JOC The Journal of Organic Chemistry

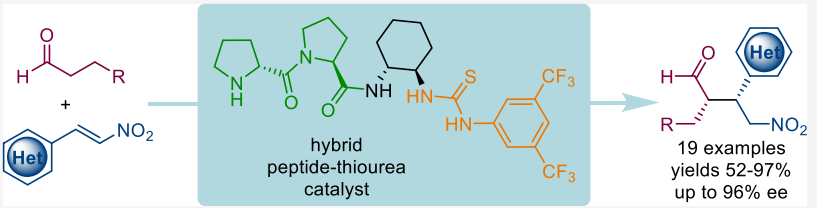
pubs.acs.org/joc Article

# Hybrid Peptide–Thiourea Catalyst for Asymmetric Michael Additions of Aldehydes to Heterocyclic Nitroalkenes

Patrícia Čmelová, Denisa Vargová, and Radovan Šebesta*

Cite This: https://dx.doi.org/10.1021/acs.joc.0c02251 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information




**ABSTRACT:** Bifunctional organocatalysis combining covalent and noncovalent activation is presented. The hybrid peptide–thiourea catalyst features a *N*-terminal proline moiety for aldehyde activation and a thiourea unit for electrophile activation. This catalyst effectively promotes asymmetric Michael additions of aldehydes to challenging but biologically relevant heterocycle-containing nitroalkenes. The catalyst can be used under solvent-free conditions. Spectroscopic and density functional theory studies elucidate the catalyst structure and mode of action.



## INTRODUCTION

Peptides and proteins occupy a central position in biology and medicine.[1] Short-chain peptides have found interesting applications in asymmetric organocatalysis.[2−7] Proline-derived secondary amine organocatalysts served as inspiration for the utilization of *N*-terminal proline moieties as a catalytically active unit within peptide catalysts. These peptide catalysts proved to be useful for asymmetric aldol reaction of ketones with aldehydes.[8−14] Enamine activation via proline-containing peptides is highly efficient for Michael additions. Wennemers and co-workers have developed peptide-catalyzed Michael additions of aldehydes to nitroalkenes,[15−21] disubstituted nitroalkenes,[22,23] or maleimides.[24] We have also shown that di- and tripeptides with a *N*-terminal proline moiety are useful for Michael additions.[25] These catalysts typically afford *syn*-configured Michael adducts because of (*E*)-*anti*-configured enamine. Interestingly, a tripeptide with *N*-terminal 5,5-dimethylpyrrolidine-2-carboxylic acid displayed antiselectivity in the Michael addition of aldehydes to nitroalkenes.[26] Kudo identified peptide aminocatalysts with a D-Pro moiety at the *N*-terminus and His residues.[27−29] Peptide organocatalysts work well also in aqueous media[30] or under solvent-free conditions.[31−33] Solid-supported peptides are attractive as recyclable catalysts[34−36] and allow flow setups of catalytic reactions.[37] Other amino acids also show interesting catalytic functions, for example, aspartic acid-based peptides are effective epoxidation catalysts.[38−41] Aspartic or glutamic acid was efficient as a secondary catalytically competent moiety within proline-based peptide aminocatalysts.[15,17] The carboxylic functional group improves the organization of reactants in the transition state via additional hydrogen bond interactions. The analyses of conformational properties of catalytically active peptides are quite complex, as was shown by Miller[42] and Wennemers.[43] Conformational flexibility and defined intramolecular arrangements of peptides offer unique possibilities for catalyst design. Hydrogen bond network as a defining catalytic motive was documented in various enzymes, for example, chorismate mutase[44] or chalcone isomerase.[45] This concept has also been recognized in small-molecule organocatalysts.[46] Thiourea is a prominent hydrogen-bond donor featuring in a number of organocatalysts, often combined with another activation unit, such as an amine, which provides a powerful tool for a variety of transformations.[47−51] Thiourea catalysts involving a tertiary amine functionality provided a blueprint for bifunctional activation. Takemoto described activation of pronucleophiles with a basic amine moiety, while electrophiles are activated by thiourea units.[52] Even though later computational and spectroscopic studies revealed a more complicated picture,[53,54] this basic idea remained the inspiration for bifunctional catalyst development. Secondary amines, such as pyrrolidines, for covalent activation of carbonyl compounds, have been realized.[55] A bifunctional proline-attached thiourea catalyst was developed for Michael additions of aldehydes to aromatic nitroalkenes.[56]

**Received:** September 18, 2020

In this context, we envisioned an organocatalyst, which would combine the enamine-activating ability of the proline residue and hydrogen-bond donating moiety, providing additional transition-state stabilization and organization to reagents. Furthermore, we hypothesized that spatial organization in a hybrid peptide−thiourea catalyst resulting from turn-inducing D-Pro-L-Pro arrangement and greater conformational flexibility of the dipeptide unit would be beneficial to catalyst performance (Figure 1).

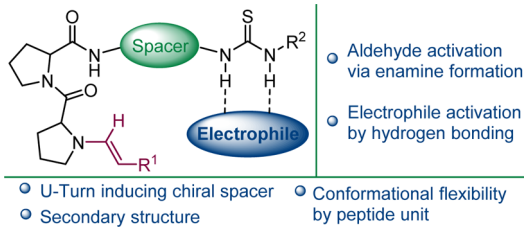



**Figure 1.** Design and proposed activation mode for the hybrid peptide−thiourea catalyst.

Herein, we present its synthesis and evaluation of its catalytic performance. This catalyst was applied to synthetically highly relevant Michael additions featuring heterocyclic moieties. There are reports mentioning isolated examples of heterocyclic nitroalkenes or those focusing on a particular structure, such as indolylnitroalkenes.[57] However, systematic investigations using heterocyclic nitroalkenes are very rare. Only very recently, Wennemers described peptide catalyzed Michael reactions of nitroalkenes bearing N-heterocycles.[58]

## RESULTS AND DISCUSSION

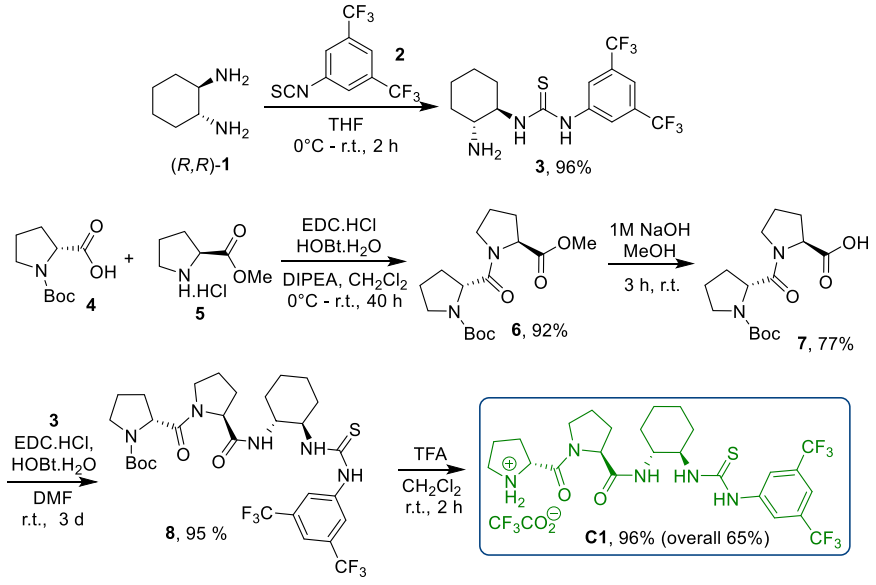
As a connecting spacer moiety between dipeptide and thiourea, we used *trans*-1,2-diaminocyclohexane (**1**), which combines desired bifunctionality, small-molecular weight and additional hydrogen bond donors. In addition, *trans*-1,2-diaminocyclohexane (**1**) is a potent stereo-inducing and U-turn-promoting unit, which has been utilized in many chiral reagents and catalysts.[59]

For the synthesis of catalyst **C1**, we envisioned a convergent approach. (1*R*,2*R*)-Cyclohexane-1,2-diamine (**1**) reacted with 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (**2**) affording thiourea fragment **3** in 96% yield. A H-(*R*)-Pro-(*S*)-Pro fragment was assembled using solution peptide coupling procedures from *N*-Boc-protected (*R*)-proline (**4**) with (*S*)-proline methyl ester (**5**). Basic ester hydrolysis of compound **6** afforded the desired dipeptide building block **7**, which was then coupled with thiourea **3** using the EDC/HOBt protocol. After the removal of the *N*-Boc-protecting group from the *N*-terminal proline moiety, catalyst **C1** was obtained in an overall yield of 65% (Scheme 1). This synthesis was performed on a gram scale, affording 1.50 g of catalyst **C1**.

To evaluate the catalytic ability of peptide−thiourea catalyst **C1**, we selected a Michael addition of 3-phenylpropanal (**9**) to indol-derived nitroalkene **10a**. Initial reaction conditions were inspired by our previous work with peptidic organocatalysts.[25] Employing 10 mol % of catalyst **C1**, this reaction afforded product **11a** as predominantly *syn*-isomer. To reach full conversion of the nitroalkene, a three-molar excess of the aldehyde was required. Solvents of medium polarity such as $CHCl_3$, DCM, and THF were adequate for this reaction. The enantioselectivity of the Michael addition decreased in highly polar DMF, which supports the notion that hydrogen bonds are crucial for the performance of catalyst **C1**. The most important results from the optimization of reaction conditions are summarized in Table 1.

Then, we tested acid additives and catalyst loading. Benzoic acid, 8 mol% of **C1**, and a temperature of −10 to 20 °C were the best reaction conditions (90% yield, 1:7 d.r. and 91% ee, see Supporting Information, Table S1). With optimum reaction conditions, we evaluated the scope of possible heterocyclic nitroalkenes **10a−i** with 3-phenylpropanal (**9**) as a model aldehyde (Scheme 2). The catalyst **C1** tolerated various heterocyclic skeletons within the nitroalkene, such as pyridine, indol, benzodioxole, thiophene, and furan. Michael adducts comprising ferrocenyl and naphthyl moiety were also obtained in good yields and high enantiomeric purities. All Michael adducts **11a−i** were obtained in synthetically relevant isolated yields (52−95%) and high enantiomeric purities (up

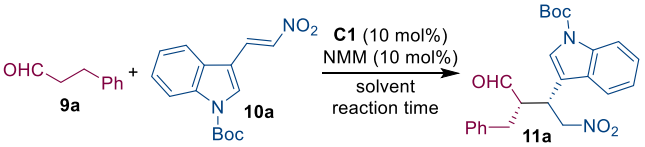
**Scheme 1. Synthesis of Catalyst C1**





https://dx.doi.org/10.1021/acs.joc.0c02251
J. Org. Chem. XXXX, XXX, XXX−XXX

**Table 1. Optimization of Reaction Conditions in the Michael Addition of Aldehyde 9a to Nitroalkene 10a**




| entry | solvent | time (h) | yield **11a** (%) | d.r.[a] | ee (syn)[b] |
|---|---|---|---|---|---|
| 1 | $CHCl_3$ | 24 | 94 | 1:7 | 91 |
| 2 | DCM | 24 | 97 | 1:7 | 91 |
| 3 | THF | 72 | 79 | 1:5 | 85 |
| 4 | DMF | 72 | 95 | 1:3.5 | 49 |
| 5 | *i*PrOH/DCM (2:1) | 24 | 96 | 1:3 | 81 |
| 6 | PhMe/DCM (7:1) | 48 | 97 | 1:6 | 90 |
| 7 | DCM/*i*PrOH (9:1) | 20 | 96 | 1:6 | 90 |
| 8 | $CHCl_3$/*i*PrOH (9:1) | 48 | 95 | 1:5 | 86 |

[a]Ratio of *anti*/*syn*-**11a** determined by $^1$H NMR of the crude reaction mixture. [b]Determined by chiral HPLC.

to 95% ee). These experiments were repeated at least two times with virtually the same yields and enantioselectivities. The practicality and synthetic applicability of catalyst **C1** and this procedure were demonstrated on a gram scale. In this experiment, 1.2 g (86%) of adduct **11c** was obtained with d.r. 1:13 and enantiomeric purities of 96 and 94% ee, respectively.

With nitroalkenes **10c** and **10d**, we have probed aldehyde scope. The peptide−thiourea catalyst **C1** worked very well for aldehydes carrying both linear and branched aliphatic chains as well as aromatic substituents. The Michael additions afforded corresponding adducts **12a−i** in high yields and enantiomeric purities (Scheme 3). Diastereomeric purities ranged from 1:23 to 1:1.5 in favor of *syn*-isomers. In the case of branched aliphatic aldehyde, the yield and enantiomeric purity of the corresponding Michael adduct **12h** was slightly compromised. Furthermore, we have also prepared compound **12j**, which has a fluorine substituent.

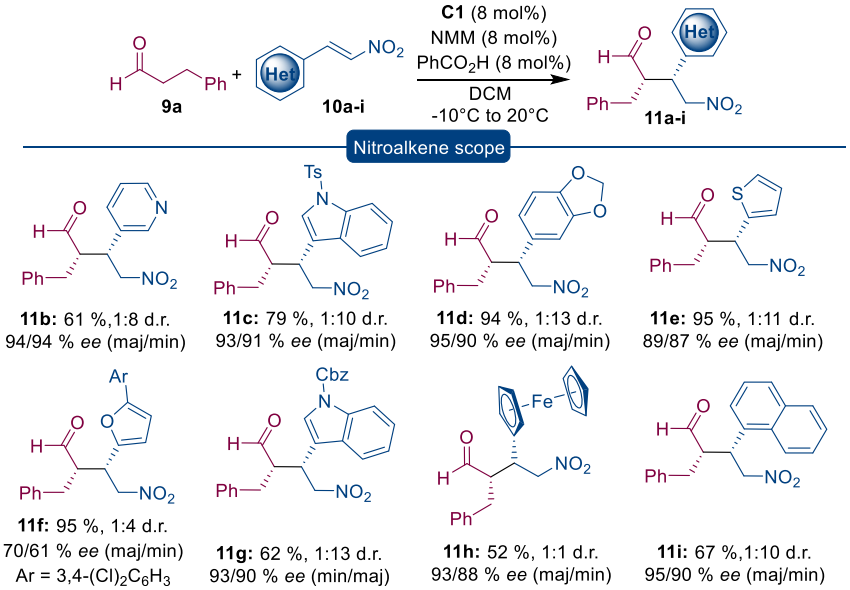
Even though Michael additions of heterocyclic nitroalkenes promoted by catalyst **C1** worked well in solvents of medium polarity, we were curious to test the effect of solvent-free ball-milling conditions. The exclusion of harmful organic solvents is an important effort toward more sustainable chemical production. Furthermore, many chemical reactions are much faster under solvent-free conditions than in solution.[60−62] Sometimes, even product selectivities might be altered with mechanochemical activation.[63] Regarding enantioselective organocatalysis, an interesting question is whether the absence of solvation can promote reactant−catalyst interactions, which are mediated by noncovalent interactions. Our previous studies showed that ball milling could be highly beneficial for Michael additions.[64,65]

Therefore, we have tested catalyst **C1** under solvent-free ball-milling conditions. Tables S2 and S3 contain results for optimization of reaction conditions under solvent-free set-up. These experiments showed that catalyst **C1** could be used under solvent-free conditions. Corresponding Michael adducts were obtained in somewhat lower yields under solvent-free conditions than in solution. Lower yields in some cases were caused by the gradual decomposition of starting materials under ball-milling conditions. Importantly, reaction times were considerably shorter in ball-milling experiments, and adducts **11** were formed with high enantiomeric purities (Scheme 4). Interestingly, also, diastereoselectivities were altered under ball-milling conditions. Overall, the exclusion of the solvent in this reaction does not lead to an increase in stereoselectivity. This result could probably be attributed to the secondary heating of the reaction mixture during milling caused by friction and ball impacts.

To demonstrate the usefulness of obtained Michael adducts, we have carried out reductive cyclization. Using activated zinc in acetic acid, corresponding 3,4-disubstituted pyrrolidines **13a** and **13b** were obtained (Scheme 5). These kind of pyrrolidines may have useful antibacterial properties.[66]

We have studied the structure of catalyst **C1** and its possible mode of action by NMR, circular dichroism (CD), and density functional theory (DFT) calculations. We have tried to identify intramolecular hydrogen bonds within catalyst **C1** by $^1$H NMR spectroscopy in various solvents (see Supporting Information

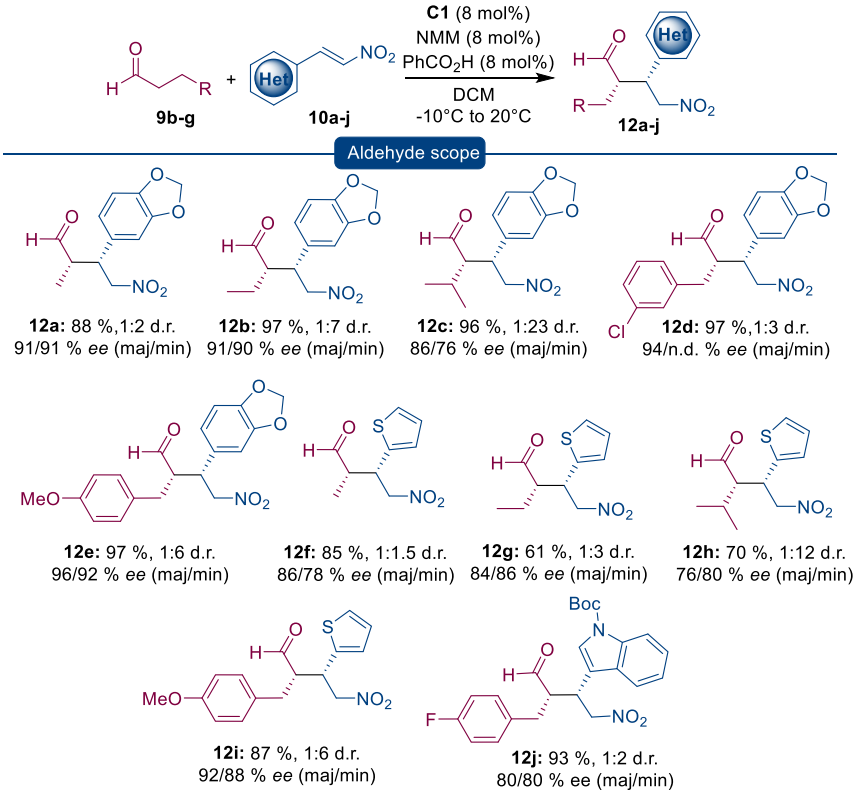
**Scheme 2. Nitroalkene Scope of the Michael Addition Catalyzed by Catalyst C1**



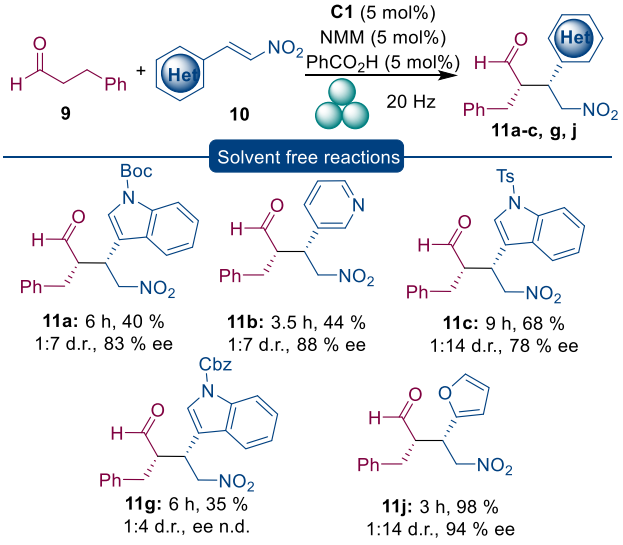


https://dx.doi.org/10.1021/acs.joc.0c02251
J. Org. Chem. XXXX, XXX, XXX−XXX

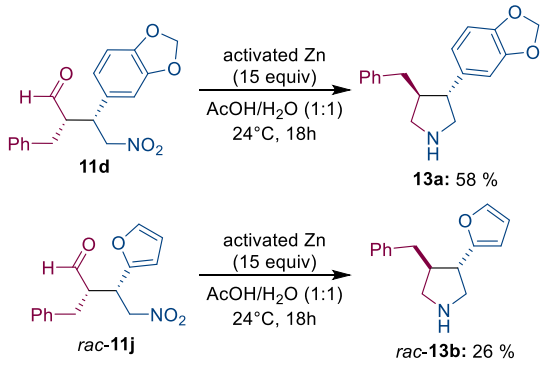
**Scheme 3. Aldehyde Scope in the Michael Addition with Heterocyclic Nitroalkenes**




**Scheme 4. Efficiency of Catalyst C1 under Solvent-Free Conditions**




**Scheme 5. Reductive Cyclization of Michael Adducts**




for more details, Figure S13) and subsequent addition of deuterium oxide. Partial H/D exchange upon $D_2O$ addition suggests that several NH protons engage in hydrogen bonding. To gain a clearer picture, we have conducted dimethyl sulfoxide (DMSO) titration.[67] In this experiment, highly Lewis-basic DMSO-$d_6$ was gradually added to a $CD_2Cl_2$ solution of catalyst **C1**. Chemical shifts of protons that rise and then gradually decrease were likely exposed to interactions with DMSO and thus were not engaged in intramolecular hydrogen bonds. DMSO titration suggests that amidic and thiourea NH protons are likely engaged in intramolecular hydrogen bonds (Figure 2a, for spectra, see Figure S11). Additional $^1$H NMR experiments suggest that catalyst **C1** does not aggregate (Figures S1–S4). $^1$H NMR measurements also support the notion that in the energetically lowest conformer, the thiourea moiety adopts anti-syn conformation, which is transferred to the reactive anti-anti conformation upon the addition of a nitroalkene (see Supporting Information for more details). An additional indication of the possible secondary structure of catalyst **C1** is provided by CD spectroscopy (Figure 2b). CD spectra of **C1** have a similar character in two different solvents (MeOH and DCM). This resemblance of CD spectra hints that catalyst **C1** features some intramolecular hydrogen bonds that are not accessible to interaction with the solvent.

We have investigated the catalyst structure by DFT calculations. The conformational analysis identified conformers, which were then geometrically optimized at the B3LYP-D3/6-31G* level and energies refined at the M06-2X/


https://dx.doi.org/10.1021/acs.joc.0c02251
J. Org. Chem. XXXX, XXX, XXX−XXX

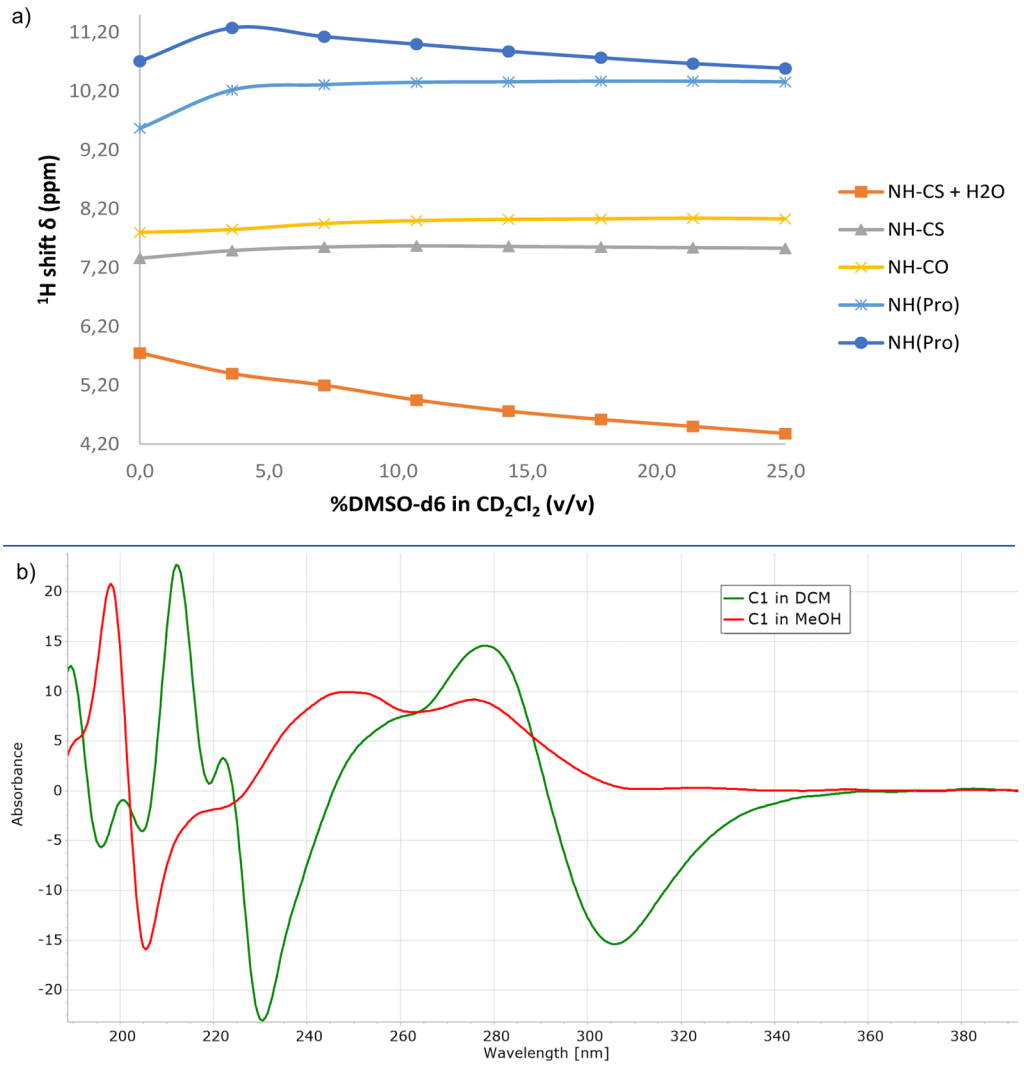



**Figure 2.** (a) DMSO titration of **C1**. (b) CD spectra of **C1** in MeOH and DCM.

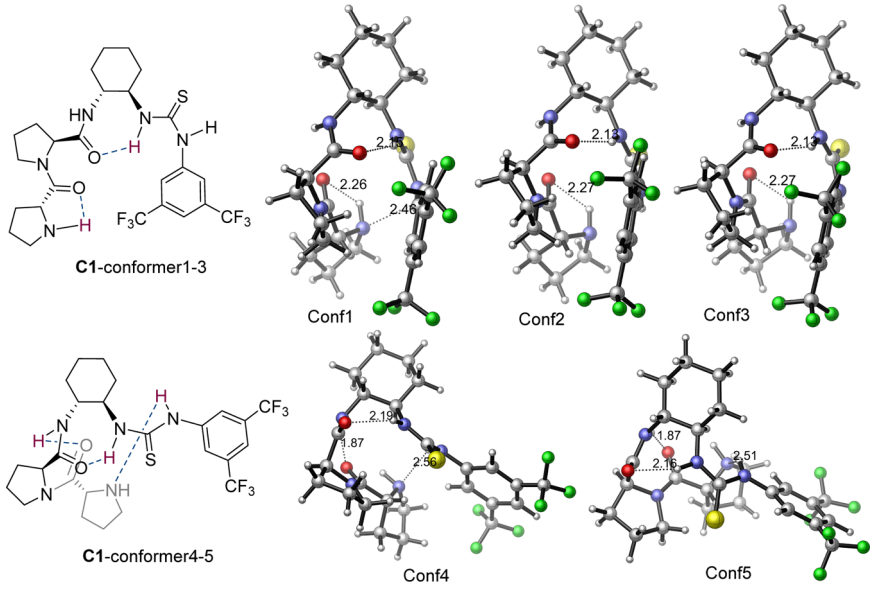



**Figure 3.** Five energetically lowest conformers of catalyst **C1** obtained at B3LYP-D3/6-31G*//M06-2X/Def2-TZVP (IEFPCM = DCM).

Def2-TZVP level. Solvent effects were accounted for by the polarizable continuum model (PCM) using the integral equation formalism variant (IEFPCM).[68] Their calculations suggest that catalyst **C1** forms a U-turn secondary structure,



https://dx.doi.org/10.1021/acs.joc.0c02251
J. Org. Chem. XXXX, XXX, XXX−XXX

which is stabilized by internal hydrogen bonds. Three energetically most favorable conformers have similar structures, which involves an intramolecular hydrogen bond between thiourea NH and amidic CO. Additionally, they have a hydrogen bond between proline moieties. Conformers 4 and 5 have a slightly different structure with a rotated thiourea moiety. Also, these structures feature a hydrogen bond between thiourea NH and amidic CO (Figure 3).

Enamine formation between catalyst **C1** and isovaleraldehyde (**9d**) was confirmed by HRMS. The peak corresponding to the $[M + H]^+$ ion at $m/z$ 648.2979 and dimeric species $[2M + H]^+$ at $m/z$ 1295.5539 was observed (see Supporting Information for more information).

DFT calculations were also utilized in the investigation of the action of catalyst **C1** in the Michael addition of aldehydes to heterocyclic nitroalkenes. For these calculations, we have employed the hybrid exchange−correlation functional B3LYP,[69] with Grimme's D3 dispersion correction,[70] which accounts well for noncovalent interactions. Energies were refined by single-point calculations at the M06-2X/Def2-TZVP (IEFPCM = DCM) level. Figure 4 shows the DFT-calculated

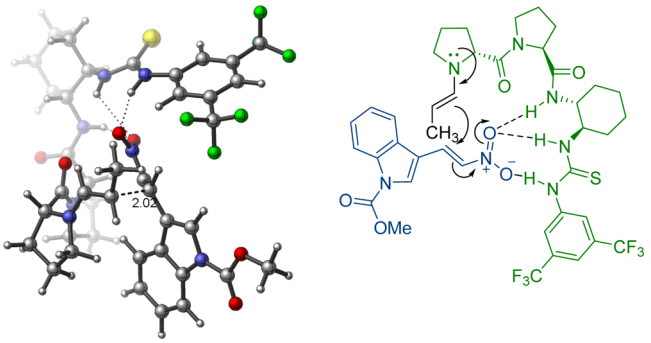



**Figure 4.** B3LYP-D3/6-31G*//M06-2X/Def2-TZVP (DCM)-calculated transition state for the **C1**-catalyzed Michael addition.

transition state, which would lead to the major stereoisomer of the Michael adduct. In this transition state, *E-anti* enamine formed at the *N*-terminal proline unit attacks nitroalkene, which is held by hydrogen bonds by the thiourea moiety and Pro-amidic proton. The most energetically favored arrangement of nitroalkene and enamine fragment is eclipsed, but it has the most hydrogen-bonding interactions with the catalyst.

The reaction of 3-(4-fluorophenyl)propanal (**9g**) with nitroalkene **10a** was monitored by $^{19}F$ NMR (Figure 5). The reaction profile shows a steady increase of the product **12j** concentration with a corresponding decrease of the concentration of the starting material. Because the aldehyde was used in excess (aldehyde/nitroalkene 3:1), the conversion of the Michael addition was practically complete.

## CONCLUSIONS

In conclusion, we have designed a hybrid peptide−thiourea catalyst featuring an enamine activation proline unit, a network of hydrogen bond donors for electrophile activation. The two fragments are connected by *trans*-cyclohexane-1,2-diamine, an additional stereogenic unit, which likely helps the catalyst to adopt a U-turn arrangement. The catalyst's secondary structure is stabilized by intramolecular hydrogen bonds. This catalyst proved to be efficient for Michael additions of aldehydes to heterocycle-containing nitroalkenes, affording the corresponding chiral heterocyclic products in high yields and diastereo-

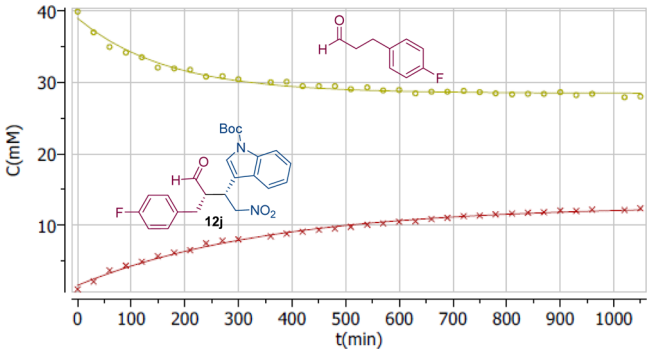



**Figure 5.** $^{19}F$ NMR reaction profile between aldehyde **9g** and nitroalkene **10a**. Catalyst **C1** (2.9 mg, 0.004 mmol) and NMM (0.4 mg, 0.004 mmol) were dissolved in $CDCl_3$ (0.6 mL). Then, nitroalkene **10j** (15 mg, 0.05 mmol) and $PhCO_2H$ (0.5 mg, 0,004 mmol) were added. The reaction mixture was stirred 10 min at room temperature, aldehyde **9g** (23.8 mg, 0.16 mmol) was added dropwise, and the resulting mixture was transferred to the NMR tube followed by $^{19}F$ NMR 24 h at 20 °C. The crude product was purified by flash chromatography ($SiO_2$, gradient 100% hexane to 90:10 hexane/EtOAc) to afford product **12j** (20.5 mg, 93%).

and enantiomeric purities. NMR and computational studies provided insights into the catalyst structure and mode of operation.

## EXPERIMENTAL SECTION

**General.** All chemicals and solvents were purchased from Alfa Aesar or Sigma-Aldrich. Reactions in solution were performed under an inert atmosphere of Ar or $N_2$. The solvents were purified and dried according to the standard techniques. Thin-layer chromatography (TLC) was performed on Merck TLC plate silica gel 60, F-254, or on $Al_2O_3$ TLC plates. Compounds were visualized by irradiation with UV light and/or by treatment with solutions of $KMnO_4$, ninhydrin, or bromocresol green reagent. Products of Michael addition from reaction mixtures after general workup were separated by flash chromatography using Isolera Biotage FSKO-1107-0010. NMR spectra were recorded on Varian NMR system 600 (600 MHz for $^1H$ and 151 MHz for $^{13}C$). Chemical shifts ($\delta$) are given in ppm relative to tetramethylsilane. Melting points were measured on an M-565 Büchi. High-resolution mass spectra were recorded on Orbitrap Elite Thermo Scientific Velos Pro in ionization mode: heated electrospray ionization (HESI). Enantiomeric excesses were determined by chiral HPLC using Daicel CHIRALCEL AS-H, OJ-H, and IC columns with isopropyl alcohol and hexane as the eluents. Optical rotations were recorded on a Jasco P-2000 polarimeter.

**Synthesis of Catalyst C1.** The peptide fragment of catalysts was prepared by solution-phase synthesis. The syntheses of peptide catalysts were carried out according to the standard methods of solution-phase synthesis of peptides.[23,71−74]

*(R)-tert-Butyl-2-((S)-2-(methoxycarbonyl)pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate* (**6**). Solution of *N*-Boc-D-Pro-OH **4** (2.0 g, 9.3 mmol), HCl·H-L-Pro-OMe **5** (1.7 g, 10.2 mmol), EDC·HCl (2.1 g, 11.2 mmol), and HOBt·$H_2O$ (1.7 g, 11.2 mmol) in anhydrous $CH_2Cl_2$ (40 mL) was cooled in ice bath under a nitrogen atmosphere. DIPEA ($i$PrNEt$_2$) (3.7 mL) was added dropwise over 10 min, and the resulting yellow solution was stirred for an additional 20 min at 0 °C. After that, the homogeneous yellow reaction mixture was warmed up to room temperature and stirred for 24 h. The mixture was diluted with 40 mL of 0.1 M HCl, and the layers were separated. The aqueous phase was extracted with DCM (3 × 20 mL). The combined organic phases were washed with 1 M $NaHCO_3$ solution (40 mL), water (40 mL), and brine (40 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product (**6**) was used in the next step without further purification.


https://dx.doi.org/10.1021/acs.joc.0c02251
J. Org. Chem. XXXX, XXX, XXX−XXX

It was obtained as a mixture of conformers (2.75 g, 91%) as a white solid. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 5.03−4.13 (m, 2H), 4.01−3.32 (m, 7H), 2.42−1.77 (m, 8H), 1.49−1.36 (m, 9H). The spectral data are in accordance with those reported in the literature.[23]

*(S)-1-((R)-1-(tert-Butoxycarbonyl)pyrrolidine-2-carbonyl)-pyrrolidine-2-carboxylic Acid (**7**).* To a solution of *N*-Boc-D-Pro-L-Pro-OMe (**6**) (0.97 g, 3.0 mmol) in MeOH (12 mL), was added 1 M NaOH (4.7 mL). The resulting colorless solution was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the resulting aqueous phase was acidified to pH 1 with 1 M solution of HCl (aq) and extracted with $CH_2Cl_2$ (3 × 12 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford the title compound. The crude product (**7**) was used in the next step without further purification.

It was obtained as a mixture of conformers, as a white solid (0.74 g, 77%). mp 195−196 °C recrystallized from EtOAc (lit.[75] 196−197 °C); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 4.62 (m, 1H), 4.45 (m, 1H), 4.48−4.43 (m, 1H), 3.77 (m, 1H), 3.61−3.43 (m, 1H), 2.50 (m, 1H), 2.29−1.85 (m, 8H), 1.44−1.40 (m, 9H). The spectral data are in accordance with those reported in the literature.[23]

*1-((1R,2R)-2-Aminocyclohexyl)-3-(3,5-bis(trifluoromethyl)-phenyl)thiourea (**3**).* Solution of (1*R*,2*R*)-cyclohexane-1,2-diamine (***R*,*R*-1**) (0.74 g, 6.5 mmol) in anhydrous THF (36 mL) was cooled to 0 °C. Then, the solution of 1-isothiocyanato-3,5-bis-(trifluoromethyl)benzene (**2**) (1.20 g, 4.3 mmol) in anhydrous THF (24 mL) was added dropwise over 20 min and the resulting homogeneous reaction mixture was stirred at 0 °C another 20 min. The resulting solution stirred at room temperature, and the reaction progress was monitored by TLC (DCM/MeOH 90:10). After 2 h, full conversion to the desired product was observed. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (DCM/MeOH 90:10) to afford the title compound **3**.

It was obtained as pale yellow foam (1.50 g, 90%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 8.03 (s, 2H), 7.58 (s, 1H), 6.29 (s, 1H), 3.38 (s, 1H), 2.71 (m, 1H), 2.06 (m, 1H), 1.96 (m, 1H), 1.79 (m, 2H), 1.37−1.20 (m, 5H). The spectral data are in accordance with those reported in the literature.[23]

*(R)-tert-Butyl-2-((S)-2-(((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)-phenyl)thioureido)cyclohexyl)carbamoyl)pyrrolidine-1-carbonyl)-pyrrolidine-1-carboxylate (**8**).* The solution of thiourea **3** (1.10 g, 2.85 mmol), dipeptide *N*-D-Pro-L-Pro-OH **7** (0.89 g, 2.85 mmol), EDC·HCl (0.65 g, 3.43 mmol), and HOBt·$H_2O$ (0.52 g, 3.43 mmol) in anhydrous DMF (7 mL) was stirred at room temperature 24 h, and the reaction progress was monitored by TLC (EtOAc/MeOH, 95:5). After full conversion to the desired product, the reaction mixture was poured into ice-cold water (approx 70 mL), and the formed precipitate was filtrated and washed with ice-cold water (3×). The crude product was purified by flash chromatography (gradient 100% EtOAc to 95:5 EtOAc/MeOH) to afford the title compound **8**.

It was obtained as a white solid (1.76 g, 91%). mp 137−139 °C $[\alpha]_D^{20}$ +32.5 (*c* 1, MeOH). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 9.66 (br s, 1H), 8.13 (s, 2H), 7.68 (br s, 1H), 7.54 (s, 1H), 7.17 (br s, 1H), 4.63−4.32 (m, 2H), 4.08−3.66 (m, 2H), 3.60−3.20 (m, 3H), 2.32 (m, 1H), 2.20−1.61 (m, 12H), 1.47 (s, 9H), 1.42−1.26 (m, 4H); $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$): $\delta$ 181.0, 172.6, 172.0, 154.6, 141.5, 131.1 (q, *J* = 34 Hz, 2C), 121.5 (q, *J* = 272 Hz, 2C), 122.5, 117.0, 79.9, 60.8, 57.9, 57.4, 53.8, 47.1, 32.7, 31.6, 29.7, 29.5, 28.6 (3C), 28.3, 25.1, 24.5, 24.5, 24.0; IR (ATR) $\nu$: 3304, 2937, 1623, 1533, 1384, 1275, 1128, 969, 884, 754, 680 cm$^{-1}$; HRMS (HESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{30}H_{39}F_6N_5O_4SNa$, 702.2519; found, 702.2520.

*(R)-2-((S)-2-(((1R,2R)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)-thioureido)cyclohexyl)carbamoyl)pyrrolidine-1-carbonyl)-pyrrolidin-1-ium (**C1**).* To the solution of *N*-Boc-PTU **8** (1.53 g, 2.25 mmol) in anhydrous $CH_2Cl_2$ (30 mL), was added TFA (5.33 mL, 52.76 mmol), and the reaction mixture was stirred for 16 h at room temperature. The volatile components were evaporated to dryness, and the oily residue was redissolved and coevaporated with toluene (3×). The resulting residue was triturated with a solution of $Et_2O$/hexane (1:2) to afford the title compound **C1**.

It was obtained as a pale brown solid (1.50 g, 96%). mp 76−79 °C; $[\alpha]_D^{20}$ +63.9 (*c* 1, MeOH); $^1$H NMR (600 MHz, $CD_3OD$): $\delta$ 8.21 (br s, 1H), 8.14 (s, 2H), 7.68 (s, 1H), 7.66 (br s, 1H), 4.51 (m, 1H), 4.41 (m, 1H) 3.72 (m, 1H), 3.46 (m, 1H), 2.49 (m, 1H), 2.22−1.87 (m, 12H), 1.82 (m, 3H), 1.45−1.27 (m, 7H); $^{13}$C{$^1$H} NMR (151 MHz, $CD_3OD$): $\delta$ 181.2, 172.5, 172.0, 167.5, 141.6, 131.2 (q, *J* = 34 Hz, 2C), 123.3 (q, *J* = 272 Hz, 2C), 123.0, 116.8, 61.2, 59.2, 54.3, 47.1, 46.3, 31.5, 31.2, 29.2, 28.0, 24.5, 24.2, 24.2, 24.0; IR (ATR) $\nu$: 3287, 3060, 2936, 1644, 1534, 1382, 1275, 1123, 967, 700, 680 cm$^{-1}$; HRMS (HESI) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{32}F_6N_5O_2S$, 580.2175; found, 580.2176.

**General Procedure for Michael Addition in Solution.** The catalyst **C1** (7.7 mg, 0.011 mmol) and NMM (1.12 mg, 0.011 mmol) were dissolved in 0.9 mL of DCM, and the reaction mixture was stirred for 10 min at room temperature. Then, nitroalkene **10** (0.14 mmol) was added, and the same mol % of the acidic additive like mol % of the catalyst was added. The reaction mixture was cooled to −10 °C, and after 10 min of stirring, an aldehyde **9** (0.42 mmol) was added dropwise, and the resulting reaction mixture was stirred at −10 °C to 20 °C. The reaction time was monitored by TLC, followed by a concentration of the reaction mixture. The crude product was purified by flash chromatography ($SiO_2$, gradient hexane to hexane/EtOAc 90:10) to afford the desired products **11** and **12**.

**General Procedure for Michael Addition in Solvent-Free Conditions.** A mixture of nitroalkene **10** (0.14 mmol), aldehyde **9** (0.83 mmol), the catalyst **C1** (9.62 mg, 0.014 mmol), NMM (1.40 mg, 0.014 mmol), and benzoic acid (1.69 mg, 0.014 mmol) was ball-milled at 20 Hz. The reaction time was monitored by TLC, and the crude product was then purified by flash chromatography ($SiO_2$, gradient hexane to hexane/EtOAc 90:10) to afford the desired product **11** in yields; diastereomeric and enantiomeric purities are reported in Scheme 4.

**Characterization Data for Michael Adducts.** Note: In NMR spectra, peaks for minor diastereomers are typed in italics.

*tert-Butyl 3-((2R,3S)-3-Benzyl-1-nitro-4-oxobutan-2-yl)-1H-indole-1-carboxylate (**11a**).* Pale yellow oil (54 mg, 93%). $[\alpha]_D^{20}$ −10.2 (*c* 1, $CHCl_3$); $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 9.74 (d, 1.9 Hz, 1H), *9.69 (d, J = 1.9 Hz, CHO—minor diastereomer)*, 8.20−8.11 (m, 1H), 7.51 (m, 1H), 7.43 (m, 1H), 7.39−7.28 (m, 2H), 7.27−7.21 (m, 3H), 7.10−7.05 (m, 2H), 4.94−4.76 (m, 2H), 4.22−4.10 (m, 1H), 3.34−3.19 (m, 1H), 3.09−2.83 (m, 2H), 1.69 (s, 9H); $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$): $\delta$ 202.9, 149.3, 137.2, 129.1, 128.9, 128.9, 128.8, 128.6, 128.5, 128.4, 128.4, 127.0, 125.1, 124.3, 123.0, 118.6, 116.1, 115.7, 84.4, 76.7, 54.5, 34.8, 34.2, 28.2; *$^{13}$C NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 202.8, 149.3, 137.2, 128.4, 128.4, 127.0, 125.1, 124.4, 123.0, 118.7, 115.6, 76.9, 53.7, 35.0, 33.5, 26.9.*; IR (ATR) $\nu$: 2924, 2853, 2731, 2114, 2092, 1942, 1721, 1603, 1551, 1496, 1451, 1369, 1309, 1255, 1220, 1151, 1095, 1020, 912, 853, 744, 698 cm$^{-1}$; HRMS (HESI) *m*/*z*: $[M - H]^-$ calcd for $C_{24}H_{25}N_2O_5$, 421.1769; found, 421.1777; HPLC: CHIRALCEL IC, hexane/*i*PrOH 80:20, 1 mL/min, $\lambda$ = 216 nm, $t_{R1(maj)}$ = 39.23, 30.09; $t_{R2(min)}$ = 13.28, 21.29 min.

*(2S,3R)-2-Benzyl-4-nitro-3-(pyridin-3-yl)butanal (**11b**).* Pale yellow oil (46 mg, 61%). $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 9.71 (d, *J* = 1.7 Hz, 1H), *9.57 (d, J = 1.7 Hz, CHO—minor diastereomer)*, 8.59−8.42 (m, 2H), 7.59−7.53 (m, 1H), 7.34−7.26 (m, 2H), 7.25−7.10 (m, 3H), 7.03−6.88 (m, 1H), 4.87 (dd, *J* = 15.0, 7.6 Hz, 1H), 4.78−4.68 (m, 1H), 3.84 (dd, *J* = 8.9, 6.0 Hz, 1H), 3.20−2.97 (m, 1H), 2.87−2.59 (m, 2H); $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$): $\delta$ 202.1, 150.2, 149.6, 136.4, 135.5, 132.8, 129.0, 128.7, 128.5, 128.5, 127.2, 123.9, 77.3, 54.7, 40.9, 34.2; *$^{13}$C NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 202.3, 149.7, 149.6, 136.5, 136.0, 132.0, 129.1, 128.7, 128.4, 127.3, 123.8, 77.1, 54.1, 41.6, 33.5*; IR (ATR) $\nu$: 3027, 2923, 2740, 1719, 1545, 1495, 1454, 1427, 1377, 1331, 1265, 1183, 1106, 1026, 989, 913, 847, 811, 749, 699, 627 cm$^{-1}$; HRMS (HESI) *m*/*z*: $[M - H]^-$ calcd for $C_{16}H_{15}N_2O_3$, 283.1093; found, 283.1088; HPLC: CHIRALCEL AS-H, hexane/*i*PrOH 70:30, 0.75 mL/min, $\lambda$ = 218 nm, $t_{R1(maj)}$ = 29.66, 31.88; $t_{R2(min)}$ = 38.40, 48.16 min.


https://dx.doi.org/10.1021/acs.joc.0c02251
J. Org. Chem. XXXX, XXX, XXX−XXX

*(2S,3R)-2-Benzyl-4-nitro-3-(1-tosyl-1H-indol-3-yl)butanal (**11c**).* Pale yellow oil (44 mg, 79%). $[\alpha]_D^{25}$ −5.26 (*c* 1, $CHCl_3$) $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.72 (d, *J* = 1.6 Hz, 1H), *9.63 (d, J = 1.6 Hz, CHO—minor diastereomer)*, 7.98 (m, 1H), 7.69 (t, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 22.0 Hz, 1H), 7.39−7.27 (m, 3H), 7.25−7.18 (m, 5H), 7.04−6.97 (m, 2H), 4.90−4.69 (m, 2H), 4.19−4.00 (m, 1H), 3.31−3.12 (m, 1H), 3.01−2.75 (m, 2H), 2.32 (s,, 3H), *2.30 (s, $CH_3$—minor diastereomer)*. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 202.5, 145.3, 137.0, 135.3, 134.6, 130.0, 129.1, 128.9, 128.8, 127.1, 126.7, 125.5, 124.9, 123.7, 119.0, 118.4, 114.2, 76.7, 54.3, 34.6, 34.1, 21.5; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 202.5, 136.8, 135.1, 134.6, 129.6, 127.1, 126.8, 125.5, 125.1, 123.7, 119.1, 117.9, 114.0, 76.7, 53.8, 34.8, 33.3, 21.6.* Spectral data agree with those in the literature.[57] HPLC: CHIRALCEL IC, hexane/*i*PrOH 70:30, 0.9 mL/min, λ = 254 nm, $t_{R1(maj)}$ = 54.33, 70.57; $t_{R2(min)}$ = 37.74, 57.94 min.

*(2S,3R)-3-(Benzo[d][1,3]dioxol-5-yl)-2-benzyl-4-nitrobutanal (**11d**).* Pale yellow oil (64 mg, 94%). $[\alpha]_D^{20}$ −3.96 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) δ 9.70 (d, *J* = 2.1 Hz, 1H), *9.55 (d, J = 2.0 Hz, CHO—minor diastereomer)*, 7.33−7.26 (m, 2H), 7.25−7.02 (m, 3H), 6.78 (dd, *J* = 17.4, 7.9 Hz, 1H), 6.69−6.60 (m, 2H), 6.00−5.96 (m, 2H), 4.84−4.60 (m, 2H), 3.74 (td, *J* = 9.5, 5.0 Hz, 1H), 3.07−2.84 (m, 2H), 2.80−2.77 (m, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 203.0, 148.4, 147.6, 137.1, 130.2, 128.9, 128.8, 128.5, 128.4, 127.0, 121.7, 108.8, 108.0, 101.4, 78.2, 55.4, 43.3, 34.3; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 203.1, 137.2, 129.3, 128.9, 128.8, 128.6, 128.4, 128.4, 127.1, 122.0, 108.7, 108.6, 78.0, 54.4, 44.3, 33.8;* IR (ATR) ν: 2901, 2733, 2121, 1718, 1604, 1549, 1488, 1443, 1377, 1246, 1105, 1037, 933, 905, 863, 813, 750, 700, 653 $cm^{-1}$; HRMS (HESI) *m*/*z*: $[M - H]^-$ calcd for $C_{18}H_{16}NO_5$, 326.1034; found, 326.1040; HPLC: CHIRALCEL IC, hexane/*i*PrOH 85:15, 1 mL/min, λ = 216 nm, $t_{R1(maj)}$ = 25.44, 33.498; $t_{R2(min)}$ = 30.68, 39.49 min.

*(2S,3S)-2-Benzyl-4-nitro-3-(thiophen-2-yl)butanal (**11e**).* Pale yellow oil (71 mg, 95%). $[\alpha]_D^{20}$ +1.56 (*c* 0.25, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.70 (d, *J* = 1.7 Hz, 1H), *9.67 (d, J = 1.6 Hz, CHO—minor diastereomer)*, 7.34−7.25 (m, 3H), 7.23 (m, 1H), 7.13 (dd, *J* = 34.8, 7.1 Hz, 2H), 6.98 (m, 1H), 6.94−6.88 (m, 1H), 4.88−4.65 (m, 2H), 4.22 (td, *J* = 8.3, 5.8 Hz, 1H), 4.22−4.10 (m, 1H), 3.14−3.02 (m, 1H), 2.88 (m, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 202.3, 139.3, 137.9, 137.1, 129.0, 128.9, 128.8, 127.6, 127.2, 127.1, 125.6, 78.3, 55.9, 39.0, 33.9; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 202.6, 139.3, 137.1, 128.9, 127.2, 127.1, 125.8, 78.4, 54.5, 39.4, 33.5;* IR (ATR) ν: 2920, 2837, 2737, 1719, 1548, 1496, 1454, 1430, 1376, 1251, 1201, 1079, 1030, 913, 850, 747, 697, 520, 486 $cm^{-1}$; HRMS (HESI) *m*/*z*: $[M - H]^-$ calcd for $C_{15}H_{14}NO_3S$, 288.0700; found, 288.0705; HPLC: CHIRALCEL IC, hexane/*i*PrOH 90:10, 1 mL/min, λ = 216 nm, $t_{R1(maj)}$ = 26.74, 39.24; $t_{R2(min)}$ = 20.97, 33.12 min.

*(2S,3S)-2-Benzyl-3-(5-(3,4-dichlorophenyl)furan-2-yl)-4-nitrobutanal (**11f**).* Pale yellow oil (56 mg, 95%). $[\alpha]_D^{20}$ −13.7 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.79 (d, *J* = 1.3 Hz, 1H), *9.77 (d, J = 1.7 Hz, CHO—minor diastereomer)*, 7.65 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.47−7.38 (m, 2H), 7.31 (m, 3H), 7.18−7.10 (m, 2H), 6.61 (dd, *J* = 8.8, 3.4 Hz, 1H), 6.32 (dd, *J* = 7.3, 3.4 Hz, 1H), 4.86−4.61 (m, 2H), 4.17−3.98 (m, 1H), 3.28−3.09 (m, 1H), 3.01−2.77 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 201.5, 151.9, 150.5, 149.9, 137.0, 133.0, 131.5, 130.8, 130.0, 129.0, 128.8, 128.3, 127.1, 125.4, 122.9, 111.8, 107.2, 75.7, 53.8, 37.7, 33.4; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 201.8, 151.9, 150.5, 149.9, 137.0, 133.1, 131.4, 130.8, 130.0, 128.8, 128.4, 127.2, 125.4, 122.9,111.3, 107.3, 75.8, 53.2, 37.3, 33.4;* IR (ATR) ν: 2922, 2852, 2731, 1719, 1603, 1550, 1496, 1465, 1437, 1376, 1340, 1278, 1180, 1135, 1066, 1027, 939, 877, 820, 789, 741, 698, 550, 486, 436 $cm^{-1}$; HRMS (HESI) *m*/*z*: $[M - H]^-$ calcd for $C_{21}H_{16}Cl_2NO_4$, 416.0462; found, 416.0461; HPLC: CHIRALCEL IC, hexane/*i*PrOH 85:15, 1 mL/min, λ = 212 nm, $t_{R1(maj)}$ = 21.47, 23.56; $t_{R2(min)}$ = 18.54, 26.44 min.

*Benzyl 3-((2R,3S)-3-Benzyl-1-nitro-4-oxobutan-2-yl)-1H-indole-1-carboxylate (**11g**).* Pale yellow oil (35 mg, 62%). $[\alpha]_D^{20}$ −3.11 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.73 (d, *J* = 1.8 Hz, 1H), *9.67 (d, J = 1.6 Hz, CHO—minor diastereomer)*, 8.19 (s, 1H), 7.54 (m, 1H), 7.50 (d, *J* = 6.9 Hz, 2H), 7.46−7.35 (m, 5H), 7.28 (m, 2H), 7.22 (m, 2H), 7.06 (dd, *J* = 8.5, 6.9 Hz, 2H), 5.46 (s, 2H), 4.94−4.73 (m, 2H), 4.22−4.05 (m, 1H), 3.35−3.19 (m, 1H), 3.01−2.80 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 202.7, 150.4, 139.2, 137.1, 134.8, 129.1, 129.0, 128.9, 128.9, 128.8, 128.8, 128.8, 128.7, 128.5, 127.1, 125.5, 125.1, 124.0, 123.4, 118.6, 115.8, 76.6, 69.1, 54.4, 34.7, 34.2, 33.5; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 202.8, 139.2, 137.1, 134.9, 129.1, 129.0, 128.9, 128.8, 128.7, 128.7, 128.6, 128.6, 128.6, 128.6, 128.5, 127.0, 125.5, 125.2, 123.4, 118.8, 115.8, 76.7, 68.9, 53.7, 34.8;* IR (ATR) ν: 3482, 3028, 2925, 2743, 1724, 1604, 1549, 1496, 1453, 1396, 1356, 1307, 1245, 1217, 1075, 1028, 944, 744, 696, 629, 578, 494, 424 $cm^{-1}$; HRMS (HESI) *m*/*z*: $[M - H]^-$ calcd for $C_{27}H_{23}N_2O_5$, 455.1612; found, 455.1621; HPLC: CHIRALCEL IC, hexane/*i*PrOH 80:20, 0.95 mL/min, λ = 220 nm, $t_{R1(maj)}$ = 59.48, 62.95; $t_{R2(min)}$ = 24.46, 38.96 min.

*(2S,3S)-2-Benzyl-3-ferrocenyl-4nitrobutanal (**11h**).* Pale yellow oil (36 mg, 52%). $[\alpha]_D^{20}$ +15.7 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$) δ 9.60 (s, 1H), *9.43 (d, J = 1.8, CHO—minor diastereomer)*, 7.28−7.26 (m, 1H), 7.25−7.16 (m, 2H), 7.13−7.05 (m, 2H), 4.99 (m, 1H), 4.72 (m, 1H), 4.25−4.15 (m, 2H), 4.12 (s, 4H), 4.02 (dt, *J* = 2.6, 1.4 Hz, 1H), 3.97 (ddd, *J* = 8.5, 5.1, 3.0 Hz, 1H), 3.87 (m, 1H), 3.06−2.84 (m, 2H), 2.81−2.53 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 202.3, 138.2, 128.9, 128.8, 128.7, 126.7, 85.3, 77.7, 69.0, 68.4, 68.3, 68.1, 66.3, 55.8, 37.8, 31.4; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 203.2, 137.8, 84.9, 77.4, 69.0, 68.8, 68.4, 68.1, 66.5, 54.7, 38.7, 32.9;* IR (ATR) ν: 3086, 3026, 2921, 2848, 2728, 2371, 2203, 2115, 1719, 1602, 1546, 1496, 1454, 1430, 1376, 1320, 1215, 1184, 1105, 1029, 1000, 911, 817, 737, 698, 598, 479 $cm^{-1}$; HRMS (HESI) *m*/*z*: $[M - H]^-$ calcd for $C_{21}H_{20}FeNO_3$, 390.0798; found, 390.0797; HPLC: CHIRALCEL IC, hexane/*i*PrOH 91:9, 0.9 mL/min, λ = 216 nm, $t_{R1(maj)}$ = 29.16, 32.07; $t_{R2(min)}$ = 34.02, 40.20 min.

*(2S,3R)-2-Benzyl-3-(naphthalen-1-yl)-4-nitrobutanal (**11i**).* Pale yellow oil (62 mg, 67%). $[\alpha]_D^{20}$ −9.87 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.78 (d, *J* = 2.0, 1H), *9.62 (s, CHO—minor diastereomer)*, (m, 1H), 8.07−7.86 (m, 1H), 7.81 (t, *J* = 8.8 Hz, 1H), 7.53−7.44 (m, 3H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.22−7.18 (m, 4H), 7.05−6.99 (m, 1H), 5.22−5.17 (m, 1H), 5.06−4.98 (m, 1H), 4.96−4.83 (m, 1H), 3.03−2.65 (m, 4H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 203.2, 142.2, 140.2, 137.2, 134.3, 129.5, 129.2, 128.9, 128.9, 128.8, 128.6, 128.5, 128.5, 127.1, 126.9, 126.2, 126.1, 125.4, 122.3, 73.3, 54.9, 45.0, 34.2; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 201.6, 141.9, 140.3, 137.4, 134.3, 129.4, 129.1, 128.5, 128.4, 127.1, 127.0, 126.3, 126.2, 125.2, 122.2, 74.4, 56.1, 45.3, 34.6;* IR (ATR) ν: 3059, 3025, 2926, 2856, 2737, 1718, 1600, 1550, 1494, 1452, 1376, 1340, 1132, 1046, 966, 950, 910, 867, 798, 778, 734, 698, 616, 530, 495, 430 $cm^{-1}$; HRMS (HESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{20}NO_3$, 334.1438; found, 334.1438; HPLC: CHIRALCEL IC, hexane/*i*PrOH 90:10, 1 mL/min, λ = 218 nm, $t_{R1(maj)}$ = 42.58, 54.85; $t_{R2(min)}$ = 39.24, 22.42 min.

*(2S,3S)-2-Benzyl-3-(furan-2-yl)-4-nitrobutanal (**11j**).* Pale yellow oil (68 mg, 98%). $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.71 (d, *J* = 1.4 Hz, 1H), *9.69 (d, J = 2.0 Hz, CHO—minor diastereomer)*, 7.40 (d, *J* = 1.8 Hz, 1H), 7.35−7.18 (m, 2H), 7.17−7.12 (m, 1H), 7.12 (d, *J* = 7.1 Hz, 2H), 6.35 (m, 1H), *6.23 (m, 1H)*, 4.79−4.66 (m, 2H), 4.08−3.95 (m, 1H), 3.17−2.97 (m, 1H), 3.05−2.88 (m, 1H), 2.84−2.73 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 202.0, 149.9, 142.8, 137.2, 129.2, 128.9, 128.9, 128.9, 127.0, 110.6, 109.1, 75.8, 53.8, 37.7, 33.4; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 202.2, 149.3, 142.9, 137.2, 128.5, 128.5, 128.4, 128.4, 127.1, 110.7, 109.5, 75.9, 53,4, 37.2, 33.3;* spectral data agree with those in the literature.[76] HPLC: CHIRALCEL AS-H, hexane/*i*PrOH 90:10, 0.7 mL/min, λ = 220 nm, $t_{R1}$ = 24.41, $t_{R2}$ = 26.52.

*(2S,3R)-3-(Benzo[d][1,3]dioxol-5-yl)-2-methyl-4-nitrobutanal (**12a**).* Pale yellow oil (46 mg, 88%). $[\alpha]_D^{20}$ +1.17 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.70 (d, *J* = 1.8 Hz, 1H), *9.53 (d, J = 1.8 Hz, CHO—minor diastereomer)*, 6.75 (dd, *J* = 7.9, 3.9 Hz, 1H), 6.69−6.60 (m, 2H), 5.96−5.94 (m, 2H), 4.77−4.57 (m, 2H), 3.72 (td, *J* = 9.3, 5.2 Hz, 1H), 2.79−2.67 (m, 1H), *1.20 (d, J = 7.3 Hz, $CH_3$—minor diastereomer)*, 1.02 (d, *J* = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (151


https://dx.doi.org/10.1021/acs.joc.0c02251
J. Org. Chem. XXXX, XXX, XXX−XXX

MHz, $CDCl_3$): δ 202.2, 148.2, 147.4, 130.1, 121.6, 108.7, 108.0, 101.3, 78.3, 48.6, 43.9, 12.2; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 202.3, 148.3, 147.4, 130.3, 121.6, 108.7, 108.2, 101.3, 77.7, 48.7, 44.8, 12.0*; IR (ATR) ν: 2971, 2900, 2834, 2729, 2117, 1842, 1720, 1610, 1549, 1504, 1488, 1443, 1377, 1279, 1248, 1193, 1126, 1037, 932, 903, 869, 813, 729, 704, 653 $cm^{-1}$; HRMS (HESI) *m/z*: $[M - H]^-$ calcd for $C_{12}H_{12}NO_5$, 250.0721; found, 250.0722; HPLC: CHIRALCEL IC, hexane/*i*PrOH 85:15, 1 mL/min, λ = 216 nm, $t_{R1(maj)}$ = 37.55, 42.15; $t_{R2(min)}$ = 26.50, 51.55 min.

***(2S,3R)-3-(Benzo[d][1,3]dioxol-5-yl)-2-ethyl-4-nitrobutanal (12b).*** Pale yellow oil (66 mg, 97%). $[\alpha]_D^{20}$ −1.47 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.71 (d, *J* = 2.7 Hz, 1H), *9.48 (d, J = 3.0 Hz, CHO—minor diastereomer)*, 6.77−6.73 (dd, *J* = 17.4, 7.9 Hz, 1H), 6.65−6.63 (m, 2H), 5.96−5.95 (m, 2H), 4.77−4.53 (m, 2H), 3.74−3.68 (m, 1H), 2.62−2.29 (m, 1H), 1.75−1.48 (m, 2H); 0.99 (t, *J* = 7.7 Hz, 3H), *0.85 (t, J = 7.7 Hz, $CH_3$—minor diastereomer)*; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 203.1, 148.2, 147.4, 130.3, 121.6, 108.7, 107.9, 101.3, 78.7, 55.1, 44.0, 20.4, 10.7; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 203.1, 148.2, 147.5, 129.8, 121.7, 108.7, 108.3, 101.3, 78.2, 55.0, 42.5, 20.7, 11.4*; IR (ATR) ν: 2967, 2881, 2734, 2064, 1838, 1718, 1610, 1551, 1488, 1443, 1375, 1278, 1247, 1176, 1133, 1038, 933, 904, 864, 814, 773, 728, 702, 682, 652 $cm^{-1}$; HRMS (HESI) *m/z*: $[M - H]^-$ calcd for $C_{13}H_{14}NO_5$, 264.0877; found, 264.0877; HPLC: CHIRALCEL IC, hexane/*i*PrOH 85:15, 1 mL/min, λ = 216 nm, $t_{R1(maj)}$ = 32.14, 35.78; $t_{R2(min)}$ = 22.17, 28.45 min.

***(2S,3R)-3-(Benzo[d][1,3]dioxol-5-yl)-2-isopropyl-4-nitrobutanal (12c).*** Pale yellow oil (56 mg, 96%). $[\alpha]_D^{20}$ −42.8 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.91 (d, *J* = 2.4 Hz, 1H), *9.50 (d, J = 3.9 Hz, CHO—minor diastereomer)*, 6.78−6.72 (m, 1H), 6.66−6.60 (m, 2H), 5.96 (s, 2H), 4.73−4.46 (m, 2H), 3.81 (td, *J* = 10.4, 4.3 Hz, 1H), 2.68 (ddd, *J* = 10.9, 4.2, 2.6 Hz, 1H), 1.81−1.74 (m, 1H), 1.11 (d, *J* = 7.0 Hz, 3H), *1.14 (d, J = 7.0 Hz, $CH_3$—minor diastereomer)*, 0.89 (d, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 204.3, 148.3, 130.6, 121.6, 108.8, 107.8, 101.3, 79.1, 58.9, 41.7, 29.7, 27.9, 21.7, 17.0; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 204.3, 147.4, 121.9, 108.7, 108.5, 78.7, 59.1, 42.5, 30.3, 27.1, 21.0, 18.8*; IR (ATR) ν: 3045, 2963, 2886, 2749, 2321, 1711, 1612, 1543, 1506, 1488, 1466, 1439, 1374, 1339, 1279, 1244, 1175, 1131, 1123, 1106, 1036, 931, 903, 860, 825, 819, 701, 683, 650, 585, 504, 465, 439 $cm^{-1}$; HRMS (HESI) *m/z*: $[M - H]^-$ calcd for $C_{14}H_{17}NO_5$, 278.1034; found, 278.1036; HPLC: CHIRALCEL IC, hexane/*i*PrOH 85:15, 1 mL/min, λ = 216 nm, $t_{R1(maj)}$ = 22.80, 24.49; $t_{R2(min)}$ = 14.13, 17.28 min.

***(2S,3R)-3-(Benzo[d][1,3]dioxol-5-yl)-2-(3-chlorobenzyl)-4-nitrobutanal (12d).*** Pale yellow oil (66 mg, 97%). $[\alpha]_D^{20}$ −2.13 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.69 (d, *J* = 2.4 Hz, 1H), *9.56 (d, J = 2.4 Hz, CHO—minor diastereomer)*, 7.24−7.12 (m, 2H), 7.03−6.99 (m, 1H), 6.94−6.90 (m, 1H), 6.78 (m, 1H), 6.67−6.60 (m, 2H), 5.98 (m, 2H), 4.84−4.59 (m, 2H), 3.73 (m, 1H), 3.06−2.96 (m, 1H), 2.86−2.70 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 202.3, 148.5, 147.7, 139.3, 134.3, 130.0, 129.8, 128.9, 127.2, 126.9, 121.7, 108.9, 107.9, 101.4, 78.2, 55.2, 43.3, 33.9; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 202.5, 148.4, 147.7, 139.4, 134.7, 130.2, 129.0, 129.0, 127.3, 127.0, 122.0, 108.8, 108.5, 77.8, 54.3, 44.4*, 33.3; IR (ATR) ν: 3063, 2901, 2734, 1844, 1719, 1597, 1548, 1503, 1487, 1442, 1375, 1279, 1245, 1181, 1124, 1105, 1079, 1036, 933, 904, 863, 812, 783, 728, 699, 683, 652, 436 $cm^{-1}$; HRMS (HESI) *m/z*: $[M-H]^-$calcd for $C_{18}H_{16}ClNO_5$, 360.0644; found, 360.0649; HPLC: CHIRALCEL OJ-H, hexane/*i*PrOH 63:37, 0.63 mL/min, λ = 216 nm, $t_{R1(maj)}$ = 75.04, 98.99; $t_{R2(min)}$ = 110.35, 114.18 min.

***(2S,3R)-3-(Benzo[d][1,3]dioxol-5-yl)-2-(4-methoxybenzyl)-4-nitrobutanal (12e).*** Pale yellow oil (71 mg, 97%). $[\alpha]_D^{20}$ −11.36 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.63 (d, *J* = 2.3 Hz, 1H), *9.47 (d, J = 2.0 Hz, CHO—minor diastereomer)*, 6.99−6.87 (m, 2H), 6.78−6.63 (m, 3H), 6.61−6.54 (m, 2H), 5.91−5.90 (m, 2H), 4.75−4.53 (m, 2H), 3.70 (s, 3H), *3.72 (s, 3H)*, 3.67−3.63 (m, 1H), 2.93−2.88 (m, 1H), 2.77−2.66 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 203.2, 158.5, 148.4, 147.5, 130.3, 129.8, 129.8, 128.9, 129.4, 121.7, 114.2, 108.8, 108.0, 101.4, 78.3, 55.6, 55.2, 43.2, 33.4; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 203.3, 158.6, 148.3, 147.5, 130.0, 129.0f, 122.0, 114.3, 108.7, 108.6, 78.0, 55.3, 54.6, 44.3, 33.0*; IR (ATR) ν: 3002, 2907, 2837, 2739, 1720, 1611, 1551, 1511, 1488, 1378, 1301, 1245, 1179, 1179, 1107, 1036, 934, 906, 845, 814, 731, 649, 565, 522 $cm^{-1}$; HRMS (HESI) *m/z*: $[M - H]^-$ calcd for $C_{19}H_{18}NO_6$, 356.1140; found, 356.1144; HPLC: CHIRALCEL AS-H, hexane/*i*PrOH 80:20, 0.75 mL/min, λ = 216 nm, $t_{R1(maj)}$ = 64.86, 85.76; $t_{R2(min)}$ = 80.13, 109.41 min.

***(2S,3S)-2-Methyl-4-nitro-3-(thiophen-2-yl)butanal (12f).*** Pale yellow oil (47 mg, 85%). $[\alpha]_D^{20}$ +2.29 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.65 (d, *J* = 1.2 Hz, 1H), *9.62 (d, J = 1.2 Hz, CHO—minor diastereomer)*, 7.24 (m, 1H), 6.96−6.94 (m, 1H), 6.93−6.88 (m, 1H), 4.81−4.65 (m, 2H), 4.26−4.15 (m, 1H), 2.85−2.77 (m, 1H), 1.26 (d, *J* = 7.3 Hz, 2H), 1.26 (d, *J* = 7.0 Hz, 3H), *1.13 (d, J = 7.0 Hz, $CH_3$—minor diastereomer)*; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 201.7, 139.9, 127.1, 126.7, 125.3, 78.4, 48.8, 39.1, 11.5; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 202.0, 139.2, 127.2, 126.8, 125.4, 78.1, 49.0, 40.1, 11.8*; IR (ATR) ν: 3168, 3105, 3049, 2978, 2936, 1720, 1670, 1625, 1548, 1464, 1372, 1325, 1275, 1171, 1130, 1107, 1004, 928, 890, 848, 670, 682, 619, 593, 567, 519 $cm^{-1}$; HRMS (HESI) *m/z*: $[M - H]^-$ calcd for $C_9H_{10}NO_3S$, 212.0387; found, 212.0386; HPLC: CHIRALCEL IC, hexane/*i*PrOH 90:10, 1 mL/min, λ = 216 nm, $t_{R1(maj)}$ = 22.25, 28.23; $t_{R2(min)}$ = 38.98, 42.17 min.

***(2S,3S)-2-Ethyl-4-nitro-3-(thiophen-2-yl)butanal (12g).*** Pale yellow oil (36 mg, 61%). $[\alpha]_D^{20}$ −6.83 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.71 (d, *J* = 2.2 Hz, 1H), *9.61 (d, J = 2.2 Hz, CHO—minor diastereomer)*, 7.25−7.22 (m, 1H), 6.95 (m, 1H), 6.91−6.90 (m, 1H), 4.83−4.61 (m, 2H), 4.20−4.14 (m, 1H), 2.73−2.66 (m, 1H), *2.60—2.56 (m, 1H)*, 1.83−1.60 (m, 2H), *1.04 (t, J = 7.5 Hz, $CH_3$—minor diastereomer)*, 0.92 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 202.5, 139.5, 127.1, 126.8, 125.3, 78.9, 55.7, 38.3, 20.3, 10.8; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 202.9, 138.5, 127.1, 127.1, 125.5, 78.5, 55.0, 39.2, 20.6, 11.6*. IR (ATR) ν: 3345, 3166, 3103, 3048, 2969, 2938, 2879, 2739, 1717, 1625, 1551, 1464, 1325, 1277, 1171, 1131, 1109, 1000, 964, 928, 891, 848, 774, 700 $cm^{-1}$; HRMS (HESI) *m/z*: $[M - H]^-$ calcd for $C_{10}H_{12}NO_3S$, 226.0543; found, 226.0543; HPLC: CHIRALCEL OJ-H, hexane/*i*PrOH 90:10, 0.57 mL/min, λ = 216 nm, $t_{R1(maj)}$ = 62.42, 66.08; $t_{R2(min)}$ = 58.09, 64.30 min.

***(2S,3S)-2-Isopropyl-4-nitro-3-(thiophen-2-yl)butanal (12h).*** Pale yellow oil (41 mg, 70%). $[\alpha]_D^{20}$ −61.8 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.90 (d, *J* = 2.0 Hz, 1H), *9.62 (d, J = 3.30 Hz, CHO—minor diastereomer)*, 7.25−7.23 (m, 1H), 6.95−6.94 (m, 1H), 6.91−6.88 (m, 1H), 4.78−4.57 (m, 2H), 4.28−4.21 (m, 1H), 2.80−2.28 (m, 1H), 2.12−1.84 (m, 1H), 1.15 (m, 3H), 1.02−0.90 (m, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 203.9, 140.1, 127.1, 126.8, 125.2, 79.4, 59.9, 37.6, 28.1, 21.6, 17.3; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 204.3, 137.9, 127.2, 127.2, 125.5, 79.0, 59.1, 38.2, 27.0, 20.7, 19.6*; IR (ATR) ν: 3172, 3104, 3049, 2964, 2873, 2743, 1716, 1551, 1465, 1439, 1372, 1326, 1278, 1174, 1132, 1043, 1000, 929, 891, 849, 700, 684 $cm^{-1}$; HRMS (HESI) *m/z*: $[M - H]^-$ calcd for $C_{11}H_{14}NO_3S$, 240.0700; found, 240.0702; HPLC: CHIRALCEL IC, hexane/*i*PrOH 85:15, 0.8 mL/min, λ = 216 nm, $t_{R1(maj)}$ = 18.43, 23.42; $t_{R2(min)}$ = 11.71, 17.18 min.

***(2S,3S)-2-(4-Methoxybenzyl)-4-nitro-3-(thiophen-2-yl)butanal (12i).*** Pale yellow oil (72 mg, 87%). $[\alpha]_D^{20}$ −35.6 (*c* 1, $CHCl_3$); $^1H$ NMR (600 MHz, $CDCl_3$): δ 9.70 (d, *J* = 1.7, 1H), *9.68 (d, J = 1.7 Hz, CHO—minor diastereomer)*, 7.28 (m, 1H), 7.09−7.01 (m, 2H), 6.99−6.97 (m, 1H), 6.93−6.89 (m, 1H), 6.87−6.81 (m, 2H), 4.87−4.66 (m, 2H), 4.22−4.10 (m, 1H), *3.80 (s, 3H)*, 3.78 (s, 3H) 3.10−2.97 (m, 1H), 2.85−2.82 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 202.6, 158.6, 139.4, 129.9, 129.9, 128.8, 127.2, 127.0, 125.5, 114.3, 78.5, 56.1, 55.3, 38.9, 33.0, 32.7; *$^{13}C$ NMR (151 MHz, $CDCl_3$, minor diastereomer): δ 202.9, 158.6, 138.0, 128.9, 127.6, 127.2, 125.8, 114.4, 78.4, 55.3, 54.7, 39.3*; IR (ATR) ν: 3200, 3166, 3105, 2930, 2838, 2116, 1720, 1611, 1551, 1512, 1465, 1372, 1325, 1278, 1247, 1174, 1130, 1107, 1032, 1004, 928, 890, 847, 764, 713, 700, 682, 619, 593, 567, 520 $cm^{-1}$; HRMS (HESI) *m/z*: $[M - H]^-$ calcd for $C_{16}H_{17}NO_4S$, 318.0806; found, 318.0808; HPLC: CHIRALCEL IC,


https://dx.doi.org/10.1021/acs.joc.0c02251
J. Org. Chem. XXXX, XXX, XXX−XXX

hexane/*i*PrOH 87:13, 1 mL/min, $\lambda$ = 216 nm, $t_{R1(maj)}$ = 27.23, 34.48; $t_{R2(min)}$ = 30.41, 40.71 min.

*tert-Butyl 3-((2R,3S)-3-(4-Fluorobenzyl)-1-nitro-4-oxobutan-2-yl)-1H-indole-1-carboxyl-ate (**12j**).* Pale yellow oil (54 mg, 93%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 9.74 (d, $J$ = 1.8 Hz, 1H), *9.69 (d, J = 1.8 Hz, CHO—minor diastereomer)*, 8.15 (m, 1H), 7.50−7.47 (m, 1H), 7.43−7.35 (m, 2H), 7.29−7.27 (m, 1H), 7.05−6.93 (m, 4H), 4.95−4.75 (m, 2H), 4.14 (m, 1H), 3.29−3.16 (m, 1H), 3.06−2.80 (m, 2H), 1.69 (s, 3H), *1.68 (s, $CH_3$—minor diastereomer)*; $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$): $\delta$ 202.5, 162.6, 149.3, 132.8, 132.8, 130.4, 130.3, 125.2, 124.4, 123.1, 118.5, 118.5, 115.8, 115.8, 115.8, 115.3, 76.7, 54.5, 34.9, 33.3, 28.2; *$^{13}$C NMR (151 MHz, $CDCl_3$, minor diastereomer): $\delta$ 202.6, 161.0, 132.9, 132.9, 129.1, 128.5, 125.2, 124.4, 123.0, 118.6, 115.6, 115.6, 115.6, 84.5, 53.8, 34.8, 32.6, 27.0*; $^{19}$F NMR (564 MHz, $CDCl_3$): $\delta$ −115.21 (m, 1F), *-117.70 (m, 1F)*; IR (ATR) $\nu$: 2980, 2926, 2858, 2729, 1721, 1603, 1551, 1509, 1475, 1450, 1369, 1309, 1255, 1220, 1151, 1097, 1065, 1018, 909, 851, 835, 765, 745, 648 cm$^{-1}$; HRMS (HESI) $m/z$: [M − H]$^-$ calcd for $C_{24}H_{24}FN_2O_5$, 439.1675; found, 439.1672. HPLC: CHIRALCEL IC, hexane/*i*PrOH 80:20, 1 mL/min, $\lambda$ = 216 nm, $t_{R1(maj)}$ = 36.43, 41.27; $t_{R2(min)}$ = 14.30, 25.25 min.

**General Procedure for Reductive Cyclization of Michael Adducts.** To the suspension of Michael adduct **11j** or **11d** (0.31 mmol) in acetic acid/water (1:1, 8 mL), was added freshly activated zinc powder (299 mg, 4.58 mmol) at 0 °C in two portions over the period of 10 min. The reaction mixture was stirred at room temperature for 18 h. When the full conversion was observed (TLC), the pH of the reaction mixture was adjusted to 12 with 4 M NaOH solution. The white colloid was filtered off, and the filtrate was extracted with DCM (4 × 25 mL). The combined organic layers were washed with brine (1 × 25 mL) and dried over anhydrous $Na_2SO_4$. The solvent was evaporated under vacuum, and the crude product was purified by flash chromatography ($SiO_2$, gradient DCM to DCM/MeOH 50:50) to afford the desired products **13a** and **13b** as pale orange oil.

*(3R,4S)-3-(Benzo[d][1,3]dioxol-5-yl)-4-benzylpyrrolidine (**13a**).* Pale orange oil (50 mg, 58%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.24−7.15 (m, 3H), 7.09−7.03 (m, 2H), 6.77−6.66 (m, 3H), 5.94 (s, 2H), 3.39−3.14 (m, 2H), 2.94−2.75 (m, 4H), 2.51−2.34 (m, 2H), 2.28 (br s, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 147.8, 146.0, 140.7, 136.7, 128.8, 128.7, 128.3, 128.3, 125.9, 120.7, 108.2, 107.6, 100.9, 55.5, 52.8, 52.1, 49.8, 39.0; IR (ATR) $\nu$ = 3059, 3024, 2911, 2876, 2117, 2067, 1944, 1603, 1485, 1439, 1339, 1243, 1189, 1125, 1098, 1037, 932, 858, 808, 747, 700, 631, 559 cm$^{-1}$; (HESI) $m/z$: [M + H]$^+$ calcd for $C_{18}H_{20}NO_2$, 282.1489; found, 282.1486.

*3-Benzyl-4-(furan-2-yl)pyrrolidine (**13b**).* Pale orange oil (11 mg, 26%). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ 7.32−7.30 (m, 1H), 7.24−7.13 (m, 5H), 6.28−6.27 (m, 1H), 6.00−5.98 (m, 1H), 3.30−2.93 (m, 4H), 2.78−2.49 (m, 4H), 1.25 (s, 1H); $^{13}$C NMR (151 MHz, $CDCl_3$): $\delta$ 141.3, 141.1, 140.6, 128.8, 128.8, 128.3, 128.3, 126.0, 110.0, 104.6, 57.7, 52.9, 47.3, 45.1, 39.6; IR (ATR) $\nu$: 3025, 2959, 2920, 2851, 2113, 1724, 1495, 1453, 1422, 1259, 1146, 1082, 1011, 798, 732, 700, 599 cm$^{-1}$; (HESI) $m/z$: [M + H]$^+$ calcd for $C_{15}H_{18}NO$, 228.1383; found, 228.1383.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02251.

Additional optimization results, additional NMR mechanistic studies, pictures of NMR spectra, HPLC chromatograms, CD and HRMS spectra, and computational details (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

**Radovan Šebesta** − *Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava, 842 15 Bratislava, Slovakia;* orcid.org/0000-0002-7975-3608; Email: radovan.sebesta@uniba.sk

### Authors

**Patrícia Čmelová** − *Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava, 842 15 Bratislava, Slovakia*

**Denisa Vargová** − *Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava, 842 15 Bratislava, Slovakia;* orcid.org/0000-0001-9923-7080

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02251


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the Slovak Research and Development Agency under the contract no. APVV-18-0242.

## ■ REFERENCES


(1) Sewald, N.; Jakubke, H.-D. *Peptides: Chemistry and Biology*, 2nd ed.; Wiley-VCH: Weinheim, 2009.

(2) Miller, S. J. In Search of Peptide-Based Catalysts for Asymmetric Organic Synthesis. *Acc. Chem. Res.* **2004**, *37*, 601−610.

(3) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. Asymmetric Catalysis Mediated by Synthetic Peptides. *Chem. Rev.* **2007**, *107*, 5759−5812.

(4) Wennemers, H. Asymmetric catalysis with peptides. *Chem. Commun.* **2011**, *47*, 12036−12041.

(5) Lewandowski, B.; Wennemers, H. Asymmetric catalysis with short-chain peptides. *Curr. Opin. Chem. Biol.* **2014**, *22*, 40−46.

(6) Shugrue, C. R.; Miller, S. J. Applications of Nonenzymatic Catalysts to the Alteration of Natural Products. *Chem. Rev.* **2017**, *117*, 11894−11951.

(7) Metrano, A. J.; Chinn, A. J.; Shugrue, C. R.; Stone, E. A.; Kim, B.; Miller, S. J. Asymmetric Catalysis Mediated by Synthetic Peptides, Version 2.0: Expansion of Scope and Mechanisms. *Chem. Rev.* **2020**, *120*, 11479−11615.

(8) Revell, J. D.; Wennemers, H. Investigating Sequence Space: How Important is the Spatial Arrangement of Functional Groups in the Asymmetric Aldol Reaction Catalyst H-Pro-Pro-Asp-NH2? *Adv. Synth. Catal.* **2008**, *350*, 1046−1052.

(9) Krattiger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. Increased Structural Complexity Leads to Higher Activity: Peptides as Efficient and Versatile Catalysts for Asymmetric Aldol Reactions. *Org. Lett.* **2005**, *7*, 1101−1103.

(10) Triandafillidi, I.; Bisticha, A.; Voutyritsa, E.; Galiatsatou, G.; Kokotos, C. G. tert-Butyl ester or benzylamide of the dipeptide Pro-Gly as organocatalysts for the asymmetric aldol reaction. *Tetrahedron* **2015**, *71*, 932−940.

(11) Bisticha, A.; Triandafillidi, I.; Kokotos, C. G. tert-Butyl esters of peptides as organocatalysts for the asymmetric aldol reaction. *Tetrahedron* **2015**, *26*, 102−108.

(12) Ahmetlli, A.; Spiliopoulou, N.; Magi-Oikonomopoulou, A.; Gerokonstantis, D.-T.; Moutevelis-Minakakis, P.; Kokotos, C. G. Proline dipeptides containing fluorine moieties as oganocatalysts for the asymmetric aldol reaction. *Tetrahedron* **2018**, *74*, 5987−5995.

(13) Psarra, A.; Kokotos, C. G.; Moutevelis-Minakakis, P. tert-Butyl esters of tripeptides based on Pro-Phe as organocatalysts for the asymmetric aldol reaction in aqueous or organic medium. *Tetrahedron* **2014**, *70*, 608−615.

(14) Bayat, S.; Tejo, B. A.; Salleh, A. B.; Abdmalek, E.; Normi, Y. M.; Rahman, M. B. A. Various Polar Tripeptides as Asymmetric Organocatalyst in Direct Aldol Reactions in Aqueous Media. *Chirality* **2013**, *25*, 726−734.

(15) Wiesner, M.; Revell, J. D.; Wennemers, H. Tripeptides as Efficient Asymmetric Catalysts for 1,4-Addition Reactions of Aldehydes to Nitroolefins—A Rational Approach. *Angew. Chem., Int. Ed.* **2008**, *47*, 1871−1874.
(16) Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H. Peptide Catalyzed Asymmetric Conjugate Addition Reactions of Aldehydes to Nitroethylene-A Convenient Entry into gamma2-Amino Acids. *J. Am. Chem. Soc.* **2008**, *130*, 5610−5611.
(17) Wiesner, M.; Neuburger, M.; Wennemers, H. Tripeptides of the Type H-D-Pro-Pro-Xaa-NH2 as Catalysts for Asymmetric 1,4-Addition Reactions: Structural Requirements for High Catalytic Efficiency. *Chem.—Eur. J.* **2009**, *15*, 10103−10109.
(18) Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. Enamine Catalysis with Low Catalyst Loadings - High Efficiency via Kinetic Studies. *J. Am. Chem. Soc.* **2010**, *132*, 6−7.
(19) Bächle, F.; Duschmalé, J.; Ebner, C.; Pfaltz, A.; Wennemers, H. Organocatalytic Asymmetric Conjugate Addition of Aldehydes to Nitroolefins: Identification of Catalytic Intermediates and the Stereoselectivity-Determining Step by ESI-MS. *Angew. Chem., Int. Ed.* **2013**, *52*, 12619−12623.
(20) Wennemers, H.; Schnitzer, T. Effect of γ-Substituted Proline Derivatives on the Performance of the Peptidic Catalyst H-dPro-Pro-Glu-NH2. *Synthesis* **2018**, *50*, 4377−4382.
(21) Wennemers, H.; Wiesner, M. Peptide-Catalyzed Conjugate Addition Reactions of Aldehydes to Nitroolefins. *Synthesis* **2010**, 1568−1571.
(22) Duschmalé, J.; Wennemers, H. Adapting to Substrate Challenges: Peptides as Catalysts for Conjugate Addition Reactions of Aldehydes to α,β-Disubstituted Nitroolefins. *Chem.—Eur. J.* **2012**, *18*, 1111−1120.
(23) Kastl, R.; Wennemers, H. Peptide-Catalyzed Stereoselective Conjugate Addition Reactions Generating All-Carbon Quaternary Stereogenic Centers. *Angew. Chem., Int. Ed.* **2013**, *52*, 7228−7232.
(24) Grünenfelder, C. E.; Kisunzu, J. K.; Wennemers, H. Peptide-Catalyzed Stereoselective Conjugate Addition Reactions of Aldehydes to Maleimide. *Angew. Chem., Int. Ed.* **2016**, *55*, 8571−8574.
(25) Poláčková, V.; Čmelová, P.; Górová, R.; Šebesta, R. Peptide-catalyzed stereoselective Michael addition of aldehydes and ketones to heterocyclic nitroalkenes. *Monatsh. Chem.* **2018**, *149*, 729−736.
(26) Schnitzer, T.; Budinská, A.; Wennemers, H. Organocatalysed conjugate addition reactions of aldehydes to nitroolefins with anti selectivity. *Nat. Catal.* **2020**, *3*, 143−147.
(27) Akagawa, K.; Sakai, N.; Kudo, K. Histidine-Containing Peptide Catalysts Developed by a Facile Library Screening Method. *Angew. Chem., Int. Ed.* **2015**, *54*, 1822−1826.
(28) Akagawa, K.; Satou, J.; Kudo, K. Exploration of Structural Frameworks for Reactive and Enantioselective Peptide Catalysts by Library Screenings. *J. Org. Chem.* **2016**, *81*, 9396−9401.
(29) Akagawa, K.; Iwasaki, Y.; Kudo, K. Library Screening in Aqueous Media To Develop a Highly Active Peptide Catalyst for Enantioselective Michael Addition of a Malonate. *Eur. J. Org. Chem.* **2016**, 4460−4464.
(30) Duschmalé, J.; Kohrt, S.; Wennemers, H. Peptide catalysis in aqueous emulsions. *Chem. Commun.* **2014**, *50*, 8109−8112.
(31) Machuca, E.; Rojas, Y.; Juaristi, E. Synthesis and Evaluation of (S)-Proline-Containing α,β-Dipeptides as Organocatalysts in Solvent-Free Asymmetric Aldol Reactions Under Ball-Milling Conditions. *Asian J. Org. Chem.* **2015**, *4*, 46−53.
(32) Avila-Ortiz, C. G.; Díaz-Corona, L.; Jiménez-González, E.; Juaristi, E. Asymmetric Michael Addition Organocatalyzed by α,β-Dipeptides under Solvent-Free Reaction Conditions. *Molecules* **2017**, *22*, 1328.
(33) Schnitzer, T.; Wennemers, H. Deactivation of Secondary Amine Catalysts via Aldol Reaction−Amine Catalysis under Solvent-Free Conditions. *J. Org. Chem.* **2020**, *85*, 7633−7640.
(34) Revell, J. D.; Gantenbein, D.; Krattiger, P.; Wennemers, H. Solid-supported and pegylated H−Pro−Pro−Asp−NHR as catalysts for asymmetric aldol reactions. *Biopolymers* **2006**, *84*, 105−113.
(35) Arakawa, Y.; Wiesner, M.; Wennemers, H. Efficient Recovery and Reuse of an Immobilized Peptidic Organocatalyst. *Adv. Synth. Catal.* **2011**, *353*, 1201−1206.
(36) Tuchman-Shukron, L.; Miller, S. J.; Portnoy, M. Polymer-Supported Enantioselective Bifunctional Catalysts for Nitro-Michael Addition of Ketones and Aldehydes. *Chem.—Eur. J.* **2012**, *18*, 2290−2296.
(37) Arakawa, Y.; Wennemers, H. Enamine Catalysis in Flow with an Immobilized Peptidic Catalyst. *ChemSusChem* **2013**, *6*, 242−245.
(38) Peris, G.; Jakobsche, C. E.; Miller, S. J. Aspartate-Catalyzed Asymmetric Epoxidation Reactions. *J. Am. Chem. Soc.* **2007**, *129*, 8710−8711.
(39) Berkessel, A. Asymmetric Epoxidation of Olefins with Hydrogen Peroxide—Catalysis by an Aspartate-Containing Tripeptide. *Angew. Chem., Int. Ed.* **2008**, *47*, 3677−3679.
(40) Jakobsche, C. E.; Peris, G.; Miller, S. J. Functional Analysis of an Aspartate-Based Epoxidation Catalyst with Amide-to-Alkene Peptidomimetic Catalyst Analogues. *Angew. Chem., Int. Ed.* **2008**, *47*, 6707−6711.
(41) Abascal, N. C.; Lichtor, P. A.; Giuliano, M. W.; Miller, S. J. Function-oriented investigations of a peptide-based catalyst that mediates enantioselective allylic alcohol epoxidation. *Chem. Sci.* **2014**, *5*, 4504−4511.
(42) Metrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Hurtley, A. E.; Miller, S. J. Diversity of Secondary Structure in Catalytic Peptides with β-Turn-Biased Sequences. *J. Am. Chem. Soc.* **2017**, *139*, 492−516.
(43) Rigling, C.; Kisunzu, J. K.; Duschmalé, J.; Häussinger, D.; Wiesner, M.; Ebert, M.-O.; Wennemers, H. Conformational Properties of a Peptidic Catalyst: Insights from NMR Spectroscopic Studies. *J. Am. Chem. Soc.* **2018**, *140*, 10829−10838.
(44) Chook, Y. M.; Ke, H.; Lipscomb, W. N. Crystal structures of the monofunctional chorismate mutase from Bacillus subtilis and its complex with a transition state analog. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8600−8603.
(45) Burke, J. R.; La Clair, J. J.; Philippe, R. N.; Pabis, A.; Corbella, M.; Jez, J. M.; Cortina, G. A.; Kaltenbach, M.; Bowman, M. E.; Louie, G. V.; Woods, K. B.; Nelson, A. T.; Tawfik, D. S.; Kamerlin, S. C. L.; Noel, J. P. Bifunctional Substrate Activation via an Arginine Residue Drives Catalysis in Chalcone Isomerases. *ACS Catal.* **2019**, *9*, 8388−8396.
(46) Fang, X.; Wang, C.-J. Recent advances in asymmetric organocatalysis mediated by bifunctional amine-thioureas bearing multiple hydrogen-bonding donors. *Chem. Commun.* **2015**, *51*, 1185−1197.
(47) Connon, S. J. Asymmetric catalysis with bifunctional cinchona alkaloid-based urea and thiourea organocatalysts. *Chem. Commun.* **2008**, 2499−2510.
(48) Zhang, Z.; Schreiner, P. R. (Thio)urea organocatalysis-What can be learnt from anion recognition? *Chem. Soc. Rev.* **2009**, *38*, 1187−1198.
(49) Siau, W.-Y.; Wang, J. Asymmetric organocatalytic reactions by bifunctional amine-thioureas. *Catal. Sci. Technol.* **2011**, *1*, 1298−1310.
(50) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. Bifunctional primary amine-thioureas in asymmetric organocatalysis. *Org. Biomol. Chem.* **2013**, *11*, 7051−7071.
(51) Zhang, Z.; Bao, Z.; Xing, H. N,N′-Bis[3,5-bis(trifluoromethyl)-phenyl]thiourea: a privileged motif for catalyst development. *Org. Biomol. Chem.* **2014**, *12*, 3151−3162.
(52) Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673.
(53) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. Theoretical Studies on the Bifunctionality of Chiral Thiourea-Based Organocatalysts: Competing Routes to C−C Bond Formation. *J. Am. Chem. Soc.* **2006**, *128*, 13151−13160.
(54) Zhu, J.-L.; Zhang, Y.; Liu, C.; Zheng, A.-M.; Wang, W. Insights into the Dual Activation Mechanism Involving Bifunctional Cinchona


https://dx.doi.org/10.1021/acs.joc.0c02251
J. Org. Chem. XXXX, XXX, XXX−XXX

Alkaloid Thiourea Organocatalysts: An NMR and DFT Study. *J. Org. Chem.* **2012**, *77*, 9813−9825.
(55) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. Pyrrolidine−Thiourea as a Bifunctional Organocatalyst: Highly Enantioselective Michael Addition of Cyclohexanone to Nitroolefins. *Org. Lett.* **2006**, *8*, 2901−2904.
(56) Bai, J.-F.; Xu, X.-Y.; Huang, Q.-C.; Peng, L.; Wang, L.-X. Highly asymmetric Michael additions of $\alpha,\alpha$-disubstituted aldehydes to $\beta$-nitroalkenes promoted by chiral pyrrolidine−thiourea bifunctional catalysts. *Tetrahedron Lett.* **2010**, *51*, 2803−2805.
(57) Chen, J.; Geng, Z.-C.; Li, N.; Huang, X.-F.; Pan, F.-F.; Wang, X.-W. Organocatalytic Asymmetric Michael Addition of Aliphatic Aldehydes to Indolylnitroalkenes: Access to Contiguous Stereogenic Tryptamine Precursors. *J. Org. Chem.* **2013**, *78*, 2362−2372.
(58) Möhler, J. S.; Wennemers, H.; Schnitzer, T. Amine Catalysis with Substrates Bearing N-Heterocyclic Moieties Enabled by Control over the Enamine Pyramidalization Direction. *Chem.—Eur. J.* **2020**, DOI: 10.1002/chem.202002966.
(59) Bennani, Y. L.; Hanessian, S. trans-1,2-Diaminocyclohexane Derivatives as Chiral Reagents, Scaffolds, and Ligands for Catalysis: Applications in Asymmetric Synthesis and Molecular Recognition. *Chem. Rev.* **1997**, *97*, 3161−3196.
(60) Do, J.-L.; Friščić, T. Mechanochemistry: A Force of Synthesis. *ACS Cent. Sci.* **2017**, *3*, 13−19.
(61) Howard, J. L.; Cao, Q.; Browne, D. L. Mechanochemistry as an emerging tool for molecular synthesis: what can it offer? *Chem. Sci.* **2018**, *9*, 3080−3094.
(62) Friščić, T.; Mottillo, C.; Titi, H. M. Mechanochemistry for Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 1018−1029.
(63) Hernández, J. G.; Bolm, C. Altering Product Selectivity by Mechanochemistry. *J. Org. Chem.* **2017**, *82*, 4007−4019.
(64) Veverková, E.; Poláčková, V.; Liptáková, L.; Kázmerová, E.; Mečiarová, M.; Toma, Š.; Šebesta, R. Organocatalyst Efficiency in the Michael Additions of Aldehydes to Nitroalkenes in Water and in a Ball-Mill. *ChemCatChem* **2012**, *4*, 1013−1018.
(65) Hestericová, M.; Šebesta, R. Higher enantioselectivities in thiourea-catalyzed Michael additions under solvent-free conditions. *Tetrahedron* **2014**, *70*, 901−905.
(66) Rodriguez, L.; Fišera, R.; Gaálová, B.; Koči, K.; Bujdáková, H.; Mečiarová, M.; Górová, R.; Jurdáková, H.; Šebesta, R. Synthesis of Chiral 3,4-Disubstituted Pyrrolidines with Antibacterial Properties. *Eur. J. Org. Chem.* **2020**, 2565−2575.
(67) Featherston, A. L.; Shugrue, C. R.; Mercado, B. Q.; Miller, S. J. Phosphothreonine (pThr)-Based Multifunctional Peptide Catalysis for Asymmetric Baeyer−Villiger Oxidations of Cyclobutanones. *ACS Catal.* **2019**, *9*, 242−252.
(68) Tomasi, J.; Mennucci, B.; Cammi, R. Quantum Mechanical Continuum Solvation Models. *Chem. Rev.* **2005**, *105*, 2999−3094.
(69) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. Ab Initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. *J. Phys. Chem.* **1994**, *98*, 11623−11627.
(70) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* **2010**, *132*, 154104.
(71) Benoiton, N. L. *Chemistry of Peptide Synthesis*; Taylor & Francis: Boca Raton, 2006.
(72) Lu, D.; Gong, Y.; Wang, W. Prolylprolinol-Catalyzed Asymmetric Michael Addition of Aliphatic Aldehydes to Nitroalkenes. *Adv. Synth. Catal.* **2010**, *352*, 644−650.
(73) Chen, F.; Huang, S.; Zhang, H.; Liu, F.; Peng, Y. Proline-based dipeptides with two amide units as organocatalyst for the asymmetric aldol reaction of cyclohexanone with aldehydes. *Tetrahedron* **2008**, *64*, 9585−9591.
(74) Hernández, J. G.; García-López, V.; Juaristi, E. Solvent-free asymmetric aldol reaction organocatalyzed by (S)-proline-containing thiodipeptides under ball-milling conditions. *Tetrahedron* **2012**, *68*, 92−97.
(75) Tsunematsu, H.; Isobe, R.; Hanazono, H.; Soeda, Y.; Inagaki, M.; Ito, N.; Higuchi, R.; Yamamoto, M. Differences in the Formation and Fragmentation of Sodium Adduct Ions between Tertiarybutoxycarbonyl-Protected Prolyproline Diastereomers in Fast Atom Bombardment Mass Spectrometry. *Chem. Pharm. Bull.* **1999**, *47*, 1040−1043.
(76) Durini, M.; Sahr, F. A.; Kuhn, M.; Civera, M.; Gennari, C.; Piarulli, U. Bifunctional 2,5-Diketopiperazines as Efficient Organocatalysts for the Enantioselective Conjugate Addition of Aldehydes to Nitroolefins. *Eur. J. Org. Chem.* **2011**, 5599−5607.


https://dx.doi.org/10.1021/acs.joc.0c02251
*J. Org. Chem.* XXXX, XXX, XXX−XXX