Rhodium-Catalyzed Alkylation of Aromatic Ketones with Allylic Alcohols and α,β-Unsaturated Ketones

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Abstract: The direct transition-metal-catalyzed addition of C–H bonds to unsaturated C=X (X=C, O, and N) bonds via C–H bond activation has been recognized as a powerful tool for the construction of C–C bonds (in terms of atom and step economy). Herein, the direct rhodium-catalyzed C–H bond addition of aromatic ketones to allylic alcohols and α,β-unsaturated ketones that affords β-aryl carbonyl compounds is described, in which a ketone carbonyl acts as a weakly coordinating directing group. It was found that the type of alkyl in aromatic ketones is crucial for the success of the reaction. This transformation provides a convenient and efficient methodology for the synthesis of 2-alkyl aromatic ketones in moderate-to-excellent yields.

Keywords: direct C–H bond addition; weakly coordinating directing group; C–H functionalization; rhodium catalysis

1. Introduction

The direct addition of C–H bonds to unsaturated C=X (X=C, O, and N) bonds catalyzed by transition-metal-catalyzed reactions has been recognized as a powerful strategy for the construction of C–C bonds in terms of atom and step economy [1–3]. Over the past two decades, remarkable achievements regarding the addition of metal-catalyzed C–H bonds to unsaturated bonds have been achieved [4,5]. As for unsaturated compounds, α,β-unsaturated ketones and allylic alcohols represent two important coupling partners to C–H reagents for C–C bond formation. In the cases of α,β-unsaturated ketones, the useful synthetic carbonyl group makes such an addition reaction more powerful in the construction of drug-related complex molecules [6]. Allylic alcohols have the advantages of commercial availability, low cost, and easy preparation. The tandem reactions of C–H bond addition to allylic alcohol, β-hydride elimination, and keto–enol tautomerism generate β-aryl carbonyl compounds [7–9], which is identical with the direct addition of C–H bonds to α,β-unsaturated ketones. Therefore, allylic alcohols have been used as substitutes for α,β-unsaturated ketones in some cases. In order to enhance the site selectivity of C–H bond functionalization, directing groups are often employed. Among the direct directing-group-assisted addition of C–H bonds to allylic alcohols and α,β-unsaturated ketones, nitrogen-based functional groups, such as quinoline N-oxide [10], pyrazolone [11], N-heterocycle [12–14], amide [15–19], pyridine [20–25], and imide [26,27], were usually utilized to promote the activation of C–H bonds owing to their good coordination ability with transition metals (Scheme 1a). In addition, Jayarajan and Maiti et al. achieved meta-C–H alkylation with allylic alcohols and long-linker-bearing pyrimidine [28–30].

Ketone moieties are widely found in many functional materials and bioactive molecules. They are often employed as versatile synthetic intermediates due to the fact that they can...
be readily converted into diverse functional groups. However, due to the weakly coordinating ability of ketone carbonyl, the application of ketone as a directing group is much rarer [31,32]. Although direct ketone-assisted additions of C–H bonds to simple alkenes [33], maleimide [34,35], and trimethoxy(vinyl)silane [36,37] have been illuminated by Martinez, Prabhu, and Murai, et al., as of now, the direct transitional-metal-catalyzed C–H bond additions of aromatic ketones to allylic alcohols and $\alpha,\beta$-unsaturated ketones that afford $\beta$-aryl carbonyl compounds, which are important synthetic precursors in synthetic organic chemistry [38], have seldom been demonstrated. Only heteroaromatic ketones containing indole were successfully explored by Yu and Punniyamurthy et al. to instigate a reaction with allylic alcohols [39,40], restricting the application of aromatic ring moiety. As a continuation from our study on the direct addition of C–H bonds to unsaturated double bonds [41,42], we herein present the direct rhodium-promoted C–H bond alkylation of aromatic ketones with allylic alcohols and $\alpha,\beta$-unsaturated ketones (Scheme 1b), generating the corresponding $\beta$-aryl carbonyl compounds.

(a) Previous work by Maiti, Jiang, Chatani, Glorius, Kim, etc.

$$\text{R} + \text{OH} \xrightarrow{\text{Catalyst: Rh, Ru, Pd}} \text{R} \xrightarrow{\text{Oxidant: Ag}_2\text{CO}_3, \text{Cu(OAc)}_2, \text{etc.}} \text{DG}$$

DG = directing group (N-based compounds)

(b) This work

$$\text{R} + \text{OH} \xrightarrow{\text{[Cp*RhCl}_2]} \text{R} \xrightarrow{\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}, \text{KOAc}, \text{TFE} \text{or NaOAc, HFIP}} \text{R}$$

Weakly coordinating ketone carbonyl acts as a directing group

Scheme 1. Alkylation reactions assisted by different directing groups.

2. Results and Discussion

We selected 2,2,2-trimethylacetophenone (1a) and 1-penten-3-ol (2a) as model substrates to optimize the reaction conditions (Scheme 2, Table 1). Initially, the expected product 3a was obtained in a 32% yield using [Cp*RhCl$_2$]$_2$ (5 mol %) as a catalyst and Cu(OAc)$_2$·H$_2$O (0.15 mmol) as an oxidant in trifluoroethanol (TFE, 0.6 mL) under an Ar atmosphere at 100 °C (Table 1, entry 1). The yield of 3a' (27%) was also observed in the crude reaction mixture. Nevertheless, several commonly used solvents, such as t-AmylOH, PhCl, 1,2-dichloroethane (DCE), CH$_3$CN, tetrahydrofuran (THF), and 1,4-dioxane, except TFE and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), failed to deliver 3a (Table 1, entries 1–8), indicating that TFE and HFIP may play an important role in the stabilization of an intermediate bearing electron-deficient metal center via coordination [43,44]. TFE was the best choice for this reaction (Table 1, entry 1). Among the different catalysts that were investigated, [Cp*RhCl$_2$]$_2$ was proven to be the best choice (Table S1 in the Supplementary Materials). The yield increased to 42% when the reaction temperature was raised to 120 °C (Table 1, entry 9). Then, several metal acetates were used to enhance the reaction efficiency. Unfortunately, AgOAc, NaOAc, KOAc, LiOAc, and Co(OAc)$_2$ afforded unsatisfactory results (Table 1, entries 10–14). To our delight, the combination of Cu(OAc)$_2$·H$_2$O and KOAc greatly enabled the reaction, and resulted in an excellent yield of 3a (76% yield, Table 1, entry 15). Subsequently, the amount of catalyst, Cu(OAc)$_2$·H$_2$O, and KOAc; the reaction time; and the solvent volume were screened to further optimize the reaction conditions. Finally, [Cp*RhCl$_2$]$_2$ (4 mol%), Cu(OAc)$_2$·H$_2$O (1.5 equiv.), KOAc (1.5 equiv.), and TFE were chosen as the best reaction conditions (78% yield, Table 1, entry 16).
propiophenone, did not yield any desired products (Figure 1, Table 1). This protocol was compatible with different 3,4-dihydronaphthalen-1(2H)-ones, such as 3,4-dihydronaphthalen-1(2H)-one, 6-methoxy-3,4-dihydronaphthalen-1(2H)-one, and 4-methyl-3,4-dihydronaphthalen-1(2H)-one, producing good targeted products (3h-3j, 54–60% yields). The reaction of 2,2-dimethyl-1-phenylpropan-1-one and but-3-en-2-ol furnished 3k in a 57% yield. To our excitement, heteroaromatic tert alkyl ketone, i.e., 2,2-dimethyl-1-(thiophen-2-yl)propan-1-one, worked well with allylic alcohol bearing different carbon chains, and successfully converted to moderate-to-excellent product yields (Figure 1, 3l-3p, 38–80% yields). However, aryl primary alkyl ketones, such as acetophenone and propiophenone, did not yield any desired products (Figure 1, 3q and 3r). This may be because the electron-donating ability of tertiary or secondary alkyl groups is stronger than that of primary alkyl groups, which is beneficial for the attack of electrophilic rhodium.

Table 1. Typical results for optimizing reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)₂·H₂O</td>
<td>TFE</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)₂·H₂O</td>
<td>HFIP</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)₂·H₂O</td>
<td>t-AmyleOH</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)₂·H₂O</td>
<td>PhCl</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)₂·H₂O</td>
<td>DCE</td>
<td>32</td>
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<td>6</td>
<td>Cu(OAc)₂·H₂O</td>
<td>CH₃CN</td>
<td>24</td>
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<tr>
<td>7</td>
<td>Cu(OAc)₂·H₂O</td>
<td>THF</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OAc)₂·H₂O</td>
<td>1,4-dioxane</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OAc)₂·H₂O</td>
<td>TFE</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>AgOAc</td>
<td>TFE</td>
<td>78</td>
</tr>
<tr>
<td>11</td>
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<td>TFE</td>
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<td>12</td>
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<td>TFE</td>
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</tr>
<tr>
<td>16</td>
<td>Cu(OAc)₂·H₂O</td>
<td>KOAc</td>
<td>78</td>
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* 2,2,2-trimethylacetophenone (0.1 mmol), pent-1-en-3-ol (0.2 mmol), [Cp*RhCl₂]₂ (5 mol%), additive (0.15 mmol), and solvent (0.6 mL) at 100 °C for 24 h under Ar conditions. ** This was determined via the ¹H NMR analysis of the crude reaction mixture, employing 1,3,5-trimethoxybenzene as an internal standard. *** ND = not detected. **** 120 °C. ***** KOAc (0.15 mmol). The 2,2-dimethyl-1-phenylpropan-1-one (0.2 mmol), 1-penten-3-ol (0.4 mmol), [RhCp*Cl₂]₂ (4 mol%), Cu(OAc)₂·H₂O (0.3 mmol), KOAc (0.3 mmol), and TFE (0.6 mL) for 24 h under Ar conditions.

After the optimal reaction conditions were established, the scope of this addition reaction was explored. Firstly, the adaptability of substituted 2,2-dimethyl-1-phenylpropan-1-one was examined. 2,2-Dimethyl-1-phenylpropan-1-one-bearing electron-donating groups at para- and meta-positions smoothly reacted with 2a to give 3a-3e (Figure 1, 39–74% yields). 2,2-Dimethyl-1-phenylpropan-1-one-bearing electron-donating groups (e.g., –CF₃, –Cl, etc.) could not deliver the addition products, which may be attributable to the decreased electron density on the benzene ring, and is unfavorable for the attack of electrophilic rhodium. Unsubstituted secondary alkyl ketones also successfully participated in this transformation, delivering products 3f and 3g in moderate yields (Figure 1, 40–51% yields). This protocol was compatible with different 3,4-dihydronaphthalen-1(2H)-ones, such as 3,4-dihydronaphthalen-1(2H)-one, 6-methoxy-3,4-dihydronaphthalen-1(2H)-one, and 4-methyl-3,4-dihydronaphthalen-1(2H)-one, producing good targeted products (3h-3j, 54–60% yields). The reaction of 2,2-dimethyl-1-phenylpropan-1-one and but-3-en-2-ol furnished 3k in a 57% yield. To our excitement, heteroaromatic tert alkyl ketone, i.e., 2,2-dimethyl-1-(thiophen-2-yl)propan-1-one, worked well with allylic alcohol bearing different carbon chains, and successfully converted to moderate-to-excellent product yields (Figure 1, 3l-3p, 38–80% yields). However, aryl primary alkyl ketones, such as acetophenone and propiophenone, did not yield any desired products (Figure 1, 3q and 3r). This may be because the electron-donating ability of tertiary or secondary alkyl groups is stronger than that of primary alkyl groups, which is beneficial for the attack of electrophilic rhodium.

Scheme 2. Alkylation of 2,2,2-trimethylacetophenone with pent-1-en-3-ol.
Inspired by the reaction results of ketones and allylic alcohol, we envisioned that by replacing allylic alcohols with α,β-unsaturated ketones, the alkylation reactions may take place under simpler reaction conditions without the oxidant. After screening several parameters, such as catalysts, additives, solvents, etc., we were pleased to find that the addition reaction between 2,2-dimethyl-1-phenylpropan-1-one and pent-1-en-3-one proceeded well when 3 mol% of \( [\text{Cp^*RhCl_2}]_2 \) was employed in combination with NaOAc (0.25 equiv.) in HFIP at 120 °C for 16 h, furnishing the targeted product 3a in an excellently isolated yield of 87% (Figure 2, 3a). Subsequently, the scope of this reaction was studied with pent-1-en-3-one by varying different aromatic ketones. Similar to the reaction using allylic alcohol as a coupling partner, aryl tert-alkyl ketones, aryl secondary alkyl ketones, and 3,4-dihydronaphthalen-1(2H)-one were all found to provide targeted products in moderate-to-excellent isolated yields (Figure 2; 3b–3j and 3s–3u, 48–80%). But-3-en-2-one and oct-1-en-3-one also furnished the corresponding products 3k and 3v in excellent yields (Figure 2; 86% and 90%, respectively). 2,2-Dimethyl-1-(thiophen-2-yl)propan-1-one reacted smoothly with pent-1-en-3-one to give 3l in a 73% yield.
In order to explicate the mechanistic insights of this transformation, several experiments were conducted. A 40% H/D exchange was observed when 2,2-dimethyl-1-phenylpropan-1-one was treated in the presence of D$_2$O under standard conditions (Scheme 3a; see Supporting Information for details). This result suggests that the cyclorhodation process via the C–H bond cleavage should be reversible. The kinetic isotope effect (KIE) was determined via parallel experiments, and a $k_H/k_D$ ratio was found to be 5.23 (Scheme 3b; see Supporting Information for details), which indicates that the C–H bond cleavage might be related to the rate-determining step.

**Scheme 3.** Mechanistic investigation results.
Based on the above experimental results and reported transition-metal-catalyzed alkylation reactions using allylic alcohol [45], a proposed mechanistic pathway for the rhodium(III)-catalyzed ketone-carbonyl-directed C–H bond addition with allylic alcohols and α,β-unsaturated ketone is depicted in Scheme 4. Initially, the dimer [Cp*RhCl₂]₂ was dissociated into an active rhodium monomer, generating a Rh(III) complex A through an ion exchange. Subsequently, with the assistance of the directing carbonyl group, regioselective electrophilic attack at the ortho position of carbonyl gave the intermediate B, releasing one HOAc molecule simultaneously. Then, the coordination of the double bond of allylic alcohol or α,β-unsaturated ketones to rhodium, followed by the migration insertion of the C–Rh bond to double bonds, delivered intermediate D or D’. The intermediate D underwent β-hydride elimination and enol isomerization to furnish the alkylation product F and Cp*Rh(I). Cp*Rh(I) was oxidized by copper (II) to start a new catalytic cycle. As for α,β-unsaturated ketones as a substrate, which does not require the involvement of copper oxidants, the final product was directly formed via the protonation of intermediate D’.

Scheme 4. Possible reaction mechanism.

3. Materials and Methods

3.1. General Remarks

The NMR spectra were recorded on a Bruker 400 MHz NMR or Bruker 600 MHz NMR, Karlsruhe, Germany. The 1H NMR and 13C NMR chemical shifts were determined using tetramethylsilane as an internal reference. The high-resolution mass spectra (HRMS) were obtained with a Bruker Compass Max instrument (ESI), Karlsruhe, Germany. All the commercial reagents were directly used without purification. The solvents used in this study were all analytical reagents.

3.2. General Process for Instigating the Reactions between Aromatic Ketones and Allylic Alcohols

The [RhCp*Cl₂]₂ (Rh*, 4.9 mg, 4 mol %, 0.008 mmol), Cu(OAc)₂·H₂O (59.9 mg, 1.5 equiv., 0.3 mmol), KOAc (29.4 mg, 1.5 equiv., 0.3 mmol), TFE (0.6 mL), aromatic ketones (0.2 mmol), and allylic alcohols (0.4 mmol) were added to the microwave vial. Then, TFE (0.6 mL) was added to microwave the vial under an Ar atmosphere. The reaction mixture was heated at 120 °C (oil bath temperature) for 24 h. The mixture was diluted with EtOAc (5 mL), and the solid in the mixture was removed by filtration. The obtained liquid was concentrated, and the residue was purified via thin-layer preparation chromatography to provide the corresponding product.
3.3. General Process for Instigating the Reactions between Aromatic Ketones and \(\alpha,\beta\)-Unsaturated Ketones

The \([\text{RhCp}^*\text{Cl}_2]\) (Rh*, 3.7 mg, 3 mol%, 0.006 mmol), NaOAc (4.1 mg, 0.25 equiv., 0.05 mmol), HFIP (1.0 mL), aromatic ketones (0.2 mmol), and \(\alpha,\beta\)-unsaturated ketones (0.3 mmol) were added to the microwave vial. Then, HFIP (1.0 mL) was added to microwave the vial under an Ar atmosphere. The reaction mixture was heated at 120 \(^\circ\) C (oil bath temperature) for 16 h. The mixture was diluted with EtOAc (5 mL), and the solid in the mixture was removed by filtration. The obtained liquid was concentrated, and the residue was purified via thin-layer preparation chromatography to provide the corresponding product.

3.4. Characterization Data of Products

3.4.1. 1-(2-Pivaloylphenyl)pentan-3-one, 3a

36.4 mg, 74% (isolated yield), or 42.6 mg, 87% (isolated yield), light yellow liquid, \(R_f = 0.51\) (n-hexane: EtOAc = 10: 1). \(^1\)H NMR (600 MHz, chloroform-d) \(\delta\) 7.29 (td, \(J = 7.8, 1.8\) Hz, 1H), 7.22 (d, \(J = 7.6\) Hz, 1H), 7.16–7.20 (m, 2H), 2.68–2.75 (m, 4H), 2.39 (q, \(J = 7.3\) Hz, 2H), 1.25 (s, 9H), and 1.04 (t, \(J = 7.3\) Hz, 3H). \(^13\)C NMR (150 MHz, chloroform-d) \(\delta\) 214.6, 210.2, 140.5, 137.5, 129.7, 128.8, 125.2, 124.6, 44.8, 44.3, 35.8, 28.3, 27.3, and 7.6. HRMS (ESI) \(m/z\): calculated for C\(_{20}\)H\(_{22}\)O\(_2\), [M + Na]\(^+\): 299.1512; found: 299.1506.

3.4.2. 1-(5-Methyl-2-pivaloylphenyl)pentan-3-one, 3b

20.4 mg, 39% (isolated yield), or 40.6 mg, 78% (isolated yield), light yellow liquid, \(R_f = 0.56\) (n-hexane: EtOAc = 5: 1). \(^1\)H NMR (600 MHz, chloroform-d) \(\delta\) 7.08 (d, \(J = 7.8\) Hz, 1H), 7.02 (s, 1H), 6.98 (d, \(J = 7.8\) Hz, 1H), 2.70–2.73 (m, 2H), 2.64–2.67 (m, 2H), 2.39 (q, \(J = 7.3\) Hz, 2H), 2.31 (s, 3H), 1.23 (s, 9H), and 1.04 (t, \(J = 7.3\) Hz, 3H). \(^13\)C NMR (150 MHz, chloroform-d) \(\delta\) 214.7, 210.5, 152.1, 137.8, 137.6, 126.9, 124.8, 45.0, 44.9, 44.6, 35.9, 28.0, 27.5, 21.2, and 7.7. HRMS (ESI) \(m/z\): calculated for C\(_{17}\)H\(_{24}\)O\(_2\), [M + Na]\(^+\): 283.1669; found: 283.1664.

3.4.3. 1-(5-(Tert-butyl)-2-pivaloylphenyl)pentan-3-one, 3c

29.7 mg, 49% (isolated yield), or 45.7 mg, 76% (isolated yield), light yellow liquid, \(R_f = 0.53\) (n-hexane: EtOAc = 5: 1). \(^1\)H NMR (600 MHz, chloroform-d) \(\delta\) 7.18–7.21 (m, 2H), 7.13 (d, \(J = 7.9\) Hz, 1H), 2.68–2.74 (m, 4H), 2.39 (q, \(J = 7.3\) Hz, 2H), 1.29 (s, 9H), 1.25 (s, 9H), and 1.04 (t, \(J = 7.3\) Hz, 3H). \(^13\)C NMR (150 MHz, chloroform-d) \(\delta\) 214.0, 210.8, 152.1, 137.8, 137.6, 126.9, 124.8, 122.3, 45.0, 44.9, 36.0, 34.7, 31.2, 28.6, 27.6, and 7.8. HRMS (ESI) \(m/z\): calculated for C\(_{20}\)H\(_{30}\)O\(_2\), [M + Na]\(^+\): 325.2138; found: 325.2136.

3.4.4. 1-(5-Methoxy-2-pivaloylphenyl)pentan-3-one, 3d

21.5 mg, 39% (isolated yield), or 44.2 mg, 80% (isolated yield), light yellow liquid, \(R_f = 0.32\) (n-hexane: EtOAc = 10: 1). \(^1\)H NMR (600 MHz, chloroform-d) \(\delta\) 7.19 (d, \(J = 8.5\) Hz, 1H), 6.75 (d, \(J = 2.5\) Hz, 1H), 6.71 (dd, \(J = 8.5, 2.5\) Hz, 1H), 3.80 (s, 3H), 2.73–2.76 (m, 2H), 2.68–2.70 (m, 2H), 2.40 (q, \(J = 7.3\) Hz, 2H), 1.24 (s, 9H), and 1.04 (t, \(J = 7.3\) Hz, 3H). \(^13\)C NMR (150 MHz, chloroform-d) \(\delta\) [ppm] = 213.9, 210.5, 159.9, 140.6, 133.0, 126.7, 115.4, 110.5, 55.2, 45.0, 44.5, 35.9, 28.3, 27.7, and 7.8. HRMS (ESI) \(m/z\): calculated for C\(_{17}\)H\(_{24}\)O\(_3\), [M + Na]\(^+\): 299.1618; found: 299.1612.

3.4.5. 1-(4-Methyl-2-pivaloylphenyl)pentan-3-one, 3e

29.3 mg, 56% (isolated yield), or 41.6 mg, 80% (isolated yield), light yellow liquid, \(R_f = 0.48\) (n-hexane: EtOAc = 10: 1). \(^1\)H NMR (600 MHz, chloroform-d) \(\delta\) 7.09 (d, \(J = 0.9\) Hz, 2H), 6.94 (s, 1H), 2.68–2.71 (m, 2H), 2.63–2.66 (m, 2H), 2.38 (q, \(J = 7.3\) Hz, 2H), 2.31 (s, 3H), 1.24 (s, 9H), and 1.03 (t, \(J = 7.3\) Hz, 3H). \(^13\)C NMR (150 MHz, chloroform-d) \(\delta\) 215.1, 210.5, 140.6, 134.9, 134.4, 129.6, 129.6, 125.2, 44.9, 44.5, 35.9, 27.6, 27.4, 21.0, and 7.7. HRMS (ESI) \(m/z\): calculated for C\(_{17}\)H\(_{24}\)O\(_2\), [M + Na]\(^+\): 283.1669; found: 283.1667.
3.4.6.  1-(2-Isobutrylphenyl)pentan-3-one, 3f

18.6 mg, 40% (isolated yield), or 30.0 mg, 65% (isolated yield), light yellow liquid, 
Rf = 0.57 (n-hexane: EtOAc = 5: 1). 1H NMR (600 MHz, chloroform-d) δ 7.54 (d, J = 7.8 Hz, 1H), 7.36–7.40 (m, 1H), 7.28 (d, J = 8.7 Hz, 2H), 3.37 (dt, J = 13.8, 6.9 Hz, 1H), 2.93 (dd, J = 9.7, 5.7 Hz, 2H), 2.80 (dd, J = 9.8, 5.6 Hz, 2H), 2.42 (q, J = 7.3 Hz, 2H), 1.17 (d, J = 6.9 Hz, 6H), and 1.05 (t, J = 7.3 Hz, 3H). 13C NMR (150 MHz, chloroform-d) δ 210.8, 209.0, 141.1, 138.3, 131.2, 130.9, 127.7, 126.0, 44.6, 38.7, 35.9, 28.4, 18.6, and 7.7. HRMS (ESI) m/z: calculated for C15H20O2, [M + Na]⁺: 255.1356; found: 255.1353.

3.4.7.  1-(2-(Cyclohexanecarboxyl)phenyl)pentan-3-one, 3g

27.7 mg, 51% (isolated yield), or 33.7 mg, 62% (isolated yield), light yellow liquid, 
Rf = 0.54 (n-hexane: EtOAc = 10: 1). 1H NMR (600 MHz, chloroform-d) δ 7.32 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 2H), 3.23 (t, J = 7.6 Hz, 2H), 2.95 (t, J = 6.1 Hz, 2H), 2.72 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 6.6 Hz, 2H), 2.44 (q, J = 7.3 Hz, 2H), 2.06–2.10 (m, 2H), and 1.04 (t, J = 7.3 Hz, 3H). 13C NMR (150 MHz, chloroform-d) δ 211.3, 200.0, 146.0, 144.3, 134.2, 135.0, 130.8, 137.4, 43.6, 41.0, 35.8, 31.0, 30.1, 22.9, and 7.8. HRMS (ESI) m/z: calculated for C15H16O2, [M + Na]⁺: 295.1669; found: 295.1657.

3.4.8.  8-(3-Oxopentyl)-3,4-dihyronaphthalen-1(2H)-one, 3h

25.5 mg, 55% (isolated yield), or 23.1 mg, 50% (isolated yield), yellow liquid, 
Rf = 0.46 (n-hexane: EtOAc = 5: 1). 1H NMR (600 MHz, chloroform-d) δ 7.32 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 2H), 3.23 (t, J = 7.6 Hz, 2H), 2.95 (t, J = 6.1 Hz, 2H), 2.72 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 6.6 Hz, 2H), 2.44 (q, J = 7.3 Hz, 2H), 2.06–2.10 (m, 2H), and 1.04 (t, J = 7.3 Hz, 3H). 13C NMR (150 MHz, chloroform-d) δ 211.3, 200.0, 146.0, 144.3, 134.2, 135.0, 130.8, 137.4, 43.6, 41.0, 35.8, 31.0, 30.1, 22.9, and 7.8. HRMS (ESI) m/z: calculated for C15H18O2, [M + Na]⁺: 253.1199; found: 253.1190.

3.4.9.  6-Methoxy-8-(3-oxopentyl)-3,4-dihyronaphthalen-1(2H)-one, 3i

28.3 mg, 54% (isolated yield), or 36.5 mg, 70% (isolated yield), yellow liquid, 
Rf = 0.13 (n-hexane: EtOAc = 5: 1). 1H NMR (600 MHz, chloroform-d) δ 6.64 (d, J = 2.4 Hz, 1H), 6.59 (d, J = 2.3 Hz, 1H), 3.82 (s, 3H), 3.23 (t, J = 7.6 Hz, 2H), 2.91 (t, J = 6.1 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.59 (t, J = 6.5 Hz, 2H), 2.45 (q, J = 7.3 Hz, 2H), 2.02–2.06 (m, 2H), and 1.04 (t, J = 7.3 Hz, 3H). 13C NMR (150 MHz, chloroform-d) δ 211.4, 198.4, 162.1, 148.7, 147.4, 124.4, 116.0, 111.7, 55.2, 43.5, 40.9, 35.7, 31.6, 30.7, 22.9, and 7.8. HRMS (ESI) m/z: calculated for C16H20O3, [M + Na]⁺: 283.1305; found: 283.1295.

3.4.10.  4-Methyl-8-(3-oxopentyl)-3,4-dihyronaphthalen-1(2H)-one, 3j

29.4 mg, 60% (isolated yield), yellow liquid, 
Rf = 0.48 (n-hexane: EtOAc = 5: 1). 1H NMR (600 MHz, chloroform-d) δ 7.36 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 7.7 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 3.20 (t, J = 7.6 Hz, 2H), 3.04–3.09 (m, 1H), 2.70–2.81 (m, 3H), 2.56–2.61 (m, 1H), 2.45 (q, J = 7.3 Hz, 2H), 2.21 (ddd, J = 14.1, 9.6, 4.9 Hz, 1H), 1.84–1.89 (m, 1H), 1.36 (d, J = 7.1 Hz, 3H), and 1.04 (t, J = 7.3 Hz, 3H). 13C NMR (150 MHz, chloroform-d) δ 211.3, 200.1, 150.5, 144.0, 132.7, 130.3, 130.1, 126.1, 43.8, 37.5, 35.7, 33.8, 30.1, 29.6, 21.2, and 7.8. HRMS (ESI) m/z: calculated for C16H19O2, [M + Na]⁺: 267.1356; found: 267.1351.

3.4.11.  4-(2-Pivaloylphenyl)butan-2-one, 3k

26.5 mg, 57% (isolated yield), or 40.0 mg, 86% (isolated yield), light yellow liquid, 
Rf = 0.35 (n-hexane: EtOAc = 10: 1). 1H NMR (600 MHz, chloroform-d) δ 7.29 (t, J = 6.8 Hz, 1H), 7.22 (d, J = 7.7 Hz, 1H), 7.18 (t, J = 8.6 Hz, 2H), 2.75 (t, J = 7.3 Hz, 2H), 2.67 (t, J = 7.3 Hz, 2H), 2.12 (s, 3H), and 1.25 (s, 9H). 13C NMR (150 MHz, chloroform-d) δ 214.8, 207.7, 140.6, 137.5, 129.8, 128.9, 125.4, 124.8, 45.8, 44.9, 29.9, 28.0, and 27.4. HRMS (ESI) m/z: calculated for C15H20O2, [M + Na]⁺: 255.1356; found: 255.1353.
3.4.12. 1-(2-Pivaloylthiophen-3-yl)pentan-3-one, 3l

40.3 mg, 80% (isolated yield), or 36.6 mg, 73% (isolated yield), light yellow liquid, Rᵣ = 0.47 (n-hexane: EtOAc = 10: 1). ¹H NMR (600 MHz, chloroform-d) δ 7.33 (d, J = 5.0 Hz, 1H), 6.96 (d, J = 5.0 Hz, 1H), 3.07 (t, J = 7.4 Hz, 2H), 2.37 (t, J = 7.5 Hz, 2H), 1.51–1.56 (m, 2H), 1.36 (s, 9H), 1.27 (dd, J = 15.0, 7.5 Hz, 2H), 1.19–1.25 (m, 2H), and 0.86 (t, J = 7.4 Hz, 3H). ¹³C NMR (150 MHz, chloroform-d) δ 210.6, 201.1, 157.8, 142.3, 126.6, 125.8, 116.7, 110.3, 55.3, 44.8, 42.4, 35.7, 27.4, 25.0, and 17.2. HRMS (ESI) m/z: calculated for C₁₄H₂₀O₂S [M + Na]⁺: 303.1389; found: 303.1385.

3.4.13. 1-(2-Pivaloylthiophen-3-yl)hexan-3-one, 3m

35.3 mg, 66% (isolated yield), light yellow liquid, Rᵣ = 0.51 (n-hexane: EtOAc = 10: 1).

3.4.14. 1-(2-Pivaloylthiophen-3-yl)heptan-3-one, 3n

38.3 mg, 68% (isolated yield), light yellow liquid, Rᵣ = 0.59 (n-hexane: EtOAc = 10: 1).

3.4.15. 1-(2-Pivaloylthiophen-3-yl)octan-3-one, 3o

39.4 mg, 67% (isolated yield), light yellow liquid, Rᵣ = 0.59 (n-hexane: EtOAc = 10: 1).

3.4.16. 2,2-Dimethyl-1-(3-(oxo-3-phenylpropyl)thiophen-2-yl)propan-1-one, 3p

22.9 mg, 38% (isolated yield), light yellow liquid, Rᵣ = 0.50 (n-hexane: EtOAc = 10: 1).

3.4.17. 1-(4-Methoxy-2-pivaloylphenyl)pentan-3-one, 3s

29.6 mg, 54% (isolated yield), light yellow liquid, Rᵣ = 0.415 (n-hexane: EtOAc = 10: 1).

3.4.18. 1-(2-Cyclopentanecarbonyl)phenyl)pentan-3-one, 3t

25.4 mg, 49% (isolated yield), light yellow liquid, Rᵣ = 0.59 (n-hexane: EtOAc = 5: 1).
3.4.19. 1-(2-(Cyclopropanecarbonyl)-5-methoxyphenyl)pentan-3-one, 3v

51.8 mg, 90% (isolated yield), light yellow liquid, Rf = 0.61 (n-hexane: EtOAc = 10: 1). 

1H NMR (600 MHz, chloroform-d) δ 7.27–7.29 (m, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.17–7.20 (m, 1H), 7.15–7.16 (m, 1H), 2.67–2.73 (m, 4H), 2.36 (t, J = 7.5 Hz, 2H), 1.53–1.58 (m, 2H), 1.20–1.31 (m, 13H), and 0.87 (t, J = 7.2 Hz, 3H). 

13C NMR (150 MHz, chloroform-d) δ 214.8, 210.2, 140.7, 137.7, 129.8, 128.9, 125.3, 124.7, 44.9, 44.7, 42.8, 31.4, 28.0, 27.4, 23.5, 22.4, and 13.9. HRMS (ESI) m/z: calculated for C19H28O2, [M + Na]+: 283.1305; found: 283.1316.

4. Conclusions

In summary, we unprecedentedly developed a reaction centered around the rhodium-catalyzed conjugate addition of aromatic ketones with allylic alcohols/α,β-unsaturated ketones using weakly coordinating ketone carbonyl as a directing group. From commercially available substrates, the approach allows for the facile access of 2-alkyl aromatic ketones using weakly coordinating ketone carbonyl as a directing group. From commercial efforts to investigate the practicality of this method are ongoing in our laboratory.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal13081157/s1, Table S1. Screening catalysts, Demonstrating the mechanistic studies, Figure S1: 1H NMR spectra of crude reaction mixture of ortho deuteration experiment, Table S2: The average yields of 3a and D2-3a, Figure S2: 1H NMR spectra of compound 3a, Figure S3: 13C NMR spectra of compound 3a, Figure S4: 1H NMR spectra of compound 3b, Figure S5: 13C NMR spectra of compound 3b, Figure S6: 1H NMR spectra of compound 3c, Figure S7: 13C NMR spectra of compound 3c, Figure S8: 1H NMR spectra of compound 3d, Figure S9: 13C NMR spectra of compound 3d, Figure S10: 1H NMR spectra of compound 3e, Figure S11: 13C NMR spectra of compound 3e, Figure S12: 1H NMR spectra of compound 3f, Figure S13: 13C NMR spectra of compound 3f, Figure S14: 1H NMR spectra of compound 3g, Figure S15: 13C NMR spectra of compound 3g, Figure S16: 1H NMR spectra of compound 3h, Figure S17: 13C NMR spectra of compound 3h, Figure S18: 1H NMR spectra of compound 3i, Figure S19: 13C NMR spectra of compound 3i, Figure S20: 1H NMR spectra of compound 3j, Figure S21: 13C NMR spectra of compound 3j, Figure S22: 1H NMR spectra of compound 3k, Figure S23: 13C NMR spectra of compound 3k, Figure S24: 1H NMR spectra of compound 3l, Figure S25: 13C NMR spectra of compound 3l, Figure S26: 1H NMR spectra of compound 3m, Figure S27: 13C NMR spectra of compound 3m, Figure S28: 1H NMR spectra of compound 3n, Figure S29: 13C NMR spectra of compound 3n, Figure S30: 1H NMR spectra of compound 3o, Figure S31: 13C NMR spectra of compound 3o, Figure S32: 1H NMR spectra of compound 3p, Figure S33: 13C NMR spectra of compound 3p, Figure S34: 1H NMR spectra of compound 3s, Figure S35: 13C NMR spectra of compound 3s, Figure S36: 1H NMR spectra of compound 3t, Figure S37: 13C NMR spectra of compound 3t, Figure S38: 1H NMR spectra of compound 3u, Figure S39: 13C NMR spectra of compound 3u, Figure S40: 1H NMR spectra of compound 3v, Figure S41: 13C NMR spectra of compound 3v.
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