## Synthesis of Solid 2-Pyridylzinc Reagents and Their Application in Negishi Reactions

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In search of alternatives to unstable or unreliable 2-pyridylboron reagents, we have explored two new varieties of solid, moderately air-stable 2-pyridylzinc reagents. Both reagents can be manipulated in air and are competent nucleophiles in Negishi cross-coupling reactions.

The 2-pyridyl group is a structural component of a variety of biologically active compounds,<sup>1</sup> functional materials,<sup>2</sup> and ligands in metal-mediated reactions.<sup>3</sup> While Suzuki–Miyaura coupling with heteroaryl boronates is a convenient and popular method for the installation of heteroaryls,<sup>4</sup> coupling of 2-pyridyl boronates<sup>5</sup> is plagued by reagent instability<sup>6</sup> and has been slow to develop. The best strategy for this problem has been the employment of 2-pyridyl MIDA<sup>5d</sup> and pinacol<sup>5e–g</sup> boronates, but a method with milder conditions and higher generality with respect to 2-pyridyl nucleophiles and electrophilic coupling partners remains highly desirable.

In contrast, 2-pyridylzinc reagents are excellent nucleophiles in cross-coupling processes and their reactions often proceed at room temperature.<sup>7</sup> Although these reagents are more basic than the corresponding boronates, their use avoids the troublesome protodeboronation issues commonly observed with 2-heteroarylboronates. We have concurrently pursued two strategies to obtain solid, airstable 2-pyridylzinc reagents, with the goal of uniting the operational simplicity of boronates and the reliability of 2-pyridylzinc halides.

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Scheme 1. Synthesis of Solid 2-Pyridylzinc Pivalates



<sup>a</sup> Complexed LiOPiv and MgOPivCl omitted for clarity.

Table 1. Air Stability of 2-Pyridylzinc Pivalates

entry	compound	$1 \ \mathrm{h}^a$
1	1	90%
2	3	86%
3	4a	69%
4	5a	70%
5	5b	72%

<sup>*a*</sup> Percentage of original titer by titration with iodine after aging for 1 h in air (see Supporting Information for details).

First, we have applied the organozinc pivalate approach<sup>8</sup> that provides reagents that are free-flowing solids, indefinitely stable when stored under an inert atmosphere, and comparable in reactivity to organozinc halides in Negishi reactions. A second, newer approach is based on the hypothesis that the use of additional ligands could provide an air-stabilized, solid organozinc halide. This is in many ways analogous to Burke's MIDA boronate method. These two conceptually different approaches have both resulted in solid reagents that are stable in air for roughly one day and are competent nucleophiles in cross-coupling reactions.

Minimal optimization was required for the synthesis of 2-pyridylzinc pivalates.<sup>8a,b</sup> Lithium– or magnesium– halogen exchange followed by transmetalation to  $Zn(OPiv)_2$  and evaporation of solvent gave compounds 1–5 in 69–97% yields (Scheme 1).<sup>9</sup> Both metal–halogen exchange methods gave reagents with air stability comparable to that of the most stable organozinc pivalates known

Scheme 2. Negishi Coupling of 2-Pyridylzinc Pivalates



<sup>a</sup> Complexed LiOPiv or MgOPivCl omitted for clarity.

(see Table 1).<sup>8b,c</sup> Notably, **5a** and **5b** had virtually identical air stabilities, even though **5b**, synthesized by magnesium– halogen exchange, is presumably complexed with an extra equivalent of hygroscopic lithium chloride (Table 1, entries 4 and 5). While the reagents cannot be stored under ambient atmosphere for long periods of time without significant decomposition, compounds 1-5 can be easily weighed in air with minimal loss of the active zinc reagent.

The solid 2-pyridylzinc pivalate reagents prepared as above exhibited excellent functional group compatibility in Negishi reactions with aryl chlorides and bromides (Scheme 2), tolerating ketones (**6b**, **6c**, **6g**), esters (**6a**, **6f**, **6i**, **6j**, **6k**), and free N–H groups (**6d**, **6h**, **6i**, **6k**). Of note, 2-chloroisonicotinonitrile was coupled to give the unsymmetrical 2,2'-bipyridyl (**6l**) in good yield. The pivalate reagents are relatively stable to trace water and oxygen under cross-coupling conditions and could be coupled

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<sup>(9)</sup> Yield of the reaction was determined by titration of a solution of the solid material with iodine. See: Krasovskiy, A.; Knochel, P. *Synthesis* 2006, *5*, 890–891.

Table 2. Evaluation of Potentially Stabilizing Ligands



<sup>*a*</sup> Complexed MgCl<sub>2</sub> and ZnCl<sub>2</sub> omitted for clarity. <sup>*b*</sup> By titration with iodine. <sup>*c*</sup> By titration with iodine after aging in air. Percentage based on yield of pyridylzinc reagent.

under air in either technical grade ethyl acetate or THF as solvent in excellent yields (**6n**, **6m**).

Looking for an alternative means to produce airstable and solid 2-pyridylzinc reagents, it was hypothesized that the addition of a ligand for zinc could provide a 2-pyridylzinc halide complex that was protected from ambient moisture and/or less basic or hygroscopic. There is significant precedent for this strategy. Charette recently prepared a series of bipyridyl-ligated zinc carbenoids that showed improved stability toward ambient atmosphere and were reactive for up to eight months.<sup>10</sup> An early example is from Sheverdina, who crystallized a variety of alkyl- and arylorganozinc compounds as the corresponding 1,4- dioxane complexes.<sup>11</sup> Subsequently, Noltes prepared a variety of ligated organozinc compounds which "seem[ed] to be less sensitive towards hydrolysis" than the unligated compounds.<sup>12</sup>

Potential ligands were added to a solution of 2-pyridylzinc chloride prepared by sequential magnesium—halogen exchange and transmetalation with zinc chloride (see Table 2).<sup>7c</sup> The resulting mixture was then concentrated under reduced pressure. The material was aged and then titrated<sup>9</sup> to determine air stability. In the absence of ligand, Scheme 3. Negishi Coupling with Dioxanate Reagent<sup>a</sup>



<sup>*a*</sup> Reaction conditions: **14**(1.3 mmol), Ar–X (1.0 mmol), **15**(2 mol %), THF (4 mL), temp, 16 h; isolated yields, average of two runs.

a sticky orange solid was obtained<sup>13</sup> that was titrated to give a reference point for the complexes prepared with additives (Table 2, entry 1). All of the ligated compounds were obtained as nondeliquescent solids and were easily manipulated. A variety of potentially chelating ligands were studied (Table 2, entries 2–7), but only the complexes formed with 2.3 equiv of 1,4-dioxane (12)<sup>14</sup> and 1,2-dimethoxyethane (13) were markedly more stable than the "ligandless" case (Table 2, entries 8 and 11), with the dimethoxyethane complex roughly half as stable as the dioxanate.

The dioxanate complex 14 was an effective nucleophile under recently developed Negishi cross-coupling conditions (see Scheme 3).<sup>7g</sup> Simple electron-poor and electronrich haloaromatics (Scheme 3, 16a, 16b, and 16c) as well as the triflate of estrone (16i) could be coupled in good yields. Moreover, the complex 14 could also be coupled with more challenging, heterocycle-containing aryl (16e, 16g, 16j) and heteroaryl (16d, 16f, 16h) bromides and chlorides in 61-95% yield.

The dioxanate **14** should be titrated to determine its concentration for use after long-term storage. However,

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<sup>(13)</sup> The "ligandless" example could have been the tetrahydrofuran (solvent) complex of the 2-pyridylzinc species.

<sup>(14)</sup> The optimized procedure for the preparation of the dioxanate reagent was performed with 30 mmol of 2-bromopyridine. No larger scales were attempted. The average yield over seven preparations at 30 mmol scale was 58% (47%-70%).

Scheme 4. Reactivity of Partially Decomposed Reagents



<sup>*a*</sup> By titration with iodine. <sup>*b*</sup> By titration with iodine after aging as described. <sup>*c*</sup> Isolated yield based on 1 mmol of aryl bromide (**17**) and 1.3 mmol of aged solid organozinc reagent (**14**); mass of solid organozinc reagent mixture used depended on concentration of active zinc reagent in mixture by titration with iodine.

decomposition products do not interfere with the reagent's efficacy. Three different samples—one stored in a glovebox for 30 days, another stored in the glovebox for 30 days and then in air for 24 h, and a third stored in a vacuum desiccator for 40 days—all gave virtually identical yields of cross-coupled product (see Scheme 4). While the aged samples have lower concentrations of an active zinc nucleophile and are presumably admixed with unreactive material, these decomposition products have no effect on the cross-coupling reaction in terms of yield.

In summary, we have developed two methods for the preparation of solid 2-pyridylzinc nucleophiles that are sufficiently air stable to be handled on the bench and viable alternatives to boronates in cross-coupling reactions. We have successfully applied the organozinc pivalate technology to the Negishi coupling of a new class of heterocycles and developed a second, new approach to solid zinc reagents. Both strategies should be applicable to other nucleophiles and may be further developed as practical surrogates for unstable or insufficiently reactive organoboron compounds.

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**Supporting Information Available.** Experimental procedures, characterizations, and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.