Enantioselective synthesis of new dimeric chromene derivatives by a ferrocene-copper catalyst system

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Novel 2-iminochromene dimers were prepared in excellent yields (93–99%) and with high to excellent enantioselectivities (89–97% *ee*) by a simple and efficient method. The precursor 2-[(3-cyano-2*H*-chromen-2-ylidene)amino]acetates and both racemic and enantioselective 2-iminochromene dimers were disclosed and characterised for the first time.

Keywords: 2-iminochromene dimer, enantioselective, ferrocene

Iminochromene derivatives are an important class of compounds, widely present in nature.[1-3] Numerous chromene-based structures are used as antibiotics,[4] fungicides,[5] and anti-inflammatory,[6] anticoagulant[7] and antitumor agents.[8] Because of their high fluorescence properties, many synthetic analogues have been made over the years.[9-13] They are widely used as brighteners, optical whitening agents, laser dyes and also as fluorescent probes in medical science.[14,15] The 2-imino analogues comprise a very important class of protein tyrosine kinase (PTK) inhibitors with low molecular weight.[16,17] As a new development, the synthesis of chiral dimeric chromene derivatives is an important target as a novel modification of existing therapeutic compounds. We have recently reported the synthesis of a siloxane-substituted ferrocenyloxazolinephosphine (FOXAP) ligand **L(f)** (Fig. 1) and successfully used it in the enantioselective 1,3-dipolar cycloaddition of azomethine ylides with alkylidene malonates.[18]

We now report a novel synthesis of chiral dimeric chromene derivatives catalysed by a combination of copper(II) salts and **L(f)**, in good yields and excellent enantioselectivities. This is a preliminary report of copper/siloxane-substituted FOXAP complexes that catalyse the self-Michael addition of 2-[(3-cyano-2*H*-chromen-2-ylidene)amino)acetates with excellent enantioselectivity.

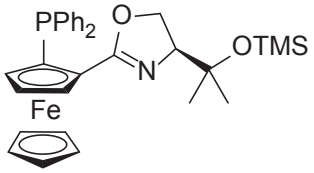


Fig. 1 Stucture of siloxane-substitued ferrocenyloxazolinephosphine (FOXAP) L(f).

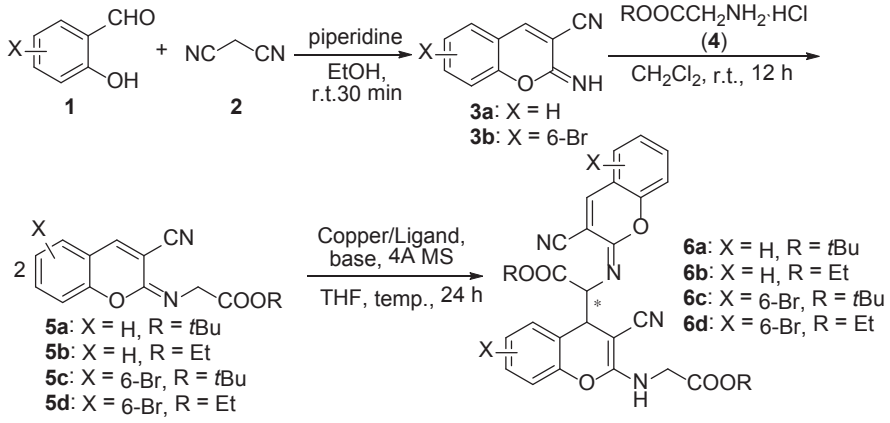
Results and discussion

Our three-step synthesis of chiral dimeric chromene derivatives is shown in Scheme 1. Compounds **3a** and **3b** are known compounds and were synthesised by a literature method[19] and then reacted with glycine ethyl (or *t*-butyl) ester hydrochloride **4** (1.0 equiv.) in CH_2Cl_2 to give iminoesters **5a–d**.

For the optimisation of the final step of the synthesis, the asymmetric self-Michael addition reaction, we chose **5a** as the model compound, and the yields of compound **6a** using various bases, two copper salts and three ligands are shown in Table 1. In a single experiment with PPh_3/Et_3N and $CuClO_4$, a moderate yield of 72% was obtained (entry 1). An organocatalyst such as cinchonine was tried, but the yield was low (entry 2). Next, several metal complexes and salts such as $CuClO_4{\cdot}4CH_3CN$, $Cu(OAc)_2{\cdot}H_2O$, and $Cu(ClO_4)_2{\cdot}6H_2O$ were examined in combination with the ligand **L(f)**. We found that $Cu(ClO_4)_2{\cdot}6H_2O$/**L(f)** gave the best result in THF at room temperature in the presence of Et_3N as a base and 4Å molecular sieves as water absorbent under the protection of N_2 for the standard time of 24 h (entry 5). At 0 °C, under the same conditions, a higher *ee* value was obtained, but the yield was lower (entry 6).

Then, the effect of the base was investigated. As shown in Table 1, $Cu(ClO_4)_2{\cdot}6H_2O$/**L(f)** performed well with Et_3N, while reactions with bases such as $KOBu^t$, K_2CO_3, and diisopropanolamine (DIPEA) gave lower yields or lower enantioselectivities (entries 7–9).

On the basis of the results reported above, the optimised reaction conditions were set as follows: 10 mol% of



Scheme 1 Catalytic enantioselective synthesis of 2-iminochromene dimmers.

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Table 1 Yields and *ee* values obtained in the optimisation of the reaction conditions (catalyst, ligand, base) for the conversion of iminoester **5a** by asymmetric self-Michael addition into chiral dimeric chromene derivative **6a** (Scheme 1)[a]

Entry	Metal	Ligand	Base	Temperature /°C	Yield /%[b]	*ee*[c] /%
1	$CuClO_4{\cdot}4CH_3CN$	PPh_3	Et_3N	0	72	–
2	–	Cinchonine	–	RT	15	ND
3	$CuClO_4{\cdot}4CH_3CN$	L(f)	Et_3N	RT	77	87.0
4	$Cu(OAc)_2{\cdot}H_2O$	L(f)	Et_3N	RT	86	75.2
5	$Cu(ClO_4)_2{\cdot}6H_2O$	L(f)	Et_3N	RT	98	91.2
6	$Cu(ClO_4)_2{\cdot}6H_2O$	L(f)	Et_3N	0	93	93.7
7	$Cu(ClO_4)_2{\cdot}6H_2O$	L(f)	*t*-BuOK	RT	98	90.6
8	$Cu(ClO_4)_2{\cdot}6H_2O$	L(f)	K_2CO_3	RT	95	88.4
9	$Cu(ClO_4)_2{\cdot}6H_2O$	L(f)	DIPEA	RT	89	92.5

[a]Reaction conditions: **5a** (0.25 mmol), base (0.025 mmol), metal (0.025 mmol), 4Å molecular sieves (two particles) and ligand (0.028 mmol) in THF (3.0 mL).
[b]Isolated yield.
[c]Determined by chiral HPLC analysis (Daicel OD-H, hexane/i-propane = 87/13, 1.0 mL min^{-1}).
ND, not determined; RT, room temperature.

Table 2 Yields and *ee* values, under the optimised conditions, for the conversion of iminoesters **5a–d** into chiral dimeric chromene derivatives **6a–d** (Scheme 1)[a]

Entry	R	X	Product	Yield[b] (%)	*ee*[c] (%)
1	*t*Bu	H	6a	98	91.2
2	Et	H	6b	93	88.7
3	*t*Bu	6-Br	6c	99	97.4
4	Et	6-Br	6d	96	89.1

[a]Reaction conditions: **5** (0.25 mmol), EtN_3 (0.025 mmol), $Cu(ClO_4)_2{\cdot}6H_2O$ (0.025 mmol), 4Å molecular sieves (two particles) and **L(f)** (0.028 mmol) in THF (3.0 mL).
[b]Isolated yield.
[c]Determined by chiral HPLC analysis (Daicel OD-H, hexane/*i*-propane).

$Cu(ClO_4)_2{\cdot}6H_2O$ and **L(f)** as the catalyst, Et_3N as the base, THF as the solvent with a substrate concentration of 0.08 M at room temperature.

Then, we applied the optimised experimental conditions to several more substrates by varying the substituents of compound **5** (Table 2). The reactions proceeded well in all cases (entries 1–4). Bulky substituents α to N (imine) impacted the results positively, due to steric hindrance (entry 1 *versus* entry 2; entry 3 *versus* entry 4). With bromine as the substituent, the substrates gave higher conversions and enantioselectivities (entry 3 99% yield and 97% *ee versus* entry 1; entry 4 *versus* entry 2). Overall, the new products were formed virtually quantitatively under the optimised conditions.

Examples of HPLC traces of the product **6a** are shown in Fig. 2. The optimised HPLC resolution condition for **6a** is Daicel OD-H column, hexane/*i*-propane (87/13) as eluent, 1.0 mL min^{-1} flow rate at room temperature.

The proposed reaction pathway is outlined in Scheme 2. Iminocoumarins **3** were prepared by Knoevenagel condensation in one-pot reactions from 2-hydroxybenzaldehyde derivatives **1** and malononitrile **2** in the presence of a catalytic amount of piperidine. The spontaneous cyclisation between the *o*-hydroxy group and the side chain cyano group of a transient intermediate led to the iminocoumarin derivatives **3**. The aldehydeamines **5** were obtained by the condensation of the imines **3** and the amino acid hydrochlorides **4**, with the precipitation of NH_4Cl. The 2-[(3-cyano-2*H*-chromen-2-ylidene)amino)acetates **5** then undergo a base catalysed intermolecular self-Michael-type reaction by attack of the α-C to N (imine) of one molecule onto the olefinic group of the other, to yield the 2-iminochromene dimers **6**. The enantioselectivity was generated from steric hindrance, which resulted from the coordination between the Cu^{II}/**L(f)** catalyst and the N (imine) atom and the ester group of **5**.

Experimental

Most of the starting materials were commercially available and were used without further purification. Solvents were dried and stored over 4 Å molecular sieves under nitrogen. Flash column chromatography was carried out on Liang Chen Gui Yuan Silica Gel 200–300 mesh and TLC on Yan Tai Jiang You plates. NMR spectra were obtained on a Bruker Avance-400 spectrometer (^1H NMR at 400 Hz, ^{13}C NMR at 100 Hz) in $CDCl_3$ using the solvent as internal reference (7.26 and 77.00 ppm, respectively for ^1H and ^{13}C). Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. Melting points were determined with an XT4 microscope electrothermal apparatus and are uncorrected. Enantiomeric excess values were determined with a Knauer S1050 HPLC instrument. Electron impact mass spectra (*m/z*, relative intensity (%)) were determined with an Agilent Technologies instrument working at 70 eV ionisation energy. IR spectra were recorded using a Bruker Alpha spectrophotometer with a ATR-Ge device. Elemental analyses were obtained on an Elementar Vario MICRO CUBE (Germany) elemental analyser.

*Synthesis of substituted 2-imino-2*H*-chromene-3-carbonitriles* **3***; general procedure* [19]

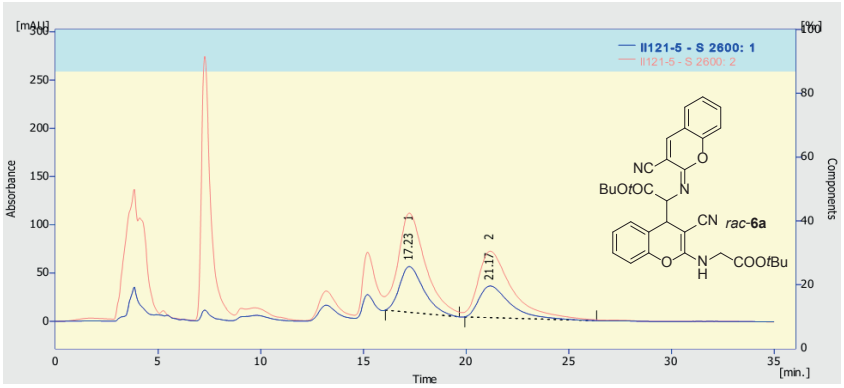
In an ice bath, malononitrile **2** (1.0 equiv.) was added to a solution of the aldehyde **1** (5.0 mmol) in EtOH (5.0 mL), and piperidine (one drop) was then added. The mixture was stirred at room temperature. Within 10 min, a pale yellow solid started to precipitate from the reaction mixture. Stirring was continued for a further 20 min. The yellow solid was filtered off and washed with petrol ether to give the pure products. **3a**: M.p. 162 °C (petrol ether) (lit.[20] 160–162 °C). **3b**: m.p. 198 °C (petrol ether) (lit.[19] 198–199 °C).

*Synthesis of substituted 2-[(3-cyano-2*H*-chromen-2-ylidene)amino) acetates* **5***; general procedure*

2-Imino-2*H*-chromene-3-carbonitrile **3** (1.5 mmol) was suspended in CH_2Cl_2 (40 mL). Glycine ester hydrochloride **4** (1.0 equiv.) was then added, and the reaction mixture became clear almost immediately but became cloudy after 1 h. The reaction was stirred at room temperature for a further 11 h. NH_4Cl was filtered off and the filtrate was concentrated and purified by flash column chromatography. Eluent: petrol ether/EtOAc = 5/1. Compounds **5** were obtained as white solids.

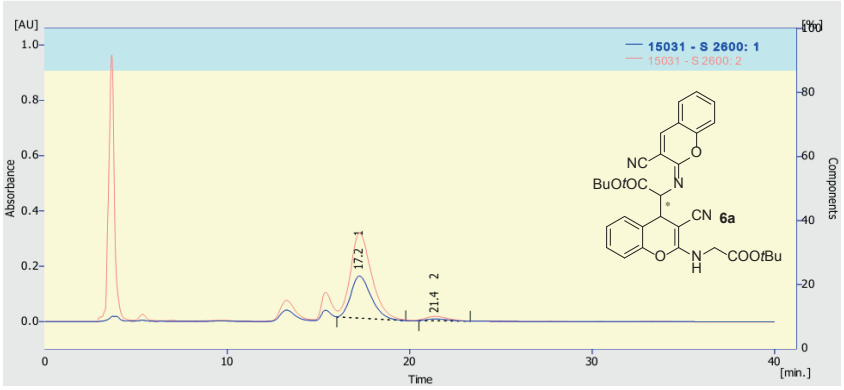
Synthesis of racemic/enantioselective substituted dimeric chromene derivatives **6***; general procedure*

THF (3.0 mL) was added to a Schlenck-type flask, containing $Cu(ClO_4)_2{\cdot}6H_2O$ (9.3 mg, 0.025 mmol) and ligand (for racemic product



Result Table (Uncal - Il121-5 - S 2600: 1)

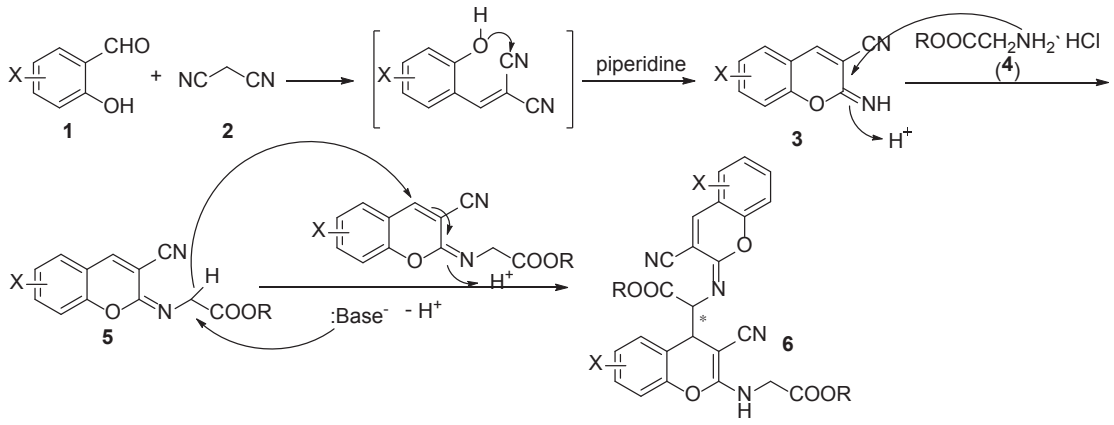
	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	17.233	3902.484	47.459	53.1	59.1	1.25	999
2	21.167	3443.058	32.804	46.9	40.9	1.52	988
	Total	7345.542	80.263	100.0	100.0		



Result Table (Uncal - 15031 - S 2600: 1)

	Reten. Time [min]	Area [mAU.s]	Height [mAU]	Area [%]	Height [%]	W05 [min]	Peak Purity [-]
1	17.233	11746.795	152.486	95.6	95.7	1.18	996
2	21.400	536.284	6.849	4.4	4.3	1.25	997
	Total	12283.078	159.335	100.0	100.0		

Fig. 2 HPLC traces of **6a.**



Scheme 2 Proposed reaction pathway for chiral 2-iminochromene dimmers.

6, PPh_3 13.1 mg, 0.050 mmol; for enantioselective product **6**, ferrocene ligand 15.6 mg, 0.028 mmol) under nitrogen. The catalyst was formed *in situ* after stirring for 15 min at room temperature. 2-[(3-cyano-2*H*-chromen-2-ylidene)amino]acetate **5** (0.250 mmol) and Et_3N (4 μL, 0.025 mmol) were added. The reaction mixture was stirred under nitrogen at room temperature for 24 h, and then allowed to warm to room temperature. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography on silica gel using mixtures of petrol ether-EtOAc as eluent.

*t-Butyl-2-[(3-cyano-*2H*-chromen-2-ylidene)amino]acetate* (**5a**): White solid; yield 97%; m.p. 105 °C (petrol ether); IR (KBr cm^{-1}): ν 2232, 1736, 1662, 1604 cm^{-1}; ^1H NMR: δ 7.73 (1H, s), 7.31 – 7.30 (1H, m), 7.11–7.09 (1H, m), 6.80–6.77 (2H, m), 3.80 (2H, s), 1.25 (9H, s); ^{13}C NMR: δ 172.6, 154.1, 151.9, 136.0, 133.2, 129.5, 124.8, 121.3, 116.5, 110.6, 97.1, 82.4, 57.6, 26.5 (3C); MS (EI, 70eV): M^+ *m/z* 285. Anal. calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85; found: C, 67.32; H, 5.86; N, 9.73%.

*Ethyl-2-[(3-cyano-*2H*-chromen-2-ylidene)amino]acetate* (**5b**): White solid; yield 56%; m.p. 99 °C (petrol ether); IR (KBr cm^{-1}): 2231, 1736,

1664; ^{1}H NMR: δ 7.74 (1H, s), 7.32–7.31 (1H, m), 7.11–7.09 (1H, m), 6.81–6.79 (2H, m), 4.37 (2H, s), 4.23 (2H, q, *J* = 7.1 Hz), 1.29 (3H, t, *J* = 7.1 Hz); ^{13}C NMR: δ 171.4, 153.6, 151.9, 136.7, 131.6, 129. 5, 122.7, 120.0, 116.4, 109.1, 97.0, 61.3, 49.2, 14.2; MS (EI, 70eV): M$^+$ *m/z* 257. Anal. calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93; found: C, 65.33; H, 4.79; N, 11.02%.

*t-Butyl-2-[(6-bromo-3-cyano-2*H*-chromen-2-ylidene)amino] acetate* (**5c**): Pale yellow solid; yield 98%; m.p. 143 °C (petrol ether); IR (KBr cm^{-1}): ν 2235, 1737, 1663, 1598; ^{1}H NMR: δ 7.65 (1H, s), 7.59 (1H, dd, *J* = 8.8, 2.3 Hz), 7.52 (1H, d, *J* = 2.3 Hz), 7.02 (1H, d, *J* = 8.8 Hz), 4.28 (2H, s), 1.50 (9H, s); ^{13}C NMR: δ 168.5, 152.6, 147.5, 142.4, 136.2, 131.0, 119.1, 117.7, 117.0, 114.0, 108.0, 81.5, 49.7, 28.1 (3C); MS (EI, 70eV): M$^+$ *m/z* 363. Anal. calcd for $C_{16}H_{15}BrN_2O_3$: C, 52.91; H, 4.16; N, 7.71; found: C, 52.80; H, 4.27; N, 7.66%.

*Ethyl-2-[(6-bromo-3-cyano-2*H*-chromen-2-ylidene)amino]acetate* (**5d**): Pale yellow solid; yield 83%; m.p. 128 °C (petrol ether); IR (KBr cm^{-1}): ν 2233, 1737, 1670, 1190; ^{1}H NMR: δ 7.68 (1H, s), 7.59 (1H, dd, *J* = 8.8, 2.3 Hz), 7.53 (1H, d, *J* = 2.2 Hz), 7.04 (1H, d, *J* = 8.8 Hz), 4.36 (2H, s), 4.23 (2H, q, *J* = 7.1 Hz), 1.30 (3H, t, *J* = 7.1 Hz); ^{13}C NMR: δ 169.5, 152.6, 147.6, 142.7, 136.3, 131.1, 119.1, 117.7, 117.1, 114.0, 107.9, 61.1, 48.9, 14.2; MS (EI, 70eV): M$^+$ *m/z* 335. Anal. calcd for $C_{14}H_{11}BrN_2O_3$: C, 50.17; H, 3.31; N, 8.36; found: C, 50.05; H, 3.44; N, 3.26%.

*t-Butyl-2-(2-[(2-(t-butoxy)-2-oxoethyl)amino]-3-cyano-4*H*-chromen-4-yl)-2-[(3-cyano-2*H*-chromen-2-ylidene)amino]acetate* (**6a**): White solid; yield 98%; m.p. 138 °C (petrol ether); IR (KBr cm^{-1}): ν 2209, 1736, 1657, 1620 cm^{-1}; ^{1}H NMR: δ 8.46 (1H, br s), 8.29 (1H, s), 7.71–7.55 (2H, m), 7.50–7.45 (2H, m), 7.33–7.17 (2H, m), 7.16–6.96 (2H, m), 4.55 (2H, s), 4.22–4.09 (1H, m), 2.33–2.21 (1H, m), 1.49 (9H, s), 1.30 (9H, s); ^{13}C NMR: δ 175.9, 168.1, 157.2, 155.4, 152.2, 145.8, 138.5, 133.3, 132.6, 128.3, 126.8, 126.2, 123.1, 121.0, 120.7, 118.4, 117.4, 117.2, 109.6, 98.3, 81.9, 81.6, 70.7, 65.4, 45.8, 42.0, 28.4 (6C); MS (EI, 70eV): M$^+$ *m/z* 569. Anal. calcd for $C_{32}H_{32}N_4O_6$: C, 67.59; H, 5.67; N, 9.85; found: C, 66.98; H, 5.73; N, 9.81%; HPLC (Daicel OD-H, hexane/*i*PrOH = 87/13, 1.0 mL min^{-1}, 215 nm) t_1 = 17 min (major), t_2 = 21 min (minor).

*Ethyl-2-(3-cyano-2-[(2-ethoxy-2-oxoethyl)amino]-4*H*-chromen-4-yl)-2-[(3-cyano-2*H*-chromen-2-ylidene)amino]acetate* (**6b**): White solid; yield 93%; m.p. 131 °C (petrol ether). IR (KBr cm^{-1}): ν 2212, 1733, 1644, 1610 cm^{-1}; ^{1}H NMR: δ 8.41 (1H, br s), 8.22 (1H, s), 7.74–7.59 (2H, m), 7.48–7.42 (2H, m), 7.36–7.19 (2H, m), 7.14–6.89 (2H, m), 4.33 (4H, s), 4.27–4.24 (4H, q, *J* = 6.8 Hz), 1.32–1.26 (6H, t, *J* = 7.1 Hz); ^{13}C NMR: δ 173.6, 170.3, 155.6, 154.1, 152.0, 147.8, 139.3, 133.6, 132.6, 129.5, 126.8, 125.4, 124.6, 121.0, 120.1, 118.2, 117.9, 117.2, 107.5, 95.4, 71.7, 62.8, 61.8, 61.2, 44.1, 41.2, 24.3, 24.2; MS (EI, 70eV): M$^+$ *m/z* 513. Anal. calcd for $C_{28}H_{24}N_4O_6$: C, 65.62; H, 4.72; N, 10.93; found: C, 65.58; H, 4.80; N, 10.88%; HPLC (Daicel OD-H, hexane/*i*PrOH = 88/12, 0.8 mL min^{-1}, 215 nm) t_1 = 21 min (major), t_2 = 26 min (minor).

*t-Butyl-2-(6-bromo-2-[(2-(t-butoxy)-2-oxoethyl]amino)-3-cyano-4*H*-chromen-4-yl)-2-[(6-bromo-3-cyano-2*H*-chromen-2-ylidene) amino]acetate* (**6c**): Yellow solid; yield 99%; m.p. 152 °C (petrol ether); IR (KBr cm^{-1}): ν 2210, 1732, 1654, 1619 cm^{-1}. ^{1}H NMR: δ 8.01 (1H, s), 7.66 (1H, s), 7.58–7.54 (2H, m), 7.47 (1H, d, *J* = 2.1 Hz), 7.31–7.29 (1H, m), 6.98–6.86 (2H, m), 4.46 (1H, d, *J* = 2.6 Hz), 4.21–4.03 (2H, m), 2.05 (1H, s), 1.49 (9H, s), 1.44 (9H, s); ^{13}C NMR: δ 170.4, 167.3, 156.7, 154.6, 152.1, 147.0, 139.8, 135.4, 134.2, 132.1, 129.1, 122.4, 121.5, 121.2, 121.1, 120.8, 118.8, 117.6, 109.5, 98.5, 82.0, 81.2, 71.0, 64.3, 45.2, 41.0, 29.1, 28.41 (6C); MS (EI, 70eV): M$^+$ *m/z* 725. Anal. calcd for $C_{32}H_{30}Br_2N_4O_6$: C, 52.91; H, 4.16; N, 7.71; found: C, 52.66; H, 4.03; N, 7.82%; HPLC (Daicel OD-H, hexane/*i*PrOH = 90/10, 1.0 mL min^{-1}, 215 nm) t_1 = 25 min (major), t_2 = 32 min (minor).

*Ethyl-2-(6-bromo-3-cyano-2-[(2-ethoxy-2-oxoethyl)amino]-4*H*-chromen-4-yl)-2-[(6-bromo-3-cyano-2*H*-chromen-2-ylidene)amino] acetate* (**6d**): Yellow solid; yield 96%; m.p. 146 °C (petrol ether); IR (KBr cm^{-1}): ν 2204, 1735, 1650, 1623 cm^{-1}; ^{1}H NMR: δ 8.22 (1H, s), 7.66 (2H, s), 7.61 (1H, d, *J* = 8.8 Hz), 7.53 (1H, s), 7.28 (1H, s), 7.06-7.04 (2H, m), 4.37 (4H, s), 4.28-4.23 (4H, q, *J* = 7.0 Hz), 1.33-1.28 (6H, t, *J* = 7.1 Hz); ^{13}C NMR: δ 173.9, 171.5, 155.6, 153.6, 152.9, 146.0, 139.4, 135.4, 134.2, 132.1, 129.8, 123.7, 121.3, 121.4, 121.1, 120.2, 119.6, 118.1, 109.5, 97.6, 71.7, 64.2, 61.7, 61.1, 45.6, 41.6, 14.7, 14.6; MS (EI, 70eV): M$^+$ *m/z* 671. Anal. calcd for $C_{28}H_{22}Br_2N_4O_6$: C, 50.17; H, 3.31; N, 8.36; found: C, 50.09; H, 3.26; N, 8.41%; HPLC (Daicel OD-H, hexane/*i*PrOH = 92/8, 1.0 mL min^{-1}, 215 nm) t_1 = 27 min (major), t_2 = 36 min (minor).

Conclusions

In summary, new 2-iminochromene dimers were successfully prepared under mild condition. In addition, siloxane-substituted FOXAP ligand **L(f)** was successfully applied in the enantioselective self-Michael reactions of **5** with satisfactory yields (up to 99%) and excellent *ee* values (up to 97% *ee*). Further investigation of the range of the substrate, the absolute configuration of the product, and the application of the dimers are underway.

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