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Stereoselective synthesis of *syn* β-hydroxy cycloalkane carboxylates: transfer hydrogenation of cyclic β-keto esters via dynamic kinetic resolution

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Abstract—The transfer hydrogenation of bicyclic and monocyclic β-keto esters using HCO_2H/Et_3N as the hydrogen source and TsDPEN-based Ru(II) catalysts proceeds with dynamic kinetic resolution to afford the corresponding cyclic β-hydroxy esters with moderate to excellent levels of diastereo- and enantioselectivities. The mild reaction conditions used make possible to preserve in most cases the *syn* relative configuration of the products, providing a complementary tool to known approaches to the synthesis of *anti* isomers.

1. Introduction

Enantiomerically pure or enriched β-hydroxy esters are of very high importance as intermediates for the synthesis of a wide variety of targets such as pharmaceuticals, pesticides, flavours, etc.[1] and, therefore, a number of highly selective methods for their synthesis have been developed. Biocatalytic approaches to these compounds are based on the reduction of β-keto esters by enzymes[2] or microorganisms,[3] or on the lipase-catalysed resolution of racemic mixtures.[4] Although high enantioselectivities may be achieved in particular applications, there are also limitations for these biocatalytic methods, mainly related with limited substrate spectrum and selectivity, the availability of only one enantiomer in most cases, and moderate yields (maximum 50%) of the required enantiomer in kinetic resolutions.

On the other hand, a variety of chemical methods have also been used. Thus, diastereoselective procedures include asymmetric aldol reactions,[5] carbomethoxylation of chiral epoxides[6] and cycloaddition of enantiopure α-oxy-*ortho*-quinodimethane-tricarbonylchromium complex intermediates with acrylates,[7] among others. The need of chiral auxiliaries or enantiopure starting materials makes these procedures unattractive for industrial applications. However, the asymmetric hydrogenation of β-keto esters by chiral ruthenium catalysts, established after the seminal work by Noyori et al.,[8] has emerged as a powerful alternative[9] that can be often combined with dynamic kinetic resolution (DKR)[10] techniques for the synthesis of α-substituted β-hydroxy esters or related compounds.

As a case of particular importance, the synthesis of *cyclic* β-hydroxy esters has been accomplished using several of these methods. The use of microorganisms for the reduction of cyclic β-keto esters or for the lipase resolution of cyclic β-hydroxy esters provided satisfactory solutions for the synthesis of *syn* or *anti* products in several cases.[11] On the other hand, ruthenium-based hydrogenation catalysts have also been used to reduce cyclic β-keto esters, but only *anti* cyclic β-hydroxy esters are available using this method,[12,9c] and, therefore, there is still interest in the development of complementary metal-catalysed hydrogenations of cyclic β-keto esters leading to *syn* products.

Asymmetric transfer hydrogenation, recently emerged as a powerful alternative for the reduction of polar C=O and C=N bonds,[13] has also been applied to the synthesis of β-hydroxy esters in a limited number of cases.[14] However, the results are in general not competitive with classical hydrogenation catalysts, most probably due to deactivation of the catalysts by the products and/or the substrate.[15] Nevertheless, our recent results on the transfer hydrogenation of β-alkyl(aryl) cyclic ketimines[16] and cyclic α-halo ketones via DKR[17] encouraged us to explore the possibility of

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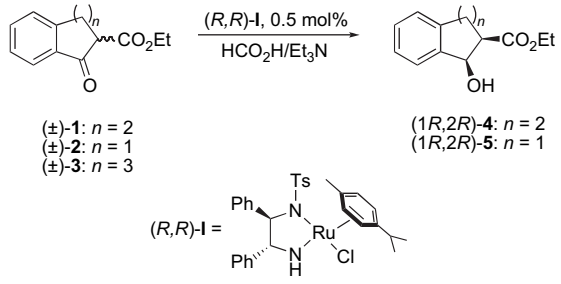
applying this method to the transfer hydrogenation of cyclic β-keto esters, as the conditions used should produce a fast racemisation of the acidic 1,3-dicarbonyl substrate, as required for the DKR process, but could eventually be mild enough as to prevent racemisation of the less acidic alcohol product. A uniform stereochemical pathway with related systems[16,17] should in this case provide products with the desired *syn* relative configuration. In this paper, we report the results collected on the basis of this hypothesis.

2. Results and discussion

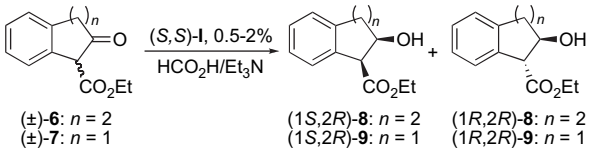
Experiments were first conducted using the 5:2 HCO_2H/Et_3N azeotropic mixture (condition A) as the solvent and the hydrogen source and Noyori/Ikariya's [(*R*,*R*)- or (*S*,*S*)-RuCl(TsDPEN)(*p*-cymene)] **I** as the catalyst.[18] Initially, β-ethoxycarbonyl-α-tetralone (±)-**1** and -α-indanone (±)-**2** were chosen as the racemic substrates taking into account the importance of the expected *syn* β-hydroxy esters as precursors of enantiopure vicinal cyclic amino alcohols of industrial interest[19] (Scheme 1). These five- and six-membered substrates reacted smoothly under these conditions using 0.5 mol % of (*R*,*R*)-**I** as the catalyst to selectively afford the corresponding *syn* β-hydroxy esters (1*R*,2*R*)-**4** and (1*R*,2*R*)-**5** in good yields (81–90%) and excellent diastereo- and enantioselectivities (Table 1, entries 1 and 2).



Scheme 1. Asymmetric transfer hydrogenation of bicyclic β-keto esters (±)-**1**–**3**.

On the other hand, attempts to accelerate the reactions by using a less acidic 1.2:1 HCO_2H/Et_3N mixture (condition B) also afforded the products **4** and **5**, but yields dropped dramatically (≈10%) under these conditions. The lower reactivity observed suggests that the higher basicity of the reaction medium results in a large proportion of unreactive enolic forms of the substrates that could also participate in deactivation pathways of the catalyst.[15] Unfortunately, no reaction was observed with seven-membered benzosuberone derivative (±)-**3** under conditions A and B, even using higher catalyst loadings (substrate/catalyst=50) and/or higher reaction temperatures.

We next turned our attention to racemic α-ethoxycarbonyl-β-tetralone and -β-indanone derivatives (±)-**6** and (±)-**7** (Scheme 2). The aliphatic nature of the carbonyl group and the higher acidity with respect to β-keto esters (±)-**1**,**2** make these compounds to appear as a more challenging type of substrates. For instance, their ^1H NMR spectra recorded in $CDCl_3$ reveal a unique set of signals corresponding to the enolic form. Consequently, the lack of reactivity found by using the standard condition A described above was not a surprise. Fortunately, it was found out that the transfer hydrogenation of these substrates takes place under condition B in reasonable rates.[20]

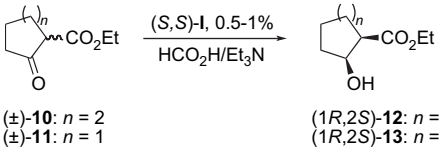


Scheme 2. Asymmetric transfer hydrogenation of bicyclic β-keto esters (±)-**6** and (±)-**7**.

Using 0.5 mol % of (*S*,*S*)-**I** as the catalyst, the β-tetralone derivative (±)-**6** afforded the corresponding β-tetralol **8** as a 1:2 mixture of *syn*-(1*R*,2*R*)-**8** and *anti*-(1*S*,2*R*)-**8**, both in ee 94% (Scheme 2, entry 3). The *anti* major isomer is supposed to proceed from the epimerization at C(1) of the *syn* product initially formed. This hypothesis is based on the relatively high acidity of the product, and is also supported by the identical enantioselectivities determined for both diastereoisomers. It was, therefore, reasoned that a higher catalyst loading, making the reaction to complete in a shorter reaction time, would leave less time for the racemisation of the product and, consequently, would increase the amount of the desired *syn* product. As expected, reaction performed with 2 mol % of catalyst afforded the product **8** in 91% yield as a 2:1 *syn*/*anti* mixture of isomers without affecting the enantioselectivity (entry 4). Interestingly, the diastereomeric mixture of **8** could be easily separated by flash chromatography to obtain the major *anti*-**8** and *syn*-**8** as single diastereomer with 94–95% ee.

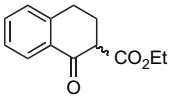
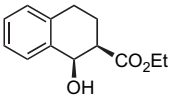
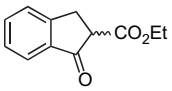
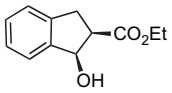
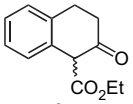
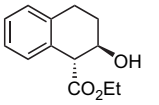
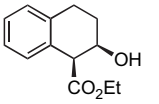
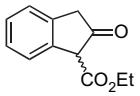
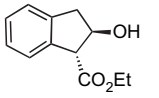
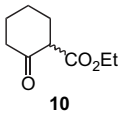
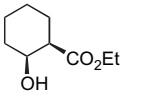
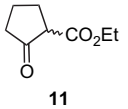
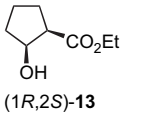
Under the same conditions, however, β-indanone (±)-**7** afforded a 15:85 mixture of *syn*-(1*R*,2*R*)-**9** and *anti*-(1*S*,2*R*)-**9** indanols with poor enantioselectivity (entry 5). In this case, the *syn* product appears to be configurationally labile and the epimerization to the *anti* isomer could not be avoided. Also in this case the diastereomeric mixture of **9** could be easily separated by flash chromatography to obtain the major *anti*-**9** in diastereomerically pure form.

Finally, the catalytic transfer hydrogenation of monocyclic substrates such as cyclohexanone and cyclopentanone derivatives (±)-**10** and (±)-**11** was investigated (Scheme 3). Noteworthy, these substrates were not either reduced under standard condition A. As in the precedent case, however, condition B was successfully applied to cyclohexanone-2-carboxylate (±)-**10** for the preparation of the corresponding cyclohexanol (1*R*,2*S*)-**12** in 80% yield with excellent *syn* selectivity (*syn*/*anti* >99:1) and moderate enantioselectivity (ee 50%) (entry 6). The enantioselectivity could be further improved to ee 70% by performing the reaction at higher concentration of substrate (*c*=8 mmol/mL, entry 7). In the same



Scheme 3. Asymmetric transfer hydrogenation of monocyclic β-keto esters (±)-**10** and (±)-**11**.

Table 1. Transfer hydrogenation of cyclic β-keto esters. Enantioselective synthesis of cyclic β-hydroxy esters via DKR

	Substrate	Method[a]/catalyst	S/C	*t* (days)	Major product	*syn*/*anti*[b]	Yield (*syn*) (%)[c]	ee_{syn} (%)[d]	Yield (*anti*) (%)[c]	ee_{anti} (%)[d]
1	 **1**	A/(*R*,*R*)-**I**	200	6	 (1*R*,2*R*)-**4**	>99:1	90	99	—	—
2	 **2**	A/(*R*,*R*)-**I**	200	6	 (1*R*,2*R*)-**5**	>99:1	81	99	—	—
3	 **6**	B/(*S*,*S*)-**I**	200	9	 (1*R*,2*R*)-**8**	1:2 (<1:99)	19[e]	94	38[e]	94
4		B/(*S*,*S*)-**I**	50	5	 (1*S*,2*R*)-**8**	2:1 (>99:1)	59	95	32	94
5	 **7**	B/(*S*,*S*)-**I**	50	6	 (1*R*,2*R*)-**9**	15:85 (<1:99)	9[f]	33	60[f]	24
6	 **10**	B/(*S*,*S*)-**I**	200	1	 (1*R*,2*S*)-**12**	>99:1	80	50	—	—
7		A[g]/(*S*,*S*)-**I**	200	6		>99:1	77	70	—	—
8	 **11**	B/(*S*,*S*)-**I**	100	0.5	 (1*R*,2*S*)-**13**	>99:1	55	20	—	—
9		B[g]/(*S*,*S*)-**I**	100	6		>99:1	95	5	—	—

[a] Method A uses 5:2 HCO_2H/Et_3N mixture; method B uses 1.2:1 HCO_2H/Et_3N mixture.
[b] Determined by ^1H NMR of the crude reaction mixtures. In parenthesis: diastereomeric ratios after column chromatography.
[c] Isolated yield after column chromatography.
[d] Determined by HPLC on chiral stationary phases.
[e] Unreacted (±)-**6** of 36% was recovered.
[f] Unreacted (±)-**7** of 18% was recovered.
[g] Reaction performed with 4 mmol of keto ester in 0.5 mL of HCO_2H/Et_3N mixture.

way, the transfer hydrogenation of the five-membered analogue (±)-**11** proceeded also with complete *syn* selectivity to afford the expected alcohol (1*R*,2*S*)-**13** in moderate 55% yield but with a low enantioselectivity (er 60:40, entry 8). In this case, a higher concentration of substrate results in a much better yield of (1*R*,2*S*)-**13** which was, however, obtained as a nearly racemic mixture (entry 9).

The absolute configuration of (1*R*,2*R*)-**4**, (1*S*,2*R*)-**9**, (1*R*,2*S*)-**12** and (1*R*,2*S*)-**13** was assigned by comparison of their NMR data and optical rotations with literature data: (1*R*,2*R*)-**4** had $[\alpha]_D^{20}$ +114.5 (*c* 0.95, EtOH) [lit.[11c] (1*R*,2*R*)-**4** (>98% ee): $[\alpha]_D^{25}$ +115.0 (*c* 1.39, EtOH)]; (1*S*,2*R*)-**9** had $[\alpha]_D^{20}$ −6.3 (*c* 0.8, $CHCl_3$) [lit.[11a] (1*R*,2*S*)-(methyl ester) (>98% ee): $[\alpha]_D^{23}$ +48.3 (*c* 1.0, $CHCl_3$)]; (1*R*,2*S*)-**12** had $[\alpha]_D^{20}$ +14.5 (*c* 0.8, $CHCl_3$) [lit.[4] (1*R*,2*S*)-**12** (>98% ee): $[\alpha]_D^{20}$ +18.2 (*c* 2.3, $CHCl_3$)]; (1*R*,2*S*)-**13** had $[\alpha]_D^{20}$ +4.5 (*c* 0.8, Et_2O) [lit.[4,21] (1*R*,2*S*)-**13** (>99% ee): $[\alpha]_D^{20}$ +22.1 (*c* 1.0, MeOH)]. Assuming a uniform stereochemical course as for **4**, the absolute configuration of (1*R*,2*R*)-**5** was assigned by analogy.[22] This assignment is also strongly supported by the well-established stereochemical model for aryl ketones, based on CH–π interactions.[23] The absolute configuration of (1*R*,2*R*)-**9** was assigned assuming that it proceeds from the *syn* (1*S*,2*R*)-**9** isomer by epimerization at C(1). Finally, the absolute configurations of (1*S*,2*R*)-**8** and (1*R*,2*R*)-**8** were tentatively assigned assuming a uniform stereochemical pathway as for (1*S*,2*R*)-**9** and (1*R*,2*R*)-**9**, respectively. This assumption is also based on the uniform stereochemical outcome observed for five- and six-membered monocyclic ketones.

3. Conclusion

In conclusion, a new entry to cyclic *syn* β-hydroxy esters from configurationally labile α-substituted keto esters has been developed. The asymmetric transfer hydrogenation of

these compounds by using Noyori/Ikariya's Ru(arene)-TsDPEN catalyst **I** and HCO_2H/Et_3N as the hydrogen source proceeds via dynamic kinetic resolution to selectively afford *syn* compounds for a variety of cyclic substrates. Remarkable results concerning the reactivity and enantioselectivities (>98% de, 99% ee) were achieved for bicyclic α-tetralone and α-indanone derivatives. This method complements the known enantioselective hydrogenation procedures leading to *anti* products.

4. Experimental section

4.1. General experimental methods

Solvents were purified and dried by standard procedures. Flash chromatography was carried out on silica gel (0.040–0.063 mm or 0.015–0.040 mm). Melting points were recorded in a metal block and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz, 400 MHz or 500 MHz; ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz or 125 MHz with the solvent peak used as the internal reference. The diastereomeric excesses (de) of the products were determined by ^{1}H NMR and the enantiomeric excess (ee) by HPLC on chiral stationary phases with *i*-PrOH/hexane mixtures as the eluent. Catalysts (*R*,*R*)-**I** and (*S*,*S*)-**I**,[18] ethyl tetral-1-one-2-carboxylate [(±)-**1**],[24] ethyl indan-1-one-2-carboxylate [(±)-**2**],[25] ethyl benzosuber-1-one-2-carboxylate [(±)-**3**][24] and ethyl tetral-2-one-1-carboxylate [(±)-**6**][24] were prepared according to literature procedures.

4.1.1. Ethyl indan-2-one-1-carboxylate [(±)-7]. Following literature procedures,[24] indan-2-one (1.32 g, 10 mmol) was added to a stirred suspension of NaH (60% dispersion, 480 mg, 12 mmol) in diethyl carbonate (13 mL, 107 mmol) under an atmosphere of argon. After effervescence had ceased, the solution was refluxed for 30 min. The resultant solid was dissolved in hydrochloric acid (2 M) and the phases were separated. The aqueous phase was extracted with ethyl acetate (3×15 mL). The organic extracts were dried ($MgSO_4$) and evaporated to dryness. Flash chromatography (EtOAc/hexane 1:30) afforded (±)-**7** (1.3 g, 64%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) for enolic form: δ 1.43 (t, 3H, *J*=7.2 Hz), 3.54 (s, 2H), 4.39 (q, 2H, *J*=7.2 Hz), 7.08 (t, 1H, *J*=7.6 Hz), 7.23 (d, 1H, *J*=7.6 Hz), 7.26 (t, 1H, *J*=7.6 Hz), 7.58 (t, 1H, *J*=7.6 Hz), 11.08 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 37.6, 60.6, 105.2, 120.2, 123.6, 123.7, 127.1, 133.2, 139.7, 169.0, 180.8. HRMS *m*/*z* calcd for $C_{12}H_{12}O_3$: 204.0786, found: 204.0788.

4.2. Transfer hydrogenation of β-keto esters: general procedures

Method A: β-keto ester (4 mmol) was added to a solution of catalyst **I** (6.5 mg, 0.02 mmol) in 5:2 HCO_2H/Et_3N (2 mL). The mixture was stirred at rt for 6 days, then diluted with CH_2Cl_2 (20 mL) and washed with H_2O (2×15 mL). The organic layer was dried and concentrated, and the residue was purified by flash chromatography.

Method B: β-keto ester (2 mmol) was added to a solution of catalyst **I** (3.3 mg, 0.01 mmol) in 1.2:1 HCO_2H/Et_3N (1 mL). The mixture was stirred at rt for 6–9 days and the reaction work-up was carried out as in method A.

Starting materials, method used for the synthesis, catalyst, eluents, yields and spectral and analytical data for compounds **4**, **5**, **8**, **9**, **12** and **13** are as follows:

4.2.1. (1*R*,2*R*)-Ethyl 1-hydroxytetraline-2-carboxylate [(1*R*,2*R*)-4]. From ethyl tetral-1-one-2-carboxylate (±)-**1** (872 mg, 4 mmol) and following method A with (*R*,*R*)-**I** as the catalyst, after 6 days the residue was purified by flash chromatography (EtOAc/hexane 1:5) to afford (1*R*,2*R*)-**4** (790 mg, 90%, dr >99:1, 99% ee) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, 3H, *J*=7.2 Hz), 2.09 (m, 1H), 2.23 (m, 1H), 2.79 (m, 2H), 2.93 (ddd, 1H, *J*=17.1, 5.4, 3.6 Hz), 3.08 (d, 1H, *J*=4.2 Hz), 4.22 (q, 2H, *J*=7.2 Hz), 5.02 (t, 1H, *J*=4.2 Hz), 7.10–7.41 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 20.3, 28.7, 45.7, 61.2, 68.1, 126.6, 128.4, 129.2, 130.2, 136.4, 137.0, 174.8. $[\alpha]_D^{20}$ +114.5 (*c* 1.0, EtOH) [lit.[11c] (1*R*,2*R*)-**4** (>98% ee): $[\alpha]_D^{25}$ +115.0 (*c* 1.4, EtOH)]. HRMS *m*/*z* calcd for $C_{13}H_{17}O_3$: 221.1178, found: 221.1192. HPLC (Chiralcel OB, propan-2-ol/hexane 6:94, flow 1 mL/min, *T*=30 °C): t_R 7.6 min (major) and 9.7 min (minor).

4.2.2. (1*R*,2*R*)-Ethyl 1-hydroxyindane-2-carboxylate [(1*R*,2*R*)-5]. From ethyl indan-1-one-2-carboxylate (±)-**2** (815 mg, 4 mmol) and following method A with (*R*,*R*)-**I** as the catalyst, after 6 days the residue was purified by flash chromatography (EtOAc/hexane 1:5) to afford (1*R*,2*R*)-**5** (670 mg, 81%, dr >99:1, 99% ee) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (t, 3H, *J*=7.2 Hz), 2.89 (d, 1H, *J*=6.3 Hz), 3.10 (m, 1H), 3.38 (m, 2H), 4.22 (q, 2H, *J*=7.2 Hz), 5.33 (t, 1H, *J*=6.3 Hz), 7.23–7.43 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 33.2, 49.7, 61.2, 76.1, 125.2, 125.3, 127.5, 129.4, 142.1, 142.9, 173.4. $[\alpha]_D^{20}$ −43.8 (*c* 1.1, EtOH). HRMS *m*/*z* calcd for $C_{12}H_{14}O_3$: 206.0943, found: 206.0938. HPLC (Chiralcel OB, propan-2-ol/hexane 5:95, flow 1 mL/min, *T*=30 °C): t_R 5.5 min (minor) and 7.8 min (major).

4.2.3. (1*S*,2*R*)- and (1*R*,2*R*)-Ethyl 2-hydroxytetraline-1-carboxylate [(1*S*,2*R*)- and (1*R*,2*R*)-8]. From ethyl tetral-2-one-1-carboxylate (±)-**6** (436 mg, 2 mmol) and following modified method B with (*S*,*S*)-**I** as the catalyst (substrate/catalyst (S/C)=50), after 6 days the residue was purified by flash chromatography (EtOAc/hexane 1:4) to afford (1*S*,2*R*)-**8** (260 mg, 59%, dr >99:1, 95% ee) and (1*R*,2*R*)-**8** (140 mg, 32%, dr >99:1, 94% ee) as light yellow syrups.

Data for (1*S*,2*R*)-**8**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J*=7.0 Hz), 1.95 (m, 1H), 2.26 (m, 1H), 2.81 (dt, 1H, *J*=17.0, 7.5 Hz), 2.99 (d, 1H, *J*=5.5 Hz), 3.04 (dt, 1H, *J*=17.0, 6.0 Hz), 3.98 (d, 1H, *J*=4.5 Hz), 4.22 (m, 3H), 7.11–7.19 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 26.8, 28.0, 50.2, 61.1, 67.8, 126.0, 127.3, 129.1, 129.5, 131.7, 136.2, 173.4. $[\alpha]_D^{20}$ −42.0 (*c* 0.8, $CHCl_3$). HRMS *m*/*z* calcd for $C_{13}H_{17}O_3$: 221.1178, found: 221.1175. HPLC (Chiralpack AD, propan-2-ol/hexane 1:99, flow 0.5 mL/min, *T*=30 °C): t_R 11.2 min (major) and 15.8 min (minor).

Data for (1*R*,2*R*)-**8**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J*=7.0 Hz), 1.82 (m, 1H), 2.09 (br s, 1H), 2.17 (m, 1H),

2.90 (dd, 2H, J=7.0, 5.5 Hz), 3.76 (d, 1H, J=8.0 Hz), 4.20–4.28 (m, 2H), 4.33 (m, 1H), 7.09–7.16 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 27.3, 29.9, 54.5, 61.2, 69.6, 126.2, 127.1, 128.4, 129.0, 131.8, 135.7, 173.5. $[\alpha]_D^{20}$ −11.0 (c 0.4, $CHCl_3$). HRMS m/z calcd for $C_{13}H_{16}O_3$: 220.1099, found: 220.1100. HPLC (Chiralpack AD, propan-2-ol/hexane 1:99, flow 1 mL/min, T=30 °C): t_R 17.6 min (minor) and 22.1 min (major).

Following method B using (*S*,*S*)-**I** as the catalyst, after 9 days the residue was purified by flash chromatography (EtOAc/hexane 1:4) to afford (1*R*,2*R*)-**8** (168 mg, 38%, dr >99:1, 94% ee) and (1*S*,2*R*)-**8** (83 mg, 19%, dr >99:1, 94% ee) as light yellow syrups. Starting material (±)-**6** of 157.0 mg (36%) was also recovered.

4.2.4. (1*R*,2*R*)- and (1*S*,2*R*)-Ethyl 2-hydroxyindane-1-carboxylate [(1*R*,2*R*)- and (1*S*,2*R*)-9]. From ethyl indan-2-one-1-carboxylate (±)-**7** (408 mg, 2 mmol) and following method B with (*S*,*S*)-**I** as the catalyst (substrate/catalyst (S/C)=50), after 6 days the residue was purified by flash chromatography (EtOAc/hexane 1:4) to afford (1*R*,2*R*)-**9** (246 mg, 60%, dr >99:1, 24% ee) and (1*S*,2*R*)-**9** (37 mg, 9%, dr >99:1, 33% ee) as yellow oils. Starting material (±)-**7** of 74 mg (18%) was also recovered.

Data for (1*R*,2*R*)-**9**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, 3H, J=7.0 Hz), 2.42 (br s, 1H), 2.90 (dd, 1H, J=16.0, 7.0 Hz), 3.33 (dd, 1H, J=16.0, 7.0 Hz), 3.94 (d, 1H, J=5.5 Hz), 4.23 (q, 2H, J=7.0 Hz), 4.89 (m, 1H), 7.11–7.24 (m, 3H), 7.38 (d, 1H, J=6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 40.3, 58.5, 61.1, 75.8, 125.0, 125.1, 127.0, 128.0, 137.8, 140.4, 172.3. $[\alpha]_D^{20}$ −5.2 (c 0.5, $CHCl_3$). HRMS m/z calcd for $C_{12}H_{15}O_3$: 207.1021, found: 207.1008. HPLC (Chiralpack AD, propan-2-ol/hexane 1:99, flow 0.5 mL/min, T=30 °C): t_R 23.2 min (major) and 25.2 min (minor).

Data for (1*S*,2*R*)-**9**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (t, 3H, J=7.0 Hz), 3.07 (dd, 1H, J=16.0, 4.0 Hz), 3.15 (dd, 1H, J=16.0, 6.0 Hz), 3.36 (br s, 1H), 4.06 (d, 1H, J=5.5 Hz), 4.25 (q, 2H, J=7.0 Hz), 4.82 (m, 1H), 7.15–7.30 (m, 3H), 7.39 (d, 1H, J=6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 40.9, 54.4, 61.1, 74.0, 125.3, 125.6, 127.0, 128.0, 137.8, 141.5, 172.3. $[\alpha]_D^{20}$ −6.3 (c 0.8, $CHCl_3$) [lit.[11a] (1*R*,2*S*)-(methyl ester) (>98% ee): $[\alpha]_D^{23}$ +48.3 (c 1.0, $CHCl_3$)]. HRMS m/z calcd for $C_{12}H_{15}O_3$: 207.1021, found: 207.1025. HPLC (Chiralpack AD, propan-2-ol/hexane 1:99, flow 0.5 mL/min, T=30 °C): t_R 19.8 min (major) and 21.6 min (minor).

4.2.5. (1*R*,2*S*)-Ethyl 2-hydroxycyclohexanecarboxylate [(1*R*,2*S*)-12]. From ethyl 2-oxocyclohexanecarboxylate (±)-**10** (680 mg, 4 mmol) and following modified method A (4 mmol, (±)-**10**/0.5 mL, HCO_2H/Et_3N 5:2) with (*S*,*S*)-**I** as the catalyst (substrate/catalyst (S/C)=100), after 6 days the residue was purified by flash chromatography (EtOAc/hexane 1:8) to afford (1*R*,2*S*)-**12** (530 mg, 77%, dr >99:1, 70% ee) as a brown oil.

Data for (1*R*,2*S*)-**12**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23 (t, 3H, J=7.1 Hz), 1.20–1.32 (m, 1H), 1.33–1.50 (m, 2H), 1.60–1.73 (m, 3H), 1.74–1.92 (m, 2H), 2.40–2.50 (m, 1H), 3.20 (m, 1H), 4.13 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.2, 20.1, 24.0, 24.8, 31.7, 46.7, 60.6, 66.7, 175.9. $[\alpha]_D^{20}$ +14.5 (c 0.8, $CHCl_3$) [lit.[4,26] (1*R*,2*S*)-**12** (>98% ee): $[\alpha]_D^{20}$ +18.2 (c 2.3, $CHCl_3$)]. Anal. calcd for $C_{17}H_{23}NO$: C 62.77, H 9.37; found: C 62.76, H 9.39. HRMS m/z calcd for $C_9H_{17}O_3$: 173.1176, found: 173.1177. HPLC (Chiralcel OD, propan-2-ol/hexane 5:95, flow 1.0 mL/min, T=30 °C): t_R for benzoate 6.4 min (major) and 7.8 min (minor).

4.2.6. (1*R*,2*S*)-Ethyl 2-hydroxycyclopentanecarboxylate [(1*R*,2*S*)-13]. From ethyl 2-oxocyclopentanecarboxylate (±)-**11** (624 mg, 4 mmol) and following modified method B (4 mmol, (±)-**11**/0.5 mL, HCO_2H/Et_3N 1.2:1.0) with (*S*,*S*)-**I** as the catalyst (substrate/catalyst (S/C)=100), after 6 days the residue was purified by flash chromatography (EtOAc/hexane 1:8) to afford (1*R*,2*S*)-**13** (600 mg, 95%, dr >99:1, 5% ee) as a brown oil.

Data for (1*R*,2*S*)-**13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 (t, 3H, J=7.1 Hz), 1.50–1.65 (m, 1H), 1.67–1.78 (m, 2H), 1.79–2.01 (m, 3H), 2.62 (m, 1H), 3.10 (m, 1H), 4.13 (q, 2H, J=7.1 Hz), 4.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 22.3, 26.6, 34.2, 49.8, 60.9, 73.9, 175.2. $[\alpha]_D^{20}$ +4.5 (c 0.8, Et_2O) [lit.[4,21] (1*R*,2*S*)-**13** (>99% ee): $[\alpha]_D^{20}$ +22.1 (c 1.0, MeOH)]. HRMS m/z calcd for $C_8H_{15}O_3$: 159.1031, found: 159.1021. HPLC (Chiralcel OD, propan-2-ol/hexane 5:95, flow 1.0 mL/min, T=30 °C): t_R for benzoate 6.4 min (major) and 7.8 min (minor).

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