Tetrahedron 69 (2013) 8579–8582

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Copper-catalyzed dehydrogenative cross-coupling reaction between unactivated ethers and simple ketones mediated by pyrrolidine

Xing-Fen Huang [a], Zhi-Qiang Zhu [a], Zhi-Zhen Huang [a,b,*]

[a] Department of Chemistry, Zhejiang University, Hangzhou 310028, PR China
[b] State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PR China

ARTICLE INFO

Article history:
Received 21 May 2013
Received in revised form 16 July 2013
Accepted 25 July 2013
Available online 1 August 2013

Keywords:
C–H functionalization
Dehydrogenative cross-coupling
Copper-catalysis
Ether
Ketone

ABSTRACT

A copper-catalyzed dehydrogenative cross-coupling reaction between unactivated ethers and simple ketones mediated by pyrrolidine has been developed. Under the catalysis of $CuBr_2$ and in the presence of pyrrolidine, either tetrahydrofuran **2a** or tetrahydropyran **2b** can react smoothly with a series of methyl aryl ketones **1a**–**m** to give desired coupling products **3aa**–**mb** using TBHP as an oxidant. The advantages of the dehydrogenative cross-coupling reaction are adoption of unmodified ethers as substrates, good tolerance of many functional groups and use of cheap copper salt as a catalyst. A plausible radical mechanism through enamine attack is proposed.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

With the rapid advancement in C–H transformations, direct α-C–H functionalizations of ethers have received considerable attention.[1a–n] Recently, the use of only C–H bonds to undergo dehydrogenative cross-coupling was considered as a new generation of C–C bond formations because dehydrogenative cross-coupling reactions avoid prefunctionalization of substrates and are more atom economic and environmentally friendly.[2] Among the α-C–H functionalizations of ethers, there have been a few literature on dehydrogenative cross-coupling reactions of ethers with simple ketones, but all these ethers bear phenyl group in α-position to activate the α-C–H bond.[1a,1e,1j,1n] In 2006, Li et al. revealed an efficient dehydrogenative cross-coupling reaction between benzyl ethers and simple ketones mediated by 2, 3-dichloro-5, 6-dicyanobenzoquinone (DDQ).[1a] Later, they also developed a dehydrogenative cross-coupling reaction of benzyl ethers with methyl ketones under the catalysis of $Cu(OTf)_2$, $InCl_3$ and *N*-hydroxyphthalimide using oxygen as a terminal oxidant.[1e] Recently, Mancheño's group found that using *N*-oxoammonium salt as oxidant, benzyl ethers performed coupling reactions with aldehydes or ketones smoothly under the catalysis of $Cu(OTf)_2$.[1j] In 2013, Lou et al. developed a dehydrogenative cross-coupling reaction of benzyl ethers with simple ketones by manganese dioxide–methanesulfonic acid oxidation system.[1n] In order to challenge the dehydrogenative cross-coupling reaction of unactivated ethers with simple ketones, which have no aryl or other functional group in α-position of ethers, we envisioned to use amine to promote the reactivity of ketone with unmodified ether. Herein, we wish to report a copper-catalyzed dehydrogenative cross-coupling reaction between tetrahydrofuran or tetrahydropyran with methyl ketones mediated by pyrrolidine synergistically.

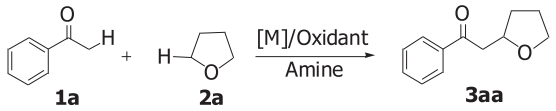
2. Results and discussion

Initially, acetophenone **1a** and THF **2a** were chosen as model substrates to explore and optimize the dehydrogenative cross-coupling reaction (Table 1). When $CuCl_2$ and pyrrolidine were employed in catalytic and stoichiometric amount, respectively, we were pleased to find that the dehydrogenative cross-coupling reaction between acetophenone **1a** and THF **2a** could occur at reflux using *t*-BuOOH (TBHP) as an oxidant, affording the coupling product **3aa** albeit in a low yield (entry 1, Table 1). Then, other transition-metal catalysts were tried in the reaction as well (For details, see Supplementary data). $CuBr_2$ was proved to be most effective to give **3aa** in 59% yields (entry 14, Table 1). Increase or decrease of the amount of $CuBr_2$ resulted in the reductions of coupling yields (entry 2, 12, 13, Table 1). Among secondary amines examined, pyrrolidine was best in yield. Using small amounts of pyrrolidine led to poor efficiency (entry 17, Table 1), and at least 70 mol % of pyrrolidine had to be employed in the reaction. Except TBHP, many oxidants, such as

* Corresponding author. Tel.: +86 0571 87951352; fax: +86 0571 87951895; e-mail addresses: huangzhizhen@zju.edu.cn, huangzz@nju.edu.cn (Z.-Z. Huang).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.07.085

Table 1
Optimization of dehydrogenative cross-coupling reaction between acetophenone **1a** and tetrahydrofuran **2a**[a]



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

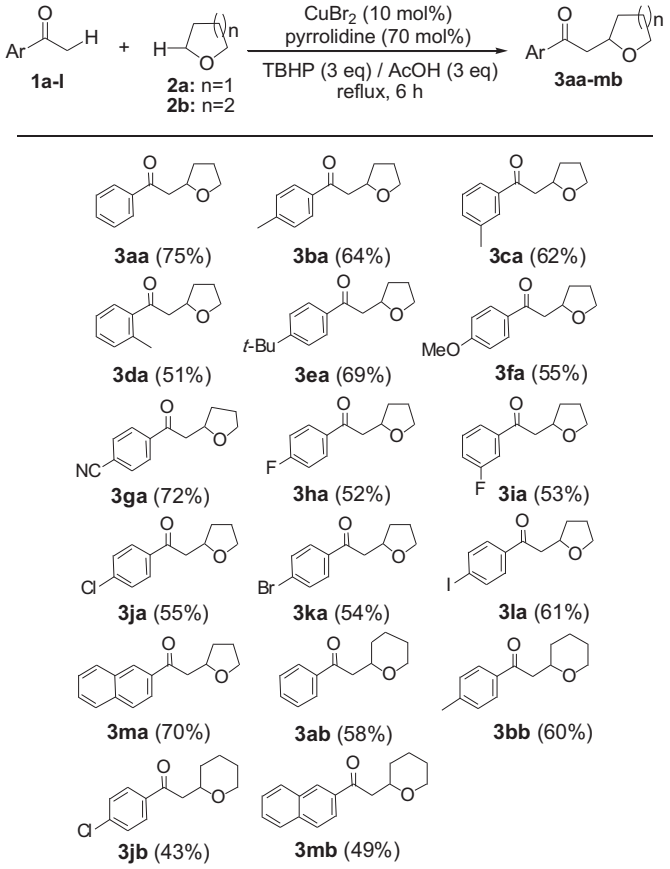
Entry	[M] (mol %)	Oxidant (equiv)	Amine (equiv)	Yield (%)[b]
1	$CuCl_2$(10)	TBHP(2)	Pyrrolidine(1)	15
2	$CuBr_2$(10)	TBHP(2)	Pyrrolidine(1)	30
3	$CuBr_2$(10)	—	Pyrrolidine(1)	Nd
4	—	TBHP(2)	Pyrrolidine(1)	Nd
5	$CuBr_2$(10)	TBHP(2)	—	Nd
6	$CuBr_2$(10)	DDQ(1)	Pyrrolidine(1)	0
7	$CuBr_2$(10)	O_2 (1)	Pyrrolidine(1)	0
8	$CuBr_2$(10)	(^{t}BuO)$_2$(3)	Pyrrolidine(1)	10
9	$CuBr_2$(10)	AIBN (1)	Pyrrolidine(1)	0
10	$CuBr_2$(10)	NMO(1)	Pyrrolidine(1)	5
11	$CuBr_2$(10)	mCPBA(1)	Pyrrolidine(1)	21
12	$CuBr_2$(5)	TBHP(2)	Pyrrolidine(1)	15
13	$CuBr_2$(20)	TBHP(2)	Pyrrolidine(1)	13
14	$CuBr_2$(10)	TBHP(3)	Pyrrolidine(1)	59
15[c]	$CuBr_2$(10)	TBHP(3)	Pyrrolidine(1)	70
16[c]	$CuBr_2$(10)	TBHP(3)	Pyrrolidine(0.7)	75
17[c,d]	$CuBr_2$(10)	TBHP(3)	Pyrrolidine(0.3)	32

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (2 ml), reflux 6 h under aerobic condition, unless otherwise noted.
[b] Yield of isolated product.
[c] 3 equiv of AcOH was added.
[d] 12 h.

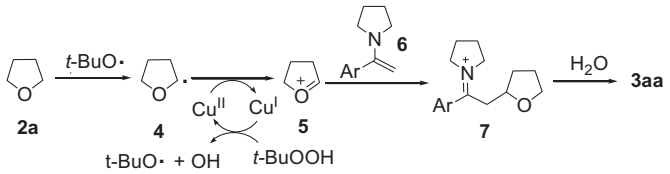
DDQ, dioxygen, *tert*-butyl peroxide, 2, 2′-azobisisobutyronitrile (AIBN), *N*-Methylmorpholine-*N*-Oxide (NMO), 3-Chloroperbenzoic acid (mCPBA) were less effective for this reaction (entry 6–11, Table 1). The addition of 3 equiv of acetic acid promoted the reaction remarkably (Entry 14, 15, Table 1). It is noteworthy that if either $CuBr_2$ or pyrrolidine was not employed, no desired product **3aa** was observed (entry 4, 5, Table 1).

After screening of reaction conditions, it can be concluded that the optimized reaction should be performed by using 10 mol % of $CuBr_2$, 70 mol % of pyrrolidine, 3 equiv of TBHP, and 3 equiv of acetic acid (entry 17, Table 1). Under the optimized conditions, we examined the scope of the copper-catalyzed dehydrogenative cross-coupling reaction. It was found that methyl aryl ketones **1a**–**l**, which bearing either electron-rich or electron-deficient groups on the benzene rings could undergo the dehydrogenative cross-coupling reaction smoothly with THF to give desired products **3aa**–**la** in the yields of 51–75% (Scheme 1). Naphthyl group instead of phenyl group also performed the coupling reaction to give α-C–H functionalized product **3ma** of tetrahydrofuran in a satisfactory yield. The coupling reaction tolerated many functions, such as methoxyl, fluoro, chloro, bromo, iodo and cyano group. When methyl alkyl ketone or ethyl ketone was employed, no coupling product was obtained under the optimized conditions. Using this strategy, tetrahydropyran **2b** can also perform the dehydrogenative cross-coupling reaction with methyl aryl ketone **1a**, **1b**, **1j**, **1m** expediently (**3ab**–**mb**, Scheme 1). However, acyclic ethers, such as diethyl ether did not undergo the coupling reaction.

Further investigation demonstrated that if 2, 6-di-*tert*-butyl-4-methyl phenol (BHT), a radical inhibitor, was added into the reaction system, the yield of coupling product **3a** was decreased dramatically from 75% to less than 5%. Thus, the mechanism of the dehydrogenative cross-coupling reaction may undergo a radical pathway, which is depicted in Scheme 2. Initially, a *tert*-butoxyl radical generated by the dissociation of *t*-BuOOH[3] may abstract α-hydrogen of **2a** to form radical **4**. A single electron transfer (SET) from **4** leads to oxonium species **5**. Then, the enamine **6** resulted



Scheme 1. Dehydrogenative cross-coupling reaction between methyl aryl ketones **1a**–**m** and tetrahydrofuran **2a** or tetrahydropyran **2b**. Reaction conditions: acetophenone (0.5 mmol), $CuBr_2$ (0.05 mmol), TBHP (3 equiv, 5–6 M in decane), pyrrolidine (0.35 mmol), AcOH (1.5 mmol), THF (2 ml)/THP (0.5 ml), 110 °C, reflux 6 h under aerobic condition. Isolated yields.



Scheme 2. Plausible mechanism of dehydrogenative cross-coupling reaction of tetrahydrofuran **2a** with methyl aryl ketone **1a**.

from methyl aryl ketone **1a** with pyrrolidine **2a** in situ attacks nucleophilically on **5** to form ammonium **7**. Finally, hydrolysis of **7** generates coupling product **3aa**.

3. Conclusion

In summary, we have developed a copper-catalyzed dehydrogenative cross-coupling reaction between unactivated ethers and simple ketones mediated by pyrrolidine synergistically. Under the catalysis of $CuBr_2$ and in the presence of pyrrolidine, either tetrahydrofuran **2a** or tetrahydropyran **2b** can react smoothly with many methyl aryl ketones **1a**–**m** to give the desired coupling products **3aa**–**mb** using TBHP as an oxidant. The advantages of the dehydrogenative cross-coupling reaction are adoption of unmodified ethers as substrates, good tolerance of many functional groups and use of cheap copper salt as a catalyst. A plausible radical mechanism through enamine attack is proposed.

4. Experimental section

4.1. General procedure for the dehydrogenative cross-coupling reaction of tetrahydrofuran 2a with methyl aryl ketone 1a–m

The mixture of $CuBr_2$ (11.1 mg, 0.05 mmol), AcOH (90.8 mg, 3 equiv), acetophenone (60.0 mg, 0.5 mmol), pyrrolidine (24.9 mg, 70 mol %) and THF (2 ml) was stirred for a couple of minutes at 110 °C. *tert*-Butyl hydroperoxide (0.28 ml, 3 equiv, 5–6 M in decane) was added to the mixture, and the reaction mixture was stirred for 6 h at this temperature. After reaction, the mixture was filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether=1:40 as eluent) to give the desired product **3aa**–**ma**.

4.1.1. 1-Phenyl-2-(tetrahydrofuran-2-yl) ethanone ***3aa***.[4] Yield 75%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.98 (d, J=7.8 Hz, 2H), 7.58 (t, J=7.6 Hz, 1H), 7.48 (t, J=7.6 Hz, 2H), 4.46–4.40 (m, 1H), 3.92 (q, J=7.2 Hz, 1H), 3.77 (q, J=7.2 Hz, 1H), 3.42 (dd, J_1=6.4 Hz, J_2=16.4 Hz, 1H), 3.08 (dd, J_1=6.4 Hz, J_2=16.0 Hz, 1H), 2.23–2.20 (m, 1H), 1.99–1.91 (m, 2H), 1.61–1.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 198.4, 136.9, 133.0, 128.5, 128.1, 75.3, 67.7, 44.6, 31.5, 25.6; MS (EI) *m*/*z* (%) 190, 162, 147, 120, 105 (100%), 91, 77, 51, 43.

4.1.2. 2-(Tetrahydrofuran-2-yl)-1-p-tolylethanone ***3ba***.[4] Yield 64%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.88 (d, J=8.4 Hz, 2H), 7.27 (d, J=6.8 Hz, 2H), 4.43–4.38 (m, 1H), 3.90 (q, J=7.2 Hz, 1H), 3.76 (q, J=7.2 Hz, 1H), 3.38 (dd, J_1=6.0 Hz, J_2=16.0 Hz, 1H), 3.04 (dd, J_1=6.8 Hz, J_2=16.0 Hz, 1H), 2.42 (s, 3H), 2.23–2.20 (m, 1H), 1.96–1.92 (m, 2H), 1.62–1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 198.0, 143.8, 134.5, 129.2, 128.2, 75.4, 67.7, 44.5, 31.5, 25.6, 21.6; MS (EI) *m*/*z* (%) 204, 161, 134, 119 (100%), 91, 71, 65, 43.

4.1.3. 2-(Tetrahydrofuran-2-yl)-1-m-tolylethanone ***3ca***.[4] Yield 62%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.75 (d, J=9.6 Hz, 2H), 7.34 (q, J=7.6 Hz, 2H), 4.42–4.38 (m, 1H), 3.89 (q, J=7.6 Hz, 1H), 3.75 (q, J=7.2 Hz, 1H), 3.38 (dd, J_1=6.0 Hz, J_2=16.4 Hz, 1H), 3.04 (dd, J_1=6.8 Hz, J_2=16.4 Hz, 1H), 2.40 (s, 3H), 2.21–2.16 (m, 1H), 1.96–1.88 (m, 2H), 1.60–1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 198.6, 138.3, 137.0, 133.8, 128.6, 128.4, 125.3, 75.3, 67.7, 44.6, 31.5, 25.6, 21.3; MS (EI) *m*/*z* (%) 204, 161, 134, 119 (100%), 91, 71, 65, 43.

4.1.4. 2-(Tetrahydrofuran-2-yl)-1-o-tolylethanone ***3da***.[4] Yield 51%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.66 (d, J=7.6 Hz, 1H), 7.37 (t, J=7.6 Hz, 1H), 7.28–7.24 (m, 2H), 4.38–4.35 (m, 1H), 3.89 (q, J=7.2 Hz, 1H), 3.75 (q, J=7.2 Hz, 1H), 3.29 (dd, J_1=6.8 Hz, J_2=16.0 Hz, 1H), 3.01 (dd, J_1=6.4 Hz, J_2=16.0 Hz, 1H), 2.51 (s, 3H), 2.19–2.14 (m, 1H), 1.96–1.90 (m, 2H), 1.60–1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 202.4, 138.1, 137.9, 131.8, 131.2128.5, 125.5, 75.4, 67.7, 47.5, 31.5, 25.5, 21.2; MS (EI) *m*/*z* (%) 204, 145, 119 (100%), 91, 71, 65, 43.

4.1.5. 1-(4-tert-Butylphenyl)-2-(tetrahydrofuran-2-yl)ethanone ***3ea***.[4] Yield 69%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.92 (d, J=8.4 Hz, 2H), 7.48 (d, J=8.4 Hz, 2H), 4.42–4.39 (m, 1H), 3.90 (q, J=7.2 Hz, 1H), 3.75 (q, J=7.6 Hz, 1H), 3.39 (dd, J_1=6.0 Hz, J_2=16.0 Hz, 1H), 3.04 (dd, J_1=6.8 Hz, J_2=16.0 Hz, 1H), 2.23–2.16 (m, 1H), 1.97–1.89 (m, 2H), 1.61–1.34 (m, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 198.0, 156.8, 134.4, 128.1, 125.4, 75.5, 67.7, 44.5, 35.0, 31.5, 31.0, 25.6; MS (EI) *m*/*z* (%) 246, 203, 161 (100%), 146, 119, 105, 91, 71, 43.

4.1.6. 1-(4-Methoxyphenyl)-2-(tetrahydrofuran-2-yl) ethanone ***3fa***.[4] Yield 55%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.96 (d, J=8.8 Hz, 2H), 6.94 (d, J=9.2 Hz, 2H), 4.42–4.39 (m, 1H), 3.91 (q, J=7.2 Hz, 1H), 3.89 (s, 3H), 3.77 (q, J=7.6 Hz, 1H), 3.36 (dd, J_1=6.4 Hz, J_2=16.0 Hz, 1H), 3.02 (dd, J_1=6.8 Hz, J_2=16.0 Hz, 1H), 2.23–2.16 (m, 1H), 1.98–1.91 (m, 2H), 1.63–1.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 196.9, 163.4, 130.4, 130.1, 113.6, 75.5, 67.7, 55.4, 44.2, 31.5, 25.6; MS (EI) *m*/*z* (%) 220, 177, 150, 135 (100%), 107, 92, 77, 71, 43.

4.1.7. 4-(2-(Tetrahydrofuran-2-yl) acetyl) benzonitrile ***3ga***.[4] Yield 72%; yellow solid; mp 55–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 8.04 (d, J=8.4 Hz, 2H), 7.75 (d, J=8.8 Hz, 2H), 4.39–4.32 (m, 1H), 3.86 (q, J=7.2 Hz, 1H), 3.74 (q, J=7.3 Hz, 1H), 3.34 (dd, J_1=6.4 Hz, J_2=16.0 Hz, 1H), 3.05 (dd, J_1=6.0 Hz, J_2=16.4 Hz, 1H), 2.21–2.16 (m, 1H), 1.96–1.89 (m, 2H), 1.59–1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 197.2, 139.9, 132.4, 128.6, 117.8, 116.2, 75.0, 67.9, 44.8, 31.5, 25.5; MS (EI) *m*/*z* (%) 215, 187, 172, 145, 130 (100%), 102, 71, 43.

4.1.8. 1-(4-Fluorophenyl)-2-(tetrahydrofuran-2-yl) ethanone ***3ha***.[4] Yield 52%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.99 (t, J=8.5 Hz, 2H), 7.13 (t, J=8.4 Hz, 2H), 4.41–4.37 (m, 1H), 3.89 (q, J=7.2 Hz, 1H), 3.75 (q, J=7.2 Hz, 1H), 3.35 (dd, J_1=6.0 Hz, J_2=16.0 Hz, 1H), 3.02 (dd, J_1=6.4 Hz, J_2=16.0 Hz, 1H), 2.22–2.16 (m, 1H), 1.97–1.90 (m, 2H), 1.62–1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 196.8, 165.7 (d, J=253.2 Hz), 133.4, 130.8 (d, J=9.3 Hz), 115.6 (d, J=21.7 Hz), 75.3, 67.8, 44.5, 31.5, 25.5; MS (EI) *m*/*z* (%) 208, 180, 165, 138, 123 (100%), 95, 71, 43.

4.1.9. 1-(3-Fluorophenyl)-2-(tetrahydrofuran-2-yl) ethanone ***3ia***.[4] Yield 53%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.75 (d, J=7.6 Hz, 1H), 7.64 (d, J=9.2 Hz, 1H), 7.45(q, J=7.2 Hz, 1H), 7.26 (t, J=7.6 Hz, 1H), 4.42–4.38 (m, 1H), 3.89 (q, J=7.2 Hz, 1H), 3.76 (q, J=7.2 Hz, 1H), 3.35 (dd, J_1=6.4 Hz, J_2=16.4 Hz, 1H), 3.04 (dd, J_1=6.4 Hz, J_2=16.4 Hz, 1H), 2.24–2.16 (m, 1H), 1.97–1.90 (m, 2H), 1.62–1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 197.1, 162.7(d, J=246.3 Hz), 139.0 (d, J=6.1 Hz), 130.2 (d, J=7.5 Hz), 123.9 (d, J=2.7 Hz), 120.0 (d, J=21.3 Hz), 114.8 (d, J=22.1 Hz),75.2, 67.8, 44.7, 31.5, 25.5; MS (EI) *m*/*z* (%) 208 (M^+), 180, 165, 138, 123 (100%), 95, 71, 43.

4.1.10. 1-(4-Chlorophenyl)-2-(tetrahydrofuran-2-yl) ethanone ***3ja***.[4] Yield 55%; light yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.93 (d, J=8.4 Hz, 2H), 7.46 (d, J=8.8 Hz, 2H), 4.42–4.39 (m, 1H), 3.91 (q, J=7.2 Hz, 1H), 3.77 (q, J=7.6 Hz, 1H), 3.36 (dd, J_1=6.4 Hz, J_2=16.4 Hz, 1H), 3.05 (dd, J_1=6.4 Hz, J_2=16.0 Hz, 1H), 2.24–2.19 (m, 1H), 1.99–1.93 (m, 2H), 1.61–1.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 197.2, 139.5, 135.3, 129.6, 128.8, 75.2, 67.8, 44.5, 31.5, 25.5; MS (EI) *m*/*z* (%) 224 (M^+), 196, 181, 154, 139 (100%), 111, 71, 43.

4.1.11. 1-(4-Bromophenyl)-2-(tetrahydrofuran-2-yl) ethanone ***3ka***.[4] Yield 54%; yellow solid; mp 39–42 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.82 (d, J=8.4 Hz, 2H), 7.59 (d, J=8.8 Hz, 2H), 4.39–4.36 (m, 1H), 3.88 (q, J=8.4 Hz, 1H), 3.74 (q, J=8.0 Hz, 1H), 3.33 (dd, J_1=6.4 Hz, J_2=16.4 Hz, 1H), 3.01 (dd, J_1=6.4 Hz, J_2=16.0 Hz, 1H), 2.21–2.16 (m, 1H), 1.94–1.90 (m, 2H), 1.60–1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 197.3, 135.7, 131.8, 129.7, 128.2, 75.2, 67.8, 44.5, 31.5, 25.5; MS (EI) *m*/*z* (%) 268 (M^+), 227, 198, 185 (100%), 155, 71, 43.

4.1.12. 1-(4-Iodophenyl)-2-(tetrahydrofuran-2-yl) ethanone ***3la***. Yield 61%; yellow solid; mp 63–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ 7.83 (d, J=8.4 Hz, 2H), 7.68 (d, J=8.4 Hz, 2H), 4.40–4.37 (m, 1H), 3.88 (q, J=8.4 Hz, 1H), 3.74 (q, J=8.0 Hz, 1H), 3.33 (dd, J_1=6.0 Hz, J_2=16.0 Hz, 1H), 3.02 (dd, J_1=6.4 Hz, J_2=16.4 Hz, 1H), 2.22–2.17 (m, 1H), 1.95–1.91 (m, 2H), 1.59–1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 197.7, 137.8, 136.2, 129.5, 101.3, 75.2, 67.8, 44.4, 31.5, 25.5; MS (EI) *m*/*z* (%) 316 (M^+), 288, 273, 246, 231 (100%), 203, 189,

104, 71, 43. HRMS (EI-TOF) $[M]^+$ calculated for $C_{12}H_{13}O_2I$ 315.9960, found 315.9951.

4.1.13. 1-(Naphthalen-2-yl)-2-(tetrahydrofuran-2-yl) ethanone ***3ma***.[4] Yield 70%; light yellow oil; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 8.49 (s, 1H), 8.04 (d, J=8.8 Hz, 1H), 7.97 (d, J=8.0 Hz, 1H), 7.88 (t, J=8.4 Hz, 2H), 7.62–7.53 (m, 2H), 4.50–4.47 (m, 1H), 3.92 (q, J=7.2 Hz, 1H), 3.78 (q, J=7.6 Hz, 1H), 3.54 (dd, J_1=6.0 Hz, J_2=16.0 Hz, 1H), 3.19 (dd, J_1=6.8 Hz, J_2=16.4 Hz, 1H), 2.26–2.19 (m, 1H), 2.00–1.93 (m, 2H), 1.66–1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 198.3, 135.5, 134.3, 132.4, 129.9, 129.5, 128.4, 128.3, 127.7, 126.7, 123.8, 75.5, 67.8, 44.6, 31.6, 25.6; MS (EI) m/z (%) 240 (M^+), 197, 170, 155 (100%), 127, 71, 43.

4.2. General procedure for the dehydrogenative cross-coupling reaction of tetrahydropyran 2b with acetophenones 1a, b, j, m

The mixture of $CuBr_2$ (11.1 mg, 0.05 mmol), AcOH (90.8 mg, 3 equiv), methyl aryl ketone (60.0 mg, 0.5 mmol), pyrrolidine (24.9 mg, 70 mol %) and THP (0.5 ml) was stirred for a couple of minutes at 120 °C. *tert*-butyl hydroperoxide (0.28 ml, 3 equiv, 5–6 M in decane) was added to the mixture, and the reaction mixture was stirred for 6 h at this temperature. After reaction, the mixture was filtered. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether=1:50 as eluent) to give the desired product **3ab**–**mb**.

4.2.1. 1-Phenyl-2-(tetrahydro-pyran-2-yl)-ethanone ***3ab***.[4] Yield 58%; light yellow oil; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 7.98 (d, J=7.6 Hz, 2H), 7.57 (t, J=7.2 Hz, 1H), 7.47 (t, J=7.6 Hz, 2H), 3.96 (q, J=7.2 Hz, 2H), 3.49 (t, J=11.2 Hz, 1H), 3.30 (dd, J_1=6.8 Hz, J_2=16.4 Hz, 1H), 2.93 (dd, J_1=6.0 Hz, J_2=16.0 Hz, 1H), 1.86 (q, J=4.0 Hz, 1H), 1.75 (d, J=12.4 Hz, 1H), 1.59–1.55 (m, 3H), 1.40–1.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 197.0, 136.7, 133.3, 128.7, 128.1, 71.7, 70.8, 66.8, 66.3, 40.6; MS (EI) m/z (%) 204 (M^+), 162, 147, 120, 105 (100%), 85, 77, 51, 41.

4.2.2. 2-(Tetrahydro-pyran-2-yl)-1-p-tolyl-ethanone ***3bb***. Yield 60%; light yellow oil; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 7.87 (d, J=8.0, 2H), 7.25 (d, J=8.0, 2H), 3.95 (d, J=10.0, 2H), 3.46 (t, J=11.2, 1H), 3.26 (dd, J_1=6.8, J_2=16.0, 1H), 2.90 (dd, J_1=5.6, J_2=16.0, 1H), 2,41 (s, 3H), 1.84 (q, J=4.4, 1H), 1,74 (d, J=12.8, 1H), 1.59–1.49 (m, 3H), 1.38–1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 198.6, 144.5, 135.5, 129.9, 129.1, 75.1, 69.3, 45.9, 32.7, 26.5, 24.1, 22.3; MS (EI) m/z (%) 218 (M^+), 176, 161, 134, 119 (100%), 91, 65, 41. HRMS (EI-TOF) $[M]^+$ calculated for $C_{14}H_{18}O_2$ 218.1307, found 218.1303.

4.2.3. 1-(4-Chloro-phenyl)-2-(tetrahydro-pyran-2-yl)-ethanone ***3jb***. Yield 43%; white solid; mp 43–45 °C; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 7.91 (d, J=7.6, 2H), 7.43 (d, J=7.6, 2H), 3.94 (d, J=10.6, 2H), 3.46 (t, J=10.4, 1H), 3.26 (dd, J_1=6.8, J_2=15.6, 1H), 2.87 (dd, J_1=5.2, J_2=16.0, 1H), 1.85 (q, J=6.0, 1H), 1.73 (d, J=13.2, 1H), 1.57–1.52 (m, 3H), 1.39–1.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 198.0, 140.1, 136.3, 130.4, 129.5, 75.0, 69.3, 46.0, 32.7, 26.5, 24.0; MS (EI) m/z (%) 238 (M^+), 196, 181, 154, 139 (100%), 111, 85, 75, 55, 41. HRMS (EI-TOF) $[M]^+$ calculated for $C_{13}H_{15}O_2Cl$ 238.0761, found 238.0760.

4.2.4. 1-Naphthalen-2-yl-2-(tetrahydro-pyran-2-yl)-ethanone ***3mb***.[5] Yield 49%; light yellow oil; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ 8.50 (s, 1H), 8.05 (d, J=8.4, 1H), 7.98 (d, J=8.0, 1H), 7.89 (t, J=8.0, 2H), 7.62–7.54 (m, 2H), 4.06–3.96 (m, 2H), 3.51–3.42 (m, 2H), 3.05 (dd, J_1=5.6, J_2=16.0, 1H), 1.87 (q, J=4.2, 1H), 1.80 (d, J=12.8, 1H), 1.62–1.54 (m, 3H), 1.48–1.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ 199.0, 136.3, 135.3, 133.2, 130.8, 130.3, 129.1, 129.0, 128.4, 127.4, 124.6, 75.2, 69.3, 46.1, 32.7, 26.5, 24.1; MS (EI) m/z (%) 254 (M^+), 170, 155 (100%), 127, 77, 41.

Acknowledgements

Financial supports from MOST of China (973 program 2011CB808600) and National Natural Science Foundation of China (No. 21072091) are gratefully acknowledged.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.07.085.

References and notes

1. For α-functionalizations of ethers, see: (a) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242–4243; (b) Zhang, Y.-H.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949–1952; (c) Tu, W. Y.; Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4184–4187; (d) Li's group reported a CDC reaction of unactivated ethers with active methylene compounds: Li, Z.; Yu, R.; Li, H. *Angew. Chem.* **2008**, *120*, 7607–7610; (e) Yoo, W. J.; Correia, C. A.; Zhang, Y.; Li, C.-J. *Synlett* **2009**, 138–142; (f) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 3069–3072; (g) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5894–5897; (h) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnürch, M. *Chem. Commun.* **2010**, 8836–8838; (i) Richter, H.; Mancheño, O. G. *Eur. J. Org. Chem.* **2010**, *23*, 4460–4467; (j) Richter, H.; Rohlmann, R.; Mancheño, O. G. *Chem.—Eur. J.* **2011**, *17*, 11622–11627; (k) Ghobrial, M.; Schnürch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2011**, *76*, 8781–8793; (l) Park, S. J.; Price, J. R.; Todd, M. H. *J. Org. Chem.* **2012**, *77*, 949–955; (m) Clausen, D. J.; Floreancig, P. E. *J. Org. Chem.* **2012**, *77*, 6574–6582; (n) Liu, X.; Sun, B.; Xie, Z.; Qin, X.; Liu, L.; Lou, H. *J. Org. Chem.* **2013**, *78*, 3104–3112.
2. For reviews on dehydrogenative cross-coupling reactions: (a) Li, C. J.; Li, Z. *Pure Appl. Chem.* **2006**, *78*, 935–945; (b) Li, C. J. *Acc. Chem. Res.* **2009**, *42*, 335–344; (c) Scheuermann, C. *Chem.—Asian J.* **2010**, *5*, 436–451; (d) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292; (e) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588–5598.
3. (a) A *tert*-butoxyl radical can be generated by a Cu(I)-catalyzed dissociation of *t*-BuOOH. A trace amount of Cu(I) can also be formed by the redox reaction of *t*-BuOOH with Cu(II). For details, see: Kharaschan, M. S.; Fono, A. *J. Org. Chem.* **1959**, *24*, 72–78; (b) A *tert*-butoxyl radical can also be generated from a homolytic cleavage of *t*-BuOOH. For an example, see: He, T.; Yu, L.; Zhang, L.; Wang, L.; Wang, M. *Org. Lett.* **2011**, *19*, 5016–5019.
4. Cheng, K.; Huang, L.-H.; Zhang, Y. H. *Org. Lett.* **2009**, *11*, 2908–2911.
5. Katritzky, A. R.; Abdel-Fattah, A. A. A.; Idzik, K. R.; Bahaa El-Gendya, E.-D. M.; Soloducho, J. *Tetrahedron* **2007**, *63*, 6477–6484.