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Copper-catalyzed intramolecular redox reaction: Asymmetric synthesis of chiral 2-(1*H*-pyrrol-1-yl)-mandelic acid esters

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ABSTRACT

An efficient approach to chiral α-hydroxy acid esters by Lewis acid-mediated asymmetric [1,5]-hydride shift and isomerization of 2-(3-pyrroline-1-yl)arylketone acid ester has been achieved in up to 96% yield and 94% ee. This protocol would be applied in the synthesis of chiral α-hydroxy acid derivatives with simplicity and high enantioselectivity.

1. Introduction

Optically active α-hydroxy acids and their derivatives as chiral building blocks are of considerable significance in pharmaceutical industry [1]. In the past decades, a number of efficient methods have been developed to access these important structural motifs [2]. Among these reported methodologies, asymmetric catalytic hydrogenations and hydrogen transfer reactions of α-ketone esters are considered as the most attractive one due to their efficiency and atom-economy [3].

Recently, [1,5]-hydride shift process has been developed as an atom-economic, efficient and rapid approach to C–H bond functionalization [4]. In 2009, the first enantioselective intramolecular redox reaction catalyzed by Lewis acids and chiral ligands was reported by Seidel (Scheme 1, a), affording chiral ring-fused tetrahydroquinolines [5]. The author speculated that an acyl oxazolidinone group in substrates was able to chelate to chiral Lewis acids in order to get the high enantioselectivity. Subsequently, other transition metal including Mg [6], Co [7], Sc [8], Au [9] and organocatalysts [10] were employed to realize enantioselective internal redox reaction. Among the reported transformations, Michael acceptors as electropositive fragments played a dominant role in the enantioselective redox reaction. And only a limited number of papers dealing with the aldehydes was reported [11]. However, the enantioselective reduction of ketones involving [1,5]-hydride shift process was rarely reported.

In our previous work, we have developed Lewis acid catalyzed intramolecular redox reaction that utilizes the inherent reducing power of 3-pyrrolines (Scheme 1, b), leading to the formation of N-aryl pyrroles via [1,5]-hydride shift and isomerization [12]. And Lewis acid activation of the dicarbonyl moiety via chelation is successfully employed in a number of asymmetric reactions [3b,13]. Herein, we envisaged that chiral Lewis acid might be applied to reduce dicarbonyl moiety involving [1,5]-hydride shift, providing access to enantioenriched α-hydroxy acid derivatives. In this paper, we describe our preliminary results.

2. Result and discussion

With this hypothesis in mind, substrate **1a** was synthesized and chosen as a model substrate for the optimization, as summarized in Table 1. On the basis of our previous work, $Sc(OTf)_3$ was selected as the catalyst, to our disappointment, when the chiral ligand **L2** was applied to this transformation, the reaction could not occur at room temperature (entry 1, Table 1). Then the temperature and catalyst loading was elevated to 50 °C and 10 mol%, respectively, the reaction proceeded smoothly, but the product was obtained in only 5%

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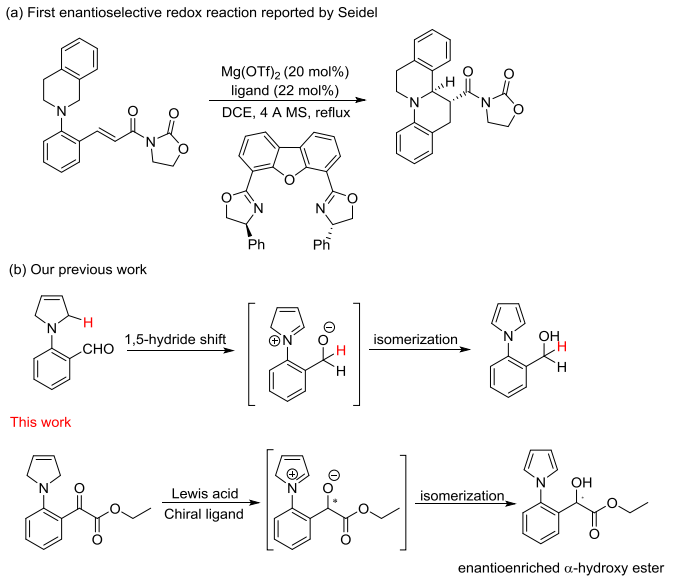


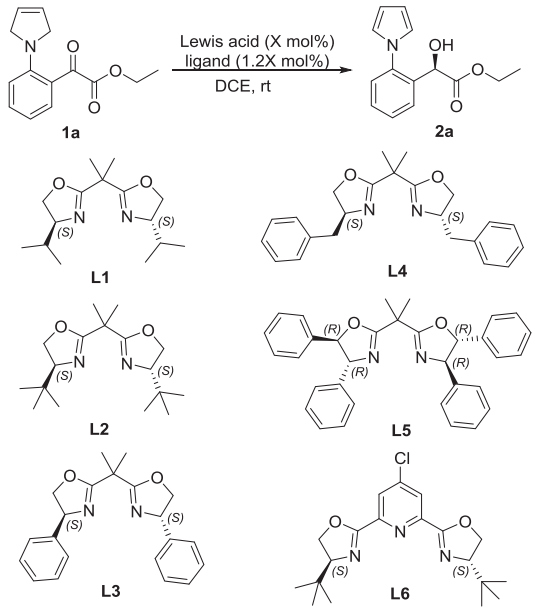
Scheme 1. Enantioselective intramolecular redox reaction and our strategy.

ee (entries 2–3, Table 1). The other Lewis acids were investigated, and we found that $Mg(ClO_4)_2$ was not efficient, giving the racemic product (entry 4, Table 1). However, when $Cu(OTf)_2$ was employed, the reaction proceeded smoothly, giving the desired product in excellent yield (82%) and enantioselectivity (90% ee) (entry 5, Table 1). Next, different chiral ligands were evaluated but could not improve the enantioselectivity. The pyridine-phox ligand **L6** had no effect on the reaction. Through examining the common solvents, including DCE, DCM, Toluene, THF and MeCN, we found that DCE was the optimal solvent while polar solvent gave a racemic result. We tried to decrease the loading of $Cu(OTf)_2$—5 mol%, and the yield was lowered to 40%, and when the temperature was increased to 50 °C, the yield and enantioselectivity of the product could be maintained. However, when we further decrease the catalyst loading to 2 mol%, the enantioselective could be kept up (90% ee), but the yield was decreased to 20%, even the reaction took place at 50 °C for 72 h (entry 18, Table 1). Finally, we determined the optimal reaction conditions as follows: **1a** (0.2 mmol), $Cu(OTf)_2$ (5 mol%), **L2** (6 mol%), DCE, 50 °C.

Reaction conditions: **1** (0.20 mmol), $Cu(OTf)_2$ (5 mol %), **L2** (6 mol%), DCE (2 mL), 50 °C.

With the optimal reaction condition established, we next evaluated the substrate scope of this transformation, as shown in Scheme 2. Different substituted esters could be tolerated in the reaction, affording the corresponding α-hydroxy acid esters (**2a-2f**) in good yields (89–98%) and ee (79–91%). The bigger benzyl group gave lower ee (79%). Next, the substrates with various substituents (4-Me, 5-Me, 4-Cl, 5-Cl, 4-F, 5-F, 5-MeO) adjacent to benzene ring were found to be proceeded smoothly, providing the desired products (**2h-2n**) in good yields (50–96%) and ee (83–91%). Product **2n** was obtained in only 50% yield, probably due to the MeO group degrading the electron withdrawing ability of carbonyl, thus leading to the low yield. It was found that the substrate with naphthalene ring gave the desired product **2g** in the highest 94% ee and 95% yield. However, for the substrate **1o** with the phenyl group on the 3-pyrroline moiety, the desired product **2o** was obtained in only 41% yield and 53% ee, the possible cause of this result is that the phenyl group affect chiral metal complex chelating with the 1,2-dicarbonyl, thus leading to low yield and ee. According to the Horeau method, we determined that the absolute configuration of the product is *R* (see the Supporting Information for details).

Table 1
Optimization of the reaction.[a]



entry	Lewis acid	X	time (h)	ligand	yield (%)	ee (%)
1	$Sc(OTf)_3$	5	24	**L2**	–	–
2	$Sc(OTf)_3$	10	24	**L2**	10	5
3[b]	$Sc(OTf)_3$	10	4.5	**L2**	88	5
4	$Mg(ClO_4)_2$	10	48	**L2**	44	0
5	$Cu(OTf)_2$	10	24	**L2**	82	90
6	$Cu(OTf)_2$	10	1	**L1**	92	55
7	$Cu(OTf)_2$	10	5	**L3**	84	74
8	$Cu(OTf)_2$	10	0.3	**L4**	90	48
9	$Cu(OTf)_2$	10	0.3	**L5**	98	−50
10	$Cu(OTf)_2$	10	24	**L6**	–	–
11[c]	$Cu(OTf)_2$	10	24	**L2**	80	90
12[d]	$Cu(OTf)_2$	10	24	**L2**	40	62
13[e]	$Cu(OTf)_2$	10	24	**L2**	32	41
14[f]	$Cu(OTf)_2$	10	24	**L2**	22	0
15[b]	$Cu(OTf)_2$	10	0.5	**L2**	92	91
16	$Cu(OTf)_2$	5	48	**L2**	40	91
17[b]	$Cu(OTf)_2$	5	1	**L2**	90	91
18[b]	$Cu(OTf)_2$	2	72	**L2**	20	90

[a] Reaction conditions: **1a** (0.2 mmol), Lewis acid, ligands, DCE (2 mL), rt.
[b] Reacted at 50 °C.
[c] Reacted in DCM.
[d] Reacted in Toluene.
[e] Reacted in THF.
[f] Reacted in MeCN.

The substrate **1p** with pyrrolidine as hydride donor was employed to this transformation, and subsequently the addition of Grignard reagents (MeMgBr) to the α-position of the amine moiety occurred, giving the corresponding product **2p** in good yield and enantioselectivity, but low diastereoselectivity (Scheme 3).

To further demonstrate the utility of this transformation involving enantioselective [1,5]-hydride shift process, the reaction of **1g** was performed on a 2 mmol scale (Scheme 4) to give product **2g** (94% ee), which could be easily hydrolyzed without further purification to the corresponding chiral α-hydroxy acid **3g** in 91% yield (two steps) and 94% ee.

3. Conclusion

In summary, Lewis acid and chiral ligand mediated-asymmetric 1,5-hydride shift and isomerization of 2-(3-pyrroline-1-yl)

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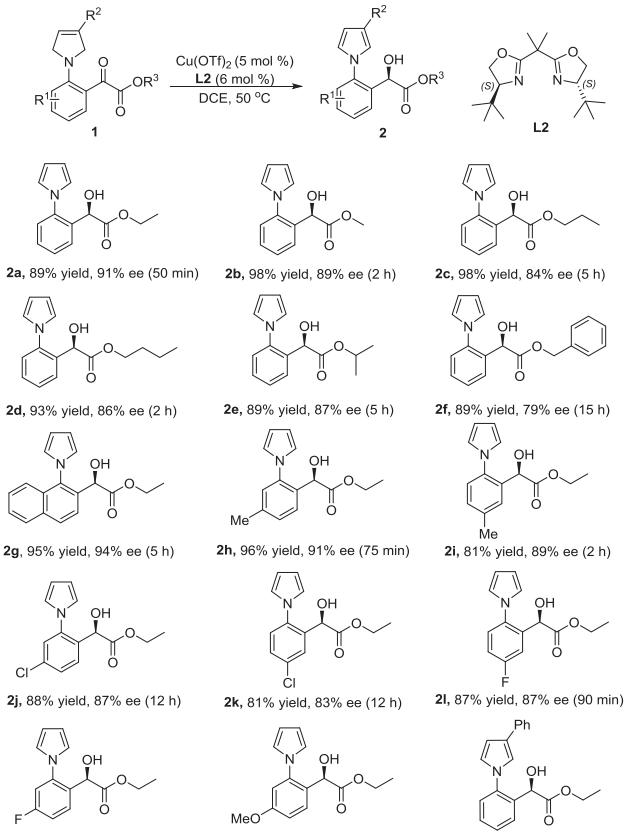
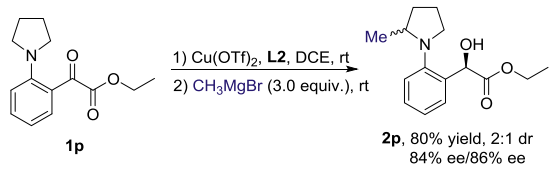
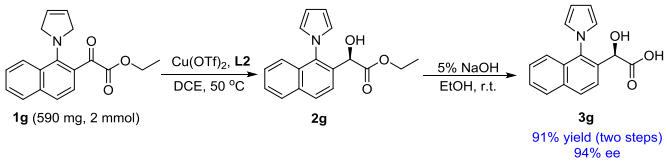


Scheme 2. Substrate scope.



Scheme 3. The reaction of the substrate 1p.



Scheme 4. Practical preparation and transformation of 2 g.

arylketone acid ester has been developed, affording an efficient approach to enantioenriched α-hydroxy acid ester derivatives. These chiral α-hydroxy acid esters could be easily transformed to the corresponding chiral α-hydroxy acids that are regarded as valuable building blocks for organic synthesis and pharmaceutical research. Further exploration of the inherent reducing power of 3-pyrroline for the synthesis of other N-aryl pyrroles is ongoing in our laboratory.

4. Experimental section

^{1}H and ^{13}C NMR spectra were recorded on an ACF* 300Q Bruker or ACF* 500Q Bruker spectrometer. Low- and high-resolution mass spectra (LRMS and HRMS) were recorded in electron impact mode. The mass analyzer type used for the HRMS measurements was TOF. Reactions were monitored by TLC on silica gel 60 F254 plates (Qingdao Ocean Chemical Company, China). Column chromatography was carried out on silica gel (200–300 mesh, Qingdao Ocean Chemical Company, China). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad singlet, coupling constant (s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Commercially available reagents and solvents were used without further purification.

4.1. General procedure for asymmetric synthesis of chiral madelic acid ester 2

$Cu(OTf)_2$ (5 mol%), chiral ligand **L2** (6 mol%) were added into the reaction flask and were dissolved in DCE (2 mL), the mixture was stirred at room temperature for 30 min, then the substrate **1** (0.20 mmol) was added, the reaction was stirred at 50 °C until complete consumption. The solvents were concentrated and purified by flash chromatography (petroleum ether/ethyl acetate = 10/1) to get the desired product **2**.

2a, light yellow oil, 44 mg, 89% yield, 91% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 92/8); flow rate = 1.0 mL/min; detection wavelength = 230 nm; t_R = 17.38 (major), 18.33 (minor) min]. $[\alpha]_D^{20}$ = +147.3 (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.23 (m, 4H), 6.96 (t, J = 3.0 Hz, 2H), 6.35 (t, J = 3.0 Hz, 2H), 5.12 (d, J = 4.2 Hz, 1H), 4.38–3.94 (m, 2H), 3.54 (d, J = 4.1 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 140.3, 134.6, 129.3, 128.2, 127.8, 127.3, 123.1, 109.2, 68.0, 62.4, 13.9; HRMS (ESI): Exact mass calcd. for $C_{14}H_{15}NO_3Na$ $[M+Na]^+$ 268.09441, found 268.09544.

2b, light yellow oil, 41 mg, 98% yield, 89% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; t_R = 18.89 (major), 17.62 (minor) min]. $[\alpha]_D^{20}$ = +166.3 (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.24 (m, 4H), 6.93 (d, J = 1.8 Hz, 2H), 6.33 (d, J = 1.8 Hz, 2H), 5.12 (s, 1H), 3.73 (s, 3H), 3.50 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 140.4, 134.5, 129.4, 128.2, 128.0, 127.4, 123.2, 109.4, 68.1, 53.0; HRMS (ESI): Exact mass calcd. for $C_{13}H_{13}NO_3Na$ $[M+Na]^+$ 254.07876, found 254.07986.

2c, colorless oil, 51 mg, 98% yield, 84% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; t_R = 15.54 (major), 16.49 (minor) min]. $[\alpha]_D^{20}$ = +126.3 (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.26 (m, 4H), 6.96 (s, 2H), 6.35 (s, 2H), 5.14 (d, J = 4.0 Hz, 1H), 4.12 (t, J = 6.6 Hz, 2H), 3.61 (d, J = 4.3 Hz, 1H), 1.67–1.54 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 140.3, 134.8, 129.2, 128.2, 127.7, 127.3, 123.1, 109.3, 67.9, 67.8, 21.7, 10.1; HRMS (ESI): Exact mass calcd. for $C_{15}H_{17}NO_3Na$ $[M+Na]^+$ 282.11006, found 282.11124.

2d, light yellow oil, 51 mg, 93% yield, 86% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; t_R = 13.43 (major), 14.80 (minor) min]. $[\alpha]_D^{20}$ = +136.0 (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.26 (m, 4H), 6.94 (s, 2H), 6.33 (s, 2H), 5.11 (d, J = 4.0 Hz, 1H), 4.15 (t, J = 6.6 Hz, 2H), 3.57 (br s, 1H), 1.68–1.43 (m, 2H), 1.39–1.08 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 140.3, 134.8, 129.2, 128.2, 127.7, 127.3, 123.1, 109.3, 67.9, 66.1, 30.3, 18.8, 13.5; HRMS (ESI): Exact mass calcd. for $C_{16}H_{19}NO_3Na$ $[M+Na]^+$ 296.12571, found 296.12717.

2e, colorless oil, 46 mg, 89% yield, 87% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; t_R = 14.04 (major), 15.21 (minor) min]. $[\alpha]_D^{20}$ = +146.3 (c 0.3, MeOH); ^{1}H NMR

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(300 MHz, $CDCl_3$) δ 7.49–7.25 (m, 4H), 6.98 (s, 2H), 6.35 (s, 2H), 5.13–5.01 (m, 2H), 3.62 (br s, 1H), 1.26 (d, $J = 6.3$ Hz, 3H), 1.14 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 140.3, 134.8, 129.1, 128.1, 127.5, 127.2, 123.1, 109.2, 70.4, 67.9, 21.5; HRMS (ESI): Exact mass calcd. for $C_{15}H_{17}NO_3Na$ $[M+Na]^+$ 282.11006, found 282.11092.

2f, colorless oil, 55 mg, 89% yield, 79% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 23.42$ (major), 27.30 (minor) min]. $[\alpha]_D^{20} = +183.0$ (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.29 (m, 8H), 7.25–7.17 (m, 1H), 6.94–6.91 (m, 2H), 6.36–6.32 (m, 2H), 5.27–5.08 (m, 2H), 4.68 (s, 1H), 3.68 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 140.4, 134.8, 134.4, 129.3, 128.5, 128.4, 128.2, 128.0, 127.9, 127.4, 127.0, 123.1, 109.3, 68.2, 67.8; HRMS (ESI): Exact mass calcd. for $C_{19}H_{17}NO_3Na$ $[M+Na]^+$ 330.11006, found 330.11111.

2g, colorless oil, 56 mg, 95% yield, 94% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 28.79$ (major), 19.49 (minor) min]. $[\alpha]_D^{20} = +203.7$ (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.89 (m, 2H), 7.54–7.47 (m, 3H), 7.29 (d, $J = 8.3$ Hz, 1H), 7.00 (d, $J = 1.2$ Hz, 1H), 6.94 (s, 1H), 6.46 (s, 2H), 5.07 (s, 1H), 4.32–3.99 (m, 2H), 3.72 (br s, 1H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 136.5, 133.6, 133.3, 131.8, 129.3, 127.7, 127.5, 127.1, 124.8, 123.8, 123.4, 109.1, 108.8, 68.4, 62.4, 14.0; HRMS (ESI): Exact mass calcd. for $C_{18}H_{17}NO_3Na$ $[M+Na]^+$ 318.11006, found 318.11054.

2h, colorless oil, 50 mg, 96% yield, 91% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 18.37$ (major), 17.33 (minor) min]. $[\alpha]_D^{20} = +127.7$ (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, $J = 7.6$ Hz, 1H), 7.21 (d, $J = 7.9$ Hz, 1H), 7.15 (s, 1H), 6.95 (d, $J = 1.7$ Hz, 2H), 6.33 (d, $J = 1.7$ Hz, 2H), 5.08 (s, 1H), 4.30–4.04 (m, 2H), 3.54 (br s, 1H), 2.39 (s, 3H), 1.26–1.18 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 140.6, 139.9, 132.0, 129.4, 128.3, 128.1, 123.5, 109.6, 68.4, 62.7, 21.4, 14.4; HRMS (ESI): Exact mass calcd. for $C_{15}H_{17}NO_3Na$ $[M+Na]+$ 282.11006, found 282.11097.

2i, colorless oil, 42 mg, 81% yield, 89% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 99/1); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 43.42$ (major), 39.91 (minor) min]. $[\alpha]_D^{20} = +107.0$ (c 0.1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.20 (s, 2H), 6.91 (d, $J = 1.8$ Hz, 2H), 6.31 (d, $J = 1.8$ Hz, 2H), 5.05 (s, 1H), 4.25–4.13 (m, 2H), 3.47 (br s, 1H), 2.39 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 138.1, 134.3, 129.9, 128.0, 127.1, 123.1, 109.0, 67.9, 62.2, 20.9, 13.9; HRMS (ESI): Exact mass calcd. for $C_{15}H_{17}NO_3Na$ $[M+Na]+$ 282.11006, found 282.11138.

2j, colorless oil, 49 mg, 88% yield, 87% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 12.63$ (major), 10.86 (minor) min]. $[\alpha]_D^{20} = +151.7$ (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (s, 2H), 7.36 (s, 1H), 6.94 (s, 2H), 6.35 (s, 2H), 5.10 (d, $J = 4.2$ Hz, 1H), 4.23–4.12 (m, 2H), 3.59 (d, $J = 4.3$ Hz, 1H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 143.9, 137.2, 135.7, 131.7, 130.9, 130.0, 125.6, 112.4, 70.2, 65.1, 16.5; HRMS (ESI): Exact mass calcd. for $C_{14}H_{14}ClNO_3Na$ $[M+Na]^+$ 302.05544, found 302.05676.

2**k**, colorless oil, 45 mg, 81% yield, 83% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 90/10); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 8.62$ (major), 7.04 (minor) min]. $[\alpha]_D^{20} = +96.3$ (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.25 (d, $J = 8.2$ Hz, 1H), 6.90 (s, 2H), 6.33 (s, 2H), 5.06 (d, $J = 3.6$ Hz, 1H), 4.40–4.08 (m, 2H), 3.57 (d, $J = 4.1$ Hz, 1H), 1.23 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 139.3, 136.7, 134.4, 129.8, 129.1, 128.4, 123.5, 110.1, 68.2, 63.1, 14.4; HRMS (ESI): Exact mass calcd. for $C_{14}H_{14}ClNO_3Na$ $[M+Na]^+$ 302.05544, found 302.05670.

2l, light yellow oil, 46 mg, 87% yield, 87% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 13.43$ (major), 14.90 (minor) min]. $[\alpha]_D^{20} = +90.7$ (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, $J = 8.6$, 5.2 Hz, 1H), 7.20–7.01 (m, 2H), 6.88 (s, 2H), 6.32 (s, 2H), 5.02 (d, $J = 3.7$ Hz, 1H), 4.27–4.12 (m, 2H), 3.62 (s, 1H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 161.8 (d, $J = 248.3$ Hz), 137.0 (d, $J = 7.6$ Hz), 136.4 (d, $J = 3.2$ Hz), 129.2 (d, $J = 8.5$ Hz), 123.2, 116.1 (d, $J = 22.8$ Hz), 114.6, 114.3 (d, $J = 23.6$ Hz), 109.8, 68.3, 63.0, 14.3; HRMS (ESI): Exact mass calcd. for $C_{14}H_{14}FNO_3Na$ $[M+Na]+$ 286.08499, found 286.08578.

2m, colorless oil, 43 mg, 82% yield, 87% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 90/10); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 8.40$ (major), 9.16 (minor) min]. $[\alpha]_D^{20}$ +119.7 (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (dd, $J = 8.4$, 6.2 Hz, 1H), 7.20–7.01 (m, 2H), 6.96 (s, 2H), 6.35 (s, 2H), 5.11 (d, $J = 3.8$ Hz, 1H), 4.41–4.08 (m, 2H), 3.51 (d, $J = 4.1$ Hz, 1H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 162.3 (d, $J = 250.0$ Hz), 141.7 (d, $J = 10.3$ Hz), 130.4 (d, $J = 3.6$ Hz), 129.5 (d, $J = 9.4$ Hz), 122.9, 115.2 (d, $J = 21.3$ Hz), 114.4 (d, $J = 23.4$ Hz), 109.8, 67.6, 62.5, 13.9; HRMS (ESI): Exact mass calcd. for $C_{14}H_{14}FNO_3Na$ $[M+Na]^+$ 286.08499, found 286.08608.

2n, brown oil, 28 mg, 50% yield, 86% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 29.71$ (major), 27.60 (minor) min]. $[\alpha]_D^{20} = +133.7$ (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, $J = 8.7$ Hz, 1H), 7.02–6.92 (m, 3H), 6.86 (d, $J = 2.2$ Hz, 1H), 6.34 (s, 2H), 5.05 (s, 1H), 4.21–4.14 (m, 2H), 3.84 (s, 3H), 3.48 (br s, 1H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 160.0, 141.4, 128.9, 126.6, 123.0, 114.3, 112.2109.3, 67.8, 62.3, 55.5, 14.0; HRMS (ESI): Exact mass calcd. for $C_{15}H_{18}NO$ $[M+H]^+$ 276.12303, found 276.12439.

2o, colorless oil, 26 mg, 41% yield, 53% ee [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 31.35$ (major), 46.64 (minor) min]. $[\alpha]_D^{20} = +80.0$ (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, $J = 7.8$ Hz, 2H), 7.49–7.30 (m, 7H), 7.19 (t, $J = 7.3$ Hz, 1H), 7.00–6.91 (m, 1H), 6.64 (dd, $J = 2.6$, 1.8 Hz, 1H), 5.20 (s, 1H), 4.32–3.90 (m, 2H), 3.52 (br s, 1H), 1.23 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 139.7, 134.9, 134.0, 128.9, 128.2, 127.9, 127.4, 126.7, 125.2, 124.6, 123.7, 119.3, 107.1, 67.5, 62.0, 13.5; HRMS (ESI): Exact mass calcd. for $C_{20}H_{20}NO_3Na$ $[M+Na]^+$ 322.14377, found 322.14264.

2p, colorless oil, 42 mg, 80% yield, 84% ee/86% ee (2/1 dr) [Daicel CHIRALPAK OJ-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 98.5/1.5); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 11.75$ (major), 27.09 (minor) min ($t_R = 15.89$ (major), 51.81 (minor) min)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.30 (m, 4H), 7.25–7.10 (m, 2H)*, 5.55 (s, 1H), 5.37 (s, 0.5H)*, 4.35–4.05 (m, 3H), 3.55–3.25 (m, 3H), 2.82 (appq, $J = 9.0$ Hz, 1H), 2.70 (appq, $J = 9.0$ Hz, 0.5 H)*, 2.25–1.80 (m, 5H), 1.70–1.50 (m, 2H), 1.23 (t, $J = 7.1$ Hz, 4.5H), 1.05 (d, $J = 6.0$ Hz, 1.5H)*, 0.99 (d, $J = 6.0$ Hz, 3H)*.

4.2. Transformation of 2 g

To a solution of **2g** (590 mg, 2 mmol) in MeOH was added NaOH (8.0 mL, 5% aq.), the mixture was stirred at room temperature until complete consumption, then purified by flash chromatography (petroleum ether/ethyl acetate = 1/1) to give **3g** as white solid. 487 mg, 91% yield, 95% ee. [Daicel CHIRALPAK AD-H (0.46 cm × 25 cm); (*n*-hexane/2-propanol = 95/5, 0.5% TFA); flow rate = 1.0 mL/min; detection wavelength = 254 nm; $t_R = 19.85$ (major), 13.64 (minor) min]. $[\alpha]_D^{20} = +170.7$ (c 0.3, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.60–7.40 (m, 3H), 7.23 (m, 1H),

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6.95 (m, 1H), 6.83 (m, 1H), 6.38 (s, 2H), 5.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 136.7, 133.8, 132.6, 131.7, 129.3, 127.7, 127.6, 127.2, 124.9, 123.8, 123.7, 123.4, 109.2, 109.0, 68.4; HRMS (ESI): Exact mass calcd. for $C_{16}H_{12}NO_3$ [M-H]$^-$ 266.08227, found 266.08273. M. p. 54–56 °C.

Notes

The authors declare no competing financial interest.

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Appendix A. Supplementary data

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