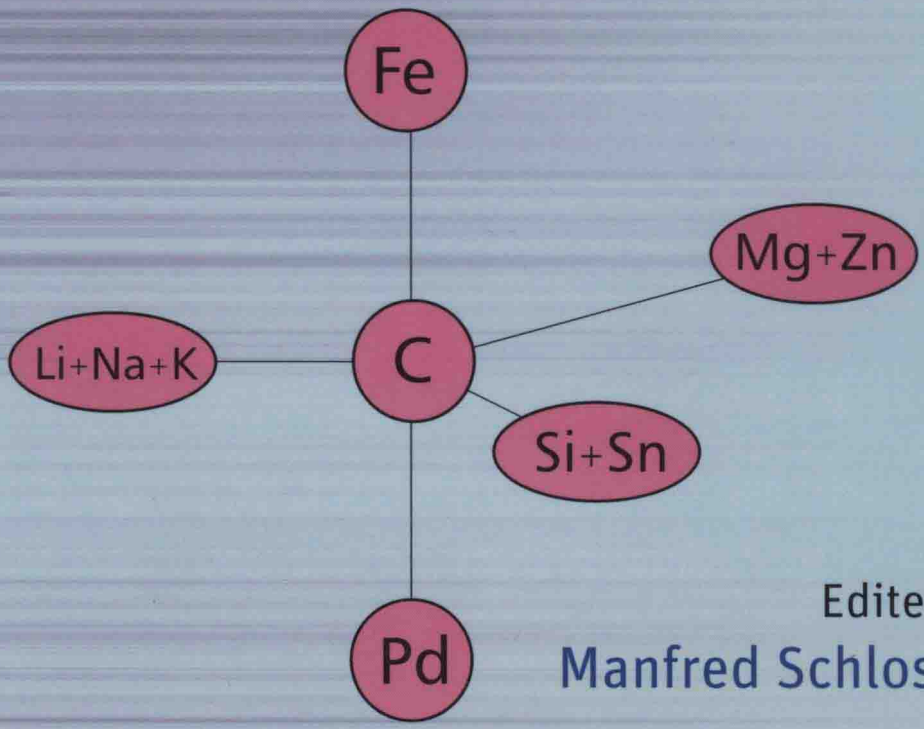
Organometallics in Synthesis

Third Manual



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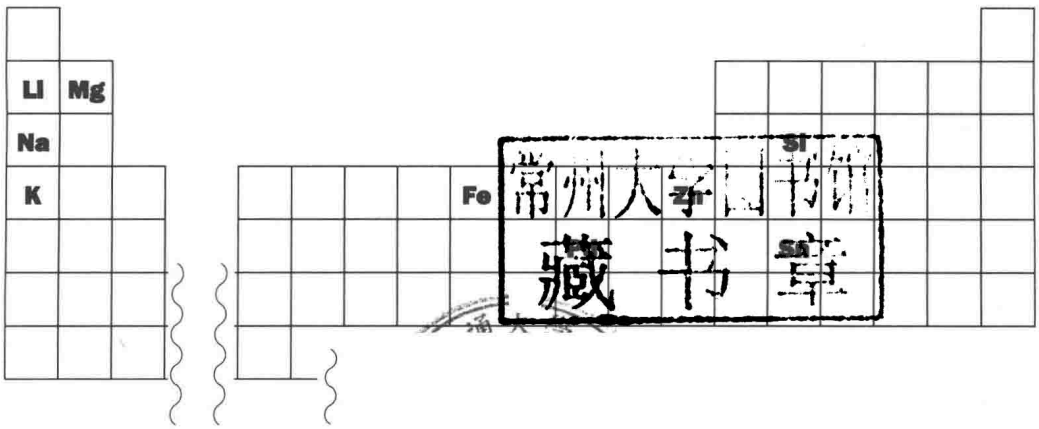

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Preface

Experimenting means arts and crafts. The creator of a cultural masterpiece and the designer of novel properties incarnated in a new chemical entity face the same challenge. Expertise, skills, and perseverance are prerequisites. Next they need a blueprint for the execution of the work and, most important for the ultimate triumph, the faculty to adapt the project continuously to the obstacles encountered on the way. To realize a tricky molecular assembly, a researcher has to master both the rational action and the intuition-guided trial-and-error approach. The bases for such conscious or subconscious decision making are *Methodology,* the critical evaluation of existing methods, and *Mechanism,* the condensing of single observations into a general and predictive concept. Methods and mechanisms were the central topics of the first *Manual* and have continued to keep this role with all follow-up volumes.

Other main characteristics of the *Manual* series remain unaltered here. The attentive reader will nevertheless discover a few innovations. The most arguable one is the revival of *n*-butyllithium. The old-German *n*-alkyl is possibly the only unforgivable sin that can be committed against modern codified nomenclature. And correct nomenclature is, as we use to tell our students, not a nonbinding recommendation but a Must. However, as an industrial executive objected, suppliers of chemicals do not sell butyllithium. They only list *n*-, *sec*-, and *tert*-butyllithium in their catalogs. Therefore, he argued, the personnel on night shift needs to know unequivocally what reagent to order and to feed into the reactor.

Before closing, I wish to share with the professional community some really good news. The *Manual* series is going to be continued soon. Bruce Lipshutz, my friend and partner for many years, is preparing a fourth volume covering copper, gold, rhodium, nickel, titanium, and zirconium. Be assured this will once again become an outstanding collection of chemical arts and crafts.

Manfred Schlosser
December 2012

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Chapter One

Organoalkali Chemistry

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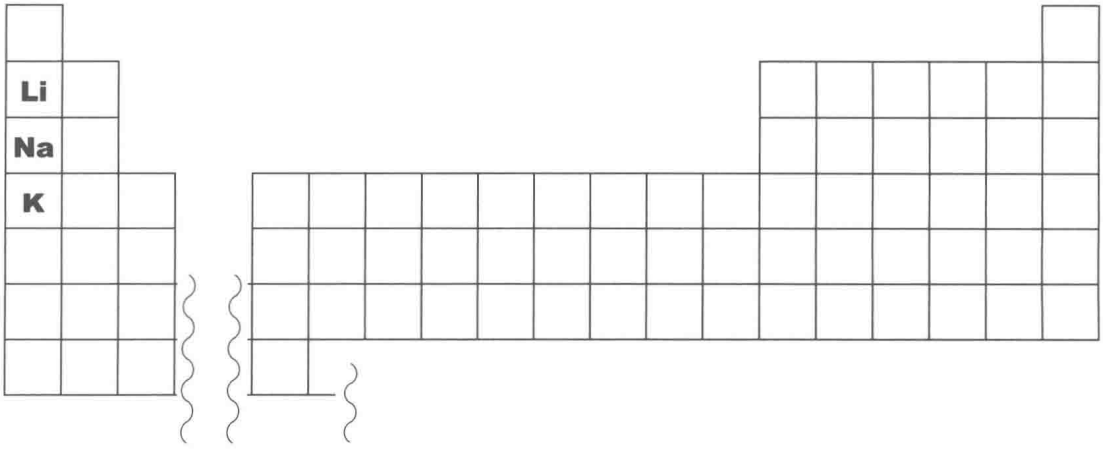

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List of Abbreviations

Ar	argon
BNZ	benzene
BOC	*tert*-butoxycarbonyl
DEE	diethyl ether
El	electrophilic part of a reagent *El*–X
El–X	electrophilic reagent
eq.	(molar) equivalent
glyme	ethylene glycol dimethyl ether
HEX	hexanes (or petroleum ether of bp ~65 °C)
LIC-KOR	superbasic 1:1 mixture of LiC_4H_9 and $KOC(CH_3)_3$
LIDA	lithium diisopropylamide
LIDMAE	lithium 2-(dimethylamino)ethoxide
LIM-KOR	superbasic mixture of $LiCH(CH_3)C_2H_5$ and $KOC(CH_3)_3$
LIT-KOR	superbasic mixture of $LiC(CH_3)_3$ and $KOC(CH_3)_3$
LITMP	lithium 2,2,6,6-tetramethylpiperid-1-ide
M-*Nu*	metal-bearing nucleophile (alkoxide, amide)
Nu	nucleophilic group
NAC-KOR	superbasic 1:1 mixture of LiC_4H_9 and $NaOC(CH_3)_3$
NMR	nuclear magnetic resonance
PMDTA	*N,N,N′,N″,N″*-pentamethyldiethylenetriamine
PEN	pentanes
R	alkyl or aryl
spec.	specifically (on this or that page)
Sv	solvent
THF	tetrahydrofuran
TOL	toluene
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine

1 Introduction

Indispensable tools in modern synthesis, organometallic reagents were perceived as exotic rarities half a century ago. What caused this profound change in attitude? The breakthrough event was without doubt the discovery of the *ortho* metalation of anisole and other heterosubstituted arenes by the pioneering work of Georg Wittig, Henry Gilman, and Charles Hauser. When in 1979, Heinz Gschwend and H. Rodriguez[1] summarized the progress made in this field, a steadily growing community of disciples in both academia and industry had recognized the potential of the new opportunities and had proliferated the underlying ideas in many directions. However, it needed more to transform episodes into a permanent success story. There are unique features that distinguish the organometallic approach to synthesis from previously existing options and establish it as an alternative or complementary concept.

The most salient particularity is presumably the better *polarity balance* inherent in reactions of polar organometallics. Saturated aliphatic hydrocarbons are totally inert toward nonradical species, and olefins or arenes are too weakly nucleophilic to combine with anything but the strongest electrophiles. This requires drastic conditions and entails poorly selective processes. In contrast, methyllithium or phenyllithium react smoothly with all kinds of electron-hungry substrates including such "lame ducks" as nitrosyl chloride or mercury acetate. This pronounced nucleophilicity widens the choice of reaction partners almost without any restriction and, as a corollary, ascertains *product flexibility*. Actually, an alkali metal attached to a carbon skeleton can be viewed like a joker in a card game destined to be traded in against something else.

The regioselective metalation of arenes at a position neighboring a heterosubstituent has been mentioned above. Deviations from the *ortho* rule do exist but are scarce.[2–5] The metal can nevertheless be systematically directed to *meta* or *para* positions if one resorts to the deployment of protective groups or similar stratagems.[6] Organometallics enable regiocontrol also in the alkenyl series. The addition of bromine onto the double bond of ω-chlorostyrene and subsequent base-mediated dehydrobromination unselectively produces a (*Z*/*E*) mixture of 1-bromo-2-chloro-1-phenylethenes. Conversely, the metalation of *cis*- and *trans*-ω-chlorostyrene (1-chloro-2-phenylethene) followed by trapping with a source of elemental bromine affords (*E*)- and (*Z*)-ω-bromo-ω-chlorostyrene, respectively.[7] These examples also shine a spotlight on the typoselectivity (or "chemoselectivity") issue. Whereas ethylene reacts with bromine under addition, vinyllithium undergoes clean substitution. In other words, the organometallic reaction avoids a two-step sequence of consecutive addition and elimination. Such a shortcut often will be welcome.

A widely overlooked aspect of organometallic reactions is their *economy*. Actually, they are widely considered to be expensive although the price of the reagent is generally negligible. To work at temperatures of liquid ammonia or dry ice has nowadays become routine. It is true that lithium has to be removed from industrial waste waters after isolation of the product. This drawback is more than compensated by major advantages. Organoalkali reactions are generally clean and high-yielding. Therefore, they frequently offer the possibility to contract two or more individual stages to a nonstop procedure. The expedient preparation of the analgetic ibuprofene in a six-step-one-flask protocol supports this view convincingly.[8]

Workup can prove to be very costly, and water, due to its high heat of evaporation, is far from being an ideal reaction medium. The solvents employed in organometallic chemistry use to be mixtures of hexanes and an ethereal cosolvent (*e.g.*, *tert*-butyl methyl ether) or toluene. They can be removed in an energy-efficient manner by distillation. The product left behind is most frequently a salt-like compound such as a metal carboxylate, metal alkoxide, or metal amide. After neutralization with a *stoichiometric* amount of an anhydrous strong acid, it can be extracted and directly purified.

2 Coverage

The present survey is exclusively devoted to the application of polar organometallic reagents to organic synthesis. This exciting subject was only accessorily treated in the chapter on "Organoalkali Chemistry" that was published as part of the Second Manual[9] of the *Organometallics in Synthesis* handbook series. A supplement was deemed appropriate if not mandatory.

Under such circumstances, it should prove helpful to start with recalling the contents of the above-mentioned chapter. It is composed of five main sections:

§ 1 Historical Background (9 pages)

§ 2 Structure and Mobility of Polar Organometallics (36 pages)

§ 3 Reactivity and Selectivity of Polar Organometallics (39 pages)

§ 4 Preparation of Organometallic Reagents and Intermediates (200 pages)

§ 5 Handling of Organoalkali Compounds (13 pages)

Before organometallic intermediates can be converted into isolable products, they need to be prepared. Their generation is hence as critical as their ultimate transformation. This explains why more than half of the allotted space, 200 out of 352 pages (references included), has been reserved for this topic. A brief overview of this cornerstone section

(§ 4) will hence be given. There are two times five methods to choose from in order to prepare a reactive organometallic species M–R from an organic precursor Z–R wherein Z represents a halogen X (Cl, Br, I), chalcogen Y (O, S, Se), metalloid Q (Hg, Sn), carbon group (C), or hydrogen (H). If used in its elemental state, the metal (M) may insert *reductively* into the Z–R bond, or alternatively, if contained in an organometallic reagent M–R', it can promote a *permutational* M/Z displacement (Table 1–1). To give an idea of the practical significance of each of these options, the number of pertinent examples and, in parentheses, working procedures selected from the literature and compiled in the Second Manual are listed (Table 1–1).

Table 1–1. Two times five methods for the generation of organometallic intermediates M–R from organic precursors Z–R.

reductive M insertion into the Z-R bond	electrofugal group Z	permutation with the M-R' reagent
43 (10)	X (halogen)	272 (6)
52 (5)	Y (chalcogen)	26 (2)
24 (4)	Q (metalloid)	87 (5)
9 (3)	C (carbon)	13 (3)
21 (1)	H (hydrogen)	663 (56)

Halogen/metal permutation and hydrogen/metal permutation (usually apostrophed as "metalation") dominate the interconversion methods. They employ organoalkali reagents such as phenyllithium, methyllithium, *n*-butyllithium, *sec*-butyllithium, or the superbasic LIC-KOR mixture. However, even if commercial, these reagents have to be made beforehand. The reaction of a chloro- or bromo-substituted hydrocarbon with lithium, sodium, or magnesium offers a standard entry to them. Thus, ultimately one always has to revert to the metal.

3 Reactions

Depending on the transformation executed, the metal of an organometallic reagent will be replaced by a hydrogen atom, another metal or metalloid, a heterosubstituent, or a carbon entity. Allowing for some further differentiation, we may classify organometallic reactions into eight prototypes (Figure 1–1). They comprise partial or complete neutralization by proton transfer from weak acids (such as hydrocarbons), moderately strong acids (such as amines), or strong acids (in particular, hydroxyl containing ones), but also cover metal/metal(loid) exchange, substitution by a heteroatom or a heterofunctional group, condensation with a carbon electrophile, nucleophilic addition onto multiple bonds, β-eliminations, and isomerizations or rearrangements.

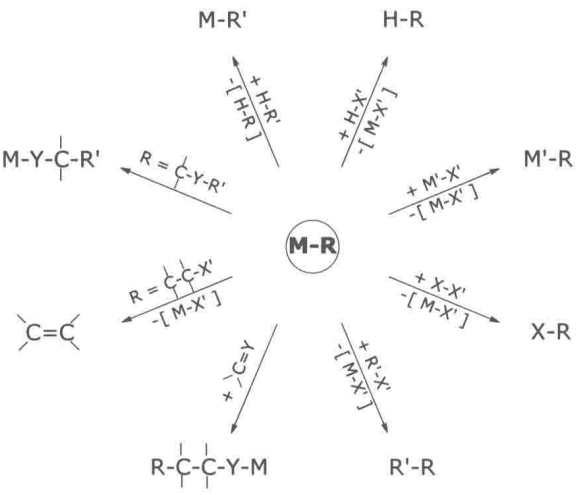

Figure 1–1. Classification of organometallic reactions into eight categories: replacement of the metal by hydrogen, another metal (or metalloid), a heterosubstituent, a carbon group, and eliminations or isomerizations.

Operationally simple as they are, such organometallic reactions have conquered a lasting place in modern organic synthesis. What makes them particularly attractive is their complementarity to well-known other methods.

3.1 Displacement of Metal by Hydrogen

An organometallic *reagent* M–R may react with a hydrocarbon H–R' under hydrogen/metal permutation to generate a new organometallic *intermediate* M–R'. Being subject to a variety of factors, the countercurrent metal and proton transfer process can proceed more or less rapidly. To make it occur at all, the substrate H–R' must be more acidic than the resulting hydrocarbon H–R.

If a metal–carbon (or metal–nitrogen) bond is quenched by a strong proton donor such as methanol or hydrochloric acid, the original reactivity potential is completely lost. The neutralization of the organometallic species is diffusion controlled under such circumstances.[10] The same is the case with an alcohol or an amine such as diisopropyamine. As a rule, OH and NH containing compounds are stronger acids than hydrocarbons. Their deprotonation is quantitative and instantaneous ($\leq$1 s) even at dry-ice temperatures (–75 °C).[11]

Although an amide base M–NR'_2 is thermodynamically less powerful than alkyl- or arylmetals, it but may prove kinetically superior. Thus, amines may be used in catalytic amounts to speed up organolithium-driven deprotonations (see example on p. 10).

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