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Organocatalytic Enantioselective Intramolecular Oxa-Michael Reaction of Enols: Synthesis of Chiral Isochromenes

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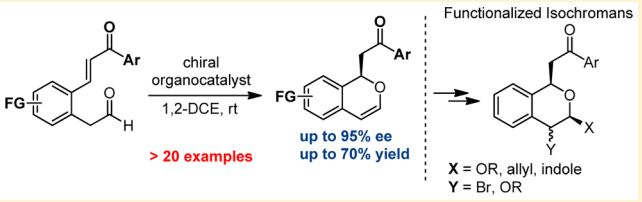
Supporting Information

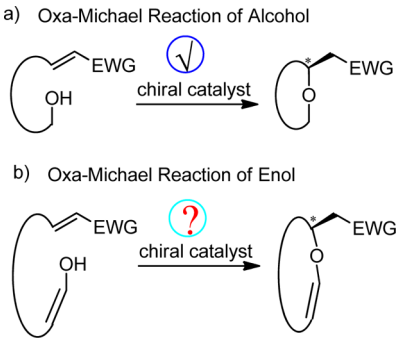
ABSTRACT: An unprecedented enantioselective intramolecular oxa-Michael reaction of enols has been described. A squaramide-containing tertiary amine based bifunctional organocatalyst efficiently activates the *o*-homoformyl chalcones to provide the chiral isochromenes in moderate yields and good to excellent enantioselectivities. Further, late-stage functionalizations of the vinyl ether moiety of the chiral isochromene products have also been exemplified.



INTRODUCTION

Intramolecular oxa-Michael reaction, one of the most fundamental organic reactions for the synthesis of O-heterocycles, allows a direct installation of new C−O bonds in a very efficient way.[1] However, the development of enantioselective oxa-Michael reactions of alcohols remained a challenge owing to its reversible addition step and poor nucleophilicity.[1b,c] To overcome this, various activation pathways have been designed and successfully implemented using either chiral Lewis acids,[2] secondary amines,[3] chiral phosphoric acids,[4] or a tertiary amine containing bifunctional organocatalysts[5] (Scheme 1a). Besides

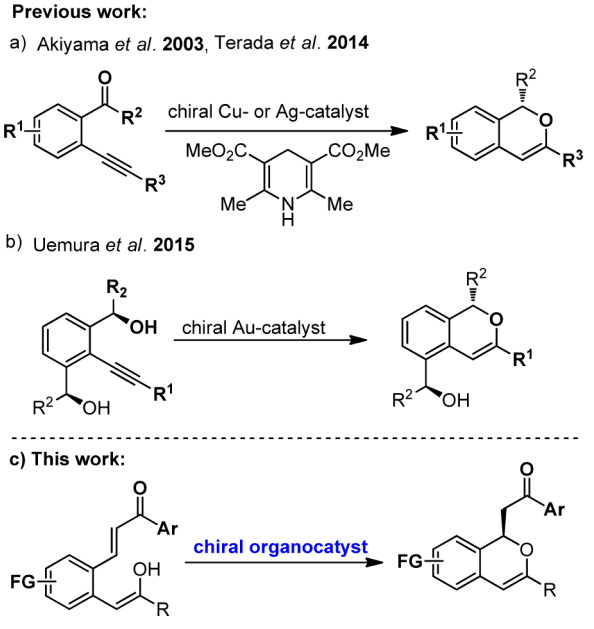
Scheme 1. Catalytic Asymmetric Oxa-Michael Reactions



alcohols, other oxo-nucleophiles such as phenols,[6a−c] oximes,[6d−f] hydroxylamines,[6i] and hydrogen peroxide[6g−i] have also been explored. However, to the best of our knowledge, the enantioselective addition of enols has not been developed to date (as depicted in Scheme 1b). Nevertheless, enols are even poorer nucleophiles compared to alcohols;[7] therefore, finding a catalytic process to enable such oxa-Michael addition in an enantiocontrolled manner is considerably challenging.

Isochromenes are important building blocks found in various natural products and molecules of biological importance.[8] Further, the presence of a "vinyl ether" counterpart in the isochromene moiety could potentially be exploited for the late-stage functionalization to provide densely functionalized isochomans, an important core of several bioactive molecules.[9] Although there are plenty of methods available for the synthesis of achiral isochromenes,[10] the enantioselective variants are extremely rare.[11] Two pioneering reports are available to date; the first one involves the enantioselective reduction/cyclization cascade of *o*-keto aryl acetylenes using chiral copper and silver catalysts (Scheme 2a).[11a] Very recently, the second strategy was

Scheme 2. Strategies for the Synthesis of Chiral Isochromenes



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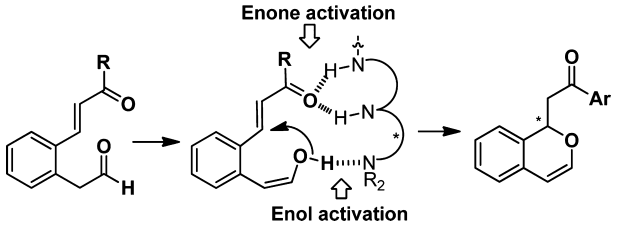
developed where the desymmetrization of 1,6-dihydroxy aryl acetylene was achieved using a chiral gold catalyst (Scheme 2b).[11b] Therefore, the development of additional catalytic asymmetric strategies remains in high demand. Our strategy, as shown in Scheme 2c, is based on the enantioselective oxa-Michael addition of enol in the presence of chiral bifunctional organocatalyst.

As a part of our ongoing programs toward the development of enantioselective oxa-Michael addition processes implying chiral organocatalysts,[12] we hypothesized a bifunctional activation of *o*-homoformyl chalcones using a thiourea/squaramide containing tertiary amine-based organocatalyst, as outlined in Scheme 3, would provide the chiral isochomenes via an enantioselective oxa-Michael addition of enol.

Scheme 3. Concept of the Catalytic Mode of Action

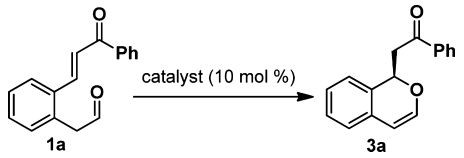


RESULTS AND DISCUSSION

First, the reaction of *o*-homoformyl chalcone **1a** was chosen as a model substrate using 10 mol % of various chiral thiourea- and squaramide-based catalysts (**2a**–**f**) derived from cinchona alkaloid (Table 1) in 1,2-DCE at rt (entries 1–6). As shown in entry 2, catalyst **2b** was shown to be the most efficient in terms of conversion and enantioselectivity. Presumably, a superior H-bond donor property of the squaramide moiety in comparison to the thiourea moiety with the enone moiety of the substrate could be the main reason for such a difference in reactivity. A similar reactivity has also been observed previously.[12] Other solvents such as toluene, chlorobenzene (PhCl), benzene, acetonitrile (MeCN), and trifluoroethanol (F_3CCH_2OH) remained less effective (entries 7–11, respectively). Decrease (5 mol %) as well as increase (15 mol %) in the catalyst loading did not provide better results (entries 13 and 14, respectively).

The optimized enantioselective oxa-Michael addition conditions (Table 1, entry 2) were screened for an array of *o*-homoformyl chalcones as shown in Scheme 4. The influence of the substitution on the aromatic ring of the α,β-unsaturated moieties was first investigated (**3a**–**l**). The observed enantioselectivities were excellent (86–95% ee) with electron-donating substitutions on the phenyl ring (**3a**–**f**). Notably, instead of an aryl moiety, a heteroaryl group such as a 2-thiophene-yl moiety provided the desired product with similar selectivity (**3f**). In general, the yields of the reaction were moderate (46–65%) due to the reversibility of the process (tested later as shown in Scheme 7).[13] Electron-deficient substituents such as *p*-F (**3g**), *p*-Cl (**3h**), *p*-Br (**3i**), *p*-I (**3j**), and *m*-F_3C (**3k**) provided the desired product with good enantiosioselectivities (80–93% ee) albeit moderate yields. Enantioselectivity increases from chloro to bromo to iodo, whereas a decrease in yields is observed (Cl, 80%; Br, 89%; and I, 93% ee). The presence of a trifluoromethyl group at the *meta*-postion gives high enantioselectivity over the *para*-position (**3k** vs **3l**).

Table 1. Optimization of the Reaction Conditions[a]



entry	2	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	**2a**	1,2-DCE	rt	4	3	79
2	**2b**	**1,2-DCE**	**rt**	**4**	**41**	**94**
3	**2c**	1,2-DCE	rt	4	16	91
4	**2d**	1,2-DCE	rt	4	12	78
5	**2e**	1,2-DCE	rt	4		
6	**2f**	1,2-DCE	rt	4	21	87
7	**2g**	1,2-DCE	rt	4	10	89
8	**2b**	toluene	rt	4	29	94
9	**2b**	PhCl	rt	4	38	92
10	**2b**	PhH	rt	4	36	87
11	**2b**	CH_3CN	rt	4	22	81
12	**2b**	F_3CCH_2OH[f]	rt	4		
13	**2b**[d]	1,2-DCE	rt	4	9	94
14	**2b**[e]	1,2-DCE	rt	4	43	86
15	**2b**	1,2-DCE	10	4	36	92

[a]All of the reactions are carried out on 0.02 mmol scale. [b]The conversion was calculated on the basis of ^{1}H NMR spectroscopy of the crude reaction mixture using anisole as the internal standard. [c]Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [d]5 mol % catalyst was used. [e]15 mol % catalyst was used. [f]CF_3CH_2OH is non-nucleophilic, as MeOH gave the exoacetal.[12c]

The scope of the internal aryl moiety was also studied in the presence of various substituents (summarized in Scheme 5). Electron-rich substituents such as 7-Me- (**3m**, 92% ee), 6,7-OCH_2O- (**3n**, 94% ee), and 6-BnO-7-MeO- (**3o**, 95% ee) and electron-withdrawing substituents such as 5-F- (**3p**, 85% ee), 6-Cl- (**3q**, 74% ee), 6-Br- (**3r**, 94% ee), and 6-F_3C- (**3s**, 92% ee) worked well to provide the desired product in good enantioselectivities and acceptable yields. Unfortunately, 6-NC- (**3t**, 48% ee) substitution was not very successful in terms of enantioselectivity. Further, instead of *o*-homoformyl chalcones when an *o*-homoacetyl chalcone (**1u**) was used, the desired 3-methyl isochrochromene (**3u**) was obtained, albeit with reduced yield and enantioselectivty. This could be because of the steric crowding of the substrate. In general, the electron-rich substitutions on terminal (such as **3a**–**f**) as well as internal (**3m**–**o**) aryl moieties makes the substrate a better H-bond acceptor, resulting a better binding with the catalyst in TS and, thus, provides better enantioselectivity.

Being we studied the substrate scope, we shifted our focus toward the derivatization of chiral isochromene (vinylogous part, Scheme 6). A simple $Bi(OTf)_3$-catalyzed diastereoselective indolization of vinyl ether provided a new C–C bond formation with no loss of enantioselectivity and excellent diastereoselectivity (>99:1). The corresponding allylic C–C bond formation was achieved by following a methoxyacetal (**5**) formation followed by allylation (**6**) with moderate distereoselectivity, keeping the enantioselectivity intact. Osmium tetraoxide catalyzed dihydroxylation followed by a simple protection leads to the formation of an enantioenriched isochroman moiety (**7**), although low distereoselectivity was observed. MTO-catalyzed epoxidation followed by a facile

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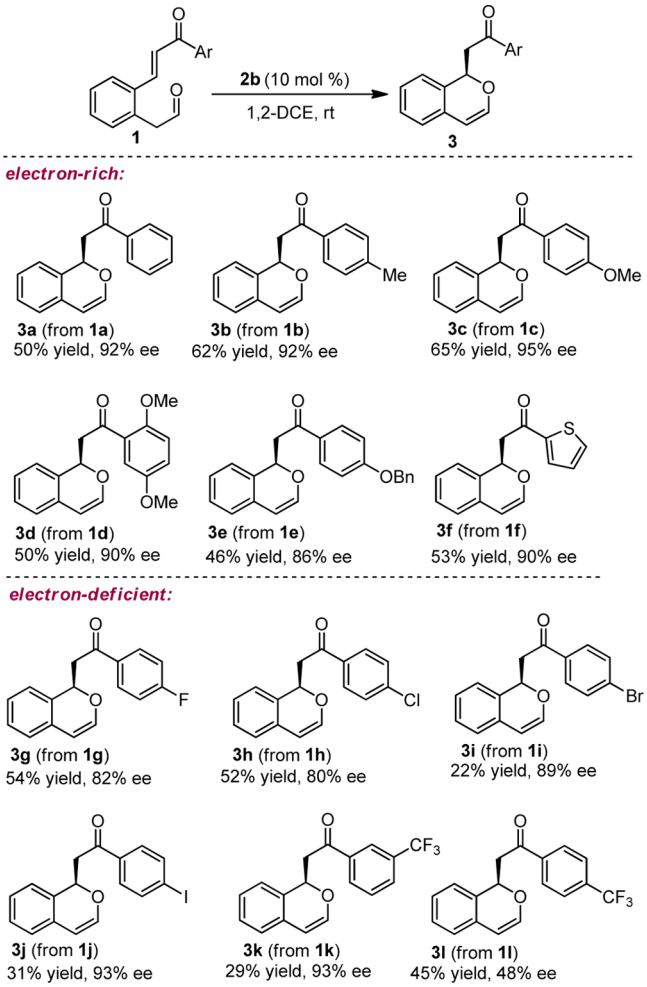
Scheme 4. Substrate Scope: Isochromenes[a−c]



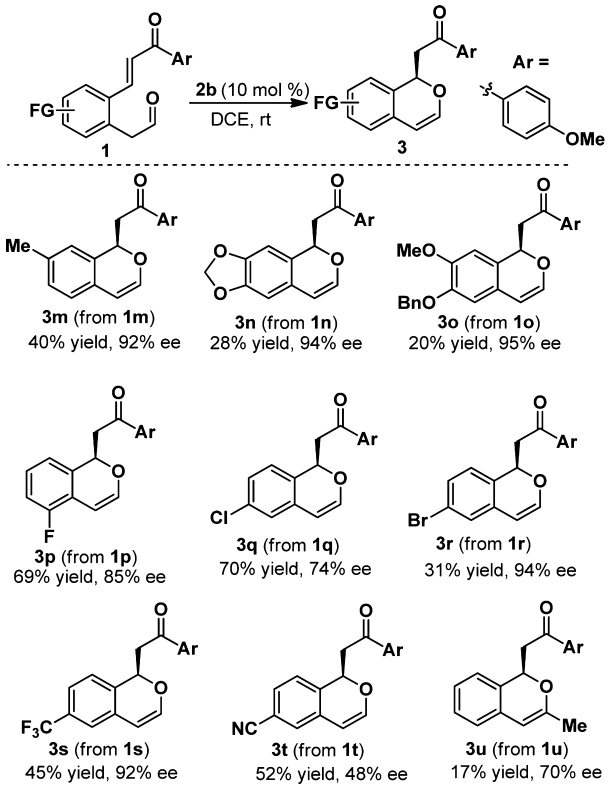
[a]Reaction conditions: **1** (0.092 mmol), **2b** (0.0092 mmol, 10 mol %) in 1,2-dichloroethane at room temperature for 3−7 h. [b]Yields shown are based on isolated products. [c]Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.

solvolysis reaction gives the isochroman (**8**), which provides the scope for further functionalization of OH group. Finally, a bromoacetoxy addition was performed to afford the desired adduct with high enantiomeric excess.

When an enantioenriched isolated isochromene product (**3c**) was treated with the catalyst **2b** under the standard reaction conditions, a slow decomposition of the isochromene, providing the mixture of starting isochromene (**3c**) and *o*-homoformyl chalcone (**1c**), was observed (Scheme 7a). This experiment implies that the reaction is reversible in nature and, thus, provides a solid reason for obtaining the lower yields in the course of reactions (Scheme 7b). The decreased in % ee in the control experiment could be explained on the basis of the reversible decomposition of the product (**3c**) in the presence of the tertiary amine moiety of the catalyst, without significant hydrogen bonding to the enone moiety of the substrate. This leads to the formation of the racemic product and, thus, reduction of the enantiselectivity.

A similar transition state which was previously proposed for the squaramide/thiourea catalysts in the oxa-Michael reaction of enone[5,12] could be used to explain the observed stereochemistry of the products.

Scheme 5. Substrate Scope: Isochromenes[a−c]



[a]The reaction conditions were same as for Scheme 4. [b]Isolated yield. [c]Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase.

CONCLUSIONS

In summary, a highly enantioselective intramolecular oxa-Michael reaction of enol has been achieved employing a chiral bifunctional organocatalyst. Enols are generated in situ by the activation of *o*-homoformyl chalcone using squaramide containing tertiary amine based bifunctional organocatalysts. The current methodology leads to highly enantioselective synthesis of isochromenes with a broad substrate scope. Further functionalization on the vinyl ether moiety of the chiral isochromenes to provide highly functionalized isochomans has also been shown.

EXPERIMENTAL SECTION

General Remarks. All reagents and solvents were used as supplied commercially. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm coated Science silica gel (EM 60-F254) plates. Visualization was accomplished with UV light (254 nm) and exposure to either ethanolic phosphomolybdic acid (PMA), anisaldehyde, or $KMnO_4$ solution, $CeSO_4$ + ammonium phosphomolybdate + 10% H_2SO_4, followed by heating. Melting points are uncorrected. ^1H NMR spectra were acquired on 400, 500, and 700 MHz spectrometers, and chemical shifts are reported relative to the residual solvent peak. ^{13}C NMR spectra were acquired on 100, 126, and 176 MHz spectrometers, 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, m = multiplet, dd = doublet of doublet), integration, coupling constant in hertz. All IR spectra were obtained as neat films, and selected absorbances are reported in cm^{-1}. High-resolution data were acquired using on a Micro TOF-Q-II mass spectrometer in MeOH as solvent or using a GC−QTOF mass spectrometer.

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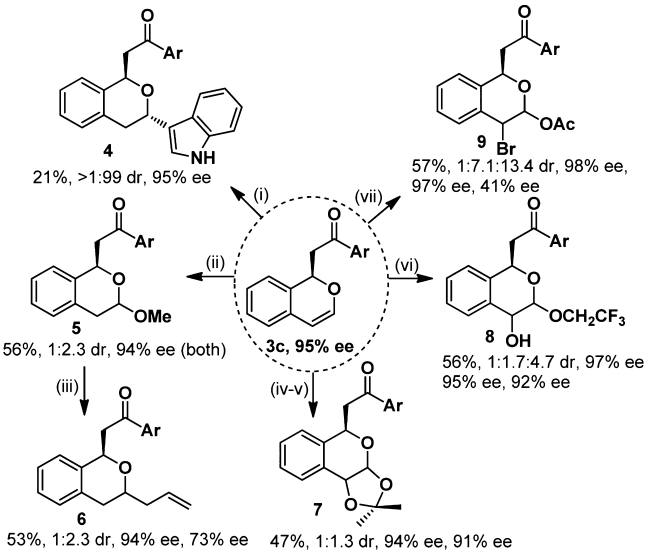
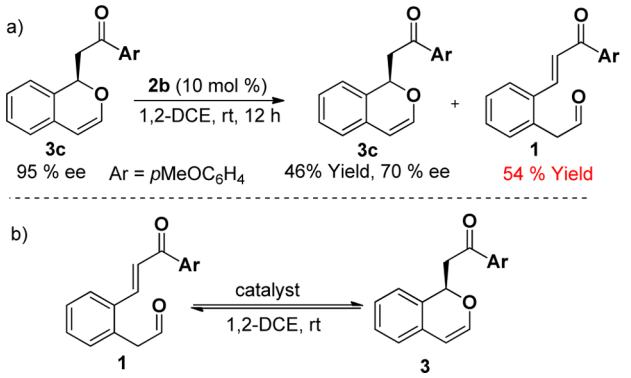
Scheme 6. Derivatization of Chiral Isochromenes[a–d]



[a]Reaction conditions: (i) Indole (1.5 equiv), $Bi(OTf)_3$ (5 mol %), CH_2Cl_2, rt, 12 h; (ii) MeOH (5 equiv), $Bi(OTf)_3$ (5 mol %), CH_2Cl_2, rt, 3 h; (iii) allyltrimethylsilane (1.5 equiv), $ZnBr_2$ (20 mol %), CH_2Cl_2, rt, 12 h; (iv) OsO_4 (10 mol %), NMO (2 equiv), acetone–H_2O, rt, 20 h; (v) 2,2-dimethoxypropane (10 equiv), *p*-TSA (10 mol %), acetone, rt, 12 h; (vi) MTO (1 mol %), pyrazole (10 mol %), 30% aq H_2O_2 (2 equiv), trifluoroethanol, rt, 6 h; (vii) NBS (1.3 equiv), AcOH (10 equiv), CH_2Cl_2, 0 °C, 30 min. [b]Isolated yield after column chromatography. [c]Enantiomeric excess were determined by HPLC analysis on a chiral stationary phase. [d]The diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of the unpurified reaction mixtures.

Scheme 7. Control Experiment



The catalysts **2a–g** were prepared according to the reported procedure.[13]

Preparation of Starting Materials 1a–i. The 2-(2-methoxyvinyl)benzaldehyde was prepared starting from the commercially available 2-bromobenzaldehydes following the procedure reported as in ref 14. The aldol reaction was performed according the procedure reported as in ref 15. The reaction protocol and the characterization data of compound **1** are given in ref 12b.

*(E)-2-(2-(3-(2,5-Dimethoxyphenyl)-3-oxoprop-1-en-1-yl)phenyl)-acetaldehyde (**1d**):* 94 mg; 55.3% yield; R_f = 0.25 (20:80 = EtOAc/*n*-hexane); brown semisolid; FT-IR (neat) 2943, 2909, 2837, 1726, 1655, 1587, 1416, 1281, 1223, 1038, 816,731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (t, J = 1.7 Hz, 1H), 7.78 (d, J = 15.6 Hz, 1H), 7.72–7.69 (m, 1H), 7.38–7.33 (m, 3H), 7.20 (dd, J = 9.2, 2.5 Hz, 2H), 7.02 (dd, J = 9.0, 3.2 Hz, 1H), 6.92 (d, J = 9.0 Hz, 1H), 3.87 (d, J = 1.6 Hz, 2H), 3.84 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 191.9, 153.7, 152.7, 139.3, 134.9, 132.1, 131.4, 130.3, 129.4, 129.3, 128.1, 127.3, 119.6, 114.4, 113.4, 56.5, 55.9, 48.1; HRMS (ESI, m/z) calcd for $C_{19}H_{19}O_4$ ([M + H]$^+$) 311.1278, found 311.1287.

*(E)-2-(2-(3-(4-(Benzyloxy)phenyl)-3-oxoprop-1-en-1-yl)phenyl)-acetaldehyde (**1e**):* 110 mg; 73.3% yield; R_f = 0.27 (20:80 = EtOAc/*n*-hexane); yellow semisolid; FT-IR (neat) 3065, 3032, 2828, 2727, 1719, 1659, 1599, 1510, 1329, 1258, 1225, 1169, 1024, 831, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.02 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 15.4 Hz, 1H), 7.77–7.74 (m, 1H), 7.47 (d, J = 15.4 Hz, 1H), 7.43 (d, J = 7.0 Hz, 2H), 7.40 (d, J = 6.9 Hz, 2H), 7.38–7.35 (m, 2H), 7.35–7.33 (m, 1H), 7.23–7.21 (m, 1H), 7.05 (d, J = 8.8 Hz, 2H), 5.14 (s, 2H), 3.91 (d, J = 1.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 188.3, 162.8, 140.4, 136.2, 134.9, 132.2, 131.5, 131.0, 130.9 (2C), 130.4, 128.7 (2C), 128.3, 128.2, 127.5 (2C), 127.2, 124.5, 114.8 (2C), 70.2, 48.2; HRMS (ESI, m/z) calcd for $C_{24}H_{21}O_3$ ([M + H]$^+$) 357.1485, found 357.1493.

*(E)-2-(2-(3-Oxo-3-(3-(trifluoromethyl)phenyl)prop-1-en-1-yl)-phenyl)acetaldehyde (**1k**):* 135 mg; 52% yield; R_f = 0.35 (20:80 = EtOAc/*n*-hexane); yellow semisolid; FT-IR (neat) 2923, 2835, 2732, 1663, 1616, 1485, 1319, 1204, 1125, 976, 761 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.24 (s, 1H), 8.17 (d, J = 7.7 Hz, 1H), 7.97 (d, J = 15.4 Hz, 1H), 7.78 (dd, J = 11.5, 4.3 Hz, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.46 (s, 1H), 7.39 (dd, J = 7.9, 6.0 Hz, 2H), 7.25–7.22 (m, 1H), 3.92 (d, J = 1.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 188.7, 142.4, 138.5, 134.4, 132.5, 131.7, 131.6, 131.3 (q, J = 32.8 Hz,1C), 131.0, 129.4, 129.3 (q, J = 3.7 Hz, 1C), 128.3, 127.3, 125.3 (q, J = 3.8 Hz, 1C), 123.7 (q, J = 272.6 Hz, 1C), 123.6, 48.2; HRMS (ESI, m/z) calcd for $C_{18}H_{14}F_3O_2$ ([M + H]$^+$) 319.0940, found 319.0948.

*(E)-2-(2-(3-Oxo-3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-phenyl)acetaldehyde (**1l**):* 60 mg; 36% yield; R_f = 0.48 (20:80 = EtOAc/*n*-hexane); yellow semisolid; FT-IR (neat) 3069, 2932, 2839, 2733, 1935, 1724, 1665, 1595, 1406, 1323, 1215, 1171, 1130, 1065, 843, 766 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, J = 1.6 Hz, 1H), 8.09 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 15.5 Hz, 1H), 7.77 (d, J = 6.3 Hz, 2H), 7.74 (s, 1H), 7.45–7.40 (m, 2H), 7.40–7.37 (m, 1H), 7.25 (d, J = 1.3 Hz, 1H), 3.92 (d, J = 1.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.9, 189.2, 142.4, 140.7, 134.4, 134.2 (q, J = 32.8 Hz, 1C), 132.4, 131.6, 131.0, 128.9 (2C), 128.3, 127.3, 125.7 (q, J = 3.7 Hz, 2C), 123.9, 123.6 (q, J = 272.8 Hz, 1C), 48.3; HRMS (ESI, m/z) calcd for $C_{18}H_{14}F_3O_2$ ([M + H]$^+$) 319.0940, found 319.0957.

*(E)-2-(2-(3-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)-4-methylphenyl)acetaldehyde (**1m**):* 129 mg; 63% yield; R_f = 0.36 (20:80 = EtOAc/*n*-hexane); yellow semisolid; FT-IR (neat) 2961, 2926, 2841, 1719, 1659, 1607, 1339, 1261, 1173, 1024, 839 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.02 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 15.4 Hz, 1H), 7.56 (s, 1H), 7.45 (d, J = 15.4 Hz, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 3.87 (s, 5H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5, 188.3, 163.6, 140.5, 137.8, 134.7, 131.4, 131.3, 130.9 (2C), 130.9, 129.2, 127.7, 124.2, 113.9 (2C), 55.5, 47.8, 21.1; HRMS (ESI, m/z) calcd for $C_{19}H_{19}O_3$ ([M + H]$^+$) 295.1329, found 295.1342.

*(E)-2-(6-(3-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)benzo[d]-[1,3]dioxol-5-yl)acetaldehyde (**1n**):* 102 mg; 50% yield; R_f = 0.30 (40:60 = EtOAc/*n*-hexane); yellow semisolid; FT-IR (neat) 2903, 2839, 1719, 1653, 1603, 1504, 1481, 1306, 1263, 1173, 1036, 976, 934, 831, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 15.2 Hz, 1H), 7.35 (d, J = 15.2 Hz, 1H), 7.23 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.66 (s, 1H), 6.00 (s, 2H), 3.87 (s, 3H), 3.85 (d, J = 1.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 188.2, 163.5, 149.9, 147.9, 139.8, 130.9, 130.8 (2C), 128.5, 127.4, 122.2, 113.9 (2C), 111.1, 106.3, 101.8, 55.5, 47.9; HRMS (ESI, m/z) calcd for $C_{19}H_{17}O_5$ ([M + H]$^+$) 325.1071, found 325.1085.

*(E)-2-(5-(Benzyloxy)-4-methoxy-2-(3-(4-methoxyphenyl)-3-oxo-prop-1-en-1-yl)phenyl)acetaldehyde (**1o**):* 108 mg; 44% yield; R_f = 0.27 (20:80 = EtOAc/*n*-hexane); light yellow semisolid; FT-IR (neat) 2963, 2938, 2839, 1719, 1657, 1597, 1514, 1458, 1265, 1169, 1107, 1022, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 15.3 Hz, 1H), 7.42 (d, J = 7.1 Hz, 2H), 7.37 (t, J = 7.3 Hz, 3H), 7.31 (d, J = 7.1 Hz, 1H), 7.25 (s, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.71 (s, 1H), 5.16 (s, 2H), 3.95 (s, 3H), 3.88 (s, 3H),

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3.81 (d, J = 1.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 188.5, 163.5, 150.4, 149.3, 140.2, 136.3, 131.0, 130.8 (2C), 128.7 (2C), 128.2, 127.5, 127.4 (2C), 125.7, 122.3, 116.0, 113.9 (2C), 110.0, 71.0, 56.3, 55.5, 47.6; HRMS (ESI, m/z) calcd for $C_{26}H_{25}O_5$ ([M + H]$^+$) 417.1697, found 417.1677.

*(E)-2-(3-Fluoro-2-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-phenyl)acetaldehyde (**1p**):* 181 mg; 62% yield; R_f = 0.18 (20:80 = EtOAc/*n*-hexane); yellow semisolid; FT-IR (neat) 2965, 2940, 2843, 2733, 1723, 1657, 1603, 1514, 1470, 1263, 1175, 1020, 835, 791 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.93 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 15.4 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 15.4 Hz, 1H), 7.25 (d, J = 5.9 Hz, 1H), 7.05 (t, J = 8.7 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 3.90 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0, 188.0, 163.7, 161.5 (d, J = 246.1 Hz, 1C) 139.2 (d, J = 3.4 Hz), 137.3 (d, J = 4.0 Hz, 1C), 130.9 (2C), 130.6, 129.1 (d, J = 9.1 Hz, 1C), 125.7, 122.8 (d, J = 3.2 Hz), 119.8 (d, J = 16.3 Hz, 1C), 116.53 (d, J = 23.0 Hz, 1C), 113.9 (2C), 55.5, 40.4 (d, J = 3.4 Hz); HRMS (ESI, m/z) calcd for $C_{18}H_{16}FO_3$ ([M + H]$^+$) 299.1078, found 299.1095.

*(E)-2-(5-Chloro-2-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-phenyl)acetaldehyde (**1q**):* 40 mg; 50% yield; R_f = 0.21 (20:80 = EtOAc/*n*-hexane); yellow semisolid; FT-IR (neat) 2959, 2932, 2839, 1722, 1659, 1605, 1510, 1497, 1339, 1260, 1173, 1024, 816, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 15.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 15.4 Hz, 1H), 7.31 (dd, J = 8.4, 2.0 Hz, 1H), 7.20 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 3.88 (d, J = 0.9 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 187.9, 163.7, 139.0, 136.1, 133.9, 133.5, 131.3, 130.9 (2C), 130.6, 128.4, 128.3, 124.7, 113.9 (2C), 55.5, 47.8; HRMS (ESI, m/z) calcd for $C_{18}H_{16}ClO_3$ ([M + H]$^+$) 315.0782, found 315.0779.

*(E)-2-(5-Bromo-2-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-phenyl)acetaldehyde (**1r**):* 116 mg; 31.7% yield; R_f = 0.21 (20:80 = EtOAc/*n*-hexane); yellow semiliquid; FT-IR (neat) 2936, 2839, 2729, 2043, 1724, 1657, 1603, 1479, 1418, 1315, 1261, 1221, 1173, 1018, 837, 814 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.97 (d, J = 8.9 Hz, 2H), 7.76 (d, J = 15.3 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.44 (s, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.33 (d, J = 1.7 Hz, 1H), 6.94−6.91 (m, 2H), 3.85 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 187.9, 163.7, 139.1, 134.2, 134.1, 133.9, 131.2, 130.9 (2C), 130.6, 128.5, 124.7, 124.4, 113.9 (2C), 55.5, 47.7; HRMS (ESI, m/z) calcd for $C_{18}H_{16}BrO_3$ ([M + H]$^+$) 359.0277, found 359.0287.

*(E)-2-(2-(3-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)-5-(trifluoromethyl)phenyl)acetaldehyde (**1s**):* 50 mg; 64.9% yield; R_f = 0.30 (20:80 = EtOAc/*n*-hexane); yellow semiliquid; FT-IR (neat) 2926, 2845, 2737,1726, 1663, 1605, 1510, 1425, 1337, 1173, 1123, 1022, 827, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.01 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 11.4 Hz, 1H), 7.82 (d, J = 4.0 Hz, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 15.4 Hz, 1H), 7.46 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 3.98 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.1, 187.9, 163.9, 138.9, 138.6, 132.8, 131.8 (q, J = 32.6 Hz, 1C), 131.0 (2C), 130.4, 128.2 (q, J = 3.8 Hz, 1C), 127.6, 126.5, 124.9 (q, J = 3.7 Hz, 1C), 123.7 (q, J = 272.5 Hz, 1C), 114.0 (2C), 55.5, 48.1; HRMS (ESI, m/z) calcd for $C_{19}H_{16}F_3O_3$ ([M + H]$^+$) 349.1046, found 349.1056

*(E)-4-(3-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)-3-(2-oxoethyl)-benzonitrile (**1t**):* 90 mg; 45% yield; R_f = 0.17(20:80 = EtOAc/*n*-hexane); brown semisolid; FT-IR (neat) 2980, 2938, 2841, 2230, 1719, 1659, 1603, 1512, 1319, 1263, 1223, 1177, 1020, 827 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.00 (d, J = 8.9 Hz, 2H), 7.81 (d, J = 2.9 Hz, 1H), 7.78 (d, J = 10.3 Hz, 1H), 7.63 (dd, J = 8.1, 1.1 Hz, 1H), 7.50 (dd, J = 8.2, 7.1 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 3.98 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 187.4, 163.9, 139.7, 138.2, 134.8, 133.3, 131.5, 131.0 (2C), 130.3, 127.8, 127.2, 118.1, 114.1 (2C), 113.4, 55.6, 47.7; HRMS (ESI, m/z) calcd for $C_{19}H_{16}NO_3$ ([M + H]$^+$) 306.1125, found 306.1122.

Procedure for Synthesis of (*E*)-3-(2-(2-Oxopropyl)phenyl)-1-phenylprop-2-en-1-one (1u). For the preparation of 2-methyl-1*H*-indene, see ref 16.

A solution of 2-methyl-1*H*-indene (160 mg, 1.2 mmol) in dichloromethane was allowed to pass though the ozone gas at −78 °C for about 20 min until complete consumption of starting material (monitored by TLC). Then, 1.3 equiv of PPh_3 was added to the reaction mixture, and it was quickly filtered through a plug of silica using dichloromethane as solvent. The solvent was evaporated , and the product was directly taken for the next step without any purification.

To the above product (145 mg, 0.9 mmol) in chloroform was added the corresponding Witting olefin (1.3 equiv), and the reaction was refluxed for 48 h. Then flash column chromatography was performed using 15:85 EtOAc/*n*-hexane to obtain (*E*)-3-(2-(2-oxopropyl)-phenyl)-1-phenylprop-2-en-1-one (**1u**) in 81% yield.

*(E)-3-(2-(2-Oxopropyl)phenyl)-1-phenylprop-2-en-1-one (**1u**):* 193 mg; 81% yield; R_f = 0.21 (20:80 = EtOAc/*n*-hexane); amber colored solid; mp 48−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.2 Hz, 2H), 7.91 (d, J = 15.5 Hz, 1H), 7.78−7.71 (m, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.50 (s, 1H), 7.48−7.40 (m, 2H), 7.39−7.30 (m, 2H), 7.19 (dd, J = 7.2, 1.3 Hz, 1H), 3.90 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.2, 190.3, 141.6, 138.0, 134.7, 134.5, 132.9, 131.4, 130.5, 128.7 (2C), 128.6 (2C), 127.8, 127.0, 124.2, 48.2, 29.7; HR-MS (ESI, m/z) calcd for $C_{18}H_{17}O_2$ ([M + H]$^+$) 265.1223, found 265.1249.

General Procedure for Synthesis of 1*H*-Isochromenes. (*E*)-2-(2-(3-Oxo-3-phenylprop-1-en-1-yl)phenyl)acetaldehyde (**1a**, 0.092 mmol) was taken in 0.5 mL of 1,2-dichloroethane in a 5 mL vial with a small magnetic bar, quinine-derived squramide catalyst **2b** (0.0092 mmol, 10 mol %) was added, and the reaction was allowed to run for 3 h 45 min at room temperature. After completion of the reaction, the product was purified by flash column chromatography using *n*-hexane/EtOAc (97:3 v/v) as eluent to afford (*R*)-2-(1*H*-isochromen-1-yl)-1-phenylethanone (**3a**, 12 mg, 50% yield). The enantiomeric excess of the product, which was determined by HPLC analysis using a chiral column, was found to be 92%.

*2-(1H-Isochromen-1-yl)-1-phenylethanone (**3a**):* 50% yield, 92% ee, R_f = 0.44 (10:90 = EtOAc/*n*-hexane); white solid; mp 69−73 °C; FT-IR (neat) 2931, 2857, 2360, 1601, 1121, 1042, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98−7.91 (m, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.20 (td, J = 7.4, 1.2 Hz, 1H), 7.14 (td, J = 7.4, 1.2 Hz, 1H), 7.03 (d, J = 7.4 Hz, 1H), 6.98 (d, J = 7.1 Hz, 1H), 6.43 (d, J = 5.7 Hz, 1H), 5.91 (dd, J = 8.3, 4.7 Hz, 1H), 5.80 (d, J = 5.7 Hz, 1H), 3.89 (dd, J = 16.3, 8.3 Hz, 1H), 3.16 (dd, J = 16.3, 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 143.9, 136.9, 133.3, 130.4, 129.3, 128.6 (2C), 128.3 (3C), 126.9, 124.2, 123.5, 104.7, 73.6, 42.9; HR-MS (ESI, m/z) calcd for $C_{17}H_{14}NaO_2$ ([M + Na]$^+$) 273.0886, found 273.0894; $[\alpha]_D^{23}$ = +137.54 (c = 0.525, $CHCl_3$, 92% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, *n*-hexane/2-propanol = 97/03, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 11.2 min (major), t_R = 16.0 min (minor).

All other isochromenes were prepared using a similar protocol.

*2-(1H-Isochromen-1-yl)-1-(p-tolyl)ethanone (**3b**):* 62% yield, 92% ee, R_f = 0.5 (10:90 = EtOAc/*n*-hexane); white solid; mp 76−78 °C; FT-IR (neat) 3015, 2883, 2835, 2334, 1677, 1605, 1432, 1289, 1226, 1046, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 7.5 Hz, 2H), 7.20 (td, J = 7.6, 1.2 Hz, 1H), 7.13 (td, J = 7.5, 1.2 Hz, 1H), 7.03 (d, J = 7.4 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.43 (d, J = 5.7 Hz, 1H), 5.90 (dd, J = 8.3, 4.7 Hz, 1H), 5.79 (d, J = 5.7 Hz, 1H), 3.86 (dd, J = 16.2, 8.4 Hz, 1H), 3.12 (dd, J = 16.2, 4.7 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 144.2, 143.9, 134.6, 130.5, 129.3 (3C), 128.4 (2C), 128.2, 126.9, 124.2, 123.4, 104.7, 73.7, 42.8, 21.7; HR-MS (ESI, m/z) calcd for $C_{18}H_{16}NaO_2$ ([M + Na]$^+$) 287.1043, found 287.1055; $[\alpha]_D^{23}$ = +150.05 (c = 0.53, $CHCl_3$, 92% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, *n*-hexane/2-propanol = 97/03, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 13.8 min (major), t_R = 18.8 min (minor).

*2-(1H-Isochromen-1-yl)-1-(4-methoxyphenyl)ethanone (**3c**):* 65% yield, 95% ee, R_f = 0.29 (10:90 = EtOAc/*n*-hexane); white solid; mp 43−46 °C; FT-IR (neat) 3030, 2942, 2857, 2362, 2092, 1641, 1397, 1118, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.9 Hz,

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2H), 7.19 (td, J = 7.4, 1.0 Hz, 1H), 7.13 (td, J = 7.4, 1.0 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 6.97 (d, J = 7.3 Hz, 1H), 6.91 (d, J = 8.9 Hz, 2H), 6.43 (d, J = 5.7 Hz, 1H), 5.89 (dd, J = 8.3, 4.7 Hz, 1H), 5.79 (d, J = 5.7 Hz, 1H), 3.89−3.80 (m, 4H), 3.09 (dd, J = 16.0, 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 163.7, 143.9, 130.6 (2C), 130.5, 130.2, 129.3, 128.2, 126.9, 124.2, 123.4, 113.8 (2C), 104.7, 73.8, 55.5, 42.5; HR-MS (ESI, m/z) calcd for $C_{18}H_{16}NaO_3$ ($[M + Na]^+$) 303.0992, found 303.1008; $[\alpha]_D^{23}$ = +140.06 (c = 0.415, $CHCl_3$, 95% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 15.3 min (major), t_R = 19.6 min (minor).

1-(2,5-Dimethoxyphenyl)-2-(1H-isochromen-1-yl)ethanone (**3d**): 50% yield, 90% ee, R_f = 0.45 (20:80 = EtOAc/n-hexane); yellow semisolid; FT-IR (neat) 3024, 2962, 2865, 2360, 1662, 1605, 1465, 1412, 1224, 1044, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 3.2 Hz, 1H), 7.18 (dd, J = 10.5, 4.3 Hz, 1H), 7.14 (td, J = 7.4, 1.2 Hz, 1H), 7.05−6.99 (m, 2H), 6.95 (d, J = 7.0 Hz, 1H), 6.88 (d, J = 9.0 Hz, 1H), 6.43 (d, J = 5.7 Hz, 1H), 5.83 (dd, J = 8.7, 4.3 Hz, 1H), 5.75 (d, J = 5.7 Hz, 1H), 3.83 (s, 3H), 3.81−3.76 (m, 4H), 3.32 (dd, J = 16.4, 4.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 153.6, 153.1, 144.1, 130.7, 129.6, 128.08, 128.06, 126.8, 124.1, 123.3, 120.5, 114.1, 113.1, 104.5, 73.7, 56.1, 55.8, 48.2; HR-MS (ESI, m/z) calcd for $C_{19}H_{19}O_4$ ($[M + H]^+$) 311.1278, found 311.1285; $[\alpha]_D^{24}$ = +76.71 (c = 0.565, $CHCl_3$, 90% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 85/15, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 13.7 min (major), t_R = 20.4 min (minor).

1-(4-(Benzyloxy)phenyl)-2-(1H-isochromen-1-yl)ethanone (**3e**): 46% yield, 86% ee, R_f = 0.53 (20:80 = EtOAc/n-hexane); light yellow solid; mp 93−95 °C; FT-IR (neat) 2967, 2851, 2363, 1676, 1599, 1510, 1456, 1256, 1225, 1171, 1047, 847, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.8 Hz, 2H), 7.41−7.36 (m, 4H), 7.34 (d, J = 6.6 Hz, 1H), 7.19 (t, J = 7.1 Hz, 1H), 7.13 (t, J = 7.0 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 6.98 (dd, J = 7.4, 5.2 Hz, 3H), 6.43 (d, J = 5.7 Hz, 1H), 5.89 (dd, J = 8.3, 4.7 Hz, 1H), 5.79 (d, J = 5.7 Hz, 1H), 5.11 (s, 2H), 3.83 (dd, J = 16.0, 8.3 Hz, 1H), 3.09 (dd, J = 16.0, 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 162.8, 143.9, 136.1, 130.6 (2C), 130.5, 130.3, 129.3, 128.7 (2C), 128.3, 128.2, 127.5 (2C), 126.9, 124.2, 123.4, 114.6 (2C), 104.7, 73.8, 70.2, 42.5; HR-MS (ESI, m/z) calcd for $C_{24}H_{21}O_3$ ($[M + H]^+$) 357.1485, found 357.1487; $[\alpha]_D^{25}$ = +117.09 (c = 0.640, $CHCl_3$, 86% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 18.9 min (major), t_R = 24.3 min (minor).

2-(1H-Isochromen-1-yl)-1-(thiophene-2-yl)ethanone (**3f**): 53% yield, 90% ee, R_f = 0.5 (20:80 = EtOAc/n-hexane); yellow solid; mp 65−67 °C; FT-IR (neat) 2984, 2909, 2835, 2364, 1651, 1590, 1414, 1118, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.66 (m, 1H), 7.65−7.63 (m, 1H), 7.20 (td, J = 7.4, 1.1 Hz, 1H), 7.13 (td, J = 7.5, 1.1 Hz, 1H), 7.10 (dd, J = 4.8, 3.9 Hz, 1H), 7.02 (d, J = 7.4 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 6.43 (d, J = 5.7 Hz, 1H), 5.87 (dd, J = 8.6, 4.6 Hz, 1H), 5.80 (d, J = 5.7 Hz, 1H), 3.80 (dd, J = 15.4, 8.7 Hz, 1H), 3.05 (dd, J = 15.4, 4.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.9, 144.5, 143.8, 134.3, 132.5, 130.1, 129.2, 128.4, 128.2, 126.9, 124.2, 123.5, 104.7, 73.9, 43.7; HR-MS (ESI, m/z) calcd for $C_{15}H_{12}O_2NaS$ ($[M + Na]^+$) 279.0450, found 279.0465; $[\alpha]_D^{21}$ = +123.34 (c = 0.560, $CHCl_3$, 90% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 95/05, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 12.6 min (major), t_R = 14.9 min (minor).

1-(4-Fluorophenyl)-2-(1H-isochromen-1-yl)ethanone (**3g**): 54% yield, 82% ee, R_f = 0.59 (20:80 = EtOAc/n-hexane); colorless solid; mp 41−45 °C; FT-IR (neat) 3087, 2958, 2857, 2369, 1677, 1607, 1456, 1394, 1228, 1050, 768 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96−7.87 (m, 2H), 7.14 (td, J = 7.4, 1.0 Hz, 1H), 7.11−7.07 (m, 1H), 7.05 (dd, J = 9.1, 5.0 Hz, 2H), 6.96 (d, J = 7.4 Hz, 1H), 6.92 (d, J = 7.3 Hz, 1H), 6.36 (d, J = 5.7 Hz, 1H), 5.83 (dd, J = 8.3, 4.7 Hz, 1H), 5.74 (d, J = 5.7 Hz, 1H), 3.79 (dd, J = 16.1, 8.3 Hz, 1H), 3.06 (dd, J = 16.1, 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 165.89 (d, J = 255.3 Hz, 1C), 143.8, 133.5 (d, J = 3.0 Hz, 1C), 130.9 (d, J = 9.4 Hz, 2C), 130.2, 129.3, 128.3, 126.9, 124.2, 123.5, 115.8 (d, J = 21.9 Hz, 2C), 104.8, 73.6, 42.8; HR-MS (ESI, m/z) calcd for $C_{17}H_{13}FNaO_2$ ($[M + Na]^+$) 291.0792, found 291.0791; $[\alpha]_D^{22}$ = +119.875 (c = 0.46, $CHCl_3$, 82% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 97/03, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 11.0 min (major), t_R = 14.8 min (minor).

1-(4-Chlorophenyl)-2-(1H-isochromen-1-yl)ethanone (**3h**). 52% yield, 80% ee, R_f = 0.37 (10:90 = EtOAc/n-hexane); light yellow semisolid; FT-IR (neat) 3069, 2926, 2855, 1684, 1628, 1587, 1489, 1456, 1360, 1287, 1227, 1096, 988, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.20 (td, J = 7.5, 1.0 Hz, 1H), 7.13 (td, J = 7.4, 1.0 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.41 (d, J = 5.7 Hz, 1H), 5.87 (dd, J = 8.3, 4.6 Hz, 1H), 5.79 (d, J = 5.7 Hz, 1H), 3.84 (dd, J = 16.2, 8.4 Hz, 1H), 3.11 (dd, J = 16.2, 4.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 143.8, 139.8, 135.3, 130.2, 129.7 (2C), 129.2, 128.9 (2C), 128.4, 127.0, 124.2, 123.5, 104.8, 73.6, 42.8; HR-MS (ESI, m/z) calcd for $C_{17}H_{13}ClNaO_2$ ($[M + Na]^+$) 307.0496, found 307.0502; $[\alpha]_D^{25}$ = +106.60 (c = 0.730, $CHCl_3$, 80% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 97/03, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 10.9 min (major), t_R = 13.9 min (minor).

1-(4-Bromophenyl)-2-(1H-isochromen-1-yl)ethanone (**3i**): 22% yield, 89% ee, R_f = 0.48 (20:80 = EtOAc/n-hexane); light yellow solid; mp 82−85 °C; FT-IR (neat) 2971, 2865, 2364, 1673, 1603, 1397, 1224, 1046, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.6 Hz, 2H), 7.20 (td, J = 7.5, 1.1 Hz, 1H), 7.14 (td, J = 7.5, 1.1 Hz, 1H), 7.01 (d, J = 7.4 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 6.41 (d, J = 5.7 Hz, 1H), 5.88 (dd, J = 8.3, 4.6 Hz, 1H), 5.80 (d, J = 5.7 Hz, 1H), 3.84 (dd, J = 16.2, 8.4 Hz, 1H), 3.11 (dd, J = 16.2, 4.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.3, 143.8, 135.7, 131.9 (2C), 130.2, 129.8 (2C), 129.2, 128.6, 128.4, 127.0, 124.2, 123.5, 104.8, 73.6, 42.8; HR-MS (ESI, m/z) calcd for $C_{17}H_{13}BrNaO_2$ ($[M + Na]^+$) 350.9991, found 351.0003; $[\alpha]_D^{23}$ = +90.43 (c = 0.6, $CHCl_3$, 89% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 95/05, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 10.3 min (major), t_R = 13.4 min (minor).

1-(4-Iodophenyl)-2-(1H-isochromen-1-yl)ethanone (**3j**): 31% yield, 91% ee, R_f = 0.61 (20:80 = EtOAc/n-hexane); yellow solid; mp 103−106 °C; FT-IR (neat) 3019, 2914, 2364, 1684, 1579, 1392, 1285, 1057, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 7.13 (t, J = 7.1 Hz, 1H), 7.01 (d, J = 7.4 Hz, 1H), 6.98 (d, J = 7.4 Hz, 1H), 6.41 (d, J = 5.7 Hz, 1H), 5.87 (dd, J = 8.3, 4.6 Hz, 1H), 5.80 (d, J = 5.7 Hz, 1H), 3.83 (dd, J = 16.2, 8.4 Hz, 1H), 3.09 (dd, J = 16.2, 4.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 143.8, 137.9 (2C), 136.2, 130.2, 129.7 (2C), 129.2, 128.4, 127.0, 124.2, 123.5, 104.8, 101.4, 73.6, 42.7; HR-MS (ESI, m/z) calcd for $C_{17}H_{13}INaO_2$ ($[M + Na]^+$) 398.9852, found 398.9846; $[\alpha]_D^{21}$ = +103.23 (c = 0.30, $CHCl_3$, 91% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 97/03, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 13.4 min (major), t_R = 16.7 min (minor).

2-(1H-Isochromen-1-yl)-1-(3-(trifluoromethyl)phenyl)ethanone (**3k**): 29% yield, 93% ee, R_f = 0.6 (20:80 = EtOAc/n-hexane); yellow semisolid; FT-IR (neat) 2980, 2883, 2364, 1695, 1609, 1452, 1329, 1125, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.21 (td, J = 7.5, 1.0 Hz, 1H), 7.14 (td, J = 7.4, 1.0 Hz, 1H), 7.03 (d, J = 7.4 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.42 (d, J = 5.7 Hz, 1H), 5.90 (dd, J = 8.3, 4.6 Hz, 1H), 5.82 (d, J = 5.7 Hz, 1H), 3.90 (dd, J = 16.2, 8.3 Hz, 1H), 3.17 (dd, J = 16.2, 4.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 143.7, 137.5, 131.38, 131.37, 130.0, 129.7 (q, J = 3.8 Hz, 1C), 129.3, 129.2, 128.5, 127.1, 125.17 (q, J = 3.9 Hz, 1C), 124.2, 123.63 (q, J = 272.5 Hz, 1C), 123.61, 104.9, 73.5, 42.9; HR-MS (ESI, m/z) calcd for $C_{18}H_{14}F_3O_2$ ($[M + H]^+$) 319.0940, found 319.0921; $[\alpha]_D^{22}$ = +69.7 (c = 0.30, $CHCl_3$, 93% ee). The enantiomeric ratio was

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determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, *n*-hexane/2-propanol = 97/03, flow rate =1.0 mL/min, λ = 254 nm; t_R = 7.3 min (major), t_R = 9.5 min (minor).

*2-(1H-Isochromen-1-yl)-1-(4-(trifluoromethyl)phenyl)ethanone (**3l**):* 45% yield, 48% ee, R_f = 0.42 (10:90 = EtOAc/*n*-hexane); light yellow semisolid; FT-IR (neat) 3071, 3067, 2922, 2851, 1694, 1630, 1512, 1487, 1329, 1130, 1063, 854, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.21 (td, *J* = 7.4, 1.0 Hz, 1H), 7.14 (td, *J* = 7.4, 1.0 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 1H), 6.41 (d, *J* = 5.7 Hz, 1H), 5.89 (dd, *J* = 8.3, 4.6 Hz, 1H), 5.81 (d, *J* = 5.7 Hz, 1H), 3.89 (dd, *J* = 16.2, 8.4 Hz, 1H), 3.17 (dd, *J* = 16.2, 4.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 143.7, 139.6 (q, *J* = 1.1 Hz, 1C), 134.6 (q, *J* = 32.8 Hz, 1C), 130.0, 129.2, 128.6 (2C), 128.5, 127.1, 125.7 (q, *J* = 3.8 Hz, 2C), 124.2, 123.6, 123.5 (q, *J* = 272.7 Hz, 1C), 104.9, 73.5, 43.1; HR-MS (ESI, *m*/*z*) calcd for $C_{18}H_{12}F_3O_2$ ($[M - H]^+$) 317.0784, found 317.0783; $[\alpha]_D^{25}$ = +42.04 (*c* = 0.515, $CHCl_3$, 48% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, *n*-hexane/2-propanol = 95/05, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 7.3 min (major), t_R = 9.4 min (minor).

*1-(4-Methoxyphenyl)-2-(7-methyl-1H-isochromen-1-yl) ethanone (**3m**):* 40% yield, 92% ee, R_f = 0.46 (20:80 = EtOAc/*n*-hexane); light yellow solid; mp 97−99 °C; FT-IR (neat) 3024, 2923, 2852, 2360, 1675, 1598, 1449, 1259, 1171, 1044, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.78 (s, 1H), 6.32 (d, *J* = 5.7 Hz, 1H), 5.78 (dd, *J* = 8.5, 4.4 Hz, 1H), 5.71 (d, *J* = 5.7 Hz, 1H), 3.82−3.75 (m, 4H), 2.98 (dd, *J* = 16.0, 4.4 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.8, 163.6, 143.0, 136.7, 130.6 (3C), 130.2, 128.8, 126.5, 124.9, 123.4, 113.8 (2C), 104.6, 73.8, 55.5, 42.6, 21.3; HR-MS (ESI, *m*/*z*) calcd for $C_{19}H_{18}NaO_3$ ($[M + Na]^+$) 317.1148, found 317.1159; $[\alpha]_D^{24}$ = +130.29 (*c* = 0.550, $CHCl_3$, 92% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, *n*-hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 10.5 min (major), t_R = 15.1 min (minor).

*2-(5H-[1,3]Dioxolo[4,5-g]isochromen-5-yl)-1-(4-methoxyphenyl)-ethanone (**3n**):* 28% yield, 94% ee, R_f = 0.38 (20:80 = EtOAc/*n*-hexane); light yellow semisolid; FT-IR (neat) 2920, 2847, 1672, 1599, 1508, 1483, 1260, 1171, 1036, 939, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.56 (s, 1H), 6.49 (s, 1H), 6.36 (d, *J* = 5.7 Hz, 1H), 5.89 (dd, *J* = 5.5, 1.2 Hz, 2H), 5.77 (dd, *J* = 7.9, 5.0 Hz, 1H), 5.69 (d, *J* = 5.7 Hz, 1H), 3.85 (s, 3H), 3.77 (dd, *J* = 16.0, 8.0 Hz, 1H), 3.07 (dd, *J* = 16.0, 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.8, 163.7, 147.4, 146.3, 142.3, 130.6 (2C), 130.2, 123.9, 123.7, 113.8 (2C), 105.5, 104.8, 104.4, 100.9, 73.9, 55.5, 42.4; HR-MS (ESI, *m*/*z*) calcd for $C_{19}H_{16}NaO_5$ ($[M + Na]^+$) 347.0890, found 347.0915; $[\alpha]_D^{26}$ = +71.91 (*c* = 0.330, $CHCl_3$, 94% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, *n*-hexane/2-propanol = 85/15, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 17.9 min (major), t_R = 22.1 min (minor).

*2-(6-(Benzyloxy)-7-methoxy-1H-isochromen-1-yl)-1-(4-methoxyphenyl)ethanone (**3o**):* 20% yield, 95% ee, R_f = 0.43 (20:80 = EtOAc/*n*-hexane); yellow semisolid; FT-IR (neat) 3059, 2924, 2855, 1670, 1599, 1510, 1458, 1423, 1260, 1121, 1042, 845, 739, 698 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 7.91 (d, *J* = 8.9 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 7.1 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 2H), 6.60 (s, 1H), 6.54 (s, 1H), 6.33 (d, *J* = 5.7 Hz, 1H), 5.82 (dd, *J* = 7.9, 5.1 Hz, 1H), 5.65 (d, *J* = 5.7 Hz, 1H), 5.10 (s, 2H), 3.85 (s, 3H), 3.81 (s, 3H), 3.79−3.72 (m, 1H), 3.08 (dd, *J* = 15.8, 5.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.0, 163.7, 148.7, 148.1, 142.1, 137.1, 130.6 (2C), 130.3, 128.6 (2C), 127.9, 127.3 (2C), 123.5, 122.2, 113.8 (2C), 109.9, 108.9, 104.3, 73.7, 71.2, 56.3, 55.5, 42.6; HR-MS (ESI, *m*/*z*) calcd for $C_{26}H_{23}O_5$ ($[M - H]^+$) 415.1540, found 415.1533; $[\alpha]_D^{25}$ = +73.04 (*c* = 0.550, $CHCl_3$, 95% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, *n*-hexane/2-propanol = 75/25, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 34.4 min (major), t_R = 25.6 min (minor).

*2-(5-Fluoro-1H-isochromen-1-yl)-1-(4-methoxyphenyl)ethanone (**3p**):* 69% yield, 85% ee, R_f = 0.31 (10:90 = EtOAc/*n*-hexane); yellow semisolid; FT-IR (neat) 2927, 2360, 1675, 1596, 1465, 1259, 1169, 1059, 1024, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 2H), 7.07 (td, *J* = 7.9, 5.5 Hz, 1H), 6.94−6.89 (m, 3H), 6.82 (d, *J* = 7.5 Hz, 1H), 6.48 (d, *J* = 5.8 Hz, 1H), 6.01 (d, *J* = 5.8 Hz, 1H), 5.89 (dd, *J* = 8.0, 4.9 Hz, 1H), 3.85 (s, 3H), 3.83−3.77 (m, 1H), 3.11 (dd, *J* = 16.2, 4.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 163.8, 156.4 (d, *J* = 248.4 Hz, 1C), 144.5 (d, *J* = 1.9 Hz, 1C), 132.5 (d, *J* = 4.6 Hz, 1C), 130.6 (2C), 130.0, 127.7 (d, *J* = 7.9 Hz, 1C), 119.9 (d, *J* = 3.3 Hz, 1C), 117.5 (d, *J* = 16.8 Hz, 1C), 114.8 (d, *J* = 20.8 Hz, 1C), 113.8 (2C), 97.4 (d, *J* = 4.7 Hz, 1C), 73.2 (d, *J* = 2.5 Hz, 1C), 55.5, 42.3; HR-MS (ESI, *m*/*z*) calcd for $C_{18}H_{15}FNaO_3$ ($[M + Na]^+$) 321.0897, found 321.0902; $[\alpha]_D^{23}$ = +100.59 (*c* = 1.050, $CHCl_3$, 85% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OD-3 column, *n*-hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 9.9 min (major), t_R = 12.2 min (minor).

*2-(6-Chloro-1H-isochromen-1-yl)-1-(4-methoxyphenyl)ethanone (**3q**):* 70% yield, 74% ee, R_f = 0.29 (10:90 = EtOAc/*n*-hexane); light yellow solid; mp 73−77 °C; FT-IR (neat) 3071, 2926, 2851, 1676, 1624, 1601, 1512, 1423, 1312, 1263, 1225, 1167, 1047, 849, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.9 Hz, 2H), 7.08 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.02−6.93 (m, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.47 (d, *J* = 5.7 Hz, 1H), 5.87 (dd, *J* = 7.8, 5.2 Hz, 1H), 5.73 (d, *J* = 5.7 Hz, 1H), 3.85 (s, 3H), 3.77 (dd, *J* = 16.2, 7.9 Hz, 1H), 3.12 (dd, *J* = 16.2, 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 163.8, 145.1, 133.9, 131.1, 130.6 (2C), 130.0, 128.7, 126.6, 125.7, 123.2, 113.8 (2C), 103.8, 73.4, 55.5, 42.4; HR-MS (ESI, *m*/*z*) calcd for $C_{18}H_{15}ClNaO_3$ ($[M + Na]^+$) 337.0602, found 337.0625; $[\alpha]_D^{25}$ = +111.02 (*c* = 0.50, $CHCl_3$, 74% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, *n*-hexane/2-propanol = 95/05, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 18.0 min (major), t_R = 21.2 min (minor).

*2-(6-Bromo-1H-isochromen-1-yl)-1-(4-methoxyphenyl)ethanone (**3r**):* 31% yield, 94% ee, R_f = 0.40 (20:80 = EtOAc/*n*-hexane); yellow solid; mp 78−81 °C; FT-IR (neat) 3069, 2963, 2922, 2847, 1674, 1624, 1595, 1510, 1420, 1314, 1263, 1173, 1047, 1026, 847, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.9 Hz, 2H), 7.23 (d, *J* = 8.9 Hz, 1H), 7.10 (d, *J* = 1.8 Hz, 1H), 6.90 (dd, *J* = 8.6, 2.7 Hz, 3H), 6.46 (d, *J* = 5.7 Hz, 1H), 5.85 (dd, *J* = 7.8, 5.2 Hz, 1H), 5.72 (d, *J* = 5.7 Hz, 1H), 3.85 (s, 3H), 3.77 (dd, *J* = 16.2, 7.9 Hz, 1H), 3.12 (dd, *J* = 16.2, 5.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 163.8, 145.1, 131.4, 130.6 (2C), 129.9, 129.6, 129.2, 126.1, 125.9, 122.0, 113.8 (2C), 103.7, 73.4, 55.5, 42.4; HR-MS (ESI, *m*/*z*) calcd for $C_{18}H_{15}BrNaO_3$ ($[M + Na]^+$) 381.0097, found 381.0110; $[\alpha]_D^{25}$ = +137.48 (*c* = 0.565, $CHCl_3$, 94% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, *n*-hexane/2-propanol = 95/05, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 19.3 min (major), t_R = 23.1 min (minor).

*1-(4-Methoxyphenyl)-2-(6-(trifluoromethyl)-1H-isochromen-1-yl)-ethanone (**3s**):* 45% yield, 92% ee, R_f = 0.48 (20:80 = EtOAc/*n*-hexane); light yellow solid; mp 79−82 °C; FT-IR (neat) 3073, 2961, 2922, 2853, 1678, 1605, 1572, 1514, 1439, 1171, 1051, 935, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.20 (s, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.51 (d, *J* = 5.7 Hz, 1H), 5.95 (dd, *J* = 7.5, 5.4 Hz, 1H), 5.83 (d, *J* = 5.7 Hz, 1H), 3.85 (s, 3H), 3.83−3.77 (m, 1H), 3.16 (dd, *J* = 16.3, 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.0, 163.8, 145.4, 133.8, 130.61 (q, *J* = 32.3 Hz, 1C), 130.60 (2C), 130.1, 129.9, 124.8, 124.0 (q, *J* = 272.2 Hz, 1C), 123.57 (q, *J* = 3.9 Hz, 1C), 120.0 (q, *J* = 3.8 Hz, 1C), 113.9 (2C), 103.9, 73.4, 55.5, 42.2; HR-MS (ESI, *m*/*z*) calcd for $C_{19}H_{16}F_3O_3$ ($[M + H]^+$) 349.1046, found 349.1028; $[\alpha]_D^{25}$ = +84.14 (*c* = 0.415, $CHCl_3$, 92% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, *n*-hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 9.5 min (major), t_R = 10.8 min (minor).

*1-(2-(4-Methoxyphenyl)-2-oxoethyl)-1H-isochromene-6-carbonitrile (**3t**):* 52% yield, 48% ee, R_f = 0.37 (20:80 = EtOAc/*n*-hexane); white solid; mp 116−119 °C; FT-IR (neat) 2961, 2922, 2845, 2232, 1672, 1624, 1599, 1512, 1261, 1171, 1051, 1026, 826, 743 cm^{-1}; ^1H

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NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.9 Hz, 2H), 7.40 (dd, J = 7.8, 1.4 Hz, 1H), 7.22 (s, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.91 (d, J = 8.9 Hz, 2H), 6.53 (d, J = 5.7 Hz, 1H), 5.93 (dd, J = 7.2, 5.8 Hz, 1H), 5.79 (d, J = 5.7 Hz, 1H), 3.85 (s, 3H), 3.77 (dd, J = 16.4, 7.5 Hz, 1H), 3.19 (dd, J = 16.4, 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 163.9, 146.0, 134.9, 130.7, 130.6 (2C), 130.5, 129.7, 126.4, 125.4, 118.6, 113.9 (2C), 112.2, 103.3, 73.3, 55.5, 42.1; HR-MS (ESI, m/z) calcd for $C_{19}H_{16}NO_3$ ([M + H]$^+$) 306.1125, found 306.1130; $[\alpha]_D^{25}$ = +35.0 (c = 0.70, $CHCl_3$, 48% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 26.3 min (major), t_R = 32.1 min (minor).

*2-(3-Methyl-1H-isochromen-1-yl)-1-phenylethanone (**3u**):* 7 mg; 17% yield; R_f = 0.49 (10:90 = EtOAc/n-hexane); colorless sticky liquid; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.98 (d, J = 7.7 Hz, 2H), 7.60 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 7.4 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 5.92 (dd, J = 8.1, 5.0 Hz, 1H), 5.68 (s, 1H), 3.85 (dd, J = 15.8, 8.4 Hz, 1H), 3.16 (dd, J = 15.8, 4.8 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 197.5, 152.5, 137.1, 133.3, 130.8, 129.3, 128.7 (2C), 128.3 (2C), 128.2, 126.0, 123.9, 122.8, 100.8, 74.5, 42.9, 19.9; HR-MS (ESI, m/z) calcd for $C_{18}H_{16}NaO_2$ ([M + Na]$^+$) 287.1043, found 287.1052; $[\alpha]_D^{25}$ = +5.68 (c = 0.220, $CHCl_3$, 70% ee). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak AD-3 column, n-hexane/2-propanol = 97/03, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 14.5 min (major), t_R = 11.4 min (minor).

Procedure for Indole Addition. As per the literature report for alcohol addition to dihydropyran,[17] 5 mol % of $Bi(OTf)_3$ was added to a solution of 2-(1*H*-isochromen-1-yl)-1-(4-methoxyphenyl)ethanone (0.096 mmol) and 1.5 equiv of indole in dichloromethane. After 12 h, the reaction was quenched with satd $NaHCO_3$ and was extracted with dichloromethane (3 × 3 mL). The organic part was collected over Na_2SO_4, solvent was removed , and then flash column chromatography was performed using EtOAc/n-hexane (25:75 v/v to 30:70) to give 2-(3-(1*H*-Indol-3-yl)isochroman-1-yl)-1-(4-methoxyphenyl)-ethanone in 21% yield.

*2-(3-(1H-Indol-3-yl)isochroman-1-yl)-1-(4-methoxyphenyl)-ethanone (**4**):* 8 mg; 21% yield; R_f = 0.21 (40:60 = EtOAc/n-hexane); FT-IR (neat) 3417, 2924, 2854, 1667, 1599, 1574, 1510, 1489, 1456, 1338, 1218, 1170, 1096, 1025, 805 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.35 (dd, J = 5.4, 3.8 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.21 (dd, J = 7.6, 4.1 Hz, 2H), 7.10−7.00 (m, 3H), 6.87 (dd, J = 9.7, 2.4 Hz, 4H), 5.29 (d, J = 7.5 Hz, 1H), 4.80 (t, J = 7.4 Hz, 1H), 3.85 (s, 3H), 3.61 (d, J = 7.4 Hz, 2H), 2.98 (dd, J = 17.7, 9.7 Hz, 1H), 2.30 (dd, J = 17.6, 2.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5, 163.8, 141.2, 138.0, 136.3, 130.5 (2C), 130.2, 127.5, 126.9, 126.5, 126.1, 122.1, 121.7, 119.9, 119.6, 119.1, 113.6 (2C), 110.9 (2C), 65.7, 55.5, 45.6, 38.3, 36.4; HR-MS (ESI, m/z) calcd for $C_{26}H_{24}NO_3$ ([M + H]$^+$) 398.1751, found 398.1745; $[\alpha]_D^{22}$ = +47.56 (c = 0.250, $CHCl_3$, 95% ee, single diastereomer). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak IC-3 column, n-hexane/2-propanol = 75/25, flow rate = 1.0 mL/min, λ = 254 nm; t_R = 13.3 min (major), t_R = 22.2 min (minor).

Procedure for Methanol Addition. As per the literature report for alcohol addition to dihydropyran,[17] 5 mol % $Bi(OTf)_3$ was added to a solution of 2-(1*H*-isochromen-1-yl)-1-(4-methoxyphenyl)-ethanone (0.075 mmol) and 5 equiv of methanol in dichloromethane. After 3 h, the reaction was quenched with satd $NaHCO_3$ and was extracted with dichloromethane (3 × 3 mL). The organic part was collected over Na_2SO_4, solvent was removed in vacuo, then flash column chromatography was performed by using EtOAc/n-hexane (07:93 v/v to 10:90) to give 2-(3-methoxyisochroman-1-yl)-1-(4-methoxyphenyl)ethanone with 56% yield.

*2-(3-Methoxyisochroman-1-yl)-1-(4-methoxyphenyl)ethanone (**5**):* 13 mg; 56% yield; R_f = 0.20 (10:90 = EtOAc/n-hexane); yellow semisolid; FT-IR (neat) 2958, 2923, 2843, 2369, 1655, 1602, 1263, 1169, 1125, 1035, 737 cm^{-1}; ^{1}H NMR (500 MHz, CDCl3) δ 8.03 (d, J = 9.0 Hz, 2H), 7.22 (d, J = 4.0 Hz, 2H), 7.15 (d, J = 4.5 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 5.54 (dd, J = 9.1, 3.2 Hz, 1H), 5.02 (dd, J = 4.6, 1.9 Hz, 1H), 3.90 (s, 3H), 3.59 (dd, J = 15.9, 9.2 Hz, 1H), 3.45 (s, 3H), 3.39 (dd, J = 16.0, 3.6 Hz, 1H), 3.20 (dd, J = 16.7, 4.6 Hz, 1H), 2.80 (d, J = 16.3 Hz, 1H); for major diastereomer; ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.6, 163.6, 136.9, 131.2, 130.6 (2C), 130.5, 129.1, 126.9, 126.3, 123.6, 113.8 (2C), 97.1, 66.4, 55.5, 55.2, 44.1, 33.6; HRMS (ESI, m/z) calcd for $C_{19}H_{20}NaO_4$ ([M + Na]$^+$) 335.1254, found 335.1264. The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 96/04, flow rate = 1.0 mL/min, λ = 254 nm; $t_{R(1)}$ = 27.1 min (major), $t_{R(1)}$ = 109.9 min (minor); $t_{R(2)}$ = 45.9 min (major), $t_{R(2)}$ = 32.6 min (minor).

Procedure for Allylation of 2-(3-Methoxyisochroman-1-yl)-1-(4-methoxyphenyl)ethanone. To a solution of 2-(3-methoxyisochroman-1-yl)-1-(4-methoxyphenyl)ethanone (0.035 mmol) and 20 mol % of $ZnBr_2$ in dichloromethane was added 1.5 equiv of allyltrimethylsilane at room temperature, the reaction was stirred for 12 h, and then flash column chromatography was performed using EtOAc/n-hexane (05:95 v/v to 07:93) to provide 2-(3-allylisochroman-1-yl)-1-(4-methoxyphenyl)ethanone with 53% yield.

*2-(3-Allylisochroman-1-yl)-1-(4-methoxyphenyl)ethanone (**6**):* 6 mg; 53% yield; R_f = 0.51 (20:80 = EtOAc/n-hexane); FT-IR (neat) 2918, 2850, 1675, 1600, 1457, 1260, 1170, 1080, 1030, 837, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.9 Hz, 2H), 7.16 (dt, J = 6.9, 3.6 Hz, 2H), 7.09 (dd, J = 5.1, 3.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 5.87−5.71 (m, 1H), 5.51−5.30 (m, 1H), 5.13−4.91 (m, 2H), 3.86 (s, 3H), 3.73 (dtd, J = 9.7, 6.2, 3.4 Hz, 1H), 3.51 (dd, J = 15.7, 7.9 Hz, 1H), 3.28 (dd, J = 15.7, 4.1 Hz, 1H), 2.72 (ddd, J = 18.7, 16.0, 6.8 Hz, 2H), 2.37 (dt, J = 13.0, 6.5 Hz, 1H), 2.30−2.21 (m, 1H); for pure diastereomer (major separated by column chromatography) ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1, 163.5, 137.9, 134.3, 134.2, 130.8 (2C), 130.7, 129.0, 126.6, 126.3, 124.2, 116.9, 113.6 (2C), 74.1, 73.9, 55.5, 45.4, 40.4, 34.3; HRMS (ESI, m/z) calcd for $C_{21}H_{22}NaO_3$ ([M + Na]$^+$) 345.1461, found 345.1484; $[\alpha]_D^{23}$ = +19.9 (c = 0.120, $CHCl_3$, 94% ee, 73% ee, 1:2.3 dr). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 93/07, flow rate = 1.0 mL/min, λ = 254 nm; $t_{R(1)}$ = 28.6 min (major), $t_{R(1)}$ = 33.7 min (minor); $t_{R(2)}$ = 11.8 min (major), $t_{R(2)}$ = 19.6 min (minor).

The dihydroxylation and protection of diol was carried out by following a similar protocol available in the literature for 5-isopropoxy-1-(4-methoxybenzyl)-1*H*-pyrrol-2(5*H*)-one.[18]

Experimental Procedure for Dihydroxylation. To a solution of 2-(1*H*-isochromen-1-yl)-1-(4-methoxyphenyl)ethanone (20 mg, 0.071 mmol), in acetone−water (9:1) mixture, were added 50% aq NMO solution (29 μL, 0.142 mmol) and 4% aq osmium tetraoxide solution (44 μL, 0.0071 mmol), and then the reaction mixture was stirred at room temperature for 20 h. After the reaction completed, the reaction mixture was extracted with dichloromethane (2 × 4 mL) and distilled water. The collected organic layer was dried with Na_2SO_4 and evaporated in vacuo. The compound was purified by flash column chromatography using 1:2 v/v EtOAc/n-hexane: yield 18.6 mg, 82%.

Experimental Procedure for the Protection of Dihydroxylation. To a solution of 2-(3,4-dihydroxyisochroman-1-yl)-1-(4-methoxyphenyl)ethanone (18.6 mg, 0.059 mmol) in acetone were added 2,2-dimethoxypropane (61.3 mg,0.59 mmol) and p-TSA (1.12 mg, 0.0059 mmol), and the mixture was stirred at room temperature for 12 h. Then the reaction mixture was extracted with dichloromethane (2 × 4 mL) and distilled water. The collected organic layer was dried with Na_2SO_4 and evaporated in vacuo. The compound was purified by flash column chromatography using 4:96 v/v EtOAc/n-hexane: yield 9.9 mg, 47%.

*2-(2,2-Dimethyl-3a,9b-dihydro-5H-[1,3]dioxolo[4,5-c]-isochromen-5-yl)-1-(4-methoxyphenyl)ethan-1-one (**7**):* 9.9 mg; 47% yield; R_f = 0.36 (20:80 = EtOAc/n-hexane); yellow semisolid; FT-IR (neat) 2980, 2918, 2361, 2343, 1675, 1600, 1576, 1508, 1374, 1260, 1217, 1170, 1031, 840, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.9 Hz, 2H), 7.41 (dd, J = 5.8, 3.0 Hz, 1H), 7.34 (d, J = 3.7 Hz, 1H), 7.30 (d, J = 2.9 Hz, 1H), 7.22−7.11 (m, 1H), 6.94 (d, J = 8.8 Hz, 2H), 5.64 (d, J = 4.8 Hz, 1H), 5.40 (t, J = 6.0 Hz, 1H), 5.11 (d, J = 4.9 Hz, 1H), 3.86 (s, 3H), 3.66 (dd, J = 16.7, 6.4 Hz, 1H), 3.48

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(dd, J = 13.9, 5.0 Hz, 1H), 1.55 (s, 3H), 1.44 (s, 3H); for major diastereomer; ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.17, 163.72, 140.91, 131.10, 130.72(2C), 130.45, 130.21, 128.99, 127.77, 124.04, 113.81(2C), 111.32, 97.71, 73.34, 70.57, 55.50, 44.12, 28.17, 26.13; HRMS (ESI, m/z) calcd for $C_{21}H_{23}O_5$ ([M + H]$^+$) 355.1540, found 355.1551; $[\alpha]_D^{23}$ = +21.717 (c = 0.495, $CHCl_3$, 94% ee, 91% ee, 1:1.35 dr). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, λ = 254 nm; $t_{R(1)}$ = 56.1 min (major), $t_{R(1)}$ = 18.2 min (minor), $t_{R(2)}$ = 39.2 min (major), $t_{R(2)}$ = 23.5 min (minor).

Experimental Procedure for Solvolysis of Epoxide. To a solution of 2-(1*H*-isochromen-1-yl)-1-(4-methoxyphenyl)ethanone (20 mg, 0.071 mmol) in trifluoroethanol were added MTO (1 mol %) and pyrazole (10 mol %), and the reaction was stirred at room temperature for 2 min. Then 30% aq H_2O_2 (2 equiv) was added and the mixture stirred for 12 h at room temperature. The reaction mixture was passed through a small silica pad with dichloromethane and evaporated in vacuo. The compound was purified by flash column chromatography using 1:4 EtOAc/n-hexane: yield 15.8 mg, 56%.

The epoxidation was performed by following literature report for epoxidation using MTO catalyst.[19]

*2-(4-Hydroxy-3-(2,2,2-trifluoroethoxy)isochroman-1-yl)-1-(4-methoxyphenyl)ethan-1-one (**8**):* 10.7 mg; 56% yield; R_f = 0.33 (30:70 = EtOAc/n-hexane); light yellow semisolid; FT-IR (neat) 2923, 2848, 2364, 1654, 1420, 1265, 1172, 1092, 1027, 976, 845, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.9 Hz, 1H), 7.42 (dd, J = 5.7, 3.2 Hz, 1H), 7.30−7.25 (m, 1H), 7.09−6.99 (m, 1H), 6.91 (d, J = 8.9 Hz, 1H), 5.37−5.25 (m, 1H), 5.18 (d, J = 1.1 Hz, 1H), 4.48 (d, J = 1.1 Hz, 1H), 4.13−3.96 (m, 1H), 3.85 (s, 2H), 3.71 (dd, J = 17.6, 5.6 Hz, 1H), 3.57 (dd, J = 17.6, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.5, 163.9, 135.4, 132.3, 130.5 (3C), 130.2, 129.9, 128.6, 127.5, 123.1, 113.8 (3C), 100.4, 66.8 (d, J = 2.9 Hz), 64.7 (q, J = 34.5 Hz), 55.5, 42.6; DEPT ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.49 (3C), 130.18, 128.63, 127.48, 123.10, 113.84 (3C), 100.44, 66.8 (d, J = 2.9 Hz), 64.7 (q, J = 34.5 Hz), 55.52, 42.63; HRMS (ESI, m/z) calcd for $C_{20}H_{19}F_3NaO_5$ ([M + Na]$^+$) 419.1077, found 419.1081; $[\alpha]_D^{22}$ = +17.280 (c = 0.535, $CHCl_3$, 97% ee, 95% ee, 92% ee, 1:1.77:4.71 dr). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 75/25, flow rate = 1.0 mL/min, λ = 254 nm; $t_{R(1)}$ = 11.2 min (major), $t_{R(1)}$ = 8.9 min (minor), $t_{R(2)}$ = 13.1 min (major), $t_{R(2)}$ = 8.1 min (minor). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OD-3 column, n-hexane/2-propanol = 70/30, flow rate = 1.0 mL/min, λ = 254 nm; $t_{R(1)}$ = 8.6 min (major), $t_{R(1)}$ = 15.4 min (minor).

Experimental Procedure Bromoacetal Formation. In a small vial, 2-(1*H*-isochromen-1-yl)-1-(4-methoxyphenyl)ethanone (20 mg, 0.071 mmol) was taken in dichloromethane and stirred at 0 °C for 2 min. Then the reaction was allowed to stir at 0 °C for 30 min after sequential addition of *N*-bromosuccinamide (1.3 equiv) and acetic acid (10 equiv). After the reaction completed, the reaction mixture was extracted with dichloromethane (2 × 5 mL) and distilled water. The collected organic layer was dried with Na_2SO_4 and evaporated in vacuo. The compound was purified by flash column chromatography using 1:9 v/v EtOAc/n-hexane: yield 16.8 mg, 56.4%.

The bromo-acetoxylation was performed by using a similar protocol available for dihydropyran.[20]

*4-Bromo-1-(2-(4-methoxyphenyl)-2-oxoethyl)isochroman-3-yl acetate (**9**):* 13.3 mg; 56.7% yield; R_f = 0.33 (20:80 = EtOAc/n-hexane); yellow semisolid; FT-IR (neat) 2923, 2852, 2364, 2342, 1673, 1598, 1261, 1169, 1072, 1029, 831, 763 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 8.00 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 3.6 Hz, 1H), 7.32 (d, J = 1.8 Hz, 1H), 7.30 (s, 1H), 7.14 (d, J = 6.7 Hz, 1H), 6.93 (d, J = 8.9 Hz, 2H), 6.46 (d, J = 1.4 Hz, 1H), 5.81 (dd, J = 8.0, 3.9 Hz, 1H), 5.07 (s, 1H), 3.85 (s, 3H), 3.77 (dd, J = 16.4, 8.2 Hz, 1H), 3.24 (dd, J = 16.4, 4.0 Hz, 1H), 1.98 (s, 3H); for major diastereomer; ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 169.2, 163.8, 135.6, 131.4, 130.8 (2C), 130.6, 130.1, 129.3, 127.7, 124.8, 113.8 (2C), 93.2, 69.2, 55.5, 45.6, 43.5, 20.9; HRMS (ESI, m/z) calcd for $C_{20}H_{19}BrNaO_5$ ([M + Na]$^+$) 441.0308, found 441.0285; calcd for $C_{20}H_{19}BrO_5$ [(M + 2) + H]$^+$ 443.0289, found 443.0262; $[\alpha]_D^{26}$ = +28.7426 (c = 0.660, $CHCl_3$, 93% ee, 1:7.10:13.47 dr). The enantiomeric ratio was determined by HPLC analysis using a Diacel Chiralpak OZ-3 column, n-hexane/2-propanol = 97/03, flow rate = 1.0 mL/min, λ = 254 nm; $t_{R(1)}$ = 72.1 min (major), $t_{R(1)}$ = 37.7 min (minor), $t_{R(2)}$ = 56.6 min (major), $t_{R(2)}$ = 91.2 min (minor), $t_{R(3)}$ = 18.3 min (major), $t_{R(3)}$ = 20.1 min (minor).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00565.

^{1}H and ^{13}C NMR spectra for all products and HPLC traces for ee determination (PDF)

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Notes

The authors declare no competing financial interest.

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