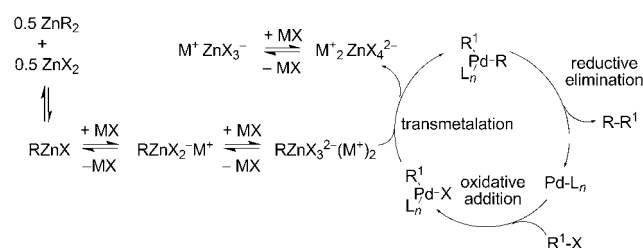


Higher-Order Zincates as Transmetalators in Alkyl–Alkyl Negishi Cross-Coupling**

Lucas C. McCann, Howard N. Hunter, Jason A. C. Clyburne, and Michael G. Organ*

Cross-coupling has been established as one of the preferred methods for generating carbon–carbon bonds in synthetic chemistry.^[1] Within this broad family of transformations, the Negishi reaction, where the organometallic partner is zinc-based, is perhaps the most facile owing to the ease of transmetalation of the organic fragment from aryl- or alkylzinc species to the catalyst metal.^[2] It has been proposed that additives, such as halide ions, can assist in transmetalation by forming “ate” complexes with the organometallic metal.^[3] This complexation likely weakens the metal–carbon bond of the organometallic partner and keeps it monomeric, thus lowering the barrier to transferring the carbon ligand. Until recently, it was taken for granted that the active transmetalator was a mono-anion (e.g., RZnX_2^- , Scheme 1).



Scheme 1. Proposed catalytic cycle for the alkyl–alkyl Negishi reaction.

Through titration studies we have demonstrated that until at least one full equivalent of MX_n (e.g., $\text{M} = \text{Li}$ or Mg , $\text{X} = \text{Cl}$ or Br) has been added to a salt-free alkylzinc reagent, there is no coupling observed.^[4] This led us to propose that the active transmetalating agent is actually a higher-order zincate (i.e., RZnX_3^{2-}) as the reaction appears to become catalytic in halide ion after 1.0 equivalent of MX_n (relative to the RZnX) has been added. This analysis is complicated by the activity of ZnX_2 , a reaction byproduct, which sequesters halide ion from solution.^[5] Indeed, if additional ZnX_2 is added to the Negishi

reaction mixture, the Schlenk equilibrium shifts away from the formation of alkyl zincate(s) and coupling terminates.^[4] So, when greater than one equivalent of LiX is used, the first full equivalent goes to form RZnX_2^- , which we believe is not an active transmetalator, and the additional LiX then produces catalytic amounts of RZnX_3^{2-} that go on to transmetalate. Once the catalytic cycle begins, when greater than one equivalent of halide has been added, each cycle liberates a halide ion from the oxidative addition partner thereby fulfilling the electrophilic needs of the inorganic zinc byproduct and allowing transmetalation to continue.

Very recently we provided the first evidence for the existence of these proposed higher-order zincates (e.g., BuZnBr_3^{2-}) in solution under alkyl Negishi cross-coupling conditions.^[6] Their formation, by the titration of salt-free BuZnBr with LiBr , was followed by both NMR spectroscopy and mass spectrometry. Further, the critical role of the solvent was explored. Not only are halide salts necessary to promote Negishi coupling, so too is a solvent of sufficient polarity to support the formation of such highly charged zincates; to our knowledge, alkyl coupling does not work without NMP (*N*-methylpyrrolidone) or DMI (*N,N*-dimethyl-2-imidazolidinone).

To this point, the existence of alkyl zincates in the Negishi reaction is speculative as they have only been formed *in situ* from the alkylzinc halide. However, the recent preparation, isolation, and characterization of ethylzinc tribromide^[7] has provided the first opportunity to study the role of zincates in the Negishi coupling through their direct synthesis and use under controlled reaction conditions. The introduction of this unique complex into the Negishi coupling cycle strongly corroborates our previous findings.

Formation of EtZnBr_3^{2-} as the tetraphenylphosphonium salt was carried out in methylene chloride following the Clyburne protocol.^[7] ^1H NMR spectra (Figure 1) show the characteristic upfield shift for the methylene group that would

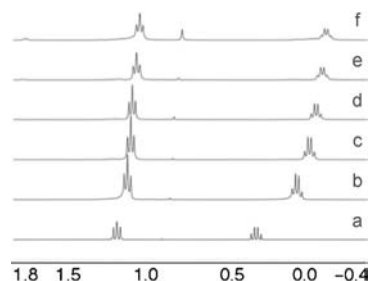


Figure 1. ^1H NMR spectra of the titration of Et_2Zn (spectrum a) with increasing equivalents of tetraphenylphosphonium bromide in CD_2Cl_2 : b) 0.5, c) 0.75, d) 1.0, e) 1.5, f) 2.5.

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be expected as the zinc center becomes increasingly electron-rich as one, and then two more halide ions coordinate to it. For example, in Figure 1 the resonance at 0.3 ppm in spectrum (a) moves progressively to −0.2 ppm in spectrum (f). The evolution of ethane (0.8 ppm),^[8] as increasing amounts of the bromide salt are added, gives mechanistic clues to this interesting transformation. One ethyl moiety is lost from Et₂Zn while three bromides are added to give a product with two singly charged counter ions. The same titration was also conducted for the tetrabutylammonium salt in methylene chloride (Figure 2A) and in THF (Figure 2B) where the identical trend in shifts was observed.

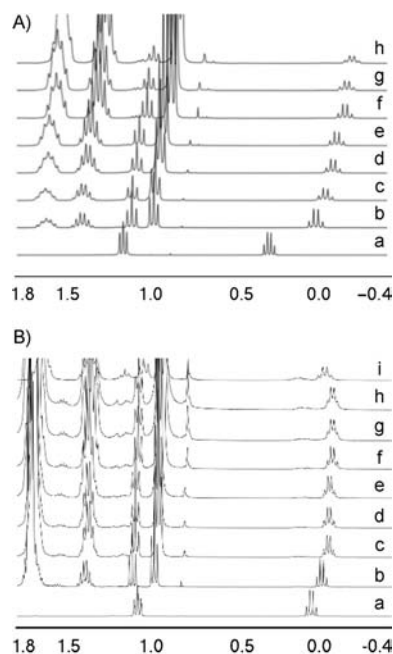


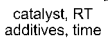
Figure 2. ¹H NMR spectra of the titration of Et₂Zn (spectrum a) in A) CD₂Cl₂ and B) [D₈]THF (spectrum a) with increasing equivalents of tetrabutylammonium bromide in CD₂Cl₂: b) 0.5, c) 0.75, d) 1.0, e) 1.5, f) 2.0, g) 2.5, h) 3.0. To the mixture in panel (B), spectrum (h), was added 1.0 equiv of dry ZnBr₂, which gave rise to spectrum (i).

With the higher-order zincates in hand, we embarked on a cross-coupling study to evaluate their reactivity, in order to provide support for their involvement in the alkyl–alkyl Negishi coupling.^[9] The first two entries in Table 1 illustrate that EtZnBr will not couple in the absence of the halide activator, which we attribute to its inability to form the higher-order zincate in situ. When the zincate **1** was subjected to the reaction, no coupling took place, either with (entry 4) or without (entry 3) LiBr. In an attempt to see whether the counter ion was playing a role in this result, the reaction was repeated with EtZnBr both with (entry 6) and without (entry 5) LiBr and no coupling was observed; the Ph₄P⁺ cation is poisoning the catalyst. When the corresponding ammonium salt was used (entry 7), while not all of **3** was consumed, cross-coupling was observed. Incomplete reaction and competing elimination and reduction of **3** encouraged us to use Pd-PEPPSI-IPent (**9**), which is less susceptible to reduction.^[10] While we have tracked the formation of **2** prior

Table 1: Negishi coupling of **3** with various ethylzinc derivatives.

$\text{Et}_2\text{Zn} + \text{PPh}_4\text{Br}$ or Bu_4NBr
 $\xrightarrow{\text{solvent}}$
 $\text{EtZnBr}_3^{2-} (\text{PPh}_4^+)_2$ **1**
or $\text{EtZnBr}_3^{2-} (\text{Bu}_4\text{N}^+)_2$ **2**

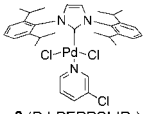
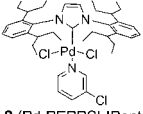
(or other organozinc, see Table 1)

add:  **3**

catalyst, RT, additives, time

 **4**
+
  **5**

 **6**
+
  **7**

 **8** (Pd-PEPPSI-IPr)
  **9** (Pd-PEPPSI-IPent)

	Zincate	Solvent	Cat. (%)	t [h]	Additive (equiv)	Ratio 3:4:5:6:7 ^[a]
1	EtZnBr	THF/DMI (2:1)	8 (4)	0.5	–	no reaction
2	EtZnBr	THF/DMI (2:1)	8 (4)	0.5	LiBr (2)	0:1:0:0:0
3	1	THF/DMI (2:1)	8 (4)	0.5	–	no reaction
4	1	THF/DMI (2:1)	8 (4)	0.5	LiBr (2)	no reaction
5	EtZnBr	THF/DMI (2:1)	8 (4)	24	PPh ₄ Br (2)	no reaction
6	EtZnBr	THF/DMI (2:1)	8 (4)	0.5	PPh ₄ Br (2) LiBr (2)	no reaction
7	2	THF/DMI (2:1)	8 (4)	0.5	–	1:3:3:3:0
8	2	THF/DMI (2:1)	9 (4)	0.5	–	0:1:0:0:0
9	2	THF/DMI (2:1)	9 (0.9)	12	–	0:1:0:0:0.04
10	Et ₂ Zn	THF/DMI (2:1)	9 (4)	12	–	1:0.2:0:0:0
11	Et ₂ Zn	THF/DMI (2:1)	9 (4)	12	LiBr (2)	1: < 0.2:0:0:0
12	2	THF only	9 (4)	2	–	< 0.1:1:0:0:0
13	EtZnBr	THF only	8 (4)	0.5	LiBr (2)	no reaction

[a] The ratio of **3** and the various products was determined by GCMS using a calibrated standard curve with undecane as an internal standard. Reactions and analyses were conducted in duplicate.

to adding **3** and **9**,^[9] we nonetheless repeated the reaction without the addition of Bu₄NBr as dialkylzincs are reported to couple on their own.^[11] Trace amounts of cross-coupled products were observed either with (entry 11) or without (entry 10) LiBr. These results confirm the unique role of Bu₄NBr in the Negishi coupling. It is not merely a source of halide ion, rather Bu₄NBr converts the dialkylzinc to the corresponding higher-order zincate, and it is this species that transmetalates and completes the catalytic cycle.

The most important control experiment carried out was the coupling of zincate **2** in straight THF (Table 1, entry 12). We have tried repeatedly to get alkyl–alkyl Negishi coupling to proceed without the necessity of polar co-solvents, such as NMP or DMI. We have never observed any coupling at all in their absence, nor have we seen reports in the literature that suggest otherwise.^[12] From our diffusion NMR studies^[6] it is clear that the role of the polar solvent changes as a steadily increasing amount of LiBr is added to the salt-free, alkylzinc halide. Initially, there is free movement of the polar solvent, but as LiBr is increased, mobility of the solvent decreases until it has a diffusion constant similar to that of the alkylzinc complex(es). This implies intimate complexation of DMI or NMP to the increasingly charged organozinc species in solution as additional Br[−] converts RZnBr through the mono-anionic zincate to the doubly charged, higher-order zincate (Scheme 1). In the current application, the formation of **2** is driven by the reaction conditions that push the equilibrium forward by the elimination of ethane, thus halting the reverse reaction. When the cross-coupling is conducted

with **2**, there is no ZnBr_2^- present to push the Schlenk equilibrium in the direction of Et_2Zn (Scheme 1). As the reaction proceeds, each catalyst turnover liberates one molecule of ZnBr_2 and one Br^- ion from **3**. This keeps the liberated electrophilic inorganic zinc saturated with Br^- ion, which can add yet another Br^- to form ZnBr_4^{2-} , thus holding the equilibrium of the alkyl component at **2** throughout the coupling until all of it has been consumed.

To prove that the Schlenk equilibrium cannot be established under the reaction conditions, i.e., pushing **2** toward Et_2Zn (see Scheme 1), we performed a back-titration of ZnBr_2 into the reaction with **2** in THF (Figure 3). The addition of ZnBr_2 , in increasing amounts, steadily shut down

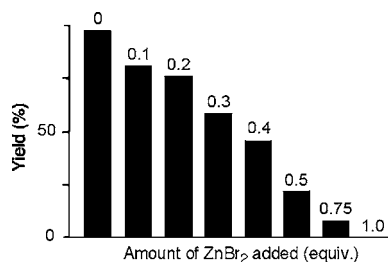


Figure 3. Back titration study of ZnBr_2 added into the cross-coupling reaction of **2** with **3** using **9** in THF at room temperature for 2 h. The reaction was performed eight times with more ZnBr_2 added each time. Yields of isolated product.

the reaction and at 1.0 equivalent cross-coupling terminated completely. So, if free ZnBr_2 was present in the reaction mixture in entry 12 (Table 1), the reaction could only proceed partially at best as the ZnBr_2 would tie up Br^- and halt coupling. However, coupling is not abated. Consistent with this observation, when 1.0 equivalent of ZnBr_2 was added at the end of the titration of Et_2Zn with Bu_4NBr in THF, the signal of the methylene protons was observed to shift back to the position of Et_2Zn itself before any Bu_4NBr was added (Figure 2B, spectrum i). This shows that the electrophilic ZnBr_2 can strip Br^- away from the more electron-rich organometallic(s), thus forming ZnBr_3^- and possibly ZnBr_4^{2-} , while the organometallic forms the less charged species EtZnBr_2^- , EtZnBr and Et_2Zn , none of which are capable of transmetalating.

In order to make sure that the results were not unique to this pairing of starting materials, a collection of products was created using diethyl- and dibutylzinc and other alkyl halides (Table 2).

The formation of simple “ate” complexes has been proposed as the role of basic additives in cross-coupling, which is thought to weaken the metal–carbon bond and aid transmetalation.^[3,4] In the case of alkyl Negishi couplings we have shown that transmetalation is rate limiting, at least with Pd–NHC (N-heterocyclic carbene) catalysts.^[13] So, we would concur that the formation of activated transmetalating species will no doubt enhance the overall observed rate of these couplings. We have shown by mass spectrometry that ample RZnBr_2^- is produced in alkyl–alkyl Negishi cross-coupling reaction mixtures containing NMP or DMI solvent when one or less equivalents of LiBr is added, yet no coupling occurs.^[6]

Table 2: Studies of the scope of alkyl–alkyl Negishi coupling using preformed tetrabutylammonium zincates in straight THF solvent.^[a]

$\text{RZnBr}_3^{2-} (\text{Bu}_4\text{N}^+)_2 + \text{R}^1\text{-Br} \xrightarrow[\text{THF, 2 h}]{\textbf{9 (4 mol \%)}} \text{R-R}^1$ (0.9 equiv)		
R = Et, 99% (92%)	R = Et, 99% (94%)	R = Et, 99% (98%)
R = Et, 99% (99%)	R = Bu, 74% (72%)	

[a] Percent conversion. Yields of isolated products are reported in brackets.

When greater than one equivalent of LiBr is added, we have demonstrated the existence of RZnBr_3^{2-} zincates by mass spectrometry under typical cross-coupling conditions (e.g., THF/DMI, 2:1) and shown by NMR spectroscopy how the role of the DMI changes as the concentration of LiBr increases. From this we attribute the ability to form higher-order zincates to strong coordination of the polar solvent, which stabilizes this highly charged species. Taken together, this suggests that the formation of higher zincates is necessary to facilitate transmetalation. Key to this theory is that “normal” alkylzinc cross-couplings with MX_n additives (e.g., LiCl, MgBr_2 , etc.) do not proceed without the polar co-solvent.

In the current study we have shown for the first time the direct involvement of higher-order zincates in the alkyl–alkyl Negishi reaction. The synthesis and isolation of pure, crystalline RZnBr_3^{2-} zincates, from non-coordinating solvents such as CH_2Cl_2 , has facilitated our study of their involvement in the Negishi reaction. It allows the strict exclusion of salts that are present in all commercially produced alkylzinc reagents. Indeed, the formation of alkylzinc halides using the Rieke protocol^[14] has previously aided in masking the role, and therefore the importance, of salt additives such as LiBr.^[4] The formation of Rieke zinc is accompanied by the production of two equivalents of LiX, a byproduct that is not a simple spectator but, in fact, is necessary to drive Negishi couplings without the need for additional additive(s). The most telling result is that the tetrabutylammonium zincate (e.g., **2**) in the absence of any salt additive, cross-couples to completion very quickly and cleanly in pure THF. Here zincate **2** can be formed in such solvents because the mechanism involved is vastly different from that seen in the Rieke^[14] or Huo^[15] protocols for alkyl zinc formation. The absence of salt, which would be required to promote equilibration to the simple zincate RZnBr_2^- , or even further to RZnBr or R_2Zn (see Scheme 1), strongly suggests that **2** is an active transmetalating species, and not RZnBr_2^- or other members of the Schlenk equilibrium.

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