One-Pot Synthesis of 1-Substituted 1H-Isochromenes by Combining Brønsted Acid with Silver Catalysis

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Dedicated to Professor Gerhard Bringmann on the occasion of his 65th birthday

Abstract A one-pot synthesis of 1-substituted 1H-isochromenes employing various 2-alkynyl-benzaldehydes and ketones as substrates under a combination of Brønsted acid and silver catalysis has been developed. The isochromenes, which are present as important heterocyclic core structures in many bioactive and natural compounds, are obtained in medium to excellent yields with diastereomeric ratios of up to 9:1. A first enantioselective variant has also been tested.

Key words isochromene, Brønsted acid catalysis, silver catalysis, organocatalysis, one-pot synthesis

Isochromenes are a common heterocyclic motif in natural products and bioactive compounds.¹ For example, compound I, containing the isochromene core structure, has been studied as an anti-inflammatory agent.² Chloroquinocin (II)³ and alnumycin-D (III)⁴ have shown activity as antibacterial and antimicrobial agents, respectively. Benzosimuline (IV)⁵ has been isolated as a natural product from the plant Formosan Zanthoxylum simulans and has been found to be active against platelet aggregation⁶ (Figure 1). In consequence, it is very important to develop new methods for the synthesis of isochromene derivatives. Various methods for the synthesis of 1-substituted 1H-isochromenes have already been reported, such as metal-catalyzed cycloisomerizations of 2-alkynylaldehydes in the presence of suitable carbon-⁶ or oxygen-nucleophiles.⁷ In addition, Yamamoto and co-workers reported on the treatment of 1-alkoxy 1H-isochromenes with a Lewis acid generating a benzopyrylium ion, which can be trapped by suitable nucleophiles leading to 1-substituted 1H-isochromene derivatives⁸ (Scheme 1). In view of the importance of the title heterocycles, one-pot syntheses of substituted 1H-isochromene derivatives are very desirable because the one-pot multicomponent domino synthesis of organic molecules has many advantages.⁹

Recently, our group has successfully combined gold/silver and organocatalysis for the one-pot synthesis of various annulated heterocycles.¹⁰ In a continuation of this, we investigated the possibility of combining the silver-catalyzed formation of benzopyrylium cation intermediates with subsequent trapping by enolizable ketones under Brønsted acid catalysis.¹¹ For the synthesis of 1-substituted 1H-isochromenes, 2-alkynyl benzaldehydes were first synthesized by using a Sonogashira coupling¹² of 2-bromo benzaldehydes and phenylacetylenes. For the initial optimization we chose 2-(2-phenylethynyl) benzaldehyde and one equiva-
lent of acetylacetone as the nucleophile. A single-neck flask charged with the 2-alkynylbenzaldehyde dissolved in toluene, 2 mol% silvercarbonate as catalyst, and 10 mol% acetic acid was stirred for 24 hours, but these conditions gave no product (Table 1, entry 1). Further heating the reaction mixture at 60 °C overnight resulted only in some consumption of the 2-(2-phenylethynyl)benzaldehyde but did not lead to any desired product (entry 2).

More Brønsted acids, for example trifluoroacetic acid (TFA), triflic acid and diphenyl phosphate (DPP), were screened (Table 1). Whereas stronger acids such as triflic acid led to the decomposition of the substrate and no desired product formation, the use of TFA resulted in 11% of the 1H-isochromene product according to NMR spectroscopic analysis. Interestingly, the combination of 2 mol% silver carbonate and 10 mol% DPP led to an increased yield of 42% product. With this initial result in hand, a range of solvents were screened. n-Hexane turned out to be the best solvent for this reaction, resulting in 66% yield of the desired isochromene. When two equivalents of acetylacetone were used instead of one equivalent, the yield increased to 86%. The combination of DPP with different silver salts such as Ag2O, AgOTf, AgBF4 and AgNO3 did not improve the yield.

It should be mentioned here that during the screening of conditions, we observed the formation of an intermediate that turned out to be the dimer of o-alkynylbenzaldehyde. This type of dimerization was previously reported by Yao and co-workers using a Brønsted acid.13 The dimer formation was dependent on the concentration and the amount of the silver catalyst. Hence, further optimization of the reaction conditions was carried out. Finally, the optimal conditions were established as stirring o-alkynylbenzaldehyde with acetylacetone (0.17 M in n-hexane), Ag2CO3 (2.5 mol%) and DPP (10 mol%) at 40 °C for 16 h, leading to 93% yield of the desired 1H-isochromene 3a (Table 1, entry 17).

With the optimized conditions in hand, we tested a range of substituted o-alkynylbenzaldehydes as well as ketones as nucleophile such as phenyl acetone, 2-phenyl cyclohexanone, and methyl cyclopentanone-2-carboxylate. The easily enolizable acetylacetone (3b; Table 2) resulted in a faster reaction and higher yield (97%) of the desired isochromene. Switching to the less enolizable nucleophile phenyl acetone (3c) required a longer reaction time and gave a lower yield of the product (54%) as a mixture of diastereomers.

Table 1  Optimization of the Reaction Conditions

<table>
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<tr>
<th>Entry</th>
<th>Ag-Salt</th>
<th>Acid</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Solvent</th>
<th>Yield (%)</th>
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<td>1</td>
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<td>AcOH</td>
<td>rt</td>
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<td>toluene</td>
<td>nr</td>
</tr>
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<td>Ag2CO3</td>
<td>AcOH</td>
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<td>24</td>
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<td>nr</td>
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<td>CF3SO3H</td>
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<td>nr</td>
</tr>
<tr>
<td>5</td>
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<td>n-hexane</td>
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<tr>
<td>11</td>
<td>–</td>
<td>DPP</td>
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<td>17</td>
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<td>40</td>
<td>16</td>
<td>n-hexane</td>
<td>93</td>
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Reactions conditions: 1a (0.4 mmol), 2a (0.4 mmol), acid (10 mol%), Ag2CO3 (0.008 mmol), n-hexane (0.3 M, 2.4 mL), 40 °C, 17 h.

Yield of isolated 3a after flash chromatography.

Acetyl acetone (2 equiv) used.

Compound 2a (0.8 mmol), Ag2CO3 (2.5 mol%) used and the concentration reduced to 0.17 M in n-hexane.
Comparing the differently substituted aldehydes, no significant influence of the substituent groups was observed; substrates bearing electron-withdrawing (3d, 95%; Table 2) or electron-donating substituents (3h, 91%), or both (3b, 97%), all gave similar yields. There was an influence of the substituents at the aldehyde when 2-phenylcyclohexanone was used as ketone nucleophile. When the aldehyde was substituted at the R4 position with an electron-donating methoxy group, the d.r. was in the range of 1:1 (3v; Table 3), but when the substituent was on R6, the d.r. increased to 9:1 (3z). Furthermore, the yields obtained for 3o–q clearly show the impact of the activation of the different nucleophiles. Methyl cyclopentanone-2-carboxylate and 2-acetylcyclopentanone, being 1,3-dicarbonyl compounds, are much more enolizable, leading to 1H-isochromene 3o (96% yield) and 3q (74% yield) in excellent or good yields, respectively. In comparison, 2-phenylcyclohexan-1-one, which is a cyclic ketone containing a sterically demanding phenyl substituent, is not easily enolizable and its use led to moderate yield and required a longer reaction time (3p; 59%, 23 h).

It is well known that under silver-catalyzed cyclization either a 5-exo-dig or a 6-endo-dig ring system can be generated. To confirm the relative configuration of the 1H-isochromenes and to evaluate whether a five- or a six-membered ring is formed, the major diastereomer of 3p was separated by preparative HPLC. Subsequent HMBC NMR experiments with the purified diastereomer of 3p were carried out, but the results were inconclusive. The proposed structure including the relative configuration was finally determined by X-ray crystal structure analysis of compound rac-3p. It was thereby confirmed that a six-membered isochromene ring system was formed (Figure 2).

![Figure 2](image)

Table 2 Synthesis of 1-Substituted 1H-isochromenes 3a–l with Open-Chain Ketones as Nucleophiles

<table>
<thead>
<tr>
<th>3</th>
<th>R1</th>
<th>R2</th>
<th>R4</th>
<th>R5</th>
<th>R6</th>
<th>R7</th>
<th>t (h)</th>
<th>Yield (%)</th>
<th>d.r.</th>
</tr>
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<td>COMe</td>
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<td>H</td>
<td>H</td>
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<td>93</td>
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</tr>
<tr>
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<td>Me</td>
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<td>H</td>
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<td>Me</td>
<td>H</td>
<td>12</td>
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<tr>
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<td>Me</td>
<td>Ph</td>
<td>H</td>
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<td>Me</td>
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<td>COMe</td>
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<td>H</td>
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*a Reaction conditions: 1 (0.4 mmol), 2 (0.8 mmol), DPP (10 mol%), Ag2CO3 (2.5 mol%), n-hexane (0.17 M), 40 °C.
*b Yield of the isolated product after flash chromatography.
*c Based on 1H NMR spectroscopic analysis.
*d Compound 1 (0.3 mmol) and 2 (0.9 mmol) used in n-hexane (0.17 M, 1.8 ml).
antioselective cyclization/reduction cascade by using a chiral Ag-catalyst.15 Recently, Uemura and co-workers reported a chiral Au-complex catalyzed desymmetrization of 2-alkynylbenzaldehydes.16 Most recently, Ghorai and co-workers reported an enantioselective synthesis of 1H-isochromenes through intramolecular oxa-Michael addition by using a chiral bifunctional organocatalyst.17 In the past years, chiral phosphoric acid catalysis has been developed

Table 3 Synthesis of 1-Substituted 1H-Isochromenes 3m–a’ with Cyclic Ketones as Nucleophiles

<table>
<thead>
<tr>
<th>3</th>
<th>R1–R3</th>
<th>R2</th>
<th>R4</th>
<th>R5</th>
<th>R6</th>
<th>R7</th>
<th>t (h)</th>
<th>Yield (%)</th>
<th>d.r.</th>
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<td>H</td>
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<td>H</td>
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<td>40 (d)</td>
<td>2.7:1</td>
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<td>46</td>
<td>92</td>
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\(a\) Reaction conditions: 1 (0.4 mmol), 2 (0.8 mmol), DPP (10 mol\%), Ag2CO3 (2.5 mol\%), n-hexane (0.17 M), 40 °C.
\(b\) Yield of the isolated product after flash chromatography.
\(c\) Based on \(^1\)H NMR spectroscopic analysis.
\(d\) Compound 1 (0.3 mmol), 2 (0.9 mmol), DPP (10 mol\%), Ag2CO3 (2.5 mol\%), n-hexane (0.17 M, 1.8 mL), 40 °C.

Scheme 2 Enantioselective synthesis of 1H-isochromene 3n (absolute configuration not determined)
as an extremely powerful tool in many asymmetric transformations, both under homogeneous and heterogeneous conditions. At present, the combination of chiral phosphoric acids with metal catalysts is of particular interest.

We envisioned that the use of a chiral phosphoric acid instead of the achiral diaryl phosphate may lead to enantioenriched 1H-isochromenes. Stirring 2-phenyl cyclohexanone-1-one with substrate 1a in the presence of 2.5 mol% Ag₂CO₃ and 10% (R)-TRIP catalyst at 40 °C for 30 minutes and then stirring at 0 °C for 3 days yielded 33% isolated product with a d.r. of 2.3:1 and 63% ee of the major diastereomer (Scheme 2). Further development and optimization of this enantioselective version is under investigation in our research group.

In conclusion, we have developed a new one-pot protocol for the synthesis of 1-substituted 1H-isochromenes involving 2-alkynyl benzaldehydes and ketone nucleophiles, such as open-chain 1,3-diketones, phenylacetone, cyclic β-ketoesters, and 2-phenylcyclohexanone, as substrates. This one-pot method combines transition-metal catalysis with organocatalytic Brønsted acid catalysis. The possibility of using water as an extremely powerful tool in many asymmetric transformations, both under homogeneous and heterogeneous conditions. At present, the combination of chiral phosphoric acids with metal catalysts is of particular interest.

All reactions were performed in oven-dried glassware. Starting materials and reagents were purchased from commercial suppliers (ABCR, Acros, Sigma Aldrich and TCI Europe), which were used without further purification unless otherwise noted. All solvents were distilled, purified, and dried according to standard procedures. Analytical TLC was performed using pre-coated silica gel plates (Merck silica gel 60 F₂₅₄). Preparative HPLC was carried out with a Knauer Azura System using a chiral stationary phase (Diacel Chiralpak IC, IA, AD, AS and IB columns). Preparative TLC was carried out with a Knaur Azura System. Optical rotation values were measured with a Perkin Elmer 241 polarimeter and melting points were obtained with a LLG MPM-H2 apparatus.

**1H-Isochromenes 3; General Procedure**

A dry single-necked flask was charged with 2-alkynylaldehyde 1 (0.4 mmol, 1 equiv), ketone 2 (0.8 mmol, 2 equiv), and diphenylphosphate (10 mg, 0.04 mmol, 10 mol %) in hexane (2.4 mL) and silver carbonate (2.75 mg, 0.01 mmol, 2.5 mol %) was added. The mixture was heated at 40 °C and stirred until the 2-alkynylaldehyde was completely consumed (progress of the reaction was monitored by TLC). The hexane was evaporated and the mixture was diluted in EtOAc (50 mL) and washed three times with water. The organic layer was dried over anhydrous Na₂SO₄ and filtered. After evaporating the EtOAc, the crude product was dissolved in dichloromethane and purified by column chromatography (sila gel; pentane/EtOAc 96:4) to give pure 1H-isochromenes 3 as yellow oils or as colorless solids. In the case of phenylaceton-2-phenylcyclohexanone as ketone nucleophiles, the crude product was directly purified by flash chromatography on silica gel.

3-(3-Phenyl-1H-isochromen-1-yl)pentane-2,4-dione (3a)

**Yield:** 112 mg (93%); colorless solid; mp 129–131 °C; Rf = 0.5 (pentane/EtOAc, 10:1); keto/enol = 1:1.3.

IR (ATR): 3426, 3048, 2969, 2926, 2658, 2325, 2097, 1917, 1677, 1621, 1519, 1471, 1218, 1054, 839, 760, 691 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ (keto) = 7.59 (d, J = 6.9 Hz, 2 H), 7.40 (t, J = 6.7 Hz, 2 H), 7.39–7.33 (m, 2 H), 7.28 (t, J = 6.2 Hz, 1 H), 7.13 (d, J = 7.5 Hz, 2 H), 7.02 (d, J = 7.9 Hz, 1 H), 6.51 (s, 1 H), 6.15 (d, J = 10.4 Hz, 1 H), 2.46 (d, J = 10.4 Hz, 1 H), 2.37 (s, 3 H), 1.90 (s, 3 H). 13C NMR (151 MHz, CDCl₃): δ = 173.5 (q), 144.0 (q), 138.4 (q), 138.0 (q), 137.5 (q), 135.4 (q), 128.2 (q), 127.9 (q), 127.0 (q), 126.8 (q), 125.1 (q), 124.9 (q), 124.8 (q), 124.5 (q), 124.1 (q), 123.5 (q), 110.1 (q), 100.7 (q), 100.6 (q), 76.3 (q), 76.3 (q), 70.7 (q), 32.1 (q), 29.0 (q).


3-(6-Fluoro-3-tolyl-1H-isochromen-1-yl)pentane-2,4-dione (3b)

**Yield:** 112 mg (93%); colorless solid; mp 129–131 °C; Rf = 0.5 (pentane/EtOAc, 10:1); keto/enol = 1:1.3.

IR (ATR): 3741, 3456, 3266, 3024, 2180, 2061, 1982, 1732, 1361, 1218, 1054, 839, 760, 691 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ (keto) = 17.32 (s, 1 H), 7.73 (d, J = 7.1 Hz, 2 H), 7.39–7.33 (m, 2 H), 7.27–7.24 (m, 1 H), 7.16 (dd, J = 7.6, 3.4, 1.1 Hz, 2 H), 6.94 (d, J = 7.5 Hz, 1 H), 6.47 (s, 1 H), 6.25 (s, 1 H), 2.21 (s, 3 H), 2.12 (s, 3 H).

13C NMR (151 MHz, CDCl₃): δ = 201.2 (C₂), 200.9 (C₁), 153.7 (C₃), 150.6 (C₅), 133.9 (C₇), 133.5 (C₉), 132.5 (C₁₀), 130.5 (C₁₁), 130.3 (C₁3), 129.2 (C₁₈), 129.0 (C₁₉), 128.9 (C₂₀), 128.5 (C₂₁), 128.4 (2C, C₂₂), 127.3 (C₂₃), 127.0 (C₂₉), 126.8 (C₂₆), 125.1 (C₂₇), 124.9 (2C, C₃₀), 124.8 (2C, C₃₁), 124.5 (C₃₂), 124.1 (C₃₃), 123.5 (C₃₄), 109.1 (C₁₄), 100.7 (CH), 100.6 (CH), 76.5 (CH), 76.3 (CH), 70.7 (CH), 32.1 (CH₃), 29.0 (CH₃).


3-(6-Fluoro-3-tolyl-1H-isochromen-1-yl)-1-phenylpropan-2-one (3c)

**Yield:** 61 mg (54%); colorless solid; mp 125 °C; Rf = 0.6 (pentane/EtOAc, 10:1); d.r. = 1:3:1.

IR (ATR): 3860, 3424, 3017, 2658, 2523, 2317, 2087, 1892, 1714, 1606, 1470, 1371, 1241, 1138, 1050, 966, 789 cm⁻¹.
HRMS (ESI): δ (minor) = 207.1, 136.45, 131.5, 131.1, 130.7, 130.2, 129.65, 129.5, 128.6, 127.8, 128.6, 128.1, 127.1, 126.5, 126.2, 116.1, 112.7, 112.6, 103.0, 79.2, 78.1, 62.25, 60.3, 30.7.

1F NMR (564 MHz, CDCl₃): δ = -114.51 (major), -115.07 (minor). HRMS (ESI): m/z [M⁺] calcd for C₂₅H₂₂O₂F: 358.1364; found: 358.1368.

3-(7-Methoxy-3-phenyl-1H-isochromen-1-yl)-pentane-2,4-dione (3f)

Yield: 127 (92%); yellow oil; Rₜ = 0.4 (n-pentane/EtOAc, 10:1).

IR (ATR): 3442, 2944, 2322, 2085, 1911, 1716, 1598, 1474, 1257, 1150, 1034, 842, 759, 693 cm⁻¹.

HRMS (ESI): δ (minor) = 207.1, 136.45, 131.5, 131.1, 130.7, 130.2, 129.65, 129.5, 128.6, 127.8, 128.6, 128.1, 127.1, 126.5, 126.2, 116.1, 112.7, 112.6, 103.0, 79.2, 78.1, 62.25, 60.3, 30.7.

1F NMR (564 MHz, CDCl₃): δ = -114.51 (major), -115.07 (minor). HRMS (ESI): m/z [M⁺] calcd for C₂₅H₂₂O₂F: 358.1364; found: 358.1368.

1-(3-Fluorophenyl)-1H-isochromen-1-yl]pentane-2,4-dione (3d)

Yield: 123 mg (95%); yellow solid; mp 122–124 °C; Rₜ = 0.48 (n-pentane/EtOAc, 10:1).

IR (ATR): 3403, 3173, 3074, 2976, 2881, 2662, 2330, 2207, 2087, 2002, 1924, 1855, 1729, 1709, 1609, 1583, 1485, 1445, 1359, 1267, 1216, 1158, 1051, 951, 873, 784, 754, 688 cm⁻¹.


3-(7-Methoxy-3-phenyl-1H-isochromen-1-yl]-1-phenylpropan-2-one (3g)

Yield: 131 mg (91%); colorless solid; mp 108–110 °C.

IR (ATR): 3794, 3455, 2971, 2180, 2041, 1740, 1588, 1367, 1218, 931, 833, 697 cm⁻¹.


1-(3-Fluorophenyl)-1H-isochromen-1-yl)-1-phenylpropan-2-one (3e)

Yield: 54 mg (50%); yellow solid; mp 123 °C; Rₜ = 0.43 (n-pentane/EtOAc, 10:1); dr = 1:4.1.

IR (ATR): 3403, 3048, 2933, 2672, 2319, 2091, 1900, 1705, 1587, 1458, 1351, 1275, 1160, 1055, 895, 773 cm⁻¹.


3-(3-Fluorophenyl)-1H-isochromen-1-yl)-1-phenylpropan-2-one (3c)

Yield: 131 mg (91%); colorless solid; mp 108–110 °C.

IR (ATR): 3912, 3779, 2959, 2646, 2321, 2177, 2062, 1992, 1921, 1714, 1603, 1406, 1361, 1265, 1208, 1110, 1044, 926, 814, 749, 698 cm⁻¹.


3-(3-Fluorophenyl)-1H-isochromen-1-yl)-1-phenylpropan-2-one (3h)

Yield: 131 mg (91%); colorless solid; mp 108–110 °C; Rₜ = 0.55 (n-pentane/EtOAc, 10:1).

IR (ATR): 3912, 3779, 2959, 2646, 2321, 2177, 2062, 1992, 1921, 1714, 1603, 1406, 1361, 1265, 1208, 1110, 1044, 926, 814, 749, 698 cm⁻¹.


3-(4-tert-Butylphenyl)-1H-isochromen-1-yl]pentane-2,4-dione (3h)

Yield: 131 mg (91%); colorless solid; mp 108–110 °C; Rₜ = 0.55 (n-pentane/EtOAc, 10:1).
1H NMR (600 MHz, CDCl3): δ (keto) = 7.51 (d, J = 8.5 Hz, 2 H), 7.39 (d, J = 8.4 Hz, 2 H), 7.29–7.26 (m, 1 H), 7.12 (d, J = 7.7 Hz, 2 H), 7.01 (d, J = 7.5 Hz, 1 H), 6.46 (s, 1 H), 6.13 (s, J = 10.3 Hz, 1 H), 4.63 (d, J = 10.4 Hz, 1 H), 2.39 (s, 3 H), 1.89 (s, 3 H), 1.32 (s, 9 H).

13C NMR (151 MHz, CDCl3): δ (enol mixture) = 201.3 (C=O), 210.0 (C=O), 153.8 (Cq), 152.4 (Cq), 150.8 (Cq), 132.7 (Cq), 131.1 (Cq), 130.6 (Cq), 130.45 (Cq), 128.9 (CH2), 128.4 (CH2), 127.2 (Cq), 126.75 (CH2), 126.6 (CH2), 125.4 (Cq), 125.35 (2C, CH2), 125.1 (Cq), 124.7 (2C, CH2), 124.65 (CH2), 124.3 (CH), 123.9 (CH2), 123.45 (CH2), 109.1 (Cq), 100.1 (CH), 99.95 (CH), 76.5 (CH), 76.2 (CH), 70.7 (CH), 34.7 (Cq), 32.15 (CH3), 31.2 (3C, CH2), 31.2 (3C, CH2), 28.9 (CH2).


1-[-(4-Methyl-phenyl)-1H-isochromen-1-yl]-1-phenylpropan-2-one (3l)

Yield: 64 mg (54%); pale-yellow solid; mp 113 °C; Rf = 0.95 (n-pentane/EtOAc, 1:1); dr = 11:1.

IR (ATR): 3872, 3547, 3327, 3041, 2646, 2301, 2088, 1905, 1746, 1634, 1493, 1245, 1008, 887, 747 cm⁻¹.

1H NMR (600 MHz, CDCl3): δ (major) = 7.50–7.48 (m, 2 H), 7.46–7.43 (m, 2 H), 7.34–7.31 (m, 4 H), 7.28–7.26 (m, 2 H), 7.21–7.16 (m, 1 H), 6.93–6.91 (m, 2 H), 4.74 (d, J = 4.3 Hz, 1 H), 4.38 (d, J = 10.5 Hz, 1 H), 4.17 (s, 1 H), 3.80 (s, 3 H), 2.12 (s, 3 H).

1H NMR (600 MHz, CDCl3): δ (minor) = 7.96–7.93 (m, 1 H), 7.54–7.52 (m, 2 H), 7.39–7.36 (m, 1 H), 7.34–7.31 (m, 1 H), 7.26–7.24 (m, 1 H), 7.21–7.16 (m, 4 H), 7.14–6.95 (m, 2 H), 6.91–6.89 (m, 1 H), 6.3 (d, J = 4.3 Hz, 1 H), 5.29 (d, J = 4.3 Hz, 1 H), 4.29 (s, 1 H), 3.74 (s, 3 H), 2.04 (s, 3 H).

13C NMR (151 MHz, CDCl3): δ (major) = 209.3, 187.3, 160.2, 137.4, 136.4, 136.3, 132.4, 130.9 (2C), 130.6, 129.6 (2C), 129.3, 128.6 (2C), 127.8, 127.6, 124.6, 114.7, 113.8 (2C), 71.9, 55.8, 50.7, 31.0.

13C NMR (151 MHz, CDCl3): δ (minor) = 207.0, 187.3, 160.2, 137.4, 136.7, 136.1, 132.4, 130.8 (2C), 129.9, 129.5 (2C), 129.0, 128.7 (2C), 128.6, 128.2, 124.6, 114.6, 113.8 (2C), 79.0, 74.0, 64.0, 29.7.


1-(6-Chloro-3-phenyl-1H-isochromen-1-yl)-1-phenylpropan-2-one (3m)

Yield: 73 mg (65%); pale-yellow solid; mp 125 °C; Rf = 0.72 (n-pentane/EtOAc, 10:1); dr = 1:1.3.

IR (ATR): 3437, 2954, 2669, 2339, 2096, 1898, 1721, 1601, 1456, 1361, 1247, 1055, 908, 701 cm⁻¹.

1H NMR (600 MHz, CDCl3): δ (major) = 7.70 (t, J = 1.3 Hz, 1 H), 7.46 (m, 2 H), 7.36–7.33 (m, 2 H), 7.30–7.24 (m, 2 H), 7.22–7.16 (m, 2 H), 7.10–7.05 (m, 2 H), 6.77 (dd, J = 8.1, 2.1 Hz, 1 H), 6.68 (s, 1 H), 6.24 (d, J = 8.0 Hz, 1 H), 6.08 (d, J = 10.3 Hz, 1 H), 4.59 (s, 1 H), 2.16 (d, J = 0.8 Hz, 3 H).

1H NMR (600 MHz, CDCl3): δ (minor) = 7.72 (d, J = 1.8 Hz, 1 H), 7.46 (m, 2 H), 7.36–7.33 (m, 2 H), 7.30–7.24 (m, 2 H), 7.22–7.16 (m, 2 H), 7.10–7.05 (m, 2 H), 6.77 (dd, J = 8.1, 2.1 Hz, 1 H), 6.61 (s, 1 H), 6.24 (d, J = 8.0 Hz, 1 H), 6.12 (d, J = 10.1 Hz, 1 H), 4.58 (d, J = 1.2 Hz, 1 H), 2.04 (s, 3 H).

13C NMR (151 MHz, CDCl3): δ (major) = 206.9, 152.0, 136.2, 134.6, 134.2, 133.6, 130.4, 130.1 (2C), 129.7 (2C), 129.0 (2C), 128.9 (2C), 127.5, 126.8, 125.9 (2C), 124.2, 100.6, 78.7, 59.9, 30.8.

13C NMR (151 MHz, CDCl3): δ (minor) = 207.0, 153.1, 134.7, 134.5, 134.2, 133.9, 130.2, 130.2 (2C), 129.6 (2C), 129.0 (2C), 128.6 (2C), 128.3, 126.2, 126.0 (2C), 124.5, 100.6, 77.6, 62.0, 30.8.

HRMS (ESI): m/z [M]+ calcd for C26H26O3Cl: 374.1068; found: 374.1069.

Methyl 2-Oxo-1-(3-phenyl-1H-isochromen-1-yl)cyclopropanecarboxylate (3n)

Yield: 125 mg (90%); colorless solid; mp 128.5–130.5 °C; Rf = 0.5 (n-pentane/EtOAc, 85:15); dr = 1:5.1.
2-Phenyl-2-(3-phenyl-1H-isochromen-1-yl)-cyclohexan-1-one (3n)

Yield: 44 mg (40%); colorless solid; mp 138 °C; Rf = 0.51 (n-pentane/EtOAc, 10:1); dr = 2:7:1.
IR (ATR): 3337, 3164, 3059, 2932, 2868, 2654, 2323, 2227, 2173, 2071, 1985, 1899, 1807, 1701, 1630, 1600, 1490, 1450, 1421, 1374, 1275, 1227, 1182, 1116, 1067, 1028, 971, 919, 854, 806, 763, 694 cm⁻¹.
1H NMR (600 MHz, CDCl₃): δ (major) = 7.68 (m, 1 H), 7.46–7.42 (m, 2 H), 7.33–7.31 (m, 3 H), 7.24–7.20 (m, 2 H), 7.19–7.17 (m, 2 H), 7.08–7.06 (m, 3 H), 6.99 (d, J = 7.6 Hz, 1 H), 6.64 (t, J = 7.6 Hz, 1 H), 6.33 (s, 1 H), 6.23 (s, 1 H), 5.54 (d, J = 7.7 Hz, 1 H), 2.60 (m, 1 H), 2.33 (m, 1 H), 2.30–2.16 (m, 1 H), 1.84 (m, 1 H), 1.67–1.61 (m, 2 H), 1.55 (m, 1 H).
1H NMR (600 MHz, CDCl₃): δ (minor) = 7.70 (m, 1 H), 7.41–7.37 (m, 3 H), 7.30–7.28 (m, 1 H), 7.28–7.25 (m, 3 H), 7.13 (d, J = 8.1, 1.4 Hz, 2 H), 7.10–7.08 (m, 2 H), 7.03 (d, J = 7.4 Hz, 1 H), 6.91 (d, J = 4.6 Hz, 1 H), 6.17 (s, 1 H), 6.13 (s, 1 H), 2.70 (m, 1 H), 2.30–2.16 (m, 2 H), 1.84 (m, 2 H), 1.67–1.61 (m, 2 H), 1.55 (m, 1 H).
13C NMR (151 MHz, CDCl₃): δ (major) = 210.4, 153.1, 136.3, 135.1, 132.9, 129.8, 129.65, 129.5, 129.3 (2C), 129.1, 128.8, 128.6, 127.7, 126.05, 125.6, 124.45, 100.6, 81.3, 79.0, 66.75, 41.0, 30.9, 30.1, 28.1, 27.5, 21.7.
13C NMR (151 MHz, CDCl₃): δ (minor) = 212.1, 153.2, 138.3, 135.1, 132.9, 129.8, 129.5, 129.4 (2C), 129.3, 128.9, 128.1, 127.9, 126.9, 126.4, 125.6, 124.8, 100.5, 82.0, 79.0, 66.75, 41.0, 30.9, 30.1, 28.1, 27.5, 22.0.

2-[6-Fluoro-3-(p-tolyl)-1H-isochromen-1-yl]-2-phenylcyclohexan-1-one (3p)

Yield: 70 mg (59%); colorless solid; mp 158 °C; Rf = 0.43 (n-pentane/EtOAc, 10:1); dr = 2:1.

For crystal growth, a preparative HPLC was used to purify one diastereomer.

Preparative HPLC (RP) [Multispher 120 RP 18 HP (250 × 20 mm); water/Methanol, 1:9; 18 mL/min; λ = 254 nm]: t_R = 20.8 (major), 22.6 (minor) min.
IR (ATR): 3393, 2940, 2322, 2085, 1889, 1702, 1604, 1477, 1321, 1065, 959, 799, 700 cm⁻¹.
1H NMR (600 MHz, CDCl₃): δ = 7.59–7.55 (m, 2 H), 7.34–7.28 (m, 3 H), 7.26 (d, J = 8.0 Hz, 2 H), 7.05–7.02 (m, 2 H), 6.70 (dd, J = 9.7, 2.7 Hz, 1 H), 6.36 (t, J = 8.7 Hz, 1 H), 6.22 (s, 1 H), 6.20 (s, 1 H), 5.55 (dd, J = 8.5, 5.7 Hz, 1 H), 2.63–2.58 (m, 1 H), 2.37 (s, 3 H), 2.34–2.29 (m, 1 H), 2.21–2.16 (m, 2 H), 1.82 (m, 1 H), 1.62 (m, 2 H), 1.59–1.48 (m, 1 H).
13C NMR (151 MHz, CDCl₃): δ (major) = 210.5, 164.2, 162.6, 154.4, 140.5, 136.1, 135.6, 132.0, 130.3 (2C), 129.7 (2C), 129.6, 129.6, 129.3 (2C), 128.7, 125.9 (2C), 122.2, 112.1, 106.1, 99.2, 66.8, 41.0, 28.4, 27.7, 21.8.
13C NMR (151 MHz, CDCl₃): δ (minor) = 210.5, 164.2, 162.6, 154.4, 140.5, 136.1, 135.6, 132.0, 130.3 (2C), 129.7 (2C), 129.6, 129.6, 129.3 (2C), 128.7, 125.9 (2C), 122.2, 112.1, 106.1, 99.2, 66.8, 41.0, 28.4, 27.7, 21.8.

2-Acetyl-2-(6-fluoro-3-p-tolyl-1H-isochromen-1-yl)cyclopentan-1-one (3q)

Yield: 107 mg (74%); colorless solid; mp 75–77 °C; Rf = 0.6 (n-pentane/EtOAc, 85:15); dr = 1:4.1.
IR (ATR): 3432, 2959, 2314, 2088, 1901, 1711, 1610, 1487, 1209, 1131, 1061, 974, 802, 731 cm⁻¹.
1H NMR (600 MHz, CDCl₃): δ (major) = 7.37 (d, J = 8.2 Hz, 2 H), 7.17 (d, J = 8.0 Hz, 2 H), 6.92–6.87 (m, 1 H), 6.84–6.76 (m, 2 H), 6.50 (s, 1 H), 6.15 (s, 1 H), 2.71 (dd, J = 12.7, 3.1 Hz, 1 H), 2.58 (s, 3 H), 2.36 (s, 3 H), 2.19 (dt, J = 8.0, 4.9 Hz, 1 H), 1.72 (ddd, J = 33.3, 20.4, 11.3 Hz, 2 H), 1.60 (tt, J = 11.2, 5.5 Hz, 2 H).
Yield: 129 mg (82%); colorless solid; mp 68–70 °C; tanecarboxylate (3r)
IR (ATR): 3380, 2954, 2742, 2329, 2095, 1902, 1698, 1591, 1469, 1254,

Ethyl 1-(6-Fluoro-3-tolyl-1H-isochromen-1-yl)-2-oxocyclo-

Methyl 1-(3-Fluorophenyl)-1H-isochromen-1-yl)-2-oxocyclo-

Yield: 137 mg (91%); colorless solid; mp 114–116 °C; Rf = 0.45 (n-pen-
tane/EtOAc, 85:15); dr = 1.25:1.
1H NMR (600 MHz, CDCl₃): δ (major) = 7.5 (d, J = 7.4 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 2 H), 7.2 (t, J = 7.1 Hz, 1 H), 7.05 (d, J = 3.7 Hz, 1 H), 6.80 (t, J = 8.2 Hz, 1 H), 6.53 (d, J = 2.5 Hz, 1 H), 6.35 (s, 1 H), 6.26 (s, 1 H), 3.88 (s, 3 H), 3.76 (s, 3 H), 2.80–2.74 (m, 1 H), 2.53–2.48 (m, 1 H), 2.44–2.35 (m, 1 H), 2.06–1.96 (m, 1 H), 1.84–1.78 (m, 1 H), 1.65 (t, J = 4.9 Hz, 1 H).

1H NMR (600 MHz, CDCl₃): δ (minor) = 7.52 (d, J = 7.4 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 2 H), 7.30 (t, J = 7.1 Hz, 1 H), 7.05 (d, J = 3.7 Hz, 1 H), 6.80 (t, J = 8.2 Hz, 1 H), 6.45 (d, J = 2.4 Hz, 1 H), 6.38 (s, 1 H), 6.12 (s, 1 H), 3.80 (s, 3 H), 3.76 (s, 3 H), 2.68 (dd, J = 13.4, 6.2 Hz, 1 H), 2.48–2.44 (m, 1 H), 2.26 (dd, J = 18.6, 7.7 Hz, 1 H), 2.06–1.96 (m, 1 H), 1.89–1.84 (m, 1 H), 1.77–1.69 (m, 1 H).

13C NMR (151 MHz, CDCl₃): δ (major) = 211.8 (C=O), 166.5 (C=O), 158.8 (Cq), 149.7 (Cq), 133.7 (Cq), 128.5 (CH₂), 128.4 (CH₂, 2C), 127.7 (Cq), 125.6 (CH₂), 125.5 (Cq), 124.5 (CH₂, 2C), 114.75 (CH₂), 110.4 (CH₃), 99.5 (CH), 80.0 (CH₂), 70.3 (Cq), 55.4 (CH₃), 53.1 (CH₃), 38.5 (CH₂), 27.1 (CH₂), 20.1 (CH₃).

13C NMR (151 MHz, CDCl₃): δ (minor) = 211.75 (C=O), 167.1 (C=O), 158.7 (Cq), 151.1 (Cq), 134.0 (Cq), 129.4 (CH₂), 128.6 (CH₂, 2C), 125.4 (CH₂), 124.7 (CH₂, 2C), 124.7 (Cq), 131.0 (CH₂), 111.2 (CH₂), 100.6 (CH), 79.6 (CH), 65.1 (Cq), 55.3 (CH₃), 53.1 (CH₃), 39.4 (CH₂), 283.2 (CH₃), 19.9 (CH₃).


2-(3-{4-[tert-Butyl]-3-isochromen-1-yl)-2-phenylcyclohexane-1-one (3v)

Yield: 71 mg (54 %); colorless solid; mp 141.0 °C; Rf = 0.77 (pentane/EtOAc, 15:1); dr = 2.2:1.

IR (ATR): 3382, 3456, 3021, 2870, 2653, 2320, 2182, 2086, 1913, 1792, 1632, 1595, 1449, 1366, 1268, 1216, 1115, 1065, 925, 789, 745, 694 cm⁻¹.

1H NMR (600 MHz, CDCl₃): δ (major) = 7.63–7.59 (m, 2 H), 7.50–7.46 (m, 2 H), 7.34–7.29 (m, 2 H), 7.27–7.24 (m, 2 H), 7.09–7.02 (m, 3 H), 6.62 (tt, J = 7.5, 0.9 Hz, 1 H), 6.29 (s, 1 H), 6.22 (s, 1 H), 5.52 (J = 7.7, 1.0 Hz), 2.59 (dq, J = 14.7, 3.2 Hz, 1 H), 2.33 (dd, J = 14.2, 3.3 Hz, 1 H), 2.30–2.15 (m, 2 H), 1.84 (m, 1 H), 1.64 (m, 2 H), 1.55 (m, 1 H), 1.33 (d, J = 0.7 Hz, 9 H, CH₃).

1H NMR (600 MHz, CDCl₃): δ (minor) = 7.34–7.29 (m, 9 H), 7.22–7.15 (m, 5 H), 7.09–7.02 (m, 3 H), 6.97 (d, J = 7.6 Hz, 1 H), 6.16 (s, 1 H), 6.09 (s, 1 H), 2.72 (dq, J = 14.7, 3.2 Hz, 1 H), 2.30–2.15 (m, 2 H), 2.21 (m, 2 H), 1.84 (m, 1 H), 1.64 (m, 2 H), 1.55 (m, 1 H), 1.28 (d, J = 0.7 Hz, 9 H, CH₃).

2-[3-([4-(tert-Butyl)phenyl]-1H-isochromen-1-yl]-2-phenylcyclopentanecarboxylate (3w)

Yield: 146 mg (90%); colorless solid; mp 89–91 °C; Rf = 0.65 (n-pentane/EtOAc, 85:15); dr = 1.1:1.
2-Phenyl-2-[3-(401.1357.]
(CHOAr, 2C), 99.5 (CH), 80.2 (CH), 64.6 (Cq), 55.3 (CH3), 53.1 (CH3), 39.4 (CH3), 27.1 (CH2), 20.0 (CH2).

IR (ATR): 3620, 2942, 2312, 2095, 1735, 1599, 1461, 1157, 758 cm
-1 H NMR (600 MHz, CDCl3): J (major) = 7.92 (d, J = 9.0 Hz, 2 H), 7.25–7.22 (m, 1 H), 7.09–7.06 (m, 2 H), 6.93 (d, J = 7.5 Hz, 1 H), 6.88 (d, J = 2.2 Hz, 2 H), 6.40 (s, 1 H), 6.17 (s, 1 H), 3.89 (s, 3 H), 3.82 (s, 3 H), 2.71–2.65 (m, 1 H), 2.45–2.36 (m, 1 H), 2.27–2.21 (m, 1 H), 1.91–1.85 (m, 1 H), 1.79–1.68 (m, 2 H).

1H NMR (600 MHz, CDCl3): δ (minor) = 7.48 (d, J = 9.0 Hz, 2 H), 7.25–7.22 (m, 1 H), 7.13–7.09 (m, 2 H), 6.90 (d, J = 2.2 Hz, 2 H), 6.83 (d, J = 7.6 Hz, 1 H), 6.27 (s, 1 H), 6.08 (s, 1 H), 3.82 (s, 3 H), 3.79 (s, 3 H), 2.83–2.77 (m, 1 H), 2.55–2.45 (m, 2 H), 2.01 (dd, J = 10.4, 6.6 Hz, 1 H), 1.67–1.59 (m, 2 H).

13C NMR (151 MHz, CDCl3): δ (major) = 211.7 (C=O), 168.7 (C=O), 160.3 (Cq), 151.7 (Cq), 132.1 (Cq), 128.9 (CHAr), 127.55 (Cq), 126.5 (CHAr), 126.35 (CHAr, 2C), 125.85 (Cq), 125.8 (CHAr), 124.0 (CHAr), 113.7 (CHAr), 98.3 (CH), 79.6 (CH), 70.4 (Cq), 55.3 (CH3), 53.15 (CH), 38.5 (CH3), 27.1 (CH2), 20.0 (CH2).

13C NMR (151 MHz, CDCl3): δ (minor) = 212.0 (C=O), 167.3 (C=O), 160.4 (Cq), 153.2 (Cq), 133.15 (Cq), 128.35 (CHAr), 126.7 (CHAr, 2C), 126.5 (Cq), 126.2 (CHAr), 126.2 (CHAr, 2C), 123.9 (CHAr), 123.4 (CHAr), 113.9 (CHAr, 2C), 99.5 (CH), 80.2 (CH), 64.6 (Cq), 55.3 (CH3), 53.1 (CH), 39.4 (CH3), 28.4 (CH2), 20.2 (CH2).


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Supporting Information

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References

(14) CCDC 1474771 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/getstructures.