

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

Moritz Balkenhohl,^[a] Dorothee S. Ziegler,^[a] Alexandre Desaintjean,^[a] Leonie J. Bole,^[b] Alan R. Kennedy,^[b] Eva Hevia,^{[c]*} and Paul Knochel^{[a]*}

Abstract: A wide range of polyfunctional diaryl- and diheteroarylzinc species have been prepared in toluene within 10 min to 5 h by an I/Zn or Br/Zn exchange reaction using bimetallic reagents of the general formula $R'_2Zn \cdot 2LiOR$ ($R' = sBu, tBu, pTol$). Highly sensitive functional groups such as a triazine, a ketone, an aldehyde or a nitro group were tolerated in these exchange reactions, giving rise to 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 $[R'_2Zn(OR)_2Li_2]$.

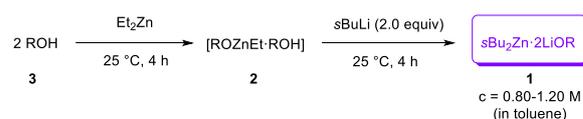
Organozinc reagents are key intermediates in organic synthesis since they tolerate many functional groups and readily participate in transition-metal-catalyzed carbon-carbon bond forming reactions.^[1] Aryl- and heteroarylzinc halides have been especially widely used organometallics for preparing complex organic molecules.^[2] Two recent alternative synthetic strategies granting access to these valuable organometallics are direct insertion of zinc powder to 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 shown ability 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 iPr_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 $iPrMgCl \cdot LiCl$ (*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 by 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, herein we report a new I/Zn and Br/Zn exchange in toluene using a novel bimetallic combination $sBu_2Zn \cdot 2LiOR$ (**1**), which allows the generation of a

wide range of polyfunctional aryl- and heteroarylzinc reagents from the corresponding organic iodides or bromides.

Firstly, Et_2Zn reacted in toluene with two equivalents of a variety of alcohols ROH (25 °C, 4 h) affording the relevant ethylzinc alkoxides, cocomplexed with the corresponding alcohol ($ROZnEt \cdot ROH$) of type **2**.^[9] These ethylzinc alkoxides (**2**) further reacted with $sBuLi$ (2.0 equiv, in cyclohexane) to produce the bimetallic reagent tentatively represented as trinuclear monozinc – dilithium complexes $sBu_2Zn \cdot 2LiOR$ (**1**, vide infra). Removal of solvents and subsequent redissolution in toluene provided a light yellow solution of **1** ($c = 0.8$ – 1.2 M in toluene; Scheme 1), which can be stored at 25 °C over months without significant loss of reactivity. Initial studies showed that complex $sBu_2Zn \cdot 2LiOR$ ($R = 2$ -octyl; **1a**) reacted with 3-iodoanisole (**4a**) in toluene^[10] within



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

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

entry	$sBu_2Zn \cdot 2LiOR$ (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] Yields of **5a** determined by GC analysis of reaction aliquots quenched with water.

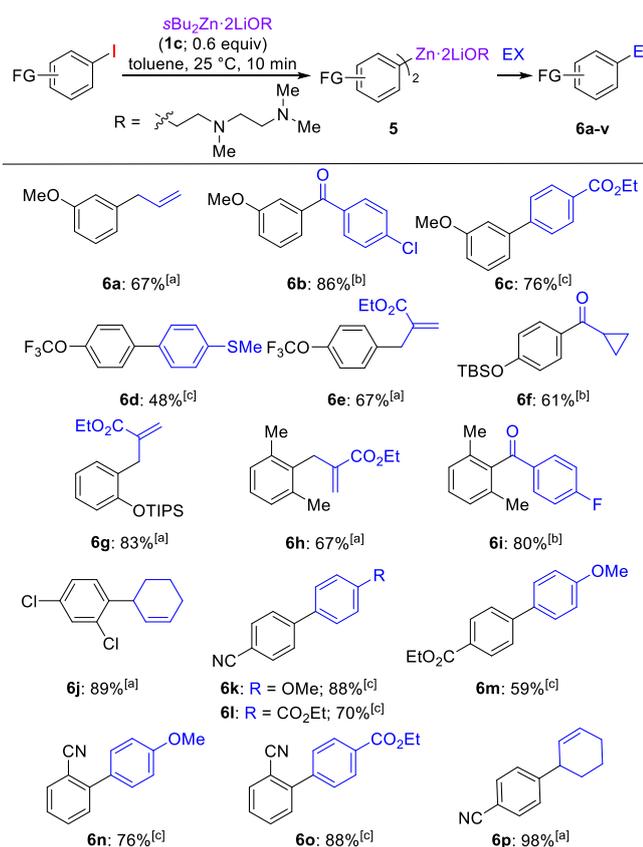
30 min at 25 °C, forming putative bis-anisylzinc complexed with 2 LiOR (**5a**) in 23% yield, as determined by GC-analysis of

[a] M. Balkenhohl, Dr. D. S. Ziegler, A. Desaintjean, Prof. Dr. P. Knochel
Ludwig-Maximilians-Universität München, Department Chemie
Butenandtstrasse 5-13, Haus F, 81377 München (Germany)
E-mail: paul.knochel@cup.uni-muenchen.de

[b] Prof. Dr. E. Hevia
Department für Chemie und Biochemie, Universität Bern,
CH3012, Bern, Switzerland
E-mail: eva.hevia@dcb.unibe.ch

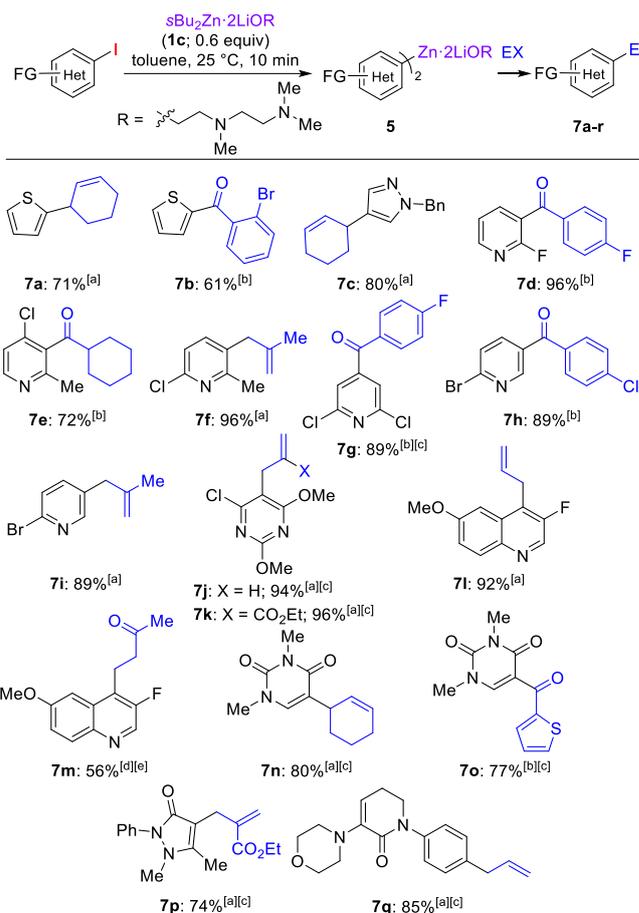
[c] L. J. Bole, Dr. A. R. Kennedy
Department of Pure and Applied Chemistry, University of
Strathclyde Glasgow, G1 1XL, UK

reaction aliquots (Table 1, entry 1). Interestingly, a striking effect was observed by 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 = -CH₂CH₂N(Et)₂) produced the diarylzinc **5a** in 95% GC-yield (entry 2); whereas using **1c** (R = -CH₂CH₂N(CH₃)CH₂CH₂N(CH₃)₂), where OR contains a second *N*-coordination site, accelerated the I/Zn exchange process affording **5a** in 99% GC-yield after just 1 minute reaction time (entries 3 and 4). Contrastingly replacing the *s*Bu group on **1c** with other alkyl groups such as Et, *n*Bu or *t*Bu groups had very little effect in the overall conversions after 30 min (ranging from 80-89%).^[12] Thus, 3-iodoanisole (**4a**) reacted with *s*Bu₂Zn·2LiOR (**1c**) in toluene at 25 °C for 10 min, to produce the bis-anisylzinc 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, leading to the biaryl **6c** in 76% yield.



^[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*Bu₂Zn·2LiOR (**1c**), followed by electrophilic functionalizations.



^[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*Bu₂Zn·2LiOR (**1c**), followed by electrophilic functionalizations.

4-(Trifluoromethoxy)iodobenzene underwent a smooth I/Zn exchange using **1c**, leading to the corresponding diarylzinc reagent **5b**. Reaction of **5b** with ethyl 2-(bromomethyl)acrylate or a palladium-catalyzed cross-coupling with 4-iodothioanisole gave functionalized arenes **6d-e** in 48-67% yield. TBS- or TIPS-protected iodophenols were treated with **1c** and the resulting zinc organometallic was allylated or acylated, providing **6f-g** in 61-83% yield. The zinc reagent obtained from sterically demanding 2-iodo-1,3-dimethylbenzene was quenched with ethyl 2-(bromomethyl)acrylate and 4-fluorobenzoyl chloride to give the 2-substituted *m*-xylenes **6h-i** in 67-80% yield. Various electron-poor aryl iodides bearing e.g. ester or nitrile groups readily reacted with **1c** and quenching of the zinc reagent of type **5** with various electrophiles gave products **6j-p** in 59-98% yield (Scheme 2).

Demonstrating the versatility of **1c**, this approach was successfully extended to a wide collection of heteroaromatic substrates to yield synthetically valuable bis-heteroarylzinc organometallics (Scheme 3). Thus, bis-thienylzinc either reacted with 3-bromocyclohexene or 2-bromobenzoyl chloride to provide

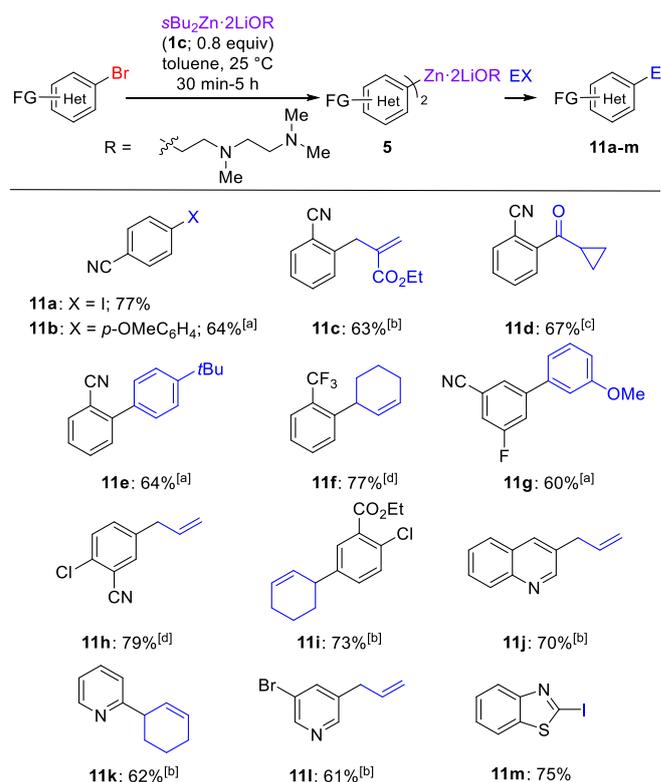
7a-b in 61-71% yield. Benzyl-protected 3-iodopyrazole reacted with **1c** to give, after allylation, **7c** in 80% yield. Also, various iodopyridines, -pyrimidines and -quinoline were converted into the corresponding zinc reagents using **1c** and quenched with several acid chlorides and allyl bromides, producing heterocyclic products **7d-i** in 72-96% yield. The organometallic obtained from an iodoquinoline underwent a copper-mediated 1,4-addition to methyl vinyl ketone in the presence of TMSCl.^[15] Subsequent enol ether cleavage using TBAF (1.1 equiv, 25 °C, 1 h) gave ketone **7m** in 56% yield over two steps. Reaction 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, Tol₂Zn·2LiOR (**9**) gave the best result.^[17] Hence, the mild exchange reagent Tol₂Zn·2LiOR (**9**, R = -CH₂CH₂N(CH₃)CH₂CH₂N(CH₃)₂; 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-nitrobenzotrile with **9** (0.6 equiv) at -15 °C for 15 min, followed by a copper-mediated allylation reaction, afforded nitroarenes **8c-d** in 71-79% yield. For converting an iodo-benzaldehyde to the corresponding zinc species, a short screening showed, that the best exchange reagent was *t*Bu₂Zn·2LiOR (**10**). Thus, the alkoxide **2c** was treated with *t*BuLi (2.0 equiv) and the resulting less nucleophilic reagent *t*Bu₂Zn·2LiOR (**10**, R = -CH₂CH₂N(CH₃)CH₂CH₂N(CH₃)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 treated with *t*Bu₂Zn·2LiOR (**10**) and the resulting zinc reagent reacted with 3-bromocyclohexene in the

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

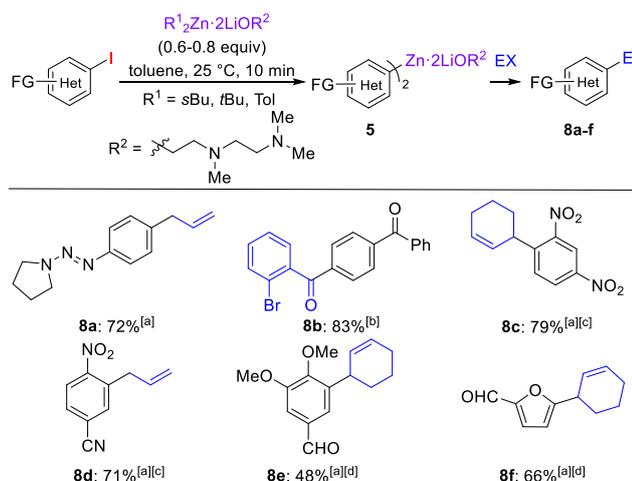
presence of CuI to give the furfural derivative **8f** in 66% yield (Scheme 4).

The excellent reactivity of these bimetallic exchange reagents led us to examine the corresponding Br/Zn exchange reaction. Thus, treatment of 4-bromobenzotrile with **1c** (0.8 equiv) at 25 °C for 5 h in toluene (1 M), provided the desired bis-arylzinc of type **5**, which, after quenching with iodine, gave 4-iodobenzotrile (**11a**) in 77% yield (Scheme 4). Reaction of the same zinc reagent with 4-iodoanisole under palladium-catalysis gave the desired biaryl **11b** in 64% yield.^[19] Allylation, acylation and cross-coupling of the zinc reagents obtained from 2-bromobenzotrile gave **11c-e** in 63-67% yield. Various bromoarenes bearing for example an ester functional group underwent a smooth Br/Zn exchange, which, after allylation or cross-coupling, produced arenes **11f-i** in 60-79% yield. Additionally, bromopyridines and a bromoquinoline were treated with **1c**. Allylation of the resulting zinc reagents gave the functionalized heteroarenes **11j-l** in 61-70% yield. Finally, 2-bromobenzothiazole was mixed with **1c** and the resulting metal species reacted with iodine to give **11m** in 75% yield (Scheme 5).



^[a]Pd(OAc)₂ (3 mol%), SPhos (6 mol%) and TMSCl (0.8 equiv) were used. ^[b]CuI (20 mol%) was used. ^[c]CuI (0.6 equiv) was used. ^[d]CuCN·2LiCl (20 mol%) was used.

Scheme 5. Reaction of various aryl bromides with *s*Bu₂Zn·2LiOR (**1**), followed by electrophilic functionalizations.



^[a]CuI (20 mol%) was used. ^[b]CuI (0.6 equiv) was used. ^[c]Tol₂Zn·2LiOR (**9**, 0.6 equiv, -15 °C, 15 min) was used. ^[d]*t*Bu₂Zn·2LiOR (**10**, 0.8 equiv, 0 °C, 10 min) was used.

Intrigued by the unique reactivity of these systems, we sought to glean some information on the constitution of **1c**. Multinuclear (^1H , ^{13}C , ^7Li) NMR studies including ^1H DOSY NMR experiments in d_8 -toluene are consistent with the formation of contacted ion pair $[\text{sBu}_2\text{Zn}(\text{OR})_2\text{Li}_2]$ (**1c**) as the major species in solution, along with another a minor ethyl complex tentatively assigned as the complex $[\text{Et}(\text{sBu})\text{Zn}(\text{OR})_2\text{Li}_2]$.^[12] The presence of this ethyl species can be rationalized considering the residual Et group present in **2** (Scheme 1) in going from type **2** to type **1**. Interestingly, ^1H 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 sBuI. $[\text{sBu}_2\text{Zn}(\text{OR})_2\text{Li}_2]$ can be envisaged as a cocomplex of sBu₂Zn and 2 equivalents 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 **1**.^[12] Cocomplexation reactions of n equivalents of LiOR ($n = 1$ and 2) with several $\text{R}'_2\text{Zn}$ ($\text{R}' = \text{Me}, \text{Et}, \text{sBu}$) in toluene were investigated spectroscopically, demonstrating in all cases the formation of mixed-metal complexes. Further evidence was obtained from X-ray crystallographic studies of the lithium diorganoalkoxyzincate $[\text{Me}_2\text{Zn}\cdot\text{LiOR}]$ (**12**, $\text{R} = -\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, Figure 1). This structure exhibits a dimeric centrosymmetric arrangement featuring 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 connect by oxygen bridges of the alkoxide groups, 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, since other alkoxide groups without N donor substituents may favour formation of higher oligomeric lithium zincates which can be expected to be less reactive.

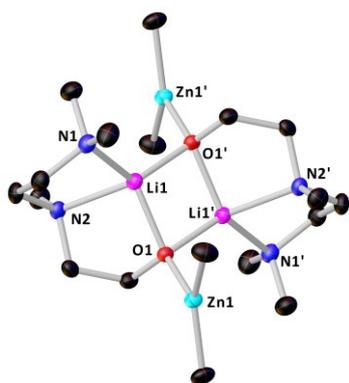


Figure 1. Molecular structure of $[\text{Me}_2\text{Zn}\cdot\text{LiOR}]$ (**12**). Hydrogen atoms are omitted for clarity and thermal ellipsoids are rendered at 50% probability.

^1H NMR monitoring studies adding variable amounts of LiOR to a solution of Et_2Zn in d_8 -toluene disclose the importance of the LiOR:alkylzinc ratio for the success of the I/Zn exchange. Thus while Et_2Zn is completely inert towards exchange with 2-iodoanisole (2 equiv.), addition of 1 equiv. of LiOR showed a conversion after 10 min of only 21%; whereas using 2 equiv. of

LiOR the reaction is almost quantitative ($\geq 99\%$). This is consistent with the formation of a more activated diorganoalkoxyzincate species $[\text{sBu}_2\text{Zn}(\text{OR})_2\text{Li}_2]$, where zinc, formally, is part of an electron-rich dianionic moiety. The excellent atom economy of the reaction, with both ethyl groups on Et_2Zn being active towards the exchange is particularly remarkable, especially when compared with the related tris(alkyl) Et_3ZnLi where only one of its three Et groups is capable of undergoing I/Zn exchange.^[12]

In summary, a new family of bimetallic reagents of type $\text{R}'_2\text{Zn}\cdot 2\text{LiOR}$ have been developed which efficiently promote I/Zn and Br/Zn exchange processes at room temperature with excellent functional group tolerance via the activation of both R' groups on Zn. Demonstrating the extensive synthetic scope of this approach, quenching the *in situ* generated zinc organometallics with various electrophiles, produced a range of functionalized (hetero)arenes. Structural and spectroscopic studies probing the constitution of these bimetallic systems to correlate reactivity with structure 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 underway in our laboratories.

Acknowledgements

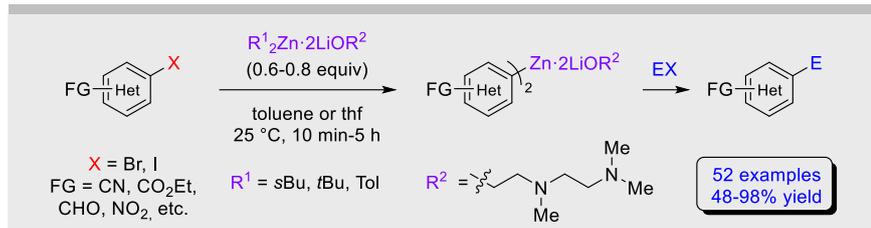
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Keywords: alkoxides • lithium • metal-halogen exchange • toluene • organozinc

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- [16] Due to poor solubility of the aryl iodides, the reactions leading to **7g,j,k,n-q** were performed in THF.
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- [19] Prior to the addition of the catalyst system and aryl iodide, TMSCl (0.8 equiv, 0 °C, 10 min) was added in order to quench the excess of alkoxide.
- [20] The arylzinc complex formed in this reaction has limited solubility in d₈-toluene but was fairly soluble in d⁹-THF. Its ¹³C NMR spectrum shows a diagnostic resonance at 155.71 ppm for Zn-C(aryl) (versus δ = 86.4 ppm for C-I in 2-iodoanisole). DOSY NMR studies are consistent with the formation of a heteroleptic [Ar₂Zn(OR)₂Li₂] species.

COMMUNICATION



Alkoxide is all you need: An efficient, atom economical I/Zn and Br/Zn exchange reaction using dialkylzinc reagents cocomplexed with lithium alkoxides is reported. Due to the covalent nature of the carbon-zinc bond, several highly sensitive functional groups including triazines, ketones, aldehydes or nitro groups were tolerated. Quenching of diarylzinc species with various electrophiles produced a plethora of functionalized arenes and heteroarenes.

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