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FULL PAPER

Focused *ortho*-Lithiation and Functionalization of *p*-Bromo- and *p*-Iodoanisole

D. W. Slocum*[a], John A. Jennings[b], Thomas K. Reinscheld[b], and Paul E. Whitley[b]

Abstract: By use of the strategy for *ortho*-lithiation (DoM) that conceptually diminishes the pK_A difference between the *ortho*-H of the substrate and the conjugate acid of the metalating agent, effective metalation of bromine and iodine bearing aryl substrates can be carried out. As a set of prototypes, *p*-bromoanisole (*p*-BrA) and *p*-iodoanisole (*p*-IA) have been successfully *ortho*-metalated in promoted hydrocarbon media using *ortho*-lithiodimethylbenzylamine (*o*-LiDMBA) as the metalating agent. No hint of exchange of either halogen was noted during these same conditions. These studies add to the emerging evidence of a hitherto unidentified acidifying effect on the proton(s) *ortho*- to a directing metalation group (DMG) by both a *p*-iodo and a *p*-bromo substituent.

Introduction

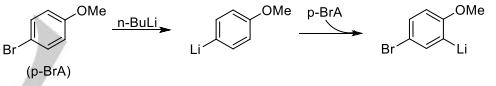
Aryllithium chemistry has gone through numerous phases since the initial *ortho*-lithiation[1] and halogen/lithium(X/Li)[1a,c,e,f, 2] exchange procedures were published. Through the decades, these procedures have become mainstays in the organic/organometallic chemist's toolbox. Overall, a varied and diverse set of protocols have been developed to bring about *ortho* C-H bond activation of a broad spectrum of substituted aryls.

Our group's preoccupation over the last two decades has been the utilization of doped hydrocarbon media, in particular cyclohexane, for both *ortho*-lithiations[3] and the halogen/lithium exchange.[4] By use of small increments of THF and/or tetramethylethylenediamine (TMEDA) as dopants, both reactions have been enabled to proceed with facility in hydrocarbon media. Incremental amounts of an ether or *bis*-chelating amine serve to deoligomerize *n*-BuLi, by far the most utilized alkyllithium reagent, in a controlled manner. By use of this strategy, controlled, fine-tuning of the reactivity of a doped hydrocarbon solution of *n*-BuLi has been achieved.[5] In addition, such solutions are much more stable to alkyllithium reagents than the currently utilized ether and ether/TMEDA solutions[6].

To further our investigations of fine-tuning of aryl metalation reactions, the concept of focused metalations has been developed. Focused metalations are realized by decreasing the pK_A difference between the conjugate acid of the organolithium base and that of the substrate. By doing so, milder metalation conditions are formed which are less prone to produce secondary metalations and / or attack of substituents. Two avenues are utilized to achieve these focused metalation conditions. One is the use of doped hydrocarbon media to modulate the basicity / reactivity of *n*-BuLi. The second is to use aryllithiums as metalating agents.

Phenyllithium (PhLi) is less basic and less nucleophilic than is *n*-BuLi (pK_A's of the conjugate acids are ~44 and ~50, respectively). As the use of PhLi was undesirable, a "surrogate" aryl metalating agent, one that did not produce benzene upon extraction of a hydrogen, was needed. Such a surrogate metalating agent could be conveniently formed either by *ortho*-lithiation or by the halogen / lithium exchange.

An initial foray into surrogate metalation was published in 2009.[7] In this paper *ortho*-lithiodimethylaniline[3a] was used as the surrogate for PhLi. Reasonable yields of eight *ortho*-substituted products of *p*-bromoanisole were isolated. This was an achievement at the time in that for seventy years, there was a fear of the intervention of a rapid halogen/lithium exchange followed by a secondary *ortho*-lithiation (equation 1). Both George Wittig[8] and Henry Gilman,[9] the co-discovers of the *ortho*-lithiation reaction, also elucidated the sequence shown below.



Equation 1.

Consideration of this sequence leads to an intriguing speculation, that the *ortho*-H of *p*-BrA must be more acidic than that of anisole. Recently, this was demonstrated by comparative surrogate metalation studies of both *p*-BrA and *p*-IA.[10] Related low-temperature experimental metalations[11] as well as computational studies[12] have afforded the insight that a bromine substituent provides a distinct acidification of the proton(s) *meta*- to it. For a *p*-substituted aryl such as anisole, this would translate as a measureable acidification of the *ortho*-proton, *i. e.*, the proton that undergoes *ortho*-lithiation.

Some success has already been realized in the *ortho*-lithiation of *p*-FA[13] and *p*-ClA,[3a,14] but it is known that other *p*-XA's (*p*-XA, *p*-haloanisoles), namely, *p*-BrA and *p*-IA, preferentially undergo the X/Li exchange if an alkyllithium reagent is utilized (equation 1). The alternative is to use a less basic, less nucleophilic organolithium. A substituted aryllithium would generate, upon its use for a metalation, a substituted benzene possessing a pK_A of its conjugate acid less than 44. Offered herein is a study of the effective *ortho*-lithiation of both *p*-BrA and *p*-IA using such a reagent where there was no indication that the halogens have been attacked.

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Our working hypothesis is that a focused metalation can be achieved if there is only a 3-5 pK_A unit difference between the acidity of the substrate and that of the conjugate acid of the metalating agent. The underlying assumption here is that such a reagent would be less aggressive and therefore less prone to attack substituents. Herein is presented an approach to a "focused" metalation procedure wherein a substituted aryllithium reagent is utilized. This approach not only gains the lower conjugate acid pK_A value of the metalating agent, but also avoids the initiation of the X/Li exchange.

This focused metalation concept was originated as a consequence of the many reports to be found in the literature describing metalations that have had their yields compromised, have generated metalations at secondary sites or have failed altogether. Many of these problems can be generalized by use of the term "over metalation". Such can be the result from use of too strong a base, too much promoter, too much base and sometimes some combination of two of these conditions. A softer touch might lead in many cases to more controlled, more focused metalations. Our success in this regard was reported recently for *ortho*-lithiation under the rubric "deficiency catalysis" where the conditions involved only *n*-BuLi in hydrocarbon media (cyclohexane) minimally activated by a deficiency (substoichiometric equiv.) of TMEDA or an equiv. or two of THF.[3a] These modulated systems avoided several competing metalations or other strong base reactions that might have intervened. Such conditions and the results therefrom provide excellent examples of the benefits provided by focused conditions for *ortho*-lithiations.

The concept of focused metalations encompasses two broad but separate categories:

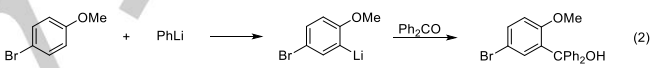
- Regiospecific metalation of designated site on an aryl where one or more potentially competing site(s) are present. This includes, but is not limited to, the related concept of "optional site selectivity".[15]
- Efficient metalation of aryls where a potentially competing reaction is suppressed.

These two categories can be further subdivided, but for our purposes, these two separate designations will suffice. Our "deficiency catalysis" paper provides many examples of the first category.[3a] In this current contribution, examples are provided that conform to the second category, *i.e.*, metalation *ortho*- to the methoxy group of *p*-bromo- and *p*-iodo-anisole (*p*-BrA and *p*-IA) with complete suppression of the X/Li exchange.

At ambient temperatures, halogens possess some stability to *ortho*-lithiation conditions, but only if located in the *p*-position. Only *p*-fluoro-[13] and *p*-chloro-aryls[3a,14] afford this stability. The *p*-F substituent in *p*-fluoroanisole was found to be a weaker director than the methoxy group using *n*-BuLi in ether at ambient temperature and so lithiation took place adjacent to the methoxy group. Earlier, both Gilman[16] and Eaborn,[17] each attained using PhLi only a 13% yield of product from the metalation of *p*-fluoroanisole after having run the metalation overnight. In each study, a black product solution was formed indicative of benzyne formation. By running the metalation over much shorter periods with *n*-BuLi, 5 h in one study[18] and 1 h in another,[13] *ortho*-substituted products were realized in 32% and 55% yields, respectively. Schlosser and coworkers performed a complete study of the lithiation of all three fluoroanisoles *ortho*- to the methoxy group.[19]

Lithiation *ortho*- to several aryl DMG's has been accomplished in the presence of a *p*-Cl substituent. These include the methoxy group[3a, 19, 20a] as well as the amide[20b] and methoxymethyl (-MOM)[20c] directing groups.

Arenes containing a DMG where either a *p*-Br or *p*-I substituent is present seldom have been subjected to *ortho*-lithiation conditions. For the most part this has been due to concern that the –Br or –I substituent will preferentially undergo rapid X/Li exchange. Both Gilman[8] and Wittig[9] attempted *ortho*-lithiation of *p*-bromoanisole with both eventually realizing that the transformation illustrated in equation 1 was occurring. Wittig[21] went on to investigate the use of PhLi for the *ortho*-lithiation of the haloanisoles, ultimately isolating the anticipated triarylcarbinol derived from *p*-BrA and benzophenone in 70% yield (equation 2). Eaborn and Walton[17] later repeated this procedure, isolating the trimethylsilyl derivative of *p*-BrA in 44% yield and that of *p*-IA in 58% yield.



Equation 2.

Sporadic reports of metalation of bromine containing aryl systems have appeared in the literature. Hirata *et al*[22] achieved regioselective lithiation of anisole (1) with a product isolated in 33% yield. Majetich and coworkers[23] attempted the X/Li exchange of compound (2) achieving as the likely result the exchange/*ortho*-lithiation sequence depicted in equation 1. In at least one case concern that a *p*-bromo substituent would undergo the halogen/lithium exchange instead of the sought *ortho*-lithiation caused a pharmaceutical research team to pursue an alternative approach.[24]

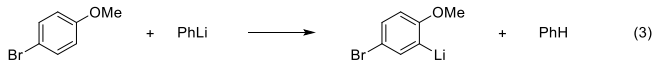
Figure 1.

Results and Discussion

The concept of use of organolithium reagents less basic than *n*-BuLi has led to some intriguing developments. Such reagents increase our ability to modulate reactivity in a controlled manner. Focused metalations using such reagents, among other attributes, would allow more substituent tolerance. Numerous substituents are too prone to side reactions with an organolithium reagent to survive either *ortho*-lithiation or halogen/lithium

exchange conditions. Exceptional substituents, aside from directing metalation groups (DMG's) themselves, which have been shown to remain intact during the course of a lithiation or exchange are –R, –SiR_3, (–F), –Cl and –D. Additional substituents, in particular ones that provide access to further functional elaboration, would be most desirable. Retention of a transformable aryl –Br or –I substituent from an *ortho*-lithiation procedure would represent a giant step towards this goal.

Most *ortho*-lithiations are carried out using *n*-BuLi or even more basic alkyllithiums. *ortho*-H's of many aryl substrates possess pK_A's between 37 and 41.[25,26] As the basicity/nucleophilic nature of an aryllithium is significantly lower than that of *n*-BuLi (pK_A of the conjugate acid, butane, is *ca.* 50), a decrease in both the aryllithium's basicity and nucleophilicity towards substituents will result. In the past PhLi was used in this regard, but this is no longer practical as PhLi generates, upon use in a metalation, benzene, a carcinogen (equation 3).

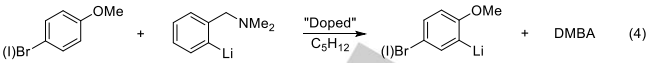


Equation 3.

By decreasing the difference in pK_A values between the conjugate acid of the metalating agent and that of the *ortho*-H of the substrate, a more focused *ortho*-lithiation can be achieved. This is the mantra to be followed in all future metalation efforts from our group. In a sense our recent publications involving *ortho*-lithiations and exchanges in activated hydrocarbon media[3,4] conforms to this mantra. Deficiencies of THF or TMEDA in hydrocarbon media were shown to provide efficient lithiations, yet the systems were much less activated than when a full equiv. of TMEDA or bulk ether solutions of *n*-BuLi were utilized.[5]

To afford a safer, greener *ortho*-lithiation procedure for the metalation of *p*-BrA, our initial investigations utilized *ortho*-lithiodimethylaniline (o-LiDMA) as the metalating agent.[7] *o*-LiDMA provided a reasonable extent-of-metalation of *p*-bromoanisole such that good yields of *ortho*- substituted products were isolated. Moreover, as the metalating agent was *o*-LiDMA, the protonated aryl generated in the reaction was dimethylaniline, not benzene. Use of this metalating agent permitted an acid/base extraction as part of the work-up, resulting in recovery of DMA for potential recycle.

To further this approach we now report the efficient *ortho*-lithiation of both *p*-BrA and *p*-IA (Tables 1 and 2, respectively) utilizing *ortho*-lithiodimethylbenzylamine (*o*-LiDMBA) as the metalating agent. DMA and DMBA each are estimated to possess a pK_A for their respective *ortho*-H's of 40.3 or greater.[25] Both provide about the same extent of metalation of *p*-bromoanisole but use of *o*-LiDMBA offers several advantages over use of *o*-LiDMA. In addition, *ortho*-lithiation of *p*-IA has been achieved using *o*-LiDMBA (equation 4). Use of *o*-LiDMA was not attempted in this latter investigation.



Equation 4.

Reproducible extents of *ortho*-lithiation of DMBA itself are 95-98% whereas those for DMA are in the area of 88-92%.[3a] *o*-LiDMBA is thus a more concentrated reagent than *o*-LiDMA. Furthermore *o*-LiDMA is formed using the "deficiency catalysis" procedure involving 0.1 equiv. of TMEDA in cyclohexane. The TMEDA would carry forward into subsequent reactions which is an undesirable feature. Its presence did not appear to be a problem in our preliminary study, but it was felt that the presence of TMEDA could present problems in future studies. *o*-LiDMBA does not present any such problem as it is generated in cyclohexane activated with an equiv. of MTBE. Moreover, the DMBA generated as a result of the metalation process is somewhat easier to extract from the reaction mixture than is the generated DMA.

Carbon-carbon and carbon-heteroatom bond formation for *ortho*-products of both *p*-bromo and *p*-iodoanisole range percentage-wise for the most part from the 60's to the high 70's (Tables 1 and 2, respectively). No clear difference was discovered between the yields of the *ortho*- products derived from the two separate substrates. No halogen/lithium exchange was observed during the *ortho*-lithiation of either substrate.

Most of these products can be further derivatized *via* the halogen/lithium exchange. In particular, the *o*-TMS derivatives of *p*-BrA and *p*-IA can be double derivatized, first by the X/Li exchange of either the bromine or iodine substituents and second by the ipso substitution of the -TMS group. In a sense, the compounds 4-Br-2-TMSA and 4-I-2-TMSA comprise a set of aryl synthons for convenient access to 2,4-disubstituted anisoles.

Dilution of the generated *ortho*-lithio intermediate with THF prior to derivatization solubilizes much of the particulate matter. Further study of this technique in general will potentially improve the percent isolated yields.

Conclusions

For decades, chemists have been seeking methods to further the effectiveness of metalation chemistry. Systems involving superbases[27] and mixed main group metals[28] have been developed for this expressed purpose. We propose a third alternative; utilization of organolithium bases whose conjugate acids are only 3-5 pK_A units less acidic than the most acidic site being metalated. Such bases can be formed by *ortho*-lithiation and/or, possibly, using chemistry yet to be explored, by the halogen/lithium exchange. The principal bases in our repertoire are *ortho*-lithiodimethylaniline (*o*-LiDMA)[7] and *ortho*-lithiodimethylbenzylamine (*o*-LiDMBA). Both of these bases can be conveniently formed by "deficiency catalysis" metalation with *n*-BuLi.[3a] By this strategy, the basicity of the *n*-BuLi is stepped down, *i.e.*, the difference between the pK_A of the conjugate acid

of the base and the pK_A of the acidic site of the substrate is reduced, ideally to a difference of 3-5 pK_A units, thereby forming a more focused metalating system.

Successful *ortho*-lithiation of both *p*-IA and *p*-BrA has afforded a series of *ortho*-substituted anisoles in modest to good yields. The two trimethylsilyl derivatives can serve as aryl synthons for the preparation of 2-, 4-disubstitued anisoles. An initial halogen/lithium exchange followed by *ipso*-substitution of the trimethylsilyl moiety of either synthon would afford access to a wide array of appropriately substituted anisoles. Under these conditions, no products from a halogen/lithium exchange were observed.

Both dimethylbenzylamine (DMBA) and dimethylaniline (DMA) have a measured *ortho*-H acidity with a pK_A of >40.3.[25] Anisole's *ortho*-H acidity possesses a measured pK_A of 39.[25] Our conjecture is that a 3-5 pK_A unit difference in acidity is necessary between the conjugate acid of the metalating agent and the acidic site of the substrate for an effective focused metalation to be achieved. Larger differences brings about unwanted side-reactions. Anisole itself is not effectively *ortho*-lithiated using *o*-LiDMBA (pK_A = 40.3 *vs* 39). This being the case, metalation of *p*-BrA and *p*-IA cannot be accomplished unless both of these halogenated anisoles are more acidic than anisole by two or three pK_A units.

These observations lead to a conundrum. The strong electronegativity of the *p*-halogen could explain the observed increase in *ortho*-H acidity of *p*-chloroanisole and *p*-fluoroanisole over that of anisole. Both can be metalated under milder conditions than anisole.[13,3a,14] The above results also indicate that both *p*-bromo- and *p*-iodoanisole possess *ortho*-protons more acidic than anisole. Yet electronegativity seemingly cannot explain this last observation. Another possibility is an opposing-*pi*-resonance contribution.[29] By opposing the *pi*-donation of the –OMe oxygen, the *p*-substituent in effect increases the localization of oxygen's electron pairs. This in turn serves to increase the contribution of alkyllithium complexion *via* the Complex-Induced Proximity Effect (CIPE)[30] leading to a perceived increase in acidity. However, it is difficult to envision how the large orbitals on –Br or –I can provide sufficient "opposing" to make the *ortho*-H's appear as acidic as those in their –F and –Cl counterparts.

So, what is the cause of the observed acidity enhancement of the *p*-bromo- and *p*-iodoanisoles? Recent experimental[11] and computational investigations[12] have indicated some generality to the observed acidifying of the position(s) *meta*- to a bromine substituent. This is exactly the relationship of the *ortho*-H to the *p*-Br substituent in *p*-BrA. Separate studies, both experimental and computation, are in progress to further our knowledge of this electronic effect, to gain more insight into its origin and, ultimately, its potential utility in synthesis.

Table 1. Here

Table 2. Here

Experimental Section

General- All research chemicals were supplied by Aldrich Chemical Co. Solvents were order anhydrous and used as received. GC analysis was performed on a capillary gas chromatograph equipped with a BP-10 capillary column (25m x 0.22mm, 0.25mm film and FID). Identities of products were confirmed by GC/MS analysis (30m x 0.32mm, 0.25 mm film) on an instrument equipped with a quadrupole mass detector and separate FID. NMR data was attained using an ECA-500 MHz instrument. Combustion analysis was performed on a CHN analyser. Several products were purified by column chromatography using silica gel (60Å, 65 x 250 mesh, 500-600 m^2/g) available from Sorbent Technologies. TLC analysis was performed using identical silica plates also available from Sorbent Technologies.

Preparation of *o*-Li-*p*-Bromoanisole- To a clean, dry nitrogen-purged round bottom flask was added a 1.33 M suspension in cyclohexane of *o*-LiDMBA (15 mL, 20 mmol; prepared as described previously[3a]) *via* 14 gauge needle. Next, MTBE (2.4 mL, 20 mmol) and *p*-bromoanisole ((2.4 mL, 19 mmol) 0.95 equiv. of *p*-BrA is used since the *o*-LiDMBA is typically 94-96% pure) was added and the reaction mixture was allowed to stir at 60°C under a positive nitrogen atmosphere for 20-30h. The prepared *o*-Li-*p*-BrA was used in subsequent derivatizations without purification. The same procedure was followed for the preparation of *o*-Li-*p*-Iodoanisole using 4.45 g (19 mmol) of *p*-iodoanisole.

General Derivatization of *o*-Li-*p*-Bromoanisole and *o*-Li-*p*-Iodoanisole- To a stirred solution of *o*-Li-*p*-bromoanisole or *o*-Li-*p*-iodoanisole (as prepared above) was slowly added 0.95 equiv. (based on *p*-BrA or *p*-IA) of the desired derivatizing agent (electrophile) *via* syringe for liquids and directly as a solid for solids. Attempts were made to maintain ambient reaction temperature with aid of a water bath or ice bath. The reaction mixture was allowed to stir at room temperature for at least 3 h. The reaction was slowly quenched with water (unless otherwise stated) and transferred to a separatory funnel with the aid of 20-30 mL of MTBE. Upon separation, the organic layer was washed with 25 mL of 1M HCl (to remove DMBA) and 25mL brine. The organic layer was then dried over sodium sulfate and concentrated *in vacuo* to provide crude product which was purified by trituration and/or recrystallization (to >95% pure by GC) as described for each individual product. In some cases, one or two additional crystallizations were necessary to obtain analytically pure samples for the combustion analysis of previously unknown compounds.

5-Bromo-2-methoxy-α-phenyl-benzenemethanol (1) - To a stirred solution of 1.1 M *o*-Li-*p*-bromoanisole (17.1 mL) was slowly added benzaldehyde (1.8 mL, 18.2 mmol) *via* syringe. The crude product was triturated with hexanes, filtered and washed with cold hexanes to afford 4.47 g, 67%. Melting point 76.0-77.4 °C (Lit. mp 76.4-78.4°C [7]); M^+ 292.0 / 294.0; Base Peak 292.0 / 294.0; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 2.69 (s, 1H, OH), 3.77 (s, 3H), 6.01 (s, 1H), 6.73-6.75 (d, J = 8.6 Hz, 1H), 7.24-7.29 (m, 1H), 7.31-7.38 (complex m, 5H), 7.444-7.450 (d, J = 2.9 Hz, 1H). ^{13}C NMR: δ = 55.8, 71.5, 112.5, 113.4, 126.6, 127.6, 128.5, 130.4, 131.4, 134.2, 142.7, 155.7; Analysis calculated for $C_{14}H_{13}BrO_2$ (293.16): C, 57.36%; H, 4.47%. Found: C, 57.36%; H, 4.56%.

5-Bromo-2-methoxy-α,α-diphenyl-benzenemethanol (2) - To a stirred solution of 1.1 M *o*-Li-*p*-bromoanisole (17.0 mL) was slowly added benzophenone (3.3 g, 18.1 mmol) as a solid. The crude product was triturated with cyclohexane, filtered and washed with cyclohexane to afford 4.47 g, 67%. Melting point 121.5-123.3 °C (Lit. mp 121.5-123.3°C [21]); M^+ 368.1 / 370.1; Base Peak 291.1; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 3.63 (s, 3H), 5.12 (s, 1H, OH), 6.635-6.641 (d, J = 2.3 Hz, 1H), 6.82-

6.84 (d, J = 9.2 Hz, 1H). ^{13}C NMR: δ = 56.1, 81.8, 113.4, 113.9, 127.4, 127.7, 128.0, 131.8, 133.0, 137.7, 145.9, 156.6.

5-Bromo-α-cyclopentyl-2-methoxy-benzenemethanol (3) - To a stirred solution of 1.0 M *o*-Li-*p*-bromoanisole (15 mL) was slowly added cyclopentanone (1.2 mL, 13.7 mmol) *via* syringe. The crude product was triturated with cyclohexane, filtered and washed with cyclohexane to afford 2.34 g, 63%. Melting point 67.9-69.0 °C (Lit. mp 67.5-69.1°C [7]); M^+ 270.1 / 272.0; Base Peak 162.1; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 1.70-2.10 (complex m, 8H), 3.32 (s, 1H, OH), 3.87 (s, 3H), 6.77-6.79 (d, J = 8.6 Hz, 1H), 7.32-7.35 (dd, J = 8.6, 2.3 Hz, 1H), 7.44-7.45 (d, J = 2.8 Hz, 1H). ^{13}C NMR: δ = 23.5, 39.2, 55.7, 82.4, 112.9, 113.4, 128.9, 130.7, 136.6, 156.5. Analysis calculated for $C_{12}H_{15}BrO_2$ (271.15): C, 53.15%; H, 5.58%. Found: C, 53.37%; H, 5.53%.

1-(5-Bromo-2-methoxy-phenyl)-cyclohexanol (4) - To a stirred solution of 1.15 M *o*-Li-*p*-bromoanisole (16 mL) was slowly added cyclohexanone (1.85 mL, 17.8 mmol) *via* syringe. The crude product was triturated with cyclohexane, filtered and washed with cyclohexane to afford 2.66 g, 53%. Melting point 98.3-98.9 °C (Lit. mp 93.9-97.6°C [7]); M^+ 284.1 / 286.1; Base Peak 162.1; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 1.15-1.28 (m, 1H), 1.57-1.97 (complex m, 9H), 3.76 (s, 1H, OH), 3.83 (s, 3H), 6.77-6.79 (d, J = 8.6 Hz, 1H), 7.31-7.33 (dd, J = 9.2, 2.9 Hz, 1 H), 7.435-7.440 (d, J = 2.8 Hz, 1H). ^{13}C NMR: δ = 21.9, 25.8, 36.5, 55.7, 73.0, 113.2, 113.8, 129.1, 130.5, 138.8, 156.4; Analysis calculated for $C_{13}H_{17}BrO_2$ (285.18): C, 54.75%; H, 6.01%. Found: C, 54.77%; H, 5.99%.

4-Bromo-1-methoxy-2-(trimethylsilyl)-benzene (5) - To a stirred solution of 0.96 M *o*-Li-*p*-bromoanisole (19 mL) was slowly added chlorotrimethylsilane ((2.5 mL, 20 mmol) A slight excess (1.1 equiv.) of ClTMS was employed since any residual can be easily hydrolyzed and removed in the aqueous work up.) *via* syringe. After 1 h the reaction mixture was quenched slowly with aqueous saturated sodium carbonate (rather than the typical water quench). The organic layer was then washed with 1M HCl, brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product was then treated with hexanes (5 mL) and allowed to sit in the refrigerator overnight whereupon needlelike crystals formed. The solution was filtered and washed with cold hexanes and afforded 2.47 g, 52% of (5-Bromo-2-methoxy-phenyl)-trimethyl-silane as clear needles. Melting point 56.7-57.7 °C (Lit. mp 58-58.5°C [17]); M^+ 258.0 / 260.0; Base Peak 258.0 / 260.0; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 0.24 (s, 9H), 3.77 (s, 3H), 6.68-6.70 (d, J = 8.0 Hz, 1H), 7.39-7.42 (m, 2H). ^{13}C NMR: δ = 1.1, 55.4, 111.5, 113.4, 131.3, 133.2, 137.4, 163.3.

5-Bromo-2-methoxy-benzaldehyde (6) - To a stirred solution of 1.0M *o*-Li-*p*-bromoanisole (16.5 mL) was slowly added N,N-dimethylformamide ((2.5 mL, 32.4 mmol) An excess of DMF was used as it can be easily removed during aqueous workup)) *via* syringe. The crude product was triturated with hexane, filtered and washed with hexane to afford 2.95 g, 73.8%. Melting point 102.0-104.0 °C (Lit. mp 107-109°C [31]); M^+ 214.0 / 216.0; Base Peak 214.0 / 216.0; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 3.91 (s, 3H), 6.88-6.9 (d, 8.6 Hz, 1H), 7.61-7.63 (dd, J = 8.6, 2.9 Hz, 1H), 7.907-7.912 (d, J = 2.8 Hz, 1H), 10.37 (s, 1H). ^{13}C NMR: δ = 56.1, 113.6, 113.8, 126.2, 131.1, 138.4, 160.8, 188.5.

(5-Bromo-2-methoxy-phenyl)-phenyl-methanone (7) - To a stirred solution of 1.0 M *o*-Li-*p*-bromoanisole (17 mL) was slowly added benzonitrile (1.6 mL, 15.5 mmol) *via* syringe. After stirring for 18 h, the reaction was quenched with water and extracted with MTBE. The organic layer was transferred to a round bottom flask and treated with 1M sulfuric acid (25 mL). Following stirring vigorously for 2 h, the reaction mixture was transferred to a sepratory funnel and the organic layer was separated. The aqueous layer was back extracted with MTBE and the combined organic layers were washed with aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product was triturated with cyclohexane, filtered and washed with cyclohexane to afford 3.0 g, 66% of a yellow solid. Melting point 101-102°C M^+ 290.0 / 292.0; Base Peak 213.0; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 3.70 (s, 3H), 6.87-6.89 (d, J = 9.2 Hz, 1H), 7.41-7.46 (m, 3H), 7.54-7.59 (m, 2H), 7.79-7.80 (d, J = 7.4 Hz, 2H). ^{13}C NMR: δ = 56.0, 112.9, 113.3, 128.5, 129.9, 130.7, 132.0, 133.5, 134.5, 137.2, 156.4. Analysis calculated for $C_{14}H_{11}BrO_2$ (291.14): C, 57.76%; H, 3.81%. Found: C, 58.09%; H, 3.93%.

5-Bromo-α-(4-chlorophenyl)-2-methoxy-benzenemethanol (8) - To a stirred solution of 1.22M *o*-Li-*p*-bromoanisole (14.8 mL) was slowly added 4-chlorobenzaldehyde (2.36g, 16.9 mmol). The crude product was triturated with hexanes, filtered and washed with cold hexanes to afford 3.03 g, 55%. Melting point 101.2-101.8°C, M^+/Base peak envelope centered at 328.0; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 2.83 (s, 1H, OH), 3.78 (s, 3H), 5.96 (s, 1H), 6.73-6.75 (d, J = 8.6 Hz, 1H), 7.25-7.41 (complex m, 6H). ^{13}C NMR: δ = 55.8, 70.1, 112.6, 113.4, 128.0, 128.6, 130.3, 131.6, 133.3, 133.8, 141.2, 155.6. Analysis calculated for $C_{14}H_{13}IO_2$ (340.16): C, 49.43%; H, 3.85%. Found: C, 49.09%; H, 3.83%.

(5-Iodo-2-methoxy-phenyl)-phenyl-methanol (9) - To a stirred solution of 1.14 M *o*-Li-*p*-iodoanisole (15.3 mL) was slowly added benzaldehyde (1.7 mL, 16.8 mmol) *via* syringe. The crude product was triturated with hexanes (5-6 mL), filtered and washed with cold hexanes to afford 3.8 g, 67%. Melting point 79.4-80.8°C, M^+/Base peak 340.1; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 2.75 (s, 1H, OH), 3.76 (s, 3H), 5.99 (s, 1H), 6.62-6.64 (d, J = 2.2 Hz, 1H). ^{13}C NMR: δ = 55.7, 71.4, 83.5, 113.2, 126.6, 127.6, 128.4, 134.6, 136.2, 137.5, 142.8, 156.5. Analysis calculated for $C_{14}H_{13}IO_2$ (340.16): C, 49.43%; H, 3.85%. Found: C, 49.09%; H, 3.83%.

5-Iodo-2-methoxy-α,α-diphenyl-benzenemethanol (10) - To a stirred solution of 1.13 M of *o*-Li-*p*-iodoanisole (10.4 mL) was slowly added benzophenone (2.6 g, 11.3 mmol) as a solid. The crude product was triturated with cyclohexane, filtered and washed with cyclohexane to afford 3.39 g, 72%. Melting point 136.3-137.4°C (Lit mp 136-137°C [21]); M^+ 416.1; Base Peak 339.1; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 3.62 (s, 3H), 5.10 (s, 1H, OH), 6.71-6.72 (d, J = 9.6 Hz, 1H), 6.780-6.784 (d, J = 2.3 Hz, 1H), 7.20-7.32 (complex m, 10H), 7.57-7.60 (dd, J = 8.6, 2.3 Hz, 1H). ^{13}C NMR: δ = 56.0, 81.7, 83.7, 177.5, 127.4, 127.7, 137.9, 138.1, 138.7, 145.9, 157.4.

5-Iodo-α-cyclopentyl-2-methoxy-benzenemethanol (11) - To a stirred solution of 1.0 M *o*-Li-*p*-iodoanisole (14.4 mL) was slowly added cyclopentanone (1.77 mL, 20.02 mmol) *via* syringe. The crude product was triturated with cyclohexane, filtered and washed with cyclohexane to afford 2.45 g, 40%. Melting point 92.4-94.1°C; M^+ 318.1; Base Peak 289.0; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 1.74-2.10 (complex m, 8H), 3.29 (s, 1H, OH), 3.87 (s, 3H), 6.66-6.68 (d, J = 8.6 Hz), 7.51-7.53 (dd, J = 8.6, 2.3, 1H), 7.60-7.61 (d, J = 2.3 Hz, 1H). ^{13}C NMR: δ = 23.5, 39.2, 55.6, 82.3, 83.3, 133.5, 134.7, 136.9, 137.0, 157.3. Analysis calculated for $C_{12}H_{15}IO_2$ (318.15): C, 45.30%; H, 4.75%. Found: C, 45.67%; H, 4.66%.

1-(5-Iodo-2-methoxy-phenyl)-cyclohexanol (12) - To a stirred solution of 1.15M *o*-Li-*p*-iodoanisole (15 mL) was slowly added cyclohexanone (1.81 mL, 17.46 mmol) *via* syringe. The crude product was triturated with cyclohexane, filtered and washed with cyclohexane to afford 3.98 g, 69%. Melting point 109.9-111.0°C; M^+ 332.1; Base Peak 289.0; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 1.21-1.24 (m, 1H), 1.57-1.62 (complex m, 2H), 1.69-1.97 (complex m, 7H), 3.65 (s, 1H, OH), 3.86 (s, 3H), 6.66-6.68 (d, J = 8.6 Hz, 1H), 7.50-7.52 (dd, J = 8.6, 2.3 Hz, 1H), 7.592-7.596 (d, J = 2.3 Hz, 1H). ^{13}C NMR: δ = 21.9, 25.8, 36.5, 55.6, 72.9, 84.2, 113.8, 134.9, 136.7, 139.2, 157.2. Analysis calculated for $C_{13}H_{17}IO_2$ (332.18): C, 47.00%; H, 5.16%. Found: C, 46.76%; H, 5.09%.

4-Iodo-1-methoxy-2-(trimethylsilyl)-benzene (13) - To a stirred solution of 1.21 M *o*-Li-*p*-Iodoanisole (15.5 mL) was slowly added chlorotrimethylsilane ((4.8 mL, 37.6 mmol) An excess (2.0 equiv.) of ClTMS was employed since any residual can be easily hydrolyzed and removed in an aqueous work up) *via* syringe. After 1 h the reaction mixture was quenched slowly with aqueous saturated sodium carbonate (rather than the typical water quench). The organic layer was then washed with 1M HCl, brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product was then triturated with hexanes (5 mL) and allowed to sit in the refrigerator overnight whereupon needlelike crystals formed. The solution was filtered and washed with cold hexanes to afford 4.46 g, 78%. Melting point 50.3-50.9°C (Lit. mp 50-50.5°C [17]); M^+ 306.0; Base Peak 289.0; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 0.24 (s, 9H), 3.77 (s, 3H), 6.59-6.61 (d, J = 8.6 HZ, 1H), 7.56-7.61 (m, 2H). ^{13}C NMR: δ = 1.1, 55.3, 84.1, 112.2, 132.0, 139.2, 143.3, 164.0.

5-Iodo-2-methoxy-benzaldehyde (14) - To a stirred solution of 1.33 M *o*-Li-*p*-iodoanisole (14.8 mL) was slowly added N,N-dimethylformamide ((2.9 mL, 38.0 mmol) An excess of DMF was used as it can be easily removed during aqueous work up) *via* syringe. The crude product was triturated with hexane, filtered and washed with hexane to afford 3.14 g, 61%. Melting point 142.0-143.5°C (Lit. mp 140-142 °C [32]); M^+ 262.0; Base Peak 262.0; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 3.91 (s, 3H), 6.77-6.79 (d, 8.6 Hz, 1H), 7.79-7.81 (dd, J = 8.6, 2.3 Hz, 1H), 8.075-8.079 (d, J = 2.3 Hz, 1H), 10.33 (s, 1H). ^{13}C NMR: δ = 56.0, 83.1, 114.2, 126.6, 137.2, 144.2, 161.5, 188.4.

(5-Iodo-2-methoxy-phenyl)-phenyl-methanone (15) - To a stirred solution of 1.28M *o*-Li-*p*-iodoanisole (15 mL) was slowly added benzonitrile (1.88 mL, 19.2 mmol) *via* syringe. After stirring for 18h, the reaction was quenched with water and extracted with MTBE. The organic layer was transferred to a round bottom flask and treated with 1M sulfuric acid (25 mL). Following stirring vigorously for 2h, the reaction mixture was transferred to a separatory funnel and the organic layers were washed with aqueous saturated sodium bicarbonate and brine, dried over sodium sulfate and concentrated *in vacuo*. The crude product was triturated with cyclohexane, filtered and washed with cyclohexane to afford 5.55 g, 86% of (5-Iodo-2-methoxy-phenyl)-phenyl-methanone as yellow solid. Melting point 79.8-81.6 °C; M^+/ Base peak 338.1; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 3.70 (s, 3 H), 6.76-6.78 (d, J = 8.6 Hz, 1H), 7.42-7.80 (complex m, 7H). ^{13}C NMR: δ = 55.9, 82.5, 113.8, 128.5, 129.9, 131.2, 133.4, 137.2, 137.7, 140.4, 157.3, 194.7. Analysis calculated for $C_{14}H_{11}IO_2$ (338.14): C, 49.73%; H, 3.28%.

5-Iodo-α-(4-chlorophenyl)-2-methoxy-benzenemethanol (16) - To a stirred solution of 1.23 M *o*-Li-*p*-iodoanisole (14.8 mL) was slowly added 4-chlorobenzaldehyde (2.38 g, 17.0 mmol). The crude product was triturated with cyclohexane overnight, filtered and washed with cold cyclohexane to afford 5.06 g, 79%. Melting point 104.7-106.4°C; M^+ 374.0; Base Peak 374.0; ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): δ = 2.76 (s, 1H, OH), 3.76 (s, 3H), 5.95 (s, 1H), 6.63-6.65 (d, J = 8.6 Hz, 1H), 7.29 (s, 4H), 7.54-7.56 (dd, J = 8.6, 2.3 Hz, 1H), 7.578-7.582 (d, J = 2.3 Hz, 1H). ^{13}C NMR: δ = 55.7, 70.9, 83.5, 113.2, 128.0, 128.6, 133.3, 134.2, 136.0, 137.7, 141.2, 156.4. Analysis calculated for $C_{14}H_{12}ClIO_2$ (374.60): C, 44.89%; H, 3.23%. Found: C, 45.16%; H, 3.19%.

2-Chloro-4-iodo-1-methoxybenzene (17) - To a stirred solution of 1.64 M *o*-Li-*p*-iodoanisole (8.0 mL) was slowly added hexachloroethane (2.79g, 11.8 mmol) as a solid. The reaction mixture was allowed to stir overnight (22 h) at 22°C. The crude product was then treated with MTBE (1 mL), poured over an evaporating dish and allowed to evaporate at room temperature (approximately 10 min.) whereupon white powder like crystals formed. Subsequent attempts (approx. 2) were completed to afford 1.11g, 35%. Melting point 88.9-90.4°C (Lit. mp 93-95°C [33]); M^+/ Base peak 268.0; Analysis calculated for C_7H_6ClIO (268.47): C, 31.31%; H, 2.25%. Found: C, 31.0%; H, 2.25.

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Keywords: ortho-lithiation • surrogate metalation • ortho-proton acidity • strong base • aryl synthesis

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Table 1

ortho-Derivatives of p-BrA

Functionalizing Reagent	Product with Designation		Isolated Yield (%)
Benzaldehyde	–CHPhOH	(1)	67
Benzophenone	–CPh_2OH	(2)	67
Cyclopentanone		(3)	63
Cyclohexanone		(4)	53
Trimethylsilylchloride	–TMS	(5)	52
N,N-Dimethylformamide	–CHO	(6)	73.8
Benzonitrile	–COPh	(7)	66
p-Chlorobenzaldehyde		(8)	55

Table 2

***ortho*-Derivatives of *p*-IA**

Functionalizing Reagent	Product with Designation		Isolated Yield (%)
Benzaldehyde	–CHPhOH	(9)	67
Benzophenone	–CPh_2OH	(10)	72
Cyclopentanone		(11)	40
Cyclohexanone		(12)	69
Ttimethylsilylchloride	–TMS	(13)	78
N,N-Dimethylformamide	–CHO	(14)	61
Benzonitrile	–COPh	(15)	86
p-Chlorobenzaldehyde		(16)	79
Hexachloroethane	–C_2Cl_6	(17)	35

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Page No. – Page No.

Title

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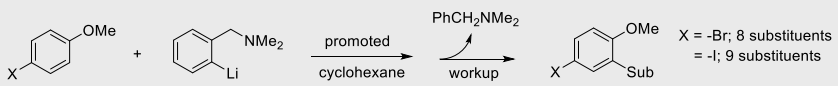

By use of the strategy for *ortho*-lithiation (DoM) that conceptually diminishes the pK_A difference between the *ortho*-H of the substrate and the conjugate acid of the metalating agent, effective metalation of bromine and iodine bearing aryl substrates can be carried out. As a set of prototypes, *p*-bromoanisole (*p*-BrA) and *p*-iodoanisole (*p*-IA) have been successfully *ortho*-metalated in promoted hydrocarbon media using *ortho*-lithiodimethylbenzylamine (*o*-LiDMBA) as the metalating agent. No hint of exchange of either halogen was noted during these same conditions. These studies add to the emerging evidence of a hitherto unidentified acidifying effect on the proton(s) *ortho*- to a directing metalation group (DMG) by both a *p*-iodo and a *p*-bromo substituent.

ortho*-lithiation

D. W. Slocum, J. A. Jennings, T. K. Reinscheld, P. E. Whitley*

Page No. – Page No.

Focused *ortho*-Lithiation and Functionalization of *p*-Bromo and *p*-Iodoanisole