A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

GDCh

www.angewandte.org

Accepted Article

Title: Quaternary β2,2-Amino Acids: Catalytic Asymmetric Synthesis and Incorporation into Peptides by Fmoc-Based Solid Phase Peptide Synthesis

Authors: Jin-Sheng Yu, Hidetoshi Noda, and Masakatsu Shibasaki

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201711143
Angew. Chem. 10.1002/ange.201711143

Link to VoR: http://dx.doi.org/10.1002/anie.201711143
http://dx.doi.org/10.1002/ange.201711143

WILEY-VCH

10.1002/anie.201711143

WILEY-VCH

Quaternary $\beta^{2,2}$-Amino Acids: Catalytic Asymmetric Synthesis and Incorporation into Peptides by Fmoc-Based Solid Phase Peptide Synthesis

Jin-Sheng Yu, Hidetoshi Noda* and Masakatsu Shibasaki*

Abstract: β-Amino acid incorporation has emerged as a promising approach to enhance the stability of parent peptides and to improve their biological activity. Owing to the lack of reliable access to $\beta^{2,2}$-amino acids in a setting suitable for peptide synthesis, most contemporary research efforts focus on the use of β^3- and certain $\beta^{2,3}$-amino acids. Herein, we report a catalytic asymmetric synthesis of $\beta^{2,2}$-amino acids and their incorporation into peptides by Fmoc-based solid phase peptide synthesis (Fmoc-SPPS). Construction of a quaternary carbon is accomplished by Pd-catalyzed decarboxylative allylation of 4-substituted isoxazolidin-5-ones. The N–O bond in the products not only acts as a traceless protecting group for β-amino acids but also undergoes amide formation with α-ketoacids derived from Fmoc-protected α-amino acids, providing expeditious access to α-$\beta^{2,2}$-dipeptides ready for Fmoc-SPPS.

The highly organized structure of proteins is closely linked with their functions. Identification of artificial molecules that form well defined three-dimensional structures has opened up the avenue for designing new functional molecules beyond what nature can create.[1] Among various foldamers, oligomers of homologated β-amino acids stand out as the most investigated class of unnatural foldamers.[2] Extensive research efforts have established the incorporation of β-amino acids as one of the most successful approaches in peptidomimetics.[3,4]

The extra carbon atom in β-amino acids restricts the conformation of the resulting peptide, inducing the formation of more rigid secondary structures than those found in α-peptides.[5] β-Amino acids are structurally classified according to their substituent position, with substituent at the β-carbon for β^3-amino acids, α-carbon for β^2-amino acids, both α- and β-carbon for $\beta^{2,3}$-amino acids, and so on (Figure 1). Almost all substitution patterns have been demonstrated to induce the formation of certain higher order structures. For instance, the seminal work of Seebach revealed that achiral $\beta^{2,2}$-amino acids cause the formation of reverse turned structures featuring 10-membered hydrogen bonding rings.[6] Given the importance of turned structures in biological settings,[7] it would be valuable to study the effect of chirality in $\beta^{2,2}$-amino acids on peptide conformation or to incorporate them into α/β-mixed peptides.[8] So far, most studies and applications employing β-amino acids have dealt with β^3- and certain $\beta^{2,3}$-amino acids, neglecting their β^2- and $\beta^{2,2}$-counterparts.[9] This apathy partly reflects the lack of available routes to these classes of β-amino acids.

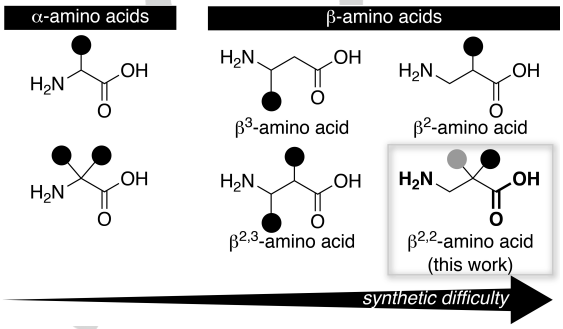


Figure 1. Structural classifications of α- and β-amino acids.

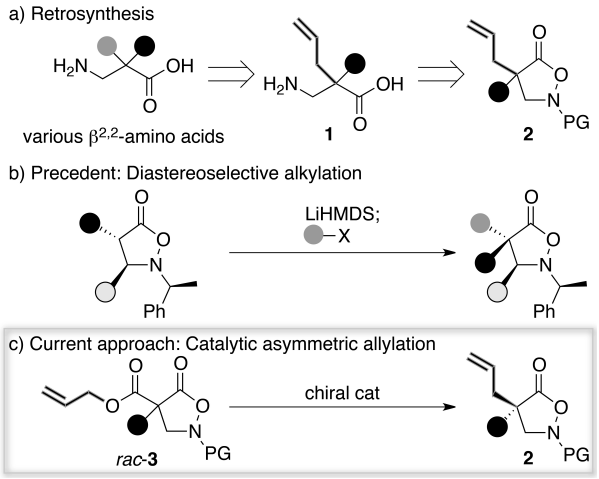
In 2009, Seebach elegantly summarized the synthetic challenges associated with the preparation of β^2-amino acids suitable for peptide synthesis,[10] and the situation has not changed since then. The enantioselective synthesis of $\beta^{2,2}$-amino acids faces even more difficulties. Most known methods resort to chiral auxiliaries to construct the all-carbon quaternary stereocenter.[11] Nevertheless several catalytic asymmetric approaches have been reported, including the conjugate addition of carbon nucleophiles to α-substituted-β-nitroacrylates[12] and the addition of α-substituted-α-cyanoacetates to carbon electrophiles.[13] Despite the tremendous efforts directed at $\beta^{2,2}$-amino acid synthesis by asymmetric catalysis, the number of available approaches remains limited, and most of them are not readily translated to peptide synthesis.[14] In this Communication, we describe catalytic asymmetric synthesis of $\beta^{2,2}$-amino acids and their incorporation into peptides by a combination of decarboxylative amide formation with α-ketoacids[15] and Fmoc-based solid phase peptide synthesis (Fmoc-SPPS).

From the outset, we sought to adopt a unified strategy that would provide a variety of quaternary $\beta^{2,2}$-amino acids from a single intermediate. Given the prospective transformations of C–C double bonds, we set compound **1** as the target structure (Scheme 1a). α-Quaternerization of racemic β^2-amino acids appears to be the most straightforward route to **1**. In such an approach, however, the low acidity of the α-protons can hamper the generation of the corresponding carboxylate-type enolate by a catalytic amount of Brønsted base. Geometric control of the resulting α,α-disubstituted enolate would also complicate the stereoselective synthesis. Substituted isoxazolidin-5-ones have often been utilized as β-amino acid precursors,[16] e.g., in the synthesis of $\beta^{2,2,3}$-amino acids by chiral auxiliary based alkylation (Scheme 1b).[17] Nevertheless, the catalytic asymmetric C–C bond formation of racemic isoxazolidin-5-ones for the synthesis of quaternary $\beta^{2,2}$-amino acids has not been reported.[18] Recent

[*] Dr. J.-S. Yu, Dr. H. Noda, Prof. Dr. M. Shibasaki
Institute of Microbial Chemistry (BIKAKEN), Tokyo
3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan
E-mail: hnoda@bikaken.or.jp; mshibasa@bikaken.or.jp

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

contributions from Stoltz, Tunge, Trost, and others have demonstrated that Pd-catalyzed decarboxylative asymmetric allylation of carbonyl compounds[19,20] is a reliable means to construct a quaternary carbon at the α-position, making this approach particularly suitable for our goal.[21] With this in mind, we selected 4-substituted isoxazolidin-5-ones as β^2-amino acid surrogates, and embarked on the development of decarboxylative asymmetric allylation of **3** (Scheme 1c).

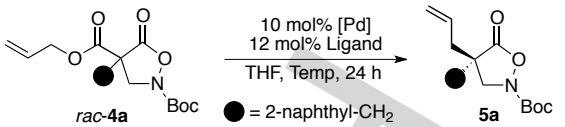


Scheme 1. Reaction design, precedents, and current approach.

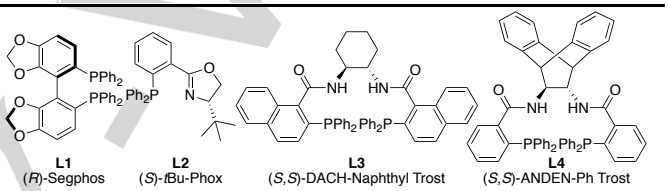
The optimization study for the decarboxylative allylation of **4a** was summarized in Table 1. Whereas most evaluated chiral ligands exhibited low to moderate selectivity, commercial (*S*,*S*)-ANDEN-Ph Trost ligand **L4** performed exceptionally well, affording **5a** in 85% ee with fair reactivity (entries 1–4). $Pd(dba)_2$ was found to present a slightly higher reactivity while preserving selectivity (entry 5). Although the origin of $Pd(dba)_2$ superiority to $Pd_2(dba)_3$ is not clear, the larger amount of dba ligand in the former precatalyst may stabilize an active Pd complex in the catalytic cycle, preventing its decomposition.[22] Lowering the reaction temperature to –20 °C further improved the enantioselectivity albeit with prolonged reaction time (entry 6). The removal of residual dba ligand from the product proved to be challenging. Fortunately Pd precatalyst containing 3,5,3',5'-dimethoxydibenzylideneacetone (dmdba) showed reactivity and selectivity comparable to those obtained in the case of $Pd(dba)_2$, with the dmdba ligand readily separated from the product by standard silica gel column chromatography (entry 7).

With the optimized conditions in hand, a series of substrates were subjected to catalytic asymmetric allylation (Table 2). Similar reactivities and selectivities were observed for 2-naphthylmethyl and benzyl substituted compounds (entries 1–2). A broad range of substituted benzyl groups also proved to be suitable for this transformation; the electronic nature and the position of substituents on the phenyl ring barely affect the reaction outcome. Both electron-withdrawing (entries 3–4) and electron-donating groups (entries 5–6) afforded the corresponding products with the same level of selectivity. The positional isomers of **5c** also produced the desired compounds with similarly high efficiency (entries 7–8). Potentially detrimental heteroaromatics were also tolerated (entries 9–10). The allylated

Table 1. Optimization of reaction conditions[a].

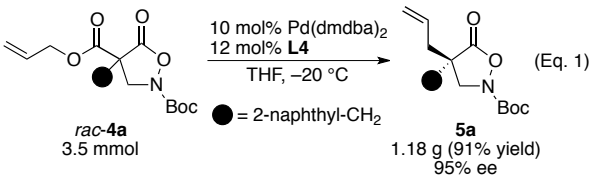


Entry	[Pd] (10 mol%)	Ligand (12 mol%)	Temp (°C)	Yield[b] (%)	Ee[c] (%)
1	$Pd_2(dba)_3$	**L1**	25	95	6
2	$Pd_2(dba)_3$	**L2**	25	96	10
3	$Pd_2(dba)_3$	**L3**	25	10	–52
4	$Pd_2(dba)_3$	**L4**	25	65	85
5	$Pd(dba)_2$	**L4**	25	75	85
6[d]	$Pd(dba)_2$	**L4**	–20	78	92
7[d,e]	$Pd(dmdba)_2$	**L4**	–20	79	93



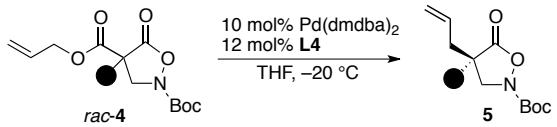
[a] 0.05 mmol scale at 0.05 M. [b] Determined by ^{1}H NMR analysis. [c] Determined with normal phase HPLC on a chiral support. [d] The reaction time equaled 48 h. [e] 0.1 mmol scale at 0.025 M. Isolated yield is reported. dba = dibenzylideneacetone, dmdba = 3,5,3',5'-dimethoxydibenzylideneacetone.

product **5f** or **5i** can be considered as analogues of β^2-tyrosine or β^2-tryptophane, respectively. Furthermore, a pyrene-containing substrate was also efficiently allylated (entry 11). The generated $\beta^{2,2}$-amino acids are potential reporter molecules due to the fluorescent nature of the pyrene ring. A substituted alkenyl chain and a simple alkyl group were both tolerated, providing the products in good selectivities (entries 12–13). The scalability of the current protocol was ascertained by synthesizing 1.18 g of **5a** in 95% ee (Eq 1). The absolute configuration of **5c** at the carbonyl α-carbon was determined as *S* by X-ray diffraction (Figure S1); the stereochemistry of other products was assigned by analogy.



10.1002/anie.201711143

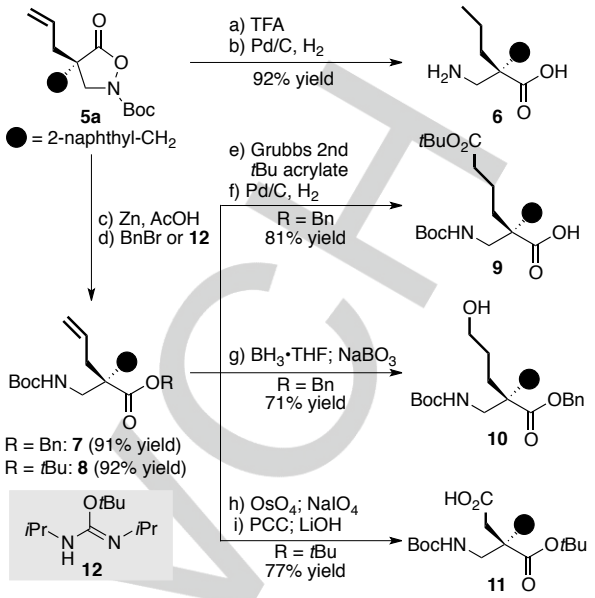
Table 2. Substrate scope of catalytic asymmetric allylation[a].



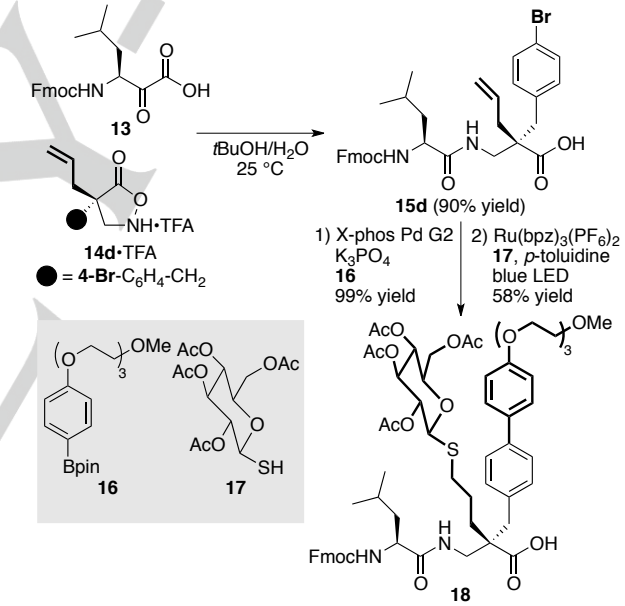
Entry	Substituent	Product	Yield (%)	Ee (%)
1	2-naphthyl-CH_2	**5a**	82	94
2	C_6H_5-CH_2	**5b**	89	92
3	4-Cl-C_6H_4-CH_2	**5c**	80	93
4	4-Br-C_6H_4-CH_2	**5d**	91	93
5	4-MeO-C_6H_4-CH_2	**5e**	88	92
6	4-*t*BuO-C_6H_4-CH_2	**5f**	85	92
7	3-Cl-C_6H_4-CH_2	**5g**	96	94
8	2-Cl-C_6H_4-CH_2	**5h**	94	90
9	*N*-Boc-3-indolyl-CH_2	**5i**	89	94
10	3-thienyl-CH_2	**5j**	76	90
11	1-pyrenyl-CH_2	**5k**	92	91
12	(*E*)-Ph-CH=CH-CH_2	**5l**	81	94
13	Me	**5m**	58	92

[a] 0.2 mmol scale at 0.025 M. Isolated yields are reported. Ee was determined with normal phase HPLC on a chiral support.

The allylated products in Table 2 were readily converted to various protected $\beta^{2,2}$-amino acids (Scheme 2). After removing the Boc group, treatment of the crude amine with Pd/C under a hydrogen atmosphere reduced the double bond in the side chain concomitant with N–O bond cleavage, producing **6** in excellent yield. Switching the reductive conditions allowed for selective cleavage of the N–O bond without disturbing the olefin moiety, which was followed by the esterification of thus obtained carboxylic acid to furnish **7** or **8**. Cross metathesis provides a convenient means to elongate the side chain with varying functionality; thus treatment with the Grubbs 2nd generation catalyst and *tert*-butyl acrylate smoothly extended the side chain. Subsequent reduction of the alkene moiety afforded **9**. Standard oxidative functionalizations of the terminal double bond also proved effective. Hydroboration with BH_3•THF produced primary alcohol **10** after oxidative workup. Carboxylic acid **11** was provided by first cleaving the terminal double bond to unveil an aldehyde, which was intramolecularly captured by the carbamate nitrogen to give the corresponding aminal. PCC oxidation to lactam and subsequent ring opening under aqueous basic conditions gave **11**. These transformations demonstrated that the allyl group in the products is a useful handle for the synthesis of various quaternary $\beta^{2,2}$-amino acids.

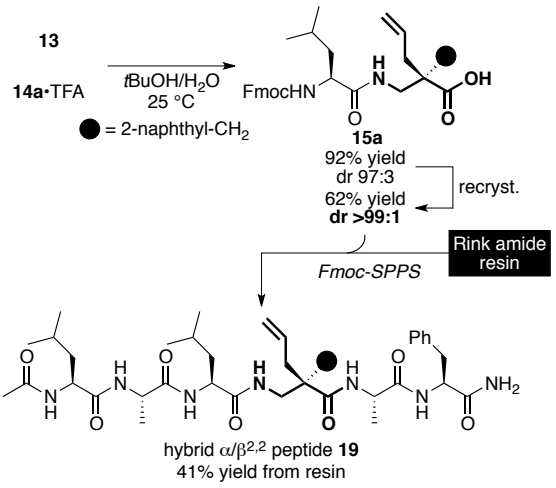


Scheme 2. Transformations to various quaternary $\beta^{2,2}$-amino acids.



Scheme 3. Synthesis of hybrid α-$\beta^{2,2}$-dipeptide **15d** and its functionalization.

The hydroxylamine moiety in the products also acts as a springboard for further transformations. Removing the Boc group makes the *O*-acyl hydroxylamines suitable for the α-ketoacid-hydroxylamine (KAHA) ligation developed by Bode and coworkers.[23] The crude mixture of TFA salt of **14d** was treated with α-ketoacid **13** derived from Fmoc-L-leucine to furnish Fmoc-protected α-$\beta^{2,2}$-dipeptide **15d** (Scheme 3). The 2nd generation Buchwald palladacycle ligated with X-phos ligand[24] smoothly promoted the Suzuki–Miyaura reaction of **15d** with PEGylated arylboronate **16** even in the presence of the base-sensitive Fmoc group. The terminal olefin in the functionalized dipeptide underwent a thiol-ene reaction with glycosyl thiol **17** under the influence of a photoredox catalyst.[25]



Scheme 4. Synthesis of hybrid $\alpha/\beta^{2,2}$ peptide by Fmoc-SPPS.

Fmoc-protected α-$\beta^{2,2}$-dipeptides **15** appeared amenable to Fmoc-SPPS. Regarding stereochemistry, peptide chemistry standards exceed those of asymmetric catalysis, requiring substrates possessing at least >99:1 stereochemical integrity. Despite the somewhat lower selectivity obtained herein, the crystalline nature of Fmoc-protected dipeptides can compensate for this drawback; a single recrystallization from hexane/Et_2O allowed for removal of the minor diastereomer, rendering dipeptide **15a** ready for Fmoc-SPPS (Scheme 4).[26] Since the growing number of applications is found in hybrid α/β peptides,[27] the facile synthesis of diastereomerically pure α-$\beta^{2,2}$-dipeptides would be advantageous. In contrast to other geminally substituted amino acids —α,α-disubstituted α-amino acids and $\beta^{3,3}$-amino acids, both of which often need to be coupled under special conditions[11]— **15** is sufficiently reactive under the standard Fmoc-SPPS conditions. Thus dipeptide **15a** was incorporated into the middle of the peptide sequence on a Rink-amide resin,[28] followed by cleavage from the polymer support and HPLC purifications to provide analytically pure peptide **19** in good overall yield. Functionalizations of the terminal olefin in the resulting peptide would also be feasible.[29]

In summary, we have documented a new entry for the catalytic asymmetric synthesis of quaternary $\beta^{2,2}$-amino acids. A proficient chiral catalyst system comprising $Pd(dmdba)_2$ and a Trost ligand promotes the decarboxylative allylation of 4-substituted isoxazolin-5-ones in a stereoselective fashion. The allylated products are converted to a range of the otherwise inaccessible $\beta^{2,2}$-amino acids. Moreover, the N–O bond in the products participates in the KAHA ligation with α-ketoacids, affording expeditious access to Fmoc-protected α-$\beta^{2,2}$-dipeptides. Finally, the standard Fmoc-SPPS procedure can routinely build up mixed $\alpha/\beta^{2,2}$ peptides, showcasing the potential of the current protocol.

Acknowledgements

This work was financially supported by JST, ACT-C (JPMJCR12YO), and JSPS KAKENHI Grant Number JP16K18856. J.-S.Y. is a JSPS International Research Fellow. H.N. thanks the Astellas Foundation for Research on Metabolic Disorders for financial support. The authors are grateful to Dr. Ryuichi Sawa, Ms. Yumiko Kubota, and Dr. Kiyoko Iijima for assistance with NMR analysis and Dr. Tomoyuki Kimura for assistance with X-ray crystallography.

Keywords: Amino acids • Asymmetric catalysis • Peptides

[1] a) S. Hecht, I. Huc, *Foldamers: structure, properties, and applications*, Wiley-VCH, Weinheim, 2007; b) D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes, J. S. Moore, *Chem. Rev.* **2001**, *101*, 3893; c) R. Gopalakrishnan, A. I. Frolov, L. Knerr, W. J. Drury III, E. Valeur, *J. Med. Chem.* **2016**, *59*, 9599.

[2] a) R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219; b) D. Seebach, J. Gardiner, *Acc. Chem. Res.* **2008**, *41*, 1366.

[3] a) E. A. Porter, X. Wang, H. S. Lee, B. Weisblum, S. H. Gellman, *Nature* **2000**, *404*, 565; b) Y. Imamura, N. Watanabe, N. Umezawa, T. Iwatsubo, N. Kato, T. Tomita, T. Higuchi, *J. Am. Chem. Soc.* **2009**, *131*, 7353; c) L. M. Johnson, S. Barrick, M. V. Hager, A. McFedries, E. A. Homan, M. E. Rabaglia, M. P. Keller, A. D. Attie, A. Saghatelian, A. Bisello, S. H. Gellman, *J. Am. Chem. Soc.* **2014**, *136*, 12848.

[4] a) J. X. Qiu, E. J. Petersson, E. E. Matthews, A. Schepartz, *J. Am. Chem. Soc.* **2006**, *128*, 11338; b) G. A. Lengyel, W. S. Horne, *J. Am. Chem. Soc.* **2012**, *134*, 15906; c) C. Mayer, M. M. Müller, S. H. Gellman, D. Hilvert, D. *Angew. Chem. Int. Ed.* **2014**, *53*, 6978; *Angew. Chem.* **2014**, *126*, 7098.

[5] Y.-D. Wu, W. Han, D.-P. Wang, Y. Gao, Y.-L. Zhao, *Acc. Chem. Res.* **2008**, *41*, 1418.

[6] D. Seebach, S. Abele, T. Sifferlen, M. Hänggi, S. Gruner, P. Seiler, *Helv. Chim. Acta* **1998**, *81*, 2218.

[7] J. D. A. Tyndall, B. Pfeiffer, G. Abbenante, D. P. Fairlie, *Chem. Rev.* **2005**, *105*, 793.

[8] Examples of $\beta^{2,2}$-amino acids bearing a heteroatom at the α-carbon. Oxygen: a) G. V. M. Sharma, K. Rajender, G. Sridhar, P. S. Reddy, M. Kanakaraju, *Carbohydr. Res.* **2014**, *388*, 8; b) F. Rodríguez, F. Corzana, A. Avenoza, J. H. Busto, J. M. Peregrina, M. M. Zurbano, *Curr. Topics Med. Chem.* **2014**, *14*, 1225. Nitrogen: c) L. Mata, A. Avenoza, J. H. Busto, F. Corzana, J. M. Peregrina, *Chem. Eur. J.* **2012**, *18*, 15822; d) N. Mazo, I. García-González, C. D. Navo, F. Corzana, G. Jiménez-Osés, A. Avenoza, J. H. Busto, J. M. Peregrina, *Org. Lett.* **2015**, *17*, 5804. Sulfur: e) I. García-González, L. Mata, F. Corzana, G. Jiménez-Osés, A. Avenoza, J. H. Busto, J. M. Peregrina, *Chem. Eur. J.* **2015**, *21*, 1156.

[9] For selected recent examples, see: a) T. Fujino, Y. Goto, H. Suga, H. Murakami, *J. Am. Chem. Soc.* **2016**, *138*, 1962; b) D. F. Kreitler, D. E. Mortenson, K. T. Forest, S. H. Gellman, *J. Am. Chem. Soc.* **2016**, *138*, 6498.

[10] D. Seebach, A. K. Beck, S. Capone, G. Deniau, U. Grošelj, E. Zass, *Synthesis* **2009**, 1.

[11] S. Abele, D. Seebach, *Eur. J. Org. Chem.* **2000**, 1.

[12] Aldehydes: a) R. Kastl, H. Wennemers, *Angew. Chem. Int. Ed.* **2013**, *52*, 7228; *Angew. Chem.* **2013**, *125*, 7369. Indoles: b) J.-Q. Weng, Q.-M. Deng, L. Wu, K. Xu, H. Wu, R.-R. Liu, J.-R. Gao, Y.-X. Jia, *Org. Lett.* **2014**, *16*, 776; c) K. Mori, M. Wakazawa, T. Akiyama, *Chem. Sci.* **2014**, *5*, 1799. Malononitrile: d) S. Chen, Q. Lou, Y. Ding, S. Zhang, W. Hu, J. Zhao, *Adv. Synth. Catal.* **2015**, *357*, 2437. 3-Alkylidene oxindoles: e) Y. Zhong, S. Ma, Z. Xu, M. Chang, R. Wang, *RSC Adv.* **2014**, *4*, 49930. Arylboronic acids: f) J.-H. Fang, J.-H. Jian, H.-C. Chang, T.-S. Kuo, W.-Z. Lee, P.-Y. Wu, H.-L. Wu, *Chem. Eur. J.* **2017**, *23*, 1830.

[13] a) S. Jautze, R. Peters, *Synthesis* **2010**, 365; b) M. D. Diaz-de-Villegas, J. A. Gálvez, R. Badorrey, P. López Ram de Víu, *Adv. Synth. Catal.* **2014**, *356*, 3261.

[14] For catalytic asymmetric transformations of pyrrolidin-2,3-diones, followed by regioselective Bayer–Villiger oxidation, see: E. Badiola, I. Olaizola, A. Vázquez, S. Vera, A. Mielgo, C. Palomo, *Chem. Eur. J.* **2017**, *23*, 8185.

[15] J. W. Bode, *Acc. Chem. Res.* **2017**, *50*, 2104.

[16] a) H.-S. Lee, J.-S. Park, B. M. Kim, S. H. Gellman, *J. Org. Chem.* **2003**, *68*, 1575; b) T. Tite, M. Sabbah, V. Levacher, J.-F. Brière, *Chem. Commun.* **2013**, *49*, 11569; c) C. Berini, M. Sebban, H. Oulyadi, M. Sanselme, V. Levacher, J.-F. Brière, *Org. Lett.* **2015**, *17*, 5408.

[17] a) T. Ishikawa, K. Nagai, T. Kudoh, S. Saito, *Synlett* **1995**, 1171; b) S. A. Bentley, S. G. Davies, J. A. Lee, P. M. Roberts, A. J. Russell, J. E. Thomson, S. M. Toms, *Tetrahedron* **2010**, *66*, 4604.

[18] For catalytic asymmetric α-sulfanylation of isoxazolidin-5-ones, see: T. Cadart, C. Berthonneau, V. Levacher, S. Perrio, J.-F. Brière, *Chem. Eur. J.* **2016**, *22*, 15261.

[19] a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921.

[20] Seminal reports on Pd-catalyzed decarboxylative allylations: a) I. Shimizu, T. Yamada, J. Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199; b) T. Tsuda, Y. Chujo, S. Nishi, K. Tawara, T. Saegusa, *J. Am. Chem. Soc.* **1980**, *102*, 6381.

[21] a) J. D. Weaver, A. Recio III, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846; b) D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044; c) J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem., Int. Ed.* **2005**, *44*, 6924; *Angew. Chem.* **2005**, *117*, 7084; d) P. Starkov, J. T. Moore, D. C. Duquette, B. M. Stoltz, I. Marek, *J. Am. Chem. Soc.* **2017**, *139*, 9615; e) E. C. Burger, J. A. Tunge, *Org. Lett.* **2004**, *6*, 4113; f) B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 17180; g) B. M. Trost, J. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2009**, *131*, 18343; h) V. Franckevičius, J. D. Cuthbertson, M. Pickworth, D. S. Pugh, R. J. K. Taylor, *Org. Lett.* **2011**, *13*, 4264; i) J. James, P. J. Guiry, *ACS Catal.* **2017**, *7*, 1397.

[22] Y. Macé, A. R. Kapdi, I. J. S. Fairlamb, A. Jutand, *Organometallics* **2006**, *25*, 1795.

[23] a) J. W. Bode, R. M. Fox, K. D. Baucom, *Angew. Chem., Int. Ed.* **2006**, *45*, 1248; *Angew. Chem.* **2006**, *118*, 1270; b) T. G. Wucherpfennig, V. R. Pattabiraman, F. R. P. Limberg, J. Ruiz-Rodríguez, J. W. Bode, *Angew. Chem. Int. Ed.* **2014**, *53*, 12248; *Angew. Chem.* **2014**, *126*, 12445.

[24] T. Kinzel, Y. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14073.

[25] E. L. Tyson, Z. L. Niemeyer, T. P. Yoon, *J. Org. Chem.* **2014**, *79*, 1427.

[26] See the Supporting Information for details.

[27] M.-I. Aguilar, A. W. Purcell, R. Devi, R. Lew, J. Rossjohn, A. I. Smith, P. Perlmutter, *Org. Biomol. Chem.* **2007**, *5*, 2884.

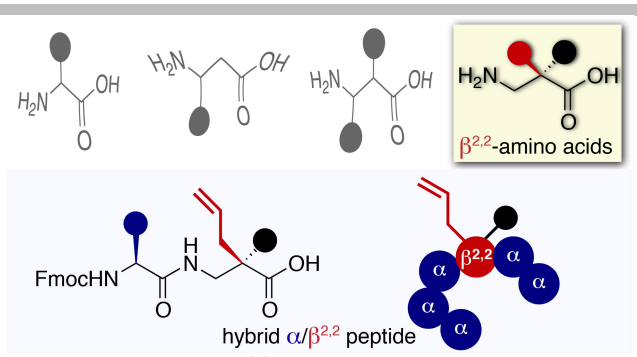
[28] F. Albericio, N. Kneib-Cordonier, S. Biancalana, L. Gera, R. I. Masada, D. Hudson, G. Barany, *J. Org. Chem.* **1990**, *55*, 3730.

[29] N. Krall, F. P. da Cruz, O. Boutureira, G. J. L. Bernardes, *Nat. Chem.* **2016**, *8*, 103.

10.1002/anie.201711143

WILEY-VCH

COMMUNICATION



Catalytic asymmetric synthesis of $\beta^{2,2}$-amino acids and their incorporation into hybrid α/β peptides are described.

Jin-Sheng Yu, Hidetoshi Noda, and Masakatsu Shibasaki**

Page No. – Page No.

Quaternary $\beta^{2,2}$-Amino Acids: Catalytic Asymmetric Synthesis and Incorporation into Peptides by Fmoc-Based Solid Phase Peptide Synthesis