Organocatalytic kinetic resolution *via* intramolecular aldol reactions: Enantioselective synthesis of both enantiomers of chiral cyclohexenones†

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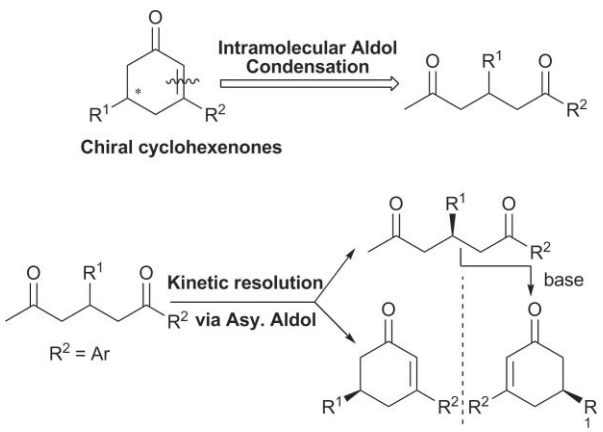
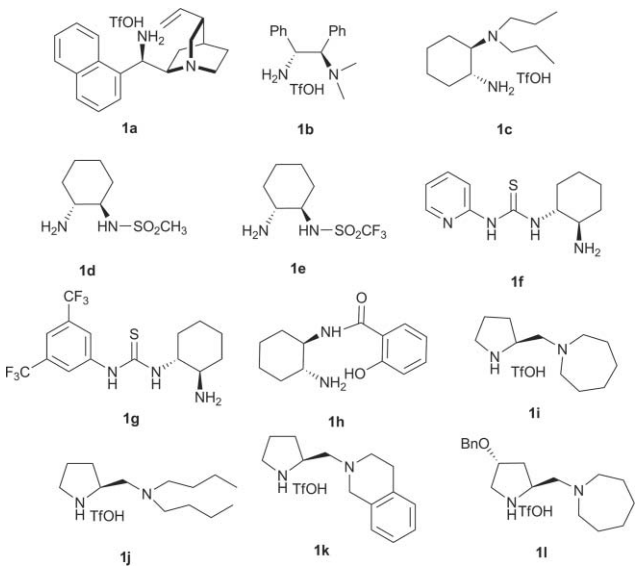
Kinetic resolution of 6-aryl-2,6-hexanediones was achieved with chiral secondary amine catalyzed intramolecular aldolization. The current kinetic resolution protocol enables the synthesis of both enantiomers of cyclohexenones with moderate to good enantioselectivity.

Introduction

Chiral cyclohexenones are versatile chiral building blocks that have been widely utilized in asymmetric natural product synthesis.[1] Retrosynthetically, intramolecular aldol condensation reaction is one of the most straightforward approaches for the synthesis of chiral cyclohexenone skeletons (Scheme 1).[2] One classical example is the Hajos–Parrish–Eder–Sauer–Wiechert reaction[3] which was developed in 1970 s for the synthesis of chiral Wieland–Miescher ketones.[4] Since this seminal work, a number of chiral catalysts have been developed for this and similar reactions that involve cyclohexenone-forming intramolecular aldol steps.[5–8] For example, based on Agami's pioneering work with proline,[5] Lerner and Barbas[6] have examined antibody 38C2 for the same aldol cyclodehydrations with good activity but only low enantioselectivity in the reactions of linear 2,6-heptanediones. Recently, List[7a] and Akiyama[7b] reported respectively chiral primary amine catalyst and chiral phosphoric acid catalyst for asymmetric desymmetrization of 2,6-heptanediones *via* intramolecular aldol condensation. Excellent catalytic activity and enantioselectivity were achieved in both examples. In a manner distinctive to these desymmetrization processes, we presented herein organocatalytic kinetic resolutions of 6-aryl-2,6-hexanediones (*e.g.* R^2 = Ar as shown in Scheme 1) *via* intramolecular aldol condensation for asymmetric synthesis of chiral cyclohexenones.[8,9] After kinetic resolution, the enantioenriched 6-aryl-2,6-hexanediones could be transformed to the same cyclohexenones with opposite chiral induction *via* a separate aldol condensation. Therefore, both enantiomers of chiral cyclohexenones can be obtained from one kinetic resolution (Scheme 1). To the best of our knowledge, such a kinetic resolution *via* intramolecular aldol condensation has not been reported so far.



Scheme 1 Kinetic resolution *via* asymmetric intramolecular aldol reaction.



Results and discussion

As a continuation to our efforts in developing chiral primary aminocatalysis,[10] we first tested a series of chiral primary amines in the kinetic resolution of racemic 6-aryl-2,6-hexanediones **2**.[11] Though good activity was obtained with our previously developed primary-tertiary diamine-Brønsted acid conjugates catalysts such as **1b** and **1c**, the reactions only gave poor resolution as reflected by the generally low $s < 5$ factors (Table 1, entries 2–3).[12] Similar results were obtained with chiral primary amine **1a** (Table 1, entry 1). In these reactions, only cyclodehydration product **3a** was observed. The use of other chiral primary amine catalyst didn't lead to any improvement, and in the cases of primary

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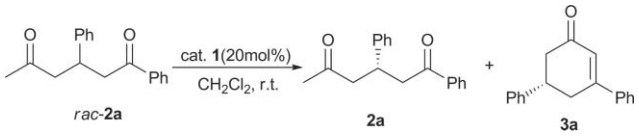
Table 1 Selected results of catalyst screening



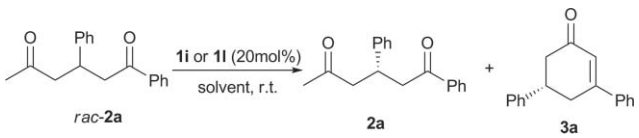
Entry[a]	Cat.	*t*/h	Conversion (%)[b]	ee (**3a**/**2a**,%)[c]	*s*[d]
1	**1a**	68	48	48/34	3
2	**1b**	55	64	20/23	1.5
3	**1c**	27	70	17/13	1.2
4	**1d**	48	N.R	—	—
5	**1e**	56	47	60/41	4
6	**1f**	48	N.R	—	—
7	**1g**	48	N.R	—	—
8	**1h**	42	46	36/37	6
9	**1i**	72	51	63/70	10
10	**1j**	168	33	39/23	0.8
11	**1k**	168	29	54/27	6
12	**1l**	72	45	67/63	15

[a] Reaction concentration: 0.1875 M. [b] Determined by ^{1}H NMR of the reaction mixture. [c] From chiral HPLC analysis. [d] Calculated by the formula $s = \ln(1 - c)(1 - ee_{sm})/\ln(1 - c)(1 + ee_{sm})$, c: convertion, ee_{sm}: ee value of starting material.

amine-thioureas such as **1f** and **1g** and primary amine–amide **1d** there were even no reactions observed (Table 1, entries 4, 6–7). After trials and errors, chiral secondary amines were found to be the catalysts of choice for the current resolution and of a series of chiral secondary amines examined catalyst **1i** and **1l**[13] gave *s* factors above 10 (Table 1, entries 9 and 12).

For practical kinetic processes, *s* factor >20 is generally preferred. We therefore further optimized the reaction conditions with the optimal catalysts **1i** and **1l** (Tables 2 and 3) in terms of solvent, concentration, temperature and additive. Both highly polar solvents such as DMSO and H_2O and nonpolar solvents such as toluene gave poor resolutions with $s < 5$ (Table 2). Chloroform was found to be the optimal solvents for **1l**-catalyzed reactions with a *s* factor 43 (Table 2, entry 7). The reaction could be further

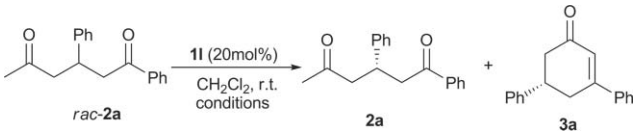
Table 2 Solvent screening



Entry[a]	Cat	Solvent	*t*/h	Conversion (%)[b]	ee (**3a**/**2a**,%)[c]	*s*[d]
1	**1i**	CH_2Cl_2	72	51	63/70	10
2	**1l**	CH_2Cl_2	72	45	67/63	15
3	**1i**	NMP	72	11	64/rac	—
4	**1i**	DMF	72	25	62/37	27
5	**1i**	$PhCH_3$	72	53	36/47	4
6	**1i**	$CHCl_3$	50	35	71/43	14
7	**1l**	$CHCl_3$	72	42	72/66	43
8	**1i**	H_2O	82	10	rac	—
9	**1i**	MeOH	26	81	25/75	3
10	**1i**	CH_3CN	50	61	35/62	4
11	**1i**	DMSO	72	25	66/21	5

[a] Reaction concentration: 0.18 M. [b] Determined by ^{1}H NMR of the reaction mixture. [c] From chiral HPLC analysis. [d] Calculated according to $s = \ln(1 - c)(1 - ee_{sm})/\ln(1 - c)(1 + ee_{sm})$.

Table 3 Reaction optimization



Entry	Condition	*t*/h	Conversion (%)[a]	ee (**3a**/**2a**,%)[b]	*s*[c]
1	0.18 M/r.t.	72	42	72/66	43
2	0.18 M/r.t./4 Å MS	72	51	62/86	29
3	0.38 M/r.t/4 Å MS	60	43	76/66	30
4	0.50 M/r.t./4 Å MS	36	57	57/93	35
5	0.75 M/r.t./4 Å MS	24	56	60/93	19
6	0.38 M/4 °C/4 Å MS	84	41	80/63	39
7	0.50 M/4 °C/4 Å MS	72	47	75/80	48
8	0.75 M/4 °C/4 Å MS	60	46	78/73	28

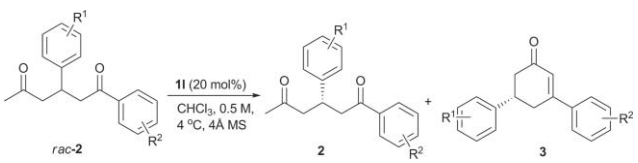
[a] Determined by ^{1}H NMR of the reaction mixture. [b] From chiral HPLC analysis. [c] Calculated by the formula $s = \ln(1 - c)(1 - ee_{sm})/\ln(1 - c)(1 + ee_{sm})$.

accelerated by the addition of 4 Å MS, albeit with a little sacrifice of stereoselectivity (Table 3, entries 1 *vs.* 2). Finally, an optimal *s* factor 48 was achieved using 0.5 M substrate at 4 °C in the presence of 4 Å MS in $CHCl_3$ (Table 3, entry 7).

With optimal conditions established, we next investigated the substrate scopes with different 6-aryl-2,6-hexanediones **2**. In the presence of 20 mol% **1l**, all the examined reactions occurred cleanly to afford the desired cyclohexenones products in 36–59% isolated yields with moderate to good enantioselectivity and the enantioenchriched starting material could be recovered with 36–49% isolated yields and 56–96% ee (Table 4).[14] In all the examined cases, only dehydrated cyclohexenones were obtained and no aldol adducts have been observed.

The absolute configuration of **3a** was determined to be *S* by comparison of optical rotation with literature results (75% ee, $[\alpha]_D^{20} = +20.0$ ($c = 0.5$, CH_2Cl_2); lit.[8a] 99% ee, $[\alpha]_D^{23} = +36.9$ ($c = 2.0$, CH_2Cl_2)). In accordance with previous reports on the

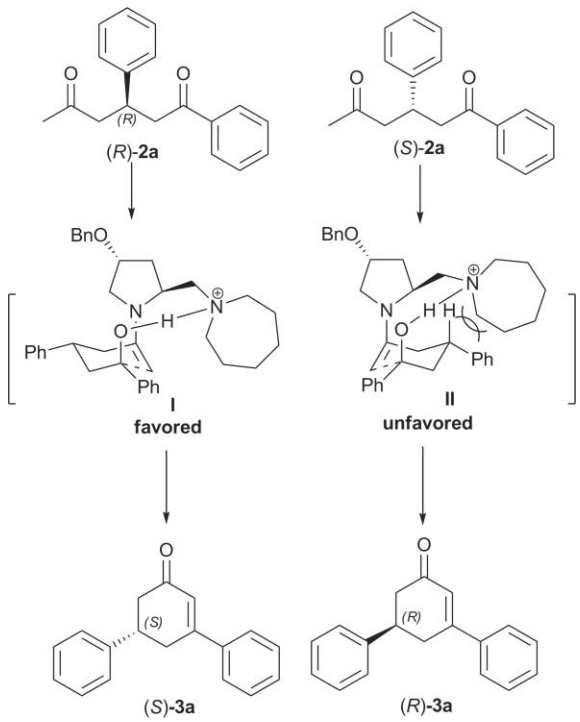
Table 4 Substrate scope



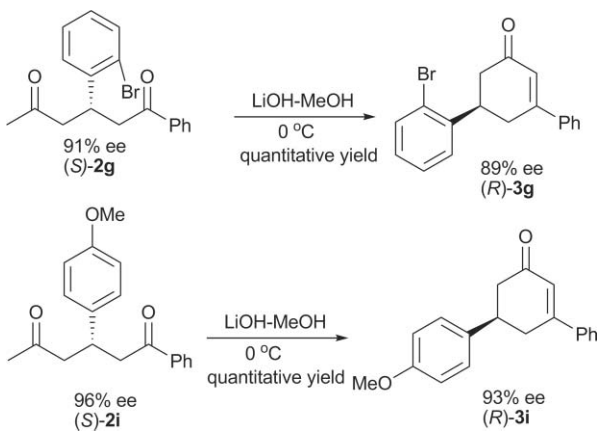
Entry	R^1	R^2	*t*/h	**3** (%)[a]	**2** (%)[b]	ee (**3**/**2**,%)[c]
1	H	H	72	**3a**/47[d]	**2a**/50[d]	75/80
2	3-Cl	4-Br	124	**3b**/54	**2b**/41	46/90
3	2,4-$(OMe)_2$	H	72	**3c**/59	**2c**/41	35/80
4	3-Cl	H	124	**3d**/50	**2d**/43	70/87
5	4-Ph	H	96	**3e**/39	**2e**/36	70/90
6	H	4-Br	72	**3f**/53	**2f**/43	32/90
7	2-Br	H	124	**3g**/43	**2g**/43	75/91
8	4-Cl	H	124	**3h**/39	**2h**/35	82/76
9	4-OMe	H	124	**3i**/59	**2i**/36	66/96
10	2-Cl	H	72	**3j**/50	**2j**/45	55/85
11	H	4-Cl	144	**3k**/50	**2k**/44	66/75
12	4-Cl	4-Cl	48	**3l**/36	**2l**/49	70/56

[a] Isolated yield of **3**. [b] Recovery of starting materials. [c] From chiral HPLC analysis. [d] Determined by ^{1}H NMR of the reaction mixture.

similar reactions,[5] cyclic chair-type transition states **I** and **II** are proposed to account for the observed stereoselectivity (Scheme 2). In this model, (*R*)-**2a** selectively forms (*S*)-**3a** *via* TS-**I**, whereas the cyclic chair TS-**II** derived from (*S*)-**2a** is disfavored due to the steric hindrance. The intramolecular aldol reaction of (*S*)-**2a** is therefore kinetically slow and (*S*)-**2a** is enriched in the resolution process. The enantioenriched (*S*)-**2** compounds could be readily transformed into the desired cyclohexenones (*R*)-**3** with quantitative yields and maintained enantioselectivity by simply treatment with LiOH in methanol (Scheme 3).



Scheme 2 Proposed transition states.



Scheme 3 Transformation of (*S*)-**2** to **3** with LiOH.

Conclusion

In conclusion, we developed a novel kinetic resolution of 6-aryl-2,6-hexanediones *via* chiral secondary amine, *e.g.* **1l**, catalyzed intramolecular aldolization. The resolution reactions afforded cleanly chiral cyclohexenones together with enantioenriched starting hexanediones with moderate to high ee and excellent isolated yields. Simple treatment of the recovered hexanediones with LiOH produced the other enantiomers of cyclohexenones. Overall, the current kinetic resolution protocol enables the synthesis of both enantiomers of cyclohexenones by using a single chiral secondary amine catalyst.

Experimental section

General

Commercial reagents were used as received, unless otherwise stated. ^{1}H and ^{13}C NMR were recorded on a Bruker-DPX 300 spectrometer, and chemical shifts are reported in ppm relative to tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations are used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. All first-order splitting patterns were assigned on the basis of the appearance of themultiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Mass spectra were obtained using a TOF or electrospray ionization (ESI) mass spectrometer. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin-Elmer 341 digital polarimeter and are reported as $[\alpha]_D^{20}$ values (*c* in g per 100 mL of solvent). IR spectra were obtained from Jasco FT/IR-480 Plus instruments; HPLC analysis was performed using Chiralcel OD-H, AS-H and OJ-H columns purchased.

General procedure for the synthesis of catalyst 1l

Catalyst **1l**: was synthesized following previous procedure.[12] $[\alpha]_D^{20}$ = 9.2 (*c* = 1.0, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (9 H, s), 2.03 (1H, q, *J* = 20.3 Hz), 2.29 (1H, s), 2.47 (2H, d, *J* = 6.1 Hz), 2.61–2.73 (4H, m), 3.15 (1H, dd, *J* = 3.1 Hz, *J* = 11.5 Hz), 3.15 (1H, d, *J* = 16.7 Hz), 3.40–3.49 (1H, m), 4.12 (1H, t, *J* = 8.1 Hz), 4.49 (2H, s), 7.25–7.36 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.1, 28.2, 37.0, 52.1, 55.5, 55.9, 63.1, 69.9, 79.6, 127.6, 128.4, 138.5; IR (KBr): 3329, 2923, 2853, 1605, 1497, 1454, 1094, 734, 697 cm^{-1}; HRMS for $C_{18}H_{28}N_2O$ (M+H$^+$), calcd 289.2280, found 289.2267.

Representative procedure for synthesis of substrate 2

Synthesis of 2a. To the solution of chalcone (1.25 g, 6 mmol) and I_2 (30.4 mg, 1.2 mmol) in 60 ml CH_2Cl_2 at 0 °C, allyltrimethylsilane was added very slowly. The mixture was then allowed to warm to room temperature and stirred overnight. Water was added to quench the reaction and the solution was extracted with CH_2Cl_2 3 times. The combined organic layer was washed with 15% solution of sodium thiosulfate and dried over anhydrous Na_2SO_4. After concentrated *in vacuo*, the residue was purified by column chromatography on silica gel to give the allylation product (750 mg, 67% yield). To a three-necked round-bottom flask, $PdCl_2$ (142 mg, 0.8 mmol), CuCl (391.6 mg, 4 mmol) and DMF–H_2O (6 ml/0.72 ml) was added and the solution was saturated with oxygen. The above obtained allylic compound was then added slowly and the resulted solution was stirred for 20 h under the

oxygen atmosphere. After completion as indicated by TLC, the reaction was quenched by the addition of water and the solution was extracted by CH_2Cl_2 for 3 times. The combined organics were washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography on silica gel gave known desired product (520 mg, 70% yield).

General procedure for the intramolecular aldol reactions

To the mixture of racemic compound **2** (0.075 mmol), **1l** (0.015 mmol) and 4 Å MS (10 mg) was added chloroform 150 μl at rt and the resulted solution was stirred at 4 °C. The reaction was monitored by TLC or ^{1}H NMR till *ca.* 50% conversion of substrate **2**. The reaction mixture was then directly loaded onto a silica gel column to afford the desired product **3** (ethyl acetate/petroleum ether = 1 : 8) and the remaining substrate **2** (ethyl acetate/petroleum ether = 1 : 4). Alternatively, the reaction mixture was first treated with sat. NH_4Cl to quench the reaction and the organic layer was separated and purified by flash chromatography after concentration.

General procedure for transformation of (*S*)-2 to 3 with LiOH

To the isolated unreacted (*S*)-**2** in MeOH, was added LiOH (10% in methanol, 150 μl) at 0 °C. The reaction was monitored by TLC. When the reaction was completed, the reaction mixture was directly loaded onto a silica gel column to afford the desired product **3** (ethyl acetate/petroleum ether = 1 : 8) in quantitative yield.

2a,[15a] **2i**,[15b] **3a**,[8a] **3h**,[15c] **3i**,[15d] **3k**[15e] and **3l**[15c,15e] are known compounds.

2b. The corresponding compound was obtained according to above procedure in 35% yield. $[\alpha]_D^{20}$ = +2.0 (*c* = 0.4, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (3H, s), 2.80 (1H, dd, *J* = 7.1 Hz, *J* = 17.1 Hz), 2.91 (1H, dd, *J* = 6.9 Hz, *J* = 17.1 Hz), 3.21 (1H, dd, *J* = 7.2 Hz, *J* = 16.7 Hz), 3.32 (1H, dd, *J* = 6.7 Hz, *J* = 16.7 Hz), 3.84 (1H, p, *J* = 6.9 Hz), 7.11–7.28 (4H, m), 7.58 (2H, d, *J* = 8.5 Hz), 7.77 (2H, d, *J* = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4, 36.2, 44.4, 49.27, 125.8, 127.0, 127.5, 128.5, 129.6, 129.9, 132.0, 134.4, 135.4, 145.7, 197.0, 206.6; IR (KBr): 1713, 1687, 1585, 812, 783, 696 cm^{-1}. HRMS for $C_{18}H_{17}BrClO_2$ (M+H$^+$), calcd. 379.0100, found 379.0099; enantioselective excess was determined to be 93% by chiral HPLC (Chiralpak OD-H, 2-propanol: hexane = 20 : 80, 25 °C, 0.5 mL min^{-1}, t_R = 9.67 min (minor), t_R = 11.60 min (major)).

2c. The corresponding compound was obtained according to above procedure in 40% yield. $[\alpha]_D^{20}$ = +7.6 (*c* = 0.5, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (3H, s), 2.86 (1H, dd, *J* = 7.4 Hz, *J* = 16.3 Hz), 2.95 (1H, dd, *J* = 6.9 Hz, *J* = 16.3 Hz), 3.30 (2H, d, *J* = 7.0 Hz), 3.78 (3H, s), 3.79 (3H, s), 4.10 (1H, p, *J* = 7.0 Hz), 6.40 (2H, dd, *J* = 2.4 Hz, *J* = 9.7 Hz), 7.07 (1H, d, *J* = 8.7 Hz), 7.41–7.45 (2H, m), 7.51–7.56 (1H, m), 7.94 (2H, dd, *J* = 1.5 Hz, *J* = 18.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.1, 31.9, 43.5, 48.2, 55.3, 55.3, 98.9, 104.0, 123.6, 128.2, 128.2, 128.9, 132.9, 137.0, 157.9, 159.5, 199.3, 208.2; IR (KBr): 1711, 1679, 1611, 1587, 1504, 1449, 835, 755, 691 cm^{-1}; HRMS for $C_{20}H_{22}O_4$ (M+H$^+$), calcd. 327.1596, found 327.1606; enantioselective excess was determined to be 80% by chiral HPLC (Chiralpak AS-H, 2-propanol: hexane=20 : 80, 25 °C, 0.5 mL min^{-1}, t_R = 24.63 min (minor), t_R = 29.22 min (major)).

2d. The corresponding compound was obtained according to above procedure in 40% yield. $[\alpha]_D^{20}$ = +2.4 (*c* = 0.5, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (3H, s), 2.81 (1H, dd, *J* = 7.4 Hz, *J* = 16.9 Hz), 2.93 (1H, dd, *J* = 6.6 Hz, *J* = 16.9 Hz), 3.25 (1H, dd, *J* = 7.0 Hz, *J* = 16.8 Hz), 3.39 (1H, dd, *J* = 7.0 Hz, *J* = 16.8 Hz), 3.87 (1H, p, *J* = 6.9 Hz), 7.13–7.25 (4H, m), 7.42–7.47 (2H, m), 7.53–7.58 (1H, m), 7.89–7.92 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.3, 36.3, 44.5, 49.3, 125.9, 126.9, 127.5, 128.1, 128.6, 129.9, 133.2, 134.4, 136.7, 145.9, 198.0, 206.6; IR(KBr): 1713, 1686, 1596, 1573, 1447, 782, 754, 693 cm^{-1}. HRMS for $C_{18}H_{18}ClO_2$ (M+H$^+$), calcd. 301.0995, found 301.1007; enantioselective excess was determined to be 87% by chiral HPLC (Chiralpak AS-H, 2-propanol: hexane=20 : 80, 25 °C, 0.5 mL min^{-1}, t_R = 23.34 min (major), t_R = 27.46 min (minor)).

2e. The corresponding compound was obtained according to above procedure in 37% yield. $[\alpha]_D^{20}$ = +3.0 (*c* = 0.5, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11 (3H, s), 2.89 (1H, dd, *J* = 7.5 Hz, *J* = 16.7 Hz), 2.99 (1H, dd, *J* = 6.7 Hz, *J* = 16.7 Hz), 3.30–3.46 (2H, m), 3.97 (1H, p, *J* = 7.0 Hz), 7.30–7.35 (3H, m), 7.41 (2H, d, *J* = 7.7 Hz), 7.46 (2H, d, *J* = 7.8 Hz), 7.50–7.57 (5H, m), 7.94 (2H, d, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4, 36.4, 44.8, 49.6, 127.0, 127.2, 127.4, 127.8, 128.1, 128.6, 128.7, 133.2, 136.8, 139.6, 140.8, 142.8, 198.5, 207.26; IR (KBr): 1710.6, 1686.4, 1594.8, 1580.4, 1486.9, 1449, 840, 766, 692 cm^{-1}; HRMS for $C_{24}H_{23}O_2$ (M+H$^+$), calcd. 343.1698, found 343.1703; enantioselective excess was determined to be 90% by chiral HPLC (Chiralpak AS-H, 2-propanol: hexane=20 : 80, 25 °C, 0.5 mL min^{-1}, t_R = 25.34 min (major), t_R = 27.90 min (minor)).

2f. The corresponding compound was obtained according to above procedure in 35% yield. $[\alpha]_D^{20}$ = −2.0 (*c* = 0.5, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11 (3H, s), 2.82 (1H, dd, *J* = 6.8 Hz, *J* = 13.9 Hz), 2.95 (1H, dd, *J* = 7.1 Hz, *J* = 16.8 Hz), 3.24 (1H, dd, *J* = 7.1 Hz, *J* = 16.4 Hz), 3.35 (1H, dd, *J* = 6.9 Hz, *J* = 16.4 Hz), 3.87 (1H, p, *J* = 7.0 Hz), 7.17–7.23 (4H, m), 7.28–7.32 (1H, m), 7.57 (2H, dd, *J* = 2.2 Hz, *J* = 7.7 Hz), 7.77 (2H, dd, *J* = 1.8 Hz, *J* = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4, 36.8, 44.8, 49.6, 126.9, 127.3, 128.3, 128.7, 129.7, 131.9, 135.5, 143.4, 197.6, 207.2; IR (KBr): 1713, 1683, 1584, 1494, 1453, 813, 759, 700 cm^{-1}; HRMS for $C_{18}H_{18}BrO_2$ (M+H$^+$), calcd. 345.0490, found 345.0491; enantioselective excess was determined to be 90% by chiral HPLC (Chiralpak OD-H, 2-propanol: hexane=20 : 80, 25 °C, 1.0 mL min^{-1}, t_R = 11.06 min (minor), t_R = 12.89 min (major)).

2g. The corresponding compound was obtained according to above procedure in 37% yield. $[\alpha]_D^{20}$ = −22.4 (*c* = 0.5, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (3H, s), 2.84–3.01 (2H, m), 3.37 (2H, dd, *J* = 1.0 Hz, *J* = 6.6 Hz), 4.31–4.40 (1H, m), 7.03–7.09 (1H, m), 7.24–7.27 (2H, m), 7.42–7.47 (2H, m), 7.53–7.57 (2H, m), 7.93–7.96 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.0, 35.9, 43.1, 48.0, 124.4, 127.7, 128.0, 128.1, 128.6, 133.2, 133.4, 136.7, 142.3, 198.2, 207.1; IR (KBr): 1713, 1684, 1597, 1447, 752, 690 cm^{-1}. HRMS for $C_{18}H_{18}BrO_2$ (M+H$^+$), calcd 345.0490, found 345.0508; enantioselective excess was determined to be 90% by chiral HPLC (Chiralpak AS-H, 2-propanol: hexane = 20 : 80,

25 °C, 0.5 mL min^{-1}, t_R = 21.09 min (minor), t_R = 24.55 min (major)).

2h. The corresponding compound was obtained according to above procedure in 40% yield. $[\alpha]_D^{20}$ = +2.0 (c = 0.5, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11 (3H, s), 2.82 (1H, dd, J = 7.5 Hz, J = 16.9 Hz), 2.94 (1H, dd, J = 6.7 Hz, J = 16.9 Hz), 3.26 (1H, dd, J = 7.2 Hz, J = 16.7 Hz), 3.36 (1H, dd, J = 6.8 Hz, J = 16.7 Hz), 3.89 (1H, p, J = 7.0 Hz), 7.18–7.26 (4H, m), 7.43–7.48 (2H, m), 7.55–7.60 (1H, m), 7.91–7.94 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4, 36.0, 44.6, 49.5, 128.1, 128.6, 128.7, 128.8, 132.4, 133.3, 136.7, 142.2, 198.1, 206.8; IR (KBr): 1580, 1495, 1447, 813, 752, 689 cm^{-1}; HRMS for $C_{18}H_{18}ClO_2$ (M+H$^+$), calcd. 301.0995, found 301.1011; enantioselective excess was determined to be 76% by chiral HPLC (Chiralpak OD-H, 2-propanol: hexane = 20 : 80, 25 °C, 0.5 mL min^{-1}, t_R = 15.37 min (major)), t_R = 16.08 min (minor)).

2j. The corresponding compound was obtained according to above procedure in 38% yield. $[\alpha]_D^{20}$ = −11.2 (c = 0.5, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12 (3H, s), 2.84–3.01 (2H, m), 3.36–3.38 (2H, dd, J = 1.7 Hz, J = 7.1 Hz), 4.31–4.40 (1H, m), 7.10–7.22 (2H, m), 7.25–7.28 (1H, m), 7.35 (1H, dd, J = 1.5 Hz, J = 7.7 Hz), 7.41–7.46 (2H, m), 7.52–7.57 (1H, m), 7.93 (2H, dd, J = 1.6 Hz, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.1, 33.4, 42.9, 47.8, 127.1, 127.9, 128.1, 128.3, 128.6, 130.1, 133.2, 133.6, 136.7, 140.6, 198.3, 207.1; IR (KBr): 1713, 1683, 1597, 1447, 751, 689 cm^{-1}. HRMS for $C_{19}H_{21}ClO_3$ (M+Na$^+$), calcd. 319.1334, found 319.1331; enantioselective excess was determined to be 85% by chiral HPLC (Chiralpak OJ-H, 2-propanol: hexane = 20 : 80, 25 °C, 1.0 mL min^{-1}, t_R = 17.19 min (minor), t_R = 27.29 min (major)).

2k. The corresponding compound was obtained according to above procedure in 41% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (3H, s), 2.85 (1H, dd, J = 7.1 Hz, J = 16.7 Hz), 2.95 (1H, dd, J = 7.0 Hz, J = 16.8 Hz), 3.25 (1H, dd, J = 7.2 Hz, J = 16.4 Hz), 3.35 (1H, dd, J = 6.8 Hz, J = 16.4 Hz), 3.87 (1H, p, J = 7.0 Hz), 7.18–7.32 (5H, m), 7.41 (2H, dd, J = 2.0 Hz, J = 8.7 Hz), 7.84–7.88 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4, 36.8, 44.8, 49.6, 126.8, 127.4, 128.7, 128.9, 129.6, 135.2, 139.5, 143.5, 197.3, 207.2; IR (KBr): 1714, 1684, 1589, 1494, 1453, 816, 761, 700 cm^{-1}; HRMS for $C_{18}H_{18}ClO_2$ (M+H$^+$), calcd. 301.0995, found 301.1006; enantioselective excess was determined to be 75% by chiral HPLC (Chiralpak AS-H, 2-propanol: hexane = 20 : 80, 25 °C, 0.5 mL min^{-1}, t_R = 24.40 min (major), t_R = 28.45 min (minor)).

2l. The corresponding compound was obtained according to above procedure in 42% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.11 (3H, s), 2.81(1H, dd, J = 7.1 Hz, J = 17.0 Hz), 2.93 (1H, dd, J = 6.9 Hz, J = 17.0 Hz), 3.21 (1H, dd, J = 7.4 Hz, J = 16.6 Hz), 3.34 (1H, dd, J = 6.6 Hz, J = 16.6 Hz), 3.85 (1H, p, J = 7.0 Hz), 7.19 (2H, dd, J = 2.0 Hz, J = 7.5 Hz), 7.24–7.28 (2H, m), 7.43 (2H, dd, J = 1.7 Hz, J = 6.9 Hz), 7.86 (2H, d, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4, 36.0, 44.5, 49.5, 128.8, 129.0, 129.4, 129.5, 132.5, 135.0, 139.7, 142.0, 197.0, 206.8; IR (KBr): 1710, 1686, 1589, 1495, 811 cm^{-1}; HRMS for $C_{18}H_{17}Cl_2O_2$ (M+H$^+$), calcd. 335.0606, found 335.0606; enantioselective excess was determined to be 56% by chiral HPLC (Chiralpak OD-H, 2-propanol: hexane = 20 : 80, 25 °C, 1.0 mL min^{-1}, t_R = 8.05 min (minor), t_R = 8.87 min (major)).

3b. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.63–2.81 (2H, m), 2.83–3.04 (2H, m), 3.39–3.49 (1H, m), 6.49 (1H, d, J = 2.0 Hz), 7.17–7.20 (1H, m), 7.28–7.34 (3H, m), 7.41 (2H, d, J = 8.6 Hz), 7.55 (2H, d, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.9, 40.7, 43.6, 124.7, 125.0, 125.4, 127.1, 127.4, 127.7, 130.2, 132.1, 134.7, 137.1, 145.0, 157.0, 198.3; IR (KBr): 1656, 1597, 1582, 1491, 1431, 1262, 805, 779 cm^{-1}; HRMS for $C_{18}H_{15}BrClO$ (M+H$^+$), calcd. 360.9995, found 360.9993; Enantioselective excess was determined to be 46% by chiral HPLC (Chiralpak OD-H, 2-propanol: hexane = 20 : 80, 25 °C, 1.0 mL min^{-1}, t_R = 19.48 min (major), t_R = 22.65 min (minor)).

3c. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.67–2.86 (2H, m), 2.89–3.08 (2H, m), 3.70–3.80 (1H, m), 3.84 (6H, s), 6.52 (3H, d, J = 2.5 Hz), 7.16 (1H, d, J = 9.1 Hz), 7.43 (3H, t, J = 6.4 Hz), 7.57–7.60 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.7, 34.7, 42.9, 55.3, 55.4, 98.9, 104.1, 123.8, 125.0, 126.2, 127.5, 128.8, 130.0, 138.7, 158.2, 159.6, 159.8, 200.3; IR (KBr): 1655, 1612, 1587, 1506, 1446, 1263, 840, 690 cm^{-1}; HRMS for $C_{20}H_{21}O3$ (M+H$^+$), calcd. 309.1941, found 309.1488; enantioselective excess was determined to be 35% by chiral HPLC (Chiralpak AS-H, 2-propanol: hexane = 20 : 80, 25 °C, 1.0 mL min^{-1}, t_R = 44.66 min (minor), t_R = 64.70 min (major)).

3d. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64–2.81 (2H, m), 2.86–3.10 (2H, m), 3.39–3.50 (1H, m), 6.52 (1H, d, J = 2.2 Hz), 7.19 (1H, dd, J = 1.8 Hz, J = 1.6 Hz), 7.27–7.34 (3H, m), 7.40–7.45 (3H, m), 7.54–7.57 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.1, 40.7, 43.7, 125.0, 125.2, 126.2, 127.1 127.3, 128.9, 130.2, 130.3, 134.4, 138.2, 145.2, 158.5, 198.6; IR (KBr): 1662, 1605, 1573, 1496, 1446, 1256, 758, 694 cm^{-1}; HRMS for $C_{18}H_{16}ClO$ (M+H$^+$), calcd. 283.0890, found 283.0891; enantioselective excess was determined to be 70% by chiral HPLC (Chiralpak AS-H, 2-propanol: hexane = 20 : 80, 25 °C, 1.0 mL min^{-1}, t_R = 26.74 min (minor), t_R = 39.87 min (major)).

3e. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.74–2.89 (2H, m), 2.95–3.18 (2H, m), 3.49–3.60 (1H, m), 6.58 (1H, d, J = 2.1 Hz), 7.36–7.50 (8H, m), 7.59–7.65 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.4, 40.7, 44.0, 125.2, 126.2, 127.1, 127.3, 127.4, 127.6, 128.9, 128.9, 130.2, 138.4, 140.1, 140.7, 142.3, 158.8, 199.2; IR (KBr): 1658, 1605, 1570, 1486, 1444, 1255, 832, 762, 694 cm^{-1}. HRMS for $C_{24}H_{21}O$ (M+H$^+$), calcd. 325.1592, found 325.1589. Enantioselective excess was determined to be 70% by chiral HPLC (Chiralpak AS-H, 2-propanol: hexane = 20 : 80, 25 °C, 1.0 mL min^{-1}, t_R = 36.60 min (minor), t_R = 53.83 min (major)).

3f. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.67–2.83 (2H, m), 2.85–3.05 (2H, m), 3.40–3.51 (1H, m), 6.49 (1H, d, J = 2.1 Hz), 7.30 (3H, d, J = 7.2 Hz), 7.36–7.43 (4H, m), 7.56 (2H, dd, J = 2.0 Hz, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.2, 41.0, 43.9, 124.6, 125.4, 126.8, 127.2, 127.7, 128.9, 132.1, 137.3, 143.0, 157.3, 199.0; IR (KBr): 1657, 1604, 1586, 1491, 1454, 1263, 808, 766, 700 cm^{-1}. HRMS for $C_{18}H_{16}BrO$ (M+H$^+$), calcd. 327.0385, found 327.0380. Enantioselective excess was determined to be 32% by chiral HPLC (Chiralpak OD-H, 2-propanol: hexane = 20 : 80, 25 °C, 1.0 mL min^{-1}, t_R = 16.46 min (major), t_R = 18.74 min (minor)).

3g. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60–2.72 (2H, m), 2.74–2.81 (1H, m), 3.08 (1H, dd, J = 4.2 Hz, J = 17.6 Hz), 3.83–3.94 (1H, m), 6.45 (1H, d, J = 2.2 Hz), 7.05–7.11 (1H, m), 7.25–7.31 (2H, m), 7.33–7.37 (3H, m), 7.46–7.55 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.8, 39.8, 42.7, 124.4, 125.2, 126.2, 127.3, 128.0, 128.6, 128.9, 130.3, 133.5, 138.3, 141.8, 158.7, 198.8; IR (KBr): 1659, 1601, 1570, 1495, 1444, 1261, 756, 689 cm^{-1}. HRMS for $C_{18}H_{16}BrO$ ($M+H^+$), calcd. 327.0385, found 327.0380. Enantioselective excess was determined to be 75% by chiral HPLC (Chiralpak AS-H, 2-propanol: hexane = 20 : 80, 25 °C, 1.0 mL min^{-1}, t_R = 73.19 min (minor), t_R = 77.66 min (major)).

3j. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68–2.77 (2H, m), 2.80–2.91 (2H, m), 3.13 (1H, dd, J = 4.7 Hz, J = 17.6 Hz), 3.93–4.04 (1H, m), 6.52 (1H, d, J = 2.2 Hz), 7.19–7.35 (3H, m), 7.37–7.44 (4H, m), 7.54–7.57 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.6, 37.2, 42.5, 125.2, 126.2, 127.2, 127.4, 128.3, 128.9, 130.1, 130.3, 133.7, 138.3, 140.2, 158.8, 198.9; IR (KBr): 1660, 1600, 1570, 1494, 1444, 1261, 755, 696 cm^{-1}; HRMS for $C_{18}H_{16}ClO$ ($M+H^+$), calcd. 283.0890, found 283.0890; enantioselective excess was determined to be 55% by chiral HPLC (Chiralpak OJ-H, 2-propanol: hexane = 20 : 80, 25 °C, 1.0 mL min^{-1}, t_R = 13.75 min (major), t_R = 14.70 min (minor)).

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