

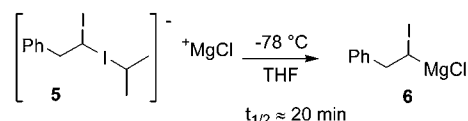
The Second Step of the Halogen/Metal Exchange Reaction

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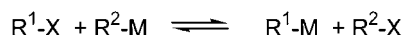
ABSTRACT



The conversion of the iodine ate-complex **5** to the Grignard reagent **6** follows a rate law first order in **5** and in magnesium ions. In addition to this normal pathway of the halogen–metal exchange process, the conversion of **5** to **6** is catalyzed by a number of diverse “electrophiles”. This points to a SET-initiated radical chain process as a second pathway for the conversion of the iodine ate-complex **5** to the Grignard reagent **6**.

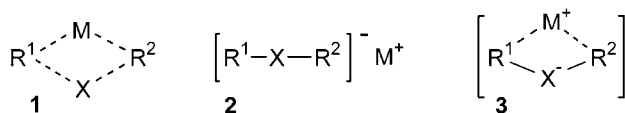
The halogen/metal exchange reaction (Scheme 1) has become, after its discovery by Wittig¹ and Gilman,² a cornerstone in the methodology of organometallic chemistry.

Scheme 1. The Halogen/Metal Exchange



Despite its importance in synthesis the mechanism(s) of the halogen/metal exchange reaction are far from being settled.^{3–5} Initial ideas pictured a four-centered transition state **1**. Later, Wittig and Schöllkopf⁶ postulated ate-complexes **2** as intermediates in the halogen/metal exchange reaction (Scheme 2). Moreover, the occurrence of free radical

Scheme 2. Intermediates and Transition States Postulated for the Halogen/Metal Exchange Reaction



processes has frequently been observed to be (directly or indirectly?) connected with the halogen/metal exchange reaction.^{3,4}

(1) Wittig, G.; Pockels, U.; Dröge, H. *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 1903–1912.

(2) Gilman, H.; Langham, W.; Jacoby, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 106–109.

Over the past decade a comprehensive picture regarding the choreography and timing of the bond-breaking and bond-forming steps began to emerge,^{3–5} cf. Figure 1.

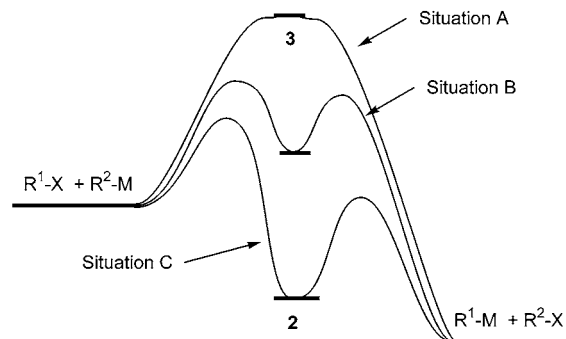


Figure 1. Reaction profiles for the halogen/metal exchange.

When the residues R^1 and R^2 are such that the ate-complex **2** can enjoy substantial thermodynamic stability, situation C may prevail, in which the ate-complex may become an

(3) For leading references see: Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1–46.

(4) For leading references see: Boche, G.; Schimeczek, M.; Cioslowski, J.; Piskorz, P. *Eur. J. Org. Chem.* **1998**, 1851–1860.

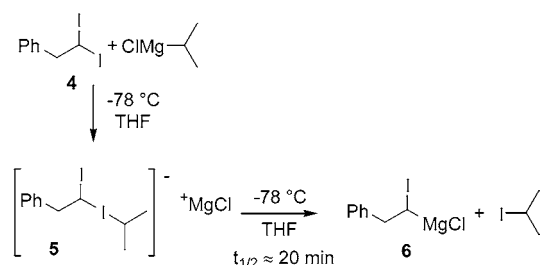
(5) For leading references see: Reich, H. J.; Bevan, M. J.; Gudmundsson, B. O.; Puckett, C. L. *Angew. Chem.* **2002**, *114*, 3586–3589; *Angew. Chem., Int. Ed.* **2002**, *41*, 3436–3439.

(6) Wittig, G.; Schöllkopf, U. *Tetrahedron* **1958**, *3*, 91–93.

observable intermediate in the reaction.⁷ The structural and kinetic stability of the ate-complexes **2** permits them to be present as solvent separated ion pairs (SSIP)⁸ or even as dissociated ions (see below). When R¹ and R² do not confer significant thermodynamic stability to the ate-complex (situation A), the transition state of the halogen/metal exchange reaction may resemble the arrangement **3**. When carbon–halogen bond formation precedes the carbon–metal bond formation, the transition state may be approximated by the contact ion pair (CIP) **3**, in which a linear dialkyl-halogenate anion is distorted by Coulombic attraction between the metal cation and the negatively charged carbon atoms.^{4,9} Figure 1 thus accommodates a spectrum of mechanistic scenarios for the halogen/metal exchange reaction, e.g. such as an intermediate situation B, differing in the stability of the ate-complex “intermediates” relative to the starting materials.

In a preceding study⁹ we found that a long-lived ate-complex **5** is formed in the iodine/magnesium exchange reaction between **4** and isopropyl Grignard (Scheme 3). This

Scheme 3. The Iodine/Magnesium Exchange on 1,1-Diiodoalkanes



gave us the opportunity to explore the chemistry of iodine ate-complexes **5** in their own right, i.e., to focus on the second step of the halogen/metal exchange reaction, the transformation of the ate-complex **5** to the product **6**.

Qualitative observations show that the conversion of the ate-complex **5** to the Grignard reagent **6** is *speeded up considerably by an excess of Grignard reagent*. The half-life of the yellow color may become as short as 2 min in the presence of 5 to 10 equiv of isopropyl or ethyl Grignard. Addition of 0.1 equiv of Mg(OTf)₂ reduced the time for decolorization to 1/4 (whereas addition of 1 or 2 equiv of

the magnesium-cation chelator 12-crown-4 doubled the time for decolorization). These effects are not due to a general salt effect, as addition of 1 equiv of lithium chloride, tetrabutylammonium tetrafluoroborate, tetrabutylammonium bromide, phenyltrimethylammonium chloride, or ethyltri-phenylphosphonium bromide did not affect the rate of conversion of **5** into **6** at $-78\text{ }^\circ\text{C}$ in THF. It thus appears that there is a common ion rate effect in the conversion of **5** to **6**, which is indicative for reactions originating from dissociated ions.¹⁰

If **5** were to be present as dissociated ions, the conversion to **6** would be first order in the concentration of the anion and first order in that of an unspecified “active” magnesium cation. During the reaction magnesium cations will be present in several species. A simplifying assumption would be that these equilibrate rapidly. In this case the concentration of the “active” magnesium cation could be proportional to the total concentration of magnesium in the system. The latter remains constant throughout the reaction. If this analysis holds, the conversion of **5** into **6** should occur in a pseudo-first-order reaction and the pseudo-first-order rate constants should be proportional to the total magnesium concentration.

The reaction of **1** with diisopropylmagnesium was then followed spectrophotometrically at 409 nm at $-80\text{ }^\circ\text{C}$.⁹ After the initial build-up phase of the color, the decay of the color followed good first-order kinetics over >2 half-lives. Varying both the initial concentration of **1** and of diisopropylmagnesium the following pseudo-first-order rate constants were recorded (Table 1):

Table 1. Pseudo-First-Order Rate Constants for the Conversion of **5** into **6** at $-78\text{ }^\circ\text{C}$ in THF

concn of 4 (mol L ⁻¹)	diisopropylmagnesium		rate constant (s ⁻¹)
	equiv	concn (mol L ⁻¹)	
8.5×10^{-3}	1	8.5×10^{-3}	1.2×10^{-4}
7×10^{-3}	2	14×10^{-3}	3.8×10^{-4}
28×10^{-3}	1	28×10^{-3}	9.5×10^{-4}
19×10^{-3}	2	38×10^{-3}	15×10^{-4}

When these rate constants were plotted against the total magnesium concentration a good linear relation was observed (cf. Figure 2):

$$10^4 \times \text{rate constant (s}^{-1}\text{)} = 458[\text{total Mg}^{2+}] - 2.76$$

Thus it appears that the conversion of the ate-complex anion into the Grignard reagent **5** is a bimolecular process involving both the anion and an unspecified cationic magnesium species. These observations relate to the normal path for the conversion of the ate-complex **5** to the product **6**.

(10) (a) Winstein, S.; Clippinger, E.; Fainberg, A. H.; Heck, R.; Robinson, G. C. *J. Am. Chem. Soc.* **1956**, *78*, 328–335. (b) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca, NY, 1969; p 500.

(7) (a) Johncock, P. J. *Organomet. Chem.* **1969**, *19*, 257–265. (b) Reich, H. J.; Phillips, N. H.; Reich, I. L. *J. Am. Chem. Soc.* **1985**, *107*, 4101–4103. (c) Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1989**, *111*, 3444–3445. (d) Reich, H. J.; Green, D. P.; Phillips, N. H. *J. Am. Chem. Soc.* **1991**, *113*, 1414–1416. (e) Uno, H.; Okada, S.-I.; Ono, T.; Shiraishi, Y.; Suzuki, H. *J. Org. Chem.* **1992**, *57*, 1504–1513 (f) Müller, M.; Stiasny, H.-C.; Brönstrup, M.; Burton, A.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1999**, 731–736. (g) Hoffmann, R. W.; Müller, M.; Menzel, K.; Gschwind, R.; Schwerdtfeger, P.; Malkina, O. L.; Malkin, V. G. *Organometallics* **2001**, *20*, 5310–5313.

(8) (a) Farnham, W. B.; Calabrese, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2449–2451. (b) Tebbe, K. F.; Fröhlich, R. Z. *Z. Anorg. Allg. Chem.* **1983**, *505*, 7–18. (c) Wiberg, K.; Sklenak, S.; Bailey, W. F. *J. Org. Chem.* **2000**, *65*, 2014–2021.

(9) Schulze, V.; Brönstrup, M.; Böhm, V. P. W.; Schwerdtfeger, P.; Schimeczek, M.; Hoffmann, R. W. *Angew. Chem.* **1998**, *110*, 869–871; *Angew. Chem., Int. Ed.* **1998**, *37*, 824–826.

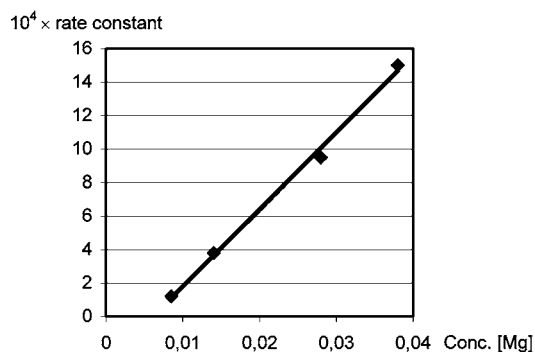
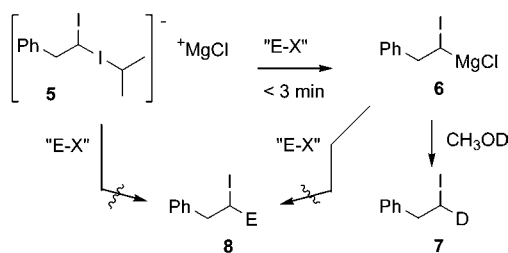


Figure 2. Dependence of the rate constant ($\times 10^4$) for the conversion of **5** into **6** at -78°C in THF on the total Mg^{2+} concentration.

That there is a second pathway for this conversion became apparent when we tested the reactivity of the ate-complex **5** toward a variety of electrophiles. Addition of 0.1 to 2 equiv of benzaldehyde, carbon tetrachloride, tosyl chloride, trimethylsilyl triflate, tributyltin chloride, nitromethane, or trimethyl borate led to a rapid (0.5–3 min)^{11,12} decolorization of the solution. CH_3OD was added 30 to 120 min after decolorization to give in all cases a high yield of **7**, indicating that the “electrophiles” had not intercepted the ate-complex to products of the type **8**, nor that the resulting Grignard **6** had reacted with the electrophiles to **8** under the reaction conditions (Scheme 4), a fact that could be substantiated by

Scheme 4. Reaction of the Ate-Complex **5** with “Electrophiles”



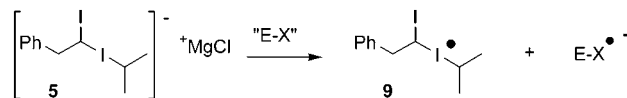
separate control experiments. Rather the electrophiles had served as catalysts which converted the ate-complex **5** into the Grignard reagent **6**. The reaction of the latter with electrophiles to give **8** does, however, occur at higher temperatures or with prolonged reaction times.

(11) In the case of reaction of **5** with 3 equiv of diethylzinc protonation with $\text{CH}_3\text{OH}/\text{CH}_3\text{OD}$ 3 min after the rapid decolorization showed the presence of **6** by the characteristic apparent isotope effect of 1.1.⁹ After 30 min a different species was present in solution, which was protonated to **7** with an apparent isotope effect of 4.0, possibly the zincate complex¹² corresponding to **6**.

(12) (a) Mobley, A. T.; Berger, S. *Angew. Chem.* **1999**, *111*, 3256–3258; *Angew. Chem., Int. Ed.* **1999**, *38*, 3070–3072. (b) Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733–8734. (c) Harada, T.; Oku, A. *Preparation and reaction of triorganozincates in Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University Press: Oxford, UK, 1999; pp 101–117.

The diverse chemical nature of these catalysts suggests that there is no specific mechanism; rather it appears that electron-transfer oxidation of the ate-complex **5** to a dialkyl-iodinanyl radical **9** may be involved (Scheme 5). The ate-

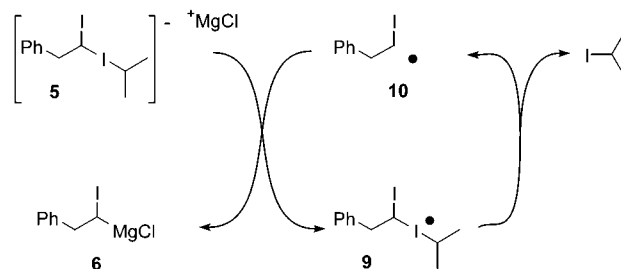
Scheme 5. One-Electron Oxidation of **5** to **9**



complex **5** with two electrons in a nonbonding or even weakly antibonding orbital may be expected to be oxidized extremely readily.

The similar efficiency of the diverse “electrophiles” in the reaction with **5** argues against a stoichiometric oxidation of **5** to **9**. Rather a small amount of **9** may be sufficient to trigger an electron transfer (radical) chain process,¹³ in which the ate-complex **5** is transformed to the Grignard reagent **6** (Scheme 6).

Scheme 6. Electron-Transfer Chain Process for the Conversion of **5** to **6**



Dialkyl-iodinanyl radicals have been discussed as intermediates in homolytic substitution reactions at an iodine atom of alkyl iodides.¹⁴ They are known to decompose almost instantaneously to an alkyl radical and an alkyl iodide.¹⁵ The alkyl radical **10** formed in this manner may be a good enough oxidant¹⁶ to oxidize the ate-complex **5** to the dialkyl-iodinanyl radical **9**, with concomitant formation of the Grignard reagent **6**.

A scenario such as the one delineated above could account for the surprising “catalysis” by diverse “electrophiles” of the conversion of the ate-complex **5** to the Grignard-reagent **6**. The “electrophiles” would merely serve as an initiator for a chain reaction. In hindsight it might not be in all cases the “electrophile” that is the actual oxidant, it could as well be

(13) (a) Astruc, D. *Electron Transfer and Radical Processes in Transition-Metal Chemistry*; VCH: Weinheim, Germany, 1995; Chapter 6.2.1, pp 414–415. (b) Astruc, D. *Angew. Chem.* **1988**, *100*, 662–680; *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 643–660.

(14) Schiesser, C. H.; Wild, L. M. *Tetrahedron* **1996**, *52*, 13265–13314.

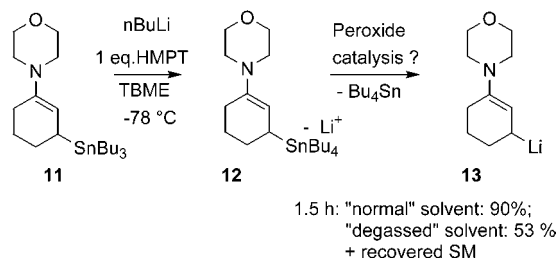
(15) Miranda, M. A.; Pérez-Prieto, J.; Font-Sanchis, E.; Scaiano, J. C. *Org. Lett.* **1999**, *1*, 1587–1589.

(16) Grimshaw, J. *Electrochemical Reactions and Mechanisms in Organic Chemistry*; Elsevier: Amsterdam, The Netherlands, 2000; p 100.

a peroxide or adventitious oxygen introduced with these reagents.¹⁷ Even if this situation were true, this would not affect the principal conclusions from this study.

In this context one should mention an observation by Fröhlich¹⁸ on the tin/lithium exchange of **11** at $-78\text{ }^{\circ}\text{C}$ (Scheme 7). Tin/lithium exchange reactions proceed via tin-

Scheme 7. Oxygen Effect on the Rate of the Tin/Lithium Exchange Reaction



ate-complexes **12**,¹⁹ The overall reaction from **11** to **13** was found to be slowed by a factor of 2 when being carried out in thoroughly degassed *tert*-butyl methyl ether, compared

(17) Slow decolorization of **5** (ca. 30 min) was attained with benzophenone, phenylacetylene, acetyl chloride, and diethylaluminum chloride.

(18) Fröhlich, C. Dissertation, Universität Giessen, 1999; personal communication by Prof. H. Ahlbrecht, Giessen.

to ordinary dry solvent. It therefore appears that a peroxidic intermediate may act as a catalyst in the tin/lithium exchange as well.

On the other hand, the conversion (decolorization) of **5** to **6** proceeded in the absence of an additive with a constant rate in numerous experiments. This indicates that the normal conversion of **5** to **6** does not involve a SET initiated chain process. But the high sensitivity of ate-complexes to enter into SET-initiated radical processes suggests a possible explanation for the observation of radical-derived products in the context of the halogen/metal exchange reaction. One should finally add that our findings have no bearing on the possible generation of free radicals from iodine ate-complexes by direct homolysis.²⁰

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(20) Cf. (a) Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 9960–9967. (b) Inoue, A.; Shinokubo, H.; Oshima, K. *Synlett* **1999**, 1582–1584. (c) Adcock, W.; Clark, C. I.; Trout, N. A. *J. Org. Chem.* **2001**, *66*, 3362–3371.