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A practical non-cryogenic process for the selective functionalization of bromoaryls

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ABSTRACT

A selective and practical bromine–metal exchange process under non-cryogenic conditions was developed by a simple modification of an existing protocol. By directly adding an alkyl lithium RLi reagent to a solution of a bromoaryl substrate ArBr and an alkylmagnesium reagent RMgX, a lithium triarylmagnesiate Ar_3MgLi complex formed that allowed for various types of functionalization and more elaborate cross-coupling reactions. The simplicity and improved safety of the method represent a significant improvement over current state of the art that uses lithium trialkylmagnesiate R_3MgLi complexes, and is especially advantageous for large-scale synthesis.

The halogen–metal exchange reaction is an often used and well established transformation prior to functionalization by either direct electrophilic quench or more elaborate metal-mediated cross-coupling reaction. In the course of our development of a robust and practical process for C–C bond forming reactions from aryl halides, we evaluated variations of commonly used halogen–metal exchange processes and their impact on the efficiency (yield, productivity) and the outcome (formation of regioisomers) of the transformation.

Numerous methods have been reported for halogen–metal exchange reactions,[1] but it still remains a challenge and an interest to the synthetic community, more particularly to process chemists. Direct metalation of aryl bromides with metallic magnesium is a strategy that is often used for the formation of aryl Grignard reagents.[2] However, the relatively limited substrate scope and the inherent safety liability of the reaction constitute process limitations. Alternatively, the bromine–lithium exchange reaction under cryogenic conditions is a strategy which relies on the rapid exchange even at low temperature and the possibility to prepare compounds that are not readily available by direct metalation.[3] The reactivity and stability of the lithiated species under the reaction conditions usually require cryogenic conditions to minimize undesired side-reactions. This becomes all the more important, for example, with aryl bromides bearing directing groups, and thus exhibiting a propensity to isomerize the lithiated intermediate species generated[4] or when aryne formation is likely to occur.[6i]

More recently, Knochel has developed attractive alternatives to prepare functionalized aryl magnesium compounds with activated forms of Grignard reagents.[5] These reagents proceed particularly well for aryl iodides and aryl bromides having electron-deficient or chelating groups, under non-cryogenic conditions and with high selectivity. In the case of aryl bromides with electron-donating groups, specific functionalization patterns, such as aromatic ethers, for example, can be reached only with difficulty and recourse to more elaborate conditions is required.[5a,b] The use of higher-order magnesiate complexes, for example, R_3MgLi that can be conveniently prepared by premixing of alkyl lithium and alkylmagnesium reagents, has here proven to be a particularly powerful solution.[6] Their enhanced reactivity generally allows a smooth bromine–magnesium exchange even in the most unfavored cases, under non-cryogenic conditions. In addition, the absence of regioisomer usually observed even in the case of densely substituted aromatic systems bearing directing groups makes it very attractive for industrial processes. However, a major drawback of this methodology is the need for the preformation of a lithium trialkylmagnesiate complex, thus requiring longer process cycle times and additional in-process controls.

The state of the art for magnesium–bromine exchange reactions prompted us to look for a new methodology which would address simultaneously the selectivity issues, the low temperature requirement, the practicality, and the safety of the process. This Letter details our recent progress in the design of a simple process that consists of a selective, net halogen–magnesium exchange reaction under non-cryogenic conditions. The scope of the new simplified and practical protocol is then illustrated.

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Our study started by a direct comparison of existing methods of bromine–metal exchange reactions on 4-bromoanisole **1**, known to be a poor substrate for bromine–magnesium exchange reactions with RMgX and R_2Mg (R = alkyl) (e.g., Refs. 5a,f). We hoped that careful monitoring of the kinetics and purity profiles for the known bromine–metal exchange reactions would lead us to an improved process. The unambiguous assignment of the product and by-products formed in the course of the reaction was made by conversion of the metalated intermediate into the corresponding benzoic acid **2** with addition of carbon dioxide.

All experiments were run in THF in order to promote a potential isomerization.[7] HPLC-conversion was monitored and results are shown in Graph 1 with the optimal conversions summarized in Table 1. The bromine–lithium exchange reaction using *n*BuLi at −78 °C proceeded very rapidly, selectively, and with high conversion to 4-methoxy benzoic acid **2** (92%, entry 1). An increase of the temperature to −40 °C resulted in a significant drop of efficiency (80% conversion, entry 2) mostly due to numerous subsequent side-reactions.[8] In the case of Grignard reagents, *i*PrMgCl proved to be poorly reactive with only *ca.* 10% conversion after 24 h at 10 °C (entry 3). The presence of lithium chloride additive only resulted in a marginal improvement of the reactivity to 55% conversion after 24 h (entry 4). The more reactive *i*Pr_2Mg·LiCl and *i*Bu_2Mg·LiCl complexes[5a,b] reacted much faster with a maximum conversion at −10 °C of 72% and 78%, respectively, after 6 h and 20 h (entries 5 and 6). The lithium trialkylmagnesiate complexes *n*Bu_3MgLi and *i*Pr*n*Bu_2MgLi[6a,b] gave the fastest and best conversions after less than an hour in 80% and 86% yield, respectively (entries 7 and 8, respectively). In the latter four entries 5–8, a decomposition of the formed aryl magnesium species was observed that reduced the conversion to 4-methoxy benzoic acid.

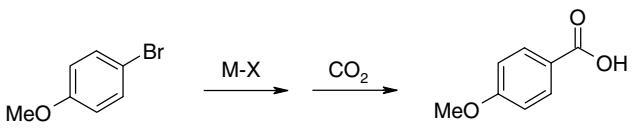
A careful examination of the purity profile and nature of impurities for all these conditions showed that decomposition resulted mostly in the reduced product (**3**), alkyl–aryl (**4** and **5**), aryl–aryl coupling (**6**), and the bis-functionalized acid (**7**) side-products (see Fig. 1).[9,10] Interestingly, only in the case of the bromine–lithium exchange with *n*BuLi did we observe migration of the lithium to the ortho position in up to 3% (compound **8**).[11]

Overall, these preliminary data showed that a bromine–magnesium exchange with Grignard reagent was not kinetically favored while bromine–lithium exchange was rapid, even at −78 °C. The high order magnesiates clearly exhibited the best purity profiles with only Wurtz-type coupling products, which could be further reduced by using branched alkyl Grignard reagents.

We therefore decided to design a system that could lead to a highly reactive lithium triaryl magnesiate intermediate without the need for preforming the lithium trialkyl magnesiate complex.[6a–c] Based on the observations described above, we envisioned that a branched alkyl magnesium halide (used here to minimize the hetero-coupling product formation) would be poorly reactive when added under non-cryogenic conditions to the solution of the aryl bromide. The addition of an alkyl lithium at a controlled rate would then result in a transient aryl lithium compound that would rapidly be transmetalled by the Grignard reagent present in solution.[12] Thus, the lithium triarylmagnesiate complex would form at the end in a process that is a net bromine–magnesium exchange reaction. We evaluated this concept on the model 4-bromoanisole **1** and were delighted to find that it proceeded very efficiently at 0–5 °C in 98% conversion without formation of the regioisomer. Compared to prior state of the art, the revised protocol displays similar efficiency; however, it is now operationally simpler and displays significant safety advantages for large-scale processes.[13]

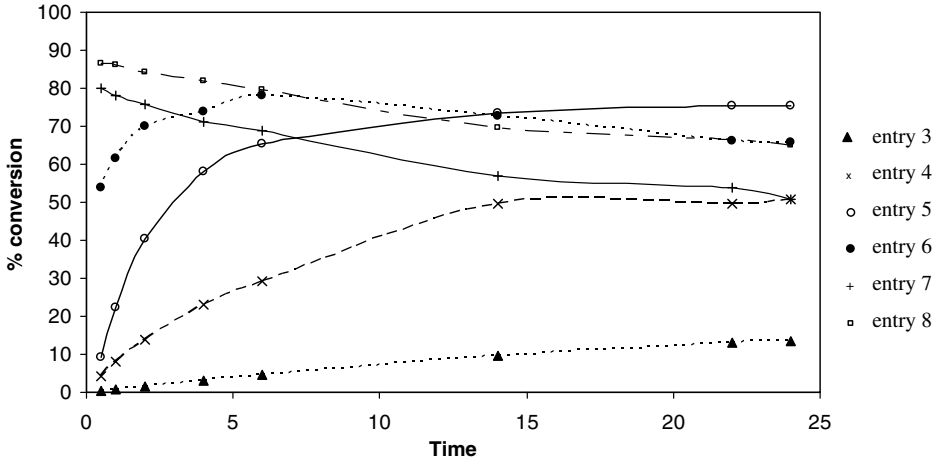
In order to demonstrate the practicality of this simplified protocol, we wanted to utilize the selectively obtained lithium triarylmagnesiate complexes in a known cross-coupling reaction such as, for example, a nickel-catalyzed Kumada–Corriu cross-coupling reaction[14] For example, 4-bromoanisole **1** under our conditions after the net bromine–magnesium exchange reaction was cross-coupled efficiently with bromobenzene in the presence of $NiCl_2$-dppp at 0 °C in 90% overall yield (Scheme 1). The interest of the method becomes clearly apparent here in view of the importance of the biphenyl unit in pharmaceutical drugs.

Table 1

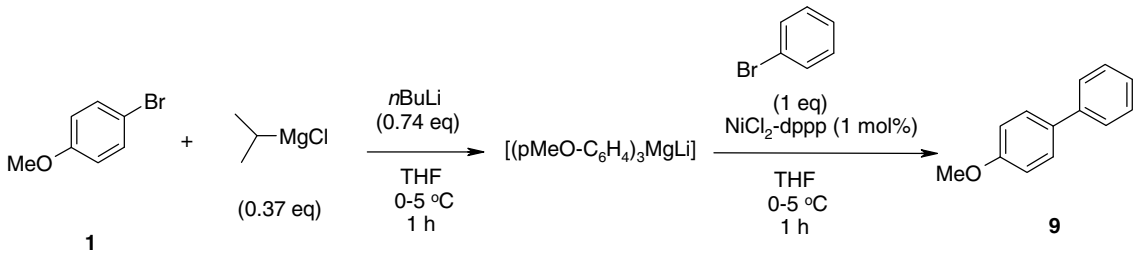


1 **2**

Entry	Conditions	Conversion to **2** (%)
1	*n*BuLi (1.1 equiv), THF, −78 °C, 1 h	92
2	*n*BuLi (1.1 equiv), THF, −40 °C, 1 h	80
3	*i*PrMgCl (1.1 equiv), THF, −10 °C, 24 h	10
4	*i*PrMgCl·LiCl (1.1 equiv), −10 °C, 24 h	55
5	*i*Pr_2Mg·LiCl (0.55 equiv), THF, −10 °C, 6 h	72
6	*i*Bu_2Mg·LiCl (0.55 equiv), THF, −10 °C, 20 h	78
7	*n*Bu_3MgLi (0.37 equiv), THF, −10 °C, 1 h	80
8	*i*Pr*n*Bu_2MgLi (0.37 equiv), THF, −10 °C, 1 h	86



Graph 1. Conversion of 4-bromoanisole **1** to 4-methoxy benzoic acid **2**.



Scheme 1.

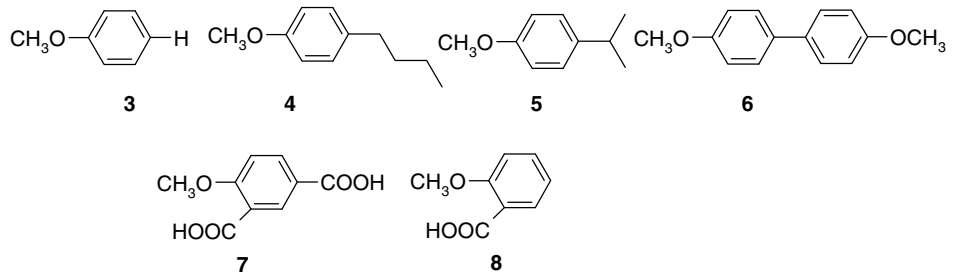
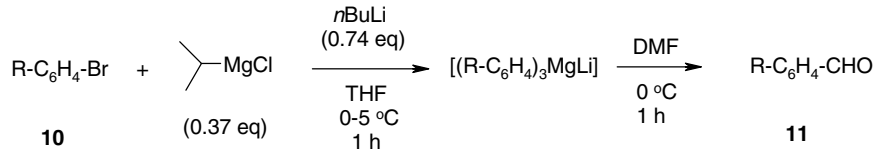


Figure 1. Observed impurities in the bromine–metal exchange reaction.

Encouraged by these results, we then investigated the scope of the revised net bromine–magnesium exchange protocol. We decided here to functionalize the aryl bromides into the corresponding aldehydes after quenching with dimethylformamide. The benzaldehyde products formed can be easily compared to commercially available reference samples. Besides, all benzaldehydes exhibit a well-resolved aldehydic proton signal on the ^{1}H NMR spectra, which allow for the unambiguous assignment of the isomer formed and the extent of the isomerization. The results are summarized in Table 2.

Bromotoluenes (entries 1–3) and bromoanisoles (entries 5–7) reacted smoothly in high yield (yields ranging from 82% to 96%) and with high selectivity as demonstrated by ^{1}H NMR. Only in the case of 3-bromoanisole did we detect formation of an isomer in less than 0.5%. The more substituted 2,6-dimethylbromobenzene (entry 4) gave results consistent with the bromotoluene series. For halobenzene bromides (entries 8 through 16), high selectivity was again observed in all cases. High yields were obtained for the meta and para substitution patterns (yields ranging from 80% to 95%) and low to mediocre for the ortho substitution pattern (yield from 12% to 48%) probably due to benzyne formation as observed by analysis of side-products. The highly selective results obtained in the fluoro series, demonstrated by careful ^{1}H and ^{19}F NMR analyses, were particularly remarkable in view of the known pronounced directing effect of the fluoride atom. Another illustration of the value of our method is the known formylation of 4,4′-bis-bromobiphenyl (entry 17).[6d] With our revised protocol, we obtained for the selective functionalization of the dibrominated substrate[8,15] the same result as those reported with the lithium trialkylmagnesiate complex (Ref. 6d, 82% yield). We then turned our attention to the effect of the trifluoromethyl substituent, also reported to be an effective directing group in halogen–metal exchange reactions (entries 18–20). The series proceeded here with the same trend as for the halobenzene bromides and resulted in modest to good yields (48–72%), and high selectivity. The more functionalized 3,5-bistrifluoromethylbromobenzene (entry 21) also reacted without formation of isomer in 55% yield.[16] The bromophenol series bearing an acidic proton

Table 2



Entry	R	Yield (%)	Entry	R	Yield (%)
1	2-Me	82	16	4-Br	95
2	3-Me	89	17	4(*p*-BrPh)	82
3	4-Me	95	18	2-CF_3	48
4	2,6-Me	94	19	3-CF_3	70
5	2-OMe	90	20	4-CF_3	72
6	3-OMe	96	21	3,5-CF_3	55
7	4-OMe	95	22	2-OH	21
8	2-F	47	23	3-OH	64
9	3-F	81	24	4-OH	56
10	4-F	82	25	2-COOEt	<5
11	2-Cl	48	26	3-COOEt	<5
12	3-Cl	80	27	4-COOEt	<5
13	4-Cl	84	28	2-CN	<5
14	2-Br	12	29	3-CN	<5
15	3-Br	90	30	4-CN	<5

(entries 22–24) gave modest to good yields (yields ranging from 21% to 64%) in addition to high selectivity.[17] In our hands, sodium hydride appeared to be a good sacrificial base to sequester the acidic proton. Finally, the bromo-methylbenzoate (entries 25–27) and the bromobenzonitrile (entries 28–30) series gave no product, presumably due to the incompatibility of the alkyl lithium with the functional groups.

In summary, we have developed a selective and practical net bromine–magnesium exchange process under non-cryogenic conditions by a simple modification of an existing protocol.[19] The lithium triarylmagnesiate complex formed allows for various types of functionalization and more elaborate cross-coupling.[18] Overall, no migration to an extent of more than 0.5% was observed in all our substrates, which compares well to the selectivity observed with lithium trialkylmagnesiate complexes.[6] The method is particularly suitable for poorly reactive aryl bromides but suffers from a poorer substrate scope as expected from the presence of a highly reactive alkyllithium and a functionalized aryl bromide at temperatures above 0 °C, in addition to modest to mediocre efficiency in the case of the *ortho* substituted substrates. The simplicity of the method nevertheless represents a significant improvement over current methodology and is especially advantageous for large-scale synthesis.

Entry	Conditions		Reactant	Product	By-products					
	T (°C)	*t* (h)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
3	20	24	2.3	13.5	<0.1	<0.1	0.4	79.9	1.2	<0.1
4	20	24	3.6	50.9	<0.1	0.4	0.5	41.7	1.0	<0.1
5	20	24	5.4	75.3	<0.1	0.3	0.8	14.6	1.0	<0.1
6	20	24	11.1	16.3	<0.1	<0.1	1.5	65.8	1.2	<0.1
7	20	24	6.8	50.8	23.8	<0.1	3.7	5.4	5.8	<0.1
8	20	24	5.8	65.0	16.1	<0.1	2.8	3.2	4.0	<0.1
7	0–5	2	2.8	80.4	8.6	<0.1	0.4	1.9	2.9	<0.1
8	0–5	2	1.8	92.2	0.9	<0.1	<0.1	1.1	0.9	<0.1

Results reported in HPLC Area % at 210 nm.
Limit of quantitation: 0.1%.

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