Alkyl aryl ketones are fundamental intermediates in the pharmaceutical, fragrance, dye, and agrochemical industries. They are usually synthesized by the traditional Friedel–Crafts acylation, which involves handling hazardous reagents and fails with electron-deficient arenes. Hydroacylation allows for direct access to these ketones from aldehydes and olefins, but generally requires chelation assistance for C–H activation and for inhibiting decarbonylation. Acylation of aryl halides offers another direct approach. However, there are only a few reported examples of acylation of aryl iodides with aldehydes; these are catalyzed by bimetallic systems and require a chelating auxiliary on the aldehydes, affording alkyl aryl ketones in low yields. In related studies, aryl boronate salts have been acylated with aldehydes to give diaryl ketones, which could also be obtained by coupling of aryl iodides with N-pyrazyl aldimines or N-tert-butylhydrazones followed by hydrolysis. Herein we disclose an efficient, palladium-catalyzed direct acylation reaction of aryl bromides with aldehydes, affording alkyl aryl ketones in one step.

The Heck reaction of aryl halides with the electron-rich olefin vinyl ethers or enamides provides yet another indirect method for accessing alkyl aryl ketones, where the aryl group inserts at the carbon α to the heteroatom and hydrolysis results in the ketone (Scheme 1). As is known, under basic conditions or in the presence of a secondary amine, an aldehyde can equilibrate with an enolate or enamine, thus generating an olefin similar to that used in the well-established Heck reaction (Scheme 1). Enlightened by this, we reasoned that, if the enolate or enamine could be formed in situ, we might be able to obtain ketones directly from aryl halides and aldehydes via the Heck coupling.

With this hypothesis in mind, we set out to examine the acylation of 1-bromo-4-methoxybenzene (1a) with octanal (2f) in the presence of various additives.

**Table 1. Screening Conditions for the Acylation of 1a with 2f**

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand additive solvent yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>dppp   KF</td>
</tr>
<tr>
<td>2</td>
<td>dppp   K2CO3</td>
</tr>
<tr>
<td>3</td>
<td>dppp   KOBu’</td>
</tr>
<tr>
<td>4</td>
<td>dppp   Et3N</td>
</tr>
<tr>
<td>5</td>
<td>dppp   l-proline</td>
</tr>
<tr>
<td>6</td>
<td>dppp   pyrrolidine</td>
</tr>
<tr>
<td>7</td>
<td>dppp   pyrrolidine, 4Å MS</td>
</tr>
<tr>
<td>8</td>
<td>dppp   n-BuNH2, 4Å MS</td>
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<tr>
<td>9</td>
<td>dppp   n-Bu2NH, 4Å MS</td>
</tr>
<tr>
<td>10</td>
<td>dppp   morpholine, 4Å MS</td>
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<tr>
<td>11</td>
<td>dppp   piperidine, 4Å MS</td>
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<tr>
<td>12</td>
<td>dppp   l-proline, 4Å MS</td>
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<tr>
<td>13</td>
<td>PPh3  pyrrolidine, 4Å MS</td>
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<tr>
<td>14</td>
<td>dppf  pyrrolidine, 4Å MS</td>
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<tr>
<td>15</td>
<td>BINAP pyrrolidine, 4Å MS</td>
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<tr>
<td>16</td>
<td>dppp   pyrrolidine, 4Å MS</td>
</tr>
<tr>
<td>17</td>
<td>dppp   pyrrolidine, 4Å MS</td>
</tr>
</tbody>
</table>

*All reactions were carried out with 1a (1.0 mmol), 2f (1.2 equiv), 2 equiv of additive, Pd(dba)2 (2 mol%), and ligand (3 mol %) in 4 mL of DMF at 115 °C for 6 h. 4Å MS: 4Å molecular sieves, 1 g when added; dppp: 1,3-bis(diphenylphosphino)propane; dppf: 1,1’-bis(diphenylphosphino)ferrocene; BINAP: 2,2’-bis(diphenylphosphino)-1,1’-binaphthalene. Isolated yields of ketone.

**Table 2. Acylation of 1a with Various Aldehydes (2a–k)**

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>2b</td>
</tr>
<tr>
<td>3</td>
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<td>10</td>
<td>2j</td>
</tr>
<tr>
<td>11</td>
<td>2k</td>
</tr>
</tbody>
</table>

*Reactions were carried out with 1a (1.0 mmol), 2a–k (1.2 equiv), pyrrolidine (2 equiv), 4Å MS (1 g), Pd(dba)2 (2 mol %), and dppp (3 mol %) in 4 mL of DMF at 115 °C for 6 h. Isolated yields. Two equivalents of aldehyde used.
We then turned attention to secondary amines, which are prone to deprotonation with a base, using Pd(dba)$_2$-phosphine as catalyst precursor. The results are summarized in Table 1. The desired ketone 3f was not isolated when using Et$_3$N led to only a small amount of product. We then tested a series of other amines, which are prone to forming enamines with the aldehyde. To our delight, an encouraging result was obtained when pyrrolidine was used (entry 6). We then tested a range of other additives under various conditions. The results show that the combination of pyrrolidine and 4Å MS affords the best yield of ketone 3f (entry 7). No reaction occurred using 2f by using 20 mol % of pyrrolidine and 1 equiv of K$_2$CO$_3$ as base under otherwise identical conditions to those above. 3f was obtained in 85% isolated yield. This compares well with the result in Table 2, suggesting that pyrrolidine indeed acts as a catalyst, presumably converting the aldehyde into a highly reactive electron-rich olefin for palladium to seize and as a base under the conditions of Tables 2 and 3 to neutralize the HBr released from the Heck reaction, as hypothesized in Scheme 1. It is interesting to note that, under similar conditions but without pyrrolidine and 4Å MS added, the coupling reaction of aldehydes with aryl bromides led to α-arylated aldehydes instead of ketones, as shown by Hartwig very recently.

Having established the optimized conditions, we then tested the acylation of 1a with various aldehydes 2a–k. The results are shown in Table 2. As may be expected, 10c ortho substitution on the arenne ring decreases the yield (entry 2). It appears that aryl bromides with electron-withdrawing or very electron-donating groups also tend to furnish lower yields. Good results were again obtained when using the aldehydes 2f–k (entries 13–15). We also examined the acylation of 2-bromothiophene (1m); a moderate yield was recorded (entry 12).

The hypothesis in Scheme 1 implies that, in the case of an enamine, the overall acylation can be catalytic in the amine since it should be regenerated following hydrolysis of the Heck coupling product. To further probe the mechanism, we then studied the acylation of 1a with 2f by using 20 mol % of pyrrolidine and 1 equiv of K$_2$CO$_3$ as base under otherwise identical conditions to those above. 3f was obtained in 85% isolated yield. This compares well with the result in Table 2, suggesting that pyrrolidine indeed acts as a catalyst, presumably converting the aldehyde into a highly reactive electron-rich olefin for palladium to seize and as a base under the conditions of Tables 2 and 3 to neutralize the HBr released from the Heck reaction, as hypothesized in Scheme 1. It is interesting to note that, under similar conditions but without pyrrolidine and 4Å MS added, the coupling reaction of aldehydes with aryl bromides led to α-arylated aldehydes instead of ketones, as shown by Hartwig very recently.

In summary, we have developed an efficient protocol for the direct acylation of aryl bromides with various aldehydes, obtaining alkyl aryl ketones in moderate to excellent yields. The reaction appears to involve co-catalysis of palladium and amine. Studies into the mechanism and further application of the reaction will be the focus of future work.

Acknowledgment. We thank the EPSRC (EP/F000316) for support.

Supporting Information Available: Experimental details and analytic data (NMR, IR, MS, and elemental analysis). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(15) Under the same conditions but in 10 h reaction time, 3k, 3l, 3m, and 3u were obtained in 75, 75, 75, and 79% isolated yield, respectively.

JA804351Z