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Strategic Application and Transformation of *ortho*-Disubstituted Phenyl and Cyclopropyl Ketones To Expand the Scope of Hydrogen Borrowing Catalysis

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Supporting Information

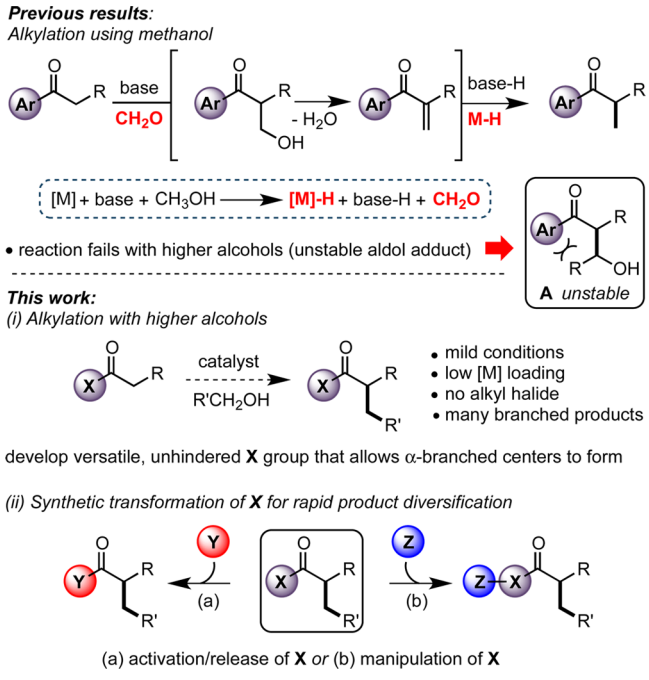
ABSTRACT: The application of an iridium-catalyzed hydrogen borrowing process to enable the formation of α-branched ketones with higher alcohols is described. In order to facilitate this reaction, *ortho*-disubstituted phenyl and cyclopropyl ketones were recognized as crucial structural motifs for C−C bond formation. Having optimized the key catalysis step, the *ortho*-disubstituted phenyl products could be further manipulated by a retro-Friedel−Crafts acylation reaction to produce synthetically useful carboxylic acid derivatives. In contrast, the cyclopropyl ketones underwent homoconjugate addition with several nucleophiles to provide further functionalized branched ketone products.

The use of hydrogen borrowing catalysis to allow the alkylation of functional groups such as amines or ketones using alcohols has become a valuable method for organic synthesis.[1] Typically, this concept relies on the use of a transition-metal catalyst to reversibly abstract hydrogen from an alcohol to generate an aldehyde *in situ*. Subsequent reaction of the aldehyde with a nucleophile (e.g., an enolate) results in bond formation. The hydrogen is then returned to a reactive intermediate (e.g., an enone) to complete the catalytic cycle and deliver alkylated compounds.

The α-alkylation of a carbonyl group (typically a ketone) using hydrogen borrowing chemistry is particularly attractive because it avoids the use of strong bases, cryogenic temperatures, and alkyl halides.[2] However, most reports of this reaction pertain to the monoalkylation of a methyl-substituted ketone. In contrast, the formation of branched products by monoalkylation of a methylene ketone is relatively underdeveloped.

Recent contributions from the groups of Donohoe,[3] Li,[4] Andersson,[5] and others[6] have shown that methanol is uniquely placed to form branched α-alkylated derivatives because of the reactive nature of the formaldehyde generated *in situ*.[7,8] However, to date few attempts to extend this protocol to other alcohols have materialized.[9] Our recent mechanistic studies showed that the intermediate aldol adducts (see **A**, Scheme 1) formed from reactions with substituted aldehydes were not stable under the reaction conditions and reverted back to the methylene ketones rather than alkylated products (i.e., the retro-aldol reaction of **A** was more favorable than elimination).

Scheme 1. General Concept for the Design of Ketones that enable α-Branched Products to form



Given that retro-aldol reactions are encouraged by a release of steric strain,[10] we set out to design a set of substrates that would form branched products with a wider range of alcohols by following two principles: (i) the ketones must be relatively unhindered to prevent retro-aldol, and (ii) any new X group that is introduced must be transformed or released easily afterward so that the products have real synthetic value (Scheme 1).

Initially we focused on aryl ketones since they were particularly effective substrates for hydrogen borrowing methylation. While phenyl ketones were not good at forming branched products with alcohols other than methanol, the addition of an *ortho*-methyl group onto the aromatic ring improved matters considerably. We rationalized this improvement to the lack of planarity imposed on the Ar−C═O system by the methyl group.

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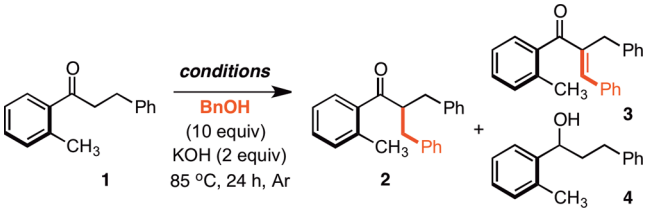
Optimization studies were performed using *ortho*-tolyl ketone **1**, KOH, BnOH, and commercially available iridium catalysts at 85 °C (Table 1, 0.3 mmol of substrate, fixed equivalents of base and alcohol are shown). The product distribution shows that, along with desired product **2**, the conjugate reduction process is interrupted and leads to enone intermediate **3** being produced in appreciable amounts. In addition to this, undesired ketone reduction was also a problem,[11] forming alcohol **4** in the process. Initially, we showed that a commercially available Ir(I) catalyst gave product **2** in 16% yield (Table 1, entry 1). The addition of a monodentate ligand increased the yield from 16% to 48% (entry 2). While the hindered additive cataCXium A [di(1-adamantyl)-*n*-butyl phosphine] did not change the product distribution, the effect of a bidentate ligand was noticeable, with BINAP, DPPE, and DPPB producing **2** in 50−63% yield (entries 4−6). Further optimization of the bidentate ligand revealed DPPBz to be the most effective, providing **2** in 70% yield using 1 mol % of Ir(I) dimer (entry 8). Pleasingly the reaction was efficient on a 5 mmol scale (entry 9), and reducing the catalyst loading to 0.5 mol % of Ir(I) dimer still gave 66% of **2** (entry 10). We discovered that an Ir(III) catalyst was viable for this alkylation forming **2** in good yield (entry 11). Finally, in contrast to previous studies,[3] performing the reaction under an O_2 atmosphere under identical conditions inhibited enone reduction to generate **3** exclusively (entry 12).[12] We postulate that the metal hydride reacts with the O_2 in preference to the enone, allowing **3** to accumulate and recycling the Ir catalyst.[13]

With the optimization complete, we applied these conditions to the alkylation of **1** with butanol. Pleasingly, this provided the corresponding butylated product in 69% yield (**5a**, Scheme 2). However, a breakthrough was made when we examined the butylation of other *ortho*-substituted aryl ketones and discovered that *ortho*-disubstituted aryl groups were superior to mono-substituted compounds (compare **5a** with **6a** and **7a**). The enhanced reactivity effect was also present on both electron-deficient (**8a**) and electron-rich (**9a**) arenes. A crystal structure of compound **7a** was obtained by single crystal X-ray diffraction, clearly indicating that the pentamethylphenyl group is twisted out of conjugation with the carbonyl.[14,15] We speculate that this is beneficial for two reasons. First, the lack of steric hindrance around the carbonyl α-carbon attenuates the rate of retro-aldol reaction, allowing the elimination reaction to compete. Second, the *ortho*-disubstitution on these aryl ketones shields the carbonyl from reduction, with no trace of reduced starting material (cf. **4**) being observed. These effects were emphasized when the lack of any *ortho*-substituent prevented efficient formation of the desired branched product, instead providing only unreacted or reduced starting material (see **10a**, Scheme 2).

We selected two *ortho*-disubstituted aryl ketones that held great potential for elaboration (2,4,6-trimethyl- and pentamethylphenyl) and synthesized a variety of substrates bearing different aliphatic side chains. These were then subjected to the hydrogen borrowing alkylation conditions with different alcohols (Scheme 3). Gratifyingly, these substrates were well tolerated under the reaction conditions, with branched products formed in consistently high yields.

Next, we sought to establish a method to functionalize these aromatic ketones. We suspected that the twist of the ketone out of the plane of the aromatic ring would facilitate *ipso* reaction with an electrophile and a retro-Friedel−Crafts acylation reaction would form an acylium ion. This reactive intermediate could then be trapped to form alternative products.[16] For example, reaction of pentamethylphenyl (abbreviated as Ph*) ketone **7a** under acidic conditions led to formation of carboxylic acid **11** (Scheme 4). The putative acylium ion intermediate could also be trapped with nucleophiles other than water, such as an electron-rich arene to give **12**. While searching for milder conditions to cleave the aryl ring, we discovered that *ipso* bromination at low temperature was particularly efficient. Reaction of **7a** with bromine at −17 °C not only resulted in release of the Ph* group but also formed the corresponding acid bromide *in situ* [see Supporting Information (SI)].[17] This could then be quenched with many different nucleophiles in a one-pot process. Ester **13**,[18] thioester **14**, amides **15**, **16**, and alcohol **17** were all formed in this procedure, greatly expanding the scope of α-branched carbonyl functional groups that can be prepared. Additional studies indicated that the 2,4,6-trimethylphenyl ketone products could also be cleaved using acid, with **6a** providing **11** (65%) and **12** (79%) under identical conditions to that shown for **7a** (see SI).

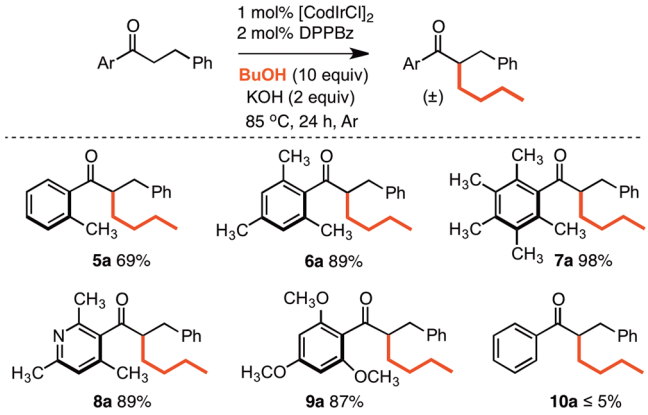
Table 1. Optimization Conditions for the α-Alkylation of Ketone 1



entry	catalyst/ligand	yields %[a] 2	3	4
1	2 mol % $[CodIrCl]_2$	16	6	74
2	2 mol % $[CodIrCl]_2$, 8 mol % PPh_3	48	6	44
3	2 mol % $[CodIrCl]_2$, 8 mol % cataCXium A	45	5	50
4	2 mol % $[CodIrCl]_2$, 4 mol % BINAP	50	13	32
5	2 mol % $[CodIrCl]_2$, 4 mol % DPPE	59	–	41
6	2 mol % $[CodIrCl]_2$, 4 mol % DPPB	63	1	36
7	2 mol % $[CodIrCl]_2$, 4 mol % DPPBz	71	–	29
8	1 mol % $[CodIrCl]_2$, 2 mol % DPPBz	70	–	30
9[b]	1 mol % $[CodIrCl]_2$, 2 mol % DPPBz	61	–	–
10	0.5 mol % $[CodIrCl]_2$,1 mol % DPPBz	66	4	30
11	2 mol % $[Cp^*IrCl_2]_2$	63	–	34
12[c]	1 mol % $[CodIrCl]_2$, 2 mol % DPPBz, O_2	–	62	–

[a]All yields are of isolated material, reactions performed on 0.3 mmol scale. [b]Reaction conducted on 5 mmol scale. [c]Reaction time was 12 h.

Scheme 2. α-Alkylation of *ortho*-Substituted Aryl Ketones



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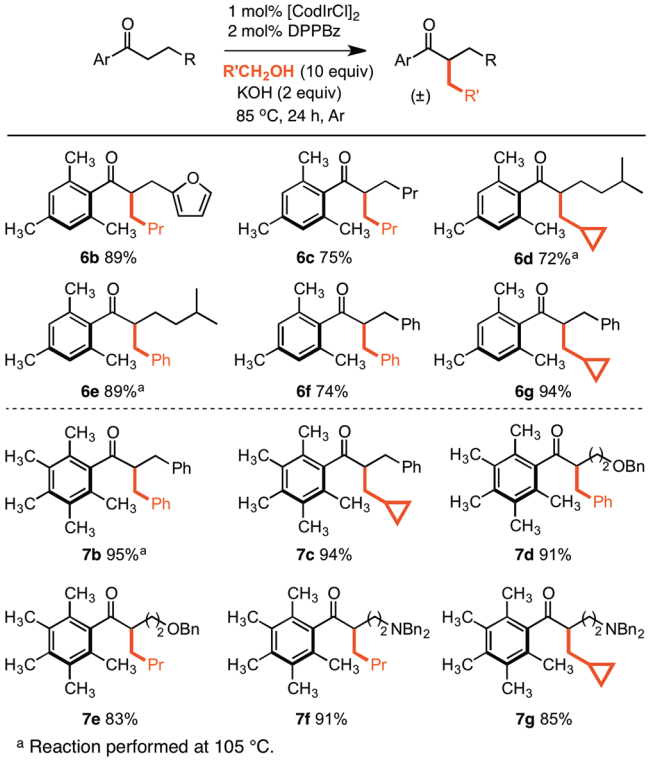
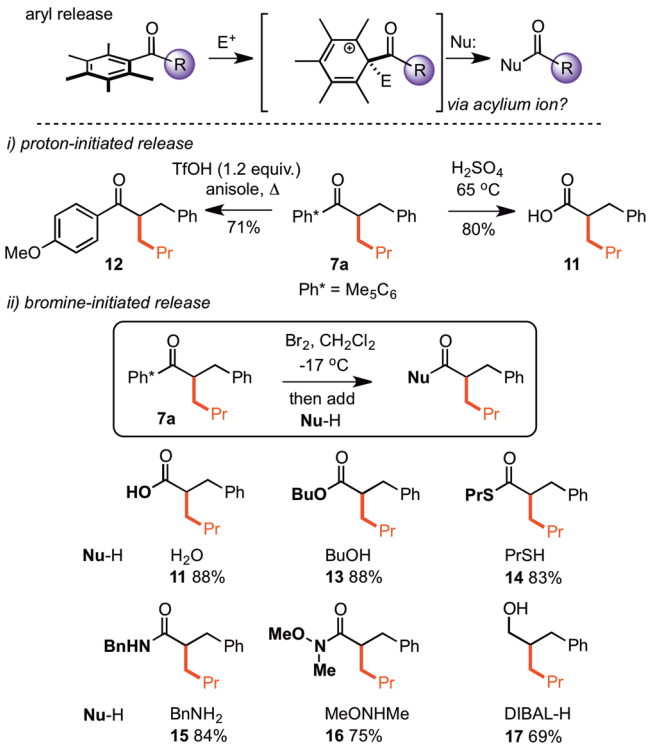
Scheme 3. Alcohol Scope with 2,4,6-Trimethyl- and Pentamethylphenyl Ketones



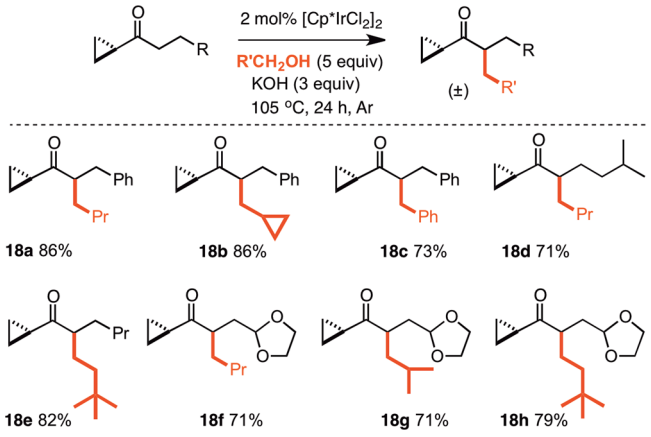
[a] Reaction performed at 105 °C.

Scheme 4. Aryl Release under Acidic or Oxidative Conditions



Investigation of other ketones that might allow the formation of branched products revealed that the cyclopropyl group was also suitable (Scheme 5). In this case slightly different conditions involving $[Cp^*IrCl_2]_2$ (2 mol %) at 105 °C proved optimal, providing the desired alkylated products in good yields. Again, a

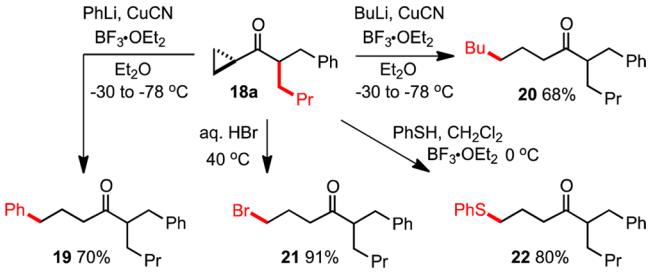
Scheme 5. α-Alkylation of Cyclopropyl Ketones



range of different ketone side chains and alcohols were compatible with this reaction, leading to diversity in the branched products. The small size and inability to easily form an enolate makes the cyclopropyl group an ideal substituent to encourage the formation of branched products on the opposite side of the ketone carbonyl.

The activated cyclopropyl groups contained in the products were easily transformed into a more general set of alkyl functionality by a homoconjugate addition reaction (Scheme 6). We discovered a variety of both carbon-based (see **19**, **20**)

Scheme 6. Homoconjugate Addition to Cyclopropyl Ketones



and heteroatom nucleophiles (see **21**, **22**) that participated in this process.[19,20] Note that the use of cyclopropyl ketones in the hydrogen borrowing procedure complements that of the previously described aryl ketones in that (after ring opening) they give access to functionalized ketones (rather than esters and amides) bearing an α-branched center.

Finally, in the absence of metal catalyst, the alkylation of three compounds (**23**–**25**) with BnOH gave the alkylated products but in lower yields [Scheme 7, see **6f** (18%) and **7b** (11%) and **18c** (49%)].[21] We also observed a significant amount of enone product that had not been reduced (cf. **3**, 10–70%). We assume that in the absence of catalyst a Meerwein–Ponndorf–Verley type mechanism is operative which shifts a hydride between the alcohol and the ketones/enones to facilitate the reaction.[21] However, the catalyst free alkylation of substrates **23** (Ar = $Me_3C_6H_2$), **24** (Ar = Ph*), and **25** is not general, and when nonbenzylic alcohols such as butanol and cyclopropylmethanol were used, the reactions gave no alkylated product. In these cases the reaction mixture consisted of mostly unreacted (Ar ketones) or reduced starting material (cyclopropyl ketones).

In conclusion, we have shown that it is now possible to α-alkylate various methylene ketones under hydrogen borrowing conditions with higher alcohols to give branched products. In

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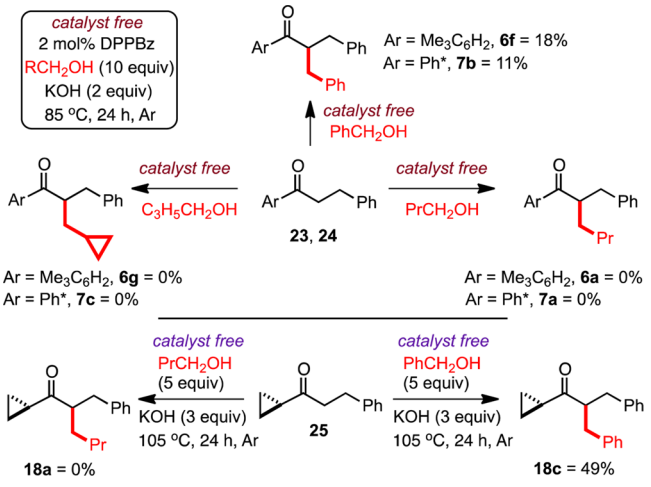
Scheme 7. Catalyst-Free Control Experiments



order to facilitate this reaction, *ortho*-disubstituted and cyclopropyl ketones were recognized as key structural motifs. These proved to be very useful synthetic handles enabling product functionalization following the catalysis step. Upon treatment with bromine, the *ortho*-disubstituted ketones underwent a retro-Friedel–Crafts reaction which, following the addition of nucleophiles, resulted in an array of carboxylic acid derivatives. Alternatively, the cyclopropyl ketone products could be opened with several nucleophiles by a homoconjugate addition sequence to give more functionalized ketones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11196.

Experimental procedures and spectroscopic data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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