Recent Advances of the Halogen–Zinc Exchange Reaction

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For the preparation of zinc organometallics bearing highly sensitive functional groups such as ketones, aldehydes or nitro groups, especially mild halogen–zinc exchange reagents have proven to be of great potential. In this Minireview, the latest research in the area of the halogen–zinc exchange reaction is reported, with a special focus lying on novel dialkylnzinc reagents complexed with lithium alkoxides. Additionally, the preparation and application of organofluorine zinc reagents and transition-metal-catalyzed halogen–zinc exchange reactions are reviewed.

Introduction

Polyfunctional organometallics are useful reagents for the preparation of a wide range of complex molecules, and therefore play an important role in modern organic chemistry.[1] In the past decades, several preparation methods of these reagents have been disclosed and the development of various halogen–metal exchange reagents have been reported.[3,2,3] Allylthium reagents (nBuLi, sBuLi, or tBuLi),[4] for example, promote efficient iodine or bromine–lithium exchange reactions, whereas the “turbo-Grimnard” (PMgCl-LiCl) has been used to prepare a plethora of magnesium organometallics.[5] However, lithium and magnesium reagents are highly reactive and therefore often lack sensitive functional group tolerance, like nitro, azido, or triazine groups, or functionalities bearing acidic protons. Hence, zinc organometallic reagents have been developed to perform efficient and yet mild halogen–zinc exchange reactions. In this Minireview, recent advances of the halogen–zinc exchange are described, with a special focus on novel activated dialkylnzinc exchange reagents.

Halogen–Zinc Exchange Using Tri- or Tetraalkylzincates (R₂ZnLi or R₄ZnLi₂)

Efficient reagents for halogen–zinc exchange reactions are tri- or tetraalkylzincates (R₂ZnLi or R₄ZnLi₂) which are prepared by mixing a dialkylnzinc with various equivalents of an organolithium RLi.[2] Thus, when dibromoalkanes of type 1 or 2 are treated with triorganozincate nBu₂ZnLi (3, 1.2 equiv) in THF at −85 °C for 3 h, a bromine–zinc exchange takes place, leading to alkynylzinc reagents 4 and 5. After hydrolysis, monobromoalkenes 6 and 7 are obtained in 82–97% yield (Scheme 1).[6]

Scheme 1. Br/Zn exchange on dibromoalkanes.

Also, dibromoalkanes 8 and 9 are suitable substrates for bromine–zinc exchange reactions using triorganozincates (Scheme 2). Thus, when being treated with nBu₂ZnLi (3) or sBu₂ZnLi (10), an initial Br/Zn exchange leads to alkylzincs 11–12, which, after rearrangement, provides dialkylnzinc reagents 13–14. After acylation or palladium-catalyzed Negishi cross-coupling[7] the functionalized alkanes 15–16 are obtained in 62–75% yield (Scheme 2).[8]

An original approach towards benzylic zinc reagents was found, when iodoarene 17 is treated with nBu₂ZnLi (3) or tBu₂ZnLi (18, Scheme 3). An I/Zn exchange takes place readily at −85 °C, producing organozincs 19–20, which, after warming to −40 °C, undergo intramolecular alkylation, leading to benzylic zinc reagents 21–22. After quenching with aldehydes, alcohols 23–24 are obtained in 56–80% yield (Scheme 3).[9]

The high reactivity of lithium zincates allows the performance of I/Zn exchange reactions on iodoarenes as disclosed by Sakamoto and Kondo (Scheme 4).[10] Thus, sensitive iodoarenes 25–26 bearing an ester and a nitro group are treated with Me₂ZnLi (27) at −78 °C for 1 h, providing the lithium arylzincates 28–29.[10] After reaction with benzaldehyde, alcohols 30–31 are obtained in 68–74% yield. Also, tBu₂ZnLi (18) reacts readily with an electron-rich aryl iodide 32, providing...
Structural and reactivity insights on magnesium zincates were reported by Hevia and co-workers. Thus, mixing tBuMgCl (3.0 equiv) with ZnCl₂ (1.0 equiv) leads to the formation of magnesium trialkylzincate 41. When aryl iodides 42–43 are treated with 41, the magnesium triarylzincates 44–45 are obtained and used in palladium-catalyzed cross-coupling reactions with aryl bromides, yielding biaryls 46–47 in 75–86% yield (Scheme 6).

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Paul Knochel was born 1955 in Strasbourg (France). He studied at the University of Strasbourg (France) and did his PhD at the ETH Zürich (D. Seebach). In 1987, he was appointed Professor at the University of Michigan. In 1992, he moved to Philippus-University at Marburg (Germany). In 1999, he then moved to the Chemistry Department of Ludwig-Maximilians-University in Munich (Germany). His research interests include the development of novel organometallic reagents and methods for use in organic synthesis, asymmetric catalysis and natural product synthesis. Prof. Knochel received many distinguished prizes as for example, the Berthelot Medal of the Académie des Sciences (Paris), the IUPAC Thieme Prize, the Otto-Bayer-Prize, the Leibniz-Prize, the Arthur C. Cope Scholar Award, Karl-Ziegler-Prize, the Nagoya Gold Medal, the H. C. Brown Award and Paul Karrer gold medal. He is member of the Académie des Sciences, the Bavarian Academy of Science, the German Academy of Sciences Leopoldina. He is author of over 900 publications.
To improve the utility and scope of these zincates, higher order reagents of type $R_4ZnLi_2$ were developed. In this way, non-activated substrates such as bromobenzene (48) are zincated using the reagent $Me_4ZnLi_2$ (49). When $Me_4ZnLi$ (27) is used as exchange reagent, no halogen–metal exchange takes place. Additionally, the resulting zincate species proves to be more reactive towards electrophilic quench reactions. When aryl iodide 51, for example, is treated with $Me_4ZnLi$ (27), merely an iodine–zinc exchange is observed. However, when 51 is treated with the higher order zincate 49, an intramolecular Michael addition proceeds after the exchange reaction, providing the indoline 52 in 66% yield (Scheme 7).

Interestingly, highly reactive zincates of type $R_4ZnLi_2$ remain fairly functional group tolerant and allow smooth halogen–zinc exchange reactions in the presence of for example, an amide or a chiral acetal (Scheme 8). When iodoarene 53 is treated with $nBu_4ZnLi_2$ (54, 1.1 equiv), an iodine–zinc exchange readily proceeds. After allylation, the chiral product 55 is isolated in 74% yield and 99% ee. Amide 56 is allylated under similar conditions, leading to the allylated product 57 in 87% yield. Remarkably, the exchange is also possible with 4-iodophenol (58), if an excess of 54 is used (2.2 equiv), which leads, after allylation, to phenol 59 in 79% yield (Scheme 8).

These methodologies were extended to N-heterocycles (Scheme 9). The more reactive zincate $nBu_4ZnLi_2$-TMEDA (60) is used to convert various bromopyridines and -quinolines (61–64) to the corresponding lithium zincates. After quenching with iodine, diphenyl disulfide or 5-bromopyrimidine in the presence of a palladium catalyst, the functionalized pyridines 65–68 are obtained in 40–75% yield. Remarkably, the halogen–zinc exchange is performed in toluene and stoichiometric exchange reagent (0.33 equiv) is used, demonstrating that three of the four alkyl groups participate in this exchange reaction.

Additionally, zincate reagents are used for the generation of benzynes, which subsequently undergo facile Diels–Alder cycloaddition reactions. Also, zincates may participate in oxovanadium(V)-induced cross-coupling reactions. 2-Thienyl zincates are used in the preparation of poly(3-hexylthiophene) (P3HT), which belongs to the class of poly-alkylthiophenes; PATs, that are of interest as organic materials.

**Halogen–Zinc Exchange Using Dialkylzincs**

Early studies towards halogen–zinc exchange reactions were reported by Nishimura and Hashimoto for the preparation of zinc carbenoids. Tetramethylethylene, for example, is treated with diethylzinc and diiodomethane, which leads to the cyclopropanated product in 53% yield. In contrast to the well-known Simmons–Smith reaction, which requires 15–70 h reaction time, this cyclopropanation proceeds within minutes. A broader substrate scope is achieved, when functionalized alkyl iodides are added to $Et_2Zn$ (5.0 equiv, neat) and stirred at elevated temperatures. Thus, alkyl iodide 69, bearing an ester functional group, is mixed with $Et_2Zn$ (70, 5.0 equiv) and stirred at 50°C for 4 h, which gives the mixed zinc species 71. After
removal of the volatiles (Et₂Zn, EtI), dialkylzinc 72 is obtained, which undergoes a Michael-addition to a nitroolefin, producing the functionalized alkane 73 in 82% yield (Scheme 10). Zinc organometallics obtained by the same22 or a similar23 method (74–75) are also used for asymmetric addition reactions in the presence of the chiral catalyst 76. The resulting dialkylics are treated with aldehydes, leading to the chiral alcohols 77–78 in 88–95% yield and up to 93% ee (Scheme 10).22,23 Notably, 78 is a prostaglandin and leukotriene building block.23a

The iodine–zinc exchange of secondary alkyl iodides 79 proceeds using iPr₂Zn (80).24 Remarkably, when the reagent is prepared from 2 iPrMgBr and ZnBr₂, leading to iPr₂Zn·2MgBr₂ (81), the exchange reaction proceeds up to 200 times faster due to the presence of this magnesium salt.24 This may be explained by the formation of the dibromozincate [iPr₂ZnBr₂]₂⁻[MgBr₂]³⁻. Thus, when secondary iodides (79a–b) are treated with iPr₂Zn (80, 1.5 equiv), the alkylzinc reagents 82a–b are obtained (Scheme 11). After transmetallation to copper using a CuCN·2LiCl solution in THF and electrophilic trapping, alkyn 83 and ketone 84 are obtained in 62–82% yield.

Menthyli iodide (79c) is used for this transformation, which, after mixing with iPr₂Zn·2MgBr₂ (81), gives the mixed zinc organometallic 82c. After copper-mediated allylation, cyclohexane 85 is isolated in 61% yield (Scheme 11).24

After the discovery, that salt additives may accelerate the rate of iodine–zinc exchange reactions,24 it was found that the combination of iPr₂Zn (80) and Li(acac) (10 mol%) in Et₂O·NMP allowed efficient halogen–magnesium exchange reactions onaryl iodides.25 Thus, various aryl iodides bearing sensitive functional groups such as isothiocyanates or aldehydes of type 86 are treated with iPr₂Zn (80) and catalytic amounts of Li(acac) (10 mol%), generating biarylzincs of type 87. Trapping with various electrophiles gives 88a–c in 60–84% yield (Scheme 12).25 From a mechanistic perspective, the acetylacetone anion may lead to the formation of a tetracoordinated zinc species. This intermediate A is reactive enough to undergo a second iodine–zinc exchange, providing zincate B, which leads to diaryl zinc 87 and Li(acac) (Scheme 12).25 Various additives play a major role in the rates of halogen–metal exchange reactions (e.g. LiCl,26 MgBr₂,24 or Li(acac)25). In most cases, it is presumed that the additive leads to the formation of a higher coordinated zincate and thus more reactive metal intermediate. In the course of our investigations towards the preparation of more efficient halogen–magnesium exchange reagents, it was found that the addition of alcoholates

Scheme 10. Generation of allylzincs using diethylzinc and their trapping reactions.

Scheme 11. Iodine–zinc exchanges of secondary alkyl iodides using iPr₂Zn (80) or iPr₂Zn·2MgBr₂ (81).

Scheme 12. Preparation of highly functionalized diarylzincs using iPr₂Zn in the presence of catalytic amounts of Li(acac).
may drastically increase the reactivity of the halogen–magnesium exchange. With this information at hand, the generation of dialkylzinc organometallics, complexed with lithium alkoxides were investigated. When an aminoalcohol ROH (89, 2.0 equiv, $R = \text{CH}_2\text{CH}_2\text{NH}-(\text{CH}_3)\text{CH}_2\text{NH}(\text{CH}_3)_2$) is treated with Et$_2$Zn in toluene, a mixed zinc species, tentatively described as [ROZnEt-ROH] (90) is obtained. Upon addition of sBuLi (2.0 equiv), di-sec-butylzinc complexed with two lithium alkoxides of the formula sBu$_2$Zn·2LiOR (91) is produced (Scheme 13).}$

This exchange reagent is highly reactive towards iodine or bromine–zinc exchange reactions. Indeed, the iodine–zinc exchange of 3-iodoanisole (92) is complete after only 1 minute, providing the diarylzinc93 (Scheme 14). After a palladium-catalyzed Negishi cross-coupling with an aryl iodide, biaryl 94 is isolated in 76% yield. Similarly, a functionalized pyridine 95 or a pyridone derivative 96 are suitable substrates for this exchange reaction, leading to zinc organometallics 97–98. After copper-mediated acylation or allylation, ketone 99 and lactam 100 are obtained in 85–96% yield (Scheme 14).$^{[27]}$

Since zinc organometallics possess a particularly unreactive carbon–zinc bond, highly sensitive functional groups such as triazines, aldehydes, ketones or nitro-groups are tolerated. Under standard reaction conditions, an aryl iodide bearing a triazine functional group (101a) is converted to the diarylzinc 102a and quenched with allyl bromide, providing 103a in 72% yield (Scheme 15).$^{[27]}$ In some cases, slight modifications of the exchange reagent are required. Thus, when 2,4-dinitroiodobenzene (101b) is treated with pTol$_2$Zn·2LiOR (104, 0.6 equiv, –15°C, 15 min), as smooth iodine–zinc exchange takes place, affording 102b, which, after allylation, leads to the dinitroarene 103b in 79% yield. For an iodine–zinc exchange to proceed in the presence of aldehydes, tBu$_2$Zn·2LiOR (105) gives the best results. Hence, 5-iodo-2-furaldehyde (101c) is treated with the exchange reagent 105 (0.8 equiv, 0°C, 10 min), leading to biarylzinc 102c. After an allylation, the furyl aldehyde 103c is obtained in 66% yield (Scheme 15).$^{[27]}$

Finally, the high reactivity of these alkoxide complexed dialkylzinc reagents allow a bromine–zinc exchange reaction. Therefore, various functionalized (hetero)aryl bromides (106a–d) are treated with 91 (0.8 equiv, 25°C, 30 min–5 h), producing diarylzincs 107a–d. After various electrophilic trapping reactions, a plethora of functionalized arenes and heteroarenies 108a–d are obtained in 60–77% yield (Scheme 16).$^{[27]}$

![Scheme 13. Preparation of the dialkylzinc reagent sBu$_2$Zn·2LiOR (91).](image1)

![Scheme 14. Generation of diarylzinc organometallics using sBu$_2$Zn·2LiOR (91).](image2)

![Scheme 15. Iodine–zinc exchange of highly sensitive substrates using exchange reagents of the general formula R$_2$Zn·2LiOR.](image3)

![Scheme 16. Bromine–zinc exchange of various (hetero)aryl bromides using sBu$_2$Zn·2LiOR (91).](image4)
Transition-Metal-Catalyzed Halogen–Zinc Exchange Reactions

The addition of transition metal salts also catalyzed the halogen–zinc exchange. Whereas without a transition metal a large excess of Et₂Zn (5.0 equiv) is required to perform an iodine–zinc exchange,[22] the addition of Cul (0.3 mol %) reduces the amount to 1.5 equivalents. Also, the rate of the exchange reaction is doubled.[28] Alkyl iodide 109, for example, when being treated with Et₂Zn (1.5 equiv) in the presence of Cul (0.3 mol %) and stirred at 50–55 °C for 8 h, undergoes a complete exchange. The resulting dialkylzinc 110 enantioselectively adds to an aldehyde in the presence of the chiral catalyst 76 (8 mol %), providing the alcohol 111 in 68% yield and 95% ee (Scheme 17).[28] It is noteworthy that the iodine–metal exchange is incomplete in absence of the copper salt and only a yield of 33% is obtained. When MnBr₂ (5 mol %) and CuCl (0.3 mol %) are simultaneously present in the reaction mixture, not only alkyl iodides but also alkyl bromides readily undergo halogen–metal exchange reactions.[29] Thus, when 4-bromobutyrate (112) is treated with Et₂Zn (0.9 equiv), MnBr₂ (5 mol %), and CuCl (0.3 mol %), alkylzinc bromide 113 is obtained. A subsequent palladium-catalyzed cross-coupling, provides the 1,2-functionalized arene 114 in 71% yield (Scheme 17).

Various transition metals are able to catalyze an I/Zn exchange and palladium(II) or nickel(II) salts are suitable additives to increase the rate of iodine–zinc exchange reactions.[30] When iodoalkane 115, which contains a remote alkene moiety, is treated with Et₂Zn (2.0 equiv) in the presence of PdCl₂(dppf) (1.5 mol %) an iodine–zinc exchange takes place, followed by cyclization, which leads to an organozinc halide 116. A copper-mediated substitution reaction produces the functionalized cyclopentane 117 in 80% yield (Scheme 18).[30] From a mechanistic perspective, it is presumed that palladium undergoes an oxidative addition to the carbon iodine bond, followed by intramolecular carbopalladation. After two ligand exchange reactions, 116 is formed, ethane and ethylene are set free, and the Pd⁶ species is regenerated (Scheme 18).[30]

Such cyclization reactions are highly stereoselective and the ring closure of iodoalkane 118, when treated with Et₂Zn in the presence of the palladium catalyst, produces, after an iodine–zinc exchange and copper-mediated allylation, the trisubstituted cyclopentane 119 in a stereoconvergent manner (Scheme 19).[30]

Nickel-catalysis proved to be beneficial for the stereoselective preparation of heterocyclic zinc reagents.[30] Thus, when the iodinated acetal 120 is treated with Et₂Zn (2.0 equiv) in the presence of Ni(acac)₂ (2 mol %) the radical intermediate 121 forms, which cyclizes to the alkylzinc iodide 122. Transmetalation to copper and trapping with ethyl propiolate provides tetrahydrofuran 123 in 63% yield and a cis:trans selectivity of 15:85 (Scheme 20).[30]

When the iodo-tetrahydrofuran 124 is used under the same reaction conditions, an iodine–zinc exchange leads to the most stable radical 125, in which the alkyl substituents at C1 and C2 are in equatorial position and the alkoxysubstituent (C3) is positioned axially. After reaction with benzoyl chloride, the bicyclic heterocycle 126 is isolated in 64% yield (exo:endo = 2:98, Scheme 21).[30]

A further extension is achieved, when electron-rich triorganozincates are combined with iron or cobalt catalysts, which enables chlorine–zinc exchange reactions.[31] Adamantyl chloride (127), for example, is treated with the zincate 128 in the presence of Fe(acac)₃ (10 mol %) and 4-fluorostyrene (20 mol %). After quenching of the resulting metal species with
MeSO_SMe, the thioether 129 is obtained in 66% yield (Scheme 22). To expand the scope of this exchange reaction, the zincate was developed. However, the catalytic system needs to be modified and Co(acac)_2 provides best results. Thus, trichlorinated arene is treated with in the presence of Co(acac)_2 (20 mol %) and 4-fluorostyrene (50 mol %) at elevated temperatures (50 °C, 5 h). Quenching of the resulting organometallic with PhSO_2 SPh produces the diarylthioether 132 in 63% yield (Scheme 22).

Generation of Fluorinated Organozinc Reagents by Halogen–Zinc Exchange Reactions

It was found, that fluorinated iodoalkanes react with diethylzinc in the presence of a Lewis-base, producing dialkyliczinc agents. A synthetic utility for these fluorinated zinc organometallics was introduced by reacting these reagents with diiodo(hetero)arenes under copper catalysis, producing fused fluorinated ring systems. Building up on these results, a dialkyliczinc reagent, designed for difluoromethylation reactions, was developed. Thus, when difluoriodomethane is treated with Et_Zn (0.5 equiv) in DMPU (N,N'-dimethylpropyleneurea), the zinc reagent 133 is obtained in 94% yield. Mixing 133 with aryl halides or triflates, such as 134–135, under nickel-catalysis in DMSO, affords the difluoromethylated (hetero)arenes 136–137 in 67–72% yield (Scheme 23).

An interesting example for a difluoromethylene bis-carbanion surrogate is accessible by a cobalt-catalyzed halogen–zinc exchange reaction. Thus, when (bromodifluoromethyl)trimethylsilane (Me_3 SiCF_2 Br, 138) is treated with iPrZnI (1.0 equiv, 58 °C, 20 h) in the presence of CoBr_2·dppe (1 mol %), the fluorinated alkylzinc organometallic 139 is generated in 88% yield. It should be noticed, that a reductive zinc insertion reaction mainly leads to homo-coupling of the zinc species. In the first step, the generated alkylzinc 139 undergoes a copper-catalyzed alkylation reaction, providing intermediate 140 in 80% yield. Next, the silyl group is activated by catalytic amounts of cesium fluoride (15 mol %) and mixed with 4-chlorobenzaldehyde, producing alcohol 141 in 98% yield (Scheme 24).
scribed by Uchiyama and Hirano. Various fluorinated halogenated arenes and alkenes (142, 2.25 equiv) are mixed with iodoarenes of type 143, and Et₃Zn (1.5 equiv), copper iodide (10 mol%), and phenanthroline (0–20 mol%) are added. After stirring at 90 °C for 16 h, the cross-coupled products 144a–d are obtained in 56–88% yield (Scheme 25).[36]

**Scheme 25.** Copper-catalyzed cross-coupling reactions of various fluorinated arenes and alkenes with aryl iodides.

**Conclusion**

The development of the halogen–zinc exchange reaction over the last decades has made considerable progress. The traditional approach to prepare alkylzinc organometallics by zinc incorporation has been significantly extended with the development of new and highly reactive halogen–zinc exchange reagents. Both the use of lower order triorganozincates of type R₂ZnLi or higher order tetraorganozincates of type R₄ZnLi allow the preparation of various functionalized organic molecules, especially since the resulting zinc species are highly reactive towards various electrophiles. A milder approach was developed by using a set of dialkylzinc reagents complexed with metallic salts such as MgBr₂, Li(acac), or lithium alkoxides. Especially diarylzinc organometallics complicated with lithium alkoxides of type R₂ZnLiOR show a large increase in reactivity in comparison with previously developed halogen–zinc exchange reagents, enabling a bromine–zinc exchange reaction in both ethereal and non-polar solvents. Also, a range of transition-metal-catalyzed halogen–zinc exchange reactions have been developed, which enable a chlorine–zinc exchange reaction. A large application field for the halogen–zinc exchange reaction has been found in the preparation of sensitive fluorinated organozinc reagents, which can be employed in difluoromethylation or cross-coupling reactions. The latest developments towards the preparation of highly reactive and yet mild diorganozinc reagents will pave the way for novel transformations, relying on the optimal balance between increasing reactivity and high functional group tolerance.

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** alkoxides • lithium • magnesium • metal-halogen exchange • zinc

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