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Enantioselective Organocatalyzed Consecutive Synthesis of Alkyl 4,5-Dihydrofuran-2-carboxylates from α -Keto Esters and (*Z*)- β -Chloro- β -nitrostyrenes

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Dedicated to Professor Dieter Enders on the occasion of his 70th birthday

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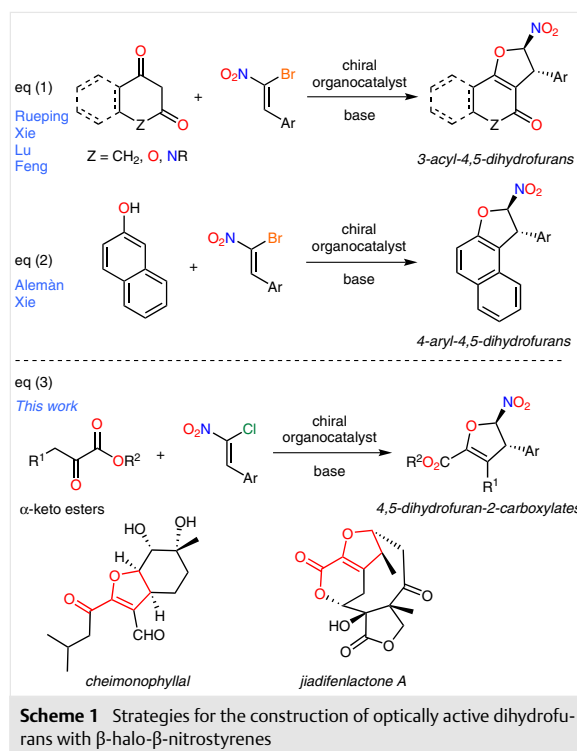
Abstract Alkyl 4,5-dihydrofuran-2-carboxylates can be efficiently obtained via an enantioselective organocatalyzed consecutive reaction between α -keto esters and (*Z*)-(2-chloro-2-nitroethenyl)benzenes. The overall sequence combines a (*R,R*)-TUC-catalyzed Michael addition with a DABCO-promoted intramolecular *O*-alkylation leading to the title products as single diastereomers with enantiomeric excesses from 86% up to 97%.

Key words dihydrofurans, organocatalysis, domino Michael/alkylation, Takemoto catalyst, (*Z*)- β -chloro- β -nitrostyrenes

Dihydrofuran is a structural subunit found in a number of important natural products and pharmaceutically relevant compounds.¹ In consequence, important efforts have been devoted towards the enantioselective synthesis of dihydrofurans derivatives.² Since the pioneer reports of Dauzonne and co-workers twenty-five years ago,³ the Michael-alkylation domino reaction between (*Z*)-(2-halo-2-nitroethenyl)benzenes and various bis-nucleophiles has become an attractive strategy to access dihydrofurans enantioselectively (Scheme 1). Hence, the groups of Rueping, Xie, Lu, and Feng employed 1,3-dicarbonyls as 1,3-bis-nucleophiles activated by an hydrogen-bonding organocatalyst to access 3-carbonyl-4,5-dihydrofurans (Scheme 1, eq 1),^{4,5} while the groups of Alemán and Xie used β -naphthols as 1,3-bis-nucleophiles to efficiently construct the corresponding 2,3-dihydrobenzofurans via a Friedel-Crafts/alkylation domino reaction (Scheme 1, eq 2).⁶

However, none of these approaches allows for the challenging introduction of a key carbonyl moiety in the 2-position of the final optically active dihydrofuran target. In-

deed, the 2-carbonyl-4,5-dihydrofuran substructure is present in various families of bioactive natural products such as cheimonophyllal,⁷ and jiadifenlactone A⁸ and no efficient enantioselective method to construct this moiety has been reported so far.⁹



Scheme 1 Strategies for the construction of optically active dihydrofurans with β -halo- β -nitrostyrenes

α -Dicarbonyl compounds are privileged substrates for the development of new multiple bond-forming transformations¹⁰ due to their high number of adjacent reactive sites that can participate in the successive creation of several bonds.^{11,12} Therefore, to address this synthetic lack, we propose a sequential enantioselective heterocyclization of α -keto esters with β -chloro- β -nitrostyrenes combining an enantioselective Michael addition promoted by a chiral H-bonding donor bifunctional catalyst¹³ with a base-promoted intramolecular *O*-alkylation (Scheme 1, eq 3).

Optimized conditions¹³ for the enantioselective Michael addition leading to **3a** were used and our initial efforts focused on the base-promoted heterocyclization from **3a** (Table 1). An encouraging result was obtained with the use of 1 equivalent of TMEDA at 60 °C leading to the desired dihydrofuran **4a** in only 27% yield, but with excellent stereoselectivities together, with the side product furan **5a** (entry 1). Lowering the amount of base to 0.2 equivalents resulted in lower yield (entry 2). Further improvements in yield were achieved using other organic bases even if in the case of DBU (entry 3) a marked erosion of both diastereo- and enantioselectivity was observed as well as an increased

proportion of undesired furan **5a** compared to the use of DABCO (entry 4). Finally, lowering the temperature had a beneficial impact on the yield (entries 5 and 6), which could be increased to 79% when conducting the reaction at 25 °C, while maintaining excellent diastereo- and enantioselectivities. In this last case, prolonged reaction time was required (72 h) to consume starting materials while keeping a limited ratio of **5a**.

Having found conditions that gave good yields and high stereoselectivities in this formal [3+2] heterocyclization, we explored alternative β -chloro- β -nitrostyrenes **1** and α -keto esters **2** (Table 2). Concerning the nitroalkene, the reaction worked well with β -substituted aromatic rings bearing either electron-donating (entries 1–5) or electron-withdrawing groups (entries 6–8), including sterically demanding *ortho* functionalization (entry 7), or a 2-naphthyl moiety (entry 9). The introduction of a heteroaromatic moiety (3-chromenyl, entry 10) was possible, but a poor yield of **4j** was obtained and the reaction was found to be very slow, both for the formation of the Michael adduct and for the heterocyclization step. On the other hand, *tert*-butyl ester as well as ethyl ester can be employed and the desired

Table 1 Optimization of the Reaction Conditions^a

Entry	Base	T (°C)	Ratio ^b 3a / 4a / 5a	Yield ^c (%)	dr ^b	ee ^d (%)
1	TMEDA	60	1:13:3	27	12:1	93
2 ^e	TMEDA	60	8:6:1	7	>20:1	– ^f
3	DBU	60	1:16:3	51	14:1	78
4	DABCO	60	1:20:4	47	>20:1	94
5	DABCO	40	1:18:1	57	>20:1	95
6 ^g	DABCO	25	1:21:1	79	>20:1	95

^a Reaction conditions: 1. **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (*R,R*)-TUC (10 mol%), EtOAc (1.0 mL), stirring, 0 °C, 24 h; 2. base (1 equiv), stirring, T (°C), 24 h; unless otherwise noted.

^b Determined by ¹H NMR analysis of the crude reaction mixture.

^c Isolated yield after column chromatography.

^d Determined by chiral HPLC analysis.

^e 0.2 equiv of base was used.

^f Not determined.

^g 72 h of reaction time after addition of base.

products were obtained in fairly good yields with excellent diastereo- and enantioselectivities (entries 11–14). We noticed also that adding steric bulk around pro-nucleophilic carbon atom of the α -keto ester (use of **2c**, **2d**, and **2e**, entries 12–14) had a negative impact on the kinetics of both the Michael addition as well as on the heterocyclization step.

To evaluate the synthetic usefulness of this methodology, the nitro group of **4a** was reduced to the primary amine moiety affording the relatively labile aminal **6** in moderate yield suffering substantial erosion of enantiomeric excess (Scheme 2). Also, an attempt to convert dihydrofuran **4a** into the corresponding lactone using the Mioskowski procedure¹⁴ resulted in the formation of nitrofuran **7** in 65% yield.

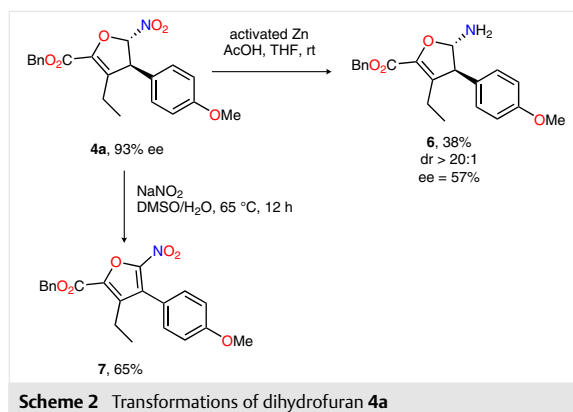
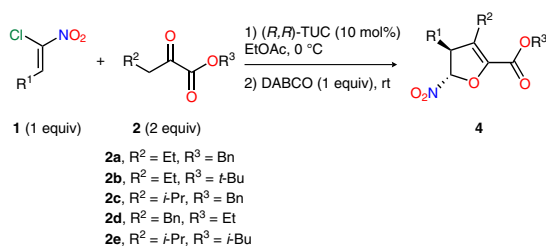


Table 2 Reaction Scope^a



Entry	R ¹	1	2	4		Time (h)	Yield ^b (%) ^b	dr ^c	ee ^d (%)
				3	4				
1	4-MeOC ₆ H ₄	1a	2a	4a		24	79	>20:1	95
2	2-MeOC ₆ H ₄	1b	2a	4b		24	54	>20:1	97
3	2-MeC ₆ H ₄	1c	2a	4c		48	48	>20:1	93
4	4-HOC ₆ H ₄	1d	2a	4d		72	48	>20:1	95
5	2-BnOC ₆ H ₄	1e	2a	4e		72	42	>20:1	94
6	4-ClC ₆ H ₄	1f	2a	4f		24	20	>20:1	93
7	2-FC ₆ H ₄	1g	2a	4g		24	62	>20:1	97
8	3-ClC ₆ H ₄	1h	2a	4h		72	43	>20:1	90
9	2-naphthyl	1i	2a	4i		48	61	>20:1	95
10 ^e	3-chromenyl	1j	2a	4j		96	20	>20:1	97
11 ^f	4-MeOC ₆ H ₄	1a	2b	4k		48	36	>20:1	94
12 ^f	4-MeOC ₆ H ₄	1a	2c	4l		72	38	>20:1	95
13 ^f	4-MeOC ₆ H ₄	1a	2d	4m		96	52	>20:1	86
14 ^f	4-MeOC ₆ H ₄	1a	2e	4n		96	26	>20:1	91

^a Reaction conditions: 1. **1** (0.1 mmol), **2** (0.2 mmol), catalyst (*R,R*)-TUC (10 mol%), EtOAc (1.0 mL) stirring, 0 °C, for the indicated time; 2. mixture brought to r.t. followed by addition of DABCO (0.1 mmol).

^b Isolated yield after column chromatography.

^c Determined by ¹H NMR analysis of the crude reaction product.

^d Determined by chiral HPLC analysis.

^e THF was used as the reaction solvent.

^f When DABCO was added, the reaction was heated to 40 °C.

In conclusion we have developed an efficient consecutive reaction to optically active alkyl *trans*-4,5-dihydrofuran-2-carboxylates by a Michael/O-alkylation sequence between α -keto esters and β -chloro- β -nitrostyrenes. This protocol nicely complements the ones existing using this strategy, making possible the introduction of an ester function in the 2 position of the dihydrofuran structure, ready for further functionalizations. The more challenging activation of α -keto esters in comparison to the well-known 1,3-dicarbonyls explains usually long reaction times for this methodology. But this is well counterbalanced by very high stereoselectivities obtained in all cases.

All reagents were weighed and handled in air at room temperature. ^1H NMR spectra were measured on a Bruker AC 400 (400 MHz) spectrometer. Data were reported as chemical shifts in ppm referenced to the internal solvent signal. ^{13}C NMR spectra were measured on a Bruker AC 400 (100 MHz) spectrometer with complete proton decoupling. High-performance liquid chromatography (HPLC) was performed on a VWR Hitachi (pump L-2130/Diode Array detector L-2455) instrument. High-resolution mass spectra (HRMS) were performed on a QStar Elite (Applied Biosystems SCIEX) spectrometer equipped with atmospheric pressure ionization source (API) pneumatically assisted. Samples were ionized by positive electrospray mode as follows: electrospray tension (ISV): 5500 V; opening tension (OR): 50 V; nebulization gas pressure (air): 20 psi. Optical rotations were measured with a Perkin-Elmer 241 micropolarimeter. Melting points (mp) were determined with a Büchi Melting-Point B-450 apparatus and were not corrected. Thin-layer chromatography (TLC) was carried out on silica Merck 60F254. Visualization was achieved under a UVP mineralight UVGL-58 lamp, and by developing the plates with *p*-anisaldehyde reagent or phosphomolybdic acid reagent. The products were purified by flash column chromatography on silica gel 60 (Merck, 230–400 mesh). All reagents were obtained from commercial suppliers unless otherwise stated.

***trans*-4,5-Dihydrofuran-2-carboxylates; General Procedure**

To a solution of nitroalkene 1 (0.1 mmol, 1.0 equiv) and α -keto ester 2 (0.2 mmol, 2.0 equiv) in EtOAc (1.0 mL) at 0 °C was added (*R,R*)-TUC (10 mol%). The reaction was stirred until complete conversion of the starting materials (monitored by TLC). Then, DABCO (0.1 mmol, 1.0 equiv) was added at 0 °C with stirring and the mixture was warmed to r.t. After completion of the reaction (monitored by ^1H NMR of the crude mixture), the reaction was quenched with sat. aq. NH_4Cl and extracted with EtOAc (3 \times 5.0 mL). The combined organic layers were then dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/PE) to afford the desired product. The diastereomeric ratio was determined by ^1H NMR spectroscopy analysis of the crude mixture and the enantiomeric excess (ee) was determined by HPLC analysis on a chiral phase.

Benzyl (4*S*,5*S*)-3-Ethyl-4-(4-methoxyphenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4a)

Isolated as a yellow oil; yield: 30 mg (79%); R_f = 0.47 (EtOAc/PE, 1:4); dr *anti/syn* >20:1; HPLC (Chiralpak IA, heptane/EtOH, 90:10, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 10.47 (major), 9.51 min (minor); 95% ee.

^1H NMR (300 MHz, CDCl_3): δ = 7.47–7.34 (m, 5 H, ArH), 7.12 (d, J = 8.7 Hz, 2 H, ArH), 6.91 (d, J = 8.7 Hz, 2 H, ArH), 5.76 (d, J = 1.9 Hz, 1 H, CHNO_2), 5.36 (d, J = 2.1 Hz, 2 H, CH_2Ph), 4.37 (d, J = 1.9 Hz, 1 H, CHAr), 3.81 (s, 3 H, OCH_3), 2.81 (dq, J = 14.9, 7.5 Hz, 1 H, CH_2CH_3), 2.04 (dq, J = 14.9, 7.5 Hz, 1 H, CH_2CH_3), 0.91 (t, J = 7.5 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, CDCl_3): δ = 160.1, 159.5, 139.9, 135.2, 134.0, 128.8 (2 C), 128.8 (2 C), 128.7, 128.6 (2 C), 127.8, 115.0 (2 C), 109.4, 67.4, 59.1, 55.5, 18.3, 12.8.

Benzyl (4*R*,5*S*)-3-Ethyl-4-(2-methoxyphenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4b)

Isolated as a light yellow oil; yield: 21 mg (54%); R_f = 0.50 (EtOAc/PE, 1:6); dr *anti/syn* >20:1; HPLC (Chiralpak IA, heptane/EtOH, 90:10, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 8.84 (major), 7.43 min (minor); 97% ee; $[\alpha]_D^{20}$ +109.76 (c 1.26, CHCl_3).

^1H NMR (300 MHz, CDCl_3): δ = 7.46–7.30 (m, 6 H, ArH), 7.01 (dd, J = 7.7, 1.8 Hz, 1 H, ArH), 6.91–6.98 (m, 2 H, ArH), 5.82 (d, J = 2.2 Hz, 1 H, CHNO_2), 5.36 (d, J = 3.6 Hz, 2 H, CH_2Ph), 4.94 (d, J = 2.2 Hz, 1 H, CHAr), 3.87 (s, 3 H, OCH_3), 2.86 (dq, J = 14.8, 7.4 Hz, 1 H, CH_2CH_3), 2.01 (dq, J = 14.8, 7.4 Hz, 1 H, CH_2CH_3), 0.93 (t, J = 7.4 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, CDCl_3): δ = 159.5, 157.0, 140.1, 135.3, 133.8, 130.1, 128.8 (2 C), 128.6, 128.5 (2 C), 128.2, 124.0, 121.3, 111.2, 109.4, 67.2, 55.7, 52.7, 18.5, 12.8.

HRMS (ESI+): m/z $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_6$: 401.1707; found: 401.1708.

Benzyl (4*S*,5*S*)-3-Ethyl-5-nitro-4-(*o*-tolyl)-4,5-dihydrofuran-2-carboxylate (4c)

Isolated as a light yellow oil; yield: 18 mg (48%); R_f = 0.35 (EtOAc/PE, 1:12); dr *anti/syn* >20:1; HPLC (Chiralpak IE, heptane/EtOH, 90:10, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 7.72 (major), 6.76 min (minor); 93% ee; $[\alpha]_D^{20}$ +168.77 (c 1.14, CHCl_3).

^1H NMR (400 MHz, CDCl_3): δ = 7.46 (d, J = 8.5 Hz, 2 H, ArH), 7.43–7.35 (m, 3 H, ArH), 7.30–7.17 (m, 3 H, ArH), 6.97 (d, J = 7.3 Hz, 1 H, ArH), 5.72 (d, J = 1.9 Hz, 1 H, CHNO_2), 5.38 (d, J = 3.5 Hz, 2 H, CH_2Ph), 4.73 (d, J = 1.9 Hz, 1 H, CHAr), 2.87 (dq, J = 15.0, 7.6 Hz, 1 H, CH_2CH_3), 2.50 (s, 3 H, CH_3), 2.02 (dq, J = 15.0, 7.6 Hz, 1 H, CH_2CH_3), 0.91 (t, J = 7.6 Hz, 3 H, CH_2CH_3).

^{13}C NMR (100 MHz, CDCl_3): δ = 159.4, 140.5, 136.5, 135.2, 134.1, 133.8, 131.4, 128.9 (2 C), 128.8, 128.7, 128.6 (2 C), 127.3, 126.9, 109.2, 67.4, 55.3, 20.0, 18.4, 12.9.

HRMS (ESI+): m/z $[\text{M} + \text{NH}_4]^+$ calcd for $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_5$: 385.1758; found: 385.1759.

Benzyl (4*S*,5*S*)-3-Ethyl-4-(4-hydroxyphenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4d)

Isolated as a light yellow oil; yield: 18 mg (48%); R_f = 0.10 (EtOAc/PE, 1:6); dr *anti/syn* >20:1; HPLC (Chiralpak IA, heptane/EtOH, 90:10, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 11.15 (major), 9.95 min (minor); 95% ee; $[\alpha]_D^{20}$ +282.58 (c 0.37, CHCl_3).

^1H NMR (300 MHz, CDCl_3): δ = 7.49–7.31 (m, 5 H, ArH), 7.06 (d, J = 8.5 Hz, 2 H, ArH), 6.84 (d, J = 8.5 Hz, 2 H, ArH), 5.75 (d, J = 1.8 Hz, 1 H, CHNO_2), 5.43–5.25 (m, 3 H, CH_2Ph , OH), 4.36 (d, J = 1.8 Hz, 1 H, CHAr), 2.81 (dq, J = 15.0, 7.6 Hz, 1 H, CH_2CH_3), 2.03 (dq, J = 15.0, 7.6 Hz, 1 H, CH_2CH_3), 0.90 (t, J = 7.6 Hz, 3 H, CH_2CH_3).

^{13}C NMR (75 MHz, CDCl_3): δ = 159.5, 156.3, 139.9, 135.1, 134.1, 129.1 (2 C), 128.8 (2 C), 128.7, 128.6 (2 C), 127.8, 116.5 (2 C), 109.4, 67.4, 59.1, 18.3, 12.8.

HRMS (ESI+): m/z [M + NH₄]⁺ calcd for C₂₀H₂₃N₂O₆: 387.1551; found: 387.1551.

Benzy (4R,5S)-4-[2-(Benzyloxy)phenyl]-3-ethyl-5-nitro-4,5-dihydrofuran-2-carboxylate (4e)

Isolated as a light yellow oil; yield: 19 mg (42%); R_f = 0.54 (EtOAc/PE, 1:5); dr *anti/syn* >20:1; HPLC (Lux-Cellulose-4, heptane/EtOH, 80/20, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 6.80 (major), 7.74 min (minor); 94% ee; $[\alpha]_D^{20}$ +117.2 (c 1.05, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 7.37–7.23 (m, 12 H, ArH), 6.99–6.91 (m, 2 H, ArH), 5.78 (d, J = 2.4 Hz, 1 H, CHNO₂), 5.25 (s, 2 H, CH₂Ph), 5.06 (s, 2 H, CH₂Ph), 4.90 (d, J = 2.4 Hz, 1 H, CHAr), 2.73 (dq, J = 14.8, 7.6 Hz, 1 H, CH₂CH₃), 1.95 (dq, J = 14.8, 7.6 Hz, 1 H, CH₂CH₃), 0.81 (t, J = 7.6 Hz, 3 H, CH₂CH₃).

¹³C NMR (75 MHz, CDCl₃): δ = 159.5, 156.1, 140.1, 136.3, 135.3, 133.9, 130.1 (2 C), 128.8 (2 C), 128.8, 128.7, 128.6, 128.5 (2 C), 128.3, 127.6 (2 C), 124.3, 121.6, 112.6, 109.4, 70.7, 67.2, 53.1, 18.5, 12.9.

HRMS (ESI+): m/z [M + NH₄]⁺ calcd for C₂₇H₂₉N₂O₆: 477.2020; found: 477.2019.

Benzy (4S,5S)-4-(4-Chlorophenyl)-3-ethyl-5-nitro-4,5-dihydrofuran-2-carboxylate (4f)

Isolated as a light yellow oil; yield: 8 mg (20%); R_f = 0.57 (EtOAc/PE, 1:6); dr *anti/syn* >20:1; HPLC (Chiralpak IA, heptane/EtOH, 90:10, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 9.21 (major), 8.43 min (minor); 93% ee; $[\alpha]_D^{20}$ +292.7 (c 0.36, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ = 7.47–7.36 (m, 7 H, ArH), 7.15 (d, J = 8.4 Hz, 2 H, ArH), 5.74 (d, J = 1.9 Hz, 1 H, CHNO₂), 5.36 (d, J = 4.0 Hz, 2 H, CH₂Ph), 4.41 (d, J = 1.9 Hz, 1 H, CHAr), 2.83 (dq, J = 15.0, 7.6 Hz, 1 H, CH₂CH₃), 2.02 (dq, J = 15.0, 7.6 Hz, 1 H, CH₂CH₃), 0.91 (t, J = 7.6 Hz, 3 H, CH₂CH₃).

¹³C NMR (100 MHz, CDCl₃): δ = 159.3, 140.4, 135.1, 135.1, 134.3, 133.2, 129.9 (2 C), 129.1 (2 C), 128.9 (2 C), 128.8, 128.6 (2 C), 108.8, 67.5, 59.0, 18.3, 12.8.

HRMS (ESI+): m/z [M + NH₄]⁺ calcd for C₂₀H₂₂ClN₂O₅: 405.1212; found: 405.1212.

Benzy (4R,5S)-3-Ethyl-4-(2-fluorophenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4g)

Isolated as a yellow oil; yield: 23 mg (62%); R_f = 0.42 (EtOAc/PE, 1:5); dr *anti/syn* >20:1; HPLC (Chiralpak IE, heptane/EtOH, 90:10, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 10.28 (major), 7.49 min (minor); 97% ee; $[\alpha]_D^{20}$ +210.0 (c 0.64, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 7.47–7.32 (m, 6 H, ArH), 7.21–7.06 (m, 3 H, ArH), 5.85 (d, J = 2.1 Hz, 1 H, CHNO₂), 5.36 (d, J = 1.8 Hz, 2 H, CH₂Ph), 4.83 (d, J = 2.1 Hz, 1 H, CHAr), 2.84 (dq, J = 15.0, 7.6 Hz, 1 H, CH₂CH₃), 2.02 (dq, J = 15.0, 7.6 Hz, 1 H, CH₂CH₃), 0.93 (t, J = 7.6 Hz, 3 H, CH₂CH₃).

¹³C NMR (75 MHz, CDCl₃): δ = 160.4 (J = 247.2 Hz), 159.3, 140.5, 135.1, 132.8, 130.8 (J = 8.25 Hz), 128.9 (2 C), 128.7, 128.7, 128.6 (2 C), 125.3 (J = 3.9 Hz), 123.0 (J = 14.3 Hz), 116.4 (J = 21.5 Hz), 108.6, 67.4, 52.0 (J = 3.75 Hz), 18.3, 12.8.

HRMS (ESI+): m/z [M + NH₄]⁺ calcd for C₂₀H₂₂FN₂O₅: 389.1507; found: 389.1506.

Benzy (4S,5S)-4-(3-Chlorophenyl)-3-ethyl-5-nitro-4,5-dihydrofuran-2-carboxylate (4h)

Isolated as a light yellow oil; yield: 17 mg (43%); R_f = 0.52 (EtOAc/PE, 1:6); dr *anti/syn* >20:1; HPLC (Chiralpak IE, heptane/EtOH, 90:10, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 8.92 (major), 6.64 min (minor); 90% ee; $[\alpha]_D^{20}$ +136.8 (c 0.90, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 7.49–7.32 (m, 7 H, ArH), 7.20 (s, 1 H, ArH), 7.14–7.08 (m, 1 H, ArH), 5.76 (d, J = 2.0 Hz, 1 H, CHNO₂), 5.37 (d, J = 1.7 Hz, 2 H, CH₂Ph), 4.40 (d, J = 2.0 Hz, 1 H, CHAr), 2.85 (dq, J = 15.0, 7.5 Hz, 1 H, CH₂CH₃), 2.01 (dt, J = 15.0, 7.5 Hz, 1 H, CH₂CH₃), 0.92 (t, J = 7.5 Hz, 3 H, CH₂CH₃).

¹³C NMR (75 MHz, CDCl₃): δ = 159.3, 140.6, 137.8, 135.7, 135.1, 133.0, 131.0, 129.4, 128.9 (2 C), 128.8, 128.6 (2 C), 127.8, 125.9, 108.7, 67.5, 59.1, 18.3, 12.8.

HRMS (ESI+): m/z [M + NH₄]⁺ calcd for C₂₀H₂₂ClN₂O₅: 405.1212; found: 405.1212.

Benzy (4S,5S)-3-Ethyl-4-(naphthalen-2-yl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4i)

Isolated as a light yellow oil; yield: 25 mg (61%); R_f = 0.43 (EtOAc/PE, 1:12); dr *anti/syn* >20:1; HPLC (Chiralpak AD-H, heptane/EtOH, 50:50, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 7.80 (major), 9.73 min (minor); 95% ee; $[\alpha]_D^{20}$ +240.08 (c 1.05, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ = 7.89 (d, J = 8.5 Hz, 1 H, ArH), 7.87–7.82 (m, 2 H, ArH), 7.69 (s, 1 H, ArH), 7.57–7.50 (m, 2 H, ArH), 7.47 (d, J = 6.8 Hz, 2 H, ArH), 7.44–7.35 (m, 3 H, ArH), 7.28 (dd, J = 8.5, 1.6 Hz, 1 H, ArH), 5.87 (d, J = 2.0 Hz, 1 H, CHNO₂), 5.40 (d, J = 3.3 Hz, 2 H, CH₂Ph), 4.60 (d, J = 2.0 Hz, 1 H, CHAr), 2.87 (dq, J = 15.0, 7.6 Hz, 1 H, CH₂CH₃), 2.07 (dq, J = 15.0, 7.6 Hz, 1 H, CH₂CH₃), 0.93 (t, J = 7.6 Hz, 3 H, CH₂CH₃).

¹³C NMR (100 MHz, CDCl₃): δ = 159.5, 140.3, 135.2, 133.7, 133.6, 133.4, 133.1, 129.9, 128.9 (2 C), 128.7, 128.6 (2 C), 128.1, 127.9, 127.2, 127.1, 126.9, 124.7, 109.2, 67.5, 59.9, 18.4, 12.9.

HRMS (ESI+): m/z [M + NH₄]⁺ calcd for C₂₄H₂₅N₂O₅: 421.1758; found: 421.1758.

Benzy (4R,5S)-3-Ethyl-5-nitro-4-(4-oxo-4H-chromen-3-yl)-4,5-dihydrofuran-2-carboxylate (4j)

Isolated as a light yellow oil; yield: 8 mg (20%); R_f = 0.10 (EtOAc/PE, 1:5); dr *anti/syn* >20:1; HPLC (Chiralpak ID, heptane/EtOH, 50:50, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 8.39 (major), 9.89 min (minor); 97% ee; $[\alpha]_D^{20}$ +61.5 (c 0.30, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ = 8.25 (d, J = 8.0 Hz, 1 H, ArH), 7.77–7.71 (m, 2 H, ArH), 7.50–7.37 (m, 7 H, ArH), 5.87 (d, J = 2.4 Hz, 1 H, CHNO₂), 5.35 (d, J = 4.7 Hz, 2 H, CH₂Ph), 4.76 (d, J = 2.4 Hz, 1 H, CHAr), 2.92 (dq, J = 14.8, 7.5 Hz, 1 H, CH₂CH₃), 2.09 (dq, J = 14.8, 7.5 Hz, 1 H, CH₂CH₃), 1.01 (t, J = 7.5 Hz, 3 H, CH₂CH₃).

¹³C NMR (100 MHz, CDCl₃): δ = 176.1, 159.1, 156.5, 154.2, 141.2, 135.1, 134.6, 131.1, 128.9 (2 C), 128.7, 128.6 (2 C), 126.2, 126.1, 123.7, 119.6, 118.4, 107.9, 67.5, 50.0, 18.4, 13.0.

HRMS (ESI+): m/z [M + NH₄]⁺ calcd for C₂₃H₂₃N₂O₇: 439.1500; found: 439.1500.

tert-Butyl (4S,5S)-3-Ethyl-4-(4-methoxyphenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4k)

Isolated as a yellow oil; yield: 25 mg (36%); R_f = 0.49 (EtOAc/PE, 1:5); dr *anti/syn* >20:1; HPLC (Chiralpak IF, heptane/EtOH, 70:30, flow rate = 1.0 mL/min, λ = 254 nm): t_R = 4.55 (major), 5.20 min (minor); 94% ee; $[\alpha]_D^{20}$ +259.3 (c 1.05, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 7.13 (d, *J* = 8.6 Hz, 2 H, ArH), 6.91 (d, *J* = 8.6 Hz, 2 H, ArH), 5.74 (d, *J* = 2.1 Hz, 1 H, CHNO₂), 4.34 (d, *J* = 2.1 Hz, 1 H, CHAr), 3.81 (s, 3 H, OCH₃), 2.73 (dq, *J* = 14.8, 7.6 Hz, 1 H, CH₂CH₃), 2.00 (dq, *J* = 14.8, 7.6 Hz, 1 H, CH₂CH₃), 1.59 (s, 9 H, *t*-Bu), 0.91 (t, *J* = 7.6 Hz, 3 H, CH₂CH₃).

¹³C NMR (75 MHz, CDCl₃): δ = 160.0, 158.8, 141.0, 131.7, 128.9 (2 C), 128.1, 114.9 (2 C), 109.3, 83.3, 59.2, 55.5, 28.3, 18.4, 12.9.

HRMS (ESI⁺): *m/z* [M + NH₄]⁺ calcd for C₁₈H₂₇N₂O₆: 367.1864; found: 367.1864.

Benzyl (4S,5S)-3-Isopropyl-4-(4-methoxyphenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4l)

Isolated as a light yellow oil; yield: 30 mg (38%); *R_f* = 0.47 (EtOAc/PE, 1:5); dr *anti/syn* >20:1; HPLC (Chiralpak IB, heptane/EtOH, 80:20, flow rate = 1.0 mL/min, λ = 254 nm): *t_R* = 6.74 (major), 6.13 min (minor); 95% ee; [α]_D²⁰ +151.4 (c 0.80, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 7.49–7.32 (m, 5 H, ArH), 7.14 (d, *J* = 8.7 Hz, 2 H, ArH), 6.89 (d, *J* = 8.7 Hz, 2 H, ArH), 5.66 (d, *J* = 1.3 Hz, 1 H, CHNO₂), 5.38 (s, 2 H, CH₂Ph), 4.42 (d, *J* = 1.3 Hz, 1 H, CHAr), 3.81 (s, 3 H, OCH₃), 3.50 (hept, *J* = 7.1 Hz, 1 H, CH), 1.03 (d, *J* = 7.1 Hz, 3 H, CH₃), 0.66 (d, *J* = 7.1 Hz, 3 H, CH₃).

¹³C NMR (75 MHz, CDCl₃): δ = 160.0, 159.5, 139.6, 138.1, 135.3, 128.9 (2 C), 128.8 (2 C), 128.7, 128.7, 128.5 (2 C), 114.9 (2 C), 109.8, 67.3, 57.5, 55.5, 25.7, 22.3, 21.5.

HRMS (ESI⁺): *m/z* [M + NH₄]⁺ calcd for C₂₂H₂₇N₂O₆: 415.1864; found: 415.1864.

Ethyl (4S,5S)-3-Benzyl-4-(4-methoxyphenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4m)

Isolated as a yellow solid (40 mg (52%); mp 104–105 °C; *R_f* = 0.51 (EtOAc/PE, 1:5); dr *anti/syn* >20:1; HPLC (Chiralpak IC, heptane/EtOH, 95:5, flow rate = 1.0 mL/min, λ = 254 nm): *t_R* = 8.66 (major), 9.35 min (minor); 86% ee; [α]_D²⁰ +256.7 (c 1.53, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 7.30–7.17 (m, 3 H, ArH), 7.08–6.98 (m, 4 H, ArH), 6.90 (d, *J* = 8.7 Hz, 2 H, ArH), 5.78 (d, *J* = 1.8 Hz, 1 H, CHNO₂), 4.51–4.39 (m, 3 H, CH₂Ph, OCH₂CH₃), 4.08 (d, *J* = 1.8 Hz, 1 H, CHAr), 3.83 (s, 3 H, OCH₃), 3.03 (d, *J* = 15.1 Hz, 1 H, CH₂Ph), 1.43 (t, *J* = 7.1 Hz, 3 H, OCH₂CH₃).

¹³C NMR (75 MHz, CDCl₃): δ = 160.1, 159.7, 140.7, 137.1, 130.6, 129.0 (2 C), 128.9 (2 C), 128.6 (2 C), 127.6, 127.1, 115.0 (2 C), 109.3, 62.0, 58.6, 55.5, 30.6, 14.3.

HRMS (ESI⁺): *m/z* [M + NH₄]⁺ calcd for C₂₁H₂₅N₂O₆: 401.1707; found: 401.1708.

Isobutyl (4S,5S)-3-Isopropyl-4-(4-methoxyphenyl)-5-nitro-4,5-dihydrofuran-2-carboxylate (4n)

Isolated as a light yellow oil; yield: 19 mg (26%); *R_f* = 0.43 (EtOAc/PE, 1:4); dr *anti/syn* >20:1; HPLC (Chiralpak AD-H, heptane/EtOH, 90:10, flow rate = 1.0 mL/min, λ = 254 nm): *t_R* = 6.17 (major), 5.11 min (minor); 91% ee; [α]_D²⁰ +198.1 (c 0.40, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 7.15 (d, *J* = 8.7 Hz, 2 H, ArH), 6.90 (d, *J* = 8.6 Hz, 2 H, ArH), 5.66 (d, *J* = 1.3 Hz, 1 H, CHNO₂), 4.41 (d, *J* = 1.3 Hz, 1 H, CHAr), 4.13 (qd, *J* = 10.7, 6.7 Hz, 2 H, OCH₂), 3.81 (s, 3 H, OCH₃), 3.50 (sept, *J* = 7.0 Hz, 1 H, CH), 2.08 (sept, *J* = 6.7 Hz, 1 H, CH), 1.05 (d, *J* = 7.0 Hz, 3 H, CH₃), 1.02 (d, *J* = 6.7 Hz, 6 H, 2 CH₃), 0.68 (d, *J* = 7.0 Hz, 3 H, CH₃).

¹³C NMR (75 MHz, CDCl₃): δ = 160.0, 159.8, 140.0, 137.2, 128.9 (2 C), 128.9, 114.9 (2 C), 109.8, 71.8, 57.5, 55.5, 27.9, 25.7, 22.4, 21.5, 19.3 (2 C).

HRMS (ESI⁺): *m/z* [M + NH₄]⁺ calcd for C₁₉H₂₉N₂O₆: 381.2020; found: 381.2024.

Benzyl (4S,5S)-5-Amino-3-ethyl-4-(4-methoxyphenyl)-4,5-dihydrofuran-2-carboxylate (6)

A solution of 4,5-dihydrofuran-2-carboxylate **4a** (0.13 mmol, 1.0 equiv) in dry THF (1.0 mL) was added activated zinc powder (18.2 mmol, 140.0 equiv), followed by the addition dropwise of AcOH (6.0 mL). The mixture was stirred for 2 h at r.t. The mixture was concentrated and extracted with sat. NaHCO₃ solution (2 × 6.0 mL). The combined aqueous phases were extracted with CH₂Cl₂ (2 × 10.0 mL) and the combined organic layers were washed with water (10.0 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc/PE, 40:60). Isolated as a light yellow oil; yield: 17 mg (38%); *R_f* = 0.37 (EtOAc/PE, 4:6); dr *anti/syn* >20:1; HPLC (Chiralpak IA, heptane/EtOH, 90:10, flow rate = 1.0 mL/min, λ = 254 nm): *t_R* = 10.83 (major), 11.91 min (minor); 57% ee (from 93% ee in the starting material); [α]_D²⁰ +65.1 (c 0.28, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 7.45–7.32 (m, 5 H, Ar-H), 7.11 (d, *J* = 8.8 Hz, 2 H, Ar-H), 6.86 (d, *J* = 8.8 Hz, 2 H, Ar-H), 5.31 (d, *J* = 3.8 Hz, 2 H), 5.11 (d, *J* = 5.3 Hz, 1 H), 3.79 (s, 3 H), 3.70 (d, *J* = 5.3 Hz, 1 H), 2.81–2.70 (m, 1 H, CH₂CH₃), 2.27 (br s, 2 H, NH₂), 2.00–1.90 (m, 1 H, CH₂CH₃), 0.89 (t, *J* = 7.5 Hz, 3 H, CH₂CH₃).

¹³C NMR (75 MHz, CDCl₃): δ = 160.1, 159.1, 138.7, 135.8, 132.0, 129.1 (2 C), 128.7 (2 C), 128.7 (2 C), 128.7, 128.5, 114.4 (2 C), 95.3, 66.8, 59.4, 55.4, 18.8, 12.9.

HRMS (ESI⁺): *m/z* [M + H]⁺ calcd for C₂₁H₂₄NO₄: 354.1700; found: 354.1699.

Benzyl 3-Ethyl-4-(4-methoxyphenyl)-5-nitrofuran-2-carboxylate (7)

A solution of the 4,5-dihydrofuran-2-carboxylate **4a** (0.13 mmol, 1.0 equiv) and NaNO₂ (0.26 mmol, 1.0 equiv) in DMSO/water (7:1, 0.4 M) was stirred at 65 °C for 12 h. The mixture was cooled to r.t. and then an equal volume of water was then added and the aqueous layer was extracted several times with Et₂O. The combined organic layers were dried (Na₂SO₄) and concentrated and the resulting crude was purified by flash column chromatography (silica gel, EtOAc/PE, 1:15) to afford the desired product.¹⁴ Isolated as a green solid; yield: 32 mg (65%); mp 91–92 °C; *R_f* = 0.61 (EtOAc/PE, 1:4).

¹H NMR (300 MHz, CDCl₃): δ = 7.44–7.50 (m, 2 H, ArH), 7.35–7.44 (m, 3 H, ArH), 7.24 (d, *J* = 8.8 Hz, 2 H, ArH), 7.00 (d, *J* = 8.8 Hz, 2 H, ArH), 5.42 (s, 2 H, CH₂Ph), 3.87 (s, 3 H, OCH₃), 2.71 (q, *J* = 7.5 Hz, 2 H, CH₂CH₃), 1.02 (t, *J* = 7.5 Hz, 3 H, CH₂CH₃).

¹³C NMR (75 MHz, CDCl₃): δ = 160.4, 158.0, 139.3 (2 C), 138.9, 135.1, 130.8 (2 C), 128.9 (2 C), 128.8, 128.7 (2 C), 128.1, 120.1, 114.3 (2 C), 67.5, 55.5, 17.7, 14.4.

HRMS (ESI⁺): *m/z* [M + NH₄]⁺ calcd for C₂₁H₂₃N₂O₆: 399.1551; found: 399.1551.

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Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0035-1562446>.

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