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Synthesis of biarylketones and phthalides from organoboronic acids and aldehydes catalyzed by cobalt complexes†

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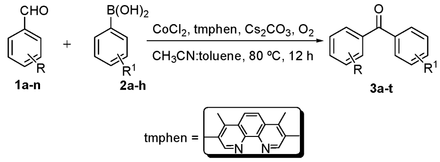
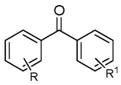
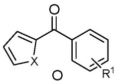
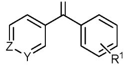
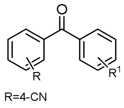
A cobalt-catalyzed addition of aryl- and alkenylboronic acids to aldehydes and phthalaldehyde to give the corresponding biarylketones and 3-aryl phthalides in good to excellent yields in one pot is described.

Biarylketones are important building blocks in both natural products and functional materials.[1] Several traditional syntheses of these compounds have been reported.[2,3] Of these approaches, transition-metal-catalyzed direct synthesis of biaryl ketones has emerged as a powerful method in organic synthesis.[4] In this context, Ishiyama and Hartwig observed a rhodium-catalyzed intermolecular Heck-type reaction of aryl iodides with *N*-heterocyclic aldimines to form the corresponding ketimines, which give ketones upon hydrolysis.[5] We also developed a Ni-catalyzed synthesis of biarylketones from the coupling of aryl iodides with aromatic aldehydes and the synthesis of polycyclic ketones from the cyclization of *o*-iodophenyl ketones with bicyclic alkenes *via* a facile β-alkyl elimination in the last step.[6] Genet and co-workers also developed a rhodium-catalyzed cross coupling reaction of potassium trifluoro(organo)borates with arylaldehydes that led to the formation of diaryl ketones.[7] Very recently, Chen and co-workers reported the synthesis of diaryl ketones by $Cu(OTf)_2$-catalyzed arylation of arylboronic acids with aldehydes under an oxygen atmosphere.[8] The development of cheap, environmentally benign alternative catalysts is still desirable. Recently, the use of cobalt complexes as inexpensive, readily available, and environmentally friendly catalysts for organic reactions has attracted considerable attention. Our continued interest in the cobalt-catalyzed coupling reactions,[9a–f] activation of boronic acids[9g,h] and synthesis of arylketones[6,9i] prompted us to explore the possibility of using low-cost cobalt complexes as the catalysts for cross coupling reactions. Herein we wish to report a direct synthesis of biarylketones and phthalides by the cobalt-catalyzed coupling of arylboronic acids with aldehydes and phthalaldehyde *via* an addition and β-hydride elimination strategy in a one-pot manner from commercially available simple starting materials.

We have earlier reported a Co-catalyzed asymmetric addition reaction of organoboronic acids with aldehydes to give diarylmethanols.[9h] During the course of our investigation, we noticed that the reaction of organoboronic acids with aldehydes could give biarylketones under certain special reaction conditions. Thus, treatment of 4-methoxycarbonylbenzaldehyde (**1a**) with phenylboronic acid (**2a**) in the presence of $CoCl_2$, tmphen (3,4,7,8-tetramethyl-1,10-phenanthroline) and Cs_2CO_3 in CH_3CN/toluene (3/1) at 80 °C under 1 atm O_2 for 12 h gave biarylketone **3a** in 91% isolated yield (Table 1, entry 1). In the absence of O_2, the reaction also gave ketone

Table 1 Results of cobalt-catalyzed coupling of aldehydes and arylboronic acids[a]



Entry	1	2		Product	Yield[b] (%)
1	**1a**	**2a**		**3a**: R = 4-CO_2Me, R^1 = H	91
2	**1b**			**3b**: R = 4-NO_2, R^1 = H	84
3	**1c**			**3c**: R = 3-CN, R^1 = H	80
4	**1d**			**3d**: R = 4-CN, R^1 = H	94
5	**1e**			**3e**: R = 2-Me, R^1 = H	65
6	**1f**			**3f**: R = 4-Me, R^1 = H	67
7	**1g**			**3g**: R = 4-OMe, R^1 = H	64
8	**1h**			**3h**: R = 4-Br, R^1 = H	73
9	**1i**			**3i**: R = 4-Cl, R^1 = H	78
10	**1j**			**3j**: R = H, R^1 = H	66
11	**1k**	**2a**		**3k**: X = O, R^1 = H	79
12	**1l**			**3l**: X = S, R^1 = H	71
13	**1m**			**3m**: Y = N, Z = C, R^1 = H	83
14	**1n**	**2a**		**3n**: Y = C, Z = N, R^1 = H	81
15	**1d**	**2b**		**3o**: R^1 = 4-Me	83
16		**2c**		**3p**: R^1 = 2-OMe	61
17		**2d**		**3q**: R^1 = 3-OMe	80
18		**2e**		**3r**: R^1 = 4-OMe	78
19		**2f**		**3s**: R^1 = 4-Cl	83
20		**2g**		**3t**: R^1 = 4-F	83

[a] Unless otherwise mentioned, all reactions were carried out using aldehyde **1** (1.00 mmol), arylboronic acid **2** (1.50 mmol), $CoCl_2$ (0.10 mmol), tmphen (0.15 mmol), Cs_2CO_3 (1.50 mmol) and CH_3CN/toluene (3 : 1, 4 ml) at 80 °C for 12 h under O_2 (1 atm at room temperature). [b] Isolated yields.

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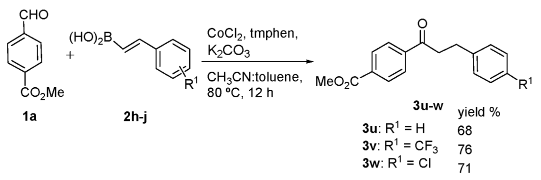
3a, but in only *ca.* 50% yield. It is noteworthy that using a phosphine ligand such as dppe, the catalytic reaction afforded only the corresponding diaryl methanol. Product **3a** was characterized by its ^{1}H, ^{13}C NMR and mass data.

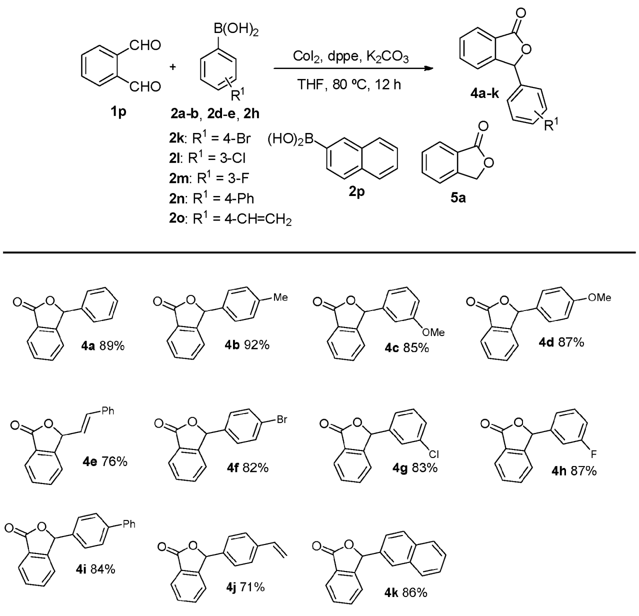
The presence of a nitrogen ligand was crucial to the reaction. Various nitrogen ligands were examined to understand the effect on the product yield. Among them, tmphen gave the best result and afforded **3a** in 91% yield. Other nitrogen ligands including 2,9-dimethyl-1,10-phenanthroline, 1,10-phenanthroline, tmeda, and 2,2′-bipyridine are less effective, giving **3a** in 61, 58, 31, and 38%, yield, respectively. No **3a** was observed in the absence of a cobalt complex, base or nitrogen ligands (see ESI† for the detailed studies).

Under similar reaction conditions for the reaction of **1a** with **2a**, various electron-withdrawing substituted benzaldehydes reacted smoothly with **2a** to give the corresponding unsymmetrical diarylketones. Thus, 4-NO$_2$-, 3-CN-, and 4-CN-substituted benzaldehydes (**1b–d**) underwent addition and β-hydride elimination reaction with **2a** to give **3b–d** in 84, 80 and 94% yield, respectively (entries 2–4). Similarly, electron-donating groups such as 2-Me-, 4-Me- and 4-Ome-substituted benzaldehydes (**1e–g**) also reacted smoothly with **2a** to give diarylketones **3e–g**, albeit in lower yields (entries 5–7). The present catalytic reaction is also compatible with bromo and chloro substituents on the aromatic ring of benzaldehyde **1**. Thus, the reaction of 4-bromo- and 4-chloro-benzaldehyde **1h–i** with **2a** gave substituted diarylketones **3h** and **3i** in 73 and 78% yield (entries 8 and 9), respectively. Benzaldehyde (**1j**) also underwent addition and elimination reaction with **2a** to afford **3j** in 66% yield (entry 10). The scope of the catalytic reaction was extended to heterocyclic aldehydes **1k–n**. Treatment of 2-formylfuran (**1k**) with **2a** gave aryl ketone **3k** in 79% yield (entry 11). Similarly, the reaction of 2-formylthiophene (**1l**) with **2a** afforded **3l** in 71% yield (entry 12). In a similar manner, both 3-formyl and 4-formylpyridines **1m–n** reacted efficiently with **2a** to provide the expected aryl ketones **3m** and **3n** in 83 and 81% yield, respectively (entries 13 and 14). In addition to **2a**, several other substituted boronic acids were tested for the addition and elimination reaction. Thus, 4-methyl-, 2-methoxy-, 3-methoxy-, 4-methoxy-, 4-chloro-, and 4-fluoro-phenylboronic acids (**2b–g**) all reacted well with 4-cyanobenzaldehyde (**1d**) to produce substituted biarylketones in good to excellent yields (entries 15–20). Alkenyl boronic acids including *trans*-2-phenyl- (**2h**), *trans*-2-(4-trifluoromethylphenyl)- (**2i**) and *trans*-2-(4-chlorophenyl)-vinylboronic acid (**2j**) also reacted with **1d** smoothly, but giving unexpected hydrogenation products **3u**, **3v** and **3w** in 68, 76 and 71% yield, respectively (Scheme 1). In these cases, K$_2$CO$_3$ was employed as the base instead of Cs$_2$CO$_3$ to improve the product yields and the reactions were carried out under a nitrogen atmosphere.



Scheme 1

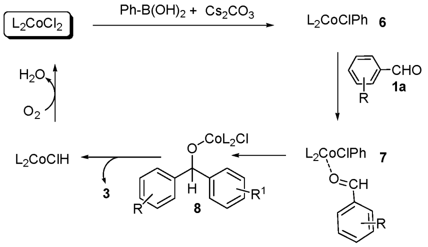
Table 2 Results of cobalt-catalyzed coupling of phthalaldehyde and arylboronic acids[a]



[a] Unless otherwise mentioned, all reactions were carried out using phthalaldehyde **1** (1.00 mmol), arylboronic acid **2** (1.50 mmol), CoI$_2$ (0.050 mmol), dppe (0.050 mmol), K$_2$CO$_3$ (1.50 mmol) and THF (3 mL) under O$_2$ (1 atm at room temperature) for 12 h.

The present cobalt-catalyzed reaction was also tested for the addition of aryl boronic acids to phthalaldehyde **1p**. The reaction of phthalaldehyde **1p** with phenylboronic acid (**2a**) in the presence of CoCl$_2$, tmphen (3,4,7,8-tetramethyl-1,10-phenanthroline) and Cs$_2$CO$_3$ in CH$_3$CN/toluene (3/1) at 80 °C under 1 atm O$_2$ gave phthalide derivative **4a** in only 62% yield along with phthalide (**5a**) in 28%. In order to increase the yield of product **4a**, we optimize the reaction by examining different metal complexes, ligands and bases (see ESI†). Finally, we found that the combination of CoI$_2$, dppe and K$_2$CO$_3$ under nitrogen is most effective giving **4a** in 89% isolated yield (Table 2, entry 1). It is interesting to note that five-membered lactones are present in various natural products that show a range of unique biological activities.[10] A number of metal-catalyzed syntheses of phthalides have been reported.[11,12] We reported a series of nickel and cobalt-catalyzed efficient syntheses of five, six, and seven-membered lactones[11a–c] and chiral phthalides.[11b] Very recently, Cheng and co-workers have developed rhodium and palladium-catalyzed cascade reactions of phthalaldehyde with arylboronic acids leading to the formation of phthalides.[12] Among the methods available, an addition and β-hydride elimination strategy for the preparation of phthalides is extremely rare.

Under the optimized reaction conditions, a variety of boronic acids reacted well with phthalaldehyde **1** to give the corresponding phthalide **4** in good yields (Table 2). Thus, boronic acids with an electron-donating group (**2b**, **2d–e**) gave **4b–d** in 92, 85 and 87% yields respectively. Phenylvinylboronic acid (**2h**) also reacted smoothly. In contrast to the results shown in Scheme 1, the carbon–carbon double bond in **2h**, is not hydrogenated. Similarly, treatment of 4-bromo, 3-chloro,



Scheme 2

3-fluoro, 4-phenyl, and 4-vinyl boronic acids **2k–o** with **1n** gave phthalide products **4f–j** in 82, 83, 87, 84 and 71% yield, respectively. Sterically bulkier 2-naphthylboronic acid **2p** also reacted smoothly with **1p** to give phthalide **4k** in high yield.

To account for the present cobalt-catalyzed reaction, a possible reaction mechanism is proposed (Scheme 2) based on the known metal-catalyzed Heck-type reactions and arylketones synthesis.[5–7] The transmetalation of phenylboronic acid (**2a**) to Co(II) in the presence of Cs_2CO_3 leads to the formation of an arylcobalt(II) species **6**. Coordination of aldehyde **7** followed by insertion into arylcobalt(II) species gives intermediate **8**. Then β-hydride elimination of intermediate **8** affords the final biarylketone **3a** and Co–H species. The Co–H species reacts with O_2 to regenerate the active Co(II) species for the next cycle.

In conclusion, we have successfully developed an effective method for the synthesis of biarylketones and 3-aryl phthalides *via* a tmphen cobalt complex catalyzed addition and β-hydride elimination of organoboronic acids with aldehydes. This method provides an opportunity for the synthesis of various unsymmetrical biarylketones and 3-aryl phthalides in one pot. Further detailed investigation on the mechanism, the substrate scope, and the application of this methodology in natural product synthesis are in progress.

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