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Palladium-Catalyzed Conjugate Addition of Arylboronic Acids to \( \beta,\beta \)-Disubstituted Enones in Aqueous Media: Formation of Bis-benzylic and ortho-Substituted Benzyl Quaternary Centers

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ABSTRACT: Palladium-catalyzed conjugate addition of arylboronic acids to \( \beta,\beta \)-disubstituted enones in aqueous media is reported. Additions of a wide range of arylboronic acids to \( \beta,\beta \)-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 \( \beta,\beta \)-disubstituted enones is a valuable approach to construct benzylic all-carbon quaternary centers. Nickel-catalyzed conjugate additions of arylaluminum reagents and copper-catalyzed additions of aryllithium, arylmagnesium, and arylzinc reagents are established methods to generate benzylic all-carbon quaternary centers. These processes involve air- and 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, arylboroxines, and arylboronic acids 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 \( \beta,\beta \)-disubstituted enones have emerged as a primary target for further development due to the stability, functional group compatibility, and commercial availability of arylboronic acids. Conjugate additions of a wide range of arylboronic acids to \( \beta,\beta \)-disubstituted enones occur in high yields when the reactions are conducted in the presence of readily accessible palladium(II) complexes of 2,2'-bipyridine \((2,2'-\text{bpy})\). In addition, Stoltz and Minnaard have developed highly enantioselective variants of these reactions using palladium(II) complexes of chiral, nonracemic pyridinoxazoline \((\text{Pyox})\) and bisoxazoline \((\text{Box})\) ligands as catalysts.

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 \( \beta,\beta \)-disubstituted enones and reactions to generate bis-benzylic quaternary centers remain challenging. Palladium-catalyzed conjugate additions of ortho-substituted arylboronic acids to \( \beta,\beta \)-disubstituted enones often result in low yields of the corresponding ketone products and require high loadings of the palladium catalyst \((\text{Scheme 1A})\). In addition, palladium-catalyzed conjugate additions of arylboronic acids to \( \beta \)-aryl \( \beta,\beta \)-disubstituted enones have not been reported to form bis-benzylic quaternary carbon centers \((\text{Scheme 1B})\). 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.
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. 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

<table>
<thead>
<tr>
<th>entry</th>
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<th>temp (°C)</th>
<th>pH</th>
<th>X</th>
<th>yield (%)</th>
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<td>1</td>
<td>9:1 MeOH:H2O</td>
<td>80</td>
<td>7</td>
<td>OAc</td>
<td>58</td>
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<td>2</td>
<td>1:1 MeOH:H2O</td>
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<td>OAc</td>
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<td>7</td>
<td>OAc</td>
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<td>TFA</td>
<td>60</td>
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</table>

*a Reaction conditions: 1a (1.0 mmol), PhB(OH)2 (1.5 mmol), PdX2 (0.010 mmol), 2,2′-bpy (0.012 mmol), reaction medium (0.33 mL), 16 h. Abbreviations: sodium acetate (NaOAc), sodium trifluoroacetate (NaTFA). *b Determined by 1H NMR spectroscopy using dibromoacetone 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:H2O 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-phenylcyclohex-2-en-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 to strongly electron-withdrawing groups enabled us to conduct the reaction under basic conditions and with only 0.5 mol % catalyst loading to synthesize the corresponding ortho-substituted ketones in good to excellent yields (Scheme 2, entries 12–14).

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

4 Reaction conditions: 1a (1.0 mmol), aryloboronic 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. *d Reaction performed with 2.0 equiv PhBpin in place of PhB(OH)2. *e 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.
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. 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 Scheme 3. Pd-Catalyzed Addition of PhB(OH)2 to Cyclic Enones 1b–1e

```
<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield</th>
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<tbody>
<tr>
<td>Et</td>
<td>2r</td>
<td>88%</td>
</tr>
<tr>
<td>i-Pr</td>
<td>2s</td>
<td>72%</td>
</tr>
<tr>
<td>CH3</td>
<td>2t</td>
<td>98%</td>
</tr>
<tr>
<td>CH3</td>
<td>2u</td>
<td>76%</td>
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</tbody>
</table>
```

“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. 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.”

Scheme 4 summarizes additions of a variety of aryloboronic 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 aryloboronic acid are required. Additions of phenyl-, 4-chlorophenyl-, and 3-chlorophenylboronic acids to 3-phenylcyclohexene 1f form ketones 2v–2x in 54–74% yield. In contrast, additions of electron-rich aryloboronic acids to 1f occur in low yields due to protodeboronation. To address this issue, we incorporated the electron-rich aryl group (Ar1 = 4-((H3C)C6H4) and 4-H3COC6H4) into the 3-aryleneone 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 aryloboronic acids to enone 1f led to low yields of the ketone products.

Our catalytic conditions also enable conjugate additions of aryloboronic acids to acyclic β,β-disubstituted enones. 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 aryloboronic 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. To our knowledge, Pd-catalyzed additions of air- and moisture-stable aryloboronic acids to cyclic β-aryl enones have not been reported. Scheme 4 summarizes additions of a variety of aryloboronic 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 aryloboronic acid are required. Additions of phenyl-, 4-chlorophenyl-, and 3-chlorophenylboronic acids to 3-phenylcyclohexene 1f form ketones 2v–2x in 54–74% yield. In contrast, additions of electron-rich aryloboronic acids to 1f occur in low yields due to protodeboronation. To address this issue, we incorporated the electron-rich aryl group (Ar1 = 4-((H3C)C6H4) and 4-H3COC6H4) into the 3-aryleneone 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 aryloboronic acids to enone 1f led to low yields of the ketone products.
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 disubstituted enones in aqueous media 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.

ACKNOWLEDGMENTS

We thank Iowa State University and the Iowa State University Center for Catalysis for financial support of this work.

REFERENCES

(14) (1a) 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-phenylcyclohexene occurs under the reaction conditions illustrated in Scheme 4 to form the corresponding ketone product in 27% yield by 1 H NMR analysis.