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A study into asymmetric Nicholas cyclisation reactions

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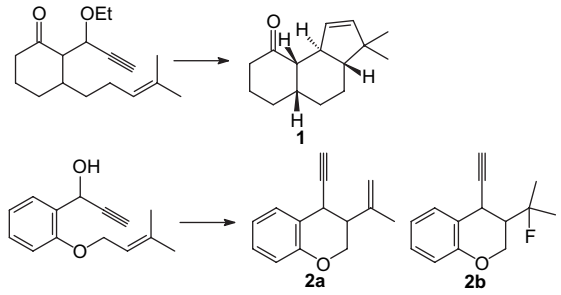
Abstract—Three systematic approaches have been employed to investigate asymmetric Nicholas reactions. We found that the use of a chiral *N*-enoyl derivative provided acceptable levels of selectivity for an intermolecular Nicholas reaction, however, we were unable to identify an auxiliary that could be utilized in an asymmetric conjugate addition and a tandem inter/intramolecular series of Nicholas reactions. The use of chiral pool non-racemic propargyl alcohols, derived from citronellal, provided enhanced levels of selectivity. As a result of these studies we developed a series of Nicholas cyclisations derived from chiral non-racemic salicylaldehyde derivatives. These underwent an extremely rapid and highly efficient cyclisation, under Nicholas conditions, to afford a range of benzopyrans. The adjacent stereogenic centres appear to be formed with high levels of stereocontrol.

1. Introduction

Previously we reported an extremely efficient and highly diastereoselective synthesis of tricyclic compounds **1**[1] and benzopyrans **2a** and **2b**[2] (Scheme 1). The chemistry, which was developed in our laboratory, involves a novel variant of an intramolecular Nicholas cyclisation reaction[3] followed by an in situ oxidative decomplexation step.

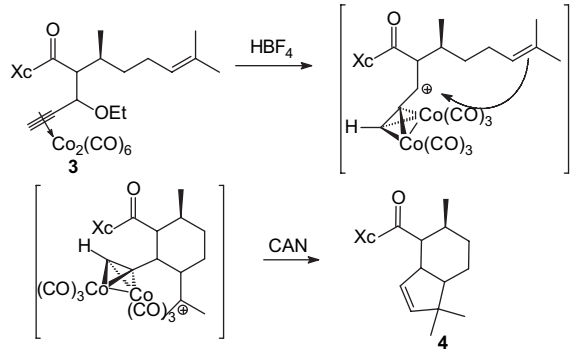


Scheme 1.

In common with others working in this area of organocobalt chemistry[4] we were keen to explore any stereoconvergent capabilities[5] of Nicholas cation in an effort to enhance the stereoselective outcome of the reaction. Most recently we have focused upon investigating an asymmetric variant of Nicholas cyclisation reactions summarized above. Three approaches are discussed involving the use of chiral auxiliary technology, substrates derived from the chiral pool and thirdly the use of chiral propargyl alcohols.

2. Results and discussion

For our initial study we envisaged that exposure of the chiral complex **3** with a Lewis acid would initiate an intramolecular Nicholas cyclisation reaction. Oxidative decomplexation of cobalt hexacarbonyl should, by analogy with the formation of **1**, facilitate a further ring closure to afford **4** (Scheme 2).



Scheme 2.

The synthesis of compound **4** should be readily achieved in three steps comprising of an asymmetric conjugate addition to an *N*-acyloxazolidinone such as **5** to provide **6**. Exposure of the boron enolate[6] derivative of **6** to hexacarbonyl[propiolaldehyde diethyl acetal]dicobalt would provide the

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cyclisation precursor **7** via an intermolecular Nicholas reaction (Fig. 1). The choice of chiral auxiliary (X_c) was crucial in order to provide optimum facial selectivity for the conjugate addition reaction as well as for both the intermolecular and intramolecular Nicholas reactions.

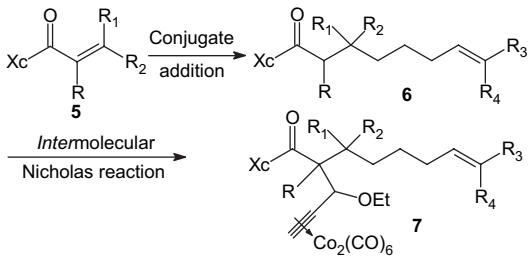
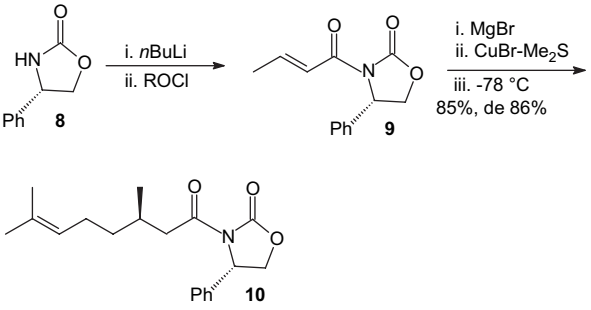


Figure 1.

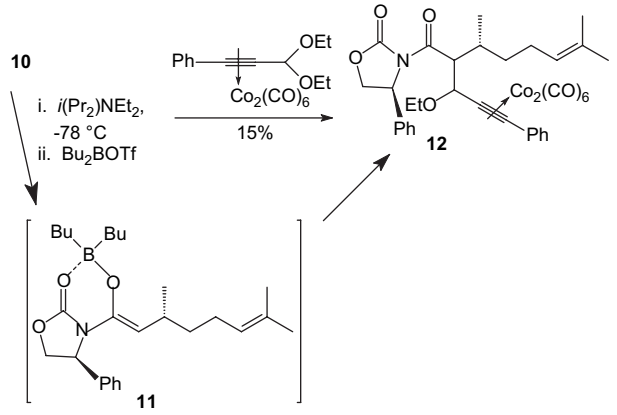
The use of organocopper reagents, in conjugate addition reactions, is of major importance as a synthetic methodology[7] and recent development in this chemistry is in the use of activating agents to promote the reaction.[8] In addition, the use of chiral 2-oxazolidinones[9] that serve as an efficient chiral auxiliaries have also made an impact in providing access to asymmetric conjugate additions.[10] Although we screened a number of chiral auxiliaries for the conjugate addition reaction[11] we obtained optimum levels of diastereoselectivity with the use of (*S*)-(−)-4-benzyl-2-oxazolidinone **8**. The method of choice[12] involves addition of a mixture containing copper(I) bromide–dimethyl sulfide complex and an appropriate Grignard derivative, maintained at −78 °C, to a precooled THF solution of the chiral *N*-enoyl derivative **9** (Scheme 3).[13]



Scheme 3.

The adduct **10** was obtained efficiently with a diastereomeric excess of 86%.[14] With the appropriately functionalised acylated auxiliary **10** in hand we turned our attention to investigate its suitability in an intermolecular Nicholas reaction. Previously it has been shown that Nicholas cation is prone to enantiomerisation as a result of the fluxional nature of the cobalt stabililised cation, which exposes both faces to the attacking nucleophile. The same authors, however, have also shown that with chiral propionimide metal enolates, such as **11**, a stereodifferentiation process results in kinetic resolution of the racemising cation.[5]

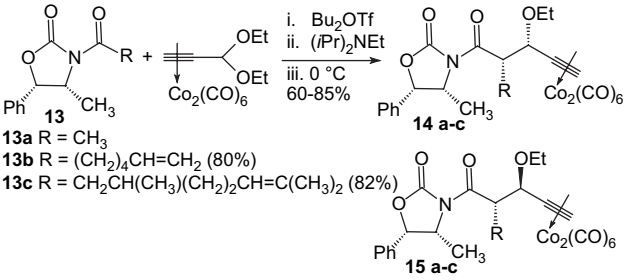
Our attempt at Nicholas reaction with a chiral boron enolate is shown (Scheme 4). The boron enolate **11** was generated by exposure of **10** with Hunig's base and dibutylboron triflate. The corresponding dicobalt hexacarbonyl complex was formed in a quantitative yield by exposure of phenylpropargyl aldehyde diethyl acetal to dicobalt octacarbonyl in dichloromethane. Analysis of the reaction mixture, by TLC, 30 min after the addition of the complex to the preformed enolate showed the presence of a new compound. This was isolated and purified to afford Nicholas adduct **12** in a very low yield.[15]



Scheme 4.

Analysis of complex **12** by ^{1}H NMR spectroscopy enabled the diastereomeric excess (de) of 50% to be determined. Our attempts to improve the unexpectedly poor yield of this rather routine transformation were thwarted. In particular we explored changes in the stoichiometry of the reagents, the temperature and solvent effects as well as the in situ generation of the boron enolate, which provided no enhancement in yield. Molecular modelling of enolate **11** (Quantam CAChe) suggested that steric hindrance between the phenyl group, at C-4 of the isoxazolidinone ring, and the β-methyl group offered an explanation. Thus although the *N*-enoyl derivative **9** provided the highest levels of diastereoselectivity for asymmetric conjugate addition reactions the corresponding intermolecular Nicholas reaction was impeded as a result of steric congestion about the alkylating centre.

In our efforts to identify a versatile auxiliary we considered the use of 4-methyl-5-phenyl-2-oxazolidinone. This has been shown to provide good levels of selectivity for intermolecular Nicholas reactions[5] involving simple *N*-acyl derivatives such as **13a**, however, our investigation required the use of more elaborate *N*-acylated compounds such as **13b/13c** (Scheme 5).



Scheme 5.

In contrast to our previous attempts Nicholas adducts were obtained in good yields and consistently enhanced diastereoselectivities **14a/15a** (60% and de of 84%),[17] **14b/15b** (80% and de of 72%) and **14c/15c** (85% and de of 80%). Alkylation reactions with this particular auxiliary have been shown to favour the major diastereoisomer bearing a *syn* relationship.[4c,5,16] In these examples the coupling constant, *J*, for the propargylic proton for the major diastereoisomer varied from 1.83 Hz (**14b**) to 4.4 Hz (**14c**). The rationale[5] proposes a double stereodifferentiation via the two *syn* cobalt cations shown as **16** and **17** (Fig. 2). Reaction of the *Z*-boron enolate with cation **16** is predicted to take place rapidly to afford the *syn* product. Cation **16** can also undergo antarafacial migration of the alkylidene moiety to afford the second *syn* cation **17**. The reaction of cation **17** with the boron enolate is predicted to be slower than **16** as a result of a 'steric mismatch' between the OEt of cation **17** and the bulky butyl group bound to the boron atom of the enolate. This coupling is predicted to afford the *anti*-isomer. The stereochemical outcome for this reaction may be explained in terms of the rapid fluxional nature of the cation. This occurs at a rate faster than the alkylation reaction itself, however, the alkylation reaction then occurs at different rates with the chiral enolate affording a kinetic resolution.

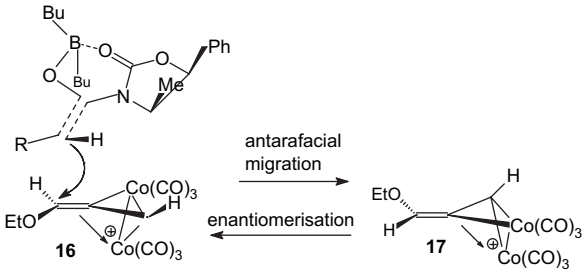
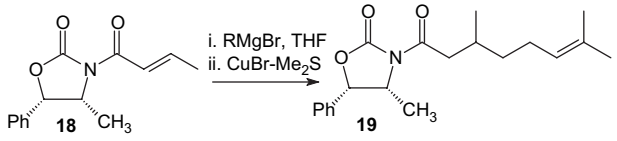


Figure 2.

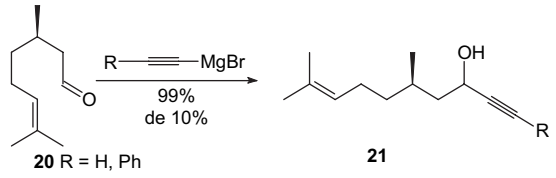
Having established the utility of 4-methyl-5-phenyl-2-oxazolidinone in a Nicholas reaction we next determined its suitability in an asymmetric conjugate addition reaction. This requirement was essential in order to extend the range of cyclisation precursors (Scheme 6). Conjugate addition to the *N*-enoyl **18** took place in a yield of 78% to afford **19** and, from our initial analysis, with excellent stereoselectivity. However, as a precaution we hydrolysed **19** to the acid for conversion to the corresponding chiral ester derivative. With the ester in hand ^{1}H NMR studies were used to determine the selectivity of the conjugate addition reaction.[18] Results from these chiral derivatisation studies showed that the conjugate addition reaction had produced an equimolar mixture of adducts with no apparent selectivity at all. Thus our endeavours to investigate a stereoselective Nicholas reaction using a chiral auxiliary to provide variation in the alkenyl derivatives, via conjugate additions, as well as stereocontrol



Scheme 6.

in the subsequent tandem inter/intramolecular Nicholas reaction/s could not be realized with these substrates.

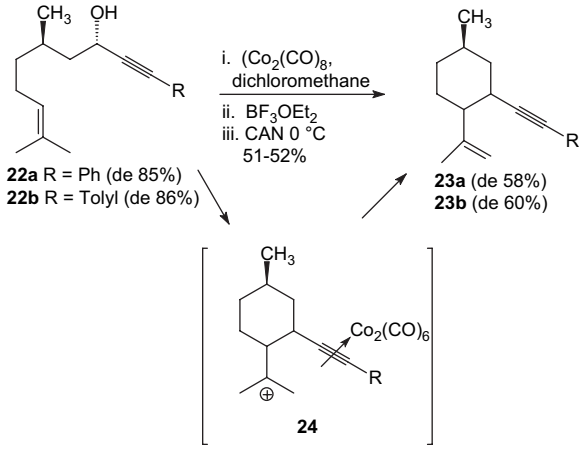
In order to pursue our goal we investigated the use of substrates derived from the chiral pool of natural products. Initially we identified citronellal **20** as a suitable candidate that could provide a chiral centre, β- to the propargyl alcohol moiety in **21**, and containing an appropriately positioned trisubstituted alkenyl group to effect an intramolecular Nicholas cyclisation. However, despite the fact that the alkynylation reactions occurred in virtually quantitative yields the levels of diastereoselectivity achieved were disappointingly low (Scheme 7).



Scheme 7.

In an attempt to overcome this we focused our attention to the synthesis of the corresponding chiral optically pure propargyl alcohols. We found that the direct asymmetric alkynylation of **20**, as described by Carreira,[19] to be a far more efficient approach than the alternative route involving an initial oxidation of propargyl alcohol **21**, to a propargyl ketone, followed by a diastereoselective reduction to a chiral propargyl alcohol.[20]

The asymmetric alkynylation involved the addition of a zinc acetylide to an aldehyde such as **20** in the presence of a stoichiometric chiral ligand such as *N*-methylephedrine. For these studies the two propargyl alcohols **22a/22b** were produced with good selectivity[17,21] and each were then subjected to our one-pot Nicholas cyclisation. This provided optically active cyclised products **23a/23b** in an average 80% yield for each of the three transformations consisting of complexation, cyclisation and oxidative decomplexation of the cobalt carbonyls (Scheme 8).



Scheme 8.

A noteworthy feature of these reactions was the predominant formation of the disubstituted alkenyl derivative **23**, derived

from cluster **24**, in preference to a more stable tetrasubstituted exocyclic double bond. The diastereoselectivity of the crude product mixtures of **23a** and **23b** was determined by GC–MS. This method of analysis provided sufficiently good separation of diastereoisomers to enable the diastereoselectivity to be ascertained. Attempts to separate the major diastereoisomer from the minor, by chromatography, met with limited success, however, we are fairly confident that both **23a** and **23b** share the same relative cis/trans configuration at the newly formed stereocentres. This deduction is based upon the similar chemical shifts for C-1 and C-2 for **23a** and **23b** in the ^{13}C NMR spectra. The use of ^{13}C NMR chemical shift data[22] for comparing the relative stereochemistry of a compound with ^{13}C NMR data from libraries of analogous compounds is not without precedent.[23] In Figure 3 the ^{13}C NMR chemical shifts for C-1 and C-2 of 2-methylcyclohexanol are shown. For the cis compound C-1 resonates at δ 71.1 ppm and C-2 at δ 35.5 ppm whereas for the corresponding trans isomer these chemical shifts are deshielded at δ 76.6 and 39.7 ppm, respectively. For compound **23a** C-1 occurred at δ 34.8 ppm and C-2 at δ 51.2 ppm whereas for **23b** C-1 resonated at δ 34.2 ppm and C-2 at δ 51.2 ppm, respectively. We were left to conclude from this study that the use of optically active propargyl alcohols, based upon citronellal derivatives, provided optically active cyclised products, however, with an optimised de of 58–60% stereochemical scrambling would limit the usefulness of these substrates.

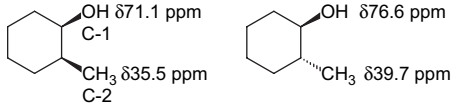


Figure 3.

In order to improve upon the observed selectivity we considered the use of a salicylaldehyde derivative. We reasoned that with this substrate both the chiral non-racemic propargyl alcohol as well as the alkenyl moiety would be constrained by the presence of an aromatic ring. The presence of a bulky substituent, R_1, in the stabilized complex, has been shown to strongly favour the formation of a cation as a single *syn*-diastereoisomer.[7] In the examples shown (Fig. 4) it may be observed that for a substituent R_1=Me the ratio of *syn*/*trans* diastereoisomers is 1.4:1, however, as the methyl substituent is replaced by a bulkier group, i.e., R_1=^{t}Bu the *syn*-diastereoisomer prevails >95:1.

We therefore concluded that this phenomenon may reduce any tendency for scrambling at the propargylic centre and

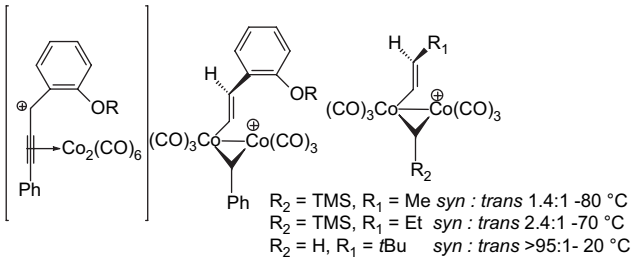
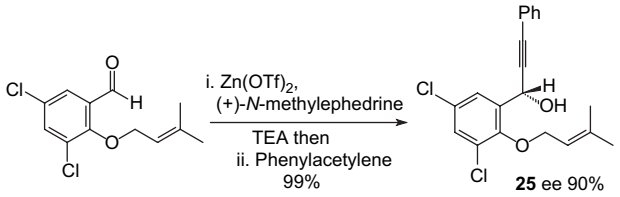


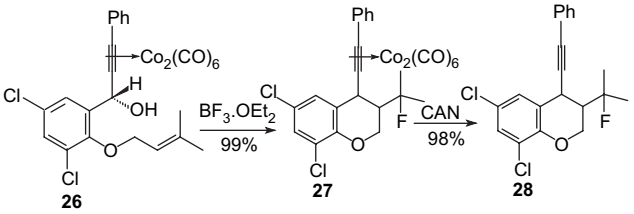
Figure 4.

hence reduce the propensity for racemisation. The selection of a suitable range of candidates for screening was based upon results obtained from our previous study on the enantioselectivity of the asymmetric alkynylation reaction. During the course of these investigations, using salicylaldehyde derivatives,[21,24] we established that both the yield and the enantioselectivity of the zinc-mediated asymmetric alkynylation reactions with salicylaldehyde derivatives were highly dependant upon the electronic nature of the aromatic ring. We found that the highest levels of enantioselectivity were observed in substrates in which the aromatic ring contains strategically placed electron withdrawing groups. On this basis our first candidate was identified (Scheme 9).



Scheme 9.

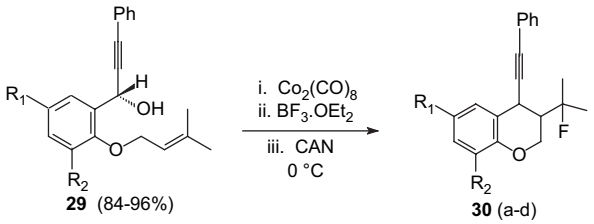
In general the chiral non-racemic propargyl alcohols used for these studies were obtained in excellent yields and with a high level of enantioselectivity,[24] for example, (*R*)-(+)-**25** was obtained in quantitative yield and with an enantiomeric excess of 90%[25] (Scheme 9). With the desired propargyl alcohol **25** in hand we were able to investigate the corresponding Nicholas cyclisation reaction. Exposure of **25** to a stirred dichloromethane solution of dicobalt octacarbonyl at an ambient temperature provided the corresponding complex **26** in a quantitative yield. Exposure of the dicobalt hexacarbonyl complex **26** to the Lewis acid, $BF_3{\cdot}OEt_2$ at 0 °C, led to an extremely rapid cyclisation reaction to afford the complexed cycloadduct **27**. The speed of the reaction was a noteworthy feature as this was completed within the time it took for us to carry out a TLC analysis (Scheme 10).



Scheme 10.

As well as the speed of the reaction, with complete conversion to products within 2-3 min by TLC analysis, we were also surprised at the efficiency of the transformation, which provided benzopyran **27** as a single optically active isolate in a quantitative yield. Polarimetry, performed upon a dilute solution of the highly coloured complex **27**, gave an $[\alpha]_D^{18}$ +50 (*c* 0.02, $CHCl_3$). Oxidative decomplexation was accomplished using ceric ammonium nitrate (CAN) to afford **28** as the sole product again in a virtually quantitative yield and with an $[\alpha]_D^{18}$ −10 (*c* 0.1, $CHCl_3$). Analysis of the crude compound **28**, using chiral HPLC[25] and ^1H NMR in the presence of a chiral shift reagent, indicated that it was synthesised as a single isomer. We were very surprised at the high

level of stereocontrol exhibited during Nicholas cyclisation with minimal scrambling at either of the newly formed asymmetric centres. We thus assume that as the cyclisation proceeds via a dicobalt hexacarbonyl stabilized cation a tandem convergence in stereochemistry occurs initially at the propargyllic position as well as in the formation of the contiguous stereogenic centre. The propargylic methine proton in **28** appeared as a doublet at δ 4.09 ppm with a coupling constant J of 5.1 Hz suggesting a cis-relationship. In order to probe the generality of the cyclisation reaction we carried out further experiments with additional chiral non-racemic propargyl alcohols **29a–d** (Scheme 11).



Scheme 11.

It was very gratifying to us that the precursors **29a–d** underwent a swift and efficient intramolecular Nicholas cyclisation reaction to afford the optically active benzopyrans **30a–d**. Having secured the synthesis of five cycloadducts we were then able to use the available spectroscopic data, obtained from the crude product, to ascertain that these benzopyrans were all stereochemically related to each other. Considering the coupling constant, J, for the benzylic proton (entries 1–5) all show consistency in magnitude. A similar trend emerges when comparing the chemical shift data for C-3 and C-4 indicating that these benzopyrans share a common relative stereochemistry (Table 1).

Table 1

Entry	Compound	J[a] Hz	δ[b]	δ[c]
1	**28**	5.1	47.17	28.99
2	**30a**	5.5	47.19	29.04
3	**30b**	5.3	47.29	28.82
4	**30c**	5.3	47.32	28.90
5	**30d**	5.8	46.64	29.21

[a] ^{1}H NMR δ (ppm) for benzyl doublet.
[b] ^{13}C NMR δ (ppm) for C-4 benzyl carbon.
[c] C-3.

3. Conclusions

During the course of these studies we have investigated three methods to effect a stereoselective Nicholas reaction. Although we were unable to find a suitable chiral auxiliary, based upon an *N*-acylated oxazolidinone, for this purpose citronellal derivatives underwent Nicholas cyclisations to afford trisubstituted cyclohexanes with acceptable diastereoselectivities. In contrast chiral non-racemic propargyl alcohols derived from salicyladehydes underwent a smooth and highly efficient intramolecular Nicholas cyclisation reaction to afford optically active benzopyrans. A most noteworthy feature in this series of cyclisations was that complete control was exerted during the formation of the two contiguous stereogenic centres.

4. Experimental

4.1. General[26]

Melting point determinations were recorded using a Stuart Scientific SMP3 digital melting point apparatus tube apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrophotometer and were calibrated using a standard polystyrene film. The spectra were recorded either as thin films for liquids between sodium chloride discs or for solids as a Nujol mull. All infrared data are quoted in wave numbers (cm^{-1}). Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz using a JEOL Eclipse 400 MHz spectrometer. Peak positions are quoted using the δ scale relative to tetramethylsilane (δ=0) as an internal standard. Carbon-13 NMR spectra (^{13}C NMR) were recorded at 100 MHz on a JEOL Eclipse 400 MHz spectrometer using deuterochloroform as an internal standard. Low resolution mass spectra were recorded on a VG TRIO-2 mass spectrometer under electron impact conditions at an ionising potential of 70 eV and/or with a Hewlett–Packard GC–MS HP5890 (GC) with capillary column and HP 5971 (MS). Accurate mass analyses were performed and reported on a VG-ZAB-E under EI conditions by the EPSRC National Mass Spectrometry Service Centre (Swansea) using the EI Peak Match on M+ method. Reactions were carried out under an atmosphere of dry nitrogen unless otherwise stated.

4.1.1. (*S*)-4-Benzyl-*N*-3-(*S*)-(3,7-dimethyloct-6-enoyl)-2-oxazolidinone (10). To a dry THF solution of 2-methyl-6-bromopent-2-ene (0.9 mL, 6.7 mmol) was added magnesium turnings (0.32 g, 12.6 mmol). The mixture was stirred at an ambient temperature for 30 min and cooled to −40 °C whereupon a copper bromide dimethylsulfide complex (0.67 g, 3.24 mmol) in dry THF (5 mL) and dimethylsulfide (3 mL) were added. The reaction was left to stir for about 15 min and then warmed to −15 °C whereupon the *N*-acyloxazolidinone **9** (0.50 g, 2.1 mmol) dissolved in dry THF (5 mL) was added via a cannula. After 30 min the cold bath was removed and the reaction mixture allowed to reach an ambient temperature over a period of 2 h. The reaction mixture was then quenched, by the addition of a saturated solution of ammonium chloride (15 mL), and the solvent removed in vacuo. Ethyl acetate was added (15 mL) and the organic layer separated and washed sequentially with a 10% aqueous solution of ammonia (2×20 mL), water (1×20 mL) and a saturated solution of sodium chloride (1×20 mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent removed in vacuo to afford the title compound as a colourless oil. Purification by chromatography on silica[27] (7:3 hexane/ethyl acetate) gave the Michael adduct **10** (0.60 g, 85%). ν_{max}/cm^{-1} (film) 2965, 1775, 1699, 1456, 1354, 1276, 1236, 1100; $[\alpha]_D^{20}$ −25.8 (*c* 0.46, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.41–7.24 (5H, m, Ar*H*), 5.42 (1H, dd, *J* 8.8, 3.7 Hz, O–CH_2), 5.06–5.01 (1H, m, C*H*=$(CCH_3)_2$), 4.66 (1H, t, *J* 8.8 Hz, N–

C*H*), 4.25 (1H, dd, *J* 8.8, 3.7 Hz, O–CH_2), 3.01 (1H, dd, *J* 16, 5.2 Hz, O=C–CH_2), 2.74 (1H, dd, *J* 16.0, 8.5 Hz, O=C–CH_2), 2.09–1.90 (3H, m, CH_2 and C*H*), 1.65 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.38–1.08 (2H, m, CH_2), 0.84–0.82 (3H, d, *J* 6.6 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 172.3, 153.7, 139.2, 131.4, 129.1, 128.9, 125.9, 124.3, 69.8, 57.6, 42.4, 36.8, 29.3, 25.7, 25.4, 19.6, 17.6; *m*/*z* (EI^+) Calcd for $C_{19}H_{25}NO_3$: 333.2173 $[M+NH_4]^+$, found: 333.2170.

4.1.2. (4*R*,5*S*)-(+)-4-Methyl-5-phenyl-*N*-(3-propionyl)-2-oxazolidinone (13a). To a stirred dry THF solution (20 mL) of (4*R*,5*S*)-(+)-4-methyl-5-phenyloxazolidinone (1.5 g, 8.47 mmol) maintained at −78 °C under an atmosphere of nitrogen was added, dropwise, *n*-BuLi (3.4 mL of a 2.5 mol solution, 8.5 mmol). When the addition was complete freshly distilled propionyl chloride (0.82 mL, 9.32 mmol) was added dropwise to the orange reaction mixture. The resulting solution was left to stir at −78 °C for 30 min and then allowed to slowly reach an ambient temperature. The reaction was quenched by the addition of a saturated solution of ammonium chloride (40 mL). The solvent was removed in vacuo and replaced with ethyl acetate (30 mL). The organic layer was extracted and washed sequentially with saturated sodium bicarbonate solution (1×20 mL) and brine (2×25 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed in vacuo. Purification of the crude product was undertaken by chromatography on silica (hexane/ethyl acetate 7:3) to afford the title compound as a white crystalline solid (1.88 g, 95%) mp 96–97 °C. ν_{max}/cm^{-1} (film) 2981, 2939, 1780, 1694, 1644, 1371, 1243, 1070; $[\alpha]_D^{20}$ +48.8 (*c* 0.25, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.42–7.27 (5H, m, Ar*H*), 5.64 (1H, d, *J* 7.3 Hz, Ph–C*H*), 4.78–4.72 (1H, m, N–C*H*), 3.04–2.86 (2H, m, CH_3–CH_2), 1.15 (3H, t, *J* 7.3 Hz, CH_3), 0.87 (3H, d, *J* 6.6 Hz, CH–CH_3); δ_C (100 MHz, $CDCl_3$) 173.8, 153.1, 133.3, 128.7, 128.6, 125.6, 78.9, 54.7, 29.2, 14.5, 8.2; *m*/*z* (EI^+) Calcd for $C_{13}H_{15}NO_3$: $[M+NH_4]^+$ 251.1390, found: 251.1390.

4.1.3. (4*R*,5*S*)-(3)-(1-Oxo-3-methyloct-7-enoyl)-4-methyl-5-phenyl-2-oxazolidinone (13b). This was prepared as previously described for **13a** to afford the title compounds as a colourless oil (0.93 g, 80%). ν_{max}/cm^{-1} (film) 2931, 1782, 1699, 1456, 1347, 1219, 1198; $[\alpha]_D^{20}$ +10.7 (*c* 0.48, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.43–7.27 (5H, m, Ar*H*), 5.85–5.75 (1H, m, C*H*=CH_2), 5.66 (1H, d, *J* 7.3 Hz, CH–Ph), 4.97 (1H, dd, *J* 17.2, 1.5 Hz, =CH_2), 4.91 (1H, dd, *J* 10.2, 1.5 Hz, =CH_2), 4.79–4.73 (1H, m, N–C*H*), 2.96 (1H, dd, *J* 16.0, 8.4 Hz, CH_2–CO), 2.91–2.80 (2H, m, CH_2), 2.67 (1H, dd, *J* 16.0, 8.4 Hz, CH_2–CO), 2.14–1.96 (3H, m, CH_2 and C*H*), 1.49 (2H, m, =CH–CH_2), 0.94 (3H, apparent dd, *J* 6.6, 5.9 Hz, N–CH–CH_3), 0.87 (3H, d, *J* 7.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 173.1, 153.2, 138.8, 135.3, 129.0, 128.7, 126.7, 114.4, 78.8, 54.7, 42.5, 36.3, 33.8, 29.2, 19.6, 14.5; *m*/*z* (EI^+) Calcd for $C_{19}H_{25}NO_3$: $[M+NH_4]^+$ 333.2173, found: 333.2169.

4.1.4. (4*R*,5*S*)-(3)-(1-Oxo-3-methyloct-7,7-dienoyl)-4-methyl-5-phenyl-2-oxazolidinone (13c). (*S*)-(−)-Citronellic (1.0 mL, 5.42 mmol), oxalyl chloride (0.8 mL, 9.02 mmol) and 1 drop of DMF were stirred at an ambient temperature under an atmosphere of nitrogen gas. Once the acid was consumed, by TLC analysis, the mixture was evaporated in vacuo and dissolved in dichloromethane (10 mL). In a separate flame-dried flask was added (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone (0.64 g, 3.61 mmol) in THF (5 mL) and maintained at a temperature of −78 °C with stirring. After 10 min BuLi (1.5 mL, 3.61 mmol) was added dropwise and left to stir for a further 10 min whereupon the acid chloride derivative was added dropwise and left stirring until the flask reached an ambient temperature. The solvent was removed in vacuo and the crude reaction mixture was purified by chromatography on silica to afford the title compound as an oil (1.18 g, 82%). ν_{max}/cm^{-1} (film) 2933, 1781, 1699, 1455, 1347, 1221, 1197, 915, 733, 700; δ_H (300 MHz, $CDCl_3$) 7.43–7.27 (5H, m, Ar*H*), 5.63 (1H, d, *J* 7.3 Hz, Ph–C*H*), 5.11–5.07 (1H, m, =C*H*), 4.80–4.73 (1H, m, N–C*H*), 2.85 (2H, d, *J* 6.9 Hz, COCH_2), 2.11–1.92 (3H, m, CH_2 and C*H*), 1.67 (3H, s, =CCH_3), 1.59 (3H, s, =CCH_3), 1.46–1.35 (1H, m, =CH–CH_2), 1.29–1.19 (1H, m, CH_2), 0.97 (3H, d, *J* 6.6 Hz, N–CH–CH_3), 0.87 (3H, d, *J* 7.2 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 172.5, 153.2, 135.4, 133.3, 128.7, 125.6, 124.3, 78.8, 54.7, 42.5, 36.8, 29.2, 25.4, 19.5, 17.6, 14.5; *m*/*z* (EI^+) Calcd for $C_{20}H_{27}NO_3$: $[M+H]^+$ 330.2064, found: 330.2068.

4.1.5. Hexacarbonyl[(4*R*,5*S*)-(*N*)-[3-ethoxy-2-methylpent-5-ynoyl]-4-methyl-5-phenyloxazolidin-2-one]dicobalt (14a). (4*R*,5*S*)-(+)-4-Methyl-5-phenyl-*N*-(3-propionyl)-2-oxazolidinone **13a** (0.5 g, 2.14 mmol) was transferred to a flame-dried round-bottomed flask under an atmosphere of argon. Dry dichloromethane (10 mL) was added and the resulting solution was cooled to −78 °C. Diisopropylamine (0.45 mL, 2.31 mmol) and dibutylboron triflate (4.75 mL of a 1.0 M solution, 4.75 mmol) were added sequentially and the mixture left to stir for 15 min. Propiolaldehyde diethyl acetal–dicobalt hexacarbonyl complex (0.90 g, 2.35 mmol) in DCM (5 mL) was added dropwise with continual stirring. The cold temperature bath was removed and the mixture allowed to warm to an ambient temperature (about 1 h) whereupon the mixture was partitioned with water. The aqueous phase was extracted with DCM (3×10 mL), and the combined organic phases dried over anhydrous magnesium sulfate and filtered in vacuo to afford the title compound as a dark red oil (0.76 g, 60%). The diastereoselectivity was determined by analysis of the NMR of the crude reaction mixture (de 84%). Major diastereoisomer: ν_{max}/cm^{-1} (film) 2965, 2930, 2355, 2093, 2056, 2030, 1783, 1694, 1339, 1192, 1118, 733; δ_H (300 MHz, $CDCl_3$) 7.41–7.27 (5H, m, Ar*H*), 6.05 (1H, s, CH), 5.62 (1H, d, *J* 7.3 Hz, Ph–C*H*), 4.83–4.69 (1H, m, N–C*H*), 4.55 (1H, d, *J* 9.8 Hz, C–C*H*), 4.24–4.17 (1H, m, CH_3–C*H*), 3.83–3.76 (1H, m, O–CH_2), 3.57–3.50 (1H, m, OCH_2), 1.24 (3H, d, *J* 6.9 Hz, CH_3), 1.14 (3H, t, *J* 7 Hz, CH_2CH_3), 0.86 (3H, d, *J* 6.8 Hz, CH–CH_3); δ_C (100 MHz, $CDCl_3$) 173.7, 153.1, 153.1, 152.5, 133.3, 128.7, 128.6, 125.6, 82.3, 78.9, 72.7, 66.7, 54.6, 44.7, 29.2, 14.8, 14.5, 8.2; *m*/*z* (EI^+) Calcd for $C_{24}H_{21}NO_{10}Co_2$: $[M-CO]^+$ 528.9613, found: 528.9620.

4.1.6. Hexacarbonyl{(4*R*,5*S*)-*N*-[2-(1-ethoxy-2-propynyl)-hept-6-enoyl]-4-methyl-5-phenyloxazolidin-2-one}dicobalt (14b). This was prepared, as previously described for **14a**, to afford the title compound as the major diastereoisomer (de 72%) isolated as a red oil (0.93 g, 80%). Major diastereoisomer: ν_{max}/cm^{-1} (film) 2977, 2933, 2341, 2095, 2054, 2029, 1785, 1695, 1456, 1397, 1339, 1192, 975,

766, 699; δ_H (400 MHz, $CDCl_3$) 7.43–7.30 (5H, m, Ar*H*), 6.04 (1H, s, alkyne-C*H*), 5.83–5.71 (1H, m, C*H*=CH_2), 5.61 (1H, d, *J* 7.3 Hz, C*H*–Ph), 5.03–4.95 (2H, m, =CH_2), 4.86–4.78 (1H, m, N–C*H*), 4.50 (1H, d, *J* 9.5 Hz, EtOCC*H*), 4.36–4.30 (1H, m, C*H*C=O), 3.81–3.74 (1H, m, O–CH_2), 3.52–3.47 (1H, m, O–CH_2), 2.08–2.03 (2H, m, =CH–CH_2), 1.85–1.66 (2H, m, CH_2), 1.49–1.30 (2H, m, CH_2), 1.05 (3H, t, *J* 7.6 Hz, O–CH_2–CH_3), 0.93 (3H, d, *J* 6.6 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 198.1, 176.5, 151.1, 136.7, 132.1, 129.0, 127.4, 124.3, 113.5, 78.8, 71.3, 65.2, 53.6, 48.5, 43.5, 38.2, 32.3, 27.8, 24.6, 13.4, 12.8; *m*/*z* obtained from a sample of the decomplexed material (EI^+) Calcd for $C_{22}H_{27}NO_4$: $[M+H]^+$ 370.2013, found: 370.2014.

4.1.7. (3*S*,5*S*)-5,9-Dimethyl-1-phenyl-dec-8-en-1-yn-3-ol (22a). A suspension of zinc triflate (2.2 g, 6.05 mmol) and (−)-*N*-methylephedrine (1.19 g, 6.62 mmol) in 0.3 M triethylamine in dry toluene was stirred for 2 h at 25 °C. After 2 h phenylacetylene (0.56 g, 0.61 mL, 5.52 mmol) was delivered to the suspension via syringe followed by (*S*)-(−)-citronellal (0.85 g, 5.52 mmol). The progress of the reaction was monitored by thin layer chromatography. Upon completion, ca. 30 h, the reaction mixture was quenched by the addition of a saturated solution of ammonium chloride (30 mL). The mixture was extracted with diethyl ether (3×30 mL) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by column chromatography on silica using hexane/ethyl acetate (8:2) gave the title compound as a colourless oil (0.99 g, 66%). The diastereoisomeric excess (de) was determined and corroborated by GC–MS, measurement of the integrations of the corresponding ^{1}H NMR spectrum of the crude reaction mixture and the ^{1}H NMR spectrum of the corresponding Mosher ester[17] and found to be de 85%. $[\alpha]_D^{20}$ +8.3 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 3422, 2929, 2202, 1664, 1489, 1444, 1379, 1285, 1069, 758; ^{1}H NMR ($CDCl_3$, 400 MHz) 7.42–7.39 (2H, m, Ar*H*), 7.30–7.27 (3H, m, Ar*H*), 5.11–5.07 (1H, m, CH=$C(CH_3)_2$, 4.67–4.62 (1H, m, HO–C*H*), 2.06–1.92 (2H, m, CH_2CH=), 1.82 (2H, dd, *J* 1.8, 5.6 Hz, CHCH_2CH–), 1.80–1.72 (1H, m, CH_3C*H*–), 1.65 (3H, s, C=CCH_3), 1.58 (3H, s, C=CCH_3), 1.4–1.33 (1H, m, CHCH_2CH_2–), 1.24–1.15 (1H, m, CHCH_2CH_2–), 0.96–0.94 (3H, d, *J* 6.4 Hz, CHCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) 131.8, 131.5, 128.4, 128.3, 124.7, 122.8, 90.3, 85.0, 61.8, 45.2, 37.2, 29.5, 25.8, 19.8, 17.8; *m*/*z* (EI^+) Calcd for $C_{18}H_{24}O$: $[M+NH_4]^+$ 274.2165, found: 274.2165.

Mosher ester derivative. To a solution of (3*S*,5*S*)-5,9-dimethyl-1-phenyl-dec-8-en-1-yn-3-ol (**22a**) (0.008 g, 0.031 mmol) were added (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetylchloride (0.018 mL, 0.09 mmol), 4-(dimethylamino)pyridine (0.003 g, 0.002 mmol), dry pyridine (0.006 mL, 0.07 mmol) and dry toluene (5 mL), and left to stir at an ambient temperature for 1 h. The reaction was quenched by the addition of water (2 mL) and the organics partitioned with ethyl acetate (4×5 mL), and washed with 10% hydrochloric acid (0.5 mL) followed by a saturated solution of sodium bicarbonate (0.5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. Purification by chromatography on silica gave the Mosher ester as an oil (0.012 g, 81%). ν_{max}/cm^{-1} 3039, 2954, 2856, 1749, 1491, 1453, 1270, 1169, 1124; δ_H (400 MHz, $CDCl_3$) 7.55–7.44 (2H, m, Ar*H*), 7.34–7.21 (8H, m, Ar*H*), 5.73 (1H, dd, *J* 5.3, 8.7 Hz, C*H*=$C(CH_3)_2$), 5.02–4.98 (1H, m, O–C*H*), 3.51 (3H, s, OCH_3), 2.01–1.85 (3H, m, CH_2C*H*), 1.68–1.61 (2H, m, CH_2), 1.59 (3H, s, C=CCH_3), 1.51 (3H, s, C=CCH_3), 1.36–1.26 (1H, m, CH_2), 1.22–1.11 (1H, m, CH_2), 0.90–0.89 (3H, d, *J* 6.2 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 165.7, 132, 131.7, 131.6, 130, 129.5, 128.8, 128.3, 128.3, 127.4, 124.2, 122.1, 86.2, 85.2, 65.4, 55.5, 41.6, 36.8, 28.9, 25.5, 25.2, 19.0, 17.6; *m*/*z* (EI^+) Calcd for $C_{28}H_{31}O_3F_3$: $[M+NH_4]^+$ 490.2564, found: 490.2561.

4.1.8. (3*S*,5*S*)-5,9-Dimethyl-1-*p*-tolyldec-8-en-1-yn-3-ol (22b). The typical procedure for the synthesis of **22a** was followed to afford the title compound as a clear oil (0.85 g, 65%). The diastereoisomeric excess (de) was determined and corroborated by GC–MS, measurement of the integrations of the corresponding ^{1}H NMR spectrum of the crude reaction mixture and found to be de 86%; $[\alpha]_D^{20}$ −10.4 (*c* 0.6, $CHCl_3$); ν_{max}/cm^{-1} 3406, 2959, 2926, 2199, 1718, 1664, 1606, 1508, 1378, 1289, 1062, 817, 755; $_{HH\eta}\delta_H$ (400 MHz, $CDCl_3$) 7.30 (2H, d, *J* 8 Hz, Ar*H*), 7.10 (2H, d, *J* 7.7 Hz, Ar*H*), 5.13–5.08 (1H, m, C*H*=$C(CH_3)_2$), 4.63 (1H, dd, *J* 5.9, 8.0 Hz, HO–C*H*), 2.34 (3H, s, ArCH_3), 2.10–1.94 (2H, m, =CHCH_2), 1.86 (2H, dd, *J* 5.5, 8.0 Hz, CH_2), 1.83–1.73 (1H, m, CH_3C*H*), 1.67 (3H, s, C=CCH_3), 1.60 (3H, s, C=CCH_3), 1.40–1.21 (2H, m, CH_2), 0.96 (3H, d, *J* 6.6 Hz, CHCH_3); δ_C (100 MHz, $CDCl_3$) 138.5, 131.7, 129.4, 124.8, 119.7, 89.9, 84.9, 61.4, 45.2, 37.0, 29.1, 26.1, 25.0, 21.3, 19.2, 18.1; Calcd for $C_{19}H_{26}O$: $[M+NH_4]^+$ 288.2322, found: 288.2324.

4.2. Asymmetric Nicholas cyclisation reaction

4.2.1. 2-Phenylethynyl-1-isopropenyl-(*S*)-4-methylcyclohexane (23a). To a 0 °C stirred solution of (3*S*,5*S*)-5,9-dimethyl-1-phenyl-dec-8-en-1-yn-3-ol (**22a**) (0.6 g, 2.34 mmol) in DCM (10 mL) maintained under an atmosphere of nitrogen was added dicobalt octacarbonyl (0.96 g, 2.8 mmol). After the evolution of carbon monoxide had subsided $BF_3\cdot OEt_2$ (0.35 mL, 2.8 mmol) was added and the progress of the reaction was monitored by TLC analysis, which revealed the presence of a new compound. A saturated solution of CAN dissolved in methanol was added dropwise until the evolution of CO was complete, observed as a change of colour from reddish brown to orange. The solvent was removed in vacuo and the base line impurities removed by chromatography on silica to afford a colourless oil (0.85 g, 55%). The diastereoisomeric excess (de) was determined by GC–MS and found to be 58%. $[\alpha]_D^{20}$ −0.45 (*c* 0.22, $CHCl_3$); ν_{max}/cm^{-1} 3075, 2924, 2868, 2199, 1664, 1490, 1443, 1276, 1069, 888, 756; $_{HH\eta}\delta_H$ (400 MHz, $CDCl_3$) 7.37–7.33 (2H m, Ar*H*), 7.28–7.22 (3H, m, Ar*H*), 4.86–4.81 (2H, m, =CH_2), 2.44 (1H, dt, *J* 3.5, 11.6 Hz, C*H*), 2.13–2.08 (2H, m, CH_2), 2.00 (1H, dt, *J* 3.5, 11.5 Hz, C*H*), 1.76 (3H, s, =CCH_3), 1.75–1.68 (2H, m, CH_2), 1.48–1.39 (1H, m, C*H*), 1.30 (1H, td, *J* 3.5, 12.4 Hz, CH_3), 0.98 (1H, td, *J* 3.5, 12.6 Hz, CH_2), 0.92 (3H, d, *J* 6.4 Hz, CH–CH_3); δ_C (100 MHz, $CDCl_3$) 148.3, 131.7, 128.1, 127.4, 124.2, 111.0, 93.3, 81.2, 51.2, 41.8, 34.8, 34.2, 32.2, 31.9, 22.3, 19.9; Calcd for $C_{18}H_{22}$: $[M+H]^+$ 239.1794, found: 239.1792.

4.2.2. 2-(4-Ethynyltoluene)-1-isopropenyl-(*S*)-4-methyl cyclohexane (23b). This was synthesised according to

compound **23a** using the following quantities: propargyl alcohol **22b** (0.89 g, 3.29 mmol), dicobalt octacarbonyl (1.35 g, 3.95 mmol), Lewis acid (0.48 mL, 3.95 mmol) and CAN (excess) to afford the title compound as a mixture of diastereoisomers as a colourless oil (0.42 g, 51%). The diastereoisomeric excess (de) was determined by GC–MS and found to be 60%. $[\alpha]_D^{20}$ +3.8 (*c* 0.79, $CHCl_3$); ν_{max}/cm^{-1} 3027, 2923, 2868, 1666, 1455, 1376, 1277, 1177, 1106, 816; $_{HH\eta}\delta_H$ (400 MHz, $CDCl_3$) 7.29–7.23 (2H, m, Ar*H*), 7.09–7.04 (2H, m, Ar*H*), 4.86–4.80 (2H, m, =CH_2), 2.43 (1H, dt, *J* 3.5, 11.3 Hz, C*H*), 2.31 (3H, s, CH_3), 2.06 (2H, m, CH_2), 1.99 (1H, dt, *J* 3.5, 11.3 Hz, C*H*), 1.76 (3H, s, =CCH_3), 1.75–1.67 (2H, m, CH_2), 1.49–1.38 (1H, m, C*H*), 1.30 (1H, dt, *J* 3.5, 12.4 Hz, CH_3), 1.04 (1H, td, *J* 3.5, 12.6 Hz, CH_2), 0.92 (3H, d, *J* 6.4 Hz, CH–CH_3); δ_C (100 MHz, $CDCl_3$) 148.4, 137.7, 131.5, 128.9, 121.1, 110.9, 92.5, 81.3, 51.2, 41.8, 34.8, 34.2, 32.2, 31.9, 22.3, 21.4, 19.9; Calcd for $C_{19}H_{24}$: $[M]^+$ 252.1873, found: 252.1876.

4.2.3. (−)-6,8-Dichloro-3-(1-fluoro-1-methylethyl)-4-(phenylethynyl)chromane (28).

4.2.3.1. Hexacarbonyl[(1*R*)-(+)-1-{3,5,dichloro-2-[3-methylbut-2-en-1-yl)oxy]phenyl}-3-phenylprop-2-yn-1-ol]dicobalt (26). To a stirred solution of (1*R*)-(+)-1-{3,5-dichloro-2-[3-methylbut-2-en-1-yl]oxy}phenyl-3-phenylprop-2-yn-1-ol (**25**) (0.169 g, 0.46 mmol) in dry dichloromethane (10 mL) was added dicobalt octacarbonyl (0.171 g, 0.50 mmol). After 1 h TLC analysis showed the presence of a new compound (R_f 0.46 (6:1 hexane/diethyl ether). The solvent was removed in vacuo to afford the corresponding cluster (**26**) (0.293 g, 99%). ν_{max}/cm^{-1} 2926, 2092, 2054, 2026, 1670, 1566, 1442, 1380, 1160; $_{HH\eta}\delta_H$ (400 MHz, $CDCl_3$) 7.66–7.03 (7H, m, Ar*H*), 6.27 (1H, br s, Ph–C–*H*), 5.42 (1H, br s, C=C–*H*), 4.52 (2H, s, CH_2), 2.54 (1H, br d, O*H*), 1.61 (6H, br ds, CH_3×2); δ_C (100 MHz, $CDCl_3$) 151.42, 140.47, 137.62, 131.81, 130.33, 129.74, 129.01, 128.90, 128.45, 126.90, 122.16, 119.31, 87.94, 87.00, 70.98, 60.87, 25.95, 15.25; LRMS (EI) *m*/*z* 590 $[M-2CO]^+$, 562, 534, 506, 478, 410, 301, 275, 235, 205.

4.2.3.2. Hexacarbonyl[(+)-6,8-dichloro-3-(1-fluoro-1-methylethyl)-4-(phenyl ethynyl)chromane]dicobalt (27). To a stirred 0 °C solution of (**26**) (0.641 g, 0.98 mmol) in dry DCM (15 mL) was added boron trifluoride diethyl etherate (0.14 g, 128 μL, 0.98 mmol). The reaction was left to stir under a nitrogen atmosphere for 5 min. TLC analysis showed the presence of a new faster moving compound (R_f 0.78 (6:1 hexane/diethyl ether). The reaction mixture was quenched by the addition of a saturated solution of sodium hydrogen carbonate (15 mL) and partitioned with DCM (15 mL). The aqueous phase was extracted with DCM (3×15 mL) and the combined organic phases were dried over anhydrous magnesium sulfate, filtered in vacuo and concentrated to afford a red oil (0.5 g, 80%); $[\alpha]_D^{18}$ +50 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} 2946, 2090, 2054, 2028, 1718, 1596, 1450, 1378, 1244; δ_H (400 MHz, $CDCl_3$) 7.52–7.22 (7H, m, Ar*H*), 6.95 (1H, br s, Ph–C–*H*), 4.48 (1H, br s, O–CH_2), 2.54 (1H, br dd, *J* 10.8 Hz, CF–C*H*), 1.48 (3H, d, J_{H-F} 22.7 Hz, CH_3), 1.29 (6H, d, J_{H-F} 22.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 148.56, 138.10, 129.14, 128.98, 128.88, 128.01, 127.10, 125.48, 122.63, 96.07 (d, $^1J_{C-F}$ 169.8 Hz), 90.38, 83.63, 63.66 (d, $^3J_{C-F}$ 9.2 Hz), 49.22 (d, $^2J_{C-F}$ 23.0 Hz), 37.17 (d, $^3J_{C-F}$ 5.4 Hz), 26.27 (d, $^2J_{C-F}$ 24.6 Hz), 24.44 (d, $^2J_{C-F}$ 23.8 Hz); LRMS (EI) *m*/*z* 620 $[M-CO]^+$ 592, 564, 536, 508, 480, 452, 362, 301, 292, 275.

4.2.3.3. (−)-6,8-Dichloro-3-(1-fluoro-1-methylethyl)-4-(phenylethynyl)chromane (28). To a stirred solution of complex (**27**) (0.484 g, 0.7 mmol) in acetone (100 mL) maintained at an ambient temperature was added CAN (2.03 g, 3.7 mmol). Stirring was maintained for about 30 min until the evolution of gas ceased. TLC analysis of the reaction mixture indicated the presence of a new compound (R_f 0.64, 6:1 hexane/diethyl ether). The reaction was quenched, by the addition of a saturated solution of sodium hydrogen carbonate (50 mL), and the mixture was extracted with diethyl ether (3×50 mL). The organic layers were recombined, dried over anhydrous magnesium sulfate, filtered and the solvent removed in vacuo to afford the title product as a viscous brown oil yield (0.27 g, 99%) and 99% de as determined by HPLC analysis (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm), t_R 5.40. *The following spectroscopic analysis was conducted on the crude product from this and all analogous cyclisation reactions.* $[\alpha]_D^{21}$ −10 (*c* 0.1, $CHCl_3$); ν_{max}/cm^{-1} 2978, 2200, 1698, 1596, 1450, 1242, 1176; δ_H (400 MHz, $CDCl_3$) 7.40–7.38 (2H, m, Ar*H*), 7.36 (1H, dd, *J* 0.9, 2.5 Hz, Ar*H*), 7.32–7.28 (3H, m, Ar*H*), 7.25 (1H, dd, *J* 0.7, 2.6 Hz, Ar*H*), 4.57 (1H, ddd, *J* 2.2, 3.3, 11.7 Hz, CH_2–*H*), 4.29 (1H, ddd, *J* 0.5, 5.7, 11.7 Hz, CH_2–*H*), 4.09 (1H, d, *J* 5.1 Hz, PhC–*H*), 2.51–2.44 (1H, m, *H*–C–F), 1.52 (3H, d, J_{H-F} 22.2 Hz, CH_3), 1.43 (3H, d, J_{H-F} 22.7 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 148.65, 131.66, 128.69, 128.49, 128.41, 128.38, 125.68, 124.82, 122.73, 122.56, 96.07 (C, d, $^1J_{C-F}$ 168.8 Hz, C–F), 90.38, 83.63, 65.39 (CH_2, d, $^3J_{C-F}$ 9.9 Hz), 47.17 (CH, d, $^2J_{C-F}$ 23.0 Hz, C–C–F), 28.99 (CH, d, $^3J_{C-F}$ 5.4 Hz, CPh), 25.85 (CH_3, d, $^2J_{C-F}$ 24.6 Hz), 25.48 (CH_3, d, $^2J_{C-F}$ 24.6 Hz); LRMS (EI) *m*/*z* 362 $[M]^+$ 327, 301, 274, 239, 176, 115, 105, 77, 61; Calcd for $C_{20}H_{17}{}^{35}Cl_2FO$ $[M]^+$ 362.0635, found: 362.0636; UV (^{i}PrOH) λ_{max1} 296 nm, λ_{max2} 239 nm.

4.2.4. (+)-6,8-Dibromo-3-(1-fluoro-1-methylethyl)-4-(phenylethynyl)chromane (30a).

This compound was synthesised according to the general procedure used for the synthesis of compound (**28**) to afford the title compound as a brown semi-solid (0.22 g, 75% over three steps). The diastereomeric excess was determined by HPLC analysis and found to be 99.5% (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm), t_R 5.42 min. $[\alpha]_D^{21}$ +10 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} 2980, 2192, 1658, 1598, 1444, 1244; δ_H (400 MHz, $CDCl_3$) 7.64–7.48 (3H, m, Ar*H*), 7.43–7.36 (2H, m, Ar*H*), 7.31–7.26 (2H, m, Ar–*H*), 4.56 (1H, ddd, *J* 2.5, 3.5, 11.9 Hz, CH–*H*), 4.29 (1H, dd, *J* 5.8, 11.9 Hz, CH–*H*), 4.10 (1H, d, *J* 5.5 Hz, PhC–*H*), 2.50–2.44 (1H, m, *H*–C–F), 1.51 (3H, d, $^3J_{H-F}$ 22.2 Hz, CH_3), 1.43 (3H, d, $^3J_{H-F}$ 22.7 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 150.01, 134.19, 132.02, 131.68, 128.68, 128.51, 128.43, 125.25, 122.73, 113.07, 111.79, 96.04 (C, d, $^1J_{C-F}$ 168.4 Hz, C–F), 90.43, 83.69, 65.60 (CH_2, d, $^3J_{C-F}$ 9.9 Hz), 47.19 (CH, d, $^2J_{C-F}$ 23.0 Hz, C–C–F), 29.04 (CH, d, $^3J_{C-F}$ 5.4 Hz, CPh), 25.87 (CH_3, d, $^2J_{C-F}$ 24.6 Hz), 25.59 (CH_3, d, $^2J_{C-F}$ 24.6 Hz); LRMS (EI) *m*/*z* 452 $[M]^+$, 384, 364, 285, 202, 176, 115, 105, 77, 61; Calcd for $C_{20}H_{17}{}^{79}Br_2FO$ $[M]^+$

449.9625, found: 449.9621; UV (^{i}PrOH) λ_{max1} 279 nm, λ_{max2} 239 nm.

4.2.5. (+)-6-Bromo-3-(1-fluoro-1-methylethyl)-4-(phenylethynyl)chromane (30b). This compound was synthesised according to the general procedure used for the synthesis of compound (**28**) to afford the title compound as a yellow waxy solid (0.26 g, 93% over three steps). The diastereomeric excess was determined by HPLC analysis and found to be 88% (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm), t_R 5.47 (major), 13.19 (minor). $[\alpha]_D^{21}$ +15 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} 2982, 2200, 1692, 1600, 1490, 1270, 1234; δ_H (400 MHz, $CDCl_3$) 7.57 (1H, dd, *J* 0.7, 2.5 Hz, Ar*H*), 7.41–7.38 (2H, m, Ar*H*), 7.31–7.28 (3H, m, Ar*H*), 7.23 (1H, ddd, *J* 0.7, 2.4, 11.7 Hz, Ar*H*), 6.62 (1H, d, *J* 8.6 Hz, Ar*H*), 4.46 (1H, ddd, *J* 2.2, 3.3, 11.7 Hz, CH–*H*), 4.17 (1H, ddd, *J* 0.5, 5.7, 11.7 Hz, CH–*H*), 4.06 (1H, d, *J* 5.3 Hz, PhC–*H*), 2.48–2.42 (1H, m, *H*–C–F), 1.50 (3H, d, $^3J_{H-F}$ 19.7 Hz, CH_3), 1.45 (3H, d, $^3J_{H-F}$ 22.7 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 153.16, 133.69, 131.67, 131.29, 128.38, 128.33, 124.05, 122.98, 118.84, 113.24, 96.29 (C, d, $^1J_{C-F}$ 169.1 Hz, C–F), 91.03, 83.19, 64.64 (CH_2, d, $^3J_{C-F}$ 9.9 Hz), 47.29 (CH, d, $^2J_{C-F}$ 23.0 Hz, C–C–F), 28.82 (CH, d, $^3J_{C-F}$ 5.4 Hz, CPh), 26.08 (CH_3, d, $^2J_{C-F}$ 24.6 Hz), 25.32 (CH_3, d, $^2J_{C-F}$ 24.6 Hz); LRMS (EI) *m*/*z* 372 $[M]^+$, 311, 285, 233, 205, 176, 151, 115, 61; Calcd for $C_{20}H_{18}{}^{79}BrFO$ $[M]^+$ 372.0520, found: 372.0521; UV (^{i}PrOH) λ_{max1} 284 nm, λ_{max2} 238 nm.

4.2.6. (+)-6-Chloro-3-(1-fluoro-1-methylethyl)-4-(phenylethynyl)chromane (30c). This compound was synthesised according to the general procedure used for the synthesis of compound (**28**) to afford the title compound as a viscous brown oil (0.41 g, 60% over three steps). The diastereomeric excess was determined by HPLC analysis and found to be 95% (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm), t_R 5.37 (major), 11.17 (minor). $[\alpha]_D^{21}$ +12.5 (*c* 0.4, $CHCl_3$); ν_{max}/cm^{-1} 2982, 2200, 1722, 1692, 1600, 1486, 1268, 1232; δ_H (400 MHz, $CDCl_3$) 7.43 (1H, dd, *J* 0.7, 2.6 Hz, Ar*H*), 7.41–7.37 (2H, m Ar*H*), 7.31–7.28 (3H, m, Ar*H*), 7.10 (1H, ddd, *J* 0.5, 2.6, 8.6 Hz, Ar*H*), 6.76 (1H, d, *J* 8.6 Hz, Ar*H*), 4.46 (1H, ddd, *J* 2.4, 3.3, 11.7 Hz, CH–*H*), 4.16 (1H, dd, *J* 5.9, 11.7 Hz, CH–*H*), 4.06 (1H, d, *J* 5.3 Hz, PhC–*H*), 2.48–2.42 (1H, m, *H*–C–F), 1.50 (3H, d, $^3J_{H-F}$ 20.0 Hz, CH_3), 1.45 (3H, d, $^3J_{H-F}$ 20.0 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 152.64, 131.66, 129.74, 128.42, 128.37, 128.33, 125.96, 123.50, 122.99, 118.37, 96.30 (C, d, $^1J_{C-F}$ 169.1 Hz, C–F), 91.01, 83.13, 64.69 (CH_2, d, $^3J_{C-F}$ 9.9 Hz), 47.32 (CH, d, $^2J_{C-F}$ 23.0 Hz, C–C–F), 28.90 (CH, d, $^3J_{C-F}$ 5.4 Hz, CPh), 26.09 (CH_3, d, $^2J_{C-F}$ 24.6 Hz), 25.31 (CH_3, d, $^2J_{C-F}$ 24.6 Hz); LRMS (EI) *m*/*z* 328 $[M]^+$, 293, 265, 233, 205, 176, 151, 61; Calcd for $C_{20}H_{18}{}^{35}ClFO$ $[M]^+$ 328.1025, found: 328.1027; UV (^{i}PrOH) λ_{max1} 284 nm, λ_{max2} 235 nm.

4.2.7. (+)-6-Nitro-3-(1-fluoro-1-methylethyl)-4-(phenylethynyl)chromane (30d). This compound was synthesised according to the general procedure used for the synthesis of compound (**28**) to afford the title compound as a yellow viscous oil (0.074 g, 84% over three steps). The diastereomeric excess was determined by HPLC analysis and found to be 84% (Chiralcel OD-H, 10% ^{i}PrOH in hexane, 254 nm), t_R 8.72 (major), 26.70 (minor). $[\alpha]_D^{21}$ +5 (*c* 0.2, $CHCl_3$); ν_{max}/cm^{-1} 2982, 2366, 1586, 1518, 1490, 1336, 1264; δ_H (400 MHz, $CDCl_3$) 8.43 (1H, dd, *J* 0.9, 2.7 Hz, Ar*H*), 8.04 (1H, dd, *J* 2.7, 8.9 Hz, Ar*H*), 7.43–7.37 (2H, m, Ar*H*), 7.33–7.27 (3H, m, Ar*H*), 6.91 (1H, d, *J* 8.9 Hz, Ar*H*), 4.59 (1H, ddd, *J* 2.0, 3.3, 11.9 Hz, CH–*H*), 4.29 (1H, ddd, *J* 0.7, 6.0, 11.9 Hz, CH–*H*), 4.16 (1H, d, *J* 5.8 Hz, PhC–*H*), 2.53–2.46 (1H, m, *H*–C–F), 1.53 (3H, d, $^3J_{H-F}$ 7.5 Hz, CH_3), 1.47 (3H, d, $^3J_{H-F}$ 8.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 159.32, 141.83, 131.67, 128.61, 128.46, 126.53, 124.37, 122.68, 122.55, 117.64, 95.95 (C, d, $^1J_{C-F}$ 169.1 Hz, C–F), 89.90, 84.22, 65.37 (CH_2, d, $^3J_{C-F}$ 9.9 Hz), 46.64 (CH, d, $^2J_{C-F}$ 23.0 Hz, C–C–F), 29.21 (CH, d, $^3J_{C-F}$ 6.2 Hz, CPh), 26.28 (CH_3, d, $^2J_{C-F}$ 24.6 Hz), 25.21 (CH_3, d, $^2J_{C-F}$ 24.6 Hz); LRMS (EI) *m*/*z* 339 $[M]^+$, 296, 276, 261, 205, 176, 115, 61; Calcd for $C_{20}H_{18}FNO_3$ $[M]^+$ 339.1265, found: 339.1267; UV (^{i}PrOH) λ_{max1} 300 nm, λ_{max2} 239 nm.

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27. To remove faster moving and base line residues only.