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Graphical Abstract

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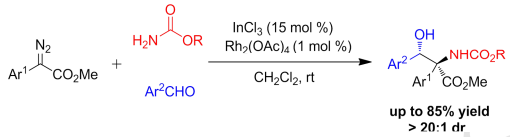

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ABSTRACT

A $Rh_2(OAc)_4$ and $InCl_3$ co-catalyzed three component reaction of diazo compounds, carbamates and aldehydes has been developed to synthesize β-hydroxyl-α-amino acid derivatives in good yields with excellent diastereoselectivity. The reaction is proceeded via trapping of active carbamate ammonium ylide intermediates by aromatic aldehydes.
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1. Introduction

β-hydroxyl-α-amino acid derivatives are important structural motifs present in many drugs, including Chloramphenicol, Thiamphenicol, and Droxidopa (Fig. 1).[1] As such, the development of efficient approaches for the construction of β-hydroxyl-α-amino acid structures with high stereoselectivity is much desirable in organic synthesis. As one of the most powerful strategies, multicomponent reactions (MCRs) can construct polyfunctional molecules that contain multiple stereogenic centers from simple substrates in a convergent and atomeconomical manner within one synthetic operation.[2]

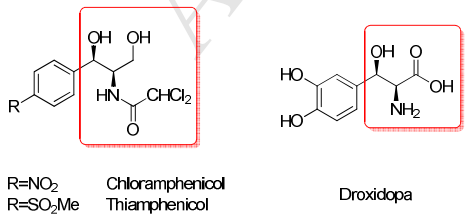
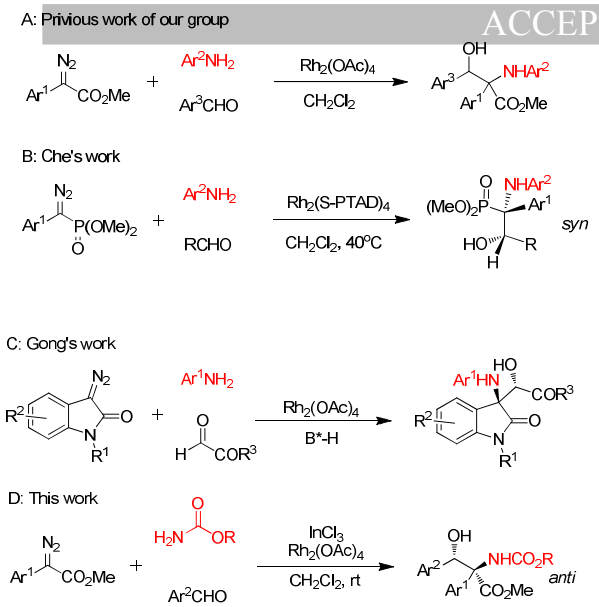


Fig. 1. Representative drugs containing a β-hydroxyl-α-amino acid fragment.

Previously, we reported a novel $Rh_2(OAc)_4$ catalyzed three-component reaction through trapping of ammonium ylides generated in situ from α-diazo esters and amines with aldehydes to afford β-hydroxyl-α-amino acid scaffolds (Scheme 1A).[3] Che and collaborators developed an asymmetric approach to chiral β-hydroxyl-α-aminophosphonates with chiral dirhodium (II) carboxamidates (Scheme 1B).[4] Gong and co-workers have reported the enantioselective Brønsted acid/rhodium(II) cooperatively catalyzed three-component aldol-type reaction of trapping ammonium ylides with glyoxylates (Scheme 1C).[5] However, only arylamines were effective in forming active ylides, and the *N*-aryl group can not be easily removed from the products, thus limiting their synthetic application. Recently, our group discovered a three-component Mannich-type reaction by trapping carbamate ammonium ylides with imines.[6] As part of our continuing interest in developing practical methods for the synthesis of β-hydroxyl-α-amino acid derivatives, we decided to extend substrates of the carbamate ammonium ylide trapping process to aldehydes. Herein, we report the reaction through trapping of carbamate ammonium ylides with aldehydes, which gives β-hydroxyl-α-amino acid derivatives in good yields with excellent diastereoselectivity (Scheme 1D).

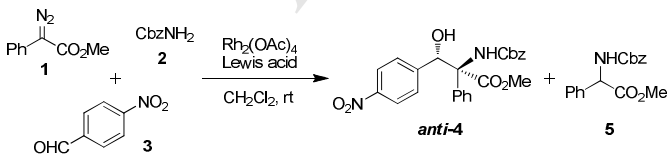


Scheme 1. Synthesize β-Hydroxyl-α-Amino acid derivatives

2. Results and discussion

In recent years, cooperative catalysis, including dual-metal and metal-organo catalysis, has proved to be an effective strategy to enhance selectivity and reactivity.[7] We have applied such a strategy to effectively control stereoselectivity in multicomponent reactions based on oxonium,[8] ammonium,[9] carbamate ammonium ylides,[6] and zwitterionic intermediates trapping process.[10] Initially, we began to investigate the reaction of methyl phenyldiazoacetate (**1**), benzyl carbamate (**2**) and 4-nitrobenzaldehyde (**3**) in the presence of $Rh_2(OAc)_4$ catalyst alone. The desired three-component product **4** was obtained in very low yield due to insufficient reactivity of 4-nitrobenzalde. Significant amount of N-H insertion product **5** (from benzyl carbamate) was isolated as a major side product (Table 1, entry 1). We envisioned that an appropriate Lewis acid co-catalyst would activate the aldehydes. To validate this hypothesis, we screened a number of Lewis acids as co-catalysts. Although $Cu(OTf)_2$ was ineffective in the reaction, we obtained the desired three-component product when we used $Mg(OTf)_2$, $Zn(OTf)_2$,$Yb(OTf)_3$, $In(OTf)_2$ and $InCl_3$ as a co-catalyst (Table 1, entries 2–7). Among the effective co-catalysts, $InCl_3$ gave the best result, with the formation of product in 55% yield with excellent diastereoselectivity in favor of the *anti* isomer (Table 1, entry 7). Control experiment revealed that $Rh_2(OAc)_4$ was indispensable for this reaction (Table 1, entry 8).

Table 1
Screening of co-catalysts[a]

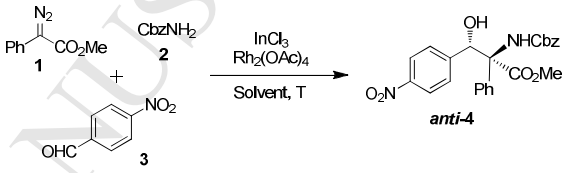


Entry	Cocat. (15 % mol)	4, Yield (%)[b]	dr[c]
1	-	<5	-
2	$Cu(OTf)_2$	<5	-
3	$Mg(OTf)_2$	10	>20:1
4	$Zn(OTf)_2$	50	>20:1
5	$Yb(OTf)_2$	24	>20:1
6	$In(OTf)_2$	50	>20:1
7	$InCl_3$	55	>20:1
8[d]	$InCl_3$	trace	-

[a] Unless otherwise noted, all reactions were carried out with 0.15 mmol scale, 1 mol % $Rh_2(OAc)_4$ and 15 mol % Lewis acids, and **1**:**2**:**3**=1.3:1.0:1.2. [b] Isolated yields were obtained after column chromatography purification. [c] The diastereomeric ratio was detected by ^{1}H NMR(400 MHz) spectroscopy. [d] In the absence of $Rh_2(OAc)_4$.

Then, various solvents were tested and CH_2Cl_2 was found to be the most efficient (Table 2, entry 1). The reaction temperature was also investigated and it has negligible effect on the reaction (Table 2, entries 4-6). The isolated product yield was slightly improved to 65% when the amount of methyl phenyldiazoacetate was increased from 1.3 to 1.9 equiv (Table 2, entry 8). It is worth mentioning that diazo compounds can be added in portions, avoiding gradual addition of diazo compounds. This change makes the synthetic protocol more practical and convenient.

Table 2
Optimization of reaction conditions[a]

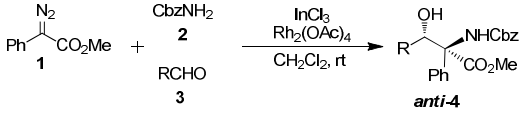


Entry	Solvent	*T* (°C)	Yield (%)[b]	dr[c]
1	DCM	rt	55	>20:1
2	$CHCl_3$	rt	39	>20:1-
3	toluene	rt	31	>20:1
4	DCM	rt	52	>20:1
5	DCM	0	51	>20:1
6	DCM	-20	48	>20:1
7[d]	DCM	rt	57	>20:1
8[e]	DCM	rt	65	>20:1

[a] Unless otherwise noted, all reactions were carried out with 0.15 mmol scale, 1 mol% $Rh_2(OAc)_4$ and 15 mol% $InCl_3$, and **1**:**2**:**3**=1.3:1.0:1.2. [b] Isolated yields were obtained after column chromatography purification. [c] The diastereomeric ratio was detected by ^{1}H NMR(400 MHz) spectroscopy. [d] 1.6 equiv of 1 was used. [e] 1.9 equiv of 1 was used.

With the optimized reaction conditions in hand, we turned to evaluate the generality of this protocol. A variety of substituted aldehydes were first examined. Benzaldehyde that bears no electron withdrawing group delivered the product in 60% yield with excellent diastereoselectivity (Table 3, entry 1). To our delight, even electron-donating 4-methoxybenzaldehyde afforded the corresponding product **4b** in 39% yield (Table 3, entry 2). Aromatic aldehydes bearing an electron withdrawing group,

Table 3
The generality of the reaction with different aldehydes[a]



Entry	R	4, Yield (%)[b]	dr[c]
1	Ph	4a, 60	>20:1
2	*p*-MeOPh	4b, 39	>20:1

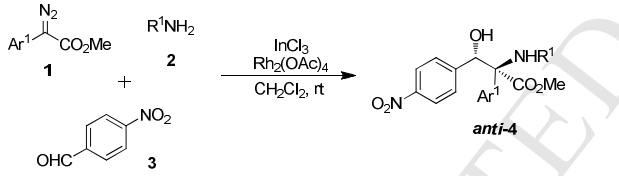
3	*p*-SO_2Ph	4c, 76	>20:1
4	*p*-BrPh	4d, 85	>20:1
5	*o*-NO_2Ph	4e, 75	>20:1
6	*m*-NO_2Ph	4f, 67	>20:1
7	*P*-NO_2Ph	4g, 65	>20:1
8	2-furyl	4h, 69	>20:1
9	2-thienyl	4i, 64	>20:1
10	cinnamonyl	4j, 62	60:40

[a] Unless otherwise noted, all reactions were carried out with 0.2 mmol scale, 1 mol % $Rh_2(OAc)_4$ and 15 mol % $InCl_3$, and **1a**:**2a**:**3a**=1.9:1.0:1.2. [b] Isolated yields were obtained after column chromatography purification. [c] The diastereomeric ratio was detected by ^{1}H NMR(400 MHz) spectroscopy.

regardless of the arene substitution (o-, m-, p-), generally gave much higher yields (Table 3, entries 3-7). When using heteroaromatic aldehydes, such as 2-furaldehyde and 2-thiophenyl aldehyde, the reactions led to products in 69% and 64% yields, respectively (Table 3, entries 8 and 9). Gratifyingly, even conjugated aldehyde, (*E*)-cinnamaldehyde reacted with methyl phenyldiazoacetate and benzyl carbamate to afford γ,δ-unsaturated β-hydroxyl-α-amino acidin 62% yield, though with decreased diastereoselectivity (Table 3, entry 10).

We next carried out screening of a series of carbamates and diazo compounds. $FmocNH_2$ and $BocNH_2$ are equally good substrates, which gave products with similar yields and stereoselectivity (Table 4, entries 2 and 3). In general, the reaction was tolerated to various substituted electron-rich and -deficient aryldiazo compounds, giving rise to the products with moderate to good yields and high diastereoselectivity (Table 4, entries 4-9).

Table 4
The generality of the reaction towards carbamates and diazo compounds[a]



Entry	Ar^1	R^1	4, Yield (%)[b]	dr[c]
1	Ph	Cbz	4g, 65	>20:1
2	Ph	Boc	4k, 58	>20:1
3	Ph	Fmoc	4l, 60	>20:1
4	*p*-MePh	Cbz	4m, 70	>20:1
5	*p*-MeOPh	Cbz	4n, 51	>20:1
6	*p*-FPh	Cbz	4o, 60	>20:1
7	*o*-BrPh	Cbz	4p, 49	>20:1
8	*m*-BrPh	Cbz	4q, 81	>20:1
9	*P*-BrPh	Cbz	4r, 52	>20:1

[a] Unless otherwise noted, all reactions were carried out with 0.2 mmol scale, 1 mol % $Rh_2(OAc)_4$ and 15 mol % $InCl_3$, and **1a**:**2a**:**3a**=1.9:1.0:1.2. [b] Isolated yields were obtained after column chromatography purification. [c] The diastereomeric ratio was detected by ^{1}H NMR(400 MHz) spectroscopy.

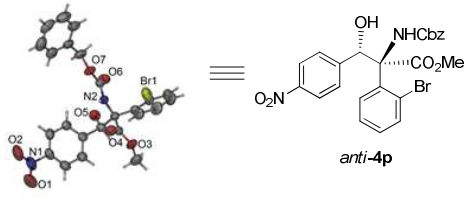
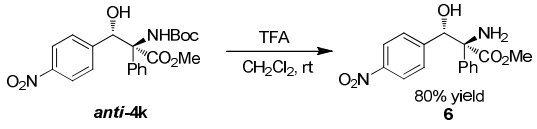


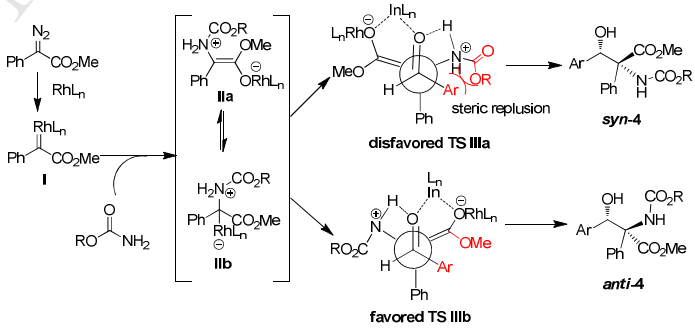
Fig. 2. X-Ray crystal structure of *anti*-**4p**.



Scheme 2. Deprotection of the product *anti*-**4k**.

The relative stereochemistry of the products was assigned as *anti* in analogy with *anti*-**4p** as determined by single-crystal X-ray diffraction (Fig. 2). Deprotection of the product was easily carried out by using TFA at room temperature in CH_2Cl_2 to give free amine in 80% yield (Scheme 2).[11]

A plausible reaction pathway for this $Rh_2(OAc)_4$ and $InCl_3$ co-catalyzd three component reaction is shown in Scheme 3. $Rh_2(OAc)_4$ decomposes diazo compounds to form the corresponding rhodium carbene species **I**, which further reacts with carbamates to give the active carbamate ammonium ylides **IIa** or **IIb**. In the presence of aromatic aldehydes that was activated by $InCl_3$, the active ylide species undergo aldol-type addition to afford the desired three component product. To have an insight into the reaction process, we carried out control experiments to exclude the possibility that the product **4g** is produced from N–H insertion product **5**. As a result, when treated the N–H insertion product **5** with aldehyde under the identical conditions, no three component product was detected. The observed stereoselective control can be explained by comparing the transition states **IIIa** and **IIIb**, as shown in Scheme 3. The *anti*-**4** is obtained from the favored transition state **IIIb** with less steric hindrance compared with the disfavored TS **IIIa**.



Scheme 3. Proposed mechanism for the three-component reaction.

3. Conclusion

In summary, by using a transision metal-Lewis acid cooperative catalysis strategy, we have realized a highly stereoselective three-component aldol-type reaction of diazo compounds and carbamates with aldehydes. The protocol provides a straightforward and efficient route to access β-hydroxyl-α-amino acid derivatives in highly stereoselective manner. This catalytic system accommodates aromatic aldehydes containing a variety of electron–donating and –withdrawing groups, heteroaromatic aldehydes, and conjugate aldehydes, demonstrating wide substrate scope. Efforts to achieve enantioselective control of this practical method is currently in progress in our laboratory.

4. Experimental section

4.1. General

HRMS (ESI) Mass spectra were recorded on Bruker micrOTOF-Q 10198 mass spectrometer. NMR spectra were recorded on a Brucker Ascend-400 MHz spectrometer. Dichloromethane was distilled over calcium hydride. Various aryl diazo compounds were prepared by the treatment of corresponding aryl acetate with *p*-acetamidobenzenesulfonylazide (*p*-ABSA) in the presence of DBU.[12]

4.2. General procedure for the three-component reaction of diazo compounds with carbamates and aldehydes

To a stirred mixture of $Rh_2(OAc)_4$ (1 mol%), $InCl_3$ (15 mol %), carbamate **1** (0.20 mmol), aldehyde **2** (0.24 mmol), and 4Å-MS (100 mg) in DCM (1.5 mL) was added diazo compound **3** (0.38 mmol) in DCM (1 mL) in portions at room temperature. After the addition of diazo compound completes, the reaction mixture was stirred for 1 h. Then, the reaction mixture was filtered and concentrated under reduced pressure. The crude product was subjected to ^{1}HNMR analysis for the determination of diastereoselectivity. The crude product was purified by column chromatography on silica gel (eluent: EtOAc /light petroleum = 1:20~1:10) to give the corresponding pure products **4.**

4.2.1. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-3-(4-nitrophenyl)-2-phenylpropanoate (anti-**4a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.7 Hz, 2H), 7.47–7.33 (m, 10H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.26 (s, 1H), 6.10 (s, 2H), 5.22 (d, *J* = 12.1 Hz, 1H), 5.07 (d, *J* = 12.1 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.09, 157.12, 147.53, 147.19, 135.68, 135.22, 130.50, 129.84, 128.78, 128.72, 128.68, 128.61, 127.89, 127.71, 123.09, 75.36, 70.34, 67.99, 53.87; HRMS (ESI) m/z calcd for $C_{24}H_{22}N_2NaO_7$ $(M+Na)^+$ 473.1308, found 473.1325.

4.2.2. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-3-(4-methoxyphenyl)-2-phenylpropanoate (anti-**4b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.1 Hz, 2H), 7.45–7.32(m, 8H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 6.36 (s, 1H), 5.95 (d, *J* = 7.4 Hz, 1H), 5.89 (d, *J* = 7.3 Hz, 1H), 5.22 (d, *J* = 12.2 Hz, 1H), 5.06 (d, *J* = 12.2 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.69, 157.17, 153.95, 142.10, 135.89, 135.78, 128.98, 128.60, 128.54, 128.35, 128.14, 127.30, 110.22, 107.70, 72.18, 69.93, 67.62, 53.94; HRMS (ESI) m/z calcd for $C_{25}H_{25}NNaO_6$ $(M+Na)^+$ 458.1580, found 458.1585.

4.2.3. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-3-(4-(methylsulfonyl)phenyl)-2-phenylpropanoate (anti-**4c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.8 Hz, 2H), 7.33–7.39 (m, 5H), 7.47–7.39, 7.22 (d, *J* = 8.0 Hz, 2H), 6.27 (s, 1H), 6.08 (s, 2H), 5.20 (d, *J* = 12.1 Hz, 1H), 5.07 (d, *J* = 12.1 Hz, 1H), 3.71 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.07, 157.15, 146.18, 139.89, 135.72, 135.31, 128.70, 128.55, 128.03, 127.19, 127.00, 126.44, 77.42, 77.10, 76.78, 75.42, 70.34, 70.11, 68.06, 67.95, 67.84, 53.90, 53.77, 53.63, 53.49, 44.53, 44.46, 44.39; HRMS (ESI) m/z calcd for $C_{25}H_{25}NNaO_7$ $(M+Na)^+$ 506.1249, found 506.1237.

4.2.4. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-(4-bromophenyl)-3-hydroxy-2-phenylpropanoate (anti-**4d**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 6.8 Hz, 2H), 7.45–7.34 (m, 8H), 7.32 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 2H), 6.32 (s, 1H), 5.97 (s, 2H), 5.21 (d, *J* = 12.2 Hz, 1H), 5.06 (d, *J* = 12.2 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.16, 157.10, 138.80, 135.86, 135.77, 131.09, 128.70, 128.65, 128.59, 128.49, 128.46, 127.29, 121.90, 75.50, 70.43, 67.79, 53.65; HRMS (ESI) m/z calcd for $C_{24}H_{22}NNaO_5Br$ $(M+Na)^+$ 506.0579, found 506.0582.

4.2.5. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-3-(2-nitrophenyl)-2-phenylpropanoate (anti-**4e**).* ^{1}H NMR (400 MHz, $CDCl_3$ δ) δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.44–7.37 (m, 8H), 7.37–7.33 (m, 3H), 7.33–7.27 (m, 2H), 6.75 (d, *J* = 5.5 Hz, 1H), 6.30 (s, 1H), 6.08 (d, *J* = 5.4 Hz, 1H), 5.26 (d, *J* = 12.3 Hz, 1H), 5.06 (d, *J* = 12.1 Hz, 1H), 3.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.12, 157.19, 149.27, 135.78, 135.60, 133.04, 131.86, 130.73, 128.81, 128.66, 128.61, 127.02, 123.90, 69.79, 69.43, 68.08, 54.00; HRMS (ESI) m/z calcd for $C_{24}H_{22}N_2NaO_7$ $(M+Na)^+$ 473.1325, found 473.1304

4.2.6. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-3-(3-nitrophenyl)-2-phenylpropanoate (anti-**4f**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.9 Hz, 1H), 7.99 (s, 1H), 7.51–7.44 (m, 2H), 7.44–7.34 (m, 10H), 6.31 (s, 1H), 6.22 (s, 1H), 6.13 (s, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.08 (d, *J* = 12.1 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.00, 157.28, 147.88, 142.10, 135.58, 135.32, 133.26, 129.00, 128.75, 128.71, 128.66, 128.51, 127.15, 122.95, 121.98, 75.36, 70.43, 68.13, 53.93; HRMS (ESI) m/z calcd for $C_{24}H_{22}N_2NaO_7$ $(M+Na)^+$ 473.1325, found 473.1311.

4.2.7. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-3-(4-nitrophenyl)-2-phenylpropanoate (anti-**4g**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.7 Hz, 2H), 7.47–7.36 (m, 10H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.26 (s, 1H), 6.14–6.02 (m, 2H), 5.22 (d, *J* = 12.1 Hz, 1H), 5.07 (d, *J* = 12.1 Hz, 1H), 3.73 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 171.09, 157.12, 147.53, 147.19, 135.68, 135.22, 128.78, 128.72, 128.69, 128.61, 127.89, 127.18, 123.09, 75.36, 70.34, 67.99, 53.88; HRMS (ESI) m/z calcd for $C_{24}H_{22}N_2NaO_7$ $(M+Na)^+$ 473.1325, found 473.1308.

4.2.8. (2R,3S*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-(furan-2-yl)-3-hydroxy-2-phenylpropanoate (anti-**4h**).* ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.4 Hz, 2H), 7.33–7.42 (m, 7H), 7.27–7.32 (m, 2H), 6.65 (s, 1H), 6.29 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.25 (d, *J* = 3.1 Hz, 1H), 6.16 (d, *J* = 10.0 Hz, 1H), 6.05 (d, *J* = 9.9 Hz, 1H), 5.15 (d, *J* = 12.3 Hz, 1H), 5.03 (d, *J* = 12.3 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.25, 159.21, 157.11, 136.23, 136.01, 131.75, 129.48, 128.60, 128.52, 128.45, 128.30, 128.11, 127.39, 113.38, 75.71, 70.72, 67.65, 55.18; HRMS (ESI) m/z calcd for $C_{22}H_{21}NNaO_6$ $(M+Na)^+$ 418.1267, found 418.1277.

4.2.9. (2R,3S*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-2-phenyl-3-(thiophen-2-yl)propanoate (anti-**4i**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.4 Hz, 2H), 7.48–7.31 (m, 8H), 7.24 (d, *J* = 5.0 Hz, 1H), 6.98–6.89 (m, 1H), 6.82 (d, *J* = 3.3 Hz, 1H), 6.62 (s, 1H), 6.34 (d, *J* = 8.1 Hz, 1H), 6.29 (d, *J* = 8.1 Hz, 1H), 5.19 (d, *J* = 12.2 Hz, 1H), 5.09 (d, *J* = 12.2 Hz, 1H), 3.71 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.73, 157.25, 143.66, 135.86, 128.72, 128.61, 128.49, 128.46, 128.33, 127.22, 126.46, 125.20, 124.89, 73.25, 70.84, 67.86, 53.83; HRMS (ESI) m/z calcd for $C_{22}H_{21}NNaO_5S$ $(M+Na)^+$ 434.1038, found 434.1059.

4.2.10. (2R,3R*,E)-methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-2,5-diphenylpent-4-enoate (anti-**4j**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.6 Hz, 2H), 7.46–7.18 (m, 13H), 6.79–6.62 (m, 2H), 6.13 (dd, *J* = 15.7, 4.9 Hz, 1H), 5.61-5.44 (m, 2H), 5.15 (d, *J* = 12.2 Hz, 1H), 5.05 (d, *J* = 12.2 Hz, 1H), 3.71 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 171.24, 156.98, 136.56, 136.10, 135.86, 132.52, 128.63, 128.60, 128.54, 128.38, 128.34, 128.14, 127.82, 127.19, 127.11, 126.73, 75.12, 70.25, 67.65, 53.86; HRMS (ESI) m/z calcd for $C_{26}H_{25}NNaO_5$ $(M+H)^+$ 454.1630, found 454.1608.

4.2.11. (2 R,3 S*,E)-methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-2,5-diphenylpent-4-enoate (syn-**4j**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.40–7.33 (m, 4H), 7.32–7.27 (m, 5H), 7.26-7.20 (m, 5H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.02 (dd, *J* = 15.9, 5.3 Hz, 1H), 5.78 (s, 1H), 5.24 (s, 1H), 5.09 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.74, 156.28, 136.47, 136.05, 133.00, 128.67, 128.51, 128.43, 128.23, 128.15, 127.82, 126.62, 126.42, 125.74, 75.70, 69.83, 67.29, 53.26; HRMS (ESI) m/z calcd for $C_{26}H_{25}NNaO_5$ $(M+H)^+$ 454.1630, found 454.1617.

4.2.12. (2R,3R*)-methyl 2-((tert-butoxycarbonyl)amino)-3-hydroxy-3-(4-nitrophenyl)-2-phenylpropanoate (anti-**4k**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.51–7.30 (m, 7H), 6.36 (s, 1H), 6.12 (d, *J* = 7.6 Hz, 1H), 6.04 (s, 1H), 3.75 (s, 3H), 1.46 (s, 9H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 171.35, 156.83, 147.75, 147.67, 135.63, 128.57, 128.02, 127.17, 123.04 (s), 81.83, 75.37, 70.28, 53.72, 28.21; HRMS (ESI) m/z calcd for $C_{21}H_{24}N_2NaO_7$ $(M+H)^+$ 439.1481, found 439.1477.

4.2.13. (2R,3R*)-methyl 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-hydroxy-3-(4-nitrophenyl)-2-phenylpropanoate (anti-**4l**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 8.1 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.43–7.30 (m, 7H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.15 (s, 1H), 6.07 (d, *J* = 6.7 Hz, 1H), 6.00 (s, 1H), 4.75–4.60 (m, 1H), 4.59–4.46 (m, 1H), 4.22 (t, *J* = 5.8 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.21, 157.11, 147.60, 147.07, 143.28, 141.52, 135.18, 128.73, 128.03, 127.23, 127.18, 127.04, 124.78, 124.69, 123.12, 120.22, 75.26, 70.10, 67.18, 53.83, 47.22; HRMS (ESI) m/z calcd for $C_{31}H_{26}N_2NaO_7$ $(M+H)^+$ 561.1638, found 561.1637.

4.2.14. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-3-(4-nitrophenyl)-2-(p-tolyl)propanoate (anti-**4m**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 2H), 7.48–7.40 (m, 3H), 7.40–7.35 (m, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 7.24–7.13 (m, 4H), 6.24 (s, 1H), 6.08 (s, 2H), 5.22 (d, *J* = 12.1 Hz, 1H), 5.06 (d, *J* = 12.1 Hz, 1H), 3.73 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.25, 157.11, 147.52, 147.29, 138.65, 135.73, 132.23, 129.41, 128.74, 128.67, 128.59, 127.92, 127.03, 123.04, 75.35, 70.16, 67.93, 53.78, 21.09; HRMS (ESI) m/z calcd for $C_{25}H_{24}N_2NaO_7$ $(M+Na)^+$ 487.1481, found 487.1490.

4.2.15. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-3-hydroxy-2-(4-methoxyphenyl)-3-(4-nitrophenyl)propanoate (anti-**4n**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.3 Hz, 2H), 7.53–7.28 (m, 7H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.23 (s, 1H), 6.06 (s, 2H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.06 (d, *J* = 12.1 Hz, 1H), 3.82 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.28, 159.69, 157.10, 147.50, 147.34, 135.71, 128.75, 128.71, 128.59, 128.44, 127.87, 127.13, 123.07, 114.04, 75.37, 69.94, 67.94, 55.30, 53.78; HRMS (ESI) m/z calcd for $C_{25}H_{24}N_2NaO_8$ $(M+H)^+$ 503.1430, found 503.1453.

4.2.16. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-2-(4-fluorophenyl)-3-hydroxy-3-(4-nitrophenyl)propanoate (anti-**4o**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.59–7.29 (m, 7H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.08 (t, *J* = 8.3 Hz, 2H), 6.28 (s, 1H), 6.13 (s, 1H), 6.06 (d, *J* = 8.0 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.05 (d, *J* = 12.1 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.71, 162.67 (d, *J* = 248.9 Hz), 157.14, 147.59, 147.10 (s), 135.55, 131.23 ((d, *J* = 2.9 Hz), 129.20 (d, *J* = 8.3 Hz), 128.85, 128.73, 128.64, 127.68, 123.20, 115.71 (d, *J* = 21.7 Hz), 75.53, 70.05, 68.10, 53.98; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.93 (s) ; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2NaO_7F$ $(M+H)^+$ 491.1230, found 491.1249.

4.2.17. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-2-(2-bromophenyl)-3-hydroxy-3-(4-nitrophenyl)propanoate (anti-**4p**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.8 Hz, 1H), 8.22–8.06 (m, 2H), 7.59 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.53–7.46 (m, 1H), 7.44 – 7.33 (m, 5H), 7.34-7.29 (m, 2H), 7.28 – 7.22 (m, 1H), 6.63 (s, 1H), 6.55 (s, 1H), 5.86 (s, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.03 (d, *J* = 12.2 Hz, 1H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.59, 157.60, 147.97, 146.62, 135.89, 135.58, 135.20, 132.06, 130.19, 128.67, 128.65, 128.62, 128.28, 127.78, 123.20, 121.71, 77.46, 70.88, 68.18, 53.90; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2NaO_7Br$ $(M+H)^+$ 551.0430, found 551.0443.

4.2.18. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-2-(3-bromophenyl)-3-hydroxy-3-(4-nitrophenyl)propanoate (anti-**4q**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.8 Hz, 2H), 7.60 (s, 1H), 7.52–7.45 (m, 1H), 7.45-7.37 (m, 4H), 7.36–7.29 (m, 2H), 7.23 (d, *J* = 4.1 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.25 (s, 1H), 6.13 (d, *J* = 7.8 Hz, 1H), 6.01 (d, *J* = 8.3 Hz, 1H), 5.18 (d, *J* = 12.1 Hz, 1H), 5.04 (d, *J* = 12.1 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.30, 157.13, 147.63, 146.91, 137.79, 135.51, 131.91, 130.38, 130.17, 128.84, 128.77, 128.58, 127.68, 126.08, 123.24, 122.86, 75.51, 70.13, 68.17 (s), 54.13; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2NaO_7Br$ $(M+H)^+$ 551.0430, found 551.0417.

4.2.19. (2R,3R*)-methyl 2-(((benzyloxy)carbonyl)amino)-2-(4-bromophenyl)-3-hydroxy-3-(4-nitrophenyl)propanoate(anti-**4r**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.48–7.41 (m, 3H), 7.41-7.32 (m, 4H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.28 (s, 1H), 6.16 (d, *J* = 7.7 Hz, 1H), 6.04 (d, *J* = 8.4 Hz, 1H), 5.21 (d, *J* = 12.1 Hz, 1H), 5.04 (d, *J* = 12.1 Hz, 1H), 3.75 (s,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.38, 157.15, 147.61, 146.99, 135.49, 134.63, 131.89, 129.05, 128.87, 128.74, 128.66, 127.63, 123.24, 123.04, 75.48, 70.24, 68.16, 54.06; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2NaO_7F$ $(M+H)^+$ 491.1230, found 491.12

4.3. *(2R*,3R*)*-methyl 2-amino-3-hydroxy-3-(4-nitrophenyl)-2-phenylpropanoate (6)

To a solution of **4k** (45 mg, 0.108 mmol) in DCM (2 mL) was added TFA (0.5 mL) at room temperature. The reaction mixture was stirred for 5h, and then solvent was removed in vacuo. The residue was diluted with DCM. pH was adjusted to about 8 with a ammonium solution (7M) in methanol and the mixture was concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc /light petroleum = 1:10~1:2) to give the product **6** (34.2 mg, 80% yield) as a white solid**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.7 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.48–7.30 (m, 5H), 5.50 (s, 1H), 3.63 (d, *J* = 1.2 Hz, 3H), 1.86 (br, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.09, 147.65, 146.59, 138.97, 128.69, 128.45, 126.47, 122.90, 5.87, 68.06, 52.73; HRMS (ESI) m/z calcd for $C_{16}H_{17}N_2O_5$ $(M+H)^+$ 317.1137, found 317.1144.

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Supplementary data

Supplementary data related to this article can be found at http://www.

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