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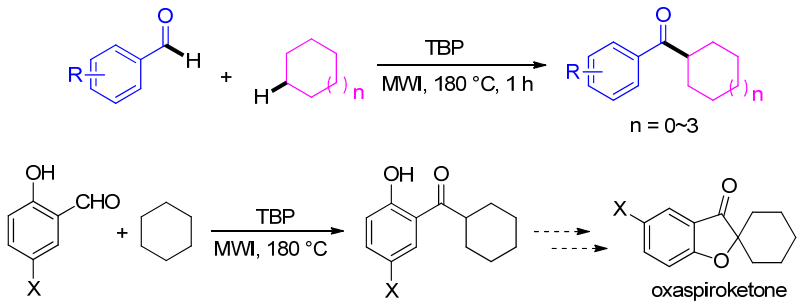
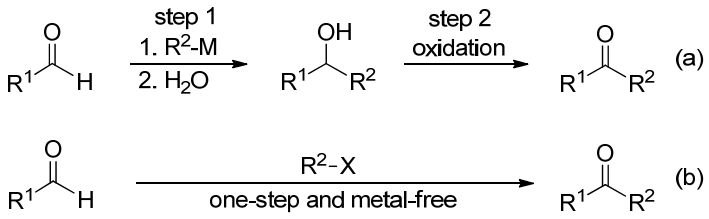


Abstract: In this paper, a novel methodology for the synthesis of ketones *via* microwave irradiation promoted direct alkylation of aldehydes by activation of the inert C(sp^3)−H bond has been developed. Notably, the reactions were accomplished under metal-free conditions and used commercially available aldehydes and cycloalkanes as substrates without pre-functionalization. By using this novel method, an alternative synthetic approach toward the key intermediates for the preparation of the pharmaceutically valuable oxaspiroketone derivatives was successfully established.

INTRODUCTION

Ketones constitute one of the most important classes of organic compounds. The significance of ketones has stimulated extensive studies to develop novel methods for their preparation.[1] As aldehyde is structurally close to ketone and there are numerous aldehydes commercially available or readily obtainable, ketone has been frequently prepared from aldehyde in both academic and industrial arena. In most cases, this protocol is realized through an initial addition of organometallic agent to aldehyde followed by an oxidation of the alcohol intermediate (Scheme 1, (a)).[2] While this approach is generally reliable and efficient, it often suffers from tedious operation procedures and the necessity of using air/moisture sensitive organometallic reagents. Therefore, to develop new synthetic methods to prepare ketones from aldehydes through a one-step procedure without using labile organometallic reagents remains an attractive but still challenging task (Scheme 1, (b)).[3]

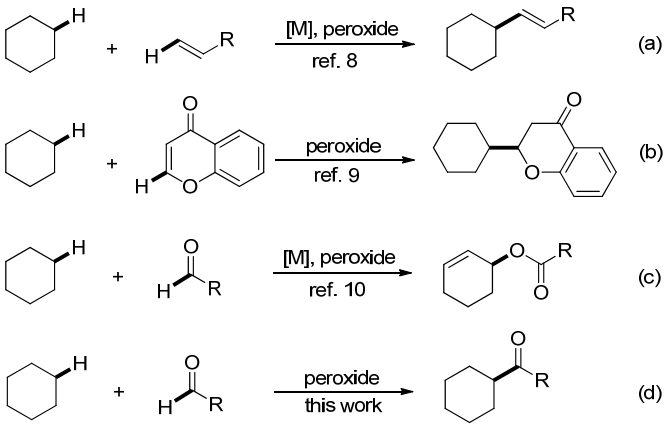
Scheme 1. One- *vs* Two-step Synthesis of Ketone from Aldehyde



Meanwhile, the development of more sustainable transformations is an extensively pursued objective for synthetic community. In this regard, an appealing strategy to replace the existing tedious multi-step protocols to meet the criteria of both atom economy and step economy is through C−H activation as this strategy usually uses the abundant and cheap hydrocarbon compounds as the starting materials without "pre-activation".[4] Among various versions of C−H activation and the following functionalizations developed so far, C−C bond formation *via* C(sp^3)−H activation deserves special attention as alkanes could be readily converted into the corresponding alkyl radicals in the presence of peroxide or other radical inductors.[5,6] In this

aspect, Zhu recently developed a metal-free cascade alkylation of *N*-phenyl-*N*-tosylmethacryl amide with simple alkanes based on a radical process.[7] Wei reported a novel copper-catalyzed direct alkenylation of simple alkanes with styrenes to give (*E*)-alkyl substituted alkenes (Scheme 2, (a)).[8] Han revealed a metal-free oxidative C(sp^3)−H bond activation of alkanes and conjugate addition to chromones (Scheme 2, (b)).[9] Han has also developed a novel synthesis of cycloallyl esters from cycloalkanes and aromatic aldehydes via copper-catalyzed C(sp^3)−H bond activation (Scheme 2, (c)).[10] Promoted by those pioneering studies and based on the fact that radical processes are valued for their excellent functional group tolerance, and inherent ability to be integrated into one-pot cascade processes, we have developed a novel synthesis of aryl cycloalkyl ketones *via* direct alkylation of aryl aldehydes with simple alkanes in the presence of peroxide under microwave irradiation (MWI) through a radical pathway (Scheme 2, (d)). Herein, we wish to report the results of this study.

Scheme 2. Some Radical Reactions of Cyclohexane

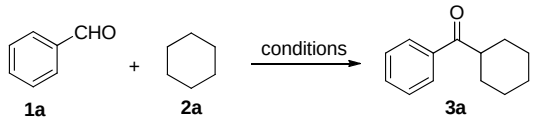


RESULTS AND DISCUSSION

Our study was initiated by treating benzaldehyde (**1a**) with cyclohexane (**2a**) in the presence of di-*tert*-butyl peroxide (TBP) at 120 ^{o}C for 24 h. However, the formation of the expected cyclohexyl(phenyl)methanone (**3a**) was not observed (Table 1, entry 1). When the reaction

temperature was elevated to 140 °C, **3a** could be obtained in a yield of 5% (entry 2). Further studies found that the efficiency improved along with increasing amounts of TBP (entries 3-5). Next, azodiisobutyronitrile (AIBN), benzoyl peroxide (BPO), *tert*-butyl hydroperoxide (TBHP) and dicumyl peroxide (DCP) were also tried. However, they were found to be less effective than TBP (entries 6-9). Considering the fact that previous studies have identified some beneficial effects of copper salts on the radical reactions of alkanes,[11] we then tried a combination of TBP with CuBr, or $Cu(OTf)_2$ as the inductor. Unfortunately, the yield of **3a** did not improve in both cases (entries 10-11). Similarly disappointing was the addition of tetrabutylammonium iodide (TBAI) as an additive (entry 12). Inspired by the fact that MWI has been used as an efficient heating method in a broad variety of chemical reactions and there appear to be good grounds to expect a synergistic alliance of homolytic and MWI methods as reviewed by McBurney,[12] the reaction of **1a** and **2a** was then tried under MWI conditions. We were very pleased to find that the yield of **3a** could be improved to 58% when the reaction was run in the presence of TBP under MWI at 180 °C for 1 h (entry 16). Lower temperatures, shorter/longer reaction period, or using AIBN, BPO, TBHP, or DCP to replace TBP, led to decreased yield (entries 13-22). In order to study the effect of metal salts on this reaction under MWI, it was also carried out in the presence of $Cu(OTf)_2$, $CuBr_2$, CuBr, CuI, $FeCl_2{\cdot}4H_2O$,[13] or $FeCl_3{\cdot}6H_2O$. However, no obvious improvement in the yield of **3a** was observed (entries 23-28). It was also found that a combination of TBHP with $FeCl_2{\cdot}4H_2O$ did not give positive result (entry 29).[13] Moreover, 365 nm cold light-emitting diodes (LED) were used to irradiate the reaction mixture for 1.5 h. It was found that under these conditions, the reaction did occur with or without TBP. However, the yields were relatively poor compared with those obtained under MWI (entries 30, 31). In summary of our optimization study, **3a** could be obtained in 58% yield by treating **1a** with **2a** in the presence of TBP under MWI at 180 °C for 1 h.

Table 1. Optimization for the Synthesis of **3a** [a]



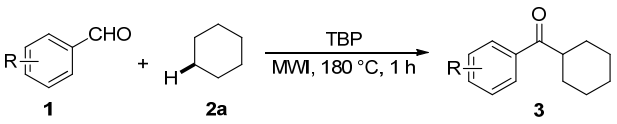
Entry	Inductor (molar ratio)	Irradiation	T/°C	t/h	Yield (%) [b]
1	TBP (2)	-	120	24	-
2	TBP (2)	-	140	24	5
3	TBP (3)	-	140	24	8
4	TBP (4)	-	140	24	12
5	TBP (6)	-	140	24	12
6	AIBN (4)	-	140	24	-
7	BPO (4)	-	140	24	6
8	TBHP (4)	-	140	24	-
9	DCP(4)	-	140	24	7
10	TBP(4)+CuBr(0.2)	-	140	24	5
11	TBP(4)+$Cu(OTf)_2$(0.2)	-	140	24	5
12	TBP(4)+TBAI(0.2)	-	140	24	11
13	TBP (4)	MWI	120	1	trace
14	TBP (4)	MWI	140	1	26
15	TBP (4)	MWI	160	1	39
16	TBP (4)	MWI	180	1	58
17	AIBN (4)	MWI	160	1	0
18	BPO (4)	MWI	160	1	32
19	TBHP (4)	MWI	160	1	0
20	DCP(4)	MWI	160	1	28
21	TBP (4)	MWI	180	0.5	40
22	TBP (4)	MWI	180	1.5	54
23	TBP(4)+$Cu(OTf)_2$(0.2)	MWI	180	1	51
24	TBP(4)+$CuBr_2$(0.2)	MWI	180	1	57
25	TBP(4)+CuBr(0.2)	MWI	180	1	58
26	TBP(4)+CuI(0.2)	MWI	180	1	52
27	TBP(4)+ $FeCl_2 \cdot 4H_2O$(0.2)	MWI	180	1	59
28	TBP(4)+ $FeCl_3 \cdot 6H_2O$ (0.2)	MWI	180	1	56

29	TBHP(4)+ $FeCl_2 \cdot 4H_2O$(0.2)	MWI	180	1	-
30	TBP(4)	UV [c]	rt	1.5	15
31	-	UV [c]	rt	1.5	8

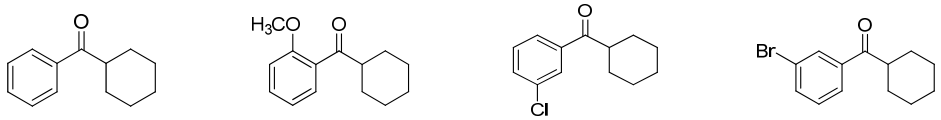
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (10 mL), N_2. [b] Isolated yield. [c] Under 365 nm cold light-emitting diodes (LED).

With the optimized reaction conditions in hand, we then studied the scope of this ketone forming reaction. Firstly, different aryl aldehydes were tested by using cyclohexane (**2a**) as a model substrate. The results listed in Table 2 showed that aldehydes bearing various functional groups including methyl, methoxy, fluoro, chloro, bromo, and trifluoromethyl on the phenyl ring took part in this reaction smoothly to give the expected ketone products in moderate yields. It was noted that substrates with electron-donating group (EDG) gave higher yield than those bearing electron-withdrawing group (EWG). The relatively lower yield of **3l** indicated that steric hindrance might also play a role. Notably, halide groups were well compatible with the reaction conditions to allow further structural elaboration of the ketone products.

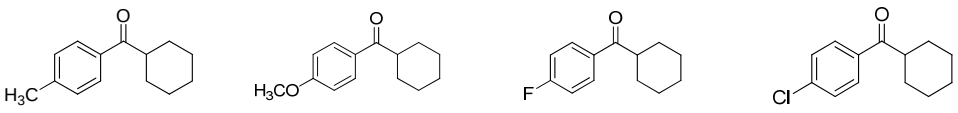
Table 2. Substrate Scope for the Preparation of **3** (I) [a,b]



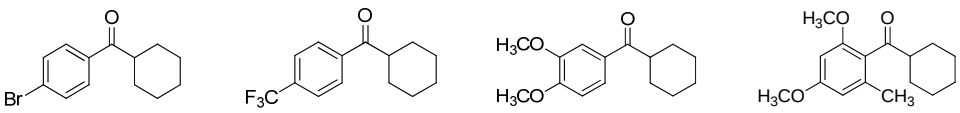
1 **2a** **3**



3a, 58% **3b**, 62% **3c**, 41% **3d**, 42%



3e, 57% **3f**, 66% **3g**, 45% **3h**, 48%

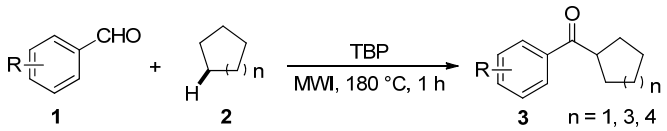


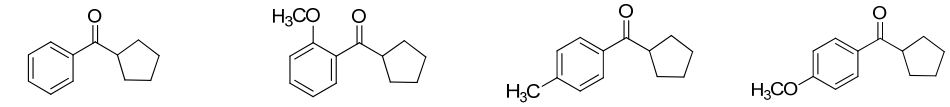
3i, 46% **3j,** 36% **3k**, 64% **3l**, 51%

[a] Reaction conditions: **1** (0.5 mmol), **2a** (10 mL), TBP (2 mmol), MWI, 180 °C, N_2, 1 h. [b] Isolated yield.

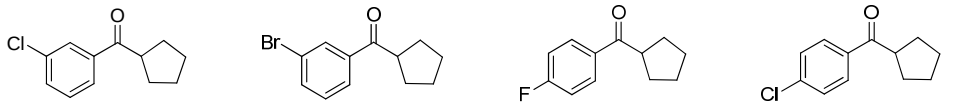
Next, the alkane substrate was extended to cyclopentane (**2b**). It turned out that the reactions of **2b** with aryl aldehydes bearing various functional groups on the phenyl ring proceeded smoothly to give the corresponding aryl cyclopentyl ketones (**3m-3v**, Table 3) in moderate yields. Similar to those of **2a**, reactions of **2b** with aryl aldehydes bearing EDG on the phenyl ring were generally more efficient than those bearing EWG. Furthermore, cycloheptane (**2c**) and cyclooctane (**2d**) were also tried, and they took part in this ketone forming reaction smoothly to give products **3w-3bb** with similar efficiency as those of **2a** and **2b**.

Table 3. Substrate Scope for the Preparation of **3** (II) [a,b]

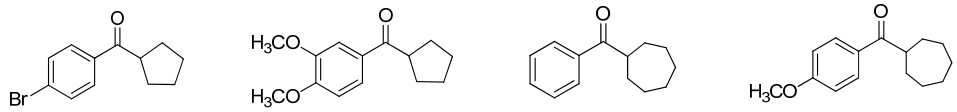




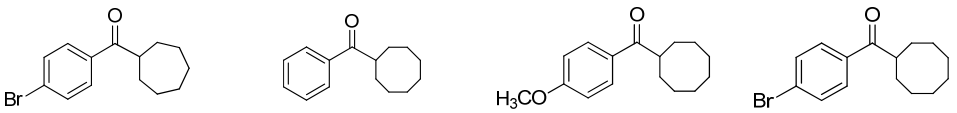
3m, 56% **3n**, 61% **3o**, 56% **3p**, 63%



3q, 39% **3r**, 38% **3s**, 43% **3t**, 44%



3u, 44% **3v**, 62% **3w**, 47% **3x**, 53%



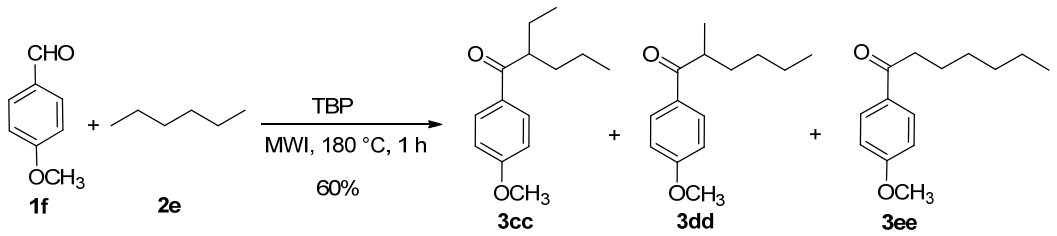
3y, 40% **3z**, 50% **3aa**, 58% **3bb**, 46%

[a] Reaction conditions: **1** (0.5 mmol), **2** (10 mL), TBP (2 mmol), MWI, 180 °C, N_2, 1 h. [b] Isolated yield.

Furthermore, the reaction of *n*-hexane (**2e**) as an example of acyclic alkane with 4-methoxy benzaldehyde (**1f**) was also tried. It turned out that the ketone forming reaction did occur albeit

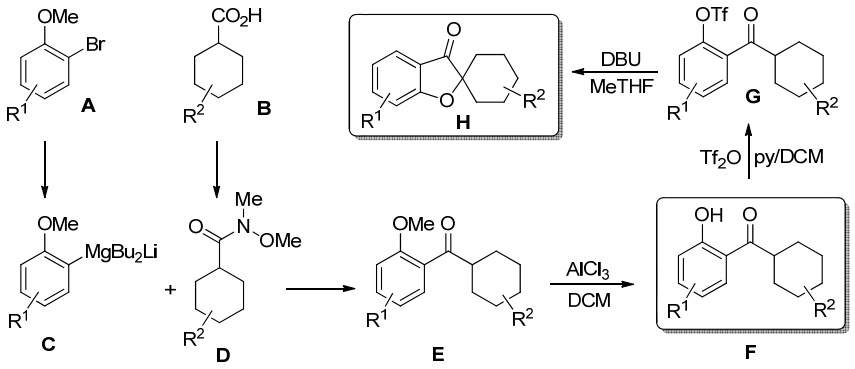
three regio-isomers were obtained as shown in Scheme 3. From these results, it was concluded that the activity of 2°-H toward acylation was much higher than that of 1°-H. The slightly higher yield of C2 acylation product compared with that of C3 acylation product should be an inflection of the steric effect.

Scheme 3. The reaction of 4-methoxybenzaldehyde with *n*-hexane



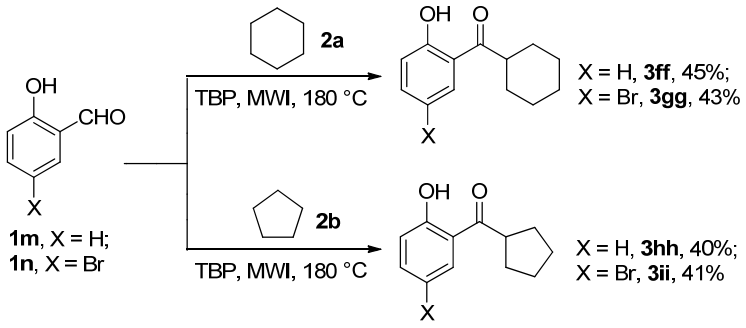
As a further aspect, it has been reported that 3*H*-spiro[benzofuran-2,1'-cyclohexan]-3-one (**H**, Scheme 4) is as a key building unit of potential drugs for the treatment of Alzheimer's disease.[14] Recent studies revealed that this oxaspiroketone derivative could be prepared through the triflation of 2-hydroxyphenyl cyclohexyl ketone (**F**) followed by an intramolecular triflate migration and ring closure of the *in situ* formed enol triflate intermediate.[15] As a key intermediate, **F** was prepared by reacting Weinreb amide **D**, derived from cyclohexyl carboxylic acid (**B)**, with organometallic reagent **C** obtained from 2-bromomethoxybenzene (**A**). While this elegant protocol is currently used by the drug development teams as an efficient and reliable methodology, its sustainability could be compromised by limited atom- and step-economy as the preparation of **F** involved a highly reactive organometallic reagent and there were a lot of atoms of the substrates not assembled into **F**.

Scheme 4. Literature Procedure Leading to Oxaspiroketone



With the aim to develop a more sustainable synthetic approach toward 2-hydroxyphenyl cyclohexyl ketones by taking advantage of the ketone formation method developed in this paper, 2-hydroxybenzaldehyde (**1m**) was treated with **2a** under the standard reaction conditions (Table 1, entry 16). To our delight, the reaction afforded 2-hydroxyphenylcyclohexyl methanone (**3ff**) in a yield of 45% (Scheme 5). Following study revealed that 5-bromo-2-hydroxybenzaldehyde (**1n**) was an equally suitable substrate to give (5-bromo-2-hydroxyphenyl)(cyclohexyl) methanone (**3gg**) in 43% yield. As a further aspect, **1m** and **1n** were found to be also able to react with **2b** to afford the desired 2-hydroxyphenylcyclopentylmethanone (**3hh**) and (5-bromo-2-hydroxyphenyl)(cyclopentyl)methanone (**3ii**) in yields of 40% and 41%, respectively.

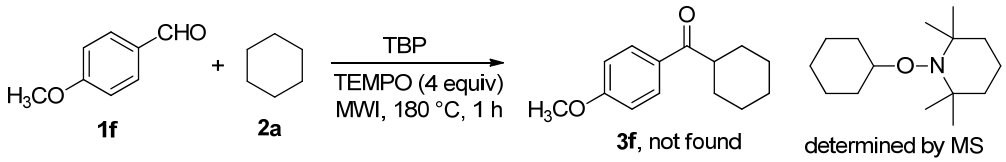
Scheme 5. An Alternative Procedure for the Preparation of 2-Hydroxyphenyl Ketone



To get some insight into the mechanism of this aldehyde alkylation process, some control experiments were carried out. Firstly, 2,2,6,6-tetramethylpiperidine oxide (TEMPO) as a radical scavenger was added in the reaction of 4-methoxybenzaldehyde (**1f**) with cyclohexane (**2a**).

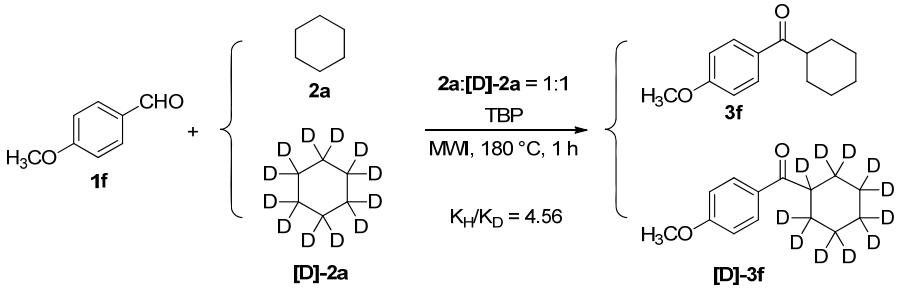
Under this circumstance, the aldehyde alkylation process was completely inhibited and the formation of **3f** was not observed (Scheme 6). This study suggests that the formation of **3f** should involve a single electron transfer (SET) process.

Scheme 6. Control Experiment (I)



Secondly, an intermolecular competing kinetic isotope effect (KIE) experiment was conducted by treating 4-methoxybenzaldehyde (**1f**) with a mixture of cyclohexane (**2a**) and [D]-cyclohexane (**[D]-2a**) under standard conditions as shown in Scheme 7. Consequently, a significant KIE was observed with k_H/k_D = 4.56 (the KIE value was determined based on ^{1}H NMR spectroscopy studies through analyzing the ratio of **3f** and **[D]-3f**). This result indicates that the C(sp^3)−H bond cleavage may be one of the rate-determining steps of this ketone formation reaction.

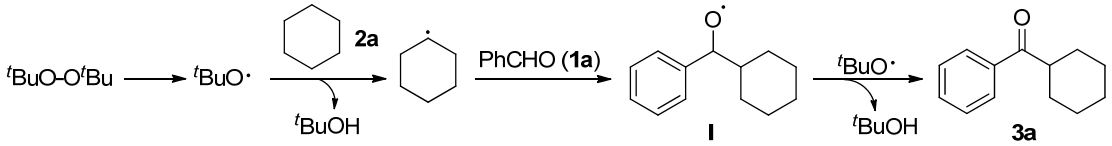
Scheme 7. Control Experiment (II)



Based on the above results and previous reports,[7-10] a plausible mechanism for the formation of **3a** from the reaction of **1a** and **2a** was proposed in Scheme 8. Initially, homolysis of the O−O bond in TBP under the assistance of MWI generates the *tert*-butyoxyl radical. The following hydrogen abstraction of **2a** by the *tert*-butyoxyl radical forms the cyclohexyl radical and

tert-butyl alcohol. Next, addition of the cyclohexyl radical onto the carbonyl group of **1a** leads to the formation of alcohoxyl radical **I**. Finally, abstraction of a hydrogen radical from **I** by another *tert*-butyoxyl radical gives the ketone product **3a**.

Scheme 8. Plausible Mechanism for the Formation of **3a**



As shown in Tables 1~3, an excess amount of cycloalkane (**2**) is usually utilized to act as both substrate and reaction medium in the ketone formation reactions. Therefore, how well to recover and reuse the excess cycloalkane is crucial in determining the sustainability of this protocol. To check the reusability of the excess cyclohexane, the resulting mixture from the reaction of **1a** (0.5 mmol) and **2a** (10 mL) was distillated under reduced pressure to recover 9.2 mL of **2a**. Then, the recovered **2a** was treated with **1a** (0.5 mmol) under standard conditions to give **3a** in a yield of 57%. The recycle test was then carried out for 3 more times, and with the recovered **2a** (8.5 mL, 7.6 mL, 6.6 mL), **3a** was obtained in yields of 55%, 56%, and 53%, respectively.

Finally, in order to showcase the applicability of this ketone forming reaction, a larger scale preparation of cyclohexyl(4-methoxyphenyl)methanone (**3f**) was carried out. Thus, 5 mmol of **1f** (0.68 g) was treated with cyclohexane (**2a**, 55 mL) under standard conditions. Upon completion, the reaction mixture was distillated under reduced pressure to recover **2a**. From the residue, **3f** was separated in a yield of 62%. Furthermore, when the reaction was run with an enlarged scale of 10 mmol (1.36g of **1f**), **3f** could be obtained in a yield of 55%.

CONCLUSION

In conclusion, a novel methodology for the synthesis of ketones *via* direct alkylation of aldehydes with simple alkanes by activation of the inert C(sp^3)−H bond has been developed in this paper. Notably, the ketone formation reactions were realized under metal-free conditions and used commercially available aldehydes and alkanes without pre-functionalization. Interestingly, by using this method, an alternative synthetic approach toward the key intermediates for the preparation of the pharmaceutically valuable oxaspiroketone derivatives was successfully established. With advantages such as economical starting materials, excellent atom-economy, and applicability to a wide range of substrates, we foresee this protocol to be useful in expanding the scaffold space of ketone derivatives as versatile intermediates in synthetic chemistry.

EXPERIMENTAL SECTION

General Methods

All the commercial reagents and solvents were used without further purification. ^{1}H and ^{13}C NMR spectra were determined as $CDCl_3$ solutions. Chemical shifts were expressed in parts per million (δ) downfield from the internal standard tetramethylsilane and were reported as s (singlet), d (doublet), t (triplet), quint (quintuplet), dd (doublet of doublet), tt (triplet of triplet), m (multiplet), etc. The coupling constants *J* were given in Hz. High resolution mass spectra (HRMS) were performed on a time-of-flight (microTOF) mass spectrometer. All reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254 0.25 mm) and components were visualized by observation under UV light (254 and 365 nm). MWI promoted reactions were performed in a commercial microwave reactor (XH-200A, Beijing Xianghu Science and Technology Development Co. Ltd, Beijing, China).

A typical procedure for the synthesis of cyclohexyl(phenyl) methanone (3a): To a reaction tube equipped with a magnetic stirring bar were added benzaldehyde (**1a**, 51 μL, 0.5 mmol), TBP (380 μL, 2 mmol) and cyclohexane (**2a**, 10 mL). The tube was then flushed with nitrogen, sealed and put into a glycerol bath inserted with an external sensor to measure the temperatures during microwave heating in the cavity of a microwave synthesis apparatus. It was then irradiated at 180 °C for 1 h. Upon completion, the resulting mixture was distillated under reduced pressure to recover **2a** for reuse. The residue was purified by column chromatography on silica gel eluting with ethyl acetate/petroleum ether (1:100) to give cyclohexyl(phenyl) methanone (**3a**). **3b**-**3ii** were obtained in a similar manner.

cyclohexyl(phenyl)methanone (3a)[16]: Eluent: ethyl acetate/petroleum ether (1:100); white solid (54.5 mg, 58%); mp: 55-56 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27-1.56 (m, 5H), 1.74-1.77 (m, 1H), 1.84-1.92 (m, 4H), 3.28 (tt, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.54-7.58 (m, 1H), 7.95-7.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.9, 26.0, 29.4, 45.6, 128.3, 128.6, 132.7, 136.4, 203.9. MS: m/z 211 $[MNa]^+$. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{16}ONa$ $[M+Na]^+$ 211.1093, found: 211.1084.

cyclohexyl(2-methoxyphenyl)methanone (3b)[17]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish liquid (67.6 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22-1.44 (m, 5H), 1.66-1.70 (m, 1H), 1.78-1.82 (m, 2H), 1.89-1.93 (m, 2H), 3.19 (tt, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H), 3.89 (s, 3H), 6.95 (d, J = 8.4 Hz, 1H), 6.99 (td, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.40-7.45 (m, 1H), 7.50 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.0, 26.1, 28.8, 50.1, 55.6, 111.3, 120.7, 129.1, 129.8, 132.4, 157.6, 207.4. MS: m/z 241 $[MNa]^+$.

(3-chlorophenyl)(cyclohexyl)methanone (3c)[18]: Eluent: ethyl acetate/petroleum ether (1:100);

yellowish liquid (45.5 mg, 41%); ^{1}H NMR (400 MHz) δ: 1.29-1.55 (m, 5H), 1.74-1.78 (m, 1H), 1.85-1.91 (m, 4H), 3.21 (tt, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.8, 25.9, 29.3, 45.8, 126.3, 128.4, 129.9, 132.7, 135.0, 138.0, 202.7. MS: m/z 245 $[MNa]^+$.

(3-bromophenyl)(cyclohexyl)methanone (3d)[19]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish liquid (55.9 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27-1.52 (m, 5H), 1.74-1.77 (m, 1H), 1.85-1.90 (m, 4H), 3.21 (tt, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 8.07 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.8, 25.9, 29.3, 45.7, 123.0, 126.7, 130.2, 131.3, 135.6, 138.0, 202.5. MS: m/z 289 $[MNa]^+$.

cyclohexyl(p-tolyl)methanone (3e)[20]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish solid (57.6 mg, 57%); mp: 62-63 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26-1.55 (m, 5H), 1.73-1.77 (m, 1H), 1.83-1.90 (m, 4H), 2.42 (s, 3H), 3.26 (tt, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H), 7.27 (d, J = 7.2 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 25.9, 26.0, 29.5, 45.5, 128.4, 129.3, 133.8, 143.6, 203.6. MS: m/z 225 $[MNa]^+$.

cyclohexyl(4-methoxyphenyl)methanone (3f)[21]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish solid (71.9 mg, 66%); mp: 64-65 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26-1.56 (m, 5H), 1.73-1.76 (m, 1H), 1.83-1.89 (m, 4H), 3.23 (tt, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H), 3.87 (s, 3H), 6.94 (dt, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 2H), 7.95 (dt, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.9, 26.0, 29.6, 45.3, 55.4, 113.7, 129.3, 130.5, 163.2, 202.5. MS: m/z 241 $[MNa]^+$.

cyclohexyl(4-fluorophenyl)methanone (3g)[20]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish liquid (46.4 mg, 45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26-1.55 (m, 5H), 1.74-1.77

(m, 1H), 1.85-1.90 (m, 4H), 3.19-3.26 (m, 1H), 7.14 (t, J = 8.8 Hz, 2H), 7.97-8.00 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.8, 25.9, 29.4, 45.6, 115.7 (d, $^2J_{C\text{-}F}$ = 22.3 Hz), 130.9 (d, $^3J_{C\text{-}F}$ = 8.7 Hz), 132.70 (d, $^4J_{C\text{-}F}$ = 2.4 Hz), 165.6 (d, $^1J_{C\text{-}F}$ = 252.5 Hz), 202.3. MS: m/z 229 $[MNa]^+$.

(4-chlorophenyl)(cyclohexyl)methanone (3h)[20]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish solid (53.3 mg, 48%); mp: 62-63 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26-1.54 (m, 5H), 1.74-1.77 (m, 1H), 1.84-1.88 (m, 4H), 3.22 (tt, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.8, 25.9, 29.4, 45.6, 128.9, 129.7, 134.7, 139.3, 202.6. MS: m/z 245 $[MNa]^+$.

(4-bromophenyl)(cyclohexyl)methanone (3i)[20]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish solid (61.2 mg, 46%); mp: 77-78 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26-1.54 (m, 5H), 1.74-1.77 (m, 1H), 1.83-1.88 (m, 4H), 3.21 (tt, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.8, 25.9, 29.3, 45.6, 127.9, 129.9, 131.9, 135.0, 202.9. MS: m/z 289 $[MNa]^+$.

cyclohexyl(4-(trifluoromethyl)phenyl)methanone (3j)[22]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish liquid (46.1 mg, 36%); ^{1}H NMR (400 MHz) δ: 1.27-1.56 (m, 5H), 1.75-1.78 (m, 1H), 1.85-1.92 (m, 4H), 3.23-3.29 (m, 1H), 7.74 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.7, 25.9, 29.2, 46.0, 123.7 (q, $^1J_{C\text{-}F}$ = 270.8 Hz), 125.7 (q, $^3J_{C\text{-}F}$ = 3.9 Hz), 128.6, 134.0 (q, $^2J_{C\text{-}F}$ = 32.6 Hz), 139.1, 202.9. MS: m/z 279 $[MNa]^+$.

cyclohexyl(3,4-dimethoxyphenyl)methanone (3k)[23]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish solid (79.4 mg, 64%); mp: 47-48 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26-1.57 (m, 5H), 1.73-1.76 (m, 1H), 1.84-1.88 (m, 4H), 3.25 (tt, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H), 3.95 (s, 3H), 3.96 (s, 3H), 6.90 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.59 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.9, 26.0, 29.7, 45.2, 56.0, 56.1, 109.9, 110.6, 122.6, 129.6, 149.4, 153.0, 202.7. MS: m/z 271 $[MNa]^+$.

cyclohexyl(2,4-dimethoxy-6-methylphenyl)methanone (3l): Eluent: ethyl acetate/petroleum ether (1:50); yellowish solid (66.8 mg, 51%); mp: 61-62 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.20-1.31(m, 3H), 1.35-1.44 (m, 2H), 1.66-1.68 (m, 1H), 1.77-1.80 (m, 2H), 1.88-1.91 (m, 2H), 2.20 (s, 3H), 2.84 (tt, J_1 = 11.2 Hz, J_2 = 3.2 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 6.31 (s, 1H), 6.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.9, 25.9, 26.0, 28.3, 51.8, 55.3, 55.6, 96.0, 107.0, 124.3, 137.7, 158.1, 160.8, 210.8. HRMS (ESI-TOF) m/z calcd for $C_{16}H_{22}O_3Na$ $[M+Na]^+$ 285.1461, found: 285.1469.

cyclopentyl(phenyl)methanone (3m)[16]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish solid (48.7 mg, 56%); mp: 140-141 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.64-1.78 (m, 4H), 1.91-1.96 (m, 4H), 3.74 (quint, J = 8.0 Hz, 1H), 7.46-7.50 (m, 2H), 7.54-7.58 (m, 1H), 7.98-8.00 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3, 30.0, 46.4, 128.48, 128.52, 132.7, 136.9, 202.9. MS: m/z 197 $[MNa]^+$.

cyclopentyl(2-methoxyphenyl)methanone (3n)[19]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish liquid (62.2 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.52-1.62 (m, 2H), 1.64-1.75 (m, 2H), 1.84-1.89 (m, 4H), 3.71 (quint, J = 8.0 Hz, 1H), 3.89 (s, 3H), 6.95 (d, J = 8.0 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 7.43 (td, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H) , 7.55 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.1, 29.6, 51.2, 55.6, 111.4, 120.6, 129.5, 129.9, 132.6, 157.8, 206.7. MS: m/z 227 $[MNa]^+$.

cyclopentyl(p-tolyl)methanone (3o)[24]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish liquid (52.7 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.63-1.76 (m, 4H), 1.90-1.95 (m, 4H),

2.43 (s, 3H), 3.71 (quint, J = 8.0 Hz, 1H), 7.27 (d, J = 6.8 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.5, 26.3, 30.0, 46.2, 128.6, 129.2, 134.5, 143.4, 202.5. MS: m/z 211 $[MNa]^+$.

cyclopentyl(4-methoxyphenyl)methanone (3p)[24]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish solid (62.3 mg, 63%); mp: 60-61 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.62-1.70 (m, 2H), 1.72-1.78 (m, 2H), 1.89-1.94 (m, 4H), 3.68 (quint, J = 8.0 Hz, 1H), 3.88 (s, 3H), 6.95 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3, 30.1, 46.0, 55.4, 113.6, 130.0, 130.7, 163.2, 201.5. MS: m/z 227 $[MNa]^+$.

(3-chlorophenyl)(cyclopentyl)methanone (3q)[25]: Eluent: ethyl acetate/petroleum ether (1:100); yellow liquid (40.6 mg, 39%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65-1.76 (m, 4H), 1.90-1.96 (m, 4H), 3.67 (quint, J = 8.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.53 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.95 (t, J = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3, 29.9, 46.5, 126.5, 128.6, 129.8, 132.7, 134.9, 138.5, 201.6. MS: m/z 231 $[MNa]^+$.

(3-bromophenyl)(cyclopentyl)methanone (3r)[19]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish liquid (47.9 mg, 38%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.64-1.76 (m, 4H), 1.89-1.95 (m, 4H), 3.66 (quint, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.68 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 8.10 (t, J = 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3, 29.9, 46.5, 122.9, 127.0, 130.1, 131.6, 135.6, 138.7, 201.4. MS: m/z 275 $[MNa]^+$.

cyclopentyl(4-fluorophenyl)methanone (3s): Eluent: ethyl acetate/petroleum ether (1:100); yellowish liquid (41.3 mg, 43%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.62-1.78 (m, 4H), 1.90-1.93 (m, 4H), 3.68 (quint, J = 8.0 Hz, 1H), 7.14 (t, J = 8.4 Hz, 2H), 8.00-8.03 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3, 30.0, 46.3, 115.6 (d, $^2J_{C\text{-}F}$ = 22.2 Hz), 131.1 (d, $^3J_{C\text{-}F}$ = 9.6 Hz),

133.3 (d, $^{4}J_{C\text{-}F}$ = 3.6 Hz), 165.5 (d, $^{1}J_{C\text{-}F}$ = 252.5 Hz), 201.2. HRMS (ESI-TOF) m/z calcd for $C_{12}H_{13}FONa$ $[M+Na]^+$ 215.0843, found: 215.0848.

(4-chlorophenyl)(cyclopentyl)methanone (3t)[26]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish liquid (45.8 mg, 44%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.62-1.78 (m, 4H), 1.91-1.95 (m, 4H), 3.67 (quint, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3, 29.9, 46.3, 128.8, 129.9, 135.2, 139.2, 201.6. MS: m/z 231 $[MNa]^+$.

(4-bromophenyl)(cyclopentyl)methanone (3u)[27]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish liquid (55.4 mg, 44%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65-1.76 (m, 4H), 1.89-1.95 (m, 4H), 3.67 (quint, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3, 29.9, 46.3, 127.8, 130.0, 131.8, 135.6, 201.7. MS: m/z 275 $[MNa]^+$.

cyclopentyl(3,4-dimethoxyphenyl)methanone (3v)[28]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish liquid (72.6 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65-1.74 (m, 4H), 1.89-1.94 (m, 4H), 3.69 (quint, *J* = 8.0 Hz, 1H), 3.94 (s, 3H), 3.95 (s, 3H), 6.90 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3, 30.3, 45.9, 55.9, 56.0, 109.9, 110.6, 122.9, 130.1, 149.0, 153.0, 201.5. MS: m/z 257 $[MNa]^+$.

cycloheptyl(phenyl)methanone (3w)[29]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish solid (47.5 mg, 47%); mp: 170-171 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.55-1.73 (m, 8H), 1.79-1.84 (m, 2H), 1.92-1.97 (m, 2H), 3.42-3.49 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.8, 28.3, 30.8, 46.6, 128.3, 128.6, 132.7, 136.5, 204.3. MS: m/z 225 $[MNa]^+$.

cycloheptyl(4-methoxyphenyl)methanone (3x)[30]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish liquid (61.5 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.53-1.72(m, 8H), 1.79-1.84 (m, 2H), 1.89-1.96 (m, 2H), 3.37-3.43 (m, 1H), 3.88 (s, 3H), 6.95 (dt, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 2H), 7.94 (dt, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.9, 28.3, 31.0, 46.3, 55.5, 113.7, 129.3, 130.6, 163.2, 203.0. MS: m/z 255 $[MNa]^+$.

(4-bromophenyl)(cycloheptyl)methanone (3y): Eluent: ethyl acetate/petroleum ether (1:100); yellowish liquid (56.0 mg, 40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54-1.69 (m, 8H), 1.79-1.83 (m, 2H), 1.90-1.95 (m, 2H), 3.35-3.42 (m, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.80-7.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.7, 28.3, 30.7, 46.6, 127.7, 129.9, 131.9, 135.1, 203.2. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{17}BrONa$ $[M+Na]^+$ 303.0355, found: 303.0359.

cyclooctyl(phenyl)methanone (3z)[31]: Eluent: ethyl acetate/petroleum ether (1:100); yellowish liquid (54.0 mg, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60-1.70 (m, 8H), 1.75-1.81 (m, 4H), 1.85-1.92 (m, 2H), 3.47-3.53 (m, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.95 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.5, 26.59, 26.61, 29.0, 44.9, 128.3, 128.6, 132.7, 136.5, 204.6. MS: m/z 239 $[MNa]^+$.

cyclooctyl(4-methoxyphenyl)methanone (3aa)[32]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish liquid (71.4 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.56-1.69 (m, 8H), 1.74-1.89 (m, 6H), 3.42-3.48 (m, 1H), 3.88 (s, 3H), 6.95 (dt, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 2H), 7.94 (dt, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.6, 26.61, 26.63, 29.3, 44.5, 55.5, 113.7, 129.3, 130.6, 163.2, 203.2. MS: m/z 269 $[MNa]^+$.

(4-bromophenyl)(cyclooctyl)methanone (3bb): Eluent: ethyl acetate/petroleum ether (1:100); yellowish liquid (67.6 mg, 46%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.59-1.66 (m, 8H), 1.73-1.89

(m, 6H), 3.39-3.46 (m, 1H), 7.59-7.63 (m, 2H), 7.79-7.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4, 26.5, 26.6, 28.9, 45.0, 127.8, 129.9, 131.9, 135.2, 203.4. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{19}BrONa$ $[M+Na]^+$ 317.0511, found: 317.0528.

2-ethyl-1-(4-methoxyphenyl)pentan-1-one (**3cc**), 2-ethyl-1-(4-methoxyphenyl)pentan-1-one (**3dd**)[33], and 1-(4-methoxyphenyl)heptan-1-one (**3ee**)[34] were obtained from the reaction of **1f** with **2e** as an unseperable mixture. The molar ratio of **3cc**, **3dd** and **3ee** is 8:10:1, which was determined by ^{1}H NMR. Eluent: ethyl acetate/ petroleum ether (1:50); colorless liquid (66.0 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85-0.89 (m, 4H), 1.17-1.19 (m, 1.5H), 1.24-1.31 (m, 3.5H), 1.42-1.58 (m, 1.5H), 1.72-1.81 (m, 1.5H), 2.91 (t, J = 7.6 Hz, 0.11H), 3.30-3.37 (m, 0.41H), 3.43 (sext, J = 6.8 Hz, 0.53H), 3.85-3.87 (m, 3H), 6.92-6.97 (m, 2H), 7.94-7.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.0, 14.0, 14.1, 14.3, 17.4, 20.8, 22.6, 22.8, 24.6, 25.6, 29.1, 29.7, 31.7, 33.7, 34.5, 38.3, 40.1, 47.0, 55.4, 113.66, 113.73, 113.74, 129.8, 130.3, 130.4, 130.5, 130.9, 163.30, 163.33, 203.2, 203.3. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{20}NaO_2$ $[M+Na]^+$ 243.1361, found: 243.1375.

cyclohexyl(2-hydroxyphenyl)methanone (3ff)[35]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish liquid (45.9 mg, 45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26-1.61 (m, 5H), 1.76-1.79 (m, 1H), 1.87-1.92 (m, 4H), 3.32 (tt, J_1 = 11.6 Hz, J_2 = 3.2 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 7.46-7.50 (m, 1H), 7.80 (d, J = 7.6 Hz, 1H), 12.61 (s , 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.78, 25.85, 29.6, 45.2, 118.3, 118.7, 118.9, 129.8, 136.3, 163.2, 210.2. MS: m/z 227 $[MNa]^+$.

(5-bromo-2-hydroxyphenyl)(cyclohexyl)methanone (3gg)[36]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish solid (60.6 mg, 43%); mp: 82-83 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ:

1.24-1.63 (m, 5H), 1.77-1.80 (m, 1H), 1.88-1.91 (m, 4H), 3.21-3.26 (m, 1H), 6.91 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.87 (s, 1H), 12.53 (s , 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.6, 25.8, 29.5, 45.2, 110.4, 119.5, 120.8, 132.0, 138.8, 162.2, 209.3. MS: m/z 305 $[MNa]^+$.

cyclopentyl(2-hydroxyphenyl)methanone (3hh)[36]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish liquid (38 mg, 40%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.67-1.80 (m, 4H), 1.94-1.99 (m, 4H), 3.77 (quint, J = 8.0 Hz, 1H), 6.90-6.94 (m, 1H), 7.00 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.45-7.50 (m, 1H), 7.82 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 12.56 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3, 30.3, 46.0, 118.5, 118.8, 119.1, 130.3, 136.0, 162.9, 209.3. MS: m/z 213 $[MNa]^+$.

(5-bromo-2-hydroxyphenyl)(cyclopentyl)methanone (3ii)[36]: Eluent: ethyl acetate/petroleum ether (1:50); yellowish liquid (54.9 mg, 41%); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.71-1.77 (m, 4H), 1.94-1.97 (m, 4H), 3.69 (quint, J = 8.0 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.90 (s, 1H), 12.46 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3, 30.3, 46.0, 110.4, 120.2, 120.6, 132.4, 138.7, 162.0, 208.5. MS: m/z 290 $[MNa]^+$.

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Supporting Information. Mechanism studies, Copies of ^{1}H and ^{13}C NMR spectra. This

material is available free of charge *via* the Internet at http://pubs.acs.org.

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