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A 2,2′-bipyridine-palladacycle catalyzed the coupling of arylboronic acids with nitroarenes

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ABSTRACT

A novel palladium-catalyzed protocol for the synthesis of diaryl ethers derivatives has been developed. In the presence of 2,2′-bipyridine-cyclopalladated ferrocenylimine complex (Cat. Ic), diaryl ethers were selectively generated by adjusting reaction parameters through the coupling of arylboronic acids and nitroarenes with yields ranging from poor to good. The efficiency of this reaction was demonstrated by its compatibility with a range of groups. Moreover, the rigorous exclusion of air or moisture was not required in these transformations.

1. Introduction

Diaryl ethers consist of an important building block in the synthesis of natural products and pharmacological active compounds as well as polymer science target molecules.[1,2] Traditionally, the synthesis of such ethers has been accomplished via Ullmann cross-couplings, which employed aryl halides and sodium or potassium aryloxides in the presence of a stoichiometric (or greater) amount of a copper species at elevated temperatures (125–220 °C).[3] Unfortunately, these relatively harsh conditions were not well tolerated for many synthetic applications. Consequently, several modifications to the original Ullmann conditions have been developed, such as rhodium,[4] palladium,[5] copper,[6] and iron[7] catalytic systems, etc. Generally aryl halides were employed as coupling partners in these improved methods. However, several problems still remain, such as high catalyst loading, elevated temperature as well as environmentally unfriendly[8] when aryl halides were used.

Organoboron reagents are ubiquitous coupling partners due to their advantages of stability to air or moisture and good functional group tolerance.[9] To the best of our knowledge, only two examples have been described in which arylboronic acids were coupled to nitroarenes catalyzed by Rhodium[10] and copper[11] to afford diaryl ethers. However, there was no report about this transformation catalyzed by palladium when nitroarenes acted as coupling partners. Thus, the development of a method that allows a general synthesis of diaryl ethers under mild conditions, while increasing the scope of applicable substrates, would be of significant interest.

In our previous report, we have developed a 2,2′-bipyridine-palladacycle Ic catalyzed arylation of aldehydes to produce secondary alcohols in good yields in neat water using a weak acid as additive (Scheme 1, Eq. 1).[12] As continuation of our interest, herein we would like to describe the phosphine-free palladacyclic complex Ic catalyzed selective synthesis of unsymmetrical diaryl ethers by adjusting reaction parameters through the coupling of arylboronic acids and nitroarenes under basic condition (Scheme 1, Eq. 2). The results showed that palladacycle Ic exhibited high efficiency with low catalyst loading.

2. Results and discussion

Previous studies regarding the synthesis of 4-(nitrophenyl)(phenyl)-methanol **4aa** from the coupling of 4-nitrobenzaldehyde **1a** with phenylboronic acid **2a** (Scheme 2) in the presence of palladacyclic complex Ic suggested 4-phenoxybenzaldehyde **3aa** occurred as a secondary product during the catalytic transformation. Based on this discovery, we began to realize the selective generation of **3aa** in the presence of Ic by

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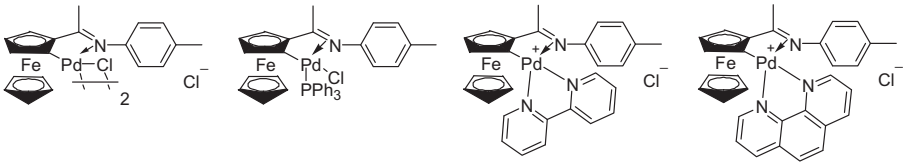
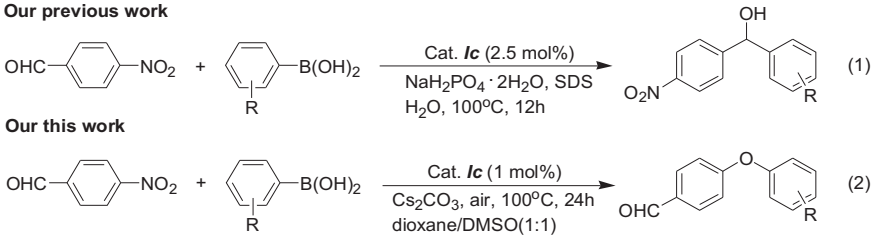
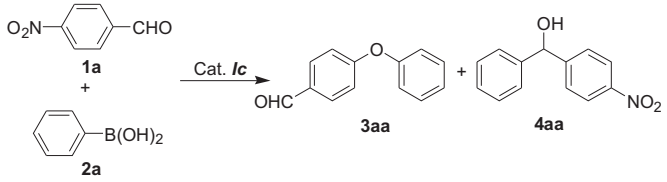




Scheme 1. Synthesis of diaryl alcohols and diaryl ethers catalyzed by Ic.

adjusting reaction parameters including palladium source, base, and solvent.

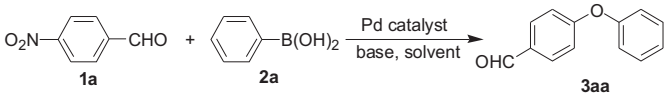


Scheme 2. Reaction of 4-nitrobenzaldehyde with phenylboronic acid.

Initial experiments were carried out by the reaction of 4-nitrobenzaldehyde **1a** with phenylboronic acid **2a** in the presence of catalyst Ic (1 mol %) when the combination of Cs_2CO_3 and DMSO was employed. To our delight, the desired product 4-phenoxybenzaldehyde **3aa** was smoothly afforded in 30% yield (Table 1, entry 1). Then we next examined the role of the solvent in this transformation. We discovered that by employing dioxane as a cosolvent in addition to DMSO (1:1), we were able to obtain biaryl ether **3aa** in consistently highest yield as compared to reactions conducted in other pure solvents, such as dioxane, toluene, DMF, CH_3NO_2, THF, and CH_3OH (Table 1, entries 1–8). As for bases tested, the use of K_2CO_3, Na_2CO_3, $CsF2H_2O$, and *t*-BuOK as bases resulted in lower yield of **3aa** (Table 1, entries 9–12 vs 8). The combination of dioxane/DMSO (1:1) and K_3PO_4 delivered **3aa** in 78% yield (Table 1, entry 13).

Among the palladium sources used including palladacyclic complex Ia–Id, $Pd(OAc)_2$, $Pd(acac)_2$, and $Pd_2(dba)_3$, 2,2′-bipyridine-palladacycle Ic exhibited the highest catalytic reactivity affording a 86% yield (Table 1, entries 8, 14–19). It is worth noting that $Pd(OAc)_2$ combined with bipyridine could be used for this transformation (Table 1, entry 20), but the yield is lower than those. So the catalyst Ic emerged as the best choice of catalyst precursors. The yields of the product decreased with decreasing the catalyst loading from 1 mol % to 0.5 mol % (Table 1, entry 21). When shortening the reaction time or reducing the reaction temperature, the yields dropped obviously (Table 1, entries 22 and 23). The yield of diaryl ether decreased with decreasing amount of phenylboronic acid (Table 1, entry 24). The excess amounts of phenylboronic acid were consumed due to the homo-coupling and protodeboronation side reactions.[13] In addition, we found that 4-phenoxybenzaldehyde (**3aa**) was isolated in a poor yield under a N_2 atmosphere (Table 1, entry 25). Furthermore, even lower yield was obtained when the

Table 1
Effect of catalysts, bases, and solvents on the selective generation of **3aa**[a]



Entry	Palladium source	Base	Solvent	Yield[b] (%)
1	Ic	Cs_2CO_3	DMSO	30
2	Ic	Cs_2CO_3	Dioxane	21
3	Ic	Cs_2CO_3	Toluene	25
4	Ic	Cs_2CO_3	DMF	55
5	Ic	Cs_2CO_3	CH_3NO_2	Trace
6	Ic	Cs_2CO_3	THF	Trace
7	Ic	Cs_2CO_3	CH_3OH	Trace
8	Ic	Cs_2CO_3	Dioxane/DMSO (1:1)	86
9	Ic	K_2CO_3	Dioxane/DMSO (1:1)	25
10	Ic	Na_2CO_3	Dioxane/DMSO (1:1)	Trace
11	Ic	$CsF·2H_2O$	Dioxane/DMSO (1:1)	10
12	Ic	*t*-BuOK	Dioxane/DMSO (1:1)	22
13	Ic	K_3PO_4	Dioxane/DMSO (1:1)	78
14	Ia	Cs_2CO_3	Dioxane/DMSO (1:1)	57
15	Ib	Cs_2CO_3	Dioxane/DMSO (1:1)	47
16	Id	Cs_2CO_3	Dioxane/DMSO (1:1)	75
17	Ia/bpy (1:4)	Cs_2CO_3	Dioxane/DMSO (1:1)	60
18	$Pd(acac)_2$	Cs_2CO_3	Dioxane/DMSO (1:1)	58
19	$Pd_2(dba)_3$	Cs_2CO_3	Dioxane/DMSO (1:1)	53
20	$Pd(OAc)_2$/bpy (1:2)	Cs_2CO_3	Dioxane/DMSO (1:1)	37
21[c]	Ic	Cs_2CO_3	Dioxane/DMSO (1:1)	58
22[d]	Ic	Cs_2CO_3	Dioxane/DMSO (1:1)	68
23[e]	Ic	Cs_2CO_3	Dioxane/DMSO (1:1)	77
24[f]	Ic	Cs_2CO_3	Dioxane/DMSO (1:1)	56
25[g]	Ic	Cs_2CO_3	Dioxane/DMSO (1:1)	12
26[h]	Ic	Cs_2CO_3	Dioxane/DMSO (1:1)	5
27[i]	Ic	Cs_2CO_3	Dioxane/DMSO (1:1)	80
28[j]	Ic	Cs_2CO_3	Dioxane/DMSO (1:1)	85

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), Pd catalyst (1 mol %), base (1.0 mmol), solvent (2.0 mL), 100 °C, air, 24 h.
[b] Isolated yield.
[c] With the catalyst loading of 0.5 mol %.
[d] For 18 h.
[e] At 80 °C.
[f] Compound **2a** (1.0 mmol) was used.
[g] Under N_2.
[h] In dry dioxane/DMSO (1:1) (2.0 mL), under N_2.
[i] In dry dioxane/DMSO (1:1) (2.0 mL), under air.
[j] 5 equiv of $^{18}OH_2$ was added to dry dioxane/DMSO (1:1) (2.0 mL), **3aa**-^{18}O was formed in 6% yield.