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Synthesis of α,β-Unsaturated δ-Lactones by Vinyl Acetate Mediated Asymmetric Cross-Aldol Reaction of Acetaldehyde: Mechanistic Insights

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A tandem asymmetric cross-aldol reaction involving the in situ generation of acetaldehyde from vinyl acetate has been developed that may resolve the challenges associated with the handling of acetaldehyde. The simple protocol, mild reaction conditions and unique harmony of an organocatalyst with a biocatalyst make this method a valuable tool for the synthesis of asymmetric β-hydroxy aldehydes. By using this methodology we have accessed α,β-unstaurated δ-lactones as well as isochromenones with high enantioselectivities from both asymmetric β-hydroxy aldehydes and ketones. Systemic density functional theory (DFT) studies were also performed to gain mechanistic insights into the role of hydrogen bonding in the asymmetric cross-aldol reaction of acetaldehyde and in the key *cis*/*trans* isomerisation step in the synthesis of δ-lactones.

Introduction

The synthesis of asymmetric β-hydroxy carbonyl compounds has enjoyed its lion's share of problems addressed throughout the history of organic synthesis. Asymmetric β-hydroxy carbonyl compounds are largely accessed through the aldol reaction,[1] which is arguably the simplest and most economic approach to C–C bond formation,[2] and has flourished over the years as a powerful tool for the synthesis of stereochemically complex molecules.[3,4] However, despite many advances, acetaldehyde, the simplest aldehyde, largely remains unexplored in this reaction owing to difficulties in its handling and dual reactivity, that is, it may act as an electrophile as well as a nucleophile. Following the pioneering work of List[5] and Hayashi and their coworkers,[6] a myriad of reports have appeared exploiting acetaldehyde as a nucleophile for cross-aldol,[7] self-aldol,[8] Michael[9,10] and alkynylation[11] reactions, which have served as an impetus to accessing scaffolds of biological significance, for example, rolipram,[12,13] baclofen,[14] pregabalin,[15,16] convolutamydines[17] and (+)-tetrahydropyrenophorol.[18] However, the use of acetaldehyde has proven difficult as a result of its tendency to polymerise, its low-boiling point and the formation of side-products. To address this issue, paraldehyde has recently been used as a source of acetaldehyde in Michael reactions. Therefore we envisaged the use of vinyl acetate (a stable liquid generally employed in *trans*-esterification reactions and considered as environmentally benign) as an alternative source of acetaldehyde for enantioselective cross-aldol reactions. Our efforts led to the identification of an organocatalyst capable of directing aldol reactions in high yields and enantioselectivities. The reactions possibly involve the lipase-catalysed in situ hydrolysis of vinyl acetate to generate acetaldehyde, followed by organocatalysed aldol reactions with aromatic aldehydes.

We also successfully extended our methodology to the asymmetric synthesis of α,β-unsaturated δ-lactones, a motif that is a characteristic underlying element of many antiproliferative agents, immunosuppressants and inhibitors of different enzymes.[19] In addition, α,β-unsaturated δ-lactones are a part of a wide variety of natural scaffolds, for example, fostriecin, callystatin, (*R*)-goniothalamin, asperlin, leptomycin B and kazusamycin A,[20] or serve as intermediates in the synthesis of bioactive molecules, such as tetrahydrolipstatin[21] and clavulactone.[22] Owing to their importance, many methods have been developed for their synthe-

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sis, such as the hetero-Diels–Alder (HDA) reactions of the Brassard diene with aldehydes or ketones,[23–26] solid-phase Diels–Alder cycloaddition,[27] the annulation of open-chain precursors,[28] N-heterocyclic-carbene-catalysed reactions of α-bromo α,β-unsaturated aldehydes,[29] reactions of homoallylic alcohols with the lithium enolate of methyl acetate[30] and enzymatic cyclisation[31] (Figure 1). Intriguingly, most of these methods suffer from poor enantioselectivity and substrate scope, and often employ environmentally hazardous metal catalysts. The biggest advantage of our method is that virtually any aldol product with a β-hydroxy carbonyl moiety can be converted enantioselectively into an α,β-unsaturated δ-lactone, which may be subsequently used for the synthesis of enantiopure valerolactones.[32] In this work we have also performed a systemic density functional theory (DFT) study to gain an understanding of the mechanism of enantioselective cross-aldol reactions of acetaldehyde as well as the formation of lactones, which is of particular intrigue because it involves the thermal isomerisation of the double bond.

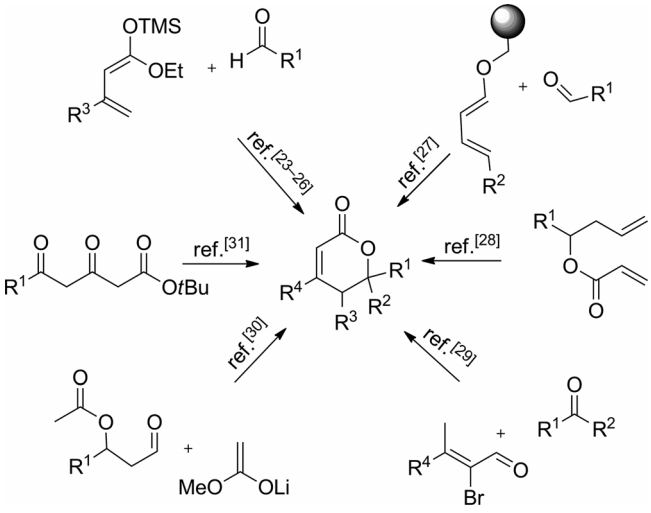
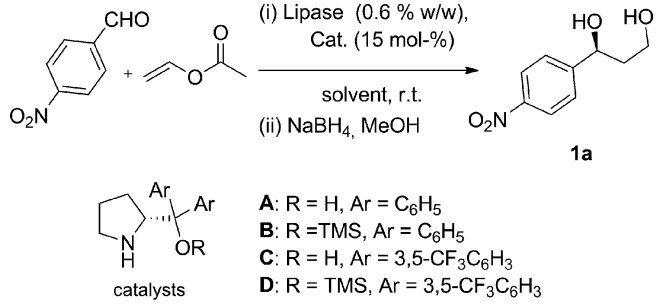


Figure 1. Methods for the synthesis of α,β-unsaturated δ-lactones.

fluoromethyl-substituted diarylprolinol silyl ether (**D**) resulted in a significant decrease in yield (entry 4, Table 1). We also examined the effect of various lipases, namely CAL-B, ABL, PPL and PSL, on the reaction, only to find N-435 to be the lipase of choice. Notably, N-435 leads to a better rate of reaction and enantioselectivity than CAL-B (recombinant from *Aspergillus oryzae*) in *i*PrOH (entries 3 and 5, Table 1). In contrast to the common assumption that the use of alcoholic solvents results in low enantioselectivity, this reaction in methanol, ethanol, isobutanol and *n*-butanol gave the corresponding product with high enantioselectivity, which suggests its possible use in the development of green methodologies.

Table 1. Effect of various lipases, catalysts and solvents on the aldol reaction of vinyl acetate and *p*-nitrobenzaldehyde.



Entry	Catalyst	Lipase[a]	Solvent[b]	Time [h]	Yield[c] [%]	*ee* [%]
1	**A**	N-435	*i*PrOH	72	20	15
2	**B**	N-435	*i*PrOH	96	<10	–
3	**C**	N-435	*i*PrOH	48	94	95
4	**D**	N-435	*i*PrOH	72	<10	–
5	**C**	CAL-B	*i*PrOH	96	28	72
6	**C**	ABL	*i*PrOH	120	<10	–
7	**C**	PPL	*i*PrOH	120	<10	–
8	**C**	PSL	*i*PrOH	96	25	64
9	**C**	N-435	MeOH	72	60	92
10	**C**	N-435	EtOH	72	72	90
11	**C**	N-435	*i*BuOH	72	86	92
12	**C**	N-435	*n*BuOH	72	88	95

[a] Lipase: 1 mg per mmol of aromatic aldehyde. [b] Solvent/vinyl acetate (1:1). [c] Isolated yields.

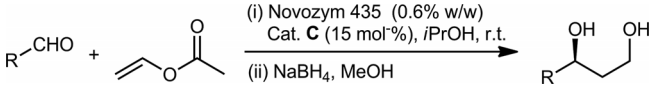
Results and Discussions

The aldol reaction of *p*-nitrobenzaldehyde and vinyl acetate (10 equiv.) as a test reaction was carried out in the presence of lipase Novozym435 (N-435, 0.5%, w/w). From our previous work we knew that proline as an organocatalyst in tandem with lipase can catalyse vinyl acetate mediated aldol reaction but with low enantioselectivity, and reaction with N-435 in the absence of catalyst gives the aldol product in 25% yield.[33] Initially, we examined the impact of catalysts on the enantioselectivity of the resulting products. The reaction with diphenylprolinol (**A**) and diphenylprolinol silyl ether (**B**) with lipase N-435 in 2-propanol (*i*PrOH) gave the corresponding products in low yields and enantioselectivities. The reaction with the trifluoromethyl-substituted diarylprolinol (**C**) provided the cross-aldol product in good yield and high enantioselectivity (entry 3, Table 1). The tri-

Having optimised the conditions, we next investigated the substituent effects of the aldehydes on the aldol reaction to identify its scope and limitations (Table 2). The reactions with aromatic aldehydes bearing electron-withdrawing groups (entries 1–3, Table 2) proceeded smoothly to afford the corresponding aldol products in excellent yields and enantioselectivities. Halogen-substituted benzaldehydes (entries 4–8, Table 2) also gave the corresponding products in good yields and with excellent enantioselectivities. Although the reaction of the electron-donating aldehyde *p*-methoxybenzaldehyde proceeded slowly and in low yield, a good enantioselectivity was observed (entry 9, Table 2). On the other hand, reactive aldehydes, such as heteroaromatic and pentafluoro-substituted aromatic aldehydes (entries 10–

13, Table 2), were found to be suitable electrophiles, giving high enantioselectivities and yields. Naphthaldehyde (entry 14, Table 2), which is less active towards cross-aldol reactions, also provided the corresponding product with high enantiopurity. Because we had been using the *R* isomer of the catalyst, we were interested to know whether the reaction system could be successfully extended to the *S* isomer. Therefore we carried out the reactions of *p*-nitro- and *m*-nitrobenzaldehyde in the presence of catalyst **E** (*S* isomer of catalyst **C**, Figure 2) under similar conditions. As expected, the reactions resulted in the formation of the corresponding products with comparably high enantiopurities and yields (entries 15 and 16, Table 2).

Table 2. Aldol reactions of various aromatic aldehydes with vinyl acetate.



Entry	R	Product	*t* [h]	Yield[a] [%]	*ee* [%]
1	4-$NO_2C_6H_4$	**1a**	48	94	95
2	2-$NO_2C_6H_4$	**1b**	48	92	97
3	3-$NO_2C_6H_4$	**1c**	48	89	93
4	3-BrC_6H_4	**1d**	96	66	99
5	3-ClC_6H_4	**1e**	96	74	87
6	2,4-$Cl_2C_6H_4$	**1f**	72	76	99
7	2,4-$F_2C_6H_4$	**1g**	72	75	99
8	3-Br-4-FC_6H_4	**1h**	72	78	99
9	4-$CH_3OC_6H_4$	**1i**	108	60	94
10	quinolin-4-yl	**1j**	72	84	99
11	quinolin-2-yl	**1k**	96	80	90
12	4-pyridyl	**1l**	72	74	90
13	2,3,4,5,6-pentafluoro	**1m**	48	80	99
14	1-naphthyl	**1n**	120	64	94
15	4-$NO_2C_6H_4$[b]	**1o**	48	95	94
16	3-$NO_2C_6H_4$[b]	**1p**	48	82	94

[a] Yields obtained after the reduction of the aldol product. [b] Reaction was performed with catalyst **E** and resulted in the cross-aldol product with the *R* configuration.

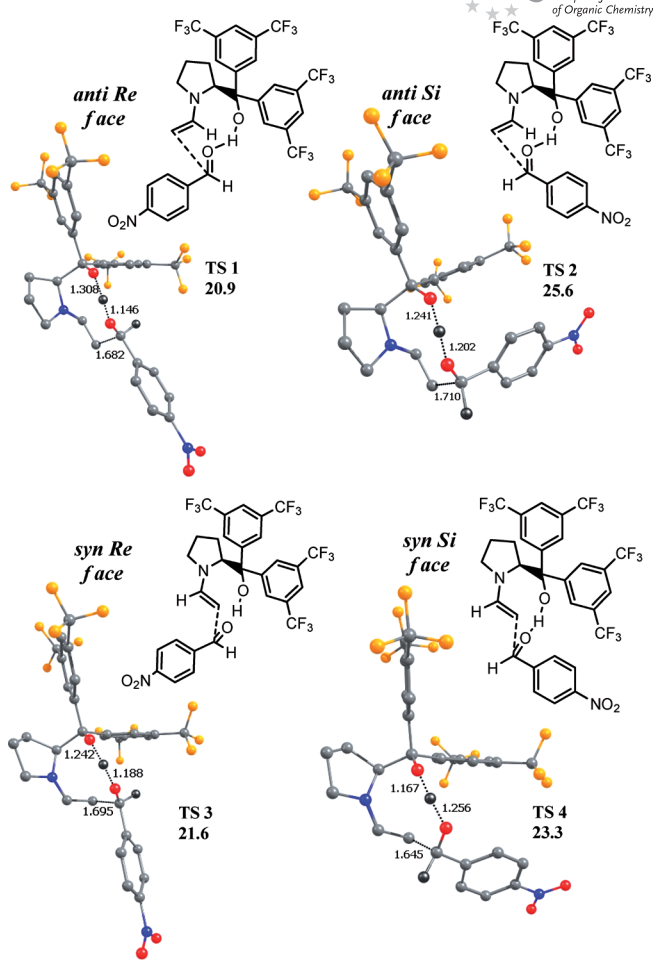


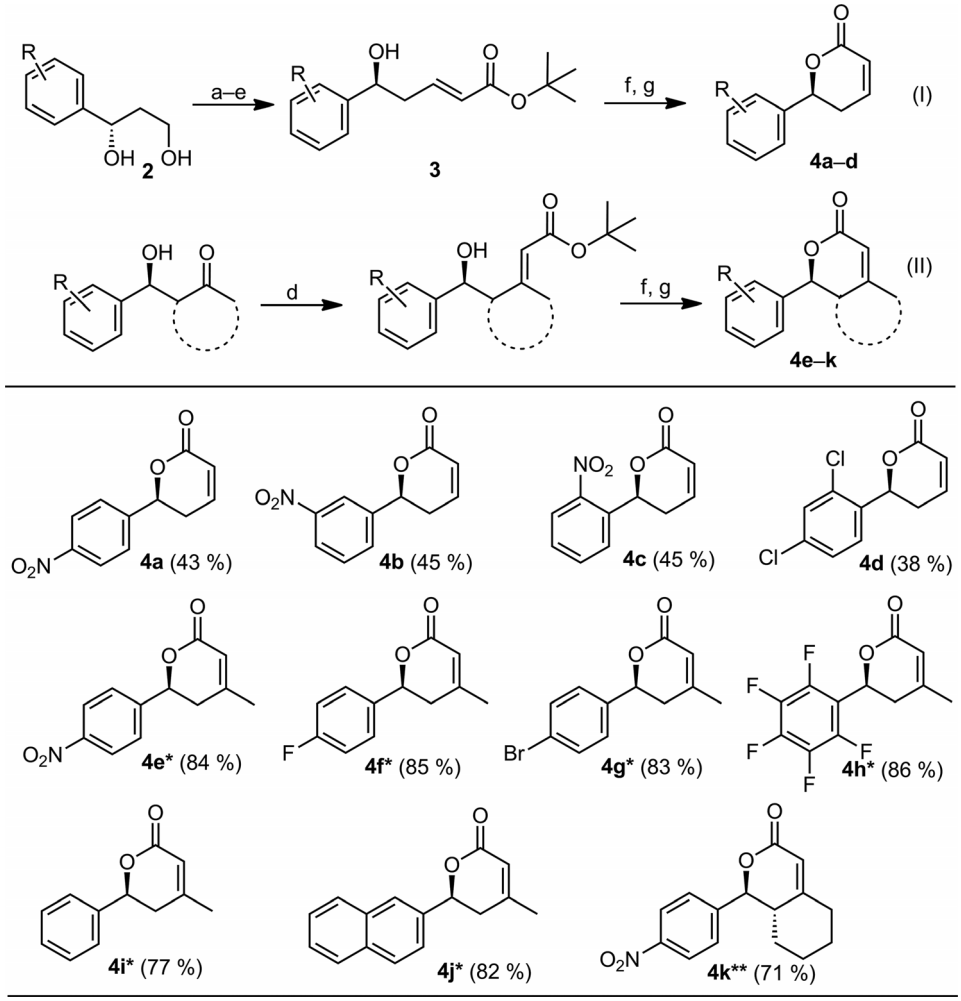
Figure 2. Optimised structures of the different transitions states for the cross-aldol reaction of acetaldehyde at the TZVP/PBE/B3LYP level of theory.

Furthermore, to shed light on the mechanism of the reaction we performed DFT calculations. The reaction starts with the interaction between acetaldehyde and catalyst **E** to form **TS1** (32.1 kcal/mol), which tautomerises to the energetically more stable enamine (11.8 kcal/mol; see Figure S1 in the Supporting Information). The resultant enamine adopts two different configurations, with the *anti*-enamine more stable than the *syn*-enamine. Furthermore, each enamine intermediate can approach the aldehyde in two different ways, resulting in four different transition states: *anti-Re* face (**TS1**), *anti-Si* face (**TS2**), *syn-Re* face (**TS3**) and *syn-Si* face (**TS4**; Figure 2). On the basis of the DFT calculations, we propose that the transition state involves hydrogen bonding between the acidic OH group of the trifluoromethyl-substituted catalyst **E** and the carbonyl of acetaldehyde, which activates the substrate for reaction as well as controlling the direction of approach. The other significant observation from the energy-minimised molecular orientations is that the bulky aryl rings discriminate the enantiofaces on the basis of steric hindrance; in the attack at the *Re* face, the aryl rings of the aldehyde and catalyst are sufficiently far apart for a stable adduct of low energy to form (20.9 kcal/mol), whereas in the case of the approach on the *Si* face, the aromatic groups of the two substrates are sufficiently close that they interact sterically leading to a less stable adduct with a higher energy (25.6 kcal/mol), and hence this approach is less favourable for bond formation. The results of the DFT studies are in agreement with the experimental results (Figure 2).

Our next aim was to extend this methodology to the synthesis of enantiopure α,β-unsaturated δ-lactones. Thus, first, the reduced cross-aldol product **2** was protected by using TBDMSCl and imidazole in DCM at 0 °C to give the TBDMS-protected diol, which was then selectively deprotected by using HF·pyridine in THF and subsequently oxidised by using Dess–martin periodinane in DCM. The resulting product was then subjected to Wittig reaction with (*tert*-butoxycarbonylmethylene)triphenylphosphorane in DCM, followed by deprotection of the secondary alcohol

by using TBAF in THF to give **3**. Compound **3** was deprotected with TFA, which, after drying, was stirred at 70 °C for 4 h in the presence of *p*-dimethylaminopyridine (DMAP) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) to accomplish the synthesis of δ-lactones **4a**–**d** [Scheme 1, Equation (I)]. The methodology with β-hydroxy ketone gave access to δ-lactones in two high-yielding steps, circumventing the need for any protection/deprotection [**4e**–**i**, Scheme 1, Equation (II)]. The methodology was also used for the synthesis of asymmetric isochromenone **4k** and hence can be used to synthesize a library of isochromenones, which are of immense biological importance, and indeed a number of methods over the years have appeared for their synthesis.[34,35] It is also imperative to mention here that these α,β-unsaturated δ-lactones are also precursors for the synthesis of δ-valerolactones.[32]

The synthesis of α,β-unsaturated δ-lactones involves a very important step, namely, the thermally induced *trans*/*cis* isomerisation of the alkene. Therefore we envisioned performing DFT calculations to gain an insight into the mechanistic aspects of this step. The calculations revealed that the rate of the lactonisation reaction mainly depends upon the concentration of the *Z* isomer as well as the relative rate of cyclisation compared with the reverse isomerisation of the *E* isomer to the *Z* isomer during the progress of the reaction. The availability of the requisite *Z* isomer of the alkene is best achieved by heating at 70 °C because the *E* isomer cannot be populated thermally due to the high $E \rightarrow Z$ thermal isomerisation barrier (3.3 kcal/mol). Thus, by providing constant heating at 70 °C the *Z* isomer state establishes a high constant *Z*/*E* ratio that favours the formation of the cyclised product (Figure 3).



Scheme 1. Reagents and conditons: a) imidazole, TBDMSCl, CH_2Cl_2, 0 °C to r.t.; b) HF/pyridine, THF; c) Dess–Martin periodinane, CH_2Cl_2, r.t.; d) (*tert*-butoxycarbonylmethylene)triphenylphosphorane, CH_2Cl_2, –10 °C; e) TBAF, THF; f) TFA, CH_2Cl_2, 0 °Cto r.t.; g) EDCI, DMAP, CH_2Cl_2, 70 °C. *Aromatic aldehydes (1 mmol), acetone (10 equiv.), D-proline (20 mol-%), DMSO, r.t.; ***p*-nitrobenzaldehyde (1 mmol), cyclohexanone (10 equiv.), cinchona amine (10 mol-%), TfOH (15 mol-%), r.t.. Note: * and ** asterisked compounds were synthesised by Equation (II); the asymmetric β-hydroxy ketones were synthesised following reported protocols.[36] The given yields correspond to overall yields of lactones **4a**–**k**.

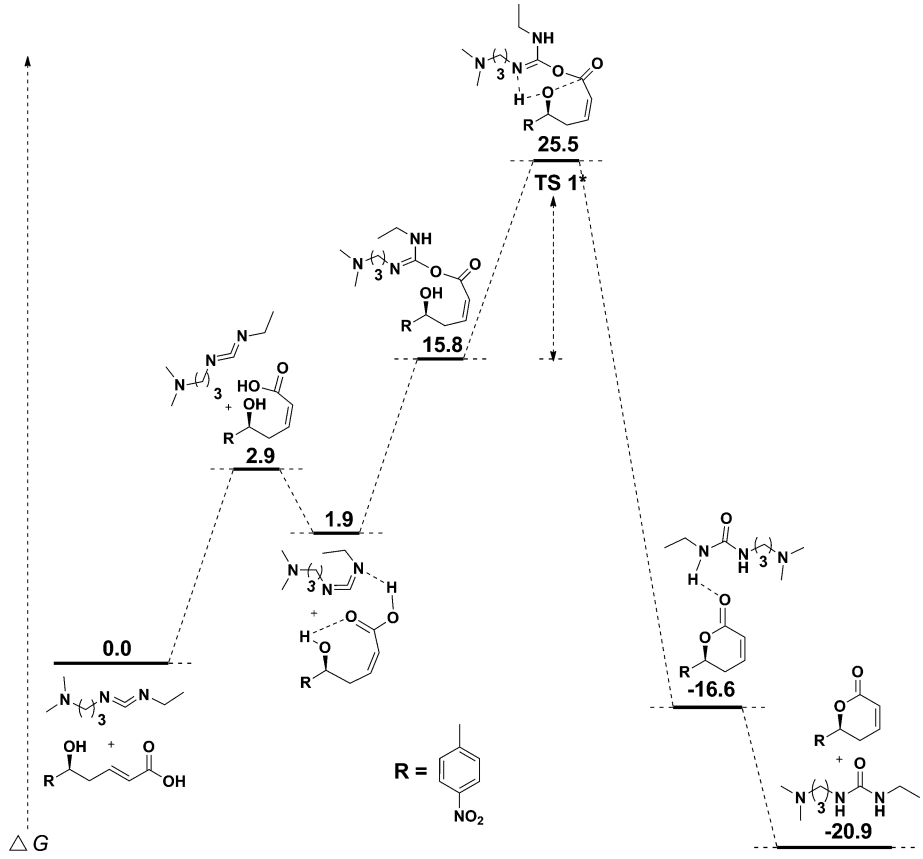


Figure 3. DFT-calculated free energy surfaces for the lactonisation process [kcal/mol].

Conclusions

The inherent challenges associated with the handling of acetaldehyde can be addressed by using vinyl acetate as its precursor. The β-hydroxy carbonyls generated by the cross-aldol reaction can give facile access to libraries of α,β-unsaturated δ-lactones in high yields and enantioselectivities. DFT calculations have provided mechanistic support for the role of hydrogen bonding between catalyst and aldehyde in the asymmetric aldol reactions and also for the *cis*/*trans* isomerisation step that occurs in the lactonisation reactions, thereby expanding our knowledge of their mechanisms. Further efforts to amplify the scope of vinyl acetate in other organocatalytic reactions are underway.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR spectra were recorded with 400 and 500 MHz spectrometers with TMS as internal standard. Chemical shifts (δ) are expressed in parts per million (ppm) and J values are given in Hz. The reagents and solvents used were mostly AR-grade. Aluminium plates coated with silica gel were used for TLC. LC-ESI-MS/MS analysis was carried out with a Triple-Quad LC–MS/MS spectrometer (model 6410).

General Procedure for the Cross-Aldol Reaction: Vinyl acetate (276 μL, 4.0 mmol) was added to a mixture of trifluoromethyl-substituted diarylprolinol (**C**; 78 mg, 15 mol-%), 2-propanol (306 μL, 4.0 mmol), Novozym435 lipase (1 mg), and *p*-nitrobenzaldehyde (151 mg, 1.0 mmol) in a sealed glass tube and agitated at room temperature. After 24 h, further vinyl acetate (276 μL, 4.0 mmol) and 2-propanol (306 μL, 4.0 mmol) were added to the reaction mixture. The reaction mixture was agitated for 48 h, then cooled to 0 °C, and then MeOH (2.0 mL) and $NaBH_4$ (226.5 mg, 6 mmol) were added. The mixture was stirred for a further 1 h at 0 °C. The reaction was quenched with pH 7.0 phosphate buffer solution, the organic materials were extracted with ethyl acetate (3×), and then the combined organic extracts were dried with anhydrous sodium sulfate and concentrated under vacuum. Purification by column chromatography gave (*S*)-1-(4′-nitrophenyl)propane-1,3-diol (**1a**) in 94% yield and 95% *ee*.

(*S*)-1-(2,4-Dichlorophenyl)propane-1,3-diol: (Table 2, entry 6): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, J = 8.4 Hz, 1 H), 7.26 (d, J = 2.1 Hz, 1 H), 7.19 (dd, J = 8.4, 2.0 Hz, 1 H), 5.18 (dd, J = 9.0, 3.0 Hz, 1 H), 3.87–3.41 (m, 1 H), 3.65 (m, 1 H), 1.82–1.74 (m, 1 H), 1.67–1.59 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 133.4, 131.8, 129.0, 128.1, 127.4, 70.8, 61.7, 38.2 ppm.

(*S*)-1-(2,4-Difluorophenyl)propane-1,3-diol: (Table 2, entry 7): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.58 (m, 1 H), 7.30–7.27 (m, 1 H), 7.09 (t, J = 8.4 Hz, 1 H), 4.97–4.93 (m, 1 H), 3.91–3.85 (m, 2 H), 1.98–1.94 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 134.7, 132.1, 129.7, 129.1, 127.0, 68.8, 61.3, 38.8 ppm.

(*S*)-1-(3-Bromo-4-fluorophenyl)propane-1,3-diol: (Table 2, entry 8): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (dd, J = 6.7, 1.9 Hz, 1 H), 7.31–7.26 (m, 1 H), 7.08 (t, J = 8.5 Hz, 1 H), 4.93–4.89 (m, 1 H), 3.87–3.77 (m, 2 H), 1.92–1.85 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 156.4, 143.1, 130.2, 126.3, 115.8, 108.0, 69.9, 69.2, 58.9, 55.5, 49.2, 41.2 ppm.

(*S*)-1-(Quinolin-4-yl)propane-1,3-diol: (Table 2, entry 10): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (d, J = 4.4 Hz, 1 H), 8.09–8.06 (m, 2 H), 7.75–7.69 (m, 2 H), 7.61–7.56 (m, 1 H), 5.72–5.69 (m, 1 H), 3.92–3.83 (m, 2 H), 2.16–2.14 (m, 1 H), 1.95–1.93 (m, 1 H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 154.3, 151.1, 148.6, 130.7, 129.8, 127.9, 126.9, 124.7, 118.7, 67.5, 59.8, 42.3 ppm.

(*S*)-1-(Quinolin-2-yl)propane-1,3-diol: (Table 2, entry 11): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, J = 8.5 Hz, 1 H), 8.08 (d, J = 8.4 Hz, 1 H), 7.84 (d, J = 8.1 Hz, 1 H), 7.77–7.72 (m, 1 H), 7.59–7.54 (m, 1 H), 7.39 (d, J = 8.5 Hz, 1 H), 5.15 (dd, J = 8.8, 3.5 Hz, 1 H), 4.02–3.87 (m, 2 H), 2.28–2.20 (m, 1 H), 1.99–1.89 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5, 146.3, 137.2, 129.8, 128.4, 127.6, 127.4, 125.4, 118.2, 72.3, 60.1, 39.9 ppm.

General Procedure for the Silyl Protection of the Reduced Cross-Aldol Products

(*S*)-1-[1,3-Bis(*tert*-butyl-dimethylsilyloxy)propyl]-4-nitrobenzene: Imidazole (431 mg, 6.33 mmol) followed by *tert*-butyldimethylsilyl chloride (838 mg, 5.57 mmol) were added to a rapidly stirred solution of (*S*)-1-(4-nitrophenyl)propane-1,3-diol (500 mg, 2.53 mmol) in dichloromethane. The resulting mixture was stirred at room temperature until TLC showed complete consumption of the starting material, and the reaction was quenched by the addition of water. The aqueous layer was extracted with Et_2O and the organic extract was washed with brine. The organic layer was dried with Na_2SO_4, the solvent was removed in vacuo and the residue was purified by column chromatography to give 950 mg (2.23 mmol, 88%) of a colourless liquid. $[\alpha]_D^{23}$ = –7.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.7 Hz, 2 H), 7.43 (d, J = 8.6 Hz, 2 H), 4.93 (dd, J = 7.9, 4.7 Hz, 1 H), 3.70 (m, 1 H), 3.50 (m, 1 H), 1.84 (m, 1 H), 1.66 (m, 1 H), 0.84 (s, 18 H), –0.02 (m, 9 H), –0.18 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 145.8, 125.4, 122.4, 69.7, 57.8, 42.7, 24.7, 24.6, 24.5, 17.1, 17.0, 16.9, –4.1, –4.2, –5.8, –6.2, –6.4, –6.5 ppm.

(*S*)-1-[1,3-Bis(*tert*-butyldimethylsilyloxy)propyl]-3-nitrobenzene: Yield 89%. $[\alpha]_D^{23}$ = –7.5 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (s, 1 H), 8.05 (m, 1 H), 7.60 (d, J = 7.6 Hz, 1 H), 7.44 (t, J = 7.9 Hz, 1 H), 4.93 (dd, J = 7.8, 4.8 Hz, 1 H), 3.70 (m, 1 H), 3.49 (m, 1 H), 1.86 (m, 1 H), 1.71 (m, 1 H), 0.86 (s, 18 H), 0.01 (s, 9 H), –0.18 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.5, 147.2, 131.2, 128.3, 121.0, 119.9, 69.9, 58.2, 43.3, 25.1, 25.0, 17.4, 17.4, –5.3, –5.7, –6.0, –6.0 ppm.

(*S*)-1-[1,3-Bis(*tert*-butyldimethylsilyloxy)propyl]-2-nitrobenzene: Yield 92%. $[\alpha]_D^{23}$ = +7.9 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (dd, J = 12.6, 8.0 Hz, 2 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.35 (t, J = 7.7 Hz, 1 H), 5.42 (dd, J = 8.8, 2.8 Hz, 1 H), 3.80 (m, 1 H), 3.70 (m, 1 H), 1.95 (m, 1 H), 1.78 (m, 1 H), 0.85 (m, 18 H), 0.03 (m, 9 H), –0.22 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 140.1, 131.7, 127.6, 126.4, 122.7, 65.5, 58.4, 42.0, 24.7, 24.6, 24.5, 17.1, 16.9, –6.1, –6.3, –6.4, –6.5 ppm.

(*S*)-1-[1,3-Bis(*tert*-butyldimethylsilyloxy)propyl]-2,4-dichlorobenzene: Yield 84%. $[\alpha]_D^{23}$ = –7.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, J = 8.4 Hz, 1 H), 7.26 (d, J = 2.1 Hz, 1 H), 7.19 (dd, J = 8.4, 2.0 Hz, 1 H), 5.18 (dd, J = 9.0, 3.0 Hz, 1 H), 3.73 (m, 1 H), 3.60 (m, 1 H), 1.78 (m, 1 H), 1.63 (m, 1 H), 0.84 (m, 18 H), 0.01 (s, 3 H), –0.20 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 132.8, 131.5, 128.8, 128.7, 127.1, 67.4, 59.2, 53.4, 42.2, 25.8, 25.8, 25.7, 18.1, 18.1, –4.8, –5.2, –5.30, –5.36 ppm.

General Procedure for the Selective Deprotection of the Primary Silyl Ethers

(*S*)-3-[(*tert*-Butyldimethylsilyloxy)-3-(4-nitrophenyl)propan-1-ol: A solution of HF/pyridine was prepared by the addition of HF·pyridine (1.3 g) to pyridine (3.1 mL) and THF (10 mL). This solution (6 mL) was added to a solution of (*S*)-1-[1,3-bis(*tert*-butyldimethylsilyloxy)propyl]-4-nitrobenzene (700 mg, 1.65 mmol) in THF (24 mL) and the mixture was stirred for 18 h at room temperature. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$, and the aqueous layer was extracted with Et_2O. The organic layer was dried with Na_2SO_4, the solvent was removed in vacuo and the residue was purified by column chromatography to give 480 mg (1.54 mmol, 94%) of (*S*)-3-(*tert*-butyldimethylsilyloxy)-3-(4-nitrophenyl)propan-1-ol as a colourless liquid. $[\alpha]_D^{23}$ = –38.0 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, J = 8.6 Hz, 2 H), 7.63 (d, J = 8.5 Hz, 2 H), 5.17 (dd, J = 7.0, 4.7 Hz, 1 H), 3.93–3.76 (m, 2 H), 2.05 (m, 2 H), 1.03 (s, 9 H), 0.21 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 147.1, 126.5, 123.7, 77.3, 77.1, 76.8, 72.6, 59.5, 42.3, 25.8, 18.1, –4.7, –5.1 ppm.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-3-(3-nitrophenyl)propan-1-ol: Yield 92%. $[\alpha]_D^{23}$ = –40.0 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (s, 1 H), 8.24 (dd, J = 8.1, 1.2 Hz, 1 H), 7.80 (d, J = 7.7 Hz, 1 H), 7.63 (t, J = 7.9 Hz, 1 H), 5.18 (dd, J = 7.2, 4.7 Hz, 1 H), 3.85 (m, 2 H), 2.06 (m, 2 H), 1.03 (s, 9 H), 0.21 (s, 3 H), –0.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2, 147.2, 131.8, 129.3, 122.2, 120.7, 72.5, 59.5, 42.3, 25.7, 18.0, –4.6, –5.1 ppm.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-3-(2-nitrophenyl)propan-1-ol: Yield 88%. $[\alpha]_D^{23}$ = +41.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (dd, J = 17.7, 8.0 Hz, 2 H), 7.84 (t, J = 7.6 Hz, 1 H), 7.61 (dd, J = 11.4, 4.1 Hz, 1 H), 5.73 (dd, J = 8.0, 3.3 Hz, 1 H), 3.98 (m, 2 H), 2.32 (m, 1 H), 2.10 (m, 1 H), 1.08 (s, 9 H), 0.25 (s, 3 H), –0.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.0, 140.4, 133.2, 128.7, 128.0, 124.1, 68.9, 60.2, 41.5, 25.7, 18.0, –4.9, –5.3 ppm.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-3-(2,4-dichlorophenyl)propan-1-ol: Yield 92%. $[\alpha]_D^{23}$ = –40.1 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.4 Hz, 1 H), 7.45 (d, J = 2.1 Hz, 1 H), 7.40 (m, 1 H), 5.43 (m, 1 H), 3.86 (m, 2 H), 2.15 (m, 1 H), 2.94 (m, 1 H), 1.02 (s, 9 H), 0.21 (s, 3 H), –0.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 133.3, 131.3, 128.9, 128.8, 127.2, 70.1, 60.1, 40.0, 25.7, 18.0, –4.8, –5.2 ppm.

General Procedure for the Oxidation of the Primary Alcohols

(*S*)-3-[(*tert*-Butyldimethylsilyloxy)-3-(4-nitrophenyl)propanal: Dess–Martin periodinane (851 mg, 2.00 mmol) was added to a cooled (0 °C) solution of (*S*)-3-(*tert*-butyldimethylsilyloxy)-3-(4-nitrophenyl)propan-1-ol (500 mg, 1.61 mmol) in dry CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 1 h and then treated with a saturated solution of $NaHCO_3$ and 20% aqueous solution of $Na_2S_2O_3$. The aqueous layer was extracted with Et_2O and the organic extract was washed with brine. The organic layer was dried with Na_2SO_4, the solvent removed in vacuo, and the residue was purified by column chromatography to give 450 mg (1.45 mmol, 91%) of (*S*)-3-(*tert*-butyldimethylsilyloxy)-3-(4-nitrophenyl)propanal as a colourless liquid. $[\alpha]_D^{23}$ = –48.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (t, J = 1.7 Hz, 1 H, CHO), 8.13 (d, J = 8.7 Hz, 2 H), 7.47 (d, J = 8.7 Hz, 2 H), 5.27 (dd, J = 7.7, 4.3 Hz, 1 H), 2.81 (m, 1 H), 2.61 (m, 1 H), 0.81 (s, 9 H), 0.00 (s, 3 H), –0.19 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 151.3, 147.4, 126.5, 123.9, 69.6, 53.7, 25.6, 18.0, –4.7, –5.1 ppm.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-3-(3-nitrophenyl)propanal: Yield 87%. $[\alpha]_D^{23}$ = –56.3 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):

δ = 9.67 (m, 1 H), 8.15 (s, 1 H), 8.03 (m, 1 H), 7.60 (d, J = 7.7 Hz, 1 H), 7.44 (m, 1 H), 5.24 (dd, J = 7.7, 4.3 Hz, 1 H), 2.81 (m, 1 H), 2.60 (m, 1 H), 0.78 (s, 9 H), –0.02 (s, 3 H), –0.21 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.8, 149.0, 133.5, 130.8, 130.2, 125.3, 123.04, 69.3, 53.7, 25.7, 17.9, –4.6, –5.1 ppm.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-3-(2-nitrophenyl)propanal: Yield 90%. $[\alpha]_D^{23}$ = +58.7 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.76 (m, 1 H), 7.92 (d, J = 8.2 Hz, 1 H), 7.83 (d, J = 7.5 Hz, 1 H), 7.62 (t, J = 7.6 Hz, 1 H), 7.40 (m, 1 H), 5.80 (dd, J = 8.1, 3.3 Hz, 1 H), 2.83 (m, 1 H), 2.72 (m, 1 H), 0.80 (s, 9 H), –0.00 (s, 3 H), –0.23 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8, 146.7, 139.7, 133.3, 128.6, 128.3, 124.2, 65.6, 52.7, 25.6, 18.0, –4.8, –5.2 ppm.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-3-(2,4-dichlorophenyl)propanal: Yield 85%. $[\alpha]_D^{23}$ = –54.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (dd, J = 2.7, 2.0 Hz, 2 H), 7.46 (m, 1 H), 7.27 (m, 1 H), 7.20 (dd, J = 8.4, 2.0 Hz, 1 H), 5.45 (m, 1 H), 2.62 (m, 2 H), 0.80 (s, 9 H), –0.04 (s, 3 H), –0.17 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.4, 139.7, 133.7, 131.5, 128.7, 128.6, 127.5, 67.8, 51.6, 25.6, 17.9, –4.8, –5.3 ppm.

General Procedure for the Wittig–Horner Reactions of Aldehydes and Ketones

***tert*-Butyl (*S,E*)-5-(*tert*-Butyldimethylsilyloxy)-5-(4-nitrophenyl)-pent-2-enoate:** (*tert*-Butoxycarbonylmethylene)triphenylphosphorane (584 mg, 1.55 mmol) was added to a cooled (0 °C) solution of (*S*)-3-(*tert*-butyldimethylsilyloxy)-3-(4-nitrophenyl)propanal (400 mg, 1.29 mmol) in dry dichloromethane (20 mL) . The resulting mixture was stirred at –10 °C until TLC showed complete consumption of the starting material, and then the reaction was quenched by the addition of water. The aqueous layer was extracted with Et_2O and the organic extract was washed with brine. The organic layer was dried with Na_2SO_4, the solvent was removed in vacuo and the residue was purified by column chromatography to give 450 mg (1.11 mmol, 85%) of *tert*-butyl (*S,E*)-5-(*tert*-butyldimethylsilyloxy)-5-(4-nitrophenyl)pent-2-enoate as a colourless liquid. $[\alpha]_D^{23}$ = –38.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 8.5 Hz, 2 H), 7.43 (d, J = 8.5 Hz, 2 H), 6.74 (dt, J = 15.1, 7.4 Hz, 1 H), 5.87 (d, J = 15.6 Hz, 1 H), 4.80 (t, J = 5.9 Hz, 1 H), 2.45 (m, 2 H), 1.41 (s, 9 H), 0.82 (s, 9 H), –0.03 (s, 3 H), –0.16 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 151.9, 147.3, 142.6, 126.5, 126.1, 123.7, 80.3, 73.4, 43.2, 28.1, 25.7, 18.2, –4.7, –5.0 ppm.

***tert*-Butyl (*S,E*)-5-(*tert*-Butyldimethylsilyloxy)-5-(3-nitrophenyl)-pent-2-enoate:** Yield 88%. $[\alpha]_D^{23}$ = –40.1 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 8.11 (m, 1 H), 7.67 (m, 1 H), 7.46 (m, 1 H), 6.80 (m, 1 H), 5.74 (m, 1 H), 4.85 (dd, J = 16.8, 10.0 Hz, 1 H), 2.54 (m, 2 H), 1.46 (s, 9 H), 0.90 (s, 9 H), 0.06 (s, 3 H), –0.10 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 146.7, 142.7, 132.8, 131.7, 129.1, 126.1, 122.3, 120.5, 80.0, 73.2, 43.4, 27.8, 25.9, 18.2, –4.7, –4.9 ppm.

***tert*-Butyl (*S,E*)-5-[(*tert*-Butyldimethylsilyloxy)-5-(2-nitrophenyl)-pent-2-enoate:** Yield 90%. $[\alpha]_D^{23}$ = +43.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, J = 8.2, 1.1 Hz, 1 H), 8.01 (dd, J = 7.9, 1.0 Hz, 1 H), 7.80 (m, 1 H), 7.58 (m, 1 H), 7.07 (m, 1 H), 5.94 (d, J = 15.6 Hz, 1 H), 5.55 (dd, J = 8.0, 3.3 Hz, 1 H), 2.85 (m, 1 H), 2.63 (m, 1 H), 1.65 (s, 9 H), 1.03 (s, 9 H), 0.19 (s, 3 H), –0.00 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 146.7, 143.3, 140.3, 133.0, 128.6, 128.0, 126.0, 124.1, 80.0, 69.2, 42.2, 28.0, 25.7, 18.0, –4.9, –5.1 ppm.

***tert*-Butyl (*S,E*)-5-[(*tert*-Butyldimethylsilyloxy)-5-(2,4-dichlorophenyl)pent-2-enoate:** Yield 83%. $[\alpha]_D^{23}$ = –40.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (m, 1 H), 7.44 (d, J = 2.1 Hz, 1 H), 7.37 (dd, J = 7.8, 2.6 Hz, 1 H), 6.97 (dt, J = 15.3, 7.5 Hz, 1 H), 5.86 (m, 1 H), 5.23 (dd, J = 8.0, 3.6 Hz, 1 H), 2.64 (m, 1 H), 2.50 (m, 1 H), 1.59 (s, 9 H), 0.99 (s, 9 H), 0.15 (s, 3 H), –0.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 143.4, 140.6, 133.2, 131.2, 128.8, 128.7, 127.2, 125.8, 80.0, 69.8, 41.1, 28.0, 25.5, 18.2, –4.8, –5.1 ppm.

***tert*-Butyl (*S,E*)-5-(4-Nitrophenyl)-5-hydroxy-3-methylpent-2-enoate (3e):** Yield 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.7 Hz, 2 H), 7.52 (d, J = 8.5 Hz, 2 H), 5.78 (s, 1 H), 4.90 (d, J = 9.2 Hz, 1 H), 3.02 (dd, J = 12.8, 9.5 Hz, 1 H), 2.60–2.48 (m, 1 H), 1.76 (t, J = 7.6 Hz, 3 H), 1.40 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 151.0, 147.2, 142.5, 126.5, 126.2, 123.7, 80.7, 71.9, 41.7, 28.0, 18.5 ppm.

***tert*-Butyl (*S,E*)-5-(4-Fluorophenyl)-5-hydroxy-3-methylpent-2-enoate (3f):** Yield 92%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 2 H), 7.11–6.92 (m, 2 H), 5.68 (s, 1 H), 4.85 (dd, J = 8.8, 4.5 Hz, 1 H), 2.57–2.35 (m, 2 H), 2.17 (d, J = 1.2 Hz, 3 H), 1.55–1.41 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 163.2, 161.2, 153.6, 139.5, 120.5, 115.4, 115.2, 80.0, 71.3, 50.9, 28.2, 28.1, 18.7 ppm.

***tert*-Butyl (*S,E*)-5-(4-Bromophenyl)-5-hydroxy-3-methylpent-2-enoate (3g):** Yield 89%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.36 (m, 2 H), 7.20 (d, J = 8.4 Hz, 2 H), 5.64 (s, 1 H), 4.79 (dd, J = 8.7, 4.6 Hz, 1 H), 2.51–2.29 (m, 2 H), 2.14 (t, J = 7.2 Hz, 3 H), 1.52–1.37 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 153.5, 142.9, 131.5, 127.4, 121.3, 120.4, 80.0, 71.2, 50.7, 28.2, 28.1, 27.9, 18.7 ppm.

***tert*-Butyl (*S,E*)-5-Hydroxy-3-methyl-5-(perfluorophenyl)pent-2-enoate (3h):** Yield 93%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.67 (s, 1 H), 5.21–5.10 (m, 2 H), 2.57 (dd, J = 13.6, 5.5 Hz, 1 H), 2.37–2.26 (m, 1 H), 2.18 (d, J = 5.5 Hz, 3 H), 1.51–1.48 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 166.1, 152.1, 144.3, 145.5, 138.4, 136.2, 121.9, 81.4, 64.8, 47.7, 28.2, 18.3 ppm.

***tert*-Butyl (*S,E*)-5-Hydroxy-3-methyl-5-phenylpent-2-enoate (3i):** Yield 85%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.20 (m, 5 H), 5.71 (s, 1 H), 4.93–4.77 (m, 1 H), 2.57–2.40 (m, 2 H), 2.18 (d, J = 3.7 Hz, 3 H), 1.56–1.39 (m, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 153.9, 143.8, 128.5, 127.7, 125.6, 120.3, 79.9, 79.4, 72.0, 50.8, 28.2, 18.7 ppm.

***tert*-Butyl (*S,E*)-5-Hydroxy-3-methyl-5-(2-naphthyl)pent-2-enoate (3j):** Yield 89%. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (td, J = 8.3, 3.8 Hz, 4 H), 7.53–7.45 (m, 3 H), 5.78 (t, J = 8.9 Hz, 1 H), 5.15–5.04 (m, 1 H), 2.64–2.55 (m, 2 H), 2.29–2.17 (m, 3 H), 1.49 (d, J = 4.3 Hz, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 154.0, 141.1, 133.2, 133.0, 128.4, 128.1, 126.0, 125.6, 124.4, 120.92, 119.7, 114.1, 80.2, 72.1, 50.8, 28.2, 18.7 ppm.

***tert*-Butyl (*E*)-2-{2-[(*S*)-Hydroxy(4-nitrophenyl)methyl]-cyclohexylidene}acetate (3k):** Yield 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.12 (m, 2 H), 7.53–7.40 (m, 2 H), 5.39–5.27 (m, 1 H), 5.21–5.12 (m, 1 H), 3.03–2.81 (m, 1 H), 2.79–2.59 (m, 1 H), 2.44–2.27 (m, 1 H), 2.16–1.94 (m, 1 H), 1.85–1.66 (m, 1 H), 1.69–1.55 (m, 1 H), 1.55–1.46 (m, 1 H), 1.43–1.38 (m, 9 H), 1.38–1.23 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 159.4, 149.0, 148.3, 127.9, 126.6, 123.6, 123.4, 113.3, 74.0, 70.1, 57.1, 56.8, 42.7, 42.6, 30.7, 27.8, 27.6, 25.9, 24.7, 24.6 ppm.

General Procedure for the Deprotection of the Secondary Alcohols

***tert*-Butyl (*S,E*)-5-Hydroxy-5-(4-nitrophenyl)pent-2-enoate (3a):** Tetra-*n*-butylammonium fluoride hydrate (TBAF, 1.06 mL, 3.68 mmol) was added to a solution of *tert*-butyl (*S,E*)-5-(*tert*-bu-

tyldimethylsilyloxy)-5-(4-nitrophenyl)pent-2-enoate (500 mg, 1.23 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 4 h. Then the reaction mixture was diluted with EtOAc and washed with water. The organic layer was dried with Na_2SO_4, the solvent was removed in vacuo and the residue was purified by column chromatography to give 265 mg (0.90 mmol, 74%) of **3a** as a colourless oil. $[\alpha]_D^{23} = -24.2$ (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.4 Hz, 2 H), 7.54 (d, J = 8.6 Hz, 2 H), 6.84 (dt, J = 15.1, 7.4 Hz, 1 H), 5.87 (d, J = 15.6 Hz, 1 H), 4.93 (t, J = 5.9 Hz, 1 H), 2.61 (m, 2 H), 1.44 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 151.1, 147.3, 142.5, 126.9, 126.6, 126.3, 123.8, 123.6, 80.78, 71.9, 41.8, 28.1, 28.0 ppm.

***tert*-Butyl (*S*,*E*)-5-Hydroxy-5-(3-nitrophenyl)pent-2-enoate (3b):** Yield 78%. $[\alpha]_D^{23} = -24.6$ (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 8.11 (m, 1 H), 7.67 (m, 1 H), 7.46 (m, 1 H), 6.81 (m, 1 H), 5.74 (m, 1 H), 4.85 (dd, J = 16.8, 10.0 Hz, 1 H), 2.4 (m, 2 H), 1.46 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.68, 148.13, 145.90, 142.58, 131.82, 129.27, 125.96, 122.34, 120.58, 80.54, 71.66, 41.54, 27.86 ppm.

***tert*-Butyl (*S*,*E*)-5-Hydroxy-5-(2-nitrophenyl)pent-2-enoate (3c):** Yield 80%. $[\alpha]_D^{23} = +25.2$ (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.1 Hz, 1 H), 7.86 (d, J = 7.7 Hz, 1 H), 7.67 (t, J = 7.6 Hz, 1 H), 7.45 (t, J = 7.7 Hz, 1 H), 6.95 (m, 1 H), 5.90 (d, J = 15.6 Hz, 1 H), 5.41 (dd, J = 8.6, 3.2 Hz, 1 H), 2.78 (m, 1 H), 2.56 (m, 1 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 147.4, 143.1, 139.4, 133.6, 128.3, 128.0, 126.0, 125.9, 124.4, 80.5, 68.2, 40.9, 28.0 ppm.

***tert*-Butyl (*S*,*E*)-5-Hydroxy-5-(2,4-dichlorophenyl)pent-2-enoate (3d):** Yield 79%. $[\alpha]_D^{23} = -25.0$ (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (t, J = 7.5 Hz, 1 H), 7.33 (dd, J = 7.7, 2.0 Hz, 1 H), 7.27 (m, 1 H), 6.89 (dt, J = 15.4, 7.3 Hz, 1 H), 5.84 (d, J = 15.6 Hz, 1 H), 5.17 (dd, J = 8.4, 3.5 Hz, 1 H), 2.65 (m, 1 H), 2.46 (m, 1 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 143.1, 139.8, 133.6, 132.0, 129.0, 128.0, 127.4, 125.8, 80.5, 68.9, 39.9, 28.0 ppm.

General Procedure for the Synthesis of α,β-Unsaturated δ-Lactones

(*S*)-6-(4-nitrophenyl)-5,6-dihydro-2*H*-pyran-2-one 4a: Ester **3a** (50 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (3 mL), and TFA (0.5 mL) was added. After 1 h, toluene (2 mL) was added and the reaction mixture was concentrated in vacuo. The resulting acid was dissolved in CH_2Cl_2 (3 mL) and EDCI (25 mg, 0.16 mmol) and DMAP (20 mg, 0.16 mmol) were added. The reaction mixture was stirred at 70 °C for 3 h. A saturated aqueous solution of $NaHCO_3$ was added and the aqueous phase was extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and the residue purified by column chromatography to give 33 mg (0.15 mmol, 90%) of **4a** as a colourless oil. $[\alpha]_D^{23} = -28.3$ (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.34–8.19 (m, 2 H), 7.62 (d, J = 8.7 Hz, 2 H), 7.01 (m, 1 H), 6.18 (m, 1 H), 5.59 (dd, J = 11.6, 4.5 Hz, 1 H), 2.82–2.54 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 147.9, 145.4, 144.4, 126.7, 124.2, 121.8, 77.8, 31.5 ppm. HRMS: calcd. for $C_{11}H_{10}NO_4$ $[M + H]^+$ 220.2009; found 220.2032.

(*S*)-6-(3-Nitrophenyl)-5,6-dihydro-2*H*-pyran-2-one (4b): Yield 92%. $[\alpha]_D^{23} = -28.5$ (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.37–8.17 (m, 2 H), 7.81 (d, J = 7.6 Hz, 1 H), 7.70–7.53 (m, 1 H), 7.10–6.96 (m, 1 H), 6.27–6.09 (m, 1 H), 5.57 (dt, J = 21.8, 11.0 Hz, 1 H), 2.84–2.56 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 147.5, 144.4, 140.5, 132.0, 129.9, 123.5, 121.8, 121.0, 77.8, 31.5 ppm. HRMS: calcd. for $C_{11}H_{10}NO_4$ $[M + H]^+$ 220.2009; found 220.2041.

(*S*)-6-(2-Nitrophenyl)-5,6-dihydro-2*H*-pyran-2-one (4c): Yield 85%. $[\alpha]_D^{23} = -29.8$ (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.89 (m, 1 H), 7.85 (t, J = 10.2 Hz, 1 H), 7.73–7.55 (m, 1 H), 7.56–7.36 (m, 1 H), 7.08–6.84 (m, 1 H), 5.84 (dd, J = 24.4, 10.7 Hz, 1 H), 5.15–5.07 (m, 1 H), 2.84–2.65 (m, 1 H), 2.60–2.47 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 147.4, 143.1, 139.4, 133.6, 128.3, 126.0, 124.4, 80.5, 40.8 ppm. HRMS: calcd. for $C_{11}H_{10}NO_4$ $[M + H]^+$ 220.2009; found 220.2032.

(*S*)-6-(2,4-Dichlorophenyl)-5,6-dihydro-2*H*-pyran-2-one (4d): Yield 88%. $[\alpha]_D^{23} = -29.5$ (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (t, J = 9.4 Hz, 1 H), 7.49–7.30 (m, 2 H), 6.98 (dd, J = 9.6, 6.2, Hz, 1 H), 6.16 (dd, J = 9.8, 2.7 Hz, 1 H), 5.84–5.69 (m, 1 H), 2.87–2.70 (m, 1 H), 2.50–2.31 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 144.7, 135.0, 134.8, 131.9, 129.3, 128.5, 121.5, 75.6, 30.2 ppm. HRMS: calcd. for $C_{11}H_9Cl_2O_2$ $[M + H]^+$ 244.0934; found 244.0956.

(*S*)-4-Methyl-6-(4-nitrophenyl)-5,6-dihydro-2*H*-pyran-2-one (4e): Yield 94%. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J = 8.6 Hz, 2 H), 7.61 (d, J = 8.7 Hz, 2 H), 5.96 (s, 1 H), 5.54 (dd, J = 11.6, 4.2 Hz, 1 H), 2.75–2.40 (m, 2 H), 2.06 (d, J = 7.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 156.6, 147.8, 145.6, 126.7, 124.0, 116.8, 77.3, 36.7, 24.1 ppm. HRMS: calcd. for $C_{12}H_{12}NO_4$ $[M + H]^+$ 234.2274; found 234.2231.

(*S*)-6-(4-Fluorophenyl)-4-methyl-5,6-dihydro-2*H*-pyran-2-one (4f): Yield 92%. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.51–7.35 (m, 2 H), 7.14–6.97 (m, 2 H), 5.94 (dd, J = 42.7, 8.5 Hz, 1 H), 5.47–5.29 (m, 1 H), 2.72–2.56 (m, 1 H), 2.55–2.38 (m, 1 H), 2.15–1.95 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 163.6, 161.6, 134.4, 127.9, 116.6, 115.6, 78.0, 36.8, 22.9 ppm. HRMS: calcd. for $C_{12}H_{12}FO_2$ $[M + H]^+$ 207.2203; found 207.2190.

(*S*)-6-(4-Bromophenyl)-4-methyl-5,6-dihydro-2*H*-pyran-2-one (4g): Yield 94%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51 (d, J = 8.4 Hz, 2 H), 7.28 (d, J = 8.4 Hz, 2 H), 5.90 (s, 1 H), 5.36 (dd, J = 12.0, 3.9 Hz, 1 H), 2.78–2.52 (m, 1 H), 2.49–2.35 (m, 1 H), 2.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 157.0, 137.7, 131.7, 127.7, 122.4, 116.7, 77.8, 36.7, 22.9 ppm. HRMS: calcd. for $C_{12}H_{12}BrO_2$ $[M + H]^+$ 268.1259; found 268.1290.

(*S*)-4-Methyl-6-(perfluorophenyl)-5,6-dihydro-2*H*-pyran-2-one (4h): Yield 93%. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.94 (s, 1 H), 5.76 (dd, J = 13.0, 3.9 Hz, 1 H), 3.16–2.89 (m, 1 H), 2.35 (dd, J = 17.8, 3.9 Hz, 1 H), 2.07 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 156.7, 145.7, 143.7, 141.5, 137.2, 115.4, 110.8, 68.2, 32.4, 22.4 ppm. HRMS: calcd. for $C_{12}H_8F_5O_2$ $[M + H]^+$ 279.1822; found 279.1843.

(*S*)-4-Methyl-6-phenyl-5,6-dihydro-2*H*-pyran-2-one (4i): Yield 90%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.29 (m, 5 H), 5.91 (s, 1 H), 5.41 (dd, J = 12.1, 3.9 Hz, 1 H), 2.73–2.56 (m, 1 H), 2.46 (dd, J = 17.9, 3.9 Hz, 1 H), 2.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 157.1, 138.6, 128.6, 128.5, 126.2, 126.0, 116.7, 78.6, 36.9, 22.7 ppm. HRMS: calcd. for $C_{12}H_{13}O_2$ $[M + H]^+$ 189.2299; found 189.2273.

(*S*)-4-Methyl-6-(2-naphthyl)-5,6-dihydro-2*H*-pyran-2-one (4j): Yield 92%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.76 (m, 4 H), 7.50 (dd, J = 9.1, 3.1 Hz, 3 H), 5.96 (s, 1 H), 5.59 (dd, J = 12.0, 3.9 Hz, 1 H), 2.84–2.64 (m, 1 H), 2.55 (dd, J = 18.0, 3.9 Hz, 1 H), 2.05 (d, J = 3.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 157.1, 135.9, 133.3, 128.5, 128.1, 127.7, 126.5, 125.1, 123.5, 116.8, 78.7, 36.9, 23.0 ppm. HRMS: calcd. for $C_{16}H_{15}O_2$ $[M + H]^+$ 239.2886; found 239.2880.

(1*S*)-1-(4-Nitrophenyl)-6,7,8,8a-tetrahydro-1*H*-isochromen-3(5*H*)-one (4k): Yield 87%. ^1H NMR (500 MHz, MeOD): δ = 8.30 (d, J

= 8.8 Hz, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 5.92 (s, 1 H), 5.79 (d, *J* = 4.6 Hz, 1 H), 3.36 (dd, *J* = 11.0, 9.4 Hz, 1 H), 2.71–2.53 (m, 1 H), 2.38 (td, *J* = 12.0, 4.9 Hz, 1 H), 2.19–2.07 (m, 1 H), 1.81 (d, *J* = 12.2 Hz, 1 H), 1.53–1.38 (m, 2 H), 1.36–1.15 (m, 2 H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 168.5, 165.5, 147.4, 143.9, 126.5, 123.6, 111.5, 78.9, 44.0, 35.7, 30.2, 29.4, 28.5, 25.4 ppm. HRMS: calcd. for $C_{15}H_{16}NO_4$ $[M + H]^+$ 274.2913; found 274.2930.

Supporting Information (see footnote on the first page of this article): HPLC, ^{1}H and ^{13}C NMR, and HRMS spectra for all relevant compounds.

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