Tetrahedron 86 (2021) 132051

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Hydrogen borrowing catalysis using 1° and 2° alcohols: Investigation and scope leading to α and β branched products

James R. Frost [a], Choon Boon Cheong [a], Wasim M. Akhtar [a], Dimitri F.J. Caputo [a], Kirsten E. Christensen [a], Neil G. Stevenson [b], Timothy J. Donohoe [a, *]

[a] Chemistry Research Laboratory, University of Oxford, Oxford, OX1 3TA, United Kingdom
[b] GlaxoSmithKline, Medicines Research Centre, Stevenage, SG1 2NY, United Kingdom

ARTICLE INFO

Article history:
Received 19 January 2021
Received in revised form
15 February 2021
Accepted 19 February 2021
Available online 5 March 2021

Dedicated to Professor J. M. J. Williams.

Keywords:
Hydrogen borrowing catalysis
Iridium
Alkylation
Cyclopentane
retro-Friedel–Crafts

ABSTRACT

The alkylation of a variety of ketones using 1° or 2° alcohols under hydrogen borrowing catalysis is described. Initial research focused on the α-alkylation of cyclopropyl ketones with higher 1° alcohols (i.e. larger than MeOH), leading to the formation of α-branched products. Our search for additional substrates with which to explore this chemistry led us to discover that di-*ortho*-substituted aryl ketones were also privileged scaffolds, with Ph* (C_6Me_5) ketones being the optimal choice. Further investigations revealed that this motif was crucial for alkylation with 2° alcohols forming β-branched products, which also provided an opportunity to study diastereoselective and intramolecular hydrogen borrowing processes.

1. Introduction

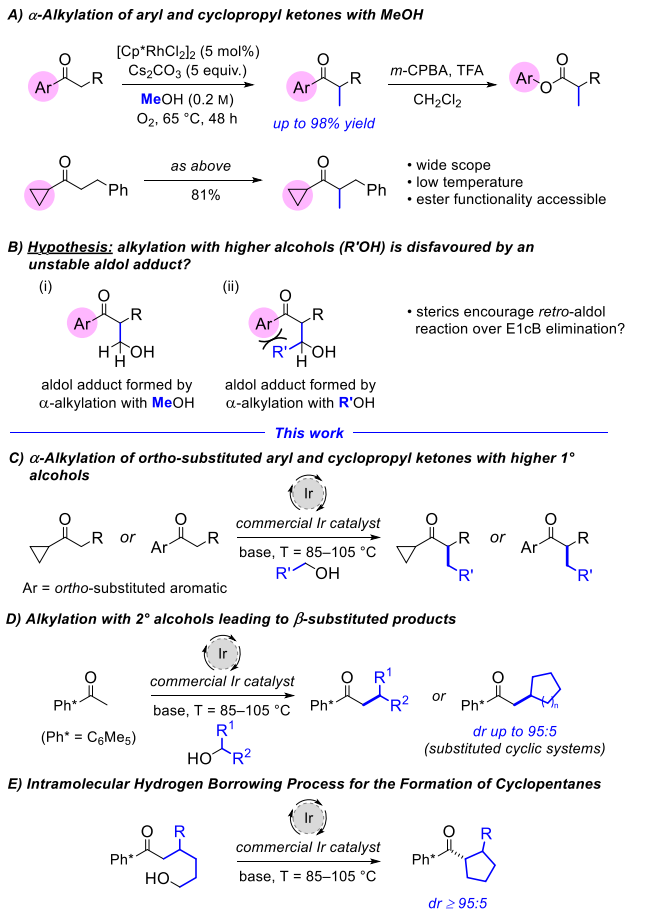
Hydrogen borrowing chemistry has emerged as a powerful method for the rapid construction of new C–C and C–N bonds under catalytic conditions [1]. In a typical one-pot reaction manifold, an alcohol functional group is initially oxidized to the corresponding carbonyl by an appropriate metal catalyst, generating a metal hydride species. The carbonyl formed *in situ* then condenses with a nucleophile (e.g. enolate or amine), and the subsequently formed compound (e.g. enone or imine) is reduced by the metal hydride to complete the catalytic cycle. The entire process involves no net change in oxidation state, and avoids laborious chemical manipulations and toxic reagents[2].

We have recently sought to expand the synthetic utility of hydrogen borrowing catalysis, and in the process develop new C–C bond forming reactions. Our initial research revealed that α-methylation of ketones could be achieved using MeOH under rhodium-catalyzed conditions (Scheme 1A) [3]. This also resulted in the formation of α-branched ketones, which at that time had little literature precedent. Further contributions by the groups of Li [4], Andersson [5], and others [6] also cemented MeOH as an appropriate alcohol with which to form α-branched (methylated) products. In order to increase the usefulness of this chemistry, we also employed a Baeyer–Villiger reaction that provided a straightforward synthesis of the corresponding α-branched esters [7].

However, initial attempts at expanding this methodology to encompass higher 1° alcohols (i.e. larger than MeOH) as alkylating agents had limited success. A subsequent literature search revealed very few examples whereby α-branching had been accomplished, with most processes pertaining to Guerbet-type reactions [8]. Furthermore, it was apparent that 2° alcohols were also not generally employed for alkylation under hydrogen borrowing conditions. A rare example of this was reported by Obora, who showed that MeCN (10 equiv.) could be alkylated with 2° alcohols, albeit at high temperatures (130–200 °C) [9]. Initially, we hypothesized that the additional steric bulk imparted by higher alcohols (both 1° and 2°) destabilized the intermediate aldol adduct, favoring the *retro*-aldol reaction over E1cB elimination (Scheme 1B). Our strategy therefore focused on the use of substrates that were less sterically hindered such that aldol condensation could occur profitably *in situ*.

* Corresponding author.
E-mail address: timothy.donohoe@chem.ox.ac.uk (T.J. Donohoe).

https://doi.org/10.1016/j.tet.2021.132051
0040-4020/



Scheme 1. Hydrogen borrowing reactions with higher 1° and 2° alcohols.

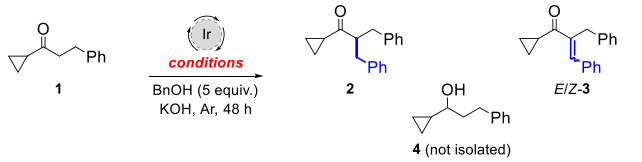
Herein we disclose our full research effort towards the development of the aforementioned α-alkylation of ketones with higher 1° alcohols (Scheme 1C). Further development of this chemistry thereafter led to a general iridium catalyzed alkylation using 2° alcohols to form β-branched products (Scheme 1D) [10,11]. Subsequent work in the literature has reported related hydrogen borrowing alkylation using a variety of metal (and earth abundant metal) catalysts [12]. This account will also highlight our preliminary studies towards the development of intramolecular hydrogen borrowing reactions (Scheme 1E) [10b].

2. Results and discussion

2.1. α-Alkylation of cyclopropyl ketones and related cycloalkyl ketones

Our study began with cyclopropyl ketone **1**, employing [Ir(cod)Cl]$_2$ (2 mol%), (±)-BINAP (4 mol%), KOH (3 equiv.) and BnOH (5 equiv.) at 65 °C under an Ar atmosphere for 48 h (Table 1, entry 1). Pleasingly, analysis of the crude ^{1}H NMR spectrum showed the desired α-alkylated product **2** (12%), as well as enone (7%, as a mixture of *E*/*Z*-**3** isomers) and unreacted starting material (47%) [13]. While ligand variation did very little to change the product distribution (select examples, entries 2–4), a breakthrough came with an increase in reaction temperature. Heating to 85 °C improved the product ratio to 41:8:20 (**2**:(*E*/*Z*)-**3**:**1**, entry 5), whilst 105 °C gave desired α-alkylated compound **2** in 74% isolated yield (entry 6). With this result in hand, we attempted to lower the stoichiometry of KOH from 3 equiv. but incomplete conversion was observed otherwise (entries 7 and 8). Whilst we replaced KOH with several different bases (K_2CO_3 and NaOMe, not shown), only KO*t*Bu gave complete conversion, albeit in inferior isolated yield (entry 9, 50%). The amount of product **2** could be marginally improved (~10%) by increasing the loading of [Ir(cod)Cl]$_2$ and (±)-BINAP (maintained in a 1:2 ratio). However, we considered this gain insufficient to justify committing additional reagents (entries 11 and 12). With this in mind, several other catalysts that were known to facilitate hydrogen borrowing chemistry without an additional ligand were also screened. Both [Cp*IrCl$_2$]$_2$ and [Cp*RhCl$_2$]$_2$ were found to be effective, with the former providing **2** in near identical yield (entry 13) to the [Ir(cod)Cl]$_2$/(±)-BINAP system (entry 6) in only 24 h. This considerable reduction in reaction time was highly desirable, and so the conditions in entry 13 were chosen to evaluate the substrate scope.

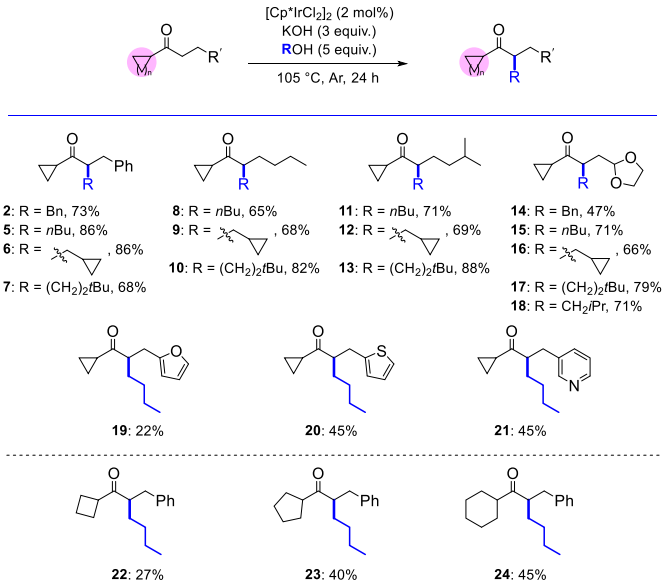
Table 1
Optimization of hydrogen borrowing conditions with cyclopropyl ketone **1** and BnOH.



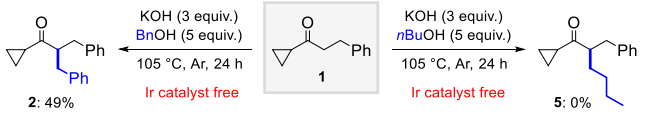
entry	catalyst (mol%)	Ligand (mol%)	KOH (equiv.)	temp. (°C)	yields (%)[a] 2	E/Z-3	1 (SM)
1	[Ir(cod)Cl]$_2$ (2)	(±)-BINAP (4)	3	65	12	7	47
2	[Ir(cod)Cl]$_2$ (2)	dppBz (4)	3	65	12	4	38
3	[Ir(cod)Cl]$_2$ (2)	DPEPhos (4)	3	65	12	8	47
4	[Ir(cod)Cl]$_2$ (2)	XantPhos (4)	3	65	6	12	35
5	[Ir(cod)Cl]$_2$ (2)	(±)-BINAP (4)	3	85	41	8	20
6	[Ir(cod)Cl]$_2$ (2)	(±)-BINAP (4)	3	105	74[b]	–	–
7	[Ir(cod)Cl]$_2$ (2)	(±)-BINAP (4)	1	105	20	10	48
8	[Ir(cod)Cl]$_2$ (2)	(±)-BINAP (4)	2	105	71	6	2
9[c]	[Ir(cod)Cl]$_2$ (2)	(±)-BINAP (4)	3	105	50[b]	–	–
10	[Ir(cod)Cl]$_2$ (1)	(±)-BINAP (2)	3	105	58	11	6
11	[Ir(cod)Cl]$_2$ (4)	(±)-BINAP (8)	3	105	82[b]	–	–
12	[Ir(cod)Cl]$_2$ (8)	(±)-BINAP (16)	3	105	84[b]	–	–
13[d]	[Cp*IrCl$_2$]$_2$ (2)	–	3	105	73[b]	–	–
14	[Cp*RhCl$_2$]$_2$ (2)	–	3	105	64[b]	–	–

[a]Yields based on ^{1}H NMR analysis, reactions performed on 0.3 mmol scale; [b]Isolated yield; [c]KO*t*Bu used instead of KOH; [d]Reaction run for 24 h.

Next, non-benzylic alcohols were assessed under the optimized conditions. Pleasingly, *n*BuOH gave α-branched compound **5** in 86% isolated yield, whilst more sterically hindered aliphatic alcohols (cyclopropylmethanol and 3,3-dimethyl-1-butanol) also worked in good to excellent yield (Scheme 2, 86% and 68% respectively). Replacing the phenyl group on the substrate sidechain with *n*Pr or *i*Bu was also tolerated in combination with these alcohols. A dioxolane ring was then incorporated into the substrate backbone, leading to compounds **14**–**18**, and thereby providing useful functionality for further synthetic manipulation. Of particular note was the use of *i*BuOH as a coupling partner (to give **18** in 71% yield), which represents one of the most sterically hindered alcohols employed to afford α-branched compounds under hydrogen borrowing conditions. Several cyclopropyl ketones bearing heterocyclic sidechains were also processed with *n*BuOH. The furan moiety was found to be the least well-tolerated substrate (Scheme 2, **19**, 22% yield), whilst thiophene and pyridine were more robust (**20** and **21**, both 45% yield).



Scheme 2. Cycloalkyl ketone substrate scope.



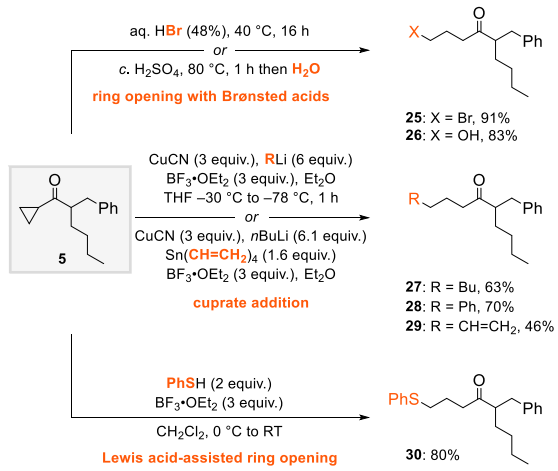
Scheme 3. Ir catalyst-free control experiments.

Having assessed cyclopropyl ketones we were also curious to determine whether other cycloalkyl ketones could be used in this reaction manifold. Thus, cyclobutyl, cyclopentyl and cyclohexyl ketones were synthesized and underwent the desired α-butylation reaction accordingly, but were lower yielding than the parent cyclopropyl ketone (**22**, **23** and **24**, 27–45% *c.f.* **5**, 86%).

Control experiments omitting $[Cp^*IrCl_2]_2$ from the reaction mixture were also performed, and to our surprise product **2** was obtained in 49% yield when BnOH was employed as a reaction partner (Scheme 3). However, this catalyst-free protocol does not appear to be a general process, since *n*BuOH did not react under these conditions. Autocatalytic hydrogen borrowing alkylation reactions are precedented [14] and are thought to proceed through Meerwein–Ponndorf–Verley–Oppenauer (MPV-O) type processes. Benzylic alcohols are presumably well-suited for this process since they undergo facile oxidation compared to their alkyl counterparts (Scheme 3).

2.2. Ring opening of the cyclopropyl ketone products

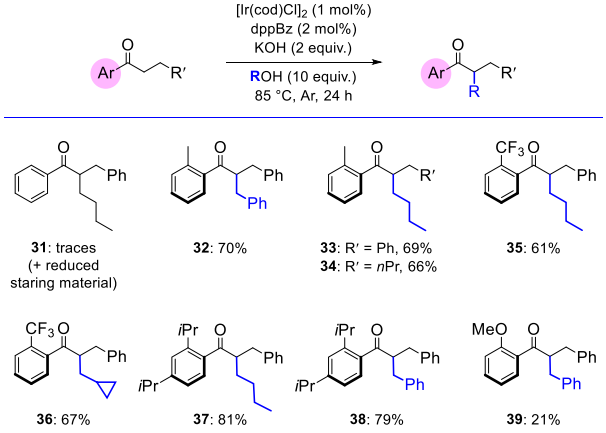
With the substrate scope complete, we also saw an opportunity to further diversify our products by ring opening of the cyclopropane. This was firstly achieved by treatment of compound **5** with either aq. HBr or H_2SO_4/H_2O [15], affording bromide and alcohol functionalities respectively. Modification of a literature procedure enabled homoconjugate addition of a Lewis acid complexed cyanocuprate, providing **27**, **28** and **29** in moderate to good yield [16]. Finally, Lewis acid-assisted ring opening with thiophenol was also successful, this time forming a C–S bond (Scheme 4).



Scheme 4. Ring opening of α-alkylated cyclopropyl ketones.

2.3. α-Alkylation of ortho-substituted aromatic ketones

During our study of cycloalkyl ketones we also chose to assess whether α-branched aryl ketones could be prepared by hydrogen borrowing alkylation. An initial lead came from 3-phenyl-1-(*ortho*-tolyl)propan-1-one, which underwent α-benzylation using similar starting conditions to those previously described for cyclopropyl ketones [10a]. This system was then optimized independently, with our final preferred conditions being $[Ir(cod)Cl]_2$ (1 mol%), dppBz (2 mol%), KOH (2 equiv.), BnOH (10 equiv.) at 85 °C under an Ar atmosphere for 24 h (Scheme 5). Pleasingly, this afforded compound **32** in 70% yield, with the remaining mass comprised of reduced starting material (3-phenyl-1-(*ortho*-tolyl)propan-1-ol). The *ortho*-methyl group was found to be critical for the success of the reaction, as its omission returned mostly unreacted substrate or its reduced form (see **31**). Since it is to be expected that *ortho*-methyl substitution on an aryl ketone results in a twisting effect whereby the aromatic ring is forced out of conjugation with the ketone, we hypothesized that this might be the reason for differing reactivity compared to unsubstituted arene **31**.



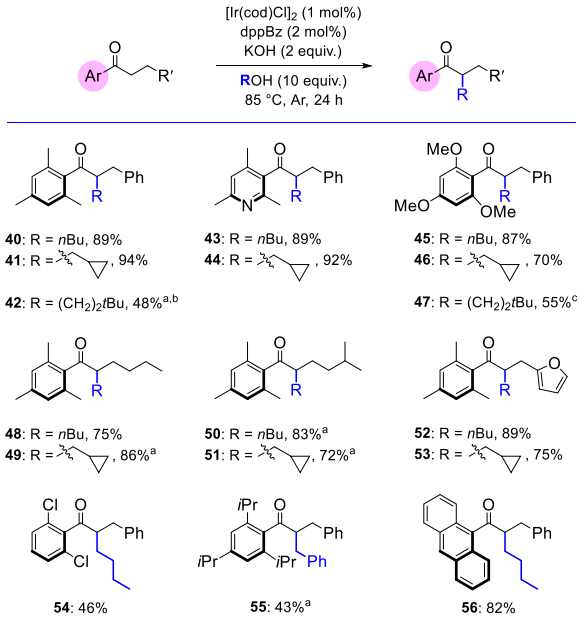
Scheme 5. *ortho*-Substituted aryl ketone substrate scope.

Variation of either the alcohol used (*n*BuOH and cyclopropylmethanol) or the substrate backbone was once again well-tolerated, although differences between various aryl *ortho*-substituents were noted. Whilst substitution with an *ortho*-CF_3 group gave similar yields to the parent *ortho*-CH_3 containing compounds (e.g. **33** and **35**), the introduction of a bulkier *ortho*-*i*Pr group improved yields and provided a cleaner reaction profile (see **37** and **38**, 81% and 79% respectively). Interestingly, no reduced starting material was detected during these reactions, with the *ortho*-*i*Pr group seeming to protect the ketone from reduction by steric shielding. In contrast, substitution with an *ortho*-methoxy group resulted in a much poorer yield of 21%, presumably since the carbonyl group is more exposed to reduction (Scheme 5) [17].

2.4. α-Alkylation of di-ortho-substituted aromatic ketones

Since steric shielding of the carbonyl appeared to be beneficial, we chose to synthesize a mesityl ketone in order to further study this feature and increase the desired twisting effect. As expected, this change delivered the α-branched products (**40** and **41**, 89% and 94% respectively, Scheme 6), with no reduced material being observed. In this instance application of 3,3-dimethyl-1-butanol under hydrogen borrowing conditions resulted in a lower yield (**42**: 48%) relative to the cyclopropyl ketone counterpart (**7**). The majority of the remaining mass balance comprised of the intermediate enone (45%), suggesting that the combination of the mesityl and *t*Bu groups hinders the final reduction step in this system (Scheme 6). Incorporation of a nitrogen atom in the aromatic ring was not detrimental (**43** and **44**), whilst addition of a further *ortho*-methoxy substituent gave satisfactory yields compared to the monosubstituted case (see **45**). Modification of the substrate backbone was again well-tolerated, with furan-containing compounds also synthesized straightforwardly under these conditions.

α-Alkylation could also be achieved even when the aromatic ring contained di-*ortho*-chloro substitution, although loss of chlorine was found to be a competing process (**54**). Having initially observed that the introduction of an *ortho*-*i*Pr group improved the reaction yield (Scheme 5), we noted that an additional *ortho*-*i*Pr substituent had the reverse effect, delivering only 43% of **55**. This example illustrates the upper limit of steric bulk necessary to obtain high yields of alkylated product. Finally, 1-anthracenyl ketone was also found to be effective under the reaction conditions (**56**). In total, this study suggested that di-*ortho*-methyl substitution was optimal, providing high yields of α-alkylated product (Scheme 6).

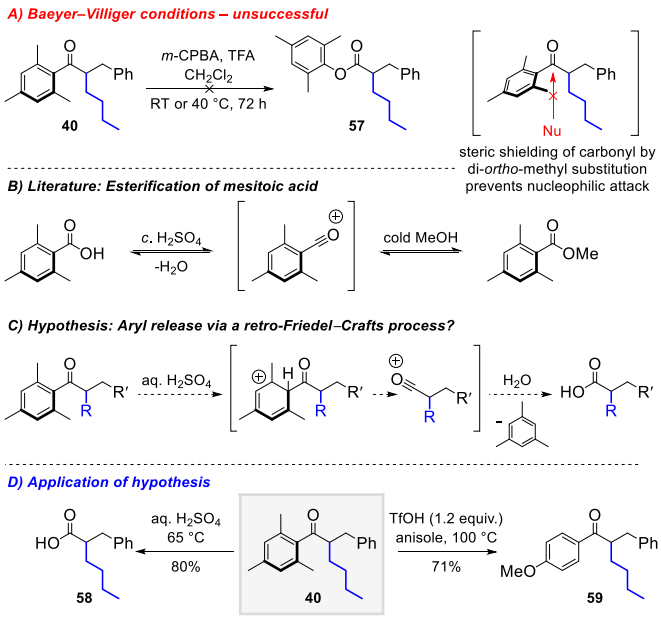


[a]Reaction performed at 105 °C; [b]An additional 45% enone was isolated; [c]An additional 25% enone was isolated.

Scheme 6. Di-*ortho*-substituted aryl ketone substrate scope.

2.5. Aryl release strategy

Whilst we had succeeded in developing a high yielding approach to α-branched aryl ketones under catalytic conditions, the products obtained appeared to represent a limited set of compounds. With this in mind, we attempted to cleave the mesityl ring by Baeyer–Villiger reaction in order to deliver the corresponding ester (Scheme 7A). However, despite several attempts, only unreacted starting material **40** was observed. Since our study of the α-alkylation reaction had shown that di-*ortho*–methyl substitution of the aromatic ring was beneficial in preventing reduction of the ketone (by virtue of the aforementioned twisting effect), it seemed likely that these methyl groups were also preventing nucleophilic attack (Scheme 7A). In our search for alternative methods, we noted that the esterification of mesitoic acid under ordinary acid catalysis conditions is similarly challenging [18]. It is well-established that in order to overcome this problem, mesitoic acid is initially treated with conc. H_2SO_4 to form an intermediate acylium ion, then the reaction mixture is poured onto cold MeOH to trap this species and form the desired methyl ester (Scheme 7B) [18]. Our α-alkylated systems bore a resemblance to this literature example, and so we hypothesized that mesityl cleavage might be possible under similar conditions but *via* a *retro*-Friedel–Crafts reaction involving *ipso* addition to the arene (Scheme 7C). A thorough literature search revealed a small set of papers whereby such a process had occurred [19], and to our delight, treatment of ketone **40** with aq. H_2SO_4 at



Scheme 7. Aryl release strategy and application to ketone **40**.

65 °C successfully converted this compound to the corresponding acid in 80% yield (**58**). Similarly, transacylation could also be achieved using TfOH (1.2 equiv.) in anisole at 100 °C to afford **59** (Scheme 7D) [20].

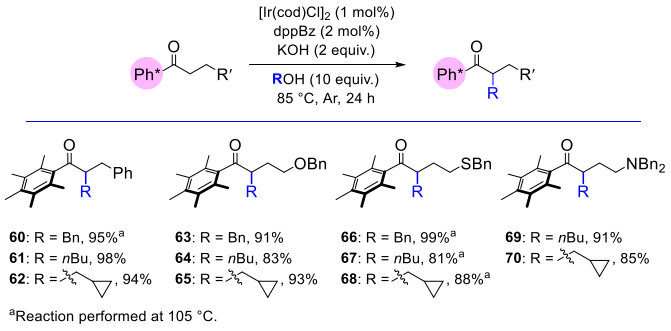
Although the twisting effect was key to the *retro*-Friedel–Crafts process, we recognized that the electron donating properties of the methyl groups also played an important role. Mechanistically, it seemed reasonable to assume that the *ipso*-position of the aromatic ring (with respect to the carbonyl) was protonated under the strongly acidic conditions, enabling an acylium ion to form and release mesitylene. To make this process more functional group tolerant and hence synthetically useful, we sought to develop non-acidic conditions for aryl cleavage, and supposed that alternative electrophiles could be employed [21]. As a proof of concept, neat bromine was quickly established as a reagent with which to trigger the *retro*-Friedel–Crafts reaction (unoptimized, not shown). This represented an important breakthrough as aryl cleavage formed a useful acid bromide *in situ* (see Section 2.6, Scheme 9). The acid bromide could then be intercepted with *n*BuOH to form the corresponding *n*Bu ester. In our hands, however, bromination of the mesityl ring was also a competing process [12f], leading to di- and tri-brominated mesitylene side-products. Thus, we decided to further refine the design of the aromatic ring.

2.6. Design of pentamethylphenyl (Ph*) ketone

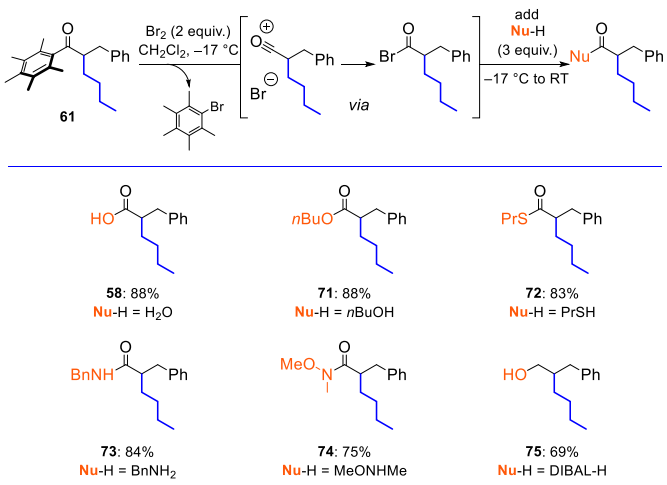
The most straightforward method to prevent unwanted bromination of the aryl ring was to block the unsubstituted positions. Therefore, in order to ensure that the aryl ring remained electron rich and amenable to cleavage by treatment with an electrophile, we chose to add additional methyl groups. Since the primary focus of our work was hydrogen borrowing catalysis, several substrates containing this pentamethylphenyl (Ph*) group were synthesized and treated under the optimized conditions. These compounds were compatible with our well-established range of alcohols, while sidechains bearing OBn, SBn and NBn_2 functionality were also tolerated (Scheme 8).

We were also pleased to note that the compounds shown in Scheme 8 were all crystalline. This proved to be a general property, with almost all of the compounds synthesized that bear the Ph* motif displaying this characteristic. This was advantageous, not only for large scale purification without chromatography, but also for straightforward determination of relative stereochemistry by single crystal X-ray diffraction (see Scheme 10 for examples).

As expected, the Ph* group underwent clean *retro*-Friedel–-Crafts reaction when treated with bromine, giving 1-bromo-2,3,4,5,6-pentamethylbenzene as the major byproduct (Scheme 9). This reaction was subsequently optimized to reduce the amount of bromine and concentration required, whilst also performing the reaction at low temperature [Br_2 (2 equiv.), CH_2Cl_2, −17 °C]. The



Scheme 8. Ph* ketone substrate scope.



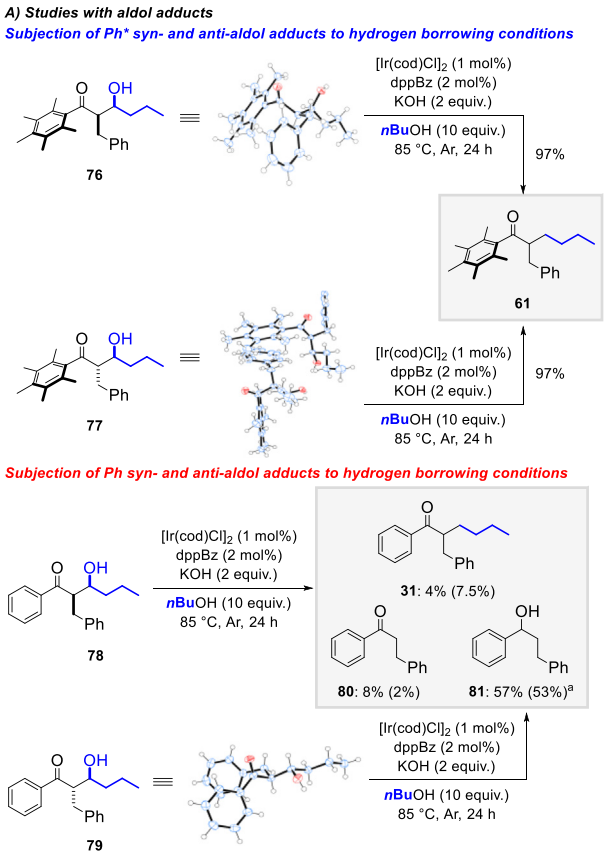
Scheme 9. Br_2-mediated cleavage of Ph* and subsequent derivatization of the acid bromide with various nucleophiles.

acid bromide generated (observed by ^{13}C NMR, see ref 10a) could then be easily intercepted *in situ* with different nucleophiles, providing a range of different carboxylic acid derivatives in a one-pot process (Scheme 9).

2.7. Further analysis of the role of the Ph* group

In order to gain additional insight into the role of Ph* in the hydrogen borrowing reaction, we synthesized separately the *syn*- and *anti*-aldol adducts (**76** and **77**) that would form as intermediates under the reaction conditions (using compound **61** as a reference). As expected, both aldol adducts were crystalline, enabling single crystal X-ray diffraction studies to be performed which supported our hypothesis that the Ph* motif was twisted out of conjugation with the carbonyl group (Scheme 10A). Subjecting either compound to the hydrogen borrowing reaction conditions then provided the anticipated product **61**. Next, we synthesized the analogous *syn*- and *anti*-aldol adducts **78** and **79** without any *ortho*-methyl substitution; the latter being crystalline with the resulting structure determined by single crystal X-ray diffraction showing the phenyl ring to be in conjugation with the ketone. This time, subjecting **78** and **79** to the hydrogen borrowing conditions resulted in only a small quantity of the desired α-alkylated product **31** being formed, with alcohol **81** being the major component of the reaction mixture (together with a small amount of ketone **80**). Taken together, several conclusions can be drawn from these results. Firstly, the product distributions obtained for phenyl-containing (i.e. non-Ph*) adducts **78** and **79** suggests that *retro*-aldol reaction is favored over E1cB elimination, with the ketone (**80**) then being reduced to the corresponding alcohol **81**. Whilst it is possible that alcohol **81** could then be re-oxidized *in situ*, the large quantity of isolated material suggests that it does not readily re-engage in the aldol process.

With these observations in mind, alcohol **81** was subjected to the hydrogen borrowing alkylation conditions (Scheme 10B). This returned **81** unchanged in 97% isolated yield. However, deuterated substrate ***d*-81** (≥95% *d*, prepared separately) returned compound **81** (11% *d* by ^1H NMR), thus suggesting that ketone **80** is formed by reversible oxidation/reduction, but does not engage in hydrogen borrowing chemistry. Interestingly, Ph*-containing alcohol **82** also only gave starting material under these conditions, without the observation of alkylated material. Since it had been well-established throughout that di-*ortho*-methyl substitution of the



Scheme 10. Subjection of various α-branching intermediates to the optimized hydrogen borrowing conditions.

aryl ring prevents carbonyl reduction, this result suggests that alcohol **82** does not undergo oxidation readily.

Taken together, these results indicate that the Ph* group enables hydrogen borrowing alkylation by protecting the adjacent carbonyl group against reduction/nucleophilic attack *in situ*. It is also possible that the twisting effect of the Ph* group expedites formation of the corresponding aldol and enone adducts, relative to their Ph counterparts.

2.8. Alkylation with pentan-3-ol

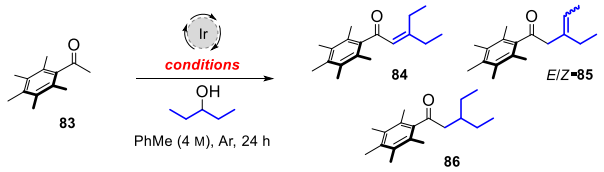
Having investigated the role of di-*ortho*-substituted aryl ketones in hydrogen borrowing chemistry, we next chose to assess 2° alcohols as alkylating agents. An initial hit was uncovered when pentamethylacetophenone (**83**) was reacted with 3-pentanol (2 equiv.) in the presence of $[Cp^*IrCl_2]_2$ (2 mol%), KOH (3 equiv.) and PhMe (4 M) at 85 °C for 24 h under Ar. This delivered the desired coupled material **86** in 12% isolated yield, with 61% unreacted **83** recovered (Table 2, entry 1). Increasing the reaction temperature to 105 °C resulted in a significantly improved yield of **86** (80%), although 115 °C was detrimental in comparison (entries 2 and 3). Analysis of the reaction mixture suggested that the solubility of KOH in PhMe may be a complicating factor, and so we chose to assess different bases at lower temperature (85 °C) (entries 4–6). Whilst NaOH was found to outperform KOH at 85 °C, KO*t*Bu and NaO*t*Bu were superior, affording **86** in 86% and 97% yield respectively. Further optimization was carried out with NaO*t*Bu, and it was quickly established that 85 °C was the ideal temperature (incomplete reaction at 65 °C, entry 7), with 2 equiv. of base required for complete conversion (entry 8). The amount of $[Cp^*IrCl_2]_2$ and 3-pentanol could also be reduced without affecting the isolated yield (entries 10 and 12). Our final conditions therefore involved treating starting material **83** with $[Cp^*IrCl_2]_2$ (0.5 mol%), 3-pentanol (1.5 equiv.), NaO*t*Bu (2 equiv.) and PhMe (4 M) at 85 °C under Ar for 24 h (entry 12). The reaction was successfully performed on 1 g scale, affording **86** in 93% isolated yield (entry 14). Finally, control experiments were run in the absence of NaO*t*Bu and $[Cp^*IrCl_2]_2$. Whilst the omission of base resulted in only recovered starting material **83** (entry 15), removing $[Cp^*IrCl_2]_2$ gave partial conversion to *E*/*Z* enones **85** (entry 16) and no reduced material (**86**) [10b].

Similar to our earlier work involving α-alkylation to form branched products, we initially studied variations of the aryl ring (Scheme 11). Compounds bearing di-*ortho*-methyl substitution once again gave the desired coupled material in good to excellent yield (see **86**, **88**, **89**, **92**, **93** and **95**). As expected, *ortho*-tolyl performed poorly (**87**, 15%), although interestingly the trimethoxyaryl system gave **90** in only 32% yield. This is in contrast to previous observations (see Scheme 6), suggesting that protection of the carbonyl using this group is suboptimal when the substrate backbone itself does not contain a longer chain (i.e. CH_2CH_2Ph, compounds **45**–**47**). Similarly, anthracenyl ketone produced **91** in poor yield. Substitution with *i*Pr groups delivered the desired coupled material in good yield (**94**, 62%), presumably since removal of the substrate backbone compensates for the increased steric bulk of these two *ortho* groups (*c.f.* **55**). Double alkylation could also be achieved, albeit with an increased loading of reagents (**95**). Lastly, we also attempted to alkylate ethyl ketone **96** with 3-pentanol. However, only unreacted starting material was returned (97%), which was in line with our earlier observations that sterics play a significant role in this chemistry. Overall, these results clearly indicated that Ph* was the preferred aryl ring for this reaction, providing the desired balance of substrate reactivity and steric protection of the carbonyl group.

2.9. Alkylation with acyclic 2° alcohols

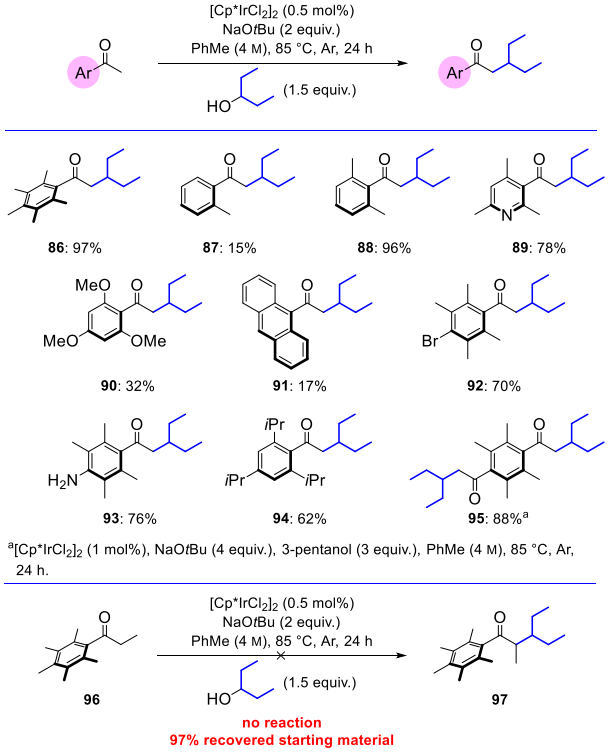
Next, we assessed the compatibility of other acyclic alcohols with Ph*COMe **83**. Alcohols bearing linear chains were readily processed (**98**–**100**), as were those containing saturated ring systems (3-membered to 6-membered rings, **101**–**104**). Phenyl substitution was also well-tolerated (**105**), whilst pyridine and thiophene-containing alcohols behaved similarly (to give **106** and **107**), albeit requiring an increased loading of reagents [$[Cp^*IrCl_2]_2$ (2 mol%), NaO*t*Bu (3 equiv.), alcohol (3 equiv.) and PhMe (4 M) at 85 °C for 24 h under Ar]. Furans could also once again be incorporated (see **52** and **53** for earlier examples), although compound **108** was only isolated in 26% yield under these conditions. Finally, long chain alcohols with distal OBn and NBn_2 groups could be combined with **83** to afford **109** and **111**. A further increase in the steric size of the alcohol (Me to Et) was also not detrimental to yield (**109** to **110**, Scheme 12). It is worth noting at this stage that no self-

Table 2
Optimization of hydrogen borrowing conditions with Ph* ketone **83** and 3-pentanol.

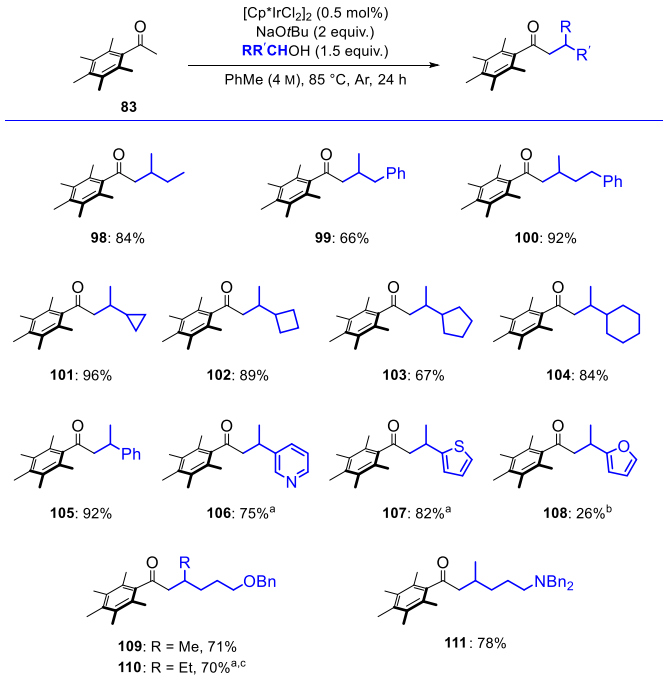


entry	catalyst (mol%)	alcohol (equiv.)	base (equiv.)	temp. (°C)	yields %[a] 83	E/Z-85	86
1	$[Cp^*IrCl_2]_2$ (2)	2	KOH (3)	85	61	–	12
2	$[Cp^*IrCl_2]_2$ (2)	2	KOH (3)	105	5	–	80
3	$[Cp^*IrCl_2]_2$ (2)	2	KOH (3)	115	21	–	65
4	$[Cp^*IrCl_2]_2$ (2)	2	NaOH (3)	85	44	–	44
5	$[Cp^*IrCl_2]_2$ (2)	2	KO*t*Bu (3)	85	–	–	86
6	$[Cp^*IrCl_2]_2$ (2)	2	NaO*t*Bu (3)	85	–	–	97
7	$[Cp^*IrCl_2]_2$ (2)	2	NaO*t*Bu (3)	65	10	11[b]	68
8	$[Cp^*IrCl_2]_2$ (2)	2	NaO*t*Bu (2)	85	–	–	97
9	$[Cp^*IrCl_2]_2$ (2)	2	NaO*t*Bu (1)	85	34	4	59
10	$[Cp^*IrCl_2]_2$ (0.5)	2	NaO*t*Bu (2)	85	–	–	97
11	$[Cp^*IrCl_2]_2$ (0.25)	2	NaO*t*Bu (2)	85	trace	–	89
12	$[Cp^*IrCl_2]_2$ (0.5)	1.5	NaO*t*Bu (2)	85	–	–	97
13	$[Cp^*IrCl_2]_2$ (0.5)	1.1	NaO*t*Bu (2)	85	8	13	73
14[c]	$[Cp^*IrCl_2]_2$ (0.5)	1.5	NaO*t*Bu (2)	85	5	–	93
15[d]	$[Cp^*IrCl_2]_2$ (0.5)	1.5	–	85	97	–	–
16[d]	–	1.5	NaO*t*Bu (2)	85	74	26	–

[a]All yields are of isolated material, reactions performed on 0.6 mmol scale; [b]Compound **84** was also observed in trace amounts at 65 °C, but could not be separated from *E*/*Z*- **85**; [c]Reaction conducted on 5.3 mmol (1 g) scale; [d]Conversion measured by ^{1}H NMR spectroscopy.



Scheme 11. Di-*ortho*-substituted aryl ketone substrate scope.



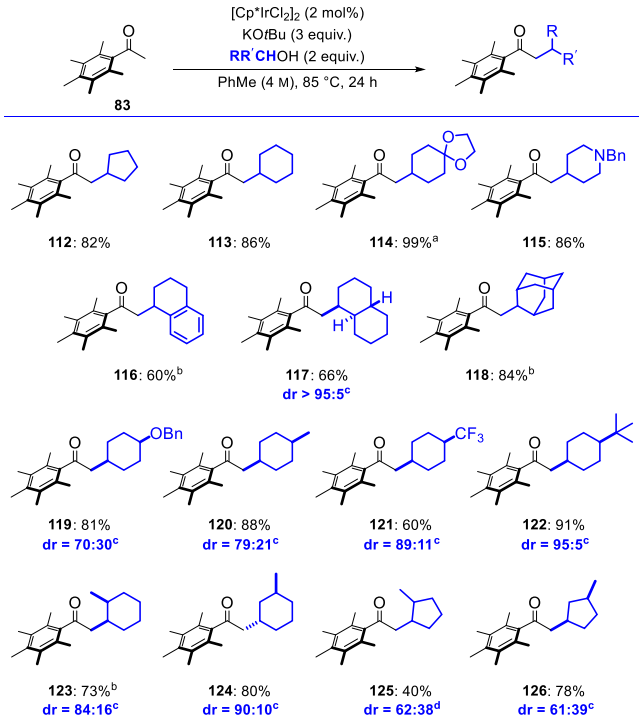
Scheme 12. Acyclic 2° alcohol scope.

condensed product (derived from **83**) was detected in any of these reactions. This suggests again that Ph* (specifically di-*ortho*-methyl substitution of the aryl ring) is key to preventing this undesired side reaction and promoting the cross-aldol process [10b].

2.10. Alkylation with cyclic 2° alcohols

Expansion of this methodology to include cyclic 2° alcohols was also possible, but this time improved yields were obtained when KO*t*Bu was used in combination with an increased loading of reagents (Scheme 13). Simple cyclopentanol and cyclohexanol were employed straightforwardly to give **112** and **113** in 82% and 86% yield respectively. As shown previously, a dioxolane ring, NBn substitution (to give the protected piperidine) and a benzylic alcohol were found to be robust under hydrogen borrowing conditions (**114**, **115** and **116**) [10b].

Substituted cyclic 2° alcohols presented an exciting opportunity to study diastereoselective hydrogen borrowing reactions, which had little literature precedent [22]. Interestingly, reaction of *cis*-decahydro-1-naphthol with **83** gave compound **117** in 66% isolated yield in dr > 95:5 (the relative stereochemistry was determined by X-ray crystallography), illustrating an initial proof of concept [23]. 4-Substituted cyclohexyl alcohols were also found to couple in high diastereoselectivity, with dr improving in line with an increase in the size of the 4-substituent (*t*Bu > CF_3>CH_3>OBn, **119**–**122**, major diastereomer shown in each case). Methyl substitution at the 2- or 3-position of the cyclohexyl ring also resulted in high diastereoselectivity (**123** and **124**). X-Ray structures were obtained for compounds **119** (major diastereomer), **121** (minor diastereomer) and **122** (*t*Bu), revealing that the CH_2COPh* group in each major diastereomer adopted an axial position (this was also true for decalin **117**). Therefore, it is reasonable to assume that the diastereoselectivity can be rationalized by equatorial attack of an Ir–H species onto an exocyclic enone, although reduction of an endocyclic (migrated) alkene cannot be ruled out [24]. In contrast to cyclohexyl-containing compounds, methyl-substituted cyclopentyl alcohols coupled in poor diastereoselectivity (see compounds **125**



Major diastereomers depicted. [a][Cp*IrCl2]2 (0.5 mol%), KO*t*Bu (2 equiv.), R^1R^2CHOH (1.5 equiv.), PhMe (4 M), 85 °C, Ar, 24 h; [b]Performed at 105 °C; [c]d.r. determined by ^{1}H NMR spectroscopic analysis of the crude mixture; [d]The identity of the major diastereomer could not be accurately determined.

Scheme 13. Cyclic 2° alcohol scope.

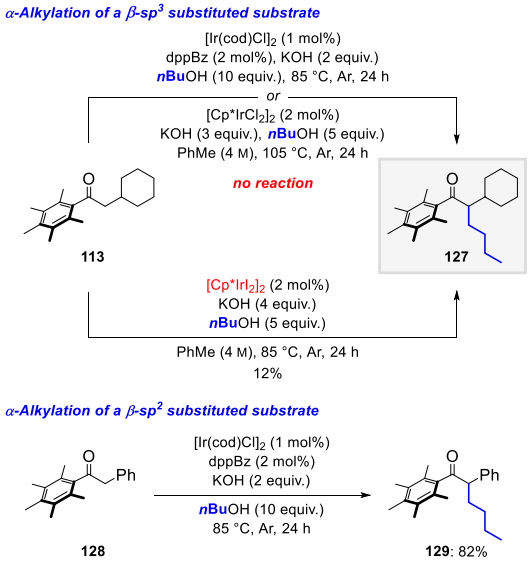
and **126**). This likely reflects the relative conformational stability of cyclohexanes over their cyclopentane counterparts.

2.11. α-Alkylation of β-substituted ketones

Since alkylation with 2° alcohols had provided a range of β-substituted ketones, it seemed appropriate to then test these compounds as substrates for α-alkylation. Thus, ketone **113** was treated under both of our optimized reaction conditions (Scheme 14). Disappointingly no α-butylated product was detected in either case, with only unreacted starting material present. Despite extensive screening, compound **127** could only be produced in 12% isolated yield (Scheme 14) [25].

In contrast, benzylic ketone **128** smoothly underwent α-alkylation to give **129** when treated with our standard set of conditions (82% yield). Once again, steric hindrance appears to be playing a significant role, with sp^3-substitution at the β-position adversely affecting reactivity.

In order to overcome the lack of reactivity at the α-position, we decided to investigate an intramolecular hydrogen borrowing reaction. β-Substituted compounds **109** and **110** were ideally suited for such an approach, as removal of the Bn-protecting group revealed the requisite 1° alcohol (Scheme 15). Treatment of both **132** and **133** under [Cp*IrCl$_2$]$_2$ conditions resulted in smooth cyclization to the corresponding cyclopentanes in good yield (**136**: 75% and **137**: 72%). Of particular note was that both compounds were formed in high diastereoselectivity (dr > 95:5), with the 1,2-*trans* relationship confirmed by X-ray crystallography [10f]. This is presumably due to reversible α-deprotonation *in situ*, leading to the thermodynamically favored product. To further investigate this intramolecular process, we attempted to synthesize additional β-alkylated substrates *via* 2° alcohols. The chain length was fixed (in order to form a cyclopentane) while the R substituent was varied. In practice Ph (**140**) and benzyl (**141**) substitution were not well-tolerated, providing messy reaction profiles and no coupled material. Incorporation of a cyclopropyl group resulted in the desired product (**130**) in 60% yield, although an increase in the ring size to cyclopentyl gave skipped enone **143** as the major product. Dioxane-containing compound **131** could also be prepared but in only moderate yield (47%), likely due to the increased steric bulk of this alcohol (Scheme 15). Deprotection of the cyclopropyl and dioxane substituted compounds proceeded without incident to give the corresponding 1° alcohols. Subjection of these substrates to hydrogen borrowing conditions then delivered the desired cyclopentanes in excellent diastereomeric ratio (**138** and **139**). Whilst an intramolecular α-alkylation approach can successfully overcome the poor reactivity profiles associated with intermolecular processes, the size of the β-sp^3 substituent still exerts a considerable influence on the reaction outcome. Nevertheless, these preliminary studies led us to consider whether diols would be appropriate partners for ring synthesis. This avenue of research proved highly successful and has been published elsewhere, so will not be discussed here [10c-e].



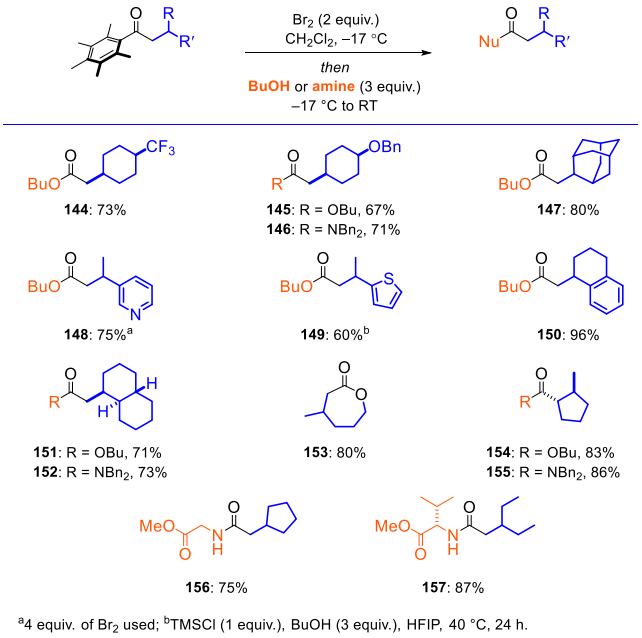
Scheme 14. α-Alkylation of β-substituted substrates.

2.12. Aryl release of Ph*

A number of structurally diverse β-substituted esters and amides were synthesized from the alkylation products following bromine-mediated release of Ph* (Scheme 16). Pleasingly, stereodefined compounds **117**, **119**, **121** and **136** underwent clean reaction without erosion of diastereoselectivity (dr > 95:5 by ^{1}H NMR). Substrates bearing pyridine (**148**) and bicyclic (**150**) backbones were also well-tolerated, but removal of Ph* in the presence of a thiophene ring was initially problematic. Further investigation of Ph* cleavage and subsequent optimization led us to develop conditions employing TMSCl/HFIP/*n*BuOH at 40 °C, giving ester **149** in 60% yield [10b,26]. Interestingly, treatment of benzyl alcohol **109** with bromine resulted in debenzylative lactonization to afford compound **153** in 80% yield. Finally, α-amino esters were also found to be suitable nucleophiles when added *in situ* to the acid bromide, providing **156** and **157** in 75% and 87% yield respectively.

3. Conclusion

In conclusion, we have presented here in full our research effort that has led to the formation of α- and β-substituted ketones under hydrogen borrowing conditions. The initial approach focused on the alkylation of cyclopropyl ketones with higher alcohols, leading to α-branched products. Our search for additional substrates led us to recognize that *ortho*-substituted aromatic ketones were also privileged scaffolds, with di-*ortho*-substitution proving optimal. We believe di-*ortho*-substitution is important for the following reasons: a) the *ortho*-substituents twist the aromatic ring out of conjugation with the ketone functionality, b) these substituents are perfectly placed to protect the parent ketone from nucleophilic attack. This latter design feature was shown to prevent competing carbonyl reduction and self-condensation, providing a clean reaction profile. To further expand the utility of our chemistry we designed Ph* (C_6Me_5) as the substituted aromatic ring of choice since this could be removed straightforwardly by a *retro*-Friedel–Crafts process using bromine. The acid bromide generated *in situ* from an intermediate acylium ion could then be intercepted in one pot with a range of nucleophiles. The Ph* group was found to be vital to further research, facilitating alkylation reactions with 2° alcohols (to form β-branched products) as well as an intramolecular ring forming process. These latter advances provided an exciting opportunity to study stereoselective hydrogen borrowing reactions, which to date remains an active area of research in our laboratory.



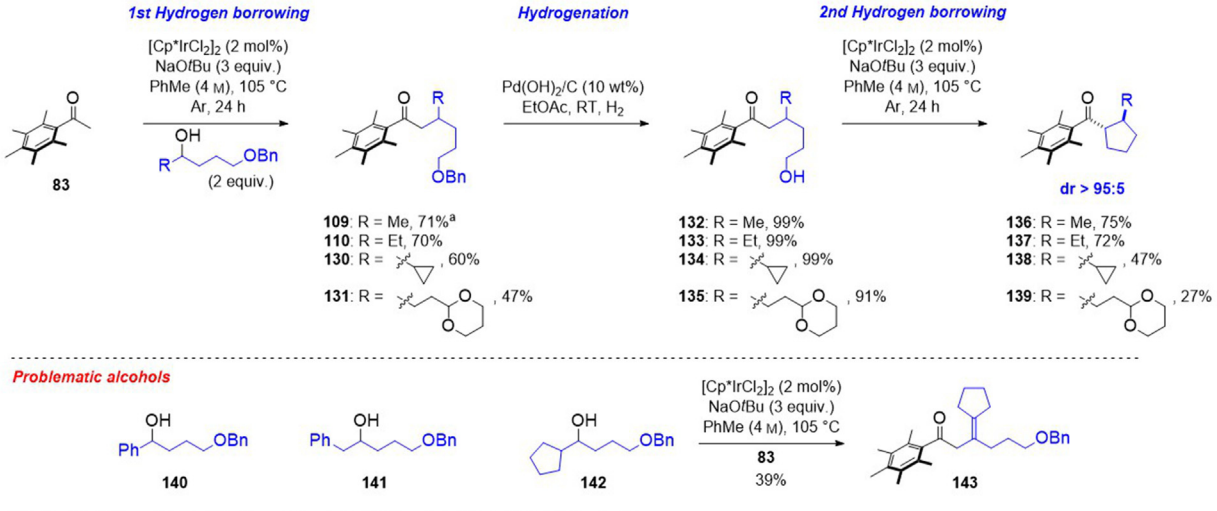
[a]4 equiv. of Br_2 used; [b]TMSCl (1 equiv.), BuOH (3 equiv.), HFIP, 40 °C, 24 h.

Scheme 16. Br_2-mediated cleavage of Ph* to give the corresponding Bu ester or amide variants.

4. Experimental section

4.1. General experimental

Unless otherwise stated, all reagents and solvents were purchased and used as supplied from Sigma-Aldrich (now Merck KGaA), Thermo Fisher Scientific (including Alfa Aesar, Fisher Scientific and Acros Organics), Fluorochem, Honeywell, Tokyo Chemical Industry, Apollo Scientific, Manchester Organics (part of Navin Fluorine Int. Ltd.), Santa Cruz Biotechnology and Strem Chemicals. All commercial reagents and solvents were used without additional purification unless indicated in the text. NMR spectroscopy was carried out using a Bruker AVIII HD 400 equipped with a 5 mm *z*-gradient BBFO probe, Bruker AVIII HD 400 equipped with a 5 mm *z*-gradient BBFO "SMART" probe, Bruker AVII 500 equipped with a 5 mm BBFO "SMART" probe or 5 mm *z*-gradient TFI probe, or Bruker AVIII HD equipped with a 5 mm triple resonance TBO probe, with the deuterated solvent acting as an internal deuterium lock. ^{1}H NMR experiments were recorded at 400 or 500 MHz with ^{19}F decoupling where appropriate, ^{13}C NMR at 101 or 126 MHz with broadband proton decoupling, and ^{19}F NMR at 377 MHz. Residual protic solvent signal acted as an internal reference for ^{1}H NMR, and deuterated solvent carbon signal acted as an internal reference for ^{13}C NMR ($CDCl_3$: ^{1}H NMR = 7.26 ppm; ^{13}C NMR = 77.16 ppm; DMSO-d_6: ^{1}H NMR = 2.50 ppm, ^{13}C NMR = 39.52 ppm. Chemical shifts are quoted in ppm with the multiplicity of a signal reported as such: s – singlet, d – doublet, t – triplet, q – quartet, quint. – quintet, sext. – sextet, sept. – septet, q_{AB} – AB quartet, m – multiplet, app. – apparent or approximate, br. – broad, v. – very, or



[a][Cp*IrCl$_2$]$_2$ (0.5 mol%), NaO*t*Bu (2 equiv.), alcohol (1.5 equiv.), PhMe (4 M), 85 °C, Ar, 24 h.

Scheme 15. Intramolecular hydrogen borrowing reaction for the synthesis of 1,2-disubstitued cyclopentanes.

combinations thereof. Coupling constants and Δ_{AB} are quoted in Hz to the nearest 0.1 Hz. Fourier-transform infrared (FT-IR) spectra were recorded from evaporated films on a Bruker Tensor 27 spectrometer equipped with a Pike Miracle Attenuated Total Reflectance (ATR) sampling accessory. Absorption maxima are quoted in wavenumbers (ν_{max}) with units of cm^{-1} and for the range of 3600–600 cm^{-1}. High resolution mass spectrometry (HRMS) under ESI conditions were recorded on a Thermo Exactive Orbitrap mass spectrometer equipped with a Waters Equity LC system, a Bruker MicroToF mass spectrometer equipped with an Agilent 1100 HPLC pump and autosampler, or on a Waters Xevo Quadrupole Time of Flight (Q-ToF) mass spectrometer. The Thermo Exactive system employs a flow rate of 0.2 mL min^{-1} using H_2O:MeOH:HCOOH (10:89.9:0.1) as eluent, with a heated electrospray ionisation (HESI-II) probe and has a resolution of 50,000 FWHM. The Bruker system uses the built-in electrospray source, while the Waters system runs on a lock-mass mode with ESI performed by a secondary electrospray source, both using conditions identical to the Thermo Exactive system. Instrument control and data processing were performed using the softwares Thermo Xcalibur for the Thermo Exactive system, Compass DataAnalysis 4.0 for the Bruker system, and MassLynx for the Waters system. Unless otherwise specified, the mass reported for HRMS is the mass-to-charge ratio containing the most abundant isotopes, with each value to 4 or 5 decimal places and within 5 ppm of the calculated mass. Single crystal X-ray diffraction was performed with a (Rigaku) Oxford Diffraction Supernovae A diffractometer using Cu-Kα radiation (λ = 1.54184 Å) and a graphite monochromator. Samples were mounted in perfluoropoly-ethyl ether oil and cooled by a Cryostream N_2 open-flow cooling device to 150 K throughout the data collection process. The diffraction patterns were integrated and reduced using the software CrysAlisPro. The software CRYSTALS for Microsoft Windows was used to obtain *ab initio* solutions using SuperFlip [27] embedded within CRYSTALS [28] and to carry out structure refinement. Melting points (m.p.) were obtained using a Leica VMTG heated-stage microscope equipped with a Testo 720 thermometer and are uncorrected.

Detailed experimental procedures, characterization data and NMR spectra for all novel alcohols, substrates and alkylated products are provided in the Supporting Information.

4.2. Representative procedure for α-alkylation of cyclopropyl ketones: synthesis of 2-butyl-1-cyclopropylhexan-1-one (**8**)

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added 1-cyclopropylhexan-1-one (42.0 mg, 0.30 mmol), $[Cp^*IrCl_2]_2$ (4.8 mg, 2 mol%), KOH (50.5 mg, 0.90 mmol) and *n*BuOH (0.14 mL, 1.50 mmol) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and purged with Ar for 5 min using a balloon. Following this, the vial (complete with an Ar balloon) was heated to 105 °C in a preheated oil bath for 24 h. The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, Pentane:Et_2O, 99:1) afforded the *title compound* **8** (38.0 mg, 65%) as a colorless oil. R_f = 0.56 (Pentane:Et_2O, 90:10), [vanillin]; IR (film) ν_{max}/cm^{-1} 3009, 2957, 2930, 2873, 2859, 1695, 1467, 1458, 1417, 1382, 1196, 1159, 1063, 1022, 997; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.59–2.50 (1H, m, C*H*CO), 1.99–1.92 (1H, m, cyclopropyl C*H*), 1.70–1.59 (2H, m, 2 × C$H_A$$H_B$CHCO), 1.49–1.39 (2H, m, 2 × CH$_A$$H_B$CHCO), 1.35–1.17 (8H, m, 2 × C$H_2$$CH_2$$CH_3$ and 2 × CH_2C$H_2$$CH_3$), 1.02–0.97 (2H, m, cyclopropyl C$_A$$H_AH_B$CH and cyclopropyl C$_B$$H_AH_B$CH), 0.88 (6H, t, *J* = 7.1 Hz, 2 × CH_3), 0.86–0.81 (2H, m, cyclopropyl C$_A$H$_A$$H_B$CH and cyclopropyl C$_BH_A$$H_B$CH); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 215.0 (C=O), 53.6 (*C*HCO), 31.7 (2C, 2 × *C*H$_2$CHCO), 29.9 (2C, 2 × *C*H$_2$CH$_2$CH$_3$), 23.0 (2C, 2 × *C*H$_2$CH$_3$), 19.5 (cyclopropyl *C*H), 14.1 (2C, 2 × *C*H$_3$), 10.8 (2C, cyclopropyl *C*$_A$H$_2$CH and cyclopropyl *C*$_B$H$_2$CH); HRMS (ESI$^+$) Found $[M+H]^+$ = 197.1901; $C_{13}H_{25}O$ requires 197.1900, Δ 0.75 ppm.

4.3. Representative procedure for α-alkylation of aromatic ketones: synthesis of 2-(cyclopropylmethyl)-1-mesitylhexan-1-one (**49**)

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added 1-mesitylhexan-1-one (50.5 mg, 0.23 mmol), $[Ir(cod)Cl]_2$ (1.54 mg, 1 mol%), dppBz (2.1 mg, 2 mol%), KOH (25.8 mg, 0.46 mmol) and cyclopropylmethanol (0.19 mL, 2.30 mmol) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and purged with Ar for 5 min using a balloon. Following this, the vial (complete with an Ar balloon) was heated to 85 °C in a preheated oil bath for 24 h. The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, Pentane:Et_2O, 99:1 → 98:2) afforded the *title compound* **49** (54.1 mg, 86%) as a colorless oil. R_f = 0.59 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$]; IR (film) ν_{max}/cm^{-1} 2955, 2929, 2859, 1689, 1611, 1571, 1457, 1428, 1378, 1355, 1305, 1297, 1274, 1240, 1231, 1212, 1160, 1133, 1103, 1077, 1034, 1016, 981; ^1H NMR ($CDCl_3$, 400 MHz) δ = 6.83 (2H, s, 2 × Ar-CH), 2.99 (1H, app. quint., *J* = 6.4 Hz, C*H*CO), 2.27 (3H, s, Ar-CH_3), 2.23 (6H, s, 2 × Ar-CH_3), 1.76–1.66 (2H, m, CH_AH$_B$CHCO and CHCH_AH$_B$CHCO), 1.53–1.43 (1H, m, CH$_A$$H_B$CHCO), 1.37–1.23 (5H, m, CHCH$_A$$H_B$CHCO, C$H_2$$CH_2$$CH_3$ and C$H_2$$CH_3$), 0.86 (3H, t, *J* = 7.2 Hz, CH_3), 0.83–0.71 (1H, m, cyclopropyl C*H*), 0.47–0.41 (2H, m, 2 × cyclopropyl CH_AH$_B$), 0.08–0.02 (2H, m, 2 × cyclopropyl CH$_A$$H_B$); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 212.7 (C=O), 138.9 (Ar–C), 138.5 (Ar–C), 133.9 (2C, 2 × Ar–C), 130.0 (2C, 2 × Ar-CH), 53.6 (CHCO), 34.7 (CHCH_2CHCO), 29.9 (CH_2CHCO), 29.7 (C$H_2$$CH_2$$CH_3$), 23.0 (C$H_2$$CH_3$), 21.2 (Ar-C$H_3$), 20.0 (2C, 2 × Ar-C$H_3$), 14.1 (C$H_3$), 9.7 (cyclopropyl *C*H), 5.4 (cyclopropyl *C*$_A$H$_2$), 5.3 (cyclopropyl *C*$_B$H$_2$); HRMS (ESI$^+$) Found $[M+H]^+$ = 273.22125; $C_{19}H_{29}O$ requires 273.22129, Δ 0.15 ppm.

4.4. Representative procedure for alkylation with 2° alcohols: synthesis of 3-cyclopropyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one (**101**)

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added 1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one **83** (114 mg, 0.60 mmol), $[Cp^*IrCl_2]_2$ (9.6 mg, 2.0 mol%), 1-cyclopropylethan-1-ol (120 mg, 1.20 mmol), PhMe (0.15 mL) and NaO*t*Bu (173 mg, 1.80 mmol) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and an Ar balloon fitted. The vial was heated to 85 °C in a preheated oil bath for 24 h. The mixture was cooled to RT, filtered through a SiO_2 plug (eluting with Et_2O) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, Pentane:Et_2O, 98:2) afforded the *title compound* **101** (149 mg, 96%) as a colourless solid. R_f = 0.38 (Pentane:Et_2O, 95:5), [UV, $KMnO_4$]; m.p. = 46–47 °C; IR (film) ν_{max}/cm^{-1} 3077, 2998, 2988, 2955, 2928, 2910, 2873, 1700, 1574, 1459, 1427, 1401, 1383, 1370, 1350, 1314, 1300, 1270, 1129, 1095, 1070, 1045, 1016, 999; ^1H NMR ($CDCl_3$, 400 MHz) δ = 2.88 (1H, dd, *J* = 19.1, 4.2 Hz, CH_AH$_B$CO), 2.65 (1H, dd, *J* = 19.1, 8.4 Hz, CH$_A$$H_B$CO), 2.23 (3H, s, Ar-C$H_3$), 2.19 (6H, s, 2 × Ar-C$H_3$), 2.12 (6H, s, 2 × Ar-C$H_3$), 1.54–1.41 (1H, m, C*H*CH$_2$CO), 1.13 (3H, d, *J* = 6.7 Hz, CH_3), 0.69–0.58 (1H, m, cyclopropyl CH), 0.49–0.36 (2H, m, cyclopropyl C$_A$$H_AH_B$ and cyclopropyl C$_B$$H_AH_B$), 0.23–0.12 (2H, m, cyclopropyl C$_A$H$_A$$H_B$ and cyclopropyl C$_B$H$_A$$H_B$); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 211.3 (C=O), 140.9 (Ar–C), 135.4 (Ar–C), 133.2 (2C, 2 × Ar–C), 127.4 (2C,

2 × Ar–C), 53.1 (CH_2CO), 33.5 ($CHCH_2CO$), 20.1 (CH_3), 18.2 (cyclopropyl *C*H), 17.1 (2C, 2 × Ar-CH_3), 16.8 (Ar-CH_3), 16.1 (2C, 2 × Ar-CH_3), 4.4 (cyclopropyl C_AH_2), 4.1 (cyclopropyl C_BH_2); HRMS (ESI^+) Found $[M+H]^+$ = 259.20575; $C_{18}H_{27}O$ requires 259.20564, Δ 0.41 ppm.

4.5. Representative procedure for Br_2-mediated cleavage: synthesis of butyl cis-2-(4-(benzyloxy)cyclohexyl)acetate (**145**)

To a 2–5 mL Biotage® microwave vial equipped with a stirrer bar was added *cis*-2-(4-(benzyloxy)cyclohexyl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one (**119**) (50.0 mg, 0.13 mmol) and CH_2Cl_2 (0.64 mL) sequentially in the open atmosphere. The reaction vessel was sealed with a microwave vial cap (containing a Reseal™ septum) and cooled to −17 °C (ice/NaCl bath). Following this, Br_2 (13.0 μL, 0.26 mmol) was added dropwise and the mixture stirred until TLC analysis indicated complete consumption of the substrate (typically 15 min). To this, was added *n*BuOH (35.0 μL, 0.38 mmol) dropwise at −17 °C, and the reaction warmed to RT and stirred for 1 h. The reaction was diluted with Et_2O (3 mL) and H_2O (3 mL). The layers were separated and the aqueous layer extracted with Et_2O (× 3). The combined organics were washed with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, Pentane:Et_2O, 95:5 → 90:10) afforded the *title compound* **145** (27.0 mg, 67%, dr > 95:5) as a colorless oil. R_f = 0.40 (Pentane:Et_2O, 90:10), [$KMnO_4$]; IR (film) ν_{max}/cm^{-1} 2957, 2928, 2859, 1731, 1496, 1454, 1444, 1389, 1373, 1356, 1331, 1310, 1286, 1256, 1215, 1156, 1108, 1091, 1064, 1028, 990; ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.38–7.31 (4H, m, Ph), 7.29–7.23 (1H, m, Ph), 4.50 (2H, s, CH_2Ph), 4.07 (2H, t, J = 6.7 Hz, CH_2O), 3.64–3.59 (1H, m, OC*H*), 2.24 (2H, d, J = 7.2 Hz, CH_2COO), 1.96–1.82 (3H, m, $CHCH_2COO$ and 2 × $OCHCH_AH_B$), 1.65–1.56 (2H, m, CH_2CH_2O), 1.55–1.44 (6H, m, 2 × $OCHCH_AH_B$ and 2 × $CH_AH_BCHCH_2COO$), 1.43–1.32 (2H, m, CH_2CH_3), 0.93 (3H, t, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 101 MHz) δ = 173.4 (C=O), 139.4 (Ar–C), 128.4 (2C, 2 × Ar-CH), 127.4 (3C, 3 × Ar-CH), 73.0 (OCH), 69.7 (CH_2Ph),64.2 (CH_2O), 41.5 (CH_2COO), 34.0 ($CHCH_2COO$), 30.8 (CH_2CH_2O), 29.3 (2C, 2 × $OCHCH_2$), 27.3 (2C, 2 × CH_2CHCH_2COO), 19.3 (CH_2CH_3), 13.9 (CH_2CH_3); HRMS (ESI^+) Found $[M+H]^+$ = 305.21149; $C_{19}H_{29}O_3$ requires 305.21112, Δ 1.20 ppm.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We are grateful to the following for financial support EPSRC [J.R.F. and T.J.D., Established Career Fellowship (EP/L023121/1)], A*STAR, Singapore (C.B.C.), GlaxoSmithKline (W.M.A.) and EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine, generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Janssen, Novartis, Pfizer, Syngenta, Takeda, UCB and Vertex (D.F.J.C., EP/L015838/1). Sean Guggiari is thanked for synthesizing compounds **128** and **129**. Dr. Roly J. Armstrong is thanked for helpful comments.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132051.

References

[1] For representative reviews on Hydrogen Borrowing Catalysis, see:. (a) M.H.S.A. Hamid, P.A. Slatford, J.M. Williams, J. Adv. Synth. Catal. 349 (2007) 1555;
(b) G.E. Dobereiner, R.H. Crabtree, Chem. Rev. 110 (2010) 681;
(c) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, ChemCatChem 3 (2011) 1853;
(d) S. Pan, T. Shibata, ACS Catal. 3 (2013) 704;
(e) C. Gunanathan, D. Milstein, Science 341 (2013) 1229712;
(f) J.M. Ketcham, I. Shin, T.P. Montgomery, M.J. Krische, Angew. Chem. Int. Ed. 53 (2014) 9142;
(g) Y. Obora, ACS Catal. 4 (2014) 3972;
(h) Q. Yang, Q. Wang, Z. Yu, Chem. Soc. Rev. 44 (2015) 2305;
(i) A. Nandakumar, S.P. Midya, V.G. Landge, E. Balaraman, Angew. Chem. Int. Ed. 54 (2015) 11022;
(j) J. Leonard, A.J. Blacker, S.P. Marsden, M.F. Jones, K.R. Mulholland, R. Newton, Org. Process Res. Dev. 19 (2015) 1400;
(k) A. Corma, J. Navas, M. Sabater, Chem. Rev. 4 (2018) 1410;
(l) T. Kwok, O. Hoff, R.J. Armstrong, T.J. Donohoe, Chem. Eur J. 26 (2020) 12912.
[2] For examples, see:. (a) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi, Y. Ishii, J. Am. Chem. Soc. 126 (2004) 72;
(b) M.S. Kwon, N. Kim, S.H. Seo, I.S. Park, R.K. Cheedrala, J. Park, Angew. Chem. Int. Ed. 44 (2005) 6913;
(c) C. Løfberg, R. Grigg, M. Whittaker, A. Keep, A. Derrick, J. Org. Chem. 71 (2006) 8023;
(d) S.J. Pridmore, J.M.J. Williams, Tetrahedron Lett. 49 (2008) 7413;
(e) Y. Iuchi, Y. Obora, Y. Ishii, J. Am. Chem. Soc. 132 (2010) 2536;
(f) L. Guo, Y. Liu, X. Yao, Z. Huang, Org. Lett. 15 (2013) 1144.
[3] (a) L.M.K. Chan, D.L. Poole, D. Shen, M.P. Healy, T.J. Donohoe, Angew. Chem. Int. Ed. 53 (2014) 761;
(b) D. Shen, D.L. Poole, C.C. Shotton, A.F. Kornahrens, M.P. Healy, T.J. Donohoe, Angew. Chem. Int. Ed. 54 (2015) 1642.
[4] F. Li, J. Ma, N. Wang, J. Org. Chem. 79 (2014) 10447.
[5] X. Quan, S. Kerdphon, P.G. Andersson, Chem. Eur J. 21 (2015) 3576.
[6] (a) Y. Iuchi, M. Hyotanishi, B.E. Miller, K. Maeda, Y. Obora, Y. Ishii, J. Org. Chem. 75 (2010) 1803;
(b) S. Ogawa, Y. Obora, Chem. Commun. 50 (2014) 2491;
(c) F.-X. Yan, M. Zhang, X.-T. Wang, F. Xie, M.-M. Chen, H. Jiang, Tetrahedron 70 (2014) 1193;
(d) K. Chakrabarti, M. Maji, D. Panja, B. Paul, S. Shee, G.K. Das, S. Kundu, Org. Lett. 19 (2017) 4750.
[7] A. Baeyer, V. Villiger, Ber. Dtsch. Chem. Ges. 32 (1899) 3625.
[8] (a) S. Musa, L. Ackermann, D. Gelman, Adv. Synth. Catal. 355 (2013) 3077;
(b) R. Madsen, I.S. Makarov, J. Org. Chem. 78 (2013) 6593;
(c) C. Chaudhari, S.M.A. Hakim Siddiki, K. Shimizu, Top. Catal. 57 (2014) 1042;
(d) K. Wang, L. Zhang, W. Tang, H. Sun, D. Xue, M. Lei, J. Xiao, C. Wang, Angew. Chem. Int. Ed. 59 (2020) 11408;
(e) T.W. Ng, G. Liao, K.K. Lau, H.-J. Pan, Y. Zhao, Angew. Chem. Int. Ed. 59 (2020) 11384.
[9] T. Sawaguchi, Y. Obora, Chem. Lett. 40 (2011) 1055.
[10] (a) J.R. Frost, C.B. Cheong, W.M. Akhtar, D.F.J. Caputo, N.G. Stevenson, T.J. Donohoe, J. Am. Chem. Soc. 137 (2015) 15664;
(b) W.M. Akhtar, C.B. Cheong, J.R. Frost, K.E. Christensen, N.G. Stevenson, T.J. Donohoe, J. Am. Chem. Soc. 139 (2017) 2577;
(c) W.M. Akhtar, R.J. Armstrong, J.R. Frost, N.G. Stevenson, T.J. Donohoe, J. Am. Chem. Soc. 140 (2018) 11916;
(d) R.J. Armstrong, W.A. Akhtar, T.A. Young, F. Duarte, T. Donohoe, J. Angew. Chem. Int. Ed. 58 (2019) 12558;
(e) R.J. Armstrong, W.M. Akhtar, J.R. Frost, K.E. Christensen, N.G. Stevenson, T.J. Donohoe, Tetrahedron 75 (2019) 130680;
(f) S. Wübbolt, C.B. Cheong, J.R. Frost, K.E. Christensen, T. Donohoe, J. Angew. Chem. Int. Ed. 59 (2020) 11339;
(g) A.E.R. Chamberlain, K.J. Paterson, R.J. Armstrong, H.C. Twin, T. Donohoe, J. Chem. Commun. 56 (2020) 3563;
(h) D.M.J. Cheang, R.J. Armstrong, W.M. Akhtar, T.J. Donohoe, Chem. Commun. 56 (2020) 3543;
(i) For related annulation reactions involving earth abundant catalysts, see: A. Kaithal, L.-L. Gracia, C. Camp, E.A. Quadrelli, W. Leitner J. Am. Chem. Soc. 141 (2019) 17487;
(j) A. Jana, K. Das, A. Kundu, P.R. Thorve, D. Adhikari, B. Maji, ACS Catal. 10 (2020) 2615;
(k) L. Bettoni, S. Gaillard, J.-L. Renaud, Chem. Commun. 56 (2020) 12909.
[11] For other recent examples of α-alkylation of ketones or similar, see:. (a) C. Schlepphorst, B. Maji, F. Glorius, ACS Catal. 6 (2016) 4184;
(b) Y. Iuchi, M. Hyotanishi, B.E. Miller, K. Maeda, Y. Obora, Y. Ishii, J. Org. Chem. 75 (2010) 1803;
(c) S. Ogawa, Y. Obora, Chem. Commun. 50 (2014) 2491;
(d) F.-X. Yan, M. Zhang, X.-T. Wang, F. Xie, M.-M. Chen, H. Jiang, Tetrahedron 70 (2014) 1193;
(e) F. Li, X. Zou, N. Wang, Adv. Synth. Catal. 357 (2015) 1405.
[12] (a) X. Cao, X. Wan, F. Yang, K. Li, X. Hao, T. Shao, X. Zhu, M. Song, J. Org. Chem. 83 (2018) 3657;
(b) L. Kabadwal, J. Das, D. Banerjee, Chem. Commun. 54 (2018) 14069;

(c) A. Kaithal, M. Schmitz, M. Hölscher, W. Leitner, ChemCatChem 11 (2019) 5287;
(d) A. Kaithal, M. Schmitz, M. Hölscher, W. Leitner, ChemCatChem 12 (2020) 781;
(e) S. Thiyagarajan, C. Gunanathan, J. Am. Chem. Soc. 141 (2019) 3822;
(f) L. Bettoni, S. Gaillard, J.-L. Renaud, Org. Lett. 22 (2020) 2064;
(g) P. Chakraborty, M.K. Gangwar, B. Emayavaramban, E. Manoury, R. Poli, B. Sundararaju, ChemSusChem 12 (2019) 3463;
(h) S. Waiba, S.K. Jana, A. Jati, A. Jana, B. Maji, Chem. Commun. 56 (2020) 8376;
(i) For an example without a metal catalyst M.B. Dambatta, J. Santos, R.R.A. Bolt, L.C. Morrill, Tetrahedron 76 (2020) 131571.

[13] Purification of the crude mixture did not allow for these three components to be easily separated, and therefore they were isolated as a mixture, with the product ratio determined based on the mass obtained and analysis of the ^{1}H NMR spectrum. We also identified alcohol 4 in the crude mixture, but this was not quantified as it was difficult to separate from excess BnOH.

[14] (a) L.J. Allen, R.H. Crabtree, Green Chem. 12 (2010) 1362;
(b) Q. Xu, J. Chen, H. Tian, X. Yuan, S. Li, C. Zhou, J. Liu, Angew. Chem. Int. Ed. 53 (2013) 225. See also ref 12i.

[15] (a) T. Nakai, E. Wada, M. Okawara, Tetrahedron Lett. 16 (1975) 1531;
(b) C.U. Pittman, S.P. McManus, J. Am. Chem. Soc. 91 (1969) 5915.

[16] C. Mioskowski, S. Manna, J.R. Falck, Tetrahedron Lett. 24 (1983) 5521.

[17] In similar fashion to cyclopropyl ketones, we also noted that α-branched product formed in the absence of catalyst when BnOH was used. Once again this occurred in lower yield compared to the optimized system, with alkyl alcohols again being unreactive in the absence of catalyst.

[18] P. Sykes, In A Guidebook to Mechanism in Organic Chemistry, John Wiley & Sons, New York, 1986.

[19] Previous conditions for the cleavage of related (mesityl) functional groups required the use of strong protic acids. For selected examples, see:. (a) W.M. Schubert, H.K. Latourette, J. Am. Chem. Soc. 74 (1952) 1829;
(b) M.L. Bender, H. Ladenheim, M.C. Chen, J. Am. Chem. Soc. 83 (1961) 123;
(c) M.L. Bender, M.C. Chen, J. Am. Chem. Soc. 85 (1963) 37.

[20] A. El-Khawaga, R. Roberts, K.M. Sweeney, J. Org. Chem. 50 (1985) 2055.

[21] (a) A.D. Andreou, R.V. Bulbulian, P.H. Gore, D.F.C. Morris, E.L. Short, J. Chem. Soc. Perkin Trans. 2 (1981) 830;
(b) M. Kazunori, K. Yasuo, T. Hisakazu, M. Toshio, T. Ichiro, K. Hidehiko, K. Takashi, Bull. Chem. Soc. Jpn. 67 (1994) 757.

[22] For examples of diastereoselective amination under hydrogen borrowing conditions, see:. (a) X. Xi, Y. Li, G. Wang, G. Xu, L. Shang, Y. Zhang, L. Xia, Org. Biomol. Chem. 17 (2019) 7651;
(b) K. Fujita, T. Fujii, R. Yamaguchi, Org. Lett. 6 (2004) 3525.

[23] We assume that *in situ* deprotonation and isomerization from cis- to trans-decalone occurred under the reaction conditions.

[24] (a) J. Sauvage, R.H. Baker, A.S. Hussey, J. Am. Chem. Soc. 82 (1960) 6090;
(b) B.E. Huff, V.V. Khau, M.E. LeTourneau, M.J. Martinelli, N.K. Nayyar, B.C. Peterson, Tetrahedron Lett. 38 (1997) 8627.

[25] Substrate **113** was also treated under our previously reported α-methylation conditions. In this instance only unreacted starting material was isolated.

[26] (a) For a review on HFIP, see: I. Colomer, A.E.R. Chamberlain, M.B. Haughey, T.J. Donohoe Nat. Rev. Chem. 1 (2017) 88;
(b) C.B. Cheong, J.R. Frost, T. Donohoe, J. Synlett. 31 (2020) 1828.

[27] L. Palatinus, G.J. Chapuis, Appl. Crystallogr. 40 (2007) 786.

[28] (a) P. Parois, R.I. Cooper, A.L. Thompson, Chem. Cent. J. 9 (2015) 30;
(b) R.I. Cooper, A.L. Thompson, D.J. Watkin, J. Appl. Crystallogr. 43 (2010) 1100.