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Direct and convenient construction of substituted (*E*)-2-methylene-3,4-cyclohexenone skeleton from cyclohexenone-MBH alcohol in the presence of DMAP

Hong-Xia Ren,[a], [b] Xiang-Jia Song,[a], [b] Lin Wu,[a], [b] Zhi-Cheng Huang,[a], [b] Ying Zou,[a], [b] Xia Li,[a], [b] Xiao-Wen Chen,[a], [b] Fang Tian*[a] and Li-Xin Wang*[a]

Abstract: An unexpected and effective DMAP catalyzed one-step construction of 3,4-cyclohexenone skeleton from simple and easily available cyclohexenone-MBH alcohol has been disclosed. A series of substituted (*E*)-2-methylene-3,4-cyclohexenones have been effectively prepared in excellent yields (up to 93%) under convenient reaction conditions. Succesful scale-up preparation and synthetic transformations have demonstrated the potentials of this new protocol.

Introduction

The 3,4-cyclohexenone skeleton, widely existed in huge numbers of bioactive natural products (Figure 1), is an important structural motif with the multiple-drug-resistance reversing activity, insecticidal and fungicidal activities, inhibition efficacy of platelet activating factor.[1-2] Those features made 3,4-cyclohexenone and their derivatives unusual attractive synthetic targets. Metal catalyzed approaches for 3,4-cyclohexenone construction from unusual starting functional materials have been successfully developed.[3-8] Murakami[3] and Yu[7] groups have reported a [5 + 1] reaction of vinylcyclopropanes with carbon monoxide catalyzed by Ir or Rh complex for the construction of 3,4-cyclohexenone skeleton. A Rhodium-catalyzed 1,3-acyloxy migration and subsequent [5 + 1] cycloaddition of cyclopropyl substituted propargyl esters for vinylidine-cyclohexenone rings has been reported by Tang.[4,6] Shi [8] and Chen [9] has also reported a special byproduct of (*E*)-2-benzylidenecyclohex-3-enone **3a** in 55% and 30 % yield respectively. Considering the limited starting materials or the lower efficiency of the mentioned preparations, concise and effective methods for the construction of 3,4-cyclohexenone skeleton are highly desirable.

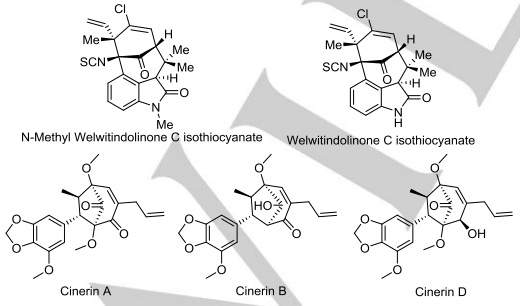
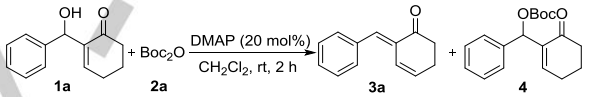


Figure 1 Selected bioactive natural products with 3,4-cyclohexenone skeleton.

Based on the applications of cyclohexenone-MBH carbonates[9-11] and our previous related work in MBH carbonates[12-13], we attempted to fulfill some enantioselective applications of cyclohexenone-MBH carbonates. Unexpectedly, when we tried to prepare cyclohexenone-MBH carbonates by treating cyclohexenone-MBH alcohol[14] with di-*tert*-butyl dicarbonate ester (Boc_2O) in the presence of DMAP for 2 hours, an unusual (*E*)-2-benzylidene-3,4-cyclohexenone **3a**, which was difficultly available from common raw materials and synthetic methods, was formed except for some expected MBH *t*-butyloxycarboryl ester **4** (Scheme 1). After prolonging reaction time, more **3a** and less **4** was observed by monitoring.



Scheme 1 The reaction between cyclohexenone MBH alcohol and Boc_2O in the presence of DMAP

Results and Discussion

Based on the preliminary results, we attempted to further understand the unexpected new reaction. Our studies were conducted with MBH alcohol **1a** and Boc_2O **2a** in CH_2Cl_2 in the presence of 20 mol% catalyst for conditioning screenings as shown in Table 1. Firstly, the reaction was not detected without catalyst (Table 1, Entry 1). Amines, such as DMAP, DABCO, DBU, Et_3N, pyridine, pyrrole, piperidine and imidazole were tested (Table 1, Entries 2-9). Only DMAP and DBU show catalytic activities, giving the target product in 48% yield for 2 d and 8% yield for 3 d respectively (Table 1, Entries 2, 4). For analogus phosphines, Bu_3P can smoothly catalyze the reaction in 24% yield after 2 days, while Ph_3P shown no catalytic activity, possibly for its less nucleophilicity (Table 1, Entries 10, 11). For inorganic bases, such as carbonates and hydroxides, no desired product was observed (Table 1, Entries 12-15). So, DMAP was chosen as the reaction promoter.

With DMAP as catalyst, solvents were furtherly screened (Table 2). Halogen hydrocarbon, such as $CHCl_3$, gave poor yield (Table 2, Entry 1). Ethers such as Et_2O, THF and 1,4-dioxane, all gave poor yields (Table 2, Entries 2-4). Other solvents, such as CH_3CN, EA, DMF, slightly higher yields were observed (Table 2, Entries 5-6) or no reaction occured (Table 2, Entry 7). MeOH gave no product (Table 2, Entry 8). However, the best result was obtained in toluene (up to 80% yield) (Table 2, Entry 9) and analogus aromatic solvents of *m*-xylene and mesitylene gave slightly reduced yields of 76% and 65% respectively, possible due to lower solubility of the substrate **1a**.

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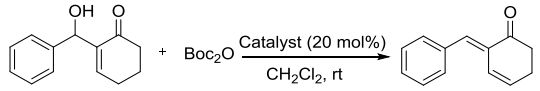
Table 1 Screenings of catalyst[a]

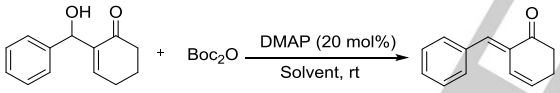


1a 2a 3a

Entry	Catalyst	Reaction time	Yield[b] (%)
1	None	3 d	NR
2	DMAP[e]	2 d	48
3	DABCO[f]	3 d	Trace[c]
4	DBU[g]	3 d	8
5	Et_3N	3 d	NR
6	Pyridine	3 d	NR
7	Pyrrole	3 d	NR
8	Piperidine	3 d	NR
9	Imidazole	3 d	NR
10[d]	Bu_3P	2 d	24
11	Ph_3P	2 d	NR
12	Cs_2CO_3	3 d	Trace[c]
13	K_2CO_3	3 d	NR
14	Na_2CO_3	3 d	NR
15	KOH	3 d	Trace[c]

[a] Unless otherwise specified, the reaction was performed on a scale of 0.2 mmol MBH alcohol **1a**, 0.22 mmol Boc_2O **2a**, 20 mmol% catalyst in 1 mL CH_2Cl_2 at room temperature. [b] Isolated yield. [c] Only **4** and trace of **3a** were detected. [d] Under N_2 atmosphere. [e] DMAP was 4-dimethylaminopyridine. [f] DABCO was 1, 4-Diazabicyclo[2.2.2]octane. [g] DBU was 1, 8-Diazabicyclo[5,4,0]undec-7-ene.

Table 2 Screenings of solvent[a]

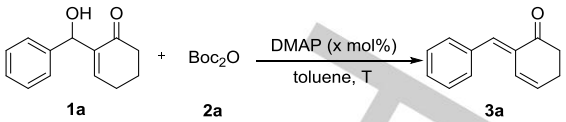


1a 2a 3a

Entry	Solvent	Reaction time	Yield[b] (%)
1	$CHCl_3$	5 d	Trace[c]
2	Et_2O	5 d	Trace[c]
3	THF[e]	2 d	20
4	1,4-Dioxane	3 d	21
5	CH_3CN	2 d	52
6	EA[f]	2 d	46
7	DMF[g]	5 d	NR
8	MeOH	5 d	NR
9	Toluene	4 d	80
10[d]	*m*-Xylene	3 d	76
11[d]	Mesitylene	5 d	65

[a] Unless otherwise specified, the reaction was performed on a scale of 0.2 mmol MBH alcohol **1a**, 0.22 mmol Boc_2O **2a**, 20 mmol% DMAP in 1 mL solvent at room temperature. [b] Isolated yield. [c] Only 4 observed. [d] Poor solubility. [e] THF was Tetrahydrofuran. [f] EA was ethyl acetate. [g] DMF was N, N-Dimethylformamide.

Table 3 Screenings of other parameters[a]



1a 2a 3a

Entry	Catalyst (x mol%)	T	**1a**:**2a**	Reaction time	Yield[b] (%)
1	50	rt	1:1.1	72 h	77
2	100	rt	1:1.1	48 h	78
3	20	50 °C	1:1.1	48 h	82
4	20	reflux	1:1.1	7 h	87
5	20	reflux	1:1	7 h	83
6	20	reflux	1:2	7 h	85
7	20	reflux	1:3	7 h	81
8	20	reflux	2:1	7 h	74
9	20	reflux	3:1	7 h	76

[a] Unless otherwise specified, the reaction was performed on a scale of 0.2 mmol MBH alcohol **1a**, y mmol Boc_2O **2a**, x mmol% catalyst in 1 mL toluene. [b] Isolated yield.

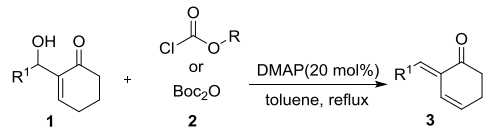
Unsatisfactorily, the reaction was not completely finished even after 4 days, so further catalyst loadings, temperature and substrate ratio were optimized. When increasing the DMAP loading to 50 mol% or 100 mol%, the reaction time was reduced to 3d and 2 d respectively with slightly decreased yields (Table 3, Entries 1, 2). The yields were increased to 82% at 50 °C for 2 d and 87% at refluxing temperature (110 °C) for 7 h (Table 3, Entries 3, 4). Changing the molar ratio of substrate **1a** and **2a**, however, no better result was observed (Table 3, Entries 5-9). Considering all the active parameters, the optimal reaction conditions were established as 0.2 mmol of **1a** and 0.22 mmol of **2a** with 20 mol% of DMAP as catalyst in 1mL toluene at refluxing terperature for 7 h (Table 3, Entry 4).

Under the optimized reaction conditions, the generality for substrates was further investigated (Table 4). Generally, most MBH alcohols **1** and **2** were well tolerated, providing corresponding products in acceptable to excellent yields. While with electron-withdrawing group of halogen atom on phenyl group (R^1) of MBH alcohols **1**, slightly decreased yields were observed (Table 4, Entries 2-6). Especially, for 4-NO_2-phenyl **1g**, only 17% yield was obtained, and when the reaction was conducted in CH_2Cl_2 at room temperature for 3 d, however, the yield increased to 52%, probably attributed to the unstability of **3g** at refluxing temperature for hours (Table 4, Entry 7). For electron-donating groups, such as methyl or methoxyl substituted on the aromatic ring, excellent yields (86-93%) were obtained (Table 4, Entries 8-11). For hetereocyclic 2-furyl MBH alcohol, good result was still achieved (Table 4, Entry 12). Changing aromatic group to hydrogen atom or methyl, only mixture or poor yields observed, possibly due to the more unstable target molecules with smaller π conjugated system (Table 4, Entries 13, 14).[15] Broadly, when chloroformate was used instead of Boc_2O, the reaction still worked well with up to 80% yields (Table 4, Entries 15-18). The configuration of the product was determined by X-ray crystal structural analysis of the representative product **3h** (Figure 2)(see the Supporting Information for details).[16]

To understand the unexpected reaction, we proposed a plausible mechanism (Scheme 2). Firstly, MBH carbonate **4** was obtained via cyclohexenone-MBH alcohol **1a** with di-*tert*-butyl dicarbonate ester in the presence of DMAP. MBH carbonate **4** was attacked by DMAP to form quaternary ammonium salt **5** and *tert*-butoxide anion after emission of CO_2. Further deprotonation of **5** by *tert*-butoxide anion, intermediate **6** was formed. The allylic hydrogen atom in **6** was transfered to the neighboring carbon to form **7**. The leaving of catalyst driven by a negative charge completed the catalytic cycle, yielding the product and setting the catalyst free.

To demonstrate the synthetic potential of this new protocol (Scheme 3), scale-up experiment was conducted on gram scale, almost equal result (84% yield) was still achieved, which may lead to a further scale-up preparation. Treating **3a** with $NaBH_4$ in THF, product **8** was afforded in 83% yield for selective reduction of carbonyl group. Under H_2 atmosphere, **3a** can be vinyl selectively reducted to **9** in 94% yield catalysed by Pd/C (5% w.t.). Carbonyl addition can be selectively occurred in the presence of Grignard reagent and product **10** was obtained in 89% yield.

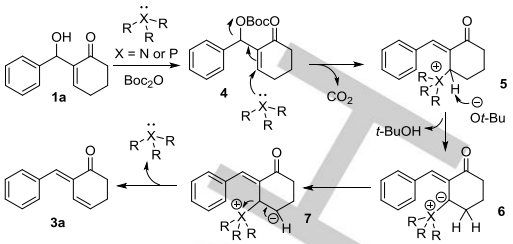
Table 4 Generality of substrates[a]



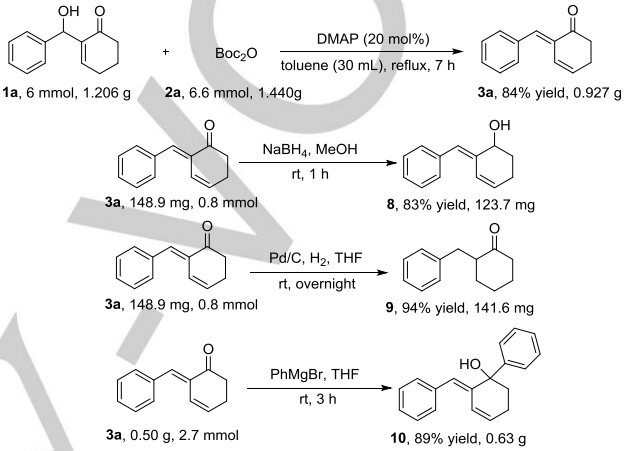
Entry	**1**/R^1	**2**	**3**/Yield[b] (%)
1	**1a**/C_6H_5	**2a**/Boc_2O	**3a**/87
2	**1b**/2-FC_6H_4	**2a**/Boc_2O	**3b**/70
3	**1c**/4-FC_6H_4	**2a**/Boc_2O	**3c**/79
4	**1d**/2-ClC_6H_4	**2a**/Boc_2O	**3d**/67
5	**1e**/4-ClC_6H_4	**2a**/Boc_2O	**3e**/58
6	**1f**/3-BrC_6H_4	**2a**/Boc_2O	**3f**/64
7	**1g**/4-$NO_2C_6H_4$	**2a**/Boc_2O	**3g**/17(52)[c]
8	**1h**/4-$CH_3C_6H_4$	**2a**/Boc_2O	**3h**/86
9	**1i**/2-$OCH_3C_6H_4$	**2a**/Boc_2O	**3i**/90
10	**1j**/3-$OCH_3C_6H_4$	**2a**/Boc_2O	**3j**/89
11	**1k**/4-$OCH_3C_6H_4$	**2a**/Boc_2O	**3k**/93
12[d]	**1l**/ Furyl	**2a**/Boc_2O	**3l**/81
13	**1m**/H	**2a**/Boc_2O	**3m**/trace
14	**1n**/Me	**2a**/Boc_2O	**1n**/47[e]
15	**1a**/C_6H_5	**2b**/$ClCO_2Bn$	**3a**/42
16	**1a**/C_6H_5	**2c**/$ClCO_2Ph$	**3a**/80
17	**1a**/C_6H_5	**2d**/$ClCO_2Et$	**3a**/46
18	**1a**/C_6H_5	**2e**/$ClCO_2$*i*-Bu	**3a**/74

[a] Unless otherwise specified, the reaction was performed on a scale of 0.2 mmol MBH alcohol **1**, 0.22 mmol ester **2**, 20 mmol% DMAP in 1 mL toluene reflux for 7 h. [b] Isolated yield. [c] The reaction condition was 0.2 mmol **1g**, 0.22 mmol **2a**, 20 mmol% DMAP in 1 mL CH_2Cl_2 at room temperature for 3 d. [d] Reacted for 2 h. [e] Detected by HPLC.

Figure 2 Representative X-ray crystallographic structure of product **3h**



Scheme 2 Plausible Mechanism



Scheme 3 Scale-up preparation and the synthetic transformations of **3a**

Conclusions

In summary, an unexpected new reaction of cyclohexenone-MBH alcohol catalyzed by DMAP has been disclosed. A series of substituted (*E*)-2-methylene-3,4-cyclohexenones have been successfully prepared in excellent yields (up to 93%) under convenient reaction conditions. After typical successful scale-up preparation and synthetic transformations, our protocol is potentially feasible for scale-up applications for concise and effective constructions of 3,4-cyclohexenone skeleton.

Experimental Section

General information

Commercial grade solvent was dried and purified by standard procedures as specified in Purification of Laboratory Chemicals, 4th Ed (Armarego, W. L. F.; Perrin, D. D. Butterworth Heinemann: 1997). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR) instrument. Data for ^{1}H NMR are reported as chemical shift (ppm, tetramethylsilane as the internal standard), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet), coupling constant (Hz). Data for ^{13}C NMR are reported as chemical shift. High resolution mass spectra were obtained with the Q-TOF-Premier mass spectrometer. Flash column chromatography was carried out using silica gel eluting with ethyl acetate and petroleum ether. Reactions were monitored by TLC and visualized with ultraviolet light.

General Procedures for the reaction of MBH alcohol 1 and 2.

A solution of 0.2 mmol MBH alcohol **1**, 0.22 mmol **2**, 20 mmol% DMAP in 1 mL toluene was stirred at reflux temperature for 7 h. After completion, the crude product was directly purified by flash chromatography to obtain the product.

(*E*)-2-benzylidenecyclohex-3-enone (3a). 87% yield, pale yellow oil, R_f = 0.28 (silica gel, petroleum ether/ethyl acetate 20:1), 1H NMR (300 MHz, DMSO-d6) δ 7.54-7.30 (m, 5H), 7.27 (s, 1H), 6.90 (dq, *J* = 10.0, 1.4 Hz, 1H), 6.23 (dtd, *J* = 10.1, 4.4, 1.8 Hz, 1H), 2.68-2.44 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 199.0, 134.8, 132.3, 130.8, 130.5, 129.8, 128.7, 128.6, 124.2, 37.7, 24.0. HRMS (ESI) m/z calcd for $C_{13}H_{13}O^+$ $(M+H)^+$ 185.09609, found 185.09572.

(*E*)-2-(*o*-fluorobenzylidenecyclohex)-3-enone (3b). 70% yield, pale yellow oil, R_f = 0.31 (silica gel, petroleum ether/ethyl acetate 20:1), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 (s, 1H), 7.35-7.25 (m, 2H), 7.13-7.02 (m, 2H), 6.73 (d, *J* = 10.0 Hz, 1H), 6.15-6.11 (m, 1H), 2.67-2.62 (m, 2H), 2.58-2.53 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 199.4, 160.7 (*J* = 249.1 Hz), 132.4, 131.5, 130.6 (*J* = 2.7 Hz), 130.2 (*J* = 8.2 Hz), 124.9 (*J* = 0.9 Hz), 124.4 (*J* = 3.5 Hz), 123.7 (*J* = 3.6 Hz), 123.1 (*J* = 13.9 Hz), 115.5 (*J* = 21.6 Hz), 38.1, 24.5. HRMS (ESI) m/z calcd for $C_{13}H_{12}FO^+$ $(M+H)^+$ 203.08667, found 203.08630.

(*E*)-2-(*p*-fluorobenzylidenecyclohex)-3-enone (3c). 79% yield, pale yellow oil, R_f = 0.23 (silica gel, petroleum ether/ethyl acetate 20:1), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50-7.36 (m, 3H), 7.16-7.05 (m, 2H), 6.89 (dq, *J* = 10.0, 1.4 Hz, 1H), 6.20 (dtd, *J* = 8.7, 4.4, 1.7 Hz, 1H), 2.76-2.66 (m, 2H), 2.66-2.54 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 200.0, 162.6 (*J* = 248.4 Hz), 131.8, 131.7, 131.5, 131.4, 131.2, 130.9, 130.7, 124.8, 115.6 (*J* = 21.5 Hz), 38.1, 24.5. HRMS (ESI) m/z calcd for $C_{13}H_{12}FO^+$ $(M+H)^+$ 203.08667, found 203.08620.

(*E*)-2-(*o*-chlorobenzylidenecyclohex)-3-enone (3d). 67% yield, pale yellow oil, R_f = 0.27 (silica gel, petroleum ether/ethyl acetate 20:1), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 (s, 1H), 7.40-7.31 (m, 2H), 7.24-7.21 (m, 2H), 6.65 (dd, *J* = 10.0, 0.9 Hz, 1H), 6.14-6.11 (m, 1H), 2.69-2.64 (m, 2H), 2.59-2.55 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 199.5, 134.7, 133.6, 132.1, 131.7, 130.6, 129.6, 129.5, 128.7, 126.2, 124.6, 38.1, 24.6. HRMS (ESI) m/z calcd for $C_{13}H_{12}ClO^+$ $(M+H)^+$ 219.05712, found 219.05673.

(*E*)-2-(*p*-chlorobenzylidenecyclohex)-3-enone (3e). 58% yield, pale yellow solid, m. p. 79.8-81.2 °C, R_f = 0.28 (silica gel, petroleum ether/ethyl acetate 20:1), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.29-7.25 (m, 5H), 6.80 (dd, *J* = 10.0, 0.8 Hz, 1H), 6.16-6.09 (m, 1H), 2.64-2.59 (m, 2H), 2.56-2.50 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 199.6, 134.2, 133.6, 131.6, 131.2, 131.0, 130.2, 128.5, 124.5, 37.9, 24.3. HRMS (ESI) m/z calcd for $C_{13}H_{12}ClO^+$ $(M+H)^+$ 219.05712, found 219.05667.

(*E*)-2-(*m*-bromobenzylidenecyclohex)-3-enone (3f). 64% yield, pale yellow oil, R_f = 0.21 (silica gel, petroleum ether/ethyl acetate 20:1), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.53 (t, *J* = 1.8 Hz, 1H), 7.49-7.39 (m, 1H), 7.3-7.27 (m, 2H), 7.23 (t, *J* = 7.8 Hz, 1H), 6.84 (dq, *J* = 10.1, 1.5 Hz, 1H), 6.19 (dtd, *J* = 10.4, 4.4, 1.7 Hz, 1H), 2.73-2.63 (m, 2H), 2.61-2.55 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 199.8, 137.4, 132.3, 132.1, 131.9, 131.2, 130.0, 129.9, 128.4, 124.5, 122.4, 38.1, 24.5. HRMS (ESI) m/z calcd for $C_{13}H_{12}BrO^+$ $(M+H)^+$ 263.00660, found 263.00616.

(*E*)-2-(*p*-nitrobenzylidenecyclohex)-3-enone (3g). 52% yield, pale yellow solid, m. p. 138.5-139.6 °C, R_f = 0.10 (silica gel, petroleum ether/ethyl acetate 20:1), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.7 Hz, 2H), 7.35 (s, 1H), 6.82 (dd, *J* = 10.0, 0.8 Hz, 1H), 6.31-6.25 (m, 1H), 2.72-2.67 (m, 2H), 2.65-2.61 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 199.3, 147.1, 142.1, 133.9, 133.3, 130.4, 128.6, 124.2, 123.6, 38.0, 24.7. HRMS (ESI) m/z calcd for $C_{13}H_{12}NO_3^+$ $(M+H)^+$ 230.08117, found 230.08183.

(*E*)-2-(*p*-methylbenzylidenecyclohex)-3-enone (3h). 86% yield, pale yellow solid, m. p. 86.1-87.4 °C, R_f = 0.29 (silica gel, petroleum ether/ethyl acetate 20:1), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 6.94 (dd, *J* = 10.0, 0.9 Hz, 1H), 6.15-6.10 (m, 1H), 2.68-2.64 (m, 2H), 2.60-2.56 (m, 2H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 200.2, 138.7, 132.4, 132.1, 130.5, 130.4, 130.0, 129.1, 125.2, 38.1, 24.4, 21.3. HRMS (ESI) m/z calcd for $C_{14}H_{15}O^+$ $(M+H)^+$ 199.11174, found 199.11122.

(*E*)-2-(*o*-methoxybenzylidenecyclohex)-3-enone (3i). 90% yield, pale yellow oil, R_f = 0.21 (silica gel, petroleum ether/ethyl acetate 20:1), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.63 (s, 1H), 7.34-7.28 (m, 2H), 6.97-6.88 (m, 2H), 6.82 (dd, *J* = 10.0, 0.8 Hz, 1H), 6.21-6.06 (m, 1H), 3.84 (s, 3H), 2.69-2.64 (m, 2H), 2.59-2.54 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 200.1, 158.3, 130.9, 130.4, 130.1, 130.1, 128.3, 125.5, 124.3, 120.0, 110.5, 55.4, 38.3, 24.5. HRMS (ESI) m/z calcd for $C_{14}H_{15}O_2^+$ $(M+H)^+$ 215.10666, found 215.10629.

(*E*)-2-(*m*-methoxybenzylidenecyclohex)-3-enone (3j). 89% yield, pale yellow oil, R_f = 0.20 (silica gel, petroleum ether/ethyl acetate 20:1), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.35 (s, 1H), 7.25 (t, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 6.91-6.88 (m, 2H), 6.83 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.13-6.07 (m, 1H), 3.76 (s, 3H), 2.65-2.60 (m, 2H), 2.56-2.50 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 199.8, 159.3, 136.4, 131.6, 131.1, 130.9, 129.2, 124.9, 122.2, 115.1, 114.0, 55.0, 38.0, 24.3. HRMS (ESI) m/z calcd for $C_{14}H_{15}O_2^+$ $(M+H)^+$ 215.10666, found 215.10645.

(*E*)-2-(*p*-methoxybenzylidenecyclohex)-3-enone (3k). 93% yield, pale yellow solid, m. p. 55.8-56.7 °C, R_f = 0.16 (silica gel, petroleum ether/ethyl acetate 20:1), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.38-7.35 (m, 3H), 6.92-6.86 (m, 3H), 6.11-6.07 (m, 1H), 3.78 (s, 3H), 2.63-2.59 (m, 2H), 2.55-2.51 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 200.0, 159.8, 131.8, 131.6, 130.0, 129.4, 127.7, 125.1, 113.8, 55.1, 38.0, 24.2. HRMS (ESI) m/z calcd for $C_{14}H_{15}O_2^+$ $(M+H)^+$ 215.10666, found 215.10622.

(*E*)-2-(furan-2-ylmethylene)cyclohex-3-en-1-one (3l). 81% yield, pale yellow oil, R_f = 0.23 (silica gel, petroleum ether/ethyl acetate 20:1), ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.59 (d, *J* = 1.4 Hz, 1H), 7.45 (d, *J* = 10.1 Hz, 1H), 7.10 (s, 1H), 6.70 (d, *J* = 3.4 Hz, 1H), 6.52-6.50 (m, 1H), 6.22-6.16 (m, 1H), 2.71-2.66 (m, 2H), 2.63-2.60 (m, 2H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ 199.5, 152.3, 144.9, 130.4, 127.2, 125.9, 117.3, 116.9, 112.2, 38.0, 24.4. HRMS (ESI) m/z calcd for $C_{11}H_{11}O_2^+$ $(M+H)^+$ 175.07536, found 175.07564.

Keywords: Cyclohexenone-MBH alcohol • Organocatalysis • Substituted (*E*)-2-methylene-3,4-cyclohexenone skeleton • Unexpected new reaction

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[15] No pure product **3m** was obtained, and its ^{1}H-NMR and ^{13}C-NMR were not available.

[16] See the ESI for the details on the single crystal X-ray analysis of **3h** in this paper, CCDC 1833125

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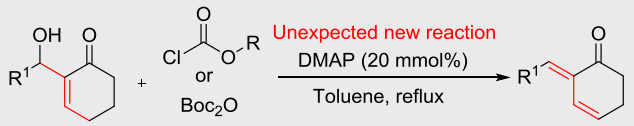

- New reaction type
- Novel construction of 3, 4-Cyclohexenone skeleton
- Convenient and effective preparation
- *E*-configuration selectivity and excellent yield
- Metal free

18 examples
up to 93% yield

An unexpected new reaction of cyclohexenone-MBH alcohol catalyzed by DMAP has been successfully disclosed to prepare a series of substituted (*E*)-2-methylene-3,4-cyclohexenones in excellent yields (up to 93%) under convenient reaction conditions. Scale-up preparation and synthetic transformations have been conducted.

Synthetic methods

Author(s), Corresponding Author(s)*

Hong-Xia Ren, Xiang-Jia Song, Lin Wu, Zhi-Cheng Huang, Ying Zou, Xia Li, Xiao-Wen Chen, Fang Tian* and Li-Xin Wang*

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Title

Direct and convenient construction of substituted (*E*)-2-methylene-3,4-cyclohexenone skeleton from cyclohexenone-MBH alcohol in the presence of DMAP