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Leaving Group Dependence of the Rates of Halogen−Magnesium Exchange Reactions

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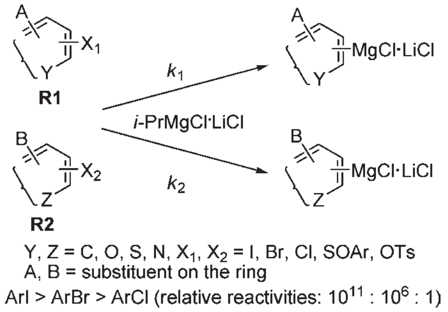
ABSTRACT



Relative reactivities and absolute rate constants of the reactions of haloarenes with *i*-PrMgCl · LiCl were investigated in THF at 0 °C. The rate of the halogen−magnesium exchange decreases in the series ArI > ArBr > ArCl (relative reactivities: 10^{11}:10^6:1). Preliminary experiments show that the *p*-tolylsulfinyl group is exchanged slightly faster than iodide, while a tosyl group is exchanged at least 10^4 times more slowly than a bromide.

Since Grignard's discovery that organometallics of the general formula RMgX can be prepared by the reactions of alkyl halides with magnesium in Et_2O,[1] organomagnesium reagents have become important reagents for the formation of C−C and carbon heteroatom bonds.[2] Currently, the most important methods for the preparation of organomagnesium compounds are (1) direct metalation of organic halides with metallic magnesium;[3] (2) deprotonation of CH-groups with strong Mg-bases;[4] (3) transmetalation of other organometallics;[5] and (4) halogen−magnesium exchange, e.g., by reactions of aryl halides with alkylmagnesium halides.[6−8]

Although halogen−magnesium exchange reactions have already been observed in the early 1930s,[6] they have not

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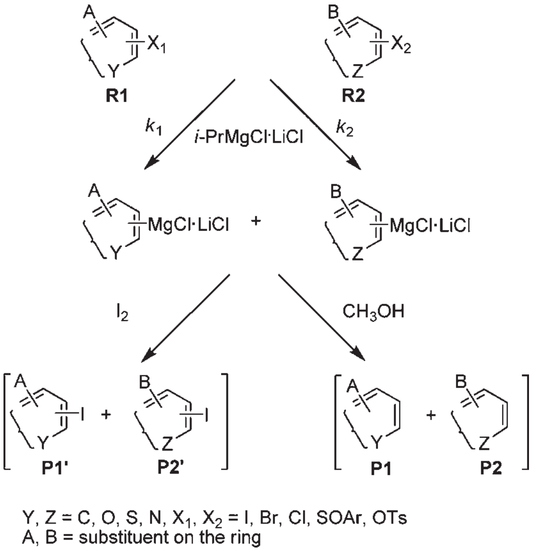
been widely used until recently. One of us[7] demonstrated the applicability of this method for the preparation of functionalized organomagnesium reagents that cannot be obtained by conventional processes. In particular, i-PrMgCl·LiCl was found to be a valuable reagent, as it exhibits a dramatically increased reactivity in halogen–magnesium exchange reactions compared to i-PrMgCl or $(i\text{-Pr})_2\text{Mg}$.[8]

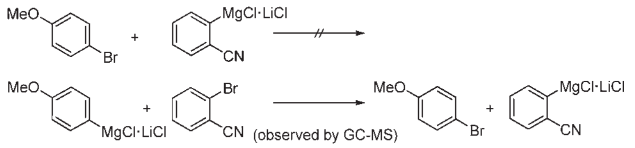
Scheme 1. Determination of the Effect of Leaving Groups on the Rates of Halogen–Magnesium Exchange Reactions



Recently, we investigated the kinetics of the reactions of substituted bromoarenes toward i-PrMgCl·LiCl in THF at 0 °C[9] and demonstrated that the rates of the bromine–magnesium exchange reactions are accelerated by electron-withdrawing substituents in the aromatic ring. The substituent effects decrease with increasing distance between bromine and the substituent under consideration (*para* < *meta* ≪ *ortho*). We now report how the rates of the halogen–magnesium exchange reactions depend on the nature of the halogens and how these data can be used for predicting the regioselectivities of halogen–magnesium exchange reactions of arene derivatives bearing different leaving groups.

The relative rates of halogen–magnesium exchange reactions were determined by competition experiments, where substoichiometric amounts of i-PrMgCl·LiCl (typically 0.33 to 0.5 equiv) were added to mixtures of two different haloarenes in THF at 0 °C. At various times, the composition of the reaction mixture was analyzed by gas chromatographic determination of the product ratios obtained by quenching either with iodine ([**P1′**]/[**P2′**]) or with methanol ([**P1**]/[**P2**]) (Scheme 1).

Scheme 2. Exchange Reactions between Aryl Grignard Reagent and Aryl Bromide



We reported[9] that 2-cyanophenylmagnesium chloride, which formed rapidly and nearly quantitatively from 2-bromobenzonitrile and i-PrMgCl·LiCl, does not undergo an exchange with 4-methoxybromobenzene (0 °C, 8 h), in line with the unfavorable thermodynamics of this reaction (Scheme 2). On the other hand, 4-methoxyphenylmagnesium chloride was observed to undergo a slow exchange with 2-bromobenzonitrile to yield approximately 2% of 2-cyanophenylmagnesium chloride and 4-methoxybromobenzene within 8 h at 0 °C (Scheme 2).

As this reaction was slow compared with the reactions of the bromoarenes with i-PrMgCl·LiCl, we had concluded that the ratios [**P1**]/[**P2**] or [**P1′**]/[**P2′**] reflect the ratios k_1/k_2 defined in Scheme 1.

However, in some cases (e.g., X = I) the product ratios [**P1**]/[**P2**] or [**P1′**]/[**P2′**] were found to depend on the reaction time, indicating that the product ratios are no longer kinetically controlled. Thus, the ratio k_1/k_2 (Scheme 1) cannot simply be derived from the product ratios when aryl derivatives Ar–X are treated with i-PrMgCl·LiCl.

Figure 1 shows that 4-methoxyphenylmagnesium chloride reacts slowly with 1-iodo-2-methylbenzene in THF at 0 °C reaching an equilibrium mixture of arylmagnesium reagents and aryl iodides within 1 h. An analogous observation was made when 2-tolylmagnesium chloride was treated with 1-iodo-4-methoxybenzene under the same conditions (Figure 2).

Both figures show that the exchange reaction between the corresponding arylmagnesium reagents and iodoarenes require about ~1 h for completion, and the degree of conversion is low within 5 min. In line with this observation, the ratio of arylmagnesium halides obtained by the fast reaction of a mixture of two competing iodoarenes with a substoichiometric amount of i-PrMgCl·LiCl was almost the same after 1 and 5 min.

If the exchange between an aryl iodide and an arylmagnesium halide is slow compared with the initial reaction, the relative reactivities of **R1** and **R2** toward i-PrMgCl·LiCl can be expressed by eq 1,[10] as reported previously.[9]

$$\kappa = \frac{k_1}{k_2} = \frac{\log([\mathbf{R1}]_0/[\mathbf{R1}]_t)}{\log([\mathbf{R2}]_0/[\mathbf{R2}]_t)} \qquad (1)$$

Substitution of $[\mathbf{R1}]_0$ and $[\mathbf{R2}]_0$ by the expressions $[\mathbf{R1}]_0 = [\mathbf{R1}]_t + [\mathbf{P1}]_t$ and $[\mathbf{R2}]_0 = [\mathbf{R2}]_t + [\mathbf{P2}]_t$ (mass balance)

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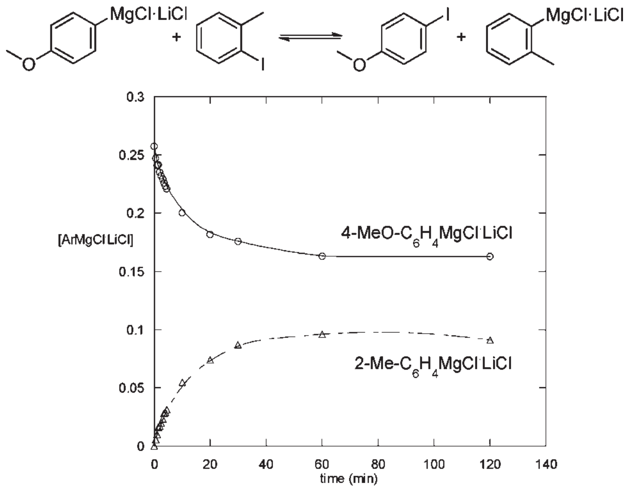

Figure 1. Time-dependent concentrations of 4-methoxyphenylmagnesium chloride (○) and 2-tolylmagnesium chloride (Δ) obtained by treatment of 4-methoxyphenylmagnesium chloride (starting concentration = 0.257 M) with 1-iodo-2-methylbenzene (starting concentration = 0.418 M) in THF at 0 °C.

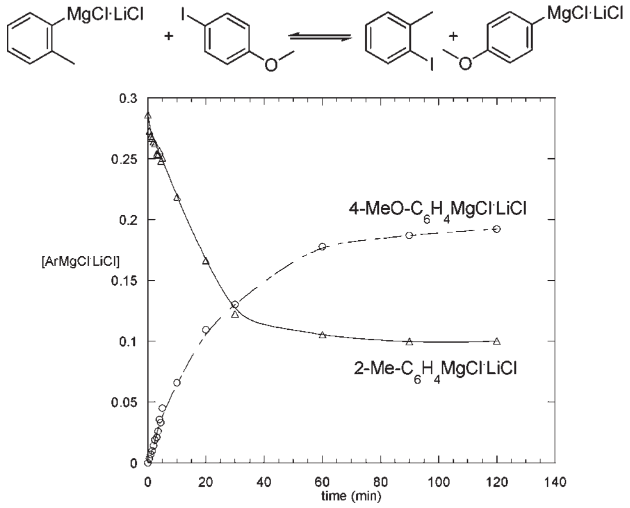

Figure 2. Time-dependent concentrations of 4-methoxyphenylmagnesium chloride (○) and 2-tolylmagnesium chloride (Δ) obtained by treatment of 2-tolylmagnesium chloride (starting concentration = 0.286 M) with 1-iodo-4-methoxybenzene (starting concentration = 0.262 M) in THF at 0 °C.

yields eq 2, which calculates the competition constant κ from the ratios $[\mathbf{P1}]_t/[\mathbf{R1}]_t$ and $[\mathbf{P2}]_t/[\mathbf{R2}]_t$, which were determined by gas chromatography.

$$\kappa = \frac{\log(1+[\mathbf{P1}]_t/[\mathbf{R1}]_t)}{\log(1+[\mathbf{P2}]_t/[\mathbf{R2}]_t)} \qquad (2)$$

Each of the six bold-printed aryl halides shown in Figure 3 was subjected to competition experiments with several

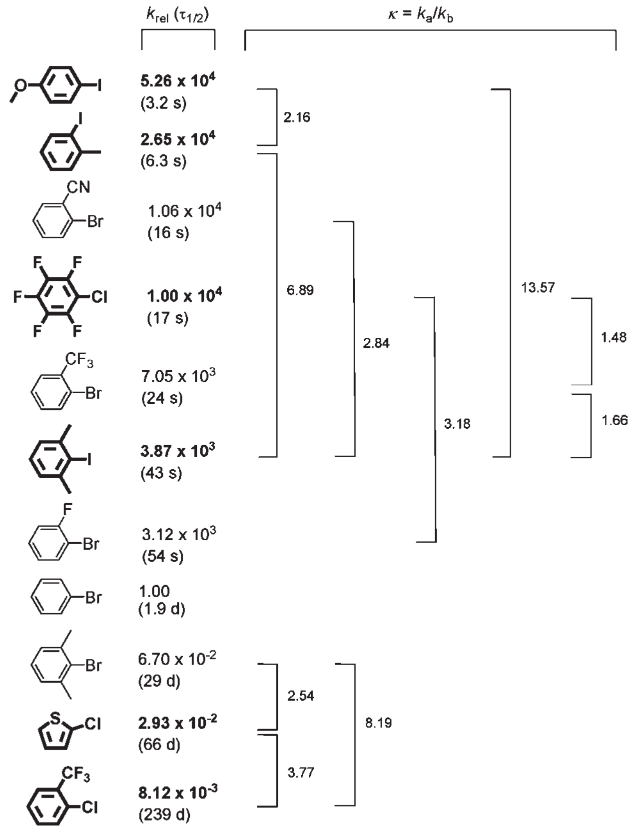

Figure 3. Relative reactivities of haloarenes toward *i*-PrMgCl·LiCl in THF at 0 °C and $\tau_{1/2}$ for 1 M solutions (PhBr = 1.0).

other aryl halides, to give the 10 competition constants κ[11] illustrated in Figure 3. The combination with the previously reported relative reactivities of differently substituted bromoarenes[9] and solving the resulting overdetermined set of linear equations (eq 3) by least-squares minimization yielded the k_{rel} values listed in the left column of Figure 3.

$$\log \kappa = \log k_a - \log k_b \qquad (3)$$

As shown in previous work,[9b] second-order rate constants for several bromine–magnesium exchange reactions have been measured directly, which allows us to estimate absolute rate constants for other aryl halides by multiplying the k_{rel} values (k_{rel} = 1.0 for bromobenzene) with 6.0×10^{-6} $M^{-1}\ s^{-1}$. In this way, we have calculated the half-reaction times[12] listed in Figure 3 for the halogen–magnesium exchange in THF solutions which are 1 M in aryl halide and 1 M in *i*-PrMgCl·LiCl, to give chemists an idea of the time needed for a specific halogen–magnesium exchange.

Though the environment of the halogens in the three analogously substituted bromo- and iodobenzenes (Scheme 3, top) differs significantly, iodine is always exchanged

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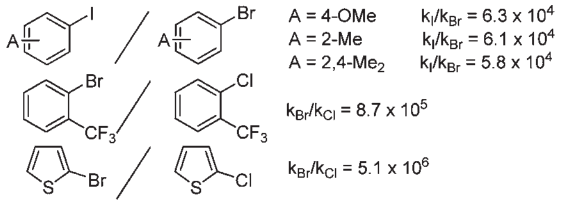
(11) Herein, κ_{calcd} have been calculated by minimizing $\Sigma\Delta^2$, where $\Delta^2 = (\kappa - \kappa_{calcd})^2$ using the program "What's Best! 4.0 Commercial" by Lindo Systems Inc.

(12) $\tau_{1/2} = 1/kc_0$ (k = second-order rate constant, c_0 = initial concentration).

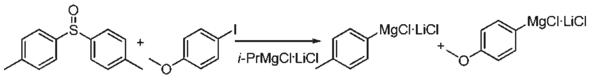
6×10^4 times faster than bromine, which is, therefore, considered to be a typical I/Br ratio. The lower two entries of Scheme 3 show that in, 2-halobenzotrifluoride and 2-halothiophenes, the Br/Cl ratio is in the same order of magnitude ($k_{Br}/k_{Cl} \approx 10^6$) which we consider an approximate value for this pair of halogens.

Scheme 3. Effect of Different Halogens on the Relative Rates of Halogen/Mg Exchange: Data from Figure 3 and Refs 9b and 9c



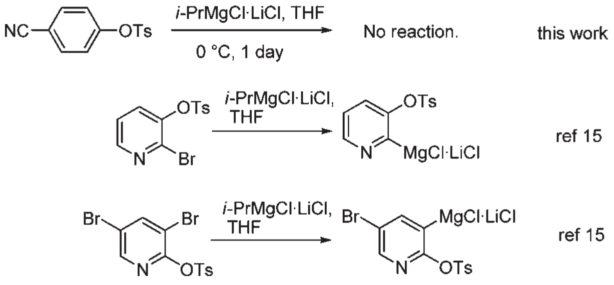
Attempts to determine the arylsulfinyl–magnesium exchange rates of bis(*p*-chlorophenyl)sulfoxide and bis(*p*-tolyl)sulfoxide by competition experiments, as described in Scheme 4, did not yield reproducible results. Probably the aryl sulfoxides are so reactive, i.e., the arylsufinyl group is exchanged so fast, that the corresponding competition constants κ depended on the rate of mixing (macroscopic diffusion control[13]). Though it is not possible to determine precise exchange rates, the approximately 3-times higher reactivity of bis(*p*-tolyl)sulfoxide compared with *p*-iodoanisole indicates that the exchange rate of the *p*-tolylsulfinyl group is of similar magnitude as that of iodine.[14]

Scheme 4. Determination of Relative Arylsulfinyl–Magnesium Exchange Rates



No exchange reaction between *p*-cyanophenyl tosylate and *i*-PrMgCl·LiCl was observed within one day. By comparison with $\tau_{1/2}$ in Figure 3, one can, therefore, conclude that k_{rel} of *p*-cyanophenyl tosylate in the listing of Figure 3 must be smaller than 10^{-1}; i.e., tosylate is exchanged at least 10^4 times more slowly than a bromide. This result is consistent with previously reported selective exchanges of bromide in the presence of tosyloxy groups (Scheme 5).[15]

Scheme 5. No Exchange Reactions between ArOTs and *i*-PrMgCl·LiCl



In summary, the qualitatively known increase of halogen–magnesium exchange rates in the order ArCl < ArBr < ArI has been quantified as $1{:}10^6{:}10^{11}$ for the reactions of haloarenes with *i*-PrMgCl·LiCl in THF at 0 °C. If one assumes that further substituents have similar effects on iodide–magnesium and chloride–magnesium exchange reactions as previously reported for bromide–magnesium exchange reactions[9] (the data in Scheme 3 support this view), one can combine the data in this work with the previously reported substituent effects to predict the most likely site of exchange in functionalized polyhalogenated arenes.

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Supporting Information Available. Experimental procedure and data for the determination of the relative exchange rates κ and determination of exchange reactions between Grignard reagent and aryl halide. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) As *p*-bromoanisole and *p*-bromotoluene have been found to be equally reactive, the same is assumed for *p*-iodoanisole and *p*-iodotoluene.

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The authors declare no competing financial interest.