Palladium-catalyzed heteroannulation approach to 7-azatryptophan with a Schöllkopf chiral auxiliary

Moon Bae Gee, Tae Seung Kim, and Eul Kgun Yum*

Department of Chemistry, Chungnam National University, Taejeon 305-764, Korea.
**E-mail: ekyum@cnu.ac.kr*
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The azaindole moiety, a bioiosostere of the indole nucleus, possesses remarkable physicochemical and pharmacological properties and has attracted considerable interest from the chemistry community.[1] Azaindole alters the electronic properties of the π-system, making such heteroaromatic rings less reactive than indoles toward electrophilic reagents. Consequently, direct functionalization at the C_3 position of an azaindole with electrophiles is not as straightforward as for indoles.[2] Although Robison *et al.*[3] described the synthesis of racemic 7-azatryptophan via 3-(*N*-dimethyl-aminomethyl)-7-azagramine in 1955, only a few other general synthetic procedures for azatryptophans have been reported.[2,4]

Recently, 7-azatryptophans have been reported to have potential as probes of protein structure and dynamics, especially for investigating protein–protein interactions,[5] in which one of the proteins involved may contain several tryptophan residues. The fluorescence emission spectra of 7-azatryptophan are significantly red-shifted from those of tryptophan due to the interaction of the 1-nitrogen of 7-azaindole with the solvent.[6]

The asymmetric preparation of 7-azatryptophan has been reported only from racemic 7-azatryptophan with chemical and chemoenzymatic methods. The first enantioselective resolution of (*R*)-7-aztryptophan was published in 1992 by Fallis *et al*. via alkylation of the (1*R*, 4*R*)-camphor imine of *tert*-butylglycinates.[7] The diastereoisomeric excess (de) was >98%, but the alkylation yield was very low. The other one was chemoenzymatic resolution of the two enantiomers with *Aspergillus* genus acylase, reported by Rolland-Fulcrand.[8]

Schöllkopf *et al*. demonstrated a particularly useful enantioselective amino acid synthetic method using L-valine as a chiral agent.[9] The Schöllkopf chiral auxiliary can be prepared readily from D- or L-valine and glycine on a large scale and is now available commercially in both enantiomeric forms.[10] Cook *et al*. reported an excellent diastereoselective, propargyl-substituted Schöllkopf chiral auxiliary.[11] They also reported the efficient asymmetric synthesis of biologically active tryptophans[12] with our palladium-mediated heteroannulation.[13] As part of our continuing organometallic approach to biologically active heterocycles, such as indoles, azaindoles, and carbazoles,[14] we examined the synthesis of 7-azatryptophan via our palladium-mediated heteroannulation with a Schöllkopf chiral auxiliary.

Results and Discussion

Larock and our group reported an excellent method for the preparation of indoles and azaindoles involving palladium-catalyzed heteroannulation of internal alkynes using *o*-iodoarylamines.[13] Although the synthetic method has been used to prepare optically active tryptophan derivatives, it has not been applied to optically active 7-azatryptophan. Our previous results on heteroannulation with unprotected 2-amino-3-iodopyridine and internal alkynes showed very low yields of the annulated product.[13c] The synthetic limitation could be due to the low nucleophilicity of the nitrogen that exists in the three tautomeric forms of 2-amino-pyridine (Scheme 1) or to the easy formation of a palladium complex with 2-aminopyridine.

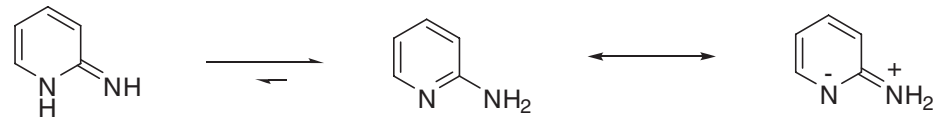
First, we examined the synthesis of the azaindole precursor, followed by reaction with a Schöllkopf chiral auxiliary (Scheme 2).

The heteroannulation of 2-amino-3-iodopyridine with an internal alkyne gave low yields of the annulated products. *N*-Benzylamino-3-iodopyridine, instead of 2-amino-3-iodo pyridine, was used to improve the heteroannulation and to allow easy deprotection of the benzyl group. The heteroannulation reaction of *N*-benzyl-2-amino-3-iodopyridine (**1**) with 3-trimethylsilyl-2-propyn-1-ol (**2**) provided a 71% yield of product **3**. The Schöllkopf chiral auxiliary (**4**), derived from L-valine and glycine, was prepared readily using a published procedure.[9] Metallation of the Schöllkopf chiral auxiliary (**4**) with *n*-BuLi in THF at –78 °C, followed by alkylation with protected methansulfonoxy-2-trimethylsilyl-1-benzyl-7-azaindole, provided a 65% yield of **5** with 5:1 (*trans*:*cis*) diastereoselectivity.

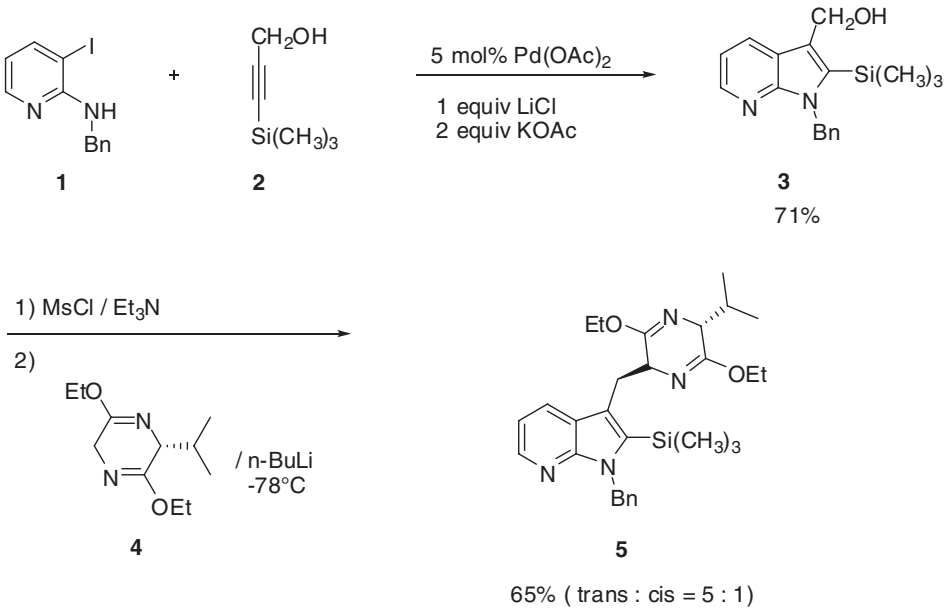
Due to the low diastereoselectivity in Scheme 2, we decided to use a direct palladium-catalyzed heteroannulation with **1** and internal alkyne-substituted Schöllkopf chiral auxiliary (**6**) (Scheme 3)

The heteroannulation provided the desired annulated product **5** in 60% yield, along with an uncyclized Sonogawasihra coupling product. After purifying product **5** by column chromatography, it was converted to 7-aza-tryptophan according to Scheme 4.

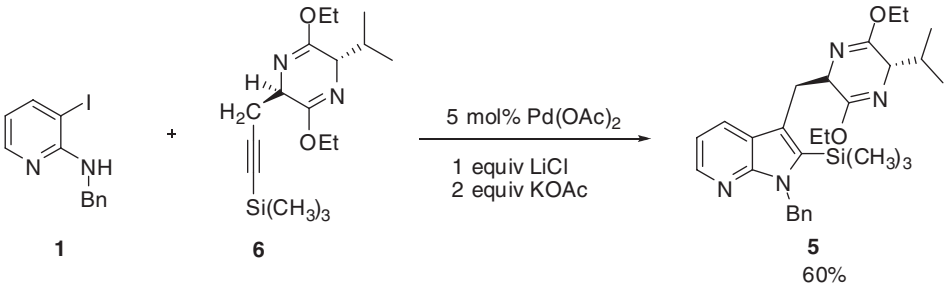
The Schöllkopf chiral auxiliary moiety of **5** was hydrolyzed to the amino acid ethyl ester (**7**) with 2 *N* HCl in THF. After desilylation with *n*-Bu_4NF/THF, the hydrolysis of 7-



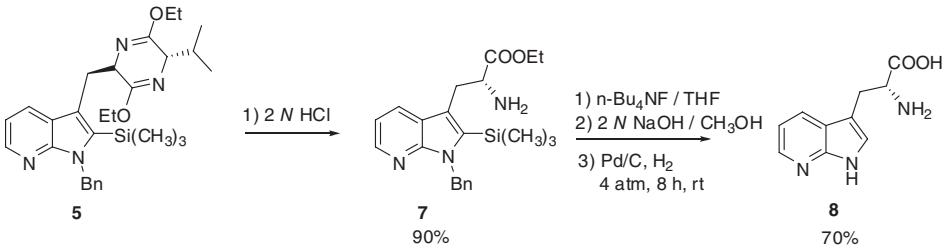
Scheme 1. Tautomeric forms of 2-aminopyridine.



Scheme 2. Intermolecular coupling with azaindole precursor and Schöllkopf chiral auxiliary.



Scheme 3. Heteroannulation with internal alkyne substituted Schöllkopf chiral auxiliary.



Scheme 4. Hydrolysis and debenzylation for 7-azatryptophan.

azatryptophan ethyl ester (**5**) was performed with 2 *N* NaOH/ethanol solution for 2 h under refluxing conditions. Then, debenzylation under 10% Pd/C provided the optically active 7-azatryptophan (**8**) with 70% yield and 81% ee.

Conclusions

A palladium-catalyzed heteroannulation with internal alkyne-substituted Schöllkopf chiral auxiliary provided optically active

7-azatryptophan. This synthetic method could be applied to optically active 1-substituted azatryptophan because of the easy preparation of various *o*-iodo-aminopyridines and commercially available (*R*)-and (*S*)-enantiomeric Schöllkopf chiral auxiliary.

Experimental

The ^{1}H NMR spectra were obtained on a Varian Gemini 200 (Varian. Inc. Korea) and a Jeol 400 MHz spectrometers (JEOL., Ltd. Japan). ^{13}C NMR spectra were recorded on a Jeol 400 MHz (100 MHz) spectrometer, and chemical shifts were referenced to tetramethylsilane (TMS) as an internal standard. Gas chromatography-mass spectrometry (GC-MS) results were obtained using a Shimadzu QP 1000 instrument (Shimadzu Co., Japan). LC-MS spectra were obtained on a LCQ Deca XP ion-trap MS. Products were purified by flash chromatography on 230–400 mesh ASTM 60 silica gel. HPLC analysis of 7-azatryptophan enantiomers was performed with an Astec Chirobiotic T column (Sigma-Aldrich, Korea) with a UV 210 nm detector. All base and palladium species were purchased from Sigma-Aldrich Chemical Co. Chemicals were used directly as obtained from commercial sources unless otherwise noted.

2-*N*-Benzylamino-3-iodopyridine (**1**)[13c]

2-Fluoro-3-iodopyridine was heated at 140 °C for 10 h in a sealed tube with excess benzylamine. Extraction of the mixture by Et_2O, drying over $MgSO_4$, solvent removal, and column chromatography over silica gel using hexane/ethyl acetate (10:1) afforded 2-benzylamino-3-iodopyridine as a yellow solid. ^{1}H NMR (200 M Hz, $CDCl_3$) δ 8.05 (dd, 1H, J = 4.4, 1.6 Hz), 7.75 (dd, 1H, J = 7.4, 1.5 Hz), 6.25 (dd, 1H, 7.6, 1.5 Hz), 4.94 (br, 1H), 2.95 (d, 3H, J = 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 147.3, 146.1, 139.0, 128.3, 128.0, 127.5, 126.9, 114.0, 46.0.

3-Hydroxymethyl-2-trimethylsilyl-1-benzylpyrrolo[2,3-*b*] pyridine (**3**)[13c]

Palladium acetate (0.25 mmol), lithium chloride (1 mmol), potassium acetate (2.0 mmol), 3-iodo-2-(benzylamino) pyridine (1 mmol), 3-(trimethylsilyl)-2-propyn-1-ol (2.0 mmol), and DMF (10 mL) were added to a tube and sealed. After heating for 8 h at 100 °C, the reaction mixture was diluted with saturated aqueous ammonium chloride and water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by silica gel column chromatography using hexane/ethyl acetate. The compound (**3**) was obtained as a yellow oil in 71% isolated yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 8.30 (dd, 1H, J = 4.5 Hz, J = 1.4 Hz), 8.05 (dd, 1H, J =7.8 Hz , 1.4 Hz), 7.26-7.15 (m, 3H), 7.05 (dd, 1H, J =7.8 Hz, 1.5 Hz), 6.75 (m, 2H), 5.71 (s, 2H), 4.95 (s, 2H), 1.90 (br, 1H), 0.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 143.9, 138.9, 128.3, 127.9, 127.0, 126.7, 125.3, 123.2, 120.5, 115.7, 63.6, 56.3, 47.0, 1.0; MS (*m/e*) 310 (M^+), 309, 293, 91 (100).

(*3S*) -Isopropyl-2,5-diethoxypyrazine (**4**)[9c]

To a stirred solution of triethoxyloxonium tetrafluoroborate (38.4 g, 0.2 mol) in methylene chloride (300 mL) was added (3*S*)-isopropyl-2,5-diketopiperazine (11.5 g, 0.075 mol). After 2 h, the reaction mixture became homogeneous. The reaction was stirred at room temperature under nitrogen for 72 h. $NaH_2PO_4{\cdot}7H_2O$ (20 g, 0.15 mol) and $Na_2HPO_4{\cdot}7H_2O$ (23.5 g, 0.9 mol) were dissolved in 750 mL of water, and the buffer solution was added to the organic solution with stirring. The organic phase was separated, and the aqueous phase was re-extracted with CH_2Cl_2 (3 ×100 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated the solvents. The residue was vacuum-distilled at 10 Torr/90 °C. The product was obtained in 78% yields. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.06 (m, 4H), 3.77 (m, 3H), 2.14 (m, 1H), 1.19 (m, 6H), 0.96 (d, 3H J = 6.8 Hz), 0.67 (d, 3H, J = 6.8 Hz), 0.84 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 162.0, 61.1, 60.8, 46.9, 32.7, 19.1, 17.1, 14.4; MS (EI) *m/e* (rel. intensity) 213 (M^+, 100).

(3*R*,6*S*)-3-[1-Benzyl-2-trimethylsilyl-3-azaindolyl] methyl-3,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (**5**)

2-(Benzylamino)-3-iodopyridine 450 mg (1.5 mmol), LiCl 62 mg (1.5 mmol), potassium acetate 285 mg (3.0 mmol), $Pd(OAc)_2$ 16 mg (0.07 mmol, 5 mol%), (2*S*,5*R*)-3,6-di-ethoxy-2-isopropyl-5-[3-(trimethylsilyl)-prop-2-ynyl] -2,5-dihydropyrazine 620 mg (2.0 mmol), and DMF (10 mL) were added to a tube and sealed. The resulting solution was stirred for 8 h at 120 °C in an oil bath. The reaction mixture was diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The ethyl acetate layer was dried over $MgSO_4$, filtered, and concentrated. The product was purified by silica gel column chromatography using hexane/ethyl acetate (1:1) as eluent. The product (**5**) was obtained in 60% yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, 1H, J = 8.0 Hz,), 8.33 (t, 1H, J = 8.0 Hz), 7.35–7.25(m, 5H), 6.81 (d, , 1H, J = 8.0 Hz), 5.79 (s, 2H), 4.39 (m, 4H), 4.10 (m, 1H), 3.90 (m, 1H), 3.35 (m, 1H), 2.30 (m, 1H), 1.35–1.10 (m, 10H), 1.08 (t, 3H, J = 8.0 Hz), 0.30 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.0, 160.8, 151.4, 144.2, 140.7, 139.4, 130.6, 129.5, 128.0, 126.7, 126.6, 123.4, 122.9, 116.2, 62.5, 60.9, 59.5, 33.6, 33.1, 30.7, 23.7, 18.4, 17.1, 14.4, 1.6. MS-ESI (*m/z*) 518.3.

(*2S,5R*)-3,6-Diethoxy-2-isopropyl-5-[3-(trimethylsilyl)-prop-2-ynyl]-2,5-dihydropyrazine (**6**)[12f]

To a solution of (*2S*)-3,6 diethoxy-2-isopropyl-2,5-dihydropyrazole (0.83 g, 3.9 mmol) in dry THF (25 mL) under nitrogen was added *n*-BuLi (2.5 M, 1.72 mL, 4.3 mmol) dropwise at −78 °C. The resulting solution was stirred at −78 °C for 30 min. The solution of diphenyl-3-(trimethyl-silyl) prop-2-ynyl phosphate (1.4 g, 3.9 mmol) in dry THF (20 mL) was added slowly to the lithiated chiral auxiliary solution, which was precooled at −78 °C. The reaction mixture was stirred for 6 h at −78 °C and quenched with ethanol. The resulting solution was removed with THF under reduced pressure, and 60 mL of ethyl ether was added. The ethyl ether was separated, and the aqueous layer was extracted with ethyl ether (2 × 30 mL). The combined ethyl ether was dried with $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by chromatography with hexane/ethyl acetate (20:1). The desired

product was obtained in 80% yield as an oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.05 (m, 5H), 3.87 (t, 1H, J = 3.4 Hz), 2.63 (m, 2H), 2.20 (m, 1H), 1.19 (m, 6H), 0.95 (d, 3H, J = 6.9 Hz), 0.61 (d, 3H, J = 6.8 Hz), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.2, 103.6. 86.6, 61.0, 60.8, 60.7, 54,6 31.6, 26.6, 19.2, 16.7, 14.8, 14.4, 0.4; MS (EI) *m/e* (rel. intensity) 322 (M^+, 13), 294(8), 279 (13) 211 (74), 169 (100).

1-Benzyl-2-trimethylsilyl-azatryptophan ethyl ester (**7**)

(3*R*,6*S*)-3-[1-Benzyl-2-trimethylsilyl-3-azaindolyl] methyl-2,6-dihydro-6-isopropyl-2,5-diethoxypyrazine (251 mg, 0.5 mmol) was dissolved in THF (20 mL). The optically active solution was cooled at −78 °C and slowly added to a solution of aqueous 2 *N* HCl (aq. 12 *N* HCl: ethanol = 1: 5). The mixture was allowed to warm to 0 °C and stirred for 2 h. Twenty milliliters of ice water was added to the solution, and pH of the reaction mixture was adjusted to 8 with aqueous concentrated NH_4OH solution at 0 °C. The mixture was then extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified by flash chromatography with hexane/EtOAc (1:1) giving 90% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, 1H, J = 8.0 Hz), 8.00 (dd, 1H, J = 8.0 Hz,), 7.35-7.25(m, 3H), 7.05 (d, 1H, J = 8.0 Hz), 6.75 (d, 1H, J = 8.0 Hz), 5.79 (s, 2H), 4.13 (m, 2H), 3.75(m, 1H), 3.34 (m, 1H), 3.13 (m, 1H), 2.30 (brs, 2H), 1.15 (m, 3H), 0.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 148.9, 142.7, 142.5, 137.5, 136.2, 127.1, 127.0, 125.9, 125.8, 125.4, 125.3, 124.0, 123.9, 119.3, 118.2, 114.0, 59.5, 55.1, 45.8, 30.3, 12.3, 0.11. MS-ESI (*m/z*) 396.5 (M + 1).

(*R*)-7-azatryptophan (**8**)[8]

1-Benzyl-2-trimethylsilyl-azatryptophan ethyl ester (181 mg, 0.5 mmol) was dissolved 2 mL of 1 *N* n-Bu_4NCl/THF and stirred 1 h at room temperature. The 2 *N* aqueous NaOH (1.0 mL)/ethanol (1.5 mL) was added to resulting solution, which was heated to 50 °C for 2 h. The progress of reaction was checked by TLC with disappeared and new material was on the base. The pH of resulting mixture was adjusted to 8 with the addition of NH_4OH. Most of the ethanol was removed under reduced pressure. The desilylated product was debenzylated with 10% Pd/C with 10 mL of ethanol solution under 4 atm for 8 h at room temperature. After removal of Pd with a silica filter, the solution was cooled and recrystallized from ethanol/water. 7-Azatryptophan was obtained with 70% yield (ee = 81%, Chiral HPLC with water/ethanol = 70:30). Mp = 261–263 °C. ^{1}H NMR (D_2O) δ 8.70 (dd, 1H, J = 8.0 Hz, J = 1.0 Hz), 8.50 (dd, 1H, J = 6.0 Hz,1.0 Hz), 7.57 (s,1H), 7.66 (dd, 1H J = 7.6 Hz, 6.2 Hz), 4.30 (t, 1H, J = 6.2 Hz), 3.60 (d, 2H, J = 6.2 Hz). MS-ESI (*m/z*) 205.2 (M+).

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References

1. (a) J. J. Song, J. T. Reeves, F. Gallou, Z. Tan, N. K. Yee, C. H. Senuanayake, *Chem. Soc. Rev.* **2007**, *36*, 1120; (b) J. Y. Merour, B. Joseph, *Curr. Org. Chem.* **2001**, *5*, 471, and references therein; (c) F. Popowycz, S. Routier, B. Joseph, J. Y. Merour, *Tetrahedron* **2007**, *63*, 1031; (d) F. Popowycz, J. Y. Merour, B. Joseph, *Tetrahedron* **2007**, *63*, 8689.
2. I. Jeanty, F. Suzenet, G. Guillaument, *J. Org. Chem.* **2008**, *73*, 7390 , and references therein.
3. M. M. Robinson, B. L. Robinson, *J. Am. Chem. Soc.* **1955**, *77*, 457.
4. F. Crestey, V. Collot, S. Stiebing, J.-F. Lohier, J. S. Oliverira Santos, S. Rault, *Tetrahedron Lett.* **2007**, *48*, 2457, and references therein.
5. (a) A. R. Offenbacher, C. V. Pagba, B. C. Polander, U. Brahmachari, B. A. Barry, *ACS Chem. Biol.* **2014**, *9*, 891 , and references therein; (b) M. G. Hoesl, M. Larregola, H. Cui, N. J. Budisa, *Pept. Sci.* **2010**, *16*, 589, and reference therein.; (c) C.-V. Wong, M. R. Eftink, *Protein Sci.* **1997**, *6*, 689; (d) K. Josephson, C. T. Hartman, J. W. Szostak, *J. Am. Chem. Soc.* **2005**, *127*, 11727; (e) S. Lepthien, B. Wiltschi, B. Bolic, N. Budisa, *Appl. Microbiol. Biotechol.* **2006**, *73*, 740; (f) M. Björklund, E. Koivunen, *Lett. Drug Des. Discov.* **2004**, *1*, 163; (g) S. Lepthien, M. G. Hoesl, L. Merkel, N. Budisa, *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 16095.
6. (a) R. L. Rich, A. V. Smirnov, A. W. Schwabacher, J. W. Petrich, *J. Am. Chem. Soc.* **1995**, *117*, 11850.
7. R. S. Obregon, A. Fallis, A. G. Szabo, *Can. J. Chem.* **1992**, *70*, 1531.
8. L. Lecointe, V. Rolland-Fulcrand, M. L. Roumestant, P. Villefont, J. Martinez, *Tetrahedron: Asymmetry* **1998**, *9*, 1753.
9. (a) U. Schölkopf, U. Groth, C. Deng, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 798; (b) U. Schöllkopf, R. Lonsky, P. Lehr, *Liebigs Ann. Chem.* **1985**, *2*, 413; (c) P. Zhang, J. M. Cook, *Synthetic Commun.* **1998**, *25*, 3883.
10. (a) J. Chen, P. Corbin, N. Holman, *Org. Process Res. Dev.* **2005**, *9*, 165; (b) A.-C. Carlsson, F. Jam, M. Tullberg, A. Pilotti, P. Ioannidis, K. Luthman, M. Grtli, *Tetrahedron Lett.* **2006**, *47*, 5199.
11. (a) C. Ma, X. Liu, S. Zhao, J. M. Cook, *Tetrahedron Lett.* **1999**, *40*, 657; (b) C. Ma, X. He, S. Yu, S. Zhao, J. M. Cook, *Tetrahedron Lett.* **1999**, *40*, 2917.
12. (a) R. Liu, P. Zhang, T. Gan, J. M. Cook, *J. Org. Chem.* **1997**, *62*, 7447; (b) C. Ma, S. Yu, X. He, X. Liu, J. M. Cook, *Tetrahedron Lett.* **2000**, *41*, 42781; (c) J. Ma, W. Yin, H. Zhou, J. M. Cook, *Org. Lett.* **2007**, *9*, 3491; (d) H. Zhou, X. Liao, J. M. Cook, *Org. Lett.* **2004**, *6*, 249; (e) S. Zhau, K. S. Smith, A. M. Deveau, C. M. Dieckhaus, M. A. Johnson, T. L. Macdonald, J. M. Cook, *J. Med. Chem.* **2002**, *45*, 1559; (f) C. Ma, X. Liu, X. Li, J. Flippen-Anderson, S. Yu, J. M. Cook, *J. Org. Chem.* **2001**, *66*, 4525; (g) X. Li, W. Yin, P. V. V. Sarma, H. Zhou, J. Ma, J. M. Cook, *Tetrahedron Lett.* **2004**, *45*, 8569.
13. (a) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689; (b) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652; (c) S. S. Park, J. K. Choi, E. K. Yum, D. C. Ha, *Tetrahedron Lett.* **1998**, *39*, 627.
14. (a) S. M. Chi, J. K. Choi, E. K. Yum, D. Y. Chi, *Tetrahedron Lett.* **2000**, *41*, 919; (b) K. B. Hong, C. W. Lee, E. K. Yum, *Tetrahedron Lett.* **2004**, *45*, 693; (c) C. S. Hong, J. Y. Seo, E. K. Yum, *Tetrahedron Lett.* **2007**, *48*, 4831; (d) J. K. Kwon, J. H. Cho, Y. S. Ryu, S. H. Oh, E. K. Yum, *Tetrahedron* **2011**, *67*, 4820.

