

Copper-Catalyzed Amination of Silyl Ketene Acetals with *N*-Chloroamines

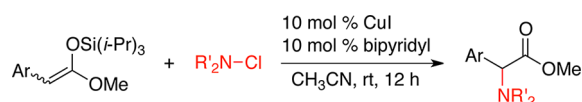
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ABSTRACT



A copper(I)/2,2'-bipyridyl complex catalyzes an amination reaction of silyl ketene acetals with *N*-chloroamines, presenting a new preparative method of α -amino esters.

Amines intrinsically possess a nucleophilic property. Their nucleophilic substitution reactions present conventional preparative methods of substituted amines. Transition-metal-catalyzed cross-coupling reactions of aryl halides with amines are also powerful methods for the formation of C–N bonds.¹ An alternative pathway to substituted amines has recently become available by the use of electrophilic amination reagents together with nucleophilic organometallic species.² For example, Johnson and co-workers have reported their pioneering research on copper- and nickel-catalyzed amination reactions of

diarylzinc compounds using *N*-hydroxyl(dialkyl)amine derivatives as the amination reagent.^{2e,f} *N*-Chloroamines are also promising amination reagents with their easy availability³ as well as high reactivity.⁴ Jarvo and co-worker reported a nickel-catalyzed amination reaction of diarylzinc compounds with *N*-chloro(dialkyl)amines, which formed tertiary anilines.^{2k} Similarly, secondary anilines are produced by the reaction of in situ-generated *N*-chloro(monoalkyl)amines with arylmagnesium reagents in the presence of an excess amount of titanium(IV) isopropoxide.^{2l,5} Furthermore, transition-metal-catalyzed direct C–H amination reactions of aromatic compounds with *N*-chloro(dialkyl)amines have been developed by Miura,⁶ Yu,⁷ and Glorius.^{8,9} It is also possible to introduce an amino group at the α -positions of carbonyl compounds by the reaction of their lithium enolates with *N*-chloroamines,^{10,11} although the substrate scope is limited probably due to the strongly basic reaction conditions

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(4) For a review on reactions of *N*-chloroamines with other nucleophiles, see: Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337.

(5) For electrophilic aminations of Grignard reagents with *N*-chloro(dialkyl)amines, see: (a) Sinha, P.; Knochel, P. *Synlett* **2006**, 3304. (b) Hatakeyama, T.; Yoshimoto, Y.; Ghorai, S. K.; Nakamura, M. *Org. Lett.* **2010**, *12*, 1516.

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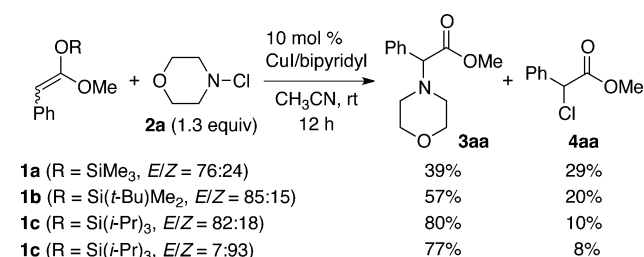
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as well as competing side reactions such as a chlorination reaction. We envisaged that an analogous amination reaction of carbonyl compounds would become feasible under milder conditions if it is assisted by transition-metal catalysts. Herein we report that a copper(I)/2,2'-bipyridyl complex successfully catalyzes an amination reaction of silyl ketene acetals with *N*-chloroamines to afford α -amino esters.

We initially attempted a direct amination reaction of methyl phenylacetate with *N*-chloromorpholine (**2a**, 1.3 equiv) in the presence of CuI (10 mol %) and 2,2'-bipyridyl (10 mol %). Various bases (2.0 equiv) such as NEt(*i*-Pr)₂, K₂CO₃, and K(OT-Bu) were examined, and the desired methyl 2-morpholino-2-phenylacetate (**3aa**) was formed in 6% (NMR) yield at best when K₂CO₃ was used. Then, methyl phenylacetate was replaced by its activated form, trimethylsilyl ketene acetal **1a** (*E/Z* = 76:24). An amination reaction proceeded in the absence of a base, and after 12 h, **3aa** was obtained in 39% yield together with methyl 2-chloro-2-phenylacetate (**4aa**, 29% yield) (Scheme 1).

Scheme 1. Effect of Silyl Group



Other sterically bulkier silyl groups were examined, and **3aa** was obtained in 80% isolated yield when triisopropylsilyl ketene acetal **1c** (*E/Z* = 82:18) was employed. It seemed that bulkier silyl groups disfavored the formation of **4aa** to improve the yield of **3aa**. A similar result was observed with **1c** of an opposite *E/Z* ratio (7:93).^{12,13} In the absence of a copper catalyst, only a small amount of

4aa (5% yield) was obtained together with the recovered **1c** (95%).

Various *N*-chloroamines **2** were subjected to the amination reaction of **1c** (*E/Z* = 7:93) (Table 1). Cyclic *N*-chloroamines **2b–f** reacted smoothly to give the corresponding products **3cb–cf** in yields ranging from 60 to 83% (entries 1–5). Acyclic *N*-chloroamines **2g–i** were also competent amination reagents (entries 6–8). On the other hand, the reaction with *N*-chloro(dibenzyl)amine (**2j**) gave the product **3cj** in only 28% yield due to a competing chlorination reaction of **1c** (entry 9).

Table 1. Cu(I)-Catalyzed Amination Reaction of Silyl Ketene Acetal **1c** with Various *N*-Chloroamines **2b–j**^a

entry	2	3	yield/% ^b
1		3cb	82
2		3cc	68
3		3cd	60
4		3ce	74
5		3cf	83
6		3cg	56 ^c
7		3ch	74
8		3ci	73
9		3cj	28 ^d

^a Conditions: **1c** (0.20 mmol), **2** (0.26 mmol), CuI (10 mol %), and 2,2'-bipyridyl (10 mol %) in CH₃CN (2 mL) at rt for 12 h, unless otherwise noted. ^b Isolated yields (averages of 2 runs). ^c Using 0.30 mmol of **2g**. ^d Chlorination product was obtained in 40% yield.

Next, the scope of silyl ketene acetals **1** was examined using **2a** (Table 2). Whereas the reaction of α -alkyl-substituted silyl ketene acetals was sluggish,¹⁴ α -aryl-substituted

(14) α -Methyl-substituted silyl ketene acetal gave the desired product in 23% yield.

(9) For transition-metal-catalyzed direct C–H amination with other electrophilic nitrogen sources, see: (a) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (b) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (c) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (d) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. (e) Liu, X.-Y.; Gao, P.; Shen, Y.-W.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 4196. (f) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110.

(10) (a) Horiike, M.; Oda, J.; Inouye, Y.; Ohno, M. *Agric. Biol. Chem.* **1969**, *33*, 292. (b) Oguri, T.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 167. See also: (c) Smulik, J. A.; Vedejs, E. *Org. Lett.* **2003**, *5*, 4187 and references therein.

(11) For reviews on α -amination of carbonyl compounds, see: (a) Greck, C.; Drouillard, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, 1377. (b) Erdik, E. *Tetrahedron* **2004**, *60*, 8747. (c) Ciganek, E. *Org. React.* **2008**, *72*, 1.

(12) Other copper catalysts such as CuCl, CuBr, Cu(OAc), CuCN, CuCl₂, Cu(acac)₂, and Cu(OAc)₂ gave inferior results.

(13) When *N*-benzoyloxymorpholine was used instead of *N*-chloromorpholine (**2a**) under the same reaction conditions, **3aa** was obtained in 80% yield.

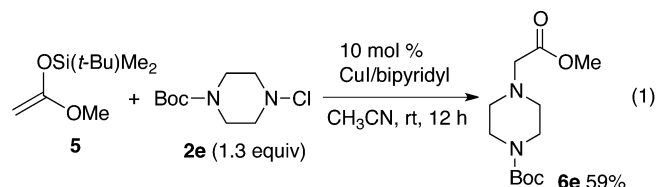
substrates successfully participated in the reaction. All three substrates **1d–f** with isomeric tolyl substituents afforded the corresponding products **3da–fa** in good yields (entries 1–3). Both electron-withdrawing and -donating groups were allowed for the aryl substituent (entries 4–6). Thienyl-substituted substrate **1j** also gave the product **3ja** in 67% yield (entry 7).

Table 2. Cu(I)-Catalyzed Amination Reaction of Various Silyl Ketene Acetals **1d–j** with 4-Chloromorpholine **2a**^a

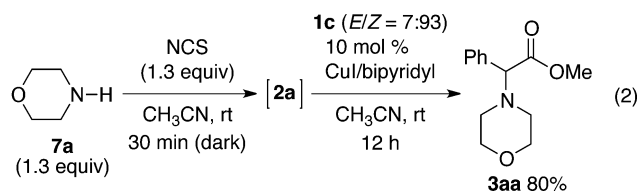
entry	1 (R, <i>E/Z</i>)	3	yield (%) ^b
1	1d (4-MeC ₆ H ₄ , 84:16)	3da	83
2	1e (3-MeC ₆ H ₄ , 81:19)	3ea	79
3	1f (2-MeC ₆ H ₄ , 68:32)	3fa	70
4	1g (4-MeOC ₆ H ₄ , 87:13)	3ga	89
5	1h (4-CF ₃ OC ₆ H ₄ , 15:85)	3ha	55 ^c
6	1i (4-ClC ₆ H ₄ , 45:55)	3ia	72
7	1j (3-thienyl, 58:42)	3ja	67

^a Conditions: **1** (0.20 mmol), **2a** (0.26 mmol), CuI (10 mol %), and 2,2'-bipyridyl (10 mol %) in CH₃CN (2 mL) at rt for 12 h, unless otherwise noted. ^b Isolated yield. ^c Using 0.36 mmol of **2a**.

The commercially available *t*-butyldimethylsilyl ketene acetal **5** produced glycine derivative **6e** in 59% yield (eq 1).

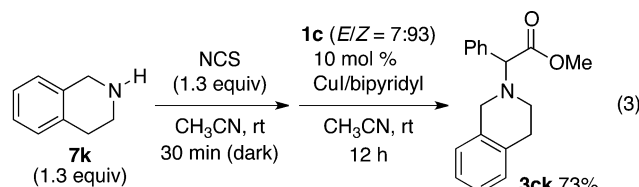


The facile availability of *N*-chloroamines from secondary amines permits a one-pot two-step synthesis starting from amines on gram scale (eq 2). Treatment of morpholine (**7a**, 0.68 g, 7.8 mmol) with *N*-chlorosuccinimide (NCS, 1.04 g, 7.8 mmol) in CH₃CN at room temperature for 30 min generated *N*-chloromorpholine (**2a**) quantitatively. Then, **1c** (1.85 g, 6.0 mmol), CuI (10 mol %), and 2,2'-bipyridyl (10 mol %) were sequentially added to the reaction mixture, which was further stirred at room temperature for 12 h. The product **3aa** (1.14 g, 4.8 mmol) was isolated in 80% yield based upon **1c**. The one-pot synthesis demonstrates another advantage from the practical standpoint.



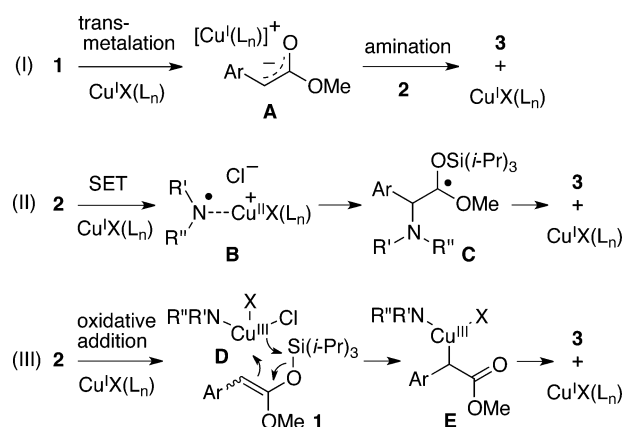
This one-pot two-step method was useful particularly when an *N*-chloroamine was too unstable to be isolated, as

exemplified in eq 3.¹⁵ The α-amino ester **3ck** was obtained in 73% yield directly from 1,2,3,4-tetrahydroisoquinoline (**7k**).



Upon the basis of experimental precedents in the literature, three plausible pathways are conceived for production of **3** from **1** and **2** (Scheme 2). In pathway (I), silyl

Scheme 2. Proposed Mechanisms for the Formation of **3** from **1** and **2**



ketene acetal **1** initially undergoes transmetalation¹⁶ with copper(I) to generate nucleophilic copper(I) enolate **A**.¹⁷ The following reaction with *N*-chloroamine **2** gives α-amino ester **3**. Pathway (II) involves single-electron transfer (SET) from copper(I) to *N*-chloroamine **2**.¹⁸ The resulting aminyl radical intermediate **B** couples with silyl ketene acetal **1**. SET back to copper(II) produces α-amino ester **3** together with triisopropylchlorosilane and copper(I). In pathway (III), *N*-chloroamine **2** initially undergoes oxidative addition to copper(I) to generate amino copper(III) species **D**.^{2h} Transmetalation with silyl ketene acetal **1** furnishes copper(III) enolate **E**, and reductive elimination ensues.

Whereas a catalytic reaction of **1c** with **2a** using CuI/1,10-phenanthroline gave **3aa** in 72% yield, a stoichiometric reaction of **2a** with copper/1,10-phenanthroline enolate **A**, generated according to the Hartwig's procedure,

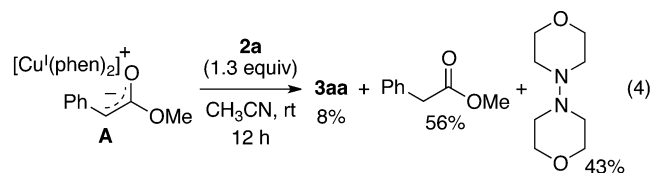
(15) When cyclohexylamine was treated with **1c** under the same one-pot reaction conditions, the desired α-amino ester was obtained in 20% yield.

(16) For transmetalation between Cu(I) and trimethylsilyl ketene acetals in the presence of a base, see: (a) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644. (b) Li, D.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 5672.

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yielded only 8% of **3aa** together with methyl phenylacetate (56% yield) and 4,4'-bimorpholine (43% yield based upon **2a**) (eq 4).



In addition, the reaction of **1c** with **2a** under the standard conditions but in the presence of TEMPO (1.0 equiv) afforded **3aa** in almost same yield (72%). Thus, we prefer pathway (III) as the most likely mechanistic scenario, albeit with no experimental evidence to support it.

In summary, we have developed a copper-catalyzed amination reaction of silyl ketene acetals with *N*-chloroamines

under mild reaction conditions. This reaction provides an efficient synthetic route to α -amino esters, which are substructures found in a variety of bioactive compounds.

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Supporting Information Available. Experimental details and spectra data for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.