Strategic application and transformation of ortho-di-substituted phenyl and cyclopropyl ketones to expand the scope of hydrogen borrowing catalysis

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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-di-substituted phenyl and cyclopropyl ketones were recognized as crucial structural motifs for C–C bond formation. Having optimized the key catalysis step, the ortho-di-substituted 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. 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. 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. However, most reports of this reaction pertain to the mono-alkylation of a methyl substituted ketone. In contrast, the formation of branched products by mono-alkylation of a methylene ketone is relatively underdeveloped.

Recent contributions from the groups of Donohoe, Li, Andersson and others have shown that methanol is uniquely placed to form branched α-alkylated derivatives because of the reactive nature of the formaldehyde generated in situ. However, to date few attempts to extend this protocol to other alcohols have materialized. 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 favourable than elimination). Given that retro-aldol reactions are encouraged by a release of steric strain, 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 afterwards so that the products have real synthetic value (Scheme 1).

Scheme 1. General concept for the design of ketones that enable α-branched products to form

Pre-existing results: Alkylation using methanol

* product distribution shows that longer alcohols are better substrates.

This work:

(i) Alkylation with higher alcohols

Develop versatile, unhindered X group that allows -branched centers to form

(ii) Synthetic transformation of X for rapid product diversification

(a) activation/release of X or (b) manipulation of X

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 (see below).

Optimization studies were performed using ortho-tolyl ketone with 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, forming alcohol 4 in the process. Initially, we showed that a commercially available Ir(I) catalyst gave product 2 but in 16% yield (Table 1, entry 1). However, this catalyst was influenced by the addition of a monodentate ligand (shown at 2 equivalents per iridium metal), which enabled an increase from 16% to 48% yield of 2 with PPh3 (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 more 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% isolated yield using 1 mol% of Ir(I) dimer catalyst (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 also discovered that an Ir(III) catalyst was viable for this alkylation forming 2 in good yield (entry 11). Finally, in contrast to previous studies, performing the reaction under an O2 atmosphere under identical conditions inhibited enone reduction to generate 3 exclusively (entry 12).

We postulate that the metal hydride reacts with the O2 in preference to the enone, allowing 3 to accumulate and recycling the Ir catalyst.

Table 1. Optimization conditions for the α-alkylation of ketone 1

| entry | catalyst/ligand | 2 | 3 | 4 |
|-------|----------------|---|---|---|
| 1     | 2 mol% [Co/Cl]2 | 16 | 6 | 74 |
| 2     | 2 mol% [Co/Cl]2, 6 mol% PPh3 | 48 | 6 | 44 |
| 3     | 2 mol% [Co/Cl]2, 8 mol% catal/Cu | 45 | 5 | 50 |
| 4     | 2 mol% [Co/Cl]2, 4 mol% BINAP | 50 | 13 | 32 |
| 5     | 2 mol% [Co/Cl]2, 4 mol% DPPE | 59 | - | 41 |
| 6     | 2 mol% [Co/Cl]2, 4 mol% DPPB | 63 | 1 | 38 |
| 7     | 2 mol% [Co/Cl]2, 4 mol% DPPBz | 71 | - | 29 |
| 8     | 1 mol% [Co/Cl]2, 2 mol% DPPBz | 70 | - | 30 |
| 9a    | 1 mol% [Co/Cl]2, 2 mol% DPPB | 61 | - | - |
| 10    | 0.5 mol% [Co/Cl]2, 1 mol% DPPBz | 66 | 4 | 30 |
| 11    | 2 mol% [Cp*Cl]2 | 63 | - | 34 |
| 12a   | 1 mol% [Cp*Cl]2, 2 mol% DPPBz, O2 | - | 62 | - |

* All yields are of isolated material, reactions performed on 0.3 mmol scale; † Reaction conducted on 5 mmol scale; ‡ Reaction time was 12 h.

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 (see 5a, Scheme 2). However, a breakthrough was made when we examined the butylation of other ortho-di-substituted aryl ketones and discovered that ortho-di-substituted aryl groups were superior to monosubstituted 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. Firstly, it is possible that the lack of steric hindrance around the carbonyl α-carbon attenuates the rate of retro-aldol reaction, thereby allowing the elimination reaction to compete. Secondly, the ortho-di-substitution present on these aryl ketones shields the carbonyl from reduction, with no trace of reduced starting material (c.f. 4) being observed. These effects were clearly emphasized when the lack of any ortho-substituent prevented efficient formation of the desired branched product, instead providing only unreacted or reduced starting material by 1H NMR (see attempted formation of 10a, Scheme 2).

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

Scheme 2. Scope of the α-alkylation of ortho-substituted aryl ketones. Structures of the (racemic) products are shown

Scheme 3. Alcohol scope with 2,4,6-trimethyl- and pentamethylphenyl ketones. Structures of the (racemic) products are shown

Having developed and optimized the alkylation of a range of ortho-di-substituted ketones using higher alcohols, we sought to establish a method to further 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 then form an acylium ion. This reactive intermediate could then be trapped to
form alternative products. For example, reaction of pentamethylphenyl (here 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) for details]. This could then be quenched with many different nucleophiles (including hydride) in a one-pot process. Ester 13, thioster 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 via hydrogen borrowing catalysis. 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 (not shown, see SI).

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*IrCl2]2 (2 mol%) at 105 °C proved optimal, providing the desired alkylated products in good yields. Again, a range of different ketone sidechains 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.

Scheme 5. Iridium catalyzed α-alkylation of cyclopropyl ketones

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) and heteroatom nucleophiles (see 21, 22) that participated in this process. 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.

Scheme 6. Homoconjugate addition to cyclopropyl ketones

Finally, in the absence of metal catalyst, the alkylation of three parent compounds (23–25) with BrOH gave the alkylated products but in lower yields [Scheme 7, see 6f (18%) and 7b (11%) and 18c (49%)]. We also observed a significant amount of enone product that had not been reduced (c.f. 3, 10–70%). According to literature precedent, we assume that in the absence of catalyst a Meerwein–Ponndorf–Verley type mechanism is operative which effectively shifts a hydride between the alcohol and the ketones/enones to facilitate the reaction. However, as expected, the catalyst free alkylation of substrates 23 (Ar = Me6C6H4), 24 (Ar = Ph*) and 25 is not general, and when non-benzylic alcohols such as butanol and cyclopropylmethanol were used the reactions gave no alkylated product. In these cases (see attempted formation of 6a, 6g, 7a, 7c, 18a, Scheme 7) the reaction mixture consisted of mostly unreacted (Ar ketones) or reduced starting material (cyclopropyl ketones).

Scheme 7. Catalyst-free control experiments
In conclusion, we have shown that it is now possible to α-alkylate various methylene ketones under hydrogen borrowing conditions with a variety of higher alcohols to give branched products. In order to facilitate this reaction, ortho-di-substituted and cyclopropyl ketones were recognized as key structural motifs. These motifs proved to be very useful synthetic handles enabling product functionalization following the catalysis step. Upon treatment with bromine, the ortho-di-substituted ketones underwent a retro-Friedel-Crafts reaction which, following the addition of various nucleophiles, resulted in an array of carboxylic acid derivatives. Alternatively, the cyclopropyl ketone products could be opened with several nucleophiles by means of a homoconjugate addition sequence to give more functionalized ketones.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via http://pubs.acs.org

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Ar\xrightarrow{\text{cat. Ir}} RCH\textsubscript{2}OH
Ar = di-ortho-substituted

X = OH, OR, SR, NR\textsubscript{2}, Ar'

aryl release

homoconjugate addition

Ar\xrightarrow{\text{cat. Ir}} RCH\textsubscript{2}OH