Hydrogen borrowing chemistry is an attractive method for C–C bond formation under catalytic conditions. In this reaction manifold, a catalyst abstracts hydrogen from an alcohol to generate the corresponding carbonyl compound in situ. After a sequence involving C–C bond formation and elimination, the catalyst “returns” the abstracted hydrogen to provide the C–C coupled product and complete the catalytic cycle. This method is popular for the formation of C–C functionalized carbonyl compounds via enolate intermediates because it avoids the use of toxic alkyl halides and lithium amide bases/cryogenic temperatures and generates water as the only byproduct.

While the alkylation of ketones using primary alcohols is widespread, the use of secondary alcohols is much more limited, with most examples pertaining to Guerbet type dimerization. However, we are not aware of a general procedure for the hydrogen borrowing alkylation with secondary alcohols. Development of the Ph* group was key for a number of reasons: (a) the di-ortho-substitution of the aromatic ring alleviated steric hindrance at the α-position by twisting out of conjugation with the ketone and (b) from a synthetic perspective Ph* was extremely versatile because treatment of the alkylated products with Br2 at −17 °C resulted in a retro-Friedel–Crafts acylation process to give an acyl bromide, which could be trapped with nucleophiles to provide carboxylic acid derivatives.

Herein, we report that Ph* ketones are especially active in hydrogen borrowing alkylation with secondary alcohols. Two factors are essential for the success of this methodology: (a) the Ph* group shields the adjacent carbonyl, thereby preventing self-condensation of the substrate, and (b) the catalytic oxidation of the secondary alcohol maintains a slow release of the second ketone which is also unavailable for self-condensation. Starting from commercially available Ph*COMe (1) we have synthesized β-functionalized carbonyl products in high yields. The ability of the Ph* group to be cleaved provides ready access to the target β-functionalized ester or amide compounds via a disconnection that does not involve conjugate addition.

Our investigations began by studying the reaction between 1 and 3-pentanol in the presence of the most promising catalyst and (c) from a synthetic perspective Ph* was extremely versatile because treatment of the alkylated products with Br2 at −17 °C resulted in a retro-Friedel–Crafts acylation process to give an acyl bromide, which could be trapped with nucleophiles to provide carboxylic acid derivatives.

**Scheme 1. Hydrogen Borrowing Alkylation with Secondary Alcohols To Form β Branched Products**

**Previous results:**

- α-Alkylation using 1 equivalents to give α-branched products
- $\text{Ph}^*\text{COMe} \rightarrow \text{Ph}^*\text{COCH}_2\text{COMe}$
- $\text{KOH} (2.0\text{ equiv})$ at $85^\circ\text{C}$ for 24 h.

**Key design features:**

- Ph* tested out of conjugation with ketone
- Reduced steric hindrance around α-carbon
- Release of Ph* by retro-Friedel–Crafts acylation

**This work:**

- α-Alkylation using 2 equivalents to give β-branched products
- $\text{Ph}^*\text{COMe} \rightarrow \text{Ph}^*\text{COR}$
- $\text{Ph}^*\text{release}$

**Key design features:**

- Ph* ensures no self-coupling of substrate
- Slow oxidation of 2 equivalents of alcohol to give $\text{Ph}^*$
- New route to β-branched carbonyls
- Low loadings of alcohol

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[5\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} and KOH [see Supporting Information (SI) for an extended optimization table]. After initial experimentation, the desired β-alkylated product 4 could be isolated in 12–80% yield depending on the temperature employed (Table 1, entries 1–3).

Table 1. Optimization Conditions for the Formation of β-Branched Product 4

| entry | catalyst (mol%) | alcohol (equiv) | base (equiv) | temp (°C) | yields % | 1/2/3 | 4 |
|-------|-----------------|----------------|-------------|-----------|----------|-------|---|
| 1     | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (2) | 2.0 | KOH (3.0) | 85 | 61 | 12 |
| 2     | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (2) | 2.0 | KOH (3.0) | 105 | 5 | 80 |
| 3     | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (2) | 2.0 | KOH (3.0) | 115 | 21 | 65 |
| 4     | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (2) | 2.0 | NaOH (3.0) | 85 | 44 | 44 |
| 5     | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (2) | 2.0 | KOtBu (3.0) | 85 | - | 86 |
| 6     | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (2) | 2.0 | NaOtBu (3.0) | 85 | - | 97 |
| 7     | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (2) | 2.0 | NaOtBu (3.0) | 65 | 10 | 11 |
| 8     | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (2) | 2.0 | NaOtBu (2.0) | 85 | - | 97 |
| 9     | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (2) | 2.0 | NaOtBu (1.0) | 85 | 34 | 4 |
| 10    | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (0.5) | 2.0 | NaOtBu (2.0) | 65 | 97 | - |
| 11    | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (0.25) | 2.0 | NaOtBu (2.0) | 65 | - | 89 |
| 12    | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (0.5) | 1.5 | NaOtBu (2.0) | 85 | - | 97 |
| 13    | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (0.5) | 1.1 | NaOtBu (2.0) | 85 | 13 | 73 |
| 14    | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (0.5) | 1.5 | NaOtBu (2.0) | 85 | 5 | 93 |
| 15\textsuperscript{a} | none | 1.5 | NaOtBu (2.0) | 85 | 26 | - |
| 16\textsuperscript{a} | [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} (0.5) | 1.5 | none | 85 | 97 | - |

\textsuperscript{a}Isolated yields, 0.6 mmol scale. \textsuperscript{b}Reaction conducted on 5.3 mmol (1.0 g) scale. \textsuperscript{c}Conversion measured by \textsuperscript{1}H NMR.

Reaction analysis indicated that the solubility of KOH in PhMe may be a complicating factor, and so we assessed different bases (entries 4–6). Pleasingly, KOtBu and NaOtBu (entries 5 and 6) both resulted in complete conversion and improved isolated yields (86% and 97% respectively) at 85 °C. The reaction was also efficient at 65 °C, but gave the β-branched product in a reduced yield (entry 7, 68% of 4). At this lower temperature we also started to observe enone 2 and skipped E/Z-enones (3), which were isolated in a combined yield of 11%.

With the temperature fixed at 85 °C the amount of NaOtBu could be reduced to 2.0 equiv, leading to complete reaction (entries 8–9). The catalyst loading (entries 10–11) and amount of alcohol (entries 12–13) could also be decreased, with 0.5 mol% of [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} and 1.5 equiv of 3-pentanol proving optimal. The reaction also proved to be equally efficient on gram scale (5.3 mmol of 1), giving 4 in 93% yield (entry 14). Control experiments whereby [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} or NaOtBu were omitted (entries 15–16) returned either starting material or partial conversion to enones 2/3 (entry 15). Replacing the Ar atmosphere with O\textsubscript{2} (see SI) resulted in the recovery of 1 and large quantities of insoluble polymeric material.

The scope of the aryl group was then explored with C\textsubscript{6}H\textsubscript{4}. The reaction was also proved to be equally efficient on gram scale (5.3 mmol of 1), giving 4 in 93% yield (entry 14). Control experiments whereby [Cp\textsuperscript{7}IrCl\textsubscript{2}]\textsubscript{2} or NaOtBu were omitted (entries 15–16) returned either starting material or partial conversion to enones 2/3 (entry 15). Replacing the Ar atmosphere with O\textsubscript{2} (see SI) resulted in the recovery of 1 and large quantities of insoluble polymeric material.

The scope of the aryl group was then explored with C−C coupling attempted on a series of ortho-substituted aryl ketones (Scheme 2). This study revealed that di-ortho methyl substituents were optimal for successful alkylation, with complex mixtures and C==O reduction products often being observed without them.\textsuperscript{10} It appears that the di-ortho methyl groups are perfectly placed to prevent self-condensation of the ketone substrate while also protecting the product carbonyl from reduction in situ. Providing that this condition was satisfied, several heteroatoms could be incorporated (7, 8, and 9). Double alkylation was also efficient when the reaction loadings were increased two-fold (10).

While the results in Scheme 2 show reasonable scope for the structure of the aryl ketone, we decided to turn our attention to Ph\textsuperscript{*}COMe (1), since it not only was higher yielding but also held greater potential for efficient removal and thereafter product derivatization. A series of acyclic secondary alcohols were employed, providing the desired β-branched products in good to excellent yield (Scheme 3). As we screened variously functionalized alcohols, we found that 2.0 equiv of alcohol and 3.0 equiv of base were sometimes required to push the reaction to completion. Pleasingly, secondary alcohols bearing heterocyclic motifs (13 and 14) or heteroatoms (16, 17, and 18) were well-tolerated.

We then moved to study a number of cyclic secondary alcohols under these conditions. Experimentation revealed that these alcohols gave superior yields when using KOtBu instead of NaOtBu (Scheme 4). Interestingly, we observed that the size and position of the substituent on the cyclohexane ring led to substrate-induced diastereoselectivity (see 22, 23, 24, and 26). In each case examined, the sense of diastereoselectivity can be predicted by equatorial attack of an [Ir−H species onto an...
exocyclic enone intermediate, although diastereoselectivity during the reduction of a migrated (endocyclic) alkene (see 3) cannot be ruled out.\(^{11,12}\)

Having shown that acyclic and cyclic alcohols perform well in this reaction manifold, we then attempted an intramolecular α-alkylation to generate cyclic structures. Therefore, compound 16 was deprotected (see SI) to provide primary alcohol 30, which was subjected to the alkylation conditions. Pleasingly, the desired cyclopentane product 31 was formed in 75% yield at 105 °C as the trans-1,2-diastereomer in d.r. > 95:5 by \(^1\)H NMR spectroscopic analysis (Scheme 5a).\(^{13}\) In a similar fashion, isomeric alcohol 32 was also found to cyclize in slightly lower yield (65%), again providing trans-1,2-cyclopentane 31 in >95:5 d.r. (Scheme 5b). With these results in hand, we also reacted 1 with 1,4-pentanediol to test the feasibility of a one-step synthesis. Compound 31 was once again produced in 49% yield as a single diastereomer (Scheme 5c). Further studies relating to the use of unsymmetrical diols and the diastereoselective synthesis of similar ring systems are currently underway in our laboratory.

Next, we sought to remove the Ph\(^*\) group by means of a retro-Friedel–Crafts acylation reaction. A selection of β-branched products were treated with Br\(^2\) (2.0 equiv) at -17 °C, generating an acid bromide in situ (Scheme 6). Interception with either BuOH or BnNH\(_2\) gave the corresponding butyl esters and benzyl amides in good to excellent yield, thereby expanding the utility of this methodology.\(^{14}\) Compounds 23, 24, 29, and 31 (major diastereomers) were straightforwardly converted to their carboxylic acid derivatives with no erosion in stereochemical purity (d.r. > 95:5 by \(^1\)H NMR analysis). Since thiophene-containing 14 was incompatible with Br\(^2\), we also developed alternative (electrophilic) conditions for Ph\(^*\) cleavage. Treatment of compound 14 with TMSCl (1.0 equiv) and BuOH (3.0 equiv) in HFIP at 40 °C provided the butyl ester 39 in good yield.

Interestingly, addition of Br\(^2\) to compound 16 resulted in debenzylation lactonization to form β-substituted seven-membered lactone 42. Although debenzylic cycloetherification has been reported for the synthesis of tetrahydrofurans,\(^{15}\) this strategy has not been employed for the synthesis of seven-membered lactones and could prove to be useful for their synthesis.\(^{16}\) The retro-Friedel–Crafts process was also shown to be applicable to peptide coupling, with \(\alpha\)-amino methyl esters coupled to give compounds 45 and 46 in good yield.

Finally, the hydrogen borrowing/Ph\(^*\) cleavage sequence was applied to the synthesis of \((\pm)-3\)-methyl-5-phenylpentanol (48), which is a common industrial fragrance compound used under various brand names. Alkylation of 1 with 4-phenyl-2-butanol provided 47 as a colorless solid in 92%. Treatment of this

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**Scheme 4. Cyclic Secondary Alcohol Alkylation Scope**

| Reaction performed at 105 °C. |
|---|
| b.d.r. determined from \(^1\)H NMR analysis of the crude reaction mixture, major isomer shown. |
| 0.5 mol % \([\text{Cp}^{*}\text{IrCl}_2]\)_2, RR'CHOH (2.0 equiv), NaO\(_2\)Bu (2.0 equiv), PhMe (4 M), 85 °C, 24 h. |
| 2.0 equiv of Br\(^2\) used. |

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**Scheme 5. α-Alkylation Using an Intramolecular Hydrogen Borrowing Approach**

| a Reaction performed at 105 °C. |
| b d.r. determined from \(^1\)H NMR analysis of the crude reaction mixture, major isomer shown. |
| c 0.5 mol % \([\text{Cp}^{*}\text{lrCl}_2]\)_2, RR'CHOH (1.5 equiv), NaO\(_2\)Bu (2.0 equiv), PhMe (4 M), 85 °C, 24 h. |
| 2.0 equiv of Br\(^2\) used. |

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**Scheme 6. β-Branched Esters and Amides by Ph\(^*\) Release**

| a 4.0 equiv of Br\(^2\) used. |
| b TMSCl (1.0 equiv), BuOH (3.0 equiv), HFIP, 40 °C, 24 h. |

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BuOH or BnNH\(_2\) gave the corresponding butyl esters and benzyl amides in good to excellent yield, thereby expanding the utility of this methodology.\(^{14}\) Compounds 23, 24, 29, and 31 (major diastereomers) were straightforwardly converted to their carboxylic acid derivatives with no erosion in stereochemical purity (d.r. > 95:5 by \(^1\)H NMR analysis). Since thiophene-containing compound 14 was incompatible with Br\(^2\), we also developed alternative (electrophilic) conditions for Ph\(^*\) cleavage. Treatment of compound 14 with TMSCl (1.0 equiv) and BuOH (3.0 equiv) in HFIP at 40 °C provided the butyl ester 39 in good yield.

Interestingly, addition of Br\(^2\) to compound 16 resulted in debenzylation lactonization to form β-substituted seven-membered lactone 42. Although debenzylic cycloetherification has been reported for the synthesis of tetrahydrofurans,\(^{15}\) this strategy has not been employed for the synthesis of seven-membered lactones and could prove to be useful for their synthesis.\(^{16}\) The retro-Friedel–Crafts process was also shown to be applicable to peptide coupling, with \(\alpha\)-amino methyl esters coupled to give compounds 45 and 46 in good yield.

Finally, the hydrogen borrowing/Ph\(^*\) cleavage sequence was applied to the synthesis of \((\pm)-3\)-methyl-5-phenylpentanol (48), which is a common industrial fragrance compound used under various brand names. Alkylation of 1 with 4-phenyl-2-butanol provided 47 as a colorless solid in 92%. Treatment of this
compound with Br₂ followed by reduction of the acid bromide with Dibal-H provided (±)-3-methyl-5-phenylpentanal (48) in 70% yield in a one-pot process (Scheme 7).

Scheme 7. Synthesis of (±)-3-Methyl-5-phenylpentanal

\[
\begin{align*}
&\text{Br}_2 (2.0 \text{ equiv.}) \quad \text{AcOH, } -77 \ ^\circ \text{C} \quad \text{then} \\
&\text{Dibal-H, } 0 \ ^\circ \text{C} \quad \text{then} \\
&\text{PhCH}_2 \text{OH} \quad \text{90%} \\
\end{align*}
\]

In conclusion, we have shown that enolate alkylation using secondary alcohols can be achieved under hydrogen borrowing conditions to provide a number of β-branched products. The use of Ph⁺ as a design element was crucial to the success of this methodology, preventing self-condensation of starting substrate I. Slow oxidation of the secondary alcohol coupling partner under the catalytic conditions then enabled the formation of the desired cross-coupled products. In several cases substrate-induced diastereoselectivity was observed which is an area for further development. Preliminary experiments have shown that an intramolecular approach is feasible for allowing α-alkylation of the β-branched products, delivering 1,2-disubstituted cyclopentane 31 in good yield and as a single diastereoisomer. Finally, the Ph⁺ group was readily cleaved to provide a series of β-branched esters and amides as well as the industrially important compound (±)-3-methyl-5-phenylpentanal.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12840.

Experimental procedures and spectroscopic data for all new compounds (PDF)
Crystallographic data (CIF)

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Notes
The authors declare no competing financial interest.

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