Synthetic Methods

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Copper-Catalyzed Amination of Ketene Silyl Acetals with Hydroxylamines: Electrophilic Amination Approach to α-Amino Acids**

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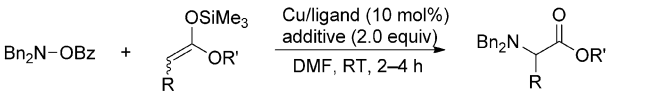
α-Amino acid derivatives are a fundamental and important structural motif in many biologically active compounds and pharmaceutical targets, especially peptide drugs. In particular, significant attention has recently been focused on unnatural α-amino acids because when used to replace natural α-amino acids in the original drug structure, the potential for the discovery of new functions as well as improved activity increases.[1] Multicomponent couplings such as the Strecker, Ugi, and Petasis reactions rank as one of the most powerful approaches to the target structure.[2] As a useful alternative, the decoration of N-protected glycine esters with organic halides under phase-transfer[3] or palladium catalysis[4] conditions has also been widely developed. These protocols generally rely on C–C bond formation. In contrast, the C–N formation at the position α to the carbonyl group can provide a complementary and potentially more efficient access to the above amino acids. A traditional halogenation α to carbonyls and subsequent nucleophilic substitution with amines is practical, but often suffers from lower efficiency and forcing conditions in the case of sterically hindered substrates, particularly, for the combination of acetates, substituted with secondary alkyl groups, and acyclic secondary amines.[5] To overcome these limitations, an electrophilic amination with azodicarboxylate esters ($RO_2CN{=}NCO_2R$) has been explored, and versatile metal-catalyzed[6] and organocatalytic[7] processes have now become available. However, the resultant N–N bond in the aminated product should undergo cleavage under relatively harsh reductive conditions, which is often problematic. Although another protocol involving the aziridination of enols with phenyl iodinane (TsN = IPh) or chloramine T[8] is reported, most of them are restricted to the aldehyde and ketone oxidation levels. Thus, there still remains a demand for further developments in C–N bond formation directed toward unnatural α-amino acid analogues. Herein, we introduce O-acylated hydroxylamine[9–11] as an effective electrophilic amination reagent for the synthesis of α-amino acid derivatives: a copper-catalyzed amination of ketene silyl acetals with hydroxylamines is described.[12] The copper catalysis allows various α-amino acid esters to be formed under very mild reaction conditions from starting materials which are at the carboxylic acid oxidation level.[13]

Our study commenced with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**1a**; 0.30 mmol) and the ketene silyl acetal **2a** (0.25 mmol) as the model substrate (Table 1). In an early experiment, a CuCl/phen (phen = 1,10-phenanthroline) system in *N*,*N*′-dimethylformamide (DMF) afforded the corresponding glycine ester **3aa** even at room temperature, albeit in only 26% yield (GC; entry 1). With the preliminary result in hand, other ancillary ligands were tested. While 2,2′-bibyridine (bpy) was ineffective (entry 2), some bidentate phosphines improved the reaction efficiency (entries 3–7), with 1,5-bis(diphenylphosphino)pentane (dpppen) proving to

Table 1: Optimization studies for copper-catalyzed amination of ketene silyl acetals **2a** and **2b** with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**1a**).[a]



1a **2a**: R = H, R' = Et; **2b**: R = Me, R' = Me (*E*/*Z* = 5:1) **3aa**: R = H, R' = Et; **3ab**: R = Me, R' = Me

Entry	2	Cu/ligand	Additive	3 Yield [%][b]
1	**2a**	CuCl/phen	none	**3aa**: 26
2	**2a**	CuCl/bpy	none	**3aa**: 0
3	**2a**	CuCl/dppbz	none	**3aa**: 27
4	**2a**	CuCl/dppe	none	**3aa**: 31
5	**2a**	CuCl/dppp	none	**3aa**: 15
6	**2a**	CuCl/dppb	none	**3aa**: 0
7	**2a**	CuCl/dpppen	none	**3aa**: 36
8[c]	**2a**	CuCl/dpppen	none	**3aa**: (56)
9[c]	**2b**	CuCl/dpppen	none	**3ab**: 0
10[c]	**2b**	$[Cu(OAc)_2]$/dpppen	$NaHCO_3$	**3ab**: (92)
11[c]	**2b**	$[Cu(OAc)_2]$/dpppen	Na_2CO_3	**3ab**: (78)
12[c]	**2b**	$[Cu(OAc)_2]$/dpppen	KOAc	**3ab**: (77)
13[c]	**2b**	$[Cu(OAc)_2]$/dpppen	LiF	**3ab**: 73
14[c]	**2a**	$[Cu(OAc)_2]$/dpppen	KOAc	**3aa**: (67)

[a] Reaction conditions: Cu (0.025 mmol), ligand (0.025 mmol), additive (0.50 mmol), **1a** (0.30 mmol), **2** (0.25 mmol), DMF (1.5 mL), N_2, RT, 2–4 h. [b] Yield estimated by GC methods. Yield of isolated product given within parentheses. [c] With **1a** (0.25 mmol) and **2** (0.50 mmol). Bz = benzoyl, Bn = benzyl, dppb = 1,4-bis(diphenylphosphino)butane, dppbz = 1,2-bis(diphenylphosphanyl)benzene, dppe = 1,2-bis(diphenylphosphanyl)ethane, dppp = 1,3-bis(diphenylphosphanyl)propane.

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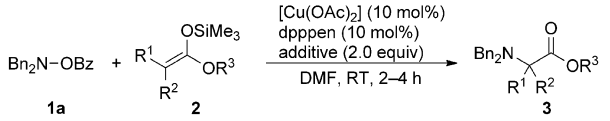
be optimal (entry 7). Investigations into the reaction stoichiometry identified that a 1:2 ratio of **1a** and **2a** increased the yield, and **3aa** was isolated in 56% yield (entry 8). However, we immediately found that the above catalyst was not applicable to the reaction with the methyl-substituted ketene silyl acetal **2b** for the synthesis of the alanine derivative **3ab** (entry 9). Thus, additional optimization studies were carried out. We were pleased to find that several combinations of basic additives and the $[Cu(OAc)_2]$/dpppen catalyst afforded the desired **3ab** in a good yield. In particular, $NaHCO_3$, Na_2CO_3, KOAc, and LiF showed high activity (entry 10–13). The best additive is dependent upon the electronic and steric nature of the hydroxylamine and ketene silyl acetal employed (see below). For example, the highest yield of **3ab** was obtained with $NaHCO_3$ (entry 10), whereas KOAc was the most effective for the synthesis of **3aa** (entry 14).[14]

Various ketene silyl acetals **2** underwent amination with **1a** to form the corresponding α-amino esters **3** (Table 2). The allyl-substituted **2c** and benzyl-substituted **2d** coupled with

Table 2: Copper-catalyzed amination of various ketene silyl acetals **2** with *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**1a**).[a]



1a **2** **3**

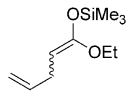
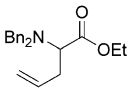
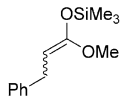
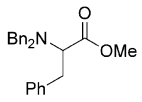
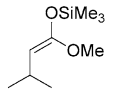
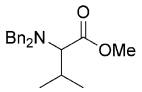
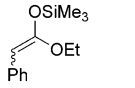
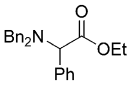
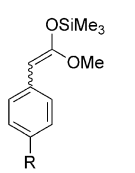
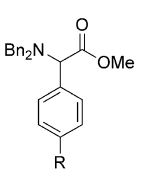
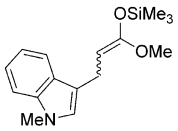
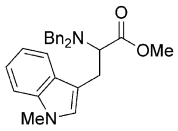
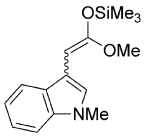
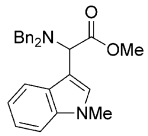
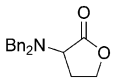
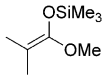
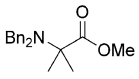
Entry	2	Additive	3	Yield [%][b]
1	 **2c** (*E*/*Z* = 5:1)	Na_2CO_3	 **3ac**	85
2	 **2d** (*E*/*Z* = 5.5:1)	Na_2CO_3	 **3ad**	79
3	 **2e** (*E*/*Z* > 20:1)	KOAc	 **3ae**	90 (42)[c]
4	 **2f** (*E*/*Z* = 3.3:1)	LiF	 **3af**	75
5	**2f** (*E*/*Z* = 1:16)	LiF	**3af**	74
6	 **2g**: R = Me (*E*/*Z* = 3.8:1)	LiF	 **3ag**: R = Me	81
7	**2h**: R = F (*E*/*Z* = 2.7:1)		**3ah**: R = F	77

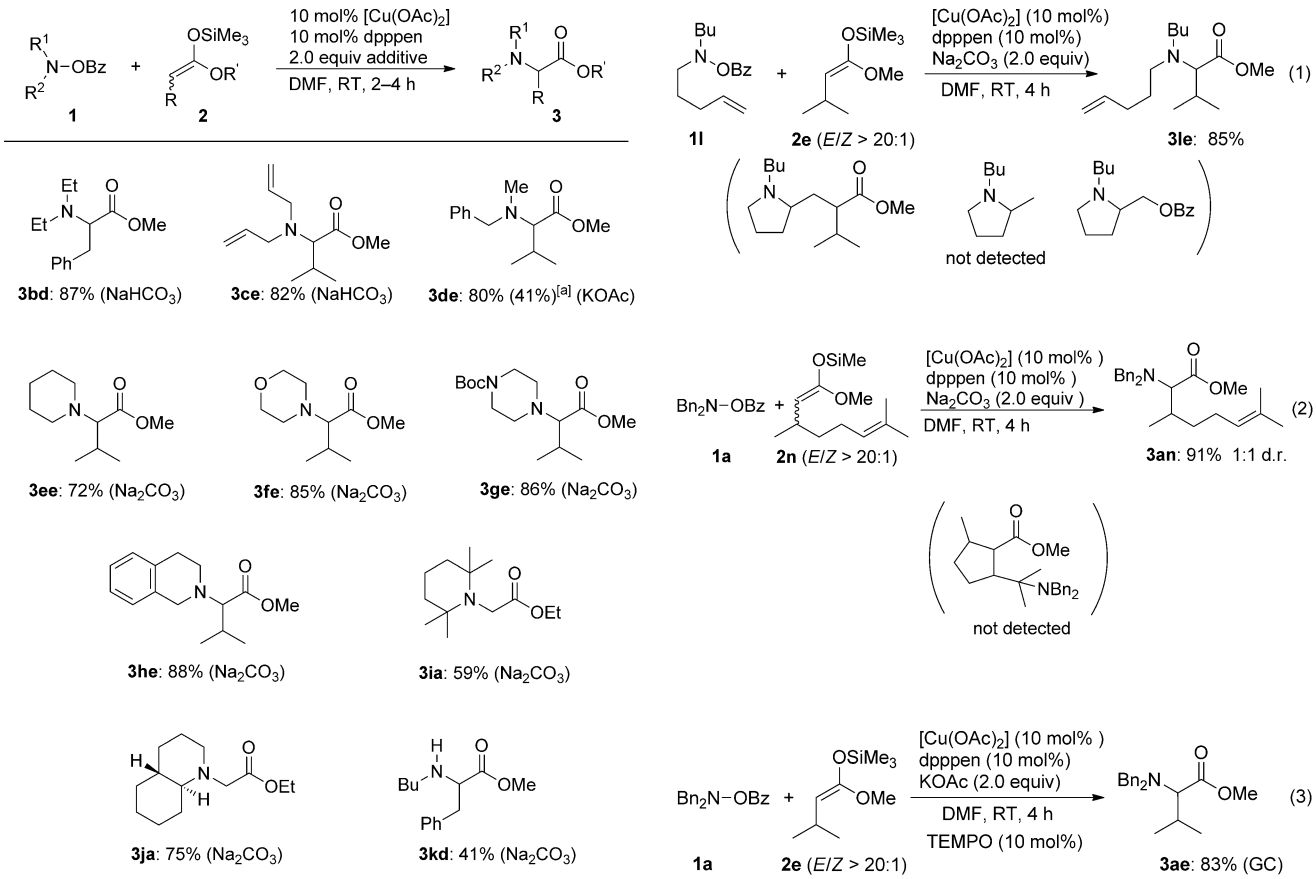
Table 2: (Continued)

Entry	2	Additive	3	Yield [%][b]
8[d]	**2i**: R = Br (*E*/*Z* = 20:1)		**3ai**: R = Br	51
9	 **2j** (*E*/*Z* = 3.5:1)	Na_2CO	 **3aj**	75
10	 **2k** (*E*/*Z* = 8.1:1)	LiF	 **3ak**	37
11	 **2l**	Na_2CO_3	 **3al**	89
12	 **2m**	KOAc	 **3am**	42

[a] Reaction conditions: $[Cu(OAc)_2]$ (0.025 mmol), dpppen (0.025 mmol), additive (0.50 mmol), **1a** (0.25 mmol), **2** (0.50 mmol), DMF (1.5 mL), N_2, RT, 2–4 h. [b] Yield of the isolated product. [c] With 0.30 mmol of **2e** and KOAc. [d] With 0.75 mmol of **2i** and LiF.

1a smoothly in the presence of Na_2CO_3 to provide the allylglycine and phenylalanine esters **3ac** (85%) and **3ad** (79%), respectively (entries 1 and 2). Notably, the substrate **2e** that bears the bulky isopropyl group also could be aminated with the assistance of KOAc, and the valine derivative **3ae** was obtained in high yield (entry 3). Aromatic substituents at the vinylic position were also tolerated to deliver the phenylglycine esters **3af**–**aj** effectively (entries 4–8). In these cases, LiF acted as a promising promoter. The amination occurred smoothly irrespective of the *E*/*Z* geometry of the starting ketene silyl acetals (entry 4 versus 5). It is worth noting that the aryl–Br bond was compatible under the reaction conditions (entry 8). Additionally, the tryptophan derivative **3aj** and its truncated analogue **3ak** were readily accessible (entries 9 and 10). The cyclic ketene silyl acetal **2l** also could be employed for the electrophilic amination without any difficulties (entry 11). The sterically demanding dimethyl-substituted **2m** was transformed into **3am** with an acceptable yield (entry 12). In sharp contrast, the present copper catalyst was insufficient for the amination of 2-trimethylsilyloxyfuran and silyl enolates derived from ketones, such as propiophenone (data not shown). While the reaction with ketene silyl acetals as the limiting reagent was unsuccessful, we succeeded by decreasing the amount of the reagent to 1.2 equivalents, albeit with a moderate yield of the aminated product (entry 3).

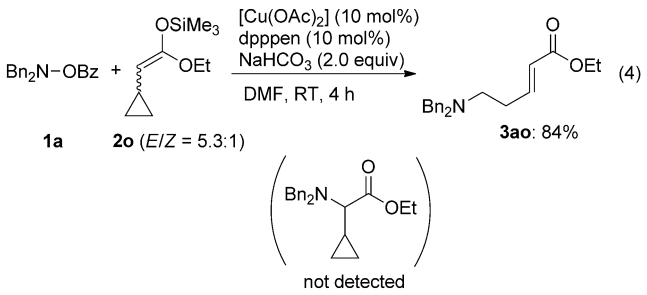
We next performed the amination with a variety of hydroxylamines (**1**; Scheme 1). In addition to **1a**, acyclic



Scheme 1. Copper-catalyzed electrophilic amination of the ketene silyl acetals **2** with various hydroxylamines (**1**) using the reaction conditions detailed in Table 2. [a] Used 1.2 equiv of **2** and KOAc. The additive is given in parentheses. Boc = *tert*-butoxycarbonyl.

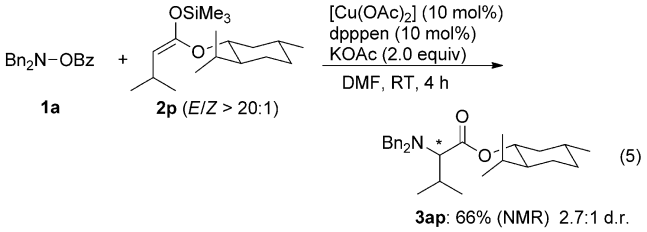
amines containing *N*,*N*-diethyl, *N*,*N*-diallyl, and *N*-benzyl-*N*-methyl substituents participated in the reaction (**3bd**, **3ce**, and **3de**). The resultant allyl and benzyl moieties can be a useful synthetic handle for further manipulations after the selective deprotection.[15] Monocyclic piperizine, morpholine, N-Boc piperazine, and bicyclic tetrahydroisoquinoline also could be introduced to the α position of esters effectively (**3ee**, **3fe**, **3ge**, and **3he**). Moreover, the hindered 2,2,6,6-tetramethylpiperizine and decahydroquinoline reacted with the ketene silyl acetal **2a** to furnish the corresponding bulky amino esters **3ia** and **3ja** in a satisfying yield. Notably, the secondary amine was also available for use (**3kd**).

To investigate whether radical intermediates are involved in the catalytic reaction, the following experiments were performed. The reaction with the *N*-4-pentenylhydroxylamine **1l** produced the usual aminated product **3le** exclusively, and no pyrrolidine-containing product from a 5-exo radical cyclization was detected [Eq. (1); Bz = benzoyl].[16] In contrast, the ketene silyl acetal **2n** also afforded the simple aminated product **3an**, thus leaving the pendant olefinic moiety untouched [Eq. (2)]. The addition of the radical scavenger 2,2,6,6,-tetramethylpiperidine 1-oxyl (TEMPO) had little influence on the outcome of the reaction [Eq. (3) versus Table 2, entry 3]. These results are inconsistent with the precedented nitrogen- and carbon-centered radical (or their copper-coordinated form) pathways.[17] Although the exact reaction mechanism remains to be elucidated, one possibility involves 1) a base-accelerated transmetalation of the copper acetate complexe with the ketene silyl acetal, thus generating a copper enolate species which exists as an equilibrium mixture of the O- and C-bound forms,[18] and 2) subsequent electrophilic amination with the hydroxylamine.[19] At present, we speculate that bases can provide an additional anionic ligand to the copper center in the catalytic cycle. Thus, the best base is highly dependent upon the electronic and steric nature of the ketene silyl acetal as well as hydroxylamine. Another possibility can be the direct attack of the ketene silyl acetal on the nitrogen center of the hydroxylamine, which is activated through coordination to $[Cu(OAc)_2]$ given its Lewis acidic nature. However, the result of the reaction with **2o** containing the cyclopropyl substituent contrasts with the above Lewis acid promoted pathway [Eq. (4)]: the reaction occurred with concomitant cyclopropyl ring opening to afford the δ-amino-α,β-unsaturated ester **3ao** as the sole product.[20] Given that a Lewis acid mediated reaction of ketene silyl acetals of the type **2o** furnished the coupling product with the cyclopropyl group left intact,[21] the phenomenon is suggestive of in situ formation of a cyclopropylmethyl copper species which is a C-bonded copper enolate. A relevant reaction mode of cyclopropylmethyl boron reagents is also reported.[22] However, we cannot exclude an alternative that includes 1) oxidative addition of



the hydroxylamine to a low-valent copper species, 2) base-assisted transmetalation with the ketene silyl acetal, and 3) productive C–N formation by reductive elimination.[10a–d,23] Efforts to clarify the details of the mechanism are ongoing.

Finally, we attempted to apply the amination protocol to the asymmetric synthesis of α-amino acids. While preliminary investigation with some representative chiral biphosphine ligands remained unsuccessful,[24] the use of readily available L-menthol as the chiral auxiliary resulted in a moderate stereoinduction [Eq. (5)]. Although insufficient at this stage,



the result shows the potential of the copper catalysis directed toward a new electrophilic amination approach to optically active unnatural α-amino acids. Development of catalytic asymmetric variants as well as additional optimization studies on the chiral auxiliary are currently underway.

In conclusion, we have developed a copper-catalyzed amination of ketene silyl acetals with O-benzoylhydroxylamines directed toward synthesis of unnatural α-amino acids. The catalysis provides a complementary C–N bond-forming approach to α-amino acids starting from substrates at the carboxylic acid oxidation level. Moreover, the reaction system is a successful example of the introduction of mild carbon nucleophiles in the electrophilic amination reaction with the hydroxylamine.

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Keywords: amination · amino acids · copper · synthetic methods · umpolung

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