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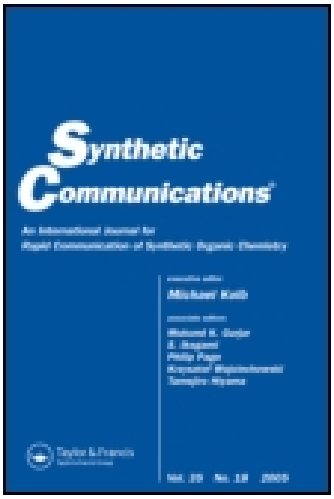

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Synthesis of the Southern Tripeptide (C_1-N_{12}) of Sanglifehrins Using Asymmetric Organocatalysis

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SYNTHESIS OF THE SOUTHERN TRIPEPTIDE (C_1–N_{12}) OF SANGLIFEHRINS USING ASYMMETRIC ORGANOCATALYSIS

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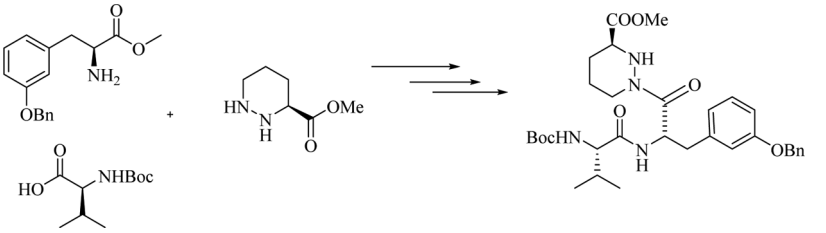
GRAPHICAL ABSTRACT



Abstract *The tripeptide southern region of the novel cyclophilin binding natural product macrolides, namely sanglifehrins, is synthesized involving asymmetric organocatalysis as chirality-inducing step. List's asymmetric α-amination was used in the synthesis of the m-hydroxyphenylalanine part, whereas α-hydrazination was used for the piperazic ester part.*

Keywords α-Amination; α-hydrazination; asymmetric organocatalysis; peptide coupling; tripeptide

INTRODUCTION

The immunosuppressive activity of cyclosporin A,[1a] FK 506, and rapamycin[1b] is attributed to immunophilin modulation, wherein the cyclosporin operates through cyclophilin binding.[1] Thus an exhaustive screening was initiated to identify novel natural products having cyclophilin binding properties. In this process, a novel class of macrolides has been isolated by Sanglier et al.[2] from actinomycete strains based on their affinity of binding to cyclophilin A, a cytosolic protein binding to cyclosporin. These macrolides are found to have 20-fold greater affinity to cyclophilin-A over the marketed drug cyclosporin A.

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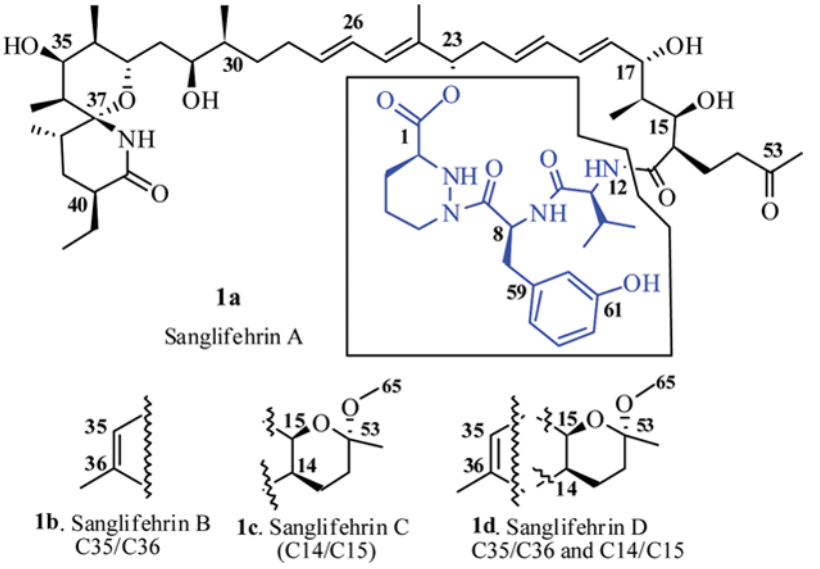

Figure 1. Structures of sanglifehrins A, B, C, and D.

Further, Kallen et al.[3] have provided mechanistic insights of this higher binding affinity through cocrystal studies and also observed that the piperazic acid moiety present in sanglifehrins is deeply buried in the hydrophobic cavity formed by the amino acids Phe^{60}, Met^{61}, Phe^{113}, and Leu^{122} of cyclophilin A.

The profound biological activities attributed to these macrolides[4] along with unprecedented type of structure having macrocyclic lactone core with two uncommon amino acids, (*S*)-3-carboxy-piperazine and (*S*)-*m*-tyrosine, naturally attracted interest from the synthetic organic chemistry community. To date, two total syntheses[5] and several partial syntheses[6] of sanglifehrin A **1a** (Fig. 1) are in print. The piperazic acids are common constituents of monamycins[7] whereas *m*-tyrosine has a profound role in probing the pathways in the central nervous system (CNS).[8] Our group has a long-term objective of evaluating the synthesis of natural products incorporating uncommon amino acids[9] and studying their biological activity. Towards this goal, we identified the southern tripeptide core of sanglifehrin A as a powerful privileged fragment for evaluating as a key synthon toward SAR studies. Herein, the synthesis of the C_1-N_{12} fragment **2** of sanglifehrins is presented using asymmetric organocatalysis, wherein chirality is introduced via (*R*)-proline.

RESULTS AND DISCUSSION

The classical retrosynthetic analysis of tripeptide **2** produced two synthetic fragments **3** and **5,** which in turn could be obtained from **6** and **7** through organocatalytic α-amination and α-hydrazination respectively (Scheme 1).

The synthesis of (*S*)-*m*-benzyloxy tyrosine methyl ester **(3)** is described in Scheme 2. The 3-(3-(benzyloxy)phenyl)propanal **(6)** was prepared following literature procedure from 3-hydroxybenzaldehyde.[10] The aldehyde **6** underwent a very

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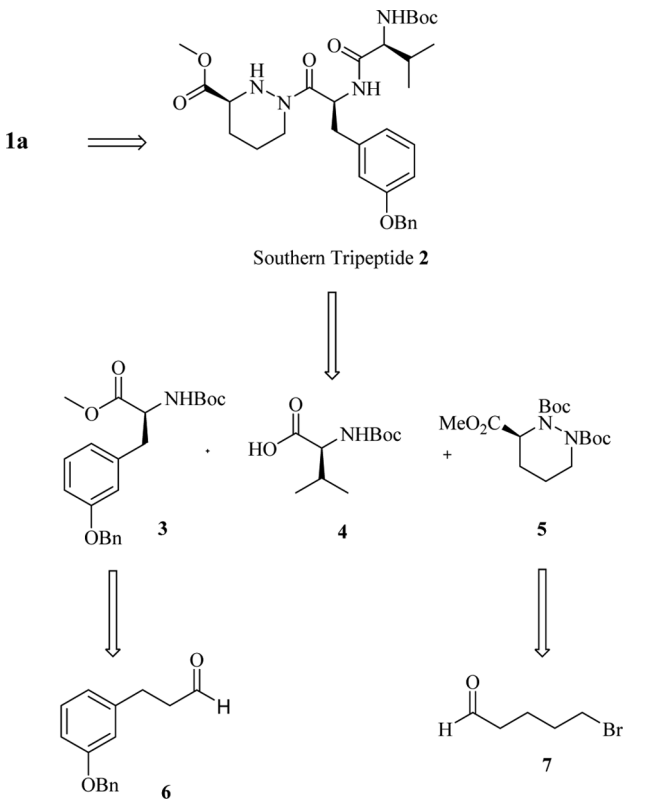
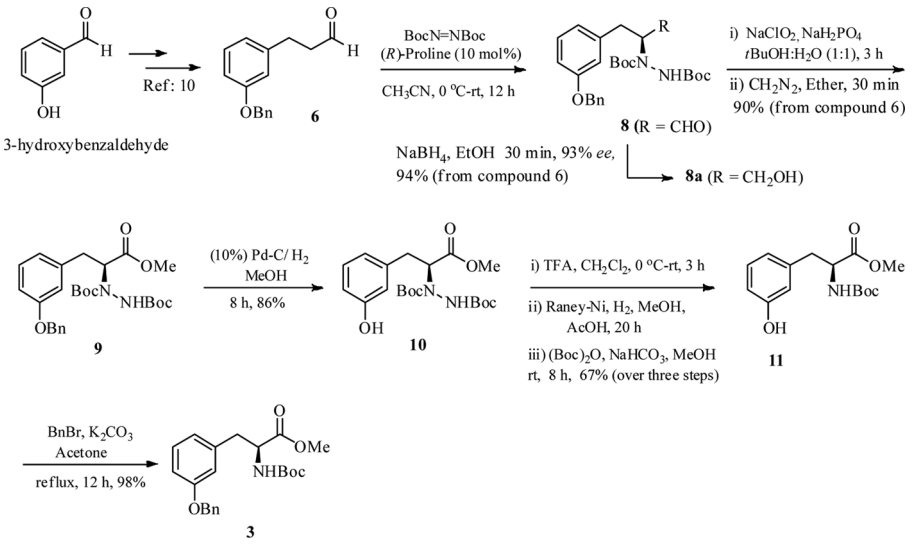


Scheme 1. Retrosynthetic analysis of tripeptide **2**.



Scheme 2. Synthesis of fragment **3**.

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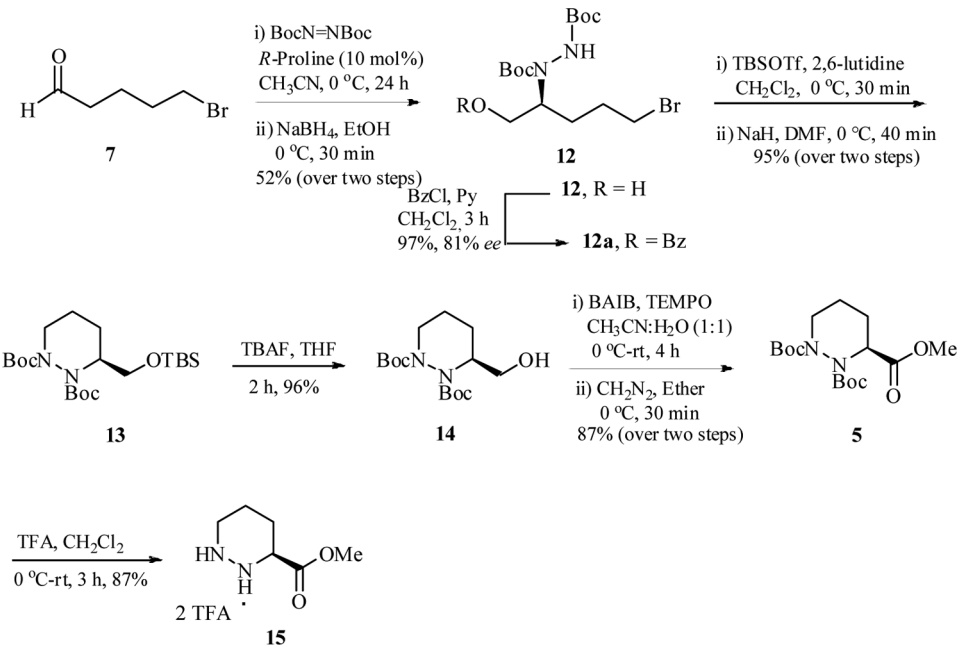
highly enantioselective organocatalytic α-amination[11] under List's conditions[11a] in the presence of (*R*)-proline (10 mol%) and di-*tert*-butyl azodicarboxylate to furnish hydrazino aldehyde **8,** which was reduced to **8a** using $NaBH_4$ for characterization. The *ee* of the product **8a** was determined to be 93%.[12] The hydrazino aldehyde **8** was oxidized to carboxylic acid, which was esterified immediately as methyl ester **9**. The catalytic hydrogenation of **9** furnished phenol **10** in 86% yield. The vicinal Boc groups on hydrazine **10** were knocked down with trifluoroacetic acid (TFA), which followed Raney–Ni hydrogenation to generate the amino ester, which was protected as a Boc amide **11**.[13] All these three transformations were carried out without engaging any purification steps with an overall yield of 67%. Rebenzylation of phenolic group in **11** was achieved in quantitative yields to furnish benzyl protected *meta*-tyrosine methyl ester **3**, for which the spectral data was matched with that reported.[14] A direct conversion of **9** to **11** was attempted, albeit in poor yields in the presence of Raney-Ni (Scheme 2).

(3*S*)-Methyl piperazate **15** was synthesized using organocatalytic α-hydrazination from 5-bromopentanal **7**, following the procedure reported by Hamada et al.,[15] except that (*R*)-proline (10 mol%) and di(Boc)-hydrazine were used to synthesize (*S*)-enantiomer. Thus, **7** on treatment with di(Boc)-hydrazine and (*R*)-proline[16] followed by $NaBH_4$ reduction furnished (*S*)-hydrazino alcohol **12**. The optical purity of **12** was determined as its benzoate ester **12a,** which was synthesized by treating **12** with BzCl and pyridine in 97% yield. The *ee* of the product **12a** was found to be 81%.[17] Exposure of **12** to TBSOTf and 2,6-lutidine followed by treatment with NaH provided piperazine derivative **13** in 95% yield for two steps. The silyl group in **13** was cleaved with TBAF to furnish alcohol **14** (96% yield),



Scheme 3. Synthesis of (3*S*)-methyl piperazate **15**.

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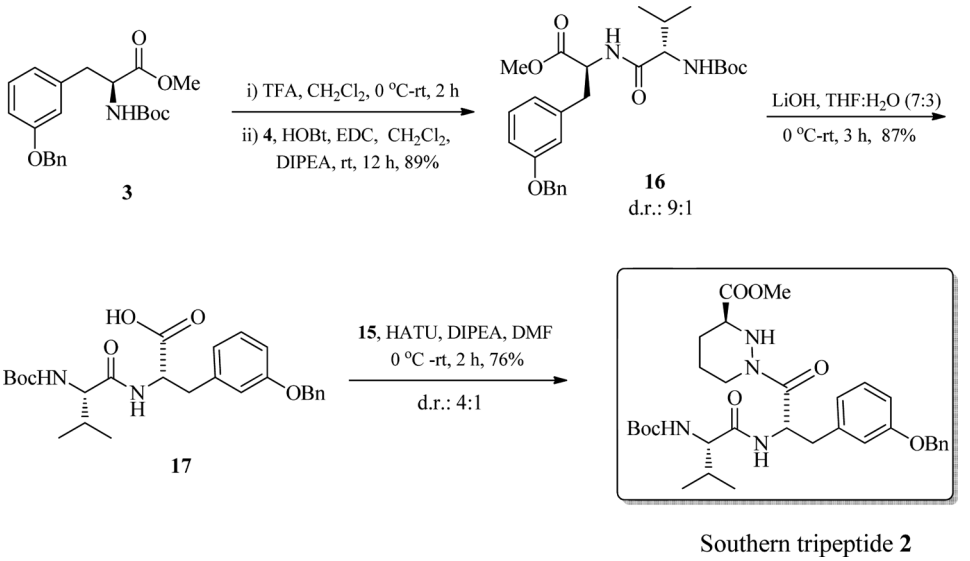

Scheme 4. Synthesis of southern tripeptide **2**.

which was oxidized to known methyl ester **5** in two steps (87% overall yield) and whose identity was fully confirmed.[6n] Exposure of **5** to TFA in CH_2Cl_2 furnished di-TFA salt of piperazic ester **15** (Scheme 3).

After establishing the synthetic procedures for the synthesis of uncommon amino acid derivatives **3** and **15**, compound **3** was exposed to TFA in CH_2Cl_2, which was further coupled with *N*-Boc (*S*)-valine **4** using HOBt (1-hydroxybenzotriazole) and EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) to furnish the required dipeptide **16** in 89% yield with excellent diastereoselectivity. The major diastereomer of the dipeptide was separated through column chromatography and subjected to hydrolysis with LiOH to furnish dipeptide acid **17** in 87% yield. Further, the dipeptide acid **17** was coupled selectively at N(1) of piperazic ester[5a,5b] **15** using HATU (*N,N,N′,N′*-tetramethyl-*O*-7-azabenzo-triazol-1-yluroniumhexafluorophosphate) and DIPEA to afford the fully and differentially protected desired tripeptide **2** (76% yield) in 4:1 diastereomeric ratio,[18] which was separated by silica-gel column chromatography. Spectral data are in agreement with the reported data[6g](Scheme 4).

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$/dimethylsulfoxide (DMSO) with 300-, 400-, 500-, or 700-MHz spectrometers at ambient temperature. Chemical shifts were measured in parts per million (ppm) and coupling constants in hertz (Hz); shifts were measured relative to the signals for residual $CHCl_3$ ($\delta = 7.26$ ppm), $CDCl_3$ ($\delta = 77.0$ ppm), DMSO ($\delta = 2.50$ ppm), and DMSO ($\delta = 39.43$ ppm). Optical rotations were measured with an Anton-Paar MCP 200 digital polarimeter by using a 1-mL cell and a 1-dm path length. FT-IR spectra were recorded as KBr discs or neat. High-resolution mass spectra (HRMS) were recorded with an Agilent Technologies

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6510 Q-TOF spectrometer. Technical-grade ethyl acetate and hexanes used for column chromatography were distilled prior to use.

Synthesis and Characterization Data of Southern Tripeptide 2[6g]

HATU (48 mg, 0.127 mmol) and DIPEA (0.06 mL, 0.37 mmol) were added to a solution of compound **17** (0.050 g, 0.01 mmol) in dry DMF (3 mL) at room temperature and stirred for 10 min. To this reaction mixture, compound **15** (16 mg, 0.01 mmol) in dry DMF (2 mL) was added and stirred for 2 h. The reaction mixture was diluted with ethyl acetate (20 mL), washed with brine (10 mL), and dried over sodium sulfate. The combined organic layer was concentrated under vacuo and purified through silica-gel column chromatography (100–200 mesh) to furnish required diastereomer **2** as a liquid (48 mg, 76%). $[\alpha]_D^{20} = -22.4$ ($c = 3.6$, MeOH). IR (KBr): $\tilde{\nu}_{max} = 3347$, 2950, 2923, 1699, 1440, 1219, 1115, 772 cm^{-1}. ^1H NMR (DMSO, 500 MHz): δ 7.66 (d, $J = 11.2$ Hz, 1H), 7.46–7.31 (m, 5H), 7.16 (m, 1H), 7.04–6.73 (m, 3H), 6.58 (d, $J = 9.4$ Hz, 1H), 5.55–5.41 (m, 1H), 5.07–4.98 (m, 2H), 3.78 (s, 3H), 3.76–3.72 (m, 1H), 3.69–3.56 (m, 1H), 3.15 (br, 1H), 2.99–2.93 (dd, $J = 13.2$, 3.5 Hz, 1H), 2.73–2.65 (dd, $J = 8.3$, 12.1 Hz, 1H), 2.47–2.41 (m, 1H), 1.91–1.83 (m, 1H), 1.80–1.72 (m, 1H), 1.70–1.47 (m, 3H), 1.35 (s, 9H), 0.76–0.72 (m, 6H) ppm. ^{13}C NMR (DMSO, 125 MHz): δ 171.4, 171.3, 170.5, 158.1, 155.2, 139.2, 137.0, 128.9, 128.3, 127.7, 127.5, 121.7, 115.7, 112.4, 78.0, 68.9, 59.9, 52.0, 51.6, 49.5, 40.4, 38.2, 30.3, 28.0, 22.0, 19.1, 19.0, 18.0 ppm. HRMS (ESI): calcd. for $C_{32}H_{45}N_4O_7$ $[M+H]^+$ 597.3282; found 597.3281.

CONCLUSION

In conclusion, organocatalytic asymmetric α-amination and hydrazination have been utilized to build the privileged tripeptide fragment of sanglifehrins.

FUNDING

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SUPPLEMENTAL MATERIAL

Full experimental details, ^1H and ^{13}C NMR, HPLC, and HRMS reports of all the compounds for this article can be accessed on the publisher's website.

REFERENCES

1. (a) For cyclophilin binding of cyclosporin A, see Handschumacher, R. E.; Harding, M. W.; Rice, J.; Drugge, R. J.; Speicher, D. W. *Science.* **1984**, *226*, 544–547; (b) for FK BP binding of FK 506 and rapamycin, see Siekierka, J. J.; Hung, S. H. Y.; Poe, M.; Lin, C. S.; Sigal, N. H. *Nature.* **1989**, *341*, 755–757.

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2. (a) Sanglier, J. J.; Quesniaux, V.; Fehr, T.; Hofmann, H.; Mahnke, M.; Memmert, K.; Schuler, W.; Zenke, G.; Gschwind, L.; Maurer, C.; Schilling, W.; *J. Antibiot.* **1999**, *52*, 466–473; (b) Fehr, T.; Kallen, J.; Oberer, L.; Sanglier, J. J.; Schilling, W. *J. Antibiot.* **1999**, *52*, 474–479.
3. Kallen, J.; Sedrani, R.; Zenke, G.; Wagner, J. *J. Biol. Chem.* **2005**, *280*(23), 21965–21971.
4. Zhang, L. H.; Liu, J. O. *J. Immunol.* **2001**, *166*, 5611–5618.
5. (a) Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Ohshima, T.; Wei, H.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc.* **2000**, *122*, 3830–3838; (b) Paquette, L. A.; Duan, M.; Konetzki, I.; Kempmann, C. *J. Am. Chem. Soc.* **2002**, *124*, 4257–4270.
6. (a) Nicolaou, K. C.; Ohshima, T.; Murphy, F.; Barluenga, S.; Xu, J.; Winssinger, N. *Chem. Commun.* **1999**, 809–810; (b) Nicolaou, K. C.; Xu, J.; Murphy, F.; Barluenga, S.; Baudoin, O.; Wei, H.-X.; Gray, D. L. F.; Ohshima, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 2447–2451; (c) Paquette, L. A.; Konetzki, I.; Duan, M. *Tetrahedron Lett.* **1999**, *40*, 7441–7444; (d) Duan, M.; Paquette, L. A. *Tetrahedron. Lett.* **2000**, *41*, 3789–3792; (e) Duan, M.; Paquette, L. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 3632–3636; (f) Cabrejas, L. M. M.; Rohrbach, S.; Wagner, D.; Kallen, J.; Zenke, G.; Wagner, J. *Angew. Chem. Int. Ed.* **1999**, *38*, 2443–2446; (g) Banteli, R.; Brun, L.; Hall, P.; Metternich, R. *Tetrahedron Lett.* **1999**, *40*, 2109–2112; (h) Metternich, R.; Denni, D.; Thai, B.; Sedrani, R. *J. Org. Chem.* **1999**, *64*, 9632–9639; (i) Wagner, J.; Cabrejas, L. M. M.; Grossmith, C. M.; Papageorgiou, C.; Senia, F.; Wagner, D.; France, J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 9255–9260; (j) Hall, P.; Brun, J.; Denni, D.; Metternich, R. *Synlett.* **2000**, 315–318; (k) Gurjar, M. K.; Chaudhuri, S. R. *Tetrahedron Lett.* **2002**, *43*, 2435–2438; (l) Sedrani, R.; Kallen, J.; Cabrejas, L. M. M.; Papageorgiou, C. D.; Senia, F.; Rohrbach, S.; Wagner, D.; Thai, B.; Eme, A. M. J.; France, J.; Oberer, L.; Rihs, G.; Zenke, G.; Wagner, J. *J. Am. Chem. Soc.* **2003**, *125*, 3849–3859; (m) Dias, L. C.; Salles Jr., A. G. *Tetrahedron Lett.* **2006**, *47*, 2213–2216; (n) White, J. D.; Suttisintong, K. *J. Org. Chem.* **2013**, *78*, 2757–2762; (o) Yadav, J. S.; Raghavendra Rao, K. V.; Kavitha, A.; Mohapatra, D. K. *Eur. J. Org. Chem.* **2013**, 2849–2858.
7. (a) Bevan, K.; Davies, J. S.; Hassall, C. H.; Morton, R. B.; Phillips, D. A. S. *J. Chem. Soc.* **1971**, 514–522 (b) Hassall, C. H.; Johnson, W. H.; Theobald, C. J. *J. Chem. Soc. Perkin Trans. 1.* **1979**, 1451–1458.
8. Bender, D. M.; Williams, R. M. *J. Org. Chem.* **1997**, *62*, 6690–6691.
9. (a) Chandrasekhar, S.; Kavitha, N.; Kumar, V. P. *Tetrahedron Lett.* **2013**, *54*, 2128–2130; (b) Chandrasekhar, S.; Satish, K.; Reddy, G. P. K.; Mainkar, P. S. *Tetrahedron: Asymmetry.* **2011**, *22*, 1568–1573; (c) Chandrasekhar, S.; Mahipal, B.; Kavitha, M. *J. Org. Chem.* **2009**, *74*, 9531–9534 (d) Chandrasekhar, S.; Lohitha Rao, Ch.; Seenaiah, M.; Naresh, P.; Jagadeesh, B.; Manjeera, D.; Arpita, S.; Bhadra, M. P. *J. Org. Chem.* **2009**, *74*, 401–404; (e) Chandrasekhar, S.; Chandrasekhar, G. *Tetrahedron: Asymmetry.* **2005**, *16*, 2209–2214; (f) Chandrasekhar, S.; Raza, A.; Takhi, M. *Tetrahedron: Asymmetry.* **2002**, *13*, 423–428.
10. Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron.* **1994**, *50*(41), 11945–11966.
11. For organocatalytic α-amination, see (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657; (b) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790–1793; (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255; (d) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun.* **2003**, 2448–2449.
12. Enantiomeric excess was determined by chiral HPLC (CHIRAL PAK-IA; 250 × 4.6 mm, 5U, Mobile phase: 20% IPA in hexane, flow rate: 1 mL/min, detection: 210 nm; major t_R 6.696 min, minor t_R 17.432 min.
13. (a) Kotkar, S. P.; Sudalai, A. *Tetrahedron: Asymmetry.* **2006**, *17*, 1738–1742; (b) Udodong, U. E.; Fraser-Reid, B. *J. Org. Chem.* **1989**, *54*, 2103–2112.

14. Wang, W.; Xiong, C.; Zhang, J.; Hruby, J. *Tetrahedron.* **2002**, *58*, 3101–3110.
15. Henmi, Y.; Makino, K.; Yoshitomi, Y.; Harab, O.; Hamada, Y. *Tetrahedron: Asymmetry.* **2004**, *15*, 3477–3480.
16. Chen, Y.; Lu, Y.; Zou, Q.; Chen, H.; Ma, D. *Org. Process Res. Dev.* **2013**, *17*, 1209–1213.
17. Enantiomeric excess of **12a** was determined by chiral HPLC (CHIRALCEL-OD-H; 250×4.6 mm, 5U, mobile phase: 5% IPA in hexane, flow rate: 0.75 mL/min, minor t_R 7.467 min, major t_R 8.291 min.
18. Diastereomeric excess was determined by HPLC analysis. Column: Atlantis dc18, 150×4.6, 5U; mobile phase: 60% ACN in H_2O (0.1% FA); detection: 210 nm; flow rate: 1.0 mL/min; major isomer t_R 9.23 min, minor isomer t_R 9.71 min.

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