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# Enantioselective Construction of the Biologically Significant Dibenzo[1,4]diazepine Scaffold *via* Organocatalytic Asymmetric Three-Component Reactions

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**Abstract:** The first catalytic asymmetric construction of the biologically important dibenzo[1,4]diazepine scaffold has been established *via* SPINOL-derived chiral phosphoric acid-catalyzed three-component reactions of aldehydes, 1,2-phenylenediamines and cyclohexane-1,3-diones, which afforded structurally complex and diverse dibenzo[1,4]diazepines in high yields and good enantioselectivities (up to 98% yield, 92:8 *er*). This transformation also represents the first catalytic asymmetric version of this three-component reaction and provides an easy access to structurally rigid seven-membered chiral heterocycles.

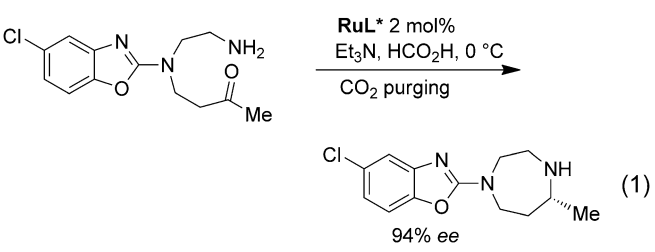
**Keywords:** asymmetric catalysis; chiral heterocycles; enantioselectivity; multicomponent reactions; organic catalysis

## Introduction

The dibenzo[1,4]diazepine scaffold is a privileged structure which is present in a variety of pharmaceutically important compounds.[1] As exemplified in Figure 1, compounds **I** and **II** represent a new class of HIV protease inhibitors.[1a] Compounds **III** and **IV** act as cystathionine β-synthase inhibitor[1b] and neuromedin B receptor antagonist,[1c] respectively. Besides, compounds **V** and **VI** have proven to be hepatitis C virus (HCV) NS5B polymerase inhibitors.[1d,e]

The prominent medicinal relevance of this type of heterocyclic architecture has led to a great demand for efficient synthetic strategies, especially those constructing enantioselective scaffolds, because one of the two enantiomers may have higher bioactivity than the other one or the mixed racemates.[2] However, a survey of the literature only revealed some reports on the synthesis of racemic products,[3] and *no catalytic asymmetric approaches affording enantioselective dibenzo[1,4]diazepines have been described as yet*. In fact, the catalytic asymmetric construction of the structurally rigid seven-membered diazepine motif had met with little success[4] until Strotman and coworkers developed a Ru-catalyzed intramolecular asymmetric reductive amination to construct a highly enantioselective diazepine framework [Eq. (1)].[5] In spite of this elegant work, the catalytic enantioselective approaches to construct a chiral diazepine moiety are still underdeveloped and full of challenges.

***Previous work on highly enantioselective construction of the diazepine motif:***




(1)

In recent years, organocatalytic enantioselective multi-component reactions (OEMCRs) have become a powerful tool to obtain structurally diverse and complex chiral compounds in a single step, which is especially important for the synthesis of pharmaceuticals without transition metal contamination of the products.[6] Therefore, it is highly desirable to develop

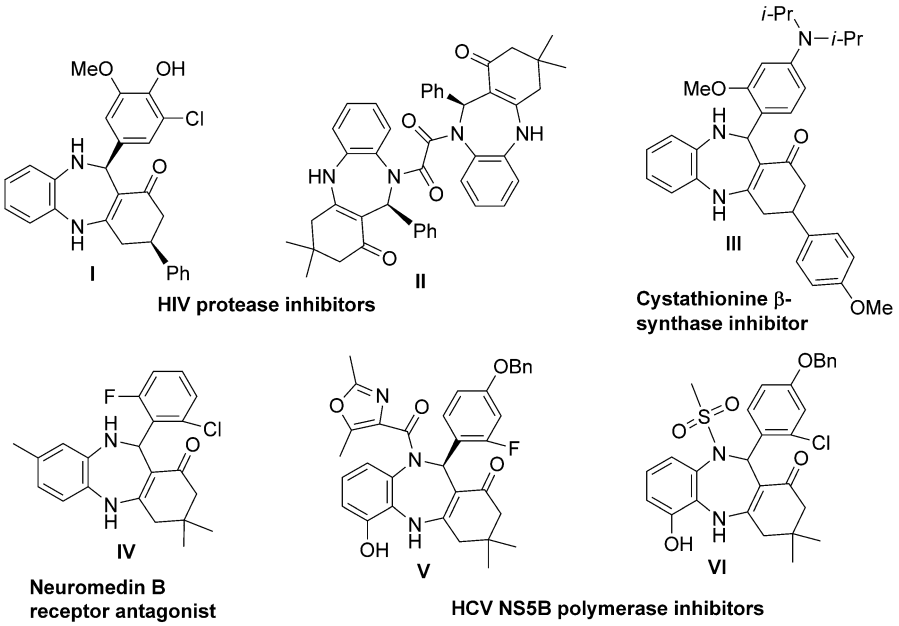
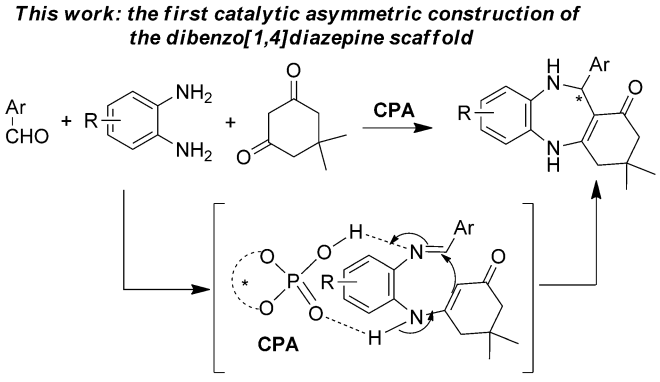



**Figure 1.** Pharmaceutically important compounds containing the dibenzo[1,4]diazepine scaffold.

OEMCRs to access optically pure diazepines from simple starting materials.

Chiral phosphoric acids (CPAs) have emerged as a class of privileged organocatalysts, which have enabled a wide range of enantioselective transformations.[7] We have established a series of CPA-catalyzed multi-component reactions for the synthesis of enantiopure heterocycles of biological importance.[8] Inspired by these success and considering that there are so far no catalytic asymmetric approaches affording enantioselective dibenzo[1,4]diazepines, we decided to employ a CPA-catalyzed three-component reaction to construct a chiral dibenzo[1,4]diazepine scaffold, wherein the nitrogen-containing intermediate should be activated by CPA *via* hydrogen-bonding interactions (Scheme 1).

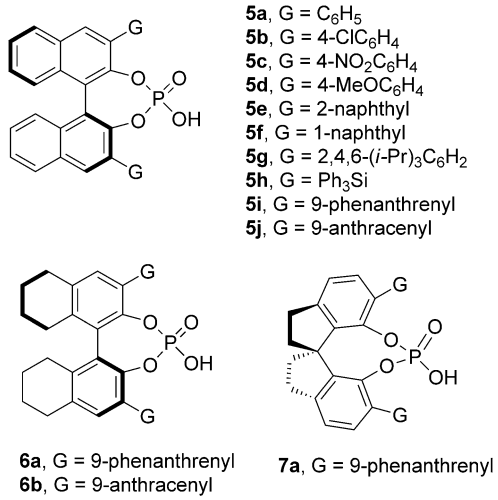
Herein, we report the first catalytic asymmetric construction of the dibenzo[1,4]diazepine scaffold *via* CPA-catalyzed three-component reactions of aldehydes, 1,2-phenylenediamines and cyclohexane-1,3-diones, which afforded structurally complex and diverse dibenzo[1,4]diazepines in high yields and good enantioselectivities (up to 98% yield, 92:8 *er*).




**Scheme 1.** Design of the CPA-catalyzed three-component reaction to construct a chiral dibenzo[1,4]diazepine scaffold.

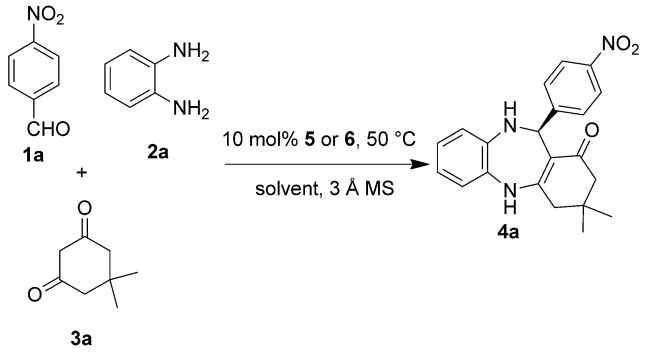
## Results and Discussion

The initial experiments to test our hypothesis commenced with a three-component reaction of 4-nitrobenzaldehyde **1a**, 1,2-phenylenediamine **2a** and 5,5-dimethylcyclohexane-1,3-dione **3a** catalyzed by a wide range of BINOL-derived CPAs **5** (in Scheme 2) at 50 °C in toluene (Table 1). Although the yields of the




**Scheme 2.** CPAs employed for the model reaction.

**Table 1.** Screening of catalysts and solvents.[a]




| Entry | CPA | Solvent | Yield [%][b] | *er*[c] |
|---|---|---|---|---|
| 1 | **5a** | toluene | 66 | 50:50 |
| 2 | **5b** | toluene | 99 | 51:49 |
| 3 | **5c** | toluene | 87 | 52:48 |
| 4 | **5d** | toluene | 92 | 51:49 |
| 5 | **5e** | toluene | 98 | 50:50 |
| 6 | **5f** | toluene | 64 | 58:42 |
| 7 | **5g** | toluene | 90 | 58:42 |
| 8 | **5h** | toluene | 69 | 58:42 |
| 9 | **5i** | toluene | 84 | 57:43 |
| 10 | **5j** | toluene | 94 | 62:38 |
| 11 | **6a** | toluene | 99 | 66:34 |
| 12 | **6b** | toluene | 90 | 65:35 |
| 13 | **6a** | DCE | 61 | 67:33 |
| 14 | **6a** | 1,4-dioxane | 90 | 78:22 |
| 15 | **6a** | THP | 90 | 57:43 |
| 16 | **6a** | anisole | 84 | 68:32 |
| 17 | **6a** | THF | 57 | 52:48 |
| 18 | **6a** | DME | 26 | 54:46 |

[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in solvent (1 mL) with 3 Å MS (100 mg) for 17 h, and the ratio of **1a**:**2a**:**3a** was 1.2:1:1.2.
[b] Isolated yield.
[c] The enantiomeric ratio (*er*) value was determined by HPLC.

reactions in the presence of catalysts **5** were good to excellent, the enantioselectivities of these reactions were frustrating (entries 1–10). In detail, CPAs **5a**–**5e** with relatively small groups at the 3,3′-positions of the BINOL backbone almost had no inducing effect on the enantioselectivity (entries 1–5), while CPAs **5f**–**5j** with bulky groups at the same positions exhibited a slightly higher catalytic activity on the enantioselective control (entries 6–10). Among them, 9-anthracenyl-substituted CPA **5j** delivered the desired product **4a** in the highest enantioselectivity of 62:38 *er* (entry 10). From these results, we assumed that the steric effect of the 3,3′-substituents and the rigidity of the BINOL backbone might play an important role in the enantioselective control of the reaction. So, we synthesized two $H_8$-BINOL-derived CPAs **6a** and **6b** with bulky groups (in Scheme 2), which are more structurally rigid than their BINOL-derived counterparts **5i** and **5j**. The employment of CPAs **6a** and **6b** as catalysts to the reaction (entries 11 and 12) improved the enantioselectivity to 66:34 *er* with a quantitative yield (entry 11).

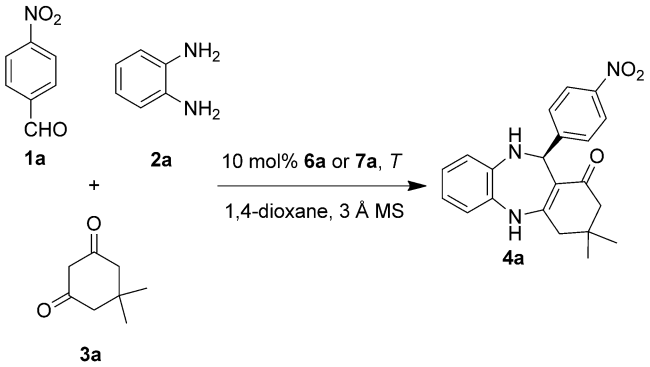
Then, in the presence of catalyst **6a**, the preliminary evaluation of other solvents such as 1,2-dichloroethane (DCE) and 1,4-dioxane disclosed that 1,4-dioxane was much superior to toluene and DCE with regard to enantioselectivity, delivering the chiral dibenzo[1,4]diazepine **4a** in 78:22 *er* (Table 1, entry 14 *vs.* 11 and 13). However, further screening of other ethers including tetrahydropyran (THP), anisole, tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) could not realise better results than 1,4-dioxane did (entries 15–18 *vs.* 14). Hence, 1,4-dioxane was chosen as the most suitable solvent for further optimization of the reaction conditions.

Next, other reaction parameters such as temperature, molecular sieves (MS) and reagent ratios were optimized for the same model reaction (Table 2). The tentative elevation of the reaction temperature in 1,4-dioxane (entries 1 and 2) revealed that 60 °C could deliver the same reaction in a higher yield of 97% with a maintained enantioselectivity of 78:22 *er* (Table 2, entry 1 *vs.* Table 1, entry 14). So, the subsequent evaluation of MS was performed at 60 °C, which indicated that 3 Å MS was better than 4 Å and 5 Å MS both in regard to enantioselectivity and reactivity (entry 1 *vs.* 3 and 4). Then, the reagent ratio was carefully tuned with the aim to enhance the enantioselectivity (entries 5–10). The presence of excess **3a** was detrimental to the enantioselectivity of the reaction (entries 5 and 6 *vs.* 1). Neither increasing nor decreasing the stoichiometry of **1a** could benefit the enantioselectivity (entries 7–9 *vs.* 1). However, reducing the stoichiometry of **1a** and **3a** at the same time resulted in a slightly improved enantioselectivity of 79:21 *er* (entry 10 *vs.* 1). Hence, the most suitable ratio of **1a**:**2a**:**3a** was set as 1:1:1.

At this stage, it seemed that the enantioselectivity of the reaction was too difficult to enhance merely by changing these reaction parameters. Modification on the structure of the catalyst has proven to be an efficient way to improve the enantioselectivity, and SPINOL-derived CPAs have recently been recognized as a type of chiral Brønsted acid possessing higher capability in enantioselective control than their BINOL-based analogues.[9] Therefore, we changed the $H_8$-BINOL backbone of catalyst **6a** to the SPINOL scaffold and employed this type of spiro-CPA **7a** (in Scheme 2) to the model reaction. Indeed, this structurally more rigid catalyst **7a** enabled the same reaction to proceed in a much more efficient and enantioselective way, delivering the targeted product **4a** in 93% yield and 89:11 *er* (Table 2, entry 11). At last, in the presence of CPA **7a**, fine-tuning the reaction temperature (entries 11–15) disclosed that 40 °C was the

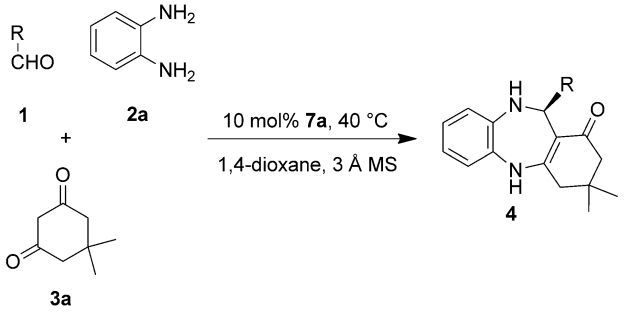
**Table 2.** Further optimization of the reaction conditions.[a]




| Entry | CPA | **1a**:**2a**:**3a** | *T* [°C] | Yield [%][b] | *er*[c] |
|---|---|---|---|---|---|
| 1 | **6a** | 1.2:1:1.2 | 60 | 97 | 78:22 |
| 2 | **6a** | 1.2:1:1.2 | 70 | 85 | 77:23 |
| 3[d] | **6a** | 1.2:1:1.2 | 60 | 96 | 75:25 |
| 4[e] | **6a** | 1.2:1:1.2 | 60 | 79 | 72:28 |
| 5 | **6a** | 1.2:1:1.6 | 60 | 97 | 71:29 |
| 6 | **6a** | 1.2:1:2 | 60 | 93 | 65:35 |
| 7 | **6a** | 1.6:1:1.2 | 60 | 95 | 74:26 |
| 8 | **6a** | 2:1:1.2 | 60 | 94 | 72:28 |
| 9 | **6a** | 1:1:1.2 | 60 | 92 | 74:26 |
| 10 | **6a** | 1:1:1 | 60 | 85 | 79:21 |
| 11 | **7a** | 1:1:1 | 60 | 93 | 89:11 |
| 12 | **7a** | 1:1:1 | 80 | 79 | 83:17 |
| 13 | **7a** | 1:1:1 | 50 | 94 | 90:10 |
| 14 | **7a** | 1:1:1 | 40 | 85 | 92:8 |
| 15 | **7a** | 1:1:1 | 30 | 77 | 84:16 |
| 16[f] | **7a** | 1:1:1 | 40 | 90 | 89:11 |
| 17[g] | **7a** | 1:1:1 | 40 | 90 | 89:11 |

[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in 1,4-dioxane (1 mL) with 3 Å MS (100 mg) for 17 h.
[b] Isolated yield.
[c] The enantiomeric ratio (*er*) value was determined by HPLC.
[d] 4 Å MS was used.
[e] 5 Å MS was used.
[f] Catalyzed by 5 mol% **7a**.
[g] Catalyzed by 15 mol% **7a**.

**Table 3.** The substrate scope of aldehydes.[a]



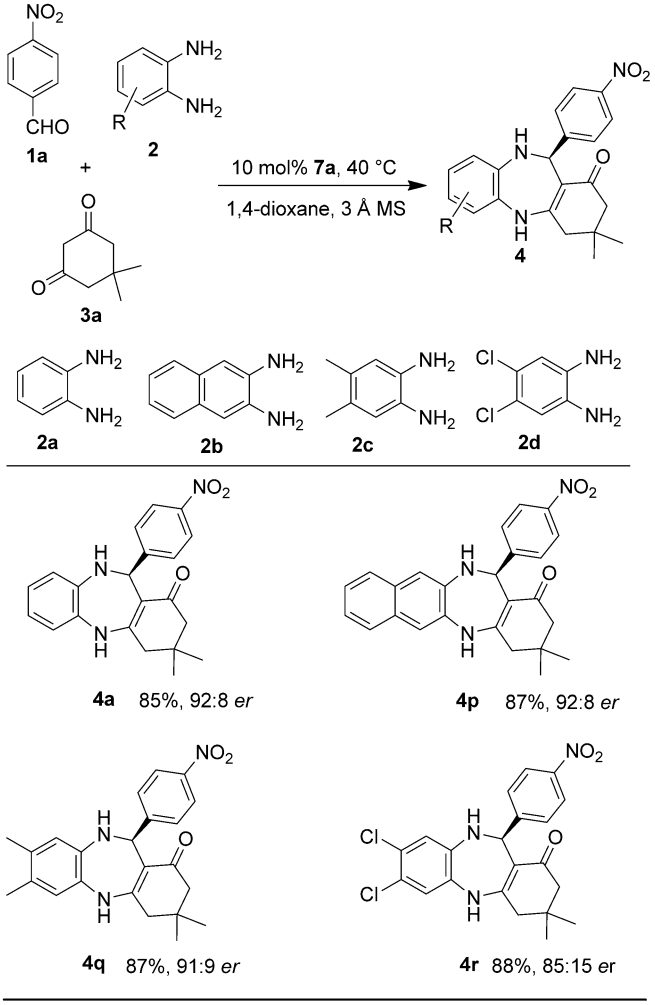

| Entry | **4** | R | Yield [%][b] | *er*[c] |
|---|---|---|---|---|
| 1 | **4a** | 4-$NO_2C_6H_4$ (**1a**) | 85 | 92:8 (>99:1)[d] |
| 2 | **4b** | 4-$CF_3C_6H_4$ (**1b**) | 78 | 91:9 |
| 3 | **4c** | 4-$MeO_2CC_6H_4$ (**1c**) | 86 | 89:11 |
| 4 | **4d** | 4-$CNC_6H_4$ (**1d**) | 84 | 87:13 |
| 5 | **4e** | 4-$FC_6H_4$ (**1e**) | 76 | 89:11 |
| 6 | **4f** | 3,4-$F_2C_6H_3$ (**1f**) | 80 | 83:17 |
| 7 | **4g** | 3-Cl-4-$FC_6H_3$ (**g**) | 98 | 84:16 |
| 8 | **4h** | 3-F-4-$ClC_6H_3$ (**1h**) | 90 | 84:16 |
| 9 | **4i** | 4-$PhC_6H_4$ (**1i**) | 55 | 91:9 |
| 10 | **4j** | $C_6H_5$ (**1j**) | 90 | 88:12 |
| 11 | **4k** | 2-naphthyl (**1k**) | 58 | 86:14 |
| 12 | **4l** | 4-$MeOC_6H_4$ (**1l**) | 61 | 91:9 |
| 13 | **4m** | 4-$MeC_6H_4$ (**1m**) | 81 | 88:12 |
| 14 | **4n** | 3-$MeC_6H_4$ (**1n**) | 60 | 83:17 |
| 15 | **4o** | 2-thiophenyl (**1o**) | 54 | 78:22 |

[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in 1,4-dioxane (1 mL) with 3 Å MS (100 mg) at 40 °C for 17 h, and the ratio of **1**:**2a**:**3a** was 1:1:1.
[b] Isolated yield.
[c] The enantiomeric ratio (*er*) value was determined by HPLC.
[d] After recrystallization.

most suitable temperature to obtain the highest enantioselectivity of 92:8 *er* (entry 14). However, either lowering or raising the catalyst loading led to slightly decreased enantioselectivity (entries 15 and 16).

With the optimal reaction conditions in hand, we then investigated the substrate scope of this catalytic asymmetric three-component reaction. Since aryl-substituted dibenzo[1,4]diazepines have exhibited significant bioactivities (Figure 1), a variety of aromatic aldehydes was employed to the reaction in order to provide structurally diverse dibenzo[1,4]diazepines **4** substituted with aryl groups. As shown in Table 3, this approach is applicable to a wide range of benzaldehydes **1** bearing either electronically poor, neutral, or rich substituents in generally high yields and fair to good enantioselectivities (55% to 98% yield, 83:17 to 92:8 *er*). Basically, there was no remarkable difference in enantioselectivity among electronically poor, neutral and rich aldehydes, since a good enantioselectivity of 91:9 *er* could be offered by all three types of aldehydes including **1b**, **1i** and **1l** (entries 2, 9 and 12). In detail, among benzaldehydes substituted with electron-withdrawing groups, *p*-nitrobenzaldehyde **1a** had the highest capability in enantioselective control, and an excellent enantioselectivity of >99:1 *er* could be obtained after simple recrystallization (entry 1, in parentheses). Disubstituted benzaldehydes **1f**–**1h** delivered the corresponding products with high yields of 80–98% albeit with slightly decreased enantioselectivities (entries 6–8). More important, benzaldehyde **1j** appeared to be a suitable substrate, offering chiral dibenzo[1,4]diazepine **4j** in a high yield of 90% and good enantioselectivity of 88:12 *er* (entry 10), which provided a good opportunity for the synthesis of HIV protease inhibitor **II** (in Figure 1) in an enantioselec-

**Table 4.** The generality for 1,2-arylenediamines.[a]




[a] Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in 1,4-dioxane (1 mL) with 3 Å MS (100 mg) at 40 °C for 17 h, and the ratio of **1a**:**2**:**3a** was 1:1:1. Yields referred to isolated yield and the enantiomeric ratio (*er*) value was determined by HPLC.

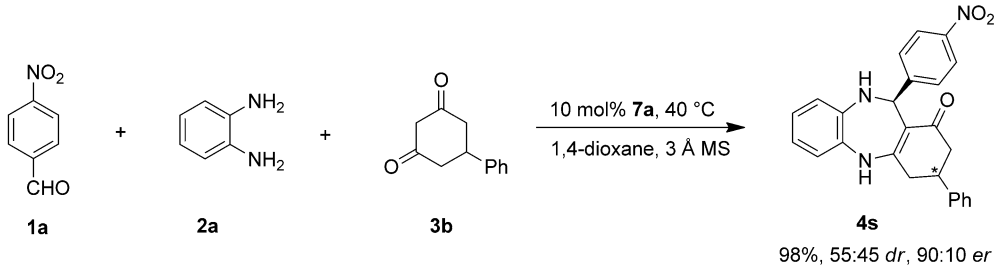
tive manner by simple treatment of **4j** with oxalyl chloride.[1a] Moreover, benzaldehyde **1l** with a strong electron-donating group was superior to other electronically rich ones in terms of enantioselectivity (entry 12 *vs.* 13 and 14), and the position of electron-donating substituents appeared to exert some impact on the enantioselectivity and the yield (entry 13 *vs.* 14). Besides, this protocol could also be applied to heteroaromatic aldehydes as exemplified by thiophene-2-carbaldehyde **1o** in an acceptable yield and enantioselectivity (entry 15).

Next, the generality for 1,2-arylenediamines **2** was examined by the reaction with 4-nitrobenzaldehyde **1a** and 5,5-dimethylcyclohexane-1,3-dione **3a**. As illustrated in Table 4, this protocol is amenable to different symmetrical 1,2-arylenediamines **2** with electron-neutral, electron-rich, or electron-withdrawing substituents on their benzene rings, giving chiral dibenzo-[1,4]diazepines **4a** and **4p**–**4r** in high yields (85–88%) and good enantioselectivities (85:15 to 92:8 *er*). In general, 1,2-arylenediamines **2a**–**2c** substituted with electron-neutral or electron-rich groups delivered higher enantioselectivity than those substituted with electron-withdrawing groups as exemplified by **2d**.

More interestingly, 5-phenyl-substituted cyclohexane-1,3-dione **3b** proved to be a reactive component and afforded the targeted product **4s** in an excellent yield of 98% and a high enantioselectivity of 90:10 *er* albeit with a moderate diastereoselectivity of 55:45 *dr* (Scheme 3). The two diastereomers could be easily separated by flash column chromatography, thereby providing a practical method for the synthesis of this type of bioactive chiral molecules such as compounds **I** and **III** (see Figure 1).

The absolute configuration of compound **4a** (>99:1 *er* after recrystallization) was unambiguously determined to be (*S*) by single-crystal X-ray diffraction analysis (Figure 2).[10] The absolute configurations of other dibenzo[1,4]diazepines **4** were assigned by analogy.

On the basis of our experimental results, we suggest a possible reaction pathway and transition state to explain the chemistry and the stereochemistry of this catalytic asymmetric three-component reaction (Scheme 4). Initially, in the presence of CPA **7a**, 1,2-arylenediamine **2** reacted with cyclohexane-1,3-dione **3** to generate an imine intermediate, which could easily isomerize to the more stable enamine intermediate **8** because of the conjugative effect of the C=C bond with the carbonyl group. Then, enamine **8**




**Scheme 3.** Reaction using 5-phenylcyclohexane-1,3-dione **3b** as substrate.

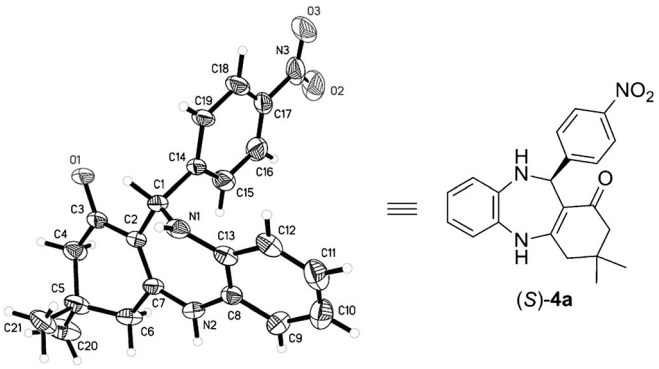


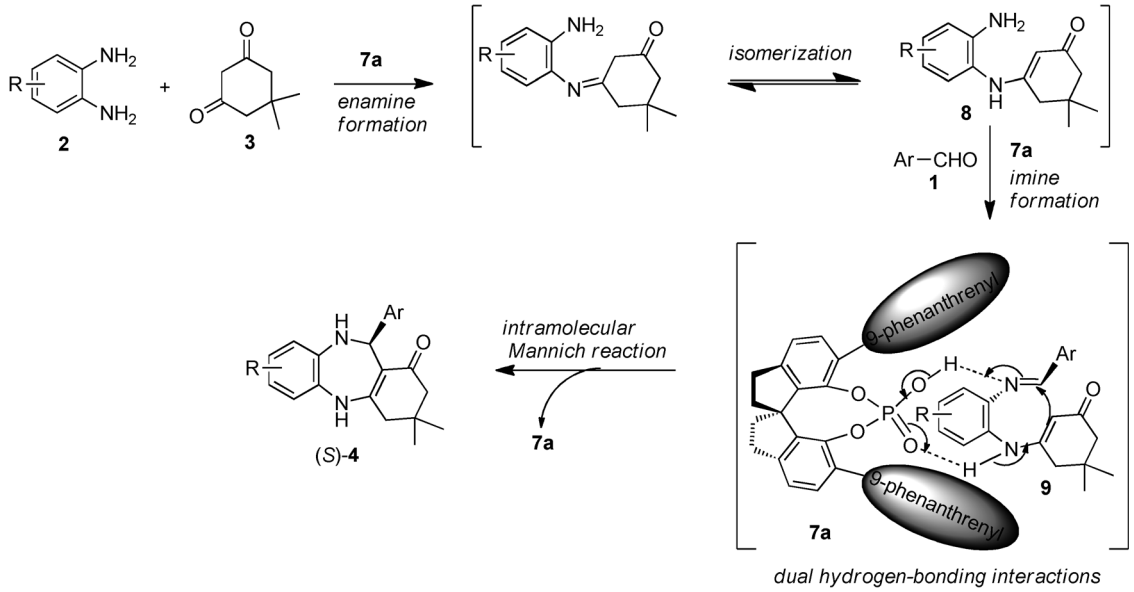

**Figure 2.** The absolute configuration of compound **4a**.

condensed with aldehyde **1** to produce the corresponding imine **9**. This key intermediate **9** possessed both the enamine and the imine functional groups, thus facilitating the subsequent intramolecular Mannich reaction, again under the catalysis of **7a**, to afford the desired dibenzo[1,4]diazepine **4**. In the proposed transition state of the intramolecular Mannich reaction, the 6,6′-bi(phenanthrenyl)phosphoric acid **7a** acted as a bifunctional catalyst to activate both the enamine and the imine groups by dual hydrogen-bonding interactions. Then, an enantioselective intramolecular Mannich reaction occurred because of the chiral environment created by (*R*)-SPINOL backbone and the bulky 6,6′-substitutents of CPA **7a**, thus providing the experimentally observed (*S*)-configured product **4**.

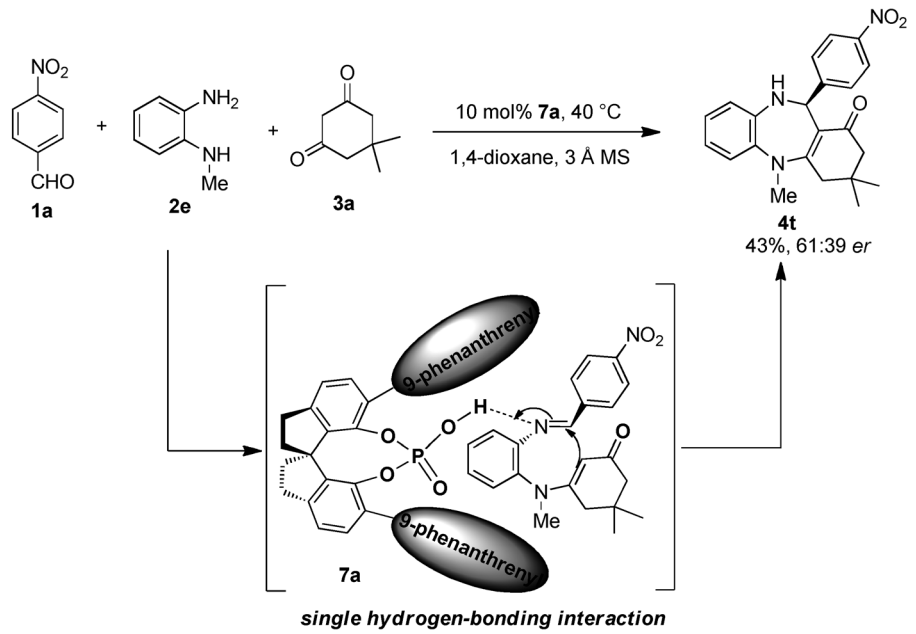
In order to test our hypothesis on the activation mode of dual hydrogen-bonding interactions as shown in Scheme 4 and to demonstrate the crucial role of $NH_2$ groups in 1,2-arylenediamine **2**, a control experiment was carried out with *N*-methyl-1,2-phenylenediamine **2e** under the optimal reaction conditions (Scheme 5). Although this three-component reaction afforded the desired dibenzo[1,4]diazepine **4t**, the yield was only 43% and the enantioselectivity was just 61:39 *er*. This result indicated that the $NH_2$ groups in 1,2-arylenediamine **2** were very important for both the reactivity and the enantioselectivity, because the existence of an *N*-methyl group allowed CPA **7a** to form just one hydrogen bond with the key intermediate, which was inferior to the dual hydrogen-bonding activation mode in reactivity and enantioselective control.

## Conclusions

In summary, we have established the first catalytic enantioselective construction of the biologically important dibenzo[1,4]diazepine scaffold in high yields and good enantioselectivities (up to 98% yield, 92:8 *er*) catalyzed by a SPNOL-derived chiral phosphoric acid. Furthermore, this transformation represents the first catalytic asymmetric version of the three-component reactions of aldehydes, 1,2-phenylenediamines and cyclohexane-1,3-diones, providing an easy access to structurally rigid seven-membered chiral heterocycles. This approach also combines the merits of organocatalysis and asymmetric multi-component reactions to afford a variety of enantioselective dibenzo-[1,4]diazepines with structural complexitzy and diversity, which should be promising candidates for chemical biology and drug discovery.




**Scheme 4.** Proposed reaction pathway and transition state.




**Scheme 5.** Control experiment involving *N*-methyl-1,2-phenylenediamine **2e**.

# Experimental Section

## General

NMR spectra were measured at 400 and 100 MHz, respectively. The solvents used for NMR spectroscopy were $CDCl_3$ and $CD_3OD$, using tetramethylsilane as the internal reference. HR-MS were recorded on an LTQ-Orbitrap mass spectrometer. Enantiomeric ratios (*er*) were determined by chiral high-performance liquid chromatography (chiral HPLC). The chiral columns used for the determination of enantiomeric ratios by chiral HPLC were Kromasil CHI-TBB and Daicel Chirapak OD-H columns. Optical rotation values were measured with instruments operating at $\lambda =$ 589 nm, corresponding to the sodium D line at the temperatures indicated. Analytical grade solvents for the column chromatography and commercially available reagents were used as received.

## Typical Procedure for the Asymmetric Synthesis of Dibenzo[1,4]diazepines 4

After a solution of 1,2-phenylenediamines **2** (0.1 mmol), cyclohexane-1,3-diones **3** (0.1 mmol), the catalyst **7a** (0.01 mmol), and 3 Å molecular sieves (100 mg) in 1,4-dioxane (0.5 mL) had been stirred at 40 °C for 2 h, the solution of aldehydes **1** (0.1 mmol) in 1,4-dioxane (0.5 mL) was added. After being stirred at 40 °C for 15 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with methanol. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure product **4**.

**(*S*)-3,3-Dimethyl-11-(4-nitrophenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4a):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 85%; yellow solid; $[\alpha]_D^{20}$: +199.2 (*c* 0.25, acetone); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta = 7.97$ (d, $J = 8.4$ Hz, 2H), 7.20 (d, $J = 8.5$ Hz, 2H), 6.82–6.70 (m, 3H), 6.58 (s, 1H), 6.48–6.31 (m, 1H), 5.98 (s, 1H), 4.48 (s, 1H), 2.63 (d, $J = 15.9$ Hz, 1H), 2.48 (d, $J = 15.9$ Hz, 1H), 2.34 (d, $J = 16.3$ Hz, 1H), 2.24 (d, $J = 16.3$ Hz, 1H), 1.17 (s, 3H), 1.08 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta = 194.0$, 153.4, 151.5, 146.5, 136.3, 130.7, 127.9, 124.4, 123.5, 121.9, 121.6, 120.2, 110.4, 57.8, 49.7, 46.5, 32.4, 28.7, 27.9; IR (KBr): $\nu = 3358$, 3566, 3393, 1698, 1683, 1647, 1636, 1541, 1522, 1508, 1385, 842, 737, 669 cm$^{-1}$; ESI-FT-MS: *m/z* 362.1512, exact mass calcd. for $(C_{21}H_{21}N_3O_3-H)^-$: 362.1499; enantiomeric ratio: 92:8, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 70/30, flow rate 1.0 mL min$^{-1}$, $T = 30$ °C, 254 nm): $t_R = 5.57$ min (major), $t_R = 6.36$ min (minor).

**(*S*)-3,3-Dimethyl-11-[4-(trifluoromethyl)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4b):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 78%; yellow solid; $[\alpha]_D^{20}$: +85.1 (*c* 0.28, acetone); $^1$H NMR ($CDCl_3/CD_3OD$, 400 MHz): $\delta = 7.36$ (d, $J = 7.5$ Hz, 2H), 7.17 (d, $J = 7.9$ Hz, 2H), 7.0–6.70 (m, 4H), 6.45 (d, $J = 7.9$ Hz, 1H), 6.02 (s, 1H), 4.58 (s, 1H), 2.65–2.50 (m, 1H), 2.44 (d, $J = 15.7$ Hz, 1H), 2.30 (d, $J = 16.2$ Hz, 1H), 2.22 (d, $J = 16.2$ Hz, 1H), 1.13 (s, 3H), 1.05 (s, 3H); $^{13}$C NMR ($CDCl_3/CD_3OD$, 100 MHz): $\delta = 194.1$, 128.7, 127.6, 125.2, 125.2, 124.3, 122.7, 122.0, 120.4, 58.1, 55.1, 46.2, 32.4, 28.9, 27.7; IR (KBr): $\gamma$ 3404, 3217, 1637, 1618, 1541, 1522, 1384, 832, 724 cm$^{-1}$; ESI-FT-MS: $m/z = 385.1543$, exact mass calcd. for $(C_{22}H_{21}F_3N_2O-H)^-$: 385.1528; enantiomeric ratio: 91:9, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T = 30$ °C, 254 nm): $t_R = 5.97$ min (major), $t_R = 6.72$ min (minor).

**(*S*)-Methyl 4-(3,3-dimethyl-1-oxo-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)benzoate (4c):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 86%; pale yellow solid; $[\alpha]_D^{20}$: +235.8 (*c* 0.29, acetone); $^1$H NMR ($CDCl_3$, 400 MHz):

$\delta$ = 7.79 (d, $J$ = 8.1 Hz, 2H), 7.12 (d, $J$ = 8.1 Hz, 2H), 6.74–6.70 (m, 4H), 6.45–6.31 (m, 1H), 5.97 (s, 1H), 4.46 (s, 1H), 3.82 (s, 3H), 2.62 (d, $J$ = 15.8 Hz, 1H), 2.43 (d, $J$ = 15.9 Hz, 1H), 2.32 (d, $J$ = 16 Hz, 1H), 2.23 (d, $J$ = 16 Hz, 1H), 1.13 (s, 3H), 1.05 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 194.0, 167.0, 153.4, 149.2, 136.7, 130.9, 129.6, 128.3, 127.2, 124.1, 121.6, 121.5, 120.0, 110.8, 58.0, 52.0, 49.7, 46.4, 32.4, 28.8, 27.7; IR (KBr): $\nu$ = 3413, 3125, 2975, 1699, 1637, 1508, 1385, 1090, 1049, 880, 741, 639 cm$^{-1}$; ESI-FT-MS: $m/z$ = 375.1684, exact mass calcd. for $(C_{23}H_{24}N_2O_3-H)^-$: 375.1709; enantiomeric ratio: 89:11, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 6.74 min (major), $t_R$ = 7.50 min (minor).

**(*S*)-3,3-Dimethyl-11-[4-(trifluoromethyl)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4d):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 84%; yellow solid; $[\alpha]_D^{20}$: +115.7 ($c$ 0.24, acetone); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.38 (d, $J$ = 7.7 Hz, 2H), 7.15 (d, $J$ = 7.9 Hz, 2H), 6.90–6.72 (m, 4H), 6.44–6.37 (m, 1H), 5.96 (s, 1H), 4.61 (s, 1H), 2.59 (d, $J$ = 15.5 Hz, 1H), 2.47 (d, $J$ = 15.8 Hz, 1H), 2.31 (d, $J$ = 16.3 Hz, 1H), 2.23 (d, $J$ = 16.3 Hz, 1H), 1.14 (s, 3H), 1.06 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 194.1, 153.9, 132.1, 130.9, 127.9, 124.3, 122.0, 121.7, 120.3, 120.3, 118.9, 110.3, 58.1, 49.7, 46.2, 32.4, 28.7, 27.8; IR (KBr): $\nu$ = 3406, 3321, 2173, 1635, 1622, 1540, 1507, 1384, 857, 716 cm$^{-1}$; ESI-FT-MS: $m/z$ 342.1631, exact mass calcd. for $(C_{22}H_{21}N_3O-H)^-$: 342.1607; enantiomeric ratio: 87:13, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 8.32 min (major), $t_R$ = 9.74 min (minor).

**(*S*)-11-(4-Fluorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4e):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 76%; pale yellow solid; $[\alpha]_D^{20}$: −9.6 ($c$ 0.24, acetone); $^1$H NMR ($CDCl_3$/$CD_3OD$, 400 MHz): $\delta$ = 7.08–6.97 (m, 2H), 6.95–6.65 (m, 6H), 6.52–6.37 (m, 1H), 6.05–5.90 (m, 1H), 4.58 (s, 1H), 2.65–2.47 (m, 1H), 2.46–2.37 (m, 1H), 2.28–2.19 (m, 2H), 1.12 (s, 3H), 1.06 (s, 3H); $^{13}$C NMR ($CDCl_3$/$CD_3OD$, 100 MHz): $\delta$ = 194.0, 162.7, 160.3, 128.8, 128.7, 124.1, 121.9, 120.3, 115.1, 114.9, 97.5, 57.7, 55.1, 46.2, 32.3, 28.9, 27.6; IR (KBr): $\nu$ = 3526, 3402, 3309, 2935, 1542, 1523, 1508, 1384, 893, 761, 703, 667 cm$^{-1}$; ESI-FT-MS: $m/z$ = 335.1573, exact mass calcd. for $(C_{21}H_{21}FN_2O-H)^-$: 335.1560; enantiomeric ratio: 89:11, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 5.77 min (major), $t_R$ = 6.39 min (minor).

**(*S*)-11-(3,4-Difluorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4f):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 80%; yellow solid; $[\alpha]_D^{20}$: +18.6 ($c$ 0.16, acetone); $^1$H NMR ($CDCl_3$/$CD_3OD$, 400 MHz): $\delta$ = 6.98–6.69 (m, 7H), 6.51–6.40 (m, 1H), 5.95–5.84 (m, 1H), 4.58 (s, 1H), 2.61–2.38 (m, 2H), 2.33–2.18 (m, 2H), 1.13 (s, 3H), 1.07 (s, 3H); $^{13}$C NMR ($CDCl_3$/$CD_3OD$, 100 MHz): $\delta$ = 194.0, 153.9, 151.2, 148.8, 124.3, 123.3, 121.9, 117.0, 116.8, 116.2, 116.0, 97.5, 57.5, 55.1, 46.2, 32.3, 28.8, 27.8; IR (KBr): $\nu$ = 3446, 3364, 3217, 2935, 2987, 1698, 1683, 1647, 1635, 1507, 1385, 933, 821, 711 cm$^{-1}$; ESI-FT-MS: $m/z$ = 353.1452, exact mass calcd. for $(C_{21}H_{21}FN_2O-H)^-$: 353.1466; enantiomeric ratio: 83:17, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 6.31 min (major), $t_R$ = 7.20 min (minor).

**(*S*)-11-(3-Chloro-4-fluorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4g):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 98%; pale yellow solid; $[\alpha]_D^{20}$: +208.3 ($c$ 0.22, acetone); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.15–7.05 (m, 1H), 6.95–6.83 (m, 2H), 6.80–6.72 (m, 3H), 6.64 (s, 1H), 6.47–6.36 (m, 1H), 5.87 (s, 1H), 4.42 (s, 1H), 2.65–2.53 (m, 1H), 2.45 (d, $J$ = 15.8 Hz, 1H), 2.32 (d, $J$ = 16.3 Hz, 1H), 2.24 (d, $J$ = 16.4 Hz, 1H), 1.15 (s, 3H), 1.08 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 194.0, 153.5, 136.7, 130.9, 129.4, 126.8, 126.7, 124.3, 121.8, 121.7, 120.1, 116.3, 116.0, 110.8, 57.3, 49.7, 46.4, 32.4, 28.7, 27.9; IR (KBr): $\nu$ = 3311, 3013, 2902, 1684, 1637, 1622, 1385, 732, 669, 617 cm$^{-1}$; ESI-FT-MS: $m/z$ = 369.1164, exact mass calcd. for $(C_{21}H_{20}ClFN_2O-H)^-$: 369.1187; enantiomeric ratio: 84:16, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 6.30 min (major), $t_R$ = 7.24 min (minor).

**(*S*)-11-(4-Chloro-3-fluorophenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4h):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 90%; pale yellow solid; $[\alpha]_D^{20}$: +214.3 ($c$ 0.23, acetone); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.19–7.07 (m, 1H), 6.88–6.64 (m, 6H), 6.49–6.34 (m, 1H), 5.88 (s, 1H), 4.44 (s, 1H), 2.65–2.52 (m, 1H), 2.44 (d, $J$ = 15.9 Hz, 1H), 2.32 (d, $J$ = 16.3 Hz, 1H), 2.23 (d, $J$ = 16.3 Hz, 1H), 1.14 (s, 3H), 1.07 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 194.0, 153.6, 136.6, 130.8, 130.2, 124.3, 123.8, 123.7, 121.8, 121.6, 120.2, 115.4, 115.1, 110.7, 57.4, 49.7, 46.3, 32.4, 28.7, 27.9; IR (KBr): $\nu$ = 3375, 3112, 2992, 1647, 1636, 1622, 1541, 1385, 832, 669, 548 cm$^{-1}$; ESI-FT-MS: $m/z$ = 369.1142, exact mass calcd. for $(C_{21}H_{20}ClFN_2O-H)^-$: 369.1164; enantiomeric ratio: 84:16, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 90/10, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 16.16 min (major), $t_R$ = 20.38 min (minor).

**(*S*)-11-[(1,1′-Biphenyl)-4-yl]-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4i):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1, then preparative thin layer chromatography, petroleum ether/ethyl acetate = 1/2; reaction time: 17 h; yield: 55%; yellow solid; $[\alpha]_D^{20}$: +32.9 ($c$ 0.23, acetone); $^1$H NMR ($CDCl_3$/$CD_3OD$, 400 MHz): $\delta$ = 7.63–7.41 (m, 3H), 7.40–7.30 (m, 5H), 7.18–7.01 (m, 2H), 6.85–6.70 (m, 3H), 6.50 (s, 1H), 6.15–5.93 (m, 1H), 4.58 (s, 1H), 2.69–2.48 (m, 1H), 2.47–2.42 (m, 1H), 2.37–2.28 (m, 1H), 2.26–2.23 (m, 1H), 1.12 (s, 3H), 1.10–1.07 (m, 3H); $^{13}$C NMR ($CDCl_3$/$CD_3OD$, 100 MHz): $\delta$ = 194.1, 140.7, 139.4, 128.7, 127.8, 127.1, 126.9, 124.1, 97.5, 58.1, 55.1, 50.9, 32.4, 29.1, 27.6; IR (KBr): $\nu$ = 3305, 3122, 1652, 1557, 1541, 1521, 1507, 1384, 921, 852, 773, 698 cm$^{-1}$; ESI-FT-MS: $m/z$ = 393.1976, exact mass calcd. for $(C_{27}H_{26}N_2O-H)^-$: 393.1967; enantiomeric ratio: 91:9, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 6.19 min (major), $t_R$ = 6.79 min (minor).

**(*S*)-3,3-Dimethyl-11-phenyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4j):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 90%; yellow solid; $[\alpha]_D^{20}$: −32.9 ($c$ 0.14,

acetone); $^1$H NMR ($CDCl_3/CD_3OD$, 400 MHz): $\delta$ = 7.16–6.99 (m, 6H), 6.82–6.68 (m, 3H), 6.51–6.39 (m, 1H), 6.12–5.93 (m, 1H), 4.58 (s, 1H), 2.54–2.31 (m, 2H), 2.29–2.12 (m, 2H), 1.11 (s, 3H), 1.06 (s, 3H); $^{13}$C NMR ($CDCl_3/CD_3OD$, 100 MHz): $\delta$ = 194.0, 128.2, 127.3, 126.8, 123.9, 122.0, 97.45, 58.3, 55.1, 46.2, 32.3, 29.1, 27.5; IR (KBr): $\nu$ = 3564, 3107, 2962, 1716, 1620, 1539, 1384, 1263, 817, 776, 703 cm$^{-1}$; ESI-FT-MS: $m/z$ = 317.1649, exact mass calcd. for $(C_{21}H_{22}N_2O-H)^-$: 317.1654; enantiomeric ratio: 88:12, determined by HPLC (Daicel Chirapak OD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 6.98 min (major), $t_R$ = 17.67 min (minor).

**(*S*)-3,3-Dimethyl-11-(naphthalen-2-yl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4k):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1, then preparative thin layer chromatography, petroleum ether/ethyl acetate = 1/2; reaction time: 17 h; yield: 58%; yellow solid; $[\alpha]_D^{20}$: −37.7 (*c* 0.21, acetone); $^1$H NMR ($CDCl_3/CD_3OD$, 400 MHz): $\delta$ = 7.70–7.56 (m, 3H), 7.47 (s, 1H), 7.37–7.32 (m, 2H), 7.24–7.12 (m, 1H), 7.01–6.57 (m, 4H), 6.46 (s, 1H), 6.31–6.05 (m, 1H), 4.58 (s, 1H), 2.70–2.47 (m, 1H), 2.46–2.43 (m, 1H), 2.37–2.27 (m, 1H), 2.26–2.22 (m, 1H), 1.10 (s, 6H); $^{13}$C NMR ($CDCl_3/CD_3OD$, 100 MHz): $\delta$ = 194.1, 133.2, 132.4, 128.0, 127.4, 125.8, 125.7, 124.1, 97.5, 55.1, 49.8, 32.4, 29.7, 27.6; IR (KBr): $\gamma$ = 3444, 3309, 2997, 1541, 1521, 1507, 1385, 831, 793, 727, 615 cm$^{-1}$; ESI-FT-MS: $m/z$ = 367.1839, exact mass calcd. for $(C_{25}H_{24}N_2O-H)^-$: 367.1811; enantiomeric ratio: 86:14, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 6.16 min (major), $t_R$ = 6.93 min (minor).

**(*S*)-11-(4-Methoxyphenyl)-3,3-dimethyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4l):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1, then preparative thin layer chromatography, petroleum ether/ethyl acetate = 1/2; reaction time: 17 h; yield: 61%; yellow solid; $[\alpha]_D^{20}$: −11.4 (*c* 0.18, acetone); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.08–6.86 (m, 3H), 6.81–6.68 (m, 3H), 6.65–6.60 (m, 2H), 6.50–6.40 (m, 1H), 6.02–5.85 (m, 1H), 4.58 (s, 1H), 3.66 (s, 3H), 2.66–2.42 (m, 1H), 2.41–2.34 (m, 1H), 2.32–2.24 (m, 1H), 2.23–2.17 (m, 1H), 1.13–1.08 (m, 3H), 1.05 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 194.0, 158.1, 128.3, 123.9, 121.9, 113.5, 57.7, 55.1, 49.8, 46.2, 32.3, 29.1, 27.6; IR (KBr): $\nu$ = 3392, 3113, 2992, 1647, 1636, 1541, 1508, 1385, 863, 733, 662 cm$^{-1}$; ESI-FT-MS: $m/z$ = 347.1786, exact mass calcd. for $(C_{22}H_{24}N_2O_2-H)^-$: 347.1760; enantiomeric ratio: 91:9, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 5.73 min (major), $t_R$ = 6.20 min (minor).

**(*S*)-3,3-Dimethyl-11-(*para*-tolyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4m):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 81%; pale yellow solid; $[\alpha]_D^{20}$: +193.2 (*c* 0.23, acetone); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.00–6.88 (m, 4H), 6.82–6.64 (m, 4H), 6.46–6.35 (m, 1H), 5.91 (s, 1H), 4.42 (s, 1H), 2.65–2.48 (m, 1H), 2.42–2.34 (m, 1H), 2.33–2.26 (m, 1H), 2.25–2.20 (m, 1H), 2.18 (s, 3H), 1.12 (s, 3H), 1.05 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 193.9, 153.2, 140.9, 137.2, 136.0, 131.0, 128.9, 127.0, 123.7, 121.59, 121.2, 119.9, 111.7, 57.8, 49.8, 46.3, 32.3, 28.9, 27.7, 21.0; IR (KBr): $\nu$ = 3327, 3001, 1733, 1698, 1647, 1558, 1508, 1457, 1385, 821, 730, 669 cm$^{-1}$; ESI-FT-MS: $m/z$ = 331.1811, exact mass calcd. for $(C_{22}H_{24}N_2O-H)^-$: 331.1805; enantiomeric ratio: 88:12, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 90/10, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 10.58 min (major), $t_R$ = 11.82 min (minor).

**(*S*)-3,3-Dimethyl-11-(*meta*-tolyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4n):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1, then preparative thin layer chromatography, petroleum ether/ethyl acetate = 1/2; reaction time: 17 h; yield: 60%; pale yellow solid; $[\alpha]_D^{20}$: +76.0 (*c* 0.24, acetone); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 6.99–6.92 (m, 2H), 6.85 (d, $J$ = 7.5 Hz, 1H), 6.81–6.69 (m, 4H), 6.68–6.57 (m, 1H), 6.46–6.36 (m, 1H), 5.90 (s, 1H), 4.41 (s, 1H), 2.64–2.51 (m, 1H), 2.40 (d, $J$ = 15.8 Hz, 1H), 2.35–2.26 (m, 1H), 2.25–2.20 (m, 1H), 2.19 (s, 3H), 1.13 (s, 3H), 1.07 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 194.0, 153.1, 143.8, 137.6, 131.0, 128.3, 127.9, 127.4, 123.8, 123.8, 121.6, 121.2, 119.9, 111.6, 58.1, 49.8, 46.4, 32.4, 28.9, 27.7, 21.5; IR (KBr): $\nu$ = 3415, 3227, 2998, 1732, 1715, 1698, 1636, 1541, 1385, 902, 862, 701 cm$^{-1}$; ESI-FT-MS: $m/z$ = 331.1806, exact mass calcd. for $(C_{22}H_{24}N_2O-H)^-$: 331.1805; enantiomeric ratio: 83:17, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 90/10, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 10.20 min (major), $t_R$ = 11.65 min (minor).

**(*R*)-3,3-Dimethyl-11-(thiophen-2-yl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4o):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1, then preparative thin layer chromatography, petroleum ether/ethyl acetate = 1/2; reaction time: 17 h; yield: 54%; pale yellow solid; $[\alpha]_D^{20}$: +75.5 (*c* 0.20, acetone); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.02–6.94 (m, 1H), 6.85–6.65 (m, 6H), 6.61–6.52 (m, 1H), 6.21 (s, 1H), 4.46 (s, 1H), 2.64–2.53 (m, 1H), 2.36 (d, $J$ = 16 Hz, 1H), 2.32 (d, $J$ = 16 Hz, 1H), 2.25 (d, $J$ = 16 Hz, 1H), 1.12 (s, 3H), 1.08 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 193.5, 153.4, 148.0, 137.0, 130.6, 126.3, 124.5, 124.0, 123.9, 121.8, 121.5, 120.2, 112.6, 53.0, 50.0, 46.2, 32.3, 29.2, 27.5; IR (KBr): $\nu$ = 3414, 3217, 2925, 1872, 1618, 1501, 1384, 912, 746, 624 cm$^{-1}$; ESI-FT-MS: $m/z$ = 323.1185, exact mass calcd. for $(C_{19}H_{20}N_2OSM->H)^-$: 323.1213; enantiomeric ratio: 78:22, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 90/10, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 12.42 min (major), $t_R$ = 13.63 min (minor).

**(*S*)-3,3-Dimethyl-13-(4-nitrophenyl)-2,3,4,5,12,13-hexahydro-1*H*-benzo[*e*]naphtho[2,3-*b*][1,4]diazepin-1-one (4p):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 87%; yellow solid; $[\alpha]_D^{20}$: +134.9 (*c* 0.21, acetone); $^1$H NMR ($CDCl_3/CD_3OD$, 400 MHz): $\delta$ = 8.10–7.71 (m, 3H), 7.60–7.46 (m, 1H), 7.42–7.36 (m, 2H), 7.23–7.17 (m, 4H), 6.87–6.82 (m, 1H), 6.13–6.00 (m, 1H), 4.98 (s, 1H), 2.82–2.59 (m, 1H), 2.54 (d, $J$ = 15.3 Hz, 1H), 2.41–2.32 (m, 1H), 2.30–2.22 (m, 1H), 1.17 (s, 3H), 1.12 (s, 3H); $^{13}$C NMR ($CDCl_3/CD_3OD$, 100 MHz): $\delta$ = 194.4, 146.6, 132.4, 130.8, 128.1, 126.3, 125.9, 125.5, 124.9, 123.6, 97.5, 57.7, 55.1, 46.3, 32.4, 28.7, 28.0; IR (KBr): $\nu$ = 3411, 3097, 1805, 1636, 1617, 1519, 1385, 932, 807, 618 cm$^{-1}$; ESI-FT-MS: $m/z$ = 412.1670, exact mass calcd. for $(C_{25}H_{23}N_3O_3-H)^-$: 412.1661; enantiomeric ratio: 92:8, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol =

80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 13.90 min (major), $t_R$ = 15.65 min (minor).

**(*S*)-3,3,7,8-Tetramethyl-11-(4-nitrophenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4q):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 87%; orange solid; $[\alpha]_D^{20}$: +163.8 (*c* 0.18, acetone); $^1$H NMR ($CDCl_3$/$CD_3OD$, 400 MHz): $\delta$ = 7.97–7.85 (m, 2H), 7.21 (d, $J$ = 8.3 Hz, 2H), 6.85–6.45 (m, 2H), 6.19 (s, 1H), 6.08–5.92 (m, 1H), 4.58 (s, 1H), 2.65–2.50 (m, 1H), 2.46–2.40 (m, 1H), 2.35–2.27 (m, 1H), 2.22 (d, $J$ = 15.7 Hz, 1H), 2.07–2.03 (m, 3H), 2.00–1.95 (m, 3H), 1.14 (s, 3H), 1.05 (s, 3H); $^{13}$C NMR ($CDCl_3$/$CD_3OD$, 100 MHz): $\delta$ = 193.9, 146.5, 133.0, 128.1, 123.5, 122.8, 121.4, 97.5, 57.9, 55.1, 50.8, 46.4, 32.3, 28.8, 18.9, 18.8; IR (KBr): $\nu$ = 3235, 2962, 2029, 1638, 1617, 1517, 1384, 1342, 1261, 932, 619 cm$^{-1}$; ESI-FT-MS: $m/z$ = 390.1845, exact mass calcd for $(C_{23}H_{25}N_3O_3-H)^-$: 390.1818; enantiomeric ratio: 91:9, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 90/10, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 22.26 min (major), $t_R$ = 26.77 min (minor).

**(*S*)-7,8-Dichloro-3,3-dimethyl-11-(4-nitrophenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4r):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 88%; orange solid; $[\alpha]_D^{20}$: +225.3 (*c* 0.39, acetone); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 8.09–8.00 (m, 2H), 7.22–7.10 (m, 2H), 6.86 (s, 1H), 6.53 (s, 1H), 6.33 (s, 1H), 5.94 (s, 1H), 4.53 (s, 1H), 2.65–2.57 (m, 1H), 2.43 (d, $J$ = 15.9 Hz, 1H), 2.35–2.30 (m, 1H), 2.24 (d, $J$ = 16.6 Hz, 1H), 1.17 (s, 3H), 1.08–1.03 (m, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 191.5, 150.5, 146.7, 135.9, 127.8, 123.8, 122.0, 120.9, 57.3, 46.2, 32.4, 28.6, 27.7, 14.1; IR (KBr): $\nu$ = 3376, 2975, 1651, 1507, 1456, 1385, 1090, 1049, 880, 801, 537 cm$^{-1}$; ESI-FT-MS: $m/z$ = 430.0751, exact mass calcd. for $(C_{21}H_{19}Cl_2N_3O_3-H)^-$: 430.0725; enantiomeric ratio: 85:15, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 14.54 min (major), $t_R$ = 16.28 min (minor).

**(11*S*)-11-(4-Nitrophenyl)-3-phenyl-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4s):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 98%; 55:45 *dr*; yellow solid; mp 125–126 °C; $[\alpha]_D^{20}$: +159.3 (*c* 0.14, acetone); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 8.00 (d, $J$ = 8.5 Hz, 2H), 7.41–7.34 (m, 2H), 7.32–7.27 (m, 4H), 7.25–7.22 (m, 1H), 6.85–6.70 (m, 3H), 6.68–6.55 (m, 1H), 6.50–6.41 (m, 1H), 6.06 (s, 1H), 4.53 (s, 1H), 3.43–3.35 (m, 1H), 3.18–3.05 (m, 1H), 2.83–2.56 (m, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 193.4, 154.7, 151.1, 146.5, 142.5, 136.4, 130.2, 129.0, 128.1, 127.3, 126.7, 124.5, 123.6, 121.9, 121.6, 120.2, 111.9, 57.3, 43.1, 40.5, 39.5; IR (KBr): $\nu$ = 3399, 2975, 1716, 1698, 1617, 1521, 1508, 1385, 1090, 1049, 857, 744 cm$^{-1}$; ESI-FT-MS: $m/z$ = 410.1520, exact mass calcd. for $(C_{25}H_{21}N_3O_3-H)^-$: 410.1505; enantiomeric ratio: 90:10, determined by HPLC (Kromasil CHI-TBB, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 13.24 min (major), $t_R$ = 17.56 min (minor).

**(*S*)-3,3,5-Trimethyl-11-(4-nitrophenyl)-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepin-1-one (4t):** Flash column chromatography eluent: petroleum ether/ethyl acetate = 1/1; reaction time: 17 h; yield: 43%; yellow solid; $[\alpha]_D^{20}$: +16.8 (*c* 0.17, acetone); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.95 (d, $J$ = 8.8 Hz, 2H), 7.12 (d, $J$ = 8.7 Hz, 2H), 6.88–6.77 (m, 3H), 6.53–6.47 (m, 1H), 6.31 (s, 1H), 5.73 (s, 1H), 3.00 (s, 3H), 2.64 (d, $J$ = 15.8 Hz, 1H), 2.49 (d, $J$ = 15.9 Hz, 1H), 2.31 (d, $J$ = 16.3 Hz, 1H), 2.20 (d, $J$ = 16.3 Hz, 1H), 1.18 (s, 3H), 1.08 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 194.1, 152.7, 148.3, 139.0, 133.1, 128.6, 124.6, 123.0, 122.6, 120.8, 120.0, 110.0, 65.6, 49.7, 46.4, 42.1, 32.5, 28.5, 28.1; IR (KBr): $\nu$ = 3413, 2992, 1775, 1638, 1618, 1510, 1265, 1050, 925, 739, 619 cm$^{-1}$; ESI-FT-MS: $m/z$ = 376.1658, exact mass calcd. for $(C_{22}H_{23}N_3O_3$-H)$^-$: 376.1656; enantiomeric ratio: 61:39, determined by HPLC (Daicel Chirapak OD-H, hexane/2-propanol = 80/20, flow rate 1.0 mL min$^{-1}$, $T$ = 30 °C, 254 nm): $t_R$ = 10.27 min (major), $t_R$ = 8.22 min (minor).

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[10] CCDC 981182 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

  

**12** Enantioselective Construction of the Biologically Significant Dibenzo[1,4]diazepine Scaffold *via* Organocatalytic Asymmetric Three-Component Reactions

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