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Catalytic asymmetric Tamura cycloadditions involving nitroalkenes†

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The first examples of asymmetric Tamura cycloaddition reactions involving singly activated alkenes are reported. Homophthalic anhydride reacts with α-methyl nitrosytrenes in the presence of an alkaloid-based catalyst to generate fused bicyclic aromatic ketone products with three new stereocentres (which are susceptible to subsequent equilibration) in 12–99% *ee*. An unusual equilibration process which occurs in methanolic medium in the absence of a recognisable base *via* proton transfer at the α-carbon of an ester was investigated experimentally and computationally.

Introduction

Some three decades ago, Tamura *et al.* reported that activated alkynes and alkenes could undergo cycloaddition reactions with enolisable anhydrides such as homophthalic anhydride (**1**) at high temperature to form (after decarboxylation) naphthol products.[1–3] Later, it was demonstrated that the same reaction could be mediated by strong bases.[4] In an intriguing example, it was shown that at 0 °C, the doubly activated olefin **2** could react with **1** on the presence of NaH to furnish the chiral bicyclic product **3** in good yield (Fig. 1A). The diastereomeric ratio was not determined. It was postulated that the reaction proceeded through either a stepwise addition–cyclisation mechanism involving the conjugate base of enol **1b** or a Diels–Alder reaction passing through the corresponding anion derived from tautomer **1c**.[4a]

While the Tamura cycloaddition has proven itself of value in the synthesis of polycyclic aromatic natural products,[5] the general lack of examples involving the generation of chiral products from activated alkenes (*i.e.* those in which stereochemically destructive aromatisation is avoided) and the requirement for activating groups at both alkene carbon atoms,[6] has limited the utility of the process considerably. In addition, neither efficient catalytic nor asymmetric variants of this process were developed until 2014. We found that the doubly activated oxindole-based Michael acceptor **4** reacted with **1** in the presence of the bifunctional squaramide-based catalyst **5** at 30 °C to yield (after *in situ* esterification) the spirocyclic

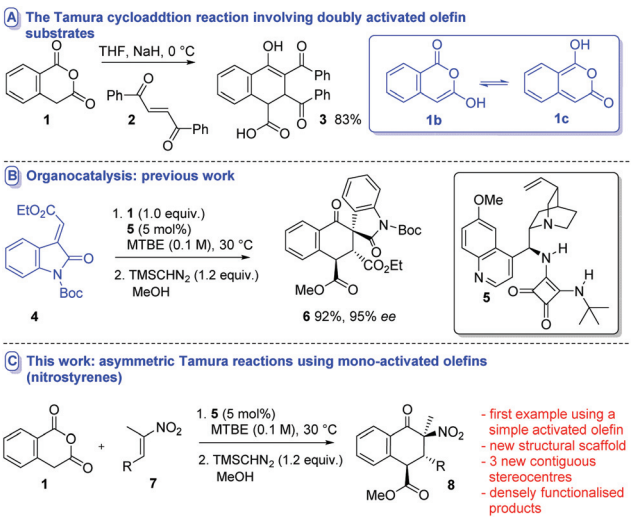

Fig. 1 Tamura cycloaddition reactions.

product **6** in excellent yield and enantiomeric excess (Fig. 1B).[7–9] To the best of our knowledge this remains the only example of this type of catalytic asymmetric Michael-type reaction involving enolisable anhydrides.

In order to probe the potential utility of this process further, we wished to extend its scope to include a less complex (but synthetically malleable) Michael acceptor – preferably one which incorporated a single activating group. This proved to be considerably less straightforward than one might expect. Herein we report the results of a study culminating in the development of a protocol for the formal cycloaddition of anhydride **1** to α-methyl nitroolefins to generate densely functionalised bicyclic products of general type **8** (Fig. 1C) with the formation of **3** contiguous stereocentres – one of which is quaternary – with a high degree of control. The exploitation of a

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highly unusual, temperature sensitive epimerisation of the esterified product is also documented.

Results and discussion

Our investigations began with the reaction of (*E*)-β-nitrostyrene (**9**) with homophthalic anhydride (**1**) in MTBE[10] at ambient temperature in the presence of the bifunctional squaramide-based catalyst **10**, which resulted in the formation of the dihydronaphthol product **11** in 53% yield as a mixture of diastereomers (Scheme 1).

While it was gratifying to obtain proof of principle that olefins possessing only one activating group could participate in the process – two drawbacks immediately presented themselves. Firstly, the high acidity of the nitroalkane favours the formation the enol **11** as the sole tautomer observable by ^{1}H NMR spectroscopy, resulting in the loss of an initially formed stereocentre. Second, **11** was not amenable to *in situ* esterification by trimethylsilyldiazomethane (which allows facile analysis of the product by CSP-HPLC and had previously proved useful in preventing retro-cycloaddition[7]); instead undergoing decomposition.

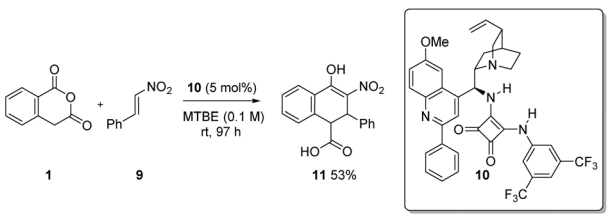
To circumvent both difficulties, the electrophile was modified to preclude keto–enol tautomerism and the formation of the reactive nitroenol unit characteristic of **11**. Repetition of the process outlined in Scheme 1 using the β-methylnitrostyrene **12** provided a considerably more successful outcome – the annulated products containing two new C–C bonds and three contiguous stereocentres (one quaternary) were formed as a diastereomeric pair (*i.e.* **13a–b**) smoothly in a relatively rapid[11] and high-yielding process (Scheme 2).

With one problem solved, another immediately presented itself: diastereocontrol was highly dependent on both reaction time and temperature, leading to what at first appeared to be irreproducible results. The minor diastereomer **13b** converts to the **13a** upon completion of the reaction. This equilibration also occurs both during and after the esterification event and even was observed during evaporation of the solvent during purification.[12]

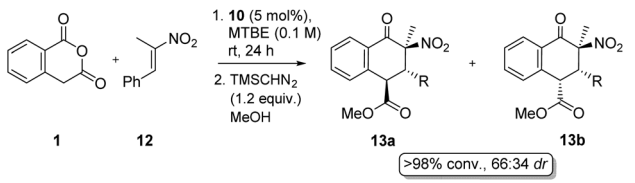
After considerable experimentation, a set of standardised conditions were developed involving reaction at 30 °C for precisely 22 h in MTBE (0.1 M) followed by esterification at 0 °C and a careful purification protocol which avoids concentration of the solvent at temperatures higher than 30 °C. When this process was strictly adhered to, the results of the cycloaddition reactions were reproducible.

The influence on the catalyst structure on the process was next examined (Table 1). While the urea-derivative **14** proved effective (entry 1), it promoted less enantio- and diastereoselective cycloaddition than the corresponding squaramide derivative **10** (entry 2). Augmentation of the bulk of the squaramide group (catalysts **15** and **16**, entries 3 and 4 respectively) led to the formation of **13a** in 84% *ee* and **13b** in almost optically pure form.

We next set about trying to exploit the amenability of **13b** to epimerisation (Table 2). Acting on the presumption that the catalyst facilitated this process, a mixture of **13a** (88% *ee*) and **13b** (>99% *ee*, *ca.* 2 : 1 dr) was treated with excess MeOH in the presence of catalyst **10** at 55 °C (entry 1). After 39 h the levels of **13b** in solution had reduced markedly, and the *ee* of **13a** had increased almost to the maximum possible based on the assumption that **13b** converts to **13a** without erosion of its enantiomeric excess. Use of the more bulky squaramide

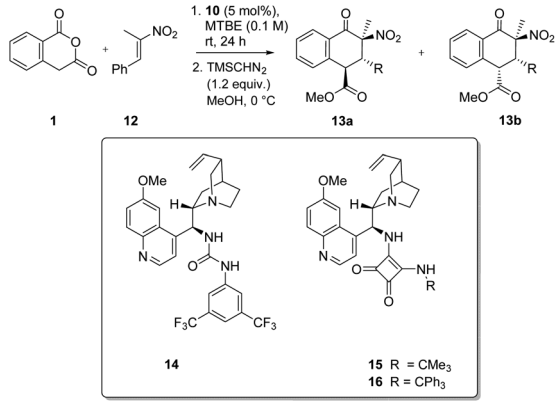


Scheme 1 Proof of principle: a catalysed reaction of a nitroolefin with homophthalic anhydride.



Scheme 2 Prevention of keto–enol tautomerism: efficient cycloaddition.

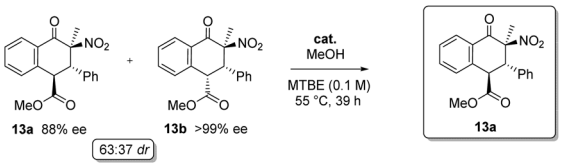
Table 1 The influence of the catalyst on stereocontrol



Entry	Cat.	Conv.[a] (%)	dr[a] **13a : 13b** (acids)	dr[a] **13a :13b** (esters)	$ee_{\mathbf{13a}}$[b] (%)	$ee_{\mathbf{13b}}$[b] (%)
1	**14**	>98	56 : 44	62 : 38	58	97
2	**10**	>98	68 : 32	72 : 28	60	97
3	**15**	>98	53 : 47	57 : 43	72	99
4	**16**	>98	63 : 37	68 : 32	84	99

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by CSP-HPLC, see Experimental section.

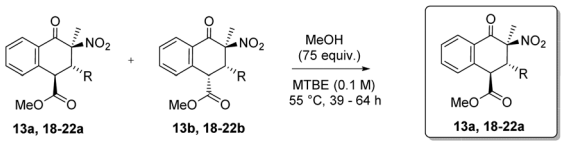
Table 2 Exploitation of the epimerisation process



Entry	Cat.	Loading (mol%)	MeOH (equiv.)	Final dr[a] **13a : 13b**	ee_{13a}[b] (%)	Yield[c] (%)
1	**10**	5	75	94 : 6	91 (92)[d]	90
2	**16**	5	75	72 : 28	n.d.	n.d.
3	**10**	5	0	65 : 35	n.d.	n.d.
4	—	0	75	92 : 8	92 (92)	89

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by CSP-HPLC, see the ESI. [c] Isolated yield of **13a**. [d] Maximum calculated *ee* (%) in parenthesis.

Table 4 Product epimerisation



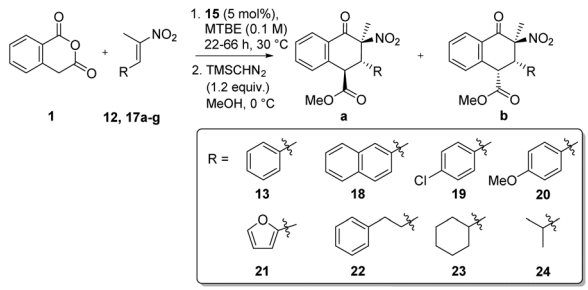
Entry	Prod.	Initial[a] **a : b**	ee_a[b] (%)	ee_b[b] (%)	Final[a] **a : b**	ee_a[b] (%)	Yield[c] (%)
1	**13**	57 : 43	72	99	96 : 4	80	91
2	**18**	56 : 44	67	96	>99 : 1	77	93
3	**19**	79 : 21	80	99	>98 : 2	83	93
4	**20**	59 : 41	74	99	96 : 4	82	92
5	**21**	86 : 14	12	96	93 : 7	28	88
6	**22**	89 : 11	51	87	89 : 11	50	82

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by CSP-HPLC, see the ESI. [c] Isolated yield of the **a** product.

derivative **16** resulted in considerably slower rates of epimerisation (entry 2). Intriguingly, repetition of the reaction involving catalyst **10** in the absence of methanol led to only trace levels of conversion of **13b** to **13a** (entry 3). Finally, upon execution of the process without an amine-based catalyst but in the presence of methanol (entry 4), efficient epimerisation allowed **13a** to be isolated in 89% yield and 92% *ee*.

Attention then turned to the issue of substrate scope. Homophthalic anhydride (**1**) was reacted with a range of methylnitroalkenes **12** and **17a–g** in the presence of (the considerably more easily prepared) catalyst **15** and the products esterified *in situ* (Table 3). Electron neutral (entries 1 and 2), activated (entry 3) and deactivated (entry 4) nitroalkenes were transformed into the bicyclic products **13** and **18–20** smoothly.

Table 3 Substrate scope



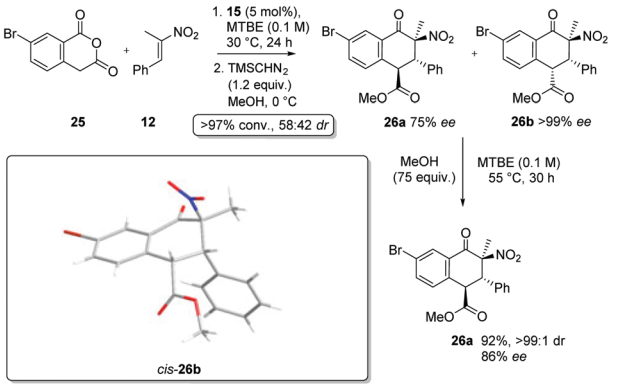
Entry	Prod.	Conv.[a] (%)	dr[a] **a : b** (acids)	dr[a] **a : b** (esters)	ee_a[b] (%)	ee_b[b] (%)
1	**13**	>98	53 : 47	57 : 43	72	99
2	**18**	>98	54 : 46	56 : 44	67	96
3	**19**	95	63 : 31	79 : 21	80	99
4	**20**	96	57 : 43	59 : 41	74	99
5	**21**	>98	77 : 23	86 : 14	12	96
6	**22**	90	88 : 12	89 : 11	51	87
7[c]	**23**	55	n.d.	98 : 2	49	—
8[d]	**24**	51	n.d.	99 : 1	52	—

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by CSP-HPLC, see the ESI. [c] 8 days reaction time. [d] 7 days reaction time.

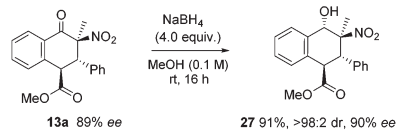
Diastereocontrol ranged from moderate to good (in the case of the product **19**) with a preference for the isomer with the β-ester group. The *ee* of disatereomers **13a** and **18–20a** were between 67 and 80%, while the minor counterparts **13b** and **18–20b** were formed with outstanding enantiocontrol.

Subsequent epimerisation of the products **13** and **18–22** under the previously established conditions (Table 4) proceeded as expected when the products were derived from nitrostyrenes (entries 1–5); leading to the isolation of **13a** and **18a–21a** in good-excellent yield, with significant enhancements in both the diastereomeric ratio and enantiomeric excess. The ester **22a** however, which incorporates an aliphatic substituent in place of an aromatic ring – proved resistant to epimerisation (entry 6).

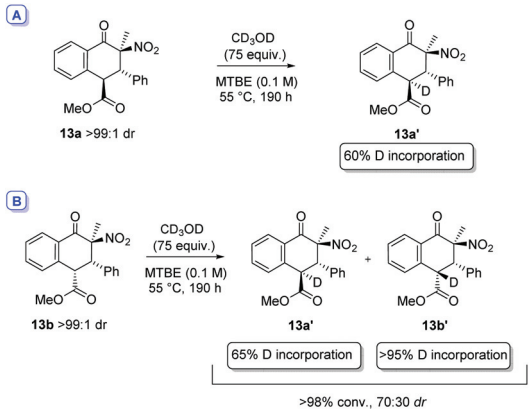
The process is also compatible with a substituted homophthalic anhydride (Scheme 3). Anhydride **25** was reacted with **12** catalysed by **15**, which, after esterification, resulted in the formation of **26a–b**. Subjection of these to the epimerisation conditions allowed the isolation of **26a** in excellent yield, >99 : 1 dr and 86% *ee*. The relative and absolute configuration of both **26a** and **26b** were confirmed using X-ray crystallographic analysis.



Scheme 3 Cycloaddition with 3-bromo-homophthalic anhydride.



Scheme 4 Selective reduction of **13a**.



Scheme 5 Deuterium incorporation experiments.

In order to demonstrate that the ketone functionality can be manipulated in a diastereocontrolled manner, α-nitroketone **13a** (89% *ee*) was reduced by sodium borohydride in methanolic solvent to produce the densely functionalised product **27** – which contains 4 contiguous stereocentres – with excellent yield and diastereocontrol, without any erosion of the enantiomeric excess (Scheme 4).

We also carried out experiments with the aim of shedding light on the mechanism of the epimerisation process (Scheme 5). Diastereomerically pure **13a** was subjected to the epimerisation conditions in the presence of CD_3OD leading to 60% incorporation of deuterium α to the ester functionality (*i.e.* **13a′**, Scheme 5A). This shows that even the more stable diastereomer **13a** undergoes proton transfer under these conditions. An identical experiment involving the kinetic diastereomer **13b** yielded different data. The expected epimerisation process occurred (70 : 30 dr); and while **13a′** was formed with 65% D incorporation, the corresponding epimer **13b′** was generated almost entirely deuterated (Scheme 5B). Therefore it seems clear that (despite the lack of a recognisable base) the proton transfer event is intermolecular and involves the protic additive. These experiments also indicate that the less stable diastereomer **13b** undergoes more facile proton transfer than its epimer **13a**, which is consistent with the epimerisation of **13b** to **13a** being driven by a proton transfer process.

Calculations

In order to provide a better understanding of the mechanism behind the epimerisation process a theoretical study (DFT) of the reaction mechanism has been carried out. Both calculation and XRD data indicated that intramolecular distance between the nitro group and the proton involved in the epimerisation process is *ca.* 2.74 Å, so a mechanism involving proton transfer mediated by the proximal nitro functional group was proposed. However, calculations indicated that this mechanism is unfavourable from the thermodynamic point of view, with a relative energy higher than 50 kcal mol^{-1} with respect to the entrance channel.

Table 5 Relative energies (Δ*E* in kcal mol^{-1}) respect to the entrance channel at B3LYP/6-311+G(d,p), computational level in PCM-diisopropylether with one and two molecules of methanol

Molecules	**2MeOH** molecules	**1MeOH** molecule
13a·2MeOH	−9.1	−2.4
TS1	18.7	35.9
28·2MeOH	1.7	12.9
TS2	21.5	35.5
13b·2MeOH	−10.7	−3.2

An alternative mechanism in which a proton transfer is assisted by explicit solvent (methanol) molecules was also considered. The energy profile corresponding to the epimerisation processes involving both one and two molecules of methanol have been studied – the relative energies of all species with respect to the entrance channel are summarised in Table 5. It was found that proton transfer aided by two molecules of MeOH was considerably more kinetically favorable than the analogous process mediated by a single additive molecule (Table 5).

Fig. 2 shows the potential energy surface for the mechanism corresponding to epimerisation process; the entrance channel (*i.e.* **13a**+**2MeOH**) represents the sum of energies associated with compound **13a** and two explicit (unbound) molecules of methanol. The first minimum (named **13a·2MeOH**) corresponds to **13a** interacting with two molecules of methanol in a complex. In the first step (**13a·2MeOH** to **28·2MeOH** *via* **TS1**), a shuttle (concerted) deprotonation-protonation process occurs involving both MeOH molecules bound to both each other and the substrate, with a barrier of

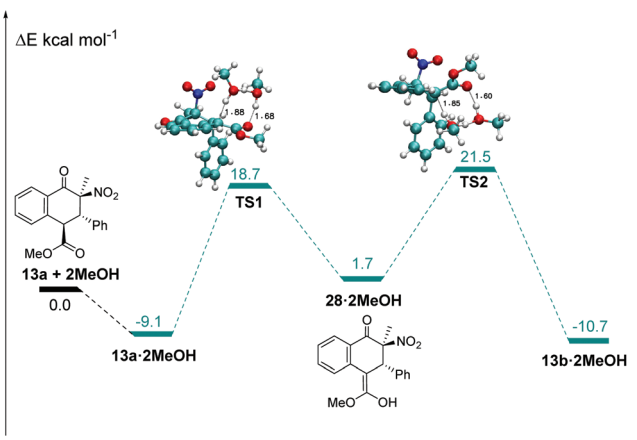
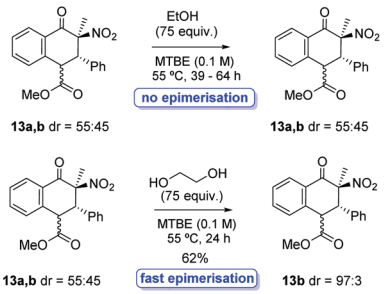


Fig. 2 Potential energy surfaces corresponding to the epimerisation reaction with two molecules of methanol.



Scheme 6 Epimerisation using ethylene glycol and ethanol.

18.7 kcal mol^{-1}. However, the barrier associated the corresponding reaction involving **13b·2MeOH** to **28·2MeOH** *via* **TS2** process is slightly higher (21.5 kcal mol^{-1}). It is noteworthy that **13b·2MeOH** is 1.6 kcal mol^{-1} more stable than **13a·2MeOH**. While these calculations represent a simplification of scenario associated with the actual epimerisation event, it is consistent with the findings from the deuteration experiments – *i.e.* that **13a** epimerises faster than **13b**, and **13b** is the more stable of the two diastereomers in the presence of MeOH additive. We would suggest that the use of 75 equivalents of MeOH mitigates against the entropic penalty associated with the assembly of the two methanol molecules around the ester functional group, without significantly altering the bulk properties of the solvent.

As the calculations indicated that two methanol molecules seem to assist in the epimerisation of **13a** in cyclical fashion, we predicted that ethylene glycol could serve as a useful substitute in which the system would incur less of an entropic penalty as catalysis proceeded. Under the standard reaction conditions the epimerisation proceeded faster with ethylene glycol than methanol giving **13b** product almost exclusively in 24 h, with partial decomposition (presumably *via* ketalisation), whereas use of EtOH as an additive provided no discernible epimerisation whatsoever (Scheme 6). We cannot rule out the possibility that more than 2 alcohol molecules are involved in the transition state, however the efficacy of ethylene glycol and our calculations indicate that a two-molecule pathway is energetically feasible.

Conclusions

The recently developed C–C bond forming asymmetric Tamura cycloaddition reaction has been extended to include nitroalkene substrates. In the presence of a bulky squaramide-based bifunctional catalyst, homophthalic anhydrides react with these electrophiles to give a pair of fused bicyclic ketone diastereomeric products (with the generation of three new stereocentres) with poor-moderate diastereocontrol and moderate-excellent enantiocontrol. The minor diastereomer is invariably formed in higher enantiomeric excess. This is the first example of an asymmetric Tamura cycloaddition reaction involving an alkene which is substituted with a single electron accepting group. An intriguing epimerisation process, which proceeds in methanol in the absence of catalysts was detected and subsequently exploited to convert the kinetic diastereomer into its thermodynamic counterpart, with concomitant improvement in product *ee*: thus the methodology allows access to both diastereomers in enantioenriched form. Deuterium isotope exchange experiments and DFT calculations have both shed light on the likely mechanism of exchange, which involves shuttle proton transfer facilitated by the protic additive.

Experimental section

Experimental details

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker DPX 400 MHz and Bruker Avance II 600 MHz spectrometers, using as solvent $CDCl_3$ or DMSO-d_6 and referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) DMSO (δ = 2.50 ppm). Chemical shifts are reported in ppm and coupling constants (J) in Hertz. Carbon NMR spectra were recorded on the same instruments (100.6 MHz and 150.9 MHz respectively) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. ESI mass spectra were acquired using a Waters Micromass LCT-time of flight mass spectrometer (TOF), interfaced to a Waters 2690 HPLC. The instrument was operated in positive or negative mode as required. EI mass spectra were acquired using a GCT Premier Micromass time of flight mass spectrometer (TOF). The instrument was operated in positive mode. APCI experiments were carried out on a Bruker microTOF-Q III spectrometer interfaced to a Dionex UltiMate 3000 LC or direct insertion probe. The instrument was operated in positive or negative mode as required. Agilent tuning mix APCI-TOF was used to calibrate the system. Flash chromatography was carried out using silica gel, particle size 0.04–0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualized by UV irradiation and $KMnO_4$ staining. Optical rotation measurements are quoted in units of 10^{-1} deg cm^2 g^{-1}. Methanol (MeOH), ethylene glycol, and isopropyl alcohol (i-PrOH) were dried over activated 3 Å molecular sieves. Commercially available anhydrous *t*-butyl methyl ether (MTBE) was used. Analytical CSP-HPLC was performed on Daicel Chiralpak, AD, AD-H, IA, or Chiralcel OD, OD-H, OJ-H (4.6 mm × 25 cm) columns. The X-ray crystallography data for crystal sample *cis*-**26b** was collected on a Rigaku Saturn 724 CCD diffractometer. Compound **12** was bought from Aldrich and was used without further purification.

Procedure for synthesis of homophthalic anhydride 1

A 100 mL round-bottomed flask containing a magnetic stirring bar was charged with homophthalic acid (2.0 g, 11.1 mmol). Acetic anhydride (25 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at 80 °C for 2 h. The excess acetic anhydride was removed *in vacuo* and the

solid obtained was triturated with diethyl ether (10 mL), filtered and dried to obtain homophthalic anhydride (**1**) as an off white solid (1.53 g, 85%). M.p. 141–142 °C (lit.[12] m.p. 143–144 °C); δ_H (400 MHz, DMSO-d_6) 8.05 (1 H, d, J = 7.9), 7.75 (1 H, app. t), 7.52 (1 H, app. t), 7.44 (1 H, d, J = 7.8), 4.28 (2 H, s); HRMS (m/z – ESI) Found: 161.0232 $(M - H)^-$ $C_9H_5O_3$ requires: 161.0239. Spectral data for this compound were consistent with those in the literature.[13]

General procedure A: preparation of nitroalkenes (12, 17a–g)

An oven-dried 25 mL round-bottomed flask containing a magnetic stirring bar under argon atmosphere was charged with dry THF (2.5 mL), *t*-butanol (2.5 mL) and nitroethane (1.1 mL, 15.0 mmol). The mixture was then cooled at 0 °C and the relevant aldehyde (10.0 mmol), followed by potassium *t*-butoxide (*t*-BuOK, 112.2 mg, 1.00 mmol – 10 mol%), were added. The reaction was allowed to warm to room temperature and was allowed to stir for 12 h. The mixture was then poured into water (10 mL) and extracted with EtOAc (3 × 10 mL), the combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the relative crude β-nitroalcohol that was used in the next step without any further purification.

The relative β-nitroalcohol obtained was dissolved in dichloromethane (10 mL) and added *via* syringe to a 50 mL oven-dried reaction vessel containing a magnetic stirring bar under argon atmosphere and cooled to −10 °C. To this solution was then added *via* syringe trifluoroacetic anhydride (TFAA, 1.5 mL, 10.5 mmol) and the reaction was allowed to stir for 30 min at −10 °C. Triethylamine (2.8 mL, 20.0 mmol) was then added dropwise and the reaction was allowed to stir for additional 30 min at −10 °C. The resulting mixture was quenched with the addition of saturated aqueous NH_4Cl solution (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were then dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a residue that was purified by flash column chromatography, eluting from 100% hexanes to 5% EtOAc in hexanes to furnish the relative nitroalkene (**12** and **17a–g**).

General procedure B: racemic preparation of products 13, 18–24

An oven-dried 10 mL reaction vessel containing a magnetic stirring bar under argon atmosphere was charged with the relevant β-methyl-(*E*)-nitroalkene (0.246 mmol) and with the relevant homophthalic anhydride (0.246 mmol). Anhydrous MTBE (2.5 mL, 0.1 M), followed by *N*,*N*-diisopropylethylamine (0.086 mL, 0.0492 mmol – 20 mol%), were then added *via* syringe and the reaction mixture was allowed to stir at room temperature for 22 h. The reaction mixture containing the corresponding carboxylic acid was then cooled to 0 °C and anhydrous MeOH (0.75 mL, 18.5 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 0.15 mL, 0.300 mmol) were added *via* syringe and the reaction was allowed to stir for 20 min. The crude reaction mixture containing the diastereomeric esters was directly loaded onto the silica column and the two major diastereomers were chromatographically isolated together. Temperature was maintained below 30 °C during the removal of the solvent under reduced pressure.

General procedure C: enantioselective preparation of products 13 and 18–24 (Tables 1 and 3)

An oven-dried 10 mL reaction vessel containing a magnetic stirring bar under argon atmosphere was charged with the relevant β-methyl-(*E*)-nitroalkene (0.246 mmol) and with a corresponding catalyst (0.0123 mmol – 5 mol%). Anhydrous MTBE (2.5 mL, 0.1 M) was then added *via* syringe and the reaction mixture was warmed to room temperature (Table 1) or the equilibrated temperature of 30 °C while stirring (Table 3). The relevant anhydride (0.246 mmol) was then added to the mixture and the reaction was allowed to stir for the time indicated in Tables 1 and 3. The diastereomeric ratio of the acid product formed was then determined by ^{1}H NMR spectroscopic analysis. The reaction was cooled to 0 °C and anhydrous MeOH (0.75 mL, 18.5 mmol), followed by trimethylsilyldiazomethane (2.0 M solution in diethyl ether, 0.15 mL, 0.300 mmol), were added *via* syringe to the reaction that was allowed to stir for 20 min. The crude reaction mixture containing the diastereomeric esters was directly loaded onto the silica column and the two diastereomers were chromatographically isolated together. Temperature was maintained below 30 °C during the removal of the solvent under reduced pressure. The diastereomeric ratio and the enantiomeric excess of the product formed, upon esterification, were then determined by CSP-HPLC using the conditions indicated in each case.

General procedure D: optimised epimerisation reaction (Tables 2 and 4)

The two isolated diastereomers of the product formed with the general procedure C were then dissolved in a mixture of MTBE (2.5 mL) and MeOH (0.75 mL) and transferred *via* syringe to an oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar. The flask was fitted with a condenser and the mixture was heated at reflux temperature for the time indicated in Tables 2 and 4. Solvent was removed *in vacuo* and the residue obtained was analysed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio of product formed upon epimerisation reaction. The major diastereomer (*trans*) was then isolated by flash column chromatography, eluting from 100% hexanes to 20% EtOAc in hexanes and the enantiomeric excess was determined by CSP-HPLC analysis using the conditions indicated in each case.

General procedure E: epimerisation reaction (Schemes 5 and 6)

The two isolated diastereomers of the product formed with the general procedure C were then dissolved in a mixture of MTBE (2.5 mL) and CD_3OD (0.75 mL) or EtOH or ethylene glycol and transferred *via* syringe to an oven-dried pressure tube containing a magnetic stirring bar. The tube was sealed and then the mixture was heated at reflux temperature for the time indicated in Schemes 5 and 6. Solvent was removed *in vacuo* and

the residue obtained was analysed by ^{1}H NMR spectroscopy to determine the diastereomeric ratio of product formed upon epimerisation reaction. Then the *P*-iodoanisole was added as an internal standard to check the deuterium insertion.

3-(*tert*-Butylamino)-4-(((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)amino)cyclobut-3-ene-1,2-dione (15). Synthesised according to the literature procedure and the spectral data for this compound were consistent with those in the literature.[7] M.p. 250 °C decomposition; TLC (EtOAc : MeOH, 9 : 1 v/v): R_f = 0.10; δ_H (400 MHz, $CDCl_3$): 8.70 (1 H, d, J = 4.0), 8.02 (1 H, d, J = 9.2), 7.78 (1 H br), 7.56 (1 H, d, J = 4.0), 7.40 (1 H, d, J = 9.2), 6.29–5.84 (1 H, m), 5.82–5.65 (1 H, m), 5.05–4.88 (2 H, m), 3.96 (3 H, s), 3.67–3.27 (2 H, m), 3.15 (1 H, app. t), 2.82–2.62 (2 H, m), 2.36–2.19 (1 H, m), 1.75–1.52 (3 H, m), 1.51–1.38 (1 H, m), 1.17 (9 H, s), 0.91–0.72 (1 H, m); HRMS (*m*/*z* – ESI): Found: 475.2712 $(M + H)^+$ $C_{28}H_{35}N_4O_3$ requires: 475.2709.

Characterisation data for synthesised of nitroalkenes (17a–g)

(*E*)-2-(2-Nitroprop-1-en-1-yl)naphthalene (17a). Prepared according to general procedure A, using recrystallised 2-naphthaldehyde (1.56 g, 10.0 mmol). After purification, product **17a** was obtained as a yellow solid (1.60 g, 75%). M.p. 86–87 °C (lit.[13] m.p. 81–83.5 °C); TLC (hexanes: EtOAc, 9 : 1 v/v): R_f = 0.43. Spectral data for this compound were consistent with those in the literature.[14] δ_H (400 MHz, $CDCl_3$): 8.26 (1 H, s), 7.95–7.84 (4 H, m), 7.61–7.50 (3 H), 2.55 (3 H); δ_C (100 MHz, $CDCl_3$): 147.9, 133.9, 133.7, 133.1, 130.7, 129.9, 128.8, 128.6, 127.9, 127.8, 127.1, 126.5, 14.3; ν_{max} (neat)/cm^{-1}: 3066, 2979, 2928, 1623, 1510, 1440, 1386, 1313, 1159, 1028, 991, 954, 930, 826, 759, 725; HRMS (*m*/*z* – APCI): Found: 214.0863 $(M + H)^+$ $C_{13}H_{12}NO_2$ requires: 214.0865.

(*E*)-1-Chloro-4-(2-nitroprop-1-en-1-yl)benzene (17b). Prepared according to general procedure A, using recrystallised 4-chlorobenzaldehyde (1.41 g, 10 mmol). After purification, product **17b** was obtained as a yellow solid (1.44 g, 73%). M.p. 81–82 °C (lit.[15] m.p. 84–85 °C); TLC (hexanes : EtOAc, 9 : 1 v/v): R_f = 0.46. Spectral data for this compound were consistent with those in the literature.[15] δ_H (400 MHz, $CDCl_3$): 8.03 (1 H, s), 7.44 (2 H, d, J = 8.8), 7.37 (2 H, d, J = 8.8), 2.44 (3 H, s); δ_C (100 MHz, $CDCl_3$): 148.2, 136.2, 132.4, 131.3, 130.9, 129.4, 14.1.

(*E*)-1-Methoxy-4-(2-nitroprop-1-en-1-yl)benzene (17c). Prepared according to general procedure IX, using freshly distilled 4-methoxybenzaldehyde (1.2 mL, 10.0 mmol). After purification, product **17c** was obtained as a yellow solid (1.26 g, 65%). M.p. 41–42 °C (lit.[15] m.p. 46–47 °C); TLC (hexanes : EtOAc, 9 : 1 v/v): R_f = 0.26. Spectral data for this compound were consistent with those in the literature.[14] δ_H (400 MHz, $CDCl_3$): 8.07 (1 H, s), 7.43 (2 H, d, J = 8.7), 6.98 (2 H, d, J = 8.7), 3.86 (3 H, s), 2.47 (3 H, s); HRMS (*m*/*z* – APCI): Found: 194.0812 $(M + H)^+$ $C_{10}H_{12}NO_3$ requires: 194.0817.

(*E*)-2-(2-Nitroprop-1-en-1-yl)furan (17d). Prepared according to general procedure A, using freshly distilled furan-2-carbaldehyde (0.828 mL, 10.0 mmol). After purification, product **17d** was obtained as a yellow solid (918.8 mg, 60%). M.p. 46–48 °C (lit.[16] m.p. 46–47 °C); TLC (hexanes : EtOAc, 9 : 1 v/v): R_f = 0.35. Spectral data for this compound were consistent with those in the literature.[16] δ_H (400 MHz, $CDCl_3$): 7.86 (1 H, s), 7.64 (1 H, d, J = 1.7), 6.82 (1 H, d, J = 3.5), 6.58 (1 H, dd, J = 1.7, 3.5), 2.60 (3 H, s); HRMS (*m*/*z* – APCI-DIP): Found: 154.0499 $(M + H)^+$ $C_7H_8NO_3$ requires: 154.0494.

(*E*)-(4-Nitropent-3-en-1-yl)benzene (17e). Prepared according to general procedure A, using freshly distilled hydrocinnamaldehyde (1.3 mL, 10.0 mmol). After purification, product **17e** was obtained as yellow oil (1.31 g, 69%). TLC (hexanes : EtOAc, 9 : 1 v/v): R_f = 0.36. Spectral data for this compound were consistent with those in the literature.[17] δ_H (400 MHz, $CDCl_3$): 7.31 (2 H, app. t), 7.23–7.18 (1 H, t, J = 7.4 H-3), 7.18–7.09 (3 H, m), 2.80 (2 H, t, J = 7.5), 2.53 (2 H, app. q), 2.03 (3 H, s); δ_C (100 MHz, $CDCl_3$): 148.3, 140.1, 135.0, 128.7, 128.5, 126.6, 34.4, 30.1, 12.5; HRMS (*m*/*z* – APCI-DIP): Found: 190.0868 $(M - H)^-$ $C_{11}H_{12}NO_2$ requires: 190.0863.

(*E*)-(2-Nitroprop-1-en-1-yl)cyclohexane (17f). Prepared according to general procedure A, using freshly distilled cyclohexanecarboxaldehyde (1.21 mL, 10.0 mmol). After purification, product **17f** was obtained as yellow oil (1.08 g, 65%). TLC (hexanes : EtOAc, 9 : 1 v/v): R_f = 0.61. Spectral data for this compound were consistent with those in the literature.[15] δ_H (400 MHz, $CDCl_3$): 6.97 (1 H, d, J = 10.0), 2.34–2.20 (1 H, m), 2.17 (3 H, s), 1.84–1.63 (5 H, m), 1.40–1.16 (5 H, m); δ_C (100 MHz, $CDCl_3$): 146.4, 141.0, 37.7, 31.8, 25.7, 25.4, 12.7; HRMS (*m*/*z* – APCI): Found: 170.1176 $(M + H)^+$ $C_9H_{16}NO_2$ requires: 170.1168.

(*E*)-4-Methyl-2-nitropent-2-ene (17g). Prepared according to general procedure A, using freshly distilled isobutyraldehyde (0.913 mL, 10.0 mmol). After purification, product **17g** was obtained as yellow oil (813.2 mg, 63%). TLC (hexanes : EtOAc, 9 : 1 v/v): R_f = 0.54. Spectral data for this compound were consistent with those in the literature.[15] δ_H (400 MHz, $CDCl_3$): 6.95 (1 H, d, J = 10.3, H-3), 2.66–2.50 (1 H, m, H-2), 2.17 (3 H, s, H-4), 1.11 (6 H, d, J = 6.7, H-1); HRMS: Analysis of product **17g** by high resolution mass spectrometry was not successful despite intensive efforts. ESI, EI, APCI and APCI-DIP techniques were all performed. Due to technical issues on the instrument, the CI technique could not be performed. As proof for the formation of **17g**, the ^{1}H NMR spectrum is attached in the ESI.†

(1*R*,2*S*,3*S*)-Methyl 3-methyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*trans*-13a, Table 4, entry 1). Prepared according to the consecutive use of general procedures C and D using catalyst **15** (5.8 mg, 0.0123 mmol – 5 mol%). Upon epimerisation, the reaction gave a diastereomeric mixture of esters in a 96 : 4 (*trans* : *cis*) ratio. The major diastereomer (*trans*-**13a**) was purified by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a white solid (75.8 mg, 91%). M. p. 180–181 °C; TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.24; $[\alpha]_D^{20}$ = +90.8 (c = 0.20, $CHCl_3$). CSP-HPLC analysis: Chiralpak AD-H (4.6 mm × 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**13a** 14.0 min (minor enantiomer) and 25.0 min (major enantiomer); *cis*-**13b**

7.9 min (major enantiomer) and 8.9 min (minor enantiomer); δ_H (400 MHz, $CDCl_3$): 8.22 (1 H, d, J = 8.0), 7.67 (1 H, app t), 7.53 (1 H, app t), 7.38–7.31 (4 H, m), 7.29–7.22 (2 H, m), 4.82 (1 H, d, J = 12.3), 4.58 (1 H, d, J = 12.3), 3.57 (3 H, s), 1.72 (3 H, s); δ_C (100 MHz, $CDCl_3$): 189.9, 171.0, 138.9, 135.4, 133.3, 129.6, 129.2, 129.1, 129.07, 129.0, 128.8, 127.3, 97.0, 52.8, 50.3, 48.9, 16.2; ν_{max} (neat)/cm^{-1}: 3008, 2955, 1732, 1692, 1598, 1550, 1453, 1345, 1211, 1166, 970, 794, 733, 700; HRMS (m/z – ESI): Found: 338.1027 $(M - H)^-$ $C_{19}H_{16}NO_5$ requires: 338.1028.

(1*S*,2*S*,3*S*)-Methyl 3-methyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*cis*-13b, Table 3, entry 1). Prepared according to general procedure C using catalyst **15** (5.8 mg, 0.0123 mmol – 5 mol%). The *cis*-diastereomer (*cis*-**13b**) was purified by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a white solid. M.p. 76–78 °C; TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.39; $[\alpha]_D^{20}$ = −76.4 (c = 0.10, $CHCl_3$); CSP-HPLC analysis: Chiralpak AD-H (4.6 mm × 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**13b** 7.6 min (major enantiomer) and 8.6 min (minor enantiomer); δ_H (400 MHz, $CDCl_3$): 8.18 (1 H, d, J = 7.8), 7.65 (1 H, app. t), 7.52 (1 H, app. t), 7.42 (1 H, d, J = 7.9), 7.22–7.26 (1 H, m), 7.18 (2 H, app. t), 6.97 (2 H, d, J = 7.4), 4.66 (1 H, d, J = 6.2), 4.58 (1 H, d, J = 6.2), 3.45 (3 H, s), 1.64 (3 H, s); δ_C (100 MHz, $CDCl_3$): 187.5, 170.8, 136.9, 134.6, 133.7, 132.2, 130.8, 129.6, 129.1, 128.9, 128.5, 128.2, 93.3, 53.1, 52.3, 46.1, 21.7; ν_{max} (neat)/cm^{-1}: 3004, 2952, 1743, 1701, 1599, 1542, 1457, 1298, 1200, 1179, 1003, 941, 816, 765, 705; HRMS (m/z – ESI): Found: 338.1026 $(M - H)^-$ $C_{19}H_{16}NO_5$ requires: 338.1028.

(1*R*,2*S*,3*S*)-Methyl 3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydro-[2,2′-binaphthalene]-1-carboxylate (*trans*-18a, Table 4, entry 2). Prepared according to the consecutive use of general procedure C and D, using β-methyl-(*E*)-nitroalkene **17a** (52.5 mg, 0.246 mmol) and anhydride **1** (39.9 mg, 0.246 mmol). Upon epimerisation, the reaction gave a diastereomeric mixture of esters in a >99 : 1 (*trans* : *cis*) ratio. The major diastereomer (*trans*-**18a**) was purified by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a white solid (88.7 mg, 93%). M.p. 205–207 °C; TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.21; $[\alpha]_D^{20}$ = +116.3 (c = 0.10, $CHCl_3$); CSP-HPLC analysis: Chiralcel OD-H (4.6 mm × 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**18a** 19.8 min (minor enantiomer) and 22.6 min (major enantiomer); *cis*-**18b** 10.5 min (major enantiomer) and 11.5 min (minor enantiomer); δ_H (400 MHz, $CDCl_3$): 8.25 (1 H, d, J = 7.9), 7.87–7.79 (3 H, m), 7.74 (1 H, s), 7.69 (1 H, app. t), 7.59–7.47 (3 H, m), 7.37 (2 H, app. d), 5.0 (1 H, d, J = 12.2), 4.72 (1 H, d, J = 12.2), 3.52 (3 H, s), 1.78 (3 H, s); δ_C (100 MHz, $CDCl_3$): 189.9, 171.0, 138.9, 135.7, 133.4, 133.3, 130.8, 129.7, 129.1, 128.9 (2C), 128.8, 128.4, 127.8, 127.3, 126.9, 126.7, 126.3, 97.1, 52.9, 50.4, 49.0, 16.4; ν_{max} (neat)/cm^{-1}: 3063, 3029, 3009, 2955, 2924, 2850, 1729, 1691, 1599, 1548, 1392, 1346, 1289, 1201, 1159, 968, 820, 733; HRMS (m/z – ESI): Found: 388.1194 $(M - H)^-$ $C_{23}H_{18}NO_5$ requires: 388.1185.

(1*R*,2*S*,3*S*)-Methyl 2-(4-chlorophenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*trans*-19a, Table 4, entry 3). Prepared according to the consecutive use of general procedures C and D, using β-methyl-(*E*)-nitroalkene **17b** (48.6 mg, 0.246 mmol) and anhydride **1** (39.9 mg, 0.246 mmol). Upon epimerisation, the reaction gave a diastereomeric mixture of esters in a >98 : 2 (*trans* : *cis*) ratio. The major diastereomer (*trans*-**19a**) was purified by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a white solid (85.6 mg, 93%). M.p. 200–202 °C; TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.24; $[\alpha]_D^{20}$ = +88.5 (c = 0.20, $CHCl_3$); CSP-HPLC analysis. Chiralpak AD-H (4.6 mm × 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**19a** 19.9 min (minor enantiomer) and 38.8 min (major enantiomer); *cis*-**19b** 8.7 min (major enantiomer) and 9.7 min (minor enantiomer); δ_H (400 MHz, $CDCl_3$): 8.22 (1 H, d, J = 7.2), 7.68 (1 H, app. t), 7.54 (1 H, app. t), 7.38–7.29 (3 H, m), 7.21 (2 H, d, J = 6.8), 4.81 (1 H, d, J = 12.3), 4.52 (1 H, d, J = 12.3), 3.60 (3 H, s), 1.70 (3 H, s); δ_C (100 MHz, $CDCl_3$): 189.5, 170.8, 138.5, 135.8, 135.2, 131.8, 130.5, 129.7, 129.4, 129.2, 128.7, 127.3, 96.8, 52.9, 49.7, 48.8, 16.1; ν_{max} (neat)/cm^{-1}: 3001, 2956, 2924, 2851, 1741, 1698, 1596, 1550, 1491, 1438, 1290, 1255, 1166, 1091, 1004, 844, 795, 740; HRMS (m/z – ESI): Found: 372.0639 $(M - H)^-$ $C_{19}H_{15}NO_5Cl$ requires: 372.0639.

(1*R*,2*S*,3*S*)-Methyl 2-(4-methoxyphenyl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*trans*-20a, Table 4, entry 4). Prepared according to the consecutive use of general procedures C and D, using β-methyl-(*E*)-nitroalkene **17c** (47.5 mg, 0.246 mmol) and anhydride **1** (39.9 mg, 0.246 mmol). Upon epimerisation, the reaction gave a diastereomeric mixture of esters in a 96 : 4 (*trans* : *cis*) ratio. The major diastereomer (*trans*-**20a**) was purified by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a white solid (83.2 mg, 92%). M.p. 193–195 °C; TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.17; $[\alpha]_D^{20}$ = +81.0 (c = 0.10, $CHCl_3$); CSP-HPLC analysis: Chiralpak AD-H (4.6 mm × 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**20a** 22.7 min (minor enantiomer) and 41.0 min (major enantiomer); *cis*-**20b** 10.9 min (major enantiomer) and 12.2 min (minor enantiomer); δ_H (400 MHz, $CDCl_3$): 8.21 (1 H, d, J = 7.9), 7.66 (1 H, app. t), 7.52 (1 H, app. t), 7.32 (1 H, d, J = 7.8), 7.18 (2 H, d, J = 8.2), 6.86 (2 H, d, J = 8.2), 4.76 (1 H, d, J = 12.4), 4.52 (1 H, d, J = 12.4), 3.79 (3 H, s), 3.58 (3 H, s), 1.70 (3 H, s); δ_C (100 MHz, $CDCl_3$): 190.1, 171.1, 159.9, 139.0, 135.6, 130.3, 129.6, 129.0, 128.9, 127.3, 125.1, 114.4, 97.2, 55.3, 52.8, 49.7, 49.1, 16.1; ν_{max} (neat)/cm^{-1}: 3000, 2960, 2927, 2849, 1739, 1693, 1595, 1550, 1513, 1438, 1385, 1344, 1294, 1250, 1182, 1107, 1027, 837, 796, 737; HRMS (m/z – ESI): Found: 368.1147 $(M - H)^-$ $C_{20}H_{18}NO_6$ requires: 368.1134.

(1*R*,2*R*,3*S*)-Methyl 2-(furan-2-yl)-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*trans*-21a, Table 4, entry 5). Prepared according to the consecutive use of general procedures C and D, using β-methyl-(*E*)-nitroalkene **17d** (37.7 mg, 0.246 mmol) and anhydride **1** (39.9 mg, 0.246 mmol). Upon

epimerisation, the reaction gave a diastereomeric mixture of esters in a 93 : 7 (*trans* : *cis*) ratio. The major diastereomer (*trans*-**21a**) was purified by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a white solid (71.1 mg, 88%). M.p. 136–138 °C; TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.22; $[\alpha]_D^{20}$ = +20.3 (c = 0.20, $CHCl_3$); CSP-HPLC analysis: Chiralpak AD-H (4.6 mm × 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**21a** 11.7 min (minor enantiomer) and 15.7 min (major enantiomer); *cis*-**21b** 8.7 min (major enantiomer) and 9.7 min (minor enantiomer); δ_H (400 MHz, $CDCl_3$): 8.18 (1 H, d, J = 7.9), 7.67 (1 H, app. t), 7.51 (1 H, app.), 7.40 (1 H, app. s), 7.36 (1 H, d, J = 7.8), 6.37–6.30 (1 H, m), 6.29–6.23 (1 H, m), 4.99 (1 H, d, J = 12.0), 4.57 (1 H, d, J = 12.0), 3.70 (3 H, s), 1.72 (3 H, s); δ_C (100 MHz, $CDCl_3$): 189.2, 171.0, 148.1, 143.6, 138.1, 135.7, 129.6, 129.1, 128.8, 127.4, 110.8, 110.5, 96.2, 53.1, 47.5, 44.6, 16.8; ν_{max} (neat)/cm^{-1}: 2954, 2923, 2852, 1732, 1694, 1598, 1549, 1436, 1347, 1293, 1206, 1160, 974, 920, 731; HRMS (m/z – ESI): Found: 328.0838 $(M - H)^-$ $C_{17}H_{14}NO_6$ requires: 328.0821.

(1*R*,2*R*,3*S*)-Methyl 3-methyl-3-nitro-4-oxo-2-phenethyl-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*trans*-22a, Table 4, entry 6). Prepared according to the consecutive use of general procedures C and D, using β-methyl-(*E*)-nitroalkene **17e** (47.0 mg, 0.246 mmol) and anhydride **1** (39.9 mg, 0.246 mmol). Upon epimerisation, the reaction gave a diastereomeric mixture of esters in a 89 : 11 (*trans* : *cis*) ratio. The major diastereomer (*trans*-**22a**) was purified by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a white solid (74.0 mg, 82%). M.p. 138–140 °C; TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.29; $[\alpha]_D^{20}$ = −38.8 (c = 0.20, $CHCl_3$); CSP-HPLC analysis: Chiralpak IA (4.6 mm × 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**22a** 11.8 min (major enantiomer) and 13.5 min (minor enantiomer); *cis*-**22b** 9.8 min (minor enantiomer) and 13.9 min (major enantiomer); δ_H (400 MHz, $CDCl_3$): 8.12 (1 H, d, J = 7.9), 7.64 (1 H, app. t), 7.48 (1 H, app. t), 7.32–7.24 (3 H, m), 7.20 (1 H, t, J = 7.3), 7.11 (1 H, d, J = 7.4), 3.94 (1 H, d, J = 10.5), 3.82 (3 H, s), 3.75–3.66 (1 H, m), 2.57 (2 H, app. t), 1.82–1.64 (5 H, m); δ_C (100 MHz, $CDCl_3$): 189.8, 172.4, 140.8, 138.4, 135.5, 129.2, 129.0, 128.9, 128.7, 128.4, 127.8, 126.5, 96.4, 53.0, 50.8, 43.4, 34.2, 32.8, 16.1; ν_{max} (neat)/cm^{-1}: 3063, 3004, 2958, 2924, 2878, 1732, 1689, 1597, 1549, 1451, 1342, 1293, 1210, 1165, 999, 969, 752, 729; HRMS (m/z – ESI): Found: 390.1335 $(M + Na)^+$ $C_{21}H_{21}NO_5Na$ requires: 390.1317.

(1*R*,2*R*,3*S*)-Methyl 2-cyclohexyl-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*trans*-23a, Table 3, entry 7). Prepared according to general procedure C, using β-methyl-(*E*)-nitroalkene **17f** (41.6 mg, 0.246 mmol), catalyst **15** (23.3 mg, 0.0492 mmol – 20 mol%) and anhydride **1** (39.9 mg, 0.246 mmol). Upon esterification, the reaction gave a diastereomeric mixture of esters in a 98 : 2 (*trans* : *cis*) ratio. The major diastereomer (*trans*-**23a**) was isolated by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a pale yellow oil which contained 17% of dimethyl homophthalate as impurity that was not possible to separate. The given yield is calculated based on the mass return of the impure sample considering the spectroscopically determined amount of the known impurity (42.2 mg, 50%). TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.38; CSP-HPLC analysis: Chiralpak AD (4.6 mm × 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**23a** 6.6 min (major enantiomer) and 7.4 min (minor enantiomer); δ_H (400 MHz, $CDCl_3$): 8.07 (1 H, d, J = 7.7), 7.60 (1 H, app. t), 7.44 (1 H, app. t), 7.31 (1 H, d, J = 7.8), 4.11 (1 H, d, J = 8.8), 3.77 (3 H, s), 3.62–3.55 (1 H, m), 1.79–1.49 (8 H, m), 1.48–1.36 (1 H, m), 1.35–0.95 (5 H, m); δ_C (100 MHz, $CDCl_3$): 189.8, 172.9, 138.9, 135.2, 129.7, 128.7, 128.6, 128.3, 96.7, 52.9, 48.2, 45.5, 39.3, 33.9, 30.0, 27.2, 26.8, 26.1, 18.2; ν_{max} (neat)/cm^{-1}: 2929, 2854, 1735, 1704, 1596, 1549, 1449, 1432, 1289, 1199, 1161, 1081, 967, 740; HRMS (m/z – ESI): Found: 344.1488 $(M - H)^-$ $C_{19}H_{22}NO_5$ requires: 344.1498.

(1*R*,2*R*,3*S*)-Methyl 2-isopropyl-3-methyl-3-nitro-4-oxo-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*trans*-24a, Table 3, entry 8). Prepared according to general procedure C, using β-methyl-(*E*)-nitroalkene **17g** (39.8 mg, 0.246 mmol) and anhydride **1** (39.9 mg, 0.246 mmol). Upon esterification, the reaction gave a diastereomeric mixture of esters in a >99 : 1 (*trans* : *cis*) ratio. The major diastereomer (*trans*-**24a**) was isolated by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a pale yellow oil which contained 3% of dimethyl homophthalate as impurity that was not possible to separate. The given yield is calculated based on the mass return of the impure sample considering the spectroscopically determined amount of the known impurity (35.2 mg, 47%). TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.37 $[\alpha]_D^{20}$ = −53.4 (c = 0.20, $CHCl_3$)*; CSP-HPLC analysis: Chiralpak AD (4.6 mm × 25 cm), hexane/IPA: 90/10, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**24a** 16.8 min (major enantiomer) and 17.7 min (minor enantiomer); δ_H (400 MHz, $CDCl_3$): 8.08 (1 H, d, J = 7.9), 7.61 (1 H, app. t), 7.45 (1 H, app. t), 7.30 (1 H, d, J = 7.8), 4.08 (1 H, d, J = 8.8), 3.77 (3 H, s), 3.71–3.63 (1 H, m), 1.87 (1 H, m), 1.74 (3 H, s), 1.05 (3 H, d, J = 7.0), 0.94 (3 H, d, J = 7.0); δ_C (100 MHz, $CDCl_3$): 189.8, 172.8, 138.9, 135.2, 129.6, 128.7, 128.6, 128.3, 96.7, 52.9, 47.9, 45.2, 28.5, 23.6, 18.8, 17.9; ν_{max} (neat)/cm^{-1}: 2970, 2894, 1737, 1697, 1599, 1550, 1453, 1386, 1288, 1158, 969, 792, 733, 659; HRMS (m/z – ESI): Found 304.1190 $(M - H)^-$ $C_{16}H_{18}NO_5$ requires: 304.1185. * $[\alpha]_D^{20}$ refers to *trans*-**24a** containing 3% impurity.

Synthesis of compound 25 7-bromoisochromane-1,3-dione

The anhydride **25** was synthesised from 5-bromo-2-(carboxymethyl) benzoic acid **25a** which was synthesised from homophthalic acid. In a three-necked 250 mL round-bottomed flask containing a magnetic stirring bar, homophthalic acid (5.00 g, 27.8 mmol) and potassium bromate (6.58 g, 39.4 mmol) were mixed in water (30 mL). The flask was then fitted with a condenser and the reaction mixture was heated at 90 °C. A mixture of sulfuric acid (24 mL, 95%) and water (40 mL) was

added dropwise to the resulting mixture at 90 °C over a period of 30 min. After completion of addition, the mixture was allowed to stir for 2 h and was cooled to the room temperature. The solid formed was isolated by suction filtration, washed with water and recrystallised from EtOAc/hexanes (4 : 1) to furnish the acid **25a** as a white solid (4.23 g, 58%). M.p. 214–216 °C (lit.[18] m.p. 216–217 °C). Spectral data for this compound were consistent with those in the literature.[18] δ_H (400 MHz, DMSO-d_6):*7.98 (1 H, d, J = 2.0), 7.71 (1 H, dd, J = 2.0, 8.1), 7.31 (1 H, d, J = 8.1), 3.91 (2 H, s). *The protic signals (H-5 and H-6) are not visible in DMSO-d_6.

An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar was charged with 5-bromo-2-(carboxymethyl)benzoic acid (**25a**, 500.0 mg, 1.93 mmol). Freshly distilled acetyl chloride (5.0 mL) was added, the flask was fitted with a condenser and the reaction mixture was heated at reflux temperature under an argon atmosphere for 16 h. The reaction was then cooled to room temperature and the excess acetyl chloride was removed *in vacuo*. The solid obtained was triturated with diethyl ether (5 mL), filtered and dried to give **25** as an off white solid (404.7 mg, 87%). M.p. 176–177 °C (lit. M.p. 171–173 °C). Spectral data for this compound were consistent with those in the literature.[19] δ_H (400 MHz, DMSO-d_6): 8.13 (1 H, d, J = 2.0), 7.94 (1 H, dd, J = 2.0, 8.3), 7.41 (1 H, d, J = 8.3), 4.23 (2 H, s); HRMS (m/z – ESI): Found: 238.9335 $(M - H)^-$ $C_9H_4BrO_3$ requires: 238.9344.

(1*R*,2*S*,3*S*)-Methyl 6-bromo-3-methyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*trans*-26a, Scheme 3). Prepared according to the consecutive use of general procedures C and D, using β-methyl-(*E*)-nitrostyrene (**12**, 40.1 mg, 0.246 mmol) and anhydride **25** (59.3 mg, 0.246 mmol). Upon epimerisation, the reaction gave a diastereomeric mixture of esters in a >99 : 1 (*trans* : *cis*) ratio. The major diastereomer (*trans*-**26a**) was purified by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a white solid (94.9 mg, 92%). M.p. 68–70 °C; TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.36; $[\alpha]_D^{20}$ = +72.2 (c = 0.20, $CHCl_3$); CSP-HPLC analysis: Chiralpak IA (4.6 mm × 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *trans*-**26a** 14.7 min (minor enantiomer) and 18.8 min (major enantiomer); *cis*-**26b** 8.0 min (minor enantiomer) and 8.6 min (major enantiomer); δ_H (400 MHz, $CDCl_3$): 8.33 (1 H, d, J = 2.1), 7.77 (1 H, dd, J = 2.1, 8.3), 7.37–7.31 (3 H, m), 7.26–7.20 (3 H, m), 4.78 (1 H, d, J = 12.0), 4.49 (1 H, d, J = 12.0), 3.57 (3 H, s), 1.71 (3 H, s); δ_C (100 MHz, $CDCl_3$): 188.8, 170.6, 138.4, 137.4, 133.0, 132.2, 130.4, 129.3, 129.2 (2C), 129.1, 123.4, 96.6, 53.0, 50.2, 48.6, 16.3; ν_{max} (neat)/cm^{-1}: 3080, 3038, 2958, 1741, 1698, 1589, 1547, 1433, 1341, 1293, 1251, 1169, 990, 907, 756, 705; HRMS (m/z – ESI): Found: 416.0125 $(M - H)^-$ $C_{19}H_{15}NO_5Br$ requires: 416.0134.

(1*S*,2*S*,3*S*)-Methyl 6-bromo-3-methyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*cis*-26b, Scheme 3). Prepared according to general procedure C, using β-methyl-(*E*)-nitrostyrene (**12**, 40.1 mg, 0.246 mmol) and anhydride **25** (59.3 mg, 0.246 mmol). Upon esterification, the reaction gave a diastereomeric mixture of esters in a 58 : 42 (*trans* : *cis*) ratio. The minor diastereomer (*cis*-**26b**) was purified by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a white solid (36.1 mg, 35%). M.p. 185–186 °C; TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.24; $[\alpha]_D^{20}$ = −69.7 (c = 0.20, $CHCl_3$); CSP-HPLC analysis: Chiralpak IA (4.6 mm × 25 cm), hexane/IPA: 95/5, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: *cis*-**26b** 8.0 min (minor enantiomer) and 8.6 min (major enantiomer); δ_H (400 MHz, $CDCl_3$): 8.30 (1 H, d, J = 1.5), 7.75 (1 H, dd, J = 1.5, 8.5), 7.34 (1 H, d, J = 8.5), 7.30–7.23 (1H, m), 7.20 (2 H, app. t), 6.93 (2 H, d, J = 7.6), 4.64 (1 H, d, J = 6.1), 4.47 (1 H, d, J = 6.1), 3.45 (3 H, s), 1.62 (3 H, s); δ_C (151 MHz, $CDCl_3$): 186.3, 170.3, 137.4, 135.6, 133.7, 133.3, 132.8, 130.8, 129.5, 129.2, 129.1, 122.9, 93.1, 53.1, 52.4, 45.7, 21.6; ν_{max} (neat)/cm^{-1}: 3088, 3000, 2948, 1745, 1705, 1593, 1543, 1433, 1196, 1176, 1003, 903, 836, 702; HRMS (m/z – ESI): Found: 416.0123 $(M - H)^-$ $C_{19}H_{15}NO_5Br$ requires: 416.0134.

(1*R*,2*S*,3*S*,4*S*)-Methyl 4-hydroxy-3-methyl-3-nitro-2-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxylate (*trans*-27, Scheme 4). An oven-dried 10 mL round-bottomed flask containing a magnetic stirring bar was charged with *trans*-**13a** (83.5 mg, 0.246 mmol) and anhydrous MeOH (2.5 mL, 0.1 M) under argon atmosphere. To the mixture was added $NaBH_4$ (37.2 mg, 0.984 mmol) and the reaction was allowed to stir at room temperature for 16 h. The excess $NaBH_4$ was then quenched by addition of a saturated aqueous NH_4Cl solution (5 mL) followed by removal of MeOH under reduced pressure. The resulting aqueous mixture was then extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford a crude diastereomeric mixture of product **27** in a >98 : 2 (*trans* : *cis*) ratio. The major diastereomer (*trans*-**27**) was purified by flash column chromatography, eluting in gradient from 100% hexanes to 20% EtOAc in hexanes, to give a white solid (76.6 mg, 91%). M.p. 197–195 °C; TLC (hexanes : EtOAc, 8 : 2 v/v): R_f = 0.27; $[\alpha]_D^{20}$ = +122.1 (c = 0.20, $CHCl_3$); CSP-HPLC analysis: Chiralcel ODH (4.6 mm × 25 cm), hexane/IPA: 90/10, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 9.2 min (major enantiomer) and 11.7 min (minor enantiomer); δ_H (400 MHz, $CDCl_3$):* 7.68 (1 H, d, J = 7.5), 7.44–7.37 (1 H, m), 7.36–7.29 (5 H, m), 7.29–7.22 (2 H, m), 5.91 (1 H, s), 4.42 (1 H, d, J = 11.8), 4.28 (1 H, d, J = 11.8), 3.57 (3 H, s), 1.49 (3 H, s); δ_C (100 MHz, $CDCl_3$): 172.3, 136.4, 134.4, 130.9, 129.1, 128.9, 128.8, 128.6, 128.5, 127.0, 126.5, 95.9, 74.9, 52.7, 50.6, 50.0, 10.8; ν_{max} (neat)/cm^{-1}: 3472, 3214, 1722, 1544, 1445, 1352, 1301, 1193, 1054, 989, 750, 702; HRMS (m/z – APCI): Found: 342.1336 $(M + H)^+$ $C_{19}H_{20}NO_5$ requires: 342.1338. *The protic signal (H-13) is not visible in $CDCl_3$.

Methyl (1*R*,2*S*,3*S*)-3-methyl-3-nitro-4-oxo-2-phenyl-1,2,3,4-tetrahydronaphthalene-1-carboxylate-1-d, 13a′. Prepared from the general procedure E. δ_H (400 MHz, $CDCl_3$): 8.22 (1 H, d, J = 8.0), 7.67 (1 H, app. t), 7.53 (1 H, app. t), 7.38–7.31 (4 H, m), 7.29–7.22 (2 H, m), 4.82 (1 H, m), 4.58 (0.6 H, 0.4D, d, J = 12.3), 3.57 (3 H, s), 1.72 (3 H, s); δ_D (400 MHz, $CDCl_3$): 4.57 (1D, s).

Computational details

The geometry of the isolated molecules as well as those of the different stationary structures of the Potential Energy Surface (PES) were optimised by using the B3LYP[20] density functional theory (DFT) approach, which combines the Becke's three-parameter nonlocal hybrid exchange potential with the nonlocal correlation functional of Lee, Yang and Parr with standard 6-311+G(d,p) basis sets.[21] Vibrational analyses were performed to confirm that the different optimized structures corresponded to true minima of the PES or to transition states. All calculations were carried out with the Gaussian09 program.[22] The self-consistent reaction field (SCRF) calculations using the PCM solvation model were carried out re-optimising the gas-phase optimised structures. The dielectric constant in the PCM calculations was set to $\varepsilon = 3.38$ to simulate diisopropylether similar to the solvent medium used in the experimental studies. All the calculations have been carried out at 342 K of temperature.

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