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Copper-Catalyzed Synthesis of Esters from Ketones. Alkyl Group as a Leaving Group

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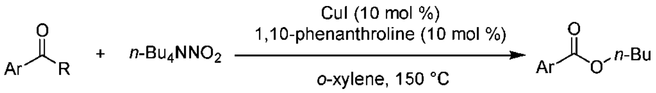
ABSTRACT



The conversion of ketones to esters has been achieved through the use of Cu catalyst and tetrabutylammonium nitrite. This reaction involves the activation of the less activated C−C bond, and the alkyl group is removed as a leaving group. Various isopropyl ketones are found to be good substrates for this reaction.

The catalytic cleavage of a carbon−carbon single bond by transition-metal complexes is a potentially useful transformation, and extensive studies have been carried out.[1] In most reactions, however, highly strained compounds such as three- or four-membered carbocycles,[2] compounds with good leaving groups which contain a carbon atom,[3] or chelating compounds[4] have been utilized as the substrates, and the catalytic cleavage of a less activated carbon−carbon bond[5] remains a challenging issue. Recently, we developed the copper-catalyzed nitration of aryl iodides by tetrabutylammonium nitrite.[6] When we carried out the Cu-catalyzed nitration of 4-iodoacetophenone, we noticed that the acetyl group was converted to butoxycarbonyl group and a small amount of a butyl ester instead of the expected nitro compound (4-nitroactophenone) was isolated. The result indicated that C−C bond was activated and an unusual alkoxylation−dealkylation reaction proceeded. We examined the reaction in detail and developed an efficient method for the conversion of ketones to esters. In this paper, we report the copper-catalyzed synthesis of esters from ketones by formal alkoxylation−dealkylation.

We studied the reaction of various aryl ketones with tetrabutylammonium nitrite (**2a**, 1.2 equiv). The results are summarized in Table 1. The reactions were carried out at 150 °C in *o*-xylene. The reaction of methyl ketone **1a** without catalyst did not proceed at all (entry 1). When the reaction was carried out in the presence of CuI (10 mol %),[7] however, the desired ester **3a** was isolated in 21% yield (entry 2). We also carried out the screening of the ligands (entries 3−9). Though various ligands were evaluated, most ligands were not effective (entries 3−7). The best result was achieved when the reaction was performed in the presence of 1,10-phenanthroline (**L1**, 20 mol %) (entry 8), and decreasing the amount of **L1** to 10 mol % did not affect the yield of **3a** (entry 9). Next, we

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(1) (a) Murai, M.; Ito, Y. *Activation of Unreactive Bonds and Organic Synthesis*; Murai, M., Ed.; Springer: Berlin, 1999; pp 99−129. (b) Jun, C.-H *Chem. Soc. Rev.* **2004**, *33*, 610–618.

(2) (a) Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. (b) Bart, S. C.; Chirik, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 886–887. (c) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976–13977.

(3) (a) Nakao, Y.; Oda, S.; Hiyama, T. *J. Am. Chem. Soc.* **2004**, *126*, 13904–13905. (b) Tobisu, M.; Kita, Y.; Chatani, N. *J. Am. Chem. Soc.* **2006**, *128*, 8152–8153.

(4) (a) Jun, C. -H.; Moon, C. W.; Lee, D.-Y. *Chem. Eur. J.* **2002**, *8*, 2422–2428. (b) Wakui, H.; Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2004**, *126*, 8658–8659.

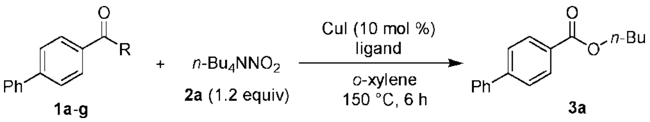
(5) Few examples on the cleavage of an unreactive carbon-carbon bond are known, see: (a) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 11368–11369. (b) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 6646–6647.

(6) Saito, S.; Koizumi, Y. *Tetrahedron Lett.* **2005**, *46*, 4715–4717.

(7) Though Cu(OAc)$_2$ and Cu(OTf)$_2$ were as effective as CuI, we chose CuI as a catalyst for this reaction due to its stability and low price. Cu bronze, CuCl, CuO, and Cu$_2$O were less effective.

10.1021/ol800576w CCC: $40.75

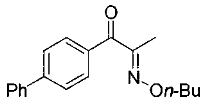
Table 1. Copper-Catalyzed Synthesis of Esters from Ketones[a]



1a-g **2a** (1.2 equiv) **3a**

entry	compd	R	ligand (mol %)	yield[b] (%)
1[c]	**1a**	Me	none	0
2	**1a**	Me	none	21
3	**1a**	Me	tri-*o*-tolylphosphine (20)	21
4	**1a**	Me	tris(2,4-di-*tert*-butylphenyl) phosphate (20)	23
5	**1a**	Me	TMEDA[d] (20)	19
6	**1a**	Me	DABCO[e] (20)	22
7	**1a**	Me	L-proline (20)	17
8	**1a**	Me	1,10-phenanthroline (**L1**) (20)	26
9	**1a**	Me	**L1** (10)	25
10	**1b**	H	**L1** (10)	3
11	**1c**	Et	**L1** (10)	14[f]
12	**1d**	*i*-Pr	**L1** (10)	76
13	**1d**[g]	*i*-Pr	**L1** (10)	81
14	**1e**[g]	Cy	**L1** (10)	64[h]
15	**1f**	*t*-Bu	**L1** (10)	0
16	**1g**	Ph	**L1** (10)	0

[a] All reactions were carried out using 1 mmol of **1** in *o*-xylene (0.5 mL) at 150 °C in a test tube sealed with a screw-cap under argon. [b] Isolated yields. A significant amount of the starting material remained unchanged when the yield of **3a** was low. [c] The reaction was carried out without catalyst. [d] TMEDA = *N*,*N*,*N*′,*N*′-tetrametylethylenediamine. [e] DABCO = 1,4-diazabicyclo[2.2.2]octane. [f] α-Oximino ketone (**4**) was isolated as the main product (54% yield). [g] A larger amount (1.8 equiv) of **2a** was used. [h] Yield determined by NMR.



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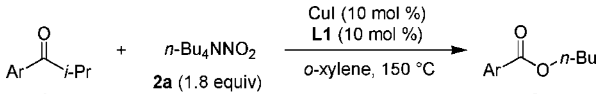
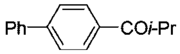
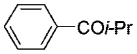
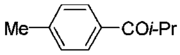
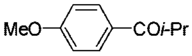
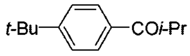
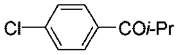
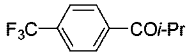
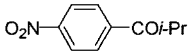
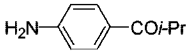
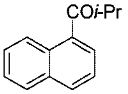
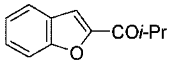
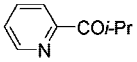
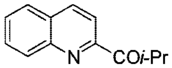
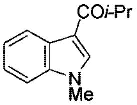
carried out the conversion of other ketones in the presence of CuI (10 mol %) and 1,10-phenanthroline (10 mol %). Aldehyde **1b** was not reactive under the reaction conditions, and only a small amount of the ester **3a** was isolated (entry 10). Though the reaction of ethyl ketone **1c** proceeded, the isolated yield of the ester **3a** was low (14% yield): the ketone **1c** was nitrosated, and α-oximino ketone (**4**) was isolated as the main product (entry 11).[8] To our surprise, isopropyl ketone **1d** was converted to the ester in high yield (entry 12). Furthermore, the yield improved by increasing the amount of **2** to 1.8 equiv (entry 13). Cyclohexyl ketone was also converted to **3a** in moderate yield (entry 14). On the other hand, the reaction of *tert*-butyl ketone **1f** or phenyl ketone **1g** did not proceed at all (entries 15 and 16). It is noteworthy that the observed leaving group ability of alkyl groups for this reaction is quite different from the migratory apititude of alkyl groups in the Baeyer–Villiger reaction.[9] Thus, the leaving group ability of alkyl groups for the copper catalyzed reaction was ranked as follows: secondary alkyl > primary alkyl ≫ aryl, tertiary alkyl. On the other hand, the migratory amplitude of the alkyl groups in the Baeyer–Villiger reaction follows the general order: tertiary alkyl > secondary alkyl, aryl > primary alkyl.[9]

As the isopropyl ketone was found to be most reactive, we next examined the generality of this reaction, and the results are summarized in Table 2. Isobutyrophenone **1h** was converted to the corresponding ester in 80% yield (entry 2). Aryl isopropyl ketones substituted with an electron-donating group such as methyl, methoxy, or *tert*-butyl group were converted to the corresponding esters in high yields (entries 3–5). Ketones substituted with an

Table 2. Copper-Catalyzed Synthesis of Esters from Ketones[a]



1 **2a** (1.8 equiv) **3**

entry	ArCO^{i}Pr		time (h)	yield[b] (%)
1		**1a**	6	81
2		**1h**	6	80
3		**1i**	6	81
4		**1j**	6	72
5		**1k**	6	80
6		**1l**	6	77
7		**1m**	6	81
8		**1n**	6	68
9		**1o**	6	trace[c,d]
10		**1p**	7	67
11		**1q**	15	57
12		**1r**	24	61
13		**1s**	24	63
14		**1t**	6	23

[a] All reactions were carried out using 1 mmol of **1** in *o*-xylene (0.5 mL) at 150 °C in a test tube sealed with a screw-cap under argon. [b] Isolated yields. [c] Determined by GC–MS analysis. [d] *n*-Butyl benzoate was isolated in 12% yield.

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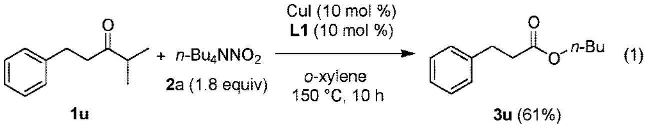
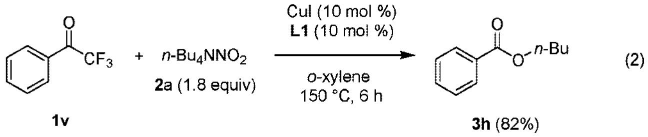
[8] It is known that the α-position of ketone was easily nitrosated by nitrites, see: Rüedi, G.; Oberli, M. A.; Nagel, M.; Weymuth, C.; Hansen, H.-J. *Synlett* **2004**, *13*, 2315–2318.

electron-withdrawing group such as chloro, trifluoromethyl, or nitro also gave the corresponding esters in good yields (entries 6−8). However, amino ketone **1o** was not a proper substrate for this transformation: the amino group was eliminated by the Sandmeyer-type reaction,[10] and *n*-butyl benzoate was isolated in 12% yield (entry 9). Naphthyl ketone **1p** also gave the corresponding ester (entry 10). As for heteroaromatic derivatives, benzofuryl, pyridyl, and quinolyl ketones were converted to the corresponding esters in moderate yields (entries 11−13), while the reactivity of *N*-methyl indolyl ketone **1t** was low. The reaction of *N*-methyl indolyl ketone (**1t**) stopped in 6 h, and further conversion was not observed even after prolonged heating (entry 14).

We next carried out the reaction of alkyl−alkyl ketone using 2-methyl-5-phenylpentan-3-one (**1u**) (eq 1). The isopropyl group was eliminated preferentially, and the corresponding ester **3u** was isolated in 61% yield. The trifluoromethyl group, as well as the isopropyl group, could be the leaving group in this reaction, and the reaction of **1v** proceeded smoothly under similar reaction conditions to give the ester in high yield (eq 2).



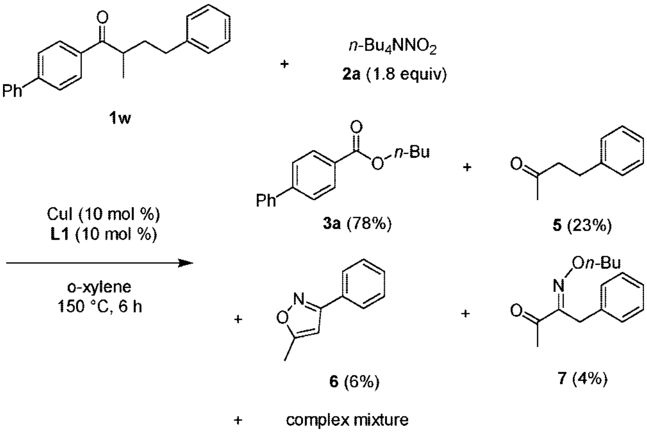
(1)



(2)

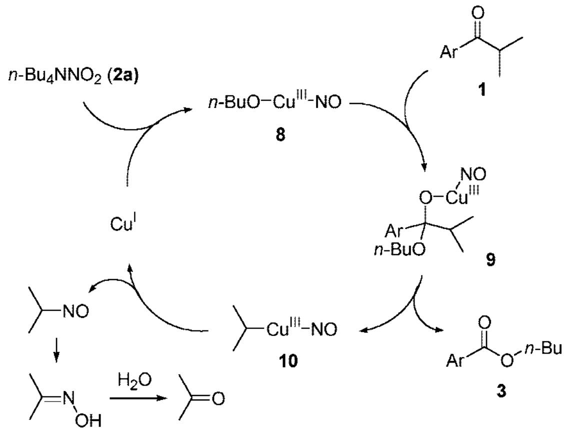
In order to understand the fate of the volatile leaving group (isopropyl group) in this reaction, we carried out the reaction of ketone **1w** and analyzed the products (Scheme 1). We obtained **3a** (78% yield), benzylacetone (**5**), and other derivatives **6** and **7**[8] from the reaction mixture.

Scheme 1. Isolation of the Products Derived from the Reaction of **1w**



Based on these results, a possible mechanism of the reaction is shown in Scheme 2. Initially, the reaction of tetrabutylammonium nitrite **2a** and Cu(I) species would occur to afford the copper complex (**8**),[11] which subsequently inserted into the carbonyl group (**1**),[12] and the ester (**3**) would be generated by the elimination of the alkyl copper species (**10**). Finally, the reductive elimination proceeded and the copper catalyst would be regenerated. The higher reactivity of isopropyl ketones compared to other ketones could be explained in terms of the bulkiness of the isopropyl group: the bulky isopropyl group would facilitate the conversion of the tetrahedral intermediate (**9**) to the ester (**3**),[13] and therefore, the rate of the reaction would be accelerated. On the other hand, *tert*-butyl ketone is so bulky that the addition of butoxy copper does not proceed to form the corresponding copper complex **9**. Although the acid-catalyzed formation of α-ketooxime from ketone in the presence of $NaNO_2$ has been reported in the literature[8] and a similar mechanism which involves the oxidation of the α-position of the ketone could be postulated, this reaction would not proceed via this pathway. It is difficult to suppose the preferential oxidation of the secondary alkyl group (isopropyl group) bound to the carbonyl group, since it was reported that the primary alkyl group, not the secondaty alkyl group, was prone to be oxidized.[8] If this reaction proceeds via the oxidation, primary alkyl groups would be better leaving groups. Furthermore, the result of the reaction of a trifluoromethyl ketone indicates that the

Scheme 2. Mechanistic Hypothesis for the Conversion of Ketones to Esters



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(9) For reviews, see: (a) ten Brink, G. J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105–4124. (b) Heaney, H. *Top. Curr. Chem.* **1993**, *164*, 1–19.

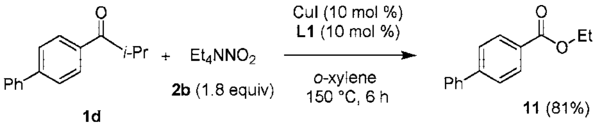
(10) Shin, H. H.; Park, Y. J.; Kim, Y. H. *Heteroatom Chem.* **1993**, *4*, 259–262.

(11) It is known that nitrite is reduced by copper complex such as copper-containig nitrite reductase to afford a Cu−NO complex, see: (a) Tocheva, E. I.; Rosell, F. I.; Mauk, A. G.; Murphy, M. E. P. *Science* **2004**, *304*, 867–870. (b) Burg, A.; Lozinsky, E.; Cohen, H.; Meyerstein, D. *Eur. J. Inorg. Chem.* **2004**, *367*, 5–3680.

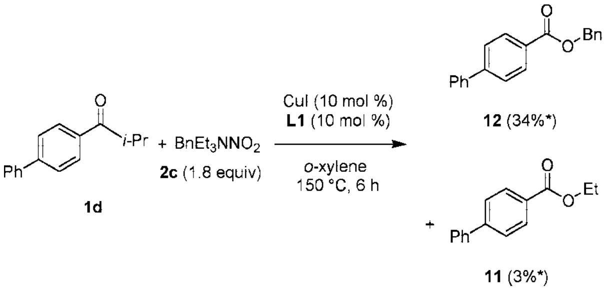
reaction proceeds via the addition−elimination pathway, rather than the oxidation pathway, since the trifluoromethyl group is a better leaving group and would not be oxygenated easily.

Finally, we carried out the synthesis of esters by using other tetraalkylammonium nitrites. Nitrite **2b** showed high reactivity as well as **2a**, and the ketone **1d** was converted to the ethyl ester **11** in 81% yield (eq 3). Although the ketone **1d** was converted to benzyl ester **12** by using **2c**, the yield was low (eq 4).

In summary, we developed an efficient method for the conversion of ketones to esters by using a copper catalyst and tetrabutylammonium nitrite. A less activated C−C bond is cleaved catalytically in the presence of a Cu catalyst, and an alkyl group is the leaving group in this reaction. The detailed mechanistic studies of this reaction are in progress.



(3)



(4)

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) An example of the insertion of an alkoxy copper complex to the carbonyl group exists, see: Kubota, M.; Yamamoto, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 146–150.

(13) This process would be the rate-determining step of this reaction.