Regioselective Bromine/Magnesium Exchange for the Selective Functionalization of Polyhalogenated Arenes and Heterocycles

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Abstract: Using the bimetallic combination sBu₂Mg·2LiOR (R = 2-ethylhexyl) in toluene enables efficient and regioselective Br/Mg exchanges with various dibromo-arenes and -heteroarenes under mild reaction conditions and provides bromo-substituted magnesium reagents. Assessing the role of Lewis donor additives in these reactions revealed that N,N,N',N''-pentamethyldiethylenetriamine (PMDTA) finely tunes the regioselectivity of the Br/Mg exchange on dibromo-pyridines and quinolines. Combining spectroscopic with X-ray crystallographic studies, light has been shed on the mixed Li/Mg constitution of the organometallic intermediates accomplishing these transformations. These systems reacted effectively with a broad range of electrophiles, including alky bromides, ketones, aldehydes, and Weinreb amides in good yields.

Functionalized halogenated arenes and heteroarenes are key tools for constructing pharmaceuticals, materials, and natural products. Several metal-mediated approaches for the functionalization of polyhalogenated substrates have been developed to access these valuable molecules, including regioselective zinc insertion in the presence of LiCl on dihalogenated (hetero)arenes. Contrastingly, halogen/magnesium exchange, one of the most powerful methods to functionalize haloarenes, has shown limited success for this type of substrates in terms of versatility and regioselective tunability. Some exceptions include the use of iPrMgCl·LiCl (1a, turbo-Grignard reagent), which can promote selective Br/Mg exchanges in THF. Improved regioselectivities have also been achieved using bulkier variations of 1a containing mesityl or 2,4,6-trisopropylphenyl substituents.

Recently, it was shown by some of us that mixed-metal compositions sBuMgOR·LiOR (1b) and to a greater extent the stoichiometric variant sBu₂Mg·2LiOR (R = 2-ethylhexyl, 1c) can promote Br/Mg exchanges in toluene or other non-polar solvents with an excellent substrate scope when operated at room temperature. While formation of lithium magnesiates was postulated, the constitution of the organometallic intermediates involved has not yet been determined. Expanding further the synthetic utility of these alkyl/alcoholate s-block metal combinations, herein, we report fast and highly regioselective Br/Mg exchanges on various dibromo-arenes and -heterocycles using sBu₂Mg·2LiOR (R = 2-ethylhexyl, 1c) in toluene. Interestingly, in some cases, the addition of Lewis donors such as PMDTA activates a regioselectivity switch, an operation that can be rationalized on consideration of the bimetallic constitution of the organometallic intermediates in these exchanges.

We commenced our studies assessing the regioselectivity of the Br/Mg exchange on 2,4-dibromoanisole (2a) with several mixed Li/Mg combinations (Table 1).

First, we treated 2a with iPrMgCl·LiCl (1a) in THF at 25°C for 2 h, giving an 85:15 ratio of the two regioisomeric magnesium species 3a and 4a, respectively, with a conversion of 87% (Table 1, entry 1). The preferential formation of 3a may be explained by assuming a coordination of the exchange reagent to the neighboring methoxy substituent, reminiscent of the complex-induced proximity effect (CIPE) in aromatic ortho-lithiations. In an attempt to improve the regioselectivity by maximizing coordination effects between the substrate and the exchange reagent, ethereal THF was replaced with ethereal toluene in the regiochemical analysis of reaction aliquots after aqueous quench.

Table 1: Screening of the regioselective Br/Mg exchange on 2,4-dibromoanisole (2a).

| Entry | Exchange reagent[a] | Solvent | t [min] | Ratio 3a/4a | Conv. [%][b] |
|-------|----------------------|---------|---------|------------|------------|
| 1     | iPrMgCl·LiCl (1a)    | THF     | 120     | 85:15      | 87[a]      |
| 2     | sBuMgOR·LiOR (1b)    | toluene | 30      | 99:1       | 75[b]      |
| 3     | sBu₂Mg·2LiOR (1c)    | toluene | 5       | 99:1       | 99[b]      |

[a] Y = Cl·LiCl. [b] Y = OR·LiOR. [c] Y = anisyI-2-LiOR. [d] R = 2-ethylhexyl, these reactions were carried out at 0.50 M using 1.2 equiv of alkylmagnesium species. Reagents are displayed according to their stoichiometry and not to their actual structure. [e] Conversion determined by GC-analysis of reaction aliquots after aqueous quench.
by non-polar toluene and sBuMgOR-LiOR\(^{[7]}\) (R = 2-ethylhexyl, 1b) was used as exchange reagent. Thus, treatment of 2a with 1b led after 30 min to the regioselective formation of 2-anisylmagnesium species 3a (3a/4a = 99:1) although with a lower conversion than 1a (75%, Table 1, entry 2). However, using the more activated reagent sBuMg2LiOR (1c, 0.6 equiv), which was readily prepared by mixing sBuLi (2.0 equiv) with Mg(OR),\(^{[7]}\) magnesiation of 2a with 1c was complete after just 5 min affording 3a (3a/4a = 99:1, Table 1, entry 3).

Different sets of substrates and electrophiles were investigated next. Thus, Cu-catalyzed allylation\(^{[11]}\) of 3a furnished 5a in 72% yield (Scheme 1). Similarly, electron-rich 2-bromoaryl ethers 2b–2d underwent complete Br/Mg exchange at the C(2) position upon treatment with 1c (25 °C, 5 min). The corresponding diarylmagnesium (3b–3d) was smoothly thiomethylated with MeSO\(_2\)SMe, acylated with N-methoxy-N-methylacetamide or allylated with methallyl bromide, producing the bromoaryl ethers 5b–5d in 64–87% yield. Analogously, 3,5-dibromo-2-methoxypyridine (2e) was regioselectively converted into the ortho-metalated compound 3e. After allylation with methallyl bromide, addition to a ketone, or transmetalation with ZnCl\(_2\)\(^{[12]}\) followed by Pd-catalyzed Negishi cross-coupling with 4-iodobenzonitrile, \(^{[13]}\) the functionalized bromopyridines 5ea–5ec were isolated in 53–81% yield. In addition, 2-bromopyridines (2f–2g) led to the corresponding 2-magnesiated pyridines (3f–3g), which gave after thiomethylation or acylation with a Weinreb amide\(^{[14]}\) the products 5f–5g in 60–66% yield. As an application, we have prepared the xanthone 5ab, a precursor of a type II dehydroquinase inhibitor (antibacterial properties).\(^{[15]}\) Thus, the selective magnesiation of 2a followed by a Cu-catalyzed acylation with 2-fluorobenzoyl chloride produced the benzophenone 5aa in 75% yield. BBr\(_3\)-deprotection of the methoxy group and mild K\(_2\)CO\(_3\)-mediated ring closure furnished the target xanthone in 96% yield (Scheme 1).\(^{[16]}\)

We next turned our attention to 2,5-dibromo-3-methylthiophene (6a), for which the exchange reagent 1c did not provide satisfactory regioselectivity (99% conversion, 7a/8a = 90:10, Scheme 2).\(^{[17]}\) Since previous works have shown that, used as additives, Lewis donors\(^{[6a,10]}\) can enhance regioselectivities in halogen/metal exchange processes, we next probed the effect of adding N,N,N',N'-tetramethylethylenediamine (TMEDA)\(^{[18]}\) or PMDTA (0.6 equiv) to 1c, which led to the formation of 7a with a better control of regioselectivity (96:4, 99% conversion for TMEDA, and 99:1, 99% conversion for PMDTA).

Trapping of 7a with 3-methoxybenzaldehyde afforded the alcohol 9a in 80% yield (Scheme 3). This donor effect was quite general and the same procedure was extended to other polyhalogenated (hetero)arenes. Thus, 6b–6d underwent complete Br/Mg exchange upon treatment with 1c·PMDTA, leading to the less sterically hindered magnesium species. After allylation or addition to Michler’s ketone, the polyfunctionalized products 9b–9d were isolated in 61–83% yield.
Interestingly, investigating the reactivity of 1c towards 2,5-dibromopyridine (10a) established that the regioselectivity of the Br/Mg exchange can be finely tuned, switching from C(2) to C(5) in the presence of Lewis donor PMDTA (Table 2).

**Table 2:** Br/Mg exchange on 2,5-dibromopyridine (10a) using various exchange reagents.

| Entry | Exchange reagent[c] | Solvent | Reaction time | Ratio | Conv. [%][a] |
|-------|---------------------|---------|---------------|-------|--------------|
| 1     | iPrMgCl·LiCl (1a)   | THF     | 120 [min]    | 11a:12a | 99:1 | 94%
| 2     | sBu2Mg·2LiOR (1c)   | toluene | 30            | 1:99   | 99%          |
| 3     | 1c·PMDTA            | toluene | 30            | 99:1   | 99%          |

[a] Y = Cl·LiCl. [b] Y = pyridyl·2LiOR·PMDTA. [c] R = 2-ethylhexyl; these reactions were carried out at 0.50 equiv using 1.2 equiv of allylmagnesium species. Reagents are displayed according to their stoichiometry and not to their actual structure. [d] Conversion determined by GC-analysis of reaction aliquots after aqueous quench.

Thus, 10a underwent selective Br/Mg exchange with turbo-Grignard iPrMgCl·LiCl (1a) at C(5) position to give the thermodynamically more favored product 11a (Table 2, entry 1). Alternatively, using sBu2Mg·2LiOR (1c) in neat toluene furnished the kinetic C(2)-magnesiation product 12a (Table 2, entry 2). While this regioselectivity is unprecedented for Br/Mg exchanges, previous studies using organolithium reagents have shown that the C(2)-lithiation product isomerises quickly to the more stable C(5)-lithiated species. Furthermore this unusual regioselectivity can be switched to C(5)-magnesiation by adding PMDTA (0.6 equiv) to 1c (Table 2, entry 3). Conditions A and B described in entries 3 and 2, respectively, of Table 2 were then applied to various dibromopyridines and -quinolines (Scheme 4).

Thus, following Conditions A (1c·PMDTA, 0.6 equiv, toluene, –20 °C, 30 min), 10a was regioselectively converted into 11a which was trapped with 3-bromocyclohexene, affording the C(5)-allylated product 13a in 72% yield. Using Conditions B (1c, 0.6 equiv, toluene, –20 °C, 30 min), 10a was regioselectively converted into 12a which was quenched with benzaldehyde, leading to the alcohol 14a in 74% yield. Analogously, the methyl-substituted pyridines 10b–10d, either using Conditions A or B, produced the expected regioisomeric pyridylmagnesium derivatives, which were trapped by allylation, thioalkylation or acylation, affording 13b–13d and 14b–14d in 52–98% yield. The electron-deficient 2,5-dibromo-4-chloro-3-fluoropyridine (10e) underwent smooth Br/Mg exchange under Conditions A or B, forming—after addition of allyl bromide—the allylated compounds 13e–14e in 72–84% yield. This Br/Mg exchange was extended to 2,4-dibromopyridine (10f) and 2,4-dibromoquinoline (10g). The expected regioisomeric products 13f–13g and 14f–14g were isolated after thioalkylation, allylation or addition of diacyclopentyl ketone in 57–78% yield.

*Scheme 4.* Reaction of various dibrominated heteroarenes with sBu2Mg·2LiOR·PMDTA (1c·PMDTA, Conditions A) or 1c alone (Conditions B), followed by electrophilic functionalization.

Intrigued by this unique reactivity and the profound effect that Lewis donors cause on the regioselectivity of the Br/Mg exchange reactions, we next studied the constitution of these organometallic intermediates prior to electrophilic interception. Firstly, 1c was prepared in situ and reacted with 2-bromoanisole (15, 2.0 equiv, toluene, 25 °C, 30 min), affording a pale yellow solution which deposited colourless crystals of [Ar2OR(Mg)Li]2 (16, Ar = o-MeO-C6H4, R = 2-ethylhexyl, Figure 1).

X-ray crystallographic studies confirmed the bimetallic constitution of 16, which exists as a centrosymmetric contact-pair dimer. Demonstrating that these reactions are genuine Br/Mg exchanges, the Mg is attached to two ortho-metalated anisole groups, occupying the position previously filled by Br atoms in 15. Alkoxide bridges complete the Mg coordination sphere. Contrastingly, the Li atom only binds to one OR ligand, achieving further coordinative stabilization via two OMe groups from the metalated anisole molecules. This special coordination of the Li atoms could be responsible for the marked Lewis donor effect observed in the regioselective control in these Br/Mg exchanges (see above). Thus, PMDTA could preferentially chelate the Li atoms, precluding their interaction with the donor substituents of the substrate, ultimately favoring the formation of solvent-separated ion pair species, which would suppress any possible Li/Mg communication. Notably, Mulvey has recently stressed that bimetallic cooperation in deprotonative metalation reactions
is key in order to achieve unique regioselectivities that cannot be replicated by single-metal reagents,[21] as illustrated by the meta-magnesiation of toluene using a sodium magnesiate base in hexane.[22] In these systems, Na acts as an intramolecular Lewis acid to engage the substrate, which, in turn, is deprotonated by the complexed magnesiate anion.

Another significant feature of 16 is that only one equivalent of the lithium alkoxide is incorporated into the final molecular arrangement despite two being present in the exchange reagent sBu2Mg·2LiOR (1c). Further insight into the formation of 16 was gained by monitoring the reactions of 1c with 15 (2.0 equiv) in [D₈]toluene (Figure 1), which showed that 16 is obtained quantitatively along with the concomitant formation of sBuBr and one equivalent of free LiOR.[17] 1H-DOSY NMR supports that the solid state structure of 16 is retained in toluene solution. The activation of both sBu groups in 1c contrasts with the sluggish reactivity of sBuMg or sBuMg(OR) towards 15, showcasing the mediating role of lithium through forming a contacted anionically activated magnesiate species of enhanced Br/Mg exchange ability.[17]

Building on these findings we next assessed the reactivities of iPrMgCl·LiCl (1a) and nBu₂Mg·2LiOR (1d) towards 2-bromo-4-iodoanisole (17, Scheme 5). For this substrate, Li-

directing effects should favor the Br/Mg exchange ortho to the donating OMe group, whereas considering purely the activation of the C—halogen bond, functionalization at the C(4) position via I/Mg exchange should be preferred. Unsurprisingly, turbo-Grignard 1a in neat THF reacts with the most activated site of 17, undergoing exclusively I/Mg exchange, affording, after allylation, the anisole derivative 18 in 85% yield. However, a completely different scenario plays out for 1d in toluene, where coordination effects dominate, encouraging reactivity ortho to the directing OMe group and hence triggering a Br/Mg exchange with a selectivity of 4:1. Subsequent allylation and chromatographical separation furnished 19 in 65% yield (Scheme 5). Supporting this interpretation, and demonstrating the importance of non-coordinating solvent toluene, addition of polydentate donor PMDTA which can chelate Li, switches off this Br/Mg exchange preference, offering an I/Mg exchange only.[17]

Finally, NMR monitoring of the reaction of 2,5-dibromopyridine (10a) with sBu₂Mg·2LiOR (1c) in [D₈]toluene at −20°C for 30 min revealed complete consumption of the starting material, as evidenced by the presence of sBuBr and a distinct set of new resonances which we can attribute to 12a, the product of regioselective C(2) Br/Mg exchange.[17] The most informative signals are those for the C(2) and C(5) positions in the 13C{¹H} NMR spectra which appear at 140.5 and 119.8 ppm, respectively for 10a (Figure 2). After 30 min, complete disappearance of the signal assigned for C(2)–Br is accompanied by emergence of a new resonance in the aromatic region at 203.5 ppm,[23] which is assigned to C(2)–Mg in 12a; whereas the chemical shift of the C(5)–Br hardly changes (118.5 ppm) with respect to the one observed for 10a.

Additionally, 1H-DOSY NMR displays co-diffusion of the three new aromatic resonances related to the metalated arene alongside the signals defined for 2-ethylhexanolate, consistent with them belonging to the same molecular entity in toluene solution with a mean diffusion coefficient of \( D = 4.349 \times 10^{-10} \text{ m}^2 \text{s}^{-1} \).[17] Final observations revealed a second set of alkoxide-related resonances in the aliphatic region of the 13C{¹H} NMR, which did not belong to 12a, but bore a striking

![Figure 1](image1.png)

**Figure 1.** a) Formation of 16 via Br/Mg exchange in [D₈]toluene at room temperature by reacting 1c with 2.0 equiv of 15 with concomitant elimination of LiOR and 2.0 equiv of sBuBr. b) Molecular structure of 16 with displacement ellipsoids at 50% probability, all hydrogen atoms omitted, and with C atoms in 2-ethylhexyl substituents and anisyl rings drawn as wire frames (except for C₃ and C₄iv) for clarity.[20]
similarity to uncomplexed LiOR, as previously observed in the formation of 16.

While 12a is thermally unstable, which precluded its crystallization, on the basis of these studies we can propose a structure similar to that of 16 (Scheme 6) but in this case the C(2) selectivity is driven by the coordination of Li to the pyridine N, guiding the Br/Mg exchange to the C(2) position. If a Lewis donor is added, this lithium-directing effect no longer operates and, as shown in Table 2 and Scheme 4, the selectivity of the Br/Mg exchange switches to the C(5) position.

Scheme 6. Reaction between 1c and 10a displaying regioselective C(2)-Br exchange facilitated by the Li–N interaction to give contacted ion pair lithium magnesiate 12a.

In conclusion, we have reported regioselective Br/Mg exchanges of dibromo(hetero)arenes performed by reagents of the type RMg·2LiOR (R = sBu, nBu, R' = 2-ethylhexyl) in toluene. Addition of a chelating ligand such as PMDTA allowed in certain cases a regioselectivity switch of the exchange. This switch can be rationalized in terms of the bimetallic cooperation between Li and Mg. The preference of Li to coordinate to the Lewis basic sites of the substrate in toluene in the absence of any donor additives guides the Br/Mg exchange to the position adjacent to these basic sites, akin to the CIPE mechanism in metatation chemistry, thus enabling new regioselectivities not available using turbo-Grignard reagents.

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Conflict of interest

The authors declare no conflict of interest.

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