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Organocatalytic, Enantioselective Synthesis of 1- and 3-Substituted Isochromans via Intramolecular Oxa-Michael Reaction of Alkoxyboronate: Synthesis of (+)-Sonepiprazole

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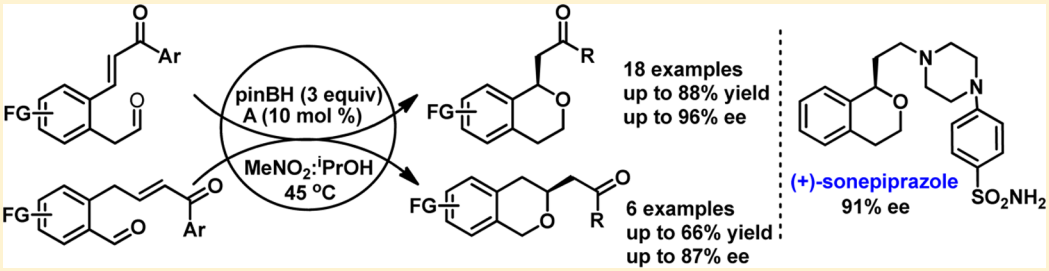
Supporting Information



ABSTRACT: The enantioselective oxa-Michael reaction of alkoxyboronate strategy was demonstrated to provide a new and practical route to enantioriched 1- and 3-substituted isochromans using a chiral bifunctional organocatalyst. Furthermore, this methodology was extended to the enantioselective synthesis of (+)-sonepiprazole, a dopamine receptor antagonist.

INTRODUCTION

Chiral 1-substituted isochromans (Figure 1) constitute the core of many natural products such as cytosporone C−D[1] and bioactive molecules sonepiprazole (U-101387), a selective dopamine D_4 receptor antagonist.[2] However, 3-substituted isochromans are a part of biologically active natural products like, DMHI,[3] a plant growth regulator and the anticoccidial isochroman,[4] found mainly in *Penicillium* species. Furthermore, 3-substituted isochromans can also be the immediate precursors for 3-substituted 3,4-dihydroisocoumarins[5] and 1,3-disubstituted isochromans,[6a,b] which are the key moieties in biologically active molecules.

While substantial progress has been achieved for the achiral synthesis of 1-substituted isochromans,[7] methods for the corresponding asymmetric variants are scarce.[8] In 2006, Jacobsen et al.[8a] developed a pioneering organocatalytic method for the enantioselective trapping of oxocarbenium ion intermediates. In 2011, Watson et al.[8b] developed the first metal-catalyzed, nucleophilic addition of phenyl acetylenes to racemic isochroman acetals. In the above two methods, the oxocarbenium ion was generated from the acid decomposition of isochroman acetals, which are difficult to synthesize and handle due to their instability. Recently, Lou and Liu et al.[8c] developed an atom economical enantioselective oxidative cross-coupling of stable benzylic ethers with aldehydes using DDQ as the oxidizing agent. It is surprising to consider that the major developments in the synthesis of these compounds have relied primarily on nucleophilic additions to a prochiral cyclic oxocarbenium ion intermediate. However, despite the importance of 3-substituted isochromans, to the best of our knowledge, their catalytic enantioselective synthesis has not been achieved and still remains a major challenge.[9]

In spite of the fact that the oxa-Michael reaction offers a straightforward route toward oxygen containing heterocycles,[10,11] the absence of corresponding enantioselective variants for the synthesis of such compounds can be attributed to the problems resulting from self-cyclization and reversibility issues.[12]

Recently, our laboratory has demonstrated a novel alkoxyboronate activation concept for the first enantioselective synthesis of substituted isobenzofurans through a push−pull strategy[13] using cinchona alkaloid based bifunctional organocatalysts (Scheme 1).[14,15] Herein, we further extend this activation concept to report an alternative route for the enantioselective synthesis of 1-substituted isochromans using relatively stable starting materials. Also, the first catalytic enantioselective synthesis of 3-substituted isochromans has been achieved using the same strategy.

RESULTS AND DISCUSSION

Exposure of (*E*)-2-(2-(3-oxo-3-phenylprop-1-en-yl)phenyl) acetaldehyde **1a** as a model substrate to the previously reported reaction conditions, using 3 equiv of pinBH and 10 mol % catalyst **A** in a mixture of $MeNO_2$/^{i}PrOH (4:1, v/v) resulted in sluggish reduction to give the corresponding alkoxyboronate (Scheme 2, first reaction). From the observation of the evolution of H_2 effervescences, we predicted that the slow rate

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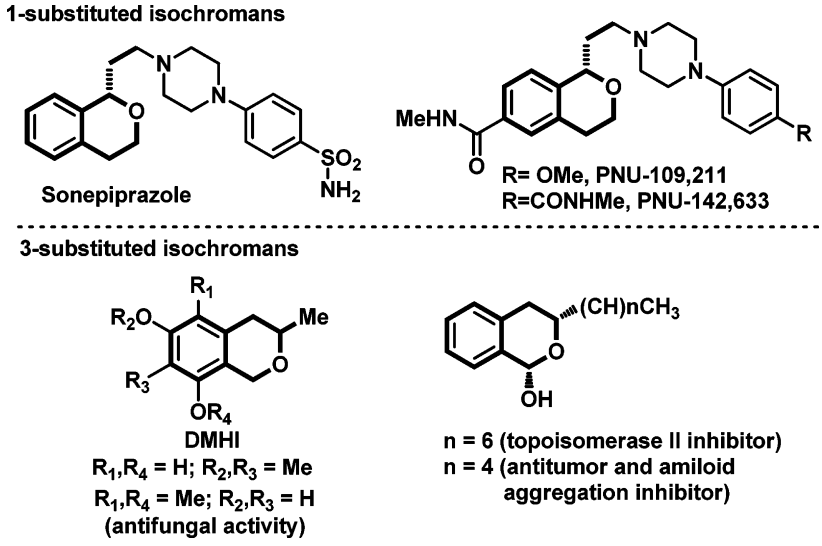
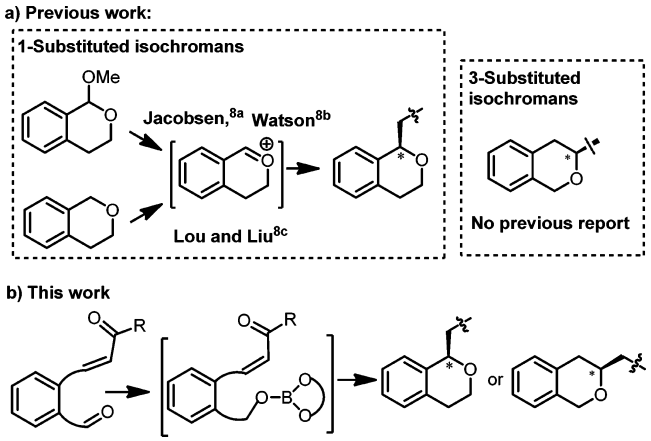
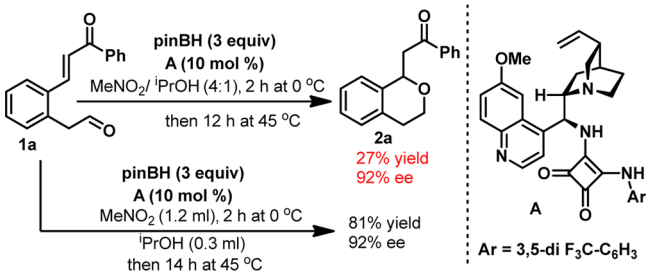


Figure 1. One- and 3-substituted isochroman structural motifs in natural products and bioactive molecules.

Scheme 1. Strategies for the Synthesis of Enantiomerically Enriched 1- and 3-Substituted Isochromans

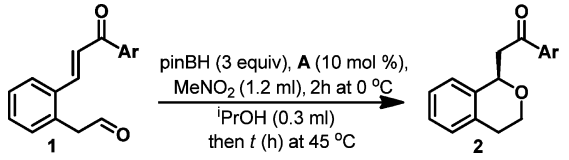


Scheme 2. Reaction Optimizations



in the reduction step may open an alternative path for the hydride of borane with the proton of i-PrOH, thus resulting in the unavailability of borane for the reduction step. As predicted, we observed a notable improvement in the reduction step, and a complete reduction of **1a** to the corresponding alkoxyboronate was observed, with the use of only $MeNO_2$ as the solvent. Further, a clean cyclization to the corresponding substituted isochroman was observed with the addition of ^{i}PrOH at 45 °C with good enantioselectivity as well as yield (Scheme 2, second reaction). With the optimized reaction conditions in hand, we examined the scope of different external aryl groups on the substrate as summarized in Table 1.

Table 1. Substrate Scope: 1-Substituted Isochromans



entry	Ar-, **1**	**2**,	t/h	(%)[b]	ee (%)[c]	
1	(**1a**)	**2a**,	14	81	92	
2	(**1b**)	**2b**,	20	71	83	
3	(**1c**)	**2c**,	21	68	89	
4	(**1d**)	**2d**,	19	83	80	
5	(**1e**)	**2e**,	19	70	91	
6	(**1f**)	**2f**,	18	64	87	>99[d]
7	(**1g**)	**2g**,	14	80	96	
8	(**1h**)	**2h**,	19	81	96	
9	(**1i**)	**2i**	18	68	94	

[a]Reaction conditions: **1** (0.225 mmol), pinBH (0.34 mmol, 1.5 equiv), **2c** (0.0225 mmol, 10 mol %) in ^{i}PrOH/CH_3NO_2 (1:4, 0.111 M) at 0 °C for 45 min then 45 °C for 2−6 h. [b]Yields shown are of isolated products. [c]Enantiomeric excess values were determined by HPLC analysis on a chiral stationary phase. [d]Enantiomeric excess after recrystallization. [e]The reduction was carried out (0 °C) for 2 h. [f]Catalyst **2e** was used instead of **2c**. [g]In parentheses, the yield and % of ee after recrystallization are shown.

Substrates with external aromatic rings having both electron-donating and electron-withdrawing groups participated successfully to give good yields and enantioselectivities (Table 1, entries 1−8). We observed that the cyclization step is sensitive to the steric nature of the external aryl group. Sterically less hindered substituents around the carbonyl generally provided

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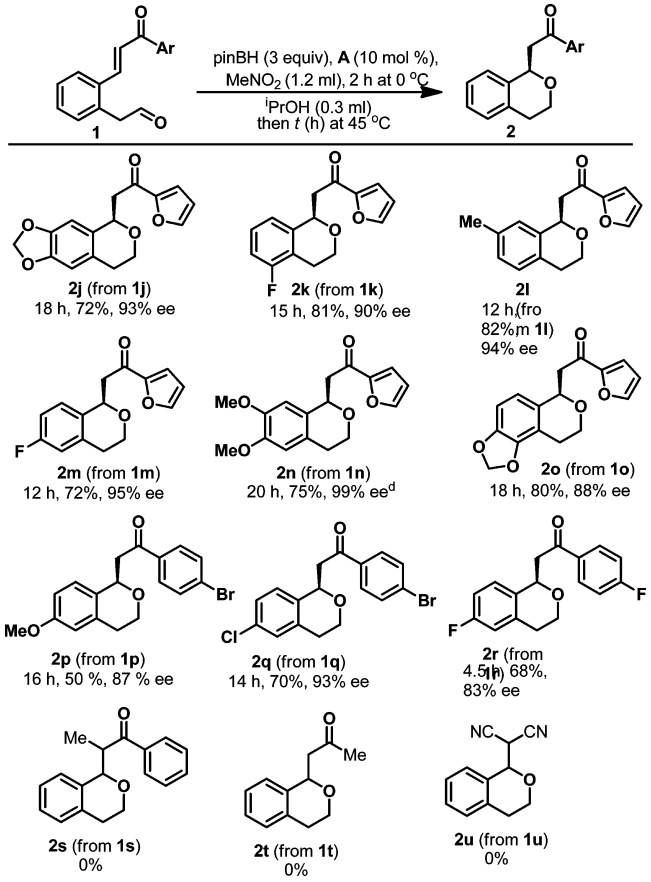
the highest level of stereocontrol; for example, furan and thiophene attached substrates provided 96% and 94% ee, respectively (entries 8 and 9).

Encouraged by the above results, we next explored the scope of internally substituted homobenzaldehydes by keeping the furyl as the external aryl group constant (Scheme 3). We were

Scheme 3. Substrate Scope: 1-Substituted Isochromans

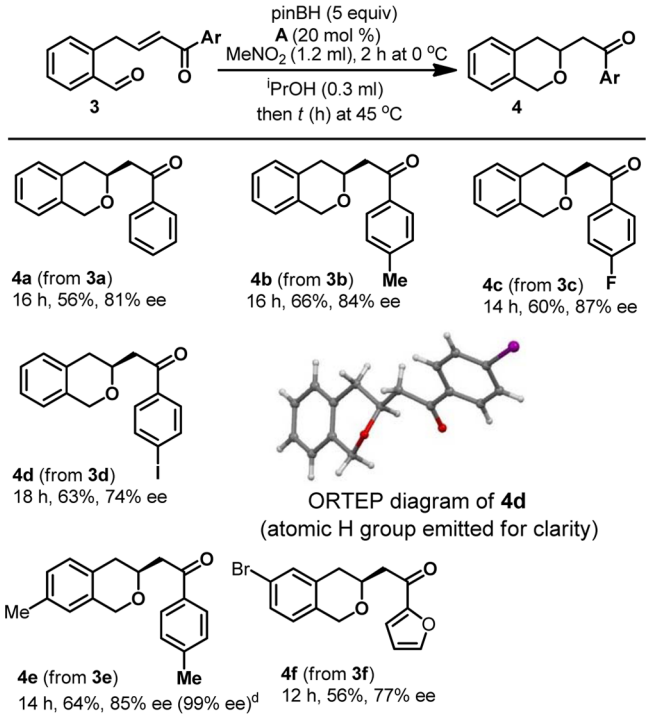


[a]The reaction conditions were the same as those in Table 1. [b]Isolated yields. [c]Enantiomeric excess were determined by HPLC analysis on a chiral stationary phase. [d]After recrystallization.

pleased to find that almost all of the substrates irrespective of the position and electronic nature of the substituents reacted well under the optimized reaction conditions to provide good yields as well as excellent enantioselectivities (**2j** to **2r**). Notably, compound **2q** is the precursor for biologically active natural product PNU-142,633, which is a 5-HT_{1D} agonist. Surprisingly, a methyl substitution at the α-position of the olefinic Michael acceptor as well as the replacement of the external aryl moiety with a methyl group hindered the cyclization from occurring (0% yield for **2s** and **2t**, respectively), although the reduction step remained successful in providing the corresponding alcohols.[21] Further, the replacement of the α,β-unasaturated ketone moiety with a malononitrile counterpart was also not effective (for compound **2u**).

Inspired by the biological importance of 3-substituted isochromans and their derivatives, we further focused our attention on the applicability of the present oxa-Michael reaction conditions for the analogoues *ortho*-formyl homo-chalcones (**3a**–**f**) as substrates (Scheme 4). To our excitement,

Scheme 4. Substrate Scope: 3-Substituted Isochromans



[a]The reaction conditions were the same as those in Table 1 except for catalyst loading and the amount of HBpin. [b]Isolated yield. [c]Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d]After recrystallization.

we found the analogues substrate **3c** reacted under the given reaction conditions to give the desired products but in lower yield due to the incomplete reduction step. Further, increase in the catalyst loading (20 mol %) as well as the reducing agent (5 equiv) resulted in the complete consumption of the aldehyde to the corresponding alkoxyboronate which cyclized at 45 °C to give the desired cyclized product in good yield and enantioselctivity.

We tested the tolerability of different substituents on both the external as well as the internal aromatic rings and were pleased to find good yields and enantioselectivities (**4a**–**4f**, Scheme 4), which prove the potentiality of the present methodology to access different 3-substituted isochromans. Further, the absolute configuration (*S*) of **4d** was determined using X-ray crystallographic analysis, thus establishing the stereochemical outcome of the current oxa-Michael addition process.[22]

A plausible mechanism, similar to our previous report,[14] for the current strategy is depicted in Scheme 5. The alkoxyboronate intermediates (**A**) were generated in situ from formyl- or homoformyl-chalcone in the presence of the neutral borane as the hydride source and a tertiary amine counterpart as the catalyst. Eventually, the alkoxyboronate **A** undergoes decomposition in the presence of the protic solvent to corresponding alcohol **C** through intermediate **B**. Finally, in the presence of the catalyst, the alcohol cyclizes to provide the desired product **3**, which is an alternative pathway, in which the direct cyclization of intermediate **B** cannot be ruled out. To explain the observed absolute stereochemistry of products, a transition state similar to our previous report has also been proposed in Scheme 6.

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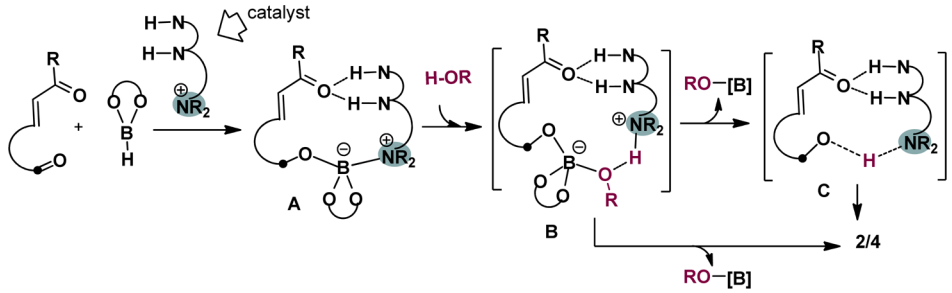
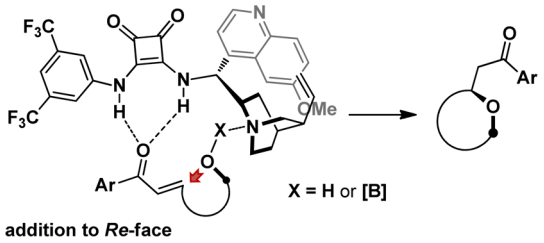
Scheme 5. Proposed Mechanism



Scheme 6. Proposed Model for the Origin of Stereoselectivity



To display the utility of chiral isochromans in the synthesis of biologically active natural products, we successfully demonstrated the synthesis of the D_4 receptor antagonist sonepiprazole[2] from 1-substituted isochroman **2a**, through a series of straightforward transformations as shown in Scheme 7.[5] Baeyer−Villiger oxidation of **2a** followed by reduction afforded the corresponding optically active alcohol **6**. Further transformation of alcohol **6** to the desired (+)-sonepiprazole **8** was achieved through mesitylation of alcohol **6** followed by the nucleophilic addition of amine **7**. However, the optical purity is thoroughly maintained here.

CONCLUSIONS

In summary, we have given an alternative method for the enantioselective synthesis of 1-substituted isochromans using stable starting materials and under an open-flask reaction conditions. The first enantioselctive synthesis of 3-substituted isochromans has also been shown. An enantioselective synthesis of sonepiprazole, a dopamine receptor antagonist, was given as a proof of synthetic applicability of the present concept.

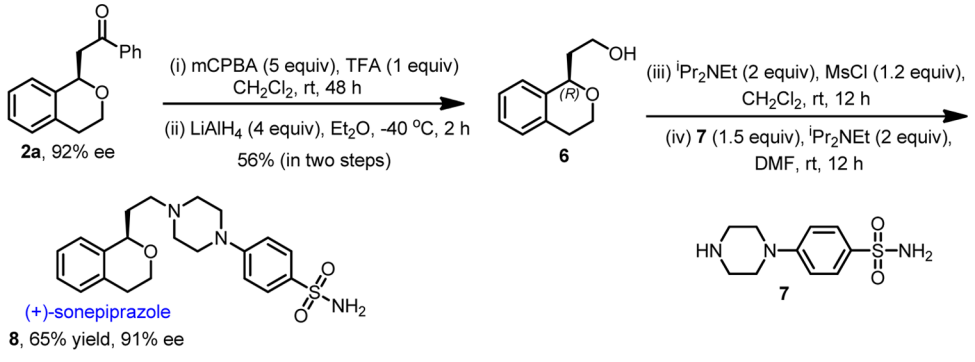
EXPERIMENTAL SECTION

General Methods. THF, DMF, and DCM solvents were all purified by a solvent purification system. All reagents and solvents were used as supplied commercially. Analytical thin-layer chromatographies (TLC) were performed on 0.2 mm coated Science silica gel (EM 60-F254) plates purchased from a supplier. Visualization was accomplished with UV light (254 nm) and exposure to ethanolic phosphomolybdic acid (PMA), anisaldehyde, or $KMnO_4$ solution, and $CeSO_4$ + ammonium phosphomolybdate + 10% H_2SO_4 followed by heating. Melting points are uncorrected. ^1H NMR spectra were acquired on a 400 MHz spectrometer, and chemical shifts are reported in parts per million relative to the residual solvent peak. ^{13}C NMR spectra were acquired at 100 MHz, and chemical shifts are reported in ppm relative to the residual solvent peak. Unless noted, NMR spectra were acquired in $CDCl_3$; individual peaks are reported as multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant in Hz. All IR spectra were obtained as neat films, and selected absorbances are reported in cm^{-1}. High-resolution data were acquired on a Micro TOF-Q-II mass spectrometer or by GC−MS (EI 70 eV) using a DB-5 column. The catalyst **A** was prepared according to the reported procedure described in ref 16.

*Preparation of Starting Materials (**1a−s**).* The 2-(2-methoxyvinyl)benzaldehyde was prepared starting from the commercially available 2-bromobenzaldehydes following the procedure reported as described in ref 17.

A solution of acetophenone (1.0 mmol, 1.0 equiv) in ethanol (3 mL) was added gradually to an aqueous solution of 10% KOH (3 mL) at 0 °C. After stirring for 15 min, 2-(2-methoxyvinyl)benzaldehyde (1.0 mmol, 1.0 equiv) was added at 0 °C and then allowed to warm to room temperature and stirred for 6 h. After completion (monitored by TLC), the reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the organic phase was subsequently washed with brine (1 × 5 mL). The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo*, and the crude was purified by column chromatography using *n*-hexane/ethyl acetate (3:97 to 10:90) as the eluent to afford 2-(2-methoxyvinyl)chalcones.

Scheme 7. Asymmetric Synthesis of (+)-Sonepiprazole[a]



[a]Absolute configuration (*R*) was determined by the comparison of optical rotation with the literature value (see Supporting Information).

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The deprotection of (2-(2-methoxyvinyl)chalcones) was carried out following the reported procedure as described in ref 18. To a solution of vinyl ether (1.0 mmol, 264 mg) in 6 mL of dichloromethane at room temperature was added Cl_3CCOOH (83 mg, 1.5 equiv) and stirred for 2 h at same temperature. Then, an additional amount of Cl_3CCOOH (63 mg, 1 equiv) was added, and the reaction was allowed to stir until the complete consumption of starting material was observed (based on TLC). All other starting materials **1b** to **1s** were prepared accordingly using the above methods.

*(E)-2-(2-(3-Oxo-3-phenylprop-1-en-1-yl)phenyl) Acetaldehyde (**1a**).* 45 mg, 30% yield; R_f = 0.24 (20:80 = EtOAc/*n*-hexane); light brown oil. FT-IR (neat): 2982, 2854, 1676, 1601, 1449, 1287, 1218, 1081, 973, 754, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.76 (t, J = 1.78 Hz, 1H), 8.01 (d, J = 7.21 Hz, 2H), 7.94 (d, J = 15.49 Hz, 1H), 7.77 (dd, J = 7.15, 1.80 Hz, 1H), 7.58 (m, 1H), 7.50 (m, 3H), 7.39 (td, J = 6.70 Hz, 1.84 Hz, 2H), 7.24 (s, 1H), 3.92 (d, J = 1.57 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.1, 190.0, 141.1, 137.9, 134.7, 133.0, 132.2, 131.5 (2C), 128.7 (2C), 128.5, 128.2, 127.2, 124.6, 48.2. HRMS (ESI, m/z): $[M - H]^+$ calculated for $C_{17}H_{13}O_2$, 249.0885; found, 249.0910.

*(E)-2-(2-(3-Oxo-3-(p-tolyl)prop-1-en-1-yl)phenyl) Acetaldehyde (**1b**).* 88 mg; 56% yield; R_f = 0.12 (20:90 = EtOAc/*n*-hexane); light yellow liquid. FT-IR (neat): 3059, 2923, 2356, 2334, 1726, 1661, 1609, 1486, 1329, 1223, 1182, 1031, 976, 821, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.74 (t, J = 0.9 Hz, 1H), 7.99−7.84 (m, 3H), 7.82−7.70 (m, 1H), 7.46 (d, J = 15.4 Hz, 1H), 7.36 (ddd, J = 10.5, 6.0, 3.7 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.23−7.19 (m, 1H), 3.90 (d, J = 1.5 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.3, 189.6, 143.94, 140.8, 135.3, 134.8, 132.2, 131.49, 130.5, 129.4 (2C), 128.7 (2C), 128.2, 127.2, 124.6, 48.2, 21.7. HRMS (ESI, m/z): calculated for $C_{18}H_{16}NaO_2$ $[M + Na]^+$, 287.1043; found, 287.1051.

*(E)-2-(2-(3-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)phenyl) Acetaldehyde (**1c**).* 87 mg; 52% yield; R_f = 0.12 (20:80 = EtOAc/*n*-hexane); light yellow semisolid. FT-IR (neat): 3064, 2937, 2841, 2731, 2359, 1725, 1659, 1603, 1511, 1420, 1335, 1261, 1223, 1172, 1022, 977, 836, 765 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.72 (t, J = 1.7 Hz, 1H), 8.00 (d, J = 8.9 Hz, 2H), 7.90 (d, J = 15.4 Hz, 1H), 7.79−7.68 (m, 1H), 7.45 (d, J = 15.4 Hz, 1H), 7.38−7.29 (m, 2H), 7.24−7.16 (m, 1H), 6.94 (d, J = 8.9 Hz, 2H), 3.89 (d, J = 1.5 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.3, 188.2, 163.6, 140.3, 134.9, 132.2, 131.5, 130.9 (2C), 130.8, 130.4, 128.1, 127.2, 124.5, 113.9 (2C), 55.5, 48.2. HRMS (ESI, m/z): calculated for $C_{18}H_{16}O_3$ $[M + H]^+$, 281.1172; found, 281.1192.

*(E)-2-(2-(3-(4-Fluorophenyl)-3-oxoprop-1-en-1-yl)phenyl) Acetaldehyde (**1d**).* 104 mg; 65% yield; R_f = 0.14 (20:80 = EtOAc/*n*-hexane); light yellow liquid. FT-IR (neat): 3072, 2846, 2357, 2329, 1728, 1665, 1603, 1328, 1218, 1157, 1026, 977, 839, 764 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.74 (t, J = 1.7 Hz, 1H), 8.07−7.99 (m, 2H), 7.92 (d, J = 15.4 Hz, 1H), 7.79−7.71 (m, 1H), 7.42 (d, J = 15.4 Hz, 1H), 7.37 (td, J = 7.2, 1.4 Hz, 2H), 7.24−7.20 (m, 1H), 7.18−7.11 (m, 2H), 3.91 (d, J = 1.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.2, 188.4, 166.7 (d, J = 254.8 Hz, 1C), 141.4, 134.6, 134.2 (d, J = 3.0 Hz, 1C), 132.3, 131.6, 131.2 (d, J = 9.3 Hz, 2C), 130.73, 128.21, 127.24, 124.08, 115.8 (d, J = 21.9 Hz, 2C), 48.22. HRMS (ESI, m/z): calculated for $C_{17}H_{13}FNaO_2$ $[M + Na]^+$, 291.0792; found, 291.0804.

*(E)-2-(2-(3-(4-Chlorophenyl)-3-oxoprop-1-en-1-yl)phenyl) Acetaldehyde (**1e**).* 116 mg; 54% yield; R_f = 0.15 (20:80 = EtOAc/*n*-hexane); light yellow liquid. FT-IR (neat): 3441, 3063, 2356, 2337, 1919, 1663, 1486, 1333, 1216, 1092, 833, 759, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.75 (t, J = 1.0 Hz, 1H), 7.96−7.90 (m, 3H), 7.75 (d, J = 7.5 Hz, 1H), 7.48−7.42 (m, 3H), 7.41−7.37 (m, 2H), 7.23 (d, J = 7.2 Hz, 1H), 3.91 (d, J = 0.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.1, 188.8, 141.7, 139.4, 136.2, 134.5, 132.3, 131.5, 130.8, 130.0 (2C), 129.0 (2C), 128.2, 127.2, 123.9, 48.2. HRMS (ESI, m/z): calculated for $C_{17}H_{13}ClNaO_2$ $[M + Na]^+$, 307.0496; found, 307.0498.

*(E)-2-(2-(3-(4-Iodophenyl)-3-oxoprop-1-en-1-yl)phenyl) Acetaldehyde (**1f**).* 169 mg; 75% yield; R_f = 0.18 (20:80 = EtOAc/*n*-hexane); colorless semisolid. FT-IR (neat): 3061, 2977, 2930, 2355, 1714, 1663, 1591, 1484, 1392, 1216, 1058, 1027, 1003, 823, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.74 (s, 1H), 7.93 (d, J = 15.4 Hz, 1H), 7.88−7.67 (5H), 7.44−7.32 (3H), 7.26−7.19 (1H), 3.91 (d, J = 1.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.0, 189.2, 141.7, 138.0 (2C), 137.1, 134.5, 132.3, 131.5, 130.8, 129.9 (2C), 128.2, 127.2, 123.9, 100.9, 48.2. HRMS (ESI, m/z): calculated for $C_{17}H_{14}IO_2$ $[M + H]^+$, 377.0033; found, 377.0043.

*(E)-2-(2-(3-(4-Bromophenyl)-3-oxoprop-1-en-1-yl)phenyl) Acetaldehyde (**1g**).* 61 mg; 31% yield; R_f = 0.26 (20:80 = EtOAc/*n*-hexane); light brown gel. FT-IR (neat): 2918, 2848, 1719, 1662, 1585, 1395, 1324, 1215, 1178, 1068, 1007, 827, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.76 (t, J = 1.65 Hz, 1H), 7.96 (d, J = 15.45 Hz, 1H), 7.87 (d, J = 8.49 Hz, 2H), 7.76 (m, 1H), 7.64 (d. J = 8.55 Hz, 2H), 7.40 (m, 3H), 7.23 (m, 1H), 3.92 (d, J = 1.45 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.0, 188.9, 141.7, 136.6, 134.6, 132.3, 132.0, 131.6, 130.8, 130.2, 130.1, 128.2, 127.3, 124.0, 48.2. HRMS (ESI+, m/z): calculated for $C_{17}H_{14}BrO_2$ ($[M + H]^+$), 329.0177; found, 329.0180.

*(E)-2-(2-(3-(Furan-2-yl)-3-oxoprop-1-en-1-yl)phenyl) Acetaldehyde (**1h**).* 88 mg; 61% yield; R_f = 0.20 (20:80 = EtOAc/*n*-hexane); light yellow liquid. FT-IR (neat): 3068, 2927, 2857, 2359, 2324, 1650, 1464, 1395, 1334, 1163, 1046, 763 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.69 (t, J = 1.7 Hz, 1H), 7.93 (d, J = 15.5 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 1.0 Hz, 1H), 7.43−7.24 (m, 4H), 7.16 (d, J = 7.2, 1H), 6.52 (dd, J = 3.5, 1.6 Hz, 1H), 3.87 (d, J = 1.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.2, 177.6, 153.5, 146.8, 140.3, 134.5, 132.3, 131.5, 130.7, 128.1, 127.3, 123.8, 117.9, 112.6, 48.1. HRMS (ESI, m/z): calculated for $C_{15}H_{13}O_3$ $[M + H]^+$, 241.0859; found, 241.0857.

*(E)-2-(2-(3-Oxo-3-(thiophen-2-yl)prop-1-en-1-yl)phenyl) Acetaldehyde (**1i**).* 61 mg, 39% yield; R_f = 0.26 (20:80 = EtOAc/*n*-hexane); light brown gel. FT-IR (neat): 2920, 2852, 1599, 1419, 1226, 978, 840, 818 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.76 (t, J = 1.70 Hz, 1H), 7.97 (d, J = 15.33 Hz, 1H), 7.86 (dd, J = 3.80, 0.76 Hz, 1H), 7.75 (m, 1H), 7.68 (m, 2H), 7.36 (m, 2H), 7.23 (m, 1H), 7.18 (m, 1H), 3.93 (d, J = 1.57 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.1, 181.7, 145.3, 140.5, 134.2, 132.3, 132.1, 131.5, 130.7, 130.3, 128.3, 128.2, 127.3, 124.4, 48.2. HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{15}H_{13}O_2S$, 257.0636; found, 257.0631.

*(E)-2-(6-(3-(Furan-2-yl)-3-oxoprop-1-en-1-yl)benzo[d][1,3] dioxol-5-yl) Acetaldehyde (Mixture of Isomers) (**1j**).* 82 mg; 48% yield; R_f = 0.10 (20:80 = EtOAc/*n*-hexane); light yellow semi solid. FT-IR (neat): 3087, 2914, 2852, 2357, 2338, 1659, 1262, 1037, 765 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.71 (t, J = 1.5 Hz, 1H), 7.90 (d, J = 15.4 Hz, 1H), 7.63 (d, J = 0.9 Hz, 1H), 7.36−7.20 (m, 3H), 6.67 (s, 1H), 6.57 (dd, J = 3.5, 1.6 Hz, 1H), 6.01 (s, 2H), 3.87 (d, J = 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.9, 177.7, 153.6, 150.1, 147.9, 146.5, 139.7, 128.1, 127.7, 121.5, 117.5, 112.6, 111.1, 106.2, 101.8, 47.8. HRMS (ESI, m/z): calculated for $C_{16}H_{13}O_5$ $[M + H]^+$, 285.0757; found, 285.0768.

*(E)-2-(2-Fluoro-6-(3-(furan-2-yl)-3-oxoprop-1-en-1-yl)phenyl) Acetaldehyde (**1k**).* 69 mg; 45% yield; R_f = 0.22 (20:80 = EtOAc/*n*-hexane); yellow oily liquid. FT-IR (neat): 3134, 2923, 2852, 2360, 2342, 1729, 1660, 1613, 1572, 1469, 1395, 1334, 1251, 1056, 768 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.77 (d, J = 1.1 Hz, 1H), 7.88 (d, J = 15.5 Hz, 1H), 7.65 (d, J = 0.9 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.41−7.27 (m, 3H), 7.14 (t, J = 8.7 Hz, 1H), 6.59 (dd, J = 3.6, 1.6 Hz, 1H), 3.99 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 196.9, 177.4, 161.5 (d, J = 246.1 Hz), 153.4, 146.9, 139.3 (d, J = 3.5 Hz), 136.8 (d, J = 4.0 Hz), 129.1 (d, J = 9.1 Hz), 125.0, 122.9 (d, J = 3.2 Hz), 120.0 (d, J = 16.4 Hz), 118.2, 116.8 (d, J = 23.0 Hz), 112.7, 40.3 (d, J = 3.5 Hz). HRMS (ESI, m/z): calculated for $C_{15}H_{12}FO_3$ $[M + H]^+$, 259.0765; found, 259.0767.

*(E)-2-(2-(3-(Furan-2-yl)-3-oxoprop-1-en-1-yl)-4-methylphenyl) Acetaldehyde (**1l**).* 60 mg; 40% yield; R_f = 0.18 (20:80 = EtOAc/*n*-hexane); colorless oily liquid. FT-IR (neat): 3133, 2922, 2732, 2358, 2334, 1717, 1649, 1496, 1469, 1394, 1335, 1251, 1162, 1087, 1048, 765 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.73 (t, J = 1.7 Hz, 1H), 7.97 (d, J = 15.5 Hz, 1H), 7.65 (s, 1H), 7.57 (s, 1H), 7.35 (m, 2H), 7.21 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 6.58 (dd, J = 3.5, 1.6 Hz, 1H), 3.88 (d, J = 1.4 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.4, 177.7, 153.5, 146.7, 140.5, 137.9, 134.2, 131.6,

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131.4, 129.4, 127.7, 123.4, 117.9, 112.6, 47.7, 21.1. HRMS (ESI, *m*/*z*): calculated for $C_{16}H_{14}NaO_3$ $[M + Na]^+$, 277.0835; found, 277.0854.

*(E)-2-(2-(3-(Furan-2-yl)-3-oxoprop-1-en-1-yl)-4,5-dimethoxyphenyl) Acetaldehyde (**1n**).* 86 mg; 48% yield; R_f = 0.12 (30:70 = EtOAc/*n*-hexane); light yellow liquid. FT-IR (neat): 3130, 2935, 2851, 2358, 2338, 1718, 1651, 1585, 1515, 1465, 1309, 1273, 1219, 1047, 766, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.70 (s, 1H), 7.93 (d, J = 15.4 Hz, 1H), 7.62 (s, 1H), 7.33−7.19 (m, 3H), 6.65 (s, 1H), 6.56 (d, J = 1.6 Hz, 1H), 3.93 (s, 3H), 3.87 (s, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.2, 177.8, 153.6, 151.5, 148.7, 146.4, 140.0, 126.6, 126.3, 121.2, 117.5, 113.7, 112.6, 109.3, 56.1, 56.0, 47.6. HRMS (ESI, *m*/*z*): calculated for $C_{17}H_{16}NaO_5$ $[M + Na]^+$, 323.0890; found, 323.0895.

*(E)-2-(5-(3-(Furan-2-yl)-3-oxoprop-1-en-1-yl)benzo[d][1,3] dioxol-4-yl) Acetaldehyde (**1o**).* 104 mg; 61% yield; R_f = 0.11 (20:80 = EtOAc/*n*-hexane); yellow semisolid. FT-IR (neat): 3132, 2912, 2357, 1727, 1650, 1588, 1470, 1261, 1070, 977, 933, 807, 764 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.74 (s, 1H), 7.82 (d, J = 15.5 Hz, 1H), 7.61 (d, J = 1.0 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.31−7.22 (m, 2H), 6.80 (d, J = 8.2 Hz, 1H), 6.56 (dd, J = 3.5, 1.7 Hz, 1H), 6.00 (s, 2H), 3.89 (d, J = 1.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.2, 177.6, 153.6, 148.9, 147.4, 146.6, 139.8, 128.5, 121.9, 121.9, 117.6, 114.0, 112.5, 108.1, 101.7, 41.1. HRMS (ESI, *m*/*z*): calculated for $C_{16}H_{13}O_5$ $[M + H]^+$, 285.0757; found, 285.0768.

*(E)-2-(2-(3-(4-Bromophenyl)-3-oxoprop-1-en-1-yl)-5-methoxyphenyl) Acetaldehyde (**1p**).* 60 mg, 28% yield; R_f = 0.19 (20:80 = EtOAc/*n*-hexane); light brown gel. FT-IR (neat): 2926, 2861, 1662, 1586, 1497, 1399, 1259, 1219, 1070, 1040, 1008, 823 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.75 (t, J = 1.80 Hz, 1H), 7.92−7.85 (m, 3H), 7.76 (d, J = 8.72 Hz, 1H), 7.63 (d, J = 8.53 Hz, 2H), 7.33 (d, J = 8.53 Hz, 1H), 6.91 (dd, J = 8.77 Hz, 2.58 Hz, 1H), 7.75 (d, J = 2.56 Hz, 1H), 3.90 (d, J = 1.54 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.8, 188.9, 161.7, 141.3, 137.0, 134.4, 131.9 (2C), 130.0 (2C), 128.9, 127.9, 126.8, 121.4, 116.6, 114.1, 55.8, 48.3. HRMS (ESI, *m*/*z*): $[M + H]^+$ calculated for $C_{18}H_{16}BrO_3$, 359.0283; found, 359.0277.

*(E)-2-(2-(3-(4-Bromophenyl)-3-oxoprop-1-en-1-yl)-4-chlorophenyl) Acetaldehyde (**1q**).* 105 mg; 48% yield; R_f = 0.22 (20:80 = EtOAc/*n*-hexane); light yellow semisolid. FT-IR (neat): 3068, 2926, 2852, 2328, 2312, 1729, 1664, 1589, 1483, 1397, 1321, 1217, 1028, 1007, 813, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.76 (t, J = 1.3 Hz, 1H), 7.91−7.78 (m, 3H), 7.69 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 15.4 Hz, 1H), 7.34 (dd, J = 8.5, 2.0 Hz, 1H), 7.23 (d, J = 2.1 Hz, 1H), 3.90 (d, J = 1.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.1, 188.6, 140.4, 136.5, 136.4, 134.0, 133.0, 132.0 (2C), 131.4, 130.0 (2C), 128.4, 128.4, 128.3, 124.1, 47.8. HRMS (ESI, *m*/*z*): calculated for $C_{17}H_{13}BrClO_2$ $[M + H]^+$, 362.9782; found, 362.9769.

*(E)-2-(5-Fluoro-2-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl) phenyl) Acetaldehyde (**1r**).* 42% yield; R_f = 0.23 (20:80 = EtOAc/*n*-hexane); light brown gel. FT-IR (neat): 2920, 2848, 1587, 1511, 1272, 1208, 1105, 1033, 1008 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.76 (s, 1H), 8.03 (m, 2H), 7.85 (d, J = 15.40 Hz, 1H), 7.76 (dd, J = 8.97 Hz, 5.71 Hz, 1H), 7.38 (d, J = 15.37 Hz, 1H), 7.16 (t, J = 8.61 Hz, 2H),7.07 (m, 1H), 6.96 (dd, J = 9.11 Hz, 2.59 Hz, 1H), 3.92 (d, J = 1.21 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.1, 188.2, 167.03 (d, J = 199 Hz, 1C), 163.5 (d, J = 196 Hz, 1C), 140.2, 134.80 (d, J = 8 Hz, 1C), 134.18 (d, J = 3 Hz, 1C), 131.17 (d, J = 9 Hz, 1C), 130.85 (d, J = 3 Hz, 1C), 129.24 (d, J = 9 Hz, 2C), 123.77 (d, J = 1 Hz, 1C), 118.34 (d, J = 22 Hz, 1C), 115.86 (d, J = 21 Hz, 2C), 115.50 (d, J = 21 Hz, 1C), 48. HRMS (ESI, *m*/*z*): $[M + H]^+$ calculated for $C_{17}H_{13}F_2O_2$, 287.0884; found, 287.0895.

*(E)-2-(2-(2-Methyl-3-oxo-3-phenylprop-1-en-1-yl)phenyl) Acetaldehyde (**1s**).* 60 mg, 54% yield; R_f = 0.31 (20:80 = EtOAc/*n*-hexane); light yellow liquid. FT-IR (neat): 3028, 2908, 2840, 1738, 1785, 1454, 1462, 1376, 1243, 1164, 1117,999, 840 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 9.62 (t, J = 2.0 Hz, 1H), 7.74 (d, J = 7.0 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.4 Hz, 2H), 7.38−7.30 (3H), 7.24 (d, J = 5.2 Hz, 1H), 7.12 (s, 1H), 3.64 (d, J = 1.9 Hz, 2H), 2.05 (d, J = 1.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, δ 199.2, 198.5, 139.9, 139.2, 137.9, 135.9, 132.0, 130.8, 130.6, 129.5, 129.3, 128.9, 128.5, 128.3, 127.6, 48.6, 14.3. HRMS (ESI, *m*/*z*): $[M - H]^+$ calculated for $C_{18}H_{15}O_2$, 263.1067; found, 263.1058.

*(E)-2-(2-(3-Oxobut-1-en-1-yl)phenyl) Acetaldehyde (**1t**).* 80 mg, 42% yield; R_f = 0.22 (20:80 = EtOAc/*n*-hexane); light brown oil. FT-IR (neat): 3015, 2909, 2101, 1717, 1644, 1360, 1259, 1175, 1121, 974, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.69 (t, J = 1.9 Hz, 1H), 7.69−7.58 (2H), 7.35 (dt, J = 19.2, 7.4 Hz, 2H), 7.22 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 16.0 Hz, 1H), 3.86 (d, J = 1.8 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.2, 198.2, 139.7, 134.3, 131.7, 131.5, 130.6, 129.3, 128.3, 127.1, 48.4, 27.8. HRMS (ESI, *m*/*z*): $[M + H]^+$ calculated for $C_{12}H_{13}O_2^+$, 189.0910; found, 189.0933.

*2-(2-(2-Oxoethyl)benzylidene)malononitrile (**1u**).* 100 mg, 51% yield; R_f = 0.24 (30:70 = EtOAc/*n*-hexane); yellow liquid. FT-IR (neat): 3017, 2905, 2839, 2231, 1638, 1590, 1452, 1368, 1228, 1197, 1113, 1052, 998, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 9.74 (s, 1H), 8.0 (d, J = 7.9 Hz, 1H), 7.93 (s, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 3.90 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.0, 158.1, 134.2, 133.4, 132.0, 130.8, 128.9, 128.7, 113.5, 112.2, 85.4, 77.4, 77.1, 76.8, 48.2. HRMS (ESI, *m*/*z*): $[M + H]^+$ calculated for $C_{12}H_9N_2O^+$, 197.0709; found, 197.0739.

*Representative Synthetic Procedure for the Synthesis of Substrates **3a**−**f**.* The indene derivatives were prepared using the representative procedure as reported in ref 19. The solution of indene derivatives (250 mg, representative case, where R = H) in dichloromethane at −78 °C was exposed to ozone for 10 min. After complete consumption of the olefin was observed (based on TLC), the reaction mixture was quenched with excess dimethylsulfide. The reaction mixture was then extracted with dichloromethane three times, dried over sodium sulfate, and the solvent removed under reduced pressure to get a colorless sticky oily like compound (248 mg, 62% yield).

To the dialdehyde (248 mg, 1.7 mmol) dissolved in dichloromethane was added the corresponding Wittig olefin (1 equiv, 634 mg), and the reaction mixture was then allowed to stir for 12 h at room temparature, after which the solvent evoparated. The crude was purified by column chromatography on silca-gel to provide the desired product **3** (152 mg, 35% yield).

*(E)-2-(4-Oxo-4-phenylbut-2-en-1-yl)benzaldehyde (**3a**).* 150 mg; 35% yield; R_f = 0.29 (20:80) = EtOAc/*n*-hexane); light yellow oily liquid. FT-IR (neat): 3024, 2920, 2360, 2324, 1940, 1652, 1492, 1452, 1070, 1028, 906, 756, 703, 540 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 10.17 (s, 1H), 7.85 (dd, J = 7.1, 1.5 Hz, 3H), 7.66−7.38 (5H), 7.32 (d, J = 7.5 Hz, 1H), 7.17 (dt, J = 15.4, 6.5 Hz, 1H), 6.79 (dt, J = 15.4, 1.4 Hz, 1H), 4.09 (dd, J = 6.5, 1.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 192.6, 190.7, 146.9, 139.8, 137.7, 134.1, 133.9, 133.9, 132.7, 131.4, 128.5, 128.5, 127.5, 127.1, 35.8. HRMS (ESI, *m*/*z*): calculated for $C_{17}H_{14}NaO_2^+$ ($[M + Na]^+$), 273.0886; found, 273.0869.

*(E)-2-(4-Oxo-4-(p-tolyl)but-2-en-1-yl)benzaldehyde (**3b**).* 172 mg; 38% yield; R_f = 0.26 (10:90) = EtOAc/*n*-hexane); yellow colored semi solid. FT-IR (neat): 3019, 2905, 2096, 1688, 1665, 1618, 1445, 1403, 1286, 1015, 976, 756, 637 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 10.17 (s, 1H), 7.84 (dd, J = 7.6, 1.1 Hz, 1H), 7.76 (d, J = 8.2 Hz, 2H), 7.55 (td, J = 7.5, 1.3 Hz, 1H), 7.46 (t, J = 7.1 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.15 (dt, J = 15.4, 6.5 Hz, 1H), 6.80 (dt, J = 15.4, 1.5 Hz, 1H), 4.07 (dd, J = 6.5, 1.1 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 192.5, 190.2, 146.3, 143.5, 140.0, 135.1, 134.0, 133.9, 133.8, 131.4, 129.2, 128.7, 127.5, 127.1, 35.7, 21.6. HRMS (ESI, *m*/*z*): calculated for $C_{18}H_{16}NaO_2^+$ ($[M + Na]^+$), 287.1043; found, 287.1065.

*(E)-2-(4-(4-Fluorophenyl)-4-oxobut-2-en-1-yl)benzaldehyde (**3c**).* 134 mg; 29% yield; R_f = 0.28 (20:80) = EtOAc/*n*-hexane); yellow colored semi solid. FT-IR (neat): 3076, 2914, 2065, 1668, 1663, 1506, 1410, 1265, 1230, 1156, 838, 756, 603 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 10.16 (s, 1H), 7.92−7.82 (3H), 7.56 (td, J = 7.5, 1.4 Hz, 1H), 7.47 (t, J = 7.1 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.22−7.05 (m, 3H), 6.77 (dt, J = 15.4, 1.5 Hz, 1H), 4.08 (dd, J = 6.5, 1.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 192.6, 189.0, 165.57 (d, J = 254.3 Hz), 147.1, 139.7, 134.1 (d, J = 6.2 Hz), 133.9, 131.5, 131.1 (d, J = 9.3 Hz), 127.6, 126.7, 115.6 (d, J = 21.9 Hz), 35.8. HRMS (ESI, *m*/*z*): calculated for $C_{17}H_{14}FO_2^+$ ($[M + H]^+$), 269.0972; found, 269.0963.

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(E)-2-(4-(4-Iodophenyl)-4-oxobut-2-en-1-yl)benzaldehyde (**3d**). 165 mg; 26% yield; R_f = 0.2 (20:80 = EtOAc/*n*-hexane); yellow colored semi solid. FT-IR (neat): 3020, 2909, 2830, 1651, 1390, 1340, 1281, 1213, 1004, 755 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 10.14 (s, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.4 Hz, 3H), 7.47 (t, J = 7.4 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.16 (dt, J = 15.3, 6.5 Hz, 1H), 6.72 (d, J = 15.4 Hz, 1H), 4.07 (d, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 192.7, 190.0, 147.6, 139.6, 137.8, 137.0, 134.2, 134.1, 133.8, 131.5, 129.9, 127.6, 126.6, 100.5, 35.9. HRMS (ESI, m/z): calculated for $C_{17}H_{12}IO_2^+$ ($[M - H]^+$), 374.9876; found, 374.9865.

(E)-2-Methyl-6-(4-oxo-4-(p-tolyl)but-2-en-1-yl)benzaldehyde (**3e**). 232 mg; 49%; R_f = 0.24 (20:80) = EtOAc/*n*-hexane); yellow colored semi solid. FT-IR (neat): 3025, 2922, 2848, 2360, 2325, 1942, 1601, 1492, 1452, 1373, 1181, 1151, 1069, 1028, 906 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 10.13 (s, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.63 (s, 1H), 7.25−7.11 (4H), 6.77 (dd, J = 15.4, 1.4 Hz, 1H), 4.02 (d, J = 5.7 Hz, 2H), 2.39 (d, J = 11.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 192.7, 190.3, 146.7, 143.5, 137.3, 137.0, 135.2, 134.8, 134.1, 133.7, 131.4, 129.2, 128.7, 127.0, 35.3, 21.6, 20.8. HRMS (ESI, m/z): calculated for $C_{19}H_{19}O_2^+$ ($[M + H]^+$), 279.1380; found, 279.1396.

(E)-4-Bromo-2-(4-(furan-2-yl)-4-oxobut-2-en-1-yl)benzaldehyde (**2f**). 80 mg; 24% yield; R_f = 0.12 (20:80 = EtOAc/*n*-hexane); yellow semisolid. FT-IR (neat): 3026, 2839, 2677, 2098, 1644, 1452, 1386, 1281, 1083, 1033, 940, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 10.11 (s, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.63−7.58 (2H), 7.48 (d, J = 1.6 Hz, 1H), 7.28−7.25 (1H), 7.22−7.18 (1H), 6.75 (dt, J = 15.4, 1.5 Hz, 1H), 6.53 (dd, J = 3.6, 1.7 Hz, 1H), 4.04 (dd, J = 6.6, 1.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 191.3, 188.1, 150.0, 146.7, 144.9, 134.9, 134.4, 133.1, 132.6, 131.4, 130.9, 126.5, 117.9, 112.4, 35.2. HRMS (ESI, m/z): calculated for $C_{15}H_{11}BrO_3Na$ $[M + Na]^+$, 340.9784; found, 340.9780.

Eanatioselective Synthesis of Isochromans: Standard Procedure for Tandem Hydroboration Intramolecular Oxa-Michael Reaction. To a solution of homobenzaldehyde **1** (0.225 mmol) and catalyst **A** (0.0225 mmol, 10 mol %) dissolved in 1.2 mL of nitromethane at 0 °C was added pinacolborane (0.67 mmol, 3 equiv). The reaction mixture was allowed to stir until the complete consumption of aldehyde was observed (TLC). Next, 0.3 mL of i-PrOH was added followed by stirring at 45 °C until the complete consumption of alkoxyboronate was observed. The solvent mixture was then evaporated *in vacuo*, and the crude was purified by column chromatography on silica-gel as the stationary phase and EtOAc/*n*-hexane as eluant.

2-(Isochroman-1-yl)-1-phenylethanone (**2a**). 35 mg; 81% yield; R_f = 0.24 (10:90 = EtOAc/*n*-hexane); colorless oil. FT-IR (neat): 3059, 2919, 2852, 2351, 1682, 1285, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.99 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.15−7.19 (m, 2H), 7.14−7.06 (m, 2H), 5.48 (dd, J = 8.6, 3.1 Hz, 1H), 4.09 (ddd, J = 11.3, 5.2, 3.8 Hz, 1H), 3.85−3.73 (m, 1H), 3.60 (dd, J = 16.2, 8.7 Hz, 1H), 3.30 (dd, J = 16.2, 3.5 Hz, 1H), 3.10−2.89 (1H), 2.69 (dt, J = 16.2, 3.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.2, 137.6, 137.3, 134.0, 133.0, 129.1, 128.6, 128., 126.6, 126.3, 124.6, 72.7, 63.4, 45.5, 28.9. HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{17}H_{17}O_2$, 253.1223; found, 253.1198; $[\alpha]_D^{26}$ = +22.64 (c = 0.1266, $CHCl_3$, 92% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.81 min (major), t_R = 13.08 min (minor).

2-(Isochroman-1-yl)-1-(p-tolyl)ethanone (**2b**). 32 mg; 71% yield; R_f = 0.26 (20:80 = EtOAc/*n*-hexane); colorless solid; mp. 95−97 °C. FT-IR (neat): 2923, 2853, 2364, 2342, 1681, 1607, 1282, 1180, 1104, 804, 750 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.90 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 7.21−7.15 (m, 2H), 7.11 (m, 2H), 5.48 (dd, J = 8.6, 3.2 Hz, 1H), 4.16−4.04 (m, 1H), 3.79 (ddd, J = 11.3, 9.6, 3.8 Hz, 1H), 3.57 (dd, J = 16.1, 8.7 Hz, 1H), 3.28 (dd, J = 16.2, 3.6 Hz, 1H), 3.05−2.95 (m, 1H), 2.70 (dt, J = 16.2, 3.5 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.8, 143.9, 137.7, 134.8, 134.0, 129.2, 129.0, 128.5, 126.5, 126.3, 124.6, 72.7, 63.4, 45.4, 28.9, 21.6. HRMS (ESI, m/z): calculated for $C_{18}H_{18}NaO_2$ ($[M + Na]^+$), 289.1199; found, 289.1207; $[\alpha]_D^{24}$ = +45.66 (c = 0.28, $CHCl_3$, 83% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 26.4 min (major), t_R = 18.8 min (minor).

2-(Isochroman-1-yl)-1-(4-methoxyphenyl)ethanone (**2c**). 32 mg; 68% yield; R_f = 0.28 (30:70 = EtOAc/*n*-hexane); light yellow liquid. FT-IR (neat): 2922, 2854, 2357, 2384, 1666, 1598, 1458, 1259, 1167, 1100, 1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.98 (d, J = 8.9 Hz, 2H), 7.21−7.15 (m, 2H), 7.15−7.07 (m, 2H), 6.93 (d, J = 8.9 Hz, 2H), 5.47 (dd, J = 8.6, 3.2 Hz, 1H), 4.10 (ddd, J = 11.3, 5.3, 3.7 Hz, 1H), 3.86 (s, 3H), 3.79 (ddd, J = 11.3, 9.6, 3.8 Hz, 1H), 3.55 (dd, J = 16.0, 8.7 Hz, 1H), 3.24 (dd, J = 16.0, 3.6 Hz, 1H), 3.05−2.95 (m, 1H), 2.70 (dt, J = 16.2, 3.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 196.6, 163.5, 137.8, 134.0, 130.7, 130.4, 129.0, 126.5, 126.2, 124.6, 113.7, 72.8, 63.5, 55.4, 45.1, 28.9. HRMS (ESI, m/z): calculated for $C_{18}H_{18}NaO_3$($[M + Na]^+$), 305.1148; found, 305.1157; $[\alpha]_D^{24}$ = +58.25 (c = 0.28, $CHCl_3$, 89% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 49.6 min (major), t_R = 32.0 min (minor).

1-(4-Fluorophenyl)-2-(isochroman-1-yl)ethanone (**2d**). 47 mg; 83% yield; R_f = 0.29 (10:90 = EtOAc/*n*-hexane); colorless liquid. FT-IR (neat): 2922, 2854, 2359, 2339, 1682, 1597, 1282, 1231, 1157, 1105, 848, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 8.02 (dd, J = 8.6, 5.5 Hz, 2H), 7.22−7.06 (m, 6H), 5.46 (dd, J = 8.5, 2.5 Hz, 1H)), 4.17−3.97 (m, 1H), 3.83−3.74 (m, 1H), 3.57 (dd, J = 16.0, 8.8 Hz, 1H), 3.27 (dd, J = 16.0, 3.4 Hz, 1H), 3.06−2.95 (m, 1H), 2.69 (dt, J = 16.2, 3.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 196.69, 165.8 (d, J = 254.9 Hz), 137.46, 134.07, 133.80 (d, J = 3.0 Hz), 131.1 (d, J = 9.3 Hz), 129.14, 126.70, 126.35, 124.54, 115.6 (d, J = 21.9 Hz), 72.86, 63.60, 45.42, 28.94. HRMS (ESI, m/z): calculated for $C_{17}H_{15}FNaO_2$($[M + Na]^+$), 293.0948; found, 293.0961; $[\alpha]_D^{23}$ = +75.18 (c = 0.72, $CHCl_3$, 86% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.6 min (major), t_R = 10.8 min (minor).

1-(4-Chlorophenyl)-2-(isochroman-1-yl)ethanone (**2e**). 35 mg; 70% yield; R_f = 0.28 (10:90 = EtOAc/*n*-hexane); coluorless solid; mp. 84−86 °C. FT-IR (neat): 3064, 2921, 2853, 2357, 1694, 1681, 1589, 1282, 1203, 1094, 845, 811, 748, 638 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.93 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.21−7.15 (m, 2H), 7.15−7.05 (m, 2H), 5.45 (dd, J = 8.7, 2.9 Hz, 1H), 4.09 (m, 1H), 3.78 (m, 1H), 3.56 (dd, J = 16.0, 8.8 Hz, 1H), 3.26 (dd, J = 16.0, 3.5 Hz, 1H), 3.09−2.92 (m, 1H), 2.69 (dt, J = 16.3, 3.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.1, 139.6, 137.3, 135.6, 134.0, 129.8, 129.1, 128.9, 126.7, 126.3, 124.5, 72.8, 63.6, 45.4, 28.9. HRMS (ESI, m/z): calculated for $C_{17}H_{15}ClNaO_2$ ($[M + Na]^+$), 309.0653; found, 309.0675; $[\alpha]_D^{23}$ = +106.06 (c = 0.5, $CHCl_3$, 91% ee) The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 15.9 min (major), t_R = 11.4 min (minor).

1-(4-Iodophenyl)-2-(isochroman-1-yl)ethanone (**2f**). 42 mg; 64% yield; R_f = 0.24 (10:90 = EtOAc/*n*-hexane); colorless crystalline solid; mp. 140−142 °C. FT-IR (neat): 2923, 2854, 2359, 1681, 1580, 1459, 1391, 1281, 1103, 805, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.82 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.18 (m, 2H), 7.15−7.10 (m, 2H), 5.44 (dd, J = 8.7, 2.7 Hz, 1H), 4.08 (ddd, J = 11.3, 5.3, 3.6 Hz, 1H), 3.88−3.67 (m, 1H), 3.54 (dd, J = 16.0, 8.9 Hz, 1H), 3.25 (dd, J = 16.0, 3.4 Hz, 1H), 3.01 (m, 1H), 2.69 (dt, J = 16.2, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.6, 137.9, 137.3, 136.6, 134.0, 129.8, 129.1, 126.7, 126.3, 124.5, 101.2, 72.8, 63.6, 45.3, 28.9. HRMS (ESI, m/z): calculated for $C_{17}H_{15}INaO_2$ ($[M + Na]^+$): 401.0009; found, 401.0026; $[\alpha]_D^{22}$ = +92.60 (c = 0.5, $CHCl_3$, 90% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 17.7 min (major), t_R = 12.7 min (minor).

1-(Furan-2-yl)-2-(isochroman-1-yl)ethanone (**2g**). 33 mg; 81% yield; R_f = 0.30 (30:70 = EtOAc/*n*-hexane); colorless liquid. FT-IR

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(neat): 2922, 2854, 2356, 2334, 1668, 1567, 1467, 1290, 1159, 1104, 1020, 752 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.58 (d, J = 0.9 Hz, 2H), 7.22 (d, J = 3.5 Hz, 2H), 7.20−7.14 (m, 2H), 7.14−7.07 (m, 2H), 5.44 (dd, J = 9.2, 3.1 Hz, 1H), 4.20−4.00 (m, 1H), 3.84−3.62 (m, 1H), 3.43 (dd, J = 15.4, 9.3 Hz, 1H), 3.17 (dd, J = 15.4, 3.5 Hz, 1H), 3.07−2.90 (m, 1H), 2.70 (dt, J = 16.3, 3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 187.0, 153.0, 146.6, 137.3, 134.0, 129.1, 126.6, 126.3, 124.6, 117.7, 112.3, 72.6, 63.2, 45.3, 28.8. HRMS (ESI, m/z): calculated for $C_{15}H_{14}NaO_3$ ($[M + Na]^+$), 265.0835; found, 265.0837; $[\alpha]_D^{24}$ = +93.26 (c = 0.85, $CHCl_3$, 96% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 34.9 min (major), t_R = 22.2 min (minor).

1-(4-Bromophenyl)-2-(isochroman-1-yl)ethanone ***(2h)***. 52 mg, 71% yield; R_f = 0.24 (10:80 = EtOAc/*n*-hexane); colorless solid; mp. 126−128 °C. FT-IR (neat): 3042, 2920, 2362, 1731, 1586, 1463, 1377, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.85 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.22−7.16 (m, 2H), 7.16−7.11 (m, 1H), 7.10−7.05 (m, 1H), 5.44 (dd, J = 8.7, 2.8 Hz, 1H), 4.08 (ddd, J = 11.3, 5.3, 3.5 Hz, 1H), 3.78 (ddd, J = 11.3, 9.9, 3.7 Hz, 1H), 3.55 (dd, J = 16.0, 8.9 Hz, 1H), 3.25 (dd, J = 16.0, 3.4 Hz, 1H), 3.11−2.83 (m, 1H), 2.69 (dt, J = 16.2, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.3, 136, 134, 131.9 (2C),129.9 (2C), 129.1, 128.3, 126.7, 126.3, 124.5, 123.0, 72.8, 63.6, 45.4, 28.9. HRMS (ESI, m/z): $[M - H]^+$ calculated for $C_{17}H_{14}BrO_2$, 329.0140; found 329.0172; $[\alpha]_D^{28}$ = +3.357 (c = 0.333, $CHCl_3$, 96% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 8.9 min (major), t_R = 6.9 min (minor).

2-(Isochroman-1-yl)-1-(thiophen-2-yl)ethanone ***(2i)***. 37 mg, 64% yield; R_f = 0.31 (10:90 = EtOAc/*n*-hexane); colorless oil. FT-IR (neat): 2924, 2852, 1654, 1414, 1283, 1105, 1013, 855, 748, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ, 7.74 (dd, J = 3.81 Hz, 0.89 Hz, 1H), 7.65 (dd, J = 4.97, 0.97 Hz, 1H), 7.18 (m, 2H), 7.12 (m, 3H), 5.46 (m, 1H), 4.11 (m, 1H), 3.79 (m, 1H), 3.50 (dd, J = 15.86, 8.96 Hz, 1H), 3.25 (dd, J = 15.63, 3.50 Hz, 1H), 2.99 (m, 1H), 2.70 (dt, J = 16.26, 3.51 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 190.9, 144.8, 137.4, 134.1, 132.5, 132.4, 129.1, 128.1, 126.7, 126.3, 124.6, 72.9, 63.5, 46.3, 28.9. HRMS (ESI, m/z): $[M + H]^+$ calculated for $C_{15}H_{15}O_2S$, 259.0787; found, 259.0792; $[\alpha]_D^{28}$ = +17.20 (c = 0.22, $CHCl_3$, 94% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 20.58 min (minor), t_R = 26.84 min (major).

2-(7,8-Dihydro-5H-[1,3]dioxolo[4,5-g]isochromen-5-yl)-1-(furan-2-yl)ethanone ***(2j)***. 36 mg; 72% yield; R_f = 0.26 (30:70 = EtOAc/*n*-hexane); colorless liquid. FT-IR (neat): 2923, 2853, 1668, 1485, 1467, 1386, 1233, 1106, 1036, 766 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.58 (s, 1H), 7.22 (d, J = 3.5 Hz, 1H), 6.56 (s, 2H), 6.52 (dd, J = 3.5, 1.6 Hz, 1H), 5.88 (s, 2H), 5.32 (dd, J = 9.0, 2.8 Hz, 1H), 4.03 (m, 1H), 3.71 (m, 1H), 3.37 (dd, J = 15.4, 9.2 Hz, 1H), 3.09 (dd, J = 15.4, 3.5 Hz, 1H), 2.92−2.79 (m, 1H), 2.59 (dt, J = 16.0, 3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 186.9, 153.0, 146.6, 146.3, 146.2, 130.1, 127.2, 117.7, 112.3, 108.7, 104.7, 100.8, 72.6, 63.0, 45.5, 28.8. HRMS (ESI, m/z): calculated for $C_{16}H_{14}NaO_5$ ($[M + Na]^+$), 309.0733; found, 309.0762; $[\alpha]_D^{22}$ = +119.66 (c = 0.83, $CHCl_3$, 93% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 70:30, flow rate 1.0 mL/min, λ = 254 nm), t_R = 34.1 min (major), t_R = 26.8 min (minor).

2-(8-Fluoroisochroman-1-yl)-1-(furan-2-yl)ethanone ***(2k)***. 21 mg; 81% yield; R_f = 0.22 (20:80 = EtOAc/*n*-hexane); colorless crystalline solid; mp. 104−106 °C. FT-IR (neat): 2921, 2853, 2355, 2337, 1651, 1468, 1246, 1100, 1019, 763, 468 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.58 (d, J = 0.9 Hz, 1H), 7.23 (d, J = 3.3 Hz, 1H), 7.14 (dd, J = 13.8, 7.9 Hz, 1H), 6.90 (t, J = 9.0 Hz, 2H), 6.53 (dd, J = 3.5, 1.7 Hz, 1H), 5.40 (dd, J = 9.0, 2.9 Hz, 1H), 4.11 (m, 1H), 3.75 (m, 1H), 3.43 (dd, J = 15.5, 9.1 Hz, 1H), 3.17 (dd, J = 15.5, 3.6 Hz, 1H), 2.92 (m, 1H), 2.73 (dt, J = 16.8, 3.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 186.6, 160.4 (d, J = 245.0 Hz), 152.9, 146.6, 139.6 (d, J = 5.4 Hz), 127.0 (d, J = 8.5 Hz), 121.7 (d, J = 19.4 Hz), 120.0 (d, J = 3.3 Hz), 117.8, 112.9 (d, J = 21.5 Hz), 112.4, 72.2 (d, J = 2.2 Hz), 62.5, 45.0, 22.0 (d, J = 3.5 Hz). HRMS (ESI, m/z): calculated for $C_{15}H_{13}FNaO_3$ ($[M + Na]^+$), 283.0741; found, 283.0765; $[\alpha]_D^{22}$ = +92.60 (c = 0.5, $CHCl_3$, 90% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 23.1 min (major), t_R = 15.6 min (minor).

1-(Furan-2-yl)-2-(7-methylisochroman-1-yl)ethanone ***(2l)***. 24 mg; 82% yield; R_f = 0.36 (10:90 = EtOAc/*n*-hexane); colorless liquid. FT-IR (neat): 2922, 2854, 2370, 1673, 1566, 1467, 1395, 1292, 1160, 1106, 1025, 808, 766, 645, 595 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.59 (d, J = 0.9 Hz, 1H), 7.23 (d, J = 3.4 Hz, 1H), 7.09 (m, 2H), 6.91 (s, 1H), 6.53 (dd, J = 3.5, 1.7 Hz, 1H), 5.40 (dd, J = 9.3, 2.6 Hz, 1H), 4.08 (m, 1H), 3.75 (m, 1H), 3.42 (dd, J = 15.4, 9.5 Hz, 1H), 3.17 (dd, J = 15.4, 3.4 Hz, 1H), 3.02 (m, 1H), 2.66 (dt, J = 16.1, 3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 187.0, 153.1, 146.6, 137.1, 135.8, 130.9, 128.9, 127.5, 125.1, 117.7, 112.3, 72.6, 63.3, 45.4, 28.5, 21.2. HRMS (ESI, m/z): calculated for $C_{16}H_{16}NaO_3$ ($[M + Na]^+$), 279.0992; found, 279.1016; $[\alpha]_D^{24}$ = +105.96 (c = 0.68, $CHCl_3$, 94% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 40.0 min (major), t_R = 21.7 min (minor).

2-(7-Fluoroisochroman-1-yl)-1-(furan-2-yl)ethanone ***(2m)***. 23 mg; 72% yield; R_f = 0.29 (20:80 = EtOAc/*n*-hexane); light yellow colored semi solid. FT-IR (neat): 2854, 2922, 2359, 1669, 1567, 1498, 1467, 1234, 1104, 1018, 764 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.58 (d, J = 1.0 Hz, 1H), 7.23 (d, J = 3.5 Hz, 1H), 7.05 (dd, J = 8.5, 5.6 Hz, 1H), 6.91−6.79 (m, 2H), 6.53 (dd, J = 3.5, 1.7 Hz, 1H), 5.38 (dd, J = 8.3, 2.4 Hz, 1H), 4.14−4.01 (m, 1H), 3.76 (m, 1H), 3.40 (dd, J = 15.5, 9.1 Hz, 1H), 3.15 (dd, J = 15.5, 3.7 Hz, 1H), 3.04−2.90 (m, 1H), 2.68 (dt, J = 16.4, 3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 186.8, 161.3 (d, J = 245.5 Hz), 153.0, 146.6, 136.2 (d, J = 7.6 Hz), 132.9 (d, J = 3.1 Hz), 126.2 (d, J = 8.2 Hz), 117.8, 115.3 (d, J = 20.7 Hz), 113.4 (d, J = 21.6 Hz), 112.4, 72.4, 62.9, 45.3, 28.9 (d, J = 1.3 Hz). HRMS (ESI, m/z): calculated for $C_{15}H_{13}FNaO_3$ ($[M + Na]^+$), 283.0741; found, 283.0763; $[\alpha]_D^{24}$ = +70.93 (c = 0.63, $CHCl_3$, 95% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 24.9 min (major), t_R = 16.9 min (minor).

2-(6,7-Dimethoxyisochroman-1-yl)-1-(furan-2-yl)ethanone ***(2n)***. 27 mg; 75% yield; R_f = 0.2 (30:70 = EtOAc/*n*-hexane); colorless crystalline solid; mp. 136−138 °C. FT-IR (neat): 2919, 2852, 2356, 2337, 1648, 1517, 1467, 1225, 1090, 1022, 994, 917, 852, 786, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.59 (s, 1H), 7.23 (d, J = 3.4 Hz, 1H), 6.58 (d, J = 11.3 Hz, 2H), 6.54−6.52 (m, 1H), 5.36 (dd, J = 8.7, 2.9 Hz, 1H), 4.07 (m, 1H), 3.82 (d, J = 18.8 Hz, 6H), 3.75 (m, 1H), 3.42 (dd, J = 15.2, 9.0 Hz, 1H), 3.11 (dd, J = 15.3, 3.6 Hz, 1H), 2.88 (m, 1H), 2.61 (d, J = 16.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 187.1, 153.1, 147.8, 147.5, 146.6, 129.0, 126.0, 117.8, 112.3, 111.6, 107.7, 72.4, 63.1, 56.0, 55.9, 45.5, 28.3. HRMS (ESI, m/z): calculated for $C_{17}H_{18}NaO_5$ ($[M + Na]^+$), 325.1046; found, 325.1076; $[\alpha]_D^{23}$ = +76.92 (c = 0.65, $CHCl_3$, 99% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 40:60, flow rate 1.0 mL/min, λ = 254 nm), t_R = 32.4 min (major), t_R = 27.9 min (minor).

2-(8,9-Dihydro-6H-[1,3]dioxolo[4,5-f]isochromen-6-yl)-1-(furan-2-yl)ethanone ***(2o)***. 28 mg; 80% yield; R_f = 0.28 (20:80 = EtOAc/*n*-hexane); colorless crystalline solid; mp. 138−140 °C. FT-IR (neat): 2921, 2853, 2320, 1667, 1568, 1467,1393, 1255, 1098, 1049, 919, 767 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ, 7.58 (d, J = 1.0 Hz, 1H), 7.22 (d, J = 3.4 Hz, 1H), 6.62 (dd, J = 37.6, 8.1 Hz, 2H), 6.53 (dd, J = 3.5, 1.7 Hz, 1H), 5.95 (s, 2H), 5.34 (dd, J = 9.1, 3.0 Hz, 1H), 4.10 (m, 1H), 3.74 (m, 1H), 3.39 (dd, J = 15.4, 9.1 Hz, 1H), 3.15 (dd, J = 15.4, 3.6 Hz, 1H), 2.82 (m, 1H), 2.64 (dt, J = 16.5, 3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 186.9, 153.0, 146.6, 145.4, 144.9, 131.2, 117.7, 117.3, 116.3, 112.3, 106.4, 101.1, 72.7, 62.6, 45.4, 22.8. HRMS (ESI, m/z): calculated for $C_{16}H_{14}NaO_5$ ($[M + Na]^+$), 309.0733; found, 309.0762; $[\alpha]_D^{23}$ = +70.07 (c = 0.56, $CHCl_3$, 88% ee). The

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enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 60:40, flow rate 1.0 mL/min, λ = 254 nm), t_R = 27.3 min (major), t_R = 19.5 min (minor).

*1-(4-Bromophenyl)-2-(6-methoxyisochroman-1-yl) ethanone (**2p**).* 39 mg, 49% yield; R_f = 0.25 (20:80 = EtOAc/*n*-hexane); colorless liquid. FT-IR (neat): 2958, 2922, 2852, 2358, 1731, 1644, 720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.85 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 6.99 (d, J = 8.5 Hz, 1H), 6.74 (dd, J = 8.5, 2.5 Hz, 1H), 6.65 (d, J = 2.3 Hz, 1H), 5.38 (dd, J = 8.6, 2.9 Hz, 1H), 4.22−3.98 (1H), 3.78 (s, 3H),3.77- 3.70 (1H), 3.51 (dd, J = 12, 8. Hz, 1H), 3.22 (dd, J = 8, 3.5 Hz, 1H), 3.05−2.89 (m, 1H), 2.65 (dt, J = 16.3, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.4, 158.2, 136.1, 135.4, 131.8 (2C), 129.9 (2C), 129.4, 128.3, 125.6, 113.6, 112.6, 72.7, 63.5, 55.0, 45.5, 29.2. HRMS (ESI, m/z): [M + H]$^+$ calculated for $C_{18}H_{18}BrO_3$, 361.0434; found, 361.0414; $[\alpha]_D^{27}$ = +83.72 (c = 0.100, $CHCl_3$, 87% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 80:20, flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.76 min (major), t_R = 12.14 min (minor).

*1-(4-Bromophenyl)-2-(7-chloroisochroman-1-yl)ethanone (**2q**).* 28 mg; 80% yield; R_f = 0.5 (10:80 = EtOAc/*n*-hexane); colorless crystalline solid; mp. 138−140 °C. FT-IR (neat): 2922, 2854, 2356, 2358, 2334, 1681, 1586, 1485, 1396, 1279, 1204, 1106, 1071, 1009, 811 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.84 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H), 7.16−7.05 (m, 2H), 7.00 (d, J = 8.2 Hz, 1H), 5.38 (dd, J = 8.4, 3.0 Hz, 1H), 4.06 (m, 1H), 3.74 (m, 1H), 3.52 (dd, J = 16.1, 8.5 Hz, 1H), 3.21 (dd, J = 16.1, 3.6 Hz, 1H), 2.97 (m, 1H), 2.66 (dt, J = 16.4, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 196.9, 135.9, 135.9, 135.8, 132.3, 131.9, 129.9, 128.8, 128.5, 126.5, 125.9, 72.5, 63.3, 45.2, 28.7. HRMS (ESI, m/z): calculated for $C_{17}H_{14}BrClNaO_2$ ([M + Na]$^+$), 386.9758; found, 386.9761; $[\alpha]_D^{23}$ = +90.70 (c = 0.75, $CHCl_3$, 93% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 16.3 min (major), t_R = 10.6 min (minor).

*2-(7-Fluoroisochroman-4-yl)-1-(4-fluorophenyl)ethanone (**2r**).* 43 mg, 68% yield; R_f = 0.24 (10:80 = EtOAc/*n*-hexane); yellowish solid. FT-IR (neat): 3030, 2923, 2852, 2360, 1683, 1596, 760 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 8.23−7.83 (m, 2H), 7.12 (t, J = 8.6 Hz, 2H), 7.04 (dd, J = 8.5, 5.6 Hz, 1H), 6.95−6.70 (m, 2H), 5.33 (d, J = 11.3 Hz, 1H), 4.12−4.03 (m, 1H), 3.76 (ddd, J = 11.4, 9.8, 3.8 Hz, 1H), 3.54 (dd, J = 16.1, 8.5 Hz, 1H), 3.23 (dd, J = 16.1, 3.7 Hz, 1H), 3.09−2.91 (1H), 2.67 (dt, J = 16.4, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 196.5, 165.8 (d, J = 254 Hz, 1C), 161.3 (d, J = 244 Hz, 1C), 136.33 (d, J = 8 Hz, 1C), 133.70 (d, J = 3 Hz, 1C), 133.12 (d, J = 3 Hz, 1C), 131.06 (d, J = 9 Hz, 2C), 126.2 (d, J = 8 Hz, 1C), 115.72 (d, J = 22 Hz, 2C), 115.4 (d, J = 20 Hz, 1C), 113.5 (d, J = 22 Hz, 1C), 72.6, 63.3, 45.4, 29.0 (d, J = 1.35 Hz, 1C). HRMS (ESI, m/z): [M + Na]$^+$ calculated for $C_{17}H_{14}F_2NaO_2$, 311.0854; found, 311.0867; $[\alpha]_D^{27}$ = +50.59 (c = 0.207, $CHCl_3$, 83% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 12.19 min (minor), t_R = 9.03 min (major).

*(E)-3-(2-(2-hydroxyethyl)phenyl)-2-methyl-1-phenylprop-2-en-1-one (**1s−OH**).* 12 mg, 78%; R_f = 0.31 (20:80 = EtOAc/*n*-hexane); light yellow liquid. FT-IR (neat): 3400, 3029, 2972, 2839, 1731, 1738, 1462, 1376, 1254, 1169, 1064, 697. ^{1}H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 8.4 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.4 Hz, 2H), 7.29−7.20 (5H), 3.68 (t, J = 6.8 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H), 2.02 (d, J = 1.2 Hz, 3H), 1.51 (s, 1H). HRMS (ESI, m/z): [M + H]$^+$ calculated for $C_{18}H_{19}O_2$, 267.1380; found, 267.1355.

*(E)-4-(2-(2-Hydroxyethyl)phenyl)but-3-en-2-one (**1t−OH**).* 35 mg, 82% yield; R_f = 0.24 (40:60 = EtOAc/*n*-hexane); oily liquid. FT-IR (neat): 3408, 3020, 2909, 1649, 1438, 1362, 1254, 1213, 1175, 1048, 1022, 906, 748 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.88 (d, J = 16.0 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.33 (t, J = 7.3 Hz, 1H), 7.26−7.21 (2H), 6.64 (d, J = 16.0 Hz, 1H), 3.81 (t, J = 6.8 Hz, 2H), 3.02 (t, J = 6.8 Hz, 2H), 2.36 (s, 3H), 1.95 (broad singlet, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 198.4, 140.6, 138.5, 133.5, 130.8, 130.4, 128.4, 127.1, 126.7, 63.4, 36.4, 28.0. HRMS (ESI, m/z): [M + H]$^+$ calculated for $C_{12}H_{15}O_2$, 191.1067; found, 191.1079.

*Representative Procedure for the Synthesis of 3-Isochromans **4a−f**.* The procedure was the same as that described for 1-substituted isochromans, except that 20 mol % of **A** and 5 equiv of pinacolborane were used.

*2-(Isochroman-3-yl)-1-phenylethanone (**4a**).* 31 mg; 56% yield; R_f = 0.39 (10:90 = EtOAc/*n*-hexane); colorless liquid. FT-IR (neat): 3029, 2923, 2360, 2334, 1943, 1601, 1492, 1451, 1373, 1070, 1028, 906, 757, 702, 540 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 8.00 (d, J = 7.2 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.18−7.13 (m, 1H), 7.11−7.07 (1H), 6.98 (dd, J = 5.0, 3.8 Hz, 1H), 4.88−4.78 (2H), 4.42−4.29 (m, 1H), 3.48 (dd, J = 16.4, 6.8 Hz, 1H), 3.12 (dd, J = 16.4, 5.7 Hz, 1H), 2.98−2.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.8, 137.1, 134.4, 133.2, 132.8, 128.8, 128.6, 128.2, 126.4, 126.1, 124.2, 71.3, 68.2, 44.8, 34.0. HRMS (ESI, m/z): calculated for $C_{17}H_{16}NaO_2^+$ ([M + Na]$^+$), 275.1043; found, 275.1029; $[\alpha]_D^{19}$ = −49.14 (c = 0.35, $CHCl_3$, 81% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak lux 5 μm cellulose-1 column (hexane/2-propanol = 98:02, flow rate 1.0 mL/min, λ = 254 nm), t_R = 22.5 min (major), t_R = 24.4 min (minor).

*2-(Isochroman-3-yl)-1-(p-tolyl)ethanone (**4b**).* 40 mg; 66% yield; R_f = 0.36 (10:90 = EtOAc/*n*-hexane); colorless solid; mp. 96−98 °C. FT-IR (neat): 3025, 2923, 2360, 2329, 1924, 1601, 1492, 1451, 1373, 1180, 1156, 1068, 1028, 906, 756, 702, 540 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.90 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.17−7.12 (m, 2H), 7.11−7.07 (m, 1H), 7.01−6.96 (m, 1H), 4.91−4.77 (m, 2H), 4.39−4.31 (m, 1H), 3.46 (dd, J = 16.3, 6.7 Hz, 1H), 3.09 (dd, J = 16.3, 5.8 Hz, 1H), 2.93−2.77 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.4, 144.0, 134.7, 134.4, 132.9, 129.3, 128.8, 128.4, 126.4, 126.0, 124.2, 71.4, 68.2, 44.7, 34.0, 21.6. HRMS (ESI, m/z): calculated for $C_{18}H_{17}O_2^+$ ([M − H]$^+$): 265.1223; found, 265.1253; $[\alpha]_D^{18}$ = −106.5 (c = 0.53, $CHCl_3$, 84% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak lux 5 μm cellulose-1 column (hexane/2-propanol = 99.5:0.5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 13.1 min (major), t_R = 11.5 min (minor).

*1-(4-Fluorophenyl)-2-(isochroman-3-yl)ethanone (**4c**).* 36 mg; 60% yield; R_f = 0.32 (10:90 = EtOAc/*n*-hexane); colorless liquid. FT-IR (neat): 3015, 2922, 2360, 2334, 1642, 1492, 1452, 1373, 1069, 1028, 906, 757, 703, 539 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 8.13−7.94 (m, 2H), 7.18−7.07 (5H), 7.01−6.95 (m, 1H), 4.94−4.70 (m, 2H), 4.38−4.31 (m, 1H), 3.45 (dd, J = 16.3, 6.9 Hz, 1H), 3.07 (dd, J = 16.3, 5.4 Hz, 1H), 2.94−2.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 196.3, 165.8 (d, J = 255.0 Hz), 133.6 (d, J = 2.9 Hz), 133.6, 132.7, 131.0, 130.9, 128.8, 126.3 (d, J = 32.8 Hz), 124.2, 115.7 (d, J = 21.9 Hz), 71.3, 6.2, 4.7, 34.0. HRMS (ESI, m/z): calculated for $C_{17}H_{14}FO_2^+$ ([M − H]$^+$), 269.0972; found, 269.0971; $[\alpha]_D^{18}$ = −14.5 (c = 0.25, $CHCl_3$, 87% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak lux 5 μm cellulose-1 column (hexane/2-propanol = 99.5:0.5, flow rate 1.0 mL/min, λ = 254 nm), t_R = 18.0 min (major), t_R = 13.8 min (minor).

*1-(4-Iodophenyl)-2-(isochroman-3-yl)ethanone (**4d**).* 45 mg; 63% yield; R_f = 0.32 (10:90 = EtOAc/*n*-hexane); colorless solid; mp. 96−98 °C. FT-IR (neat): 3021, 2914, 2329, 1675, 1594, 1579, 1443, 1390, 1254, 1096, 1057, 746 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.83 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 7.16 (dd, J = 5.6, 3.4 Hz, 2H), 7.12−7.07 (m, 1H), 6.98 (dd, J = 5.0, 3.8 Hz, 1H), 4.88−4.73 (m, 2H), 4.33 (m, 1H), 3.42 (dd, J = 16.3, 7.0 Hz, 1H), 3.05 (dd, J = 16.3, 5.4 Hz, 1H), 2.93−2.76 (2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.2, 137.9, 136.4, 134.3, 132.7, 129.7, 128.8, 126.5, 126.1, 124.2, 101.3, 71.3, 68.2, 44.6, 33.9. HRMS (ESI, m/z): calculated for $C_{17}H_{15}INaO_2^+$ ([M + Na]$^+$), 401.0009; found, 401.0005; $[\alpha]_D^{19}$ = −92.91 (c = 0.83, $CHCl_3$, 74% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak lux 5 μm cellulose-1 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 21.3 min (major), t_R = 17.1 min (minor).

*2-(8-Methylisochroman-3-yl)-1-(p-tolyl)ethanone (**4e**).* 42 mg; 64% yield; R_f = 0.32 (10:90 = EtOAc/*n*-hexane); colorless crystalline solid; mp. 121−123 °C. FT-IR (neat): 3024, 2923, 2360, 2334, 1943, 1602, 1492, 1452, 1181, 1153, 1069, 1028, 906, 757, 703 cm^{-1}. ^{1}H

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NMR (400 MHz, $CDCl_3$): δ, 7.90 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 6.98 (s, 2H), 6.80 (s, 1H), 4.88−4.73 (m, 2H), 4.37−4.30 (m, 1H), 3.45 (dd, J = 16.3, 6.8 Hz, 1H), 3.08 (dd, J = 16.3, 5.7 Hz, 1H), 2.93−2.69 (m, 2H), 2.35 (d, J = 46.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 197.5, 144.0, 135.6, 134.7, 134.2, 129.8, 129.3, 128.6, 128.4, 127.2, 124.7, 71.6, 68.2, 44.7, 33.7, 21.6, 21.0. HRMS (ESI, m/z): calculated for $C_{19}H_{21}O_2^+$ ($[M + H]^+$), 281.1536; found, 281.1561; $[\alpha]_D^{18}$ = −61.6 (c = 0.90, $CHCl_3$, 85% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak lux 5 μm cellulose-1 column (hexane/2-propanol = 98:2, flow rate 1.0 mL/min, λ = 254 nm), t_R = 23.1 min (major), t_R = 16.2 min (minor).

*2-(6-Bromoisochroman-3-yl)-1-(furan-2-yl)ethanone (**4f**).* 40 mg; 56% yield; R_f = 0.4 (20:80 = EtOAc/*n*-hexane); yellow semisolid. FT-IR (neat): 3016, 2918, 2364, 2087, 1642, 1493, 1465, 1456, 1261, 1158, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.60 (d, J = 0.9 Hz, 1H), 7.29−7.25 (3H), 6.85 (d, J = 8.1 Hz, 1H), 6.55 (dd, J = 3.5, 1.6 Hz, 1H), 4.74 (s, 2H), 4.32−4.24 (m, 1H), 3.31 (dd, J = 15.8, 7.4 Hz, 1H), 2.95 (dd, J = 15.8, 5.3 Hz, 1H), 2.85−2.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 186.4, 152.9, 146.7, 135.1, 133.3, 131.5, 129.2, 125.9, 120.0, 117.7, 112.4, 70.8, 67.8, 44.4, 33.6. HRMS (ESI, m/z): calculated for $C_{15}H_{13}BrO_3Na$ $[M + Na]^+$, 342.9940; found, 342.9929; $[\alpha]_D^{20}$ = −9.1 (c = 0.32, $CHCl_3$, 77% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 14.5 min (major), t_R = 15.8 min (minor).

Synthesis of (+)-Sonepiprazole. Alcohol **6** was prepared following the Baeyer−Villiger oxidation followed by the LAH reduction protocol as discussed in the case of **3zb**.[13g]

*2-(Isochroman-1-yl)ethanol (**6**).*[20] 56% yield in two steps; R_f = 0.29 (30:70 = EtOAc/*n*-hexane); colorless oil. FT-IR (neat): 3223, 2925, 1722, 1607, 1455, 1295, 1120, 1032, 760, 697 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ, 7.18−7.03 (m, 4H), 5.99 (dd, J = 8.70, 1.93 Hz, 1H), 4.17 (m, 1H), 3.80 (m, 3H), 3.03 (m, 2H), 2.68 (dt, J = 16.27, 2.29 Hz, 1H),2.22 (m, 1H), 2.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 137.4, 133.7, 129.0, 126.5, 126.3, 124.5, 76.4, 63.7, 61.0, 37.5, 29.0. HRMS (ESI, m/z): calculated for $C_{11}H_{13}O_2$ ($[M - H]^+$): 177.0916; found, 177.0910; $[\alpha]_D^{26}$ = +45.47 (c = 0.45, $CHCl_3$, 88% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 90:10, flow rate 1.0 mL/min, λ = 254 nm), t_R = 13.58 min (major), t_R = 15.21 min (minor).

The comparison of the optical rotation value of **6** with the literature value (*R*)-(+)[20] provided the absolute configuration of our synthesized isochromans.

*Synthetic Procedure for 4-(Piperazin-1-yl)benzenesulfonamide (**7**).* It was prepared according to the reported literature as follows.[20] A mixture of 4-fluorobenzenesulfonamide (5 mmol, 1 equiv) and piperazine (20 mmol, 4 equiv) in water (30 mL) was heated at 100 °C overnight. The solid was then filtered, washed with water and toluene, and dried under reduced pressure to give the pure product.

*Synthetic Procedure for 4-(4-(2-(Isochroman-1-yl)ethyl)-piperazin-1-yl)benzenesulfonamide (**8**).*[20] The mesitylation of alcohol **6** was carried out according to the reported method.[20] A 5 mL round-bottomed flask was charged with 2-(isochroman-1-yl)-ethanol (0.25 mmol, 1 equiv) and CH_2Cl_2 (1 mL). The mixture was cooled using an ice/water bath. DIEA (0.5 mmol, 2 equiv) was added to the mixture followed by dropwise addition of methanesulfonyl chloride (0.3 mmol, 1.2 equiv). The mixture was stirred for 12 h at room temperature. Once the starting material was completely consumed, it was diluted with CH_2Cl_2. The diluted reaction mixture was washed with 1 N HCl (1 mL). The organic layer was dried with $MgSO_4$ and filtered through Celite to get the product which was used for the next step without further purification.

A DMF (1 mL) solution of the above product (0.2 mmol, 1 equiv), 4-(piperazin-1-yl)benzene sulphonamide **7** (0.3 mmol, 1.5 equiv), and *N*,*N*-diisopropylethylamine (0.4 mmol, 2 equiv) was stirred for 12 h at room temperature. Once starting material completely disappeared (on TLC), the volatile component was removed in vacuum. The residue was partitioned between CH_2Cl_2 and water, and the organic layer was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography using the solvent system MeOH/CH_2Cl_2 (2:98 to 10:90) to afford the title compound as a white solid.

*4-(4-(2-(Isochroman-1-yl)ethyl)piperazin-1-yl) benzenesulfonamide (**8**).* 65% yield; R_f = 0.34 (05:95 = MeOH/CH_2Cl_2); colorless solid; mp 66−69 °C. FT-IR (neat): 3409, 2924, 2853, 1651, 1594, 1463, 1191, 1155, 1025, 999, 826, 766 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-D_6): δ, 8.11 (s, 1H), 7.65 (dd, J = 10.85, 9.09 Hz, 3H), 7.20 (m, 2H), 7.05 (m, 3H), 4.78 (d, J = 8.40 Hz, 1H),4.06 (m, 1H), 3.69 (m, 1H), 3.53 (m, 2H), 3.30 (m, 8H), 2.88 (m, 1H), 2.68 (m, 1H), 2.41 (m, 1H), 2.11 (m, 1H), 1.91 (m, 1H). ^{13}C NMR (100 MHz, DMSO-D_6): δ, 166.2, 158.0, 157.7, 143.3, 138.9, 137.9, 133.9, 132.3, 131.2, 129.9, 119.6, 118.8, 78.8, 67.5, 59.4, 57.8, 53.3, 52.3, 39.4, 37.8, 33.7. HRMS (ESI, m/z): calculated for $C_{21}H_{28}N_3O_3S$ ($[M + H]^+$), 402.1851; found, 402.1865; $[\alpha]_D^{28}$ = +20.20 (c = 0.40, MeOH, 91% ee). The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralpak IC-3 column (hexane/2-propanol = 50:50, flow rate 1.0 mL/min, λ = 254 nm), t_R = 51.91 min (minor), t_R = 57.93 min (major).

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic data of **4d**, the copies of ^{1}H and ^{13}C NMR spectra for all products, and HPLC-traces for ee determination. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00719.

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Notes

The authors declare no competing financial interest.

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(21) Even the corresponding alcohols (**2s-OH** and **2t-OH** from **1s** and **1t**, respectively) were found to be stable toward column chromatography.
(22) Crystallographic data for catalyst **4d** is available free of charge from the Cambridge Crystallographic Data Centre, accession number CCDC-1400567.

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