Palladium-catalysed addition of potassium phenyltrifluoroborate to dinitriles: synthesis of diketone compounds

Xingyong Wang[a], Qingzong Wang[a], Jiuxi Chen[a], Miaochang Liu[a]*, Jinchang Ding[a,b] and Huayue Wu[a]

[a] *College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou 325035, P. R. China*

[b] *Wenzhou Vocational and Technical College, Wenzhou 325035, P. R. China*

$Pd(OAc)_2$/1,10-phenanthroline-catalysed addition of potassium phenyltrifluoroborate to aliphatic dinitriles in 2-MeTHF has been developed, achieving diphenyl diones in moderate to excellent yields. The scope of the developed approach was successfully explored toward the addition of potassium phenyltrifluoroborate to aromatic dinitriles. Additionally, a plausible pathway for the formation of the diones has been proposed.

Keywords: palladium, addition, potassium phenyltrifluoroborate, dinitriles, diketones, diphenyl diones

It is well-known that transformations of nitriles play an important role in both the laboratory and industry due to their well-recognised chemical versatility.[1] However, the nitrile group is generally inert in organometallic reactions and thus acetonitrile or benzonitrile usually participate as solvents or ligands[2] in many metal-catalysed reactions. The insertion into nitrile groups by Grignard reagents[3] and organolithium reagents[4] is a powerful tool for the construction of arylketones and heterocyclic compounds, but the rigorous conditions of these reactions have 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.[5–7] Although transition metal-catalysed addition reactions of organoboronic acids and aromatic nitriles or activated nitriles had been well-studied,[8–15] palladium-catalysed coupling of organoboron reagents with aliphatic dinitriles has not been reported thus far, which may be ascribed to the fact that aliphatic nitriles tend to be deprotonated in the presence of palladium catalysts leading to α-arylation products.[16,17] Thus, the addition reaction of aliphatic dinitriles is generally more challenging than that of aromatic nitriles.

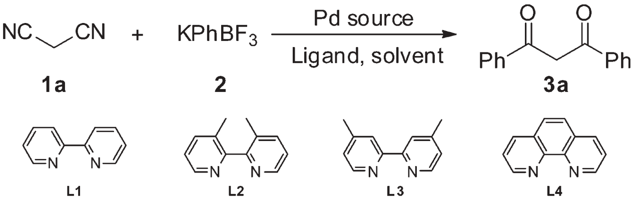
As part of the continuing efforts in our laboratory towards the development of novel transition-metal-catalysed addition or coupling reactions with organoboron reagents,[18] we report here a new method for the synthesis of diketones (or benzophenones) by palladium-catalysed addition reaction of organoboron reagents with aliphatic dinitriles (or aromatic dinitriles).

We began our study by examining the reaction between malononitrile (**1a**) and potassium phenyltrifluoroborate (**2**) to obtain the optimal reaction conditions including catalysts, ligands and solvents (Table 1). Initially, several palladium sources, including $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd(acac)_2$ $Pd(TFA)_2$, and $Pd(OAc)_2$ were investigated (Table 1, entries 1–6). Screening revealed that $Pd(OAc)_2$ exhibited the highest catalytic reactivity, affording the desired product 1,3-diphenylpropane-1,3-dione (**3a**) in 67% yield (Table 1, entry 6). The choice of ligand was also vital to the success of the catalytic reaction (Table 1, entries 6–9). We found that the use of 1,10-phenanthroline (**L4**) as ligand achieved the best result (Table 1, entry 9). Subsequently, the effect of solvents was examined (Table 1, entries 9–15). The results showed that various solvents, including 1,4-dioxane, toluene, xylene, EtOH, and DMF, were less effective than THF and 2-methyl-tetrahydrofuran (2-MeTHF). We were delighted to find that the yield could be improved to 84% when the combination of $Pd(OAc)_2$ and **L4** was employed in 2-MeTHF under an N_2 atmosphere (Table 1, entry 15). It is worth noting that the expected product **3a** could not be detected in the absence of palladium catalysts.

Having the optimised reaction conditions in hand, we next investigated the scope and generality of the addition reaction using various dinitriles and potassium phenyltrifluoroborate (Table 2).

As shown in Table 2, palladium-catalysed addition of other aliphatic dinitriles, such as glutaronitrile (**1b**), succinonitrile (**1c**) and adiponitrile (**1d**) to potassium phenyltrifluoroborate (**2**) was examined (Table 2, entries 2–4). The transformations of substrates **1c** and **1d** with potassium phenyltrifluoroborate also proceeded successfully to provide the corresponding products 1,5-diphenylpentane-1,5-dione (**3c**) and 1,6-diphenylhexane-1,6-dione (**3d**) in 91% and 89% yields respectively (Table 2, entries 3 and 4). However, 1,4-diphenylbutane-1,4-dione (**3b**) was produced in moderate yield accompanied by a small amount of *N*-phenylpyrrole when glutaronitrile (**1b**) was treated with potassium phenyltrifluoroborate (Table 2, entry 2). Next, the scope of the developed approach was

Table 1 Optimisation of reaction conditions[a]



Entry	Pd source	Ligand	Solvent	Yields/%[b]
1	$Pd(PPh_3)_4$	**L1**	1,4-Dioxane	Trace
2	$PdCl_2(PPh_3)_2$	**L1**	1,4-Dioxane	Trace
3	$Pd(acac)_2$	**L1**	1,4-Dioxane	43
4	$PdCl_2$	**L1**	1,4-Dioxane	Trace
5	$Pd(TFA)_2$	**L1**	1,4-Dioxane	65
6	$Pd(OAc)_2$	**L1**	1,4-Dioxane	67
7	$Pd(OAc)_2$	**L2**	1,4-Dioxane	57
8	$Pd(OAc)_2$	**L3**	1,4-Dioxane	56
9	$Pd(OAc)_2$	**L4**	1,4-Dioxane	72
10	$Pd(OAc)_2$	**L4**	Toluene	12
11	$Pd(OAc)_2$	**L4**	Xylene	18
12	$Pd(OAc)_2$	**L4**	EtOH	43
13	$Pd(OAc)_2$	**L4**	THF	82
14	$Pd(OAc)_2$	**L4**	DMF	21
15	$Pd(OAc)_2$	**L4**	2-MeTHF	84
16	none	**L4**	2-MeTHF	0

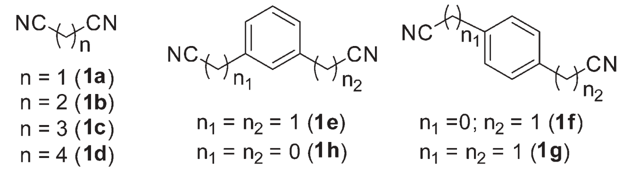
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), Pd source (10 mol %), ligand (20 mol %), solvent (2 mL), TFA/H_2O (0.4 mL/0.4 mL), 80 °C, 48 h, N_2. [b] Isolated yield.

---

* Correspondent. E-mail: mcl@wzu.edu.cn

Table 2 Palladium-catalysed synthesis of diketones[a]

$$\underset{\mathbf{1}}{\text{dinitriles}} + \underset{\mathbf{2}}{KPhBF_3} \xrightarrow[\text{2-MeTHF, 80 °C, 48 h, } N_2]{Pd(OAc)_2/\mathbf{L4}\text{, TFA-}H_2O} \underset{\mathbf{3}}{\text{diketones}}$$



Entry	Dinitrile (**1**)	Product (**3**)	Yield/%[b]
1	**1a**	**3a**	84
2	**1b**	**3b**	57
3	**1c**	**3c**	91
4	**1d**	**3d**	89
5	**1e**	**3e**	91
6	**1f**	**3f**	93
7	**1g**	**3g**	95
8	**1h**	**3h**	93

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), $Pd(OAc)_2$ (10 mol %), **L4** (20 mol %), 2-MeTHF (2 mL), TFA/H_2O (0.4 mL/ 0.4mL), 80 °C, 48 h, N_2.

[b] Isolated yield.

explored toward the addition of potassium phenyltrifluoroborate to aromatic dinitriles. For example, 2,2′-(1,3-phenylene)-diacetonitrile (**1e**), 4-(cyanomethyl)benzonitrile (**1f**), terephthalonitrile (**1g**) and isophthalonitrile (**1h**) bearing two nitrile groups on different positions of the phenyl ring afforded the corresponding products **3e**–**h** in 91%, 93%, 95% and 90% yield, respectively (Table 2, entries 5–8).

A tentative pathway for the formation of diketones is proposed in Scheme 2. The first step may involve the transmetallation of Pd(II) with organoboron reagent **2** to afford an organopalladium intermediate **A**, which gives the intermediate **B** by the coordination of aliphatic dinitrile **1**. Next, carbopalladation of the aliphatic dinitrile **1** forms the corresponding imine–Pd(II) complex **C**. Finally, protonation of the imine–Pd(II) complex **C** by TFA affords the diketimine intermediate **D** and regenerates the Pd(II) catalyst. Hydrolysis of the diketimine intermediate **D** delivers the corresponding diketones **3** as the products.

Conclusion

In summary, we have developed a palladium-catalysed addition of organoboron reagent with aliphatic dinitriles, achieving diketone compounds in moderate to good yields. Moreover, this process also tolerated several aromatic dinitriles to construct benzophenone derivatives in excellent yields. Further efforts to expand the scope of the chemistry are currently underway in our laboratory.

Experimental

Chemicals were either purchased or purified by standard techniques without special instructions. ^{1}H NMR and ^{13}C NMR spectra were measured 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 tetramethylsilane (TMS) as the internal standard at room temperature. 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). All compounds are known. For analytical spectra (^{1}H and ^{13}C NMR) of all compounds see E;lectronic Supplementary Information (ESI).

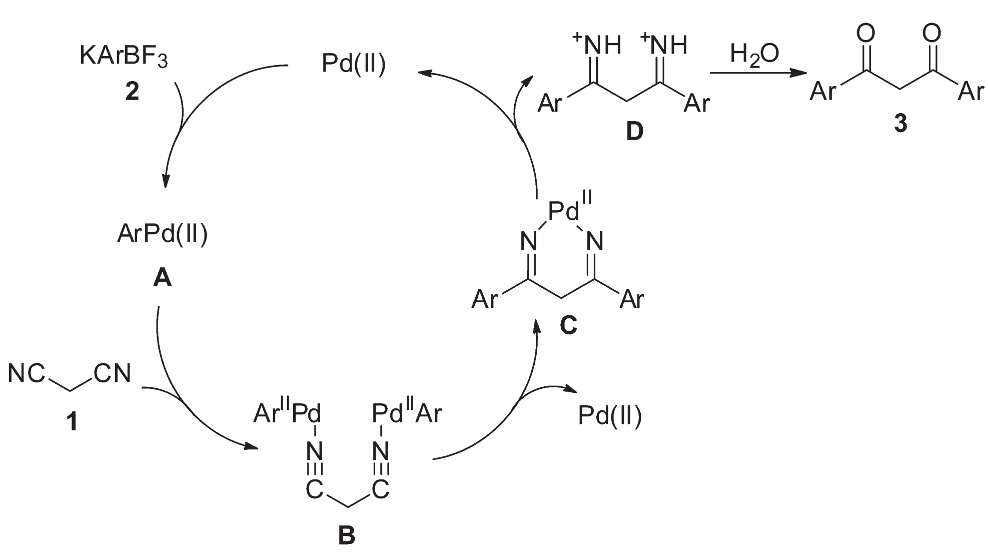
Synthesis of diketone compounds; general procedure

Under N_2 atmosphere, dinitrile **1** (0.2 mmol), potassium phenyltrifluoroborate **2** (147 mg, 0.8 mmol), $Pd(OAc)_2$ (4.49 mg, 10 mol %), **L4** (7.2 mg, 20 mol %), TFA/H_2O (0.4 mL/0.4mL), and 2-MeTHF (2 mL) were successively added into a Schlenk reaction tube. The reaction mixture was stirred vigorously at 80 °C for 48 h. After the completion of the reaction, the mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (2 × 10 mL) and then brine (1 × 10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired products **3**. The physical and spectroscopic data of compounds **3a**–**h** follow.

1,3-Diphenylpropane-1,3-dione (**3a**): Yellowish powder, m.p. 78–79 °C (lit.[19] 77–78 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.99 (d, *J* = 7.1 Hz, 4H), 7.55 (t, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 4H), 6.86 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.8, 135.6, 132.5, 128.7, 127.2, 93.2.

1,4-Diphenylbutane-1,4-dione (**3b**): White powder, m.p. 142–143 °C (lit.[20] 145–146 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (d, *J* = 8.6 Hz, 4H), 7.58 (t, *J* = 7.4 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 4H), 3.46 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.8, 135.6, 132.5, 128.7, 127.2, 93.2.

1,5-Diphenylpentane-1,5-dione (**3c**): Yellowish powder, m.p. 65–66 °C (lit.[21] 65–66 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, *J* = 7.3 Hz, 4H), 7.55 (t, *J* = 7.4 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 4H), 3.12



Scheme 1 A tentative pathway for the formation of diketones.

(t, J = 7.0 Hz, 4H), 2.23–2.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.9, 136.9, 133.1, 128.6, 128.1, 37.6, 18.8.

1,6-Diphenylhexane-1,6-dione (**3d**): Yellowish powder, m.p. 116–117 °C (lit.[22] 122–123 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.96 (d, J = 8.3 Hz, 4H), 7.55 (t, J = 7.4 Hz, 2H), 7.46 (t, J = 7.7 Hz, 4H), 3.04 (t, J = 7.0 Hz, 4H), 1.87–1.83 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.0, 137.0, 133.0, 128.6, 128.0, 38.4, 23.9.

2,2′-(1,3-Phenylene)bis(1-phenylethanone) (**3e**): Yellowish powder, m.p. 84–85 °C (lit.[23] no report). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.99 (d, J = 7.2 Hz, 4H), 7.55 (t, J = 7.4 Hz, 2H), 7.44 (t, J = 7.7 Hz, 4H), 7.28 (t, J = 7.6 Hz, 1H), 7.19–7.15 (m, 3H), 4.26 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.6, 136.6, 135.0, 133.2, 130.7, 129.0, 128.7, 128.6, 128.1, 45.4.

2-(4-Benzoylphenyl)-1-phenylethanone (**3f**): Yellowish powder, m.p. 122–123 °C (lit.[24] 126 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (d, J = 7.6 Hz, 2H), 7.80–7.78 (m, 4H), 7.60–7.56 (m, 2H), 7.50–7.45 (m, 4H), 7.39 (d, J = 8.1 Hz, 2H), 4.38 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.8, 196.3, 139.4, 137.7, 136.4, 133.5, 132.4, 130.5, 130.0, 129.6, 128.8, 128.6, 128.3, 45.3.

1,4-Phenylenebis(phenylmethanone) (**3g**): Yellowish powder, m.p. 156–158 °C (lit.[25] 160–161 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (s, 4H), 7.85 (d, J = 7.2 Hz, 4H), 7.62 (t, J = 7.4 Hz, 2H), 7.52 (t, J = 7.7 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.0, 140.7, 137.0, 133.0, 130.2, 129.8, 128.5.

1,3-Phenylenebis(phenylmethanone) (**3h**): Yellowish powder, m.p. 98–99 °C (lit.[25] 100 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.19 (s, 1H), 8.03 (d, J = 7.7 Hz, 2H), 7.82 (d, J = 8.4 Hz, 4H), 7.65–7.59 (m, 3H), 7.50 (t, J = 7.7 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.8, 137.9, 137.1, 133.5, 132.9, 131.2, 130.1, 128.6, 128.5.

Electronic Supplementary Information

NMR spectra of the products have been deposited in the ESI available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

We thank the National Natural Science Foundation of China (Nos. 21172175 and 21272176) and Natural Science Foundation of Zhejiang Province (No. LY12B02011) for financial support.

Received 24 March 2013; accepted 26 May 2013
Paper 1301855 doi: 10.3184/174751913X13730099043760

References

1 V.Y. Kukushkin and A.J.L. Pombeiro, *Chem. Rev.*, 2002, **102**, 1771.
2 S.F. Rach and F.E. Kühn, *Chem. Rev.*, 2009, **109**, 2061.
3 W. Clegg, R.P. Davies, L. Dunbar, N. Feeder, S.T. Liddle, R.E. Mulvey, R. Snaith and A.E.H. Wheatley, *Chem. Commun.*, 1999, 1401.
4 M.S. Malamas, J. Erdei, I. Gunawan, K. Barnes, M. Johnson, Y. Hui, J. Turner, Y. Hu, E. Wagner, K. Fan, A. Olland, J. Bard and A.J. Robichaud, *J. Med. Chem.*, 2009, **52**, 6314.
5 A. Suzuki, *Acc. Chem. Res.*, 1982, **15**, 178.
6 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
7 A. Suzuki, *J. Organomet. Chem.*, 1998, **576**, 147.
8 K. Ueura, S. Miyamura, T. Satoh and M. Miura, *J. Organomet. Chem.*, 2006, **691**, 2821.
9 C. Zhou and R.C. Larock, *J. Am. Chem. Soc.*, 2004, **126**, 2302.
10 C. Zhou and R.C. Larock, *J. Org. Chem.*, 2006, **71**, 3551.
11 B. Zhao and X. Lu, *Tetrahedron Lett.*, 2006, **47**, 6765.
12 B. Zhao and X. Lu, *Org. Lett.*, 2006, **8**, 987.
13 Y.C. Wong, K. Parthasarathy and C.H. Cheng, *Org. Lett.*, 2010, **12**, 1736.
14 H. Shimisu and M. Murakami, *Chem. Commun.*, 2007, 2855.
15 G.C. Tsui, Q. Glenadel, C. Lau and M. Lautens, *Org. Lett.*, 2011, **13**, 208.
16 D.A. Culkin and J.F. Hartwig, *Acc. Chem. Res.*, 2003, **36**, 234.
17 D.A. Culkin and J.F. Hartwig, *J. Am Chem. Soc.*, 2002, **124**, 9330.
18 J.X. Chen, Y. Peng, M.C. Liu, J.C. Ding, W.K. Su and H.Y. Wu, *Adv. Synth. Catal.*, 2012, **354**, 2117.
19 B.A. Trofimov, L.N. Sobenina, A.I. Mikhaleva, I.A. Ushakov, T.I. Vakul'skaya, Z.V. Stepanova, D.D. Toryashinova, A.G. Mal'kina and V.N. Elokhina, *Synthesis*, 2003, 1272.
20 S. Kotani, K. Osakama, M. Sugiura and M. Nakajima, *Org. Lett.*, 2011, **13**, 3968.
21 D. Mousset, I. Gillaizeau, A. Sabatié, P. Bouyssou and G. Coudert, *J. Org. Chem.*, 2006, **71**, 5993.
22 P. Tomboulian, *J. Org. Chem.*, 1961, **26**, 2652.
23 E. Georges and C. Paul, *Macromolecules*, 1979, **12**, 803.
24 A. Battace, M. Feuerstein, M. Lemhadri, T. Zair, H. Doucet and M. Santelli, *Eur. J. Org. Chem.*, 2007, 3122.
25 M.J. Lo Fiego, M.A. Badajoz, G.F. Silbestri, M.T. Lockhart and A.B. Chopa, *J. Org. Chem.*, 2008, **73**, 9184.