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Unique building blocks for organic synthesis

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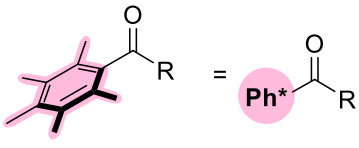

pentamethylphenyl (Ph*) ketones

- ✓ *easy to prepare*
- ✓ *highly crystalline*
- ✓ ***twisted structure leads to unique reactivity***
- ✓ *cleavage to other FGs*

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Pentamethylphenyl (Ph*) ketones: Unique building blocks for organic synthesis

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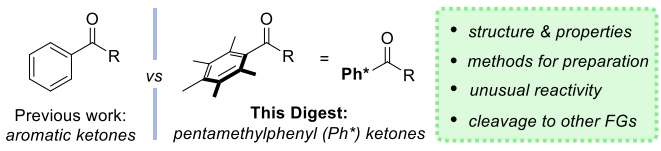
ABSTRACT

Pentamethylphenyl (Ph*) ketones are rapidly emerging as versatile and useful building blocks for organic synthesis. The *ortho*-methyl substituents force the aromatic ketone to twist out of planarity with the carbonyl, and consequently these molecules display a unique pattern of reactivity which is completely distinct to that of traditional aromatic ketones. The primary aim of this Digest is to highlight examples where new chemical reactivity is unlocked through the use of Ph* ketones, and a wide range of examples are presented including hydrogen borrowing catalysis, aldol addition and organocatalysis. Finally, methods to cleave the Ph* group to a range of other functionality are surveyed.

Dedicated to Professor S. F. Martin

Introduction

Pentamethylphenyl (Ph*) ketones are an unusual class of carbonyl compounds bearing a per-methylated aromatic ring (Scheme 1). These materials have been known in the literature for over 130 years, initially studied out of simple structural curiosity.[1] However, in recent years it has become increasingly apparent that Ph* ketones display a unique pattern of reactivity that is distinct to that of other aromatic ketones. This has enabled the development of a wide range of valuable new chemical transformations of Ph* ketones that cannot be easily achieved with other carbonyl substrates. Moreover, the Ph* group can readily be converted to a series of other functional groups (e.g. esters, amides, alcohols and aldehydes), which greatly expands their utility and makes them exciting building blocks for organic synthesis.



Scheme 1. Pentamethylphenyl (Ph*) ketones – useful building blocks for organic synthesis

This Digest begins by introducing the fundamental reactivity and properties of Ph* ketones framed in the context of their structure and conformation. A brief survey of the methods available for the preparation of simple Ph* ketones is then presented. We then move on to explore the unique chemistry that can be achieved with Ph* ketones, which is the primary focus of this Digest. A variety of different processes are discussed including hydrogen borrowing catalyzed alkylation, annulation, aldol addition and organocatalysis – the focus is upon processes that are made possible or enhanced by the Ph* group. Finally, a critical survey of state-of-the-art methods to cleave the Ph* group is presented. The emphasis is placed upon pentamethylphenyl ketones, but where it is particularly relevant, examples involving related 2,6-dimethylphenyl- and 2,4,6-trimethylphenyl ketones are also presented.

Structure and reactivity of Ph ketones*

Typical aryl ketones (e.g. acetophenone) preferentially adopt a planar conformation, which enables conjugation between the aromatic ring and the carbonyl group. In contrast, for Ph* ketones, such a planar conformation leads to a strongly destabilizing steric interaction between the two *ortho*-methyl substituents and the ketone (Scheme 2A). As a result, Ph* ketones (and other *ortho*-disubstituted ketones) instead favour a twisted conformation – essentially all of the unusual reactivity of Ph* ketones stems from this altered conformational preference. Key evidence for the orthogonality between the carbonyl and aromatic ring can be seen in the infrared stretch of the carbonyl group, which is typically 10-20 cm^{-1} higher for Ph* ketones than their Ph-substituted analogues (e.g. **2** vs **1**), implying a lack of conjugation between the Ph* ring and the C=O group. Moreover, single crystal X-ray analysis of a variety of Ph* ketones has revealed that, in the solid state, a twisted conformation is unanimously preferred. A key consequence of this 90° twist is that the *ortho*-methyl groups project above and below the plane

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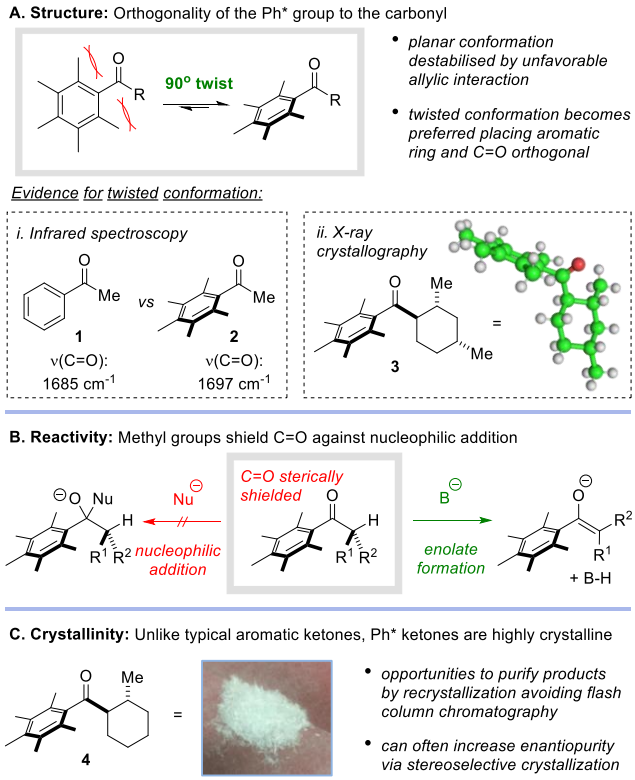
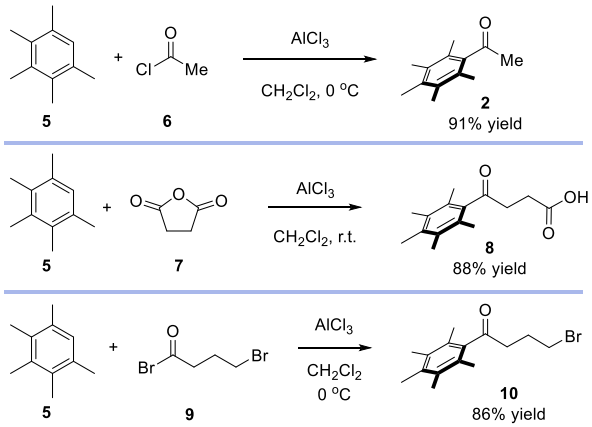
of the carbonyl and protect it against nucleophilic addition (Scheme 2B). As a result, Ph* ketones will only react with the most reactive nucleophiles (e.g. $LiAlH_4$) or require forcing conditions. In contrast, the α-position of the ketone is still comparatively sterically accessible and the acidic hydrogens can readily be removed by a base to form the corresponding enolate. This ability to undergo selective deprotonation without competing addition of nucleophiles is at the heart of much of the unusual chemistry set out in the subsequent sections. Finally, Ph* ketones display a very high degree of crystallinity compared to other ketones (Scheme 2C). This affords an opportunity to purify products by recrystallization, thereby negating the requirement for column chromatography and also providing an opportunity to increase the enantiomeric purity of scalemic mixtures.



Scheme 2. Ph* ketones: important building blocks with unusual structure, reactivity and crystallinity

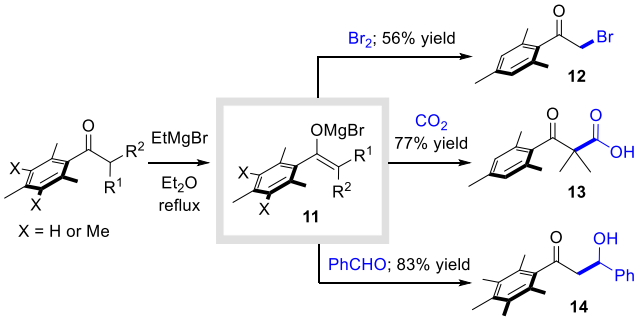
Synthesis of Ph ketone building blocks*

Simple Ph* ketones can readily be prepared by Friedel-Crafts acylation between commercially available pentamethylbenzene (**5**) and activated carboxylic acid derivatives under standard conditions (three representative examples are provided in Scheme 3). For example, the important building block pentamethylacetophenone (**2**) can readily be prepared from **5** and acetyl chloride in 91% yield (N.B. **2,** CAS: 2040-01-9, is also commercially available from Santa-Cruz Biotechnology).[2,3] In a similar manner, pentamethylbenzene can be reacted with cyclic anhydrides to afford Ph*-substituted γ-keto-acids such as **8** in excellent yields.[4] Alkyl halide-containing acid bromides (e.g. **9**) are also good substrates for this chemistry, undergoing acylation with no evidence of any competing Friedel-Crafts alkylation processes.[4] We have a number of unpublished results which show that this chemistry is not limited to commercially available activated acids – acid chlorides can be generated from the corresponding carboxylic acids and employed without purification for the Friedel-Crafts acylation. In such cases, we have found superior results are generally obtained using $SOCl_2$ to generate the acid chloride rather than oxalyl chloride.



Scheme 3. Representative examples of synthesis of Ph* ketones *via* Friedel-Crafts acylation

Conveniently, the magnesium enolates of *ortho*-disubstituted phenyl ketones can be straightforwardly prepared by deprotonation with EtMgCl (the more typical 1,2-addition pathway is prevented by the shielding effect of the *ortho*-methyl substituents).[5] Detailed mechanistic studies suggest that the deprotonation proceeds *via* initial precomplexation between the ketone and Grignard reagent followed by intramolecular deprotonation.[6] The resulting intermediates (**11**) display unusual reactivity more akin to Grignard reagents than ketone enolates and can be trapped with a range of electrophiles including bromine, acid chlorides, esters, carbon dioxide, aldehydes and ketones (a selection of these reactions are shown in Scheme 4). The majority of work has been focused on mesityl ketones (e.g. formation of **12** and **13**),[5] but we have shown that Ph* ketones are also effective substrates for this chemistry, which gives convenient access to α-substituted Ph* ketones (e.g. **14**).[7]

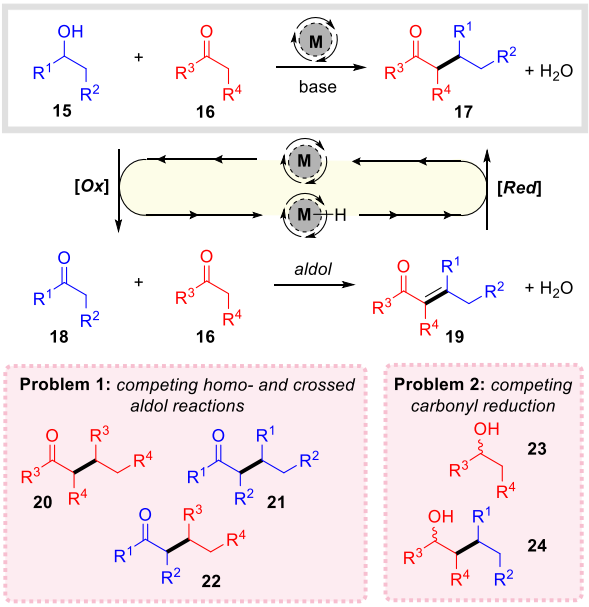


Scheme 4. Formation and reactivity of magnesium enolates of *ortho*-disubstituted aromatic ketones.

Hydrogen borrowing reactions enabled by Ph ketones*

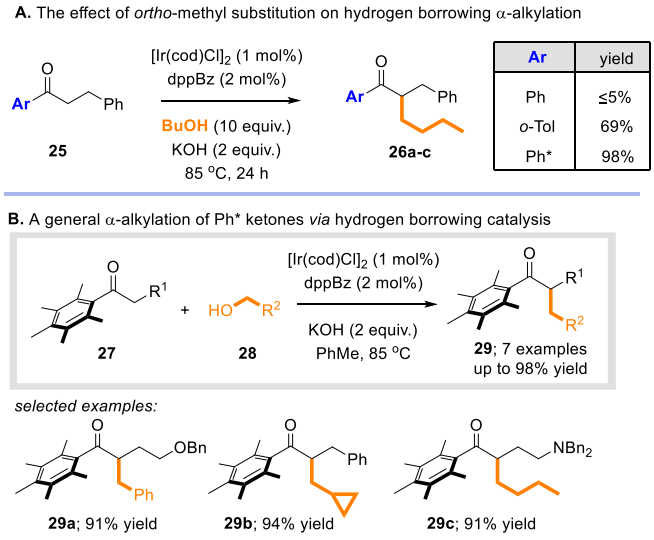
The most widespread application of Ph* ketones to date has been in the field of hydrogen borrowing catalysis.[8] This chemistry is of great contemporary interest as it provides an environmentally friendly alternative to classical enolate alkylation, enabling α-alkylation to be performed with non-toxic, unactivated alcohols. A generalized process is shown in Scheme 5 in which a ketone (**16**) undergoes alkylation with an alcohol (**15**) to generate an alkylated product (**17**). Such reactions rely upon a transition metal catalyst (**M**), which initiates the process by oxidizing the alcohol to form the corresponding carbonyl compound (**18**) along with a metal hydride. In the presence of a base (e.g. KOH), the oxidized intermediate can then undergo aldol condensation with the ketone starting material. The resulting enone (**19**) is then reduced by the metal hydride to form α-alkylated product **17** and close the catalytic cycle. This is an

extremely green process, the sole byproduct being the water that is produced during the aldol step. However, there are some serious limitations. Firstly, the crossed-aldol step between **16** and **18** presents an inherent chemoselectivity challenge, as competing homo- and hetero-aldol reactions would lead (after reduction) to the formation of undesired products **20**-**22**. As a consequence, the majority of studies have focused on reactions of simple methyl ketones with benzylic (non-enolizable) alcohols. A second important issue is that the efficiency of the method is often challenged by competing 1,2-reduction of the carbonyl in both the ketone starting material and product.



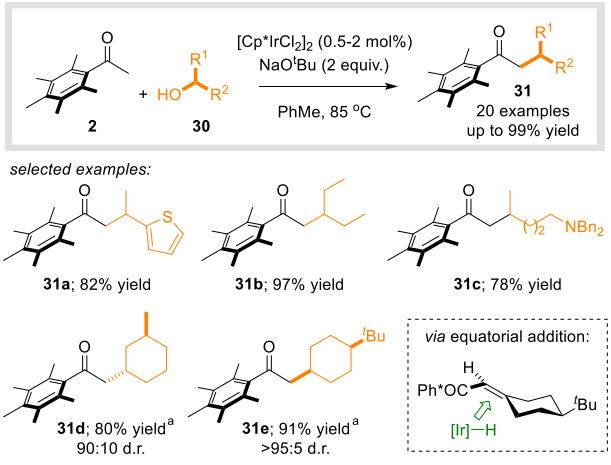
Scheme 5. A generic example of hydrogen borrowing catalyzed enolate alkylation, mechanism and possible pitfalls.

In 2017, our group set out to investigate whether the hydrogen borrowing method could be expanded beyond methyl ketone alkylation to target α-branched ketone products. Building upon previous studies of α-methylation, we tested the alkylation of a series of dihydrochalcones (**25**) with *n*-butanol in the presence of an Ir(I)-catalyst and 1,2-bis(diphenylphosphino)-benzene (dppBz) (Scheme 6A).[4,9] Simple phenyl ketones did not afford any of the desired α-branched product, but a starting material bearing a single *ortho*-methyl substituent reacted to afford the ketone product in 69% yield. Even more remarkably, with a Ph* ketone, the α-alkylated product was isolated in near quantitative yield. These results can be rationalized on the basis that the Ph* group is able to shield the carbonyl against 1,2-addition, which prevents the undesired aldol addition and 1,2-reduction processes discussed above. This proved to be a remarkably general approach and a variety of Ph* ketone starting materials could be cleanly alkylated with primary alcohols to afford α-branched ketone products in excellent yields (Scheme 6B). Both benzylic and non-benzylic alcohols could be employed (e.g. **29a**-**29c**) and a variety of ether and amine containing ketones were well tolerated. Another very important benefit of the Ph* group is that it can be readily cleaved to a variety of other functional groups *via* retro-Friedel-Crafts reaction (this chemistry is discussed later in detail).



Scheme 6. Synthesis of α-branched Ph* ketones *via* hydrogen borrowing catalysis.

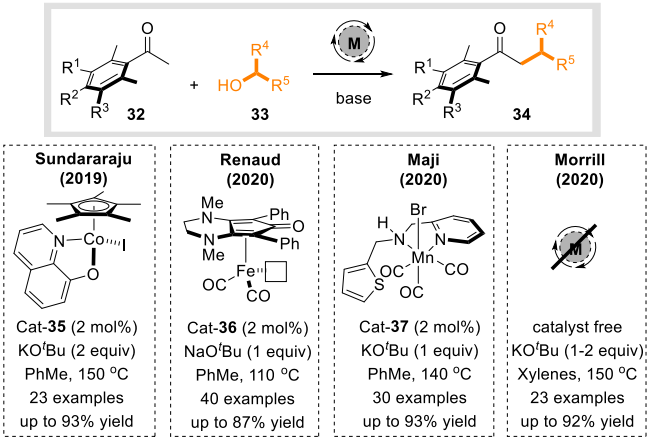
We have also investigated challenging hydrogen borrowing reactions between pentamethylacetophenone and secondary alcohols to form β-branched products (Scheme 7).[10] Optimization revealed that the commerically available complex $[Cp^*IrCl_2]_2$ is able to efficiently mediate this process, and a series of acyclic β,β-disubstituted ketones (e.g. **31a**-**31c**) were prepared in very high yields. The Ph* group was again essential to prevent undesired aldol and reduction processes, and inferior results were obtained with less substituted aromatic ketones. Notably, self-condensation of the secondary alcohol partner was also minimal under these conditions, which is presumably because the corresponding ketone is released slowly by oxidation and is therefore present at low concentration throughout the reaction. Reactions of cyclic secondary alcohols afforded cyclohexenes (e.g. **31d** and **31e**) with high levels of diastereoselectivity. This relative stereochemistry was rationalized on the basis of equatorial addition of iridium hydride to an exocyclic enone intermediate.



Scheme 7. Ir-catalyzed alkylation of Ph* ketones with secondary alcohols. [a] With KO^{t}Bu (3 equiv.) instead of NaO^{t}Bu.

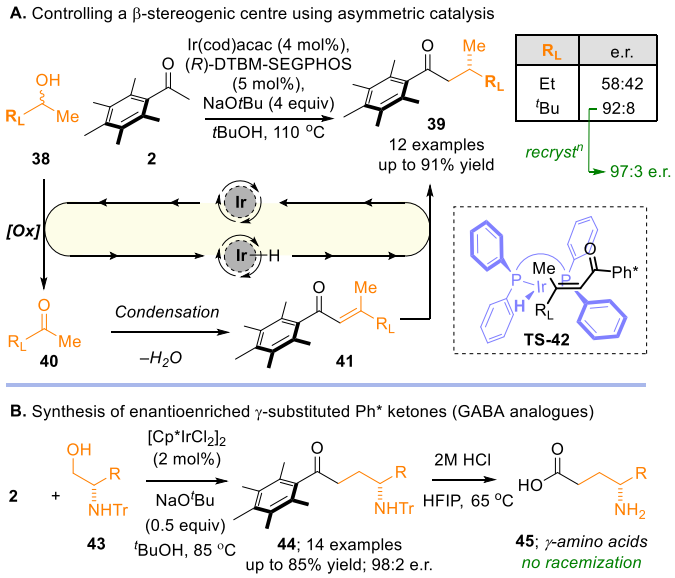
Following our initial report of iridium-catalyzed alkylation with secondary alcohols, several other groups have reported elegant earth-abundant catalyst systems, which are capable of performing similar chemistry (Scheme 8). For example, in 2019, Sundararaju and co-workers reported that

high-valence Co(III) catalyst **35** can efficiently promote the alkylation of pentamethylacetophenone with a variety of secondary alcohols.[11] One year later, Renaud and co-workers disclosed a similar process mediated by iron catalyst **36**, which was prepared *in situ* by treatment of the corresponding tricarbonyl complex with trimethylamine N-oxide.[12] Under these conditions, alkylation of both Ph* and mesityl ketones with secondary alcohols proceeded in excellent yields. Almost simultaneously, Maji and co-workers reported that Manganese(I) complex **37** was also able to efficiently promote similar chemistry.[13] Interestingly, it was found that the hemilabile thiophene group of the ligand was critical to achieve efficient alkylation. Very recently, Morrill and co-workers reported that alkylation of *ortho*-disubstituted ketones can proceed at high temperature (150 °C) without any transition metal catalyst.[14] Presumably under these forcing conditions, the usual transition metal catalyzed "hydrogen borrowing" and "hydrogen retuning" steps are replaced by Oppenauer oxidation and Meerwein-Ponndorf-Verley reduction respectively.



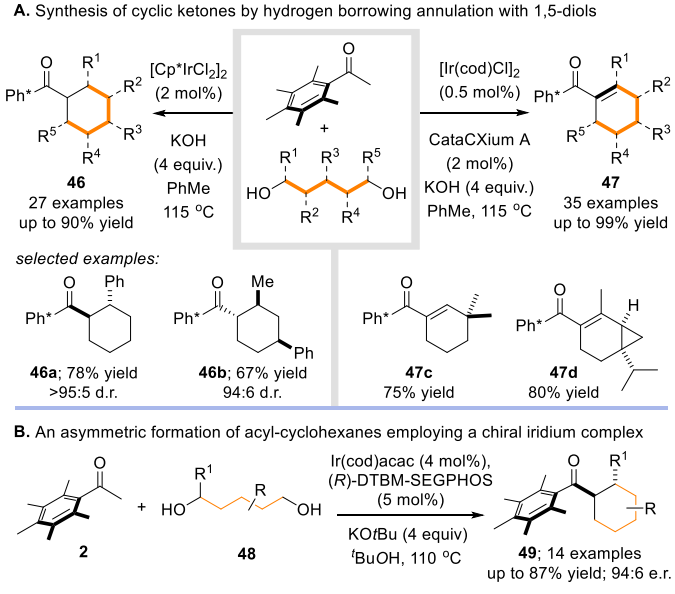
Scheme 8. Earth-abundant and catalyst-free systems for alkylation of *ortho*-disubstituted aromatic ketones.

We have also developed a catalytic asymmetric variant of this chemistry employing an iridium(I) catalyst modified by the commercially available chiral ligand (*R*)-DTBM-SEGPHOS (Scheme 9A).[15] A variety of methyl substituted secondary alcohols could be employed to afford enantioenriched β-branched Ph* ketones in high yields. The enantiodetermining step involves hydrogenation of achiral enone intermediate **41** via transition state **TS-42**, which places the bulky Ph* group in the least hindered quadrant to avoid unfavorable steric interactions with the chiral ligand. A clear correlation was observed between the size of the non-methyl substituent (R_L) and enantioselectivity, with the best results achieved with very bulky *tert*-alkyl groups. This is presumably because bulky groups favour the formation of a single *E*-enone isomer – with smaller groups, a mixture of enone intermediates are produced leading to non-selective reduction. Very recently, we also reported that it is also possible to employ hydrogen borrowing alkylation to prepare enantiopure γ-amino Ph* ketones **44** (Scheme 9B).[16] Initial experiments led to extensive racemization of the sensitive stereogenic centre (α to an aldehyde after oxidation), but racemization could be almost completely suppressed by protecting the nitrogen with a bulky trityl group. Treatment the resulting enantioenriched ketones with acid resulted in both trityl deprotection and Ph* cleavage (*vide infra*) to release valuable enantiopure γ-amino acids **45**. In both of these processes (Scheme 9A and B), the Ph* group imparts a high degree of crystallinity to the products, enabling stereoselective crystallization to enhance enantiomeric purity.



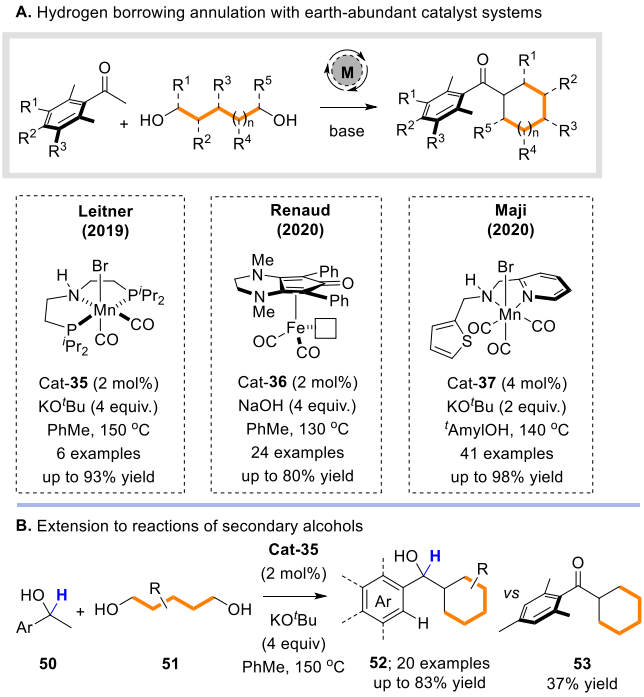
Scheme 9. Alkylation of Ph* ketones to form enantioenriched products bearing a β- or γ-stereogenic centre.

We have also shown that pentamethylacetophenone can undergo annulative hydrogen borrowing reactions with 1,5-diols (Scheme 10A). Employing an iridium(III) catalyst along with KOH enabled the formation of cyclohexane products in excellent yields and with very high levels of control over relative stereochemistry.[17] We subsequently discovered that by employing a Ir(I)-catalyst in combination with the bulky trialkyl phosphine ligand CataCXium A, the final reduction process could be disrupted leading to valuable cyclohexenes.[18] Detailed mechanistic analysis revealed that neither of these processes proceed by the expected pathway of two sequential hydrogen borrowing pathways, and instead take place *via* an unusual cascade involving an intramolecular 1,5-hydride shift. We have also shown that the final reduction step can be rendered asymmetric by introducing a chiral bisphosphine ligand (Scheme 10B).[19] This enabled the synthesis of a wide range of chiral non-racemic cyclohexanes with excellent levels of diastereo- and enantioselectivity.



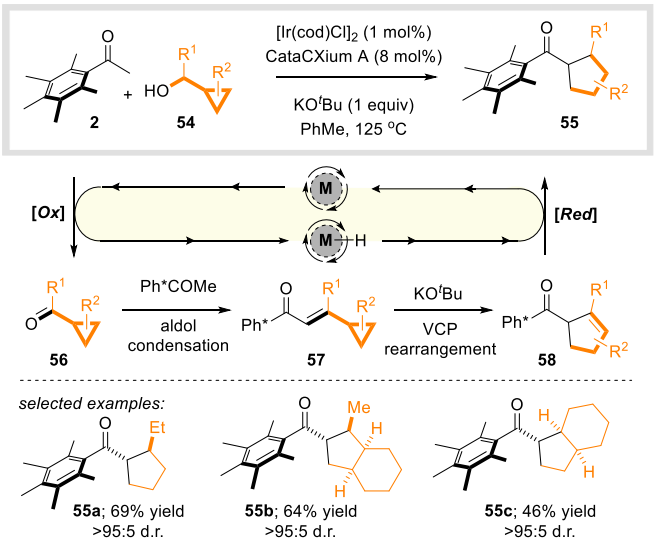
Scheme 10. Annulative hydrogen borrowing reactions between pentamethylacetophenone and 1,5-diols.

Several other research groups have subsequently reported important developments in this area, which allow the annulation of Ph* ketones to be carried out without a precious metal catalyst (Scheme 11A). For example, in 2019, Leitner and co-workers reported that manganese pincer complex **35** is capable of catalyzing the reaction between pentamethylacetophenone and various diols to form 5, 6 and 7-membered cycloalkane products.[20] Later, Renaud and Maji reported iron and manganese catalysts that are also able to promote similar chemistry.[21,22] Leitner and co-workers also investigated analogous reactions of secondary benzylic alcohols **50** with diols (Scheme 11B).[20] In this case, oxidation of the secondary alcohol liberates an extra equivalent of hydride, and consequently a final reduction process was observed to form secondary alcohol products. Interestingly, this chemistry could be performed without *ortho*-disubstituted starting materials, and when a mesityl ketone was employed the final reduction process did not occur. This outcome highlights the important resilience of *ortho*-disubstituted ketones to reduction.



Scheme 11. Earth-abundant and catalyst-free systems for annulation of *ortho*-disubstituted aromatic ketones and alcohols.

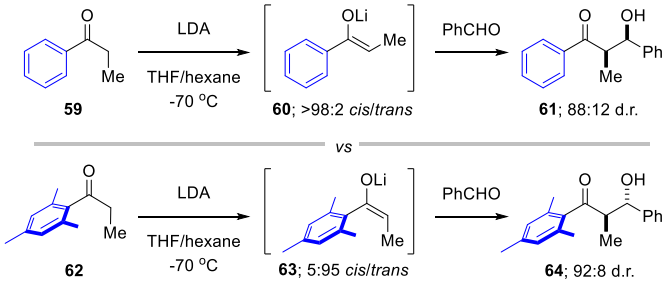
Very recently, we reported an unusual iridium catalyzed reaction between pentamethylacetophenone (**2**) and cyclopropyl alcohols to afford acyl cyclopentanes **55** (Scheme 12).[23] This reaction is believed to proceed *via* iridium mediated oxidation of the cyclopropyl alcohol to the corresponding ketone followed by aldol condensation with pentamethylacetophenone. The resulting enone intermediate **57** can then undergo a vinyl cyclopropane (VCP) rearrangement to form a skipped enone **58**. Base mediated isomerization of the alkene into conjugation with the carbonyl followed by reduction generates the cyclopentane product and closes the catalytic cycle. Detailed mechanistic interrogation revealed the vinyl cyclopropane rearrangement is not catalyzed by iridium and an alternative mechanism was proposed in which rearrangement is triggered by single electron reduction of the vinyl cyclopropane. The multisubstituted alicyclic ketone products were obtained in high yields with excellent levels of diastereocontrol. A variety of cyclopentane products could be obtained in very high yields such as 1,2-*trans*-disubstituted product **55a** as well as complex bicyclic examples (e.g. **55b**-**55c**).



Scheme 12. A vinyl cyclopropane rearrangement embedded within a hydrogen borrowing alkylation.

Other reactions enabled by Ph ketones*

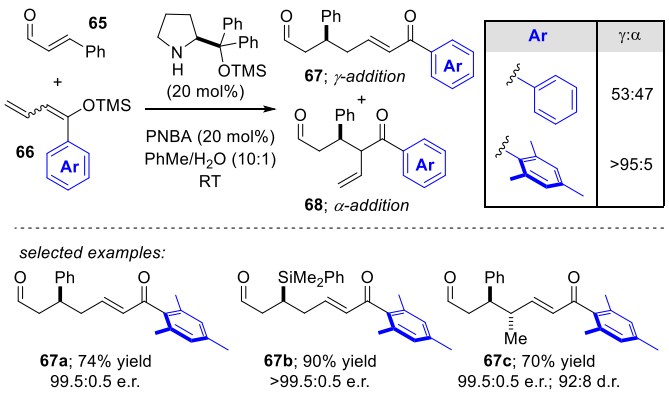
It is well established that deprotonation of most α-substituted ketones with LDA preferentially affords the *cis*-enolate.[24] For example, the lithium enolate of propiophenone **60** is formed as a single *cis*-isomer, and upon addition of benzaldehyde, reacts to form the *syn* aldol-adduct **61** via a Zimmerman-Traxler transition state (Scheme 13).[25] In contrast, Heathcock and co-workers have reported that under identical conditions, mesityl ethyl ketone **62** undergoes deprotonation to form the *trans*-enolate **63**.[25] This remarkable inversion of selectivity was rationalized on the basis that the twisted nature of the mesityl group reduces its effective size, and allows it to behave more like the analogous esters, which typically form *trans*-enolates. After addition of benzaldehyde, the *anti*-aldol product **64** was obtained in 92:8 d.r. Stereodefined *trans*-enolate equivalents derived from **62** have subsequently been utilized in a variety of other processes, such as 1,4-additions,[26] Mukiyama aldol,[27] and Tsuji-Trost allylation.[28]



Scheme 13. An unusual formation of *trans*-enolates by deprotonation of mesityl ketones.

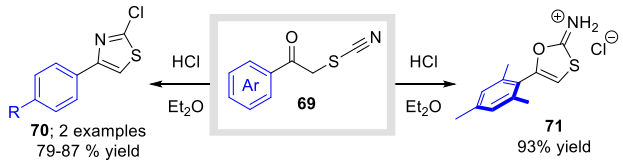
Schneider and co-workers have reported an elegant study on the catalytic asymmetric vinylogous Michael addition of dienol silyl ethers to α,β-unsaturated aldehydes (Scheme 14).[29] This reaction was mediated by 20 mol% of the Hayashi-Jørgensen catalyst along with *para*-nitrobenzoic acid (PNBA) as a co-catalyst. Both the unsaturated aldehyde and enol ether starting materials possess two reactive sites, and therefore up to four regioisomeric products could be formed in this process. In practice, excellent selectivity was observed for Michael addition to the aldehyde, but with a phenyl-substituted silyl enol ether, approximately equal amounts of α- and γ-addition were observed. It was found that switching to the corresponding mesityl ketone completely

solved this problem and enabled exclusive formation of the γ-addition product. A variety of aldehydes and silyl enol ethers were well tolerated in this process and gave very high levels of enantioselectivity (e.g. **67a-67c**). Schneider and co-workers subsequently applied a similar approach to develop vinylogous conjugate additions of sterically encumbered 2,5-dimethylsubstituted *N*-acyl pyrroles.[30]



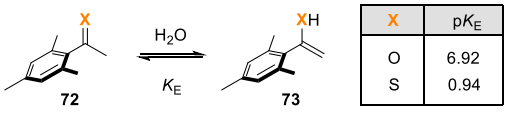
Scheme 14. Organocatalytic asymmetric vinylogous Michael addition reactions.

The cyclization of thiocyanatoacetophenones to form 2-chlorothiazoles is a well-documented process, and a variety of products (e.g. **70**) can be isolated in very high yields (Scheme 15). In contrast, Merijanian and co-workers have shown that the analogous mesityl ketone undergoes a completely different mode of cyclization to form 1,3-oxathiole hydrochlorides **71** in 93% yield.[31] Presumably, the normal cyclization mode cannot occur because the mesityl group protects the carbonyl from 1,2-addition. When thiocyanatoacetophenones bearing a single *ortho*-substituent were employed as starting materials, competition between these two pathways was observed, resulting in a mixture of the corresponding chlorothiazole and oxathiole products.



Scheme 15. Alternative pathways in the cyclization of thiocyanatoacetophenones

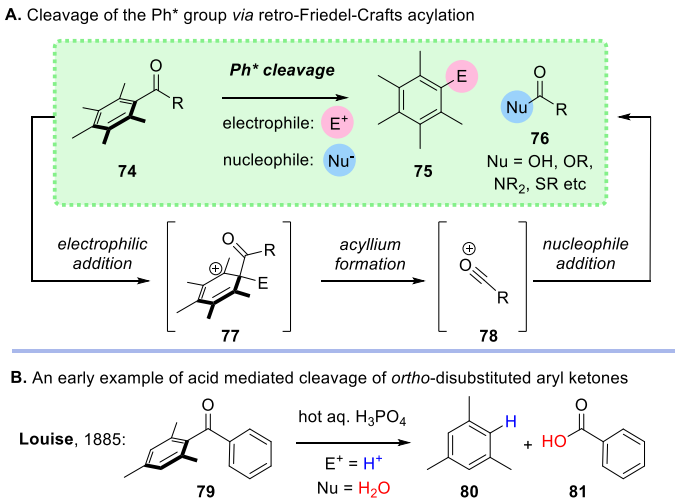
Kresge and Meng have performed detailed studies into the keto-enol tautomerism of *ortho*-disubstituted aromatic thioketones **72** in water (Scheme 16).[32] Normally such measurements are complicated by very rapid hydrolysis of the thioketone, which occurs on a timescale that competes with keto-enol tautomerism. However, it was discovered that thioacetyl mesitylene does not undergo this process, presumably because the two *ortho*-methyl substituents prevent the attack of water at the thiocarbonyl carbon. This enabled a detailed study to be performed on thioacetyl mesitylene, which revealed that enol formation is significantly more facile for the thioketone than its oxygen analogue.



Scheme 16. A study of keto-enol tautomerism in thioacetyl mesitylene

Cleavage of Ph ketones*

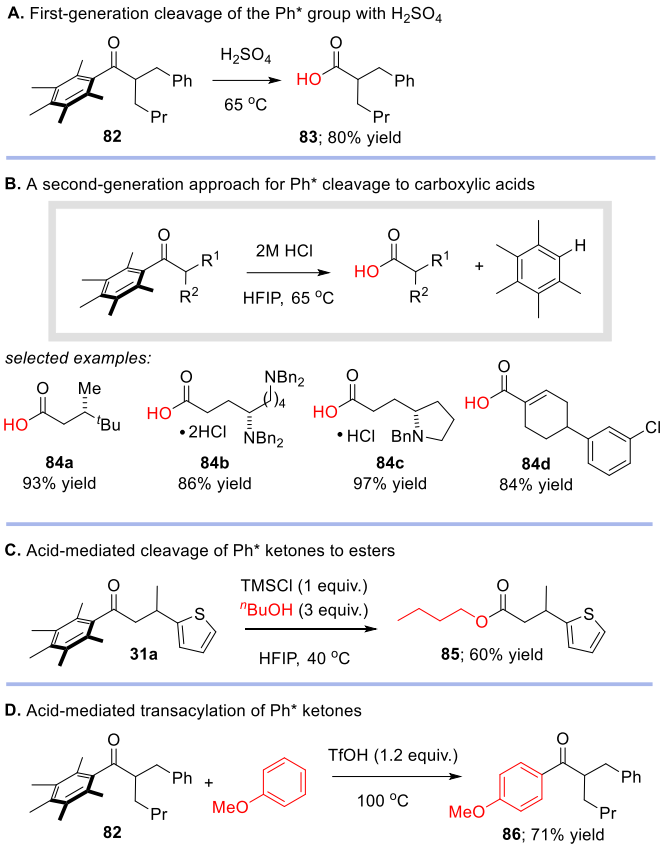
Pentamethylphenyl ketones have a final, and very important property that has not yet been discussed – they are precursors for carboxylic acid derivatives *via* retro-Friedel-Crafts acylation (Scheme 17A). The combination of five methyl substituents, as well as a carbonyl that is twisted out of conjugation renders the aromatic ring comparatively electron rich, such that *ipso*-addition to electrophiles ($\mathbf{E}^+$) is possible. The resulting Wheland intermediate **77** can then undergo fragmentation to form an acylium ion **78** which can finally be captured by a nucleophile to form acyl derivatives. The origins of this chemistry can be traced back to the 19th century when Louise reported that treatment of benzoyl mesitylene **79** with hot phosphoric acid resulted in formation of mesitylene and benzoic acid (Scheme 17B).[33] In this case, a proton serves as the electrophile and water acts as the nucleophile. Following this initial report, several other groups reported related cleavages with various other strong acids, e.g. H_2SO_4, TfOH, CF_3COOH and Nafion-H.[34] Most of these studies employed simple acyl groups, and the emphasis was placed on obtaining the deacylated arene products rather than the carboxylic acids.



Scheme 17. General strategy for cleavage of Ph* ketones by retro-Friedel-Crafts acylation and an early example

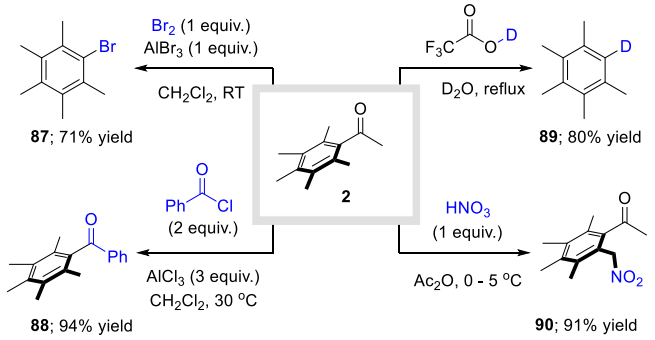
This retro-Friedel-Crafts acylation strategy provides a perfect opportunity to convert complex Ph* ketone derivatives to the corresponding carboxylic acids. For example, in our early work, we showed that α-branched Ph* ketone **82** could be cleaved to the corresponding carboxylic acid **83** in 80% yield by heating to 65 °C in concentrated sulfuric acid (Scheme 18A).[4] Perhaps unsurprisingly, these strongly acidic conditions displayed somewhat limited functional group tolerance. We therefore developed a milder set of second-generation conditions in which Ph* ketones are treated with aqueous HCl in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at 65 °C (Scheme 18B).[15,16,18] Presumably this process is facilitated by stabilization of the key Wheland and acylium intermediates by HFIP, which is known to be particularly effective at facilitating carbocation formation.[35] Using these conditions, we have been able to cleave a variety of sensitive enantioenriched Ph* ketones (e.g. **84a**–**84c**), as well as alkene containing examples (e.g. **84d**). The acylium ion formed after protonation can also be intercepted by other nucleophiles. For example, we have shown that esters can be obtained by treating Ph* ketones with alcohols in HFIP along with anhydrous HCl (generated *in situ* by addition of trimethylsilyl chloride) to form ester **85** (Scheme 18C).[4,7] Electron rich arenes can also act

as nucleophiles, and a variety of transacylation processes have been reported, such as the acid mediated reaction of **82** with anisole shown in Scheme 18D.[4,36]



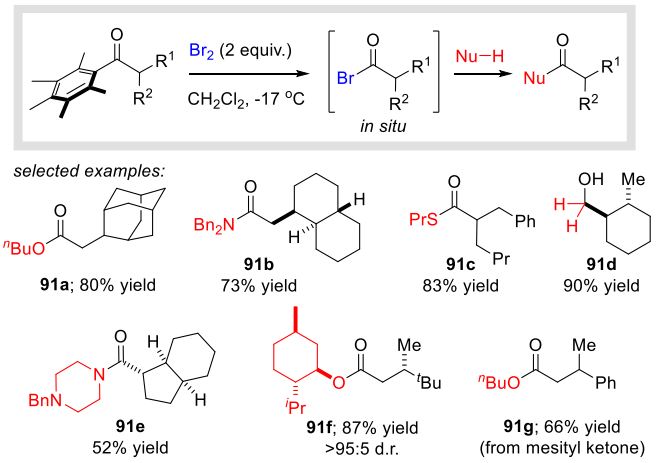
Scheme 18. Acid-mediated cleavage of Ph* ketones to carboxylic acids, esters and ketones.

Retro-Friedel-Crafts acylation with other electrophiles is also possible, and Kitijama and co-workers have carried out a systematic study of the reaction between *ortho*-disubstituted aryl ketones and various electrophiles (Scheme 19).[37] They found that treatment of pentamethylacetophenone **2** with Br_2 in the presence of $AlBr_3$ resulted in clean conversion to bromopentamethylbenzene **87** in 71% yield. Analogous reactions with acid chlorides delivered transacylated products such as **88** in very high yields.[37,38] With deuterated trifluoroacetic acid, deutereopentamethylbenzene **89** was formed in 80% yield. Surprisingly, Kitijama and others have reported that nitration of pentamethylacetophenone does not proceed *via* the expected *ipso*-addition pathway, but instead nitration of one of the *ortho*-methyl groups is observed.[37,39] Mechanistically, it was proposed that this process occurs by oxidation to form a radical cation, followed by deprotonation and radical recombination.



Scheme 19. Cleavage of pentamethylacetophenone with various electrophiles

The byproduct of Kitijama's bromination chemistry is presumably acetyl bromide, and we recognized that for more complex Ph* ketones (e.g. those discussed in the proceeding sections of this Digest), it would be extremely valuable to apply a similar approach to form acid bromides, which are versatile intermediates that could react with a variety of nucleophiles. After some optimization, we discovered that cleavage of Ph* ketones to the acid bromide can be straightforwardly achieved by treatment with Br_2 in dichloromethane at –17 °C. The *in situ* formed acid bromides (observed by ^{13}C NMR spectroscopy) could be directly converted to a variety of other useful functional groups (Scheme 20).[4] For example, addition of an alcohol, amine or thiol afforded esters, amides and thioesters respectively (e.g. **91a-91c**).[10,4] The acid bromides could be reduced to the corresponding alcohols with $LiAlH_4$ (e.g. **91d**)[19] and examples bearing stereochemical information at the α-position reacted without any epimerization (e.g. **91e**).[23] Enantiopure β-substituted Ph* ketones could be converted to the corresponding acid bromide and trapped with chiral, non-racemic nucleophiles to generate products such as **91f** as a single diastereoisomer.[15] In our experience, the Br_2 mediated cleavage of mesityl ketones is generally less effective than the reactions of the analogous Ph* ketones, but Renaud and co-workers have reported that β-branched mesityl ketones can be successfully cleaved to provide products such as **91g** in up to 66% yield.[12] This cleavage chemistry has also been used outside of hydrogen borrowing catalysis. For example, Ph* ketones have been employed as masked esters to carry out various processes such as Rh-catalyzed C-H insertion or reductive couplings of cyclopropanes, followed by bromine-mediated Ph* cleavage.[40]



Scheme 20. One-pot bromine-mediated cleavage of Ph* ketones to a variety of functional groups

Conclusion and outlook

Pentamethylphenyl (Ph*) ketones are emerging new materials with exciting applications in synthetic organic chemistry. These molecules often display unique reactivity, which stems from their twisted structure, which protects the carbonyl against 1,2-addition whilst still allowing enolate formation. This aim of this Digest is to highlight the chemistry that is made possible with Ph* ketones that could not be achieved with other traditional ketones (where particularly relevant, examples involving other *ortho*-disubstituted ketones are also included). A variety of different chemistry is described, including hydrogen borrowing catalysis, aldol condensation and organocatalysis. The final section presents state-of-the-art methods available for the cleavage of Ph* ketones to other functional groups. We believe that the unique reactivity of these materials, coupled with an

expanding range of methods to convert them to other functional groups, will inspire many exciting new developments in the area of Ph* chemistry.

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