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Palladium-Catalyzed Conjugate Addition of Arylboronic Acids to β,β-Disubstituted Enones in Aqueous Media: Formation of Bis-benzylic and *ortho*-Substituted Benzylic Quaternary Centers

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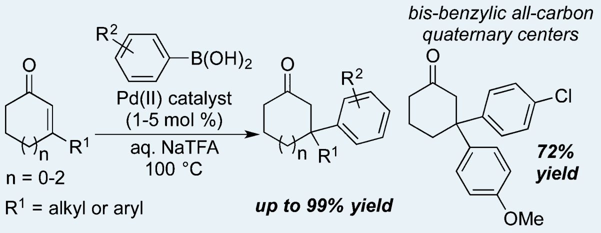
Supporting Information

ABSTRACT: Palladium-catalyzed conjugate addition of arylboronic acids to β,β-disubstituted enones in aqueous media is reported. Additions of a wide range of arylboronic acids to β,β-disubstituted enones occur to form ketone products bearing benzylic all-carbon quaternary centers. These reactions are promoted by a simple catalyst prepared from palladium trifluoracetate and 2,2′-bipyridine. The use of aqueous sodium trifluoracetate as the reaction medium significantly enhances reactivity and enables the formation of challenging bis-benzylic and *ortho*-substituted benzylic all-carbon quaternary centers.

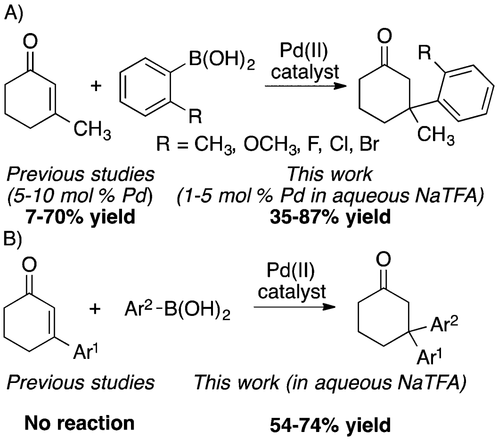


KEYWORDS: *conjugate addition, quaternary center, palladium, aqueous media, arylboronic acid*

Transition-metal-catalyzed conjugate addition of aryl nucleophiles to β,β-disubstituted enones is a valuable approach to construct benzylic all-carbon quaternary centers.[1] Nickel-catalyzed conjugate additions of arylaluminum reagents[2] and copper-catalyzed additions of arylaluminum,[3] arylmagnesium,[4] and arylzinc[5] reagents are established methods to generate benzylic all-carbon quaternary centers. These processes involve air- and/or moisture-sensitive organometallic nucleophiles and typically do not occur in aqueous media. In contrast, rhodium- and palladium-catalyzed conjugate additions of air- and moisture-stable tetraarylborates,[6] arylboroxines,[7] and arylboronic acids[8,9] form the corresponding ketones containing benzylic quaternary carbon centers in high yields and, in several cases, with high enantioselectivities.

In recent years, palladium-catalyzed conjugate additions of arylboronic acids to β,β-disubstituted enones have emerged as a primary target for further development due to the stability, functional group compatibility, and commercial availability of arylboronic acids.[9−11] Conjugate additions of a wide range of arylboronic acids to β,β-disubstituted enones occur in high yields when the reactions are conducted in the presence of readily accessible palladium(II) complexes of 2,2′-bipyridine (2,2′-bpy).[9] In addition, Stoltz and Minnaard have developed highly enantioselective variants of these reactions using palladium(II) complexes of chiral, nonracemic pyridinooxazoline (Pyox)[10] and bisoxazoline (Box)[11] ligands as catalysts.

Scheme 1. Current Challenges in Pd-Catalyzed Conjugate Addition of Arylboronic Acids to β,β-Disubstituted Enones



Although current palladium catalysts promote conjugate additions of arylboronic acids to form ketones containing benzylic quaternary carbon centers, additions of *ortho*-substituted arylboronic acids to β,β-disubstituted enones and reactions to generate bis-benzylic quaternary centers remain challenging. (Scheme 1). Palladium-catalyzed conjugate additions of *ortho*-substituted arylboronic acids to β,β-disubstituted enones often result in low yields of the corresponding ketone products and require high loadings of the palladium catalyst (Scheme 1A).[10b,c,11b] In addition, palladium-catalyzed conjugate additions of arylboronic acids to β-aryl β,β-disubstituted enones have not been reported to form bis-benzylic quaternary carbon centers (Scheme 1B). Herein, we report studies to identify a combination of palladium catalyst and aqueous reaction conditions to address these limitations and enable the formation of ketones

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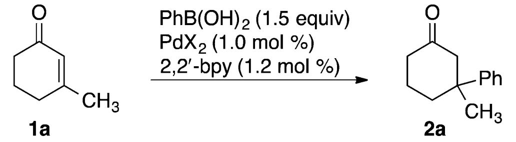
containing sterically encumbered benzylic and bis-benzylic all-carbon quaternary centers.

At the outset of our studies, we noted a report by Stoltz indicating that the presence of water increases the overall rate of palladium-catalyzed conjugate additions to *β*,*β*-disubstituted enones.[10c] We hypothesized that the choice of aqueous reaction medium may also function to enhance the reactivity of palladium catalysts such that *ortho*-substituted benzylic and bis-benzylic all-carbon quaternary centers could be readily formed in these reactions. To test our hypothesis, we evaluated the Pd(II)-catalyzed addition of phenylboronic acid to 3-methylcyclohex-2-en-1-one **1a** in a variety of aqueous reaction media (Table 1).

Table 1. Identification of Reaction Conditions[a]



entry	reaction medium	temp (°C)	pH	X	yield (%)[b]
1	9:1 MeOH:H_2O	80	7	OAc	58
2	1:1 MeOH:H_2O	80	7	OAc	53
3	1:9 MeOH:H_2O	80	7	OAc	52
4	1:9 MeOH: 50 mM NaOAc	80	7	OAc	70
5	50 mM NaOAc	80	7	OAc	85
6	50 mM NaTFA	80	7	OAc	88
7	50 mM NaTFA	100	7	OAc	95
8	50 mM NaTFA	100	7	TFA	97
9[c]	50 mM NaTFA	100	7	TFA	91
10[c]	50 mM NaTFA	100	6.5	TFA	62
11[c,d]	50 mM NaTFA	100	8.2	TFA	99
12[c,e]	50 mM NaTFA	100	8.2	TFA	99
13[c,f]	50 mM NaTFA	100	8.2	TFA	60

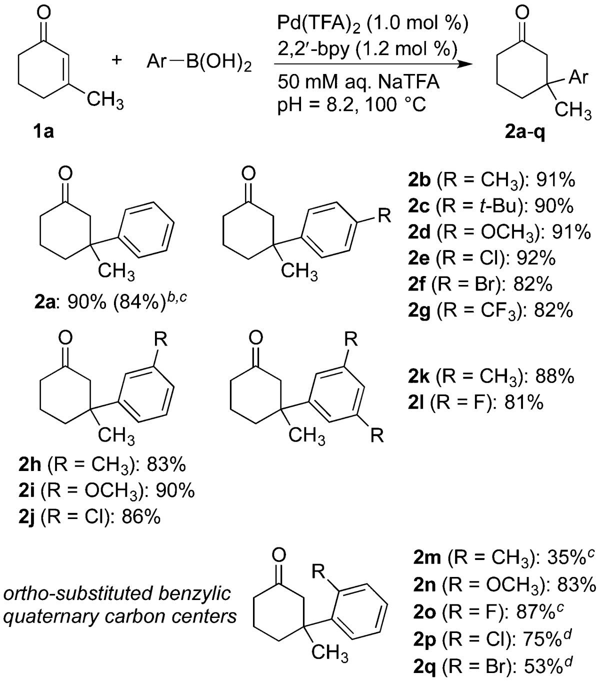
[a] Reaction conditions: **1a** (1.0 mmol), $PhB(OH)_2$ (1.5 mmol), PdX_2 (0.010 mmol), 2,2′-bpy (0.012 mmol), reaction medium (0.33 mL), 16 h. Abbreviations: sodium acetate (NaOAc), sodium trifluoracetate (NaTFA). [b] Determined by ^1H NMR spectroscopy using dibromomethane as an internal standard. [c] Reactions performed with 1.2 equiv of $PhB(OH)_2$. [d] Reaction run for 2 h. [e] Reaction run for 4 h in the presence of 0.5 mol % $Pd(TFA)_2$ and 0.6 mol % 2,2′-bpy. [f] Reaction run for 8 h in the presence of 0.25 mol % $Pd(TFA)_2$ and 0.3 mol % 2,2′-bpy.

The reaction of **1a** with 1.5 equiv of phenylboronic acid in the presence of a catalyst prepared from palladium acetate ($Pd(OAc)_2$) and 2,2′-bipyridine was initially evaluated in MeOH:H_2O mixtures ranging from 9:1 to 1:9 (entries 1−3). The ratio of MeOH to water has little impact on the yields of 3-methyl-3-phenylcyclohexan-1-one **2a** (52−58%). However, increasing the ionic strength of the aqueous reaction medium has a dramatic impact on the yield of **2a** (entries 4−6). For example, the addition of phenylboronic acid to **1a** formed **2a** in 88% when the reaction was conducted in the presence of 50 mM aqueous sodium trifluoroacetate (NaTFA) (pH = 7) (entry 6).

The reaction temperature, pH of the aqueous reaction medium, and the identity of the Pd(II) salt also impact the efficiency of the Pd(II)-catalyzed addition of phenylboronic acid to **1a**. Ketone **2a** is formed in 95−97% yield when the reaction is conducted in 50 mM aqueous NaTFA at 100 °C with catalysts generated from 2,2′-bipyridine and either $Pd(OAc)_2$ or palladium trifluoroacetate ($Pd(TFA)_2$) (entries 7 and 8). The combination of a palladium catalyst generated from $Pd(TFA)_2$ and a higher reaction temperature enabled us to lower the loading of phenylboronic acid to 1.2 equiv with only a modest decrease in the yield of **2a** (entry 9). The pH of the reaction medium dramatically influences the efficiency of the model reaction (entries 10 and 11). The addition of phenylboronic acid to **1a** under slightly acidic conditions leads to a significant decrease in the yield of **2a** (62% yield, entry 10). In contrast, the model reaction forms **2a** in nearly quantitative yield when the reaction is conducted under basic conditions (99% yield, entry 11). Under these reaction conditions, the loading of the palladium catalyst can be lowered to 0.5 mol % without impacting the yield of **2a**, but a decrease in reaction efficiency is observed upon lowering the catalyst loading to 0.25 mol % (entries 12 and 13).

We chose to proceed with studies to evaluate additions of a variety of arylboronic acids to **1a** under the reaction conditions identified in entry 11 of Table 1. These results are summarized in Scheme 2. As noted above, the addition of phenylboronic acid to **1a** occurs to form **2a** in high yield. The addition of the related phenylboronic acid pinacol ester to **1a** occurs to form **2a** in 84% yield when the reaction is conducted with 2 mol % Pd catalyst. Additions of 4-substituted phenylboronic acids containing substituents ranging from strongly electron-donating

Scheme 2. Pd-Catalyzed Addition of Arylboronic Acids to 1a in Aqueous NaTFA[a]



[a] Reaction conditions: **1a** (1.0 mmol), arylboronic acid (1.2 mmol), palladium trifluoroacetate ($Pd(TFA)_2$) (0.010 mmol), 2,2′-bpy (0.012 mmol), 50 mM aq NaTFA (0.33 mL, pH = 8.2), 100 °C, 2−24 h. Isolated yields are reported after purification by flash column chromatography. [b] Reaction performed with 2.0 equiv PhBpin in place of $PhB(OH)_2$. [c] Reaction run in the presence of 2.0 mol % $Pd(TFA)_2$ and 2.4 mol % 2,2′-bpy with 2.0 equiv $ArB(OH)_2$. [d] Reaction run in the presence of 5 mol % $Pd(TFA)_2$ and 6 mol % 2,2′-bpy with 2.0 equiv $ArB(OH)_2$.

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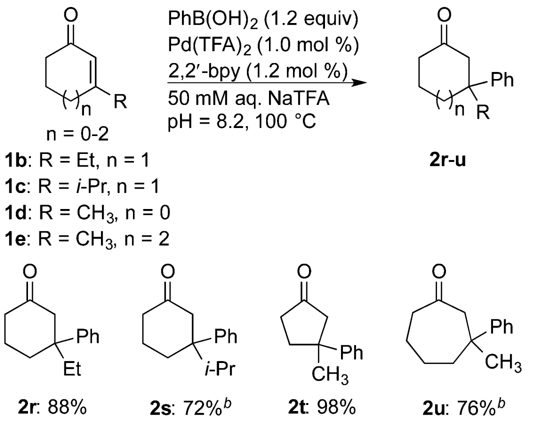
to strongly electron-withdrawing form ketones **2b**−**2g** in 82−92% yield. Additions of a variety of 3-substituted and 3,5-disubstituted phenylboronic acids form the corresponding ketones **2h**−**2l** in high yields (81−90% yield).

Additions of 2-substituted phenylboronic acids to *β*,*β*-disubstituted enones often occur in low yields with previously developed palladium catalyst and reaction systems.[10b,c,11b] However, additions of a range of 2-substituted phenylboronic acids to **1a** occur in the presence of 1−5 mol % catalyst when the reactions are conducted in aqueous NaTFA. These reactions form ketones **2m**−**2q** containing *ortho*-substituted benzylic quaternary carbons in 35−87% yield. Additions of 2,6-disubstituted phenylboronic acids to **1a** did not occur to form the corresponding ketone products.

Additions of phenylboronic acid to a variety of 3-substituted enones also occur in good to excellent yields (Scheme 3). The additions of phenylboronic acid to 3-ethylcyclohexenone and 3-isopropylcyclohexenone form ketones **2r** (R = Et) and **2s** (R = *i*-Pr) in 88% and 72% yield. Additions of phenylboronic acid to 5- and 7-membered enones also occur to form ketones containing benzylic quaternary carbons. The addition to 3-methylcyclopentenone forms ketone **2t** in 98% yield under our standard reaction conditions. The addition to 3-methylcycloheptenone forms ketone **2u** in 76% yield. However, 3-methylcycloheptenone is less reactive than the corresponding 5- and 6-membered ketones, and 2 mol % catalyst is required to drive this reaction toward completion.

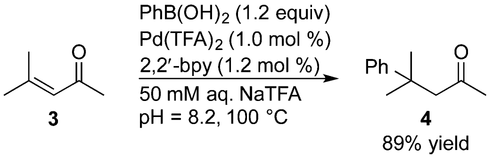
Scheme 3. Pd-Catalyzed Addition of $PhB(OH)_2$ to Cyclic Enones 1b−1e[a]



[a]Reaction conditions: **1b**−**1e** (1.0 mmol), $PhB(OH)_2$ (1.2 mmol), $Pd(TFA)_2$ (0.010 mmol), 2,2′-bpy (0.012 mmol), 50 mM aq NaTFA (0.33 mL, pH = 8.2), 100 °C, 16−24 h. Isolated yields are reported after purification by flash column chromatography. [b]Reaction run in the presence of 2.0 mol % $Pd(TFA)_2$ and 2.4 mol % 2,2′-bpy with 2.0 equiv of $PhB(OH)_2$.

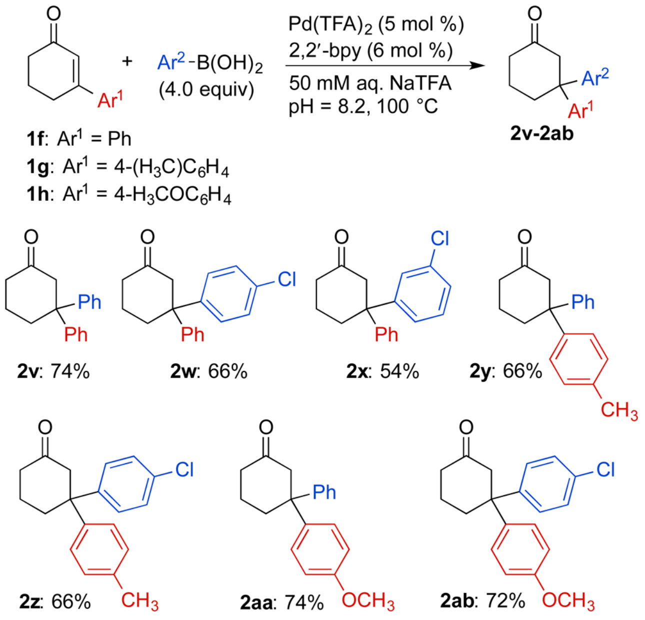
Our catalytic conditions also enable conjugate additions of arylboronic acids to acyclic *β*,*β*-disubstituted enones.[12] For example, the addition of phenylboronic acid to 4-methylpent-3-en-2-one **3** occurs under our standard reaction conditions to form ketone **4** in 89% yield eq 1.

The ability to form challenging *ortho*-substituted benzylic quaternary carbons through Pd-catalyzed conjugate additions of arylboronic acids led us to investigate whether our reaction system would enable the formation of bis-benzylic quaternary carbon centers. Formation of this class of quaternary carbon center by conjugate addition of aryl nucleophiles to cyclic *β*-aryl enones typically requires air- and/or moisture-sensitive organometallic reagents.[3c,13] To our knowledge, Pd-catalyzed additions of air- and moisture-stable arylboronic acids to cyclic *β*-aryl enones have not been reported.[14]

 (1)

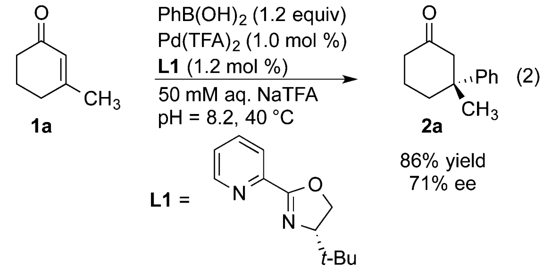
Scheme 4 summarizes additions of a variety of arylboronic acids to cyclic *β*-aryl enones **1f**−**1h** to form bis-benzylic quaternary carbon centers in aqueous media. These reactions form the *β*,*β*-diaryl ketone products **2v**−**2ab** in moderate to good yields, but 5 mol % palladium catalyst and 4.0 equiv of the arylboronic acid are required. Additions of phenyl-, 4-chlorophenyl-, and 3-chlorophenylboronic acids to 3-phenylcyclohexenone **1f** form ketones **2v**−**2x** in 54−74% yield. In contrast, additions of electron-rich arylboronic acids to **1f** occur in low yields due to protodeboronation. To address this issue, we incorporated the electron-rich aryl group (Ar^1 = 4-$(H_3C)C_6H_4$ (**1g**) and 4-$H_3COC_6H_4$ (**1h**)) into the 3-arylenone substrates. Additions of phenyl- and 4-chlorophenylboronic acid to enones **1g** and **1h** form the corresponding ketones **2y**−**2ab** containing bis-benzylic quaternary carbons in 66−74% yield. Attempts to construct bis-benzylic quaternary centers containing an *ortho*-substituted aryl group by addition of *ortho*-substituted arylboronic acids to enone **1f** led to low yields of the ketone products.[15]

Scheme 4. Pd-Catalyzed Addition of Arylboronic Acids to *β*-aryl Cyclohex-2-enones 1f−1h.[a]



[a]Reaction conditions: **1f**−**1h** (0.50 mmol), $Ar^2B(OH)_2$ (2.0 mmol), $Pd(TFA)_2$ (0.025 mmol), 2,2′-bpy (0.030 mmol), 50 mM NaTFA (0.17 mL, pH = 8.2), 100 °C, 16−20 h. Isolated yields are reported after purification by flash column chromatography.

We have demonstrated that a catalytic, enantioselective addition of phenylboronic acid to enone **1a** occurs in high yield with good enantioselectivity under our aqueous reaction conditions. This reaction occurs in the presence of a chiral, nonracemic catalyst generated from 1.0 mol % Pd(TFA)$_2$ and 1.2 mol % pyridinooxazoline ligand **L1** to form ketone **2a** in 86% yield with 71% ee eq 2. To our knowledge, this reaction represents the first enantioselective example of conjugate addition to form a benzylic, all-carbon quaternary center under completely aqueous conditions.



In summary, we have developed a set of catalytic reaction conditions for palladium-catalyzed conjugate addition of arylboronic acids to *β*,*β*-disubstituted enones in aqueous media. Additions of a wide range of arylboronic acids to *β*,*β*-disubstituted enones occur to form ketone products bearing benzylic all-carbon quaternary centers in moderate to high yields. The use of aqueous NaTFA as the reaction medium significantly enhances reactivity and enables the formation of challenging bis-benzylic and *ortho*-substituted benzylic quaternary centers. Studies to develop enantioselective, Pd-catalyzed conjugate additions to set bis-benzylic quaternary carbon stereocenters in aqueous media are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01272.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) Additions of phenylboronic acid to *β*-aryl- and *β*-heteroarylcyclohexenones formed trace ketone product or no conversion when the reactions were conducted in the presence of a catalyst prepared from Pd(TFA)$_2$ and a pyridinooxazoline ligand. See reference 10b for details.

(15) As an example, the addition of *ortho*-fluorophenylboronic acid to 3-phenylcyclohexenone occurs under the reaction conditions illustrated in Scheme 4 to form the corresponding ketone product in 27% yield by ^{1}H NMR analysis.