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Palladium-Catalyzed Hydroalkylation of Styrenes with Organozinc Reagents to Form Carbon-Carbon sp^3 - sp^3 Bonds under Oxidative Conditions

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Abstract

An unconventional route for the formation of sp^3 - sp^3 C-C bonds from various styrene and an organozinc reagents in a formal alkene hydroalkylation process is detailed. Mechanistically this process is proposed to proceed by initial transmetalation followed formation of a Pd-H which is subsequently trapped with the styrene.

The metal-catalyzed cross-coupling of simple alkyl electrophiles with various organometallic reagents has received significant attention over the last several years due to extensive synthetic applications of such a reaction type.¹ To initiate the catalysis, a low valent metal complex promotes oxidative addition of the electrophilic compound to access a metal-alkyl intermediate (Scheme 1).² The development of these reactions is considered to be particularly difficult due to the slow rate of oxidative addition of the alkyl electrophile and the ease with which the resultant metal alkyl species undergoes β -hydride elimination.² Nickel based systems have generally overcome these issues³ but the use of palladium to affect the coupling of secondary alkyl nucleophiles and electrophiles is still considered challenging.⁴ Herein we present an alternative approach to alkyl-alkyl cross coupling reactions using a Pd-catalyzed hydroalkylation of styrenes with alkylzinc reagents wherein a primary-secondary C-C bond is formed.

Our approach is to use a conjugated alkene to replace the alkyl halide as the coupling partner thereby removing the challenge of slow oxidative addition (Scheme 1). In parallel, we aim to take advantage of the propensity that unfunctionalized Pd-alkyls undergo β -hydride elimination to access a Pd-hydride (**B** $\rightarrow$ **C**) that could be subsequently trapped by the conjugated alkene to yield a stabilized Pd-alkyl similar to **D**. We have recently reported this type of process is indeed possible using an aerobic alcohol oxidation to generate the Pd-hydride.⁵ However, in these reports only sp^2 -coupling partners, generally aryl organometallic reagents, were successfully added. In the current study, we hypothesized that the organometallic reagent could act both as the hydride source and the ultimate coupling partner, along with a styrene derivative as the alkene. It should be noted that the system must be compatible with a terminal oxidant to reform Pd(II).

To initiate the investigation, 4-methyl styrene and Bu_4Sn were submitted to the conditions recently reported for the oxidative diarylation of terminal alkenes using aryl organostannanes.

⁶ We were excited to observed 25% GC yield of the hydroalkylation product providing proof

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Supporting Information Available: Optimization data, experimental procedures, and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

of concept (Table 1 entry 1). However, we reasoned that the use of Bu_4Sn for further optimization would not be practical. Therefore, the use of the analogous alkylzinc reagents was investigated which are commonly used in Negishi-type cross-coupling reactions.⁷ Initial screening with commercial *n*-BuZnBr under aerobic oxidative conditions did not yield the hydroalkylation product or result in any consumption of the styrene (entry 2). To the best of our knowledge, the only example of utilizing organozinc reagents in an oxidative cross-coupling type reaction was performed with desyl chloride as the terminal oxidant.⁸ However, no appreciable hydroalkylation product is observed under our conditions (entry 3). Benzoquinone (BQ), a common terminal oxidant in Pd-oxidative catalysis, was next investigated.^{9a} To our delight, a 30% GC yield was achieved of the desired product using this oxidant with incomplete consumption of starting material (entry 4). Initial attempts to enhance the reaction conversion by modifying the reaction conditions did not prove fruitful. One possible reason for this is the absence of two protons to facilitate the oxidation Pd(0) to Pd(II) with benzoquinone, which are not available in this system. Indeed, addition of Brønsted acids to reactions employing benzoquinone as the terminal oxidant typically results in rate enhancements.^{9b} However, since strong Brønsted acids are incompatible with alkyl zinc reagents, Lewis acids were explored, wherein $\text{Zn}(\text{OTf})_2$ was found to enhance the performance of the system with a product GC yield of 70% (entry 5). To further optimize the system, other sources of *n*-BuZnBr were evaluated due to the potential of the commercial sources to contain excess halide ions which were found to inhibit this reaction.¹⁰ A halide-free *n*-BuZnBr reagent was prepared using Rieke zinc to considerably enhance the yield of the reaction to 97% (entry 6). Additionally, *n*-BuZnBr prepared using the method of Fu again lead to an excellent yield of 98% (entry 7) and, considering the ease of this route, it was used throughout the remainder of the study.¹¹

The substrate scope of reaction under the optimized conditions was examined by first exploring the nature of the styrene derivative. Both electron rich and poor substituents on the styrene (**3a–3f**) are tolerated and generally lead to high yields.. Also, ortho substitution is allowed with a 93% yield of **3g** observed. Various alkyl zinc reagents were then explored, including the successful use of cyclohexylmethyl zinc bromide which contains substitution at the β -position (**3h**). Functionalized organozinc reagents were examined, wherein an alkyl chloride, a TBDPS protected alcohol, and an ester containing alkylzinc reagent are competent coupling partners (**3j–3l**). The reaction is not limited to terminal alkenes wherein substituted styrenes, including indene and a β -methyl styrene derivative, undergo the hydroalkylation reaction in good yields. Finally, the reaction of a 1,1-disubstituted styrene proceeds to furnish an all-carbon quaternary center albeit in reduced yield. Of note, we do not observe any constitutional isomers by GC.

To determine the origin of the hydrogen incorporated into the product and probe our mechanistic hypothesis, a perdeuterated alkyl zinc reagent was prepared and submitted to the hydroalkylation reaction conditions. Approximately one deuterium atom is incorporated into the product as determined by ^1H NMR spectroscopy, which is consistent with the hydrogen added to the alkene originating from the organozinc reagent. Interestingly, incorporation of deuterium is observed at both the methyl and methine position, which indicates insertion of the alkene occurs from either side, but the resultant Pd-alkyl most likely rearranges via β -hydride elimination to the more stable π -benzyl intermediate (Scheme 1, **D**).

In conclusion, we have described an alternative method for the formation of sp^3 - sp^3 carbon-carbon bonds via cross-coupling, which avoids the difficulty of oxidative addition of unactivated alkyl halides and takes advantage of the inherent ease of β -hydride elimination of Pd-alkyls. The scope of the process reveals excellent tolerance of styrene functionalization and the ability to form a quaternary carbon center. Isotopic labeling experiments indicate that the hydroalkylation process most likely proceeds by initial transmetalation of the alkylzinc reagent, followed by formation of a Pd-H, which is trapped with a styrene. An interesting aspect of this process is that the alkene is formally reduced under oxidative conditions. Future work is focused on expanding the scope of coupling partners that can be utilized in this process and development of an enantioselective variant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Conventional sp^3 - sp^3 Cross-Coupling **Hydroalkylation of Styrenes with Alkyl Organometallics** **Mechanistic Hypothesis** **Scheme 1.**Conventional route and our approach to sp^3 - sp^3 cross coupling reactions.

Table 1

Optimization for the hydroalkylation of 4-methyl styrene

Entry	Conditions	% Conv. ^a	% 3a ^b
1 ^c	3 eq $\text{Sn}(n\text{-Bu})_4$, 25 mol% Cu(OTf)_2 , O_2	40	25
2	4 eq $n\text{-BuZnBr}$, O_2	<2	<1
3	4 eq $n\text{-BuZnBr}$, 2 eq desyl chloride	<2	<1
4	4 eq $n\text{-BuZnBr}$, 2 eq BQ	55	30
5	4 eq $n\text{-BuZnBr}$, 1 eq Zn(OTf)_2 , 4 eq BQ	80	70
6 ^d	4 eq $n\text{-BuZnBr}$, 1 eq Zn(OTf)_2 , 4 eq BQ	99	97
7 ^e	4 eq $n\text{-BuZnBr}$, 1 eq Zn(OTf)_2 , 4 eq BQ	99	98

^a Measured by GC using an internal standard.^b GC yield.^c Reaction performed at 55° C.^d $n\text{-BuZnBr}$ made from Rieke zinc.^e $n\text{-BuZnBr}$ made using Huo and Fu method (ref ¹¹)

Table 2

Substrate Scope of the Pd-catalyzed hydroalkylation of styrene derivatives.

Yields are average isolated yields of at least two experiments