# Role of LiCl in Generating Soluble Organozinc Reagents

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Ⓢ *Supporting Information*

**ABSTRACT:** The sensitivity provided by fluorescence microscopy enabled the observation of surface intermediates in the synthesis of soluble organozinc reagents by direct insertion of alkyl iodides to commercial zinc powder. Five hypotheses were examined for the mechanistic role of lithium chloride in enabling this direct insertion. The data are consistent with lithium chloride solubilizing organozinc reagents from the surface of the zinc after oxidative addition.

O rganometallic reagents have revolutionized organic synthesis by enabling diverse carbon−carbon bond forming reactions. The generation of soluble organomagnesium reagents (Grignard reagents) by oxidative addition of organohalides to magnesium turnings was an enabling early advance.[1,2] The analogous direct insertion of organohalides to commercially available powders of other metals would provide the simplest route for the synthesis of valuable reagents with higher functional group tolerance, complementary reactivity, or catalytic activity (e.g., organozinc, -copper, -calcium, -manganese, -indium, -aluminum, and -palladium complexes). Yet generalization of this direct insertion process has long been hampered by the resistance of commercial powders of other metals[3] toward direct insertion of organohalides. The primary failure methods are believed to be recalcitrant oxidative addition to these metal surfaces due to passivation from surface impurities[4] or inherent inactivity,[5,6] and/or low solubility of the products once formed, which are then sluggish to dissociate from the metallic surface.[7]

Given the challenges with in operando characterization of small quantities of intermediates in mixtures of metal powders with organohalides, progress in extending direct insertion to other metals has been largely empirical to date. For example, in 2006 Knochel established that addition of lithium chloride enabled the synthesis of highly functionalized, soluble organozinc reagents via oxidative addition to metallic zinc (Scheme 1).[8] Organozinc reagents have a variety of uses in organic synthesis, e.g., as Negishi coupling partners,[9] and the reagents produced through this pathway (denoted as bimetallic RZnI·LiCl, **5**[8,10]) are synthetically useful.[11−13] In a subsequent series of discoveries by Knochel, addition of lithium chloride enabled the direct insertion of organohalides into manganese,[14] aluminum,[15] and indium[16] powders, often in conjunction with other additives such as TMSCl[8,15] or metal halide catalysts.[14]

Despite this method's widespread use, the reason why the insertion is ineffective in the absence of lithium chloride remains speculative and has not been experimentally established.[10,17] We herein describe fluorescence microscopy experiments with sensitivity as high as up to single-molecules[18−32] that rule out

Scheme 1. Prior Work and the Experiment Schematic of This Study, Illustrating Different Mechanistic Hypotheses for the Role of Lithium Chloride
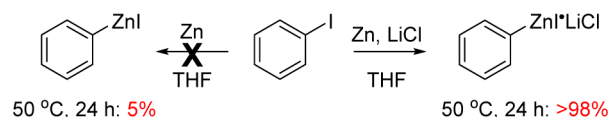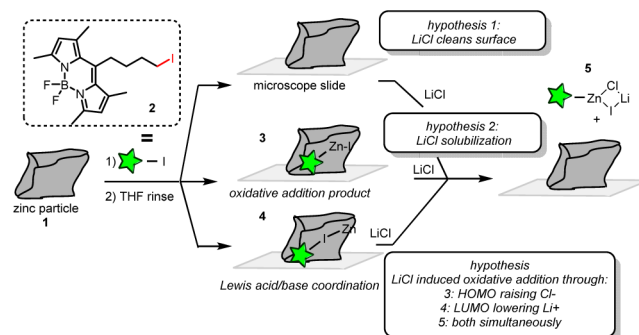


mechanistic possibilities and rationalize why the synthetic system optimized to LiCl rather than a different salt. It is anticipated that this improved understanding of the mechanistic basis for the effect will facilitate the future development of currently unknown organometallic reagents by direct insertion into presently recalcitrant metals.

Five mechanistic possibilities were herein considered for the role of lithium chloride in the formation of soluble organozinc reagents from alkyl iodides and zinc powder: (1) lithium chloride cleans impurities from the surface of the zinc powder before coordination or reaction of the alkyl iodide (similar to the role of $I_2$ to activate magnesium metal in Grignard reagent formation);[4] (2) lithium chloride solubilizes surface organozinc reagents after oxidative addition, thus producing the solution-phase reagent and exposing the zinc surface to another molecule of alkyl iodide;[8] and lithium chloride accelerates oxidative addition (3) through binding of chloride to the zinc surface (HOMO raising); (4) through binding of lithium cation to iodide (LUMO lowering); or (5) through simultaneous LUMO lowering/ HOMO raising with both lithium and chloride required, as suggested previously through calculation[6] (Scheme 1).

We designed an alkyl iodide probe (**2**) to differentiate between these mechanistic roles through fluorescence microscopy

imaging (Scheme 1). The green BODIPY fluorophore in **2** serves as a bright "beacon" that enables determination of the location of the alkyl group throughout the multiple physical phase changes and chemical changes of the overall reaction. The fluorophore is a spectator in the reaction and is not directly attached to the iodide in order to reduce the chance of quenching or other undesired/interfering reactivity of the fluorophore upon reaction with the zinc surface.

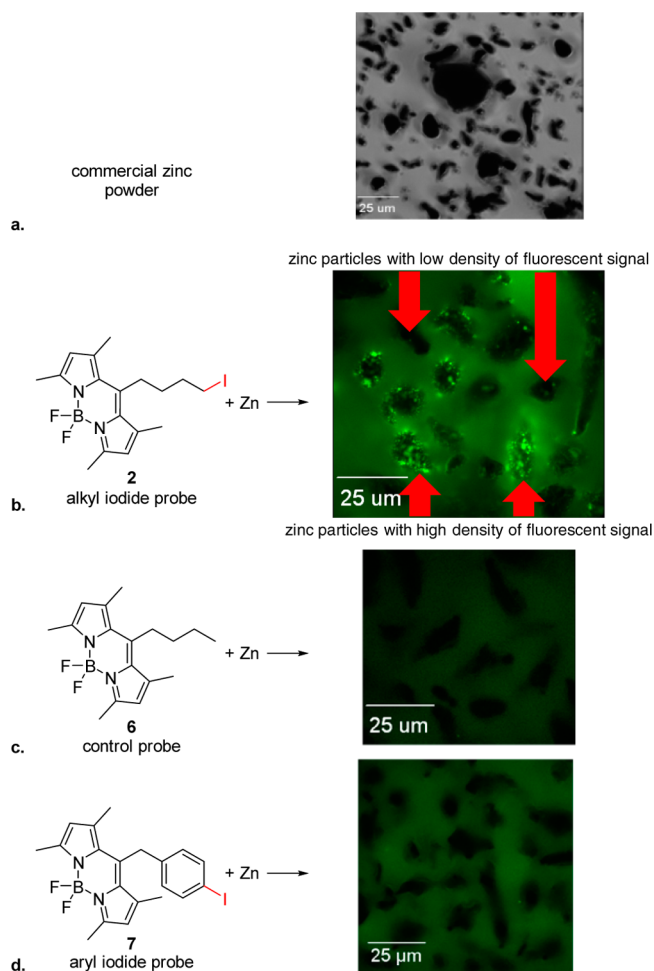Commercial zinc metal powder (**1**, Figure 1a) from the same supplier and of the same mesh as previously employed by



**Figure 1.** Ambient light illumination: (a) zinc powder as received from commercial supplier. Fluorescence microscopy: (b) zinc powder after soaking in a solution of **2**, (c) zinc powder after soaking in a solution of control probe **6**, and (d) zinc powder after soaking in a solution of control probe **7**.

Knochel[8] was treated with TMSCl per the reported protocol[8] and then soaked in a solution of alkyl iodide **2** in THF for 24 h. The mother liquor containing residual **2** was then decanted, and the remaining zinc particles were rinsed three times with THF. The zinc particles were suspended in clean THF and transferred to a reaction vial with a thin glass bottom suitable for fluorescence microscopy imaging of the sample under air-free conditions.

Material containing the fluorophore was clearly visible as bright green spots on the surface of the dark irregular zinc particles (Figure 1b). Notably, the zinc particles displayed heterogeneous reactivity with the probe, with some particles—and some locations on each particle—displaying significantly

higher reactivity than others, likely due to differences in surface composition or local environments.[33,34]

The background appears light green rather than black because of illumination from fluorescent spots on out-of-focus nearby zinc particles and residual fluorescent material in solution, in combination with the extremely high sensitivity of the camera to detect low levels of fluorescence. On the basis of the fluorescence intensity and photophysical behavior of these spots on the zinc particles, it is possible to clearly assign the brightest spots as many molecules of probe and not single molecules.[35]

The presence of these organic groups on the surface of the zinc *prior* to addition of lithium chloride is inconsistent with the hypothesis that lithium chloride must be present prior to surface attachment of organohalides in order to clean the zinc surface of impurities and expose reactive surface (hypothesis 1).

Control probe **6** is similar to **2** but lacks the carbon–iodide bond; thus, zinc cannot oxidatively insert into this probe. Zinc particles prepared identically except with control probe **6** instead of **2** are dark in comparison and do not show similar high quantities of bright green spots from organic material on their surface (Figure 1b). This data indicated the chemoselectivity of the surface attachment process and is consistent with the assignment of the chemical structure of the fluorescent molecules on the surface as iodide-requiring **3** or **4**, rather than nonspecifically physisorbed material.

To differentiate between surface structures **3** and **4**, reaction of the zinc with control probe **7** was next investigated. Surface structure **3** is the product of direct insertion/oxidative addition and contains a zinc–carbon bond. Surface structure **4**, in contrast, is the product of simple coordination of the iodide lone pair to Lewis acidic zinc. Control probe **7** contains an aryl iodide rather than an alkyl iodide. Aryl iodides that lack electron withdrawing groups are significantly less reactive toward direct insertion of metallic zinc than are alkyl iodides, requiring 50 °C rather than ambient temperature for reaction.[8] Thus, direct insertion of control probe **7** should not occur under otherwise identical conditions. Control probe **7**, however, does contain iodide lone pairs and thus would be expected to coordinate similarly to zinc as probe **2**, if simple ligand coordination were responsible for the bright green spots from buildup of organic material on the surface of the zinc. Zinc particles prepared identically except being treated with aryl iodide **7** are dark and do not show similar high quantities of bright spots of fluorescent material on their surface (Figure 1d). Thus, the material on the surface in Figure 1b is assigned as structure **3**, the product of direct insertion, rather than structure **4**, the product of simple ligand coordination.

The next question was if this observable surface material constituted reaction intermediates in the synthesis of organozinc reagents. In order to examine this question and remaining hypothesis 2, four different solid salts were then added to four separate samples of zinc particles previously treated with alkyl iodide probe **2**—LiCl, LiOTf, NaCl (control experiment since salt is only sparingly soluble), and $Bu_4NCl$—and the effect of these salts on the bright green spots on the surface of the zinc was examined (Figure 2).

At $t = 600$ s after salt addition, the imaging region was moved to a new area that had not been exposed to the laser, in order to prevent any significant photobleaching[35] from convoluting the data analysis. The sample treated with lithium chloride showed a dramatic decrease in the quantity of probe on the surface of the zinc, as seen by the lack of bright spots at $t = 600$ s, consistent
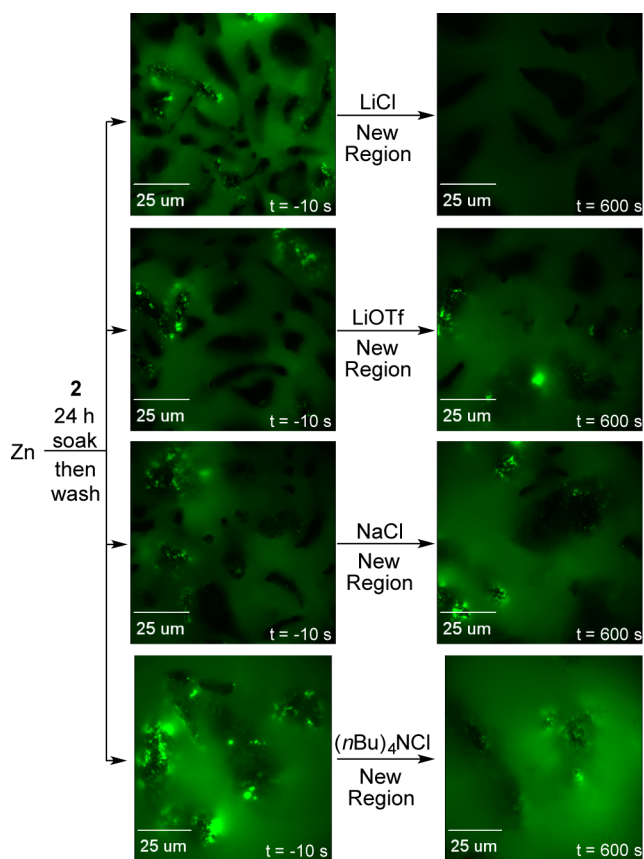
**Figure 2.** Addition of solid salts to different aliquots of a Zn sample in THF, with LiCl, LiOTf, NaCl, and Bu$_4$NCl (top to bottom). Negative times indicate the time before addition of the salt.

with assignment of the bright green material as reaction intermediates that could be transformed by lithium chloride.

In contrast, at $t = 600$ s, organic probe remained on the surface of the zinc in all other samples after addition of LiOTf (lithium cation but no chloride), NaCl (insoluble control), and Bu$_4$NCl (chloride anion but no lithium cation), as seen by the presence of similar numbers and intensities of bright green spots at $t = -10$ and $t = 600$ s. Representative data from one run is shown in Figure 2; data from triplicate runs are included in the Supporting Information. These results established that both lithium and chloride are required concomitantly for transformation of the organic surface material, which is further consistent with hypothesis 2 (Scheme 1) but inconsistent with hypotheses 3 or 4. Thus, the role of LiCl has been assigned as solubilization of otherwise persistent surface intermediate 3.

The data further provided a rationale for why the synthetic system optimized to LiCl rather than another salt. Concurrent complexation of both lithium and chloride to enhance the solubility, as shown in complex 5, is a plausible requirement, because the other tested salts contain either weakly coordinating anions or cations.[36]

**Quenching Control Experiments.** An alternative explanation for the decrease in the fluorescence of the sample is that the added lithium chloride, or liberated byproducts zinc iodide or zinc chloride, could quench the fluorescence of the fluorophore, leading to a decrease in fluorescence signal even though the fluorescently tagged alkyl or alkyl iodide were still present on the surface of the zinc.[37] Three control experiments therefore quantified the bulk fluorescence of a sample of BODIPY

fluorophore 2 in THF in the absence of lithium chloride and in a saturated solution of lithium chloride, and separately at several concentrations of zinc iodide and zinc chloride. The three samples displayed identical fluorescence at multiple concentrations (LiCl and ZnI$_2$ in Figure 3; ZnCl$_2$ in Supporting Information). Thus, the disappearance of the fluorescence signal is attributed to removal of the organic probe from the surface and not to quenching.
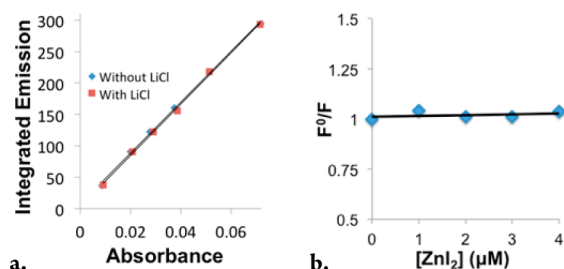


**Figure 3.** Fluorescence of a sample of 2 is not affected by reagents or byproduct quenching: (a) in the presence and absence of saturated lithium chloride, at varying [2] or (b) at fixed [2] and varying low concentrations of ZnI$_2$, as would be expected in a microscopy sample.

**Additional Characterization of the Surface through Downstream Reactivity.** In contrast to the high signal that makes fluorescence imaging of small numbers of molecules and thus detection of these intermediates possible, though we attempted to use surface Raman spectroscopy to detect surface intermediates, it proved insufficiently sensitive. We therefore turned to chemical methods to provide additional characterization of the nature of the surface.

To a sample of the zinc particles treated with 2 was added three drops of water during microscopy imaging. This addition resulted in complete and immediate removal of intermediates on the surface, consistent with protodemetalation/protonation of a Zn–C surface bond in 3 to release 6 into solution (eq 1, Figure 4), analogous to the facile protonation of solution
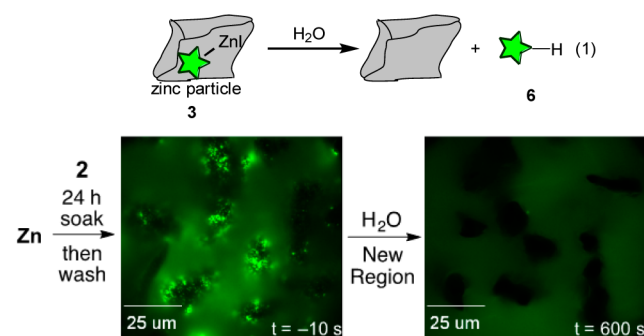


**Figure 4.** Addition of water to zinc treated with 2 results in complete removal of fluorescent material from surface of the zinc.

organozinc complexes with ambient moisture.[8] BODIPY fluorophores retain their fluorescence in solutions with water cosolvents.[22] This chemical experiment is therefore further consistent with direct insertion occurring in the absence of lithium chloride (hypothesis 2).

**Characterization of Ultimate Organic Product.** Treatment of probe 2 with the same zinc powder and lithium chloride in a standard bench experiment followed by NH$_4$Cl quench led to the expected protodemetalated product 6, using a similar GC-

MS identification process to Knochel (eq 2).[8] This result established that **2** does indeed form the corresponding organozinc reagent **5** upon treatment with zinc metal and lithium chloride in our studied system.
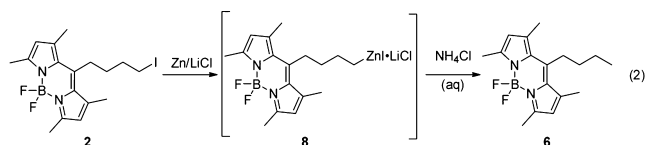


In conclusion, we demonstrated a sensitive new tool for investigating the roles of additives in the synthesis of organometallic reagents through direct metal insertion. This disclosure is the first example of fluorescence microscopy—already well-established in biology—as a tool to determine the mechanistic role of a reagent in organic/organometallic synthesis. This sensitivity permitted detection of surface intermediates for the first time in reactions of commercial zinc powder with organohalides.

An initial reaction between the zinc surface and an alkyl iodide occurred in the absence of LiCl, inconsistent with hypothesis 1 (data in Figure 1b). An aryl iodide did not generate surface intermediates, inconsistent with hypotheses 3−5 (data in Figure 1d). Both lithium and chloride were required to transform the surface species, further ruling out hypotheses 3 and 4 (data in Figure 2). Not all locations on the surface of zinc were equally reactive, and addition of LiCl removed the organic material from these most reactive locations on the zinc surface, thus plausibly re-exposing the more reactive zinc locations to further substrate direct insertion during the synthetic procedure, consistent with hypothesis 2 (data in Figure 2).[8] The mechanistic role for the lithium chloride additive is thus indicated as the solubilization of otherwise persistent organometallic intermediates from the surface of the zinc. These studies bring mechanistic understanding to an area of chemistry that is currently progressing empirically.

## ■ ASSOCIATED CONTENT

**Ⓢ Supporting Information**
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08465.

Experimental details, replicate data, and compound characterization (PDF)

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**Notes**
The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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