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Palladium-Catalyzed Synthesis of Aryl Ketones from Carboxylic Acids and Arylboronic Acids Using EEDQ

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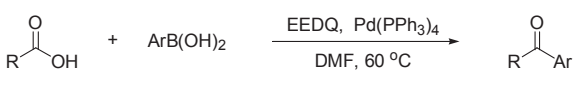
Aryl ketones are important structural motifs found in a number of natural and unnatural products of biological and medicinal interest.[1] A traditional method for the preparation of arylketones is Friedel-Crafts acylation.[2] However, it has major drawbacks, such as limited regioselectivity, difficulty of regioisomer separation, harsh reaction condition, and incompatibility with other functional groups.[2(d)] Arylketones can also be prepared by the nucleophilic addition of organometallics such as magnesium, lithium, zinc, copper, boron, tin or cadmium reagents to a variety of carboxylic acid derivatives including thioesters, nitrile, amides, and acid halides.[3] However, harsh condition and low yields due to the formation of tertiary alcohols as side products are the serious problems.[7] The recently reported mild methods are palladium-catalyzed cross-coupling reaction of activated carboxylic acid derivatives, for example, acid chlorides,[4,7] thioesters,[5] 2-pyridyl esters,[6] and anhydrides[7,8(b)] with boronic acids or other organoboranes. These methods are mild, efficient, and regioselective. However, there are several limitations of these methods. The acid derivatives are not commercially available and anhydride is inefficient to use because the half part of carboxylic anhydride is lost as a leaving group. Gooßen and his coworkers reported a palladium-catalyzed synthesis of aryl ketones directly by the reaction of boronic acids with active ester or anhydride of carboxylic acid generated *in situ* using activating group, such as disuccinimidyl carbonate, pivalic anhydride, or dimethyl dicarbonate.[8] These approaches give good yields even for sensitive functionalized substrates and save one reaction step in comparison to the standard processes. However, the reagent is expensive, difficult to handle, and generating acid. In addition, the reaction is not efficient and needs specific catalytic systems depending on substrates. Therefore, alternative and complementary approach is demanding. *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) has been known to be a coupling reagent in the peptide synthesis,[9] a reagent in the protection of 2-hydroxycarboxylic acid,[10] and a substrate for the synthesis of dihydroquinoline derivatives.[11] The key intermediates in the reactions are reported to be a mixed anhydride generated *in situ*. It occurs to us that the mixed anhydride generated *in situ* might be used for the synthesis of aryl ketone *via* the palladium catalyzed cross coupling reaction of carboxylic acid with boronic acid. Here, we report an efficient coupling reaction of carboxylic acids with aryl boronic acids in DMF in the presence of EEDQ, $Pd(PPh_3)_4$, and water at 60 °C to give the corresponding aryl ketones (Scheme 1). Our method might be a nice alternative to the methods developed recently.

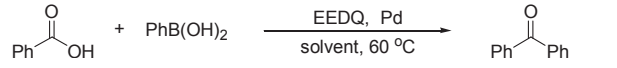


1 **2** **3**

Scheme 1

The coupling reaction of benzoic acid with benzeneboronic acid in the presence of EEDQ and 2.5 equiv. of water[8c] was conducted using palladiums such as $Pd(OAc)_2$, $Pd_2(dba)_3{\cdot}CH_3Cl$, $Pd(acac)_2$, $Pd(PPh_3)_4$ and phosphine ligands such as PPh_3, $(o\text{-tolyl})_3P$, $(furyl)_3P$, BINAP, dppf in THF for 15 h and the results are listed in Table 1 (entries 1-11). $Pd(PPh_3)_4$ was identified to be the best palladium catalyst in the coupling reaction and 2.5 equiv. of water is necessary for the efficient reaction (entries 2 and 11). The reaction was examined in the other solvents such as DMF, acetonitrile, and dioxane. DMF and acetonitrile were proved to be the most effective solvents in the

Table 1. The reaction[a] of benzoic acid and benzeneboronic acid at 60 °C



Entry	Palladium (Pd) / Ligand	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$ / PPh_3	THF	63
2[c]	$Pd(OAc)_2$ / PPh_3	THF	40
3	$Pd(OAc)_2$ / $(o\text{-tolyl})_3P$	THF	13
4	$Pd(OAc)_2$ / $(furyl)_3P$	THF	33
5	$Pd(OAc)_2$ / $P(OPh)_3$	THF	27
6[d]	$Pd(OAc)_2$ / BINAP	THF	10
7[d]	$Pd(OAc)_2$ / dppf	THF	trace
8	$Pd_2(dba)_3{\cdot}CH_3Cl$ / PPh_3	THF	14
9	$Pd(acac)_2$/ PPh_3	THF	7
10	$Pd(PPh_3)_4$	THF	73
11[c]	$Pd(PPh_3)_4$	THF	47
12	$Pd(PPh_3)_4$	Dioxane	43
13	$Pd(PPh_3)_4$	CH_3CN	90
14	$Pd(PPh_3)_4$	DMF	93
15	$Pd(PPh_3)_4$ (without EEDQ)	DMF	No reaction

[a]Reaction conditions: benzoic acid (100 mg, 0.82 mmol), benzeneboronic acid (120 mg, 0.98 mmol), EEDQ (247 mg, 1.23 mmol), H_2O (37 μL, 2.05 mmol), palladium catalyst (3.0 mol %), ligand (6.6 mol %), solvent (1 mL), 15 h, 60 °C. [b]Isolated yield. [c]Water was not added. [d]3.3 mol % ligand.

Table 2. Reaction[a] of carboxylic acids with arylboronic acids under the optimum condition

Entry	R	Ar	Ketones[b]	Product	Yield[c] (%)
1	4-$MeOC_6H_4$	Ph	4-$MeOC_6H_4COPh$	**3a**	84[d]
2	4-MeC_6H_4	Ph	4-MeC_6H_4COPh	**3b**	82
3	2,3-diMeC_6H_3	Ph	2,3-diMeC_6H_3COPh	**3c**	83[e]
4	2-Cl C_6H_4	Ph	2-ClC_6H_4COPh	**3d**	84
5	3-Cl C_6H_4	Ph	3-ClC_6H_4COPh	**3e**	84
6	4-Cl-2-$MeOC_6H_3$	Ph	4-Cl-2-$MeOC_6H_4COPh$	**3f**	73[e]
7	1-naphthyl	Ph	1-naphthyl-COPh	**3g**	82
8	$CH_3(CH_2)_4$	Ph	$CH_3(CH_2)_4$-COPh	**3h**	77[f]
9	CH_3CH_2	Ph	CH_3CH_2-COPh	**3i**	79[f]
10	Ph	4-$MeOC_6H_4$	4-$MeOC_6H_4COPh$	**3j**	96
11	4-MeC_6H_4	4-$MeOC_6H_4$	4-$MeOC_6H_4COPh$-4-Me	**3k**	90[d]
12	2-Cl C_6H_4	4-$MeOC_6H_4$	4-$MeOC_6H_4COPh$-2-Cl	**3l**	79
13	3-Cl C_6H_4	4-$MeOC_6H_4$	4-$MeOC_6H_4COPh$-3-Cl	**3m**	97
14	Ph	4-MeC_6H_4	4-$MeOC_6H_4COPh$	**3n**	99
15	Ph	4-ClC_6H_4	4-ClC_6H_4COPh	**3o**	97
16	Ph	2-thienyl	2-thienyl-COPh	**3p**	79

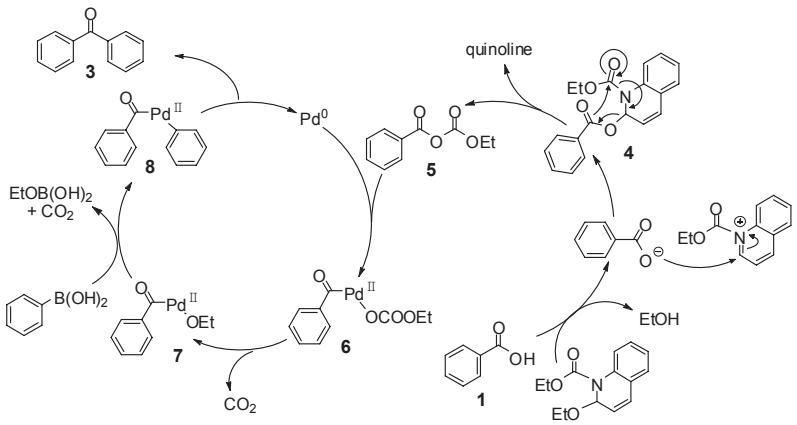
[a]Conditions: 1.0 mmol carboxylic acid, 1.2 equiv. arylboronic acid, 1.5 equiv. EEDQ, 2.5 equiv. H_2O, 3.0 mol % $Pd(PPh_3)_4$, DMF (1 mL), 60 °C, 15 h. [b]Spectroscopic data of all products were consistent with those of corresponding known compounds. [c]Isolated yield. [d]Reaction time for 30 h. [e]at 80 °C. [f]2.5 equiv. benzeneboronic acid.

coupling reaction. The mixed anhydride of carboxylic acid was detected by TLC during the reaction and the ethyl ester of benzoic acid as a side product was not observed under the reaction condition.

To investigate the scope and limitations, the reaction of a variety of carboxylic acids with a variety of boronic acids in DMF[12] at 60 °C were studied and the results are listed in Table 2. Generally, the reactions work well with both electron rich and poor carboxylic acid as well as electron rich and poor boronic acid. The benzoic acid with substituent at *ortho* position is less reactive, probably resulting from steric crowdness and therefore the reaction was conducted at 80 °C to give the corresponding ketones in high yields (entries 3 and 6). Excess amount of boronic acid in the reaction of hexanoic and propanoic acids has been used due to the formation of large amount of biphenyl as a side product from the homocoupling of arylboronic acid, probably resulting from the low reactivity of mixed anhydride of hexanoic and propanoic acids (entries 8 and 9).

The plausible mechanism is shown in Scheme 2 based on the reported one.[13] The coupling reaction is proceeded through a mixed anhydride **5** formed *in situ via* adduct **4** generated from the reaction of carboxylic acid with EEDQ. The mixed anhydride **5** is oxidatively added to palladium (0) generating an acylpalladium carbonate complex **6**. It might be decarboxylated and transmetallated with arylboronic acid to give palladium complex **8** which was isomerized to *cis* isomer and reductively eliminated to give a coupling product **3**.

Carboxylic acid derivatives are successfully coupled with arylboronic acids in the presence of EEDQ as an activating reagents and $Pd(PPh_3)_4$ as a catalyst in 2 equiv. H_2O and DMF at 60 °C to give diarylketone in high to excellent yields. Our catalytic coupling system is general, simple and efficient. Therefore, our method might be a nice alternative to that developed by others.



Scheme 2

Experimental Section

A typical procedure of the synthesis of 4-methoxybenzophenone (3a).[7(a)] To a solution of 4-methoxybenzoic acid (100 mg, 0.66 mmol), EEDQ (244 mg, 0.99 mmol) and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) in DMF (1 mL) and water (30 μL, 1.66 mmol) in a 5 mL reaction vessel was added phenylboronic acid (96 mg, 0.79 mmol) and the resulting solution was purged with argon. The reaction mixture was stirred for 15 h at 60 °C and the reaction was monitored by TLC (ethyl acetate : *n*-hexane = 1 : 10). After the reaction, the mixture was quenched with water (5 mL), and the aqueous solution was extracted with ethyl acetate (5 mL) three times. The combined ethyl acetate phases were concentrated and further purification of the product was achieved by flash column chromatography on silica gel (ethyl acetate : *n*-hexane = 1 : 10) to give a 4-methoxybenzophenone **3a** (84 %) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 6.9 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.47 (dd, J = 6.9 and 7.2 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 3.89 (s, 3H).

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