Grignard Reagents

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Highly Efficient Reagents for Br/Mg Exchange**

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Dedicated to Professor Bernd Giese on the occasion of his 65th birthday

Functionalized aryl and heteroaryl magnesium compounds have become readily available from the corresponding organic iodides through an iodine–magnesium exchange by using *i*PrMgCl in THF.^[1] Recently, we reported that aryl and heteroaryl bromides also undergo a bromine–magnesium exchange if the mixed complex *i*PrMgCl·LiCl (1) is used.^[2a] Herein, we report the exceptional reactivity of the new exchange reagent *i*Pr₂Mg·LiCl (2) and the principles on which its reactivity is based. Synthetic applications as well as quantum-chemical calculations provide a rationalization for the reactivity differences and insight into the mechanism of the halogen–magnesium exchange.

We have speculated that the high reactivity of the bimetallic reagent **1** is due to the magnesiate character of this reagent solution in THF.^[2,3] Indeed, our quantumchemical model calculations of halogen–metal exchange reactions predict that the energy of the reaction barrier decreases with increased electronic saturation at the magnesium center.^[4] Both a higher magnesium coordination number as well as more-strongly electron-donating ligands dramatically facilitate the formation of 10-valence-electron ate transition states (Scheme 1, Figure 1, and Table 1).

Experimentally, iodine ate complexes have been either observed or isolated as intermediates.^[5] In contrast, quantumchemical studies on halogen–metal exchange reactions with 'naked' lithium counter ions have so far only predicted hypervalent halogen ate transition states.^[6] Our model calculations involve a more reasonable metal coordination environment (Figure 1 and Table 1). Both pathways now appear to be competitive alternatives (Figure 2).

The enthalpic stabilization of ate intermediates owing to the additional magnesium-solvent bond is, however, entropically unfavorable. Thus, low temperatures and strong donor

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Scheme 1. Halogen-metal exchange reactions through a one-step transition-state pathway or a two-step ate complex intermediate mechanism.



Figure 1. Calculated halogen ate transition states and intermediates.

Table 1: Calculated total electronic energies E_0 [kJ mol⁻¹] for any halides and organometallic substrates, hypervalent halides, and products.^[a]

	Х	М	Hypervalent halide [C ₆ H ₅ XiPr] ⁻ M ⁺ transition state	Products $C_6H_5M + iPrX$ ΔE_0 (reaction)
\mathbf{A}^{\pm}	Br	Mg(µ-Cl) ₂ Li(OMe ₂)	147.7	-42.7
\mathbf{B}^{\pm}	Br	Mg(OMe ₂) ₂ Cl	129.3	-37.3
\mathbf{C}^{\dagger}	Br	MgCl ₂ ⁻	99.2	-55.7
\mathbf{D}^{\dagger}	Br	$Mg(OMe_2)Cl_2^-$	84.5	-58.0
D	Br	$Mg(OMe_2)_2Cl_2^-$	(49.3) ^[b]	-
\mathbf{E}^{\pm}	Br	MgCl(iPr) ⁻	81.9	-57.5
F	Br	Li(OMe ₂) ₃	19.3 ^[c]	-64.6
\mathbf{G}^{+}	1	MgCl ₂ ⁻	69.1	-56.1
н	I.	Li (OMe ₂) ₃	-11.5 ^[c]	-65.0

[a] Gibbs free activation energies will be higher, as two substrate molecules have to combine in one entropically disfavored transitionstate molecule. As a consequence, the Gibbs free activation energies are highly temperature-dependent. Energy values are given relative to the energies of the substrates $C_6H_5X + iPrM$; [b] Ion pair, local minimum (NIMAG 0), energy relative to $PrMgCl_2(OMe_2)^-$, PhBr, and Me_2O model structures. [c] Contact ion pair, local minimum (NIMAG 0).



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Figure 2. Ball-and-stick model structures of the transition state \mathbf{D}^{*} and the intermediate $\mathbf{D}.$

solvents favor two-step pathways via ate intermediates, whereas high temperatures and weak donor ligands support one-step reactions with ate transition states.

To increase the effective negative charge at the magnesium center through separation of the lithium cation from the magnesiate anion, we added various strong σ donors, particularly chelating ethers. Li⁺ selective [12]crown-4 is not, however, efficient, and only a small rate enhancement was observed. This therefore indicates that 1 is already an ionic reagent, presumably with the formula [Li(thf)₄]⁺[Mg(thf)-(*i*Pr)Cl₂]⁻. Nevertheless, other additives such as 1,4-dioxane or [15]crown-5 lead to a higher reactivity through the enforcement of an 'anionic Schlenk equilibrium' with the formation of a MgCl₂·additive precipitate and a solution containing 2, presumably as $[Li(thf)_4]^+[Mg(thf)(iPr)_2Cl]^{-}$.^[7] We prepared reagent 2 by mixing *i*PrMgCl (2 equiv), LiCl (1 equiv), and 1,4-dioxane (10 vol%) in THF, and the resultant precipitate was removed by filtration. The solution of 2 gave the same results as that prepared in situ. The new reagent 2 displays exceptional reactivity for the conversion of various aryl bromides into the corresponding Grignard reagents (Scheme 2 and Table 2).

Interestingly, no significant rate enhancements are observed in Br/Mg-exchange reactions with iPr_2Mg prepared from iPrMgCl and 1,4-dioxane relative to reactions with iPrMgCl. Apparently, the reactive species in solutions of iPrMgCl is iPr_2Mg , which is formed in a Schlenk equilibrium and thermodynamically shifted to the right side by the higher magnesium coordination number of the MgCl₂ by-product (Scheme 3).^[8] Schlenk equil

Whereas the reaction of 1 with 4-bromoanisole (3) produces the corresponding Grignard reagent 4 in 24 h with only 31 % conversion, the addition of [15]crown-5 (1 equiv) to 1 leads to complete conversion within 6 h (Table 2, entries 1 and 2). The use of the larger [18]crown-6 leads to 77% conversion after 24 h. This correlates with a stronger complexation of MgCl₂ by [15]crown-5, which has the perfect size for a seven-coordinated Mg^{II} center (Scheme 3).^[9] Conveniently, ethylene glycol derivatives as PEG250, such Me- $(OCH_2CH_2)_4OMe$, or dimethoxyethane (DME) also give significant rate enhancement (Table 2, entries 4-6). However, the addition of 1,4-dioxane (\approx 1.2 equiv, 10 vol%) provides 100% conversion after 10 h (Table 2, entry 7). Finally, additive: [15]crown-5, PEG250, 1,4-dioxane, TMEDA, DMPU

$$2 \text{ MeO} \xrightarrow{\text{Br}} + i \text{Pr}_2 \text{Mg} \cdot \text{LiCl}$$

$$3 \xrightarrow{\text{THF}, 25 \text{ °C}, 6-24 \text{ h}}_{-2 i \text{PrBr}} (\text{MeO} \xrightarrow{\text{Mg}}_2 \text{Mg} \cdot \text{LiCl}$$



Table 2: Effect of chelating additives on the conversion of the Br/Mg-exchange reaction of 4-bromoanisole.^[a]

Entry	Additive	Amount	Conversion [%] ^[b]
1	-	-	31
2	[15]crown-5	1.0 equiv	100 ^[c]
3	[18]crown-6	1.0 equiv	77
4	PEG250	10 vol %	55
5	Me(O CH ₂ CH ₂) ₄ OMe	10 vol %	60
6	DME	10 vol %	70
7	1,4-dioxane	10 vol %	100 ^[d]
8	DMPU	10 vol %	60
9	TMEDA	10 vol%	77

[[]a] After 24 h at 25 °C; [b] The conversion of the reaction was determined by gas chromatographic analysis of reaction aliquots; precision $\pm 2\%$; [c] After 6 h; [d] After 10 h.

related complexing molecules such as N,N'-dimethyl-N,N'-propylene urea (DMPU) or N,N,N',N'-tetramethylethylenediamine (TMEDA) similarly enhanced the exchange rate (Table 2, entries 8 and 9).^[10]

Several electron-rich aryl bromides, which react only slowly with **1**, undergo a smooth Br/Mg-exchange reaction with **2**. Thus, the reaction of 1-bromo-4-trimethylsilylbenzene

Schlenk equilibrium

2 i

$$\Pr{Mg(thf)_2Cl} \xrightarrow{+ (n-2) THF} i\Pr_2Mg(thf)_2 + MgCl_2(thf)_r$$

- (n-2) THF n = 2, 3, or 4

Anionic Schlenk equilibrium/ Magnesiate equilibrium



 $\textit{Scheme 3.}\ Schlenk equilibrium (without <math display="inline">\mu\text{-chloro dimers})$ and the proposed magnesiate equilibrium.

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undergo Br/Mg



Scheme 4. Br/Mg exchanges with iPr_2Mg ·LiCl (2) generated by the addition of 1,4-dioxane (10 vol%) to iPrMgCl·LiCl (1).

(5) with 2 (0.525 equiv), generated by adding 1,4-dioxane (10 vol %) to 1 (1.05 equiv), is completed within 24 h at 25 °C (Scheme 4). The same exchange with 1 in THF led to a conversion of only 36%. The reaction of the resultant Grignard reagent 6 with furfural provided the alcohol 7 in 92% yield. Strongly electron-donating amine substituents slow down the Br/Mg exchange considerably. However, the reaction of 4-bromo-N,N-dimethylanilin (8) with 2, prepared in the same way, furnishes the Grignard reagent 9 within 48 h at 25 °C, whereas the use of 1 results in only 16% conversion. Quenching of 9 with benzaldehyde leads to the benzhydrol 10 in 95% yield. For benzylic alcohols such as 11, the Br/Mg exchange is nonselective with 1. On the other hand, the reaction of the unprotected alcohol 11 with 2 in THF/dioxane

(9:1) provides cleanly the Grignard reagent **12** within 24 h at 25 °C. Its reaction with *t*BuCHO furnishes the diol **13** in 90 % yield and as a separable mixture of two diastereomers (1:1 ratio).

On the basis of these these results, we independently prepared the dialkyl magnesiate reagent sBu₂Mg·LiCl (14) directly by combining sBuLi (1 equiv) with sBuMgCl (1 equiv) in THF at 25°C (Scheme 5). No precipitate was formed, and the resulting clear solution (1.0 M in THF) is stable at 25°C and again proved to be a superior reagent for of Br/Mgexchange reactions. For example, the reaction of 3 with 14 (0.55 equiv) results in the formation of the corresponding diaryl magnesium reagent 4 within 6 h at 25°C. Also, the highly electron-rich aryl bromide 15 is smoothly converted into the diaryl magnesium reagent 16, which (after trapping with benzaldehyde) affords the alcohol 17 in 90% yield (Scheme 5). Alkenyl bromides

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with previously exchange known magnesium reagents; however, the reaction of 14 (0.55 equiv) with α -bromostyrene (18) provides the desired magnesium reagent within 1 h at 25°C. 19 Ouenching with benzaldehyde leads to the allylic alcohol 20 in 93% yield. Finally, 14 allows the facile preparaof dimagnesium tion reagents. After 2 h at 25°C in Me(OCH₂CH₂)₄OMe, the reaction of 1,4-diiodobenzene (21) with 14 (1.3 equiv) furnishes the corresponding magnesium reagent 22, which in the presence of excess allyl bromide forms the 1,4-diallylbenzene (23) in 85% vield.

In summary, we have presented model calculations that correlate the structure of magnesium reagents and their reactivity in Br/Mg-exchange reactions. Efficient procedures for the shifting of alkyl magnesiate–dialkyl magnesiate equilibria by additives or the alternative direct preparations of dialkyl magnesiates have been developed. Compounds 2 and 14 display exceptional reactivities for otherwise challenging Br/Mg-exchange reactions, thus giving dialkyl magnesiates general synthetic value.

sBu₂Mg∙LiCl

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do

not

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sBuMgCl + sBuLi

THE 14 (1 M solution) MeC MeO MeC PhCHO 14 (1.1 equiv) 2 MeO Mg·LiCl MeC MeO THF, 25 °C, 2 h MeC MeO MeC 2 15 17: 90 % 16 OH B (1.1 equiv) PhCHO Mg∙LiCl THF, 25 °C, 1 h 2 20: 93 % 19 18 14 (1.3 equiv) Me(OCH₂CH₂)₄OMe CuCN-LiC -LiCl 25 °C, 2 h n 23: 85 % 21 22 Scheme 5. Preparation and reactivity of sBu₂Mg·LiCl (14) in halogen-magnesium exchange reactions.

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Keywords: bromine-magnesium exchange · density functional calculations · Grignard reaction · lithium · Schlenk equilibrium

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- [10] Solutions of tBuMgCl·LiCl (1M in THF) and tBu₂Mg·LiCl (1M in THF) were also prepared and applied in Br/Mg-exchange reactions with 3. However, these tert-butyImagnesiates featured slightly lower reaction rates than the secondary reagents 1 and 14. For full conversion of the aryl bromides into the Grignard reagents, 1.1 equiv of both types of reagents was enough, therefore indicating that no elimination of HBr from the tBuBr byproduct by magnesiates takes place. Further work on magnesiates with different alkyl groups is in progress in our laboratories.