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Asymmetric Desymmetrization of 1,3-Diketones via Intramolecular Benzoin Reaction

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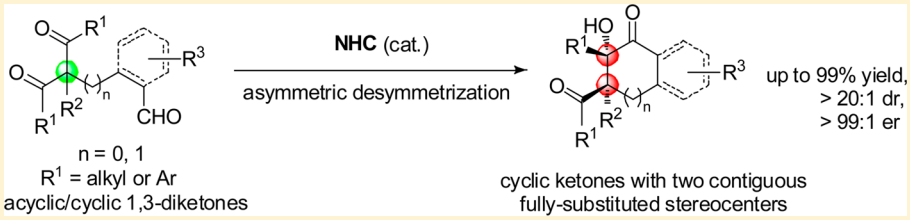
Supporting Information



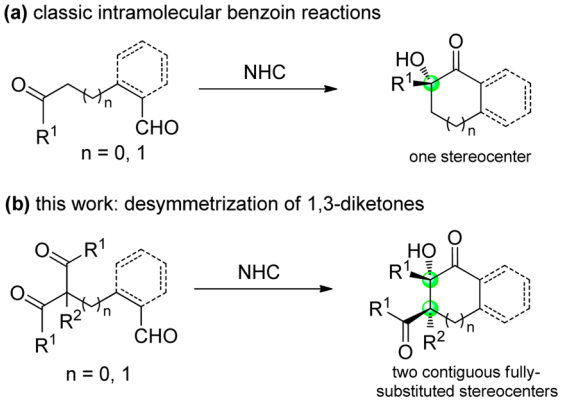
ABSTRACT: A general method for the asymmetric desymmetrization of 1,3-diketone substrates via chiral N-heterocyclic carbene catalyzed intramolecular benzoin reactions was developed. Five- and six-membered cyclic ketones bearing two contiguous fully substituted stereocenters were generated with excellent diastereoselectivities and moderate to excellent enantioselectivities.

INTRODUCTION

Desymmetrization is an unique organic synthesis strategy that has been widely used in the field of asymmetric catalysis. The substrates' ready availability, theoretical 100% yield, and formation of multiple stereogenic centers in one step make this strategy very promising in the field of asymmetric catalysis.[1] Furthermore, desymmetrization has shown special importance in the construction of fully substituted stereocenters.[2] Therefore, a series of catalysts, including both transition metal catalysts and organocatalysts, have been employed to realize the transformations of prochiral substances to chiral molecules through the strategy of desymmetrization.[3]

N-heterocyclic carbene (NHC) catalysis has drawn global research interests in the field of asymmetric catalysis, owning to its unique reaction modes, various activation approaches, and highly selective transformations.[4] Thus, the combination of the desymmetrization and NHC catalysis will certainly provide more opportunities in new methodology development. There have been several reports concerning the NHC catalyzed desymmetrization from the groups of Rovis, Scheidt, You, and Ema.[5] These reactions utilized intramolecular Stetter reaction, enolate mediated aldol reaction, and benzoin reaction to realize the asymmetric transformations of structurally symmetric molecules. To be noted, benzoin reaction (Scheme 1a)[6] is one of the earliest reported and mostly studied reaction types in NHC catalysis, but the potential of the benzoin reaction in asymmetric desymmetrization has not been fully studied. For example, in 2012, Ema and co-workers reported the NHC-catalyzed intramolecular crossed benzoin reaction of symmetrical cyclic 1,3-diketones, with bicyclic compounds formed.[5e] In their work, the substrates scope is limited to cyclic ketones and aliphatic aldehdyes. The usage of commonly seen acyclic 1,3-diketones and aromatic aldehdyes in NHC catalyzed desymmerization through benzoin reaction remains elusive so far. As is known, the acyclic 1,3-diketones have more flexible structure than the rigid cyclo-1,3-diketones, which makes the control of the stereoselectivity more challenging. And the reactivity of aromatic aldehydes in NHC catalyzed reactions is different to that of aliphatic ones in most cases.[4]

Scheme 1. NHC Catalyzed Intramolecular Benzoin Reaction



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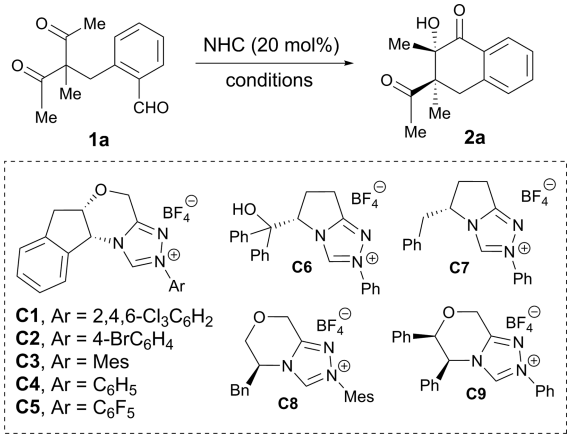
Furthermore, Ema's work employed almost four different conditions to get optimal results, and no general approach was developed. Considering the urgency and necessity of developing a more general approach of NHC catalyzed desymmetric benzoin reaction, we recently conducted the project shown in Scheme 1b. To be noted, the corresponding products are cyclic ketones with multiple stereogenic centers and functional groups, which are widely used synthons in organic synthesis and commonly found key units in natural products and pharmaceuticals.[7]

RESULTS AND DISCUSSION

We started our project with **1a** as the model substrate to optimize the reaction conditions, and the results are shown in Table 1. When Rovis' triazolium salt **C1**[8] was used as the catalyst, DBU as the base, and CH_2Cl_2 as the solvent, the reaction proceeded smoothly to furnish the desired product **2a** in 57% yield and with 81:19 er (Table 1, entry 1). Further catalysts screening indicated that 4-bromophenyl, mesityl, and phenyl substituted catalysts **C2**–**C4**[9] did not show any reactivities (Table 1, entry 2). Rovis catalyst **C5**,[10] with a C_6F_5 substituent, showed better result, and the product was isolated in 80% yield and with 89:11 er (Table 1, entry 3). Then, we examined more solvents such as CH_3CN and toluene, and the latter gave a slightly higher yield (Table 1, entries 4 and 5). Replacement of the base of DBU with organic base (e.g., Et_3N) and inorganic bases (e.g., NaOAc and KOAc) did not show optimal results (Table 1, entries 6–8). Further effort of base screen showed that KHMDS was a good choice, and the product was obtained with 91:9 er (Table 1, entry 9). Then, it was found that lowering the reaction temperature was beneficial for the improvement of the enantioselectivity without decreasing the yield (Table 1, entries 10 and 11). Chiral catalysts **C6**–**C9**[9a,11] were also tested, but they were proved to be ineffective (Table 1, entry 12), so the optimal conditions were finally set at −20 °C; product **2a** can be provided in 95% yield and with 97:3 er (Table 1, entry 11).

Table 1. Condition Optimization[a]



entry	NHC	base	solvent	yield (%)[b]	er[c]
1	**C1**	DBU	CH_2Cl_2	57	81:19
2	**C2**–**C4**	DBU	CH_2Cl_2	trace	-
3	**C5**	DBU	CH_2Cl_2	80	89:11
4	**C5**	DBU	CH_3CN	74	87:13
5	**C5**	DBU	toluene	82	89:11
6	**C5**	NaOAc	toluene	92	87.5:12.5
7	**C5**	KOAc	toluene	87	89.5:10.5
8	**C5**	Et_3N	toluene	94	85.5:14.5
9	**C5**	KHMDS[d]	toluene	87	91:9
10[e]	**C5**	KHMDS[d]	toluene	90	95:5
11[f]	**C5**	KHMDS[d]	toluene	95	97:3
12	**C6**–**C9**	DBU	CH_2Cl_2	trace	-

[a]Reaction condition: **1a** (0.1 mmol), NHC (0.02 mmol), base (0.02 mmol), solvent (2 mL), rt, argon protection, overnight. Diastereomeric ratio was determined by ^{1}H NMR. [b]Isolated yields based on **1a**. [c]Determined via HPLC analysis on a chiral stationary phase; the absolute configuration was determined via X-ray single crystal structure of **2e** (Table 2). [d]1.0 M in toluene. [e]0 °C. [f]−20 °C.

With the optimized conditions in hand, the substrate scope was then evaluated. When R^2 group in substrate **1** was changed from Me to Et or allyl groups, the corresponding products were obtained with quantitative yields and good er (Table 2, **2b** and **2c**). Enantioselectivity dropped to moderate 80.5:19.5 er when substituted 1,3-diethylketone was used as the substrate (Table 2, **2d**). The enantioselective induction was found to be sensitive to the steric bulkiness of the R^2 substituent (similar result was also observed in NHC catalyzed desymmetric enolate reaction[5c]). But excellent yields and good er were observed when the aryl units in substrate **1** were substituted by both electron-rich and electron-poor groups (Table 2, **2e**–**2g**), and the absolute configuration of **2e** was determined via X-ray single crystal structure. The synthesis of chiral fluoro compounds has drawn much attention of organic chemists because of their unique properties in pharmaceuticals, agrochemicals, and medicinal chemistry.[12] We were glad to find that when fluoro atom was introduced into the substrate, the desymmetrization can occur smoothly to afford the chiral fluoro product in 96% yield and with 93.5:6.5 er (Table 2, **2h**). 4-Chromanones widely exist in natural products, and many efforts have been made to synthesize this type of compounds.[13] Our NHC catalyzed desymmetrization strategy can also be applied to the synthesis of fully substituted 4-chromanone derivative, with excellent yield and moderate er obtained (Table 2, **2i**). When 1,3-diphenylketone was used as the substrate, moderate 83:17 er and 45% yield were produced (Table 2, **2j**). To be noted, our method can also be applicable to cyclic 1,3-diketones, with the corresponding products liberated in good to excellent yields and with good er (Table 2, **2k**–**2m**).

To further explore the generality of this method, we then examined the substrates with aliphatic aldehyde moieties. To our delight, the reaction worked well with catalyst **C5** under the slightly modified condition (NaOAc was used as the base in place of KHMDS and the reactions were conducted at room temperature). As shown in Table 3, cyclopentanone **4a** was obtained in good yield and with excellent > 99:1 er (Table 3, **4a**). Enantioselectivites dropped when R^2 group became bigger (Table 3, **4b**–**4c**). But aromatic 1,3-diketones were also good candidates for the asymmetric desymmetrization (Table 3, **4d**–**4f**); in most cases, about 95:5 er was observed. To be noted, product **4e**, with fluoro substituent in phenyl ring, was produced with 1.5:1 dr (Table 3, **4e**), possibly because the strong F–H hydrogen bond[14] was formed in the reaction intermediate. Attempts to get chiral cyclohexanone **4g** were not successful (Table 3, **4g**); starting material remained in most of the conditions we tested.[15]

Versatile derivatizations of the chiral ketone products can be easily accessed (Scheme 2). For example, chemoselective nucleophilic addition of **2a** with Grignard reagent resulted in the formation of 1,3-diol **5a** in 90% yield and with 96.5:3.5 er.

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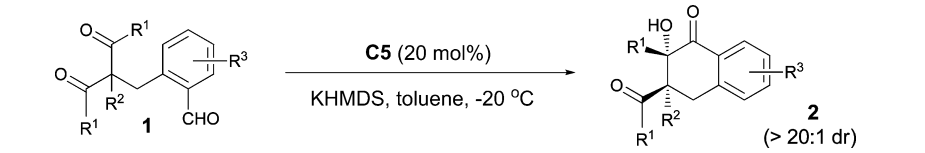
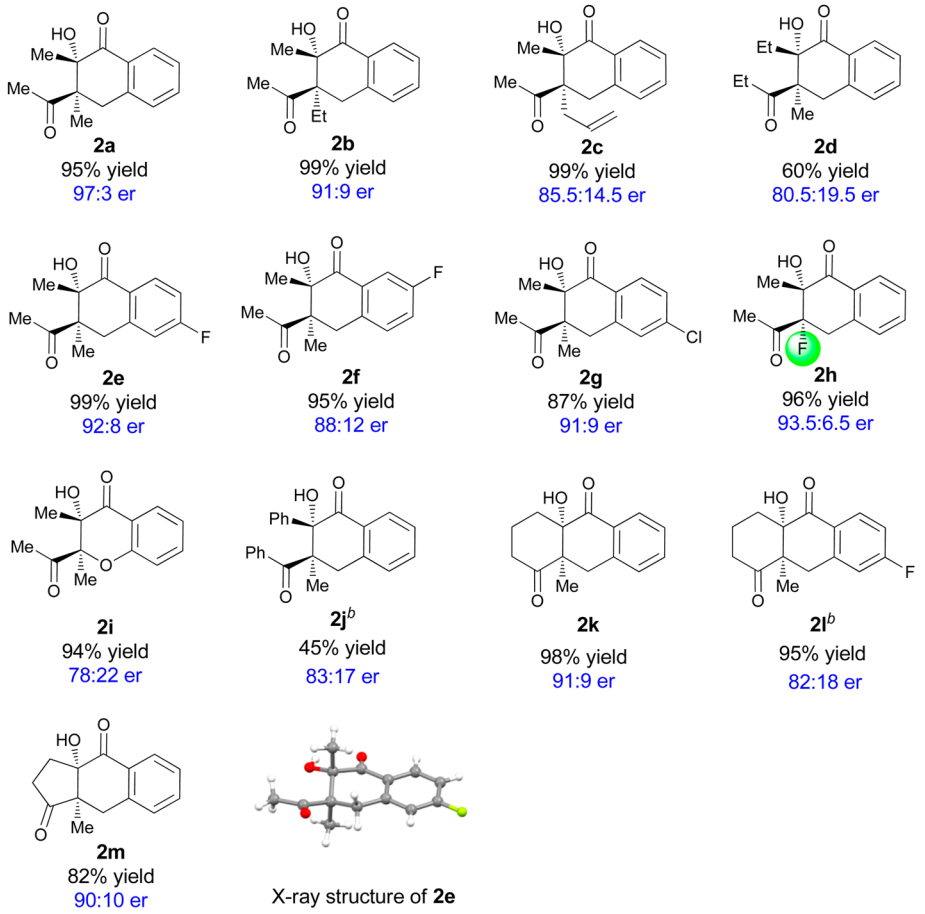
Table 2. Scope of Substrates with Aromatic Aldehyde Groups[a]





[a]Reaction condition: **1** (0.1 mmol), **C5** (0.02 mmol), KHMDS (0.02 mmol, 1.0 M in toluene), toluene (2 mL), −20 °C, argon protection, overnight. Diastereomeric ratios were determined by ^{1}H NMR. All yields were of isolated products based on **1**. Enantiomer ratios were determined via HPLC analysis on a chiral stationary phase. [b]NaOAc (0.02 mmol) was used as base and the reaction was conducted at rt.

Highly diastereoselective reduction of methylketone moiety of **2a** by DIBAL-H released product **5b** in excellent yield and without any erosion of the enantioselectivity.[16] Furthermore, the methylketone unit can also react selectively with hydroxylamine to form the oxime and then undergo the Beckmann rearrangement to furnish amide **5c**, with the chirality retained.[17] All these highly selective transformations make the derivatizations of the products easier, since no protection−deprotection steps are needed.

CONCLUSION

In conclusion, a general method for the asymmetric desymmetrization of 1,3-diketones via the NHC catalyzed intramolecular benzoin reaction was developed. Both aromatic and alphatic aldehydes were tolerable in this chiral NHC catalyzed transformation. Cyclic ketones bearing two consecutive fully substituted stereogenic centers were formed in high diastereoselectivities and moderate to excellent enantioselectivities. Further application of the desymmetrization strategy in NHC catalyzed transformations is ongoing in our research group.

EXPERIMENTAL SECTION

Commercially available materials were used as received, unless otherwise noted, and all reactions and manipulations involving air- or moisture-sensitive compounds were performed using standard Schlenk techniques. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a 400 MHz spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 100 MHz spectrometer. High-resolution mass spectral analysis (HRMS) was performed on aLTQFT Ultra mass spectrometer. Optical rotations were measured using a 1 mL cell with a 5 dm path length and are reported as follows: $[\alpha]^{rt}_D$ (c in g per 100 mL solvent). All starting materials (**1** and **3**) were prepared from the reactions of 1,3-diketones with bromides or iodides under basic conditions, followed by hydrolysis of the acetals to release the aldehydes.

General Method for the Synthesis of 2a−2i, 2k, 2m−2n through Benzoin Reaction. To a 25 mL, two-necked, oven-dried flask was added triazolium salt **C5** (9.34 mg, 0.02 mmol). The flask was then vacuumized and refilled with dry argon. Anhydrous toluene (2 mL) was added. Then, the reaction mixture was cooled to −20 °C,

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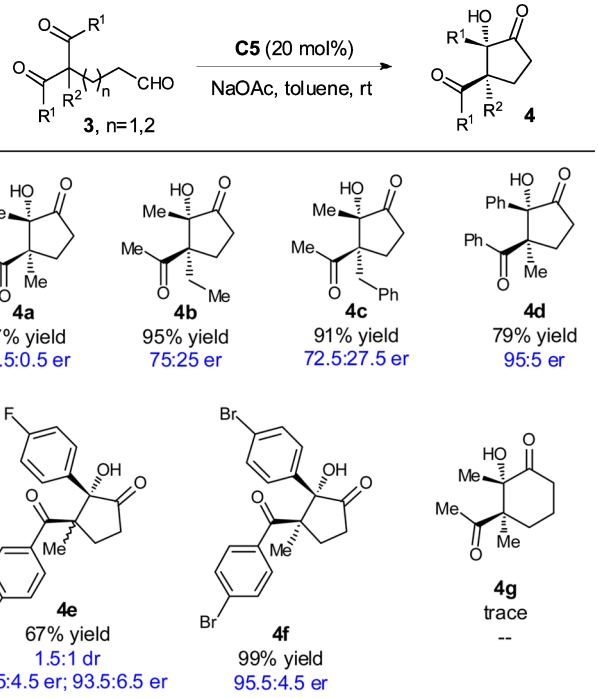
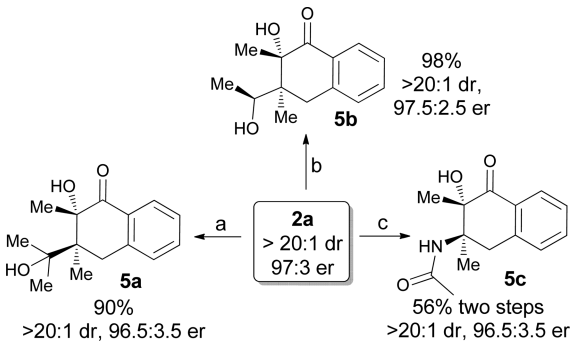
Table 3. Scope of Substrates with Aliphatic Aldehyde Groups[a]



[a]Reaction condition: **3** (0.1 mmol), **C5** (0.02 mmol), NaOAc (0.02 mmol), toluene (2 mL), rt, argon protection, overnight. Diastereomeric ratios were determined by ^{1}H NMR. All yields were of isolated products based on **3**. Enantiomer ratios were determined via HPLC analysis on a chiral stationary phase.

Scheme 2. Derivatization of Product 2a[a]



[a]Reaction condition: (a) CH_3MgBr, Et_2O, −30 °C to rt. (b) DIBAL-H, CH_2Cl_2, −45 °C. (c) $NH_2OH{\cdot}HCl$, pyridine, 0 °C to rt; then TsCl, Et_3N, CH_2Cl_2, 0 °C to rt, SiO_2.

and followed by an injection of KHMDS (40 μL, 0.02 mmol). After 20 min, **1a** (23.21 mg, 0.10 mmol) was added. The mixture was stirred at −20 °C for 10−20 h. Solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (10:1 v/v) as eluent to afford the benzoin product of **2a**. Racemic products were synthesized via similar procedure using racemic catalyst **C5** at room temperature.

*(2S,3R)-3-Acetyl-2-hydroxy-2,3-dimethyl-3,4-dihydronaphthalen-1(2H)-one (**2a**).* White solid (22.1 mg, 95% yield). Mp 57−60 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 6H), 2.39 (s, 3H), 2.71 (d, J = 18.0 Hz, 1H), 3.78 (d, J = 18.0 Hz, 1H), 4.24 (s, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 22.5, 28.5, 35.5, 56.6, 126.8, 127.8, 128.5, 129.9, 134.8, 141.3, 200.6, 210.8; HRMS (ESI, m/z): calcd for $C_{14}H_{16}O_3H^+$ 233.1172, found 233.1171. $[\alpha]^{20}_D$: 67.2 (c 1.7, $CHCl_3$). HPLC analysis: 94% ee (Chiralcel AD-H, 10:90 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 4.0 min, R_t (minor) = 3.6 min.

*(2S,3R)-3-Acetyl-3-ethyl-2-hydroxy-2-methyl-3,4-dihydronaphthalen-1(2H)-one (**2b**).* Yellow oil (24.4 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (t, J = 6.0 Hz, 3H), 1.22 (s, 4H), 2.25−2.39 (m, 1H), 2.39 (s, 3H), 2.95 (d, J = 20.0 Hz, 1H), 3.54 (d, J = 20.0 Hz, 1H), 4.27 (s, 1H), 7.29−7.36 (m, 2H), 7.56 (t, J = 8.0 Hz, 1H), 8.00 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 21.3, 23.0, 28.7, 30.4, 61.4, 126.9, 127.8, 128.7, 129.8, 134.9, 141.2, 200.8, 211.0; HRMS (ESI, m/z): calcd for $C_{15}H_{18}O_3H^+$ 247.1329, found 247.1327. $[\alpha]^{20}_D$: 95.5 (c 0.7, $CHCl_3$). HPLC analysis: 82% ee (Chiralcel AD-H, 10:90 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 3.7 min, R_t (minor) = 3.1 min.

*(2S,3R)-3-Acetyl-3-allyl-2-hydroxy-2-methyl-3,4-dihydronaphthalen-1(2H)-one (**2c**).* Yellow oil (25.6 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.95 (dd, J = 8.0, 16.0 Hz, 1H), 2.42 (s, 3H), 2.95 (d, J = 18.0 Hz, 1H), 3.00 (dd, J = 8.0, 16.0 Hz, 1H), 3.57 (d, J = 18.0 Hz, 1H), 4.30 (s, 1H), 4.85 (d, J = 18.0 Hz, 1H), 5.02 (d, J = 8.0 Hz, 1H), 5.41−5.52 (m, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 29.0, 31.2, 33.4, 60.7, 76.7, 119.5, 126.9, 127.8, 128.6, 129.8, 132.5, 135.0, 141.0, 200.5, 210.0; HRMS (ESI, m/z): calcd for $C_{16}H_{18}O_3H^+$ 259.1329, found 259.1327. $[\alpha]^{20}_D$: 41.5 (c 1.8, $CHCl_3$). HPLC analysis: 71% ee (Chiralcel AD-H, 10:90 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 3.7 min, R_t (minor) = 3.0 min.

*(2S,3R)-2-Ethyl-2-hydroxy-3-methyl-3-propionyl-3,4-dihydronaphthalen-1(2H)-one (**2d**).* White solid (15.6 mg, 60% yield). Mp 44−47 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56 (t, J = 8.0 Hz, 3H), 0.98 (t, J = 8.0 Hz, 3H), 1.14 (s, 3H), 1.32−1.42 (m, 1H), 1.63−1.72 (m, 1H), 2.51−2.63 (m, 2H), 2.82−2.92 (m, 1H), 3.85 (d, J = 16.0 Hz, 1H), 4.21 (s, 1H), 7.17−7.24 (m, 2H), 7.46 (td, J = 1.3, 7.8 Hz, 1H), 7.85 (dd, J = 1.0, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.3, 8.0, 17.7, 26.7, 33.3, 35.5, 56.8, 79.8, 126.8, 127.4, 129.0, 129.9, 134.6, 141.3, 200.5, 213.3; HRMS (ESI, m/z): calcd for $C_{16}H_{20}O_3H^+$ 261.1485, found 261.1484. $[\alpha]^{20}_D$: 48.9 (c 0.6, $CHCl_3$). HPLC analysis: 61% ee (Chiralcel AD-H, 10:90 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 3.4 min, R_t (minor) = 3.0 min.

*(2S,3R)-3-Acetyl-6-fluoro-2-hydroxy-2,3-dimethyl-3,4-dihydronaphthalen-1(2H)-one (**2e**).* White solid (24.8 mg, 99% yield). Mp 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.23 (s, 3H), 2.39 (s, 3H), 2.69 (d, J = 20.0 Hz, 1H), 3.77 (d, J = 20.0 Hz, 1H), 4.20 (s, 1H), 6.96 (d, J = 8.0 Hz, 1H), 7.01−7.06 (m, 1H), 8.01−8.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 22.6, 28.5, 35.63, 35.64, 56.5, 114.9 (d, J = 22.0 Hz), 116.3 (d, J = 21.0 Hz), 125.1 (d, J = 3.0 Hz), 130.9 (d, J = 10.0 Hz), 144.7 (d, J = 9.0 Hz), 166.7 (d, J = 255.0 Hz), 199.2, 210.5; HRMS (ESI, m/z): calcd for $C_{14}H_{15}FO_3H^+$ 251.1078, found 251.1077. $[\alpha]^{20}_D$: 53.9 (c 1.7, $CHCl_3$). HPLC analysis: 84% ee (Chiralcel AD-H, 20:80 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 3.3 min, R_t (minor) = 3.0 min.

*(2S,3R)-3-Acetyl-7-fluoro-2-hydroxy-2,3-dimethyl-3,4-dihydronaphthalen-1(2H)-one (**2f**).* White solid (23.8 mg, 95% yield). Mp 83−85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 6H), 2.40 (s, 3H), 2.72 (d, J = 20.0 Hz, 1H), 3.74 (d, J = 20.0 Hz, 1H), 4.16 (s, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 22.4, 28.5, 35.0, 56.6, 113.6 (d, J = 22.0 Hz), 122.3 (d, J = 22.0 Hz), 130.0 (d, J = 8.0 Hz), 131.8 (d, J = 8.0 Hz), 137.0 (d, J = 3.0 Hz), 161.5 (d, J = 246.0 Hz), 199.8, 210.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −114.5; HRMS (ESI, m/z): calcd for $C_{14}H_{15}FO_3H^+$ 251.1078, found 251.1076. $[\alpha]^{20}_D$: 67.2 (c 1.7, $CHCl_3$). HPLC analysis: 76% ee (Chiralcel AD-H, 20:80 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 3.6 min, R_t (minor) = 3.2 min.

*(2S,3R)-3-Acetyl-6-chloro-2-hydroxy-2,3-dimethyl-3,4-dihydronaphthalen-1(2H)-one(**2g**).* White solid (23.1 mg, 87% yield). Mp 122−125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.22 (s, 3H), 2.38 (s, 3H), 2.67 (d, J = 20.0 Hz, 1H), 3.75 (d, J = 20.0 Hz, 1H), 4.17 (s, 1H), 7.27−7.32 (m, 2H), 7.93 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 22.5, 28.5, 35.3, 56.4, 126.9, 127.5, 129.4, 129.8, 141.2, 143.0, 199.6, 210.4; HRMS (ESI, m/z): calcd for

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$C_{14}H_{15}ClO_3H^+$ 267.0782, found 267.0780. $[\alpha]^{20}_D$: 71.4 (*c* 1.9, $CHCl_3$). HPLC analysis: 82% ee (Chiralcel AD-H, 1:99 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 12.6 min, R_t (minor) = 8.3 min.

(2R,3S)-3-Acetyl-3-fluoro-2-hydroxy-2-methyl-3,4-dihydronaphthalen-1(2H)-one (**2h**). White solid (22.7 mg, 96% yield). Mp 106−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H), 2.44 (d, *J* = 8.0 Hz, 3H), 3.18 (dd, *J* = 20.0, 14.0 Hz, 1H), 3.82 (dd, *J* = 40.0, 14.0 Hz, 1H), 3.99 (s, 1H), 7.25−7.27 (m, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0 (d, *J* = 6.0 Hz), 27.8, 34.5 (d, *J* = 22.0 Hz), 77.5 (d, *J* = 22.0 Hz), 103.9 (d, *J* = 187.0 Hz), 127.5, 127.8, 128.8, 129.4, 134.9, 137.6, 198.37, 198.41, 206.3 (d, *J* = 31.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −170.4; HRMS (ESI, *m*/*z*): calcd for $C_{13}H_{13}FO_3H^+$ 237.0921, found 237.0920. $[\alpha]^{20}_D$: −55.2 (*c* 1.7, $CHCl_3$). HPLC analysis: 87% ee (Chiralcel AD-H, 5:95 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 4.9 min, R_t (minor) = 4.5 min.

(2R,3S)-2-Acetyl-3-hydroxy-2,3-dimethylchroman-4-one (**2i**). Yellow oil (22.0 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.49 (s, 3H), 2.49 (s, 3H), 4.04 (s, 1H), 7.09 (t, *J* = 8.4 Hz, 2H), 7.57 (td, *J* = 1.6, 8.8 Hz, 1H), 7.87 (dd, *J* = 1.2, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 21.7, 27.6, 75.2, 89.9, 117.7, 118.6, 122.1, 127.4, 137.1, 157.7, 194.7, 207.0; HRMS (ESI, *m*/*z*): calcd for $C_{13}H_{14}O_4H^+$ 235.0965, found 235.0964. $[\alpha]^{20}_D$: 19.5 (*c* 1.5, $CHCl_3$). HPLC analysis: 56% ee (Chiralcel OD-H, 10:90 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 4.3 min, R_t (minor) = 4.8 min.

(4aS,9aR)-4a-hydroxy-9a-methyl-2,3,4,4a,9,9a-hexahydroanthracene-1,10-dione (**2k**). Yellow oil (23.9 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.53−1.57 (m, 1H), 1.97−2.01 (m, 1H), 2.19−2.52 (m, 3H), 2.76−2.85 (m, 2H), 3.65 (d, *J* = 16.0 Hz, 1H), 3.70 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.56−7.60 (m, 1H), 8.06 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 20.6, 31.0, 36.3, 37.9, 54.1, 80.5, 127.3, 128.1, 129.2, 129.4, 134.8, 139.9, 199.2, 210.6; HRMS (ESI, *m*/*z*): calcd for $C_{15}H_{16}O_3H^+$ 245.1172, found 245.1171. $[\alpha]^{20}_D$: −6.7 (*c* 2.4, $CHCl_3$). HPLC analysis: 82% ee (Chiralcel AD-H, 7:93 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 8.3 min, R_t (minor) = 10.4 min.

(3aS,9aR)-3a-hydroxy-9a-methyl-3,3a,9,9a-tetrahydro-1H-cyclopenta[b]naphthalene-1,4(2H)-dione (**2m**). White solid (18.9 mg, 82% yield). Mp 99−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 3H), 2.02−2.08 (m, 1H), 2.32−2.40 (m, 1H), 2.63−2.74 (m, 3H), 3.05 (d, *J* = 20.0 Hz, 1H), 3.79 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.58 (td, *J* = 8.0, 1.2 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 31.4, 33.9, 34.8, 57.0, 81.7, 127.6, 127.9, 128.8, 129.7, 135.1, 139.6, 198.7, 215.7; HRMS (ESI, *m*/*z*): calcd for $C_{14}H_{14}O_3H^+$ 231.1016, found 231.1014. $[\alpha]^{20}_D$: −11.5 (*c* 1.9, $CHCl_3$). HPLC analysis: 80% ee (Chiralcel OJ-H, 10:90 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 11.1 min, R_t (minor) = 12.6 min.

General Method for the Synthesis of 2j, 2l, and 4a−4f through Benzoin Reaction. Typically, to a 25 mL, two-necked, oven-dried flask were added triazolium salt **C5** (9.34 mg, 0.02 mmol) and NaOAc (1.64 mg, 0.02 mmol). The flask was then vacuumized and refilled with dry argon. Anhydrous toluene (2 mL) was added. After 20 min, **3a** (17.01 mg, 0.10 mmol) was added. The mixture was stirred at room temperature until **3a** was consumed up by TLC analysis. Solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (5:1 v/v) as eluent to afford the benzoin product **4a**. Racemic products were synthesized via similar procedure using racemic catalyst **C5** at room temperature.

(2S,3R)-3-Benzoyl-2-hydroxy-3-methyl-2-phenyl-3,4-dihydronaphthalen-1(2H)-one (**2j**). White solid (16.0 mg, 45% yield). Mp 41−46 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 3H), 2.78 (d, *J* = 18.0 Hz, 1H), 3.88 (d, *J* = 18.0 Hz, 1H), 7.14−7.21 (m, 5H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.41−7.52 (m, 4H), 7.65 (t, *J* = 7.0 Hz, 1H), 8.06 (d, *J* = 7.2 Hz, 2H), 8.18 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 38.1, 58.5, 81.8, 126.6, 127.3, 127.8, 127.9, 128.0, 128.2, 129.3, 130.2, 130.8, 131.4, 135.2, 139.3, 139.6, 143.1, 198.7, 204.8; HRMS (ESI, *m*/*z*): calcd for $C_{24}H_{20}O_3H^+$ 357.1485, found 357.1482. $[\alpha]^{20}_D$: 30.5 (*c* 1.0, $CHCl_3$). HPLC analysis: 66% ee (Chiralcel OJ-H, 1:99 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 31.5 min, R_t (minor) = 25.9 min.

(4aS,9aR)-7-Fluoro-4a-hydroxy-9a-methyl-2,3,4,4a,9,9a-hexahydroanthracene-1,10-dione (**2l**). White solid (24.9 mg, 95% yield). Mp 88−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.55 (d, *J* = 12.0 Hz, 1H), 1.98−1.99 (m, 1H), 2.20 (t, *J* = 12.0 Hz, 1H), 2.30−2.36 (m, 1H), 2.48 (d, *J* = 16.0 Hz, 1H), 2.74−2.78 (m, 2H), 3.61−3.67 (m, 2H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 8.08 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 20.5, 31.0, 36.2, 37.8, 53.8, 80.4, 115.3 (d, *J* = 22.0 Hz), 115.9 (d, *J* = 22.0 Hz), 125.7 (d, *J* = 3.0 Hz), 131.2 (d, *J* = 10.0 Hz), 143.1 (d, *J* = 9.0 Hz),165.5 (d, *J* = 256.0 Hz), 197.7, 210.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.8; HRMS (ESI, *m*/*z*): calcd for $C_{15}H_{15}FO_3H^+$ 263.1078, found 263.1076. $[\alpha]^{20}_D$: −22.1 (*c* 2.1, $CHCl_3$). HPLC analysis: 64% ee (Chiralcel AD-H, 5:95 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 12.7 min, R_t (minor) = 13.7 min.

(2S,3R)-3-Acetyl-2-hydroxy-2,3-dimethylcyclopentanone (**4a**). White solid (14.8 mg, 87% yield). Mp 98−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.14 (s, 3H), 1.60−1.66 (m, 1H), 2.23−2.32 (m, 4H), 2.41−2.52 (m, 2H), 2.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 20.8, 24.7, 26.9, 30.0, 57.5, 80.1, 210.5, 218.1; HRMS (ESI, *m*/*z*): calcd for $C_9H_{14}O_3H^+$ 171.1016, found 171.1015. $[\alpha]^{20}_D$: −71.7 (*c* 0.8, $CHCl_3$). HPLC analysis: 99% ee (Chiralcel AD-H, 10:90 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 11.8 min, R_t (minor) = 13.0 min.

(2S,3R)-3-Acetyl-3-ethyl-2-hydroxy-2-methylcyclopentanone (**4b**). White solid (17.5 mg, 95% yield). Mp 84−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (t, *J* = 6.0 Hz, 3H), 1.06 (s, 3H), 1.79−1.84 (m, 1H), 2.08−2.46 (m, 8H), 3.04 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.5, 19.5, 21.3, 22.0, 27.0, 29.8, 62.1, 80.2, 210.3, 218.5; HRMS (ESI, *m*/*z*): calcd for $C_{10}H_{16}O_3H^+$ 185.1172, found 185.1171. $[\alpha]^{20}_D$: −20.2 (*c* 1.5, $CHCl_3$). HPLC analysis: 50% ee (Chiralcel AS-H, 30:70 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 4.4 min, R_t (minor) = 8.4 min.

(2S,3S)-3-Acetyl-3-benzyl-2-hydroxy-2-methylcyclopentanone (**4c**). White solid (22.4 mg, 91% yield). Mp 99−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.78−1.84 (m, 1H), 2.06−2.16 (m, 2H), 2.22−2.30 (m, 1H), 2.40−2.50 (m, 5H), 2.97 (s, 1H), 3.36 (d, *J* = 15.2 Hz, 1H), 7.00 (d, *J* = 6.4 Hz, 2H), 7.20−7.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 21.5, 28.0, 30.1, 36.2, 62.3, 80.7, 127.0, 128.6, 129.3, 136.1, 210.0, 218.0; HRMS (ESI, *m*/*z*): calcd for $C_{15}H_{18}O_3H^+$ 247.1329, found 247.1328. $[\alpha]^{20}_D$: −27.7 (*c* 1.3, $CHCl_3$). HPLC analysis: 45% ee (Chiralcel AD-H, 10:90 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 8.1 min, R_t (minor) = 5.1 min.

(2S,3R)-3-Benzoyl-2-hydroxy-3-methyl-2-phenylcyclopentanone (**4d**). White solid (23.2 mg, 79% yield). Mp 113−116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 3H), 2.00 (t, *J* = 12.0 Hz, 1H), 2.58−2.68 (m, 1H), 2.74−2.81 (m, 1H), 2.96 (q, *J* = 12.0 Hz, 1H), 3.57 (s, 1H), 7.17 (s, 5H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.46−7.50 (m, 1H), 8.01 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 28.5, 32.5, 59.3, 84.6, 126.1, 128.0, 128.1, 128.3, 129.1, 132.1, 137.3, 138.5, 203.7, 217.0; HRMS (ESI, *m*/*z*): calcd for $C_{19}H_{18}O_3H^+$ 295.1329, found 295.1326. $[\alpha]^{20}_D$: −59.5 (*c* 1.4, $CHCl_3$). HPLC analysis: 90% ee (Chiralcel OD-H, 5:95 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 6.2 min, R_t (minor) = 6.8 min.

(2S,3R)-3-(4-Fluorobenzoyl)-2-(4-fluorophenyl)-2-hydroxy-3-methylcyclopentanone (**4e**) *(dr 1.5:1)*. White solid (22.1 mg, 67% yield). Mp 114−116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 3H), 1.97−2.02 (m, 1H), 2.61−2.81 (m, 2H), 2.90−3.01 (m, 1H), 3.63 (s, 0.35H), 3.66 (s, 0.5H), 6.86 (t, *J* = 8.0 Hz, 1H), 7.05−7.14 (m, 4H), 7.37 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 8.14−8.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 21.5, 28.30, 28.33, 32.15, 32.20, 59.3, 59.4, 83.9, 115.2 (d, *J* = 21.0 Hz), 115.4 (d, *J* = 22.0 Hz), 127.3, 127.7, 127.8, 128.46, 128.52, 130.8, 132.1, 132.2, 133.0, 134.2, 135.1, 137.0, 138.8, 165.2 (d, *J* = 253.0 Hz), 201.2, 201.9, 216.6, 216.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ −113.2, −105.9; HRMS (ESI, *m*/*z*): calcd for $C_{19}H_{16}F_2O_3H^+$ 331.1140, found 331.1139. $[\alpha]^{20}_D$: −48.6 (*c* 0.9, $CHCl_3$). HPLC analysis for the major isomer: 91% ee (Chiralcel OD-H, 5:95 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 17.1 min, R_t (minor) = 20.0 min; HPLC analysis for the minor isomer: 87% ee (Chiralcel

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OD-H, 5:95 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 15.8 min, R_t (minor) = 20.3 min.

*(2S,3R)-3-(4-Bromobenzoyl)-2-(4-bromophenyl)-2-hydroxy-3-methylcyclopentanone (**4f**).* White solid (44.5 mg, 99% yield). Mp 143−149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.95−2.04 (m, 1H), 2.61−2.80 (m, 2H), 2.90−2.98 (m, 1H), 3.69 (s, 1H), 7.02 (d, J = 8.0 Hz, 2H), 7.28 (t, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 28.2, 32.2, 59.3, 83.9, 122.5, 127.56, 127.60, 130.9, 131.47, 131.48, 135.4, 137.4, 201.9, 216.4; HRMS (ESI, m/z): calcd for $C_{19}H_{16}Br_2O_3H^+$ 450.9539, found 450.9535. $[\alpha]^{20}_D$: −65.4 (c 0.3, $CHCl_3$). HPLC analysis: 91% ee (Chiralcel AD-H, 10:90 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 4.2 min, R_t (minor) = 5.4 min.

*(2S,3S)-2-Hydroxy-3-(2-hydroxypropan-2-yl)-2,3-dimethyl-3,4-dihydronaphthalen-1(2H)-one (**5a**).* To a 25 mL round-bottom flask was added **2a** (23.2 mg, 0.100 mmol). The flask was vacuumized and refilled with dry argon. Anhydrous Et_2O (3 mL) was added and the solution was cooled to −30 °C. Then, CH_3MgBr (0.4 mL, 0.400 mmol) was added to the flask. After addition was complete, the reaction was allowed to warm to room temperature and was stirred for 8 h under argon atmosphere. The reaction was diluted with saturated NH_4Cl aqueous solution (3 mL) and extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel with petroleum ether/ethyl acetate (5:1 v/v) as eluent afforded 22.3 mg (90% yield) of compound **5a**. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.38 (s, 3H), 1.48 (s, 3H), 1.50 (s, 3H), 2.82 (d, J = 17.5 Hz, 1H), 3.11 (s, 1H), 3.42 (d, J = 17.5 Hz, 1H), 4.34 (s, 1H), 7.24−7.25 (m, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 24.1, 27.4, 29.0, 36.5, 47.8, 76.8, 81.1, 126.6, 127.6, 129.4, 129.7, 134.3, 141.7, 202.0; HRMS (ESI, m/z): calcd for $C_{15}H_{20}O_3H^+$ 249.1485, found 249.1485. $[\alpha]^{20}_D$: −62.0 (c 0.3, $CHCl_3$). HPLC analysis: 93% ee (Chiralcel AD-H, 3:97 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 12.6 min, R_t (minor) = 10.5 min.

*(2S,3S)-2-Hydroxy-3-((R)-1-hydroxyethyl)-2,3-dimethyl-3,4-dihydronaphthalen-1(2H)-one (**5b**).* To a 25 mL round-bottom flask was added **2a** (23.2 mg, 0.100 mmol). The flask was vacuumized and refilled with dry argon. Anhydrous CH_2Cl_2 (2 mL) was added, and the solution was cooled to −45 °C. Then, DIBAL-H (0.27 mL, 0.400 mmol) was added to the flask. The reaction mixture was stirred at −45 °C for 6 h before warming to room temperature. The reaction was diluted with HCl aqueous solution (3 mL) and extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel with petroleum ether/ethyl acetate (5:1 v/v) as eluent afforded 22.9 mg (98% yield) of compound **5b**. White solid. Mp 134−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.19 (d, J = 6.1 Hz, 3H), 1.39 (s, 3H), 2.70 (d, J = 17.3 Hz, 1H), 2.86 (d, J = 17.3 Hz, 1H), 4.30 (s, 1H), 4.37 (q, J = 6.1 Hz, 1H), 4.46 (s, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.2 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 16.3, 20.8, 37.8, 45.0, 70.2, 80.6, 127.0, 127.6, 129.0, 129.8, 134.6, 140.4, 201.4; HRMS (ESI, m/z): calcd for $C_{14}H_{18}O_3H^+$ 235.1329, found 235.1327. $[\alpha]^{20}_D$: 25.8 (c 0.7, $CHCl_3$). HPLC analysis: 95% ee (Chiralcel AD-H, 3:97 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 11.9 min, R_t (minor) = 9.9 min.

*N-((2R,3S)-3-Hydroxy-2,3-dimethyl-4-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (**5c**).* To a 25 mL round-bottom flask were added **2a** (25.0 mg, 0.109 mmol) and NH_2OH·HCl (45.3 mg, 0.652 mmol). The flask was vacuumized and refilled with dry argon. Then, pyridine (1 mL) was added at 0 °C. After addition was complete, the reaction was allowed to warm to room temperature and was stirred at room temperature overnight. Pyridine was then evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (5:1 v/v) as eluent afforded (2*R*,3*R*)-2-hydroxy-3-((*E*)-1-(hydroxyimino)ethyl)-2,3-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one. Then, (2*R*,3*R*)-2-hydroxy-3-((*E*)-1-(hydroxyimino)ethyl)-2,3-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one and 4-methylbenzene-1-sulfonyl chloride (45.6 mg, 0.240 mmol) were added into a 25 mL round-bottom flask. The flask was vacuumized and refilled with dry argon. Then, CH_2Cl_2 (2 mL) and Et_3N (66.8 uL, 0.480 mmol) were added to the flask at 0 °C. After addition was complete, the reaction was allowed to warm to room temperature and stirred overnight. Then, CH_2Cl_2 was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel with petroleum ether/ethyl acetate (1:1 v/v) as eluent afforded 15.1 mg (56% yield) of compound **5c**. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.40 (s, 3H), 2.04 (s, 3H), 3.43 (d, J = 18.0 Hz, 1H), 4.13 (s, 1H), 4.20 (d, J = 18.0 Hz, 1H), 5.99 (s, 1H), 7.29−7.36 (m, 2H), 7.55 (td, J = 1.2, 7.6 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 21.1, 24.6, 38.6, 60.5, 78.6, 126.9, 127.5, 128.9, 129.9, 134.8, 140.9, 171.0, 200.0; HRMS (ESI, m/z): calcd for $C_{14}H_{17}NO_3H^+$ 248.1281, found 248.1280. $[\alpha]^{20}_D$: −60.7 (c 0.3, $CHCl_3$). HPLC analysis: 93% ee (Chiralcel AD-H, 3:97 ^{i}PrOH/hexane, 1 mL/min), R_t (major) = 18.0 min, R_t (minor) = 14.8 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02829.

X-ray structure of **2e** (CIF)
X-ray structure of **4a** (CIF)
NMR and HPLC spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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