

# Generation of Iminyl Copper Species from $\alpha$ -Azido Carbonyl Compounds and Their Catalytic C–C Bond Cleavage under an Oxygen Atmosphere

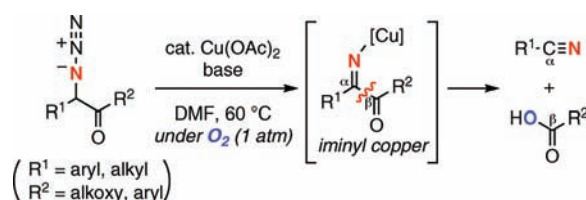
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Received March 3, 2010

## ABSTRACT



A copper-catalyzed reaction of  $\alpha$ -azidocarbonyl compounds under an oxygen atmosphere is reported where nitriles are formed via C–C bond cleavage of a transient iminyl copper intermediate. The transformation is carried out by a sequence of denitrogenative formation of iminyl copper species from  $\alpha$ -azidocarbonyl compounds and their C–C bond cleavage, where molecular oxygen (1 atm) is a prerequisite to achieve the catalytic process and one of the oxygen atoms of  $O_2$  was found to be incorporated into the  $\beta$ -carbon fragment as a carboxylic acid.

Transition-metal-catalyzed C–C bond cleavage has attracted attention as a versatile tool in organic synthesis, and various modes of catalytic processes have been reported to activate inert C–C bonds.<sup>1</sup> Among them,  $\beta$ -carbon elimination of iminyl metal species ( $[M]-N=C_\alpha-C_\beta \rightarrow N\equiv C_\alpha + C_\beta-[M]$ ) has recently been disclosed, where release of ring strain or formation of a relatively stable  $C_\beta-[M]$  bond by cleavage

of the  $C_\alpha-C_\beta$  bond contributes significantly to the driving force of such reactions, although the examples are particularly rare.<sup>2,3</sup> Herein, we report a copper-catalyzed reaction of  $\alpha$ -azido carbonyl compounds under an oxygen atmosphere, providing nitriles<sup>4</sup> via C–C bond cleavage of a transient iminyl copper intermediate (Scheme 1). The present transformation is carried out by a sequence of denitrogenative formation of iminyl copper species from  $\alpha$ -azido carbonyl compounds and their C–C bond cleavage, where molecular oxygen is a prerequisite to achieve the catalytic process and

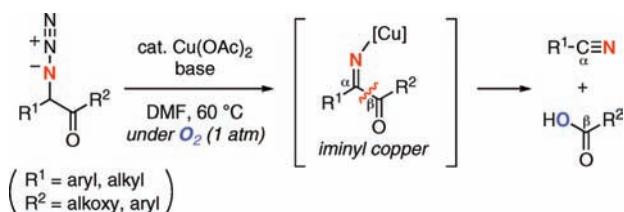
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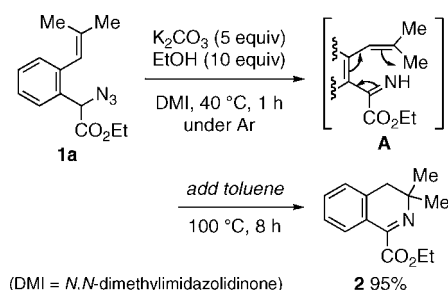
**Scheme 1.** Copper-Catalyzed Nitrile Formation from  $\alpha$ -Azido Carbonyl Compounds under an Oxygen Atmosphere



one of the oxygen atoms of  $O_2$  was found to be incorporated into the  $\beta$ -carbon fragment as a carboxylic acid.

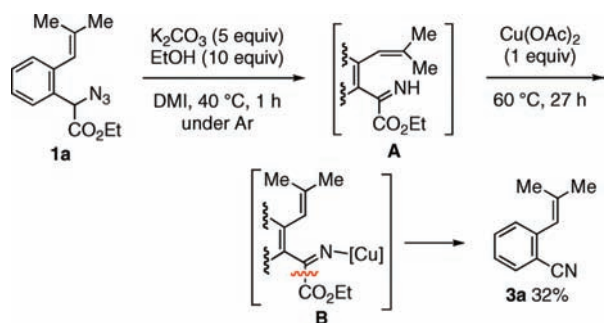
We have recently reported the synthesis of isoquinoline derivatives from  $\alpha$ -azido carbonyl compounds possessing a 2-alkenylaryl moiety at the  $\alpha$ -position. The reaction proceeded via  $6\pi$ -electrocyclization of  $N$ -H imine intermediates **A**, which are formed by treatment of azide such as **1a** with  $K_2CO_3$  in the presence of EtOH as a proton source (Scheme 2).<sup>5</sup>

**Scheme 2.** Isoquinoline Formation from  $\alpha$ -Azido Carbonyl Compounds Possessing a 2-Alkenylaryl Moiety at the  $\alpha$ -Position



The current study focused on generation of iminyl metal species by trapping this  $N$ -H imine **A** with transition metals<sup>2a</sup> and exploring their chemical reactivity. During the course of this study, it was found that treatment of generated  $N$ -H imine **A** with 1 equiv of  $Cu(OAc)_2$  at 60 °C under an Ar atmosphere afforded unexpected aryl nitrile **3a** in 32% yield instead of isoquinoline **2** (Scheme 3). The formation of nitrile

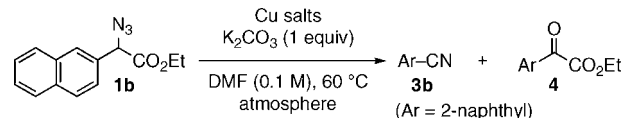
**Scheme 3.** Unexpected Nitrile Formation Mediated by  $Cu(OAc)_2$



**3a** apparently occurred by elimination of an ethoxycarbonyl group<sup>6,7</sup> presumably via  $\beta$ -carbon elimination of an iminyl copper intermediate **B**.

Further optimization of this nitrile formation was investigated by using ethyl 2-azido-2-(naphthalen-2-yl)acetate (**1b**) (Table 1). Treatment of **1b** with  $Cu(OAc)_2$  (1 equiv) and

**Table 1.** Optimization of Reaction Conditions



entry	copper salts (equiv)	atmosphere (1 atm)	time (h)	yield <sup>a</sup> (%)	
				<b>3b</b>	<b>4</b>
1 <sup>b</sup>	$Cu(OAc)_2$ (1.0)	Ar	24	78	3
2 <sup>b</sup>	$Cu(OAc)_2$ (0.2)	Ar	24	11	12
3 <sup>b,c</sup>	$Cu(OAc)_2$ (1.0)	Ar	11	71	6
4	$Cu(OAc)_2$ (1.0)	Air	4	89	0
5	$Cu(OAc)_2$ (1.0)	$O_2$	4	94	0
6	$Cu(OAc)_2$ (0.2)	Air	25	70	2
7	$Cu(OAc)_2$ (0.2)	$O_2$	7.5	90	0
8	$Cu(OAc)_2$ (0.1)	$O_2$	24	83	0
9	$Cu(OTf)_2$ (0.2)	$O_2$	29	45	6
10	$Cu(acac)_2$ (0.2)	$O_2$	25	32	32
11	$CuCl_2$ (0.2)	$O_2$	32	38	41
12	$CuTC$ (0.2)	$O_2$	5	83	0
13	$CuI$ (0.2)	$O_2$	25	52	26
14	$CuCl$ (0.2)	$O_2$	24	43	41

<sup>a</sup> Isolated yield. <sup>b</sup> Degassed DMF was used. <sup>c</sup>  $PhI(OAc)_2$  (1 equiv) was used as an additive. TC: thiophene-2-carboxylate.

$K_2CO_3$  (1 equiv) in DMF at 60 °C directly delivered 2-naphthonitrile (**3b**) in 78% yield along with 3% yield of  $\alpha$ -keto ester **4**, which should be formed by hydrolysis of the corresponding iminyl copper or  $N$ -H imine intermediate (Table 1, entry 1). In this case, coordination of  $Cu(OAc)_2$  to the internal nitrogen of the azido moiety might induce denitrogenative formation of iminyl copper (see Scheme 1).<sup>8</sup> A catalytic amount of  $Cu(OAc)_2$  under an Ar atmosphere could not complete the reaction (entry 2). It was found that the reaction of 1 equiv of  $Cu(OAc)_2$  in the presence of  $PhI(OAc)_2$  provided nitrile **3b** in shorter reaction time (entry 3). Moreover, the reaction was dramatically accelerated in the presence of molecular oxygen with excellent yields of **3b** (entries 4 and 5). Under an oxygen atmosphere (1 atm), nitrile **3b** was obtained in 90% yield by using 20 mol % of  $Cu(OAc)_2$  (entry 7), while lower catalytic loading (10 mol %) needed longer time (entry 8).  $Cu(II)$  salts bearing the

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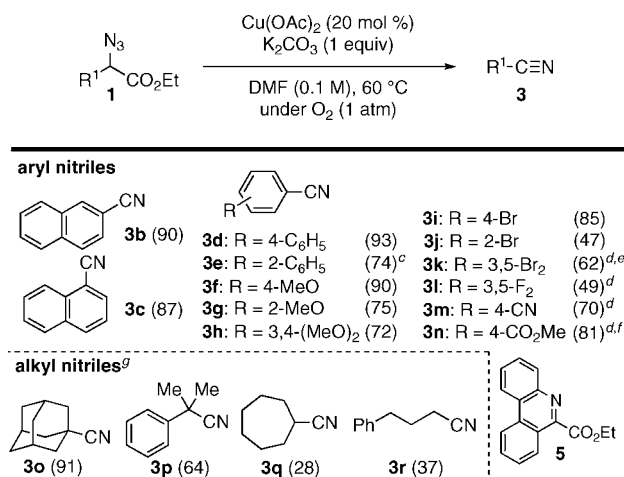
(7) For examples of C–C bond cleavage with elimination of a carbonyl moiety, see: (a) Ram, R. N.; Singh, L. *Tetrahedron Lett.* **1995**, *36*, 5401. (b) Jin, S.-J.; Arora, P. K.; Sayre, L. M. *J. Org. Chem.* **1990**, *55*, 3011.

(8) For a report on the coordination of the internal nitrogen of azido moiety with a  $Cu(II)$  complex, see: Barz, M.; Herdweck, E.; Thiel, W. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 2262.

other counteranions were not effective for this reaction (entries 9–11). Cu(I) species also exhibited catalytic activity (entries 12–14) in which copper(I) thiophene-2-carboxylate (CuTC) provided good yield (entry 12). Other metal salts like Pd(II), Mn(III), Co(II), and Fe(III) were not viable catalysts for this transformation (see the Supporting Information for more detailed studies).

With the optimized catalytic conditions in hand, we next examined the generality of this catalytic method for the synthesis of substituted nitriles using  $\alpha$ -azido esters **1** (Table 2). The process could provide decarboxylated one-carbon

**Table 2.** Synthesis of Nitriles



<sup>a</sup> Reactions were carried out using 0.3–0.55 mmol of **1**. <sup>b</sup> Isolated yields are recorded in parentheses. <sup>c</sup> 1 equiv of Cu(OAc)<sub>2</sub> was used, and phenanthridine **5** was obtained in 20% yield. In the case of 40 mol % of Cu(OAc)<sub>2</sub>, **3e** and **5** were obtained in 55 and 41% yields, respectively. <sup>d</sup> The reactions were run using the corresponding bromide (for **3k**) or mesylates (for **3l**, **3m**, **3n**) by treatment with NaN<sub>3</sub> followed by Cu(OAc)<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub> under O<sub>2</sub> (1 atm). <sup>e</sup> 40 mol % of Cu(OAc)<sub>2</sub> was used at 80 °C. <sup>f</sup> A methyl ester was used as a starting material. <sup>g</sup> 1 equiv of NaOEt was used as a base.

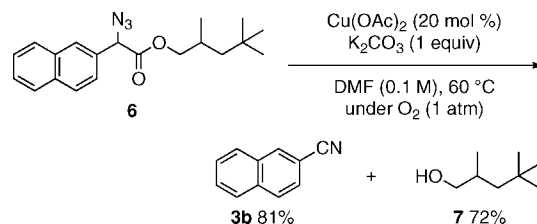
shorter nitriles from the corresponding carboxylic acid derivatives. For synthesis of aryl nitriles, the reaction allowed installing both electron-donating (**3b–h**) and -withdrawing groups (**3i–n**). When R is a 2-biphenyl group, nitrile **3e** was formed in 55% yield along with 41% yield of phenanthridine **5** using 40 mol % of Cu(OAc)<sub>2</sub>, while a stoichiometric use of Cu(OAc)<sub>2</sub> improved the yield of nitrile **3e** to 74% (with 20% yield of **5**).<sup>9</sup> Halogen atoms like Br and F were successfully incorporated with keeping the carbon–halogen bond intact (**3i–l**). Alkyl nitriles were also accessed utilizing NaOEt as a base. In particular, formation of tertiary nitriles proceeded with good yields (**3o**, **3p**), while secondary and primary nitriles were obtained in moderate yields (**3q**, **3r**).

To probe the reaction mechanism of this catalytic cycle, especially for elucidation of co-products derived from the carbonyl fragment after C–C bond cleavage and the role of

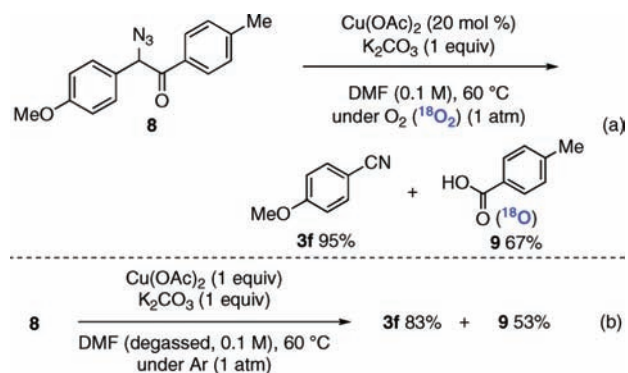
(9) For proposed mechanisms on the formation of phenanthridine **5**, see the Supporting Information.

molecular oxygen, substrates **6**, **8**, and **10** were employed (Schemes 4–6).

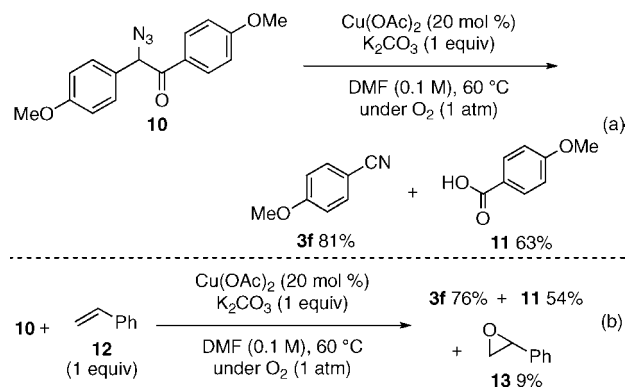
**Scheme 4.** Reaction of 2,4,4-Trimethyl-1-pentyl Ester **6**



**Scheme 5.** Reactions of  $\alpha$ -Keto Azides **8**



**Scheme 6.** Reactions of  $\alpha$ -Keto Azides **10**



The reaction of 2,4,4-trimethyl-1-pentyl ester **6** afforded nitrile **3b** and 2,4,4-trimethyl-1-pentanol (**7**) in 81% and 72% yields, respectively (Scheme 4).

Interestingly, treatment of  $\alpha$ -keto azide **8** instead of  $\alpha$ -azido esters provided nitrile **3f** and the corresponding benzoic acid **9** in good yields (Scheme 5a). Utilization of <sup>18</sup>O<sub>2</sub> revealed that one of the oxygen atoms from O<sub>2</sub> is incorporated into the benzoic acids (see the Supporting Information).<sup>10</sup> A reaction of azide **8** with 1 equiv of Cu(OAc)<sub>2</sub> under an Ar atmosphere also delivered nitriles **3f** and benzoic acid **9** (Scheme 5-b). In this case, acid **9** might

be formed via air oxidation of the resulting acylcopper species (see ref 14) during the workup process.

$\alpha$ -Keto azide **10** also provided nitrile **3f** and acid **11** (Scheme 6a). The reaction of **10** in the presence of styrene (**12**) (1 equiv) under the present catalytic conditions gave **3f** (76%) and **11** (54%) along with styrene oxide (**13**) in 9% yield (analyzed by GC), which suggested that acylperoxy copper species might be involved in the catalytic cycle (Scheme 6b).<sup>11,12</sup>

Based on these results, we propose a mechanistic possibility of this Cu(OAc)<sub>2</sub>-catalyzed reaction under an O<sub>2</sub> atmosphere as shown in Scheme 7. Denitrogenative forma-

moiety to induce C–C bond cleavage to deliver nitrile **3** and acylperoxy copper **IV**. Protonation of acylperoxy copper **IV** provides carboxylic acid **V** with regeneration of Cu(II) salts, while we are not certain as to the mechanism of this oxidation process.<sup>14</sup> When ester substrates are utilized, further decarboxylation of **V** occurs to afford the alcohols.

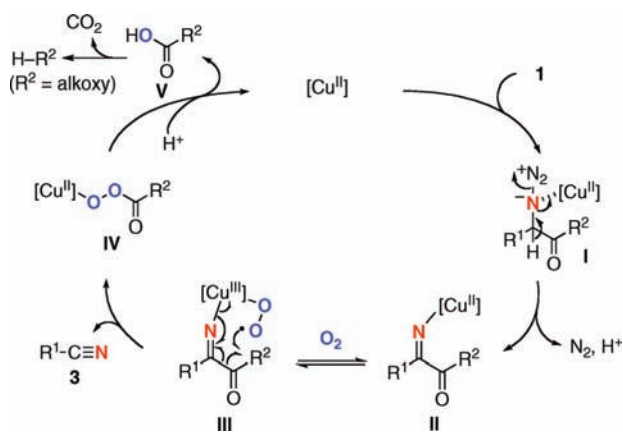
Continuous studies on the scope, mechanistic evaluation, and synthetic applications of the present C–C bond cleavage as well as further exploitation of new chemical reactivity of iminyl metals are in progress.

**Acknowledgment.** This work was supported by funding from Nanyang Technological University and Singapore Ministry of Education.

**Supporting Information Available:** Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Scheme 7. A Proposed Catalytic Cycle



tion of iminyl copper intermediate **II**<sup>13</sup> from **1** followed by oxidation of **II** with O<sub>2</sub> affords peroxycopper(III) species **III**, which subsequently adds to the intramolecular carbonyl

(10) For copper-mediated incorporation of the oxygen atom into carboxylic acid derivatives from O<sub>2</sub>, see: (a) Kim, S.; Lee, J. I. *J. Chem. Soc., Chem. Commun.* **1981**, 1231. (b) van Koten, G.; Noltes, J. G. *J. Chem. Soc., Chem. Commun.* **1972**, 59.

(11) For the chemical reactivity of acylperoxy metals, see: Cornell, C. N.; Sigman, M. S. In *Activation of Small Molecules*; Tolman, W. B., Ed.; Wiley: Weinheim, 2006; pp 159–186 and references therein.

(12) It was confirmed that the reaction of styrene (**12**) under the present catalytic conditions without azide **10** did not form styrene oxide (**13**) at all.

(13) For generation of iminyl lithium species from  $\alpha$ -azido carbonyl compounds, see: Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1980**, *45*, 4952. For iminyl titanium(IV) species, see: Ciez, D. *Org. Lett.* **2009**, *11*, 4282.

(14) The stoichiometric reactions under an Ar atmosphere (Table 1, entry 1 and Scheme 5b) indicated that iminyl copper(II) **II** could form nitrile **3** and acylcopper **VI** by  $\beta$ -carbon elimination (path A). Based on these results, it was speculated as another mechanistic possibility (path B) that peroxycopper **III** undergoes  $\beta$ -fission to lead formation of nitrile **3** and acylperoxy copper **IV**, which isomerizes to acylperoxy copper **IV**.

