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Formation of optically active chromanes by catalytic asymmetric tandem oxa-Michael addition–Friedel–Crafts alkylation reactions

Hester L. van Lingen,[a,b] Wei Zhuang,[a] Tore Hansen,[a] Floris P. J. T. Rutjes*[b] and Karl Anker Jørgensen*[a]

[a] *Danish National Research Foundation, Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark. E-mail: kaj@chem.au.dk; Fax: 45.8619.6199; Tel: 45.8942.3910*

[b] *Department of Organic Chemistry, NSRIM, University of Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands. E-mail: rutjes@sci.kun.nl; Fax: 31.2436.53393; Tel: 31.2436.53202*

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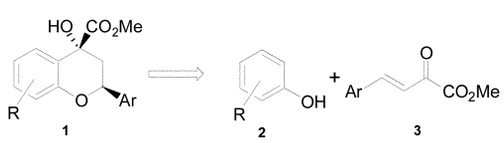
A novel tandem reaction involving an oxa-Michael addition, followed by a Friedel–Crafts alkylation has been developed. This catalytic tandem reaction, which provides facile and efficient access to optically active functionalised chromanes, proceeds under the influence of bisoxazoline-based catalysts to give diastereomerically pure products in enantioselectivities up to 81% and excellent yields. The optimisation studies, the scope of the reaction, and a model that on the basis of PM3 calculations predicts the outcome of the reaction will be detailed.

Introduction

One of the challenges in organic chemistry is the development of tandem reactions that provide complex molecules from readily available starting compounds.[1] A further challenge is to perform these reactions in a diastereo- and/or enantioselective manner. Thus, starting from prochiral substrates and with an enantiomerically pure catalyst may provide enantioselectivity, after which the newly generated stereocenter will control the diastereoselectivity. In this contribution, we wish to detail a novel tandem reaction, involving conjugate addition and subsequent Friedel–Crafts alkylation resulting in diastereomerically pure chromanes (dihydrobenzopyrans) **1** in enantioselectivities up to 81% ee (Scheme 1).



Scheme 1 Retrosynthesis.

Functionalised chromanes possess potentially useful biologically properties.[2] An evident example of a naturally occurring chromane is vitamin E (**A**, Fig. 1), which acts as an antioxidant.[3] A similar structural moiety is found in chromanes **B** which are able to inhibit a multidrug transporter that decreases drug accumulation in resistant cells.[4] Chromane **C** (Ro 23–3544), containing an acid and an acetyl moiety, is a potential peptidoleukotriene antagonist and biosynthesis inhibitor.[5] Furthermore, this compound is thought to possess a potential utility in the treatment of asthma. Another example of a biologically active chromane is sorbinil (**D**), which functions as an aldose reductase inhibitor.[6] In order to circumvent undesired side effects of sorbinil – probably caused by the spirohydantoin ring moiety – chromane **E** was synthesized. Indeed, this compound possessed similarly high aldose reductase activity and so far no evidence of side effects has been observed.

Although numerous synthetic routes towards highly functionalised chromenes and chromanes have been reported over the past decades,[7] we wish to detail a new efficient route starting from readily available compounds. This route, depicted in Scheme 2, initially involves a Lewis acid-catalysed oxa-Michael

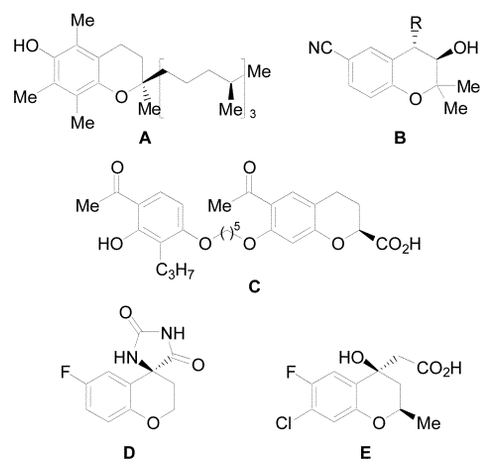
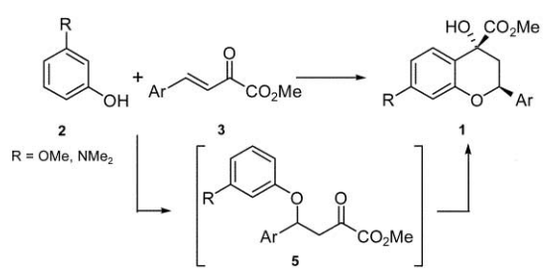


Fig. 1 Examples of biologically active chromanes.



Scheme 2 The consecutive steps of the tandem process.

addition of phenols **2** to the β,γ-unsaturated α-ketoesters **3**. The Michael adduct **5** immediately undergoes intramolecular Friedel–Crafts alkylation to form the chromanes **1** as single diastereomers.

Although several examples of oxa-Michael additions are known, only three asymmetric catalytic versions have been reported by Ishikawa and coworkers.[8] They constructed a chromanone unit *via* intramolecular addition of a phenol moiety to an α,β-unsaturated enone in the presence of chiral bases such as quinine.

Bisoxazolines[9] have been frequently used as chiral ligands in combination with different Lewis acids as catalysts for a

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Table 1 Variation of ligand and solvent in the tandem reaction

Entry	Ligand	Solvent	Yield **1a** (%)	Ee **1a** (%)	Yield **6a** (%)
1	**4a**	CH_2Cl_2	57	36	nd
2	**4b**	CH_2Cl_2	58	16	21
3	**4c**	CH_2Cl_2	49	21	21
4	**4c**	THF	26	16	43
5	**4c**	Et_2O	31	4	37
6	**4c**	Toluene	65	28	20

number of reaction types, such as Michael additions[10] and Friedel–Crafts alkylations.[11] Generally, the catalysis proceeds by the Lewis acidic properties of the metal, while the stereochemical outcome is determined by the steric properties of the chiral ligand. Since bisoxazoline based systems have been shown to be useful catalysts for each of these reaction types, we reasoned that such catalysts may be well-suited to apply in a tandem version of these reactions.[12] Beside the commercially available *tert*-butyl- and phenyl-box ligands **4a** and **4b**, we included the readily available more bulky box ligands **4c**[13] and **4d**.[14] The 1-naphthyl ligand **4c** was chosen since we anticipated that this ligand would be optimally suited for reactions where the reacting center is relatively remote from the coordination site (Fig. 2).[13]

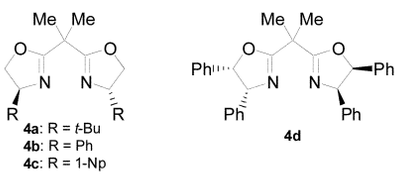
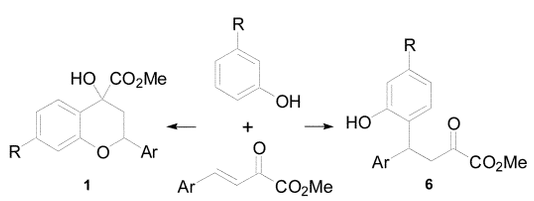


Fig. 2 Bisoxazoline ligands applied in the tandem reaction.

Results and discussion

A variety of Lewis acids in combination with the chiral ligands **4a**–**d** were evaluated as catalysts. Preliminary studies suggested that especially the C_2-symmetric bisoxazolines (box) were the best ligands for the tandem reaction. Other chiral ligands, *e.g.* (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (DBFOX)/Ph, BINOL and salen-type ligands[15] in combination with various Lewis acids did not induce enantioselectivity, nor catalyse the reaction toward the tandem product.

Initially, we subjected a mixture of *m*-methoxyphenol **2a** and the β,γ-unsaturated α-ketoester **3a** to a catalyst that was prepared from $Cu(OTf)_2$ and the box ligands **4**; this led to the formation of chromane **1a** as a single diastereomer in moderate yields (Table 1). In addition to the desired tandem product, we observed the Friedel–Crafts alkylation product **6a**, which resulted from *C*-nucleophilic 1,4-addition of the phenol to the α,β-unsaturated carbonyl compound (Scheme 3).[11c] The desired tandem product could be readily separated from the Friedel–Crafts product by flash column chromatography. In the purification, the 1-Np-box ligand (**4c**), could be quantitatively recovered, whereas the other box ligands were filtered off together with the Lewis acid during workup.



Scheme 3 Tandem process *vs.* *C*-conjugate addition.

Although it is clear from Table 1 that the best enantiomeric excess was obtained in the presence of *t*-Bu-box (only 36% ee), we anticipated that the 1-Np-box eventually would afford the tandem product with higher enantioselectivities under optimised conditions. Variation of the solvent revealed that toluene was the best solvent, giving both the highest enantiomeric excess (62% ee) and highest yield (65%) (Table 2). Moreover, the undesired Friedel–Crafts *C*-alkylation of the α,β-unsaturated ketone was optimally reduced in toluene.

Replacement of $Cu(OTf)_2$ by $Zn(OTf)_2$ led to a clear decrease of enantioselectivity, whereas $Mg(OTf)_2$ resulted in a remarkable increase of the enantiomeric excess to 62% ee (Table 2). In the presence of $Mg(OTf)_2$ and 1-Np-box, toluene appeared to be the most appropriate solvent (Table 2). The tandem reaction did not proceed at all in THF and Et_2O; only starting material was recovered. On the other hand, we observed a good conversion into chromane **1a** in dichloromethane and dichloroethane, but the enantioselectivity was significantly reduced to 47% ee and 45% ee, respectively. In the presence of other Mg(II)-salts, *i.e.* using different counter ions, a decrease of enantioselectivity was observed.

By applying other commercially and readily available box ligands under the aforementioned reaction conditions we tried to optimise the best result so far (Table 3, entry 3, $Mg(OTf)_2$, 1-Np-box **4c**, toluene). In all cases, however, lower enantioselectivities were obtained. Inversely, decreasing the temperature to 0 °C led to an enhanced enantioselectivity of 74% ee with a slightly lower yield (entry 5). In addition, at this temperature the formation of the Friedel–Crafts *C*-alkylation product **6a** was reduced. Further decrease of the temperature led to a complete loss of reactivity; at −14 °C no reaction took place.

Previously, it was found in other nucleophilic addition reactions that the yield and enantiomeric excess can be dependent on the presence of a base.[17] Probably the base facilitates the addition of the nucleophile by deprotonation. For example, in the presence of 10 mol% of Et_3N, the yield of **1a** was improved to 87% compared to 39% without an additive (Table 4). The concomitant decrease of enantioselectivity (from 74% ee to 63% ee) was probably due to a background reaction.[18] In order to diminish this undesired background reaction, the amount of Et_3N was reduced to 2 mol%, affording chromane **1a** in a somewhat lower yield (61%) and similar enantioselectivity.

In order to investigate the role of the base, the sodium salt of *m*-methoxyphenol was subjected to the tandem reaction conditions. In the absence of Lewis acid, only starting material was recovered; in the presence of the catalyst that was prepared from $Mg(OTf)_2$ and 1-Np-box ligand (**4c**), the tandem product was obtained in good yield, but without enantioselectivity. Probably, the phenolate anion of **2a** is sufficiently nucleophilic to give (non-selective) conjugate addition, which is then followed by Lewis acid-catalysed formation of the chromane.

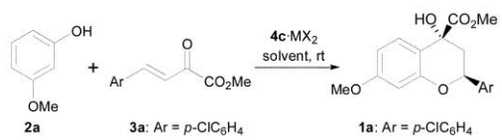
In the presence of KO*t*Bu (10 mol%), the tandem product was formed with an enantioselectivity of 73% ee (Table 4, entry 4). However, the yield was only slightly better and even lower than in the presence of Et_3N. Other bases such as *N*-methylmorpholine (NMO) and 1,4-diazabicyclo[2.2.2]octane (DABCO) resulted in a decrease of enantioselectivity and lower yields. This was partially due to relatively large yields for the Friedel–Crafts *C*-alkylation product. Use of proton sponge (1,8-bis(dimethylamino)naphthalene) resulted in an enhanced enantioselectivity of 81% ee. Unfortunately, the rate of the Friedel–Crafts *C*-alkylation reaction was also increased, affording mainly side product (**6a**) and only 21% of the desired tandem product.

Addition of other amine-based additives such as Hünig's base and phenyldibenzylamine did not improve the enantioselectivity, and even resulted in a decrease of the yield. Finally, in the presence of *p*-methyl-*N*,*N*-dimethylaniline, the tandem reaction proceeded smoothly affording chromane **1a** in similar enantioselectivity and increase of the yield to 89%, rendering this the method of choice.

Using these optimised reaction conditions, *m*-methoxyphenol was reacted with a range of aryl-substituted β,γ-unsaturated α-ketoesters (**3b**–**d**, Table 5, entries 1–4) to give the tandem products in high yields as single diastereoisomers, as proven by ^{1}H-NMR studies. For the phenyl-substituted enone **3b** a decrease of both yield and enantiomeric excess was observed in the absence of *p*-methyl-*N*,*N*-dimethylaniline (compare entry 1 and entry 2), which is similar to the results for β,γ-unsaturated α-ketoesters **3a** (Table 4). The enantioselectivity appeared to be weakly dependent on the aryl substituent, resulting in enantiomeric excesses ranging from 66% to 80%. In contrast, replacement of the aryl substituent by a simple methyl group resulted in formation of a mixture of diastereoisomers (4 : 1) with low enantioselectivity; this shows the importance of a large substituent on the alkene.

In order to vary the nucleophile, the methoxy substituent of phenol **2a** was replaced with a dimethylamine group. *m*-*N*,*N*-Dimethylaminophenol **2b** was reacted with both aryl-

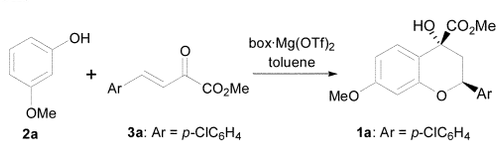
Table 2 Different solvents and different metal salts



Entry	Lewis acid	Solvent	Yield **1a** (%)	Ee (%)
1	$Cu(OTf)_2$	Toluene	65	28
2	$Zn(OTf)_2$	Toluene	32	17[a]
3	$Mg(OTf)_2$	Toluene	53	62
4	$Mg(OTf)_2$	Et_2O	0	—
5	$Mg(OTf)_2$	THF	0	—
6	$Mg(OTf)_2$	CH_2Cl_2	60	47
7	$Mg(OTf)_2$	$ClCH_2CH_2Cl$	57	45
8	$Mg(ClO_4)_2$	Toluene	66	40
9	MgI_2	Toluene	62	24
10[b]	MgI_2[c]	Toluene	64	42

[a] The opposite enantiomer was obtained. [b] The reaction was started at 0 °C and allowed to warm up to rt. [c] The addition of iodide (0.5 equiv with respect to MgI_2) is known to activate MgI_2, thereby improving the outcome of the reaction.[16]

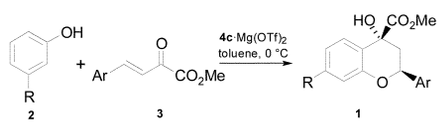
Table 3 Comparison of different ligands under optimized reaction conditions



Entry	Ligand	Reaction temp./°C	Yield (%)	Ee (%)
1	**4a**	RT	67	2[a]
2	**4b**	RT	32	44
3	**4c**	RT	53	62
4	**4d**	RT	20	50[a]
5	**4c**	0	39	74
6	**4c**	−14	0	–

[a] The opposite enantiomer was obtained.

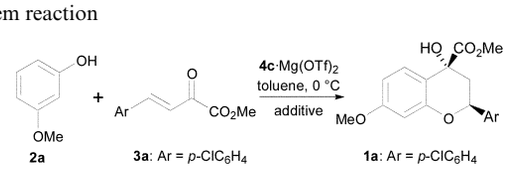
Table 5 Variation of the Michael donor and acceptor molecule



Entry	R	Ar	Product	Yield (%)	Ee (%)
1	OMe	Ph	**1b**	67	73
2[a]	OMe	Ph	**1b**	77	80
3[a]	OMe	*p*-FC_6H_4	**1c**	43	74
4[a]	OMe	*p*-BrC_6H_4	**1d**	45	66
5	NMe_2	*p*-ClC_6H_4	**1e**	>95	<18
6	NMe_2	Ph	**1f**	>95	13

[a] The reaction was performed in the presence of *p*-methyl-*N*,*N*-dimethylaniline.

Table 4 Influence of additives on the tandem reaction

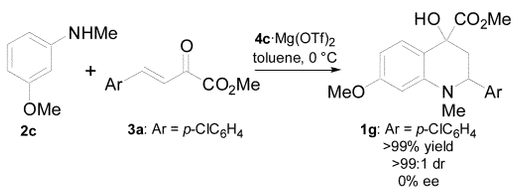


Entry	Additive	Mol%	Yield **1a** (%)	Ee (%)	Yield **6a** (%)
1	None	—	39	74	6
2	Et_3N	10	87	63	nd
3	Et_3N	2	61	74	15
4	KO*t*Bu	10	59	73	28
5	NMO	10	31	56	24
6	DABCO	10	24	59	65
7	Proton sponge[a]	10	21	81	74
8	$EtNiPr_2$	10	30	72	43
9	$PrNBn_2$	10	31	69	<5
10	*p*-$TolNMe_2$	10	89	73	<5

[a] Proton sponge = 1,8-bis(dimethylamino)naphthalene.

substituted β,γ-unsaturated α-ketoesters **3a** (R = Cl) and **3b** (R = H), affording the corresponding chromanes as single diastereoisomers in excellent yield (>95%), but with low enantioselectivity (<20% ee). Most likely, due to the higher electron-donating character of the dimethylamine substituent (compared to the methoxy group) the nucleophile is sufficiently reactive to give an uncatalysed (non-selective) oxa-Michael addition resulting in a dramatic decrease of the enantioselectivity.

In an attempt to prepare tetrahydroquinolines in a similar process, *m*-methoxy-*N*-methylaniline was reacted with β,γ-unsaturated α-ketoesters **3a** (Scheme 4). Indeed, the corresponding tetrahydroquinoline (**1g**) was formed quantitatively and in diastereomerically pure form, but unfortunately without enantioselectivity. The high yield and the lack of enantioselectivity were probably due to the higher nucleophilicity of the amine moiety. Because of the high aniline nucleophilicity, the Friedel–Crafts *C*-alkylation reaction was completely suppressed giving straightforward access to the tetrahydroquinoline structure.



Scheme 4 Formation of the tetrahydroquinoline **1g**.

Close examination of the tandem products **1** revealed that the second reaction step was completely diastereoselective. The enantioselectivity of the reaction is determined in the oxa-Michael addition, which appears to be a reversible reaction. The equilibrium of this first reaction step lies heavily at the side of the starting materials, which hampered our attempts to detect intermediate **5** with NMR-studies.

The relative stereochemistry of chromane **1a** was deduced from a NOESY-experiment (Fig. 3). The two-dimensional spectrum revealed that H^2 is in close proximity to both H^1 and OH. Since H^3 showed no NOE-correlations to either H^1 and OH, we concluded that H^1 and OH are *cis* with respect to each other, resulting in the diastereoisomer depicted in Fig. 3. This is in line with results from simple MM2-modeling studies showing that this is the thermodynamically most stable conformation.

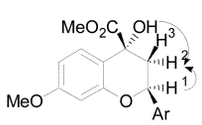


Fig. 3 Elucidation of the relative stereochemistry by NOESY-studies.

Recently, the X-ray structures of several chiral bisoxazoline-copper(II) complexes were published.[19] To compare the 1-Np-box with the more commonly used *t*Bu- and Ph-box ligands, crystals of $[CuCl_2(1\text{-Np-box})]$[20] and $[CuBr_2(1\text{-Np-box})]$[21] complexes were prepared †. Because both structures showed the same trend, only the X-ray crystal structure of the $[CuCl_2(1\text{-Np-box})]$ complex is depicted (Fig. 4). Similar to the structures of the $[CuCl_2(t\text{Bu-box})]$ and $[CuCl_2(\text{Ph-box})]$ complexes,[19] the chlorides or – more general – halides coordinate to the copper, resulting in a geometry that is in between square planar and tetrahedral. Taking the orientation of the oxazoline rings into account, the $[CuX_2(1\text{-Np-box})]$ complexes mostly resemble the $[CuX_2(\text{Ph-box})]$ complexes.

† CCDC reference numbers 206608 and 206609. See http://www.rsc.org/suppdata/ob/b3/b303353h/ for crystallographic data in .cif or other electronic format.

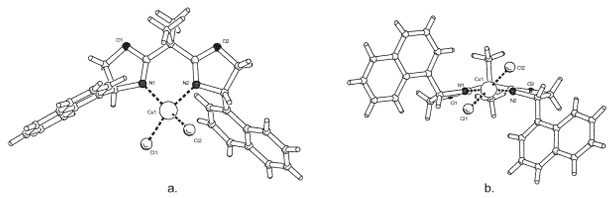


Fig. 4 X-Ray structure of $[CuCl_2(1\text{-Np-box})]$.

In order to gain insight into the enantiodifferentiation of the reaction, we performed PM3-level calculations[22] on the proposed intermediate: 1-naphthyl-box–magnesium(II) catalyst with β,γ-unsaturated a-ketoester **3b** as the complexing compound (Fig. 5). Replacement of copper(II) by magnesium(II) directly resulted in a change of the geometry to (distorted) tetrahedral.

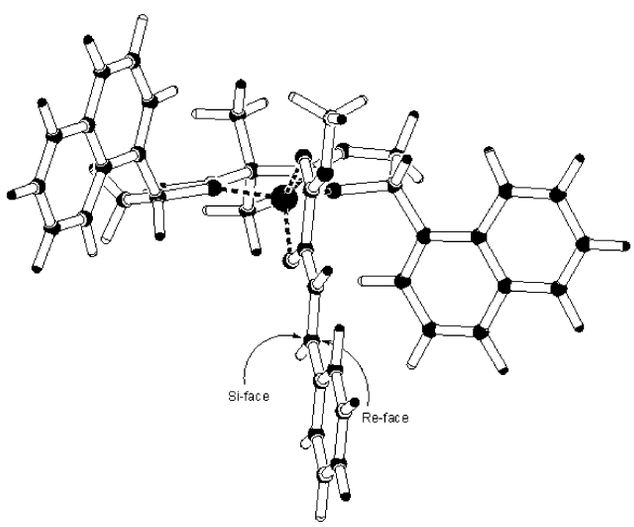


Fig. 5 PM3 model of [Mg(II)(1-Np-box)] complex with **3b**.

As clearly depicted in Fig. 5, the 1-naphthyl box ligand **4c** is oriented perpendicular to the plane of the picture, having both naphthyl substituents sticking out of the plane. The *Re*-face of the β,γ-unsaturated α-ketoester **3b**, coordinated to magnesium perpendicular to the box ligand, is blocked from attack by an incoming nucleophile due to the naphthyl substituent on the right side. This suggests a favorable attack on the *Si*-face, resulting in the (*S*)-enantiomer of the Michael adduct **5b**.

Conclusions

In summary, we have developed a novel enantio- and diastereoselective catalytic tandem reaction involving an oxa-Michael addition and subsequent Friedel–Crafts alkylation providing facile access to optically active functionalised chromanes **1**. The oxa-Michael reaction is reversible, having an equilibrium that lies heavily at the side of the starting materials. The second step – the Friedel Crafts alkylation – is completely diastereoselective, since the tandem products were formed as single diastereoisomers. In addition, *C*-nucleophilic 1,4-addition of the phenol to the α,β-unsaturated carbonyl compound occurred in some cases resulting in side product **6**.

This reaction represents the first example where the bulky 1-naphthyl bisoxazoline ligand **4c** gives results that are superior in comparison to the existing bisoxazoline ligands under optimised conditions ($Mg(OTf)_2$, 0 °C, toluene). Further optimisation led to the optimal reaction conditions using 1-Np box in combination with $Mg(OTf)_2$ as the catalyst (10 mol%) in toluene at 0 °C, in the presence of 10 mol% of *p*-methyl-*N*,*N*-dimethylaniline.

Variation of the nucleophile revealed that replacement of the methoxy substituent by the more electron-donating

dimethylamine group, resulted in a dramatic decrease of enantioselectivity. Applying somewhat less reactive *m*-methoxy-*N*-methylaniline, afforded exclusively the desired tetrahydroquinoline, although with no enantioselectivity.

Using NOESY studies, the relative stereochemistry of the tandem products was established. So far, we were unable to establish the absolute configuration of the products: on the basis of PM3 calculations, we developed a model, which tentatively predicts the stereochemical outcome of the reaction.

Experimental

General methods

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and relative to the central $CDCl_3$ resonance ($\delta = 77.07$) for ^{13}C NMR. Coupling constants (J) are given in Hz. Flash chromatography (FC) was carried out using Merck silica gel 60 (230–400 mesh). Optical rotations were measured on a Perkin-Elmer 241 polarimeter and are recorded in units of 10^{-1}deg cm^2 g^{-1}. The enantiomeric excess (ee) of the products were determined by HPLC using Daciel Chiralcel OD columns with hexane–*i*-PrOH as eluent.

Materials

m-Methoxyphenol, and *m*-*N*,*N*-dimethylaminophenol were purchased from Aldrich and used as received. Solvents were distilled over the appropriate drying agents. Aryl-substituted β,γ-unsaturated α-ketoesters were synthesized by our group. 2,2′-Isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], (*R*)-2,2′-isopropylidenebis(4-phenyl-2-oxazoline), 2,2′methylenebis-[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline], $Mg(OTf)_2$ and $Cu(OTf)_2$ from Aldrich were stored under an inert atmosphere and used without further purification.

Representative experimental procedure

To a flame-dried Schlenk tube was added $Mg(OTf)_2$ (8.0 mg, 0.025 mmol) and (*S*)-**4c** (12 mg, 0.028 mmol). The mixture was dried under vacuum for 0.5 h and distilled anhydrous toluene (0.5 ml) was added. After stirring for 0.5 h, **3a** (58 mg, 0.25 mmol) and *p*-methyl-*N*,*N*-dimethylaniline (3.6 µl, 0.025 mmol) were added and the mixture was cooled to 0 °C. After addition of **2a** (55 µl, 0.50 mmol), the mixture was stirred overnight at 0 °C. Flash chromatography (20% Et_2O in pentane) afforded **1a** as a colourless oil (77 mg, 89%) in an enantiomeric excess of 73% ee (detected by HPLC: OD column; hexane–*i*-PrOH 95 : 5; t_R(major) = 12.9 min, t_R(minor) = 14.4 min).

2-(4-Chlorophenyl)-4-hydroxy-7-methoxychroman-4-carboxylic acid methyl ester (1a)

Chromane **1a** was isolated as a colourless oil; $[\alpha]_D^{rt} = +0.28$ (c = 0.63 g per 100 mL, $CHCl_3$, 73% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, dt, J = 2.0, 8.4, Ar), 7.19 (2H, dt, J = 2.0, 8.4, Ar), 6.60 (1H, dd, J = 0.8, 8.8, Ar), 6.45–6.41 (2H, m, Ar), 4.43 (1H, d, J = 2.0, O*H*), 4.27 (1H, dd, J = 6.0, 13.2, C*H*Ar), 3.90 (3H, s, CO_2CH_3), 3.74 (3H, s, OCH_3), 2.38 (1H, td, J = 2.0, 13.2, CH_2), 2.24 (1H, dd, J = 5.6, 13.2, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.8, 152.4, 142.3, 132.9, 130.4, 130.1, 129.1, 117.4, 108.8, 102.1, 101.9, 94.6, 55.6, 55.5, 53.8, 36.9, 36.8; HRMS [M$^+$Na] calcd 371.0662; found 371.0665.

2-Phenyl-4-hydroxy-7-methoxychroman-4-carboxylic acid methyl ester (1b)

Chromane **1b** was isolated as a colourless oil; $[\alpha]_D^{rt} = +1.36$ (c = 1.55 g per 100 mL, $CHCl_3$, 80% ee), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.17 (5H, m, Ar), 6.56 (1H, d, J = 8.4, Ar), 6.38–6.33 (2H, m, Ar), 4.38 (1H, s, O*H*), 4.21 (1H, dd, J = 5.6, 13.2, C*H*Ar), 3.83 (3H, s, OCH_3), 3.67 (3H, s, CO_2CH_3), 2.38 (1H, t, J = 13.2, CH_2), 2.24 (1H, dd, J = 5.6, 13.2, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 159.6, 152.3, 143.7, 130.2, 129.1, 129.0, 128.8, 127.2, 118.0, 108.7, 108.0, 106.6, 101.9, 94.8, 55.5, 53.8, 37.0; HRMS [M$^+$Na] calcd 337.1052; found 337.1044.

2-(4-Fluorophenyl)-4-hydroxy-7-methoxychroman-4-carboxylic acid methyl ester (1c)

Chromane **1c** was isolated as a colourless oil; $[\alpha]_D^{rt} = +0.09$ (c = 0.85 g per 100 mL, $CHCl_3$, 74% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.18 (2H, m, Ar), 7.03–6.99 (2H, m, Ar), 6.60–6.58 (1H, m, Ar), 6.43–6.40 (2H, m, Ar), 4.35 (1H, d, J = 1.2, O*H*), 4.25 (1H, dd, J = 5.2, 13.2, C*H*Ar), 3.89 (3H, s, CO_2CH_3), 3.73 (3H, s, OCH_3), 2.38 (1H, td, J = 1.2, 13.2, CH_2), 2.22 (1H, dd, J = 5.6, 14.4, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 163.3, 160.8, 159.7, 152.3, 139.4, 130.5, 130.0, 117.7, 115.9, 115.7, 108.8, 102.0, 94.6, 55.6, 53.9, 37.1, 36.6; HRMS [M$^+$Na] calcd 355.0958; found 355.0966.

2-(4-Bromophenyl)-4-hydroxy-7-methoxychroman-4-carboxylic acid methyl ester (1d)

Chromane **1d** was isolated as a colourless oil; $[\alpha]_D^{rt} = +0.23$ (c = 0.94 g per 100 mL, $CHCl_3$, 66% ee), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (2H, dd, J = 2.0, 8.0, Ar), 7.13 (2H, dd, J = 2.0, 8.0, Ar), 6.60 (1H, dd, J = 0.8, 8.8, Ar), 6.44–6.41 (2H, m, Ar), 4.45 (1H, d, J = 2.0, O*H*), 4.25 (1H, dd, J = 6.0, 13.2, C*H*Ar), 3.90 (3H, s, OCH_3), 3.74 (3H, s, CO_2CH_3), 2.38 (1H, td, J = 2.0, 13.2, CH_2), 2.24 (1H, dd, J = 6.0, 13.2, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.8, 152.3, 142.8, 132.1, 130.8, 130.0, 120.9, 117.3, 108.8, 102.0, 94.5, 55.6, 53.9, 36.8; HRMS [M$^+$Na] calcd 415.0157; found 415.0173.

2-(4-Chlorophenyl)-4-hydroxy-7-(*N*,*N*-dimethylamino)chroman-4-carboxylic acid methyl ester (1e)

Chromane **1e** was isolated as a purple oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.19 (4H, m, Ar), 6.55 (1H, d, J = 8.4, Ar), 6.34–6.21 (2H, m, Ar), 4.25 (1H, dd, J = 5.6, 12.8, C*H*Ar), 3.89 (3H, s, CO_2CH_3), 2.90 (3H, s, NCH_3), 2.89 (3H, s, NCH_3), 2.38 (1H, t, J = 12.8, CH_2), 2.24 (1H, dd, J = 5.6, 13.2, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.2, 151.0, 142.8, 132.7, 130.4, 130.2, 129.7, 129.0, 113.3, 107.3, 100.8, 94.6, 53.8, 40.8, 37.2, 36.7; HRMS [M$^+$Na] calcd 384.0979; found 384.0986.

2-Phenyl-4-hydroxy-7-(*N*,*N*-dimethylamino)chroman-4-carboxylic acid methyl ester (1f)

Chromane **1f** was isolated as a purple oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (3H, m, Ar), 6.60 (1H, d, J = 8.0, Ar), 6.34–6.22 (3H, m, Ar), 4.28 (1H, dd, J = 5.6, 13.2, C*H*Ar), 3.89 (3H, s, CO_2CH_3), 2.90 (3H, s, NCH_3), 2.89 (3H, s, NCH_3), 2.44 (1H, t, J = 12.8, CH_2), 2.28 (1H, dd, J = 5.6, 13.2, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 152.3, 150.1, 144.2, 130.2, 129.9, 129.1, 128.9, 127.0, 114.0, 107.3, 105.6, 104.1, 100.8, 94.7, 53.7, 40.9, 37.3, 37.2; HRMS [M$^+$Na] calcd 350.1368; found 350.1377.

2-(4-Chlorophenyl)-4-hydroxy-7-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline-4-carboxylic acid methyl ester (1g)

Chromane **1g** was isolated as a colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (2H, d, J = 8.0, Ar), 7.18 (2H, d, J = 8.0, Ar), 6.39 (1H, d, J = 8.0, Ar), 6.29 (1H, d, J = 2.0, Ar), 6.17 (1H, dd, J = 2.0, 8.0, Ar), 4.16 (1H, s, OH), 4.08 (1H, dd, J = 4.0, 14.0, C*H*Ar), 3.84 (3H, s, CO_2CH_3), 3.75 (3H, s, NCH_3), 2.84 (3H, s, NCH_3), 2.29 (1H, t, J = 12.8, CH_2), 2.08 (1H, dd, J = 4.0, 12.8, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 159.6, 144.8, 141.8, 132.8, 130.5, 130.1, 129.0, 128.9, 128.3, 120.5, 102.1, 99.1, 85.9, 55.5, 54.0, 42.1, 38.0, 33.7; HRMS [M$^+$Na] calcd 384.0979; found 384.0982.

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21 Reference number of the [$CuBr_2$(1-Np-box)] complex in the Cambridge Crystallographic Data Centre: CCDC 206609. $C_{26}H_{26}Br_2CuN_2O_2$, M = 657.91, crystallises in the orthorhombic space group $P2_12_12_1$, with a = 10.2389(9) Å, b = 13.089(1) Å, c = 19.466(2) Å, V = 2608.8(4) Å^3, T = 120 K, Z = 4, μ = 3.940 mm^{-1}; 24177 reflections were measured, giving 7639 independent, of which 5147 with $I > 3\sigma(I)$ were used in the refinements. The internal agreement had R = 0.079, the final R = 0.033, Rw = 0.035, GOF = 0.90, for the significant reflections.

22 Optimisations were performed using Spartan (version 5.1.3). Counterions and solvent were omitted during calculations.