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Mild and efficient formation of symmetric biaryls via Pd(II) catalysts and Cu(II) oxidants

Jay P. Parrish, Vincent L. Flanders, Ryan J. Floyd and Kyung Woon Jung*

Department of Chemistry, University of South Florida, 4202 E. Fowler Avenue, Tampa, FL 33620-5250, USA Received 22 June 2001; revised 4 September 2001; accepted 10 September 2001

Abstract—Described herein is a mild and efficient palladium-catalyzed synthesis of symmetric biaryls from organostannanes. This methodology offers products rapidly in very high yields. © 2001 Elsevier Science Ltd. All rights reserved.

Carbon–carbon bond formation is an essential process in organic chemistry. Of particular importance to natural product synthesis are reactions that form new *sp* and *sp*² bonds. Examples of these include Stille, Heck, Suzuki, and Sonogashira couplings.¹ Interestingly, many of these palladium-catalyzed carbon–carbon bond-forming reactions have been known to give an oxidative dimerization side product.² This 'homocoupling' reaction has been developed into a useful tool for the preparation of a number of symmetric materials such as biaryls, 1,3-dienes and 1,3-diynes.^{3,4}

Recently, we described a modification of the Heck reaction that employs aryl stannanes as surrogates for aryl halides.⁵ This methodology offers a milder approach to C–C bond formation, delivering di- and trisubstituted olefins at room temperature in short reaction times. During the development of the reaction parameters, aryl–aryl dimerization products were noticed. These products formed via a standard homocoupling reaction and often competed directly with desired olefin formation. More importantly, it was found that when the reaction was run without adding any olefin source, homocoupling was the exclusive product.

Reported herein is the development of the palladiumcatalyzed homocoupling reaction into a useful C–C bond-forming tool, which prepares symmetric biaryls, dienes and diynes in high yields and very short reaction times. Likewise, our methodology allows for the synthesis of certain sterically hindered biphenyl systems.

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First, we undertook reaction optimization using commercially available tributylphenyltin 1 as the homocoupling partner. It was found that $Pd(OAc)_2$ and Pd_2dba_3 were the most effective catalysts for this transformation, providing biphenyl 2 in 94% yield or greater in less than 15 minutes. $Pd(OAc)_2$ was the catalyst of choice due to its lower cost and greater air and water stability when compared to Pd_2dba_3 . Catalyst amounts as low as 1 mol% could be used with little drop off in yield and reaction time. Additionally, it was found that THF was the optimal solvent for the reaction. Other solvents like EtOH, DMF, and benzene did not work well.

Of the catalyst reoxidants screened, $CuCl_2$ was the most effective. FeCl₃ gave lower yields, and MnO₂ was completely inactive. As shown in Table 1, the reaction of **1**

Table 1. Effect of reoxidant amount on reaction yield

PhSnI 1	Bu ₃ — Pd(OAc) ₂ , 0 — THF, 23	Pd(OAc) ₂ , CuCl ₂ THF, 23 °C	
entry	amount of CuCl ₂	time	yield
1	0 equiv.	24 h	20%
2	0.5 equiv.	24 h	45%
3	1.0 equiv.	2 h	94%
4	2.0 equiv.	15 min	97%
5	3.0 equiv.	15 min	96%
1	CuCl ₂ , THF 23 °C, 24 h	→ Z (No re	2 action)

Keywords: biaryls; catalysis; dienes; diynes; homocoupling.

^{*} Corresponding author. Tel.: 1-813-974-7306; fax: 1-813-974-1733; e-mail: kjung@chuma.cas.usf.edu

with varying amounts of $CuCl_2$ gave us insight into the course of the reaction. With submolar amounts of the reoxidant, yields of biphenyl were retarded and the reaction did not go to completion (entry 2). Additionally, 1 equivalent of $CuCl_2$ provided **2** in high yield at a reasonable rate (entry 3). From these results, 2 equivalents of the reoxidant appears to be optimal in terms of reaction time and yield (entry 4). Adding more $CuCl_2$ does not provide any increase in product formation (entry 5).

With these results in hand, several control experiments were performed to glean additional insight. The $Pd(OAc)_2$ catalyst delivers the product in low yield when run in the absence of reoxidant (entry 1). Furthermore, many examples of Cu(I) and Cu(II) initiated oxidative dimerizations of organostannanes have been reported providing homocoupling products.⁴ In order to determine the role of CuCl₂ in our methodology, **1** was treated with only the reoxidant and no sign of biphenyl was detected after 24 hours.

Next, as shown in Table 2, synthesis of various biphenyls proceeded at room temperature in good yields and in short reaction times. Sterically encumbered (2-methoxyphenyl)-tributylstannane gave the corresponding biaryl in 95% after 7 min, showing little steric effects from the *ortho* methoxy group (entry 1).⁶ Additionally, electron rich (3,4-dimethoxyphenyl)-tributylstannane was an efficient substrate, providing the coupled compound in 93% yield (entry 2).⁷

Next, stannanes with electron withdrawing groups were screened. (4-Trifluoromethylphenyl)tributylstannane offered the coupled biphenyl in 94% after 20 min (entry 3). Also, air- and moisture-sensitive (4-tributylstannyl)benzaldehyde was found to give 77% of desired biphenyl after 3 h (entry 4). Despite careful handling, the aldehyde moiety on the phenyl ring reacted with atmospheric moisture to give both acid and alcohol side products resulting from the Cannizzaro reaction.

These results demonstrate that our methodology offers one of the mildest conditions for symmetric biphenyl formation to date. With the exception of a few examples, reaction conditions are not moisture sensitive and an inert atmosphere was not required. Furthermore, stannanes with varying degrees of electron density and steric hindrance worked well with our conditions.

Having obtained excellent results with biaryl formation, we next focused our attention on coupling of other stannane classes as shown in Table 3. First, we screened heterocyclic stannanes, and 2,2'-bipyridine was synthesized from its corresponding stannane in 89% yield after 1 h (entry 1). Next, 2-(tributylstannyl)thiophene was screened and found to give high yields of the biaryl in 25 min (entry 2). Additionally, 2-(tributylstannyl)furan delivered 2,2'-bifuran in 91% after only 15 min (entry 3). We found this material was air-sensitive as reported by Larock.⁸

We then turned our attention to the synthesis of 1,3dienes and 1,3-diynes. First, (E)-2-(tributylstannyl)styrene was subjected to our conditions, and after 2.5 h gave 93% of (1E,3E)-1,4-diphenyl-1,3-butadiene (entry 4). Based on ¹H NMR analysis, only this isomer was detected. Next, 1,4-diphenylbutadiyne was prepared from its corresponding stannane in 94% after 25 min (entry 5). Our synthesis of dienes and diynes is both mild and efficient, and offers access to Diels–Alder precursors and other important materials.⁹

Based on our observations, the proposed catalytic cycle is shown in Scheme 1. The initial step involves transmetallation of the stannane by a Pd(II) catalyst. The intermediate RPdX then undergoes a second

	ArSnBu ₃ 3 Pd(OAc) ₂ , THF, 23	CuCl₂ 3 °C ►	Ar—Ar 4
entry	stannane	time	yield
1	OMe SnBu ₃	7 min	95%
2	MeO MeO-SnBu ₃	30 min	93%
3	F ₃ C-SnBu ₃	20 min	94%
4	OHC - SnBu ₃	3 h	77%

Table 2. Formation of biphenyls from aryl stannanes

Table 3. Formation of biaryls, dienes, and diynes fromstannanes

		RSnBu ₃ Pd(OA THI 5	AC) ₂ , CuCl ₂ → R−F F, 23 °C → R−F 6	2
-	entry	stannane	time	yield
	1	N SnBu ₃	1 h	89%
	2	S SnBu ₃	25 min	99%
	3	O SnBu ₃	15 min	91%
	4	Ph SnBu ₃	2.5 h	93%
	5	Ph SnBu ₃	25 min	94%



Scheme 1. Proposed catalytic cycle for homocoupling.

transmetallation with a second mole of stannane to provide RPdR. This then undergoes a reductive elimination to provide the homocoupled product and Pd(0). The Cu(II) additive then oxidizes the palladium species back to Pd(II), which reenters the cycle and continues the process. Our methodology has proven to be milder and more rapid than others and does not require additional additives to facilitate the coupling. We attribute this factor to the relative ease of transmetallation with the Pd(II) catalyst and the rapid reoxidation that the Cu(II) provides.

In summary, we have developed a mild and efficient method for the oxidative dimerization of organostannanes. Our methodology offers rapid access to symmetric biaryls along with dienes and diynes in high yields and short reaction times.

Acknowledgements

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- 7. Representative experimental procedure: Tributylphenyltin (0.16 mL, 0.5 mmol, 1 equiv.) was dissolved in tetrahydrofuran (2.5 mL, 0.2 M solution) and rapid stirring was begun. Into the clear solution was added CuCl₂ (134 mg, 1.0 mmol, 2 equiv.) and Pd(OAc)₂ (11 mg, 0.05 mmol, 0.1 equiv.). The suspension was stirred at room temperature for 5 min, after which the mixture was diluted with diethyl ether (10 mL), filtered through a plug of neutral alumina, and washed with diethyl ether (3×10 mL). The filtrate was then concentrated in vacuo, and followed by flash chromatography (30 g SiO₂, eluted with petroleum ether (100 mL), then 9:1 hexanes/EtOAc) to afford biphenyl (35 mg, 97%).
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