Supporting Information for

Copper-catalyzed asymmetric 1,2-addition of Grignard reagents to 3-acyl 2H-chromenes

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Experimental Section

General experimental

All reactions were performed under nitrogen atmosphere, using dried glassware and dry solvents. t-BuOMe and THF were taken from an MBraun solvent purification system (SPS-800). All other reagents were purchased from Sigma-Aldrich, Acros Organics and Combi-Blocks and were used without further purification. Racemic products, required to establish a separation method on chiral HPLC, were synthesized by reacting the substrates with the corresponding Grignard reagent in t-BuOMe at −10 °C. 1H-NMR and 13C-NMR were recorded on a Varian AMX400 (400 and 100.6 MHz, respectively) using CDCl3 as the solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl3: δ 7.26 for 1H, δ 77.0 for 13C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration.

Melting points were measured with a Buchi melting point B-545. High-resolution mass spectra (HRMS) were recorded on a FTMS orbitrap (Thermo Fisher Scientific) mass spectrometer. Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g / 100 mL). Enantiomeric excesses were determined by Shimadzu LC-20AD with columns Chiralpack OD-H and Chiracel AD-H.

Flash chromatography: Merck silica gel type 9385 230-400 mesh. TLC: Merck silica gel 60, 0.25 mm. Compounds were visualized by UV, Seebach’s reagent (phosphomolybdic acid, 25 g; cerium sulfate, 7.5 g; H2O, 500 mL; H2SO4, 25 mL) and p-anisaldehyde staining (15 mL of AcOH and 3.5 mL of p-anisaldehyde in 350 mL EtOH). Prepared Grignard reagents were titrated according to literature procedures (Lin, H. S.; Paquette, L. A.; Synth. Commun., 1994, 24, 2503.) Compounds 2, 6 and 1 were prepared according to literature procedures and their spectral data are consistent with the literature.15,16

General procedure for the synthesis of the substrates:

1-(2H-chromen-3-yl)propan-1-one (8):
To a round-bottom flask charged with a magnetic stirrer was added salicylaldehyde (7.3 mmol, 1.27 g), dissolved in 40 mL of 1,4-dioxane. K2CO3 (8.8 mmol, 1.22 g) was then added to the solution. Ethyl vinyl ketone (14.7 mmol, 1.24 g) was added and the mixture was left to reflux for 24 h, followed by the addition of 1.5 eq of ethyl vinyl ketone and reflux for another 24 h. The reaction was allowed to cool down to rt and then 1,4-dioxane was removed at reduced pressure. Water and EtOAc were added to the flask, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over MgSO4, filtered, and concentrated at reduced pressure to afford 8 in 36% yield as a yellow oil after flash chromatography (SiO2, n-pentane : EtOAc (95:5)).

1H NMR (400 MHz, CDCl3) δ 7.28 – 7.22 (m, 1H), 7.15 (dd, J = 7.5, 1.6 Hz, 1H), 6.93 (td, J = 7.5, 1.2 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 5.01 (s, 2H), 2.78 (q, J = 7.4 Hz, 2H), 1.17 (t, J = 7.3 Hz, 3H). 13C NMR (101 MHz, CDCl3) δ 198.8, 155.5, 132.7, 132.3, 130.2, 129.1, 121.7, 120.8, 116.3, 64.4, 30.2, 8.4. HRMS (ESI+, m/z): calcd. for [C12H12O2+ H+]+ = 189.091 found: 189.090.

1-(2H-chromen-3-yl)ethanone (9):
The product was obtained as a yellow solid in 60% yield after column chromatography (SiO2, n-pentane: EtOAc (92 : 8)).

1H NMR (400 MHz, CDCl3) δ 7.31 (s, 1H), 7.29 – 7.23 (m, 1H), 7.17 (dd, J = 7.5, 1.6 Hz, 1H), 6.94 (td, J = 7.5, 0.8 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 5.01 (d, J = 1.2 Hz, 2H), 2.41 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 195.9, 155.6, 133.9, 132.4, 130.8, 129.1, 121.8, 120.7, 116.3, 64.2, 25.0. mp= 47 °C (reported 48-50 °C).17 HRMS (ESI+, m/z): calcd. for [C13H10O2 + H]+ = 175.075; found: 175.075. The spectral data correspond to those reported in literature.17

1-(6-methyl-2H-chromen-3-yl)ethanone (10):
The product was obtained as a yellow solid in 27% yield after column chromatography (SiO2, n-pentane: EtOAc (90:10)).
**1-(6-chloro-2H-chromen-3-yl)ethanone (11):**
The product was obtained as a yellow solid in 45% yield after column chromatography (SiO₂, n-pentane: EtOAc (90:10)).

1H NMR (400 MHz, CDCl₃) δ 7.24 – 7.16 (m, 2H), 7.14 (d, J = 2.5 Hz, 1H), 6.80 (dd, J = 8.6 Hz, 1H), 5.00 (d, J = 1.3 Hz, 2H), 2.41 (s, 3H).

13C NMR (101 MHz, CDCl₃) δ 195.9, 153.4, 134.1, 132.7, 132.6, 129.0, 121.4, 120.2, 117.2, 70.2, 25.1, 19.6.

HRMS (ESI+, m/z): calcd. for [C₁₁H₁₀O₂ + H]^+ = 189.091; found: 189.090.

1-(6-fluoro-2H-chromen-3-yl)ethanone (12):
The product was obtained as a yellow solid in 62% yield after column chromatography (SiO₂, n-pentane: EtOAc (90:10)).

1H NMR (400 MHz, Chloroform-d) δ 7.23 (s, 1H), 6.96 (td, J = 8.6, 3.0 Hz, 1H), 6.89 (dd, J = 8.0, 3.0 Hz, 1H), 6.81 (dd, J = 8.9, 4.5 Hz, 1H), 4.98 (d, J = 1.2 Hz, 1H), 2.41 (s, 3H).

13C NMR (101 MHz, CDCl₃) δ 195.7, 156.2, 152.1, 151.5, 132.8, 132.8, 132.0, 121.6, 121.6, 118.8, 118.5, 117.4, 117.3, 114.8, 114.6, 64.3, 25.1. mp = 54 °C. HRMS (ESI+, m/z): calcd. for [C₁₁H₁₀FO₂ + H]^+ = 193.065; found: 193.065.

**General procedure for the enantioselective 1,2-addition:**

1-(2-(2H-chromen-3-yl)-4-methylpentan-2-ol (14):

To a flame dried Schlenk tube, containing a magnetic stirring bar, CuBr·SMₑ₂ (15 μmol, 3.1 mg), (L1) (18 μmol, 10.7 mg) and 3 mL of dry r-BuOMe were added. The mixture was left to stir for 10 min. Subsequently, 9 (0.3 mmol, 52 mg) was added to the solution. The mixture was left to stir for 30 min at −78 °C. Isobutylmagnesium bromide (2 M in Et₂O, 1.7 eq, 0.25 mL) was then added dropwise over 15 min and the reaction was left to stir for 3 to 4 h at −78 °C. The reaction was quenched with water (2 mL), allowed to warm up to rt and diluted with Et₂O. NH₄Claq was added and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic layers were dried over MgSO₄, filtered, and concentrated at reduced pressure to afford 14 in 70% yield as a yellowish oil after flash chromatography (SiO₂, n-pentane : Et₂O (90:10)). ee = 80% Retention times on chiral HPLC: 28.2 min and 31.8 min.
The product was obtained as a yellowish oil in 91% yield after column chromatography (SiO₂, n-pentane: Et₂O (90:10)). ee = 80%. Retention times on chiral HPLC: 23.8 min and 27.1 min.

The product was obtained as a yellowish oil in 97% yield after column chromatography (SiO₂, n-pentane: Et₂O (90:10)). ee = 84%. Retention times on chiral HPLC: 48.3 min and 50.6 min.

The product was obtained as a yellowish oil in 70% yield after column chromatography (SiO₂, n-pentane: EtOAc (96:4)). ee = 80%. Retention times on chiral HPLC: 13.2 min and 14.4 min.
m/z): calcd. for \([C_{16}H_{22}O_2 + H]^+ = 247.169;\] found: 247.169.

4-methyl-2-(2-methyl-2H-chromen-3-yl)pentan-2-ol (22):
The product was obtained as a mixture of diastereomers as a yellowish oil in 62% yield after column chromatography (SiO₂, n-pentane: EtOAc (96:4)). \(de = 68\%\ er = 70\%\) (of the major diastereomer) \(er = 74\%\) (of the minor diastereomer). Retention times on chiral HPLC: 15.5 min and 17.6 min (of the major diastereomer) 14.4 min and 15.9 min (of the minor diastereomer).

(7:3 mixture of diastereomers) \(^1H\) NMR (400 MHz, CDCl₃) δ 7.12 (td, \(J = 7.7, 1.6\) Hz, 2H), 7.08 – 7.00 (m, 2H), 6.92 – 6.77 (m, 3H), 6.45 (s, 1H), 6.29 (s, 1H), 5.06 (q, \(J = 6.4\) Hz, 1H), 4.91 (q, \(J = 6.4\) Hz, 1H), 1.90 – 1.64 (m, 2H), 1.61 (dd, \(J = 9.8, 5.7\) Hz, 2H), 1.58 – 1.53 (m, 1H), 1.50 (s, 3H), 1.40 – 1.33 (m, 7H), 1.00 – 0.93 (m, 10H). \(^13C\) NMR (101 MHz, CDCl₃) δ 151.3, 151.1, 144.3, 144.1, 128.8, 128.7, 126.6, 126.6, 122.9, 122.7, 121.1, 121.0, 117.2, 116.8, 116.5, 116.5, 74.9, 74.5, 70.9, 70.8, 51.1, 49.9, 29.8, 28.4, 24.6, 24.6, 24.6, 24.4, 24.3, 20.5, 20.0. HRMS (ESI+, m/z): calcd. for \([C_{16}H_{22}O_2 + Na]^+ = 269.151;\) found: 269.151.

2-(6-fluoro-2H-chromen-3-yl)-3-methylbutan-2-ol (23):
The product was obtained as a yellowish oil in 70% yield after column chromatography (SiO₂, n-pentane: EtOAc (96:4)). \(ee = 18\%). Retention times on chiral HPLC: 27.1 min and 29.8 min.

\(^1H\) NMR (400 MHz, CDCl₃) δ 6.82 – 6.69 (m, 3H), 6.36 (d, \(J = 1.5\) Hz, 1H), 4.70 (dd, \(J = 4.3, 1.3\) Hz, 2H), 1.90 – 1.71 (m, 1H), 1.36 (s, 2H), 0.96 – 0.92 (m, 7H). \(^13C\) NMR (101 MHz, CDCl₃) δ 158.8, 156.4, 149.1, 141.7, 130.9, 124.1, 124.0, 117.7, 117.7, 116.1, 116.1, 114.7, 114.5, 112.9, 112.7, 76.1, 65.7, 34.7, 29.7, 23.6, 17.0, 16.9. \([\alpha]_D^{20} = -1.6\) (c = 0.15, CHCl₃). HRMS (ESI+, m/z): calcd. for \([C_{16}H_{18}O_2 - H]^+ = 235.113;\) found: 235.113.

2-(2H-chromen-3-yl)-1-cyclohexylpropan-2-ol (19):
The product was obtained as a yellowish oil in 78% yield after column chromatography (SiO₂, n-pentane: EtOAc (96:4)). \(ee = 58\%\) Retention times on chiral HPLC: 40.5 min and 43.2 min.

\(^1H\) NMR (400 MHz, CDCl₃) δ 7.11 (td, \(J = 7.7, 1.6\) Hz, 1H), 7.03 (dd, \(J = 7.5, 1.6\) Hz, 1H), 6.89 (td, \(J = 7.5, 1.2\) Hz, 1H), 6.82 (d, \(J = 8.0\) Hz, 1H), 6.44 (s, 1H), 4.73 (d, \(J = 1.3\) Hz, 2H), 1.86 – 1.69 (m, 2H), 1.70 – 1.49 (m, 6H), 1.39 (s, 3H), 1.30 – 1.07 (m, 4H), 1.06 – 0.83 (m, 2H). \(^13C\) NMR (101 MHz, CDCl₃) δ 158.8, 156.4, 149.1, 141.7, 130.9, 124.1, 124.0, 117.7, 117.7, 116.1, 116.1, 114.7, 114.5, 112.9, 112.7, 76.1, 65.7, 34.7, 29.7, 23.6, 17.0, 16.9. \([\alpha]_D^{20} = -1.6\) (c = 0.15, CHCl₃). HRMS (ESI+, m/z): calcd. for \([C_{16}H_{20}O_2 - H]^+ = 273.185;\) found: 273.184.
1-(2-methyl-2H-chromen-3-yl)ethan-1-one (X):
1-(2H-chromen-3-yl)ethan-1-one (X):
1-(2H-chromen-3-yl)propan-1-one (X):
1-(6-methyl-2H-chromen-3-yl)ethan-1-one (X):
1-(6-chloro-2H-chromen-3-yl)ethan-1-one (X):
1-(6-fluoro-2H-chromen-3-yl)ethan-1-one (X):
(S)-2-(2H-chromen-3-yl)-4-methylpentan-2-ol (X):
Analysis Report

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- Method Filename: C5_90_2_40 min.icm
- Batch Filename: 0
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Analysis Report

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Chromatogram

[Graph of chromatogram with peaks at 37.811 and 39.722 minutes]

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![Chromatogram Graph]

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30-9-2015 16:13:59 Page 1 / 1
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Sample Type: Unknown
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Processed by: System Administrator

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PDA Ch1 254nm

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PDA Multi 1 254nm,4nm
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Sample Name: BCG153 rac
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Data Filename: BCG153_99_160min.lcd
Method Filename: C299_1f05_80min.lcm
Batch Filename: 20140627.lcb
Vial #: 1-4
Injection Volume: 4 µL
Date Acquired: 1-8-2014 17:49:59
Date Processed: 1-8-2014 18:50:04

Sample Type: Unknown
Acquired by: System Administrator
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PDA Ch1 254nm
(2S)-4-methyl-2-(2-methyl-2H-chromen-3-yl)pentan-2-ol (X):
Analysis Report

<Sample Information>
Sample Name: 
Sample ID: 
Data Filename: BCG160 rac.lcd
Method Filename: C2 98_2 fi0,5 40 min.lcm
Batch Filename: 20140627.lcb
Vial #: 1-7
Injection Volume: 5 uL
Date Acquired: 13-8-2014 12:03:38
Date Processed: 13-8-2014 13:03:41
Sample Type: Unknown
Level: 1
Acquired by: System Administrator
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PDA Ch1 254nm

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Analysis Report

Sample Information:
- Sample Name: 
- Sample ID: 
- Data Filename: BCG160.lcd
- Method Filename: C298_2fi0.540 min.lcm
- Batch Filename: 20140627.lcb
- Vial #: 1-8
- Injection Volume: 5 uL
- Date Acquired: 13-8-2014 13:34:18
- Date Processed: 13-8-2014 14:19:55
- Sample Type: Unknown
- Level: 1
- Acquired by: System Administrator
- Processed by: System Administrator

Chromatogram:

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PDA Ch1 254nm
(S)-3-(2H-chromen-3-yl)-5-methylhexan-3-ol (X):
Analysis Report

Sample Information:
- Sample Name: Herbertendiol ACA
- Sample ID: Herbertendiol ACA
- Data Filename: BCG167_97.5_2.5,lcd
- Method Filename: C2 97.5 2.5 f10,5 30 min,lcm
- Batch Filename: 20140824,lcb
- Vial #: 1-7
- Injection Volume: 5 uL
- Date Acquired: 29-8-2014 16:15:49
- Date Processed: 29-8-2014 16:45:53
- Sample Type: Unknown
- Level: 1
- Acquired by: System Administrator
- Processed by: System Administrator

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(S)-2-(2H-chromen-3-yl)-1-cyclohexylpropan-2-ol
Analysis Report

<Sample Information>
Sample Name: BCG 134  
Sample ID: BCG 134  
Data Filename: BCG134_60min.lcm  
Method Filename: C5 98.2 fl 0.5 60 min.lcm  
Batch Filename: 20140823.lcb  
Vial #: 1-2  
Injection Volume: 3 uL  
Date Acquired: 23-6-2014 10:02:02  
Date Processed: 23-6-2014 11:02:07  
Sample Type: Unknown  
Acquired by: System Administrator  
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<PD Ch: 254nm>

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Analysis Report

Sample Information

Sample Name: BCG309
Sample ID: BCG309
Data Filename: BCG309.lcd
Method Filename: C5 98-2 fl 0.5 60 min.lcm
Batch Filename: Bea_12-10-2015.lcb
Vial #: 1-1
Injection Volume: 10 μL
Date Acquired: 12-10-2015 17:30:29
Date Processed: 12-10-2015 18:30:31
Sample Type: Unknown
Level: 3
Acquired by: System Administrator
Processed by: System Administrator

<Peak Table>
PDA Ch1 254nm

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(-2-(6-fluoro-2H-chromen-3-yl)-3-methylbutan-2-ol
Analysis Report

Sample Information:
- Sample Name: BCG 171 rac
- Sample ID: BCG 171 rac
- Data Filename: BCG171 rac.lcd
- Method Filename: C2 98_2 fl0,5 40 min.lcm
- Batch Filename: 20140916.lcb
- Vial #: 148
- Injection Volume: 5 μL
- Date Acquired: 24-9-2014 17:48:24
- Date Processed: 24-9-2014 10:40:28
- Sample Type: Unknown
- Level: 1
- Acquired by: System Administrator
- Processed by: System Administrator

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Analysis Report

Sample Information:
- Sample Name: BCG 171 enantio
- Sample ID: BCG 171 enantio
- Data Filename: BCG171 enantio.ldc
- Method Filename: C2 98_2 f0.5 40 min.1cm
- Batch Filename: 20140916.lcb
- Vial #: 1-49
- Injection Volume: 5 µL
- Date Acquired: 24-9-2014 19:10:07
- Date Processed: 24-9-2014 20:19:11
- Sample Type: Unknown
- Level: 1
- Acquired by: System Administrator
- Processed by: System Administrator

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