JOC The Journal of Organic Chemistry

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α-Oxo-γ-Butyrolactam, *N*-Containing Pronucleophile in Organocatalytic One-Pot Assembly of Butyrolactam-Fused Indoloquinolizidines

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Supporting Information

ABSTRACT: The ambident reactivity of α-oxo-γ-butyrolactam has been explored in an organocatalytic one-pot Michael/Pictet–Spengler sequence. The synthetically interesting and medicinally important pentacyclic butyrolactam-fused indoloquinolizidines can be efficiently constructed in a highly stereocontrolled manner. Importantly, the chemistry described herein provides a general catalytic method for the enantioselective synthesis of butyrolactam-incorporated chemical entities.

The development of new and efficient approaches to functionalized molecules with structural complexity or biological importance continues to be a crucial, yet challenging, target in modern organic synthesis.[1] The identification of new substrate with diverse reactivity is essential to achieve this goal. Chiral butyrolactams is a common motif found in numerous naturally occurring molecules and biologically active compounds.[2] Established strategies for catalytic asymmetric synthesis of this important target were mostly limited to α,β-unsaturated γ-butyrolactam and 2-siloxypyrrole-related transformations.[3] Hence, discovery of new and general catalytic method for direct formation of chiral butyrolactam is still in demand.

In the field of organocatalysis, compared to 1,3-dicarbonyl compounds,[4] there were only a handful of examples exploiting 1,2-dicarbonyl compounds (1,2-diketone, α-ketoester, and α-ketoamide) as carbon-centered nucleophiles despite their diverse reactivity and synthetic value.[5] In hopes of developing a straightforward approach to functionalized chiral butyrolactams and related five-membered nitrogen-containing heterocycles, we decided to explore the reactivity of α-ketobutyrolactam[6] (Figure 1), which featured both the reaction pattern of α-ketoamide and the synthetic value of butyrolactam-type *N*-heterocycles. From the synthetic point of view, this cyclic α-ketoamide combines both nucleophilic and electrophilic characteristics, which enables various sequential or cascade transformations with suitable nucleophiles or electrophiles leading to valuable synthetic intermediates with increased complexity and diversity, such as α-/β-functionalized or ring-fused butyrolactams.

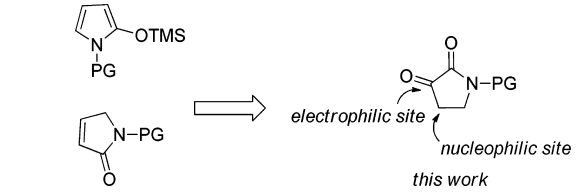


Figure 1. Development of new nucleophiles for the synthesis of chiral butyrolactams and related N-heterocycles.

Developing more effective strategies to generate molecule libraries for biological screening is a challenging and significant exploitation for organic chemists. This ambition could be achieved through a facile modification of a single privileged scaffold, such as transformation of functional groups or substitution of ring patterns. Indoloquinolizidine[7] constitutes one key structural backbone of a large number of medicinally interesting natural indole alkaloids such as normacusine, reserpine, mitragynine, dihydroantirhine, and tangutorine (Figure 2). The combination of butyrolactam and indoloquinolizidine may introduce improved molecular diversity and potential biological applications. However, to our knowledge, butyrolactam-fused indoloquinolizidines have not been investigated. Over the past several years, the organocatalyzed one-pot strategies[8] have paved the way for the direct construction of indoloquinolizidine scaffold from simple starting materials.[9] In connection with our interest in the facile and stereoselective construction of functionalized chiral molecules by means of organocatalysis, herein we present a organocatalytic one-pot Michael/Pictet–Spengler sequence for the rapid construction of pentacyclic butyrolac tam-fused indoloquinolizidine with highly stereochemical control.

We envisaged that α-oxo-γ-butyrolactam **2** could be utilized as readily available *N*-containing pronucleophile, and the unprecedented butyrolactam-fused indoloquinolizidine could be constructed by means of organocatalyzed three-component coupling reaction of **2**, α,β-unsaturated aldehyde **3**, and tryptamine. On the basis of the iminium ion activation

Received: June 22, 2012
Published: August 13, 2012

dx.doi.org/10.1021/jo301192d | J. Org. Chem. 2012, 77, 7737–7743

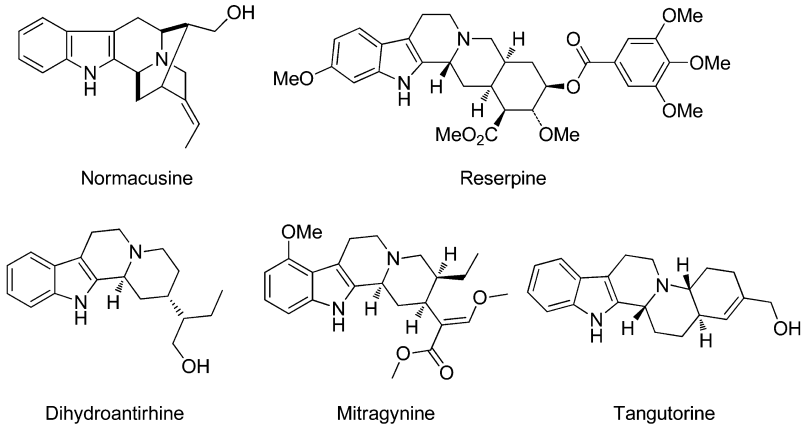
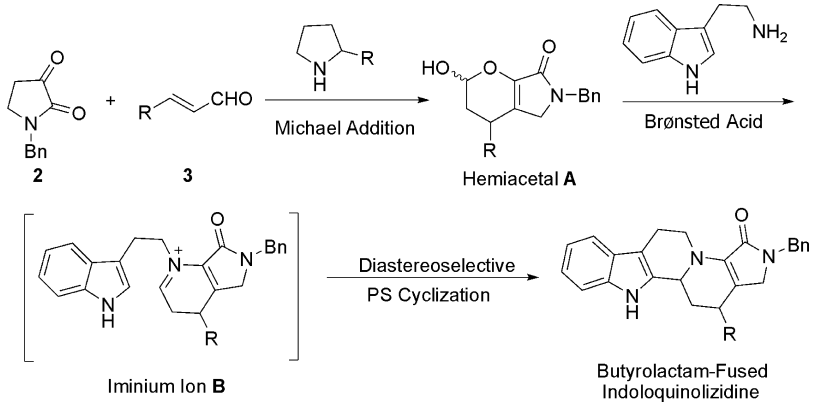


Figure 2. Representative natural products incorporating the indoloquinolizidine scaffold.

Scheme 1. Proposed Sequential Michael Addition/Pictet–Spengler Cyclization to Butyrolactam-Fused Indoloquinolizidine Scaffold



strategy,[10] secondary amine catalyzed Michael addition of **2** to **3** would initiate the reaction sequence to deliver the chiral hemiacetal **A**. Under the acidic conditions, the activated hemiacetal **A** reacts with tryptamine to generate the iminium ion **B**, which then undergoes a diastereoselective Pictet–Spengler reaction[11] to afford the anticipated butyrolactam-fused indoloquinolizidine (Scheme 1).

With this speculation in mind, we began the investigation by testing the model reaction between **2a** and **3a** in the presence of diarylprolinol TMS ether[12] **1b**. After complete formation of the hemiacetal, benzoic acid and tryptamine were added. We were pleased to find that further reaction proceeded smoothly at room temperature to furnish the desired butyrolactam-fused indoloquinolizidine with good yield and high stereoselectivity.

The successful implementation of one-pot transformation in a cascade process requires the optimization of the first step to make it compatible with the consecutive ones. In order to simplify the reaction system of the first step, we switched the ratio of **3a** to **2a** from 2:1 to 2:3. After an initial screening of several solvents for this entire one-pot sequence performed at room temperature, it was found that dichloromethane was the most suitable one in terms of both diastereo- and enantioselectivities. With the optimal solvent, various diarylprolinol-derived catalysts were screened briefly in the model reaction. The enantioselectivities varied depending on the organocatalysts used. As expected, the use of **1a** and **1b** gave the same results only with a slightly different yield. For the second step, the final desired product could also be obtained utilizing CSA or TFA, but the yield was lower than that in the case of benzoic acid. The results are summarized in Table 1.

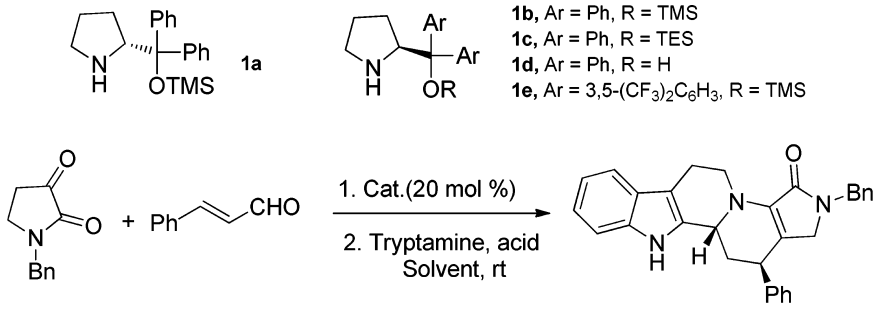
The extension of this one-pot procedure to various substrates was then investigated under the established conditions. The results are summarized in Table 2. For α-oxo-γ-butyrolactam **2**, a wide range of α,β-unsaturated aldehydes with β-aryl groups, either bearing electron-withdrawing or electron-donating substitutions, could be efficiently utilized. With respect to aryl substitution, *ortho*-, *para*-, and *meta*-substituents were all well tolerated, leading to desired products with moderate to high yields and high enantioselectivities. However, aldehydes bearing electron-donating substituents on the phenyl ring delivered lower diastereoselectivities. To our delight, for 2-furylacrolein, the desired product was also obtained with 76% yield and low diastereoselectivity (entry 16). The absolute configuration of **4o** was determined to be (2*R*,13b*R*) according to the X-ray crystal structure of compounds **4o** and **5**.[13]

To further illustrate the synthetic value of α-oxo-γ-butyrolactam, *o*-aminobenzylamine was employed as a reaction partner with two nucleophilic sites to trap the hemiacetal **A** in this organocatalytic one-pot sequence. The interesting heterocyclic architecture, butyrolactam-incorporated pyridoquinazoline, can be efficiently generated in moderate yield and with high enantioselectivity (Scheme 2). The absolute configuration of **5** was determined to be (4*R*,5a*R*) by the X-ray crystal structure of compound **5**.[13]

With regard to the mechanism of this reaction sequence, we assume that initially enal **3** is activated by catalyst **1a** through

dx.doi.org/10.1021/jo301192d | J. Org. Chem. 2012, 77, 7737–7743

Table 1. Optimization of the One-Pot Reaction Conditions

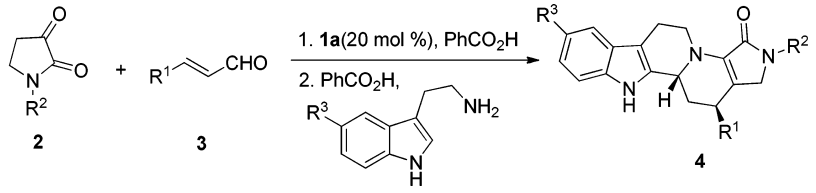


2a **3a** **4a**

entry[a]	solvent	cat.	yield[b] (%)	dr[c]	ee[d] (%)
1	toluene	**1a**	74	4:1	94
2	THF	**1a**	32	3:1	93
3	MeCN	**1a**	14		
4	EtOH	**1a**	<10		
5	DCE	**1a**	81	4:1	94
6	DCM	**1a**	87	4:1	95
7	DCM	**1b**	85	4:1	−95
8	DCM	**1c**	81	4:1	−94
9	DCM	**1d**	86	4:1	−87
10	DCM	**1e**	18		

[a]Unless otherwise noted, the reaction was carried out as follows: (step 1) **2** (0.3 mmol), **3** (0.2 mmol), **1** (0.04 mmol), $PhCO_2H$ (0.04 mmol); (step 2) tryptamine (0.24 mmol), $PhCO_2H$ (0.24 mmol) in dry CH_2Cl_2 (1.5 mL) at room temperature. [b]Isolated yields. [c]Determined by ^1H NMR or HPLC analysis. [d]Determined by HPLC analysis of the main diastereomer.

Table 2. Scope of the Reaction



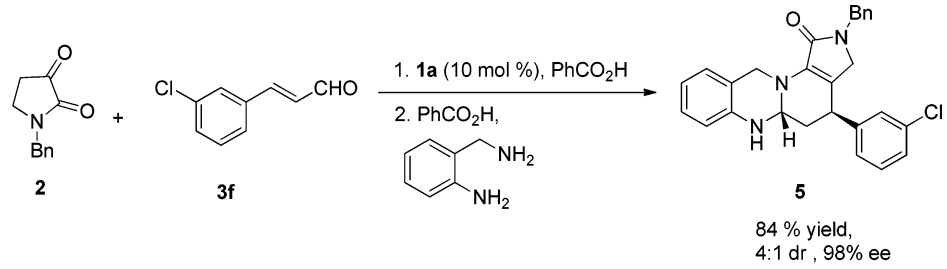
entry[a]	R^1, R^2, R^3	**4**	yield[b] (%)	dr[c]	ee[d] (%)
1	Ph, Bn, H	**4a**	87	4:1	95
2	*o*-MeOPh, Bn, H	**4b**	74	4:1	96
3	*p*-MeOPh, Bn, H	**4c**	71	4:1	96
4	*p*-MePh, Bn, H	**4d**	75	3:1	96
5	*p*-BrPh, Bn, H	**4e**	81	15:1	95
6	*m*-ClPh, Bn, H	**4f**	72	>20:1	95
7	*p*-ClPh, Bn, H	**4g**	79	17:1	96
8	*p*-FPh, Bn, H	**4h**	69	8:1	93
9	2,4-diChloroPh, Bn, H	**4i**	83	3:1	95
10	*p*-CNPh, Bn, H	**4j**	76	8:1	97
11	Ph, allyl, H	**4k**	62	>20:1	93
12	*p*-MePh, allyl, H	**4l**	62	>20:1	93
13	*p*-BrPh, allyl, H	**4m**	53	>20:1	93
14	*p*-CNPh, allyl, H	**4n**	60	8:1	93
15	Ph, Bn, MeO	**4o**	84	2:1	95
16	2-furyl, Bn, H	**4p**	76	3:1	90

[a]General conditions: (step 1) α-oxo-γ-butyrolactam (0.3 mmol), enal (0.2 mmol), **1a** (0.04 mmol), $PhCO_2H$ (0.04 mmol) in CH_2Cl_2 (1.5 mL). (step 2) Tryptamine (0.24 mmol), $PhCO_2H$ (0.24 mmol). [b]Isolated yield after column chromatography. [c]Determined by ^1H NMR or HPLC. [d]Determined by the HPLC analysis of the major diastereomer.

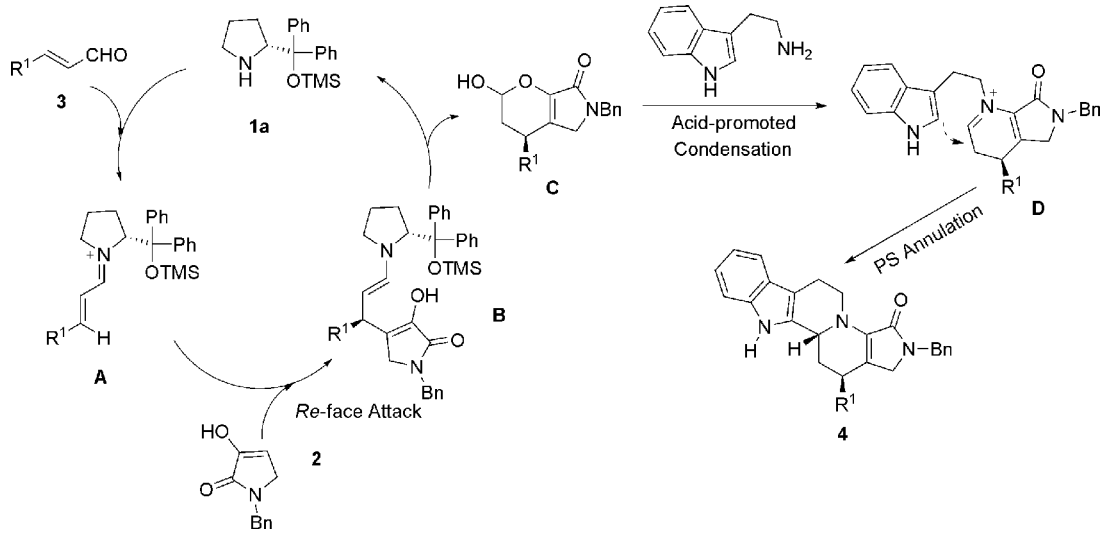
the reactive iminium ion **A**. Because of the shielding effect of catalyst **1a**, subsequent stereoselective *Re*-facial Michael addition by α-oxo-γ-butyrolactam **2** occurs and generates intermediate **B**, which undergoes subsequent tautomerization and hydrolysis to form **C**. The masked 1,5-dicarbonyl compounds **C** could efficiently condense with tryptamine to give rise to iminium ion **D** under acidic conditions, and intermediate **D** performs diastereoseletive Pictet−Spengler

dx.doi.org/10.1021/jo301192d | J. Org. Chem. 2012, 77, 7737−7743

Scheme 2. Further Investigation of the Reaction Potential



Scheme 3. Plausible Catalytic Cycle of One-Pot Michael/Pictet–Spengler Sequence



cyclization to afford butyrolactam-fused indoloquinolizidine **4** owing to the steric hindrance of the R^1 group (Scheme 3).

In conclusion, we have developed an organocatalytic one-pot strategy for the stereoselective construction of synthetically interesting and medicinally important pentacyclic butyrolactam-fused indoloquinolizidines. Promoted by simple chiral secondary amine and benzoic acid, the multicomponent coupling reaction of α-oxo-γ-butyrolactam, α,β-unsaturated aldehyde, and tryptamine proceeded efficiently with highly stereochemical control. For the first time, α-oxo-γ-butyrolactam was exploited as reactive pronucleophile to directly assemble chiral butyrolactams. This chemistry provides a general catalytic method for the enantioselective synthesis of butyrolactam-incorporated chemical entities. The results presented here potentially have an impact on new reaction design and scaffold diversity synthesis of five-membered N-heterocyclic systems.

■ EXPERIMENTAL SECTION

General Remarks. Chemicals and solvents were either purchased from commercial suppliers or purified by standards techniques. Analytical thin-layer chromatography (TLC) was performed on silica gel plates with F-254 indicator, and compounds were visualized by irradiation with UV light. Flash chromatography was carried out utilizing silica gel 200–300 mesh. ^{1}H NMR and ^{13}C NMR spectra were recorded on ^{1}H 400 MHz and ^{13}C 100 MHz spectrometers. The spectra were recorded in $CDCl_3$ as solvents; ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to either the residual solvent peak (^{13}C) (δ = 77.00 ppm) or TMS (^{1}H) (δ = 0 ppm) as an internal standard. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported as chemical shift. IR spectra are reported in wavenumbers (cm^{-1}). HRMS were performed on FT-ICRMS mass instrument (ESI). Enantiomeric excess values were determined by HPLC with employing a Daicel Chirapak AD-H, OD-H, and AS-H and eluting with *i*-PrOH and *n*-hexane. Optical rotation was measured on polarimeter with $[\alpha]_D$ values reported in degrees; concentration (c) is in g/100 mL. α-Oxo-γ-butyrolactam **2** were prepared according to the previously reported methods.[14]

General Procedure for the Synthesis of 4. To a solution of compound **2** (0.3 mmol) and catalyst **1** (0.04 mmol) in CH_2Cl_2 (1.5 mL) were added enal **3** (0.2 mmol) and benzoic acid (0.04 mmol), and the mixture was stirred at room temperature. The reaction was monitored by TLC analysis. After full conversion of **3**, tryptamine or substituted tryptamine (0.24 mmol) and benzoic acid (0.24 mmol) were added to the solution. After completion of the reaction, the mixture was subjected directly to flash column chromatography yielding the corresponding products.

4a: 77.4 mg (87% yield); gray-white solid; mp 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (s, 1H), 7.46–7.41 (m, 1H), 7.39–7.18 (m, 7H), 7.14–7.09(m, 4H), 7.08–7.03 (m, 2H), 4.76–4.68 (m, 2H), 4.47 (d, J = 6.8 Hz, 1H), 4.36 (d, J = 15.2 Hz, 1H), 3.58 (t, J = 5.6 Hz, 1H), 3.48–3.35 (m, 3H), 2.86–2.70 (m, 2H), 2.43–2.35 (m, 1H), 2.25–2.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.4, 143.6, 137.8, 137.3, 135.9, 132.7, 128.8, 128.6, 128.0, 127.9, 127.4, 127.3, 127.0, 123.6, 121.7, 119.6, 118.2, 110.8, 110.3, 51.4, 49.0, 46.4, 43.6, 37.8, 34.9, 21.3 ppm; IR (KBr) = 3287, 3027, 2840, 2357, 2049, 2024, 1664, 1493, 1452, 1402, 1360, 1253, 1225, 920, 744, 702, 571, 424 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{27}N_3O$ $[M + Na]^+$ 468.2046, found 468.2062; $[\alpha]^{20}_D$ = −31.1 (c 2.25, CH_2Cl_2, 95% ee. The enantiomeric excess was determined by HPLC with an AD-H column. (*n*-hexane/*i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 23.4 min, minor enantiomer t_R = 33.0 min.

4b: 70.3 mg (74% yield); gray-white solid; mp 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 (s, 1H), 7.49–7.43 (m, 1H), 7.29–7.19 (m, 7H), 7.12–7.05 (m, 3H), 6.89–6.86 (m, 2H), 4.69 (d, J =

dx.doi.org/10.1021/jo301192d | J. Org. Chem. 2012, 77, 7737–7743

14.8 Hz, 1H), 4.64−4.59 (m, 1H), 4.50 (d, J = 14.8 Hz, 1H), 4.38−4.35 (m, 1H), 4.06 (t, J = 4.8 Hz, 1H), 3.81 (s, 3H), 3.57 (d, J = 18.0 Hz, 1H), 3.51−3.43 (m, 2H), 2.91−2.79 (m, 2H), 2.23−2.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5, 156.7, 138.3, 137.4, 135.9, 133.1, 131.5, 129.2, 128.6, 128.3, 127.9, 127.4, 127.3, 124.1, 121.5, 120.5, 119.3, 118.1, 110.7, 110.4, 109.9, 55.2, 51.2, 49.1, 46.3, 43.3, 32.7, 31.6, 21.5 ppm; IR (KBr) = 3277, 3028, 2910, 2837, 2049, 2023, 1664, 1490, 1454, 1401, 1288, 1243, 1113, 1095, 1028, 743, 702, 571, 437 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}N_3O_2$ [M + H]$^+$ 476.2333, found 476.2337; $[\alpha]^{20}_D$ = 20.0 (c 1.0, CH_2Cl_2, 96% ee. The enantiomeric excess was determined by HPLC with an OD-H column (n-hexane/i-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 30.5 min, minor enantiomer t_R = 23.9 min.

4c: 67.4 mg (71% yield); gray-white solid; mp 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16 (s, 1H), 7.48−7.46 (m, 1H), 7.26−7.20 (m, 4H), 7.15−7.03 (m, 6H), 6.81−6.79 (m, 2H), 4.75−4.66 (m, 2H), 4.47(d, J = 5.6 Hz, 1H), 4.38 (d, J = 15.2 Hz, 1H), 3.74 (s, 1H), 3.55 (t, J = 5.6 Hz, 1H), 3.49−3.36 (m, 3H), 2.85−2.71 (m, 2H), 2.39−2.33 (m, 1H), 2.22−2.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5, 158.4, 137.4, 137.2, 135.9, 135.4, 132.9, 128.8, 128.5, 127.7, 127.3, 127.2, 124.7, 121.4, 119.3, 118.1, 114.1, 110.9, 109.8, 55.1, 51.6, 48.9, 46.2, 43.7, 36.8, 34.7, 21.2 ppm; IR (KBr) = 3286, 2913, 2838, 2021, 1665, 1510, 1454, 1249, 1176, 1033, 835, 741, 702, 568, 429 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_2$ [M + H]$^+$ 476.2333, found 476.2321; $[\alpha]^{20}_D$ = −67.7 (c 0.9, CH_2Cl_2, 96% ee). The enantiomeric excess was determined by HPLC with an AD-H column (n-hexane/i-PrOH = 65:35), 1.0 mL/min; major enantiomer t_R = 10.2 min, minor enantiomer t_R = 22.8 min.

4d: 68.8 mg (75% yield); gray-white solid; mp 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (b, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.29−7.19 (m, 4H), 7.18−7.14 (m, 2H), 7.13−7.03 (m, 4H), 7.07−7.03 (m, 2H), 4.75−4.69 (m, 2H), 4.47 (d, J = 5.6 Hz, 1H), 4.41 (d, J = 15.2 Hz, 1H), 3.58 (t, J = 5.6 Hz, 1H), 3.53−3.38 (m, 3H), 2.88−2.75 (m, 2H), 2.37−2.31 (m, 4H), 2.23−2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.5, 140.5, 137.6, 137.3, 136.6, 135.9, 132.8, 129.4, 128.6, 127.8, 127.4, 127.3, 124.3, 121.6, 119.4, 118.1, 110.8, 110.1, 110.0, 51.5, 49.0, 46.4, 43.7, 37.4, 34.9, 21.3, 20.9 ppm; IR (KBr) = 3302, 3029, 2921, 2845, 2022, 1657, 1513, 1452, 1399, 1317, 1224, 1103, 817, 739, 701, 569, 434 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}N_3O$ [M + H]$^+$ 460.2383, found 460.2387; $[\alpha]^{20}_D$ = 43.3 (c 1.2, CH_2Cl_2, 96% ee). The enantiomeric excess was determined by HPLC with an AS-H column. (n-hexane/i-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 27.0 min, minor enantiomer t_R = 18.8 min.

4e: 84.7 mg (81% yield); gray-white solid; mp 134−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.24 (b, 1H), 7.48−7.38 (m, 3H), 7.28−7.21 (m, 4H), 7.15−7.05(m, 4H), 7.05−7.01 (m, 2H), 4.81−4.76 (m, 1H), 4.70(d, J = 15.2 Hz, 1H), 4.45−4.37 (m, 2H), 3.55 (t, J = 5.6 Hz, 1H), 3.47−3.33 (m, 3H), 2.86−2.71 (m, 2H), 2.41−2.34 (m, 1H), 2.22−2.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 142.4, 137.8, 137.1, 135.9, 132.5, 131.8, 129.6, 128.6, 127.8, 127.4, 127.2, 123.0, 121.6, 120.7, 119.5, 118.2, 110.9, 110.0, 51.5, 48.8, 46.3, 43.6, 37.2, 34.6, 21.2 ppm; IR (KBr): = 3265, 3058, 2910, 2842, 2049, 2022, 1661, 1553, 1487, 1458, 1402, 1262, 1223, 1071, 1009, 924, 827, 739, 568, 530, 438 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}BrN_3O$ [M + H] $^+$ 524.1332, found 524.1333; $[\alpha]^{20}_D$ = −70.0 (c 2.4, CH_2Cl_2, 95% ee). The enantiomeric excess was determined by HPLC with an AD-H column (n-hexane/i-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 16.5 min, minor enantiomer t_R = 35.4 min.

4f: 68.9 mg (72% yield); gray-white solid; mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 (b, 1H), 7.48−1.47 (m, 1H), 7.29−7.21 (m, 6H), 7.16−7.02 (m, 6H), 4.82−4.76 (m, 1H), 4.73 (d, J = 15.2 Hz, 1H), 4.47 (d, J = 6.4 Hz, 1H), 4.40 (d, J = 15.2 Hz, 1H), 3.58 (t, J = 5.6 Hz, 1H), 3.51−3.35 (m, 3H), 2.87−2.72 (m, 2H), 2.35−2.42 (m, 1H), 2.24−2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 145.6, 137.9, 137.1, 135.9, 134.6, 132.5, 130.0, 128.6, 128.1, 127.7, 127.4, 127.2, 127.1, 126.1, 122.7, 121.7, 119.5, 118.2, 110.9, 110.1, 51.5, 48.9, 46.4, 43.6, 37.5, 34.6, 21.2 ppm; IR (KBr) = 3306, 2913, 2031, 1662, 1453, 1317, 1225, 1112, 1062, 745, 699 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}ClN_3O$ [M + H]$^+$: 480.1837, found: 480.1826; $[\alpha]^{20}_D$ = −33.0 (c 1.0, CH_2Cl_2, 95% ee). The enantiomeric excess was determined by HPLC with an AD-H column. (n-hexane/i-PrOH = 70:30), 1.0 mL/min; major enantiomer t_R = 10.6 min, minor enantiomer t_R = 17.7 min.

4g: 75.7 mg (79% yield); gray-white solid; mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09 (b, 1H), 7.49−7.43 (m, 1H), 7.28−7.22 (m, 6H), 7.16−7.14 (m, 2H), 7.12−7.06 (m, 3H), 4.81−4.75(m, 1H), 4.69 (d, J = 15.2 Hz, 1H), 4.46 (d, J = 6.0 Hz, 1H), 4.41 (d, J = 15.2 Hz, 1H), 3.57 (t, J = 5.6 Hz, 1H), 3.48−3.35 (m, 3H), 2.88−2.73 (m, 2H), 2.41−2.34 (m, 1H), 2.22−2.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 141.9, 137.8, 137.1, 135.9, 133.4, 132.7, 132.5, 130.1, 129.3, 128.9, 128.6, 127.8, 127.4, 121.6, 119.5, 118.1, 110.9, 110.1, 51.5, 48.9, 46.3, 43.7, 37.2, 34.7, 21.2 ppm; IR (KBr) = 3292, 3030, 2918, 2843, 2044, 2023, 1666, 1491, 1453, 1405, 1310, 1225, 1094, 1012, 833, 744, 701, 571 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}ClN_3O$ [M + H] $^+$ 480.1837, found 480.1830; $[\alpha]^{20}_D$ = −65.0 (c 1.4, CH_2Cl_2, 96% ee). The enantiomeric excess was determined by HPLC with an AD-H column (n-hexane/i-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 16.3 min, minor enantiomer t_R = 32.9 min.

4h: 63.9 mg (69% yield); gray-white solid; mp 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (b, 1H), 7.50−7.48 (m, 1H), 7.29−7.22 (m, 4H), 7.17−7.07 (m, 6H), 7.01−6.96 (m, 2H), 4.82−4.71 (m, 1H), 4.71 (d, J = 14.8 Hz, 1H), 4.48 (d, J = 6.0 Hz, 1H), 4.42 (d, J = 15.2 Hz, 1H), 3.60 (t, J = 5.6 Hz, 1H), 3.49−3.37 (m, 3H), 2.88−2.75 (m, 2H), 2.41−2.34 (m, 1H), 2.23−2.18 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 161.7 (d, J = 244.0 Hz), 139.1, 137.7, 137.2, 135.9, 132.5, 129.4, 128.6, 127.8, 127.4, 123.4, 121.7, 119.5, 118.2, 115.7, 115.5, 110.8, 110.2, 51.5, 48.9, 46.4, 43.6, 37.0, 34.9, 21.2 ppm; IR (KBr) = 3669, 3311, 3031, 2912, 2842, 2049, 2023, 1661, 1508, 1453, 1401, 1225, 1157, 1109, 838, 741, 701, 651, 570, 429 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{26}FN_3O$ [M + H]$^+$ 464.2133, found 464.2136; $[\alpha]^{20}_D$ = −30.3 (c 1.45, CH_2Cl_2, 93% ee). The enantiomeric excess was determined by HPLC with an AD-H column (n-hexane/i-PrOH = 70:30), 1.0 mL/min; major enantiomer t_R = 9.2 min, minor enantiomer t_R = 15.8 min.

4i: 85.1 mg (83% yield); gray-white solid; mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (b, 1H), 7.50−7.41 (m, 2H), 7.29−7.18 (m, 7H), 7.12−7.06 (m, 3H), 4.76−4.70 (m, 2H), 4.48 (d, J = 14.8 Hz, 1H), 4.33 (d, J = 8.8 Hz, 1H), 4.13−4.07 (m, 1H), 3.58−3.42 (m, 3H), 2.92−2.78 (m, 2H), 2.34−2.27(m, 1H), 2.19(d, J = 13.6 Hz, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.1, 139.4, 139.1, 137.1, 135.9, 134.1, 133.3, 132.2, 130.7, 129.7, 128.7, 128.0, 127.5, 127.3, 127.2, 121.7, 120.6, 119.5, 118.2, 110.8, 110.1, 50.8, 48.8, 46.4, 43.1, 34.5, 32.9, 21.5 ppm; IR (KBr) = 3607, 3302, 3059, 2919, 2843, 2049, 2024, 1668, 1557, 1494, 1465, 1404, 1309, 1225, 1201, 1102, 1048, 869, 820, 737, 571, 434 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{25}Cl_2N_3O$ [M + H] $^+$ 514.1447, found 514.1439; $[\alpha]^{20}_D$ = 4.6 (c 1.95, CH_2Cl_2, 95% ee). The enantiomeric excess was determined by HPLC with an AD-H column (n-hexane/i-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 25.1 min, minor enantiomer t_R = 29.3 min.

4j: 71.4 mg (76% yield); gray-white solid; mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 (b, 1H), 7.55−7.47 (m, 3H), 7.29−7.24 (m, 6H), 7.17−7.08 (m, 4H), 4.87−4.82 (m, 1H), 4.69 (d, J = 14.8 Hz, 1H), 4.47−4.41 (m, 2H), 3.67 (t, J = 6.2 Hz, 1H), 3.43−3.36 (m, 3H), 2.88−2.74 (m, 2H), 2.45−2.39 (m, 1H), 2.28−2.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.1, 149.1, 138.2, 137.0, 135.9, 132.5, 132.2, 128.8, 128.6, 127.8, 127.5, 127.2, 121.7, 121.1, 119.5, 118.4, 118.2, 110.9, 110.7, 110.1, 51.4, 48.7, 46.4, 43.5, 37.9, 34.5, 21.3 ppm; IR (KBr) = 3296, 2916, 2842, 2227, 2022, 1671, 1452, 1405, 1305, 1225, 1102, 841, 744, 701, 565, 433 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{26}N_4O$ [M + H$^+$] 471.2179, found 471.2168; $[\alpha]^{20}_D$ = −81.4 (c 1.4, CH_2Cl_2, 96% ee). The enantiomeric excess was determined by HPLC with an AD-H column (n-hexane/i-PrOH = 70:30), 1.0 mL/min; major enantiomer t_R = 13.7 min, minor enantiomer t_R = 28.4 min.

4k: 49.0 mg (62% yield); gray-white solid; mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (b, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.36−7.19 (m, 6H), 7.15−7.07 (m, 2H), 5.76−5.69 (m, 1H), 5.12−5.06 (m, 2H), 4.75−4.71 (m, 1H), 4.50 (d, J = 5.6 Hz, 1H), 4.11−4.05 (m, 1H), 3.95−3.90 (m, 1H), 3.67 (t, J = 5.6 Hz, 1H), 3.58−3.52 (m,

dx.doi.org/10.1021/jo301192d | J. Org. Chem. 2012, 77, 7737−7743

2H), 3.41−3.35 (m, 1H), 2.83−2.76 (m, 2H), 2.43−2.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.2, 143.5, 137.7, 135.8, 133.2, 132.7, 128.8, 128.1, 127.3, 127.0, 123.8, 121.6, 119.5, 118.2, 117.4, 110.8, 110.1, 51.5, 49.1, 45.1, 43.6, 37.8, 34.8, 21.2 ppm; IR (KBr) = 3273, 2926, 2845, 2022, 1661, 1456, 1400, 1315, 1223, 1144, 924, 744, 702, 567, 435 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{25}N_3O$ [M + H]$^+$ 396.2070, found 396.2075; $[\alpha]^{20}_D$ = −25.7 (*c* 1.05, CH_2Cl_2, 93% ee). The enantiomeric excess was determined by HPLC with an OD-H column (*n*-hexane/*i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 29.2 min, minor enantiomer t_R = 15.4 min.

4l: 50.7 mg (62% yield); gray-white solid; mp 105−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (s, 1H), 7.49−7.47 (m, 1H), 7.29−7.24 (m, 1H), 7.16−7.08 (m, 6H), 5.77−5.67 (m, 1H), 5.11−5.05 (m, 2H), 4.72−4.67 (m, 1H), 4.49 (d, *J* = 6.0 Hz, 1H), 4.07 (dd, *J* = 6.0, 15.2 Hz, 1H), 3.92 (dd, *J* = 6.0, 15.2 Hz, 1H), 3.62 (t, *J* = 5.6 Hz, 1H), 3.58−3.46 (m, 2H), 3.41−3.37 (m, 1H), 2.82−2.76 (m, 2H), 2.37−2.34 (m, 4H), 2.25−2.20(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 140.5, 137.7, 136.6, 135.8, 133.3, 132.9, 129.4, 127.9, 127.3, 124.3, 121.6, 119.4, 118.1, 117.4, 110.8, 110.1, 51.5, 49.1, 45.1, 43.6, 37.3, 34.8, 21.2, 20.9 ppm; IR (KBr) = 3399, 3282, 2918, 2844, 2045, 2023, 1664, 1511, 1457, 1402, 1308, 1223, 1171, 1065, 992, 930, 818, 741, 670, 566, 528, 434 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{27}N_3O$ [M + H]$^+$ 410.2227, found 410.2225; $[\alpha]^{20}_D$ = −53.7 (*c* 0.8, CH_2Cl_2, 93% ee). The enantiomeric excess was determined by HPLC with an AD-H column. (*n*-hexane/*i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 11.34 min, minor enantiomer t_R = 9.6 min.

4m: 50.1 mg (53% yield); gray-white solid; mp 126−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (b, 1H), 7.49−7.45 (m, 3H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.24−7.07 (m, 4H), 5.74−5.66 (m, 1H), 5.12−5.06 (m, 2H), 4.78−7.74 (m, 1H), 4.48 (d, *J* = 6.0 Hz, 1H), 4.05 (dd, *J* = 6.0, 15.6 Hz, 1H), 3.92 (dd, *J* = 6.0, 15.6 Hz, 1H), 3.63 (t, *J* = 5.6 Hz, 1H), 3.51 (s, 2H), 3.38−3.33 (m, 1H), 2.82−2.72(m, 2H), 2.44−2.37 (m, 1H), 2.25−2.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.1, 142.5, 137.9, 135.9, 133.1, 132.5, 131.9, 129.7, 127.2, 122.8, 121.6, 120.8, 119.5, 118.2, 117.6, 110.9, 110.1, 51.5, 48.9, 45.1, 43.6, 37.3, 34.7, 21.2 ppm; IR (KBr): = 3601, 3277, 2910, 2841, 2359, 2047, 2023, 1661, 1486, 1458, 1403, 1313, 1224, 1070, 1008, 922, 828, 741, 569, 438 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{24}BrN_3O$ [M + H] $^+$ 474.1176, found 474.1173; $[\alpha]^{20}_D$ = −66.0 (*c* 1.0, CH_2Cl_2, 93% ee). The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 70:30), 1.0 mL/min; major enantiomer t_R = 11.9 min, minor enantiomer t_R = 6.7 min.

4n: 50.4 mg (60% yield); gray-white solid; mp 136−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (b, 1H), 7.64−7.48 (m, 3H), 7.36−7.25 (m, 3H), 7.17−7.08 (m, 2H), 5.78−5.69 (m, 1H), 5.14−5.08(m, 2H), 4.89−4.83 (m, 1H), 4.48 (d, *J* = 6.0 Hz, 1H), 4.08 (dd, *J* = 6.0, 15.6 Hz, 1H), 3.94(dd, *J* = 6.0, 15.2 Hz, 1H), 3.75 (t, *J* = 5.2 Hz, 1H), 3.51 (s, 2H), 3.39−3.33 (m, 1H), 2.88−2.74 (m, 2H), 2.47−2.40 (m, 1H), 2.30−2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.7, 149.2, 138.4, 135.9, 133.1, 132.6, 132.1, 128.9, 127.2, 121.9, 120.6, 119.6, 118.5, 118.3, 117.7, 111.0, 110.8, 110.4, 51.4, 48.7, 45.1, 43.5, 38.0, 34.7, 21.3 ppm; IR (KBr) = 3582, 3272, 3058, 2841, 2229, 2046, 2018, 1660, 1459, 1404, 1309, 1224, 929, 841, 740, 569 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{24}N_4O$ [M + H]$^+$ 421.2023, found 421.2017; $[\alpha]^{20}_D$ = −110.6 (*c* 0.75, CH_2Cl_2, 93% ee). The enantiomeric excess was determined by HPLC with an AS-H column (*n*-hexane/*i*-PrOH = 60:40), 1.0 mL/min; major enantiomer t_R = 21.2 min, minor enantiomer t_R = 9.5 min.

4o: 79.8 mg (84% yield); gray-white solid; mp 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (b, 1H), 7.29−7.22 (m, 6H), 7.18−7.14 (m, 5H), 6.94 (d, *J* = 2.4 Hz, 1H), 6.77(dd, *J* = 2.4, 8.8 Hz, 1H), 4.78−4.70 (m, 2H), 4.47 (d, *J* = 6.0 Hz, 1H), 4.41 (d, *J* = 15.2 Hz, 1H), 3.84 (s, 3H), 3.61 (t, *J* = 5.6 Hz, 1H), 3.52−3.37 (m, 3H), 2.82−2.71 (m, 2H), 2.39−2.33 (m, 1H), 2.24−2.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.4, 154.1, 143.5, 137.7, 137.3, 133.7, 130.9, 128.8, 128.6, 128.3, 128.0, 127.9, 127.7, 127.4, 126.9, 123.9, 111.6, 109.9, 100.3, 55.9, 51.6, 49.0, 46.4, 43.7, 37.8, 34.8, 21.3 ppm; IR (KBr) = 3308, 2942, 2047, 2024, 1659, 1456, 1320, 1214, 1148, 1066, 802, 704, 629, 570 cm^{-1}; HRMS (ESI) calcd for $C_{31}H_{29}N_3O_2$ [M + H]$^+$ 476.2333, found 476.2338; $[\alpha]^{20}_D$ = −75.3 (*c* 1.5, CH_2Cl_2, 95% ee). The enantiomeric excess was determined by HPLC with an OD-H column (*n*-hexane/*i*-PrOH = 70:30), 1.0 mL/min; major enantiomer t_R = 28.5 min, minor enantiomer t_R = 19.9 min

4p: 66.1 mg (76% yield); gray-white solid; mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 (b, 1H), 7.50−7.48 (m, 1H), 7.32−7.19 (m, 7H), 7.13−7.08 (m, 2H), 6.27 (dd, *J* = 2.0, 2.8 Hz, 1H), 6.01 (d, *J* = 2.8 Hz, 1H), 4.74−4.68 (m, 2H), 4.49−4.43 (m, 2H), 3.70 (t, *J* = 5.2 Hz, 1H), 3.66−3.52 (m, 2H), 3.44−3.37 (m, 1H), 2.85−2.75 (m, 2H), 2.42−2.37 (m, 1H), 2.28−2.21 (m, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 155.9, 141.8, 137.4, 137.3, 135.9, 132.6, 130.1, 128.7, 128.4, 127.9, 127.4, 127.3, 121.7, 119.5, 118.2, 110.9, 110.3, 106.2, 51.8, 49.2, 46.4, 43.4, 31.6, 31.1, 21.3 ppm; IR (KBr) = 3319, 2930, 2829, 2049, 2023, 1668, 1644, 1452, 1316, 1226, 1139, 1008, 741, 725, 598, 557, 429 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{25}N_3O_2$ [M + H$^+$] 436.2020, found 436.2022; $[\alpha]^{20}_D$ = −44.5 (*c* 1.1, CH_2Cl_2, 90% ee). The enantiomeric excess was determined by HPLC with an OD-H column. (*n*-hexane/*i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 22.2 min, minor enantiomer t_R = 16.8 min.

Experimental Procedure for the Synthesis of 5. To a solution of compound **2** (0.3 mmol) and catalyst **1a** (0.04 mmol) in dichloromethane (1.5 mL) were added enal **3** (0.2 mmol) and $PhCO_2H$ (0.04 mmol), and the mixture was stirring at room temperature. The reaction was monitored by TLC analysis. After full conversion of **3**, 2-(aminomethyl)aniline (0.24 mmol) and BzOH (0.24 mmol) were added to the solution. After completion of the reaction, the mixture was subjected directly to flash column chromatography yielding the corresponding products.

5: 74.1 mg (84% yield); gray-white solid; mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27−7.14 (m, 7H), 7.04−6.99 (m, 3H), 6.75−6.69 (m, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 5.97 (d, *J* = 16.8 Hz, 1H), 4.66−4.64 (m, 1H), 4.60 (d, *J* = 14.8 Hz, 1H), 4.42 (d, *J* = 15.2 Hz, 1H), 4.30 (d, *J* = 16.4 Hz, 1H), 3.87−3.79 (m, 2H), 3.38 (d, *J* = 2.4 Hz, 2H), 2.26−2.20 (m, 1H), 2.15−2.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.9, 144.8, 142.6, 137.1, 135.8, 134.6, 130.0, 128.6, 128.1, 127.9, 127.4, 127.2, 127.1, 126.9, 126.0, 121.8, 121.1, 118.8, 115.1, 64.4, 48.4, 46.4, 46.3, 36.6, 36.3 ppm; IR (KBr) = 3431, 2922, 2854, 1673, 1495, 1296, 1228, 750, 701, 584, 403 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{24}ClN_3O$ [M + H]$^+$ 442.1681, found 442.1670; $[\alpha]^{20}_D$ = −146.5 (*c* 0.43, CH_2Cl_2, 98% ee). The enantiomeric excess was determined by HPLC with an OD-H column (*n*-hexane: *i*-PrOH = 70:30), 1.0 mL/min; major enantiomer t_R = 31.5 min, minor enantiomer t_R = 41.6 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, spectra data for the products, and X-ray crystallographic data (CIF file of **4o**: CCDC 873633, CIF file of **5**: CCDC 881242). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the NSFC (21032005, 20972058, 21172097), the National Basic Research Program of China (No. 2010CB833203), and the "111" program from MOE of P. R. China.

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