Preparation of chiral 3-oxocycloalkanecarbonitrile and its derivatives by crystallization-induced diastereomer transformation of ketals with chiral 1,2-diphenylethane-1,2-diol†

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Chiral 3-oxocycloalkanecarbonitriles were prepared by fractional crystallization and crystallization-induced diastereomer transformation (CIDT) of diastereomeric ketals with (1R,2R)-1,2-diphenylethane-1,2-diol. Investigation of the crystal structures by X-ray diffraction analysis revealed that the difference in hydrogen bonds caused the discrepancy of the solubilities between (R) and (S) diastereomers. Furthermore, CIDT to afford the (R)-diastereomer in good yield (95% yield) and with high diastereoselectivity (97% de) was accomplished, which is the first example of CIDT of neutral compounds via formation of the diastereomeric ketal with (1R,2R)-1,2-diphenylethane-1,2-diol.

Introduction

In recent years, the structure of active pharmaceutical ingredients and fine chemicals has become more complicated. To meet the demands for synthesizing organic molecules with a sophisticated design, building blocks containing chiral carbons as a component are widely used. Developing a new chiral building block will enable the synthesis of a new compound and provide benefits to both the chemical and pharmaceutical industries.

As new candidate building blocks, we focus on 3-oxocycloalkanecarbonitriles, 1a,1b and 1b† (Fig. 1). In fact, active pharmaceutical ingredients or intermediates containing 3-oxocycloalkanecarbonitriles or its derivatives have been reported,†,‡ which implies that 1 has potential as a building block. In spite of its structural simplicity, the preparation of enantiomerically pure 1 remains a challenging task.

Although 3-cyanoketones 1 are easily prepared from Michael addition of cyanide ions to z,β-unsaturated ketones,†,‡ there are a few articles reporting the preparation of chiral 3-cyanoketones by catalytic enantioselective conjugate addition of cyanide to enones. Specifically, 1b was obtained in 81% ee and 90% yield,§ and nucelophilic addition of formaldehyde dialkylhydrazones to conjugated enones has been reported.** However, no optical resolution of these neutral compounds has been reported, as these compounds are not applicable for diastereomeric salt separation, which is the most popular method to resolve racemic compounds. In fact, 3-oxocyclopentanecarboxylic acid as an acidic compound was resolved by diastereomeric salt formation with (−)-brucine, but four sequential crystallizations were required to obtain (R)-enantiomer in 98% ee.ε

In order to introduce chiral moiety onto 1 and apply diastereomeric separation, we use chiral ketals as not only a protecting group but also chiral resolving auxiliary. Among several 1,2-diols, commercially available (1R,2R)- or (1S,2S)-1,2-diphenylethane-1,2-diol (dihydrobenzoin) shows great promise as a chiral auxiliary. In fact, several articles reported the separation of two isomers via formation of the diastereomeric ketals, and subsequent isolation either by column chromatography or crystallization.ε–r

Preliminarily, we synthesized diastereomeric mixtures of 2, but unfortunately, it was oily substance, which indicated that diastereomer separation by recrystallization was not applicable.

Fig. 1 Chiral separation of racemic 3-oxocycloalkanecarbonitriles.
Therefore, we transformed nitriles 2 into amides 3, which are generally expected to solidify due to the formation of hydrogen bonds. First, we examined the preparation of chiral 3-oxocycloalkanecarbonitrile and their derivatives via ketalization with (1R,2R)-1,2-diphenylethane-1,2-diol through fractional crystallization (Fig. 1). Even if separation of diastereomer is achieved through fractional crystallization, half of the diastereomeric mixture would remain as an undesired diastereomer. To our delight, 3 turned out to be racemized under basic conditions. Therefore, we performed crystallization-induced diastereomer transformation (CIDT)\textsuperscript{13} on 3 and demonstrated the successful transformation of these compounds while keeping stereochemistry (Fig. 2).

### Results and discussion

#### Synthesis of ketal

In accordance with the literature,\textsuperscript{7a} 3-cyanocyclopentanone 1a was prepared from Michael addition of cyanide ions to 2-cyclopentenenone in 92%. In the case of 2-cyclohexenone, 3-cyanocyclohexanone 1b was obtained in lower yield (63%), but the value is comparable in the reported yield\textsuperscript{14} (Scheme 1). Then, acid-catalyzed ketalization of 3-cyanocyclopentanone with 1,2-diphenylethane-1,2-diol was performed by pyridinium p-toluene sulfonylate (PPTS).\textsuperscript{10a,b} Using an optimized reaction condition, namely, 1a (1.00 g, 9.20 mmol) with the diol (1.3 equiv.) and PPTS (0.1 equiv.) in toluene (30 mL) at 110 °C for 23 h, ketalization of 1a proceeded in 78% yield. Similarly, ketalization of 1b proceeded in 39% yield. Insufficient yield in ketalization of 1b is due to the contamination in 1b.\textsuperscript{15} Both diastereomeric mixtures of 2 were oily substance.

For the purpose of applying the diastereomer separation by fractional crystallization, we hydrated nitriles 2 with a combination of hydrogen peroxide and potassium carbonate\textsuperscript{12} to obtain crystalline amides 3.

#### Fractional crystallization

To obtain a single diastereomer, we performed fractional crystallization on these amides 3 from the solution (toluene/CHCl\textsubscript{3} = 2/3, Table 1). First, fractional crystallization of diastereomeric mixture 3a provided (R)-3a\textsuperscript{15} with 84% de (32% yield). An additional crystallization of the (R)-3a (84% de) achieved de of 99% (total yield 16%). In contrast, first fractional crystallization (toluene/CHCl\textsubscript{3} = 2/3) of diastereomeric mixture 3b was performed to obtain (R)-3b\textsuperscript{14} with only 30% de (46% yield). Second and third fractional crystallization (toluene/CHCl\textsubscript{3} = 2/3) provided (R)-3b with 87% de and 99% de (total yield 14%). As shown in this result, both diastereomeric mixtures were separated by simple crystallization, and diastereomers of five-membered ketal 3a were more easily separated than those of six-membered 3b.

#### Investigation of crystal structures by single-crystal X-ray diffraction analysis

To determine the stereochemistry of these diastereomers and to clarify why (R)-diastereomer crystallized preferably, we investigated the crystal structures of their diastereomers by single-crystal X-ray diffraction (SXRD) analysis. To obtain both diastereomers of 3, we first tried to separate the diastereomeric mixture of 3a by recycling preparative HPLC. However, 3a was inseparable due to the similar retention time of the diastereomers. In contrast, the corresponding nitriles 2a could be satisfactorily separated by recycling preparative HPLC. Here, we confirmed that both diastereomers of 2a were definitely oil. Then, (R)-2a and (S)-2a were transformed to crystalline amides (R)-3a and (S)-3a under the basic conditions mentioned above without epimerization.\textsuperscript{12} In sharp contrast with 2a, even ten cycles of recycling preparative HPLC could not separate 2b. After transformation to the corresponding amide 3b, diastereomeric

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**Table 1**: Fractional crystallization of 3a and 3b\textsuperscript{a}

| Starting material | Crystallizations |
|-------------------|------------------|
|                   | None | 1st | 2nd | 3rd |
| (R)-3a            | % de\textsuperscript{b} | 3   | 84  | >99 |
|                   | Yield (%)   | —   | 32  | 16  |
| (R)-3b            | % de\textsuperscript{b} | 10  | 30  | 87  | >99 |
|                   | Yield (%)   | —   | 46  | 26  | 14  |

\textsuperscript{a} In toluene/CHCl\textsubscript{3} = 2/3. \textsuperscript{b} % de was determined by HPLC.
mixtures of 3b were satisfactorily separated into (R)-3b and (S)-3b by recycling preparative HPLC.

All amides 3 were crystallized to obtain crystals suitable for SXRD analysis and we were able to determine the stereochemistry (Fig. 3 and 4). As shown in Fig. 3, both (R)-3a and (S)-3a had the same space group (P2₁) and a similar molecular arrangement to construct hydrogen bonding networks. Their amide groups act as hydrogen donor and acceptor to construct the same number of hydrogen bonds, namely, two amide protons bound to two oxygen atoms of the amide and the ketal. While the cis proton against the carbonyl oxygen in (R)-3a constructed hydrogen bonds with the amide functional group, the trans one did in (S)-3a. The parameters of the hydrogen bonds in (R)-3a and (S)-3a are summarized in Table 2. The hydrogen bonding distances in (R)-3a crystals were shorter than those of (S)-3a. The crystals of (R)-3a (mp 139–140 °C, 1.26 g cm⁻³) had a higher melting point and larger calculated density than those of (S)-3a (mp 135–136 °C, 1.23 g cm⁻³). We performed solubility tests on each diastereomer in toluene at 25 °C and found that the values of (R)-3a and (S)-3a were 16.0 g L⁻¹ and 21.5 g L⁻¹, respectively, as anticipated. These results suggest that the difference of strength of the hydrogen bonds caused the discrepancy of the solubility and consequently enabled fractional crystallization providing (R)-3a.

As shown in Fig. 4, the crystals of (R)-3b and (S)-3b had space groups of P2₁ and P2₁2₁2₁, respectively. Similar molecular arrangements of constructing hydrogen bonding networks were observed in both diastereomers. While the cis proton against the carbonyl oxygen in (R)-3b constructed hydrogen bonds with amide functional groups, the cis one did not in (S)-3b. In other words, a cis proton of (S)-3b did not bind to an oxygen atom of the ketal. The crystals of (R)-3b (mp 164–165 °C) had a higher melting point than those of (S)-3b (mp 152–154 °C), but both had the same calculated density (1.24 g cm⁻³). Solubility tests on each diastereomer in toluene at 25 °C revealed that the values of (R)-3b and (S)-3b were 35.3 g L⁻¹ and 49.0 g L⁻¹, respectively. As discussed above, we conclude that the different hydrogen bonding networks caused the difference in both melting point and solubility and enabled fractional crystallization providing (R)-3b.

![Fig. 3 X-ray crystallographic structure: (a) (R)-3a, (b) (S)-3a.](image1)

![Fig. 4 X-ray crystallographic structure: (a) (R)-3b, (b) (S)-3b.](image2)

| Table 2 | Hydrogen-bonding distances and angles of (R)-3a, (S)-3a, (R)-3b, and (S)-3b |
|---------|-------------------------------------|
|         | N···Oamide interaction | N···Oketal interaction |
|         | N···O (H···O)/Å | N–H···O° | N···O (H···O)/Å | N–H···O° |
| (R)-3a  | 2.829 (1.983) | 160.80 | 3.099 (2.295) | 157.21 |
| (S)-3a  | 3.195 (2.311) | 151.76 | 3.239 (2.352) | 178.40 |
| (R)-3b  | 2.878 (2.001) | 175.90 | 3.071 (2.194) | 175.14 |
| (S)-3b  | 2.917 (2.039) | 176.77 | — | — |

* (S)-3b did not bind to an oxygen atom of the ketal.
Table 1 shows that the separation capacity of 3a is superior to that of 3b in the aspect of fractional crystallization. To elucidate the reason for this difference, both diastereomeric mixtures (3a and 3b) were crystallized simply from the solution (toluene/CHCl₃ = 2/3) and the precipitated solid was analyzed using powder X-ray diffraction (PXRD) analysis. Fig. 5 shows the PXRD patterns of the crystallized diastereomeric mixture of 3 along with those of each single diastereomer as well as their simulated patterns calculated from SXRD. In the case of 3a, the PXRD pattern showed a superposition pattern of each diastereomer component of (R)-3a and (S)-3a, which means the two diastereomers deposited separately. In contrast, the PXRD pattern of the solid precipitation of 3b shows a broad pattern with a partial component of (R)-3b. The pattern of (S)-3b was particularly hard to identify. These results suggest that the mixture of (R)-3b and (S)-3b might exist as an amorphous material and be what caused the broad PXRD pattern. If so, it would explain why the separation capacity of 3a is superior to that of 3b.

Epimerization and crystallization-induced diastereomer transformation (CIDT)

Even if a racemic compound is optically resolved by the diastereomer method, half of the undesired diastereomer remains in the filtrate. Therefore, epimerization of the remaining diastereomer (S)-3 into (R)-3 is desirable from the viewpoint of yield. The screening of the epimerization conditions using (S)-3a and (S)-3b is summarized in Table 3. DBU in toluene and potassium t-butoxide in dioxane or THF were not effective (entries 1–3). (S)-3a (>99% de) was smoothly epimerized with potassium t-butoxide (2 equiv.) at 50 °C for 3.5 h in t-butanol, and the opposite diastereomer (R)-3a was slightly enriched with 7% de (entry 4). Under the same conditions, epimerization of (S)-3b (>99% de) proceeded more slowly than (S)-3a, where the % de of (S)-3b was 20% even after 7 h (entry 5). Other bases such as NaH and KOH were not effective (entries 6 and 7). The combination of potassium t-butoxide and t-butanol for CIDT has been reported, so we consider strong basic and protic conditions appropriate for this epimerization. This positive result encouraged us to apply CIDT (Table 4). The treatment of 3a (0.25 mmol, 2% de) with potassium t-butoxide (0.5 equiv.) in t-butanol (0.20 mL) at room temperature precipitated (R)-3a with 80% de (87% yield, entry 1). An increased amount of t-butanol (0.40 mL) with an extended stirring time (96 h) improved % de to 97% (95% yield, entry 2). Meanwhile, a similar procedure to entry 2 using 3b precipitated (R)-3b with 14% de (85% yield, entry 3). Although the attempt to increase the reaction temperature to 80 °C in order to accelerate CIDT with addition of l-octane as a poor solvent provided better % de (44% de and 51% de, entries 4 and 5), these figures were not as high as those of 3a. As with the fractional crystallization of 3, the CIDT of 3a was superior to 3b. Anyway, we are convinced that the ketal moiety acted as not only a protecting group but also a chiral resolving auxiliary which is a useful tool for CIDT.

Deprotection and derivatization of ketals

In order to show synthetic applications, derivatization of (R)-3a and (R)-3b was demonstrated (Scheme 2). (R)-3a and (R)-3b were dehydrated into nitrile (R)-2a and (R)-2b by treatment with trifluoroacetic anhydride and triethylamine in 92% and 91% yield, respectively. Subsequent deprotection of ketal groups by usual acidic condition provided 3-oxocycloalkanecarbonitriles (R)-1a and (R)-1b without epimerization.

Meanwhile, (R)-2a was reduced by hydrogenation using sponge cobalt to give primary amine (R)-4a which was immediately converted into benzoylated derivative (R)-5a. Deprotected ketone (R)-6a was finally obtained by usual acidic condition in 93% yield with 98% ee.

Table 3  Screening of epimerization conditions of 3a

| Entry | Base  | Solvent | Temp. (°C) | Time (h) | % de a |
|-------|-------|---------|------------|----------|--------|
| 1     | (S)-3a| DBU     | Toluene    | 110      | 24     | 98     |
| 2     | (S)-3a| t-BuOK  | Dioxane    | 100      | 24     | 98     |
| 3     | (S)-3a| t-BuOK  | THF        | 50       | 48     | 87     |
| 4     | (S)-3a| t-BuOK  | t-BuOH     | 50       | 3.5    | –7     |
| 5     | (S)-3b| t-BuOK  | t-BuOH     | 50       | 7      | 20     |
| 6     | (S)-3b| NaH     | THF        | 50       | 24     | 96     |
| 7     | (S)-3b| KOH     | EtOH       | 50       | 8      | 88     |

a Conditions: (S)-3a or (S)-3b (>99% de, 0.050 mmol), base (2.0 equiv.), and solvent (1.5 mL) was used. a % de was determined by HPLC.
Conclusions

We have synthesized chiral 3-oxocycloalkanecarbonitrile and 3-oxocycloalkanecarboxamide by fractional crystallization of ketal derivatives with (1R,2R)-1,2-diphenylethane-1,2-diol. Investigation of the crystal structures by X-ray diffraction analysis revealed that the difference in hydrogen bonds caused the discrepancy of the solubilities between the (R) and (S) diastereomers. Furthermore, CIDT to obtain (R)-3a in good yield (95% yield) and with high diastereoselectivity (97% de) was accomplished. Finally, successful derivatization of functional group and deprotection of ketals were performed without epimerization. To the best of our knowledge, we demonstrated the first example of CIDT of neutral compounds via formation of the diastereomeric ketal with (1R,2R)-1,2-diphenylethane-1,2-diol. These findings can be applied for synthesizing chiral and neutral building blocks containing carbonyl group.

Experimental section

General information

Starting materials, reagents, and solvents were obtained from commercial suppliers and used without further purification. Optical rotations were measured with a JASCO DIP-140 digital polarimeter at 20 °C using the sodium D line, and optical rotation data were reported as follows: [α]D (concentration c = g/100 mL, solvent). 1H and 13C NMR spectra were acquired with a Varian Gemini 2000 NMR spectrometer at 300 MHz and 75 MHz, respectively. Chemical shifts (δ) of 1H NMR were expressed in parts per million (ppm) relative to tetramethylsilane (δ = 0) as an internal standard. Multiplicities are indicated as br (broadened), s (singlet), d (doublet) and m (multiplet), and coupling constants (J) are reported in Hz unit. Chemical shifts (δ) of 13C NMR were expressed in ppm downfield or upfield from CDCl3 as an internal standard (δ = 77.0). Infrared spectra were acquired using in KBr disk with a JASCO FT/IR-460 plus spectrometer. Mass spectra were acquired with a Thermo Fisher Scientific Exactive spectrometer. Powder X-ray diffraction were acquired with a Bruker D8 ADVANCE. Single-crystal X-ray diffraction were acquired with Bruker APEX II and Bruker APEXII Ultra CCD diffractometers. Recycling preparative HPLC was performed with a JAI LC-908. Enantiomeric excess (ee) and diastereomeric excess (de) were determined by chiral HPLC analysis with a JASCO LC-2000Plus system and a SHIMAZU LC-2010 system.

Table 4  Crystallization-induced diastereomer transformation (CIDT) of 3a

| Entry | % de<sup>a</sup> | t-BuOK (equiv.) | Solvent (mL) | Temp. (°C) | Time (h) | % de<sup>b</sup> | Yield (%) |
|-------|----------------|----------------|--------------|------------|----------|----------------|-----------|
| 1     | 3a (2)         | 0.50           | t-BuOH 0.20  | rt         | 30       | 80             | 87        |
| 2     | 3a (2)         | 0.50           | t-BuOH 0.40  | rt         | 96       | 97             | 95        |
| 3     | 3b (5)         | 0.50           | t-BuOH 0.40  | rt         | 40       | 14             | 85        |
| 4     | 3b (9)         | 0.25           | t-BuOH 0.05  | 80         | 96       | 44             | 75        |
| 5     | 3b (9)         | 0.25           | t-BuOH 0.10  | 80         | 72       | 51             | 54        |

<sup>a</sup> 0.25 mmol scale.  <sup>b</sup> % de was determined by HPLC.

Scheme 2 Synthesis of 3-oxocyclopentanecarbonitrile and its derivatives.
solution of methanol (12 mL) and water (10 mL). A solution of cyclopenten-2-one (4.17 g, 50.8 mmol) in methanol (8 mL) was added dropwise over 30 min at rt. The reaction mixture was stirred at rt for 2 h, and then acidified with 4 M HCl aqueous solution. After extraction with CHCl₃ (20 mL × 5), the combined organic layer was dried over MgSO₄, filtered and concentrated under vacuum to give 1a (5.10 g, 46.7 mmol, 92% yield). A solution of 1a (1.00 g, 9.20 mmol) in toluene (30 mL) was added pyridinium p-toluene sulfonate (230 mg, 0.920 mmol) and (1R,2R)-1,2-diphenylethane-1,2-diol (2.54 g, 11.9 mmol). The mixture was stirred at 110 °C in a Dean–Stark apparatus for 23 h. After cooling, the reaction mixture was washed with 5 wt% NaHCO₃ aqueous solution (10 mL). The organic layer was dried over MgSO₄, filtered and concentrated under vacuum. Toluene (30 mL) was added and the precipitated solid was separated by filtration. The filtrate was concentrated under vacuum and purified by silica gel column chromatography (n-heptane–AcOEt) to give 2a (2.17 g, 7.10 mmol, 78% yield from 1a) as a diastereomeric mixture. 1H NMR (CDCl₃) δ 7.34–7.32 (m, 6H), 7.22–7.17 (m, 4H), 4.76–4.65 (m, 2H), 3.14–2.92 (m, 1H), 2.60–2.26 (m, 4H), 2.23–2.04 (m, 2H); 13C NMR (CDCl₃) δ 136.1, 136.0, 135.8, 135.7, 128.49, 128.46, 128.4, 126.64, 126.60, 126.5, 126.4, 122.1, 119.7, 116.77, 85.6, 85.5, 85.4, 41.7, 41.4, 36.5, 36.2, 28.3, 28.0, 25.54, 25.45; HRMS (ESI) m/z [M + Na]⁺ calcd for C₂₀H₂₃N₂O₂ 323.1760, found 323.1754.

(2R,3R,7R)-2,3-Diphenyl-1,4-dioxsapir[4.4]nonane-7-carboxamide (3a)

A solution of 2a (307 mg, 1.01 mmol) in dimethylsulfoxide (8 mL) was added 30 wt% H₂O₂ aqueous solution (0.7 mL) and K₂CO₃ (554 mg, 4.01 mmol) in ice bath. The reaction mixture was stirred at rt for 19 h, followed by addition of water for quenching. After extraction with CHCl₃ (15 mL × 3), the combined organic layer was dried over MgSO₄, filtered and concentrated under vacuum. The residue was crystallized with a mixed solution of acetone and n-hexane to give 3a (314 mg, 0.971 mmol, 96% yield) as a diastereomeric mixture. 1H NMR (CDCl₃) δ 7.34–7.31 (m, 6H), 7.24–7.19 (m, 4H), 5.85–5.49 (m, 2H), 4.78–4.67 (m, 2H), 3.04–2.83 (m, 1H), 2.47–1.97 (m, 4H); 13C NMR (CDCl₃) δ 177.8, 177.3, 136.5, 136.3, 128.5, 128.4, 126.74, 126.71, 126.5, 118.34, 118.27, 85.6, 85.5, 42.9, 42.5, 41.0, 40.6, 37.1, 36.8, 27.6, 27.5; HRMS (ESI) m/z [M + H]⁺ calcd for C₂₀H₂₂NO₃ 324.1600, found 324.1593.

(2R,3R,7R)-2,3-Diphenyl-1,4-dioxsapir[4.4]nonane-7-carboxamide ((R)-3a)

(R)-3a was prepared in 88% yield (121 mg, 0.374 mmol, >99% de) from (R)-2a (130 mg, 0.425 mmol, >99% de) according to the procedure similar to that mentioned in 3a. Mp 139–140 °C; [α]D²⁰ + 23.2 (c = 0.99, CHCl₃); 1H NMR (CDCl₃) δ 7.35–7.31 (m, 6H), 7.24–7.19 (m, 4H), 5.70 (brs, 1H), 5.35 (brs, 1H), 4.73 (d, J = 8.5 Hz, 1H), 4.69 (d, J = 8.5 Hz, 1H), 2.95–2.84 (m, 1H), 2.47–1.96 (m, 6H); 13C NMR (CDCl₃) δ 177.3, 136.5, 136.3, 128.5 (large intensity), 128.3, 126.7, 126.5, 118.3, 85.59, 85.56, 42.9, 41.0, 37.1, 27.6; FTIR (KBr, cm⁻¹) 3447, 3206, 3028, 2896, 1699, 1655, 1496, 1452, 1435, 1335; HRMS (ESI) m/z [M + H]⁺ calcd for C₂₀H₂₂NO₃ 324.1600, found 324.1593; HPLC condition, CHIRALCEL OJ-H 250 mm × 4.6 mm, 5 μm, n-hexane-2-propanol =
(2R,3R,7S)-2,3-Diphenyl-1,4-dioxaspiro[4.4]nonane-7-carboxamide ((S)-3a)

(S)-3a was prepared in 90% yield (135 mg, 0.417 mmol, >99% de) from (S)-2a (141 mg, 0.461 mmol, 99% de) according to the procedure similar to that mentioned in 3a. Mp 135-136 °C; [α]D 20 + 47.9 (c = 1.00, CHCl3); 1H NMR (CDCl3) δ 7.34-7.31 (m, 6H), 7.24-7.19 (m, 4H), 5.84 (brs, 1H), 5.40 (brs, 1H), 4.77 (d, J = 8.5 Hz, 1H), 4.72 (d, J = 8.5 Hz, 1H), 3.04-2.93 (m, 1H), 2.46-2.04 (m, 6H); 13C NMR (CDCl3) δ 177.7, 136.6, 136.3, 128.49 (large intensity), 128.45, 128.3, 126.7, 126.5, 118.4, 85.5 (large intensity), 42.6, 40.6, 36.8, 27.5; FTIR (KBr, cm−1) 3455, 3352, 3031, 2979, 1670, 1607, 1456, 1439, 1334, 1122; HRMS (ESI) m/z [M + H]+ calcd for C28H28NO5 338.1751, found 338.1754.

Fractional crystallization to give (2R,3R,7R)-2,3-diphenyl-1,4-dioxaspiro[4.4]nonane-7-carboxamide (R)-3a

A solution of 3a (50 mg, 0.155 mmol) in a mixed solution of CHCl3 (0.6 mL) and toluene (0.4 mL) was left under slow evaporation conditions at rt for 2 d. The precipitated solid was collected by filtration. The procedure described above was repeated to give (R)-3a (8.0 mg, 0.025 mmol, >99% de, 16% yield).

Fractional crystallization to give (2R,3R,7R)-2,3-diphenyl-1,4-dioxaspiro[4.4]decane-7-carboxamide ((R)-3b)

A solution of 3b (50 mg, 0.148 mmol) in a mixed solution of CHCl3 (0.60 mL) and toluene (0.40 mL) was left slow evaporation conditions at rt for 3 d. The precipitated solid was collected by filtration. The procedure described above was repeated twice to give (R)-3b (7.0 mg, 0.021 mmol, >99% de, 14% yield).

Synthesis of (R)-3a by crystallization-induced diastereomer transformation (CIDT)

A mixture of 3a (76.0 mg, 0.235 mmol) and t-butanol (0.40 mL) was added potassium t-butoxide (14 mg, 0.125 mmol) in a sealed vial. The mixture was stirred at rt for 96 h. The precipitated solid was collected by filtration to give (R)-3a (72.0 mg, 0.223 mmol, 97% de, 95% yield).

Fractional crystallization to give (2R,3R,7R)-2,3-diphenyl-1,4-dioxaspiro[4.4]decane-7-carboxamide ((R)-3b)

A mixture of 3b (81 mg, 0.240 mmol), t-butanol (0.10 mL) and i-octane (0.70 mL) was added potassium t-butoxide (7 mg, 0.062 mmol) in a sealed vial. The mixture was stirred at 80 °C for 72 h. The precipitated solid was collected by filtration to give (R)-3b (44.0 mg, 0.130 mmol, 51% de, 54% yield).

Synthesis of (R)-3b by CIDT

A solution of (R)-3a (77 mg, 0.238 mmol, >99% de) in CHCl3 (2 mL) was added triethylamine (0.07 mL, 0.502 mmol) and trifluoroacetic anhydride (0.04 mL, 0.284 mmol) in ice bath. The reaction mixture was stirred at rt for 3 h. Triethylamine (0.07 mL, 0.502 mmol) and trifluoroacetic anhydride (0.04 mL, 0.284 mmol) were added to the reaction mixture in ice bath, and the mixture was stirred at rt for 18 h. After extraction with CHCl3 (10 mL × 3), the combined organic layer was washed with water (10 mL × 3), dried over MgSO4, filtered and concentrated under vacuum to give (R)-2a (67 mg, 0.219 mmol, yield 92%, >99% de).

Synthesis of (R)-2a by dehydration

(R)-2b was prepared in 91% yield (69 mg, 0.216 mmol, >99% de) from (R)-3b (76 mg, 0.225 mmol, >99% de) according to the procedure similar to that mentioned in (R)-2a by dehydration.
(R)-3-Oxocyclooctane-carbonitrile ((R)-1a)

A solution of (R)-2a (162 mg, 0.530 mmol, >99% de) in acetone (5 mL) was added to 1.5 M HCl aqueous solution (1 mL). The reaction mixture was stirred at 50 °C for 48 h. After reaction with AcOEt (10 mL × 3), the combined organic layer was dried over MgSO₄, filtered, and concentrated under vacuum. The crude was purified by silica gel column chromatography (n-heptane–AcOEt) to give (R)-1a (49 mg, 0.449 mmol, 85% yield, >99% ee). [a]D° + 41.7 (c = 1.00, CHCl₃); ¹H NMR (CDCl₃) δ 3.6–3.15 (m, 1H), 2.68–2.42 (m, 2H), 2.38–2.21 (m, 2H); ¹³C NMR (CDCl₃) δ 121.7, 120.8, 114.1, 108.4; FTIR (KBr, cm⁻¹) 3480, 2984, 2921, 2243, 1747, 1461, 1405, 1152, 1141, 908; HRMS (ESI) m/z [M + H⁺]⁺ calec for C₇H₁₀NO₂ 171.0582, found 171.0582.

Chiral HPLC conditions, CHIRALCEL OD-RH 150 mm × 4.6 mm, 5 μm, elution A, 0.1% HClO₄ aqueous solution, elution B, MeCN, gradient 50% A to 5% A over 25 min, flow rate 0.1 mL min⁻¹, at 40 °C, wavelength 254 nm, retention times (R)-1a 11.6 min, (S)-1a 12.3 min.

(R)-3-Oxocyclohexanecarbonitrile ((R)-1b)

(R)-1b was prepared in 45% yield (19 mg, 0.154 mmol, >99% de) from (R)-2b (110 mg, 0.344 mmol, >99% de) according to the procedure similar to that mentioned in (R)-1a. [α]D° − 33.3 (c = 1.00, CHCl₃); ¹H NMR (CDCl₃) δ 3.08–2.99 (m, 1H), 2.72–2.55 (m, 2H), 2.43–2.39 (m, 2H), 2.22–1.98 (m, 3H), 1.89–1.81 (m, 1H); ¹³C NMR (CDCl₃) δ 205.3, 120.1, 43.2, 40.7, 28.6, 28.1, 23.7; FTIR (KBr, cm⁻¹) 2957, 2873, 2241, 1718, 1451, 1419, 1362, 1325, 1261, 1225; HRMS (ESI) m/z [M + H⁺]⁺ calec for C₇H₁₀NO₂ 168.1171, found 168.1170.

HPLC condition, CHIRALPAK IC 250 mm × 4.6 mm, 5 μm, n-hexane/ethanol = 90/10, flow rate 0.80 mL min⁻¹, at 25 °C, wavelength 225 nm, retention times (R)-1b 13.8 min, (S)-1b 15.9 min.

N-(([(2R,3R,7R)-2,3-Diphenyl-1,4-dioxaspiro[4.4]nonan-7-yl)methyl]benzamide ((R)-5a)

A mixture of (R)-2a (400 mg, 1.31 mmol, 95% de), sponge cobalt (Nikko Rica R-400, 0.80 g), 28 wt% ammonia aqueous solution (0.80 mL) and methanol (3.2 mL) was stirred at 25 °C for 10 h under hydrogen atmosphere (7 bar) in an autoclave. The catalyst was removed by filtration and the filtrate was concentrated under vacuum followed by azotropic distillation with methyl t-butyl ether (8.0 mL × 3) under vacuum to give (R)-4a. The mixture of (R)-4a, methyl t-butyl ether (8.0 mL) and 20 wt% K₂CO₃ aqueous solution (8.0 mL) were added benzyl chloride (183 μL, 1.58 mmol) in ice bath, and the reaction mixture was stirred at rt for 13 h. After phase separation, the aqueous layer was extracted with methyl t-butyl ether (4.0 mL). The combined organic layer was dried over MgSO₄, filtered and concentrated under vacuum. The crude was purified by silica gel column chromatography (n-heptane–AcOEt) to give (R)-5a (496 mg, 1.20 mmol, 92% yield, 98% de). Mp 129–130 °C; [α]D° − 7.1 (c = 1.00, CHCl₃); ¹H NMR (CDCl₃) δ 7.70–7.68 (m, 2H), 7.42–7.30 (m, 7H), 7.26–7.17 (m, 6H), 6.61 (brs, 1H), 4.74 (d, J = 8.5 Hz, 1H), 4.70 (d, J = 8.3 Hz, 1H), 3.65–3.45 (m, 2H), 2.60–2.51 (m, 1H), 2.44–2.36 (m, 1H), 2.24–1.94 (m, 4H), 1.68–1.54 (m, 1H); ¹³C NMR (CDCl₃) δ 167.7, 136.6, 136.3, 134.4, 131.2, 128.6, 128.50, 128.44, 128.35, 128.3, 126.8, 126.5, 118.5, 85.67, 85.65, 44.4, 41.6, 37.6, 31.27, 27.0; FTIR (KBr, cm⁻¹) 3300, 3033, 2961, 2865, 1628, 1605, 1580, 1549, 1492, 1466; HRMS (ESI) m/z [M + H⁺]⁺ calec for C₂₇H₃₄NO₃ 414.2069, found 414.2062.

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