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Recent advances in the use of pentamethylphenyl (Ph*) ketones in organic synthesis

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Pentamethylphenyl (Ph*) ketones have gained prominence as versatile and valuable motifs in organic synthesis. The presence of the two *ortho*-methyl groups forces the aromatic ring to adopt a twisted conformation relative to the carbonyl group and gives Ph* ketones a distinctive and unconventional reactivity profile, differentiating them from traditional aromatic ketones. The main goal of this feature article is to demonstrate how the properties of Ph* ketones facilitate innovative chemical transformations. A range of applications are explored, concentrating not only on hydrogen borrowing catalysis, but also including acceptorless dehydrogenation, dynamic kinetic resolution and reduction chemistry, thereby showcasing the exceptional potential that these compounds exhibit. Furthermore, a detailed review of strategies for cleaving the Ph* group into a variety of functional derivatives is presented, highlighting their broad synthetic utility.

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1. Introduction

Pentamethylphenyl (Ph*) substituted ketones **2** represent a distinctive type of carbonyl compound characterised by a fully methylated aromatic ring. Although first documented over a century ago due to their intriguing structure, recent studies have unveiled their exceptional behaviour in chemical reactions.[1,2] Their distinct reactivity has its origins in the non-planar nature of the Ar and C=O groups which sets Ph* ketones **2** apart from other aromatic ketones **1**; it enables a range of novel and valuable transformations that are otherwise challenging to accomplish with standard carbonyl substrates. Notably, the pentamethylphenyl group (Ph*) can be efficiently converted into diverse functional groups such as carboxylic acids, esters, amides, alcohols, and aldehydes. This versatility

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Timothy J. Donohoe

Tim studied at the University of Oxford for a DPhil with Prof. Steve Davies and in 1993–1994 did postdoctoral work in the US with Prof. Phil Magnus. In 1994, he was appointed as a Lecturer at the University of Manchester, being promoted to Reader in 2000. In 2001, he moved to the University of Oxford as a Lecturer and Fellow of Magdalen College. In 2004, he was appointed as the Professor of Chemistry and he was the Head of Organic Chemistry at the University of Oxford (2006–2011). Tim's research interests lie in the field of redox chemistry, catalysis and the application of this methodology to natural product synthesis.

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significantly broadens the synthetic utility of Ph* ketones **2**, positioning them as powerful motifs in organic synthesis. Previously, we have reviewed the fundamental properties and reactivity of Ph* ketones **2**, with particular attention being paid to the influence that their conformation holds over reactivity.[2] We also provided a concise overview of established methods for synthesising simple Ph* ketones and their applications in synthesis. In this current feature article, we highlight recently reported reactions that are facilitated or enhanced by the Ph* group, concentrating on hydrogen-borrowing (HB) alkylation, acceptorless dehydrogenation, and including annulation, dynamic kinetic resolution and their applications in total synthesis, all emphasising the remarkable reactivity demonstrated by this class of compounds. Finally, state-of-the-art strategies for cleaving Ph* (and derivative) groups are also reviewed here. While our primary focus remains on pentamethylphenyl (Ph*) ketones **2**, relevant examples involving structurally related ketones, such as 2,6-dimethylphenyl and 2,4,6-trimethylphenyl ketones, are also discussed where applicable.

Aryl ketones **1**, such as acetophenone, typically adopt a planar conformation that facilitates conjugation between the aromatic ring and the carbonyl group. However, this is not the case for Ph* ketones **2**. In these compounds, a planar conformation would result in significant steric hindrance due to interactions between the ketone and the two bulky *ortho*-methyl substituents (Fig. 1A). Consequently, Ph* ketones **2**, as well as other *ortho*-disubstituted ketones, preferentially assume a non-planar conformation. This deviation from planarity is the root of their distinctive reactivity because the *ortho* methyl groups can now effectively shield the ketone C=O against nucleophilic attack. One key piece of evidence supporting the orthogonality between the carbonyl group and the aromatic ring is found using infrared spectroscopy: the carbonyl stretches for Ph* ketones **2** is typically shifted 10–20 cm^{-1} higher compared to their Ph-substituted counterparts (*e.g.*, **2** *vs.* **1**, Fig. 1).[3] This shift indicates a lack of conjugation between the C=O group and the Ph* ring (Fig. 1B).

In addition to the robustness endowed by Ph* ketones **2**, they offer another advantage with their tendency to crystallise; this facilitates the obtaining of crystal structures to determine the structure and enables straightforward purification by crystallisation.

One of the principal applications of Ph* ketones **2** lies in HB alkylation, together with multiple variants of this methodology. The high yields that Ph* ketones **2** give here are almost certainly due to their non-electrophilic character in the face of reactions conducted with a base at high temperatures. In our experience, the yields obtained with Ph* ketones **2** (and their close variants) cannot be matched using more conventional ketones.[4–7] Moreover, after any HB methodology is complete, simple and efficient methods for transforming Ph* groups into a diverse array of functional groups greatly enhance their value in the synthesis of complex molecules.[8–10]

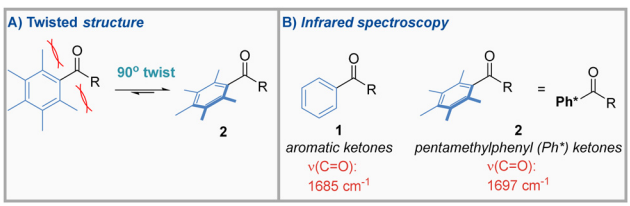


Fig. 1 General structure of pentamethylphenyl (Ph*) ketone **2**.

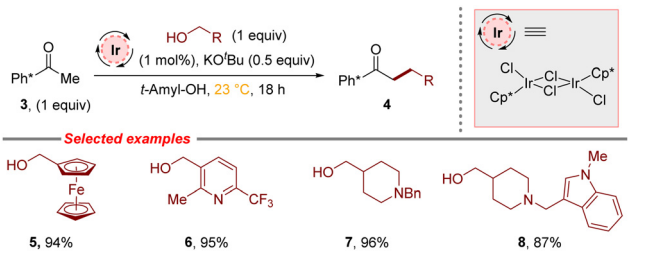
2. Functional group tolerant hydrogen borrowing

2.1 Anaerobic hydrogen borrowing catalysis

Performing HB alkylation under anaerobic conditions has revealed remarkable efficiency in reactions between Ph*COMe **3** and various alcohol substrates under mild, room-temperature conditions using catalytic $[Cp^*IrCl_2]_2$ (Scheme 1).[11] These conditions expand the range of compatible substrates and enable the successful alkylation of alcohols containing sensitive functional groups such as heterocycles, amines, and even TBS silyl ethers. Remarkably, the anaerobic conditions (achieved by degassing the reaction vessel) are essential for the increased reaction efficiency. Without this precaution, the reaction yields drop drastically, as demonstrated by the stark contrast between high yields under degassed conditions and negligible yields in air.

We then extended this work by showcasing how higher reaction temperatures (typically 85 °C) together with anaerobic conditions can overcome limitations posed by some coordinating and heterocyclic alcohols (see selected examples, Scheme 2).[11] Alcohol substrates containing pyridines, oxazoles, and other nitrogen-containing heterocycles, which are prone to catalyst deactivation through complexation, have now become viable. This aspect demonstrates the versatility of the methodology in alkylating functionalised alcohols. These findings have implications for synthesising complex molecules especially those relevant to pharmaceuticals and mark a significant advancement in hydrogen borrowing catalysis.

Our mechanistic studies confirmed the pivotal role of an iridium hydride intermediate in the hydrogen borrowing process. This intermediate is highly sensitive to oxygen and degassing is essential to prevent its degradation, thereby



Scheme 1 Room temperature anaerobic HB catalysis using functionalised alcohols (Donohoe, 2024).[11]

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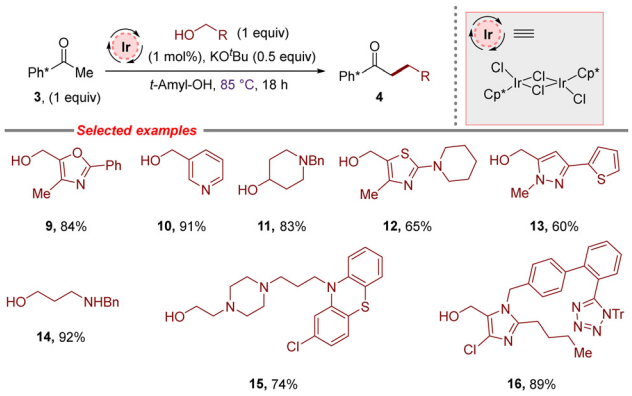
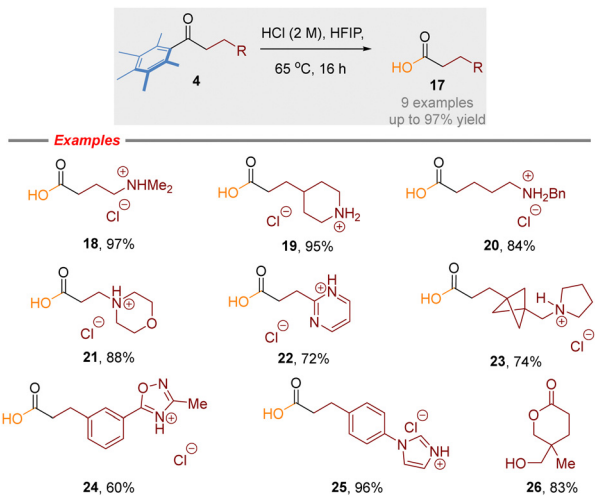


Scheme 2 Higher temperature anaerobic HB catalysis using functionalised alcohols (Donohoe, 2024).[11]

maintaining efficient catalytic activity. Exposure to air leads to the formation of modified catalyst species which are inactive at room temperature but retain limited activity at elevated temperatures. These findings underscore the critical importance of anaerobic conditions for ensuring optimal reaction performance, especially at lower temperatures.[11]

Finally, this study also demonstrated that the Ph* group can be smoothly removed using aqueous HCl in hexafluoroisopropanol (HFIP), enabling conversion of the alkylated intermediates into a variety of functionalised carboxylic acids **18–25** (Scheme 3). This process exhibits broad substrate tolerance, accommodating sensitive functional groups such as tertiary amines, alkyl halides, and aromatic heterocycles while maintaining high yields and selectivity. Importantly, the methodology is scalable (at a 10 mmol scale), yielding lactone **26** in 83% yield over two steps. These results reveal the potential of this approach in synthesising biologically relevant molecules (Scheme 3).[11]



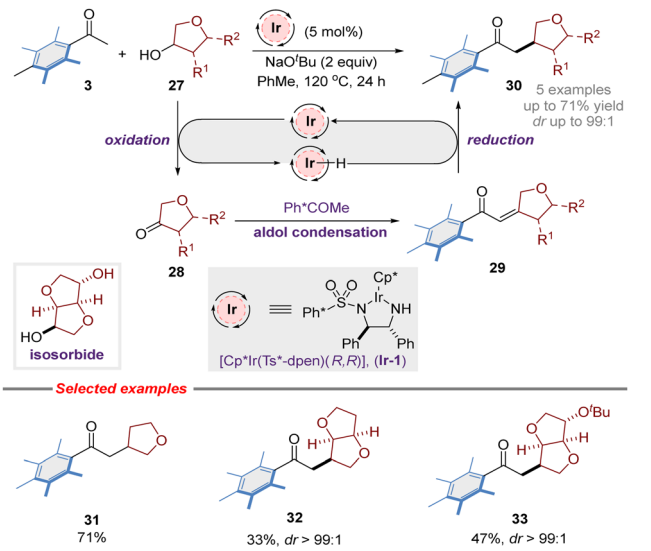
Scheme 3 Formation of carboxylic acids *via* Ph* cleavage of **4** (Donohoe, 2024).[11]

3. Hydrogen borrowing using secondary alcohols

In 2023, Popowycz and coworkers disclosed the first instance of direct C–C hydrogen-borrowing functionalisation of an isosorbide alcohol, building on their earlier work on the diastereoselective Ir-catalysed amination of isohexides.[12] In fact, direct functionalisation of the isosorbide skeleton poses a significant challenge in biomass valorisation, mainly due to the difficulty in achieving high selectivity. Using an iridium-based homogeneous organometallic catalyst, they achieved C–C alkylation with remarkable diastereoselectivity (Scheme 4). A Noyori type catalyst, [Cp*Ir(Ts*-dpen)(*R*,*R*)](**Ir-1**), was found to be more effective than $[Cp^*IrCl_2]_2$ in catalysing this HB system. Thus, treatment of Ph*COMe **3** with substituted 3-hydroxytetrahydrofuran derivatives **27** in the presence of **Ir-1** catalyst (5 mol%) and NaO^{t}Bu produced the desired products in moderate to good yields (see **31–33**, Scheme 4). It was also observed that substitution on the THF ring influenced both the reactivity and diastereoselectivity of this HB reaction.

As per the usual mechanism proposed for hydrogen borrowing, the reaction involves a catalytic sequence beginning with oxidation of the alcohol to form a reactive ketone intermediate **28**. This is followed by *in situ* aldol condensation and elimination, culminating in enone **29** hydrogenation to yield the desired alkylated product **30** and regenerate the catalyst.[12]

The group conducted a computational mechanistic study at the DFT level to investigate the factors underlying the observed diastereoselectivity. Their analysis revealed the critical role of the sodium counter-cation, which coordinates with the substrate's oxygen and controls hydride addition. This work provides a deeper understanding of the factors governing selectivity in HB chemistry and underscores the importance of using sterically hindered ketones such as Ph* in HB catalysis.[12]



Scheme 4 HB alkylation of tetrahydrofuran and isosorbide alcohol derivatives (Popowycz, 2023).[12]

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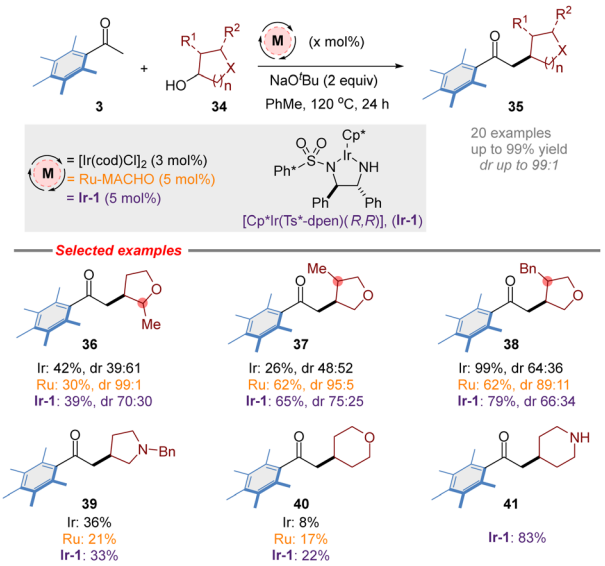
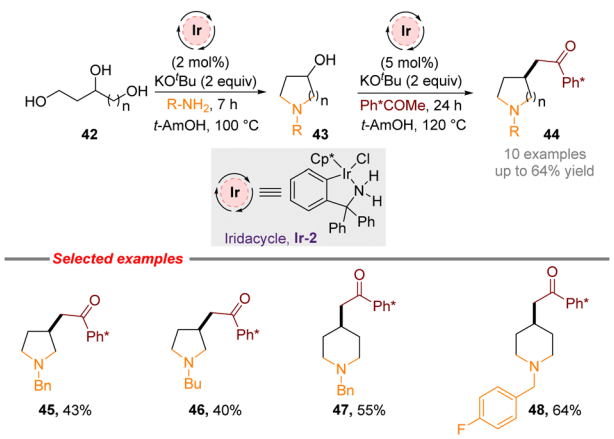


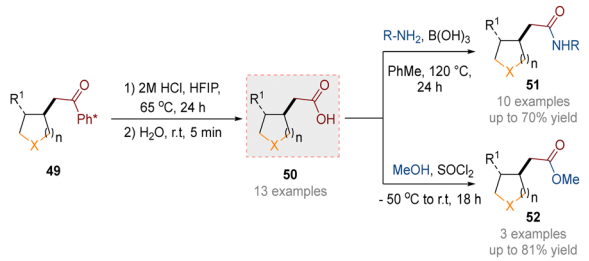
Scheme 5 HB alkylation of substituted tetrahydrofurans (THFs), pyrrolidines, and piperidines (Popowycz, 2024).[13]

In subsequent work (2024), Popowycz and coworkers built upon their earlier studies to expand the scope of this HB chemistry. The authors developed three distinct catalytic systems – [IrCODCl]$_2$ [(3 mol%)], Ru-MACHO® (5 mol%), and [**Ir-1** (5 mol%)] which all proved to be effective. Using these catalysts, a range of substituted tetrahydrofurans (THFs), pyrrolidines, and piperidines, **36–41,** were synthesised in good to high yields using HB alkylation with Ph*COMe **3** (Scheme 5).[13]

Furthermore, the authors investigated the HB cyclisation of triols **42** (here 1,2,4-butanetriol and 1,3,5-pentanetriol) with benzylic and aliphatic amines using iridacycle **Ir-2** as a catalyst. This C–N bond forming approach enabled efficient access to a variety of N-heterocycles **43** (Scheme 6) with distinct structural and functional properties.[13] This annulation is a valuable strategy for synthesising *N*-protected heterocycles with a free hydroxyl group, which then underwent *C*-alkylation with Ph*COMe **3** (see **45–48**, Scheme 6).



Scheme 6 Synthesis of pyrrolidines and piperidines from triols (Popowycz, 2024).[13]



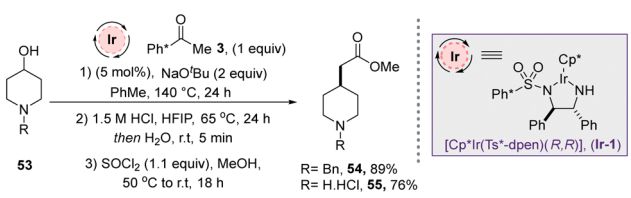
Scheme 7 Ph* cleavage and functionalisation of carboxylic acids (Popowycz, 2024).[13]

Finally, Popowycz and co-workers employed previously reported conditions[8–11,14–16] for Ph* cleavage to achieve post-functionalisation of their HB products. Under mild conditions, using HCl in HFIP, a range of acid products **50** was obtained and used without purification in a following step. Subsequent transformations of acid **50** into amides **51** and ester derivatives **52** were accomplished in good yields (Scheme 7).[13]

In a sequential approach, the HB reaction shown in Scheme 8 progressed directly from a piperidinol derivative **53** into the functionalised esters **54** and **55** without the need for purifying any intermediates. This sequence meant that **54** was obtained in 89% yield over three steps (compared to 50% yield when purification was required). Similarly, piperidin-4-ol **53** was converted into **55** with an overall yield of 76%, offering further opportunities for modifying the amino group (Scheme 8).[13]

These results demonstrate that sequential HB alkylation combined with post-reaction functionalisation is a promising method, offering advantages in reaction efficiency and serving as an effective tool for synthesising functionalised molecules.

In related work, the Srimani group recently developed redox-active Zn(II)-complexes for the efficient hydrogen borrowing α-alkylation of Ph*COMe **3** using secondary alcohols **56**.[17] This method demonstrated excellent functional group compatibility and chemoselectivity, particularly for distally unsaturated compounds, affording the desired products **58–63** in good to excellent yields (Scheme 9). Aromatic secondary alcohols yielded β-disubstituted ketones with excellent efficiency, tolerating a range of substituents on the aromatic ring. In their original paper, they showed that electron-donating groups (*e.g.* methoxy) and electron-withdrawing halogens (*e.g.* fluoro, chloro, and bromo) are well-tolerated, showcasing the system's robustness. Moreover, the halogenated products can undergo subsequent functionalisation *via* cross-coupling reactions, adding synthetic value. Finally, the authors demonstrated that



Scheme 8 Sequential formation of piperidinyl methyl esters (Popowycz, 2024).[13]

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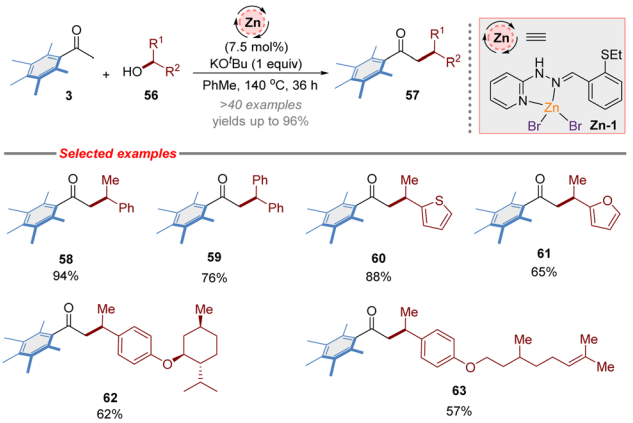
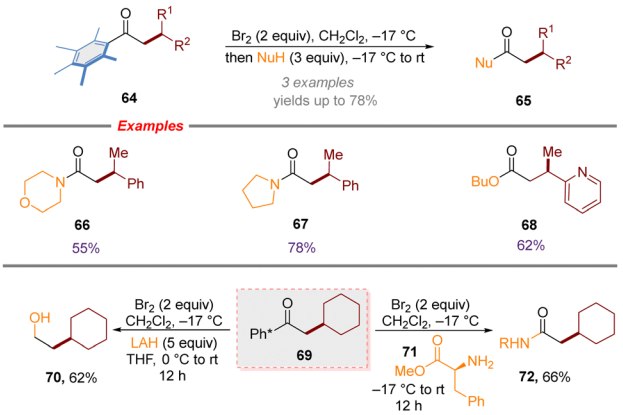


Scheme 9 HB alkylation of a wide range of alcohols using a zinc catalyst (Srimani, 2024).[17]



Scheme 10 Ph* cleavage and functionalisation of products (Srimani, 2024).[17]

aliphatic secondary alcohols, including cyclic and acyclic variants, also performed effectively in this alkylation.[17]

Pleasingly, substituted cyclic alcohols, such as cyclohexanol derivatives, exhibit good diastereoselectivity during this HB alkylation, while long-chain alcohols such as 2-decanol and 2-octanol give high yields. The method's chemoselectivity preserves many functional groups, enabling its application to more complex molecules such as menthol and cholesterol derivatives (as shown in their original paper).[17] The scalability of the reaction was also highlighted by a successful gram-scale synthesis of the products.

Control experiments, including kinetic studies, were conducted to better understand the catalyst's role and the reaction mechanism. The authors identified that KO^{t}Bu is essential for activating the catalyst through dehydrobromination and single electron transfer to the precatalyst. Notably, the use of non-toxic, cost-effective, and biocompatible Zn(II) for the base-mediated synthesis of β-disubstituted carbonyl compounds positions this procedure as a potentially sustainable approach.

Using a bromine-assisted retro Friedel–Crafts acylation, the Ph* group was then efficiently cleaved to yield acid bromide intermediates. These intermediates reacted with nucleophiles such as amines and alcohols to produce amides **66–67** and esters **68**, respectively. Additionally, the protocol enabled reduction of the acid bromide intermediates to alcohol **70** using lithium aluminum hydride (LAH) and coupling to amino acid derivative **71** as shown in Scheme 10.[17]

4. Acceptorless dehydrogenation

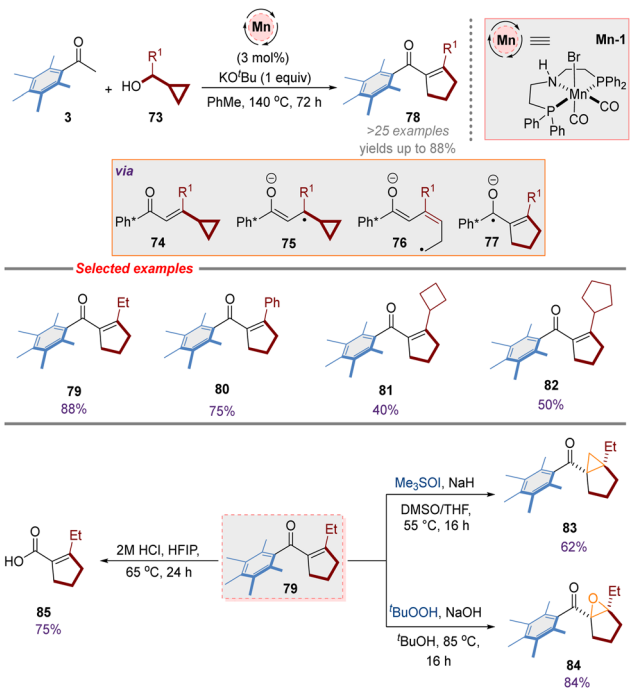
Acceptorless dehydrogenation (AD) is a catalytic process that removes hydrogen atoms from organic molecules without the need for external oxidants or hydrogen acceptors, releasing hydrogen gas (H_2) as the by-product. This method is considered environmentally friendly and atom-efficient, as it avoids the use of stoichiometric oxidants.[18,19] In our research group, we have extensively investigated acceptorless dehydrogenation (AD) processes. In 2020, we developed a tandem reaction sequence initiated by an iridium-catalysed acceptorless dehydrogenation (AD) of 1,5-diols to generate hydroxyaldehydes, which then engage in a redox-neutral [1,5]-hydride shift cascade to afford acyl-cyclohexenes.[20]

4.1 Cyclopentene synthesis

In 2024, Maji and co-workers reported the first successful synthesis of acyl cyclopentene derivatives **78** through the AD reaction of sterically hindered ketones (Scheme 11).

Utilising Ph*COMe **3**, and cyclopropane methanol **73** manganese complex (**Mn-1**) served as the key catalyst in this innovative approach.[21]

This method delivered the desired cyclopentene products in moderate to high yields (see **79–82**, Scheme 11), showcasing a



Scheme 11 Synthesis of cyclopentenes and product derivatisation (Maji, 2024).[21]

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sustainable and practical route for the construction of these valuable intermediates.[21]

The reaction mechanism, elucidated through in-depth experimental and computational studies, involved several pivotal steps. These included manganese-catalysed acceptorless alcohol dehydrogenation of **73**, subsequent aldol condensation with **3** to form a vinyl cyclopropane intermediate **74**, and a single-electron transfer (SET)-mediated ring expansion proceeding *via* **75–77**. The careful optimisation of reaction conditions, including the steric and electronic properties of the ketone substrate, was critical for steering the reaction toward the formation of cyclopentene derivatives **78**.[21]

This reaction enabled the selective isolation of unsaturated cyclopentene products while preventing over-reduction to their saturated cyclopentane counterparts.[22] This unique selectivity emphasises the significance of the manganese catalyst in mediating a complex cascade of transformations. Furthermore, this study not only advanced the understanding of catalytic ring-expansion strategies but also provided an outline for designing similar transformations using earth-abundant metal catalysts, making it an environmentally and economically appealing alternative for synthetic chemists.[21]

The authors also illustrated the synthetic utility of the cyclopentenes derived from Ph* ketones through various functionalisation reactions. These cyclopentene motifs underwent diverse transformations, including Corey–Chaykovsky cyclopropanation to form a bicyclic product **83** in 62% yield. Finally, epoxidation of the cyclopentenes afforded tetra-substituted epoxide **84** in 84% yield (Scheme 11).[21]

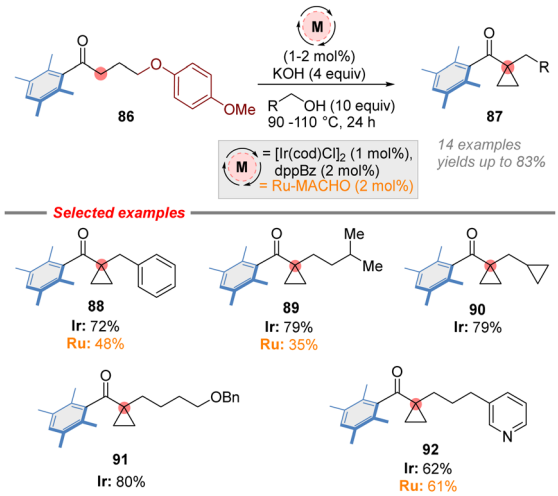
5. Construction of quaternary centres

5.1 Construction of quaternary centres *via* hydrogen borrowing catalysis

In 2023, we reported an operationally simple method for the α-cyclopropanation of ketones, employing HB catalysis (Scheme 12). This approach involves HB alkylation of a sterically hindered ketone **86**, followed by intramolecular displacement of a precisely positioned leaving group to yield a cyclopropanated product **87**.

Notably, the leaving group can be introduced into either the ketone or the alcohol component of the hydrogen borrowing system, enabling the synthesis of α-cyclopropyl ketones through two distinct pathways.[23] Importantly, this is the first reported example in the literature of cyclopropane synthesis utilising HB catalysis.[23]

In this study, the tetramethylphenyl (Ph^x) group was used instead of Ph* because the bromine or acid-catalysed methods for removing the Ph* protecting group were unsuccessful, due to concomitant decomposition of the cyclopropane unit. However, replacing Ph* with the 2,3,5,6-tetramethylphenyl group (Ph^x) provided a solution, as the Ph^x group can be removed cleanly under mild two-step conditions, yielding the desired carboxylic acid **97** and maintaining the integrity of the cyclopropane moiety, *vide infra*. As expected, the Ph^x group performed comparably to Ph* under the iridium-catalysed HB

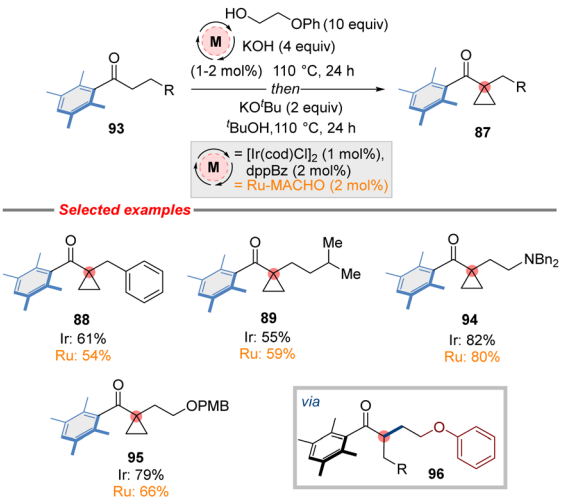


Scheme 12 HB alkylation enables the formation of α-cyclopropyl ketones (Donohoe, 2023).[23]

alkylation conditions. We also found that the commercially available catalysts [Cp*IrCl$_2$]$_2$ and Ru-MACHO® were both highly effective in promoting this transformation, and a series of α-cyclopropyl ketones **88–92** were prepared in good to high yields (Scheme 12).[23]

In the first pathway, treatment of hindered ketone substrate **86**, with a range of aliphatic and benzylic alcohols in the presence of [Cp*IrCl$_2$]$_2$ and Ru-MACHO® catalysts facilitated HB alkylation and cyclisation to afford cyclopropane products **88–92** in good to high yields (Scheme 12).

Next, we established a separate alcohol prefunctionalisation pathway for cyclopropane synthesis. Pleasingly, the previously optimised conditions were compatible with a phenoxy leaving group placed on the alcohol component delivering the best results (Scheme 13). The use of KO^{t}Bu as the base in the second stage of the reaction consistently provided good to high yields of cyclised products from intermediate **96**. This strategy proved



Scheme 13 HB alkylation toward the formation of α-cyclopropyl ketones using a prefunctionalised alcohol (Donohoe, 2023).[23]

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to be compatible with a range of Ph^x ketones highlighting the utility of this method.[23]

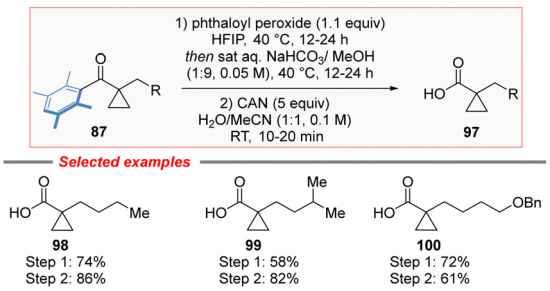
After alkylation, the Ph^x group was removed efficiently in two steps to yield the desired carboxylic acids **97**. In the first step, oxidation of the aryl ring with phthaloyl peroxide in HFIP produced the corresponding *para*-phenol in moderate to good yields. These phenols were then treated with CAN, leading to the formation of carboxylic acids (**98–100**) in good to excellent yields with the cyclopropane ring remaining unaffected (Scheme 14).[23]

5.2 Construction of quaternary centres *via* acceptorless dehydrogenation

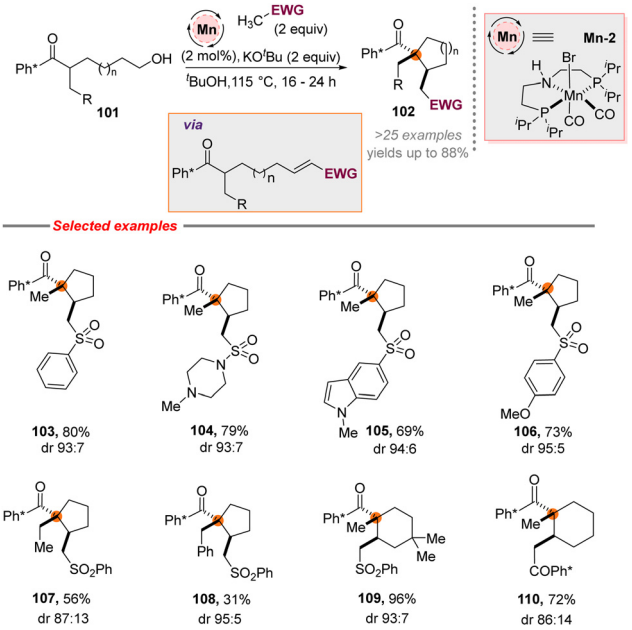
In 2025, we developed another approach for constructing quaternary stereocenters using a manganese-catalysed tandem acceptorless dehydrogenation-cyclisation cascade (Scheme 15).[24] Here, an AD reaction of an alcohol substrate **101** is followed by condensation with a nucleophilic component (CH_3-EWG) to form a key unsaturated intermediate. This unsaturated intermediate then cyclises under the basic reaction conditions, and the bulkiness of the Ph*CO group ensured excellent diastereoselectivity while forming five and six-membered rings, achieving yields of up to 96%. Moreover, this reaction exhibits impressive tolerance for various nucleophiles (see CH_3-EWG, Scheme 15), including sulfones, sulfonamides, and ketones, underscoring the versatility of this method in constructing functionalised carbocyclic scaffolds bearing a quaternary stereocentre.[24]

This study also investigated the divergent reactivity of benzylic alcohol substrates under related catalytic conditions. Using Ru-MACHO® catalysis, the reaction predominantly formed five membered carbocycles with exocyclic alkenes *via* cyclisation and elimination of sulfinate. In contrast, $[Cp^*IrCl_2]_2$ catalysis favored the formation of six-membered carbocycles (Scheme 16). The Ru-catalysed sequence accommodated a range of substituents on both the aromatic ring and the benzylic alcohol. Substituents such as methyl, ethyl, and electron-withdrawing groups are well tolerated, yielding exocyclic alkenes in moderate to high yields. Similarly, electron-rich benzylic alcohols also undergo efficient cyclisation in up to 92% yield.[24]

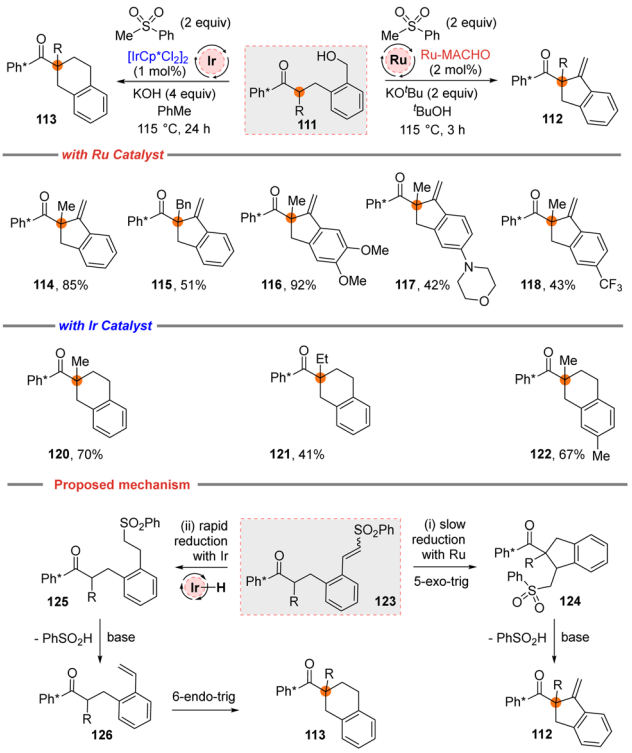
For the Ir-catalysed pathway, only simpler aromatic substituents were tolerated, and the scope for generating six-membered carbocycles is narrower, with lower yields observed



Scheme 14 Formation of cyclopropane carboxylic acids by Ph^x removal (Donohoe, 2023).[23]



Scheme 15 Synthesis of highly functionalised carbocyclic derivatives (Donohoe, 2025).[24]



Scheme 16 Distinct pathways for benzylic alcohols in HB alkylation (Donohoe, 2025).[24]

for bulkier or more electron-rich substrates (Scheme 16). This variation in products (6-membered rings *vs.* 5-membered rings) highlights how catalyst selection can fine-tune the reaction and demonstrates the robustness of Ph* ketones in navigating

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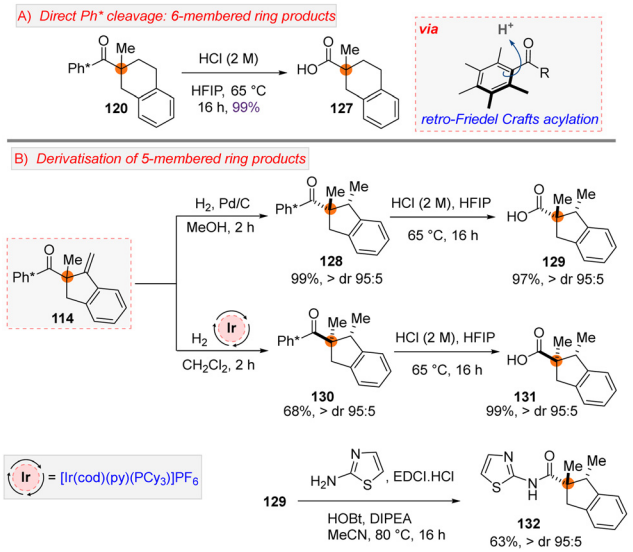


Scheme 17 Ph* cleavage and the formation of functionalised five and six-membered rings (Donohoe, 2025).[24]

different reaction pathways (see **114–122**, Scheme 16).[24] We then investigated the mechanism underlying the formation of products **112** and **113**, and proposed that intermediate **123**—generated *via* alcohol oxidation followed by condensation with the sulfone—plays a key role (Scheme 16). We suggest that the competition between reduction and cyclisation of **123** determines the product outcome. When Ru MACHO® is used, reduction of the alkene within **123** proceeds more slowly than cyclisation, favouring five membered ring formation **112**. This route involves deprotonation adjacent to the ketone, followed by a 5-*exo-trig* cyclisation to generate intermediate **124**. Conversely, rapid reduction of intermediate **123** with an Ir catalyst allows subsequent elimination of sulfinate from **125** and then 6-*endo-trig* cyclisation of an enolate from **126** to generate the six membered ring products **113**.

Once again, we showed that the Ph* group can be efficiently removed without compromising the integrity of the final products. Selective cleavage from cyclic products enabled access to carboxylic acids and their derivatives, allowing for additional functionalisation. This versatility allowed for the synthesis of biologically relevant compounds, such as glucocorticoid receptor modulator **132**, which was obtained in 63% yield (Scheme 17).[24]

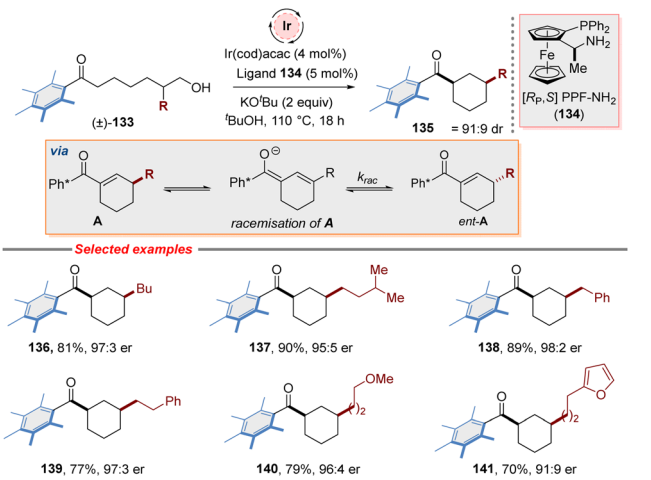
6. Dynamic kinetic resolution *via* HB catalysis

In 2025, we reported a study on the synthesis of enantiopure γ-substituted cyclohexyl ketones **135** using dynamic kinetic resolution (DKR) in asymmetric HB reactions.[25] While previous strategies allowed stereocontrol at the α-, β-, and δ-centres on the six membered ring, the γ-centre was unaddressed due to its susceptibility to racemisation under basic conditions.[7,10] This study turns that limitation into an advantage by starting from a racemic linear alcohol **133**, and exploiting *in situ* racemisation of the key intermediate **A**. This scenario enables the selective reduction of one enantiomer of **A** using an iridium catalyst (Ir(cod)acac) and a chiral ligand, [R_P,*S*]-PPF-NH_2 **134**. The unreactive enantiomer (*ent*-**A**) can racemise *in situ* and thus the HB method allows racemic alcohols to be converted efficiently into γ-substituted ketones with excellent yields and enantioselectivity (Scheme 18).[25]

The substrate scope was investigated using a series of racemic linear alcohols, as shown in Scheme 18. The methodology delivered eight distinct products with consistently high yields (ranging from 70% to 87%) and excellent enantioselectivities, reaching up to 98 : 2 er (see **136–141**, Scheme 18). The success of the dynamic kinetic resolution (DKR) process relied on the [R_P,*S*]-PPF-NH_2 ligand, which outperformed other ligands such as DTBM-SEGPHOS. Additionally, the presence of the Ph* group not only contributed to the high stereoselectivity and yield but also enhanced product crystallinity, enabling structural confirmation *via* X-ray analysis and allowing enantiopurity to be improved through recrystallisation.[25]

We also rationalised the high enantioselectivity through DFT calculations performed on the hydride transfer step from Ir–H to the coordinated enone (*i.e.* **A** *versus ent*-**A**). The mechanism proceeds *via* a stepwise pathway: first, hydride migration to the β-carbon forms an Ir σ-complex, followed by a rearrangement to a π-allylic enolate. Among the four reactive configurations possible, both the *Re*-(*S*) and the *Si*-(*S*) pathways emerged as the lowest energy routes with either the first or the second step becoming rate limiting and enantioselectivity determining. This conclusion was underpinned by favourable non-covalent interactions and π-stacking found between the ligand aryl phosphine and the Ph* group.

Finally, the Ph* group was removed *via ipso* bromination to generate an acid bromide intermediate, which underwent nucleophilic addition to form diverse derivatives such as carboxylic acids **142**, alcohols **143**, esters **144–145**, and amides **146–147**. These reactions proceed efficiently, with retention of



Scheme 18 HB alkylation enables the synthesis of enantiopure γ-substituted ketones using a dynamic kinetic resolution (Donohoe, 2025).[25]

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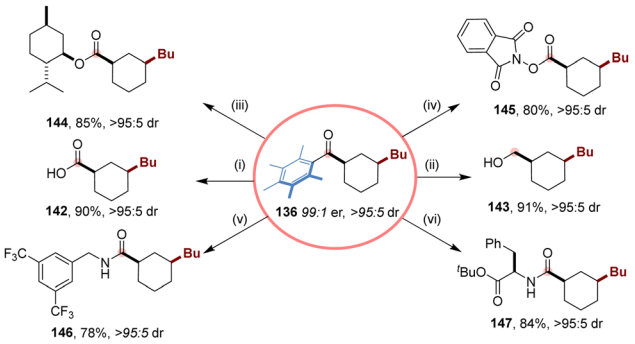


Scheme 19 Derivatisation of the Ph* group. Br_2 (2 equiv.) CH_2Cl_2, −20 °C then add (i) aq. $NaHCO_3$; (ii) $LiAlH_4$; (iii) L-(−)-menthol; (iv) *N*-hydroxyl phthalimide; (iv) 3,5-ditrifluoromethyl benzylamine (v) H-D-Phe-O*t*Bu·HCl.

stereochemistry; therefore, employing enantiopure nucleophiles in these transformations produced amide and ester products as single diastereoisomers (Scheme 19).[25]

7. Utility in total synthesis

In 2022, we reported an asymmetric synthesis of (−)-γ-lycorane **152**, and the first total synthesis featuring HB alkylation as the pivotal step (Scheme 20).[26]

We recognised that a fused 6,5-lactam ring system **E** was well-suited for construction by a HB alkylation reaction employing a cyclic amino alcohol **B** as a novel alkylating agent (Scheme 20A). Indeed, the successful alkylation of Ph*COMe **3** with 1,2-aziridinyl alcohols (see **B** → **C**) offered a promising strategy for synthetic exploration.

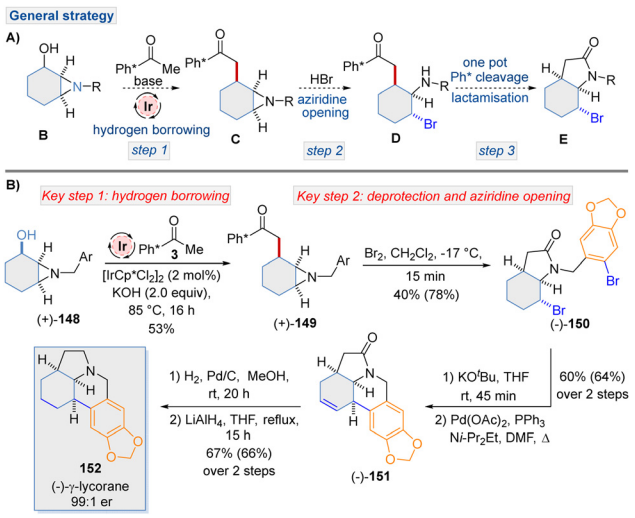
In the forward synthesis, 1,2-aziridinyl alcohol (+)-**148** was prepared in four steps from cyclohexanone with an overall yield of 37%. Pleasingly, the HB alkylation of Ph*COMe **3** using 1,2-aziridinyl alcohol **148** then produced **149** as a single diastereoisomer in 53% yield (and e.r. 98 : 2). The Ph* group was efficiently removed using Br_2, triggering an aziridine ring opening and lactamisation *in situ* to form the *cis*-fused 6,5-lactam bicyclic motif **150** in 40% yield (aryl ring bromination was also facilitated in this step). This sequence was followed by regioselective elimination from the alkyl bromide and a regio- and stereoselective intramolecular Heck reaction, which constructed the final carbon–carbon bond and formed compound **151** in 60% yield. Finally, catalytic hydrogenation of the alkene with Pd/C, followed by amide reduction using $LiAlH_4$, completed the synthesis of (−)-γ-lycorane **152** in 67% yield as a single enantiomer (e.r. 99 : 1) as shown in Scheme 20B.[26]

8. Asymmetric transfer hydrogenation

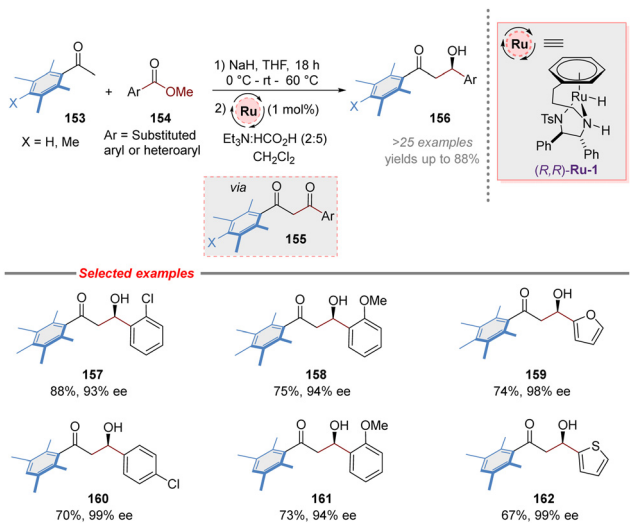
The asymmetric transfer hydrogenation (ATH) of ketones using ruthenium-based catalysts has become a key method in synthetic chemistry.[27,28] A wide range of ketone classes have been found to exhibit excellent compatibility with the ATH reduction when using chiral Ru-based catalysts such as **Ru-1**.[29]

In 2024, Wills and co-workers reported a highly selective approach for the asymmetric transfer hydrogenation (ATH) of diarylketones, achieving regio- and enantioselective reduction of one carbonyl group in the presence of another, Scheme 21.[30] This strategy takes advantage of using hindered ketones such as Ph* ketones and Ph^x ketones to selectively deactivate one carbonyl, allowing the other to undergo smooth reduction using a Ru-based ATH catalyst (**Ru-1**) under mild conditions[31–33] (here formic acid/triethylamine).[30]

This study begins by establishing that certain ketones with *ortho*-substituted aromatic rings, such as di-*ortho*-methoxyphenyl or Ph* ketones, are completely resistant[34,35] to ATH using the **Ru-1** ruthenium catalyst in a formic acid/triethylamine azeotrope. Such resistance to the ATH reaction is presumably a consequence of steric shielding caused by the *ortho* substituents when the aromatic ring does not lie in conjugation with the



Scheme 20 Total synthesis of (−)-γ-lycorane **152** (Donohoe, 2022).[26] Yields in parentheses are for the racemic material.



Scheme 21 Synthesis of enantiopure β-hydroxyketones *via* the ATH method (Wills, 2024).[30]

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carbonyl group. This discovery forms the basis for the new strategy: incorporating such hindered arylketones into a diarylketone scaffold so that only the less hindered carbonyl group is reduced. In their original report, Wills outlined a synthetic route to a series of diaryl 1,3-diketones, prepared by the reaction of enolates from hindered aryl ketones **153** with esters **154**. These diketones were then subjected to ATH using 1 mol% of the **Ru-1** catalyst system (Scheme 21).[30] The reactions proceeded under mild conditions, delivering the corresponding enantiopure hydroxyketones (**157–162**) in moderate to excellent yields. This synthetic strategy enabled the systematic variation of both the sterically hindered aryl group and the substituent on the reducible carbonyl moiety, allowing access to a well-defined scope of diketones for evaluating regio- and enantioselectivity.

The results demonstrate excellent regioselectivity and enantioselectivity across a broad substrate scope. Substrates bearing unsubstituted, *para*-substituted, and even heteroaromatic groups afforded products with high enantiomeric excess (up to 99% ee), with selected examples illustrated in Scheme 21.[30]

Importantly, diketones incorporating Ph* and Ph^x motifs consistently gave high yields and excellent ee, confirming their effectiveness as steric blocks for one carbonyl group. In their report, the absolute configuration of several products was confirmed by X-ray crystallography, supporting the proposed mechanistic model involving CH/π interactions with the η^6-arene ligand of the catalyst and steric shielding by the *ortho*-substituents of the substrate.

The aryl functional group tolerance was notably broad. Both electron-donating and electron-withdrawing substituents were well tolerated, including halogens, methoxy groups and heterocycles. Even mono-*ortho*-substituted arenes gave good enantioselectivity, though with a modest drop compared to their *para*-substituted analogs.[30]

9. Conclusions

Pentamethylphenyl (Ph*) ketones represent a unique class of functional groups with significant untapped potential in synthetic organic chemistry. Their unusual reactivity arises from their sterically hindered and twisted structure, which prevents nucleophilic addition to the carbonyl group during reactions. This review highlights the recent applications of Ph* ketones, alongside comparisons to other related sterically hindered ketones, in diverse catalytic and synthetic methodologies.

Ph* ketones demonstrate exceptional versatility, allowing the development of new pathways in hydrogen borrowing (HB) catalysis such as dynamic kinetic resolution, and applications in total synthesis. Recently, in HB catalysis, Ph* ketones have been effectively used to achieve selective C–C bond formation under mild and sustainable conditions, highlighting their practical utility. These reactions are recognised for their sustainable nature, as they produce H_2 and/or water as by-products. Beyond serving as tolerant intermediates for hydrogen borrowing and other reactions, they act as strategic platforms for further functionalisation. Operationally, simple methods for converting Ph* groups into a wide range of functionalities, including carboxylic acids, esters, amides, alcohols, amines, and heterocycles, significantly expand their utility in the synthesis of complex molecules with pharmaceutical and materials science applications. Another advantage of Ph* ketones is their ability to integrate hydrogen borrowing alkylation with subsequent functionalisation steps without requiring intermediate purification techniques. Finally, their crystalline nature can be used advantageously in purification and enantiomeric upgrade processes. We anticipate that the utility of these ketone derivatives will continue to expand in hydrogen borrowing catalysis and beyond into other fundamentally different classes of chemical reactions.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results are included and no new data were generated or analysed as part of this review.

Acknowledgements

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