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Note

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NHC-Catalyzed Asymmetric Benzoin Reaction in Water

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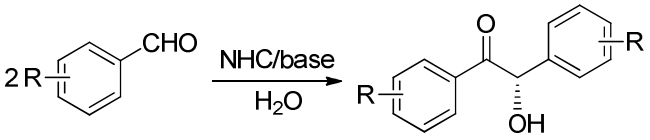
Supporting Information



ABSTRACT: A chiral NHC-catalyzed benzoin condensation reaction in water was developed, thereby affording α-hydroxy ketones in good to high yields and high enantioselectivities. Water was proposed as a proton shuttle in the aqueous asymmetric condensation reaction.

In nature, the largest number of biochemical reactions are enzymatic catalytic ones, which are complex, highly efficient and highly selective reactions occurring in aqueous conditions. One of the most well-known biotransformations is the nucleophilic acylation reaction catalyzed by transketolase enzyme[1] in the presence of coenzyme thiamine (vitamin B1).[2] Until 1943, Ugai proposed that the coenzyme thiamine was actually a natural thiazolium salt used as a catalyst in the acylation reaction, the so-called benzoin reaction.[3] To organic chemists, one of the important research aims is to develop synthetic reactions that mimic enzymatic processes such as this enzymatic system.[4] Consequently, significant developments in the last decade have been made in enabling organic reactions in aqueous media with the application of chiral organocatalysts, such as aldol condensations, Michael reactions and Mannich reactions.[5] Aqueous reactions have various advantages for instance: reduced pollution, lower cost and simpler processing compared to reactions carried out in organic solvents. Furthermore,

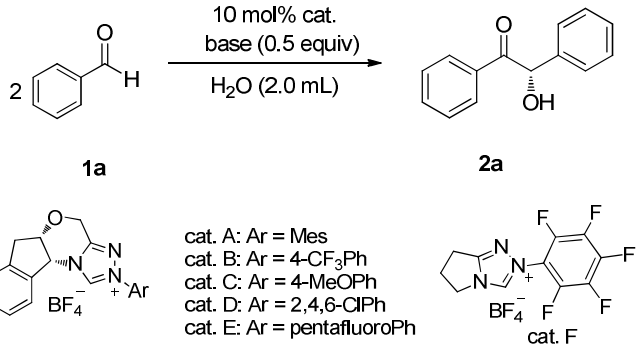
water is widespread and extremely attractive as a renewable green medium for organic synthesis.

N-Heterocyclic carbenes (NHCs), with their special electronic characteristics, not only serve as excellent ligands in organometallic catalysis,[6] but also act as organocatalysts.[7] Over the past decade, NHCs have received significant interest in organocatalyzed reactions due to their special electronic characteristics.[8] Making use of intriguing organocatalytic activation of NHC for new bond-formation opens up a new avenue for the synthesis of target molecules. For example, the traditional a^1-d^1 umpolung (benzoin condensation and Stetter reaction)[9] and a^3-d^3 umpolung (homoenolate cycloaddition[10]) approaches have been well-documented. We have disclosed a series of chiral NHC-catalyzed reactions[11] and our ongoing interest on this topic prompted us to go back to investigate the well-known, direct and useful benzoin condensation reaction in water with a chiral environment. Many reports on carrying out NHC-catalyzed reactions have been prepared, due to their ability to produce acyl anion equivalents.[12] The benzoin condensation catalyzed by NHCs has been intensively investigated. Since the first asymmetric benzoin condensation reactions reported by Sheehan and Hunneman,[13] there have been further reports on this topic.[14] Furthermore, benzoin condensation reactions have been carried out in aqueous media.[15] However, to the best of our knowledge, NHC-catalyzed asymmetric benzoin condensation reactions in water have never been investigated or successfully achieved. Herein, we report a NHC-catalyzed asymmetric benzoin condensation reaction catalyzed by a pentafluorophenyl substituted triazolium salt in water to afford α-hydroxy ketones in good to high yields and high enantioselectivities.

To investigate this chiral benzoin condensation reaction, we first surveyed the simple substrate benzaldehyde (**1a**) in the presence of different catalysts and bases with water as the solvent. The screening of different chiral triazolium catalysts was carried out and the results are summarized in

Table 1. When catalyst **A** (with Mes), with K_2CO_3 as base in water was used, the reaction could proceed smoothly and afforded the desired product α-hydroxycarbonyl, albeit with moderate yield (65%) and low enantioselectivity (55:45 *er*) (entry 1). When a catalyst with a strong electron withdrawing group (4-CF_3) or a strong electron donating group (4-MeO) on a phenyl ring was used, only a trace amount of the desired product was obtained. To our delight, when catalyst **D** was used, a significantly better result was obtained (80% yield, 90:10 *er*, Table 1, entry 4). Subsequent screening of catalyst indicated that catalyst **E** was the best catalyst, which led to the desired product in higher yield and enantioselectivity (entry 6). The screening of different bases revealed that organic bases were deemed to be unsuitable for the reaction as they led to only a trace amount of the desired product. This is likely because of the very low solubility of the organic bases in water. Accordingly, Na_2CO_3 was found to be the best base. When DCM was employed as the solvent, the yield decreased dramatically to 40%. Furthermore, a mixed solvent of water and DCM in a 1:3 or 3:1 ratio led to only a trace amount of the desired product (Table 1, entries 17 and 18), while brine promoted the reaction and afforded a higher yield of 85% (entry 15) and no change in the enantioselectivity was observed.

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	base	solvent	reaction time (h)	yield[b] (%)	*er*[c]
1	A	K_2CO_3	H_2O	8	65	55:45

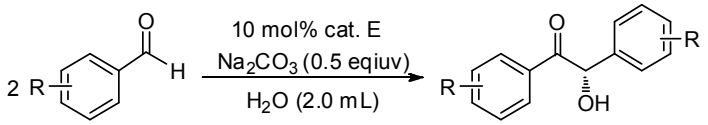
2	B	K_2CO_3	H_2O	24	trace	n.d.
3	C	K_2CO_3	H_2O	24	trace	n.d.
4	D	K_2CO_3	H_2O	8	80	90:10
5	E	K_2CO_3	H_2O	8	65	92:8
6	E	Na_2CO_3	H_2O	8	75	93:7
7	E	CS_2CO_3	H_2O	7	50	92:8
8	E	Et_3N	H_2O	24	trace	n.d.
9	E	DIPEA	H_2O	24	trace	n.d.
10	E	AcONa	H_2O	9	63	93:7
11	E	AcOK	H_2O	9	61	92:8
12	E	KOH	H_2O	10	52	90:10
13	E	NaOH	H_2O	10	46	91:9
14	E	K_3PO_4	H_2O	10	64	89:11
15	E	Na_2CO_3	Brine	7	85	93:7
16	E	Na_2CO_3	DCM	24	40	91:9
17	E	Na_2CO_3	DCM/H_2O (1:3)	24	trace	n.d.
18	E	Na_2CO_3	DCM/H_2O (3:1)	24	trace	n.d.

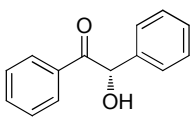
[a] Unless otherwise specified, the reaction was performed by using 0.2 mmol aldehyde in water (2.0 mL) at rt, and the racemic version was catalyzed by cat. F. [b] Yields of isolated products. [c] *er* values determined by HPLC analysis on Chiralcel column (see the Experimental Section).

With the optimal reaction conditions established, we evaluated the substrate scope (**Table 2**) of this NHC-catalyzed asymmetric benzoin condensation reaction in water. The reaction proceeded smoothly for a broad spectrum of substituted benzaldehydes to afford the desired products in good yields and high enantioselectivities. Both electron-donating and electron-withdrawing substituents on the phenyl group were tolerated. The reaction proceeded smoothly for substituted benzaldehydes bearing electron-withdrawing group on phenyl ring (**2b**, **2c** and **2e**). Similarly, electron-donating substituents were also tolerated, with 4-methyl and 4-ethyl substituted benzaldehydes giving the highest enantioselectivities (94:6 *er*) with good yields (**2f** and **2h**). When a substrate with a bulkier group was

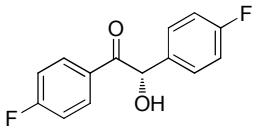
used, the desired product was provided with a lower enantioselectivity and lower yield (**2k**). The position of the substituent on phenyl ring seemed to have little influence on the reaction outcomes (**2c, 2d**, **2f** and **2g**). Replacing the phenyl group with a heteroaryl, such as furan-2-yl, thiophene-2-yl, did

Table 2. Substrate Scope of the Asymmetric Condensation Reaction in Water

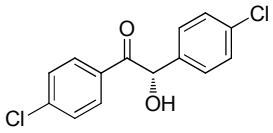




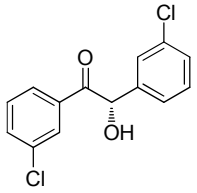
2a, 75% yield, 93:7 *er*



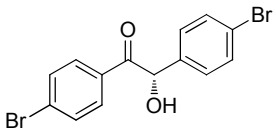
2b, 28% yield, 90:10 *er*



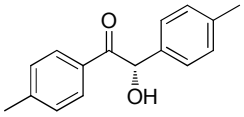
2c, 78% yield, 89:11 *er*



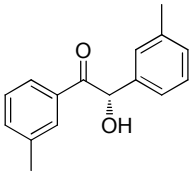
2d, 77% yield, 85:15 *er*



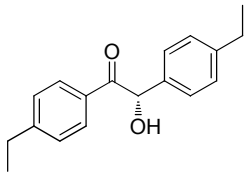
2e, 80% yield, 90:10 *er*



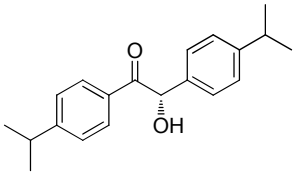
2f, 71% yield, 94:6 *er*



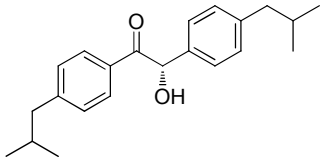
2g, 79% yield, 93:7 *er*



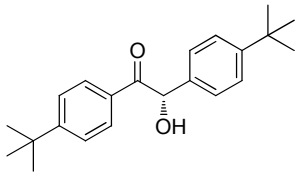
2h, 64% yield, 94:6 *er*



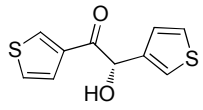
2i, 80% yield, 91:9 *er*



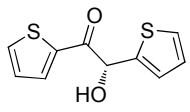
2j, 56% yield, 84:16 *er*



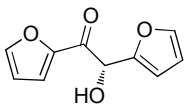
2k, 59% yield, 80:20 *er*



2l, 52% yield, 90:10 *er*



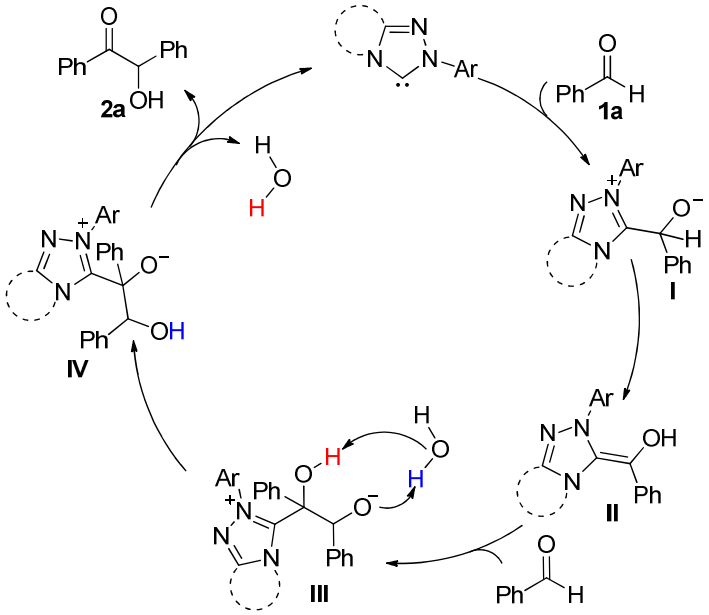
2m, 55% yield, 90:10 *er*



2n, 57% yield, 84:16 *er*

not change the reaction result in terms of yields and enantioselectivities (**2m** and **2n**). A thiophene-3-yl heteroaryl was also well tolerated, giving the yield and enantioselectivity (**2l**) similar to those of thiophene-2-yl aldehyde (**2m**). The absolute configuration of the benzoin condensation products was confirmed to be S (with exception of **2m** for R) by comparison with the optical rotation data reported in the literature.[17]

Figure 1. Proposed Mechanism and Water Was Proposed as a Proton Shuttle



To understand the asymmetric benzoin condensation reaction in aqueous conditions, we proposed a mechanism (Figure 1). In which, the addition of NHC to benzaldehyde (**1a**) provides a zwitterion of triazolium salt adduct **I**. The proton transfer from carbon to oxygen leads to the formation of an enol-type Breslow intermediate **II**. The Breslow intermediate **II** is actually an acylation reagent, which reacts with another benzaldehyde **1a** to provide an intermediate **III**. Water was deemed to be a proton shuttle in a 1,4-H shift process by simultaneously providing one proton to the oxygen and obtaining another from the hydroxyl group to give an intermediate **IV**. This is followed by the regeneration of the NHC catalyst and elimination of the benzoin product **2a**. As such, when dichloromethane was

employed as a solvent, a low yield of 40% was obtained in contrast to a higher yield of 75% when the reaction was carried out in water. Furthermore, when brine was selected as the solvent, the reaction could be accelerated slightly in 85% yield, thereby indicating the presence of a hydrophobic effect.[16]

In conclusion, an asymmetric benzoin condensation reaction of benzaldehydes in water has been developed. This transformation provides rapid access to optically enriched α-hydroxy carbonyl products that are found common in bioactive compounds. Water was proposed as a proton shuttle in the aqueous asymmetric condensation reaction.

Experimental Section

^{1}H and ^{13}C NMR spectra were measured at 500 and 125 MHz, respectively. The solvent used for NMR spectroscopy was $CDCl_3$, using tetramethylsilane as the internal reference. HRMS (Quadrupole, ESI, m/z) was determined by an HRMS/MS instrument. Analytical grade solvents for the column chromatography were used after distillation, and commercially available reagents were used as received.

To a 10 mL vial was added 2.0 mL water, aldehyde (21.2 mg, 0.20 mmol, 1.0 equiv), cat. E (9.3 mg, 0.02 mmol, 10 mol%) and Na_2CO_3 (10.5 mg, 0.10 mmol, 0.5 equiv). Then the resulting solution was stirred under at room temperature, until complete disappearance of the starting material monitored by TLC. The reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography using EtOAc/PE = 1:15 as eluent to afford the desired product **2**.

(S)-2-hydroxy-1,2-diphenylethan-1-one (2a).[17a] White solid, 75% yield (15.9 mg), reaction time 8 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, J = 8.4, 1.3 Hz, 2H), 7.54 – 7.49 (m, 1H), 7.39 (*t*, J = 7.8 Hz, 2H), 7.35 – 7.29 (m, 4H), 7.29 – 7.26 (m, 1H), 5.95 (d, J = 6.1 Hz, 1H), 4.55 (d, J = 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 139.3, 134.6, 133.8, 129.5, 129.5, 129.0, 128.9, 128.1, 76.6. HRMS

m/z calculated for $C_{14}H_{11}O_2$ $[M-H]^-$: 211.0765, found: 211.0758. HPLC: Chiralcel OD (n-hexane/i-PrOH, 90/10, flow rate 0.7 mL/min, λ= 254 nm), t_R (major) = 18.2 min, t_R (minor) = 13.3 min; 93:7 *er*, $[\alpha]_D^{25}$ = +94.5 (*c* = 0.50, $CHCl_3$); lit[17a]: > 99.5:0.5 *er*, $[\alpha]_D^{22}$ = +123.3 (*c* = 1.51, MeOH) for (S)-**2a**. Melting point: 116 - 117 °C.

(S)-1,2-bis(4-fluorophenyl)-2-hydroxyethan-1-one (2b).[17b] White solid, 28% yield (6.5 mg), reaction time 19 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.81 (m, 2H), 7.35 – 7.26 (m, 2H), 7.14 – 6.94 (m, 4H), 5.90 (s, 1H), 4.51 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 15.8 (d, *J* = 422.1 Hz), 163.8 (d, *J* = 413.3 Hz), 135.2 (d, *J* = 2.5 Hz), 133.1 (d, *J* = 3.8 Hz), 132.2 (d, *J* = 8.8 Hz), 130.0 (d, *J* = 2.5 Hz), 129.9 (d, *J* = 8.8 Hz), 116.52 (d, *J* = 42.84 Hz), 116.5, 75.7. HRMS *m/z* calculated for $C_{14}H_9F_2O_2$ $[M-H]^-$: 247.0576, found: 247.0579. HPLC: Chiralcel IC (n-hexane/i-PrOH, 90/10, flow rate 1 mL/min, λ= 254 nm), t_R (major) = 9.4 min, t_R (minor) = 7.9 min; 90:10 *er*, $[\alpha]_D^{25}$ = +56.8 (*c* = 0.50, $CHCl_3$); lit[17b]: 92:8 *er*, $[\alpha]_D^{26}$ = +98.3 (*c* = 0.6, $CHCl_3$) for (S)-**2b**. Melting point: 78 - 79 °C.

(S)-1,2-bis(4-chlorophenyl)-2-hydroxyethan-1-one (2c). [17b] White solid, 78% yield (21.9 mg), reaction time 6 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.42 – 7.35 (m, 2H), 7.33 – 7.28 (m, 2H), 7.26 – 7.23 (m, 2H), 5.88 (d, *J* = 5.9 Hz, 1H), 4.48 (d, *J* = 5.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 141.1, 137.5, 135.1, 131.9, 130.8, 129.8, 129.6, 129.4, 75.8. HRMS *m/z* calculated for $C_{14}H_9Cl_2O_2$ $[M-H]^-$: 278.9985, found: 278.9991. HPLC: Chiralcel IC (n-hexane/i-PrOH, 90/10, flow rate 1.0 mL/min, λ= 254 nm), t_R (major) = 9.2 min, t_R (minor) = 7.6 min; 89:11 *er*. $[\alpha]_D^{25}$ = +44.0 (*c* = 0.50, $CHCl_3$); lit[17b]: 87:13 *er* $[\alpha]_D^{25}$ = +34.3 (*c* = 0.28, MeOH) for (S)-**2c**. Melting point: 84 - 85 °C.

(S)-1,2-bis(3-chlorophenyl)-2-hydroxyethan-1-one (2d). [17a] White solid, 77% yield (21.6 mg), reaction time 6 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (t, *J* = 1.9 Hz, 1H), 7.74 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.52 (ddd, *J* = 8.0, 2.2, 1.0 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.32 (q, *J* = 1.4 Hz, 1H), 7.28 – 7.26 (m,

2H), 7.20 (dq, *J* = 5.3, 1.7 Hz, 1H), 5.88 (d, *J* = 6.0 Hz, 1H), 4.45 (d, *J* = 6.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 140.6, 135.6, 135.5, 135.1, 134.5, 130.9, 130.5, 129.4, 129.4, 128.2, 127.5, 126.2, 76.0. HRMS *m/z* calculated for $C_{14}H_9Cl_2O_2$ $[M-H]^-$: 278.9985, found: 278.9988. HPLC: Chiralcel IC (n-hexane/i-PrOH, 95/5, flow rate 1.0 mL/min, λ= 254 nm), t_R (major) = 15.4 min, t_R (minor) = 12.7 min; 85:15 *er*, $[\alpha]_D^{25}$ = +29.8 (*c* = 0.50, $CHCl_3$); lit[17a]: 93:7 *er*, $[\alpha]_D^{25}$ = +93.4 (*c* = 1.82, $CHCl_3$) for (S)-**2d**. Melting point: 78 - 79 °C.

(S)-1,2-bis(4-bromophenyl)-2-hydroxyethan-1-one (2e).[17b] White solid, 80% yield (29.4 mg), reaction time 6 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.69 (m, 2H), 7.59 – 7.51 (m, 2H), 7.49 – 7.42 (m, 2H), 7.21 – 7.14 (m, 2H), 5.85 (s, 1H), 4.47 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 138.0, 132.8, 132.6, 132.3, 130.8, 129.9, 129.7, 123.3, 75.9. HRMS *m/z* calculated for $C_{14}H_9Br_2O_2$ $[M-H]^-$: 366.8975, found: 366.8977. HPLC: Chiralcel IC (n-hexane/i-PrOH, 90/10, flow rate 1.0 mL/min, λ= 254 nm), t_R (major) =9.9 min, t_R (minor) = 8.1 min; 90:10 *er*, $[\alpha]_D^{25}$ = +31.64 (*c* = 0.50, $CHCl_3$); lit[17b]: 93:7 *er*, $[\alpha]_D^{25}$ = +14.2 (*c* = 0.50, $CHCl_3$) for (S)-**2e**. Melting point: 93 - 94 °C.

(S)-2-hydroxy-1,2-di-p-tolylethan-1-one (2f).[17b] White solid, 71% yield (17.1 mg), reaction time 10 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2H), 7.19 (dd, J = 14.7, 8.0 Hz, 4H), 7.11 (d, J = 7.8 Hz, 2H), 5.89 (d, J = 6.1 Hz, 1H), 4.53 (d, J = 6.1 Hz, 1H), 2.35 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 145.2, 138.7, 136.7, 131.3, 130.1, 129.7, 129.6, 128.0, 76.1, 22.1, 21.5. HRMS *m/z* calculated for $C_{16}H_{15}O_2$ $[M-H]^-$: 239.1078, found: 239.1070. HPLC: Chiralcel IC (n-hexane/i-PrOH, 90/10, flow rate 1.0 mL/min, λ= 254 nm), t_R(major) = 20.6 min, t_R (minor) = 16.8 min; 94:6 *er*, $[\alpha]_D^{25}$ = +31.6 (*c* = 0.5, $CHCl_3$); lit[17b]: 95.5:4.5 *er*, $[\alpha]_D^{25}$ = +81.0 (*c* = 0.3, $CHCl_3$) for (S)-**2f**. Melting point: 85 - 86 °C.

(S)-2-hydroxy-1,2-di-m-tolylethan-1-one (2g).[17a] White solid, 79% yield (19.0 mg), reaction time 10

h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 6.7 Hz, 2H), 7.07 (d, *J* = 7.5 Hz, 1H), 5.90 (d, *J* = 6.1 Hz, 1H), 4.52 (d, *J* = 6.1 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 139.3, 139.2, 138.9, 135.0, 133.8, 129.9, 129.7, 129.3, 128.8, 128.6, 126.8, 125.3, 76.5, 21.7, 21.7. HRMS *m/z* calculated for $C_{16}H_{15}O_2$ [M-H]$^-$: 239.1078, found: 239.1089. HPLC: Chiralcel IC (n-hexane/i-PrOH, 90/10, flow rate 1.0 mL/min, λ= 254 nm), t_R (major) = 16.3 min, t_R (minor) = 13.9 min; 93:7 *er*, $[\alpha]_D^{25}$ = +70.4 (*c* = 0.50, $CHCl_3$); lit[17a]: 98:2 *er*, $[\alpha]_D^{22}$ = +95.6 (*c* = 1.03, MeOH) for (S)-**2g**. Melting point: 73 - 74 °C.

(S)-1,2-bis(4-ethylphenyl)-2-hydroxyethan-1-one (2h). White solid, 64% yield (17.2 mg), reaction time 10 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.3 Hz, 2H), 7.23 (dd, J = 16.0, 8.1 Hz, 4H), 7.15 (d, J = 8.0 Hz, 2H), 5.90 (d, J = 6.2 Hz, 1H), 4.53 (d, J = 6.2 Hz, 1H), 2.65 (q, J = 7.6 Hz, 2H), 2.59 (q, J = 7.6 Hz, 2H), 1.23 – 1.16 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 151.3, 144.6, 136.9, 131.5, 129.8, 129.0, 128.5, 128.0, 76.2, 29.3, 28.9, 15.7, 15.3. HRMS *m/z* calculated for $C_{18}H_{19}O_2$ [M-H]$^-$: 267.1391, found: 267.1381. HPLC: Chiralcel IC (n-hexane/i-PrOH, 90/10, flow rate 1.0 mL/min, λ= 254 nm), t_R (major) = 19.9 min, t_R (minor) = 16.9 min; 94:6 *er*, $[\alpha]_D^{25}$ = +68.9 (*c* = 0.50, $CHCl_3$); lit[17a]: 97:3 *er*, $[\alpha]_D^{22}$ = +58.8 (*c* = 1.47, MeOH) for (S)-**2h**. Melting point: 88 - 89 °C.

(S)-2-hydroxy-1,2-bis(4-isopropylphenyl)ethan-1-one (2i).[17c] White solid, 80% yield (23.7 mg), reaction time 12 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.81 (m, 2H), 7.27 – 7.23 (m, 4H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.90 (d, *J* = 6.2 Hz, 1H), 4.52 (d, *J* = 6.2 Hz, 1H), 2.87 (dh, *J* = 27.7, 6.9 Hz, 2H), 1.24 – 1.16 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 155.9, 149.6, 137.0, 131.6, 129.8, 128.0, 127.6, 127.2, 76.1, 34.6, 34.1, 24.2, 24.2, 23.9, 23.8. HRMS *m/z* calculated for $C_{20}H_{23}O_2$ [M-H]$^-$: 295.1693, found: 295.1706. HPLC: Chiralcel IC (n-hexane/i-PrOH, 95/5, flow rate 1.0 mL/min, λ= 254 nm), t_R

(major) = 25.6 min, t_R (minor) = 20.8 min; 91:9 *er*, $[\alpha]_D^{25}$ = +20.2 (*c* = 0.50, $CHCl_3$). Melting point: 91 - 92 °C.

(S)-2-hydroxy-1,2-bis(4-isobutylphenyl)ethan-1-one (2j). White solid, 56% yield (18.2 mg), reaction time 12 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.78 (m, 2H), 7.26 – 7.22 (m, 2H), 7.18 – 7.13 (m, 2H), 7.11 – 7.06 (m, 2H), 5.89 (d, *J* = 6.1 Hz, 1H), 4.54 (d, *J* = 6.2 Hz, 1H), 2.47 (d, *J* = 7.2 Hz, 2H), 2.41 (d, J = 7.2 Hz, 2H), 1.76 – 1.89 (m, 2H), 0.86 (dd, *J* = 8.4, 6.6 Hz, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.9, 148.9, 142.5, 136.9, 131.6, 130.2, 129.7, 129.5, 127.9, 76.2, 45.8, 45.4, 30.5, 30.3, 22.7, 22.7. HRMS *m/z* calculated for $C_{22}H_{27}O_2$ $[M-H]^-$: 323.2017, found: 323.2034. HPLC: Chiralcel IC (n-hexane/i-PrOH, 95/5, flow rate 1.0 mL/min, λ= 254 nm), t_R (major) = 14.1 min, t_R (minor) = 11.7 min; 84:16 *er*. $[\alpha]_D^{25}$ = +29.8 (*c* = 0.50, $CHCl_3$). Melting point: 94 - 95 °C.

(S)-1,2-bis(4-(tert-butyl)phenyl)-2-hydroxyethan-1-one (2k).[17a] White solid, 59% yield (19.1 mg), reaction time 12 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 5.91 (d, J = 5.0 Hz, 1H), 4.51 (d, J = 6.2 Hz, 1H), 1.29 (s, 9H), 1.27 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 158.1, 151.8, 136.6, 131.2, 129.6, 127.7, 126.4, 126.0, 76.0, 35.6, 34.9, 31.6, 31.3. HRMS *m/z* calculated for$C_{22}H_{27}O_2$ $[M-H]^-$: 323.2017, found: 323.2043. HPLC: Chiralcel IC (n-hexane/i-PrOH, 95/5, flow rate 1.0 mL/min, λ= 254 nm), t_R (major) = 15.2 min, t_R (minor) = 12.2 min; 80:20 *er*, $[\alpha]_D^{25}$ = +45.6 (*c* = 0.50, $CHCl_3$); lit[17a]: 98:2 *er*, $[\alpha]_D^{25}$ = +54.8 (c = 2.37, $CHCl_3$) for (S)-**2k**. Melting point: 111 - 112 °C.

(S)-2-hydroxy-1,2-di(thiophen-3-yl)ethan-1-one (2l).[17d] White solid, 52% yield (11.6 mg) , reaction time 14 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (dd, J = 3.0, 1.3 Hz, 1H), 7.52 (dd, J = 5.2, 1.3 Hz, 1H), 7.33 (dd, J = 3.0, 1.3 Hz, 1H), 7.29 (ddd, J = 5.1, 2.9, 0.9 Hz, 2H), 7.00 (dd, J = 5.0, 1.4 Hz, 1H), 5.84 (d, J = 6.0 Hz, 1H), 4.34 (d, J = 6.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 138.9, 136.9, 133.2,

126.2, 126.1, 125.6, 125.2, 123.2, 71.4. HRMS *m/z* calculated for $C_{10}H_7O_2S_2$ [M-H]$^-$: 222.9893, found: 222.9894. HPLC: Chiralcel IC (n-hexane/i-PrOH, 90/10, flow rate 1.0 mL/min, λ= 254 nm), t_R (major) = 21.5 min, t_R (minor) = 16.9 min; 90:10 *er*. $[\alpha]_D^{25}$ = +67.84 (*c* = 0.50, $CHCl_3$); lit[17d]: > 99.5:0.5 *er*, $[\alpha]_D^{25}$ = -103.96 (*c* = 0.005, $CHCl_3$) for (R)-**2l**. Melting point: 103 - 104 °C.

(R)-2-hydroxy-1,2-di(thiophen-2-yl)ethan-1-one (2m).[17e] White solid, 55% yield (12.3 mg), reaction time 14 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.70 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.30 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.13 – 7.06 (m, 2H), 6.97 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.03 (d, *J* = 6.4 Hz, 1H), 4.35 (d, *J* = 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3, 142.4, 139.6, 135.7, 134.6, 128.7, 127.6, 127.3, 127.2, 72.0. HRMS *m/z* calculated for $C_{10}H_7O_2S_2$ [M-H]$^-$: 222.9893, found: 222.9911. HPLC: Chiralcel IC (n-hexane/i-PrOH, 90/10, flow rate 1.0 mL/min, λ= 254 nm), t_R (major) = 22.2 min, t_R (minor) = 19.7 min; 90:10 *er*, $[\alpha]_D^{25}$ = +22.8 (*c* = 0.50, $CHCl_3$); lit[17e]: 97.5:2.5 *er* for (S)-**2m**, $[\alpha]_D^{25}$ = -380 (*c* = 0.1, $CHCl_3$). Melting point: 114 - 115 °C.

(S)-1,2-di(furan-2-yl)-2-hydroxyethan-1-one (2n).[17d] White solid, 57% yield (11.0 mg), reaction time 12 h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.58 (m, 1H), 7.37 (dd, J = 1.9, 0.9 Hz, 1H), 7.25 (d, J = 3.9 Hz, 1H), 6.54 (dd, J = 3.7, 1.7 Hz, 1H), 6.40 (d, J = 3.3 Hz, 1H), 6.35 (dd, J = 3.3, 1.8 Hz, 1H), 5.80 (s, 1H), 4.18 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.7, 151.6, 150.0, 148.1, 143.5, 120.5, 113.0, 111.1, 109.5, 69.6. HRMS *m/z* calculated for $C_{10}H_7O_4$ [M-H]$^-$: 191.0350; found: 191.0347. HPLC: Chiralcel IA (n-hexane/i-PrOH, 90/10, flow rate 1.0 mL/min, λ= 254 nm), t_R (major) = 16.6 min, t_R (minor) = 20.1 min; 84:16 *er*, $[\alpha]_D^{25}$ = +38.7 (*c* = 0.5, $CHCl_3$); lit[17d]: 98.5:1.5 *er*, $[\alpha]_D^{25}$ = -110.8 (*c* = 0.0066, $CHCl_3$) for R-**2n**. Melting point: 99 - 100 °C.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^{1}H NMR, ^{13}C NMR and HPLC spectra for all the products (**2a**-**2n**) (PDF).

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Notes

The authors declare no competing financial interest.

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