

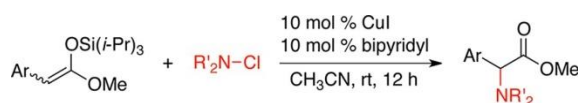
Copper-Catalyzed Amination of Silyl Ketene Acetals with *N*-Chloroamines

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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.

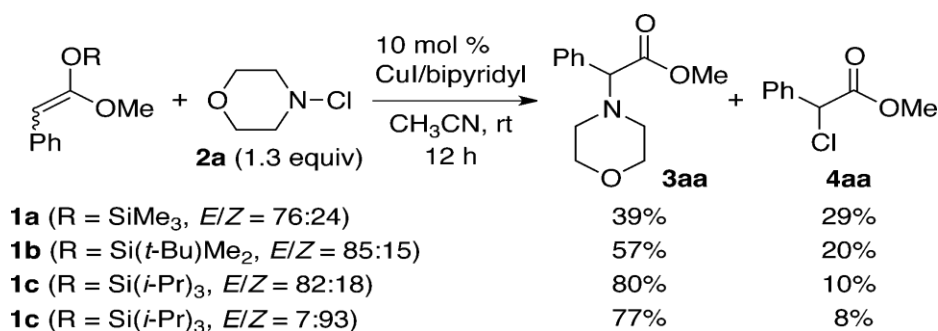
Amines intrinsically possess a nucleophilic property. Their nucleophilic substitution reactions present conventional preparative methods of substituted amines. Transition-metal-catalyzed cross-coupling reactions of aryl halides with amines are also powerful methods for the formation of C-N bonds.¹ An 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 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 *R*-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(*O**t*-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

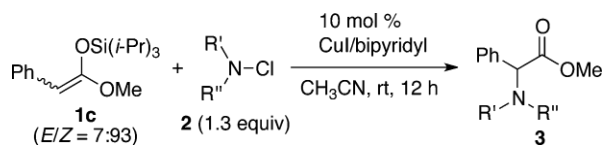


Other sterically bulkier silyl groups were examined, and 3aa was obtained in 80% isolated yield when triisopropylsilyl ketene acetal 1c (*E/Z* = 82:18) was employed. It seemed that bulkier silyl groups disfavored the formation of 4aa to improve the yield of 3aa. A similar result was observed with 1c 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

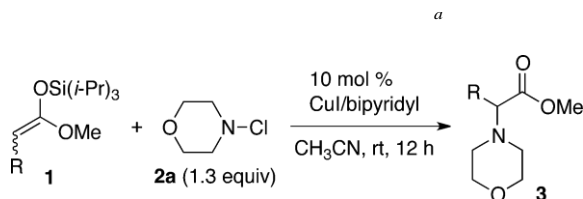


entry	2	3	yield/% ^b	
1		2b	3cb	82
2		2c	3cc	68
3		2d	3cd	60
4		2e	3ce	74
5		2f	3cf	83
6		2g	3cg	56 ^c
7		2h	3ch	74
8		2i	3ci	73
9		2j	3cj	28 ^d

^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 R-alkyl-substituted silyl ketene acetals was sluggish,¹⁴ R-aryl-substituted 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).

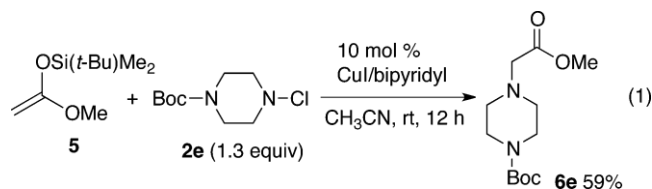
Table 2. Cu(I)-Catalyzed Amination Reaction of Various Silyl Ketene Acetals **1d–j** with 4-Chloromorpholine **2a**



entry	1 (R, <i>E/Z</i>)	3	yield (%) ^{<i>b</i>}
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 ^{<i>c</i>}
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**.

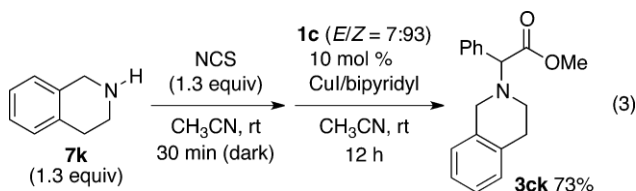
The commercially available *t*-butyldimethylsilyl ketene acetal **5** produced glycine derivative **6e** in 59% yield (eq 1).



The facile availability of *N*-chloroamines from second-ary 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

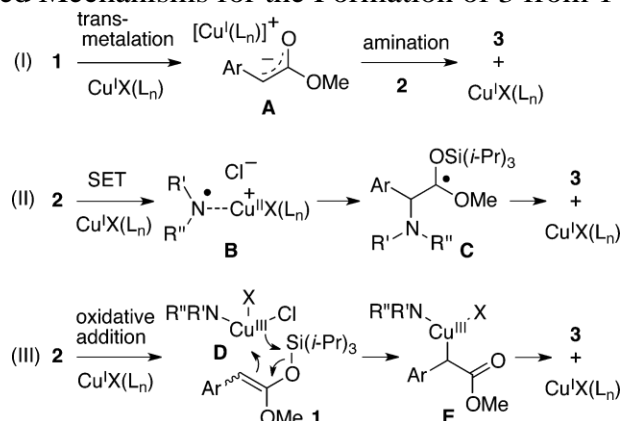
reaction mixture, which was further stirred at room temperature for 12 h. The product **3aa** (1.14 g, 4.8 mmol) was isolated in 80% yield based upon **1c**. The one-pot synthesis demonstrates another advantage from the practical standpoint.

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



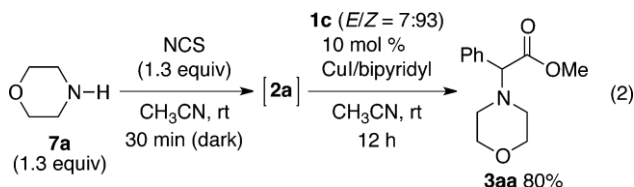
Upon the basis of experimental precedents in the literature, three plausible pathways are conceived for production of **3** from **1** and **2** (Scheme 2). In pathway (I), silyl

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

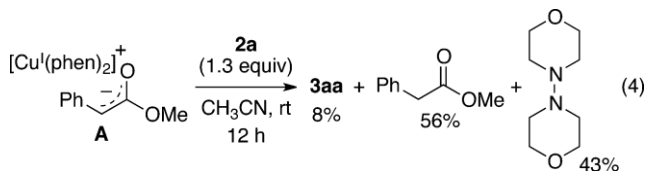


ketene acetal **1** initially undergoes transmetalation¹⁶ with copper(I) to generate nucleophilic copper(I) enolate **A**.¹⁷ The following reaction with *N*-chloroamine **2** gives *R*-amino ester **3**. Pathway (II) involves single-electron transfer (SET) from copper(I) to *N*-chloroamine **2**.¹⁸ The resulting aminyl radical intermediate **B** couples with silyl ketene acetal **1**. SET back to copper(II) produces *R*-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, 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.

under mild reaction conditions. This reaction provides an efficient synthetic route to R-amino esters, which are sub- structures found in a variety of bioactive compounds. exemplified in eq 3.¹⁵ The R-amino ester 3ck was obtained in 73% yield directly from 1,2,3,4-tetrahydroisoquino- line (7k).

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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*-chloro- morpholine (**2a**) under the same reaction conditions, **3aa** was obtained in 80% yield.
14. *R*-Methyl-substituted silyl ketene acetal gave the desired product in 23% yield.

