JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Catalytic Asymmetric Conjugate Addition and Sulfenylation of Diarylthiazolidin-2,4-diones

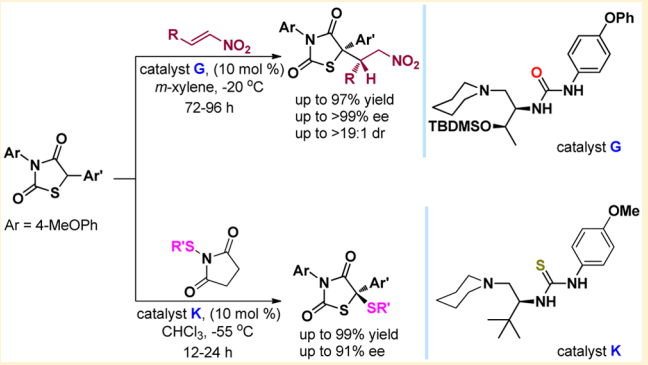
Lihui Jiao,[†,§] Liwei Bu,[†,§] Xinyi Ye,[‡] Xiaowei Zhao,[†] and Zhiyong Jiang*[,†]

[†]Key Laboratory of Natural Medicine and Immuno-Engineering of Henan Province, Henan University, Kaifeng, Henan 475004, P.R. China

[‡]Division of Chemistry and Biological Chemistry, Nanyang Technological University, 21 Nanyang Link, 637371 Singapore

Supporting Information

ABSTRACT: This work reports the first application of diarylthiazolidin-2,4-diones as nucleophiles in asymmetric catalysis. By utilizing chiral amino acid-based (thio)urea–tertiary amines as the catalysts, we successively established asymmetric conjugate addition to nitroolefins and sulfenylation to *N*-(sulfanyl)-succinimides of diarylthiazolidin-2,4-diones. Two series of biologically important 5-aryl-5-substituted thiazolidin-2,4-diones were obtained with high enantio- and diastereoselectivities (up to >99% ee and >19:1 dr). The enantioenriched adducts were found to show satisfactory anticancer activities against three different cancer cell lines using the MTT assay. All of these successes depended on the development of a general and expedient synthetic strategy to provide diverse 5*H*-thiazolidin-2,4-diones.



INTRODUCTION

Thiazolidinediones,[1] also known as glitazones,[2] are important heterocyclic compounds for the treatment of type II diabetes mellitus. More complex compounds such as 5-aryl-5-substituted thiazolidin-2,4-diones bearing fully substituted stereogenic centers on the 5-position are also important as they are promising drug candidates as inhibitors of lactamase[3a] and aldose reductase,[3b] agrochemical fungicides,[3c] and angiotensin-II receptor antagonists[3d] (compounds **I**–**IV**, Figure 1). To our knowledge, the asymmetric synthesis of chiral 5-aryl-5-substituted thiazolidin-2,4-diones has not been established yet.

Structurally, catalytic asymmetric reaction using the enolizable 5-aryl-substituted thiazolidin-2,4-diones as nucleophiles would provide the most direct approach to the desired chiral 5-aryl-5-substituted thiazolidin-2,4-diones. Wheeler's synthetic method of making diarylthiazolidin-2,4-diones (*N*-aryl-5-aryl-substituted thiazolidin-2,4-diones) can be dated back to more than a century ago.[4] From then on, no reports of these heterocyclic molecules in catalytic reactions were further pursued.[5] In this context, the development of an asymmetric reaction using diarylthiazolidin-2,4-diones as reagents remains highly desirable and challenging given their less-known chemical reactivity.

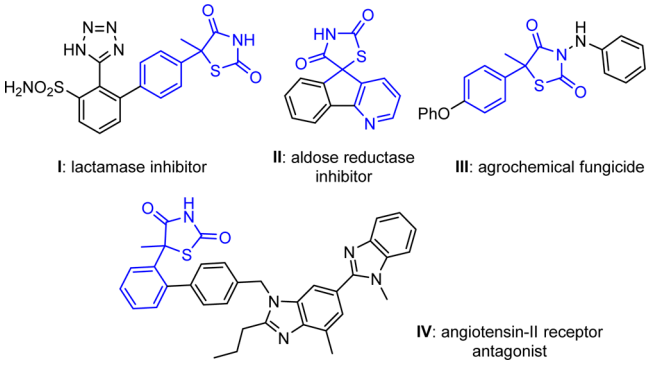


Figure 1. Representative examples of bioactive compounds.

In recent years, we have invested great efforts in developing organocatalytic asymmetric strategies to access biologically important chiral molecules with heteroquaternary (thia[6] and oxa[7]) stereogenic centers. As an extension of these works, we herein report the first catalytic asymmetric reaction of diarylthiazolidin-2,4-diones, including conjugate addition to nitroolefins and sulfenylation to *N*-(sulfanyl)-succinimides, thus leading to the desired chiral 5-aryl-5-substituted thiazolidin-2,4-diones with high stereoselectivity. To this end, a general and efficient synthetic method of 5*H*-thiazolidin-2,4-diones is reported for the first time.

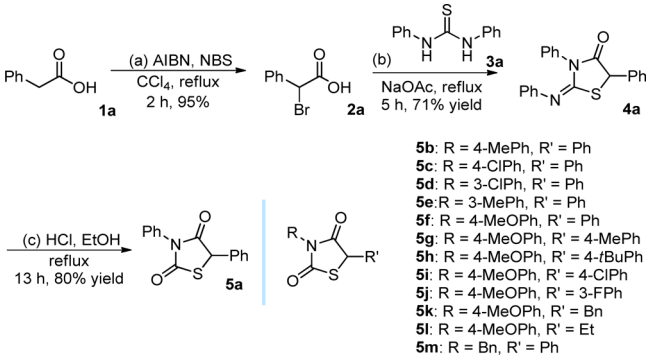
RESULTS AND DISCUSSION

Reported synthetic protocols[4,8] for 5-aryl-substituted thiazolidin-2,4-diones lack the product scope, thus reigniting our interest in this work. As shown in Scheme 1, the representative

Received: July 8, 2016
Published: September 23, 2016

DOI: 10.1021/acs.joc.6b01637
J. Org. Chem. 2016, 81, 9620–9629

Scheme 1. Representative Synthesis of 5*H*-Thiazolin-2,4-diones

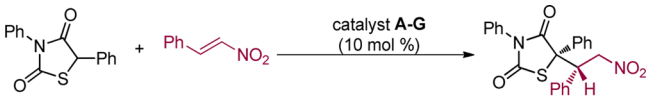


diphenylthiazolidin-2,4-dione **5a** could be prepared from commercially available phenylacetic acid **1a** through a simple three-step process. Treatment of AIBN and NBS could transform **1a** to α-bromo carboxylic acid **2a** in 95% yield. Subsequently, **2a** was condensed with diphenyl thiourea **3a** in the presence of NaOAc to form 2-(phenylimino)-4-thiazolidinone **4a** in 71% yield. After hydrolysis with HCl, diphenylthiazolidin-2,4-dione **5a** was obtained satisfactorily. It is noteworthy that this methodology is versatile and suitable to provide a series of 5*H*-thiazolidin-2,4-diones with diverse *N*-functionalized groups and 5-aryl, benzyl, and alkyl substituents (**5b**−**m**, see the Supporting Information).

To explore the reactivity of 5*H*-thiazolidin-2,4-diones, we first attempted catalytic asymmetric conjugate addition to the most commonly used electrophiles, i.e. nitroolefins. The reaction between diphenylthiazolidin-2,4-dione **5a** and nitroolefin **6a** was chosen as the model reaction (Table 1). Our recent works have revealed that *L*-amino acid-based urea−tertiary amines as efficient bifunctional Brønsted base catalysts could be conveniently prepared.[7d−f] Therefore, *L*-*tert*-leucine-based urea−tertiary amine **A** (Figure 2) was first screened as the catalyst (entry 1). It was found that the reaction worked smoothly in toluene at 25 °C, and the desired conjugate adduct **7a** was obtained in 77% yield after 24 h. While enantio- and diastereoselectivity were poor, the good reactivity encouraged us to further examine the asymmetric reaction with catalysts **B** and **C**, containing pyrrolidine and diethylamine as the tertiary amine moiety, respectively (entries 2−3). Catalysts **B** and **C** did not give improved results. Next, we examined catalyst **D** with *L*-threonine as the chiral skeleton and *tert*-butyldimethylsilyl (TBDMS) as the alcohol protecting group, and the ee value of **7a** was increased to 30% (entry 4). We also observed that the analogous thiourea **E** slightly improved the enantioselectivity, but the reaction became sluggish (Table 1, entry 5). The effect of the substituent of urea was then investigated (catalysts **F** and **G**, entries 6 and 7, respectively). It was detected that catalyst **G** with a 4-PhO-Ph urea moiety could further increase the enantioselectivity (entry 7), indicating that different substituents of urea affected the H-bond interactions between urea and the substrate (Figure 3), thus leading to distinct stereoselective outcomes.

In the presence of 10 mol % catalyst **G**, a range of solvents, including THF, ether, dichloromethane and *m*-xylene, were evaluated (Table 1, entries 8−11), and *m*-xylene was the best, providing **7a** in 85% yield with 60% ee and 64:36 dr (entry 11). When the temperature was decreased, both enantio- and diastereoselectivity were improved (Table 1, entries 12 and

Table 1. Screening Studies[a]



entry	catalyst	solvent	t (h)	yield (%)[b]	ee (%)[c]	dr[c]
1	**A**	toluene	24	77	18/6	48:52
2	**B**	toluene	24	49	15/4	57:43
3	**C**	toluene	24	81	17/4	47:53
4	**D**	toluene	24	62	30/12	52:48
5	**E**	toluene	24	27	32/13	46:54
6	**F**	toluene	24	73	32/13	52:48
7	**G**	toluene	24	71	36/27	53:47
8	**G**	THF	24	76	23/17	51:49
9	**G**	Et_2O	24	87	27/8	54:46
10	**G**	CH_2Cl_2	24	82	35/15	48:52
11	**G**	*m*-xylene	24	85	60/9	64:36
12	**G**	*m*-xylene	48	89	77/7	78:22
13	**G**	*m*-xylene	48	64	81/1	82:18
14[d]	**G**	*m*-xylene	60	91	87/11	83:17
15[e]	**G**	*m*-xylene	60	89	84/9	86:14
16[f]	**G**	*m*-xylene	60	92	89/4	90:10

[a]The reaction was carried out with 0.05 mmol of **5a**, 0.06 mmol of **6a**, and 0.005 mmol of catalyst in 0.5 mL of solvent. Entries 1−11, T = 25 °C; entry 12, T = 0 °C; entries 13−16, T = −20 °C. [b]Isolated yield. [c]Determined by HPLC methods. [d]25 mg of 4 Å molecular sieves were used. [e]NaCl (10 mol %) was used. [f]Both 25 mg of 4 Å molecular sieves and 10 mol % NaCl were used.

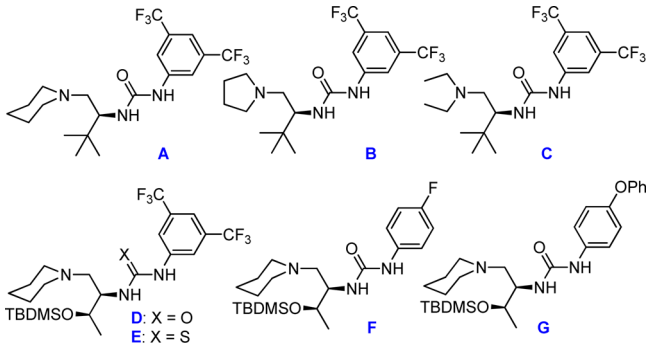


Figure 2. Structures of catalysts **A**−**G**.

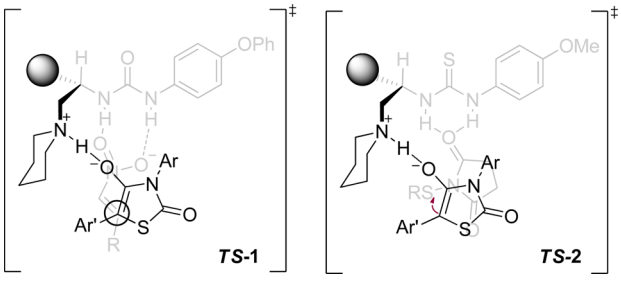


Figure 3. Plausible transition states of two reactions.

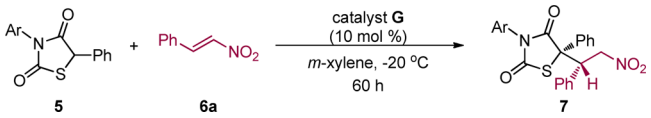
13); at −20 °C, **7a** with 81% ee and 82:18 dr was attained (entry 13). The effect of additive was examined (entries 14−16). Molecular sieves (4 Å; 10 mg) boosted the enantioselectivity but gave similar diastereoselectivity (entry 14).[7b] NaCl was shown to be effective in enhancing diastereoselectivity (entry 15). The combination of 4 Å molecular sieves and NaCl

DOI: 10.1021/acs.joc.6b01637
J. Org. Chem. 2016, 81, 9620−9629

optimally provided **7a** in 92% yield with 89% ee and 90:10 dr (entry 16).

Subsequently, we anticipated improving the stereoselectivity by modifying the *N*-substituent from *N*-phenyl of **5a** to other aryl groups. As shown in Table 2, the introduction of 4-MePh

Table 2. Investigation on the Effect of *N*-Aryl Groups of 5[a]



5 **6a** **7**

entry	5	7	yield (%)[b]	ee (%)[c]	dr[c]
1	**5b**	**7b**	87	87	92:8
2	**5c**	**7c**	83	85	87:13
3	**5d**	**7d**	N.R.		
4	**5e**	**7e**	71	87	90:10
5	**5f**	**7f**	90	98	90:10

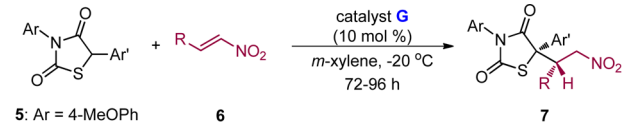
[a]The reaction was carried out with 0.05 mmol of **5**, 0.06 mmol of **6a**, 0.005 mmol of catalyst **G**, 0.005 mmol of NaCl, and 25 mg of 4 Å molecular sieves in 0.5 mL of *m*-xylene. [b]Isolated yield. [c]Determined by HPLC methods. N.R. = no reaction.

(**5b**) and 4-ClPh (**5c**) on the *N*-position led to similar enantio- and diastereoselectivities (Table 2, entries 1 and 2). Surprisingly, no reaction was observed for **5d** (3-ClPh) (entry 3). The best results were obtained with 4-MeOPh (**5e**) substituent on the *N*-position, and the corresponding product **7f** was attained in 90% yield with 98% ee and 90:10 dr (entry 5). These results indicated that the *N*-substituted aryl groups are pivotal for modulating the reactivity and stereoselectivity.

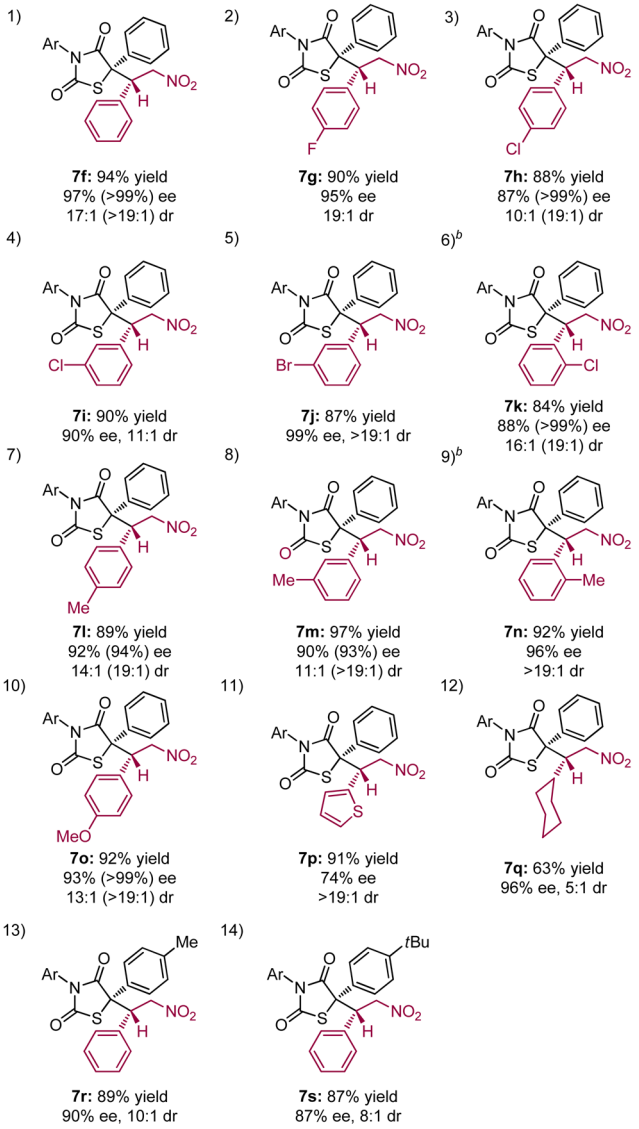
With the optimized reaction conditions in hand, the reaction scope was expanded (Table 3). First, we evaluated the conjugate addition of **5e** with a variety of nitroolefins **6** in the presence of 10 mol % catalyst **G** at −20 °C in *m*-xylene solvent, employing 4 Å molecular sieves and NaCl as additives (Table 3, entries 1−12). The corresponding conjugate adducts **7f−q** were obtained in 63−97% yield with 74−99% ee and 5:1 to >19:1 dr within 72−96 h. 2-Thienyl nitroolefin (**7p**, Table 3, entry 11) was found to suppress enantioselectivity. With 15 mol % catalyst **G**, enantiomeric pure adduct **7n** was obtained (Table 3, entry 9). Next, diarylthiazolidin-2,4-diones with 4-MePh (**5f**) and 4-*t*BuPh (**5g**) on the 5-position were subjected to conjugate addition reaction with **6a**, affording adducts **7r−s** with excellent enantioselectivities and slightly lower but satisfactory diastereoselectivities (Table 3, entries 13 and 14). Unfortunately, 5-benzyl and ethyl-substituted as well as *N*-benzyl-substituted thiazolidin-2,4-diones (**5j−l**) were unreactive under the established reaction conditions. The absolute configurations of conjugate adducts **7** were assigned based on X-ray crystallographic analysis of a single crystal of **7f**.[9]

In recent years, asymmetric sulfenylation[6a,b,10] has been demonstrated as one of the most efficient strategies to build optically active sulfur-containing compounds. As a continuation of the success in conjugate addition, we were subsequently engaged in surveying sulfenylation of diarylthiazolidin-2,4-diones to facilitate the first asymmetric synthesis of 5-sulfur-5-aryl-disubstituted thiazolidin-2,4-diones and 5-sulfone-5-aryl-disubstituted thiazolidin-2,4-diones, which were tested as inhibitors for farnesyl-protein transferase.[11] Under the established reaction conditions toward conjugate addition, we attempted sulfenylation of diphenylthiazolidin-2,4-dione **5a**

Table 3. Substrate Scope of Conjugate Addition to Nitroolefins[a]



5: Ar = 4-MeOPh **6** **7**



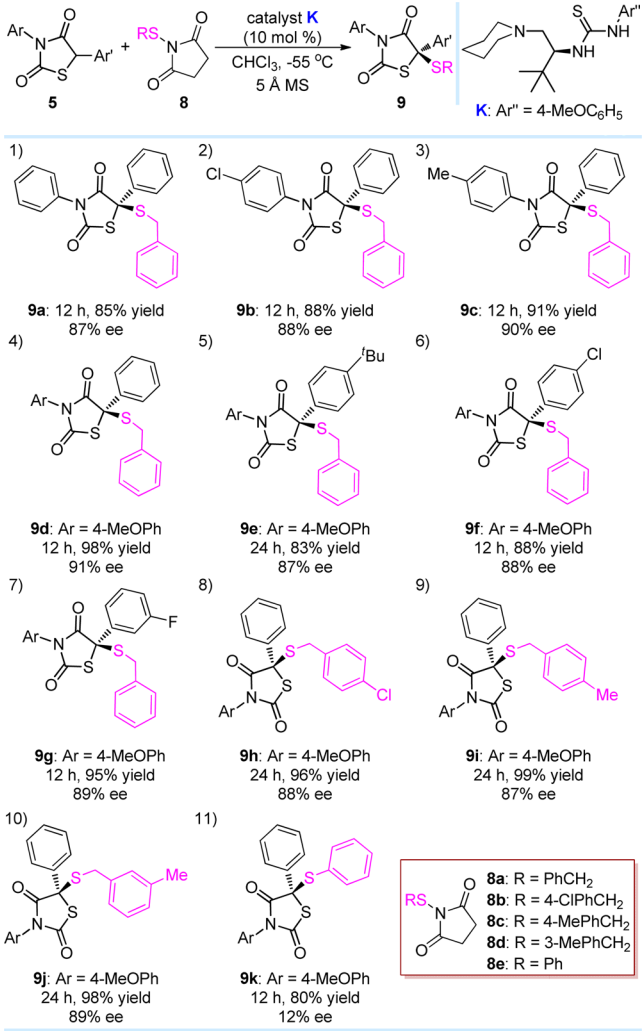
[a]The reaction was carried out with 0.1 mmol of **5**, 0.12 mmol of **6**, 0.01 mmol of **G**, 0.01 mmol of NaCl and 50 mg of 4 Å molecular sieves in 1.0 mL *m*-xylene. Yields of isolated products are presented. The dr was determined by ^{1}H NMR analysis. Ee values were determined by HPLC using chiral stationary phase. The data in parentheses were obtained after a single recrystallization. [b]15 mol % of catalyst **G** was utilized.

using *N*-(benzylthio)succinimide **8a** as the sulfenylating reagent. However, the reaction became very sluggish, indicating that the amino acid-based urea−tertiary amine catalyst is not optimal for sulfenylation. We next screened amino acid-based thiourea−tertiary amines, which is another class of important bifunctional Brønsted base catalysts.[12,13] We were pleased to find that the reaction worked, and the sulfenylated adduct **9a** was isolated in 85% yield with 87% ee after 12 h when *L*-*tert*-leucine-based thiourea−tertiary amine **K** was employed as the

DOI: 10.1021/acs.joc.6b01637
J. Org. Chem. 2016, 81, 9620−9629

catalyst and 5 Å molecular sieves were employed as the additive in $CHCl_3$ at −55 °C (Table 4, entry 1). Moreover, **5e** was found to yield higher enantioselectivity (entry 4, see also the Supporting Information). The substituents on aromatic rings at the 5-position of thiazolidin-2,4-diones (**5g−i**) and of *N*-(benzylthio)succinimides (**8b−d**) did not affect the reactivity and enantioselectivity (entries 5−10). However, for *N*-(arylthio)succinimides, only 12% ee of **9k** was obtained when *N*-(phenylthio)succinimide **8e** was used as the sufenylating reagent. (entry 11).

Table 4. Substrate Scope of Sulfenylation[a]



[a]The reaction was carried out with 0.1 mmol of **5**, 0.2 mmol of **8**, 0.01 mmol of **K**, and 10 mg of 5 Å molecular sieves in 0.5 mL of $CHCl_3$. Yields of isolated products are presented. The ee values were determined by HPLC using chiral stationary phase.

On the basis of our previous investigations,[7] the plausible transition states (TS) of two reactions were proposed (Figure 3). First, the enolates of diarylthiazolidin-2,4-diones were generated after protonation and would bind to the R_3NH^+ arm of catalyst **G** or **K**. Two N−H bonds of the (thio)urea unit could activate the LUMO of nitroolefins (TS-1) or *N*-(sulfanyl)-succinimides (TS-2) through two H-bonding interactions. The conjugate adducts **7** and sulfenylated adducts **9** were thus obtainable with the observed absolute configurations after nucleophilic addition. The used additives, such as 4 and 5 Å molecular sieves as well as NaCl, should affect the solution environment to increase the free energy differences between the transition states, thus leading to slightly improved enantio- and diastereoselectivity in two transformations.

To demonstrate the utility of the methodology, we endeavored to evaluate the biological activities of adducts. A variety of chiral 5-aryl-5-substituted thiazolidin-2,4-diones, including **7f−h**, **7j**, and **7l**, were subjected to cytotoxic activity measurements for three human cancer cell lines employing the MTT assay. A summary of the IC50 values is shown in Table 5.

Table 5. IC_{50} Values of Chiral Conjugate Adducts 7 on the Growth of Human Cancer Cell Lines[a]

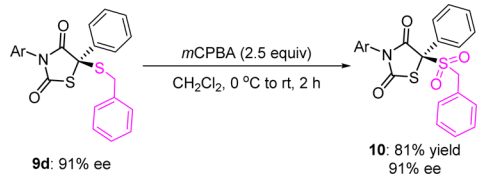
compound	7f	7g	7h	7j	7l	7m	7n
H22	21	55	20	25	18	40	9.9
HCT116	36	94	45	73	60	94	30
K562	29	>100	>100	>100	>100	>100	45

[a]Values are means of three experiments each done in duplicate. IC_{50} values are described in μM.

The analogues **7f**, **7h**, **7j**, and **7l** showed inhibitory effects on the H22 line with IC_{50} values of 18−25 μM. Moreover, **7n** gave a lower IC_{50} value of 9.9 μM. While **7n** and **7f** presented weaker inhibitory activity (IC_{50} = 30 and 29 μM) on the HCT116 and K562 cell lines, respectively, they were still overall the most effective compounds. The distinct cytotoxicities suggested that the cancer cell lines exhibited different sensitivities to chiral 5-aryl-5-substituted thiazolidinediones.

We also attempted transformation of adducts **9** to verify the synthetic utility of the method. Using *m*CPBA in dichloromethane, the oxidation of the sulfenylated adduct **9d** was performed, as shown in Scheme 2. After 2 h, when the reaction completed, the sulfone **10** could be readily achieved in 81% yield with no loss of enantiomeric purity. The absolute configurations of sulfenylated adducts **9** could be assigned based on X-ray crystallographic analysis of a single crystal of sulfone **10**.[9]

Scheme 2. Transformation of Adducts 9



CONCLUSION

In summary, we established the pioneer work of employing diarylthiazolidin-2,4-diones as nucleophiles in asymmetric synthesis. By utilization of an *L*-amino acid-based tertiary amine as a bifunctional Brønsted base catalyst, asymmetric conjugate addition of diarylthiazolidin-2,4-diones to nitroolefins afforded a series of chiral 5-aryl-5-substituted thiazolidin-2,4-diones, which structurally feature two contiguous thia-quaternary and tertiary stereogenic centers with high enantio- and diastereoselectivities (up to >99% ee and >19:1 dr). Several conjugate adducts were observed to show potential anticancer activities. Moreover, a highly enantioselective sulfenylation of diarylthiazolidin-2,4-diones to *N*-(sulfanyl)-succinimides was developed, leading to chiral 5-sulfur-5-aryl-disubstituted

DOI: 10.1021/acs.joc.6b01637
J. Org. Chem. 2016, 81, 9620−9629

thiazolidin-2,4-diones and 5-sulfone-5-aryl-disubstituted thiazolidin-2,4-diones. Given our devised expedient synthetic approach to various 5*H*-thiazolidin-2,4-diones with highly tunable *N*-substituents, we anticipate that such novel nucleophilic reagents will find application in more kinds of reaction requiring access to diverse chiral 5,5-disubstituted thiazolidinediones with potentially positive biological and pharmaceutical activities.

EXPERIMENTAL SECTION

General Information. *General Procedures and Methods.* Experiments involving moisture and/or air sensitive components were performed under a positive pressure of nitrogen in oven-dried glassware equipped with a rubber septum inlet. Dried solvents and liquid reagents were transferred by oven-dried syringes or hypodermic syringe cooled to ambient temperature in a desiccator. Reactions mixtures were stirred in 10 mL sample vial with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in nonvolatile reagents/compounds was removed in high *vacuo* by means of an oil pump and subsequent purging with nitrogen. Solvents were removed in vacuo under ∼30 mmHg and heated with a water bath at 30−35 °C using rotary evaporator with aspirator. The condenser was cooled with running water at 0 °C.

All experiments were monitored by analytical thin layer chromatography (TLC). TLC was performed on precoated plates. After elution, plate was visualized under UV illumination at 254 nm for UV active material. Further visualization was achieved by staining $KMnO_4$, ceric molybdate, or anisaldehyde solution. For those using the aqueous stains, the TLC plates were heated on a hot plate.

Columns for flash chromatography (FC) contained silica gel 200−300 mesh. Columns were packed as slurry of *silica gel* in petroleum ether and equilibrated solution using the appropriate solvent system. The elution was assisted by applying pressure of about **2** atm with an air pump.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) and carbon NMR (^{13}C NMR) were recorded in $CDCl_3$ otherwise stated. ^{1}H (300 MHz) and ^{13}C (75 MHz) were performed on (300 MHz) spectrometers. Chemical shifts are reported in parts per million (ppm), using the residual solvent signal as an internal standard: $CDCl_3$ (^{1}H NMR: δ 7.26, singlet; ^{13}C NMR: δ 77.0, triplet). Multiplicities were given as *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *quintet*, *m* (multiplets), *dd* (doublet of doublets), *dt* (doublet of triplets), and *br* (broad). Coupling constants (*J*) were recorded in Hertz (Hz). The number of proton atoms (*n*) for a given resonance was indicated by *n*H. The number of carbon atoms (*n*) for a given resonance was indicated by *n*C. HRMS (analyzer: TOF) was reported in units of mass of charge ratio (*m*/*z*). Optical rotations were recorded on a polarimeter with a sodium lamp of wavelength 589 nm and reported as follows; $[\alpha]_\lambda^{ToC}$ (*c* = g/100 mL, solvent). Melting points were determined on a microscopic melting point apparatus.

Enantiomeric excesses were determined by chiral High Performance Liquid Chromatography (HPLC) analysis. UV detection was monitored at 254 nm. HPLC samples were dissolved in HPLC grade isopropanol (IPA) unless otherwise stated.

Materials. All commercial reagents were purchased with the highest purity grade. They were used without further purification unless specified. All solvents used, mainly petroleum ether (PE) and ethyl acetate (EtOAc) were distilled. Anhydrous DCM and MeCN were freshly distilled from CaH_2 and stored under N_2 atmosphere. THF, Et_2O, *m*-xylene and toluene were freshly distilled from sodium/benzophenone before use. Anhydrous methanol and etanol were distilled from Mg. All compounds synthesized were stored in a−20 °C freezer and light-sensitive compounds were protected with aluminum foil.

General Procedure for the Synthesis of 2. A flame-dried 50 mL two-necked round bottomed flask equipped with a reflux condenser, a Teflon-coated magnetic stirring bar, a rubber septum, and an inlet adapter with three-way stopcock was charged with **1** (2.77 mmol), NBS (540 mg, 3.05 mmol), and CCl_4 (5.5 mL). To the solution was added AIBN (23 mg, 0.14 mmol). The mixture was heated at reflux for 2 h, then diluted with hexanes and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was purified by *silica gel* column chromatography (hexanes-Et_2O = 2:1) to afford **2** as a white solid.

General Procedure for the Synthesis of 4. A mixture of **2** (white solid, 2.0 mmol), thiourea (2.0 mmol), sodium acetate (2.0 mmol) and ethanol (10 mL) was stirred under reflux for 5 h, and concentrated *in vacuo*. The residue was neutralized with saturated aqueous sodium bicarbonate, and Et_2O (10 mL) with hexane (50 mL) were then added. The mixture was stirred at room temperature for 15 min, and the imino compounds were collected by filtration.

General Procedure for the Synthesis of 5. A mixture of **4** (0.1 mmol), 4 *N* HCl (1.0 mL) and ethanol (5.0 mL) was stirred under reflux for 13 h. The reaction mixture was concentrated *in vacuo*. The residue was diluted with water, neutralized with saturated aqueous sodium bicarbonate and extracted with chloroform. The organic layer was then washed with brine, dried with anhydrous magnesium sulfate and concentrated in vacuo to give the title compounds.

General Procedure for the Synthesis of 7. 5-Argio-3-(4-methoxyphenyl)thiazolidine-2,4-dione **5** (0.1 mmol, 1.0 equiv), nitroolefin **6** (0.12 mmol, 1.2 equiv), **G** (0.01 mmol, 0.1 equiv), NaCl (0.1 equiv) and 4 Å molecular sieves (50 mg) were dissolved in *m*-xylene (1.0 mL). The reaction mixture was stirred at −20 °C for 72−96 h and monitored by TLC. Upon complete consumption of **5**, the reaction mixture was concentrated under reduced pressure. The crude material was subsequently purified by flash column chromatography on *silica gel* with PE/EtOAc mixture (20:1−5:1 ratio, the crude material was completely dissolved in CH_2Cl_2/PE before loaded on *silica gel*). After removing the solvent in *vacuo*, the product **7** could be obtained.

General Procedure for the Synthesis of 9. 5-Argio-3-(4-methoxyphenyl)thiazolidine-2,4-dione **5** (0.1 mmol, 1.0 equiv), **8** (0.2 mmol, 2 equiv), **K** (0.01 mmol, 0.1 equiv), and 5 Å molecular sieves (10 mg) were dissolved in $CHCl_3$ (0.5 mL). The reaction mixture was stirred at −55 °C for 12−24 h and monitored by TLC. Upon complete consumption of **9**, the reaction mixture was concentrated under reduced pressure, the recovered crude material was subsequently purified by flash column chromatography on silica gel with PE/EtOAc mixture (20:1−5:1 ratio, the crude material was completely dissolved in CH_2Cl_2/PE before loaded on *silica gel*). After removing the solvent in *vacuo*, the product **9** could be obtained.

General Procedure for the Synthesis of 10. A solution of **9d** (210 mg, 0.5 mmol) in dichloromethane (5 mL) was cooled to 0 °C and *m*CPBA (215 mg, 1.25 mmol) was added. After stirring for 10 min, the solution was warmed to room temperature, ant then stirred for 2 h. The solvent was removed under vacuum, and the residue was purified by column chromatography on *silica gel* to give **11** as a white solid.

General Methods for the Procedure of the Biological Studies. H22, HCT116 and K562 cells were seeded at a density of 4000−5000 cells in 96-well plates. Compounds were added 24 h after seeding. After 2 days in culture, the MTT stock solution (5 mg/mL in PBS) was added to each well and incubated at 37 °C for 4 h. The medium was removed carefully, and dimethyl sulfoxide was added to each well to dissolve formazan. The absorbance of each well at 490 nm was measured by using a BioTek microplate reader.

*3,5-Diphenylthiazolidine-2,4-dione (**5a**, see the Supporting Information).* White solid; mp 169.2−171.0 °C; 216.3 mg (1 mmol), 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.39 (m, 8H), 7.31 (dd, *J* = 10.0, 3.1, 2H), 5.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 170.4, 134.2, 132.8, 129.5, 129.4 (two peaks), 129.3, 128.3, 127.3, 53.0; HRMS (ESI) *m*/*z* 270.0588 (M + H^+), calcd for $C_{15}H_{12}NO_2S$ 270.0589.

*5-Phenyl-3-(p-tolyl)thiazolidine-2,4-dione (**5b**).* White solid; mp 187.0−188.2 °C; 235.6 mg (1 mmol), 83% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.38 (m, 5H), 7.28 (t, *J* = 11.7, 2H), 7.16 (d, *J* = 7.8, 2H), 5.43 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 170.5, 139.5, 134.3, 130.2, 130.1, 129.3, 129.2, 128.3, 127.0, 53.0, 21.3;

DOI: 10.1021/acs.joc.6b01637
J. Org. Chem. 2016, 81, 9620−9629

HRMS (ESI) m/z 284.0746 (M + H^+), calcd for $C_{16}H_{14}NO_2S$ 284.0745.

*3-(4-Chlorophenyl)-5-phenylthiazolidine-2,4-dione (**5c**).* White solid; mp 133.5−134.7 °C; 251.5 mg (1 mmol), 83% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.31 (m, 6H), 7.16 (d, J = 8.9, 3H), 5.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 170.0, 135.3, 133.8, 131.2, 129.7, 129.4, 129.4, 128.6, 128.2, 53.1; HRMS (ESI) m/z 304.0201 (M + H^+), calcd for $C_{15}H_{11}ClNO_2S$ 304.0199.

*3-(3-Chlorophenyl)-5-phenylthiazolidine-2,4-dione (**5d**).* White solid; mp 125.0−126.3 °C; 227.3 mg (1 mmol), 75% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.39 (m, 7H), 7.32 (s, 1H), 7.24−7.16 (m, 1H), 5.41 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 173.0, 170.8, 135.7, 134.3, 132.6, 130.4, 130.1, 129.7, 129.5, 129.4, 129.3, 125.7, 53.1; HRMS (ESI) m/z 304.0197 (M + H^+), calcd for $C_{15}H_{11}ClNO_2S$ 304.0199.

*5-Phenyl-3-(m-tolyl)thiazolidine-2,4-dione (**5e**).* White solid; mp 154.3−155.3 °C; 224.4 mg (1 mmol), 79% yield; ^{1}H NMR (300 MHz, DMSO) δ 6.58 (d, J = 6.9, 2H), 6.43 (t, J = 8.1, 4H), 6.31 (d, J = 7.4, 1H), 6.22 (d, J = 12.2, 2H), 4.96 (s, 1H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 173.2, 171.0, 139.4, 135.8, 133.8, 130.3, 129.6, 129.5, 129.3, 128.8, 125.6, 53.0, 21.2; HRMS (ESI) m/z 284.0743 (M + H^+), calcd for $C_{16}H_{14}NO_2S$ 284.0745.

*3-(4-Methoxyphenyl)-5-phenylthiazolidine-2,4-dione (**5f**).* White solid; mp 169.7−171.0 °C; 243.2 mg (1 mmol), 81% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.35 (m, 5H), 7.23−7.12 (m, 2H), 6.99 (d, J = 9.0, 2H), 5.42 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 170.6, 160.0, 134.3, 129.4, 129.3, 128.5, 128.3, 125.4, 114.8, 55.6, 53.0; HRMS (ESI) m/z 300.0695 (M + H^+), calcd for $C_{16}H_{14}NO_3S$ 300.0694.

*3-(4-Methoxyphenyl)-5-(p-tolyl)thiazolidine-2,4-dione (**5g**).* White solid; mp 162.3−163.5 °C; 266.1 mg (1 mmol), 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.1, 2H), 7.37−7.15 (m, 4H), 7.14−6.85 (m, 2H), 5.47 (s, 1H), 3.91 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 170.7, 160.0, 139.3, 131.2, 130.0, 128.5, 128.1, 125.4, 114.7, 55.6, 52.8, 21.2; HRMS (ESI) m/z 314.0852 (M + H^+), calcd for $C_{17}H_{16}NO_3S$ 314.0851.

*5-(4-(tert-Butyl)phenyl)-3-(4-methoxyphenyl)thiazolidine-2,4-dione (**5h**).* White solid; mp 182.9−184.1 °C; 287.6 mg (1 mmol), 81% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (q, J = 8.6, 4H), 7.25−7.12 (m, 2H), 7.05−6.87 (m, 2H), 5.41 (s, 1H), 3.83 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 170.8, 160.0, 152.4, 131.2, 128.6, 127.9, 126.4, 125.4, 114.7, 55.6, 52.7, 34.7, 31.3; HRMS (ESI) m/z 356.1321 (M + H^+), calcd for $C_{20}H_{22}NO_3S$ 356.1320.

*5-(4-Chlorophenyl)-3-(4-methoxyphenyl)thiazolidine-2,4-dione (**5i**).* White solid; mp 169.2−170.4 °C; 259.8 mg (1 mmol), 78% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 4H), 7.17 (d, J = 8.5, 2H), 6.99 (d, J = 8.4, 2H), 5.40 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, D_6-acetone) δ 172.3, 170.1, 160.0, 134.6, 134.2, 130.6, 129.1, 126.2, 114.3, 55.0, 51.9; HRMS (ESI) m/z 334.0306 (M + H^+), calcd for $C_{16}H_{13}ClNO_3S$ 334.0305.

*5-(3-Fluorophenyl)-3-(4-methoxyphenyl)thiazolidine-2,4-dione (**5j**).* White solid; mp 139.7−141.3 °C; 256.8 mg (1 mmol), 81% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, J = 13.8, 7.9, 2H), 7.25−7.10 (m, 4H), 7.02 (d, J = 8.9, 2H), 5.44 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 170.1, 164.7, 161.4, 160.1, 136.4, 136.3, 131.0, 130.9, 128.4, 125.2, 124.1, 124.1, 116.5, 116.3, 115.6, 115.3, 114.8, 55.6, 52.4; HRMS (ESI) m/z 318.0601 (M + H^+), calcd for $C_{16}H_{13}FNO_3S$ 318.0600.

*5-Benzyl-3-(4-methoxyphenyl)thiazolidine-2,4-dione (**5k**).* White solid; mp 138.2−139.6 °C; 247.3 mg (1 mmol), 79% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.20 (m, 5H), 6.96 (s, 4H), 4.60 (dd, J = 8.2, 3.4, 1H), 3.80 (s, 3H), 3.53−3.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 170.6, 160.0, 135.3, 129.6, 128.7, 128.5, 127.7, 125.2, 114.7, 55.5, 51.0, 38.6; HRMS (ESI) m/z 314.0852 (M + H^+), calcd for $C_{17}H_{16}NO_3S$ 314.0851.

*5-Ethyl-3-(4-methoxyphenyl)thiazolidine-2,4-dione (**5l**, see the Supporting Information).* White solid; mp 87.8−88.4 °C; 195.8 mg (1 mmol), 78% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.6, 2H), 6.99 (d, J = 8.6, 2H), 4.33 (dd, J = 8.0, 4.1, 1H), 3.82 (s, 3H), 2.38−1.95 (m, 2H), 1.12 (t, J = 7.3, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 171.1, 159.9, 128.5, 125.3, 114.7, 55.5, 50.9, 26.4, 10.7; HRMS (ESI) m/z 252.0695 (M + H^+), calcd for $C_{12}H_{14}NO_3S$ 252.0694.

*3-Benzyl-5-phenylthiazolidine-2,4-dione (**5m**).* White solid; mp 148.8−150.3 °C; 189.6 mg (1 mmol), 67% yield; ^{1}H NMR (300 MHz, DMSO) δ 7.73−7.03 (m, 10H), 5.96 (s, 1H), 4.76 (s, 2H); ^{13}C NMR (75 MHz, DMSO) δ 173.6, 171.4, 136.0, 135.6, 129.5, 129.2, 129.1, 129.1, 128.3, 128.0, 52.8, 45.3; HRMS (ESI) m/z 284.0746 (M + H^+), calcd for $C_{16}H_{14}NO_2S$ 284.0745.

*(S)-5-((S)-2-Nitro-1-phenylethyl)-3,5-diphenylthiazolidine-2,4-dione (**7a**).* White solid; mp 139.4−140.2 °C; 89% ee; dr =9:1; 36.4 mg (0.1 mmol), 87% yield; $[\alpha]_D^{22}$ + 27.3 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.5, 2H), 7.70−7.28 (m, 11H), 6.51 (d, J = 7.2, 2H), 5.08−4.74 (m, 2H), 4.44−4.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 167.4, 134.3, 132.4, 132.2, 131.6, 130.1, 129.9, 129.6, 129.4, 129.3, 128.9, 128.0, 127.1, 75.7, 69.0, 53.0; HRMS (ESI) m/z 419.1064 (M + H^+), calcd for $C_{23}H_{19}N_2O_4S$ 419.1066. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm) + CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 25.8 min (minor, major diastereomer), 28.7 min (minor diastereomer), 33.5 min (major, major diastereomer), 40.2 min (minor diastereomer).

*(S)-5-((S)-2-Nitro-1-phenylethyl)-5-phenyl-3-(p-tolyl)thiazolidine-2,4-dione (**7b**).* White solid; mp 153.3−154.5 °C; 86% ee; dr = 7:1; 35.1 mg (0.1 mmol), 81% yield; $[\alpha]_D^{22}$ + 24.6 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.4, 2H), 7.66−7.34 (m, 8H), 7.11 (d, J = 7.6, 2H), 6.38 (d, J = 7.5, 2H), 4.99−4.73 (m, 2H), 4.43−4.40 (m, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ172.8, 167.5, 139.7, 134.3, 132.4, 130.1, 129.9, 129.8, 129.6, 129.5, 128.8, 128.0, 126.8, 75.7, 69.0, 53.0, 21.2; HRMS (ESI) m/z 433.1223 (M + H^+), calcd for $C_{24}H_{21}N_2O_4S$ 433.1222. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 95/5; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 21.2 min (minor diastereomer), 32.9 min (minor, major diastereomer), 37.7 min (major, major diastereomer), 42.3 min (minor diastereomer).

*(S)-3-(4-Chlorophenyl)-5-((S)-2-nitro-1-phenylethyl)-5-phenylthiazolidine-2,4-dione (**7c**).* White solid; mp 144.6−146.0 °C; 82% ee; dr = 6:1; 42.2 mg (0.1 mmol), 94% yield; $[\alpha]_D^{22}$ + 21.2 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO) δ 8.01 (d, J = 7.2, 2H), 7.56−7.44 (m, 10H), 6.57 (d, J = 8.2, 2H), 5.31−5.21 (m, 1H), 4.84 (d, J = 11.1, 1H), 4.66 (d, J = 13.2, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 167.1, 135.5, 134.0, 132.4, 130.5, 130.0, 130.0 129.9, 129.6, 129.5, 128.9, 128.4, 128.0, 75.6, 69.1, 53.0; HRMS (ESI) m/z 453.0673 (M + H^+), calcd for $C_{23}H_{18}ClN_2O_4S$ 453.0676. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 12.9 min (minor, major diastereomer), 17.4 min (minor diastereomer), 29.4 min (major, major diastereomer), 32.7 min (minor diastereomer).

*(S)-5-((S)-2-Nitro-1-phenylethyl)-5-phenyl-3-(m-tolyl)-thiazolidine-2,4-dione (**7e**).* White solid; mp 227.8−228.2 °C; 87% ee; dr = 9:1; 30.8 mg (0.1 mmol), 71% yield; $[\alpha]_D^{22}$ + 30.5 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 7.3, 2H), 7.54−7.26 (m, 8H), 7.23−7.01 (m, 2H), 6.50−6.04 (m, 2H), 5.05−4.69 (m, 2H), 4.48−4.40 (m, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 167.4, 139.5, 134.3, 132.5, 132.0, 130.3, 130.1, 129.9, 129.6, 129.5, 129.0, 128.9, 128.0, 127.7, 124.1, 75.7, 69.1, 53.0, 21.1; HRMS (ESI) m/z 433.1223 (M + H^+), calcd for $C_{24}H_{21}N_2O_4S$ 433.1222. The ee was determined by HPLC analysis. Nu-Analytical INA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 95/5; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 24.7 min (minor, major diastereomer), 29.3 min (minor diastereomer), 31.3 min (minor diastereomer), 34.4 min (major, major diastereomer).

*(S)-3-(4-Methoxyphenyl)-5-((S)-2-nitro-1-phenylethyl)-5-phenylthiazolidine-2,4-dione (**7f**).* White solid; mp 144.6−146.0 °C; 97% ee; dr = 16:1 (after a single recrystallization, ee >99%, dr >19:1); 42.2 mg (0.1 mmol), 94% yield; $[\alpha]_D^{22}$ + 21.2 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, J = 7.0,2H), 7.54−7.41 (m, 8H), 6.81 (d, J = 8.9, 2H), 6.41 (d, J = 8.9, 2H), 5.02−4.75 (m, 2H), 4.43−4.40 (m, 1H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 167.7, 160.1, 134.3, 132.5, 130.1, 130.0, 129.6, 129.5, 128.9, 128.3, 128.1, 124.6,

DOI: 10.1021/acs.joc.6b01637
J. Org. Chem. 2016, 81, 9620−9629

114.6, 75.7, 68.9, 55.5, 53.0; HRMS (ESI) m/z 449.1176 (M + H$^+$), calcd for $C_{24}H_{21}N_2O_5S$ 449.1171. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm) + CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 29.6 min (minor, major diastereomer), 37.6 min (minor diastereomer), 51.7 min (major, major diastereomer), 56.8 min (minor diastereomer).

*(S)-5-((S)-1-(4-Fluorophenyl)-2-nitroethyl)-3-(4-methoxyphenyl)-5-phenylthiazolidine-2,4-dione (**7g**).* White solid; mp 97.3−98.9 °C; 95% ee; dr >19:1; 41.9 mg (0.1 mmol), 90% yield; $[\alpha]_D^{22}$ + 20.6 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, J = 8.1, 1.3, 2H), 7.68−7.41 (m, 5H), 7.11 (t, J = 8.6, 2H), 6.94−6.76 (m, 2H), 6.49 (d, J = 8.9, 2H), 4.95−4.68 (m, 2H), 4.41 (dd, J = 12.8, 3.5, 1H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 167.4, 163.2 (d, 1JC-F = 248.3 Hz), 160.2, 134.2, 131.9 (d, 1JC-F = 8.2 Hz), 129.9, 129.6, 128.1, 127.9, 124.5, 116.0, 115.8, 114.7, 75.7, 68.8, 55.5, 52.2;HRMS (ESI) m/z 467.1072 (M + H$^+$), calcd for $C_{24}H_{20}FN_2O_5S$ 467.1077. The ee was determined by HPLC analysis. Nu-Analytical INA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 95/5; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 41.6 min (minor diastereomer), 43.3 min (minor, major diastereomer), 48.8 min (major, major diastereomer), 70.0 min (minor diastereomer).

*(S)-5-((S)-1-(4-Chlorophenyl)-2-nitroethyl)-3-(4-methoxyphenyl)-5-phenylthiazolidine-2,4-dione (**7h**).* White solid; mp 163.1−164.6 °C; 87% ee; dr =11:1 (after a single recrystallization, ee >99%, dr >19:1); 42.4 mg (0.1 mmol), 88% yield; $[\alpha]_D^{22}$ + 19.9 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.1, 1.4, 2H), 7.64−7.19 (m, 7H), 6.96−6.76 (m, 2H), 6.56−6.43 (m, 2H), 5.00−4.73 (m, 2H), 4.44 (dd, J = 12.6, 3.2, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 167.3, 160.2, 135.7, 134.1, 131.4, 130.9, 129.9, 129.6, 129.1, 128.0, 124.5, 114.7, 75.5, 68.7, 55.5, 52.4; HRMS (ESI) m/z 483.0778 (M + H$^+$), calcd for $C_{24}H_{20}ClN_2O_5S$ 483.0781. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm) + CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 30.1 min (minor diastereomer), 39.4 min (minor, major diastereomer), 53.4 min (major, major diastereomer), 65.8 min (minor diastereomer).

*(S)-5-((S)-1-(3-Chlorophenyl)-2-nitroethyl)-3,5-diphenylthiazolidine-2,4-dione (**7i**).* White solid; mp 74.1−75.7 °C; 90% ee; dr = 19:1; 43.4 mg (0.1 mmol), 90% yield; $[\alpha]_D^{22}$ + 21.2 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (dd, J = 8.1, 1.5, 2H), 7.97−7.42 (m, 7H), 7.21−7.02 (m, 2H), 6.90−6.67 (m, 2H), 5.37−4.88 (m, 2H), 4.66 (dd, J = 12.8, 3.2, 1H), 4.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 167.2, 160.2, 134.9, 134.0, 133.4, 132.7, 130.3, 130.0, 129.6, 128.3, 128.2, 128.0, 124.5, 122.8, 114.7, 75.3, 68.5, 55.5, 52.4; HRMS (ESI) m/z 483.0781 (M + H$^+$), calcd for $C_{24}H_{20}ClN_2O_5S$ 483.0782. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm) + CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 24.6 min (minor, major diastereomer), 31.4 min (minor diastereomer), 35.9 min (minor diastereomer), 41.4 min (major, major diastereomer).

*(S)-5-((S)-1-(3-Bromophenyl)-2-nitroethyl)-3-(4-methoxyphenyl)-5-phenylthiazolidine-2,4-dione (**7j**).* White solid; mp 116.7−118.1 °C; 99% ee; dr >19:1; 45.8 mg (0.1 mmol), 87% yield; $[\alpha]_D^{22}$ + 20.8 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (dd, J = 8.1, 1.5, 2H), 8.00−7.63 (m, 6H), 7.54 (dd, J = 13.1, 5.2, 1H), 7.22−6.96 (m, 2H), 6.93−6.51 (m, 2H), 5.17−4.95 (m, 2H), 4.66 (dd, J = 12.8, 3.2, 1H), 4.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 167.2, 160.2, 134.9, 134.0, 133.4, 132.7, 130.3, 130.0, 129.6, 128.3, 128.2, 128.0, 124.5, 122.8, 114.7, 75.3, 68.5, 55.5, 52.4; HRMS (ESI) m/z 527.0285 (M + H$^+$), calcd for $C_{24}H_{20}BrN_2O_5S$ 527.0276. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm) + CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2-propanol = 95/5; flow rate 0.5 mL/min; 25 °C; 254 nm t_R = 30.4 min (minor diastereomer), 32.8 min (major, major diastereomer), 55.6 min (minor, major diastereomer), 62.6 min (minor diastereomer).

*(S)-5-((S)-1-(2-Chlorophenyl)-2-nitroethyl)-3-(4-methoxyphenyl)-5-phenylthiazolidine-2,4-dione (**7k**).* White solid; mp 156.3−157.1 °C; 88% ee; dr = 16:1 (after a single recrystallization, ee >99%, dr >19:1); 40.5 mg (0.1 mmol), 84% yield, $[\alpha]_D^{22}$ + 23.2 (c 1.00, $CHCl_3$);^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17−7.98 (m, 2H), 7.67−7.30 (m, 7H), 6.81 (d, J = 8.9, 2H), 6.46 (d, J = 8.9, 2H), 5.66 (dd, J = 11.1, 4.0, 1H), 4.93−4.68 (m, 1H), 4.58 (dd, J = 13.2, 4.1, 1H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 167.5, 160.2, 137.0, 134.7, 131.7, 130.9, 130.5, 129.9, 129.4, 128.2, 127.2, 124.8, 114.6, 134.9, 68.4, 55.5, 52.9, 47.5; HRMS (ESI) m/z 483.0781 (M + H$^+$), calcd for $C_{24}H_{20}ClN_2O_5S$ 483.0780. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm) + CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 13.7 min (minor, major diastereomer), 14.7 min (major, major diastereomer), 22.8 min (minor diastereomer), 36.1 min (minor diastereomer).

*(S)-3-(4-Methoxyphenyl)-5-((S)-2-nitro-1-(p-tolyl)ethyl)-5-phenylthiazolidine-2,4-dione (**7l**).* White solid; mp 159.5−161.1 °C; 92% ee; dr = 14:1 (after a single recrystallization, ee =94%, dr =19:1); 41.1 mg (0.1 mmol), 89% yield; $[\alpha]_D^{22}$ + 24.0 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09−7.85 (m, 2H), 7.59−7.26 (m, 5H), 7.28−7.09 (m, 2H), 6.78 (d, J = 9.0, 2H), 6.41 (t, J = 6.0, 2H), 4.95−4.66 (m, 2H), 4.37−4.34 (m, 1H), 3.75 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 167.8, 160.1, 139.5, 134.4, 129.9, 129.8, 129.5, 129.3, 128.3, 128.1, 124.7, 114.5, 75.8, 69.1, 55.5, 52.8, 21.2; HRMS (ESI) m/z 463.1321 (M + H$^+$), calcd for $C_{25}H_{23}N_2O_5S$ 463.1328. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm) + CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 46.6 min (minor, major diastereomer), 50.4 min (minor diastereomer), 69.0 min (major, major diastereomer), 82.3 min (minor diastereomer).

*(S)-3-(4-Methoxyphenyl)-5-((S)-2-nitro-1-(m-tolyl)ethyl)-5-phenylthiazolidine-2,4-dione (**7m**).* White solid; mp 143.6−145.2 °C; 90% ee; dr = 11:1 (after a single recrystallization, ee =93%, dr >19:1); 44.8 mg (0.1 mmol), 97% yield; $[\alpha]_D^{22}$ + 25.0 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 7.0, 2H), 7.59−7.38 (m, 3H), 7.40−7.11 (m, 4H), 6.78 (d, J = 8.9, 2H), 6.39 (d, J = 8.9, 2H), 4.98−4.69 (m, 2H), 4.41−4.34 (m, 1H), 3.72 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 167.8, 160.1, 138.6, 134.4, 132.4, 130.9, 130.2, 129.8, 129.5, 128.7, 128.3, 128.2, 126.8, 124.7, 114.5, 75.7, 69.0, 55.5, 53.0, 21.5; HRMS (ESI) m/z 463.1318 (M + H$^+$), calcd for $C_{25}H_{23}N_2O_5S$ 463.1328. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm) + CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 22.9 min (minor, major diastereomer), 33.2 min (minor diastereomer), 38.9 min (major, major diastereomer), 44.5 min (minor diastereomer).

*(S)-3-(4-Methoxyphenyl)-5-((S)-2-nitro-1-(o-tolyl)ethyl)-5-phenylthiazolidine-2,4-dione (**7n**).* White solid; mp 142.9−144.0 °C; 99% ee; dr >19:1; 42.5 mg (0.1 mmol), 92% yield; $[\alpha]_D^{22}$ + 20.4 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13−7.86 (m, 3H), 7.61−7.46 (m, 3H), 7.36−7.27 (m, 3H), 6.89−6.67 (m, 2H), 6.65−6.09 (m, 2H), 5.24 (dd, J = 11.3, 3.8, 1H), 4.87 (dd, J = 13.0, 11.3, 1H), 4.48 (dd, J = 13.1, 3.8, 1H), 3.74 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 167.8, 160.1, 139.6, 135.1, 131.8, 129.8, 129.5, 129.4, 129.2, 128.5, 128.3, 128.2, 129.5, 114.6, 68.9, 55.5, 52.9, 47.2, 20.1; HRMS (ESI) m/z 485.1148 (M+Na$^+$), calcd for $C_{25}H_{23}N_2O_5S$ 485.1147. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm) + CHIRALPAK IE (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 27.1 min (major, major diastereomer), 31.6 min (minor, major diastereomer), 55.6 min (minor diastereomer), 58.5 min (minor diastereomer).

*(S)-3-(4-Methoxyphenyl)-5-((S)-1-(4-methoxyphenyl)-2-nitroethyl)-5-phenylthiazolidine-2,4-dione (**7o**).* White solid; mp 81.0−82.3 °C; 93% ee; dr = 12:1 (after a single recrystallization, ee >99%, dr >19:1); 44.0 mg (0.1 mmol), 92% yield; $[\alpha]_D^{22}$ + 21.7 (c 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, J = 8.1, 1.2, 2H), 7.65−7.36 (m, 5H), 7.06−6.70 (m, 4H), 6.66−6.27 (m, 2H), 4.85−4.79 (m, 2H), 4.40−4.36 (m, 1H), 3.82 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 167.8, 160.4, 160.1, 134.4, 131.2,129.8, 129.6, 129.5, 128.3, 128.0, 124.7, 124.1, 114.2, 75.8, 69.2, 55.5, 55.4, 52.4; HRMS (ESI) m/z 479.1270 (M + H$^+$), calcd for $C_{25}H_{23}N_2O_6S$ 479.1277. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. ×

DOI: 10.1021/acs.joc.6b01637
J. Org. Chem. 2016, 81, 9620−9629

250 mm) + CHIRALPAK ID-3 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 70/30; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 36.7 min (minor, major diastereomer), 46.4 min (minor diastereomer), 52.3 min (major, major diastereomer), 65.5 min (minor diastereomer).

*(S)-3-(4-Methoxyphenyl)-5-((R)-2-nitro-1-(thiophen-2-yl)ethyl)-5-phenylthiazolidine-2,4-dione (**7p**).* White solid; mp 105.3−106.6 °C; 74% ee; dr >19:1; 41.3 mg (0.1 mmol), 91% yield; $[\alpha]_D^{22}$ + 18.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17−7.98 (m, 2H), 7.62−7.37 (m, 4H), 7.34−7.20 (m, 1H), 7.09 (dd, *J* = 5.1, 3.6, 1H), 6.96−6.78 (m, 2H), 6.67−6.43 (m, 2H), 5.28 (dd, *J* = 11.3, 3.5, 1H), 4.74 (dd, *J* = 12.9, 11.4, 1H), 4.43 (dd, *J* = 13.0, 3.5, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 167.8, 160.2, 134.6, 133.8, 130.3, 130.0, 129.6, 128.3, 128.0, 127.2, 126.9, 124.7, 114.7, 68.9, 55.5, 49.5; HRMS (ESI) *m*/*z* 455.0727 (M + H$^+$), calcd for $C_{22}H_{19}N_2O_5S_2$ 455.0735. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 13.7 min (minor diastereomer), 22.8 min (minor diastereomer), 31.2 min (minor, major diastereomer), 35.3 min (major, major diastereomer).

*(S)-5-((S)-1-Cyclohexyl-2-nitroethyl)-3-(4-methoxyphenyl)-5-phenylthiazolidine-2,4-dione (**7q**).* White solid; mp 126.0−127.2 °C; 96% ee; dr = 5:1; 28.6 mg (0.1 mmol), 63% yield; $[\alpha]_D^{22}$ − 25.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97−7.80 (m, 2H), 7.54−7.34 (m, 3H), 7.13−6.88 (m, 4H), 4.33−4.15 (m, 2H), 3.81 (s, 3H), 3.70−3.47 (m, 1H), 1.98−1.57 (m, 6H), 1.29−1.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 169.2, 160.1, 135.8, 129.7, 129.4, 128.3, 127.8, 125.1, 114.8, 73.9, 69.1, 55.6, 50.5, 40.5, 33.8, 30.0, 27.1, 26.6, 25.8; HRMS (ESI) *m*/*z* 455.1649 (M + H$^+$), calcd for $C_{24}H_{27}N_2O_5S$ 455.1641. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 12.8 min (minor diastereomer), 17.4 min (major, major diastereomer), 18.9 min (minor, major diastereomer), 22.3 min (minor diastereomer).

*(S)-3-(4-Methoxyphenyl)-5-((S)-2-nitro-1-phenylethyl)-5-(p-tolyl)-thiazolidine-2,4-dione (**7r**).* White solid; mp 108.6−110.1 °C; 90% ee; dr = 13:1; 41.1 mg (0.1 mmol), 89% yield; $[\alpha]_D^{22}$ + 21.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4, 2H), 7.60−7.12 (m, 7H), 6.90−6.67 (m, 2H), 6.56−6.24 (m, 2H), 4.99−4.76 (m, 2H), 4.44−4.41 (m, 1H), 3.75 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 167.7, 160.1, 140.0, 132.5, 131.3, 130.2, 130.1, 129.4, 128.8, 128.3, 127.9, 124.9, 114.5, 75.7, 68.8, 55.5, 52.9, 21.0; HRMS (ESI) *m*/*z* 463.1335 (M + H$^+$), calcd for $C_{25}H_{23}N_2O_5S$ 463.1328. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm) + CHIRALPAK ID-3 (4.6 mm i.d. × 250 mm); hexane/2-propanol = 70/30; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 29.1 min (minor, major diastereomer), 45.5 min (minor diastereomer), 57.9 min (major, major diastereomer), 82.4 min (minor diastereomer).

*(S)-5-(4-(tert-Butyl)phenyl)-3-(4-methoxyphenyl)-5-((S)-2-nitro-1-phenylethyl)thiazolidine-2,4-dione (**7s**).* White solid; mp 108.6−110.2 °C; 87% ee; dr = 12:1; 43.8 mg (0.1 mmol), 87% yield; $[\alpha]_D^{22}$ + 23.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.7, 2H), 7.61−7.37 (m, 7H), 6.87−6.68 (m, 2H), 6.51−6.21 (m, 2H), 5.05−4.74 (m, 2H), 4.46−4.43 (m, 1H), 3.75 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 167.8, 160.2, 153.0, 132.5, 131.2, 130.1, 129.4, 128.8, 128.3, 127.7, 126.5, 124.7, 114.5, 75.7, 68.7, 55.5, 52.8, 34.7, 31.2; HRMS (ESI) *m*/*z* 505.1801 (M + H$^+$), calcd for $C_{28}H_{29}N_2O_5S$ 505.1797. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 8.3 min (minor, major diastereomer), 11.1 min (minor diastereomer), 13.7 min (major, major diastereomer), 41.3 min (minor diastereomer).

*(S)-5-(Benzylthio)-3,5-diphenylthiazolidine-2,4-dione (**9a**).* Colorless oil; 87% ee; 33.2 mg (0.1 mmol), 85% yield; $[\alpha]_D^{22}$ − 25.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.3, 2H), 7.53−7.25 (m, 6H), 7.18 (dd, *J* = 17.3, 8.8, 7H), 4.00 (d, *J* = 11.8, 1H), 3.66 (d, *J* = 11.8, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 167.8, 135.6, 134.8, 132.8, 129.5, 129.4, 129.4, 129.4, 129.2, 128.8, 127.7, 127.5, 127.4, 66.3, 37.6; HRMS (ESI) *m*/*z* 392.0780 (M + H$^+$), calcd for $C_{22}H_{18}NO_2S_2$ 392.0779. The ee was determined by HPLC analysis. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 12.8 min (minor), 20.0 min (major).

*(S)-5-(Benzylthio)-3-(4-chlorophenyl)-5-phenylthiazolidine-2,4-dione (**9b**).* Colorless oil; 88% ee; 37.4 mg (0.1 mmol), 88% yield; $[\alpha]_D^{22}$ − 20.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 7.4, 2H), 7.44−7.24 (m, 5H), 7.23−6.99 (m, 7H), 3.96 (d, *J* = 12.0, 1H), 3.65 (d, *J* = 12.0, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 167.6, 135.4, 135.3, 134.8, 131.1, 129.7, 129.5, 129.4, 129.2, 128.8, 128.7, 127.8, 127.5, 66.3, 37.7; HRMS (ESI) *m*/*z* 426.0390 (M + H$^+$), calcd for $C_{22}H_{17}ClNO_2S_2$ 426.0389. The ee was determined by HPLC analysis. CHIRALPAK IF (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 8.0 min (minor), 10.4 min (major).

*(S)-5-(Benzylthio)-5-phenyl-3-(p-tolyl)thiazolidine-2,4-dione (**9c**).* Colorless oil; 90% ee; 36.8 mg (0.1 mmol), 91% yield; $[\alpha]_D^{22}$ − 21.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.4, 2H), 7.46−7.27 (m, 5H), 7.20−7.15 (m, 5H), 7.05 (d, *J* = 7.9, 2H), 4.00 (d, *J* = 11.8, 1H), 3.66 (d, *J* = 11.8, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 167.9, 139.7, 135.7, 134.9, 130.2, 130.1, 129.4, 129.3, 129.2, 128.7, 127.7, 127.5, 127.1, 66.3, 37.6, 21.3; HRMS (ESI) *m*/*z* 406.0934 (M + H$^+$), calcd for $C_{23}H_{20}NO_2S_2$ 406.0935. The ee was determined by HPLC analysis. CHIRALPAK IF (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 10.2 min (minor), 12.6 min (major).

*(S)-5-(Benzylthio)-3-(4-methoxyphenyl)-5-phenylthiazolidine-2,4-dione (**9d**).* Colorless oil; 91% ee; 41.3 mg (0.1 mmol), 98% yield; $[\alpha]_D^{22}$ − 24.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.4, 2H), 7.42−7.23 (m, 3H), 7.22−6.99 (m, 7H), 6.91 (d, *J* = 8.3, 2H), 4.00 (d, *J* = 11.8, 1H), 3.70 (d, *J* = 17.5, 3H), 3.66 (d, *J* = 11.8, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 168.1, 160.2, 135.7, 134.9, 129.4, 129.4, 129.2, 128.8, 128.6, 127.7, 127.5, 125.4, 114.8, 66.2, 55.6, 37.6; HRMS (ESI) *m*/*z* 422.0884 (M + H$^+$), calcd for $C_{23}H_{20}NO_3S_2$ 422.0885. The ee was determined by HPLC analysis. CHIRALPAK IF (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 11.6 min (minor), 16.6 min (major).

*(S)-5-(Benzylthio)-5-(4-(tert-butyl)phenyl)-3-(4-methoxyphenyl)-thiazolidine-2,4-dione (**9e**).* Colorless oil; 87% ee; 39.6 mg (0.1 mmol), 83% yield; $[\alpha]_D^{22}$ − 20.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7, 2H), 7.44 (d, *J* = 7.8, 2H), 7.26 (s, 5H), 7.19 (d, *J* = 7.9, 2H), 7.02 (d, *J* = 8.1, 2H), 4.10 (d, *J* = 11.9, 1H), 3.85 (s, 3H), 3.80 (s, 1H), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 168.2, 160.2, 152.5, 135.1, 132.6, 129.4, 128.7, 128.6, 127.6, 127.2, 126.1, 125.5, 114.8, 66.2, 55.6, 37.6, 34.7, 31.2; HRMS (ESI) *m*/*z* 478.1517 (M + H$^+$), calcd for $C_{27}H_{28}NO_3S_2$ 478.1511. The ee was determined by HPLC analysis. CHIRALPAK IF (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 9.3 min (minor), 11.5 min (major).

*(S)-5-(Benzylthio)-5-(4-chlorophenyl)-3-(4-methoxyphenyl)-thiazolidine-2,4-dione (**9f**).* Colorless oil; 88% ee; 40.0 mg (0.1 mmol), 88% yield; $[\alpha]_D^{22}$ − 31.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.2, 2H), 7.29 (d, *J* = 8.3, 2H), 7.28−6.94 (m, 7H), 6.92 (d, *J* = 8.5, 2H), 3.99 (d, *J* = 12.0, 1H), 3.76 (s, 3H), 3.69 (d, *J* = 12.0, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 167.6, 160.2, 135.4, 134.7, 134.2, 129.3, 129.2, 129.0, 128.8, 128.5, 127.7, 125.3, 114.8, 65.6, 55.6, 37.7; HRMS (ESI) *m*/*z* 456.0492 (M + H$^+$), calcd for $C_{23}H_{19}ClNO_3S_2$ 456.0495. The ee was determined by HPLC analysis. CHIRALPAK IF (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 15.0 min (minor), 16.8 min (major).

*(S)-5-(Benzylthio)-5-(3-fluorophenyl)-3-(4-methoxyphenyl)-thiazolidine-2,4-dione (**9g**).* Colorless oil; 89% ee; 41.7 mg (0.1 mmol), 95% yield; $[\alpha]_D^{22}$ − 29.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 2H), 7.29 (d, *J* = 7.7, 1H), 7.21−7.03 (m, 7H), 7.03−6.85 (m, 3H), 3.99 (d, *J* = 11.9, 1H), 3.75 (s, 3H), 3.69 (d, *J* = 11.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 167.6, 162.8 (d, 1JC-F = 246.4 Hz), 160.2, 138.1 (d, 1JC-F = 7.3 Hz), 134.7, 130.7 (d, 1JC-F = 8.2 Hz), 129.3, 128.8, 128.5, 127.7, 125.2, 123.3 (d, 1JC-F = 3.0 Hz), 114.6 (d, 1JC-F = 21.0 Hz), 115.0 (d, 1JC-F = 24.2 Hz), 114.8, 65.4, 55.6, 37.7; HRMS (ESI) *m*/*z* 440.0791 (M + H$^+$), calcd for

DOI: 10.1021/acs.joc.6b01637
J. Org. Chem. 2016, 81, 9620−9629

$C_{23}H_{19}FNO_3S_2$ 440.0790. The ee was determined by HPLC analysis. CHIRALPAK IF (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 10.4 min (minor), 12.8 min (major).

*(S)-5-((4-Chlorobenzyl)thio)-3-(4-methoxyphenyl)-5-phenylthiazolidine-2,4-dione (**9h**).* Colorless oil; 88% ee; 43.6 mg (0.1 mmol), 96% yield; $[\alpha]_D^{22}$ − 30.2 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.0, 2H), 7.31 (d, *J* = 6.8, 3H), 7.19−7.00 (m, 6H), 6.92 (d, *J* = 8.3, 2H), 3.94 (d, *J* = 12.3, 1H), 3.75 (s, 3H), 3.65 (d, *J* = 12.2, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 167.8, 160.2, 135.6, 133.6, 133.5, 130.7, 129.3, 129.2, 128.9, 128.5, 127.5, 125.3, 114.8, 66.0, 55.6, 37.0; HRMS (ESI) *m*/*z* 456.0490 (M + H^+), calcd for $C_{23}H_{19}ClNO_3S_2$ 456.0495. The ee was determined by HPLC analysis. CHIRALPAK IF (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 13.1 min (minor), 25.8 min (major).

*(S)-3-(4-Methoxyphenyl)-5-((4-methylbenzyl)thio)-5-phenylthiazolidine-2,4-dione (**9i**).* Colorless oil; 87% ee; 42.2 mg (0.1 mmol), 99% yield; $[\alpha]_D^{22}$ − 10.0 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.0, 2H), 7.44 (d, *J* = 7.9, 3H), 7.14 (dt, *J* = 16.1, 8.1, 6H), 7.02 (d, *J* = 7.5, 2H), 4.08 (d, *J* = 11.6, 1H), 3.85 (s, 3H), 3.75 (d, *J* = 11.9, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 166.2, 158.2, 135.5, 133.9, 129.7, 127.5, 127.4, 127.2, 126.7, 125.6, 123.5, 112.8, 64.4, 53.7, 35.4, 19.2; HRMS (ESI) *m*/*z* 436.1042 (M + H^+), calcd for $C_{24}H_{22}NO_3S_2$ 436.1041. The ee was determined by HPLC analysis. CHIRALPAK IF (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 13.7 min (minor), 29.3 min (major).

*(S)-3-(4-Methoxyphenyl)-5-((3-methylbenzyl)thio)-5-phenylthiazolidine-2,4-dione (**9j**).* Colorless oil; 89% ee; 42.6 mg (0.1 mmol), 98% yield; $[\alpha]_D^{22}$ − 19.4 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.0, 2H), 7.52−7.34 (m, 3H), 7.20 (d, *J* = 8.8, 3H), 7.03 (d, *J* = 10.0, 5H), 4.08 (d, *J* = 11.7, 1H), 3.86 (s, 3H), 3.74 (d, *J* = 11.8, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 166.2, 158.2, 136.5, 133.8, 132.8, 128.2, 127.4, 127.2, 126.7, 126.7, 126.5, 125.6, 124.5, 123.5, 112.8, 64.4, 53.7, 35.6, 19.4; HRMS (ESI) *m*/*z* 436.1037 (M + H^+), calcd for $C_{24}H_{22}NO_3S_2$ 436.1041. The ee was determined by HPLC analysis. CHIRALPAK IF (4.6 mm i.d. × 250 mm); hexane/2-propanol = 90/10; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 13.9 min (minor), 17.4 min (major).

*(S)-3-(4-Methoxyphenyl)-5-phenyl-5-(phenylthio)thiazolidine-2,4-dione (**9k**).* Colorless oil; 12% ee; 32.5 mg (0.1 mmol), 80% yield; $[\alpha]_D^{22}$ − 5.1 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.2, 2H), 7.70 (d, *J* = 7.5, 2H), 7.60−7.33 (m, 6H), 6.88 (d, *J* = 8.5, 2H), 6.66 (d, *J* = 8.4, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 167.9, 160.0, 137.7, 135.5, 131.1, 129.5, 129.3, 129.1, 128.4, 127.7, 125.0, 114.6, 72.2, 55.5; HRMS (ESI) *m*/*z* 408.0729 (M + H^+), calcd for $C_{22}H_{18}NO_3S_2$ 408.0728. The ee was determined by HPLC analysis. CHIRALPAK IF (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 13.3 min (major), 16.3 min (minor).

*(R)-5-(Benzylsulfonyl)-3-(4-methoxyphenyl)-5-phenylthiazolidine-2,4-dione (**10**).* White solid; mp 133.1−134.5 °C; 91% ee; 183.5 mg (0.5 mmol), 81% yield; $[\alpha]_D^{22}$ − 21.1 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.45 (s, 3H), 7.29−7.02 (m, 8H), 6.98 (d, *J* = 8.2, 2H), 4.66 (d, *J* = 12.9, 1H), 3.92 (d, *J* = 12.9, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 167.4, 160.6, 131.5, 130.7, 130.6, 129.5, 129.2, 128.8, 128.7, 128.3, 125.0, 124.8, 115.0, 83.8, 55.6, 55.2; HRMS (ESI) *m*/*z* 454.0705 (M + H^+), calcd for $C_{23}H_{20}NO_5S_2$ 454.0703; The ee was determined by HPLC analysis. CHIRALPAK IF (4.6 mm i.d. × 250 mm); hexane/2-propanol = 80/20; flow rate 1.0 mL/min; 25 °C; 254 nm; t_R = 22.6 min (minor), 30.1 min (major).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01637.

General information, optimization of the reaction conditions of sulfenylation, determination of the absolute configuration by X-ray crystallography, copies of HPLC and NMR spectra (PDF)

Crystallographic information (CIF)

Crystallographic information (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chmjzy@henu.edu.cn.

Author Contributions

§L.J. and L.B. made equal contributions to this work

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the grants from NSFC (21072044 and 21672052) and Henan province (14IRTSTHN006, 152300410057, and 162300410002).

■ REFERENCES

(1) (a) Lesyk, R. B.; Zimenkovsky, B. S. *Curr. Org. Chem.* **2004**, *8*, 1547. (b) Murugan, R.; Anbazhagan, S.; Narayanan, S. S. *Eur. J. Med. Chem.* **2009**, *44*, 3272. (c) Tomasic, L. P.; Masic, L. *Curr. Med. Chem.* **2009**, *16*, 1596. (d) Mohler, D. L.; Shen, G.; Dotse, A. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2239. (e) Giles, R. G.; Lewis, N. J.; Quick, J. K.; Sasse, M. J.; Urquhart, M. W. J.; Youssef, L. *Tetrahedron* **2000**, *56*, 4531. (f) Kaminskyy, D.; Zimenkovsky, B.; Lesyk, R. *Eur. J. Med. Chem.* **2009**, *44*, 3627.

(2) Saltiel, A. R.; Olefsky, J. M. *Diabetes* **1996**, *45*, 1661.

(3) (a) Mandal, M.; Tang, H.; Xiao, L.; Su, J.; Li, G.; Yang, S.-W.; Pan, W.; Tang, H.; Dejesus, R.; Hicks, J.; Lombardo, M.; Chu, H.; Hagmann, W.; Pasternak, A.; Gu, X.; Jiang, J.; Dong, S.; Ding, F.-X.; London, C.; Biswas, D.; Young, K.; Hunter, D. N.; Zhao, Z.; Yang, D. PCT Int. Appl. WO 2015112441 A1 20150730, 2015. (b) York, B. M., Jr. U.S. Patent US 5070100 A 19911203, 1991. (c) Iwataki, I.; Rudchenko, V. F.; Kurz, T.; Semer, C. R.; Kucharek, T. A.; Geffken, D. U.S. Patent US 6476055 B1 20021105, 2002. (d) Mihm, G.; Hauel, N.; Ries, U.; Meel, J.; van Wienen, W.; Entzeroth, M. Ger. Offen DE 4408497 A1 19950921, 1995. (e) Desai, R. C.; Han, W.; Metzger, E. J.; Bergman, J. P.; Gratale, D. F.; MacNaul, K. L.; Berger, J. P.; Doebber, T. W.; Leung, K.; M?ller, D. E.; Heck, J. V.; Sahoo, S. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2795. (f) Falk, K.; Roetzschke, O. PCT Int. Appl. WO 2006029891 A2 20060323, 2006. (g) Pedras, M. S. C.; Hossain, M. *Org. Biomol. Chem.* **2006**, *4*, 2581. (h) Pedras, M. S. C.; Hossain. *Bioorg. Med. Chem.* **2007**, *15*, 5981.

(4) (a) Wheeler, H. L. *J. Am. Chem. Soc.* **1901**, *23*, 223. (b) Wheeler, H. L.; Johnson, T. B. *J. Am. Chem. Soc.* **1902**, *24*, 680.

(5) Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron* **1982**, *38*, 3255.

(6) (a) Han, Z.; Chen, W.; Dong, S.; Yang, C.; Liu, H.; Pan, Y.; Yan, L.; Jiang, Z. *Org. Lett.* **2012**, *14*, 4670. (b) Qiao, B.; Liu, X.; Duan, S.; Yan, L.; Jiang, Z. *Org. Lett.* **2014**, *16*, 672. (c) Huang, L.; Li, J.; Zhao, Y.; Ye, X.; Liu, Y.; Yan, L.; Tan, C.-H.; Liu, H.; Jiang, Z. *J. Org. Chem.* **2015**, *80*, 8933. (d) Zhu, B.; Qiu, S.; Li, J.; Coote, M. L.; Lee, R.; Jiang, Z. *Chem. Sci.* **2016**, *7*, 6060.

(7) (a) Zhang, W.; Tan, D.; Lee, R.; Tong, G.; Chen, W.; Qi, B.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 10069. (b) Zhu, B.; Zhang, W.; Lee, R.; Han, Z.; Yang, W.; Tan, D.; Huang, K.-W.; Jiang, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 6666. (c) Qiao, B.; An, Y.; Liu, Q.; Yang, W.; Liu, H.; Shen, J.; Yan, L.; Jiang, Z. *Org. Lett.* **2013**, *15*, 2358. (d) Bai, X.; Jing, Z.; Liu, Q.; Ye, X.; Zhang, G.; Zhao, X.; Jiang, Z. *J. Org. Chem.* **2015**, *80*, 12686. (e) Zhu, B.; Lee, R.; Li, J.; Ye, X.; Hong, S.-N.; Qiu, S.; Coote, M. L.; Jiang, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 1299. (f) Jiao, L.; Zhao, X.; Liu, H.; Ye, X.; Li, Y.; Jiang, Z. *Org. Chem. Front.* **2016**, *3*, 470.

DOI: 10.1021/acs.joc.6b01637
J. Org. Chem. 2016, 81, 9620−9629

(8) (a) Taylor, E. C.; Berchtold, G. A.; Goeckner, N. A.; Stroehmann, F. G. *J. Org. Chem.* **1961**, *26*, 2715. (b) Taylor, E. E., Jr.; Wolinsky, J.; Lee, H.-H. *J. Am. Chem. Soc.* **1954**, *76*, 1866. (c) Potts, K. T.; Chen, S. J.; Kane, J.; Marshall, J. L. *J. Org. Chem.* **1977**, *42*, 1633. (d) Majcen Le Maréchal, A.; Robert, A.; Leban, I. *Tetrahedron* **1990**, *46*, 453.

(9) CCDC1430350 (**7f**) and CCDC1489694 (**11**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(10) For selected examples on asymmetric sulfenylation: (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (c) Liao, K.; Zhou, F.; Yu, J.-S.; Gao, W.-M.; Zhou, J. *Chem. Commun.* **2015**, *51*, 16255. For selected reviews, see: (d) Zhao, X.; Shen, J.; Jiang, Z. *Mini-Rev. Org. Chem.* **2014**, *11*, 424. (e) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Rev.* **2014**, *114*, 8807.

(11) Salaski, E. J.; Salaski, E. J.; Ayral-Kaloustian, S.; Epstein, J. W. PCT Int. Appl. WO 2003018011 A1 20030306, 2003.

(12) For the selected reviews, see: (a) Chai, Z.; Zhao, G. *Catal. Sci. Technol.* **2012**, *2*, 29. (b) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051. (c) Zhao, X.; Zhu, B.; Jiang, Z. *Synlett* **2015**, *26*, 2216.

(13) Vallejos, J. C.; Legrand, O.; Christidis, Y. *Bull. Soc. Chim. Fr.* **1997**, *134*, 101.

DOI: 10.1021/acs.joc.6b01637
J. Org. Chem. 2016, 81, 9620−9629