JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

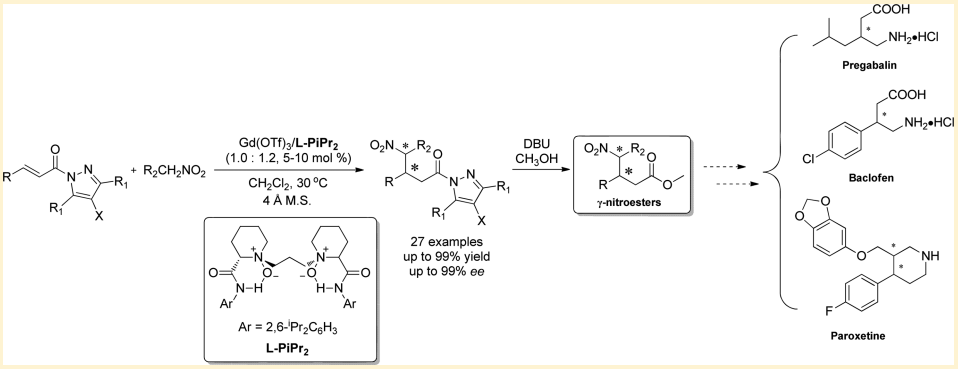
N,N′-Dioxide/Gadolinium(III)-Catalyzed Asymmetric Conjugate Addition of Nitroalkanes to α,β-Unsaturated Pyrazolamides

Qian Yao,[†] Zhen Wang,[†] Yuheng Zhang,[†] Xiaohua Liu,[†] Lili Lin,[†] and Xiaoming Feng*[,†,‡]

[†]Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China

[‡]Collaborative Innovation Center of Chemical Science and Engineering, Tianjin 300072, People's Republic of China

Supporting Information



ABSTRACT: A highly efficient *N,N′*-dioxide/Gd(III) complex has been developed for the enantioselective conjugate addition of nitroalkanes to α,β-unsaturated pyrazolamides. Under mild reaction conditions, a series of γ-nitropyrazolamides were obtained in good to excellent yields (up to 99%) with excellent enantioselectivities (up to 99% ee). What's more, the optically active products could be easily transformed into γ-nitroesters which were key intermediates for the preparation of paroxetine, pregabalin and boclofen.

INTRODUCTION

The asymmetric conjugate additions are powerful and efficient methods for the construction of carbon−carbon bonds.[1] Among them, the conjugate addition of nitroalkanes to α,β-unsaturated carbonyl compounds attracts widespread attention since the obtained γ-nitrocarbonyl componds are very useful intermediates in organic synthesis.[2] On the other hand, optically pure γ-nitroesters are very important precursors in asymmetric synthesis because they can be easily transformed into valuable structural motifs, such as γ-aminobutyric acids (**GABAs**), 2-piperidones, and 2-pyrrolidones (Figure 1).[3] In particular, some γ-aminobutyric acids and their derivatives have emerged as inhibitory active pharmaceuticals in the nervous system and have been used for clinical treatment.[4] For instance, 3-(aminomethyl)-5-methylhexanoic acid, commercially named pregabalin, has found widespread use for treatment of central nervous system disorders, and 4-amino-3-(4-chlorophenyl)-butanoic acid, also named baclofen, possesses therapeutically valuable abilities. As a result, continuous efforts have been devoted to the synthesis of optically pure γ-nitroesters. Theoretically, one of the most efficient routes to obtain chiral γ-nitroesters is the Michael addition of nitroalkanes to conjugate esters. Cobb's group has shown an enantioselective intramolecular Michael addition of nitronates to conjugated esters.[5] However, the enantioselective intermolecular addition of nitroalkanes to simple α,β-unsaturated esters has never been reported for the inherent lower reactivity and imposed challenge to coordinate/activate these substrates with a suitable chiral catalyst.[6] Therefore, some other methods were developed. Jørgensen's group developed a one-pot asymmetric amino catalyzed addition between nitroalkanes and α,β-unsaturated aldehydes followed by an oxidative esterification using NBS as the oxidant.[7] Deng's group provided a conjugate addition of malonates and α-ketoesters to nitroalkenes.[8] In 2002, Kanemasa reported a Michael addition of nitromethane to α,β-unsaturated pyrazolamides by a catalytic double-activation method using chiral Lewis acid and achiral amine catalysts.[9] We envisaged that the γ-nitropyrazolamides, which function as not only a good directing group but also a better leaving group, might be a good means to form γ-nitroesters. In addition, *N,N′*-dioxide/metal complexes, developed by our group, have been used to catalyze a number of enantioselective reactions, and they were also proven to be efficient for the enantioselective conjugate addition of nitroalkanes with chalcone and its derivatives.[10] Herein, we developed a *N,N′*-dioxide/Gd(III) complex for the asymmetric conjugate addition of nitroalkanes to α,β-unsaturated pyrazolamides to

Received: March 23, 2015
Published: April 29, 2015

DOI: 10.1021/acs.joc.5b00649
J. Org. Chem. 2015, 80, 5704−5712

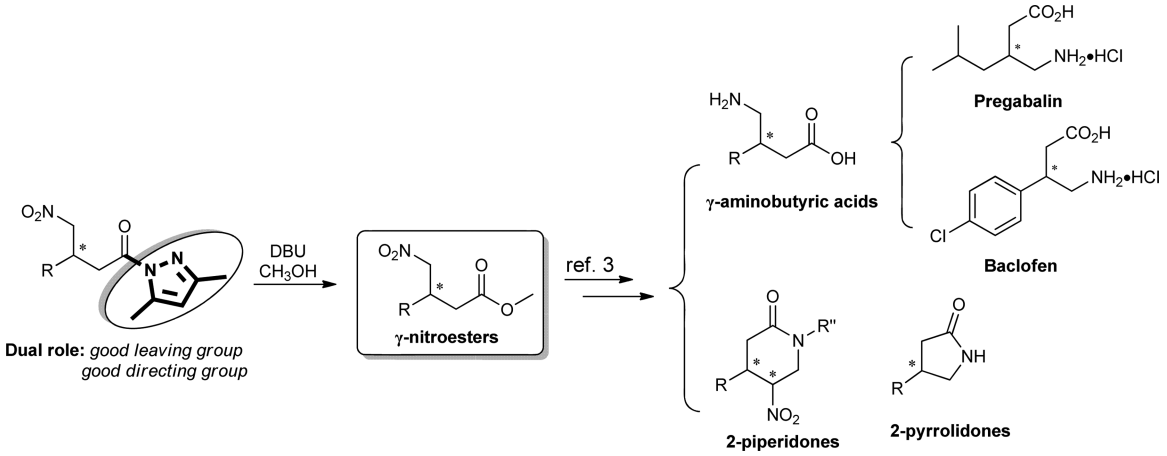


Figure 1. Transformation of γ-nitropyrazolamides to γ-nitroesters and then their derivatives.

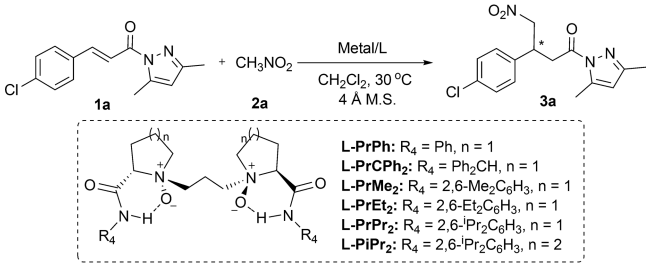
synthesize the γ-nitropyrazolamides, and then the pyrazole moiety of the products was displaced by methoxyl to form γ-nitroesters following the transformation to 2-piperidones, 2-pyrrolidones, and γ-aminobutyric acids.

RESULTS AND DISCUSSION

Our investigation began with the reaction of 3,5-dimethyl-1-[3-(4-chlorophenyl)propanonyl]pyrazole (**1a**) with nitromethane as the model reaction to optimize the reaction conditions. Initially, by using $Sc(OTf)_3$ as the metal salt, a screening of the chiral ligands was carried out. It revealed that the amide moiety of the ligand affected the reaction greatly. The amide moiety of the ligands with less steric hindered amide subunits, such as aniline, 1,1-diphenylmethylamine, or 2,6-dimethylaniline, only a trace amount of product was detected (Table 1, entry 1−3). Increasing the steric hindrance of the amide moieties to 2,6-diethylaniline could promote the reaction in 9% yield with 99% ee value (Table 1, entry 4). Moreover, the *N*,*N*′-dioxide **L-PrPr$_2$** bearing more steric hindered 2,6-diisopropylaniline raised the yield to 30% without affecting the ee value (Table 1, entry 5). To our delight, other lanthanide metal salts, such as $Er(OTf)_3$, $Ho(OTf)_3$, $Yb(OTf)_3$, $Y(OTf)_3$, and $Gd(OTf)_3$, gave much higher yields (73−93%) with excellent ee values (97−99% ee) (Table 1, entries 6−10), and the complex of $Gd(OTf)_3$ gave the highest yield and 97% ee. Excitingly, when L-proline-derived **L-PrPr$_2$** was changed to *S*-pipecolic acid derived **L-PiPr$_2$**, a quantitative yield (99%) was obtained with the ee maintained (98% ee) (Table 1, entry 11). The ratio of **L-PiPr$_2$** and $Gd(OTf)_3$ also affected the reactivity greatly. A small excess of **L-PiPr$_2$** to $Gd(OTf)_3$ increased the reactivity (Table 1, entry 11). An equal amount or small excess of $Gd(OTf)_3$ to **L-PiPr$_2$** led to a sharp drop in reactivity (Table 1, entries 12 and 13). By reducing the amount of catalyst loading to 7.5 mol % and the nitromethane to 9.3 equiv, the yield could be maintained by extending the reaction time from 2 days to 3 days (Table 1, entry 14).

Under the optimized reaction conditions, a series of 3,5-dimethyl-1-(3-arylpropanonyl)pyrazoles (**1a−n**) were examined. The phenyl rings bearing both electron-withdrawing and electron-donating groups could produce the versatile 3,5-dimethyl-1-(3-arylpropanonyl)pyrazoles in high to excellent yields (83%−99%) with excellent ee values (97%−99%) (Table 2, entries 3−12). Additionally, the 4-chloro- and 4-fluoro-substituted products **3a** and **3b** (Table 2, entries 1 and 2), which could be transformed to baclofen and paroxetine, also

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	metal	yield[b](%)	ee[c] (%)
1	**L-PrPh**	$Sc(OTf)_3$	trace	n.d.
2	**L-PrCPh$_2$**	$Sc(OTf)_3$	trace	n.d.
3	**L-PrMe$_2$**	$Sc(OTf)_3$	trace	n.d.
4	**L-PrEt$_2$**	$Sc(OTf)_3$	9	99
5	**L-PrPr$_2$**	$Sc(OTf)_3$	30	99
6	**L-PrPr$_2$**	$Er(OTf)_3$	87	98
7	**L-PrPr$_2$**	$Ho(OTf)_3$	74	97
8	**L-PrPr$_2$**	$Yb(OTf)_3$	91	98
9	**L-PrPr$_2$**	$Y(OTf)_3$	73	98
10	**L-PrPr$_2$**	$Gd(OTf)_3$	93	97
11	**L-PiPr$_2$**	$Gd(OTf)_3$	99	98
12[d]	**L-PiPr$_2$**	$Gd(OTf)_3$	25	97
13[e]	**L-PiPr$_2$**	$Gd(OTf)_3$	11	81
14[f]	**L-PiPr$_2$**	**$Gd(OTf)_3$**	**98**	**98**

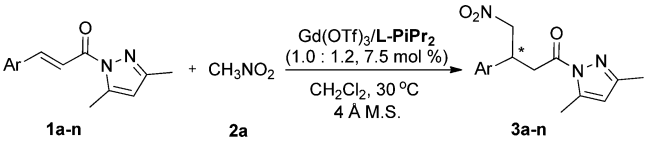
[a]Unless otherwise noted, the reactions were carried out with the ligand **L** (12 mol %), metal (10 mol %), 4 Å MS (30 mg), **1a** (0.1 mmol) and **2a** (0.3 mL, 5.6 mmol) in CH_2Cl_2 (0.4 mL) at 30 °C for 2 days. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Change of the ratio of $Gd(OTf)_3$/**L-PiPr$_2$** to 1:1. [e]Change of the ratio of $Gd(OTf)_3$/**L-PiPr$_2$** to 1.25:1. [f]The reaction was carried out with the ligand **L-PiPr$_2$** (9 mol %), metal (7.5 mol %), 4 Å MS (30 mg), **1a** (0.1 mmol), and **2a** (50 μL, 0.93 mmol) in CH_2Cl_2 (0.4 mL) at 30 °C for 3 days.

obtained perfect results (**3a**: 98% yield with 98% ee; **3b**: 99% yield with 99% ee). Heterocyclo substituents, 2-furyl and 2-thienyl, also gave excellent ee values (97% ee and 98% ee respectively) albeit with a moderate yields (56% and 58%, respectively).

Encouraged by the results obtained from the aryl-substituted α,β-unsaturated pyrazolamides, 3-alkyl-, 3-ethoxyl-, and 3-carbethoxy-substituted propanonylpyrazoles were explored under the same conditions (Scheme 1). Gratifyingly, not only the linear but also the branched 3-alkyl substituents could be

DOI: 10.1021/acs.joc.5b00649
J. Org. Chem. 2015, 80, 5704−5712

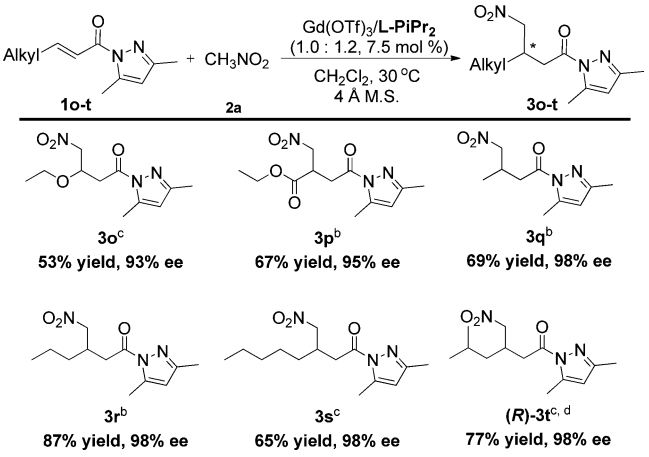
Table 2. Substrate Scope for the 3, 5-Dimethyl-1-(3-arylpropanonyl)pyrazole Derivatives[a]



entry	Ar	yield[b] (%)	ee[d] (%)
1	4-ClC_6H_4 (**3a**)	98	98 (*S*)[e]
2	4-FC_6H_4 (**3b**)	99	99 (*S*)[e]
3	C_6H_5 (**3c**)	99	99
4	4-BrC_6H_4 (**3d**)	96	98
5	4-MeC_6H_4 (**3e**)	95	99
6	4-$MeOC_6H_4$ (**3f**)	89	99
7	3-BrC_6H_4 (**3g**)	98	98
8	3-MeC_6H_4 (**3h**)	96	99
9	2-BrC_6H_4 (**3i**)	99	99
10	2-$MeOC_6H_4$ (**3j**)	99	99
11	3,4-$Cl_2C_6H_3$ (**3k**)	96	99
12	3,4-$(MeO)_2C_6H_3$ (**3l**)	83	99
13	2-furyl (**3m**)	56	97
14	2-thienyl (**3n**)	58	98

[a]Unless otherwise noted, reactions were carried out with **L-PiPr$_2$** (9 mol %), $Gd(OTf)_3$ (7.5 mol %), 4 Å MS (30 mg), **1** (0.1 mmol), and **2a** (50 μL, 0.93 mmol) in CH_2Cl_2 (0.4 mL) at 30 °C for 3 days. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis. [e]The absolute configuration of **3a** and **3b** were determined by the corresponding esters **5a** and **5b**.

Scheme 1. Substrate Scope for the 3,5-Dimethyl-1-(3-alkylpropanonyl)pyrazole Derivatives[a]

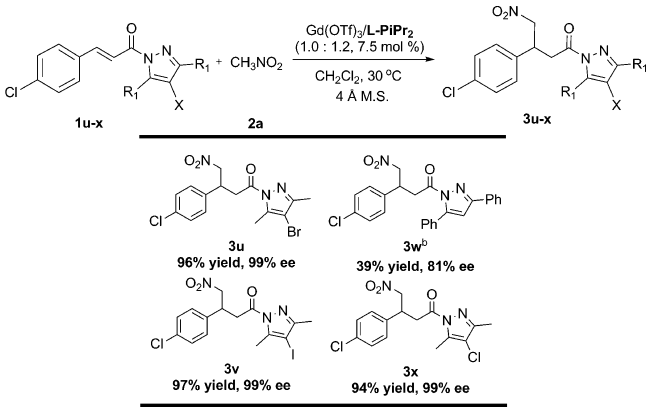


[a]The *Z*/*E* ratios of **1q** (1/3), **1s** (1/10), and **1t** (1/12) were detected by ^{1}H NMR analysis. [b]The reactions were carried out with **L-PiPr$_2$** (9 mol %), $Gd(OTf)_3$ (7.5 mol %), 4 Å MS (30 mg), **1** (0.1 mmol), and **2a** (50 μL, 0.93 mmol) in CH_2Cl_2 (0.4 mL) at 30 °C for 3 days. [c]The reactions were carried out with **L-PiPr$_2$** (12 mol %), $Gd(OTf)_3$ (10 mol %), 4 Å MS (for **1o**, **1s**: 60 mg; for **1t**: 100 mg), **1** (0.1 mmol), and **2a** (50 μL, 0.93 mmol) in CH_2Cl_2 (0.4 mL) at 30 °C for 3 days. [d]The configuration was determined by compound **6c**.

compatible, providing the products in moderate to good yields (65−87%) with 98% ee. Notably, 3-isobutylpropanonylpyrazole **1t** was further transformed to pregabalin in 77% yield with 98% ee. Ethoxyl-substituted **1o** and 3-carbethoxy-substituted **3p** could also afford the corresponding products in moderate yields with 93% ee and 95% ee, respectively.

Further investigation was focused on the substituent effect on the pyrazole (Scheme 2). More sterically hindered 3,5-

Scheme 2. Substrate Scope for the 1-[3-(4-Chlorophenyl)propanonyl]pyrazole Derivatives[a]

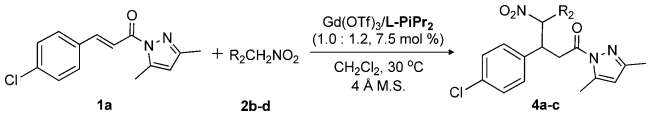


[a]Unless otherwise noted, reactions were carried out with **L-PiPr$_2$** (9 mol %), $Gd(OTf)_3$ (7.5 mol %), 4 Å M. S. (30 mg), **1** (0.1 mmol), and **2a** (50 μL, 0.93 mmol) in CH_2Cl_2 (0.4 mL) at 30 °C for 3 days. [b]The catalyst loading was 10 mol %.

diphenylpyrazole decreased the yield and ee value sharply (39%, 81% ee). Halo atom (F, Cl, Br) substituents at the 4-position of 3,5-dimethylpyrazole had little influence on the yields (94−97%) and ee values (99% ee).

To further expand the scope of the reaction, several nitroalkanes were tested (Table 3). Nitroethane, nitropropane,

Table 3. Substrate Scope for the Nitroalkanes[a]



entry	R_2	yield[b] (%)	ee[c] (%)	dr[d]
1	CH_3 (**4a**)	94	98/98	1.6/1
2	C_2H_5 (**4b**)	87	99/98	1.2/1
3	$C_6H_5CH_2$ (**4c**)	98	99/98	1.1/1

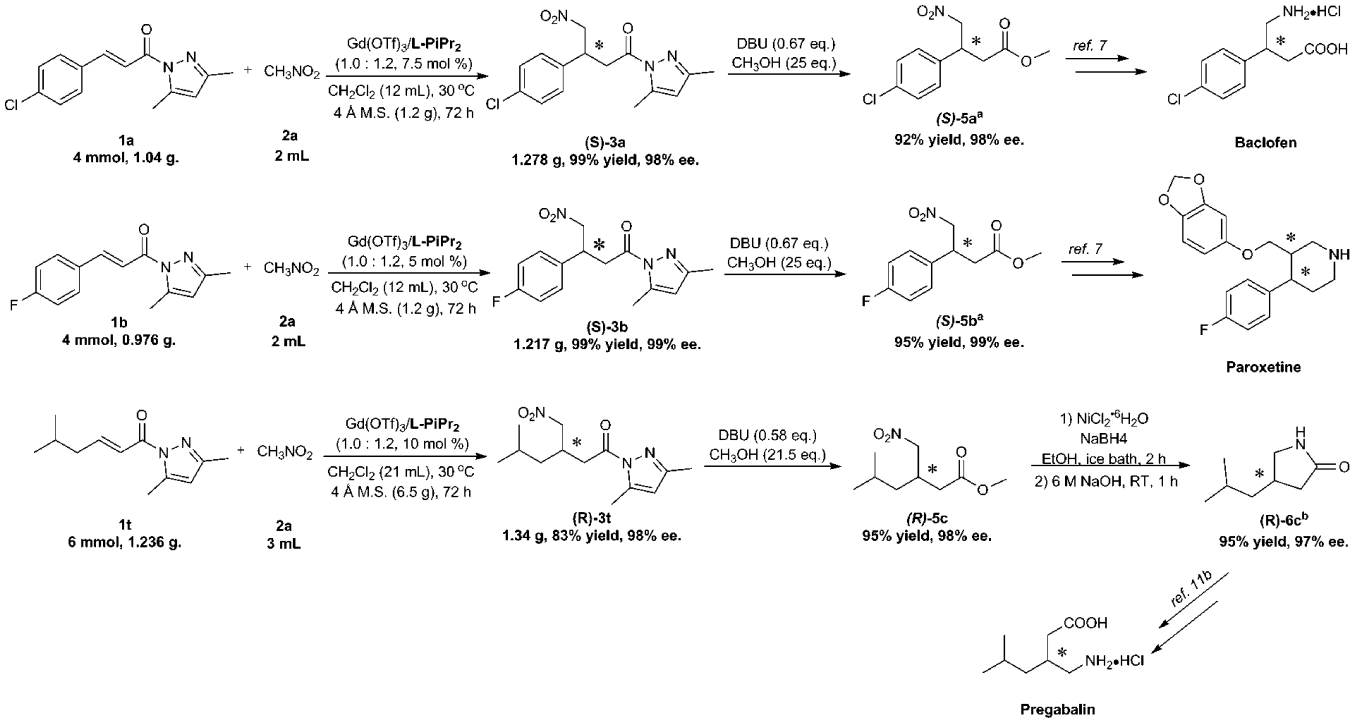
[a]Unless otherwise noted, reactions were carried out with **L-PiPr$_2$** (9 mol %), $Gd(OTf)_3$ (7.5 mol %), 4 Å MS (30 mg), **1a** (0.1 mmol), and **2** (0.93 mmol) in CH_2Cl_2 (0.4 mL) at 30 °C for 3 days. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Determined by ^{1}H NMR analysis.

and 2-phenylnitroethane could promote the reaction in high to excellent yields and excellent enantioselectivities. Despite the low diastereomeric ratio, the diastereomers could be isolated by silica gel chromatography.

To show the synthetic potential of this strategy, the products **3a**, **3b**, and **3t** were carried out on large scale (Scheme 3). Under the slightly modified conditions, 4 mmol of **1a**, 4 mmol of **1b**, and 6 mmol of **1t** reacted smoothly with 9.3 equiv of nitromethane to provide the gram-scaled **3a**, **3b**, and **3t** without any loss of yield or enantiomeric excesses. Furthermore, the 3,5-dimethylpyrazole moiety could be easily displaced by methanol in the presence of DBU to form γ-nitroesters (Scheme 3). Then, the obtained ester **5a** and **5b** could be transformed into the hydrochloride salts of baclofen and paroxetine, respectively, according to ref 7, and a reductive

DOI: 10.1021/acs.joc.5b00649
J. Org. Chem. 2015, 80, 5704−5712

Scheme 3



[a]The configuration was determined by HPLC analysis according to ref 7. [b]The configuration was determined by HPLC analysis according to ref 11b.

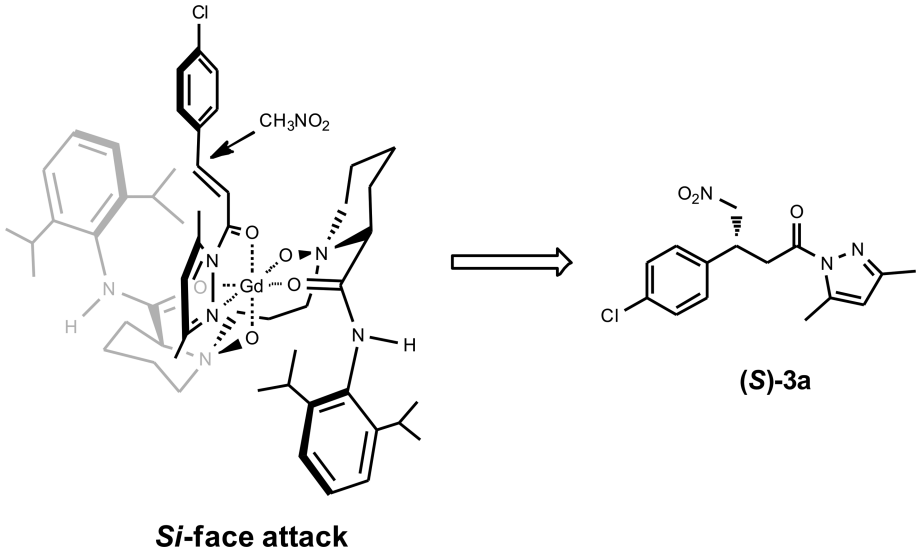


Figure 2. Proposed transition model.

cyclization of the 3-isobutyl-substituted product **5c** could be easily achieved by hydrogenation using $NiCl_2/NaBH_4$ to afford the 2-pyrrolidone **6c** in 95% yield. The lactam **6c** could then be hydrolyzed using 6 M HCl to afford the hydrochloride salt of pregabalin according to ref 11b, which is a therapeutically important GABA receptor agonist.[11] In addition, the products **6c** also provide access to 2-pyrrolidones which are key intermediates for the preparation of pharmaceutically important drug candidates.[12]

On the basis of our previous work[10e,h] and the absolute configuration of the product **3a**, a possible transition model was proposed to explain the high selectivities. As shown in Figure 2, the *N*-oxides and amide oxygens of **L-PiPr$_2$** coordinated to Gd^{III} in a tetradentate manner to form six-membered chelate rings. Meanwhile, pyrazolamide **3a** coordinated with the metal in a bidentate manner. The *Re* face of pyrazolamide **1a** was shielded by the neighboring 2,6-diisopropylphenyl group of the ligand **L-PiPr$_2$**, and the nucleophile attacked from the *Si* face predominantly to give the *S*-configured product **3a**.

CONCLUSION

In conclusion, we have developed an *N*,*N*′-dioxide/Gd(III) complex to catalyze the highly enantioselective conjugate addition of nitroalkanes to *α*,*β*-unsaturated pyrazolamides, synthesizing the *γ*-nitropyrazolamides in good to excellent yields with excellent enantioselectivities. The system displayed

DOI: 10.1021/acs.joc.5b00649
J. Org. Chem. 2015, 80, 5704−5712

great tolerance toward a number of aromatic as well as aliphatic substrates. What's more, the products could be easily transformed to γ-nitroesters, which were used for the preparation of paroxetine, pregabalin, and boclofen.

EXPERIMENTAL SECTION

General Remarks. ^{1}H NMR spectra were recorded on commercial instruments (400 MHz). Chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constants (Hz), integration. ^{13}C NMR data were collected on commercial instruments (100 MHz) with complete proton decoupling. The enantiomeric excesses were determined by HPLC analysis on chiral DAICEL CHIRALPAK IB, CHIRALPAK IC, CHIRALPAK IE, or CHIRALPAK ADH columns at 210 or 254 nm. HRMS was recorded on a commercial apparatus (ESI Source). Optical rotations are measured on a commerical polarimeter and are reported as follows: $[\alpha]_D^T$ (c = g/100 mL, CH_2Cl_2). MS (4 Å) was powdered <50 μm, which was activated at 450 °C for 3 h and stored under nitrogen. Solvents were dried according to standard procedures. Nitroalkanes were obtained from commercial sources and used with further purification (by distilled, except 2-phenylnitroethane by column chromatographic separation on silica gel). Racemic samples were prepared with 10 mol % of DBU as the catalyst under rt condition. All reactions were performed in sealed oven-dried glass tubes under an atmosphere of nitrogen unless otherwise noted.

General Procedure for the Preparation of α,β-Unsaturated Pyrazolamides 1. Method 1: Under an atmosphere of nitrogen, a CH_2Cl_2 (5 mL) solution of thionyl chloride (13 mmol) was added dropwise to a mixture of pyrazole (10 mmol), carboxylic acid (13 mmol), and Et_3N (40 mmol) in CH_2Cl_2 (25 mL) at 0 °C. After being continuously stirred for overnight at rt, the reaction was quenched with water. The organic layer was washed successively with dilute HCl, aq NaOH, and aq NaCl, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatographic separation on silica gel (ethyl acetate/petroleum ether 1:20−1:4) to afford the desired product.

Method 2: A CH_2Cl_2 (5 mL) solution of pyzaole (10 mmol) was added dropwise to a mixture of carboxylic acid (12 mmol), DMAP (1 mmol), and DCC (12 mmol) in CH_2Cl_2 (25 mL) at rt. After being continuously stirred for 5 h, the reaction was filtered and concentrated in vacuo. The crude product was purified by column chromatographic separation on silica gel (ethyl acetate/petroleum ether 1:20−1:4) to afford the desired product.

General Procedure for the Catalytic Asymmetric Conjugate Addition Reactions. A dry reaction tube was charged with **L-PiPr$_2$** and **Gd(OTf)$_3$** (1.2/1, 7.5 mol %, unless otherwise noted), pyrazolamides **1** (0.1 mmol), and 4 Å MS (30 mg, unless otherwise noted), and then CH_2Cl_2 (0.3 mL) and nitroalkanes (0.93 mmol) were added sequentially, followed by the addition of CH_2Cl_2 (0.1 mL), and the mixture was allowed to stir at 30 °C for 3 days. The reaction mixture was purified by column chromatographic separation on silica gel (ethyl acetate/petroleum ether 1/20−1/4) to afford the desired product. The enantiomeric excess (ee) was determined by high-performance liquid chromatography (HPLC) with Chiralcel IC or Chiralcel IE. The *anti/syn* ratio was determined by ^{1}H NMR spectroscopy analysis.

General Procedure for the Transformations. *(1). 3,5-Dimethylpyrazole Moiety Displaced by Methanol in One-Pot Reaction (**5a** and **5b**).* After the catalytic asymmtric conjugate additions were reacted for 3 days, DBU (10 ul, 0.67 equiv) and CH_3OH (100 ul, 25 equiv) were added to the reaction mixture sequentially, and the mixture was allowed to stir at 30 °C for overnight. The reaction mixture was purified by column chromatographic separation on silica gel (ethyl acetate/petroleum ether 1:20−1:4) to afford the desired product.

*Methyl 3-(4-Chlorophenyl)-4-nitrobutanoate (**5a**)[7] (Scheme 3).* $C_{11}H_{12}ClNO_4$, colorless oil (23.6 mg), 92% isolated yield with 98% ee. $[\alpha]_D^{20}$ = −13.20 (c = 0.46 in CH_2Cl_2). HPLC (chiral IB column), *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 210 nm, t_R (major) = 16.79 min, t_R (minor) = 14.76 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.27 (m, 2H), 7.22−7.11 (m, 2H), 4.72 (dd, J = 12.8, 6.8, 1H), 4.61 (dd, J = 12.4, 8.0, 1H), 4.03−3.90 (m, 1H), 3.63 (s, 3H), 2.80−2.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 136.8, 134.0, 129.4, 128.8, 79.2, 52.2, 39.6, 37.4.

*Methyl 3-(4-Fluorophenyl)-4-nitrobutanoate (**5b**)[7] (Scheme 3).* $C_{11}H_{12}FNO_4$, colorless oil (22.9 mg), 95% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −20.78 (c = 0.45 in CH_2Cl_2). HPLC (chiral IC column), *n*-hexane/*i*-PrOH = 95/5, flow rate 0.8 mL/min, λ = 210 nm, t_R (major) = 26.89 min, t_R (minor) = 25.03 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25−7.14 (m, 2H), 7.07−6.96 (m, 2H), 4.72 (dd, J = 12.4, 6.8, 1H), 4.60 (dd, J = 12.4, 8.0, 1H), 4.05−3.88 (m, 1H), 3.62 (s, 3H), 2.80−2.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 163.6, 161.2, 134.1, 134.1, 129.1, 129.1, 116.2, 116.0, 79.4, 52.1, 39.6, 37.6.

*(2). 3,5-Dimethylpyrazole Moiety Displaced by Methoxyl in Multistep Reaction (**5c**).* A dry reaction tube was charged with **3t** (46.2 mg, 0.173 mmol), CH_2Cl_2 (0.3 mL), CH_3OH (150 μL, 21.5 equiv), and DBU (15 μL, 0.58 equiv) were added sequentially, followed by the addition of CH_2Cl_2 (0.2 mL), and the mixture was stirred at room temperature for 5 h. The reaction mixture was purified by column chromatographic separation on silica gel (ethyl acetate/petroleum ether 1:9) to afford the desired product **5c** in 95% yield and 98% ee.

*Methyl 3-Isobutyl-4-nitrobutanoate (**5c**)[11i] (Scheme 3).* $C_9H_{17}NO_4$, colorless oil (19.3 mg), 95% isolated yield with 98% ee. $[\alpha]_D^{20}$ = −9.24 (c = 0.66 in CH_2Cl_2). HPLC (chiral IE column), *n*-hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 210 nm, t_R (major) = 7.79 min, t_R (minor) = 9.12 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.53−4.38 (m, 2H), 3.68 (s, 3H), 2.73−2.59 (m, 1H), 2.43 (d, J = 6.4, 2H), 1.67−1.60 (m, 1H), 1.25 (dd, J = 14.0, 7.6, 2H), 0.91 (dd, J = 7.6, 6.4, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 78.8, 77.4, 51.9, 40.6, 35.9, 32.2, 25.2, 22.6, 22.4.

*(3). (R)-4-Isobutylpyrrolidin-2-one (**6c**).* To a solution of **5c** (68.82 mg, 0.339 mmol) and $NiCl_2{\cdot}6H_2O$ (80.6 mg, 0.339 mmol) in EtOH (2.0 mL) was added $NaBH_4$ (140.9 mg, 3.73 mmol) at 4 °C. The reaction was stirred at 4 °C for 2 h before it was diluted with EtOH (1.0 mL). A solution of 6 M NaOH (1 mL) was added, and the mixture was stirred for 1 h at rt before it was quenched with 2 M HCl. The solution was extracted with CH_2Cl_2 (4 × 6 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to afford the lactam **6c**. **4-Isobutylpyrrolidin-2-one (6c)**[11b] (Scheme 3): $C_8H_{15}NO$, colorless oil (13.4 mg), 95% isolated yield with 97% ee. $[\alpha]_D^{20}$ = +1.19 (c = 0.50 in CH_2Cl_2). HPLC (chiral ADH column), *n*-hexane/*i*-PrOH = 96/4, flow rate 1.0 mL/min, λ = 210 nm, t_R (major) = 16.79 min, t_R (minor) = 14.76 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 1H), 3.45 (t, J = 8.8, 1H), 2.96 (dd, J = 9.6, 7.2, 1H), 2.56−2.45 (m, 1H), 2.38 (dd, J = 16.4, 8.4, 1H), 1.95 (dd, J = 16.8, 8.4, 1H), 1.59−1.47 (m, 1H), 1.35−1.28 (m, 2H), 0.87 (dd, J = 6.8, 4.4, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9, 48.5, 43.9, 37.2, 33.0, 26.2, 22.8, 22.6.

3,5-Dimethyl-1-[4-nitro-3-(4-chlorophenyl)butanoyl]-pyrazole (3a) (Table 2, Entry 1). $C_{15}H_{16}ClN_3O_3$, white solid (31.6 mg) in 98% isolated yield with 98% ee. $[\alpha]_D^{20}$ = −61.32 (c = 0.49 in CH_2Cl_2). HPLC (chiral IE column), *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 12.90 min, t_R (minor) = 9.14 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (dd, J = 24.8, 8.4, 4H), 5.88 (s, 1H), 4.71 (dd, J = 12.8, 6.8, 1H), 4.57 (dd, J = 12.4, 8.4, 1H), 4.18−4.00 (m, 1H), 3.56 (dd, J = 17.6, 7.6, 1H), 3.41 (dd, J = 17.6, 7.2, 1H), 2.40 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 152.8, 144.4, 137.4, 133.9, 129.3, 129.1, 111.7, 79.5, 39.2, 38.6, 14.5, 13. 9. HRMS (ESI-TOF): calcd for $C_{15}H_{17}{}^{35}ClN_3O_3^+$ ([M + H]$^+$) 322.0958, found 322.0957; for $C_{15}H_{17}{}^{37}ClN_3O_3^+$ ([M + H]$^+$) 324.0929, found 323.9940.

3,5-Dimethyl-1-[4-nitro-3-(4-fluorophenyl)butanoyl]-pyrazole (3b) (Table 2, Entry 2). $C_{15}H_{16}FN_3O_3$, white solid (30.3 mg) in 99% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −58.37 (c = 0.51 in CH_2Cl_2). HPLC (chiral IE column), *n*-hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 10.35 min, t_R (minor) = 8.52 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (dd, J = 8.0, 5.6, 2H),

DOI: 10.1021/acs.joc.5b00649
J. Org. Chem. 2015, 80, 5704−5712

7.02 (t, J = 8.4, 2H), 5.95 (s, 1H), 4.78 (dd, J = 12.4, 6.4, 1H), 4.64 (dd, J = 12.4, 8.8, 1H), 4.25−4.10 (m, 1H), 3.63 (dd, J = 17.6, 7.2, 1H), 3.48 (dd, J = 17.2, 6.8, 1H), 2.47 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 163.6, 161.1, 152.7, 144.4, 134.6, 134.6, 129.4, 129.3, 116.2, 116.0, 111.7, 79.7, 39.1, 38.7, 14.5, 13.9. HRMS (ESI-TOF): calcd for $C_{15}H_{17}FN_3O_3^+$ ([M + H]$^+$) 306.1248, found 306.1246.

3,5-Dimethyl-1-(4-nitro-3-phenyl)butanoyl)pyrazole (3c)[9] (Table 2, Entry 3). $C_{15}H_{17}N_3O_3$,white solid (28.5 mg) in 99% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −57.98 (c = 0.53 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 10.60 min, t_R (minor) = 9.19 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.26 (m, 5H), 5.96 (s, 1H), 4.81 (dd, J = 12.8, 6.8, 1H), 4.69 (dd, J = 12.4, 8.0, 1H), 4.27−4.12 (m, 1H), 3.68 (dd, J = 17.6, 6.8, 1H), 3.53 (dd, J = 17.6, 7.2, 1H), 2.49 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 152.6, 144.3, 138.9, 129.1, 128.0, 127.7, 111.6, 79.7, 39.8, 38.7, 14.5, 13.9.

3,5-Dimethyl-1-[4-nitro-3-(4-bromophenyl)butanoyl]-pyrazole (3d) (Table 2, Entry 4). $C_{15}H_{16}BrN_3O_3$, white solid (35.1 mg) in 96% isolated yield with 98% ee. $[\alpha]_D^{20}$ = −57.56 (c = 0.51 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 14.47 min, t_R (minor) = 9.92 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.4, 2H), 7.19 (d, J = 8.4, 2H), 5.95 (s, 1H), 4.78 (dd, J = 12.8, 6.4, 1H), 4.64 (dd, J = 12.8, 8.4, 1H), 4.23−4.07 (m, 1H), 3.64 (dd, J = 18.0, 7.6, 1H), 3.47 (dd, J = 17.6, 7.2, 1H), 2.47 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 152.8, 144.4, 137.9, 132.3, 129.5, 122.0, 111.7, 79.4, 39.2, 38.5, 14.5, 13.9. HRMS (ESI-TOF): calcd for $C_{15}H_{16}{}^{79}BrN_3NaO_3^+$ ([M + Na]$^+$) 388.0273, found 388.0255; for $C_{15}H_{16}{}^{81}BrN_3NaO_3^+$ ([M + Na]$^+$) 390.0252, found 390.0258.

3,5-Dimethyl-1-[4-nitro-3-(4-methylphenyl)butanoyl]-pyrazole (3e) (Table 2, Entry 5). $C_{16}H_{19}N_3O_3$, white solid (28.7 mg), 95% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −59.77 (c = 0.53 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 10.68 min, t_R (minor) = 9.56 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (dd, J = 21.2, 8.0, 4H), 5.94 (s, 1H), 4.77 (dd, J = 12.4, 6.8, 1H), 4.65 (dd, J = 12.4, 8.4, 1H), 4.22−4.08 (m, 1H), 3.65 (dd, J = 17.2, 6.8, 1H), 3.49 (dd, J = 17.6, 7.2, 1H), 2.48 (s, 3H), 2.31 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 152.5, 144.3, 137.7, 135.9, 129.8, 127.5, 111.5, 79.9, 39.4, 38.7, 21.2, 14.5, 13.9. HRMS (ESI-TOF): calcd for $C_{16}H_{20}N_3O_3^+$ ([M + H]$^+$) 302.1499, found 302.1505.

3,5-Dimethyl-1-[4-nitro-3-(4-methoxyphenyl)butanoyl]-pyrazole (3f) (Table 2, Entry 6). $C_{16}H_{19}N_3O_4$, white solid (28.3 mg), 89% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −60.51 (c = 0.39 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 17.35 min, t_R (minor) = 14.56 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, J = 8.4, 2H), 6.86 (d, J = 8.4, 2H), 5.94 (s, 1H), 4.76 (dd, J = 12.4, 6.8, 1H), 4.63 (dd, J = 12.4, 8.4, 1H), 4.21−3.05 (m, 1H), 3.78 (s, 3H), 3.63 (dd, J = 17.2, 7.2, 1H), 3.47 (dd, J = 17.6, 7.2, 1H), 2.48 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 159.2, 152.6, 144.3, 130.8, 128.8, 114.5, 111.5, 80.0, 55.4, 39.1, 38.8, 14.6, 13.9. HRMS (ESI-TOF): calcd for $C_{16}H_{20}N_3O_4^+$ ([M + H]$^+$) 318.1448, found 318.1454.

3,5-Dimethyl-1-[4-nitro-3-(3-bromophenyl)butanoyl]-pyrazole (3g) (Table 2, Entry 7). $C_{15}H_{16}BrN_3O_3$, white solid (35.8 mg), 98% isolated yield with 98% ee. $[\alpha]_D^{20}$ = −50.14 (c = 0.72 in CH_2Cl_2). HPLC (chiral IC column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 9.92 min, t_R (minor) = 8.45 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.26 (m, 2H), 7.22−7.08 (m, 2H), 5.88 (s, 1H), 4.72 (dd, J = 12.8, 6.4, 1H), 4.58 (dd, J = 12.8, 8.4, 1H), 4.18−3.94 (m, 1H), 3.56 (dd, J = 17.6, 7.2, 1H), 3.41 (dd, J = 18.0, 7.6, 1H), 2.41 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 152.8, 144.4, 141.2, 131.2, 130.8, 130.7, 126.5, 123.1, 111.7, 79.3, 39.4, 38.5, 14.5, 13.9. HRMS (ESI-TOF): calcd for $C_{15}H_{16}{}^{79}BrN_3NaO_3^+$ ([M + Na]$^+$) 388.0273, found 388.0274; for $C_{15}H_{16}{}^{81}BrN_3NaO_3^+$ ([M + Na]$^+$) 390.0252, found 390.0233.

3,5-Dimethyl-1-[4-nitro-3-(3-methylphenyl)butanoyl]-pyrazole (3h) (Table 2, Entry 8). $C_{16}H_{19}N_3O_3$, white solid (28.9 mg), 96% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −62.89 (c = 0.58 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 8.35 min, t_R (minor) = 7.79 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (t, J = 7.6, 1H), 7.17−6.91 (m, 3H), 5.95 (s, 1H), 4.78 (dd, J = 12.4, 6.8, 1H), 4.66 (dd, J = 12.4, 8.4, 1H), 4.21−4.05 (m, 1H), 3.65 (dd, J = 17.6, 6.8, 1H), 3.49 (dd, J = 17.2, 7.2, 1H), 2.48 (s, 3H), 2.33 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 152.6, 144.3, 138.8, 138.8, 129.0, 128.8, 128.4, 124.6, 111.5, 79.8, 39.7, 38.7, 21.6, 14.5, 13.9. HRMS (ESI-TOF): calcd for $C_{16}H_{20}N_3O_3^+$ ([M + H]$^+$) 302.1499, found 302.1497.

3,5-Dimethyl-1-[4-nitro-3-(2-bromophenyl)butanoyl]-pyrazole (3i) (Table 2, Entry 9). $C_{15}H_{16}BrN_3O_3$ white solid (36.3 mg) 99% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −58.29 (c = 0.72 in CH_2Cl_2). HPLC (chiral IC column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 8.81 min, t_R (minor) = 7.56 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.0, 1H), 7.41−7.21 (m, 2H), 7.20−6.93 (m, 1H), 5.96 (s, 1H), 4.82 (d, J = 6.8, 2H), 4.73−4.53 (m, 1H), 3.77−3.53 (m, 2H), 2.49 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 152.7, 144.4, 137.7, 133.8, 129.4, 128.1, 124.7, 111.6, 77.8, 38.5, 37.4, 14.5, 13.9. HRMS (ESI-TOF): calcd for $C_{15}H_{17}{}^{79}BrN_3O_3^+$ ([M + H]$^+$) 366.0453, found 366.0453; for $C_{15}H_{17}{}^{81}BrN_3O_3^+$ ([M + H]$^+$) 368.0433, found 368.0439.

3,5-Dimethyl-1-[4-nitro-3-(2-methoxyphenyl)butanoyl]-pyrazole (3j) (Table 2, Entry 10). $C_{16}H_{19}N_3O_4$, white solid (31.4 mg), 99% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −30.76 (c = 0.63 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 11.00 min, t_R (minor) = 10.45 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (dd, J = 13.6, 7.2, 2H), 7.01−6.73 (m, 2H), 5.94 (s, 1H), 4.95−4.73 (m, 2H), 4.46−4.26 (m, 1H), 3.86 (s, 3H), 3.73 (dd, J = 17.6, 6.8, 1H), 3.60 (dd, J = 18.0, 7.6, 1H), 2.48 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 157.4, 152.3, 144.3, 129.6, 129.1, 126.5, 120.9, 111.4, 111.1, 78.0, 55.5, 36.9, 36.3, 14.6, 13.9. HRMS (ESI-TOF): calcd for $C_{16}H_{20}N_3O_4^+$ ([M + H]$^+$) 318.1448, found 318.1458.

3,5-Dimethyl-1-[4-nitro-3-(3,4-dichlorophenyl)butanoyl]-pyrazole (3k) (Table 2, Entry 11). $C_{15}H_{15}Cl_2N_3O_3$, white solid (34.1 mg), 96% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −59.65 (c = 0.68 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 9.90 min, t_R (minor) = 9.35 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 8.0, 2H), 7.16 (dd, J = 8.4, 1.6, 1H), 5.96 (s, 1H), 4.78 (dd, J = 12.8, 6.4, 1H), 4.64 (dd, J = 12.8, 8.8, 1H), 4.26−4.04 (m, 1H), 3.63 (dd, J = 18.0, 7.6, 1H), 3.47 (dd, J = 17.6, 6.8, 1H), 2.48 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 152.9, 144.4, 139.1, 133.2, 132.3, 131.1, 129.8, 127.2, 111.8, 79.1, 77.5, 77.2, 76.8, 39.0, 38.4, 14.5, 13.9. HRMS (ESI-TOF): calcd for $C_{15}H_{15}{}^{35}Cl_2N_3NaO_3^+$ ([M + Na]$^+$) 378.0388, found 378.0388; for $C_{15}H_{15}{}^{37}Cl_2N_3NaO_3^+$ ([M + Na]$^+$) 380.0359, found 380.0357.

3,5-Dimethyl-1-[4-nitro-3-(3,4-dimethoxyphenyl)butanoyl]-pyrazole (3l) (Table 2, Entry 12). $C_{17}H_{21}N_3O_5$, white solid (28.8 mg), 83% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −63.97 (c = 0.58 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 29.00 min, t_R (minor) = 27.78 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (dd, J = 14.4, 8.4, 3H), 5.94 (s, 1H), 4.76 (dd, J = 12.4, 6.8, 1H), 4.64 (dd, J = 12.4, 8.4, 1H), 4.19−4.07 (m, 1H), 3.85 (d, J = 9.2, 6H), 3.68 (dd, J = 17.6, 7.6, 1H), 3.44 (dd, J = 17.6, 7.2, 1H), 2.47 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 152.6, 149.2, 148.7, 144.3, 131.2, 119.6, 111.6, 111.5, 110.9, 80.0, 56.0, 56.0, 39.5, 38.6, 14.5, 13.9. HRMS (ESI-TOF): calcd for $C_{17}H_{22}N_3O_5^+$ ([M + H] $^+$) 348.1554, found 348.1557.

3,5-Dimethyl-1-[3-(2-furyl)-4-nitrobutanoyl)]pyrazole (3m)[9] (Table 2, entry 13). $C_{13}H_{15}N_3O_4$, colorless oil (15.5 mg), 56% isolated yield with 97% ee. $[\alpha]_D^{20}$ = −38.78 (c = 0.31 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 11.04 min, t_R (minor) = 9.80 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 1.2, 1H), 6.29 (dd, J = 3.2, 2.0, 1H), 6.21 (d, J = 3.6, 1H), 5.97 (s, 1H), 4.77 (d, J = 7.2, 2H), 4.33−424 (m, 1H), 3.68 (dd, J = 18.0, 6.8, 1H), 3.52 (dd, J = 18.0, 7.2,

DOI: 10.1021/acs.joc.5b00649
J. Org. Chem. 2015, 80, 5704−5712

1H), 2.51 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 152.8, 151.7, 144.4, 142.5, 111.7, 110.6, 107.4, 77.3, 36.4, 33.6, 14.6, 13.9.

3,5-Dimethyl-1-[3-(2-thienyl)-4-nitrobutanoyl)]pyrazole (3n)[9] (Table 2, Entry 14). $C_{13}H_{15}N_3O_3S$, colorless oil (17.0 mg), 58% isolated yield with 98% ee. $[\alpha]_D^{20} = -62.50$ (c = 0.34 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 9.19 min, t_R (minor) = 10.60 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (dd, J = 4.8, 0.8, 1H), 7.03−6.97 (m, 1H), 6.94 (dd, J = 4.8, 3.6, 1H), 5.96 (s, 1H), 4.81 (dd, J = 12.8, 6.4, 1H), 4.69 (dd, J = 12.8, 8.0, 1H), 4.56−4.44 (m, 1H), 3.71 (dd, J = 17.6, 6.8, 1H), 3.56 (dd, J = 17.6, 6.8, 1H), 2.50 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 152.8, 144.4, 141.6, 127.2, 125.7, 124.9, 111.7, 80.0, 39.6, 35.2, 14.6, 13.9.

3,5-Dimethyl-1-(3-ethoxy-4-nitrobutanoyl)pyrazole (3o) (Scheme 1). $C_{11}H_{17}N_3O_4$, colorless oil (13.6 mg), 53% isolated yield with 93% ee. $[\alpha]_D^{20} = -28.87$ (c = 0.14 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 7.58 min, t_R (minor) = 6.12 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 (s, 1H), 4.67−4.51 (m, 3H), 3.75−3.65 (m, 1H), 3.61−3.50 (m, 2H), 3.35−3.20 (m, 1H), 2.52 (d, J = 0.8, 3H), 2.22 (s, 3H), 1.13 (t, J = 7.2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 152.7, 144.3, 111.7, 78.6, 72.8, 66.2, 37.8, 15.3, 14.5, 13.9. HRMS (ESI-TOF): calcd for $C_{11}H_{17}N_3NaO_4^+$ ([M + Na] $^+$) 278.1111, found 278.1116.

3,5-Dimethyl-1-(3-carboxylate-4-nitrobutanoyl)pyrazole (3p)[9] (Scheme 1). $C_{12}H_{17}N_3O_5$, colorless oil (19.0 mg), 67% isolated yield with 95% ee. $[\alpha]_D^{20} = +12.57$ (c = 0.38 in CH_2Cl_2). HPLC (chiral IC column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 18.00 min, t_R (minor) = 20.25 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.98 (s, 1H), 4.87 (dd, J = 14.4, 6.8, 1H), 4.71 (dd, J = 14.4, 5.2, 1H), 4.28−4.16 (m, 2H), 3.76−3.65 (m, J = 23.5, 15.1, 5.6, 2H), 3.55−3.45 (m, 1H), 2.51 (s, 3H), 2.22 (s, 3H), 1.25 (t, J = 6.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.740, 153.0, 144.4, 111.7, 74.7, 62.0, 38.8, 34.5, 14.5, 14.1, 13.9.

3,5-Dimethyl-1-(3-methyl-4-nitrobutanoyl)pyrazole (3q)[9] (Scheme 1). $C_{10}H_{15}N_3O_3$, colorless oil (15.5 mg), 69% isolated yield with 98% ee. $[\alpha]_D^{20} = +8.65$ (c = 0.31 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 9.19 min, t_R (minor) = 8.76 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 (s, 1H), 4.55 (dd, J = 12.0, 6.0, 1H), 4.38 (dd, J = 12.4, 7.6, 1H), 3.31−3.11 (m, 2H), 3.04−2.88 (m, 1H), 2.53 (s, 3H), 2.22 (s, 3H), 1.16 (d, J = 6.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 152.5, 144.3, 111.6, 80.5, 38.9, 29.1, 17.7, 14.6, 13.9.

3,5-Dimethyl-1-(4-nitro-3-propylbutanoyl)pyrazole (3r)[9] (Scheme 1). $C_{12}H_{19}N_3O_3$, colorless oil (22.0 mg), 87% isolated yield with 98% ee. $[\alpha]_D^{20} = -9.55$ (c = 0.44 in CH_2Cl_2). HPLC (chiral IC column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 7.16 min, t_R (minor) = 6.38 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.96 (s, 1H), 4.56 (dd, J = 12.4, 6.4, 1H), 4.48 (dd, J = 12.0, 6.4, 1H), 3.37−3.13 (m, 2H), 2.93−2.77 (m, 1H), 2.53 (s, 3H), 2.22 (s, 3H), 1.54−1.35 (m, 4H), 0.93 (t, J = 7.2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 152.5, 144.3, 111.5, 78.8, 36.8, 33.9, 33.6, 19.8, 14.6, 14.0, 13.9.

3,5-Dimethyl-1-(4-nitro-3-pentylbutanoyl)pyrazole (3s) (Scheme 1). $C_{14}H_{23}N_3O_3$, colorless oil (18.3 mg), 65% isolated yield with 98% ee. $[\alpha]_D^{20} = -13.40$ (c = 0.19 in CH_2Cl_2). HPLC (chiral IC column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 6.52 min, t_R (minor) = 5.82 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 (s, 1H), 4.59 (dd, J = 12.0, 9.0, 1H), 4.43 (dd, J = 12.4, 6.4, 1H), 3.36−3.13 (m, 2H), 2.88−2.75 (m, 1H), 2.53 (s, 3H), 2.23 (s, 3H), 1.49 (dd, J = 14.4, 7.2, 2H), 1.43−1.34 (m, 2H), 1.29 (dd, J = 6.4, 3.2, 4H), 0.88 (t, J = 6.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.000, 152.5, 144.3, 111.5, 78.9, 36.8, 33.9, 31.7, 26.3, 22.6, 14.7, 14.1, 13.9. HRMS (ESI-TOF): calcd for $C_{14}H_{23}N_3NaO_3^+$ ([M + Na]$^+$) 304.1632, found 304.1631.

3,5-Dimethyl-1-(3-isobutyl-4-nitrobutanoyl)pyrazole (3t) (Scheme 1). $C_{13}H_{21}N_3O_3$, colorless oil (20.6 mg), 77% isolated yield with 98% ee. $[\alpha]_D^{20} = -11.43$ (c = 0.21 in CH_2Cl_2). HPLC (chiral IC column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 6.66 min, t_R (minor) = 5.74 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.97 (s, 1H), 4.56 (dd, J = 12.4, 6.4, 1H), 4.48 (dd, J = 12.0, 6.0, 1H), 3.34−3.13 (m, 2H), 2.93−2.82 (m, 1H), 2.54 (s, 3H), 2.23 (s, 3H), 1.76−1.67 (m, 1H), 1.41−1.28 (m, 2H), 1.01−0.86 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 152.5, 144.3, 111.5, 79.1, 41.0, 37.0, 31.8, 25.2, 22.8, 22.3, 14.7, 13.9. HRMS (ESI-TOF): calcd for $C_{13}H_{21}N_3NaO_3^+$ ([M + Na]$^+$) 290.1475, found 290.1480.

4-Bromo-3,5-dimethyl-1-[4-nitro-3-(4-chlorophenyl)-butanoyl]pyrazole (3u) (Scheme 2). $C_{15}H_{15}BrClN_3O_3$, white solid (38.4 mg), 96% isolated yield with 99% ee. $[\alpha]_D^{20} = -41.02$ (c = 0.77 in CH_2Cl_2). HPLC (chiral IC column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 9.89 min, t_R (minor) = 9.02 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.4, 2H), 7.23 (d, J = 8.4, 2H), 4.76 (dd, J = 12.8, 6.8, 1H), 4.64 (dd, J = 12.4, 8.0, 1H), 4.22−4.09 (m, 1H), 3.64 (dd, J = 17.6, 7.6, 1H), 3.46 (dd, J = 18.0, 7.2, 1H), 2.49 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 151.4, 141.6, 137.1, 134.0, 129.4, 129.1, 102.9, 79.4, 39.1, 37.9, 13.5, 12.9. HRMS (ESI-TOF): calcd for $C_{15}H_{15}{}^{79}BrClN_3NaO_3^+$ ([M + Na]$^+$) 421.9883, found 421.9882; for $C_{15}H_{15}{}^{81}BrClN_3NaO_3^+$ ([M + Na]$^+$) 423.9863, found 423.9890.

3,5-Dimethyl-4-iodo-1-[4-nitro-3-(4-chlorophenyl)-butanoyl]pyrazole (3v) (Scheme 2). $C_{15}H_{15}ClIN_3O_3$, white solid (43.4 mg), 97% isolated yield of products, 99% ee. $[\alpha]_D^{20} = -29.12$ (c = 0.86 in CH_2Cl_2). HPLC (chiral IC column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 10.50 min, t_R (minor) = 9.61 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 8.0, 2H), 7.23 (d, J = 8.4, 2H), 4.76 (dd, J = 12.4, 6.8, 1H), 4.64 (dd, J = 12.4, 8.0, 1H), 4.22−4.08 (m, 1H), 3.65 (dd, J = 17.6, 7.6, 1H), 3.47 (dd, J = 17.6, 6.8, 1H), 2.53 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 154.0, 145.3, 137.1, 134.0, 129.4, 129.1, 79.4, 73.8, 39.2, 37.9, 15.6, 14.6. HRMS (ESI-TOF): calcd for $C_{15}H_{16}{}^{35}ClIN_3O_3^+$ ([M + H] $^+$) 447.9925, found 447.9918; for $C_{15}H_{16}{}^{37}ClIN_3O_3^+$ ([M + H]$^+$) 449.9895, found 449.9914.

3,5-Diphenyl-1-[4-nitro-3-(4-chlorophenyl)butanoyl]-pyrazole (3w) (Scheme 2). $C_{25}H_{20}ClN_3O_3$, white solid (17.4 mg), 39% isolated yield with 81% ee. $[\alpha]_D^{20} = -44.25$ (c = 0.53 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 19.88 min, t_R (minor) = 12.47 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89−7.71 (m, 2H), 7.48−7.08 (m, 12H), 6.64 (s, 1H), 4.71 (dd, J = 12.4, 6.8, 1H), 4.58 (dd, J = 12.8, 8.4, 1H), 4.17−4.03 (m, 1H), 3.71 (dd, J = 17.6, 7.2, 1H), 3.58 (dd, J = 17.2, 7.2, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 154.2, 147.7, 137.1, 134.0, 131.4, 130.6, 129.6, 129.4, 129.2, 129.0, 129.0, 128.1, 126.4, 110.4, 79.4, 39.3, 38.9. HRMS (ESI-TOF): calcd for $C_{25}H_{20}{}^{35}ClN_3NaO_3^+$ ([M + Na]$^+$) 468.1085, found 468.1092; for $C_{25}H_{20}{}^{37}ClN_3NaO_3^+$ ([M + Na]$^+$) 470.1055, found 470.1085.

4-Chloro-3,5-dimethyl-1-[4-nitro-3-(4-chlorophenyl)-butanoyl]pyrazole (3x) (Scheme 2). $C_{15}H_{15}Cl_2N_3O_3$, white solid (33.4 mg), 94% isolated yield with 99% ee. $[\alpha]_D^{20} = -49.56$ (c = 0.67 in CH_2Cl_2). HPLC (chiral IC column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 9.59 min, t_R (minor) = 8.71 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.27 (m, 2H), 7.26−7.20 (m, 2H), 4.76 (dd, J = 12.8, 6.8, 1H), 4.64 (dd, J = 12.8, 8.4, 1H), 4.22−4.09 (m, 1H), 3.64 (dd, J = 17.6, 7.6, 1H), 3.45 (dd, J = 17.6, 6.8, 1H), 2.47 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 150.2, 139.5, 137.0, 134.0, 129.4, 129.1, 115.3, 79.4, 39.1, 37.9, 12.5, 11.9. HRMS (ESI-TOF): calcd for $C_{15}H_{15}{}^{35}Cl_2N_3NaO_3^+$ ([M + Na] $^+$) 378.0388, found 378.0390; for $C_{15}H_{15}{}^{37}Cl_2N_3NaO_3^+$ ([M + Na] $^+$) 380.0359, found 380.0423.

3,5-Dimethyl-1-[3-(4-chlorophenyl)-4-nitropentanoyl)]-pyrazole (4a) (Table 3, Entry 1). $C_{16}H_{18}ClN_3O_3$, colorless oil (31.5 mg), 94% isolated yield of mixture products. The ratio was determined to be 1.6/1 by ^{1}H NMR analysis of the mixture products. **Major products.** $C_{16}H_{18}ClN_3O_3$, white solid (19.4 mg), 58% isolated yield with 98% ee. $[\alpha]_D^{20} = -82.19$ (c = 0.32 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 11.20 min, t_R (minor) = 7.19 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.27 (m, 2H), 7.24−7.15 (m, 2H), 5.90 (s, 1H), 4.90−4.77 (m, 1H), 3.97−3.87 (m, 1H), 3.78 (dd, J = 17.2, 10.0,

DOI: 10.1021/acs.joc.5b00649
J. Org. Chem. 2015, 80, 5704−5712

1H), 3.31 (dd, J = 17.2, 4.0, 1H), 2.40 (d, J = 0.8, 3H), 2.21 (s, 3H), 1.36 (d, J = 6.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 152.5, 144.2, 136.6, 133.8, 129.9, 129.2, 111.5, 86.7, 45.0, 38.3, 17.7, 14.5, 13.9. **Minor products.** $C_{16}H_{18}ClN_3O_3$, colorless oil (12.1 mg), 36% isolated yield with 98% ee. $[\alpha]_D^{20}$ = −78.21 (c = 0.23 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 10.39 min, t_R (minor) = 8.79 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.23 (m, 3H), 7.22−7.13 (m, 2H), 5.94 (s, 1H), 4.99−4.87 (m, 1H), 3.94−3.85 (m, 1H), 3.66 (dd, J = 17.6, 8.8, 1H), 3.54 (dd, J = 17.6, 5.6, 1H), 2.43 (s, 3H), 2.23 (s, 3H), 1.61 (d, J = 6.4, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 152.6, 144.3, 136.8, 133.8, 129.7, 129.0, 111.6, 86.9, 44.8, 36.9, 17.2, 14.5, 13.9. HRMS (ESI-TOF): calcd for $C_{16}H_{18}{}^{35}ClN_3NaO_3^+$ ([M + Na]$^+$) 358.0934, found 358.0936; for $C_{16}H_{18}{}^{37}ClN_3NaO_3^+$ ([M + Na]$^+$) 360.0905, found 360.0903.

3,5-Dimethyl-1-[3-(4-chlorophenyl)-4-nitrohexanoyl)]-pyrazole (4b) (Table 3, Entry 2). $C_{17}H_{20}ClN_3O_3$, colorless oil (30.4 mg), 87% isolated yield of mixture products. The ratio was determined to be 1.2/1 by ^{1}H NMR analysis of the mixture products. **Major products.** $C_{17}H_{20}ClN_3O_3$, white solid (16.6 mg), 47% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −63.11 (c = 0.33 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 9.62 min, t_R (minor) = 8.11 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.13 (m, 4H), 5.93 (s, 1H), 4.84−4.69 (m, 1H), 3.92−3.83 (m, 1H), 3.67−3.51 (m, 2H), 2.42 (d, J = 0.8, 3H), 2.22 (s, 3H), 2.07−1.90 (m, 2H), 0.99 (t, J = 7.2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 152.6, 144.2, 137.0, 133.7, 129.7, 128.9, 111.5, 93.9, 43.9, 37.5, 24.9, 14.4, 13.9, 10.4. **Minor products.** $C_{17}H_{20}ClN_3O_3$ colorless oil (13.8 mg) 40% isolated yield with 98% ee. $[\alpha]_D^{20}$ = −56.60 (c = 0.29 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 13.74 min, t_R (minor) = 6.65 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.14 (m, 4H), 5.89 (s, 1H), 4.79−4.56 (m, 1H), 4.03−3.72 (m, 2H), 3.26 (dd, J = 16.4, 2.4, 1H), 2.38 (d, J = 0.8, 3H), 2.20 (s, 3H), 1.90−1.75 (m, 1H), 1.60−1.45 (m, 1H), 0.87 (t, J = 7.2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 152.3, 144.1, 137.0, 133.7, 129.8, 129.2, 111.4, 93.9, 44.3, 38.4, 25.5, 14.4, 13.8, 10.3. HRMS (ESI-TOF): calcd for $C_{17}H_{20}{}^{35}ClN_3NaO_3^+$ ([M + Na]$^+$) 372.1091, found 372.1089; for $C_{17}H_{20}{}^{37}ClN_3NaO_3^+$ ([M + Na]$^+$) 374.1061, found 374.1070.

3,5-Dimethyl-1-[3-(4-chlorophenyl)- 4-nitro-5-phenylpentanoyl)]pyrazole (4c) (Table 3, Entry 3). $C_{22}H_{22}ClN_3O_3$ colorless oil (40.3 mg) 98% isolated yield of mixture products. The ratio was determined to be 1.1/1 by ^{1}H NMR analysis of the mixture products. **Major products.** $C_{22}H_{22}ClN_3O_3$, colorless oil (21.1 mg), 51% isolated yield with 99% ee. $[\alpha]_D^{20}$ = −77.39 (c = 0.40 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 6.13 min, t_R (minor) = 5.76 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.18 (m, 7H), 7.04−6.96 (m, 2H), 5.89 (s, 1H), 5.02−4.92 (m, 1H), 4.01−3.95 (m, 1H), 3.84 (dd, J = 17.2, 10.4, 1H), 3.31 (dd, J = 17.2, 3.6, 1H), 3.09 (dd, J = 14.4, 11.2, 1H), 2.80 (dd, J = 14.4, 2.8, 1H), 2.39 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 152.5, 144.2, 136.8, 135.4, 134.0, 129.9, 129.5, 128.9, 128.6, 127.6, 111.5, 94.0, 44.7, 38.4, 38.3, 14.4, 13.9. **Minor products.** $C_{22}H_{22}ClN_3O_3$, colorless oil (19.2 mg), 47% isolated yield with 98% ee. $[\alpha]_D^{20}$ = −6.61 (c = 0.35 in CH_2Cl_2). HPLC (chiral IE column), n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, t_R (major) = 7.27 min, t_R (minor) = 6.60 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.11 (m, 9H), 5.94 (s, 1H), 5.18−5.08 (m, 1H), 3.97 (dd, J = 7.2, J = 14.4, 1H), 3.76−3.63 (m, 2H), 3.28−3.15 (m, 2H), 2.44 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 152.7, 144.3, 136.5, 135.3, 134.0, 129.8, 129.0, 129.0, 128.9, 127.6, 111.7, 93.3, 44.3, 37. 6, 14.5, 13.9. HRMS (ESI-TOF): calcd for $C_{22}H_{22}{}^{35}ClN_3NaO_3^+$ ([M + Na]$^+$) 434.1247, found 434.1248; for $C_{22}H_{22}{}^{37}ClN_3NaO_3^+$ ([M + Na]$^+$) 436.1218, found 436.1219.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra and HPLC data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00649.

■ AUTHOR INFORMATION

Corresponding Author

*Fax: + 86 28 85418249. E-mail: xmfeng@scu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We appreciate the National Natural Science Foundation of China (Nos. 21172151, 21321061, and 21432006) for financial support.

■ REFERENCES

(1) For reviews of conjugate reactions, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992. (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: New York, 1999. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (d) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (e) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (f) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933. (g) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (h) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123.

(2) For some examples on conjugate addition of nitroalkanes to α,β-unsaturated carbonyl compounds, see: (a) Kwiatkowski, P.; Cholewiak, A.; Kasztelan, A. *Org. Lett.* **2014**, *16*, 5930. (b) Rodrigo, E.; Ruano, J. L. G.; Cid, M. B. *J. Org. Chem.* **2013**, *78*, 10737. (c) Quintavalla, A.; Lanza, F.; Montroni, E.; Lombardo, M.; Trombini, C. *J. Org. Chem.* **2013**, *78*, 12049. (d) Jia, Z. X.; Luo, Y. C.; Cheng, X. N.; Xu, P. F.; Gu, Y. C. *J. Org. Chem.* **2013**, *78*, 6488. (e) Lu, R. J.; Yan, Y. Y.; Wang, J. J.; Du, Q. S.; Nie, S. Z.; Yan, M. *J. Org. Chem.* **2011**, *76*, 6230. (f) Vakulya, B.; Varga, S.; Soós, T. *J. Org. Chem.* **2008**, *73*, 3475. (g) Dai, Q. P.; Huang, H. C.; Zhao, J. C-G. *J. Org. Chem.* **2013**, *78*, 4153.

(3) (a) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243. (b) Otera, J. *Esterification: Methods, Reactions and Applications*; Wiley: New York, 2003.

(4) Brenner, M.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 2365.

(5) Nodes, W. J.; Nutt, D. R.; Chippindale, A. M.; Cobb, A. J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16016.

(6) Monge, D.; Jiang, H.; Alvarez-Casao, Y. *Chem.—Eur. J.* **2015**, *21*, 1.

(7) Jensen, K. L.; Poulsen, P. H.; Donslund, B. S.; Morana, F.; Jørgensen, K. A. *Org. Lett.* **2012**, *14*, 1516.

(8) Li, H. M.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906.

(9) (a) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394. (b) Hasegawa, M.; Ono, F.; Kanemasa, S. *Tetrahedron Lett.* **2008**, *49*, 5220.

(10) For reviews on chiral N-oxides in asymmetric catalysis, see: (a) Malkov, A. V.; Kočovský, P. *Curr. Org. Chem.* **2003**, *7*, 1737. (b) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry.* **2004**, *15*, 1373. (c) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29. (d) Feng, X. M.; Liu, X. H. In *Scandium: Compounds, Productions and Applicatons*; Greene, V. A., Ed.; Nova Science: New York, 2011; pp 1−48. (e) Liu, X. H.; Lin, L. L.; Feng, X. M. *Acc. Chem. Res.* **2011**, *44*, 574. (f) Shen, K.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem. Sci.* **2012**, *3*, 327. (g) Liu, X. H.; Lin, L. L.; Feng, X. M. *Org. Chem. Front.* **2014**, *1*, 298. For some examples on Michael additions, see: (h) Wang, Z.; Yao, Q.; Kang, T. F.; Feng, J. H.; Liu, X. H.; Lin, L.

DOI: 10.1021/acs.joc.5b00649
J. Org. Chem. 2015, 80, 5704−5712

L.; Feng, X. M. *Chem. Commun.* **2014**, *50*, 4918. (i) Wang, L. W.; Zhang, Q.; Zhou, X.; Liu, X. H.; Lin, L. L.; Qin, B.; Feng, X. M. *Chem.—Eur. J.* **2010**, *16*, 7696. (j) Wang, Z.; Zhang, Z. L.; Yao, Q.; Liu, X. H.; Cai, Y. F.; Lin, L. L.; Feng, X. M. *Chem.—Eur. J.* **2013**, *19*, 8591. (k) Wang, Z.; Chen, D. H.; Yang, Z. G.; Bai, S.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem.—Eur. J.* **2010**, *16*, 10130.

(11) For recent reviews, see: (a) Chen, Y. S.; Li, X.; Cheng, R. N.; Zhao, S. Y. *Chin. J. Org. Chem.* **2011**, *10*, 1582. (b) Liu, J. M.; Wang, X.; Ge, Z. M.; Sun, Q.; Cheng, T. M.; Li, R. T. *Tetrahedron* **2011**, *67*, 636. (c) Poe, S. L.; Kobaslija, M.; Mc, Q. T. D. *J. Am. Chem. Soc.* **2007**, *129*, 9216. (d) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (e) Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 5820. (f) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (g) Burk, M. J.; De, K. P. D.; Grote, T. M.; Hoekstra, M. S.; Hoge, G.; Jennings, R. A.; Kissel, W. S.; Le, T. V.; Lennon, I. C.; Mulhern, T. A.; Ramsden, J. A.; Wade, R. A. *J. Org. Chem.* **2003**, *68*, 5731. (h) Zhang, G. L.; Yang, X. P.; Liu, B. F. *Chin. J. Pharm.* **2007**, *38*, 617. (i) Wang L. X.; Xu X. Y.; Gang L. X.; Li X. G.; Huang Q. C.; Wang W.; Tian F.; He G. Y. CN 102115449, 2011.

(12) Xu, F.; Corley, E.; Murry, J. A.; Tschaen, D. M. *Org. Lett.* **2007**, *9*, 2669.

DOI: 10.1021/acs.joc.5b00649
J. Org. Chem. 2015, 80, 5704−5712