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Enantioselective Synthesis of a Novel Chiral 2,9-Disubstituted 1,10-Phenanthroline and First Applications in Asymmetric Catalysis

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The asymmetric synthesis of a novel, C_2-symmetric, tetradentate 1,10-phenanthroline is described; it is based on the stereoselective preparation of two functionalized pyridine subunits, which were subsequently joined through two consecutive carbon–carbon bond-forming reactions to assemble the heteroaromatic system. Some initial applications of this new chiral ligand in metal-catalyzed, enantioselective ring-opening reactions of *meso*-epoxides and aminations of β-keto esters are presented.

Introduction

The design and synthesis of novel chiral ligands and their application in enantioselective, metal-catalyzed reactions continues to be an important area of research in the field of organic synthesis.[1] Through careful fine-tuning of the electronic and steric properties of a ligand its coordination to a metal can easily be modulated, with the aim of creating a chiral environment within the metal–ligand complex that leads to a high enantioselectivity in a given reaction. Nitrogen-based chiral ligands have become extremely popular in asymmetric metal catalysis on the basis of their efficient and well-documented coordination to late-transition metals and their facile preparation, typically starting from natural amino acids. Prominent examples in this respect include chiral bisoxazolines,[2] pyridine-2,6-bisoxazolines,[3] and 2,2′-bipyridines,[4] in addition to various mixed P,N- and N,S-type ligands, all of which have proven to provide excellent levels of enantioselectivity in various reactions.

1,10-Phenanthrolines occupy a prominent position in organometallic chemistry as very rigid ligands that are known to coordinate tightly to several metal ions in a chelate fashion.[5] Accordingly, they have been used for a broad range of metal-catalyzed reactions such as the Mizoroki–Heck reaction,[6] aryl and alkenyl aminations and amidations,[7] oxidation of alcohols,[8] conjugate addition reactions,[9] and cyclopropanations.[10] Only a few reports, however, have dealt with the use of chiral 1,10-phenanthroline ligands in asymmetric catalysis, which is mainly due to difficulties in synthesizing these compounds in enantiomerically pure form. The majority of reported synthetic routes to chiral phenanthrolines are based either upon the modification of the phenanthroline core by appendage or upon annulations with one or two chiral units.[4b,11] The heteroaromatic systems of the phenanthroline cores, however, have remained intact throughout these modifications. Some of the important applications of chiral phenanthroline derivatives in asymmetric catalysis, which have mainly come from the Chelucci group, include Pd-catalyzed allylic alkylation of allylic acetates,[12] Cu-catalyzed cyclopropanation of styrenes,[13] Rh-catalyzed asymmetric hydrosilylation[14] and transfer hydrogenation of ketones,[15] and Cu-catalyzed allylic oxidation of alkenes.[16] In addition, Helquist and coworkers recently reported the synthesis of a functionalized chiral phenanthroline in 17–42% yield through SmI_2-mediated coupling of the parent 1,10-phenanthroline with (*R*)-1,2-epoxybutane.[11j] However, no application of this ligand in asymmetric catalysis has yet been reported in the literature.

In recent years we have developed scandium- and indium-bipyridine-catalyzed ring-opening reactions of *meso*-epoxides with alcohols, amines, thiols, and selenols, to furnish 1,2-diol monoethers, 1,2-amino alcohols, 1,2-hydroxy sulfides, and 1,2-hydroxy selenides, respectively, in part with excellent enantioselectivities (Scheme 1).[17] As chiral ligand we employed the 2,2′-bipyridine **1** with appended hydroxyalkyl groups, first synthesized and introduced into the field of asymmetric catalysis by Bolm and co-workers.[18]

Here we report the straightforward synthesis of a conformationally rigid C_2-symmetric phenanthroline ligand with appended hydroxyalkyl groups, resembling the Bolm bipyridine ligand **1**. In contrast with previous approaches to such structures we first assembled two completely functionalized pyridine subunits and subsequently joined them to form the phenanthroline core through two consecutive C–C-coupling reactions. Some initial applications of this new chiral ligand in metal-catalyzed epoxide-opening reactions and in aminations of β-keto esters are also presented.

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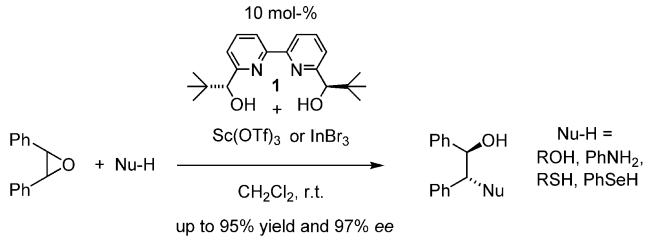
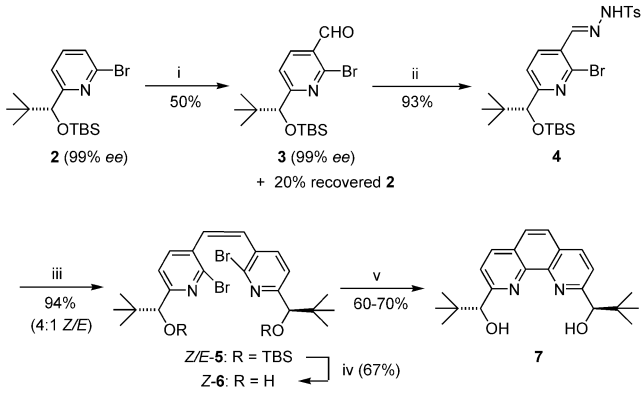


Scheme 1. Enantioselective ring-opening reactions of *meso*-epoxides catalyzed by scandium or indium together with bipyridine **1**.[17]



Scheme 2. Synthesis of the chiral phenanthroline **7**: i) LDA, THF, –78 °C, 2 h, then DMF, –78 °C, 4 h; ii) *p*TsNHNH$_2$, CH_2Cl_2, 2 d; iii) a) $(C_6H_5CH_2)Et_3N^+Cl^-$, NaOH (aq., 14%), toluene, 65 °C, 2 h; b) $Rh_2OAc)_4$, –20 to 0 °C, 16 h; iv) TBAF·3 H_2O, THF, 6 h (pure *Z*); v) $PdCl_2(PhCN)_2$ (20 mol-%), TDAE, DMF, 75 °C, 48 h. TDAE = tetrakis(dimethylamino)ethylene.

Results and Discussion

Generally, one method for the synthesis of 2,9-disubstituted 1,10-phenanthrolines is through the attachment of the 2- and 9-substituents to a commercially available or easily prepared 1,10-phenanthroline derivative. One of the problems with this approach is the inherent reactivity of the phenanthroline ring towards undesired nucleophilic imine addition to furnish 1,2-addition products, especially with organometallic reagents, which eventually foiled this approach.[4] The alternative option, which we ultimately pursued, called for the stereoselective synthesis of two fully functionalized pyridine units, later to be coupled with each other to yield the desired phenanthroline skeleton. A similar approach was recently reported for simpler systems by Chelucci and co-workers, who employed a Wittig olefination to construct the 5,6-double bond within the phenanthroline backbone.[19]

We started the synthesis from the known TBS-protected 2-bromo pyridyl alcohol **2** (Scheme 2),[17b] readily prepared through enantioselective Noyori hydrogenation of the corresponding ketone in good yield and with excellent enantioselectivity,[20] and subsequent silylation. The introduction of the aldehyde moiety was achieved by the highly regioselective metalation of the pyridine ring in **2** with LDA in THF at –78 °C and subsequent treatment with DMF to afford the 3-pyridyl carbaldehyde **3** in 50% yield, along mainly with unreacted starting material.[21] Despite many attempts to optimize the conversion of this reaction (e.g., by the addition of more base and electrophile) the yield could not be increased beyond this mark. Along with some dehalogenated starting material we isolated as the main byproduct in this reaction the starting material in significant amounts which we could submit again in this reaction. It is important to note here that the metalation had not affected the chiral center in the pyridyl silyl ether, because the enantiomeric excesses both of the recovered material and of the product were determined to be 99% *ee*.

Aldehyde **3** was then converted into the corresponding sulfonyl hydrazone **4** by treatment with *p*-toluenesulfonyl hydrazide. The sulfonyl hydrazone **4** was in turn converted under phase-transfer conditions into the corresponding diazoalkane, which was subsequently dimerized through the action of catalytic amounts of $Rh_2(OAc)_4$ to afford a 4:1 mixture of the *Z*- and *E*-alkenes **5** in 94% yield.[22] The *Z* and *E* isomers were best separated by chromatography after removal of the silyl ethers with TBAF in THF, which afforded the pure *Z*-stilbene **6** in 67% yield.

The final Ullmann-type coupling reaction in this sterically quite congested situation proved to be challenging. Although the conditions developed by Bolm for the synthesis of 2,2′-bipyridines were not suitable in this particular situation the protocol used by Kobayashi for similar pyridine coupling reactions worked much better.[20] Thus, in the presence of $PdCl_2(PhCN)_2$ (20 mol-%) and stoichiometric amounts of tetrakis(dimethylamino)ethylene used simultaneously as ligand and reductant, the intramolecular Ullmann coupling of the *Z*-stilbene **6** afforded the chiral phenanthroline **7** in 60–70% isolated yield by direct crystallization. Any attempt to purify this highly polar product by chromatography resulted in significant loss of material. Subsequently we were able to obtain a crystal structure of this new ligand, which established its structure unequivocally (Figure 1).[23]

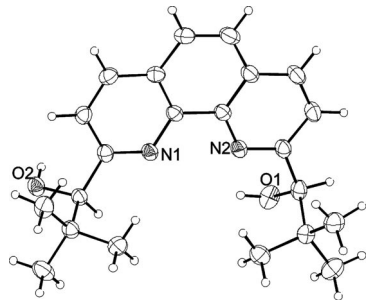
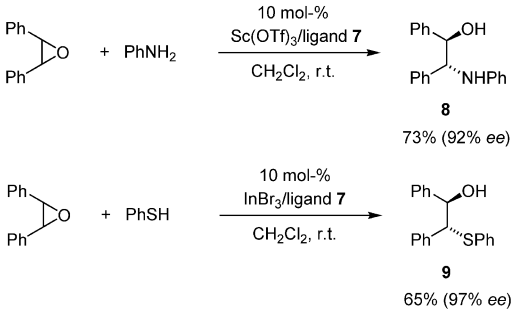


Figure 1. X-ray crystal structure of the phenanthroline **7**.

As a first test of this novel chiral ligand in asymmetric catalysis we chose scandium- and indium-catalyzed enantioselective ring-openings of *meso*-epoxides with aniline and thiophenol, respectively (Scheme 3).[17] Treatment of *cis*-stilbene oxide with aniline in the presence of $Sc(OTf)_3$ (10 mol-%) and **7** (10 mol-%) in CH_2Cl_2 at room temperature thus

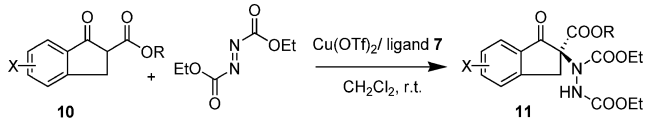
afforded the 1,2-amino alcohol **8** in 73% yield and 92% *ee*. Likewise, the thiolysis reaction in the presence of a catalyst system composed of $InBr_3$ and **7** (each 10 mol-%) furnished the 1,2-hydroxy sulfide **9** in 65% yield and 97% *ee*. The results obtained with the new phenanthroline ligand thus did not differ much from those obtained previously with the bipyridine **1**.



Scheme 3. Enantioselective amine and thiol additions to *cis*-stilbene oxide catalyzed by scandium or indium and the phenanthroline **7**.

As a novel application of this chiral phenanthroline ligand in asymmetric metal catalysis we found it to be highly suitable for the copper-catalyzed amination of β-keto esters.[24] Thus, when the β-keto ester **10a** was treated with diethyl azodicarboxylate (DEAD) and with 10 mol-% $Cu(OTf)_2$ and phenanthroline **7** each in CH_2Cl_2 at room temp., the α-hydrazino-β-keto ester **11a** was obtained in 85% yield and with 93% *ee* (Table 1, Entry 1). It is especially noteworthy that even the more commonly used methyl ester and the commercially available reagent DEAD were already giving rise to a highly enantioselective reaction. Other chiral catalysts that have been developed for this reaction frequently require the use of bulkier and less convenient β-keto esters and/or bulky azo compounds such as the corresponding diisopropyl or di-*tert*-butyl derivatives to achieve high enantioselectivities. This protocol was subsequently applied to the asymmetric α-amination of the other β-keto esters **10b**–**e**, which proceeded with uniformly high levels of enantioselectivity (Table 1).

Table 1. Enantioselective α-aminations of the β-keto esters **10**, catalyzed by copper(II) and the phenanthroline **7**.



Entry	X	R	Product	Yield [%][a]	*ee* [%][b]
1	H	Me	**11a**	85	93
2	H	Et	**11b**	84	93
3	5-OMe	Me	**11c**	88	98
4	6-OMe	Me	**11d**	86	95
5	6-Me	Me	**11e**	82	95

[a] Yield of isolated product after flash column chromatography. [b] Determined by chiral HPLC analysis.

Conclusions

We have synthesized the novel chiral tetradentate 2,9-disubstituted 1,10-phenanthroline **7** through two consecutive carbon–carbon coupling reactions starting from two fully elaborated pyridine subunits. Additionally, we have revealed some initial applications of this chiral ligand in asymmetric ring-openings of *meso*-epoxides, as well as in asymmetric aminations of β-keto esters. Because of its rigid structure and the additional coordination sites in the form of the hydroxy groups this novel ligand might offer some advantages over existing chiral ligands and may be applicable in reactions that are intractable with other known ligands. Further work to explore the potential of this novel chiral ligand in asymmetric catalysis fully is in progress in our laboratory.

Experimental Section

General Methods: All reactions were performed under nitrogen in oven-dried glassware. ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 2000 (200, 300, or 400 MHz) NMR spectrometer. NMR spectra were obtained in $CDCl_3$ as solvent. Chemical shifts are given in the δ scale with tetramethylsilane or the $CHCl_3$ proton as the internal standard. IR spectra were obtained with a FTIR spectrometer (Genesis ATI Mattson/Unicam). UV spectra were recorded with a UV spectrometer (DU-650 Beckmann). Optical rotations were measured with a Polarotronic polarimeter (Schmidt & Haensch). HPLC analyses were performed with a JASCO MD-2010 plus instrument with a chiral stationary phase column (Chiralcel OD column). Solvents were purified by distillation from appropriate drying agents. All ESI mass spectra were recorded with a Bruker APEX II FT-ICR instrument. All EI mass spectra were recorded with a Finnigan MAT 8230 instrument. Melting points were determined with a Boetius heating table and are uncorrected.

2-Bromo-6-[(*R*)-1-(*tert*-butyldimethylsiloxy)-2,2-dimethylpropyl]pyridine-3-carbaldehyde (3): LDA (2.63 g, 24.6 mmol), was added dropwise under argon at –78 °C to a solution of 2-bromo-6-[(*R*)-1-(*tert*-butyldimethylsiloxy)-2,2-dimethylpropyl]pyridine (**2**, 2.93 g, 8.19 mmol) in dry THF (50 mL) and the solution was stirred for 2 h at –78 °C. Dry DMF (2.39 g, 32.8 mmol) was then added dropwise over a period of 10 min and the reaction mixture was stirred at –78 °C for another 4 h, after which it was hydrolyzed with a degassed aqueous solution of KH_2PO_4 (10%, 20 mL). It was then allowed to warm to room temperature and was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, concentrated, and purified by flash chromatography on a silica gel column. Elution with ethyl acetate/hexane (2%) afforded aldehyde **3** as a viscous, light yellow liquid (1.59 g, 50%) along with unreacted starting material that could be used again for this reaction. $[\alpha]_D^{22}$ = +33 (*c* = 1, $CHCl_3$). HPLC (Daicel Chiracel OD-phase, 95:5 *n*-hexane/propan-2-ol, flow rate 0.5 mL min^{-1}): t_R (major) 19.56 min (99% *ee*) and t_R (minor) 21.78 min. ^1H NMR (400 MHz, $CDCl_3$): δ = –0.30 (s, 3 H, CH_3), 0.06 (s, 3 H, CH_3), 0.90 [s, 9 H, $C(CH_3)_3$], 0.91 [s, 9 H, $C(CH_3)_3$], 4.50 (s, 1 H, CH), 7.54 (d, *J* = 8.4 Hz, 1 H, ArH), 8.11 (d, *J* = 8.4 Hz, 1 H, ArH), 10.31 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.91, –4.27, 18.40, 26.18, 26.28, 36.75, 82.97, 121.5, 126.3, 138.0, 165.2, 191.2 ppm. IR (film): $\tilde{\nu}$ = 2955, 2930, 2858, 1698, 1582, 1544, 1471, 1445, 1392, 1353, 1252, 1235, 1184, 1122, 1091, 1055, 1030, 1006 cm^{-1}. UV ($CHCl_3$): λ_{max} (lg ε) = 248 (3.926), 290 (3.811) nm. MS (EI, 70 eV): *m*/*z* (%) = 410.1 [M

+ Na + 1]$^+$. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{17}H_{28}BrNO_2Si$: 386.11454; found 386.11432.

Toluenesulfonylhydrazone 4: *p*-Toluenesulfonylhydrazide (176 mg, 0.95 mmol) was added to a solution of aldehyde **3** (365 mg, 0.95 mmol) in CH_2Cl_2 and the reaction mixture was stirred for 48 h at room temperature. After completion of the reaction (TLC), the solvent was evaporated and the crude product was purified by flash chromatography (ethyl acetate/hexane 30%) to give rise to hydrazone **4** (490 mg, 93%) as a colorless solid; m.p. 70–72 °C. $[\alpha]_D^{22}$ = +50 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.32 (s, 3 H, CH_3), 0.04 (s, 3 H, CH_3), 0.86 [s, 9 H, $C(CH_3)_2$], 0.90 [s, 9 H, $C(CH_3)_2$], 2.43 (s, 3 H, CH_3), 4.41 (s, 1 H, –CH), 7.33–7.42 (m, 3 H, ArH, NH), 7.86–7.89 (m, 2 H, ArH, CH=N), 8.03–8.09 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.91, –4.23, 18.38, 21.99, 26.15, 26.26, 36.93, 82.76, 122.1, 128.3, 130.1, 135.4, 135.5, 140.6, 144.5, 166.7 ppm. IR (KBr): $\tilde{\nu}$ = 3196, 2955, 2929, 2856, 1585, 1539, 1471, 1435, 1393, 1362, 1321, 1251, 1216, 1185, 1168, 1126, 1086, 1048, 1030, 1006 cm^{-1}. UV (MeOH): λ_{max} (lg ε) = 222 (4.221), 279 (4.160), 303 (4.188) nm. MS (EI, 70 eV): *m*/*z* (%) = 578 [M + Na]$^+$, 554 [M]$^+$. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{24}H_{36}BrN_3O_3SSi$: 554.15028; found 554.14970.

***Z*/*E*-Stilbene 5:** Benzyltriethylammonium chloride (154 mg, 0.68 mmol) and aqueous NaOH (14%, 30 mL) were added to a solution of hydrazone **4** (2.88 g, 5.20 mmol) in toluene (30 mL). After the reaction mixture had been heated for 2 h at 65 °C, the red colored organic layer was separated and dried with anhydrous $MgSO_4$. The reaction mixture was then cooled to –20 °C, $Rh_2(OAc)_4$ (10 mg) was added, and the reaction mixture was allowed to warm slowly to 0 °C and then to room temp. The organic layer was separated and dried with anhydrous $MgSO_4$, and the solvent was removed under vacuum. The product **5** was isolated as a colorless solid (1.82 g, 94%, 4:1 *Z*/*E*) by flash chromatography on a silica column (ethyl acetate/hexane 3%). Data for the *Z*-stilbene: m.p. 119–120 °C. $[\alpha]_D^{23}$ = +23 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.32 (s, 3 H, CH_3), 0.32 (s, 3 H, CH_3), 0.83 [s, 18 H, $C(CH_3)_3$], 0.87 [s, 18 H, $C(CH_3)_3$], 4.41 (s, 2 H, CH), 6.78 (s, 2 H, CH=CH), 7.11 (m, 2 H, ArH), 7.18 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.99, –4.10, 18.37, 26.17, 26.24, 36.77, 82.66, 121.2, 130.4, 131.9, 138.1, 141.1, 164.1 ppm. IR (KBr): $\tilde{\nu}$ = 2956, 2930, 2884, 2857, 1584, 1575, 1539, 1471, 1462, 1393, 1355, 1253, 1207, 1182, 1127, 1101, 1088, 1056, 1031, 1007 cm^{-1}. UV ($CHCl_3$): λ_{max} (lg ε) = 216 (4.027), 225 (3.808), 279 (4.272) nm. MS (EI, 70 eV): *m*/*z* (%) = 739.3 [M]$^+$. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{34}H_{56}Br_2N_2O_2Si_2$: 739.23198; found 739.23326.

***Z*-Stilbene 6:** TBAF·3 H_2O (4.63 g, 14.6 mmol) was added to a solution of the *Z*/*E* mixture of **5** (1.81 g, 2.44 mmol) in THF. The reaction mixture was stirred at room temp. for 6 h and the solvent was removed under vacuum. The crude product was dissolved in CH_2Cl_2 and washed with water. The organic layer was collected and dried with anhydrous $MgSO_4$, and the solvents were evaporated. Purification of the crude product by flash chromatography (ethyl acetate/hexane 30%) on a basic alumina column afforded the *Z*-stilbene **6** as a light yellow solid (843 mg, 67%); m.p. 85–87 °C. $[\alpha]_D^{22}$ = –50 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 [s, 18 H, $C(CH_3)_3$], 3.59 (d, *J* = 7.2 Hz, 2 H, –CH), 4.24 (d, *J* = 7.2 Hz, 2 H, OH), 6.77 (s, 2 H, CH=CH), 6.91 (d, *J* = 7.6 Hz, 2 H, ArH), 7.11 (d, *J* = 7.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.11, 36.65, 80.52, 121.6, 130.5, 132.5, 138.5, 142.0, 161.2 ppm. IR (KBr): $\tilde{\nu}$ = 3356, 3042, 2951, 2866, 1697, 1581, 1541, 1477, 1455, 1440, 1393, 1344, 1272, 1230, 1213, 1172, 1131, 1062, 1015 cm^{-1}. UV ($CHCl_3$): λ_{max} (lg ε) = 278 (4.071) nm. MS (EI, 70 eV): *m*/*z* (%) = 535 [M + Na]$^+$. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{22}H_{28}Br_2N_2O_2$: 511.05903; found 511.05874.

(*R*,*R*)-2,9-Bis(1-hydroxy-2,2-dimethylpropyl)-1,10-phenanthroline-(7): The *Z*-stilbene **6** (222 mg, 0.44 mmol) and tetrakis(dimethylamino)ethylene (TDAE, 176 mg, 0.88 mmol) were added at room temperature to a solution of $PdCl_2(PhCN)_2$ (34 mg, 20 mol-%) in degassed DMF (2 mL). The reaction mixture was heated at 75 °C for 24 h and was then allowed to cool to room temperature. The reaction mixture was then filtered through a short celite column with CH_2Cl_2 and the solvents were evaporated under high vacuum. Crystallization of the product from the crude reaction mixture in CH_2Cl_2 afforded **7** (93–102 mg, 60–70%) as colorless crystals; m.p. 228–230 °C. $[\alpha]_D^{22}$ = –254 (*c* = 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 [s, 18 H, $C(CH_3)_2$], 4.72 (d, *J* = 6.8 Hz, 2 H, CH), 5.92 (d, *J* = 6.8 Hz, 2 H, OH), 7.42 (d, *J* = 8.4 Hz, 2 H, ArH), 7.62 (s, 2 H, CH=CH), 7.93 (d, *J* = 8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.50, 36.82, 82.18, 122.9, 125.9, 127.8, 135.3, 144.0, 161.5 ppm. IR (KBr): $\tilde{\nu}$ = 3354, 3279, 3042, 2949, 2885, 1619, 1608, 1589, 1552, 1497, 1477, 1464, 1444, 1419, 1390, 1363, 1327, 1304, 1240, 1175, 1146, 1139, 1096, 1072, 1059, 1016 cm^{-1}. UV ($CHCl_3$): λ_{max} (lg ε) = 205 (4.095), 236 (4.031), 272 (4.097) nm. MS (EI, 70 eV): *m*/*z* (%) = [M + Na]$^+$ 375.1. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{22}H_{28}N_2O_2$: 353.22235; found 353.22202.

Typical Procedure for the α-Amination of β-Keto Esters 10: A solution of $Cu(OTf)_2$ (1.8 mg, 10 mol-%) and the chiral phenanthroline **7** (1.94 mg, 11 mol-%) in CH_2Cl_2 (2 mL) was stirred for 45 min at room temperature. Subsequently one of the β-keto esters **10** (0.05 mmol) and DEAD (9.57 mg, 55 μmol) were added and the solution was stirred for 12 h at room temperature. The crude product was purified by flash chromatography over silica gel (ethyl acetate/hexane 30%) to afford the α-aminated products **11** as viscous liquids.

Data for 11a: $[\alpha]_D^{23}$ = +140 (*c* = 0.5, $CHCl_3$). HPLC (Daicel Chiracel OD-phase, *n*-hexane/propan-2-ol 95:5, flow rate 1 mL min^{-1}): t_R (major) 19.53 min (93% *ee*) and t_R (minor) 23.60 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (m, 6 H, CH_3), 3.73 (s, 3 H, CH_3), 4.16 (mc, 6 H, OCH_2, CH_2), 6.97 (br. s, 1 H, NH), 7.34 (m, 1 H, ArH), 7.46 (d, *J* = 7.5 Hz, 1 H, ArH), 7.60 (t, *J* = 7.5 Hz, 1 H, ArH), 7.74 (d, *J* = 7.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.39, 36.01, 53.67, 62.13, 62.34, 63.37, 76.54, 81.49, 125.3, 126.6, 127.8, 133.2, 136.5, 154.2, 156.0, 167.5, 195.0 ppm. IR (KBr): $\tilde{\nu}$ = 3316, 2983, 1731, 1608, 1590, 1466, 1379, 1337, 1305, 1237, 1172, 1154, 1082, 1060, 1042 cm^{-1}. HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd. for $C_{17}H_{20}N_2O_7$: 387.11627; found 387.11651.

Data for 11b: $[\alpha]_D^{23}$ = +144 (*c* = 0.5, $CHCl_3$). HPLC (Daicel Chiracel OD-phase, 95:5 *n*-hexane/propan-2-ol, flow rate 1 mL min^{-1}): t_R (major) 14.39 min (93% *ee*) and t_R (minor) 18.24 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 9 H, CH_3), 3.75–4.22 (m, 8 H, CH_2, OCH_2), 7.00 (br. s, 1 H, NH), 7.35 (t, *J* = 7.5 Hz,1 H, ArH), 7.47 (d, *J* = 7.5 Hz, 1 H, ArH), 7.62 (t, *J* = 7.5 Hz, 1 H, ArH), 7.73–7.75 (m, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.72, 14.09, 36.67, 62.02, 62.56, 62.95, 76.34, 77.92, 124.9, 126.2, 127.5, 133.0, 135.5, 136.1, 154.1, 155.9, 167.0, 194.8 ppm. IR (KBr): $\tilde{\nu}$ = 3312, 2983, 2937, 1726, 1608, 1590, 1466, 1445, 1402, 1377, 1337, 1304, 1237, 1201, 1173, 1154, 1095, 1081, 1041, 904, 860, 787, 760, 617 cm^{-1}. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{18}H_{23}N_2O_7$: 379.14998; found 379.14993.

Data for 11c: $[\alpha]_D^{23}$ = +176 (*c* = 0.5, $CHCl_3$). HPLC (Daicel Chiracel OD-phase, *n*-hexane/propan-2-ol 95:5, flow rate 1 mL min^{-1}): t_R (major) 37.68 min (98% *ee*) and t_R (minor) 45.44 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17–1.29 (m, 6 H, CH_3), 3.75 (s, 3 H, OCH_3), 3.78 (br. s, 1 H, CH_2), 3.89 (s, 3 H, OCH_3), 3.98–4.24 (m, 5 H, CH_2, OCH_2), 6.91 (s, 2 H, ArH), 6.97 (s, 1 H, NH), 7.69 (br.

s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.40, 38.79, 53.66, 55.86, 62.05, 62.32, 63.28, 78.43, 109.3, 116.6, 125.4, 126.5, 127.2, 134.3, 154.3, 156.2, 166.8, 192.9 ppm. IR (KBr): $\tilde{\nu}$ = 3314, 2982, 1717, 1600, 1491, 1466, 1445, 1404, 1337, 1259, 1173, 1152, 1082, 1062, 1041 876, 787, 762, 656, 621 cm^{-1}. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{18}H_{23}N_2O_8$: 395.14489; found 395.14499.

Data for 11d: $[\alpha]_D^{23}$ = +156 (*c* = 0.5, $CHCl_3$). HPLC (Daicel Chiracel OD-phase, *n*-hexane/propan-2-ol 95:5, flow rate 1 mL min^{-1}): t_R (minor) 40.51 min and t_R (major) 48.49 min (95% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.34 (m, 6 H, CH_3), 3.69–3.71 (m, 1 H, CH_2), 3.75 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.97–4.24 (m, 5 H, CH_2, OCH_2), 6.96 (br. s, 1 H, NH), 7.16–7.25 (m, 2 H, ArH), 7.37 (d, *J* = 8.4 Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.35, 38.05, 53.64, 55.62, 62.03, 62.35, 63.28, 78.75, 106.2, 125.4, 126.1, 127.2, 134.2, 147.4, 156.1, 159.6, 167.5, 194.4 ppm. IR (KBr): $\tilde{\nu}$ = 3316, 2983, 1722, 1618, 1494, 1466, 1433, 1404, 1377, 1339, 1302, 1238, 1161, 1084, 1060, 1030, 861, 788, 762 cm^{-1}. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{18}H_{23}N_2O_8$: 395.14489; found 395.14454.

Data for 11e: $[\alpha]_D^{23}$ = +148 (*c* = 0.5, $CHCl_3$). HPLC (Daicel Chiracel OD-phase, *n*-hexane/propan-2-ol 95:5, flow rate 1 mL min^{-1}): t_R (minor) 24.16 min and t_R (major) 27.06 min (95% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91–1.27 (m, 6 H, CH_3), 2.38 (s, 3 H, CH_3), 3.74 (s, 3 H, OCH_3), 3.78 (br. s, 1 H, CH_2), 4.11–4.20 (m, 5 H, CH_2, OCH_2), 7.07 (br. s, 1 H, NH), 7.38 (d, *J* = 7.5 Hz, 1 H, ArH), 7.46 (d, *J* = 7.5 Hz, 1 H, ArH), 7.56 (br. s, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.33, 21.05, 38.40, 53.60, 62.07, 62.30, 63.24, 78.41, 125.1, 126.1, 127.3, 133.3, 137.1, 137.8, 151.5, 156.1, 167.4, 194.4 ppm. IR (KBr): $\tilde{\nu}$ = 3311, 2983, 2954, 1727, 1619, 1584, 1494, 1405, 1377, 1338, 1238, 1174, 1150, 1085, 1042, 872, 762, 682, 605, 501 cm^{-1}. HRMS-ESI: *m*/*z* [M + H]$^+$ calcd. for $C_{18}H_{23}N_2O_7$: 379.14998; found 379.15002.

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