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Kinetics of Bromine−Magnesium Exchange Reactions in Substituted Bromobenzenes

Lei Shi, Yuanyuan Chu, Paul Knochel, and Herbert Mayr*

Department Chemie und Biochemie der Ludwig-Maximilians-Universität München, Butenandtstrasse 5-13 (Haus F), 81377 München, Germany

herbert.mayr@cup.lmu.de

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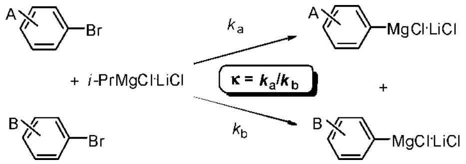

Competition experiments have been performed to determine the relative reactivities of substituted bromobenzenes, bromonaphthalenes, and 9-bromoanthracene toward *i*-PrMgCl·LiCl in THF at 0 °C. The rates of the bromine−magnesium exchange reactions are accelerated by electron-acceptor substituents, the activating efficiency of which increases in the order *para* < *meta* ≪ *ortho*. The activation free enthalpies of the bromine−magnesium exchange reactions correlate fairly ($r^2 = 0.83$) with the proton affinities of analogously substituted aryllithiums (slope 0.8). The kinetics of two representative bromoarenes with *i*-PrMgCl·LiCl were found to be first-order in both bromoarene and *i*-PrMgCl·LiCl. Combination of the resulting second-order rate constants with the k_{rel} values from competition experiments allowed us to calculate reaction times for the bromine−magnesium exchange reactions of a large variety of bromoarenes.

Introduction

Bromine−magnesium exchange reactions provide a straightforward access to aromatic Grignard reagents including functionalized derivatives.[1,2] A particularly efficient way to achieve this conversion is the treatment of bromoarenes with *i*-PrMgCl·LiCl.[3] In a recent communication we reported competition experiments that revealed the influence of substituents on the rates of these reactions.[4] Though it was evident that electron-withdrawing substituents facilitated the exchange process, the relative magnitude of these substituent effects, in particular the ranking *para* < *meta* ≪ *ortho* did not correlate with Hammett's σ values or related substituent constants.[5]

We have now extended this work to donor-substituted and multiply substituted benzenes, as well as to naphthalene and anthracene derivatives. In order to give synthetic chemists a clue what reaction times to expect for certain exchange reactions, we have also determined absolute rate constants for some of these reactions that allowed us to convert the relative reactivities determined in this and the earlier work into absolute reaction times.

Results and Discussion

Relative Reactivities by Competition Experiments. Competition experiments were carried out by adding *i*-PrMgCl·LiCl in THF to an excess of two differently substituted bromobenzenes (approximately 2 equiv). The ratio of the resulting arylmagnesium chlorides was then derived from the gas-chromatographically determined product ratio obtained after quenching with methanol (Scheme 1).

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(1) (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem.* **2003**, *115*, 4438–4456; *Angew. Chem., Int. Ed.* **2003**, *42*, 4302−4320. (b) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565–569.

(2) (a) Silverman, G. S.; Rakita, P. *Handbook of Grignard Reagents*; Marcel Dekker: New York, 1996. (b) Richey, H. G., Jr. *Grignard Reagents: New Developments*; Wiley: New York, 1999. (c) Yamamoto, H.; Oshima, K. *Main Group Metals in Organic Synthesis*; Wiley: New York, 2004. (d) Knochel, P. *Handbook of Functionalized Organometallics*; Wiley: Weinheim, 2005.

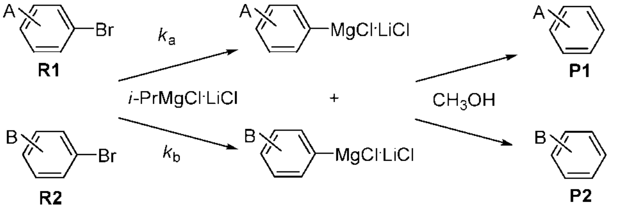
(3) (a) Krasovskiy, A.; Knochel, P. *Angew. Chem.* **2004**, *116*, 3396–3399; *Angew. Chem., Int. Ed.* **2004**, *43*, 3333−3336. (b) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem.* **2006**, *118*, 165–169; *Angew. Chem., Int. Ed.* **2006**, *45*, 159−162. (c) Hauk, D.; Lang, S.; Murso, A. *Org. Process Res. Dev.* **2006**, *10*, 733–738. (d) Li, F.; Castle, S. L. *Org. Lett.* **2007**, *9*, 4033–4036. (e) Hirner, S.; Panknin, O.; Edefuhr, M.; Somfai, P. *Angew. Chem.* **2008**, *120*, 1933–1935; *Angew. Chem., Int. Ed.* **2008**, *47*, 1907−1909. (f) Huang, L.; Wu, S.; Qu, Y.; Geng, Y.; Wang, F. *Macromolecules* **2008**, *41*, 8944–8947. (g) Rauhut, C. B.; Melzig, L.; Knochel, P. *Org. Lett.* **2008**, *10*, 3891–3894. (h) Duan, X.-F.; Ma, Z.-Q.; Zhang, F.; Zhang, Z.-B. *J. Org. Chem.* **2009**, *74*, 939–942. (i) For iodine-magnesium exchange reactions using *i*-PrMgCl·LiCl, see: Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844–3845.

(4) Shi, L.; Chu, Y.; Knochel, P.; Mayr, H. *Angew. Chem.* **2008**, *120*, 208–210; *Angew. Chem., Int. Ed.* **2008**, *47*, 202−204.

(5) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.

10.1021/jo802770h CCC: $40.75

SCHEME 1. Competition Experiment for Determining the Relative Reactivities of Bromoarenes toward *i*-PrMgCl·LiCl



The relative reactivity of **R1** and **R2** can be expressed by the competition constant κ, which is defined by eq 1:[6]

$$\kappa = \frac{k_a}{k_b} = \frac{\log([\mathbf{R1}]_0/[\mathbf{R1}]_t)}{\log([\mathbf{R2}]_0/[\mathbf{R2}]_t)} \quad (1)$$

Substitution of $[\mathbf{R1}]_0$ and $[\mathbf{R2}]_0$ by the expressions in eqs 2 and 3 (mass balance) yields eq 4:

$$[\mathbf{R1}]_0 = [\mathbf{R1}]_t + [\mathbf{P1}]_t \quad (2)$$

$$[\mathbf{R2}]_0 = [\mathbf{R2}]_t + [\mathbf{P2}]_t \quad (3)$$

$$\kappa = \frac{\log(1 + [\mathbf{P1}]_t/[\mathbf{R1}]_t)}{\log(1 + [\mathbf{P2}]_t/[\mathbf{R2}]_t)} \quad (4)$$

Competition constants calculated according to eq 4 from the chromatographically determined ratios $[\mathbf{P1}]_t/[\mathbf{R1}]_t$ and $[\mathbf{P2}]_t/[\mathbf{R2}]_t$ are used to evaluate the relative reactivities.

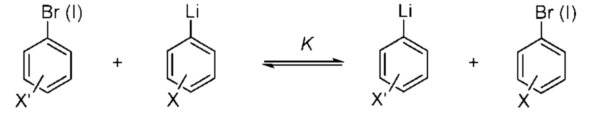
Because κ, as defined by eq 4, was found to be independent of the reaction times, one can conclude that subsequent reactions of the arylmagnesium halides with bromoarenes do not take place, i.e., that the competition constants are the result of kinetic control.

Each of the 38 bromoarenes listed in Figure 1 was subjected to competition experiments with several other bromoarenes as illustrated in Scheme 1. The resulting 58 competition constants κ, 22 of which (marked by asterisks) have been reported previously,[4] are summarized in Figure 1. Solving the resulting overdetermined set of linear equations (eq 5) by least-squares minimization[7] yielded the k_{rel} values given in Figure 1.[8]

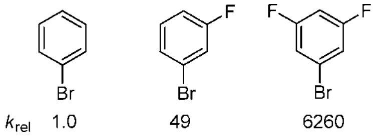
$$\log \kappa = \log k_a - \log k_b \quad (5)$$

From the fact that electron-withdrawing groups generally accelerate the bromine−magnesium exchange but that 3-CN and 3-CF_3 accelerate more than 4-CN and 4-CF_3, respectively, we had previously concluded that there is no correlation between the effects of substituents on the rates of exchange and Hammett's substituent constants. This statement can now be refined because data for donor substituents have now become available. When log k_{rel} for all investigated *meta*- and *para*-substituted bromobenzenes is plotted against σ, a rather poor correlation is observed. Individual treatment of the *meta*- and *para*-substituted bromobenzenes (Figure 2) leads to a significant improvement of the correlations, particularly for the *meta*-substituted compounds ($r^2 = 0.97$) and less for the *para*-substituted compounds ($r^2 = 0.92$). From the reaction constants, $\rho = 5.38$ for the *meta*-substituted compounds, and $\rho = 2.65$ for the *para*-substituted compounds, one can derive that the bromine−magnesium exchange is predominantly accelerated by inductively withdrawing substituents. Because the σ_m values exclusively reflect inductive effects, the resulting ρ value is larger than that derived from σ_p, which includes inductive as well as mesomeric effects.

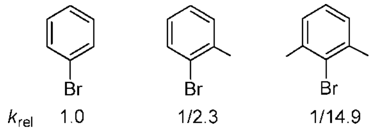
SCHEME 2. Assessment of Relative Aryllithium Basicities by Schlosser[9]



SCHEME 3. Effect of 3-F Substitution on Relative Rates of Br−Mg Exchange



SCHEME 4. Effect of *o*-Methyl Groups on Relative Rates of Br−Mg Exchange



Schlosser and Gorecka−Kobylinska have just reported relative aryllithium basicities that were derived from equilibrium constants for the reactions described in Scheme 2.[9]

Figure 3 shows a fair correlation between log k_{rel} for the bromine−magnesium exchange reactions and the relative aryllithium basicities. When the slope of this correlation is multiplied by $-2.303RT = -1.245$, a ratio $\Delta\Delta G^{\ddagger}/\Delta\Delta G^0 = 0.80$ is obtained, indicating a transition state with a charge distribution in the aryl ring that closely resembles that of the corresponding aryllithium compounds.

From the regioselectivities of the exchange reactions in dibromo-substituted benzenes, we had previously derived approximate additivities of the substituent effects.[4] Rough additivity is also observed for 3-fluorine substituents as shown by the comparison in Scheme 3, where the second fluorine atom is demonstrated to cause a somewhat stronger acceleration than the first fluorine ($49^2 = 2401$).

Because of the small effects of methyl and methoxy groups in *meta*- and *para*-positions, it is not surprising that also two or three methyl or methoxy groups in *meta*- or *para*-positions relative to bromine affect the reactivity by less than a factor of 3. Steric shielding is probably responsible for the fact that two methyl groups in positions *ortho* to bromine retard by a factor of 15, whereas one *o*-methyl reduces the exchange rate of Br by a factor of only 2.3 (Scheme 4).

As in electrophilic aromatic substitutions, naphthalene is more reactive than benzene, and the 1-position of naphthalene is more reactive than the 2-position. Annelation of a second benzene

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(6) Huisgen, R. *Angew. Chem.* **1970**, *82*, 783–794; *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 751−762.

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

(8) Actually, some additional competition constants for brominated heteroarenes have also been included for the calculation of k_{rel}. In this way we intend to avoid reoptimization when publishing exchange rates for further classes of compounds.

(9) Gorecka-Kobylinska, J.; Schlosser, M. *J. Org. Chem.* **2009**, *74*, 222–229.

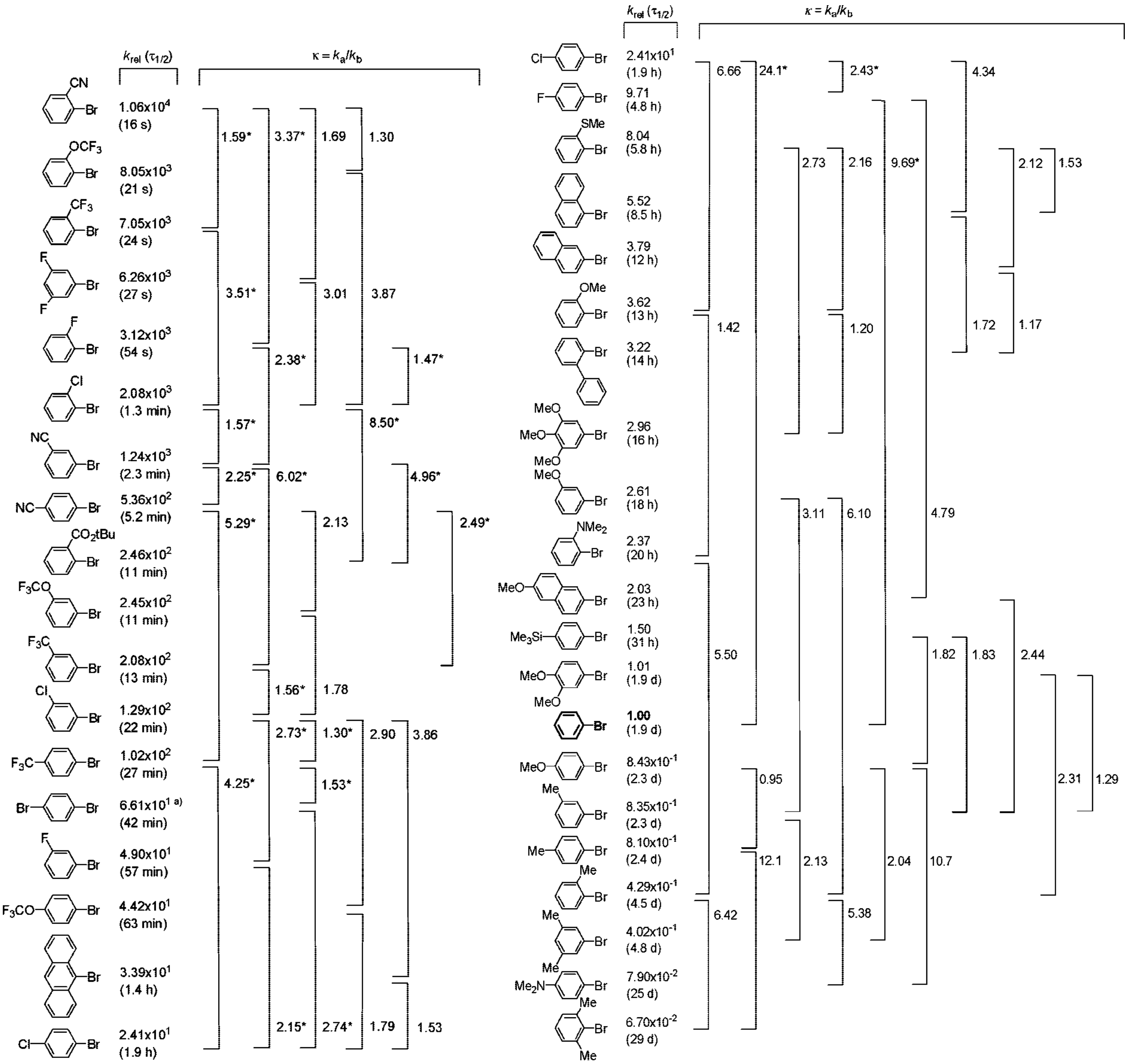
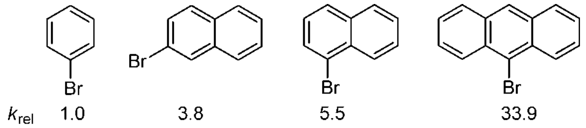


FIGURE 1. Relative reactivities of substituted bromobenzenes toward *i*-PrMgCl·LiCl in THF at 0 °C and $\tau_{1/2}$ for 1 M solutions (κ marked with an asterisk were taken from ref 4). (a) k_{rel} not statistically corrected.

SCHEME 5. Relative Reactivities of Bromobenzene, Bromonaphthalenes, and 9-Bromoanthracene toward *i*-PrMgCl·LiCl



ring to bromobenzene (→ 9-bromoanthracene) has a slightly larger effect than annelation of the first benzene ring (Scheme 5).

Determination of Absolute Rate Constants. To convert the relative rate constants listed in Figure 1 into absolute rate constants, we have determined the kinetics of the Br−Mg exchange reactions of 4-bromobenzonitrile and 1-bromo-3-chlorobenzene with *i*-PrMgCl·LiCl at 0 °C (Scheme 6).

For that purpose, THF solutions that were 0.01 M in bromoarene and 0.1−0.5 M in *i*-PrMgCl·LiCl were prepared. After appropriate times, aliquots of these solutions were taken with gastight syringes, injected into methanol, and the ratio [product]/[reactant], i.e., [benzonitrile]/[4-bromobenzonitrile] and [chlorobenzene]/[1-bromo-3-chlorobenzene], respectively, was analyzed by GC, from which the concentration of the reactant was calculated by eq 6:

$$[\mathbf{R}] = \frac{[\mathbf{R}]_0}{1 + f_{RP}(A_P/A_R)} \qquad (6)$$

[**R**] is the concentration of the reactant (bromoarene), $[\mathbf{R}]_0$ is the concentration of the bromoarene at $t = 0$, i.e., $[\mathbf{R}]_0 = [\mathbf{R}] + [\mathbf{P}]$, and $f_{RP} = (A_R[\mathbf{P}])/(A_P[\mathbf{R}])$ is the response factor, which was determined from the GC peak areas A_R and A_P of artificial mixtures of reactant **R** and product **P**, respectively.

For the consumption of **R**, the general rate law (eq 7) is considered:

$$\frac{-\mathrm{d}[\mathbf{R}]}{\mathrm{d}t} = k[\mathbf{R}]^n[i\text{-PrMgCl·LiCl}]^m \qquad (7)$$

Because the ratio [*i*-PrMgCl·LiCl]/[bromoarene] varied between 10 and 50, the concentration [*i*-PrMgCl·LiCl] is almost constant, and $k[i\text{-PrMgCl·LiCl}]^m$ was replaced by k_{obs}, i.e.,

$$\frac{-\mathrm{d}[\mathbf{R}]}{\mathrm{d}t} = k_{\mathrm{obs}}[\mathbf{R}]^n \quad \text{with } k_{\mathrm{obs}} = k[i\text{-PrMgCl}\cdot\text{LiCl}]^m \qquad (8)$$

From the linearity of the plots of $-\ln[\mathbf{R}]$ versus t (Figure 4), one can derive that the reactions are first order in bromoarenes **R**, i.e., $n = 1$.

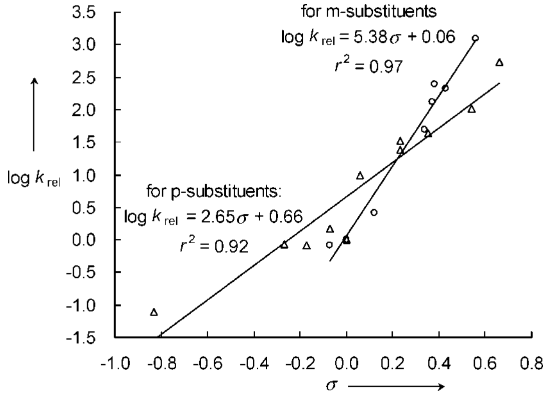


FIGURE 2. Plot of the logarithm of relative rates, log k_{rel}, against Hammett's σ values.

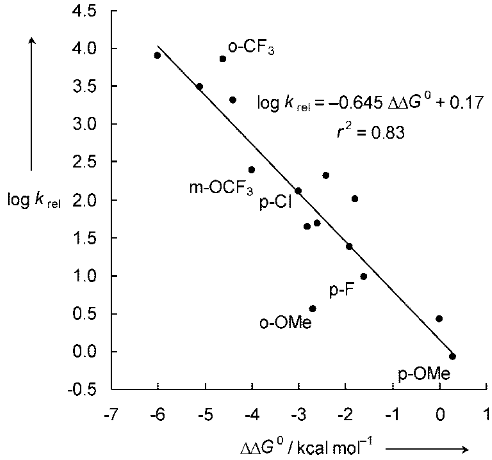
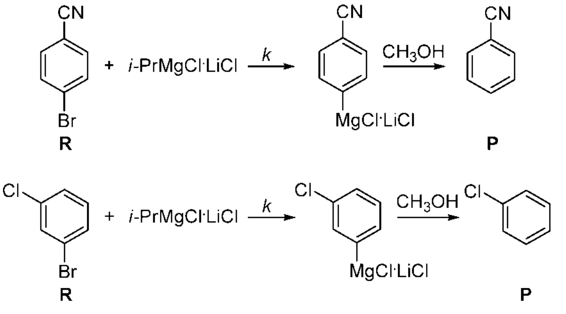


FIGURE 3. Correlation between log k_{rel} for the bromine−magnesium exchange reactions (0 °C, THF, data from Figure 1) and $\Delta\Delta G^0$ for the relative aryllithium basicities (Scheme 2). Data used for this correlation are given in Table S14 of Supporting Information.

SCHEME 6. Determination of the Kinetics of Bromine−Magnesium Exchange



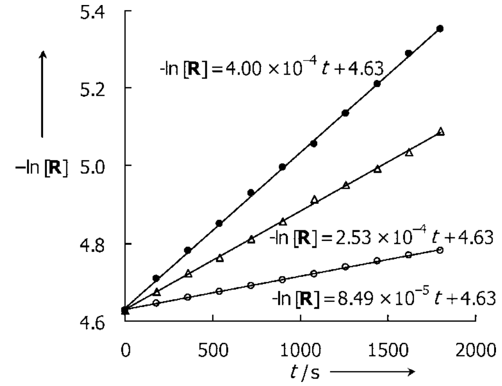


FIGURE 4. Plot of $-\ln[\mathbf{R}]$ versus time for the reaction of 1-bromo-3-chlorobenzene ($[\mathbf{R}] = 0.01$ M) with variable concentrations of i-PrMgCl·LiCl [(○) 0.1 M, (Δ) 0.3 M, (●) 0.5 M; all three linear correlations with $r^2 > 0.999$] in THF at 0 °C.

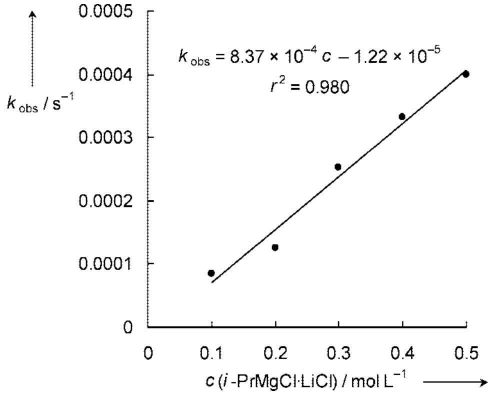


FIGURE 5. Dependence of the pseudo-first-order rate constants k_{obs} for the reaction of 1-bromo-3-chlorobenzene with i-PrMgCl·LiCl on the concentration of i-PrMgCl·LiCl (in THF at 0 °C).

Plots of the resulting first-order rate constants k_{obs} versus [i-PrMgCl·LiCl] were almost linear, indicating first-order dependence on the concentration of the organomagnesium reagent, i.e., $m = 1$ in eqs 7 and 8. Obviously, the nature of the organometallic does not alter in this concentration range. Analogous observations have been made for reactions of Grignard reagents with carbonyl compounds[10] and chlorosilanes[11] in THF. The slope of the correlation shown in Figure 5 gave the second-order rate constant for the reaction of i-PrMgCl·LiCl with 1-bromo-3-chlorobenzene (8.37×10^{-4} M^{-1} s^{-1}), and an analogous evaluation of the reaction of 4-bromobenzonitrile with i-PrMgCl·LiCl in THF gave a second-order rate constant of 2.97×10^{-3} M^{-1} s^{-1}. The ratio of the directly determined rate constants (3.55) is 14% smaller than the ratio derived from the competition experiments (4.14). Using the average value, one can now convert the k_{rel} values of Figure 1 into second-order rate constants by multiplying k_{rel} with 6.0 $\times$ 10^{-6} M^{-1} s^{-1}. Under typical reaction conditions,[3a] the THF solutions are 1 M in both bromoarene and i-PrMgCl·LiCl. With the assumption that the second-order rate law derived above also holds at these concentrations, one can calculate the reaction times needed for conversion. A conversion of 50% is then reached within $t = 1/(k[\mathbf{R}]_0)$, i.e., within 16 s for 2-bromobenzonitrile, the most reactive compound of this series, and within 29 days for 2-bromo-1,3-dimethylbenzene, the least reactive compound of this series. In order to reach 90% conversion, a

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(10) (a) Yamataka, H.; Matsuyama, T.; Hanafusa, T. *J. Am. Chem. Soc.* **1989**, *111*, 4912–4918. (b) Holm, T. *J. Org. Chem.* **2000**, *65*, 1188–1192. (c) Shimizu, M.; Yamataka, H. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1757–1761.

(11) (a) Rudolph, S. E.; Charbonneau, L. F.; Smith, S. G. *J. Am. Chem. Soc.* **1973**, *95*, 7083–7093. (b) Tuulmets, A.; Nguyen, B. T.; Panov, D.; Sassian, M.; Jaerv, J. *J. Org. Chem.* **2003**, *68*, 9933–9937. (c) Tuulmets, A.; Nguyen, B. T.; Panov, D. *J. Org. Chem.* **2004**, *69*, 5071–5076.

(12) This value comes from $kt = 1/[\mathbf{R}]_t - 1/[\mathbf{R}]_0$ for bimolecular reactions with equal concentrations $[\mathbf{R}]_0$ for the two reactions partners.

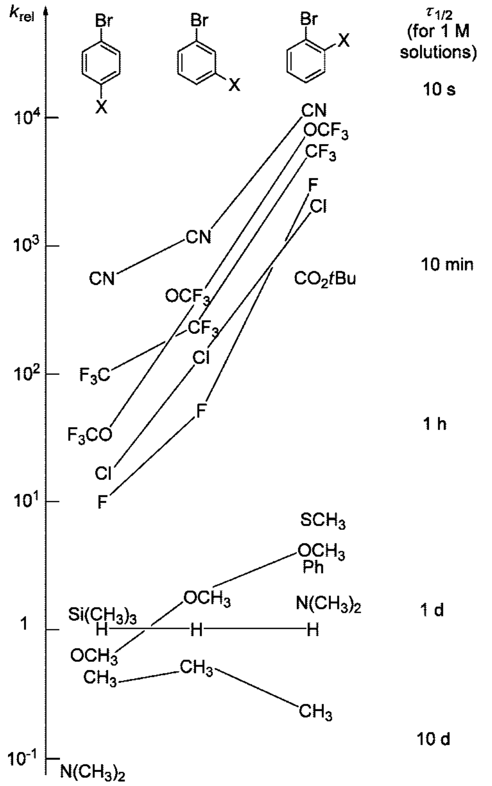


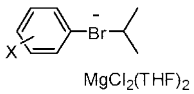
FIGURE 6. Substituent effects on the reactivities of bromobenzene derivatives toward *i*-PrMgCl·LiCl (0 °C, THF).

reaction time of 9/(k[**R**]$_0$) is needed,[12] i.e., the times listed in Figure 1 have to be multiplied by a factor of 9.

For the reaction of *i*-PrMgCl·LiCl with 1-bromo-3-chlorobenzene in THF/1,4-dioxane (9/1), a second-order rate constant of 3.08×10^{-3} M^{-1} s^{-1} was determined at 0 °C. The addition of 10 vol % 1,4-dioxane thus accelerated the bromine−magnesium exchange by a factor of 3.7, which allows one to significantly reduce the reaction times listed in Figure 1.

Conclusion

Bromine−magnesium exchange reactions in substituted bromobenzenes with *i*-PrMgCl·LiCl are strongly accelerated by electron-withdrawing substituents. From the increasing effect in the series *para* < *meta* ≪ *ortho* (Figure 6), one can derive that it is mostly the inductive substituent effect that is responsible for the activation of the bromine−magnesium exchange, in line with a transition state resembling the hypervalent halogen complex **A**.[3b]



A

From the slope of 0.8 for the plot of log k_{rel} versus the relative basicities (log K) of the corresponding aryllithiums, one can derive a transition state where the charge distribution in the aryl ring is comparable to that in the analogous aryllithium compounds. Schlosser's explanation of the large ortho effect by σ-polarization[9] may be applied analogously.

Experimental Section

Procedure for Determination of Relative Exchange Rates κ. A dry and nitrogen-flushed 25-mL flask, equipped with a magnetic stirrer, was charged with 2-bromobenzonitrile **R1** (1.3 mmol, 237 mg), 1-bromo-2-(trifluoromethoxy)benzene **R2** (1.3 mmol, 313 mg), and internal standard (n-$C_{14}H_{30}$) in THF (4.20 mL). The reaction mixture was cooled to 0 °C. *i*-PrMgCl·LiCl (1.3 mmol, 1.00 mL solution in THF) was added in one portion. After certain times (e.g., 60 min), ca. 0.2 mL of the reaction mixture was taken with a gastight syringe and injected in methanol. The reaction mixture was washed with saturated aqueous NaCl solution (30 mL). The aqueous phase was extracted with diethyl ether (ca. 25−30 mL). The etheral solutions were dried over Na_2SO_4 and analyzed by GC.

Procedure for Determination of Pseudo-First-Order Rate Constants. A solution of 1-bromo-3-chlorobenzene (37.4 mg, 0.195 mmol) and n-$C_{14}H_{30}$ (internal standard, 9.8 mg, 0.0493 mmol) in dry THF (12.31 mL) was combined with a 1.30 M solution of *i*-PrMgCl·LiCl in THF (7.69 mL) at 0 °C to give a solution with the concentration listed in Table S2 of Supporting Information. The mixture was stirred under a nitrogen atmosphere at 0 °C, and after variable times (typically every 3 min), 1.5 mL of this mixture was taken with a gastight syringe and injected into 3 mL of methanol. The mixture was extracted with diethyl ether and then analyzed by GC.

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Supporting Information Available: Experimental procedure and data for the determination of the relative exchange rates κ and determination of absolute rate constants. This material is available free of charge via the Internet at http://pubs.acs.org.

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