Negishi Reaction Mechanism

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On The Remarkably Different Role of Salt in the Cross-Coupling of Arylzincs From That Seen With Alkylzincs**

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Abstract: *The role of halide salt additives has been investigated in the Negishi reaction involving aryl zinc reagents. Diarylzincs readily transmetallate to Pd in relatively non-polar media (e.g., THF) with zero salt present and coupling proceeds. Arylzinc halides (ArZnX) fail to couple in THF without salt, but do couple with it. However, unlike alkylzincs that form higher-order zincates in order to facilitate transmetallation, all that is required with arylzincs in an increase in solvent dielectric as even* ZnX_2 *works as an additive, which completely terminates alkylzinc coupling.*

The cross-coupling of organozinc compounds with organohalides (i.e., the Negishi reaction)[1] is a useful reaction in the class of cross-coupling transformations.[2] While organozincs are not as air and moisture stable as their organoboron counterparts (i.e., the Suzuki–Miyaura reaction),[3] organozinc reagents nonetheless exhibit very high functional-group tolerance.[4] In light of this reaction's importance, the mechanism and identification of key additives that are essential for efficient coupling has been the subject of extensive investigation. The necessity for salt (e.g. LiCl/Br) for the Negishi reaction has been investigated by a number of groups. Knochel and co-workers found that LiCl accelerated the formation of organozinc reagents that were prepared by using a Br/Mg exchange method.[5] Studies by Oshima and co-workers suggested that LiCl enhanced the reactivity of organozinc halides toward transmetallation.[6] The existence of zincates in Negishi reaction mixtures has been investigated by Koszinowski using mass spectrometry and his group has demonstrated the existence of $RZnX_2^-$ where R is alkyl.[7] In related studies, our group has shown not only the presence of $RZnX_2^-$, but also the existance of higher-order zincates ($RZnX_3^{-2}$) by mass spectrometry, NMR spectroscopy, and by titration studies using LiBr.[8] This led us to propose that it is not $RZnX_2^-$ that transmetallates with alkylzinc reagents, as has been believed for many years,[6] but rather that the formation of $RZnX_3^{-2}$ is necessary to promote transmetallation.[9] The interrelationship between the Schlenk equilibrium and the cross-coupling catalytic cycle is depicted in Figure 1. Energetically, the lower-order zincate would be expected to form fully before the dianionic, higher-order species will begin to form. In the absence of one full equivalent of MX, the equilibrium populates with the lower-order zincate, but none of $RZnX_3^{-2}$ forms and no coupling is observed.[9] This is consistent with the fact that a highly polar co-solvent (e.g., *N,N'*-dimethyl-2-imidazolidinone; DMI) is necessary with THF (tetrahydrofuran) in order for coupling to occur, even with several equivalents of the MX salt present.[8,9] It was not until Clyburne developed a method for the independent preparation of $RZnX_3^{-2}$,[10] which in essence short-circuits the Schlenk equilibrium, that cross-couplings could take place without the need for additional MX and, more impressively, without the need for the polar co-solvent (i.e., THF only).[9b]

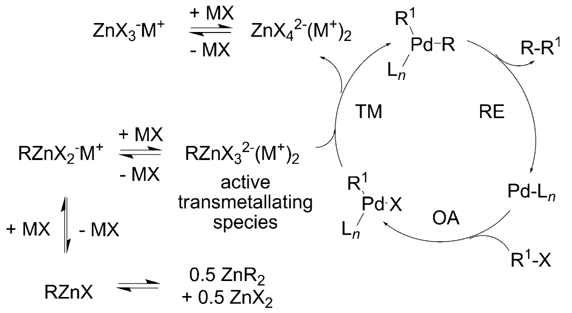

Figure 1. Proposed catalytic cycle for the alkyl–alkyl Negishi reaction.[9b] R = alkyl, M = Mg, Li, Bu_4N, X = Cl, Br. OA = oxidative addition, TM = transmetallation, RE = reductive elimination.

The coupling of sp^2-hybridized zincs is viewed as an easier transmetallation (TM) than their sp^3 counterparts.[2] However, the detailed study of organozincs is confounded by the fact that they are invariably obtained by the transmetallation of the corresponding organolithium or Grignard compound.[11] Unlike the alkyl variants that can be obtained by direct Zn insertion (e.g., the Hou protocol),[12] thus eliminating salt byproducts, this cannot be done with vinyl- and arylzinc halides directly. Here we detail the preparation of salt-free arylzinc reagents and the systematic evaluation of the necessity and role of salts in the coupling of sp^2 organozincs. These efforts have led to some striking observations regarding the transmetallation of these organometallics.

When PhMgBr (**1**) was treated with $ZnCl_2$, one full equivalent (presumably) of MgX_2 (X = Cl and/or Br) was seen to come out of solution following TM resulting in a slurry of PhZnBr (**2**, Scheme 1a). Upon addition of Pd-PEPPSI-IPent precatalyst and 2-bromoanisole (**3**) the suspension dissipates and **4** was produced quantitatively. In a separate operation, a transmetallated solution of **2** was cooled to −78 °C to ensure the complete precipitation of all MgX_2. After centrifugation,[13] the now clear solution of cold **2** was

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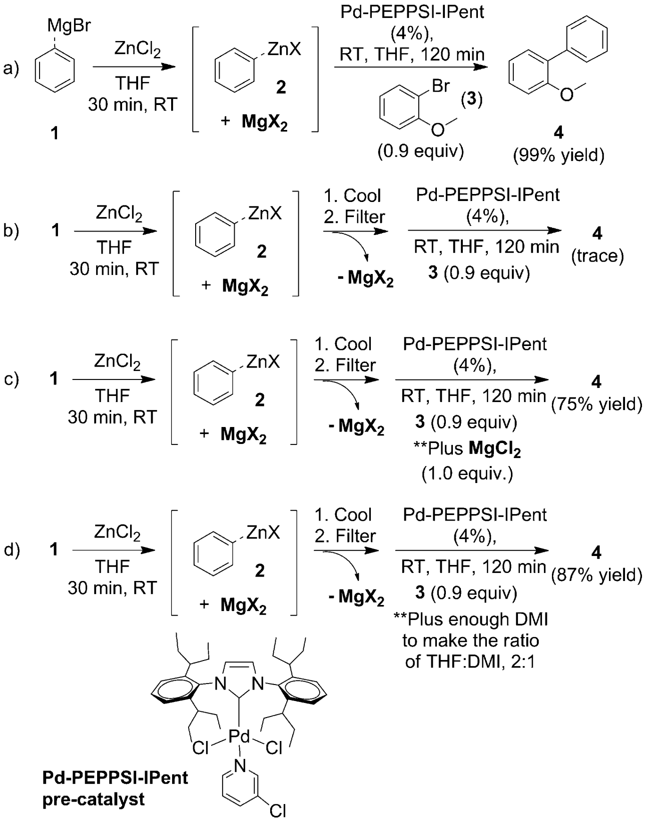
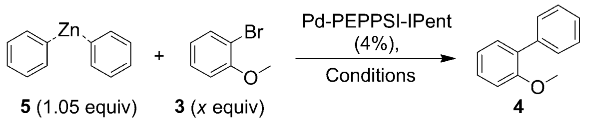


Scheme 1. Effect of magnesium halide salts on the cross-coupling of phenyl zinc bromide with arylhalides using Pd-PEPPSI-IPent catalyst.

carefully cannulated, so as not to disturb the salt pellet, into another flask containing the precatalyst and **3** and the cross-coupling failed (Scheme 1b). Next, a MgX_2-free solution of **2** was added to a flask containing $MgCl_2$, in addition to **3** and the IPent precatalyst, and cross-coupling activity was fully restored (Scheme 1c). These experiments confirm the necessity of the halide salt. In this respect, the requirement of additonal halide ions for the alkylzinc system,[6,8,9] on the surface, appears to mirror the situation with arylzinc substrates.

Despite the seemingly similar mechanism in the alkyl and aryl systems, we were forced to revisit the role of ZnX_2 as zinc salts are the natural byproduct of all Negishi couplings (Figure 1). In the case of alkyl couplings, we have shown a direct correlation between the amount of ZnX_2 present in a coupling mixture and the success of that coupling.[9] Specifically, ZnX_2, which is much more electrophilic than RZnX, shuts down the coupling, presumably by sequestering all halide ions out of solution and forming ZnX_3^- and ZnX_4^{2-}. This prevents the necessary organic zincates from forming (see above), which suppresses TM, and no coupling can occur. In stark contrast to this, we discovered previously that unless an excess of $ZnCl_2$ (at least an additional 40 mol%) was present following transmetallation of aryl Grignard reagents in THF, the ensuing coupling result was poor.[11] When this much additional $ZnCl_2$ was added to a similar alkyl coupling, the typically quantitative yield dropped to 50%, and an additional 35 mol% (75 mol% of total $ZnCl_2$) terminated coupling all together.[9b] Conversely, the addition of the same amount of $ZnCl_2$ to aryl coupling mixtures leads to essentially quantitative couplings.[11] Clearly the role of the salts in the alkyl and aryl systems cannot be the same.

Table 1: Cross-coupling of diphenylzinc under different conditions.[a]



Entry	**3** (equiv)	Solvent	Time	Additives	Yield[d]
1	1.0	THF	8 h	–	98%
2	2.0	THF	8 h	–	47%
3	2.0	THF	8 h	LiBr (1.0)[b]	87%
4	2.0	THF	8 h	$ZnBr_2$ (1.0)[b]	90%
5	2.0	THF/DMI, 2:1	8 h	–	80%
6[c]	2.0	1. THF, then 2. add DMI	2 h 6 h	–	81%

[a] Aryl bromide **3**, diphenylzinc (**5**, sublimed), Pd-PEPPSI-IPent precatalyst, and solvent were mixed and stirred for the indicated period of time at RT. [b] The salt was added at the same time as **3**. [c] The protocol was set up with THF as solvent and the reaction stirred for 2 h after which DMI was added and stirring continued for 6 h. [d] Percent yield was determined by flash-column of purified material.

To examine this, we decided to bring the organozinc into the Schlenk equilibrium at a different entry point than via transmetallation of the Grignard. We chose diphenylzinc for the next series of experiments, which we sublimed to ensure that it was salt-free (see Supporting Information). When we performed the coupling in THF we saw full conversion to **4** based on **3** as the limiting reagent (Table 1, entry 1, also see Supporting Information for additional examples). In this case, there are two equivalents of phenyl present in the reaction mixture that could be capable of being transferred to Pd. So, it was not yet clear whether all of the transmetallated phenyl came from PhZnPh, or whether any came from the byproduct of the first TM, that is, PhZnBr. At no point in this reaction should there ever be $ZnBr_2$ present, especially at the beginning, thus there is no chance of converting the PhZnPh to PhZnBr via some Schlenk-type transfer process, which would then be the actual transmetallating agent. So, even if only at the beginning of the transformation, all TM should be coming from PhZnPh. To address this point we tried the reaction with two equivalents of **3** (entry 2) and approximately half of it (47%) was coupled, which strongly suggests that under these salt-free conditions in THF, PhZnPh can transmetallate, but PhZnBr cannot. When we added LiBr to the same reaction conditions used in entry 2, near full consumption of all phenyl groups present was observed (entry 3). This would support the growing notion that the PhZnPh can transfer the first phenyl group under salt-free conditions, but that the second one (now as PhZnBr) requires LiBr.

On the surface of it, the coupling of arylzincs was beginning to look very much like the situation with alkylzinc halides that require enough halide ion to form the requisite higher order zincate to transmetallate.[9] However, the next experiment (entry 4) cast doubt on this as the same excellent result was attained with one equivalent of $ZnBr_2$ present, something that completely suppresses alkyl coupling, even when two equivalents of LiBr are also added to the same coupling mixture.[9] This led us to postulate that the formation of a halide-derived zincate is not necessary with PhZnBr, but rather the salt is responsible for increasing the solvent dielectic and that triggers TM with sp^2 organozincs. This was supported by experiments in polar solvent without additives. A THF/DMI mixture (entry 5) led to high conversion and when we added the solvent in stages (entry 6), the results were instructive. The experiment in entry 2 was essentially repeated and monitored for 2 h and coupling proceeded approximately half way. Upon addition of enough DMI to bring the solvent ratio to 2:1 THF:DMI, again high conversion was observed at the end of the reaction. In the analogous alkyl couplings the identical co-solvent system in the absence of LiBr failed to intiate any coupling.[9] In the final polar solvent effect experiment, de-salted PhZnBr (**2**) was added to the catalyst in a solution containing enough DMI to bring the final ratio of THF:DMI to 2:1 and very high conversion was attained (Scheme 1 d).

That the TM of alkyl- and arylzinc reagents appears so different is unanticipated and striking. Based on our extensive studies with the alkyl system, both in carfeully titrated control reactions[9] and organozinc structural analysis,[8,9] we anticipated that similar zincates were forming when the necessity for LiX or MgX_2 surfaced. Similar to what we observed in the alkylzinc case, when increasing amounts of LiBr were added to a solution of salt-free PhZnBr we observed significiant and progressive shifts in the ^1H NMR spectra of the aryl protons (see Supporting Information for ^1H NMR titration spectra). In the alkyl case, there was overwhelming evidence that these shifts were the result of zincate formation. In the aryl case, we do not believe that this is the case as simply adding increasing amounts of DMI caused identical changes to the ^1H NMR spectra (see SI). Further, the positive cross-coupling result (Table 1, entry 4) with $ZnBr_2$, which breaks down organic zincates,[9b] also casts doubt on this necessity of arylzincate formation. So, we propose that the changes in structure detected by NMR spectroscopy are in fact primarily the result of the breakdown of aggregates.

Adding to the complexity is why Ph_2Zn transmetallates and couples in low dielectric solvent without salt, while PhZnBr does not. Considering first diarylzincs, they are less likely to form strong aggregates owing to the less polarized C−Zn bond relative to the Zn−Br case where aggregation minimizes dipoles and imparts necessary stabilization. Thus, any Ar_2Zn aggregates that form would be more readily broken down to facilitate TM in a non-polar solvent such as THF (dielectricity constant ε THF = 7.5). Second, as the zinc partner is the nucleophile in TM, the presence of two carbon-based ligands on Zn, rather than the electronegative halide of ArZnX, should make it more likely to undergo smooth ligand transfer with the electrophilic Pd^{II} center in the catalytic cycle (Figure 2). Consequently, ArZnX species require a high dielectric, which can be by the nature of the solvent itself (e.g., ε DMI = 37.6)[14] or by dissolving salt in a less polar solvent, as is seen when $ZnBr_2$, $MgBr_2$, or LiBr are present in THF.

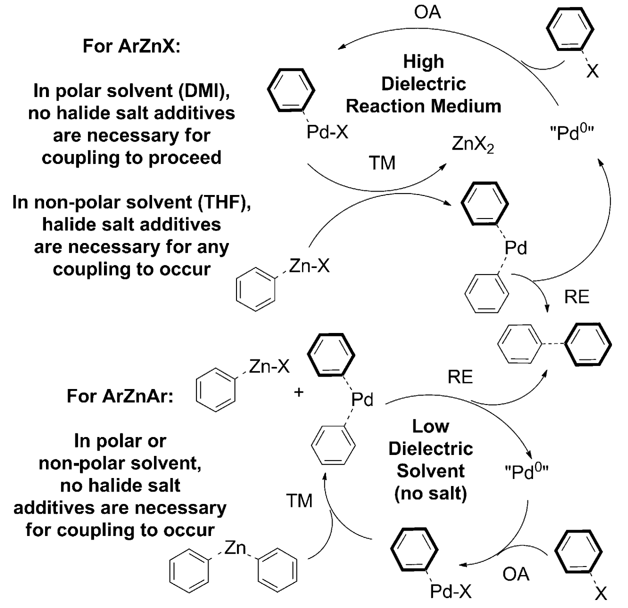


Figure 2. Proposed catalytic cycle(s) for the Negishi coupling of aryl zinc reagents including the role of salt additives and solvent dielectric.

In summary, a significant difference in the nature of TM of arylzinc compounds relative to alkylzincs has been uncovered. Diarylzinc compounds are capable of transmetallating in low dielectric solvent without the aid of salt, whereas ArZnX compounds require either a high dielectric solvent or a lower polarity solvent loaded with enough salt to increase the medium's ion-solubilizing ability to break down residual ArZnX aggregates. These results are in stark contrast to alkylzinc species that require both salt and a high dielectric solvent and dialkylzincs (R_2Zn) are not capable of transmetallating at all, despite literature claims to the contrary.[9] While higher-order zincates have been shown to form and are the postulated transmetallating species in alkylzinc couplings, there is no evidence to support their requirement in the coupling of aryl zinc reagents.

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