

Halogen–magnesium exchange of *m*- and *p*-iodo or bromo-arenes bearing *ortho*-directing groups through ate complexes

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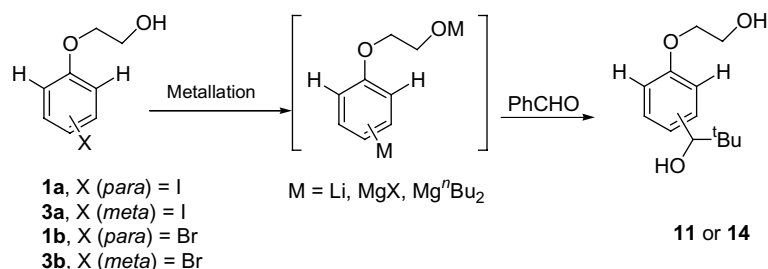
Abstract—*m*- or *p*-Iodinated, or brominated ω -phenoxyalcohols and phenols as well as halogenated indoles were subjected to halogen–magnesium exchange reactions with isopropyl magnesium bromide ($^i\text{PrMgBr}$) or isopropyl magnesium di-*n*-butyl lithium ate complexes ($^i\text{PrMg}^n\text{Bu}_2\text{Li}$) at -78°C to room temperature. $^i\text{PrMg}^n\text{Bu}_2\text{Li}$ proved superior to prevent *ortho*-metallation of these substituted arenes.

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Additional functional groups in organolithium arenes considerably enhance their synthetic utility,¹ but also increase the complexity of their formation especially when an ionizable functional group is present. Typical examples include ω -phenoxyalcohols, phenols, and amides. While *ortho*-lithiation of ω -phenoxyalcohols and ω -phenoxyalkanethiols was reported in the literature,² lithiation of *meta*- or *para*-halogenated ω -phenoxyalcohols (**1–4**) and phenols (**5–6**) by halogen–lithium exchange is nonselective using *n*-butyllithium or by other reductive procedures. One possible competing reaction to the halogen–lithium exchange of *m*- or *p*-halogenated ω -phenoxyalcohols and similar substrates is the *ortho*-lithiation of the aromatic ring.³ To address this issue,

we conducted studies on the metallation of *m*- or *p*-halogenated ω -phenoxyalcohols as well as halogenated phenols and indoles with various organometallic reagents. In our studies, the formed organometallic species were quenched with simple electrophiles such as aldehydes, benzyl bromide and allyl bromide.

A typical example of this effort is shown in Scheme 1. As expected, when *meta*- or *para*-substituted phenoxyalcohols **1a**, **1b**, or **3a**, **3b** were treated with 2 equiv of $^n\text{BuLi}$ at -20°C , halogen–lithium exchange followed by reaction with benzaldehyde, only 3–37% of the desired product **11** or **14** was obtained, along with several by-products associated with nonselective lithiation



Scheme 1.

Keywords: Magnesium–halogen exchange; *ortho*-Directing groups; Ate complexes; Phenoxy alcohols; Phenols.

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Table 1. Iodine–magnesium exchange of aryl iodides

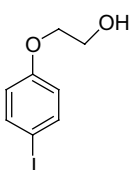
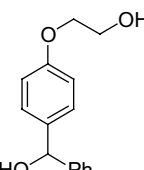
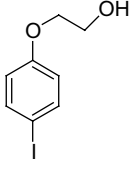
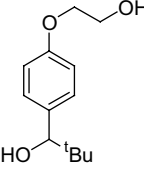
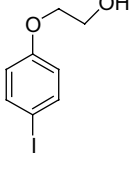
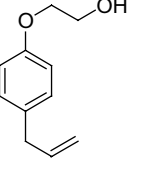
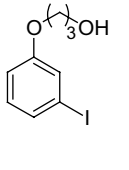
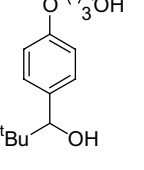
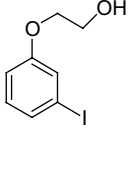
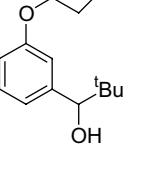
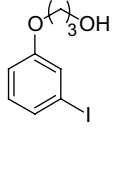
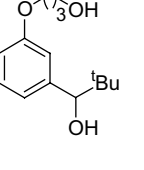
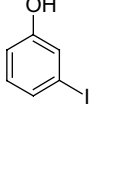
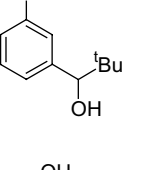
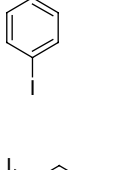
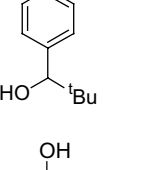
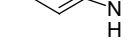
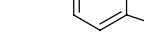
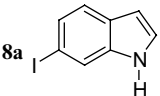
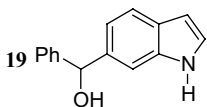
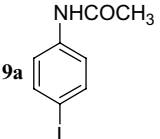
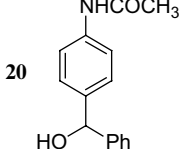
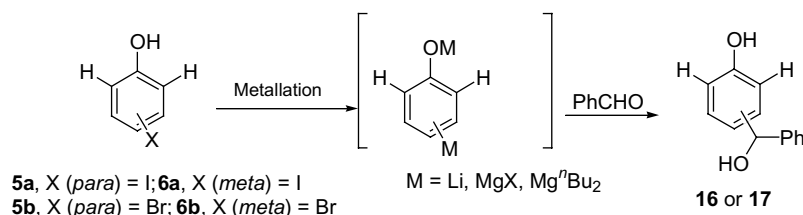
Substrate	Electrophile	Product	Reagent	Condition for M–X exchange	Yield (%)
 1a	PhCHO	 10	ⁿ BuLi	–30 °C, 3 h	3–6
			ⁱ PrMgBr	–10 °C, 3 h	81
			ⁱ PrMgCl	–10 °C, 3 h	57
			ⁱ PrMg ⁿ Bu ₂ Li	–78 °C, 4 h	82
			ⁱ PrMgN ⁱ Pr ₂	–78 °C, 4 h	82
ⁱ PrMg(N ⁱ Pr ₂) ₂	–78 °C, 4 h	82			
 1a	Me ₃ CCHO	 11	ⁱ PrMgCl	–10 °C, 3 h	57
			ⁱ PrMg ⁿ Bu ₂ Li	–78 °C, 4 h	82
			ⁱ PrMgN ⁱ Pr ₂	–10 °C, 4 h	82
 1a	Allyl bromide	 12	ⁱ PrMgCl	–10 °C, 3 h	57
			ⁱ PrMg ⁿ Bu ₂ Li	–78 °C, 4 h	82
			ⁱ PrMgN ⁱ Pr ₂	–10 °C, 4 h	82
 2a	Me ₃ CCHO	 13	ⁿ BuLi	–78 to –10 °C, 3–6 h	5–12
			ⁱ PrMgBr	–10 °C, 3 h	46
			ⁱ PrMg ⁿ Bu ₂ Li	–78 °C, 5 h	77
			ⁱ PrMg ⁿ Bu ₂ Li	–78 °C, 8 h	88
 3a	Me ₃ CCHO	 14	ⁱ PrMgBr	–10 °C, 3 h	66
			ⁱ PrMg ⁿ Bu ₂ Li	–10 °C, 3 h	88
			ⁱ PrMgN ⁱ Pr ₂	–10 °C, 3 h	88
 4a	Me ₃ CCHO	 15	ⁱ PrMgBr	–10 °C, 3 h	66
			ⁱ PrMg ⁿ Bu ₂ Li	–10 °C, 3 h	78
			ⁱ PrMgN ⁱ Pr ₂	–10 °C, 3 h	88
 5a	Me ₃ CCHO	 16	ⁱ PrMgCl	65 °C, 10 min	44
			ⁱ PrMg ⁿ Bu ₂ Li	RT, 1 h	28
 6a	Me ₃ CCHO	 17	ⁱ PrMgBr	65 °C, 10 min	29
			ⁱ PrMg ⁿ Bu ₂ Li	RT, 1 h	44
 7a	PhCHO	 18	ⁱ PrMgBr	65 °C, 10 min	21
			ⁱ PrMg ⁿ Bu ₂ Li	–10 °C, 1 h	94

Table 1 (continued)

	PhCHO		$^i\text{PrMgBr}$ $^i\text{PrMg}^n\text{Bu}_2\text{Li}$	65°C, 10 min –10°C, 1 h	41 84
	PhCHO		$^i\text{PrMgBr}$ $^i\text{PrMg}^n\text{Bu}_2\text{Li}$	65°C, 10 min –10°C, 1 h	41 84



Scheme 2.

(Table 1). We were unable to eliminate the by-products by lowering the temperature. In fact, at –78°C, no reaction was observed for most of the substrates.

We reasoned that in order to suppress these undesired reactions, the metallation potential of butyllithium should be decreased. Very recently, Knochel and co-workers^{4,5} have shown that poly-functional aryl- and alkenylmagnesium reagents⁶ can be prepared by halogen–magnesium exchange reactions with $^i\text{PrMgBr}$. We thought these reagents would be ideal to suppress the undesired side reactions associated with the *ortho*-lithiation of compounds 1–4. We were pleased to find that iodophenoxy alcohols 1a and 3a upon treating with 2.0 equiv of $^i\text{PrMgBr}$ or $^i\text{PrMgCl}$ provided the corresponding organomagnesium reagents in good yields. Normally the reaction was carried out at –10°C to room temperature. Iodine–magnesium exchange for compounds 5a–9a was carried out at 65°C as illustrated in Table 1. To optimize the halogen–magnesium exchange reactions, we also studied the influence of several modified magnesium reagents such as $^i\text{PrMg-N}^i\text{Pr}_2$ and $^i\text{Pr}_2\text{MgN}^i\text{Pr}_2$.

Even though $^i\text{PrMgX}$ and $^i\text{PrMgN}^i\text{Pr}_2$ gave satisfactory results in iodine–magnesium exchange reactions for phenoxyalcohols 1a, 2a, and 4a, poor yields were observed with iodophenols (Scheme 2, 5a and 6a) and iodoindole 7a and 8a (Table 1). All attempts for bromine–magnesium exchange reactions of the corresponding bromo phenoxyalcohols, phenols, and indoles using $^i\text{PrMgX}$ or $^i\text{PrMgN}^i\text{Pr}_2$ were unsuccessful. In order to develop a general method for metallation of aromatic halides containing incompatible functional groups for lithiation, we turned our attention to magnesium ate

complexes such as R_3MgLi . The utility of organometallic ate complexes such as R_2CuLi , R_3ZnLi , R_4AlLi , and R_3MnLi in organic synthesis is well documented.⁷ These complexes are known to induce metal–halogen exchange reactions in some cases.⁸ However, the application of magnesium ate complexes was very little studied since the first report in 1951 until very recently.^{9,10} Indeed, iodine–magnesium exchange of phenoxyalcohols with ate complexes such as $^i\text{PrMg}^n\text{Bu}_2\text{Li}$ proceeded smoothly under mild conditions. For example, treatment of 4a by freshly prepared $^i\text{PrMg}^n\text{Bu}_2\text{Li}$ in THF at –78°C for 3 h gave the corresponding magnesium reagent in very good yield. Much to our delight, bromine–magnesium exchange of the bromo arenes through magnesium ate complexes gave excellent results. For example, 1b, 5b, 6b, and 7b, the bromo analogs of 1a, 5a, 6a, and 7a, gave compounds 10, 16, 17, and 18 in 82%, 74%, 64%, and 100% yields, respectively, when treated with $^i\text{PrMg}^n\text{Bu}_2\text{Li}$ in THF, followed by reactions with appropriate electrophiles. Generally, elevated temperatures were required to perform the bromine–magnesium exchange reactions.^{11b}

It is worth mentioning that this procedure can be extended to other halogenated arenes, which bear an *ortho*-directing group as shown with *p*-iodoacetanilide 9a (Table 1) as well as its bromo analog 9b (88%, structure not shown).

In summary, *m*- and *p*-iodinated, or brominated ω -phenoxyalcohols can be transformed into the corresponding magnesium ω -(*m*- and *p*-magnesiumphenoxy) alkoxides by successive deprotonation followed by halogen–magnesium exchange with $^i\text{PrMgBr}$, $^i\text{PrMgN}^i\text{Pr}_2$, or $^i\text{PrMg}^n\text{Bu}_2\text{Li}$ under mild conditions without

ortho-metallation side reactions. Among the magnesium reagents studied, magnesium ate complexes such as ${}^i\text{PrMg}^n\text{Bu}_2\text{Li}$ are the most efficient reagents for this transformation, suitable for both iodinated and brominated arenes. Subsequent reactions with aldehydes and allyl bromides afforded chemo selective C-alkylated product. This halogen–magnesium exchange procedure can also be extended to functionalize aryl iodides containing phenols, amines, and amides that are known to be difficult substrates for halogen–lithium exchange.

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- (a) *Iodine–magnesium exchange of 1a, a general procedure for iodinated arenes*: To a solution of 2-(4-iodo-phenoxy)-ethanol **1a** (400 mg, 1.51 mmol) in dry THF (10 mL) at -10°C , ${}^i\text{PrMgBr}$ (3.02 mL, 1.0 M, in THF, 3.02 mmol) was added slowly. After 30 min of stirring at -10°C , the reaction mixture was cooled to -78°C and trimethyl acetaldehyde (256 mg, 3.0 mmol) in THF (2 mL) was added to the white suspension and stirred for 3 h. The reaction was quenched with saturated aqueous ammonium chloride solution and washed with brine. The organic layer was dried with sodium sulfate and the solvent was evaporated after filtration. Purification by flash column chromatography (SiO_2 , 1:1 hexanes–EtOAc) yielded **11** as a colorless oil (275 mg, 81%); (b) *Bromine–magnesium Exchange of 2b, a general procedure for brominated arenes*: To a solution of ${}^i\text{PrMgCl}$ (0.6 mL, 2.0 M in THF, 1.2 mmol) in THF (2 mL), was added n -butyllithium (1.5 mL, 1.6 M solution in hexane, 2.4 mmol) at 0°C , and the mixture was stirred for 30 min and cooled to -10°C . A solution of **2b** (130 mg, 0.6 mmol) in THF (2 mL) was added dropwise. After stirring for 0.5 h at -10°C , the mixture was cooled to -78°C and benzaldehyde (0.37 mL, 3.6 mmol, neat) was added. After stirring for 0.5 h at -78°C , the reaction was quenched with saturated aqueous NH_4Cl . The mixture was extracted with ethyl acetate, and the combined organic layers were dried with anhydrous Na_2SO_4 . Concentration and purification by chromatography provided compound **10** (122 mg, 0.56 mmol, 82%).