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Regioselective Aldehyde Decarbonylation through Palladium-Catalyzed Nitrile Boronic Acid Cross-Coupling

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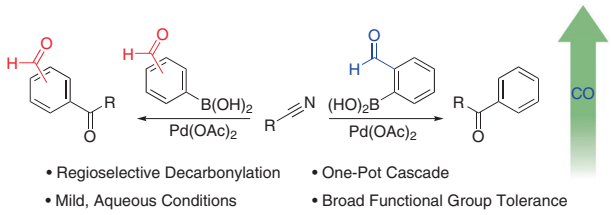

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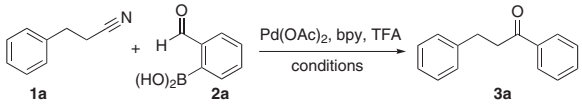
Abstract Aldehyde decarbonylation is a vital chemical transformation in the synthesis of natural products. Nature accomplishes this process through a family of decarbonylase enzymes, while in the laboratory, harsh transition metals and elevated temperatures are required. Herein, we report a mild aldehyde decarbonylation reaction that exhibits its exclusive selectivity for *ortho*-aldehydes during a tandem nitrile boronic acid cross-coupling reaction. A wide substrate scope is displayed that includes regioselective removal of the *ortho*-aldehyde from phenyl boronic acids in the presence of *meta*- or *para*-aldehydes. A mechanistic investigation of the observed regioselectivity for *ortho*-aldehydes by density functional theory (DFT) calculations shows that the CO ligand extrusion is energetically more favorable for the *ortho* position as compared to the *para* position.

Key words decarbonylation, aldehydes, boronic acids, nitriles, palladium

Aldehyde decarbonylation involving the loss of CO was first developed by Eschinazi and co-workers in the 1950s,[1] and has been a crucial transformation in the synthesis of natural products. Aldehydes are often introduced during total synthesis as handles to promote improved reactivity for numerous organic reactions including Diels–Alder,[2] oxa-Michael additions,[3] C–H activations,[4] and many more.[5] However, the removal of aldehydes is challenging and often requires harsh conditions and metals including Rh,[6] Ni,[7] Ru,[8] Ir,[9] and Pd.[10] More recently, nanoparticles,[11] photocatalysts,[12] and microwave conditions[13] have been employed to overcome the high cost and harsh conditions associated with these catalysts. Additionally, many reports utilize an aldehyde scavenger to minimize catalyst poisoning.[14] Yet, despite its high cost and use in stoichiometric amounts, Wilkinson's Rh catalyst remains the reagent of choice for this transformation.[15]

Regardless of these numerous methods for aldehyde decarbonylation, none are capable of differentiating various aldehydes and indiscriminately remove CO from all formyl groups, often requiring chemists to mask desired aldehydes in different oxidation states, lengthening synthetic routes.[16]

Table 1 Aldehyde Decarbonylation of Formyl Phenyl Boronic Acid (**2a**) via a Nitrile Boronic Acid Cross-Coupling Reaction[a]



Entry	$Pd(OAc)_2$ (mol%)	bpy (mol%)	Temp (°C)	Time (h)	Yield[a]
1	10	20	60	48	72%
2	10	20	80	24	81%
3	10	20	90	12	74%
4	20	40	80	24	79%
5	20	40	90	12	72%

[a] All reactions were conducted with 50 mg of **1a**, 4 equiv. of **2a**, and 10 equiv. of TFA in 5:1 THF:H_2O.
[b] Yield refers to chromatographically pure compounds.

While investigating the substrate scope of a cross-coupling reaction between nitrile **1a** and an aryl boronic acid **2a** using $Pd(OAc)_2$,[17] we serendipitously noticed the disappearance of the aldehyde group (Table 1, entry 1). Encouraged by the one-pot nature of this aldehyde decarbonylation, we sought to explore this reaction further. Increasing the temperature from 60 °C to 90 °C decreased the reaction time from 48 hours to 12 hours without significant change in the yield of the reaction (Table 1, entries 2 and 3). Increasing the catalyst loading to 20 mol% $Pd(OAc)_2$ with 40 mol% bipyridine ligand did not produce any significant difference in the yield or reaction time (Table 1, entries 4 and

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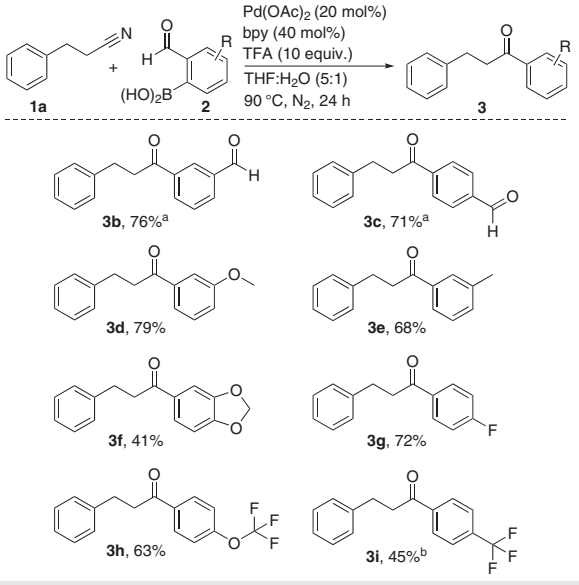
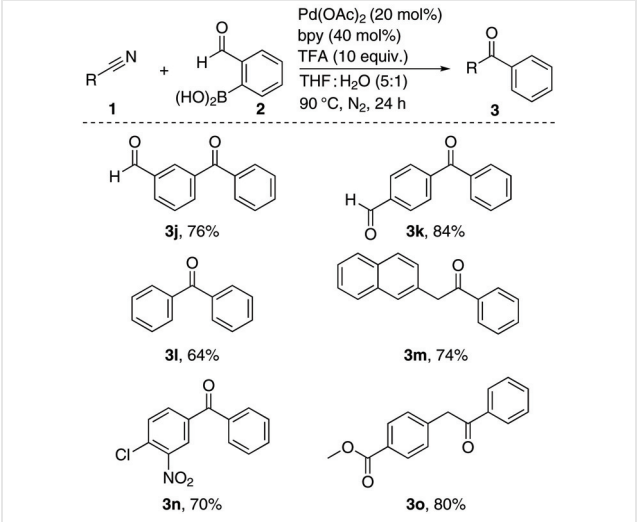
5). All reactions were purged under N_2 to mitigate unproductive oxidative homocoupling of the phenyl boronic acid, which hinders reaction progress.[18]

Aldehyde decarbonylation using $Pd(OAc)_2$ has been reported previously by Maiti and collaborators,[10f] but they required high temperatures up to 140 °C, while we observed the decarbonylation of aldehydes at lower temperatures of 60 °C. Interestingly, the cross-coupling reaction with *meta*-formyl phenyl boronic acid (**2b**) did not lead to any decarbonylation under the reaction conditions, only generating ketone **3b** in high yield (76%) (Scheme 1). Literature regarding regioselective decarbonylation is absent, leading us to further investigate this unique reactivity. Similar to the *meta*-substituted aldehyde, no aldehyde decarbonylation occurred with *para*-formyl phenyl boronic acid (**2c**) and only cross-coupled product **3c** (71%) was observed under the reaction conditions. This observation motivated us to further explore the substrate scope of this regioselective aldehyde decarbonylation reaction. To determine the scope and role of substituents in *ortho*-selective aldehyde decarbonylation, we explored substrates with electron-donating (**2d–f**) and electron-withdrawing (**2g–i**) groups at varying positions with respect to the aldehyde handle. All the reactions successfully underwent aldehyde decarbonylation with nitrile **1a** under the developed reaction conditions and yielded ketone products **3d–i** (Scheme 1).

ortho-formyl phenyl boronic acids containing electron-withdrawing substituents, particularly trifluoromethyl, gave modestly lower yields after 48 hours (e.g., **3i**, 45%)



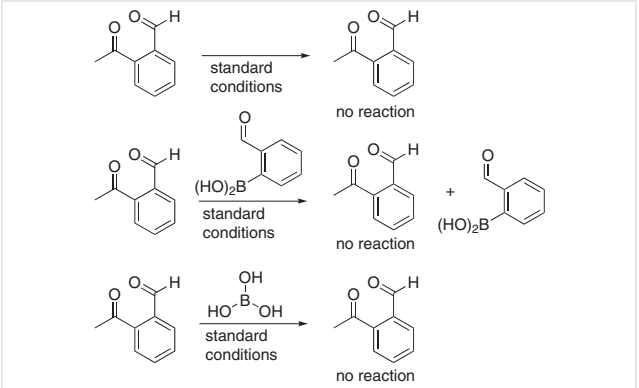
Scheme 1 Scope of boronic acids in the regioselective *ortho*-aldehyde decarbonylation reaction. Yields refer to chromatographically pure compounds. [a] 12 hours. No decarbonylation was observed with substrates containing an aldehyde group at the *meta* (**2b**) and *para* (**2c**) positions of the phenyl boronic acid. [b] 48 hours.



Scheme 2 Scope of nitriles in the regioselective *ortho*-aldehyde decarbonylation reaction. Yields refer to chromatographically pure compounds.

(Scheme 1). We mainly attribute the lower conversion to the slower rate of the initial oxidative addition with the nitrile group.[17] However, the reaction does require an aromatic boronic acid, as vinylic boronic acids gave no reaction.

Next, we evaluated the substrate scope of this reaction with various nitriles (**1b–g**) by reaction with *ortho*-formyl phenyl boronic acid (**2a**) (Scheme 2). Phenyl nitriles **1b–d** and naphthyl nitrile **1e** yielded the decarbonylated ketone products **3j–m** in good yields (64–84%). An electron-withdrawing functionality on the nitrile **1f** was well tolerated and generated the decarbonylated product **3n** in high yield (70%) under the reaction conditions. Most notably, we were able to selectively decarbonylate the *ortho*-aldehyde of the phenyl boronic acid **2a** in the presence of *meta*- and *para*-aldehydes on the phenyl nitrile **1b**,**c** to generate the corresponding ketone products **3j**,**k** in high yields. To the best of

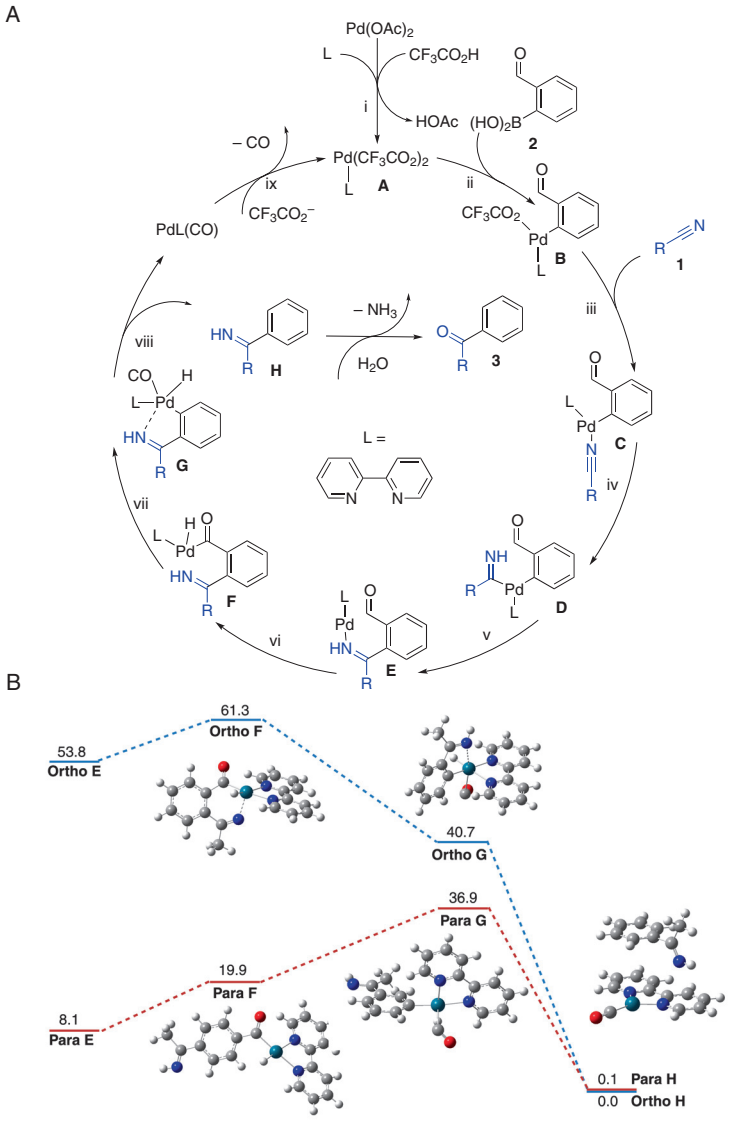


Scheme 3 Control reactions to investigate the mechanistic pathway. Reactions were conducted on 50 mg scale of 2-acetylbenzaldehyde at 80 °C for 24 hours. No conversion was observed for all conditions.

our knowledge, these are the first examples of regioselective decarbonylation. Additionally, a reactive carbonyl moiety was retained, as seen with the ester group in **3o**. Interestingly, nitrile substrates with β-carbonyl functionality were not tolerated.

In order to investigate the role of the boronic acid in aldehyde decarbonylation, we attempted the reaction with 2-acetylbenzaldehyde as a model substrate and subjected it to the optimized conditions (Scheme 3). No decarbonylation was observed and starting material 2-acetylbenzaldehyde was fully recovered under the conditions. We then postulated that the boronic acid may be supporting the coordination of palladium to facilitate the decarbonylation. However, the addition of 2-formylphenylboronic acid or boric acid externally in the presence of 2-acetylbenzaldehyde did not lead to any decarbonylation (Scheme 3). These experiments suggest that the *ortho* decarbonylation stems from the cross-coupling reaction of the nitrile with the boronic acid in a concerted manner.

Based on these experimental results and literature precedent for the nitrile cross-coupling reaction[19] and aldehyde decarbonylation,[20] we proposed a plausible reaction mechanism (Scheme 4A). In the first step, $Pd(OAc)_2$ coordinates with bipyridine and trifluoroacetate to generate the active



Scheme 4 Reaction Pathway. (A) Proposed mechanistic pathway. (B) Energy landscape. Values are in kcal/mol relative to the **Ortho E** intermediate. Computations conducted at B3LYP/LanL2DZ theory and basis set.

Pd(II) catalyst **A**, which further undergoes transmetalation with aryl boronic acid **2**, resulting in the Pd-aryl species **B** (steps i and ii, Scheme 4A). The coordination of nitrile **1** with Pd-aryl species **B** generates intermediate **C**, which is followed by intramolecular carbopalladation to form the corresponding imine Pd(II) complex **D** before undergoing reductive elimination, yielding imine complex **E** (steps iii–v, Scheme 4A). The oxidative addition of Pd into the *ortho*-formyl C–H bond generates intermediate **F**, after which migratory deinsertion gives complex **G** (steps vi and vii, Scheme 4A). This is followed by reductive elimination, resulting in the generation of decarbonylated imine product **H** and a Pd catalyst CO complex (step viii, Scheme 4A). Imine **H** further undergoes hydrolysis to generate the decarbonylated ketone product **3**, while Pd dissociates from CO to regenerate the active catalyst **A** with trifluoroacetate ligands (step ix, Scheme 4A).

Given the high regioselectivity for *ortho*-aldehydes, we decided to investigate a plausible explanation using density functional theory (DFT) calculations (B3LYP/LanL2DZ) on *ortho*- and *para*-imine intermediates **E**–**H**, where R = CH_3. Scheme 4B displays the energies in kcal/mol of each intermediate relative to the **Ortho H** intermediate. While the C–H oxidative addition on **Ortho E** and **Para E** intermediates (step vi, forming intermediates **Ortho F** and **Para F**) is unfavorable for both substrates, the CO ligand extrusion is a favorable process (step vii) for the **Ortho F** system, generating **Ortho G**, which has ~20 kcal/mol lower energy than **Ortho F**. Conversely, the transformation from **Para F** to generate **Para G** is unfavorable by ~17 kcal/mol. Overall, the CO ligand extrusion process is the rate-determining step,[20] and is ~37 kcal/mol more favorable for the formation of **Ortho G** as compared to **Para G** (step vii). We postulated that **Ortho G** is likely stabilized by the electron donation from the imine in a 5-membered transition state, giving palladium 18 electrons, the preferred electronic configuration for palladium.[21] These computations are in agreement with the excellent regioselectivity of this method, compared to the traditional global decarbonylation approaches.

In summary, we report a regioselective aldehyde decarbonylation, the first to our knowledge, via a nitrile boronic acid cross-coupling reaction under mild conditions.[22] On the basis of experimental and computational analysis, we concluded that the exclusive *ortho* selectivity is due to the lower activation energy for the decarbonylation of *ortho*-aldehydes over *meta*- or *para*-aldehydes. The substrate scope was explored with a variety of boronic acids and diverse nitriles, demonstrating the broad compatibility of this reaction. This method exhibits the ability to transform and remove functionality in a one-pot manner under mild conditions with low catalyst loading, while demonstrating the potential for other directing groups to promote selective decarbonylation.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0042-1751562.

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(22) **Aldehyde Decarbonylation; General Procedure**
To a mixture of THF:H_2O (5:1) in a 35 mL high-pressure tube, TFA (10 equiv.) was added followed by the addition of nitrile **1** (1 equiv.), formyl phenyl boronic acid **2** (4 equiv.), and 2,2′-bipyridyl ligand (40 mol%). The mixture was left to stir until all compounds had dissolved, after which N_2 was bubbled for 5 minutes. Finally, $Pd(OAc)_2$ (20 mol%) was transferred to the reaction vessel (order of addition reduces oxidative homocoupling of boronic acid). The high-pressure tube was again flushed with N_2 and the contents left to stir for 24 hours at 80 °C. The reaction progress was monitored by TLC. After completion of the reaction, the mixture was diluted with EtOAc (10 mL), extracted with brine (3 × 15 mL), dried over Na_2SO_4, and evaporated. The crude reaction mixture was then purified by silica gel column chromatography (EtOAc/hexane gradient), and the resulting products were characterized by NMR.