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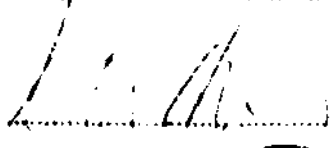
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Thomas Michael Cooper

ENTITLED Selective Lixiation of Dibrominated Species

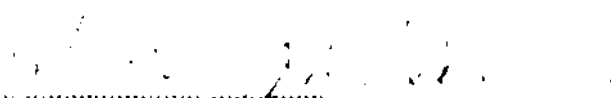
IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Bachelor of Science in Chemistry



Instructor in Charge

APPROVED:



HEAD OF DEPARTMENT OF

**SELECTIVE LITHIATION
OF
DIBROMINATED SPECIES**

**BY
THOMAS MICHAEL COOPER**

**THESIS
FOR THE
DEGREE OF BACHELOR OF SCIENCE
IN
CHEMISTRY**

**COLLEGE OF LIBERAL ARTS AND SCIENCES
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS**

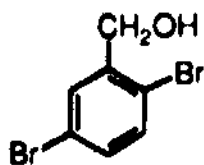
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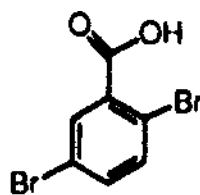
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INTRODUCTION

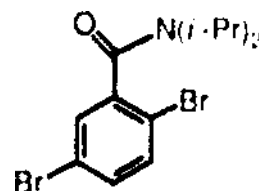
The selective use of halogen-metal exchange to prepare organolithium reagents is a topic of synthetic importance and mechanistic interest. In previous unreported work it was found that halogen-metal exchange on 2-bromobenzyl alcohol was slower than expected.¹ It was decided to examine intramolecular competitive halogen-metal exchange of a dibromobenzyl alcohol. The compound 2,5-dibromobenzyl alcohol, 1, was chosen along with 2,5-dibromobenzoic acid, 2, for comparison purposes. Another compound, *N,N*-diisopropyl-2,5-dibromobenzamide, 3, which lacks an acidic proton, but has a strong directing group, was also chosen for comparison. The purpose of these studies was to determine if the two bromine sites of the three compounds could be selectively exchanged in halogen-metal exchange involving a minimal amount of butyllithium.



1



2

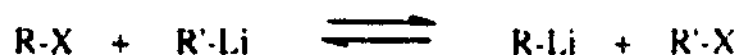


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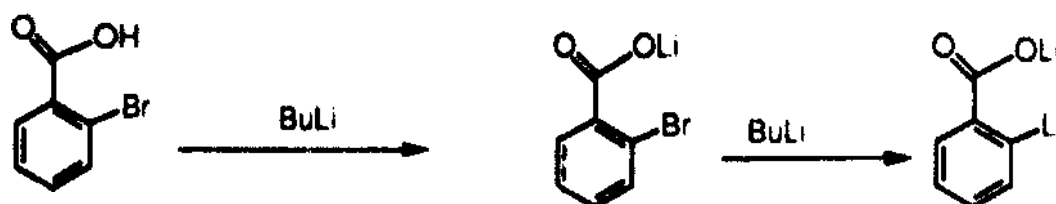
HISTORICAL

In 1938 Wittig and Gilman discovered simultaneously and independently that organohalides can react with simple organolithium compounds to form new organolithium reagents and new organohalides (Scheme I).^{2,3} Early studies showed that when the halides are bromine and iodine the reaction proceeds rapidly.⁴ Gilman first proposed the idea of nucleophilic attack on the halogen atom by the lithium reagent.⁵ This mechanism could lead to a stable "ate" complex intermediate which will then proceed into the exchanged products.⁶ It has been reported that with treatment of two equivalents of butyllithium, bromobenzoic acid undergoes halogen-metal exchange.⁷ Removal of the acidic proton would consume one equivalent of the butyl lithium; the second equivalent would carry out the halogen metal exchange on the bromocarboxylate salt (Scheme II).⁸

Scheme I



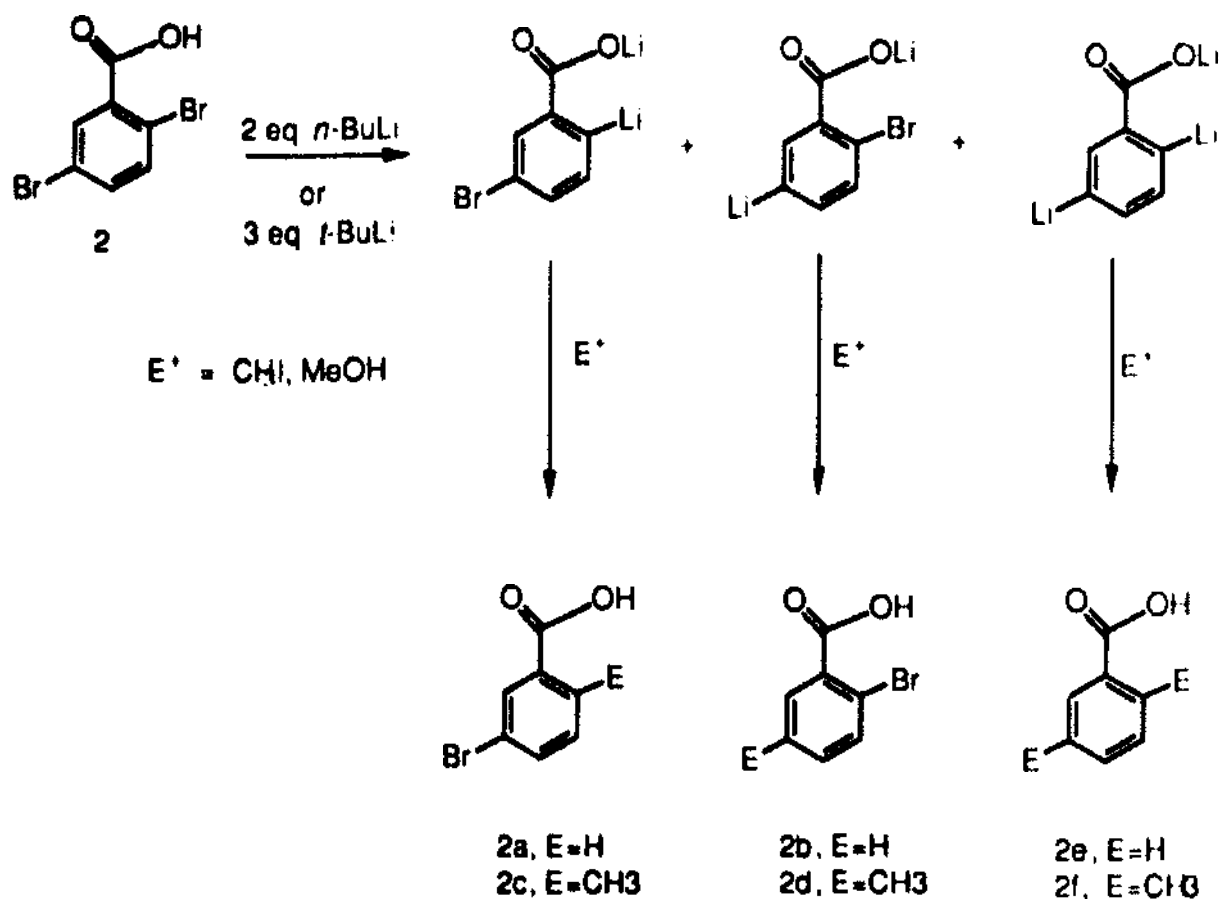
Scheme II



RESULTS AND DISCUSSION

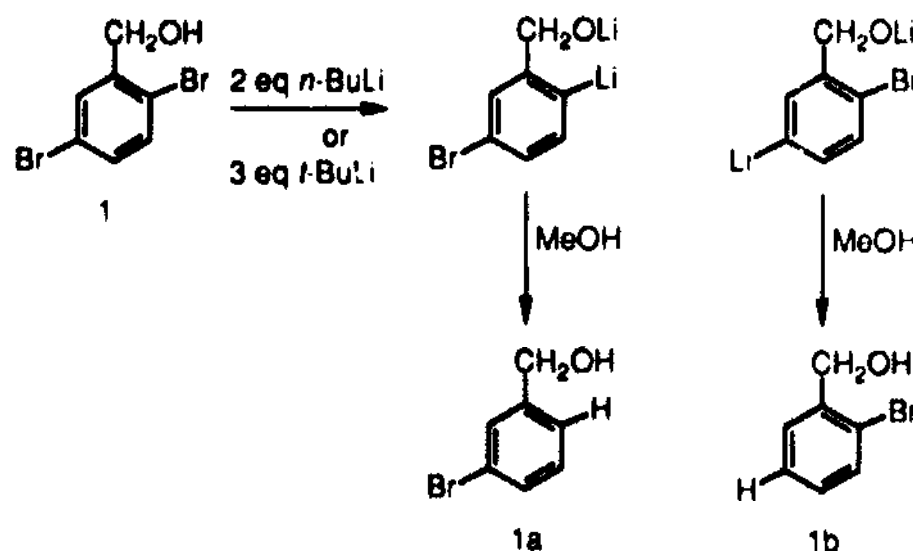
Initially 2,5-dibromobenzoic acid, **2**, was investigated. If this compound is reacted with two equivalents of butyllithium, there should only be attack at one of the two bromine positions on the ring because only one equivalent of organolithium reagent remains after the first equivalent is used to attack the acidic proton (Scheme III). If methanol is used as the electrophile, this will produce 3-bromobenzoic acid, **2a**, and/or 2-bromobenzoic acid, **2b**. Benzoic acid, **2e**, is the product from the disubstituted product. Accordingly, if methyl iodide is used as the electrophile the compounds 3-bromo-2-methyl benzoic acid, **2c**, and/or 2-bromo-3-methyl benzoic acid, **2d**, will be produced. In this situation the disubstituted product is 2,5-dimethyl benzoic acid, **2f**.

Scheme III



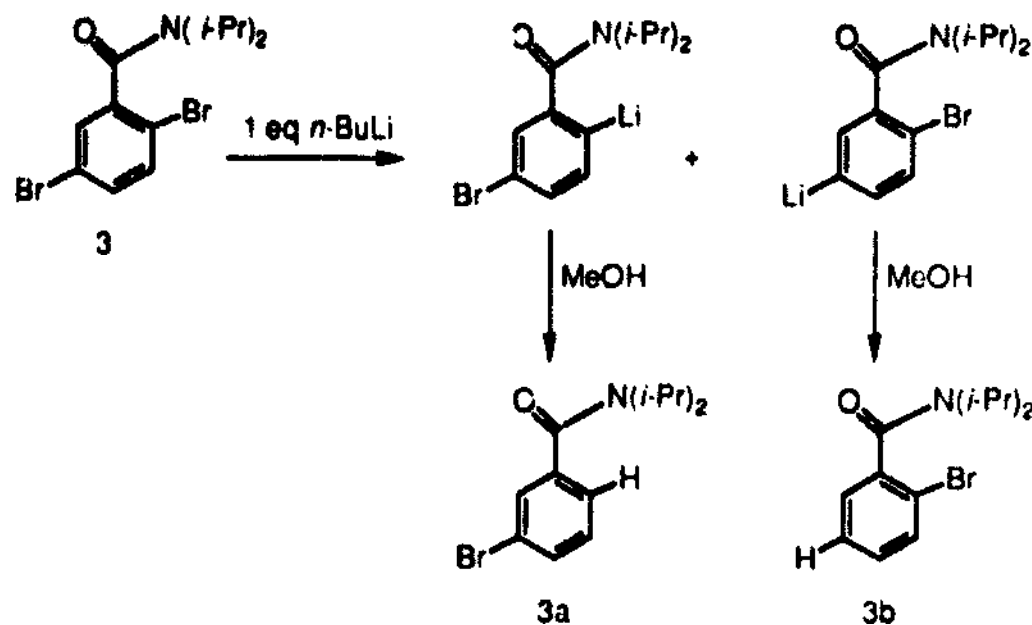
If 2,5-dibromobenzyl alcohol, 1, is reacted under the same conditions the result would be similar (Scheme IV). Again the methanol trap would produce 3-bromobenzyl alcohol, 1a, and/or 2-bromobenzyl alcohol, 1b.

Scheme IV



Similar results would be expected in the reaction of N,N -diisopropyl-2,5-dibromobenzamide, 3, (Scheme V). This time only one equivalent of butyllithium is needed in order to carry out the halogen-metal exchange because there is no acidic proton to react with the butyllithium. The methanol trap would produce N,N -diisopropyl-3-bromobenzamide, 3a, and/or N,N -diisopropyl-2-bromobenzamide, 3b. With these experiments it is hoped to determine optimal functional groups for directed lithiation in these systems.

Scheme V



For the competitive halogen-metal exchange reactions on the 2,5-dibromobenzoic acid, 2, the acid was dissolved in freshly distilled THF and then reacted with 2 equivalents of *n*-butyl lithium (*n*-BuLi), followed by addition of methanol. Analysis by GC with coinjection of 2, 3-bromobenzoic acid, 2a, and 2-bromobenzoic acid, 2b, gave the following results. The acid, 2a, accounted for 78% of the overall product; 2b was 2% of the product; and 3% of the product was recovered 2. This experiment indicates that halogen-metal exchange of 2 is an extremely selective process. The exchange was almost exclusive at the ortho position on the ring.

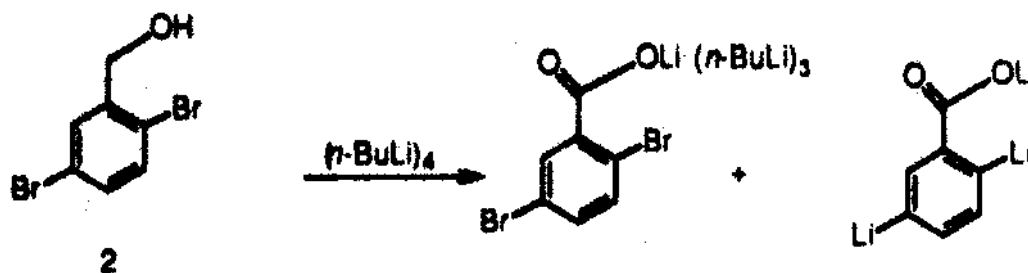
One interesting result was also found in this reaction. When the product was coinjected with benzoic acid it was found that 13% of the product was benzoic acid, 2c. In order to get the formation of benzoic acid from 2 an extra 3 equivalents of *n*-BuLi must be used. The first for the acidic proton and one for each of the two bromines.

The above reaction was repeated in order to confirm the results. The *n*-BuLi was titrated and freshly distilled THF was used as the solvent. The reaction was trapped with

methanol. The results, confirmed by coinjection of standards, were very similar to the above reaction. The acid, 2a, once again accounted for 78% of the product; 2b was 2% of the product; 5% of the product was starting material; and 12% of the product was benzoic acid.

These results confirmed that somehow a second equivalent of *n*-BuLi was being used to form benzoic acid. One possible reason for this result was that *n*-BuLi exists as a tetramer. Thus if *n*-BuLi reacts with 2 the initial *n*-BuLi will attack at the acidic proton and form a complex with the acid (Scheme VI). The remaining *n*-BuLi in the complex may then react at the ortho position and the meta position. This possible explanation would then account for the formation of benzoic acid while using only two equivalents of *n*-BuLi.

Scheme VI



In order to test this possible mechanism the reaction was repeated using the more reactive *t*-butyl lithium (*t*-BuLi). It has been reported that this organolithium exists as a monomer at -108°C so that if the explanation outlined above is correct, then there should not be any benzoic acid formed assuming the *t*-BuLi was a monomer at -78°C . The acid, 2, was again dissolved in THF and allowed to react with 3 equivalents of *t*-BuLi. In this situation, 3 equivalents are necessary because the third equivalent is needed to react with the *t*-butyl bromide formed upon addition of the second equivalent of organolithium. Upon being trapped with methanol the following results were obtained via GC. The acid, 2a, accounted for only 9% of the product. The remaining 91% of the product was

benzoic acid. Even though this may rule out the above explanation as a possibility, there might be another cause for this result. The third equivalent of *t*-BuLi may react at a faster rate with the reactants than it reacts with the *t*-butyl bromide thus producing the disubstituted benzoic acid.

The next experiment on 2 was a reaction with methanol-*d*. The acid was allowed to react with 2 equivalents of *n*-BuLi and then trapped with deuterated methanol. The results obtained are as follows: 5-bromo-2-deuterobenzoic acid accounted for 40% of the product; there was no deuterium incorporation on the meta position of the acid, 2; 34% of the product was the di-deutero benzoic acid. Once again, these results were consistent with those obtained in the methanol traps. When the mono substituted product is considered, the lithium halogen exchange was almost exclusive on the ortho position of the acid. Also, there was a large quantity of the disubstituted benzoic acid in the product.

Another possible explanation for the formation of benzoic acid as a product was within the experiment itself. Since the base was being added to 2 there is a chance that a very large local concentration of the base reacts with a low concentration of 2. Thus all of the lithium-halogen exchange was being incorporated onto a small amount of the acid. If a reverse addition reaction was attempted (i.e. the acid was added to the base), then this possibility wouldn't be a factor.

A reverse addition was the next attempted reaction. The acid, 2, was added to 2 equivalents of *n*-BuLi dissolved in THF. The reaction was again trapped with methanol-*d*. This time the reaction gave slightly different results. Exchange at the ortho position produced 5-bromo-2-deutero benzoic acid in 51% yield; starting material accounted for 14% of the product; there was no incorporation at only the meta position; and 10% of the product was the dideuterobenzoic acid.

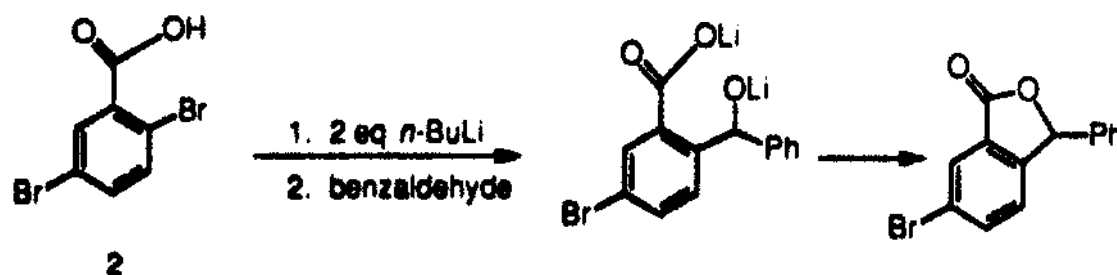
Next, methyl iodide was attempted as a trap with 2. This reaction was initiated by adding 2 equivalents of *n*-BuLi to the acid dissolved in THF. The reaction was then trapped with methyl iodide and 57% of the product was 2c and the remaining 43% was

2,5-dimethylbenzoic acid, 2f. This is once again consistent with the results obtained from the proton trap reactions. In other words, there was exchange largely at the ortho position along with a substantial amount of disubstituted product.

Once again the methyl iodide trap was attempted using *t*-BuLi as the reagent. The acid, 2, was dissolved in THF and then 3 equivalents of *t*-BuLi were added and the reaction was trapped with methyl iodide. Analysis of the reaction by GC showed a complex mixture of products. Halogen exchange at the ortho position was found by GC to be only 10% and the remainder of the product was divided into a complex mixture of products that contained no starting material.

Another type of electrophile used for these reactions was the benzaldehyde trap. If benzaldehyde reacts with the ortho lithio species then cyclization should occur on workup (Scheme VII). Attack at the meta position, on the other hand, could not give this cyclization. The reaction was attempted with 2 equivalents of *n*-BuLi as the lithiating reagent. The results were identified via GC analysis. Of over twenty different peaks present in the GC trace, not one them was greater than 15% of the product. Therefore, this trap wasn't able to give any substantial information about the reaction.

Scheme VII



With 2,5-dibromobenzoic acid the overall results were reasonably consistent. The lithium-halogen exchange occurs primarily at the ortho position of the ring accompanied by a percentage of the product that has exchanged at both positions on the ring.

The halogen-metal exchange reactions were then attempted with the 2,5-dibromobenzyl alcohol, 1. The alcohol was dissolved in freshly distilled THF and then reacted with 2 equivalents of *n*-BuLi. Once again the first equivalent was to deprotonate the alcohol proton; the second equivalent was for halogen-metal exchange of one of the two bromines on the ring structure. After addition of the organolithium, the reaction was trapped with methanol. The results of this proton trap indicates that the alcohol was largely unreactive. When the product was injected onto the GC and then coinjected with the appropriate standards it was found that 83% of the product was unreacted starting material. One of the products was found to be 10% of 1a, indicative of proton trapping of the ortho lithio species. Another 5% of the product was the isomer 1b indicating reaction at the meta position. Even though very little of 1 reacted, it was apparent that this reaction didn't have the selectivity found in the halogen-metal exchange reactions involving 2.

The reaction was then repeated with the stronger lithiating reagent *t*-BuLi. It was hoped that this organolithium would allow a greater percentage of 1 to react. Because *t*-BuLi was being used, 3 equivalents of the reagent was used for the reaction. The alcohol was again trapped with methanol. This time a much greater percentage of 1 reacted with the base. Upon coinjection on the GC it was found that 46% of the product was unreactive starting material. The product was almost evenly divided between two isomers. Exchange at the ortho position on the ring, producing 1a, corresponded to 23% of the product and the isomer 1b then accounted for 22% of the product. In this reaction 3% of the disubstituted benzyl alcohol was found. Once again, it was shown that the halogen-metal exchange of the alcohol is not as selective as the acid. In the reaction the two isomers accounted for nearly an equal percentage of the product. Even though a greater percentage of the alcohol reacted with the *t*-BuLi as opposed to the weaker lithiating reagent *n*-BuLi, 46% of the reactant was still unreacted.

In order to attempt to get a larger percentage of the alcohol to react, it was decided to repeat the reaction with a greater amount of *t*-BuLi. In this situation, we didn't concern ourselves with the selectivity of the reaction. This was because our previous results showed the reaction was for the most part not selective between the two halogen sites. We were interested in finding out if a greater percent of reaction could occur by increasing the concentration of the organolithium. The alcohol, 1, was reacted with 4 equivalents of *t*-BuLi in THF and trapped with methanol. Upon completion of workup, this product was injected on the GC and it was observed that only starting material was present.

To confirm this intriguing result, the reaction was repeated with 4 equivalents of *t*-BuLi in diethyl ether. In many reactions, the choice of solvent has had a drastic difference in the results of the reaction. Thus, the solvent was changed from THF to diethyl ether to observe if there were any solvent effects. The trap in use was methanol-*d*. The results showed that 92% of the product was unreactive starting material, and the remainder was unidentified. None of the expected products were found. This reaction showed that there was no real solvent effects upon the reaction between the two solvents.

The final reaction attempted used *N,N*-diisopropyl-2,5-dibromobenzamide, 3 as the reactant. Because there is no acidic proton on this molecule only 2 equivalents of *t*-BuLi was used to react with the amide. The reaction was quenched with methanol. The results of this proton trap indicates that 3 has slightly similar selective halogen-metal exchange properties to the acid 2. Upon coinjection on the GC with standards it was observed that 24% of the product corresponded to 3a, while only 9% of the product was 3b. That is to say that 24% of the product involved halogen-metal exchange at the ortho position on the ring. This was the same position in which 2 had almost exclusive selectivity. Recovered starting material accounted for 28% of the product in this reaction.

In order to examine whether the amide reacts at a faster rate than the acid an equimolar mixture of the two starting materials was prepared. This was dissolved in

THF and reacted with one equivalent of *n*-BuLi. The reaction was then trapped with methanol. Upon coinjection with the appropriate standards it was found that absolutely none of the acid, 2, reacted. For 3, 10% of the product corresponded to exchange at the ortho position on the ring--product 3a. This shows that the amide reacts at a faster rate than the acid.

When the results of the experiments are considered a possible general explanation of the results can be proposed. In general it was found that the amide reacted at a faster rate than the acid which reacted to a much greater extent than the alcohol. This reason for this may be that the amide, being a neutral species, is a better directing group than the acid. This is consistent with regular ortho-lithiation results. The acid functional group must then also be a better directing group than the alcohol.

Conclusion

In conclusion these series of experiments showed that the halogen-metal exchange reactions of 2,5-dibromobenzoic acid are quite selective. The selective lithiation reactions produced exchange almost exclusively at the ortho position. However, 2,5-dibromobenzyl alcohol, was not selective in halogen-metal exchange reactions, and is reluctant to undergo any reaction. *N,N*-diisopropyl-2,5-dibromobenzamide also exhibited selective halogen-metal exchange at the ortho position on the ring and the amide also reacted at a faster rate than the acid in an equimolar mixture reaction.

EXPERIMENTAL

Materials: All reagents used were of reagent grade quality and used without further purification. Dry tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone. *n*-butyl lithium and *t*-butyl lithium were both titrated using *N*-pivaloyl-*O*-Toluidine prior to use.

General Procedure for the Titration of Lithium Reagents: All organo lithium reagents were titrated before use. Approximately 150 mg of *N*-pivaloyl-*o*-toluidine was weighed into a dry round bottom flask, dissolved in 2.5 ml of THF, placed under a positive pressure of nitrogen, and magnetically stirred. A solution of the lithium reagent was added dropwise until the solution turned yellow and persisted for at least 10 seconds. The molarity of lithium solution is given by $(\text{mass of } N\text{-pivaloyl-}o\text{-toluidine}) / (191.275 \text{ g/mol}) \times (\text{Volume of Lithium reagent})$.

General Procedure for the Addition Reaction of Substrates with Butyllithium: Approximately 1 mmol of the substrate was then dissolved in about 20 ml of solvent. The solution was magnetically stirred and cooled to -78°C under nitrogen while being placed in a dry ice/isopropanol slurry bath. The desired amount of butyllithium solution was then added dropwise via syringe. The solution was stirred for 30 minutes and then trapped with the electrophile. The solution was left to stir for a minimum of 2 hours and then quenched with NH_4Cl . The standard workup involves addition of water to the solution and then the water layer was extracted with Et_2O (3 x 40 ml). The ether layers were collected, dried over MgSO_4 and concentrated in vacuo to give a mixture of products.

Addition Reaction of 2 with *n*-Butyl lithium in THF (MeOH trap) (1): To 0.1949 g (0.70 mmol) of 2 dissolved in 20 ml of dry THF at -78° C under N₂ was added a solution of 0.88 ml of 1.6 M *n*-BuLi (1.40 mmol). The reaction was trapped with 1 ml of methanol. The products were analyzed by GC analysis and coinjected with standards. 2a 78%; 2b 2%; starting material 3%; benzoic acid 13%

Addition Reaction of 2 with *n*-Butyl lithium in THF (MeOH trap) (2): To 0.1477 g (0.528 mmol) of 2 dissolved in 15 ml of dry THF at -78° C under N₂ was added a solution of 0.56 ml of 1.9 M *n*-BuLi (1.055 mmol). The reaction was trapped with 1 ml of methanol. The products were analyzed by GC and coinjected with standards. 2a 78%; 2b 2%; starting material 5%; benzoic acid 12%.

Addition Reaction of 2 with *t*-butyl lithium in THF (MeOH trap): To 0.1820 g (0.650 mmol) of 2 dissolved in 15 ml of dry THF at -78° C under N₂ was added a solution of 1.4 ml of 1.4 M *t*-BuLi (1.96 mmol). The reaction was trapped with 1 ml of methanol. The products were analyzed by GC and coinjected with standards. 2a 9%; benzoic acid 91%.

Addition Reaction of 2 with *n*-Butyl lithium in THF (MeOD trap): To 0.1445 g (0.516 mmol) of 2 dissolved in 22 ml of dry THF at -78° C under N₂ was added a solution of 0.61 ml of 1.7 M *n*-BuLi (1.032 mmol). The reaction was trapped with 0.15 ml of methanol-*d*. The products were analyzed by GC and coinjected with standards. 2a 40%; benzoic acid 34%.

Reverse Addition Reaction of 2 with *n*-Butyl lithium in THF (MeOD trap): 0.1263 g (0.451 mmol) of 2 dissolved in 20 ml of dry THF was added to a solution of 0.56 ml of 1.6 M *n*-Butyl lithium (0.902 mmol) dissolved in 2 ml of dry THF at -78° C under N₂.

The reaction was trapped with 0.15 ml of methanol-*d*. The products were analyzed by GC and coinjected with standards. 2a 51%; starting material 14%; benzoic acid 10%.

Addition Reaction of 2 with *n*-Butyl lithium in THF (CH₃I trap): To 0.2012 g (0.719 mmol) of 2 dissolved in 20 ml of dry THF at -78° C under N₂ was added a solution of 0.76 ml of 1.89 M *n*-BuLi (1.438 mmol). The reaction was trapped with 0.25 ml of methyl iodide. The products were analyzed by GC and coinjected with standards. 2c 57%; 2,5-dimethyl benzoic acid 43%.

Addition Reaction of 2 with *t*-butyl lithium in THF (CH₃I trap): To 0.2228 g (0.800 mmol) of 2 dissolved in 15 ml of dry THF at -78° C under N₂ was added a solution of 2.18 ml of 1.1 M *t*-BuLi (2.400 mmol). The reaction was trapped with 0.25 ml of methyl iodide. The products were analyzed by GC and coinjected with standards. 2c 10%.

Addition Reaction of 2 with *n*-Butyl lithium in THF (Benzaldehyde trap): To 0.1802 g (0.672 mmol) of 2 dissolved in 15 ml of dry THF at -78° C under N₂ was added a solution of 0.71 ml of 1.9 M *n*-BuLi (1.345 mmol). The reaction was trapped with 0.15 ml of benzaldehyde. The products were analyzed by GC and coinjected with standards.

Addition Reaction of 1 with *n*-Butyl lithium in THF (MeOH trap): To 0.0563 g (0.209 mmol) of 1 dissolved in 15 ml of dry THF at -78° C under N₂ was added a solution of 0.22 ml of 1.89 M *n*-BuLi (0.417 mmol). The reaction was trapped with 1 ml of methanol. The products were analyzed by GC and coinjected with standards. 1a 10%; 1b 5%; starting material 83%.

Addition Reaction of 1 with *t*-butyl lithium in THF (MeOH trap): To 0.0275 g (0.102 mmol) of 1 dissolved in 3 ml of dry THF at -78° C under N₂ was added a solution of 0.28

ml of 1.1 M *t*-BuLi (0.306 mmol). The reaction was trapped with 1 ml of methanol. The products were analyzed by GC and coinjected with standards. 1a 23%; 1b 22%; starting material 46%.

Addition Reaction of 1 with *t*-butyl lithium in THF (MeOH trap) (xs base): To 0.0171 g (0.063 mmol) of 1 dissolved in 3 ml of dry THF at -78°C under N₂ was added a solution of 0.17 ml of 1.5 M *t*-BuLi (0.253 mmol). The reaction was trapped with 1 ml of methanol. The products were analyzed by GC and coinjected with standards. Starting material 100%.

Addition Reaction of 1 with *t*-butyl lithium in Et₂O (MeOD trap) (xs base): To 0.0156 g (0.058 mmol) of 1 dissolved in 4 ml of dry Et₂O at -78°C under N₂ was added a solution of 0.15 ml of 1.5 M *t*-BuLi (0.231 mmol). The reaction was trapped with 0.15 ml of methanol-*d*. The products were analyzed by GC and coinjected with standards. Starting material 92%.

Addition Reaction of 3 with *t*-butyl lithium in THF (MeOH trap): To 0.1037 g (0.286 mmol) of 3 dissolved in 5 ml of dry THF at -78°C under N₂ was added a solution of 0.39 ml of 1.45 M *t*-BuLi (0.571 mmol). The reaction was trapped with 1 ml of methanol. The products were analyzed by GC and coinjected with standards. 3a 24%; 3b 9%; starting material 28%.

Equimolar Addition Reaction of 2 and 3 with *n*-Butyl lithium in THF (MeOH trap): To 0.085 g (0.3036 mmol) of 2 and 0.1102 g (0.3036 mmol) of 3 dissolved in 10 ml of dry THF at -78°C under N₂ was added a solution of 0.12 ml of 2.5 M *n*-BuLi (0.3036 mmol). The reaction was trapped with 1 ml of methanol. The products were analyzed by GC and coinjected with standards.

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