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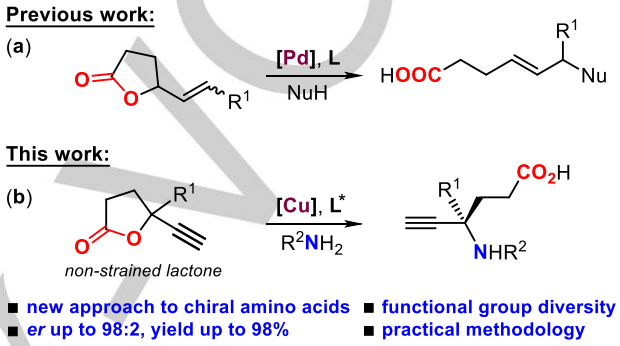
Copper-Catalyzed Synthesis of γ-Amino Acids Featuring Quaternary Stereocenters

José Enrique Gómez,[a] Wusheng Guo,*[a] Silvia Gaspa,[a] and Arjan W. Kleij*[a][b]

Abstract: The first general asymmetric synthesis of γ,γ-disubstituted γ-amino acids via Cu-catalyzed ring opening of non-strained lactones with amines is reported. This approach features ample scope, operational simplicity and wide functional group diversity. The catalytic process allows to access a series of highly functionalized enantioenriched γ-amino acids featuring quaternary stereocenters with excellent enantiomeric ratios up to 98:2 and excellent yields up to 98%.

Significant efforts have been devoted towards the synthesis of γ-amino acids due to their important applications in pharmaceutical industry and peptide chemistry.[1-4] Various biologically active γ-amino acids are used as drugs including 4-methylpregabalin, vigabatrin, baclofen and γ-aminobutyric acid (GABA).[3] The γ-amino acid scaffolds are also frequently encountered in biologically active short peptides such as pepstatin, hapalosin and dolastatins.[4] Recently, oligomers constructed from γ-amino acid synthons have demonstrated great potential in material science as these protein-like foldamers display interesting functional properties; specifically, the stereodefined γ-amino acid monomers are highly essential to control the folding patterns.[5] Although appreciable progress has been noted in the synthesis of γ-amino acids (mostly analogues or precursors), the enantioselective synthesis of γ,γ-disubstituted amino acids featuring a quaternary stereocenter is still quite challenging and underdeveloped.[6] Thus, designing new catalytic methods toward the synthesis of these challenging chiral scaffolds will prospectively reinforce their use in pharmaceutical development and peptide chemistry.

Despite the highly stable nature of non-strained five-membered lactones,[7] the Pd-catalyzed nucleophilic ring opening of vinyl-lactones toward the (amino) acid formation has been achieved (Scheme 1a).[8] Furthermore, Cu-catalyzed transformation of propargylic compounds via Cu-allenylidene intermediates has been extensively studied in synthetic chemistry; this protocol enables the installation of synthetically versatile alkyne functionality.[9] Inspired by the Pd-catalyzed carboxylic acid formation from vinyl-lactones[8] (Scheme 1a) and also our own work on challenging amine synthesis,[10,11] we envisaged that the asymmetric synthesis of γ,γ-disubstituted γ-amino acids would be feasible through a Cu-allenylidene mediated ring opening of non-strained five-membered lactones (Scheme 1b).



Scheme 1. Transition metal-catalyzed ring opening of five-membered lactones with nucleophiles.

To test our working hypothesis, the reaction of lactone **A** and aniline was selected as a model reaction (Table 1). The Trost ligand **L1** using THF as solvent at rt was probed first and promisingly, the desired amino acid **1** could be isolated in 47% yield with 60:40 *er* (entry 1). Decreasing the reaction temperature to 0ºC resulted in higher enantioselectivity though low conversion (<15%, entries 2–3). Changing the solvent to MeOH at 0ºC led to quantitative product formation with a lower *er* value (entries 3-7, entries 3 *vs* 6). The utilization of a mixed solvent MeOH/THF (1:3) gave promising result with 40% yield and 87:13 *er* (entries 8–10). The Cu-catalyst precursor and type of base also showed significant effect towards the reaction outcome (entries 9 *vs* 10, see also Tables S1 and S2 in the supporting information (SI)). We were pleased to find that the use of Pybox ligand **L6** resulted in quantitative yield of product **1** and excellent enantioselectivity (entries 11–16). Lowering the reaction temperature, concentration and catalyst loading had positive effects (entries 17-22). Notably, the reaction could be performed open to air without any special precautions, requiring only 3 mol% of Cu (entry 23: 94% yield and 97:3 *er*) which is a significant advantage compared to other Cu-catalyzed reactions generally requiring 10 mol% of metal loading.[9]

With the optimized reaction conditions in hand (Table 1, entry 23), the scope in lactone substrates was first investigated (Figure 1). The catalytic system proved to be efficient in the conversion of lactones with electron-withdrawing (**2**, **3**, **5** and **7**) or -donating groups (**4**, **7**, **9** and **10**) present in the aryl-substituents and gave rise to the amino acids generally with *er* values higher than 95:5. The presence of *meta*-substituted aryl substituents in the lactones (**7** and **9**) allowed the formation of γ-amino acids with high

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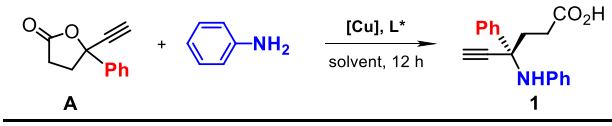
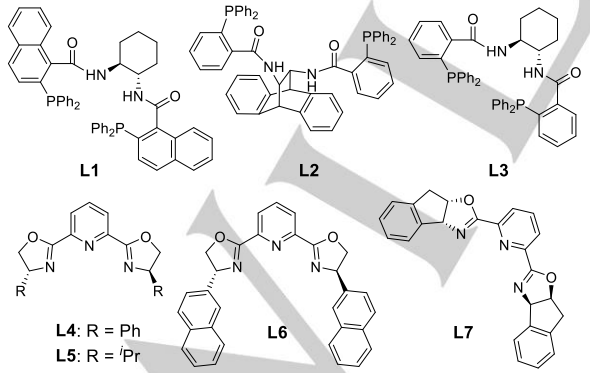
Table 1: Selected screening data for the formation of chiral γ,γ-disubstituted γ-amino acid **1**.[a]



A **1**

Entry	L	Solvent	T [°C]	Yield[b]	*er*[c]
1	**L1**	THF	25	47	60:40
2	**L1**	THF	10	15	73:27
3	**L1**	THF	0	10	77.5:22.5
4	**L1**	Acetone	0	46	69:31
5	**L1**	Et_2O	0	20	62.5:37.5
6	**L1**	MeOH	0	96	60.5:39.5
7	**L1**	iPrOH	0	50	68:32
8	**L1**	MeOH/THF (1:1)	0	96	77:23
9	**L1**	MeOH/THF (1:3)	0	54	80.5:19.5
10	**L1**	MeOH/THF (1:3)	0	40	87:13
11	**L2**	MeOH/THF (1:3)	0	38	60:40
12	**L3**	MeOH/THF (1:3)	0	88	74:26
13	**L4**	MeOH/THF (1:3)	0	98	73:27
14	**L5**	MeOH/THF (1:3)	0	98	56:44
15	**L6**	MeOH/THF (1:3)	0	98	90:10
16	**L7**	MeOH/THF (1:3)	0	98	61.5:38.5
17[d]	**L6**	MeOH/THF (1:3)	-5	98	91.5:8.5
18[d]	**L6**	MeOH/THF (1:3)	-10	98	92:8
19[d]	**L6**	MeOH/THF (1:3)	-20	98	93:7
20[d,e]	**L6**	MeOH/THF (1:3)	-20	98	94:6
21[d,f]	**L6**	MeOH/THF (1:3)	-20	98	95:5
22[d,f,g]	**L6**	MeOH/THF (1:3)	-20	97	96:4
23[d,f,h]	**L6**	MeOH/THF (1:3)	-20	94	97:3



[a] Reaction conditions unless otherwise noted: lactone **A** (0.2 mmol), aniline (0.30 mmol, 1.5 equiv), solvent (200 μL), $^iPr_2NEt$ (0.24 mmol, 1.2 equiv), Cu catalyst precursor (10 mol%; entries 1-9 using $Cu(OTf)_2$, entries 10-23 using $Cu(ACN)_4(OTf)$), **L** (11 mol%). [b] Isolated yield. [c] Determined by UPC2. [d] Aniline (0.22 mmol). [e] Solvent (400 μL). [f] Solvent (600 μL). [g] $Cu(ACN)_4(OTf)$ (5 mol%), **L6** (6 mol%). [h] $Cu(ACN)_4(OTf)$ (3 mol%), **L6** (4 mol%), 24 h.

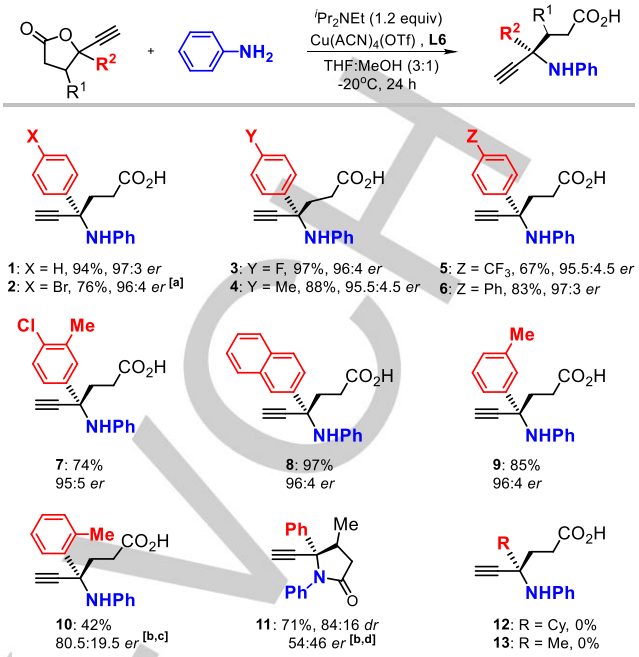


Figure 1. Scope in lactones (0.2 mmol scale). Reaction performed under the optimized conditions (Table 1, entry 23). The *er* values were determined by UPC2. [a] $Cu(ACN)_4(OTf)$ (5 mol%), **L6** (6 mol%). [b] $Cu(ACN)_4(OTf)$ (10 mol%), **L6** (11 mol%), solvent (200 μL). [c] 0°C. [d] Performed at rt; lactam **11** was isolated instead of the amino acid (SI for details).

enantioselectivity and isolated yield, while the *ortho*-Me-substituted lactone is less reactive (**10**). The presence of a bulky naphthyl group did not reduce the efficiency of the catalysis (**8**). Substitution at the *β*-position (R^1) of the lactone is possible as exemplified by the successful isolation of compound **11**. The lactones bearing a cyclohexyl or methyl group proved to be unproductive, not even at higher reaction temperatures of up to 50°C and higher catalyst loading up to 10 mol% (**12** and **13**), suggesting an significant electronic effect within this catalytic process.

Various amine nucleophiles were then examined (Figure 2). The use of aryl amines bearing electron-donating groups afforded the γ-amino acids in both high yield and enantioselectivity (**14**–**17**, **26**). In contrast, the aryl amines equipped with strongly electron-withdrawing substituents such as nitro, ester and trifluoromethyl, gave rise to only trace amount of product under the optimized conditions; performing these reactions at higher reaction temperature (products **22**–**24**), however, significantly improved the reaction outcome. The incorporation of a heterocycle in the final product proved to be feasible (**25**) which is of interest in pharmaceutical development.[12] The installation of boro- and halogen-functionality (**18** and **20**) is potentially useful for the application of these γ-amino acid products in Suzuki-coupling reactions. The presence of *meta*- or *ortho*-substituents in the aryl amine (**15**, **16**, **23**, **24** and **26**) is tolerated towards efficient amino acid formation. The reactions with morpholine and propargylic amine at –20°C for 24 h displayed low conversions (<5%), while reasonable reactivity was observed at 0°C though with lower enantio-discrimination or none (**28** and **29**).

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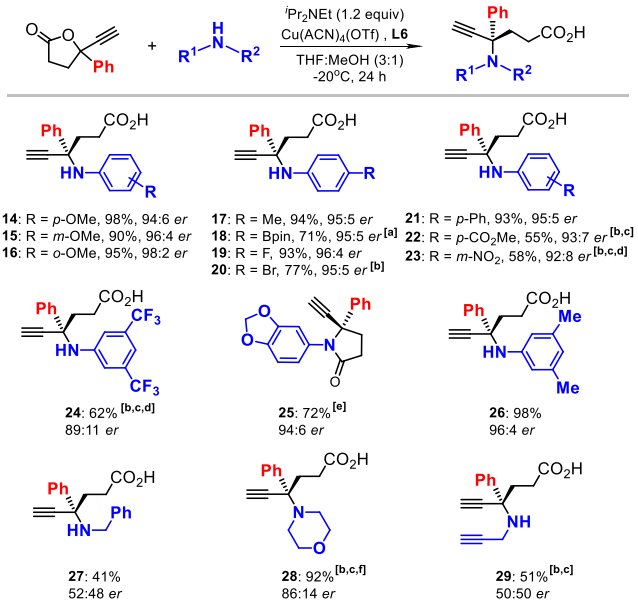


Figure 2. Scope in amine partners (0.2 mmol scale). Reaction performed under the optimized conditions (Table 1, entry 23); *er* values determined by UPC2. [a] $Cu(ACN)_4(OTf)$ (5 mol%), **L6** (6 mol%). [b] $Cu(ACN)_4(OTf)$ (10 mol%), **L6** (11 mol%). [c] 0ºC. [d] Solvent (200 μL). [e] Lactam **25** was isolated instead of the amino acid, see SI for details. [f] The *er* value was determined by using a chiral shift reagent, see SI for details.

The pendant alkyne functional group in these amino acid scaffolds (products **1**–**29**) creates potential for *in vivo* bio-orthogonal reactions through click chemistry.[13] These amino acids could be easily converted into various valuable enantioenriched products (Figure 3) such as lactams **30** and **31**, pyrrolidine **32** and triazole **33**. Notably, chiral lactams are very important building blocks in pharmaceutical development (also see products **11** and **25**).[14] The absolute configuration of the amino acid product (*R*) was deduced from X-ray diffraction analysis of lactam **30** (inset in Figure 3).[15]

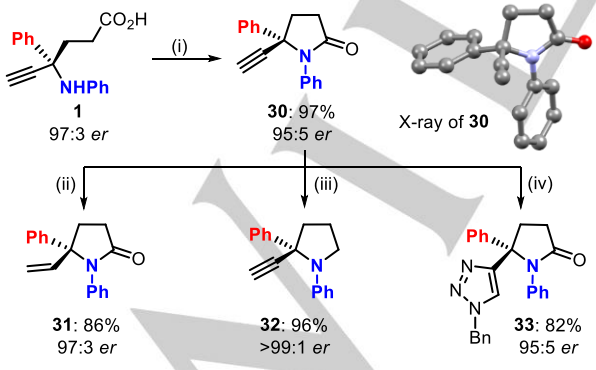
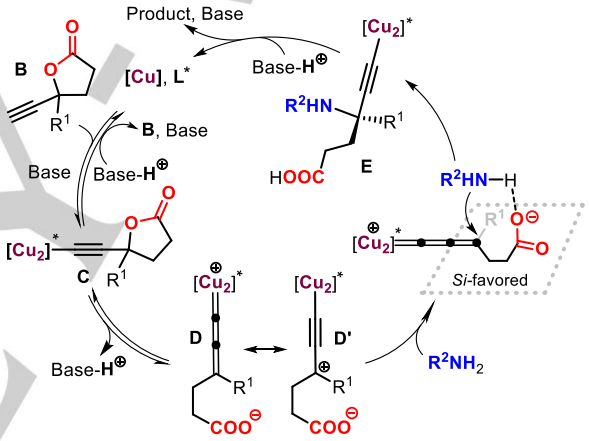


Figure 3. Synthetic conversions of chiral amino acid **1**. Reaction conditions: (i) KOH, DMSO, rt, 1 h; then MeI, rt, 1 h. (ii) Lindlar catalyst (2 mol%), H_2 (balloon), EtOAc, rt, 30 min. (iii) $LiAlH_4$ (5 equiv), $AlCl_3$ (2 equiv), THF, 0ºC–rt, 2 h. (iv) CuTC (10 mol%), BnN_3 (1.2 equiv), toluene, rt, 1 h. See SI for details.

Based on previous mechanistic investigations on related chemistry[9e-f,9h-i,16] and our experimental observations, a plausible mechanism is proposed in Scheme 2. First, the Cu-complex activates the alkyne group of lactone **B** generating a Cu-acetylide species **C** in the presence of $^{i}Pr_2NEt$. Then, isomerization of **C** leads to a zwitterionic species **D**, which is in dynamic equilibrium with **D'** providing resonance stabilization. Considering the thermodynamically stable nature of five-membered lactone,[7] the back conversion of intermediate **D** into starting material **B** through intermediate **C** is likely dominant over the nucleophilic attack of the amine;[8c-e] thus, a hydrogen bond assisted amine attack may be involved (**D** to **E**) enabling the formation of the Cu-bound product **E**.[17] Hereafter, the amino acid product is obtained upon a proton-transfer process with regeneration of the catalyst and ligand. The asymmetric induction may be rationalized by a well-established bimetallic model[9e-f,9i,16,18] in which the amine attacks on the *Si*-face of the Cu-allenylidene intermediate is favored thus resulting in the (*R*)-amino acid as major product.



Scheme 2. Plausible mechanism for the formation of the γ-amino acid product from lactone **B**.

In conclusion, we herein present the first general approach toward the asymmetric synthesis of γ,γ-disubstituted γ-amino acids through Cu-catalyzed ring opening of non-strained lactones with amine nucleophiles. The protocol features ample reaction scope, wide functional group tolerance and high asymmetric induction with typical *er* values >95:5. The resultant amino acids can be easily converted into other important building blocks as exemplified by the synthesis of chiral lactams **30** and **31**, and pyrrolidine **32**. Importantly, this procedure is user-friendly (no special precautions required) and thus marks a great step forward in the challenging synthesis of chiral γ-amino acids featuring quaternary stereocenters.

Acknowledgements

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Keywords: amino acids • asymmetric synthesis • copper • lactam • lactone

[1] For the syntheses and applications of γ-amino acids please refer to: a) M. Ordóñez, C. Cativiela, *Tetrahedron: Asymmetry* **2007**, *18*, 3; b) P. G. Vasudev, S. Chatterjee, N. Shamala, P. Balaram, *Chem. Rev.* **2011,** *111,* 657; c) P. Conti, L. Tamborini, A. Pinto, A. Blondel, P. Minoprio, A. Mozzarelli, C. De Micheli, *Chem. Rev.* **2011,** *111,* 6919; d) A. Isidro-Llobet, M. Álvarez, F. Albericio, *Chem. Rev.* **2009,** *109,* 2455; e) K. Maruoka, T. Ooi, *Chem. Rev.* **2003,** *103,* 3013.

[2] For synthesis of γ-amino acids and their derivatives or analogues, please refer to recent examples: a) K. Akagawa, K. Kudo, *Angew. Chem. Int. Ed*. **2012**, *51*, 12786; b) J. H. Sim, C. E. Song, *Angew. Chem. Int. Ed*. **2017**, *56*, 1835; c) Y. Tahara, M. Michino, M. Ito, K. S. Kanyiva, T. Shibata, *Chem. Commun*. **2015**, *51*, 16660; d) R. Kastl, H. Wennemers, *Angew. Chem. Int. Ed*. **2013**, *52*, 7228; e) L.-T. Shen, L.-H. Sun, S. Ye, *J. Am. Chem. Soc.* **2011**, *133*, 15894; f) G. K. Friestad, K. Banerjee, *Org. Lett.* **2009**, *11*, 1095; g) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608; h) A. Baschieri, L. Bernardi, A. Ricci, S. Suresh, M. F. A. Adamo, *Angew. Chem. Int. Ed*. **2009**, *48*, 9342; i) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *117*, 119; j) M. Wiesner, J. D. Revell, S. Tonazzi, H. Wennemers, *J. Am. Chem. Soc.* **2005**, *130*, 5610; k) L. Guo, Y. Chi, A. M. Almeida, I. A. Guzei, B. K. Parker, S. H. Gellman, *J. Am. Chem. Soc.* **2009**, *131*, 16018; l) J. A. Gurak, K. S. Yang, Z. Liu, K. M. Engle, *J. Am. Chem. Soc.* **2016**, *138*, 5805.

[3] Please refer to the following references and therein: a) G. H. Fromm, C. F. Terrence, A. S. Chattha, J. D. Glass, *Arch. Neurol.* **1980**, *37*, 768; b) B. A. Sachais, J. N. Logue, M. S. Carey, *Arch. Neurol.* **1977**, *34*, 422; c) R. B. Silverman, *Angew. Chem. Int. Ed.* **2008**, *47*, 3500; d) P. Yuen, G. D. Kanter, C. P. Taylor, M. G. Vartanian, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 823; e) I. Lapin, *CNS Drug Rev.* **2001**, *7*, 471.

[4] a) D. H. Rich, *J. Med. Chem.* **1985**, *28*, 263; b) H. Umezawa, T. Aoyagi, H. Morishima, M. Matsuzaki, M. Hamada, T. Takeuchi, *J. Antibiot.* **1970**, *23*, 259; c) K. Stratmann, D. L. Burgoyne, R. E. Moore, G. M. L. Patterson, *J. Org. Chem.* **1994**, *59*, 7219; d) G. R. Pettit, Y. Kamano, C. L. Herald, A. A. Tuinman, F. E. Boettner, H. Kizu, J. M. Schmidt, L. Baczynskyj, K. B. Tomer, R. J. Bontems, *J. Am. Chem. Soc.* **1987**, *109*, 6883.

[5] For the formation of γ-peptide foldamers from γ-amino acids, see: a) B. F. Fisher, S. H. Gellman, *J. Am. Chem. Soc.* **2016**, *138*, 10766; b) H. Awada, C. M. Grison, F. Charnay-Pouget, J.-P. Baltaze, F. Brisset, R. Guillot, S. Robin, A. Hachem, N. Jaber, D. Naoufal, O. Yazbeck, D. J. Aitken, *J. Org. Chem.* **2017**, *82*, 4819; c) L. Mathieu, B. Legrand, C. Deng, L. Vezenkov, E. Wenger, C. Didierjean, M. Amblard, M.-C. Averlant-Petit, N. Masurier, V. Lisowski, J. Martinez, L. T. Maillard, *Angew. Chem. Int. Ed.* **2013**, *52*, 6006; d) C. M. Grison, J. A. Miles, S. Robin, A. J. Wilson, D. J. Aitken, *Angew. Chem. Int. Ed*. **2016**, *55*, 11096; e) B. F. Fisher, L. Guo, B. S. Dolinar, I. A. Guzei, S. H. Gellman, *J. Am. Chem. Soc.* **2015**, *137*, 6484. Please also refer to Ref. [2k].

[6] The construction of quaternary stereocenters represents a challenging task: a) X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou, J. Zhou, *Chem. Rev*. **2016**, *116*, 7330; b) K. Fuji, *Chem. Rev*. **1993**, *93*, 2037.

[7] a) D. Myers, A. Cyriac, C. K. Williams, *Nature Chem.* **2016**, *8*, 3; b) M. Hong, E. Y.-X. Chen, *Nature Chem.* **2016**, *8*, 42.

[8] a) B. M. Trost, T. P. Klun, *J. Am. Chem. Soc.* **1979**, *101*, 6756; b) J. L. Nallasivam, R. A. Fernandes, *J. Am. Chem. Soc.* **2016**, *138*, 13238; conversion of bicyclic 5- and 6-membered lactones, please refer to: c) V. K. Aggarwal, N. Monteiro, G. J. Tarver, S. D. Lindell, *J. Org. Chem.* **1996**, *61*, 1192; d) B. M. Trost, T. Zhang, *Angew. Chem. Int. Ed.* **2008**, *47*, 3759; e) B. M. Trost, T. Zhang, *Chem. Eur. J.* **2011**, *17*, 3630.

[9] Please refer to: a) R. J. Detz, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2009**, 6263; b) D.-Y. Zhang, X.-P. Hu, *Tetrahedron Lett.* **2015**, *56*, 283; c) Y. Nishibayashi, *Synthesis* **2012**, 489; d) C.-H Ding, X.-L, Hou, *Chem. Rev.* **2011**, *111*, 1914. Research articles, please refer to: e) K. Nakajima, M. Shibata, Y. Nishibayashi, *J. Am. Chem. Soc.* **2015**, *137*, 2472; f) Q. Wang, T.-R. Li, L.-Q. Lu, M.-M. Li, K. Zhang, W.-J. Xiao, *J. Am. Chem. Soc.* **2016**, *138*, 8360; g) Y. Miyake, S. Endo, T. Moriyama, K. Sakata, Y. Nishibayashi, *Angew. Chem. Int. Ed.* **2013**, 52, 1758; h) R. J. Detz, M. M. E. Delville, H. Hiemstra, J. H. van Maarseveen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3777; i) K. Zhang, L.-Q. Lu, S. Yao, J.-R. Chen, D.-Q. Shi, W.-J. Xiao, *J. Am. Chem. Soc.* **2017**, *139*, 12847.

[10] a) A. Cai, W. Guo, L. Martínez-Rodríguez, A. W. Kleij, *J. Am. Chem. Soc.* **2016**, *138*, 14194; b) W. Guo, J. Gónzalez-Fabra, N. A. G. Bandeira, C. Bo, A. W. Kleij, *Angew. Chem. Int. Ed*. **2015**, *54*, 11686; c) W. Guo, L. Martínez-Rodríguez, R. Kuniyil, E. Martin, E. C. Escudero-Adán, F. Maseras, A. W. Kleij, *J. Am. Chem. Soc.* **2016**, *138*, 11970; d) W. Guo, A. Cai, J. Xie, A. W. Kleij, *Angew. Chem. Int. Ed*. **2017**, DOI: 10.1002/anie.201705825.

[11] We recently reported on amide synthesis from non-strained lactones: W. Guo, J. E. Gómez, L. Martínez-Rodríguez, N. A. G. Bandeira, C. Bo, A. W. Kleij, *ChemSusChem* **2017**, *10*, 1969.

[12] The 1,3-benzodioxole motif is frequently encountered in pharmaceuticals, see for example: J. D. Bloom, M. D. Dutia, B. D. Johnson, A. Wissner, M. G. Burns, E. E. Largis, J. A. Dolan, T. H. Claus, *J. Med. Chem.* **1992**, *35*, 3081.

[13] For click reactions in bio-orthogonal applications: a) C. R. Becer, R. Hoogenboom, U. S. Schubert, *Angew. Chem. Int. Ed*. **2009**, *48*, 4900; b) M. Yang, J. Li, P. R. Chen, *Chem. Soc. Rev.* **2014**, *43*, 6511; c) R. K. V. Lim, Q. Lin, *Chem. Commun.* **2010**, *46*, 1589.

[14] Chiral lactams are frequently encountered in drugs: a) L.-W. Ye, C. Shu, F. Gagosz, *Org. Biomol. Chem.* **2014**, *12*, 1833; b) C. Kammerer, G. Prestat, D. Madec, G. Poli, *Acc. Chem. Res.* **2014**, *47*, 3439; c) J. Caruano, G. G. Muccioli, R. Robiette, *Org. Biomol. Chem.* **2016**, *14*, 10134. For their asymmetric syntheses, see: d) D. Q. Tan, K. S. Martin, J. C. Fettinger, J. T. Shaw, *Proc. Natl. Acad. Sci.* **2011**, *108*, 6781.

[15] See the SI and CCDC-1574299 for more details.

[16] a) J. Díez, M. P. Gamasa, M. Panera, *Inorg. Chem.* **2006**, *45*, 10043; b) M. Panera, J. Díez, I. Merino, E. Rubio, M. P. Gamasa, *Inorg. Chem.* **2009**, *48*, 11147. Please also see Refs. [9e,9f].

[17] For hydrogen-bond assisted processes, see: a) B. M. Trost, C. Jiang, K. Hammer, *Synthesis* **2005**, 3335; b) B. M. Trost, R. C. Bunt, R. C. Lemoine, T. L. Calkins, *J. Am. Chem. Soc.* **2000**, *122*, 5968; also see Refs. [10a,10c].

[18] A non-linear relationship was observed upon using **L6** (having different *ee* values) and the corresponding enantioenriched amino acid product **1**, suggesting the involvement of a dinuclear copper complex as a key reactive species, see also Refs. [9e,9f] and supporting information for details.

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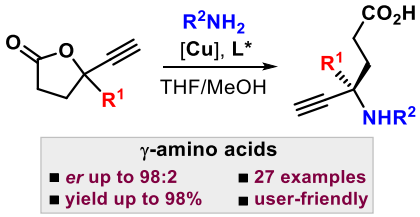
Entry for the Table of Contents:

COMMUNICATION

Amino acid: The first general asymmetric synthesis of γ,γ-disubstituted γ-amino acids through Cu-catalyzed ring opening of non-strained lactones by amines is reported. This catalytic system allows the synthesis of a series of highly functionalized enantio-enriched γ-amino acids featuring quaternary stereocenters with excellent enantiomeric ratios up to 98:2 and yields of up to 98%.



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Page No. – Page No.

Copper-Catalyzed Synthesis of γ-Amino Acids Featuring Quaternary Stereocenters