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Bifunctional AgOAc/ThioClickFerrophos catalyzed asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides to nitroalkenes

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ABSTRACT

AgOAc/ThioClickFerrophos (TCF) complex catalyzed the 1,3-dipolar cycloaddition of azomethine ylides (glycine imino ester) to nitroalkenes. The corresponding *endo*-cycloadducts (88:12–98:2 *endo/exo*) were afforded in good yields with high enantioselectivities, up to 98% ee, without addition of external amine. AgOAc/TCF works as a bifunctional (Lewis acid and base) catalyst.

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1. Introduction

The asymmetric 1,3-dipolar cycloaddition of azomethine ylides to activated alkenes provides a beneficial method for the synthesis of highly substituted pyrrolidines, which can lead to discovery of new biologically active compounds. Chiral metal complexes have been developed for catalyzing this reaction,¹ with various activated alkenes like acrylates and maleimides, employed as good dipolarophiles. Nitroalkenes are also good dipolarophiles, affording biologically interesting nitro-containing pyrrolidines.² The 1,3dipolar cycloaddition of glycine imino ester 1 with 2-substituted-1-nitroethene 2 potentially affords up to eight diastereomers of a pyrrolidine ring bearing four stereogenic centers. While it appears difficult to generate a single isomer out of eight possible diastereoisomers, the use of the (E)-nitroethene can fix the stereoconjunction between the 3- (R^2) and 4-positions (NO_2) in a *trans* conformation. The groups at the 5-position (R¹, from the substituent of the imino group) and 2-position (the ester group) are usually arranged cis to each other, with an exception involving catalysis by a solid-supported imidazoline-aminophenol/Ni(OAc)₂ complex (Fig. 1).³ Thus, the focus of stereoselectivity is simplified to the 4- and 5-positions, with two diastereoisomers (exo and endo) possible; epimers of exo and endo isomers can be excluded.⁴

There has previously been success in controlling the stereochemistry at the 4- and 5-positions of pyrrolidine in cycloaddition of azomethine ylide to a nitroalkene was achieved using CuClO₄/ FeSulphos,⁵ CuPF₆/Segphos,⁶ CuClO₄/Taniaphos,⁷ Cu(OTf)₂/chiral phosphoramidite,⁸ and CuClO₄/Imidazolium-FcPHOX.⁹ Oh et al. prepared an *exo*-pyrrolidine ring via consecutive Michael addition of glycine imino ester to a nitroalkene and intramolecular Mannich reaction with a CuOAc/brucine-derived amino alcohol complex.¹⁰ Waldman et al. first reported the asymmetric reaction of a cyclic azomethine ylide to a nitroalkene affording *exo*-cycloadducts as the major product,¹¹ while *endo*-selective cycloaddition has been achieved using Cu(OTf)₂/PyBidine complex.¹² Hou et al. succeeded in switching the *endo/exo*-selectivity in the CuClO₄/FcPHOX complexcatalyzed reaction by tuning the electron density of the phosphine moiety.¹³ Cossio et al. also succeeded in *endo/exo*-switching in the



Fig. 1. *exo* and *endo* Isomers in the 1,3-dipolar cycloaddition of azomethine ylide with nitroalkene.

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CuPF₆/chiral ferrocene pyrrolidine ligand-catalyzed reaction by alternating ligand stereochemistry.¹⁴

Despite the success of copper-complex-catalyzed diastereo- and enantio-selective cyclization reactions, development of highly stereoselective cycloadditions of azomethine ylides to nitroalkenes remains challenging. There had been no reports of a successful asymmetric silver-catalyzed cycloaddition of imino esters to nitroalkenes with high diastereo- and enantio-selectivities before the recent work by Xu and co-workers.¹⁵ They developed a new chiral phosphine, based on non-biaryl atropisomers, and achieved *exo*-selective cycloaddition using the AgF complex.¹⁶

In our series of studies on 1,3-dipolar cycloadditions of azomethine ylides catalyzed by silver/ThioClickFerrophos (TCF, a chiral P,S-ferrocene ligand) complex, we have reported that the reaction with β -nitrostyrene afforded a mixture of *endo*- and *exo*-cycloadducts (65:35 endo/exo) in low yield (36%).¹⁷ Although enantioselectivity in the endo-isomer was high (91% ee), we abandoned optimization of the reaction, concluding that the catalyst was not suitable for the reaction with nitroalkenes because of poor diastereoselectivity and low yield. Later we found that, in the reaction of a ketimine ester with a nitroalkene, AgOAc/TCF gave the cycloadduct in good yield under base-free conditions, or the Michael adduct in the presence of base.¹⁸ We suspected that the base-free conditions could be essential for successful cycloaddition to nitroalkenes, and chose to re-examine the reaction. It was indeed found that AgOAc/TCF works as a bifunctional catalyst,¹⁹ giving endocycloadducts, both diastereo- and enantioselectively, in good yields under base-free conditions. In this paper, we report the optimization of reaction conditions and scope of substrates.

2. Results and discussion

We first optimized the reaction conditions in the model reaction of imino methyl ester **1a** and β -nitrostyrene **2a** using 5 mol % of AgOAc/TCF catalyst (Scheme 1). The reactions were carried out at room temperature for 10 h, with various solvents, in the absence or presence of base; results are shown in Table 1.²⁰ The endo/exoisomer ratio was determined by ¹H NMR integration of the methyl group peak. Enantiomeric excess was determined by chiral HPLC. The absolute configuration of endo-isomer 3aa was determined as (2S, 3R, 4S, 5S) by comparing optical rotation and HPLC retention time with reported compounds.^{10,13} The reaction in 1,4-dioxane (DOX) in the absence of base gave 79% isolated yield of endoproduct. The *endo*-isomer was produced selectively (94:6 *endo/exo*) with high enantioselectivity (96% ee) (Table 1, entry 1). The reactions in tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), and diethyl ether yielded the endo-isomer preferentially, again with high ee, but in lower yields (Table 1, entries 2, 5, and 6). The reaction in THF in the presence of triethylamine had a lower yield than its base-free counterpart, but showed no significant change in diastereo- or enantio-selectivity (Table 1, entry 3). Dichloromethane and toluene were not suitable solvents, affording poor yields under even base-free conditions (Table 1, entries 7–9). Thus, DOX was the solvent of choice. In our previous study on the



Scheme 1. The 1,3-dipolar cycloaddition of glycine imino ester 1a with β -nitrostyrene 2a.

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| Entry | Solvent | Yield (%) ^b | endo/exo ^c | ee (%) (<i>endo</i>) ^d |
|------------------|-------------------|------------------------|-----------------------|-------------------------------------|
| 1 | DOX | 74 | 94:6 | 96 |
| 2 | THF | 61 | 92:8 | 96 |
| 3 ^e | THF | 64 | 91:9 | 91 |
| 4^{f} | DOX | 42 | 95:5 | 91 |
| 5 | DME | 60 | 90:10 | 95 |
| 6 | Et ₂ O | 62 | 94:6 | 88 |
| 7 | CH_2Cl_2 | 43 | 72:28 | 95 |
| 8 ^{e,g} | CH_2Cl_2 | 36 | 65:35 | 91 |
| 9 | toluene | 39 | 96:4 | 75 |

^a **1a** (0.20 mmol), **2a** (0.22 mmol), AgOAc (0.01 mmol, 5.0 mol%), (*R*,*S*_{*p*})-TCF (0.011 mmol, 5.5 mol%), solvent (2.0 mL): rt, 10 h.

^b Isolated yield of the *endo*-isomer.

^c Determined by ¹H NMR.

^d Determined by HPLC (Daicel Chiralpak AS-H).

^e Et₃N (20 mol %) was added.

^f Imino *tert*-butyl ester **1a**' was used.

^g Data from the literature.¹⁷

cycloaddition of ketimine esters with nitroalkenes, imino *tert*-butyl ester was a better azomethine ylide source than the corresponding methyl ester. However, the methyl ester was better suited in this reaction as an aldimine ester.

Having established optimal reaction conditions for the cycloaddition of imino ester **1a** to nitroalkene **2a**, the scope of the reaction was examined using different imino esters **1b–1k** in the reaction with **2a**. The results are summarized in Table 2.

All reactions afforded the *endo*-isomer (**3aa**–**3ka**) as the major product, in ratios ranging from 88:12–96:4 *endo/exo*. Yields were always high for aryl substrates bearing electron-donating groups, with ee values for *endo*-adducts ranged from 94 to 97% (Table 2, entries 2–5). The position of the methyl group slightly affected the reaction; the more sterically hindered *o*-methyl group gave the *endo*-isomer in high yield with good ee, as did the *m*- and *p*substituted substrates. Moderate yields of *endo*-isomers were obtained in reactions with halogen-substituted aryl substrates (Table 2, entries 6–8). The 1-napthyl ester, **1i**, and the heteroaryl imino esters (2-thienyl; **1j**) were also appropriate substrates, achieving good yields of *endo*-adducts with up to 91% ee (Table 2, entry 10). The reaction with alkyl imino esters such as **1k** afforded low product yields, but exhibited high *endo*-selectivity and enantioselectivity (Table 2, entry 11).

Table 2

Scope of glycine imino esters 1 in cycloaddition with nitroalkene 2a^a

| | Ph 0 ₂ N 2a + − R ^{1 ^} N ^CO ₂ Me 1a−1k | AgOAc/TCF (5 mol%) DOX rt, 10 h | O ₂ N, Ph R ¹ N CO H 3aa–3ka | I ₂ Me |
|-------|---|--|--|-------------------------------------|
| Entry | R ¹ | Yield (%) ^b | endo/exo ^c | ee (%) (<i>endo</i>) ^d |
| 1 | Ph, 1a | 3aa , 70 | 94/6 | 96 |
| 2 | o-MeC ₆ H ₄ , 1b | 3ba , 74 | 96/4 | 94 |
| 3 | <i>m</i> -MeC ₆ H ₄ , 1c | 3ca , 86 | 95/5 | 96 |
| 4 | <i>p</i> -МеС ₆ Н ₄ , 1d | 3da , 71 | 96/4 | 97 |
| 5 | <i>p</i> -МеОС ₆ Н ₄ , 1е | 3ea , 82 | 94/6 | 97 |
| 6 | p-FC ₆ H ₄ , 1f | 3fa , 67 | 94/6 | 96 |
| 7 | p-ClC ₆ H ₄ , 1g | 3ga , 80 | 95/5 | 96 |
| 8 | <i>p</i> -BrC ₆ H ₄ , 1h | 3ha , 51 | 94/6 | 96 |
| 9 | 1-Naphtyl, 1i | 3ia , 80 | 96/4 | 86 |
| 10 | 2-thienyl, 1j | 3ja , 80 | 91/9 | 91 |
| 11 | Cy, 1k | 3ka , 47 | 88/12 | 93 |

^a **1** (0.20 mmol), **2a** (0.22 mmol), AgOAc (0.01 mmol, 5.0 mol%), (R_sS_p)-TCF (0.011 mmol, 5.5 mol%), solvent (2.0 mL): rt, 10 h.

^b Isolated yield of the *endo*-isomer.

^c Determined by ¹H NMR.

^d Determined by HPLC (Daicel Chiralpak AS-H or IB).

The substrate scope for nitroalkenes was also examined under optimized conditions (Table 3). Reactions of imino ester **1a** with various (*E*)-2-aryl-1-nitroalkenes, with *o*- or *p*-substituents on the phenyl ring, proceeded with *endo*-selectivities of 89:11–98:2 and enantioselectivities of 80–98%. Nitroalkenes with non-alkyl substituents on the aromatic ring also gave the *endo*-adduct as the major product, although the electronic properties of these substituents caused a reduction in diastereo- and enantio-selectivity. The ferrocenyl **1g** and heteroaryl substrate such as 2-furyl nitroalkene **1h** could be used, giving corresponding *endo*-adducts with high enantioselectivities (Table 3, entries 6–7).

Table 3

Entry

Scope of nitroalkenes 2 in cycloaddition with imino ester 1a^a

| O ₂ N 2b−h + Ph ^{(¬} N [^] CO ₂ Me 1a | AgOAc/TCF (5 mol%) DOX rt, 10 h | O_2N , R^2 Ph N CO H 3ab-3ah | l₂Me |
|--|--|--|----------------------------|
| R ² | Yield (%) ^b | endo/exo ^c | ee (%) ^d (endo) |
| о-МеС ₆ Н ₄ , 2b | 3ab , 81 | 97/3 | 97 |

| 1 | o-MeC ₆ H ₄ , 2b | 3ab , 81 | 97/3 | 97 | |
|---|--|-----------------|-------|----|--|
| 2 | <i>p</i> -MeC ₆ H ₄ , 2с | 3ac , 60 | 93/7 | 98 | |
| 3 | <i>p</i> -MeOC ₆ H ₄ , 2d | 3ad , 64 | 90/10 | 97 | |
| 4 | p-ClC ₆ H ₄ , 2e | 3ae , 40 | 93/7 | 90 | |
| 5 | p-BrC ₆ H ₄ , 2f | 3af , 60 | 90/10 | 80 | |
| 6 | Fc, 2g | 3ag , 80 | 98/2 | 95 | |
| 7 | 2-furyl, 2h | 3ah , 50 | 89/11 | 91 | |
| | | | | | |

^a **1a** (0.20 mmol), **2** (0.22 mmol), AgOAc (0.01 mmol, 5.0 mol%), (*R*,*S*_{*p*})-TCF (0.011 mmol, 5.5 mol%), solvent (2.0 mL): rt, 10 h.

^b Isolated yield of the *endo*-isomer.

^c Determined by ¹H NMR.

^d Determined by HPLC (Daicel Chiralpak AS-H or IB).

If *tetra*-coordinated transition state could be proposed as shown in Fig. 2 based on the absolute configuration of the *endo*-cycloadduct, the azomethine ylide would coordinate to silver atom with the preferred orientation where the nitrogen atom is oriented *trans* to the phosphine group (the oxygen atom is oriented *trans* to the sulfur atom). A reverse orientation in which the nitrogen atom is *trans* to the sulfur atom would not be preferred because of the steric repulsion between the phosphine phenyl group and the substituent (R^1) of the azomethine ylide. The nitroalkene would come from the *si* face of the azomethine ylide avoiding the bulky *tert*-butylthio group, thus affording the *endo*-(2*S*, 3*R*, 4*S*, 5*S*)-configured adduct.



Fig. 2. Plausible transition structure of the reaction.

3. Conclusion

AgOAc/ThioClickFerrophos (TCF) complex is an effective bifunctional catalyst for the 1,3-dipolar cycloaddition of azomethine ylides to nitroalkenes under base-free conditions. The corresponding *endo*-cycloadducts were afforded preferentially (88:12–98:2 *endo/exo*) with high enantioselectivities (up to 98% ee). Substituents on the nitroalkene 2-aryl group had little effect on the stereochemistry and product yield.

4. Experimental section

4.1. General

¹H and ¹³C NMR spectra recorded with a Varian Mercury 300 or 400 MHz using CDCl₃ as a solvent. The chemical shifts are reported in δ units downfield from (SiMe₄) and are referenced to CHCl₃ as an internal standard (δ =0.00 ppm for ¹H, δ =77.16 ppm for ¹³C). All coupling constants (1) are absolute values and are expressed in Hz. Enantiomeric excesses were determined by chiral HPLC analysis on the Chiralpak columns. The GC-MS analyses were carried out with an Agilent 5975B/6890N instrument equipped with a capillary column (helium as the carrier gas). Endo/exo ratios of cycloadducts were determined by integration of the methyl ester signals of ¹H NMR. Preparative TLC was conducted on a 20 cm square glass sheet coated with a 1 mm thick layer of silica gel. AgOAc was purchased from Wako Chemicals Inc. ThioClickFerrophos was prepared by the literature method.²¹ Nitroalkene **2a** was purchased from TCI Company. Nitroalkenes **2b**-g were prepared according to literature procedures.²² Dry 1,4-dioxane (DOX) was purified by distillation after the pre-drying with LiAlH₄.

4.2. General procedure for the asymmetric 1,3-dipolar cycloaddition 3

The following provide a typical experimental procedure of asymmetric 1,3-dipolar cycloaddition of azomethine ylide with nitroalkenes. All reactions were carried out under nitrogen atmosphere with oven-dried glassware. In a 20 mL Schlenk tube containing a stirring bar, AgOAc (1.66 mg, 0.01 mmol), (R,Sp)-TCF (6.92 mg, 0.011 mmol) were dissolved in dry 1,4-dioxane (2.0 mL) and stirred at room temperature for 30 min. Then, **1a** (35.4 mg, 0.20 mmol) and **2a** (32.8 mg, 0.22 mmol) were added successively. The resulting mixture was stirred at the same temperature for 10 h and then filtered through Celite and concentrated in vacuo. The residue was isolated by PTLC (n-hexane/EtOAc=3/1) to afford **3aa** as yellow oil.

4.2.1. **3aa** (R^1 =Ph). Yellow oil; 45.6 mg, 70% yield. ¹H NMR δ 7.43–7.24 (m, 10H), 5.27 (dd, *J*=3.6, 6.5 Hz, 1H), 4.90 (m, 1H), 4.21 (dd, *J*=3.6, 7.5 Hz, 1H), 4.15 (m, 1H), 3.79 (s, 3H), 3.35 (br s, 1H); ¹³C NMR δ 172.1, 138.9, 134.7, 129.7, 134.7, 129.6, 129.5, 128.5, 127.9, 126.8, 97.4, 68.2, 67.8, 55.8, 53.0; HPLC: Daicel Chiralpak AS-H (hexane/2-propanol=70/30, 0.7 mL/min, 220 nm); t_R =21.9 min (major), t_R =30.4 min (minor); $[\alpha]_D^{27}$ =-29.2 (*c*=0.11, CHCl₃); HRMS (ESI) calcd for C₁₈H₁₉N₂O₄ [M+H]⁺327.1345, found: 327.1347.

4.2.2. **3ba** (R^1 =o-MeC₆H₄). Yellow oil; 50.4 mg, 74% yield. ¹H NMR δ 7.43–7.15 (m, 9H), 5.33 (dd, *J*=3.5, 6.6 Hz, 1H), 5.00 (dd, *J*=6.6, 10.7 Hz, 1H), 4.27 (dd, *J*=3.5, 7.7 Hz, 1H), 4.09 (t, *J*=8.0 Hz, 1H), 3.79 (s, 3H), 3.32 (t, *J*=10.2 Hz, 1H), 2.38 (s, 3H); ¹³C NMR δ 171.6, 138.7, 135.3, 132.2, 130.5, 129.3, 128.5, 128.0, 127.4, 126.5, 125.0, 95.5, 67.2, 64.9, 55.3, 52.6, 15.4; HPLC: Daicel Chiralpak AD-H column (hexane/2-propanol=70/30, 0.7 mL/min, 220 nm); *t*_R=13.7 (minor), *t*_R=18.2 min (major); [α]_D²⁵=-4.89 (*c*=0.11, CHCl₃). HRMS (ESI) calcd for C₁₉H₂₀N₂NaO₄ [M+Na]⁺ 363.1321, found: 363.1303.

4.2.3. **3ca** (R^1 =m- MeC_6H_4). White oil; 58.5 mg, 86% yield. ¹H NMR δ 7.44–7.13 (m, 9H), 5.27 (dd, J=3.3, 6.5 Hz, 1H), 4.87 (dd, J=6.5, 11.3 Hz, 1H), 4.20 (dd, J=3.3, 7.4 Hz, 1H), 4.14 (dd, J=7.4, 8.8 Hz, 1H), 3.82 (s, 3H), 3.36 (t, J=10.7 Hz, 1H), 2.35 (s, 3H); ¹³C NMR δ 171.7, 138.6, 138.4, 134.2, 129.4, 129.2, 128.5, 128.0, 127.4, 127.1, 123.4, 97.0, 67.8, 67.5, 55.5, 52.6, 21.4; HPLC: Daicel Chiralpak AS-H (hexane/2-propanol=70/30, 0.7 mL/min, 220 nm); t_R =16.6 (major),

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 t_R =21.7 min (minor); $[\alpha]_D^{25}$ =-35.3 (*c*=0.09, CHCl₃); HRMS (ESI) calcd for C₁₉H₂₁N₂O₄ [M+H]⁺ 341.1501, found: 341.1506.

4.2.4. **3da** (R^1 =p- MeC_6H_4). Yellow solid, mp=115-117 °C; 48.3 mg, 71% yield. ¹H NMR δ 7.34–7.07 (m, 9H), 5.17 (dd, *J*=3.5, 6.5 Hz, 1H), 4.80 (m, 1H), 4.13 (dd, *J*=3.5, 7.4 Hz, 1H), 4.08 (m, 1H), 3.72 (s, 3H), 3.25 (m, 1H), 2.25 (s, 3H); ¹³C NMR δ 171.8, 138.6, 138.5, 131.3, 129.4, 129.3, 128.0, 127.5, 126.3, 97.1, 67.7, 67.4, 55.4, 52.6, 21.1. HPLC: Daicel Chiralpak AS-H (hexane/2-propanol=70/30, 0.7 mL/min, 220 nm); t_R =19.3 (major), t_R =18.2 min (minor); $[\alpha]_D^{26}$ =-42.9 (*c*=0.12, CHCl₃); HRMS (ESI) calcd for C₁₉H₂₀KN₂O₄ [M+K]⁺ 379.1060, found: 379.1056.

4.2.5. **3ea** ($R^1 = p$ -MeOC₆H₄). Yellow oil; 58.4 mg, 82% yield. ¹H NMR δ 7.41–7.28 (m, 7H), 6.88 (d, J=8.0 Hz, 1H), 5.23 (dd, J=3.6, 6.5 Hz, 1H), 4.88 (dd, J=6.5, 11.0 Hz, 1H), 4.22 (dd, J=3.4 Hz, 7.4 Hz, 1H), 4.13 (t, J=8.6 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 3.28 (t, J=9.8 Hz, 1H); ¹³C NMR δ 171.8, 159.8, 138.6, 129.6, 128.1127.7, 127.5, 126.3, 114.1, 97.1, 67.4, 67.4, 67.3, 55.2, 52.6. HPLC: Daicel Chiralpak AD-H (hexane/2-propanol=70/30, 0.7 mL/min, 220 nm); t_R =29.3 (major), t_R =41.9 min (minor); $[\alpha]_D^{26}$ =-29.1 (*c*=0.12, CHCl₃); HRMS (ESI) calcd for C₁₉H₂₀KN₂O₅ [M+K]⁺ 395.1009, found: 395.1023.

4.2.6. **3fa** (R^1 =p- FC_6H_4). Yellow oil; 46.1 mg, 67% yield. ¹H NMR δ 7.53–7.02 (m, 9H), 5.25 (dd, *J*=3.8, 6.6 Hz, 1H), 4.89 (m, 1H), 4.23 (dd, *J*=3.8, 7.5 Hz, 1H), 4.14 (m, 1H), 3.80 (s, 3H), 3.24 (m, 1H); ¹³C NMR δ 171.7, 162.8 (d, *J*=250 Hz), 138.3, 130.4, 129.3, 128.4, 128.2 (d, *J*=11.4 Hz), 127.5, 115.7 (d, *J*=21.7 Hz), 96.8, 67.1, 66.8, 54.9, 52.7; HPLC: Daicel Chiralpak AS-H (hexane/2-propanol=70/30, 0.7 mL/min, 220 nm); t_R =28.5 (major), t_R =36.7 min (minor); [α]_D²⁷=–41.2 (*c*=0.12, CHCl₃); HRMS (ESI) calcd for C₁₈H₁₇FNaN₂O₄ [M+Na]⁺ 367.1070, found: 367.1079.

4.2.7. **3ga** (R^1 =p-*ClC*₆ H_4). White solid, mp=126-127 °C; 57.7 mg, 80% yield. ¹H NMR δ 7.51-7.26 (m, 9H), 5.26 (dd, *J*=3.8, 6.6 Hz, 1H), 4.89 (dd, *J*=6.6, 10.3 Hz, 1H), 4.23 (dd, *J*=3.8, 7.5 Hz, 1H), 3.81 (s, 3H), 3.26 (t, *J*=9.8 Hz, 1H); ¹³C NMR δ 171.6, 138.2, 134.7, 133.1, 129.3, 128.9, 128.2, 127.9, 127.5, 96.7, 67.1, 66.8, 55.0, 52.7. HPLC; Daicel Chiralpak AS-H (hexane/2-propanol=70/30, 0.7 mL/min, 220 nm); t_R =22.1 min (major), t_R =30.4 min (minor); $[\alpha]_D^{27}$ =-27.6 (*c*=0.12, CHCl₃); HRMS calcd for C₁₈H₁₈ClN₂O₄ [M+H]⁺ 361.0955, found: 361.0969.

4.2.8. **3ha** (R^1 =p- BrC_6H_4). White solid, mp=132–134 °C; 41.3 mg, 51% yield. ¹H NMR δ 7.50–7.23 (m, 9H), 5.25 (dd, *J*=3.8, 6.6 Hz, 1H), 4.87 (dd, *J*=6.6, 10.2 Hz, 1H), 4.22 (dd, *J*=3.8, 7.5 Hz, 1H), 4.13 (t, *J*=8.1 Hz, 1H), 3.79 (s, 3H), 3.24 (t, *J*=9.6 Hz, 1H); ¹³C NMR δ 171.6, 138.2, 133.7, 131.9, 129.3, 128.2, 128.2, 127.5, 122.8, 96.6, 67.1, 66.8, 54.9, 52.7; HPLC: Daicel Chiralpak AS-H column (hexane/2-propanol=70/30, 0.7 mL/min, 220 nm); t_R =42.6 (major), t_R =55.8 min (minor); $[\alpha]_D^{27}$ =-47.1 (*c*=0.12, CHCl₃); HRMS (ESI) calcd for C₁₈H₁₈BrN₂O₄ [M+H]⁺ 405.0450, found: 405.0444.

4.2.9. **3ia** (R^1 =1- C_8H_9). Yellow solid, mp=85–88 °C; 60.2 mg, 80% yield. ¹H NMR δ 7.91–7.67 (m, 4H), 7.28–7.67 (m, 8H), 5.65 (d, *J*=6.2 Hz, 1H), 5.54 (dd, *J*=3.2, 6.1 Hz, 1H), 4.35 (dd, *J*=3.0, 7.3 Hz, 1H), 4.15 (d, *J*=7.3 Hz, 1H), 3.80 (s, 3H); ¹³C NMR δ 171.8, 139.0, 133.6, 130.7, 129.5, 129.4, 128.2, 127.7, 126.9, 126.0, 125.5, 123.7, 121.8, 96.6, 67.1, 64.1, 55.4, 52.8. HPLC: Daicel Chiralpak IB (hexane/2-propanol=90/10, 0.8 mL/min, 220 nm); t_R =15.0 min (minor), t_R =22.5 min (major); $[\alpha]_D^{27}$ =+46.3 (*c*=0.05, CHCl₃); HRMS (ESI) calcd for C₂₂H₂₀KN₂O₄ [M+K]⁺ 415.1060, found: 415.1047.

4.2.10. **3***ja* (R^1 =2-thienyl). Yellow oil; 53.2 mg, 80% yield. ¹H NMR δ 7.43–7.26 (m, 7H), 6.99–7.07 (m, 1H), 5.27 (dd, *J*=4.1, 6.5 Hz, 1H), 5.12 (d, *J*=6.5 Hz, 1H), 4.26 (dd, *J*=4.1, 7.4 Hz, 1H), 4.14 (m, 1H), 3.80 (s, 3H); ¹³C NMR δ 171.6, 138.2, 137.5, 129.4, 128.2, 127.6, 127.4, 125.8,

125.4, 96.3, 67.1, 63.4, 54.7, 52.8; HPLC: Daicel Chiralpak IB (hexane/ 2-propanol=95/5, 0.7 mL/min, 220 nm); t_R =12.2 min (minor), t_R =13.5 min (major); $[\alpha]_D^{26}$ =+12.9 (*c*=0.01, CHCl₃); HRMS (ESI) calcd for C₁₆H₁₇N₂O₄S [M+H]⁺ 333.0909, found: 333.0900.

4.2.11. **3ka** (R^1 =Cy). Yellow oil; 31.2 mg, 47% yield. ¹H NMR δ 7.41–7.19 (m, 5H), 5.07 (d, *J*=4.9 Hz, 1H), 3.96 (s, 2H), 3.78 (s, 1H), 2.27 (m, 1H), 2.88 (br s, 1H), 1.04–2.11 (m, 11H); ¹³C NMR δ 171.9, 139.7, 129.4, 128.1, 127.5, 95.3, 71.5, 68.4, 57.1, 52.7, 38.5, 31.5, 31.1, 26.2, 25.8, 25.6; HPLC: Daicel Chiralpak IB (hexane/2-propanol=95/5, 1 mL/min, 220 nm); t_R =6.53 min (major), t_R =7.16 min (minor); $[\alpha]_D^{27}$ =-48.4 (*c*=0.05, CHCl₃); HRMS (ESI) calcd for C₁₈H₂₄N₂NaO₄ [M+Na]⁺ 355.1634, found: 355.1634.

4.2.12. **3ab** ($R^2 = o - MeC_6H_4$). Yellow oil; 55.1 mg, 81% yield. ¹H NMR δ 7.37–7.23 (m, 9H), 5.14 (dd, J=3.4, 6.5 Hz, 1H), 4.94 (dd, J=6.5, 10.9 Hz, 1H), 4.55 (dd, J=3.4, 7.0 Hz, 1H), 4.21 (dd, J=7.0, 8.5 Hz, 1H), 3.81 (s, 3H), 3.38 (t, J=9.2 Hz, 1H), 2.35 (s, 3H); ¹³C NMR δ 172.1, 137.1, 134.4, 131.1, 130.7, 129.1, 128.8, 127.9, 127.1, 126.5, 126.0, 97.2, 67.8, 67.2, 52.7, 51.0, 19.9. HPLC: Daicel Chiralpak AS-H (hexane/2-propanol=70/30, 0.7 mL/min, 220 nm); $t_R=19.0$ (minor), $t_R=22.0$ min (major); $[\alpha]_D^{27}=-23.4$ (c=0.13, CHCl₃); HRMS (ESI) calcd for C₁₉H₂₁N₂O₄ [M+H]⁺ 341.1501, found: 341.1503.

4.2.13. **3ac** ($R^2 = p$ -MeC₆H₄). Yellow oil; 40.8 mg, 60% yield. ¹H NMR δ 7.55–7.06 (m, 9H), 5.20–5.30 (m, 1H), 4.90–4.92 (m, 1H), 4.11–4.19 (m, 2H), 3.81 (s, 3H), 2.37 (s, 3H); ¹³C NMR δ 171.8, 138.0, 135.6, 130.0, 129.6, 128.7, 127.9, 127.3, 126.4, 87.2, 67.8, 67.5, 55.2, 52.6, 21.1; HPLC: Daicel Chiralpak AS-H (hexane/2-propanol=70/30, 0.7 mL/min, 220 nm); t_R =20.8 (major), t_R =25.9 min (major); $[\alpha]_D^{27}$ =-35.2 (*c*=0.06, CHCl₃); HRMS (ESI) calcd for C₁₉H₂₁N₂O₄ [M+H]⁺ 341.1501, found: 341.1550.

4.2.14. **3ad** (R^2 =*p*-*MeOC*₆*H*₄). Yellow oil; 45.6 mg, 64% yield. ¹H NMR δ 7.43–7.25 (m, 5H), 7.23 (d, *J*=8.0 Hz, 2H), 6.93 (d, *J*=8.0 Hz, 2H), 5.24 (dd, *J*=3.3, 6.5 Hz, 1H), 4.90 (dd, *J*=6.5, 11.1 Hz, 1H), 4.11–4.19 (m, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.35 (m, 1H); ¹³C NMR δ 172.0, 159.5, 134.7, 130.7, 128.9, 128.9, 128.8, 126.7, 114.8, 97.4, 67.8, 67.6, 55.5, 55.0, 52.8. HPLC: Chiralpak AS-H (hexane/2-propanol=80/20, 1.0 mL/min, 220 nm); t_R =31.1 (major), t_R =39.2 min (minor); $[\alpha]_D^{26}$ =–34.9 (*c*=0.08, CHCl₃); HRMS (ESI) calcd for C₁₉H₂₁N₂O₅ [M+H]⁺ 357.1451, found: 357.1455.

4.2.15. **3ae** ($R^2 = p - ClC_6H_4$). Yellow oil; 28.9 mg, 40% yield. ¹H NMR δ 7.51–7.26 (m, 9H), 5.26 (dd, *J*=3.8, 6.6 Hz, 1H), 4.89 (dd, *J*=6.6, 10.3 Hz, 1H), 4.23 (dd, *J*=3.8, 7.5 Hz, 1H), 3.81 (s, 3H); ¹³C NMR δ 171.6, 137.0, 134.5, 134.2, 129.6, 129.0, 129.0, 128.9, 126.6, 96.6, 67.7, 67.4, 54.6, 52.9; HPLC: Chiralpak IB (hexane/2-propanol=95/5, 1.0 mL/min, 220 nm); t_R =32.6 (minor), t_R =36.2 min (major); $[\alpha]_D^{27}$ =-28.4 (*c*=0.12, CHCl₃); HRMS (ESI) calcd for C₁₈H₁₈ClN₂O₄ [M+H]⁺ 361.0955, found: 361.0949.

4.2.16. **3af** ($R^2 = p - BrC_6H_4$). Yellow oil; 48.6 mg, 60% yield. ¹H NMR δ 7.54 (d, J=8.5 Hz, 2H), 7.47–7.33 (m, 5H), 7.18 (d, J=8.5 Hz, 1H), 5.24 (dd, J=4.1, 6.4 Hz, 1H), 4.89 (d, J=7.0 Hz, 1H), 4.17–4.20 (m, 1H), 4.07–4.10 (m, 1H), 3.81 (s, 3H); ¹³C NMR δ 171.6, 137.5, 134.4, 132.6, 129.4, 129.0, 128.9, 126.6, 122.3, 96.8, 68.1, 67.8, 54.7, 52.9; HPLC: Chiralpak IB (hexane/2-propanol=95/5, 1.0 mL/min, 220 nm); t_R =15.9 (minor), t_R =20.2 min (major); $[\alpha]_D^{27}$ =-36.9 (*c*=0.10, CHCl₃); HRMS (ESI) calcd for C₁₈H₁₇BrKN₂O₄ [M+K]⁺ 443.0009, found: 443.0031.

4.2.17. **3ag** ($R^2 = C_{10}H_9Fe$). Yellow solid, mp=152-154 °C; 82.5 mg, 80% yield. ¹H NMR δ 7.37-7.32 (m, 5H), 5.26 (m, 1H), 4.75 (d, J=5.5 Hz, 1H), 4.26 (m, 4H), 4.23 (s, 5H), 4.12 (m, 1H), 4.03 (m, 1H), 2.91 (s, 3H); ¹³C NMR δ 172.3, 134.2, 128.9, 126.4, 96.8, 87.2, 69.0,

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68.5, 67.9, 67.8, 67.6, 66.1, 52.8, 51.0; HPLC: Chiralpak IB (hexane/2-propanol=95/5, 1.0 mL/min, 220 nm); t_R =24.2 (minor), t_R =35.5 min (major); [α]_D²⁷=96.1 (c=0.10, CHCl₃); HRMS (ESI) calcd for C₂₂H₂₃FeN₂O₄ [M+Na]⁺ 437.0827, found 457.0839.

4.2.18. **3ah** (R^2 =2-*furyl*). Yellow oil; 30.0 mg, 50% yield. ¹H NMR δ 7.44–7.30 (m, 6H), 6.39–6.37 (m, 2H), 6.30 (d, *J*=3.2 Hz, 2H), 5.34 (dd, *J*=3.0, 6.1 Hz, 1H), 4.86 (m, 1H), 4.30 (dd, *J*=3.0, 6.7 Hz, 1H), 4.20 (m, 1H), 3.79 (s, 3H), 3.31 (m, 1H); ¹³C NMR δ 171.4, 150.9, 143.1, 134.0, 128.9, 128.2, 126.5, 110.9, 108.0, 94.2, 67.7, 64.9, 52.9, 49.0. HPLC: Daicel Chiralpak IB (hexane/2-propanol=95/5, 1.0 mL/min, 220 nm); t_R =17.9 (minor), t_R =19.9 min (major); $[\alpha]_D^{27}$ =-35.1 (*c*=0.11, CHCl₃); HRMS (ESI) calcd for C₁₆H₁₆N₂O₅ [M+Na]⁺ 339.0957, found: 339.0950.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.08.002.

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