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An Asymmetric Tandem Conjugative Addition-Intramolecular Cyclisation Process to Provide Functionalised 3,6-Dihydropyrans and 4,5-Epoxytetrahydropyrans

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The synthesis of 3,6-dihydropyrans and 4,5-epoxytetrahydropyrans starting from enantiomerically pure β-hydroxy aldehyde (prepared by an organocatalytic aldol reaction) is described. The key step is a tandem sequence, which consists of a base-promoted conjugative addition to a vinyl onium salt, followed by either an intramolecular Wittig process to provide 3,6-dihydropyran derivatives or an intramolecular cyclisation/epoxidation process to afford 4,5-epoxytetrahydropyran scaffolds. The products obtained by this method are common substructures in polyketide natural products.

Introduction

Pyran derivatives are a common structural motif in numerous polyketide natural products, some of which have shown interesting biological activities. For example, the laulimalide family of macrolides contain the dihydropyran framework as a characteristic element. Laulimalide (**1**) and Fijianolide G (**2**) (Figure 1) were found to be a potent microtubule-stabilising agents and thereby inhibit the proliferation of several tumour cancer cell lines in a similar manner to Paclitaxel.[1] Owing to the importance of the pyran framework several strategies towards its preparation have been developed, including Prins cyclisations,[2] hetero Diels–Alder reactions,[3] ring closing metathesis,[4] Ferrier-type reactions,[5] and intramolecular nucleophilic reactions.[6]

Thus far, only a few organocatalytic syntheses have been described.[7] Asymmetric organocatalysis has emerged as a powerful tool to synthesise optically pure substances in a simple manner.[8] Among the enantioselective reactions promoted by chiral amines, aldol reactions are of particular value. The direct combination of two carbonyl substrates leads to important building blocks and often proceeds with excellent chemo- and stereoselectivity.[9]

We have recently used these methods for the preparation of chiral 1,2-oxazines and pyridazines.[10] Starting from achiral aldehydes and ketones, an α-oxyamination with nitrosobenzene in presence of pyrrolidinyl-tetrazole followed by conjugative addition to a vinylphosphonium salt generates an ylide. This then cyclises to give the dihydro-1,2-oxazine in this one-pot process. Similarly, chiral pyridazines were prepared by applying α-amination instead of oxyamination in the first part of the transformation. The products of these reactions were obtained in good to excellent yield with high enantioselectivity. Herein, we have designed a related route directed towards the synthesis of pyran derivatives from aldol adducts **6** and various onium salts **7** (Scheme 1).

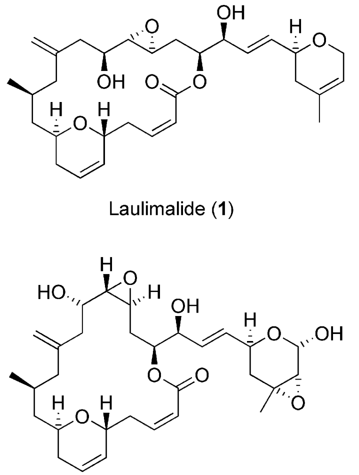

Figure 1. Pyran-containing polyketide natural products.

Reaction of a β-hydroxy aldehyde **6** with a vinylphosphonium salt **7a** should lead to the formation of 3,6-dihydropyrans **8** whereas the corresponding and complimentary sulfur derivatives **7b** were expected to afford access to 4,5-epoxytetrahydropyrans **9**.

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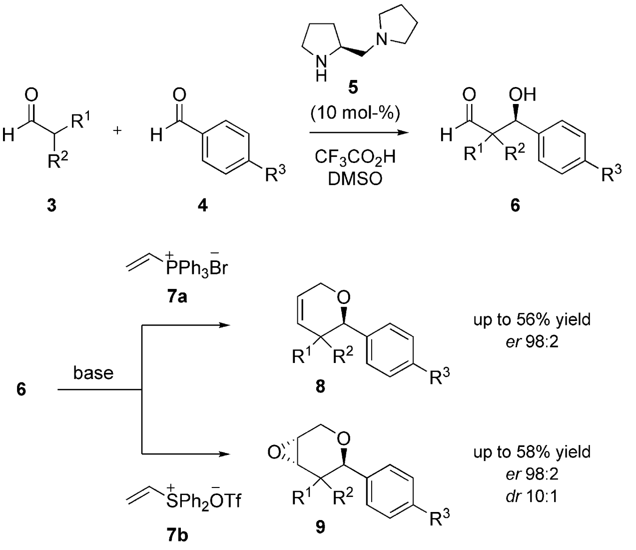
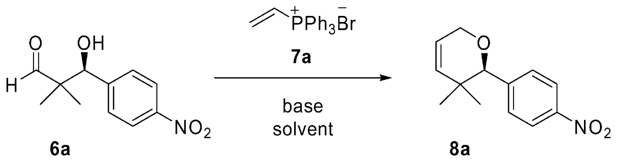


Scheme 1. Synthesis of pyran derivatives from β-hydroxy aldehydes and vinyl ylides.

Table 1. Base screening for the synthesis of 3,6-dihydropyran **8a** from β-hydroxy aldehyde **6a**.[a]



Entry	Base [equiv.]	Solvent [0.1 M]	Method[c]	Yield **8a** [%]
1	KH [2.0]	THF/DMSO[b]	A	17
2	KN(TMS)$_2$ [2.5]	DMSO	A	30
3	K_2CO_3 [2.5]	DMF	B	11
4	K_2CO_3 [2.5]	DMF	A	40
5	Cs_2CO_3 [2.5]	DMF	B	12
6	Cs_2CO_3 [2.5]	DMF	A	43
7	Li_2CO_3 [2.5]	DMSO	A	0
8	DBU [2.0]	DMSO	A	38

[a] All reactions were performed with 1.5 equiv. of vinylphosphonium salt **7a** at room temp. with reaction times of 1–4 h. [b] Mixture of THF/DMSO [1:1], 0.05 M. [c] Method A: base was added to a stirred solution of **6a** and **7a**; Method B: deprotonation of **6a** first, followed by addition of **7a**.

Results and Discussion

The initial β-hydroxy aldehydes **6** can be synthesised with a well established asymmetric aldol reaction between an α,α-dialkyl aldehyde **3** with an aromatic aldehyde **4**. Although this method could be applied to different α,α-dialkyl aldehydes we have limited our study to the *gem*-dimethyl group. This transformation was then followed by a base-promoted nucleophilic attack of the resulting hydroxy group to a vinylphosphonium salt[11] **7a** to provide a transient ylide intermediate, which was cyclised through an intramolecular Wittig reaction to furnish the 3,6-dihydropyran product **8**.

Using the same conditions that had been successfully applied to the preparation of chiral 1,2-oxazines (KH, THF/DMSO, 1:1),[10c] the desired product **8a** was only isolated in an unacceptable 17% yield (Table 1, Entry 1). While an improvement of the yield was observed using potassium bis(trimethylsilyl)amide, competing retro-aldol reaction was found to significantly limit the outcome of the process (Table 1, Entry 2). To circumvent this problem, milder bases such as K_2CO_3 or Cs_2CO_3 were examined. In this study we were able to determine that both the order of base addition, as well as the counterion, were of utmost importance. Initial deprotonation of the hydroxy aldehyde **6a**, followed by subsequent reaction with the phosphonium salt **7a** resulted in low yields (Table 1, Entry 3 and 5). However, by direct base addition to a reagent mixture the yield was increased to 43% (Table 1, Entry 4 and 6). Comparable results were obtained with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base (Table 1, Entry 8). Interestingly, with Li_2CO_3 the retro-aldol reaction prevailed and no dihydropyran formation occurred (Table 1, Entry 7).[12]

Because the results with K_2CO_3 and Cs_2CO_3 were promising an extensive solvent screening was undertaken. These experiments showed that the reaction did not work well in ethereal solvents such as dioxane, dimethoxethane or THF (Table 2, Entry 1–3) and varying yields were obtained with polar aprotic solvents (Table 2, Entry 4–7, and 10). DMSO was eventually chosen to be the best solvent, yielding dihydropyran **8a** in 48% yield after 1 h at room temperature. Similar results were obtained in 1,2-dichloroethane (Table 2, Entry 9) and dichloromethane was less effective. However, due to the toxicity of these halogenated solvents no further investigation was carried out.

Table 2. Solvent screening.[a]

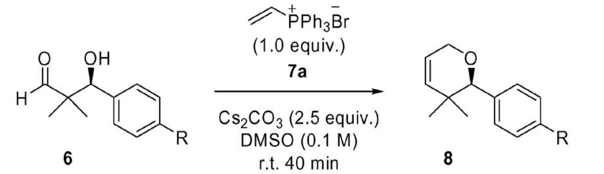
Entry	Solvent [0.1 M]	Yield **8a**[c] [%]
1	dioxane	25
2	dimethoxyethane	traces
3	THF/DMF	traces
4	DMSO	48
5	DMSO[b]	43
6	DMPU	23
7	*N*-methyl-2-pyrrolidone (NMP)	19
8	CH_2Cl_2	33
9	1,2-dichloroethane	47
10	CH_3CN	24
11	1-butyl-3-methylimidazolin tetrafluoroborate	10

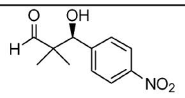
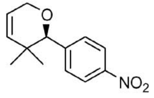
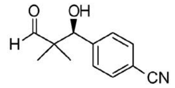
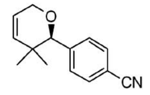
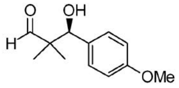
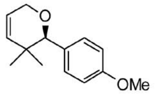
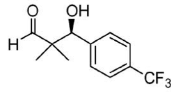
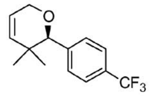
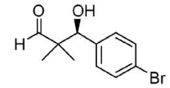
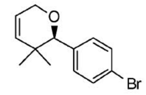
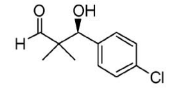
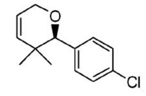
[a] All reactions were performed according to method A on substrate **6a** with 1.5 equiv. of **7a** and 2.5 equiv. of Cs_2CO_3 at room temp. with reaction times of 1–4 h. [b] K_2CO_3 was used as the base. [c] Yield of isolated product based on β-hydroxy aldehyde **6a**.

The influence of additives on the reaction was then investigated. Firstly it was found that addition of phase-transfer catalysts, such as tetrabutylammonium salts, crown ethers or molecular sieves had no effect on the reaction profile. Interestingly, the process was completely inhibited when conducted in presence of lithium salts, again showing the significant influence of the counterion. Furthermore, the transformation was shown to be not markedly water-sensitive, because dihydropyran **8a** was isolated in 48% yield by using either freshly dried or moist DMSO and Cs_2CO_3.

We also observed that the relative proportion of the reagents was crucial for achieving acceptable yields. When the reaction was performed in presence of 15 equiv. of **7a** in DMSO only 19% of the desired product **8a** was obtained. Pleasingly however we were able to increase the yield to 56% using stoichiometric amounts of phosphonium salt **7a** (Table 3, Entry 1). The amount of Cs_2CO_3 used in the reaction was also varied although 2.5 equiv. were found to be optimal with regard to temperature. At 0 °C the conjugate addition and Wittig reaction were slower and retro-aldol process was found to dominate, whereas at temperatures above room temperature decomposition of the starting material was observed prior to any coupling reaction.

Table 3. Substrate scope for the synthesis of 3,6-dihydropyrans **8**.



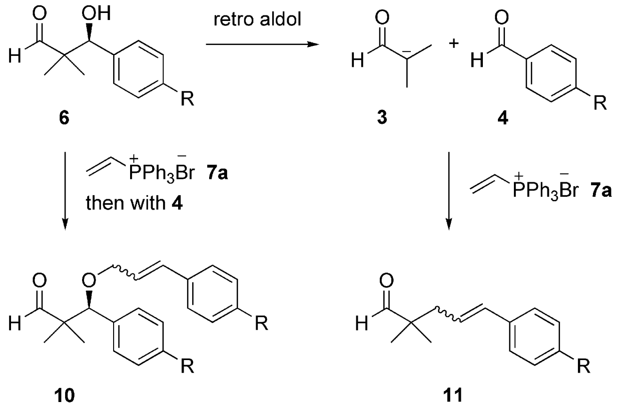
Entry	6	8	Yield[a] [%]	er[b] [S:R]
1	 **6a**	 **8a**	56	4:96
2	 **6b**	 **8b**	48	5:95
3	 **6c**	 **8c**	43	2:98
4	 **6d**	 **8d**	34	–[c]
5	 **6e**	 **8e**	48	4:96
6	 **6f**	 **8f**	40	2:98

[a] Yield of isolated product based on β-hydroxy aldehyde **6**. [b] Determined by HPLC analysis on a chiral phase (Chiralpak AS, AD-H). [c] Incompletely separated enantiomeric mixture.

We also tested the susceptibility of aldehyde **6a** towards racemisation in the presence of Cs_2CO_3. Although the substrate racemises under these conditions the conjugate addition–cyclisation process is sufficiently fast to maintain high enantiomeric excess in the product. Dihydropyran **8a** was isolated with *er* 96:4 starting from 97:3 enantiomerically enriched β-hydroxy aldehyde **6a** which was obtained according to the previously reported procedure of Barbas.[13a]

Encouraged by these results, we further explored the scope of this reaction with a series of aromatic β-hydroxy aldehydes under the optimised conditions. A solution of the respective substrate **6**[13] and vinylphosphonium salt **7a** in DMSO was treated with Cs_2CO_3 at room temperature. The results of these studies are depicted in Table 3.

All reactions proceeded with moderate to good yields of 34–56% with the *p*-nitro-substituted aldehyde **6a** giving the best. The competing retro-aldol reaction could not be further suppressed and formation of **10** and **11** limited the overall outcome of the process (Scheme 2).



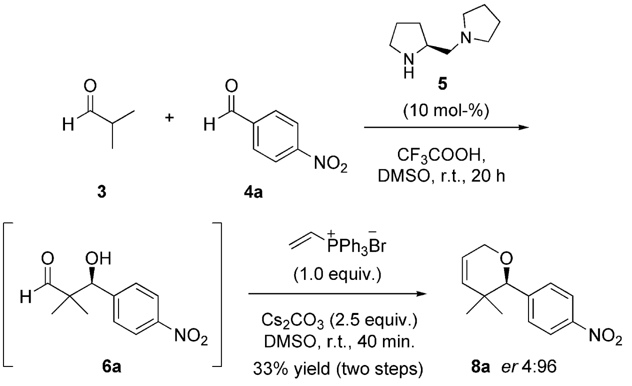
Scheme 2. Side reactions in the synthesis of 3,6-dihydropyrans.

The initial β-hydroxy aldehyde **6** can either react with vinylphosphonium salt **7a**, followed by an *intermolecular* Wittig reaction with the aromatic aldehyde **4** to give **10** as *E*/*Z* mixture, or the retro-aldol products **3** and **4** can be transformed into aldehyde **11** in a similar manner. Nevertheless the yields of the cyclised product **8** were considered acceptable given the structural features incorporated into the product.

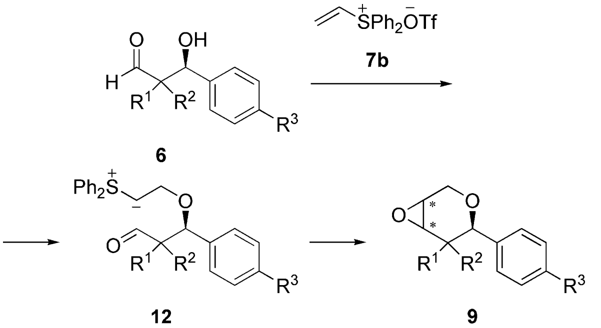
We have also shown that the synthesis of 3,6-dihydropyrans can be performed as a one-pot process (Scheme 3). Starting from isobutyraldehyde (**3**) and *p*-nitrobenzaldehyde (**4a**) the product was obtained in an isolated 33% yield and excellent *er*.

Aggarwal and co-workers have recently demonstrated the use of vinylsulfonium salts in stereocontrolled asymmetric synthesis of epoxide- and aziridine-fused heterocycles.[14] Starting from α,β- and γ-amino aldehydes and ketones five-, six- and seven-membered epoxide-fused rings were obtained in high yields. In addition, by using alanine-derived amido ketones a highly *syn*-diastereoselective epoxy annulation has been developed.[15]

We envisioned that 4,5-epoxy-tetrahydropyrans could be prepared by a related process as shown in Scheme 4.



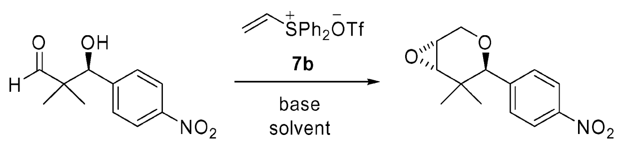
Scheme 3. One pot process to synthesis 3,6-dihydropyran **8a**.



Scheme 4. An annulation reaction mediated by a vinylsulfonium salt for the synthesis of 4,5-epoxy-tetrahydropyrans **9**.

We began our studies towards the synthesis of 4,5-epoxy-tetrahydropyrans **9** by applying conditions, which were deemed optimal in Aggarwal's epoxy-annulation procedure.[14] Initially, a solution of β-hydroxy aldehyde **6a** and 1.2 equiv. of sulfonium salt **7b** were treated with 2.0 equiv. of DBU at 0 °C. The reaction was warmed to room temperature and afforded the desired epoxide **9a** in 45% (Table 4, Entry 1). By contrast, the use of lower temperatures led to poor yields (Table 4, Entry 2), as in the case of the dihydropyrans **8**. The best result was observed at room temperature with a yield of 56%. Increasing the amount of sulfonium salt also lowered the yield (Table 4, Entry 4) and the use of solvents other than dichloromethane did not lead to improvement (Table 4, Entry 5 and 6). For comparison, the reaction with Cs_2CO_3 as base afforded only 37% yield of the epoxy product (Table 4, Entry 7).

Table 4. Screening for the synthesis of 4,5-epoxy-tetrahydropyrans **9a** from β-hydroxy aldehyde **6a**.[a]



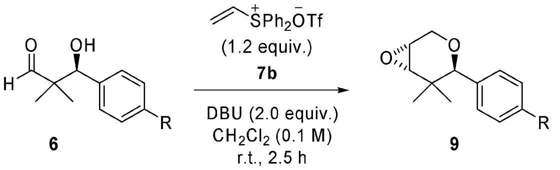
Entry	Base	Solvent	7b [equiv.]	T [°C]	Yield 9a [%]
1	DBU	CH_2Cl_2	1.2	0 → room temp.	45
2	DBU	CH_2Cl_2	1.2	–10	14
3	DBU	CH_2Cl_2	1.2	room temp.	58
4	DBU	CH_2Cl_2	1.8	room temp.	47
5	DBU	1,2-dichloroethane	1.2	room temp.	35
6	DBU	DMSO	1.2	room temp.	29
7	Cs_2CO_3[b]	CH_2Cl_2	1.2	room temp.	37

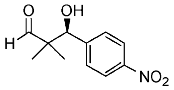
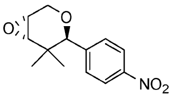
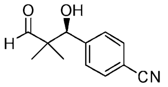
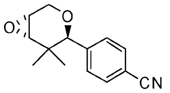
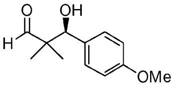
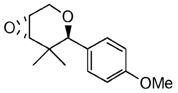
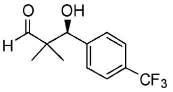
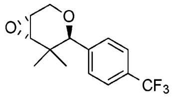
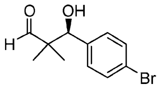
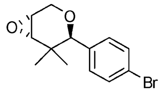
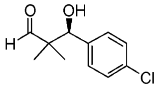
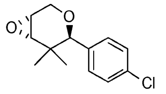
[a] 2.0 equiv. of base was added to a stirred solution (0.1 M) of hydroxy aldehyde **6a** and vinylsulfonium salt **7b** and the reaction stirred for 1–3 h. [b] Reaction was carried out with 2.5 equiv. of Cs_2CO_3.

The product was formed in a diastereomeric ratio (*dr*) of 10:1 with the *anti*-epoxide being the major isomer. In addition, we explored the scope of the reaction with a series of aromatic β-hydroxy aldehydes under the optimised conditions (Table 4, Entry 3).

9b–**9f** were also formed as a diastereomeric mixture [10:1]; the major isomer was always the *anti*-epoxide easily separable by flash column chromatography. The yields obtained in these studies are slightly lower, but comparable to those reported for the synthesis of dihydropyrans using phosphonium salts (Table 3). *p*-Nitro substitution at the

Table 5. Substrate scope for the synthesis of 4,5-epoxy-tetrahydropyrans **9**.



Entry	6	9	Yield[a] [%]	er[b] [S:R]
1	 6a	 9a	58	98:2
2	 6b	 9b	46	98:2
3	 6c	 9c	25	97:3
4	 6d	 9d	35	97:3
5	 6e	 9e	30	97:3
6	 6f	 9f	24	98:2

[a] Yield of isolated *anti*-epoxide (major). [b] Determined by HPLC analysis on a chiral phase (Chiralpak AS and Chiralcel OD, OD-H).

aromatic ring of β-hydroxy aldehyde was found optimal and the desired product **9a** was isolated in 58% yield (Table 5, Entry 1). Although this tandem transformation also suffers from the reto-aldol reaction we did not notice any other side products that could be readily characterised.

The structure and relative configuration of the major product isomer **9a** was also confirmed by single-crystal X-ray diffraction analysis.

Conclusions

In this work, a new method for the preparation of pyran derivatives **8** and **9** starting from aldol adducts **6** and onium salts was developed, which consists of a tandem conjugate addition–cyclisation process. Reaction of aromatic β-hydroxy aldehydes **6** and vinylphosphonium salts in presence of Cs_2CO_3 affords 3,6-dihydropyrans in moderate to good yields. Using optically pure aldol adducts **6** as starting material a high enantiomeric excess in the product can be conserved. This reaction was performed as one-pot process to generate the β-hydroxy aldehyde in situ. However, reto-aldol reaction was found to be a significant side process leading to the formation of unwanted products. The method was extended to the diastereoselective formation of 4,5-epoxy-tetrahydropyrans. Conjugate addition of aldol adduct **6** to a vinylsulfonium salt, followed by a subsequent cyclisation process gave the epoxides in good yields and high diastereoselectivity in presence of DBU as a base.

Experimental Section

General Information: All reactions were performed under argon unless otherwise stated. Solvents: tetrahydrofuran (THF) was distilled from lithium aluminium hydride using triphenylmethane as indicator; 1,2-dimethoxyethane (DME), acetonitrile and dichloromethane (CH_2Cl_2) from calcium hydride prior to use. Anhydrous dimethyl sulfoxide (DMSO), dimethylformamide (DMF), dioxane, *N*-methyl-2-pyrrolidone (NMP) and 1,2-dichloroethane were used as supplied. "PE" refers to petroleum ether with a boiling range of 40–60 °C. Reagents: were used as supplied or purified using standard procedures as necessary. Chromatography: flash column chromatography was carried out using silica gel 60 (0.040–0.063 mm) 230–400 mesh under pressure unless otherwise indicated. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F254) and visualised by ultraviolet radiation (254 nm), acidic ceric ammonium molybdate, or basic potassium permanganate solutions as appropriate. Data collection: melting points were performed with a Reichert hot-stage apparatus, and are uncorrected. Optical rotations were measured with a Perkin–Elmer 343 digital polarimeter using a sodium lamp (589 nm) as the light source, $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded as thin films with a Perkin–Elmer Spectrum One FT-IR 1600 spectrometer fitted with an ATR sampling accessory. ^{1}H NMR spectra were recorded at 400 MHz with Bruker Advance DPX-400 spectrometer with residual protic solvent $CDCl_3$ as the internal reference (δ_H = 7.26 ppm) and are reported as follows: chemical shift δ/ppm (number of protons, multiplicity, coupling constant *J*/Hz, assignment). ^{13}C NMR spectra were recorded at 100 MHz with Bruker Advance DPX- 400 spectrometer. The resonance of $CDCl_3$ (δ_C = 77.0 ppm, t) was used as an internal reference. ^{13}C DEPT-135 and two-dimensional (COSY and HMQC) NMR experiments were used where appropriate, to support the assignment of signals in the ^{1}H and ^{13}C spectra. Mass spectra and accurate mass data were obtained on an LCT Premier spectrometer by Waters using a Micromass MS software at the Department of Chemistry, University of Cambridge. The enantiomeric ratios (*er*) were determined by high-performance liquid chromatography (HPLC), performed with Hewlett–Packard Agilent 1100 chromatographs, or by supercritical fluid chromatography (SFC) with a Berger Minigram using a Chiralpak AS (0.46 × 25 cm), Chiralpak ADH (0.46 × 25 cm), Chiralcel OD (0.46 × 25 cm) or Chiralcel OD-H (0.46 × 25 cm) column as noted. The diastereomeric ratios (*dr*) were determined by ^{1}H NMR spectroscopy of crude products. The racemic materials were prepared using pyrrolidine as catalyst in the presence of acetic acid according to literature.[16]

General Procedure for the Synthesis of 3,6-Dihydropyrans 8: Caesium carbonate (179 mg, 0.55 mmol) was added to a stirred solution of the appropriate aldol adduct **6a–f** (0.22 mmol) and triphenylvinylphosphonium bromide (81.2 mg, 0.22 mmol) in anhydrous DMSO (2.2 mL). The resulting suspension was stirred vigorously at room temperature under argon until TLC analysis indicated complete conversion of the starting material **6a–f**. The reaction mixture was quenched with water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine and dried with Mg_2SO_4. The solvent was evaporated to dryness and the resultant residue was purified by column chromatography on silica gel with PE/EtOAc (50:1) mixture to provide the dihydropyrans **8**.

(*R*)-3,6-Dihydro-3,3-dimethyl-2-(4-nitrophenyl)-2*H*-pyran (8a): White solid; yield 56% (28.6 mg); m.p. 70–72 °C. R_f = 0.56 (PE 40–60/EtOAc, 4:1). $[\alpha]_D^{25}$ = +143.1 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2843, 1605, 1512, 1465, 1344, 1150, 1092, 1030, 997, 861, 851, 796 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.78 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3), 4.30 (d, $J_{H,H}$ = 16.5 Hz, 1 H, CH_2), 4.37 (d, $J_{H,H}$ = 16.5 Hz, 1 H, CH_2), 4.39 (s, 1 H, OCH), 5.65–5.72 (m, 2 H, CH=CH), 7.50 (d, $J_{H,H}$ = 8.7 Hz, 2 H, Ar-CH), 8.19 (d, $J_{H,H}$ = 8.7 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.0, 25.8, 35.8, 66.6, 83.7, 122.7, 123.4, 128.4, 136.2, 146.7, 147.3 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}NO_3$ $[M + H]^+$ 234.1124; found 234.1130. SFC (Chiralpak AS, 10% *i*PrOH in CO_2, 2 mL min^{-1}, 100 bar, 254 nm) t_R(major) = 38.0 min, t_R(minor) = 48.0 min.

4-[(*R*)-3,6-Dihydro-3,3-dimethyl-2*H*-pyran-2-yl]benzonitrile (8b): White solid; yield 48% (22.6 mg); m.p. 114–116 °C. R_f = 0.57 (PE 40–60/EtOAc, 3:1). $[\alpha]_D^{25}$ = +143.8 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2963 (m), 2818 (m), 1725 (w), 1361 (w), 1148 (m), 1086 (s), 1032 (m), 903 (m), 859 (s), 796 (m), 710 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.77 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 4.28 (d, $J_{H,H}$ = 16.5 Hz, 1 H, CH_2), 4.33 (s, 1 H, OCH), 4.36 (d, $J_{H,H}$ = 16.5 Hz, 1 H, CH_2), 5.64–5.70 (m, 2 H, CH=CH), 7.44 (d, $J_{H,H}$ = 8.2 Hz, 2 H, Ar-CH), 7.62 (d, $J_{H,H}$ = 8.2 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 22.0, 25.8, 35.8, 66.6, 83.9, 111.1, 118.9, 123.4, 128.3, 131.4, 136.2, 144.7 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NONa$ $[M + Na]^+$ 236.1053; found 236.1046. HPLC (Chiralpak AS, 99:1 hexane/*i*PrOH, 1 mL min^{-1}, 230 nm) t_R(major) = 8.6 min, t_R(minor) = 14.2 min.

(*R*)-3,6-Dihydro-2-(4-methoxyphenyl)-3,3-dimethyl-2*H*-pyran (8c): White solid; yield 43% (20.7 mg); m.p. 54–56 °C. R_f = 0.63 (PE 40–60/EtOAc, 3:1). $[\alpha]_D^{25}$ = +89.1 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2954, 2928, 1725, 1610, 1513, 1467, 1439, 1300, 1247, 1175, 1117, 1085, 1037, 994, 899, 803, 694 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.83 (s, 3 H, CH$_3$), 0.90 (s, 3 H, CH$_3$), 3.81 (s, 3 H, OCH$_3$), 4.25 (s, 1 H, OCH), 4.28 (d, $J_{H,H}$ = 16.6 Hz, 1 H, CH$_2$), 4.34 (d, $J_{H,H}$ = 16.6 Hz, 1 H, CH$_2$), 5.66 (s, 2 H, CH=CH), 6.86 (d, $J_{H,H}$ = 8.6 Hz, 2 H, Ar-CH), 7.24 (d, $J_{H,H}$ = 8.7 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 22.2, 25.9, 35.8, 55.3, 66.8, 84.3, 113.0, 123.3, 128.7, 131.5, 136.8, 158.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}O_2Na$ [M + Na]$^+$ 241.1208; found 241.1199. HPLC (Chiralcel OD-H, 99:1 hexane/*i*PrOH, 1 mL min^{-1}, 215 nm) t_R(major) = 5.4 min, t_R(minor) = 7.8 min.

(*R*)-3,6-Dihydro-3,3-dimethyl-2-[4-(trifluoromethyl)phenyl]-2*H*-pyran (8d): Colourless oil; yield 34% (19.2 mg). R_f = 0.56 (PE 40–60/EtOAc, 4:1). $[\alpha]_D^{25}$ = +43.0 (c = 0.7, CHCl$_3$). IR (neat): $\tilde{\nu}_{max}$ = 2966, 1621, 1323, 1163, 1119, 1067, 1018, 849, 796, 707, 661 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.80 (s, 3 H, CH$_3$), 0.94 (s, 3 H, CH$_3$), 4.29 (d, $J_{H,H}$ = 16.4 Hz, 1 H, CH$_2$), 4.35 (s, 1 H, OCH), 4.35–4.39 (m, 1 H, CH$_2$), 5.67 (d, $J_{H,H}$ = 11.2 Hz, 1 H, CH), 5.70 (d, $J_{H,H}$ = 11.2 Hz, 1 H, CH), 7.44 (d, $J_{H,H}$ = 8.1 Hz, 2 H, Ar-CH), 7.58 (d, $J_{H,H}$ = 8.2 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 22.0, 25.8, 35.7, 66.7, 84.1, 123.4, 124.3 ($^{1}J_{C,F}$ = 276.4 Hz), 124.5 ($^{3}J_{C,F}$ = 3.8 Hz), 127.9, 136.5, 143.3 ($^{5}J_{C,F}$ = 1.3 Hz) ppm. HRMS (ESI): calcd. for $C_{14}H_{15}F_3ONa$ [M + Na]$^+$ 279.0973; found 279.0981. Incompletely separated enantiomeric mixture.

(*R*)-2-(4-Bromophenyl)-3,6-dihydro-3,3-dimethyl-2*H*-pyran (8e): White solid; yield 48% (28.2 mg); m.p. 58–60 °C. R_f = 0.63 (PE 40–60/EtOAc, 3:1). $[\alpha]_D^{25}$ = +72.5 (c = 0.9, CHCl$_3$). IR (neat): $\tilde{\nu}_{max}$ = 2957, 1725, 1487, 1467, 1402, 1360, 1238, 1165, 1088, 1009, 896, 837, 720 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.79 (s, 3 H, CH$_3$), 0.91 (s, 3 H, CH$_3$), 4.25 (s, 1 H, OCH), 4.28 (d, $J_{H,H}$ = 16.8 Hz, 1 H, CH$_2$), 4.35 (dd, $J_{H,H}$ = 16.7, 1.9 Hz, 1 H, CH$_2$), 5.63–5.69 (m, 2 H, CH=CH), 7.19 (d, $J_{H,H}$ = 8.6 Hz, 2 H, Ar-CH), 7.45 (d, $J_{H,H}$ = 8.6 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 22.0, 25.8, 35.6, 66.7, 84.0, 121.2, 123.3, 129.3, 130.6, 136.5, 138.3 ppm. HRMS (ESI): calcd. for $C_{13}H_{15}BrONa$ [M + Na]$^+$ 289.0196; found 289.0203. HPLC (Chiralpak AD-H, 0.2% *i*PrOH in hexane, 0.2 mL min^{-1}, 230 nm) t_R(major) = 21.8 min, t_R(minor) = 23.2 min.

(*R*)-2-(4-Chlorophenyl)-3,6-dihydro-3,3-dimethyl-2*H*-pyran (8f): White solid; yield 40% (19.5 mg); m.p. 85–87 °C. R_f = 0.63 (PE 40–60/EtOAc, 3:1). $[\alpha]_D^{25}$ = +128.7 (c = 0.7, CHCl$_3$). IR (neat): $\tilde{\nu}_{max}$ = 2957, 2839, 1727, 1490, 146 (m), 1407, 1360, 1239, 1166, 1090, 1026, 1011, 896, 839, 788, 720 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.80 (s, 3 H, CH$_3$), 0.91 (s, 3 H, CH$_3$), 4.27–4.37 (m, 3 H, OCH and CH$_2$), 5.66 (s, 2 H, CH), 7.25 (d, $J_{H,H}$ = 8.6 Hz, 2 H, Ar-CH), 7.31 (d, $J_{H,H}$ = 8.6 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 22.1, 25.9, 35.7, 66.7, 84.0, 123.3, 127.7, 129.0, 133.0, 136.6, 137.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}ClO$ [M + H]$^+$ 223.0882; found 223.0890. HPLC (Chiralpak AD-H, 0.2% *i*PrOH in hexane, 0.2 mL min^{-1}, 230 nm) t_R(major) = 21.5 min, t_R(minor) = 20.6 min.

General Procedure for the Synthesis of 4,5-Epoxytetrahydropyrans 9: DBU (67 µL, 0.44 mmol) was added to a stirred solution of the appropriate aldol adduct **6a**–**f** (0.22 mmol) and diphenylvinylsulfonium trifluoromethanesulfonate (95.6 mg, 0.26 mmol) in anhydrous CH$_2$Cl$_2$ (2.2 mL). The resulting solution was stirred at room temperature under argon until the reaction was determined to be complete by TLC. The reaction mixture was quenched with water (10 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic phase was washed with brine, dried with Mg$_2$SO$_4$, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel with PE/EtOAc (10:1) mixture to provide the epoxides **9**.

(1*S*,3*S*,6*R*)-2,2-Dimethyl-3-(4-nitrophenyl)-4,7-dioxabicyclo[4.1.0]heptane (9a): White solid; yield 58% (31.8 mg); m.p. 59–61 °C. R_f = 0.65 (PE 40–60/EtOAc, 3:1). $[\alpha]_D^{25}$ = +33.1 (c = 1.0, CHCl$_3$). IR (neat): $\tilde{\nu}_{max}$ = 2967, 2985, 16004, 1513, 1470, 1343, 1144, 1102, 1000, 864, 849, 744, 674 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.86 (s, 3 H, CH$_3$), 1.03 (s, 3 H, CH$_3$), 3.08 (d, $J_{H,H}$ = 4.2 Hz, 1 H, C*H*OCHCH$_2$), 3.39 (d, $J_{H,H}$ = 4.1 Hz, 1 H, CHOC*H*CH$_2$), 4.07 (d, $J_{H,H}$ = 13.5 Hz, 1 H, CH$_2$), 4.31 (d, $J_{H,H}$ = 13.5 Hz, 1 H, CH$_2$), 4.37 (s, 1 H, C*H*OCH$_2$), 7.39 (d, $J_{H,H}$ = 8.8 Hz, 2 H, Ar-CH), 8.15 (d, $J_{H,H}$ = 8.8 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 17.9, 22.9, 35.3, 52.7, 60.9, 65.4, 78.4, 122.7, 128.4, 145.9, 147.3 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}NO_4$ [M + H]$^+$ 250.1085; found 250.1074. HPLC (Chiralpak AS, 99:1 hexane/*i*PrOH, 1 mL min^{-1}, 230 nm) t_R(major) = 16.9 min, t_R(minor) = 21.3 min.

4-[(1*S*,3*S*,6*R*)-2,2-Dimethyl-4,7-dioxabicyclo[4.1.0]heptan-3-yl]benzonitrile (9b): White solid; yield 46% (23.1 mg); m.p. 99–101 °C. R_f = 0.53 (PE 40–60/EtOAc, 3:1). $[\alpha]_D^{25}$ = +61.0 (c = 1.0, CHCl$_3$). IR (neat): $\tilde{\nu}_{max}$ = 2971, 2874, 2229, 1708, 1610, 1470, 1365, 1148, 1018, 849, 830, 772, 700 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.85 (s, 3 H, CH$_3$), 1.01 (s, 3 H, CH$_3$), 3.07 (d, $J_{H,H}$ = 4.3 Hz, 1 H, C*H*OCHCH$_2$), 3.38 (d, $J_{H,H}$ = 4.2 Hz, 1 H, CHOC*H*CH$_2$), 4.06 (d, $J_{H,H}$ = 13.6 Hz, 1 H, CH$_2$), 4.30 (dd, $J_{H,H}$ = 13.9, 4.0 Hz, 1 H, CH$_2$), 4.31 (s, 1 H, C*H*OCH$_2$), 7.34 (d, $J_{H,H}$ = 8.6 Hz, 2 H, Ar-CH), 7.59 (d, $J_{H,H}$ = 8.6 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 18.0, 22.9, 35.3, 52.7, 61.0, 65.4, 78.6, 111.3, 118.8, 128.3, 131.3, 143.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NO_2Na$ [M + Na]$^+$ 252.0997; found 252.0995. HPLC (Chiralcel OD-H, 99:1 hexane/*i*PrOH, 1 mL min^{-1}, 215 nm) t_R(major) = 18.8 min, t_R(minor) = 15.9 min.

(1*S*,3*S*,6*R*)-3-(4-Methoxyphenyl)-2,2-dimethyl-4,7-dioxabicyclo[4.1.0]heptane (9c): White solid; yield 25% (12.9 mg); m.p. 70–72 °C. R_f = 0.47 (PE 40–60/EtOAc, 3:1). $[\alpha]_D^{25}$ = +47.6 (c = 0.87, CHCl$_3$). IR (neat): $\tilde{\nu}_{max}$ = 2971, 2859, 1684, 1609, 1513, 1442, 1300, 1246, 1177, 1147, 1036, 1021, 996, 911, 845, 831, 774 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.91 (s, 3 H, CH$_3$), 0.97 (s, 3 H, CH$_3$), 3.06 (d, $J_{H,H}$ = 4.3 Hz, 1 H, C*H*OCHCH$_2$), 3.36 (d, $J_{H,H}$ = 4.2 Hz, 1 H, CHOC*H*CH$_2$), 3.79 (s, 3 H, OCH$_3$), 4.07 (d, $J_{H,H}$ = 13.7 Hz, 1 H, CH$_2$), 4.22 (s, 1 H, C*H*OCH$_2$), 4.28 (dd, $J_{H,H}$ = 13.7, 4.1 Hz, 1 H, CH$_2$), 6.83 (d, $J_{H,H}$ = 8.8 Hz, 2 H, Ar-CH), 7.14 (d, $J_{H,H}$ = 8.7 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 18.2, 23.0, 35.2, 52.9, 55.3, 61.3, 65.5, 78.8, 112.9, 128.7, 132.0, 158.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{18}O_3Na$ [M + Na]$^+$ 257.1157; found 257.1148. HPLC (Chiralcel OD-H, 99:1 hexane/*i*PrOH, 1 mL min^{-1}, 230 nm) t_R(major) = 8.7 min, t_R(minor) = 11.9 min.

(1*S*,3*S*,6*R*)-2,2-Dimethyl-3-[4-(trifluoromethyl)phenyl]-4,7-dioxabicyclo[4.1.0]heptane (9d): Colourless oil; yield 35% (20.9 mg). R_f = 0.55 (PE 40–60/EtOAc, 3:1). $[\alpha]_D^{25}$ = +19.8 (c = 0.8, CHCl$_3$). IR (neat): $\tilde{\nu}_{max}$ = 2973, 1622, 1513, 1472, 1350, 1163, 1107, 1067, 999, 850, 830, 661 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 0.88 (s, 3 H, CH$_3$), 1.02 (s, 3 H, CH$_3$), 3.08 (d, $J_{H,H}$ = 4.1 Hz, 1 H, C*H*OCHCH$_2$), 3.39 (d, $J_{H,H}$ = 4.1 Hz, 1 H, CHOC*H*CH$_2$), 4.08 (d, $J_{H,H}$ = 13.6 Hz, 1 H, CH$_2$), 4.30 (dd, $J_{H,H}$ = 13.6, 3.3 Hz, 1 H, CH$_2$), 4.33 (s, 1 H, C*H*OCH$_2$), 7.35 (d, $J_{H,H}$ = 8.1 Hz, 2 H, Ar-CH), 7.56 (d, $J_{H,H}$ = 8.1 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 18.0, 22.9, 35.1, 52.8, 61.0, 65.5, 78.7, 124.2 ($^{1}J_{C,F}$ = 272 Hz), 124.4 ($^{3}J_{C,F}$ = 4 Hz), 127.9, 129.6 ($^{2}J_{C,F}$ = 32 Hz), 142.5 ($^{5}J_{C,F}$ = 2 Hz) ppm. HRMS (ESI): calcd. for $C_{14}H_{15}F_3O_2Na$ [M + Na]$^+$ 295.0913; found 295.0916. HPLC

(Chiralcel OD-H, 0.1% *i*PrOH in hexane, 1 mL min^{-1}, 215 nm) t_R(major) = 12.2 min, t_R(minor) = 10.3 min.

(1*S*,3*S*,6*R*)-3-(4-Bromophenyl)-2,2-dimethyl-4,7-dioxabicyclo[4.1.0]-heptane (9e): White solid; yield 30% (18.6 mg); m.p. 81–84 °C. R_f = 0.73 (PE 40–60/EtOAc, 5:1). $[\alpha]_D^{25}$ = +68.7 (c = 0.6, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2970, 2869, 1490, 1470, 1147, 1109, 998, 837, 827, 771, 668 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.87 (s, 3 H, CH_3), 0.98 (s, 3 H, CH_3), 3.06 (d, $J_{H,H}$ = 4.2 Hz, 1 H, C*H*OCHCH$_2$), 3.37 (d, $J_{H,H}$ = 4.2 Hz, 1 H, CHOC*H*CH$_2$), 4.06 (d, $J_{H,H}$ = 13.7 Hz, 1 H, CH_2), 4.23 (s, 1 H, C*H*OCH$_2$), 4.28 (dd, $J_{H,H}$ = 13.7, 4.2 Hz, 1 H, CH_2), 7.09 (d, $J_{H,H}$ = 8.4 Hz, 2 H, Ar-CH), 7.42 (d, $J_{H,H}$ = 8.4 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.0, 22.9, 35.1, 52.8, 61.1, 65.5, 78.6, 121.3, 129.3, 130.6, 137.4 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}BrO_2$ [M + H]$^+$ 283.0326; found 283.0328. HPLC (Chiralcel OD-H, 0.1% *i*PrOH in hexane, 1 mL min^{-1}, 230 nm) t_R(major) = 22.4 min, t_R(minor) = 19.9 min.

(1*S*,3*S*,6*R*)-3-(4-Chlorophenyl)-2,2-dimethyl-4,7-dioxabicyclo[4.1.0]-heptane (9f): White solid; yield 24% (12.6 mg); m.p. 104–106 °C. R_f = 0.49 (PE 40–60/EtOAc, 3:1). $[\alpha]_D^{25}$ = +61.4 (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2971, 2969 (w), 1594, 1489, 1469, 1365, 1146, 1113, 1010, 997, 893, 830, 767 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 0.88 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 3.06 (d, $J_{H,H}$ = 4.2 Hz, 1 H, C*H*OCHCH$_2$), 3.37 (d, $J_{H,H}$ = 4.2 Hz, 1 H, CHOC*H*CH$_2$), 4.07 (d, $J_{H,H}$ = 13.6 Hz, 1 H, CH_2), 4.25 (s, 1 H, C*H*OCH$_2$), 4.28 (dd, $J_{H,H}$ = 13.6, 4.0 Hz, 1 H, CH_2), 7.16 (d, $J_{H,H}$ = 8.4 Hz, 2 H, Ar-CH), 7.27 (d, $J_{H,H}$ = 8.4 Hz, 2 H, Ar-CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 18.0, 22.9, 35.1, 52.8, 61.1, 65.5, 78.6, 127.7, 128.9, 133.1, 136.9 ppm. HRMS (ESI): calcd. for $C_{13}H_{16}ClO_2$ [M + H]$^+$ 239.0836; found 239.0833. HPLC (Chiralcel OD, 0.1% *i*PrOH in hexane, 0.5 mL min^{-1}, 230 nm) t_R(major) = 36.4 min, t_R(minor) = 33.3 min.

Supporting Information (see also the footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra for **8a**–**f** and **9a**–**f**.

Acknowledgments

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