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Preparation of Polyfunctional Zinc Organometallics Using an Fe- or Co-Catalyzed Cl/Zn-Exchange

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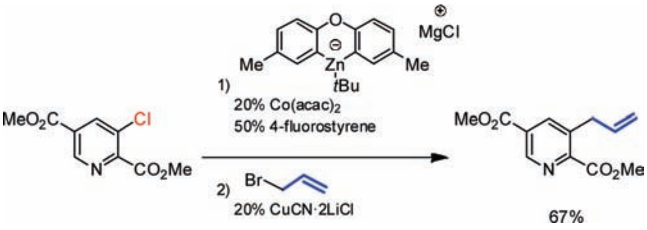
ABSTRACT



A new Fe- or Co-catalyzed Cl/Zn-exchange reaction allows the direct transformation of aryl, heteroaryl, and also alkyl chlorides into the corresponding zinc reagents. The method tolerates functional groups such as a nitrile or an ester. Remarkably, secondary and tertiary alkyl chlorides are suitable substrates for the Cl/Zn exchange.

Zinc organometallics are of great importance since these reagents tolerate the presence of many functional groups.[1] Direct zinc insertion,[2] base directed metalation,[3] boron–zinc exchange,[4] transmetalation,[5] and halide/zinc-exchange performed with iPr$_2$Zn,[6] Et$_2$Zn,[7] or zincates such as Bu$_4$ZnLi$_2$[8] have been used for their preparation. The halogen/zinc-exchange was successful mostly with aryl iodides and in some cases with aryl bromides.[6−9] Although aryl chlorides are ideal precursors in light of their good availability, stability, and low price in comparison to the corresponding bromides and especially iodides, these substrates, however, are reluctant to undergo a

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(9) (a) For a Cl/Li-exchange, see: Gillet, J. P.; Sauvêtre, R.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 3999. (b) For a Cl/Mg-exchange, see: Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618.

(10) (a) Cahiez, G.; Moyeux, A. *Chem. Rev.* **2010**, *10*, 1435. (b) Affo, W.; Ohmiya, H.; Fujioka, T.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Inamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068. (c) Ohmiya, H.; Yorimitu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 1240. (d) Fillon, F.; Gosmini, C.; Périchon, J. *J. Am. Chem. Soc.* **2003**, *125*, 3867. (e) Gosmini, C.; Moncomble, A. *Isr. J. Chem.* **2010**, *50*, 568. (f) Gosmini, C.; Amatore, M.; Claudel, S.; Périchon, J. *Synlett* **2005**, 2171. (g) Kazmierski, I.; Gosmini, C.; Paris, J.-M.; Périchon, J. *Synlett* **2006**, 881.

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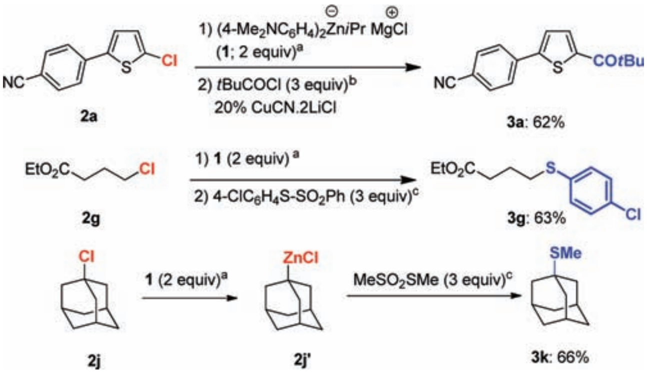
Cl/Zn-exchange. Interestingly, related Cl/Li- or Cl/Mg-exchanges also proceed, but only for specific substrates.[9]

Various cobalt[10] and iron[11] salts have been used in organic synthesis as versatile catalysts for several organic transformations. We also reported a Co-catalyzed sulfonate/copper-exchange, allowing the synthesis of functionalized arylcopper derivatives.[12] This led us to investigate the Cl/Zn-exchange reaction using transition-metal catalysis.

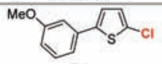
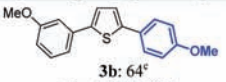
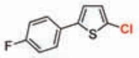
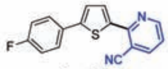
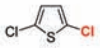
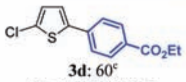
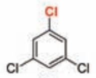
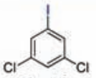
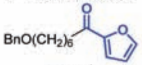
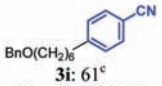
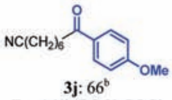
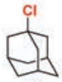
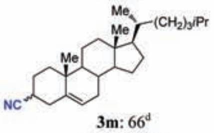
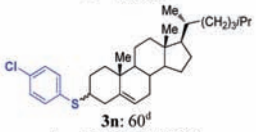
Herein, we report new iron(III) and cobalt(II)-catalyzed Cl/Zn-exchange reactions on aryl, heteroaryl, and alkyl chlorides as substrates using a triorganozincate[13] as an exchange reagent. We have selected the chloromagnesium triorganozincate $(4\text{-}Me_2NC_6H_4)_2Zn(i\text{Pr})MgCl$ (**1**), since the hydrolyzed zincate and the resulting quenching byproduct with electrophiles are readily removed by an acidic workup. After numerous optimization reactions, we have found that the treatment of a heterocyclic chloride such as the 2-chlorothiophene **2a** with the zincate **1** (2.0 equiv) in the presence of 10% $Fe(acac)_3$ and 20% 4-fluorostyrene[14] provides under mild conditions (THF, 25 °C, 16 h) a zinc organometallic species that reacts with typical electrophiles such as pivaloyl chloride (3.0 equiv) in the presence of 20% $CuCN \cdot 2LiCl$,[15] leading to the expected acylated thiophene **3a** in 62% isolated yield (Scheme 1). The presence of a catalytic amount of 4-fluorostyrene[14] increases the Cl/Zn-exchange rate and improves the reaction yield.[16] Interestingly, 2,5-dichlorothiophene (**2d**) undergoes a selective monoexchange under these conditions, providing the thiophene **3d** in 60% yield after a Pd(0)-catalyzed cross-coupling (Table 1, entry 3). Also electron-deficient aromatic chlorides such as 1,3,5-trichlorobenzene (**2e**) undergo a selective monoexchange, affording the aryl iodide **3e** in 56% yield after iodolysis (entry 4).

Scheme 1. Fe-Catalyzed Cl/Zn-Exchange of Organic Chlorides **2a,g,j** and Reaction with Electrophiles



[a] 10% $Fe(acac)_3$, 20% 4-fluorostyrene, THF, 25 °C, 16 h. [b] THF, −20 °C, 30 min. [c] THF, 25 °C, 30 min.

Table 1. Fe-Catalyzed Cl/Zn-Exchange of Aryl, Heteroaryl, and Alkyl Chlorides and Reaction with Electrophiles

entry	substrate	product, yield [%]^{a}, electrophile
1	 **2b**	 **3b**: 64^{c} E = $4\text{-}IC_6H_4OMe$
2	 **2c**	 **3c**: 62^{c} E = 2-chloronicotinonitrile
3	 **2d**	 **3d**: 60^{c} E = $4\text{-}IC_6H_4CO_2Et$
4	 **2e**	 **3e**: 56 E = I_2
5	 **2f**	 **3f**: 66^{b} E = $4\text{-}ClC_6H_4COCl$
6	$BnO(CH_2)_6Cl$ **2h**	 **3h**: 63^{b} E = furoyl chloride
7	**2h**	 **3i**: 61^{c} E = $4\text{-}BrC_6H_4CN$
8	$NC(CH_2)_6Cl$ **2i**	 **3j**: 66^{b} E = $4\text{-}MeOC_6H_4COCl$
9	 **2j**	 **3l**: 61 E = I_2
10	Cholesteryl-Cl **2k**	 **3m**: 66^{d} E = TosCN
11	**2k**	 **3n**: 60^{d} E = $4\text{-}ClC_6H_4S\text{-}SO_2Ph$

[a] Yield of isolated analytically pure product; 3 equiv of the electrophile were used. [b] 20% $CuCN \cdot 2LiCl$ used as catalyst. [c] 2% $Pd(PPh_3)_4$ used as catalyst. [d] dr = 1.4:1.

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(13) For the use of zincates for performing I/Zn and Br/Zn exchange reactions, see: (a) Nakamura, S.; Liu, C.-Y.; Muranaka, A.; Uchiyama, M. *Chem.—Eur. J.* **2009**, *15*, 5686. (b) Chau, N. T. T.; Meyer, M.; Komagawa, S.; Chevallier, F.; Fort, Y.; Uchiyama, M.; Mongin, F.; Gros, P. C. *Chem.—Eur. J.* **2010**, *16*, 12425. (c) Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733. (d) Naka, H.; Ito, K.; Ueno, M.; Kobayashim, K.; Kondo, Y. *New J. Chem.* **2010**, *34*, 1700.

(14) (a) Piber, M.; Jensen, A. E.; Rottländer, M.; Knochel, P. *Org. Lett.* **1999**, *1*, 1323. (b) Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79. (c) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 9717. (d) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840.

(15) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, T. *J. Org. Chem.* **1988**, *53*, 2390.

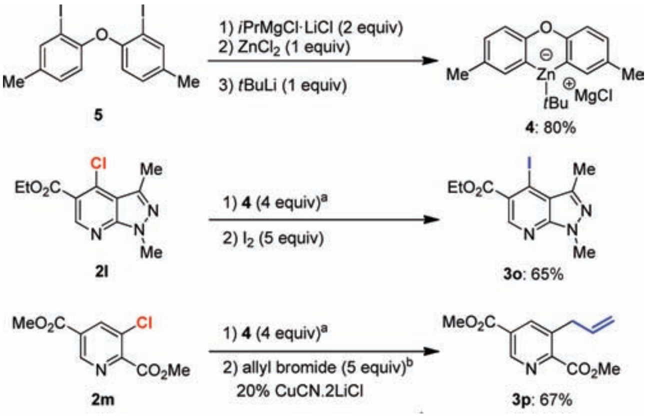
Performing the Cl/Zn-exchange protocol with chloropentafluorobenzene (**2f**) leads to the ketone **3f** in 65% yield after acylation (entry 5). Remarkably, using these conditions, alkyl chlorides could also be converted to organozincs. Therefore, ethyl 4-chlorobutanoate (**2g**) reacted with zincate **1** (THF, 25 °C, 16 h) and furnished the alkyl aryl sulfide **3g** in 63% yield after quenching of the resulting alkylzinc reagent with a thiosulfonate (Scheme 1). Other functionalized chlorides such as the benzyl-protected 6-chlorohexanol **2h** underwent the Cl/Zn-exchange (25 °C, 18 h). The resulting organozinc reagent could either be acylated with furoyl chloride to yield functionalized furan **3h** in 63% yield (entry 6) or be submitted to a Pd(0)-catalyzed cross-coupling to form the benzonitrile derivative **3i** in 61% yield (entry 7). Also the nitrile-substituted alkyl chloride **2i** led to an alkylzinc species (25 °C, 16 h), which after acylation with 4-methoxybenzoyl chloride gave the ketone **3j** in 66% yield (entry 8).

Preparatively useful is the performance of a Cl/Zn-exchange on tertiary chlorides, which are generally known to be difficult to convert into organometallic species.[17] Hence, the reaction of 1-chloroadamantane (**2j**) furnishes a tertiary organozinc reagent **2j′** under our conditions (25 °C, 24 h), which after quenching with *S*-methyl methanesulfonothioate resulted in the thiomethyl adamantane **3k** (66% yield, Scheme 1). Alternatively, quenching the adamantylzinc species with iodine furnished 1-iodoadamantane (**3l**) in 61% yield (Table 1, entry 9). Finally, a secondary chloride like cholesteryl chloride (**2k**) smoothly undergoes a Cl/Zn-exchange (25 °C, 24 h). Trapping the zinc reagent with tosyl cyanide or a thiosulfonate led to the functionalized steroids **3 m,n** in 60–66% yield as a mixture of two diastereomers (entries 10 and 11).

The scope of the Fe-catalyzed Cl/Zn-exchange was satisfactory for alkyl chlorides. However, we found some limitations for aryl chlorides and chloro-substituted N-heterocycles. This led us to investigate an alternative transition metal catalyst. $Co(acac)_2$ was found to be the most appropriate salt. Although zincate **1** was an efficient exchange reagent for Fe-catalysis, we found that the readily available zincate **4** performed better on most aryl and N-heterocyclic chlorides. This zincate was prepared from 4,4′-oxybis(3-iodo-1-methylbenzene) (**5**) by an I/Mg-exchange with *i*PrMgCl·LiCl (2.0 equiv, THF, −78 °C, 1 h), followed by transmetalation with $ZnCl_2$ and addition of *t*BuLi (1.0 equiv, THF, 0 °C, 0.5 h, Scheme 2).

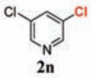
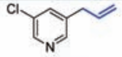
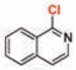
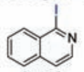
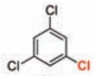
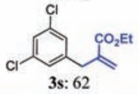
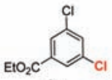
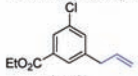
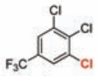
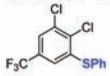
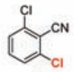
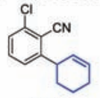
Thus, the pyrazolopyridine **2l** underwent a Cl/Zn-exchange reaction using zincate **4** (4.0 equiv) and 20% Co-$(acac)_2$ (50% 4-fluorostyrene, THF, 50 °C, 5 h). The resulting zinc species reacted with iodine, furnishing the functionalized N-heterocycle **3o** in 65% yield. Furthermore, the 3-chloro-pyridine derivative **2m** was converted into a zinc species using the same conditions. Quenching with allyl bromide furnished the trisubstituted pyridine **3p** in 67% yield. Moreover, we performed the Cl/Zn-exchange on 3,5-dichloropyridine (**2n**, 50 °C, 5 h). After Cu-catalyzed allylation the desired heterocycle **3q** was obtained in 64% yield (Table 2, entry 1).

Scheme 2. Preparation of Zincate **4** and Co-Catalyzed Cl/Zn-Exchange of Heterocyclic Chlorides **2l,m**



[a] 20% $Co(acac)_2$, 50% 4-fluorostyrene, THF, 50 °C, 5 h. [b] THF, −20 °C, 30 min.

Table 2. Co-Catalyzed Cl/Zn-Exchange of Heteroaryl and Aryl Chlorides and Reaction with Electrophiles (E)

entry	substrate	product, yield [%][a]
1	 **2n**	 **3q**: 64 $E = Br\text{-}CH_2CH{=}CH_2$[b]
2	 **2o**	 **3r**: 59 $E = I_2$
3	 **2p**	 **3s**: 62 $E = Br\text{-}CH_2C(CO_2Et)CH_2$[b]
4	 **2q**	 **3t**: 62 $E = Br\text{-}CH_2CH{=}CH_2$[b]
5	 **2r**	 **3u**: 63 $E = PhSO_2\text{-}SPh$[b]
6	 **2s**	 **3v**: 57 E = 3-Bromocyclohex-1-ene[b]

[a] Yield of isolated analytically pure product; 5 equiv of electrophile were used. [b] 20% CuCN·2LiCl used as catalyst.

Also 1-chloroisoquinoline (**2o**) undergoes the Cl/Zn-exchange reaction (50 °C, 5 h). Quenching with iodine

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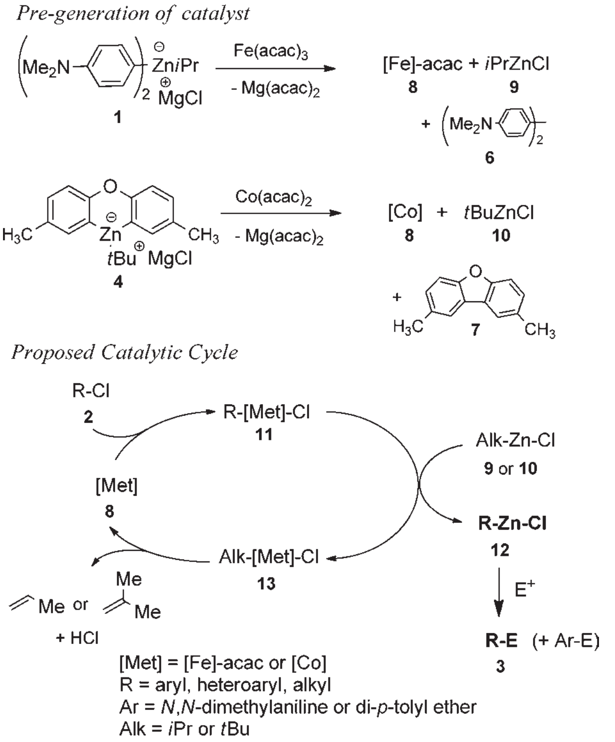
(16) We assume that 4-fluorostyrene facilitates the reductive elimination step during the catalytic cycle. Its presence is essential for the Cl/Zn-exchange. Apparently, 4-fluorostyrene is not consumed during the reaction, as shown by GC analysis using an internal standard.

(17) For the preparation of adamantyllithium and adamantylmagnesium reagents, see: (a) Molle, G.; Dubois, J.-E.; Bauer, P. *Tetrahedron Lett*. **1978**, *19*, 3177. (b) Molle, G.; Bauer, P.; Dubois, J.-E. *J. Org. Chem.* **1983**, *48*, 2975.

(18) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.

Scheme 3. Proposed Mechanism for the Cl/Zn-Exchange



Pre-generation of catalyst

Proposed Catalytic Cycle

[Met] = [Fe]-acac or [Co]
R = aryl, heteroaryl, alkyl
Ar = *N*,*N*-dimethylaniline or di-*p*-tolyl ether
Alk = *i*Pr or *t*Bu

furnished the 2-iodoisoquinoline **3r** (59% yield, entry 2). The Co-catalyzed Cl/Zn-exchange protocol using zincate **4** also proceeds well with nonheteroaromatic chlorides. This Cl/Zn-exchange protocol gives access to 1,3,5-trisubstituted arenes, which are tedious to prepare by classical methods.[19] An ester function is well tolerated in the exchange: the dichlorobenzene **2q** was converted after Cl/Zn-exchange and subsequent allylation to ethyl 3-allyl-5-chlorobenzoate (**3t**) in 62% yield (entry 4).

A selective monoexchange is also possible on 1,2,3-trichloro-5-(trifluoromethyl)benzene (**2r**, 50 °C, 5 h). Quenching with $PhSO_2$−SPh furnished the trisubstituted thioether **3u** in 63% yield (entry 5). The Cl/Zn-exchange reaction was suitable for aryl chlorides bearing a nitrile group. So the benzonitrile derivative **2s** was converted to a zinc reagent (50 °C, 5 h), which after Cu-catalyzed allylation gives the 1,2,3-trisubstituted benzene **3v** in 57% yield (entry 6).

A tentative catalytic cycle is proposed for this new Cl/Zn-exchange (Scheme 3). Under the reaction conditions, we anticipate the formation of a reduced active metal catalyst [Met] (Met = FeL_n, CoL_n) **8**.[20] The formation of biphenyldiamine derivative **6** and dimethylbenzofuran **7** is mostly complete by mixing the reagents. The organic chloride **2** may initially undergo an oxidative addition to the metal catalyst (**8**) resulting in the formation of the organometallic **11**. The reaction of **11** with either zinc reagent **9** or **10** transfers the R group from the transition metal center to zinc leading to the new zinc reagent **12** and to the *i*Pr- or *t*Bu-organometallic intermediate **13** (Alk-[Met]-Cl; Alk = *i*Pr or *t*Bu). After β-hydride elimination with formation of propene or isobutylene, the active metal catalyst (**8**) is regenerated and is available for a new catalytic cycle.[21]

In summary, we have developed a new Cl/Zn-exchange reaction allowing the direct transformation of aryl, heteroaryl, and also alkyl chlorides into the corresponding zinc reagents. The method tolerates several functional groups such as a nitrile or an ester. Remarkably, also secondary and even tertiary chlorides are suitable substrates for the exchange protocol. The synthetic scope of this new method is currently being investigated in our laboratories.

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Supporting Information Available. Experimental procedure and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) By using the zincate $(4\text{-}Me_2NC_6H_4)_2Zn(Oct)MgCl$ as an exchange reagent we have observed a constant increase of the formation of octene during the course of the reaction. This elimination was observed only if an organic chloride is added to the mixture of the exchange reagent (zincate) and the catalytic system.