JOC The Journal of Organic Chemistry

Article

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Asymmetric Synthesis of (2*S*,3*S*)-α-(1-Oxoisoindolin-3-yl)glycines under Low-Basicity "Kinetic" Control

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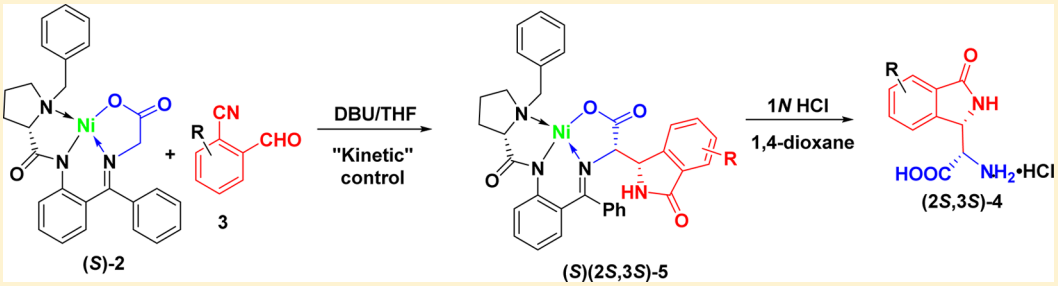
Supporting Information

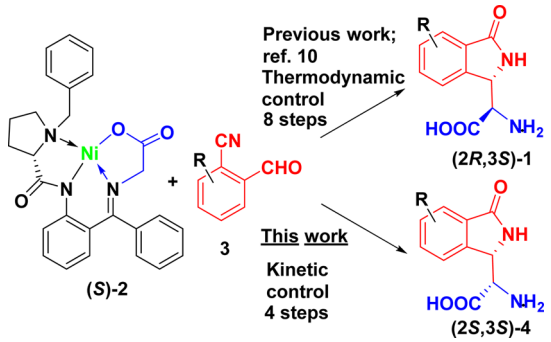


ABSTRACT: The previously illusive (2*S*,3*S*)-configured α-(1-oxoisoindolin-3-yl)glycines can be prepared under mild DBU-catalyzed, low-basicity conditions. The overall process includes a cascade of aldol addition, cyclization, rearrangement, and conjugate addition reactions, leading to the target products with moderate to good chemical yields and diastereoselectivity.

INTRODUCTION

Due to the paramount role of α-amino acids in the development of life, biological evolution, and sustenance of human health, synthesis of this class of organic compounds continues to attract considerable attention.[1] In fact, interest in development of new methods for preparation of tailor-made[2] α-amino acids (α-AAs) in enantiomerically pure form is at an all-time high[3] because of the rapidly growing number of pharmaceutical products incorporating α-AAs in the their structures.[4] For quite some time, the research in our groups[5,6] has been focused on the development of general asymmetric methodology for asymmetric synthesis of α- and β-amino acids via homologation of chiral equivalents of glycine[7] and β-alanine.[8] In particular, drawing inspiration from the recent work by Massa et al.,[9] we reported synthesis of (2*R*,3*S*)-α-(1-oxoisoindolin-3-yl)glycines **1** (Scheme 1) via addition reactions between chiral Ni(II) glycine complex **2** and 2-cyanobenzaldehydes **3**.[10] Amino acids of type **1** embody the least studied structural class of sterically constrained α-amino acids as their synthesis, especially in enantiomerically pure form, still remains quite a challenging undertaking. The major synthetic hurtle associated with the preparation of amino acids of type **1**, is not only the two consecutive stereogenic centers and the sensitive polyfunctional nature, but rather the fact that this structure cannot be assembled in one reaction step, requiring a cascade of successive transformations and multiple intermediates. On the other hand, these α-amino acids are of very significant pharmacological interest, allowing for an efficient control of peptide-space side conformations.[11] Consequently, building on our earlier success in the synthesis of (2*R*,3*S*)-**1**, we were highly motivated to accomplish synthesis of yet another diastereomer

Scheme 1. Synthesis of Diastereomers (2*R*,3*S*)-1 and (2*S*,3*S*)-4 under the Conditions of Thermodynamic and Kinetic Control, Respectively



Received: July 8, 2015
Published: November 2, 2015

DOI: 10.1021/acs.joc.5b01730
J. Org. Chem. 2015, 80, 11275−11280

Scheme 2. Four Diastereomeric Products in the Reaction of Ni(II) Complex (*S*)-2 with Aldehyde 3a

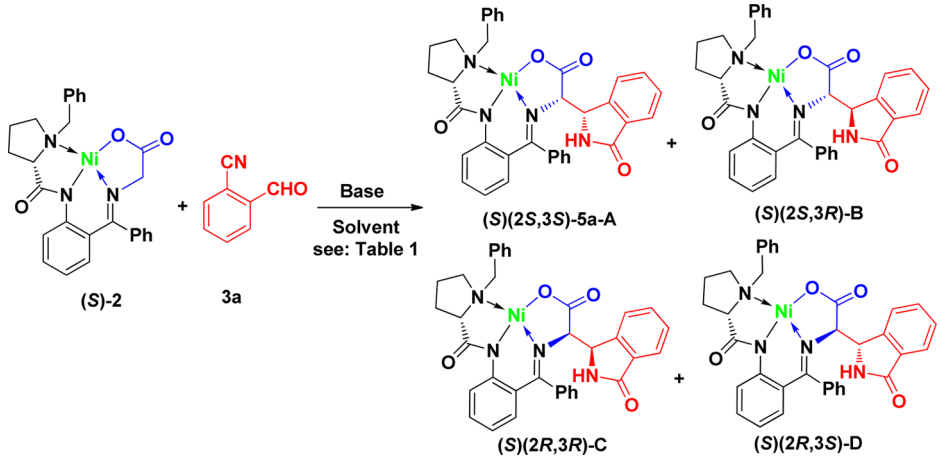
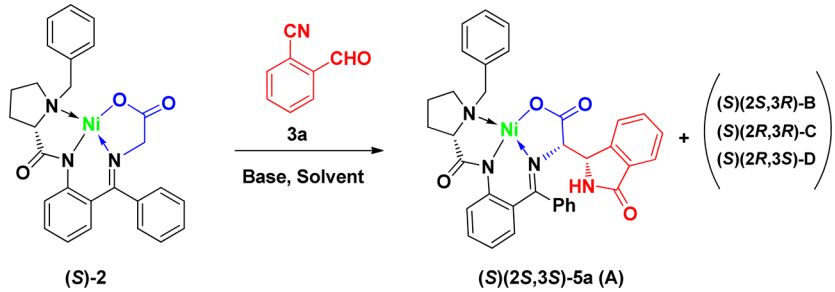


Table 1. Optimization of the Reaction Conditions for Preparation of Diastereomer (2*S*,3*S*)-5a[a]



entry	bases	solvents	time (h)	temp (°C)	yield[b] (%)	A/B/C/D dr[c]
1	DBU	DCM	20	rt	56.9	50/18/5/27
2	DBU	CH_3CN	20	rt	48	52/17/3/28
3	DBU	acetone	20	rt	43	47/18/3/32
4	DBU	THF	20	rt	62.8	52/22/5/22
5	DBU	THF	20	0	51.2	34/28/13/25
6	DBU	THF	20	40	69.5	71/9/2/18
7	DBU	THF	20	60	50.9	88/6/2/4
8	DBU	THF	14	80	29.5	61/29/5/5

[a]Reactions conditions: (*S*)-**2** (0.2 mmol), **3a** (0.22 mmol) and base (0.24 mmol) were run in solvent (2 mL). [b]Combined yield of isolated crude products. [c]Determined by LC/MS analysis of the crude products.

(2*S*,3*S*)-**4** (Scheme 1), which we failed to prepare in the previous work.[10] The diastereomer(2*S*,3*S*)-**4** is thermodynamically unfavorable and, therefore, stereochemically more challenging.

One may agree that the development of a procedure for preparation of diastereomer (2*S*,3*S*)-**4**, along with the previous work,[10] will provide access to all four possible enantiomers (2*R*,3*S*)-/(2*S*,3*R*)-**4** and (2*S*,3*S*)-/(2*R*,3*R*)-**4**, starting correspondingly from (*S*)- or (*R*)-**2**, affording a stereochemically complete study of biological properties of these amino acids. Thus, owing both to practical importance and scientific curiosity, we sought to develop the method for preparation of diastereomer (2*S*,3*S*)-**4**. Herein, we describe the results of this study.

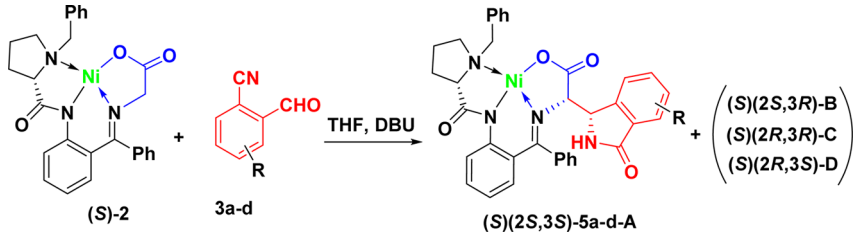
As demonstrated previously by Massa et al.[9] and us,[10] the formation of target structure **5a** (Scheme 2), from staring Ni(II) complex (*S*)-**2** and aldehyde **3a**, proceeds via the consecutive sequence of at least four reactions: aldol addition, cyclization, rearrangement, and conjugate addition. Due to such reaction complexity, all four theoretically possible diastereomers (*S*)(2*S*,3*S*)-**5a** (**A**), (*S*)(2*S*,3*R*)-**B**, (*S*)(2*R*,3*R*)-**C**, and (*S*)(2*R*,3*S*)-**D**[12] are usually observed in the reaction mixture.

RESULTS AND DISCUSSION

All four reactions involved in the formation of products are base-catalyzed and can be accelerated at an elevated temperature. As established previously,[10] application of strong bases, such as NaOMe in MeOH, at 80 °C led to relatively rapid (~10 h) thermodynamic control (relative ratios of the diastereomers ceased to change) strongly favoring (2*R*,3*S*)-diastereomers **D**. Taking into account the cascade of various transformations taking place in the reaction of (*S*)-**2** with **3a**, one might agree that the sense of kinetic control in such processes is somewhat ambiguous. Nevertheless, diastereomer (2*S*,3*S*)-**5a** repetitively appeared as a prevailing isomer in the early reaction stages, rendering it rather "kinetic" as compared with the thermodynamically favored (2*R*,3*S*)-**D**. Numerous experiments designed to screen various bases and solvents revealed that strong inorganic bases (NaH, KOH, NaOH, *t*-BuONa, *t*-BuOK), needed to catalyze the chain of the consecutive reactions, led to

DOI: 10.1021/acs.joc.5b01730
J. Org. Chem. 2015, 80, 11275−11280

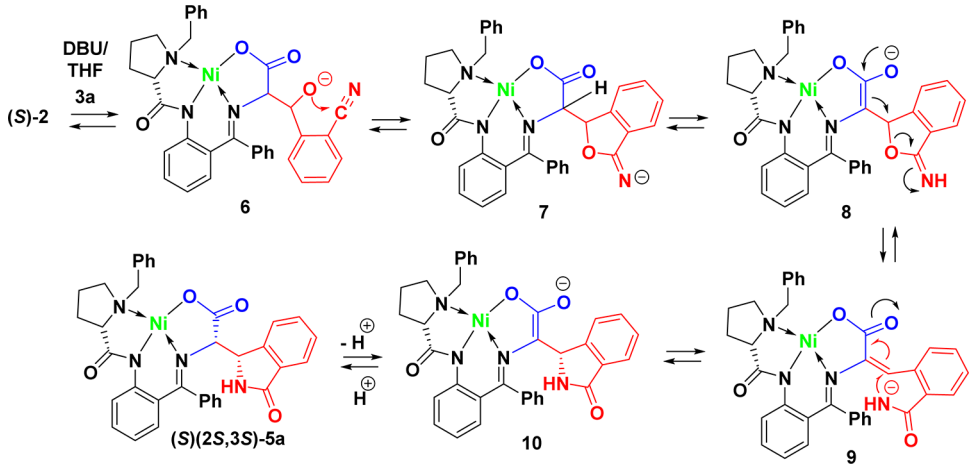
Table 2. Scope of the Reaction between Schiff Base Ni(II) Complex (*S*)-2 and Aldehydes 3a−d[a]



entry	R	time (h)	5a−d	yield[b] (%)	dr (A/B/C/D)[c]
1	H	20	**5a**	50.9	88/6/2/4
2	4-F	8	**5b**	47.9	80/13/2/5
3	4-MeO	22	**5c**	70.6	73/15/1/11
4	4-Me	30	**5d**	72.6	85/12/1/2

[a]Reactions conditions: (*S*)-**2** (0.2 mmol), **3a−d** (0.22 mmol), and DBU (0.24 mmol) were run in THF (2 mL). [b]Combined yield of isolated crude products. [c]Determined by LC/MS analysis of the crude products.

Scheme 3. Mechanistic Considerations Accounting for the Formation of (*S*)(2*S*,3*S*)-5a



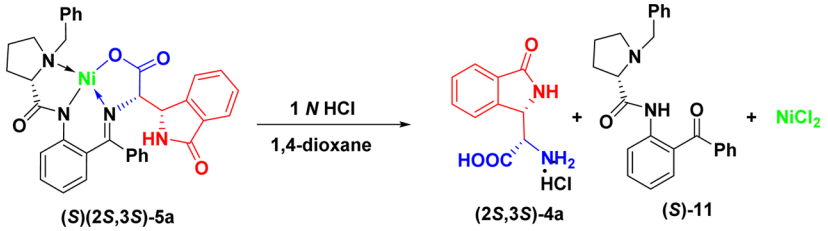
thermodynamic control and rapid disappearance of the target diastereomer (2*S*,3*S*)-**5a**. On the other hand, relatively weak organic bases (TEA, DABCO, DBN) were generally ineffective as the catalysts. Eventually, we found that application of DBU might be promising to realize a synthetic opportunity for preparation of (2*S*,3*S*)-**5a**. Some key and selected results are presented in Table 1.

For example, the reaction of (*S*)-**2** and **3a**, conducted in DCM and catalyzed by DBU (entry 1), took place at an ambient temperature with fairly slow rate. The best ratio of the diastereomers, with respect to the relative amount of diastereomer (2*S*,3*S*)-**A**, was observed at about 20 h of the reaction time. A similar stereochemical outcome, but with slightly lower yields, was recorded for the DBU-catalyzed reactions conducted in acetonitrile (entry 2) and acetone (entry 3). In contrast, the use of THF, as a reaction solvent, gave noticeably better results furnishing the diastereomeric mixture (entry 4) in 62.8% yield with (2*S*,3*S*)-**A** as a major product. Quite unexpectedly, lowering the reaction temperature to 0 °C (entry 5) decreased both the reaction yield and relative ratio of (2*S*,3*S*)-**A**. Following this trend we conducted the reaction at elevated (40 °C; entry 6) temperature. To our delight, the yield and stereochemical outcome were both markedly improved, clearly rendering the target diastereomer (2*S*,3*S*)-**A** as a major reaction product. Further increase of the reaction temperature to 60 °C (entry 7) gave even better results in terms of the diastereoselectivity, albeit the yield was lower. Finally, an attempt to conduct the reaction at even higher temperature (80 °C) was rather disappointing (entry 8), leading to decreased yield and stereoselectivity. According to these results, application of DBU as a base and use of THF as a solvent at 60 °C were considered as the optimized conditions providing for synthetically meaningful yield and stereochemical control. With the aim of understanding reaction progress and stereochemical outcome under optimized conditions, we monitored the reaction using HPLC analysis. The main product (2*S*,3*S*)-**5a** (**A**) was afforded as a kinetically favored isomer. Over time, the relative amounts of the diastereomer (2*S*,3*S*)-**5a** (**A**) steadily increased, reached a peak at 20 h, and decreased when the reaction time was prolonged to 27 h (see Table S1 in the Supporting Information).

With the optimized reaction conditions thus established, we decided to evaluate briefly the scope of this procedure for preparation of several analogues containing various substituents on the phenyl ring of the oxoisoindolinyl moiety. The results are presented in Table 2. In general, the presence of electron-withdrawing/donating substituents on the starting benzaldehydes **3a−d** has no effect on the kinetic stereochemical preferences, favoring in these reactions the (*S*)(2*S*,3*S*) configured products **5a−d** (**A**) as major diastereomers (Table 2, entries 1−4).

DOI: 10.1021/acs.joc.5b01730
J. Org. Chem. 2015, 80, 11275−11280

Scheme 4. Disassembly of Product (2*S*,3*S*)-5a, Isolation of Target Free Amino Acid (2*S*,3*S*)-4a, and Recycling of the Chiral Ligand 11



On the other hand, a clear tendency for higher yields and stereochemical outcome could be noticed for the reactions of aldehydes bearing electron-donating substituents (entries 3, 4 vs 1, 2). Thus, the best yield and relative ratio of major product (*S*)(2*S*,3*S*)-**5d** was observed in the reaction of *p*-Me-substituted derivative.

On the basis of the mechanism suggested by Massa et al.[9] as well as our previous work,[10] we can assume that the initial reaction step results in the formation of expected aldol product **6** (Scheme 3).

Next, the ionized form of **6** might undergo cyclization with the *o*-CN group to produce intermediate cyclic compound **7**, rearrangement of which, via an E1cb mechanism, gives rise to ionized amide **8**/**9**. Intramolecular conjugate addition of **9** was realized through acetamide anion attacked from the *Si*-face of the Michael acceptor with smaller steric hindrance and faster kinetic rate, which would lead to recyclization with the formation of (3*S*)-enolate **10** as major products. The final step in this reaction cascade would be the protonation of enolate **10** furnishing neutral product (*S*)(2*S*,3*S*)-**5a**, which has preferred (2*S*)-configuration avoiding mutual repulsion with chiral ligand residue.

Aldol addition reactions of glycine Schiff base Ni(II) complex (*S*)- or (*R*)-**2** were previously studied, however, only on simple examples,[1b] not like in the present case where we have the chain of subsequent transformations. However, the mechanistic rational and the stereochemical outcome giving preference for (*S*)(2*S*,3*S*) stereochemistry is consistent with general mode of the stereocontrol of chiral Ni(II) complex, strongly favoring (*S*)-configuration of an amino acid residue.[1,10,13]

It should be noted that considering the fact that this developed one-pot procedure actually includes a consecutive chain of aldol addition, cyclization, rearrangement, and conjugate addition reactions, the obtained yields (Table 1 and 2) are rather good allowing synthetically attractive preparation of the target products.

As a final goal of this study, diastereomerically pure Ni(II) complex (*S*)(2*S*,3*S*)-**5a** was disassembled (Scheme 4) under the standard conditions[1b] using 1 N HCl to furnish free amino acid (2*S*,3*S*)-**4a** (Scheme 1) in 82.5% yield with 97.7% ee. At the same time, chiral ligand (*S*)-**11** was recycled with 86% yield and used again for preparation of starting glycine Schiff base Ni(II) complex (*S*)-**2**.

CONCLUSIONS

In summary, we demonstrate that previously illusive α-(1-oxoisoindolin-3-yl)glycines of (2*S*,3*S*) absolute configuration can be prepared under specially designed DBU-catalyzed, low-basicity protocol, favoring "kinetic" stereochemical outcome. The developed one-pot procedure actually includes a consecutive chain of aldol addition, cyclization, rearrangement and conjugate addition reactions. Regardless the chemical complexities of this procedure, the yields and diastereoselectivity are generally moderate to good allowing preparation of target amino acids of high pharmaceutical potential.

EXPERIMENTAL SECTION

General Information. The chemicals were purchased from commercial sources and used without further purification. Analytical thin-layer chromatography (TLC) was performed on HSGF 254 (0.15−0.2 mm thickness). All products were characterized by NMR and MS spectra. ^{1}H and ^{13}C NMR spectra were recorded in deuterochloroform ($CDCl_3$), dimethyl sulfoxide-d_6 (DMSO-d_6), or deuterium oxide (D_2O) on a 400 or 500 MHz instrument. Chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton-coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (p), doublet of triplets (dt), and multiplet (m). High-resolution mass spectra (HRMS) were measured on a Q-TOF spectrometer. The determination of dr was performed via LC/MS analysis. The determination of ee was performed via HPLC analysis. Optical rotations were measured using a 1 mL cell with a 10 mm path length on matic polarimeter and were reported as follows: $[\alpha]\ ^{25}_{D}$ (c: g/100 mL, in solvent). Melting points were measured on melting point apparatus. All physicochemical data reported for the Ni(II) complexes are due to the single diastereomer after purification by chromatography.

General Procedure. *General Procedure for the Synthesis of(S)(2S,3S)-**5a**.* (*S*)-**2** (100 mg, 0.20 mmol) was dissolved in THF (2 mL) at ambient conditions followed by 2-cyano benzaldehyde **3a** (28.9 mg, 0.22 mmol) and DBU (36.0 mmL, 0.24 mmol). The solution was stirred at 60 °C. After 20 h, the reaction was cooled and quenched by pouring it into 5 mL of aq satd NH_4Cl. The suspension was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (CH_2Cl_2/acetone = 1/5, v/v) to give (*S*)(2*S*, 3*S*)-**5a** as a red solid (64.3 mg, yield 50.9%).

*Disassembly of Ni(II) Complex (S)(2S,3S)-**5a**.* To a stirring solution of (*S*)(2*S*,3*S*)-**5a** (385 mg, 0.6 mmol) in 1,4-dioxane (10 mL) was added 1 N HCl (20 mL) at 70 °C for 20 min, the solution was evaporated, and the solid residue was dissolved in water. Then the precipitate ((*S*)-**11**) was filtered, and the filtrate was extracted with CH_2Cl_2 to recover extra (*S*)-**11**. The aqueous phase was concentrated. Water (5 mL) was added to the residue, which was purified by reversed-phase preparative chromatography (MeOH/water = 5/95, v/v) resulting in optically pure product (2*S*,3*S*)-**4a**·HCl as a white solid (109 mg, 86.5%).

Analytical Characterization Data of Products. *Ni(II)−(S)-BPB/(S)-2-Amino-2-((S)-1-oxoisoindolin-3-yl)acetic Acid Schiff Base Complex (**5a**).* Red solid (64.3 mg, yield 50.9%). Mp: 264.5−266.5 °C. $[\alpha]^{25}_{D}$ = +2810 (*c* 0.05 g/100 mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 8.7, 1.1 Hz, 1H), 8.10−8.02 (m, 2H), 7.86−7.79 (m, 1H), 7.56 (td, *J* = 7.6, 1.4 Hz, 1H), 7.52−7.27 (m, 7H), 7.25−7.20 (m, 1H), 7.19−7.12 (m, 2H), 6.86−6.82 (m, 1H), 6.72−6.63 (m, 2H), 6.31 (d, *J* = 7.7 Hz, 1H), 4.99 (d, *J* = 5.0 Hz, 1H), 4.42 (d, *J* = 12.7 Hz, 1H), 4.17 (d, *J* = 5.2 Hz, 1H), 3.67−3.44 (m, 4H), 2.88−2.75 (m, 1H), 2.64−2.50 (m, 1H), 2.29−2.17 (m, 1H), 2.15−2.05 (m, 1H). ^{13}CNMR (100 MHz, $CDCl_3$) δ 180.2, 174.4, 172.3, 170.9, 142.8, 142.6, 133.4, 132.8, 132.2, 131.6, 131.3, 131.2, 129.5,

DOI: 10.1021/acs.joc.5b01730
J. Org. Chem. 2015, 80, 11275−11280

128.8, 128.7, 128.4, 127.4, 127.0, 125.7, 123.7, 123.0, 122.7, 120.2, 72.4, 69.8, 62.7, 59.2, 56.8, 30.5, 23.1. LRMS (ESI) $[M + Na]^+$ found m/z 651.1. HRMS (ESI) calcd for $C_{35}H_{31}N_4NiO_4^+$ $[M + H]^+$ 629.1693, found 629.1690. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 34.266 min, t_R (minor diastereomers) = 35.255 min, 37.036 min, 40.754 min, respectively. dr = 88:6:2:4.

Ni(II)−(S)-BPB/(S)-2-Amino-2-((S)-6-fluoro-1-oxoisoindolin-3-yl)-acetic Acid Schiff Base Complex ***5b***. Red solid (62.2 mg, yield 47.9%). Mp: 299.4−300.3 °C. $[\alpha]^{25}_D$ = +2759 (*c* 0.05 g/100 mL, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.30 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 7.5 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.57−7.45 (m, 3H), 7.40−7.28 (m, 3H), 7.22−7.08 (m, 2H), 6.95 (td, *J* = 8.6, 2.5 Hz, 1H), 6.79−6.66 (m, 2H), 6.57 (d, *J* = 7.6 Hz, 1H), 6.31 (dd, *J* = 8.4, 4.2 Hz, 1H), 4.67−4.57 (m, 1H), 4.50 (d, *J* = 12.8 Hz, 1H), 4.23 (d, *J* = 3.9 Hz, 1H), 3.61−3.38 (m, 4H),, 2.84 (p, *J* = 7.3 Hz, 1H), 2.53−2.40 (m, 1H), 2.15−2.05 (m, 1H), 2.04−1.96 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 174.0, 172.2, 169.6, 162.4 (d, *J* = 248.9 Hz), 142.6, 138.2, 133.3, 132.5, 132.1, 131.2, 129.6, 128.7, 128.6, 128.3, 127.2, 127.0, 125.8, 124.1, 124.1, 122.9, 120.1, 119.1 (d, *J* = 23.5 Hz), 110.2 (d, *J* = 23.5 Hz), 71.9, 69.5, 62.5, 58.4, 56.5, 30.5, 22.9. LRMS (ESI) $[M + Na]^+$ found m/z 669.0. HRMS (ESI): calcd for $C_{35}H_{30}FN_4NiO_4^+$ $[M + H]^+$ 647.1599, found 647.1595. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min), t_R (major diastereomer) = 36.461 min, t_R(minor diastereomers) = 38.326 min, 40.367 min, 44.662 min, respectively. dr = 80/13/2/5.

Ni(II)−(S)-BPB/(S)-2-Amino-2-((S)-6-methoxy-1-oxoisoindolin-3-yl)acetic Acid Schiff Base Complex ***5c***. Red solid (93.5 mg, yield 70.6%). Mp: 305.1−306.5 °C. $[\alpha]^{25}_D$ = +2404 (*c* 0.05 g/100 mL, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.7 Hz, 1H), 7.98 (d, *J* = 7.4 Hz, 2H), 7.69 (s, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.32−7.21 (m, 5H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.04−6.99 (m, 1H), 6.85 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.66−6.58 (m, 2H), 6.55−6.47 (m, 2H), 4.75 (d, *J* = 4.7 Hz, 1H), 4.35 (d, *J* = 12.8 Hz, 1H), 4.11 (d, *J* = 4.7 Hz, 1H), 3.76 (s, 3H), 3.53−3.34 (m, 4H), 2.71−2.58 (m, 1H), 2.46−2.33 (m, 1H), 2.13−2.04 (m, 1H), 2.01−1.93 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1, 174.5, 172.2, 170.2, 160.0, 142.5, 134.7, 133.4, 133.3, 132.8, 132.7, 132.3, 131.0, 129.5, 128.6, 128.4, 127.2, 126.8, 123.7, 122.9, 120.3, 120.1, 106.3, 72.6, 69.9, 62.7, 59.0, 56.8, 55.2, 30.5, 23.1. LRMS (ESI) $[M + Na]^+$ found m/z 681.0. HRMS (ESI) calcd for $C_{36}H_{33}N_4NiO_5^+$ $[M + H]^+$ 659.1799, found 659.1787. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 36.345 min, t_R (minor diastereomers) = 37.891 min, 39.412 min, 46.171 min, respectively. dr =73/15/1/11.

Ni(II)−(S)-BPB/(S)-2-Amino-2-((S)-6-methyl-1-oxoisoindolin-3-yl)-acetic Acid Schiff Base Complex ***5d***. Red solid (93.7 mg, yield 72.6%). Mp: 295.2−296.7 °C. $[\alpha]^{25}_D$ = +2625 (*c* 0.05 g/100 mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.7 Hz, 1H), 8.11−8.03 (m, 2H), 7.63 (s, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.52−7.45 (m, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.29 (s, 1H), 7.25−7.20 (m, 3H), 7.19−7.12 (m, 2H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.71−6.63 (m, 2H), 6.33 (d, *J* = 7.7 Hz), 4.96 (d, *J* = 5.2 Hz, 1H), 4.42 (d, *J* = 12.7 Hz, 1H), 4.15 (d, *J* = 5.2 Hz, 1H), 3.64−3.43 (m, 4H), 2.87−2.77 (m, 1H), 2.64−2.52 (m, 1H), 2.40 (s, 3H, CH_3), 2.28−2.17 (m, 1H), 2.15−2.03 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 174.5, 172.2, 170.9, 142.5, 140.0, 138.5, 133.4, 133.4, 132.8, 132.7, 132.2, 131.4, 131.1, 129.5, 128.8, 128.7, 128.4, 128.4, 127.3, 127.0, 125.6, 123.9, 123.0, 122.4, 120.3, 72.6, 69.9, 62.7, 59.1, 56.8, 30.5, 23.1, 21.0. LRMS (ESI) $[M + Na]^+$ found m/z 665.1. HRMS (ESI): calcd for $C_{36}H_{33}N_4NiO_4^+$ $[M + H]^+$ 643.1850, found 643.1867. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 37.772 min, t_R (minor diastereomers) = 38.638 min, 41.103 min, 47.841 min, respectively. dr = 85/12/1/2.

(S)-2-Amino-2-((S)-1-oxoisoindolin-3-yl)acetic Acid ***4a***·*HCl*. White solid (109 mg, yield 86.5%). Mp: 295.3−297.1 °C. $[\alpha]^{25}_D$ = −26 (*c* 0.10 g/100 mL, H_2O). ^1H NMR (500 MHz, D_2O + CF_3COOH) δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 5.16 (d, *J* = 3.4 Hz, 1H), 4.57 (d, *J* = 3.3 Hz, 1H). ^{13}C NMR (125 MHz, D_2O + CF_3COOH) δ 172.1, 167.9, 139.6, 132.9, 130.7, 129.6, 123.4, 123.0, 55.1, 53.7. LRMS (ESI) $[M-H]^-$ found m/z 205.1. HRMS (ESI): calcd for $C_{10}H_{11}N_2O_3^+$ $[M + H]^+$ 207.0764, found 207.0770. The ee was determined through its corresponding methyl 2-amino-2-(3-oxoisoindolin-1-yl)acetic acid by HPLC with a Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 90/10, λ = 254 nm, 1.0 mL/min). t_R (major enantiomer) = 29.491 min, t_R (minor enantiomer) = 37.558 min, 97.7% ee.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01730.

Stereochemical outcome over time, HPLC spectra for dr determination, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the National Natural Science Foundation of China (Grant Nos. 21021063, 91229204, and 81025017) and the National S&T Major Projects (Nos. 2012ZX09103101-072, 2012ZX09301001-005, 2013ZX09507-001, and 2014ZX09507002001).

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