Decarbonylative Suzuki-Miyaura Cross-Coupling of Aroyl Chlorides

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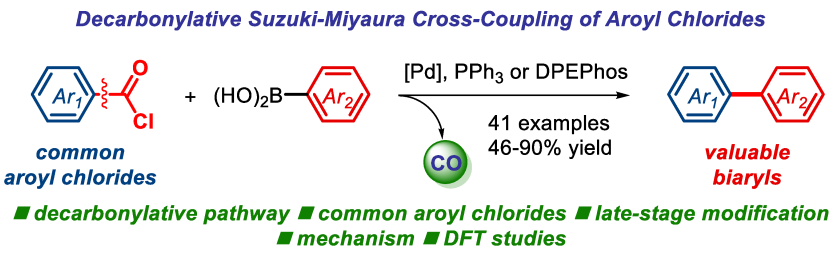
Supporting Information



ABSTRACT: Herein, we report a catalyst system for Pd-catalyzed decarbonylative Suzuki-Miyaura cross-coupling of aroyl chlorides with boronic acids to furnish biaryls. This strategy is suitable for a broad range of common aroyl chlorides and boronic acids. The synthetic utility is highlighted in the direct late-stage functionalization of pharmaceuticals and natural products capitalizing on the presence of carboxylic acid moiety. Extensive mechanistic and DFT studies provide key insight into the reaction mechanism and high decarbonylative cross-coupling selectivity.

The Suzuki-Miyaura cross-coupling of aryl chlorides is one of the most powerful reactions developed (Figure 1A).[1,2] On the other hand, very little progress has been made in the development of the biaryl Suzuki-Miyaura cross-coupling of aroyl chlorides.[3] To date, only one catalyst system has been developed by Sanford and co-workers using Pd[P(*o*-tol)$_3$]$_2$/BrettPhos,[4] however, it involves a sequential decarbonylative chlorination/aryl chloride cross-coupling rather than direct decarbonylative cross-coupling. This Suzuki reaction was successful in only two examples of electronically-activated aroyl chlorides.

Herein, we report to the best of our knowledge the first catalytic system for the direct decarbonylative Suzuki-Miyaura cross-coupling of aroyl chlorides (Figure 1B). The method employs [Pd(η^3-1-*t*-Bu-ind)Cl]$_2$/PPh$_3$ or DPEPhos and NaHCO$_3$ as a weak base to slow down transmetallation relative to decarbonylation.[1d] The utility of this method is highlighted in the direct functionalization of pharmaceuticals and natural products that capitalize on the presence of the carboxylic acid moiety to introduce the biaryl motif in a decarbonylative fashion (Figure 1C). Furthermore, we present detailed mechanistic and DFT studies to elucidate the mechanistic pathway and provide benchmark for the development of future synthetic methods.

In general, aroyl chlorides, R–C(O)Cl are the most fundamental and ubiquitous carboxylic acid derivatives.[3] Despite some limitations, such as stability, aroyl chlorides are the most common acyl transfer reagents used on daily basis in academic and industrial laboratories worldwide.[5,6] In particular, nucleophilic acyl substitution using aroyl chlorides is among the most popular synthetic methods at present,[3] however, an arsenal of acyl cross-couplings of aroyl chlorides has also been developed permitting access to biaryl ketones.[7]

In contrast to these methods, the direct arylation of aroyl chlorides remains a major challenge. Although decarbonylative cross-couplings have been developed as a powerful reactivity manifold, few methods involving simple aroyl chlorides have been established.[8] In this context, although aroyl chlorides are the most fundamental carboxylic acid derivatives,[3,5,6] the biaryl Suzuki–Miyaura cross-coupling – one of the most powerful synthetic transformations within the field of chemistry[1,2] – using aroyl chlorides as electrophiles remains a challenging goal.

Within our program on decarbonylative cross-coupling reactions,[9] we questioned whether decarbonylative Suzuki-Miyaura cross-coupling of aroyl chlorides might be accomplished using versatile Pd catalysis.[10–14] Notable features of our study include (1) the first example of a direct decarbonylative Suzuki-Miyaura cross-coupling of aroyl chlorides. Aroyl chlorides represent a fundamental functional group in organic synthesis. The reaction involves a fundamental elementary step, oxidative addition of an acyl-Cl bond (cf. acyl-OCOR bond).[9f] (2) a new catalytic system for decarbonylative cross-coupling of aroyl electrophiles (cf. acid anhydrides), which we believe would be useful for the development of future cross-coupling methods.

Our studies were initiated by the examination of the cross-coupling of benzoyl chloride with 4-methoxyphenyl boronic acid as the nucleophile (eq 1). The key challenge in decarbonylative cross-coupling is the reactivity of acyl- and aryl-metal intermediates in elementary organonometallic steps. After very extensive optimization (see Tables S1-S10, SI), we have identified a catalyst system consisting of [Pd(η^3-1-*t*-Bu-ind)Cl]$_2$ as the Pd source, PPh$_3$ or DPEPhos as a phosphine ligand and NaHCO$_3$ as a base. Under the optimized conditions, the biaryl product was formed in 93% yield with >95:5 selectivity for the

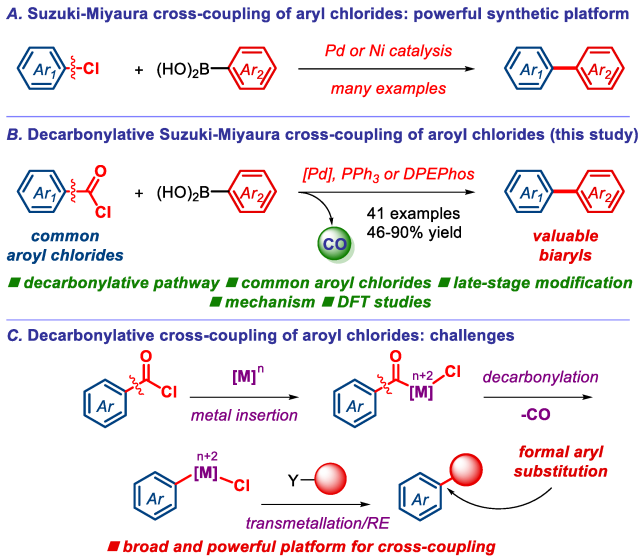
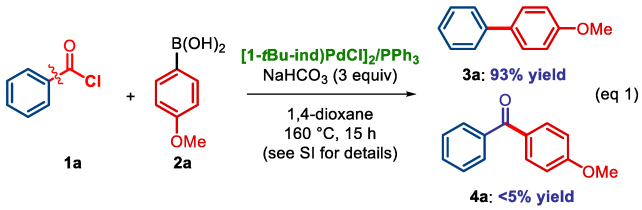


Figure 1. (a) Suzuki cross-coupling of aryl chlorides. (b-c) This study: Decarbonylative Suzuki–Miyaura cross-coupling of aroyl chlorides.



biaryl vs. acyl coupling. In the model cross-coupling, the same yield was observed using preformed (η^3-1-*t*-Bu-ind)Pd(Cl)(PPh_3) and the catalyst formed in situ from [Pd(η^3-1-*t*-Bu-ind)Cl]$_2$ and PPh_3. To our knowledge, this is the first example of a beneficial effect of allyl-supported precatalysts in decarbonylative cross-coupling, a finding which may lead to the development of more effective Pd(II) precatalysts in this catalysis platform.[15–17]

It is further interesting to note that a comprehensive optimization of η^3-allyl throw-away ligands,[15] such as η^3-allyl, η^3-cin, η^3-ind, η^3-1-*t*-Bu-ind in [Pd(η^3-allyl)Cl]$_2$ catalysts across various boronic acids was conducted and confirmed the beneficial effect of η^3-1-*t*-Bu-ind in all cases examined (see SI).

With the optimized conditions in hand, the scope and limitations of this Suzuki–Miyaura cross-coupling were investigated (Scheme 1). As shown, the scope of the reaction is very broad using unbiased electrophile and accommodates a significant electronic and steric variation. As such, electron-rich (**3a-3b**) and electron-deficient (**3c-3h**) boronic acids are well-tolerated. It is noteworthy that the reaction readily accommodates electrophilic groups, such as ketones (**3c**), esters (**3d**), chlorides (**3g**), aldehydes (**3h**). In particular, the tolerance to aryl chloride (**3g**) highlights the orthogonal nature of decarbonylative cross-coupling vs. the conventional aryl chloride cross-coupling. Furthermore, steric-hindrance (**3i-3j**) and a variety of other substrates (**3k-3t**), including heterocycles (**3r-3t**) are readily accommodated by this decarbonylative cross-coupling. Importantly, the scope with respect to the aroyl chloride component is similarly broad (**3u-3ak**), including electrophilic substrates such as chloride (**3z**), ester (**3ab**) or cyano (**3ah-3aj**). Several additional points and limitations should be noted.[18] At this stage, mono-ortho-substitution on acyl chlorides is tolerated, while di-ortho-substituted aroyl chlorides are not suitable substrates. The 4-nitro substituent on the boronic acid allows for the cross-coupling (4-nitro-1,1'-biphenyl, 42% yield). The ratio of **3**:**4** = 81:19 is consistent with the electron-withdrawing effect of the nitro group. The 4-nitro group on aroyl chloride is tolerated (4-methoxy-4'-nitro-1,1'-biphenyl, 31% yield, **3**:**4** >95:5). It should also be noted that aroyl chlorides are potential lachrymators (LC_{50} inhalation, rat, 1.45 mg/L) and have several other hazards.[18d]

The synthetic utility is highlighted in the direct late-stage functionalization of pharmaceuticals and natural products that feature carboxylic acid moiety that is readily converted in situ to aroyl chlorides using thionyl chloride – a classic sequence in nucleophilic acyl additions[3,5,6,14] (Scheme 2). The synthesis of biaryls from probenecid (**3al**, antihyperuricemic), bexarotene (**3am**, antineoplastic), methone (**3an**, monoterpene) and cholesterol (**3ao**, steroid) illustrate the capacity of this coupling in the synthesis of biaryls with a range of potential applications.[19]

To study the mechanism, we conducted stoichiometric experiments with isolated intermediates (Scheme 3 and SI).

A. To gain insight into the facility of decarbonylation, we prepared acyl-palladium complex **6** and subjected this complex to the cross-coupling (Scheme 3A). Decarbonylation of **6** occurs at 80 °C, while full conversion is achieved at 160 °C after 30 min. Furthermore, we have independently prepared aryl-Pd complex **7** (Scheme 3A).[20] The reverse reaction of **7** to give **6** occurs under atmospheric pressure of CO within 2 h at rt. These findings confirm that decarbonylation of acyl-palladium **6** can occur under mild conditions at 80 °C.[21] Decarbonylation of **6** is not observed at lower temperatures than 80 °C (see SI).

B. Stoichiometric experiments using benzoyl chloride in the presence of palladium precursor and phosphine ligand using [Pd] (1 equiv) ($Pd(dba)_2$ or [Pd(η^3-1-*t*-Bu-ind)Cl]$_2$) and PPh_3 (2 equiv) give aryl-Pd complex **7** exclusively (Scheme 3B), consistent with fast decarbonylation of acyl-palladium **6**.[21]

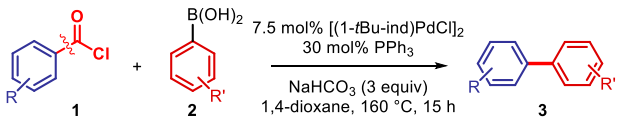
C. Experiments with acyl-Pd complex **6** in the presence of boronic acid and base under different conditions show that at rt only ketone **4a** resulting from acyl coupling was formed, however, at higher temperatures only biaryl **3a** was observed, even after short reaction times, reaching full conversion at 160 °C after 15 min (Scheme 3C).

D. Stoichiometric experiments with **7** in the presence of boronic acid and base show full conversion of aryl-palladium **7** to biaryl **3a** after 15 min at 160 °C (Scheme 3D).

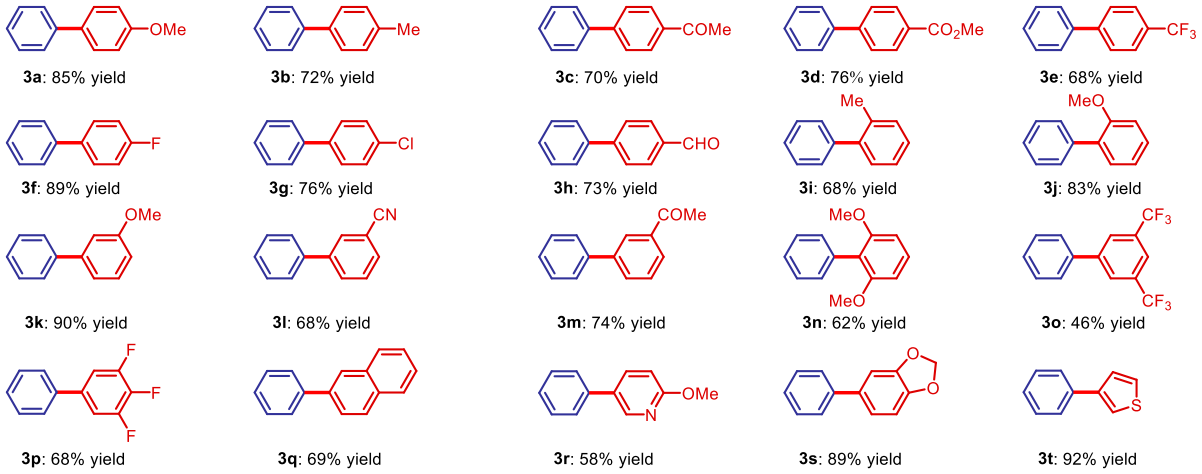
E-F. Further experiments probing the effect of CO (Scheme 3E) and the potential of acyl-palladium complex **6** as a catalyst (Scheme 3F) demonstrate that acyl coupling is more facile than aryl coupling and that **6** is catalytically active, consistent with **6** as a catalytic intermediate in the cross-coupling. Scheme 4 presents a summary of stoichiometric studies. The results suggest that decarbonylation precedes transmetallation. Decarbonylation is facile and occurs at temperatures as low as 80 °C. The results indicate transmetallation as the rate-limiting step.

To gain further insight into the mechanism of this novel cross-coupling, we have performed extensive computational studies to delineate the origin of high reactivity and the energies of elementary steps. The DFT-computed free energy profile of Pd/PPh_3-catalyzed decarbonylative biaryl Suzuki-Miyaura

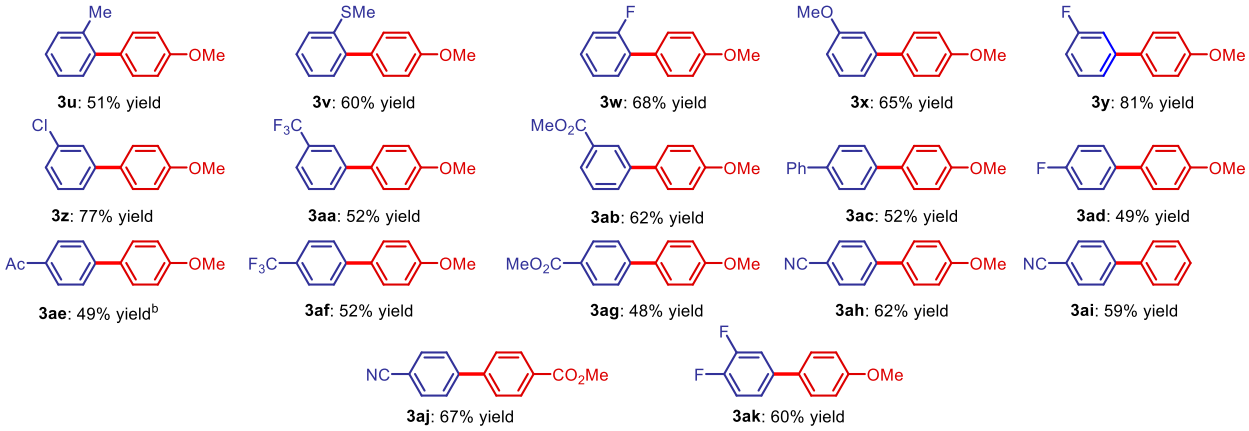
Scheme 1. Scope of Decarbonylative Suzuki–Miyaura Cross-Coupling of Aroyl Chlorides[a]



A: Scope of boronic acids

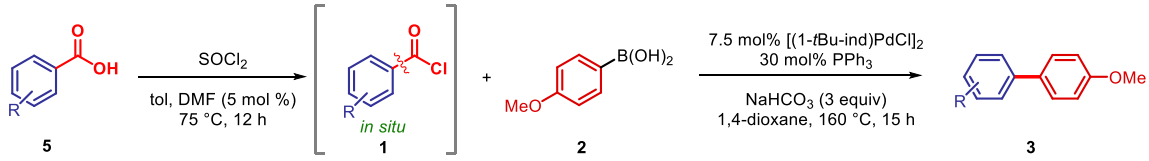


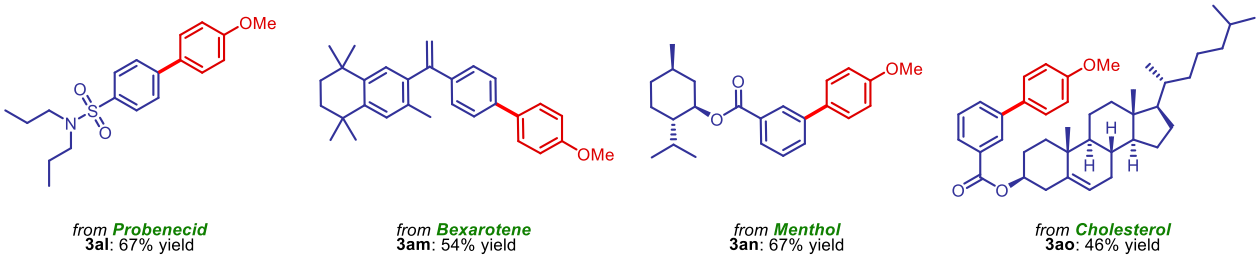
B: Scope of acid chlorides



[a]Conditions: acyl chloride (1.0 equiv), boronic acid (1.5 equiv), $NaHCO_3$ (3 equiv), $[(1\text{-}t\text{-Bu-ind})PdCl]_2$ (7.5 mol%), 30 mol% PPh_3, dioxane (0.10 M), 160 °C, 15 h. Isolated yields. [b]20 mol% DPEPhos. See SI for details.

Scheme 2. Late-Stage Functionalization of Pharmaceuticals and Natural Products[a]





[a]Conditions: carboxylic acid (1.0 equiv), $SOCl_2$, DMF, toluene, 75 °C, 12 h, then boronic acid (1.5 equiv), $NaHCO_3$ (3 equiv), $[(1\text{-}t\text{-Bu-ind})PdCl]_2$ (7.5 mol%), 30 mol% PPh_3, dioxane (0.10 M), 160 °C, 15 h. Isolated yields. See SI for details.

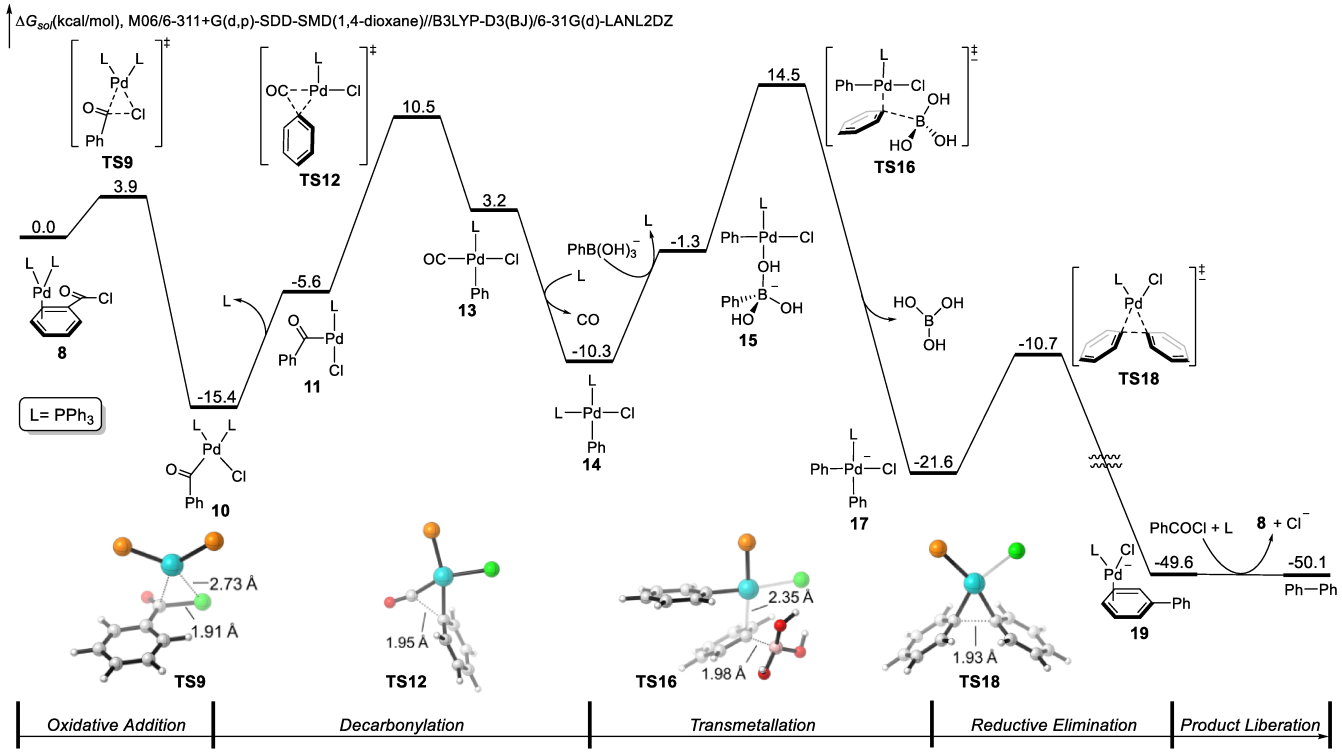
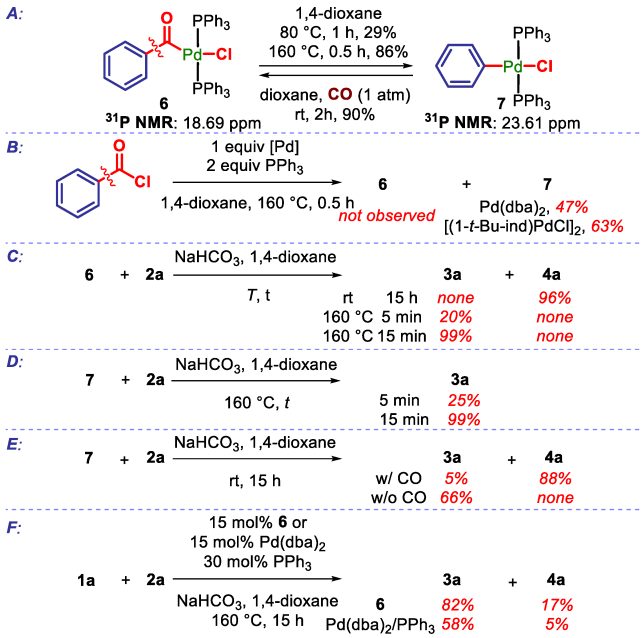
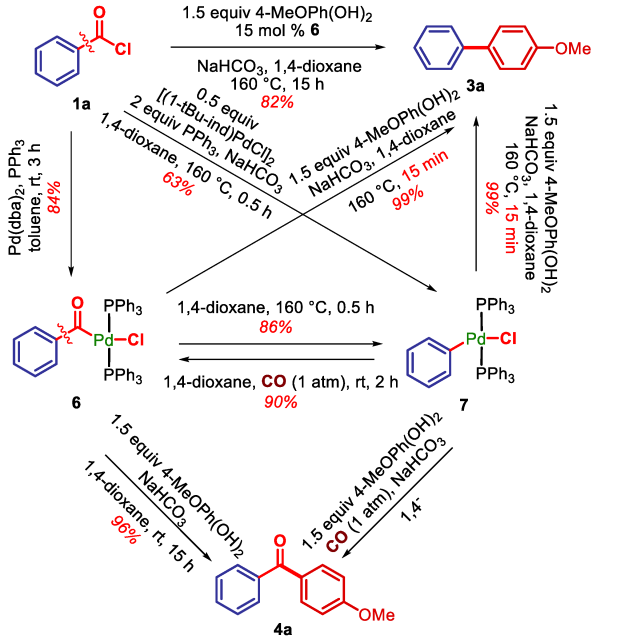


Figure 2. DFT-computed free-energy-profile of Pd/PPh_3-catalyzed decarbonylative biaryl Suzuki-Miyaura coupling of benzoyl chloride. See SI for details.

Scheme 3. Mechanistic Studies with Isolated Intermediates



Scheme 4. Summary of Mechanistic Studies[a]



cross-coupling with benzoyl chloride is shown in Figure 2. From the substrate-coordinated complex **8**, the oxidative addition of benzoyl chloride through **TS9** is very facile, generating the acyl-palladium intermediate **10**. **10** dissociates one of the phosphine coordinates to allow the subsequent decarbonylation via **TS12**, and the ligand-CO exchange leads to the bisligated aryl-palladium species **14**. From **14**, the base-promoted transmetallation occurs via an outer-sphere mechanism (**TS16**) to generate the biaryl-palladium intermediate **17**. The alternative base-free, bicarbonate-facilitated, or inner-sphere transmetallation processes were found less favorable (Figure S1). **17** undergoes a facile aryl-aryl reductive elimination through **TS18** to produce the produce-coordinated complex **19**. Subsequent product liberation regenerates the palladium catalyst and completes the catalytic cycle. We want to emphasize that the isolated chloride anion is a simplification of its form in the catalytic system, complexation with cationic species could further stabilize the dissociated chloride anion and make the product liberation more exergonic. Based on the DFT-computed free energy profile, the rate-determining step of the

catalytic cycle is the transmetallation step via **TS16**. This step requires an overall barrier of 29.9 kcal/mol comparing with the on-cycle resting state acyl-palladium intermediate **10**.

An additional point is the speciation of Pd catalyst at 160 °C. Decarbonylation of **6** to **7** occurs at 60 ºC (1 h, 13%) and the entire reaction at 100 ºC (**3a**, 21%). Therefore, we can make a reasonable assumption of catalyst speciation between 25-80 °C and apply it to our reaction conditions. Moreover, considering the boiling point of 1,4-dioxane, the system temperature should be close to 120 °C in the stoichiometric transformation. Furthermore, we have made attempts to determine the fate of the Pd in stoichiometric reactions of **7**. Preliminary studies indicate the formation of $Pd(PPh_3)_2$ in the cross-coupling of **7** (0.5 h, 17%).

In summary, we have identified a new catalyst system for the decarbonylative Suzuki–Miyaura cross-coupling of aroyl chlorides. Synthetically, aroyl chlorides are the most fundamental carboxylic acid derivatives. This report demonstrates that aroyl chlorides could be successfully utilized in the powerful Suzuki-Miyaura biaryl cross-coupling manifold. The synthetic utility has been highlighted in the direct functionalization of pharmaceuticals and natural products capitalizing on the presence of carboxylic acid moiety. Mechanistic and DFT studies have provided insight into the high reaction selectivity and established facile decarbonylation, and decarbonylation preceding transmetallation. Our future studies will be focused on expanding the scope of coupling partners in this process.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, computational details, coordinates and energies of DFT-computed stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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