JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

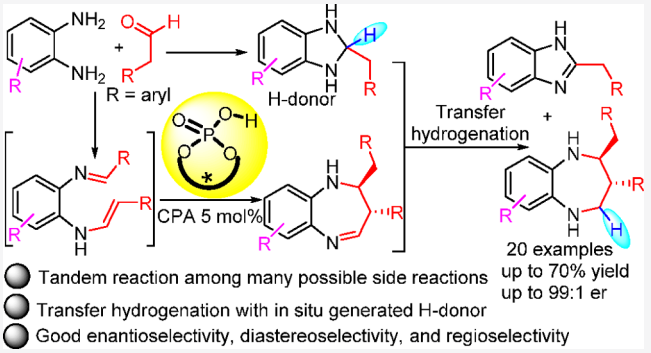
Regioselective, Diastereoselective, and Enantioselective One-Pot Tandem Reaction Based on an in Situ Formed Reductant: Preparation of 2,3-Disubstituted 1,5-Benzodiazepine

Gao-feng Yang, Guang-xun Li,* Jin Huang, Ding-qiang Fu, Xiao-kang Nie, Xin Cui, Jin-zhong Zhao, and Zhuo Tang*

Cite This: J. Org. Chem. 2021, 86, 5110–5119 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The 1,5-benzodiazepines are important skeletons frequently contained in medicinal chemistry. Herein, we described an unexpected tandem cyclization/transfer hydrogenation reaction for obtaining chiral 2,3-disubstituted 1,5-benzodiazepines. The enolizable aryl aldehydes were chosen as substrates to react with symmetric and unsymmetric *o*-phenylenediamines. The unforeseen tandem reaction occurred among many possible latent side reactions under chiral phosphoric acid catalysis and affords the corresponding products in moderate yields and regioselectivities, good diastereoselectivities, and enantiomeric ratio (up to 99:1).



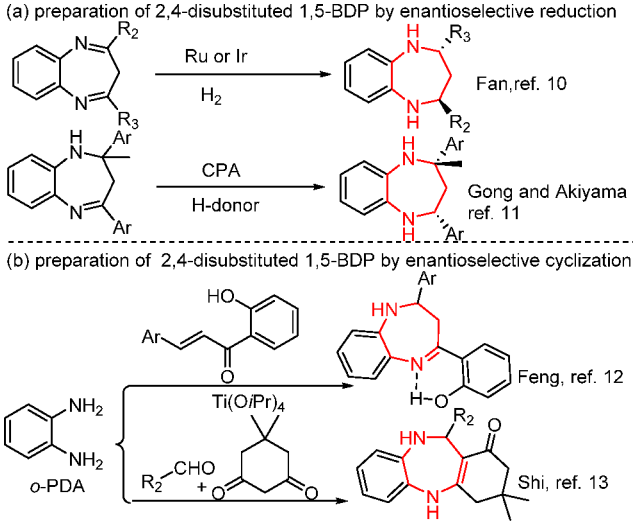
INTRODUCTION

The 1,5-benzodiazepines (1,5-BDPs) and their polycyclic derivatives have received great attention, because of their wide range of therapeutic and pharmacological properties.[1] For example, some of them were recognized as HCV NS5B inhibitors,[2] Caspase-1 (ICE) inhibitor,[3] antimicrobial,[4] diet pills, etc.;[5] thus, these are referred to as "privileged structures," a term first used to describe the benzodiazepine.[6] Because of their wide range of biological and synthetic applications, several methods have been developed.[7] Among these reactions, domino reactions of *o*-phenylenediamine (*o*-PDA) with carbonyl compounds[8] were systematically investigated, including the use of Lewis acids as catalysts, and the employment of microwave irradiation.[9] A series of functionalized 1,5-BDP derivatives were obtained as racemates. Though chiral 1,5-BDPs were a fundamental skeleton in many bioactive molecules, relatively few of these scaffolds have been enantioselectively synthesized.

Generally, the preparation of chiral 1,5-BDP can be divided into two categories including the enantioselective reduction of the obtained cyclic imine and the enantioselective construction of the seven-membered ring. Fan and co-workers[10] developed a useful asymmetric hydrogenation strategy, which could obtain both enantiomers with the same enantiomer of the ligand but in the presence of different achiral counteranions (Scheme 1a).

Gong and Akiyama[11] developed a similar way via the dynamic kinetic asymmetric transfer hydrogenation of racemic cyclic imine (Scheme 1a). The above methods elegantly

Scheme 1. Selected Examples of Enantioselective Synthesis of 1,5-BDP



Received: December 31, 2020
Published: March 16, 2021

https://dx.doi.org/10.1021/acs.joc.0c03064
J. Org. Chem. 2021, 86, 5110–5119

ensured the preparation of 2,4-disubstituted 1,5-BDP through the enantioselective reduction of the cyclized imine substrates in different ways. On the other hand, researchers were trying to construct the 1,5-BDP ring directly in an enantioselective way. Feng and co-workers[12] developed an enantioselective domino reaction of *o*-PDA and chalcone derivatives, which produced the corresponding 1,5-BDP ring in one step in up to 82% ee (Scheme 1b). Shi and co-workers[13] developed an interesting way for enantioselective construction of the 1,5-BDP ring through a chiral phosphoric acid catalyzed tandem reaction with reactive 5,5-dimethyl cyclohexane-1,3-dione, *o*-PDA, and aromatic aldehyde or isatin as substrates (Scheme 1b). The reaction proceeded through the formation of the key enamine intermediate, which was followed by an enantioselective intramolecular Mannich reaction. These methods ensured the enantioselective construction of 1,5-BDP possessing only one chiral center by ingeniously utilizing a special substrate according to the difference of the reactivity. However, the efficient synthesis of 2,3-disubstituted 1,5-BDPs has not been investigated. Herein, a unique tandem cyclization/transfer hydrogenation reaction was unexpectedly found to be an efficient way to construct 2,3-disubstituted 1,5-BDP, and its chiral derivatives could be obtained with high enantioselectivity by using phosphoric acid as catalysts.

RESULTS AND DISCUSSION

Imidazoline was used as an interesting hydride donor in the literature.[14] When we intended to prepare alkyl substituted imidazoline **3a′**, to our surprise, the obtained main product was 1,5-BDP **3a** with aromatized imidazole **4a** (Scheme 2a). Moreover, the high diastereoselectivity (>25:1) was observed for product **3a**. This unexpected result inspired us to investigate the reaction deeply. We speculated that the key imine enamine intermediate **A** could be formed, which could be cyclized to afford the seven-membered 1,5-BDP ring **B** with two adjacent chiral centers through the similar mechanism report by the Shi group.[13] Then the cyclic imine intermediate **B** was reduced probably by the in situ formed imidazoline **3a′**, yielding the 1,5-BDP **3a** and imidazole **4a**, respectively.[15] If the reaction proceeds according to the speculated mechanism, the outcome observed is completely incredible due to the fact that there are many possible side reactions (Scheme 2b): (i) the possible reductive amination between *o*-PDA and aldehydes; (ii) the formation of imidazolines with *o*-PDA, and the following reductive amination to yield *N*-substituted *o*-PDA; (iii) the direct formation of imidazoles; (iv) aldol reaction to yield *β*-hydroxyl aldehyde or *α*,*β*-unsaturated aldehyde, which might react with *o*-PDA as roads i−iii to get more complicated products. However, the reaction afforded 2,3-disubstituted 1,5-BDP as the unanticipated main product; thus, we optimized the reaction conditions for obtaining 1,5-BDP **3a** in the tandem one-pot reaction (Table S1; see Supporting Information). According to the result, the reaction could be catalyzed under catalytic diphenyl phosphate (5 mol %), and the corresponding product **3a** could be obtained in 63% yield in high diastereoselectivity (>25:1).

Then, we moved on to investigate the corresponding enantioselective reaction with chiral phosphoric acid as catalyst (Table 1). First, the phosphoric acid catalysts **5a**−**5g** were

Scheme 2. The Discovery and the Property of the Reaction

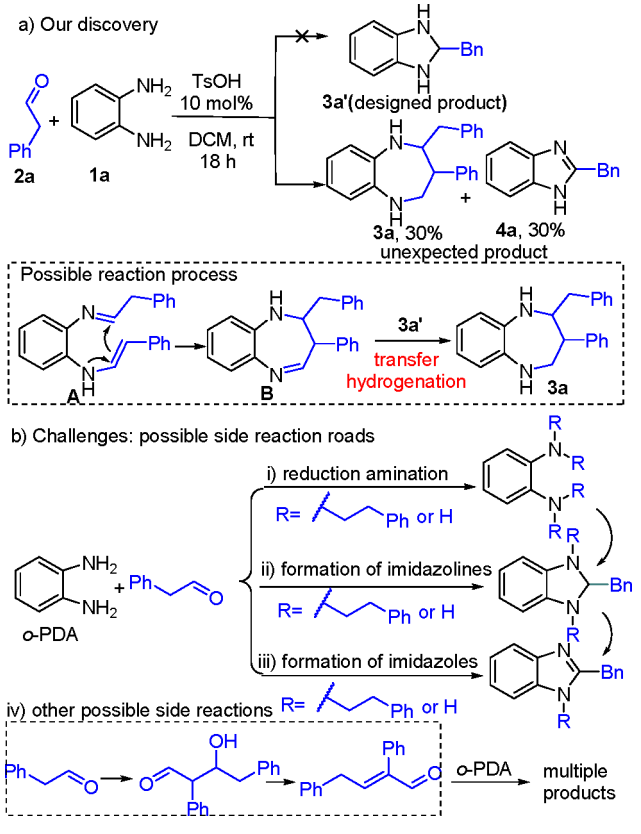
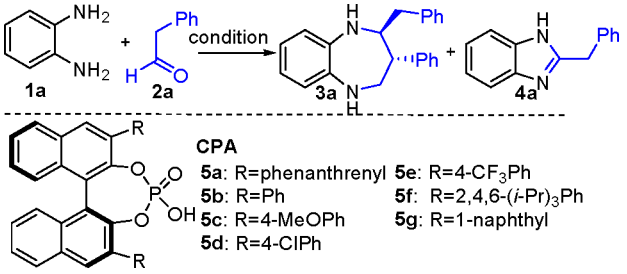


Table 1. Optimization of Reaction Conditions



entry[a]	cat	*T* (°C)	solvent	yield (%)[b]	er[c]
1	**5a**	15	DCM	30	68:32
2	**5b**	15	DCM	40	63:37
3	**5c**	15	DCM	34	57:43
4	**5d**	15	DCM	39	59:41
5	**5e**	15	DCM	42	63:37
6	**5f**	15	DCM	43	78:22
7	**5g**	15	DCM	29	65:35
8[d]	**5f**	15	ACN	55	87:13
9	**5f**	0	ACN	32	68:16
10[e]	**5f**	15	ACN	63	95:5
11[e]	**5f**	15	ACN/$CHCl_3$ (1/1)	65	99:1
12[e]	**5f**	15	ACN/DCM (1/1)	55	96:4
13[e]	**5f**	15	ACN/$PhCH_3$ (1/1)	53	98:2
14[f]	**5f**	15	ACN/DCM (1/1)	55	96:4
15[g]	**5f**	15	ACN/$PhCH_3$ (1/1)	53	98:2

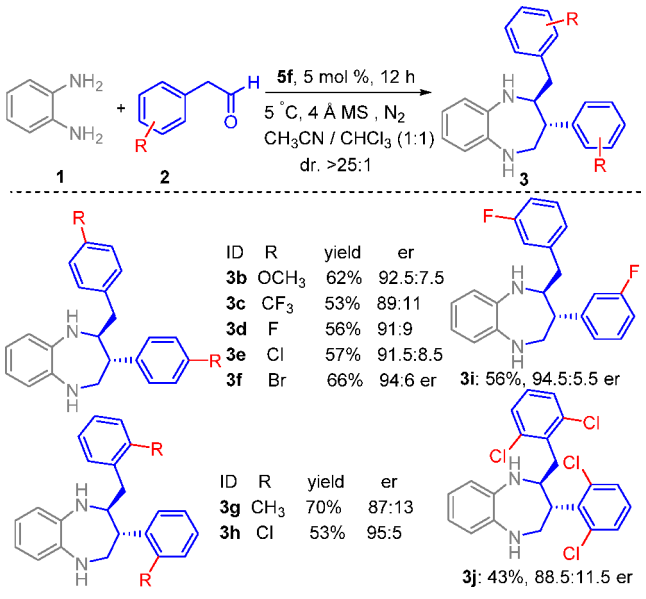
[a]Condition: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (5 mol %), solvent 2 mL, under a N_2 atmosphere overnight. [b]Calculated based on purification with silicon column; dr value was analyzed based on crude ^{1}H NMR (>25:1). [c]Analyzed by chiral HPLC. [d]ACN is the short name of CH_3CN. [e]4 Å molecular sieves were added. [f]HEH (1.2 equiv) was added. [g]BTL (1.2 equiv) was added.

https://dx.doi.org/10.1021/acs.joc.0c03064
J. Org. Chem. 2021, 86, 5110−5119

screened (entries 1−7). Fortunately, both the enantioselectivity and yield were improved with **5f** as a catalyst. Then the reaction solvents were screened with **5f** as a catalyst. The reaction yield and er value were slightly improved when we used acetonitrile (CH_3CN) as solvent (entry 8). However, the reaction yield and er value were decreased after decreasing the reaction temperature to 0 °C (entry 9). To improve the reaction yield and er value, when 4 Å molecular sieves were used for absorbing the produced water, both the reaction yield and er value could be improved (entry 10). Next, mixed solvents were investigated, which demonstrated that the mixture of CH_3CN:$CHCl_3$ (1:1) was the optimal solvent (entries 11−13). Then the addition of extra reduction reagents such as Hantzch ester (HEH)[16] or 2-phenyl-2,3-dihydrobenzo-[*d*]thiazole (BTL)[17] were investigated (entries 14 and 15). However, the reaction yield was not increased and the aromatized Hantzch pyridine or thiazole was not found. On the basis of this result, we realized that the in situ formed imidazoline (BBI)[14] was an irreplaceable hydride donor due to the fact that its reduction ability is generally higher than that of the HEH[18] and BTL.[19] Therefore, the optimal reaction conditions were obtained as follows: 1 equiv of *o*-PDA **1** and 1.5 equiv of phenylacetaldehyde **2** reacted in the mixture of CH_3CN:$CHCl_3$ (1:1) with catalytic **5f** (5 mol %) at 15 °C for 12 h without the addition of external H-donor. On the basis of the optimal reaction conditions, the 2,3-disubstituted-1,5-BDP **3a** could be obtained in 65% yield, good dr value (>25:1), and excellent er value (99:1).

Having the optimal conditions in hand, we began to explore the scope of the aromatic phenylacetaldehydes. From the results presented in Scheme 3, we could see that all chosen substrates reacted with **1** to give desired products (**3b**−**3j**) in excellent dr values (>25:1), moderate yields (43−70%), and moderate to good er values (87:13−95:5). Initially, the *para*-substituents of the phenylacetaldehydes were evaluated, which demonstrated that the reaction proceeded well with an electron-donating (**3b**) or electron-withdrawing (**3c**) group.

Scheme 3. Investigation of the Phenylacetaldehyde Substrate[a]

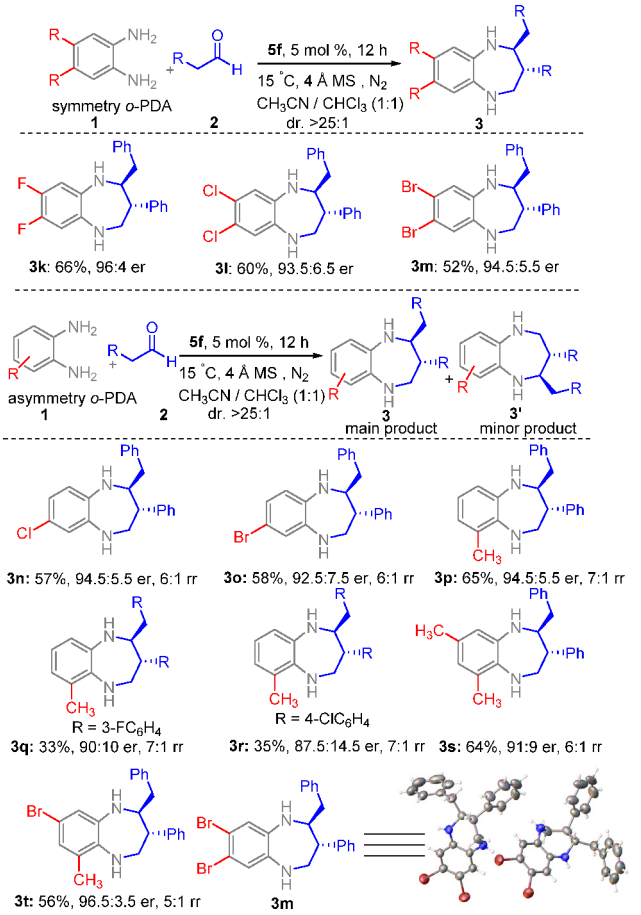


[a]The reaction temperature was decreased to 5 °C for better er.

In addition, various halogen substituents (F, Cl, Br) were also investigated, which proved that the desired products were obtained with moderate yields and good er values (**3d**−**3f**). Then the *ortho*-substituents were evaluated, which demonstrated the *o*-methyl substituent was good for high yield (70%) and bad for er value (87:13, **3g**). However, the *ortho*-Cl substituent was good for high er value (95:5, **3h**). In addition, the *meta*-F substituent was investigated, which also afforded the corresponding product with a pleasant er value (94.5:5.5, **3i**). Meanwhile, *ortho*-disubstituted phenylacetaldehyde with big steric hindrance was evaluated, which afforded the desired product **3j** in slightly lower yield (43%) and moderate er value (88.5:11.5).

Then we turned to investigate the reaction with substituted *o*-PDAs as substrates (Scheme 4). To our delight, symmetric

Scheme 4. Investigation of the Reaction with Symmetric and Unsymmetric *o*-PDA as Substrate



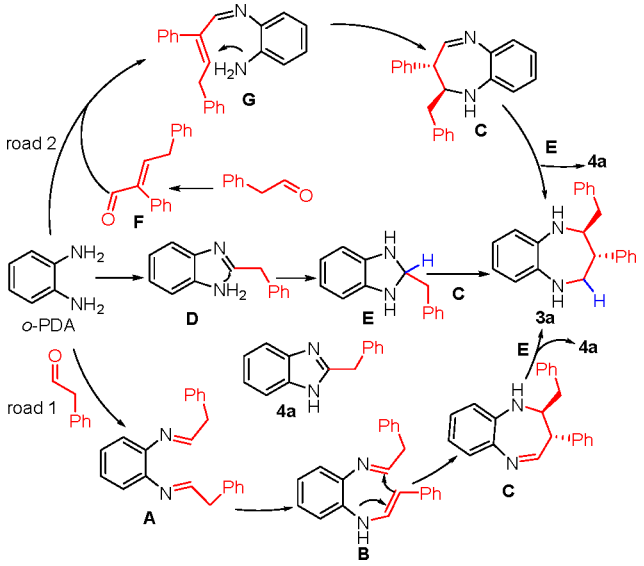
disubstituted *o*-PDAs (e.g., fluoro, chloro, bromo) performed well in this transformation, affording the corresponding products (**3k**−**3m**) in excellent dr values (>25:1), moderate yields (52−66%), and good er values (93.5:6.5−96:4). Meanwhile, the absolute configuration of **3m** was confirmed by X-ray single crystal analysis and other products were assigned by analogy. The universalities of the reaction prompted us to investigate the reaction with unsymmetric *o*-PDAs as substrate (Scheme 4). The reaction would become very complicated due to the incorporation of regioselectivity,[20] diastereoselectivity, and enantioselectivity. To our surprise, 4-Cl-*o*-PDA and 4-Br-*o*-PDA reacted smoothly, affording the

https://dx.doi.org/10.1021/acs.joc.0c03064
J. Org. Chem. 2021, 86, 5110−5119

corresponding products (**3n**, **3o**) in pleasant regioselectivity (6:1) and moderate yields. Moreover, high diastereoselectivity (>25:1) and good enantioselectivity were maintained. Then the 3-CH_3-*o*-PDA was investigated, which afforded **3p** in better regioselectivity (7:1), high diastereoselectivity (>25:1), and good enantioselectivity (94.5:5.5). Meanwhile, other substituted phenylacetaldehydes were used to react with 3-CH_3-*o*-PDA, and the corresponding products (**3q**, **3r**) were obtained in good regioselectivity (7:1), high diastereoselectivity (>25:1), moderate yield, and good enantioselectivity as well. On the basis of this unique regioselectivity, other unsymmetric disubstituted *o*-PDAs were evaluated. Interestingly, the 3,5-di-CH_3-*o*-PDA proceeded well and afforded **3s** in good regioselectivity (6:1) and moderate er value (91:9). Meanwhile, 5-Br-3-CH_3-*o*-PDA afforded the corresponding product **3t** in moderate regioselectivity (5:1) and good er value (96.5:3.5). The structures of these products were affirmed based on 2D NMR (see Supporting Information). Interestingly, when *N*-CH_3-*o*-PDA was used as substrate, the corresponding product was not obtained.

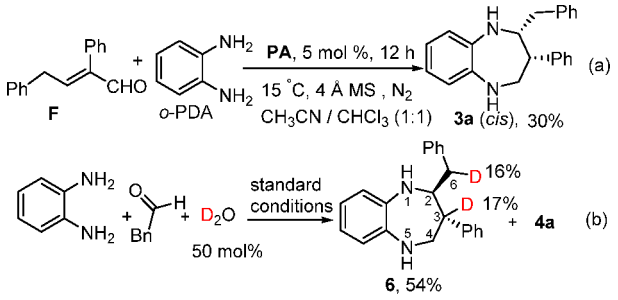
Then, we moved on to investigate the reaction mechanism. On the basis of the reaction results as well as the previous literature,[11,21] two possible reaction roads were proposed (Scheme 5). On the first road, *o*-PDA reacts with phenylacetaldehyde to form imine intermediate **A**, which could easily isomerize into intermediate **B** through imine/enamine isomerization. Next, cyclic imine **C** is formed through the intramolecular enantioselective Mannich reaction under the chiral phosphoric catalyst. Finally, the in situ formed imidazoline **E** selectively reduces the imine **C** and affords the final product **3a** and the corresponding aromatized imidazole **4a**. On the second road, α,β-unsaturated aldehyde **F** might be formed from **2a** by aldol condensation. Then, α,β-unsaturated imine **G** is formed, which reacts through intramolecular Michael reaction to form the cyclic imine intermediate **C**. Finally, intermediate **C** is reduced with **E** to afford the product **3a**.

Scheme 5. Plausible Reaction Mechanism



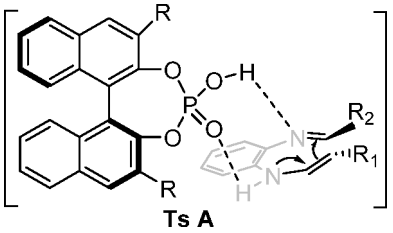
In order to verify the reaction road 2, α,β-unsaturated aldehyde **F** was prepared and used as a substrate under the optimal reaction conditions (Scheme 6a). Interestingly, the obtained product was *cis*-**3a** rather than *trans*-**3a**. According to this result, we concluded that the reaction proceeded via road 2. Meanwhile, the production of the reaction intermediate **B** was detected via the NMR experiment (Figure S1; see Supporting Information). Moreover, the imine/enamine isomerization could be proved via the deuteration experiment (Scheme 6b). Therefore, road 1 might be the reasonable reaction process.

Scheme 6. Investigation of the Reaction Mechanism



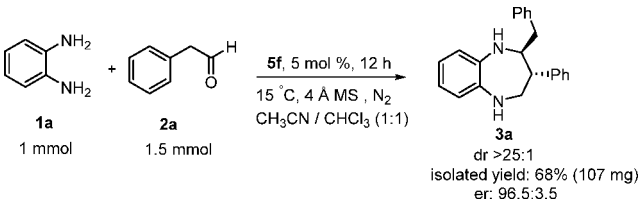
According to the reaction mechanism and the previous report,[22] the chirality of the reaction might be formed through the intramolecular Mannich reaction. Therefore, we proposed that the bifunctional nature of the chiral phosphoric acid is responsible for concurrent activation of both the enamine nucleophile and the imine electrophile through hydrogen bonding[23] (Scheme 7, **TsA**).

Scheme 7. Proposing the Reasonable Transition State



To demonstrate the synthetic practicality of this approach, a large-scale synthesis of **3a** was performed. The reaction proceeded smoothly to give the corresponding product in 68% isolated yield with high dr value (>25:1) and only a slight loss in er value (96.5:3.5) (Scheme 8).

Scheme 8. Large-Scale Synthesis of 3a



CONCLUSIONS

In summary, we have developed an unexpected tandem reaction for efficient preparation of 2,3-disubstituted-1,5-BDPs which was incompetent with previous ways. There was no need to add any extra reductant to reduce the imine intermediate, and the in situ formed imidazoline was the irreplaceable reductant for the reaction. A series of 2,3-

https://dx.doi.org/10.1021/acs.joc.0c03064
J. Org. Chem. 2021, 86, 5110−5119

disubstituted-1,5-BDP were obtained in good er (up to 99:1), good dr (>25:1), and especially acceptable rr (up to 7:1) for the unsymmetric *o*-PDAs. The reaction mechanism was investigated which demonstrated that the reaction probably proceeds through the enantioselective intramolecular Mannich reaction/transfer hydrogenation tandem reaction.

EXPERIMENTAL SECTION

General Information. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agent prior to use. All kinds of phenylenediamines are commercially available. All chiral phosphoric acid was purchased from DAICEL CHIRAL TECHNOLOGIES (CHINA) CO., Ltd. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. The heating reaction condition was performed under an oil bath with a magnetic stirrer DF-101T. The cooling reaction condition was performed with a ChangCheng cooler DFY-5L. Melting points are uncorrected and recorded on a digital melting point apparatus WRS-1B. Reactions were monitored by thin layer chromatography using 0.25 mm Merck silica gel precoated plates (60F-254). Visualization was accomplished by irradiation with UV light at 254 nm. Column chromatography was performed using Macherey-Nagel silica gel 60 M (particle size 0.040−0.063 mm). Chemical yields refer to pure isolated substances. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on Bruker spectrometers at 400 or 101 MHz, respectively, using $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal reference. Structural assignments were made with additional information from gHMBC, and gDEPT 135° experiments. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, b = broad. HRMS (ESI) determinations were performed on a Bruker micrOTOF II spectrometer (TOF analyzer). X-ray crystallographic structure determination was carried out on a Bruker SMART CCD. Enantiomeric ratios (er) were determined by chiral HPLC using Daicel CHIRALCEL OJ-H, AD-H, and AS-H columns with hexane/2-propanol as the eluents. Optical rotations were measured on an Autopol IV Polarimeter and reported as follows: $[\alpha]_D^{20}$ (*c* in g per 100 mL, solvent).

Synthesis of Phenylacetaldehydes. Phenylacetaldehyde **2a** was purchased. Others (**2b−j**)[24] were prepared by oxidation of the corresponding aryl ethanol according to a reported literature. IBX (10 mmol) was added to a solution of aryl ethanol (5 mmol) in CH_3CN (15 mL) at room temperature. Then the reaction mixture was moved to an oil bath, which was refluxed at 80 °C under a N_2 atmosphere for 2.5 h. After cooling to room temperature, filtration, and evaporation, followed by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1−7/1), the desired product was obtained.

Preparation of Chiral 2,3-Disubstituted 1,5-BDPs with Different Phenylacetaldehydes (3a−3j). To a tube were added a solution of *o*-DPA (0.2 mmol, 1.0 equiv), 4 Å MS (50 mg), acid catalyst **5f** (7.5 mg, 10 μmol, 0.05 equiv), and 1 mL of mixed solvent (CH_3CN:$CHCl_3$ = 1:1); the tube was sealed with a septum, evacuated, and backfilled with nitrogen three times. Next, phenylacetaldehyde (0.3 mmol, 1.5 equiv) was dissolved in 1 mL of mixed solvent (CH_3CN:$CHCl_3$ = 1:1), which was added into the above solution by syringe under a nitrogen atmosphere, and it was stirred at 5 °C overnight, Next, the reaction mixture was concentrated. The desired product was isolated by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 15/1−8/1). The enantiomeric ratio of the product was determined by HPLC analysis.

*(2S,3R)-2-Benzyl-3-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]-diazepine (**3a**).* Prepared according to the general procedure, but the reaction temperature was 15 °C, and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (20 mg, yield 65%), with er 99:1 (HPLC, Daicel Chiralcel OJ-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 17.8 min; t_{R2} = 20.4 min; $[\alpha]_D^{20}$ = +35° (*c* 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dt, *J* = 14.9, 7.4 Hz, 4H), 7.30 (dt, *J* = 13.4, 7.3 Hz, 4H), 7.16 (d, *J* = 7.2 Hz, 2H), 6.76 (t, *J* = 7.0 Hz, 1H), 6.66 (dd, *J* = 14.1, 6.9 Hz, 2H), 6.30 (d, *J* = 7.6 Hz, 1H), 3.85 (dd, *J* = 13.2, 4.2 Hz, 1H), 3.77−3.51 (m, 2H), 3.13 (dd, *J* = 13.2, 6.2 Hz, 1H), 2.94−2.79 (m, 2H), 2.53 (dd, *J* = 14.3, 11.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.5, 140.4, 138.7, 138.6, 128.9, 128.8, 128.7, 128.0, 126.8, 126.7, 121.3, 120.6, 119.6, 118.4, 62.2, 53.4, 52.6, 40.8. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{22}H_{23}N_2$ 315.1856; Found 315.1862.

*(2S,3R)-2-(4-Methoxybenzyl)-3-(4-methoxyphenyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3b**).* Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (10:1) to afford a yellow oil (23 mg, yield 62%), with er 92.5:7.5 (HPLC, Daicel Chiralcel AD-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 12.4 min; t_{R2} = 23.4 min; $[\alpha]_D^{20}$ = +43° (*c* 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.79 (dt, *J* = 14.7, 7.4 Hz, 2H), 6.71 (t, *J* = 7.3 Hz, 1H), 6.33 (d, *J* = 7.5 Hz, 1H), 3.83 (d, *J* = 5.1 Hz, 7H), 3.60−3.45 (m, 1H), 3.08 (dd, *J* = 13.1, 7.0 Hz, 1H), 2.90 (t, *J* = 9.9 Hz, 1H), 2.77 (dd, *J* = 14.2, 2.3 Hz, 1H), 2.44 (dd, *J* = 14.3, 11.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 158.5, 158.3, 139.4, 135.1, 130.5, 129.9, 128.9, 121.5, 120.0, 119.1, 114.1, 114.0, 62.6, 55.3, 52.9, 52.0, 39.8. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{24}H_{27}N_2O_2$ 375.2067; Found 375.2061.

*(2S,3R)-2-(4-(Trifluoromethyl)benzyl)-3-(4-(trifluoromethyl)-phenyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3c**).* Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (10:1) to afford a yellow oil (24 mg, yield 53%), with er 89:11 (HPLC, Daicel Chiralcel OJ-H column, 95:5 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 26.9 min; t_{R2} = 35.2 min); $[\alpha]_D^{20}$ = +51° (*c* 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.59−7.54 (m, 4H), 7.29−7.23 (m, 2H), 6.81−6.73 (m, 1H), 6.67 (t, *J* = 7.6 Hz, 2H), 6.37−6.31 (m, 1H), 3.96 (dd, *J* = 13.4, 4.5 Hz, 1H), 3.88 (ddd, *J* = 10.7, 9.2, 3.3 Hz, 3H), 3.18 (dd, *J* = 13.4, 5.0 Hz, 1H), 2.98 (dt, *J* = 9.2, 4.7 Hz, 1H), 2.86 (dd, *J* = 14.5, 2.7 Hz, 1H), 2.72 (dd, *J* = 14.5, 10.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.7, 142.5, 139.6, 137.5, 129.3 (C-F, $^{2}J_{C-F}$ = 33.3 Hz), 129.2, 128.3, 125.7 (C-F, $^{3}J_{C-F}$ = 4.0 Hz), 124.1 (C-F,$^{1}J_{C-F}$ = 273.7 Hz), 121.4, 120.5, 119.3, 118.1, 61.8, 52.5, 51.6, 40.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.4, −62.5. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{24}H_{21}F_2N_2$ 451.1603; Found 451.1591.

*(2S,3R)-2-(4-Fluorobenzyl)-3-(4-fluorophenyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3d**).* Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (20 mg, yield 56%), with er 91:9 (HPLC, Daicel Chiralcel AD-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 9.2 min; t_{R2} = 16.8 min); $[\alpha]_D^{20}$ = +146° (*c* 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.15−7.04 (m, 4H), 7.01 (t, *J* = 8.6 Hz, 2H), 6.77 (t, *J* = 7.4 Hz, 1H), 6.72−6.59 (m, 2H), 6.32 (d, *J* = 7.3 Hz, 1H), 3.89 (dd, *J* = 13.3, 4.3 Hz, 1H), 3.75−3.19 (m, 3H), 3.11 (dd, *J* = 13.3, 5.7 Hz, 1H), 2.88 (dt, *J* = 9.6, 5.0 Hz, 1H), 2.83−2.69 (m, 1H), 2.53 (dd, *J* = 14.4, 11.1 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.8 (C-F,$^{1}J_{C-F}$ = 245.4 Hz), 168.7 (C-F,$^{1}J_{C-F}$ = 245.4 Hz), 139.8, 139.3 (C-F, $^{4}J_{C-F}$ = 3.0 Hz), 138.3, 134.1 (C-F, $^{4}J_{C-F}$ = 3.0 Hz), 130.3 (C-F, $^{3}J_{C-F}$ = 7.1 Hz), 129.3 (C-F, $^{3}J_{C-F}$ = 8.1 Hz), 121.4, 120.7, 119.5, 118.3, 115.6 (C-F, $^{2}J_{C-F}$ = 21.2 Hz), 115.5 (C-F, $^{2}J_{C-F}$ = 20.2 Hz), 62.5, 52.3, 52.1, 40.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.0, −116.1. HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{22}H_{21}F_2N_2$ 351.1667; Found 351.1664.

*(2S,3R)-2-(4-Chlorobenzyl)-3-(4-chlorophenyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3e**).* Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (12:1) to afford a yellow oil (22 mg, yield 57%), with er 91.5:8.5 (HPLC, Daicel Chiralcel AD-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 8.7 min; t_{R2} = 10.9 min); $[\alpha]_D^{20}$ = +28° (*c* 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.32 (m, 4H), 7.29 (d, *J* = 4.2 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.76 (t, *J* = 7.0 Hz, 1H), 6.66 (t, *J* =

https://dx.doi.org/10.1021/acs.joc.0c03064
J. Org. Chem. 2021, 86, 5110−5119

6.9 Hz, 2H), 6.32 (d, J = 7.3 Hz, 1H), 3.89 (dd, J = 13.3, 4.4 Hz, 1H), 3.78−3.20 (m, 3H), 3.11 (dd, J = 13.3, 5.4 Hz, 1H), 2.85 (dt, J = 9.4, 4.8 Hz, 1H), 2.78 (dd, J = 14.4, 2.6 Hz, 1H), 2.54 (dd, J = 14.4, 11.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.1, 139.8, 138.0, 136.9, 132.6, 132.5, 130.2, 129.3, 128.9, 128.8, 121.4, 120.6, 119.4, 118.2, 62.1, 52.2, 52.0, 40.2. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{22}H_{21}Cl_2N_2$ 383.1076; Found 383.1071.

(2S,3R)-2-(4-Bromobenzyl)-3-(4-bromophenyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3f**). Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (31 mg, yield 66%), with er 94:6 (HPLC, Daicel Chiralcel AD-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 9.7 min; t_{R2} = 11.6 min); $[\alpha]_D^{20}$ = +88° (c 0.04, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.2 Hz, 2H), 6.83−6.73 (m, 1H), 6.67 (t, J = 6.7 Hz, 2H), 6.33 (d, J = 7.7 Hz, 1H), 3.89 (dd, J = 13.3, 4.4 Hz, 1H), 3.78−3.20 (m, 3H), 3.11 (dd, J = 13.3, 5.4 Hz, 1H), 2.85 (dt, J = 9.3, 4.7 Hz, 1H), 2.76 (dd, J = 14.4, 2.7 Hz, 1H), 2.53 (dd, J = 14.4, 11.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.6, 139.7, 138.0, 137.4, 131.8, 130.6, 129.7, 121.4, 120.7, 120.6, 120.5, 119.5, 118.2, 62.0, 52.2, 51.9, 40.3. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{22}H_{21}Br_2N_2$ 471.0066; Found 471.0060.

(2S,3R)-2-(2-Methylbenzyl)-3-(o-tolyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3g**). Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (24 mg, yield 70%), with er 87:13 (HPLC, Daicel Chiralcel AD-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 5.8 min; t_{R2} = 16.2 min; $[\alpha]_D^{20}$ = +26° (c 0.04, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.0 Hz, 1H), 7.27−7.22 (m, 2H), 7.18 (dd, J = 7.4, 3.4 Hz, 5H), 6.78 (t, J = 7.0 Hz, 1H), 6.69 (dd, J = 12.9, 6.8 Hz, 2H), 6.41−6.30 (m, 1H), 3.73 (dd, J = 13.2, 4.1 Hz, 2H), 3.69−3.53 (m, 2H), 3.29 (ddd, J = 9.7, 7.0, 4.2 Hz, 1H), 3.07 (dd, J = 13.2, 7.0 Hz, 1H), 2.78 (dd, J = 14.4, 2.5 Hz, 1H), 2.60 (dd, J = 14.4, 11.2 Hz, 1H), 2.48 (s, 3H), 2.12 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 141.5, 140.6, 139.0, 136.9, 136.7, 135.9, 130.8, 130.5, 129.3, 126.8, 126.5, 126.3, 126.1, 121.5, 120.8, 119.9, 118.6, 61.2, 52.4, 47.9, 37.7, 20.5, 19.4. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{24}H_{27}N_2$ 343.2169; Found 343.2165.

(2S,3R)-2-(2-Chlorobenzyl)-3-(2-chlorophenyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3h**). Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (20 mg, yield 53%), with er 95:5 (HPLC, Daicel Chiralcel AD-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 7.1 min; t_{R2} = 11.8 min); $[\alpha]_D^{20}$ = +33° (c 0.04, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.36−7.29 (m, 2H), 7.19 (t, J = 7.4 Hz, 4H), 6.77−6.70 (m, 1H), 6.68−6.60 (m, 2H), 6.38 (d, J = 7.3 Hz, 1H), 3.96 (dq, J = 9.3, 4.4 Hz, 2H), 3.68 (dt, J = 9.0, 4.5 Hz, 3H), 3.14 (dd, J = 13.4, 4.6 Hz, 1H), 2.95−2.84 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.9, 138.0, 136.6, 131.0, 129.8, 129.4, 128.7, 128.1, 127.7, 127.1, 126.9, 121.0, 120.2, 119.2, 118.0, 61.0, 51.0, 46.8, 38.1. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{22}H_{21}Cl_2N_2$ 383.1076; Found 383.1072.

(2S,3R)-2-(3-Fluorobenzyl)-3-(3-fluorophenyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3i**). Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (15:1) to afford a yellow oil (20 mg, yield 56%), with er 94.5:5.5 (HPLC, Daicel Chiralcel AD-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 7.5 min; t_{R2} = 15.8 min; $[\alpha]_D^{20}$ = +30° (c 0.04, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.31 (m, 1H), 7.30 (d, J = 4.7 Hz, 1H), 7.19 (t, J = 7.3 Hz, 2H), 7.05−6.89 (m, 3H), 6.85 (d, J = 9.8 Hz, 1H), 6.77 (t, J = 7.4 Hz, 1H), 6.69 (dd, J = 16.1, 7.8 Hz, 2H), 6.33 (d, J = 7.6 Hz, 1H), 3.91 (dd, J = 13.3, 4.3 Hz, 1H), 3.77−3.23 (m, 2H), 3.14 (dd, J = 13.3, 5.6 Hz, 1H), 2.91 (dt, J = 9.4, 4.8 Hz, 1H), 2.82 (dd, J = 14.4, 2.6 Hz, 1H), 2.58 (dd, J = 14.4, 11.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.1 (C-F, $^1J_{C\text{-}F}$ = 246.4 Hz), 163.0 (C-F, $^1J_{C\text{-}F}$ = 247.5 Hz), 145.9 (C-F, $^3J_{C\text{-}F}$ = 7.1 Hz), 141.0 (C-F, $^3J_{C\text{-}F}$ = 7.1 Hz), 139.4, 138.2, 130.3 (C-F, $^3J_{C\text{-}F}$ = 8.1 Hz), 130.2 (C-F, $^3J_{C\text{-}F}$ = 8.1 Hz), 124.5 (C-F, $^4J_{C\text{-}F}$ = 2.0 Hz), 123.7 (C-F, $^4J_{C\text{-}F}$ = 3.0 Hz), 121.5, 120.9, 119.5, 118.5, 115.7 (C-F, $^2J_{C\text{-}F}$ = 21.2 Hz), 114.7 (C-F, $^2J_{C\text{-}F}$ = 22.2 Hz), 113.8 (C-F, $^2J_{C\text{-}F}$ = 21.2 Hz), 113.7 (C-F, $^2J_{C\text{-}F}$ = 21.2 Hz), 62.0, 52.5, 52.0, 40.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.7, −112.8. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{22}H_{21}F_2N_2$ 351.1667; Found 351.1669.

(2S,3R)-2-(2,6-Dichlorobenzyl)-3-(2,6-dichlorophenyl)-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3j**). Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (19 mg, yield 43%), with er 88.5:11.5 (HPLC, Daicel Chiralcel AD-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 9.7 min; t_{R2} = 27.3 min); $[\alpha]_D^{20}$ = +31° (c 0.04, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.0 Hz, 1H), 7.33 (dd, J = 18.1, 8.0 Hz, 3H), 7.16 (dt, J = 11.7, 8.0 Hz, 2H), 6.77 (ddt, J = 21.7, 14.4, 7.2 Hz, 3H), 6.40 (d, J = 7.5 Hz, 1H), 4.32 (td, J = 10.3, 2.8 Hz, 1H), 4.23 (td, J = 9.5, 2.9 Hz, 1H), 3.90 (dd, J = 12.5, 10.0 Hz, 3H), 3.44−3.29 (m, 2H), 2.84 (dd, J = 13.7, 2.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 141.8, 139.2, 137.3, 136.3, 134.9, 134.6, 130.2, 128.8, 128.6, 128.5, 128.4, 122.1, 121.4, 121.2, 119.6, 57.2, 52.6, 49.2, 35.7. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{22}H_{19}Cl_4N_2$ 451.0297; Found 451.0290.

Preparation of Chiral 2,3-Disubstituted 1,5-BDPs with Different *o*-DPAs (3k−3t). To a tube were added a solution of different *o*-DPA (0.2 mmol, 1.0 equiv), 4 Å MS (50 mg), acid catalyst **5f** (7.5 mg, 10 μmol, 0.05 equiv), and 1 mL of mixed solvent (CH_3CN:$CHCl_3$ = 1:1); the tube was sealed with a septum, evacuated, and backfilled with nitrogen three times. Next, phenylacetaldehyde (0.3 mmol, 1.5 equiv) was dissolved in 1 mL of mixed solvent (CH_3CN:$CHCl_3$ = 1:1), which was added into the above solution by syringe under a nitrogen atmosphere, and it was stirred at 15 °C overnight. Next, the reaction mixture was concentrated. The desired product was isolated by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 15/1−8/1). The enantiomeric ratio of the product was determined by HPLC analysis. X-ray quality crystals were obtained by slow evaporation of solvent from a saturated solution in hexanes. This compound was further characterized by X-ray crystallography.

(2S,3R)-2-Benzyl-7,8-difluoro-3-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3k**). Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (23 mg, yield 66%), with er 96:4 (HPLC, Daicel Chiralcel AD-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 9.6 min; t_{R2} = 17.0 min; $[\alpha]_D^{20}$ = +38° (c 0.04, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 4.2 Hz, 4H), 7.36−7.32 (m, 2H), 7.29 (s, 2H), 7.15 (d, J = 7.2 Hz, 2H), 6.48 (dd, J = 11.2, 7.7 Hz, 1H), 6.07 (dd, J = 11.2, 7.8 Hz, 1H), 3.76 (dd, J = 13.3, 4.0 Hz, 1H), 3.68−3.37 (m, 3H), 3.09 (dd, J = 13.3, 6.8 Hz, 1H), 2.93−2.76 (m, 2H), 2.49 (dd, J = 14.2, 11.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.6 (C-F, $^1J_{C\text{-}F}$ = 227.3 Hz), 144.4 (C-F, $^1J_{C\text{-}F}$ = 227.3 Hz), 142.6, 138.2, 135.9 (C-F, $^3J_{C\text{-}F}$ = 7.1 Hz), 135.8 (C-F, $^3J_{C\text{-}F}$ = 7.1 Hz), 135.2 (C-F, $^3J_{C\text{-}F}$ = 6.1 Hz), 135.1 (C-F, $^3J_{C\text{-}F}$ = 6.1 Hz), 128.9, 128.8, 128.7, 127.9, 127.1, 127.0, 108.1 (C-F, $^2J_{C\text{-}F}$ = 19.2 Hz), 107.2 (C-F, $^2J_{C\text{-}F}$ = 20.2 Hz), 62.41, 53.22, 52.80, 40.61. ^{19}F NMR (376 MHz, $CDCl_3$) δ −147.8, −147.9, −148.7, −148.8. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{22}H_{21}F_2N_2$ 351.1667; Found 351.1667.

(2S,3R)-2-Benzyl-7,8-dichloro-3-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3l**). Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (23 mg, yield 60%), with er 93.5:6.5 (HPLC, Daicel Chiralcel AS-H column, 98:2 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 18.7 min; t_{R2} = 26.5 min; $[\alpha]_D^{20}$ = +28° (c 0.04, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44−7.38 (m, 3H), 7.38−7.31 (m, 3H), 7.30−7.25 (m, 2H), 7.18−7.07 (m, 2H), 6.69 (s, 1H), 6.32 (s, 1H), 3.87 (dd, J = 13.4, 4.4 Hz, 1H), 3.83−3.69 (m, 2H), 3.55 (s, 1H), 3.14 (dd, J = 13.4, 5.5 Hz, 1H), 2.86 (ddd, J = 14.3, 8.1, 4.0 Hz, 2H), 2.52 (dd, J = 14.5, 11.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.1,

https://dx.doi.org/10.1021/acs.joc.0c03064
J. Org. Chem. 2021, 86, 5110−5119

139.8, 138.3, 138.2, 128.9, 128.8, 128.7, 127.9, 127.1, 127.0, 123.1, 122.2, 120.0, 118.8, 62.1, 52.6, 51.9, 40.7. HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{22}H_{21}Cl_2N_2$ 383.1076; Found 383.1077.

*(2S,3R)-2-Benzyl-7,8-dibromo-3-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3m**).* Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (24. mg, yield 52%), with er 94.5:5.5 (HPLC, Daicel Chiralcel AS-H column, 98:2 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 12.2 min; t_{R2} = 15.5 min; $[\alpha]_D^{20}$ = +41° (c 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.37 (m, 3H), 7.34 (dd, J = 9.4, 7.7 Hz, 2H), 7.28 (d, J = 9.7 Hz, 3H), 7.16−7.08 (m, 2H), 6.86 (s, 1H), 6.48 (s, 1H), 3.88 (dd, J = 13.4, 4.5 Hz, 1H), 3.84−3.70 (m, 2H), 3.55 (s, 1H), 3.14 (dd, J = 13.3, 5.3 Hz, 1H), 2.92−2.77 (m, 2H), 2.52 (dd, J = 14.5, 11.0 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.2, 140.5, 139.0, 128.9, 128.8, 128.7, 127.9, 127.1, 127.0, 122.9, 121.8, 62.0, 52.4, 51.8, 40.7. HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{22}H_{21}Br_2N_2$ 471.0066; Found 471.0076.

*(2S,3R)-2-Benzyl-7-chloro-3-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3n**).* Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (20 mg, yield 57%), with er 94.5:5.5 (HPLC, Daicel Chiralcel AS-H column, 98:2 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 13.0 min; t_{R2} = 17.7 min; $[\alpha]_D^{20}$ = +30° (c 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.29 (m, 8H), 7.14 (d, J = 7.1 Hz, 2H), 6.68 (dd, J = 8.3, 2.3 Hz, 1H), 6.56 (d, J = 8.3 Hz, 1H), 6.26 (d, J = 2.3 Hz, 1H), 3.83 (dd, J = 13.3, 4.3 Hz, 1H), 3.77−3.68 (m, 1H), 3.59 (s, 1H), 3.11 (dd, J = 13.3, 6.0 Hz, 1H), 2.86 (ddd, J = 17.1, 12.0, 4.2 Hz, 2H), 2.52 (dd, J = 14.4, 11.1 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.2, 139.8, 138.7, 138.3, 128.9, 128.8, 128.7, 127.9, 127.0, 126.9, 124.9, 120.8, 119.2, 119.0, 62.0, 53.0, 52.4, 40.8. HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{22}H_{22}Cl_2N_2$ 349.1466; Found 349.1447.

*(2S,3R)-2-Benzyl-7-bromo-3-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3o**).* Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (23 mg, yield 58%), with er 92.5:7.5 (HPLC, Daicel Chiralcel AD-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 11.3 min; t_{R2} = 36.1 min); $[\alpha]_D^{20}$ = +33° (c 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (q, J = 8.1, 7.5 Hz, 4H), 7.35−7.26 (m, 4H), 7.14 (d, J = 7.2 Hz, 2H), 6.86−6.78 (m, 1H), 6.51 (d, J = 8.2 Hz, 1H), 6.43−6.37 (m, 1H), 3.84 (dd, J = 13.3, 4.2 Hz, 1H), 3.78−3.47 (m, 3H), 3.12 (dd, J = 13.3, 5.8 Hz, 1H), 2.94−2.76 (m, 2H), 2.52 (dd, J = 14.2, 11.1 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.3, 140.0, 139.3, 138.3, 128.9, 128.8, 128.7, 127.9, 126.9, 126.8, 123.6, 121.7, 119.4, 111.9, 62.0, 52.9, 52.3, 40.8. HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{22}H_{22}BrN_2$ 393.0961; Found 393.0963.

*(2S,3R)-2-Benzyl-6-methyl-3-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3p**).* Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (13:1) to afford a yellow oil (21 mg, yield 65%), with er 94.5:5.5 (HPLC, Daicel Chiralcel AD-H column, 98:2 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 12.3 min; t_{R2} = 18.7 min; $[\alpha]_D^{20}$ = +43° (c 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.42 (m, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.31 (td, J = 3.4, 2.0 Hz, 3H), 7.27−7.21 (m, 1H), 7.19−7.11 (m, 2H), 6.68 (d, J = 7.4 Hz, 1H), 6.53 (t, J = 7.6 Hz, 1H), 6.19 (dd, J = 7.8, 1.4 Hz, 1H), 4.00 (dd, J = 13.3, 4.4 Hz, 1H), 3.78 (ddd, J = 11.0, 9.5, 3.0 Hz, 3H), 3.16 (dd, J = 13.3, 5.4 Hz, 1H), 2.94−2.80 (m, 2H), 2.54 (dd, J = 14.4, 11.0 Hz, 1H), 2.19 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.8, 138.7, 138.4, 128.9, 128.7, 128.6, 128.1, 126.8, 126.6, 124.5, 123.0, 119.5, 117.8, 62.2, 53.1, 51.9, 40.8, 17.8. HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{23}H_{25}N_2$ 329.2012; Found 329.2019.

*(2S,3R)-(2S,3R)-2-(3-Fluorobenzyl)-3-(3-fluorophenyl)-6-methyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3q**).* Prepared according to the general procedure, but the reaction temperature was 5 °C, and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (12:1) to afford a yellow oil (12 mg, yield 33%), with er 86.5:13.5 (HPLC, Daicel Chiralcel AD-H column, 95:5 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 10.1 min; t_{R2} = 13.5 min; $[\alpha]_D^{20}$ = +15° (c 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dt, J = 12.1, 5.9 Hz, 1H), 7.28−7.15 (m, 3H), 7.06−6.97 (m, 1H), 6.94 (t, J = 6.5 Hz, 2H), 6.85 (d, J = 9.7 Hz, 1H), 6.69 (d, J = 7.3 Hz, 1H), 6.56 (t, J = 7.6 Hz, 1H), 6.23 (d, J = 7.6 Hz, 1H), 4.05 (dd, J = 13.4, 4.4 Hz, 1H), 3.89−3.35 (m, 3H), 3.19 (dd, J = 13.4, 4.5 Hz, 1H), 2.98−2.77 (m, 2H), 2.59 (dd, J = 14.3, 11.0 Hz, 1H), 2.20 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.1 (C-F, $^1J_{C\text{-}F}$ = 246.4 Hz), 163.0 (C-F, $^1J_{C\text{-}F}$ = 248.5 Hz), 146.2 (C-F, $^3J_{C\text{-}F}$ = 7.1 Hz), 141.1 (C-F, $^3J_{C\text{-}F}$ = 8.1 Hz), 137.8, 137.7, 130.2 (C-F, $^3J_{C\text{-}F}$ = 8.1 Hz), 130.1 (C-F, $^3J_{C\text{-}F}$ = 8.1 Hz), 124.6, 124.5 (C-F, $^4J_{C\text{-}F}$ = 3.0 Hz), 123.83 (C-F, $^4J_{C\text{-}F}$ = 3.0 Hz), 123.2, 119.6, 117.7, 115.7 (C-F, $^2J_{C\text{-}F}$ = 20.2 Hz), 114.7 (C-F, $^2J_{C\text{-}F}$ = 21.2 Hz), 113.8 (C-F, $^2J_{C\text{-}F}$ = 21.2 Hz), 113.7 (C-F, $^2J_{C\text{-}F}$ = 21.21 Hz), 62.0, 52.3, 51.3, 40.5, 17.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ −112.8, −112.9. HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{23}H_{23}F_2N_2$ 365.1824; Found 365.1817.

*(2S,3R)-(2S,3R)-2-(4-Chlorobenzyl)-3-(4-chlorophenyl)-6-methyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3r**).* Prepared according to the general procedure, but the reaction temperature was 5 °C, and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (15:1) to afford a yellow oil (14 mg, yield 35%), with er 87.5:14.5 (HPLC, Daicel Chiralcel AD-H column, 95:5 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 12.6 min; t_{R2} = 15.2 min; $[\alpha]_D^{20}$ = +25° (c 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (q, J = 8.6 Hz, 4H), 7.28 (d, J = 1.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 6.68 (d, J = 7.1 Hz, 1H), 6.55 (t, J = 7.6 Hz, 1H), 6.21 (d, J = 7.0 Hz, 1H), 4.03 (dd, J = 13.4, 4.5 Hz, 1H), 3.76 (td, J = 11.0, 3.1 Hz, 3H), 3.15 (dd, J = 13.4, 4.6 Hz, 1H), 2.89−2.74 (m, 2H), 2.54 (dd, J = 14.5, 11.0 Hz, 1H), 2.18 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 142.2, 137.8, 137.7, 136.9, 132.6, 132.4, 130.1, 129.4, 128.8, 124.5, 119.5, 117.6, 62.1, 52.0, 51.4, 40.1, 17.8. HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{23}H_{23}Cl_2N_2$ 397.1233; Found 397.1236.

*(2S,3R)-2-Benzyl-6,8-dimethyl-3-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3s**).* Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (15:1) to afford a yellow oil (19 mg, yield 56%), with er 91:9 (HPLC, Daicel Chiralcel AD-H column, 98:2 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 10.7 min; t_{R2} = 15.6 min; $[\alpha]_D^{20}$ = +25° (c 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.35 (m, 4H), 7.32 (q, J = 6.1, 5.2 Hz, 3H), 7.28−7.23 (m, 1H), 7.16 (d, J = 7.0 Hz, 2H), 6.52 (s, 1H), 6.02 (s, 1H), 3.90 (dd, J = 13.2, 4.3 Hz, 1H), 3.71 (td, J = 11.0, 2.9 Hz, 1H), 3.11 (dd, J = 13.2, 6.0 Hz, 1H), 2.94−2.79 (m, 2H), 2.53 (dd, J = 14.4, 11.1 Hz, 1H), 2.17 (s, 3H), 2.12 (s, 3H). ^{13}C{^{1}H}NMR (101 MHz, $CDCl_3$) δ 143.7, 138.7, 138.6, 136.2, 129.1, 128.9, 128.7, 128.6, 128.1, 126.8, 126.6, 124.9, 123.9, 118.4, 62.1, 53.5, 52.4, 40.9, 20.4, 17.8. HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{24}H_{27}N_2$ 343.2169; Found 343.2165.

*(2S,3R)-2-Benzyl-8-bromo-6-methyl-3-phenyl-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepine (**3t**).* Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (12:1) to afford a yellow oil (26 mg, yield 64%),with er 96.5:3.5 (HPLC, Daicel Chiralcel AD-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 7.9 min; t_{R2} = 8.8 min; $[\alpha]_D^{20}$ = +28° (c 0.04, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 13.4, 7.1 Hz, 4H), 7.32 (d, J = 6.9 Hz, 4H), 7.13 (d, J = 6.9 Hz, 2H), 6.78 (s, 1H), 6.30 (s, 1H), 3.97 (dd, J = 13.6, 3.4 Hz, 1H), 3.85−3.56 (m, 3H), 3.16 (dd, J = 13.2, 4.4 Hz, 1H), 2.90−2.83 (m, 2H), 2.59−2.48 (m, 1H), 2.14 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.5, 139.6, 138.4, 137.4, 128.9, 128.8, 128.7, 128.0, 126.9, 126.8, 126.2, 125.2, 119.8, 110.8, 62.0, 52.6, 51.7, 40.8, 17.7. HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{23}H_{24}BrN_2$ 407.1117; Found 407.1115.

*2-Benzyl-1H-benzo[d]imidazole (**4a**).* Prepared according to the general procedure and purified by column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (5:1) to afford a white solid (8 mg, yield 38%, mp 243−244 °C). ^{1}H NMR (400 MHz, (DMSO-d_6) δ 12.29 (s, 1H), 7.48 (s, 2H), 7.33 (d, J = 6.4 Hz, 4H), 7.27−7.21 (m, 1H), 7.13 (dd, J = 5.9, 3.1 Hz, 2H), 4.18 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, (DMSO-d_6) δ 154.0, 138.1, 129.2, 128.9,

https://dx.doi.org/10.1021/acs.joc.0c03064
J. Org. Chem. 2021, 86, 5110−5119

127.0, 121.7, 35.4. HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{14}H_{13}N_2$ 209.1073; Found 209.1075.

Large-Scale Synthesis of 3a. To a tube were added a solution of *o*-DPA (1.0 mmol, 1.0 equiv), 4 Å MS (250 mg), acid catalyst **5f** (37 mg, 50 μmol, 0.05 equiv), and 5 mL of mixed solvent (CH_3CN:$CHCl_3$ = 1:1); the tube was sealed with a septum, evacuated, and backfilled with nitrogen three times. Next, phenylacetaldehyde (1.5 mmol, 1.5 equiv) was dissolved in 5 mL of mixed solvent (CH_3CN:$CHCl_3$ = 1:1), which was added into the above solution by syringe under a nitrogen atmosphere, and it was stirred at 15 °C overnight, Next, the reaction mixture was concentrated. The desired product was isolated by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 13/1), to afford a yellow oil (107 mg, yield 68%), with er 96.5:3.5 (HPLC, Daicel Chiralcel OJ-H column, 80:20 hexane/2-propanol, 1 mL/min, 254 nm; t_{R1} = 17.2 min; t_{R2} = 21.1 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c03064.

Figures S1−S4, Table S1, copies of NMR spectra data of all compounds, crystal information for compound **3m**, and HPLC spectra of all the compounds (PDF)

Accession Codes

CCDC 1958302 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Guang-xun Li − *Natural Products Research Center, Chengdu Institution of Biology, Chinese Academy of Science, Chengdu, Sichuan 610041, China;* orcid.org/0000-0001-6782-2066; Email: Ligx@cib.ac.cn

Zhuo Tang − *Natural Products Research Center, Chengdu Institution of Biology, Chinese Academy of Science, Chengdu, Sichuan 610041, China;* orcid.org/0000-0002-5845-3569; Email: Tangzhuo@cib.ac.cn

Authors

Gao-feng Yang − *Natural Products Research Center, Chengdu Institution of Biology, Chinese Academy of Science, Chengdu, Sichuan 610041, China; University of Chinese Academy of Sciences, Beijing 100049, China*

Jin Huang − *Natural Products Research Center, Chengdu Institution of Biology, Chinese Academy of Science, Chengdu, Sichuan 610041, China*

Ding-qiang Fu − *Natural Products Research Center, Chengdu Institution of Biology, Chinese Academy of Science, Chengdu, Sichuan 610041, China*

Xiao-kang Nie − *Natural Products Research Center, Chengdu Institution of Biology, Chinese Academy of Science, Chengdu, Sichuan 610041, China*

Xin Cui − *Natural Products Research Center, Chengdu Institution of Biology, Chinese Academy of Science, Chengdu, Sichuan 610041, China*

Jin-zhong Zhao − *College of Art and Sciences, Shanxi Agricultural University, Taigu, Shanxi 030800, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c03064

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported financially by the Youth Innovation Promotion Association CAS (2018402) and the West Light Foundation of the Chinese Academy of Sciences (25E0C304).

■ REFERENCES

(1) (a) Grossi, G.; Di Braccio, M.; Roma, G.; Ballabeni, V.; Tognolini, M.; Calcina, F.; Barocelli, E. 1,5-Benzodiazepines: Part XIII. Substituted 4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepin-5-amines and 4H-imidazo[1,2-a][1,5]benzodiazepin-5-amines as analgesic, anti-inflammatory and/or antipyretic agents with low acute toxicity. *Eur. J. Med. Chem.* **2002**, *37*, 933−944. (b) Ha, S. K.; Shobha, D.; Moon, E.; Chari, M. A.; Mukkanti, K.; Kim, S.-H.; Ahn, K.-H.; Kim, S. Y. Anti-neuroinflammatory activity of 1,5-benzodiazepine derivatives. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3969−3971.

(2) Nyanguile, O.; Pauwels, F.; Van den Broeck, W.; Boutton, C. W.; Quirynen, L.; Ivens, T.; van der Helm, L.; Vandercruyssen, G.; Mostmans, W.; Delouvroy, F.; Dehertogh, P.; Cummings, M. D.; Bonfanti, J.-F.; Simmen, K. A.; Raboisson, P. 1,5-Benzodiazepines, a Novel Class of Hepatitis C Virus Polymerase Nonnucleoside Inhibitors. *Antimicrob. Agents Chemother.* **2008**, *52*, 4420−4431.

(3) Lauffer, D. J.; Mullican, M. D. A practical synthesis of (S) 3-tert-Butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-1,5-benzodiazepine-1-acetic acid methyl ester as a conformationally restricted dipeptido-Mimetic for caspase-1 (ICE) inhibitors. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1225−1227.

(4) Parmar, N. J.; Barad, H. A.; Pansuriya, B. R.; Teraiya, S. B.; Gupta, V. K.; Kant, R. An efficient one-pot synthesis, structure, antimicrobial and antioxidant investigations of some novel quinolyldibenzo[b,e][1,4]diazepinones. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3816−3821.

(5) Insuasty, B.; Ramírez, J.; Becerra, D.; Echeverry, C.; Quiroga, J.; Abonia, R.; Robledo, S. M.; Vélez, I. D.; Upegui, Y.; Muñoz, J. A.; Ospina, V.; Nogueras, M.; Cobo, J. An efficient synthesis of new caffeine-based chalcones, pyrazolines and pyrazolo[3,4-b][1,4]-diazepines as potential antimalarial, antitrypanosomal and antileishmanial agents. *Eur. J. Med. Chem.* **2015**, *93*, 401−413.

(6) (a) Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. Design of potent, orally effective, nonpeptidal antagonists of the peptide hormone cholecystokinin. *Proc. Natl. Acad. Sci. U. S. A.* **1986**, *83*, 4918−4922. (b) Smith, S. G.; Sanchez, R.; Zhou, M.-M. Privileged Diazepine Compounds and Their Emergence as Bromodomain Inhibitors. *Chem. Biol.* **2014**, *21*, 573−583.

(7) (a) Lee, J.; Gauthier, D.; Rivero, R. A. Solid-Phase Synthesis of 3,4,5-Substituted 1,5-Benzodiazepin-2-ones. *J. Org. Chem.* **1999**, *64*, 3060−3065. (b) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. Synthesis of Medium Ring Nitrogen Heterocycles via a Tandem Copper-Catalyzed C−N Bond Formation−Ring-Expansion Process. *J. Am. Chem. Soc.* **2004**, *126*, 3529−3533. (c) Murai, K.; Nakatani, R.; Kita, Y.; Fujioka, H. One-pot three-component reaction providing 1,5-benzodiazepine derivatives. *Tetrahedron* **2008**, *64*, 11034−11040. (d) Sotoca, E.; Allais, C.; Constantieux, T.; Rodriguez, J. User-friendly stereoselective one-pot access to 1,4-diazepane derivatives by a cyclodehydrative three-component reaction with 1,3-dicarbonyls. *Org. Biomol. Chem.* **2009**, *7*, 1911−1920. (e) Bhattacharya, A. K.; Rana, K. C.; Raut, D. S.; Mhaindarkar, V. P.; Khan, M. I. An efficient synthesis of benzodiazepinyl phosphonates as clostripain inhibitors via $FeCl_3$ catalyzed four-component reaction. *Org. Biomol. Chem.* **2011**, *9*, 5407−5413. (f) Rahmati, A.; Ahmadi, S.; Ahmadi-Varzaneh, M. One-pot synthesis of 1,2,4,5-tetrahydro-2,4-dioxobenzo[b][1,4]diazepine and malonamide derivatives using multi-component reactions. *Tetrahedron* **2014**, *70*, 9512−9521. (g) Praveen Kumar, C.; Reddy,

T. S.; Mainkar, P. S.; Bansal, V.; Shukla, R.; Chandrasekhar, S.; Hügel, H. M. Synthesis and biological evaluation of 5,10-dihydro-11H-dibenzo[b,e][1,4]diazepin-11-one structural derivatives as anti-cancer and apoptosis inducing agents. *Eur. J. Med. Chem.* **2016**, *108*, 674−686.

(8) (a) Baraldi, P. G.; Ruggiero, E.; Tabrizi, M. A. New Synthesis of Diazepino[3,2,1-ij]quinoline and Pyrido[1,2,3-de]quinoxalines via Addition−Elimination Followed by Cycloacylation. *J. Heterocycl. Chem.* **2014**, *51*, 101−105. (b) Sarkar, S.; Deka, J. K. R.; Hazra, J. P.; Khan, A. T. Bromodimethylsulfonium Bromide (BDMS)-Catalyzed Synthesis of 1,5-Benzodiazepines Using a Multi-Component Reaction Strategy. *Synlett* **2013**, *24*, 2601−2605. (c) Wang, Y. F.; He, C. Y.; Hou, L. L.; Tian, P.; Lin, G. Q.; Tong, X. F. Facile Access to 1,5-Benzodiazepines via Amine-Promoted (4 + 3) Annulations of delta-Acetoxy Allenoates with o-Diaminobenzenes under Mild Conditions. *Synlett* **2018**, *29*, 1176−1180.

(9) Castillo, J.-C.; Presset, M.; Abonia, R.; Coquerel, Y.; Rodriguez, J. Microwave-Assisted Domino Benzannulation of α-Oxo Ketenes: Preparation of 1,3-Dihydro-2H-1,5-benzodiazepin-2-ones. *Eur. J. Org. Chem.* **2012**, *2012*, 2338−2345.

(10) (a) Ding, Z.-Y.; Chen, F.; Qin, J.; He, Y.-M.; Fan, Q.-H. Asymmetric Hydrogenation of 2,4-Disubstituted 1,5-Benzodiazepines Using Cationic Ruthenium Diamine Catalysts: An Unusual Achiral Counteranion Induced Reversal of Enantioselectivity. *Angew. Chem., Int. Ed.* **2012**, *51*, 5706−5710. (b) Ma, B.; Ding, Z.; Liu, J.; He, Y.; Fan, Q.-H. Highly Enantioselective Hydrogenation of 2,4-Diaryl-1,5-Benzodiazepines Catalyzed by Dendritic Phosphinooxazoline Iridium Complexes. *Chem. - Asian J.* **2013**, *8*, 1101−1104.

(11) (a) Han, Z.-Y.; Xiao, H.; Gong, L.-Z. Dynamic kinetic asymmetric transfer hydrogenation of racemic 2,4-diaryl-2,3-dihydrobenzo[b][1,4]diazepines catalyzed by chiral phosphoric acids. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3729−3732. (b) Horiguchi, K.; Yamamoto, E.; Saito, K.; Yamanaka, M.; Akiyama, T. Dynamic Kinetic Resolution Approach for the Asymmetric Synthesis of Tetrahydrobenzodiazepines Using Transfer Hydrogenation by Chiral Phosphoric Acid. *Chem. - Eur. J.* **2016**, *22*, 8078−8083.

(12) Fu, X.; Feng, J.; Dong, Z.; Lin, L.; Liu, X.; Feng, X. Enantioselective Synthesis of 2-Substituted-1,5-Benzodiazepines through Domino Reaction of o-Phenylenediamine and Chalcone Derivatives. *Eur. J. Org. Chem.* **2011**, *2011*, 5233−5236.

(13) (a) Wang, Y.; Tu, M.-S.; Shi, F.; Tu, S.-J. Enantioselective Construction of the Biologically Significant Dibenzo[1,4]diazepine Scaffold via Organocatalytic Asymmetric Three-Component Reactions. *Adv. Synth. Catal.* **2014**, *356*, 2009−2019. (b) Wang, Y.; Shi, F.; Yao, X.-X.; Sun, M.; Dong, L.; Tu, S.-J. Catalytic Asymmetric Construction of 3,3′-Spirooxindoles Fused with Seven-Membered Rings by Enantioselective Tandem Reactions. *Chem. - Eur. J.* **2014**, *20*, 15047−15052.

(14) (a) Chikashita, H.; Morita, Y.; Itoh, K. An Efficient Method for the Selective Reduction of 2-Aryl-1-Nitroalkenes to 2-Aryl-1-Nitroalkanes by 2-Phenylbenzimidazoline. *Synth. Commun.* **1985**, *15*, 527−533. (b) Zhu, X.-Q.; Zhang, M.-T.; Yu, A.; Wang, C.-H.; Cheng, J.-P. Hydride, Hydrogen Atom, Proton, and Electron Transfer Driving Forces of Various Five-Membered Heterocyclic Organic Hydrides and Their Reaction Intermediates in Acetonitrile. *J. Am. Chem. Soc.* **2008**, *130*, 2501−2516. (c) Khan, I. A.; Balaramnavar, V. M.; Saxena, A. K. Identification and optimization of novel pyrimido-isoxazolidine and oxazine as selective hydride donors. *Tetrahedron* **2012**, *68*, 10122−10129.

(15) For selected examples of asymmetric transfer hydrogenation of an in situ formed imine: (a) Shi, F.; Gong, L.-Z. Relay Catalysis Enables Hydrogen Gas to Participate in Asymmetric Organocatalytic Hydrogenation. *Angew. Chem., Int. Ed.* **2012**, *51*, 11423−11425. (b) Zhang, Y.-C.; Zhao, J.-J.; Jiang, F.; Sun, S.-B.; Shi, F. Organocatalytic Asymmetric Arylative Dearomatization of 2,3-Disubstituted Indoles Enabled by Tandem Reactions. *Angew. Chem., Int. Ed.* **2014**, *53*, 13912−13915. (c) Meng, F.-J.; Shi, L.; Feng, G.-S.; Sun, L.; Zhou, Y.-G. Enantioselective Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones through Organocatalytic Transfer Hydrogenation of 2-Hydroxypyrimidines. *J. Org. Chem.* **2019**, *84*, 4435−4442.

(16) (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. Remarkably Low Catalyst Loading in Brønsted Acid Catalyzed Transfer Hydrogenations: Enantioselective Reduction of Benzoxazines, Benzothiazines, and Benzoxazinones. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751−6755. (b) Rueping, M.; Antonchick, A. P.; Theissmann, T. A Highly Enantioselective Brønsted Acid Catalyzed Cascade Reaction: Organocatalytic Transfer Hydrogenation of Quinolines and their Application in the Synthesis of Alkaloids. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683−3686. (c) Guo, Q.-S.; Du, D.-M.; Xu, J. The Development of Double Axially Chiral Phosphoric Acids and Their Catalytic Transfer Hydrogenation of Quinolines. *Angew. Chem., Int. Ed.* **2008**, *47*, 759−762. (d) Kim, K.-H.; Lee, C.-Y.; Cheon, C.-H. Enantioselective Synthesis of β-Arylamines via Chiral Phosphoric Acid-Catalyzed Asymmetric Reductive Amination. *J. Org. Chem.* **2015**, *80*, 6367−6374. (e) Abudu Rexit, A.; Luo, S.; Mailikezati, M. Chiral Phosphoric Acid-Catalyzed Enantioselective Reductive Amination of 2-Pyridyl Ketones: Construction of Structurally Chiral Pyridine-Based Ligands. *J. Org. Chem.* **2016**, *81*, 11384−11388. (f) Reid, J. P.; Simón, L.; Goodman, J. M. A Practical Guide for Predicting the Stereochemistry of Bifunctional Phosphoric Acid Catalyzed Reactions of Imines. *Acc. Chem. Res.* **2016**, *49*, 1029−1041.

(17) (a) Wen, W.; Zeng, Y.; Peng, L.-Y.; Fu, L.-N.; Guo, Q.-X. Asymmetric Synthesis of α-Amino Ketones by Brønsted Acid Catalysis. *Org. Lett.* **2015**, *17*, 3922−3925. (b) Zhu, C.; Saito, K.; Yamanaka, M.; Akiyama, T. Benzothiazoline: Versatile Hydrogen Donor for Organocatalytic Transfer Hydrogenation. *Acc. Chem. Res.* **2015**, *48*, 388−398.

(18) (a) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. Enantioselective Organocatalytic Transfer Hydrogenation Reactions using Hantzsch Esters. *Acc. Chem. Res.* **2007**, *40*, 1327−1339. (b) Rueping, M.; Dufour, J.; Schoepke, F. R. Advances in catalytic metal-free reductions: from bio-inspired concepts to applications in the organocatalytic synthesis of pharmaceuticals and natural products. *Green Chem.* **2011**, *13*, 1084−1105. (c) Zheng, C.; You, S.-L. Transfer hydrogenation with Hantzsch esters and related organic hydride donors. *Chem. Soc. Rev.* **2012**, *41*, 2498−2518. (d) Faísca Phillips, A. M.; Pombeiro, A. J. L. Recent advances in organocatalytic enantioselective transfer hydrogenation. *Org. Biomol. Chem.* **2017**, *15*, 2307−2340.

(19) Zhu, C.; Falck, J. R. Benzothiazoline: The Surrogate of Hantzsch Ester. *ChemCatChem* **2011**, *3*, 1850−1851.

(20) Shi, F.; Tan, W.; Zhang, H.-H.; Li, M.; Ye, Q.; Ma, G.-H.; Tu, S.-J.; Li, G. Asymmetric Organocatalytic Tandem Cyclization/Transfer Hydrogenation: A Synthetic Strategy for Enantioenriched Nitrogen Heterocycles. *Adv. Synth. Catal.* **2013**, *355*, 3715−3726.

(21) Fu, X.; Feng, J.; Dong, Z.; Lin, L.; Liu, X.; Feng, X. Enantioselective Synthesis of 2-Substituted-1,5-Benzodiazepines through Domino Reaction of *o*-Phenylenediamine and Chalcone Derivatives. *Eur. J. Org. Chem.* **2011**, *2011*, 5233−5236.

(22) (a) Terada, M.; Machioka, K.; Sorimachi, K. High Substrate/Catalyst Organocatalysis by a Chiral Brønsted Acid for an Enantioselective Aza-Ene-Type Reaction. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254−2257. (b) Terada, M.; Machioka, K.; Sorimachi, K. Chiral Brønsted Acid-Catalyzed Tandem Aza-Ene Type Reaction/Cyclization Cascade for a One-Pot Entry to Enantioenriched Piperidines. *J. Am. Chem. Soc.* **2007**, *129*, 10336−10337. (c) Li, G.; Fronczek, F. R.; Antilla, J. C. Catalytic Asymmetric Addition of Alcohols to Imines: Enantioselective Preparation of Chiral N,O-Aminals. *J. Am. Chem. Soc.* **2008**, *130*, 12216−12217. (d) Baudequin, C.; Zamfir, A.; Tsogoeva, S. B. Highly enantioselective organocatalytic formation of a quaternary carbon center via chiral Brønsted acid catalyzed self-coupling of enamides. *Chem. Commun.* **2008**, 4637−4639. (e) Terada, M.; Machioka, K.; Sorimachi, K. Activation of Hemiaminal Ethers by Chiral Brønsted Acids for Facile Access to Enantioselective Two-Carbon Homologation Using Enecarbamates. *Angew. Chem., Int. Ed.* **2009**, *48*, 2553−2556. (f) Jarrige, L.; Glavač,

https://dx.doi.org/10.1021/acs.joc.0c03064
J. Org. Chem. 2021, 86, 5110−5119

D.; Levitre, G.; Retailleau, P.; Bernadat, G.; Neuville, L.; Masson, G. Chiral phosphoric acid-catalyzed enantioselective construction of structurally diverse benzothiazolopyrimidines. *Chem. Sci.* **2019**, *10*, 3765−3769.

(23) (a) Akiyama, T.; Itoh, J.; Fuchibe, K. Recent Progress in Chiral Brønsted Acid Catalysis. *Adv. Synth. Catal.* **2006**, *348*, 999−1010. (b) Taylor, M. S.; Jacobsen, E. N. Asymmetric Catalysis by Chiral Hydrogen-Bond Donors. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−154. (c) Akiyama, T. Stronger Brønsted Acids. *Chem. Rev.* **2007**, *107*, 5744−5758. (d) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047−9153. (e) Akiyama, T.; Mori, K. Stronger Brønsted Acids: Recent Progress. *Chem. Rev.* **2015**, *115*, 9277−9306. (f) Wu, H.; He, Y.-P.; Shi, F. Recent Advances in Chiral Phosphoric Acid Catalyzed Asymmetric Reactions for the Synthesis of Enantiopure Indole Derivatives. *Synthesis* **2015**, *47*, 1990−2016. (g) Li, S.; Xiang, S.-H.; Tan, B. Chiral Phosphoric Acid Creates Promising Opportunities for Enantioselective Photoredox Catalysis. *Chin. J. Chem.* **2020**, *38*, 213−214. (h) Xia, Z.-L.; Xu-Xu, Q.-F.; Zheng, C.; You, S.-L. Chiral phosphoric acid-catalyzed asymmetric dearomatization reactions. *Chem. Soc. Rev.* **2020**, *49*, 286−300.

(24) (a) Hesse; Revelant, G.; Dunand, S.; Kirsch, G. Microwave-Assisted Synthesis of 5-Substituted 2-Aminothiophenes Starting from Arylacetaldehydes. *Synthesis* **2011**, *2011*, 2935−2940. (b) Zhuangyu; Yi, P.; Honwen, H.; Tsi-yu, K. A Facile Approach to Arylacetaldehydes via Polymeric Palladium Catalyst. *Synthesis* **1991**, *1991*, 539−542.

https://dx.doi.org/10.1021/acs.joc.0c03064
J. Org. Chem. 2021, 86, 5110−5119