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Highly efficient synthesis of 1,2-disubstituted acetylenes derivatives from the cross-coupling reactions of 1-bromoalkynes with organoalane reagents

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ABSTRACT

A Highly efficient route for the synthesis of 1,2-disubstituted acetylene derivatives has been developed by palladium catalyzed cross-couplings of alkynyl halides with (hetero)aryl aluminium reagents under mild conditions. This has given corresponding cross-coupling products good to excellent isolated yields of up to 99%. The aryls bearing electron-donating or electron-withdrawing groups in either alkynylhalides or arylaluminum substrates gave cross-coupling products good yields. This process was simple and easily performed, which provides an efficient method for the synthesis of 1,2-disubstituted acetylenes derivatives. On the basis of the experimental results, a possible catalytic cycle has been proposed.

1. Introduction

Palladium-catalyzed cross-coupling reactions are found to be extremely powerful in constructing new C–X (X = C, N, O, etc.) bonds [1]. Among these reactions, Sonogashira coupling reaction [2], which was discovered in the early 1970s has been emerged as one of the most potent transformations [3]. The corresponding acetylenic products are important synthetic units in the preparation of potential bioactive compounds [4], new materials [5], and natural products as well [6]. Concerning the importance of this reaction, researchers have directed their efforts towards the development of more efficient or single metal catalyst systems, milder reaction conditions, and other such objectives during the past decades [7]. Although, these efforts have provided alternative methods for the synthesis of alkynes, these reactions still suffer from excess bases, co-catalysts, high temperature, relatively long reaction times, and the special reaction medium. The development of more efficient and atom economical approaches for the synthesis of alkynes remains as desirable work. Aryl halides, especially aryl iodides and bromides, and alkynes are the preferred coupling partners in these reactions. Particularly, 1-bromoalkynes, which is easily synthesized from terminal alkynes, has been widely applied in cross-coupling reactions [8]. Recently, the synthesis of 1, 2-disubstituted acetylenes by copper or nickel-catalyzed cross-coupling of Grignard reagents with alkynyl bromides has been described [9]. In addition to the above reagents, organoalane reagents have been extensively used as nucleophiles for organic reactions [10].

In recent times, metal-catalyzed cross-coupling reactions of electrophiles with alkynylmetallic reagents have provided an alternative route for the preparation of alkyne compounds [11]. Previous studies show that organoalane reagents are a highly efficient nucleophiles for cross-coupling reactions with aromatic halides [12] or benzylic halides. [13] While, the synthesis based on direct coupling of alkynyl halide with organoalane reagents using palladium as catalyst is developed rarely. To continue our efforts in developing coupling reactions using reactive organometallic reagents [9b,10c,13,14], and develop a more efficient and convenient procedures for the preparation of 1, 2-disubstituted acetylenes, herein, we wish to report a new method for the synthesis of 1, 2-disubstituted acetylenes via palladium-catalyzed cross-couplings between 1-bromoalkynes and organoalane reagents in the presence of $Pd(PPh_3)_4$ (1 mol%) and DPPE (2 mol%) at 60 °C. Notably, in our procedure palladium is used as the single catalyst and neither base nor additive is needed to obtain 1,2-disubstituted acetylenes

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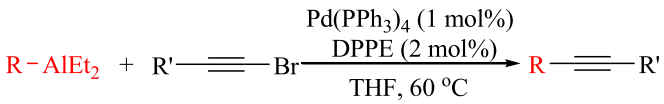


Scheme 1. Palladium-catalyzed cross-coupling reactions of 1-bromoalkyne derivatives with organoalane nucleophiles.

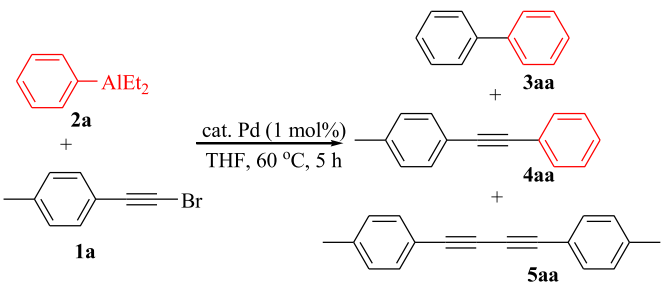
in good to excellent isolated yields (Scheme 1).

2. Results and discussion

In our initial research, we performed the reaction between 1-(2-bromoethynyl)-4-methylbenzene (p-$MeC_6H_4C{\equiv}CBr$)(**1a,** 0.5 mmol) with diethylphenylaluminum ($C_6H_5AlEt_2$) (**2a,** 1.0 mmol) in the presence of $Pd(OAc)_2$ (1 mol%) in THF at 60 °C for 5 h. To our delight, 16% isolated yield of the desired 1-methyl-4-(2-phenylethynyl)-benzene was obtained (**4aa**) (Table 1, entry 1). Then, different palladium salts were examined (Table 1, entries 2–6). Notably, $Pd(PPh_3)_4$ gave the best result among the tested palladium salts (Table 1, entry 3). The product ratio is about 33:66:1 in favor of the coupling product **4aa**. To further understand the nature of this catalysis, we tested the reaction of **1a** with **2a** under various conditions and the results are listed in Tables 1 and 2. The effect of various ligands in the generation of **4aa** using $Pd(PPh_3)_4$ as catalyst is shown in Table 1 (Table 1, entries 7–11). Although the highest isolated yield of coupling product **4aa** (82% yield) was obtained when DPPP was used, the product ratio is only about 16:78:6 (Table 1, entry 9). While, the isolated yield of coupling product **4aa** was only 74% when using DPPE as ligand, but the product ratio is up to 9:90:1 in favor of the coupling product **4aa**. Other ligands such as PPh_3, PCy_3 and DPPB were less effective than DPPE (Table 1, entries 7, 8, 10).

The molar ratio of metal and ligand was examined. It was found that a $Pd(PPh_3)_4$/DPPE ratio of 1.0/2.0 gave the coupling product **4aa** in good isolated yield of 74% with a ratio of 9:90:1 in favor of the coupling product **4aa** (Table 2, entry 2). A brief examination of the influence of solvent on the isolated yield of the coupling product **4aa** and reaction selectivity revealed that THF was the solvent of choice. In toluene, hexane, or DME, the isolated yield of the coupling product **4aa** was low and reaction selectivity was poor (Table 2, entries 5–7). Further studies indicated that the catalyst loading dramatically influenced the isolated yield of the coupling product **4aa**. It was found that the most favorable catalyst loading is 1 mol% $Pd(PPh_3)_4$/2 mol% DPPE (Table 2, entry 2). It is particularly interesting that the addition of K_2CO_3 as a base could somewhat decrease the isolated yield of the coupling product **4aa** and reaction selectivity (Table 2, entry 8). The desired coupling product **4aa** was obtained in 77% isolated yield with good selectivity for the 1,2-disubstituted acetylenes **4aa** when **1a** and **2a** (molar ratio 0.5: 0.8) were stirred in THF in the presence of $Pd(PPh_3)_4$ at 60 °C for 5 h (Table 2, entry 9). It is worth noting that the desired coupling product **4aa** was obtained in 77% isolated yield with excellent selectivity when the reaction time is shortened from 5 h to 4 h (Table 2, entry 12). However, the isolated yield of the coupling product **4aa** and reaction selectivity were decreased when the reaction time was extended to 6 h (Table 2, entry 11). Although excellent selectivity can be obtained at room temperature, the isolated yield of the coupling product **4aa** is only 8% (Table 2, entry 13). Extensive screening showed that the optimized coupling conditions were 1 mol% $Pd(PPh_3)_4$/2 mol% DPPE, 0.5 mmol **1a**, 0.8 mmol **2a** in THF at 60 °C for 4 h (Table 2, entry 9).

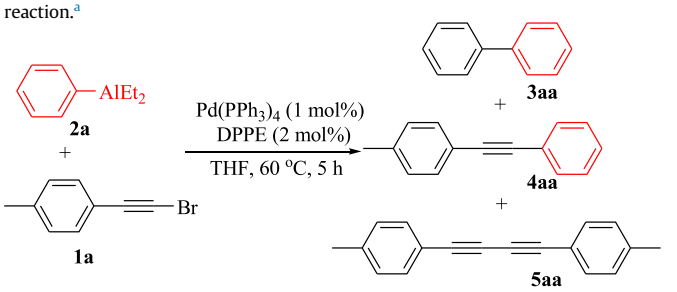
Table 1
Effect of the palladium salt and the ligand on the cross-coupling reaction.[a]



Entry	Cat.	Ligand	Yield **4aa** (%)[b]	**3aa/4aa/5aa**[c]
1	$Pd(OAc)_2$	–	16	55/42/3
2	$Pd(PPh_3)_2Cl_2$	–	37	45/51/4
3	$Pd(PPh_3)_4$	–	78	33/66/1
4	$PdCl_2$	–	16	50/44/6
5	$Pd(dppf)Cl_2$	–	43	41/56/3
6	Pd^{2+}(acac)	–	30	47/48/5
7	$Pd(PPh_3)_4$	PCy_3	43	29/67/4
8	$Pd(PPh_3)_4$	PPh_3	50	37/59/4
9	$Pd(PPh_3)_4$	DPPP	82	16/78/6
10	$Pd(PPh_3)_4$	DPPB	55	18/78/4
11	$Pd(PPh_3)_4$	DPPE	74	9/90/1

[a] **1a**/**2a**/Cat/Ligand = 0.5/1.0/0.005/0.01 mmoL, THF 2 mL.
[b] Isolated.
[c] Ratio of isolated yield.

Table 2
Effect of the solvent and the molar ratio of $Pd(PPh_3)_4$/DPPE on the cross-coupling reaction.[a]



Entry[a]	**2a**(mmol)	Solvent	Yield **4aa** (%)[b]	**3aa/4aa/5aa**[c]
1[d]	1	THF	51	21/74/5
2[e]	1	THF	74	9/90/1
3[f]	1	THF	49	13/78/8
4[g]	1	THF	60	7/90/3
5	1	hexane	37	32/64/4
6	1	toluene	30	23/75/2
7	1	DME	47	34/63/3
8[h]	1	THF	38	3/63/34
9	0.8	THF	77	9/90/1
10	0.5	THF	31	5/79/16
11[i]	0.8	THF	67	10/78/12
12[j]	0.8	THF	77	3/96/1
13[k]	0.8	THF	8	1/98/1

[a] **1a**/$Pd(PPh_3)_4$/Ligand = 0.5/0.005/0.01 mmol, 60 °C, 5 h.
[b] Isolated.
[c] Ratio of isolated yield.
[d] $Pd(PPh_3)_4$/DPPE = 1/1.
[e] $Pd(PPh_3)_4$/DPPE = 1/2.
[f] $Pd(PPh_3)_4$/DPPE = 1/3.
[g] $Pd(PPh_3)_4$/DPPE = 0.01/0.02 mmol.
[h] 2.0 equiv K_2CO_3.
[i] 6 h.
[j] 4 h.
[k] r.t, 4 h.

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