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A new cost-effective Ru-chloramphenicol base derivative catalyst for the asymmetric transfer hydrogenation/dynamic kinetic resolution of *N*-Boc α-amino-β-ketoesters and its application to the synthesis of the chiral core of vancomycin†

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Herein we describe the application of a series of newly developed Ru-chloramphenicol base derivative complexes as catalysts for the highly diastereo- and enantioselective transfer hydrogenation of *N*-Boc α-amino-β-ketoesters for the asymmetric synthesis of *anti*-*N*-Boc-β-hydroxy-α-amino esters. This report highlights the utility of this catalytic methodology for the preparation of pharmaceutical compounds bearing a *N*-Boc α-amino-β-hydroxy substructure with two stereocenters.

Introduction

The stereocontrolled construction of chiral vicinal amino alcohol motifs remains an active area of research in modern organic chemistry. Compounds containing this motif not only represent valuable building blocks, ligands and chiral auxiliaries in asymmetric synthesis, but also exhibit a variety of interesting biological activities. Chiral vicinal amino alcohols can also be found in a wide range of natural products, including, for example, (+)-lactacystin, symbioramide, vancomycin antibiotics and sphingosine (Fig. 1).[1] Among the synthetic methods available for the construction of optically pure vicinal amino alcohol subunits, the asymmetric transfer hydrogenation (ATH) of α-amino-β-keto ester accompanied by dynamic kinetic resolution (DKR) is considered to be the most efficient approach.[2]

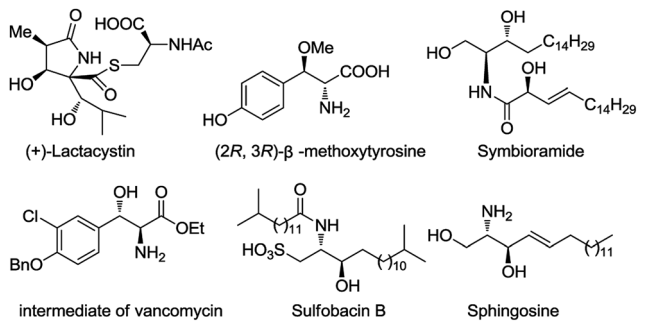

Fig. 1 Examples of biologically active molecules containing an *anti*-vicinal amino alcohol fragments.

In 1989, the Noyori group[3] reported the first asymmetric transfer hydrogenation of α-acylamino-β-keto esters using a Ru-(*R*)-BINAP complex to afford the corresponding *syn*-selective β-hydroxyl-α-amino esters with excellent diastereo- and enantioselectivity. In a subsequent publication, Genet's group[4] reported the similar results with other sophisticated ligands, such as MeO-BIPHEP, TsDPEN, SUNPHOS, SYNPHOS. During the last decade, Hamada and co-workers[5] have developed a series of Ru-catalysts for the *anti*-selective asymmetric transfer hydrogenation of α-amino-β-keto ester hydrochlorides through a DKR process to afford the corresponding *anti*-selective α-amino-β-hydroxyl esters. Somfai *et al.*[6] recently reported the asymmetric transfer hydrogenation of α-amido-β-keto esters in water in the presence of a phase transfer catalyst with an expensive (*S*,*S*)-BnDPAE ligand. Although vicinal amino alcohol can be prepared in good yields using an ATH/DKR process with high diastereo- and enantioselectivity, the application of this process has been limited by its required for expensive ligand. The development of readily available and in expensive ligands for preparation of β-hydroxy-α-amino esters *via* ATH/DKR under mild reaction conditions is therefore highly desired.

(1*S*,2*S*)-2-Amino-1-(4-nitrophenyl)-propane-1,3-diol (chloramphenicol base), which is produced as a chiral waste product during the manufacture of chloramphenicol,[7] has a similar structure to that of (*S*,*S*)-BnDPAE. We previously reported the use of chloramphenicol base derivatives as a chiral ligand for the synthesis of florfenicol.[8] As part of our ongoing interest in the stereoselective synthesis of vicinal amino alcohol using an ATH/DKR approach, we set out to achieve the *anti*-selective transfer hydrogenation of α-amido-β-ketoesters with high

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diastereo- and enantioselectivity using Ru-chloramphenicol base derivative complex as a catalyst.

Herein, we describe our recent work towards the use of Ru-chloramphenicol base derivative complexes as catalysts for the preparation of *anti*-*N*-Boc β-hydroxyl-α-amino esters. Notably, the transfer hydrogenation strategy described in this paper was successfully applied to the synthesis of a key intermediate of vancomycin.

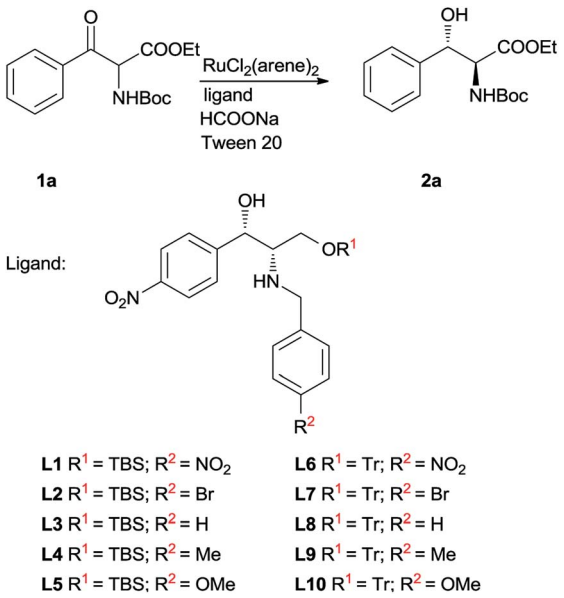
Results and discussion

Our initial investigation focused on evaluating various Ru-chloramphenicol base derivative complexes as catalysts for the asymmetric transfer hydrogenation of racemic of *N*-Boc α-amino-β-ketoesters **1a** in the presence of sodium formate (10 equiv.) and Tween 20 (20%) in water at 40 °C (Table 1). All of the catalysts evaluated in this screen performed effectively to afford **2a** with excellent diastereoselectivity (up to 91%) and moderate enantioselectivity (66%) with high isolated yield. The relative and absolute stereochemistry of **2a** was confirmed by high-performance liquid chromatography (HPLC) analysis based on a comparison with an authentic sample.[8] The results clearly showed that the stereochemistry outcome of the reaction is affected by the nature of chiral ligand. We initially investigated the impact of the R^2 substituent of the ligand on the stereochemical outcome of the reaction. The introduction of an electron-withdrawing or electron-donating group at the R^2 position of the phenyl ring did not lead to an increase in the diastereo- or enantioselectivity of the reaction (Table 1, entries 1–5). This result could be attributed to unfavored steric hindrance between the R^2 group of ligand and **1a** during the reaction. We subsequently proceeded to investigate the impact of changing the R^1 group to a bulky OTr group. Ligand **L8** bearing a proton at R^2 led to low level of asymmetric induction (Table 1, entry 8).

Notably, the introduction of $[RuCl_2(benzene)]_2$ as a pre-catalyst led to a slight decrease in the stereoselectivity of **2a** (Table 1, entry 11). Among these catalysts, $[RuCl_2(p\text{-cymene})]_2$-**L3** was found to be the most effective for the ATH reaction of **1a**, affording the product **2a** with 90% de and 66% ee in 82% yield (Table 1, entry 3).

Encouraged by these results, we proceeded to investigate the effect of varying the phase transfer catalyst (PTC), temperature and catalyst loading, with the aim of improving the enantioselectivity (Table 2). It has been reported that phase transfer catalysts played a critical role in determining the diastereo- and enantioselectivity in ATH/DKR reactions.[9] several phase transfer catalysts were examined in this transformation in an attempt to enhance the diastereo- and enantioselectivity. The addition of PEG-400 or PEG-600 had very little impact on the stereoselectivity, with the latter leading to a considerable decrease in the yield (Table 2, entries 4 and 5). Several other PTCs were also screened, but found to have an adverse impact on the reaction. We then examined the effect of temperature on the outcome of reaction and found that reducing the temperature to 25 °C led to an increase in the enantioselectivity of **2a** increased to 74% with $[RuCl_2(p\text{-cymene})]_2$-**L3** as the catalyst

Table 1 Screening of the asymmetric transfer hydrogenation of **1a** with chiral $[RuCl_2(arene)]_2$-chloramphenicol base derivative catalysts[a]



L1 R^1 = TBS; R^2 = NO_2 **L6** R^1 = Tr; R^2 = NO_2
L2 R^1 = TBS; R^2 = Br **L7** R^1 = Tr; R^2 = Br
L3 R^1 = TBS; R^2 = H **L8** R^1 = Tr; R^2 = H
L4 R^1 = TBS; R^2 = Me **L9** R^1 = Tr; R^2 = Me
L5 R^1 = TBS; R^2 = OMe **L10** R^1 = Tr; R^2 = OMe

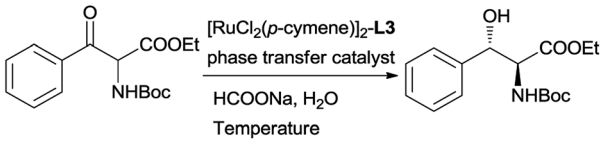
Entry	Arene/ Ligand	Temp. (°C)	Yield[b] (%)	de[c] (*anti*)	ee[c] (*anti*, %)
1	*p*-Cymene/ **L1**	40	82	91	58
2	*p*-Cymene/ **L2**	40	81	88	60
3	*p*-Cymene/ **L3**	40	82	90	66
4	*p*-Cymene/ **L4**	40	82	86	64
5	*p*-Cymene/ **L5**	40	86	87	61
6	*p*-Cymene/ **L6**	40	81	84	60
7	*p*-Cymene/ **L7**	40	74	82	48
8	*p*-Cymene/ **L8**	40	80	85	55
9	*p*-Cymene/ **L9**	40	85	88	43
10	*p*-Cymene/ **L10**	40	88	87	60
11	Benzene/**L3**	40	80	82	62

[a] All of these reactions were carried out with **1a** (2 mmol), HCOONa (5 equiv.) and catalyst (10%) for 48 h. [b] Isolated yield. [c] The diastereo- and enantioselectivity were determined by HPLC analysis with a Daicel Chiralcel AD-H column.

(Table 2, entries 8–11). However, further reducing of the temperature to 20 °C led to a slight decrease in the de, ee and yield of **2a**. Decreasing of the catalyst loading lead to a significant decrease of the enantioselectivity. It is noteworthy that increasing the catalyst loading caused nearly no increase of the enantioselectivity of the reaction (Table 2, entries 12 and 13).

It has been shown that the pH value can affect the reaction rate and stereoselectivity of ATH in water.[10] Under present

Table 2 Optimization of the reaction conditions for the ATH of **1a** with $[RuCl_2(p\text{-cymene})]_2$-**L3** complex[a]



1a **2a**

Entry	PTC	Temp. (°C)	Catalyst loading	Yield[b] (%)	de[c] (*anti*)	ee[c] (%)
1	Tween 20	40	10	82	90	66
2	SDS	40	10	60	70	40
3	CTAB	40	10	54	80	51
4	PEG-400	40	10	75	87	63
5	PEG-600	40	10	52	86	61
6	TBAB	40	10	35	72	42
7	TEBAC	40	10	41	80	55
8	Tween 20	35	10	74	92	69
9	Tween 20	30	10	75	88	72
10	Tween 20	25	10	80	92	74
11	Tween 20	20	10	76	91	71
12	Tween 20	25	5	76	90	64
13	Tween 20	25	20	80	92	75

[a] All of these reactions were carried out with **1a** (2 mmol), HCOONa (5 equiv.) and catalyst (10%) for 48 h. [b] Isolated yield. [c] The diastereo- and enantioselectivity were determined by HPLC analysis with a Daicel Chiralcel AD-H column.

Table 3 Effect of initial pH values of the solution on the ATH of **1a** catalyzed by $[RuCl_2(p\text{-cymene})]_2$-**L3** complex[a]

Entry	pH	Conv. (%) (h)	de[c] (%)	ee[c] (%)
1	2.0	15 (48 h)	—	—
2	3.0	60 (48 h)	—	—
3	4.0	72 (48 h)	80	70
4	5.0	90 (12 h)	94	75
5	6.0	99 (12 h)	96	79
6	7.0	95 (24 h)	93	74
7	8.0[b]	86 (24 h)	92	71

[a] All of these reaction were carried out with substrate (2 mmol), catalyst (10%), tween 20 (20%) in water with a HCOOH–HCOONa buffer. [b] This reaction was carried out at pH 8.0 in HCOONa–NaOH buffer. [c] Determined by HPLC analysis with a Daicel Chiralcel AD-H.

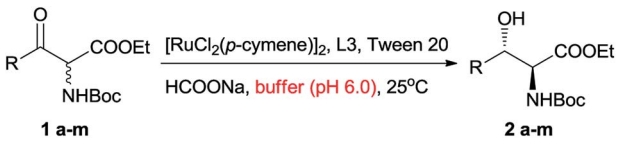
conditions, the initial pH value of the reaction mixture was about 7 and this transfer hydrogenation of **1a** was sluggish. So we intend to improve the reaction rate of **1a** by adjusting pH value and the results were shown in Table 3. We found that the reaction rate of **1a** was indeed strongly affected by the pH values of the solution, with the maximum conversion in 12 h observed at pH 6.0 (Table 3, entry 5) and little compromise in stereoselectivity. Deviating from pH 6.0 for $[RuCl_2(p\text{-cymene})]_2$-**L3** resulted in rapid decrease in the reduction rates.

Based on these results, the optimized reaction conditions were determined to be as follows: 10 mol% of $[RuCl_2(p\text{-cymene})]_2$-**L3** as the catalyst, Tween 20 as the phase transfer catalyst with HCOOH–HCOONa buffer (pH 6.0) at 25 °C for 12 h.

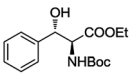
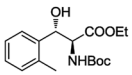
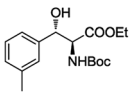
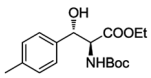
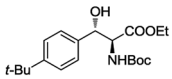
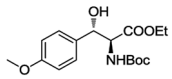
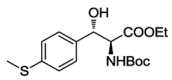
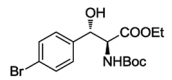
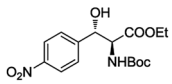
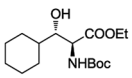
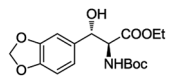
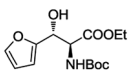
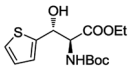
With optimized conditions in hand, we proceeded to examine the scope of this Ru-catalyzed ATH/DKR reaction using a series of different α-amido-β-ketoesters **1a–m** (Table 4). All of these substrates reacted efficiently to afford the corresponding chiral vicinal amino alcohol **2a–m** as the *anti*-products in good yield with excellent diastereoselectivity and good enantioselectivity. Notably, the introduction of a methyl group at the *ortho*- or *meta*-position of the phenyl ring of the substrate resulted in a significant decrease in the enantioselectivity (Table 4, entries 2–4). This decrease in the enantioselectivity was attributed to steric hindrance between the catalytic complex and the substituents at these positions. Notably, the introduction of a bulky *tert*-butyl group at the *para*-position of the phenyl ring had very little impact on the diastereoselectivity and enantioselectivity (Table 4, entries 4 and 5). Electron-withdrawing and electron-donating substituents at the *para*-position both resulted in high yields and good enantioselectivities (Table 4, entries 6–9). Specifically, the 4-bromo substrate **1h** gave the highest ee value of all of the substrates tested in the current study (up to 87%, Table 4, entry 8). However, the replacement of the 4-bromo group with a more strongly electron-withdrawing 4-nitro group led to a slightly lower enantioselectivity (Table 4, entry 9). The cyclohexyl substrate **1j** (Table 4, entry 10) gave a slightly lower yield and enantioselectivity than its aromatic counterpart **1a**.

Heteroaromatics substrates performed poorly under the optimized conditions, as exemplified by the furan and thiophene substrates **1l** and **1m**, which both resulted in low diastereoselectivity observed in these cases could be explained by the heteroatoms of these ring forming six-membered cyclic intermediate in combination with the Ru-chloramphenicol base derivative complex.[4g]

Table 4 *anti*-Selective asymmetric hydrogenation catalyzed by Ru-**L3** complex[a]

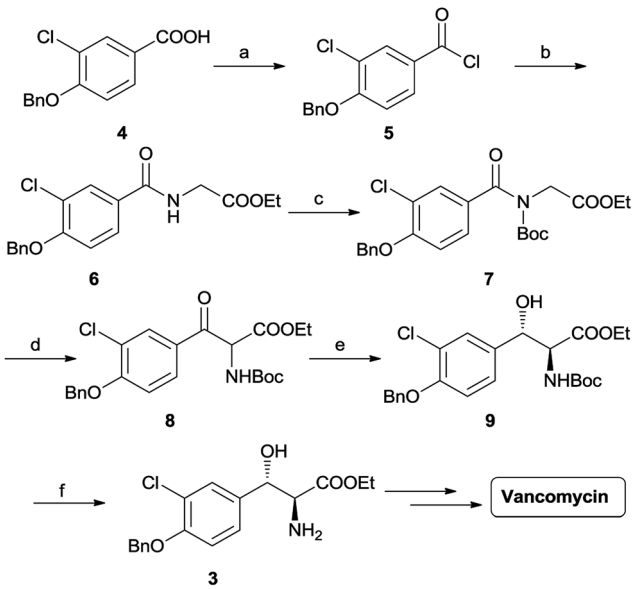


1 a-m **2 a-m**

Entry	ATH product **2**	Yield[b] (%)	de[c] (*anti*)	ee[d] (*anti*, %)
1		80	96	79
2		79	93	43
3		80	96	68
4		85	90	73
5		80	94	79
6		92	89	71
7		88	94	78
8		85	90	87
9		88	96	67
10		81	82	68
11		87	94	82
12		85	63	60
13		79	80	66

[a] All of these reactions were carried out with substrate **1a–m** (2 mmol), catalyst (10%), Tween 20 (20%) HCOONa–HCOOH (pH 6.0, 5 equiv.) at 25 °C for 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis with a Daicel Chiralcel AD-H or OD-H column.

To demonstrate the utility of the methodology developed in this study, we investigated its application to the synthesis of **3**, which is a key building block in the construction of the



Scheme 1 Reagent and conditions: (a) $SOCl_2$, DMF (cat.), DCM, reflux., 3 h; (b) glycine ethyl ester hydrochloride, Na_2CO_3, EA/H_2O, r.t., 2 h; (c) Boc_2O, DMAP (cat.), CH_3CN, r.t., 10 h; (d) *t*-BuOK, THF, 10 °C, 1 h, 63% (over 4 steps); (e) $[RuCl_2(p\text{-cymene})]_2$, Tween 20, HCOONa, H_2O, 25 °C, 48 h, 88%, 76% of ee and 95% of de; (f) TFA, DCM, 0 to 20 °C, 4 h, 91%, 99% of ee and 99% of de after crystallized from MTBE.

antibiotic agent vancomycin[12,13] (Scheme 1). Briefly, 4-(benzyloxy)-3-chlorobenzoic acid **4** was prepared according to a literature procedure.[12] The subsequent treatment of **4** with thionyl chloride in refluxing dichloromethane in the presence of a catalytic amount of DMF afforded the corresponding acyl chloride **5**. The treatment of **5** with glycine, followed by the *N*-Boc-protection of the resulting amide gave the *N*-Boc α-amino-β-ketoesters **8**.[11] The ATH/DKR reaction of **8** under our optimized condition afford compound **9** with 76% ee and 95% of de in 88% yield. The optical purity of **9** was improved to 92% by recrystallized from petroleum ether/ethyl acetate (1/1, v/v). The subsequent deprotection of the Boc group in **9** with TFA in dichloromethane at room temperature to give the *anti*-(2*S*,3*S*) amino alcohol **3** in 91% yield. After crystallized from MTBE, the desired **3** was obtained with 99% of ee and 99% of de.

Conclusions

In conclusion, we have successfully developed a novel series of readily available Ru-chloramphenicol base derivative complexes as catalysts for the ATH/DKR of *N*-Boc α-amino-β-ketoester to afford *anti*-selective *N*-Boc β-hydroxyl-α-amino esters with excellent diastereoselectivity and good enantioselectivity. This protocol showed good functional group tolerance towards a wide variety of aromatic, heteroaromatic and alkyl substrates. The utility of this methodology was demonstrated by its application to the stereoselective synthesis of a key building block in the preparation of the antibiotic vancomycin.

Experimental section

All reagents and solvent were obtained from commercial sources and used without further purification. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR were recorded on a Bruker Avance 400 spectrometer using TMS or $CDCl_3$ as internal standards, IR spectra were recorded on a Nicolet iS5 FT-IR spectrometer, optical rotations were measured by a JASCO P1020 digital polarimeter. EI-MS were recorded on an Agilent 6890N/5975 spectrometer and ESI-MS were recorded on a Waters Micromass Quattro Micro spectrometer. The pH values were recorded on a PHS-3C. HRMS were recorded on a Bruker microTOF spectrometer.

General procedure for the preparation of transfer hydrogenation substrates 1a–m

1a–m was synthesized according to known procedure from the corresponding acid.[11]

Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-oxo-3-phenylpropanoate (1a). The compound **1a** was prepared in 70% yield as a white solid. Mp 68.0–69.2 °C. FT-IR (ATR): ν 3358, 2980, 2946, 1751, 1680, 1521, 1288, 1158, 1030, 942, 891, 698, 590. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–8.13 (m, 5H), 5.95 (s, 2H), 4.16–4.20 (m, 2H), 1.47 (s, 9H), 1.14 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 166.4, 154.4, 133.6, 128.9, 128.1, 79.9, 61.7, 58.8, 27.6, 13.2. HRMS (ESI) calcd for $C_{16}H_{21}NNaO_5$ $[M + Na]^+$ 330.1317, found 330.1310.

Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-oxo-3-(*o*-tolyl)propanoate (1b). The compound **1b** was prepared in 68% yield as a white solid. Mp 56.0–58.0 °C. FT-IR (ATR): ν 3355, 2969, 1754, 1680, 1515, 1331, 1280, 1158, 1013, 729, 584. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, J = 7.6 Hz, 1H), 7.25–7.44 (m, 3H), 5.92 (d, J = 6.8 Hz, 1H), 5.79 (d, J = 7.6 Hz, 1H), 4.05–4.16 (m, 2H), 2.45 (s, 3H), 1.45 (s, 9H), 1.05 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 166.7, 154.8, 139.0, 134.8, 132.1, 131.6, 129.4, 125.5, 80.3, 61.9, 53.2, 28.0, 20.7, 13.6. HRMS (ESI) calcd for $C_{17}H_{23}NNaO_5$ $[M + Na]^+$ 344.1474, found 344.1489.

Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-oxo-3-(*m*-tolyl)propanoate (1c). The compound **1c** was prepared in 75% yield as a white solid. Mp 70.2–72.1 °C. FT-IR (ATR): ν 3344, 2977, 1757, 1683, 1521, 1282, 1197, 1152, 953, 729. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 2H), 7.39–7.45 (m, 3H), 5.95 (s, 2H), 4.14–4.19 (m, 2H), 2.43 (s, 3H), 1.47 (s, 9H), 1.15 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.8, 166.9, 154.8, 138.4, 134.9, 134.0, 129.8, 128.4, 126.6, 80.4, 62.1, 59.3, 28.0, 21.1, 13.7. HRMS (ESI) calcd for $C_{17}H_{23}NNaO_5$ $[M + Na]^+$ 344.1474, found 344.1467.

Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-oxo-3-(*p*-tolyl)propanoate (1d). The compound **1d** was prepared in 70% yield as a white solid. Mp 92.6–94.0 °C. FT-IR (ATR): ν 3327, 2983, 1757, 1677, 1603, 1527, 1291, 1160, 1055, 947, 828, 737, 621. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 5.93 (s, 2H), 4.14–4.19 (m, 2H), 2.44 (s, 3H), 1.46 (s, 9H), 1.15 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 167.5, 155.3, 145.7, 131.9, 129.9, 129.6, 80.7, 62.5, 59.6, 28.5, 22.0, 14.1. HRMS (ESI) calcd for $C_{17}H_{23}NNaO_5$ $[M + Na]^+$ 344.1474, found 344.1482.

Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-(4-(*tert*-butyl)phenyl)-3-oxopropanoate (1e). The compound **1e** was prepared in 69% yield as a white solid. Mp 118.0–120.3 °C. FT-IR (ATR): ν 3341, 2972, 1757, 1674, 1603, 1518, 1288, 1155, 1053, 842, 615. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 5.95 (s, 2H), 4.17–4.20 (m, 2H), 1.47 (s, 9H), 1.36 (s, 9H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.0, 167.0, 158.1, 154.8, 131.3, 129.8, 129.3, 125.5, 125.2, 80.3, 62.0, 59.1, 35.1, 30.9, 30.8, 28.0, 13.7. HRMS (ESI) calcd for $C_{20}H_{29}NNaO_5$ $[M + Na]^+$ 386.1943, found 386.1943.

Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-(4-methoxyphenyl)-3-oxopropanoate (1f). The compound **1f** was prepared in 74% yield as a white solid. Mp 60.1–62.3 °C. FT-IR (ATR): ν 3324, 2977, 1748, 1674, 1600, 1535, 1266, 1158, 1033, 947, 840, 587. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 5.95 (d, J = 7.6 Hz, 1H), 5.88 (d, J = 8.0 Hz, 1H), 4.16–4.19 (m, 2H), 3.89 (s, 3H), 1.46 (s, 9H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.3, 166.7, 163.9, 154.4, 131.4, 126.4, 113.3, 79.8, 61.6, 58.5, 54.9, 27.6, 13.3. HRMS (ESI) calcd for $C_{17}H_{23}NNaO_6$ $[M + Na]^+$ 360.1423, found 360.1434.

Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-(4-(methylthio)phenyl)-3-oxopropanoate (1g). The compound **1g** was prepared in 70% yield as a white solid. Mp 83.0–84.5 °C. FT-IR (ATR): ν 3324, 2977, 1748, 1674, 1600, 1535, 1266, 1158, 1033, 947, 840, 587. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 5.88–5.93 (m, 2H), 4.17–4.20 (m, 2H), 2.55 (s, 3H), 1.47 (s, 9H), 1.17 (t, J = 7.2 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9, 166.6, 154.4, 147.4, 129.3, 124.2, 79.9, 61.7, 58.6, 27.7, 14.0, 13.3. HRMS (ESI) calcd for $C_{17}H_{23}NNaO_5S$ $[M + Na]^+$ 376.1195, found 376.1196.

Ethyl-3-(4-bromophenyl)-2-((*tert*-butoxycarbonyl)amino)-3-oxopropanoate (1h). The compound **1h** was prepared in 78% yield as a white solid. Mp 101.0–102.8 °C. FT-IR (ATR): ν 3329, 2983, 1757, 1677, 1586, 1527, 1288, 1158, 1055, 950. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 5.89 (s, 2H), 4.17–4.20 (m, 2H), 1.46 (s, 9H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.0, 166.6, 154.8, 132.9, 131.9, 130.7, 129.5, 80.6, 62.3, 59.2, 28.0, 13.7. HRMS (ESI) calcd for $C_{16}H_{20}BrNNaO_5$ $[M + Na]^+$ 408.0423, found 408.0429.

Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-(4-nitrophenyl)-3-oxopropanoate (1i). The compound **1i** was prepared in 78% yield as a yellow solid. Mp 62.0–64.5 °C. FT-IR (ATR): ν 3327, 2986, 1751, 1677, 1524, 1334, 1155, 1058, 868, 851, 703, 598. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, J = 8.8 Hz, 2H), 8.26 (d, J = 8.8 Hz, 2H), 5.88 (s, 2H), 4.20–4.22 (m, 2H), 1.46 (s, 9H), 1.16 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 166.0, 154.7, 150.6, 138.9, 130.2, 123.6, 80.8, 62.6, 61.1, 59.5, 28.0, 13.6. HRMS (ESI) calcd for $C_{16}H_{20}N_2NaO_7$ $[M + Na]^+$ 375.1168, found 375.1188.

Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-cyclohexyl-3-oxopropanoate (1j). The compound **1j** was prepared in 66% yield as a oil. FT-IR (ATR): ν 3358, 2975, 1748, 1660, 1518, 1197, 1053, 947, 723, 587. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (d, J = 6.8 Hz, 1H), 5.12 (d, J = 7.6 Hz, 1H), 4.21–4.27 (m, 2H), 2.76–2.79 (m, 1H), 1.97–1.93 (m, 1H), 1.69–1.78 (m, 5H), 1.46 (s, 9H), 1.26–1.30

(m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9, 167.1, 155.1, 80.6, 62.5, 62.4, 48.5, 43.0, 28.4, 25.9, 25.3, 14.2. HRMS (ESI) calcd for $C_{16}H_{27}NNaO_5$ $[M + Na]^+$ 336.1787, found 336.0883.

Ethyl-3-(benzo[*d*][1,3]dioxol-5-yl)-2-((*tert*-butoxycarbonyl) amino)-3-oxopropanoate (1k). The compound **1k** was prepared in 52% yield as a white solid. Mp 100.0–101.0 °C. FT-IR (ATR): ν 3321, 2977, 1762, 1669, 1532, 1441, 1370, 1263, 1158, 1030, 930, 837, 567. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.0 Hz, 1H), 7.55 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.08 (s, 1H), 5.92 (d, J = 8.0 Hz, 1H), 5.83 (d, J = 8.4 Hz, 1H), 4.17–4.21 (m, 2H), 1.46 (s, 9H), 1.18 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.9, 167.5, 155.3, 153.2, 148.6, 129.1, 126.9, 109.1, 108.3, 102.4, 80.8, 62.5, 59.4, 28.5, 14.2. HRMS (ESI) calcd for $C_{17}H_{25}NNaO_7$ $[M + Na]^+$ 374.1216, found 374.1218.

Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-(furan-2-yl)-3-oxopropanoate (1l). The compound **1l** was prepared in 76% yield as a white solid. Mp 84.2–85.7 °C. FT-IR (ATR): ν 3366, 3139, 2989, 1748, 1657, 1512, 1329, 1158, 1050, 777, 590. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (s, 1H), 7.49 (s, 1H), 6.60 (t, J = 1.6 Hz, 1H), 5.83 (d, J = 7.6 Hz, 1H), 5.68 (d, J = 8.0 Hz, 1H), 4.17–4.22 (m, 2H), 1.45 (s, 9H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.7, 166.5, 154.7, 150.1, 147.9, 120.7, 112.6, 80.4, 62.2, 59.2, 28.0, 13.7. HRMS (ESI) calcd for $C_{14}H_{19}NNaO_6$ $[M + Na]^+$ 320.1110, found 320.1117.

Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-oxo-3-(thiophen-2-yl) propanoate (1m). The compound **1m** was prepared in 75% yield as a white solid. Mp 74.0–75.5 °C. (Lit.[3] mp 75.5–76 °C). FT-IR (ATR): ν 3358, 2975, 1748, 1660, 1518, 1197, 1053, 947, 723, 587. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 3.6 Hz, 1H), 7.77 (d, J = 4.8 Hz, 1H), 7.18 (t, J = 4.8 Hz, 1H), 5.90 (d, J = 7.6 Hz, 1H), 5.75 (d, J = 8.4 Hz, 1H), 4.19–4.24 (m, 2H), 1.46 (s, 9H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.9, 166.7, 154.7, 140.8, 135.8, 134.9, 128.3, 80.4, 62.3, 60.1, 28.0, 13.7. HRMS (ESI) calcd for $C_{14}H_{19}NNaO_5S$ $[M + Na]^+$ 336.0882, found 336.0888.

General procedure for the ATH/DKR procedure (2a–m)

A mixture of $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 0.05 mmol), ligand **L3** (42 mg, 0.1 mmol), Tween 20 (69 mg, 0.2 mmol) and water (5 mL) were stirred at 40 °C under N_2 for 2 h and cooled to room temperature, **1a–m** (1 mmol) and HCOOH–HCOONa buffer (pH 6.0, 5 mmol) were added. The reaction mixture was stirred at 25 °C for 12 h. Ethyl acetate (10 mL) was added to the reaction mixture and stirred for 30 min. The organic layer was separated, the aqueous layer was extracted with ethyl acetate (10 mL × 3), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo*, and the crude product was purified by flash chromatography (petroleum ether/ethyl acetate 3 : 1, v/v) to give **2a–m** (Y = 79–92%).

For the synthesis of the racemic amino alcohols for the ee assay, the TsDPEN ligand (0.2 equiv.) and $[RuCl_2(p\text{-cymene})]_2$ (0.1 equiv.) were used as the catalyst and the reaction was run at 45 °C following the procedure outlined above.[6]

(2*S*,3*S*)-Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-phenylpropanoate (2a). The compound **2a** was prepared in 90% yield as a white solid. Mp 88.0–89.2 °C. HPLC (Daicel AD-H, hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, detection at 225 nm, 30 °C): *anti*: t_R (major) = 14.1 min, t_R (minor) = 15.1 min; *syn*: t_R = 16.4 min, t_R = 17.4 min. FT-IR (ATR): ν 3466, 3321, 2975, 1723, 1677, 1504, 1294, 1186, 1158, 1007, 871, 703. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.35 (m, 5H), 5.33 (d, J = 6.0 Hz, 1H), 5.21 (s, 1H), 4.71 (s, 1H), 4.13–4.19 (q, 2H), 4.07 (s, 1H), 1.45 (s, 9H), 1.19 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 156.3, 139.2, 128.1, 126.0, 80.5, 75.0, 61.6, 59.7, 28.2, 13.9. HRMS (ESI) calcd for $C_{16}H_{23}NNaO_5$ $[M + Na]^+$ 332.1474, found 332.1473.

(2*S*,3*S*)-Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(*o*-tolyl)propanoate (2b). The compound **2b** was prepared in 80% yield afford **2b** (3.3 g, 85%) as a white solid. Mp 90.0–91.5 °C. HPLC (Daicel AD-H, hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, detection at 225 nm, 30 °C): t_R (major) = 13.3 min, t_R (minor) = 16.4 min. FT-IR (ATR): ν 3471, 3381, 2983, 1697, 1515, 1376, 1189, 1160, 1061, 752, 519. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.41 (m, 1H), 7.13–7.21 (m, 3H), 5.56 (d, J = 7.2 Hz, 1H), 5.27 (s, 1H), 4.56 (s, 1H), 3.99–4.07 (m, 2H), 3.51 (s, 1H), 2.37 (s, 3H), 1.44 (s, 9H), 1.04 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 155.3, 137.4, 134.6, 130.2, 127.5, 125.6, 80.0, 71.4, 61.1, 57.7, 53.2, 28.0, 18.8, 13.5. HRMS (ESI) calcd for $C_{17}H_{25}NNaO_5$ $[M + Na]^+$ 346.1630, found 346.1620.

(2*S*,3*S*)-Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(*m*-tolyl)propanoate (2c). The compound **2c** was prepared in 76% yield as a white solid. Mp 75.4–76.8 °C. HPLC (Daicel AD-H, hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, detection at 225 nm, 30 °C): t_R (major) = 13.3 min, t_R (minor) = 16.4 min. FT-IR (ATR): ν 3466, 3335, 2977, 1731, 1677, 1512, 1370, 1291, 1158, 1016, 791. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.25 (m, 1H), 7.06–7.11 (m, 3H), 5.33 (d, J = 6.4 Hz, 1H), 5.18 (s, 1H), 4.67 (s, 1H), 4.14–4.19 (m, 2H), 4.05 (s, 1H), 2.35 (s, 3H), 1.46 (s, 9H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 156.2, 139.0, 137.6, 128.5, 127.9, 126.5, 122.9, 80.3, 74.9, 61.4, 59.6, 53.2, 28.0, 21.2, 13.8. HRMS (ESI) calcd for $C_{17}H_{25}NNaO_5$ $[M + Na]^+$ 346.1630, found 346.1612.

(2*S*,3*S*)-Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(*p*-tolyl)propanoate (2d). The compound **2d** was prepared in 84% yield as a white solid. Mp 94.0–95.1 °C. HPLC (Daicel AD-H, hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, detection at 225 nm, 30 °C): t_R (major) = 13.7 min, t_R (minor) = 15.2 min. FT-IR (ATR): ν 3471, 3332, 2975, 1725, 1680, 1521, 1370, 1291, 1160, 1010, 825, 541. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (s, 4H), 5.30 (d, J = 6.0 Hz, 1H), 5.17 (s, 1H), 4.68 (s, 1H), 4.14–4.19 (q, 2H), 4.00 (s, 1H), 2.34 (s, 3H), 1.45 (s, 9H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 155.8, 137.0, 135.6, 128.4, 128.3, 125.4, 79.9, 74.3, 61.1, 59.2, 27.6, 20.5, 13.4. HRMS (ESI) calcd for $C_{17}H_{25}NNaO_5$ $[M + Na]^+$ 346.1630, found 346.1640.

(2*S*,3*S*)-Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-(4-(*tert*-butyl) phenyl)-3-hydroxypropanoate (2e). The compound **2e** was prepared in 80% yield as a oil. HPLC (Daicel AD-H, hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, detection at 225 nm, 30 °C): t_R (major) = 11.6 min, t_R (minor) = 13.5 min. FT-IR (ATR): ν 3437, 2963, 1697, 1510, 1365, 1251, 1158, 1021, 859, 573. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, J = 8.0 Hz 2H), 7.21 (d, J = 7.6 Hz 2H), 5.33 (s, 1H), 5.15 (s, 1H), 4.67 (s, 1H), 4.11–4.17 (m, 2H), 3.86 (d, J = 4.4 Hz 1H), 1.44 (s, 9H), 1.31 (s, 9H), 1.15 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 169.9, 156.1, 150.8, 136.1, 125.7, 80.3, 74.7, 61.5, 60.3, 59.5, 34.4, 31.2, 28.2, 20.9, 13.8. HRMS (ESI) calcd for $C_{20}H_{31}NNaO_5$ $[M + H]^+$ 388.2100, found 388.2097.

(2*S*,3*S*)-Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(4-methoxyphenyl)propanoate (2f). The compound **2f** was prepared in 92% yield as a white solid. Mp 101.5–102.0 °C. HPLC (Daicel AD-H, hexane/i-PrOH = 90/10, 0.6 mL min^{-1}, detection at 254 nm, 30 °C): t_R (major) = 30.1 min, t_R (minor) = 31.0 min. FT-IR (ATR): ν 3361, 2983, 1746, 1688, 1612, 1512, 1362, 1246, 1155, 999, 828, 539. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.29 (d, J = 7.6 Hz, 1H), 5.15 (s, 1H), 4.66 (s, 1H), 4.14–4.19 (q, 2H), 3.96 (s, 1H), 3.80 (s, 3H), 1.45 (s, 9H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 159.6, 156.6, 113.9, 80.8, 74.9, 61.9, 60.0, 55.5, 28.5, 14.3. HRMS (ESI) calcd for $C_{17}H_{25}NNaO_6$ $[M + Na]^+$ 362.1580, found 362.1587.

(2*S*,3*S*)-Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(4-(methylthio)phenyl)propanoate (2g). The compound **2g** was prepared in 88% yield as a brown solid. Mp 116.0–117.4 °C. HPLC (Daicel OD-H, hexane/i-PrOH = 95/5, 0.5 mL min^{-1}, detection at 254 nm, 30 °C): t_R (major) = 18.5 min, t_R (minor) = 19.8 min. FT-IR (ATR): ν 3364, 2980, 1740, 1686, 1510, 1248, 1152, 1001, 820, 666. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 4H), 5.31 (d, J = 6.0 Hz, 2H), 5.17 (s, 1H), 4.67 (s, 1H), 4.14–4.19 (q, 2H), 4.11 (s, 1H), 2.48 (s, 3H), 1.45 (s, 9H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 156.7, 138.4, 136.4, 126.9, 80.9, 75.0, 62.0, 60.0, 28.5, 16.0, 14.3. HRMS (ESI) calcd for $C_{17}H_{25}NNaO_5S$ $[M + Na]^+$ 378.1351, found 378.1349.

(2*S*,3*S*)-Ethyl-3-(4-bromophenyl)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxypropanoate (2h). The compound **2h** was prepared in 88% yield as a white solid. Mp 123.0–124.2 °C. HPLC (Daicel OD-H, hexane/i-PrOH = 95/5, 0.5 mL min^{-1}, detection at 254 nm, 30 °C): t_R (major) = 15.4 min, t_R (minor) = 16.4 min. FT-IR (ATR): ν 3389, 2986, 1697, 1515, 1251, 1158, 1030, 1004, 823. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 1H), 5.33 (d, J = 6.4 Hz, 1H), 5.18 (s, 1H), 4.67 (s, 1H), 4.27 (s, 1H), 4.15–4.20 (q, 2H), 1.45 (s, 9H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 156.8, 138.7, 131.5, 128.1, 122.1, 81.1, 74.9, 62.2, 59.9, 28.5, 14.3. HRMS (ESI) calcd for $C_{16}H_{22}BrNNaO_5$ $[M + Na]^+$ 410.0579, found 410.0563.

(2*S*,3*S*)-Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(4-nitrophenyl)propanoate (2i). The compound **2i** was prepared in 95% yield as a yellow solid. Mp 107.7–108.4 °C. HPLC (Daicel OD-H, hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, detection at 225 nm, 30 °C): t_R (major) = 8.9 min, t_R (minor) = 10.9 min. FT-IR (ATR): ν 3392, 2989, 1686, 1515, 1348, 1246, 1155, 1033, 840, 709, 573. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 1H), 5.40 (d, J = 6.4 Hz, 1H), 5.34 (s, 1H), 4.72 (s, 1H), 4.55 (s, 1H), 4.18–4.23 (q, 2H), 1.46 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 156.4, 146.7, 126.9, 123.1, 81.0, 74.5, 62.0, 59.7, 28.0, 13.8. HRMS (ESI) calcd for $C_{16}H_{22}N_2NaO_7$ $[M + Na]^+$ 377.1325, found 377.1311.

(2*S*,3*S*)-Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-cyclohexyl-3-hydroxypropanoate (2j). The compound **2j** was prepared in 80% yield as a white solid. Mp 75.4–76.8 °C. HPLC (Daicel AD-H, hexane/i-PrOH = 90/10, 0.6 mL min^{-1}, detection at 210 nm, 30 °C): t_R (major) = 14.0 min, t_R (minor) = 17.0 min. FT-IR (ATR): ν 2929, 2853, 1697, 1498, 1365, 1254, 1160, 1027, 553. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.56 (d, J = 6.8 Hz, 1H), 4.43 (d, J = 4.8 Hz, 1H), 4.15–4.27 (m, 2H), 3.50 (s, 1H), 2.79 (s, 1H), 2.02 (s, 1H), 1.66–1.76 (m, 4H), 1.43 (s, 9H), 0.99–1.28 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 155.4, 79.8, 61.2, 55.6, 40.5, 28.0, 26.0, 25.5, 13.9. HRMS (ESI) calcd for $C_{16}H_{29}NNaO_5$ $[M + H]^+$ 338.1943, found 338.1958.

(2*S*,3*S*)-Ethyl-3-(benzo[*d*][1,3]dioxol-5-yl)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxypropanoate (2k). The compound **2k** was prepared in 86% yield as a white solid. Mp 70.3–72.3 °C. HPLC (Daicel AD-H, hexane/i-PrOH = 85/15, 0.8 mL min^{-1}, detection at 230 nm, 30 °C): t_R (major) = 16.5 min, t_R (minor) = 17.0 min. FT-IR (ATR): ν 3466, 3321, 2980, 1720, 1686, 1504, 1370, 1229, 1158, 1030, 1007, 925. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (s, 1H), 6.71–6.75 (m, 2H), 5.94 (s, 2H), 5.32 (d, J = 7.2 Hz 1H), 5.10 (s, 1H), 4.62 (s, 1H), 4.10–4.19 (m, 2H), 1.44 (s, 9H), 1.21 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 169.6, 156.3, 147.5, 147.1, 133.2, 119.4, 107.8, 106.7, 100.9, 80.5, 74.7, 61.6, 60.3, 59.7, 28.1, 20.9, 13.9. HRMS (ESI) calcd for $C_{17}H_{23}NNaO_7$ $[M + H]^+$ 376.1372, found 376.1366.

(2*S*,3*R*)-Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-(furan-2-yl)-3-hydroxypropanoate (2l). The compound **2l** was prepared in 85% yield as a oil. HPLC (Daicel AD-H, hexane/i-PrOH = 90/10, 0.6 mL min^{-1}, detection at 210 nm, 30 °C): t_R (major) = 19.2 min, t_R (minor) = 21.2 min. FT-IR (ATR): ν 3403, 2977, 1703, 1504, 1370, 1163, 1058, 1027, 740. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, J = 6.4 Hz, 2H), 6.30–6.32 (m, 2H), 5.44 (d, J = 6.8 Hz, 1H), 5.17 (s, 1H), 4.72 (s, 1H), 4.16–4.20 (m, 2H), 1.43 (s, 9H), 1.20 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 156.2, 152.7, 152.5, 142.1, 110.0, 107.4, 80.4, 69.2, 68.3, 61.6, 58.0, 28.0, 13.8. HRMS (ESI) calcd for $C_{14}H_{21}NNaO_6$ $[M + Na]^+$ 322.1267, found 322.1263.

(2*S*,3*S*)-Ethyl-2-((*tert*-butoxycarbonyl)amino)-3-hydroxy-3-(thiophen-2-yl)propanoate (2m). The compound **2m** was prepared in 79% yield as a oil. Mp 70.0–71.1 °C. HPLC (Daicel AD-H, hexane/i-PrOH = 90/10, 0.8 mL min^{-1}, detection at 225 nm, 30 °C): t_R (major) = 16.3 min, t_R (minor) = 17.9 min. FT-IR (ATR): ν 3446, 3324, 2977, 1723, 1680, 1524, 1291, 1160, 999, 703. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.27 (m, 1H), 6.90–7.05 (m, 2H), 5.48 (s, 1H), 5.41–5.42 (m, 1H), 4.76 (s, 1H), 4.53 (s, 1H), 4.18–4.24 (m, 2H), 1.46 (s, 9H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 169.0, 156.6, 142.6, 126.4, 124.9, 124.0, 80.7, 71.8, 70.4, 61.8, 61.6, 59.4, 28.0, 13.8. HRMS (ESI) calcd for $C_{14}H_{21}NNaO_5S$ $[M + H]^+$ 338.1038, found 338.1047.

Ethyl-2-(4-(benzyloxy)-3-chlorobenzamido)acetate (6). To a stirred suspension of Na_2CO_3 (4.0 g, 37.7 mmol) in water (60 mL) and ethyl acetate (50 mL) was added glycine ethyl ester hydrochloride (4.8 g, 34.3 mmol) at 0 °C in portions over 30 min. After stirring for an additional 30 min, **5** (8.8 g, 31.4 mmol) was then added in portions over 30 min. The reaction mixture was warmed to room temperature and formed homogenous biphasic solution. The separated organic phase was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford **6** as a white solid, which could be used in the next step without further

purification. Mp 97.0–98.1 °C. FT-IR (ATR): ν 3295, 1753, 1634, 1542, 1491, 1260, 1196, 995, 918, 646. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H), 7.65 (d, J = 6.4 Hz, 1H), 7.35–7.47 (m, 5H), 6.96 (d, J = 8.4 Hz, 1H), 6.75 (br, 1H), 5.21 (s, 2H), 4.24–4.29 (q, 2H), 4.20 (d, J = 5.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 165.7, 156.7, 135.7, 129.4, 128.6, 128.1, 127.0, 126.9, 123.2, 113.0, 70.7, 61.6, 41.8, 14.1. HRMS (ESI) calcd for $C_{18}H_{18}ClNNaO_4$ $[M + Na]^+$ 370.0822, found 370.0814.

Ethyl-2-(4-(benzyloxy)-*N*-(*tert*-butoxycarbonyl)-3-chlorobenzamido)acetate (7). The crude **6** (6.94 g, 20 mmol) and DMAP (122 mg, 1.0 mmol) were dissolved in acetonitrile (60 mL) under N_2. Boc_2O (5.2 g, 24 mmol) was added at 0 °C dropwise over 1 h. The reaction mixture was stirred at room temperature for 3 h, and the solvent was evaporated under reduced pressure to give crude **7** as a light yellow solid, which was used in the next step without further purification. Mp 87.2–88.4 °C. FT-IR (ATR): ν 2979, 1738, 1669, 1597, 1500, 1357, 1320, 1212, 1146, 1008, 731. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 1H), 7.53 (d, J = 6.8 Hz, 1H), 7.32–7.48 (m, 5H), 6.97 (d, J = 8.4 Hz, 1H), 5.25 (s, 2H), 4.51 (s, 2H), 4.22–4.27 (q, 2H), 1.31 (t, J = 6.8 Hz, 3H), 1.22 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 168.7, 156.3, 152.5, 135.6, 130.3, 129.8, 128.5, 128.0, 126.8, 122.5, 112.6, 83.5, 70.5, 61.3, 46.4, 27.2, 13.9. HRMS (ESI) calcd for $C_{23}H_{26}ClNNaO_6$ $[M + Na]^+$ 470.1346, found 470.1325.

Ethyl-3-(4-(benzyloxy)-3-chlorophenyl)-2-((*tert*-butoxycarbonyl)amino)-3-oxopropanoate (8). A solution of *t*-BuOK (2.4 g, 21.6 mmol) in THF (20 mL) was added to a solution of crude **7** (8.0 g, 18 mmol) in THF (80 mL) at 0 °C dropwise over 1 h under N_2. After aging at 0–10 °C for 1 h, then adjusted to pH = 7 with 10% citric acid, and the organic layer was washed with brine (50 mL × 3), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Recrystallized from MTBE afforded **8** (5.6 g, 63%, over three steps) as a white solid. Mp 78.0–80.5 °C. FT-IR (ATR): ν 3363, 2936, 1751, 1683, 1522, 1493, 1271, 1157, 1057, 1016, 734, 583. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1H), 8.02 (d, J = 7.2 Hz, 1H), 7.36–7.48 (m, 5H), 7.04 (d, J = 8.8 Hz, 1H), 5.91 (d, J = 8.0 Hz, 1H), 5.85 (d, J = 8.0 Hz, 1H), 5.27 (s, 2H), 4.18–4.21 (m, 2H), 1.47 (s, 9H), 1.17 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.5, 167.1, 158.9, 155.1, 135.5, 131.9, 130.3, 127.1, 123.9, 112.8, 80.7, 71.0, 62.5, 59.3, 28.4, 14.0. HRMS (ESI) calcd for $C_{23}H_{26}ClNNaO_6$ $[M + Na]^+$ 470.1346, found 470.1344.

(2*S*,3*S*)-Ethyl-3-(4-(benzyloxy)-3-chlorophenyl)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxypropanoate (9). A mixture of $[RuCl_2(p\text{-cymene})]_2$ (61 mg, 0.1 mmol), ligand **L3** (83 mg, 0.2 mmol), Tween 20 (0.14 g, 0.4 mmol) and water (10 mL) were stirred at 40 °C under N_2 for 2 h and cooled to room temperature, compound **8** (0.89 g, 2 mmol) and HCOOH–HCOONa buffer (pH 6.0, 10 mmol) were added. The reaction mixture was stirred at room temperature for 12 h. Ethyl acetate (20 mL) and 20% citric acid (10 mL) were added to the reaction mixture and stirred for 30 min. The organic layer was separated, the aqueous layer was extracted with ethyl acetate (15 mL × 3), and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo*, and the crude product was purified by flash chromatography (petroleum ether/ethyl acetate 3 : 1, v/v) to give **9** (0.79 g, 88%) as a white solid. The ee value of **9** was improved to 92% after a crystallization from petroleum ether/ethyl acetate (1/1, v/v). Mp 92.0–94.6 °C. $[\alpha]_D^{20.8}$ = +70.4(c 1.0, $CHCl_3$). FT-IR (ATR): ν 3295, 1753, 1634, 1542, 1491, 1260, 1196, 995, 918, 646. HPLC (Daicel AD-H, hexane/i-PrOH = 85/15, 0.8 mL min^{-1}, detection at 225 nm, 30 °C): t_R (minor) = 19.8 min, t_R (major) = 24.2 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.48 (m, 6H), 7.08 (d, J = 7.6 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 5.37 (d, J = 6.8 Hz, 1H), 5.16 (s, 2H), 4.64 (d, J = 3.2 Hz, 1H), 4.28 (s, 1H), 4.15–4.21 (q, 2H), 3.22 (s, 1H), 1.46 (s, 9H), 1.21 (t, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 156.3, 153.6, 136.2, 132.7, 128.4, 128.1, 127.8, 126.8, 125.1, 122.9, 113.4, 80.6, 74.1, 72.6, 64.1, 61.7, 59.6, 49.2, 28.0, 26.7, 25.1, 13.8. HRMS (ESI) calcd for $C_{23}H_{28}ClNNaO_6$ $[M + Na]^+$ 472.1503, found 472.1501.

(2*S*,3*S*)-Ethyl-2-amino-3-(4-(benzyloxy)-3-chlorophenyl)-3-hydroxypropanoate (3). To a solution of **9** (0.89 g, 2 mmol) in dichloromethane (10 mL) was added TFA (1 mL) at 0 °C under N_2. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with sat. $NaHCO_3$ (10 mL) and diluted with dichloromethane (20 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **3** (0.64 g, 91%) as a white solid with 92% ee, which was upgraded to 99% de and 99% ee after recrystallized from MTBE. Mp 99.5–100.8 °C. FT-IR (ATR): ν 3291, 2857, 1718, 1504, 1255, 1189, 1014, 940, 816, 728, 693. HPLC (Daicel AD-H, hexane/i-PrOH = 75/25, 0.8 mL min^{-1}, detection at 225 nm, 30 °C): t_R (minor) = 10.0 min, t_R (major) = 11.7 min. $[\alpha]_D^{25}$ = −6.6 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.48 (m, 6H), 7.11 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.16 (s, 2H), 4.89 (d, J = 5.2 Hz, 1H), 4.12–4.18 (q, 2H), 3.77 (d, J = 5.2 Hz, 1H), 2.37 (br, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 153.7, 136.2, 133.2, 128.2, 127.8, 126.9, 125.5, 123.0, 113.5, 73.0, 70.6, 61.1, 59.5, 13.9. HRMS (ESI) calcd for $C_{18}H_{20}ClNNaO_4$ $[M + Na]^\backslash$ 372.0979, found 372.0975.

Notes and references

1 (*a*) S. C. Bergmeier, *Tetrahedron*, 2000, **56**, 2561–2576; (*b*) G. O. K. Karjalainen and A. M. P. Koskinen, *Org. Biomol. Chem.*, 2012, **10**, 4311–4326.

2 (*a*) H. Pellissier, *Tetrahedron*, 2008, **64**, 1563–1601; (*b*) Y. Hamada, *Chem. Rec.*, 2014, **14**, 235–250; (*c*) C. G. Goodman, D. T. Do and J. S. Johnson, *Org. Lett.*, 2013, **15**, 2446–2449; (*d*) Y. J. Seo, J. A. Kim and H. K. Lee, *J. Org. Chem.*, 2015, **80**, 8887–8902; (*e*) Z. Q. Liu, C. S. Shultz, C. A. Sherwood, S. Krska, P. G. Dormer, R. Desmond, C. Lee, E. C. Sherer, J. Shpungin, J. Cuff and F. Xu, *Tetrahedron Lett.*, 2011, **52**, 1685–1688; (*f*) B. Mohar, A. Valleix, J. R. Desmurs, M. Felemez, A. Wagner and C. Mioskowski, *Chem. Commun.*, 2001, 2572–2573; (*g*) X. M. Tao, W. F. Li, X. M. Li, X. M. Xie and Z. G. Zhang, *Org. Lett.*, 2013, **15**, 72–75; (*h*) J. H. Xie, S. Liu, W. L. Kong, W. J. Bai, X. C. Wang, L. X. Wang and Q. L. Zhou, *J. Am.*

Chem. Soc., 2009, **131**, 4222–4223; (*i*) A. W. Lei, S. L. Wu, M. S. He and X. M. Zhang, *J. Am. Chem. Soc.*, 2004, **126**, 1626–1627.

3 R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Takatomi and H. Kumobayashi, *J. Am. Chem. Soc.*, 1989, **111**, 9134–9135.

4 (*a*) J. P. Genet, C. Pinel, S. Mallart, S. Juge, S. Thorimbert and J. A. Laffite, *Tetrahedron: Asymmetry*, 1991, **2**, 555–567; (*b*) V. Ratovelomanana-Vidal and J. P. Genet, *Can. J. Chem.*, 2000, **78**, 846–851; (*c*) C. Mordant, P. Dunkelmann, V. Ratovelomanana-Vidal and J. P. Genet, *Eur. J. Org. Chem.*, 2004, **14**, 3017–3026; (*d*) C. Mordant, P. Dunkelmann, V. Ratovelomanana-Vidal and J. P. Genet, *Chem. Commun.*, 2004, 1296–1297; (*e*) E. Coulon, M. Cristina, C. D. Andrade, V. Ratovelomanana-Vidal and J. P. Genet, *Tetrahedron Lett.*, 1998, **39**, 6467–6470; (*f*) M. Perez, P. G. Echeverria, E. M. Arripe, M. E. Zoubir, R. Touati, Z. G. Zhang, J. P. Genet, P. Phansavath, T. Ayad and V. Ratovelomanana-Vidal, *Eur. J. Org. Chem.*, 2015, 5949–5958; (*g*) P. G. Echeverria, J. Cornil, C. Ferard, A. Guerinot, J. Cossy, P. Phansavath and V. Ratovelomanana-Vidal, *RSC Adv.*, 2015, **5**, 56815–56819.

5 (*a*) K. Makino, T. Goto, Y. Hiroki and Y. Hamada, *Angew. Chem., Int. Ed.*, 2004, **43**, 882–884; (*b*) K. Makino, Y. Hiroki and Y. Hamada, *J. Am. Chem. Soc.*, 2005, **127**, 5784–5875; (*c*) K. Makino, T. Goto, Y. Hiroki and Y. Hamada, *Tetrahedron: Asymmetry*, 2008, **19**, 2816–2828; (*d*) Y. Hamada and K. Makino, *Yuki Gosei Kagaku Kyokaishi*, 2008, **66**, 1057–1065.

6 (*a*) B. Seashore-Ludlow, P. Villo, C. Hacker and P. Somfai, *Org. Lett.*, 2010, **12**, 5274–5277; (*b*) B. Seashore-Ludlow, F. Saint-Dizier and P. Somfai, *Org. Lett.*, 2012, **14**, 6334–6337; (*c*) B. Seashore-Ludlow, P. Villo and P. Somfai, *Chem.–Eur. J.*, 2012, **18**, 7219–7223.

7 (*a*) B. Jiang and Y. G. Si, *Angew. Chem., Int. Ed.*, 2004, **43**, 216–218; (*b*) K. H. Yang, H. Fang, J. Z. Gong, L. Su and W. F. Xu, *Mini-Rev. Med. Chem.*, 2009, **9**, 1329–1341; (*c*) M. R. Jia, K. H. Yang, Y. Q. Jiang, L. L. Sun and W. F. Xu, *Chin. J. Med. Chem.*, 2010, **20**, 543–549; (*d*) S. X. Wang and F. E. Chen, *Adv. Synth. Catal.*, 2009, **351**, 547–552.

8 X. L. Wang, L. J. Xu, L. J. Yan, H. F. Wang, S. Han, Y. Wu and F. E. Chen, *Tetrahedron*, 2016, **72**, 1787–1793.

9 (*a*) H. F. Zhou, Q. H. Fan, Y. Y. Huang, L. Wu, Y. M. He, W. J. Tang, L. Q. Gu and A. C. Chan, *J. Mol. Catal. A: Chem.*, 2007, **275**, 47–53; (*b*) J. S. Wu, F. Wang, Y. P. Ma, X. Cui, L. F. Cun, J. Zhu, J. G. Deng and B. L. Yu, *Chem. Commun.*, 2006, 1766–1768.

10 (*a*) X. F. Wu, X. G. Li, F. King and J. L. Xiao, *Angew. Chem., Int. Ed.*, 2005, **44**, 3407–3411; (*b*) X. F. Wu, X. H. Li, A. Z. Gerosa, A. Pettman, J. K. Liu, A. J. Mills and J. L. Xiao, *Chem.–Eur. J.*, 2008, **14**, 2209–2222; (*c*) X. F. Wu, J. K. Liu, D. D. Tommaso, J. A. Iggo, C. R. A. Catlow, J. Bacsa and J. L. Xiao, *Chem.–Eur. J.*, 2008, **14**, 7699–7715; (*d*) T. Abura, S. Ogo, Y. Watanabe and S. Fukuzumi, *J. Am. Chem. Soc.*, 2003, **125**, 4149–4154; (*e*) M. A. Ariger and E. M. Carreira, *Org. Lett.*, 2012, **14**, 4522–4524.

11 (*a*) S. D. Lee, T. H. Chan and K. S. Kwon, *Tetrahedron Lett.*, 1984, **25**, 3399–3402; (*b*) O. Hara, M. Ito and Y. Hamada, *Tetrahedron Lett.*, 1998, **39**, 5537–5540; (*c*) D. Farran, I. Parrot, L. Toupet, J. Martinez and G. Dewynter, *Org. Biomol. Chem.*, 2008, **6**, 3989–3996; (*d*) F. Xu, J. Y. L. Chung, J. C. Moore, Z. Q. Liu, N. Yoshikawa, R. S. Hoerrner, J. Lee, M. Royzen, E. Cleator, A. G. Gibson, R. Dunn, K. M. Maloney, M. Alam, A. Goodyear, J. Lynch, N. Yasuda and P. N. Devine, *Org. Lett.*, 2013, **15**, 1342–1345.

12 N. Trisovic, J. Antanasijevic, T. T. Katona, M. Kohout, M. Salamonczyk, S. Sprunt, A. Jakli and K. F. Csorba, *RSC Adv.*, 2015, **5**, 64886–64891.

13 (*a*) T. Isoda, R. Akiyama, H. Oyamada and S. Kobayashi, *Adv. Synth. Catal.*, 2006, **348**, 1813–1817; (*b*) K. C. Nicolaou, C. N. C. Boddy, S. Brase and N. Winssinger, *Angew. Chem., Int. Ed.*, 1999, **38**, 2096–2152.