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Polymer-Supported Chiral *Cis*-Disubstituted Pyrrolidine Catalysts and Their Application to Batch and Continuous-Flow Systems

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ABSTRACT: Polymer-supported *cis*-pyrrolidine catalysts were developed that allowed for high enantioselectivity and diastereoselectivity compared with those obtained from common *trans*-pyrrolidine catalysts. Not only configurational but also polymeric effects contribute to the high diastereoselectivity and enantioselectivity. Polymer catalysts were also successfully applied in a continuous-flow process. Acceleration of the reaction rate, an increase in diastereoselectivity, and an improvement in durability were observed in continuous-flow operation compared with the batch system.

KEYWORDS: *chiral organocatalyst, diphenylmethylpyrrolidine, polymer-supported catalyst, continuous-flow process, asymmetric Michael reaction, trans-β-nitrostyrene, butyraldehyde*

INTRODUCTION

Chiral pyrrolidine derivatives, readily derived from inexpensive prolines, are among the most important asymmetric organocatalysts and are frequently used for asymmetric syntheses of complex molecules, including active pharmaceutical ingredients (APIs), agrochemicals, and natural products.[1] They are generally stable, readily available, and environmentally friendly, and therefore, they have attracted the interest of many synthetic chemists in industrial and academic fields. One of the most distinguished catalysts is diphenylprolinol silyl ether, also known as the Jørgensen−Hayashi catalyst.[2,3]

Meanwhile, the immobilization of chiral catalysts on polymer supports has also been attracting considerable interest.[4] These polymer-supported chiral catalysts are largely insoluble in most reaction solvents, which allows for easy recovery and recycling of the catalysts. To date, much effort has been devoted to the design and development of polymer-immobilized chiral pyrrolidine catalysts, aiming for high catalytic performance as well as high reusability.[5] In line with recent developments, some of these catalysts were extended to continuous-flow processes, making them further attractive tools from the viewpoints of operational simplicity, environmental compatibility, and cost efficiency.[6]

As described above, a wide variety of polymer-supported chiral pyrrolidine catalysts have been investigated, but the configuration of substituents on the pyrrolidine ring of the diphenylmethylpyrrolidine moiety has not been well-investigated to date. In most cases, *trans*-2,4-disubstituted pyrrolidine catalysts have been used for polymer-supported asymmetric catalysts, initially because of their easy availability and cost efficiency.

However, at this point we envisioned that the polymer-supported *cis*-2,4-disubstituted pyrrolidine catalysts derived from *cis*-4-hydroxyproline would provide higher enantioselectivity and diastereoselectivity than their polymer-supported *trans* analogues (Figure 1, left) because of the enhanced facial selectivity caused by arranging the substituents on the same face of the pyrrolidine ring (Figure 1, right).[2a,7] In the case of nonpolymeric 2,4-disubstituted pyrrolidine catalysts, it is reported that a *cis*-2,4-disubstituted catalyst was superior to the corresponding *trans*-2,4-disubstituted catalyst in terms of enantioselectivity and diastereoselectivity.[8] As polymer-supported catalysts, we expected that in addition to the reaction site, the polymer chain would further improve the steric bias by acting as a bulky substituent. This hypothesis (i.e., polymeric effect) is partly supported by recent reports on the asymmetric addition of a hydroxylamine derivative[9] and malonate[10] to enals catalyzed by polystyrene-supported *cis*-2,4-disubstituted diphenylprolinol silyl ether.

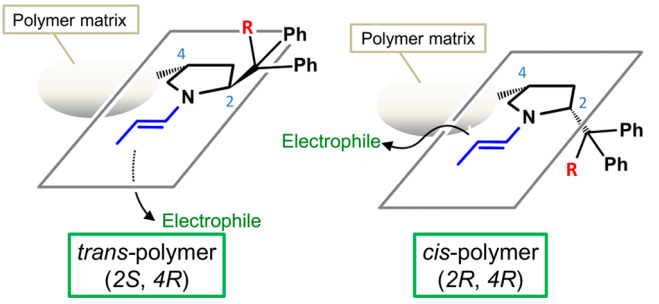

Figure 1. Our concept: *cis*-2,4-disubstituted pyrrolidines.

On the basis of this background, we embarked on the synthesis of polymer-supported *cis*-pyrrolidine derivatives as efficient catalysts for asymmetric reactions with the intention

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of expanding the application of these catalysts to continuous-flow synthesis.

RESULTS AND DISCUSSION

Following the aforementioned concept, we have designed three types of *cis*-2,4-disubstituted polymer catalysts with a range of substituents (**1-*cis*-OTMS**, **1-*cis*-OMe**, and **1-*cis*-H**) and their corresponding *trans* polymers (**2-*trans*-OTMS**, **2-*trans*-OMe**, and **2-*trans*-H**) for comparison. Cross-linked polystyrene was chosen as a polymer support because of its mechanical stability and easily tunable properties. These six polymer catalysts were synthesized by radical polymerization of monomers bearing a styrene derivative, styrene, and divinylbenzene (Figure 2; for the synthesis of the polymer catalysts, see the Supporting Information).

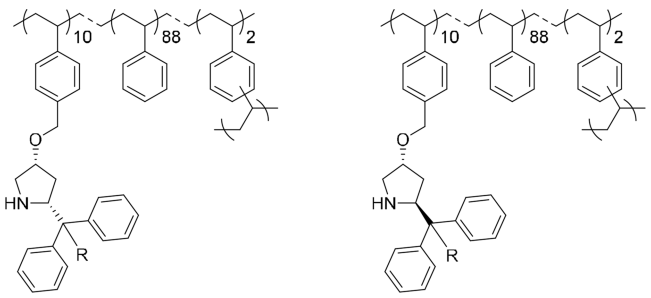


Figure 2. Polymer-supported chiral pyrrolidine catalysts.

Optimization of the Reaction Conditions in the Batch System Utilizing 1-*cis*-OTMS. After screening of the reaction conditions using **1-*cis*-OTMS**, it was found that our polymer efficiently catalyzed the asymmetric Michael addition of an aldehyde to nitrostyrene in a heterogeneous batch system (Table 1). Stirring a mixture of *trans*-β-nitrostyrene (**3**) (1.0 mmol, 1 equiv), butyraldehyde (**4**) (5.0 mmol, 5.0 equiv), benzoic acid (0.10 mmol, 10 mol %), and **1-*cis*-OTMS** (0.05 mmol, 5.0 mol %) in CH_2Cl_2 at 25 °C for 24 h afforded the desired product (2*S*,3*R*)-2-ethyl-4-nitro-3-phenylbutanal (**5**) in good yield with excellent diastereoselectivity and enantioselectivity (Table 1, entry 1). The reactivity of the polymer catalyst was strongly influenced by the solvent, which was partly attributed to swelling of the polymer gel. Since **1-*cis*-OTMS** is a hydrophobic gel-type polymer, it easily swells in low-polarity solvents (CH_2Cl_2, hexane, etc.), which would maximize the potential of the catalyst (entries 1 and 2 and Table S1). High conversion was not achieved when high-polarity solvents were used, partly because the substrate and reagents cannot approach the active site inside of a nonswollen polymer catalyst (entries 3−5 and Table S1, entries 5−8). Decreasing the reaction temperature had little effect on the diastereoselectivity and enantioselectivity and only decreased the reaction rate (entry 6 and Table S2, entry 2). The addition of acid was critical to the catalyst activity, which was attributed to accelerated generation of the imine as the reactive intermediate (entry 7 and Table S3).[2e] Reducing the amount of catalyst resulted in incomplete conversion even with a prolonged reaction time, suggesting deactivation of the polymer catalyst (entry 8 and Table S4).

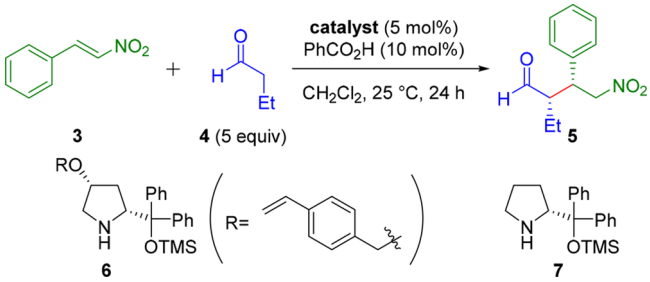
Table 1. Screening of the Reaction Conditions

entry	solvent	yield (%)[a]	dr[b]	% ee[c]
1	CH_2Cl_2	93	>20:1	99.0
2	hexane	51	19:1	97.8
3	THF	3	7:1	95.7
4	EtOAc	10	9:1	95.4
5	MeOH	0	–	–
6[d]	CH_2Cl_2	79	>20:1	98.9
7[e]	CH_2Cl_2	32	8:1	98.2
8[f]	CH_2Cl_2	30	>20:1	98.9

[a]Isolated yields. [b]The dr (*syn*:*anti*) values were determined by NMR spectroscopy. [c]The ee values of the *syn* isomer were determined by chiral HPLC. [d]The reaction was performed at 0 °C. [e]The reaction was performed in the absence of $PhCO_2H$. [f]A 1 mol % loading of the catalyst was used. The reaction time was 96 h.

Configurational Effect and Polymeric Effect. With the optimal conditions in hand, we next focused on evaluating the effect of the configuration on the pyrrolidine ring by comparison of *cis* and *trans* polymers in the same reaction (Tables 2 and S5−S7). As we anticipated, *cis* polymers exhibited higher reactivity,[11] diastereoselectivity, and enantioselectivity compared with the corresponding *trans* polymers (entries 1, 2, and 5−8), showing the configurational effect. To evaluate the polymeric effect, **1-*cis*-OTMS** and monomeric catalysts **6** and **7** were also tested (entries 2−4). The results suggest that the diastereoselectivity and enantioselectivity were enhanced by having the substituent on the same face of the pyrrolidine ring at C-4 (entries 3 and 4) and that polymer

Table 2. Investigation of the Steric Effect of the Substituent



entry	catalyst	yield (%)[a]	dr[b]	% ee[c]	*config.*
1	**2-*trans*-OTMS**	28	6:1	90.3	(2*R*,3*S*)
2	**1-*cis*-OTMS**	93	>20:1	99.0	(2*S*,3*R*)
3[d]	**6**	90	13:1	98.0	(2*S*,3*R*)
4[e]	**7**	97	7:1	97.3	(2*S*,3*R*)
5	**2-*trans*-H**	95	5:1	78.7	(2*R*,3*S*)
6	**1-*cis*-H**	96	5:1	87.0	(2*S*,3*R*)
7	**2-*trans*-OMe**	51	4:1	95.2	(2*R*,3*S*)
8	**1-*cis*-OMe**	99	16:1	95.5	(2*S*,3*R*)

[a]Isolated yields. [b]The dr (*syn*:*anti*) values were determined by NMR spectroscopy. [c]The ee values of the *syn* isomer were determined by chiral HPLC. [d]The reaction time was 2 h. [e]The reaction time was 1 h.

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chain works as a bulky substituent and further enhances the facial selectivity (entries 2 and 3), as we hypothesized in Figure 1.

Application to Continuous-Flow Process. Encouraged by the batch-mode results with our polymeric *cis* catalysts, including the clear polymeric and configurational effects, we turned our attention to the application of these polymer catalysts to a continuous-flow process as illustrated in Figure 3.

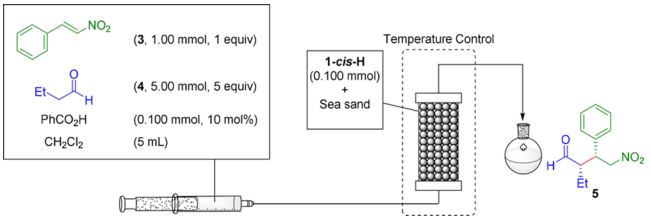

Figure 3. Illustration of the continuous-flow process for asymmetric Michael addition.

A packed-bed reactor was filled with a preground mixture of **1-*cis*-H** (0.100 mmol, 10 mol %) and sea sand. The sea sand was used as a spacer in order to control the residence time and to restrict clogging. The temperature of the packed-bed column was controlled by an HPLC column oven.

A solution[12] of **3** (1.0 mmol, 1 equiv), benzoic acid (0.10 mmol, 10 mol %), and **4** (5.0 mmol, 5.0 equiv) in CH_2Cl_2 (5 mL) was passed through the packed-bed column at the indicated flow rate and temperature. After the injection of the substrate solution was completed, CH_2Cl_2 (5 mL) was passed through the column for washout at the same flow rate and temperature. After evaporation and purification, the resulting **5** was analyzed by NMR spectroscopy, HPLC, and chiral HPLC. These results are shown in Table 3.

For comparison between the batch and continuous-flow systems, the results of experiments performed in the batch system using 10 mol % **1-*cis*-H** can be seen in entry 0. In the batch system, the conversion was only 69% at 50 min (Table 3, entry 0, top), and reaction completion required almost 180 min to afford **5** in good yield (entry 0, bottom). Following these results, it was found that a higher catalyst loading gave a higher diastereoselectivity and enantioselectivity, suggesting that the higher loading provided suppression of an undesired background reaction (Table 2, entry 6). In the continuous-flow process using **1-*cis*-H** as the catalyst, the asymmetric Michael addition proceeded smoothly to afford **5** (entry 1). Reduction of the residence time from 100 to 50 min increased the reaction rate compared with the batch system (entry 2). This can be explained by the relatively high local concentration of the catalyst. Reducing the residence time further while increasing the dr value could not achieve high conversion (entry 3). Increasing the concentration of the reactant showed improvement in the productivity (entry 4). Increasing the flow rate resulted in decreased conversion and an increased dr value (entry 5), while decreasing the flow rate resulted in high conversion but also a decreased yield, which shows a non-negligible diffusion effect against the flow direction (entry 6). Decreasing the reaction temperature resulted in increased diastereoselectivity as well as enantioselectivity (entry 7).

Durability Study. The durability of the polymer catalyst **1-*cis*-H** was investigated in both batch and continuous-flow operations. The result of the recycling test under batch conditions can be seen in Table S8. In the batch system, all of the catalysts have low reusability, suggesting fast deactivation of the catalyst, and it was found that the presence of butyraldehyde is the main contributor to the deactivation. This is presumably explained by the generation of an inactive species such as β,β-disubstituted enamine **S23** and hemiaminal ether **S25** (see Table S9 and Scheme S5). This hypothesis is also supported by the recent report by Schnitzer and Wennemers.[13]

On the other hand, improved durability of the catalyst was observed in continuous-flow operation (Figure 4). As can be seen in Figure 4, the continuous-flow reaction showed a decrease in reaction conversion (red line) and a slight decrease in diastereomeric ratio (blue line) as time passed, but interestingly, the turnover number was obviously superior to that of the batch system without any processing of the catalyst.

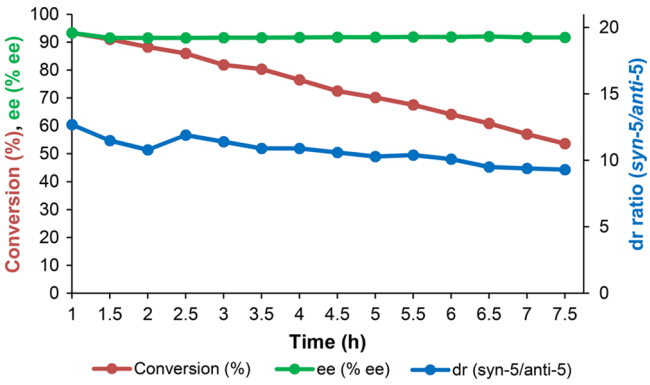

Figure 4. Durability study of **1-*cis*-H** in continuous-flow operation.

Table 3. Asymmetric Michael Addition Using the Continuous-Flow System

entry[a]	T (°C)	flow rate (mL/min)	column volume (mL)	residence time (min)	conc. (M)	yield (%)[b]	conv. (%)[c]	dr (*syn*:*anti*)[d]	% ee[e]
0	25	batch	–	50[f]	0.2	–	69.3	–	–
				180[f]		91.7	100	11:1	91.1
1	25	0.05	5.0	100	0.2	86.2	98.6	9:1	95.6
2	25	0.05	2.5	50	0.2	86.5	94.9	10:1	91.8
3	25	0.05	1.0	20	0.2	68.4	82.2	11:1	92.3
4	25	0.05	2.5	50	0.4	89.4	96.1	12:1	91.3
5	25	0.10	5.0	50	0.2	62.0	73.6	16:1	92.4
6	25	0.025	5.0	200	0.2	77.1	99.4	13:1	91.1
7	5	0.05	5.0	100	0.2	48.3	72.9	17:1	93.6

[a]**1-*cis*-H** (0.100 mmol) was used. [b]Isolated yields. [c]Determined by HPLC [area/(area + area^{SM})]. [d]Determined by ^{1}H NMR spectroscopy (integration of peak area). [e]The ee values of the *syn* isomer were determined by chiral HPLC. [f]The reaction time is indicated.

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It should be mentioned that the enantiomeric excess (green line) did not change even after extended reaction times. Although the durability test using **1-*cis*-OTMS** showed a similar trend, the reaction conversion was relatively low compared with that of **1-*cis*-H**, suggesting that steric hindrance at the reaction site influences the reactivity (Figures S3 and S4).[14] It should be noted that increasing the catalyst loading resulted in increased conversion in the case of **1-*cis*-OTMS** (Figures S3 and S4), suggesting that further increases in reaction conversion would be possible.

Investigation of Epimerization. Continuous-flow operation (as described in Table 3) shows an increase in diastereoselectivity in line with a decrease in the residence time as well as an increase in the flow rate. This suggests that reducing the contact time of the reaction mixture with the catalyst is important for high dr values. This can be partly attributed to limiting the undesired epimerization of the product by minimizing the exposure to the catalyst. In order to investigate this epimerization effect, the dr value was evaluated upon treatment with **1-*cis*-H** in the batch system, as shown in Figure 5 (see Table S14). In the presence of **1-*cis*-H** and

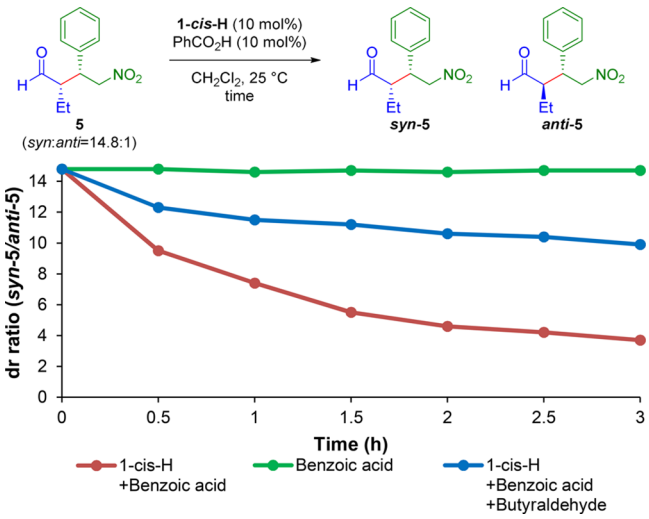

Figure 5. Investigation of epimerization.

benzoic acid, the dr value of **5** decreased over time (red line). On the other hand, in the absence of **1-*cis*-H**, the dr value did not decrease as expected (green line), suggesting that the interaction of product **5** with the catalyst caused undesired epimerization. The addition of butyraldehyde resulted in partial restriction of undesired epimerization (blue line), suggesting competitive enamine formation from butyraldehyde and **1-*cis*-H**.

CONCLUSION

An array of polymer-supported *cis*-2,4-diphenylmethylpyrrolidine derivatives were designed and synthesized, with the *cis* polymers showing higher diastereoselectivity and enantioselectivity than the *trans* polymers using the asymmetric Michael addition of butyraldehyde to *trans*-β-nitrostyrene as a model reaction. It was also found that the polymer chain plays an important role in the high selectivity. Moreover, expanded investigation of these catalysts to a continuous-flow process was explored and showed an improvement in durability and increases in reaction rate diastereoselectivity compared with the batch system results. These findings lend themselves well to efficient synthesis of APIs, agrochemicals, etc. using these catalysts in continuous-flow mode, and further investigation of the substrate scope and scale-up application to specific APIs is underway.

EXPERIMENTAL SECTION

General Procedure for Asymmetric Michael Addition of Butyraldehyde to Nitrostyrene. To a solution of *trans*-β-nitrostyrene (**3**) (149 mg, 1.00 mmol, 1 equiv) in a solvent (5 mL) were added an acid (0.100 mmol, 0.10 equiv), butyraldehyde (**4**) (361 mg, 5.00 mmol, 5.0 equiv), and a polymer catalyst (0.0500 mmol, 5.0 mol %) at 25 °C. After 24 h of stirring at the same temperature, the reaction mixture was filtered to remove the polymer catalyst. The eluent was concentrated under reduced pressure to obtain the crude mixture, which was purified by silica gel column chromatography (5:1 *n*-Hex/EtOAc) to afford a diastereomixture of 2-ethyl-4-nitro-3-phenylbutanal (**5**) as a colorless oil. The dr value of **5** (*syn*-**5**:*anti*-**5**) was determined by ^{1}H NMR spectroscopyy (integration of peak area). The ee value of *syn*-**5** was determined by chiral HPLC.

General Procedure for Continuous-Flow Synthesis. *Preliminary Preparation.* A mixture of **1-*cis*-H** (0.100 mmol, 10 mol %) and sea sand was ground in a mortar and charged into a glass column. CH_2Cl_2 (ca. 10 mL) was passed through the packed-bed column for swelling of **1-*cis*-H** in advance. The temperature of the packed-bed column was controlled by a column oven for HPLC.

Continuous-Flow Experiment. A solution of **3** (149 mg, 1.00 mmol, 1 equiv), benzoic acid (12.2 mg, 0.100 mmol, 10 mol %), and **4** (361 mg, 5.00 mmol, 5.0 equiv) in CH_2Cl_2 (5 mL) was passed through the packed-bed column at the indicated flow rate and temperature. After the injection of the substrate solution was complete, CH_2Cl_2 (5 mL) was passed through the column at the same flow rate and temperature for washout. The eluent was concentrated under reduced pressure to obtain a crude mixture, which was purified by silica gel column chromatography (5:1 *n*-Hex/EtOAc) to afford a diastereomixture of **5** as a colorless oil. The dr value of **5** (*syn*-**5**:*anti*-**5**) was determined by ^{1}H NMR spectroscopy (integration of peak area). The ee value of *syn*-**5** was determined by chiral HPLC.

HPLC Method. High-performance liquid chromatography (HPLC) was performed on an LC-2030 Plus chromatograph with a YMC-triart C18 column (250 mm × 4.6 mm i.d.). The column oven was set at 40 °C, and the UV detector was set at 210 nm. Mobile phases A (0.1% aqueous phosphoric acid) and B (acetonitrile) were utilized at a flow rate of 1.5 mL/min. Mobile phase B was increased linearly from 15% to 80% over 22.5 min and maintained at 80% for 5 min. Retention times: **3** (15.5 min), *syn*-**5** (16.0 min), *anti*-**5** (16.6 min).

Chiral HPLC Method. The optical purity (enantiomeric excess) of **5** (*syn* isomer) was analyzed on an LC-2030 Plus chromatograph with a Chiralpak OD-H column (250 mm × 4.6 mm i.d.). The column oven was set at 25 °C, and the UV detector was set at 215 nm. Isocratic flow (80:20 *n*-Hex/IPA) at a flow rate of 0.8 mL/min was used. Retention times: (2*S*,3*R*)-**5** (17.7 min), (2*R*,3*S*)-**5** (22.6 min).

syn-**5**. ^{1}H NMR ($CDCl_3$) δ 9.72 (dd, *J* = 2.6, 1.4 Hz, 1H), 7.36−7.27 (m, 3H), 7.19−7.17 (m, 2H), 4.72 (dd, *J* = 12.6, 4.9 Hz, 1H), 4.63 (dd, *J* = 12.6, 9.8 Hz, 1H), 3.80 (td, *J* = 9.8, 4.9 Hz, 1H), 2.71−2.66 (m, 1H), 1.55−1.46 (m, 2H), 0.83 (td, *J* = 7.5, 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 203.2 (1CH), 136.7

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(1C), 129.1 (2CH + 1CH), 127.9 (2CH), 78.5 ($1CH_2$), 54.9 (1CH), 42.6 (1CH), 20.3 ($1CH_2$), 10.6 ($1CH_3$).

anti-5. ^{1}H NMR ($CDCl_3$) δ 9.48 (dd, J = 3.0, 1.0 Hz, 1H), 7.36−7.27 (m, 3H), 7.16−7.17 (m, 2H), 4.81 (ddd, J = 13.0, 6.1, 0.6 Hz, 1H), 4.76 (dd, J = 13.0, 9.2 Hz, 1H), 3.84−3.77 (m, 1H), 2.60−2.55 (m, 1H), 1.77−1.63 (m, 2H), 0.98 (td, J = 7.5, 1.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 203.3 (1CH), 136.2 (1C), 129.1 (1CH), 128.2 (2CH), 128.1 (2CH), 77.9 ($1CH_2$), 54.9 (1CH), 44.0 (1CH), 20.5 ($1CH_2$), 11.4 ($1CH_3$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00268.

General information, experimental procedure, and characterization (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All of the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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