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Cu(II)-Catalyzed Intermolecular Amidation of *C*-Acylimine: A Convenient Access to *gem*-Diamino Acid Derivatives

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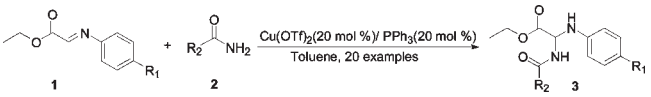
ABSTRACT



***C*-Acylimines 1 undergo intermolecular amidation with amides 2 to produce monoacyl *gem*-diamino acid derivatives 3 upon treatment with $Cu(OTf)_2$ (20 mol %)/ PPh_3 (20 mol %) under mild conditions. This method provides an efficient access to *gem*-diamino acid equivalents with good to excellent yields.**

Transition-metal-catalyzed C−N bond-forming reactions starting from imine derivatives are among the most straightforward strategies for constructing various nitrogen-containing units, which could be found in many complex natural products, synthetic biologically active compounds, and pharmaceuticals.[1] Imines have served as versatile acceptors of nucleophiles; their corresponding addition reactions with carbon radicals, organometallic reagents, Mannich donors, etc. are commonly utilized in many crucial steps.[2] However, although much progress toward the transformation scope of imines has been made, the amidation of imine derivatives has attracted much less attention because of the poor nucleophilicity and higher pK_a values (17−25) of amides.[3] Considering the wide application of nitrogen-containing intermediates, especially for *gem*-diamino carboxylic acid derivatives, which are an important class of core structures of biological molecules,[4] such as, among others, the inhibitors of HIV-1 protease[4d] and *E. coli*[4e,g] (Figure 1), the exploration of new activation methods for imino compounds and subsequent imine amidation reactions under mild conditions therefore is always desirable.

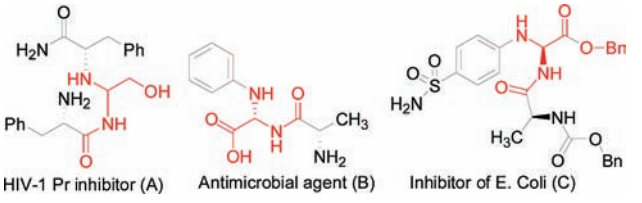


Figure 1. *gem*-Diamino unit-containing drugs.

(1) For a review, see: Martin, S. F. *Pure Appl. Chem.* **2009**, *81*, 195 and references therein.

(2) For selective reviews, see: (a) Shimizu, M.; Hachiya, I.; Mizota, I. *Chem. Commun.* **2009**, 874. (b) Miyabe, H.; Yoshioka, E.; Kohtani, S. *Curr. Org. Chem.* **2010**, *14*, 1254. (c) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (d) Dickstein, J. S.; Kozlowski, M. C. *Chem. Soc. Rev.* **2008**, *37*, 1166. (e) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541. (f) Kobayashi, S.; Ishitahi, H. *Chem. Rev.* **1999**, *99*, 1069. (g) Blay, G.; Mo- nleon, A.; Pedro, J. R. *Curr. Org. Chem.* **2009**, *13*, 1498. For selective recent examples, see:(h) Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500. (i) Ueno, S.; Ohtsubo, M.; Kuwano, R. *J. Am. Chem. Soc.* **2009**, *131*, 12904. (j) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650.

(3) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(4) For reviews, see: (a) Goodman, M.; Chorev, M. *Acc. Chem. Res.* **1979**, *12*, 1. (b) Chorev, M.; Goodman, M. *Acc. Chem. Res.* **1993**, *26*, 266. For selective examples, see:(c) Hernandez, J. F.; Soleihac, J. M.; Roques, B. P.; Fournie- Zaluski, M. C. *J. Med. Chem.* **1988**, *31*, 1825. (d) Marastoni, M.; Salvadori, S.; Bortolotti, F.; Tomatis, R. *J. Peptide Res.* **1997**, *49*, 538. (e) Kingsbury, W. D.; Boehm, J. C.; Perry, D.; Gilvary, C. *Proc. Natl. Acad. Sci. U.S.A.* **1984**, *81*, 4573. (f) Nishimura, Y.; Shitara, E.; Adachi, H.; Toyashima, M.; Nakajima, M.; Okami, Y.; Takeuchi, T. *J. Org. Chem.* **2000**, *65*, 2. (g) Hwang, S. Y.; Berges, D. A.; Taggart, J. J.; Gilvarg, C. *J. Med. Chem.* **1989**, *32*, 694. (h) Han, Y.; Giragossian, C.; Mierke, D. F.; Chorev, M. *J. Org. Chem.* **2002**, *67*, 5085. (i) Fletcher, M. D.; Campbell, M. M. *Chem. Rev.* **1998**, *98*, 763.

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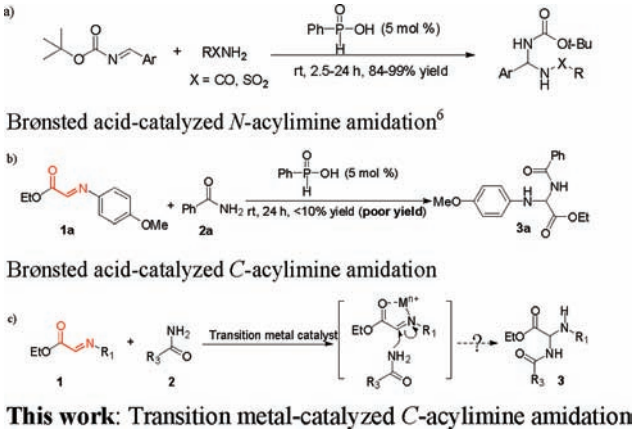
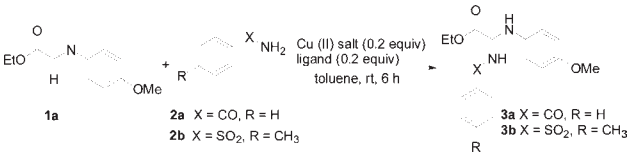
Scheme 1. Catalytic Amidation of Imines



Among the different types of C−N bond-forming reactions, aza-Michael addition of amides to enones provides a convenient approach to make β-amido carbonyl compounds in the presence of transition metal salts that act as Lewis acid catalyst to activate enone.[5] Recently, the Antilla group found that a Brønsted acid could efficiently catalyze intermolecular amidation of *N*-acylimines to give *N*,*N*-aminals in good to excellent yields (see Scheme 1a). There are only a few reports about imine amidation up to present,[6] and transition-metal-catalyzed imine amidation was also previously unknown. Unfortunately, when we tried to use Antilla's method to make *gem*-diamino acid derivative **3a** via Brønsted acid catalyzed amidation of *C*-acylimine **1a**, only traces of target product **3a** was formed (see Scheme 1b).[7] The above combined results about transition-metal-catalyzed aza-Michael addition and Brønsted acid catalyzed imine amidation encouraged us to envision that transition metal salts could possibly activate the carbon−nitrogen double bond of *C*-acylimine via the coordination with carbonyl oxygen and imine nitrogen and then enhanced addition of amide nitrogen nucleophile to *C*-acylimine carbon to produce α-amido-α-amino acid derivates (**3**) (see Scheme 1c). Although different methods to make *gem*-diamino acid derivatives via Curtius- or Hoffman-type rearrangements of protected amino acid equivalents[4a,b] or a benzotriazole-mediated approach[8] were developed successively, these synthetic methods suffer from disadvantages of multistep procedures (more than three steps) and low overall yield.[8,9] Herein we report an efficient synthetic method of *gem*-diamino residues via copper(II)-catalyzed amidation of *C*-acylimine.

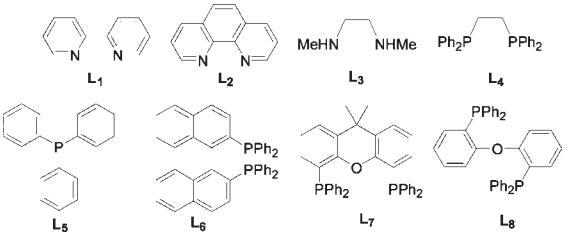
(4-Methoxy-phenylimino)-acetic acid ethyl ester (**1a**) was first used as the model substrate to screen the reaction conditions for the optimization of the catalyst, ligand, solvent, and temperature under Ar atmosphere. As shown in Table 1, when **1a** (0.1 mmol), which formed from ethyl

Table 1. Optimization of Reaction Conditions for Amidation of *C*-Acylimine[a]



entry	catalyst	ligand	yield (%)[b]
1	$Cu(OAc)_2.H_2O$		5
2	$Cu(OAc)_2$		6
3	$CuCl_2$		15
4	$CuBr_2$		27
5	$Cu(OTf)_2$		32
6	$Cu(OTf)_2$		trace[c]
7	$Cu(OTf)_2$	L_1	61
8	$Cu(OTf)_2$	L_2	55
9	$Cu(OTf)_2$	L_3	62
10	$Cu(OTf)_2$	L_4	66
11	$Cu(OTf)_2$	L_5	84
12		L_5	trace
13	$Cu(OTf)_2$	L_6	66
14	$Cu(OTf)_2$	L_7	72
15	$Cu(OTf)_2$	L_8	58
16	$Cu(OTf)_2$	L_5	41[d]
17	$Cu(OTf)_2$	L_5	49[e]
18	$Cu(OTf)_2$	L_5	61[f]
19	$Cu(OTf)_2$	L_5	67[g]

[a] Reaction conditions: unless stated otherwise, all reactions were carried out with *C*-acylimine **1a** (0.2 mmol), amide **2a** (0.3 mmol), catalyst (20 mol %), ligand (20 mol %), and toluene (2.0 mL) under Ar atmosphere at 25 °C for 6 h. [b] Isolated yield. [c] Substrate **2b** (0.3 mol) was used. [d] Reaction temperature 10 °C. [e] Reaction temperature 50 °C. [f] 10 mol % $Cu(OTf)_2$ and 10 mol % PPh_3 were used. [g] 30 mol % $Cu(OTf)_2$ and 30 mol % PPh_3 were used.



(5) For selective examples, see: (a) Gaunt, M. J.; Spencer, J. B. *Org. Lett*. **2001**, *3*, 25. (b) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett*. **2002**, *4*, 1319. (c) Srivastava, N.; Banik, B. K. *J. Org. Chem*. **2003**, *68*, 2109. (d) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett*. **2004**, *6*, 1861. (e) Wabnitz, T. C.; Yu, J. Q.; Spencer, J. B. *Chem.—Eur. J*. **2004**, *10*, 484. (f) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez- Bengoa, E.; García, J. M. *J. Am. Chem. Soc*. **2004**, *126*, 9188. (g) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2006**, *128*, 9328.

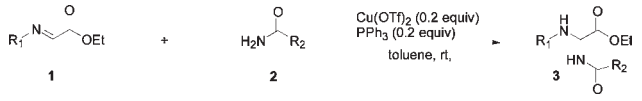
(6) (a) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc*. **2005**, *127*, 15696. (b) Liang, Y.; Rowland, E. B.; Rowland, G. B.; Perman, J. A.; Antilla, J. C. *Chem. Commun*. **2007**, 4477.

(7) When we also tried to use some stronger acids such as H_3PO_4 and HOTf as catalyst using Antilla's reaction conditions, the best yield was only up to 15% (see Supporting Information for more details).

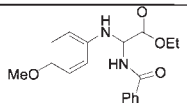
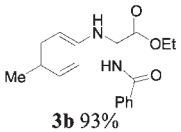
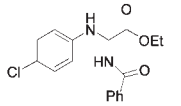
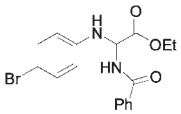
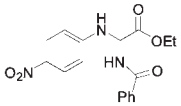
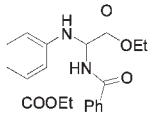
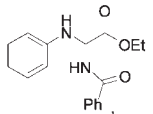
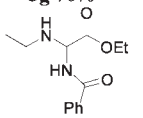
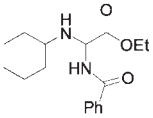
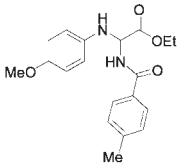
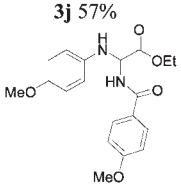
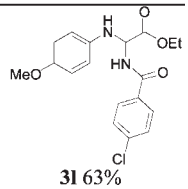
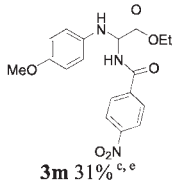
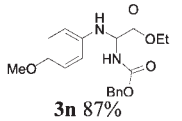
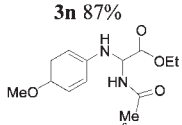
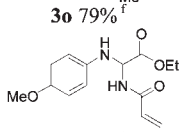
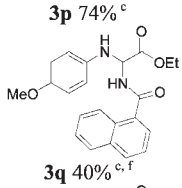
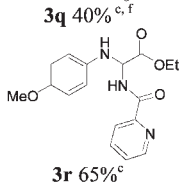
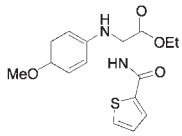
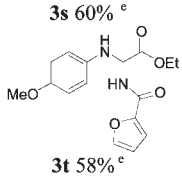
(8) Katritzky, H. R.; Urogdi, L.; Mayence, A. *J. Org. Chem*. **1990**, *55*, 2206.

(9) Chorev, M.; Willson, C. G.; Goodman, M. *J. Am. Chem. Soc*. **1977**, *99*, 8075.

Table 2. Copper(II)-Catalyzed Intermolecuar Amidation of *C*-Acylimine[a]



1 + 2 → 3

entry	R_1	R_2	time (h)	product yield (%)[b]
1	4-$MeOC_6H_4$	Ph	6	 **3a** 84%
2	4-MeC_6H_4	Ph	6	 **3b** 93%
3	4-ClC_6H_4	Ph	6	 **3c** 98%
4	4-BrC_6H_4	Ph	6	 **3d** 87%
5	4-$NO_2C_6H_4$	Ph	12	 **3e** 96%[c]
6	3-$CO_2EtC_6H_4$	Ph	12	 **3f** 95%
7	Ph	Ph	12	 **3g** 70%[d]
8	*i*Pr	Ph	12	 **3h** 46%
9	Cy	Ph	12	 **3i** 53%
10	4-$MeOC_6H_4$	4-MeC_6H_4	24	 **3j** 57%
11	4-$MeOC_6H_4$	4-$MeOC_6H_4$	24	 **3k** 80%
12	4-$MeOC_6H_4$	4-ClC_6H_4	12	 **3l** 63%
13	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	12	 **3m** 31%[c, e]
14	4-$MeOC_6H_4$	Cbz	6	 **3n** 87%
15	4-$MeOC_6H_4$	Me	12	 **3o** 79%[f]
16	4-$MeOC_6H_4$	Vinyl	12	 **3p** 74%[c]
17	4-$MeOC_6H_4$	1-Naphthyl	12	 **3q** 40%[c, f]
18	4-$MeOC_6H_4$	1-Pyridyl	36	 **3r** 65%[c]
19	4-$MeOC_6H_4$	1-Thienyl	12	 **3s** 60%[e]
20	4-$MeOC_6H_4$	1-Furyl	12	 **3t** 58%[e]

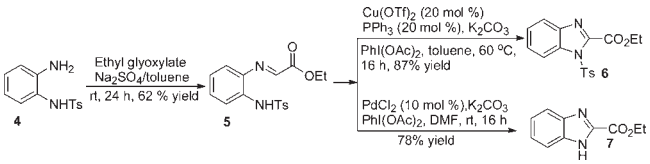
[a] Unless otherwise noted, all reactions were performed under argon at 25 °C for the given time; *C*-acylimine, 0.2 mmol; amide, 0.3 mmol; $Cu(OTf)_2$, 20 mol %; PPh_3, 20 mol %; solvent, toluene (2.0 mL). [b] Isolated yield. [c] Reaction temperature 45 °C. [d] K_2CO_3(1.0 equiv) was added. [e] 3.0 equiv of amide was used. [f] 30 mol % $Cu(OTf)_2$ and 30 mol % PPh_3 were used.

oxoacetate and 4-methoxyaniline, was treated with 1.5 equiv of benzamide (**2a**) in toluene (2.0 mL) at room temperature (25 °C) for 6 h in the presence of copper salts (20 mol %) such as $Cu(OAc)_2$, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2 \cdot H_2O$, and $Cu(OTf)_2$ (entries 1−5), the use of $Cu(OTf)_2$ provided a 32% yield of the desired product, monoacyl *gem*-diamino acid derivative (**3a**) (entry 5).[10] No desired **3a** was detected by TLC and ^1H NMR methods in the absence of copper salts even after 24 h. When we switched substrate benzamide to 4-toluenesulfonamide (**2b**), the sulfonamidation of *C*-acylimine **1a** did not take place due possibly to less nucleophilic property of sulfonamide compared with carbonamide **2a** (entry 6).[3] Subsequently, we investigated the effect of ligand on the copper(II)-catalyzed amidation of *C*-acylimine in order to improve the reaction yield, we soon found nitrogen- or phosphate-containing ligands (**L_1**−**L_8**) significantly improved yield of **3a** (compare entries 5 and 7−15); among the tested ligands, PPh_3 (**L_5**) showed the best cocatalyzed activity (entry 11). Notably, PPh_3 could not enhance efficiently the transformation to occur in absence of $Cu(OTf)_2$ (entry 12). Encouraged by these positive results, we further investigated other reaction conditions to define the reaction parameters. When the reaction temperature was lowered to 10 °C or increased to 50 °C, the yield decreased due to incomplete reaction or decomposition of *C*-acylimine, respectively (compare entries 11, 16, and 17). A catalyst loading of 20 mol % was found to be effective to achieve satisfied yield (compare entries 11, 18, and 19). The effect of the solvent was also investigated, and THF, dioxane, and ethyl acetate were the better solvents, with toluene being the best (see Supporting Information for more details).

With the optimized reaction conditions in hand, the scope of this transformation was subsequently investigated. As shown in Table 2, this new method could be applied to a wide range of substrates. The catalysis proceeded well with benzamide irrespective of the electronic effects of substituent at the iminoaromatic ring. Thus, *C*-acylimine with methyl, methoxyl, chloro, bromo, esteryl, and nitro substituents at the 4-position or 3-position of phenyl ring reacted to afford the corresponding α-amido-α-amino acid derivates in yields up to 98% (entries 1−7). On the contrary, significant substituent effect for benzamide substrate was observed, and the reaction with 4-nitro- benzamide gave only 31% yield of the target compound **3l** (entries 1, 10−13). In the case of 1-naphthylamide, lower reactivity was observed possibly due to steric influence of naphthyl group (entry 17). Moreover, *N*-alkyl *C*-acylimine, aliphatic amide, and acrylamide were also investigated, and the corresponding target compounds were obtained in moderate to good yields (entries 8, 9, 14−16).[11] It is worth noting that heterocyclic amide such as 2-pyridinecarboxamide, 2-furancarboxamide, and 2-thiophenecarboxamide could also be used in this transformation and gave the corresponding monoacyl *gem*-diamino acid derivates in moderate yields (entries 18−20). The structure of **3n** was unambiguously assigned by single crystal X-ray analysis (see Supporting Information for more details).

Esteryl 2-benzimidazole and its corresponding derivatives belong to an important precursor for assembling biological molecules.[12] Cu(II)-catalyzed intramolecular amidation/dehydrogenation of *C*-acylimine **5** could occur and gave the *N*-protected 2-esteryl benzimidazole **6** in 87% yield. When Pd(II)/$PhI(OAc)_2$ system was employed in this reaction, *N*-unprotected 2-esteryl benzimidazole **7** was produced in 78% yield via one-pot cascade intramolecular amidation/oxidation/desulfonylation. This two-step reaction process starting from *o*-phenylenediamine derivative **4** has an overall yield of 48−54% (see Scheme 2).

Scheme 2. Synthesis of Esteryl 2-Benzoimidazole via Transition-Metal-catalyzed Intramolecular Amidation of *C*-Acylimine



In conclusion, we have developed the first copper(II)-catalyzed intermolecular amidation of *C*-acylimine under mild conditions. A range of electron-rich and electron-poor *C*-acylimine and amide derivatives participate. The protocol uses readily available *C*-acylimines (synthesized by the reaction of ethyl oxoacetate with amines) and amides as the starting material and provides the corresponding monoacyl *gem*-diamino acid derivatives in moderate to excellent yields. The further studies about transition-metal-catalyzed intramolecular amidation of *C*-acylimine are underway in our laboratory.

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Supporting Information Available. Details for experiments conditions, characterization data, copies of ^1H and ^{13}C NMR spectra for all isolated compounds, and crystallographic data for **3n** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) The compound **3a** was found to be stable in air atmosphere even under heat treatment condition (100 °C) for 12 h.

(11) It should be noted that the amidation of *C*-alkyl or *C*-arylimines with **2a** is limited possibly due to the poor electrophilicity of imine carbon, and also the amidation of **1a** with *N*-phenyl-acetamide or *N*-ethyl-benzamide did not proceed smoothly even at 45 °C for 24 h.

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