11	Ph	<i>p</i> -ClPh	Me	1k , 65
12	<i>p</i> -MePh	<i>p</i> -ClPh	Me	1l , 72

^a Reaction carried out at room temperature on a 1.5-mmol scale in dry DCM (for detailed procedure, see ref 14). ^b Isolated yield based on alcohol.

ether linkages are tolerated in the reactions. In all cases, only propargylic allylation products were isolated. The high regioselectivity of this propargylic allylation is presumably due to the absence of Brønsted acids. In traditional routes to cations from alcohols, the existence of a Brønsted acid in the reaction mixture is unavoidable regardless of what type of acid is used. Apparently, the Brønsted acid free reaction conditions stabilize the propargylic cation. The presence of LiCl in the reaction is not a factor because the observed regioselectivity is retained when NaH is used in place of *n*-BuLi. Using NEt₃ as a base led only to the recovery of the propargyl alcohol.

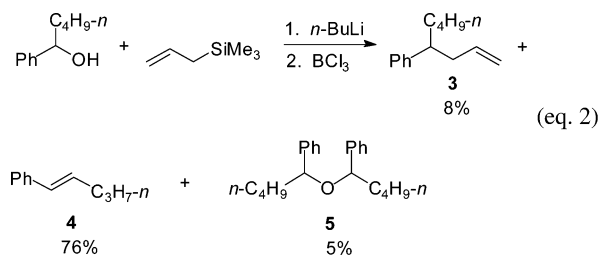
This new and novel reaction is also applicable to benzylic and allylic alcohols (Scheme 1).

Scheme 1. Allylation of Lithium Benzyloxides and Allyloxides



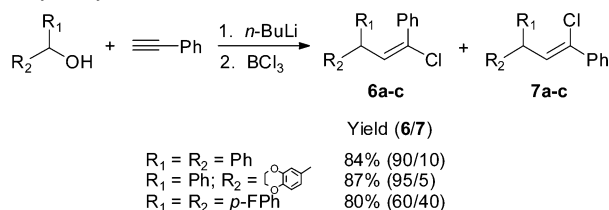
No reaction occurs between allyltrimethylsilane and boron trichloride, which precludes the formation of an intermediate allylboron dichloride. In addition, it is well-known that allylation reactions involving allyltrimethylsilane proceed through a cationic mechanism.¹⁵ Evidence supporting a cation intermediate was provided by the isolation of pent-1-enylbenzene (**4**) in the allylation of 1-phenylpentan-1-ol (eq 2).¹⁶

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Formation of a cation intermediate was further supported by the successful coupling of a lithium alkoxide with an alkyne in the presence of boron trichloride. Contrary to the reaction of alkoxides with alkenylboron dichloride,^{3a-c} reaction of alkoxides with alkynes in the presence of boron trichloride gave *E*-alkenyl chlorides as major products (Scheme 2). In the literature, similar reactions using

Scheme 2. BCl₃-Mediated Coupling of Lithium Alkoxides with Phenylacetylene



alcohols have rarely been achieved due to the existence of a Brønsted acid in reaction mixture.¹⁷ Our method successfully solved the problems associated with the selective generation of a cation from an alcohol in the presence of unsaturated carbon–carbon bonds.

In conclusion, we have discovered that cations can be generated from the corresponding alkoxides in the presence of boron trichloride. The absence of a Brønsted acid makes regioselective allylations quite straightforward. The reaction conditions make the coupling of alcohols to alkenes and alkynes feasible. As to the generation of cations instead of complexes B(OR)_{*n*}Cl_{3-*n*}, we believe there are two factors leading to weakening of the C–O bond and its subsequent cleavage: steric hindrance between the R group and chloride lengthens the C–O bond, and the high electronegativity of chlorine strengthens the B–O bond. Further investigations of this Brønsted acid free route to carbocations are under way.

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Supporting Information Available: Experimental procedures for synthesis and full characterization for compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (4) Evidence for the presence of a cationic intermediate include ring opening reactions of cyclopropyl derivatives and racemization of chiral benzylic alcohols. See ref 3a.
- (5) As noted, alkenylboron dichlorides were used in our earlier studies to generate carbocations (see 3a), and a stronger Lewis acid (BCl₃) would be expected to react similarly. The appearance of a dark red color upon addition of BCl₃ provides further evidence for the formation of a cation.
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- (13) Control experiments revealed that no coupling occurs between allyltrimethylsilane and 1,3-diphenylpropargyloxide in the absence of BCl₃.
- (14) **Typical Experimental Procedure.** A solution of propargyl alcohol (1.5 mmol) in dry dichloromethane (10 mL) was treated with *n*-butyllithium (1.0 mL of a 1.6 M solution in hexanes) at 0 °C and warmed to room temperature. After stirring at room temperature for 30 min, allyltrimethylsilane (1.8 mmol) and boron trichloride (1.5 mmol) were added. The mixture was allowed to stir 10 h at room temperature. Water (20 mL) was added to quench the reaction. The reaction mixture was extracted with ethyl acetate, and the extracts were dried over anhydrous MgSO₄. The solvent was removed in vacuo, and the product was purified by silica gel column chromatography using hexane as an eluent to provide **1a**.
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- (16) Although **4** could, in theory, be formed via an E2 elimination involving the initially formed benzyloxyboron dichloride intermediate, the absence of a base under these acidic conditions would appear to make this unlikely.
- (17) Brønsted acids react with the alkyne (or alkene) starting materials in a competitive fashion that generally leads to more complex product mixtures.

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