Synthesis Q. Llopis et al. Paper

Rhodium-Catalyzed *anti* and *syn* Enantio- and Diastereoselective Transfer Hydrogenation of α-Amino β-Keto Ester Hydrochlorides through Dynamic Kinetic Resolution

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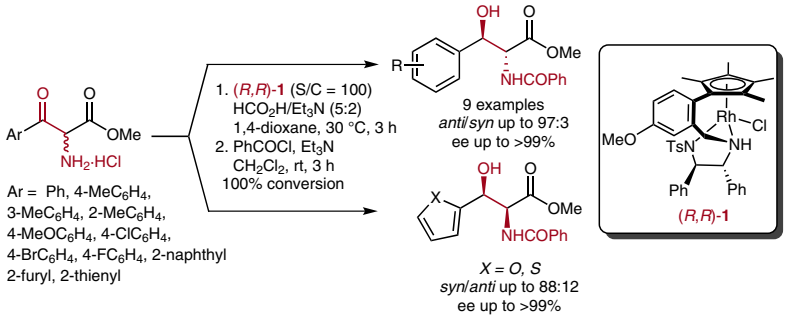
In memory of Professor Jean Normant with profound respect



Received: 13.05.2016
Accepted after revision: 06.06.2016
Published online: 21.07.2016
DOI: 10.1055/s-0035-1562444; Art ID: ss-2016-c0351-op

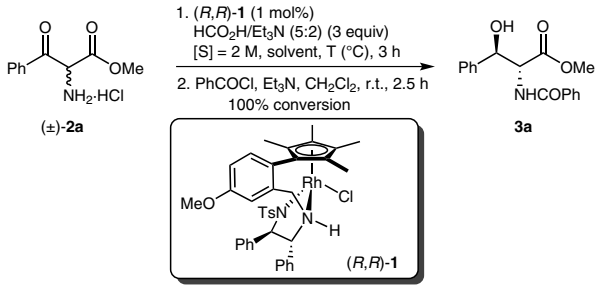
Abstract A mild catalytic asymmetric transfer hydrogenation of a series of α-amino β-keto ester hydrochlorides catalyzed by a rhodium(III) complex is reported. The use of the formic acid/triethylamine system as the hydrogen donor source provided the corresponding *anti* and *syn* amino alcohols with complete conversions, fair diastereoselectivities (up to 97:3 dr), and high enantioselectivities (ee up to >99%).

Key words rhodium, asymmetric catalysis, transfer hydrogenation, amino alcohols, diastereoselectivity, enantioselectivity

Transition-metal-catalyzed asymmetric transfer hydrogenation (ATH) is among the most atom-efficient and powerful methods for the synthesis of chiral compounds in enantiomerically enriched form.[1] In conjunction with a dynamic kinetic resolution (DKR) process and by starting from racemic substrates bearing a labile stereocenter, the reaction permits the installation of two contiguous stereogenic centers in a single operation.[2] In particular, an elegant path to β-hydroxy α-amino acids, important as building blocks in natural products and pharmaceuticals,[3] relies on the transition-metal-catalyzed ATH of α-amino β-keto ester derivatives. In this field, only few groups have described the reduction of these compounds in their N-protected forms through Ru-catalyzed ATH.[4] In this context, we have previously reported the first example of a Ru-catalyzed ATH of α-amino β-keto ester hydrochlorides[5] by using a tethered ruthenium complex developed by Wills and co-workers.[6] As part of our long-standing program directed toward the development of efficient catalytic systems for the reduction/DKR process[7] and their applications in total syntheses,[8] we now describe the asymmetric transfer hydrogenation of α-amino β-keto ester hydrochlorides with the Rh(III) complex (*R*,*R*)-**1**, which contains a TsDPEN ligand and an η^5-cyclopentadiene moiety connected through a carbon tether, recently developed in our group[9] (Table 1). We have previously shown that (*R*,*R*)-**1** exhibits an excellent catalytic performance in terms of reactivity and stereoselectivity for the ATH of ketones, and we were keen to investigate its behavior in the ATH of functionalized ketones, particularly in the reduction of α-amino β-keto ester hydrochlorides through DKR.

Our exploration commenced with the examination of the reaction parameters by using compound **2a**, bearing a phenyl substituent on the ketone function, as the standard substrate (Table 1). The reaction, which proceeded readily in a wide variety of solvents, was initially conducted in acetonitrile at room temperature in the presence of 1 mol% of the complex (*R*,*R*)-**1** and a HCO_2H/Et_3N (5:2) azeotropic mixture as the hydrogen source. Under these conditions, the ATH proceeded with full conversion, delivering, after N-benzoylation, the corresponding *anti* β-hydroxy α-amido ester **3a** in 65% yield, a 81:19 diastereomeric ratio, and an 80% enantiomeric excess (Table 1, entry 1). Interestingly, upon increasing the reaction temperature to 30 °C, a higher yield was obtained (79%) without affecting the stereochemical outcome of the reaction (entry 2). Using these reaction conditions, we next examined the effect of the solvent on the DKR (entries 3–15). Of all the solvents explored, methanol and 1,4-dioxane gave the highest yields of 81% and 82%, respectively (entries 4 and 15).

Table 1 Optimization of the Reaction Conditions for the ATH of **2a** with (*R*,*R*)-**1**[a]



Entry	Solvent	Temp (°C)	Yield (%)	dr[b]	ee[c] (%)
1	MeCN	r.t.	65	81:19	80
2	MeCN	30	79	79:21	82
3	*i*-PrOH	30	57	80:20	91
4	MeOH	30	81	82:18	90
5	CH_2Cl_2	30	43	88:12	75
6	DMC[d]	30	71	75:25	91
7	DEC[e]	30	55[f]	76:24	85
8	EtOAc	30	80[f]	74:26	92
9	DMF	30	78	66:34	98
10	–[g]	30	62[f]	85:15	70
11	THF	30	61	68:32	97
12	2-MeTHF[h]	30	67	68:32	98
13	MTBE	30	67[f]	79:21	82
14	Et_2O	30	76	80:20	77
15	1,4-dioxane	30	82	74:26	99
16	1,4-dioxane	r.t.	77	75:25	99
17	1,4-dioxane	10	75	81:19	88
18	1,4-dioxane	50	80	68:32	99
19	1,4-dioxane	80	74	57:43	98
20[i]	1,4-dioxane	30	80	71:29	97
21[j]	1,4-dioxane	30	89	46:54	98
22[k]	1,4-dioxane	30	0	—	—
23[l]	1,4-dioxane	30	72	71:29	98

[a] Reaction conditions: (1) **2a** (0.44 mmol), (*R*,*R*)-**1** (1 mol%), HCO_2H/Et_3N (5:2) (3 equiv), 3 h. (2) Crude ATH product (0.44 mmol), BzCl (0.48 mmol), Et_3N (1.32 mmol), CH_2Cl_2 (2 mL), r.t., 2.5 h.(N-benzoylation was required for analytical purpose).
[b] Determined by ^1H NMR of the crude ATH product.
[c] Determined by supercritical fluid chromatography (SFC).
[d] Dimethyl carbonate.
[e] Diethyl carbonate.
[f] Compound **3a** was contaminated with byproducts.
[g] HCO_2H/Et_3N (5:2) azeotropic mixture (10 equiv) was used as the solvent.
[h] 2-Methyltetrahydrofuran.
[i] Five equivalents of the HCO_2H/Et_3N (5:2) azeotropic mixture were used.
[j] HCO_2Na was used as the hydrogen source.
[k] HCO_2NH_4 was used as the hydrogen source.
[l] The reaction was performed with 0.5 mol% of (*R*,*R*)-**1**.

Whereas the reaction afforded a better diastereomeric ratio in methanol (82:18 dr versus 74:26 dr for 1,4-dioxane), excellent enantioselectivity of 99% ee (versus 90% ee for methanol) was achieved in 1,4-dioxane. DMF and 2-methyltetrahydrofuran both gave high enantioselectivities (98% ee; Table 1, entries 9 and 12), but lower yields and lower diastereoselectivities (66:34 and 68:32 dr, respectively; entries 9 and 12) were observed in these solvents. The other solvents investigated (isopropanol, dichloromethane, dimethyl carbonate, diethyl carbonate, ethyl acetate, tetrahydrofuran, methyl *tert*-butyl ether, and diethyl ether) all gave less satisfactory results than 1,4-dioxane in terms of yields and asymmetric inductions (entries 3, 5–8, 11, 13 and 14). When the reaction was performed in the absence of a solvent (in this case, 10 equivalents of the formic acid/triethylamine (5:2) azeotropic mixture were used), an enantiomeric excess of only 70% was observed (entry 10) and the reduced compound was formed in 62% yield alongside uncharacterized byproducts.

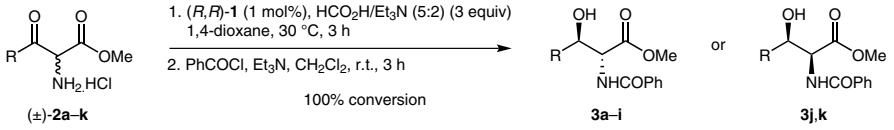
Having established that 1,4-dioxane is the most appropriate solvent for the ATH of α-amino β-keto ester hydrochloride **2a** with catalyst (*R*,*R*)-**1**, we next sought the optimal reaction parameters. The influence of the reaction temperature was first examined. Running the reduction at room temperature led to a slightly lower yield with no change in stereoselectivity (Table 1, entry 16). Higher temperatures provided markedly lower diastereoselectivities (50 and 80 °C; entries 18 and 19), whereas decreasing the temperature to 10 °C resulted in a better dr of 81:19, albeit with a significant drop in enantioselectivity (entry 17). The use of five equivalents instead of three equivalents of the HCO_2H/Et_3N (5:2) azeotropic mixture did not notably affect the outcome of reaction (entry 20). Other hydrogen sources were then investigated. Sodium formate gave a higher yield, but at the expense of the diastereoselectivity (entry 21), whereas ammonium formate produced no conversion (entry 22). Changing the catalyst loading to 0.5 mol% of (*R*,*R*)-**1** did not improve the diastereoselectivity, but the β-hydroxy ester **3a** was obtained in lower yield (entry 23). In light of these results, having defined conditions to control the stereoselectivity and product distribution, the optimized reaction conditions for the ATH of α-amino β-keto ester hydrochloride **2a** were set as follows: 1 mol% of the tethered Rh complex (*R*,*R*)-**1**, 3 equiv of the HCO_2H/Et_3N (5:2) azeotropic mixture as the hydrogen source, 1,4-dioxane as the solvent, a reaction temperature of 30 °C, and a reaction time of three hours.

With these optimized reaction conditions in hand, we further explored the substrate scope and limitations of the reaction. A variety of aromatic substrates[10] were surveyed (Table 2). The results from these studies indicated that the current reaction conditions were generally tolerant of substrates containing either electron-donating (Table 2, entries 2, 3, 5, and 9) or electron-withdrawing groups (entries 6–8). Diastereomeric ratios in these instances varied from

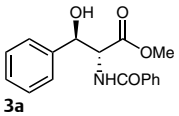
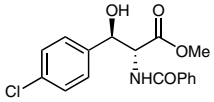
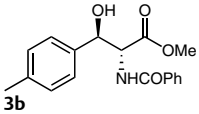
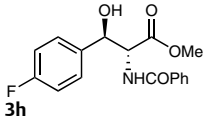
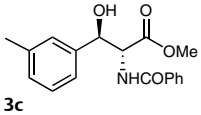
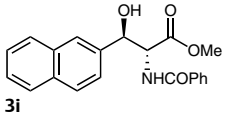
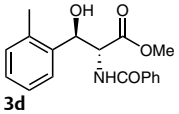
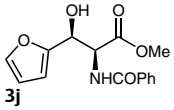
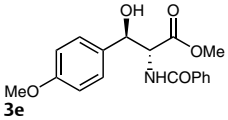
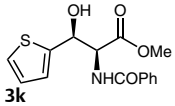
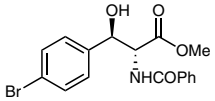
63:37 to 74:26 in favor of the *anti* compound, whereas excellent enantioinductions were generally achieved (96% to >99% ee). In the case of an *ortho*-substituted benzene ring, a high level of diastereoselection was attained (97:3 dr; entry 4) with no significant erosion in the enantioselectivity (94% ee; entry 4), although the more sterically hindered position induced a lower yield of **3d**. This result stands in sharp contrast with the related Ru-catalyzed asymmetric transfer hydrogenation of compound **2d**, because we previously reported that the reaction was inefficient in this instance. Furthermore, ATH of the heteroaromatic substrates **2j** and **2k** led to a reversal of the diastereoselection. The corresponding reduced furan and thiophene derivatives **3j** and **3k** were produced in 55% yields with 14:86 dr and 12:88 dr, respectively, in favor of the *syn* products, and with excellent enantioselectivities toward the major isomer in both cases (99% ee; entries 10 and 11).[11,12]

Interestingly, higher diastereoselectivities were observed than for the previously reported Ru-promoted ATH, which gave diastereomeric ratios of 41:59 and 32:68 for compounds **3j** and **3k**, respectively. In addition, upon scale-up (gram scale), a slight improvement in both enantioselectivity and yield (99% ee and 74% yield versus 96% ee and 70% yield; Table 2, entry 3) was observed for α-amino β-hydroxy ester **3c**, whereas the diastereoselectivity of the reaction remained unchanged.

Table 2 ATH of α-Amino β-Keto Ester Hydrochlorides **2a–k** Catalyzed by the Rh Catalyst (*R*,*R*)-**1**[a]



(±)-**2a–k** **3a–i** **3j,k**

Entry	ATH product[b]	Yield[c] (%)	dr[d]	ee[e] (%)	Entry	ATH product[b]	Yield[c] (%)	dr[d]	ee[e] (%)
1	 **3a**	82	74:26	99	7	 **3g**	75	70:30	>99
2	 **3b**	75	63:37	>99	8	 **3h**	84	75:25	>99
3	 **3c**	70	70:30	96	9	 **3i**	72	74:26	98
4	 **3d**	41	97:3	94	10	 **3j**	55	14:86	>99[f]
5	 **3e**	60	64:36	>99	11	 **3k**	55	12:88	99[f]
6	 **3f**	68	72:28	>99					

[a] Reaction conditions: (1) **2a** (0.44 mmol), (*R*,*R*)-**1** (1 mol%), HCO_2H/Et_3N (5:2) (3 equiv), 3 h. (2) crude ATH product (0.44 mmol), BzCl (0.48 mmol), Et_3N (1.32 mmol), CH_2Cl_2 (2 mL), r.t., 2.5 h. The conversion was determined by ^1H NMR of the crude ATH product.
[b] The relative and absolute configurations of compounds **3a–k** were assigned by comparison with reported analytical data or on the basis of the general observed trends in enantio- and diastereoselectivities.
[c] Isolated yield.
[d] The *anti*/*syn* ratio was determined by ^1H NMR of the crude product after the ATH reaction.
[e] Determined by HPLC or SFC analysis.
[f] ee of the *syn* isomer.

In summary, we have shown that aromatic α-amino β-keto ester hydrochlorides undergo ATH induced by the Rh complex (*R*,*R*)-**1** with good yields, fair diastereoselection, and excellent enantioselectivities through a DKR process. The Rh(III) complex (*R*,*R*)-**1** containing the TsDPEN ligand and an η^5-arene connected through a carbon tether was efficiently used in combination with the formic acid/triethylamine (5:2) system as the hydrogen donor source. The reaction generally afforded good yields of the corresponding *anti* α-amino β-hydroxy ester derivatives with fair diastereoselectivities and a high level of enantioselectivity (ee up to >99%). Moreover, we observed an interesting reversal of diastereoselection for heteroaromatic compounds under the standard reaction conditions. In these instances, the *syn* products were formed with good diastereoselectivities and excellent enantioselectivities. This transformation serves as an atom-economical and stereoselective method to prepare *anti* and *syn* α-amino β-hydroxy ester derivatives found in natural products and bioactive molecules with a high level of enantioinduction (ee up to >99%).

All reactions were performed under argon. Reaction vessels were oven dried, cooled under vacuum, and flushed with argon before use. 1,4-Dioxane was distilled over calcium hydride. CH_2Cl_2 was dried over alumina columns in an Innovative Technologies apparatus. Reagent-grade hexane and methanol were purchased and used without further purification. Reagents were purified according to the methods described in the literature. Acros Silica Gel 60 (0.0040–0.0063 mm) was used for flash column chromatography. Analytical TLC was carried out on commercial silica-gel plates (Merck 60 F_{254}), which were viewed by using UV light (λ = 254 nm) and $KMnO_4$ or *p*-anisaldehyde staining solutions. NMR spectra were recorded on a Bruker AVANCE 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) instrument. Chemical shifts are expressed in ppm referenced to residual chloroform (7.26 ppm for ^{1}H and 77.16 for ^{13}C). Supercritical fluid chromatography (SFC) analyses were performed on a Berger apparatus equipped with Daicel CHIRALCEL or CHIRALPAK columns coupled with a dual-wavelength (215/254 nm) Waters 2489 UV detector. HPLC analyses were performed on a Waters Alliance e2695 system equipped with Daicel CHIRALPAK columns and a UV detector operating at 215 nm. Mass spectra (EI, Na) were recorded at ENSCP Chimie ParisTech.

α-Amino β-Hydroxy Ester Hydrochlorides 3a–k: General Procedure

A round-bottomed tube fitted with a rubber septum equipped with a balloon of argon was charged with the appropriate α-amino β-keto ester hydrochloride **2** (0.44 mmol) and the rhodium complex (*R*,*R*)-**1** (0.0044 mmol, 1 mol%). The solids were subjected to three vacuum/argon cycles before distilled 1,4-dioxane (2 mL) was added, and another three vacuum/argon cycles were then performed. HCO_2H/Et_3N (5:2) azeotropic mixture (110 µL, 1.32 mmol, 3 equiv) was added, the mixture was stirred at 30 °C for 3 h, and the solvent was removed under reduced pressure. The conversion and diastereomeric excess were determined by ^{1}H NMR analysis of the crude product.

A solution of the crude α-amino β-hydroxy ester hydrochloride (0.44 mmol) in anhyd CH_2Cl_2 (2 mL) was treated with BzCl (0.48 mmol, 1.1 equiv) and Et_3N (1.32 mmol, 3 equiv) at 0 °C. The mixture was stirred at 0 °C for 1.5 h and at r.t. for 1 h, then diluted with CH_2Cl_2. The reaction was quenched with sat. aq NH_4Cl, the mixture was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$). The crude protected product was purified by flash chromatography. The enantiomeric excess was determined by SFC or HPLC analysis of the purified product (on a CHIRALCEL OD-H or CHIRALPAK IA, IC or AD-H column).

Methyl (2*R*,3*R*)-2-(Benzoylamino)-3-hydroxy-3-phenylpropanoate (3a)[13]

White solid; yield: 116 mg (82%); R_f = 0.31 (pentane–EtOAc, 6:4); *anti*/*syn* = 74:26; ee_{anti} = 99%.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti*) = 7.76–7.69 (m, 2 H), 7.56–7.50 (m, 1 H), 7.47–7.36 (m, 2 H), 7.29–7.18 (m, 5 H), 6.88 (d, *J* = 7.0 Hz, 1 H), 5.40 (dd, *J* = 5.9, 3.4 Hz, 1 H), 5.23 (dd, *J* = 7.0, 3.4 Hz, 1 H), 4.59 (d, *J* = 5.9 Hz, 1 H), 3.79 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 169.9, 168.4, 139.0, 133.0, 132.0, 128.6, 128.2, 128.0, 127.1, 125.8, 75.0, 59.3, 52.5.

MS (ESI): *m*/*z* = 312 $[M + Na]^+$.

SFC: CHIRALPAK AD-H, $scCO_2$/MeOH (85:15), 3 mL/min, P = 150 bar, λ = 215 nm; t_R [*syn*] = 7.47 min, t_R [*syn*] = 8.32 min, t_R [*anti*-(*R*,*R*)] = 9.72 min (major), t_R [*anti*-(*S*,*S*)] = 10.73 min.

Methyl (2*R*,3*R*)-2-(Benzoylamino)-3-hydroxy-3-(4-methylphenyl)propanoate (3b)[13]

White solid; yield: 103 mg (75%); R_f = 0.58 (pentane–EtOAc, 1:1); *anti*/*syn* = 63:37, ee_{anti} > 99%.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti*) = 7.74 (d, *J* = 7.0 Hz, 2 H), 7.55–7.26 (m, 4 H), 7.17–7.10 (m, 3 H), 6.91 (d, *J* = 7.2 Hz, 1 H), 5.32 (br s, 1 H), 5.20 (dd, *J* = 7.2, 3.6 Hz, 1 H), 4.52 (br s, 1 H), 3.75 (s, 3 H), 2.32 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 170.0, 168.5, 137.8, 136.0, 133.1, 132.1, 129.0, 128.6, 127.2, 125.8, 75.1, 59.4, 52.6, 21.1.

MS (ESI): *m*/*z* = 336 $[M + Na]^+$.

SFC: CHIRALPAK AD-H, $scCO_2$/MeOH (89:11), 3 mL/min, P = 150 bar, λ = 215 nm; t_R [*syn*] = 9.07 min, t_R [*syn*] = 20.56 min, t_R [*anti*-(*S*,*S*)] = 21.76 min, t_R [*anti*-(*R*,*R*)] = 24.06 min (major).

Methyl (2*R*,3*R*)-2-(Benzoylamino)-3-hydroxy-3-(3-tolyl)propanoate (3c)[13]

Pale-yellow solid; yield: 102 mg (70%); R_f = 0.44 (pentane–EtOAc, 6:4); *anti*/*syn* = 70:30, ee_{anti} = 96%.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti*) = 7.74 (d, *J* = 6.9 Hz, 2 H), 7.53–7.35 (m, 3 H), 7.26–7.18 (m, 2 H), 7.10–7.03 (m, 2 H), 6.90 (d, *J* = 7.5 Hz, 1 H), 5.33 (br s, 1 H), 5.17 (dd, *J* = 7.5, 3.7 Hz, 1 H), 4.47 (br s, 1 H,), 3.75 (s, 3 H), 2.31 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 170.0, 168.3, 139.0, 137.8, 133.1, 132.0, 128.8, 128.5, 128.1, 127.1, 126.5, 122.9, 74.9, 59.3, 52.4, 21.3.

MS (ESI): *m*/*z* = 336 $[M + Na]^+$.

SFC: CHIRALPAK AD-H, $scCO_2$/MeOH (80:20), 4 mL/min, P = 150 bar, λ = 215 nm; t_R [*syn*] = 2.37 min, t_R [*anti*-(*S*,*S*)] = 4.06 min, t_R [*syn*] = 4.51 min, t_R [*anti*-(*R*,*R*)] = 5.63 min (major).

Methyl (2*R*,3*R*)-2-(Benzoylamino)-3-hydroxy-3-(2-methylphenyl)propanoate (3d)[13]

Pale-yellow solid; yield: 54 mg (41%); R_f = 0.63 (pentane–EtOAc, 1:1); *anti*/*syn* = 97:3, ee_{anti} = 94%.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti*) = 7.88–7.76 (m, 2 H), 7.57–7.36 (m, 4 H), 7.23–7.14 (m, 3 H), 7.08 (d, *J* = 7.5 Hz, 1 H), 5.47 (br s, 1 H), 5.11 (dd, *J* = 7.5, 3.5 Hz, 1 H), 3.62 (s, 3 H), 3.54 (br s, 1 H), 2.40 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 170.6, 167.8, 137.4, 134.9, 133.5, 132.2, 130.8, 128.8, 128.1, 127.3, 125.9, 125.9, 71.8, 57.6, 52.4, 19.1.

MS (ESI): *m*/*z* = 336 [M + Na]$^+$.

HPLC: CHIRALPAK IA, hexane–*i*-PrOH (90:10), 1 mL/min, λ = 215 nm; t_R [*syn*] = 11.83 min, t_R [*syn*] = 12.73 min, t_R [*anti*-(*R*,*R*)] = 18.82 min (major), t_R [*anti*-(*S*,*S*)] = 20.90 min.

Methyl (2*R*,3*R*)-2-(Benzoylamino)-3-hydroxy-3-(4-methoxyphenyl)propanoate (3e)[9]

White solid; yield: 83 mg (60%); R_f = 0.35 (pentane–EtOAc, 6:4); *anti*/*syn* = 64:36, ee_{anti} > 99%.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti*) = 7.73 (d, *J* = 7.3 Hz, 2 H), 7.56–7.38 (m, 3 H), 7.19 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 7.3 Hz, 1 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 5.30 (s, 1 H), 5.19 (dd, *J* = 7.3, 3.7 Hz, 1 H), 4.48 (br s, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H),

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 169.9, 168.7, 136.6, 133.6, 133.13, 133.1, 133.06, 132.2, 128.7, 128.1, 128.0, 127.7, 127.2, 126.2, 126.1, 125.0, 123.7, 75.4, 59.5, 52.7.

MS (ESI): *m*/*z* = 352 [M + Na]$^+$.

SFC: CHIRALPAK IA, $scCO_2$/MeOH (85:15), 4 mL/min, P = 150 bar, λ = 215 nm; t_R [*syn*] = 7.01 min, t_R [*syn*] = 8.83 min, t_R [*anti*-(*S*,*S*)] = 9.66 min, t_R [*anti*-(*R*,*R*)] = 13.03 min (major).

Methyl (2*R*,3*R*)-2-(Benzoylamino)-3-(4-bromophenyl)-3-hydroxypropanoate (3f)[9]

White solid; yield: 114 mg (68%); R_f = 0.44 (pentane–EtOAc, 6:4); *anti*/*syn* = 74:26, ee_{anti} > 99%.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti*) = 7.74 (d, *J* = 7.7 Hz, 2 H), 7.54–7.24 (m, 5 H), 7.13 (d, *J* = 7.7 Hz, 2 H), 6.93 (d, *J* = 7.2 Hz, 1 H), 5.33 (br s, 1 H), 5.17 (dd, *J* = 7.0, 3.4 Hz, 1 H), 4.86 (s, 1 H), 3.78 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 169.6, 168.5, 138.3, 132.7, 132.2, 131.3, 128.6, 127.6, 127.1, 121.9, 74.5, 59.3, 52.7.

MS (ESI): *m*/*z* = 402 [M + Na]$^+$.

SFC: CHIRALPAK AD-H, $scCO_2$/MeOH (80:20), 4 mL/min, P = 150 bar, λ = 215 nm; t_R [*syn*] = 3.56 min, t_R [*syn*] = 5.93 min, t_R [*anti*-(*S*,*S*)] = 9.56 min, t_R [*anti*-(*R*,*R*)] = 12.38 min (major).

Methyl (2*R*,3*R*)-2-(Benzoylamino)-3-(4-chlorophenyl)-3-hydroxypropanoate (3g)[9]

White solid; yield: 109 mg (75%); R_f = 0.36 (pentane–EtOAc, 6:4); *anti*/*syn* = 70:30, ee_{anti} > 99%.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti*) = 7.75–7.66 (m, 2 H), 7.46–7.16 (m, 7 H), 6.89 (d, *J* = 7.2 Hz, 1 H), 5.35 (br s, 1 H), 5.18 (dd, *J* = 7.2, 3.4 Hz, 1 H), 4.81 (br s, 1 H), 3.78 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 169.7, 168.6, 137.7, 133.7, 132.8, 132.4, 128.7, 128.4, 127.3, 127.1, 74.5, 59.4, 52.7.

MS (ESI): *m*/*z* = 356 [M + Na]$^+$.

SFC: CHIRALPAK AD-H, $scCO_2$/MeOH (85:15), 4 mL/min, P = 150 bar, λ = 215 nm; t_R [*syn*] = 4.60 min, t_R [*syn*] = 7.71 min, t_R [*anti*-(*S*,*S*)] = 11.82 min, t_R [*anti*-(*R*,*R*)] = 14.97 min (major).

Methyl (2*R*,3*R*)-2-(Benzoylamino)-3-(4-fluorophenyl)-3-hydroxypropanoate (3h)[9]

White solid; yield: 117 mg (84%); R_f = 0.44 (pentane–EtOAc, 6:4); *anti*/*syn* = 75:25, ee_{anti} > 99%.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti*) = 7.64 (d, *J* = 7.0 Hz, 2 H), 7.45–7.11 (m, 5 H), 6.94–6.85 (m, 3 H), 5.24 (d, *J* = 3.5 Hz, 1 H), 5.07 (dd, *J* = 7.1, 3.5 Hz, 1 H), 4.71 (br s, 1 H), 3.65 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 169.8, 168.6, 162.4 (d, $^1J_{CF}$ = 246.2 Hz), 134.9 (d, $^4J_{CF}$ = 3.0 Hz), 132.8, 132.2, 128.7, 127.5, 127.1 (d, $^3J_{CF}$ = 8.1 Hz), 115.2 (d, $^2J_{CF}$ = 21.6 Hz), 74.5, 59.4, 52.7.

MS (ESI): *m*/*z* = 340 [M + Na]$^+$.

SFC: CHIRALPAK AD-H, $scCO_2$/MeOH (85:15), 4 mL/min, P = 150 bar, λ = 215 nm; t_R [*syn*] = 3.14 min, t_R [*syn*] = 4.53 min, t_R [*anti*-(*S*,*S*)] = 5.93 min, t_R [*anti*-(*R*,*R*)] = 8.23 min (major).

Methyl (2*R*,3*R*)-2-(Benzoylamino)-3-hydroxy-3-(2-naphthyl)propanoate (3i)[13]

White solid; yield: 107 mg (72%); R_f = 0.35 (pentane–EtOAc, 6:4); *anti*/*syn* = 74:26, ee_{anti} = 98%.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*anti*) = 7.87–7.66 (m, 6 H), 7.55–7.34 (m, 6 H), 6.93 (d, *J* = 7.1 Hz, 1 H), 5.56 (br s, 1 H), 5.33 (dd, *J* = 7.1, 3.4 Hz, 1 H), 4.69 (d, *J* = 5.3 Hz, 1 H), 3.78 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 169.9, 168.7, 136.6, 133.6, 133.13, 133.1, 133.06, 132.2, 128.7, 128.1, 128.0, 127.7, 127.2, 126.2, 126.1, 125.0, 123.7, 75.4, 59.5, 52.7.

MS (ESI): *m*/*z* = 372 [M + Na]$^+$.

SFC: CHIRALPAK IA, $scCO_2$/MeOH (80:20), 4 mL/min, P = 150 bar, λ = 215 nm; t_R [*syn*] = 3.49 min, t_R [*syn*] = 4.95 min, t_R [*anti*-(*S*,*S*)] = 5.41 min, t_R [*anti*-(*R*,*R*)] = 6.15 min (major).

Methyl (2*S*,3*S*)-2-(Benzoylamino)-3-(2-furyl)-3-hydroxypropanoate (3j)[9]

Orange solid; yield: 71 mg (55%); R_f = 0.23 (pentane–EtOAc, 6:4); *anti*/*syn* = 14:86, ee_{syn} > 99%, ee_{anti} = 96%.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*syn*) = 7.76–7.72 (m, 2 H), 7.51–7.31 (m, 4 H), 7.15 (d, *J* = 8.8 Hz, 1 H), 6.32–6.27 (m, 1 H), 6.25 (dd, *J* = 3.3, 1.8 Hz, 1 H), 5.35–5.33 (m, 1 H), 5.17 (dd, *J* = 8.8, 3.2 Hz, 1 H), 4.07 (br s, 1 H), 3.74 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*syn*) = 170.5, 167.8, 152.6, 142.4, 133.6, 131.7, 128.4, 127.1, 110.2, 107.2, 68.2, 56.4, 52.7.

MS (ESI): *m*/*z* = 312 [M + Na]$^+$.

SFC (er measurement for the *anti* compound): CHIRALPAK IC, $scCO_2$/MeOH (90:10), 4 mL/min, P = 150 bar, λ = 215 nm; t_R [*syn* × 2] = 4.28 min, t_R [*anti*] = 6.39 min, t_R [*anti*] = 7.46 min.

SFC (er measurement for the *syn* compound): CHIRALCEL OD-H, $scCO_2$/MeOH (95:5), 2 mL/min, P = 150 bar, λ = 215 nm; t_R [*syn*-(*S*,*S*)] = 11.30 min (major), t_R [*anti* × 2] = 12.25 min, t_R [*syn*-(*R*,*R*)] = 15.04 min.

Methyl (2*S*,3*S*)-2-(Benzoylamino)-3-hydroxy-3-(2-thienyl)propanoate (3k)[9]

Orange solid; yield: 73 mg (55%); R_f = 0.23 (pentane–EtOAc, 6:4); *anti*/*syn* = 12:88, ee_{syn} = 99%, ee_{anti} = 96%.

^{1}H NMR (300 MHz, $CDCl_3$): δ (*syn*) = 7.78–7.74 (m, 2 H,), 7.48–7.34 (m, 4 H), 7.24 (d, *J* = 8.8 Hz, 1 H), 7.18 (d, *J* = 8.9 Hz, 1 H), 6.99–6.88 (m, 1 H), 5.63 (br s, 1 H), 5.28–5.25 (m, 1 H), 5.13 (dd, *J* = 8.8, 3.2 Hz, 1 H), 3.74 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*syn*) = 170.5, 167.8, 152.6, 142.4, 133.6, 131.7, 128.4, 127.1, 110.2, 107.2, 68.2, 56.4, 52.7.

MS (ESI): *m/z* = 312 $[M + Na]^+$.

SFC: CHIRALPAK AD-H, $scCO_2$/MeOH (80:20), 4 mL/min, P = 150 bar, λ = 215 nm; t_R [*syn*-(*S*,*S*)] = 2.98 min (major), t_R [*syn*-(*R*,*R*)] = 3.83 min, t_R [*anti*] = 5.26 min, t_R [*anti*] = 5.85 min.

Acknowledgment

Q.L. is grateful to PCAS for a grant (2014-2017). We are grateful to Dr. M.-N. Rager for carrying additional NMR experiments.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562444.

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