Access to cyclic β -amino acids by amine-catalyzed enantioselective addition of the γ -carbon atoms of α,β -unsaturated imines to enals

Luo, Guoyong; Huang, Zhijian; Zhuo, Shitian; Mou, Chengli; Wu, Jian; Jin, Zhichao; Chi, Robin Yonggui

2019

Luo, G., Huang, Z., Zhuo, S., Mou, C., Wu, J., Jin, Z., & Chi, R. Y. (2019). Access to cyclic β -amino acids by amine-catalyzed enantioselective addition of the γ -carbon atoms of α,β -unsaturated imines to enals. *Angewandte Chemie International Edition*, 58(48), 17189-17193. doi:10.1002/ange.201908896

<https://hdl.handle.net/10356/137752>

<https://doi.org/10.1002/anie.201908896>

This is the peer reviewed version of the following article: Luo, G., Huang, Z., Zhuo, S., Mou, C., Wu, J., Jin, Z., & Chi, R. Y. (2019). Access to cyclic β -amino acids by amine-catalyzed enantioselective addition of the γ -carbon atoms of α,β -unsaturated imines to enals. *Angewandte Chemie International Edition*, 58(48), 17189-17193, which has been published in final form at <https://doi.org/10.1002/anie.201908896>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

Access to Cyclic β -Amino Acids by Amine-Catalyzed Enantioselective Addition of the γ -Carbon Atoms of α,β -Unsaturated Imines to Enals

Guoyong Luo,[†] [a,b] Zhijian Huang,[†] [b] Shitian Zhuo,^[b] Chengli Mou,^[a,b] Jian Wu,^{*} [c] Zhichao Jin,^[c] and Yonggui Robin Chi^{*[b,c]}

Abstract: Disclosed here is a new catalytic approach for a most efficient access to cyclic β -amino acids widely found in bioactive small molecules and peptidic foldamers. Our method involves addition of the remote γ -carbon atoms of α,β -unsaturated imines to enals via iminium organic catalysis. This highly chemo- and stereo-selective reaction affords cyclic β -amino aldehydes that can be converted to amino acids bearing quaternary stereocenters with exceptional optical purities. Our study demonstrates the unique power of organic catalytic remote carbon reactions in rapid synthesis of functional molecules.

The addition of carbon nucleophiles to electron-deficient alkenes is a common step in forming new carbon-carbon bonds. Among the electron-deficient alkenes, α,β -unsaturated aldehydes (enals) can be readily activated by organic catalysts for asymmetric reactions with various nucleophiles. For example, reactions of enals with primary or secondary amine catalysts form α,β -unsaturated iminium intermediates that can undergo addition reactions with carbon or heteroatom nucleophiles.^[1,2] With N-heterocyclic carbenes (NHCs) as organic catalysts,^[3,4] in the presence of oxidants, enals can be converted to α,β -unsaturated azolium ester intermediates for further reactions.^[5] The majority of the carbon nucleophiles in organic catalytic 1,4-addition to enals (and related electron-deficient alkenes) are the α -carbon atoms of carbonyl compounds or their derivatives and analogues (Figure 1a).^[6] Vinylogous Michael donors^[7] have also found interesting use for construction of C-C bonds at the γ -carbon centers of carbonyl compounds^[8] or their derivatives and analogues.^[9] However, most of vinylogous Michael donors are restricted to cyclic substrates with at least one of the electron-rich double bonds incorporated in the ring systems (Figure 1a).^[8,9] It remains less explored to use acyclic linear vinylogous Michael donors in asymmetric addition to enals (via α,β -unsaturated iminium or azolium ester intermediates) (Figure

1a).^[10,11]

(a) Carbon nucleophiles in organic catalytic 1,4-addition reactions with enals

(b) Addition of remote γ -carbon atoms of α,β -unsaturated imines to enals (this work)

(c) Bioactive molecules and peptidic foldamers containing cyclic β -amino acids

Figure 1. Access to cyclic β -amino acids by addition of remote carbon atoms of unsaturated imines to enals.

Here we disclose that the γ -carbon atoms of α,β -unsaturated imines (linear substrates) can directly undergo nucleophilic addition to enals under the catalysis of chiral secondary amine catalysts (Figure 1b). Key steps include the reaction of enal (**1**) with amine catalyst to form unsaturated iminium intermediate **I**, and γ -CH deprotonation of unsaturated imine substrate (**2**) to form dienamine intermediate **II**. Addition of the γ -carbon atom of **II** to unsaturated iminium intermediate **I** affords intermediate **III** that can undergo further intramolecular Mannich reaction to form intermediate **IV**. Hydrolysis of the iminium component of intermediate **IV** leads to cyclic amino aldehyde product (**3**) with the regeneration of amine catalyst. In this cascade reaction, multiple atoms of both the enal and unsaturated imine substrates are involved with the formation of two new carbon-carbon bonds. The cyclic amino aldehyde products (**3**), obtained as essentially single enantiomers with up to 99% ee, can be readily transformed to cyclic β -amino acids after oxidations. Notably, cyclic amino acids (such as 6-

- [a] Dr. G. Luo, Dr. C. Mou,
School of Pharmacy, Guizhou University of Traditional Chinese
Medicine, Huaxi District, Guiyang 550025, China
- [b] Dr. G. Luo, Dr. Z. Huang, Dr. S. Zhuo, Dr. C. Mou, Prof. Dr. Y. R.
Chi
Division of Chemistry and Biological Chemistry, School of Physical
and Mathematical Sciences, Nanyang Technological University,
Singapore 637371, Singapore.
E-mail: robinchi@ntu.edu.sg
- [c] Prof. Dr. J. Wu, Prof. Dr. Z. Jin, Prof. Dr. Y. R. Chi
Laboratory Breeding Base of Green Pesticide and Agricultural
Bioengineering, Key Laboratory of Green Pesticide and Agricultural
Bioengineering, Ministry of Education, Guizhou University, Huaxi
District, Guiyang 550025, China
E-mail: wujian2691@126.com
- [†] These authors contributed equally to this work.

Supporting information for this article is given via a link at the end of the document.

membebered cyclic β -amino acid BAY 9379,^[12] Tilidin,^[13] and oryzoxymycin^[14] exhibit medicinally significant bioactivities (Figure 1c).^[15] These amino acids are also key components in many pharmaceutical leads such as CEP-28122,^[16] VX-787,^[17] VLA-4 Antagonist^[18] and 11-methoxytabersonine^[19]. In the field of foldamers research, Gellman and co-workers have pioneered the creation of new peptidic structures by employing cyclic non-natural amino acids^[20] that include six-membered β -amino acids^[21]. Our new catalytic reaction provides an efficient approach to this class of cyclic β -amino acids.

Table 1. Condition optimizations.^[a]

Entry	Catalyst	Base	Additive	Yield [%] 3a ^[c] / 4a ^[d]	Ee ^[e] 3a / 4a
1	A	KH ₂ PO ₄	-	64 / 6	99 / 93
2	A	K ₂ HPO ₄	-	trace / -	- / -
3	A	K ₂ HPO ₄ , KH ₂ PO ₄ ^[b]	-	23 / 10	99 / 94
4	A	K ₃ PO ₄ , KH ₂ PO ₄ ^[b]	-	trace / -	- / -
5	A	K ₂ CO ₃ , KH ₂ PO ₄ ^[b]	-	trace / -	- / -
6	A	KH ₂ PO ₄	NaCl	56 / -	99 / -
7	A	K ₂ HPO ₄ , KH ₂ PO ₄ ^[b]	NaCl	72 (69) ^[d] / 4	99 / 93
8	A	K ₂ HPO ₄ , KH ₂ PO ₄ ^[b]	LiBr	55 / 7	99 / 86
9	B	As entry 7	-	trace / -	- / -
10	C	As entry 7	-	20 / -	29 / -
11	D	As entry 7	-	0 / -	- / -

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.1 mmol), amine (0.03 mmol), base (0.1 mmol), additive (0.1 mmol) in 1 mL CH₃OH/H₂O (99:1) at 60 °C for 12 h. [b] 100 mol% of each base was used. [c] NMR yield based on **2a** using trimethoxybenzene as internal standard. [d] Isolated yields of **3a** and **4a** based on **2a**. [e] Enantiomeric excess of **3a** and **4a** was determined via HPLC analysis on chiral stationary phase.

We started by using enal **1a** and α,β -unsaturated imine **2a** as model substrates to develop the γ -carbon addition and cascade reaction (Table 1). Our original attempt in using NHC catalysts under oxidative condition to realize a similar transformation was unsuccessful. We then moved to examine chiral secondary amines as the catalysts. We were delighted to find that by using the Hayashi-Jørgensen type prolinol TMS ether^[22] as the amine catalyst, KH₂PO₄ as the base, the proposed cyclic amino aldehyde product (**3a**) could be obtained as essentially a single enantiomer with 64% yield and 99% ee (entry 1). A mixture of CH₃OH with water (99:1 v/v) was found as an optimal solvent (see Table S1 in SI for examples of other solvents). Trace product was observed when KH₂PO₄ was replaced with K₂HPO₄ (entry 2). Dual basic additives were then examined for further condition optimization (entries 3-5).

Optically enriched products (**3a**, 99% ee) were obtained in trace to 23% yields when using KH₂PO₄ together with K₂HPO₄, K₃PO₄ or K₂CO₃ as the basic additives (entries 3-5, for more details, see Table S1 in SI). Through the addition of NaCl as a salt additive, the yield of **3a** dropped to 56% when KH₂PO₄ alone was used as the base (entry 6). However, the yield of the product **3a** could be dramatically increased by the addition of NaCl with K₂HPO₄/KH₂PO₄ as the bases (entries 7 vs 3). Other inorganic salts (e.g., entry 8, see Table S1 in SI for more details) were also tested as additives for this reaction. As a technical note, adduct **4a** was obtained as the major side product, and its formation was suppressed by the addition of NaCl (entries 7 vs 3). Several other amine catalysts (**B**, **C** and **D**) we tested were not effective (entries 9-11).

Scheme 1. Substrate scope.

With an acceptable condition (Table 1, entry 7) in hand, we examined the generality of the reactions with regards to both substrates (Scheme 1). With **2a** as a model unsaturated imine substrate, we first tested derivatives of cinnamaldehyde as the enal substrates (**3b-3f**). Placing various substituents on the para position of the β -phenyl group of cinnamaldehyde were well tolerated, with the corresponding products obtained in 66-73% yields and excellent ee values (**3b-3e**). When a methyl unit was placed on the ortho-carbon of the β -phenyl ring of cinnamaldehyde, a longer reaction time was needed with a drop

on product yield (**3f**, 43% yield) likely due to the steric hindrance. Changing the phenyl group into other heteroaryl (**3g**) and naphthyl (**3h**) substituents did not influence the reaction outcomes. The phenyl group of cinnamaldehyde could also be replaced by an alkene unit (**3i**). Aliphatic enal could give the desired product (**3j**) in a low yield (12%) even after an extended reaction time.

We next moved to examine the imine substrates (**2**) using cinnamaldehyde (**1a**) as a model electrophile. Placing halogen substituents on the phenyl ring of the unsaturated imine substrates led to the corresponding products **3k** and **3l** with 44% and 65% yield respectively. The β -phenyl substituent of the unsaturated imine could be replaced by a naphthyl unit (**3m**). The β -aryl substituent of the imine can be changed to an alkyl (**3n**) or a carboxylic ester (**3o**) unit, albeit with yields decreased. The γ -phenyl substituted imine could give the desired product (**3p**) in a low yield (16%). We also investigated imines with other *N*-protecting groups. Both 2- and 4-nitrobenzenesulfonyl protected imines (**3q** and **3r**) were tolerated to give the corresponding products in 68% and 59% yield respectively. Interestingly, diphenylphosphinyl imine substrate also reacted fine to give **3s** with 34% yield (isolated after reduction of the aldehyde to alcohol due to the instability of the amino aldehyde adduct). No desired product was observed when aldimine was employed as the substrate under the current reaction condition.

In all these catalytic reactions (**3a-s**), the cyclic β -amino aldehyde products were obtained as single diastereomers. The reaction likely gave *trans*-Mannich adduct that subsequently underwent an epimerization to the thermodynamically more stable isomer with excellent diastereoselectivity (see SI for a detailed mechanistic discussion).

The reaction is amenable for scale up without loss in yields or ee values. Here we demonstrated a preparation of **3a** in 1.5 gram scale with 67% yield and 99% ee.

Scheme 2. Control experiments.

To understand the reaction pathway for the formation of by-product **4a** and the role of NaCl, multiple control experiments were conducted (Scheme 2). Under the optimized reaction condition, **3a** was employed as the reaction starting material, and the yield of by-product **4a** was monitored by ^1H NMR. As shown in Scheme 2a, without the addition of NaCl, **4a** could be afforded from **3a** in moderate yields under otherwise identical reaction conditions. However, the formation of **4a** was significantly suppressed by the addition of NaCl. This might

because that the salt additive can facilitate the precipitation of product **3a** from the reaction solution and thus suppress its transformation to the side-product **4a**. Only trace formation of **4a** was observed from the reaction of **1a** and the enone substrate **2a'** (Scheme 2b). Notably, the formation of **3a'** and **3a''** were not observed in our model reactions while using unsaturated imine **2a** as the substrate, showing that hydrolysis of unsaturated imine is minimal under our optimal reaction conditions (see SI for additional control experiments). Based on these results, the side-product **4a** is expected to be afforded via elimination of TsNH_2 from **3a**, rather than from the reaction between enal **1a** and enone **2a'** (generated in situ via hydrolysis of **2a** during the catalytic reaction).

The amino aldehyde adducts from our catalytic reactions could be converted to the corresponding cyclic β -amino acids. As a technical note, it was easier to remove the nitrobenzenesulfonyl (nosyl, Ns) protecting group of the amine than the toluenesulfonyl (tosy, Ts) group. The aldehyde moiety of the Ns protected amino aldehyde **3r** could be readily oxidized to the corresponding carboxylic acid (**5**) in 84% yield. The Ns group on the amino group could be removed in the presence of a thiophenol and base^[23] to give the unprotected amino acid (**6**) in 80% yield. In both transforming steps (from **3r** to **5** and to **6**), the optical purity of the products was not affected (Scheme 3).

Scheme 3. Conversion of **3r** to unprotected cyclic amino acids.

In summary, we have developed a new reaction between α,β -unsaturated imines and enals. Key steps in this catalytic process involves 1,4-addition of the remote γ -carbon atoms of unsaturated imines to enals under the catalysis of chiral amines. The reaction affords cyclic β -amino aldehydes with exceptional chemo- and stereoselectivities. The amino aldehydes can be converted to cyclic β -amino acids bearing quaternary stereocenters that are difficult to prepare using previous methods. We expect this study to encourage further exploration of remote carbon atoms in organic catalytic reactions for rapid assembly of useful molecules.

Acknowledgements

We acknowledge financial support from the National Natural Science Foundation of China (No. 21772029, 21562012, 21762012, 21801051), National Key Technologies R&D Program (No. 2014BAD23B01), "Thousand Talent Plan", The 10 Talent Plan (Shicengci) of Guizhou Province, S&T Planning Project of Guizhou Province (No. [2017]1402, [2017]5788), the Department of Science and Technology of Guizhou Province for Basic Research (No. [2019]1020), Guizhou Province Returned Oversea Student Science and Technology Activity Program, Guizhou University, the Guizhou Province First-Class Disciplines

Project (Yiliu Xueke Jianshe Xiangmu)-GNYL(2017)008, Guizhou University of Traditional Chinese Medicine (China), Open Fund of Guizhou Key Laboratory of Miao Medicine (QMYYY[2017]101), Guizhou University of Traditional Chinese Medicine (China). Singapore National Research Foundation (NRF-NRFI2016-06), the Ministry of Education of Singapore (MOE2013-T2-2-003; MOE2016-T2-1-032; RG108/16), A*STAR Individual Research Grant (A1783c0008), Nanyang Research Award Grant, and Nanyang Technological University.

Keywords: cyclic β -amino acid • remote γ carbon • direct vinylogous Michael addition • acyclic vinylogous Michael donor • amine catalysis

- [1] For selected reviews, see: a) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416-5470; b) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590-1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570-1581.
- [2] For selected examples, see: a) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874-9875; b) M. Marigo, T. Schulte, J. Franzén, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710-15711; c) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861-863; d) S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299-4301; *Angew. Chem. Int. Ed.* **2006**, *45*, 4193-4195; e) X. Jiang, B. Tan, C. F. Barbas III, *Angew. Chem.* **2013**, *125*, 9431-9435; *Angew. Chem. Int. Ed.* **2013**, *52*, 9261-9265; f) Q. Liu, L. Zu, *Angew. Chem.* **2018**, *130*, 9649-9653; *Angew. Chem. Int. Ed.* **2018**, *57*, 9505-9509.
- [3] For selected reviews, see: a) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485-496; b) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307-9387.
- [4] For selected examples, see: a) N. T. Reynolds, J. R. de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518-9519; b) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418-8420; c) D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem.* **2006**, *118*, 1491-1495; *Angew. Chem. Int. Ed.* **2006**, *45*, 1463-1467; d) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766-771; e) Z. Q. Fu, J. F. Xu, T. S. Zhu, W. W. Y. Leong, Y. R. Chi, *Nat. Chem.* **2013**, *5*, 835-839; f) H. Lv, W.-Q. Jia, L.-H. Sun, S. Ye, *Angew. Chem.* **2013**, *125*, 8769-8772; *Angew. Chem. Int. Ed.* **2013**, *52*, 8607-8610; g) A. Patra, S. Mukherjee, T. K. Das, S. Jain, R. G. Gonnade, A. T. Biju, *Angew. Chem.* **2017**, *129*, 2774-2778; *Angew. Chem. Int. Ed.* **2017**, *56*, 2730-2734.
- [5] For selected examples, see: a) J. Guin, S. De Sarkar, S. Grimme, A. Studer, *Angew. Chem.* **2008**, *120*, 8855-8858; *Angew. Chem. Int. Ed.* **2008**, *47*, 8727-8730; b) A. G. Kravina, J. Mahatthananchai, J. W. Bode, *Angew. Chem.* **2012**, *124*, 9568-9572; *Angew. Chem. Int. Ed.* **2012**, *51*, 9433-9436; c) J. Mo, L. Shen, Y. R. Chi, *Angew. Chem.* **2013**, *125*, 8750-8753; *Angew. Chem. Int. Ed.* **2013**, *52*, 8588-8591; d) Z.-Q. Liang, D.-L. Wang, H.-M. Zhang, S. Ye, *Org. Lett.* **2015**, *17*, 5140-5143.
- [6] For selected examples of α -carbon nucleophiles, see: a) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, 4928-4930; b) C. Palomo, A. Landa, A. Mielgo, M. Oiarbide, Á. Puente, S. Vera, *Angew. Chem.* **2007**, *119*, 8583-8587; *Angew. Chem. Int. Ed.* **2007**, *46*, 8431-8435; c) Y. Hayashi, M. Toyoshima, H. Gotoh, H. Ishikawa, *Org. Lett.* **2009**, *11*, 45-48; d) V. Blanco, D. A. Leith, U. Lewandowska, B. Lewandowski, V. Marcos, *J. Am. Chem. Soc.* **2014**, *136*, 15775-15780; e) S. Duce, I. Alonso, A. M. Lamsabhi, E. Rodrigo, S. Morales, J. L. G. Ruano, A. Poveda, P. Mauleón, M. B. Cid, *ACS Catal.* **2018**, *8*, 22-34.
- [7] For selected reviews, see: a) C. Schneider, F. Abels, *Org. Biomol. Chem.* **2014**, *12*, 3531-3543; b) Y. Yin, Z. Jiang, *ChemCatChem* **2017**, *9*, 4306-4318.
- [8] For selected examples for 1,4-addition of cyclic vinylogous Michael donors to enals via direct approach, see: a) X. Feng, H.-L. Cui, S. Xu, L. Wu, Y.-C. Chen, *Chem. Eur. J.* **2010**, *16*, 10309-10312; b) A. Quintard, A. Lefranc, A. Alexakis, *Org. Lett.* **2011**, *13*, 1540-1543; c) L. Dell'Amico, L. Albrecht, T. Naicker, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2013**, *135*, 8063-8070; d) L. Dell'Amico, G. Rassu, V. Zambrano, A. Sartori, C. Curti, L. Battistini, G. Pelosi, G. Casiraghi, F. Zanardi, *J. Am. Chem. Soc.* **2014**, *136*, 11107-11114; e) S. R. Yetra, S. Mondal, S. Mukherjee, R. G. Gonnade, A. T. Biju, *Angew. Chem.* **2016**, *128*, 276-280; *Angew. Chem. Int. Ed.* **2016**, *55*, 268-272; f) Z.-L. Jia, Y. Wang, C.-G. Zhao, X.-H. Zhang, P.-F. Xu, *Org. Lett.* **2017**, *19*, 2130-2133.
- [9] For selective examples for 1,4-addition of cyclic vinylogous Michael donors to enals via indirect approach, see: a) S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192-1194; b) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051-15053; c) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2011**, *133*, 4694-4697.
- [10] Examples for 1,4-addition of acyclic linear vinylogous Michael donors to enals via indirect approach: a) V. Gupta, S. T. Mandal, C. Schneider, *Angew. Chem.* **2012**, *124*, 12778-12781; *Angew. Chem. Int. Ed.* **2012**, *51*, 12609-12612; b) S. Basu, V. Gupta, J. Nickel, C. Schneider, *Org. Lett.* **2014**, *16*, 274-277.
- [11] Examples for 1,4-addition of linear vinylogous Michael donors to enals via direct approach: a) Y. Gu, Y. Wang, T.-Y. Yu, Y.-M. Liang, P.-F. Xu, *Angew. Chem.* **2014**, *126*, 14352-14355; *Angew. Chem. Int. Ed.* **2014**, *53*, 14128-14131; b) Q. Guo, A. J. Fraboni, S. E. Brenner-Moyer, *Org. Lett.* **2016**, *18*, 2628-2631.
- [12] F. Kunisch, P. Babczinski, D. Arlt, M. Plempel, Ger. Offen. DE 4028046 A1, **1992**; *Chem. Abstr.* **1992**, *117*, 20486.
- [13] A. Trojan, H. Beil, *Drug Alcohol Depen.* **1978**, *3*, 383-391.
- [14] T. Hashimoto, S. Kondo, T. Takita, M. Hamada, T. Takeuchi, Y. Okami, H. Umezawa, *J. Antibiot.* **1968**, *21*, 653-658.
- [15] a) F. Fülöp, *Chem. Rev.* **2001**, *101*, 2181-2204; b) L. Kiss, F. Fülöp, *Chem. Rev.* **2014**, *114*, 1116-1169.
- [16] M. Cheng, M. R. Quail, D. E. Gingrich, G. R. Ott, L. Lu, W. Wan, M. S. Albom, T. S. Angeles, L. D. Aimone, F. Cristofani, R. Machiorlatti, C. Abele, M. A. Ator, B. D. Dorsey, G. Inghirami, B. A. Ruggeri, *Mol. Cancer Ther.* **2012**, *11*, 670-679.
- [17] M. P. Clark, M. W. Ledebor, I. Davies, R. A. Byrn, S. M. Jones, E. Perola, A. Tsai, K. Jacobs, K. Nti-Addae, U. K. Bandarage, M. J. Boyd, R. S. Bethiel, J. J. Court, H. Deng, J. P. Duffy, W. A. Dorsch, L. J. Farmer, H. Gao, W. Gu, K. Jackson, D. H. Jacobs, J. M. Kennedy, B. Ledford, J. Liang, F. Maltis, M. Murcko, T. Wang, M. W. Wannamaker, H. B. Bennett, J. R. Leeman, C. McNeil, W. P. Taylor, C. Memmott, M. Jiang, R. Rijnbrand, C. Bral, U. Germann, A. Nezami, Y. Zhang, F. G. Salituro, Y. L. Bennani, P. S. Charifson, *J. Med. Chem.* **2014**, *57*, 6668-6678.
- [18] L. L. Chang, Q. Truong, G. A. Doss, M. MacCoss, K. Lyons, E. McCauley, R. Mumford, G. Forrest, S. Vincent, J. A. Schmidt, W. K. Hagmann, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 597-601.
- [19] T. Feng, Y. Li, Y.-Y. Wang, X.-H. Cai, Y.-P. Liu, X.-D. Luo, *J. Nat. Prod.* **2010**, *73*, 1075-1079.
- [20] For selected reviews, see: a) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173-180; b) R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219-3232.
- [21] For selected examples, see: a) D. H. Appella, L. A. Christianson, D. A. Klein, D. R. Powell, X. Huang, J. J. Barchi, S. H. Gellman, *Nature* **1997**, *387*, 381-384; b) D. H. Appella, L. A. Christianson, D. A. Klein, M. R. Richards, D. R. Powell, S. H. Gellman, *J. Am. Chem. Soc.*, **1999**, *121*, 7574-7581; c) E. A. Porter, X. Wang, H.-S. Lee, B. Weisblum, S. H. Gellman, *Nature*, **2000**, *404*, 565.

- [22] a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284-4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215; b) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804-807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794-797.
- [23] a) T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373-6374; b) A. Kessler, H. Faure, M. C. Roussanne, S. Ferry, M. Ruat, P. Dauban, R. H. Dodd, *ChemBioChem* **2004**, *5*, 1131-1136.
-

Layout 2:

COMMUNICATION

Direct Vinylogous Michael addition of the remote γ -carbon atoms of α,β -unsaturated imines to enals is realized via iminium organic catalysis, providing a quick access to enantiopure cyclic amino acids.

Guoyong Luo,[†] Zhijian Huang,[†] Shitian Zhuo, Chengli Mou, Jian Wu,^{*} Zhichao Jin, and Yonggui Robin Chi^{*}

Page No. – Page No.

Access to Cyclic β -Amino Acids by Amine-Catalyzed Enantioselective Addition of the γ -Carbon Atoms of α,β -Unsaturated Imines to Enals