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

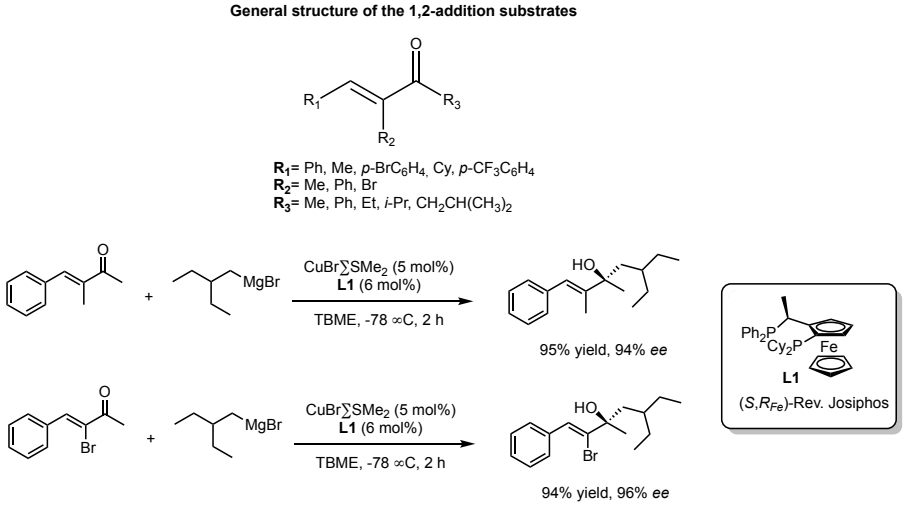
Introduction

Complementary to the well-known asymmetric copper-catalyzed conjugate addition (1,4-addition) of Grignard reagents[1] we reported in 2011 on a copper-diphosphine catalyst that performs enantioselective 1,2-addition reactions of Grignard reagents to enones.[2,3,4] The alkylcopper species apparently outcompetes the Grignard reagent in the addition to the carbonyl group, and for several types of enones the yields and *ee´*s obtained are very high.[5] Until then, just a few examples of enantioselective 1,2-addition reactions employing Grignard reagents had been described. Seebach had reported on the use of stoichiometric Taddol ligand combined with alkyl Grignard reagents and organolithium reagents for the enantioselective 1,2-addition to ketones.[6] A catalytic enantioselective 1,2-addition of Grignard reagents to ketones had been reported in 2006 by Hatano *et al..*[7] In this system, the addition of catalytic $ZnCl_2$ to the alkyl Grignard reagents is required. More recent examples, also using aryl Grignard reagents, were reported by the groups of Yus[8] and Gilheany.[9]

It turned out that the substrate scope of the alkyl Grignard reagent/copper-diphosphine catalyst system could be considerably expanded with arylalkyl ketones,[10] aryl heteroaryl ketones,[11] acylsilanes,[12] silyl ketimines,[13] alkenyl- substituted aromatic N-heterocycles,[14] and ketimines.[15] In addition, the method was applied in natural product synthesis.[16]

(B. C. Calvo and A.J. Minnaard; **2017**, *Synlett.*; 28 (19), p. 2624)

The originally used enone substrates, however, had a rather fixed substitution pattern with a methyl, phenyl or bromide substituent at the α-position of the double bond (Scheme 1). In order to get more insight into the substrate requirements for this reaction, and to expand the substrate scope, we desired to vary the substituent at the α-position and study the effect on the selectivity and the enantioselectivity of the copper-catalyzed Grignard addition reaction.



Scheme 1: Substrates previously used in the enantioselective Cu-catalyzed 1,2-addition of Grignard reagents.

Results and discussion

A hydroxy-methylene unit at the α-position, as in 1 (Figure 1), was chosen as a suitable expansion of the substrate scope.

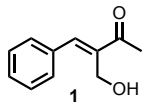
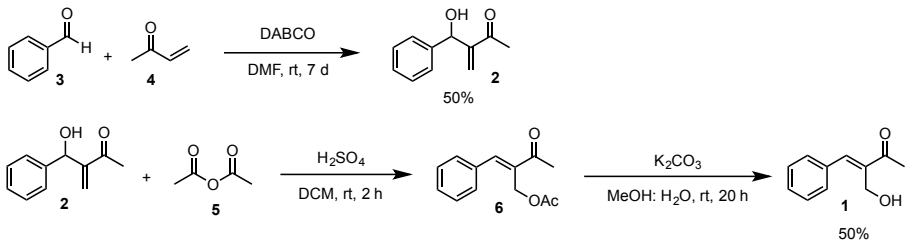


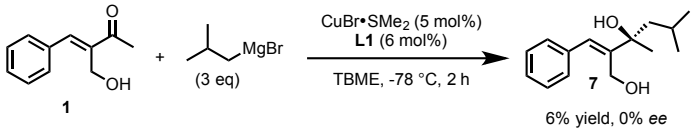
Figure 1: Target substrate for the 1,2-addition reaction.

The synthesis of 1 proceeded according to literature (Scheme 2).[17] Baylis-Hillman reaction of benzaldehyde and methyl vinyl ketone afforded 2, although due to concomitant polymerization of the methyl vinyl ketone the yield was with 50% just moderate. As the starting materials are low cost, this was compensated for by performing the reaction at a large scale. Subsequent acetylation, rearrangement, and acetate hydrolysis,[18] gave 1 in 50% yield over two steps.



Scheme 2: Synthesis of enone (1).

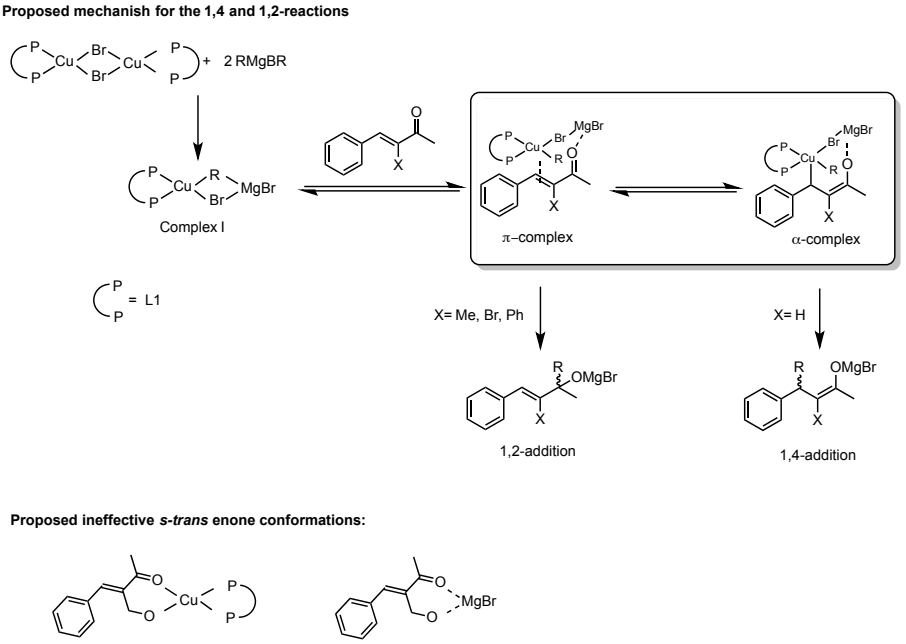
With 1 in hands, the 1,2-addition reaction was studied at low temperature employing isobutylmagnesium bromide, one of the Grignard reagents that gave the highest ee´s in this reaction with the previous substrates employed. Tertiary alcohol 7 was obtained in a very low yield, however, and turned out to be racemic (Scheme 3). Mainly unreacted starting material was observed, even with an excess of Grignard reagent.



Scheme 3: Cu-catalyzed 1,2-addition of isobutylmagnesium bromide to enone (1).

From previous studies we know that enolisation of the substrate takes over if the addition reaction is slow. We speculate that the lack of reactivity is due to coordination of the magnesium alkoxide, formed upon deprotonation by the Grignard reagent, to the ketone. This coordination results in a change of conformation of the enone from the (preferred) *s-cis* conformation to the *s-trans* conformation (Scheme 4), the last one being apparently ineffective in the reaction. Alternatively, the copper-catalyst is inhibited by bidentate coordination to this alkoxy ketone. As depicted in Scheme 4, the reaction mechanism for the 1,2 and 1,4-addition reactions probably both run via Cu-Grignard complex I. It forms a π-complex with the double bond of the *s-cis* enone and, upon alkyl transfer, the 1,2-addition product is formed.

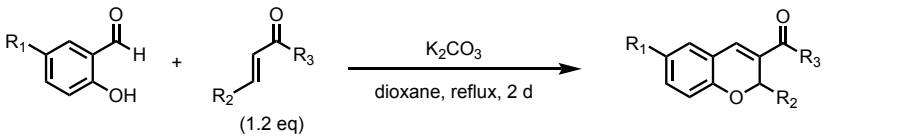
The reaction was subsequently studied using the TBDMS-protected derivative of 1, but the result was the same; a low yield and absence of enantioselectivity. We assume, that as long as the oxygen can participate in bidentate coordination of either the magnesium or the copper, this will prohibit (enantioselective) addition.



Scheme 4: The proposed mechanism for the 1,2 and 1,4-addition reaction.

To challenge this hypothesis, it was decided to "lock" the oxygen in a cyclic ether, so that the *s-trans* conformation could no longer be stabilized by coordination of the alkoxy group and the ketone to the copper/magnesium. The 3-acyl substituted 2*H*-chromenes 8 to 13 were synthesized by reacting a series of substituted salicyl aldehydes with methyl vinyl ketone under basic conditions (Scheme 5).[19] The deprotonated hydroxyl group of the salicyl aldehyde adds in a Michael-type addition reaction to the enone. Subsequent aldol condensation gives the corresponding 2*H*-chromenes.

These substrates are interesting as the 2*H*-chromene core is pharmacologically important and is found in natural products.[20,21,22] Nevertheless, except for 9, the synthesis of which gave in our hands a somewhat lower yield than reported, the other compounds had not been described before. 3-Acyl substituted 2*H*-chromenes have not been used in 1,4- or 1,2-addition reactions.



8; R_1= H, R_2= H, R_3= Et, 36%

9; R_1= H, R_2= H, R_3= Me, 60%

10; R_1= Me, R_2= H, R_3= Me, 27%

11; R_1= Cl, R_2= H, R_3= Me, 45%

12; R_1= F, R_2= H, R_3= Me, 62%

13; R_1=H, R_2= Me, R_3= Me, 33%

Scheme 5: Synthesis of the desired substrates for the asymmetric 1,2 addition reaction.

The copper-catalyzed asymmetric 1,2-addition to 9 was carried out employing isobutylmagnesium bromide. Product 14 was obtained in good yield and a high *ee* of 80% (entry 1, Table 1). This result supports our hypothesis that preventing the alkoxide or ether from coordinating to the catalyst or magnesium, leads to (a larger amount of) the *cis* enone and in turn to an enantioselective addition reaction. The yields and the enantioselectivities are slightly lower compared to the previous studied substrates, the α-bromo and α-methyl substituted enones. With the same substrate we performed the reaction with the linear Grignard

reagent ethylmagnesium bromide and product 15 was obtained in a lower yield and a considerably lower *ee*, in line with our previous reports.[4]

Subsequently, we decided to study the effect of substituents on the aromatic ring of the substrate on the yield and enantioselectivity of the addition reaction. Substrates 10, 11 and 12 were reacted with isobutylmagnesium bromide, and in all cases the products were obtained in good yields and high *ee´*s. Varying the substituent on the ring apparently does not have a large influence on the *ee*, a similar trend as observed for asymmetric 1,2-addition reactions to methyl arylketones.[10]

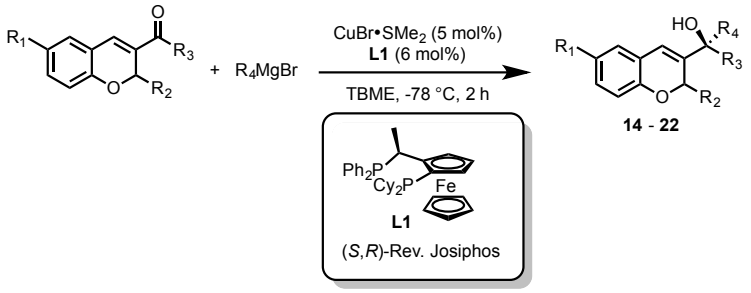
Subsequently, we used different branched Grignard reagents in combination with 9. Cyclohexylmethylmagnesium bromide was employed, giving the expected product with a lower *ee* compared to isobutylmagnesium bromide. When isopropylmagnesium bromide was used, the product was obtained with very low *ee* (entry 7, table 1). Isopropylmagnesium bromide is an α-branched Grignard reagent, that consistently gives low enantioselectivities in asymmetric 1,2-addition reactions.[5] Apparently the highest *ee´*s are obtained with β-branched Grignard reagents.

Next, the steric effect of a larger substituent on the carbonyl function was studied. The combination of 8, in which the 2*H*-chromene has a propionyl instead of an acyl substituent, with isobutylmagnesium bromide afforded the product with the same yield and *ee* as for 9. Increasing the sterics at that position apparently does not affect the *ee*. Finally, steric effects at the 2-position were studied. When the reaction was performed with rac-13, the product was obtained with a de of 68%

and an *ee* of 70%. Apparently, a substituent at the 3-position does have an effect on the asymmetric 1,2-addition and leads to some extend to a kinetic resolution.

Unfortunately, the absolute configuration of the products could not be determined despite attempts to obtain crystals suitable for X-ray diffraction or chemical correlation to a compound of known configuration. The absolute configuration is therefore conferred from that of the substrates studied previously (Scheme 1).

Table 1: 1,2-additions of various Griganard reagents to the desired substrates.



Entry	Starting material	R_1	R_2	R_3	R_4	product	Yield (%)	Ee (%)[b]
1	**9**	H	H	Me	Isobutyl	**14**	70	80
2	**9**	H	H	Me	Ethyl	**15**	50	40
3	**11**	Cl	H	Me	Isobutyl	**16**	91	80
4	**12**	F	H	Me	Isobutyl	**17**	97	84
5	**10**	Me	H	Me	Isobutyl	**18**	80	80

6	**9**	H	H	Me	CH_2-Cy	**19**	78	58
7	**9**	H	H	Me	Isopropyl	**20**	70	18
8	**8**	H	H	Et	Isobutyl	**21**	70	80
9	**13**[c]	H	Me	Me	Isobutyl	**22**	62	70

[a] Isolated yield. [b] Enantiomeric excess determined by chiral HPLC. [c]*dr*= 84:16.

Conclusions

In this study, the substrate scope of the enantioselective Cu/diphosphine-catalyzed 1,2-addition of Grignard reagents has been enlarged. Employing substrates with a CH_2OH or $CH_2OTBDMS$ group at the α-position of the double bond, led to very poor conversions and no enantioselectivity. We hypothesize that this is due to coordination of this oxygen to copper or magnesium, leading to a substrate conformation that is not suitable for asymmetric 1,2-addition. Upon locking the oxygen substituent in a 2*H*-chromene core, thereby preventing chelation, high *ee´*s and good yields are obtained. The regioselectivity for the reaction was remarkable; no conjugate addition product was observed. The observation that the 2*H*-chromene core can be equipped with an enantio-enriched tertiary hydroxyl group might be interesting for medicinal chemistry applications, all the more so because methods to prepare enantio-enriched tertiary alcohols are still scarce.

Experimental Section

General experimental

All reactions were performed under nitrogen atmosphere, using flame-dried glassware and dry solvents. *t*-BuOMe and THF were taken from a 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 were synthesized by reacting the substrates with the corresponding Grignard reagent in MTBE at –10 °C. ^{1}H-NMR and ^{13}C-NMR were recorded on a Varian AMX400 (400 and 100.6 MHz, respectively) using $CDCl_3$ as the solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). 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 AEI-MS-902 and 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 Chiracal 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; H_2O, 500 mL; H_2SO_4, 25 mL) and *p*-anisaldehyde staining (15 ml of AcOH and 3.5 mL of *p*-anisaldehyde to 350 mL ice cold EtOH. Cautiously add

50 mL concentrated H_2SO_4 dropwise over 60 min). Synthetized Grignard reagents were titrated according to literature procedures.[12] Compounds (2), (6) and (1) were prepared according to literature procedures and their spectral data are consistent with the literature.[8,9]

General procedure for the synthesis of the substrates:

1-(2H-chromen-3-yl)propan-1-one (8):

To a roundbottom flask charged with a magnetic stirrer was added salicylaldehyde (7.3 mmol, 1.27 g) that was dissolved in 40 mL of 1,4-dioxane. K_2CO_3 (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, then an additional 1.5 eq of ethyl vinyl ketone was added and the mixture was left to 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 $MgSO_4$, filtered, and concentrated at reduced pressure to afford (8) in 36% yield as a yellow oil after flash chromatography (SiO_2, *n*-pentane : EtOAc (95:5)).

^{1}H 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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 $[C_{12}H_{12}O_2 + H]^+$ = 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 (SiO_2, *n*-pentane: EtOAc (92 : 8)).

^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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).[10] HRMS (ESI+, m/z): calcd. for $[C_{11}H_{10}O_2 + H]^+$ = 175.075; found: 175.075. The spectral data correspond to those reported in literature.[10]

1-(6-methyl-2H-chromen-3-yl)ethanone (10):

The product was obtained as a yellow solid in 27% yield after column chromatography (SiO_2, *n*-pentane: EtOAc (90:10)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 4.97 (d, J = 1.2 Hz, 2H), 2.40 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 153.4, 134.1, 133.1, 131.1, 130.8, 129.4, 120.6, 116.0, 64.2, 25.0, 20.4. mp = (50 – 52) ˚C. HRMS (ESI+, m/z): calcd. for $[C_{12}H_{12}O_2 + H]^+$ = 189.091; found: 189.091.

1-(6-chloro-2H-chromen-3-yl)ethanone (11):

The product was obtained as a yellow solid in 45% yield after column chromatography (SiO_2, *n*-pentane: EtOAc (90:10)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.16 (m, 2H), 7.14 (d, J = 2.5 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 5.00 (d, J = 1.3 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 154.0, 132.5, 131.9, 131.7, 128.3, 126.5, 122.0, 117.6, 64.4, 25.1. mp = (49 – 51) ˚C. HRMS (ESI+, m/z): calcd. for $[C_{11}H_9ClO_2 + H]^+$ = 209.036; found: 209.037.

1-(6-fluoro-2H-chromen-3-yl)ethanone (12):

The product was obtained as a yellow solid in 62% yield after column chromatography (SiO_2, *n*-pentane: EtOAc (90:10)).

^{1}H 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). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 158.6, 156.2, 151.5, 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 = (53 – 55) ˚C. HRMS (ESI+, m/z): calcd. for $[C_{11}H_9FO_2 + H]^+$ = 193.065; found: 193.065.

1-(2-methyl-2H-chromen-3-yl)ethanone (13):

The product was obtained as a yellow oil in 33% yield after column chromatography (SiO_2, *n*-pentane: EtOAc (97:03)).

^{1}H NMR (400 MHz, Chloroform-d) δ 7.30 – 7.23 (m, 2H), 7.17 (dd, J = 7.6, 1.6 Hz, 1H), 6.93 (td, J = 7.5, 1.1 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 5.46 (q, J = 6.5 Hz, 1H), 2.40 (s, 3H), 1.29 (d, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 195.9, 153.7, 135.1, 132.7, 132.6, 129.0, 121.4, 120.2, 117.2, 70.2, 25.1, 19.6.
HRMS (ESI+, m/z): calcd. for $[C_{12}H_{12}O_2 + H]^+$ = 189.091; found: 189.090.

(*E*)-3-(((tert-butyldimethylsilyl)oxy)methyl)-4-phenylbut-3-en-2-one (23):

Compound (1) (2.02 g, 10.5 mmol) was diluted in 50 mL of DCM and imidazole (2.18 g, 31.5 mmol) and TBDMS chloride (3.2 g, 21 mmol) were added. The reaction mixture was left to stir at rt for 20 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, pentane:Et_2O (97:3)) to give the product as a yellow oil in 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.62 – 7.58 (m, 2H), 7.46 – 7.34 (m, 3H), 4.47 (s, 2H), 2.46 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 142.4, 139.6, 135.0, 129.9, 129.2, 128.4, 56.6, 26.4, 25.9, 18.3, –5.3. HRMS (ESI+, m/z): calcd. for $[C_{17}H_{26}O_2Si + H]^+$ = 313.159; found: 313.159

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•SMe_2 (15 µmol, 3.1 mg), (L1) (18 µmol, 10.7 mg) and 3 mL of dry *t*-BuOMe were added. The mixture was left to stir for 10 min. After that, compound (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 Et_2O, 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 H_2O (2 mL), allowed to warm up to rt and diluted with Et_2O. NH_4Cl_{aq} was added and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated at reduced pressure to afford (14) in 70% yield as a yellowish oil after flash chromatography (SiO_2, *n*-pentane : Et_2O (90:10)). *er* = 90:10 Retention times on chiral HPLC: 28.2 min and 31.8 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (td, J = 7.5, 1.3 Hz, 1H), 7.03 (dd, J = 7.4, 1.5 Hz, 1H), 6.92 – 6.86 (m, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.46 (s, 1H), 4.73 (d, J = 0.7 Hz, 2H), 1.75 (m, 1H), 1.57 (dd, J = 5.9, 2.2 Hz, 3H), 1.40 (s, 3H), 0.96 (t, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 134.0, 128.7, 126.8, 123.0, 121.5, 117.7, 115.4, 74.3, 65.6, 48.8, 28.0, 24.5, 24.5, 24.4. $[\alpha]_D^{20}$ = –7.8 (c =1.0, $CHCl_3$). HRMS (ESI–, m/z): calcd. for $[C_{15}H_{20}O_2 - H]^-$ = 231.139; found: 231.138.

2-(2H-chromen-3-yl)butan-2-ol (15):

The product was obtained as a yellowish oil in 50% yield after column chromatography (SiO_2, *n*-pentane: Et_2O (90:10)). *er* = 70:30 Retention times on chiral HPLC: 37.8 min and 39.7 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (td, J = 7.5, 1.4 Hz, 1H), 7.02 (dd, J = 7.4, 1.5 Hz, 1H), 6.88 (t, J = 7.4 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 6.41 (s, 1H), 4.74 (s, 2H), 1.67 (q, J = 7.5 Hz, 2H), 1.40 (s, 3H), 0.90 (t, J = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 139.3, 128.7, 126.7, 121.5, 118.1, 115.4, 74.1, 65.4, 32.9, 26.5, 22.3, 8.2. $[\alpha]_D^{20}$ = –10.4 (c = 1.0, $CHCl_3$). HRMS (ESI-, m/z): calcd. for $[C_{13}H_{16}O_2 - H]^-$ = 203.107; found: 203.143.

4-methyl-2-(6-methyl-2H-chromen-3-yl)pentan-2-ol (18):

The product was obtained as a yellowish oil in 80% yield after column chromatography (SiO_2, *n*-pentane: Et_2O (90:10)). *er* = 90:10. Retention times on chiral HPLC: 27.4 min and 30.9 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (dd, J = 8.1, 1.6 Hz, 1H), 6.84 (d, J = 1.9 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.42 (s, 1H), 4.69 (d, J = 1.2 Hz, 2H), 2.26 (s, 3H), 1.74 (m, 6.6 Hz, 1H), 1.56 (dd, J = 6.0, 2.8 Hz, 3H), 1.39 (s, 3H), 0.95 (dd, J = 7.8, 6.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0, 140.1, 130.7, 129.1, 127.2, 122.8, 117.7, 115.1, 74.3, 65.6, 48.8, 28.0, 24.5, 24.4, 20.6. $[\alpha]_D^{20}$ = –8.0 (c = 1.0, $CHCl_3$). HRMS (ESI–, m/z): calcd. for $[C_{16}H_{22}O_2 - H]^-$ 245.154; found: 245.154.

2-(6-chloro-2H-chromen-3-yl)-4-methylpentan-2-ol (16):

The product was obtained as a yellowish oil in 91% yield after column chromatography (SiO_2, *n*-pentane: Et_2O (90:10)). *er* = 90:10 Retention times on chiral HPLC: 23.8 min and 27.1 min.

^{1}H NMR (400 MHz, Chloroform-d) δ 7.06 – 7.01 (m, 1H), 6.98 (d, J = 2.5 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 6.39 (s, 1H), 4.71 (d, J = 1.4 Hz, 2H), 1.72 (dh, J = 13.1, 6.5 Hz, 1H), 1.55 (dd, J = 5.8, 2.4 Hz, 2H), 1.38 (s, 3H), 0.95 (dd, J = 8.1, 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7, 141.4, 128.2,

126.3, 126.2, 124.4, 116.9, 116.6, 74.2, 65.8, 48.8, 27.9, 24.4, 24.4. $[\alpha]_D^{20}$ = –11.6 (c = 1.0, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $[C_{15}H_{19}ClO_2 + H]^+$ = 267.114; found: 267.113.

2-(6-fluoro-2H-chromen-3-yl)-4-methylpentan-2-ol (17):

The product was obtained as a yellowish oil in 97% yield after column chromatography (SiO_2, *n*-pentane: Et_2O (90:10)). *er* = 92:8 Retention times on chiral HPLC: 48.3 min and 50.6 min.

^1H NMR (400 MHz, $CDCl_3$) δ 6.81 – 6.70 (m, 3H), 6.41 (s, 1H), 4.69 (s, 2H), 1.74 (m, 1H), 1.56 (dd, J = 5.9, 3.4 Hz, 2H), 1.39 (s, 3H), 0.96 (dd, J = 7.9, 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 156.4, 149.0, 149.0, 141.7, 124.1, 124.0, 117.2, 117.1, 116.2, 116.1, 114.7, 114.5, 112.9, 112.7, 74.2, 65.7, 48.8, 28.0, 24.5, 24.4, 24.4. $[\alpha]_D^{20}$ = –14.4 (c = 1.0, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $[C_{15}H_{19}FO_2 + H]^+$ = 251.144; found: 251.143.

3-(2H-chromen-3-yl)-5-methylhexan-3-ol (21):

The product was obtained as a yellowish oil in 70% yield after column chromatography (SiO_2, *n*-pentane: EtOAc (96:4)). *er* = 90:10 Retention times on chiral HPLC: 13.2 min and 14.4 min.

^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (td, J = 7.7, 1.7 Hz, 1H), 7.04 (dd, J = 7.5, 1.6 Hz, 1H), 6.90 (td, J = 7.4, 1.1 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.48 (s, 1H), 4.63 (s, 2H), 1.86 – 1.74 (m, 1H), 1.64 – 1.46 (m, 5H), 0.99 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101

MHz, $CDCl_3$) δ 153.1, 138.1, 128.6, 126.7, 123.0, 121.5, 119.0, 115.4, 65.8, 47.9, 32.9, 24.6, 24.4, 24.2, 7.5. $[\alpha]_D^{20}$ = +11.0 (c = 1.0, $CHCl_3$). HRMS (ESI+, 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 (SiO_2, *n*-pentane: EtOAc (96:4)). *dr* = 84:16 *er* = 85:15 (of major diastereomer) *er* = 87:13 (of minor diastereomer). Retention times on chiral HPLC: 15.5 min and 17.6 min (of major diastereomer) 14.4 min and 15.9 min (of minor diastereomer).

(7:3 mixture of diastereomers) ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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, 24.6, 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-(2H-chromen-3-yl)-1-cyclohexylpropan-2-ol (19):

The product was obtained as a yellowish oil in 78% yield after column chromatography (SiO_2, *n*-pentane: EtOAc (96:4)). *er* = 79:21 Retention times on chiral HPLC: 40.5 min and 43.2 min.

^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 140.2, 128.7, 126.8, 123.0, 121.5, 117.5, 115.4, 74.3, 65.6, 47.6, 35.0, 34.9, 33.7, 28.0, 26.3, 26.2. $[\alpha]_D^{20}$ = –11.2 (c = 1.0, $CHCl_3$). HRMS (ESI+, m/z): calcd. for $[C_{18}H_{24}O_2 + H]^+$ = 273.185; found: 273.184.

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 (SiO_2, *n*-pentane: EtOAc (96:04)). *er* = 59:41. Retention times on chiral HPLC: 27.1 min and 29.8 min.

^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (101 MHz, $CDCl_3$) 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, $CHCl_3$). HRMS (ESI-, m/z): calcd. for $[C_{14}H_{18}O_2 - H]^-$ = 235.113; found: 235.113.

References:

(1) Villacorta, G. M.; Rao, Ch. P.; Lippard, S. J.; *J. Am. Chem. Soc*., **1988**, 110, p.3175

(2) Harutyunyan, S. R.; Lopez, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L.; *J. Am. Chem. Soc*.; **2006**, 128, p. 9103

(3) Madduri, A. V. R.; Harutyunyan, S. R.; Minnaard, A. J.; *Chem. Comm.*, **2012**, 48, p.1478

(4) Madduri, A. V. R.; Minnaard, A. J.; Harutyunyan, S. R.; *Org. Biomol. Chem*., **2012**, 10, p.2878

(5) Weber, B., Seebach, D., *Angew. Chem.*, **1992**, p.96

(6) Hanato, M.; Suzuki, S., Ishihara, K., *J. Am. Chem. Soc*., **2006**, p.9998

(7) Madduri, A. V. R.; Harutyunyan, S. R.; Minnaard, A. J.; *Drug. Discov. Today.,* **2013**, 10, p.21

(8) De Paula, B. R. S.; Zampieri, D. S.; Rodrigues, J. A. R.; Moran, O. J. S.; *Tetrahedron: Asymmetry*, **2013**, 24, p.973

(9) Lee, K. Y., GowriSankar, S., Kim, J. M., *Bull. Korean Chem. Soc*., **2004**, p.413

(10) Brenna, E.; Gatti, F. G.; Malpezzi, L.; Monti, D.; Parmeggiani, F.; Sacchetti, A.; *J. Org. Chem*., **2013**, 78, p.4811

(11) Madduri, A. V. R.; Harutyunyan, S. R.; Minnaard, A. J.; *Angew. Chem. Int. Ed.*, **2012**, 51, p.3164

(12) Lin, H. S.; Paquette, L. A.; *Synth. Commun.*, **1994**, 24, p.2503