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# Palladium-phosphinous acid-catalyzed cross-coupling of aliphatic and aromatic acyl chlorides with boronic acids

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ABSTRACT

The cross-coupling of aromatic and aliphatic acyl chlorides with arylboronic acids in the presence of 2.5 mol % of $(t\text{-Bu}_2\text{POH})_2\text{PdCl}_2$ (POPd) provides rapid access to ketones that are obtained in up to 93% yield. This palladium-phosphinous acid-catalyzed reaction is completed within 10 min when microwave irradiation is used, and it overcomes typical drawbacks of Friedel–Crafts acylation procedures such as harsh reaction conditions, untunable regiocontrol, and low substrate scope.



In recent years, phosphinous acid ligands have been successfully introduced to a wide range of transition metal-catalyzed transformations.[1] In particular, nickel and palladium complexes bearing phosphinous acids have proved to be very powerful catalysts for carbon–carbon and carbon-heteroatom bond formation, but their use in coupling reactions with acyl chlorides has remained unexplored.[2–4] While most Stille, Negishi and Suzuki couplings involve aryl halides, the introduction of acyl halides further extends the application spectrum of these reactions. The cross-coupling of acyl chlorides with organometallic reagents provides convenient access to ketones that can often not be prepared otherwise, for example, via Friedel–Crafts acylation methods. Few transition metal-catalyzed coupling reactions of acyl halides with stannanes,[5] boronic acids[6] and organozinc,[7] arylbismuth,[8] and Grignard reagents[9] are known. Typical disadvantages of previously reported procedures include (1) incompatibility with several functionalities, including aryl halide bonds that compete with the acyl halide group for oxidative addition to the transition metal catalyst and subsequent carbon–carbon bond formation, (2) the use of toxic reagents, and (3) the need for high reaction temperatures and long reaction times.

Initially, we compared the catalytic activity of palladium-phosphinous acid, POPd, and its chlorophosphine analog PXPd, as well as complexes formed in situ from $\text{Pd(dba)}_2$ and phosphine oxides **1**–**5** (Fig. 1). Phosphine oxides are well known to rapidly tautomerize to the corresponding phosphinous acids that form active palladium catalysts after stirring with a palladium source, such as $\text{Pd(dba)}_2$, at room temperature for 2–4 h (Scheme 1).

We found that POPd is most effective in catalyzing the coupling of benzoyl chloride, **6**, and phenylboronic acid, **7**, providing benzophenone, **8**, with superior yields and shorter reaction time. Further screening of catalyst loading, solvent, temperature, and base revealed that **8** can be obtained in 93% yield within 1 h when 2.5 mol % of POPd and stoichiometric amounts of $K_2CO_3$ are used in a toluene-dioxane solvent mixture heated to 80 °C (Table 1, entry 1).[10]

Under these conditions, a wide range of electron-rich and electron-deficient benzoyl chloride derivatives were successfully converted to benzophenones **10**, **12**, **15**, **16**, **18**, **20**, and **21** (entries 2–8). It is noteworthy that this procedure tolerates the presence of aryl chloride and bromide bonds in both the acyl halide substrate and the arylboronic acid (entries 9–13). For example,

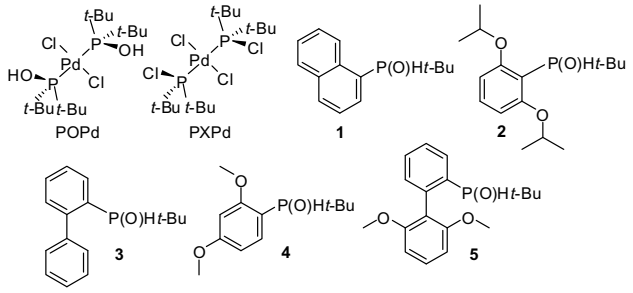
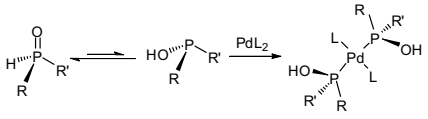



**Figure 1.** Structures of palladium catalysts used in this study.



**Scheme 1.** Formation of palladium-phosphinous acids from phosphine oxides.

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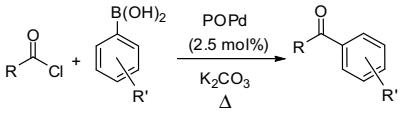
**Table 1**
POPd-catalyzed Suzuki-Miyaura cross-coupling of acyl chlorides and boronic acids[a]



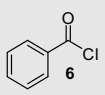
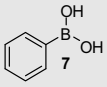
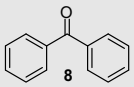
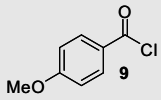
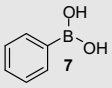
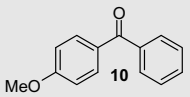
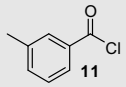
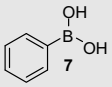
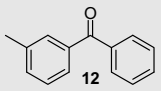
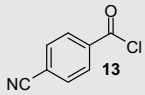
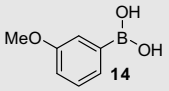
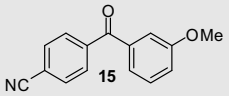
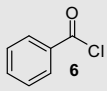
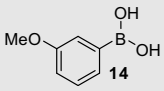
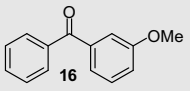
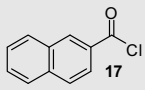
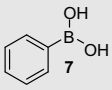
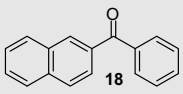
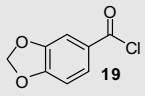
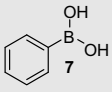
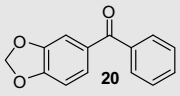
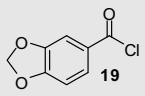
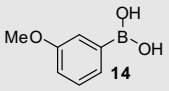
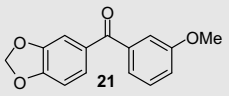
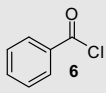
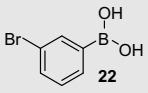
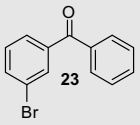
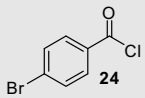
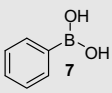
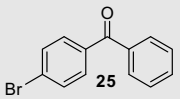
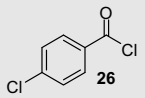
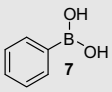
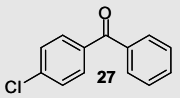
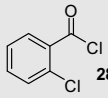
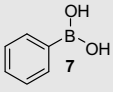
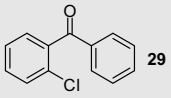
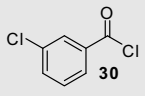
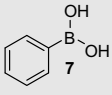
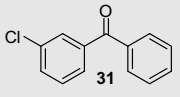
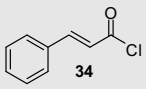
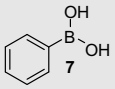
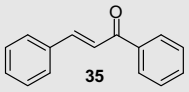
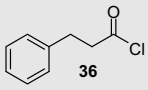
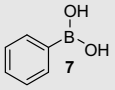
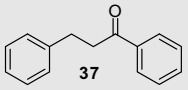
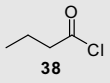
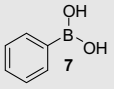
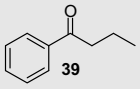

| Entry | Acyl chloride | Boronic acid | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  **6** |  **7** |  **8** | 93 |
| 2 |  **9** |  **7** |  **10** | 84 |
| 3[b] |  **11** |  **7** |  **12** | 81 |
| 4 |  **13** |  **14** |  **15** | 83 |
| 5 |  **6** |  **14** |  **16** | 85 |
| 6 |  **17** |  **7** |  **18** | 86 |
| 7 |  **19** |  **7** |  **20** | 87 |
| 8 |  **19** |  **14** |  **21** | 80 |
| 9 |  **6** |  **22** |  **23** | 80 |
| 10 |  **24** |  **7** |  **25** | 90 |
| 11 |  **26** |  **7** |  **27** | 88 |
| 12 |  **28** |  **7** |  **29** | 82 |
| 13 |  **30** |  **7** |  **31** | 87 |
| 14 |  **6** |  **32** |  **33** | 73 |

**Table 1** (*continued*)

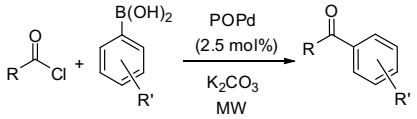
| Entry | Acyl chloride | Boronic acid | Product | Yield (%) |
|---|---|---|---|---|
| 15 |  **34** |  **7** |  **35** | 75 |
| 16 |  **36** |  **7** |  **37** | 78 |
| 17 |  **38** |  **7** |  **39** | 65 |

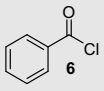
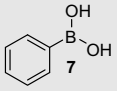
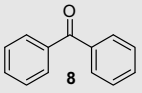
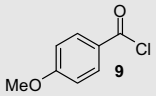
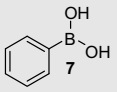
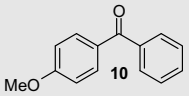
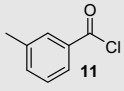
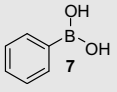
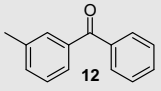
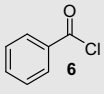
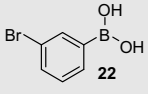
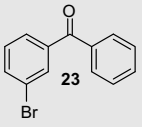
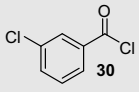
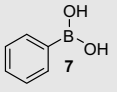
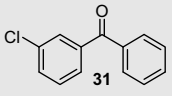
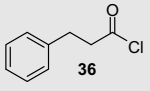
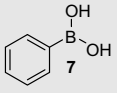
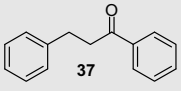
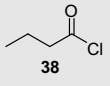
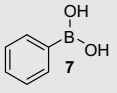
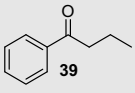
[a] All reactions were carried out with 150 mg of acyl chloride, 1.3 equiv of boronic acid, 2.5 mol % of POPd, 1.6 equiv of $K_2CO_3$ in 1.75 mL of toluene: 1,4-dioxane (2:1, v/v) at 80 °C for 1 h.

coupling of **6** with 3-bromophenylboronic acid, **22**, and 4-bromobenzoyl chloride, **24**, with boronic acid **7** gave 3-bromoacetophenone, **23**, and 4-bromoacetophenone, **25**, in 80 and 90% yield, respectively. Unsaturated ketones can be prepared in good yields either from a styrylboronic acid, such as **32**, or from cinnamoyl chloride, **34**, and its analogs (entries 14 and 15). In addition to the successful synthesis of benzophenone derivatives from benzoyl chlorides and arylboronic acids, our POPd-catalyzed method affords significantly better results with aliphatic acyl chlorides than previously reported Suzuki-type coupling procedures (entries 16 and 17).[6]

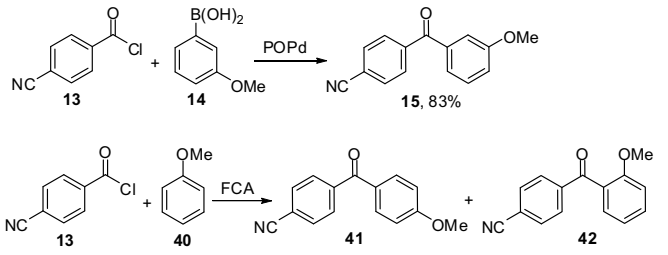
The POPd-catalyzed cross-coupling of acyl chlorides and boronic acids also proceeds upon microwave irradiation, providing biaryl ketones in yields that are similar to those obtained by conventional heating (Table 2). Under otherwise identical conditions, the formation of benzophenones and acetophenones was

**Table 2**
Microwave-assisted POPd-catalyzed cross-coupling of acyl chlorides with boronic acids[a]




| Entry | Acyl chloride | Boronic acid | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  **6** |  **7** |  **8** | 90 |
| 2 |  **9** |  **7** |  **10** | 81 |
| 3 |  **11** |  **7** |  **12** | 80 |
| 4 |  **6** |  **22** |  **23** | 73 |
| 5 |  **30** |  **7** |  **31** | 84 |
| 6 |  **36** |  **7** |  **37** | 72 |
| 7 |  **38** |  **7** |  **39** | 61 |

[a] All reactions were carried out with 150 mg of acyl chloride, 1.3 equiv of boronic acid, 2.5 mol % of POPd, and 1.6 equiv of $K_2CO_3$ in 1.75 mL of toluene: 1,4-dioxane (2:1, v/v) at 80 °C in the microwave (100 W) for 10 min.




**Scheme 2.** Comparison of the POPd-catalyzed synthesis of **15** with traditional FCA.

completed in very short reaction times. For example, benzoyl chloride and phenylboronic acid gave **8** in 90% yield in 10 min.

The synthetic usefulness of transition metal-catalyzed ketone formation from readily available boronic acids becomes apparent through a comparison with traditional Friedel–Crafts acylation (FCA). Using our method, 4-cyano-3′-methoxybenzophenone, **15**, can be prepared in 83% yield in a single step. By contrast, Lewis acid-promoted acylation of anisole, **40**, with 4-cyanobenzoyl chloride, **13**, would favor the formation of regioisomers **41** and **42**. Similarly, FCA with benzonitrile, **43**, and 3-methoxybenzoyl chloride, **44**, would be sluggish and produce **15** only in minor amounts (Scheme 2). Nucleophilic additions of Grignard reagents or organocopper, lithium, and cadmium analogs to carboxylic acid derivatives provide other viable synthetic alternatives toward ketones such as **15**.[11] However, these methods generally show limited functional group compatibility and often afford low yields due to significant formation of tertiary alcohols.

In summary, we have introduced a palladium-phosphinous acid-catalyzed Suzuki-type cross-coupling method that furnishes benzophenone and acetophenone derivatives in good to high yields from aromatic and aliphatic acyl chlorides, respectively. The POPd-catalyzed ketone formation utilizes readily available boronic acids and is generally completed within 10 min when it is conducted in a microwave. This approach overcomes typical drawbacks of procedures based on Friedel–Crafts acylation or nucleophilic addition of organometallic reagents to carboxylic acid derivatives such as harsh reaction conditions, limited substrate scope, reduced functional group tolerance and synthetic limitations due to substituent-directing effects inherent to electrophilic aromatic substitution.

## Acknowledgement

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## Supplementary data

Synthesis and characterization of all products including NMR spectra are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.115.

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10. *General procedure for the synthesis of 4-cyano-3′-methoxybenzophenone* **15**: 4-Cyanobenzoyl chloride **13** (174 mg, 1.05 mmol), 3-methoxyphenylboronic acid **14** (213 mg, 1.4 mmol), POPd (2.5 mol %) and $K_2CO_3$ (241 mg, 1.7 mmol) were dissolved in 1.75 mL of toluene: 1,4-dioxane (2:1, v/v). The reaction mixture was heated to 80 °C for 1 h, quenched with 1 mL of water and extracted with methylene chloride. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography using hexanes:methylene chloride (1:2, v/v) as mobile phase gave 175.1 mg of **15** as a white powder (0.79 mmol, 83%). $^1$H NMR: $\delta$ 3.88 (s, 3H), 7.17 (dd, $J$ = 3.6 Hz, 6.6 Hz, 1H), 7.18–7.30 (m, 2H), 7.21 (dd, $J$ = 4.5 Hz, 6.6 Hz, 1H), 7.81 (d, $J$ = 8.7 Hz, 2H), 7.90 (d, $J$ = 8.7 Hz, 2H). $^{13}$C NMR: $\delta$ 55.5, 114.3, 115.6, 118.0, 119.7, 122.8, 129.5, 130.2, 137.5, 141.2, 159.8, 194.7. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.60; H, 4.36, N, 5.72.
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