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Communication

Copper-Catalyzed Tertiary Alkylative Cyanation for the Synthesis of Cyanated Peptide Building Blocks

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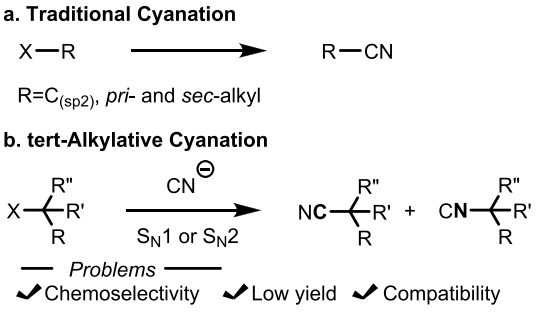
ABSTRACT: In this paper, we report efficient cyanation of various peptides containing the α-bromocarbonyl moiety using a Cu-catalyzed radical-based methodology employing zinc cyanide as the cyanide source. Mechanistic studies revealed that in situ formed CuCN was a key intermediate during the catalytic cycle. Our method could be useful for the synthesis of modified peptides containing quaternary carbons.

The modification of peptides, including those containing natural and unnatural amino acid moieties, is essential for protein chemistry.[1,2] Thus, overcoming the challenges to incorporate various functional groups into peptides contributes to not only the new synthetic methodology but also protein chemistry. In this context, cyanation of peptides is a key strategy because the cyano group can be easily converted to amine, aldehyde, ketone, and carboxylic acid groups. However, cyanation reaction on peptide derivatives could be limited by incompatible functional groups on the peptides and steric issues, since the reaction needs to occur at a tertiary carbon atom.

Cyanide, a small but reactive nucleophile, is useful to carry out a substitution reaction (S_N2) with primary and secondary alkyl halides.[3] Although the formation of a C_{sp^2}−CN bond by a transition metal catalyst has been well investigated (Scheme 1a),[4,5] the reaction of a tertiary-alkyl halide with cyanide is still unexplored (Scheme 1b). In 1981, Reetz and co-workers reported an S_N1 reaction of *tert*-alkyl halides and TMSCN (Me_3SiCN) in the presence of $SnCl_4$ as a strong Lewis acid.[6] However, they had used only nonfunctionalized and specific alkyl groups due to poor compatibility with functional groups. Moreover, the reported yields were low to moderate. Furthermore, cyanation via S_N1 reaction has the risk of isocyanation.[7] Recent progress in this area includes the use of a photoredox system to produce nonfunctionalized alkyl cyanide,[8] boron enolate to provide α-ketocyanide,[9] and enantioselective benzylic C−H cyanation to obtain sec-alkyl cyanide.[10] Additionally, issues with cyanation at the tertiary carbon atom include the following: (1) low yield, (2) chemoselectivity, (3) functional group compatibilities, and (4) α-cyanation of carboxamides for modification of peptides.

Scheme 1. Cyanation Reactions and Their Limitations



Recently, we demonstrated the coupling of fluoride, amine, and alkyne with α-bromocarboxamides containing a *tert*-alkyl structure.[11] In these reactions, copper fluoride, copper amide, and alkynyl copper were key intermediates. Based on these findings, we hypothesized that α-bromocarboxamide could react with copper cyanide, generated in situ (Scheme 2). α-Bromocarbonyl compounds are useful building blocks as a quaternary carbon precursor, but they cannot react with a cyanide via the S_N1 or S_N2 mechanism. Herein, we show the coupling reaction of α-bromocarboxamides and their peptide derivatives with zinc cyanide in the presence of a copper catalyst. The advantages of this methodology are that it uses $Zn(CN)_2$, a stable and safe cyanide source, and it allows

Scheme 2. This work

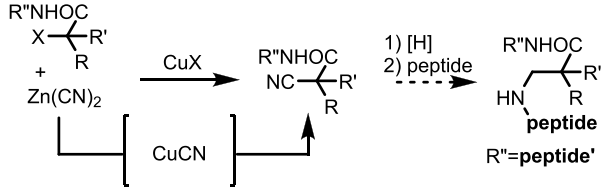


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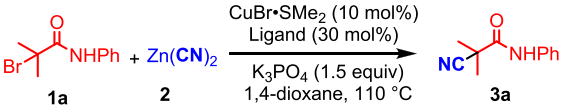
Table 1. Ligand Effect



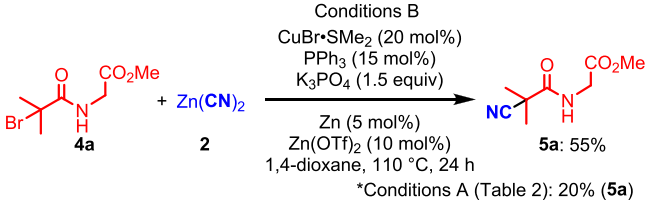
Ligands			
none: 11%	PPh_3: 33%	2,2′-bpy: 23%	$N(CH_2$2-Py$)_3$ (TPMA): 9%
$(CH_2NMe_2)_2$ (TMEDA): 81% (93%,[b] 88%[c])			$MeN(CH_2CH_2NMe_2)_2$ (PMDETA): 44%

[a]All reactions were conducted with **1** (1.0 equiv), $Zn(CN)_2$ (**2**: 1.0 equiv), CuBr·SMe_2 (10 mol %), ligand (30 mol %), K_3PO_4 (1.5 equiv), in 1,4-dioxane for 24 h at 110 °C. Yields were determined by ^{1}H NMR analysis. [b]THF was used instead of 1,4-dioxane in a sealed tube. [c]1.5 equiv of $Zn(CN)_2$ was used.

incorporation of an unnatural β-amino acid moiety into oligopeptides.

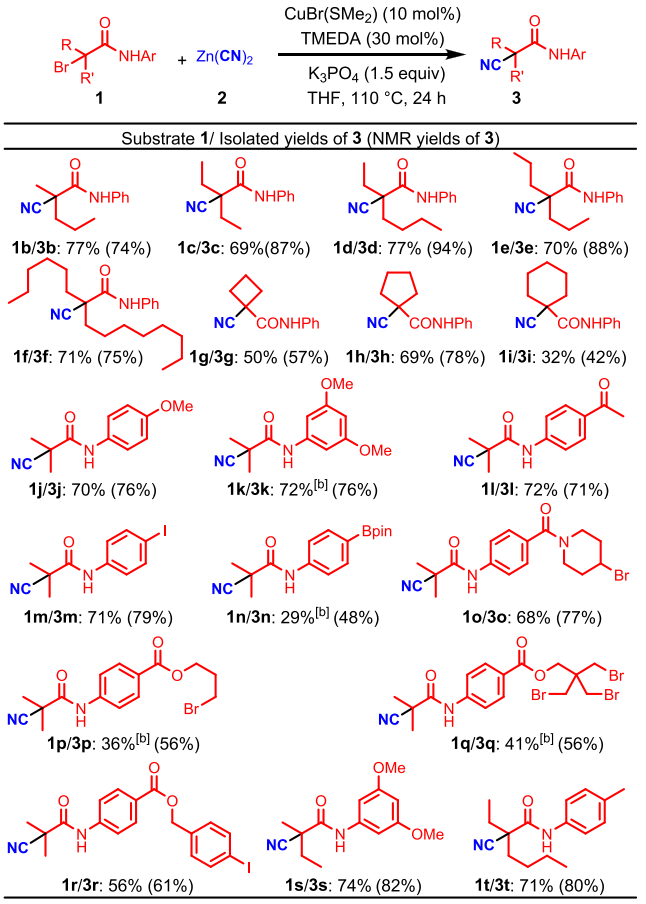
Initially, we screened various candidates as the CN source, such as $Zn(CN)_2$(**2**), TMSCN,[12] cyanohydrins, and iron cyanides for the reaction of α-bromocarboxamide (**1a**), and found $Zn(CN)_2$ (**2**) to be a good CN source, in the presence of a copper catalyst. In Cu-catalyzed reactions, the use of $Zn(CN)_2$(**2**), even in reactions involving sp^2 hybridized carbon (Csp^2-CN), is limited by its poor solubilitty.[13] We also tried the reaction with the stoichiometric amounts of CuCN, which is known as a source of Lipshutz's reagent (CN as a dummy group);[14] however, the yield of **3a** was low and Lewis acidic CuCN caused the hydration of CN (discussed later, see Scheme 6II). In this reaction, both a ligand and a base need to undergo the cyanation reaction (see SI: Table S1). The accurate role of base was not clear at this stage, but K_3PO_4 showed high reactivity. Other bases mainly produced acrylamide, which is the elimination product of **1**. The reaction without a ligand gave an 11% yield of **3a**. Phosphorus and nitrogen ligands were screened, and TMEDA resulted in the highest yield of **3a**. Increasing the amount of **2** was ineffective; however, using THF instead of 1,4-dioxane produced the best yield. In previous studies, we showed that multidentate nitrogen ligands, such as TPMA and PMDETA, generate alkyl radicals from α-bromocarbonyls.[11,15] Therefore, we expected that multidentate nitrogen ligands could be effective in this reaction. However, TMEDA, a bidentate ligand, was found to be the most effective ligand (Table 1 and Scheme 3). The reactivity of $Zn(CN)_2$ was low for **1a** in the absence of a catalyst. Therefore, Cu catalyst was necessary to carry out the cyanation reaction. We expected that the current cyanation reaction could involve a radical species, but considering the ligand effect, the reaction cannot be a simple radical reaction. A cation reaction, S_N1, was one of the possibilities, but the isonitrile product, which would be generated from the reaction of a carbocation and cyanide, was not obtained.

Scheme 3. Cyanation of α-Bromocarboxamide 4a



The reactivities of various α-bromocarboxamides (**1**) were examined under the optimized reaction conditions (Table 2). Sterically hindered bromides (**1b**–**1f**) showed good yields of

Table 2. Substrate Scope[a]



[a]See SI. Isolated product yields are reported. Yields shown in parentheses were determined by ^{1}H NMR analysis. [b]Isolated yields by GPC.

3b–**3f**. For example, **1f** possessing long alkyl chains at the α-position of carbonyl group resulted in a 71% yield of **3f**. However, cyclic bromides (**1g**–**1h**) resulted in moderate yields of **3g**–**3h** because of preferential HBr eliminations from **1** to give methacrylamide derivatives. Transition metal cyanide showed various reactivities,[5,16] but our cyanation reaction provided good functional group compatibility (**3j**–**3r**). Although ArI reacts with cyanide under copper-catalyzed conditions,[5,16] Ar–I bonds remained intact (**3m** and **3r**). On the other hand, borylated **1n** did not show good reactivity; the carbon–boron bond cleavage was detected. In this reaction, free cyanide might not be generated. When **1o**–**1q** possessing alkyl-Br bonds were employed for the cyanation, no S_N2 reactions at alkyl-Br bonds with cyanide were observed. The

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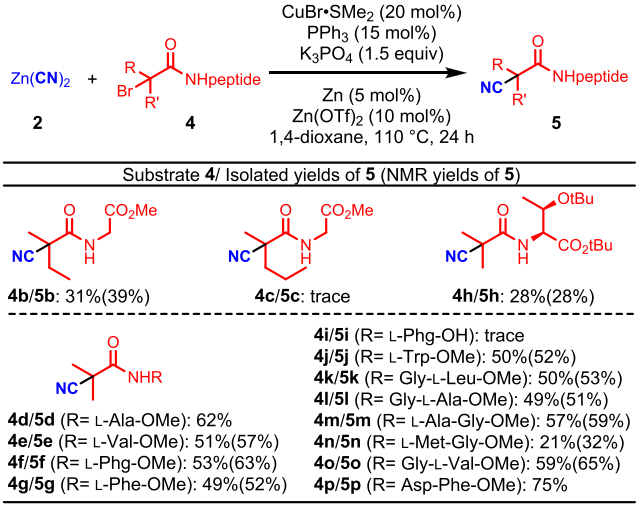
yields of **3o**−**3q** were moderate to good because of HBr elimination of **1**. Other combinations using **1s** and **1t** resulted in 74% and 71% isolated yields of **3s** and **3t**, respectively. The NMR yields of **3** were good, but isolated yields were moderate to good because the purification was sometimes difficult due to inseparable side products such as products of reduction and H−Br elimination of **1**. The substituents on amide is necessary to carry out our cyanation reaction. Cyanation at a primary- or secondary-carbon atom is well-established, but we were not able to detect any cyanations with α-bromocarbonyls possessing a primary- or secondary-carbon atom. Under our conditions, primary- and secondary-alkyl radical species could not be generated and the starting materials partly remained or decomposed. Next, we examined the cyanation reaction with α-bromocarboxamide **4a** (monopeptide) (Scheme 3), but the reactivity was not good under optimized conditions (Conditions A in Table 1). We speculated that this result was attributed to strong ligation (chelation) of **4a** to copper, which might have decreased the catalytic activity of the copper salt. Avoidance of catalyst poisoning could be challenging during cyanation of peptides containing an α-bromocarboxamide. For this, we screened various additives and ligands. Zinc additives and the PPh_3 ligand were suitable for the cyanation of **4a** with a peptide moiety. The yield of **5a** was improved (see SI: Table S2). We speculate that Zn might bind to peptides to replace Cu allowing recovery of its activity. Sterically hindered and highly functionalized peptides are not considered to be ideal substrates, especially for transition-metal-catalyzed cyanation reaction because cyanide is also a catalyst poison for copper and other metal catalysts. Thus, these results could provide the next generation cyanation protocol.

Using optimized conditions (Conditions B in Scheme 3), various peptides possessing an α-bromocarboxamide were cyanated (**4b**−**4p**) (Table 3). In this study, isolations were difficult due to generation of side products (elimination and reduction of **4**). Therefore, NMR yields were higher than isolation yields. Although catalyst poisoning was high in the reactions with peptide derivatives **4**, yields were mostly reasonable. For example, **4d**−**4g**, **4j**−**4m**, **4o**, and **4p** gave

Table 3. Cyanations of Peptide with an α-Bromocarboxamide[a]

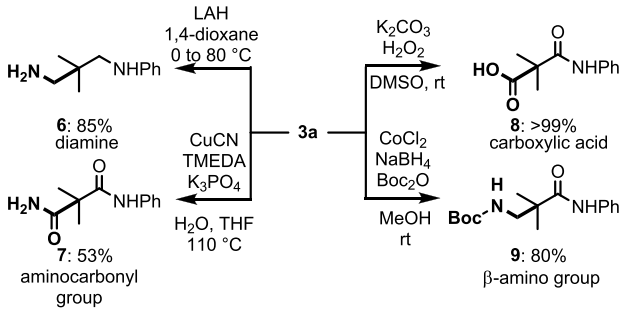


[a]See SI. Isolated product yields are reported. Yields shown in parentheses were determined by ^{1}H NMR analysis.

around 50% to 60% yield of **5d**−**5g**, **5j**−**5m**, **5o**, and **5p**, respectively. We did not observe epimerization of chiral amino acid units in **5p**. Reactions of highly sterically congested and functionalized peptide **4b**, **4c**, **4h**, and **4n** did not show good reactivities. Peptide-containing free carboxylic acid **4i** was sluggish.

Our cyanation reaction is useful to synthesize functionalized building blocks because the CN group can easily access various functional groups such as amine and carboxylic acid. We demonstrated four chemical transformations of **3a** in Scheme 4

Scheme 4. Transformation of CN Group[a]

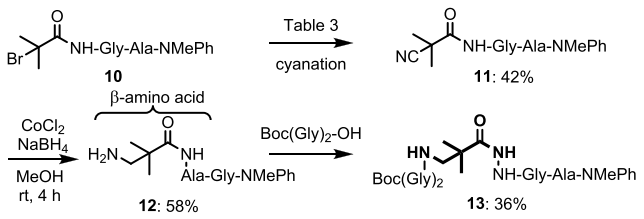


[a]Isolated yields are reported.

as examples. The reaction of **3a** in the presence of $LiAlH_4$ (LAH) resulted in the formation of a diamine **6** in 85% yield. The reaction of **3a** and stoichiometric amounts of CuCN produced the corresponding amide compound in 53% yield. Hydrolysis of CN group to give **8** was easy in the presence of H_2O_2. The reduction of **3a** in the presence of Co salt and $NaBH_4$ resulted in **9**, which contained a β-amino group, in 80% yield.

Recently, peptides with natural α-amino acid moieties have been synthesized by using active aminocarbonyl or aminonitrile derivatives[2,17,18] or a special catalyst system.[19] The current cyanation methodology provides a synthetic route for a modified peptide that has a β-amino acid moiety incorporated within it. The cyanation of **10** possessing dipeptide fragment gave a 42% yield of **11** (Scheme 5). After Co-mediated

Scheme 5. Synthesis of Modified Peptide Having α-Amino Acid[a]



[a]Isolated yields are reported.

reduction of **12**, the modified peptide **13** having a β-amino acid moiety was obtained in 36% yield. The chemical yield of **13** was not high probably because **13** might be decomposed during aqueous workup.

An outline for plausible copper-catalyzed cyanation mechanisms is shown in Figure 1. The reaction of CuX and $Zn(CN)_2$ could give copper cyanide (**A**). The resulting **A** could react with **1** to generate **3** via a transient intermediate

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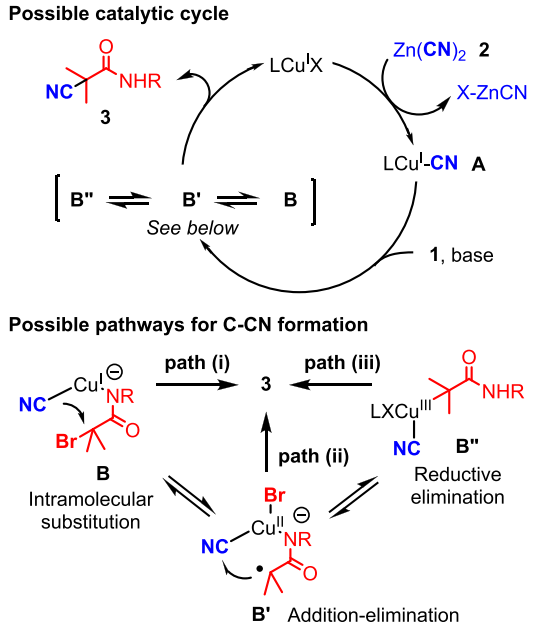
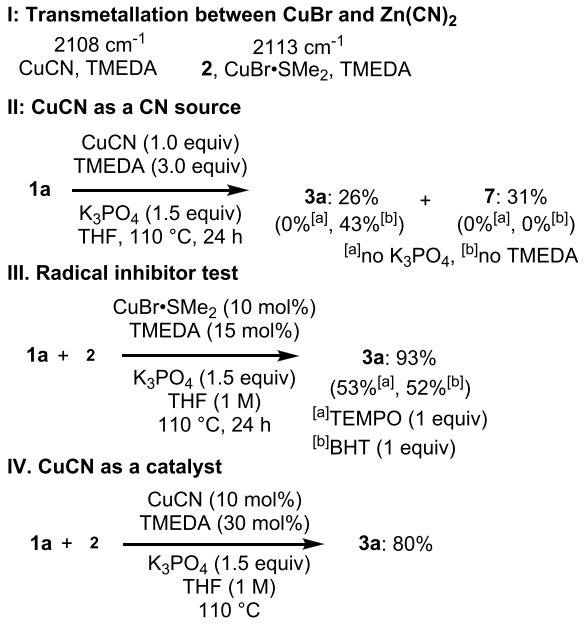


Figure 1. Possible mechanism

Scheme 6. Control Experiments[a]



[a]Isolated yields are reported.

(**B**, **B**′, or **B**′′). Although the overall reaction mechanism is still unclear, we conducted control experiments to support our postulated mechanism (Scheme 6). The transmetalation between CuX and $Zn(CN)_2$ is known, and the resulting product should be CuCN or a multinuclear metal complex.[20] IR studies revealed the generation of CuCN from the reaction of **2** and CuBr·SMe_2. The mixture of CuCN and TMEDA showed a CN peak at 2108 cm^{-1}. A similar peak (2113 cm^{-1}) was observed when **2** was reacted with CuBr·SMe_2 (Scheme 6I). Next, the reactivity of CuCN (**A**) was checked (Scheme 6II). When the reaction of CuCN (**A**) and **1a** was carried out in the presence/absence of K_3PO_4 and TMEDA, the corresponding product **3a** was obtained in 26% yield with concomitant formation of hydrolyzed product **7** in 31% yield. The Lewis acidity of CuCN[15] could accelerate the reaction of **3** and K_3PO_4 to generate **7** (Scheme 4). This is the reason why stoichiometric CuCN was not a good CN source compared with $Zn(CN)_2$. We also tried the reaction in the absence of K_3PO_4, but no product was obtained. In the absence of TMEDA, a 43% yield of **3a** was obtained. Thus, TMEDA plays an important role in the formation of **7** because the reaction without TMEDA did not give **7**. Based on these observations, three possible pathways for the C−CN formation step could be considered (Figure 1 bottom).

Path (i): **B** could be generated via deprotonation of NH followed by the ligation of CuCN. Compound **3** could be generated via an intramolecular substitution reaction. Path (ii): **B**′ could be obtained via intramolecular single electron transfer of **B**. **B**′ could undergo a radical addition to CN followed by elimination to produce **3**. Path (iii): **B**′′ could be obtained via migratory insertion of **B**′. Next **B**′′ could undergo reductive elimination to produce **3**. We tried to detect each intermediate but failed. For example, the reaction of **1a** and copper salt in the presence of K_3PO_4 did not yield any metal complex (**1a** was recovered completely). Although we have no direct proof of the existence of a radical species, the cyanation reaction was moderately inhibited by the addition of BHT or TEMPO, which indicated the involvement of a short-lifetime radical species (Scheme 6III). Finally, we used CuCN (**A**) as a catalyst in the reaction of **1a** and **2** under the optimized conditions. As a result, **3a** was obtained in 80% yield (Scheme 6IV). This result indicated that CuCN (**A**) could be the key intermediate in the catalytic cycle.

In summary, we successfully demonstrated Cu-catalyzed cyanation of α-bromocarboxamides and their peptide derivatives in the presence of zinc cyanide. Cyanation at a highly congested and functionalized reaction site was found to be difficult; however, the Cu catalyst system enabled efficient cyanation via CuCN which is formed by a transmetalation reaction between CuBr and zinc cyanide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b11349.

Screening data, experimental details, characterization of new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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