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PAPER

Organocatalytic asymmetric direct vinylogous Michael addition of α,β-unsaturated γ-butyrolactam to nitroolefins†

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The first organocatalytic enantioselective direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactam to nitroolefins is developed using cinchona alkaloids as the catalysts. Both product enantiomers are accessible with moderate to good enantioselectivity.

Vinylogous reactivity of unsaturated carbonyl compounds has always received a great deal of attention since the introduction of the concept of vinylogy due to the generation of synthetically useful γ-functionalized carbonyl compounds.[1] Whereas the acyclic metal dienolates and the corresponding dienolsilanes suffer from potential α- *vs.* γ-selectivity problem, their cyclic counterparts are generally γ-selective.[2] In this regard, extensive research has been carried out with silyloxyfuran[3] and to a lesser extent with γ-butenolides.[4] However, the use of their corresponding aza-analogues: silyloxypyrroles and α,β-unsaturated γ-butyrolactams in vinylogous reactions remained relatively rare, despite the wide abundance of 5-substituted 3-pyrrolidin-2-ones in complex targets.[5] As part of our research program on catalytic asymmetric vinylogous reactivity of cyclic systems,[6] we became interested in direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactams. In 2010, Matsunaga, Shibasaki and coworkers reported a highly enantioselective direct vinylogous Michael reaction of an α,β-unsaturated γ-butyrolactam with nitroolefins using a dinuclear nickel catalyst.[7] Asymmetric vinylogous Michael reaction of the same nucleophile to enals and enones have also been realized under metal and organocatalytic conditions.[8,9] There are also reports of direct as well as Mukaiyama-type enantioselective vinylogous aldol and Mannich reactions.[7,10] However, to the best of our knowledge, there is no report on organocatalytic direct addition of α,β-unsaturated γ-butyrolactam to nitroolefins. Considering the general importance of chiral compounds containing butyrolactam moiety, it is of great interest to develop new methods for the asymmetric synthesis of such class of compounds.

Herein, we present the first organocatalytic asymmetric direct vinylogous Michael reaction of an α,β-unsaturated γ-butyrolactam with nitroolefins. Both the product enantiomers are accessible with impeccable diastereoselectivity and moderate to good enantioselectivity using quinidine and a modified quinine derivative, respectively.

We began our investigation with the screening of various cinchona alkaloids and their derivatives for the direct vinylogous Michael addition of Boc-protected α,β-unsaturated γ-butyrolactam **1** to ω-nitrostyrene **2a** (Table 1). Cinchona alkaloids were chosen as potential catalyst candidates taking their well-established bifunctional character into consideration.[11] We envisioned that enolization through general base catalysis by the tertiary amine group would activate butyrolactam for nucleophilic attack to nitroolefin, the electrophilicity of which would be enhanced through the hydrogen bonding from the catalyst hydroxyl group (*vide infra*). Such a bifunctional activation mode was indeed found to be operative as quinidine **I** turned out to be an efficient catalyst for this Michael reaction: with 10 mol% of **I**, complete conversion to the Michael adduct **3a** was observed within 23 h when equimolar amount of **1** and **2a** were stirred at r.t. in toluene (Table 1, entry 2). The Michael addition was found to be highly diastereoselective as only the single diastereomer of the product could be detected by ^{1}H-NMR of the crude reaction mixture. However, enantioselectivity was only moderate (79 : 21 er). The relative and absolute configuration of the product was established by comparison with literature (see ESI† for detail).[7] A solvent screening (entries 2–7) established trifluorotoluene as the suitable reaction medium, furnishing **3a** with drastically enhanced enantioselectivity (entry 7). Such a solvent effect is not entirely surprising, particularly in the context of fluorinated solvents, and well-precedented in the recent literature.[12] Slight improvement in enantioselectivity could be achieved by carrying out the reaction at 0 °C; however further lowering of temperature had no favourable influence (entries 8 and 9). Several quinidine derivatives including 9-*epi*-quinidine **VI**, β-isocupreidine **VII**,[13] β-isoquinidine **VIII** and a dimeric quinidine derivative $(QD)_2$PHAL **IX** were tested (entries 10–17). We were surprised to find that **VIII** and **IX**, both lacking the hydroxyl group, were also efficient catalysts and in both the cases the product was obtained with fairly

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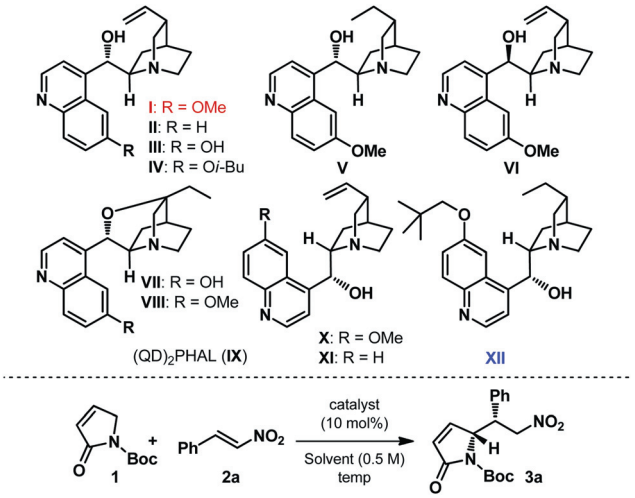
†Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all relevant compounds together with HPLC traces for all products. See DOI: 10.1039/c2ob25832c

Table 1 Catalyst optimization for the direct asymmetric vinylogous Michael reaction of *N*-Boc-butyrolactam **1** to nitrostyrene **2a**[a]



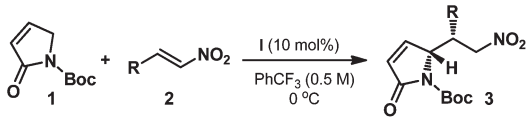
Entry	Catalyst	Solvent	T (°C)	t (h)[b]	dr[c]	er[d]
1	—	Toluene	25	[e]	—	—
2	**I**	Toluene	25	23	>20 : 1	79 : 21
3	**I**	C_6H_6	25	20	>20 : 1	82.5 : 17.5
4	**I**	CH_2Cl_2	25	23	>20 : 1	87 : 13
5	**I**	TBME	25	22	>20 : 1	84 : 16
6	**I**	PhCl	25	23	>20 : 1	89 : 11
7	**I**	$PhCF_3$	25	26	>20 : 1	93 : 7
8	**I**	$PhCF_3$	0	31	>20 : 1	94.5 : 5.5
9	**I**	$PhCF_3$	−20	42	>20 : 1	94.5 : 5.5
10	**II**	$PhCF_3$	25	20	>20 : 1	80 : 20
11	**III**	$PhCF_3$	25	18	>20 : 1	58 : 42
12	**IV**	$PhCF_3$	25	19	>20 : 1	86 : 14
13	**V**	$PhCF_3$	25	18	>20 : 1	89 : 11
14	**VI**	$PhCF_3$	25	53	>20 : 1	55 : 45
15	**VII**	$PhCF_3$	25	42	>20 : 1	45 : 55
16	**VIII**	$PhCF_3$	25	30	>20 : 1	87 : 13
17	**IX**	$PhCF_3$	25	42	>20 : 1	11 : 89
18	**X**	$PhCF_3$	25	19	>20 : 1	14 : 86
19	**XI**	$PhCF_3$	25	28	>20 : 1	19 : 81
20	**XII**	$PhCF_3$	25	49	>20 : 1	18 : 92

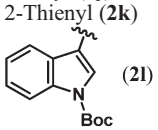
[a] Reactions carried out using 1.0 equiv. of **1** and 1.0 equiv. of **2a**. [b] Time required for complete conversion of starting materials. [c] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis using a stationary phase chiral column (see ESI†). [e] No conversion after 48 h.

modest enantioselectivity. However, quinidine **I** itself remained the optimum catalyst. With the objective of attaining the other antipode of the Michael adduct (*ent*-**3a**), the pseudoenantiomeric quinine **X**, cinchonidine **XI** and a dihydroquinine derivative **XII** were tested (entries 18–20). Even though with quinine **X** itself, *ent*-**3a** was obtained with only 86 : 14 er, simple modification of dihydroquinine afforded **XII**, a significantly more selective catalyst. With the dihydroquinine derivative **XII**, *ent*-**3a** was obtained in good enantioselectivity, however the reaction in this case was somewhat slower compared to quinine **X** as the catalyst.

With optimized reaction conditions for both the catalysts **I** and **XII** in hand, we decided to explore the scope and limitations of this reaction in terms of its applicability to various nitroolefins. Table 2 illustrates the scope of nitroolefin for this vinylogous

Table 2 Asymmetric direct vinylogous Michael reaction of *N*-Boc-butyrolactam **1** with various nitroolefins catalyzed by quinidine **I**[a]



Entry	R	t (h)	Product	Yield[b] (%)	er[c]
1	Ph (**2a**)	31	**3a**	81	94.5 : 5.5
2	4-MeC_6H_4 (**2b**)	37	**3b**	79	91 : 9
3	4-FC_6H_4 (**2c**)	33	**3c**	76	85 : 15
4	4-ClC_6H_4 (**2d**)	39	**3d**	78	82.5 : 17.5
5	4-BrC_6H_4 (**2e**)	31	**3e**	81	90 : 10
6	4-OMeC_6H_4 (**2f**)	39	**3f**	74	86 : 14
7	3-ClC_6H_4 (**2g**)	31	**3g**	81	90 : 10
8	2,4-$Cl_2C_6H_3$ (**2h**)	35	**3h**	79	80 : 20
9	2-Naphthyl (**2i**)	36	**3i**	82	86 : 14
10	2-Furyl (**2j**)	32	**3j**	82	92 : 8
11	2-Thienyl (**2k**)	29	**3k**	81	92 : 8
12	 (**2l**)	33	**3l**	82	92 : 8
13	*c*-Hex (**2m**)	33	**3m**	84	82.5 : 17.5
14	*i*-Bu (**2n**)	29	**3n**	79	87 : 13
15	*i*-Pr (**2o**)	31	**3o**	76	84 : 16

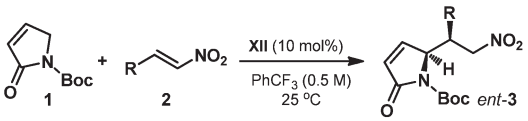
[a] Reactions carried out using 1.0 equiv. of **1** and 1.0 equiv. of **2**. [b] Isolated yield of the products after column chromatography. In all cases products were obtained with >20 : 1 dr. [c] Determined by HPLC analysis using a stationary phase chiral column (see ESI†).

Michael reaction using quinidine **I** as the catalyst. As evident from Table 2, both aromatic, heteroaromatic and aliphatic nitroolefins are suitable substrate for this reaction. In general, products with higher enantioselectivities were obtained for aromatic nitroolefins as the substrate (entries 1–9), except for *ortho*-substituted nitroolefin **2h** where the enantioselectivity was found to be significantly lower (entry 8). Nitroolefins with heteroaromatic substituent were equally efficient and the products were acquired with good enantioselectivity (entries 10–12). Acceptable enantioselectivities were observed for aliphatic nitroolefins (entries 13–15). In all the above cases, the products were obtained as a single diastereomer.

After exploring the scope and limitations of the quinidine-catalyzed vinylogous Michael reaction, we next focused on the scope of the reaction using dihydroquinine derivative **XII** as the catalyst. The results are summarized in Table 3. With **XII** as the catalyst, in general, adducts were obtained in lower enantioselectivities as compared to quinidine **I**. However, excellent diastereoselectivity (>20 : 1 dr) was maintained for all nitroolefins tested. The highest enantioselectivity was obtained with ω-nitrostyrene **2a** as the Michael acceptor (92 : 8 er, entry 1). Irrespective of the nature of nitroolefins, in all other cases the enantiomeric products were obtained with moderate to acceptable enantioselectivities (entries 2–7).

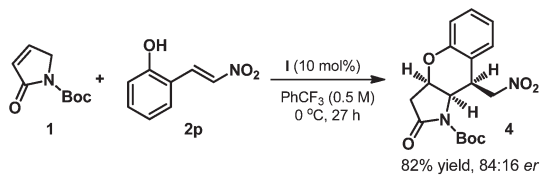
An interesting aspect of this reaction is that even though *N*-Boc butyrolactam **1** is used as the nucleophilic component in this reaction, the α,β-unsaturated moiety of the butyrolactam is also a potential Michael acceptor, particularly in the product. To explore the potential Michael acceptor behaviour of

Table 3 Asymmetric direct vinylogous Michael reaction of *N*-Boc-butyrolactam **1** with various nitroolefins catalyzed by dihydroquinine derivative **XII**[a]

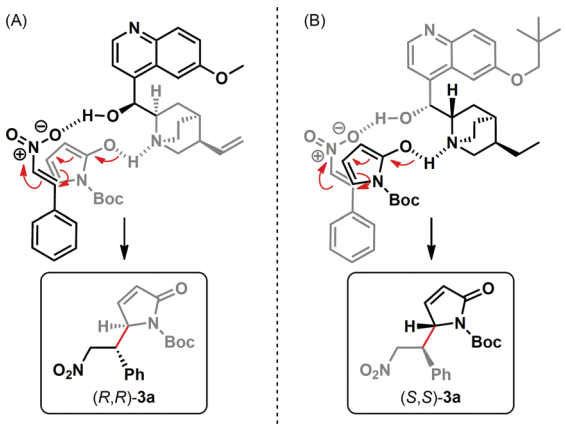


Entry	R	*t* (h)	Product	Yield[b] (%)	er[c]
1	Ph (**2a**)	49	*ent*-**3a**	81	92 : 8
2	4-MeC_6H_4 (**2b**)	56	*ent*-**3b**	82	90 : 10
3	4-BrC_6H_4 (**2e**)	59	*ent*-**3e**	78	78 : 22
4	3-ClC_6H_4 (**2g**)	62	*ent*-**3g**	72	80 : 20
5	2-Furyl (**2j**)	54	*ent*-**3j**	81	85 : 15
6	2-Thienyl (**2k**)	56	*ent*-**3k**	81	84 : 16
7	*i*-Bu (**2n**)	58	*ent*-**3n**	88	77 : 23

[a] Reactions carried out using 1.0 equiv. of **1** and 1.0 equiv. of **2**. [b] Isolated yield of the products after column chromatography. In all cases products were obtained with >20 : 1 dr. [c] Determined by HPLC analysis using a stationary phase chiral column (see ESI†).



Scheme 1 Michael–Michael cascade sequence to the tricyclic product **4**.



Scheme 2 Proposed stereochemical model of the direct vinylogous Michael reaction.

butyrolactam, we designed a Michael–Michael cascade sequence using *ortho*-hydroxynitrostyrene **2p** as the substrate (Scheme 1). We realized that after the initial vinylogous Michael reaction, the nucleophilic hydroxyl group in the product could engage itself into a diastereoselective intramolecular oxa-Michael addition, generating a tricyclic system. The cascade product **4** was indeed formed as a single diastereomer in good yield, albeit with only modest enantioselectivity (84 : 16 er).

Our current speculation regarding the mechanism of this Michael reaction is based on the well-known bifunctional properties of the cinchona alkaloids.[11] As illustrated in Scheme 2, the activation of the nitroolefin can be expected *via* hydrogen bonding from the Brønsted acidic hydroxyl group whereas the Brønsted basic tertiary amine provides nucleophilic activation. The stereochemical outcome of the Michael adducts is dictated by the orientation of the vicinal tertiary amine and hydroxyl groups in the catalyst. In the case of quinidine **I**, the *Si*-face of nitroolefin is attacked by the *Si*-face of enolated butyrolactam, resulting in the formation of (*R*,*R*)-enantiomer as the major product (Scheme 2A). Not surprisingly, the (*S*,*S*)-adduct is generated due to the enantiomeric relationship of the same two catalytically relevant functional groups in the modified dihydroquinine derivative **XII** (Scheme 2B), thereby favouring the *Re*–*Re*-facial interaction between the two reactants.

Conclusions

In summary, we have developed the first organocatalytic direct vinylogous Michael reaction of α,β-unsaturated γ-butyrolactam to nitroolefins. Using quinidine and a simple modified dihydroquinine derivative, both product enantiomers are accessible as single diastereomer in moderate to good enantioselectivity. A Michael–Michael cascade sequence for the synthesis of a tricyclic compound is also presented. We are currently investigating the possibility to develop a more efficient and selective catalyst for this transformation.

Experimental

General remarks

Unless stated otherwise, all reactions were carried out with distilled and dried solvents under an atmosphere of N_2 or argon, oven (120 °C) dried glassware with standard vacuum line techniques. Organic solvents used for carrying out reactions were dried using standard methods. All work up and purification were carried out with reagent grade solvents in air. Thin-layer chromatography was performed using Merck silica gel 60 F_{254} pre-coated plates (0.25 mm). Column chromatography was performed using silica gel (230–400 or 100–200 mesh). Infrared (FT-IR) spectra were recorded on a Perkin Elmer Spectrum BX spectrophotometer, reported in cm^{-1} and the bands are characterized as broad (br), strong (s), medium (m), and weak (w). NMR spectra were recorded on Bruker Ultrashield spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$: δ 7.26, CD_3OD: δ 3.31 for ^{1}H-NMR and $CDCl_3$: δ 77.16 for ^{13}C NMR). For ^{1}H NMR, data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectrometry was performed on Micromass Q-TOF Micro instrument. Optical rotations were measured on JASCO P-1020 polarimeter. Melting points were measured using ANALAB μ-Thermocal 10 melting point apparatus. All melting points were measured in open glass capillary and values are uncorrected. Enantiomeric ratios were determined by HPLC

analysis using Daicel chiral columns (4.6 mm × 250 mm) in comparison with authentic racemic materials.

Representative procedure for the catalytic enantioselective direct vinylogous Michael addition of *N*-Boc α,β-unsaturated γ-butyrolactam 1 to ω-nitrostyrene 2a

A Schlenk tube was heated to 150 °C under vacuum for 30 min, cooled to r.t. under vacuum and purged with argon. *N*-Boc α,β-unsaturated γ-butyrolactam **1** (55 mg, 0.3 mmol) and quinidine **I** (9.7 mg, 0.03 mmol) was dissolved in 0.2 mL of $PhCF_3$. The resulting mixture was cooled to 0 °C and nitrostyrene **2a** (45 mg, 0.3 mmol) in 0.4 mL $PhCF_3$ was added over a period of 6 h using syringe pump. The resulting solution was stirred at 0 °C until TLC (20% EtOAc in toluene) revealed complete consumption of nitrostyrene (31 h). The reaction mixture was allowed to attain r.t., the solvent was removed *in vacuo* and the residue was purified by silica gel (100–200 mesh) column chromatography using 8% EtOAc in toluene as eluent to obtain **3a** as a colorless oil (81 mg, 0.243 mmol; 81% yield).

(*R*)-*tert*-Butyl 2-((*R*)-2-nitro-1-phenylethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3a (Table 2, entry 1). Purification by silica gel column chromatography (8% EtOAc in toluene) afforded pure **3a** as a viscous oil (81 mg, 0.243 mmol; 81% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2924 (s), 2855 (m), 1778 (s), 1746 (s), 1554 (s), 1366 (m), 1315 (m), 1283 (m), 1157 (s), 1106 (m), 1019 (s), 916 (w), 826 (w), 765 (w), 704 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66 (s; 9H), 4.50–4.52 (m; 1H), 4.64–4.73 (m; 2H), 4.87–4.88 (m; 1H), 6.18 (dd, J = 1.5, 6.2 Hz; 1H), 7.03 (dd, J = 1.9, 6.2 Hz; 1H), 7.27–7.43 (m; 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1, 43.8, 65.1, 73.3, 84.1, 127.7, 128.5, 128.6, 129.2, 134.8, 146.2, 149.4, 168.3. Spectral data are in agreement with the literature.[7] HRMS (ESI+): Calculated for $C_{17}H_{20}N_2NaO_5^+$ ([M + Na]$^+$): 355.1270, found: 355.1270; $[\alpha]_D^{27}$ +138 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 94.5 : 5.5 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 9.23 min, τ_{minor} = 12.67 min).

(*S*)-*tert*-Butyl 2-((*S*)-2-nitro-1-phenylethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate *ent*-3a (Table 3, entry 1). Purification by silica gel column chromatography (8% EtOAc in toluene) afforded pure *ent*-**3a** as a viscous oil (81 mg, 0.243 mmol; 81% yield). Diastereomeric ratio was determined by ^{1}H-NMR analysis of the crude product. $[\alpha]_D^{27}$ −130.2 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 92 : 8 er [Lit[7]: $[\alpha]_D^{24}$ −155 (c 0.93, $CHCl_3$)]. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{minor} = 9.37 min, τ_{major} = 13.18 min).

(*R*)-*tert*-Butyl 2-((*R*)-2-nitro-1-(*p*-tolyl)ethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3b (Table 2, entry 2). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3b** as a white solid (82 mg, 0.237 mmol; 79% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. Melting point: 73 °C; FT-IR (neat): ν 2980 (m), 2923 (m), 1784 (s), 1746 (m), 1713 (m), 1557 (s), 1457 (w), 1369 (s), 1316 (m), 1257 (w), 1156 (s), 1107 (m), 1031 (m), 920 (w), 842 (w), 778 (w), 795 (w), 736 (w), 700 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (s; 9H), 2.33 (s; 3H), 4.48 (dd, J = 4.2, 12.3 Hz; 1H), 4.58–4.69 (m; 2H), 4.84–4.85 (m; 1H), 6.16 (dd, J = 1.1, 6.1 Hz; 1H), 7.03 (dd, J = 1.5, 6.1 Hz; 1H), 7.13 (d, J = 8.0 Hz; 1H), 7.20 (d, J = 8.0 Hz; 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 28.0, 43.5, 65.1, 73.4, 84.1, 127.5, 128.5, 129.9, 131.6, 138.3, 146.3, 149.2, 168.3; HRMS (ESI+): Calculated for $C_{18}H_{22}N_2NaO_5^+$ ([M + Na]$^+$): 369.1426, Found: 369.1426; $[\alpha]_D^{27}$ +110.7 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 91 : 9 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 9.88 min, τ_{minor} = 15.43 min).

(*S*)-*tert*-Butyl 2-((*S*)-2-nitro-1-(*p*-tolyl)ethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate *ent*-3b (Table 3, entry 2). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure *ent*-**3b** as a white solid (85 mg, 0.246 mmol; 82% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. $[\alpha]_D^{27}$ −108 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 90 : 10 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{minor} = 9.91 min, τ_{major} = 15.53 min).

(*R*)-*tert*-Butyl 2-((*R*)-1-(4-fluorophenyl)-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3c (Table 2, entry 3). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3c** as a viscous oil (80 mg, 0.228 mmol; 76% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2925 (m), 2853 (w), 1783 (s), 1749 (s), 1717 (m), 1604 (w), 1558 (s), 1513 (m), 1369 (s), 1339 (m), 1318 (m), 1287 (m), 1259 (m), 1229 (m), 1158 (s), 1108 (m), 1032 (m), 918 (w), 843 (w), 825 (m), 799 (w), 749 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (s; 9H), 4.54 (dd, J = 2.7, 10.6 Hz; 1H), 4.60–4.69 (m; 2H), 4.85–4.86 (m; 1H), 6.18 (dd, J = 1.4, 6.1 Hz; 1H), 7.02 (dd, J = 1.9, 6.1 Hz; 1H), 7.08–7.12 (m; 2H), 7.22–7.26 (m; 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1, 43.3, 64.9, 73.6, 84.4, 116.4 (d, J = 22 Hz), 128.9, 129.4 (d, J = 8 Hz), 130.5 (d, J = 3 Hz), 146.0, 149.4, 162.5 (d, J = 249 Hz), 168.0; HRMS (ESI+): Calculated for $C_{17}H_{19}FN_2NaO_5^+$ ([M + Na]$^+$): 373.1176, Found: 373.1175; $[\alpha]_D^{26}$ −75 (c 0.1, $CHCl_3$) for an enantiomerically enriched sample with 85 : 15 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 7.96 min, τ_{minor} = 11.52 min).

(*R*)-*tert*-Butyl 2-((*R*)-1-(4-chlorophenyl)-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3d (Table 2, entry 4). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3d** as a viscous oil (94 mg, 0.234 mmol; 78% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2922 (m), 1779 (s), 1747 (m), 1591 (m), 1557 (s), 1369 (m), 1282 (m), 1258 (m), 1156 (s), 1096 (w), 1015 (s), 823 (w), 668 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s; 9H), 4.53 (dd, J = 3.9, 11.8 Hz; 1H), 4.58–4.69 (m; 2H), 4.84 (br s; 1H), 6.17 (dd, J = 1.3, 6.1 Hz; 1H), 7.00 (dd, J = 1.7, 6.1 Hz; 1H), 7.19 (d, J = 8.2 Hz;

2H), 7.37 (d, J = 8.2 Hz; 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1, 29.6, 43.4, 64.7, 73.4, 84.4, 129.0, 129.5, 133.2, 134.5, 145.9, 149.4, 168.0; HRMS (ESI+): Calculated for $C_{17}H_{19}ClN_2NaO_5^+$ ([M + Na]$^+$): 389.0880, found: 389.0880; $[\alpha]_D^{27}$ −66.4 (c 0.1, $CHCl_3$) for an enantiomerically enriched sample with 82.5 : 17.5 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 8.26 min, τ_{minor} = 12.30 min).

(*R*)-*tert*-Butyl 2-((*R*)-1-(4-bromophenyl)-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3e (Table 2, entry 5). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3e** as a viscous oil (100 mg, 0.243 mmol; 81% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2921 (s), 2851 (m), 1782 (s), 1773 (s), 1749 (s), 1717 (m), 1557 (s), 1369 (m), 1339 (m), 1317 (m), 1281 (m), 1259 (m), 1156 (s), 1105 (w), 1012 (s), 822 (w), 795 (w), 749 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s; 9 H), 4.53 (dd, J = 4.3, 12.1 Hz; 1H), 4.57–4.69 (m; 2H), 4.84 (s; 1H), 6.17 (dd, J = 1.0, 6.1 Hz; 1H), 7.00 (dd, J = 1.4, 6.1 Hz; 1H), 7.14 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 8.3 Hz; 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1, 43.5, 64.7, 73.3, 84.4, 122.7, 128.9, 129.3, 132.5, 133.8, 145.9, 149.4. Spectral data are in agreement with the literature.[7] HRMS (ESI+): Calculated for $C_{17}H_{19}BrN_2NaO_5^+$ ([M + Na]$^+$): 433.0375, Found: 433.0374; $[\alpha]_D^{27}$ +93.1 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 90 : 10 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 8.58 min, τ_{minor} = 13.05 min).

(*S*)-*tert*-Butyl 2-((*S*)-1-(4-bromophenyl)-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate *ent*-3e (Table 3, entry 3). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure *ent*-**3e** as a viscous oil (96 mg, 0.234 mmol; 78% yield). Diastereomeric ratio was determined by ^{1}H-NMR analysis of the crude product. $[\alpha]_D^{27}$ −63.5 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 78 : 22 er [Lit[7]: $[\alpha]_D^{24}$ −114 (c 0.50, $CHCl_3$)]. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{minor} = 8.56 min, τ_{major} = 12.77 min).

(*R*)-*tert*-Butyl 2-((*R*)-1-(4-methoxyphenyl)-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3f (Table 2, entry 6). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3f** as a viscous oil (80 mg, 0.222 mmol; 74% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2921 (m), 1779 (s), 1749 (m), 1586 (m), 1557 (s), 1515 (w), 1368 (s), 1313 (s), 1256 (s), 1156 (s), 1119 (w), 1030 (s), 1017 (s), 912 (w), 826 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.65 (s; 9H), 3.81 (s; 3H), 4.50 (dd, J = 4.0, 11.8 Hz; 1H), 4.56–4.67 (m; 2H), 4.83–4.84 (m; 1H), 6.17 (dd, J = 1.5, 6.2 Hz; 1H), 6.92 (d, J = 8.6 Hz; 2H), 7.04 (dd, J = 2.0, 6.2 Hz; 1H), 7.17 (d, J = 8.6 Hz; 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1, 43.3, 55.3, 65.2, 73.7, 84.3, 114.7, 126.5, 128.7, 128.8, 146.4, 149.4, 159.6, 168.2. Spectral data are in agreement with the literature.[7] HRMS (ESI+): Calculated for $C_{18}H_{22}N_2NaO_5^+$ ([M + Na]$^+$): 385.1376, Found: 385.1374; $[\alpha]_D^{27}$ +68.0 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 86 : 14 er [Lit[7]: $[\alpha]_D^{24}$ −94.7 (c 0.50, $CHCl_3$) for *ent*-**3f**]. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.4 mL min^{-1}, τ_{major} = 17.48 min, τ_{minor} = 25.04 min).

(*R*)-*tert*-Butyl 2-((*R*)-1-(3-chlorophenyl)-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3g (Table 2, entry 7). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3g** as a viscous oil (87 mg, 0.237 mmol; 81% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2922 (s), 2853 (m), 1774 (s), 1749 (s), 1652 (s), 1555 (s), 1543 (s), 1366 (w), 1315 (w), 1259 (w), 1156 (s), 1107 (w), 1019 (s), 912 (w), 826 (w),795 (w), 747 (w), 669 (w), 623 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (s; 9H), 4.53 (dd, J = 3.8, 12.0 Hz; 1H), 4.60–4.70 (m; 1H), 4.86–4.87 (m; 1H), 6.19 (dd, J = 1.2, 6.1 Hz; 1H), 7.02 (dd, J = 1.7, 6.1 Hz; 1H), 7.14–7.17 (m; 2H), 7.32–7.37 (m; 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1, 43.5, 64.7, 73.1, 84.5, 125.7, 128.0, 128.9, 129.0, 130.6, 135.3, 136.8, 145.8, 149.4, 167.9; HRMS (ESI+): Calculated for $C_{17}H_{19}N_2NaO_5^+$ ([M + Na]$^+$): 389.0880, found: 389.0883; $[\alpha]_D^{24}$ −99 (c 0.1, $CHCl_3$) for an enantiomerically enriched sample with 87 : 13 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 8.53 min, τ_{minor} = 12.66 min).

(*S*)-*tert*-Butyl 2-((*S*)-1-(3-chlorophenyl)-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate *ent*-3g (Table 3, entry 4). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure *ent*-**3g** as a viscous oil (77 mg, 0.216 mmol; 72% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. $[\alpha]_D^{24}$ +80 (c 0.1, $CHCl_3$) for an enantiomerically enriched sample with 80 : 20 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{minor} = 8.54 min, τ_{major} = 12.54 min).

(*R*)-*tert*-Butyl 2-((*R*)-1-(2,4-dichlorophenyl)-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3h (Table 2, entry 8). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3h** as a white solid (95 mg, 0.237 mmol; 79% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. Melting point: 123 °C; FT-IR (neat): ν 2982 (m), 2924 (m), 2852 (m), 1783 (s), 1745 (s), 1721 (s), 1589 (m), 1558 (s), 1476 (m), 1393 (m), 1370 (s), 1314 (m), 1285 (m), 1258 (m), 1196 (m), 1157 (s), 1106 (m), 1047 (m), 1033 (m), 921 (w), 869 (w), 822 (m), 789 (w), 735 (w), 689 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (s; 9H), 4.68–4.71 (m; 2H), 5.04–5.09 (m; 2H), 6.11 (dd, J = 1.2, 6.2 Hz; 1H), 6.96 (dd, J = 1.8, 6.2 Hz; 1H), 7.06 (d, J = 8.4 Hz; 1H), 7.29 (dd, J = 2.1, 8.4 Hz; 1H), 7.47 (d, J = 2.1 Hz; 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1, 40.4, 62.0, 73.8, 84.6, 127.8, 128.6, 128.7, 130.5, 130.6, 135.2, 135.5, 146.4, 149.7, 168.2; HRMS (ESI+): Calculated for $C_{17}H_{18}Cl_2N_2NaO_5^+$ ([M + Na]$^+$): 423.0490, Found: 423.0490; $[\alpha]_D^{24}$ +159 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 80 : 20 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 9.29 min, τ_{minor} = 14.31 min).

(*R*)-*tert*-Butyl 2-((*R*)-1-(naphthalen-2-yl)-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3i (Table 2, entry 9). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3i** as a viscous oil (94 mg, 0.246 mmol; 82% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2926 (m), 2850 (w), 1778 (w), 1658 (m), 1560 (w), 1402 (w), 1158 (w), 1113 (w), 1018 (s), 913 (w), 683 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (s; 9H), 4.56–4.62 (m; 1H), 4.80–4.87 (m; 2H), 4.97 (br s; 1H), 6.19 (dd, J = 1.3, 6.3 Hz; 1H), 7.06 (dd, J = 1.6, 6.1 Hz; 1H), 7.39 (d, J = 8.4 Hz; 1H), 7.52–7.54 (m; 2H), 7.70 (br s; 1H), 7.81–7.86 (m; 2H), 7.90 (d, J = 8.4 Hz; 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1, 43.8, 65.1, 73.3, 84.3, 125.3, 126.6, 126.7, 126.9, 127.7, 128.8, 129.3, 132.3, 132.9, 133.2, 146.2, 149.4, 168.2; HRMS (ESI+): Calculated for $C_{21}H_{22}N_2NaO_5^+$ ([M + Na]$^+$): 405.1426, Found: 405.1424; $[\alpha]_D^{26}$ −85.4 (c 0.1, $CHCl_3$) for an enantiomerically enriched sample with 86 : 14 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 10.02 min, τ_{minor} = 12.98 min).

(*R*)-*tert*-Butyl 2-((*R*)-1-(furan-2-yl)-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3j (Table 2, entry 10). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3j** as a viscous oil (79 mg, 0.246 mmol; 82% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2979 (w), 2929 (w), 1774 (s), 1744 (m), 1559 (s), 1370 (s), 1315 (w), 1257 (w), 1157 (s), 1107 (w), 1016 (w), 914 (w), 828 (w), 748 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (s; 9H), 4.33 (dd, J = 4.3, 13.3 Hz; 1H), 4.54 (dd, J = 9.7, 13.3 Hz; 1H), 4.72–4.77 (m; 1H), 4.96–4.97 (m; 1H), 6.21 (dd, J = 1.1, 6.2 Hz; 1H), 6.30 (d, J = 3.2 Hz; 1H), 6.36–6.38 (m; 1H), 7.19 (dd, J = 1.7, 6.2 Hz; 1H), 7.42 (br s; 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 38.1, 63.4, 72.5, 84.3, 108.9, 110.8, 128.6, 143.2, 146.9, 148.9, 149.1, 168.1. Spectral data are in agreement with the literature.[7] HRMS (ESI+): Calculated for $C_{15}H_{18}N_2NaO_5^+$ ([M + Na]$^+$): 345.1063, Found: 345.1062; $[\alpha]_D^{27}$ +150.2 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 92 : 8 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 8.24 min, τ_{minor} = 9.65 min).

(*S*)-*tert*-Butyl 2-((*S*)-1-(furan-2-yl)-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate *ent*-3j (Table 3, entry 5). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure *ent*-**3j** as a viscous oil (78 mg, 0.243 mmol; 81% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. $[\alpha]_D^{27}$ −125 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 85 : 15 er [Lit[7]: $[\alpha]_D^{24}$ −179 (c 1.11, $CHCl_3$)]. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{minor} = 8.33 min, τ_{major} = 9.77 min).

(*R*)-*tert*-Butyl 2-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3k (Table 2, entry 11). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3k** as a viscous oil (82 mg, 0.243 mmol; 81% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2927 (m), 1776 (s), 1654 (w), 1559 (s), 1459 (w), 1281 (s), 1261 (s), 1157 (s), 915 (w), 826 (m), 799 (w), 628 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (s; 9H), 4.50 (dd, J = 5.0, 13.5 Hz; 1H), 4.58 (dd, J = 9.6, 13.5 Hz; 1H), 4.89–4.93 (m; 1H), 4.95–4.96 (m; 1H), 6.21 (dd, J = 1.1, 6.1 Hz; 1H), 6.98 (d, J = 3.3 Hz; 1H), 7.02 (dd, J = 3.6, 5.0 Hz; 1H), 7.16 (dd, J = 1.7, 6.1 Hz; 1H), 7.31 (d, J = 5.1 Hz; 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1, 39.9, 64.9, 75.0, 84.5, 125.8, 126.3, 127.4, 129.0, 137.3, 146.3, 149.3, 168.1. Spectral data are in agreement with the literature.[7] HRMS (ESI+): Calculated for $C_{15}H_{18}NaO_5S^+$ ([M + Na]$^+$): 361.0834, Found: 361.0834; $[\alpha]_D^{27}$ +154.5 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 92 : 8 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 9.02 min, τ_{minor} = 12.93 min).

(*S*)-*tert*-Butyl 2-((*S*)-2-nitro-1-(thiophen-2-yl)ethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate *ent*-3k (Table 3, entry 6). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure *ent*-**3k** as a viscous oil (82 mg, 0.243 mmol; 81% yield). Diastereomeric ratio was determined by ^{1}H-NMR analysis of the crude product. $[\alpha]_D^{27}$ −125.1 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 84 : 16 er [Lit[7]: $[\alpha]_D^{24}$ −184 (c 1.03, $CHCl_3$)]. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{minor} = 9.13 min, τ_{major} = 13.16 min).

***tert*-Butyl 3-((*R*)-1-((*R*)-1-(*tert*-butoxycarbonyl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)-2-nitroethyl)-1*H*-indole-1-carboxylate 3l (Table 2, entry 12).** Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3l** as a viscous oil (116 mg, 0.246 mmol; 82% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2979 (w), 2929 (m), 1738 (s), 1559 (m), 1459 (w), 1369 (m), 1313 (m), 1273 (m), 1259 (m), 1156 (s), 1109 (m), 1019 (m), 826 (w), 748 (w), 722 (w), 685 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69 (s; 18H), 4.53 (dd, J = 5.2, 13.3 Hz; 1H), 4.65 (dd, J = 9.5, 13.3 Hz; 1H), 5.00–5.04 (m; 1H), 5.13–5.14 (m; 1H), 6.20 (dd, J = 1.2, 6.1 Hz; 1H), 7.06 (dd, J = 1.6, 6.1 Hz; 1H), 7.32–7.41 (m; 2H), 7.51 (s; 1H), 7.84 (d, J = 7.7 Hz; 1H), 8.14 (d, J = 7.1 Hz; 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.17, 28.21, 35.54, 62.94, 73.16, 84.50, 84.62, 115.40, 115.61, 119.20, 122.71, 123.22, 125.46, 128.92, 135.48, 146.61, 149.31, 149.73, 167.98; HRMS (ESI+): Calculated for $C_{24}H_{29}N_3NaO_7^+$ ([M + Na]$^+$): 494.1903, Found: 494.1901; $[\alpha]_D^{24}$ +38.8 (c 0.1, $CHCl_3$) for an enantiomerically enriched sample with 92 : 8 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, 1 : 1 *n*-hexane–EtOH, 1.0 mL min^{-1}, τ_{minor} = 11.09 min, τ_{major} = 13.04 min).

(*R*)-*tert*-Butyl 2-((*R*)-1-cyclohexyl-2-nitroethyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3m (Table 2, entry 13). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3m** as a white solid (86 mg, 0.255 mmol; 85% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. Melting point: 82 °C; FT-IR (neat): ν 2930 (s), 2856 (m), 1782 (s), 1774 (s), 1555 (m), 1453 (w), 1368 (m), 1313 (m), 1287 (m), 1159 (s), 1104 (w), 1032 (m), 912 (w), 845 (w), 825 (w), 804 (w), 751 (w) cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$): δ 1.08–1.14 (m; 1H), 1.28–1.31 (m; 1H), 1.41–1.50 (m; 1H), 1.57 (s; 9H), 1.68–1.71 (m; 1H), 1.77–1.83 (m; 3H), 1.93–1.96 (m; 1H), 3.16–3.22 (m; 1H), 3.88 (dd, J = 4.1, 13.8 Hz; 1H), 4.13 (dd, J = 7.1, 13.8 Hz; 1H), 4.95–4.96 (m; 1H), 6.20 (dd, J = 1.4, 6.2 Hz; 1H), 7.09 (dd, J = 1.6, 6.2 Hz; 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0, 28.0, 30.7, 30.8, 39.1, 42.8, 61.7, 73.3, 83.9, 129.2, 146.3, 148.9, 168.3; HRMS (ESI+): Calculated for $C_{17}H_{26}N_2NaO_5^+$ ([M + Na]$^+$): 361.1739, Found: 361.1741; $[\alpha]_D^{24}$ −36.8 (c 0.1, $CHCl_3$) for an enantiomerically enriched sample with 82.5 : 17.5 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 8.99 min, τ_{minor} = 13.25 min).

(*R*)-*tert*-Butyl 2-((*R*)-4-methyl-1-nitropentan-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3n (Table 2, entry 14). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure **3n** as a yellowish liquid (74 mg, 0.237 mmol; 79% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2961 (m), 2934 (m), 2873 (w), 1781 (s), 1743 (s), 1717 (w), 1557 (s), 1370 (s), 1339 (m), 1314 (s), 1282 (m), 1257 (m), 1159 (s), 1105 (m), 1048 (m), 1033 (m), 910 (w), 843 (m), 792 (w), 771 (w), 750 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J = 7.0 Hz; 6H), 1.27–1.41 (m; 2H), 1.54 (s; 9H), 1.65–1.75 (m; 1H), 3.33–3.41 (m; 1H), 3.96 (dd, J = 7.5, 13.0 Hz; 1H), 4.09 (dd, J = 5.2, 13.0 Hz; 1H), 4.74–4.75 (m; 1H), 6.19 (dd, J = 1.2, 6.2 Hz; 1H), 7.12 (dd, J = 1.6, 6.2 Hz; 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 22.7, 25.3, 28.0, 35.9, 39.2, 63.1, 75.4, 83.9, 129.1, 145.9, 149.0, 168.4; HRMS (ESI+): Calculated for $C_{15}H_{24}N_2NaO_5^+$ ([M + Na]$^+$): 335.1583, Found: 335.1586; $[\alpha]_D^{27}$ +109.2 (c 0.1, $CHCl_3$) for an enantiomerically enriched sample with 87 : 13 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 7.87 min, τ_{minor} = 10.71 min).

(*S*)-*tert*-Butyl 2-((*S*)-4-methyl-1-nitropentan-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate *ent*-3n (Table 3, entry 7). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded pure *ent*-**3n** as a yellowish viscous oil (82 mg, 0.264 mmol; 88% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. $[\alpha]_D^{27}$ −79.7 (c 0.1, $CHCl_3$) for an enantiomerically enriched sample with 77 : 23 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{minor} = 7.84 min, τ_{major} = 10.61 min).

(*R*)-*tert*-Butyl 2-((*R*)-3-methyl-1-nitrobutan-2-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate 3o (Table 2, entry 15). Purified by silica gel column chromatography (10% EtOAc in toluene) afforded **3o** as a viscous oil (68 mg, 0.228 mmol; 76% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2975 (m), 2934 (m), 2879 (w), 1780 (s), 1746 (s), 1717 (m), 1557 (s), 1370 (s), 1338 (m), 1314 (m), 1285 (m), 1257 (m), 1160 (s), 1048 (m), 1033 (m), 902 (w), 844 (w), 825 (w), 771 (w), 751 (w), 705 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (d, J = 6.7 Hz; 3H), 1.14 (d, J = 6.7 Hz; 3H), 1.57 (s; 9H), 1.75–1.84 (m; 1H), 3.10–3.16 (m; 1H), 3.91 (dd, J = 4.2, 13.8 Hz; 1H), 4.13 (dd, J = 6.9, 13.8 Hz; 1H), 4.92–4.93 (m; 1H), 6.21 (dd, J = 1.4, 6.2 Hz; 1H), 7.10 (dd, J = 1.9, 6.2 Hz; 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.56, 20.64, 27.97, 29.49, 61.99, 73.53, 83.92, 129.24, 146.11, 148.89, 168.31. Spectral data are in agreement with the literature.[7] HRMS (ESI+): Calculated for $C_{14}H_{22}N_2NaO_5^+$ ([M + Na]$^+$): 321.1426, Found: 321.1428; $[\alpha]_D^{27}$ +120.3 (c 0.5, $CHCl_3$) for an enantiomerically enriched sample with 84 : 16 er [Lit[7]: $[\alpha]_D^{24}$ −177 (c 1.0, $CHCl_3$) for *ent*-**3o**]. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{major} = 8.19 min, τ_{minor} = 11.64 min).

(3a*R*,9*S*,9a*R*)-*tert*-Butyl 9-(nitromethyl)-2-oxo-3,3a,9,9a-tetrahydrochromeno[3,2-*b*]pyrrole-1(2*H*)-carboxylate 4. Purified by silica gel column chromatography (20% EtOAc in petroleum ether) afforded pure **4** as a viscous oil (86 mg, 0.246 mmol; 82% yield). Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. FT-IR (neat): ν 2925 (m), 2852 (w), 1793 (s), 1654 (w), 1559 (m), 1475 (w), 1374 (w), 1282 (m), 1253 (m), 1202 (w), 1151 (s), 1113 (w), 1020 (s), 913 (w), 883 (w), 841 (w), 766 (w), 707 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (s; 9H), 2.88 (dd, J = 5.7, 18.9 Hz; 1H), 3.14 (dd, J = 9.2, 18.9 Hz; 1H), 4.37–4.42 (m; 1H), 4.48 (t, J = 10.3 Hz; 1H), 4.57 (dd, J = 4.5, 11.9 Hz; 1H), 4.65–4.76 (m; 2H), 7.02 (d, J = 7.9 Hz; 1H), 7.06 (t, J = 7.5 Hz; 1H), 7.18 (d, J = 7.2 Hz; 1H), 7.30 (t, J = 7.9 Hz; 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9, 38.4, 39.2, 59.9, 70.4, 84.9, 118.2, 124.2, 125.2, 129.4, 130.2, 149.2, 154.6, 170.2; HRMS (ESI+): Calculated for $C_{17}H_{20}N_2NaO_5^+$ ([M + Na]$^+$): 371.1219, Found: 371.1216; $[\alpha]_D^{28}$ −60.2 (c 0.1, $CHCl_3$) for an enantiomerically enriched sample with 84 : 16 er. Enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak-IC column, 254 nm, EtOH, 0.7 mL min^{-1}, τ_{minor} = 7.93 min, τ_{major} = 14.94 min).

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