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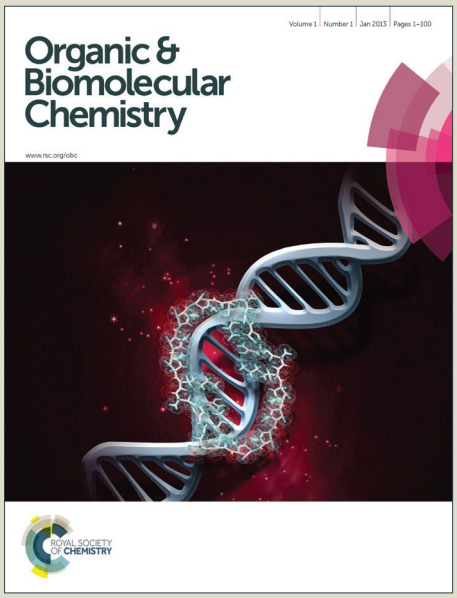

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ARTICLE

Iron (III) chloride hexahydrate-promoted selective hydroxylation and chlorination of benzyl ketone derivatives for construction hetero-quaternary scaffolds

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A novel and tunable α-hydroxylation/α-chlorination of benzyl ketone derivatives has been developed for the construction of hetero-quaternary carbon center by Iron(III) chloride hexahydrate mediated selective transformations through the application of different oxidants, especially the crystal water in catalyst as OH source is firstly reported in this hydroxylation.

Introduction

Selective functionalization of C-H bond at the α-position of ketones has been a classical and important research topic in organic synthesis.[1] Especially, the construction of tertiary α-heteroatom-substituted carbonyl compound through direct functionalization of ketones has attracted the interests of synthetic communities.[2] Among the resulting products, two motifs are of great importance to academic research and industrial field: one is the tertiary α-hydroxyl ketones, and the other is the tertiary α-chloro ketones.

The tertiary α-hydroxyl ketones not only exist in many bioactive compounds (Figure 1), but also serve as the building block for the syntheses of functional molecules.[3] Especially, the rearrangement of these scaffolds and their variants could provide various products via the migration of corresponding alkyl or aryl groups.[4] Although many methods for the preparation of these unique scaffolds have been explored, direct oxidation of the activated C-H bond at the α-position of the easily available ketones is one of the most common strategy.[5] For example, Ritter[5a] and Schoenebeck[5b] reported hydroxylation of C-H bond through Pd- or Cu-catalyzed oxidation of ketone, respectively, while Jiao[5c] and Zhao[5d] independently have developed the base catalyzed similar transformations. However, some drawbacks are involved in these transformations, such as the application of precious metal catalyst, the requirement of relative poisonous reductant, and the preformation under the basic reaction conditions. Therefore, the development of new synthetic method especially under acidic reaction conditions for the preparation of these important units is highly needed.

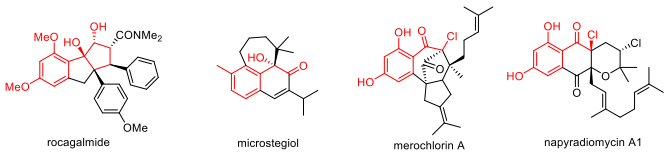

Fig. 1 The selective natural products containing tertiary α-hydroxyl- or α-chloro- ketone scaffold.

In analogy to the tertiary α-hydroxyl ketones, the tertiary α-chlorinated ketones have been used as valuable intermediates and ligands in organic synthesis[6] and are also common scaffolds in numerous bioactive molecules[7] (Figure 1), so the construction of these challenging units has also been an active area in organic synthesis. In many developed synthetic methods, the direct introduction of a chlorine atom in the corresponding ketones is a commonly used approach.[8] However, some shortcomings still exist. Consequently, the exploitation of new approach for the preparation of the tertiary α-chlorinated ketones is of great necessary.

Considering two abovementioned valuable synthetic motifs, and our continuing research interests in "three birds with one stone" chemical reagents,[9] we speculated that $FeCl_3·6H_2O$,[10] which has shown excellent properties, such as inexpensiveness, easily availability, low-toxicity, insensitivity for moisture and air in organic synthesis, could be used as both Lewis acid and OH or Cl source for the construction of the tertiary α-hydroxyl ketones or the tertiary α-chlorinated analogues under suitable reaction conditions. Herein, we report $FeCl_3·6H_2O$ mediated selective hydroxylation/chlorination of benzyl ketones through the switch of reaction conditions.

Results and discussion

Initially, we started our research for the hydroxylation of the commercially available 2-phenylcyclohexanone. However, there were some tough problems to be solved in this

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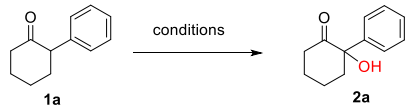
Table 1. Selected optimization of reaction condition[a]



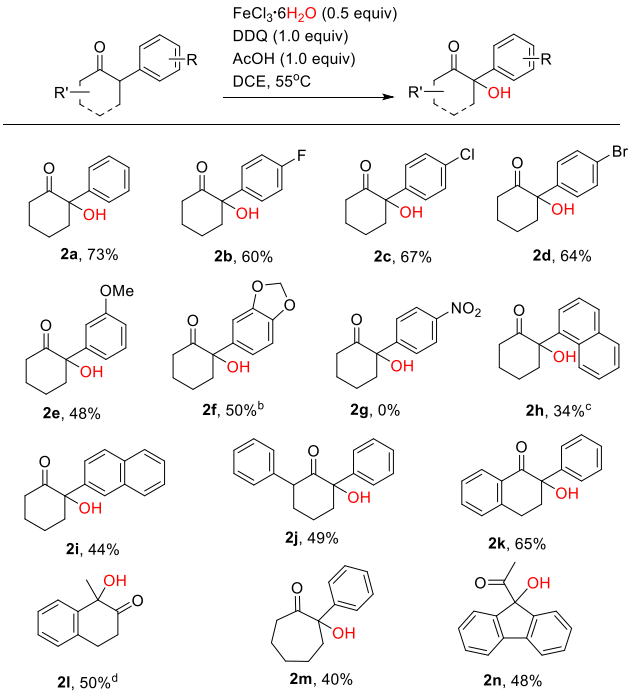
entry	cat. (0.5 equiv)	solv.	ox. (equiv)	additives (equiv)	temp.	yield[b]
1	$FeCl_3·6H_2O$	DCE	DDQ[c] (1.0)	-	RT	48%
2	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	-	45°C	55%
3	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	-	55 °C	56%
4	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	-	65 °C	61%
5	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	-	75 °C	57%
6	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	-	85 °C	36%
7	$FeCl_3·6H_2O$	DMF	DDQ (1.0)	-	65 °C	0
8	$FeCl_3·6H_2O$	DMSO	DDQ (1.0)	-	65 °C	0
9	$FeCl_3·6H_2O$	THF	DDQ (1.0)	-	65 °C	0
10	$FeCl_3·6H_2O$	CH_3NO_2	DDQ (1.0)	-	65 °C	trace
11	$FeCl_3·6H_2O$	toluene	DDQ (1.0)	-	65 °C	trace
12	$FeCl_3·6H_2O$	hexane	DDQ (1.0)	-	65 °C	trace
13	$FeCl_3·6H_2O$	CH_3CN	DDQ (1.0)	-	65 °C	19%
14	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	$PhCO_2H$ (1.0)	55 °C	70%
15	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	Picolinic acid(1.0)	55 °C	18%
16	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	Me_3CCO_2H (1.0)	55 °C	64%
17	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	HCO_2H (1.0)	55 °C	71%
18	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	CH_3CO_2H (1.0)	55 °C	73%
19	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	CF_3CO_2H (1.0)	55 °C	70%
20	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	CH_3CO_2H (0.5)	55 °C	56%
21	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	CH_3CO_2H (2.0)	55 °C	48%
22	$FeCl_3·6H_2O$	DCE	DDQ (1.0)	CH_3CO_2H (4.0)	55 °C	40%
23	$FeCl_3·6H_2O$	DCE	-	CH_3CO_2H (1.0)	55 °C	trace
24	-	DCE	DDQ (1.0)	CH_3CO_2H (1.0)	55 °C	0
25	$Fe(OTs)_3·6H_2O$	DCE	DDQ (1.0)	CH_3CO_2H (1.0)	55 °C	35%
26	$Fe(NO_3)_3·9H_2O$	DCE	DDQ (1.0)	CH_3CO_2H (1.0)	55 °C	trace
27	$FeCl_3$[d]	DCE	DDQ (1.0)	CH_3CO_2H (1.0)	55 °C	trace
28	$FeCl_3$[e]	DCE	DDQ (1.0)	CH_3CO_2H (1.0)	55 °C	62%
29	$FeCl_3·6H_2O$[f]	DCE	DDQ (1.0)	CH_3CO_2H (1.0)	55 °C	29%

a) Reactions were performed using 2-phenylcyclohexanone (0.2 mmol) in 2.0 mL solvent at the noted temperature under an argon atmosphere; b) isolated yield; c) DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; d) the anhydrous $FeCl_3$ was prepared according the reported method; e) 0.5 equiv $FeCl_3$ and 3.0 equiv H_2O was used; f) Reaction was performed under air atmosphere.

transformation: 1) the competitive C-C bond cleavage of the α-position of the ketone other than C-H bond hydroxylation or chlorination have been reported;[2d,5b,11] 2) the intermolecular oxidative self-coupling product would be produced in the presence of $FeCl_3$;[12] 3) to our best knowledge, crystal water contained in the hydrated metal salt serves as OH source was seldom investigated,[13] although free water has been extensively studied and applied as the same purpose; 4) especially, how to control the selectivity of hydroxylation and chlorination through the adjustment of experimental parameters is a challenging issue. To our delight, the desired product **2a** was isolated in 48% yield in the presence of 50% $FeCl_3·6H_2O$ in 1,2-dichloroethane (DCE) under an argon atmosphere at room temperature after 2 days (entry 1, Table 1). Encouraged by this initial result, we conducted the reaction at various temperatures, and the results indicated that the product **2a** was obtained with 61% yield at 65 °C, and decreasing or increasing reaction temperature are adverse for this transformation (entries 2-6, Table 1). Then the reaction were performed in different solvents, and it was revealed that solvent strongly affected this transformation; no reaction occurred in DMF, DMSO and THF (entries 7-9, Table 1), might be due to the strong coordinating effect between iron (III) and oxygen atom in DMSO, DMF, THF, and CH_3NO_2 which reduced the Lewis acid activity of Iron (III), resulting in the suppressing of the initial enloted process, while product **2a** could be isolated with 19% yield in CH_3CN (entry 13, Table 1). Other oxidants did not give better result.[14] When the acidic additives were introduced to the reaction systems at 65 °C, no obvious improvement of the yield was observed, however, the additives were beneficial for this reaction at 55 °C, in which the best yield of 73% was obtained by the use of acetic acid (entries 14-19, Table 1); So the amount of acetic acid was further investigated, however, no superior results were obtained (entries 20-22, Table 1). The loading of $FeCl_3·6H_2O$ did not affect obviously the yield of product.[14] In the absence of $FeCl_3·6H_2O$ or DDQ, no desired product **2a** was isolated (entries 23-24, Table 1). Other Iron salt hydrates were also tested.[14] Among them, 50% $Fe(OTs)_3·6H_2O$ could promote the reaction in 35% yield, while $Fe(NO_3)_3·9H_2O$ was inefficient (entries 25-26, Table 1). Further screening other metal salt hydrates or the addition of water (entry 28, table 1) could not improve the yield.[14] So 50% $FeCl_3·6H_2O$, DDQ (1.0 eq.) and AcOH (1.0 eq.) in DCE at 55°C under an argon atmosphere were selected as the optimal reaction conditions.

With the optimal reaction conditions in hand, we turned our attention to expand the substrate scope, and the reaction results were shown in Scheme 1. The substituents on the aryl ring had an obvious effect on the reaction results. For examples, the substrates bearing the slight electronic-withdrawing F, Cl or

Scheme 1 Scope of hydroxylation substrates [a]



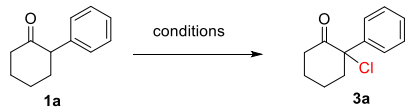
a) Unless noted, reactions were performed using 2-phenylcyclohexanone derivatives (0.2 mmol) in 2.0 mL DCE at 55 °C under an argon atmosphere; b) the reaction was performed at 18 °C; c) the reaction was performed at 0 °C; d) the reaction was performed at rt.

Br group at the *p*-position afforded the expected product **2b**-**2d** in good yield. Similarly, the electronic-donating OMe or piperonyl group on the aryl ring were tolerated, led to the desired product **2e** and **2f** in 48% and 50% yield, respectively. However, strong electronic-withdrawing NO_2 group on the aryl ring didn't afford the desired product **2g**. Substrates with a naphthyl ring reacted smoothly, although the yield of 1-naphthyl product **2h** was slightly lower than that of 2-naththyl analogue **2i**, which might be due to the steric hindrance effect. Interestingly, the mono-hydroxylated product **2j** was isolated in 49% yield, even though dual reaction positions existed in 2, 6-diphenylcyclohexanone. When 2-phenyl-3, 4-dihydronaphthalen-1(*2H*)-one was subjected to the optimal conditions, the expected product **2k** was obtained in 65% yield. *α*-Methyl-*β*-tetralone also afforded the *α*-hydroxy-*α*-methyl-*β*-tetralone **2l** at room temperature. The derivative of cycloheptanone gave the expected product **2m**, albeit with 40% yield. It is noteworthy that non-cyclic 1-(*9H*-fluoren-9-yl) ethan-1-one was also an ideal substrate, producing the desired product **2n** in 48% yield.

Interestingly, the chlorinated product **3a** was isolated in 52% yield using Dess-Martin periodinane (DMP) as oxidant and DCE as solvent in the investigative processes of the hydroxylation reaction (entry 1, Table 2). Therefore, after completing the substrates investigation of the hydroxylation, we turned our efforts to explore the optimal conditions for chlorination of 2-phenylcyclohexanone (Table 2). Solvents screening demonstrated that the best result was obtained in a mixture solvent (ethyl acetate/AcOH = 1 : 1) at room temperature, while no product **3a** was isolated when the reaction was conducted in THF, DMSO, or CF_3CO_2H (entries 2-9, Table 2). Further screening of oxidants indicated that the similar result was obtained using IBX to replace DMP, while only trace amount of product **3a** was observed using Na_2IO_4, $K_2S_2O_8$ or H_2O_2 as oxidant (entries 11-13, Table 2). Notably, O_2 or air using as oxidant led to the unexpected C-C bong cleavage process, resulting in the cycle-opening product[2d, 5b] (entries 14-15, Table 2). The amount of $FeCl_3{\cdot}6H_2O$ obviously affected the yield of product **3a** (entries 16-19, Table 2). Replacement of $FeCl_3{\cdot}6H_2O$ with other metal hydrate were inefficient for this transformation (entries 20-22, Table 2), but the product **3a** was isolated in 13% yield in the presence of $FeCl_2{\cdot}4H_2O$ (entry 23, Table 2). Increasing or lowing the amount of DMP was not beneficial for this transformation (entries 24-26, Table 2). Therefore, 200% $FeCl_3{\cdot}6H_2O$, DMP (1.2 equiv) in EA/AcOH at room temperature under an argon atmosphere (entry 9, Table 2) were used as the optimal chlorination conditions for the next investigation.

Under the optimal reaction conditions, a series of substrates were tested, and the results are summarized in Scheme 2. Among the substrates tested, the corresponding products **3a**-**3d** and **3f**-**3i** were isolated in moderate to good yield. The slight electronic-drawing groups on the aryl ring did not affect the reaction results, and the desired products bearing *p*-F, *p*-Cl, and *p*-Br on the aryl ring could be isolated in good yields. It is noteworthy that the product **3e** bearing strong electron-donating OMe at *meta*-position was not isolated, while the product **3f** bearing strong electron-withdrawning NO_2 on aryl ring was obtained in 34% yield, which are different from the results of hydroxylation. Similar to the hydroxylation, the mono-chlorinated product **3g** was also isolated as a major product. Non-cyclic ketone could afford the products **3h** under the optimal

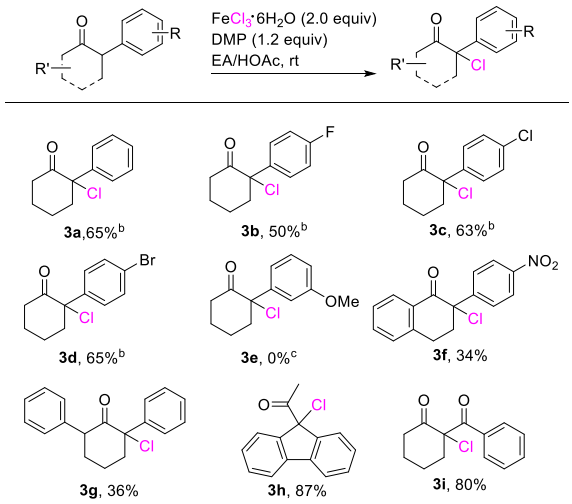
Table 2. Selected optimization of reaction condition[a]



Entry	Metal hydrate (equiv)	Oxidant (equiv)	Solvent	Yield (%)[b]
1	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP[c] (1.2)	DCE	52
2	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP (1.2)	hexane	45
3	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP (1.2)	toluene	31
4	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP (1.2)	DMSO	trace
5	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP (1.2)	THF	trace
6	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP (1.2)	ethyl acetate	63
7	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP (1.2)	AcOH	71
8	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP (1.2)	CF_3CO_2H	trace
9	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP (1.2)	EA/AcOH	72
10	$FeCl_3{\cdot}6H_2O$ (2.0)	IBX (1.2)	EA/AcOH	70
11	$FeCl_3{\cdot}6H_2O$ (2.0)	H_2O_2 (1.2)	EA/AcOH	trace
12	$FeCl_3{\cdot}6H_2O$ (2.0)	Na_2IO_4 (1.2)	EA/AcOH	57
13	$FeCl_3{\cdot}6H_2O$ (2.0)	$K_2S_2O_8$ (1.2)	EA/AcOH	13
14	$FeCl_3{\cdot}6H_2O$ (2.0)	O_2	EA/AcOH	trace
15	$FeCl_3{\cdot}6H_2O$ (2.0)	air	EA/AcOH	trace
16	$FeCl_3{\cdot}6H_2O$ (1.0)	DMP (1.2)	EA/AcOH	58
17	$FeCl_3{\cdot}6H_2O$ (1.5)	DMP (1.2)	EA/AcOH	60
18	$FeCl_3{\cdot}6H_2O$ (2.5)	DMP (1.2)	EA/AcOH	66
19	$FeCl_3{\cdot}6H_2O$ (3.0)	DMP (1.2))	EA/AcOH	57
20	$CoCl_2{\cdot}6H_2O$ (2.0)	DMP (1.2)	EA/AcOH	0
21	$NiCl_2{\cdot}6H_2O$ (2.0)	DMP (1.2)	EA/AcOH	trace
22	$CuCl_2{\cdot}2H_2O$ (2.0)	DMP (1.2)	EA/AcOH	trace
23	$FeCl_2{\cdot}4H_2O$ (2.0)	DMP (1.2)	EA/AcOH	13
24	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP (0.8)	EA/AcOH	66
25	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP (1.5)	EA/AcOH	72
26	$FeCl_3{\cdot}6H_2O$ (2.0)	DMP (2.0)	EA/AcOH	62
27	$FeCl_3{\cdot}6H_2O$ (2.0)	-	EA/AcOH	trace

a) Reactions were performed using 2-phenylcyclohexanone (0.2 mmol) in 2.0 mL solvent at the room temperature under an argon atmosphere; b) the NMR yield; c) DMP = Dess-Martin periodinane; d) IBX = 2-Iodoxybenzoic acid; e) EA = Ethyl acetate

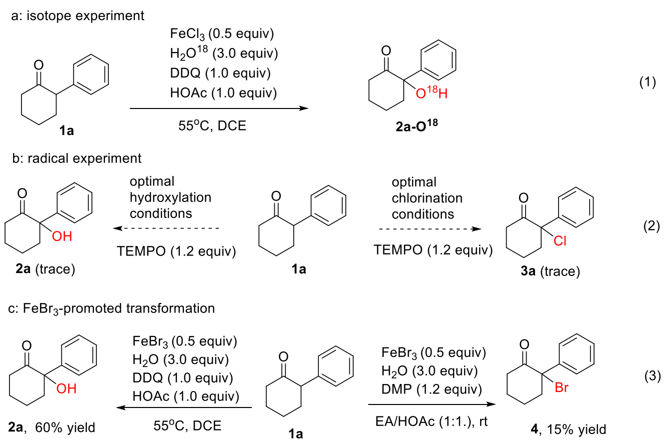
Scheme 2. Scope of hydroxylation substrates[a]



a) Unless noted, reactions were performed using 2-phenylcyclohexanone derivatives (0.2 mmol) in 2.0 mL EA/HOAc (v/v = 1:1) at rt under an argon atmosphere; b) Isolated by HPLC; c) the complex mixture was observed.

conditions. Notably, 1,3-dicarboyl compound was also an ideal substrate, providing the expected product **3i** in 80% yield. Because some functional groups such as F, Cl, Br, NO_2 on the aryl ring could be tolerated in this transformation, the resulting products could be further convert to other valuable synthetic intermediates or couple with other reaction partner for the construction of more complex functional molecules.

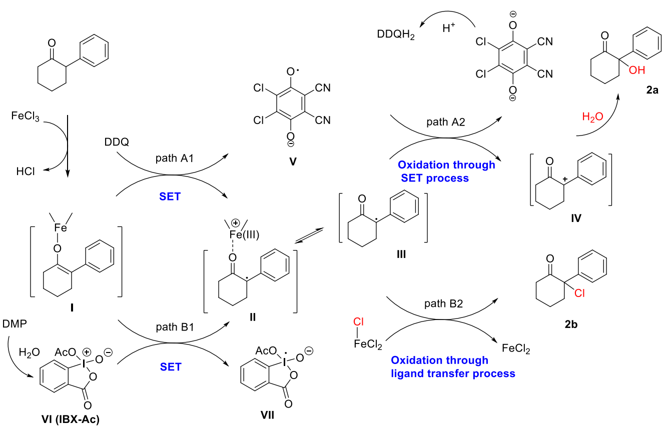
In order to elucidate the reaction mechanism, some control experiments were carried out. When $FeCl_3{\cdot}6H_2O$ was replaced by anhydrous $FeCl_3$[15] (entry 27, Table 1), only trace amount of product **2a** was observed, and the result proved that the hydroxyl group in product **2a** should be derived from the crystal water in $FeCl_3{\cdot}6H_2O$. Moreover, the product **2a** was isolated in 62% yield when the additional water was introduced in reaction system (entry 27, Table 1). In order to further prove the source of hydroxyl group, the isotope experiment was performed. When the combination of $FeCl_3$ (0.5 equiv) and H_2O^{18} (3.0 equiv) was used under the optimal hydroxylation reaction conditions, the product **2a-O^{18}** could be isolated (eq. 1, Scheme 3). This result confirmed that the OH group was derived from water. While the model reaction was conducted under air atmosphere, the product **2a** was isolated in only 29% yield (entry 28, Table 1), stating that air suppress obviously the hydroxylation reaction, hence a radical process maybe involve in this transformation. Moreover, in the presence of radical scavenger 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), the desired product **2a** or **3a** was observed only in trace amount (eq. 2, Scheme 3), indicating a radical intermediate could be involved in the both of hydroxylation and chlorination processes. Furthermore, the obvious substituent effect on the aryl ring demonstrated that the hydroxylation and chlorination might go through two different approaches (Scheme 1 and 2). Replacing $FeCl_3{\cdot}6H_2O$ with weak Lewis acid $CoCl_2{\cdot}6H_2O$, $CuCl_2{\cdot}2H_2O$, or $NiCl_2{\cdot}6H_2O$ were inefficient for both of the hydroxylation and the chlorination transformation,[14] revealing that the enolization process would be vital in above two transformations. Importantly, the replacement $FeCl_3{\cdot}6H_2O$ with $FeBr_3$ and H_2O, the hydroxylation product **2a** was isolated in 60% yield under the optimal hydroxylation conditions (eq. 3, Scheme 3), while the bromation product **4**[16] was also obtained under the optimal chloronation conditions, albeit with 15% yield. Additionally, *o*-iodoxybenzoic acid (IBX) as oxidant couldn't obviously effect the



Scheme 3. Some control experiments.

chlorination results (entry 9, Table 3), demonstrating that the IBX-Ac, serves as the possible active oxidant, involve the chlorination process.

Based on these experiment results and the previous studies,[17] a plausible reaction mechanism is proposed, although other possible mechanisms cannot be excluded at this stage. The substrate **1a** is enolized inspired by $FeCl_3$, which serves as Lewis acid, and the intermediate enolate is oxidized by DDQ to give α-keto radical **II**. The resulted radical **II** could be further oxidized to anion **IV**[17e] by oxidant **V** derived from DDQ, and the anion **IV** is trapped by H_2O to provide the hydroxylation product **2a**. For the chlorination process, the DMP reacted with water to produce compound **VI** (IBX-Ac),[18] which act as active oxidant to oxidize the enolized intermediate **I**, and the α-keto radical **III** is generated through a SET process. The resulting radical **III** could be further oxidized by $FeCl_3$ to give the product **3a**, in which $FeCl_3$ serves as a ligand transfer reagent.[6a, 17a-d]



Scheme 4. The proposed reaction mechanism.

Conclusions

In summary, we have developed a controllable and direct $FeCl_3{\cdot}6H_2O$ mediated α-hydroxylation/α-chlorination of benzylketone derivatives through the switch of different oxidants, in which the $FeCl_3{\cdot}6H_2O$ serves as both Lewis acid and OH or Cl source. The procedure could provide the products bearing a hetero-quaternary motif in moderate to good yield. Especially, the crystal water in catalyst as OH source is firstly reported in the hydroxylation process.

Experimental section

General Information

All solvents were purified using standard techniques and distilled prior to use. All reagents obtained from commercial sources and were directly used without further purification, unless otherwise noted.

All reactions were monitored by thin-layer chromatography (TLC). Flash chromatography was carried out on 200–300 mesh silica gel, eluting with a mixture of petroleum ether (b.p. 60–90 °C) and ethyl acetate or petroleum ether (b.p. 60–90 °C) and dichloromethane, unless otherwise noted.

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^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on 400 spectrometer or a 300BB spectrometer. Coupling constants (*J*) were reported in hertz (Hz). Electron ionization mass spectra (EI-MS) were measured on a spectrometer by direct inlet at 70 eV and signals were given in m/z with relative intensity (%) in brackets. High-resolution mass spectra (HRMS) were measured on a Mass Spectrometer by means of the ESI technique. High Performance Liquid Chromatography (HPLC) equipped with a UV-detector.

Preparation of substrates

Besides commercially available 2-phenylcyclohexan-1-one, 2-(3-methoxyphenyl)cyclohexan-1-one, 2,6-diphenylcyclohexan-1-one, 1-methyl-3,4-dihydronaphthalen-2(1H)-one and 2-benzoylcyclohexan-1-one, other substrates were prepared according to the reported procedures.[19-26]

General Hydroxylation Procedure.

Under an argon atmosphere, to a stirred suspension of 2-phenylcyclohexan-1-one (34.9 mg, 0.20 mmol), DDQ (45.4 mg, 0.20 mmol, 1.0 equiv) and $FeCl_3{\cdot}6H_2O$ (27.0 mg, 0.10 mmol, 0.5 equiv) in DCE (2.0 mL) was added acetic acid (11.4 μL, 0.20 mmol, 1.0 equiv) at room temperature, then the mixture was stirred at 55 °C. After the starting material disappeared, the reaction mixture was allowed to cool to room temperature, and diluted with 1.0 mL petroleum ether. The crude product was directly purified by flash column chromatography with petroleum ether/ethyl acetate as eluent to afford the desired product **2a**.

2-hydroxy-2-phenylcyclohexan-1-one (**2a**).[5c] 73% yield, 27.8 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41-7.38 (m, 2 H), 7.34-7.30 (m, 3 H), 4.48 (s, 1 H), 3.02-2.98 (m, 1 H), 2.56-2.52 (m, 1 H), 2.47-2.39 (m, 1 H), 2.09-2.03 (m, 1 H), 1.90-1.82 (m, 2 H), 1.81-1.68 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.9, 140.1, 129.3, 128.5, 126.5, 80.2, 39.1, 39.0, 28.5, 23.2; **MS** (EI) *m/z* (%): 55 (42), 77 (72), 91 (28), 105 (81), 120 (100), 190 (24).

2-(4-fluorophenyl)-2-hydroxycyclohexan-1-one (**2b**). 60% yield, 25.1 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.27 (m, 2 H), 7.10-7.06 (m, 2 H), 4.51 (s, 1 H), 2.97-2.93 (m, 1 H), 2.56-2.52 (m, 1 H), 2.44-2.36 (m, 1 H), 2.11-2.04 (m, 1 H), 1.91-1.83 (m, 2 H), 1.77-1.71 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.6, 162.2 (d, *J* = 246 Hz), 136.0 (d, *J* = 3 Hz), 128.4 (d, *J* = 8 Hz), 116.2 (d, *J* = 22 Hz), 79.6, 39.2, 38.9, 28.5, 23.2; **MS** (EI) *m/z* (%): 123 (53), 138 (40), 151 (100), 180 (62), 208 (15); **HRMS** (ESI) *m/z* calculated for $C_{12}H_{13}FO_2Na$ [M+Na$^+$] 231.0792, found 231.0789.

2-(4-chlorophenyl)-2-hydroxycyclohexan-1-one (**2c**). 67% yield, 30.1 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.4 Hz, 2 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 4.51 (s, 1 H), 2.96-2.91 (m, 1 H), 2.57-2.53 (m, 1 H), 2.43-2.35 (m, 1 H), 2.10-2.05 (m, 1 H), 1.91-1.83 (m, 2 H), 1.77-1.68 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.3, 138.7, 134.4, 129.4, 128.0, 79.6, 39.1, 38.9, 28.4, 23.2; **MS** (EI) *m/z* (%): 111 (11), 139 (61), 154 (48), 167 (100), 169 (35), 196 (31), 224 (12); **HRMS** (ESI) *m/z* calculated for $C_{12}H_{13}ClO_2Na$ [M+Na$^+$] 247.0496, found 247.0494.

2-(4-bromophenyl)-2-hydroxycyclohexan-1-one (**2d**). 64% yield, 34.5 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 4.51 (s, 1 H), 2.96-2.91 (m, 1 H), 2.57-2.53 (m, 1 H), 2.43-2.34 (m, 1 H), 2.10-2.06 (m, 1 H), 1.89-1.82 (m, 2 H), 1.76-1.70 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.3, 139.2, 132.4, 128.3, 122.6, 79.7, 39.0, 38.9, 28.4, 23.2; **MS** (EI) *m/z* (%): 25 (25), 77 (27), 132 (100), 183 (35), 198 (34), 211 (31), 240 (18), 268 (12); **HRMS** (ESI) *m/z* calculated for $C_{12}H_{17}BrO_2N$ [M+NH$_4^+$] 286.0437, found 286.0433.

2-hydroxy-2-(3-methoxyphenyl) cyclohexan-1-one (**2e**). 48% yield, 21.2 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.29 (m, 1 H), 6.89-6.85 (m, 3 H), 4.50 (s, 1 H), 3.80 (s, 3 H), 3.00-2.95 (m, 1 H), 2.55-2.40 (m, 2 H), 2.08-2.02 (m, 1 H), 1.88-1.67 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.7, 160.3, 141.5, 130.3, 118.7, 113.5, 112.5, 80.0, 55.4, 39.0, 38.9, 28.4, 23.2; **MS** (EI) *m/z* (%): 55 (100), 65 (27), 77 (58), 107 (42), 135 (94), 150 (64), 163 (83), 192 (47), 220 (34); **HRMS** (ESI) *m/z* calculated for $C_{13}H_{16}O_3Na$ [M+Na$^+$] 243.0992, found 243.0989.

2-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxycyclohexan-1-one (**2f**). The reaction was performed at 18°C. 50% yield, 23.4 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.83-6.75 (m, 3 H), 5.97 (s, 2 H), 4.45 (s, 1 H), 2.93-2.89 (m, 1 H), 2.54-2.43 (m, 2 H), 2.09-2.03 (m, 1 H), 1.87-1.69 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 212.7, 148.5, 147.6, 134.0, 120.2, 108.8, 107.0, 101.4, 79.9, 39.2, 38.9, 28.4, 23.2; **MS** (EI) *m/z* (%): 55 (50), 65 (33), 91 (22), 149 (100), 164 (73), 177 (60), 206 (35), 234 (34); **HRMS** (ESI) *m/z* calculated for $C_{13}H_{14}O_4Na$ [M+Na$^+$] 257.0784, found 257.0782.

2-hydroxy-2-(naphthalen-1-yl)cyclohexan-1-one (**2h**). The reaction was performed at 0 °C. 34% yield, 16.5 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.96-7.94 (m, 1 H), 7.87-7.85 (m, 2 H), 7.81-7.79 (m, 1 H), 7.53-7.44 (m, 3 H), 4.61 (s, 1 H), 3.30-2.48 (m, 1 H), 2.47-2.44 (m, 1 H), 2.26-2.19 (m, 1 H), 2.10-2.05 (m, 1 H), 1.98-1.76 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 216.2, 134.9, 134.1, 132.0, 129.9, 129.2, 126.8, 125.84, 125.80, 124.9, 124.8, 82.0, 43.6, 39.4, 30.3, 23.7; **MS** (EI) *m/z* (%): 127 (38), 141 (29), 155 (100), 165 (42), 183 (43), 212 (27), 240 (28); **HRMS** (ESI) *m/z* calculated for $C_{16}H_{16}O_2Na$ [M+Na$^+$] 263.1043, found 263.1040.

2-hydroxy-2-(naphthalen-2-yl)cyclohexan-1-one (**2i**). 44% yield, 21.2 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.88-7.81 (m, 4 H), 7.52-7.50 (m, 2 H), 7.37-7.34 (m, 1 H), 4.61 (s, 1 H), 3.17-3.13 (m, 1 H), 2.60-2.55 (m, 1 H), 2.50-2.42 (m, 1 H), 2.09-2.04 (m, 1 H), 1.99-1.75 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 213.0, 137.3, 133.4, 133.1, 129.3, 128.4, 127.7, 126.8, 126.6, 125.7, 124.2, 80.3, 39.13, 39.07, 28.5, 23.3; **MS** (EI) *m/z* (%): 127 (50), 141 (21), 155 (92), 170 (78), 183 (100), 212 (50), 240 (36); **HRMS** (ESI) *m/z* calculated for $C_{16}H_{16}O_2Na$ [M+Na$^+$] 263.1043, found 263.1041.

2-hydroxy-2,6-diphenylcyclohexan-1-one9 (**2j**).[5f] 49% yield, 25.9 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47-7.43 (m, 2 H), 7.39-7.33 (m, 5 H), 7.31-7.27 (m, 1 H), 7.11-7.09 (m, 2 H), 4.64 (s, 1 H), 3.79-3.74 (m, 1 H), 3.17-3.13 (m, 1 H), 2.28-2.22 (m, 1 H), 2.15-1.96 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 211.7, 140.2, 137.3, 129.5, 128.61, 128.56, 127.5, 126.5, 80.5, 53.9, 39.2, 36.4, 22.9; **MS** (EI) *m/z* (%): 51 (13), 77 (43), 91 (28), 105 (81), 120 (100), 133 (33), 266 (34).

2-hydroxy-2-phenyl-3,4-dihydronaphthalen-1(2*H*)-one (**2k**).[27] 65% yield, 30.8 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19-8.17 (m, 1 H), 7.54-7.50 (m, 1 H), 7.41-7.37 (m, 1 H), 7.30-7.26 (m, 5 H), 7.21-7.19 (m, 1 H), 4.20 (s, 1 H), 2.94-2.88 (m, 1 H), 2.76-2.67 (m, 2 H), 2.49-2.41 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.9, 144.5, 141.1, 134.4, 131.8, 129.2, 128.7, 128.3, 127.8, 127.2, 126.2, 77.9, 36.7, 26.7; **MS** (EI) *m/z* (%): 77 (22), 90 (32), 105 (100), 118 (95), 133 (36), 150 (64), 220 (64), 238 (34).

1-hydroxy-1-methyl-3,4-dihydronaphthalen-2(1*H*)-one (**2l**).[5a] The reaction was performed at rt. 50% yield, 17.5 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.67-7.65 (m, 1 H), 7.34-7.30 (m, 1 H), 7.27-7.24 (m, 1 H), 7.17-7.15 (m, 1 H),3.94 (s, 1 H), 3.35-3.27 (m, 1 H), 3.11-

3.04 (m, 1 H), 2.98-2.91 (m, 1 H), 2.69-2.60 (s, 1 H), 1.55 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 213.1, 140.9, 133.9, 127.81, 127.77, 127.65, 125.5, 76.2, 33.6, 28.0, 27.9; **MS** (EI) *m/z* (%): 77 (28), 91 (46), 105 (26), 121 (58), 133 (100), 158 (54), 176 (9).

2-hydroxy-2-phenylcycloheptan-1-one (**2m**).[28] 40% yield,16.2 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46-7.44 (m, 2 H), 7.38-7.34 (m, 2 H), 7.31-7.27 (m, 1 H), 4.57 (d, *J* = 1.2 Hz, 1 H), 2.87-2.80 (m, 1 H), 2.51-2.46 (m, 1 H), 2.37-2.25 (m, 2 H), 2.05-1.99 (m, 3 H), 1.54-1.36 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 213.9, 141.8, 128.8, 128.1, 125.9, 82.5, 39.7, 36.6, 30.7, 28.0, 23.8; **MS** (EI) *m/z* (%): 55 (38), 77 (37), 105 (46), 133 (100), 176 (15), 204 (6).

1-(9-hydroxy-9*H*-fluoren-9-yl)ethan-1-one (**2n**).[3g] 48% yield, 21.7 mg, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75-7.73 (m, 2 H), 7.48-7.44 (m, 2 H), 7.35-7.31 (m, 4 H), 5.11 (s, 1 H), 1.65 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 207.2, 144.5, 141.6, 130.0, 128.6, 124.0, 120.7, 88.4, 22.6; **MS** (EI) *m/z* (%): 152 (28), 165 (15), 181 (100), 199 (18), 224 (8).

General Chlorination Procedure.

Under an argon atmosphere, to a stirred suspension of 2-phenylcyclohexan-1-one (34.9 mg, 0.20 mmol) and DMP (101.8 mg, 0.24 mmol, 1.2 equiv) in the mixed solvent (EtOAc /AcOH = 1:1, 2.0 mL) was added $FeCl_3·6H_2O$ (108.1 mg, 0.40 mmol, 2.0 equiv) at room temperature. The mixture was then stirred at this temperature. After the starting material disappeared, the reaction mixture was quenched with a saturated aqueous solution of Na_2CO_3. The mixture was extracted with EtOAc (40 mL × 2) and the combined organic layers were washed successively with water and brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The mixture was preliminarily purified by flash column chromatography with petroleum ether/ethyl acetate as eluent to afford crude product **3a**, and continuously isolated by HPLC with acetonitrile/water as eluent to afford the product **3a** (27.1 mg, 65% yield, an amorphous solid). The pure products **3b**-**3d** were obtained through the same procedure for preparation of **3a**, while the pure products **3f**-**3i** could be isolated by flash column chromatography with petroleum ether/ethyl acetate as eluent.

2-chloro-2-phenylcyclohexan-1-one (**3a**).[29] 65% yield, 27.0 mg, amorphous solid. Isolated by HPLC (SunFire™ Prep C18 OBD™, 10 μm, 19×150 mm Column, H_2O-CH_3CN 60:40, 20 mL/min, t_r = 26.3 min, 210 nm.). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41-7.33 (m, 5 H), 2.99-2.92 (m, 1 H), 2.89-2.83 (m, 1 H), 2.48-2.41 (m, 2 H), 2.04-2.00 (m, 1 H), 1.94-1.89 (m, 2 H), 1.86-1.80 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.5, 138.7, 128.9, 128.7, 127.2, 41.9, 39.2, 27.5, 22.8; **MS** (EI) *m/z* (%): 77 (32), 91 (93), 103 (50), 115 (87), 129 (100), 145 (40), 164 (20), 173 (19), 208 (10).

2-chloro-2-(4-fluorophenyl)cyclohexan-1-one (**3b**). 50% yield, 22.7 mg, amorphous solid. Isolated by HPLC (SunFire™ Prep C18 OBD™, 10 μm, 19×150 mm Column, H_2O-CH_3CN 60:40, 20 mL/min, t_r = 31.3 min, 210 nm.). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41-7.37 (m, 2 H), 7.10-7.06 (m, 2 H), 2.96-2.91 (m, 1 H), 2.82-2.78 (m, 1 H), 2.51-2.40 (m, 2 H), 2.06-1.81 (m, 4 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.3, 162.7 (d, *J* = 247 Hz), 134.8 (d, *J* = 3 Hz), 129.3 (d, *J* = 8 Hz), 115.7 (d, *J* = 21 Hz), 75.8, 42.0, 38.8, 27.4, 22.6; **MS** (EI) *m/z* (%): 57 (18), 109 (100), 147 (60), 163 (40), 182 (33), 226 (18); **HRMS** (ESI) *m/z* calculated for $C_{12}H_{16}ClFON$ [M+NH_4^+] 244.0899, found 244.0893.

2-chloro-2-(4-chlorophenyl)cyclohexan-1-one (**3c**). 63% yield, 30.4 mg, amorphous solid. Isolated by HPLC (SunFire™ Prep C18 OBD™, 10 μm, 19×150mm Column, H_2O-CH_3CN 60:40, 20 mL/min, t_r = 59.6 min, 210 nm.). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38-7.33 (m, 4 H), 2.97-2.92 (m, 1 H), 2.79-2.75 (m, 1 H), 2.49-2.39 (m, 2 H), 2.10-2.07 (m, 1 H), 1.98-1.97 (m, 1 H), 1.90-1.80 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.1, 137.5, 134.7, 128.90, 128.85, 75.7, 41.9, 38.8, 27.3, 22.5; **MS** (EI) *m/z* (%): 101 (22), 125 (100), 153 (52), 179 (43), 198 (40), 242 (30); **HRMS** (ESI) *m/z* calculated for $C_{12}H_{12}Cl_2ONa$ [M+Na^+] 265.0157, found 265.0153.

2-(4-bromophenyl)-2-chlorocyclohexan-1-one (**3d**). 65% yield, 37.1 mg, amorphous solid. Isolated by HPLC (SunFire™ Prep C18 OBD™, 10 μm, 19×150 mm Column), H_2O-CH_3CN 60:40, 20 mL/min, t_r = 71.1 min, 210 nm.). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53-7.50 (m, 2 H), 7.30-7.27 (m, 2 H), 2.98-2.92 (m, 1 H), 2.78-2.74 (m, 1 H), 2.49-2.39 (m, 2 H), 2.10-2.07 (m, 1 H), 1.99-1.97 (m, 1 H), 1.90-1.80 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.0, 138.0, 131.9, 129.2, 122.9, 75.7, 41.9, 38.7, 27.3, 22.5; **MS** (EI) *m/z* (%): 102 (60), 115 (100), 128 (65), 179 (43), 169 (60), 244 (88), 288 (62); **HRMS** (ESI) *m/z* calculated for $C_{12}H_{12}BrClONa$ [M+Na^+] 308.9652, found 308.9649.

2-chloro-2-(4-nitrophenyl)-3,4-dihydronaphthalen-1(2*H*)-one (3f). 34% yield, 20.6 mg, amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.8 Hz, 2 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 7.72 (d, *J* = 8.8 Hz, 2 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.41 (t, *J* = 7.6 Hz, 1 H), 7.29 (d, *J* = 7.6 Hz, 1 H), 3.47-3.39 (m, 1 H), 3.00-2.90 (m, 2 H), 2.76-2.70 (m, 1 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.1, 147.8, 146.5, 142.7, 134.6, 130.4, 129.4, 129.0, 128.7, 127.6, 123.5, 72.3, 39.5, 26.5; **MS** (EI) *m/z* (%): 90 (38), 118 (100), 266 (15), 301 (28). **HRMS** (ESI) *m/z* calculated for $C_{16}H_{13}ClNO_3$ [M+H^+] 302.0578, found 302.0574.

2-chloro-2,6-diphenylcyclohexan-1-one (**3g**). 36% yield, 20.3 mg, amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48-7.45 (m, 2 H), 7.37-7.30 (m, 5 H), 7.27-7.23 (m, 1 H), 7.18-7.16 (m, 2 H), 4.71 (dd, *J* = 13.6 Hz, *J* = 5.6 Hz, 1 H), 2.71-2.66 (m, 2 H), 2.52-2.48 (m, 1 H), 2.36-2.32 (m, 1 H), 2.12-2.00 (m, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 202.9, 139.2, 138.2, 128.9, 128.4, 128.3, 128.2, 127.9, 127.3, 75.8, 52.3, 42.0, 35.3, 21.9; **MS** (EI) *m/z* (%): 77 (12), 91 (23), 117 (84), 129 (26), 221 (100), 248 (15), 284 (44); **HRMS** (ESI) *m/z* calculated for $C_{18}H_{17}ClONa$ [M+Na^+] 307.0860, found 307.0859.

1-(9-chloro-9*H*-fluoren-9-yl)ethan-1-one (**3h**). 87% yield, 42.1 mg, amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.6 Hz, 2 H), 7.52-7.47 (m, 4 H), 7.38 (td, *J* = 7.6 Hz, *J* = 0.8 Hz, 2 H), 1.77 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.5, 143.8, 140.6, 130.4, 129.0, 125.2, 120.9, 78.2, 24.5; **MS** (EI) *m/z* (%): 81 (8), 163 (36), 199 (100), 242 (18); **HRMS** (ESI) *m/z* calculated for $C_{15}H_{11}ClONa$ [M+Na^+] 265.0391, found 265.0390.

2-benzoyl-2-chlorocyclohexan-1-one (3i).[8g] 80% yield, 37.6 mg, amorphous solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98-7.96 (m, 2 H), 7.57-7.53 (m, 1 H), 7.44-7.40 (m, 2 H), 3.09-3.05 (m, 1 H), 2.81-2.77 (m, 1 H), 2.25-2.19 (m, 1 H), 2.15-2.09 (m, 1 H), 2.02-1.98 (m, 1 H), 1.94-1.85 (m, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 203.6, 190.9, 134.4, 133.7, 130.2, 128.7, 77.2, 41.5,

41.3, 28.5, 23.1. **MS** (EI) *m/z* (%): 77 (32), 105 (100), 173 (10), 201 (4), 236 (0.5).

2-bromo-2-phenylcyclohexan-1-one (4).[16] 15% yield, 7.7 mg, amorphous solid. Isolated by HPLC (SunFire™ Prep C18 OBD™, 10 μm, 19×150 mm Column, H_2O-CH_3CN 40:60, 20 mL/min, t_r = 6.7 min, 210 nm.). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.43-7.31 (m, 5 H), 3.02-2.95 (m, 2 H), 2.65-2.61 (m, 1 H), 2.51-2.46 (m, 1 H), 2.00-1.83 (m, 4 H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 202.8, 139.3, 128.7, 128.5, 127.5, 72.5, 42.5, 38.7, 27.3, 23.3; **MS** (EI) *m/z* (%): 55 (100), 69 (85), 81 (75), 91 (76), 115 (70), 172 (41), 173 (45). **HRMS** (ESI) *m/z* calculated for $C_{12}H_{13}BrONa$ [M+Na$^+$] 275.0042, found 275.0043.

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A tunable α-hydroxylation/α-chlorination of benzylketone derivatives for the construction hetero-quaternary units have been developed by Iron(III) chloride hexahydrate-mediated selective transformations.