# General and Greener Route to Ketones by Palladium-Catalyzed Direct Conversion of Carboxylic Acids with Organoboronic Acids

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Cross-coupling reaction of carboxylic acids with organoboron compounds catalyzed by palladium complexes in the presence of an activator such as dimethyl dicarbonate under mild conditions gives ketones in excellent yields except for certain substrates.

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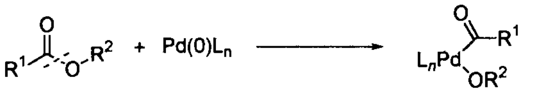
Ketones occupy pivotal positions as intermediates in organic synthesis as well as end products for various commercial uses. Although quite a variety of synthetic methods are available, most methods entail some shortcomings in efficiency and environmental problems.[1]

The C–O bond in various oxygen-containing compounds can be cleaved by transition metal complexes.[2] We have previously found that the C–O bonds in carboxylic esters and anhydrides are readily cleaved on interaction with Pd(0) complexes to give acylpalladium aryloxides or carboxylates (eq 1).[3,4]

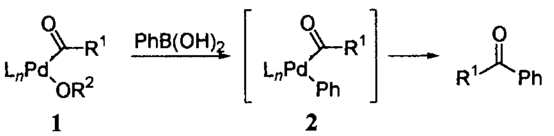


(1)

**1**

The acylpalladium complexes react with organoboronic acids to yield ketones. On further application of the findings we could develop catalytic synthesis of ketones from carboxylic anhydrides and activated esters.[5,6]

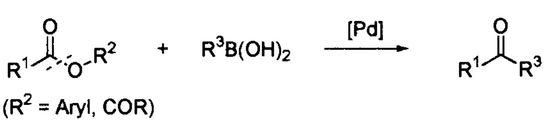
The catalytic synthesis of ketones is based on the reaction of the acylpalladium complex **1** to undergo exchange of the aryloxido or carboxylato ligand with phenylboronic acids to yield acyl(phenyl)palladium species **2** that readily releases the phenyl ketone on reductive elimination (eq 2).



(2)

**1** **2**

We have constructed catalytic processes on the basis of these elementary processes to convert various carboxylic anhydrides and aryl esters into ketones using palladium complexes (eq 3).[5,6]



(3)

We have previously observed that treatment of carboxylic acids with less reactive carboxylic anhydride such as pivalic anhydride (2,2-dimethylpropanoic anhydride) leads to the anhydride mixture, which can be subjected to the C–O bond cleavage process and further hydrogenolysis to yield aldehydes.[7] By application of the similar concept we now developed the new catalytic method of directly converting carboxylic acids into mixed ketones using organoboronic acids.[8]

We first examined the effects of various activators in promotion of direct conversion of heptanoic acid into heptanophenone with phenylboronic acid in the presence of [Pd(PPh$_3$)$_4$]. Strong effects of the nature and molar amounts of the activators added to the catalyst system on the yields of ketone were noted.

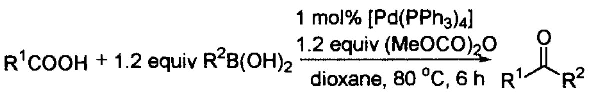
Pivalic anhydride that was most suitable for aldehyde synthesis[7] proved to be not the best activator, giving 83% yield of the ketone. Among the activators examined, dimethyl dicarbonate was most effective giving 95% yield of the ketone with usage of 1.2 equiv of dimethyl dicarbonate per heptanoic acid. With further decrease in the amount of the activator down to 1.0 equiv a slight decrease in the yield was noted. Other additives such as acetic anhydride and di-*tert*-butyl dicarbonate showed poor to moderate activities.

The catalyst system composed of [Pd(PPh$_3$)$_4$] and 1.2 equiv of (MeOCO)$_2$O was effective affording a variety of ketones as summarized in Table 1 by treating carboxylic acids and organoboronic acids in the presence of the activator in dioxane at 80 °C for 6 h.

The present process is applicable to various aromatic, heterocyclic, and aliphatic carboxylic acids with organoboron compounds and is tolerant to a variety of functional groups. Benzoic acid derivatives having functional groups such as methoxy, chloro, formyl, cyano, and nitro groups at the para positions can be catalytically converted into the corresponding ketones in excellent yields on treatment with arylboronic acids in the presence of dimethyl dicarbonate and [Pd(PPh$_3$)$_4$]. Heterocyclic carboxylic acids such as 2-thiophenecarboxylic acid, 3-furoic acid and nicotinic acid readily coupled with phenylboronic acid under standardized conditions to give the corresponding ketones in good yields. *trans*-Cinnamic acid having the double bond that may interact with the palladium center could be also used, although the yield was moderate. Various aliphatic carboxylic acids such as heptanoic acid are converted smoothly into heptanophenone in combination with phenylboronic acid, whereas a bulky aliphatic carboxylic acid such as 2,2-dimethylpropanoic acid resulted in a low yield probably due to the less reactivity of its mixed anhydride in oxidative addition to a Pd(0) species.

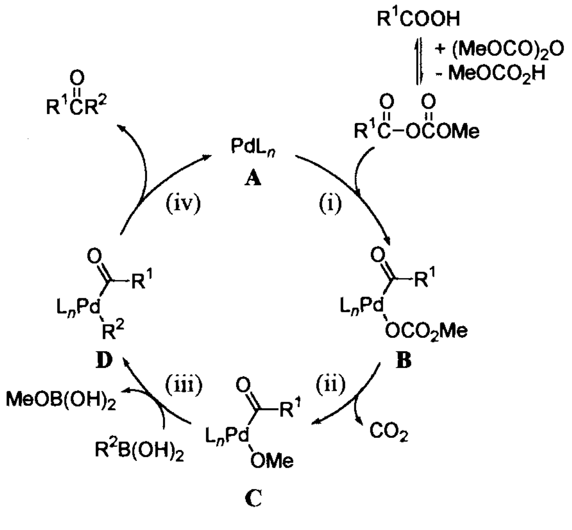
We propose the catalytic cycle consisted of several elementary processes as shown in Scheme 1 to account for the catalytic formation of ketones from carboxylic acids and organoboron

**Table 1.** Synthesis of unsymmetrical ketones by the palladium-catalyzed cross-coupling of carboxylic acids with organoboronic acids in the presence of dimethyl dicarbonate



| Entry | $R^1$ | $R^2$ | Yield / %[a] |
|---|---|---|---|
| 1 | Ph | Ph | 97 |
| 2 | *p*-$MeOC_6H_4$ | Ph | 96 (86) |
| 3 | *p*-$ClC_6H_4$ | Ph | (88) |
| 4 | *p*-$HCOC_6H_4$ | *p*-$MeC_6H_4$ | (88) |
| 5 | *p*-$NCC_6H_4$ | Ph | 98 |
| 6 | *p*-$O_2NC_6H_4$ | Ph | 96 |
| 7 | Ph | *p*-$MeOC_6H_4$ | 97 |
| 8 | Ph | *p*-$F_3CC_6H_4$ | 98 |
| 9 | furan-3- | Ph | (85) |
| 10 | thiophene-2- | Ph | 99 (88) |
| 11 | pyridine-3- | Ph | 85 |
| 12 | *trans*-PhCH=CH | Ph | 56 |
| 13 | $^nC_6H_{13}$ | Ph | 96 |
| 14 | $^t$Bu | Ph | 20 |

[a] Typical conditions: a mixture containing carboxylic acid (1 mmol), organoboronic acid (1.2 mmol), dimethyl dicarbonate (1.2 mmol), $[Pd(PPh_3)_4]$ (0.01 mmol) and dioxane (5 $cm^3$) was stirred in a Schlenk tube under argon at 80 °C for 6 h. Standard work-up procedure was performed after the end of experiment and GC yields based on carboxylic acids are given. The isolated yields are in the parentheses.

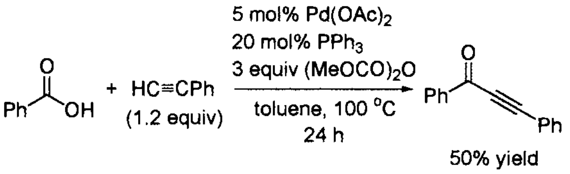


**Scheme 1**. Catalytic cycle for the formation of ketones.

compounds in the presence of dimethyl dicarbonate.

The carboxylic acid employed is considered to undergo the exchange reaction with dimethyl dicarbonate to form a mixed anhydride, whose acyl–O bond is cleaved on interaction with Pd(0) complex **A** to give **B**. The acylpalladium complex **B** may undergo decarboxylation (ii), transmetallation (iii) and reductive elimination (iv) producing the product and the catalyst.

The similar concept can be applied to $\alpha,\beta$-alkynyl ketone synthesis, suggesting wide applicability of the process (eq 4).



(4)

The process is not limited to homogeneous systems. The combination of Pd/$BaSO_4$ used in the presence of 4 equiv of $PPh_3$ gave 88% yield of benzophenone from benzoic acid with phenylboronic acid and dimethyl dicarbonate in dioxane at 90 °C for 6 h.

The present process does not require the prior synthesis of carboxylic acid derivatives such as acyl halides, anhydrides, nor needs any extra base. The versatility of the process, mild experimental conditions, a wide scope of applications, and environmentally benign nature makes the process promising as one of the useful synthetic methods of ketones.

## References and Notes

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8 While preparing the paper, we found that Gooβen et al. independently succeeded in catalytic preparation of ketones directly from carboxylic acids and organoboronic acids using pivalic anhydride as the activator on the basis of similar concept as described here. L. J. Gooβen and K. Ghosh, *Angew. Chem. Int. Ed.*, **40**, 3458 (2001).