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Facile Reaction of *o*-Carboranyllithium Reagents with Functionalized Alkyl Halides

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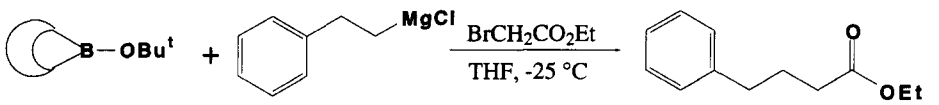
Abstract: *Unlike the normal organolithium reagents, o-carboranyllthium derivatives can tolerate many functional groups, such as ketones, nitriles and esters. This chemoselectivity is utilized in synthesizing a wide variety of o-carborane derivatives containing functional groups by reacting o-carboranyllithium reagents with functionalized alkyl halides, such as ethyl bromoacetate.*

Synthesis of substituted icosahedral 1,2-carborane derivatives is currently of interest due to their potential use in boron neutron capture therapy, BNCT[2], a binary method for cancer treatment based on the cytotoxic boron-neutron capture reaction, ^{10}B (n, α) ^{7}Li. In continuation of work designed to synthesize biologically active carboranes which would promote its localization into tumors for BNCT program,[3] *o*-carboranes with functional groups were considered. *o*-Carborane derivatives are generally prepared by the reaction of alkynes with decaborane. However, with disubstituted alkynes the reaction generally gives poor yields of the *o*-carborane derivatives.[4] Additionally, the limited availability of suitably substituted alkynes makes this procedure less attractive. Alternatively, substituted *o*-carboranes can be prepared by the reaction of *o*-carboranyllithiums with electrophiles.[5] However, the use of *o*-carboranyllithium derivatives for these alkylation reactions discouraged earlier workers from utilizing functionalized alkyl halides for the synthesis of substituted *o*-carboranes containing functional groups.

The presence of functional groups, such as X, OR, OAc, CN etc., poses a problem in substitution reactions involving organometallic reagents as a mixture of products is often produced.[6] Even though transmetallations using either cuprous bromide or dilithium tetrachlorocuprate as catalysts have been employed for controlling the chemoselectivity of these reactions,[7] cross coupling reaction between organometallic compounds and functionalized alkyl halides containing acidic protons, such as ethyl bromoacetate, has not been reported so far.

Yet, *o*-carborane derivatives containing carboxylic acid derivatives are useful in the synthesis of biologically active ^{10}B carriers, such as netropsin containing *o*-carborane using an *o*-carboranylacetic acid derivative.[8] It appeared desirable, therefore, to explore convenient procedures for the synthesis of functionalized carboranes from the corresponding *o* - carboranyllthium reagents and functional group containing alkyl halides. We have recently found that organolithium reagents and Grignard reagents can undergo *B-tert*-BuO-9-borabicyclo[3.3.1]nonane (*B*-BuO-9-BBN) promoted cross coupling reaction with ethyl bromoacetate (eq. 1).[9]

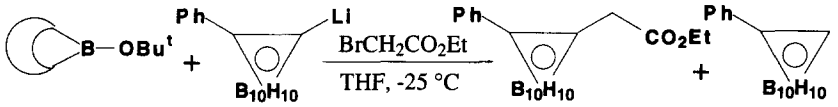


(1)

85% yield

Consequently, we checked the possibility of synthesizing functionalized *o*-carborane derivatives using *B*-BuO-9-BBN promoted alkylation of *o*-carboranyllithium derivatives with functionalized alkyl halides. For this study, we selected 2-methyl, 2-phenyl and 2-dibenzyloxyglyceroxymethyl *o*-carborane and unsubstituted *o*-carborane for the generation of the carboranyllithium reagents. We chose ethyl bromoacetate, 4-cyanobenzyl bromide and phenacyl bromide as representative functionalized alkyl halides.

Initially, we studied the reaction of 2-phenyl *o*-carboranyllithium with ethyl bromoacetate in the presence of an equivalent amount of *B*-BuO-9-BBN. 2-Phenyl *o*-carboranyllithium was generated from the corresponding carborane and butyllithium at 0 °C.[4] Analysis of the reaction product showed that the desired product was formed in 50% yield along with regenerated 2-phenyl *o*-carborane in 45% yield (eq. 2).

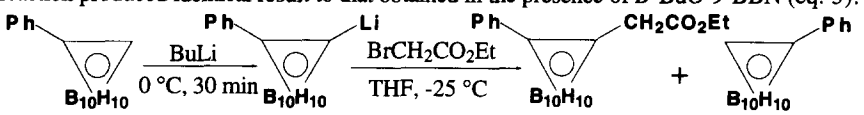


(2)

50% 45%

Similarly, reaction of 2-phenyl *o*-carboranyllithium with phenacyl bromide in the presence of an equivalent amount of *B*-BuO-9-BBN gave the desired ketone in 30% yield along with the regenerated 2-phenyl *o*-carborane in 66% yield. The diminished yields and the regeneration of the parent *o*-carboranes puzzled us.

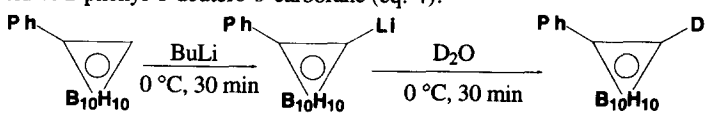
Subsequent ^{11}B NMR analysis revealed that 2-substituted *o*-carboranyllithium reagents are sterically too demanding to form an 'ate' complex with *B*-BuO-9-BBN. We realized that products are formed from an unprecedented, direct cross coupling between 2-phenyl *o*-carboranyllithium and ethyl bromoacetate and phenacyl bromide. Consequently, we reacted 2-phenyl *o*-carboranyllithium directly with ethyl bromoacetate. This reaction produced identical result to that obtained in the presence of *B*-BuO-9-BBN (eq. 3).



(3)

50% 45%

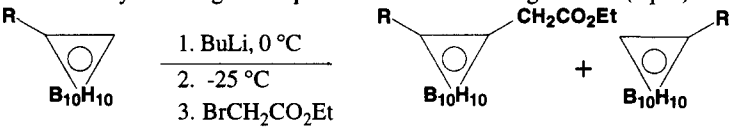
Additionally, reaction of 2-phenyl *o*-carboranyllithium with phenacyl bromide gave the desired ketone in 30% yield along with the regenerated 2-phenyl *o*-carborane in 66% yield. No products arising from the addition to the ester or the keto group was present in the reaction mixture. We suspected that the formation of unreacted 2-phenyl *o*-carborane could be due to an incomplete formation of 2-phenyl *o*-carboranyllithium reagent. However, quenching the 2-phenyl *o*-carboranyllithium with deuterium oxide produced a quantitative yield of 2-phenyl-1-deutero-*o*-carborane (eq. 4).



(4)

>99%

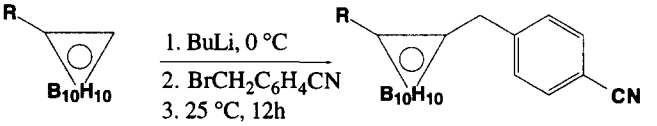
Apparently, the regeneration of starting *o*-carborane derivative is due to proton abstraction either from the product *o*-carboranylacetate or the reactant ethyl bromoacetate. Even though this proton abstraction leading to the unreacted starting *o*-carborane is an annoying side reaction, the *o*-carborane can be recovered quantitatively and recycled. Encouraged by these results, we studied the generality of this reaction. All the *o*-carborane derivatives used in our reaction behaved similarly to afford the corresponding *o*-carboranylacetate derivatives around 50% yield along with equal amount of the starting material (eq. 5).[10]



(5)

R = H,	42%	44%
R = Me,	45%	48%
R = $CH_2O[CH(CH_2OBn)_2]$,	47%	48%

Reaction of unsubstituted 2-lithio-*o*-carborane gave some disubstituted compound (diethyl 2-*o*-carboranyl-succinate, 13%) with ethyl bromoacetate. We did not observe this over alkylated product with the other *o*-carborane derivatives. Just like esters and ketones, nitriles were inert toward *o*-carboranyllithium reagents. However, reaction of 4-bromobutyronitrile with all the *o*-carboranyllithium derivatives gave exclusively the product of an elimination reaction instead of the cross coupled product and use of CuCN:2LiCl catalyst did not promote this reaction.[11] Fortunately, 4-cyanobenzyl bromide reacted readily with these *o*-carboranyllithium derivatives and gave essentially the desired S_N2-products (eq. 6).[12]



(6)

R = H, 70%; Me, 65%; Ph, 65%; $CH_2O[CH(CH_2OBn)_2]$, 75%

Our study has shown clearly, for the first time, that *o*-carboranyllithium derivatives can tolerate many functional groups, such as ketones, esters and nitriles. We have utilized this chemoselectivity to prepare a wide variety of substituted *o*-carborne derivatives containing functional groups. *o*-Carborane derivatives, such as 2-dibenzyloxyglyceroxymethyl *o*-carboranylacetate, are useful in synthesizing biologically active ^{10}B carriers.

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10. **General Procedure for the Reaction of Carboranyllithium with Ethyl Bromoacetate:** The following procedure for the reaction of 2-(dibenzyloxyglyceroxymethyl)-*o*-carboranyllithium with ethyl bromoacetate is representative. To a stirred solution of 2-(dibenzyloxyglyceroxymethyl)-*o*-carborane (0.43 g, 1 mmol) in tetrahydrofuran (THF, 4 mL), cooled at 0 ℃ under argon atmosphere, *n*-BuLi (0.6 mL, 1 mmol) was added with stirring. After 30 min. at 0 ℃, the reaction mixture was cooled to -25 ℃ and ethyl bromoacetate (0.11 mL, 1 mmol) was added and the reaction mixture was allowed to warm to 25 ℃ slowly (3h). The reaction mixture was diluted with ether (10 mL), decanted into a separatory funnel, washed with water (2x5 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure (25 ℃, 10 Torr) and the residue was purified by column chromatography [silica gel, methylene chloride-hexane (5:1) as eluent] to give the regenerated 2-(dibenzyloxyglyceroxymethyl)-*o*-carborane (0.23g, 48%) and the product ethyl 2-(dibenzyloxyglyceroxymethyl)-*o*-carboranylacetate (0.24g, 47%): IR (Neat) 1741, 2584 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.01-3.12 (br. signal, 10H), 1.27 (t, J = 7Hz, 3H), 3.14 (s, 2H), 3.58 (dd, J = 4, 7Hz, 4H), 3.78 (quintet, J = 6 Hz, 1H), 4.12 (q, J = 7Hz, 2H), 4.26 (s, 2H), 4.51 (s, 4H), 7.32 (m, 10H); ^{13}C NMR ($CDCl_3$)δ 14.0, 40.4, 61.7, 70. 4, 70.8, 71.5, 73.5, 78.1, 79.3, 127.8, 128.5, 137.8, 166.9.
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12. **General Procedure for the Reaction of Carboranyllithium with 4-Cyanobenzyl Bromide:** The following procedure for the reaction of 2-methyl-*o*- carboranyllithium with 4-cyanobezyl bromide is typical. To a stirred solution of 2-methyl-*o*- carborane (0.15g, 1 mmol) in THF (4 mL), cooled at 0 ℃ under argon atmosphere, *n*-BuLi (0.6 mL, 1 mmol) was added with stirring. After 30 min. at 0 ℃, 4-cyanobenzyl bromide in THF (0.5 M, 2 mL) was added and the reaction mixture was stirred for 12h at 25 ℃. The reaction mixture was diluted with ether (10 mL), decanted into a separatory funnel, washed with water (2x5 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure (25 ℃, 10 Torr) and the residue was purified by column chromatography [silica gel, hexane-methylene chloride (1:1) as eluent] to give the product 2-(4'-cyanobenzyl)-1-methyl-*o*- carborane (0.18g, 65%): IR (KBr) 2211, 2582; ^1H NMR ($CDCl_3$) δ 1.01-3.12 (br. signal, 10H), 2.18 (s, 3H), 3.51 (s, 2H), 7.52 (ABq, J = 4, 8Hz); ^{13}C NMR ($CDCl_3$) δ 23.7, 40.9, 74.8, 75.9, 112.3, 118.2, 131.1, 132.4, 139.9.

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