JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

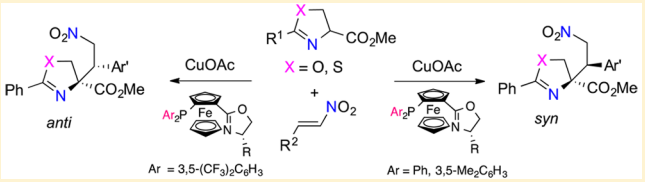
Ligand-Controlled Stereodivergent, Enantioselective Conjugate Addition of 2-Oxazoline- and 2-Thiazoline-4-carboxylate to Nitroalkene Catalyzed by Chiral Copper Complexes

Yukiko Matsuda, Akihiro Koizumi, Ryosuke Haraguchi, and Shin-ichi Fukuzawa*

Department of Applied Chemistry, Institute of Science and Engineering, Chuo University, 1-13-27 Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan

Supporting Information

ABSTRACT: The copper-catalyzed asymmetric conjugate addition of 2-oxazoline- and 2-thiazoline-4-carboxylate to a nitroalkene proceeded to give either the *syn* or *anti* adduct selectively in high enantiomeric excess when an appropriate chiral ligand was used. Subsequent reduction of the nitro group followed by hydrolysis of the oxazoline ring yielded an optically active γ-lactam of protected α-quaternary serine derivative.



INTRODUCTION

α,α-Disubstituted amino acids (α-quaternary amino acids) have been of interest as nonproteinogenic amino acids and as useful substrates for modified peptides and unnatural proteins.[1] The synthetic study of chiral α-quaternary amino acids could provide potential biologically active substrates that can be useful in drug discovery. An oxazolone is an extremely useful building block to access chiral α-quaternary amino acids. There are numerous examples of organocatalytic aldol, Michael, and alkylation reactions of oxazolones that provide chiral α-quaternary amino acids when an appropriate electrophile is used.[2] Recently, the Fu and Lu research groups independently reported the chiral phosphine-catalyzed γ-addition of oxazolones to allenoates, which affords the corresponding oxazolones with a chiral quaternary carbon and provides ready access to protected α-quaternary amino acids.[3]

2-Oxazoline-4-carboxylate is an alternative building block of α-quaternary amino acids; it should be a framework of protected α-quaternary serine derivatives. Park and co-workers reported the chiral phase-transfer-catalyzed Michael addition of 2-oxazoline-4-carboxylate with acrylate. Subsequent hydrolysis of the resulting conjugate adduct yielded a chiral α-quaternary glutamic acid.[4] Overman and co-workers reported the diastereoselective Michael addition of chiral 5-methyl-2-oxazoline-4-carboxylate to an unsaturated ester; the adduct, upon treatment with LDA, gives a chiral α-quaternary serine derivative after hydrolysis.[5] 2-Thiazoline-4-carboxylates are also good building blocks for α-quaternary cysteine derivatives.[6]

Deng[7] and our[8] research groups independently succeeded in achieving the stereodivergent asymmetric conjugate addition of 1-pyrroline-5-carboxylate to nitroalkenes, where the diastereoselectivity (*syn*/*anti*-selectivity) is controlled by a chiral copper or silver catalyst. The corresponding pyrrolidine product with a spiro-γ-lactam-bearing chiral quaternary center was obtained after hydrogenation of the Michael adduct. Inspired by the success of the metal-catalyzed asymmetric conjugate addition of 1-pyrroline-5-carboxylates to nitroalkenes, we envisaged that 2-oxazoline-4-carboxylates, which are analogous to 1-pyrroline-5-carboxylates, would give chiral α-quaternary serine derivatives when subjected to metal-catalyzed Michael addition with nitroalkenes. As stated earlier, chiral α-quaternary amino acids have grown increasingly important, and the metal-catalyzed methodology described here will provide a versatile route for the synthesis of this class of compounds. Further, the synthesis of α-quaternary amino acids with varied electronic properties as well as diverse stereochemistry is a challenging subject.

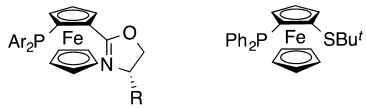
In this paper, we report the first stereodivergent copper-catalyzed asymmetric Michael addition of 2-oxazoline- and 2-thiazoline-4-carboxylates to nitroalkenes by choosing an appropriate chiral ligand. We also report the transformation of the Michael adduct to its corresponding γ-lactam of protected α-quaternary serine derivative.

RESULTS AND DISCUSSION

We first examined the reaction of methyl 2-phenyl-2-oxazoline-4-carboxylate **1** with *trans*-β-nitrostyrene **2** using combinations of several copper salts and chiral ligands (Figure 1). Table 1 summarizes the results of the reaction with various chiral copper complexes. The reaction was carried out in THF at room temperature for 24 h using 5 mol % copper salt and 5.5 mol % chiral ligand. The combination of CuOAc and chiral *P*,*N*-ligand *i*-Pr-FcPHOX **L1** gave a mixture of the *syn*-**3a** and *anti*-**4a** adducts in 82:18 ratio and 76% combined yield, and *syn*-**3a** was produced in 88% ee (entry 1). The *syn*-to-*anti* ratio of the adducts was determined by ^{1}H NMR integration of the

Received: July 19, 2016
Published: August 5, 2016

DOI: 10.1021/acs.joc.6b01722
J. Org. Chem. 2016, 81, 7939−7944

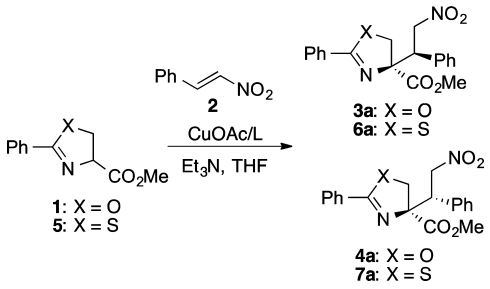


(*S*,*Sp*)-FcPHOX FeSulphos
L5

L1: Ar = Ph, R = *i*-Pr
L2: Ar = Ph, R = *t*-Bu
L3: Ar = 3,5-$Me_2C_6H_3$, R = *i*-Pr
L4: Ar = 3,5-$(CF_3)_2C_6H_3$, R = *i*-Pr

Figure 1. Chiral *P*,*N*- and *P*,*S*-ligands.

Table 1. Reaction of 2-Oxazoline- and 2-Thiazoline-4-carboxylates with Nitroalkene[a]



entry	1 or 5	L	yield (%)[b]	*syn*/*anti*[c]	ee (%)[d]
1	1	L1	76	82:18	88 (*syn*)
2	1	L2	66	88:12	93 (*syn*)
3	1	L3	53	83:17	97 (*syn*)
4	1	L4	68	3:97	97 (*anti*)
5	1	L5	63	21:79	95 (*anti*)
6[e]	1	L2	40	89:11	89 (*syn*)
7[e]	1	L4	65	5:95	81 (*anti*)
8[e]	1	L5	60	19:81	93 (*anti*)
9	5	L1	85	92:8	99 (*syn*)
10	5	L2	86	86:14	98 (*syn*)
11	5	L3	82	85:15	82 (*syn*)
12	5	L4	88	5:95	97 (*anti*)
13	5	L5	88	10:90	97 (*anti*)

[a]Conditions: **1** (0.20 mmol), **2** (0.22 mmol), CuOAc (5 mol %), **L** (5.5 mol %), Et_3N (0.04 mmol), THF (1.0 mL), rt, 24 h. [b]Combined isolated yield of *syn*- and *anti*-isomers. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC. [e]$CuBF_4$ was used as a copper salt.

methylene signal of the oxazoline ring and/or the methyl ester signal. As in our previous report,[7] the *syn*/*anti*-stereochemistry is defined by the relative configuration of the imino and phenyl groups. The relative and absolute configuration of all the other adducts was assumed by analogy to that of the product obtained in the reaction with 1-pyrroline-5-carboxylate. The stereoisomeric adducts with upfield (4.0 ppm) and downfield (4.4 ppm) benzyl signals were assigned *syn* and *anti* stereochemistry, respectively. The absolute configuration of *syn*-**3a** was temporarily assigned as (4*R*, 1′*R*) (and confirmed by X-ray crystallography of the corresponding thiazoline analogue, as discussed later). The chiral complex with *t*-Bu-FcPHOX **L2** ligand improved the *syn* selectivity and enantiomeric excess of *syn*-**3a** (93% ee) (entry 2). The use of the more hindered FcPHOX ligand **L3** (two -CH_3 groups attached to each phenyl moiety) decreased the reaction yield but had a minor effect on the *syn* selectivity with the ee of *syn*-**3a** being almost the same as that obtained with **L2** (entry 3). The use of electron-poor FcPHOX ligand **L4** (two electron withdrawing -CF_3 groups attached to each phenyl moiety) dramatically switched the diastereoselectivity in favor of the *anti* adduct (*syn*/*anti* = 3:97); *anti*-**4a** was produced as the major product with 97% ee (entry 4). A similar diastereo-switch was reported in the asymmetric 1,3-dipolar cycloaddition of azomethine ylide with nitroalkenes: electron-rich ligands gave the *exo*-cycloadduct whereas electron-poor ligands gave the *endo*-cycloadduct.[9] The *anti* adduct was produced when chiral *P*,*S*-ligand FeSulphos **L5** was used, and the relative and absolute configuration of the adduct was the same as **4a** (entry 5). The *anti*-selectivity observed with ligand **L5** is not clearly understood. However, it has been reported in the literature that the diastereo-fashion depends on the nature of alkenes in the copper/**L5**-catalyzed reactions with azomethine ylide.[10] A similar stereochemical outcome was observed when $CuBF_4$ copper salt was used but the yields, diastereoselectivities, and ee values were slightly lower than that with CuOAc (entries 6−8); the chiral catalyst with ligands **L2** and **L4** favors *syn* and *anti* selectivity, respectively.

The reaction of methyl 2-thiazoline-4-carboxylate **5** with **2** was then examined under the same reaction conditions using CuOAc and chiral ligands **L1**−**L5**. The thiazoline ring did not affect the reaction outcome, although the coordinating sulfur atom could interact with copper. Similar to the results obtained in the reactions with **1**, in these reactions the *syn*-adducts were also obtained in good yields and enantioselectivities when the electron-rich ligand **L1** was used (entries 9−11), whereas the electron-poor ligand **L4** resulted in *anti* selectivity (entry 12). *P*,*S*-Ligand **L5** also gave the *anti*-adduct (entry 13).

Table 2 summarizes the optimization experiments; the reaction was examined by using various solvents and bases. In

Table 2. Optimization of the Reaction[a]

entry	1 or 5	L	solvent	base	yield (%)[b]	*syn*/*anti*[c]	ee (%) (*syn*)[d]
1	1	L2	THF		66	84:16	96
2	1	L2	THF	NEt_3	66	88:12	93
3	1	L2	THF	pyridine	65	79:21	97
4	1	L2	THF	DIPEA	61	81:19	96
5	1	L2	THF	Cs_2CO_3	52	63:37	94
6	1	L2	Et_2O		72	80:20	94
7	1	L2	DME		72	97:3	94
8	1	L2	DCM		68	87:13	79
9	1	L2	toluene		76	96:4	95
10[e]	5	L1	THF		81	90:10	99
11[e]	5	L1	THF	NEt_3	86	95:5	99
12[e]	5	L1	THF	pyridine	86	89:11	99
13[e]	5	L1	THF	DIPEA	83	89:11	99
14[e]	5	L1	THF	Cs_2CO_3	71	50:50	72
15[e]	5	L1	Et_2O	NEt_3	85	94:6	99
16[e]	5	L1	DME	NEt_3	85	95:5	99
17[e]	5	L1	DCM	NEt_3	76	90:10	97
18[e]	5	L1	toluene	NEt_3	83	93:7	99

[a]Conditions: **1** or **5** (0.20 mmol), **2** (0.22 mmol), CuOAc (5 mol %), **L** (5.5 mol %), solvent, rt, 24 h. [b]Combined isolated yield of *syn*- and *anti*-isomers. [c]Determined by ^1H NMR. [d]Determined by HPLC. [e]The reaction was carried out at −20 °C for 24 h.

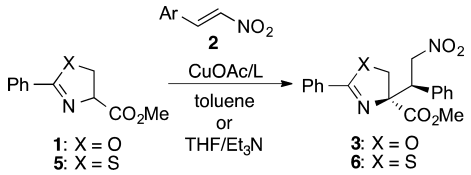
entries 1−9 and 10−18, the results of the reaction of **1** and **5** with **2a** are shown, respectively. For the reaction of **1**, every solvent gave moderate to good yields with high *syn* selectivities and high ee, and we decided that toluene was the choice of solvent considering a total yield and ee, and additional base had limited effect on the reaction. For the reaction of **5**, a good yield

DOI: 10.1021/acs.joc.6b01722
J. Org. Chem. 2016, 81, 7939−7944

and stereoselectivity were obtained with every combination of solvent and a base, and we determined that the combination of THF and Et_3N was the optimized conditions considering the highest yield and stereoselectivity. It must be noted that the reaction should be carried out at −20 °C to obtain a high ee.

To evaluate the scope of the *syn*-selective Michael addition of **1** and **5**, we examined a variety of (*E*)-nitroalkenes with differing electronic and steric properties under the optimized reaction conditions. The reaction with **1** was carried out in toluene at room temperature for 24 h using **L2** in the absence of Et_3N, and the reaction with **5** was carried out in THF at −20 °C for 24 h using **L1** in the presence of Et_3N. The results are summarized in Table 3. The sterically hindered *o*-methyl

Table 3. Scope of Nitroalkenes[a]



entry	1 or 5	Ar in 2	yield (%)[b]	*syn*/*anti*[c]	ee (%) (*syn*)[d]
1	**1**	Ph	76, **3a**	96:4	95
2	**1**	*o*-MeC_6H_4	68, **3b**	63:37	99
3	**1**	*m*-MeC_6H_4	81, **3c**	91:9	99
4	**1**	*p*-MeC_6H_4	77, **3d**	93:7	98
5	**1**	*p*-$MeOC_6H_4$	78, **3e**	94:6	99
6	**1**	*p*-ClC_6H_4	80, **3f**	93:7	93
7	**1**	*p*-BrC_6H_4	68, **3g**	79:21	94
8	**1**	*p*-$NO_2C_6H_4$	53, **3h**	83:17	95
9	**1**	2-thienyl	75, **3i**	99:1	96
10[e]	**1**	*p*-$MeOC_6H_4$	83, **4e**	6:94	89[f]
11[e]	**1**	*p*-$NO_2C_6H_4$	59, **4h**	3:97	85[f]
12	**5**	Ph	86, **6a**	95:5	98
13	**5**	*p*-$MeOC_6H_4$	87, **6b**	94:6	98
14	**5**	*p*-ClC_6H_4	83, **6c**	95:5	98
15	**5**	*p*-BrC_6H_4	88, **6d**	95:5	92
16	**5**	*p*-$NO_2C_6H_4$	60, **6e**	93:7	98
17	**5**	2-thienyl	85, **6f**	99:1	96
18	**5**	Fc	58, **6g**	86:14	97
19[e]	**5**	Fc	62, 7g	2:98	91[f]

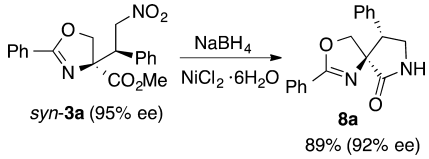
[a]Conditions for entries 1−11: **1** (0.20 mmol), **2** (0.22 mmol), CuOAc (5 mol %), **L2** (5.5 mol %), toluene (1.0 mL), rt, 24 h. Conditions for entries 12−19: **5** (0.20 mmol), **2** (0.22 mmol), CuOAc (5 mol %), **L1** (5.5 mol %), Et_3N (0.04 mmol), THF (1.0 mL), −20 °C, 24 h. [b]Combined isolated yield of *syn*- and *anti*-isomers. [c]Determined by ^1H NMR. [d]Determined by chiral HPLC. [e]**L4** used as a ligand. [f]ee for the *anti*-isomer.

substituent on the phenyl group decreased the yield and *syn*-selectivity in the reaction with **1** (entry 2). The electron-donating halogen and *m*-substituents had a limited effect on the reaction, yielding high *syn*- and enantioselectivities (entries 3−7). The electron-withdrawing *p*-nitro substituent decreased the yield (entry 8). When a heteroaryl derivative containing a 2-thienyl group was used as a substrate, good yields were obtained with high *syn*- and enantioselectivities (entry 9). When electron-poor ligand **L4** was used, a switch in diastereoselectivity was realized regardless of the electronic properties of the substituents on the phenyl group; the *anti*-isomers were produced as the major product in the reaction of substrates with *p*-methoxy and *p*-nitro substituents (entries 10−11 and 19). All nitroalkenes used in the reaction with **1** were usable in the reaction with **5**; all substituents, except the nitro group, hardly affected the reaction regardless of their electronic properties (entries 12−17).

We were successful obtaining X-ray structures of the ferrocene-substituted *syn*- and *anti*-Michael adducts obtained by the reaction of 2-thiazoline-4-carboxylate with ferrocene-substituted nitroalkene and were able to assign the relative and absolute configurations of *syn*-**6g** and *anti*-**7g** (obtained in entries 18−19) as (4*R*, 1′*S*) and (4*R*, 1′*R*), respectively (see Supporting Information). If the ferrocenyl group were to be replaced by phenyl, then the absolute configuration of *syn*-**6a** would be (4*R*, 1′*R*).

We finally examined the reduction of the nitro group in *syn*-**3a**. The reduction of *syn*-**3a** (95% ee) by $NiCl_2{\cdot}6H_2O/NaBH_4$ afforded spiro-γ-lactam **8a** in 89% yield with 92% ee. Thus, **8a**, optically active-protected α-quaternary serine derivative, was obtained with little racemization (Scheme 1).

Scheme 1. Conversion of the Michael Adduct to the Spiro-γ-lactam



CONCLUSIONS

The copper-catalyzed conjugate addition of 2-oxazoline- and 2-thiazoline-4-carboxylates with nitroalkenes can yield either the *syn*- or *anti*-adduct selectively in high enantiomeric excess when an appropriate chiral ligand is chosen. The electron-neutral and electron-rich chiral *P,N*-ligands **L1**−**L3** afforded the *syn* adduct, whereas the electron-poor *P,N*-ligand **L4** and chiral *P,S*-ligand **L5** afforded the *anti*-adduct selectively. The chiral Michael adduct thus obtained could be transformed to the corresponding γ-lactam of the protected α-quaternary serine derivative with little racemization. This methodology paves the way for a substrate divergent as well as stereodivergent synthesis of α-quaternary amino acid γ-lactams and would prove to be valuable for the discovery of new biologically active compounds.

EXPERIMENTAL SECTION

Typical Experimental Procedure for the Reaction of 2-Oxazoline-4-carboxylate 1 with Nitroalkene 2. All reactions were carried out under a nitrogen atmosphere with oven-dried glassware. To a 20 mL Schlenk tube containing a stirring bar were added **L2** (5.45 mg, 0.011 mmol) and CuOAc (1.20 mg, 0.011 mmol), and dry toluene (1.0 mL) was introduced from the rubber septum (1.0 mL). After stirring at room temperature for 30 min, **1** (41.0 mg, 0.20 mmol) and *trans*-β-nitrostyrene **2a** (32.8 mg, 0.22 mmol) were successively added to the solution. The resulting mixture was stirred at the same temperature for 24 h and then filtered through Celite and concentrated in vacuo. The residue was subjected to short silica gel column chromatography (hexane/EtOAc = 2:1 as eluent), and a mixture of *syn*-**3a** and *anti*-**4a** were obtained (combined yield, 54 mg, 76%); a *syn*/*anti* ratio of the crude mixture was determined by ^1H NMR (*syn*/*anti* = 82:18). The mixture was further subjected to PTLC to isolate pure *syn*-**3a**, and its enantiomeric excess was determined by HPLC. Racemate of all products for HPLC analyses were prepared using $CuOAc/PPh_3$.

DOI: 10.1021/acs.joc.6b01722
J. Org. Chem. 2016, 81, 7939−7944

(*R*)-Methyl 4-((*R*)-2-Nitro-1-phenylethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 3a. Yellow solid; 54.0 mg, 76% yield; mp 85−86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 2H), 7.56−7.51 (m, 1H), 7.46−7.41 (m, 2H), 7.31 (m, 5H), 5.26 (dd, J = 3.8, 13.7 Hz, 1H), 5.08 (dd, J = 10.6, 13.7 Hz, 1H), 4.74 (d, J = 9.8 Hz, 1H), 4.47 (d, J = 9.5 Hz, 1H), 3.86 (dd, J = 3.8, 10.6 Hz, 1H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 166.1, 134.9, 132.5, 129.2, 129.0, 128.9, 128.8, 128.6, 126.6, 80.5, 76.9, 73.8, 53.0, 52.4; HPLC (Daicel Chiralpak IB, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min) t_R = 17.0 min (minor), 21.5 min (major); $[\alpha]_D^{26}$ −4.82 (c 0.05, $CHCl_3$); HRMS (ESI-TOF) calcd for $C_{19}H_{19}N_2O_5$ $[M + H]^+$ 355.1294, found 355.1310.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-(2-methylphenyl)ethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 3b. Brown solid; 50.1 mg, 68% yield; mp 78−88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 7.0 Hz, 2H), 7.57−7.52 (m, 1H), 7.49−7.42 (m, 3H), 7.24−7.14 (m, 3H), 5.11 (dd, J = 4.0, 13.2 Hz, 1H), 4.95 (dd, J = 10.3, 13.2 Hz, 1H), 4.73 (d, J = 9.9 Hz, 1H), 4.39 (d, J = 9.5 Hz, 1H), 4.28 (dd, J = 4.0, 10.3 Hz, 1H), 3.65 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 166.0, 137.6, 133.9, 132.5, 131.2, 129.0, 128.6, 128.4, 127.2, 126.9, 126.6, 80.7, 77.4, 73.7, 52.9, 46.3, 20.0; HPLC (Daicel Chiralpak IB, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min) t_R = 12.0 min (minor), 29.4 min (major); $[\alpha]_D^{26}$ +40.7 (c 0.10, $CHCl_3$); HRMS (ESI-TOF) calcd for $C_{20}H_{21}N_2O_5$ $[M + H]^+$ 369.1451, found 369.1453.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-(3-methylphenyl)ethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 3c. Yellow oil; 59.7 mg, 81% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 7.1 Hz, 2H), 7.56−7.41 (m, 3H), 7.25−7.20 (m, 1H), 7.06−7.12 (m, 3H), 5.29 (dd, J = 4.3, 13.5 Hz, 1H), 5.10 (dd, J = 10.8, 13.5 Hz, 1H), 4.74 (d, J = 9.3 Hz, 1H), 4.46 (d, J = 9.8 Hz, 1H), 3.81 (dd, J = 4.3, 10.8 Hz, 1H), 3.72 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 164.8, 137.6, 133.6, 131.3, 128.6, 128.4, 127.9, 127.8, 127.4, 125.5, 124.5, 79.3, 75.8, 72.6, 51.7, 51.2, 20.4; HPLC (Daicel Chiralpak IB, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min) t_R = 11.1 min (minor), 15.9 min (major); $[\alpha]_D^{26}$ −24.5 (c 0.16, $CHCl_3$); HRMS (ESI-TOF) calcd for $C_{20}H_{20}N_2Na_1O_5$ $[M + Na]^+$ 391.1288, found 391.1270.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-(4-methylphenyl)ethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 3d. Yellow oil; 56.7 mg, 77% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 6.9 Hz, 2H), 7.56−7.51 (m, 1H), 7.46−7.41 (m, 2H), 7.19−7.12 (m, 4H), 5.28 (dd, J = 4.1, 13.6 Hz, 1H), 5.08 (dd, J = 10.6, 13.6 Hz, 1H), 4.74 (d, J = 10.6 Hz, 1H), 4.46 (d, J = 10.6 Hz, 1H), 3.79−3.84 (dd, J = 4.1, 10.6 Hz, 1H), 3.72 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 166.0, 138.6, 132.4, 131.7, 129.9, 129.0, 128.7, 128.6, 126.7, 80.5, 77.0, 73.8, 52.9, 52.1, 21.2; HPLC (Daicel Chiralpak IB, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min) t_R = 13.8 min (minor), 17.5 min (major); $[\alpha]_D^{26}$ −20.5 (c 0.11, $CHCl_3$); HRMS (ESI-TOF) calcd for $C_{20}H_{20}N_2Na_1O_5$ $[M + Na]^+$ 391.1270, found 391.1264.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-(4-methoxylphenyl)ethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 3e. Yellow solid; 60.0 mg, 78% yield; mp 130−132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 7.0 Hz, 2H), 7.56−7.51 (m, 1H), 7.46−7.41 (m, 2H), 7.23 (d, J = 8.9 Hz, 2H), 6.86 (d, J = 8.9 Hz, 2H), 5.22 (dd, J = 4.0, 13.4 Hz, 1H), 5.04 (dd, J = 10.8, 13.4 Hz, 1H), 4.74 (d, J = 9.7 Hz, 1H), 4.46 (d, J = 9.7 Hz, 1H), 3.78−3.83 (m, 4H), 3.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 166.0, 159.8, 132.4, 130.0, 128.9, 128.6, 126.7, 114.5, 80.6, 77.4, 77.0, 73.8, 55.3, 52.9, 51.7; HPLC (Daicel Chiralpak IB, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min) t_R = 28.3 min (minor), 31.6 min (major); $[\alpha]_D^{26}$ −3.74 (c 0.095, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{20}H_{21}N_2O_6$ $[M + H]^+$ 385.1400, found 385.1381.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-(4-chlorophenyl)ethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 3f. Yellow oil; 62.2 mg, 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 7.1 Hz, 2H), 7.57−7.42 (m, 3H), 7.34−7.27 (m, 4H), 5.15 (dd, J = 4.1, 13.6 Hz, 1H), 4.99 (dd, J = 11.0, 13.6 Hz, 1H), 4.73 (d, J = 9.9 Hz, 1H), 4.45 (d, J = 9.9 Hz, 1H), 3.84−3.89 (dd, J = 4.1, 11.0 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 166.3, 134.8, 133.6, 132.6, 130.4, 129.3, 128.9, 128.6, 126.4, 80.3, 76.6, 73.7, 53.0, 51.5; HPLC (Daicel Chiralpak IB, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min) t_R = 21.5 min (minor), 37.2 min (major). $[\alpha]_D^{26}$ +8.28 (c 0.11, $CHCl_3$); HRMS (ESI-TOF) calcd for $C_{19}H_{18}Cl_1N_2O_5$ $[M + H]^+$ 389.0904, found 389.0899.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-(4-bromophenyl)ethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 3g. Yellow oil; 58.9 mg, 68% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 6.8 Hz, 2H), 7.57−7.42 (m, 5H), 7.26−7.22 (m, 2H), 5.16 (dd, J = 3.7, 13.5 Hz, 1H), 4.99 (dd, J = 10.6, 13.5 Hz, 1H), 4.73 (d, J = 9.6 Hz, 1H), 4.45 (d, J = 9.3 Hz, 1H), 3.82−3.88 (dd, J = 3.7, 10.6 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 166.3, 134.1, 132.6, 132.3, 130.7, 129.0, 128.7, 126.4, 123.0, 80.3, 76.6, 73.8, 53.0, 51.6. HPLC (Daicel Chiralpak IB, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min) t_R = 22.9 min (minor), 38.6 min (major); $[\alpha]_D^{26}$ +7.73 (c 0.14, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{19}H_{18}Br_1N_2O_5$ $[M + H]^+$ 433.0399, found 433.0420.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-(4-nitrophenyl)ethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 3h. Yellow solid; 42.3 mg, 53% yield; mp 53−54 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 8.7 Hz, 2H), 8.02 (d, J = 7.3 Hz, 2H), 7.64−7.44 (m, 5H), 5.09 (dd, J = 3.7, 13.5 Hz, 1H), 4.97 (dd, J = 10.7, 13.5 Hz, 1H), 4.74 (d, J = 10.0 Hz, 1H), 4.50 (d, J = 9.5 Hz, 1H), 4.06 (dd, J = 3.7, 10.7 Hz, 1H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 166.7, 148.2, 142.7, 132.8, 130.3, 129.0, 128.7, 126.1, 124.1, 80.2, 76.3, 73.8, 53.2, 51.3; HPLC (Daicel Chiralpak IB, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min) t_R = 27.6 min (minor), 48.2 min (major); $[\alpha]_D^{26}$ +41.1 (c 0.074, $CHCl_3$); HRMS (ESI-TOF) calcd for $C_{19}H_{18}N_3O_7$ $[M + H]^+$ 400.1145, found 400.1140.

(*R*)-Methyl 4-((*R*)-2-Nitro-1,2-thienylethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 3i. White solid; 54.1 mg, 75% yield; mp 83−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 7.0 Hz, 2H), 7.56−7.51 (m, 1H), 7.46−7.41 (m, 2H), 7.27−7.25 (m, 1H), 7.01−6.95 (m, 2H), 5.38 (dd, J = 3.7, 13.7 Hz, 1H), 5.12 (dd, J = 10.4, 13.7 Hz, 1H), 4.86 (d, J = 8.8 Hz, 1H), 4.49 (d, J = 9.5 Hz, 1H), 4.19 (dd, J = 3.7, 10.4 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 166.5, 136.8, 132.5, 129.0, 128.6, 128.2, 127.2, 126.5, 80.5, 78.0, 77.4, 74.3, 53.2, 48.0. HPLC (Daicel Chiralpak IB, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min) t_R = 14.6 min (minor), 17.8 min (major); $[\alpha]_D^{26}$ −71.1 (c 0.086, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{17}H_{17}N_2O_5S_1$ $[M + H]^+$ 361.0858, found 361.0875.

(*R*)-Methyl 4-((*S*)-2-Nitro-1-phenylethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 4a. Yellow oil; 53.2 mg, 68% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.90 (d, J = 7.1 Hz, 2H), 7.56−7.51 (m, 1H), 7.45−7.40 (m, 2H), 7.25−7.21 (m, 5H), 5.09−4.94 (m, 2H), 4.56−4.52 (d, J = 9.1 Hz, 1H), 4.31−4.25 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 166.9, 134.4, 132.4, 129.4, 129.0, 128.8, 128.7, 128.6, 126.6, 80.0, 76.8, 72.6, 53.4, 49.0. HPLC (Daicel Chiralpak ID-3, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min) t_R = 13.6 min (minor), 18.2 min (major); $[\alpha]_D^{25}$ −151 (c 0.057, $CHCl_3$); HRMS (ESI-TOF) calcd for $C_{19}H_{18}N_2Na_1O_5$ $[M + Na]^+$ 377.1113, found 377.1129.

(*R*)-Methyl 4-((*S*)-2-Nitro-1-(4-methoxyphenyl)ethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 4e. Yellow oil; 54.6 mg, 71% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 7.1 Hz, 2H), 7.55−7.50 (m, 2H), 7.44−7.40 (m, 2H), 7.14 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 5.05−4.90 (m, 2H), 4.53 (d, J = 9.3 Hz, 1H), 4.24 (m, 2H), 3.84 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 166.8, 159.7, 132.3, 130.5, 128.8, 128.6, 126.6, 126.1, 114.4, 80.1, 77.1, 72.7, 55.3, 53.4, 48.5; HPLC (Daicel Chiralpak ID-3, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min) t_R = 22.5 min (minor), 30.3 min (major). $[\alpha]_D^{25}$ +1.83 (c 0.060, $CHCl_3$); HRMS (ESI-TOF) calcd for $C_{20}H_{21}N_2O_6$ $[M + H]^+$ 385.1400, found 385.1381.

(*R*)-Methyl 4-((*S*)-2-Nitro-1-(4-nitrophenyl)ethyl)-2-phenyl-4,5-dihydrooxazole-4-carboxylate 4h. Yellow solid; 54.1 mg, 59% yield; mp 138−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, J = 8.8 Hz, 2H), 7.92−7.89 (m, 2H), 7.59−7.54 (m, 1H), 7.47−7.42 (m, 4H), 5.14−4.99 (m, 2H), 4.55−4.52 (d, J = 9.2 Hz, 1H), 4.42−4.37 (dd, J = 4.9, 4.9 Hz,1H), 4.18−4.15 (d, J = 9.2 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 167.5, 148.2, 142.1, 132.8, 130.6,

DOI: 10.1021/acs.joc.6b01722
J. Org. Chem. 2016, 81, 7939−7944

128.8, 128.8, 126.0, 124.0, 79.5, 76.5, 72.9, 53.7, 48.8; HPLC (Daicel Chiralpak ID-3, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min) t_R = 29.5 min (minor), 49.2 min (major); $[\alpha]_D^{26}$ −7.58 (*c* 0.066, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{19}H_{18}N_3O_7$ $[M + H]^+$ 400.1145, found 400.1139.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-phenylethyl)-2-phenyl-4,5-dihydrothiazole-4-carboxylate 6a. White solid; 63.8 mg, 86% yield; mp 101−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 6.7 Hz, 2H), 7.55−7.42 (m, 3H), 7.33 (m, 5H), 5.29 (dd, *J* = 4.1, 13.7 Hz, 1H), 5.06 (dd, *J* = 10.4, 13.7 Hz, 1H), 4.04 (dd, *J* = 4.1, 10.4 Hz, 1H), 3.87 (d, *J* = 12.2 Hz, 1H), 3.68 (s, 3H), 3.48 (d, *J* = 12.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.9, 135.4, 132.5, 132.3, 129.1, 129.0, 128.9, 128.8, 90.2, 77.3, 53.0, 51.1, 39.4; HPLC (Daicel Chiralpak ID-3, hexane/2-propanol = 98:2, 1.0 mL/min, 250 nm, flow rate = 1.0 mL/min); t_R = 16.3 min (major), 17.9 min (minor); $[\alpha]_D^{26}$ +33.3 (*c* 0.065, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{19}H_{19}N_2O_4S$ $[M + H]^+$ 371.1066, found 371.1061.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-(4-methylphenyl)ethyl)-2-phenyl-4,5-dihydrothiazole-4-carboxylate 6b. Yellow oil; 69.6 mg, 87% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 6.9 Hz, 2H), 7.53−7.42 (m, 3H), 7.33 (m, 5H), 7.26 (m, 2H), 7.24 (m, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.24 (dd, *J* = 4.2, 13.4 Hz, 1H), 5.02 (dd, *J* = 10.8, 13.4 Hz, 1H), 3.98 (dd, *J* = 4.2, 10.8 Hz, 1H), 3.87 (d, *J* = 12.2 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.48 (d, *J* = 12.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.7, 159.8, 132.6, 132.3, 130.24, 128.9, 128.8, 127.3, 114.42, 90.4, 77.5, 55.4, 53.0, 50.6, 39.4; HPLC (Daicel Chiralpak ID-3, hexane/2-propanol = 95:5, 1.0 mL/min, 250 nm, flow rate = 1.0 mL/min); t_R = 23.8 min (major), 31.7 min (minor); $[\alpha]_D^{26}$ +31.1 (*c* 0.054, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{20}H_{20}N_2NaO_5S$ $[M + Na]^+$ 423.0991, found 423.1006.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-(4-chlorophenyl)ethyl)-2-phenyl-4,5-dihydrothiazole-4-carboxylate 6c. White solid; 67.1 mg, 83% yield; mp 113−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 6.9 Hz, 2H), 7.56−7.42 (m, 3H), 7.32 (m, 4H), 5.19 (dd, *J* = 4.0, 13.9 Hz, 1H), 4.97 (dd, *J* = 10.8, 13.9 Hz, 1H), 4.03 (dd, *J* = 4.0, 10.8 Hz, 1H), 3.88 (d, *J* = 12.3 Hz, 1H), 3.65 (s, 3H), 3.46 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 170.9, 134.7, 134.6, 134.1, 134.0, 132.3, 130.5, 129.1, 128.8, 89.9, 77.0, 52.9, 50.6, 39.5. HPLC: Daicel Chiralpak IB (hexane/2-propanol = 99:1, 1.0 mL/min, 250 nm, flow rate = 1.0 mL/min); t_R = 16.8 min (minor), 60.8 min (major); $[\alpha]_D^{26}$ +29.2 (*c* 0.100, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{19}H_{18}ClN_2O_4S$ $[M + H]^+$ 405.0676, found 405.0682.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-(4-bromophenyl)ethyl)-2-phenyl-4,5-dihydrothiazole-4-carboxylate 6d. Yellow oil; 78.8 mg, 88% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 6.9 Hz, 2H), 7.56−7.43 (m, 5H), 7.26 (d, *J* = 8.4 Hz, 2H), 5.19 (dd, *J* = 4.1, 13.7 Hz, 1H), 4.97 (dd, *J* = 10.6, 13.7 Hz, 1H), 4.01 (dd, *J* = 4.1, 10.6 Hz, 1H), 3.88 (d, *J* = 12.3 Hz, 1H), 3.66 (s, 3H), 3.46 (d, *J* = 12.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 171.0, 134.6, 132.4, 132.3, 132.2, 130.8, 128.9, 128.8, 123.0, 89.9, 77.0, 53.1, 50.7, 39.5. HPLC: Daicel Chiralpak IB (hexane/2-propanol = 99:1, 1.0 mL/min, 250 nm, flow rate = 1.0 mL/min); t_R = 18.6 min (minor), 64.1 min (major); $[\alpha]_D^{26}$ +39.5 (*c* 0.090, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{19}H_{18}BrN_2O_4S$ $[M + H]^+$ 449.0171, found 449.0178.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-(4-nitrophenyl)ethyl)-2-phenyl-4,5-dihydrothiazole-4-carboxylate 6e. Yellow oil; 49.8 mg, 60% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.59−7.53 (m, 1H), 7.50−7.45 (m, 2H), 5.15 (dd, *J* = 4.1, 13.8 Hz, 1H), 4.96 (dd, *J* = 10.6, 13.8 Hz, 1H), 4.20 (dd, *J* = 4.1, 10.6 Hz, 1H), 3.92 (d, *J* = 12.4 Hz, 1H), 3.62 (s, 3H), 3.46 (d, *J* = 12.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 170.9, 148.1, 143.2, 132.7, 132.1, 130.4, 128.9, 124.0, 89.6, 76.7, 53.2, 51.0, 39.9. HPLC (Daicel Chiralpak IB, hexane/2-propanol = 95:5, 1.0 mL/min, 250 nm, flow rate = 1.0 mL/min); t_R = 17.6 min (minor), 63.2 min (major); $[\alpha]_D^{26}$ +42.6 (*c* 0.084, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{19}H_{18}N_3O_6S$ $[M + H]^+$ 416.0916, found 416.0913.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-thienylethyl)-2-phenyl-4,5-dihydrothiazole-4-carboxylate 6f. Yellow oil; 63.9 mg, 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.0 Hz, 2H), 7.55−7.42 (m, 3H), 7.28 (d, *J* = 5.2 Hz, 1H), 7.04 (d, *J* = 3.5 Hz, 1H), 6.97 (dd, J = 3.5, 5.2 Hz, 1H), 5.33 (dd, *J* = 3.9, 13.8 Hz, 1H), 5.04 (dd, *J* = 9.9, 13.8 Hz, 1H), 4.39 (dd, *J* = 3.9, 9.9 Hz, 1H), 3.96 (d, *J* = 12.1 Hz, 1H), 3.79 (s, 3H), 3.53 (d, *J* = 12.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 170.6, 137.6, 132.4, 128.9, 128.8, 126.6, 127.1, 126.6, 90.3, 78.5, 53.2, 46.7, 39.2. HPLC (Daicel Chiralpak ID-3, hexane/2-propanol = 95:5, 1.0 mL/min, 250 nm, flow rate = 1.0 mL/min) t_R = 13.7 min (major), 17.3 min (minor); $[\alpha]_D^{26}$ +41.1 (*c* 0.087, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{17}H_{17}N_2O_4S_2$ $[M + H]^+$ 377.0630, found 377.0639.

(*R*)-Methyl 4-((*R*)-2-Nitro-1-ferrocenylethyl)-2-phenyl-4,5-dihydrothiazole-4-carboxylate 6g. Yellow solid; 55.5 mg, 58% yield; mp 59−61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.3 Hz, 2H), 7.51−7.38 (m, 3H), 5.55 (dd, *J* = 7.1, 14.1 Hz, 1H), 5.13 (dd, *J* = 3.5, 14.1 Hz, 1H), 4.27 (m, 1H), 4.23 (m, 1H), 4.20 (m, 1H), 4.16 (s, 5H), 4.09 (dd, *J* = 3.5, 7.1 Hz, 1H), 3.90 (m, 1H), 3.65 (s, 3H), 3.46 (d, *J* = 11.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.4, 132.5, 132.0, 128.7, 128.7, 77.5, 69.9, 69.1, 69.1, 68.9, 68.3, 66.3, 52.8, 44.5, 38.7, 29.8. HPLC (Daicel Chiralpak AS-3, hexane/2-propanol = 95:5, 1.0 mL/min, 250 nm, flow rate = 1.0 mL/min) t_R = 18.8 min (major), 45.5 min (minor); $[\alpha]_D^{24}$ +7.03 (*c* 0.061, $CHCl_3$); HRMS (ESI-TOF) calcd for $C_{23}H_{23}FeN_2O_4S$ $[M + H]^+$ 479.0728, found 479.0738. CCDC: 1484419.

(*R*)-Methyl 4-((*S*)-2-Nitro-1-phenylethyl)-2-phenyl-4,5-dihydrothiazole-4-carboxylate 7a. White solid; 65.1 mg, 88% yield; mp 96−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 6.9 Hz, 2H), 7.54−7.40 (m, 3H), 7.24 (m, 5H), 5.13 (dd, *J* = 10.4, 13.6 Hz, 1H), 5.00 (dd, *J* = 4.5, 13.6 Hz, 1H), 4.36 (dd, *J* = 4.5, 10.4 Hz, 1H), 3.81 (s, 3H), 3.60 (d, *J* = 11.7 Hz, 1H), 3.31 (d, *J* = 11.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 172.3, 134.8, 132.5, 132.1, 129.6, 128.9, 128.8, 128.7, 128.5, 89.8, 77.8, 53.5, 50.4, 39.3. HPLC (Daicel Chiralpak ID-3, hexane/2-propanol = 95:5, 1.0 mL/min, 250 nm, flow rate = 1.0 mL/min) t_R = 11.0 min (minor), 13.4 min (major); $[\alpha]_D^{23}$ −169 (*c* 0.087, $CHCl_3$); HRMS (ESI-TOF) calcd for $C_{19}H_{19}N_2O_4S$ $[M + H]^+$ 371.1066, found 371.1050.

(*R*)-Methyl 4-((*S*)-2-Nitro-1-ferrocenylethyl)-2-phenyl-4,5-dihydrothiazole-4-carboxylate 7g. Yellow solid; 59.2 mg, 62% yield; mp 148−152 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.0 Hz, 2H), 7.47−7.36 (m, 3H), 5.11 (dd, *J* = 3.9, 14.0 Hz, 1H), 5.03 (dd, *J* = 6.8, 14.0 Hz, 1H), 4.27 (m, 1H), 4.53 (dd, *J* = 3.9, 6.8 Hz, 1H), 4.20−4.14 (m, 7H), 3.84 (m, 1H), 3.78 (s, 3H), 3.72 (d, *J* = 12.1 Hz, 1H), 3.30 (d, *J* = 12.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 171.1, 132.4, 132.0, 128.7, 128.6, 91.7, 85.0, 77.3, 69.7, 69.2, 68.9, 68.2, 66.6, 53.2, 45.1, 36.8; HPLC (Daicel Chiralpak ID-3, hexane/2-propanol = 95:5, 1.0 mL/min, 250 nm, flow rate = 1.0 mL/min) t_R = 17.1 min (minor), 26.6 min (major); $[\alpha]_D^{26}$ +39.4 (*c* 0.107, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{23}H_{23}FeN_2O_4S$ $[M + H]^+$ 479.0728, found 479.0739. CCDC: 1484418.

Transformation of the Michael Adduct to the γ-Lactam. Under a nitrogen atmosphere, to a 20 mL Schlenk tube containing a stirring bar was added *syn*-**3a** (95% ee, 70.9 mg, 0.20 mmol), and THF (2 mL) and MeOH (1 mL) were introduced through the rubber septum. $NiCl_2{\cdot}6H_2O$ (47.6 mg, 0.20 mmol) was added to the mixture, and after stirring at 0 °C for 20 min, then $NaBH_4$ (37.8 mg, 1.0 mmol) was added portion by portion to result in a black solution at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by aqueous K_2CO_3 (110.6 mg, 0.8 mmol)/H_2O (1 mL), and the mixture was stirred at room temperature for 2 h. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography to afford **8a**.

(5*R*,9*R*)-2,9-Diphenyl-3-oxa-1,7-diazaspiro[4.4]non-1-en-6-one 8a. White solid; 51.9 mg, 89% yield; mp 169−170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.0 Hz, 2H), 7.52−7.28 (m, 6H), 7.22−7.17 (m, 2H), 7.08 (br, 1H), 4.48 (d, *J* = 8.9 Hz, 2H), 4.12 (dd, *J* = 7.1, 9.7 Hz, 1H), 3.98 (d, *J* = 9.7 Hz, 1H), 3.69 (dd, *J* = 3.3, 7.1 Hz,1H), 3.57 (dd, *J* = 3.3, 9.7 Hz,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 165.6, 139.0, 131.9, 129.3, 128.8, 128.4, 127.9, 127.7, 127.2, 79.7, 70.0, 50.5, 46.3. HPLC (ESI-TOF) (Daicel Chiralpak OD-H,

DOI: 10.1021/acs.joc.6b01722
J. Org. Chem. 2016, 81, 7939−7944

hexane/2-propanol = 70:30, flow rate = 0.8 mL/min) t_R = 20.2 min (minor), 24.5 min (major); $[\alpha]_D^{25}$ −276 (*c* 0.054, $CHCl_3$). HRMS (ESI-TOF) calcd for $C_{18}H_{16}N_2NaO_2$ $[M + Na]^+$ 315.1110, found 315.1116.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01722.

Optimization of the reaction, ^1H and ^{13}C NMR spectra, and HPLC analytical data for products **3a**−**3h**, **4a**, **4e**, **4h**, **6a**−**6g**, **7a**, and **7g** (PDF)
Crystallographic data for **6g** (CIF)
Crystallographic data for **7g** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: orgsynth@kc.chuo-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the Japan Society for the Promotion of Science (JSPS) Grant-in-Aid No. 16K05704 for scientific research.

■ REFERENCES

(1) For reviews, see: (a) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406. (b) Metz, A. E.; Kozlowski, M. C. *J. Org. Chem.* **2015**, *80*, 1.
(2) For a review, see: (a) de Castro, P. P.; Carpanez, A. G.; Amarante, G. W. *Chem. - Eur. J.* **2016**, *22*, 10294. (b) Fisk, J. S.; Mosey, R. A.; Tepe, J. *Chem. Soc. Rev.* **2007**, *36*, 1432.
(3) (a) Kalek, M.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9438. (b) Wang, T.; Yu, Z.; Hoon, D. L.; Phee, C. Y.; Lan, Y.; Lu, Y. *J. Am. Chem. Soc.* **2016**, *138*, 265.
(4) (a) Jew, S.-s.; Lee, Y.-J.; Lee, J.; Kang, M. J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Kim, M.-J.; Choi, S.-h.; Ku, J.-M.; Park, H.-g. *Angew. Chem., Int. Ed.* **2004**, *43*, 2382. (b) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, T.-S.; Lee, J.; Ku, J.-M.; Jew, S.-s.; Park, H.-g. *Org. Lett.* **2005**, *7*, 3207.
(5) Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J. A.; Ng, F. W.; Overman, L. E. *J. Am. Chem. Soc.* **2007**, *129*, 11987.
(6) (a) Kim, T.-S.; Lee, Y.-J.; Jeong, B.-S.; Park, H.-g.; Jew, S.-s. *J. Org. Chem.* **2006**, *71*, 8276. (b) Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13321.
(7) Li, C.-Y.; Yang, W.-L.; Luo, X.; Deng, W.-P. *Chem. - Eur. J.* **2015**, *21*, 19048.
(8) Koizumi, A.; Kimura, M.; Arai, Y.; Tokoro, Y.; Fukuzawa, S.-i. *J. Org. Chem.* **2015**, *80*, 10883.
(9) Yan, X.-X.; Peng, Q.; Zhang, Y.; Zhang, K.; Hong, W.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1979.
(10) Cabrera, S.; Arrayás, R. G.; Martín-Matute, B.; Cossío, F. P.; Carretero, J. C. *Tetrahedron* **2007**, *63*, 6587.

DOI: 10.1021/acs.joc.6b01722
J. Org. Chem. 2016, 81, 7939−7944