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# Recent advances in asymmetric synthesis with boronic esters

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Abstract – The reaction of chiral diol boronic esters with (dichloromethyl)lithium to form diol α-chloro boronic esters in high diastereomeric purity has been improved by the use of diols of $C_2$ symmetry. Reaction of the resulting α-chloro boronic esters with alkyl Grignard reagents provides a further kinetic resolution in which the minor isomer is not converted to diastereomer but to an air-sensitive borinic ester. The final diastereomeric ratio can exceed 1000:1, and a diastereomeric pair of insect pheromones has been synthesized in unusually high purity. Other recent applications of α-chloro boronic ester chemistry in asymmetric synthesis will also be discussed. Diol boronic esters of $C_2$ symmetry are useful in the conversion of α-chloro boronic esters via α-alkoxy tin compounds to α-lithio ethers, which in turn can be coupled to α-chloro boronic esters to provide a stereospecific convergent coupling of two chiral carbon chains. New applications of the older pinanediol ester technology have also been explored. These include syntheses of phenylalanine and of glycerol bearing stereospecific deuterium labels. Preparations of chiral tertiary alcohols have given useful stereoselectivity with some structures and not with others. A supplementary discovery is that solvent free dichloroborane can be generated from boron trichloride and trialkylsilanes and is an efficient hydroborating agent.

## INTRODUCTION

Chiral boronic esters yield exceptionally high asymmetric inductions in the reaction with (dichloromethyl)lithium, which inserts a chiral CHCl group into the boron–carbon bond with diastereoselection in the 100:1 range. A recent discovery is that with chiral directors of $C_2$ symmetry, inherent kinetic resolution in the displacement of chloride by a nucleophile can raise isomer ratios above 1000:1.

Another recent development is the convergent connection of two chains of chiral centers. The α-halo boronic ester, which may be regarded as a chiral carbocation synthon, is converted via tin intermediates to an α-lithio ether, a chiral carbanion equivalent. The α-lithio ether and an α-halo boronic ester can then be coupled stereospecifically.

Previously established useful features of this chemistry include sequential installation of several adjacent chiral carbons, chemist's choice of absolute configuration at each chiral center, a wide variety of accessible structure types, generally high yields, and recyclable chiral directors obtainable in substantial quantities.[1]

Cyclic boronic esters of 1,2-diols are stable intermediates which can generally be treated as ordinary organic compounds. As a class, they do not require any handling precautions beyond what would be used for typical aldehydes, and they do not present any known special hazards.

### THE BASIC PROCESS OF CARBON CHAIN EXTENSION

The fundamental process for inserting a CHCl group into the B–C bond has been reviewed in detail elsewhere,[1,2] and only a brief description will be provided here. Our first work was done with pinanediol boronic esters, which lack $C_2$ symmetry and have certain limitations as a result.

Reaction of a pinanediol boronic ester (**1**) with (dichloromethyl)lithium at low temperature results in formation of a borate complex (**2**), which on warming rearranges to an α-chloro boronic ester (**3**). Zinc chloride increases the rate of rearrangement and greatly improves the diastereoselection, so that **3** are

typically formed in 97-99% diastereomeric excess. Reaction of **3** with R²M, which may be a Grignard or alkyllithium reagent, a lithium alkoxide, or other appropriate nucleophile, yields a borate complex (**4**), which at room temperature rearranges to a chirally substituted boronic ester (**5**). One option with **5** (if R² is alkyl or aryl) is oxidation with hydrogen peroxide to the secondary alcohol (**6**). Otherwise, **5** is the same as **1** with a different R¹ group, and a second application of the reaction sequence introduces a second chiral carbon in the same manner.
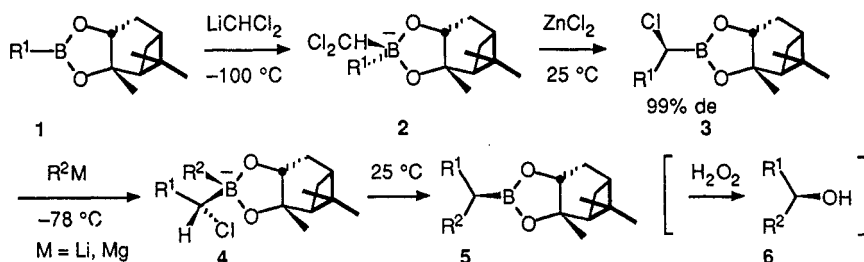


## STEREOSPECIFIC COUPLING OF CHIRAL CARBONS

The synthesis with boronic esters and (dichloromethyl)lithium can be repeated in order to assemble a sequence of two or more chiral carbons. Multiple repetition of this linear strategy ultimately leads to poor yields. A means of converting an α-halo boronic ester to a carbanion so that it can be joined to another α-halo boronic ester is needed in order to assemble larger molecules.

In the successful route, α-chloro boronic esters (**7**) are converted to α-hydroxy tin compounds (**9**). Still and Sreekumar had previously resolved one example of **9** and converted it to an α-lithio ether with full retention of configuration.[3] We have found that conversions of α-tributylstannyl boronic esters (**8**) to the corresponding α-hydroxy tin compounds (**9**) and on to (*R*)-α-lithio ethers (**10**) proceed smoothly.[4]

Coupling of an α-lithio ether (**10**) having R = *n*-butyl with an α-chloroboronic ester (**7**) also having R = *n*-butyl proceeded easily. However, the same reaction gave low yields when first tested with **7** and **10** each having R = isopropyl. Much tributylstannyl ether (**9**) was recovered. It was then found that the reaction of butyllithium with **9** is reversible. The sterically hindered boronic ester **7** (R = isopropyl) reacts faster with the small equilibrium concentration of butyllithium than with **10** at –78 °C, but by mixing the reactants at –100 °C this problem was overcome and the coupling product **11** was obtained in 69% yield.
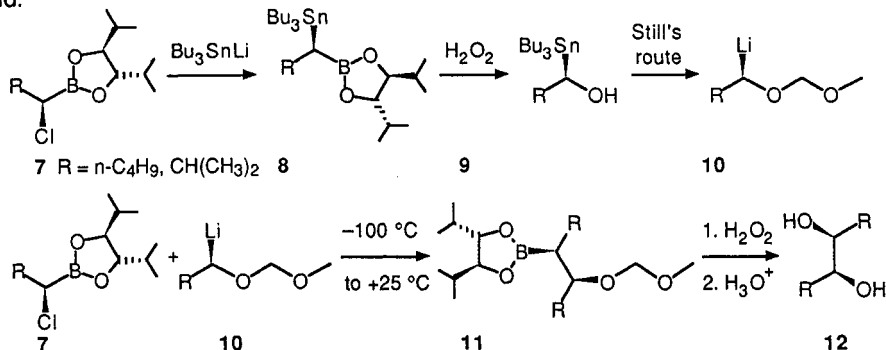


In order to confirm the diastereomeric purity of **12**, the lithio ether *ent*-**10** (R = isopropyl) was coupled with **7** to make **13**, the precursor to the *meso*-diol **14**.
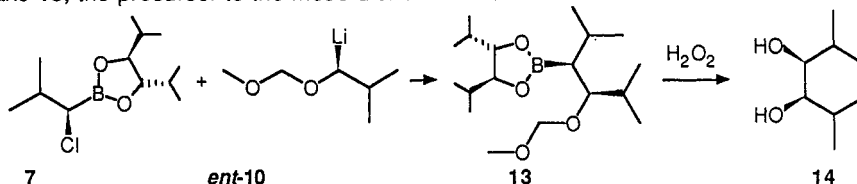


Prior to the development of the diisopropylethanediol esters illustrated, it was found that pinanediol esters are too hindered to serve as good sources of α-hydroxy tin compounds. Both the displacement of chloride by (tributylstannyl)lithium and the deboronation with hydrogen peroxide proved sluggish and inefficient.

Finally, the assembly of four chiral centers was demonstrated by the conversion of the propylboronic ester (**15**) to α-chloroboronic ester (**16**) followed by conversion of part of the **16** to the tin and lithio derivatives (see **9** and **10** above) and coupling to form boronic ester **17**.
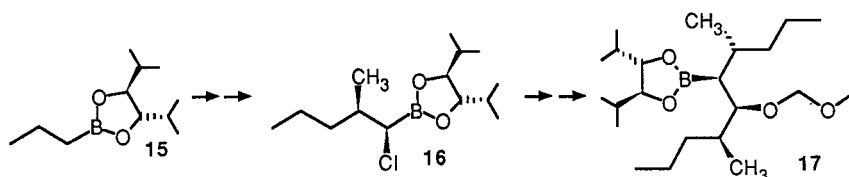


## ULTRA HIGH ENANTIOMERIC AND DIASTEREOMERIC PURITY

The reaction of diisopropylethanediol ("DIPED") boronic esters with (dichloromethyl)lithium and subsequent transformations have led to unexpectedly high stereoselection.[5] The result of interest was first encountered as a failure of an attempted synthesis.

What was attempted was the replacement of an (*R,R*)-diol as chiral director by an (*S,S*)-diol, which would lead to the diastereomer of the normal pair of chiral centers. Thus, (2*R*,3*R*)-2,3-butanediol (1*S*)-(1-chlorobutyl)boronate (**18**) was transesterified to the crystalline diethanolamine ester **19**, which was hydrolyzed with cold dilute acid to the boronic acid **20** and esterified with (*S,S*)-DIPED to form (*S,S*)-DIPED (1*S*)-(1-chlorobutyl)boronate (**21**), the diastereomer of the (1*R*)-(1-chlorobutyl)boronate that is derived from (*S,S*)-DIPED propylboronate and (dichloromethyl)lithium.

The unexpected result was that treatment with methylmagnesium bromide in the usual manner did not yield the expected product, (*S,S*)-DIPED (1*S*)-(1-methylbutyl)boronate (**25**), but (*S,S*)-DIPED methylboronate (**24**) instead. It was then shown by NMR that cyclic borinic ester **23** is the initial product, and that it oxidizes very rapidly on contact with air to form butyraldehyde and **24**. Evidently the borate intermediate **22** exists in a conformation **22A** which can only rearrange via ring expansion to **23**, and there is only a minor concentration of the conformer **22B**, which leads to a very small amount of the normally expected product **25**.
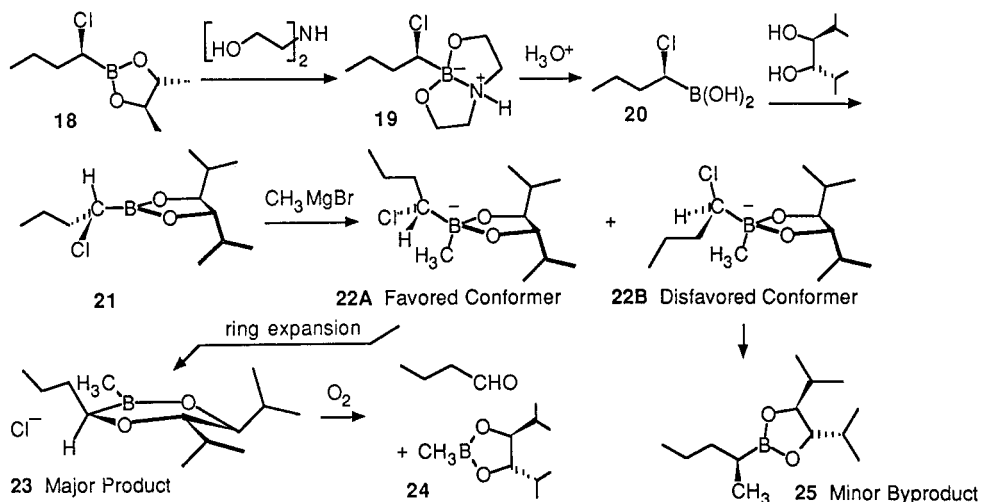


## ISOTOPIC LABELS AT CHIRAL SITES

The reaction of boronic esters with (dichloromethyl)lithium is well suited for the introduction of isotopic labels at specific sites in chiral molecules. The development of a general synthesis of amino acids via boronic ester chemistry[6] opened the way to application of this approach to stereospecifically labeled amino acids. For a demonstration of the feasibility, specifically deuterated phenylalanine (**33**) was prepared.[7] This synthesis began with the known conversion of pinanediol phenylboronate (**26**) to the α-chloro benzylboronate (**27**).[8] The crude **27** is generally a few percent epimerized by the time it is isolated, but it is easily recrystallized to high diastereomeric purity. Reduction of **27** with lithium triethylborodeuteride yielded stereospecifically deuterated benzylboronic ester **28**, which was shown to be of ≥98% diastereomeric purity by conversion to deuterated benzyl alcohol.
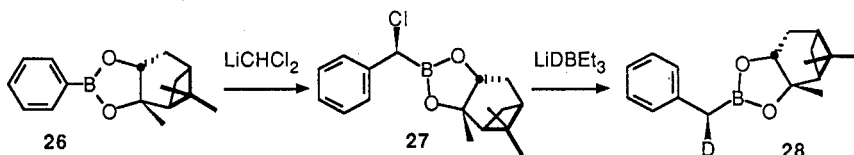
Chain extension of **28** with (dichloromethyl)lithium in the usual manner yielded α-chloro boronic ester **29**, which reacted with sodium azide in dichloromethane–water under phase transfer conditions to form the α-azido boronic ester **30**. Epimerization is a problem in this step, and a large excess of sodium azide must be used. Another chain extension yielded α-chloro boronic ester **31**, which was oxidized with sodium chlorite (a known reagent for oxidizing aldehydes to acids,[9] but new to boronic ester chemistry) to form the α-azido carboxylic acid **32**. Hydrogenation of **32** then yielded (2S,3S)-phenylalanine-3-*d* (**33**).
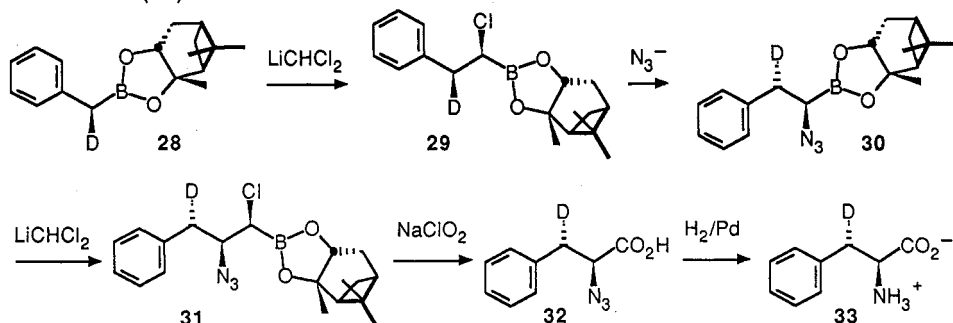


This approach to chiral deuterium labeling has been further developed in the synthesis of labeled glycerol. The first step was the efficient preparation of diisopropyl (chloromethyl)boronate (**34**) via addition of butyllithium to a solution of chloroiodomethane and triisopropyl borate in THF at −78 °C, conditions under which unstable (chloromethyl)lithium is generated and captured.[10] Conversion to the pinanediol ester **35** was followed by displacement of chloride by lithium benzyloxide to form the [(benzyloxy)methyl]boronic ester **36**. Preparation of **38** via (dichloromethyl)lithium and the chlorine analogue of **37** proved somewhat inefficient, and the use of (dibromomethyl)lithium formed by addition of lithium diisopropylamide to dibromomethane in the presence of **36** proved superior.[11] The diastereomeric ratio at this carbon was only ~97:3, which is unusually poor for pinanediol esters.
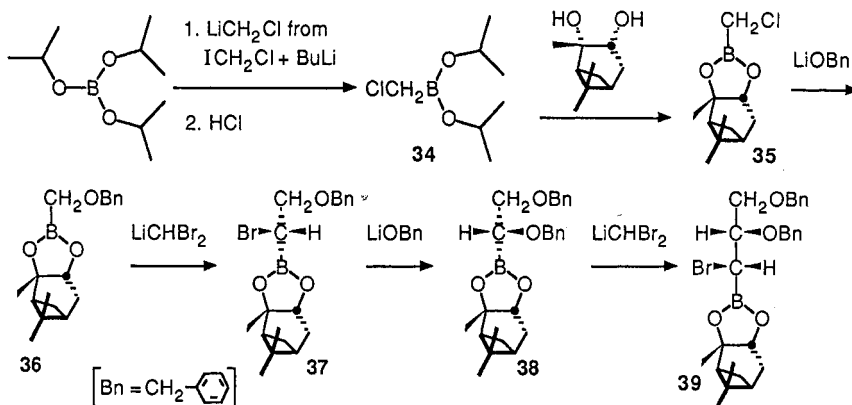


Repetition of the (dibromomethyl)lithium reaction yielded three-carbon intermediate **39**, which was reduced with potassium triisopropoxyborodeuteride to form the labeled intermediate **40** with ~99% chiral selectivity at the labeled carbon.[12] The remaining steps, peroxidic deboronation to dibenzyl ether **41** and catalytic hydrogenolysis to labeled glycerol **42**, are well known procedures.
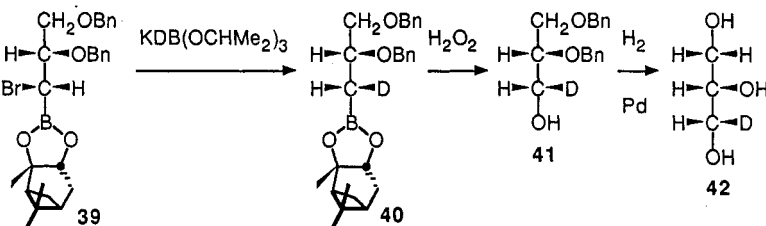


The diastereomerically labeled glycerol **46** was prepared by reversing the order of introduction of protium and deuterium. Thus, intermediate **38** with (deuterodibromomethyl)lithium from dideutero-dibromomethane yielded deuterated bromo compound **43**, which with lithium triethylborohydride

formed **44**, diastereomeric to **41** with respect to the label. Conversion to **45** and labeled glycerol **46** was accomplished in the same manner as with the diastereomers.
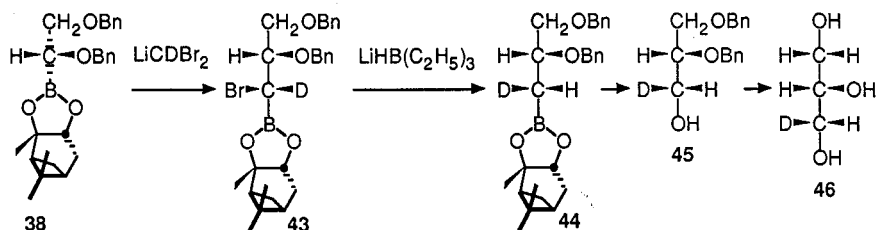


The labeled glycerol isomers **42** and **46** are those which could be converted enzymatically into glucose having a stereospecific deuterium label in the terminal hydroxymethyl group. The amounts of **42** and **46** actually prepared were a few hundred milligrams of each, more than enough for most biochemical research, though it would be a simple matter to scale up the synthesis to produce multigram quantities.

### CHIRAL TERTIARY ALCOHOLS

Preparation of (1,1-dichloroethyl)lithium from lithium diisopropylamide and 1,1-dichloroethane in the presence of a pinanediol boronic ester followed by the usual zinc chloride treatment yields the corresponding α-chloro boronic ester. However, the stereochemistry depends on the structure of the boronic ester. Ethylboronate **47** leads to the (αR)-α-chloro boronic ester **48**, which corresponds to the usual (αS)-isomer where there is hydrogen in place of the methyl group, the R designation being an artifact of the reordering of priorities, ethyl > methyl > boron as opposed to ethyl > boron > hydrogen. The diastereomeric ratio was ~9:1.

Phenylboronate **50** yielded the (αS)-α-chloro boronic ester **51**, which is opposite the configuration produced by (dichloromethyl)lithium, in ~25:1 diastereomeric ratio. These relationships were unequivocally proved by reactions of **48** with phenylmagnesium bromide and of **51** with ethylmagnesium bromide to produce identical boronic ester **49** and derived tertiary alcohol **52** in both cases.[13] In contrast to routes to tertiary alcohols, there was some loss of diastereomeric purity in the conversion of **51** to **49** as indicated by the rotation of the final product **52**, which was obtained in only 84% enantiomeric excess. The analogous conversion of **48** to **52** was stereospecific within experimental error.
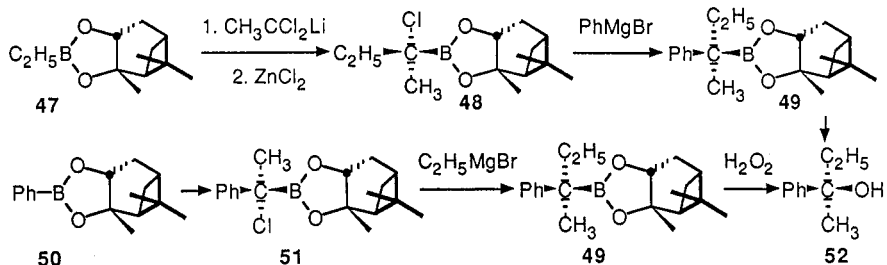


The change of sign of stereoselectivity between ethylboronic and phenylboronic esters implied that some intermediate size of substituent would result in little diastereoselection. In accord with this expectation, primary alkylboronic esters having chains longer than ethyl yielded useless ~1:1 isomer mixtures. Some preliminary evidence was obtained that secondary alkyl boronic esters may generally lead to useful diastereoselection. However, simple α-branched tertiary alcohols of known stereochemistry and optical rotation are not common in the literature, and proof of this expectation awaits considerable further experimental effort.

### OTHER RECENT DISCOVERIES

The reaction of (1,1-dichloroethyl)lithium with trimethyl borate produces the (1,1-dichloroethyl)boronic ester **53**.[14] This has been converted to the pinanediol ester **54**, which with lithium chloride in hot dimethylformamide forms the (1-chlorovinyl)boronic ester **55**.[15] The reaction of **55** with (dichloromethyl)lithium proceeds normally.
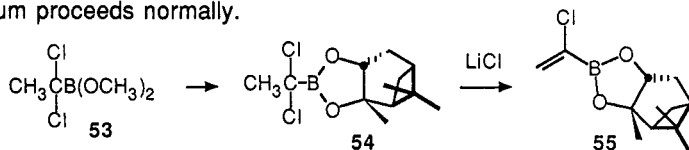
The (1-methoxyvinly)boronic ester **57** has been prepared from pinanediol methoxyboronate (**56**) and the corresponding lithium reagent. However, this very labile boronic ester fails to yield any α-chloro boronic ester with (dichloromethyl)lithium.[15]
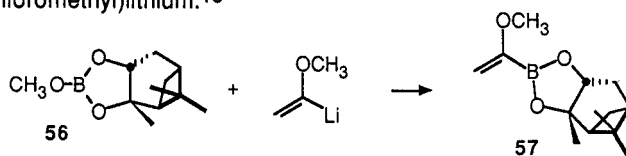


A short investigation has provided a new practical route to simple alkylboron dihalides, boronic esters, and related compounds. The reaction of di- or trialkylsilanes with boron trichloride in the presence of an alkene results in rapid hydroboration, presumably via the unstable intermediate $HBCl_2$.[16] For example, 1-hexene reacts rapidly at temperatures as low as -100 °C, or more conveniently at higher temperatures up to the boiling point of boron trichloride (+12 °C), to form hexylboron dichloride (**58**). In general, alkylboron dichlorides such as **58** react at 0 °C or above with trialkylsilanes to form the intermediate (alkyl)(chloro)borane (**59**), which readily hydroborates the same or a different alkene, as illustrated by the formation of (hexyl)(cyclohexyl)(chloro)borane (**60**). This new technique can also be used with acetylenic compounds, as illustrated by the hydroboration of 1-hexyne to 1-hexenylboron dichloride (**61**), which can be prepared as a clean single product, or which with excess reagent is converted to 1,1-bis(dichloroboryl)hexane (**62**).
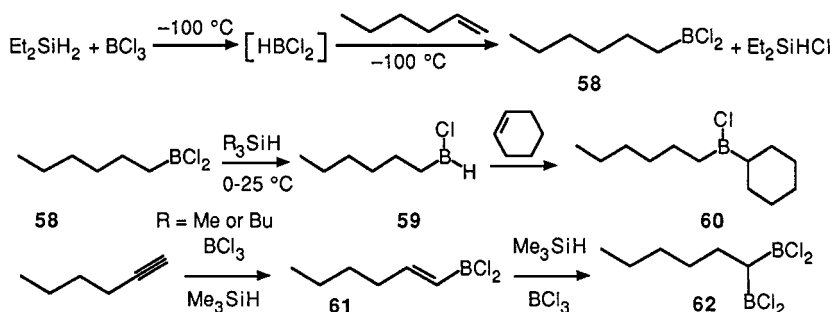


### Acknowledgement

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