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Highly efficient synthesis of α-amino amidines from ynamides by the Cu-catalyzed three-component coupling reactions

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Abstract

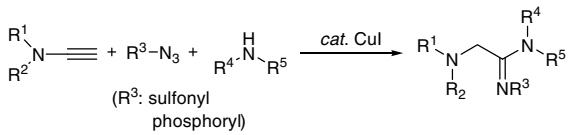
Using ynamides as one of the reacting components, the Cu-catalyzed three-component reaction of sulfonyl or phosphoryl azides and amines affords α-amino amidines in high yields under mild conditions. Synthetic utility of the produced compounds was demonstrated in the diastereoselective alkylation of α-amino amidines bearing a chiral oxazolidinone moiety. It was also shown that α-amino imidates could be readily prepared by employing alcohols instead of amines.

Keywords: α-Amino amidines; Ynamides; Three-component reactions; Copper catalysis

α-Amino amidines are widely found in natural products,[1] and used as important synthetic building units in the synthesis of iminopeptides[2] and antitumor or antibiotic compounds.[3] However, only a few synthetic methods for the α-amino amidine compounds have been developed.[4] For instance, Keung et al. presented a novel procedure for the synthesis of α-amino amidine via Sc-mediated Ugi condensation reactions.[4c] We recently developed the three-component synthesis of *N*-sulfonylamidines by the copper-catalyzed coupling reaction of alkynes, sulfonyl azides, and amines.[5] Imidates and amides were also prepared under the similar conditions with the use of alcohols[6] or water[7] instead of amines. More recently, phosphoryl azides were also found to be a facile reacting partner in the catalytic three-component reactions.[8]

Along with this line, we envisioned that α-amino amidines could be readily prepared by the Cu-catalyzed three-component coupling reactions when ynamides are employed as a source of terminal triple bonds. Hsung and Cintrat independently reported the highly efficient Cu-catalyzed [3+2] cycloaddition reactions between ynamides and alkyl- or aryl azides producing 4-amino-1,2,3-triazoles.[9] However, no example of utilizing ynamides in the catalytic three-component coupling reactions has been shown to afford α-amino amidines, which will be described herein (Scheme 1).

Since ynamides or ynamines bearing electron-deficient substituents have been shown to be highly useful synthetic precursors,[10–12] several preparative routes are reported. For instance, Witulski paved the way for the synthesis of electronically tunable 1-alkynylamides using iodonium triflate salts in reaction with electron-deficient amines.[13] Hsung demonstrated that N-alkynylation of oxazolidinones and lactams with alkynyl halides can be catalyzed by CuCN.[14] Danheiser developed a modified procedure of N-alkynylation of carbamates, ureas, and sulfonamides



Scheme 1.

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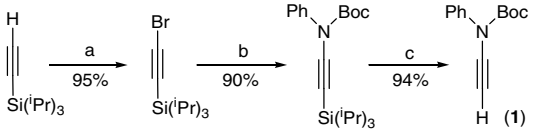
using stoichiometric amounts of KHMDS and CuI.[15] Urabe and Sato reported a route to *N*-(1-alkynyl)sulfonamides based on the Cu catalysis.[16] Hsung's approach for the cross-coupling of amides with alkynyl bromides using catalytic amounts of $CuSO_4$ and 1,10-phenanthroline significantly broadened the availability of ynamides.[17] Tam subsequently developed a method for the facile synthesis of acyclic ynamides by the slow addition of KHMDS to CuI catalytic systems.[18]

Following Tam's procedure with a slight modification, we were able to prepare a variety of ynamides in high yields substituted with several functional groups such as oxazolidinones, acyclic carbamates, and sulfonamides. A representative example is shown in Scheme 2. Cross-coupling of *N*-Boc-aniline and bromo(triisopropylsilyl)acetylene, which can be obtained by bromination of TIPS-acetylene with NBS,[19] was successfully achieved by the action of CuI and 1,10-phenanthroline catalysts under the slow addition conditions.[20] Subsequent desilylation was readily-carried out with tributylammonium fluoride, thus leading to the desired *N*-ethynyl-*N*-phenyl-(*tert*-butyl) carbamate (**1**) in 80% overall yield. Other substrates of ynamide derivatives could be readily prepared in similar yields using the same procedure.

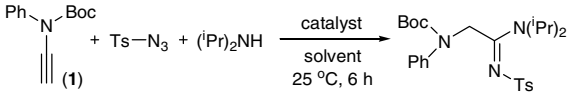
With ynamides in our hands, we tried to optimize the reaction conditions for the synthesis of α-amino amidines using the Cu-catalyzed three-component reaction (Table 1). Initially, catalytic activity of various Cu species was examined in THF to reveal that CuI and CuCN were especially effective for the three-component reaction, leading to the desired product with high yields (entries 3 and 4, respectively). However, copper(II) complexes displayed reduced catalytic activities (entries 5–7). Among several solvents screened, chloroform turned out to be the best one with CuI catalyst (entry 9) while polar media were less effective (entries 11–13). Interestingly, no significant effects of external ligands were observed (entry 14).[21,22]

Under the optimized conditions, a wide range of ynamides, azides, and amines were smoothly reacted to afford the corresponding α-amino amidine products in good yields (Table 2).[23] In addition to acyclic *N*-ethynyl carbamate (entry 1), cyclic analogs such as ynamides of oxazolidinone could also be readily employed as a viable type of substrates (entries 2–5). Interestingly, steric variation on the cyclic skeleton in these substrates does not alter efficiency of the coupling reactions. For instance, reactions with substrates bearing various substituents such as benzyl,



Scheme 2. Reagents and conditions: (a) *N*-Bromosuccinimide (1.2 equiv), $AgNO_3$ (0.1 equiv), acetone, 25 °C, 2 h; (b) *N*-Boc-aniline (0.8 equiv), CuI (0.25 equiv), 1,10-phenanthroline (0.3 equiv), KHMDS (1.1 equiv), toluene, 90 °C, 12 h; (c) TBAF (2.0 equiv), THF, 0 °C, 1 h.

Table 1
Optimization of the α-amino amidine synthesis[a]



Entry	Catalyst	Solvent	Yield[b] (%)
1	CuCl	THF	35
2	CuBr·SMe_2	THF	<1
3	CuI	THF	78
4	CuCN	THF	80
5	$Cu(acac)_2$	THF	53
6	$Cu(OAc)_2$	THF	59
7	$Cu(OTf)_2$	THF	<1
8	CuI	CH_2Cl_2	66
9	CuI	$CHCl_3$	82
10	CuCN	$CHCl_3$	66
11	CuI	DMF	43
12	CuI	CH_3CN	71
13	CuI	1,4-Dioxane	62
14[c]	CuI	$CHCl_3$	74

[a] A mixture of *p*-toluenesulfonyl azide (0.6 mmol), **1** (0.5 mmol), diisopropylamine (0.6 mmol), and Cu catalyst (10 mol %) in solvent (1.0 mL) was stirred at 25 °C for 6 h.
[b] H NMR yield (internal standard: 1,3-benzodioxole).
[c] 20 Mol % of tris(benzyltriazolylmethyl)amine was added.

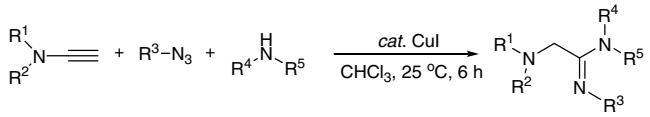
isopropyl, or *tert*-butyl group on the 4-position of oxazolidinone provided the corresponding products with high yields in all cases (entries 3–5, respectively). *N*-Sulfonamido acetylene was also employed as a substrate to afford α-sulfonamido amidine in a moderate yield (entry 6).

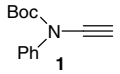
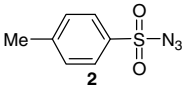
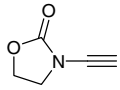
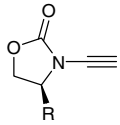
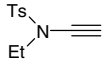
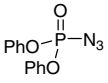
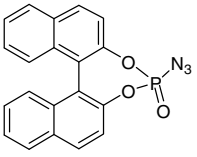
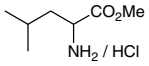
It was revealed that, like arenesulfonyl azides, alkylsulfonyl azides were also smoothly reacted leading to *N*-alkylsulfonyl amidines in high yields as demonstrated in entry 7. We were pleased to observe that phosphoryl azides displayed similar reactivity with ynamides to afford the corresponding α-amino-*N*-phosphoryl amidines in excellent yields (entries 8 and 9). It should be mentioned that the scope of amine species was very broad. Aniline derivatives as well as aliphatic amines were shown to be efficiently coupled in the presence of triethylamine (entry 10). Primary amines and amino esters were also readily employed in this coupling (entries 11 and 12, respectively).

The produced α-amino amidine compounds can be regarded as α-amino acid isosteres. For further synthetic applications, asymmetric alkylation of optically active α-amino amidines was next investigated (Table 3). It was especially interesting to see any steric influence of 4-substituents of the oxazolidinone skeleton on the diastereoselectivity during the alkylation process.[24] After examining various reaction conditions, it was found that deprotonation of the chiral α-amino amidines with LHMDS (in THF) followed by alkylation with electrophiles provided monoalkylated products in moderate to good chemical yields.

Not surprisingly, the observed diastereoselectivity turned out to be dependent on the steric environment on the oxazolidinone moiety despite the fact that the extent

Table 2
Cu-catalyzed three-component coupling reactions for the synthesis of α-amino amidines[a]



Entry	Ynamide	Azide	Amine	Yield[b] (%)
1	 **1**	 **2**	$(i\text{-Pr})_2NH$ **3**	82
2		**2**	**3**	83
3	 (R: Bn)	**2**	**3**	89
4	(R: *i*-Pr)	**2**	**3**	78
5	(R: *t*-Bu)	**2**	**3**	85
6		**2**	**3**	65
7	**1**		**3**	90
8	**1**		**3**	90
9	**1**		**3**	86
10[c]	**1**	**2**	PhNHMe	87
11	**1**	**2**	*i*-$PrNH_2$	75
12[c]	**1**	**2**		74

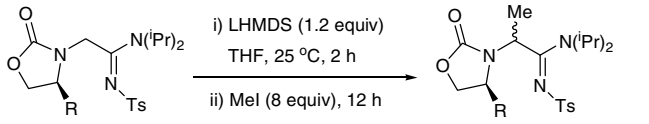
[a] Ynamide (0.5 mmol), azide (0.6 mmol), amine (0.6 mmol), and CuI (10 mol %) in $CHCl_3$ (1.0 mL) at 25 °C for 6 h.
[b] Isolated yield after column chromatography.
[c] Et_3N (1.2 equiv to alkyne) was added.

of stereoselectivity was not significantly changed. A moderate diastereomeric ratio (2.7:1) was obtained from the methylation reaction of a chiral α-amino amidine bearing 4-isopropyloxazolidinone moiety (entry 1). When the isopropyl group was replaced by a benzyl substituent, the corresponding diastereoselectivity was increased to 4.0:1 under the identical conditions. This ratio was not further significantly improved upon the introduction of *tert*-butyl substituent on the oxazolidinone (entry 3).

It is postulated that a carbonyl oxygen of oxazolidinone ring and a nitrogen of sulfonenamido species, which is generated upon deprotonation of α-amino amidine with LHMDS, are chelated to lithium metal to form a seven-membered transition state during the α-alkylation process (Fig. 1).[25] Accordingly, the major diastereomer product is predicted to form by the alkylation from the less congested face of the proposed transition state.[26]

In addition to the synthesis of α-amino amidines, we used ynamides as a coupling partner in the imidate-forming reactions by employing alcohols instead of amines. We were pleased to observe that imidates were readily produced under the similar conditions except that triethylamine is required to complete the conversion. For example, the Cu-catalyzed reaction of ynamide **1** with

Table 3
α-Methylation of chiral α-amino amidine derivatives



Entry	R	Yield[a] (%)	d.r.[b]
1	$CH(CH_3)_2$	57	2.7:1
2	CH_2Ph	51	4.0:1
3	$C(CH_3)_3$	68	4.1:1

[a] Isolated yield.
[b] Diastereomeric ratio was determined by HPLC.

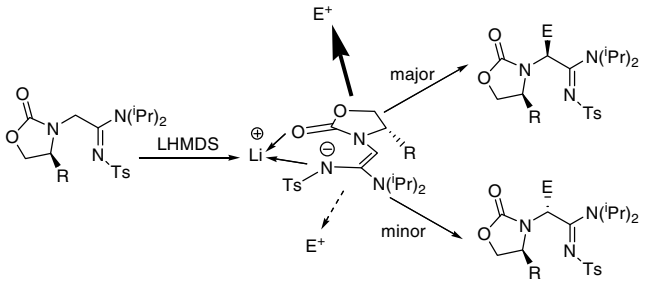
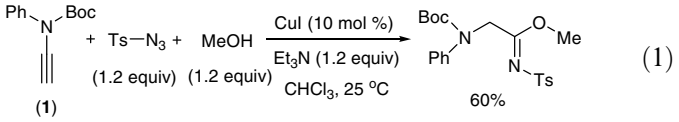


Fig. 1. Proposed transition state of the asymmetric α-alkylation.

p-toluenesulfonyl azide and methanol resulted in the corresponding α-amino imidate in 60% yield (Eq. 1).



(1)

In summary, we have demonstrated that ynamides can be utilized as a new type of reacting partner in the Cu-catalyzed three-component coupling reactions for the preparation of α-amino amidines and imidates. The substrate scope is very broad including a wide range of ynamides, sulfonyl or phosphoryl azides, and amines or alcohols. Synthetic applicability of the produced α-amino amidines was demonstrated by the diastereoselective α-alkylation.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.073.

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23. *General procedure for the synthesis of α-amino amidines*: To a stirred mixture of azide (0.6 mmol), ynamide (0.5 mmol), and CuI (0.05 mmol) in $CHCl_3$ (1 mL) was slowly added amine nucleophile (0.6 mmol) at room temperature under an N_2 atmosphere. Triethylamine (0.6 mmol) was added after the addition of amine, if necessary (entries 10 and 12 of Table 2). After 6 h, the reaction mixture was diluted by adding CH_2Cl_2 (3 mL) and aqueous NH_4Cl solution

(3 mL). The mixture was stirred for an additional 30 min and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatograph with an appropriate eluting solvent system. Spectroscopic data for representative compound: N^1,N^1-diisopropyl-N^2-(diphenylphosphoryl)-2-[*N*-(1,1-dimethylethoxy)carbonyl-*N*-phenyl]amino acetamidine (Table 2, entry 8): light orange liquid; isolated yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.23 (m, 4H), 7.21–7.13 (m, 5H), 7.05–6.99 (m, 6H), 5.10 (s, 2H), 4.32 (m, 1H), 3.34 (m, 1H), 1.35 (s, 9H), 1.16 (d, $J = 6.5$ Hz, 6H), 0.95 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 163.4, 154.1, 151.7, 151.6, 139.8, 129.1, 128.5, 127.4, 126.7, 123.8, 120.5, 81.1, 50.1, 49.7, 47.6, 28.0, 20.5, 19.2; IR (NaCl) ν 2972, 1692, 1579, 1491, 1251, 1203, 1058, 921, 692 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{31}H_{41}N_3O_5P$ $[M+H]^+$: 566.2784, found: 566.2781.

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