Lewis Acid-Catalyzed Enantioselective Friedel–Crafts Alkylation of Pyrrole in Water

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ABSTRACT: Highly enantioselective Friedel–Crafts alkylation of pyroles with 2-enoyl-pyridine N-oxides in water/chloroform (10:1) was developed under catalysis of Lewis acid. The Friedel–Crafts alkylation products can be obtained in high yields and excellent enantioselectivities. Moreover, several control experiments were carried out to study the reaction mechanism.

INTRODUCTION

Pyrrole derivatives that contain chiral centers are prevalent moieties in many natural products and active pharmaceuticals. Because the biological activities are strongly linked with stereochemistry, the catalytic asymmetric reaction remains a topic of ongoing research in synthetic organic chemistry. As a type of this reaction, Friedel–Crafts alkylation of pyrrole has emerged as an important synthetic strategy for the construction of stereogenic carbon centers. For instance, the organocatalyzed Friedel–Crafts alkylation of pyrroles was reported by Paras and MacMillan and Enders et al. Later, enantioselective Friedel–Crafts alkylation of pyrroles catalyzed by metal complexes was developed greatly in the past few decades. Palomo et al., Arai et al., Fu et al., and George and Reddy developed enantioselective Friedel–Crafts alkylation of pyrroles catalyzed by copper complexes. Recently, Evans and Fandrick and Feng et al. disclosed similar reactions with scandium complexes. Very recently, the Friedel–Crafts alkylation of pyrroles catalyzed by zinc complexes was reported by Singh and Singh and Chang et al. However, all of these Friedel–Crafts alkylation of pyrroles catalyzed by metal complexes were developed in organic solvents. Constructing a chiral center by virtue of Friedel–Crafts alkylation in aqueous media is still a challenge for organic synthesis. Our group has been focusing on the asymmetric organic reaction in water for a long time, and many water-chiral catalysts were synthesized and investigated. As our continuing interest, we herein report our recent efforts in developing enantioselective Friedel–Crafts alkylation of pyrrole with 2-enoyl-pyridine N-oxides in aqueous media (Scheme 1).

RESULTS AND DISCUSSION

Our investigation began with the reaction of 2-enoyl-pyridine N-oxide 1a and pyrrole 2 in water/chloroform (10:1) (Tables 1 and 2). First of all, the Schiff base ligand L1 was employed with various metal salts at 0 °C for this reaction. To our delight, Zn(OTf)$_2$ could perform well to afford the target product 3a with high yield and good enantioselectivity, while the other metal salts gave poor results (Table 1, entries 1–9).

Subsequently, ligand L2 was investigated in this reaction, and the target product 3a was obtained with good yield but lower ee value (Table 1, entries 2 and 10). To further optimize the reaction conditions, ligand L1 was chosen as the optimal ligand and different temperatures were examined. Raising the
temperature resulted in the decrease in the ee values despite a few increases in reaction yield (Table 1, entries 11 and 12). To increase the solubility of the reactants in water, various kinds of solvents were added to the reaction mixture. It was found that 1.0 mL of H2O containing 0.1 mL of CHCl3 was the best choice (Table 2, entries 1−5). To further enhance the stereoselectivity of this reaction, different phase transfer catalysts (PTCs) and weak base additives were examined (Table 2, entries 6−10). PTCs had a negative effect on the reaction, while weak base additives could enhance the stereoselectivity (Table 2, entries 6−16). Especially, the use of piperidine gave the target product 3a in 92% yield with 96% ee (Table 2, entry 10). After investigation, the optimal conditions were decided as below: Zn(OTf)2 with the chiral ligand L1 as the catalyst, piperidine as the additive, and the reaction being carried out in an aqueous medium at 0 °C.

With the optimal conditions in hand, the substrate scope of 2-enoyl-pyridine N-oxides 1 was studied (Table 3). Initially, the electronic effect of the substrates was investigated by varying the para-substituent groups of R. It was found that the substrates with electron-donating groups in the para-position of the phenyl ring gave the desired products with high yields and excellent enantioslectivities (entries 2 and 3). Meanwhile, the substrates bearing electron-withdrawing halogen groups in the para-position of the phenyl ring led to almost no change in the yield and ee value (entries 4−6). With the exchange of halogen groups to strong electron-withdrawing trifluoromethyl group, excellent enantioselectivity of the Friedel–Crafts adducts could be maintained, albeit with a slight erosion of yield (entry 7). As for the substrate 1h, bearing a nitro group on the phenyl ring also worked well in the reaction (entry 8). Afterward, different positions for the substituents of R were investigated. The products bearing para- and meta-substituents could be obtained in high yields and excellent enantioslectivities (entries 2−11). However, when the sterically encumbered ortho-substituent was employed, a trace of the corresponding product 3i was detected, which indicated that hindrance had a great negative influence on the reaction (entry 12). On the other hand, a multisubstituted group could also be compatible, affording products 3m with excellent enantioselectivity (>99% ee). More importantly, the naphthalene substrate 1n, the thiophene substrate 1o, and the furan substrate 1p could also be converted into interesting products 3n−3p with high yields and excellent enantioslectivities (entries 14−16). In addition, the absolute configuration of the product 3 was confirmed through HPLC data and specific rotation data.7a

To obtain insight into the reaction mechanism, several control experiments were carried out (Scheme 2). First, the reaction of N-methylpyrrole with 2-enoyl-pyridine N-oxide 1a was performed under standard conditions. However, no reaction was observed (entry 1). When the reaction of 2,4-dimethylpyrrole with 2-enoyl-pyridine N-oxide 1a was carried out under standard conditions, the corresponding product 3q could be obtained in 96% yield with 32% ee (entry 2). These experimental results indicated that the NH in pyrrole played a crucial role in the formation of the chiral center, perhaps due to the fact that this NH group promoted the formation of a hydrogen bond to direct the attack orientation (entries 1 and 2). On the other hand, when the hydrophobic ligand L3 without the dimethylamino groups was examined instead of
the ligand L1 in this reaction, the desired product could be obtained in 19% yield with 43% ee. This experiment suggested that the dimethylamino groups on the ligand L1, which act as hydrophilic groups to promote the formation of the emulsion, favored this reaction in water (entry 3).

On the basis of the control experiments and our previous mechanism study,10 a plausible structure of the transition state was proposed (Scheme 3). The hydrophilic dimethylamino groups were dissolved in the water phase, while the 2-enoyl-pyridine N-oxide was activated by chelating with a metal center in the catalyst complex, and the NH in pyrrole served as a hydrogen bond-donating group to direct the alkylation at the si face of the 2-enoyl-pyridine N-oxide, affording the corresponding product in S-configuration.

Subsequently, to probe the practicability of this asymmetric addition in water/chloroform (10:1), a gram-scale experiment was carried out under standard conditions (Scheme 4). To our delight, the desired product 3c was obtained with 1.31 g quantity, 90% yield, and 96% ee.

**CONCLUSIONS**

In conclusion, Lewis acid-catalyzed asymmetric Friedel–Crafts alkylation of pyrrole with 2-enoyl-pyridine N-oxide in water/chloroform (10:1) was developed under mild reaction conditions. A series of Friedel–Crafts alkylation products were obtained with excellent enantioselectivities and high yields. Moreover, a gram scale of the asymmetric Friedel–Crafts alkylation in aqueous media could be achieved.

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**EXPERIMENTAL SECTION**

**General Information.** 1H NMR and 13C NMR were recorded on a Bruker-400 MHz spectrometer (1H NMR: 400 MHz; 13C NMR: 100 MHz) using TMS as an internal reference. The chemical shifts (δ) and coupling constants (J) were expressed in ppm and Hz, respectively. UV−Vis spectrophotometry was carried out on a Shimadzu UV-3000. HPLC analysis was carried out on an Agilent 1100 series HPLC with a multiple wavelength detector. Chiralpak AS-H, AD-H, and OD-H columns were purchased from Daicel Chemical Industries, Ltd. Optical rotations were measured on a PerkinElmer polarimeter (model 343). HRMS (ESI) was recorded on Waters Q-TOF Premier and Thermo Scientific LTQ Orbitrap XL Hybrid Ion Trap-Orbitrap mass spectrometers. Commercially available compounds were used without further purification. Solvents were purified according to the standard procedures, unless otherwise noted. Commercial pyrrole should be distilled for the use of the reactions.

Ligands9d,10b and various 2-enoyl-pyridine N-oxides2,11 were prepared according to literature procedures.

**General Procedures for Friedel–Crafts Alkylation of Pyrroles with 2-Enoyl-pyridine N-Oxides in Aqueous Media.** A mixture of ligand L1 (0.02 mmol) and Zn(OTf)2 (0.02 mmol) in water (2.0 mL) was stirred for 2 h under an ambient atmosphere, and then 2-enoyl-pyridine N-oxides 1 (0.2 mmol), CHCl3 (0.2 mL), and piperidine (0.02 mmol) were added. The resulting mixture was cooled to 0 °C. After 30 min, the corresponding pyrrole 2 (40 μL, 0.6 mmol) was added to the mixture. The reaction was left to stir for 2 h under an ambient atmosphere, and then the product was isolated by column chromatography.
added slowly using a syringe. After the reactions were finished (monitored by TLC), the organic phase was separated and evaporated in vacuo. Purification by column chromatography afforded Friedel–Crafts alkylation adducts.

Table 2. Optimization of the Solvents, PTCs, and Bases of the Reaction

| entry | solvent                  | PTC        | base        | yield (%) | ee (%) |
|-------|--------------------------|------------|-------------|-----------|--------|
| 1     | H₂O/CHCl₃                |            |             | 84        | 86     |
| 2     | H₂O                      |            |             | 52        | 56     |
| 3     | H₂O/toluene              |            |             | 86        | 84     |
| 4     | H₂O/CH₂Cl₂               |            |             | 84        | 79     |
| 5     | H₂O/MeOH                 |            |             | 74        | 51     |
| 6     | H₂O/CHCl₃                | Bu₄NBr     |             | 87        | 84     |
| 7     | H₂O/CHCl₃                | Bu₄NPF₆    |             | 91        | 82     |
| 8     | H₂O/CHCl₃                | SDS        |             | 80        | 81     |
| 9     | H₂O/CHCl₃                |            | NEt₃       | 87        | 89     |
| 10    | H₂O/CHCl₃                | piperidine |             | 92        | 96     |
| 11    | H₂O/CHCl₃                | DBU        |             | 88        | 94     |
| 12    | H₂O/CHCl₃                | Na₂CO₃     |             | 83        | 90     |
| 13    | H₂O/CHCl₃                | Cs₂CO₃     |             | 79        | 92     |
| 14    | H₂O/CHCl₃                | Bu₄NBr     |             | 93        | 81     |
| 15    | H₂O/CHCl₃                | Bu₄NPF₆    | piperidine  | 97        | 91     |
| 16    | H₂O/CHCl₃                | SDS        | piperidine  | 84        | 91     |

*Unless otherwise noted, the reactions of 1a (0.1 mmol) and 2 (0.3 mmol) were performed in the presence of L1 (10 mol %), Zn(OTf)₂ (10 mol %), PTC (10 mol %), and base (10 mol %) in solvent (1.0/0.1 mL) at 0 °C for 24 h.*

Table 3. Scope of 2-Enoyl-pyridine N-Oxides

| entry | R (1)               | 3     | time* (h) | yield (%) | ee (%) |
|-------|---------------------|-------|-----------|-----------|--------|
| 1     | Ph (1a)             | 3a    | 24        | 92        | 96     |
| 2     | p-MeC₆H₄ (1b)       | 3b    | 48        | 90        | 94     |
| 3     | p-MeOC₆H₄ (1c)      | 3c    | 48        | 84        | 98     |
| 4     | p-FC₆H₄ (1d)        | 3d    | 30        | 95        | 97     |
| 5     | p-CIC₆H₄ (1e)       | 3e    | 24        | 88        | 93     |
| 6     | p-BrC₆H₄ (1f)       | 3f    | 24        | 92        | >99    |
| 7     | p-CF₂C₆H₄ (1g)      | 3g    | 24        | 72        | >99    |
| 8     | p-NO₂C₆H₄ (1h)      | 3h    | 24        | 74        | 93     |
| 9     | m-MeC₆H₄ (1i)       | 3i    | 36        | 91        | 97     |
| 10    | m-CIC₆H₄ (1j)       | 3j    | 24        | 88        | 96     |
| 11    | m-NO₂C₆H₄ (1k)      | 3k    | 30        | 95        | 95     |
| 12    | o-MeC₆H₄ (1l)       | 3l    | 48        | trace     |        |
| 13    | 3,4-(OMe)₂C₆H₄ (1m) | 3m    | 48        | 78        | >99    |
| 14    | 2-naphthyl (1n)     | 3n    | 24        | 98        | >99    |
| 15    | 2-thienyl (1o)      | 3o    | 24        | 81        | 99     |
| 16    | 2-furyl (1p)        | 3p    | 30        | 87        | 96     |

*Unless otherwise noted, the reactions of 1 (0.2 mmol) and 2 (0.6 mmol) were performed in the presence of L1 (10 mol %), Zn(OTf)₂ (10 mol %), and piperidine (10 mol %) in H₂O/CHCl₃ (2.0/0.2 mL) at 0 °C for the time indicated.*

*Detemined by TLC detection.*

*Isolated yields.*

*Determined by chiral HPLC analysis.*
Experimental Data of Friedel–Crafts Products. (S)-2-(3-Phenyl-3-(1H-pyrrol-2-yl)propanoyl)pyridine 1-Oxide (3a). The title compound was prepared according to the general working procedure and purified by column chromatography (ethyl acetate = 1) to give the product as a light yellow solid (92% yield); mp = 110–111 °C; [α]D25 5.6 (c = 1.00, THF, 96% ee); HPLC: Daicel Chiralpak OD-H; hexane/2-propanol = 90:10; flow rate = 1.0 mL/min; T = 30 °C; UV = 240 nm; tR = 35.82 min (minor); tR = 41.78 min (major); 1H NMR (400 MHz, CDCl3): δ 8.60 (br s, 1H), 8.16 (d, J = 6.5 Hz, 1H), 7.36 (dd, J = 7.7, 2.2 Hz, 1H), 7.34–7.29 (m, 1H), 7.28–7.18 (m, 6H), 6.64–6.62 (m, 1H), 6.07 (dd, J = 5.8, 2.8 Hz, 1H), 5.92–5.90 (m, 1H), 4.73 (dd, J = 8.5, 6.5 Hz, 1H), 4.12 (dd, J = 17.1, 8.4 Hz, 1H), 3.69 (dd, J = 17.1, 6.5 Hz, 1H), 2.29 (s, 3H). 13C NMR (100 MHz, CDCl3): δ 196.5, 146.8, 143.0, 140.3, 133.6, 128.6, 127.9, 127.9, 126.8, 126.8, 126.0, 117.1, 108.1, 105.8, 48.6, 40.0; HRMS (ESI-TOF) m/z: [M + H]+ calcd for C18H16N2O2H, 293.1285; found, 293.1282.

(S)-2-(3-(1H-Pyrrol-2-yl)-3-(p-tolyl)propanoyl)pyridine 1-Oxide (3b). The title compound was prepared according to the general working procedure and purified by column chromatography (ethyl acetate = 1) to give the product as a light yellow solid (90% yield); mp = 135–136 °C; [α]D25 1.6 (c = 0.90, THF, 94% ee); HPLC: Daicel Chiralpak AS-H; hexane/2-propanol = 70:30; flow rate = 1.0 mL/min; T = 30 °C; UV = 240 nm; tR = 20.51 min (major); tR = 34.02 min (minor); 1H NMR (400 MHz, CDCl3): δ 8.56 (br s, 1H), 8.26–8.04 (m, 1H), 7.38–7.28 (m, 2H), 7.27–7.21 (m, 1H), 7.12–7.05 (m, 4H), 6.75–6.52 (m, 1H), 6.07 (dd, J = 5.8, 2.9 Hz, 1H), 5.95–5.81 (m, 1H), 4.77–4.65 (m, 1H), 4.10 (dd, J = 17.1, 8.4 Hz, 1H), 3.68 (dd, J = 17.1, 6.6 Hz, 1H), 2.29 (s, 3H). 13C NMR (100 MHz, CDCl3): δ 196.6, 146.8, 140.3, 139.9, 136.3, 133.8, 129.3, 127.8, 127.8, 126.8, 126.0, 117.0, 108.1, 105.7, 48.7, 39.6, 21.0; HRMS (ESI-TOF) m/z: [M + H]+ calcd for C19H18N2O2H, 307.1441; found, 307.1434.

(S)-2-(3-(4-Methoxyphenyl)-3-(1H-pyrrol-2-yl)propanoyl)pyridine 1-Oxide (3c). The title compound was prepared according to the general working procedure and purified by column chromatography (ethyl acetate = 1) to give the product as a light yellow solid (94% yield); mp = 119–120 °C; [α]D25 5.6 (c = 1.00, THF, 94% ee); HPLC: Daicel Chiralpak AS-H; hexane/2-propanol = 90:10; flow rate = 1.0 mL/min; T = 30 °C; UV = 240 nm; tR = 35.82 min (minor); tR = 41.78 min (major); 1H NMR (400 MHz, CDCl3): δ 8.60 (br s, 1H), 8.16 (d, J = 6.5 Hz, 1H), 7.36 (dd, J = 7.7, 2.2 Hz, 1H), 7.34–7.29 (m, 1H), 7.28–7.18 (m, 6H), 6.64–6.62 (m, 1H), 6.07 (dd, J = 5.8, 2.8 Hz, 1H), 5.92–5.90 (m, 1H), 4.73 (dd, J = 8.5, 6.5 Hz, 1H), 4.12 (dd, J = 17.1, 8.4 Hz, 1H), 3.69 (dd, J = 17.1, 6.5 Hz, 1H), 2.29 (s, 3H). 13C NMR (100 MHz, CDCl3): δ 196.5, 146.8, 140.3, 139.9, 136.3, 133.8, 129.3, 127.8, 127.8, 126.8, 126.0, 117.0, 108.1, 105.7, 48.7, 39.6, 21.0; HRMS (ESI-TOF) m/z: [M + H]+ calcd for C19H18N2O2H, 307.1441; found, 307.1434.
Scheme 4. Asymmetric Friedel–Crafts Alkylation on a Gram Scale**

column chromatography (ethyl acetate = 1) to give the product as a light yellow oil (84% yield); [α]_D^20 = 2.0 (c = 1.05, THF, 98% ee); HPLC: Daicel Chiralpak AS-H; hexane/2-propanol = 70:30; flow rate = 1.0 mL/min; T = 30 °C; UV = 230 nm; t_R = 39.68 min (major); t_f = 68.70 min (minor); ^1H NMR (400 MHz, CDCl₃): δ = 8.57 (br s, 1H), 8.16 (d, J = 6.4 Hz, 1H), 7.37–7.29 (m, 2H), 7.26–7.21 (m, 1H), 7.18–7.09 (m, 2H), 6.83–6.74 (m, 2H), 6.64–6.59 (m, 1H), 6.10–6.03 (m, 1H), 5.91–5.87 (m, 1H), 4.67 (t, J = 7.5 Hz, 1H), 4.07 (dd, J = 17.0, 8.2 Hz, 1H), 3.76 (s, 3H), 3.67 (dd, J = 17.0, 6.8 Hz, 1H). ^13C NMR (100 MHz, CDCl₃): δ = 196.6, 156.3, 148.6, 140.3, 135.0, 134.0, 128.9, 126.8, 125.9, 117.0, 113.9, 108.0, 105.6, 55.3, 48.8, 39.2; HRMS (ESI-TOF) m/z: [M + H]^+ calcd for C₁₉H₁₆F₃N₂O₂H, 327.1390; found, 327.1394.

"Unless otherwise noted, the reactions of 1a (5 mmol) and 2 (15 mmol) were performed in the presence of L1 (10 mol %), Zn(OTf)₂ (10 mol %), and piperidine (10 mol %) in H₂O/CHCl₃ (25/2.5 mL) at 0 °C for 24 h. Isolated yields. Determined by chiral HPLC analysis.
The title compound was prepared according to the general working procedure and purified by column chromatography (ethyl acetate = 1) to give the product as a light yellow oil (98% yield); \([\alpha]_D^{25} = -5.2 (c = 0.90, THF, 99\% ee)\); HPLC: Daicel Chiralpak AS-H; hexane/2-propanol = 70:30; flow rate = 1.0 mL/min; T = 30 °C; UV = 240 nm; tf = 26.02 min (minor); fg = 31.30 min (major); \(^1\)H NMR (400 MHz, CDCl₃): δ 8.59 (d, J = 6.6 Hz, 1H), 7.53–7.39 (m, 1H), 6.69–6.60 (m, 1H), 6.10–6.06 (m, 1H), 5.96–5.87 (m, 1H), 4.67 (t, J = 7.5 Hz, 1H), 4.08 (dd, J = 17.0, 8.2 Hz, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.72 (dd, J = 17.0, 6.9 Hz, 1H). \(^13\)C NMR (100 MHz, CDCl₃): δ 196.9, 149.0, 147.8, 146.8, 140.3, 135.4, 133.8, 127.8, 126.8, 126.0, 119.9, 117.1, 111.1, 111.1, 108.1, 105.6, 55.9, 55.8, 48.7, 39.7; HRMS (ESI-TOF) m/z: [M + H]+ calcld for C₁₉H₁₈N₂O₂H, 343.1496; found, 353.1497.

\((S)-2-(3-(Naphthalen-2-yl)-3-(1H-pyrrol-2-yl)propanoyl)pyridine 1-Oxide (3n)\). The title compound was prepared according to the general working procedure and purified by column chromatography (ethyl acetate = 1) to give the product as a light yellow oil (88% yield); \([\alpha]_D^{25} = -5.2 (c = 0.90, THF, 99\% ee)\); HPLC: Daicel Chiralpak AS-H; hexane/2-propanol = 70:30; flow rate = 1.0 mL/min; T = 30 °C; UV = 240 nm; tf = 26.02 min (minor); fg = 31.30 min (major); \(^1\)H NMR (400 MHz, CDCl₃): δ 8.66 (br s, 1H), 8.12 (d, J = 6.4 Hz, 1H), 7.79–7.70 (m, 3H), 7.69–7.66 (m, 1H), 7.47–7.39 (m, 2H), 7.46 (td, J = 8.4, 2.0 Hz, 2H), 7.29–7.21 (m, 1H), 7.19–7.12 (m, 1H), 6.69–6.59 (m, 1H), 6.12–6.08 (m, 1H), 5.99–5.93 (m, 1H), 4.90 (dd, J = 8.3, 6.6 Hz, 1H), 4.20 (dd, J = 17.2, 8.3 Hz, 1H), 3.81 (dd, J = 17.2, 6.6 Hz, 1H). \(^13\)C NMR (100 MHz, CDCl₃, δ 196.4, 146.7, 140.4, 140.3, 133.5, 133.4, 132.4, 128.4, 127.8, 127.8, 127.6, 126.8, 126.4, 126.2, 125.5, 125.7, 117.3, 108.2, 106.0, 48.4, 40.1; HRMS (ESI-TOF) m/z: [M + H]+ calcld for C₂₀H₂₀N₂O₄H, 353.1441; found, 343.1436.

\((S)-2-(3-(Nitrophenyl)-3-(1H-pyrrol-2-yl)propanoyl)pyridine 1-Oxide (3k)\). The title compound was prepared according to the general working procedure and purified by column chromatography (ethyl acetate = 1) to give the product as a brown oil (95% yield); \([\alpha]_D^{25} = 15.1 (c = 0.80, THF, 95\% ee)\); HPLC: Daicel Chiralpak AS-H; hexane/2-propanol = 70:30; flow rate = 1.0 mL/min; T = 30 °C; UV = 254 nm; tf = 26.16 min (major); fg = 36.64 min (minor); \(^1\)H NMR (400 MHz, CDCl₃): δ 8.97 (br s, 1H), 8.21 (d, J = 6.4 Hz, 1H), 8.15–8.01 (m, 2H), 7.61 (d, J = 7.7 Hz, 1H), 7.54–7.48 (m, 1H), 7.46–7.42 (m, 1H), 7.43–7.29 (m, 2H), 6.73–6.62 (m, 1H), 6.17–6.04 (m, 1H), 5.94–5.85 (m, 1H), 4.89 (t, J = 7.5 Hz, 1H), 4.21 (dd, J = 17.5, 8.5 Hz, 1H), 3.73 (dd, J = 17.5, 6.4 Hz, 1H). \(^13\)C NMR (100 MHz, CDCl₃): δ 195.4, 148.3, 146.3, 145.5, 140.5, 134.3, 132.1, 129.6, 128.3, 127.1, 126.3, 122.8, 121.9, 117.8, 108.4, 106.5, 48.2, 39.6; HRMS (ESI-TOF) m/z: [M + H]+ calcld for C₁₈H₁₄N₂O₂SH, 327.0985; found, 345.0845.

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1H NMR and 13C NMR spectra for all the products along with HPLC profiles for the title compound were prepared according to the general working procedure and purified by column chromatography (ethyl acetate = 1) to give the product as a yellow oil (96% yield); \( \delta^1H = 0.2 \) (c = 1.0, THF, 3% ee); HPLC: Daicel Chiralpak OD-H; hexane/2-propanol = 90:10; flow rate = 1.0 mL/min; T = 30 °C; UV = 230 nm; \( t_R = 20.08 \text{ min (minor)}; t_R = 27.52 \text{ min (major)}; \) 1H NMR (400 MHz, CDCl\(_3\)): δ 8.71 (br s, 1H), 8.15 (d, \( J = 6.3 \) Hz, 1H), 7.38–7.27 (m, 1H), 7.27–7.19 (m, 6H), 7.17–7.12 (m, 1H), 5.57 (d, \( J = 2.7 \) Hz, 1H), 4.75 (dd, \( J = 9.9, 6.3 \) Hz, 1H), 4.21 (dd, \( J = 16.3, 9.9 \) Hz, 1H), 3.54 (dd, \( J = 16.3, 6.3 \) Hz, 1H), 2.11 (s, 3H), 1.87 (s, 3H). 13C NMR (100 MHz, CDCl\(_3\)): δ 196.7, 146.7, 145.3, 143.4, 140.0, 128.6, 127.7, 127.3, 126.6, 126.5, 126.3, 114.9, 107.9, 46.9, 38.5, 13.0, 11.0. HRMS (ESI-TOF) m/z: [M + H]** calculated for \( \text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2\text{H} \) 321.1598, found, 321.1594.

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