

Facile access to hetero-poly-functional arenes and *meta*-substituted arenes via two-step dimetalation and Mg/halogen-exchange protocol

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Dedication **Dedicated to Professor Robert Mulvey on the occasion of his 60th birthday. A tremendous chemist, colleague and friend.**

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Abstract: The Grignard reagent, ⁱPrMgCl and its lithium chloride-enhanced 'turbo' derivative ⁱPrMgCl·LiCl have been employed to investigate the single iodo/magnesium exchange reactions of the trisubstituted arenes, 2,5-diiodo-*N,N*-diisopropylbenzamide **1**, 1,4-diiodo-2-methoxybenzene **2**, and 1,4-diiodo-2-(trifluoromethyl)benzene **3**. These three arenes themselves were initially prepared by a double *ortho*-, *meta*'-deprotonation of *N,N*-diisopropylbenzamide, anisole and (trifluoromethyl)benzene respectively, using a sodium magnesiate reagent, and subsequent electrophilic quenching with iodine/THF solution. Thus, by following a combined deprotonation and magnesium/halogen exchange strategy, the simple monosubstituted arenes can be converted to trisubstituted diiodoarenes, which can ultimately be transformed into the corresponding mono-magnesiated arenes, in THF at -40°C, within seconds in good yields. The other functional group (OMe, NⁱPr₂ or CF₃ respectively) present on the di-iodoarenes helps direct the exchange reaction to the *ortho* position whereas subsequent addition of different electrophiles permits the preparation of hetero-poly-functional-arenes, with three different substituents in their structure. Intriguingly, if water is used as the electrophile, a new and facile route to prepare *meta*-substituted arenes, which cannot be easily obtained by conventional processes, is forthcoming. In contrast to directed *ortho*-metalation (DoM) chemistry, this reaction sequence can be thought of as InDirect *meta*-Metalation (IDmM). The scope of the chemistry has been tested further by exposing the initial unreacted iodo-functionality at the *meta*-position to a second Mg/I-exchange reaction and subsequent functionalization.

Introduction

Haloarenes are core building blocks of modern organic synthesis,^[1] primarily due to their role as precursors for the synthesis of organometallic compounds (e.g., Grignard reagents),^[2] for nucleophilic substitution reactions^[3] and for reagents in cross-coupling chemistry.^[4] They are fundamentally key to the syntheses of many natural products,^[5] agrochemicals and pharmaceuticals.^[6] The preparation of *meta*-haloarenes, is

particularly desirable and challenging, as they cannot be easily obtained by conventional processes. For instance, metalation (conversion of a C-H bond into a C-metal bond), is one of the most widely used chemical reactions to functionalize arene rings;^[7] however, it has generally been confined to a single position, *i.e.*, the *ortho*-position. The Directed *ortho*-Metalation (DoM) reaction,^[8] is a highly efficient and selective methodology which enables arene metalation to occur adjacent to a directing group (DG). The reaction was first discovered independently by Gilman^[9] and Wittig^[10] and has been developed extensively in the intervening years.^[11] Turning to other metalation patterns, Schlosser noted, "deviations from the *ortho*-rule do exist but are scarce" in his masterwork on polar organometallic chemistry,^[7a] highlighting the difficulties in activating *meta*- or *para*-positions of arene rings. In recent years, the functionalization of these sites has emerged as a topic of paramount importance, as the compounds are key intermediates in pharmaceuticals, agrochemicals, and novel materials. Focusing on *meta*-functionalization, it has been achieved through palladium-,^[12] ruthenium-,^[13] and copper-catalyzed processes.^[14]

We have focused recently on the use of mixed alkali metal magnesiates in metalation chemistry. Most success has revolved around the sodium magnesiate [Na₄Mg₂(TMP)₆(ⁿBu)₂] (where TMP is 2,2,6,6-tetramethylpiperidide) which can regioselectively perform a double metalation of functionalized arenes^[15] (including amides or carbamates in positions 2 and 5, through a directing *ortho-meta*' metalation, *DomM*; or anilines in positions 3 and 5 through a directing *meta-meta*' metalation, *DmmM*). In addition unfunctionalized polyaryl systems are also subject to metalation at the *meta-meta*' sites,^[16] to generate 'inverse crowns'^[17] whereby the metalated arene dianions are trapped within a cationic ring. With the aim of generating aromatic carbon-halogen bonds and new polyfunctional arenes, the organometallic species thus obtained can be subsequently exposed to an electrophilic addition reaction with iodine, forming *ortho-meta*'- or *meta-meta*' diiodoarenes.^[15-16]

Also pertinent to this study, polyfunctional arenes can be prepared via metal-halogen exchange reactions (*i.e.*, transforming C-halogen bonds to C-metal bonds). The lithium-

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halogen exchange reaction has been known since the 1930s.^[9-10, 18] The main disadvantage of using lithium reagents is that the subsequent aryllithium is generally highly reactive, due to the high ionicity of the C-Li bond formed, and is thus not compatible with many functional groups. Over the past two decades, the Knochel group has widely explored the metal-halogen exchange reaction using various organometallic reagents, focusing primarily on magnesium reagents.^[18-19] This has proven to be a valuable methodology in the synthesis of polyfunctional organometallic intermediates^[2b, 18-20] due to the less ionic character of C-Mg bonds, allowing for a considerably slower, but often more selective, exchange for magnesium reagents in comparison to their lithium counterparts. To maximize efficiency and selectivity Knochel and co-workers developed the chemistry of lithium salt-enhanced 'turbo'-Grignard reagents (e.g., ⁱPrMgCl·LiCl), where the LiCl additive considerably improves the efficiency of Mg insertion into various aromatic and heterocyclic carbon-iodine and carbon-bromine bonds.^[18, 19b, 21] ⁱPrMgCl·LiCl has also shown great functional group tolerance under mild reaction conditions as well as delivering high levels of chemoselectivity. Recently we have reported the first examples of metal-halogen exchange using bimetallic sodium-magnesiates which incorporate chiral phenoxide ligands.^[22] Zn-halogen exchange reactions of aromatic halides have also been investigated to prepare arylzinc compounds, which can then be used, for instance, in Negishi cross-coupling transformations.^[23] The C-Zn bond is relatively covalent and tolerates most of the functional groups; however, the less polar dialkylzinc compounds used require additives, such as Li(acac), (acac is acetylacetonate) for the Zn/I-exchange reaction to occur effectively. An important example was published by Hevia, based on a magnesium tris(*tert*-butyl) zincate reagent, that efficiently promotes Zn/I-exchange reactions of different functionalized aromatic halides in THF, avoiding the use of additives and in a high atom economic exchange process.^[24]

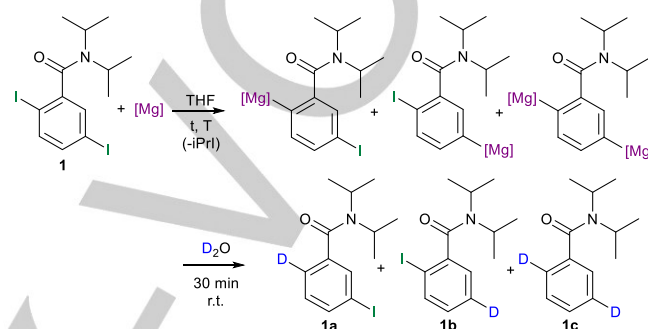
Despite the examples discussed here, the number of regioselective metal/halogen-exchange reactions, which occur when there are at least two identical halogens present in inequivalent positions of an aromatic ring, is relatively scarce.^[21a, 25] On the basis of these precedents, we envisioned that we could use the diiodo-compounds, which we have prepared previously via templated metalation,^[15] and attempt to subject these to regioselective metal/halogen-exchange reactions. As such this dual metalation/metal-halogen strategy acts as a convenient tool to prepare hitherto difficult to synthesize arenes with at least three different substitutions. Additionally, the protocols have also allowed us to develop a complementary tool to DoM, which can be thought of as InDirect *meta*-Metalation (IDmM).

Results and Discussion

The optimization of the work in this paper focused on: (i) choice of diiodo-aryl reagent; (ii) choice of organometallic reagent to initiate the metal-halogen exchange reaction; and (iii) choice of electrophile. Our study commenced by focusing on the single-iodo exchange reaction screening with the electron-poor 2,5-diiodo-*N,N*-diisopropylbenzamide (**1**).^[15] The presence of a strong electron withdrawing substituent in the aromatic ring, such as the amido group, usually accelerates the rates of the halogen-magnesium exchange reactions.^[25a] Our first task was to optimize

the organometallic reagent used to initiate the metal-halogen exchange. The turbo Grignard Reagent ⁱPrMgCl·LiCl, reported by Knochel,^[18, 19b, 21] was employed primarily as it is well known to display high functional group tolerance and can be used under mild conditions.

After performing the metal-iodine exchange reaction, (Scheme 1) the new arylmagnesium reagent was quenched with the simple electrophile D₂O for the initial optimization, primarily due to its commercial availability, ease of use and the considerable recent interest in deuterium incorporation in medicinal chemistry over the past decade.^[26] Of particular note, the Food and Drug Administration (FDA) has recently approved the first deuterium-labelled drug.^[27]



Scheme 1. Mg/I-exchange reaction of 2,5-diiodo-*N,N*-diisopropylbenzamide (**1**) with ⁱPrMgCl·LiCl or ⁱPrMgCl, at different temperatures and times, and subsequent quench with D₂O.

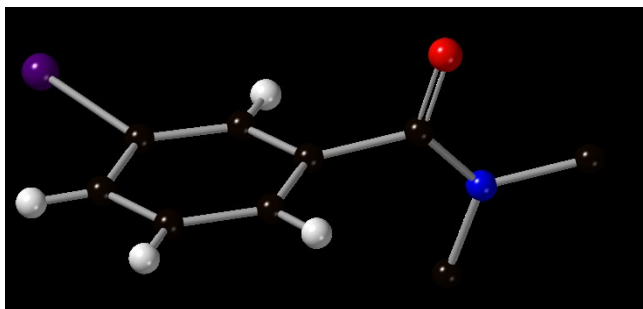
The single magnesium/iodo exchange reaction of diiodoarene **1** with one equivalent of ⁱPrMgCl·LiCl was performed in THF using various reaction times and temperatures. The reaction performed at -20°C for 30 minutes, which was then quenched with D₂O, produced three different products (Scheme 1 and Figure S34). They were isolated and subsequently identified via flash column chromatography, by both NMR spectroscopy and mass spectrometry. The products were identified as the two single exchange reaction isomers **1a** (*ortho*-D) and **1b** (*meta*-D) and the double exchange reaction product **1c** (*ortho*-, *meta*-D) (Scheme 1). In addition to the characterization of the major organic product **1a** by multinuclear NMR spectroscopy, its solid-state structure was determined using X-ray crystallography, unequivocally demonstrating that metal/*ortho*-halogen exchange had occurred (Figure 1). Thus, it appears that the functional group helps direct the exchange reaction to the *ortho* position, obtaining 2-deutero-5-iodo-*N,N*-diisopropylbenzamide **1a** as the major product.

Focusing on the minor isomer **1b**, its NMR spectra are considerably different from those of **1a**. Both ¹H and ¹³C NMR spectra of isomer **1b** show the anticipated signals for the amido group (Figures S6 and S7) due to the presence of the more hindered iodine substituent in the *ortho*-position of the ring.^[28] This group hampers the rotation of both bonds, with a higher barrier to rotation, resulting in clear and discrete sets of signals in the NMR spectra at 300 K. However, isomer **1a** and compound **1c**, with a less hindered deuterium atom in the *ortho*-position to the amido group, present a considerably lower barrier to rotation, which gives rise to broad and unresolved signals (Figures S1 and S9). This observation is in agreement with the assignment of 2-deutero-5-iodo-*N,N*-diisopropylbenzamide **1a** as the major isomer obtained from the Mg/I exchange reaction. Performing a variable

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temperature NMR spectroscopy study helped resolve the NMR spectra for both **1a** and **1c** (see Figures S2, S4, S10 and S11). For instance, ^1H NMR spectrum of **1a**, in CDCl_3 at 300 K, shows two broad peaks (from δ 0.9 to δ 1.8 ppm and from δ 3.3 to 4.0 ppm) for the *iso*-propyl groups ($-\text{CH}_3$ and $-\text{CH}$, respectively). In the meantime, at low temperature, 243 K in CDCl_3 , slow rotation on the NMR timescale occurs and well-resolved and discrete NMR signals are observed at δ 1.13 and 1.50 ppm (doublets of the $-\text{CH}_3$ groups) and at δ 3.48 and 3.78 ppm (septets of the $-\text{CH}$ groups).

Figure 1. Crystal structure of **1a**. Structure further discussed in Figure S70 and Table S1.



Turning to the optimization process, it was observed that both time and temperature play an important role in the final ratio of the three products. The ratio of the undesired di-halogen metal exchange product **1c** considerably increased with longer reaction time and/or higher temperature (Figures S35 and S36) and can be obtained as the major product if the reaction is performed at ambient temperature for 1 hour (Figure 2). On the other hand, both at -20°C and ambient temperature, the desired compound **1a** is formed in a higher ratio after a reaction time of only 10 seconds (*i.e.*, the minimum time required to perform the addition of D_2O to the Mg-organometallic species). This rapid rate of reaction was not unexpected due to the highly electron-withdrawing substituent accelerating the halogen-Mg exchange process, resulting in fast metal-iodine exchange. However, the fact that this reaction is almost instantaneous precludes the study of the organometallic species formed after the iodine-magnesium exchange, limiting the NMR spectroscopic investigation to the deuterated products formed after work up with D_2O .

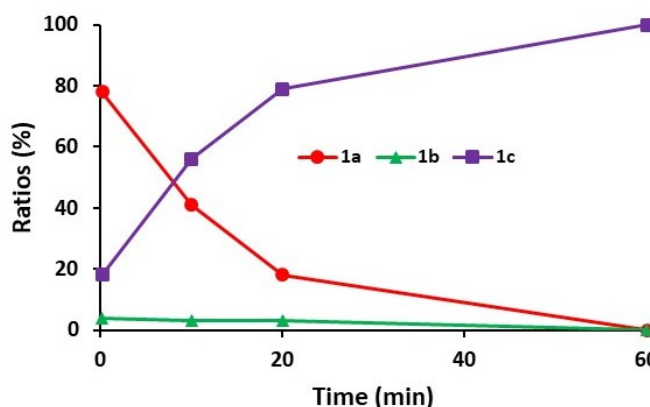


Figure 2. ^1H NMR integration ratios of the Mg/I-exchange reactions of 2,5-diiodo-*N,N*-diisopropylbenzamide (**1**) with $^i\text{PrMgCl}\cdot\text{LiCl}$ performed at ambient temperature for different times, after quenching with D_2O . The first values correspond to 10s reactions.

It is important to highlight here that during this optimization process another crucial factor to consider was the order of addition of the reagents. When a solution of the di-iodo compound **1** in THF is added to a THF solution of the turbo Grignard reagent, the synthesis of **1a** and **1b** is favored; however, when the order of addition is reversed (*i.e.*, the turbo-Grignard is added to the diiodo compound) the formation of the di-magnesium product **1c** after D_2O quench appears to be favored. Presumably, this is due to the fact that when the double metal-halogen exchange is favored when an excess of C-I bonds is available.

A more in-depth look at the effect of reaction temperature (Table 1) revealed that after 10 seconds at -78°C a small quantity of some unreacted compound **1** (5 %) is still present. The yield of desired compound **1a** is 67% yield (against FeCp_2 internal standard), whilst after 60 s, no unreacted compound was observed and the yield of **1a** had modestly increased to 73%. A 60 s reaction at -40°C yields higher amounts of the undesired di-deuterated compound **1c** but when the time is reduced to 10 s at this temperature, the highest yield of isomer **1a** was obtained (75%). The ratio of the other isomer (**1b**) seems to remain almost unchanged.

Table 1. Reaction conditions of the Mg/I-exchange reaction of 2,5-diiodo-*N,N*-diisopropylbenzamide (**1**) with $^i\text{PrMgCl}\cdot\text{LiCl}$ or $^i\text{PrMgCl}$ after D_2O quench.

Entry	Reaction Conditions			Yield (%) ^[a]			
	[Mg]	T ($^\circ\text{C}$)	t (s)	1a	1b	1c	1
1	$^i\text{PrMgCl}\cdot\text{LiCl}$	-78	10	67	5	3	5
2	$^i\text{PrMgCl}\cdot\text{LiCl}$	-78	60	73	4	9	0
3	$^i\text{PrMgCl}\cdot\text{LiCl}$	-40	10	75	5	7	0
4	$^i\text{PrMgCl}\cdot\text{LiCl}$	-40	60	70	5	12	0
5	$^i\text{PrMgCl}$	-78	10	77	5	2	7
6	$^i\text{PrMgCl}$	-78	60	78	6	6	0
7	$^i\text{PrMgCl}$	-40	10	80	6	5	0
8	$^i\text{PrMgCl}$	-40	60	75	6	9	0

[a] ^1H NMR yields (against FeCp_2 internal standard).

To assess whether the alkyl groups of the Grignard reagents, affected the reaction, $^t\text{BuMgCl}$ was also tested. In stark contrast to using $^i\text{PrMgCl}$, the reaction of **1a** with $^t\text{BuMgCl}$ only showed unreacted starting material **1** after 40 min at -40°C . When the same reaction was performed at ambient temperature for either 40 min or 2 h, a complex mixture of products was obtained (Figures S45-S47), including unreacted compound **1**, isomers **1a** and **1b**, di-deuterated compound **1c**, among other unidentified products. Consequently, even though $^t\text{BuMgCl}$ is able to perform the Mg/I-exchange reaction of **1** at ambient temperature, the reaction is slow and completely lacks regioselectivity.

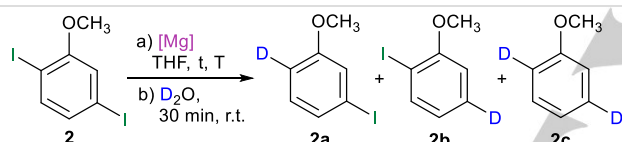
The single lithium/iodine exchange reaction of **1** was also investigated with an equivalent of $^t\text{BuLi}$ at low temperature, but in this case, after D_2O quench, the di-deuterium species **1c**, together with the two possible isomers of the butyl- and deuterium-containing *N,N*-diisopropylbenzamide were formed (Figure S48), as suggested by NMR and GCMS studies of the crude product.^[29] It appears that following this method, a substitution reaction of the

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generated ArLi with ⁿBul occurs, as has been observed in previous studies.^[30] In summary, the optimized conditions for the single Mg/I-exchange reaction of 2,5-diiodo-*N,N*-diisopropylbenzamide (**1**) employs the Grignard reagent, ^tPrMgCl, and is performed at -40°C for only 10 s.

We next investigated the scope of the diiodo-arenes. The two-step dimetalation and Mg/I-exchange protocol was firstly extended to a more electron rich substrate, anisole. Despite the importance of anisoyl fragments in pharmaceuticals (for instance, as a component of the analgesic Tramadol,^[31] and the antidepressant Moxifetin hydrogen maleate^[32]), before 2014 it had only been possible to directly mono-metalate anisole at the *ortho*-position.^[33] Through the sodium magnesiate template approach, our group managed to 2,5-dimetalate anisole and after work-up with iodine produce 1,4-diiodo-2-methoxybenzene (**2**).^[15] In contrast to 2,5-diiodo-*N,N*-diisopropylbenzamide (**1**), the single Mg/I-exchange reaction of **2** with the turbo Grignard reagent ^tPrMgCl·LiCl is considerably slower, likely due to the electron-donating character of the methoxy directing group, and after 10 s unreacted compound is still observed. Longer reaction times, 6 min, allow complete conversion to the two isomers **2a** and **2b** at -40°C, formed in 61% and 31% yield, respectively (Table 2, entry 3). Perhaps surprisingly given the results found with **1**, there is no evidence that the double exchange reaction occurs when **2** is utilized.

Table 2. Reaction conditions of the Mg/I-exchange reaction of 1,4-diiodo-2-methoxybenzene (**2**) with ^tPrMgCl·LiCl or ^tPrMgCl after D₂O quench.



Entry	Reaction Conditions			Yield (%) ^[a]			
	[Mg]	T (°C)	t (min)	2a	2b	2c	2
1	^t PrMgCl·LiCl	-78	5	23	10	0	60
2	^t PrMgCl·LiCl	-78	35	56	28	0	8
3	^t PrMgCl·LiCl	-40	6	61	31	0	0
4	^t PrMgCl	-78	15	66	7	0	16
5	^t PrMgCl	-78	35	80	11	0	2
6	^t PrMgCl	-40	15	82	10	0	0

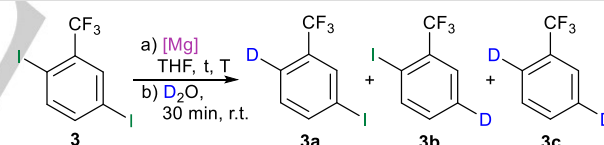
[a] ¹H NMR yields (against FeCp₂ internal standard)

As expected, when the Grignard reagent ^tPrMgCl was used as the exchange reagent, longer reaction times were required but encouragingly **2a**, with the deuterium atom in the *ortho* position, is obtained, after quenching with D₂O, in a higher yield (82%). Isomer **2b** was only formed in a yield of 10%. Unreacted diiodo-anisole **2** was always observable where the same reaction conditions were carried out, even after 35 min at -78 °C (Table 2, entry 5). To a greater extent than that which was observed for **1**, the absence of LiCl is even more favorable for the formation of **2a**, at -40°C. An attempt to force the double Mg/I-exchange reaction of **2** with two equivalents of ^tPrMgCl·LiCl for 5 h at ambient temperature, failed: with only **2a** and **2b** being observed. This suggests that the second Mg/I-exchange is more difficult to

achieve for the electron-rich diiodo-anisole **2**, than for electron-deficient **1**, indicating that the most electron poor iodine undergoes the reaction faster and substituent effects decrease with increasing distance from the reaction center, in agreement with the observations of the Knochel group.^[34]

We next focused on 1,4-diiodo-2-(trifluoromethyl)benzene (**3**), which has a strongly electron withdrawing CF₃ group. This trifluoromethyl group presents a relatively sterically demanding, highly hydrophobic and electron-rich nature, and therefore offers a distinctive chemical and physiological stability,^[35] with important applications in medicinal chemistry and drug discovery.^[36] Due to the anticipated low boiling points of the expected products, we considered it appropriate to perform these reactions in D₈-THF, in order to avoid solvent removal. Thus, yields were directly obtained by ¹H NMR experiments of the reaction crudes in D₈-THF, against a FeCp₂ internal standard. Mg/I-exchange reactions of **3** with either ^tPrMgCl·LiCl or ^tPrMgCl proceed slower than the same reactions using **1** as substrate, after 10s at -40°C the ¹H NMR spectra reveal some unreacted starting diiodo species **3** (Table 3, entries 1 and 3). When the reaction time is increased to 60 s (^tPrMgCl·LiCl) or 70 s (for ^tPrMgCl) all of the starting material was consumed (it was not observed by either ¹H NMR spectroscopy nor GCMS experiments) giving the corresponding 1-deutero-4-iodo-2-(trifluoromethyl)benzene **3a** in 71% and 79% yield, respectively (Table 3, entries 2 and 4). The isomer **3b** and the di-deuterium product **3c** were observed in 3% and 10% yields, respectively, when ^tPrMgCl·LiCl was used, and in 2% and 5% yields when the Mg source is employed in the absence of LiCl. The double exchange product (**3c**) could be obtained in a 75% yield after a two-hour reaction time at ambient temperature employing two equivalents of ^tPrMgCl·LiCl (Table 3, entry 5).

Table 3. Reaction conditions of the Mg/I-exchange reaction of 1,4-diiodo-2-(trifluoromethyl)benzene (**3**) with ^tPrMgCl·LiCl or ^tPrMgCl after D₂O quench.



Entry	Reaction Conditions			Yield (%) ^[a]			
	[Mg]	T (°C)	t (s)	3a	3b	3c	3
1	^t PrMgCl·LiCl	-40	10	66	3	8	7
2	^t PrMgCl·LiCl	-40	60	71	3	10	0
3	^t PrMgCl	-40	10	73	2	5	6
4	^t PrMgCl	-40	70	79	2	5	0
5	2 ^t PrMgCl·LiCl	r.t.	2 h	0	0	81	0

[a] ¹H NMR yields (against FeCp₂ internal standard).

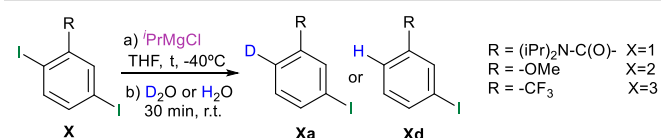
Once the two-step protocol combining dimetalation and Mg/halogen-exchange reactions was successfully implemented in different substrates (**1-3**), and after quenching with D₂O new deuterium-containing species could be obtained, we decided to simply use H₂O. Considering that the Mg/I-exchange arises selectively, under the conditions tested, in the iodine *ortho* to the functional group for **1-3**, if water is used as the electrophile, a facile route to obtain *meta*-substituted arenes is forthcoming. This

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objective is particularly desirable and challenging since *meta*-substituted arenes cannot be easily obtained by conventional processes. We applied this indirect *meta*-metalation process to diiodo-arenes **1-3**, combining the template base dimetalation with the I/Mg-exchange reaction (under the effective reaction conditions for each case) and quenching the organometallic intermediate species thus obtained with water. *Meta*-iodo products **1d**, **2d**, **3d** were obtained in good yields (against FeCp₂ internal standard) 79%, 81% and 80%, respectively.

Following the optimal conditions, it was possible to increase the reaction scale thus allowing isolation and purification of the desired products via column chromatography (Table 4). The isolated yields were consistent with the calculated NMR spectroscopic yields against FeCp₂ internal standard, in all the cases. In addition, H₂O could be used as the electrophile to produce the desired proto-arene (**1d**, **2d** and **3d**).

Table 4. Scaled up reactions of **1-3** (0.33 mmol) using ⁱPrMgCl at -40°C for specified times (t) followed by D₂O quench.

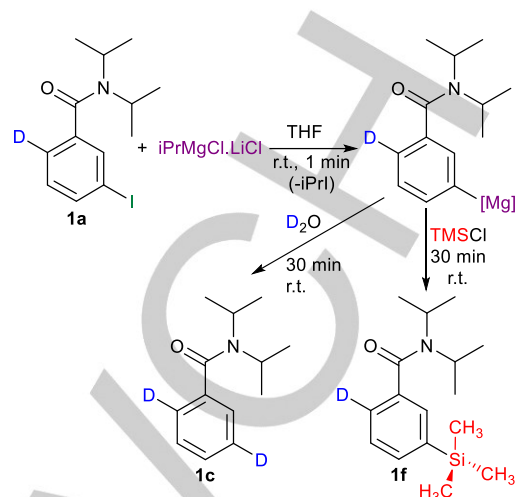


Entry	Substrate ^[a]	Electrophile	t	Product	Yield (%) ^[b]
1	1	D ₂ O	10 s	1a	81
2	2	D ₂ O	15 min	2a	81
3	3	D ₂ O	70 s	3a	78 ^[c]

[a] 0.33 mmol. [b] Isolate yield by mass [c] ¹H NMR spectroscopic yield (against FeCp₂ internal standard) due to product volatility.

Finally, the obtained deuterio-iodo-arenes can participate in another Mg/I-exchange reaction, thus significantly expanding the scope of *meta*-arene chemistry. As proof of concept, we exposed 2-deutero-5-iodo-*N,N*-diisopropylbenzamide (**1a**) to one equivalent of ⁱPrMgCl·LiCl for a 1 min reaction at room temperature (Scheme 3). After this time the corresponding Mg-species were quenched with both D₂O and TMSCl, obtaining only the di-deutero species **1c** (93% ¹H NMR yield) and the new species **1f** (91% ¹H NMR yield). In addition, this reaction proves that a great range of new, and so far, difficult to obtain, *meta*-substituted arenes can be more easily accessible by this tandem template metalation and Mg/I-exchange reactions.

Scheme 2. Mg/I-exchange reaction of 2-deutero-5-iodo-*N,N*-diisopropylbenzamide **1a** with ⁱPrMgCl·LiCl, at ambient temperature for 1 min, and subsequent quench with D₂O and TMSCl.



Conclusion

In summary, we have reported an efficient combined strategy, based on the tandem template metalation and Mg/I-exchange reactions, for converting di-iodoarenes into the corresponding mono-magnesiates into the corresponding mono-magnesiates into the corresponding mono-magnesiates into the corresponding mono-magnesiates in THF at -40°C, within seconds (or minutes) and in good yields. The functional group of the di-iodoarenes helps direct the exchange reaction to the *ortho* position, leaving an unreacted iodo-functionality in the *meta* position that can experiment a second Mg/I-exchange reaction. A facile indirect route to obtain *meta*-substituted arenes is available when H₂O is used as the electrophile to quench the magnesiate intermediate.

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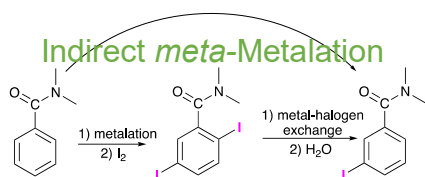
Keywords: metalation • metal-halogen exchange • alkali metals • magnesium • *meta*-activation

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Entry for the Table of Contents



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A tandem template metalation and Mg/I-exchange strategy has been used to convert simple arenes into the corresponding *meta*-substituted arenes in good yields.

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