Note

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Asymmetric Organocatalytic Cyclopropanation of Cinnamone Derivatives with Stabilized Sulfonium Ylides

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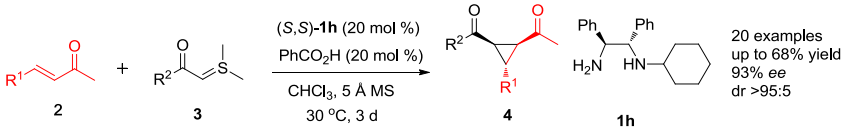


ABSTRACT: A simple chiral diamine catalyst **1h** was successfully applied in the asymmetric cyclopropanation of cinnamone derivatives with stabilized sulfur ylides. The desired cyclopropanation adducts were obtained in moderate yields (up to 68%) with good enantioselectivities (67–93% *ees*) and excellent diastereoselectivities (>95:5) under mild conditions.

Cyclopropanes and their derivatives are common units presented in a large number of biologically active pharmaceutical agents and natural products. They could serve as versatile and important building blocks in organic synthesis because of their unique combination of reactivity and structural properties.[1] Therefore, enormous effort has been invested in diastereo- and enantioselective synthesis of functionalized cyclopropanes. The carbenoid-mediated reactions, such as Lewis acid catalyzed Simmons-Smith type cyclopropanation, and metallocarbenoid-mediated cyclopropanation from diazo compounds, are the most often used.[2] On the other hand, catalytic-ylide-based cyclopropanation has also been employed successfully for this purpose, which could date back to work by Corey in 1965.[3] A variety of ylide species as cyclopropanation reagents has been

developed to construct substituted three-membered carboncyclic rings. Of the methods developed, the catalytic asymmetric cyclopropanation of electron-deficient olefins with ylides is less. The first catalytic asymmetric cyclopropanation of α,β-unsaturated aldehydes with stabilized sulfonium ylides was reported by the MacMillan group based on iminium catalysis.[5a] Chiral dihydroindol derivative was also proven useful.[5b] Zhao's group utilized a diphenylprolinol silyl ether to promote the cyclopropanation between α,β-unsaturated aldehydes and arsonium ylides.[5c] Later, the Shibasaki group successfully accomplished asymmetric cyclopropanation of enones with dimethyloxosulfonium methylide catalyzed by a La-Li(biphenyldiolate)$_3$/NaI complex.[6] Recently, Xiao's group reported C_2-symmetric ureas-catalyzed asymmetric cyclopropanation of β,γ-unsaturated α-ketoesters via a cooperative effect of the hydrogen-bond catalysis.[7] Chiral amine catalysis[8] offers a powerful strategy in useful organocatalysis based on the selective activation of aldehyde. Despite these achievements, little progress has been achieved in the corresponding organocatalytic transformations of cinnamone derivatives, mainly because of the inherent difficulties in generating congested covalent intermediates from amines and ketones.[6, 9] In the mechanism study by Aggarwal's group, it showed that the reactions of stabilized sulfonium ylides with acyclic enones unexpectedly gave low *ee*. Following addition of a stabilized ylide to the Michael acceptor, rapid and reversible intramolecular proton transfer within the betaine intermediate, prior to ring closure, results in an erosion of *ee*.[10] In addition, The activation of α,β-unsaturated ketones with primary amine catalyst toward an iminium-enamine sequence[11] might afford a formal [4+1] addition/cyclization byproduct.[12] Therefore, developing for an efficient catalytic system to generate trisubstituted cyclopropanes in high stereoselectivity is still challenging and interesting. Herein, we describe the first example of organocatalytic asymmetric cyclopropanation of cinnamone derivatives with stabilized sulfonium ylides. In the presence of an easily available chiral primary-secondary diamine catalyst, a series of

1,2,3-trisubstituted cyclopropanes was obtained with good results (up to 65% yield, 93% *ee*, >95:5 dr), meanwhile, a byproduct of 3,4-disubstituted cyclopentanone derivative was detected.

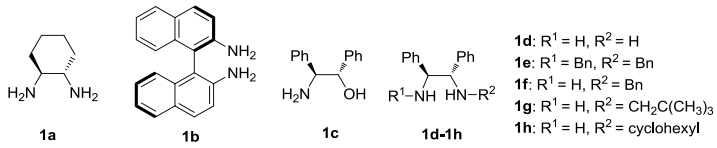
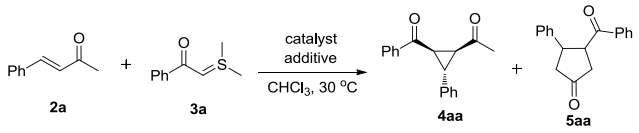


Figure1. Chiral Organocatalysts Used for the Reaction

Table 1. Optimization of the Reaction Conditions



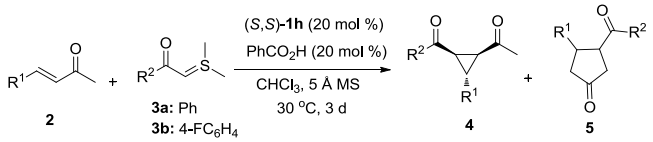
entry[a]	catalyst	additive	yield[b](%)	*ee*[c](%)	*dr*[d]
1	**1a**	$PhCO_2H$	60	49	>95:5
2	**1b**	$PhCO_2H$	No reaction	--	--
3	**1c**	$PhCO_2H$	15	44	>95:5
4	**1d**	$PhCO_2H$	8	73	>95:5
5	**1e**	$PhCO_2H$	trace	--	--
6	**1f**	$PhCO_2H$	40	50	>95:5
7	**1g**	$PhCO_2H$	24	46	>95:5
8	**1h**	$PhCO_2H$	61	85	>95:5
9	**1h**	--	trace	--	--
10	**1h**	TsOH	8	0	--
11	**1h**	AcOH	22	75	>95:5
12	**1h**	HCOOH	55	55	>95:5
13	**1h**	salicylic acid	64	47	>95:5
14[e]	**1h**	$PhCO_2H$/5 Å MS	62	90	>95:5
15[e,f]	**1h**	$PhCO_2H$/5 Å MS	68	90	>95:5

[a] Unless otherwise noted, reactions were carried out with **2a** (0.10 mmol), **3a** (0.12 mmol), diamine (20 mol %) and acidic additive (20 mol %) in $CHCl_3$ (1.0 mL) at 30 °C for 2 days. [b] Isolated yield of the product **4aa**. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR. [e] 5 Å MS (15.0 mg) was added. [f] Reaction time was 3 days.

The cyclopropanation between stabilized sulfonium ylide **3a** with a ketone unit and cinnamone **2a** was used as the model reaction to screen the optimal conditions. We envisioned that the iminium catalysis and hydrogen activation of the two substrates in concert would provide access to the desired products. Firstly,

various chiral diamine catalysts assisted with identical equivalence of benzoic acid were selected for the reaction. Chiral primary diamine catalysts bearing different backbones were investigated. The desired product **4aa** was obtained in 60% yield, 49% *ee*, and >95:5 dr when (*S*,*S*)-cyclohexylenediamine **1a** was used as the catalyst (Table 1, entry 1). Trace amount of five-membered carboncyclic rings product **5aa** was detected as a racemate. Axial chiral binaphthyl diamine **1b** was inert to the cyclopropanation (Table 1, entry 2). The use of chiral amino alcohol **1c** as the catalyst resulted in 15% yield, 44% *ee*, and >95:5 dr (Table 1, entry 3). Excitingly, (*S*,*S*)-1,2-diphenylethylenediamine (Dpen) **1d** showed superior in enantioselectivity (73% *ee*) (Table 1, entry 4). To further improve the reactivity of the reaction, diamine catalysts **1e**–**h**, formed by modification of the primary diamine were introduced. Trace amount of cyclopropanation product was obtained in the presence of secondary diamine **1e.** Primary-secondary diamine catalyst **1h** containing one cyclohexyl substituent showed the best results in both the yield and the enantioselectivity (Table 1, entry 8 vs entries 5–7). Additionally, in the absence of the acidic additive, the product was generated in extremely low yield, which indicated that the acid was crucial in the activation process (Table 1, entry 9 vs entry 8). Other reaction conditions to improve the yield were examined.[13] The acidity of the additive affected the yield and enantioselectivity greatly, and enhancing the acidity led to the loss of the enantiomeric excess (Table 1, entries 10–13). Pleasingly, the addition of 5 Å molecular sieves (MS) improved the *ee* value to 90% *ee* (Table 1, entry 14). Finally, a slight higher yield was achieved when the reaction time was prolonged to 3 days (Table 1, entry 15). It should be noteworthy that in all cases high diastereoselectivity (up to 95:5) was achieved.

Table 2. Asymmetric Cyclopropanations of Sulfonium Ylides with Various Cinnamone Derivatives



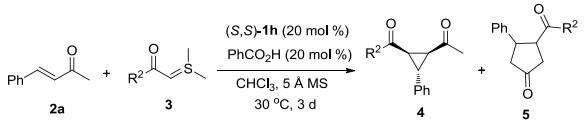
entry[a]	R^1	R^2	**4**	yield[b] (%)	*ee*[c](%)	*dr*[d]
1	Ph	Ph	**4aa**	68(40)	90(98)[f]	>95:5
2[e]	4-FC_6H_4	Ph	**4ba**	63(40)	90(99)[f]	>95:5
3[e]	4-ClC_6H_4	Ph	**4ca**	56(34)	90(98)[f]	>95:5
4[e]	4-BrC_6H_4	Ph	**4da**	53(31)	90(99)[f]	>95:5
5	4-FC_6H_4	4-FC_6H_4	**4bb**	60(38)	92(98)[f]	>95:5
6[e]	4-ClC_6H_4	4-FC_6H_4	**4cb**	57(35)	92(98)[f]	>95:5
7[e]	4-BrC_6H_4	4-FC_6H_4	**4db**	52(30)	93(98)[f]	>95:5
8	3-$CF_3C_6H_4$	4-FC_6H_4	**4eb**	60	89	>95:5
9	4-PhC_6H_4	4-FC_6H_4	**4fb**	61(39)	90(98)[f]	>95:5
10	3-$MeOC_6H_4$	4-FC_6H_4	**4gb**	65	91	>95:5
11		4-FC_6H_4	**4hb**	51	86	>95:5
12	2-naphthyl	4-FC_6H_4	**4ib**	55(33)	88(98)	>95:5
13	2-furyl	4-FC_6H_4	**4jb**	50	90	>95:5
14	*n*-Pr	4-FC_6H_4	**4kb**	67	71	>95:5
15	*i*-Pr	4-FC_6H_4	**4lb**	57	67	>95:5

[a] Unless otherwise noted, reactions were carried out with **2** (0.20 mmol), **3** (0.24 mmol), **1h**/$PhCO_2H$ (1/1, 20 mol %), and 5 Å MS (30.0 mg) in $CHCl_3$ (2.0 mL) at 30 °C for 3 days. [b] Isolated yield of the product **4**, and the yield in parenthesis was that after recrystallization. [c] Determined by chiral HPLC. [d] Determined by ^1H NMR. [e] The yield of **4** was determined by ^1H NMR analysis of the isolated mixture of **4** and **5** which could not be separated. [f] The data in parenthesis was determined after recrystallization.

The optimized reaction conditions were applicable to a variety of cinnamone derivatives with sulfonium ylides **3a** and **3b**. The corresponding cyclopropanation products were gained in moderate yields, good *ee* values and excellent diastereoselectivites (>95:5). In general, moderate yields (51–68%) and good *ee* values (86–93%) were obtained, regardless of the electronic properties of substituents at the aryl group of enones (Table 2, entries 1–11). Notably, a disubstituted cinnamone derivative **2h** was also tolerated in the reaction, although the enantioselectivity of the adduct **4hb** was slightly reduced (86% *ee*, Table 2, entry 11). Optical pure products could be afforded (up to 98% *ee*) after recrystallization procedure. A fused-ring

aromatic-substituted enone, such as **2i**, could also be employed successfully in this transformation, giving the corresponding product **4ib** with 88% *ee* (Table 2, entry 12). Heteroaromatic enone **2j** was a suitable substrate to generate the desired product **4jb** with 90% *ee* (Table 2, entry 13). In addition, *β*-alkyl substituted enones **2k** and **2l** were also investigated, and underwent the reaction well in moderate yields with 71% *ee* and 67% *ee*, respectively (Table 2, entries 14–15).

Table 3. Asymmetric Cyclopropanations of Cinnamone **2a** with Various Sulfonium Ylides



entry[a]	R^2	**4**	yield[b] (%)	*ee*[c](%)	*dr*[d]
1	4-FC_6H_4	**4ab**	65(41)	90(99)[f]	>95:5
2[e]	4-ClC_6H_4	**4ac**	62(40)	91(98)[f]	>95:5
3[e]	4-BrC_6H_4	**4ad**	63(40)	90(98)[f]	>95:5
4	4-$CH_3C_6H_4$	**4ae**	55(32)	89(98)[f]	>95:5
5	2-naphthyl	**4af**	65	89	>95:5

[a] Unless otherwise noted, reactions were carried out with **2a** (0.20 mmol), **3** (0.24 mmol, 1.2 equiv), **1h**/$PhCO_2H$ (1/1, 20 mol %), and 5 Å MS (30.0 mg) in $CHCl_3$ (2.0 mL) at 30 °C for 3 days. [b] Isolated yield of the product **4**, and the yield in parenthesis was that after recrystallization. [c] Determined by chiral HPLC. [d] Determined by ^1H NMR. [e] The yield of **4** was determined by ^1H NMR analysis of the isolated mixture of **4** and **5**. [f] The data in parenthesis was determined after recrystallization.

Significantly, structural variation in the sulfonium ylide components can also be tolerated in the reaction. As shown in Table 3, various sulfonium ylides were proven to be suitable for this catalytic asymmetric cyclopropanation reaction. For example, electron-withdrawing substituents in the benzoyl group of sulfonium ylides **3b**–**d** proceeded well, generating the corresponding products in moderate yields (62–65%) and stereoselectivities (89–91% *ee*s, >95:5 dr) (Table 3, entries 1–3). Introducing an electron-donating group (e.g., methyl) to the benoyl unit of sulfonium ylide **3e** could also give the desired product **4ae** in slightly reduced

yield with 89% *ee* and >95:5 dr (Table 3, entry 4). Moreover, the cyclopropanation of a fused-ring substituted sulfonium ylide **3f** gave the product **4af** in 65% yield and 89% *ee* (Table 3, entry 5). In most cases, five-membered byproducts **5** were detected as nearly racemates.

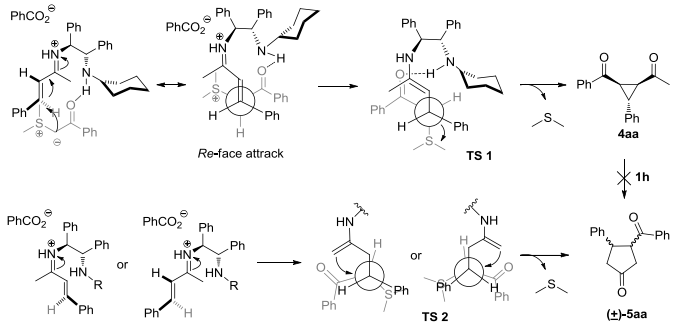
Scheme 1. Gram-Scale Version of Cyclopropanation of Sulfonium Ylide **3a** to Cinnamone **2a**

In order to show the synthetic utility of the catalytic system, a gram-scale synthesis of **4aa** was performed. As shown in Scheme 1, by treatment of **2a** (10.0 mmol) and **3a** (12.0 mmol) under the optimal reaction conditions, the desired product **4aa** was obtained in 60% yield with 90% *ee* and > 95:5 dr. The absolute configuration of the major enantiomer was established by X-ray crystallography analysis as (1*S*,2*R*,3*S*) (Scheme 1).[14]

A bifunctional catalytic model for the cyclopropanation reaction between cinnamone **2a** and sulfonium ylide **3a** was proposed. As shown in Figure 2, the primary moiety associating with the Brønsted acid additive could activate the cinnamone by forming the iminium ion intermediate (Table 1, entry 5). On the other hand, the secondary amine moiety directed the addition of sulfonium ylide through hydrogen bonding. The formation of the Michael adduct by approach of the sulfonium ylide **3a** from the *β-Re*-face of the cinnamone was favored. Finally, the corresponding (1*S*,2*R*,3*S*)-**4aa** as the major product was afforded after an intramolecular S_N2 displacement and release of dimethylsulfane. When the isolated product **4aa** was resubjected to the catalyst system, the cyclopentanone derivative was not detected, which exclude the byproduct formation via vinyl cyclopropane rearrangement, following enolization or enamine formation.

Based on the fact that only racemic *trans*-3,4-disubstituted cyclopentanones were given, we postulated that the side reaction might undergo a single activation model without facial selectivity. Following the addition of sulfonium ylide to the iminium-ion of cinnamon, competitive transformation to enamine intermediates TS2 with the terminal methyl group formed. Subsequently, the intermediate underwent an intramolecular S_N2 displacement to afford a formal [4+1] ylide annulation product as racemate.

Figure 2. Proposed Catalytic Models



In summary, we have developed the first highly enantioselective cyclopropanation of cinnamone derivatives with stabilized sulfonium ylides catalyzed by an easily available primary-secondary diamine. A series of cyclopropanation adducts were obtained in moderate yields (up to 68%) with good enantioselectivities (67–93% *ee*s) and excellent dr values (>95:5) under mind conditions. This strategy provides a potential method for the formation of 1,2,3-trisubstituted cyclopropane compounds.

EXPERIMENTAL SECTION

General Details. Unless otherwise noted, ^{1}H and ^{13}C NMR spectra are internally referenced to residual solvent signals (^{1}H 400 MHz, $CDCl_3$; ^{13}C 100 MHz, $CDCl_3$). Spectra were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Diastereoisomeric ratios were determined by ^{1}H NMR. Enantiomeric excesses (*ee*) were determined by HPLC analysis using chiralpak

columns. Optical rotations were reported as follows: $[a]_D^{25}$ (*c* g/100 mL, CH_2Cl_2). HRMS was recorded on a commercial apparatus (ESI Source: TOF).

Typical Procedure for Asymmetric Cyclopropanation of Cinnamone Derivatives with Stabilized Sulfonium Ylides. Catalyst **1h** (11.8 mg, 0.04 mmol), benzoic acid (4.8 mg, 0.04 mmol), 5 Å (30 mg), sulfonium ylide **3a** (43.2 mg, 0.24 mmol) were mixed in dry $CHCl_3$ (2 mL). After stirring at 30 °C for 0.5 h, cinnamone **2a** (29.2 mg, 0.2 mmol) was added directly. The reaction mixture was stirred at 30 °C for 3 days and purified by flash column chromatography on silica gel (petroleum ether/ethyl ether (6:1) to give the corresponding pure product **4aa** in 68% yield (35.9 mg) as white solid. The diastereoisomer ratio (>95:5) was determined by ^{1}H NMR and enantiomeric excesses (*ee*) were determined by chiral HPLC (Daicel Chirapak IA, hexane/2-propanol 80/20).

1-(2-benzoyl-3-phenylcyclopropyl)ethanone (4aa) 35.9 mg, 68% yield; 90% *ee*; >95:5 dr; (After recrystallization: 21.1 mg, 40% yield; 98% *ee*); white solid: 110–112 °C; $[a]_D^{25}$ = +3.77 (*c* 0.32, CH_2Cl_2) for 98% *ee*; HPLC Daicel chiralpack IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 9.52 min, $t_{(minor)}$ 10.57 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.27 (t, *J* = 7.1 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 2H), 3.37 (t, *J* = 6.1 Hz, 1H), 3.21 (t, *J* = 7.5 Hz, 1H), 2.88 – 2.73 (m, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 194.3, 138.3, 136.9, 133.4, 128.8, 128.7, 128.4, 127.2, 126.4, 39.6, 37.2, 31.1, 30.9, 25.3; HRMS (ESI-TOF) m/z: Calcd for $[C_{18}H_{16}O_2+K]^+$: 303.0782, found: 303.0791.

1-(2-benzoyl-3-(4-fluorophenyl)cyclopropyl)ethanone (4ba) 35.6 mg, 63% yield; 90% *ee*; >95:5 dr; (After recrystallization: 22.6 mg, 40% yield; 99% *ee*); white solid: 136–138 °C; $[a]_D^{25}$ = +7.14 (*c* 0.18, CH_2Cl_2) for 99% *ee*; HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 19.98 min, $t_{(minor)}$ 24.40

min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.52 – 7.40 (m, 4H), 7.09 (d, *J* = 8.2 Hz, 2H), 3.33 (t, *J* = 6.1 Hz, 1H), 3.16 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.77 (dd, *J* = 9.2, 6.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 193.8, 137.4, 136.8, 133.5, 131.9, 128.7, 128.4, 128.2, 121.0, 39.4, 37.1, 30.9, 30.3; HRMS (ESI-TOF) m/z: Calcd for $[C_{18}H_{15}FO_2+K]^+$: 321.0688, found: 321.0675.

1-(2-benzoyl-3-(4-chlorophenyl)cyclopropyl)ethanone (4ca) 33.5 mg, 56% yield; 90% *ee*; >95:5 dr; (After recrystallization: 20.3 mg, 34% yield; 98% *ee*); white solid: 164–166 ^{o}C; $[a]_D^{25}$ = +9.06 (*c* 0.28, CH_2Cl_2) for 98% *ee*; HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 21.40 min, $t_{(minor)}$ 29.94 min.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 0H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.17 (d, *J* = 8.2 Hz, 1H), 3.37 (t, *J* = 6.1 Hz, 0H), 3.18 (dd, *J* = 9.2, 6.4 Hz, 0H), 2.79 (dd, *J* = 9.2, 6.2 Hz, 0H), 2.48 (s, 0H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 193.8, 136.8, 136.8, 133.5, 133.0, 129.0, 128.7, 128.4, 127.8, 39.5, 37.1, 30.9, 30.24; HRMS (ESI-TOF) m/z: Calcd for $[C_{18}H_{15}{}^{34.9689}ClO_2+Na]^+$: 321.0653, found: 321.0664.

1-(2-benzoyl-3-(4-bromophenyl)cyclopropyl)ethanone (4da) 36.4 mg, 53% yield; 90% *ee*; >95:5 dr; (After recrystallization: 21.3 mg, 31% yield; 99% *ee*); white solid: 186–188 ^{o}C; $[a]_D^{25}$ = +7.93 (*c* 0.29, CH_2Cl_2) for 99% *ee*; HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 21.40 min, $t_{(minor)}$ 29.94 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.52 – 7.40 (m, 4H), 7.09 (d, *J* = 8.2 Hz, 2H), 3.33 (t, *J* = 6.1 Hz, 1H), 3.16 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.77 (dd, *J* = 9.2, 6.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 193.8, 137.4, 136.8, 133.5, 131.9, 128.7, 128.4, 128.2, 121.0, 39.4, 37.1, 30.9, 30.3; HRMS (ESI-TOF) m/z: Calcd for $[C_{18}H_{15}{}^{78.9183}BrO_2+Na]^+$: 365.0148, found: 365.0151.

1-(2-(4-fluorobenzoyl)-3-(4-fluorophenyl)cyclopropyl)ethanone (4bb) 36.0 mg, 60% yield; 92% *ee*; >95:5 dr; (After recrystallization: 22.8 mg, 38% yield; 98% *ee*); white solid: 132–134 °C; $[a]_D^{25}$ = +5.29 (*c* 0.45, CH_2Cl_2) for 98% *ee*; HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 16.38 min, $t_{(minor)}$ 18.50 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.22 – 7.09 (m, 4H), 7.04 (t, *J* = 8.6 Hz, 2H), 3.34 (t, *J* = 6.2 Hz, 1H), 3.08 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.76 (dd, *J* = 9.3, 6.1 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 192.4, 131.0, 130.9, 128.1, 128.0, 116.0, 115.869, 115.8, 115.657, 39.4, 36.9, 30.9, 30.3; HRMS (ESI-TOF) m/z: Calcd for $[C_{18}H_{14}F_2O_2+Na]^+$: 323.0854, found: 323.0858.

1-(2-(4-chlorophenyl)-3-(4-fluorobenzoyl)cyclopropyl)ethanone (4cb) 36.1 mg, 57% yield; 92% *ee*; >95:5 dr; (After recrystallization: 22.2 mg, 35% yield; 98% *ee*); white solid: 174–176 °C; $[a]_D^{25}$ = −11.35 (*c* 0.52, CH_2Cl_2) for 98% *ee*; HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 18.53 min, $t_{(minor)}$ 21.01 min.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.95 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.13 (t, *J* = 8.5 Hz, 4H), 3.32 (t, *J* = 6.2 Hz, 1H), 3.09 (dd, *J* = 9.4, 6.3 Hz, 1H), 2.76 (dd, *J* = 9.4, 6.1 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 192.2, 136.6, 133.1, 131.0, 130.9, 129.0, 127.8, 116.0, 115.8, 39.3, 37.0, 30.9, 30.3; HRMS (ESI-TOF) m/z: Calcd for $[C_{18}H_{14}{}^{34.9689}ClFO_2+Na]^+$: 339.0559, found: 339.0562.

1-(2-(4-bromophenyl)-3-(4-fluorobenzoyl)cyclopropyl)ethanone (4db) 37.6 mg, 52% yield; 93% *ee*; >95:5 dr; (After recrystallization: 21.7 mg, 30 % yield; 98% *ee*); white solid: 186–188 °C; $[a]_D^{25}$ = −2.71 (*c* 0.33, CH_2Cl_2) for 98% *ee*; HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 20.24 min, $t_{(minor)}$ 23.17 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.93 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.19 – 7.03 (m, 4H), 3.30 (t, *J* = 6.2 Hz, 1H), 3.09 (dd, *J* = 9.4, 6.3 Hz, 1H), 2.77 (dd, *J* = 9.4, 6.1 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 191.2, 136.2, 130.9, 130.0, 129.9, 127.1, 120.0, 115.0, 114.8, 38.3, 36.0, 29.9, 29.3; HRMS (ESI-TOF) m/z: Calcd for $[C_{18}H_{14}{}^{78.9183}BrFO_2+Na]^+$: 383.0053, found: 383.0058.

1-(2-(4-fluorobenzoyl)-3-(3-(trifluoromethyl)phenyl)cyclopropyl)ethanone (4eb) 42.0 mg, 60% yield; 89% *ee*; >95:5 dr; white solid: 62–64 °C; $[a]_D^{25}$ = −15.0 (*c* 0.10, CH_2Cl_2); HPLC Daicel chiralpack ADH, *n*-hexane/*i*-PrOH 90/10, 1.0 mL/min, $t_{(minor)}$ 10.60 min, $t_{(major)}$ 13.00 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.58 – 7.40 (m, 4H), 7.15 (t, *J* = 8.5 Hz, 2H), 3.42 (t, *J* = 6.1 Hz, 1H), 3.18 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.86 (dd, *J* = 9.3, 6.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 191.9, 139.2, 131.1, 131.0, 130.20, 129.4, 124.1, 124.1, 122.9, 122.9, 116.1, 115.8, 39.4, 36.9, 31.0, 30.2; HRMS (ESI-TOF) m/z: Calcd for $[C_{19}H_{14}F_4O_2+Na]^+$: 373.0822, found: 373.0827.

1-(2-([1,1'-biphenyl]-4-yl)-3-(4-fluorobenzoyl)cyclopropyl)ethanone (4fb) 43.7 mg, 61% yield; 90% *ee*; >95:5 dr; (After recrystallization: 28.0 mg, 39% yield; 98% *ee*); white solid: 174–176 °C; $[a]_D^{25}$ = +4.87 (*c* 0.31, CH_2Cl_2) for 98% *ee*; HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 28.12 min, $t_{(minor)}$ 36.02 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.59 (d, *J* = 7.9 Hz, 4H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.14 (t, *J* = 8.6 Hz, 2H), 3.39 (t, *J* = 6.2 Hz, 1H), 3.18 (dd, *J* = 9.3, 6.3 Hz, 1H), 2.84 (dd, *J* = 9.3, 6.1 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 192.6, 140.5, 140.3, 137.2, 131.1, 131.0, 128.9, 127.6, 127.5, 127.0, 126.8, 116.0, 115.8, 39.5, 37.2, 31.0, 30.9; HRMS (ESI-TOF) m/z: Calcd for $[C_{24}H_{19}FO_2+Na]^+$: 381.1261, found: 381.1266.

1-(2-(4-fluorobenzoyl)-3-(3-methoxyphenyl)cyclopropyl)ethanone (4gb) 40.6 mg, 65% yield; 91% *ee*; >95:5 dr; white solid: 88–90 °C; $[a]_D^{25}$ = −20.70 (*c* 0.31, CH_2Cl_2); HPLC Daicel chiralpack IA, *n*-hexane/*i*-PrOH 70/30, 1.0 mL/min, $t_{(major)}$ 8.10 min, $t_{(minor)}$ 9.34 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.27 (dd, *J* = 8.7, 7.1 Hz, 1H), 7.13 (t, *J* = 8.6 Hz, 2H), 6.80 (m, 3H), 3.82 (s, 3H), 3.31 (t, *J* = 6.2 Hz, 1H), 3.12 (dd, *J* = 9.3, 6.3 Hz, 1H), 2.79 (dd, *J* = 9.3, 6.1 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 203.0, 192.6, 160.0, 139.8, 131.1, 131.0, 129.90, 118.40, 116.0, 115.7, 112.495, 112.4, 55.3, 39.4, 37.1, 31.1, 31.0; HRMS (ESI-TOF) m/z: Calcd for $[C_{19}H_{17}FO_3+K]^+$: 351.0793, found: 351.0792.

1-(2-(benzo[d][1,3]dioxol-5-yl)-3-(4-fluorobenzoyl)cyclopropyl)ethanone (4hb) 33.3 mg, 51% yield; 86% *ee*; >95:5 dr; white solid: 114–116 °C; $[a]_D^{25}$ = −7.0 (*c* 0.10, CH_2Cl_2); HPLC Daicel chiralpack IA, *n*-hexane/*i*-PrOH 70/30, 1.0 mL/min, $t_{(major)}$ 10.83 min, $t_{(minor)}$ 15.72 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.13 (t, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.70 (m, 2H), 5.97 (s, 2H), 3.27 (t, *J* = 6.2 Hz, 1H), 3.05 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.72 (dd, *J* = 9.3, 6.1 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 192.6, 148.2, 146.9, 131.9, 131.1, 131.0, 119.9, 116.0, 115.7, 108.5, 106.7, 101.2, 39.3, 37.0, 31.1, 31.0; HRMS (ESI-TOF) m/z: Calcd for $[C_{19}H_{15}FO_4+K]^+$: 365.0586, found: 365.0583.

1-(2-(4-fluorobenzoyl)-3-(naphthalen-2-yl)cyclopropyl)ethanone (4ib) 36.6 mg, 55% yield; 88% *ee*; >95:5 dr; (After recrystallization: 21.9 mg, 33% yield; 98% *ee*); white solid: 148–150 °C; $[a]_D^{25}$ = −4.0 (*c* 0.10, CH_2Cl_2) for 98% *ee*; HPLC Daicel chiralpack IA, *n*-hexane/*i*-PrOH 90/10, 1.0 mL/min, $t_{(major)}$ 56.77 min, $t_{(minor)}$ 61.77 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.1, 5.7 Hz, 2H), 7.82 (dd, *J* = 13.3, 8.2 Hz, 3H), 7.68 (s, 1H), 7.56 – 7.41 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.13 (t, *J* = 8.5 Hz, 2H), 3.51 (t, *J* = 6.1 Hz, 1H), 3.24 (dd, *J* = 9.1, 6.5 Hz, 1H), 2.92 (dd, *J* = 9.1, 6.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 192.0, 135.5, 133.4, 132.6, 131.1, 131.0, 128.7, 127.7, 127.5, 126.6, 126.0, 125.2, 124.3, 116.0, 115.7, 39.4, 37.2, 31.4, 31.0; HRMS (ESI-TOF) m/z: Calcd for $[C_{22}H_{17}FO_2+K]^+$: 371.0844, found: 371.0846.

1-(2-(4-fluorobenzoyl)-3-(furan-2-yl)cyclopropyl)ethanone(4jb) 27.2 mg, 50% yield; 90% *ee*; >95:5 dr; yellow solid: 112–114 °C; $[a]_D^{25}$ = +9.84 (*c* 0.12, CH_2Cl_2); HPLC Daicel chiralpack ADH, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 11.51 min, $t_{(minor)}$ 12.54 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.3, 5.6 Hz, 2H), 7.31 (s, 1H), 7.14 (t, *J* = 8.5 Hz, 2H), 6.35 (s, 1H), 6.25 (d, *J* = 2.9 Hz, 1H), 3.34 (t, *J*

= 6.0 Hz, 1H), 3.26 (dd, *J* = 9.2, 6.3 Hz, 1H), 2.90 (dd, *J* = 9.3, 6.0 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 192.1, 151.2, 141.5, 131.1, 131.0, 116.0, 115.8, 110.9, 106.8, 37.3, 35.0, 30.9, 24.4; HRMS (ESI-TOF) m/z: Calcd for $[C_{16}H_{13}FO_3+Na]^+$: 295.0741, found: 295.0745.

1-(2-(4-fluorobenzoyl)-3-propylcyclopropyl)ethanone (4kb) 33.3 mg, 67% yield; 71% *ee*; >95:5 dr; yellow solid: 44–46 °C; $[a]_D^{25}$ = +12.74 (*c* 0.42, CH_2Cl_2); HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(minor)}$ 9.98 min, $t_{(major)}$ 11.46 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.89 (m, 2H), 7.10 – 6.99 (m, 2H), 2.58 (dd, *J* = 8.7, 6.6 Hz, 1H), 2.27 – 2.15 (m, 2H), 2.14 – 2.08 (m, 3H), 1.42 (m, 4H), 0.94 – 0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 192.7, 129.8, 129.7, 114.8, 114.6, 37.4, 34.0, 33.5, 29.6, 26.8, 21.0, 12.7; HRMS (ESI-TOF) m/z: Calcd for $[C_{15}H_{17}FO_2+K]^+$: 287.0844, found: 287.0846.

1-(2-(4-fluorobenzoyl)-3-isopropylcyclopropyl)ethanone (4lb) 28.3 mg, 57% yield; 67% *ee*; >95:5 dr; yellow solid: 46–48 °C; $[a]_D^{25}$ = +8.65 (*c* 0.21, CH_2Cl_2); HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(minor)}$ 9.31 min, $t_{(major)}$ 10.28 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 2H), 7.06 (t, *J* = 8.6 Hz, 2H), 2.63 (dd, *J* = 9.2, 6.2 Hz, 1H), 2.24 (dd, *J* = 9.1, 6.4 Hz, 1H), 2.12 (s, 3H), 2.05 (dt, *J* = 8.3, 6.3 Hz, 1H), 1.34 – 1.23 (m, 1H), 1.00 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 193.8, 130.9, 130.8, 115.8, 115.6, 37.7, 35.6, 33.8, 31.6, 30.5, 21.5, 21.4; HRMS (ESI-TOF) m/z: Calcd for $[C_{15}H_{17}FO_2+K]^+$: 287.0844, found: 287.0845.

1-(2-(4-fluorobenzoyl)-3-phenylcyclopropyl)ethanone (4ab) 36.7 mg, 65% yield; 90% *ee*; >95:5 dr; (After recrystallization: 23.1 mg, 41% yield; 99% *ee*); white solid: 102–104 °C; $[a]_D^{25}$ = −6.04 (*c* 0.49, CH_2Cl_2) for 99% *ee*; HPLC Daicel chiralpack IA, *n*-hexane/*i*-PrOH 90/10, 1.0 mL/min, $t_{(major)}$ 18.86 min, $t_{(minor)}$ 20.92 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (t, *J* = 6.2 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 2H), 7.12 (t, *J* = 7.9 Hz, 2H), 3.34 (t, *J* = 6.1 Hz, 1H), 3.13 (t, *J* = 7.8 Hz, 1H), 2.80 (t, *J* =

7.6 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 191.6, 137.1, 130.0, 129.9, 127.8, 126.3, 125.35, 114.9, 114.7, 38.4, 36.1, 30.2, 29.9; HRMS (ESI-TOF) m/z: Calcd for $[C_{18}H_{15}FO_2+K]^+$: 321.0688, found: 321.0691.

1-(2-(4-chlorobenzoyl)-3-phenylcyclopropyl)ethanone (4ac) 37.0 mg, 62% yield; 91% *ee*; >95:5 dr; (After recrystallization: 23.9 mg, 40% yield; 98% *ee*); white solid: 136–138 ^{o}C; $[a]_D^{25}$ = −11.48 (*c* 0.22, CH_2Cl_2) for 98% *ee*; HPLC Daicel chiralpack ADH, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(minor)}$ 17.40 min, $t_{(major)}$ 18.80 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 2H), 3.34 (t, *J* = 6.1 Hz, 1H), 3.12 (dd, *J* = 9.2, 6.4 Hz, 1H), 2.81 (dd, *J* = 9.2, 6.2 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 193.1, 139.9, 138.0, 135.2, 129.8, 129.0, 128.9, 127.3, 126.4, 39.5, 37.1, 31.3, 31.0; HRMS (ESI-TOF) m/z: Calcd for $[C_{18}H_{15}{}^{34.9689}ClO_2+Na]^+$: 321.0653, found: 321.0661.

1-(2-(4-bromobenzoyl)-3-phenylcyclopropyl)ethanone (4ad) 43.2 mg, 63% yield; 90% *ee*; >95:5 dr; (After recrystallization: 27.5 mg, 40% yield; 98% *ee*); white solid: 152–154 ^{o}C; $[a]_D^{25}$ = –17.02 (*c* 028, CH_2Cl_2) for 98% *ee*; HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 21.36 min, $t_{(minor)}$ 25.94 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.29 (d, *J* = 7.1 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 2H), 3.33 (t, *J* = 6.2 Hz, 1H), 3.11 (dd, *J* = 9.3, 6.4 Hz, 1H), 2.81 (dd, *J* = 9.3, 6.1 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 193.3, 138.0, 135.7, 132.0, 129.9, 128.9, 128.6, 127.3, 126.4, 39.5, 37.0, 31.3, 31.0; HRMS (ESI-TOF) m/z: Calcd for $[C_{18}H_{15}{}^{78.9183}BrO_2+Na]^+$: 365.0148, found: 365.0152.

1-(2-(4-methylbenzoyl)-3-phenylcyclopropyl)ethanone (4ae) 30.6 mg, 55% yield; 89% *ee*; >95:5 dr; (After recrystallization: 17.8 mg, 32% yield; 98% *ee*); white solid: 136−138 ^{o}C; $[a]_D^{25}$ = −4.00 (*c* 0.10, CH_2Cl_2)

for 98% *ee*; HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 27.12 min, $t_{(minor)}$ 32.47 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.30 – 7.18 (m, 5H), 3.36 (t, *J* = 6.2 Hz, 1H), 3.18 (dd, *J* = 9.4, 6.3 Hz, 1H), 2.77 (dd, *J* = 9.4, 6.2 Hz, 1H), 2.41 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 193.8, 144.3, 138.4, 134.4, 129.4, 128.8, 128.5, 127.2, 126.4, 39.5, 37.2, 31.0, 30.9, 21.7; HRMS (ESI-TOF) m/z: Calcd for $[C_{19}H_{18}O_2+K]^+$: 317.0938, found: 317.0913.

1-(2-(2-naphthoyl)-3-phenylcyclopropyl)ethanone (4af) 40.9 mg, 65% yield; 89% *ee*; >95:5 dr; (After recrystallization: 25.8 mg, 41% yield; 98% *ee*); white solid: 154–156 °C; $[a]_D^{25}$ = −39.58 (*c* 0.05, CH_2Cl_2) for 98% *ee*; HPLC Daicel chiralpack ID, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{(major)}$ 28.02 min, $t_{(minor)}$ 32.75 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.05 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.98 – 7.84 (m, 3H), 7.58 (dt, *J* = 23.7, 6.9 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.29 (m, 3H), 3.44 (t, *J* = 6.2 Hz, 1H), 3.34 (dd, *J* = 9.4, 6.3 Hz, 1H), 2.88 (dd, *J* = 9.4, 6.2 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 194.1, 138.3, 135.7, 134.3, 132.5, 130.2, 129.6, 128.9, 128.7, 128.6, 127.9, 127.3, 126.9, 126.5, 124.0, 39.6, 37.3, 31.3, 30.9; HRMS (ESI-TOF) m/z: Calcd for $[C_{22}H_{18}O_2+K]^+$: 353.0938, found: 353.0945.

3-benzoyl-4-phenylcyclopentanone (5aa) White solid: 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.24 – 7.10 (m, 5H), 4.14 (q, *J* = 8.6 Hz, 1H), 3.79 (dd, *J* = 18.2, 8.6 Hz, 1H), 2.81 (dd, *J* = 18.6, 8.3 Hz, 1H), 2.65 (m, 2H), 2.53 (dd, *J* = 18.6, 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 199.0, 140.5, 135.1, 132.5, 127.9, 127.7, 127.4, 126.2, 126.0, 49.6, 44.3, 44.0, 41.8; HRMS (ESI-TOF) m/z: Calcd for $[C_{18}H_{16}O_2+Na]^+$: 287.1043, found: 287.1047.

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Supporting Information

Full optimization details, ^{1}H and ^{13}C NMR spectra, HPLC data and CD data are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) CCDC 932350 (**4aa**) contains the supplementary crystallographic data for this paper. The data can

be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.