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Efficient catalytic-free method to produce α-aryl cycloalkanones through highly chemoselective coupling of aryl compounds with oxyallyl cations†

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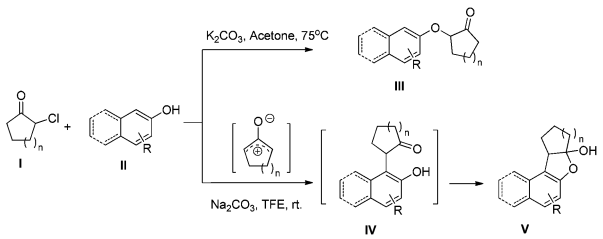
Catalytic-free coupling of aryl compounds and α-halo cycloketones *via in situ* generated oxyallyl cation intermediates is reported here. The reactions efficiently afford α-naphthol cycloalkanones with moderate to excellent yields. Electron-rich aromatic compounds are also used to produce the corresponding α-aryl cycloalkanones, and in some cases, analytically pure products are obtained after simple filtration followed by evaporation.

Introduction

α-Aryl cycloalkanones are important building blocks for concise preparation of medicines or organic functional materials, such as naphthonone,[1] brazan,[2] and electroluminescence devices.[3] The synthesis of α-aryl cycloalkanones, particularly α-naphthol cycloalkanones, can be realized by nucleophilic substitution of α-hydroxylketones with oxygen protected naphthols *via* Grignard reagents and final deprotection,[4] or by direct electrophilic substitution of α-hydroxylketones with phenols under acidic conditions.[5] α-Arylation of β-dicarbonyl compounds, as a powerful technology, needs to be catalyzed by transition metals,[6] organocatalysts[7] or enzymes.[8] Pappo and colleagues have recently reported an efficient cross-dehydrogenative coupling reaction between phenols and α-substituted β-ketoesters catalyzed by iron trichloride.[9]

It has been reported that reaction of β-naphthol with α-cyclohexanone in xylene under refluxing temperature produces compound **V** directly.[10] However, a high temperature is necessary, the yield is moderate (22–57%), and a large amount of by-product **III** is evolved. It is worth noting that direct substitution of α-haloketones with naphthols under basic conditions produces phenol ethers **III** (Scheme 1) as the main product.[11]

Here we report an efficient catalyst-free coupling of unprotected naphthols and oxyallyl cation intermediates generated from α-halocycloketones at room temperature. Oxyallyl cations have been extensively explored for more than half a century.[12]



Scheme 1 Different reaction pathways of α-haloketones with naphthols.

The literature is replete with examples of cycloaddition reactions of such species, especially (4 + 3) cycloaddition reactions.[13] Moreover, aromatic groups have been extensively used to trap oxyallyl cations in the context of Nazarov cyclization.[14] However, there are only a few reports on the interrupted cycloaddition reactions of aromatic compounds with oxyallyl cations derived from α-halo ketones.[15] Recently, MacMillan and colleagues and ourselves both reported an efficient synthesis of α-indole carbonyl compounds *via* electrophilic aromatic substitution of unprotected indoles to *in situ* generated oxyallyl cations.[16] To further expand the reaction scope, we started to use naphthols as nucleophiles to react with oxyallyl cations generated from α-halo cycloalkanones. To our delight, the reaction proceeded smoothly and produced α-naphthol cycloalkanones **IV** (Scheme 1) which are eventually transformed to product **V** (Scheme 1) with high yield.

Results and discussion

We first explored the reaction between 2-chlorocyclohexanone (**Ia**) and 2-naphthol (**IIb**). At room temperature, most of the starting materials remain unreacted in common organic solvents such as DMF, DMSO, THF, toluene, Et_2O, CH_2Cl_2,

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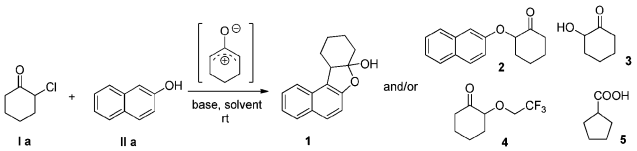
† Electronic supplementary information (ESI) available: Chemical shifts assignments, and spectral data for compounds. See DOI: 10.1039/c4ra01043d

Table 1 Model reaction optimization[a]



Entry	Base	Solvent	Temperature (°C)	Time (h)	Product[b] (yield%)
1	Na_2CO_3	Solvents[c]	25	48	**1** (<5)
2	Na_2CO_3	Xylene	25	48	**1** (<5)
3	Na_2CO_3	Xylene	140	24	**1/2** (42/33)[d]
4	Na_2CO_3	H_2O	25	12	**1/3** (8/85)[d]
5	Na_2CO_3	TFE	25	12	**1** (91)[e]
6	Na_2CO_3	TFE	80	10	**1/4** (88/5)[d]
7	Na_2CO_3	HFIP	25	10	**1** (86)[e]
8	$NaHCO_3$	TFE	25	48	**1** (<5)
9	NaOH	TFE	25	4	**1/5** (48/5)[d]
10	Pyrrolidine	TFE	25	48	**1/4** (71/6)[d]
11	Et_3N	TFE	25	48	**1/4** (80/6)[d]

[a] Reaction condition: **I** (0.5 mmol), **II** (0.5 mmol), base (0.6 mmol) in solvent (1 mL). [b] Isolated yields. [c] DMF, DMSO, THF, Et_2O, toluene, CH_2Cl_2, EtOAc, CH_3CN. [d] Yield of minor product was determined by crude NMR integration. [e] No other product was isolated. TFE = 2,2,2-trifluoroethanol; HFIP = hexafluoro-2-propanol.

EtOAc, CH_3CN, toluene and xylene (Table 1, entries 1 and 2). Although cough medicine, product **1**, is evolved when xylene is used as a solvent under high temperature, 33% yield of ether by-product **2**, which is not transformed to product **1** within the prolonged reaction time, is also obtained (Table 1, entry 3). In the case where water was used as a solvent, hydrolysis of 2-chlorocyclohexanone becomes the preferred reaction pathway to produce compound **3** serving as the main product,[17] while very little of compound **1** could be isolated (Table 1, entry 4). Owing to their high ionizing power and low nucleophilicity, fluorinated alcohols, such as trifluoroethanol (TFE) and hexafluoro isopropanol (HFIP), are the best solvents for generation of oxyallyl cations.[18] So the fluorinated alcohols were then evaluated (Table 1, entries 5–11). Under the reaction conditions of Na_2CO_3 in TFE at room temperature, a clean reaction with high yield is realized (Table 1, entry 5). Higher temperature (Table 1, entry 6) or higher ionizing power (Table 1, entry 7) is beneficial for the reaction rate rather than the reaction efficiency. With TFE as the solvent, the choice of base has a significant effect on the reaction purity and yield. Organic bases, *e.g.* pyrrolidine and Et_3N, effectively initiate the reaction (Table 1, entries 10 and 11). However, when a relatively weak base, *e.g.* sodium bicarbonate, was chosen, virtually no reaction takes place (Table 1, entry 8). In contrast, when a strong base, *e.g.* NaOH, was used, the reaction becomes complex with formation of Favorskii rearrangement adduct **5** among the side products (Table 1, entry 9).[19]

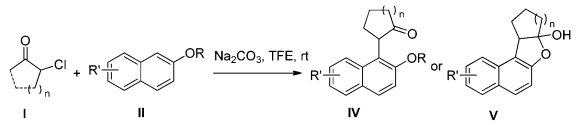
Then we examined various naphthols in reaction with 2-chlorocyclopentanone. Both protected and unprotected β-naphthols are alkylated at C-1 to produce compounds **IV** or **V** in moderate to excellent yields (Table 2, entries 1–6). Bromo-substituted naphthols show excellent outcomes no matter what the substitution position of bromo is (Table 2, entries 3–5). For α-naphthols, the reaction shows excellent chemoselectivity, naphthols are regioselectively alkylated at C-4, and no C-2 alkylated product is obtained (Table 2, entries 7 and 8). To further examine the regioselectivity, 4-chloro-1-naphthol was selected as substrate (Table 2, entry 8). No C-2 alkylated product was detected under our standard reaction conditions. Most of the starting material is recovered after reacting for 12 h.

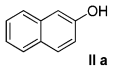
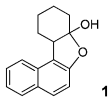
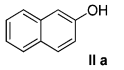
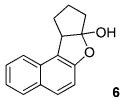
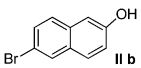
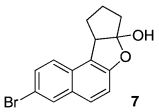
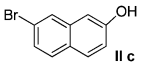
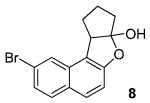
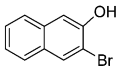
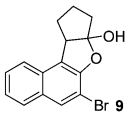
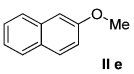
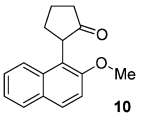
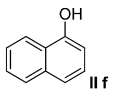
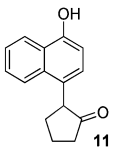
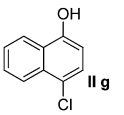
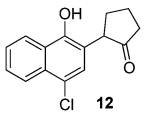
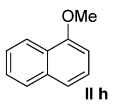
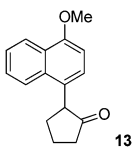
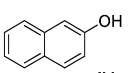
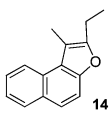
Noncyclic haloketones were also examined. Unfortunately, when 1,1-dichloropropan-2-one or 1,3-dichloropropan-2-one was used, we found that most of the 2-naphthol remained unreacted. Similarly, for substrates 1,3-dibromo-3-methylbutan-2-one and 1-chloro-1,3-diphenylpropan-2-one, a small amount of 2-naphthol is consumed without isolating any desired products. Only 2-bromo-3-pentanone produces a small amount of condensed product **14** in the presence of excessive haloketone (Table 2, entry 10).

To explore the reaction scope further, we screened different hydroxyquinolines, wherein 5-hydroxy and 7-hydroxy isoquinoline gave acceptable yields of α-aryl cycloalkanones along with their corresponding ether products **III** (Table 3, entries 1 and 2). It should be noted that product **16** is the ketone isomer, not the hemiketal form. When excessive haloketone **Ib** was used, disubstituted product **22** was obtained as a mixture of stereoisomers (Table 3, entry 3).

We think that the reaction mechanism is just like that of Friedel–Crafts alkylation, so we used different types of aromatic compound to react with 2-chlorocyclopentanone. We found that an electron-rich system of aromatic compounds plays an important role in the reaction efficiency. When phenol (**IIm**) was used as a substrate, only ether product **23** is obtained (Table 4, entry 1). For the reaction of substrates **IIn** and **IIo**, the

Table 2 Addition of naphthols to α-halo alkanones[a,b]

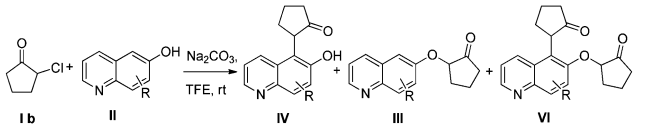


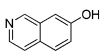
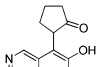
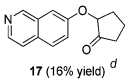
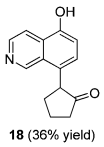
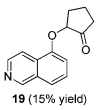
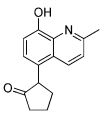
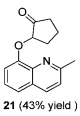
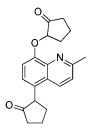
Entry	Haloketone	Naphthol	Product	Yield
1	 I a	 II a	 1	91% (dr > 20 : 1)[c]
2	 I b	 II a	 6	92% (dr = 10 : 1)[c]
3	 I b	 II b	 7	93% (dr = 10 : 1)[c]
4	 I b	 II c	 8	93% (dr = 8 : 1)[c]
5	 I b	 II d	 9	94% (dr = 8 : 1)[c]
6	 I b	 II e	 10	88%
7	 I b	 II f	 11	89%[d,e]
8	 I b	 II g	 12	—[f]
9	 I b	 II h	 13	87%[d,g]
10	 I c	 II i	 14	11%[h,i]

[a] **I** (0.5 mmol), **II** (0.5 mol), Na_2CO_3 (0.6 mmol) in TFE (1 mL). [b] Isolated yields. [c] Ratio of diastereomers was determined by integration of benzylic proton signals in ^1H NMR spectrum. [d] No another isomer was detected. [e] The structure is confirmed by 2D NMR spectra (COSY, HMQC and HMBC). [f] No desired product is obtained. [g] The ^1H and ^{13}C NMR spectra are the same as that reported in the literature.[4a] [h] **Ic** (1.0 mmol), **IIi** (0.5 mol), Na_2CO_3 (1.1 mmol) in HFIP (1 mL). [i] The ether product (**15**), 2-(naphthalen-2-yloxy)pentan-3-one, is also isolated.

main products are, respectively, ether **24** and amine **25**, both of which are accompanied by several other complex compounds. However, when the more electron-rich compound **IIp** was used, an almost quantitative reaction takes place. After simple filtration followed by evaporation, analytically pure product **26** is obtained (Table 4, entry 4). The reaction efficiency is

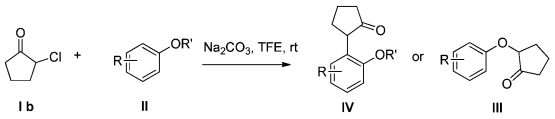
Table 3 Addition of hydroxyquinolines to α-chloropentanone[a]

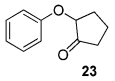
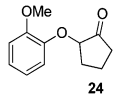
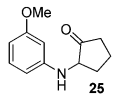
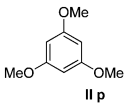
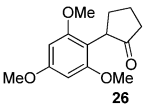
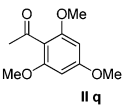
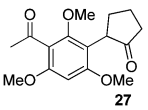
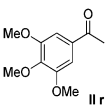
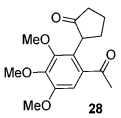


Entry	Quinine	Product **IV**	Product **III**	Product **VI**
1[b]	 II j	 16 (33% yield)	 17 (16% yield) [d]	—[e]
2[b]	 II k	 18 (36% yield)	 19 (15% yield)	—[e]
3[c]	 II l	 20 (13% yield)	 21 (43% yield)	 22 (11% yield) [f,g] (dr=1:1)

[a] Isolated yield. [b] **I** (0.5 mmol), **II** (0.5 mol), Na_2CO_3 (0.6 mmol) in TFE (1 mL). [c] **I** (1.5 mmol), **II** (0.5 mol), Na_2CO_3 (1.6 mmol) in TFE (1 mL). [d] Yield of product **15** was determined by integration of proton signals in ^{1}H NMR spectrum. [e] Not detected. [f] Ratio of diastereomers was determined by integration of proton signals in ^{1}H NMR spectrum. [g] The structure is confirmed by 2D NMR spectra (COSY, HMQC and HMBC).

Table 4 Addition of aryl compounds to α-chloropentanone[a,b]



Entry	Aryl compounds	Product	Yield
1	 II m	 23	46%
2	 II n	 24	38%
3	 II o	 25	32%
4	 II p	 26	99%
5	 II q	 27	48%
6	 II r	 28	—[c]

[a] **I** (0.5 mmol), **II** (0.5 mol), Na_2CO_3 (0.6 mmol) in TFE (1 mL). [b] Isolated yields. [c] Not detected.

dramatically lowered if there is an electron-withdrawing group on the arene ring. Moderate yield is obtained in the presence of substrate **IIq**, while no reaction occurs for substrate **IIr** (Table 4, entries 5 and 6).

Conclusions

We developed a highly efficient and practical method for chemoselective coupling of α-halo cycloalkanones with electron-rich aromatic compounds, especially naphthols, at room temperature. No protection of naphthol substrates and no catalysts are required in our protocol. α-Aryl cycloalkanone **26** is obtained in quantitative yield, and analytically pure products are obtained after simple filtration followed by evaporation. An electron-rich system of aryl compounds plays an important role in the reaction efficiency. Further research on the interrupted cycloaddition reaction of oxyallyl cations is being pursued in our lab.

Experimental section

General information

Nuclear magnetic resonance spectra (^{1}H and ^{13}C) were recorded on JEOL ECA400 (400 MHz), Bruker AV300 (300 MHz), AV400 (400 MHz), AV500 (500 MHz) or BBFO400 (400 MHz) spectrometers. ^{1}H NMR chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or DMSO ($\delta = 2.50$, singlet), and the splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), *etc.* All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted were designated as multiplet (m) or broad (br). High resolution mass spectral analysis (HRMS) was performed on a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plates (0.2 mm thickness). Visualization was performed using a UV lamp or chemical stains such as $KMnO_4$ and 2,4-dinitrophenyl hydrazine solutions.

Commercially available materials purchased from Alfa Aesar or Aldrich were used as received, apart from α-haloketones that were further purified *via* distillation or column chromatography over silica gel prior to use. Some of the α-chloroketones (2-bromo-3-pentanone and 1,3-dibromo-3-methylbutan-2-one) were prepared using a literature method.[20]

Typical procedure for metal-free coupling of aromatic compounds with α-haloketones

A 4 mL vial equipped with a magnetic stir bar was charged with fresh distilled α-halo ketone **I** (0.5–1.5 mmol), aromatic compound **II** (0.5 mmol) and TFE or HFIP (1.0 mL). Anhydrous Na_2CO_3 (0.6–1.6 mmol) was added to the reaction mixture and stirred at room temperature. After completion of the reaction (about 12–24 h, monitored by TLC or crude ^{1}H NMR analysis), the reaction mixture was filtered through a celite pad using Et_2O or CH_2Cl_2 and the filtrate was concentrated under reduced pressure. The crude residue was further purified by silica gel flash chromatography using EtOAc/hexanes as eluent to give pure products. In some cases, analytically pure products could be obtained merely by simple filtration and evaporation under reduced pressure.

7*a*,8,9,10,11,11*a*-Hexahydronaphtho[2,1-*b*]benzofuran-7*a*-ol (1). White solid, Mp: 136–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (d, J = 8.3 Hz, 1H), 7.69 (t, J = 9.2 Hz, 2H), 7.45 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.31 (ddd, J = 8.1, 6.8, 1.1 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 3.41 (dd, J = 10.2, 6.8 Hz, 1H), 3.26 (d, J = 3.1 Hz, 1H), 2.46–2.27 (m, 2H), 1.90 (ddd, J = 14.1, 12.3, 5.2 Hz, 1H), 1.85–1.74 (m, 1H), 1.64–1.28 (m, 4H), 1.15 (dddd, J = 14.0, 12.0, 10.3, 3.9 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.23, 130.61, 129.91, 129.04, 126.72, 124.64, 123.18, 122.79, 113.05, 109.78, 46.62, 33.37, 30.86, 21.79, 21.76 ppm. HRMS (ESI) calcd for $C_{16}H_{17}O_2$ (M + 1)$^+$: 241.1229, found: 241.1233.

2-(Naphthalen-2-yloxy)cyclohexanone (2).[11a] White solid, Mp: 104–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (dd, J = 2.8, 9.2 Hz, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.10 (dd, J = 2.4, 8.8 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 4.72–4.65 (m, 1H), 2.59–2.52 (m, 1H), 2.34–2.21 (m, 2H), 2.01–1.89 (m, 3H), 1.74–1.62 (m, 2H) ppm.

2-Hydroxycyclohexanone (3).[21] White solid; Mp: 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.13 (dd, J = 11.9, 7.0 Hz, 1H), 3.64 (s, 1H), 2.57 (ddt, J = 13.8, 4.3, 2.3 Hz, 1H), 2.52–2.43 (m, 1H), 2.36 (tdd, J = 13.7, 6.4, 1.5 Hz, 1H), 2.16–2.06 (m, 1H), 1.96–1.84 (m, 1H), 1.81–1.68 (m, 1H), 1.68–1.58 (m, 2H), 1.56–1.40 (m, 2H) ppm.

2-(2,2,2-Trifluoroethoxy)cyclohexanone (4).[22] Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.20 (dq, J = 12.7, 9.0 Hz, 1H), 4.01 (dd, J = 10.4, 5.8 Hz, 1H), 3.76 (dq, J = 12.7, 8.5 Hz, 1H), 2.58–2.45 (m, 1H), 2.30 (dtd, J = 12.3, 5.4, 2.4 Hz, 2H), 2.08–1.88 (m, 2H), 1.85–1.62 (m, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.47, 128.00, 125.23, 122.45, 119.68, 83.86, 67.88, 67.54, 67.20, 66.86, 40.53, 34.23, 27.25, 23.22 ppm. HRMS (ESI) calcd for C $_8H_{12}F_3O_2$ (M + 1)$^+$: 197.0789, found: 197.0784.

8,9,10,10*a*-Tetrahydro-7*aH*-cyclopenta [*b*] naphtha [1,2-*d*] furan-7*a*-ol (6). White solid; Mp: 128–129 °C; further purification could be realized by recrystallization using ethanol. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.46 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.31 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 3.84 (dd, J = 9.3, 3.0 Hz, 1H), 3.33 (s, 1H), 2.49–2.19 (m, 2H), 2.11 (ddd, J = 13.0, 10.9, 6.4 Hz, 1H), 1.93 (dddd, J = 8.6, 6.5, 5.4, 3.3 Hz, 1H), 1.81 (dtd, J = 9.6, 6.3, 3.0 Hz, 1H), 1.72–1.58 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.38, 130.48, 129.62, 129.35, 128.96, 126.78, 123.01, 122.44, 121.74, 121.24, 111.83, 51.48, 40.03, 32.71, 24.84 ppm. HRMS (ESI) calcd for $C_{15}H_{15}O_2$ (M + 1)$^+$: 227.1072, found: 227.1069.

3-Bromo-8,9,10,10*a*-tetrahydro-7*aH*-cyclopenta[*b*]naphtha [1,2-*d*]furan-7*a*-ol (7). White solid; Mp: 86–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.49 (q, J = 8.7 Hz, 2H), 7.08 (d, J = 8.8 Hz, 1H), 3.79 (d, J = 8.9 Hz, 1H), 3.60–3.30 (brs, 1H), 2.48–2.17 (m, 2H), 2.10 (dd, J = 18.1, 11.9 Hz, 1H), 1.94–1.73 (m, 2H), 1.74–1.52 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.76, 130.87, 130.72, 130.03, 128.93, 128.53, 124.11, 121.86, 121.58, 116.51, 112.87, 51.38, 40.07, 32.78, 24.87 ppm. HRMS (ESI) calcd for $C_{15}H_{14}BrO_2$ (M + 1)$^+$: 306.1745, found: 306.1744.

2-Bromo-8,9,10,10*a*-tetrahydro-7*aH*-cyclopenta[*b*]naphtha [1,2-*d*]furan-7*a*-ol (8). Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.75 (s, 1H), 7.65 (dd, J = 8.6, 3.6 Hz, 2H), 7.37 (dd, J = 8.7, 1.8 Hz, 1H), 7.07 (dd, J = 8.7, 3.4 Hz, 1H), 3.81–3.70 (m, 1H), 3.50–3.40 (brs, 1H), 2.49–2.34 (m, 1H), 2.34–2.20 (m, 1H), 2.19–2.04 (m, 1H), 1.94–1.72 (m, 2H), 1.64 (dq, J = 10.6, 6.3 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.09, 131.62, 130.61, 129.39, 127.93, 126.38, 124.57, 122.02, 121.22, 120.68, 112.18, 51.13, 40.02, 32.70, 24.80 ppm. HRMS (ESI) calcd for $C_{15}H_{14}BrO_2$ (M + 1)$^+$: 306.1745, found: 306.1742.

6-Bromo-8,9,10,10*a*-tetrahydro-7*aH*-cyclopenta[*b*]naphtha [1,2-*d*]furan-7*a*-ol (9). Colorless oil, 94% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.90 (s, 1H), 7.71 (t, J = 10.8 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.47 (dd, J = 8.1, 7.1 Hz, 1H), 7.33 (dd, J = 8.1, 7.0 Hz, 1H), 3.99–3.88 (m, 1H), 3.51 (d, J = 10.4 Hz, 1H), 2.52–2.35 (m, 2H), 2.19–2.08 (m, 1H), 1.99–1.88 (m, 1H), 1.83 (ddd, J = 12.7, 6.4, 3.5 Hz, 1H), 1.76–1.64 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.39, 131.06, 130.53, 129.43, 128.02, 127.00, 123.93, 122.92, 122.61, 122.23, 104.75, 52.34, 40.20, 32.80, 24.94 ppm. HRMS (ESI) calcd for $C_{15}H_{14}BrO_2$ (M + 1)$^+$: 306.1745, found: 306.1740.

2-(2-Methoxynaphthalen-1-yl)cyclopentanone (10). White solid; Mp: 92–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.79 (dd, J = 8.5, 4.4 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.39–7.30 (m, 1H), 7.30–7.22 (m, 2H), 3.85 (s, 3H), 2.60 (ddd, J = 18.4, 11.9, 8.6 Hz, 1H), 2.45 (ddd, J = 19.3, 12.4, 8.0 Hz, 2H), 2.33–2.10 (m, 2H), 2.09–1.84 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 219.87, 129.62, 128.98, 128.76, 126.69, 123.51, 122.48, 114.12, 56.07, 47.79, 38.22, 30.83, 22.08 ppm. HRMS (ESI) calcd for $C_{15}H_{17}O_2$ (M + 1)$^+$: 241.1229, found: 241.1230.

2-(1-Hydroxynaphthalen-4-yl)cyclopentanone (11). Yellow solid; Mp: 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.22–8.08 (m, 1H), 7.78 (dd, J = 8.4, 3.4 Hz, 1H), 7.57–7.34 (m, 2H), 6.96 (dd, J = 9.8, 7.9 Hz, 1H), 6.59 (dd, J = 15.7, 7.8 Hz, 1H), 5.99 (brs, 1H), 4.06–3.88 (m, 1H), 2.71–2.53 (m, 2H), 2.53–2.36 (m, 1H), 2.30–2.10 (m, 2H), 2.10–1.89 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 221.02, 151.09, 132.87, 127.01, 126.41, 125.37, 125.12, 124.74, 123.33, 122.64, 108.31, 52.34, 39.10, 32.48, 21.06 ppm. HRMS (ESI) calcd for $C_{16}H_{17}O_2$ (M + 1)$^+$: 241.1229, found: 241.1231.

2-(4-Methoxy naphthalen-2-yl)cyclopentanone (13).[4a] Colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (dd, J = 8.3, 1.2 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.60–7.38 (m, 2H), 7.14 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 4.01–3.93 (m, 1H), 3.98 (s, 3H),

2.68–2.51 (m, 2H), 2.51–2.35 (m, 1H), 2.30–2.12 (m, 2H), 2.04 (dddd, J = 14.1, 12.2, 7.1, 3.3 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 219.12, 154.76, 132.88, 127.33, 126.58, 126.16, 125.12, 125.02, 123.46, 122.78, 103.47, 55.54, 52.03, 38.94, 32.45, 21.08 ppm. HRMS (ESI) calcd for $C_{15}H_{17}O_2$ $(M + 1)^+$: 241.1229, found: 241.1234.

2-Ethyl-1-methyl-1,2-dihydronaphtho[2,1-*b*] furan-2-ol (14). Freshly distilled 2-chloro-3-pentanone (1.0 mmol) was added into the solution of 2-naphthol (0.5 mmol), anhydrous Na_2CO_3 (0.6 mmol) and HFIP (1.0 mL). The mixture was stirred at r.t. over 2 days, and then filtered through a celite pad using CH_2Cl_2. The filtrate was concentrated under reduced pressure and separated by silica gel flash chromatography to give two pure products. Product **13** was white solid, Mp: 101–103 °C, 11% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.66–7.50 (m, 3H), 7.44 (t, J = 7.6 Hz, 1H), 2.84 (dd, J = 15.2, 7.6 Hz, 2H), 2.57 (s, 3H), 1.33 (t, J = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.04, 157.26, 130.32, 128.43, 127.51, 125.75, 124.22, 124.10, 123.09, 122.21, 121.72, 113.01, 27.90, 25.00, 23.93 ppm. HRMS (ESI) calcd for $C_{17}H_{19}O_2$ $(M + 1)^+$: 211.1123, found: 211.1125.

2-(Naphthalen-2-yloxy)pentan-3-one (15). Brown oil, 7% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.81–7.72 (m, 2H), 7.69 (d, J = 8.2 Hz, 1H), 7.48–7.41 (m, 1H), 7.39–7.30 (m, 1H), 7.17 (dd, J = 8.9, 2.5 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 4.80 (q, J = 6.9 Hz, 1H), 2.73 (dq, J = 18.9, 7.2 Hz, 1H), 2.47 (dq, J = 18.9, 7.3 Hz, 1H), 2.20–2.04 (m, 1H), 1.56 (d, J = 7.0 Hz, 3H), 1.01 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 213.20, 155.48, 134.33, 129.94, 129.26, 127.63, 126.89, 126.63, 124.10, 118.75, 107.42, 79.13, 29.89, 18.07, 7.11 ppm. HRMS (ESI) calcd for $C_{15}H_{17}O_2$ $(M + 1)^+$: 229.1229, found: 229.1224.

2-(7-Hydroxyisoquinolin-8-yl)cyclopentanone (16). Yellow solid; Mp: 92–93 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.28 (s, 1H), 8.50 (d, J = 5.8 Hz, 1H), 8.14 (d, J = 5.8 Hz, 1H), 7.16 (dd, J = 17.2, 8.2 Hz, 1H), 7.07–6.96 (m, 1H), 4.14–4.02 (m, 1H), 2.71–2.52 (m, 2H), 2.52–2.34 (m, 1H), 2.22 (tt, J = 17.4, 6.0 Hz, 2H), 2.12–2.03 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 218.72, 152.19, 147.69, 140.26, 129.17, 128.13, 127.12, 126.39, 116.83, 112.65, 51.10, 38.65, 32.18, 20.98 ppm. HRMS (ESI) calcd for $C_{14}H_{14}NO_2$ $(M + 1)^+$: 228.1025, found: 228.1022.

2-(5-Hydroxyisoquinolin-8-yl)cyclopentanone (18). White solid, Mp: 103–104 °C, 36% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.92 (s, 1H), 8.15 (d, J = 5.6 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.45 (d, J = 5.6 Hz, 1H), 7.21 (d, J = 5.6 Hz, 1H), 3.87 (t, J = 6.8 Hz, 1H), 2.43–2.34 (m, 2H), 2.23–2.18 (m, 1H), 1.84–1.81 (m, 2H), 1.71–1.52 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 205.73, 157.01, 146.54, 138.91, 131.63, 130.83, 130.24, 127.65, 121.76, 108.57, 50.42, 39.91, 33.32, 24.56 ppm. HRMS (ESI) calcd for $C_{14}H_{14}NO_2$ $(M + 1)^+$: 228.1025, found: 228.1026.

2-(Isoquinolin-5-yloxy)cyclopentanone (19). Colorless oil, 15% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.14 (s, 1H), 8.42 (d, J = 5.7 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.59 (d, J = 5.7 Hz, 1H), 7.42 (dd, J = 8.9, 2.5 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 4.79 (t, J = 8.4 Hz, 1H), 2.70–2.57 (m, 1H), 2.51–2.31 (m, 2H), 2.31–2.17 (m, 1H), 2.13–1.88 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 213.42, 156.68, 151.17, 141.44, 131.80, 129.63, 128.24, 123.89, 120.26, 107.63, 79.54, 35.28, 29.42, 17.33 ppm. HRMS (ESI) calcd for $C_{14}H_{14}NO_2$ $(M + 1)^+$: 228.1025, found: 228.1027.

2-(8-Hydroxy-2-methylquinolin-5-yl)cyclopentanone (20). With an excess amount of α-haloketone, three products were obtained. Product **19** was a white solid, Mp: 114–115 °C, 15% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 (d, J = 8.7 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 3.88 (dd, J = 10.4, 8.7 Hz, 1H), 2.72 (s, 3H), 2.63–2.48 (m, 2H), 2.41 (ddd, J = 19.1, 10.4, 8.6 Hz, 1H), 2.32–2.13 (m, 2H), 2.13–1.95 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 218.07, 156.53, 150.89, 138.08, 133.04, 125.50, 124.98, 124.87, 122.50, 109.19, 51.27, 38.51, 31.50, 24.73, 21.04 ppm. HRMS (ESI) calcd for $C_{15}H_{16}NO_2$ $(M + 1)^+$: 242.1181, found: 242.1177.

2-((2-Methylquinolin-8-yl)oxy)cyclopentanone (21). White solid, Mp: 87–89 °C, 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (d, J = 8.4 Hz, 1H), 7.47–7.33 (m, 2H), 7.33–7.28 (m, 1H), 7.22 (dd, J = 7.5, 1.2 Hz, 1H), 5.09–4.89 (m, 1H), 2.77 (s, 3H), 2.72–2.58 (m, 1H), 2.46–2.36 (m, 1H), 2.28 (dddd, J = 14.1, 10.3, 6.6, 4.7 Hz, 2H), 2.13–1.79 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 214.01, 158.31, 153.25, 140.07, 136.16, 127.82, 125.49, 122.51, 121.08, 112.90, 81.11, 35.38, 29.37, 25.60, 17.20 ppm. HRMS (ESI) calcd for $C_{15}H_{16}NO_2$ $(M + 1)^+$: 242.1181, found: 242.1180.

2-((2-Methyl-5-(2-oxocyclopentyl)quinolin-8-yl)oxy)cyclopentanone (22). White solid, mixture of two diastereomers (dr = 1 : 1), Mp: 76–79 °C, 11% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 (dd, J = 11.5, 8.8 Hz, 1H), 7.31 (dd, J = 8.7, 3.2 Hz, 1H), 7.20–7.08 (m, 2H), 5.07–4.82 (m, 1H), 3.92 (dd, J = 18.8, 8.8 Hz, 1H), 2.76 (d, J = 2.1 Hz, 3H), 2.67–2.49 (m, 3H), 2.49–2.33 (m, 3H), 2.33–2.13 (m, 4H), 2.13–1.98 (m, 1H), 1.98–1.80 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 218.07, 217.80, 214.13, 213.94, 157.91, 157.86, 152.57, 152.51, 140.74, 140.52, 132.69, 132.52, 128.47, 128.26, 126.70, 126.58, 124.15, 123.85, 122.30, 122.21, 113.27, 112.37, 81.38, 81.16, 51.47, 51.07, 38.71, 38.61, 35.44, 35.39, 31.80, 31.69, 29.40, 25.40, 21.04, 21.02, 17.22 ppm. HRMS (ESI) calcd for $C_{20}H_{22}NO_3$ $(M + 1)^+$: 324.1600, found: 324.1603.

2-Phenoxycyclopentanone (23).[11a] White solid; Mp: 69–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.28 (t, J = 8.1 Hz, 2H), 6.96–7.00 (m, 3H), 4.58–4.63 (m, 1H), 2.46–2.55 (m, 1H), 2.33–2.41 (m, 2H), 2.11–2.19 (m, 1H), 1.89–2.04 (m, 2H).

2-(2-Methoxyphenoxy)cyclopentanone (24). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.08–6.94 (m, 2H), 6.94–6.82 (m, 2H), 4.60 (dd, J = 9.2, 8.0 Hz, 1H), 3.85 (s, 3H), 2.51–2.40 (m, 1H), 2.35 (dt, J = 9.5, 6.8 Hz, 2H), 2.21–2.08 (m, 1H), 2.10–1.98 (m, 1H), 1.95–1.76 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 213.77, 150.31, 147.32, 122.81, 120.82, 117.09, 112.34, 81.00, 55.95, 35.24, 29.53, 17.20 ppm. HRMS (ESI) calcd for $C_{12}H_{15}O_3$ $(M + 1)^+$: 207.1021, found: 207.1024.

2-((3-Methoxyphenyl) amino)cyclopentanone (25). White solid; Mp: 121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.10 (t, J = 8.1 Hz, 1H), 6.37–6.27 (m, 2H), 6.22 (t, J = 2.3 Hz, 1H), 4.42 (s, 1H), 3.77 (s, 3H), 3.69 (dd, J = 11.4, 7.9 Hz, 1H), 2.76 (ddd, J = 12.5, 7.6, 6.3 Hz, 1H), 2.56–2.41 (m, 1H), 2.21 (dd, J = 19.5, 9.4 Hz, 1H), 2.17–2.07 (m, 1H), 1.99–1.84 (m, 1H), 1.58 (qd, J = 12.3, 6.8 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 215.63, 160.86, 148.85, 130.09, 106.57, 103.21, 99.66, 61.96, 55.15, 34.68, 31.83,

17.79 ppm. HRMS (ESI) calcd for $C_{12}H_{16}NO_2$ $(M + 1)^+$: 206.1181, found: 206.1180.

2-(2,4,6-Trimethoxyphenyl)cyclopentanone (26). Freshly distilled α-chlorocyclopentanone (0.5 mmol) was added into the solution of 1,3,5-trimethoxybenzene (0.5 mmol), anhydrous Na_2CO_3 (0.6 mmol) and TFE (1.0 mL). After stirring at r.t. for 8 h, a white solid was obtained merely by filtration through a celite pad using dichloromethane and evaporation under reduced pressure. Mp: 117–118 °C, ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 6.12$ (s, 2H), 3.79 (s, 3H), 3.74 (s, 6H), 3.68 (dd, $J = 11.0$, 8.7 Hz, 1H), 2.37 (dd, $J = 9.6$, 5.5 Hz, 2H), 2.28–2.17 (m, 1H), 2.09 (ddt, $J = 16.8$, 11.7, 4.2 Hz, 2H), 1.93–1.75 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) $\delta = 220.63$, 160.28, 158.55, 109.34, 91.18, 55.61, 55.35, 45.06, 38.05, 29.92, 21.82 ppm. HRMS (ESI) calcd for $C_{14}H_{19}O_4$ $(M + 1)^+$: 251.1283, found: 251.1280.

2-(3-Acetyl-2,4,6-trimethoxyphenyl)cyclopentanone (27). White solid, Mp: 86–87 °C, 48% yield. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 6.25$ (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 3.57 (dd, $J = 10.6$, 9.0 Hz, 1H), 2.50 (s, 3H), 2.38 (dd, $J = 9.8$, 4.5 Hz, 2H), 2.31–2.20 (m, 1H), 2.20–2.08 (m, 2H), 1.95–1.81 (m, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) $\delta = 219.98$, 201.97, 159.24, 157.22, 157.11, 114.77, 91.82, 55.90, 55.63, 45.66, 37.96, 32.51, 30.25, 21.72 ppm. HRMS (ESI) calcd for $C_{16}H_{21}O_5$ $(M + 1)^+$: 293.1389, found: 293.1390.

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