

Organometallic Chemistry | *Reviews Showcase*

## Recent Advances of the Halogen–Zinc Exchange Reaction

Moritz Balkenhohl and Paul Knochel\*<sup>[a]</sup>

**Abstract:** 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 halo-

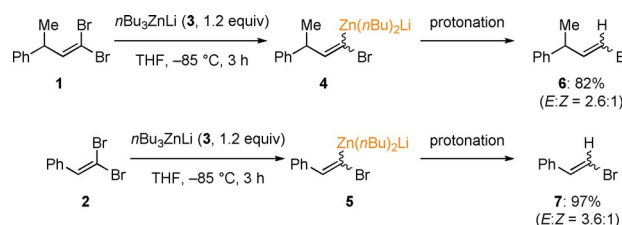
gen–zinc exchange reaction is reported, with a special focus lying on novel dialkylzinc reagents complexed with lithium alkoxides. Additionally, the preparation and application of organofluorine zinc reagents and transition-metal-catalyzed halogen–zinc exchange reactions are reviewed.

## 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.<sup>[1]</sup> 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.<sup>[1,2,3]</sup> Alkyl lithium reagents (*n*BuLi, *s*BuLi, or *t*BuLi),<sup>[4]</sup> for example, promote efficient iodine or bromine–lithium exchange reactions, whereas the “turbo-Grignard” *i*PtMgCl·LiCl has been used to prepare a plethora of magnesium organometallics.<sup>[5]</sup> 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 dialkylzinc exchange reagents.

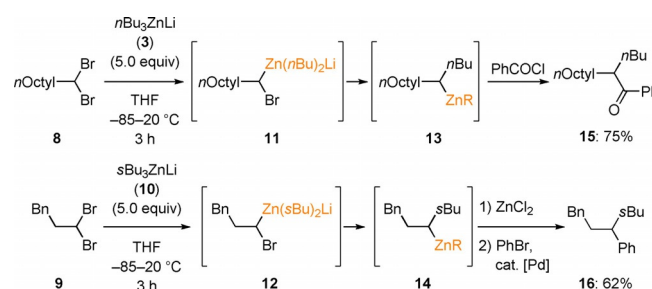
## Halogen–Zinc Exchange Using Tri- or Tetraalkylzincates (R<sub>3</sub>ZnLi or R<sub>4</sub>ZnLi<sub>2</sub>)

Efficient reagents for halogen–zinc exchange reactions are triorgano- (R<sub>3</sub>ZnLi, R = alkyl) or tetraorganozincates (R<sub>4</sub>ZnLi<sub>2</sub>) which are prepared by mixing a dialkylzinc with various equivalents of an organolithium RLi.<sup>[2]</sup> Thus, when dibromoalkenes of type **1** or **2** are treated with triorganozincate *n*Bu<sub>3</sub>ZnLi (**3**, 1.2 equiv) in THF at –85 °C for 3 h, a bromine–zinc exchange takes place, leading to alkenylzinc reagents **4** and **5**. After hydrolysis, monobromoalkenes **6** and **7** are obtained in 82–97% yield (Scheme 1).<sup>[6]</sup>



**Scheme 1.** Br/Zn exchange on dibromoalkenes.

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



**Scheme 2.** Br/Zn exchange on dibromoalkanes, followed by intramolecular alkylation and electrophilic quenching.

An original approach towards benzylic zinc reagents was found, when iodoarene **17** is treated with *n*Bu<sub>3</sub>ZnLi (**3**) or *t*Bu<sub>3</sub>ZnLi (**18**, Scheme 3). An I/Zn exchange takes place readily at –85 °C, producing organozinc **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).<sup>[9]</sup>

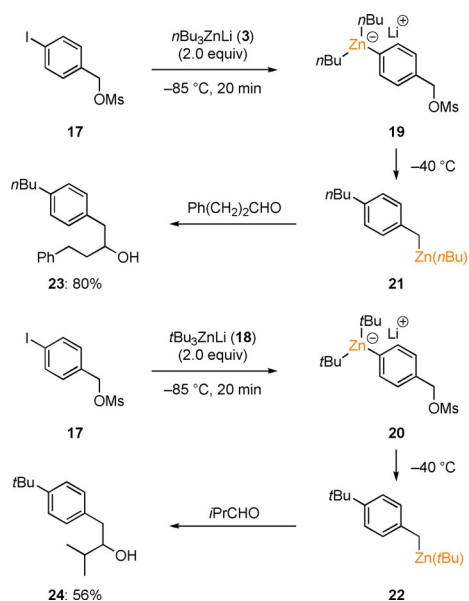
The high reactivity of lithium zincates allows the performance of I/Zn exchange reactions on iodoarenes as disclosed by Sakamoto and Kondo (Scheme 4).<sup>[10]</sup> Thus, sensitive iodoarenes **25–26** bearing an ester and a nitro group are treated with Me<sub>3</sub>ZnLi (**27**) at –78 °C for 1 h, providing the lithium arylzincates **28–29**.<sup>[10]</sup> After reaction with benzaldehyde, alcohols **30–31** are obtained in 68–74% yield. Also, *t*Bu<sub>3</sub>ZnLi (**18**) reacts readily with an electron-rich aryl iodide **32**, providing

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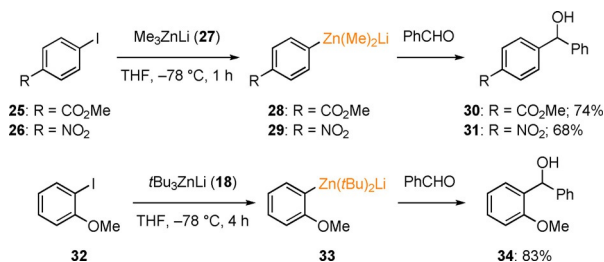
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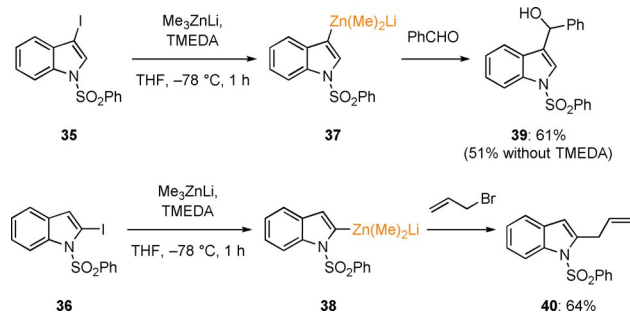
**Scheme 3.** I/Zn exchange on aryl halides bearing a remote mesylate leaving group, affording benzylic zinc reagents after intramolecular alkylation.



**Scheme 4.** I/Zn exchange on aryl iodides bearing sensitive electrophilic functional groups as well as an I/Zn exchange on 2-iodoanisole.

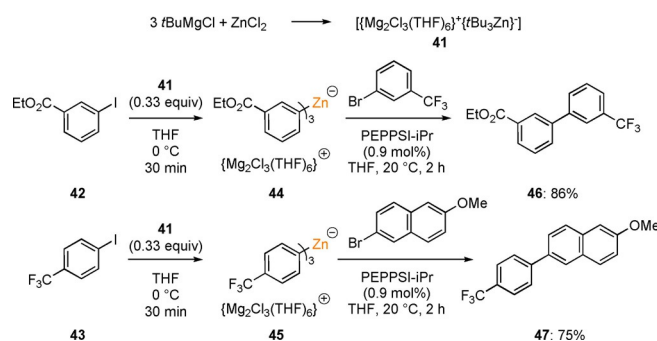
the zincate **33**, which leads to **34** after quenching with benzaldehyde in 83% yield (Scheme 4).<sup>[11]</sup>

Also, protected indoles (**35–36**) are suitable for such an exchange (Scheme 5).<sup>[12]</sup> Interestingly, the yield is increased by 10% by adding one equivalent of TMEDA (tetramethylethylenediamine) to  $\text{Me}_3\text{ZnLi}$  (**27**). After halogen–metal exchange, the zincates **37–38** are quenched with benzaldehyde or allyl bromide, giving rise to functionalized indoles **39–40** in 61–64% yield (Scheme 5).<sup>[12]</sup>



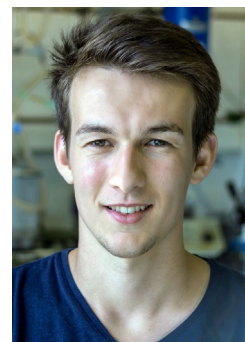
**Scheme 5.** I/Zn exchange reactions on indoles, using  $\text{Me}_3\text{ZnLi}$ -TMEDA.

Structural and reactivity insights on magnesium zincates were reported by Hevia and co-workers.<sup>[13]</sup> Thus, mixing  $t\text{BuMgCl}$  (3.0 equiv) with  $\text{ZnCl}_2$  (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).<sup>[13]</sup>



**Scheme 6.** I/Zn exchange using a magnesium triorgano zincate followed by cross-coupling reactions.

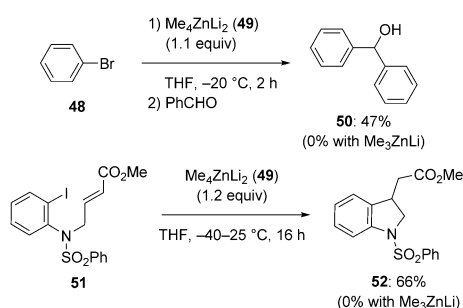
Moritz Balkenhohl was born 1992 in Speyer (Germany). He studied chemistry at the Julius-Maximilians-Universität Würzburg and at Imperial College London. In 2015 he joined the group of Prof. Paul Knochel for his Master thesis in Munich and started his PhD thesis in 2016. After having finished his PhD in 2019, he remained in the laboratory of Prof. Knochel as a postdoctoral researcher, and will now join the group of Prof. Erick M. Carreira at the ETH Zürich for his postdoctoral placement. His research focuses on the functionalization of challenging heterocycles, and halogen–metal exchange reactions.



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). He spent 4 years at the University Pierre and Marie Curie in Paris (J.-F. Normant) and one year at Princeton University (M. F. Semmelhack). In 1987, he was appointed Professor at the University of Michigan. In 1992, he moved to Philipps-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 Academie 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.

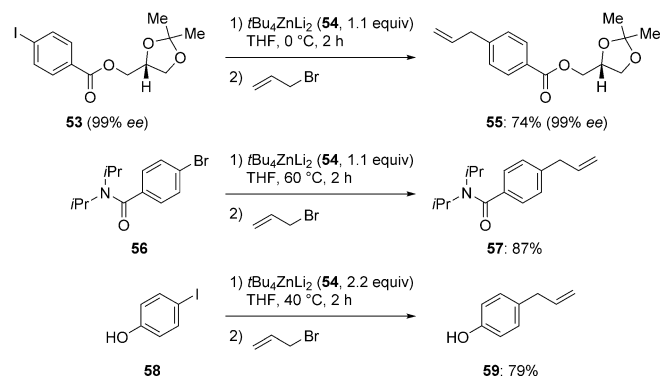


To improve the utility and scope of these zincates, higher order reagents of type  $R_4ZnLi_2$  were developed.<sup>[14]</sup> In this way, non-activated substrates such as bromobenzene (**48**) are zincated using the reagent  $Me_4ZnLi_2$  (**49**,  $-20^\circ\text{C}$ , 2 h) and, after quenching with benzaldehyde, alcohol **50** is obtained in 47% yield (Scheme 7).<sup>[14]</sup> When  $Me_3ZnLi$  (**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  $Me_3ZnLi$  (**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).<sup>[14]</sup>



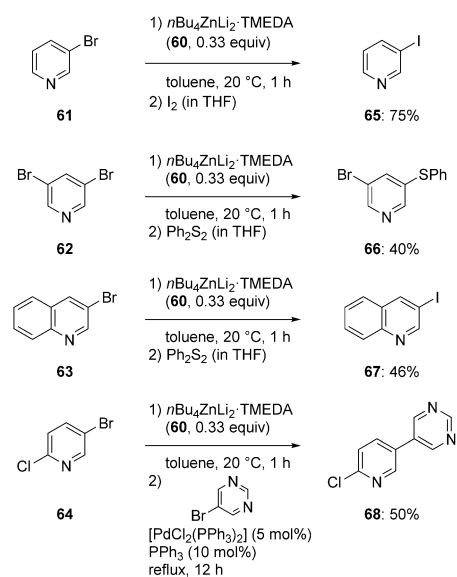
**Scheme 7.** Halogen–zinc exchange using the higher order zincate  $Me_4ZnLi_2$  (**49**).

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).<sup>[15]</sup> When iodoarene **53** is treated with  $tBu_4ZnLi_2$  (**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).<sup>[15]</sup>



**Scheme 8.** Halogen–zinc exchange of sensitive aryl halides and of an unprotected phenol.

These methodologies were extended to N-heterocycles (Scheme 9).<sup>[16]</sup> The more reactive zincate  $nBu_4ZnLi_2$ ·TMEDA (**60**) is used to convert various bromo-pyridines 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.<sup>[16]</sup> Remarkably, the halogen–zinc exchange is performed in toluene and substoichiometric exchange reagent (0.33 equiv) is used, demonstrating that three of the four alkyl groups participate in this exchange reaction.<sup>[16]</sup>



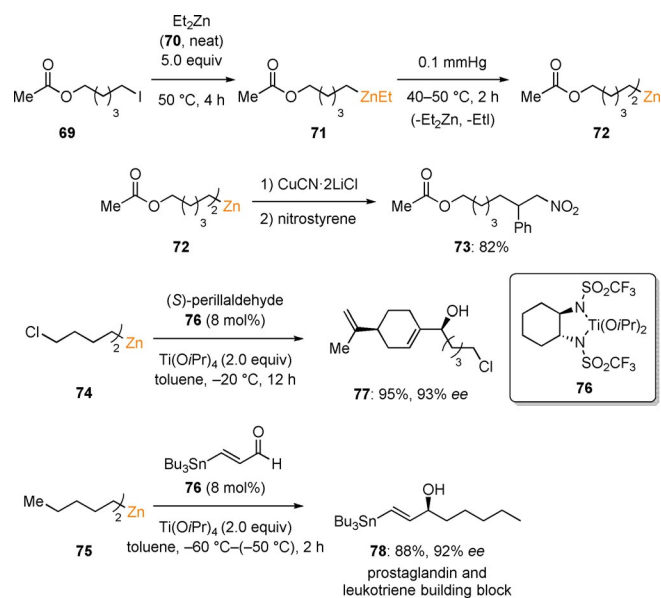
**Scheme 9.** Bromine–zinc exchange on various bromo-pyridines and -quinolines using  $nBu_4ZnLi_2$ ·TMEDA (**60**).

Additionally, zincate reagents are used for the generation of benzynes, which subsequently undergo facile Diels–Alder cycloaddition reactions.<sup>[17]</sup> Also, zincates may participate in oxovanadium(V)-induced cross-coupling reactions.<sup>[18]</sup> 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.<sup>[19]</sup>

## Halogen–Zinc Exchange Using Dialkylzincs

Early studies towards halogen–zinc exchange reactions were reported by Nishimura and Hashimoto for the preparation of zinc carbenoids.<sup>[20]</sup> Tetramethylethylene, for example, is treated with diethylzinc and diiodomethane, which leads to the cyclopropanated product in 53% yield.<sup>[20a]</sup> In contrast to the well-known Simmons–Smith reaction,<sup>[21]</sup> 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.<sup>[22]</sup> Thus, alkyl iodide **69**, bearing an ester functional group, is mixed with  $Et_2Zn$  (**70**, 5.0 equiv) and stirred at  $50^\circ\text{C}$  for 4 h, which gives the mixed zinc species **71**. After

removal of the volatiles (Et<sub>2</sub>Zn, 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 same<sup>[22]</sup> or a similar<sup>[23]</sup> method (**74–75**) are also used for asymmetric addition reactions in the presence of the chiral catalyst **76**. The resulting dialkylzincs are treated with aldehydes, leading to the chiral alcohols **77–78** in 88–95% yield and up to 93% *ee* (Scheme 10).<sup>[22,23]</sup> Notably, **78** is a prostaglandin and leukotriene building block.<sup>[23a]</sup>

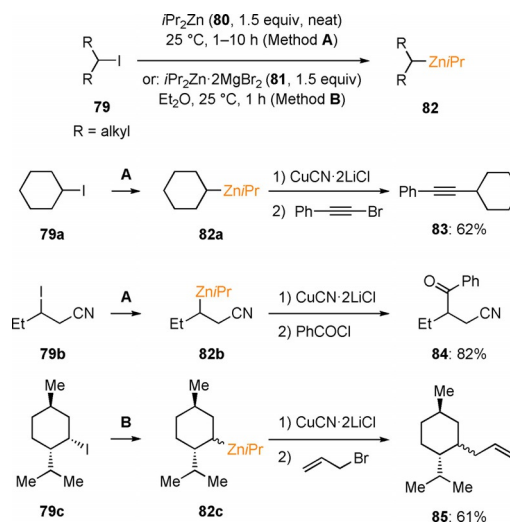


**Scheme 10.** Generation of alkylzincs using diethylzinc and their trapping reactions.

The iodine–zinc exchange of secondary alkyl iodides **79** proceeds using *i*Pr<sub>2</sub>Zn (**80**).<sup>[24]</sup> Remarkably, when the reagent is prepared from 2 *i*PrMgBr and ZnBr<sub>2</sub>, leading to *i*Pr<sub>2</sub>Zn·2MgBr<sub>2</sub> (**81**), the exchange reaction proceeds up to 200 times faster due to the presence of this magnesium salt.<sup>[24]</sup> This may be explained by the formation of the dibromozincate [*i*Pr<sub>2</sub>ZnBr<sub>2</sub>]<sup>2-</sup>[Mg<sub>2</sub>Br<sub>2</sub>]<sup>2+</sup>. Thus, when secondary iodides (**79 a–b**) are treated with *i*Pr<sub>2</sub>Zn (**80**, 1.5 equiv), the alkylzinc reagents **82 a–b** are obtained (Scheme 11). After transmetalation to copper using a CuCN·2LiCl solution in THF and electrophilic trapping, alkyne **83** and ketone **84** are obtained in 62–82% yield.

Menthyl iodide (**79 c**) is used for this transformation, which, after mixing with *i*Pr<sub>2</sub>Zn·2MgBr<sub>2</sub> (**81**), gives the mixed zinc organometallic **82 c**. After copper-mediated allylation, the cyclohexane **85** is isolated in 61% yield (Scheme 11).<sup>[24]</sup>

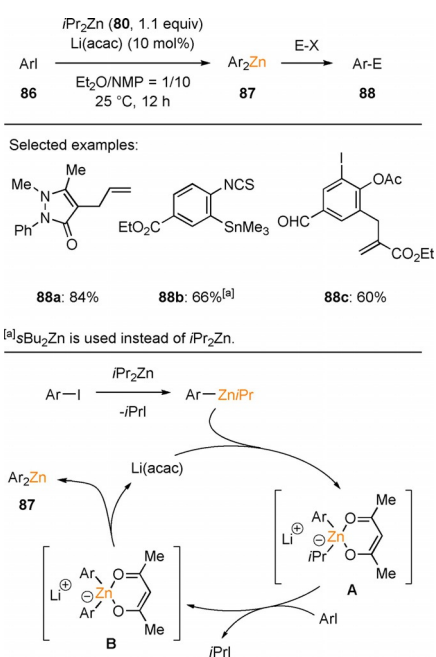
After the discovery, that salt additives may accelerate the rate of iodine–zinc exchange reactions,<sup>[24]</sup> it was found that the combination of *i*Pr<sub>2</sub>Zn (**80**) and Li(acac) (10 mol%) in Et<sub>2</sub>O:NMP allowed efficient halogen–zinc exchange reactions on aryl iodides.<sup>[25]</sup> Thus, various aryl iodides bearing sensitive functional groups such as isothiocyanates or aldehydes of type **86** are treated with *i*Pr<sub>2</sub>Zn (**80**) and catalytic amounts of Li(acac) (10 mol%), generating biarylzincs of type **87**. Trapping with



**Scheme 11.** Iodine–zinc exchanges of secondary alkyl iodides using *i*Pr<sub>2</sub>Zn (**80**) or *i*Pr<sub>2</sub>Zn·2MgBr<sub>2</sub> (**81**).

various electrophiles gives **88 a–c** in 60–84% yield (Scheme 12).<sup>[25]</sup> From a mechanistic perspective, the acetylacetonate 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 diarylzinc **87** and Li(acac) (Scheme 12).<sup>[25]</sup>

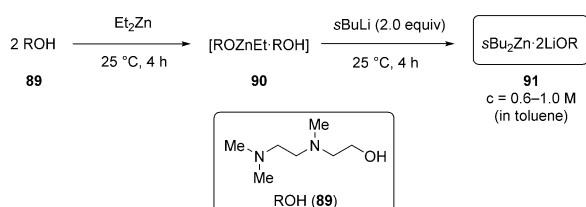
Various additives play a major role in the rates of halogen–metal exchange reactions (e.g. LiCl,<sup>[5]</sup> MgBr<sub>2</sub>,<sup>[24]</sup> or Li(acac)<sup>[25]</sup>). In most cases, it is presumed that the additive leads to the formation of a higher coordinated zincate and thus more reactive metal 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 12.** Preparation of highly functionalized diarylzincs using *i*Pr<sub>2</sub>Zn in the presence of catalytic amounts of Li(acac).

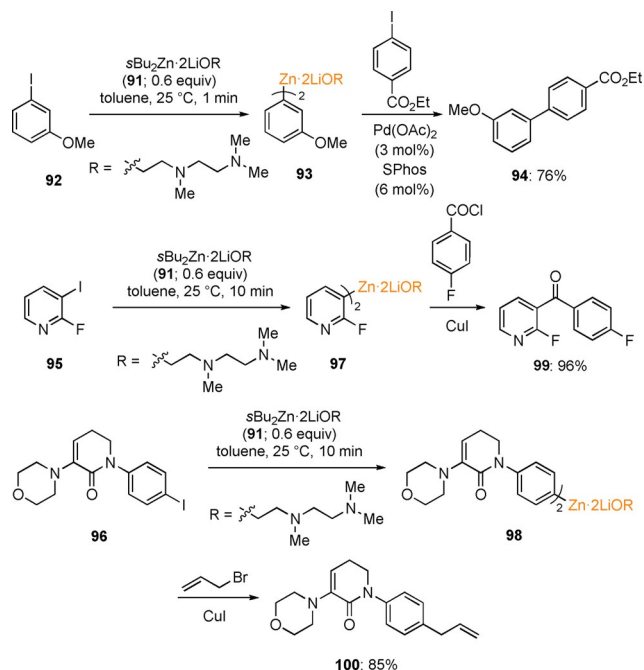
may drastically increase the reactivity of the halogen–magnesium exchange.<sup>[26]</sup> With this information at hand, the generation of dialkylzinc organometallics, complexed with lithium alkoxides were investigated.<sup>[27]</sup> When an aminoalcohol ROH (**89**, 2.0 equiv, R = CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>) is treated with Et<sub>2</sub>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<sub>2</sub>Zn·2LiOR (**91**) is produced (Scheme 13).<sup>[27]</sup>



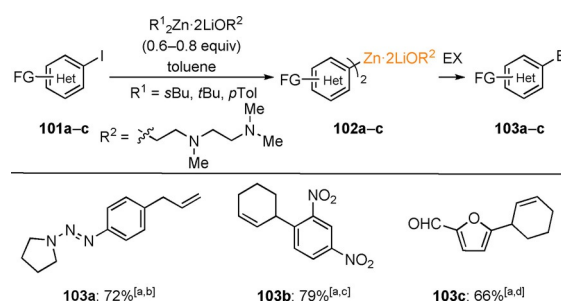
Scheme 13. Preparation of the dialkylzinc reagent sBu<sub>2</sub>Zn·2LiOR (**91**).

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 diarylzinc **93** (Scheme 14). After a palladium-catalyzed Negishi cross-coupling with an aryl iodide,<sup>[7]</sup> 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).<sup>[27]</sup>



Scheme 14. Generation of diarylzinc organometallics using sBu<sub>2</sub>Zn·2LiOR (**91**).

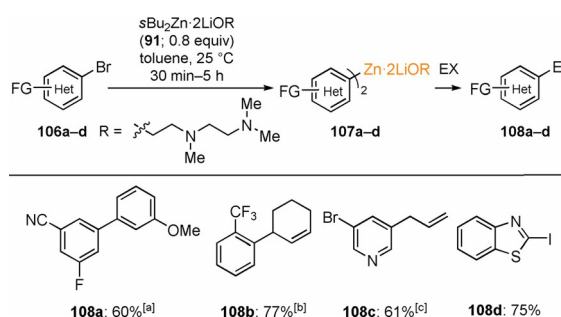
Since zinc organometallics possess a particularly unreactive carbon–zinc bond, highly sensitive functional groups such as triazines, aldehydes, ketones or nitro-groups are tolerated. Under standard reaction conditions, an aryl iodide bearing a triazine functional group (**101 a**) is converted to the diarylzinc **102 a** and quenched with allyl bromide, providing **103 a** in 72% yield (Scheme 15).<sup>[27]</sup> In some cases, slight modifi-



Scheme 15. Iodine–zinc exchange of highly sensitive substrates using exchange reagents of the general formula R<sub>2</sub>Zn·2LiOR. [a] CuI (20 mol%) is used. [b] sBu<sub>2</sub>Zn·2LiOR (**91**, 0.6 equiv, 25 °C, 10 min). [c] pTol<sub>2</sub>Zn·2LiOR (**104**, 0.6 equiv, –15 °C, 15 min) is used. [d] tBu<sub>2</sub>Zn·2LiOR (**105**, 0.8 equiv, 0 °C, 10 min) is used.

cations of the exchange reagent are required. Thus, when 2,4-dinitroiodobenzene (**101 b**) is treated with pTol<sub>2</sub>Zn·2LiOR (**104**, 0.6 equiv, –15 °C, 15 min), a smooth iodine–zinc exchange takes place, affording **102 b**, which, after allylation, leads to the dinitroarene **103 b** in 79% yield. For an iodine–zinc exchange to proceed in the presence of aldehydes, tBu<sub>2</sub>Zn·2LiOR (**105**) gives the best results. Hence, 5-iodo-2-furaldehyde (**101 c**) is treated with the exchange reagent **105** (0.8 equiv, 0 °C, 10 min), leading to biarylzinc **102 c**. After an allylation, the furyl aldehyde **103 c** is obtained in 66% yield (Scheme 15).<sup>[27]</sup>

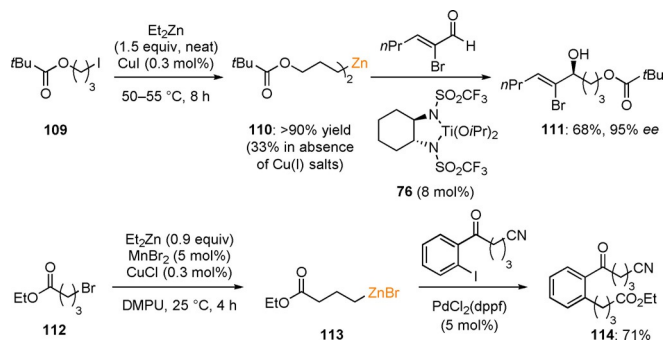
Finally, the high reactivity of these alkoxide complexed dialkylzinc reagents allow a bromine–zinc exchange reaction. Therefore, various functionalized (hetero)aryl bromides (**106 a–d**) are treated with **91** (0.8 equiv, 25 °C, 30 min–5 h), producing biarylzincs **107 a–d**. After various electrophilic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



Scheme 16. Bromine–zinc exchange of various (hetero)aryl bromides using sBu<sub>2</sub>Zn·2LiOR (**91**). [a] Pd(OAc)<sub>2</sub> (3 mol%), SPhos (6 mol%) and TMSCl (0.8 equiv) are used. [b] A 1 M CuCN·2LiCl solution in THF is used (20 mol%). [c] CuI (20 mol%) is used.

## 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  $\text{Et}_2\text{Zn}$  (5.0 equiv) is required to perform an iodine–zinc exchange,<sup>[22]</sup> the addition of  $\text{CuI}$  (0.3 mol%) reduces the amount to 1.5 equivalents. Also, the rate of the exchange reaction is doubled.<sup>[28]</sup> Alkyl iodide **109**, for example, when being treated with  $\text{Et}_2\text{Zn}$  (1.5 equiv) in the presence of  $\text{CuI}$  (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).<sup>[28]</sup> It is noteworthy that the iodine–metal ex-

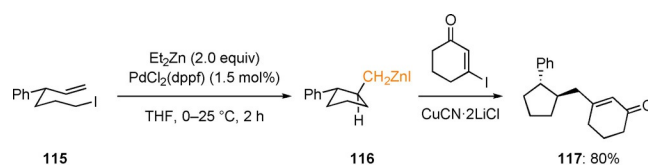


**Scheme 17.** Copper- and manganese-catalyzed halogen–zinc exchange reactions.

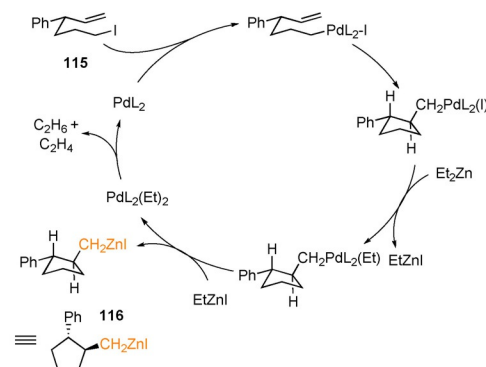
change is incomplete in absence of the copper salt and only a yield of 33% is obtained. When  $\text{MnBr}_2$  (5 mol%) and  $\text{CuI}$  (0.3 mol%) are simultaneously present in the reaction mixture, not only alkyl iodides but also alkyl bromides readily undergo halogen–metal exchange reactions.<sup>[29]</sup> Thus, when 4-bromobutyrate (**112**) is treated with  $\text{Et}_2\text{Zn}$  (0.9 equiv),  $\text{MnBr}_2$  (5 mol%), and  $\text{CuCl}$  (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.<sup>[30]</sup> When iodoalkane **115**, which contains a remote alkene moiety, is treated with  $\text{Et}_2\text{Zn}$  (2.0 equiv) in the presence of  $\text{PdCl}_2(\text{dppf})$  (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).<sup>[30]</sup> 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  $\text{Pd}^0$  species is regenerated (Scheme 18).<sup>[30]</sup>

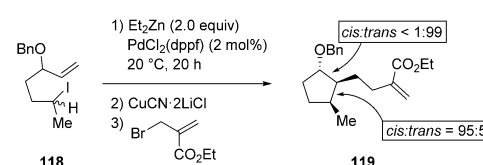
Such cyclization reactions are highly stereoselective and the ring closure of iodoalkane **118**, when treated with  $\text{Et}_2\text{Zn}$  in the presence of the palladium catalyst, produces, after an iodine–



Proposed reaction mechanism:



**Scheme 18.** Palladium catalyzed iodine–zinc exchange reactions, leading to functionalized cyclopentanes.



1:1 mixture of diastereomers

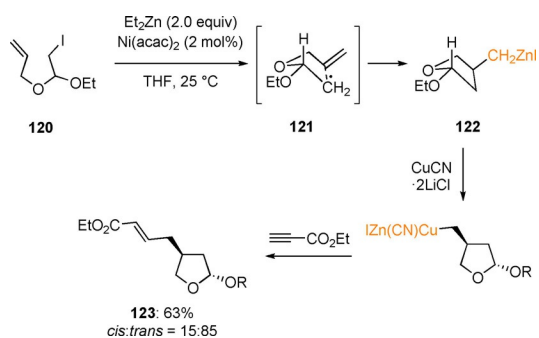
**Scheme 19.** Stereoselective preparation of a trisubstituted cyclopentane by radical cyclization after iodine–zinc exchange.

zinc exchange and copper-mediated allylation, the trisubstituted cyclopentane **119** in a stereoconvergent manner (Scheme 19).<sup>[30b]</sup>

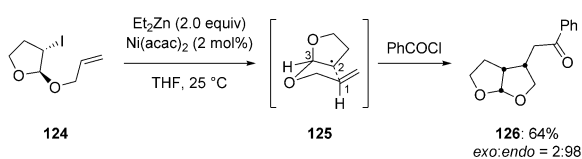
Nickel-catalysis proved to be beneficial for the stereoselective preparation of heterocyclic zinc reagents.<sup>30d</sup> Thus, when the iodinated acetal **120** is treated with  $\text{Et}_2\text{Zn}$  (2.0 equiv) in the presence of  $\text{Ni}(\text{acac})_2$  (2 mol%) the radical intermediate **121** 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).<sup>[30d]</sup>

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 alkoxy substituent (C3) is positioned axially. After reaction with benzoyl chloride, the bicyclic heterocycle **126** is isolated in 64% yield (*exo:endo* = 2:98, Scheme 21).<sup>30d</sup>

A further extension is achieved, when electron-rich triorganozincates are combined with iron or cobalt catalysts, which enables chlorine–zinc exchange reactions.<sup>[31]</sup> Adamantyl chloride (**127**), for example, is treated with the zincate **128** in the presence of  $\text{Fe}(\text{acac})_2$  (10 mol%) and 4-fluorostyrene (20 mol%). After quenching of the resulting metal species with

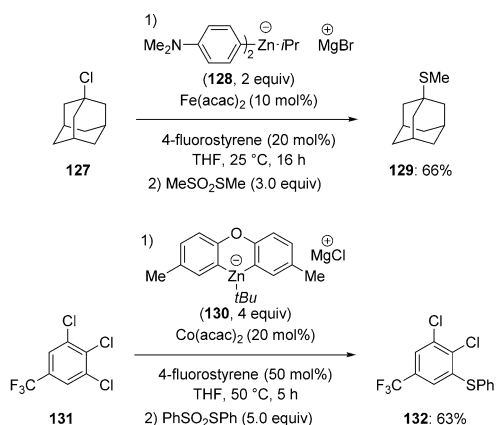


**Scheme 20.** Nickel-catalyzed iodine–zinc exchange for the stereoselective preparation of tetrahydrofuran derivatives.



**Scheme 21.** Stereoselective cyclization of an iodo-tetrahydrofuran using a nickel-catalyzed iodine–zinc exchange.

MeSO<sub>2</sub>SMe, the thioether **129** is obtained in 66% yield (Scheme 22).<sup>[31]</sup> To expand the scope of this exchange reaction, the zincate **130** was developed. However, the catalytic system needs to be modified and Co(acac)<sub>2</sub> provides best results. Thus, trichlorinated arene **131** is treated with **130** in the presence of Co(acac)<sub>2</sub> (20 mol%) and 4-fluorostyrene (50 mol%) at elevated temperatures (50 °C, 5 h). Quenching of the resulting organometallic with PhSO<sub>2</sub>SPh produces the diarylthioether **132** in 63% yield (Scheme 22).<sup>[31]</sup>

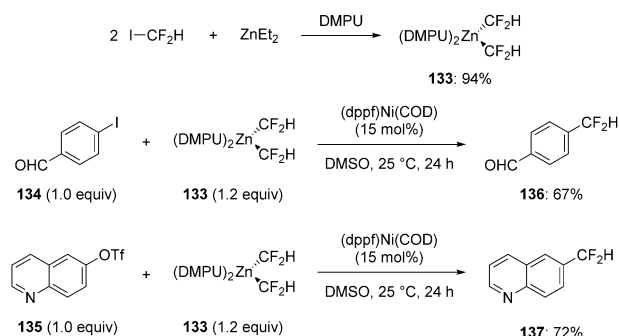


**Scheme 22.** Iron- and cobalt-catalyzed chlorine–zinc exchange reactions using electron-rich triorganozincates.

## 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 dialkylzinc re-

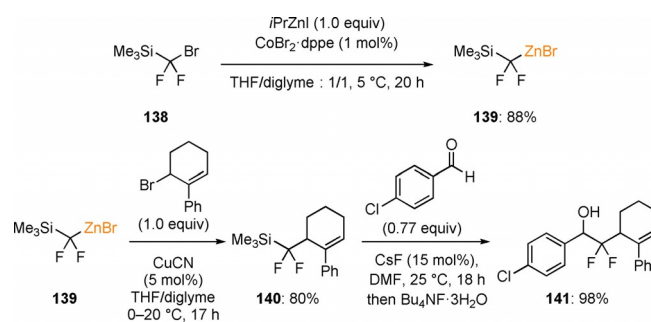
agents.<sup>[32]</sup> A synthetic utility for these fluorinated zinc organometallics was introduced by reacting these reagents with diido(hetero)arenes under copper catalysis, producing fused fluorinated ring systems.<sup>[33]</sup> Building up on these results, a dialkylzinc reagent, designed for difluoromethylation reactions, was developed.<sup>[34]</sup> Thus, when difluoroiodomethane is treated with Et<sub>2</sub>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).<sup>[34]</sup>



**Scheme 23.** Preparation of the difluoromethylation reagent **133** by iodine–zinc exchange reaction and further cross-coupling reactions.

An interesting example for a difluoromethylene bis-carbanion surrogate is accessible by a cobalt-catalyzed halogen–zinc exchange reaction.<sup>[35]</sup> Thus, when (bromodifluoromethyl)trimethylsilane (Me<sub>3</sub>SiCF<sub>2</sub>Br, **138**) is treated with *i*PrZnI (1.0 equiv, 5 °C, 20 h) in the presence of CoBr<sub>2</sub>-dpppe (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 allylation 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).<sup>[35]</sup>

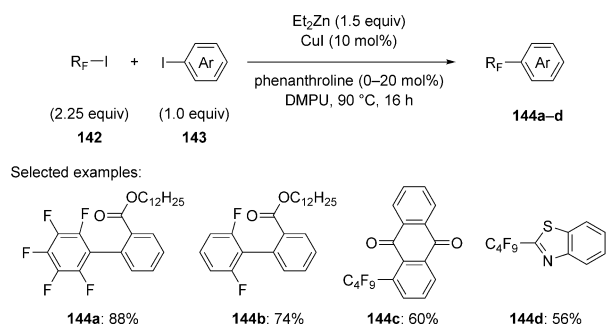
An example for the preparation of in situ generated fluorinated alkylzinc organometallics by iodine–zinc exchange is de-



**Scheme 24.** Preparation of geminal difluoro derivatives by a bromine–zinc exchange.



scribed by Uchiyama and Hirano.<sup>[36]</sup> Various fluorinated halogenated arenes and alkenes (**142**, 2.25 equiv) are mixed with iodoarenes of type **143**, and Et<sub>2</sub>Zn (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).<sup>[36]</sup>



**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 insertion 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 R<sub>3</sub>ZnLi or higher order tetraorganozincates of type R<sub>4</sub>ZnLi<sub>2</sub> 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 MgBr<sub>2</sub>, Li(acac), or lithium alkoxides. Especially dialkylzinc organometallics complexed with lithium alkoxides of type R<sub>2</sub>Zn·2LiOR 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.

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