JOC The Journal of Organic Chemistry

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Development and Application of α-Heteroatom Ketones in Asymmetric Michael Reaction with β-*trans*-Nitroalkenes

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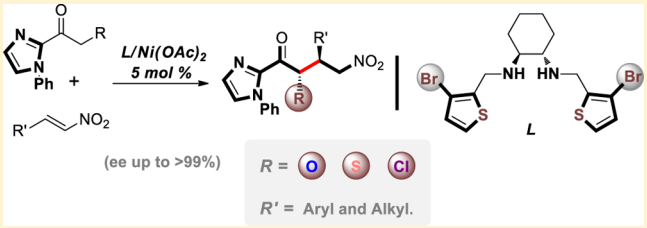
Supporting Information

ABSTRACT: The successful design and application of a new type of *N*-phenyl-imidazole-modified α-heteroatom ketones in asymmetric *anti*-selective Michael reactions with β-*trans*-nitroalkenes is reported. High yields and enantioselectivities could be obtained, and the corresponding conjugate adducts could be further transformed into related chiral esters and cyclopropane derivatives with excellent enantioselectivities.

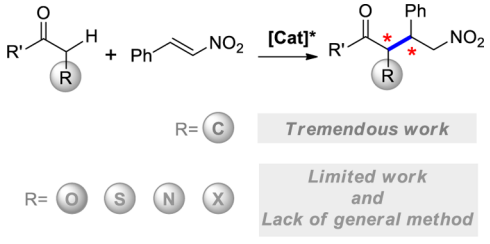


INTRODUCTION

Direct asymmetric α-function of carbonyl compounds with β-*trans*-nitroalkenes has been studied in detail as a classic transformation and fundamental approach in developing novel chiral catalysts and affording useful optical moleculars bearing two typical functional groups. Over the past decade, tremendous methods involving various type of carbonyl compounds have been devoted to realizing the asymmetric C−C bond formation process with β-*trans*-nitroalkenes.[1] It is well-known that aldehydes,[2] ketones,[3] ketoesters,[4] and types of cyclic carbonyl compounds[5] have been reported as powerful nucleophiles in the direct asymmetric conjugate addition with nitroalkenes. However, in comparison with the well-documented studies of α-carbon type nucleophiles, the reaction with the utility of α-heteroatom nucleophiles, especially for simple linear aldehydes[6] and ketones,[7,8] has not been studied as extensively (Scheme 1).

On the basis of our recent work on the application of *N*-phenyl-imidazole-modified ketones in asymmetric Michael reaction with β-nitroalkenes by demonstrating a newly developed 3-bromothiophene-modified chiral diamine ligand,[9] and considering our recent studies on *N*,*O*-bidentate effects on metal-mediated asymmetric reactions,[10] here we report a relatively general method of *N*-phenyl-imidazole-modified α-heteroatom ketones in enantioselective conjugate reaction with β-nitroalkenes.

Scheme 1. Different Types of Nucleophiles in Asymmetric Michael Reactions with β-*trans*-Nitroalkenes



RESULTS AND DISCUSSION

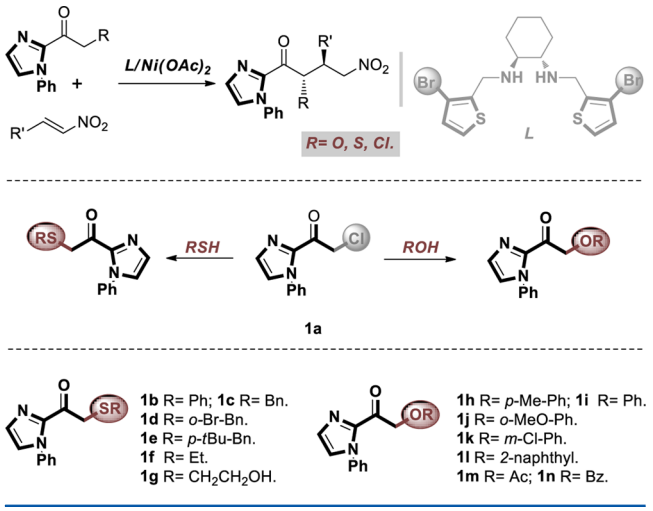
As illustrated in Scheme 2, the imidazole-modified α-heteroatom ketones could be easily prepared by simple substitution reactions of α-chloroketone **1a** with different phenols, acids, thiophenols, and thiols.[11]

Having built the synthetic method of types of imidazole-modified α-heteroatom ketones, we next evaluated the conjugate reaction of ketone **1b** with β-*trans*-nitroalkenes **2a** using the diamine/Ni(OAc)$_2$ catalysts prepared from chiral diamine ligands and Ni(OAc)$_2$ in a 1:1 ratio.[12] As the results show in Table 1, serials of chiral diamine derivatives (Scheme 3) were screened to effect the desired conjugate reaction. A 3-bromothiophene-modified chiral diamine ligand **L7** was proven to be better at introducing highly enantioselectivity as compared to other diamine units (Table 1, entries 1−10). Solvent changing from THF to DCM, *i*PrOH, and dioxane did not give more potential results (Table 1, entries 11−13). Changing the reaction's concentration from 0.2 to 0.05 M would slightly decrease the ee values (Table 1, entries 14 and 15). Further screening process displayed that the reactions carried out under 0 °C could enhance the result and further selection process of additives found the introduction of 4 Å MS into the reaction would improve the ee value to 97% (Table 1, entries 16−21). To our delight, the reaction could also proceed smoothly with 5.0

Received: January 7, 2015
Published: April 8, 2015

DOI: 10.1021/acs.joc.5b00013
J. Org. Chem. 2015, 80, 4336−4348

Scheme 2. Design of Strategies of α-Heteroatom Ketones in Enantioselective Conjugate Reaction with β-*trans*-Nitroalkenes

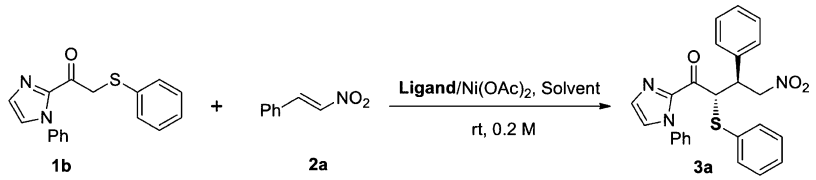


mol % catalyst without decreasing the ee value (Table 1, entry 22).

After the optimized conditions were established as aforementioned, the substrate generality of the *N*-phenylimidazole-modified α-thioketones with an array of β-nitroalkenes was examined. As illustrated in Table 2, a serials of aromatic nitroalkenes were tested in the conjugate reaction, and the corresponding adducts **3a**−**3j** were obtained in good to excellent yields and enantioselectivities (Table 2). For heterocyclic substrates, such as 2-furyl- and 2-thienyl-derived nitroalkenes, the conjugate products were obtained in decreased diastereoselectivities while maintaining a high level of ee values, respectively (Table 2, **3k**,**3l**). Two representative aliphatic β-nitroalkenes were also tried in the conjugate reaction; the desired adducts could be obtained in relatively lower diastereoselectivities (Table 2, **3m**,**3n**). The reaction scope with respect to different types of α-thioketones then was also investigated (Table 2). As the results show in the table, ketones equipped with different benzylthio groups could also be applied to the catalytic asymmetric conjugate reactions. The desired conjugate adducts **3o**, **3p**, and **3q** were smoothly generated in moderate diastereoselectivities and excellent enantioselectivities, respectively. The use of an α-ethanethioketone also led to good results, and the absolute stereochemistry of the corresponding product **3r** was unambiguously determined to be (*S*,*S*) by X-ray crystallographic analysis,[13] bearing the same absolute configuration of our previous studies of carbon substituent *N*-phenylimidazole-modified ketones in conjugate reactions with β-nitroalkenes.[9] Additionally, 2-hydroxyethanethiol was also an alternative sulfur source for this catalytic system, affording the desired conjugate adduct **3s** with acceptable results.

Encouraged by the above results obtained from the α-thioketones, we next focused our attention on the adaptability of *N*-phenylimidazole-modified α-oxyketones in this asymmetric conjugate reaction. To our delight, the conjugate reaction proceeded smoothly for the α-oxyketones. As the results show in Table 3, aromatic nitroalkenes bearing either electron-deficient or electron-rich substituents are equally applicable, and generated the desired adducts in good to excellent diastereoselectivities and enantioselectivities (Table 3, **4a**−**4m**). To be noted, aromatic nitroalkenes with *ortho*-substituents or heterocyclic groups displayed relative lower diastereoselectivities. Also, aliphatic β-nitroalkenes that were also tolerable in the conjugate reaction resulted in moderate yields and good diastereoselectivities and enantioselectivities (Table 3, **4n**,**4o**). Furthermore, the use of different α-oxyketones also led to good results, and the desired products **4p**−**4s** were obtained in good yields and ee values. It is notable that an acetic-modified ketone could be applied to the conjugated reaction and generated the corresponding product **4t** smoothly with good results, while the ketone equipped with a benzoate group cannot perform the transformation and no desired product **4u** was detected by TLC

Table 1. Screening for the Optimized Conditions[a]



entry	ligand	solvent	ee (%)[b]	entry	ligand	solvent	ee (%)
1	**L1**	THF	75	12	**L7**	dioxane	87
2	**L2**	THF	84	13	**L7**	*i*PrOH	79
3	**L3**	THF	82	14[c]	**L7**	THF	79
4	**L4**	THF	78	15[c]	**L7**	dioxane	81
5	**L5**	THF	72	16[d]	**L7**	THF	91
6	**L6**	THF	82	17[d,e]	**L7**	THF	85
7	**L7**	THF	87	18[d,f]	**L7**	THF	81
8	**L8**	THF	76	19[g]	**L7**	THF	91
9	**L9**	THF	72	20[d,h]	**L7**	THF	90
10	**L10**	THF	74	21[d,i]	**L7**	THF	97
11	**L7**	DCM	40	22[d,i,j]	**L7**	THF	97

[a]General conditions: **1b** (0.10 mmol), **2a** (0.15 mmol), ligand/$Ni(OAc)_2$ (10 mol %) in THF (0.20 M) at rt, 18 h. [b]ee values were determined by HPLC analysis. [c]Reaction carried out with 0.05 M. [d]Reaction carried out in 0 °C. [e]Reaction carried out with 0.40 M. [f]20 mol % TEA was introduced into the reaction. [g]Reaction carried out at −10 °C. [h]Reaction carried out with 0.10 M. [i]100 mg of 4 Å MS was introduced into the reaction. [j]Reaction carried out with 5.0 mol % ligand/$Ni(OAc)_2$.

DOI: 10.1021/acs.joc.5b00013
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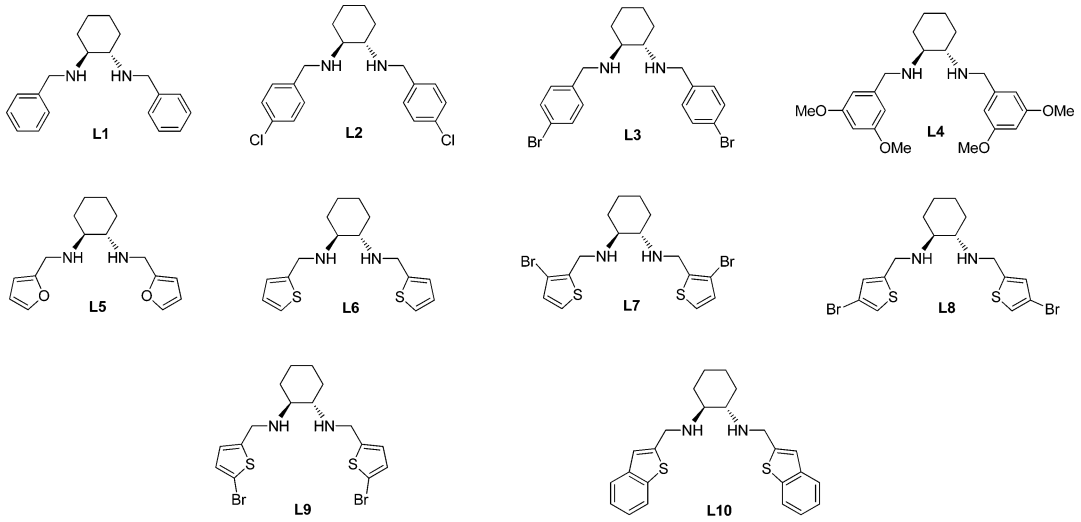
Scheme 3. Screening of Chiral Diamine Ligands



analysis and ^{1}H NMR studies, and we have not found any side reactions and the relative starting materials could be recovered.

We next explored the application of the α-chloroketone **1a** in this reaction. We found the related conjugate adducts could be formed smoothly and resulted in acceptable diastereoselectivities and good to excellent enantioselectivities (Table 4). The major diastereoisomer's absolute configuration was determined to be (*S*,*S*) by X-ray crystallographic analysis.[13]

Our further trial of α-azoketones failed. It was found that using this type of *N*-phenylimidazole-modified ketones could not furnish the desired conjugate adducts under the current conditions.[14] No other side reactions were observed, but only the relative starting materials were recovered. Now we are trying other catalytic systems to realize this type of transformation.

Next, some further transformations of the conjugate products have been carried out. As shown in Scheme 4, the conjugate adduct **3a** and **4a** could be transformed into esters after the cleavage of the *N*-phenylimidazole group with the corresponding alcohols. It should be noted the the diastereoselectivities of the product would be dramatically dropped in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene. So it is obvious that the reverse process of diastereoselectivity easily occurred when the heteroatom was equipped in adducts. To our delight, the adduct **5a** could be easily transformed into cyclopropane derivatives after treating it with a simple base such as potassium carbonate, and the relative stereochemistry of **8** and **9** was determined by NOESY analysis[15] (Scheme 5).

Finally, a possible mechanism for this Ni(II)-catalyzed conjugate reaction is proposed in Scheme 6. After the enolization process of the α-heteroatom ketone and the coordination results determined by the chiral environment of the catalyst, the conjugate reaction would occur between the activated ketone and nitroalkenes. On the basis of the absolute stereochemistry of the conjugate products, we speculated the in situ generated (*Z*)-enolate should be more stable than (*E*)-enolate due to the sterically hindered effects between the imidazole group and the heteroatoms.

CONCLUSION

In summary, we have disclosed a relatively general method for asymmetric conjugate Michael reaction of α-heteroatom ketones with β-*trans*-nitroalkenes. Synthesis of the related α-heteroatom ketones is easily handled, and the successful utilization of these types of ketones in the conjugate reaction is described by employing a 3-bromothiophene-derived chiral diamine/Ni-$(OAc)_2$ catalysis. The conjugate reactions of α-thio-, α-oxy-, and α-chloro-ketones with nitroalkenes have been realized, but the α-azoketones failed to perform the reaction under current conditions, and still need further investigation. Additionally, the corresponding adducts could be further transformed into related chiral esters and cyclopropane derivatives with excellent enantioselectivity; these compounds could act as key precursors of a serial of chiral amino acids.[16]

EXPERIMENTAL SECTION

General Remarks. Unless stated otherwise, all reactions were carried out in flame-dried glassware. All solvents were purified and dried according to standard methods prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a spectrometer (300 and 75 MHz, respectively) and internally referenced to tetramethylsilane signal or residual protio solvent signals. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet or unresolved, coupling constant (s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). IR spectra were recorded on a FT-IR spectrometer, and only major peaks were reported in cm^{-1}. High-resolution mass spectra (HRMS) were obtained by the ESI ionization sources with a time-of-flight mass analyzer. The ee value determination was carried out using chiral HPLC with a UV-detector.

Synthesis Procedure of α-Heteroatom Ketones. *2-Chloro-1-(1-phenyl-1H-imidazol-2-yl)ethanone (**1a**).* To 100 mL of vacuum flame-dried RBF was added *N*-phenylimidazole (10.0 mmol, 1.0 equiv) under an argon atmosphere. The solution was cooled to −78 °C, and *n*-butyllithium in hexanes (2.5 M, 10.0 mmol, 1.0 equiv) was added to the flask. The reaction mixture then was allowed to warm to rt over a 30 min period. The reaction was cooled to −78 °C for 20 min before *tert*-butylchloroacetate (12.5 mmol, 1.25 equiv) was added as a single portion. The reaction was stirred at −40 °C for 5.0 h. The reaction was quenched with 3 mL of H_2O and diluted with 50 mL of EtOAc and 50 mL of brine. The aqueous layer was separated and extracted with 2 × 30 mL of EtOAc. The organic layers were combined and dried with Na_2SO_4. The drying agent was removed by filtration, and the filtrate was concentrated in vacuo. The crude reaction mixture was purified with a short SiO_2 column to produce the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.46 (m, 3H), 7.32−7.28 (m, 3H), 7.26 (s, 1H), 4.96 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.5, 140.1, 137.5, 130.2, 129.1, 129.0, 127.8, 125.8, 46.8 ppm; HRMS (ESI): $C_{11}H_9ClN_2O$ [M + Na]$^+$ calcd, 243.0296; found, 243.0304.

DOI: 10.1021/acs.joc.5b00013
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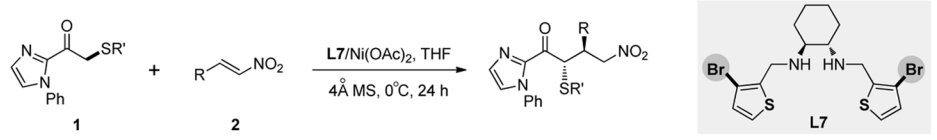
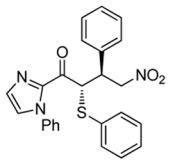
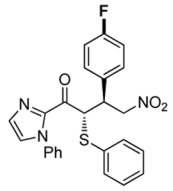
Table 2. Substrates Scope with Respect to α-Thioketones[a]

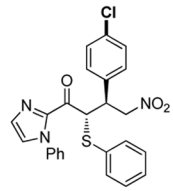




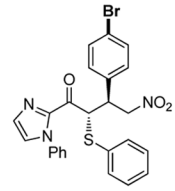
3a. 98% (84%),[b] 7.0:1 (>20:1) dr,[c] 97% ee.[d]



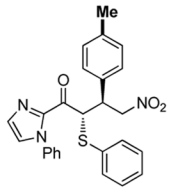
3b. 94% (78%), 6.2:1 (>20:1) dr, 98% ee.



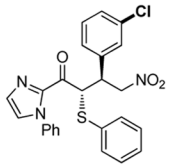
3c. 99% (81%), 5.6:1 (15:1) dr, 97% ee.



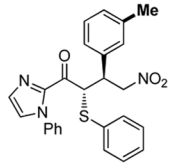
3d. 97% (80%), 5.2:1 (14:1) dr, 98% ee.



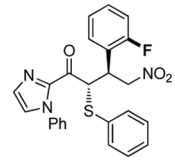
3e. 87% (52%), 4.0:1 (18:1) dr, 93% ee.



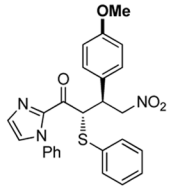
3f. 86% (50%), 4.7:1 (11:1) dr, 95% ee.



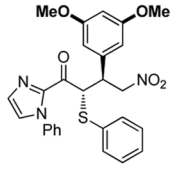
3g. 89% (66%), 3.5:1 (>20:1) dr, 96% ee.



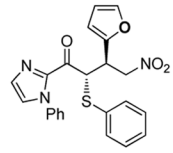
3h. 61% (50%), 3.2:1(5.0:1) dr, 94% ee/89% ee.



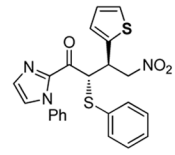
3i. 90%,[e] 2.8:1 dr, 94% ee/-.



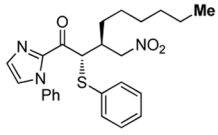
3j. 84%,[e] 2.9:1 dr, 94% ee/-.



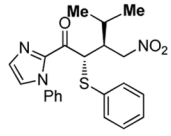
3k. 94%,[e] 1.5:1 dr, 92% ee/92% ee.



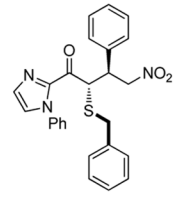
3l. 79% (55%), 2.0:1 (4.0:1) dr, 95% ee/96% ee.



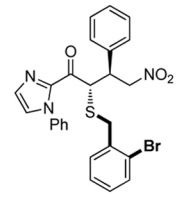
3m. 84%,[e] 1.6:1 dr, 94% ee/92% ee.



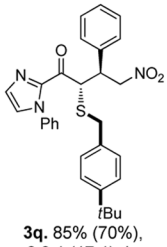
3n. 87%,[e] 2.2:1 dr, 94% ee/-.



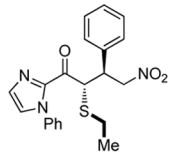
3o. 90% (70%), 3.7:1 (>20:1) dr, 95% ee.



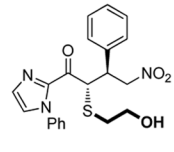
3p. 89% (77%), 9.5:1 (>20:1) dr, 91% ee.



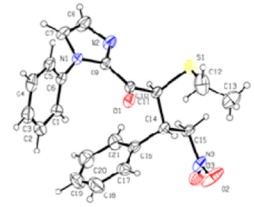
3q. 85% (70%), 6.0:1 (17:1) dr, 95% ee.



3r. 94% (80%), 7.4:1 (>20:1) dr, 97% ee.



3s. -% (77%),[f] 4.4:1 (10:1) d.r., 83% ee.



*X-Ray analysis of **3r**.*

[a]General conditions: **1** (0.10 mmol), **2** (0.15 mmol), ligand/$Ni(OAc)_2$ (5 mol %) in THF (0.20 M) at 0 °C for 24 h. [b]Isolated yields of the major diastereoisomers were included in parentheses. [c]Determined by ^1H NMR analysis of crude reaction mixtures and isolated major diastereoisomers; the dr values of the isolated major diastereoisomers were included in parentheses. [d]ee values were determined by HPLC analysis. [e]Combined yields of diastereoisomers. [f]The reaction was carried out under 10 mol % catalyst.

Representative Procedure A for the Synthesis of *N*-Phenylimidazole-Modified α-Heteroatom Ketones. To 10 mL of vacuum flame-dried RBF were added **1a** (1.0 mmol, 1.0 equiv), K_2CO_3 (1.0 mmol, 1.0 equiv), and DMF (2.0 mL), the reaction mixtures was stirred at rt, then the substituent reagent (phenthiols or thioalcohols) (1.5 mmol, 1.5 equiv) was added to the reaction mixture and stirred at this temperature, until the reaction was complete (monitored by TLC). The reaction was quenched by the addition of NH_4Cl and extracted with EA, dried over Na_2SO_4, and concentrated under reduced pressure. The

DOI: 10.1021/acs.joc.5b00013
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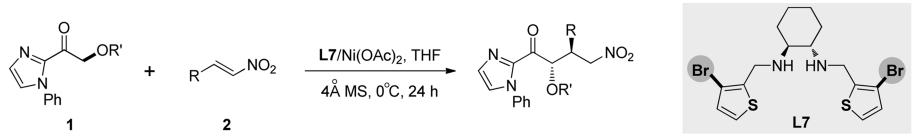
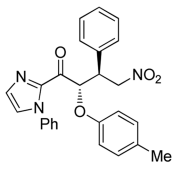
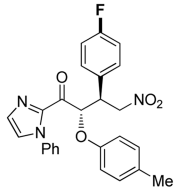
Table 3. Substrates Scope of *N*-Phenylimidazole-Modified α-Oxyketones[a]

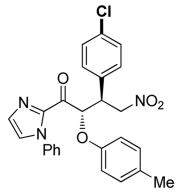




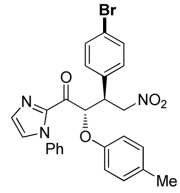
4a. 89% yield,[b] 18:1 dr,[c] 92% ee.[d]



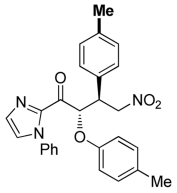
4b. 85% yield, >20:1 dr, 91% ee.



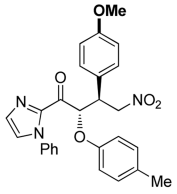
4c. 84% yield, >20:1 dr, 90% ee.



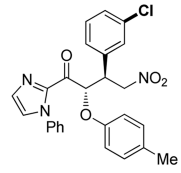
4d. 82% yield, >20:1 dr, 93% ee.



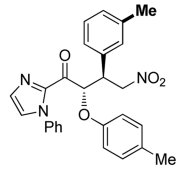
4e. 80% yield, 10:1 dr, 90% ee.



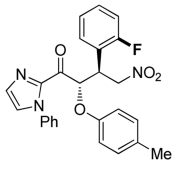
4f. 94% yield, >20:1 dr, 85% ee.



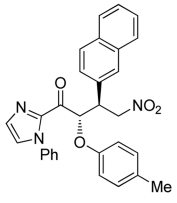
4g. 79% yield, >20:1 dr, 87% ee.



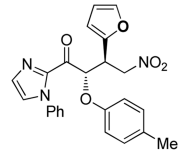
4h. 66% yield, >20:1 dr, 88% ee.



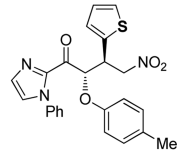
4i. 59% yield, 10:1 dr, 87% ee.



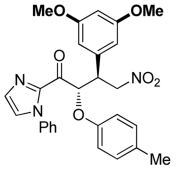
4j. 64% yield, 9:1 dr, 87% ee.



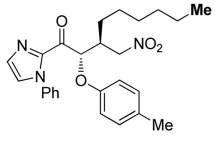
4k. 75% yield, 17:1 dr, 80% ee.



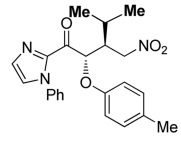
4l. 70% yield, 12:1 dr, >99% ee.



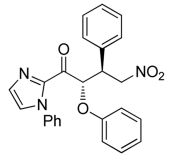
4m. 63% yield, >20:1 dr, 76% ee.



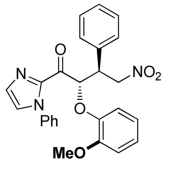
4n. 54% yield, 16:1 dr, 86% ee.



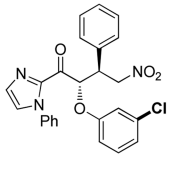
4o. 53% yield, >20:1 dr, 94% ee.



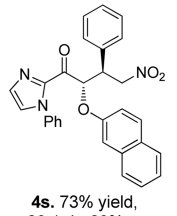
4p. 71% yield, >20:1 dr, 88% ee.



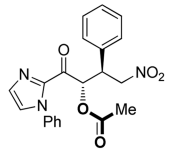
4q. 67% yield, >20:1 dr, 91% ee.



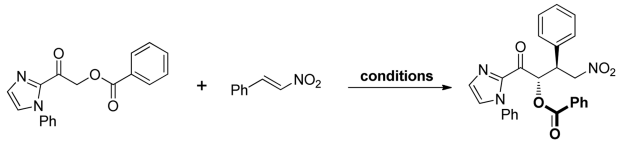
4r. 68% yield, >20:1 dr, 90% ee.



4s. 73% yield, >20:1 dr, 83% ee.



4t. 67% yield, >20:1 dr, 90% ee.



4u. no reaction.

DOI: 10.1021/acs.joc.5b00013
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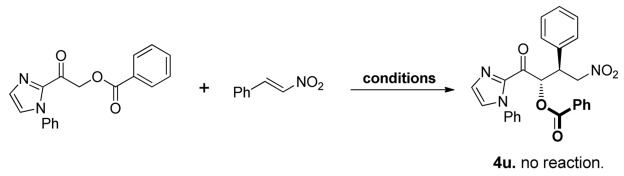
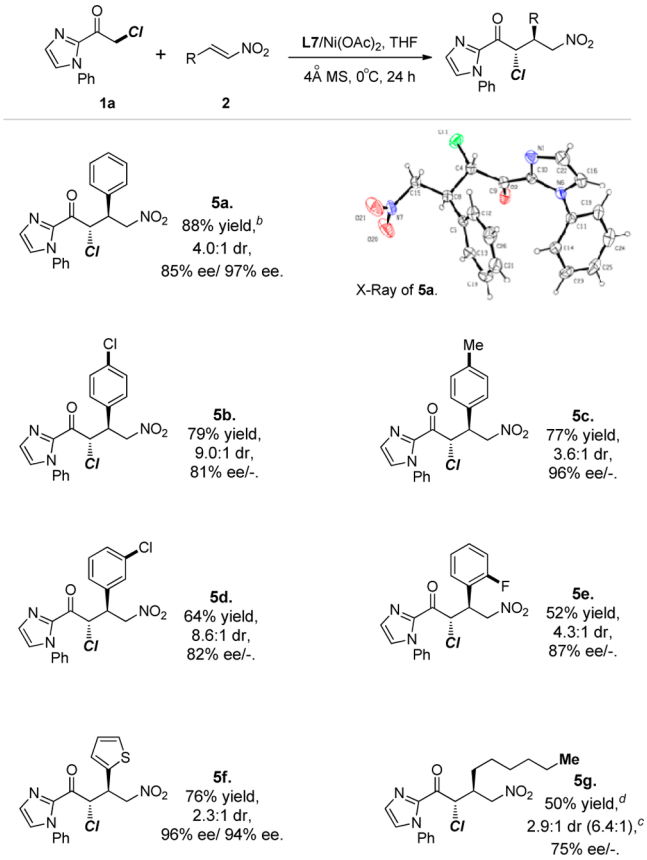
Table 3. continued



[a]General conditions: **1** (0.10 mmol), **2** (0.15 mmol), ligand/$Ni(OAc)_2$ (5 mol %) in THF (0.20 M) at 0 °C for 24 h. [b]Isolated yields the products. [c]Determined by ^1H NMR analysis of crude reaction mixtures. [d]ee values were determined by HPLC analysis.

Table 4. Substrates Scope with Respect to α-Chloroketone 1a[a]



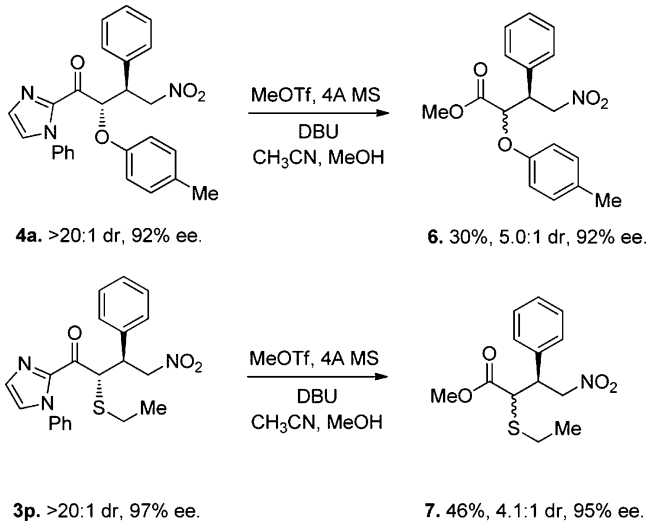
[a]General conditions: **1a** (0.10 mmol), **2** (0.15 mmol), ligand/$Ni(OAc)_2$ (5 mol %) in THF (0.20 M) at 0 °C for 24 h. [b]Combined yields of diastereoisomers. [c]dr value of isolated product was summarized in parentheses. [d]The reaction was carried out under 10 mol % catalyst.

residue was purified by chromatography on silica gel using petroleum/EtOAc as the eluent to afford compound **1**. General yield > 70%.

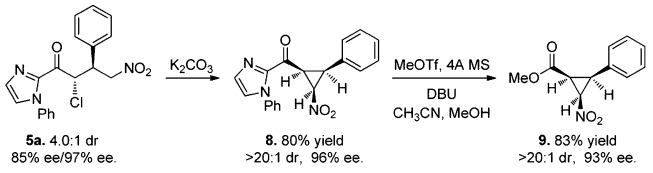
Representative Procedure B for the Synthesis of *N*-Phenylimidazole-Modified α-Heteroatom Ketones. To 10 mL of vacuum flame-dried RBF were added **1a** (1.0 mmol, 1.0 equiv), K_2CO_3 (1.0 mmol, 1.0 equiv), and DMF (2.0 mL), the reaction mixtures was stirred at rt, then the substituent reagent (phenols) (1.5 mmol, 1.5 equiv) was added to the reaction mixtures and stirred at this temperature, until the reaction was complete (monitored by TLC). The reaction was quenched by the addition of NH_4Cl and extracted with EA, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using petroleum/EtOAc as the eluent to afford compound **1**. General yield > 80%.

Representative Procedure C for the Synthesis of *N*-Phenylimidazole-Modified α-Heteroatom Ketones. To 10 mL of vacuum flame-dried RBF were added **1a** (1.0 mmol, 1.0 equiv), the substituent reagent (acids) (1.5 mmol, 1.5 equiv), and acetone (1.5 mL), the

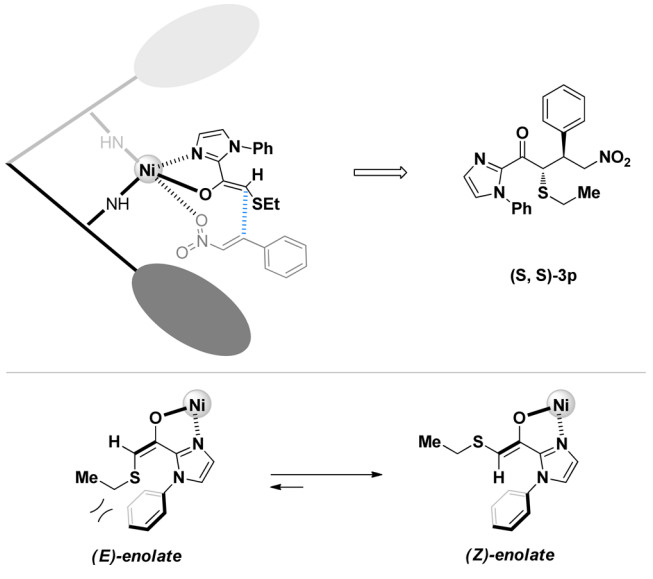
Scheme 4. Transformation of the Conjugate Products to Esters



Scheme 5. Transformation of the Conjugate Products to Cyclopropane Derivatives



Scheme 6. Proposed Mechanism of the Conjugate Reaction



DOI: 10.1021/acs.joc.5b00013
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reaction mixture was stirred at rt, then Et_3N (2.5 mmol, 2.5 equiv) was added to the reaction mixtures and stirred at this temperature, until the reaction was complete (monitored by TLC). The reaction was quenched by the addition of NH_4Cl and extracted with EA, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using petroleum/EtOAc as the eluent to afford compound **1**.

*1-(1-Phenyl-1H-imidazol-2-yl)-2-(phenylthio)ethanone (**1b**).* Synthesized according to representative procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 5.8 Hz, 5H), 7.27 (d, J = 10.3 Hz, 3H), 7.21 (s, 4H), 4.46 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 142.0, 137.9, 135.3, 129.9, 129.6, 129.0, 128.9, 128.8, 127.4, 126.5, 125.7, 40.8 ppm; HRMS (ESI): $C_{17}H_{14}N_2OS$ $[M + H]^+$ calcd, 295.0900; found, 295.0909.

*2-(Benzylthio)-1-(1-phenyl-1H-imidazol-2-yl)ethanone (**1c**).* Synthesized according to representative procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.44 (m, 3H), 7.36−7.30 (m, 4H), 7.30−7.26 (m, 3H), 7.23 (d, J = 6.9 Hz, 1H), 7.20 (s, 1H), 3.81 (s, 2H), 3.76 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 142.1, 138.1, 137.6, 129.8, 129.3, 129.1, 128.9, 128.5, 127.4, 127.1, 125.7, 36.2, 36.1 ppm; HRMS (ESI): $C_{18}H_{16}N_2OS$ $[M + H]^+$ calcd, 309.1056; found, 309.1068.

*2-((2-Bromobenzyl)thio)-1-(1-phenyl-1H-imidazol-2-yl)ethanone (**1d**).* Synthesized according to representative procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 7.9, 1.1 Hz, 1H), 7.51−7.45 (m, 3H), 7.42 (dd, J = 7.6, 1.6 Hz, 1H), 7.33 (m, J = 4.3, 3.4 Hz, 2H), 7.29 (d, J = 0.9 Hz, 1H), 7.26−7.19 (m, 2H), 7.10 (td, J = 7.7, 1.7 Hz, 1H), 3.88 (s, 2H), 3.86 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 142.1, 138.1, 137.0, 133.3, 131.2, 129.9, 129.1, 128.9, 128.8, 127.5, 127.3, 125.7, 124.7, 36.5, 36.3 ppm; HRMS (ESI): $C_{18}H_{16}N_2O_2$ $[M + H]^+$ calcd, 293.1285; found, 293.1294.

*2-((4-(tert-Butyl)benzyl)thio)-1-(1-phenyl-1H-imidazol-2-yl)-ethanone (**1e**).* Synthesized according to representative procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (m, J = 6.6, 3.8 Hz, 3H), 7.31 (m, J = 4.8, 3.1 Hz, 4H), 7.27 (d, J = 6.1 Hz, 3H), 7.21 (s, 1H), 3.82 (s, 2H), 3.74 (s, 2H), 1.29 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 150.0, 142.2, 138.2, 134.5, 129.8, 129.1, 128.9, 128.8, 127.4, 125.7, 125.4, 36.2, 35.8, 34.5, 31.3 ppm; HRMS (ESI): $C_{22}H_{24}N_2OS$ $[M + H]^+$ calcd, 365.1682; found, 365.1698.

*2-(Ethylthio)-1-(1-phenyl-1H-imidazol-2-yl)ethanone (**1f**).* Synthesized according to representative procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, J = 6.8, 3.8 Hz, 3H), 7.37−7.28 (m, 3H), 7.21 (s, 1H), 3.94 (s, 2H), 2.60 (q, J = 7.4 Hz, 2H), 1.25 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 142.1, 138.1, 129.8, 129.0, 128.8, 127.4, 125.7, 37.0, 26.4, 14.3 ppm; HRMS (ESI): $C_{13}H_{14}N_2OS$ $[M + H]^+$ calcd, 247.0900; found, 247.0906.

*2-((2-Hydroxyethyl)thio)-1-(1-phenyl-1H-imidazol-2-yl)ethanone (**1g**).* Synthesized according to representative procedure A. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.45 (m, 3H), 7.32−7.28 (m, 3H), 7.23 (d, J = 0.7 Hz, 1H), 4.03 (s, 2H), 3.79 (t, J = 5.6 Hz, 2H), 2.80 (t, J = 5.6 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7, 138.0, 129.9, 129.1, 129.0, 127.7, 125.7, 61.1, 37.2, 35.8 ppm; HRMS (ESI): $C_{13}H_{14}N_2O_2S$ $[M + H]^+$ calcd, 263.0849; found, 263.0861.

*1-(1-Phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)ethanone (**1h**).* Synthesized according to representative procedure B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.37 (m, 3H), 7.31 (s,3H), 7.26 (s, 1H), 7.05 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.48 (s, 2H), 2.26 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 155.9, 140.7, 130.6, 130.0, 129.9, 129.0^2, 129.0, 127.4, 125.9, 114.5, 70.0, 20.5 ppm; HRMS (ESI): $C_{18}H_{16}N_2O_2$ $[M + H]^+$ calcd, 293.1285; found, 293.1294.

*2-Phenoxy-1-(1-phenyl-1H-imidazol-2-yl)ethanone (**1i**).* Synthesized according to representative procedure B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.38 (m, 3H), 7.32 (d, J = 0.8 Hz, 2H), 7.27 (m, J = 10.7, 7.6, 4.5 Hz, 4H), 7.03−6.87 (m, 3H), 5.51 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 158.0, 140.6, 137.5, 130.1, 129.5, 129.0^4, 129.0, 127.4, 125.9, 121.3, 114.7, 69.8 ppm; HRMS (ESI): $C_{17}H_{14}N_2O_2$ $[M + H]^+$ calcd, 279.1128; found, 279.1137.

*2-(2-Methoxyphenoxy)-1-(1-phenyl-1H-imidazol-2-yl)ethanone (**1j**).* Synthesized according to representative procedure B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.37 (m, 3H), 7.28 (d, J = 14.8 Hz, 4H), 6.88 (ddd, J = 18.9, 9.8, 3.8 Hz, 4H), 5.59 (s, 2H), 3.85 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.4, 149.4, 147.4, 140.6, 137.5, 129.9, 128.9^4, 128.9, 127.3, 125.8, 121.8, 120.6, 113.5, 111.9, 70.6, 55.8 ppm; HRMS (ESI): $C_{18}H_{16}N_2O_3$ $[M + H]^+$ calcd, 309.1234; found, 309.1246.

*2-(3-Chlorophenoxy)-1-(1-phenyl-1H-imidazol-2-yl)ethanone (**1k**).* Synthesized according to representative procedure B. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50−7.42 (m, 3H), 7.31 (m, J = 4.3, 2.5 Hz, 4H), 7.20−7.12 (m, 1H), 6.93 (m, J = 4.3, 2.3 Hz, 2H), 6.83 (dd, J = 8.3, 1.7 Hz, 1H), 5.50 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 184.0, 158.7, 140.5, 137.4, 134.9, 130.2^6, 130.2^1, 129.1, 127.6, 125.9, 121.6, 115.1, 113.2, 69.9 ppm; HRMS (ESI): $C_{17}H_{13}ClN_2O_2$ $[M + H]^+$ calcd, 313.0738; found, 313.0751.

*2-(Naphthalen-2-yloxy)-1-(1-phenyl-1H-imidazol-2-yl)ethanone (**1l**).* Synthesized according to representative procedure B. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81−7.64 (m, 3H), 7.51−7.37 (m, 4H), 7.37−7.20 (m, 6H), 7.18 (s, 1H), 5.62 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 155.9, 140.7, 134.3, 130.2, 129.6, 129.3, 129.1, 127.6, 127.5, 126.7, 126.4, 125.9, 123.9, 118.8, 107.1, 69.9 ppm; HRMS (ESI): $C_{21}H_{16}N_2O_2$ $[M + H]^+$ calcd, 329.1285; found, 329.1296.

*2-Oxo-2-(1-phenyl-1H-imidazol-2-yl)ethyl Acetate (**1m**).* Synthesized according to representative procedure C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.39 (m, 3H), 7.31 (m, J = 5.8 Hz, 3H), 7.24 (s, 1H), 5.49 (s, 2H), 2.14 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.9, 170.4, 140.3, 137.5, 130.2, 129.1, 127.3, 125.9, 66.1, 20.5 ppm; HRMS (ESI): $C_{13}H_{12}N_2O_3$ $[M + Na]^+$ calcd, 267.0740; found, 267.0749.

Preparation of Isolated Nickel−Diamine Complex.[12a] A mixture of diamine (**L**) (1.0 equiv) and nickel acetate tetrahydrate (1.0 equiv) in ethanol was stirred for 2.0 h at room temperature. The resulting solution was filtered through a membrane filter. The filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane and concentrated under reduced pressure to give the complex as a blue powder.

General Procedure for the Asymmetric *anti*-Selective Conjugate Reactions between Phenylimidazole-Modified Ketones and Nitroalkenes. Ketones (0.10 mmol), $Ni(OAc)_2$/L7 (5 mol %, 0.005 mmol), nitroalkenes (0.15 mmol, 1.5 equiv), and 4 Å MS (100 mg) were weighed together in a flame-dried round-bottom flask. THF (0.5 mL) was then added to the mixture, and the resulting solution was stirred at 0 °C. After the starting material (ketones) was completely consumed as monitored by TLC, the reaction mixture was filtered through a short pad of Celite (ethyl acetate), and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EA/PE = 1:4) to give adducts **3**.

*(2S,3S)-4-Nitro-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)butan-1-one (**3a**).* White solid, mp 119−120 °C; 37.3 mg, 84% yield; 96.8% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 11.9 min, t_{major} = 7.3 min); $[\alpha]^{rt}_D$ = −70.2 (c = 1.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.54−7.48 (m, 2H), 7.42−7.35 (m, 2H), 7.35−7.29 (m, 4H), 7.24−7.17 (m, 6H), 7.11 (d, J = 0.9 Hz, 1H), 6.92 (dd, J = 8.1, 1.5 Hz, 2H), 5.51−5.33 (m, 2H), 4.76 (dd, J = 12.7, 10.8 Hz, 1H), 4.15 (td, J = 11.1, 3.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.7, 147.8, 141.9, 137.6, 137.0, 133.3, 132.3, 129.8, 129.3, 128.9, 128.8, 128.7, 128.4, 128.0, 127.5, 125.4, 79.1, 54.5, 45.0 ppm; IR (neat) 3356, 2925, 2400, 1554, 1403, 1262, 1104, 1042, 766, 696 cm^{-1}; HRMS (ESI): $C_{25}H_{21}N_3O_3S$ $[M + H]^+$ calcd, 444.1376; found, 444.1387.

*(2S,3S)-3-(4-Fluorophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)butan-1-one (**3b**).* Colorless oil; 36.0 mg, 78% yield; 98% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 10.0 min, t_{major} = 6.7 min); $[\alpha]^{rt}_D$ = −44.1 (c = 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.53−7.47 (m, 2H), 7.38 (dt, J = 5.5, 3.6 Hz, 3H), 7.35−7.29 (m, 3H), 7.24−7.14 (m, 4H), 7.02 (dd, J = 7.8, 1.6 Hz, 2H), 6.95−6.84 (m, 2H), 5.50−5.32 (m, 2H), 4.72 (dd, J = 12.7, 10.9 Hz, 1H), 4.12 (td, J = 11.3, 3.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.4, 158.3 (d, J = 354.2 Hz), 141.9, 137.6, 133.4, 132.3 (d, J = 54.2 Hz), 130.1, 130.0, 129.9, 129.4, 129.0, 128.9, 128.8, 127.7, 125.4, 115.8 (d, J = 6.1 Hz), 80.0, 54.4, 44.1 ppm; IR (neat) 3356, 2924, 2368, 1883, 1684, 1554, 1403, 1219, 761, 693 cm^{-1}; HRMS (ESI): $C_{25}H_{20}FN_3O_3S$ $[M + H]^+$ calcd, 462.1282; found, 462.1296.

DOI: 10.1021/acs.joc.5b00013
J. Org. Chem. 2015, 80, 4336−4348

*(2S,3S)-3-(4-Chlorophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)butan-1-one (**3c**).* Colorless oil; 38.7 mg, 81% yield; 97% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 11.4 min, t_{major} = 7.2 min); $[\alpha]^{rt}_D$ = −29.2 (*c* = 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.55−7.46 (m, 3H), 7.39 (d, *J* = 7.1 Hz, 3H), 7.36−7.30 (m, 3H), 7.24 (s, 1H), 7.18 (t, *J* = 5.6 Hz, 4H), 7.03 (d, *J* = 6.1 Hz, 2H), 5.41 (dd, *J* = 19.1, 7.7 Hz, 2H), 4.72 (dd, *J* = 12.7, 3 (s) 11.0 Hz, 1H), 4.10 (td, *J* = 11.3, 3.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.2, 141.8, 137.5, 135.5, 133.9, 133.5, 131.8, 129.9, 129.7, 129.4, 129.0, 128.9[3], 128.9, 127.7, 125.4, 78.8, 54.2, 44.2 ppm; IR (neat) 3353, 2922, 2371, 1684, 1554, 1493, 1402, 757, 693, 531 cm^{-1}; HRMS (ESI): $C_{25}H_{20}ClN_3O_3S$ $[M + H]^+$ calcd, 478.0987; found, 478.1002.

*(2S,3S)-3-(4-Bromophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)butan-1-one (**3d**).* Colorless oil; 41.8 mg, 80% yield; 98% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 12.3 min, t_{major} = 7.4 min); $[\alpha]^{rt}_D$ = −14.6 (*c* = 0.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 (dd, *J* = 7.1, 2.3 Hz, 3H), 7.39 (d, *J* = 7.1 Hz, 3H), 7.33 (dd, *J* = 5.1, 3.4 Hz, 4H), 7.24 (s, 1H), 7.16 (s, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 6.0 Hz, 2H), 5.49−5.31 (m, 2H), 4.77−4.65 (m, 1H), 4.16−4.03 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.2, 141.8, 137.5, 136.1, 133.5, 133.4, 131.9, 131.8, 130.0, 129.9, 129.4, 129.0, 128.9, 127.7, 125.4, 122.1, 78.8, 54.2, 44.3 ppm; IR (neat) 3351, 2925, 2370, 1554, 1403, 1217, 1112, 1043, 766, 692 cm^{-1}; HRMS (ESI): $C_{25}H_{20}BrN_3O_3S$ $[M + H]^+$ calcd, 522.0482; found, 522.0501.

*(2S,3S)-4-Nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)-3-(p-tolyl)butan-1-one (**3e**).* Colorless oil; 23.8 mg, 52% yield; 93% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 11.4 min, t_{major} = 52.6 min); $[\alpha]^{rt}_D$ = −101.6 (*c* = 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.51 (m, *J* = 6.5, 2.8 Hz, 2H), 7.42−7.27 (m, 6H), 7.23 (s, 1H), 7.14−7.05 (m, 3H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 7.0 Hz, 2H), 5.54−5.19 (m, 2H), 4.81−4.62 (t, 1H), 4.12 (m, *J* = 11.2, 3.8 Hz, 1H), 2.23 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.7, 141.9, 137.7, 137.6, 133.8, 133.3, 132.4, 129.8, 129.5, 129.3, 128.9, 128.8, 128.7, 128.2, 127.4, 125.4, 79.2, 54.7, 44.6, 21.1 ppm; IR (neat) 3353, 2924, 2372, 1685, 1554, 1402, 1217, 1024, 758, 693 cm^{-1}; HRMS (ESI): $C_{26}H_{23}N_3O_3S$ $[M + H]^+$ calcd, 458.1533; found, 458.1554.

*(2S,3S)-3-(3-Chlorophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)butan-1-one (**3f**).* Colorless oil; 23.9 mg, 50% yield; 95% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 7.1 min, t_{major} = 29.3 min); $[\alpha]^{rt}_D$ = −42.4 (*c* = 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 (dd, *J* = 6.4, 2.9 Hz, 2H), 7.68−7.41 (m, 4H), 7.43−7.35 (m, 3H), 7.34−7.29 (m, 3H), 7.41−7.04 (m, 14H), 7.28−7.23 (m, 2H), 7.18−7.10 (m, 4H), 7.04−6.92 (m, 2H), 7.05−6.96 (m, 2H), 5.52−5.32 (m, 2H), 5.50−5.34 (m, 2H), 4.74 (dd, *J* = 12.9, 10.9 Hz, 1H), 4.74 (dd, *J* = 12.9, 10.9 Hz, 1H), 4.10 (td, *J* = 11.2, 3.8 Hz, 1H), 4.10 (td, *J* = 11.2, 3.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.3, 141.8, 139.1, 137.5, 134.6, 133.4, 131.9, 130.1, 130.0, 129.4, 129.0, 128.9, 128.8[8], 128.8[5], 128.3, 127.8, 126.2, 125.4, 78.6, 54.2, 44.6 ppm; IR (neat) 3349, 2924, 2372, 1684, 1554, 1402, 1217, 1085, 758, 693 cm^{-1}; HRMS (ESI): $C_{25}H_{20}ClN_3O_3S$ $[M + H]^+$ calcd, 478.0987; found, 478.1004.

*(2S,3S)-4-Nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)-3-(m-tolyl)butan-1-one (**3g**).* Colorless oil; 30.1 mg, 66% yield; 95% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 8.8 min, t_{major} = 6.2 min); $[\alpha]^{rt}_D$ = −58.9 (*c* = 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.52 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.42−7.35 (m, 2H), 7.32 (dd, *J* = 6.1, 3.4 Hz, 4H), 7.23 (s, 1H), 7.13−7.05 (m, 2H), 6.99 (t, *J* = 8.5 Hz, 3H), 6.91 (d, *J* = 6.8 Hz, 2H), 5.49−5.34 (m, 2H), 4.75 (dd, *J* = 12.6, 10.8 Hz, 1H), 4.10 (td, *J* = 11.2, 3.8 Hz, 1H), 2.22 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.8, 142.0, 138.4, 137.6, 136.8, 133.3, 132.3, 129.8, 129.4, 129.3, 128.9, 128.8, 128.7, 128.6[7], 128.6[4], 127.4, 125.4, 125.1, 79.1, 54.5, 45.0, 21.3 ppm; IR (neat) 3354, 3021, 2924, 2402, 1685, 1554, 1403, 1217, 758, 694 cm^{-1}; HRMS (ESI): $C_{26}H_{23}N_3O_3S$ $[M + H]^+$ calcd, 458.1533; found, 458.1550.

*(2S,3S)-3-(2-Fluorophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)butan-1-one (**3h**).* Colorless oil; 28.6 mg, 61% yield; 94%/88% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 7.0 min, t_{major} = 7.9 min); $[\alpha]^{rt}_D$ = −31.3 (*c* = 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 (m, *J* = 6.3, 3.0 Hz, 2H), 7.37 (t, *J* = 6.7 Hz, 2H), 7.34−7.28 (m, 3H), 7.24 (d, *J* = 11.5, 5.3 Hz, 3H), 7.20−7.10 (m, 3H), 6.97 (m, *J* = 15.3, 7.0 Hz, 3H), 5.68 (t, *J* = 9.8 Hz, 1H), 5.35 (dd, *J* = 13.0, 4.0 Hz, 1H), 4.98 (dd, *J* = 12.9, 10.1 Hz, 1H), 4.30 (td, *J* = 10.5, 4.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.5, 161.0 (d, *J* = 245.8 Hz), 141.7, 137.6, 133.0, 131.5 (d, *J* = 4.2 Hz), 130.0, 129.9 (d, *J* = 8.6 Hz), 129.4, 129.2, 129.0, 128.9, 128.8, 128.7, 127.6, 125.4, 124.4 (d, *J* = 3.3 Hz), 123.8 (d, *J* = 12.8 Hz), 116.1(d, *J* = 21.8 Hz), 53.3, 41.0. IR (neat) 3351, 2925, 2370, 1683, 1554, 1403, 1217, 1106, 760, 692 cm^{-1}; HRMS (ESI): $C_{25}H_{20}FN_3O_3S$ $[M + H]^+$ calcd, 462.1282; found, 462.1303.

*(2S,3S)-3-(4-Methoxyphenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)butan-1-one (**3i**).* Colorless oil; 42.2 mg, 90% yield (2.8:1 dr); 94% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate =1.0 mL/min, t_{minor} = 8.2 min, t_{major} = 37.2 min); $[\alpha]^{rt}_D$ = −37.9 (*c* = 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.56−7.45 (m, 2H), 7.39−7.21 (m, 7H), 7.16−7.06 (m, 3H), 7.02−6.91 (m, 2H), 6.82−6.67 (d, 2H), 5.53 (dd, *J* = 9.5 Hz, 2H), 4.91−4.63 (dd, 1H), 4.18−3.93 (m, 1H), 3.72 (s, *J* = 18.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 185.5, 183.7, 159.2, 141.9, 137.8, 137.6, 133.9, 133.3, 132.3, 130.1, 129.8, 129.6, 129.4, 129.3, 129.2, 129.1, 129.0, 128.8, 128.7[2], 128.7, 128.6, 128.3, 127.9, 127.5, 125.6, 125.4, 114.2, 114.1, 79.2, 55.7, 55.2, 55.1, 54.6, 44.6, 44.3. IR (neat) 3369, 2924, 2853, 2369, 1797, 1553, 1254, 1120, 1033, 762 cm^{-1}; HRMS (ESI): $C_{26}H_{23}N_3O_4S$ $[M + H]^+$ calcd, 474.1482; found, 474.1496.

*(2S,3S)-3-(3,5-Dimethoxyphenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)butan-1-one (**3j**).* Colorless oil; 42.3 mg, 84% yield (2.9:1 dr); 94% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 9.8 min, t_{major} = 32.8 min); $[\alpha]^{rt}_D$ = −72.0 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.57−7.45 (m, 2H), 7.41−7.19 (m, 7H), 7.13 (s, *J* = 0.5 Hz, 1H), 6.97 (dd, *J* = 7.9, 2 Hz, 1H), 6.40−6.21 (m, 3H), 5.43 (dd, *J* = 17.5, 16.5, 6.6 Hz, 2H), 4.91−4.66 (dd, 1H), 4.13−3.93 (m, 1H), 3.66 (d, *J* = 11.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 185.3, 183.6, 160.8, 142.0, 139.3, 138.7, 137.6, 133.8, 133.4, 132.1, 130.1, 129.8, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.5, 128.0, 127.5, 125.6, 125.4, 106.7, 106.1, 100.4, 99.9, 79.1, 77.7, 55.4, 55.3, 54.0, 45.4, 45.6, 45.2. IR (neat) 3366, 2925, 2854, 2370, 1738, 1596, 1461, 1155, 1027, 761 cm^{-1}; HRMS (ESI): $C_{27}H_{25}N_3O_5S$ $[M + H]^+$ calcd, 504.1588; found, 504.1603.

*(2S,3R)-3-(Furan-2-yl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)butan-1-one (**3k**).* Colorless oil; 40.9 mg, 94% yield (1.5:1 dr); 92%/92% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 7.2/8.0 min, t_{major} = 9.7/16.6 min); $[\alpha]^{rt}_D$ = −10.8 (*c* = 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.44 (m, *J* = 12.7, 6.2, 2.9 Hz, 5H), 7.34−7.24 (m, 6H), 7.22−7.12 (m, 2H), 6.32−6.04 (m, 2H), 5.51 (d, *J* = 10.9 Hz, 1H), 5.35−4.76 (m, 2H), 4.30 (td, *J* = 10.4, 3.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 184.8, 183.6, 149.9, 142.5, 141.9, 141.6, 137.7, 133.9, 133.2, 131.9, 130.2, 130.0, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.0, 127.7, 125.6, 110.4, 109.2, 76.2, 75.8, 53.9, 52.9, 39.3, 38.6 ppm; IR (neat) 3298, 2924, 2372, 1683, 1555, 1402, 1148, 1016, 758, 693 cm^{-1}; HRMS (ESI): $C_{23}H_{19}N_3O_4S$ $[M + H]^+$ calcd, 434.1169; found, 434.1186.

*(2S,3S)-4-Nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)-3-(thiophen-2-yl)butan-1-one (**3l**).* Colorless oil; 35.5 mg, 79% yield (2.0:1 dr); 95%/95% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 13.2 min, t_{major} = 8.3 min); $[\alpha]^{rt}_D$ = −54.9 (*c* = 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50−7.47 (m, 2H), 7.40 (s, 2H), 7.34−7.28 (m, 4H), 7.26 (s, 2H), 7.16 (s, 1H), 7.04 (m, *J* = 7.6, 1.6 Hz, 2H), 6.89 (t, *J* = 2.8 Hz, 2H), 5.44 (d, *J* = 11.4 Hz, 1H), 4.93 (d, *J* = 6.5 Hz, 1H), 4.76 (dd, *J* = 12.8, 10.3 Hz, 1H), 4.49 (td, *J* = 10.7, 3.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 184.0, 182.2, 140.7, 138.4, 136.6, 132.8, 132.3, 130.9, 129.2, 128.9, 128.3, 128.1[3], 128.1, 128.0, 127.9, 127.8, 127.7, 127.0, 126.6, 126.1, 125.9, 125.8, 124.5, 124.4, 124.3, 78.3, 77.3, 55.5, 54.0, 40.0, 39.2, 0.0 ppm; IR (neat) 3351, 2924, 2854, 1684, 1555, 1402,

DOI: 10.1021/acs.joc.5b00013
J. Org. Chem. 2015, 80, 4336−4348

1306, 1217, 759, 694 cm^{-1}; HRMS (ESI): $C_{23}H_{19}N_3O_3S_2$ $[M + H]^+$ calcd, 450.0941; found, 450.0959.

*(2S,3S)-3-(Nitromethyl)-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)nonan-1-one (**3m**).* Colorless oil; 38.2 mg, 85% yield (1.6:1 dr); 94%/92% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 4.3/4.6 min, t_{major} = 5.2/8.1 min); $[\alpha]^{rt}_D$ =19.5(c = 0.97, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.57−7.52 (m, 1H), 7.50−7.42 (m, 4H), 7.34−7.24 (m, 6H), 7.24 (s, 1H), 5.44 (d, J = 37.3, 7.7 Hz, 1H), 4.93 (dd, J = 16.3, 13.1, 3.7 Hz, 1H), 4.61 (dd, J = 27.1, 13.1, 8.0 Hz, 1H), 3.04−2.62 (m, 1H), 1.54−1.40 (m, 2H), 1.38−1.27 (m, 2H), 1.24−1.10 (m, 6H), 0.84 (m, J = 11.6, 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 185.3, 142.1, 137.9, 133.4, 132.9, 130.0, 129.3−128.7 (m), 128.5, 128.2, 127.9, 125.6, 76.5, 54.2, 53.9, 39.4, 38.5, 31.4, 30.1, 29.0, 26.1, 22.5, 14.0 ppm; IR (neat) 3348, 2927, 2858, 2374, 1681, 1551, 1445, 1402, 757, 693 cm^{-1}; HRMS (ESI): $C_{25}H_{29}N_3O_3S$ $[M + H]^+$ calcd, 452.2002; found, 452.2020.

*(2S,3S)-4-Methyl-3-(nitromethyl)-1-(1-phenyl-1H-imidazol-2-yl)-2-(phenylthio)pentan-1-one (**3n**).* Colorless oil; 35.8 mg, 87% yield; 94% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 5.5 min, t_{major} = 5.0 min); $[\alpha]^{rt}_D$ = 59.1 (c = 1.07, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.61 (dd, J = 6.4, 2.9 Hz, 1H), 7.46 (m, J = 8.4, 5.7 Hz, 4H), 7.37−7.29 (m, 2H), 7.29−7.21 (m, 5H), 5.33 (d, J = 9.8 Hz, 1H), 4.95 (dd, J = 14.1, 3.9 Hz, 1H), 4.54 (dd, J = 14.1, 7.1 Hz, 1H), 3.09 (m, J = 10.5, 3.5 Hz, 1H), 1.99−1.75 (m, 1H), 0.98−0.79 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 185.2, 183.7, 141.0, 136.8, 132.5, 132.1, 131.8, 129.0, 128.5−127.8 (m), 127.6, 127.1, 126.6, 124.5, 76.4, 76.0, 75.6, 74.9, 73.5, 52.6, 45.1, 42.1, 28.4, 19.4, 18.9, 18.6, 16.6 ppm; IR (neat) 3343, 2963, 2399, 1682, 1553, 1401, 1261, 1024, 758, 693 cm^{-1}; HRMS (ESI): $C_{22}H_{23}N_3O_3S$ $[M + H]^+$ calcd, 410.1533; found, 410.1540.

*(2S,3S)-2-(Benzylthio)-4-nitro-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**3o**).* Colorless oil; 31.7 mg, 69% yield; 95% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 10.2 min, t_{major} = 9.1 min); $[\alpha]^{rt}_D$ = −210.3 (c = 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.47 (d, J = 7.0 Hz, 2H), 7.37 (m, J = 11.0, 8.8, 4.5 Hz, 6H), 7.27 (s, 1H), 7.21−7.10 (m, 6H), 6.98 (dd, J = 7.7, 1.6 Hz, 2H), 5.03 (d, J = 11.4 Hz, 1H), 4.92−4.84 (m, 1H), 4.12−3.95 (m, 2H), 3.87 (q, J = 13.1 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.4, 142.4, 137.7, 137.6, 137.4, 129.8, 129.4[4], 129.4[1], 129.0, 128.9, 128.8[8], 128.8, 128.2, 127.9, 127.5, 125.2, 78.8, 49.5, 43.0, 35.9 ppm; IR (neat) 3349, 2924, 2373, 1681, 1552, 1382, 1261, 1099, 760, 698 cm^{-1}; HRMS (ESI): $C_{26}H_{23}N_3O_3S$ $[M + H]^+$ calcd, 458.1533; found, 458.1538.

*(2S,3S)-2-((2-Bromobenzyl)thio)-4-nitro-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**3p**).* Colorless oil; 41.5 mg, 77% yield; 91% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate =1.0 mL/min, t_{minor} = 27.2 min, t_{major} = 24.5 min); $[\alpha]^{rt}_D$ = −167.0 (c = 1.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.59 (t, J = 9.2 Hz, 2H), 7.42−7.31 (m, 4H), 7.26 (s, 1H), 7.23−7.11 (m, 7H), 7.00 (dd, J = 7.6, 1.5 Hz, 2H), 5.16−4.95 (m, 2H), 4.29−4.15 (m, 1H), 4.07 (dd, J = 11.5, 3.6 Hz, 1H), 4.01 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.3, 142.4, 137.7, 137.3, 136.4, 133.6, 131.5, 129.8, 129.6, 129.0, 128.8, 128.2, 127.9, 127.6, 127.5, 125.2, 124.9, 78.8, 49.5, 43.1, 36.4 ppm; IR (neat) 3346, 2924, 2395, 1683, 1552, 1493, 1379, 1027, 758, 697 cm^{-1}; HRMS (ESI): $C_{26}H_{22}BrN_3O_3S$ $[M + H]^+$ calcd, 536.0638; found, 536.0643.

*(2S,3S)-2-((4-(tert-Butyl)benzyl)thio)-4-nitro-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**3q**).* Colorless oil; 36.1 mg, 70% yield; 95% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 8.0 min, t_{major} = 6.5 min); $[\alpha]^{rt}_D$ = −169.2 (c = 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.49−7.32 (m, 8H), 7.30−7.23 (m, 2H), 7.15 (m, J = 18.3, 6.6 Hz, 6H), 6.99 (dd, J = 7.7, 1.7 Hz, 2H), 5.09−4.97 (m, 1H), 4.91−4.75 (m, 1H), 4.01−3.90 (m, 2H), 3.80 (dd, J = 26.8, 13.8 Hz, 2H), 1.33 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.3, 151.1, 142.4, 137.8, 137.7, 134.3, 129.8, 129.2, 129.0, 128.8, 128.2, 127.8, 127.4, 125.8, 125.2, 78.7, 49.6, 42.9, 35.7, 34.7, 31.4 ppm; IR (neat) 3347, 2964, 2370, 1684, 1554, 1494, 1404, 1217, 758, 697 cm^{-1}; HRMS (ESI): $C_{30}H_{31}N_3O_3S$ $[M + H]^+$ calcd, 514.2159; found, 514.2166.

*(2S,3S)-2-(Ethylthio)-4-nitro-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**3r**).* White solid, mp 163−165 °C; 31.7 mg, 80% yield; 97% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t = 6.3 min); $[\alpha]^{rt}_D$ = −138.0 (c = 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.41−7.31 (m, 3H), 7.28−7.23 (m, 4H), 7.23−7.18 (m, 2H), 7.11 (d, J = 0.7 Hz, 1H), 6.94 (dd, J = 7.9, 1.5 Hz, 2H), 5.32 (dd, J = 12.8, 4.0 Hz, 1H), 5.12 (d, J = 11.8 Hz, 1H), 4.79 (dd, J = 12.7, 10.5 Hz, 1H), 4.08 (ddd, J = 11.6, 10.6, 4.0 Hz, 1H), 2.83−2.53 (m, 2H), 1.25 (t, J = 7.5 Hz, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.0, 142.2, 137.7, 137.4, 129.7, 129.0, 128.8, 128.7, 128.2, 128.0, 127.4, 125.2, 79.3, 49.6, 43.0, 24.4, 14.1 ppm; **IR** (neat) 3342, 2923, 2375, 1594, 1545, 1382, 1112, 771, 700, 627 cm^{-1}; HRMS (ESI): $C_{21}H_{21}N_3O_3S$ $[M + H]^+$ calcd, 396.1376; found, 396.1382.

*(2S,3S)-2-((2-Hydroxyethyl)thio)-4-nitro-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**3s**).* Colorless oil; 31.9 mg, 77% yield; 83% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 9.3 min, t_{major} = 6.6 min); $[\alpha]^{rt}_D$ = −88.8 (c = 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.43−7.29 (m, 4H), 7.22 (d, J = 10.9 Hz, 5H), 7.12 (s, 1H), 6.86 (d, J = 7.0 Hz, 2H), 5.41−5.28 (m, 2H), 4.88 (dd, J = 12.7, 10.4 Hz, 1H), 4.38 (s, 1H), 4.09 (td, J = 10.7, 4.2 Hz, 1H), 3.88 (s, 2H), 2.86 (t, J = 5.3 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) = 184.1, 141.7, 137.5, 137.4, 129.5, 129.2, 129.1, 128.9, 128.3, 128.0, 127.5, 125.2, 78.8, 62.6, 49.7, 44.7, 35.3 ppm; IR (neat) 3343, 2923, 2370, 1677, 1596, 1550, 1382, 1068, 767, 697 cm^{-1}; HRMS (ESI): $C_{21}H_{21}N_3O_4S$ $[M + H]^+$ calcd, 412.1326; found, 412.1331.

*(2S,3S)-4-Nitro-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)butan-1-one (**4a**).* Colorless oil; 39.4 mg, 89% yield; 92% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 8.1 min, t_{major} = 12.1 min); $[\alpha]^{rt}_D$ = 10.9 (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.45−7.33 (m, 5H), 7.33−7.22 (m, 4H), 7.10−7.02 (m, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.29 (d, J = 5.1 Hz, 1H), 4.97 (m, J = 22.8, 13.6, 7.1 Hz, 2H), 4.45−4.22 (m, 1H), 2.21 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.7, 155.1, 141.5, 137.4, 136.4, 131.2, 130.5, 130.0, 129.0, 128.8, 128.6, 128.2, 127.9, 125.7, 115.3, 79.2, 77.5, 46.5, 20.5 ppm; IR (neat) 3370, 2924, 2374, 1554, 1223, 760, 697, 520 cm^{-1}; HRMS (ESI): $C_{26}H_{23}N_3O_4$ $[M + H]^+$ calcd, 442.1761; found, 442.1773.

*(2S,3S)-3-(4-Fluorophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)butan-1-one (**4b**).* Colorless oil; 39.2 mg, 85% yield; 91% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 6.1 min, t_{major} = 8.4 min); $[\alpha]^{rt}_D$ = 14.4 (c = 0.97, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.46−7.35 (m, 5H), 7.33 (s, 1H), 7.21 (s, 1H), 7.11 (m, J = 6.3, 2.5 Hz, 2H), 6.98 (t, J = 8.0 Hz, 4H), 6.80 (d, J = 8.4 Hz, 2H), 6.24 (d, J = 4.8 Hz, 1H), 4.94 (m, J = 23.1, 13.6, 7.2 Hz, 2H), 4.34 (m, J = 9.5, 4.8 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.4, 162.5 (d, J = 245.7 Hz), 154.9, 141.3, 137.3, 132.3 (d, J = 3.2 Hz), 131.4, 130.6, 130.3 (d, J = 8.2 Hz), 130.1, 129.1 (overlapped), 128.0, 125.7, 115.8 (d, J = 2.1 Hz), 115.2, 79.2, 76.1, 45.7, 20.5. IR (neat) 3364, 2925, 2367, 1693, 1555, 1510, 1229, 1107, 761, 694 cm^{-1}; HRMS (ESI): $C_{26}H_{22}FN_3O_4$ $[M + H]^+$ calcd, 460.1667; found, 460.1687.

*(2S,3S)-3-(4-Chlorophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)butan-1-one (**4c**).* Colorless oil; 40.0 mg, 84% yield; 90% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 6.5 min, t_{major} = 7.5 min); $[\alpha]^{rt}_D$ = 42.6 (c = 1.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.44−7.31 (m, 6H), 7.25 (m, J = 10.5, 7.8 Hz, 3H), 7.16−7.07 (t, 2H), 6.99 (d, J = 8.3 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 6.23 (d, J = 4.5 Hz, 1H), 4.94 (m, J = 13.8, 7.2 Hz, 2H), 4.34 (m, J = 9.4, 4.7 Hz, 1H), 2.21 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.2, 154.8, 141.2, 137.2, 135.1, 134.1, 131.3, 130.5, 130.0, 129.8, 128.9[9], 128.9[6], 128.0, 125.6, 115.1, 79.1, 75.7, 45.6, 20.4 ppm; IR (neat) 3366, 2925, 2373, 1694, 1555, 1509, 1403, 1219, 759, 694 cm^{-1}; HRMS (ESI): $C_{26}H_{22}ClN_3O_4$ $[M + H]^+$ calcd, 476.1372; found, 476.1392.

*(2S,3S)-3-(4-Bromophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)butan-1-one (**4d**).* Colorless oil; 42.6 mg, 82% yield; 93% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-

DOI: 10.1021/acs.joc.5b00013
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propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 6.4 min, t_{major} = 7.0 min); $[\alpha]^{rt}_D$ = 43.5 (c = 0.97, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.40 (m, J = 9.5, 6.4 Hz, 5H), 7.32 (m, J = 14.0, 5.8 Hz, 3H), 7.22 (s, 1H), 7.16−7.07 (m, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 6.22 (d, J = 4.5 Hz, 1H), 4.94 (m, J = 13.8, 7.2 Hz, 2H), 4.32 (m, J = 9.3, 4.7 Hz, 1H), 2.22 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.3, 154.9, 141.2, 137.3, 135.7, 132.0, 131.4, 130.6, 130.3, 130.1, 129.1, 128.1, 125.7, 122.4, 115.2, 79.2, 75.7, 45.8, 20.5 ppm; IR (neat) 3367, 2925, 2371, 1695, 1555, 1509, 1403, 1229, 1013, 759, 694 cm^{-1}; HRMS (ESI): $C_{26}H_{22}BrN_3O_4$ $[M + H]^+$ calcd, 520.0866; found, 520.0888.

*(2S,3S)-4-Nitro-1-(1-phenyl-1H-imidazol-2-yl)-3-(p-tolyl)-2-(p-tolyloxy)butan-1-one (**4e**).* Colorless oil; 36.4 mg, 80% yield; 90% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 5.9 min, t_{major} = 6.5 min); $[\alpha]^{rt}_D$ = 20.7 (c = 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.42−7.34 (m, 3H), 7.32 (s, 1H), 7.27 (t, J = 6.9 Hz, 2H), 7.18 (d, J = 0.6 Hz, 1H), 7.13−7.02 (m, 4H), 6.98 (d, J = 8.4 Hz, 2H), 6.25 (d, J = 5.0 Hz, 1H), 4.95 (qd, J = 13.5, 7.2 Hz, 2H), 4.30 (dt, J = 9.6, 5.0 Hz, 1H), 2.28 (s, 3H), 2.23 (d, J = 7.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.8, 155.1, 141.5, 137.9, 137.4, 133.3, 131.2, 130.4, 130.0, 129.5, 129.0, 128.9, 128.4, 127.8, 125.7, 115.2, 79.3, 76.4, 46.1, 21.1, 20.5 ppm; IR (neat) 3366, 2924, 1879, 1692, 1554, 1510, 1403, 1229, 758, 694 cm^{-1}; HRMS (ESI): $C_{27}H_{25}N_3O_4$ $[M + H]^+$ calcd, 456.1918; found, 456.1922.

*(2S,3S)-3-(4-Methoxyphenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)butan-1-one (**4f**).* Colorless oil; 44.4 mg, 94% yield; 86% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 8.5 min, t_{major} = 12.7 min); $[\alpha]^{rt}_D$ = 25.2 (c = 1.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.38 (m, J = 8.6, 3.1 Hz, 3H), 7.32 (m, J = 7.8, 5.3 Hz, 3H), 7.17 (s, 1H), 7.06 (m, J = 4.5, 3.3 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.82 (t, J = 8.7 Hz, 4H), 6.25 (d, J = 5.3 Hz, 1H), 4.93 (m, J = 22.8, 13.4, 7.2 Hz, 2H), 4.28 (m, J = 9.7, 5.0 Hz, 1H), 3.74 (s, 3H), 2.21 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.9, 159.4, 155.1, 141.5, 137.4, 131.2, 130.5, 130.0, 129.7, 129.0, 128.2, 127.9, 125.7, 115.2, 114.2, 79.3, 76.6, 55.3, 45.9, 20.5 ppm; IR (neat) 3301, 2925, 2373, 1690, 1553, 1511, 1253, 1033, 762, 695 cm^{-1}; HRMS (ESI): $C_{27}H_{25}N_3O_5$ $[M + H]^+$ calcd, 472.1867; found, 472.1872.

*(2S,3S)-3-(3-Chlorophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)butan-1-one (**4g**).* Colorless oil; 37.7 mg, 79% yield; 88% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 7.0 min, t_{major} = 8.7 min); $[\alpha]^{rt}_D$ = 22.3 (c = 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.44−7.37 (m, 4H), 7.36−7.29 (m, 2H), 7.25−7.21 (m, 2H), 7.20 (d, J = 0.9 Hz, 1H), 7.11 (m, J = 4.4, 3.5 Hz, 2H), 6.99 (d, J = 8.3 Hz, 2H), 6.84−6.77 (m, 2H), 6.25 (d, J = 4.8 Hz, 1H), 5.01 (dd, J = 13.9, 4.9 Hz, 1H), 4.90 (dd, J = 13.9, 9.4 Hz, 1H), 4.31 (dt, J = 9.5, 4.9 Hz, 1H), 2.22 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.2, 154.9, 141.3, 138.5, 137.3, 134.6, 131.4, 130.6, 130.1, 130.0, 129.1, 129.0, 128.5, 128.1, 126.7, 125.7, 115.2, 78.9, 75.7, 46.1, 20.5 ppm; IR (neat) 3359, 2925, 2370, 1694, 1555, 1509, 1403, 1219, 1089, 762, 694 cm^{-1}; HRMS (ESI): $C_{26}H_{22}ClN_3O_4$ $[M + H]^+$ calcd, 476.1372; found, 476.1377.

*(2S,3S)-4-Nitro-2-phenoxy-1-(1-phenyl-1H-imidazol-2-yl)-3-(m-tolyl)butan-1-one (**4h**).* Colorless oil; 30.2 mg, 66% yield; 87% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 6.1 min, t_{major} = 7.1 min); $[\alpha]^{rt}_D$ = 9.9 (c = 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.41−7.30 (m, 4H), 7.16 (d, J = 6.6 Hz, 4H), 7.02 (m, J = 6.9, 3.8, 1.8 Hz, 4H), 6.97 (s, 1H), 6.86 (d, J = 5.6 Hz, 2H), 6.29 (d, J = 5.5 Hz, 1H), 5.02 (dd, J = 13.5, 5.0 Hz, 1H), 4.90 (dd, J = 13.5, 9.3 Hz, 1H), 4.36−4.18 (m, 1H), 2.29 (s, 3H), 2.21 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.8, 155.0, 141.6, 138.4, 137.3, 136.0, 131.1, 130.3, 129.9, 129.4, 128.9, 128.6, 127.7, 125.6, 115.2, 78.9, 76.4, 46.5, 21.3, 20.4 ppm; IR (neat) 3364, 2924, 2374, 1695, 1555, 1509, 1403, 1228, 760, 695 cm^{-1}; HRMS (ESI): $C_{27}H_{25}N_3O_4$ $[M + H]^+$ calcd, 456.1918; found, 456.1923.

*(2S,3S)-3-(2-Fluorophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)butan-1-one (**4i**).* White solid, mp 103−105 °C; 27.1 mg, 59% yield; 87% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 6.4 min, t_{major} = 9.9 min); $[\alpha]^{rt}_D$ = 5.1 (c = 0.99, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.46−7.34 (m, 4H), 7.34−7.17 (m, 3H), 7.15 (s, 1H), 7.06 (m, J = 5.5, 3.9 Hz, 3H), 7.00 (d, J = 8.7 Hz, 3H), 6.85 (d, J = 8.5 Hz, 2H), 6.36 (d, J = 6.4 Hz, 1H), 5.09 (dd, J = 13.7, 5.2 Hz, 1H), 4.96 (dd, J = 13.7, 8.9 Hz, 1H), 4.60 (m, J = 9.0, 5.8 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.5, 161.0 (d, J = 246.3 Hz), 154.9, 141.5, 137.4, 131.3, 130.6 (d, J = 4.0 Hz), 130.5, 130.1 (J = 8.2 Hz), 130.0, 129.0, 127.9, 125.7, 124.5 (J = 3.8 Hz), 123.0 (d, J = 14.3 Hz), 116.0 (J = 21.8 Hz), 115.1, 77.5, 75.3 (overlapped), 41.2, 20.5. IR (neat) 3367, 2963, 2407, 1693, 1556, 1403, 1221, 1110, 759, 694 cm^{-1}; HRMS (ESI): $C_{26}H_{22}FN_3O_4$ $[M + H]^+$ calcd, 460.1667; found, 460.1672.

*(2S,3S)-3-(Naphthalen-2-yl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)butan-1-one (**4j**).* Colorless oil; 31.3 mg, 64% yield; 85% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 10.4 min, t_{major} = 11.3 min); $[\alpha]^{rt}_D$ = 62.7 (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.77 (m, J = 10.2, 5.2 Hz, 4H), 7.55 (dd, J = 8.5, 1.3 Hz, 1H), 7.49−7.42 (m, 2H), 7.35 (m, J = 16.8, 9.7, 4.1 Hz, 4H), 7.08 (s, 1H), 6.98 (d, J = 8.5 Hz, 2H), 6.89 (m, J = 13.5, 7.9 Hz, 4H), 6.39 (d, J = 5.4 Hz, 1H), 5.07 (m, J = 13.6, 7.2 Hz, 2H), 4.56−4.43 (m, 1H), 2.21 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.7, 155.1, 141.6, 137.2, 133.5, 133.3, 133.0, 131.3, 130.4, 130.0, 129.0, 128.9, 128.6, 128.2, 128.0, 127.9, 127.6, 126.4, 125.9, 125.7, 115.3, 79.1, 76.3, 46.8, 20.5 ppm; IR (neat) 3298, 2924, 2405, 1690, 1553, 1510, 1223, 1016, 759, 694 cm^{-1}; HRMS (ESI): $C_{30}H_{25}N_3O_4$ $[M + H]^+$ calcd, 492.1918; found, 492.1926.

*(2S,3S)-3-(Furan-2-yl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)butan-1-one (**4k**).* Colorless oil; 32.5 mg, 75% yield; 80% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 5.9 min, t_{major} = 7.6 min); $[\alpha]^{rt}_D$ = 14.1 (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.56−7.38 (m, 3H), 7.32 (s, 2H), 7.24−7.11 (m, 3H), 6.99 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.37 (d, J = 5.8 Hz, 1H), 6.23 (s, 2H), 4.95 (qd, J = 13.8, 6.9 Hz, 2H), 4.52 (dt, J = 8.3, 5.5 Hz, 1H), 2.23 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.3, 155.0, 149.2, 142.8, 141.3, 137.4, 131.3, 130.6, 130.0, 129.1, 128.0, 125.7, 115.2, 115.2, 110.5, 77.5, 74.1, 40.7, 20.5 ppm; IR (neat) 3369, 2924, 2450, 1695, 1556, 1509, 1404, 1229, 760, 694 cm^{-1}; HRMS (ESI): $C_{24}H_{21}N_3O_5$ $[M + H]^+$ calcd, 432.1554; found, 432.1558.

*(2S,3S)-4-Nitro-2-phenoxy-1-(1-phenyl-1H-imidazol-2-yl)-3-(thiophen-2-yl)butan-1-one (**4l**).* Colorless oil; 31.4 mg, 70% yield; >99% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 9.3 min, t_{major} = 10.5 min); $[\alpha]^{rt}_D$ = −13.4 (c = 0.97, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.46−7.38 (m, 3H), 7.38−7.33 (d, 1H), 7.25 (s, J = 0.9 Hz, 1H), 7.22−7.14 (m, 3H), 7.09−7.04 (t, 1H), 7.00 (d, J = 8.3 Hz, 2H), 6.91 (dd, J = 5.1, 3.5 Hz, 1H), 6.83 (d, J = 5.7 Hz, 2H), 6.29 (d, J = 3.7 Hz, 1H), 4.97 (dd, J = 13.4, 4.5 Hz, 1H), 4.83 (dd, J = 13.3, 8.9 Hz, 1H), 4.74 (m, J = 8.6, 4.2 Hz, 1H), 2.23 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.0, 154.8, 141.2, 138.6, 137.4, 131.4, 130.7, 130.0, 129.1, 128.1, 127.2, 126.7, 125.9, 125.7, 115.2, 79.4, 76.8, 42.0, 20.5 ppm; IR (neat) 3343, 2925, 2373, 1694, 1556, 1403, 1218, 1040, 763, 699 cm^{-1}; HRMS (ESI): $C_{24}H_{21}N_3O_4S$ $[M + H]^+$ calcd, 448.1326; found, 448.1332.

*(2S,3S)-3-(3,5-Dimethoxyphenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)butan-1-one (**4m**).* Colorless oil; 31.5 mg, 63% yield; 76% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 6.0 min, t_{major} = 6.7 min); $[\alpha]^{rt}_D$ = 12.9 (c = 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.47−7.27 (m, 5H), 7.17 (d, J = 0.7 Hz, 1H), 7.06 (m, J = 7.0, 3.1 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.85 (m, J = 8.2, 6.0 Hz, 2H), 6.52 (d, J = 2.2 Hz, 2H), 6.38−6.23 (m, 2H), 4.95 (m, J = 22.7, 13.6, 7.1 Hz, 2H), 4.31−4.10 (m, 1H), 3.72 (s, 6H), 2.22 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.7, 160.9, 155.0, 141.7, 138.3, 137.3, 131.2, 130.4, 130.0, 129.0, 127.8, 125.7, 115.2, 114.5, 106.7, 100.3, 78.8, 76.3, 55.3, 46.8, 20.5 ppm; IR (neat) 3370, 2927, 2450, 1695, 1597, 1555, 1229, 1155, 759, 694 cm^{-1}; HRMS (ESI): $C_{28}H_{27}N_3O_6$ $[M + H]^+$ calcd, 502.1973; found, 502.1979.

*(2S,3S)-3-(Nitromethyl)-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)nonan-1-one (**4n**).* White solid, mp 92−94 °C; 24.1 mg, 54% yield; 86% ee determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 90/10, flow rate = 1.0 mL/min, t_{minor} = 6.0 min, t_{major} = 9.5 min); $[\alpha]^{rt}_D$ = 1.9 (c = 1.07, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.50−7.38 (m, 3H), 7.36 (s, 1H), 7.33−7.21 (m, 3H), 7.02

DOI: 10.1021/acs.joc.5b00013
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(d, J = 13.8 Hz, 2H), 6.76 (d, J = 8.2 Hz, 2H), 6.18 (s, 1H), 4.70 (dd, J = 13.9, 4.3 Hz, 1H), 4.42 (dd, J = 13.8, 7.5 Hz, 1H), 3.09 (s, 1H), 2.23 (s, 3H), 1.84−1.70 (m, 1H), 1.66−1.45 (m, 4H), 1.28 (m, 6H), 0.87 (m, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.4, 154.2, 140.1, 136.5, 129.8, 129.4, 128.9, 128.1, 128.0, 126.9, 124.7, 113.8, 74.6, 39.0, 30.5, 29.5, 28.0, 25.4, 21.6, 19.4, 13.0, 0.0 ppm; IR (neat) 3369, 2927, 2857, 2366, 1696, 1553, 1509, 1233, 760, 694 cm^{-1}; HRMS (ESI): $C_{26}H_{31}N_3O_4$ $[M + H]^+$ calcd, 450.2387; found, 450.2395.

*(2S,3S)-4-Methyl-3-(nitromethyl)-1-(1-phenyl-1H-imidazol-2-yl)-2-(p-tolyloxy)pentan-1-one (**4o**).* White solid, mp 151−153 °C; 21.7 mg, 53% yield; 94% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 7.1 min, t_{major} = 6.1 min); $[\alpha]^{rt}_D$ = −8.5(c = 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.54−7.34 (m, 4H), 7.27 (m, J = 6.0, 3.3 Hz, 3H), 6.99 (d, J = 8.2 Hz, 2H), 6.83−6.68 (m, 2H), 6.30 (d, J = 1.6 Hz, 1H), 4.80 (dd, J = 14.6, 4.1 Hz, 1H), 4.51 (dd, J = 14.6, 6.6 Hz, 1H), 2.94 (m, J = 6.5, 4.6 Hz, 1H), 2.22 (s, 3H), 2.06 (m, J = 13.1, 6.7 Hz, 1H), 1.12 (m, J = 6.7, 2.9 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 187.6, 154.8, 141.0, 137.6, 130.8, 130.4, 130.0, 129.1, 129.0, 128.0, 125.8, 114.6, 73.8, 45.3, 30.3, 20.5, 20.3, 19.7 ppm; IR (neat) 3368, 2964, 2407, 1695, 1553, 1510, 1403, 1233, 761, 694 cm^{-1}; HRMS (ESI): $C_{23}H_{25}N_3O_4$ $[M + H]^+$ calcd, 408.1918; found, 408.1924.

*(2S,3S)-4-Nitro-2-phenoxy-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**4p**).* White solid, mp 122−124 °C; 30.6 mg, 71% yield; 88% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 5.2 min, t_{major} = 7.6 min); $[\alpha]^{rt}_D$ = 27.4 (c = 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.44−7.34 (m, 5H), 7.34−7.23 (m, 4H), 7.23−7.15 (m, 3H), 7.10−7.04 (m, 2H), 6.92 (m, J = 12.3, 4.5 Hz, 3H), 6.34 (d, J = 5.0 Hz, 1H), 4.98 (qd, J = 13.6, 7.1 Hz, 2H), 4.48−4.25 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.5, 157.1, 141.4, 137.3, 136.3, 130.5, 129.6, 129.0, 128.9, 128.6, 128.3, 127.9, 125.7, 121.9, 115.3, 79.0, 76.2, 46.3 ppm; IR (neat) 3369, 2925, 2408, 1694, 1596, 1554, 1403, 1227, 754,695 cm^{-1}; HRMS (ESI): $C_{25}H_{21}N_3O_4$ $[M + H]^+$ calcd, 428.1605; found, 428.1610.

*(2S,3S)-2-(2-Methoxyphenoxy)-4-nitro-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**4q**).* Colorless oil; 30.8 mg, 67% yield; 92% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 9.7 min, t_{major} = 7.1 min); $[\alpha]^{rt}_D$ = −17.2 (c = 0.93, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.46−7.34 (m, 5H), 7.31−7.20 (m, 4H), 7.15 (s, 1H), 7.11−6.97 (m, 2H), 6.96−6.80 (m, 3H), 6.78−6.65 (m, 1H), 6.24 (d, J = 5.7 Hz, 1H), 5.18 (dd, J = 13.7, 4.6 Hz, 1H), 5.01 (dd, J = 13.7, 9.9 Hz, 1H), 4.35 (dt, J = 10.1, 5.0 Hz, 1H), 3.77 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.5, 150.2, 146.7, 141.7, 137.5, 136.3, 130.4, 129.9, 128.8, 128.7, 128.1, 127.7, 125.7, 123.0, 120.7, 116.8, 112.6, 80.3, 76.4, 55.9, 46.7 ppm; IR (neat) 3363, 2924, 2378, 1690, 1553, 1501, 1381, 1257, 1025, 759, 698 cm^{-1}; HRMS (ESI): $C_{26}H_{23}N_3O_5$ $[M + H]^+$ calcd, 458.1710; found, 458.1720.

*(2S,3S)-2-(3-Chlorophenoxy)-4-nitro-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**4r**).* White solid, mp 120−122 °C; 31.5 mg, 68% yield; 90% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 10.8 min, t_{major} = 13.9 min); $[\alpha]^{rt}_D$ = 13.1 (c = 1.07, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.44−7.36 (m, 5H), 7.35 (s, 1H), 7.31 (m, J = 11.1, 4.9 Hz, 3H), 7.21 (s, 1H), 7.09 (m, J = 7.8, 6.2 Hz, 3H), 6.98 (t, J = 2.1 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 6.81 (dd, J = 8.3, 2.4 Hz, 1H), 6.32 (d, J = 5.0 Hz, 1H), 4.96 (m, J = 13.6, 7.1 Hz, 2H), 4.43−4.31 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 185.9, 157.7, 141.4, 137.2, 136.1, 135.0, 130.6, 130.4, 129.1, 129.0, 128.9, 128.5, 128.4, 128.1, 125.7, 122.2, 116.2, 113.4, 79.2, 75.9, 46.4 ppm; IR (neat) 3369, 2962, 2374, 1692, 1555, 1381, 1222, 1092, 767, 698 cm^{-1}; HRMS (ESI): $C_{25}H_{20}ClN_3O_4$ $[M + H]^+$ calcd, 462.1215; found, 462.1220.

*(2S,3S)-2-(Naphthalen-2-yloxy)-4-nitro-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**4s**).* White solid, mp 167−169 °C; 34.7 mg, 73% yield; 83% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 8.6 min, t_{major} = 9.7 min); $[\alpha]^{rt}_D$ = −60.4 (c = 1.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.75−7.66 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.45−7.38 (m, 3H), 7.37 (s, 3H), 7.35−7.28 (m, 4H), 7.25 (d, J = 7.1 Hz, 2H), 7.23−7.15 (m, 2H), 7.08−6.97 (m, 2H), 6.50 (d, J = 5.3 Hz, 1H), 5.03 (ddd, J = 22.7, 13.6, 7.1 Hz, 2H), 4.52−4.34 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 186.5, 155.0, 141.6, 137.4, 137.3, 136.2, 134.1, 130.5, 129.8, 129.5, 129.0, 128.9, 128.6, 128.3, 128.0, 127.6, 127.0, 126.4, 125.7, 124.1, 118.6, 108.6, 79.0, 76.3, 46.5 ppm; IR (neat) 3368, 2962, 2398, 1692, 1555, 1380, 1258, 1216, 757, 697 cm^{-1}; HRMS (ESI): $C_{29}H_{23}N_3O_4$ $[M + H]^+$ calcd, 478.1761; found, 478.1767

*(2S,3S)-4-Nitro-1-oxo-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)-butan-2-yl Acetate (**4t**).* Colorless oil; 26.3 mg, 67% yield; 90% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 5.6 min, t_{major} = 9.9 min); $[\alpha]^{rt}_D$ = 99.0 (c = 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.46 (m, J = 6.5, 3.8 Hz, 3H), 7.43−7.36 (m, 3H), 7.35 (s, 2H), 7.32 (m, J = 2.3 Hz, 1H), 7.22 (m, J = 6.8, 2.7 Hz, 3H), 6.37 (d, J = 3.6 Hz, 1H), 4.94−4.77 (m, 2H), 4.49 (m, J = 9.0, 5.6, 3.6 Hz, 1H), 2.10 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 184.2, 169.7, 140.7, 137.6, 136.5, 130.6, 129.1, 129.0, 128.9, 128.3, 128.2, 127.7, 125.8, 77.0, 75.0, 44.4, 20.4 ppm; IR (neat) 3376, 2962, 2445, 1749, 1697, 1556, 1405, 1228, 759, 698 cm^{-1}; HRMS (ESI): $C_{21}H_{19}N_3O_5$ $[M + H]^+$ calcd, 394.1397; found, 394.1402.

*(2S,3S)-2-Chloro-4-nitro-3-phenyl-1-(1-phenyl-1H-imidazol-2-yl)-butan-1-one (**5a**).* White solid, mp 146−148 °C; 36.4 mg, 88% yield (4.0:1 dr); 95%/97% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 9.3/10.2 min, t_{major} = 8.1/11.6 min); $[\alpha]^{rt}_D$ = 43.8 (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41 (m, J = 5.6, 3.7 Hz, 3H), 7.30−7.24 (m, 6H), 7.18 (d, J = 0.7 Hz, 1H), 6.99 (dd, J = 7.9, 1.6 Hz, 2H), 6.12 (d, J = 9.5 Hz, 1H), 5.13 (dd, J = 13.2, 4.4 Hz, 1H), 4.87 (dd, J = 13.2, 10.1 Hz, 1H), 4.31 (m, J = 9.8, 4.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.8, 140.9, 137.3, 135.3, 130.6, 129.1^2, 129.1^1, 129.0, 128.6, 128.5, 125.4, 59.7, 57.9, 46.3 ppm; IR (neat) 3370, 2925, 2366, 1696, 1556, 1403, 1217, 1090, 761, 696 cm^{-1}; HRMS (ESI): $C_{19}H_{16}ClN_3O_3$ $[M + H]^+$ calcd, 370.0953; found, 370.0959.

*(2S,3S)-2-Chloro-3-(4-chlorophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**5b**).* White solid, mp 133−135 °C; 32 mg, 79% yield (3.6:1 dr); 81% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 40/60, flow rate = 1.0 mL/min, t_{minor} = 6.5 min, t_{major} = 15.3 min); $[\alpha]^{rt}_D$ = 91.3 (c = 1.03, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.49−7.39 (m, 3H), 7.30 (d, J = 0.8 Hz, 1H), 7.26−7.20 (m, 4H), 7.11−7.04 (m, 2H), 6.07 (d, J = 9.3 Hz, 1H), 5.11 (dd, J = 13.3, 4.4 Hz, 1H), 4.83 (dd, J = 13.3, 10.2 Hz, 1H), 4.30 (td, J = 9.8, 4.3 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.5, 140.7, 137.2, 134.5, 133.9, 130.7, 129.9, 129.2,129.1,128.7, 125.4, 77.2, 57.7, 45.5 ppm; IR (neat) 3365, 2925, 2370, 1695, 1556, 1402, 1380, 1095, 759, 694 cm^{-1}; HRMS (ESI): $C_{19}H_{15}Cl_2N_3O_3$ $[M + H]^+$ calcd, 404.0563; found, 404.0569.

*(2S,3S)-2-Chloro-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-3-(p-tolyl)butan-1-one (**5c**).* White solid, mp 117−119 °C; 29.5 mg, 77% yield; 96% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 6.5 min, t_{major} = 10.6 min); $[\alpha]^{rt}_D$ = 62.4 (c = 0.98, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.46−7.39 (m, 3H), 7.29 (s, 1H), 7.18 (d, J = 3.5 Hz, 2H), 7.15 (s, 1H), 7.10 (d, J = 5.4 Hz, 2H), 7.00 (dd, J = 7.8, 1.6 Hz, 2H), 6.08 (d, J = 9.5 Hz, 1H), 5.10 (dd, J = 13.1, 4.4 Hz, 1H), 4.84 (dd, J = 13.1, 10.1 Hz, 1H), 4.27 (td, J = 9.8, 4.4 Hz, 1H), 2.27 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.9, 140.9, 138.3, 137.3, 132.2, 130.6, 129.7, 129.1, 129.0, 128.4, 125.4, 77.7, 57.9, 45.9, 21.1 ppm; IR (neat) 3341, 2925, 2373, 1696, 1556, 1402, 1380, 1020, 760, 693 cm^{-1}; HRMS (ESI): $C_{20}H_{18}ClN_3O_3$ $[M + H]^+$ calcd, 384.1109; found, 384.1116.

*(2S,3S)-2-Chloro-3-(3-chlorophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**5d**).* White solid, mp 131−133 °C; 25.9 mg, 64% yield (8.6:1 dr); 82% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 6.4 min, t_{major} = 12.4 min); $[\alpha]^{rt}_D$ = 62.8 (c = 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.52−7.40 (m, 3H), 7.30 (dd, J = 3.6, 1.1 Hz, 2H), 7.25−7.18 (m, 4H), 7.12−7.01 (m, 2H), 6.08 (d, J = 9.0 Hz, 1H), 5.12 (dd, J = 13.5, 4.3 Hz, 1H), 4.85 (dd, J = 13.5, 10.1 Hz, 1H), 4.34−4.20 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.5, 140.7, 137.4, 137.2, 134.8, 130.7, 130.2, 129.2, 129.1, 128.8, 128.7, 126.4, 125.4, 76.9, 57.8, 45.8 ppm; IR (neat) 3366, 2924, 2403, 1695, 1556, 1402, 1217, 1019, 760, 693 cm^{-1}; HRMS (ESI): $C_{19}H_{15}Cl_2N_3O_3$ $[M + H]^+$ calcd, 404.0563; found, 404.0569.

DOI: 10.1021/acs.joc.5b00013
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*(2S,3S)-2-Chloro-3-(2-fluorophenyl)-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)butan-1-one (**5e**).* Colorless oil; 20.1 mg, 52% yield; 87% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 6.9 min, t_{major} = 13.6 min); $[\alpha]^{rt}_D$ = 20.5 (*c* = 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.42 (d, *J* = 7.2 Hz, 2H), 7.31 (s, 1H), 7.29−7.22 (m, 3H), 7.21 (s, *J* = 3.1 Hz, 1H), 7.10−6.99 (m, 4H), 6.24 (d, *J* = 9.9 Hz, 1H), 5.16 (dd, *J* = 13.4, 4.5 Hz, 1H), 5.09−4.94 (dd, 2H), 4.47 (td, *J* = 9.7, 4.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.7, 160.8 (d, *J* = 246.3 Hz), 140.7, 137.3, 131.3 (d, *J* = 4.1 Hz), 130.7, 130.4 (d, *J* = 8.5 Hz), 129.2, 129.1, 128.5, 125.3, 124.6 (d, *J* = 3.4 Hz), 122.2 (d, *J* = 13.2 Hz), 116.2 (d, *J* = 22.0 Hz), 76.0, 56.3, 41.9. IR (neat) 3336, 2926, 2373, 1696, 1556, 1402, 1218, 1099, 759, 694 cm^{-1}; HRMS (ESI): $C_{19}H_{15}ClFN_3O_3$ $[M + H]^+$ calcd, 388.0859; found, 388.0865.

*(2S,3S)-2-Chloro-4-nitro-1-(1-phenyl-1H-imidazol-2-yl)-3-(thiophen-2-yl)butan-1-one (**5f**).* White solid, mp 115−117 °C; 28.6 mg, 76% yield (2.3:1); 96%/94% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 8.2/8.7 min, t_{major} = 7.4/11.8 min); $[\alpha]^{rt}_D$ = 41.4 (*c* = 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.49−7.39 (m, 3H), 7.33 (dd, *J* = 4.1, 0.8 Hz, 1H), 7.29−7.18 (m, 2H), 7.17−7.07 (m, 2H), 6.93 (m, *J* = 13.9, 7.0, 3.3 Hz, 2H), 6.10 (d, *J* = 8.7 Hz, 1H), 5.13 (dd, *J* = 13.3, 4.1 Hz, 1H), 5.01 (m, *J* = 7.2, 3.6 Hz, 1H), 4.83 (dd, *J* = 13.3, 9.5 Hz, 1H), 4.63 (td, *J* = 9.1, 4.1 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 181.6, 140.7, 137.3, 136.4, 130.8, 129.2, 128.6, 127.5, 126.1, 126.0, 125.4, 78.0, 57.9, 41.4 ppm; IR (neat) 3370, 2923, 2403, 1695, 1556, 1402, 1095, 1038, 760, 695 cm^{-1}; HRMS (ESI): $C_{17}H_{14}ClN_3O_3S$ $[M + H]^+$ calcd, 376.0517; found, 376.0523.

*(2S,3S)-2-Chloro-3-(nitromethyl)-1-(1-phenyl-1H-imidazol-2-yl)-nonan-1-one (**5g**).* Colorless oil; 18.9 mg, 50% yield (6.4:1 dr); 75% ee determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 60/40, flow rate = 1.0 mL/min, t_{minor} = 5.6 min, t_{major} = 5.2 min); $[\alpha]^{rt}_D$ = 22.9 (*c* = 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.49 (m, *J* = 6.6, 3.6 Hz, 3H), 7.35 (m, *J* = 1.7 Hz, 1H), 7.30 (m, *J* = 7.0, 2.6 Hz, 3H), 6.01 (d, *J* = 4.6 Hz, 1H), 4.72 (dd, *J* = 13.8, 4.5 Hz, 1H), 4.38 (dd, *J* = 13.8, 6.9 Hz, 1H), 3.11 (m, *J* = 10.6, 4.9 Hz, 1H), 1.68−1.46 (m, 4H), 1.35−1.26 (m, 6H), 0.89 (t, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 183.1, 140.7, 137.6, 130.6, 129.2, 128.6, 125.7, 125.6, 75.6, 60.1, 39.9, 31.5, 30.5, 28.9, 26.2, 22.5, 14.1 ppm; IR (neat) 3372, 2928, 2370, 1696, 1554, 1401, 1306, 1037, 761, 694 cm^{-1}; HRMS (ESI): $C_{19}H_{24}ClN_3O_3$ $[M + H]^+$ calcd, 378.1584; found, 378.1586.

*(3S)-Methyl 4-Nitro-3-phenyl-2-(p-tolyloxy)butanoate (**6**).* **4a** (0.14 mmol, 61.9 mg, 1.0 equiv), 4 Å molecular sieves (70 mg), and acetonitrile (1.4 mL) were combined in an oven-dried airtight flask. The suspension was stirred vigorously under a positive pressure of nitrogen for 2 h. Methyl trifluoromethanesulfonate (56 μL) then was added. After 2 h another 14 μL of methyl trifluoromethanesulfonate was added, and the reaction was stirred an additional 30 min. The reaction then was cooled to 0 °C. MeOH (62.7 μL, 1.4 mmol, 10.0 equiv) and DBU (56.6 μL, 3.0 equiv) then were added stepwise. The reaction was stirred at 0 °C for 1 h before being quenched by 1 M HCl (10 mL) and extracted with EA (3 × 15 mL), and the combined organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed in vacuo. The product was purified by flash chromatography (PE:EA = 20:1) to give the product **6**, 13.2 mg, 30% yield (5.0:1 dr). White solid, mp 103−105 °C; 92% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 8.9 min, t_{major} = 9.7 min); $[\alpha]^{rt}_D$ = −67.8 (*c* = 0.58, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.33 (s, 5H), 7.06 (d, *J* = 8.3 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 5.05 (dd, *J* = 13.5, 5.5 Hz, 1H), 4.90 (dd, *J* = 13.5, 9.0 Hz, 1H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.16 (m, *J* = 9.0, 5.7 Hz, 1H), 3.62 (s, 3H), 2.27 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.0, 154.9, 135.6, 132.0, 130.2, 129.1, 128.6, 128.2, 115.1, 78.9, 76.1, 52.5, 46.5, 20.5 ppm; IR (neat) 3342, 2961, 2372, 1752, 1556, 1381, 1261, 1090, 760, 701 cm^{-1}; HRMS (ESI): $C_{18}H_{19}NO_5$ $[M + Na]^+$ calcd, 352.1155; found, 352.1162.

*(3S)-Methyl 2-(Ethylthio)-4-nitro-3-phenylbutanoate (**7**).* Synthesis from **3p** (0.1 mmol) and MeOH. White solid, mp 87−89 °C; 14.0 mg, 46% yield (4.1:1 dr); 95% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 95/5, flow rate = 1.0 mL/min, t_{minor} = 12.8 min, t_{major} = 13.7 min); $[\alpha]^{rt}_D$ = −80.4 (*c* = 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.32 (m, *J* = 10.4, 2.9 Hz, 3H), 7.25−7.19 (m, 2H), 5.18 (dd, *J* = 12.9, 4.3 Hz, 1H), 4.75 (dd, *J* = 13.0, 9.8 Hz, 1H), 3.99−3.87 (m, 1H), 3.62 (d, *J* = 11.3 Hz, 1H), 3.52 (s, 3H), 2.73 (q, *J* = 7.4 Hz, 2H), 1.29 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.5, 136.7, 129.0, 128.4, 127.8, 78.3, 52.3, 49.4, 44.4, 25.6, 14.3 ppm; IR (neat) 3428, 2968, 2402, 1723, 1537, 1432, 1264, 1160, 763, 703 cm^{-1}; HRMS (ESI): $C_{13}H_{17}NO_4S$ $[M + Na]^+$ calcd, 306.0770; found, 306.0776.

*((1S,2R,3S)-2-Nitro-3-phenylcyclopropyl)(1-phenyl-1H-imidazol-2-yl)methanone (**8**).* **5a** (0.50 mmol, 184.5 mg, 1.0 equiv), K_2CO_3 (0.50 mmol, 69.0 mg, 1.0 equiv), and DMF (2.0 mL) were combined in an oven-dried airtight flask. The reaction mixture was stirred at rt and monitored by TLC before being quenched by NH_4Cl (10 mL) and extracted with EA (3 × 15 mL), and the combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The product was purified by flash chromatography to give the product **8**, 133.2 mg, 80% yield. Colorless oil. 96% ee determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 13.4 min, t_{major} = 14.2 min); $[\alpha]^{rt}_D$ = 76.7 (*c* = 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.41−7.33 (m, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.25 (m, *J* = 6.6, 3.5 Hz, 3H), 7.19 (m, *J* = 3.8 Hz, 3H), 6.89 (t, *J* = 5.4 Hz, 2H), 5.37−5.26 (m, 1H), 4.75 (dd, *J* = 11.7, 3.8 Hz, 1H), 3.94 (dd, *J* = 11.7, 4.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 180.6, 142.7, 137.4, 131.0, 130.5, 128.9[2], 128.9[1], 128.8, 128.5, 127.9, 127.7, 125.4, 62.8, 37.4, 36.9 ppm; IR (neat) 3343, 3026, 2964, 2363, 1680, 1548, 1415, 1046, 759, 693 cm^{-1}; HRMS (ESI): $C_{19}H_{15}N_3O_3$ $[M + H]^+$ calcd, 334.1186; found, 334.1194.

*(1S,2R,3S)-Methyl 2-Nitro-3-phenylcyclopropanecarboxylate (**9**).* Synthesis from **8** (0.26 mmol) and MeOH. Colorless oil; 47.5 mg, 83% yield; 93% ee determined by HPLC on a Chiralpak IA-H column (hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, t_{minor} = 6.2 min, t_{major} = 6.4 min); $[\alpha]^{rt}_D$ = −38.3 (*c* = 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 7.40−7.28 (m, 3H), 7.28−7.18 (m, 2H), 5.18 (dd, *J* = 4.8, 3.6 Hz, 1H), 3.66 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.54 (s, 3H), 3.23 (dd, *J* = 11.4, 3.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.3, 131.2, 128.7, 128.5, 128.3, 62.9, 52.5, 34.8, 32.1 ppm; IR (neat) 3341, 2957, 2373, 1738, 1552, 1371, 1206, 1063, 758, 697 cm^{-1}; HRMS (ESI): $C_{11}H_{11}NO_4$ $[M + Na]^+$ calcd, 244.0580; found, 244.0585.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra, copies of HPLC results, and crystallographic data (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSFC (91213302, 91413107, 81473095, 21432003), the National S&T Major Project of China (2012ZX09504001-003), and the Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT1137), and the Innovation Group of Gansu Province (1210RIIA002).

■ REFERENCES

(1) For pioneering works, see: (a) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Enders, D.; Seki, A. *Synlett* **2002**, 26. (d) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.

(2) For selected recent examples, see: (a) Avilaa, A.; Chinchillaa, R.; Fiser, B.; Gómez-Bengoa, E.; Nájera, C. *Tetrahedron: Asymmetry* **2014**, *25*, 462. (b) Bächle, F.; Duschmal, J.; Ebner, C.; Pfaltz, A.; Wennemers,

DOI: 10.1021/acs.joc.5b00013
J. Org. Chem. 2015, 80, 4336−4348

H. *Angew. Chem., Int. Ed.* **2013**, *52*, 12619. (c) Geertsema, E. M.; Miao, Y.; Tepper, P. G.; Haan, P.; Zandvoort, E.; Poelarends, G. J. *Chem.—Eur. J.* **2013**, *19*, 14407. (d) Xu, K.; Zhang, S.; Hu, Y.; Zha, Z.; Wang, Z. *Chem.—Eur. J.* **2013**, *19*, 3573. (e) Sahoo, G.; Rahaman, H.; Madarsz, Á.; Pápai, I.; Melarto, M.; Valkonen, A.; Pihko, P. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 13144. (f) Zheng, Z.; Perking, B. L.; Ni, B. *J. Am. Chem. Soc.* **2010**, *132*, 50. (g) Han, B.; Xiao, Y.; He, Z.; Chen, Y.-C. *Org. Lett.* **2009**, *11*, 4660. (h) Wu, J.; Ni, B.; Headley, A. D. *Org. Lett.* **2009**, *11*, 3354. (i) Laars, M.; Ausmess, K.; Uudsemaa, M.; Tamm, T.; Kanger, T.; Lopp, M. *J. Org. Chem.* **2009**, *74*, 3772. (j) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545. (k) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. (l) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966. (m) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (n) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369.

(3) For selected examples, see: (a) Lu, A.; Liu, T.; Wu, R.; Wang, Y.; Wu, G.; Zhou, Z.; Fang, J.; Tang, C. *J. Org. Chem.* **2011**, *76*, 3872. (b) Ting, Y.-F.; Chang, C.; Reddy, R.; Magar, D.; Chen, K. *Chem.—Eur. J.* **2010**, *16*, 7030. (c) Jiang, X.; Zhang, Y.; Chan, A. S. C.; Wang, R. *Org. Lett.* **2009**, *11*, 153. (d) Almas, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2006**, *17*, 2064. (e) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624. (f) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093. (g) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901. (h) Xu, Y.-M.; Córdova, A. *Chem. Commun.* **2006**, 460. (i) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808. (j) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558.

(4) (a) Raimondi, W.; Baslé, O.; Constantieux, T.; Bonne, D.; Rodriguez, J. *Adv. Synth. Catal.* **2012**, *354*, 563. (b) Baslé, O.; Raimondi, W.; Sanchez Duque, M.; Bonne, D.; Constantieux, T.; Rodriguez, J. *Org. Lett.* **2010**, *12*, 5246. (c) Xu, Y.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 3246. (d) Nakamura, A.; Lectard, S.; Shiizu, R.; Hamashima, Y.; Sodeoka, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2064.

(5) For selected examples, see: (a) Kato, Y.; Furutachi, M.; Chen, Z.; Mitsunuma, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9168. (b) Bui, T.; Syed, S.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2009**, *131*, 8758. (c) He, R.; Shirakawa, S.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 16620. (d) Wang, C.; Yang, X.; Enders, D. *Chem.—Eur. J.* **2012**, *18*, 4832. (e) Liu, X.; Song, H.; Chen, Q.; Li, W.; Yin, W.; Kai, M.; Wang, R. *Eur. J. Org. Chem.* **2012**, 6647. (f) Trost, B. M.; Hirano, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 6480. (g) Qiao, B.; An, Y.; Liu, Q.; Yang, W.; Liu, H.; Shen, J.; Yan, L.; Jiang, Z. *Org. Lett.* **2013**, *15*, 2358. (h) Diosdado, S.; Etxabe, J.; Izquierdo, J.; Landa, A.; Mielgo, A.; Olaizola, I.; López, R.; Palomo, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 11846.

(6) (a) Albertshofer, K.; Thayumanavan, R.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III. *Tetrahedron Lett.* **2007**, *48*, 693. (b) Uehara, H.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2009**, *48*, 9848.

(7) (a) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559. (b) Trost, B. M.; Hisaindee, S. *Org. Lett.* **2006**, *8*, 6003. (c) Mossé, S.; Alexakis, A. *Org. Lett.* **2006**, *8*, 3577. (d) Jiang, X.; Zhang, B.; Zhang, Y.; Lin, L.; Yan, W.; Wang, R. *Chirality* **2010**, *22*, 625.

(8) For our recent interest in asymmetric reactions of linear ketones, see: (a) Yang, D.; Wang, L.; Han, F.; Zhao, D.; Wang, R. *Chem.—Eur. J.* **2014**, *20*, 8584. (b) Yang, D.; Wang, L.; Han, F.; Zhao, D.; Zhang, B.; Wang, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 6739.

(9) Yang, D.; Wang, L.; Li, D.; Han, F.; Zhao, D.; Wang, R. *Chem.—Eur. J.* **2015**, *21*, 1458.

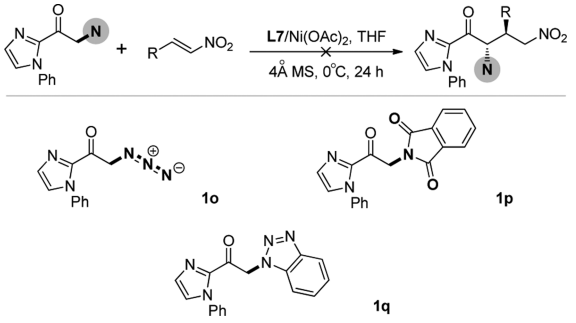
(10) (a) Zhao, D.; Wang, L.; Yang, D.; Zhang, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7523. (b) Yang, D.; Wang, L.; Han, F.; Li, D.; Zhao, D.; Cao, Y.; Ma, Y.; Kong, W.; Sun, Q.; Wang, R. *Chem.—Eur. J.* **2014**, *20*, 16478. (c) Wang, L.; Yang, D.; Han, F.; Li, D.; Zhao, D.; Wang, R. *Org. Lett.* **2015**, *17*, 176. (d) Yang, D.; Wang, L.; Han, F.; Li, D.; Zhao, D.; Wang, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 2185.

(11) See the Supporting Information for the synthesis of ketones **1**.

(12) For selected examples employing diaminocyclohexane-Ni$(OAc)_2$ catalyst in asymmetric reactions, see: (a) Nakamura, A.; Lectard, S.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4036. (b) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *Chem.—Eur. J.* **2011**, *17*, 14922. (c) Li, W.; Liu, X.; Mao, Z.; Chen, Q.; Wang, R. *Org. Biomol. Chem.* **2012**, *10*, 4767. (d) Zhang, H.; Hong, L.; Kang, H.; Wang, R. *J. Am. Chem. Soc.* **2013**, *135*, 14098.

(13) CCDC 1041792 (**3r**) and CCDC 1041793 (**5a**) contain the supplementary crystallographic data for this Article. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The Supporting Information also contains the X-ray crystal structure details of products **3r** and **5a**.

(14) There is no reaction between these substrates:



(15) See the Supporting Information for the NOESY analysis.

(16) For our group's recent interest in asymmetric synthesis of non-natural amino acids precursors and modification of the activities of peptides with these amino acids, see: (a) Zhao, D.; Yang, D.; Wang, Y.; Wang, L.; Mao, L.; Wang, R. *Chem. Sci.* **2011**, *2*, 1918. (b) Liu, X.; Wang, Y.; Xing, Y.; Yu, J.; Ji, H.; Kai, M.; Wang, Z.; Wang, D.; Zhang, Y.; Zhao, D.; Wang, R. *J. Med. Chem.* **2013**, *56*, 3102. (c) Wang, Y.; Xing, Y.; Liu, X.; Ji, H.; Kai, M.; Chen, Z.; Yu, J.; Zhao, D.; Ren, H.; Wang, R. *J. Med. Chem.* **2012**, *55*, 6224.

DOI: 10.1021/acs.joc.5b00013
J. Org. Chem. 2015, 80, 4336−4348