$Rh_2(OAc)_4$ and Chiral Phosphoric Acid Cocatalyzed Highly Diastereo- and Enantioselective Four-Component Reactions: Facile Synthesis of Chiral α,β-Diamino Acid Derivatives

Changcheng Jing, Dong Xing, Yu Qian, Wenhao Hu*

Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, and Department of Chemistry, East China Normal University, Shanghai, 200062, P. R. of China
Fax +86(21)62221235; E-mail: whu@chem.ecnu.edu.cn

Received: 02.02.2014; Accepted: 25.02.2014

Abstract: A highly diastereo- and enantioselective four-component reaction of a diazo ketone with two molecules of anilines and ethyl glyoxylate was achieved under $Rh_2(OAc)_4$ and chiral phosphoric acid cocatalyzed conditions. This transformation proceeds through a Mannich-type trapping of the ammonium ylide generated from metal carbene and one molecule of aniline with iminoester derived from another molecule of aniline and ethyl glyoxylate. With this method, a series of chiral α,β-diamino acid derivatives were efficiently constructed in good yields and with good to excellent diastereo- and enantioselectivities.

Key words: four-component reaction, metal carbene, chiral Brønsted acid, ammonium ylide, chiral α,β-diamino acid

Chiral α,β-diamino acid scaffolds are present widely in natural products and biologically active compounds, and have received extensive attention from the synthetic community (Figure 1).[1] As a result, an array of useful methods have been developed to construct α,β-diamino acid derivatives through carbon–carbon bond formation or carbon–nitrogen bond formation processes.[1,2] These methods include Mannich reaction of nucleophiles with imines,[2a–d] dimerization of glycinates,[2e–g] amino functionalization of cyclic intermediates,[2h–j] and amination of α,β-unsaturated alkenoates or functionalized alkanoates.[2k–m] Despite these achievements, however, facile and efficient enantioselective approaches to chiral α,β-diamino acid derivatives from simple starting materials, are still highly desirable.

Multicomponent reactions (MCRs) have been widely recognized as step- and atom-economic ways to construct multiple chemical bonds from three or more starting materials in a single operation.[3] As part of our continuous interest in maximizing synthetic efficiency to construct structurally diversified molecules, recently we have developed a novel type of MCR by trapping active onium ylides or zwitterionic intermediates generated from metal carbene[4] with electrophiles.[5,6] The use of either chiral metal catalysts or metal/organo cooperative catalysis has further broadened the synthetic potentials of such types of MCRs by providing expedient access to chiral polyfunctional molecules.[7,8] Among these progress, enantioselective trapping of ammonium ylides with electrophiles has been developed for synthesizing chiral nitrogen-containing molecules. Che and co-workers developed an enantioselective three-component coupling reaction of diazophosphonates, anilines, and electron-deficient aldehydes catalyzed by chiral rhodium catalysts.[8a] Gong and co-workers reported an enantioselective aldol-type three-component reaction of 3-diazooxindoles with anilines and glyoxylates by using rhodium/chiral Brønsted acid co-operative catalysis.[8c] Our group realized several Mannich-type enantioselective three-component reaction of diazoacetates with anilines or carbamates and imines under rhodium/chiral Brønsted acid cocatalyzed conditions.[9] Despites these progresses, however, the construction of chiral nitrogen-containing molecules based on ylide-trap-

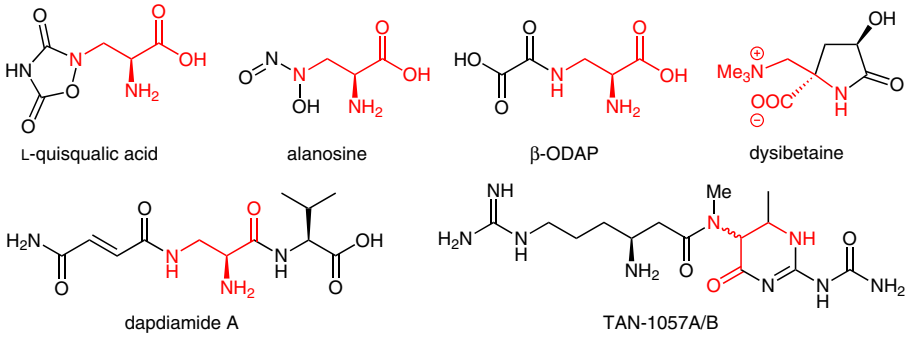


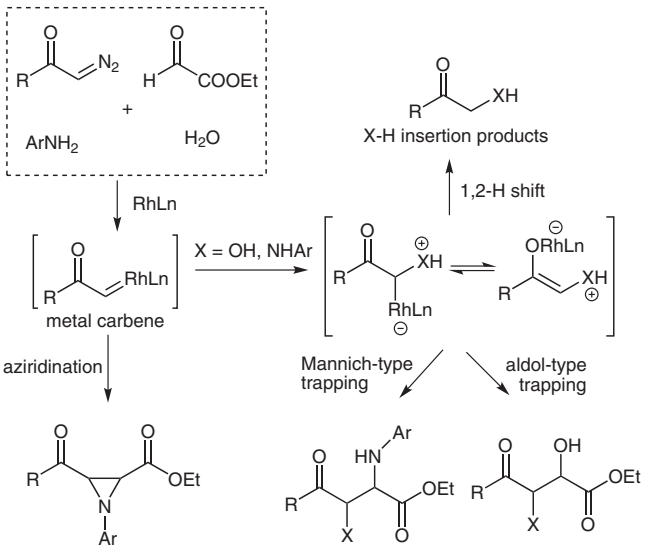
Figure 1 Natural products and biologically active compounds containing α,β-diamino acid scaffolds

SYNTHESIS 2014, 46, 1348–1354
Advanced online publication: 27.03.2014
DOI: 10.1055/s-0033-1341051; Art ID: SS-2014-C0085-OP

ping MCRs, especially those using diazo ketones as the carbene sources to generate ammonium ylides, are relatively rare. As a result, we focused our attention on the seeking of an enantioselective process starting from diazo ketones, anilines, and glyoxylates for the efficient synthesis of α,β-diamino acid derivatives.

To construct optically active α,β-diamino acid derivatives, a rhodium(II) and chiral Brønsted acid cocatalyzed four-component reaction of a diazo ketone with two molecules of anilines and ethyl glyoxylate was designed (Scheme 1). Within this transformation, an ammonium ylide intermediate **I** would be generated in situ from a diazo ketone and one molecule of aniline in the presence of a rhodium catalyst, on the other hand, another molecule of aniline would react with ethyl glyoxylate to afford an iminoester, which could be further activated into an iminium ion **II** by the assistance of a chiral phosphoric acid. A Mannich-type trapping of the ammonium ylide **I** with the iminium ion **II** would then occur to afford the desired four-component product **4**. In order to make this designed transformation to occur smoothly, one of the biggest challenges need to overcome is the chemoselectivity issue, such as N–H and O–H insertion reactions, aziridination,[10] Mannich-type addition of diazo compounds to iminoesters,[11] hydrolysis of the iminoesters[8c,12] as well as the four-component reaction of diazo ketones, water, anilines, and glyoxylates; [13] all these are possible competitive side reaction pathways (Scheme 2). On the other hand, due to the high reactivity of acceptor carbene derived from diazo ketones, it would be difficult to achieve high level of enantioselective control for this four-component reaction.[14]

With these concerns in mind, our initial investigations began by choosing diazoacetophenone (**1a**), two molecules of aniline (**2a**) (2.2 equiv) and ethyl glyoxylate (**3**) as the substrates to react under $Rh_2(OAc)_4$-catalyzed conditions. To our delight, the desired four-component reaction proceeded smoothly in the presence of 4 Å molecular sieves at 25 °C with toluene as the solvent, affording **4a** in 73% yield with 83:17 dr. The addition of 5 mol% racemic phosphoric acid **5a** (Figure 2) as a cocatalyst further improved the yield as well as the diastereoselectivity of this four-component reaction probably via facilitating the formation of iminoester (Scheme 3). The presence of 4 Å molecular sieves and racemic phosphoric acid was crucial in efficiently inhibiting undesired side reactions; as a result, under such reaction conditions, the formation of any other obvious by-products was not observed.



Scheme 2 Possible reaction pathways of diazo ketones, anilines, and ethyl glyoxylate in the presence of $Rh_2(OAc)_4$ catalyst

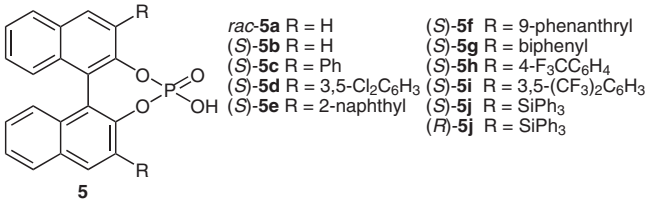
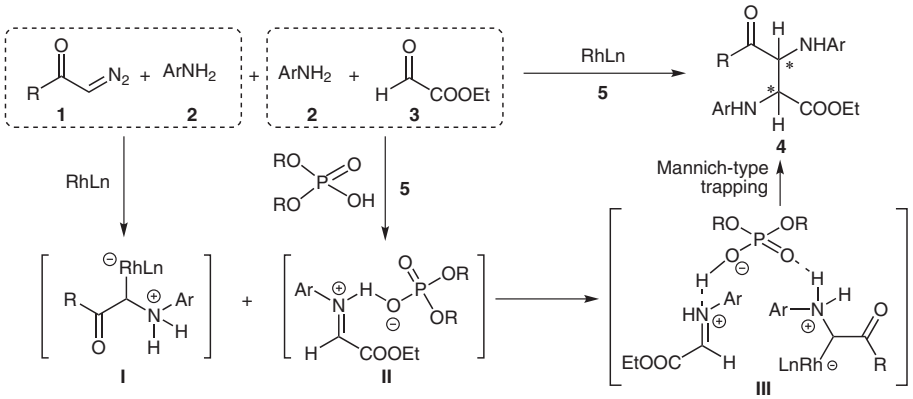
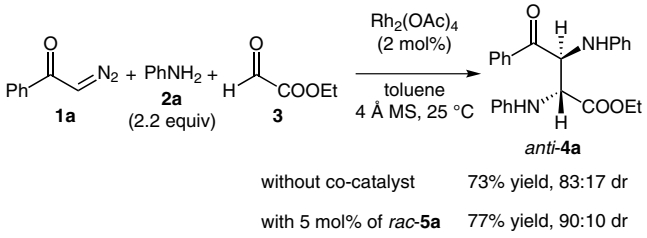


Figure 2 Chiral phosphoric acid cocatalysts **5**

With these preliminary results, different chiral phosphoric acids were screened for enantioselective transformations. Among the different chiral phosphoric acids being tested, (*S*)-**5j** bearing bulky 3,3′-$SiPh_3$ substituents gave satisfactory result, yielding the desired four-component product in 84% yield with 86:14 dr and 94% ee (Table 1, entries



Scheme 1 Designed rhodium(II)/chiral PPA cocatalyzed four-component reaction of diazo ketones, anilines, and ethyl glyoxylate for the synthesis of α,β-diamino acids



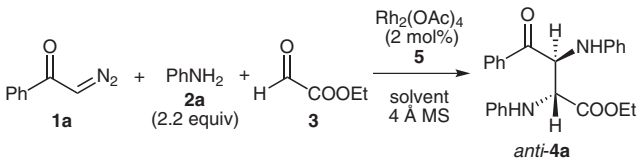
Scheme 3 Initial results of the four-component reaction of diazoacetophenone (**1a**), two molecules of aniline (**2a**), and ethyl glyoxylate (**3**)

1–9). When the amount of chiral phosphoric acid (*S*)-**5j** was decreased from 5 mol% to 2 mol%, the enantioselectivity was decreased to 71% (entry 10). The screening of different solvents and temperatures revealed that the use of toluene as the solvent at 40 °C was the most optimal (entries 11–14). The use of 5 mol% of (*R*)-**5j** as the cocatalyst gave (2*S*,3*R*)-*anti*-**4a** in 84% yield with 84:16 dr and 92% ee (entry 15).

With the optimized reaction conditions in hand, the substrate scope of this $Rh_2(OAc)_4$/chiral phosphoric acid cocatalyzed four-component reaction was investigated. When anilines bearing different substituents were applied, the desired four-component reactions proceeded smoothly, providing the desired products in high level of diastereo- and enantioselective control (Table 2, entries 1–6). The highest diastereomeric ratio was achieved when 3,4-difluoroaniline (**2f**) was used as the substrate, affording the desired product **4f** in 72% yield with 95:5 dr and 91% ee (entry 6). On the other hand, different diazo ketones were also tested. The results indicated that the existence of either electron-donating or electron-withdrawing substituents on the aromatic ring of diazo ketone **1** could all afford the desired products in good yield with high dr and ee (entries 7–11). When styryl-substituted diazo ketone **1f** was used, the desired product was obtained in 50% yield with 92:8 dr, albeit with 67% ee (entry 12). The absolute configurations of the four-component products were tentatively established as 2*R*,3*S* by comparing the circular dichroism spectrum of *anti*-**4h** with a known compound.[13,15]

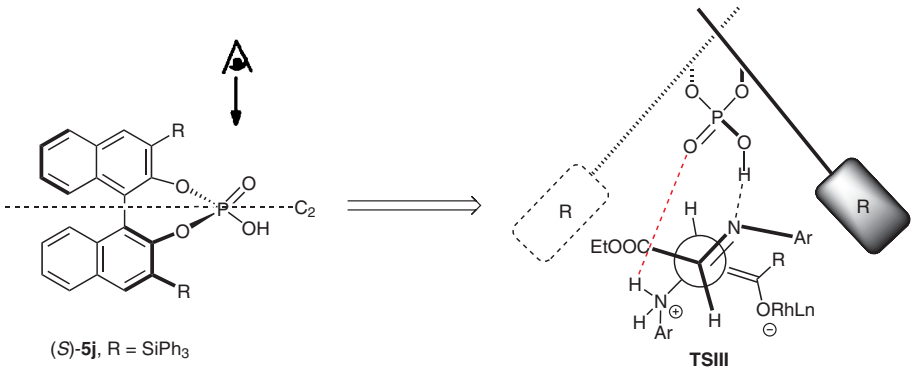
In order to rationalize the high diastereo- and enantioselectivity observed in this $Rh_2(OAc)_4$/chiral phosphoric

Table 1 Catalyst Screening and Optimization of Reaction Conditions for the Four-Component Reaction of **1a**, **2a** (2.2 equiv), and **3**[a]



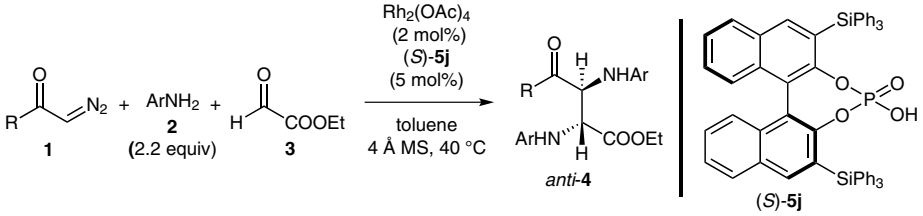
Entry	**5** (mol%)	Solvent	Temp (°C)	Yield (%)[b]	dr[c] (*anti*/*syn*)	ee (%)[d]
1	(*S*)-**5b** (5)	toluene	25	78	91:9	19
2	(*S*)-**5c** (5)	toluene	25	76	88:12	65
3	(*S*)-**5d** (5)	toluene	25	78	82:18	73
4	(*S*)-**5e** (5)	toluene	25	79	85:15	67
5	(*S*)-**5f** (5)	toluene	25	81	83:17	89
6	(*S*)-**5g** (5)	toluene	25	80	84:16	54
7	(*S*)-**5h** (5)	toluene	25	83	85:15	33
8	(*S*)-**5i** (5)	toluene	25	86	81:19	89
9	(*S*)-**5j** (5)	toluene	25	84	86:14	94
10	(*S*)-**5j** (2)	toluene	25	76	90:10	71
11	(*S*)-**5j** (5)	DCE	25	84	67:33	91
12	(*S*)-**5j** (5)	CH_2Cl_2	25	78	70:30	89
13	(*S*)-**5j** (5)	toluene	40	86	87:13	95
14	(*S*)-**5j** (5)	toluene	0	83	88:12	90
15	(*R*)-**5j** (5)	toluene	40	84	84:16	–92

[a] The reactions were carried out on a 0.10 mmol scale, **1a**/**2a**/**3a** = 1.2:2.2:1.0. Diazoacetophenone **1a** (0.12 mmol) in 0.5 mL of solvent was added to a mixture of **2a** (0.22 mmol), **3** (0.10 mmol), **5** (5.0 mol%), $Rh_2(OAc)_4$ (2.0 mol%), and 4 Å MS (100 mg) in 0.5 mL of solvent within 1 h via a syringe pump.
[b] Isolated yield of **4a**.
[c] The dr for **4a** was determined by chiral HPLC with an IA column.
[d] The ee for *anti*-**4a** was determined by chiral HPLC with an IA column.



Scheme 4 Proposed preferential conformation for transition state

Table 2 Enantioselective Four-Component Mannich-Type Reactions of Diazo Ketones **1**, Anilines **2** (2.2 equiv) and Ethyl Glyoxylate (**3**)[a]



Entry	**1**	Ar	**4**	Yield (%)[b]	dr[c] (*anti*/*syn*)	ee (%)[d]
1	**1a** (R = Ph)	Ph	**4a**	86	87:13	95
2	**1a** (R = Ph)	4-BrC_6H_4	**4b**	82	91:9	92
3	**1a** (R = Ph)	4-ClC_6H_4	**4c**	86	90:10	94
4	**1a** (R = Ph)	3,4-$Cl_2C_6H_3$	**4d**	71	85:15	97
5	**1a** (R = Ph)	4-FC_6H_4	**4e**	77	92:8	88
6	**1a** (R = Ph)	3,4-$F_2C_6H_3$	**4f**	72	95:5	91
7	**1b** (R = 4-ClC_6H_4)	4-ClC_6H_4	**4g**	69	87:13	94
8[e]	**1c** (R = 4-$MeOC_6H_4$)	4-ClC_6H_4	**4h**	65	87:13	92
9	**1d** (R = 3-BrC_6H_4)	4-ClC_6H_4	**4i**	62	91:9	94
10[e]	**1c** (R = 4-$MeOC_6H_4$)	4-BrC_6H_4	**4j**	62	89:11	93
11	**1e** (R = β-naphthyl)	4-BrC_6H_4	**4k**	74	88:12	93
12	**1f** (R = *trans*-styryl)	4-BrC_6H_4	**4l**	50	92:8	67

[a] The reactions were carried out on a 0.20 mmol scale, **1**/**2**/**3** = 1.2:2.2:1.0. Diazo compound **1** (0.24 mmol) in 1.0 mL of toluene was added to a mixture of **2** (0.44 mmol), **3** (0.20 mmol), (*S*)-**5j** (5.0 mol%), $Rh_2(OAc)_4$ (2.0 mol%), and 4 Å MS (200 mg) in 1.0 mL of toluene at 40 °C within 1 h via a syringe pump.
[b] Isolated yield of **4**.
[c] The dr for **4** was determined by chiral HPLC with an IA column.
[d] The ee for *anti*-**4** was determined by chiral HPLC with an IA column.
[e] The dr for **4** was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

acid cocatalyzed four-component reaction, a plausible preferential conformation for transition state was proposed (Scheme 4). Iminoester that was protonated by phosphoric acid would accept a nucleophilic attack from ammonium ylide intermediate to afford *anti*-products as the major product through preferential conformation for transition state **III** (**TSIII**). A weak hydrogen bond between the Lewis basic phosphoryl oxygen atom and the acidic NH proton in the ammonium yilde intermediate was believed to be the key interaction to define the stereochemical outcome of this transformation.[16]

In summary, we have developed a highly diastereo- and enantioselective four-component reaction of a diazo ketone with two equivalents of anilines and ethyl glyoxylate in the presence of $Rh_2(OAc)_4$ and chiral phosphoric acid catalysts. $Rh_2(OAc)_4$ plays a role to catalyze the diazo decomposition reaction of the diazo ketone and the aniline to generate an ammonium ylide intermediate. In the meantime, reaction of an additional equivalent of aniline with ethyl glyoxylate promoted by the chiral phosphoric acid allowed to form an iminium ion of iminoester. The desired transformation proceeds through a Mannich-type trapping of the ammonium ylide by the phosphoric acid activated iminoester. With this co-operative catalytic system, a series of chiral α,β-diamino acid derivatives were efficiently produced from simple starting materials in good yields and with good to excellent diastereo- and enantioselectivities.

All NMR spectra were recorded on a Bruker spectrometer at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR), a Bruker spectrometer at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) or JNM-EX at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). Chemical shifts (δ values) were reported in ppm downfield from internal TMS. HRMS (ESI) mass spectra were recorded on a Bruker micrOTOF II instrument. HPLC analysis was performed on Waters-Breeze (2487 Dual Absorbance Detector and 1525 Binary HPLC Pump) and Shimadzu (SPD-20AV UV-VIS Detector and LC-20AT Liquid Chromatograph Pump). Chiralpak IA was purchased from Daicel Chemical Industries, LTD. CD spectra were recorded on a JASCO J-810 spectropolarimeter.

The racemic standards used in HPLC studies were prepared according to the general procedure by using a racemic BINOL-derivatized phosphoric acid catalyst.

Four-Component Mannich-Type Reactions of Diazo Ketones 1, Anilines 2, and Ethyl Glyoxylate (3); General Procedure

A mixture of $Rh_2(OAc)_4$ (1.77 mg, 2 mol%), chiral phosphoric acid (*S*)-**5** (5 mol%), aniline **2** (0.44 mmol, 2.2 equiv), ethyl glyoxylate **3** (40.8 mg, 0.20 mmol, 1.0 equiv), and 4 Å MS (200 mg) in solvent (1.5 mL) was heated to 40 °C, then the diazo compound **1** (0.24 mmol, 1.2 equiv) in solvent (1.5 mL) was added over 1 h via a syringe pump. The reaction mixture was purified by flash chromatography on silica gel to give the corresponding four-component reaction product.

Ethyl (2*R*,3*S*)-4-Oxo-4-phenyl-2,3-bis(phenylamino)butanoate (4a); Typical Procedure

A mixture of $Rh_2(OAc)_4$ (1.77 mg, 2 mol%), chiral phosphoric acid (*S*)-**5j** (8.65 mg, 5 mol%), aniline (**2a**; 40.98 mg, 0.44 mmol, 2.2 equiv), ethyl glyoxylate (**3**; 40.8 mg, 0.20 mmol, 1.0 equiv), and 4 Å MS (200 mg) in toluene (1.0 mL) was heated to 40 °C. Then, the diazo compound **1a** (35.08 mg, 0.24 mmol, 1.2 equiv) in toluene (1.0 mL) was added over 1 h via a syringe pump. The reaction mixture was purified by flash chromatography on silica gel (eluent: PE–EtOAc, 40:1 to 10:1) to give **4a**; yield: 66.82 mg (86%); 87:13 dr (*anti*/*syn*); 95% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min, hexane–*i*-PrOH (95:5); 254 nm; t_R (minor) = 22.4 min, t_R (major) = 27.5 min].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.4 Hz, 2 H), 7.61 (t, *J* = 7.3 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 2 H), 7.21–7.12 (m, 4 H), 6.82–6.74 (m, 4 H), 6.61 (d, *J* = 7.8 Hz, 2 H), 5.54 (dd, *J* = 9.8, 3.5 Hz, 1 H), 4.78 (d, *J* = 10.0 Hz, 1 H), 4.68–4.59 (m, 2 H), 4.04–4.01 (m, 2 H), 1.13 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.08, 170.98, 146.73, 146.53, 135.67, 133.87, 129.56, 129.37, 128.92, 128.50, 119.40, 119.24, 114.59, 114.52, 61.59, 60.55, 58.83, 13.97.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{24}N_2O_3$ + Na: 411.1679; found: 411.1674.

Ethyl (2*R*,3*S*)-2,3-Bis(4-bromophenylamino)-4-oxo-4-phenylbutanoate (4b)

Yield: 89.59 mg (82%); 91:9 dr (*anti*/*syn*); 92% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min, hexane–EtOH (80:20), 254 nm; t_R (minor) = 12.0 min, t_R (major) = 15.0 min].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.4 Hz, 2 H), 7.63 (t, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 7.7 Hz, 2 H), 7.28 (d, *J* = 8.7 Hz, 2 H), 7.23 (d, *J* = 8.7 Hz, 2 H), 6.65 (d, *J* = 8.7 Hz, 2 H), 6.47 (d, *J* = 8.7 Hz, 2 H), 5.47 (dd, *J* = 10.1, 4.1 Hz, 1 H), 4.78 (d, *J* = 10.1 Hz, 1 H), 4.65 (d, *J* = 10.4 Hz, 1 H), 4.51 (dd, *J* = 10.4, 4.1 Hz, 1 H), 4.03–3.99 (m, 2 H), 1.13 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.44, 170.44, 145.57, 145.29, 135.29, 134.11, 132.31, 132.10, 128.98, 128.39, 116.00, 115.95, 111.24, 111.09, 61.80, 60.13, 58.49, 13.92.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{22}Br_2N_2O_3$ + Na: 566.9889; found: 566.9923.

Ethyl (2*R*,3*S*)-2,3-Bis(4-chlorophenylamino)-4-oxo-4-phenylbutanoate (4c)

Yield: 78.66 mg (86%); 90:10 dr (*anti*/*syn*); 94% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min, hexane–*i*-PrOH (80:20), 254 nm; t_R (minor) = 15.5 min, t_R (major) = 19.8 min].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.3 Hz, 2 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.17–7.14 (m, 2 H), 7.12–7.08 (m, 2 H), 6.73–6.70 (m, 2 H), 6.54–6.51 (m, 2 H), 5.47 (dd, *J* = 10.0, 3.9 Hz, 1 H), 4.76 (d, *J* = 10.2 Hz, 1 H), 4.64 (d, *J* = 10.5 Hz, 1 H), 4.51 (dd, *J* = 10.5, 4.2 Hz, 1 H), 4.07–3.99 (m, 2 H), 1.14 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.55, 170.54, 145.15, 144.87, 135.32, 134.13, 129.45, 129.26, 129.00, 128.42, 124.19, 124.02, 115.62, 115.56, 61.81, 60.33, 58.67, 13.93;

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{22}Cl_2N_2O_3$ + Na: 479.0900; found: 479.0930.

Ethyl (2*R*,3*S*)-2,3-Bis(3,4-dichlorophenylamino)-4-oxo-4-phenylbutanoate (4d)

Yield: 74.73 mg (71%); 85:15 dr (*anti*/*syn*); 97% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min, hexane–*i*-PrOH–EtOH (80:10:10), 254 nm; t_R (minor) = 9.7 min, t_R (major) = 13.6 min].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.87 (m, 2 H), 7.62–7.58 (m, 1 H), 7.50–7.46 (m, 2 H), 7.17 (d, *J* = 8.8 Hz, 1 H), 7.12 (d, *J* = 8.6 Hz, 1 H), 6. 78 (d, *J* = 2.7 Hz, 1 H), 6.61 (d, *J* = 2.7 Hz, 1 H), 6.53 (dd, *J* = 8.8, 2.7 Hz, 1 H), 6.38 (dd, *J* = 8.8, 2.7 Hz, 1 H), 5.37 (dd, *J* = 9.8, 3.9 Hz, 1 H), 4.76 (d, *J* = 10.0 Hz, 1 H), 4.60 (d, *J* = 10.2 Hz, 1 H), 4.43 (dd, *J* = 10.2, 4.1 Hz, 1 H), 4.02–3.96 (m, 2 H), 1.10 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.90, 169.87, 145.79, 145.69, 135.14, 134.36, 133.28, 133.08, 131.04, 130.90, 129.14, 128.39, 122.31, 122.11, 115.57, 115.49, 114.03, 114.01, 62.10, 59.99, 58.40, 13.94.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{20}Cl_4N_2O_3$ + Na: 547.0120; found: 547.0101.

Ethyl (2*R*,3*S*)-2,3-Bis(4-fluorophenylamino)-4-oxo-4-phenylbutanoate (4e)

Yield: 65.37 mg (77%); 92:8 dr (*anti*/*syn*); 88% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min, hexane–*i*-PrOH–EtOH (90:5:5), 254 nm; t_R (minor) = 19.9 min, t_R (major) = 25.6 min].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.1 Hz, 2 H), 7.65–7.61 (m, 1 H), 7.51 (t, *J* = 7.7 Hz, 2 H), 6.93–6.84 (m, 4 H), 6.77–6.72 (m, 2 H), 6.57–6.54 (m, 2 H), 5.43 (dd, *J* = 10.5, 4.2 Hz, 1 H), 4.68 (d, *J* = 10.5 Hz, 1 H), 4.57 (d, *J* = 10.8 Hz, 1 H), 4.48 (dd, *J* = 10.8, 4.2 Hz, 1 H), 4.06–3.98 (m, 2 H), 1.13 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.96, 170.88, 158.05, 155.68, 142.90, 142.71, 142.68, 135.47, 133.99, 128.94, 128.40, 115.92, 115.88, 115.85, 61.62, 61.26, 59.48, 13.92.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{22}F_2N_2O_3$ + Na: 447.1491; found: 447.1489.

Ethyl (2*R*,3*S*)-2,3-Bis(3,4-difluorophenylamino)-4-oxo-4-phenylbutanoate (4f)

Yield: 66.30 mg (72%); 95:5 dr (*anti*/*syn*); 91% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min, hexane–*i*-PrOH–EtOH (90:5:5), 254 nm; t_R (minor) = 16.4 min, t_R (major) = 23.0 min].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.3 Hz, 2 H), 7.66 (t, *J* = 7.5 Hz, 1 H), 7.53 (t, d, *J* = 7.8 Hz, 2 H), 7.03–6.91 (m, 2 H), 6.63–6.58 (m, 1 H), 6.47–6.38 (m, 2 H), 6.30–6.28 (m, 1 H), 5.39 (dd, *J* = 10.2, 4.1 Hz, 1 H), 4.74 (d, *J* = 10.2 Hz, 1 H), 4.61 (d, *J* = 10.5 Hz, 1 H), 4.44 (dd, *J* =10.5, 4.1 Hz, 1 H), 4.08–4.00 (m, 2 H), 1.15 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.32, 170.34, 152.01, 149.56, 143.38, 135.21, 134.28, 129.08, 128.38, 118.01, 117.81, 117.62, 109.96, 109.93, 109.79, 103.70, 103.61, 103.49, 103.41, 61.93, 60.71, 59.01, 13.91.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{20}F_4N_2O_3$ + Na: 483.1302; found: 483.1282.

Ethyl (2*R*,3*S*)-4-(4-Chlorophenyl)-2,3-bis(4-chlorophenylamino)-4-oxobutanoate (4g)

Yield: 67.80 mg (69%); 87:13 dr (*anti*/*syn*); 94% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min,

hexane–*i*-PrOH–EtOH (90:5:5), 254 nm; t_R (minor) = 28.4 min, t_R (major) = 41.0 min].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.5 Hz, 2 H), 7.48 (d, *J* = 8.5 Hz, 2 H), 7.17 (d, *J* = 8.7 Hz, 2 H), 7.10 (d, *J* = 8.7 Hz, 2 H), 6.70 (d, *J* = 8.7 Hz, 2 H), 6.51 (d, *J* = 8.7 Hz, 2 H), 5.42 (dd, *J* = 10.4, 4.2 Hz, 1 H), 4.71 (d, *J* = 10.4 Hz, 1 H), 4.63 (d, *J* = 10.5 Hz, 1 H), 4.48 (d, *J* = 10.5, 4.2 Hz, 1 H), 4.08–4.03 (m, 2 H), 1.15 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.49, 170.61, 145.19, 144.61, 140.68, 133.58, 129.86, 129.53, 129.31, 129.26, 124.40, 124.16, 115.62, 115.58, 61.88, 60.37, 58.64, 13.96.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{21}Cl_3N_2O_3$ + Na: 513.0510; found: 513.0505.

Ethyl (2*R*,3*S*)-2,3-Bis(4-chlorophenylamino)-4-(4-methoxyphenyl)-4-oxobutanoate (4h)

Yield: 63.36 mg (65%); 87:13 dr (*anti*/*syn*); 92% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min, hexane–*i*-PrOH–EtOH (80:10:10), 254 nm; t_R (minor) = 28.6 min, t_R (major) = 38.6 min].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.8 Hz, 2 H), 7.14 (d, *J* = 8.7 Hz, 2 H), 7.08 (d, *J* = 8.7 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 6.69 (d, *J* = 8.7 Hz, 2 H), 6.51 (d, *J* = 8.8 Hz, 2 H), 5.43 (dd, *J* = 10.3, 4.2 Hz, 1 H), 4.76 (d, *J* = 10.3 Hz, 1 H), 4.65 (d, *J* = 10.6 Hz, 1 H), 4.49 (dd, *J* = 10.6, 4.2 Hz, 1 H), 4.04–4.00 (m, 2 H), 3.89 (s, 3 H), 1.12 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.69, 170.74, 164.33, 145.25, 144.89, 130.87, 129.40, 129.18, 128.08, 123.98, 123.84, 115.54, 115.49, 114.17, 61.70, 59.60, 58.62, 55.57, 13.93.

HRMS (ESI): *m*/*z* [M + Na]$^+$calcd for $C_{25}H_{24}Cl_2N_2O_4$ + Na: 509.1005; found: 509.0992.

Ethyl (2*R*,3*S*)-4-(3-Bromophenyl)-2,3-bis(4-chlorophenylamino)-4-oxobutanoate (4i)

Yield: 66.50 mg (62%); 91:9 dr (*anti*/*syn*); 94% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min, hexane–*i*-PrOH–EtOH (92:6:2), 254 nm; t_R (minor) = 23.9 min, t_R (major) = 33.5 min].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06–7.91 (m, 1 H), 7.87–7.81 (m, 1 H), 7.75–7.59 (m, 1 H), 7.46–7.38 (m, 1 H), 7.16–7.10 (m, 4 H), 6.69 (d, *J* = 7.5 Hz, 2 H), 6.52 (d, *J* = 7.9 Hz, 2 H), 5.40–5.39 (m, 1 H), 4.72 (d, *J* = 10.0 Hz, 1 H), 4.61 (d, *J* = 10.0 Hz, 1 H), 4.51–4.49 (m, 1 H), 4.07–4.05 (m, 2 H), 1.17 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.52, 196.44, 170.45, 170.42, 145.07, 145.05, 144.63, 136.88, 135.35, 133.98, 131.42, 130.55, 130.31, 129.52, 129.31, 128.51, 126.90, 126.45, 124.41, 124.18, 123.29, 115.65, 61.97, 60.64, 58.70, 13.99.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{21}BrCl_2N_2O_3$ + Na: 557.0005; found: 556.9993.

Ethyl (2*R*,3*S*)-2,3-Bis(4-bromophenylamino)-4-(4-methoxyphenyl)-4-oxobutanoate (4j)

Yield: 71.46 mg (62%); 89:11 dr (*anti*/*syn*); 93% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min, hexane–*i*-PrOH–EtOH (240:15:50), 254 nm; t_R (minor) = 26.1 min, t_R (major) = 32.9 min].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.3 Hz, 2 H), 7.28–7.21 (m, 4 H), 6.96 (d, *J* = 8.5 Hz, 2 H), 6.64 (d, *J* = 8.2 Hz, 2 H), 6.47 (d, *J* = 8.3 Hz, 2 H), 5.44–5.42 (m, 1 H), 4.77 (d, *J* = 9.4 Hz, 1 H), 4.66 (d, *J* = 10.0 Hz, 1 H), 4.49 (d, *J* = 10.2 Hz, 1 H), 4.04–4.01 (m, 2 H), 3.88 (s, 3 H), 1.12 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.62, 170.66, 164.35, 145.70, 145.32, 132.29, 132.07, 130.87, 128.09, 115.97, 115.92, 114.18, 111.09, 110.97, 61.71, 59.44, 58.51, 55.57, 13.93.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{24}Br_2N_2O_4$ + Na: 596.9995; found: 596.9985.

Ethyl (2*R*,3*S*)-2,3-Bis(4-bromophenylamino)-4-(naphthalen-2-yl)-4-oxobutanoate (4k)

Yield: 88.25 mg (74%); 88:12 dr (*anti*/*syn*); 93% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min, hexane–*i*-PrOH–EtOH (80:10:10), 254 nm; t_R (minor) = 23.1 min, t_R (major) = 27.4 min].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (s, 1 H), 7.99–7.89 (m, 4 H), 7.67–7.58 (m, 2 H), 7.31–7.23 (m, 4 H), 6.70 (d, *J* = 8.0 Hz, 2 H), 6.50 (d, *J* = 8.0 Hz, 2 H), 5.62 (dd, *J* = 12.0, 4.0 Hz, 1 H), 4.85 (d, *J* = 8.0 Hz, 1 H), 4.69 (d, *J* = 12.0 Hz, 1 H), 4.59 (dd, *J* = 8.0, 4.0 Hz, 1 H), 4.05–3.96 (m, 2 H), 1.11 (t, *J* = 6.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.34, 170.49, 145.57, 145.46, 136.01, 132.66, 132.41, 132.38, 132.20, 130.20, 129.65, 129.21, 129.09, 127.93, 127.30, 123.86, 116.15, 116.04, 111.34, 111.19, 61.86, 60.33, 58.79, 13.96.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{24}Br_2N_2O_3$ + Na: 617.0046; found: 617.0072.

Ethyl (2*R*,3*S*,5*E*)-2,3-Bis(4-bromophenylamino)-4-oxo-6-phenylhex-5-enoate (4l)

Yield: 57.23 mg (50%); 92:8 dr (*anti*/*syn*); 67% ee (*anti*) determined by HPLC [Daicel Chiralpak IA, flow rate 1.0 mL/min, hexane–*i*-PrOH (90:10), 254 nm; t_R (minor) = 18.0 min, t_R (major) = 19.4 min].

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 15.9 Hz, 1 H), 7.54–7.53 (m, 2 H), 7.41–7.39 (m, 3 H), 7.32–7.30 (m, 2 H), 7.24–7.22 (m, 3 H), 6.98 (d, *J* = 15.9 Hz, 1 H), 6.63 (d, *J* = 8.8 Hz, 1 H), 6.56–6.55 (m, 1 H), 6.51 (d, *J* = 8.8 Hz, 1 H), 4.86 (dd, *J* = 9.9, 3.8 Hz, 1 H), 4.71 (d, *J* = 9.9 Hz, 1 H), 4.56 (d, *J* = 10.0 Hz, 1 H), 4.50–4.49 (m, 1 H), 4.20–4.15 (m, 2 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.75, 170.85, 145.83, 145.27, 145.19, 133.90, 132.37, 132.11, 131.95, 131.24, 129.04, 128.68, 121.85, 116.65, 115.91, 115.68, 111.10, 111.07, 63.25, 61.97, 58.23, 14.06.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{24}Br_2N_2O_3$ + Na: 593.0046; found: 593.0045.

Acknowledgment

We are grateful for the financial support from NSF of China (21125209 and 21332003), the MOST of China (2011CB808600), STCSM (12JC1403800), specialized Research Fund for the Doctoral Program of Higher Education (20100076110005 and 20130076120031), Shanghai Postdoctoral Scientific Program (13R21412800), and the Scholarship Award for Excellent Doctoral Student granted by East China Normal University (XRZZ2013021). We also thank Prof. X. F. Mei for the CD analysis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) For a review on synthesis and biological significance of α,β-diamino acids, see: Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2011**, *111*, 1. (b) For a review on vicinal diamines, see: Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580.

(2) (a) Wang, J.; Shi, T.; Deng, G.; Jiang, H.; Liu, H. *J. Org. Chem.* **2008**, *73*, 8563. (b) Wang, J.; Lin, D. Z.; Shi, J. M.; Ding, X.; Zhang, L.; Jiang, H. L.; Liu, H. *Synthesis* **2010**, 1205. (c) Hernández-Toribio, J.; Arrayás, R. G.; Carretero,

J. C. *J. Am. Chem. Soc.* **2008**, *130*, 16150. (d) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866. (e) Alvarez-Ibarra, C.; Csákÿ, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478. (f) Zeitler, K.; Steglich, W. *J. Org. Chem.* **2004**, *69*, 6134. (g) Chen, Y.; Yudin, A. K. *Tetrahedron Lett.* **2003**, *44*, 4865. (h) Palomo, C.; Aizpurua, J. M.; Galarza, R.; Mielgo, A. *Chem. Commun.* **1996**, 633. (i) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813. (j) Liu, W.-J.; Chen, X.-H.; Gong, L.-Z. *Org. Lett.* **2008**, *10*, 5357. (k) Chong, A. O.; Oshima, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 3420. (l) Han, H.; Yoon, J.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 2045. (m) Li, G. G.; Wei, H.-X.; Kim, S. H.; Carducci, M. D. *Angew. Chem. Int. Ed.* **2001**, *40*, 4277. (n) Tranchant, M.-J.; Dalla, V. *Tetrahedron* **2006**, *62*, 10255.

(3) For reviews on multi-component reactions, see: (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899.

(4) For recent reviews on metal carbenes, see: (a) Li, A. H.; Dai, L. X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (c) Sun, X. L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937. (d) Zhu, S.-F.; Zhou, Q.-L. *Acc. Chem. Res.* **2012**, *45*, 1365. (e) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.* **2012**, *48*, 10162.

(5) For a review on electrophilic trapping of onium ylides, see: Guo, X.; Hu, W. H. *Acc. Chem. Res.* **2013**, *46*, 2427.

(6) For a review on electrophilic trapping of zwitterionic intermediates, see: Xing, D.; Hu, W. H. *Tetrahedron Lett.* **2014**, *55*, 777.

(7) For recent examples developed by our group, see: (a) Jiang, J.; Guan, X. Y.; Liu, S. Y.; Ren, B. Y.; Ma, X. C.; Guo, X.; Lv, F. P.; Wu, X.; Hu, W. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 1539. (b) Xing, D.; Jing, C. C.; Li, X. F.; Qiu, H.; Hu, W. H. *Org. Lett.* **2013**, *15*, 3578. (c) Jing, C. C.; Xing, D.; Qian, Y.; Shi, T. D.; Zhao, Y.; Hu, W. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 9289.

(8) For recent examples developed by others, see: (a) Zhou, C.-Y.; Wang, J.-C.; Wei, J. H.; Xu, Z.-J.; Guo, Z.; Low, K-H.; Che, C.-M. *Angew. Chem. Int. Ed.* **2012**, *51*, 11376. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Callejo, R.; Ruiz, M. P.; Torres, M. R. *Eur. J. Org. Chem.* **2012**, 2359. (c) Ren, L.; Lian, X.-L.; Gong, L.-Z. *Chem. Eur. J.* **2013**, *19*, 3315. (d) Mei, L.-Y.; Tang, X.-Y.; Shi, M. *Org. Biomol. Chem.* **2014**, *12*, 1149.

(9) (a) Wang, Y. H.; Zhu, Y. X.; Chen, Z. Y.; Mi, A. Q.; Hu, W. H.; Doyle, M. P. *Org. Lett.* **2003**, *5*, 3923. (b) Jiang, J.; Xu, H. D.; Xi, J. B.; Ren, B. Y.; Lv, F. P.; Guo, X.; Jiang, L. Q.; Zhang, Z. Y.; Hu, W. H. *J. Am. Chem. Soc.* **2011**, *133*, 8428. (c) Jiang, J.; Ma, X. C.; Liu, S. Y.; Qian, Y.; Lv, F. P.; Qiu, L.; Wu, X.; Hu, W. H. *Chem. Commun.* **2013**, *49*, 4238. (d) Jiang, L. Q.; Zhang, D.; Wang, Z. Q.; Hu, W. H. *Synthesis* **2013**, *45*, 452.

(10) (a) Hashimoto, T.; Uchiyama, N.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 14380. (b) Lu, Z.-J.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185.

(11) (a) Hashimoto, T.; Maruoka, K. *Synthesis* **2008**, 3703. (b) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054.

(12) Zhang, X.; Guo, X.; Yang, L. P.; Hu, W. H. *Chin. Chem. Lett.* **2009**, *20*, 1299.

(13) Qian, Y.; Jing, C. C.; Liu, S. Y.; Hu, W. H. *Chem. Commun.* **2013**, *49*, 2700.

(14) (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Wardrop, D. J.; Forslund, R. E. *Tetrahedron Lett.* **2002**, *43*, 737. (c) Nicolas, I.; Roisnel, T.; Maux, P. L.; Simonneaux, G. *Tetrahedron Lett.* **2009**, *50*, 5149. (d) Xu, X. F.; Qian, Y.; Yang, L. P.; Hu, W. H. *Chem. Commun.* **2011**, *47*, 797.

(15) For detailed analysis of circular dichroism spectra, see the Supporting Information.

(16) (a) Simon, L.; Goodman, J. M. *J. Org. Chem.* **2011**, *76*, 1775. (b) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J.-P. *J. Am. Chem. Soc.* **2009**, *131*, 4598. (c) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5565. (d) Xu, B.; Zhu, S.-F.; Xie, X.-L.; Shen, J.-J.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2011**, *50*, 11483.

