J|A|C|S COMMUNICATIONS

Published on Web 11/24/2009

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

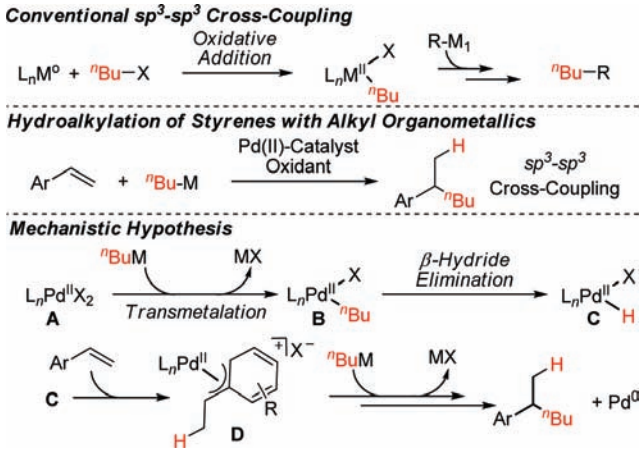
Kaveri Balan Urkalan and Matthew S. Sigman*

Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, Utah 84112-085

Received October 7, 2009; E-mail: sigman@chem.utah.edu

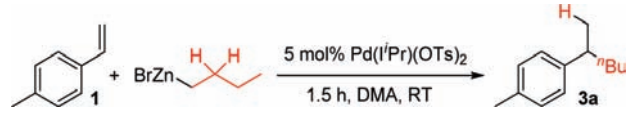
Metal-catalyzed cross-coupling of simple alkyl electrophiles with various organometallic reagents has received significant attention over the last several years because of the extensive synthetic applications of such a reaction type.[1] To initiate the catalysis, a low-valent metal complex promotes oxidative 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 because of 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] Ni-based systems have generally overcome these issues,[3] but the use of Pd to affect the coupling of secondary alkyl nucleophiles and electrophiles is still considered challenging.[4] Herein we present an alterative 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.

Scheme 1. Conventional Route and Our Approach to sp^3−sp^3 Cross-Coupling Reactions



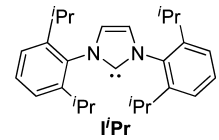
Our approach involves using a conjugated alkene to replace the alkyl halide as the coupling partner, thereby removing the challenge of slow oxidative addition (Scheme 1). In parallel, we aim to take advantage of the propensity of unfunctionalized Pd−alkyls to undergo β-hydride elimination to access a Pd hydride (**B** → **C**) that could subsequently be trapped by the conjugated alkene to yield a stabilized Pd−alkyl similar to **D**. We have recently reported that 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 as both 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 re-form Pd(II).

Table 1. Optimization of the Hydroalkylation of 4-Methylstyrene



entry	conditions	% conv.[a]	% **3a**[b]
1[c]	$Sn(n\text{-}Bu)_4$ (3 equiv), $Cu(OTf)_2$ (25 mol %), O_2	40	25
2	*n*-BuZnBr (4 equiv), O_2	<2	<1
3	*n*-BuZnBr (4 equiv), desyl chloride (2 equiv)	<2	<1
4	*n*-BuZnBr (4 equiv), BQ (2 equiv)	55	30
5	*n*-BuZnBr (4 equiv), $Zn(OTf)_2$ (1 equiv), BQ (4 equiv)	80	70
6[d]	*n*-BuZnBr (4 equiv), $Zn(OTf)_2$ (1 equiv), BQ (4 equiv)	99	97
7[e]	*n*-BuZnBr (4 equiv), $Zn(OTf)_2$ (1 equiv), BQ (4 equiv)	99	98

[a] Measured by GC using an internal standard. [b] GC yield. [c] Reaction performed at 55 °C. [d] *n*-BuZnBr made from Rieke zinc. [e] *n*-BuZnBr made using the method of Fu and Huo.[11]

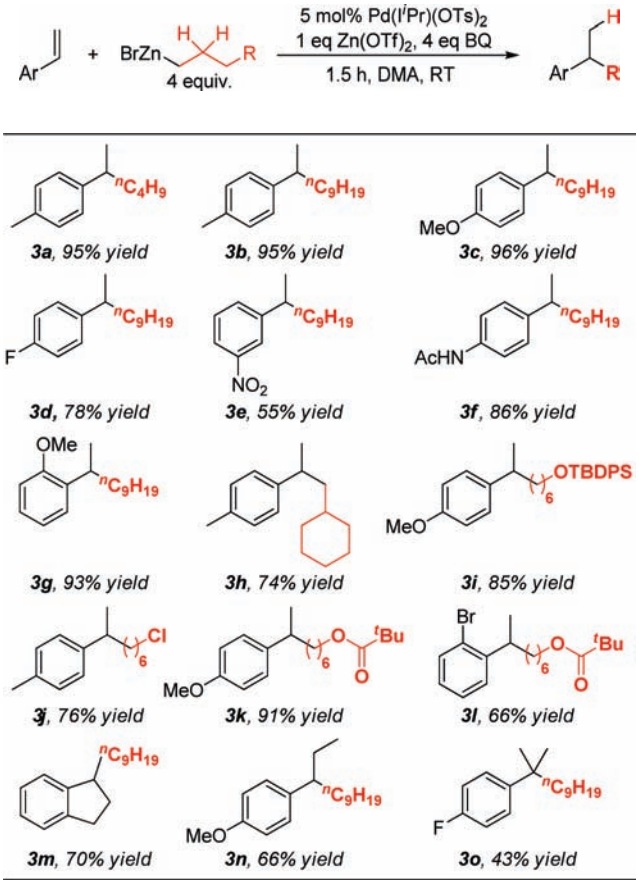


To initiate the investigation, 4-methylstyrene and Bu_4Sn were submitted to the conditions recently reported for the oxidative diarylation of terminal alkenes using aryl organostannanes.[6] We were excited to observe a 25% GC yield of the hydroalkylation product, providing proof of concept (Table 1, entry 1). However, we reasoned that the use of Bu_4Sn for further optimization would not be practical and therefore investigated the use of the analogous alkylzinc reagents, 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 the use of organozinc reagents in an oxidative cross-coupling-type reaction was performed with desyl chloride as the terminal oxidant.[8] However, no appreciable hydroalkylation product was 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 of the desired product was achieved using this oxidant, with incomplete consumption of the 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 was the absence of two protons to facilitate the oxidation of Pd(0) to Pd(II) with BQ, which are not available in this system. Indeed, addition of Brønsted acids to reactions employing BQ as the terminal oxidant typically results in rate enhancements.[9b] However, since strong Brønsted acids are incompatible with alkylzinc reagents, Lewis acids were explored, wherein $Zn(OTf)_2$ was found to

10.1021/ja908545b

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 because of 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 prepared using Rieke zinc was found to considerably enhance the yield of the reaction to 97% (entry 6). Additionally, *n*-BuZnBr prepared using the method of Fu and Huo[11] again led to an excellent yield of 98% (entry 7); considering the ease of this route, it was used throughout the remainder of the study.

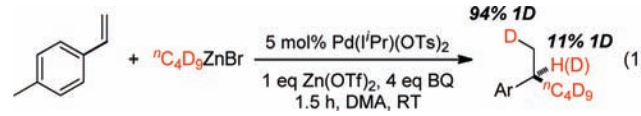
Table 2. Substrate Scope of the Pd-Catalyzed Hydroalkylation of Styrene Derivatives[a]



[a] Yields are average isolated yields of at least two experiments.

The substrate scope of the reaction under the optimized conditions was then examined (Table 2). First, the nature of the styrene derivative was explored. Both electron-rich and -poor substituents on the styrene (**3a**−**f**) were tolerated and generally led to high yields. Also, ortho substitution is allowed, as a 93% yield of **3g** was observed. Various alkylzinc reagents were then explored, including the successful use of cyclohexylmethylzinc 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 were competent coupling partners (**3j**−**l**). The reaction is not limited to terminal alkenes, as substituted styrenes, including indene and a β-methyl styrene derivative, underwent the hydroalkylation reaction in good yields. Finally, the reaction of a 1,1-disubstituted styrene proceeded to furnish an all-carbon quaternary center, albeit in reduced yield. Notably, we did 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 alkylzinc reagent was prepared and submitted to the hydroalkylation reaction conditions (eq 1):



(1)

Approximately one D atom was incorporated into the product, as determined by ^{1}H NMR spectroscopy, which is consistent with the hydrogen added to the alkene originating from the organozinc reagent. Interestingly, incorporation of D was observed at both the methyl and methine positions, indicating that insertion of the alkene occurs from either side, but the resultant Pd−alkyl species most likely rearranges via β-hydride elimination to the more stable π-benzyl intermediate (**D** in Scheme 1).

In conclusion, we have described an alternative method for the formation of sp^3−sp^3 C−C 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 species, which is trapped by the styrene. An interesting aspect of this process is that the alkene is formally reduced under oxidative conditions. Future work will focus on expanding the scope of coupling partners that can be utilized in this process and development of an enantioselective variant.

Acknowledgment. This work was supported by the National Institutes of Health (NIGMS RO1 GM3540). We are grateful to Johnson Matthey for the gift of various Pd salts.

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.

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JA908545B