Grignard Reagents

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Relative Rates of Bromine–Magnesium Exchange Reactions in Substituted Bromobenzene Derivatives**

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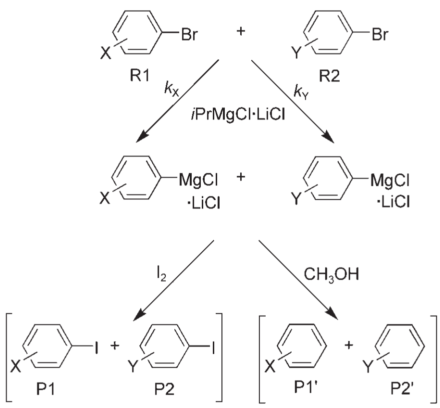
Dedicated to Professor Klaus Hafner on the occasion of his 80th birthday

The accessibility of functionalized Grignard reagents has opened new dimensions in organic synthesis.[1] One of us has previously demonstrated that treatment of substituted bromoarenes with *i*PrMgCl·LiCl provides a straightforward access to functionalized aryl Grignard reagents by bromine–magnesium exchange.[2] In accord with the suggested mechanism for these reactions,[3] electron-acceptor groups have been observed to facilitate this conversion. We have now determined the relative rates of such exchange reactions to facilitate a targeted use of these reactions on polyfunctional compounds.

The influence of substituents on the rates of bromine–magnesium exchange has been determined by competition experiments. For this purpose, mixtures of two differently substituted bromobenzene derivatives have been combined with less than one equivalent of *i*PrMgCl·LiCl in THF. The ratio of the resulting aryl magnesium chlorides was then derived by gas chromatographic determination of the product ratio obtained after quenching with iodine ([P1]/[P2]) or methanol ([P1′]/[P2′]; Scheme 1).



Scheme 1. Determination of relative bromine–magnesium exchange rates. X, Y = H, F, Cl, Br, CF_3, CO_2tBu, CN.

The relative reactivities of R1 and R2 towards *i*PrMgCl·LiCl can be calculated by Equation (1),[4] which also holds under conditions where the ratio [R1]/[R2] during the reaction with *i*PrMgCl·LiCl varies. Substitution of $[R1]_0$ and $[R2]_0$ by Equations (2) and (3) yields Equation (4), which calculates the competition constant κ (termed $\kappa 1$ in the Supporting Information) from the ratios $[P1]_t/[R1]_t$ and $[P2]_t/[R2]_t$ determined by gas chromatography.

$$\kappa = \frac{k_x}{k_y} = \frac{\lg([R1]_0/[R1]_t)}{\lg([R2]_0/[R2]_t)} \tag{1}$$

$$[R1]_0 = [R1]_t + [P1]_t \tag{2}$$

$$[R2]_0 = [R2]_t + [P2]_t \tag{3}$$

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

Alternative ways to calculate κ, for example, by substituting the absolute concentrations $[R1]_0$, $[R1]_t$, $[R2]_0$, and $[R2]_t$ into Equation (1), usually gave less reproducible results, and are presented in the Supporting Information for comparison. In several cases, control experiments were performed to demonstrate that the mode of quenching did not affect the results (Table 1 and Supporting Information). The independence of the product ratios on the reaction time is evidence that the product ratio is under kinetic control, that is, no exchange reactions take place between bromoarenes and aryl magnesium chlorides (Scheme 2, Table 1, and Supporting Information). Furthermore, the exchange depicted in Scheme 2 has been excluded by treating 3-cyanophenylmag-

Table 1: Relative reactivities of 3-bromobenzonitrile (R1) and 4-bromobenzonitrile (R2) toward *i*PrMgCl·LiCl in THF at 0 °C.

$[R1]_0$ [M]	$[R2]_0$ [M]	[*i*PrMgCl·LiCl]$_0$ [M]	*t* [h]	$\kappa(I_2)$[a]	κ(MeOH)[b]
0.25	0.25	0.25	0.33	2.09	2.37
			2	2.20	2.22
			5	2.23	2.17
0.50	0.50	0.50	0.33	2.32	2.40
			2	2.33	2.42
			5	2.40	2.32
0.25	0.50	0.25	0.67		2.55
0.50	1.00	0.50	0.67		2.43

[a] From Equation (4). [b] From Equation (1).

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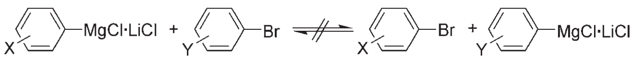
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Evidence for kinetic product control.

nesium chloride with 4-bromobenzonitrile and by treatment of 4-cyanophenylmagnesium chloride with 3-bromobenzonitrile (see the Supporting Information). From the fact that the competition constants κ are independent of the concentrations of the reactants, it can be further concluded that the nature of the reactive organomagnesium species does not change in the concentration range investigated.

Each of the 15 bromobenzenes listed in Figure 1 was subjected to competition experiments with several other bromobenzene derivatives to give the 22 competition constants κ listed in Figure 1. Solving the resulting overdetermined set of linear equations [Eq. (5)] by least-squares minimization yielded the k_{rel} values listed in Figure 1.

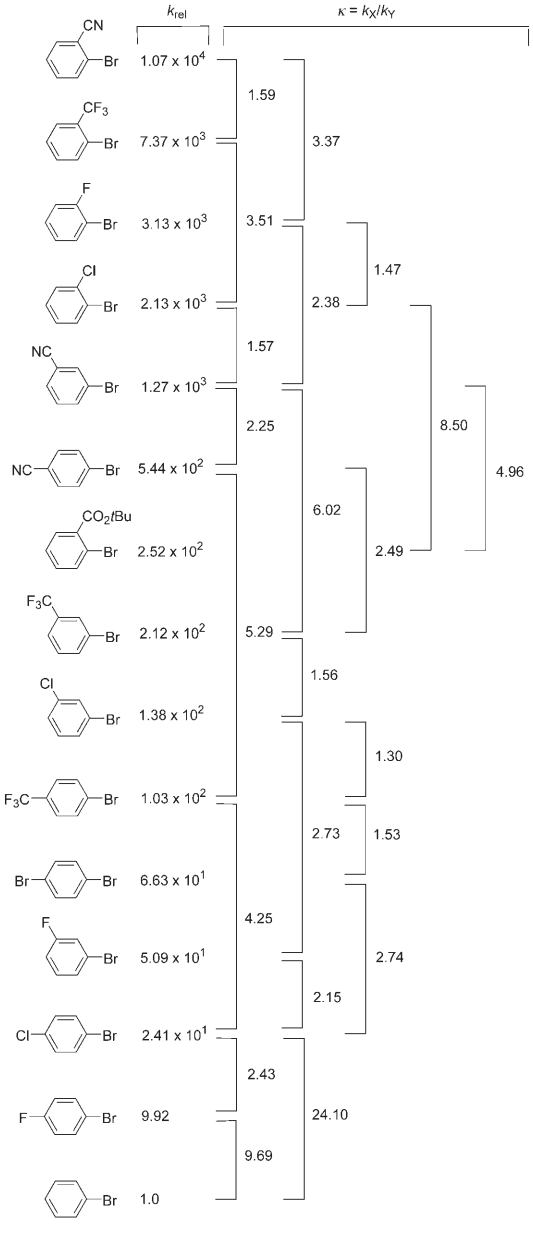


Figure 1. Relative reactivities of substituted bromobenzene derivatives toward *i*PrMgCl·LiCl (THF, 0 °C).

$$\lg k_X - \lg k_Y = \lg \kappa \tag{5}$$

Figure 1 shows a reactivity range of 10^4, from bromobenzene, the least reactive compound, to 2-bromobenzonitrile, the most reactive compound of this series. Unlike in typical electrophilic and nucleophilic aromatic substitutions, where the activating and deactivating *ortho*- and *para*-substituent effects are much greater than the corresponding *meta* effects,[5] now the *meta* effects lie in between the *ortho* and *para* effects (Figure 2), which means that the substituent effects decrease with increasing distance from the reaction center. Clearly mesomeric effects do not play an important role in the halogen–metal exchange reactions. The order of the substituent effects ($CO_2tBu < F \approx Cl < CF_3 < CN$) is in line with this conclusion, and there is no significant correlation with any of the Hammett substituent constants.[6]

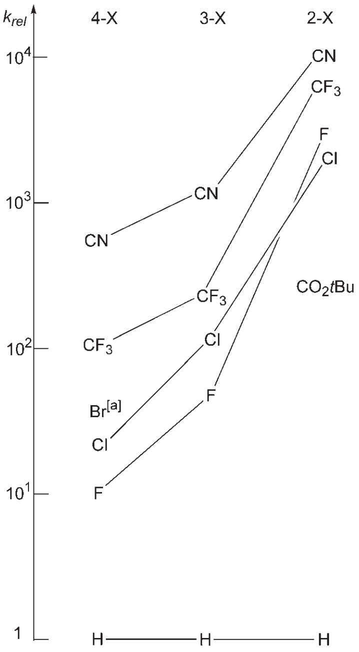
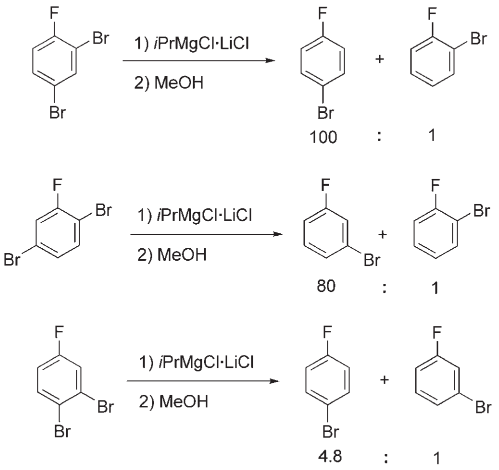


Figure 2. Substituent effects on the reactivities of bromobenzene derivatives toward *i*PrMgCl·LiCl (THF, 0 °C). [a] Statistically corrected. The solid lines serve as guides for the eye.

The substituent effects shown in Figures 1 and 2 can now be used to rationalize the regioselectivities in reactions with multiply substituted benzene derivatives. In line with the considerably greater *ortho*-F effect (3130) relative to the *para*- (9.9) and the *meta*-F effects (51), almost selective exchange of bromine in the *ortho* position to fluorine has been observed in the top two examples of Scheme 3. The selectivity observed in the bottom example of Scheme 3 is much smaller, and the observed ratio of 4.8:1 nicely reflects the ratio of the *meta*- (51) to the *para*-F effect (9.9) shown in Figure 1.

We intend to extend these studies to exchange reactions of other substituents on benzene as well as to the analogous



Scheme 3. Intramolecular competition experiments.

syntheses of heteroaryl- and vinylmagnesium halides. We thus aim to provide a method which allows one to predict the selectivity of halogen–magnesium exchange reactions of polyfunctional compounds.[7] Attempts to determine the kinetics of these reactions to reveal details of the reaction mechanisms have so far not been conclusive.

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[1] a) H. Yamamoto, K. Oshima, *Main Group Metals in Organic Synthesis*, Wiley, New York, **2004**; b) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem.* **2003**, *115*, 4438–4456; *Angew. Chem. Int. Ed.* **2003**, *42*, 4302–4320; c) A. E. Jensen, W. Dohle, I. Sapountzis, D. M. Lindsay, V. A. Vu, P. Knochel, *Synthesis* **2002**, 565–569.

[2] a) A. Krasovskiy, P. Knochel, *Angew. Chem.* **2004**, *116*, 3396–3399; *Angew. Chem. Int. Ed.* **2004**, *43*, 3333–3336; b) review: D. Hauk, S. Lang, A. Murso, *Org. Process Res. Dev.* **2006**, *10*, 733–738.

[3] A. Krasovskiy, B. F. Straub, P. Knochel, *Angew. Chem.* **2006**, *118*, 165–169; *Angew. Chem. Int. Ed.* **2006**, *45*, 159–162.

[4] R. Huisgen, *Angew. Chem.* **1970**, *82*, 783–794; *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 751–762.

[5] a) F. Terrier, *Nucleophilic Aromatic Displacements: The Influence of the Nitro Group*, VCH, New York, NY, **1991**; b) R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, Chichester, **1990**.

[6] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.

[7] For a review on organometallic methods for the regiochemical functionalization of arenes, see M. Schlosser, *Angew. Chem.* **2005**, *117*, 380–398; *Angew. Chem. Int. Ed.* **2005**, *44*, 376–393.