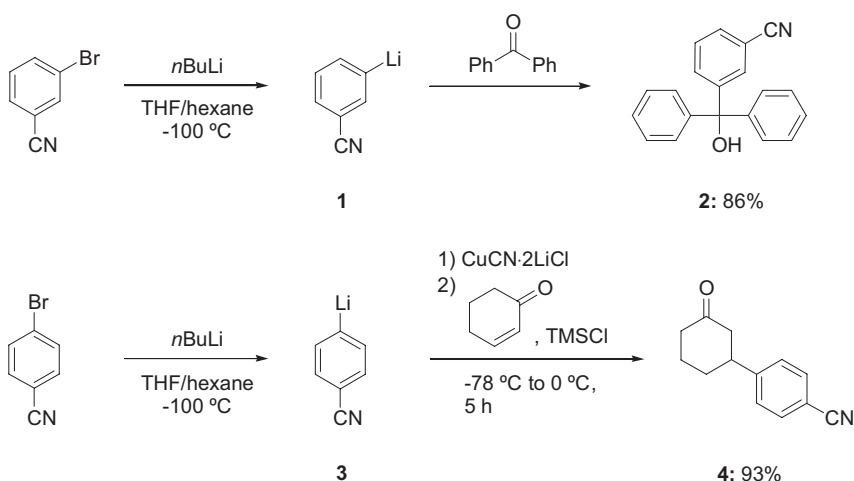


1

Introduction

Paul Knochel and Felix Kopp

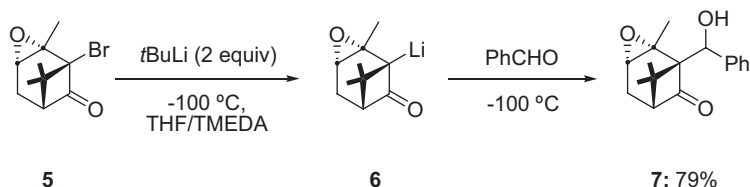
Achieving selectivity in chemical reactivity is one of the most important goals in synthetic chemistry. This holds especially true for organometallic compounds in which the carbon attached to the metallic center behaves as a nucleophile. The nature of the metal or of the metallic moiety (MetL_n) is exceedingly important for tuning this reactivity. An ionic character of the carbon–metal bond leads to a polarity of this bond and to a high reactivity towards electrophilic species. This high reactivity precludes the presence of many functional groups in organometallics like organolithiums. However, by lowering the reaction temperature and using a solvent of moderate polarity, it is also possible to prepare functionalized organolithiums. Especially interesting was the pioneering work of Parham, who showed that a bromine–lithium exchange can be readily performed at -100°C in a THF–hexane mixture leading to the functionalized organolithium compound **1**.



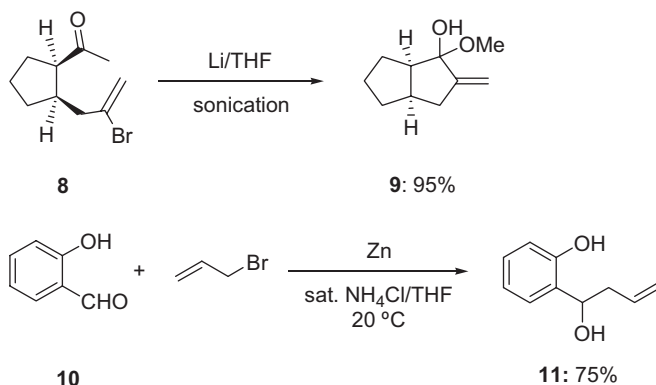
Scheme 1.1 Preparation of nitrile-functionalized aryllithiums by a low-temperature Br–Li exchange.

Its reaction with benzophenone provides the desired alcohol **2** in 86% yield [1]. The need for keeping the highly reactive lithium intermediate **1** at $-100\text{ }^{\circ}\text{C}$ is a preparative limitation, which can be avoided by performing a transmetalation of the functionalized aryllithium to a less electropositive metal, such as zinc or copper. The resulting organometallic species is stable at much higher temperatures (0 – $25\text{ }^{\circ}\text{C}$), but still reactive enough to undergo efficient conjugated 1,4-addition. Thus, the cyano-substituted aryllithium **3**, readily prepared by a bromine–lithium exchange at $-100\text{ }^{\circ}\text{C}$, reacts within a few minutes at this low temperature with the THF-soluble salt $\text{CuCN}\cdot 2\text{LiCl}$ [2] and provides a functionalized copper reagent that reacts smoothly with cyclohexanone in the presence of TMSCl and provides the Michael-adduct **4** in 93% yield (Scheme 1.1) [3].

Even many sensitive functional groups, such as a ketone and an epoxide, can be present in a polar organometallic species, like an organolithium. Thus, the bicyclic bromide **5** undergoes an efficient Br–Li exchange reaction at $-100\text{ }^{\circ}\text{C}$ in THF/TMEDA affording the unstable polyfunctional lithium reagent **6**, which is trapped with benzaldehyde affording the benzylic alcohol **7** in 79% yield (Scheme 1.2) [4]. Low temperature allows the preparation of highly reactive organometallics, but only very active electrophiles react with these reagents at low temperature, which is a serious limitation. Furthermore, large-scale syntheses involving very low temperatures are difficult to set up and to apply in industry. An alternative constitutes a Barbier procedure [5], in which the reactive polyfunctional lithi-



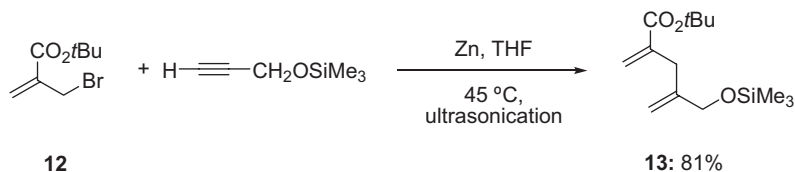
Scheme 1.2 Low-temperature preparation of an organolithium species bearing an epoxide and a ketone.



Scheme 1.3 Barbier reactions using polyfunctional substrates.

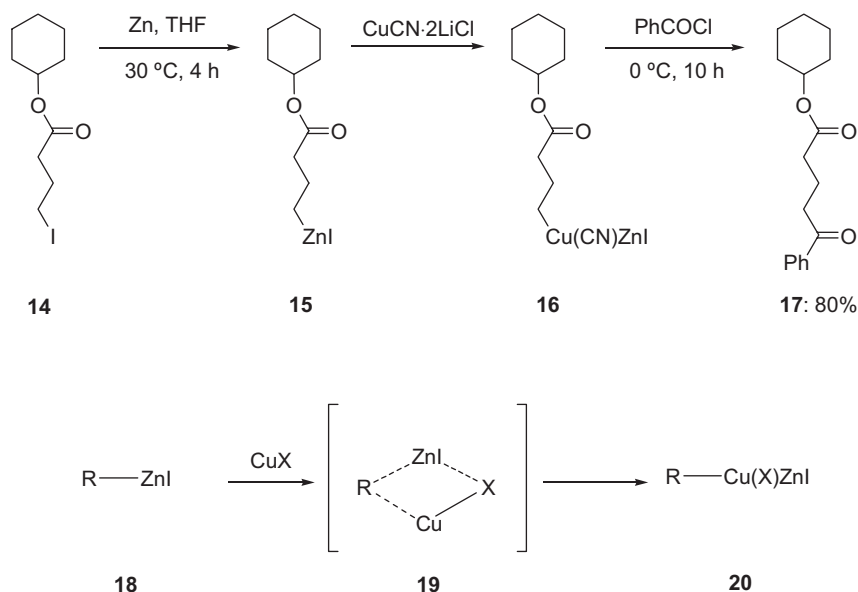
umorganic is directly generated in the presence of the electrophile. Thus, the sensitive bromoketone **8** can be converted *in situ* to the corresponding lithium species by the direct treatment with lithium metal when sonication is applied, leading to the bicyclic tertiary alcohol **9** in 95% yield [6].

Barbier reactions allow the generation of organometallic intermediates that are difficult to store or to generate in the absence of an electrophile. Thus, it was possible to perform the addition of an allylzinc moiety to an aldehyde, such as **10**, bearing a free hydroxy group in a 5:1 mixture of saturated aq. NH_4Cl /THF at room-temperature affording the product in 75% yield without the need of a protecting group (Scheme 1.3) [7]. New types of reactions, such as carbozincation reactions of alkynes using functionalized allylic zinc reagents can be readily accomplished. Thus, the reaction of a silylated propargyl alcohol with *t*-butyl(2-bromomethyl)acrylate (**12**) in the presence of zinc in THF at 45 °C under sonication provides the addition product **13** in 81% yield with excellent regioselectivity (Scheme 1.4) [8].



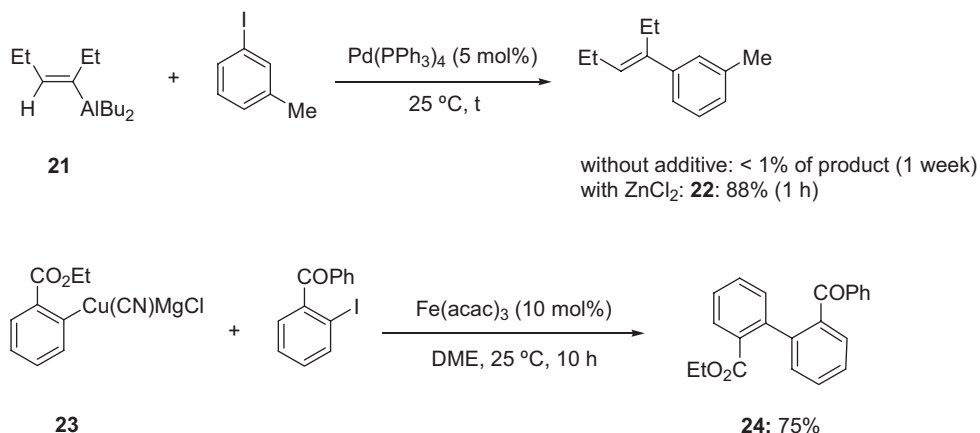
Scheme 1.4 Regioselective addition of a functionalized allylic bromide to alkynes.

The examples above show that the preparation of polyfunctional lithium reagents can be mastered in many cases, but often low temperature and very careful control of the reaction conditions have to be applied. The use of protecting groups is mandatory and reduces the overall yield of the reaction sequences including the protection and deprotection steps. The use of organometallics bearing more covalent carbon–metal bonds would avoid extreme reaction conditions. In 1988 it was found that organozinc iodides bearing numerous functional groups, such as an ester or a ketone can be readily prepared by the direct insertion of zinc dust at 45–50 °C. The resulting organozinc species has unfortunately a moderate reactivity and a transmetallation is required to adjust the intrinsic low reactivity of the zinc reagent. Therefore, the reaction of the functionalized alkyl iodide **14** with zinc dust produces within 4 h at 30 °C the corresponding alkylzinc iodide **15**. It is important in this reaction to keep the reaction temperature below 35 °C in order to avoid competitive deprotonation of the comparably acidic protons in the alpha position to the carbonyl group. Under these conditions, the desired zinc reagent can be prepared in high yield. The addition of $\text{CuCN}\cdot 2\text{LiCl}$ allows the preparation of the corresponding copper reagent **16** within a few minutes, which is readily acylated with PhCOCl providing the desired product **17** in 80% yield (Scheme 1.5) [2].



Scheme 1.5 Fine tuning of the reactivity of functionalized organometallic species by transmetalation.

The success of this transmetalation for adjusting the reactivity of the zinc organometallic relies on two main facts. Organozincs **18** undergo a series of transmetalations with transition metal salts due to the presence of empty p-orbitals of appropriate energy that facilitate 4-membered transition states such as **19**, leading to the copper–zinc species **20**. Secondly, the resulting copper reagent, although being thermodynamically more stable (more covalent carbon–copper bond) is also more reactive due to the presence of nucleophilic, nonbonding d-electrons that interact in an oxidative process with the electrophile and catalyze the formation of the new carbon–carbon bond. This concept is quite general and Negishi has shown the importance of sequential transmetalations for adjusting the reactivity in cross-coupling reactions [9]. Thus, the reaction of alkenylalane **21** with 3-iodotoluene does not proceed directly. After one week at 25 °C less than 1% of the cross-coupling product is obtained. On the other hand, in the presence of zinc chloride rapid cross-coupling takes place within one hour leading to the styrene derivative **22** in 88% yield. This reaction takes place via an alkenylzinc species that is readily obtained by transmetalation from the alkenylalane **21** (Scheme 1.5). This example shows the importance of mixed metal catalysis. Recently, it was found that, while the cross-coupling of arylmagnesium derivatives with aryl iodides catalyzed by $\text{Fe}(\text{acac})_3$ produces only homo-coupling products, the reaction of the corresponding magnesium cuprate **23** furnishes smoothly the desired cross-coupling product **24** in 75% yield (Scheme 1.6) [10].



Scheme 1.6 Mixed metal catalysis for efficient cross-coupling reactions.

These general concepts can be applied to a number of organometallic compounds and over the years have allowed the development of an arsenal of synthetic methods for preparing polyfunctional organometallics and for selective reactions of these versatile intermediates. This book intends to cover the broad aspects of this chemistry that should find broad application in industry and universities.

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