

Article

Development of Guanidine-Bisurea Bifunctional Organocatalyst Bearing Chirality at the Inner and Outer Sides of the Urea Groups, and Application to Enantioselective α -Hydroxylation of Pyranoindolizine Intermediate for Camptothecin Synthesis

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Abstract: Pyranoindolizine is a tricyclic structure found in various biologically active compounds, such as camptothecin (CPT) and its derivatives. In the case of CPTs, the chirality at the α -position in the α -hydroxyl lactone moiety of pyranoindolizine is important for the antitumor activity. This paper deals with enantioselective oxidation of the α -position in pyranoindolizine lactone, which corresponds at C20 in CPT, with cumene hydroperoxide (CHP) in the presence of newly synthesized guanidine-bisurea bifunctional organocatalysts bearing chirality on both the inner and outer sides of the urea groups.

Keywords: α -hydroxylation; pyranoindolizine; camptothecin; organocatalyst

1. Introduction

Camptothecin (CPT **1**, Figure 1), which was isolated from *Camptotheca acuminata* by Wani and Wall in 1966 [1], exhibits potent antitumor activity by inhibiting DNA topoisomerase I (Topo I) [2–5]. To date, two camptothecin analogues, *i.e.*, irinotecan (**2**) [6–9] and topotecan (**3**) [10–12], have been approved by the FDA to treat cancers. Structurally, CPTs contain a pyranoindolizine tricyclic structure (the C-D-E ring system) with a *tert*-hydroxyl group at C20, and the stereochemistry at C20 is important

for their biological activity. Thus, stereoselective construction of this *tert*-hydroxyl group is an important issue in the synthesis of CPTs.

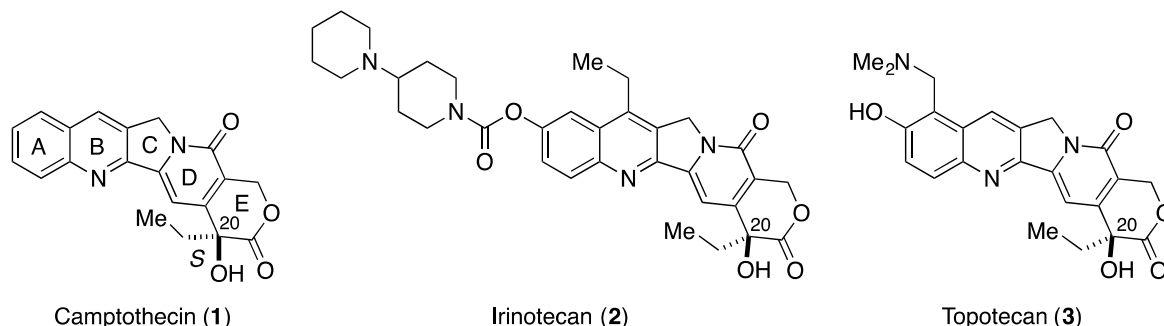
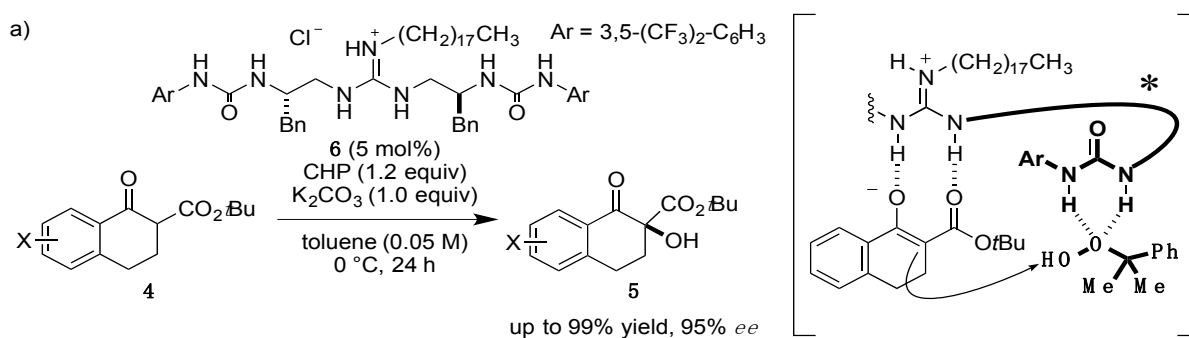
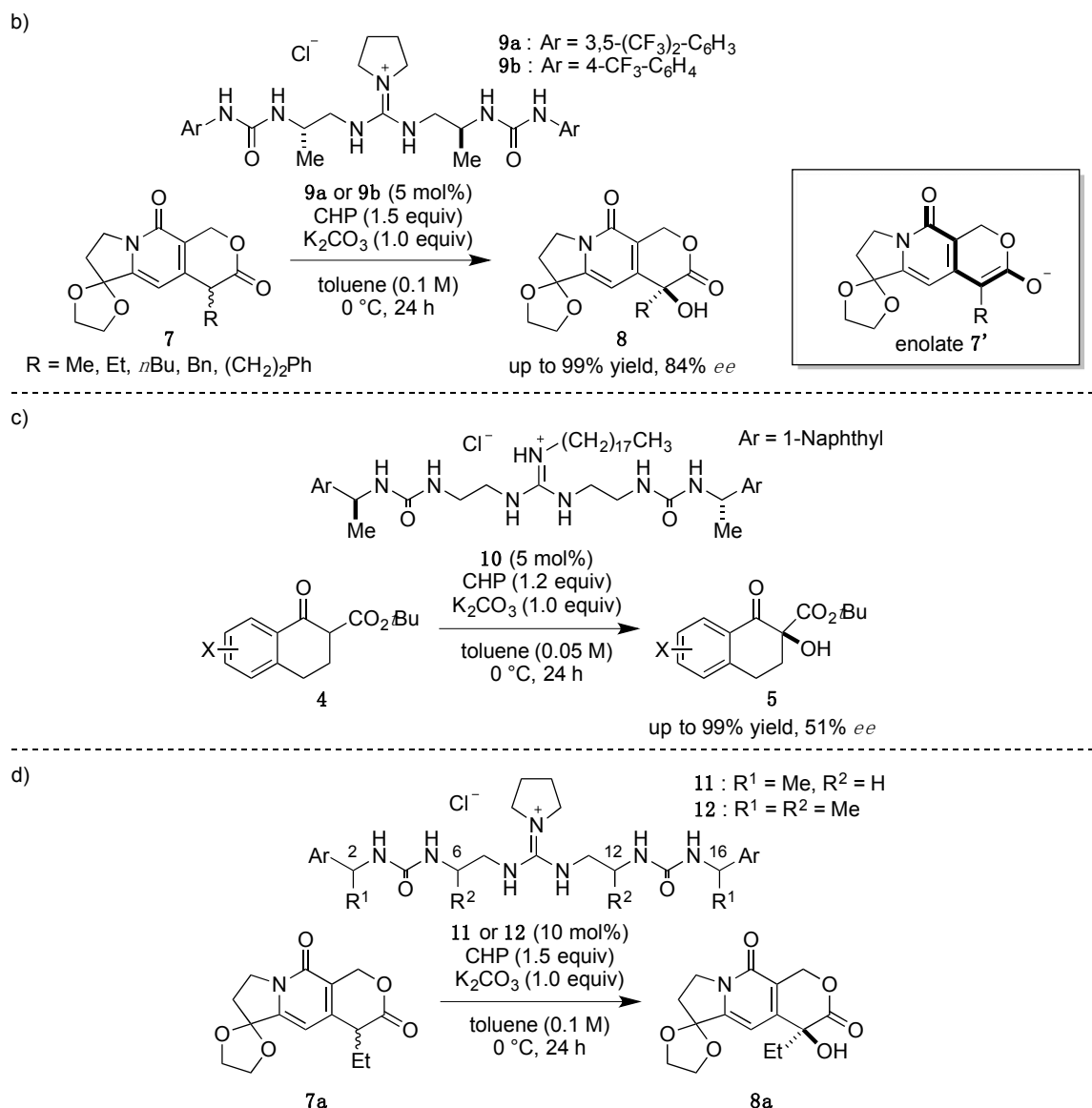


Figure 1. Structures of camptothecin (1) and its analogs 2 and 3.

Recently, we have reported α -hydroxylation of tetralone-derived β -ketoesters **4** using cumene hydroperoxide (CHP) in the presence of guanidine-bisurea bifunctional organocatalyst **6** (Scheme 1a) [13]. In this reaction, the guanidine group and urea group were suggested to interact with the enolate of tetralone and the oxidant CHP, respectively. Based upon the proposed transition state model, we further applied this reaction to the α -hydroxylation of pyranoindolidine derivatives **7** to obtain the corresponding hydroxylated compounds **8** via the extended enolate **7'** with high enantioselectivity (Scheme 1b). The products **8** are key synthetic intermediates in the Friedländer condensation approach to CPT derivatives [14–22]. Subsequently, we developed the novel guanidine-bisurea bifunctional organocatalyst **10** (Scheme 1c) bearing a chiral center at the outer side of the urea groups [23]. Although it is conformationally more flexible than **6**, we found that **10** catalyzed the α -hydroxylation of tetralone-derived β -ketoesters **4** with moderate enantioselectivity. Moreover, the catalyst **10** lacks a CF_3 group in the Ar moiety, which had been believed to be mandatory for effective activation of the oxidant; nevertheless, the catalyst **10** gave the oxidative product **5** in excellent yield. Therefore, we set out to examine the effect of chirality at the outer side of urea in the newly designed catalyst **11**. Herein, we described α -hydroxylation of pyranoindolidine derivative **7a** in the presence of catalyst **11** bearing a chiral center at the outer side of the urea groups. We also examined the effectiveness of catalyst **12** possessing chirality at both the inner and outer sides of the urea groups (Scheme 1d).



Scheme 1. Cont.



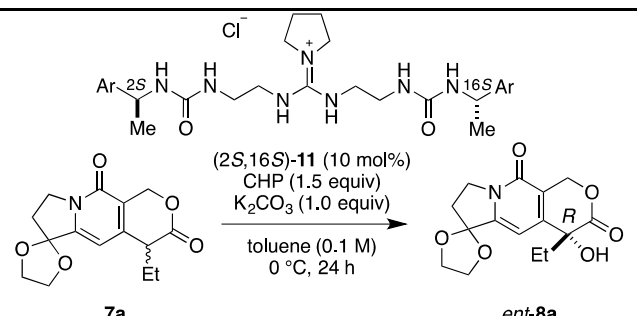
Scheme 1. (a–c) Asymmetric α -hydroxylation using a series of guanidine-bisurea bifunctional organocatalysts (previous work); (d) α -Hydroxylation of pyranoindolizine derivatives **7a** using guanidine-bisurea bifunctional organocatalysts **11** and **12** (this work).

2. Results and Discussion

Catalysts **11** and **12** were synthesized according to the procedure previously reported by our group [23]. With catalysts **11** and **12** in hand, we commenced our investigation of α -hydroxylation of the pyranoindolizine derivative **7a** with catalyst (2*S*,16*S*)-**11**, which has chiral methyl groups with *S* configuration at the outer side of the urea groups, and various Ar groups. In the case of (2*S*,16*S*)-**11a** with phenyl as Ar, α -hydroxylation of **7a** proceeded efficiently, and *ent*-**8a** was obtained in 77% yield with 50% *ee* in *R* configuration (Table 1, entry 1). With the catalyst (2*S*,16*S*)-**11b**, having 4-methoxyphenyl as Ar, the enantioselectivity increased to 61% *ee* with 88% yield (entry 2); however, when the electron-donating 4-methoxy group was replaced with the electron-withdrawing 4-nitro group, *i.e.*, (2*S*,16*S*)-**11c**, the selectivity was drastically decreased to 31% *ee* (88% yield, entry 3). Since the nature of the Ar group in (2*S*,16*S*)-**11** clearly affected the selectivity, introduction of naphthyl groups was

investigated (entries 4 and 5). In the case of 1-naphthyl-substituted (2*S*,16*S*)-**11d**, a relatively high selectivity of 69% *ee* was obtained, but the 2-naphthyl-substituted catalyst of (2*S*,16*S*)-**11e** showed little selectivity for hydroxylated *ent*-**8a**, although very high catalytic activities (over 90% yield) were observed with both catalysts.

Table 1. α -Hydroxylation of **7a** using guanidine-bisurea bifunctional organocatalyst (2*S*,16*S*)-**11**.^a

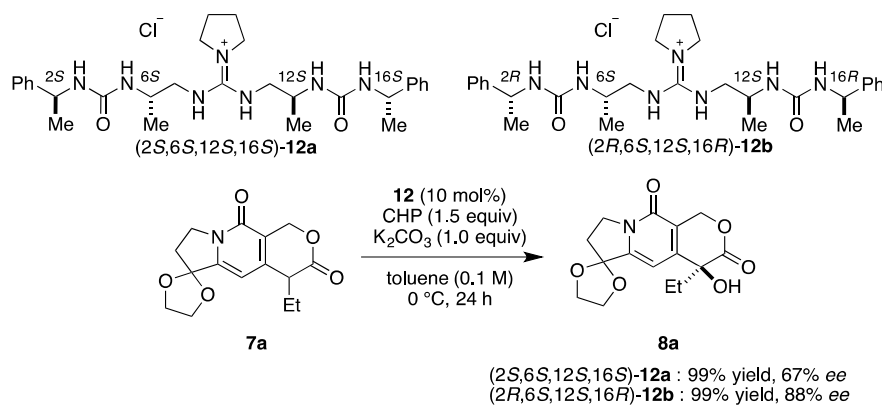


Entry	(2 <i>S</i> ,16 <i>S</i>)- 11		<i>ent</i> - 8a	
		Ar	yield (%) ^b	<i>ee</i> (%) ^c
1	(2 <i>S</i> ,16 <i>S</i>)- 11a	C ₆ H ₅	77	50
2	(2 <i>S</i> ,16 <i>S</i>)- 11b	4-MeO-C ₆ H ₄	88	61
3	(2 <i>S</i> ,16 <i>S</i>)- 11c	4-NO ₂ -C ₆ H ₄	88	31
4	(2 <i>S</i> ,16 <i>S</i>)- 11d	1-Naphthyl	92	69
5	(2 <i>S</i> ,16 <i>S</i>)- 11e	2-Naphthyl	91	51

Notes: ^a Reaction conditions: **7a** (0.1 mmol), CHP (0.15 mmol) and K₂CO₃ (0.1 mmol) in the presence of (2*S*,16*S*)-**11** (10 mol%) in toluene (1.0 mL) at 0 °C for 24 h; ^b Isolated yield; ^c Determined by HPLC analysis using a chiral stationary phase.

Then, we investigated the cooperative effect of inner-side chirality in the presence of outer-side chirality with (2*S*,6*S*,12*S*,16*S*)-**12a** and (2*R*,6*S*,12*S*,16*R*)-**12b**. Based on previously reported results together with the above results, inner- and outer-side chiralities with *S* configuration tend to induce *R* and *S* configuration of the product **8a**, respectively. Therefore, (2*R*,6*S*,12*S*,16*R*)-**12b** should be a good matched pair for cooperation, and was expected to give the hydroxylated product **8a** more selectively as compared with **12a**.

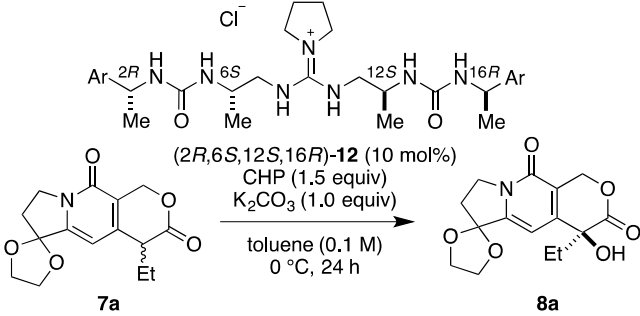
Indeed, (2*S*,6*S*,12*S*,16*S*)-**12a** gave the α -hydroxylation product with moderate enantioselectivity (67% *ee*), while (2*R*,6*S*,12*S*,16*R*)-**12b** gave 88% *ee* with 99% yield (Scheme 2).



Scheme 2. α -Hydroxylation of **7a** using (2*S*,6*S*,12*S*,16*S*)-**12a** and (2*R*,6*S*,12*S*,16*R*)-**12b**.

Then, we further investigated the effect of the aromatic group in (2*R*,6*S*,12*S*,16*R*)-**12b** on the selectivity (Table 2). The phenyl group in (2*R*,6*S*,12*S*,16*R*)-**12b** was varied to a 4-methoxyphenyl group (2*R*,6*S*,12*S*,16*R*)-**12c**, 1-naphthyl group (2*R*,6*S*,12*S*,16*R*)-**12d**, and 2-naphthyl group (2*R*,6*S*,12*S*,16*R*)-**12e**. High enantioselectivity (89% *ee*) was obtained in all cases (Table 2, entries 1–3).

Table 2. Screening of aromatic group of (2*R*,6*S*,12*S*,16*R*)-**12**.^a

				
Entry	(2 <i>R</i> ,6 <i>S</i> ,12 <i>S</i> ,16 <i>R</i>)- 12	Ar	yield (%) ^b	<i>ee</i> (%) ^c
1	(2 <i>R</i> ,6 <i>S</i> ,12 <i>S</i> ,16 <i>R</i>)- 12c	4-MeO-C ₆ H ₄	99	89
2	(2 <i>R</i> ,6 <i>S</i> ,12 <i>S</i> ,16 <i>R</i>)- 12d	1-Naphthyl	95	89
3	(2 <i>R</i> ,6 <i>S</i> ,12 <i>S</i> ,16 <i>R</i>)- 12e	2-Naphthyl	75	89

Notes: ^a Reaction conditions: **7a** (0.1 mmol), CHP (0.15 mmol) and K₂CO₃ (0.1 mmol) in the presence of (2*R*,6*S*,12*S*,16*R*)-**12** (10 mol%) in toluene (1.0 mL) at 0 °C for 24 h; ^b Isolated yield; ^c Determined by HPLC analysis using a chiral stationary phase.

3. Experimental Section

3.1. General Remarks

Flash chromatography was performed using silica gel 60 (spherical, particle size 0.040–0.100 mm, Kanto Co., Tokyo, Japan) or NH silica gel (spherical, particle size 0.06 mm, Fuji Silysia Chemical, Tokyo, Japan). Optical rotations were measured on a JASCO P-2200 polarimeter (JASCO, Tokyo, Japan). ¹H and ¹³C NMR spectra were recorded on AL300 (JEOL), ECX400 (JEOL), or AVANCE400 (Bruker) instruments (JEOL, Tokyo, Japan). Chemical shifts in [d₄]MeOH was reported in the scale relative to [d₄]MeOH (δ = 3.30 ppm) for ¹H NMR spectroscopy. For ¹³C NMR spectra, chemical shift was reported in the scale relative to [d₄]MeOH (δ = 49.0 ppm) (internal reference). Mass spectra were recorded on a JMS-T100LC (JEOL) spectrometer (JEOL, Tokyo, Japan). HPLC analysis on a chiral stationary phase was performed on JASCO 800-series instruments (JASCO, Tokyo, Japan). A Daicel Chiralpak IA column was used with hexane/ethanol as the eluent.

3.2. Typical Procedure for *α*-Hydroxylation of Pyranoindolizine Derivative

A test tube equipped with a magnetic stirring bar was charged with catalyst **11** (0.01 mmol), pyranoindolizine derivative **7a** (0.1 mmol), K₂CO₃ (0.1 mmol), and toluene (1.0 mL) at room temperature. The mixture was cooled to 0 °C and stirred for 10 min. Then, cumene hydroperoxide (0.15 mmol) was added, and stirring was continued at 0 °C for 24 h. The reaction was quenched by addition of 10% Na₂S₂O₃ solution (2 mL) and acetic acid (0.2 mL), and the mixture was vigorously

stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted three times with chloroform. The combined organic solution was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate 1:1 to chloroform/methanol 100:1) to give the product **8a**. Enantiomeric excess and absolute configuration were determined by HPLC analysis of the product on a chiral column (DAICEL Chiralpak IA) with *n*-hexane/ethanol.

3.3. Characterizations of Guanidine-Bisurea Bifunctional Organocatalysts **11** and **12**

3.3.1. Catalyst (2*S*,16*S*)-**11a**

$[\alpha]^{25}_{\text{D}} = -25.6$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CD_3OD) δ 7.34–7.30 (m, 8H), 7.26–7.21 (m, 2H), 4.82 (q, $J = 7.0$ Hz, 2H), 3.37–3.19 (m, 12H), 1.88–1.79 (m, 4H), 1.41 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 161.6, 158.4, 147.4, 130.4, 128.7, 127.7, 51.8, 50.9, 47.3, 41.7, 27.1, 24.6; HRMS (ESI, M-Cl) calcd for $\text{C}_{27}\text{H}_{40}\text{N}_7\text{O}_2$ 494.3243, found 494.3293.

3.3.2. Catalyst (2*S*,16*S*)-**11b**

$[\alpha]^{25}_{\text{D}} = -28.9$ ($c = 0.66$, CHCl_3); ^1H NMR (300 MHz, CD_3OD) δ 7.20 (d, $J = 8.6$ Hz, 4H), 6.85 (d, $J = 8.6$ Hz, 4H), 4.74 (q, $J = 7.2$ Hz, 2H), 3.75 (s, 6H), 3.27–3.18 (m, 12H), 1.85–1.81 (m, 4H), 1.36 (d, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.71, 160.02, 157.61, 138.52, 127.98, 114.81, 55.71, 50.37, 46.45, 40.32, 32.5, 26.25, 23.73; HRMS (ESI, M-Cl) calcd for $\text{C}_{29}\text{H}_{44}\text{N}_7\text{O}_4$ 554.3454, found 554.3411.

3.3.3. Catalyst (2*S*,16*S*)-**11c**

$[\alpha]^{25}_{\text{D}} = -21.1$ ($c = 0.49$, CHCl_3); ^1H NMR (300 MHz, CD_3OD) δ 8.17 (d, $J = 8.6$ Hz, 4H), 7.53 (d, $J = 8.6$ Hz, 4H), 4.9 (q, $J = 7.2$ Hz, 2H), 3.27–3.17 (m, 12H), 1.89–1.82 (m, 4H), 1.42 (d, $J = 7.2$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.52, 157.54, 154.64, 148.09, 128.00, 124.61, 50.77, 46.33, 40.38, 26.2, 23.19; HRMS (ESI, M-Cl) calcd for $\text{C}_{27}\text{H}_{38}\text{N}_6\text{O}_6$ 584.2945, found 584.2930.

3.3.4. Catalyst (2*S*,16*S*)-**11d**

$[\alpha]^{25}_{\text{D}} = 56.4$ ($c = 0.50$, CHCl_3); ^1H NMR (300 MHz, CD_3OD) δ 8.13–8.10 (m, 2H), 7.88–7.83 (m, 2H), 7.74 (d, $J = 7.5$ Hz, 2H), 7.52–7.39 (m, 8H), 5.63 (q, $J = 6.8$ Hz, 2H), 3.27–3.11 (m, 12H), 1.62–1.57 (m, 4H), 1.51 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.49, 157.18, 142.12, 135.22, 131.76, 129.80, 128.47, 127.10, 126.59, 126.52, 124.01, 123.05, 79.48, 46.82, 46.37, 40.16, 25.90, 22.99; HRMS (ESI, M-Cl) calcd for $\text{C}_{35}\text{H}_{44}\text{N}_7\text{O}_2$ 594.3556, found 594.3589.

3.3.5. Catalyst (2*S*,16*S*)-**11e**

$[\alpha]^{25}_{\text{D}} = -34.6$ ($c = 0.62$, CHCl_3); ^1H NMR (300 MHz, CD_3OD) δ 7.80–7.71 (m, 8H), 7.46–7.40 (m, 6H), 4.93 (q, $J = 6.8$ Hz, 2H), 3.24–3.01 (m, 12H), 1.52–1.40 (m, 4H), 1.45 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.79, 157.31, 144.05, 134.80, 133.99, 129.25, 128.78, 128.61,

127.17, 126.68, 125.53, 124.99, 51.17, 49.76, 46.50, 40.23, 25.87, 23.55; HRMS (ESI, M-Cl) calcd for $C_{35}H_{44}N_7O_2$ 594.3556, found 594.3589.

3.3.6. Catalyst (2*S*,6*S*,12*S*,16*S*)-**12a**

$[\alpha]^{25}_D = -29.6$ ($c = 0.96$, $CHCl_3$); 1H NMR (300 MHz, CD_3OD) δ 7.34–7.18 (m, 10H), 4.8 (q, $J = 6.8$ Hz, 2H), 3.91–3.80 (m, 2H), 3.41–3.39 (m, 4H), 3.24 (dd, $J = 13.4, 8.6$ Hz, 4H), 2.00–1.98 (m, 4H), 1.4 (d, $J = 6.8$ Hz, 6H), 1.17 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.14, 157.62, 146.32, 129.49, 127.89, 126.81, 51.52, 50.80, 50.16, 47.07, 32.49, 26.36, 23.72; HRMS (ESI, M-Cl) calcd for $C_{29}H_{44}N_7O_2$ 522.3556, found 522.3561.

3.3.7. Catalyst (2*R*,6*S*,12*S*,16*R*)-**12b**

$[\alpha]^{25}_D = 26.0$ ($c = 0.68$, $CHCl_3$); 1H NMR (300 MHz, CD_3OD) δ 7.32–7.17 (m, 10H), 7.49 (q, $J = 6.8$ Hz, 2H), 3.90–3.70 (m, 4H), 3.22–2.92 (m, 8H), 1.63–1.59 (m, 4H), 1.38 (d, $J = 6.8$ Hz, 6H), 1.11 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.12, 157.27, 146.70, 129.53, 127.89, 126.78, 51.82, 50.90, 49.75, 46.82, 26.07, 23.98, 18.76; HRMS (ESI, M-Cl) calcd for $C_{29}H_{44}N_7O_2$ 522.3556, found 522.3582.

3.3.8. Catalyst (2*R*,6*S*,12*S*,16*R*)-**12c**

$[\alpha]^{25}_D = 28.4$ ($c = 0.59$, $CHCl_3$); 1H NMR (300 MHz, CD_3OD) δ 7.19 (d, $J = 8.6$ Hz, 4H), 6.85 (d, $J = 8.6$ Hz, 4H), 4.74 (q, $J = 6.8$ Hz, 2H), 3.24–2.95 (m, 4H), 1.67–1.65 (m, 2H), 1.36 (d, $J = 6.8$ Hz, 6H), 1.12 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.13, 160.02, 157.36, 138.63, 127.98, 114.87, 55.72, 51.87, 50.35, 49.85, 46.88, 26.13, 23.93, 18.79; HRMS (ESI, M-Cl) calcd for $C_{31}H_{48}N_7O_4$ 582.3767, found 582.3767.

3.3.9. Catalyst (2*R*,6*S*,12*S*,16*R*)-**12d**

$[\alpha]^{25}_D = -63.1$ ($c = 0.54$, $CHCl_3$); 1H NMR (300 MHz, CD_3OD) δ 8.12 (d, $J = 7.2$ Hz, 2H), 7.87–7.84 (m, 2H), 7.7 (d, $J = 7.9$ Hz, 2H), 7.53–7.37 (m, 8H), 5.65 (q, $J = 6.8$ Hz, 2H), 3.87–3.68 (m, 2H), 3.15–2.84 (m, 8H), 1.5 (d, $J = 6.8$ Hz, 6H), 1.03 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.08, 157.01, 142.47, 135.26, 131.71, 129.71, 129.85, 128.44, 127.14, 126.66, 126.58, 123.97, 123.00, 79.49, 51.88, 46.74, 25.62, 23.21, 18.65; HRMS (ESI, M-Cl) calcd for $C_{37}H_{48}N_7O_4$ 622.3869, found 622.3851.

3.3.10. Catalyst (2*R*,6*S*,12*S*,16*R*)-**12e**

$[\alpha]^{25}_D = -40.0$ ($c = 0.67$, $CHCl_3$); 1H NMR (300 MHz, CD_3OD) δ 7.79–7.61 (m, 8H), 7.46–7.37 (m, 6H), 4.9 (q, $J = 6.8$ Hz, 2H), 3.90–3.74 (m, 2H), 3.51–2.74 (m, 8H), 1.44 (d, $J = 7.2$ Hz, 6H), 1.08 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 160.20, 156.87, 144.18, 134.74, 133.92, 129.28, 128.74, 128.60, 127.16, 126.67, 125.50, 124.95, 51.95, 51.12, 49.38, 46.75, 25.50, 23.76, 18.72; HRMS (ESI, M-Cl) calcd for $C_{37}H_{48}N_7O_4$ 622.3869, found 622.3876.

4. Conclusions

New guanidine-bisurea bifunctional organocatalysts **11** bearing chirality at the outer side of the urea groups were effective for enantioselective α -hydroxylation of pyranoindolizine derivative **7a**. Catalysts bearing an aryl group with an electron-donating substituent or a 1-naphthyl group provided selectivity of 61%–69% *ee*. Based on these results, we synthesized catalysts **12** bearing chirality at both the outer and inner sides of the urea groups. They showed even higher enantioselectivity. Thus, chirality on the inner side of the urea groups showed a cooperative effect with outer-side chirality in the catalysts for improving stereoselectivity in the α -hydroxylation of pyranoindolizine.

Supplementary Materials

Copies of ^1H and ^{13}C NMR spectra for all new compounds.

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Author Contributions

Minami Odagi and Tatsuya Watanabe performed the synthetic works; Kazuo Nagasawa contributed to the whole studies in this manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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