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Enabling the Development of *N*-Heterocyclic Carbene (NHC) Catalyzed Reactions: Practical Methods for the Preparation of 1-Acyl-2-Alkylcycloalkenes from Cycloalkanones

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The synthesis of 1-acyl-2-alkylcycloalkenes from a variety of cycloalkanones has been achieved via either β-keto enol phosphates or β-bromoenones. Both methods exploit simple and readily scalable transformations allowing the preparation of the desired compounds to be achieved in three, or four steps, respectively. The utility of these strategies has been examined, resulting in the preparation of 17 disubstituted cycloalkenes.

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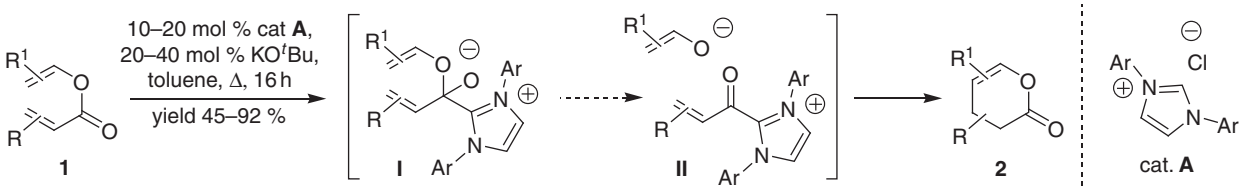
Introduction

N-Heterocyclic carbenes (NHCs) have great utility, with roles at the frontiers of transition metal and organo- catalysis.[1] In the later field, NHC-mediated carbonyl umpolung has a long history.[1a,b] More recently rich and diverse reactivity has been accessed by combining both normal and reverse polarity events in a single reaction cascade.[1b–g] Our studies have focussed on the use of NHCs as Lewis bases capable of catalyzing transformations without carbonyl umpolung.[2] In 2009 we realized this concept, demonstrating that α,β-unsaturated enol esters **1** are rearranged by diaryl imidazolium-derived NHCs to provide dihydropyranones **2** (Scheme 1).[2a] Mechanistically, this isomerization likely proceeds via formation of hemiacetal **I**, followed by either a 3,3-sigmatropic rearrangement, or fragmentation to the α,β-unsaturated acyl azolium[3] enolate ion pair **II** followed by conjugate addition. Last year Bode reported a related transformation and, from kinetic analysis, postulated a mechanism involving a 3,3-sigmatropic rearrangement.[3l,o] While both may proceed via a common pathway, significant differences regarding the reaction conditions raise the possibility that distinct mechanisms may be operative. Although the mechanism of this transformation is not yet clear, its utility has been examined through the total synthesis of 7-deoxyloganin.[2b]

Earlier this year we reported the NHC-triggered formation of acyl azoliums and dienolates in studies focussed on the development of [4 + 2] cycloadditions (Scheme 2).[2c] In this transformation NHC-mediated substitution of acyl fluoride **4** triggers desilylation of TMS dienol ether **3** to provide the ion pair **III**. These undergo a highly *endo* selective coupling to presumably provide β-lactone **IV**, which then decarboxylates to give the observed cyclohexadienes **5**. In addition to providing an additional example of the use of NHCs to catalyze reactions without polarity inversion, this transformation provides a powerful method to valuable cyclohexadienes.

To develop the [4 + 2] cycloaddition, access to the starting materials **3** and **4** was required. Acid fluorides **4** are available in one step from the corresponding acid,[4] and the TMS enol ethers **3** are accessible by γ-deprotonation of the 1-acyl-2-alkylcycloalkenes (i.e. **6**, Scheme 3).[2c,5] Unfortunately, we were surprised to find limited reports on the synthesis of the later compounds.[6,7] Furthermore, these methods were plagued by combinations of poor yield, restricted scope, and the requirement of nontrivial starting materials or reagents.[7] To allow a meaningful examination of the NHC-catalyzed [4 + 2] cycloaddition, scalable methods for the preparation of 1-acyl-2-alkylcycloalkenes (i.e. **6**) were required. Herein, we report our studies on this topic with two strategies that allow the preparation of a broad range of 1-acyl-2-alkylcycloalkenes **6**. Both methods exploit cheap and readily available reagents, making them achievable in a variety of laboratories, across a range of scales.



Scheme 1. NHC catalyzed pyranone synthesis.[2a]

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Results and Discussion

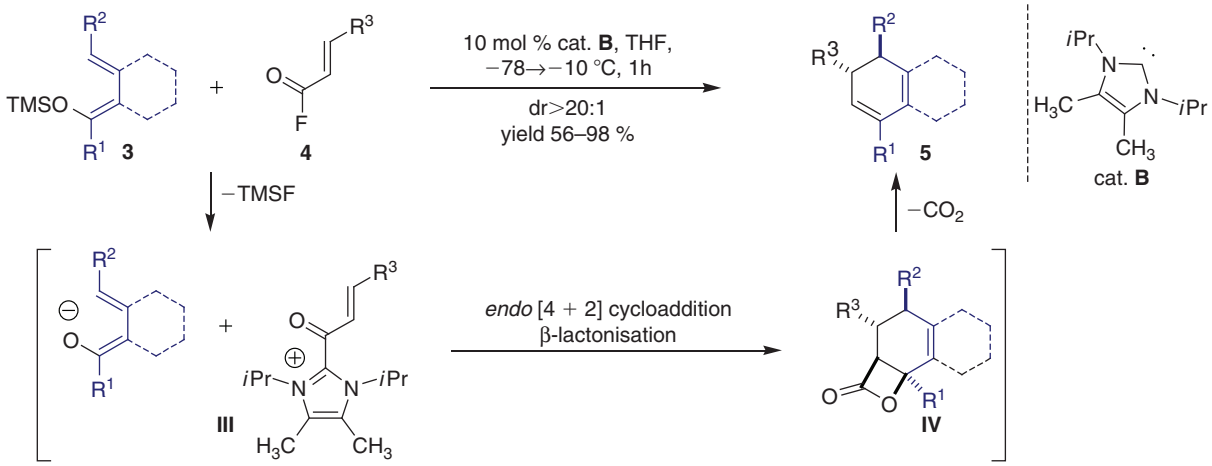
*Method 1: Preparation of 1-acyl-2-alkylcycloalkenes **6** via enol phosphates **7***

While dialkylcuprate coupling of enol phosphates derived from β-ketoesters and symmetrical β-diketones was first reported in 1979,[8a] this transformation is yet to be applied to phosphates derived from unsymmetrical β-diketones. This situation presumably arises due to difficulties, or perceived difficulties, associated with regioselective β-keto enol phosphate formation.[9] If regioselectivity could be achieved, then a viable approach to 1-acyl-2-alkylcycloalkenes **6**, from the corresponding β-keto enol phosphates (i.e. **7a**) should be possible. To explore this strategy the formation of phosphate **7a** (and the undesired **7a′**) from benzoyl cyclohexanone **8a** was examined. It was hypothesized that generation of **7a** should be favoured over **7a′** due to buttressing of the phosphate residue with the carbonyl group in the latter compound. When β-diketone **8a** was subjected to conditions developed for the conversion of β-ketoesters,[8] we were pleased to discover that **7a** was the major product. Unfortunately, this effect was only modest, with products **7a** and **7a′** generated in a 3:2 ratio (Scheme 4). By extending the equilibration time before addition of phosphoryl chloride enol phosphate, **7a** now formed in an improved 4:1 ratio, and in an isolated yield of 72 % (Table 1, entry 1). Subsequent conversion of phosphate **7a** to 1-acyl-2-alkylcycloalkenes **6a** was achieved with $LiMe_2Cu$ in excellent yield (Table 1, entry 1),[8] demonstrating the viability of this approach.

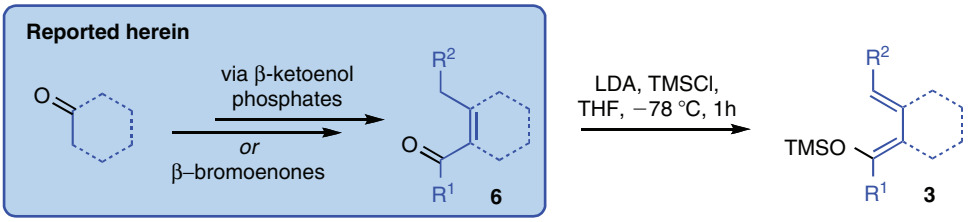
To explore the generality of this reaction sequence, a range of β-diketones **8** were required. In our hands, the acylation of the corresponding ketone[10a] or enamine[10b] proved convenient for their preparation. Exploiting the optimized conditions, a variety of enol phosphates **7** were prepared (Table 1, entries 1–8). The regioisomeric composition of the enol phosphate products was at worst 4:1 (Table 1, entries 1, 2 and 7), with most examples occurring with ≥ 8:1 selectivity for the desired enol phosphate. Substituted aromatic starting materials were tolerated, with electron poor aroyl-cyclohexanones affording enol phosphates **7c** and **d** in good yield (Table 1, entries 3–5). Similarly, cinnamoylcyclohexanone **8e** and furoyl-cyclohexenone **8f** were compatible with the reaction conditions (Table 1, entries 5 and 6). Finally, incorporation of additional degrees of unsaturation and the use of bicyclic substrates proved suitable, allowing enol phosphates **7 g** and **h** to be prepared in good yields with excellent regioselectivity (Table 1, entries 7 and 8). The formation of the β-keto enol phosphates **7** was remarkably reliable, performing well over a range of scales. This transformation was regularly performed on 0.05 mol of β-diketones **8** without modification to the reaction conditions.

The enol phosphates were next subjected to dialkylcuprate coupling using conditions developed by Weiler.[8] While $LiMe_2Cu$ provided products **6a**, **c**, **d** and **f-h** in good yields (Table 1, entries 1, 3, 4 and 6–8), when cinnamoyl phosphate **7e** was reacted a mixture of products resulted (Table 1, entry 5), presumably due to undesired conjugate addition pathways. In addition, $LiBu_2Cu$ could be used to install a butyl side chain, albeit in lower yields (Table 1, entry 2).

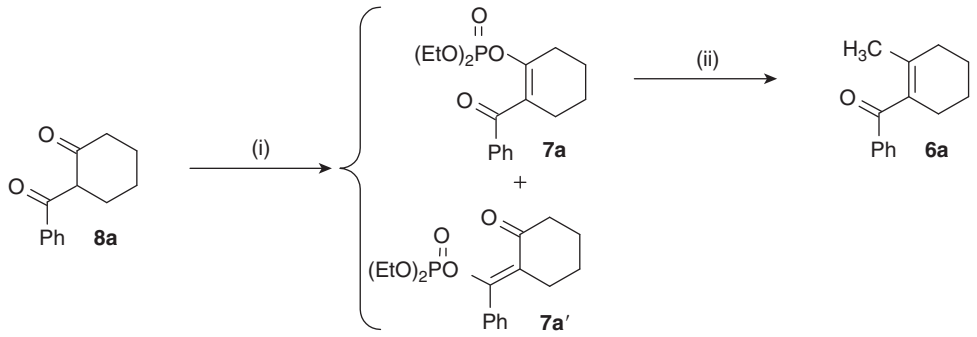
Although this strategy allows the conversion of cycloalkanones to the desired 1-acyl-2-alkylcycloalkenes, it suffers from limitations. Most significantly the incorporation of the butyl group could only be achieved in low yield. Whether this result was indicative of restricted reactivity with non-methyl alkyl lithiums was not examined further. This was due to restricted availability of alkyl lithium reagents compared with the Grignard reagents, materials that served as the key coupling partner in the second approach.



Scheme 2. NHC catalyzed [4 + 2] cycloaddition/decarboxylation.[2c]



Scheme 3. Strategy for the synthesis of 1-acyl-2-alkylcycloalkenes **6**.



Scheme 4. Reagents and Conditions: (i) NaH, Et_2O, 0 → 18 °C, 1.5 h, then $(EtO)_2$ PO(Cl), 18 °C, 2 h. (ii) $LiMe_2Cu$, Et_2O, –78 °C, 1 h

*Method 2: Preparation of 1-acyl-2-alkylcycloalkenes **6** via β-bromo enones **9***

Since the pioneering work of Kochi,[11a] iron catalyzed coupling of vinyl bromides with alkylmagnesium halides has seen extensive investigation.[11] The use of inexpensive iron catalysts in association with a range of Grignard reagents, makes this an attractive strategy for the preparation of substituted alkenes.[11,12] In addition, cross-couplings proceed with exquisite chemoselectivity, for example certain ketones and esters are able to couple without any direct carbonyl addition.[11f] To test whether iron catalyzed cross-coupling could furnish 1-acyl-2-alkylcycloalkenes (i.e. **6**) we chose to target bromide **9a**. When the coupling reaction was attempted, the desired methylketone **6a** was formed in 99 % yield without any addition into the ketone functionality.

To explore the breadth of this reaction, a variety of β-bromoenones **9** were required. In all cases they were prepared from the bromoaldehydes **10**, themselves accessed via haloformylation of the corresponding cycloalkanone.[13] This was followed by treatment with an appropriate Grignard reagent and oxidation of the resulting alcohol with PCC, to give **9** (Table 2). When β-bromoenone **9a** was subjected to iron-catalyzed coupling with the methyl, ethyl, propyl and butenyl Grignard reagents, ketones **6a**, **i**, **j** and **k** formed in good yields (Table 2, entry 1–4). Unfortunately, when the cross-coupling was attempted with allyl magnesium bromide addition into the ketone gave the allylic alcohol as the only isolable product (Table 1, entry 5). Attention was next turned to variations in the β-bromoenone **9**. Those containing alkyl or substituted aromatic substituents proved successful when reacted with methyl magnesium bromide, providing ketones **6l-n** (Table 2, entries 6–8). In addition the ring expanded bromide **9o** and bicyclic bromides **9p** and **q** reacted smoothly (Table 2, entries 9–11).

As with the transformations described in method 1, the cross-coupling could be performed on a range of scales, and was regularly conducted on 20 mmol of β-bromenone **9** without modification of the reaction conditions.

Conclusions

The development of new chemical transformations requires simple procedures that provide rapid access to substrates. During the course of studies into a novel NHC-catalyzed [4 + 2] cycloaddition, we required access to a range of 1-acyl-2-alkylcycloalkenes **6**. Herein, we report the development of approaches for the preparation of these materials from cycloalkanones via either the β-keto enol phosphate **7**, in 3 steps, or the β-bromo enone **9**, in 4 steps. The first strategy was possible due to the preference for formation of endocyclic enol phosphates from non-symmetrical β-diketones. While this strategy was useful, it was less successful in delivering non-methyl β-alkylated compounds. Our second strategy addressed this limitation through use of an iron-catalyzed cross coupling between β-bromoenones and a diverse range of Grignard reagents. Remarkably, this reaction provided the desired products without any direct addition to the carbonyl group in all but one case. Combined, these two methods provided access to 17 cycloalkenes in good to excellent yields. In addition to enabling our studies on the NHC-catalyzed [4 + 2] cycloaddition, these procedures provide a valuable resource for the synthesis of 1-acyl-2-alkylcycloalkenes (i.e. **6**).

Experimental Section

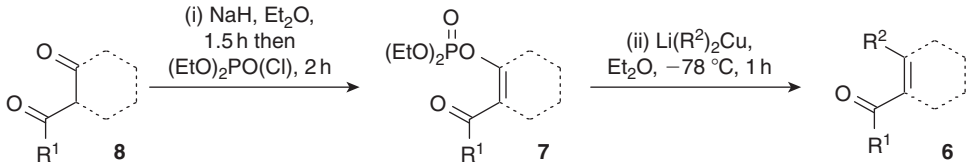
Unless otherwise specified, proton (^1H) and carbon (^{13}C) NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei or a Varian DRX 500 spectrometer operating at 500 MHz for proton and 125 MHz for carbon. Signals arising from the residual protio-forms of the solvent were used as the internal standard. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer RXI FTIR Spectrometer. Samples were analyzed as thin films on NaCl plates. High resolution mass spectra (HRMS) (ESI) were recorded on a Bruker BioApex 47e FTMS fitted with an analytical electrospray source using NaI for accurate mass calibration. HRMS (EI) were recorder on an Agilent 7890A GC, Waters GCT Premier TOF-MS with an ion source temperature of 200°C and electron impact energy (70 eV). Flash column chromatography was performed on silica gel (Davisil LC60A, 40–63 μm silica media) using compressed air or nitrogen. Thin-layer chromatography (TLC) was performed using aluminium or plastic backed plates coated with 0.2 mm silica (Merck, DC-Platten, Kieselgel; 60 F_{254} plates). Eluted plates were visualized using a 254-nm UV lamp and by treatment with a suitable stain followed by heating.

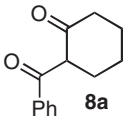
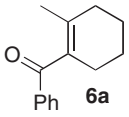
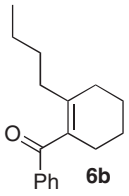
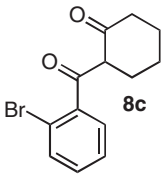
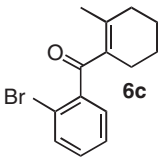
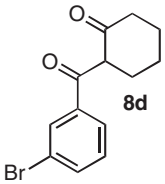
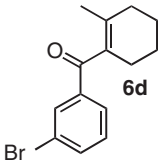
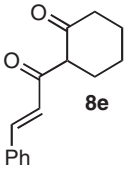
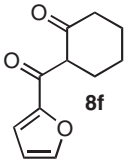
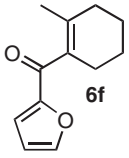
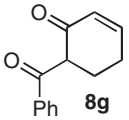
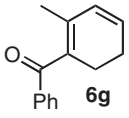
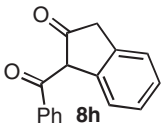
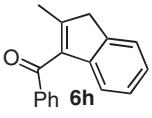
Starting materials and reagents were purchased from Sigma-Aldrich and were used as supplied or, in the case of some liquids, distilled. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. Concentration under reduced pressure was performed on a rotary evaporator with the water bath temperature not exceeding 40°C. β-Diketones **8** were prepared using reported procedures.[10]

Procedure for the synthesis of β-keto enol phosphates 7

Using a modification to the procedure reported by Weiler,[8] β-diketones **8** (12.0 mmol) in diethyl ether (2 mL) were added to a suspension of NaH (528 mg of a 60 % suspension in mineral oil, 13.2 mmol) in diethyl ether (20 mL) at 0°C. The mixture was

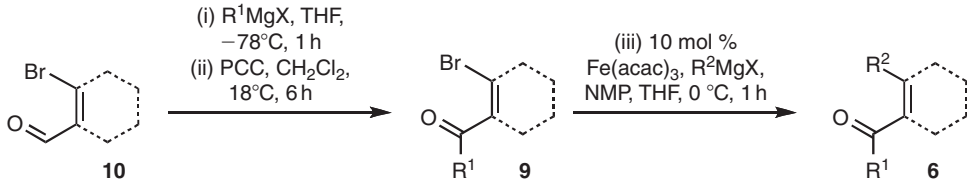
Table 1. Scope of 1-acyl-2-alkylcycloalkenes 6 synthesis via β-keto enol phosphates 7

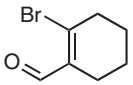
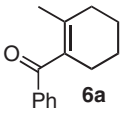
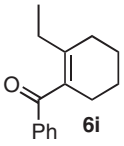
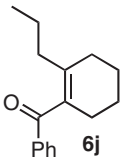
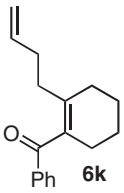
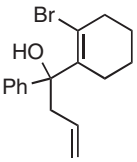
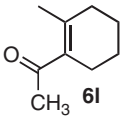
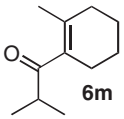
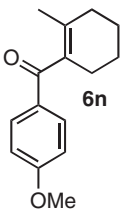


Entry	Starting Material 8	Ratio 7:7′[a]	Yield 7[b]	R^2	Product[c]	Yield 6[b]
1	 **8a**	4:1	72 %	Me	 **6a**	94 %
2	‘	4:1	72 %	Bu	 **6b**	25 %
3	 **8c**	1:0	53 %	Me	 **6c**	73 %
4	 **8d**	1:0	42 %	Me	 **6d**	55 %
5	 **8e**	9:1	74 %	Me	–	–
6	 **8f**	8:1	65 %	Me	 **6f**	76 %
7	 **8g**	4:1	62 %	Me	 **6g**	81 %
8	 **8h**	9:1	57 %	Me	 **6h**	83 %

[a]Ratio of **7**:**7′** was determined by analysis of the crude ^{1}H NMR spectrum. [b]Isolated yield following flash column chromatography. [c]Lithium dialkylcuprate generated according to Weiler.[8]

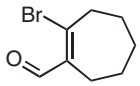
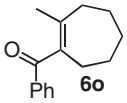
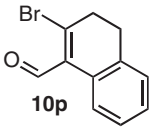
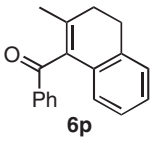
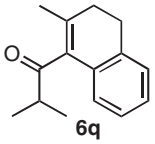
Table 2. Scope of 1-acyl-2-alkylcycloalkenes 6 synthesis via β-bromo enones 9



Entry	SM 10	R^1	Yield 9[a,b]	R^2	Product	Yield 6[a]
1	 **10a**	Ph	86 %	Me	 **6a**	99 %
2	‘	‘	‘	Et	 **6i**	99 %
3	‘	‘	‘	Pr	 **6j**	31 %
4	‘	‘	‘	But-en-yl	 **6k**	77 %
5	‘	‘	‘	Allyl		-[c]
6	‘	Me	54 %	Me	 **6l**	52 %
7	‘	*i*Pr	60 %	Me	 **6m**	74 %
8	‘	4-OMePh	67 %	Me	 **6n**	82 %

(*Continued*)

Table 2. (Continued)

Entry	SM 10	R^1	Yield 9[a,b]	R^2	Product	Yield 6[a]
9	 **10o**	Ph	62 %	Me	 **6o**	81 %
10	 **10p**	Ph	71 %	Me	 **6p**	77 %
11	‘	*i*Pr	47 %	Me	 **6q**	68 %

[a]Isolated yield following flash column chromatography. [b]Yield was calculated for the two steps. [c]Identified in variable yields as the only product.

allowed to warm to room temperature, and stirring continued for a further hour. After this time, phosphoryl chloride (2.28 g, 13.2 mmol) was slowly added and the mixture stirred for an additional 2 h. The suspension was quenched with NH_4Cl (5 mL of a saturated aqueous solution) and extracted with diethyl ether (3 × 10 mL), the combined organic layers were dried ($MgSO_4$), filtered, and the volatiles evaporated. The crude residue was purified by flash column chromatography (4:1, v/v EtOAc/hexanes) to provide the title compound β-keto enol phosphates **7** along with the regioisomeric product. Yields and ratios of **7**:**7′** are reported in Table 1.

*2-Benzoylcyclohex-1-en-1-yl diethyl phosphate (**7a**).* Clear colourless oil. R_f 0.3 (4:1, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 3490, 2985, 1660, 1449, 1283, 1132, 1034. δ_H (300 MHz, $CDCl_3$) 7.93–7.90 (m, 2H), 7.58–7.51 (m, 1H), 7.47–7.42 (m, 2H), 3.79–3.65 (m, 4H), 2.60–2.52 (m, 2H), 2.41–2.36 (m, 2H), 1.90–1.81 (m, 2H), 1.76–1.68 (m, 2H), 1.11 (dt, *J* 6.6, 1.2, 6H). δ_C (75 MHz, $CDCl_3$) 196.8, 147.2 (d, *J* 7.1), 136.9, 132.8, 129.1, 128.2, 121.9 (d, *J* 8.6), 63.9 (d, *J* 6.3), 27.5, 26.2, 22.4, 21.4, 15.6 (d, *J* 6.8). *m/z* (HR-ESI) Found $(M+H)^+$ 339.1358, $C_{17}H_{23}O_5P$ requires $(M+H)^+$ 339.1361.

*(Z)-diethyl ((2-oxocyclohexylidene)(phenyl)methyl) phosphate (**7a′**).* Clear colourless oil. R_f 0.2 (4:1, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 3490, 2932, 1699, 1445, 1272, 1026. δ_H (300 MHz, $CDCl_3$) 7.49–7.38 (m, 5H), 4.05–3.97 (m, 4H), 2.60 (t, *J* 6.6, 2H), 2.43 (td, *J* 6.6, 2.7, 2H), 1.93 (quint., *J* 6.6, 2H), 1.76 (quint., *J* 6.6, 2H), 1.17 (td, *J* 6.6, 0.6, 6H). δ_C (75 MHz, $CDCl_3$) 202.5, 145.1 (d, *J* 7.1), 133.8, 129.5, 129.4, 128.3, 126.6 (d, *J* 7.4), 64.3 (d, *J* 6.0), 43.4, 30.9, 25.8, 25.5, 15.9 (d, *J* 7.4). *m/z* (HR-ESI) Found $(M+H)^+$ 339.1359, $C_{17}H_{23}O_5P$ requires $(M+H)^+$ 339.1361.

*2-(2-Bromobenzoyl)cyclohex-1-en-yl diethyl phosphate (**7c**).* Clear colourless oil. Prepared using the procedure described for compound **7a**. R_f 0.2 (3:2, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 3563, 2938, 1652, 1367, 1294, 1137, 1033. δ_H (300 MHz, $CDCl_3$) 7.57 (dd, *J* 7.8, 1.2, 1H), 7.44 (dd, *J* 7.8, 2.1, 1H), 7.35 (td, *J* 7.8, 1.2, 1H), 7.24 (td, *J* 7.8, 2.1, 1H), 3.92–3.78 (m, 4H), 2.57–2.52 (m, 2H), 2.49–2.44 (m, 2H), 1.82–1.75 (m, 2H), 1.72–1.66 (m, 2H), 1.20 (td, *J* 7.2, 1.2, 6H). δ_C (75 MHz, $CDCl_3$) 195.5, 153.6 (d, *J* 6.6), 142.4, 133.0, 130.8, 129.5, 127.1, 121.8 (d, *J* 8.6), 119.2, 64.1 (d, *J* 6.2), 28.5, 25.2, 22.2, 21.5, 15.9 (d, *J* 7.1). *m/z* (HR-ESI) Found $(M+H)^+$ 417.0464, $C_{17}H_{22}BrO_5P$ requires $(M+H)^+$ 417.0467.

*2-(3-Bromobenzoyl)cyclohex-1-en-yl diethyl phosphate (**7d**).* Prepared using the procedure described for compound **7a**. Clear colourless oil. R_f 0.2 (3:2, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 3501, 2939, 1667, 1567, 1361, 1285, 1032. δ_H (300 MHz, $CDCl_3$) 7.99 (t, *J* 1.8, 1H), 7.80 (dt, *J* 7.8, 1.8, 1H), 7.65 (dq, *J* 7.8, 0.9, 1H), 7.33 (t, *J* 7.8, 1H), 3.83–3.71 (m, 4H), 2.60–2.52 (m, 2H), 2.41–2.36 (m, 2H), 1.88–1.83 (m, 2H), 1.75–1.68 (m,2H), 1.15 (td, *J* 6.9, 0.9, 6H). δ_C (75 MHz, $CDCl_3$) 195.6, 148.6 (d, *J* 7.1), 139.1, 135.2, 131.6, 129.8, 127.7, 122.3, 121.4 (d, *J* 8.3), 63.9 (d, *J* 6.6), 27.6, 26.0, 22.3, 21.3, 15.6 (d, *J* 7.1). *m/z* (HR-ESI) Found $(M+H)^+$ 417.0462, $C_{17}H_{22}BrO_5P$ requires $(M+H)^+$ 417.0467.

*(E) 2-Cinnamoylcyclohex-1-en-yl diethyl phosphate (**7e**).* Prepared using the procedure described for compound **7a**. Clear colourless oil. R_f 0.2 (3:2, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 2939, 1647, 1598, 1367, 1285, 1032. δ_H (300 MHz, $CDCl_3$) 7.59–7.54 (m, 3H), 7.35–7.33 (m, 3H), 7.13 (d, *J* 16.2, 1H), 4.09–3.97 (m, 4H), 2.54–2.49 (m, 2H), 2.37–2.34 (m, 2H), 1.77–1.72 (m, 2H), 1.63–1.60 (m, 2H), 1.80 (dt, *J* 6.0, 0.9, 6H). δ_C (75 MHz, $CDCl_3$) 193.2, 150.8 (d, *J* 7.4), 142.6, 134.9, 130.1, 128.7, 128.2, 126.6, 123.8 (d, *J* 8.6), 64.4 (d, *J* 6.0), 28.4, 25.4, 22.5, 21.5, 15.8 (d, *J* 6.9). *m/z* (HR-ESI) Found $(M+H)^+$ 365.1516, $C_{19}H_{25}O_5P$ requires $(M+H)^+$ 365.1518.

*Diethyl (2-(furan-2-carbonyl)cyclohex-1-en-yl) phosphate (**7f**).* Prepared using the procedure described for compound **7a**. Clear colourless oil. R_f 0.3 (1:1, v/v EtOAc/hexane). ν_{max}/cm^{-1} 2940, 1760, 1644, 1463, 1263, 1032. δ_H (300 MHz, $CDCl_3$) 7.54–7.51 (m, 1H), 7.14–7.10 (m, 1H), 6.54–6.42 (m, 1H), 3.84–3.74 (m, 4H), 2.40–2.38 (m, 2H), 2.30–2.19 (m, 2H), 1.76–1.62 (m, 2H), 1.60–1.53 (m, 2H), 1.31–1.05 (m, 6H). δ_C (75 MHz, $CDCl_3$) 183.7, 152.0, 147.6 (d, *J* 7.13), 146.8, 121.6 (d, *J* 8.55), 119.7, 112.0, 64.0 (d, *J* 6.52), 27.5, 25.8, 22.2, 21.3, 15.6 (d, *J* 6.83). *m/z* (HR-ESI) Found $(M+H)^+$, 329.1154, $C_{15}H_{21}O_6P$, requires $(M+H)^+$, 329.1149.

*2-Benzoylcyclohexa-1,5-dien-1-yl diethyl phosphate (**7g**).* Prepared using the procedure described for compound **7a**. Clear colourless oil. R_f 0.2 (4:1, v/v EtOAc/hexanes). ν_{max}/cm^{-1}

3494, 2985, 1643, 1579, 1367, 1288, 1030. δ_H (300 MHz, $CDCl_3$) 7.86 (dt, *J* 6.0, 1.2, 2H), 7.56–7.51 (m, 3H), 6.33–6.23 (m, 2H), 3.62–3.51 (m, 4H), 2.52–2.44 (m, 2H), 2.24–2.17 (m, 2H), 1.12 (td, *J* 7.1, 1.2, 6H). δ_C (75 MHz, $CDCl_3$) 196.0, 146.3 (d, *J* 7.7), 138.5, 135.5, 132.4, 129.1, 128.2, 122.9 (d, *J* 1.7), 118.4 (d, *J* 8.6), 64.3 (d, *J* 6.6), 24.6, 22.6, 15.8 (d, *J* 6.9). *m/z* (HR-ESI) Found $(M+Na)^+$ 359.1017, $C_{17}H_{21}O_5P$ requires $(M+Na)^+$ 359.1024.

*3-Benzoyl-1*H*-inden-2-yl diethyl phosphate (**7h**).* Prepared using the procedure described for compound **7a**. Clear colourless oil. R_f 0.3 (1:1, v/v EtOAc/hexane). ν_{max}/cm^{-1} 2985, 1731, 1602, 1450, 1222, 1035. δ_H (300 MHz, $CDCl_3$) 7.94–7.91 (m, 2H), 7.60–7.22 (m, 7H), 3.93–3.87 (m, 4H), 2.04 (s, 2H), 1.23–1.17 (m, 6H). δ_C (75 MHz, $CDCl_3$) 196.9, 178.4 (d, *J* 8.52), 143.2, 138.3, 137.7, 134.7, 129.3, 128.5, 127.9, 126.8, 125.6, 125.4, 107.8 (d, *J* 7.75), 63.3 (d, *J* 6.63), 42.2, 15.8 (d, *J* 6.83). *m/z* (HR-EI) Found $(M)^+$, 372.1131, $C_{20}H_{21}O_5P$, requires $(M)^+$, 372.1127.

Procedure for the haloformylation reaction

PBr_3 (10.8 mL, 115 mmol) was added dropwise to a stirred solution of DMF (9.8 mL, 128 mmol) in chloroform (75 mL) at 0°C. The reaction mixture was allowed to stir for 1 h, at which time the appropriate ketone (50 mmol) was added and the mixture heated to reflux for an additional 3 h. The solution was then cooled to room temperature, transferred to a flask of ice water and neutralized with solid $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers washed with $NaHCO_3$ (2 × 20 mL of a saturated aqueous solution), dried ($MgSO_4$) and the volatiles evaporated. The resulting residue was purified by flash column chromatography to afford, after concentration of the appropriate fractions, compounds **10a**,[14] **10o**[15] and **10p**,[16] which matched previously reported data.

Procedure for the Grignard addition reaction

The appropriate bromoaldehyde **10a**, **o** or **p** (15 mmol) was added dropwise to a stirred solution of R^1MgX (23 mmol) in THF (40 mL) at −78°C. The reaction mixture was maintained at this temperature, with stirring, for 1 h. At this time it was quenched with NH_4Cl (10 mL of a saturated aqueous solution). The aqueous solution was extracted with EtOAc (3 × 20 mL) and the combined organic layers washed with brine (20 mL), dried ($MgSO_4$) and the volatiles evaporated. The resulting residue was purified by flash column chromatography to afford, after concentration of the appropriate fractions, the title bromo alcohols.

(2-Bromocyclohex-1-en-yl(phenyl)methanol (Table 2, entries 1–5) was prepared as a clear colourless oil using the procedure described above and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[17]

1-(2-Bromocyclohex-1-en-1-yl)ethanol (Table 2, entry 6) was prepared as a clear colourless oil using the procedure described above and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[15]

1-(2-Bromocyclohex-1-en-1-yl)-2-methylpropan-1-ol (Table 2, entry 7) was prepared using the procedure described above. White low melting solid. R_f 0.3 (1:9, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 3308, 2933, 1728, 1447, 1334, 1257, 1025. δ_H (300 MHz, $CDCl_3$) 4.37 (d, *J* 9.3, 1H), 2.54–2.49 (m, 2H), 2.34–2.26 (m, 1H), 2.05–1.96 (m, 1H), 1.83–1.59 (m, 5H), 1.04 (d, *J* 6.9, 3H), 0.82 (d, *J* 6.9, 3H). δ_C (75 MHz, $CDCl_3$) 136.9, 121.6, 80.1, 37.2, 31.7, 25.5, 25.0, 22.3, 19.5, 18.7. *m/z* (HR-EI) Found $(M^\bullet)^+$, 232.0458, $C_{10}H_{17}BrO$ requires $(M^\bullet)^+$, 232.0463.

(2-Bromocyclohex-1-en-1-yl)(4-methoxyphenyl)methanol (Table 2, entry 8) was prepared using the procedure described above. Clear colourless oil. R_f 0.3 (1:4, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 3427, 2934, 1725, 1611, 1509, 1247, 1036. δ_H (300 MHz, $CDCl_3$) 7.35 (d, *J* 8.7, 2H), 6.88 (d, *J* 8.7, 2H), 5.97 (s, 1H), 3.80 (s, 3H), 2.57–2.55 (m, 2H), 2.32–2.23 (m, 1H), 1.87–1.53 (m, 5H)/ δ_C (75 MHz, $CDCl_3$) 158.9, 137.7, 133.8, 126.8, 121.2, 113.7, 75.1, 55.4, 37.1, 25.3, 24.9, 22.2. *m/z* (HR-ESI) Found $(M^\bullet)^+$, 296.0241, $C_{14}H_{17}BrO_2$ requires $(M^\bullet)^+$, 296.0412.

(2-Bromocyclohept-1-en-1-yl)(phenyl)methanol (Table 2, entry 9) was prepared using the procedure described above. Clear colourless oil. R_f 0.3 (3:7, v/v EtOAc/hexane). ν_{max}/cm^{-1} 3390, 2934, 1448, 1332, 1017. δ_H (300 MHz, $CDCl_3$) 7.47–7.27 (m, 5H), 6.04 (s, 1H), 2.83 (d, *J* 6.3, 2H), 2.26–2.06 (m, 2H), 1.79–1.55 (m, 4H), 1.37–1.18 (m, 2H). δ_C (75 MHz, $CDCl_3$) 142.8, 141.3, 128.1, 127.1, 125.2, 124.4, 76.4, 41.6, 31.5, 27.8, 26.4, 25.2. *m/z* (HR-ESI) Found $(M+H)^+$, 281.0535, $C_{14}H_{17}BrO$, requires $(M+H)^+$, 281.0536.

(2-Bromo-3,4-dihydronaphthalen-1-yl)(phenyl)methanol (Table 2, entry 10) was prepared using the procedure described above. Clear colourless oil. R_f 0.2 (3:7, v/v EtOAc/hexane). ν_{max}/cm^{-1} 3387, 3027, 2831, 1491, 1448, 1239, 1026. δ_C (300 MHz, $CDCl_3$) 7.56–7.52 (m, 2H), 7.42–7.36 (m, 2H), 7.33–7.25 (m, 2H), 7.16–7.12 (m, 2H), 7.04–6.98 (m, 1H), 6.46 (d, *J* 5.7, 1H), 3.12–2.86 (m, 4H), 2.70 (d, *J* 5.7, 1H, -OH). δ_C (75 MHz, $CDCl_3$) 141.24, 136.08, 135.56, 131.64, 128.37, 127.51, 127.06, 126.92, 126.33, 126.18, 125.63, 125.20, 74.38, 35.93, 29.52. *m/z* (HR-EI) Found $(M+H)^+$, 314.0308, $C_{17}H_{15}BrO$, requires $(M+H)^+$, 314.0306.

1-(2-Bromo-3,4-dihydronaphthalen-1-yl)-2-methylpropan-1-ol (Table 2, entry 11) was prepared using the procedure described above. Clear colourless oil. R_f 0.3 (3:7, v/v EtOAc/hexane). ν_{max}/cm^{-1} 3448, 3061, 2957, 1480, 1016. δ_H (300 MHz, $CDCl_3$) 7.98–7.95 (m, 1H), 7.19–7.12 (m, 3H), 4.84 (d, *J* 10.2, 1H), 2.94–2.72 (m, 4H), 2.37–2.24 (m, 1H), 2.13 (s, 1H, -OH), 1.17 (d, *J* 6.6, 3H), 0.74 (d, *J* 6.6, 3H). δ_C (75 MHz, $CDCl_3$) 136.0, 133.0, 127.7, 127.4, 126.5, 126.2, 125.8, 119.9, 81.2, 36.5, 32.3, 30.1, 20.2, 19.2. *m/z* (HR-EI) Found $(M^\bullet)^+$, 281.0533, $C_{14}H_{17}BrO$, requires $(M^\bullet)^+$, 281.0536.

Procedure for the PCC oxidation to provide β-bromo ketones 9

Bromoalcohols as prepared above (10 mmol) were dissolved in CH_2Cl_2 (30 mL), pyridiniumchloro chromate (2.59 g, 12 mmol) was then added and the mixture allowed to stir for 6–18 h at room temperature. The solution was then diluted with ether (10 mL) and passed through a plug of neutral alumina. The filtrate was concentrated under reduced pressure and the crude residue purified by flash column chromatography to afford, after concentration of the appropriate fractions, the bromo ketones **9**. Yields in Table 2 correspond to the formation of these compounds in two-steps from the starting β-bromo aldehyde.

*(2-Bromocyclohex-1-en-1-yl)(phenyl)methanone (**9a**)* was prepared as a pale yellow oil using the procedure described above and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[17]

*1-(2-Bromocyclohex-1-en-1-yl)ethenone (**9l**)* was prepared as a pale yellow oil using the procedure described above and

provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[18]

1-(2-Bromocyclohex-1-en-1-yl)-2-methylpropan-1-one ***(9m)*** was prepared using the procedure described above. Pale yellow oil. R_f 0.3 (1:9, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 2935, 1695, 1466, 1203, 980. δ_H (300 MHz, $CDCl_3$) 3.13 (quint., *J* 7.2, 1H), 2.55–2.50 (m, 2H), 2.30–2.25 (m, 2H), 1.79–1.68 (m, 4H), 1.14 (d, *J* 7.2, 6H). δ_C (75 MHz, $CDCl_3$) 211.0, 139.6, 119.7, 39.6, 36.1, 29.9, 24.3, 21.5, 18.1.

(2-Bromocyclohex-1-en-1-yl)(4-methoxyphenyl)methanone ***(9n)*** was prepared using the procedure described above. Pale yellow oil. R_f 0.3 (1:9, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 2935, 1660, 1598, 1508, 1253, 1170. δ_H (300 MHz, $CDCl_3$) 7.91 (d, *J* 9.0, 2H), 6.96 (d, *J* 9.0, 2H), 3.88 (s, 3H), 2.62–2.58 (m, 2H), 2.35–2.31 (m, 2H), 1.86–1.77 (m, 4H). δ_C (75 MHz, $CDCl_3$) 196.4, 164.2, 138.1, 132.1, 127.6, 119.7, 114.2, 55.6, 35.6, 29.8, 24.4, 21.6. *m/z* (HR-ESI) Found $(M+H)^+$, 295.0326, $C_{14}H_{15}BrO_2$ requires $(M+H)^+$, 295.0334.

(2-Bromocyclohept-1-en-1-yl)(phenyl)methanone ***(9o)*** was prepared using the procedure described above. Pale yellow oil. R_f 0.3 (1:19, v/v EtOAc/hexane). ν_{max}/cm^{-1} 2925, 1667, 1595, 1448, 1260. δ_H (300 MHz, $CDCl_3$) 7.94–7.91 (m, 2H), 7.56–7.51 (m, 1H), 7.46–7.41 (m, 2H), 2.87–2.84 (m, 2H), 2.35–2.32 (m, 2H), 1.78–1.69 (m, 6H). δ_C (75 MHz, $CDCl_3$) 197.2, 141.8, 134.0, 133.3, 129.3, 128.5, 123.5, 41.4, 31.6, 30.4, 25.8, 25.4. *m/z* (HR-ESI) Found $(M+H)^+$, 279.0379, $C_{14}H_{15}BrO$, requires $(M+H)^+$, 279.0379.

(2-Bromo-3,4-dihydronaphthanen-1-yl)(phenyl)methanone ***(9p)*** was prepared, then directly subjected to cross-coupling, at which point full characterization was performed on **6p**.

1-(2-Bromo-3,4-dihydronaphthalen-1-yl)-2-methylpropan-1-one ***(9q)*** was prepared using the procedure described above. Pale yellow oil. R_f 0.2 (1:19, v/v EtOAc/hexane). ν_{max}/cm^{-1} 3061, 1670, 1593, 1484, 1280. δ_H (300 MHz, $CDCl_3$) 7.20–7.12 (m, 3H), 6.89–6.86 (m, 1H), 3.09 (quint., *J* 6.9, 1H), 2.99–2.93 (m, 2H), 2.86–2.80 (m, 2H), 1.20 (d, *J* 6.9, 6H). δ_C (75 MHz, $CDCl_3$) 209.5, 140.0, 133.2, 131.5, 128.0, 127.9, 126.9, 123.8, 120.6, 41.0, 34.3, 29.2, 17.9. *m/z* (HR-ESI) Found $(M+H)^+$, 279.0379, $C_{14}H_{15}BrO$, requires $(M+H)^+$, 279.0379.

General procedures for the preparation of 1-acyl-2-alkylcycloalkenes 6

Method A: From β-keto enol phosphate 7

1-Acyl-2-alkylcycloalkenes **6** were prepared according to the procedure of Weiler,[8] from the corresponding enol phosphate intermediate **7**. Thus, MeLi (4.0 equiv. of a 1.6-M solution in Et_2O) was added to a stirred solution of CuI (2.0 equiv.) in dry Et_2O at 0°C. The resulting clear solution was cooled to −78°C and phosphate **5** (1.0 equiv.), slowly added. The mixture was maintained at this temperature for 1 h after which time it was quenched with NH_4Cl (saturated aqueous solution), extracted with Et_2O, washed with dilute NH_3 in brine, then brine, the organics were dried ($MgSO_4$), filtered, concentrated, and the crude residue purified via flash column chromatography. Yields of isolated material are reported in Table 1.

Method B: From β-bromo cycloalkenone 9

1-Acyl-2-alkylcycloalkenes **6** were prepared according to Cahiez,[11f] through iron catalyzed coupling with the corresponding β-bromo ketones **9**. Thus, R^2MgBr (1.5 equiv.) was slowly added to a stirred solution of $Fe(acac)_3$ (0.01 equiv.), NMP (9.0 equiv.) and β-bromoketone **7** (1.0 equiv.) in THF at 15°C. The mixture was stirred at room temperature for 1 h then quenched with HCl (1 M aqueous solution) and the phases separated. The aqueous layer was extracted with diethyl ether and washed with $NaHCO_3$ (saturated aqueous solution). The combined organic layers were dried ($MgSO_4$), and the volatiles evaporated. The resulting residue was purified by flash column chromatography. Yields of isolated material are reported in Table 2.

(2-Methylenecyclohex-1-en-1-yl)(phenyl)methanone ***(6a)*** was prepared as a clear colourless oil using both methods A and B and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[2c]

(2-Butylcyclohex-1-en-1-yl)(phenyl)methanone ***(6b)*** was prepared using method A. Clear colourless oil. R_f 0.3 (1:9, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 2928, 1660, 1447, 1277, 1246. δ_H (300 MHz, $CDCl_3$) 7.91–7.88 (m, 2H), 7.59–7.53 (m, 1H), 7.48–7.43 (m, 2H), 2.22–2.19 (m, 2H), 2.14–2.11 (m, 2H), 1.87 (t, *J* 7.8, 2H), 1.74–1.69 (m, 4H), 1.36–1.26 (m, 2H), 1.56–1.08 (m, 2H), 0.74 (t, *J* 7.2, 3H). δ_C (75 MHz, $CDCl_3$) 201.5, 138.3, 136.8, 132.9, 132.3, 129.2, 128.4, 34.7, 30.1, 28.3, 27.5, 22.5, 22.4, 22.2, 13.7. *m/z* (HR-EI) Found $(M)^+$, 242.1666, $C_{17}H_{22}O$ requires $(M)^+$, 242.1671.

(2-Bromophenyl)(2-methylcyclohex-1-en-1-yl)methanone ***(6c)*** was prepared using method A. Clear colourless oil. R_f 0.3 (1:9, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 2932, 1667, 1644, 1430, 1289, 1236. δ_H (300 MHz, $CDCl_3$) 7.57–7.54 (m, 1H), 7.36–7.33 (m, 2H), 7.27–7.21 (m, 1H), 2.23–2.18 (m, 2H), 2.14–2.13 (m, 2H), 1.71–1.70 (m, 3H), 1.66–1.61 (m, 4H). δ_C (75 MHz, $CDCl_3$) 198.9, 145.5, 142.4, 133.3, 132.1, 131.0, 129.2, 127.4, 119.4, 33.5, 26.9, 22.3, 22.1, 21.7. *m/z* (HR-ESI) Found $(M+Na)^+$, 301.0190, $C_{14}H_{15}BrO$ requires $(M+Na)^+$, 301.0204.

(3-Bromophenyl)(2-methylcyclohex-1-en-1-yl)methanone ***(6d)*** was prepared as a clear colourless oil using method A and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[2c]

Furan-2-yl(2-methylcyclohex-1-en-1-yl)methanone ***(6f)*** was prepared using method A. Clear colourless oil. R_f 0.3 (1:19, v/v EtOAc/hexane). ν_{max}/cm^{-1} 2933, 1759, 1643, 1463, 1294, 1018. δ_H (300 MHz, $CDCl_3$) 7.57–7.55 (m, 1H), 7.05–7.03 (m, 1H), 6.48–6.45 (m, 1H), 2.27–2.16 (m, 2H), 2.06–1.97 (m, 2H), 1.64–1.58 (m, 4H), 1.56 (s, 3H). δ_C (75 MHz, $CDCl_3$) 188.5, 152.5, 146.3, 135.9, 131.6, 119.3, 112.1, 31.1, 27.0, 22.3, 22.1, 20.9. *m/z* (HR-ESI) Found $(M+H)^+$, 191.1068, $C_{12}H_{14}O_2$, requires $(M+H)^+$, 191.1067.

(2-Methylcyclohexa-1,3-dien-1-yl)(phenyl)methanone ***(6g)*** was prepared as a clear colourless oil using method A and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[2c]

*(2-methyl-1*H*-inden-3-yl)(phenyl)methanone* ***(6h)*** was prepared as a clear colourless oil using method A and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[2c]

(2-Ethylcyclohex-1-en-1-yl)(phenyl)methanone ***(6i)*** was prepared as a clear colourless oil using method B and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[2c]

Phenyl(2-propylcyclohex-1-en-1-yl)methanone ***(6j)*** was prepared as a clear colourless oil using method B. R_f 0.3 (1:9, v/v EtOAc/hexanes). ν_{max}/cm^{-1} 2929, 1663, 1448, 1245. δ_H (300 MHz, $CDCl_3$) 7.91–7.89 (m, 2H), 7.59–7.50 (m, 1H), 7.46–7.41 (m, 2H), 2.23–2.20 (m, 2H), 2.13–2.10 (m, 2H), 1.86 (t, *J* 7.5, 2H), 1.75–1.66 (m, 4H), 1.42–1.30 (m, 2H), 0.73 (t, *J* 7.5, 3H). δ_C (75 MHz, $CDCl_3$) 201.4, 138.0, 136.9, 132.9, 129.2, 128.4, 127.0, 36.9, 28.2, 27.6, 22.5, 22.2, 21.1,

13.9. *m/z* (HR-EI) Found $(M^{\bullet})^{+}$, 228.1530, $C_{16}H_{20}O$ requires $(M^{\bullet})^{+}$, 228.1514.

(2-(But-3-en-1-yl)cyclohex-1-en-1-yl)(phenyl)methanone ***(6k)*** was prepared as a clear colourless oil using method B and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[2c]

1-(2-Methylcyclohex-1-en-1-yl)methanone ***(6l)*** was prepared as a clear colourless oil using method B and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[19]

2-Methyl-1-(2-methylcyclohex-1-en-1-yl)propan-1-one ***(6m)*** was prepared as a clear colourless oil using method B and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[2c]

(4-Methoxyphenyl)(2-methylcyclohex-1-en-1-yl)methanone ***(6n)*** was prepared as a clear colourless oil using method B and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[2c]

(2-Methylcyclohept-1-en-1-yl)(phenyl)methanone ***(6o)*** was prepared as a clear colourless oil using method B and provided ^{1}H- and ^{13}C-NMR spectra consistent with the reported structure.[2c]

(2-Methyl-3,4-dihydronaphthalen-1-yl)(phenyl)methanone ***(6p)*** was prepared as a clear colourless oil using method B. R_f 0.2 (1:19, v/v EtOAc/hexane). ν_{max}/cm^{-1} 3063, 2957, 1667, 1596, 1448, 1018. δ_H (300 MHz, $CDCl_3$) 8.06–8.02 (m, 2H), 7.58–7.52 (m, 1H), 7.46–7.41 (m, 2H), 7.19 (d, *J* 7.5, 1H), 7.12 (dt, *J* 7.5, 1.2, 1H), 7.04 (dt, *J* 7.5, 1.2, 1H), 6.84 (d, *J* 7.5, 1H), 2.97 (t, *J* 8.4, 2H), 2.42 (t, *J* 8.4, 2H), 1.85 (s, 3H). δ_C (75 MHz, $CDCl_3$) 199.3, 136.9, 136.6, 133.7, 133.3, 133.1, 132.7, 129.3, 128.5, 127.4, 126.5, 126.3, 124.0, 29.5, 27.7, 20.8. *m/z* (HR-ESI) Found $(M+H)^{+}$, 249.1270, $C_{18}H_{16}O$, requires $(M+H)^{+}$, 249.1274.

2-Methyl-1-(2-methyl-3,4-dihydronaphthalen-1-yl)propan-1-one ***(6q)*** was prepared using method B. Clear colourless oil. R_f 0.3 (1:19, v/v EtOAc/hexane). ν_{max}/cm^{-1} 3061, 2957, 1671, 1448, 1282, 1018. δ_H(300 MHz, $CDCl_3$) 7.15–7.11 (m, 3H), 6.80–6.77 (m, 1H), 2.91 (quint., *J* 6.6, 1H), 2.80 (t, *J* 8.1, 2H), 2.28 (d, *J* 8.1, 2H), 1.88 (s, 3H), 1.15 (d, *J* 6.6, 6H). δ_C (75 MHz, $CDCl_3$) 212.9, 136.4, 135.3, 134.5, 132.4, 127.5, 126.7, 126.5, 123.6, 40.9, 29.9, 27.9, 20.8, 18.0. *m/z* (HR-ESI) Found $(M+H)^{+}$, 215.1431, $C_{15}H_{18}O$, requires $(M+H)^{+}$, 215.1430.

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