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Mechanism of an Elusive Solvent Effect in Organozinc Reagent Synthesis

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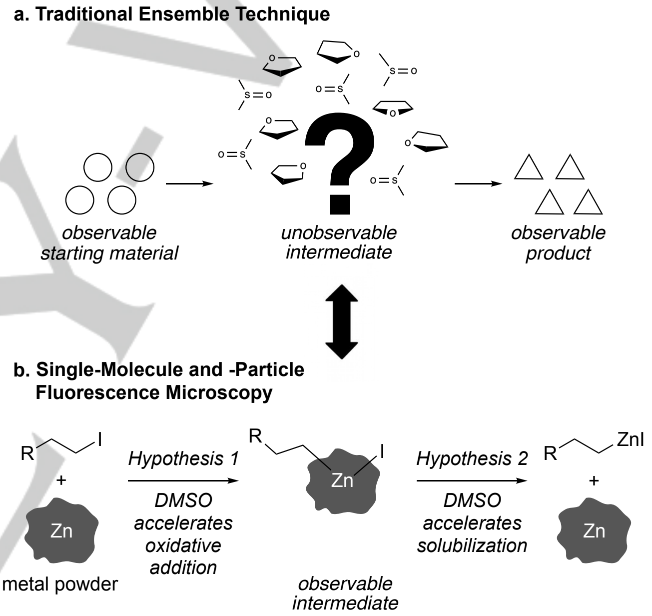
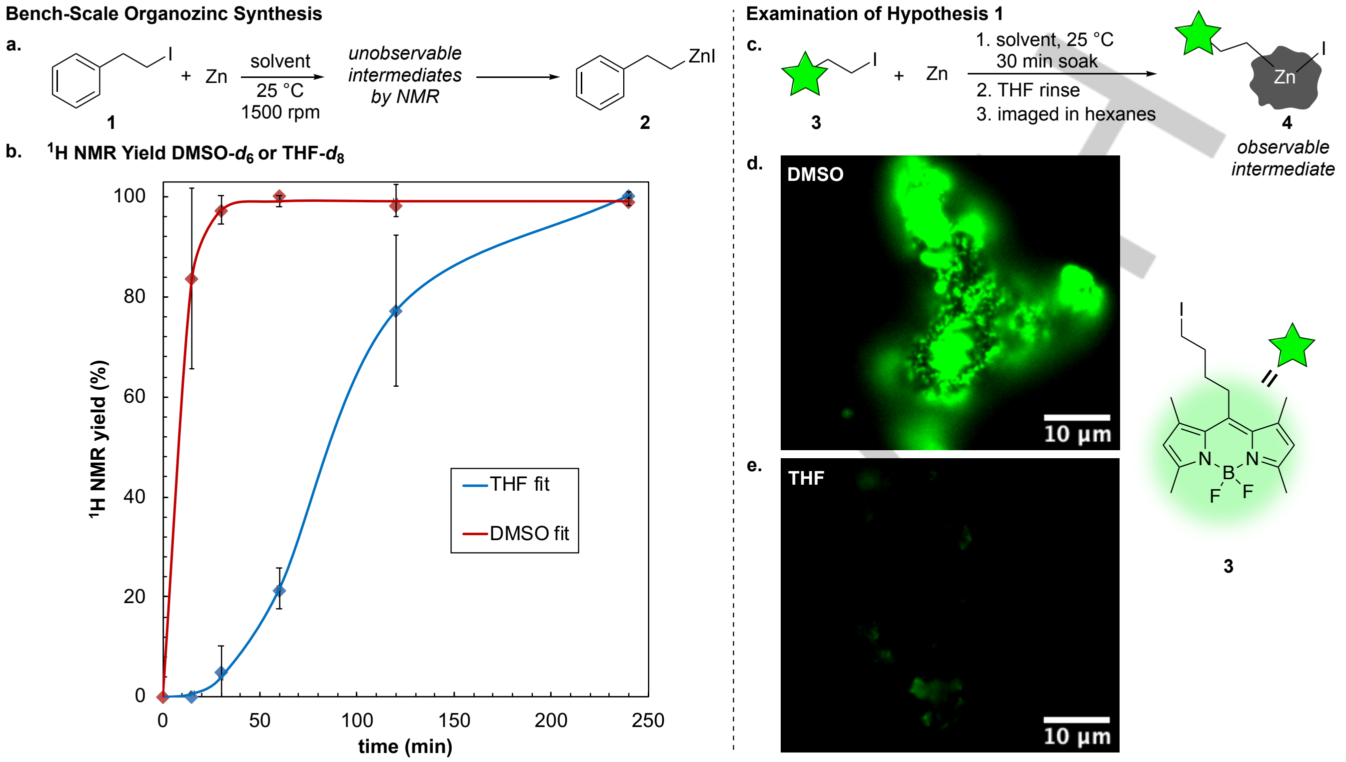
Abstract: Solvent effects are often difficult to understand in cases where reaction intermediates, and thus their differential behaviour in different solvents, are not directly observable by traditional ensemble analytical techniques. Herein, the sensitivity of single-particle fluorescence microscopy uniquely enables direct observation of organozinc intermediates and solvent effects on their build-up and persistence. When combined with NMR spectroscopy, these imaging data pinpoint the previously elusive mechanistic origin of solvent effects in the synthesis of widely used organozinc reagents. These findings characterize the acceleration of oxidative addition of the starting organoiodide to the surface of zinc metal in DMSO relative to THF, but once formed, surface intermediates display similar persistence in either solvent. The current studies are the first demonstration of a highly sensitive, single-particle fluorescence microscopy technique to pinpoint otherwise elusive solvent effects in synthetic chemistry.

Solvent effects are powerful tools for enhancing chemical reaction rates and selectivities.[1–4] Yet, the mechanistic basis[5] of these effects can be elusive. For this reason, synthetic methods are often optimized through purely empirical solvent screening approaches. These approaches typically provide insufficient mechanistic understanding for underpinning future reaction design. Fundamentally, the lack of understanding in these cases arises from the inability of traditional ensemble analytical techniques to observe low quantities of intermediates due to insufficient sensitivity or dynamic range. Thus, the effect of solvent on the generation and persistence of these intermediates cannot be determined by direct observation (Scheme 1a). The formation of organozinc reagents from zinc metal and organohalides in different solvents is one of these cases. The reaction has been the focus of study for over 50 years, due to the synthetic importance of these compounds in Negishi cross-coupling and other C−C bond forming reactions.[6–11] Initially, polar aprotic solvents (e.g., mixtures with DMSO[12,13], or DMF[7,14]) were required. This requirement was circumvented later by Knochel, who showed that LiCl salt additive enabled direct insertion in THF.[15] Yet, the origin of these solvent effects remains poorly understood. Determination of the origin would provide guiding principles for expanding practical direct insertion chemistry to diverse metal powders, a desirable but currently limited area of synthetic chemistry.



Scheme 1. (a) Schematic of the broader mechanistic problem with traditional ensemble analytical techniques. (b) Two mechanistic hypotheses for solvent effects in organozinc synthesis.

Harnessing single-particle fluorescence microscopy with up to single-molecule sensitivity, we now combine bench-scale NMR spectroscopy kinetics and structural studies with imaging studies, enabling correlation of macroscale reaction solvent effects with microscale effects on intermediates. We previously detected organozinc surface intermediates from the combination of zinc metal with organoiodides. Those prior studies demonstrated a mechanism of reaction acceleration of the salt additive, LiCl, in THF as solubilization of intermediates from the surface of zinc *after oxidative addition*.[16–18] It remained unanswered, then, if the two known synthetic routes to organozinc reagents from zinc metal (e.g., LiCl in THF, or polar aprotic solvent) function by the same mechanism (i.e., increase solubility of the surface organozinc intermediate, Hypothesis 2, Scheme 1b), or if the two routes function by different mechanisms (e.g., LiCl in THF accelerates



Scheme 2. (a) Bench-scale chemical reaction monitored by NMR spectroscopy. (b) NMR spectroscopy yield relative to internal standard vs time, in DMSO-d_6 (red) and THF-d_8 (blue). (c) Chemical reaction for fluorescence microscopy experiments. (d) Representative zinc particle in DMSO after 30 min, fluorescence microscopy image. (e) Representative zinc particle in THF after 30 min, fluorescence microscopy image. Green "hot spots" of observable intermediate **4**, and the full chemical structure of imaging agent **3**. Images *d* and *e* are displayed at the same brightness/contrast settings for direct comparison.

solubilization of intermediates, but polar aprotic solvents accelerate oxidative addition, Hypothesis 1). Previous experimental data, obtained through indirect stereochemical and radical-clock experiments, strongly suggest that oxidative addition of alkyl iodides to zinc proceeds through single-electron transfer pathways.[19] The resulting transient charged intermediates would plausibly be stabilized by polar solvents, lending credence to a mechanistic possibility wherein polar solvents could act through acceleration of oxidative addition.[20]

Given the range of reported literature procedures in organozinc reagent synthesis, with variables including reaction stir rate, zinc particle size and supplier, and presence or absence of a zinc pretreatment step, a robust comparison of bench-scale synthetic reaction rates in DMSO and THF was not readily available in the existing literature. NMR spectroscopy kinetics comparing synthetic conditions were therefore performed in-house. Specifically, the kinetics of the reaction of 2-iodoethylbenzene (**1**, [100 mM]) and zinc powder in DMSO-d_6 and separately in THF-d_8, to generate organozinc **2** were examined (Scheme 2a). To simplify this direct comparison, we opted to avoid a pretreatment step with TMSCl or iodine[7], which partially removes the inactive surface layer but which generates additional variability during handling.[16–18] ^{1}H NMR spectroscopy kinetics were measured in triplicate in each solvent relative to an internal standard (Scheme 2b).

Consistent with the heterogeneous nature of the reaction, replicate runs showed some variation in numerical yields at each time point. Nevertheless, clear, reproducible trends were observed, which were significantly larger than the variation in the measurement: 1) Formation of **2**, identifiable by the substantial upfield shift of its α-zinc methylene protons, was significantly faster in DMSO-d_6 than in THF-d_8. After 30 min, the ^{1}H NMR spectra indicate nearly complete conversion in DMSO-d_6, but only 3% conversion in THF-d_8. The reaction in THF-d_8 reaches 96% yield only after 4 h (Scheme 2b). 2) Regardless of solvent, only starting material **1** and product **2** are observable by ^{1}H NMR spectroscopy. No reaction intermediates are observable. Thus, the solvent effect cannot be pinned to impact on a specific reaction step or intermediate by NMR spectroscopy alone. This unobservability of intermediates highlights the broader mechanistic challenge; and 3) An induction period is evident in THF-d_8 but not in DMSO-d_6.

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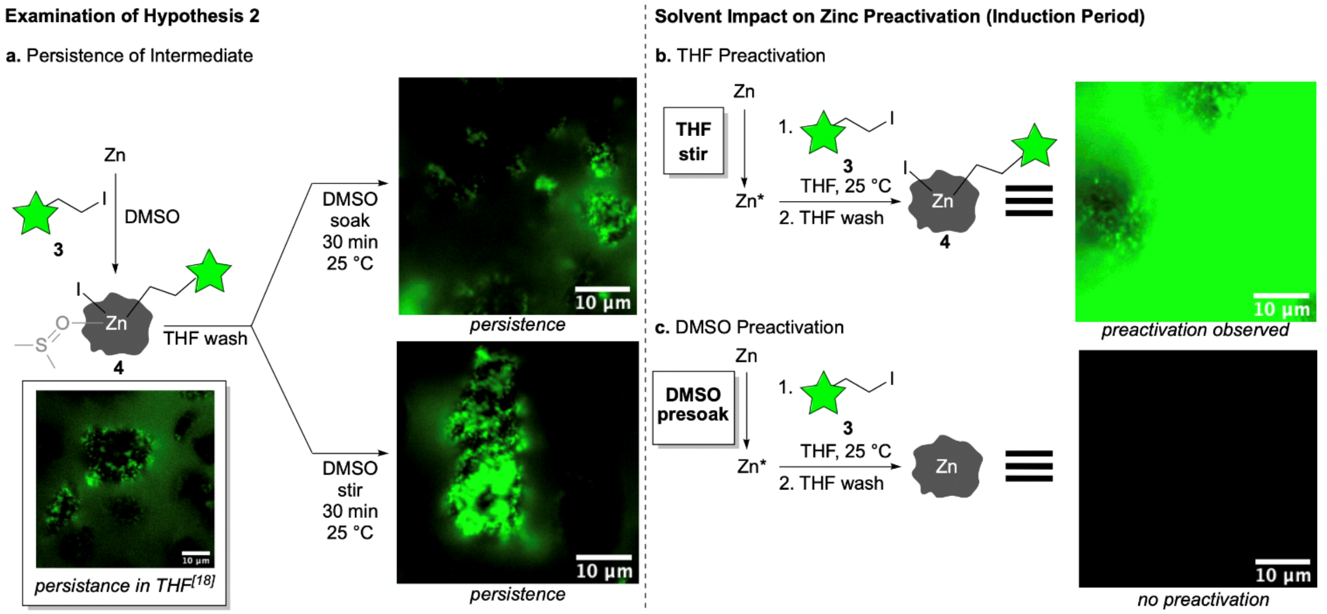


Scheme 3. Fluorescence microscopy: (a) Relative persistence of oxidative addition intermediate **4** in DMSO at ambient temperature. (b) Activation of Zn surface (shown as Zn*) by stirring in THF, consistent with removal of a surface oxide layer being the source of the induction period observed in THF in *Scheme 2b*. (c) No activation of Zn surface with DMSO upon presoaking.

With a robust understanding of the solvent effect on the reaction *overall*, we next investigated the impact of solvent on the build-up and persistence of organozinc surface intermediates by single-particle fluorescence microscopy. These experiments harnessed organohalide reagents with sensitive and chemoselective spectral handles to observe organozinc surface intermediates by fluorescence microscopy that were not observable by NMR spectroscopy. An alkyl iodide tagged with a green spectator boron dipyrromethene (BODIPY) fluorophore, **3** (2 mM), reacted with zinc metal to form observable surface oxidative addition intermediate **4** (Scheme 2c).[16–18] Intermediate **4** was characterized as bright green "hot spots" on the surface of otherwise dark zinc particles. In THF, these intermediates are persistent,[16–18] unless the sample is treated with lithium salts, heating, or strong stirring.[18] The brightness on a particle in these fluorescence microscopy images is a measure of the quantity of **4**. Thus, through this imaging technique, the impact solvents have on the build-up and persistence of intermediate **4** could now be characterized by direct observation of changes in quantity of **4**.

Examination of Hypothesis 1: DMSO accelerates oxidative addition. The rate of build-up of intermediate **4** in DMSO and in THF was examined by fluorescence microscopy. Two parallel samples of zinc powder were soaked in solutions of oxidative addition imaging agent **3** in DMSO or THF for 30 min (Scheme 2c). Both zinc samples were then rinsed and transferred into hexanes, an inert solvent, to prevent potential data convolution by differential solubilization of **4** during imaging. Reactions in DMSO and THF were each performed in triplicate to characterize the range of brightness inherent to the heterogeneous nature of the reaction system (see SI for triplicate data).

Single-particle imaging enabled direct comparison between the two samples. Outcomes for samples reacted in DMSO and THF starkly contrasted: DMSO produced substantially greater build-up of oxidative addition surface intermediate **4** than did THF, as observed by the significantly higher intensities and fuller spatial distributions of the bright green "hot spots" of fluorescence on zinc particles in DMSO. The images in Figure 2d,e show two representative zinc particles from these samples.

Together, these data are consistent with Hypothesis 1: DMSO leads to faster generation of oxidative addition surface intermediate **4** compared to THF, providing a step-specific mechanistic explanation for the higher efficiency of DMSO previously observed in macroscale synthesis.

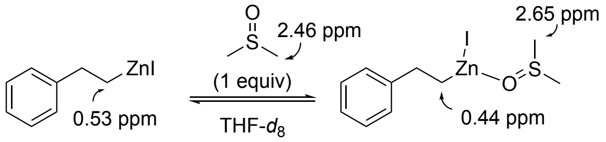
Control Experiments. In order to determine if the fluorescent spots on the DMSO-soaked particles in Scheme 2d were indeed oxidative addition intermediate **4**[16–18], control experiments were conducted with the same conditions but employing different fluorophores. These control fluorophores were identical except they had either no carbon−iodide bond, and therefore could not undergo oxidative addition, or a less reactive sp^2 carbon−iodide bond, which would undergo oxidative addition more slowly (see SI). All control samples showed little fluorescence compared to the samples treated with **3** (see SI).[17]

Examination of Hypothesis 2: DMSO accelerates solubilization of surface intermediate. The operation of the mechanism in Hypothesis 1 does not, on its own, exclude the concurrent operation of the mechanism in Hypothesis 2. To examine Hypothesis 2, the persistence of surface intermediate **4** in these two solvents was compared. In both DMSO and THF, intermediate **4** was largely persistent upon standing or stirring for 2 h at ambient temperature (Scheme 3a; THF established previously[18]). Thus, there is not a significant solvent effect on solubilization of the surface intermediate and the mechanism in Hypothesis 2 is not co-implicated.

These data therefore indicate two different and complimentary mechanisms for the reported rate accelerations of organozinc reagent generation in the two synthetic literature preparations: polar solvent accelerates oxidative addition whereas LiCl in THF accelerates solubilization.

Coordination environment of the organozinc reagent formed in DMSO. The coordination environment of the organozinc species in the two different solvents was next examined. The ligand coordination environment around organozinc reagents formed through these direct insertion reactions is of the utmost importance, as it dictates the downstream reactivity of the reagent (e.g., in metalation[21] and Negishi cross-coupling reactions[6,10]). DMSO, for example, has been crystallographically characterized in *O*-bound Zn(II) complexes.[22]

To explore the coordination environment in DMSO, a stoichiometric amount of DMSO was added into a THF-d_8 solution of **2** (eq 1). Monoorganozinc iodides like **2** have been previously characterized as monomeric in THF.[18,23] New compound **5** is structurally similar and therefore also likely to be monomeric. The resulting NMR spectrum showed an upfield shift in the product peaks of the organozinc[3] (from 0.53 to 0.44 ppm) and a downfield shift in the product DMSO peak (from 2.46 to 2.65 ppm), consistent with DMSO complexation to form **5**. Mass spectrometry data from this sample showed evidence for ions derived from both **2** and **5** (eq 1).



(1)

2 [PhCH$_2$CH$_2$ZnI$_2$]$^-$ *m/z* = 422.8

5 [PhCH$_2$CH$_2$Zn(DMSO)]$^+$ *m/z* = 247.0

A continued shift of these resonances upon titration with a second equivalent of DMSO was consistent with an equilibrium between complexes **2** and **5** (product organozinc to 0.39 ppm, and product DMSO to 2.60 ppm). This complexation suggests solvent-coordinated structures similar to **5** as the major coordination environment in neat and mixtures of DMSO relevant to applications in organic synthesis.[12,13] These data establish that the coordination environment of **5**, and plausibly also of the surface intermediate **4** by extension (potential coordination shown in grey in Scheme 3a), are different in DMSO than in THF.

The possibility that the alkyl iodide substrate is first activated in solution by nucleophilic displacement of iodide by DMSO, creating a potentially faster reacting oxidative addition partner, was considered. Such intermediates are proposed at elevated temperatures (150 °C) in Kornblum oxidations of primary alkyl iodides to aldehydes by DMSO solvent.[24] As the potential solution intermediate was not observable at ambient temperature in THF or DMSO by ^{1}H NMR spectroscopy, however, this possibility could not currently be examined further.

The mechanistic origin of the solvent-dependent induction period in Scheme 2b was next identified. For these studies, “preactivation” of the zinc was examined by both mechanical and chemical methods. In the first experiment, zinc powder was stirred vigorously in THF in the absence of other reagents, and then treated with a solution of imaging agent **3**. The resulting mechanically “preactivated” particles of zinc displayed significantly enhanced build-up of intermediate **4** (compare images in Scheme 2e with Scheme 3b). These data are consistent with the induction period in THF arising from the time needed for mechanical etching of the inactive surface layer[25] during vigorous stirring to expose the reactive zinc surface toward oxidative addition. These results provide a clearer mechanistic basis for the high efficiency of ultrasonic treatment of zinc towards oxidative addition substrates,[26,27] and as such, are potentially important for additional heterogeneous reactions with metals that may be activated towards reaction intermediate generation by vigorous mechanical processes.

Second, preactivation by dissolution of the inactive surface layer in DMSO was examined (Scheme 3c). Presoaking the zinc in DMSO without stirring (which avoided a convoluting vigorous mechanical processes) followed by reaction in THF did not lead to enhanced intermediate formation, which ruled out fast chemical or solubilization removal of the inactive surface layer by DMSO. This observation is consistent instead with the idea that, in DMSO, the more rapid chemical process of oxidative addition causes etching that is sufficiently rapid itself to expose additional reactive zinc surface, leading to the absence of an observable induction period in DMSO.

In conclusion, single-particle fluorescence data combined with NMR spectroscopy data characterized solvent effects on overall reaction rates and induction periods, pinpointed the mechanistic origin of rate acceleration in DMSO to oxidative addition (Hypothesis 1) and not to solubilization (Hypothesis 2), and identified solvent-dependent differences in coordination environment of the generated organozinc reagents. These data indicate two different and complimentary mechanisms for the rate accelerations of organozinc reagent generation in the two reported synthetic literature preparations: polar solvent accelerates oxidative addition whereas adding LiCl in THF[15] accelerates solubilization[16]. Such mechanistic information aids in the design and optimization of desirable direct insertion chemistry to metal powders. This advance in sensitive imaging technology opens avenues for obtaining further elusive mechanistic solvent effect information, enabling predictive reaction design.

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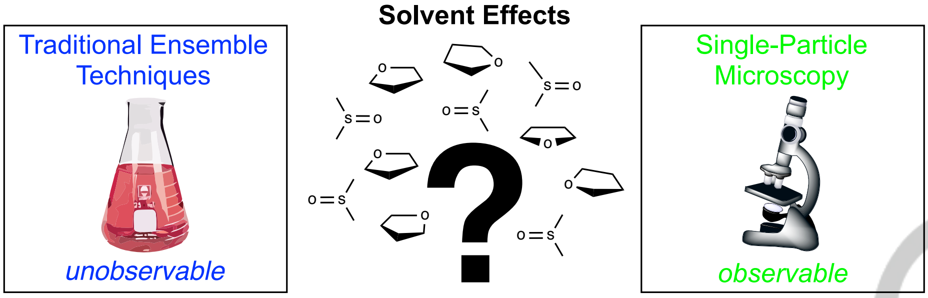

Sensitive single-particle fluorescence microscopy experiments enable understanding solvent effects by direct observation of previously “unobservable” organometallic surface intermediates. Combination of this microscopy technology with ^{1}H NMR spectroscopy characterizes the solvent effect on the synthesis of widely used organozinc reagents.