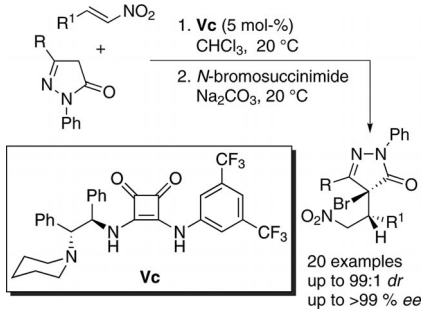
EurJOC European Journal of Organic Chemistry

Asymmetric Synthesis

A one-pot synthesis of optically active brominated pyrazol-5-one derivatives bearing contiguous quaternary and tertiary stereocenters has been developed. The asymmetric, sequential Michael addition/dearomative bromination reaction of pyrazol-5-ones and nitro olefins is catalyzed by a bifunctional squaramide.



Keywords: Organocatalysis / Michael addition / Nitrogen heterocycles / Nitro olefins

DOI: 10.1002/ejoc.201300460

Bifunctional Squaramide-Catalyzed One-Pot Sequential Michael Addition/Dearomative Bromination: Convenient Access to Optically Active Brominated Pyrazol-5(4*H*)-ones with Adjacent Quaternary and Tertiary Stereocenters

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Keywords: Organocatalysis / Michael addition / Nitrogen heterocycles / Nitro olefins

The organocatalytic asymmetric, one-pot, sequential Michael addition/dearomative bromination reaction of pyrazol-5-ones to nitro olefins and *N*-bromosuccinimide (NBS) has been developed. Under the catalysis of a chiral bifunctional squaramide, a wide variety of chiral brominated pyrazol-5-one derivatives with contiguous quaternary and tertiary stereocenters was obtained in high yields (up to >99 %) with good to excellent diastereoselectivities (62:38–99:1 *dr*) and uniformly high levels of enantioselectivity (92 to >99 % *ee*). This experimentally simple process facilitates access to various enantioenriched, multiply substituted pyrazolin-5-one derivatives, potential biologically active molecules, starting from readily available starting materials.

Introduction

Pyrazolone derivatives, an important class of five-membered, lactam-containing ring with two contiguous nitrogen atoms, can be used as pharmaceutical candidates and as biologically important structural components.[1] For example, edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one, also known as MCI-186) has been developed as a medical drug for brain ischemia[2] and has also been reported to be effective for myocardial ischemia.[3] Because of their biological significance, the development of asymmetric methods to access optically active pyrazolone derivatives is therefore of considerable interest. The most convenient access to chiral pyrazolone derivatives is the catalytic asymmetric direct functionalization of achiral pyrazolones. However, relatively few examples have been documented for catalytic asymmetric transformations by using pyrazolone as a nucleophile. These methods involve a cinchona alkaloid catalyzed tandem Michael addition/cyclization between 2-pyrazolin-5-ones and benzylidenemalononitriles to generate 6-amino-5-cyanodihydropyrano[2,3-*c*]pyrazoles,[4] the enantioselective synthesis of β-(3-hydroxypyrazol-1-yl) ketones through an organocatalyzed aza-Michael addition of 2-pyrazolin-5-ones to acyclic aliphatic α,β-unsaturated ketones,[5] the organocatalytic diastereo- and enantioselective Michael addition of 4-substituted pyrazolin-5-ones to nitro olefins,[6] a highly enantioselective Michael addition of 4-substituted pyrazolones and 4-oxo-4-arylbutenoates catalyzed by chiral metal/*N*,*N*′-dioxide complexes,[7] the synthesis of chiral spiropyrazol-3-ones through an organocatalyzed Michael/Michael/aldol cascade reaction,[8] the amination of pyrazol-3-ones through nucleophilic attack of diazodicarboxylates catalyzed by Gd salts,[9] the asymmetric Michael addition of pyrazolones to maleimides catalyzed by bifunctional thiourea catalysts,[10] and the one-pot asymmetric synthesis of tetrahydropyrano[2,3-*c*]pyrazoles through a secondary amine catalyzed asymmetric Michael/Wittig/oxa-Michael reaction sequence.[11] Despite this promising progress, it is still highly desirable to broaden the diversity of functionalized pyrazolones and to develop new efficient catalytic asymmetric methods to access chiral multifunctionalized pyrazolone species. In addition, the stereocontrolled construction of contiguous quaternary and tertiary stereocenters, which are common structural motifs in complex natural products, has proven to be a formidable challenge in asymmetric organic synthesis.[12] Consequently, exploring highly efficient approaches to optically active building blocks containing such contiguous quaternary and tertiary stereocenters has been a hot point of research in catalytic asymmetric transformations. Herein, we wish to report the first highly enantioselective one-pot sequential Michael addition/dearomative bromination of 4-substituted pyrazol-5-ones by using a chiral bifunctional squaramide as the catalyst to generate optically active brominated pyrazol-5(4*H*)-ones with adjacent quaternary and tertiary stereocenters.[13,14] High yields (up to 99 %), good to excellent dia-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300460.

stereoselectivities (up to 99:1 *dr*), and excellent enantioselectivities (up to >99% *ee*) were achieved for a wide range of nitro olefins at 5 mol-% catalyst loading.

Results and Discussion

Bifunctional tertiary amine squaramide catalysts[15] **I**–**V** (Figure 1) were evaluated for the Michael addition of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**1a**, 1.0 equiv.) to *trans*-β-nitrostyrene (**2a**, 1.1 equiv.) in chloroform at 20 °C, and the results are summarized in Table 1.

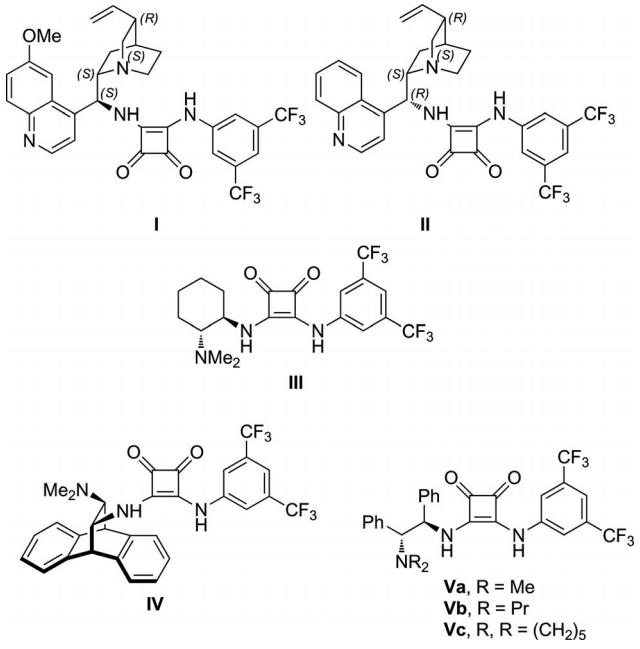
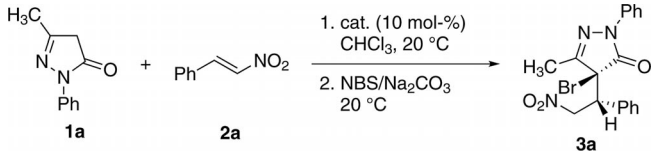


Figure 1. Catalyst candidates.

Indeed, the model reaction ran smoothly to give the corresponding conjugate addition intermediate in the presence of quinine-based squaramide catalyst **I** (10 mol-%). Although analysis by NMR spectroscopy indicated that the addition intermediate was a mixture of tautomers, to our delight, this mixture could be further brominated with *N*-bromosuccinimide (NBS) to afford brominated chiral pyrazo-5(4*H*)-one **3a** in high yield with good diastereo- (80:20 *dr*) and enantioselectivity (76% *ee*) within 5 min (Table 1, entry 1). Screening of other squaramide catalysts demonstrated that the chiral diamine backbone significantly affected the enantioselectivity of the reaction. A similar stereochemical outcome was observed for cinchonine-derived squaramide catalyst **II** (Table 1, entry 2). The use of catalyst **III**, incorporating (1*R*,2*R*)-1,2-cyclohexanediamine, resulted in a clearly decreased *ee* value (Table 1, entry 3). Squaramide catalyst **IV** bearing a structurally rigid 9,10-ethylene-9,10-dihydroanthracene skeleton, which had previously been successfully employed for the Michael addition of 4-hydroxycoumarins to β,γ-unsaturated α-ketophosphonates, demonstrated much lower catalytic activity, and it gave product **3a** in 47 h with quite low enantioselectivity (18% *ee*; Table 1, entry 4). We then turned our attention to

Table 1. Catalyst evaluation.[a]



Entry	Catalyst	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**I**	1	94	80:20	76
2	**II**	0.33	97	81:19	77
3	**II**	16	98	90:10	43
4	**IV**	47	90	80:20	18
5	**Va**	6	99	82:18	81
6	**Vb**	5	99	80:20	93
7	**Vc**	1.5	99	83:17	98

[a] All reactions were carried out with pyrazol-5-one (**1a**, 0.20 mmol), nitrostyrene (**2a**, 0.22 mmol), and the squaramide catalyst (10 mol-%) in chloroform (1 mL) at 20 °C for the time indicated. Then, *N*-bromosuccinimide (NBS, 0.3 mmol) and Na_2CO_3 (0.24 mmol) were added at the same temperature, and the resulting mixture was stirred for 5 min. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by ^1H NMR spectroscopy or HPLC analysis. [d] Determined by chiral HPLC analysis.

squaramides derived from chiral 1,2-diphenylethane-1,2-diamine. It was gratifying that a slightly better enantioselectivity was obtained if catalyst **Va** was employed (81% *ee*; Table 1, entry 5). To investigate the effect of the tertiary amino group, squaramide-based catalysts **Vb**, and **Vc** containing a dipropylamino and a piperidinyl group, respectively, were prepared and screened. Satisfactorily, squaramides **Vb** and **Vc** gave access to the desired products with excellent enantioselectivities (93 and 98% *ee*, respectively; Table 1, entries 6 and 7). Catalyst **Vc** afforded the highest enantioselectivity of 98% *ee* and was selected as the best catalyst for further optimization.

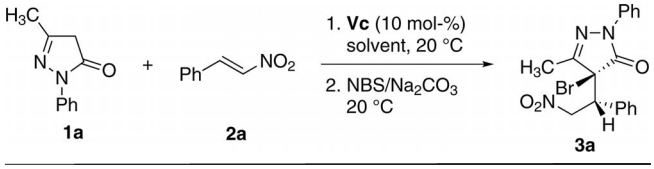
With promising catalyst **Vc** in hand, other reaction parameters, such as solvent, catalyst loading, and reaction temperature (Table 2, entries 1–11), were further optimized, and the results are summarized in Table 2.

Variation of the solvent had a significant effect on the enantioselectivity of the reaction. The common solvents, such as $CHCl_3$, CH_2Cl_2, THF, and ethyl acetate, gave excellent enantioselectivities (92–98% *ee*; Table 2, entries 1–3, 6). Performing the reaction in either nonpolar toluene or polar acetonitrile led to clearly decreased *ee* values (Table 2, entries 4 and 5). As expected, EtOH resulted in a dramatic decrease in the enantioselectivity (51% *ee*; Table 2, entry 7) because it is often a poor solvent in hydrogen-bond-controlled organocatalysis. Finally, by decreasing the temperature to –20 °C and by adjusting the catalyst loading to 5 mol-%, we achieved excellent yields and almost perfect enantioselectivity in this reaction (Table 2, entry 11).

After having established the optimal reaction conditions (5 mol-% **Vc** in $CHCl_3$ at –20 °C), the scope and limitations of this enantioselective synthesis were next examined, and the results are collected in Table 3.

As shown in Table 3, this asymmetric one-pot multistep reaction is compatible with a wide range of nitro olefin sub-

Table 2. Optimization of the reaction conditions.[a]

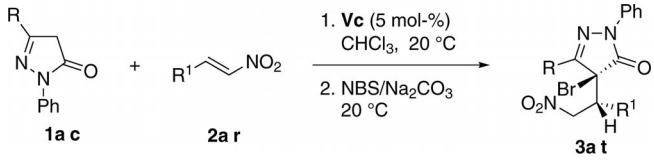


Entry	Solvent	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	$CHCl_3$	1.5	99	80:20	98
2	CH_2Cl_2	2	99	81:19	96
3	THF	4	90	80:20	95
4	$PhCH_3$	10	87	80:20	80
5	CH_3CN	10	92	82:18	87
6	AcOEt	17	90	78:22	92
7	EtOH	17	77	75:25	51
8[e]	$CHCl_3$	2	99	80:20	98
9[f]	$CHCl_3$	8	99	82:18	98
10[g]	$CHCl_3$	3	99	82:18	99
11[h]	$CHCl_3$	8	99	83:17	>99

[a] Unless otherwise noted, all reactions were carried out with pyrazol-5-one (**1a**, 0.20 mmol), nitrostyrene (**2a**, 0.22 mmol), and squaramide catalyst **Vc** (10 mol-%) in solvent (1 mL) at 20 °C for the time indicated. Then, NBS (0.30 mmol) and Na_2CO_3 (0.24 mmol) were added at the same temperature, and the resulting mixture was stirred for 5 min. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by ^{1}H NMR spectroscopy or HPLC analysis. [d] Determined by chiral HPLC analysis. [e] With a catalyst loading of 5 mol-%. [f] With a catalyst loading of 2 mol-%. [g] Reaction was performed at 0 °C with a catalyst loading of 5 mol-%. [h] Reaction was performed at –20 °C with a catalyst loading of 5 mol-%.

strates, as brominated pyrazol-5-ones **3a**–**r** were generated in 82 to >99% yields with 95 to >99% enantioselectivities and good to excellent diastereoselectivities (Table 3, entries 1–18). It appeared that the electronic properties of the substituents on the aromatic rings had a very limited influence on the stereoselectivities of the reactions (Table 3, entries 2–14). Substrates with electron-withdrawing (Table 3, entries 2–9), electron-donating (Table 3, entries 10–13), and electron-neutral (Table 3, entries 1 and 14) groups participated in this reaction efficiently to deliver the brominated pyrazolin-5-ones bearing contiguous quaternary and tertiary stereocenters with uniformly high enantioselectivities (*ee* values ranging from 96 to >99%) regardless of the substitution pattern. For example, the most sterically demanding substrate, β-mesityl-substituted nitroethylene **2k**, worked well to give product **3k** in 96% yield with 95:5 *dr* and 96% *ee* (Table 3, entry 11). Not only aromatic groups but also heteroaromatic groups such as furyl and thienyl could be successfully employed to afford the respective chiral pyrazol-5-one derivatives with excellent enantioselectivities (Table 3, entries 15 and 16). Notably, less reactive aliphatic nitro olefins, such as (*E*)-1-nitrobut-1-ene (**2q**) and (*E*)-4-methyl-1-nitropent-1-ene (**2r**), were also tolerated in this reaction, and they afforded the desired products with almost the same high level of enantioselectivities at the expense of reaction time (Table 3, entries 17 and 18). Furthermore, by using nitro olefin **2a** as the reaction partner, the one-pot sequential reaction also proceeded smoothly if pyrazolone **1a** was replaced with either **1b** or **1c** (Table 3, entries 19 and 20).

Table 3. **Vc**-catalyzed cascade Michael addition/dearomative bromination reaction of pyrazolones **1** and nitro olefins **2**.[a]



Entry	**3** (R, R^1)	Time [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**3a** (CH_3, Ph)	8	99	83:17	>99
2	**3b** (CH_3, 4-FC_6H_4)	5.5	99	85:15	99
3	**3c** (CH_3, 2-ClC_6H_4)	5.5	>99	97:3	>99
4	**3d** (CH_3, 3-ClC_6H_4)	5	94	86:14	>99
5	**3e** (CH_3, 4-ClC_6H_4)	11	97	84:16	99
6	**3f** (CH_3, 2,4-$Cl_2C_6H_3$)	72	82	93:7	96
7	**3g** (CH_3, 2-BrC_6H_4)	5	>99	94:6	99
8	**3h** (CH_3, 4-$NO_2C_6H_4$)	72	93	94:6	99
9	**3i** (CH_3, 4-$CF_3C_6H_4$)	32	98	82:18	>99
10	**3j** (CH_3, 4-MeC_6H_4)	6.5	>99	85:15	97
11	**3k** (CH_3, 2,4,6-$Me_3C_6H_2$)	120	96	95:5	96
12	**3l** (CH_3, 3-$MeOC_6H_4$)	17	>99	88:12	98
13	**3m** (CH_3, 4-Me-OC_6H_4)	26	91	88:12	98
14	**3n** (CH_3, 1-naphthyl)	86	>99	82:18	>99
15	**3o** (CH_3, 2-furyl)	12	89	80:20	99
16	**3p** (CH_3, 2-thienyl)	12.5	82	97:3	>99
17	**3q** (CH_3, Et)	168	86	84:16	95
18	**3r** (CH_3, *i*Bu)	48	90	62:38	98
19	**3s** (CF_3, Ph)	144	87	99:1	92
20	**3t** (Ph, Ph)	2.5	>99	97:3	99

[a] All reactions were carried out with pyrazol-5-one (**1a**, 0.20 mmol), nitrostyrene (**2a**, 0.22 mmol), and squaramide catalyst (5 mol-%) in chloroform (1 mL) at –20 °C for the time indicated. Then, NBS (0.30 mmol) and Na_2CO_3 (0.24 mmol) were added at 20 °C, and the resulting mixture was stirred for 5 min. [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by ^{1}H NMR spectroscopy or HPLC analysis. [d] Determined by chiral HPLC analysis.

The relative and absolute configuration of product **3d** was unequivocally established by X-ray analysis (Figure 2), and the remaining configurations were assumed by analogy.[16]

Conclusions

In conclusion, we have developed a facile organocatalytic, enantioselective synthesis of highly functionalized chiral pyrazol-5(4*H*)-ones with contiguous quaternary and tertiary stereocenters by a one-pot sequential Michael addition/dearomative bromination strategy. Under the catalysis of a bifunctional tertiary amine squaramide, a series of optically active brominated pyrazol-5-ones bearing adjacent quaternary and tertiary stereocenters were obtained in high yields (82 to >99%) and good to excellent diastereoselectivities (62:38–99:1 *dr*) with high levels of enantioselectivity (92 to >99% *ee*).

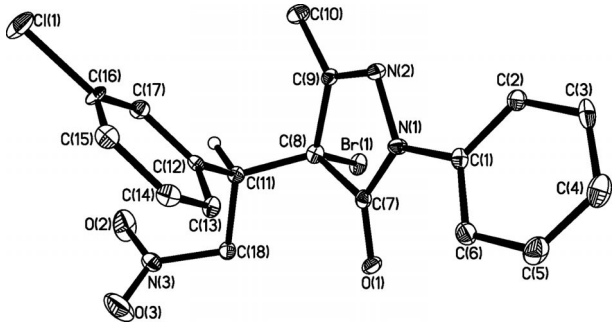


Figure 2. X-ray crystal structure of (4*R*,1′*R*)-**3d**. Most of the hydrogen atoms are omitted for clarity.

Experimental Section

General Methods: All reagents and solvents were commercial grade and were purified prior to use if necessary. NMR spectra were acquired with a Varian 400 MHz instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ = 7.26 ppm and δ = 77.0 ppm ($CDCl_3$) or δ = 2.50 ppm and δ = 39.43 ppm ([D_6]DMSO). Specific rotations were measured with a Perkin–Elmer 341MC polarimeter. Enantiomeric excesses were determined with an HP-1100 instrument (chiral column, mobile phase = hexane/*i*PrOH). HRMS was performed with a Varian QFT-ESI instrument. Melting points were determined with a Taike X-4 melting point apparatus.

Synthesis of Squaramide Catalyst Vb and Vc: To a solution of the corresponding (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (4.8 mmol) in CH_2Cl_2 (40 mL) was added 3-[3,5-bis(trifluoromethyl)phenylamino]-4-methoxycyclobut-3-ene-1,2-dione (4.0 mmol) in one portion. The resulting mixture was stirred at room temperature until completion of the reaction (monitored by TLC). The precipitate was filtered and dried in the vacuum to obtain the product.

Vb: White solid, 63% yield, m.p. 204–206 °C, $[a]_D^{20}$ = –216 (*c* = 0.2, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.2 Hz, 6 H), 1.30–1.39 (m, 2 H), 1.45–1.53 (m, 2 H), 1.99–2.06 (m, 2 H), 2.52–2.59 (m, 2 H), 4.31 (d, *J* = 11.6 Hz, 1 H), 5.86 (br. s, 1 H), 7.10–7.24 (m, 8 H_{arom}), 7.31 (d, *J* = 7.6 Hz, 2 H_{arom}), 7.67 (s, 1 H_{arom}), 8.08 (s, 2 H_{arom}), 8.22 (br. s, 1 H), 10.21 (br. s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 11.5, 21.0, 51.2, 58.1, 67.1, 114.7, 118.0, 121.7, 124.4, 126.9, 127.4, 127.6, 128.4, 129.1, 131.3 (q, *J* = 32.8 Hz), 134.7, 140.0, 140.9, 162.0, 168.9, 179.6, 184.6 ppm. HRMS (ESI): calcd. for $C_{32}H_{32}F_6N_3O_2$ [M + H]$^+$ 604.2393; found 604.2395.

For Vc: Yellow solid, 66% yield, m.p. 228–206 °C, $[a]_D^{20}$ = –136 (*c* = 0.1, DMSO). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (br. s, 2 H), 1.39 (br. s, 2 H), 1.47 (br. s, 2 H), 2.21 (br. s, 2 H), 2.50 (br. s, 2 H), 4.18 (d, *J* = 15.2 Hz, 1 H), 5.81 (br. s, 1 H), 7.09–7.31 (m, 10 H_{arom}), 7.67 (s, 1 H_{arom}), 8.08 (s, 2 H_{arom}), 8.33 (br. s, 1 H), 10.32 (br. s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 24.0, 25.9, 26.0, 49.8, 57.4, 72.1, 114.7, 118.1, 121.7, 124.4, 127.0, 127.4, 127.5, 127.6, 128.3, 129.2, 131.2 (q, *J* = 33.1 Hz), 133.2, 139.9, 141.0, 162.2, 169.3, 180.0, 184.5 ppm. HRMS (ESI): calcd. for $C_{31}H_{28}F_6N_3O_2$ [M + H]$^+$ 588.2080; found 588.2085.

General Procedure for Bifunctional Squaramide Vc-Catalyzed Asymmetric One-Pot Sequential Michael Addition/Dearomative Bromination Reactions: To a stirring mixture of catalyst **Vc** (0.010 mmol) and nitro olefin **2** (0.22 mmol) in chloroform (1 mL) was added pyrazol-5-one **1** (0.20 mmol) at –20 °C. Upon completion of the reaction (monitored by TLC), NBS (0.30 mmol) and Na_2CO_3 (0.24 mmol) were added at 20 °C, and the resulting mixture was stirred at the same temperature for 5 min. The reaction mixture was concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel [200–300 mesh, petroleum ether (PE)/EtOAc = 20:1] to afford chiral brominated pyrazol-5-one **3**. The title compounds were fully characterized by ^{1}H NMR and ^{13}C NMR spectroscopy, HRMS, and specific rotation. Diastereomeric ratios and enantiomeric excess values of the products were determined by chiral HPLC analysis.

(*R*)-4-Bromo-3-methyl-4-[(*R*)-2-nitro-1-phenylethyl]-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3a): Yellow solid, 98% yield, m.p. 45–47 °C, $[a]_D^{20}$ = +90.2 (*c* = 1.0, $CHCl_3$), 83:17 *dr*, >99% *ee* for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 0.51 H), 2.14 (s, 2.49 H), 4.06 (dd, *J* = 5.2, 9.6 Hz, 0.83 H), 4.22 (dd, *J* = 3.2, 11.6 Hz, 0.17 H), 4.96 (dd, *J* = 11.6, 13.2 Hz, 0.17 H), 5.34–5.44 (m, 1.83 H), 7.10–7.24 (m, 6 H_{arom}), 7.31 (t, *J* = 8.0 Hz, 2 H_{arom}), 7.54 (d, *J* = 8.4 Hz, 0.34 H_{arom}), 7.61 ppm (d, *J* = 8.0 Hz, 1.66 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.6 (major isomer), 15.8 (minor isomer), 48.0 (minor isomer), 48.8 (major isomer), 56.4 (major isomer), 57.7 (minor isomer), 75.9 (major isomer), 76.0 (minor isomer), 119.1 (minor isomer), 119.2 (major isomer), 126.0 (minor isomer), 126.1 (major isomer), 127.8 (major isomer), 128.6 (minor isomer), 128.9 (minor isomer), 129.0 (major isomer), 129.1 (minor isomer), 129.4 (major isomer), 129.5 (minor isomer), 129.6 (major isomer), 131.9 (minor isomer), 132.2 (major isomer), 136.7 (minor isomer), 136.8 (major isomer), 155.7 (minor isomer), 156.8 (major isomer), 168.3 (minor isomer), 168.7 ppm (major isomer). HRMS (ESI): calcd. for $C_{18}H_{16}BrN_3NaO_3$ [M + Na]$^+$ 424.0627; found 424.0624. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 12.03 (minor, major isomer), 15.53 (major, major isomer), 18.48 (major, minor isomer), 19.66 min (minor, minor isomer).

(*R*)-4-Bromo-4-[(*R*)-1-(4-fluorophenyl)-2-nitroethyl]-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3b): Yellow solid, 99% yield, m.p. 56–58 °C, $[a]_D^{20}$ = +110.6 (*c* = 1.0, $CHCl_3$), 85:15 *dr*, 99% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 0.45 H), 2.23 (s, 2.55 H), 4.15 (t, *J* = 7.2 Hz, 0.85 H), 4.31 (d, *J* = 11.2 Hz, 0.15 H), 4.99 (t, *J* = 12.4 Hz, 0.15 H), 5.42–5.49 (m, 1.85 H), 6.96 (d, *J* = 8.0 Hz, 1.70 H_{arom}), 7.02 (d, *J* = 8.0 Hz, 1.70 H_{arom}), 7.19–7.26 (m, 3 H_{arom}), 7.41 (t, *J* = 7.6 Hz, 2 H_{arom}), 7.65 (d, *J* = 7.6 Hz, 0.30 H_{arom}), 7.71 ppm (d, *J* = 8.0 Hz, 1.70 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.6 (major isomer), 15.7 (minor isomer), 47.4 (minor isomer), 48.0 (major isomer), 56.2 (major isomer), 57.4 (minor isomer), 75.8 (major isomer), 76.0 (minor isomer), 116.3 (d, *J* = 21.8 Hz, minor isomer), 116.7 (d, *J* = 21.7 Hz, major isomer), 119.0 (minor isomer), 119.1 (major isomer), 126.1 (minor isomer), 126.2 (major isomer), 127.8 (d, *J* = 3.7 Hz, minor isomer), 128.0 (d, *J* = 3.3 Hz, major isomer), 128.9 (minor isomer), 129.0 (major isomer), 129.7 (d, *J* = 8.6 Hz, major isomer), 130.6 (d, *J* = 8.3 Hz, minor isomer), 136.6 (minor isomer), 136.7 (major isomer), 155.5 (minor isomer), 156.6 (major isomer), 163.1 (d, *J* = 250.5 Hz), 168.2 (minor isomer), 168.6 ppm (major isomer). HRMS (ESI): calcd. for $C_{18}H_{15}BrN_3NaO_3$ [M + Na]$^+$ 442.0173; found 442.0175. HPLC (Chiralpak AD-H, hexane/2-propanol = 98:2, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 21.72 (minor, major isomer), 24.19 (major, major isomer), 38.35 min (major, minor isomer).

(*R*)-4-Bromo-4-[(*R*)-1-(2-chlorophenyl)-2-nitroethyl]-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3c): Yellow solid, 91% yield, m.p. 36–38 °C, $[a]_D^{20}$ = +117.2 (*c* = 1.0, $CHCl_3$), 97:3 *dr*, >99% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 4.97 (dd, *J* = 3.2, 10.8 Hz, 1 H), 5.37 (dd, *J* = 10.8, 13.6 Hz, 1 H), 5.53 (dd, *J* = 3.2, 13.6 Hz, 1 H), 7.11 (dt, *J* = 1.2, 7.6 Hz, 1 H_{arom}), 7.19–7.26 (m, 3

H_{arom}), 7.41 (t, J = 7.6 Hz, 3 H_{arom}), 7.73 ppm (d, J = 7.6 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.7, 43.7, 56.4, 76.0, 119.1, 126.2, 127.0, 128.1, 129.0, 130.6, 130.9, 131.0, 134.4, 136.7, 157.1, 168.7 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}BrClN_3NaO_3$ [M + Na]$^+$ 457.9878; found 457.9874. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 11.79 (minor, major isomer), 18.26 (major, major isomer), 30.77 min (major, minor isomer).

(*R*)-4-Bromo-4-[(*R*)-1-(3-chlorophenyl)-2-nitroethyl]-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3d): Yellow solid, 94% yield, m.p. 118–119 °C, $[\alpha]_D^{20}$ = +90.8 (c = 1.0, $CHCl_3$), 86:14 *dr*, >99% *ee*. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 0.42 H), 2.22 (s, 2.58 H), 4.10 (t, J = 7.2 Hz, 0.86 H), 4.23 (d, J = 10.8 Hz, 0.14 H), 4.98 (t, J = 7.6 Hz, 0.14 H), 5.42 (d, J = 7.2 Hz, 1.86 H), 7.08 (d, J = 7.2 Hz, 1 H_{arom}), 7.18–7.26 (m, 4 H_{arom}), 7.39 (t, J = 7.6 Hz, 2 H_{arom}), 7.67 ppm (d, J = 8.0 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.6 (major isomer), 15.7 (minor isomer), 47.5 (minor isomer), 48.4 (major isomer), 56.0, 75.6 (major isomer), 75.7 (minor isomer), 119.4, 125.7, 126.4, 128.3, 129.0, 130.0, 130.8, 134.3, 135.4, 136.6, 156.5, 168.5 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}BrClN_3NaO_3$ [M + Na]$^+$ 457.9878; found 457.9875. HPLC (Chiralpak AD-H, hexane/2-propanol = 97:3, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 15.74 (minor, major isomer), 19.00 (major, major isomer), 23.55 (major, minor isomer), 26.14 min (minor, minor isomer).

(*R*)-4-Bromo-4-[(*R*)-1-(4-chlorophenyl)-2-nitroethyl]-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3e): Yellow solid, 97% yield, m.p. 50–51 °C, $[\alpha]_D^{20}$ = +101.4 (c = 1.0, $CHCl_3$), 84:16 *dr*, 99% *ee*. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 0.48 H), 2.24 (s, 2.52 H), 4.14 (t, J = 7.2 Hz, 0.84 H), 4.29 (d, J = 11.6 Hz, 0.16 H), 5.00 (t, J = 12.4 Hz, 0.16 H), 5.45 (d, J = 7.2 Hz, 1.84 H), 7.16 (d, J = 8.0 Hz, 1.68 H_{arom}), 7.24–7.32 (m, 3.32 H_{arom}), 7.42 (t, J = 7.6 Hz, 2 H_{arom}), 7.67 (d, J = 7.6 Hz, 0.32 H_{arom}), 7.72 ppm (d, J = 8.0 Hz, 1.68 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.6 (major isomer), 15.7 (minor isomer), 47.4 (minor isomer), 48.1 (major isomer), 56.0 (major isomer), 57.2 (minor isomer), 75.7 (major isomer), 75.8 (minor isomer), 119.1 (major isomer), 119.4 (minor isomer), 126.1 (minor isomer), 126.2 (major isomer), 128.9 (minor isomer), 129.0 (major isomer), 129.2 (major isomer), 129.4 (minor isomer), 129.8 (major isomer), 130.1 (minor isomer), 130.6 (minor isomer), 130.7 (major isomer), 135.7 (minor isomer), 135.8 (major isomer), 136.6 (minor isomer), 136.7 (major isomer), 155.4 (minor isomer), 156.5 (major isomer), 168.1 (minor isomer), 168.5 ppm (major isomer). HRMS (ESI): calcd. for $C_{18}H_{15}BrClN_3NaO_3$ [M + Na]$^+$ 457.9878; found 457.9873. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 11.39 (major, major isomer), 14.28 (minor, major isomer), 21.31 (major, minor isomer), 23.11 min (minor, minor isomer).

(*R*)-4-Bromo-4-[(*R*)-1-(2,4-dichlorophenyl)-2-nitroethyl]-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3f): Yellow solid, 72% yield, m.p. 140–142 °C, $[\alpha]_D^{20}$ = +120.0 (c = 1.0, $CHCl_3$), 93:7 *dr*, 96% *ee*. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 4.91 (dd, J = 3.2, 10.8 Hz, 1 H), 5.37 (dd, J = 10.8, 13.6 Hz, 1 H), 5.52 (dd, J = 3.2, 13.6 Hz, 1 H), 7.11 (dd, J = 2.0, 8.8 Hz, 1 H_{arom}), 7.19 (d, J = 8.4 Hz, 1 H_{arom}), 7.27 (t, J = 7.6 Hz, 1 H_{arom}), 7.41–7.45 (m, 3 H_{arom}), 7.75 ppm (d, J = 7.6 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.7, 43.2, 56.0, 75.8, 119.1, 126.3, 127.9, 128.5, 129.1, 129.6, 130.8, 135.2, 136.1, 136.6, 156.9, 168.5 ppm. HRMS (ESI): calcd. for $C_{18}H_{14}BrClN_3NaO_3$ [M + Na]$^+$ 491.9488; found 491.9495. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 7.20 (major, major isomer), 8.29 (minor, major isomer), 14.41 (minor, minor isomer), 15.88 min (major, minor isomer).

(*R*)-4-Bromo-4-[(*R*)-1-(2-bromophenyl)-2-nitroethyl]-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3g): Yellow solid, 91% yield, m.p. 48–49 °C, $[\alpha]_D^{20}$ = +132.0 (c = 0.5, $CHCl_3$), 94:6 *dr*, 99% *ee*. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 4.97 (dd, J = 3.2, 10.8 Hz, 1 H), 5.33 (dd, J = 10.8, 13.2 Hz, 1 H), 5.55 (dd, J = 3.2, 13.2 Hz, 1 H), 7.13–7.19 (m, 2 H_{arom}), 7.21–7.27 (m, 2 H_{arom}), 7.42 (t, J = 8.0 Hz, 2 H_{arom}), 7.60 (dd, J = 1.6, 7.6 Hz, 1 H_{arom}), 7.75 ppm (d, J = 8.0 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.2, 46.7, 56.3, 76.2, 119.2, 125.2, 126.2, 127.0, 128.8, 129.0, 130.9, 133.1, 134.4, 136.8, 157.2, 168.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}Br_2N_3NaO_3$ [M + Na]$^+$ 501.9372; found 501.9370. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 12.70 (minor, major isomer), 23.85 (major, major isomer), 32.28 min (major, minor isomer).

(*R*)-4-Bromo-3-methyl-4-[(*R*)-2-nitro-1-(4-nitrophenyl)ethyl]-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3h): Yellow solid, 93% yield, m.p. 66–68 °C, $[\alpha]_D^{20}$ = +85.0 (c = 1.0, $CHCl_3$), 92:8 *dr*, >99% *ee*. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.23 (s, 0.24 H), 2.25 (s, 2.76 H), 4.12 (dd, J = 7.2, 14.4 Hz, 0.08 H), 4.28 (dd, J = 5.2, 8.8 Hz, 1 H), 5.42–5.55 (m, 2 H), 7.26 (t, J = 7.6 Hz, 1 H_{arom}), 7.39–7.44 (m, 4 H_{arom}), 7.66 (d, J = 7.6 Hz, 0.16 H_{arom}), 7.70 (d, J = 8.0 Hz, 1.84 H_{arom}), 8.12 (d, J = 8.8 Hz, 1.84 H_{arom}), 8.19 ppm (d, J = 8.8 Hz, 0.16 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.6, 48.3, 55.5, 75.4, 119.0, 124.6, 126.4, 129.0, 129.1, 136.5, 139.5, 148.4, 156.2, 168.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{15}BrN_4NaO_5$ [M + Na]$^+$ 469.0118; found 469.0114. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 23.82 (major, major isomer), 44.62 (minor, major isomer), 52.16 (minor, minor isomer), 57.12 min (major, minor isomer).

(*R*)-4-Bromo-4-{(*R*)-1-[4-(trifluoromethyl)phenyl]-2-nitroethyl}-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3i): Yellow solid, 98% yield, m.p. 46–48 °C, $[\alpha]_D^{20}$ = +75.6 (c = 0.5, $CHCl_3$), 82:18 *dr*, >99% *ee*. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 0.54 H), 2.24 (s, 2.46 H), 4.23 (t, J = 7.2 Hz, 0.82 H), 4.36 (d, J = 10.8 Hz, 0.18 H), 5.00–5.12 (m, 0.18 H), 5.48 (d, J = 7.2 Hz, 1.82 H), 7.26 (t, J = 7.6 Hz, 1 H_{arom}), 7.35 (d, J = 7.6 Hz, 2 H_{arom}), 7.41 (d, J = 8.0 Hz, 2 H_{arom}), 7.54 (d, J = 8.0 Hz, 2 H_{arom}), 7.70 ppm (d, J = 8.0 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.6, 48.5, 55.9, 75.6 119.2, 126.4, 126.5 (q, J = 3.6 Hz), 128.4, 129.0, 129.1, 129.3, 136.5, 136.6, 156.4, 168.5 ppm. HRMS (ESI): calcd. for $C_{19}H_{15}BrF_3N_3NaO_3$ [M + Na]$^+$ 492.0141; found 492.0139. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 220 nm): t_R = 7.97 (major, major isomer), 13.57 (minor, major isomer), 18.29 (minor, minor isomer), 20.65 min (major, minor isomer).

(*R*)-4-Bromo-3-methyl-4-[(*R*)-2-nitro-1-*p*-tolylethyl]-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3j): Yellow solid, >99% yield, m.p. 50–51 °C, $[\alpha]_D^{20}$ = +84.4 (c = 1.0, $CHCl_3$), 85:15 *dr*, 97% *ee*. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 0.45 H), 2.23 (s, 2.55 H), 2.25 (s, 2.55 H), 2.27 (s, 0.45 H), 4.11 (dd, J = 4.4, 9.6 Hz, 0.85 H), 4.27 (t, J = 3.6, 12.0 Hz, 0.15 H), 5.40–5.52 (m, 2 H), 7.04 (d, J = 8.0 Hz, 1.70 H_{arom}), 7.08 (d, J = 8.4 Hz, 1.70 H_{arom}), 7.11 (d, J = 8.4 Hz, 0.30 H_{arom}), 7.19 (d, J = 8.0 Hz, 0.30 H_{arom}), 7.24 (t, J = 7.6 Hz, 1 H_{arom}), 7.41 (t, J = 8.0 Hz, 2 H_{arom}), 7.66 (d, J = 8.0 Hz, 0.30 H_{arom}), 7.72 ppm (d, J = 8.4 Hz, 1.70 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.5 (major isomer), 15.8 (minor isomer), 21.1, 47.7 (minor isomer), 48.5 (major isomer), 56.5, 76.0 (major isomer), 76.1 (minor isomer), 119.1 (minor isomer), 119.2 (major isomer), 125.9 (minor isomer), 126.1 (major isomer), 127.6 (major isomer), 128.0 (minor isomer), 128.5 (major isomer), 128.7 (minor isomer), 128.9 (minor isomer), 129.0 (major isomer), 129.9 (minor isomer), 130.2 (major isomer), 136.8 (minor isomer), 136.9 (major

isomer), 139.6 (minor isomer), 139.7 (major isomer), 155.8 (minor isomer), 156.9 (major isomer), 168.4 (minor isomer), 168.8 ppm (major isomer). HRMS (ESI): calcd. for $C_{19}H_{18}BrN_3NaO_3$ [M + Na]$^+$ 438.0424; found 438.0424. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 15.25 (minor, major isomer), 17.65 (major, major isomer), 24.11 (major, minor isomer), 28.45 min (minor, minor isomer).

(*R*)-4-Bromo-4-[(*R*)-1-mesityl-2-nitroethyl]-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3k): Yellow solid, 96% yield, m.p. 114–115 °C, $[\alpha]_D^{20}$ = +104.9 (*c* = 0.89, $CHCl_3$), 95:5 *dr*, 96% *ee* for major isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (s, 3 H), 2.07 (s, 3 H), 2.20 (s, 3 H), 2.46 (s, 3 H), 5.03 (dd, *J* = 10.8, 4.0 Hz, 1 H), 5.27 (dd, *J* = 12.8, 11.2 Hz, 1 H), 5.75 (dd, *J* = 12.8, 4.0 Hz, 1 H), 6.74 (s, 1 H_{arom}), 6.84 (s, 1 H_{arom}), 7.26 (t, *J* = 7.6 Hz, 1 H_{arom}), 7.44 (t, *J* = 8.0 Hz, 2 H_{arom}), 7.83 ppm (d, *J* = 8.0 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 20.0, 20.6, 21.9, 46.3, 56.3, 74.1, 118.9, 126.0, 127.7, 129.1, 130.4, 131.9, 136.0, 137.0, 138.4, 138.7, 157.4, 169.5 ppm. HRMS (ESI): calcd. for $C_{21}H_{22}BrN_3NaO_3$ [M + Na]$^+$ 466.0737; found 466.0732. HPLC (Chiralpak AS-H, hexane/2-propanol = 98:2, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 8.78 (minor, major isomer), 10.01 (major, minor isomer), 11.40 (minor, minor isomer), 13.00 min (major, major isomer).

(*R*)-4-Bromo-4-[(*R*)-1-(3-methoxyphenyl)-2-nitroethyl]-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3l): Yellow solid, >99% yield, m.p. 103–105 °C, $[\alpha]_D^{20}$ = +85.2 (*c* = 0.5, $CHCl_3$), 88:12 *dr*, 98% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 3.60 (s, 3 H), 4.12 (dd, *J* = 6.8, 7.6 Hz, 1 H), 5.43–5.45 (m, 2 H), 6.70 (s, 1 H_{arom}), 6.76–6.82 (m, 2 H_{arom}), 7.16 (t, *J* = 8.0 Hz, 1 H_{arom}), 7.24 (t, *J* = 6.4 Hz, 1 H_{arom}), 7.40 (t, *J* = 8.0 Hz, 2 H_{arom}), 7.72 ppm (d, *J* = 8.4 Hz, 1 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.7 (major isomer), 15.8 (minor isomer), 47.8 (minor isomer), 49.0 (major isomer), 55.1, 56.4, 75.9, 113.0, 115.4, 119.2, 120.0, 126.1, 129.0, 130.6, 133.6, 136.9, 156.9, 160.2, 168.9 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}BrN_3NaO_4$ [M + Na]$^+$ 454.0373; found 454.0374. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 13.48 (minor, major isomer), 16.56 (major, major isomer), 21.13 (major, minor isomer), 22.60 min (minor, minor isomer).

(*R*)-4-Bromo-4-[(*R*)-1-(4-methoxyphenyl)-2-nitroethyl]-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3m): Yellow solid, 91% yield, m.p. 63–64 °C, $[\alpha]_D^{20}$ = +123.2 (*c* = 0.5, $CHCl_3$), 88:12 *dr*, 98% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17 (s, 0.36 H), 2.23 (s, 2.64 H), 3.72 (s, 2.64 H), 3.74 (s, 0.36 H), 4.09 (dd, *J* = 4.8, 10.0 Hz, 0.88 H), 4.26 (dd, *J* = 3.6, 11.6 Hz, 0.12 H), 5.00 (dd, *J* = 11.6, 13.2 Hz, 0.12 H), 5.39–5.50 (m, 1.88 H), 6.76 (d, *J* = 8.4 Hz, 1.76 H_{arom}), 6.82 (d, *J* = 8.4 Hz, 0.24 H_{arom}), 7.12 (d, *J* = 8.8 Hz, 2 H_{arom}), 7.24 (t, *J* = 7.6 Hz, 1 H_{arom}), 7.40 (t, *J* = 7.6 Hz, 2 H_{arom}), 7.66 (d, *J* = 8.4 Hz, 0.24 H), 7.72 ppm (d, *J* = 8.4 Hz, 1.76 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.6 (major isomer), 15.9 (minor isomer), 47.4 (minor isomer), 48.1 (major isomer), 55.2, 56.4, 76.0 (major isomer), 76.2 (minor isomer), 114.5 (minor isomer), 114.9 (major isomer), 119.1 (minor isomer), 119.2 (major isomer), 123.5 (minor isomer), 123.7 (major isomer), 126.0 (minor isomer), 126.1 (major isomer), 128.9 (minor isomer), 129.0 (major isomer), 129.1 (major isomer), 129.9 (minor isomer), 136.8 (minor isomer), 136.9 (major isomer), 156.9, 160.3, 168.8 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}BrN_3NaO_4$ [M + Na]$^+$ 454.0373; found 454.0378. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 14.02 (major, major isomer), 17.34 (minor, major isomer), 25.12 (minor, minor isomer), 27.48 min (major, minor isomer).

(*R*)-4-Bromo-3-methyl-4-[(*R*)-1-(naphthalen-1-yl)-2-nitroethyl]-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3n): Yellow solid, >99% yield, m.p. 57–58 °C, $[\alpha]_D^{20}$ = +190.0 (*c* = 1.0, $CHCl_3$), 82:18 *dr*, >99% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (s, 0.54 H), 1.91 (s, 2.46 H), 5.15 (dd, *J* = 10.4, 12.8 Hz, 0.18 H), 5.23 (dd, *J* = 3.2, 10.8 Hz, 0.82 H), 5.28 (s, 0.18 H), 5.54 (dd, *J* = 10.4, 14.0 Hz, 0.82 H), 5.69 (dd, *J* = 3.2, 14.0 Hz, 0.82 H), 5.81 (dd, *J* = 3.2, 13.2 Hz, 0.18 H), 7.23–7.28 (m, 2 H_{arom}), 7.33 (t, *J* = 8.0 Hz, 0.54 H_{arom}), 7.41 (t, *J* = 8.0 Hz, 2.46 H_{arom}), 7.52 (t, *J* = 8.0 Hz, 1 H_{arom}), 7.64 (t, *J* = 8.4 Hz, 1 H_{arom}), 7.69–7.77 (m, 3 H_{arom}), 7.83 (d, *J* = 8.0 Hz, 1 H_{arom}), 8.14 (d, *J* = 8.8 Hz, 0.18 H_{arom}), 8.25 ppm (d, *J* = 8.8 Hz, 0.82 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.7 (major isomer), 15.4 (minor isomer), 40.1 (minor isomer), 42.0 (major isomer), 56.9 (major isomer), 58.4 (minor isomer), 76.8, 119.0 (minor isomer), 119.2 (major isomer), 122.3 (minor isomer), 122.4 (major isomer), 124.0 (major isomer), 124.9 (minor isomer), 125.4 (major isomer), 125.9 (minor isomer), 126.2 (major isomer), 126.4 (major isomer), 12126.5 (minor isomer), 127.3 (major isomer), 127.5 (minor isomer), 128.9 (minor isomer), 129.0 (major isomer), 129.4, 129.6, 130.3, 131.1 (major isomer), 132.0 (minor isomer), 133.8 (minor isomer), 134.1 (major isomer), 136.8 (minor isomer), 136.9 (major isomer), 156.4 (minor isomer), 156.9 (major isomer), 168.5 (minor isomer), 169.0 ppm (major isomer). HRMS (ESI): calcd. for $C_{22}H_{18}BrN_3NaO_3$ [M + Na]$^+$ 474.0424; found 474.0421. HPLC (Chiralpak AS-H, hexane/2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 11.21 (minor, major isomer), 14.56 (major, minor isomer), 16.72 min (major, major isomer).

(*R*)-4-Bromo-4-[(*R*)-1-(furan-2-yl)-2-nitroethyl]-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (3o): Brown oil, 89% yield, m.p. 38–40 °C, $[\alpha]_D^{20}$ = +57.4 (*c* = 1.0, $CHCl_3$), 80:20 *dr*, 99% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 0.60 H), 2.23 (s, 2.40 H), 4.29 (d, *J* = 10.8 Hz, 0.80 H), 4.44 (d, *J* = 10.8 Hz, 0.20 H), 5.06 (t, *J* = 12.4 Hz, 0.20 H), 5.27–5.41 (m, 1.80 H), 6.18–6.28 (m, 2 H_{arom}), 7.16 (t, *J* = 7.2 Hz, 1 H_{arom}), 7.19 (s, 1 H_{arom}), 7.33 (t, *J* = 7.2 Hz, 2 H_{arom}), 7.66 ppm (d, *J* = 7.2 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.2 (major isomer), 15.0 (minor isomer), 41.8 (minor isomer), 42.4 (major isomer), 54.5 (major isomer), 55.8 (minor isomer), 73.8 (major isomer), 74.2 (minor isomer), 109.9 (major isomer), 111.0 (major isomer), 111.2 (minor isomer), 111.5 (minor isomer), 119.0 (minor isomer), 119.1 (major isomer), 126.0, 128.9, 136.8 (minor isomer), 136.9 (major isomer), 143.5 (minor isomer), 143.7 (major isomer), 145.0 (minor isomer), 145.5 (major isomer), 156.2 (minor isomer), 156.6 (major isomer), 168.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}BrN_3NaO_4$ [M + Na]$^+$ 414.0060; found 414.0058. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 18.04 (minor, major isomer), 23.93 (major, minor isomer), 25.77 (major, major isomer), 33.78 min (minor, minor isomer).

(*R*)-4-Bromo-4-[(*R*)-2-nitro-1-(thiophen-2-yl)ethyl]-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (3p): Brown solid, 82% yield, m.p. 38–40 °C, $[\alpha]_D^{20}$ = +87.6 (*c* = 1.0, $CHCl_3$), 97:3 *dr*, >99% *ee*. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 4.47 (t, *J* = 7.2 Hz, 1 H), 5.46 (d, *J* = 7.2 Hz, 2 H), 6.88 (t, *J* = 3.6 Hz, 1 H_{arom}), 6.98 (d, *J* = 3.6 Hz, 1 H_{arom}), 7.21 (d, *J* = 5.2 Hz, 1 H_{arom}), 7.25 (t, *J* = 7.6 Hz, 1 H_{arom}), 7.41 (t, *J* = 7.6 Hz, 2 H_{arom}), 7.75 ppm (d, *J* = 8.4 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.5, 43.7, 55.5, 76.7, 119.1, 126.1, 127.0, 127.5, 127.8, 129.0, 133.1, 136.9, 156.6, 168.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{14}BrN_3NaO_3S$ [M + Na]$^+$ 429.9831; found 429.9830. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 13.52 (minor, major isomer), 15.59 (major, major isomer), 28.32 (major, minor isomer), 29.84 min (minor, minor isomer).

(*R*)-4-Bromo-3-methyl-4-[(*R*)-1-nitrobutan-2-yl]-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3q): Pale yellow oil, 86% yield, $[\alpha]_D^{20}$ = –45.6 (*c* =

0.5, $CHCl_3$), 70:30 *dr*, 95% *ee*. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93–1.00 (m, 3 H), 1.36–1.74 (m, 2 H), 2.27 (s, 0.90 H), 2.34 (s, 2.10 H), 3.02 (br. s, 0.70 H), 3.11 (br. s, 0.30 H), 4.46 (dd, J = 7.6, 13.6 Hz, 0.30 H), 4.75 (dd, J = 7.6, 14.8 Hz, 0.70 H), 4.82 (d, J = 13.6 Hz, 0.30 H), 5.37 (d, J = 14.8 Hz, 0.70 H), 7.24 (t, J = 8.0 Hz, 1 H_{arom}), 7.42 (t, J = 7.6 Hz, 2 H_{arom}), 7.84 ppm (d, J = 8.0 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 10.9 (major isomer), 11.5 (minor isomer), 13.3 (major isomer), 14.9 (minor isomer), 22.7 (major isomer), 22.8 (minor isomer), 42.7 (major isomer), 43.0 (minor isomer), 57.5 (major isomer), 58.3 (minor isomer), 75.2 (major isomer), 76.0 (minor isomer), 118.8 (major isomer), 118.9 (minor isomer), 125.9, 129.0, 137.1, 156.3 (minor isomer), 157.4 (major isomer), 168.6 (minor isomer), 168.7 ppm (major isomer). HRMS (ESI): calcd. for $C_{14}H_{16}BrN_3NaO_3$ $[M + Na]^+$ 376.0267; found 376.0266. HPLC (Chiralpak AS-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 8.94 (minor, major isomer), 11.48 (major, major isomer), 13.37 (major, minor isomer), 15.71 min (minor, minor isomer).

(*R*)-4-Bromo-3-methyl-4-[(*R*)-4-methyl-1-nitropentan-2-yl]-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3r): Pale yellow oil, 90% yield, $[\alpha]_D^{20}$ = –42.0 (c = 0.5, $CHCl_3$), 62:38 *dr*, 98% *ee*. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87–0.94 (m, 6 H), 1.26–1.56 (m, 3 H), 2.28 (s, 1.14 H), 2.33 (s, 1.86 H), 3.16 (br. s, 0.62 H), 3.24 (br. s, 0.38 H), 4.40 (dd, J = 6.4, 13.6 Hz, 0.38 H), 4.53 (dd, J = 5.6, 15.2 Hz, 0.62 H), 4.80 (dd, J = 4.4, 13.6 Hz, 0.37 H), 5.48 (dd, J = 3.6, 15.2 Hz, 0.60 H), 7.24 (t, J = 7.2 Hz, 1 H_{arom}), 7.43 (t, J = 7.6 Hz, 2 H_{arom}), 7.86 ppm (d, J = 7.6 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.2 (major isomer), 14.8 (minor isomer), 21.1 (minor isomer), 21.2 (major isomer), 23.4 (minor isomer), 23.7 (major isomer), 25.5 (major isomer), 25.9 (minor isomer), 38.7 (minor isomer), 39.0 (major isomer), 39.1 (major isomer), 39.5 (minor isomer), 57.5 (major isomer), 58.5 (minor isomer), 75.9 (major isomer), 76.7 (minor isomer), 118.8 (major isomer), 118.9 (minor isomer), 125.9, 129.0, 137.1, 156.2 (minor isomer), 157.3 (major isomer), 168.6 ppm. HRMS (ESI): calcd. for $C_{16}H_{20}BrN_3NaO_3$ $[M + Na]^+$ 404.0580; found 404.0586. HPLC (Chiralpak AS-H, hexane/2-propanol = 90:10, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 5.67 (minor, major isomer), 6.47 (major, major isomer), 7.44 min (inseparable minor isomer).

(*R*)-4-Bromo-3-trifluoromethyl-4-[(*R*)-2-nitro-1-phenylethyl]-1-phenyl-1*H*-pyrazol-5(4*H*)-one (3s): Pale yellow oil, 87% yield, $[\alpha]_D^{20}$ = +18.0 (c = 0.5, $CHCl_3$), 99:1 *dr*, 92% *ee*. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.46 (dd, J = 6.4, 8.4 Hz, 1 H), 5.45 (s, 1 H), 5.46 (d, J = 2.0 Hz, 1 H), 7.22 (d, J = 7.2 Hz, 2 H_{arom}), 7.30 (t, J = 7.2 Hz, 3 H_{arom}), 7.44 (t, J = 8.0 Hz, 3 H_{arom}), 7.59 ppm (d, J = 8.4 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 48.3, 51.0, 75.0, 119.8, 127.5, 127.9, 129.3, 129.6, 130.1, 131.4, 135.7, 168.0 ppm. HRMS (ESI): calcd. for $C_{23}H_{18}BrN_3NaO_3$ $[M + Na]^+$ 486.0424; found 486.0417. HPLC (Chiralpak AS-H, hexane/2-propanol = 80:20, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 6.08 (minor, major isomer), 7.63 (major, major isomer), 9.39 min (inseparable minor isomer).

(*R*)-4-Bromo-4-[(*R*)-2-nitro-1-phenylethyl]-1,3-diphenyl-1*H*-pyrazol-5(4*H*)-one (3t): Yellow solid, >99% yield, m.p. 55–57 °C, $[\alpha]_D^{20}$ = +102.4 (c = 0.5, $CHCl_3$), 98:2 *dr*, 99% *ee* for major isomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.56 (dd, J = 4.8, 10.0 Hz, 1 H), 5.54–5.65 (m, 2 H), 6.81 (d, J = 7.6 Hz, 2 H_{arom}), 7.05 (t, J = 7.6 Hz, 2 H_{arom}), 7.16 (t, J = 7.6 Hz, 1 H_{arom}), 7.27 (t, J = 7.6 Hz, 1 H_{arom}), 7.44 (t, J = 7.6 Hz, 2 H_{arom}), 7.49–7.56 (m, 3 H_{arom}), 7.78 (d, J = 8.0 Hz, 2 H_{arom}), 7.96 ppm (d, J = 7.2 Hz, 2 H_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 48.8, 53.9, 75.4, 119.5, 126.4, 126.9, 128.2, 128.9, 129.0, 129.3, 131.3, 131.4, 136.8, 154.7, 169.2 ppm. HRMS (ESI): calcd. for $C_{23}H_{18}BrN_3NaO_3$ $[M + Na]^+$ 486.0424; found 486.0417. HPLC (Chiralpak AD-H, hexane/2-propanol = 95:5, flow rate = 1.0 mL min^{-1}, λ = 254 nm): t_R = 12.26 (minor, major isomer), 15.06 (major, major isomer), 19.86 (minor, minor isomer), 21.88 min (major, minor isomer).

Supporting Information (see footnote on the first page of this article): Copies of the NMR and HRMS spectra as well as chiral HPLC traces for the prepared optically active pyrazol-5-ones.

Acknowledgments

The authors are grateful to the National Natural Science Foundation of China (NSFC) (grant numbers 20972070, 21121002), the National Basic Research Program of China (973 program, grant number 2010CB833300), the Program for New Century Excellent Talents in University (grant number NCET-11-0265), and the Key Laboratory of Elemento-Organic Chemistry for generous financial support of our programs.

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Received: March 29, 2013
Published Online: ■

