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Dynamic kinetic resolution of β′-keto-β-amino esters using Ru–DTBM–Sunphos catalyzed asymmetric hydrogenation

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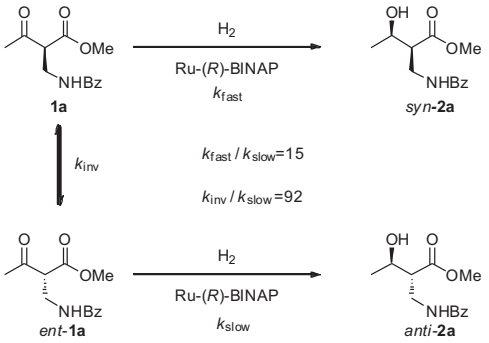
ABSTRACT

A convenient method for the enantioselective synthesis of β′-hydroxy-β-amino esters was developed through intensive investigations of the reaction conditions. Dichloromethane (DCM)/2,2,2-trifluoroethanol (TFE) and 1,2-dichloroethane (DCE)/TFE combinations were found to be the appropriate co-solvents for the reaction. In this mixed solvent system, $[Ru(cymene)Cl_2]_2$–Sunphos exhibited unusually higher activity and selectivity than the corresponding $[Ru(cymene)I_2]_2$–Sunphos. In situ generated catalyst could be used for this transformation. Asymmetric hydrogenation of a series of β′-keto-β-amino esters derivatives using Ru–Sunphos complexes via dynamic kinetic resolution led to the corresponding β′-hydroxy-β-amino esters with ee up to 99.6% and de up to 98.8% (*S*/*C*=1000).

1. Introduction

Enantiomerically pure β-amino acids are useful building blocks for the asymmetric synthesis of biologically active compounds.[1] More specifically, β′-hydroxy-β-amino acids play a crucial role in the syntheses of carbapenem derivatives and other types of β-lactams.[2] Chemical[1,3] and enzymatic approaches[1,4] have been developed to perform the enantio- and diastereo-selective preparation of β′-hydroxy-β-amino acids from the corresponding β′-keto-β-amino acids. Among them, the Takasago's industrial production of 4-acetoxyazetidin-2-one has been successfully achieved through the asymmetric hydrogenation of racemic 2-substituted β-ketoesters using dynamic kinetic resolution (DKR, Scheme 1),[5] which was first reported by Noyori et al.[6]

Takaya and co-workers[7] further investigated the factors controlling the activity and stereoselectivity by using a variety of dihalo–Ru(arene)–Binap complexes as catalysts. They found that the stereochemical outcome of the reaction strongly depended on both the nature of halide counter anions of the catalyst ($I^->Br^->Cl^-$), and the nature of the aryl substituents at the phosphorus atom. Particularly, the nature of the substituents on the phenyl rings of the phosphorus of the Binap-type ligands plays a crucial role in the reaction. A combination of $[Ru(cymene)I_2]_2$ and (*R*)-3,5-*t*-Bu_2-Binap gives *syn*-**2a** in 99% ee and 98% de. These



Scheme 1. Asymmetric hydrogenation of **1** in DCM via DKR process.

results inspired other groups to improve the efficiency and selectivity of new catalytic systems. The catalytic properties of several ligands, such as Segphos,[8] Bitiop,[9] and Diophep[10] and the use of different counter anions[11] have been evaluated for this transformation. However, most of the reported catalytic methods used the expensive $[Ru(cymene)I_2]_2$ and required careful manipulations. Our group has focused on the studies of asymmetric hydrogenation and developed a series of effective methods for the enantioselective reduction of α- and β-ketoesters, β-ketosulfones, and polyfunctionalized ketones.[12] We report herein the application of DTBM–Sunphos for the enantioselective synthesis of β′-hydroxy-β-amino acids via DKR process.

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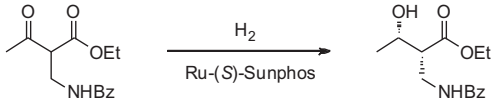
2. Results and discussion

Ethyl 2-(benzamidomethyl)-3-oxobutanoate **1b** was chosen as the model substrate and [Ru(cymene)Cl_2]$_2$–(*S*)-Sunphos was set as the catalyst to investigate the dynamic kinetic resolution reaction. Given that large k_{fast}/k_{slow} and k_{inv}/k_{slow} are crucial parameters for the success of this reaction, solvent, temperature, catalyst and the factors affecting the reaction rate must be carefully considered. Because significant solvent effects have been observed in Noyori's protocol,[6] preliminary studies using the Ru–Sunphos catalytic system began with a solvent screen (Table 1). When using single solvents, no desirable ee and de could be obtained. Although alcohols exhibited high enantioselectivities, none of them led to good diastereoselectivities (Table 1, entries 1–4). 2,2,2-Trifluoroethanol (TFE),[13] which is more acidic than methanol and ethanol gave better de up to 83.2% but lower ee up to 92.9% compare to MeOH or EtOH (entries 1, 2 vs 5). As for aprotic solvents, DCM and 1,2-DCE afforded good ee and much better *syn*/*anti* diastereoselectivity than the corresponding alcohols (entries 9–10). Noyori et al. reported that the reaction could be carried out in a mixed solvent of DCM/MeOH.[6] Consequently, several experiments using either DCM or DCE and alcohols as co-solvents were conducted (entries 12–23). No remarkable enhancement was made using DCM/MeOH, DCM/EtOH or DCE/EtOH although a significant improvement was obtained using DCM/TFE with 98.9% ee and 95/5 *syn*/*anti* diastereoselectivity using a volumetric ratio of DCM/TFE=3/1 (entry 18). A co-solvent of DCE/TFE=3/1 showed comparable result (entry 23). Moreover, the enantioselectivity decreased when the ratio of DCM/TFE changed from 3/1 to 1/7 (entries 18–22). Therefore, the co-solvent of DCM/TFE=3/1 was selected to perform the hydrogenation.

Table 1
Solvent screen[a]



1b **2b**

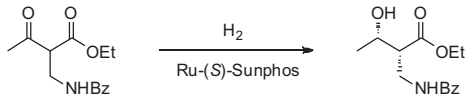
Entry	Solvent	Conversion (%)	ee (2*R*,3*S*, %)	de (%)
1	MeOH	100	98.3	23.2
2	EtOH	100	98.7	19.8
3	*n*-PrOH	100	95.1	28.2
4	*i*-PrOH	100	61.9	33.6
5	TFE	100	92.9	83.2
6[b]	Toluene	27.7	76.3	−74.8
7[b]	EtOAc	60.8	44.5	−8.2
8[b]	THF	51.2	72.8	−80.4
9	DCM	100	98.7	73.8
10	1,2-DCE	100	97.9	73.2
11	1,4-Dioxane	89.6	66.0	37.8
12	DCM/MeOH=7/1	100	99.4	61.6
13	DCM/EtOH=7/1	100	98.0	62.2
14	1,2-DCE/EtOH=7/1	100	99.4	60.0
15	DCM/TFE=9/1	100	94.5	82.4
16	DCM/TFE=7/1	100	98.8	84.6
17	DCM/TFE=5/1	100	97.9	86.0
18	DCM/TFE=3/1	100	98.9	90.0
19	DCM/TFE=1/1	100	96.9	83.6
20	DCM/TFE=1/3	100	95.2	84.8
21	DCM/TFE=1/5	100	95.5	84.6
22	DCM/TFE=1/7	100	93.3	82.6
23	1,2-DCE/TFE=3/1	100	99.2	88.6

[a] Catalyst=[Ru(cymene)Cl_2]$_2$–(*S*)-Sunphos (preformed), *S*/*C*=100, *c*=0.25 M, *P*=50 bar, *T*=70 °C, *t*=20 h, ee and de were determined by HPLC, the absolute configuration was determined by comparison with Ref. [9]. de=[(*syn*-**2b**)–(*anti*-**2b**)]/[(*syn*-**2b**)+(*anti*-**2b**)].

[b] *(2R,3S)*-**2b** was not the major product.

Taking into account that the temperature plays a crucial role in the stereochemical outcome of the hydrogenation (Table 2), compound **2** was prepared with a slightly better ee and de by lowering the reaction temperature to 60 °C, albeit with a lower conversion (entry 1) although higher temperature up to 110 °C (Table 2, entries 3–4) led to a roughly 10% decreased diastereoselectivity down to 80.3%, thus 70 °C was chosen as the preferred temperature.

Table 2
Optimization of reaction temperature[a]



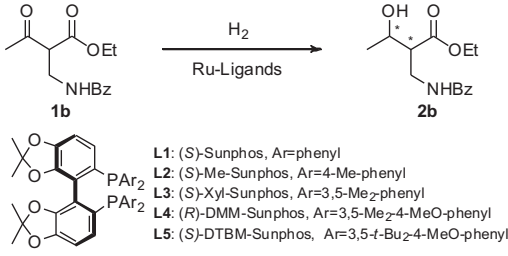
1b **2b**

Entry	Temperature (°C)	Conversion (%)	ee (2*R*,3*S*, %)	de (%)
1	60	79.7	99.3	91.5
2	70	100	98.9	90.0
3	90	100	98.6	81.5
4	110	100	98.7	80.3

[a] Catalyst=[Ru(cymene)Cl_2]$_2$–(*S*)-Sunphos (preformed), *S*/*C*=100, *c*=0.25 M, solvent: DCM/TFE=3/1, *P*=50 bar, *t*=20 h, ee and de were determined by HPLC.

The reaction was not influenced by the hydrogen pressure, and similar ee and de of the products were obtained when the hydrogen pressure varied from 10 to 70 bar. Therefore, the optimized condition of hydrogenation using [Ru(cymene)Cl_2]$_2$–(*S*)-Sunphos as catalyst was set as: 70 °C, 50 bar of H_2, in a 0.25 M solution of a mixed solvent of DCM/TFE=3/1 (v/v). Under these conditions, an extensive number of Ru-complexes bearing diphosphine ligands were tested (Table 3). In all cases, the reaction proceeded smoothly to give the desired product **2b** with good to excellent enantio- and diastereo-selectivity. Atropisomeric diphosphine ligands, such as Binap,[14] Segphos,[8] Synphos,[15] MeO-Biphep,[16] and C_3-Tunephos[17] led to high enantioselectivities up to 98.7% and diastereoselectivities up to 90.2% (Table 3, entries 1–5, preformed

Table 3
Asymmetric hydrogenation of **1b** with Ru(II) complexes



1b **2b**

L1: (*S*)-Sunphos, Ar=phenyl
L2: (*S*)-Me-Sunphos, Ar=4-Me-phenyl
L3: (*S*)-Xyl-Sunphos, Ar=3,5-Me_2-phenyl
L4: (*R*)-DMM-Sunphos, Ar=3,5-Me_2-4-MeO-phenyl
L5: (*S*)-DTBM-Sunphos, Ar=3,5-*t*-Bu_2-4-MeO-phenyl

Entry	Ligand	Conversion (%)	ee (%)	de (%)
1	(*R*)-Binap	100	98.1 (2*S*,3*R*)	87.2
2	(*S*)-Segphos	100	98.2 (2*R*,3*S*)	84.2
3	(*R*)-Synphos	100	92.4 (2*S*,3*R*)	87.4
4	(*S*)-MeO-Biphep	100	98.7 (2*R*,3*S*)	87.8
5	(*S*)-C_3-Tunephos	100	98.7 (2*R*,3*S*)	90.2
6	**L1**	100	98.9 (2*R*,3*S*)	90.0
7	**L2**	100	96.7 (2*R*,3*S*)	89.7
8	**L3**	100	97.3 (2*R*,3*S*)	89.5
9	**L4**	100	98.1 (2*S*,3*R*)	92.3
10	**L5**	100	99.3 (2*R*,3*S*)	99.4
11[a]	**L1**	100	99.0 (2*R*,3*S*)	90.5
12[a]	**L5**	100	98.7 (2*R*,3*S*)	97.5
13[b]	**L1**	100	99.2 (2*R*,3*S*)	90.7
14[c]	**L1**	90.5	95.9 (2*R*,3*S*)	88.0

[a] Catalysts were in situ formed. [Ru(cymene)Cl_2]$_2$ and ligands were added together with substrates and used directly for hydrogenation.

[b] [Ru(benzene)Cl_2]$_2$.

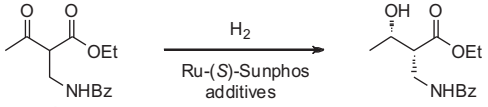
[c] [Ru(cymene)I_2]$_2$.

catalysts). Better results were obtained in term of enantioselectivities with the Sunphos family of ligands **L4** and **L5** demonstrating that the in situ generated chiral ruthenium catalysts could be efficiently used for such hydrogenation reaction. Substituent effects were investigated by changing the nature of the substituents on the phenyl rings of the phosphorus of the Sunphos ligands. (*S*)-Me-Sunphos **L2** (entry 7) (*S*)-xyl-Sunphos **L3** (entry 8) and (*S*)-DMM-Sunphos **L4** (entry 9) led to similar results both in enantio- and diastereo-selectivities. Pleasingly, better results were obtained with bulkier DTBM–Sunphos **L5** leading to **2b** with an excellent enantio- and diastereo-facial discrimination up to 99.3% ee and 99.4% de (entry 10). To the best of our knowledge, such level of enantio- and diastereo-selectivity has never been attained for such process using in situ generated Ru–Cl complexes. Comparable results were obtained when performing the hydrogenation reaction of **1b** by mixing $[Ru(cymene)Cl_2]_2$, Ligands **L1** or **L5**, substrate **1b** and DCM/TFE=3/1 (entries 6, 10 vs entries 11, 12). $[Ru(cymene)Cl_2]_2$ and $[Ru(benzene)Cl_2]_2$ gave similar results regarding the stereochemical outcome of the reaction (entry 6 vs entry 13). Surprisingly, $[Ru(cymene)I_2]_2$ was not efficient compare to $[Ru(cymene)Cl_2]_2$ (entry 6 vs entries 14) resulting in a lower selectivity and slower reaction rate, the conversion being not complete under 50 bar of hydrogen pressure after 20 h (entry 14).

Acids have been reported to promote the hydrogenation of functionalized ketones.[7b,12d,18] Particularly, Lewis acids could improve the diastereoselectivity in similar reactions.[19] Recently, Ackermann[20] disclosed the positive effect of carboxylic acids or carboxylates as additives in ruthenium-catalyzed reactions. Thus, a series of additives were tested and the results are illustrated in Table 4. None of these acids was effective in the reaction (Table 4, entries 1–8). On the contrary, the presence of Lewis acids (entries 4–6) enhanced the transesterification between substrates and TFE.[21] Carboxylic acids and phenols did not improve the selectivity (entries 7–10) either. As for counter anions, AcOK and ^{t}BuONa led to a dramatic decrease in the enantio- and diastereo-selectivity (entries 11, 12). No conversion was observed using $AgBF_4$ (entry 13), which is in agreement with Maheswaran and co-worker's report.[11b] They found that hydrogenation of **1a** with Ru(H)(*p*-cymene)((*R*)-DTBM–Segphos)(SbF_6) as catalyst afforded **2a** in 94% ee and 90% de in EtOH while no product could be obtained in a co-solvent of DCM/MeOH. Therefore, halogen ions remain to be the appropriate counter anions in such mixed solvent systems. Bases have been widely used to accelerate the racemization between enantiomers.[5], which may led in this case to a higher k_{inv}/k_{slow}. However, the use of K_2CO_3, NEt_3 or DBU gave complete conversions albeit with low selectivities (entries 14–16). We had previously demonstrated that $CaCO_3$ was advantageous to neutralize HCl generated during hydrogenation.[12g] However, no significant effect of $CaCO_3$ was found in the hydrogenation reaction (entry 17). Addition of 0.5% (v/v) of water led to an excellent ee up to 99% with a decreased de of 86.2% (entry 18).

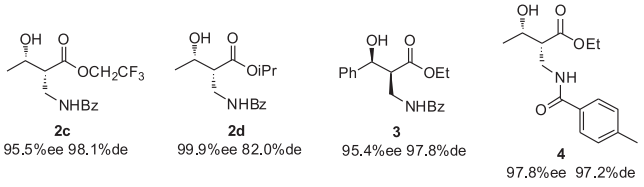
Following these careful investigations, the *S*/*C* ratio was changed from 100 to 1000 and the hydrogenation reaction was carried out with preformed Ru-(*S*)-DTBM–Sunphos in DCE/TFE (3/1) under 70 bar of H_2. Pleasingly, Reactions of **1a** and **1b** could be accomplished with a complete conversion within 72 h, giving, respectively, **2a** in 96.6% ee, 98.4% de and **2b** in 99.6% ee, 98.8% de. However, hydrogenation of **1b** under the same reaction conditions with the in situ prepared catalyst at *S*/*C*=1000 gave **2b** in 87.5% conversion, 98.3% ee and 96.3% de, suggesting higher substrate/diphosphine loading might inhibit the formation of active catalytic species. Finally, we evaluated the scope of this hydrogenation reaction and demonstrated that this dynamic kinetic resolution using the Ru–DTBM–Sunphos catalytic system could be successfully extended to other β′-keto-β-amino esters leading to the corresponding β′-hydroxy-β-amino esters **2c**, **2d**, **3** and **4** with excellent enantioselectivities up to 99.9% and diastereoselectivities up to 98.1% using our experimental conditions (Scheme 2).

Table 4
Additives screen[a]



Entry	Additives	Conversion (%)	ee (2*R*,3*S*, %)	de (%)
1[b]	HCl	100	99.8	84.3
2	I_2	99.3	100	66.1
3	HBF_4	94.8	96.6	57.4
4	LiCl	100	98.0	84.5
5	$ZnCl_2$	100	89.8	76.9
6	$CeCl_3 \cdot 7H_2O$	100	95.6	70.0
7	PhCOOH	100	97.3	86.2
8	^{t}BuCOOH	100	96.8	87.2
9	Phenol	100	98.3	87.4
10	2,6-*t*-Bu_2-Phenol	100	98.9	87.5
11	AcOK	92.5	−1.8	−2.6
12	^{t}BuONa	32.7	73.1	−88.2
13	$AgBF_4$	ND	—	—
14	K_2CO_3	100	−11.0	39.9
15	NEt_3	100	66.2	52.8
16	DBU	100	11.2	0.2
17	$CaCO_3$	100	98.1	88.5
18[c]	H_2O	100	99.0	86.2

[a] Catalyst=$[Ru(cymene)Cl_2]_2$–(*S*)-Sunphos (preformed), *S*/*C*=100, *c*=0.25 M, solvent: DCM/TFE=3/1, *T*=70 °C, *P*=50 bar, *t*=20 h, additives/catalyst=10/1 (exception: $AgBF_4$/catalyst=1/1), all additives were added together with substrates, ee and de were determined by HPLC.
[b] 1 M in DCM.
[c] 0.5% v/v.



Catalyst: $[Ru(cymene)Cl_2]_2$-(*S*)-DTBM-Sunphos for **2c**, **3d** and **4**, $[Ru(cymene)Cl_2]_2$-(*S*)-Sunphos for **3**. Catalysts were preformed. S/C=200, DCM/TFE = 3/1, 70 °C, 50 bar of H_2, 0.25 mol/L, 20h.

Scheme 2. Substrate scope of the Ru–DTBM–Sunphos catalytic system.

3. Conclusion

In conclusion, a convenient and practical method for the enantio- and diastereo-selective synthesis of β′-hydroxy-β-amino acids has been developed using the in situ generated $[Ru(cymene)Cl_2]_2$–Sunphos as catalyst. We demonstrated that $[Ru(cymene)Cl_2]_2$ associated to atropisomeric diphosphines in DCM/TFE and DCE/TFE combinations of solvent was more efficient than the corresponding $[Ru(cymene)I_2]_2$ in DCM/MeOH and DCM/EtOH for common diphosphine ligands. These unusual experimental conditions have been applied to the synthesis of a series of enantioenriched β′-hydroxy-β-amino acids with high level of enantio- and diastereoselectivites.

4. Experimental section

4.1. General

All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques or in a nitrogen-filled glovebox, unless otherwise noted. ^{1}H NMR spectra were recorded at 400 MHz,

with TMS as internal standard. ^{13}C NMR spectra were obtained at 100 MHz and referenced to the central peak of 77.0 ppm for $CDCl_3$. Coupling constants (J) are reported in Hertz and refer to apparent peak multiplications. Flash column chromatography was performed on silica gel (300–400 mesh). Commercially available reagents were used throughout without further purification other than those detailed below. The solvents used in catalyst preparation and hydrogenation reactions were pretreated and degassed by literature methods.[22] Compound **1a** and **1b** were synthesized according to the literature.[23]

4.2. Typical procedure for the asymmetric hydrogenation

To a 25 mL Schlenk tube were added $[Ru(cymene)Cl_2]_2$ (12 mg, 0.02 mmol) and (*S*)-SunPhos (30 mg, 0.045 mmol). The tube was vacuumed and purged with nitrogen three times before addition of freshly distilled and degassed $EtOH/CH_2Cl_2$ (2 mL/2 mL). The resulting mixture was heated at 50 °C for 1.5 h and then cooled to room temperature. The solvent was removed under vacuum to give the catalyst. The catalyst was dissolved in a mixture of degassed DCM and TFE (12 mL/4 mL) and then the solution was equally put into eight vials, in which compound **1b** (132 mg, 0.5 mmol) was pre-introduced, and then the vials were taken into an autoclave. The autoclave was purged three times with H_2 and stirred under specified reaction conditions. After being cooled to ambient temperature and release of the hydrogen, the autoclave was opened and the solvent was evaporated. The ee was determined by HPLC after passing the samples through a short pad of silica gel with pure ethyl acetate.

4.3. The hydrogenation with in situ prepared catalyst

To a 50 mL Schlenk tube were added $[Ru(cymene)Cl_2]_2$ (6 mg, 0.01 mmol), (*S*)-SunPhos (15 mg, 0.022 mmol), and compound **1b** (526 mg, 2 mmol). The tube was vacuumed and purged with nitrogen three times before addition of freshly distilled and degassed DCM and TFE (6 mL/2 mL). The resulting solution was taken into an autoclave. The autoclave was purged three times with H_2 and stirred under specified reaction conditions.

*4.3.1. Methyl 2-(benzamidomethyl)-3-oxobutanoate (**1a**).*[23] ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.69 (m, 2H), 7.53–7.46 (m, 1H), 7.45–7.38 (m, 2H), 6.79 (s, 1H), 4.00–3.82 (m, 3H), 3.77 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 169.2, 167.7, 134.0, 131.8, 128.7, 127.1, 58.3, 52.9, 37.8, 30.1.

*4.3.2. (2R,3S)-Methyl 2-(benzamidomethyl)-3-hydroxybutanoate (**1b**).*[6a,7b] ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.75 (m, 2H), 7.54–7.49 (m, 1H), 7.46–7.44 (m, 2H), 6.96 (s, 1H), 4.18–4.11 (m, 2H), 4.01–3.98 (m, 1H), 3.73 (s, 3H), 3.60–3.55 (m, 1H), 2.64–2.60 (m, 1H), 1.26 (d, J=6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 132.0, 128.8, 127.2, 65.6, 52.7, 52.1, 38.0, 20.9. $[\alpha]_D^{20}$ −45.3 (*c* 1.0, $CHCl_3$, 96.6% ee, 98.4% de). HPLC: (Chiralcel AD-H column, hexane/*i*-PrOH: 85/15, 0.5 mL/min, 230 nm, 30 °C) t_1=15.1 min, t_2=16.1 min (major), t_3=17.4 min, t_4=18.8 min.

*4.3.3. Ethyl 2-(benzamidomethyl)-3-oxobutanoate (**2a**).*[9] ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.68 (m, 2H), 7.52–7.45 (m, 1H), 7.45–7.37 (m, 2H), 6.84 (s, 1H), 4.27–4.13 (m, 2H), 4.01–3.81 (m, 3H), 2.32 (s, 3H), 1.27 (t, J=7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.8, 168.7, 167.7, 134.0, 131.8, 128.7, 127.0, 62.0, 58.5, 37.8, 30.1, 14.2.

*4.3.4. (2R,3S)-Ethyl 2-(benzamidomethyl)-3-hydroxybutanoate (**2b**).*[9] ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.66 (m, 2H), 7.57–7.30 (m, 3H), 7.10 (s, 1H), 4.42–3.88 (m, 5H), 3.61–3.56 (m, 1H), 2.60–2.56 (m, 1H), 1.36–1.14 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 168.8, 133.8, 131.9, 128.7, 127.1, 65.8, 61.1, 52.7, 38.0, 20.9, 14.3. $[\alpha]_D^{20}$ −46.7 (*c* 1.0, $CHCl_3$, 99.3% ee, 99.4% de). HPLC: (Chiralcel AD-H column, hexane/*i*-PrOH: 85/15, 0.5 mL/min, 230 nm, 30 °C) t_1=14.1 min, t_2=15.4 min (major), t_3=17.6 min, t_4=18.4 min.

*4.3.5. (2R,3S)-2,2,2-Trifluoroethyl 2-(benzamidomethyl)-3-hydroxybutanoate (**2c**).*[6a,6c] ^1H NMR (400 MHz, $CDCl_3$) δ 7.79–7.74 (m, 2H), 7.56–7.50 (m, 1H), 7.48–7.41 (m, 2H), 6.81 (s, 1H), 4.64–4.43 (m, 2H), 4.31–4.14 (m, 2H), 4.08–3.93 (m, 1H), 3.65–3.53 (m, 1H), 2.76–2.64 (m, 1H), 1.30–1.28 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 169.1, 133.6, 132.1, 128.8, 127.1, 122.9 (q, J_{FC}=277.7 Hz), 65.6, 60.4 (q, J_{FC}=36.6 Hz), 52.8, 38.0, 21.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.1 (t, J=8.4 Hz). HRMS (QTOF-ESI) calcd for $C_{14}H_{17}NO_4F_3$, (M+H): 320.1110, found: 320.1108. $[\alpha]_D^{20}$ −40.1 (*c* 1.0, $CHCl_3$, 95.5% ee, 98.1% de). HPLC: (Chiralcel AD-H column, hexane/*i*-PrOH: 92/08, 0.6 mL/min, 230 nm, 30 °C) t_1=19.9 min, t_2=21.3 min, t_3=25.1 min, t_4=28.5 min.

*4.3.6. (2R,3S)-Isopropyl 2-(benzamidomethyl)-3-hydroxybutanoate (**2d**).*[6a,6c] ^1H NMR (400 MHz, $CDCl_3$) δ 7.82–7.74 (m, 2H), 7.55–7.38 (m, 3H), 7.04 (s, 1H), 5.07–5.01 (m, 1H), 4.20–3.88 (m, 3H), 3.65–3.51 (m, 1H), 2.62–2.48 (m, 1H), 1.30–1.21 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 168.8, 133.8, 131.9, 128.8, 127.1, 68.7, 65.7, 52.8, 38.0, 21.9, 20.8. HRMS (QTOF-ESI) calcd for $C_{15}H_{21}NO_4$ (M+H): 280.1549, found: 280.1571. $[\alpha]_D^{20}$ +27.4 (*c* 1.0, MeOH, 99.9% ee, 82.0% de). HPLC: (Chiralcel OD-H column, hexane/*i*-PrOH: 90/10, 0.5 mL/min, 230 nm, 30 °C) t_1=14.3 min, t_2=15.3 min (major), t_3=16.3 min, t_4=17.0 min.

*4.3.7. (2S,3S)-Ethyl 2-(benzamidomethyl)-3-hydroxy-3-phenylpropanoate (**3**).*[4c] ^1H NMR (400 MHz, $CDCl_3$) δ 7.78–7.70 (m, 2H), 7.53–7.46 (m, 1H), 7.42–7.40 (m, 2H), 7.36–7.21 (m, 5H), 7.09 (s, 1H), 4.96–4.94 (m, 1H), 4.50–4.49 (m, 1H), 4.15–3.88 (m, 3H), 3.65–3.61 (m, 1H), 2.99–2.95 (m, 1H), 0.99 (t, J=7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 168.5, 141.1, 133.9, 131.8, 128.7, 128.5, 127.9, 127.1, 126.3, 60.9, 52.9, 38.1, 13.9. $[\alpha]_D^{20}$ −12.6 (*c* 1.0, $CHCl_3$, 95.4% ee, 97.8% de). HPLC: (Chiralcel IA-3 column, hexane/*i*-PrOH: 85/15, 0.5 mL/min, 230 nm, 25 °C) t_1=20.9 min, t_2=22.2 min, t_3=27.5 min, t_4=33.5 min.

*4.3.8. (2R,3S)-Ethyl 3-hydroxy-2-((4-methylbenzamido)methyl)butanoate (**4**).*[6a,6c] ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.63 (m, 2H), 7.24–7.17 (m, 2H), 7.01 (s, 1H), 4.24–4.04 (m, 3H), 3.97–3.95 (m, 1H), 3.56–3.54 (m, 1H), 2.58–2.56 (m, 1H), 2.37 (s, 3H), 1.30–1.21 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 168.8, 142.4, 130.9, 129.4, 127.1, 65.6, 61.0, 52.8, 37.9, 21.6, 20.9, 14.3. HRMS (QTOF-ESI) calcd for $C_{15}H_{21}NO_4$ (M+H): 280.1549, found: 280.1576. $[\alpha]_D^{20}$ +23.6 (*c* 1.0, MeOH, 97.8% ee, 97.2% de). HPLC: (Chiralcel AD-H column, hexane/*i*-PrOH: 85/15, 0.5 mL/min, 230 nm, 30 °C) t_1=20.0 min, t_2=21.5 min (major), t_3=25.2 min, t_4=28.8 min.

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Supplementary data

Copies of ^1H NMR and ^{13}C NMR spectra of compounds **1**–**4** are available in Supplementary data. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.136.

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