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A Zinc Catalyzed C(sp³)-C(sp²) Suzuki-Miyaura Cross-Coupling Reaction Mediated by Aryl-Zincates

Richard J. Procter^[a], Jay J. Dunsford^[a], Philip J. Rushworth^[b], David G. Hulcoop^[b], Richard A. Layfield^[a] and Michael J. Ingleson^[a]*

Abstract: The Suzuki-Miyaura (SM) reaction is one of the most important methods for C-C bond formation in chemical synthesis. In this communication, we show for the first time that the low toxicity, inexpensive element zinc is able to catalyze SM reactions. The cross coupling of benzyl bromides with aryl-borates is catalyzed by ZnBr₂, in a process free from added ligand, and that is compatible with a range of functionalized benzyl bromides and aryl boronic acid pinacol esters. Initial mechanistic investigations indicate that the selective in-situ formation of triaryl zincates is crucial to promote selective cross-coupling reactivity, which is facilitated by employing an arylborate of optimal nucleophilicity.

The selective formation of carbon-carbon bonds is arguably the most important transformation in synthetic chemistry. Among the most widely used C-C bond forming reactions is the Suzuki-Miyaura (SM) cross coupling reaction,^[1,2] which is even utilized on large scale in industry.^[3] This powerful method couples a boron based organic nucleophile with an organic electrophile, typically catalyzed by Pd or Ni compounds.^[4] Recently, catalysts based on other metals, particularly less toxic metals (relative to Pd/Ni),^[5] e.g. copper^[6] and iron (which has the lowest toxicity rating),^[7] that offer alternative reactivity profiles, and/or reduced costs, have gained increasing attention. However, zinc catalyzed SM reactions are, to the best of our knowledge, unknown. This is despite the attractive features of zinc which include: (i) low toxicity (in contrast to Ni compounds, zinc has the same toxicity rating as iron),^[5] and (ii) relatively high abundance, thus zinc compounds are inexpensive and have low supply risk.^[8]

The use of *stoichiometric* organozinc reagents in coupling reactions is well established, particularly the Pd catalyzed Negishi reaction.^[9] More recently, stoichiometric organozinc reagents have been used in coupling reactions that do not require transition metal catalysts.^[10] Of specific relevance to this work is the coupling of arylboronic acids with benzylbromides in the presence of excess Et₂Zn (Scheme 1a). The proposed mechanism involves a zinc cation activating benzyl bromides for S_N2 substitution.^[11] Diaryl zinc species have also been reacted with alkyl halides (including benzylic) to form $C(sp^2)-C(sp^3)$ bonds in the abscence of a catalyst, provided the reaction was carried out in weakly-coordinating aromatic solvents (Scheme1b).^[12] These recent developments, while notable, all

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Scheme 1. Zinc compounds in "catalyst-free" coupling reactions.

use stoichiometric (or super-stoichiometric) quantities of zinc reagents. The use of sub-stoichiometric zinc compounds in C-C coupling is extremely rare, with the only example, to the best of our knowledge, being the coupling of alkyl Grignard reagents with α - hydroxy ester triflates catalyzed by ZnCl₂ (Scheme 1c).^[13] We sought to develop a catalytic in zinc cross coupling reaction that uses aryl boron nucleophiles. This requires an arylborate able to convert zinc halide by-products from cross coupling back to arylzinc species that are effective for cross coupling with organic electrophiles. Herein we realize this goal using readily accessible arylborate nucleophiles derived from aryl boronic acid pinacol esters, with ZnBr₂ proving an effective catalyst for coupling these arylborates with benzyl halides.

While neutral aryl-boranes exchange aryl for alkyl on reaction with dialkylzinc reagents, [14,15] in order to transmetallate to zinc halides more strongly nucleophilic aryl-boranes are required.^[16,17] Attempts using aryl boronic esters activated by alkoxides led to transfer of the alkoxide group to zinc in preference to the aryl group (see Figure S2). In contrast, the lithium borate, 1a (Scheme 2), selectively and rapidly (< 30 min for complete consumption of 1a) transfers an aryl group to zinc dihalides (halide = Br or Cl) in ether solvents, as indicated by the formation of *tert*-butylboronic acid pinacol ester (^tBuBPin) by NMR spectroscopy (no PhBPin is observed precluding Zn-^tBu formation). An alternative pathway, rapid alkyl transfer from 1a to form Zn-Bu species followed by rapid reaction of these with AryIBPin to form AryI-Zn species is precluded based on the slow reaction between ZnEt₂ and ArylBpin (< 5 % aryl transfer after 30 mins).

With an effective boron to ZnX_2 transmetallating agent in hand the transmetallation from boron to zinc in arene solvents was attempted, but it did not proceed significantly being hindered by the low solubility of the aryl borate reagent and zinc halides. Arene solvents were essential in previous work coupling COMMUNICATION

stoichiometric Ar₂Zn with alkyl halides, whereas in ether solvents coupling was effectively quenched.^[12] By performing the transmetallation in cyclopentyl methyl ether (CPME) and then replacing CPME with benzene, the arylzinc product reacted with 3-methoxybenzyl bromide (**2a**) to generate the desired product (**3a**) within 1 h at 20°C. Subsequently, we found that using 10 mol% of zinc dihalide both steps can be performed in CPME, with heating enabling the cross coupling step (Scheme 2), albeit with a lower hetero:homo coupling ratio. In contrast, using ArylBPin / ZnEt₂ mixtures with **2a** as the electrophile led to minimal C(sp²)-C(sp³) cross coupling after 18 h at 60°C.



Scheme 2. Transmetallation followed by cross-coupling

The transmetallation and cross-coupling steps in ether solvents was optimized using 4-fluorobenzyl bromide, 2b (enabling quantitative in-situ analysis by ¹⁹F NMR spectroscopy). This revealed that lower temperatures and other ether solvents resulted in high selectivity for heterocoupling (see Table 1). It is noteworthy that successful cross coupling was observed using dioxane as the solvent (entry 3), whereas ZnPh₂ effectively does not undergo cross coupling with benzylbromides in dioxane even at 60 °C over 18 h.[11] While highly selective cross coupling was observed in dioxane and 2-MeTHF, 2-MeTHF was utilized for this study due to its superior safety profile. Control reactions were performed next to examine the possibility of trace metal catalysis.^[18] ZnBr₂ obtained from multiple sources and of different purity (including 99.999% purity) produced similar coupling outcomes. When the reaction is performed without $ZnBr_2$ no **3b** is formed, with only minor homocoupling (4b) observed (entry 6). Catalysis by trace copper or nickel impurities is disfavored on the basis of lower hetero- : homo-coupling selectivity (entries 7 and 8). FeBr₂ was examined and significant heterocoupling was observed (entry 9). However, FeBr₂ is precluded as a "trace metal catalyst" in this chemistry due to significant reactivity differences compared to ZnBr₂ (e.g. FeBr₂ is an effective catalyst for heterocoupling using 1a and arylGrignard reagents, whereas ZnBr2 does not couple arylGrignard reagents with benzylbromides, see SI for further discussion). A Pd catalyst also gave high heterocoupling selectivity (entry 10). However, in the coupling of 4bromobenzylbromide (an electrophile containing both an aryl C-Br and benzylic C-Br bond) with 1a, ZnBr2 selectively couples through the benzylic carbon. In contrast, under identical conditions Pd(PPh₃)₄ cross-couples through both the C(sp²)-Br and the C(sp³)-Br, thus precluding Pd impurities as the catalyst in this protocol (see SI). Finally, under these conditions MgBr₂ led to no heterocoupling (entry 11). These results strongly support a zinc catalyzed cross coupling between 1a and 2b.

Table 1. Optimization and impurity catalysis controls



Entry	Solvent	T / ℃	catalyst (x mol%)	3b ∕%ª	4b ∕%ª
1	THF	60	ZnBr ₂ (10)	47	3
2	Benzene : THF 10:1	75	ZnBr ₂ (10)	70	3
3	Dioxane	60	ZnBr ₂ (10)	86	1
4	2-MeTHF	60	ZnBr ₂ (10)	90	1
5	2-MeTHF	80	ZnBr ₂ (10)	87	3
6	2-MeTHF	60	No catalyst	0	16
7	2-MeTHF	60	CuBr (13)	45	26
8	2-MeTHF	60	$NiBr_2(PPh_3)_2(3)$	26	27
9	2-MeTHF	60	FeBr ₂ (11)	84	8
10	2-MeTHF	60	Pd(PPh ₃) ₄ (3)	93	2
11	2-MeTHF	60	MgBr ₂ (10)	<1	12
12 ^b	2-MeTHF	60	ZnBr ₂ (10)	47	<1

^aBy ¹⁹F NMR spectroscopy and GCMS. ^busing Li[ⁿBuB(Pin)Ph], **5**, instead of **1a**.

Optimization of the boron nucleophile also was explored and while the "butyl congener of 'butyl borate **1a**, i.e. Li["BuB(Pin)Ph], **5**, cleanly formed **3b** the reaction was slower than that using **1a** (entry 12). In contrast, using the alternative phenyl source Na[BPh₄] led to minimal conversion to **3b** after 18 h (< 15 % **3b**, see SI). Finally, 1.5 eq. of **1a** was found to be optimal (lower equivalents of **1a** did not lead to full consumption of the electrophile).

This zinc catalyzed cross-coupling was compatible with electron withdrawing and electron donating groups (Table 2). It was also tolerant of halide, CF₃, OCF₃, alkyl, ether, thioether and heteroaryl groups with excellent heterocoupling selectivity throughout. Electron withdrawing groups on the arylborate, e.g. p-(OCF₃), are compatible but result in a slower reaction (only 30 % heterocoupling after 24 h), so need longer reaction times. While ketone and aldehyde functional groups proved to be incompatible, esters and acetals were both amenable. Benzyl chlorides reacted slower than the analogous bromides, as did 2° benzyl electrophiles, however, both are also viable substrates if longer reaction times are used. Bromodiphenylmethane and methylallyl bromide were also effectively cross-coupled, however, octylbromide and cycloheptylbromide were not amenable. The formation of 30 was highly selective (> 95 %) with minimal products from *cine* or *tele* substitution observed. indicating an organometallic ipso couplina process dominates.^[10g] The observed scope is consistent with an $S_N 2$ mechanism and the minor amounts of homocoupling observed (< 5 %) is attributed to a zinc free reaction based on Table 1 entry 6. Radical scavengers such as 9,10-dihydroanthracene

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(used in zinc mediated radical borylations),^[19] and styrene (a scavenger used in radical reactions involving arylborates)^[20] did not inhibit heterocoupling.



 Table 2. Substrate scope for the zinc catalyzed C(sp³)-C(sp²) coupling

 ^aWith benzyl chloride. ^b72 hours.

With a closed shell mechanism favored and neutral di arylzinc reagents precluded as the active species (as ZnPh2 and 2a do not cross-couple in dioxane)[11] the formation of anionic arylzincates from 1a was explored in 2-MeTHF. Anionic zincates are more nucleophilic than Ar₂Zn species and are often more effective in the transfer of aryl groups to electrophiles,^[21] e.g. [^tBu₂PhZn]Li cleanly arylates Mel.^[22] To assess for zincate formation two eq. of 1a were reacted with ZnBr₂ at 20°C, which in < 10 mins had completely formed ^tBuBPin (by NMR spectroscopy) indicating transfer of two eq. of phenyl to zinc. The likely composition of the ensuing zincate species will predominantly be of the form ${[Ph_xZnBr_y]}_n$ (x+y = 3 n = 1 or higher aggregates), although only a single set of ¹H and ¹³C phenyl resonances were observed which is consistent with rapid exchange on the NMR timescale (as is the case throughout these experiments).^[23] The zincate assignment is supported by significant changes in the ¹H and ¹³C{¹H} NMR spectra on addition of one eq. of LiBr to ZnPh₂, whereas a second eq. of LiBr results in only very minor chemical shift changes (indicating minimal formation of $[Ph_xZnBr_y]^{2-}$ (x+y = 4) species).



To determine if an aryl group can be transferred from 1a to a diarylzinc species, equimolar ZnPh₂ and **1a** were reacted. This resulted in slow (at 20°C) transfer to form [ZnPh₃]⁻ (with a diagnostic $\delta^{13}C = 168.8$ for the ipso C_{phenyl} in 2-MeTHF)^[24] and ^tBuBpin. At 60 °C approximately 2 h were required for formation of [ZnPh₃]⁻ from ZnPh₂ and **1a**. Li[ZnPh₃], synthesized from ZnPh₂ and one eq. of PhLi has a closely comparable $\delta^{13}C_{ipso}$ for the Zn-Ph moiety (169.5 ppm in 2-MeTHF). Transmetallation still proceeds in the presence of LiBr, for example using a 1:2 mixture of ZnPh2 : LiBr 35 % aryl transfer from 1a to zinc occurs after 1 h at 60°C, thus aryl transfer to {[Ph_xZnBr_y]}_n species does occur. Li[ZnPh₃] only interacts weakly with 1 eq. of LiBr (as indicated by very minor changes in the ¹H and ¹³C NMR resonances, max $\Delta \delta$ = 0.02 ppm, addition of a second eq. of LiBr results in no observable $\Delta\delta$). As $[Ar_4Zn]^{2-}$ are documented ^[24,25] attempts to form [Ph₄Zn]²⁻ using **1a** were explored. However, the addition of **1a** to [Ph₃Zn]⁻ (made in-situ) did not lead to any observable aryl transfer (by NMR spectroscopy) disfavoring formation of $[Ph_4Zn]^{2-}$ under these conditions. In our hands attempts to crystallise these zincates failed, nevertheless, the above reactions indicate that a major Zn species present during catalysis is $[ZnPh_3]^{-}$. However, $[Ph_xZnBr_y]^{n-}$ (x+y = 3 or 4, n = 1 or 2, y≥1) will also be present and presumably will increase in concentration as catalysis proceeds due to the formation of LiBr as a by-product from cross coupling. It is notable that $1a / ZnX_2$ does not produce any observable [Ph₄Zn]²⁻ in contrast to using PhLi, thereby using borate **1a** allows [Ar₃Zn]⁻ to be selectively accessed without any dianioic zincate formation.[24] It is also notable that Na[BPh₄] gives drastically different transmetallation outcomes to 1a, as it does not transfer an aryl to ZnPh₂ in 2-MeTHF (at 20°C or 60°C), and thus does not produce any observable [Ph₃Zn]⁻. A relative nucleophilicity scale in 2-MeTHF for these nucleophiles is shown in Scheme 4, with 1a uniquely positioned between the monoanionic triaryl and dianionic tetraaryl zincates.

PhLi >
$$[Ph_4Zn]^{2-}$$
 > Bu_BO_{O} > $[Ph_3Zn]^{-}$ > $[BPh_4]^{-}$

increasing relative nucleophilicity

Scheme 4: Relative aryl nucleophilicity (in 2-MeTHF)

The stoichiometric coupling reactivity of various zincates with **2b** was assessed to identify if any lead to heterocoupling. In each case benzylbromide **2b** was combined with a zincate mixture containing a specific ratio, e.g. ZnPh_yBr_x, generated by combining ZnPh₂ (or ZnBr₂) with PhLi (or **1a**) and LiBr. On combining [ZnPh₄]²⁻ (formed from PhLi and ZnPh₂)^[24] and **2b** in 2-MeTHF, **2b** was consumed within 20 min at 25°C. However, this led exclusively to homocoupled product **4b** (Table 3, entry 1). Therefore for selective heterocoupling [Ar₄Zn]²⁻ species have to be avoided, presumably as these are more reducing thus lead to single electron transfer reactivity. In contrast, [ZnPh₃]⁻ (made from PhLi and ZnPh₂) on combination with **2b** led to predominantly heterocoupling (entry 2). Repeating in the presence of LiBr also led to formation of [ZnPh₃]⁻ (by comparable δ^{13} C for the ipso C_{phenvl}, entry 4) and a comparable coupling

Table 3. Zincate reactivity with 2b

ZnPh ₂ or ZnBr to generate 1 Zn	2+ PhLi + LiBr 72 + PhLi + LiB e a speciifc rat 1 : xPh : yBr	r F	Br 2b MeTHF F 1.5 h	3b	+ F	4b
Entry	<i>x</i> Ph	<i>y</i> Br	δ ¹³ C (ipso)	Temp / ℃	3b / % ^a	4b / % ^a
1	4	0	171.4	25 ^b	0	100
2	3	0	169.5	60	59	11
3 ^c	3	0	168.8	60	69	9
4	3	2	169.4	60	63	11
5	2	2	160.4	60	3	10
6	1	3	158.7	60	0	0

^aYields by ¹⁹F NMR spectroscopy and GC-MS, mass balance where appropriate is unreacted 2b. b 20 min c = from ZnPh₂ and borate 1a

outcome. Notably, a 1:1 mixture of 1a:ZnPh₂ (post heating at 60°C for 18 h) when reacted with **2b** produced predominantly **3b**, with a slightly improved hetero:homo coupling ratio (entry 3 vs 2, or 4), suggesting that ¹BuBPin may subtly effects the catalytic process and thus the overall selectivity. A number of mixed zincates, [Ph_xZnBr_y]ⁿ (with δ^{13} C resonances supporting Zn-Br moieties),^[26] were reacted with **2b** with reactivity slow at 60 °C and giving more **4b** than **3b** (entry 5) or no reaction observed at all (entry 6). Therefore the triarylzincates appear essential for leading to significant heterocoupling. This is consistent with the increased efficacy of 1.5 eq. of **1a** relative to 1.1 eq. in the catalysis as otherwise low activity bromide-zincates will dominate as the reaction progresses.

Previously, zinc Lewis acids were proposed to activate benzylbromides by coordination to bromide and thus facilitate S_N2 substitution by arylborates or zincates.^[11] To assess if Lewis acids are present during catalysis, Et₃PO was added (using the conditions from Table 1 entry 4) after 3 h. The ³¹P{¹H} NMR spectrum showed a downfield shift of 12.44 ppm compared to free Et₃PO, confirming Lewis acidic species are present. However, this may well be due to lithium Lewis acids as a similar $(\Delta \delta = 13.98 \text{ ppm})$ downfield shift was observed on addition of Et₃PO to LiBr in 2-MeTHF. Furthermore, a 2:1 mixture of ZnPh2:1a was heated in 2-MeTHF until 1a was consumed, targeting a 1:1 mixture of Lewis acidic ZnPh₂(solvent)_n and zincate [ZnPh₃]. To this mixture was added 2b with heating to 60°C for 1 h leading to poor coupling selectivity (3b:4b of 2.8 : 1). Therefore under these conditions zinc Lewis acid mediated coupling is disfavored and a mechanism involving S_N2 substitution by a triarylzincate is preferred, possibly involving substrate activation by Li⁺ salts.

In conclusion, benzyl halides can be coupled with aryl borates using ZnBr₂ as catalyst. To the best of our knowledge this is the first zinc catalyzed Suzuki – Miyaura reaction. Initial studies indicate a S_N2 mechanism with triarylzincates the key nucleophiles. Our findings represent an advance in the development of less toxic, base-metal cross-coupling catalysts as alternatives to established methodologies using noble metals,

and further investigations into the detailed mechanism and scope of the reaction are ongoing.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: cross coupling • alkylation • transmetallation • boron • zincate

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Entry for the Table of Contents

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Suzuki-Miyaura cross coupling, cheap, low toxicity catalyst, no ligand required

The cross coupling of benzyl bromides with aryl-borates is catalyzed by ZnBr₂, in a process that is compatible with a range of functionalized benzyl bromides and aryl boronic acid pinacol esters. Mechanistic investigations indicate that the *in-situ* formation of triaryl zincates is crucial to promote selective cross-coupling reactivity,

R. J. Procter, J. J. Dunsford, P. J. Rushworth, D. G. Hulcoop, R. A. Layfield and M. J. Ingleson*

Page No. – Page No.

A Zinc Catalyzed C(sp³)-C(sp²) Suzuki-Miyaura Cross-Coupling Reaction Mediated by Aryl-Zincates