Palladium-Catalyzed Reaction of Arylboronic Acids with Aliphatic Nitriles: Synthesis of Alkyl Aryl Ketones and 2-Arylbenzofurans

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Received: 31.03.2013; Accepted after revision: 29.04.2013

Abstract: An efficient palladium-catalyzed addition of arylboronic acids to aliphatic nitriles has been developed, providing a wide range of alkyl aryl ketones in moderate to excellent yields. It is noteworthy that sequential addition and intramolecular annulation reaction of 2-(2-hydroxyphenyl)acetonitriles with arylboronic acids are also conducted smoothly to afford 2-arylbenzofurans in good yields under the standard conditions.

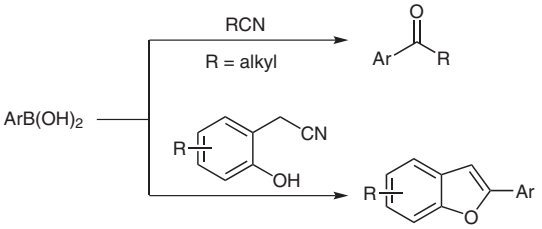
Key words: palladium, aliphatic nitriles, arylboronic acids, alkyl aryl ketones, 2-arylbenzofurans

Generally, the nitrile group is inert in organometallic reactions and thus acetonitrile or benzonitrile are usually used as solvents or ligands in many metal-catalyzed reactions. However, transformations of nitriles play an important role in both the laboratory and industry due to their well-recognized chemical versatility.[1] Transition-metal-catalyzed insertion of nitriles offers an attractive route for the creation of novel carbon–carbon and carbon–heteroatom bonds. Recently, a few examples of rhodium,[2] palladium,[3] and nickel-catalyzed[4] additions of arylboronic acids to nitriles became known; however, the substrate scope is usually limited to aromatic nitriles, and activated nitriles [e.g., cyanoformate[2b] and (benzyl-/arylsulfonyl)acetonitriles[2c]]. Compared to the reactions of aromatic nitriles, one of the main problems encountered in nucleophilic addition reactions of aliphatic nitriles is the insufficient electrophilic activation to perform the addition. On the other hand, aliphatic nitriles tend to be deprotonated in the presence of palladium catalysts leading to α-arylation products.[5] Thus, the addition reaction of aliphatic nitriles is generally more challenging than that of aromatic nitriles.

The insertions of nitrile groups by Grignard reagents[6] and organolithium reagents[7] are powerful tool for the construction of aryl ketones and heterocyclic compounds; however, the rigorous conditions have sometimes restricted their applications and the variety of substrates. Compared to the reactions using Grignard reagents and organolithium reagents, organoboron reagents are highly regarded due to their advantages of stability to air and moisture as well as good functional group tolerance.[8]

SYNTHESIS 2013, 45, 2241–2244
Advanced online publication: 11.06.2013
DOI: 10.1055/s-0033-1338909; Art ID: SS-2013-F0255-OP

As part of the continuing efforts in our laboratory towards the development of novel transition metal-catalyzed reactions under participation of organoboron reagents,[9] we herein report a new method for the synthesis of alkyl aryl ketones by palladium-catalyzed addition of arylboronic acids to aliphatic nitriles (Scheme 1). Furthermore, the scope of the developed approach is successfully explored toward one-step synthesis of 2-arylbenzofurans via sequential addition and intramolecular annulation reaction.

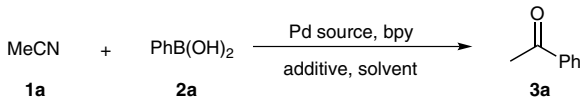


Scheme 1 Palladium-catalyzed reaction of arylboronic acids with aliphatic nitriles

To optimize the reaction conditions, initial studies were concentrated on treatment of acetonitrile (**1a**) with phenylboronic acid (**2a**) as a model reaction. As shown in Table 1, the best result was observed with palladium(II) acetate as the catalyst in the presence of 2,2′-bipyridine (bpy) in this transformation (Table 1, entry 9). In contrast, the yield of the desired product **3a** was decreased to some extent when the reactions were carried using other palladium sources in tetrahydrofuran (entries 1–7). On the other hand, the effect of solvents was also tested. Among all the solvents screened (e.g., THF, 1,4-dioxane, DMSO, DMF, toluene, and xylenes), tetrahydrofuran was determined to be the most effective medium for the generation of **3a** (entries 9–14). Then, various acids were screened as the additive to examine their effect on the reaction. Screening revealed that various additives, including acetic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, and benzoic acid were less effective than trifluoroacetic acid (entries 15–18). It was one of the major reasons that the use of trifluoroacetic acid as additive facilitates the generation of highly cationic $[Pd(II)O_2CCF_3]$[10] species to form palladium–aryl complexes through transmetalation of arylboronic acids.

Having the optimized reaction conditions in hand, we explored the substrate scope of aliphatic nitriles and arylboronic acids for this transformation (Table 2). Initially, the

Table 1 Screening for Optimal Reaction Conditions[a]



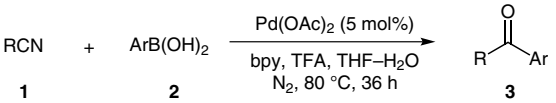
Entry	Pd source	Additive	Solvent	Yield (%)[b]
1	$Pd(PPh_3)_4$	CF_3CO_2H	THF	trace
2	$Pd_2(dba)_3$	CF_3CO_2H	THF	trace
3	$Pd(dba)_2$	CF_3CO_2H	THF	trace
4	$PdCl_2(dppe)$	CF_3CO_2H	THF	trace
5	$PdCl_2(PPh_3)_2$	CF_3CO_2H	THF	trace
6	$PdCl_2$	CF_3CO_2H	THF	trace
7	$Pd(acac)_2$	CF_3CO_2H	THF	48
8	$Pd(TFA)_2$	CF_3CO_2H	THF	83
9	$Pd(OAc)_2$	CF_3CO_2H	THF	88
10	$Pd(OAc)_2$	CF_3CO_2H	1,4-dioxane	71
11	$Pd(OAc)_2$	CF_3CO_2H	DMSO	25
12	$Pd(OAc)_2$	CF_3CO_2H	DMF	0
13	$Pd(OAc)_2$	CF_3CO_2H	toluene	41
14	$Pd(OAc)_2$	CF_3CO_2H	xylenes	37
15	$Pd(OAc)_2$	CF_3CO_2H	THF	12
16	$Pd(OAc)_2$	$PhCO_2H$	THF	14
17	$Pd(OAc)_2$	CF_3SO_3H	THF	72
18	$Pd(OAc)_2$	$4\text{-}MeC_6H_4SO_3H$	THF	42

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.8 mmol), Pd source (5 mol%), bpy (10 mol%), additive (10 equiv), solvent (2 mL), H_2O (0.4 mL), 80 °C, 36 h, N_2.
[b] Isolated yield.

reaction between acetonitrile (**1a**) and various arylboronic acids **2b–j** was investigated under the standard conditions (Table 2, entries 1–10). As shown in Table 2, the monosubstituent positions at the aryl moiety of arylboronic acids were evaluated, and the results demonstrated that steric effects of substituents affected the yields of the reaction to some extent. For example, the coupling of **1a** with 4-, 3- and 2-tolylboronic acid was examined, 89% of **3b** and 83% of **3c** were isolated, while the yield of **3d** was decreased to 51% (entries 2–4). In general, the arylboronic acids possessing electron-donating groups afforded a higher yield than electron-withdrawing arylboronic acids. For example, substrates **2e** and **2f**, bearing a 4-methoxyphenyl or 4-chlorophenyl group, reacted with substrate **1a** to give the corresponding products in 93% and 75% yield, respectively (entries 5, 6). It is noteworthy that biarylboronic acids such as 4-phenylphenylboronic acid (**2h**), 1-naphthylboronic acid (**2i**), and 2-naphthylboronic acid (**2j**) also afforded the corresponding **3h**, **3i**, and **3j** in 81%, 87%, and 82% yield, respectively (entries 8–10).

Subsequently, other aliphatic nitriles bearing α-alkyl substituents (e.g., **1b–e**) or α-aryl substituents (e.g., **1f–i**) were evaluated (Table 2, entries 11–18). The results disclosed that primary α-alkylnitriles, such as pentanenitrile (**1b**) and octanenitrile (**1c**), are suitable substrates, leading to the corresponding products in good yields (entries 11, 12). The transformation of secondary α-alkylnitriles, such as isobutyronitrile (**1d**) or cyclopropylnitrile (**1e**) with **2a** also proceeded successfully to provide the respective products in 84% and 83% yield, respectively (entries 13, 14). Excellent yields were observed when α-aryl substituted nitriles **1f–h** bearing either an electron-rich phenyl or electron-deficient phenyl group were used as substrate (entries 15–17). Interestingly, treatment of 2-(2-hydroxyphenyl)acetonitrile (**1i**) with **2a** under the standard condi-

Table 2 Palladium-Catalyzed Synthesis of Alkyl Aryl Ketones[a]



Entry	1	R	2	Ar	Product	Yield (%)[b]
1	**1a**	Me	**2a**	Ph	**3a**	88
2	**1a**	Me	**2b**	$4\text{-}MeC_6H_4$	**3b**	89
3	**1a**	Me	**2c**	$3\text{-}MeC_6H_4$	**3c**	83
4	**1a**	Me	**2d**	$2\text{-}MeC_6H_4$	**3d**	51
5	**1a**	Me	**2e**	$4\text{-}MeOC_6H_4$	**3e**	93
6	**1a**	Me	**2f**	$4\text{-}ClC_6H_4$	**3f**	75
7	**1a**	Me	**2g**	$4\text{-}BrC_6H_4$	**3g**	67
8	**1a**	Me	**2h**	$4\text{-}PhC_6H_4$	**3h**	81
9	**1a**	Me	**2i**	1-naphthyl	**3i**	87
10	**1a**	Me	**2j**	2-naphthyl	**3j**	82
11	**1b**	*n*-Bu	**2a**	Ph	**3k**	94
12	**1c**	$n\text{-}C_7H_{15}$	**2a**	Ph	**3l**	96
13	**1d**	*i*-Pr	**2a**	Ph	**3m**	84
14	**1e**	*c*-Pr	**2a**	Ph	**3n**	83
15	**1f**	Bn	**2a**	Ph	**3o**	97
16	**1g**	$4\text{-}MeC_6H_4CH_2$	**2a**	Ph	**3p**	92
17	**1h**	$4\text{-}O_2NC_6H_4CH_2$	**2a**	Ph	**3q**	99
18	**1i**	$2\text{-}HOC_6H_4CH_2$	**2a**	Ph	**4a**	94[c]

[a] Unless otherwise noted, reaction conditions were as follows: **1** (0.4 mmol), **2** (0.8 mmol), $Pd(OAc)_2$ (5 mol%), bpy (10 mol%), TFA (10 equiv), THF (2 mL), H_2O (0.4 mL), 80 °C, 36 h, N_2.
[b] Isolated yield.
[c] 2-Phenylbenzofuran was obtained in 94% yield.

tions afforded the unexpected 2-phenylbenzofuran (**4a**) in 94% yield instead of alkyl aryl ketone product (entry 18).

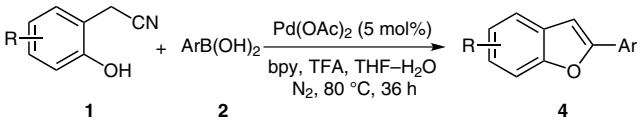
Benzofurans are abundant in numerous natural products and possess many important biological activities.[11] As an application of our chemistry, we next explored a simple and efficient approach to other 2-arylbenzofurans, which involves ketone formation from the addition of 2-hydroxyphenylacetonitriles with arylboronic acids, followed by intramolecular cyclization under mild conditions. As shown in Table 3, the electronic properties of the groups on the phenyl ring of arylboronic acids had some effect on the reaction. Electron-rich arylboronic acids with a methyl or methoxy group at the *para* position proved to be good substrates for this transformation, affording the corresponding 2-arylbenzofurans **4b** and **4c** in higher yields (Table 3, entries 2, 3). Having an electron-withdrawing substituent (e.g., fluoro, chloro, bromo, and phenyl) at the *para* position afforded a slightly lower yield of the desired products **4d**–**g** (entries 4–7). Notably, the fluoro, chloro, and bromo moieties (commonly used for cross-coupling reactions) in arylboronic acids were all tolerated and afforded a novel route to compounds **4d**–**f** in good yields, making further elaborations of the corresponding biarylbenzofuran derivatives possible.

Next, the addition reactions of several 2-hydroxyphenylacetonitriles with phenylboronic acid (**2a**) were investigated. As expected, the groups on the phenyl ring of 2-hydroxyphenylacetonitriles, such as methyl, chloro, bromo, and methoxy, were quite compatible under the optimized reaction conditions. Generally, 2-hydroxyphenylacetonitriles having an electron-donating substituent (e.g., methyl and methoxy) on the phenyl group (Table 3, entries 8, 9) gave a slightly higher yield of the desired 2-arylbenzofurans than those analogues bearing electron-withdrawing substituent (e.g., chloro and bromo; entries 10, 11).

In summary, we have developed a new catalytic protocol to synthesize alkyl aryl ketones by palladium-catalyzed addition reaction of arylboronic acids with aliphatic nitriles in moderate to excellent yields. The scope of this chemistry is successfully explored toward one-step synthesis of 2-arylbenzofurans via sequential addition and intramolecular annulation reaction. Investigations on the further applications in the future for rapidly constructing other useful heterocyclic compounds are currently underway in our laboratory.

All chemicals were either purchased or purified by standard techniques. Melting points were measured on Digital Melting Point Apparatus WRS-1B and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 MHz Bruker spectrometer (^{1}H 500 MHz and ^{13}C 125 MHz), using $CDCl_3$ or DMSO-d_6 as the solvent with TMS as the internal standard at r.t. Chemical shifts are given in δ relative to TMS, the coupling constants *J* are given in Hz. Column chromatography was performed using EM Silica gel 60 (300–400 mesh).

Table 3 Palladium-Catalyzed Synthesis of 2-Arylbenzofurans[a]



1 2 4

Entry	1	R	2	Ar	Product	Yield (%)[b]
1	**1i**	H	**2a**	Ph	**4a**	94
2	**1i**	H	**2b**	4-MeC_6H_4	**4b**	91
3	**1i**	H	**2e**	4-MeOC_6H_4	**4c**	92
4	**1i**	H	**2k**	4-FC_6H_4	**4d**	86
5	**1i**	H	**2f**	4-ClC_6H_4	**4e**	84
6	**1i**	H	**2g**	4-BrC_6H_4	**4f**	81
7	**1i**	H	**2h**	4-PhC_6H_4	**4g**	85
8	**1j**	4-Me	**2a**	Ph	**4h**	91
9	**1k**	3-MeO	**2a**	Ph	**4i**	89
10	**1l**	4-Cl	**2a**	Ph	**4j**	81
11	**1m**	4-Br	**2a**	Ph	**4k**	80

[a] Reaction conditions: **1** (0.4 mmol), **2** (0.8 mmol), $Pd(OAc)_2$ (5 mol%), bpy (10 mol%), TFA (10 equiv), THF (2 mL), H_2O (0.4 mL), 80 °C, 36 h, N_2.
[b] Isolated yield.

Alkyl Aryl Ketones 3 and 2-Arylbenzofurans 4; General Procedure

To a Schlenk tube with a magnetic stirring bar were charged the respective nitrile **1** (0.4 mmol), arylboronic acid **2** (0.8 mmol), $Pd(OAc)_2$ (5 mol%), bpy (10 mol%), TFA (10 equiv), THF (2 mL), and H_2O (0.4 mL) under N_2 atmosphere. The reaction mixture was stirred at 80 °C for 36 h. After cooling to r.t., the mixture was poured into EtOAc (5 mL), which was washed with sat. aq $NaHCO_3$ (2 × 10 mL) and then brine (1 × 10 mL). After extracting the aqueous layer with EtOAc (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), and evaporated under vacuum. The residue was purified by flash column chromatography (hexane–EtOAc) to afford the desired products **3** or **4**. All known compounds afforded analytical data identical to those reported literature previously (see Supporting Information for further details).

Acetophenone (3a)

Yield: 42.3 mg (88%); colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.1 Hz, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.4 Hz, 2 H), 2.61 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.2, 137.2, 133.1, 128.6, 128.3, 26.6.

2-Phenylbenzo[*b*]furan (4a)

Yield: 72.9 mg (94%); white solid; mp 119−120 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.4 Hz, 2 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.52 (d, *J* = 8.1 Hz, 1 H), 7.43 (t, *J* = 7.8 Hz, 2 H), 7.34 (t, *J* = 7.4 Hz, 1 H), 7.28 (t, *J* = 7.6 Hz, 1 H), 7.22 (t, *J* = 7.4 Hz, 1 H), 7.10 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0, 154.9, 130.5, 129.3, 128.8, 128.6, 125.0, 124.3, 123.0, 120.9, 111.2, 101.3.

Acknowledgment

We thank the National Natural Science Foundation of China (No. 21102105) and Natural Science Foundation of Zhejiang Province (No. LY12B02011) for financial support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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