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Copper-Catalyzed Cleavage of Unstrained C–C Bonds for the Synthesis of 1-Acyloxy-2,2,6,6-tetramethylpiperidines from Cyclic or Acyclic Ketones

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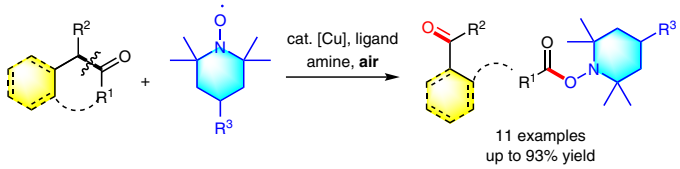

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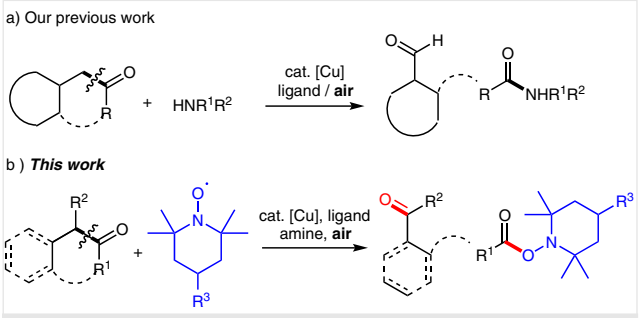
Abstract A copper-catalyzed approach for the synthesis of 1-acyloxy-2,2,6,6-tetramethylpiperidines through the C–C bond cleavage of cyclic or acyclic ketones was developed. In this chemistry, a combination of $CuCl_2·2H_2O$, 1,10-phenanthroline monohydrate, and aniline was crucial for the formation of the desired products by the reaction of ketones with TEMPO. This research provides a new strategy for the further transformation of α-aryl cyclic or acyclic ketones.

Key words copper catalysis, acyloxypiperidines, C–C bond cleavage, ketones, TEMPO

The importance of investigations on the cleavage of C–C bonds stems from the unique potential of this reaction for efficient rearrangements or multifunctionalizations of the carbon skeletons of organic compounds.[1,2] Compared with strained C–C bonds, the cleavage of unstrained C–C bonds is challenging from the energy point of view, but more desirable in terms of its synthetic applications and the easy availability of starting materials.[3]

In the past few decades, a great deal of attention has been focused on the cleavage of C–C(CO) bonds, because carbonyl compounds such as ketones and aldehydes exist widely in nature[4] and are also commercially available or readily accessible through chemical synthesis. The development of transformations based on C–C bond cleavage of ketones will undoubtedly enrich the range of tools available for the utilization of carbonyl compounds.[5]

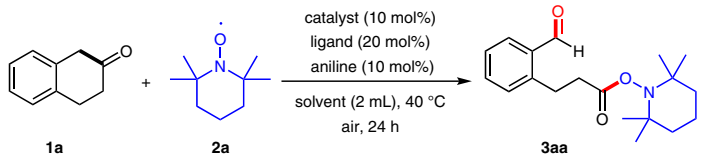
In relation to green and sustainable chemistry, the copper/air catalytic system has many merits and is considered an ideal choice for organic transformations.[6] In the past decade, copper-catalyzed cleavage of nonstrained open-chain ketones for the synthesis of amides,[7] aldehydes,[8] or other compounds[9] has been achieved. In addition, Jiao and coworkers conducted pioneering research on the copper-catalyzed esterification of 1,3-diones[10a] and simple ketones.[10b] However, these methods could be successfully applied to acyclic ketones only. We recently developed a copper-catalyzed oxidative C–C bond cleavage reaction of unstrained ketones with air and amines (Scheme 1, Path a),[11] in which both cyclic and acyclic ketones are well tolerated to give oxo amides or aldehydes and amides as products. In mechanistic studies, we found that in the presence of a stoichiometric amount of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), β-tetralone [3,4-dihydronaphthalen-2(1*H*)-one] was converted into a 1-acyloxy-2,2,6,6-tetramethylpiperidine derivative rather than the corresponding oxo amide. In a continuing effort to explore this reaction, we report here a copper-catalyzed synthesis of 1-acyloxy-2,2,6,6-tetramethylpiperidines from cyclic or acyclic ketones (Scheme 1, Path b).



Scheme 1 Copper-catalyzed cleavage of unstrained C–C bonds

After a slight change from the standard conditions previously reported, namely, the use of acetonitrile as a solvent, we obtained 2-{3-oxo-3-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propyl}benzaldehyde (**3aa**) in 93% isolated yield by the reaction of β-tetralone with TEMPO (Table 1, entry 4).[12] The combination of a copper catalyst ($CuCl_2·2H_2O$), a

Table 1 Screening of Reaction Conditions[a]



Entry	Catalyst	Ligand	Solvent	Yield[b] (%)
1	$Cu(OTf)_2$	1,10-phen·H_2O	MeCN	81
2	$Cu(OAc)_2·H_2O$	1,10-phen·H_2O	MeCN	55
3	CuI	1,10-phen·H_2O	MeCN	88
4	**$CuCl_2·2H_2O$**	**1,10-phen·H_2O**	**MeCN**	**93**
5	none	1,10-phen·H_2O	MeCN	0
6	$CuCl_2·2H_2O$	none	MeCN	0
7[c]	$CuCl_2·2H_2O$	1,10-phen·H_2O	MeCN	0
8[d]	$CuCl_2·2H_2O$	1,10-phen·H_2O	MeCN	10
9	$CuCl_2·2H_2O$	pyridine	MeCN	69
10	$CuCl_2·2H_2O$	2,2′-bipyridyl	MeCN	81
11	$CuCl_2·2H_2O$	TMEDA	MeCN	69
12	$CuCl_2·2H_2O$	1,10-phen·H_2O	DCE	53
13	$CuCl_2·2H_2O$	1,10-phen·H_2O	acetone	88
14	$CuCl_2·2H_2O$	1,10-phen·H_2O	DMSO	39
15[e]	$CuCl_2·2H_2O$	1,10-phen·H_2O	MeCN	87
16[f]	$CuCl_2·2H_2O$	1,10-phen·H_2O	MeCN	43

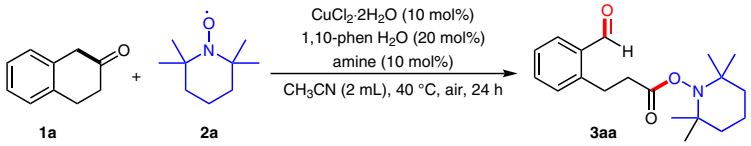
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.25 mmol), catalyst (0.025 mmol), ligand (0.05 mmol), aniline (0.025 mmol), solvent (2 mL), stirring, 40 °C, 24 h, under air (1 atm).
[b] Isolated yield.
[c] Without aniline.
[d] 10 mol% of 1,10-phen·H_2O was used.
[e] At r.t.
[f] At 50 °C.

bidentate ligand (1,10-phenanthroline monohydrate; 1,10-phen·H_2O), and aniline proved to be crucial for this transformation (entries 5–7). Note that the reaction became sluggish when the amount of 1,10-phenanthroline monohydrate was decreased to 10 mol% (entry 8). Other combinations of copper salts with nitrogen-containing ligands also catalyzed this reaction, albeit with lower efficiencies (entries 1–3 and 9–11). In addition, changing the solvent or temperature had significant impacts on the yield (entries 12–16).

Having noted the perplexing role of aniline in this reaction, we screened a variety of amines to probe the exact function of the amine (Table 2). For primary amines, an aniline with an electron-donating substituent gave a better result than one with an electron-withdrawing substituent (Table 2, entries 1 and 2). A slight decrease in yield was observed when butylamine or *tert*-butylamine was used (Table 2, entries 4 and 5). As for secondary amines, the reaction proceeded in the presence of diaryl or dialkyl amines, providing similar outcomes (entries 6–8). Moreover, tertiary amines also mediated this transformation (entries 9 and 10). Taken in combination with the observed negative effect of decreasing the loading of the ligand (Table 1, entry 8), these results imply that the amine might serve as a base rather than as a ligand. However, the mechanistic details of this chemistry are still unclear.

With the optimum reaction conditions in hand, we commenced an exploration of the substrate scope (Table 3). β-Tetralones bearing various substituents on the aromatic ring were successfully converted into the desired products in moderate to good yields (Table 3, entries 1–5). As for benzo ketones, although indan-2-one was tolerated (entry 6), 2-benzosuberone (5,7,8,9-tetrahydro-6*H*-benzocyclohepten-6-one) was incompatible (not shown). When α-phenyl cyclic ketones with six- to eight-membered rings were employed, decreased yields of the corresponding products were obtained (entries 7–9). The scope could be extended to an open-chain ketone (entry 10); in this reaction, the over-quantitative yield of aldehyde **3ja′** originates

Table 2 Screening of Amines[a]



Entry	amines	Yield[b] of **3aa** (%)
1	(4-methoxyphenyl)amine	90
2	4-aminobenzonitrile	69
3	1-naphthylamine	76
4	$BuNH_2$	83
5	*t*-$BuNH_2$	79
6	Ph_2NH	82
7	PhNHMe	73
8	morpholine	73
9	Ph_3N	71
10	Et_3N	67

[a] Reaction conditions, **1a** (0.5 mmol), **2a** (0.25 mmol), $CuCl_2·2H_2O$ (0.025 mmol), 1,10-phen·H_2O (0.05 mmol), amine (0.025 mmol), MeCN (2 mL), stirring 40 °C, 24 h, under air (1 atm).
[b] Isolated yield.

from the side reaction of excess ketone.[13] However, α-tetralone could not be used successfully in this transformation (entry 11).

Moreover, this reaction provides ready access to 1-acyloxy-2,2,6,6-tetramethylpiperidines with various substituents in the 4-position of the piperidine ring (Scheme 2).

Table 3 Substrate Scope of Ketones[a]

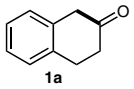
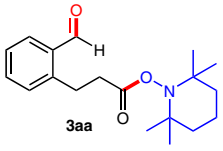
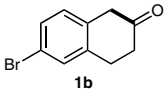
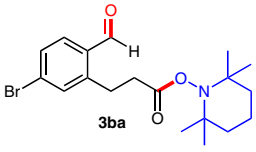
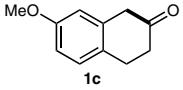
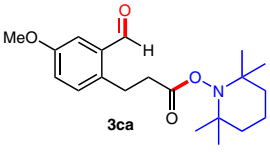
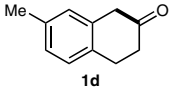
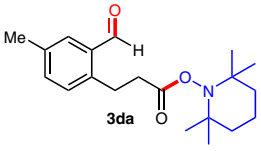
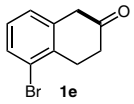
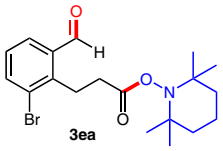
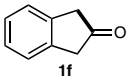
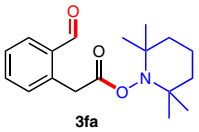
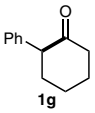
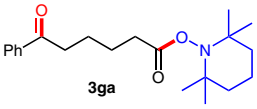
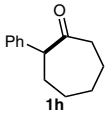
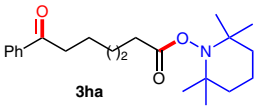
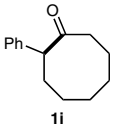
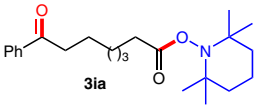
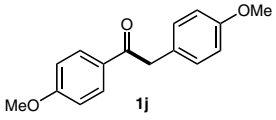
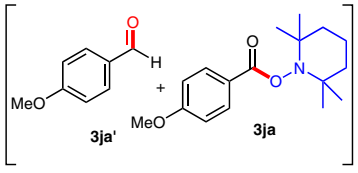
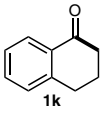
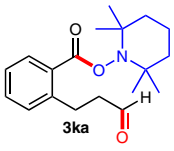
Entry	Substrate	Product	Yield[b] (%)
1	 1a	 3aa	93
2	 1b	 3ba	81
3	 1c	 3ca	76
4	 1d	 3da	80

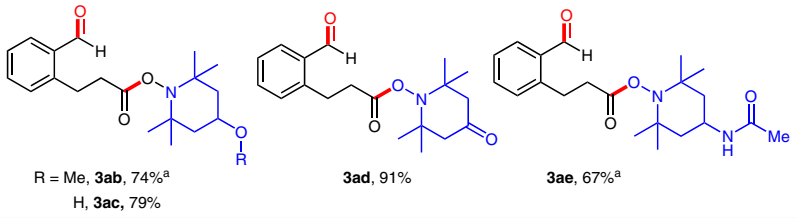
Table 3 (continued)

Entry	Substrate	Product	Yield[b] (%)
5	 **1e**	 **3ea**	72
6[c]	 **1f**	 **3fa**	53
7[d]	 **1g**	 **3ga**	50
8[e]	 **1h**	 **3ha**	22
9[e]	 **1i**	 **3ia**	36
10[f]	 **1j**	 **3ja'** + **3ja**	74 (**3ja**) 109 (**3ja'**)
11	 **1k**	 **3ka**	(not detected)

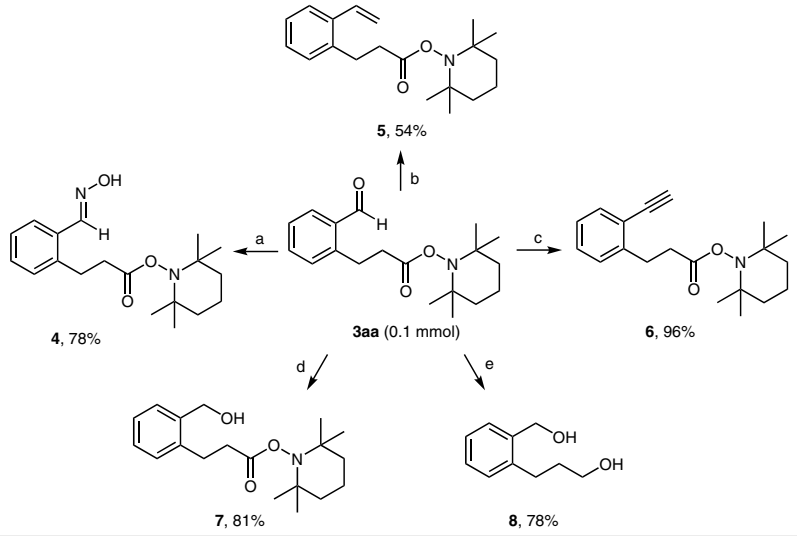
[a] For reaction conditions, see Table 1, entry 4.
[b] Isolated yield.
[c] PhNHAc and MeCN–acetone (3:1) were used as the amine and solvent, respectively, at r.t.
[d] 60 °C, 48 h.
[e] 80 °C, 48 h.
[f] 60 °C, 36 h.

Finally, a set of reactions was conducted to demonstrate the synthetic value of this transformation (Scheme 3). Product **3aa** was converted into oxime **4** by condensation with hydroxylamine. The terminal alkene **5** and alkyne **6** were readily synthesized by reaction of **3aa** with a Wittig reagent and the Ohira–Bestmann reagent [$MeCOC(=N_2)P(O)(OMe)_2$], respectively. Sodium borohydride selectively reduced **3aa** to give the benzyl alcohol derivative **7**. Complete reduction of the two carbonyl groups of **3aa** to give diol **8** was achieved by treatment with $LiAlH_4$ in THF.

In conclusion, we have developed a copper/air catalytic system for the cleavage of unstrained C–C bonds of cyclic or acyclic ketones. The results of this research will enrich range of tools available for the utilization of α-aryl cyclic or acyclic ketones.



Scheme 2 Scope of TEMPO derivatives. *Reaction Conditions*: see Table 1, entry 4. Isolated yields are reported. [a] 48 h.



Scheme 3 Further transformations. *Reagents and conditions*: (a) $NH_2OH{\cdot}HCl$, $NaHCO_3$, EtOH–H_2O, r.t., overnight; (b) Ph_3PCH_3Br, *t*-BuOK, anhyd THF, 0 °C to r.t., 16 h; (c) Ohira–Bestmann reagent, K_2CO_3, MeOH, r.t.; (d) $NaBH_4$, THF–H_2O; (e) $LiAlH_4$, THF.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590805.

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(12) **2-{3-Oxo-3-[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]propyl}benzaldehyde (3aa); Typical Procedure**

A tube equipped with a condenser was successively charged with 2-tetralone (**1a**, 0.5 mmol, 73.1 mg), TEMPO (**2a**, 0.25 mmol, 39.1 mg), $CuCl_2$·2 H_2O (0.025 mmol, 4.3 mg), 1,10-phenanthroline monohydrate (0.05 mmol, 9.9 mg), aniline (0.025 mmol, 2.3 mg, 2.3 µL), and MeCN (2 mL), and the mixture was stirred at 40 °C under air. When the reaction was complete (TLC), the mixture was cooled to r.t., dried under vacuum, and purified by column chromatography [silica gel, PE–EtOAc (5:1)] to give a solid; yield: 74 mg (93%); mp 56–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.23 (s, 1 H), 7.81 (d, *J* =7.6 Hz, 1 H), 7.50 (t, *J* = 7.4 Hz, 1 H), 7.44–7.36 (m, 2 H), 3.41 (t, *J* = 7.6 Hz, 2 H), 2.69 (t, *J* = 7.6 Hz, 2 H), 1.72–1.35 (m, 6 H), 1.09 (s, 6 H), 0.95 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.7, 172.3, 142.7, 133.8, 133.7, 133.6, 131.5, 127.0, 59.8, 38.8, 34.0, 31.8, 28.2, 20.4, 16.9.

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