Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201400243

Continuous Synthesis of Organozinc Halides Coupled to Negishi Reactions

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Received: March 9, 2014; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201400243.

Abstract: The Negishi cross-coupling is a powerful C–C bond forming reaction. The method is less commonly used relative to other cross-coupling methods in part due to lack of availability of organozinc species. While organozinc species can be prepared, problems with reproducibility and handling of these sensitive species can complicate these reactions. Herein, we describe the continuous formation, using an activated packed-bed of metallic zinc, and subsequent use of organozinc halides. We demonstrate that a single column of zinc can provide excellent yields of organozinc halides and that they can be used downstream in subsequent Negishi cross-couplings. The preparation of the zinc column and the scope of the reaction are discussed.

Keywords: cross-coupling; flow chemistry; Negishi reaction; organozinc halides; supported catalysts

Transition metal-based cross-coupling reactions are powerful synthetic tools for forming C–C bonds.[1] While organoboranes (Suzuki) are often the first choice in cross-coupling partner, organozincs (Negishi) often show superior reaction rates and are used when organoboranes are too unreactive. Moreover, the Negishi reaction facilitates the coupling of *sp*^{3} carbons, increasing their prevalence in drug discovery compounds and thus allowing medicinal chemists to access new chemical space.[2] Despite outstanding innovations with regard to organozinc synthesis, the paucity of commercially available organozinc species compared to the abundance of organoboranes limits use of the Negishi reaction.[3] In our experience, the stability of organozinc species even compared to organolithium and organomagnesium species is low and that solutions of organozinc species decompose readily. This feature contributes to the lack of commercially available organozinc species and may also contribute to less wide-spread use of the Negishi reaction.

We hypothesized that an ideal situation would be to avoid handling organozinc reagents altogether and instead create a continuous system whereby an organozinc reagent is prepared from a shelf-stable organohalide and immediately used in a subsequent reaction.[4] It is well documented that continuous flow is an ideal tool for handling unstable and highly reactive intermediates, integrating several steps into one single streamlined process.[5] The key challenge is to define zinc metal activation conditions that would enable an organozinc halide to be produced within a column of zinc metal (Figure 1) and then to pass the organozinc halide directly into a column of supported transition metal catalyst to facilitate a Negishi reaction. Recently, we have demonstrated that NHC-copper(I) transition metal complexes could be readily formed by passing a solution of imidazolium chloride through a packed-bed of copper(I) oxide.[6] The desired complexes were formed in high yield and could then be coupled to downstream catalytic reactions. We speculated that this concept could be applied to the forma-

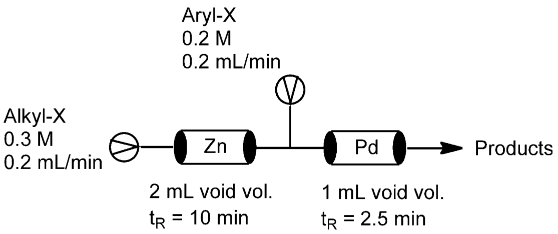


Figure 1. Experimental set-up of the flow system (t_R = residence time).

tion of a wide range of organometallic species such as the formation of organozinc halides.

Herein, we demonstrate that organozinc halides can be rapidly formed with reproducible titers by simply passing organohalides through a column of appropriately active zinc metal. The organozinc halides can then be used in downstream Negishi couplings. Not only is the two-step process rapid and high yielding, the method also enables a wide range of Negishi couplings without the need to handle the sensitive organozinc reagents.

When creating a reactive packed-bed for use in a continuous reaction the following factors must be considered.

Particle size of the packed-bed material: in general we have found that solids with mesh sizes similar to silica gel form beds that enable reasonable flow rates without high back pressures. For this reaction, we found that zinc dust works poorly while zinc particles or powder with a size of ~30 mesh works well.

Metal activation is another crucial consideration: commerical zinc granules often arrive with a passivating layer that must be etched away. We found that common activation strategies work well; however, activation with TMSCl (2 M, 10 mL), 1,2-dibromoethane (1 M, 10 mL) followed by washing with THF (20 mL) provided the most active column.

Column packing is best achieved by using a column with removable ends similar to an HPLC column (we prefer Omni-fit columns). We place an inert material such as silica gel or cotton at the end of the column to prevent zinc fines from exiting the column and fouling the downstream reaction.

Column heating must be considered: we have used HPLC column heaters, nichrome heating tape and commercial heaters associated with flow chemistry systems. The ideal heater will uniformly heat the column without forming hot spots.

Integrating these considerations, we filled a 10 mm internal diameter Omni-fit column with 12 g of zinc and placed it in a Vapourtec R2+R4 system.[7] The performance of the column was assessed by pumping 0.63 M benzyl bromide (**1a**) in THF through the zinc and measuring the consumption *via* GC. Figure 2 illustrates that the column has an induction period where total consumption of **1a** is not complete until ~3 min into the run. In this case, the column was activated using dilute HCl followed by washing with dry THF. The induction period can be eliminated by switching the column activation wash from dilute HCl, black diamonds, to TMSCl/dibromoethane, grey squares (see the Supporting Information). Selected data points were titrated using the Knochel method.[8] The titrations indicated a 1:1 correlation between consumption of **1a** and organozinc halide (**2a**) formation.

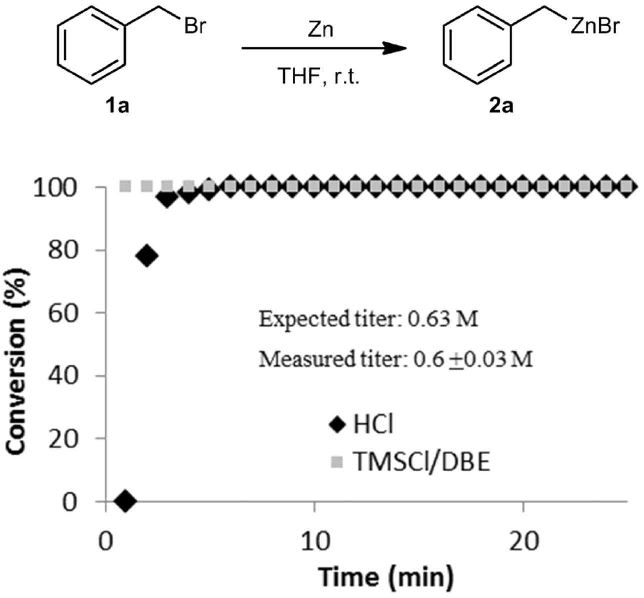


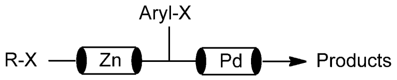
Figure 2. Activation of zinc column: HCl wash (black diamonds) and TMSCl/dibromoethane wash (grey squares).

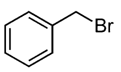
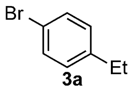
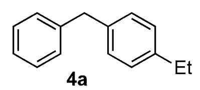
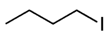
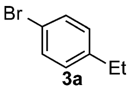
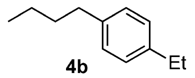
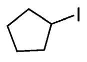
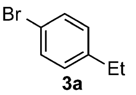
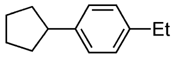
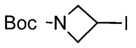
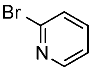
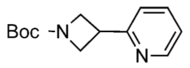
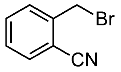
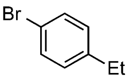
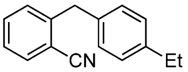
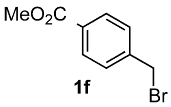
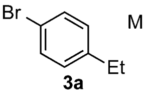
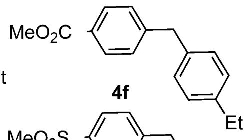
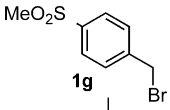
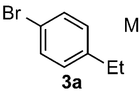
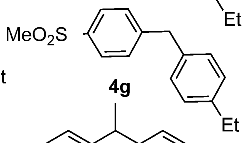
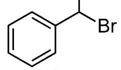
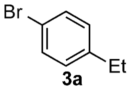
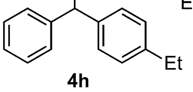
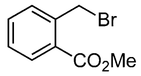
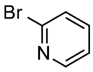
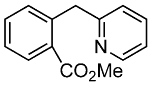
We have determined that a zinc column, activated as described above (see the Supporting Information for more detail), yields quantitative formation of organozinc halides at room temperature when benzyl and allylic halides are used and between 30–60 °C when alkyl iodides are used. Aryl halides under the conditions we examined do not yield organozinc halides even above 110 °C. We are now examining alternative conditions that might enable formation of arylzinc halides.

While organozinc halides are suitable nucleophiles for use in a wide range of reactions, we concentrated our efforts towards coupling the formation of organozinc halides. In particular, a Negishi reaction that allowed introduction of functional alkyl groups for easy access to more complex compounds. With this in mind, we examined the formation of organozinc halides using THF as the solvent as this will support both the zinc reagent formation and the subsequent Negishi reaction.

We have recently published a series of manuscripts describing efficient and rapid continuous cross-coupling reactions using supported palladium complexes.[9] In particular, SiliaCat DPP-Pd[10] was found to support a wide range of Negishi reactions.[9b] We proceeded to leverage this knowledge by creating a two column reactor system whereby the zinc packed-bed was placed upstream of a 6.6 mm internal diameter Omni-fit column containing 1 g of SiliaCat DPP-Pd (Table 1). We started examining the performance of this two column system by surveying the range of coupling partners that could undergo successful cross-coupling. As shown in Table 1, Negishi cross-couplings between aryl halides and organozinc halides formed from alkyl (**1b**–**1d**) and benzylic hal-

Table 1. Initial survey of coupling partners supported by a two column system (scale 0.8 mmol).

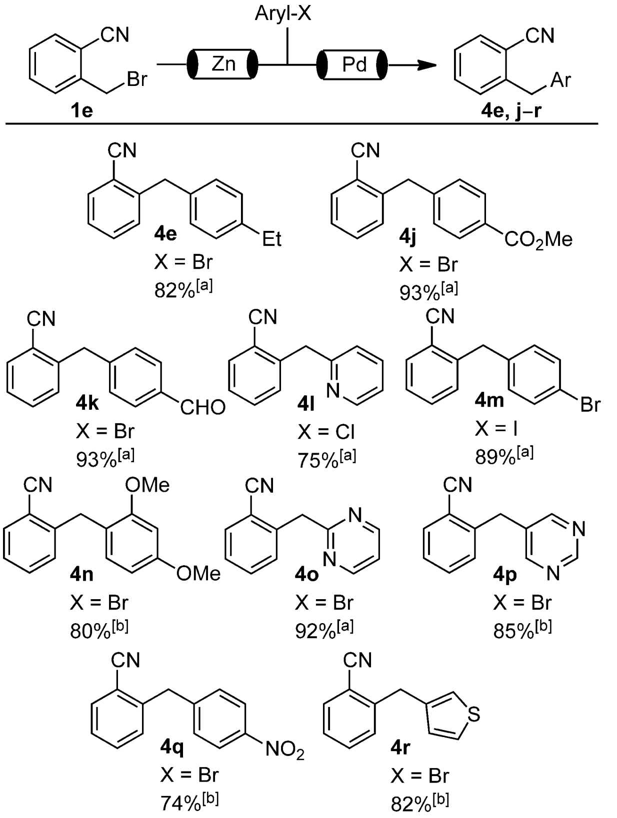


Entry	R-X	Aryl-X	Product	Yield [%]
1[a]	 **1a**	 **3a**	 **4a**	81
2[b]	 **1b**	 **3a**	 **4b**	74
3[c]	 **1c**	 **3a**	 **4c**	83
4[d]	 **1d**	 **3b**	 **4d**	71
5[a]	 **1e**	 **3a**	 **4e**	81
6[a]	 **1f**	 **3a**	 **4f**	79
7[b]	 **1g**	 **3a**	 **4g**	82
8[b]	 **1h**	 **3a**	 **4h**	84
9[a]	 **1i**	 **3b**	 **4i**	86

[a] Zn column, r.t.; Silicat DPP-Pd column 60 °C.
[b] Zn column, 60 °C; Silicat DPP-Pd 60 °C.
[c] Zn column, 60 °C and LiCl (1 equiv.) as additive; Silicat DPP-Pd column, 80 °C.
[d] Zn column, 110 °C and LiCl (1 equiv.) as additive; Silicat DPP-Pd column, 60 °C.
[e] Zn column, r.t.; Silicat DPP-Pd column, 80 °C.

ides (**1a**, **1e**–**1i**) proceeded in good to high yields. It is worth highlighting that many functionalized alkyl and benzyl species performed well, such as Boc-protected azetidine (entry 4), as well as secondary benzyl halides (entry 8). We have only identified that nitro groups are incompatible with the organozinc halide forming step which is consistent with previously described organozinc chemistry.[3]

Table 1 demonstrates that our hypothesis, organozinc halides can be prepared continuously and immediately used downstream, is valid. We proceeded to examine a range of aryl halide-based coupling reactions to examine the functional group tolerance of the system (Scheme 1). In this way, electron-rich and electron-poor aryl substrates react in good to excellent yields. In addition, the process is tolerant of five- and six-membered ring heterocyclic coupling partners under mild reaction conditions. In contrast to the zinc insertion step, nitro groups are well tolerated as coupling partners (**4q**). In the case of bromo-iodo derivatives, coupling proceeded selectively at the iodine atom (**4m**). The data presented thus far indicate that a two column system whereby a shelf-stable organohalide is passed through a suitably activated zinc column can be used to perform Negishi couplings. What we have yet to demonstrate is that the system can be used to form meaningful volumes of material. To address the issue of scale, we have examined two aspects of this system.



[a] Zn column, r.t.; Silicat DPP-Pd column 60 °C.
[b] Zn column, r.t.; Silicat DPP-Pd column 80 °C.

Scheme 1. Survey of functional group tolerance: scale 0.8 mmol.

The first aspect of scale we examined was organozinc halide production. Using the Omnifit column filled with 12 g of zinc, we were able to prepare 150 mL of a 0.5 M solution of benzylzinc bromide **2a** in THF. During this procedure about 5 g of zinc were

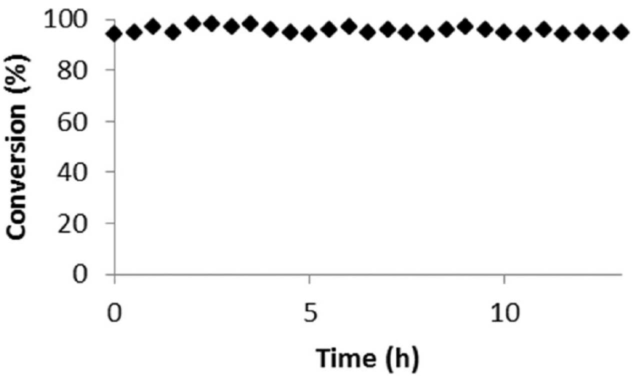


Figure 3. Long-term stability assessment.

consumed. This volume is very practical on the laboratory scale as most organometallic reagents are sold in 100 mL volumes. These data suggest that use of the zinc column to produce organozinc halides will be broadly applicable to reactions beyond the Negishi reaction.

The second aspect of scale examined was overall protocol stability with respect to the two column system. In this case, we measured the formation of Negishi product as a function of time (Figure 3). The reaction was performed such that 3.3 mmol h^{-1} was achieved. The calculated turnover number of the catalyst for the overall process was 175. The isolated yield of the reaction was 94% and the reaction was stable over the 13 h that we monitored. These data demonstrate that this approach is valid on development scales. We perceive that with larger zinc and catalyst columns the reaction could be scaled to manufacturing volumes.

In conclusion, we have demonstrated that organozinc halides can be produced from shelf-stable halides and used *in situ* in a continuous packed-bed approach. The data shown in Figure 2 demonstrate that high and reproducible titers can be realized when the zinc is appropriately activated. The scope data indicate that a variety of substrate types are readily converted into organozinc halides and that coupling the formation of the zinc species with a Negishi reaction is a productive approach. The two column system is tolerant of many functional groups including those of interest from a medicinal chemistry perspective (heterocycles such as azetidine **1d**). The formation of organozinc halides is broadly useful as the approach can support the formation of 150 mL of 0.5 M reagent. Finally, the two stage zinc insertion/Negishi reaction functions at the high end of laboratory scale with ease suggesting that the approach is stable and robust enough to support much larger scale chemistry. Further expansion of both zinc insertion and coupling steps will be the topic of future endeavors.

Experimental Section

General Flow Procedure for Zinc Insertion and Negishi Cross-Coupling

A solution of alkyl halide 0.3 M in dry THF (when required 1 equiv. of LiCl was added as additive) was passed through a 10 mm internal diameter Omni-fit column containing Zn (12 g) using the R2+R4 system[7] at the desired temperature and a flow rate of 0.2 mL min^{-1} (t_R = 10 min). The outlet solution was mixed in a T piece with a solution of haloarene 0.2 M in dry THF at 0.2 mL min^{-1} and passed through a 6.6 mm internal diameter Omni-fit column containing Siliacat DPP-Pd (1 g) at the required temperature (t_R = 2.5 min). The crude of the reaction was quenched with a saturated solution of ammonium chloride and extracted with AcOEt. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated under vacuum. The crude products were purified by column chromatography using silica to yield the desired products.

Acknowledgements

The authors thank NSF (CHE-1152020), Chemring, Inc., Prof. Frank Gupton for helping the contact. Prof. Antonio de la Hoz, Prof. Angel Diaz Ortiz, Prof. Wim de Borggraeve and Dr. Brecht Egle for their help in the Negishi protocol. D. Miguel A. Peña Piñon and Dr. Alberto Nuñez Ocaña for their help in the large scale preparation of organozinc compounds. Duncan Guthrie, Chris Butters, David Griffin, Adrian Clarkson, and Lillian Auchincloss from Vapourtec Ltd. are thanked for their assistance throughout this project.

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[10] For further information about SiliaCat catalyst visit: http://www.silicycle.com (last checked 2014-03-04).

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Adv. Synth. Catal. **2014**, *356*, 1 – 6

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