Exchange Reactions | **Very Important Paper**

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Preparation of Polyfunctional Arylzinc Organometallics in Toluene by Halogen/Zinc Exchange Reactions

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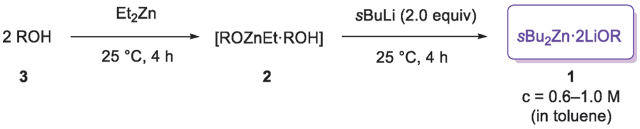
Abstract: *A wide range of polyfunctional diaryl- and diheteroarylzinc species were prepared in toluene within 10 min to 5 h through an I/Zn or Br/Zn exchange reaction using bimetallic reagents of the general formula* $R'_2Zn{\cdot}2\,LiOR$ *(R′ = sBu, tBu, pTol). Highly sensitive functional groups, such as a triazine, a ketone, an aldehyde, or a nitro group, were tolerated in these exchange reactions, enabling the synthesis of a plethora of functionalized (hetero)arenes after quenching with various electrophiles. Insight into the constitution and reactivity of these bimetallic mixtures revealed the formation of highly active lithium diorganodialkoxyzincates of type* $[R'_2Zn(OR)_2Li_2]$.

Organozinc reagents are key intermediates in organic synthesis as they tolerate many functional groups and readily participate in transition-metal-catalyzed carbon–carbon bond-forming reactions.[1] Aryl- and heteroarylzinc halides have been particularly widely used as organometallic reagents for preparing complex organic molecules.[2] Two recently developed alternative synthetic strategies granting access to these valuable organometallics are the direct insertion of zinc powder into organic halides[3] and deprotonative metalation using TMP-zinc bases (TMP = 2,2,6,6-tetramethylpiperidyl).[4] Lithium alkylzincates such as "lower-order" R_3ZnLi and "higher-order" R_4ZnLi_2 have been shown to be able to promote halogen/zinc exchange reactions towards aryl halides.[5] Furthermore, an I/Zn exchange of aryl and heteroaryl iodides can be accomplished by adding substoichiometric amounts of Li(acac) to $i\mathrm{Pr}_2Zn$ in NMP.[6] Contrasting with the enhanced reactivity of these mixed-metal combinations, monometallic R_2Zn reagents on their own fail to promote these type of transformations.

For preparing related organomagnesium derivatives, the exchange reagent $i\mathrm{PrMgCl{\cdot}LiCl}$ ("turbo-Grignard") has been extensively used and leads to high rates of Br/Mg exchange.[7] This exchange can be accelerated further by replacing LiCl with a stronger donor additive, namely a lithium alkoxide (ROLi; R = 2-ethylhexyl). Furthermore, this exchange could be performed in the industrially friendly solvent toluene.[8]

Opening new ground in this evolving area, we herein report a new I/Zn and Br/Zn exchange in toluene based on the use of a novel bimetallic combination $s\mathrm{Bu}_2Zn{\cdot}2\,LiOR$ (**1**), which allows the generation of a wide range of polyfunctional aryl- and heteroarylzinc reagents from the corresponding organic iodides or bromides.

First, Et_2Zn reacted in toluene with two equivalents of a variety of alcohols ROH (25 °C, 4 h), affording the relevant ethylzinc alkoxides co-complexed with the corresponding alcohol (ROZnEt·ROH) of type **2**.[9] These ethylzinc alkoxides (**2**) further reacted with *s*BuLi (2.0 equiv, in cyclohexane) to produce the bimetallic reagent tentatively represented as the trinuclear monozinc–dilithium complexes $s\mathrm{Bu}_2Zn{\cdot}2\,LiOR$ (**1**, see below). Removal of the solvents and subsequent redissolution in toluene provided a light yellow solution of **1** ($c = 0.6$–$1.0\,\mathrm{M}$ in toluene; Scheme 1), which can be stored at 25 °C for months without significant loss of reactivity. Initial studies showed that the complex $s\mathrm{Bu}_2Zn{\cdot}2\,LiOR$ (R = 2-octyl; **1a**) reacted with 3-iodoanisole (**4a**) in toluene[10] within 30 min at 25 °C, forming putative bis(anisyl)zinc complexed with 2 LiOR (**5a**) in 23 % yield, as determined by GC analysis of reaction aliquots (Table 1, entry 1). Interestingly, a striking effect was observed upon varying the alkoxide component of **1**. Using alcohols bearing N-coordination sites[11] led to a significant improvement in the efficiency of the I/Zn exchange process. Thus complex **1b** ($R = CH_2CH_2N(Et)_2$) produced the diarylzinc species **5a** in 95 % GC yield (entry 2) while the use of **1c** ($R = CH_2CH_2N(CH_3)CH_2CH_2N(CH_3)_2$), where OR contains a second N-coordination site, accelerated the I/Zn exchange process, affording **5a** in 99 % GC yield after just 1 min (entries 3 and 4). Contrastingly, replacing the *s*Bu group on **1c** with other alkyl groups such as Et, *n*Bu, or *t*Bu had very little effect on



Scheme 1. Preparation of mixed-metal reagents of type **1**.

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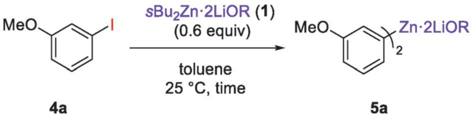
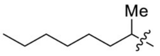
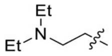
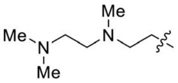
Table 1: Optimization of the reaction conditions for the I/Zn exchange using dialkylzinc reagents of type **1**.

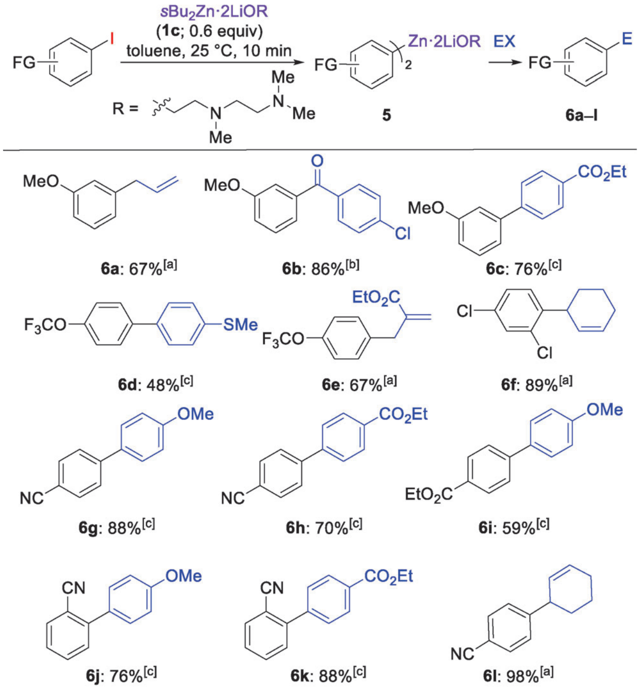


Entry	*s*Bu$_2$Zn·2 LiOR (**1**)	Time [min]	Yield [%][a]
1	**1a**; R = 	30	23
2	**1b**; R = 	30	95
3	**1c**; R = 	30	99
4	**1c**	1	99

[a] Yield of **5a** determined by GC analysis of reaction aliquots quenched with water.

the overall conversions after 30 min (ranging from 80 to 89 %).[12]

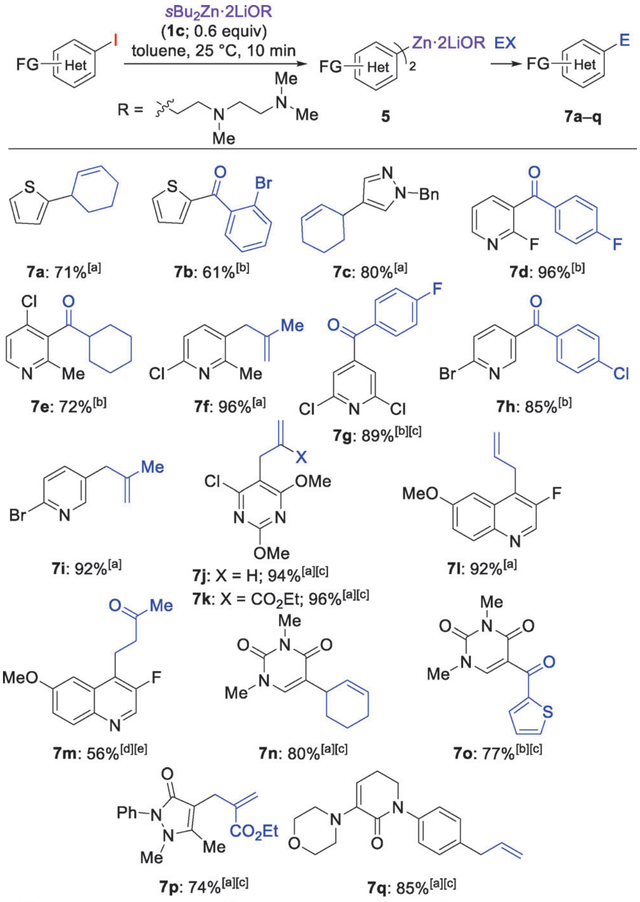
Thus 3-iodoanisole (**4a**) reacted with *s*Bu$_2$Zn·2 LiOR (**1c**) in toluene at 25 °C for 10 min to produce the bis(anisyl)zinc reagent **5a**. Reaction of **5a** with allyl bromide in the presence of CuI (20 mol %) gave the allylated arene **6a** in 67 % yield (Scheme 2). Transmetalation of **5a** to copper using CuI (0.6 equiv), followed by addition of 4-chlorobenzoyl chloride, gave the acylated anisole **6b** in 86 % yield. When the zinc species **5a** was mixed with ethyl 4-iodobenzoate, Pd(OAc)$_2$ (3 mol %), and SPhos (6 mol %),[13] a palladium-catalyzed Negishi cross-coupling[14] took place, generating biaryl **6c** in 76 % yield. 4-(Trifluoromethoxy)iodobenzene underwent a smooth I/Zn exchange with **1c**, giving the corresponding diarylzinc reagent **5b**. Reaction of **5b** with ethyl 2-(bromomethyl)acrylate or a palladium-catalyzed cross-coupling with 4-iodothioanisole gave the functionalized arenes **6d** and **6e** in 48 and 67 % yield, respectively. Various electron-poor aryl iodides bearing, for example, ester or nitrile groups readily reacted with **1c**, and quenching of the zinc reagents of type **5** with various electrophiles gave products **6f–l** in 59–98 % yield (Scheme 2).[15]



[a]CuI (20 mol%) was used. [b]CuI (0.6 equiv) was used. [c]Pd(OAc)$_2$ (3 mol%) and SPhos (6 mol%) was used.

Scheme 2. Reaction of various aryl iodides with *s*Bu$_2$Zn·2 LiOR (**1c**), followed by electrophilic functionalization.

To demonstrate the versatility of **1c**, this approach was extended to a wide collection of heteroaromatic substrates to yield synthetically valuable bis(heteroaryl)zinc organometallics (Scheme 3). Thus, bis(thienyl)zinc reacted with either 3-bromocyclohexene or 2-bromobenzoyl chloride to provide **7a** and **7b** in 71 and 61 % yield, respectively. Benzyl-protected 3-iodopyrazole reacted with **1c** to give, after allylation, **7c** in 80 % yield. Also, various iodopyridines, -pyrimidines, and -quinolines were converted into the corresponding zinc reagents using **1c**, which were quenched with several electrophiles, including acid chlorides and allyl bromides to produce the heterocyclic products **7d–m** in 56–96 % yield. Reactions

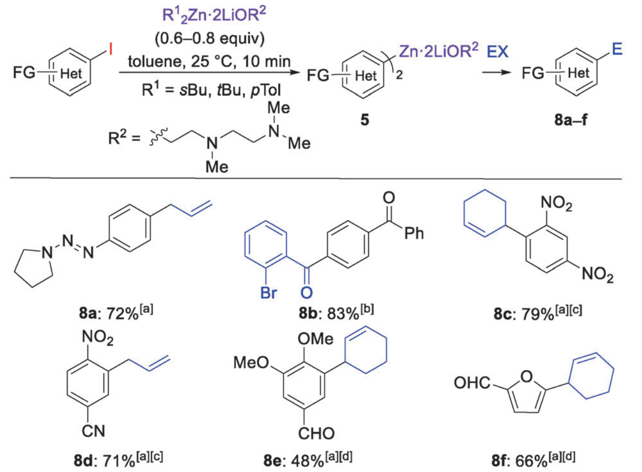


[a]CuI (20 mol%) was used. [b]CuI (0.6 equiv) was used. [c]The reaction was run in THF. [d]Yield over two steps. [e]Reaction conditions: 1) CuI, methyl vinyl ketone, TMSCl 2) TBAF.

Scheme 3. Reaction of various heteroaryl iodides with *s*Bu$_2$Zn·2 LiOR (**1c**), followed by electrophilic functionalization.

of more complex iodinated N-heterocycles, namely pyrazolone, uracil, or 5,6-dihydropyridone, gave the expected bis-zinc reagents of type **5**, which, after allylation or acylation, provided **7n–q** in 74–85 % yield (Scheme 3).[16]

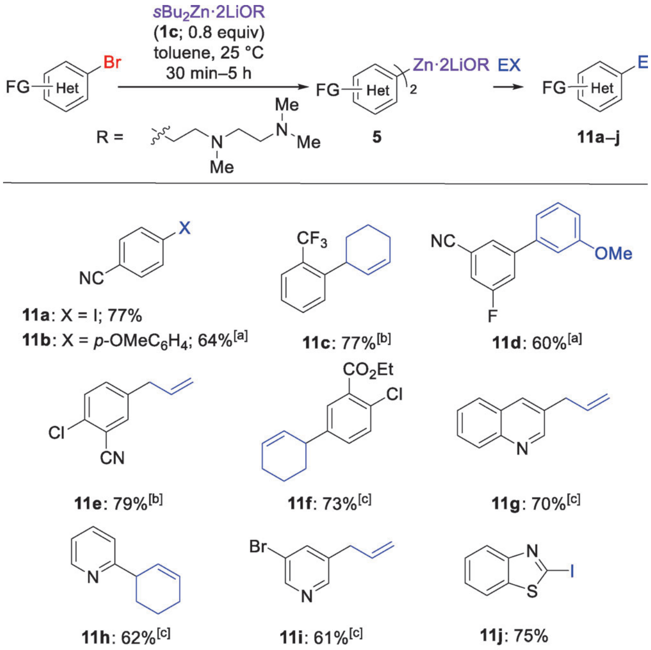
Expanding even further the scope of this approach, the I/Zn exchange process proved tolerant to different highly sensitive functional groups. Thus mixing an aryl iodide bearing a triazine moiety with **1c**, followed by allylation, gave arene **8a** in 72 % yield (Scheme 4). Next, the diarylzinc species generated from 4-iodobenzophenone was allylated, providing ketone **8b** in 83 % yield. In the case of nitro-substituted aryl iodides, $p\text{Tol}_2\text{Zn}\cdot 2\,\text{LiOR}$ (**9**) gave the best result.[17] Hence, the mild exchange reagent $p\text{Tol}_2\text{Zn}\cdot 2\,\text{LiOR}$ (**9**, $\text{R} = \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$; $p\text{Tol} = p$-tolyl) was prepared by mixing the alkoxide **2c** with tolyllithium (2.0 equiv).[18] Treatment of 2,4-dinitroiodobenzene or 3-iodo-4-nitrobenzonitrile with **9** (0.6 equiv) at −15 °C for 15 min, followed by a copper-mediated allylation reaction, afforded nitroarenes **8c** and **8d** in 79 and 71 % yield, respectively. For the conversion of an iodo-substituted benzaldehyde into the corresponding zinc species, a short screening showed that the best exchange reagent was $t\text{Bu}_2\text{Zn}\cdot 2\,\text{LiOR}$ (**10**). Thus alkoxide **2c** was treated with *t*BuLi (2.0 equiv), and the resulting less nucleophilic reagent $t\text{Bu}_2\text{Zn}\cdot 2\,\text{LiOR}$ (**10**, $\text{R} = \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$) was obtained as a 1 M solution in toluene. Reaction of 5-iodo-veratraldehyde with **10** (0.8 equiv; 0 °C, 10 min) afforded a diarylzinc organometallic of type **5**, which, after allylation, provided the vanillin derivative **8e** in 48 % yield. 4-Iodofuraldehyde was also treated with $t\text{Bu}_2\text{Zn}\cdot 2\,\text{LiOR}$ (**10**), and the resulting zinc reagent reacted with 3-bromocyclohexene in the presence of CuI to give the furfural derivative **8f** in 66 % yield (Scheme 4).



[a]CuI (20 mol%) was used. [b]CuI (0.6 equiv) was used. [c]$p\text{Tol}_2\text{Zn}\cdot 2\text{LiOR}$ (**9**, 0.6 equiv, −15 °C, 15 min) was used. [d]$t\text{Bu}_2\text{Zn}\cdot 2\text{LiOR}$ (**10**, 0.8 equiv, 0 °C, 10 min) was used.

Scheme 4. The I/Zn exchange reaction on various (hetero)aryl iodides bearing highly sensitive functional groups.

The excellent reactivity of these bimetallic exchange reagents led us to examine the corresponding Br/Zn exchange reaction. Treatment of 4-bromobenzonitrile with **1c** (0.8 equiv) at 25 °C for 5 h in toluene (1 M) provided the desired bis(aryl)zinc reagent of type **5**, which, after quenching with iodine, gave 4-iodobenzonitrile (**11a**) in 77 % yield (Scheme 5). The reaction of the same zinc reagent with 4-iodoanisole under palladium catalysis gave the desired biaryl **11b** in 64 % yield.[19] Various bromoarenes bearing, for example, an ester functional group underwent smooth Br/Zn exchange, which, after allylation or cross-coupling, produced arenes **11c–f** in 60–79 % yield. Additionally, bromopyridines and a bromoquinoline were treated with **1c**. Allylation of the resulting zinc reagents gave the functionalized heteroarenes **11g–i** in 61–70 % yield. Finally, 2-bromobenzothiazole was mixed with **1c**, and the resulting metal species reacted with iodine to give **11j** in 75 % yield (Scheme 5).[15]



[a]Pd(OAc)_2 (3 mol%), SPhos (6 mol%) and TMSCl (0.8 equiv) were used.
[b]A 1 M $\text{CuCN}\cdot 2\text{LiCl}$ solution in THF was used (20 mol%).
[c]CuI (20 mol%) was used.

Scheme 5. Reaction of various aryl bromides with $s\text{Bu}_2\text{Zn}\cdot 2\,\text{LiOR}$ (**1**), followed by electrophilic functionalization.

Intrigued by the unique reactivity of these systems, we sought to gain some information on the constitution of **1c**. The results of multinuclear (^{1}H, ^{13}C, ^{7}Li) NMR studies including ^{1}H DOSY NMR experiments in [D$_8$]toluene are consistent with the formation of the contact ion pair lithium zincate $[s\text{Bu}_2\text{Zn}(\text{OR})_2\text{Li}_2]$ (**1c**) as the major species in solution, along with a minor ethyl complex tentatively assigned as the complex $[\text{Et}(s\text{Bu})\text{Zn}(\text{OR})_2\text{Li}_2]$.[12] The presence of this ethyl species can be rationalized by considering the residual Et group present in **2** (Scheme 1) in going from type **2** to type **1**. Interestingly, ^{1}H NMR monitoring of the reaction of this zincate mixture with 2-iodoanisole showed that both bimetallic complexes are active towards the I/Zn exchange as evidenced by the almost immediate consumption of the aryl iodide, affording an arylzinc species,[20] with concomitant formation of EtI and *s*BuI. $[s\text{Bu}_2\text{Zn}(\text{OR})_2\text{Li}_2]$

(**1c**) can be envisaged as a co-complex of $s\mathrm{Bu}_2\mathrm{Zn}$ and 2 equiv of LiOR; in fact, this combination of single-metal reagents in toluene showed very similar reactivity towards I/Zn exchange with 3-iodoanisole to that found for **1c**.[12]

Co-complexation reactions of n equiv of LiOR ($n = 1$ and 2) with several $\mathrm{R'}_2\mathrm{Zn}$ ($\mathrm{R'} = \mathrm{Me}$, Et, sBu) reagents in toluene were investigated spectroscopically, demonstrating in all cases the formation of mixed-metal complexes (see the Supporting Information). Further evidence was obtained from X-ray crystallographic studies of the lithium diorganoalkoxyzincate [$\mathrm{Me_2Zn{\cdot}LiOR}$] (**12**, $\mathrm{R = CH_2CH_2N(CH_3)CH_2CH_2N(CH_3)_2}$; Figure 1).[21] This structure contains an eye-catching 5,5,4,5,5 fused ring system where each zinc in **12** binds to two methyl groups and one alkoxide ligand. Both Li atoms are connected to the OR groups via oxygen bridges, and complete their coordination sphere by binding to the two N atoms present in the multidentate alkoxide chain. This special coordination to Li can be influential for the marked alkoxide effect seen in Table 1 as other OR groups without N donor substituents may favor formation of higher oligomeric lithium zincates, which can be expected to be less reactive.

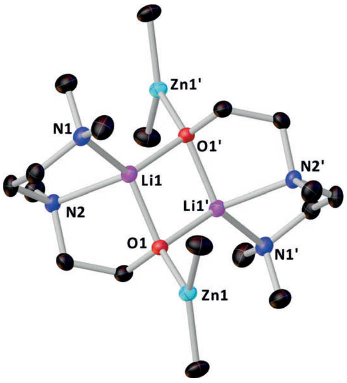


Figure 1. Molecular structure of [$\mathrm{Me_2Zn{\cdot}LiOR}$] (**12**). Hydrogen atoms are omitted for clarity. Thermal ellipsoids set at 50% probability.

^{1}H NMR monitoring studies with addition of variable amounts of LiOR to a solution of $\mathrm{Et_2Zn}$ in [$\mathrm{D_8}$]toluene disclose the importance of the LiOR/alkylzinc ratio for the success of the I/Zn exchange. While $\mathrm{Et_2Zn}$ is completely inert towards exchange with 2-iodoanisole (2 equiv), addition of 1 equiv of LiOR gave a conversion of only 23% after 10 min; on the other hand, with 2 equiv of LiOR, the reaction is almost quantitative (95%). This is consistent with the formation of a more activated diorganodialkoxyzincate species [$s\mathrm{Bu_2Zn(OR)_2Li_2}$], where zinc is formally part of an electron-rich dianionic moiety. The excellent atom economy of the reaction, with both ethyl groups on $\mathrm{Et_2Zn}$ being active towards the exchange, is particularly remarkable, especially when compared with the related tris(alkyl) reagent $\mathrm{Et_3ZnLi}$,[22] where only one of the three Et groups can undergo I/Zn exchange.[12]

In summary, a new family of bimetallic reagents of type $\mathrm{R'_2Zn{\cdot}2\,LiOR}$ have been developed that efficiently promote I/Zn and Br/Zn exchange processes at room temperature with excellent functional group tolerance through the activation of both R′ groups on Zn. Quenching of the in situ generated zinc organometallics with various electrophiles produced a range of functionalized (hetero)arenes, demonstrating the extensive synthetic scope of this approach. Structural and spectroscopic studies probing the constitution of these bimetallic systems support the formation of highly reactive lithium bis(alkyl)bis(alkoxy)zincates and shed light on the key role of each component in the mixture for the success of the I/Zn exchange. Further extensions of this bimetallic research are currently being studied in our laboratories.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkoxides · lithium · metal/halogen exchange · organozinc reagents · toluene

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[9] Co-complex [EtZn(OR)·ROH] ($R = CH_2CH_2N(CH_3)CH_2CH_2N(CH_3)_2$) has been spectroscopically characterized by ^1H and ^{13}C NMR analysis; see the Supporting Information. The structure of the neutral complex EtZn(OR) has been previously established by X-ray crystallography; see: M. S. Hill, G. Kociok-Köhn, K. C. Molloy, D. C. Stanton, *Main Group Met. Chem.* **2015**, *38*, 61.

[10] A solvent screen showed that the halogen/zinc exchange cannot only be performed in hydrocarbons such as toluene or hexane, but also in other industrially friendly ethereal solvents such as 2-methyl-THF or MTBE.

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[15] Further examples can be found in the Supporting Information.

[16] Because of the poor solubility of the aryl iodides, the reactions generating **7g**,**j**,**k**, and **n**–**q** were performed in THF.

[17] When 2,4-dinitroiodobenzene was treated with **1c**, decomposition of the starting material was observed.

[18] *p*Tolyllithium was prepared by a direct lithium insertion into 4-chlorotoluene; see: C. G. Screttas, B. R. Steele, M. Micha-Screttas, G. A. Heropoulos, *Org. Lett.* **2012**, *14*, 5680–5683.

[19] Prior to addition of the catalyst system and the aryl iodide, TMSCl (0.8 equiv; 0 °C, 10 min) was added to quench the excess alkoxide.

[20] The arylzinc complex formed in this reaction has limited solubility in [D$_8$]toluene but was fairly soluble in [D$_8$]THF. Its ^{13}C NMR spectrum shows a diagnostic resonance at $\delta = 155.71$ ppm for Zn$-$*C*(aryl) (vs. $\delta = 86.4$ ppm for *C*$-$I in 2-iodoanisole). DOSY NMR studies are consistent with the formation of a heteroleptic $[Ar_2Zn(OR)_2Li_2]$ species.

[21] CCDC 1918845 (**12**) and 1918846 (**13**, see the Supporting Information), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[22] Et_3ZnLi was prepared in [D$_8$]toluene by co-complexation of EtLi and Et_2Zn. Its reaction with three equiv of 2-iodoanisole was monitored by ^1H NMR spectroscopy, revealing the formation of an $ArEt_2ZnLi$ species; see the Supporting Information for details.

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Communications

Exchange Reactions

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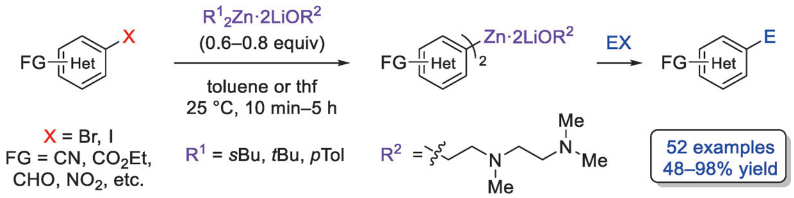
Preparation of Polyfunctional Arylzinc Organometallics in Toluene by Halogen/Zinc Exchange Reactions



Alkoxide is all you need: Atom-economic I/Zn and Br/Zn exchange reactions were developed by using dialkylzinc reagents co-complexed with lithium alkoxides. Because of the covalent nature of the carbon–zinc bond, several sensitive functional groups, including triazines, ketones, aldehydes, and nitro groups, were tolerated. Quenching of the diarylzinc species with various electrophiles produced a plethora of functionalized (hetero)arenes.