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钴催化芳基烯烃氧烷基化反应: 快速获得 α-烷基取代苯乙酮衍生物

周 鹏[a] 朱伟明[a] 张建涛*[,a,b] 肖朵朵[a] 郭祥峰[a] 刘卫兵*[,a]
([a]广东石油化工学院化学学院 广东茂名 525000)
([b]茂名绿色化工研究院 广东茂名 525099)

摘要 烷基芳基酮是化学和生物学中一类有价值的化合物, 被广泛应用于制药、香料、染料、农药、功能材料以及有机合成行业. 发展了钴催化芳基烯烃与叔丁基过氧化氢(TBHP)以及环醚的氧烷基化反应. 该方法适用于各种带有吸电子基团或给电子基团的烯烃底物, 并且以中等产率得到 α-烷基取代苯乙酮衍生物. 该方案具有广泛的底物适用范围及灵活性, 在温和条件下即可快速构建一系列增值的苯乙酮衍生物.

关键词 烷基芳基酮; 钴催化; 氧烷基化; 苯乙酮衍生物

Cobalt-Catalyzed Oxyalkylation Reaction of Styrenes: Rapid Access to α-Alkyl Substituted Acetophenone Derivatives

Zhou, Peng[a] Zhu, Weiming[a] Zhang, Jiantao*[,a,b] Xiao, Duoduo[a]
Guo, Xiangfeng[a] Liu, Weibing*[,a]
([a] *College of Chemistry, Guangdong University of Petrochemical Technology, Maoming, Guangdong 525000*)
([b] *Maoming Green Chemical Industry Research Institute, Maoming, Guangdong 525099*)

Abstract Alkyl aryl ketones are a class of valuable compounds in chemistry and biology, which are widely used in the pharmaceutical, spice, dye, pesticide, functional materials, and organic synthesis industries. A cobalt-catalyzed oxyalkylation reaction of aryl olefin with *tert*-butyl hydroperoxide (TBHP) and cyclic ethers was developed. Various substrates with electron-withdrawing or electron-donating groups were tolerated in this protocol to provide the α-alkyl substituted acetophenones in moderate yields. The present protocol features broad substrate scope, and flexibility, allowing rapid assembly of a series of value-added acetophenone derivatives under mild conditions with good reaction efficacy.

Keywords alkyl aryl ketone; cobalt-catalysis; oxyalkylation; acetophenone derivative

1 Introduction

As a class of bioactive skeleton compounds, aromatic ketones and their derivatives widely exist in nature, and many natural products and drug molecules contain this skeleton structure. Due to the excellent biological activity of aryl ketones, scientists have conducted a lot of research on the synthesis of their structural diversity.[1-5]

On the other hand, alkenes are abundant organic molecules and useful chemical feedstock, and the methods for their direct, selective functionalization are attractive as an important means to assemble more complex and valuable compounds.[6-9] Three-component difunctionalization of alkenes in one step is an attractive method to construct highly functionalized molecules. With the renaissance of radical chemistry, the radical three component difunctionalization of alkenes receives more and more attention and has been intensively studied these years.[10-15] In 2009, Zhang *et al.*[10] described a copper-catalyzed protocol for the oxyalkylation of vinylarenes with cyclic ethers. In 2012, Wang and Zha *et al.*[11] reported an oxyalkylation of vinylarenes by using SMONP-1 as the catalyst. As a cheap and easily available metal catalyst, cobalt has shown similar or even unique activity to precious metals in recent years, thus receiving great attention.[16] In 2019, Li *et al.*[12] developed a cobalt-catalyzed difunctionalization of styrenes

* Corresponding authors. E-mail: zhangjt@gdupt.edu.cn; lwb409@gdupt.edu.cn
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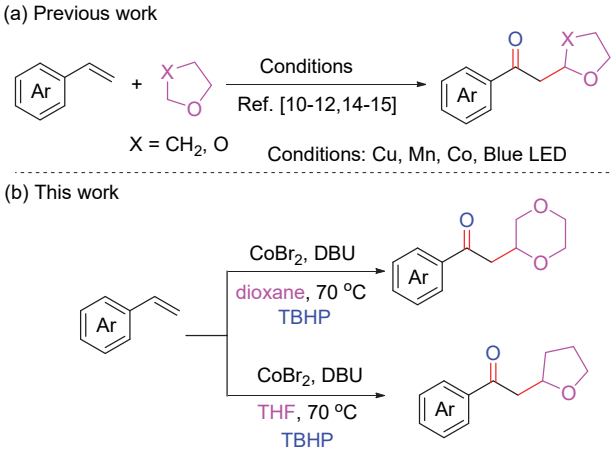
with ethers, which initiated through α-C(sp^3)—H bond activation of ethers. In the following year, Hajra *et al.*[14] developed a visible-light-promoted oxidative coupling of styrene with cyclic ethers. Later, Chen and co-workers[15] developed a cobalt-catalyzed intermolecular oxidative alkylation from styrenes and ethers, which furnished a rapid method for the synthesis of γ-ether ketone compounds. However, there are drawbacks such as low yields or the usage of large amounts of peroxides in the reported methods. As a continuation of our research group's work on radical functionalization of olefin,[17-21] herein, we would like to describe a $CoBr_2$-catalyzed oxyalkylation reactions of styrenes for the synthesis of α-alkyl substituted acetophenone derivatives (Scheme 1, b).



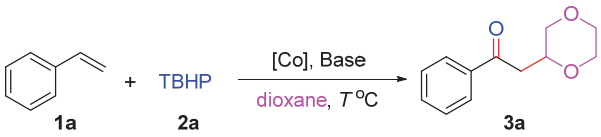
Scheme 1 Synthesis of acetophenone derivatives from olefins

2 Results and discussion

Exploratory studies were carried out employing styrene (**1a**) and *tert*-butyl hydroperoxide (TBHP, **2a**) as benchmarking substrates and $CoCl_2$ as the catalyst in dioxane to screen for optimized reaction conditions. Pleasingly, the reaction delivered the desired product **3a** in 53% yield (Table 1, Entry 1). After a brief screening of cobalt salts, $CoBr_2$ performed better than the other cobalt salts for this conversion (Entries 2～4). Different types of bases were subjected to the reaction, and it showed that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was the best base while other bases yield less amount of the product (Entries 5～8). There was no improvement when increasing or decreasing the amount of TBHP (Entries 9～12) or DBU (Entries 13, 14). Reaction performed at room temperature did not afford the desired product (Entry 15). It was found that the desired product could not be formed without Co catalyst (Entry 16). In the absence of the base, the reaction still provided product **3** in 8% yields (Entry 17).

Having optimal conditions in hand, the substrate scope of this one-pot three component reaction protocol has been examined by employing different arenes with varying substituents on the aryl rings (Table 2). It was noticed that all the substrates with an electron-donating (OCH_3, CH_3, ^{t}Bu)

Table 1 Optimization of reaction conditions[a]



Entry	[Co]	Base	TBHP/equiv.	Yield[b]/%
1	$CoCl_2$	DMAP	3.0	53
2	$Co(acac)_2$	DMAP	3.0	43
3	$Co(PPh_3)_2Cl_2$	DMAP	3.0	50
4	$CoBr_2$	DMAP	3.0	59
5	$CoBr_2$	Et_3N	3.0	35
6	$CoBr_2$	*t*-BuOK	3.0	0
7	$CoBr_2$	Na_2CO_3	3.0	12
8	**$CoBr_2$**	**DBU**	**3.0**	**74**
9	$CoBr_2$	DBU	1.0	22
10	$CoBr_2$	DBU	2.0	55
11	$CoBr_2$	DBU	4.0	72
12	$CoBr_2$	DBU	5.0	75
13[c]	$CoBr_2$	DBU	3.0	70
14[d]	$CoBr_2$	DBU	3.0	74
15[e]	$CoBr_2$	DBU	3.0	0
16	—	DBU	3.0	0
17	$CoBr_2$	—	3.0	8

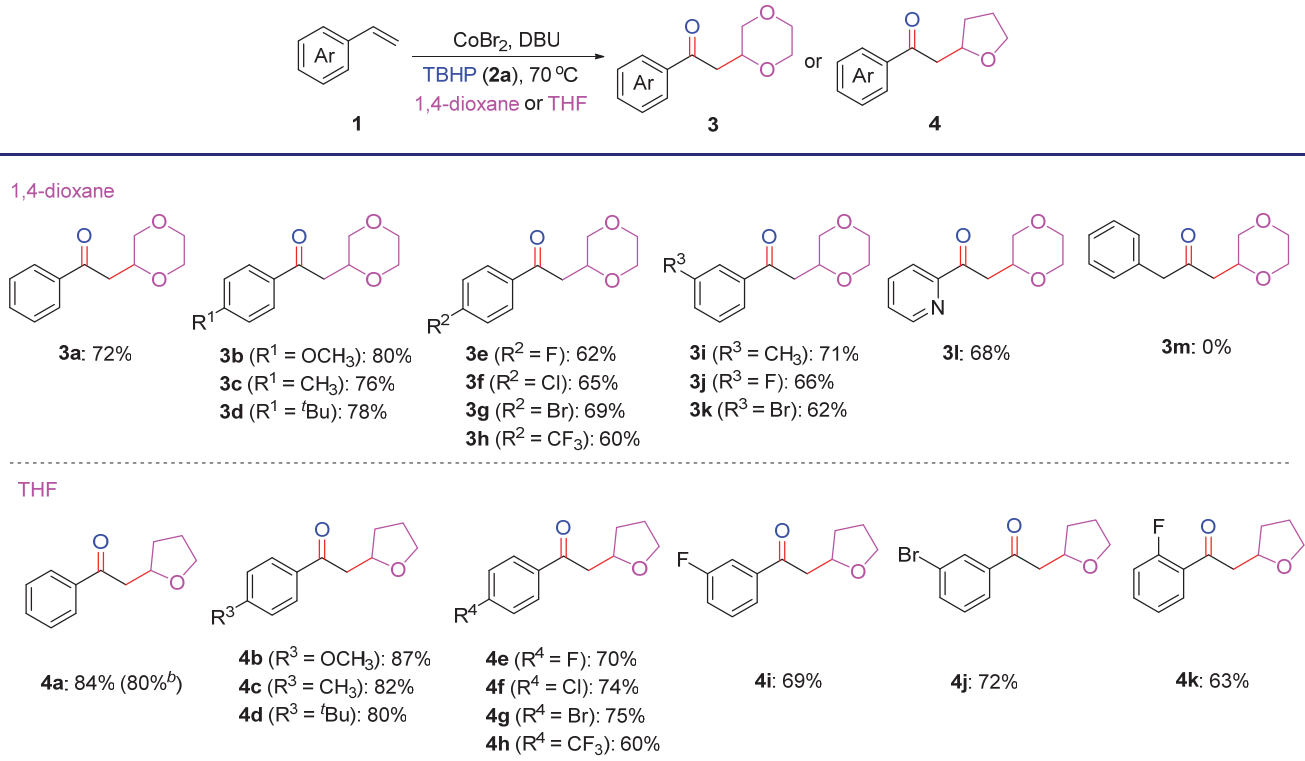
[a] Reaction conditions: **1a** (0.5 mmol), TBHP (3.0 equiv.), Co catalyst (10 mol%), base (2.0 equiv.), the reaction was performed at 70 °C in dioxane (2.0 mL) for 12 h; [b] GC yield; [c] 1.5 equiv. of DBU was used. [d] 3.0 equiv. of DBU was used. [e] The reaction was performed at room temperature.

or electron-withdrawing (F, Cl, Br, CF_3) group at the *para* and *meta* positions of the phenyl ring could be smoothly transformed to the corresponding desired products in good to high yields (**3b**～**3k**). Alkenes with electron-donating group (**3b**～**3d**) gave superior results than those with electron-withdrawing group (**3e**～**3h**). In addition, the heterocycle substrate was also investigated, and the corresponding product was obtained in 68% yields (**3l**). However, aliphatic alkene was not good candidate for this transformation, and **1m** could not furnish **3m** under the optimized conditions. The scope of alkenes with tetrahydrofuran (THF) was also briefly examined. A wide range of multisubstituted alkenes containing different kinds of substituents on different substituted positions showed good efficiency to afford the expected products in good yields (**4a**～**4k**).

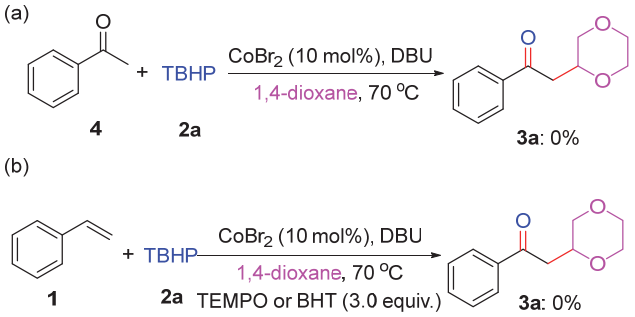
To clarify the mechanism, several control experiments were conducted. When acetophenone **4** was subjected to the reaction under standard conditions, **3a** was not detected, which suggested that acetophenone was not the intermediate of this reaction (Scheme 2, a). In addition, the radical scavenger effect was also examined, and the addition of 3.0 equiv. of 2,2,6,6-tetramethylpiperidoxyl (TEMPO) or butylated hydroxytoluene (BHT) as a radical scavenger completely suppressed this reaction, indicating that the reaction probably proceeded via a free radical process (Scheme 2, b).

Based on the above results and the reports from the literature,[12,15] a possible mechanism for the synthesis of

Table 2 Substrate scope for the synthesis of **3** and **4**[a]

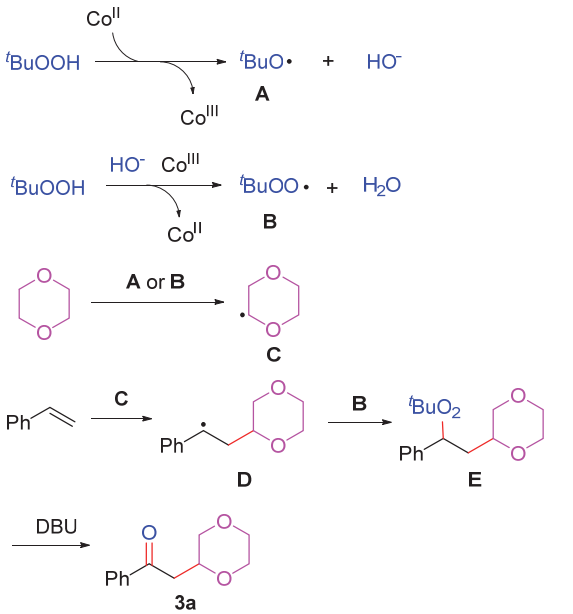


[a] All of these reactions were carried out at 70 ℃ on a 1.0 mmol scale by using dioxane or THF (2.0 mL) as solvent; TBHP (3.0 equiv.), $CoBr_2$ (10 mol%), DBU (2.0 equiv.), isolated yields. [b] Yield of 10 mmol (1.04 g) scale.



Scheme 2 Control experiments

substituted acetophenones is proposed (Scheme 3). First, ^{t}BuO• (**A**) and ^{t}BuOO• (**B**) were formed from TBHP at the aid of $CoBr_2$. They promoted dioxane to give intermediate **C**. Subsequently, the following addition of **C** to alkene led to intermediate **D**, which was then captured by species **B**, giving the intermediate **E**. Finally, intermediate **E** would witness a Kornblum-DeLaMare rearrangement in the presence of DBU to provide the desired product **3a**.



Scheme 3 Proposed mechanism for the reaction

3 Conclusions

In conclusion, we have developed a cobalt-catalyzed oxyalkylation reaction of styrenes with TBHP and cyclic ethers. Various substrates with electron-withdrawing or electron-donating groups were tolerated in this protocol to provide the α-alkyl substituted acetophenones in moderate yields. The present protocol features broad substrate scope, and flexibility, allowing rapid assembly of a series of value-added acetophenone derivatives under mild conditions with good reaction efficacy.

4 Experimental section

4.1 General information

All the reactions were carried out at 70 ℃ for 12 h in a

round-bottom flask equipped with a magnetic stir bar. Unless specified otherwise, all the reagents were used as received from commercial sources, and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 (400 MHz for ^{1}H NMR; 100 MHz for ^{13}C NMR). ^{1}H NMR and ^{13}C NMR chemical shifts were determined relative to internal standard TMS at δ 0.0. Mass spectra were obtained from a highresolution ESI mass spectrometer. HR-MS was obtained on a Q-TOF micro spectrometer.

4.2 General procedure for the oxyalkylation of styrenes

Taking the synthesis of compound **3a** as an example, to a solution of **1a** in dioxane or THF was added $CoBr_2$ (10 mol%), DBU (2.0 equiv.) and TBHP (3.0 equiv.) at room temperature. Then the solution mixture was stirred at 70 ℃ for 12 h. After completion of the reaction, the solvent was removed under reduced pressure and the crude product was subjected to silica gel column chromatography with petroleum ether/ethyl acetate (V∶V=10∶1) as the eluent to afford products **3a**. Products **3b**～**3l** and **4** were obtained using the same procedure as yellow oil liquid.

2-(1,4-Dioxan-2-yl)-1-phenylethan-1-one (**3a**):[14] 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, J=8.1 Hz, 2H), 7.63～7.56 (m, 1H), 7.48 (t, J=7.6 Hz, 2H), 4.32～4.19 (m, 1H), 3.93 (dd, J=11.3, 2.3 Hz, 1H), 3.85～3.71 (m, 3H), 3.68～3.61 (m, 1H), 3.46～3.36 (m, 1H), 3.26 (dd, J=16.5, 6.5 Hz, 1H), 2.90 (dd, J=16.5, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.1, 136.9, 133.4, 128.7, 128.2, 71.8, 70.9, 66.9, 66.4, 40.7.

2-(1,4-Dioxan-2-yl)-1-(4-methoxyphenyl)ethan-1-one (**3b**):[3] 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, J=8.7 Hz, 2H), 6.96 (d, J=8.7 Hz, 2H), 4.41～4.15 (m, 1H), 3.93 (dd, J=11.5, 2.4 Hz, 1H), 3.89 (s, 3H), 3.83～3.78 (m, 2H), 3.75 (d, J=11.0 Hz, 1H), 3.69～3.61 (m, 1H), 3.46～3.34 (m, 1H), 3.22 (dd, J=16.3, 6.5 Hz, 1H), 2.85 (dd, J=16.3, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.6, 163.7, 130.6, 130.0, 113.8, 72.0, 71.0, 66.9, 66.5, 55.5, 40.4.

2-(1,4-Dioxan-2-yl)-1-(p-tolyl)ethan-1-one (**3c**):[14] 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (d, J=8.0 Hz, 2H), 7.27 (d, J=8.0 Hz, 2H), 4.32～4.18 (m, 1H), 3.92 (dd, J=11.3, 2.2 Hz, 1H), 3.79 (dd, J=7.7, 3.3 Hz, 2H), 3.74 (d, J=11.1 Hz, 1H), 3.69～3.59 (m, 1H), 3.40 (t, J=10.6 Hz, 1H), 3.23 (dd, J=16.5, 6.5 Hz, 1H), 2.87 (dd, J=16.5, 6.1 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.7, 144.2, 134.4, 129.3, 128.3, 71.9, 71.0, 66.9, 66.4, 40.6, 21.7.

1-(4-(*tert*-Butyl)phenyl)-2-(1,4-dioxan-2-yl)ethan-1-one (**3d**): 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (d, J=8.4 Hz, 2H), 7.50 (d, J=8.4 Hz, 2H), 4.36～4.12 (m, 1H), 3.93 (dd, J=11.4, 2.5 Hz, 1H), 3.83～3.71 (m, 3H), 3.69～3.60 (m, 1H), 3.49～3.36 (m, 1H), 3.24 (dd, J=16.4, 6.4 Hz, 1H), 2.89 (dd, J=16.4, 6.2 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.7, 157.1, 134.3, 128.2, 125.6, 71.9, 71.0, 66.9, 66.4, 40.7, 35.2, 31.1; HRMS (ESI) calcd for $C_{16}H_{22}NaO_3$ $[M+Na]^+$ 285.1461, found 285.1470.

2-(1,4-Dioxan-2-yl)-1-(4-fluorophenyl)ethan-1-one (**3e**):[3] 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (dd, J=8.6, 5.5 Hz, 2H), 7.15 (t, J=8.5 Hz, 2H), 4.29～4.16 (m, 1H), 3.91 (dd, J=11.4, 2.4 Hz, 1H), 3.82～3.71 (m, 3H), 3.64 (ddd, J=11.6, 9.6, 4.4 Hz, 1H), 3.48～3.33 (m, 1H), 3.22 (dd, J=16.4, 6.7 Hz, 1H), 2.86 (dd, J=16.4, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.5, 165.9 (d, J=255.1 Hz), 133.4 (d, J=3.0 Hz), 130.9 (d, J=9.4 Hz), 115.8 (d, J=21.9 Hz). 71.8, 70.9, 66.9, 66.4, 40.6.

1-(4-Chlorophenyl)-2-(1,4-dioxan-2-yl)ethan-1-one (**3f**):[3] 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, J=8.6 Hz, 2H), 7.46 (d, J=8.6 Hz, 2H), 4.31～4.15 (m, 1H), 3.91 (dd, J=11.4, 2.5 Hz, 1H), 3.81～3.73 (m, 3H), 3.64 (m, 1H), 3.41 (dd, J=11.3, 9.9 Hz, 1H), 3.22 (dd, J=16.5, 6.8 Hz, 1H), 2.86 (dd, J=16.5, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.0, 139.9, 135.2, 129.7, 129.0, 71.8, 70.9, 66.9, 66.4, 40.7.

1-(4-Bromophenyl)-2-(1,4-dioxan-2-yl)ethan-1-one (**3g**):[14] 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, J=8.5 Hz, 2H), 7.63 (d, J=8.5 Hz, 2H), 4.29～4.18 (m, 1H), 3.91 (dd, J=11.4, 2.5 Hz, 1H), 3.80～3.73 (m, 3H), 3.67～3.61 (m, 1H), 3.40 (dd, J=11.2, 10.0 Hz, 1H), 3.21 (dd, J=16.4, 6.8 Hz, 1H), 2.85 (dd, J=16.4, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.2, 135.6, 132.0, 129.8, 128.6, 71.8, 70.9, 66.9, 66.4, 40.6.

2-(1,4-Dioxan-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-one (**3h**):[3] 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, J=8.3 Hz, 2H), 7.75 (d, J=8.3 Hz, 2H), 4.30～4.20 (m, 1H), 3.92 (dd, J=11.4, 2.5 Hz, 1H), 3.82～3.71 (m, 3H), 3.67～3.61 (m, 1H), 3.42 (dd, J=11.2, 10.0 Hz, 1H), 3.27 (dd, J=16.5, 6.9 Hz, 1H), 2.90 (dd, J=16.5, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.3, 139.5, 134.6 (dd, J=65.4, 32.7 Hz), 128.6, 125.7 (q, J=3.7 Hz), 124.9, 122.2, 71.7, 70.8, 66.8, 66.4, 40.9.

2-(1,4-Dioxan-2-yl)-1-(m-tolyl)ethan-1-one (**3i**): 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, J=9.5 Hz, 2H), 7.39 (dt, J=14.8, 7.5 Hz, 2H), 4.30～4.22 (m, 1H), 3.93 (dd, J=11.4, 2.5 Hz, 1H), 3.83～3.78 (m, 2H), 3.77～3.72 (m, 1H), 3.68～3.62 (m, 1H), 3.41 (dd, J=11.3, 9.9 Hz, 1H), 3.25 (dd, J=16.5, 6.5 Hz, 1H), 2.90 (dd, J=16.5, 6.1 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.3, 138.5, 136.9, 134.1, 128.7, 128.5, 125.5, 71.9, 71.0, 66.9, 66.5, 40.8, 21.4; HRMS (ESI) calcd for $C_{13}H_{16}NaO_3$ $[M+Na]^+$ 243.0992, found 243.0997.

2-(1,4-Dioxan-2-yl)-1-(3-fluorophenyl)ethan-1-one (**3j**): 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, J=7.8 Hz, 1H), 7.70～7.60 (m, 1H), 7.47 (td, J=8.0, 5.5 Hz, 1H), 7.29 (td, J=7.9, 2.5 Hz, 1H), 4.29～4.19 (m, 1H), 3.91 (dd, J=11.4, 2.5 Hz, 1H), 3.82～3.71 (m, 3H), 3.67～3.61 (m, 1H), 3.40 (dd, J=11.3, 10.0 Hz, 1H), 3.22 (dd, J=16.5, 6.7 Hz, 1H), 2.87 (dd, J=16.5, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.9 (d, J=2.1 Hz), 162.8 (d, J=248.1 Hz), 139.0 (d, J=6.2 Hz), 130.3 (d, J=7.6 Hz), 124.0 (d, J=3.0 Hz), 120.4 (d, J=21.5 Hz), 115.0 (d, J=22.4 Hz), 71.7, 70.8, 66.8, 66.4, 40.8; HRMS (ESI) calcd for $C_{12}H_{13}$-

$FNaO_3$ $[M+Na]^+$ 247.0741, found 247.0739.

1-(3-Bromophenyl)-2-(1,4-dioxan-2-yl)ethan-1-one (**3k**): 62% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.10 (t, J=1.8 Hz, 1H), 7.89 (d, J=7.8 Hz, 1H), 7.78～7.68 (m, 1H), 7.37 (t, J=7.9 Hz, 1H), 4.30～4.18 (m, 1H), 3.91 (dd, J=11.4, 2.6 Hz, 1H), 3.83～3.71 (m, 3H), 3.68～3.61 (m, 1H), 3.41 (dd, J=11.3, 9.9 Hz, 1H), 3.22 (dd, J=16.5, 6.8 Hz, 1H), 2.86 (dd, J=16.5, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.8, 138.6, 136.2, 131.3, 130.2, 126.8, 123.0, 71.7, 70.8, 66.8, 66.4, 40.7; HRMS (ESI) calcd for $C_{12}H_{13}BrNaO_3$ $[M+Na]^+$ 306.9940, found 306.9946.

2-(1,4-Dioxan-2-yl)-1-(pyridin-2-yl)ethan-1-one (**3l**): 68% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.68～8.66 (m, 1H), 8.04 (dt, J=7.9, 1.0 Hz, 1H), 7.83 (td, J=7.7, 1.7 Hz, 1H), 7.49～7.45 (m, 1H), 4.30～4.24 (m, 1H), 3.85 (dd, J=11.4, 2.6 Hz, 1H), 3.75 (dd, J=7.6, 2.2 Hz, 2H), 3.70 (dt, J=11.5, 1.7 Hz, 1H), 3.66～3.58 (m, 1H), 3.51～3.40 (m, 2H), 3.14 (dd, J=16.6, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.7, 153.1, 149.0, 136.9, 127.3, 121.9, 71.8, 70.8, 66.8, 66.4, 39.7; HRMS (ESI) calcd for $C_{11}H_{14}NO_3$ $[M+Na]^+$ 208.0968, found 208.0966.

1-Phenyl-2-(tetrahydrofuran-2-yl)ethan-1-one (**4a**):[12] 84% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.06～7.94 (m, 2H), 7.59 (t, J=7.4 Hz, 1H), 7.48 (t, J=7.6 Hz, 2H), 4.54～4.37 (m, 1H), 3.92 (dd, J=15.0, 6.8 Hz, 1H), 3.78 (dd, J=14.9, 7.4 Hz, 1H), 3.42 (dd, J=16.3, 6.1 Hz, 1H), 3.08 (dd, J=16.3, 6.7 Hz, 1H), 2.22 (dt, J=19.4, 6.2 Hz, 1H), 2.04～1.89 (m, 2H), 1.63～1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.5, 137.1, 133.1, 128.6, 128.2, 75.4, 67.9, 44.7, 31.7, 25.7.

1-(4-Methoxyphenyl)-2-(tetrahydrofuran-2-yl)ethan-1-one (**4b**):[12] 87% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.22～7.83 (m, 2H), 7.05～6.81 (m, 2H), 4.49～4.35 (m, 1H), 3.94～3.90 (m, 1H), 3.89 (s, 3H), 3.77 (dd, J=14.9, 7.5 Hz, 1H), 3.37 (dd, J=16.0, 6.1 Hz, 1H), 3.02 (dd, J=16.0, 6.8 Hz, 1H), 2.20 (dt, J=19.6, 6.2 Hz, 1H), 1.99～1.88 (m, 2H), 1.63～1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.0, 163.5, 130.5, 130.2, 113.7, 75.6, 67.8, 55.5, 44.3, 31.6, 25.7.

2-(Tetrahydrofuran-2-yl)-1-(*p*-tolyl)ethan-1-one (**4c**):[12] 82% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, J=8.2 Hz, 2H), 7.27 (d, J=8.1 Hz, 2H), 4.49～4.36 (m, 1H), 3.91 (dd, J=15.0, 6.9 Hz, 1H), 3.77 (dd, J=14.8, 7.5 Hz, 1H), 3.39 (dd, J=16.1, 6.0 Hz, 1H), 3.05 (dd, J=16.1, 6.8 Hz, 1H), 2.43 (s, 3H), 2.21 (dt, J=19.6, 6.2 Hz, 1H), 1.99～1.89 (m, 2H), 1.63～1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.1, 143.9, 134.6, 129.3, 128.3, 75.5, 67.8, 44.6, 31.6, 25.7, 21.7.

1-(4-(*tert*-Butyl)phenyl)-2-(tetrahydrofuran-2-yl)ethan-1-one (**4d**):[12] 80% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.93 (d, J=8.4 Hz, 2H), 7.50 (d, J=8.5 Hz, 2H), 4.50～4.37 (m, 1H), 3.92 (dd, J=15.0, 6.9 Hz, 1H), 3.77 (dd, J=14.9, 7.5 Hz, 1H), 3.41 (dd, J=16.1, 6.0 Hz, 1H), 3.05 (dd, J=16.1, 6.9 Hz, 1H), 2.22 (dt, J=19.5, 6.3 Hz, 1H), 2.07～1.88 (m, 2H), 1.61～1.52 (m, 1H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.1, 156.9, 134.5, 128.2, 125.6, 75.6, 67.8, 44.6, 35.1, 31.7, 31.1, 25.7.

1-(4-Fluorophenyl)-2-(tetrahydrofuran-2-yl)ethan-1-one (**4e**):[12] 70% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.05～7.97 (m, 2H), 7.15 (t, J=8.6 Hz, 2H), 4.45～4.37 (m, 1H), 3.91 (dd, J=15.0, 6.9 Hz, 1H), 3.77 (dd, J=15.0, 7.3 Hz, 1H), 3.37 (dd, J=16.1, 6.3 Hz, 1H), 3.04 (dd, J=16.1, 6.4 Hz, 1H), 2.21 (dt, J=19.2, 6.3 Hz, 1H), 2.00～1.89 (m, 2H), 1.63～1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.9, 165.8 (d, J=254.8 Hz), 133.5 (d, J=3.1 Hz), 130.9 (d, J=9.3 Hz), 115.7 (d, J=21.9 Hz). 75.4, 67.9, 44.6, 31.6, 25.6.

1-(4-Chlorophenyl)-2-(tetrahydrofuran-2-yl)ethan-1-one (**4f**):[12] 74% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.93 (d, J=8.5 Hz, 2H), 7.46 (d, J=8.5 Hz, 2H), 4.47～4.33 (m, 1H), 3.91 (dd, J=15.0, 6.9 Hz, 1H), 3.77 (dd, J=15.0, 7.4 Hz, 1H), 3.36 (dd, J=16.2, 6.3 Hz, 1H), 3.04 (dd, J=16.2, 6.3 Hz, 1H), 2.21 (dt, J=19.2, 6.3 Hz, 1H), 2.04～1.88 (m, 2H), 1.68～1.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.3, 139.6, 135.4, 129.7, 128.9, 75.3, 67.9, 44.6, 31.6, 25.6.

1-(4-Bromophenyl)-2-(tetrahydrofuran-2-yl)ethan-1-one (**4g**)[12]: 75% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, J=8.5 Hz, 2H), 7.62 (d, J=8.5 Hz, 3H), 4.46～4.36 (m, 1H), 3.91 (dd, J=15.0, 6.9 Hz, 1H), 3.77 (dd, J=15.0, 7.4 Hz, 1H), 3.35 (dt, J=15.7, 7.8 Hz, 2H), 3.04 (dd, J=16.2, 6.3 Hz, 2H), 2.21 (td, J=12.7, 6.4 Hz, 2H), 1.99～1.89 (m, 2H), 1.62～1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.5, 135.8, 131.9, 129.8, 128.3, 75.3, 67.9, 44.6, 31.6, 25.6.

2-(Tetrahydrofuran-2-yl)-1-(4-(trifluoromethyl)phenyl)-ethan-1-one (**4h**)[15]: 60% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, J=8.1 Hz, 2H), 7.75 (d, J=8.2 Hz, 2H), 4.48～4.37 (m, 1H), 3.91 (dd, J=15.0, 6.9 Hz, 1H), 3.77 (dd, J=15.0, 7.4 Hz, 1H), 3.40 (dt, J=12.5, 6.2 Hz, 1H), 3.10 (dd, J=16.3, 6.1 Hz, 1H), 2.23 (td, J=12.6, 6.3 Hz, 1H), 2.00～1.91 (m, 1H), 1.65～1.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.6, 139.7, 134.6, 134.2, 128.6, 125.7 (q, J=3.8 Hz), 75.2, 68.0, 44.9, 31.6, 25.6.

1-(3-Fluorophenyl)-2-(tetrahydrofuran-2-yl)ethan-1-one (**4i**)[15]: 69% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, J=7.7 Hz, 1H), 7.67 (dd, J=9.5, 2.0 Hz, 1H), 7.47 (td, J=8.0, 5.6 Hz, 1H), 7.29 (dd, J=16.4, 2.6 Hz, 1H), 4.47～4.34 (m, 1H), 3.92 (dd, J=15.0, 6.9 Hz, 1H), 3.78 (dd, J=14.9, 7.4 Hz, 1H), 3.38 (dd, J=16.3, 6.3 Hz, 1H), 3.06 (dd, J=16.3, 6.4 Hz, 1H), 2.22 (dt, J=19.3, 6.3 Hz, 1H), 2.03～1.89 (m, 2H), 1.66～1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.2, 162.9 (d, J=247.9 Hz), 139.2 (d, J=6.0 Hz), 130.3 (d, J=7.6 Hz), 124.0 (d, J=3.0 Hz), 120.2 (d, J=21.5 Hz), 115.0 (d, J=22.3 Hz), 75.3, 67.9, 44.8, 31.7, 25.7.

1-(3-Bromophenyl)-2-(tetrahydrofuran-2-yl)ethan-1-one (**4j**):[15] 72% yield. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.11 (t, J=1.7 Hz, 1H), 7.90 (d, J=7.8 Hz, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.36 (t, J=7.9 Hz, 1H), 4.46～4.37 (m, 1H), 4.47～4.33 (m, 1H), 3.91 (dd, J=15.1, 6.9 Hz, 1H), 3.77 (dd, J=14.9, 7.4 Hz, 1H), 3.36 (dd, J=16.3, 6.4 Hz, 1H), 3.04 (dt, J=12.9, 6.5 Hz, 1H), 2.21 (dt, J=19.4, 6.3 Hz, 2H), 2.00～1.91 (m, 1H), 1.63～1.54 (m, 1H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ: 197.1, 138.8, 136.0, 131.3, 130.2, 126.8, 123.0, 75.2, 67.9, 44.7, 31.6, 25.6.

1-(2-Fluorophenyl)-2-(tetrahydrofuran-2-yl)ethan-1-one (**4k**):[15] 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (td, J=7.6, 1.8 Hz, 1H), 7.58～7.47 (m, 1H), 7.24 (t, J=7.6 Hz, 1H), 7.14 (dd, J=11.1, 8.4 Hz, 1H), 4.48～4.38 (m, 1H), 3.96～3.85 (m, 1H), 3.77 (dd, J=14.6, 7.6 Hz, 1H), 3.39～3.32 (m, 1H), 3.18～3.12 (m, 1H), 2.20 (td, J=12.3, 6.2 Hz, 1H), 2.01～1.88 (m, 2H), 1.63～1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.6, 161.9 (d, J=254.4 Hz), 134.6 (d, J=9.1 Hz), 130.7 (d, J=2.5 Hz), 125.7 (d, J=13.0 Hz), 124.5 (d, J=3.4 Hz), 116.6 (d, J=23.8 Hz), 74.9, 67.9, 49.7, 49.6, 31.6, 25.7.

Supporting Information ^{1}H NMR and ^{13}C NMR spectra of all products. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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(Zhao, C.)

