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Construction of All-Carbon Quaternary Stereocenters *via* Asymmetric Cyclopropanations: Synthesis of Chiral Carbocyclic Pyrimidine Nucleosides

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ABSTRACT: An efficient route to synthesize chiral carbocyclic pyrimidine nucleoside analogues containing all-carbon quaternary stereocenters has been established *via* the asymmetric intermolecular cyclopropanation of N1-vinylpyrimidines and α-aryl diazoesters. With 2 mol% of chiral dirhodium (II) carboxylate complex as the catalyst, a variety of chiral carbocyclic cytosine or uracil nucleoside analogues were obtained in good yields (up to 96% yield), high diastereoselectivities (>20:1 dr), and excellent enantioselectivities (up to 99% *ee*).

Keywords: All-carbon quaternary stereocenter; Asymmetric catalysis; cyclopropanation; nucleoside; pyrimidine.

Chiral nucleosides have shown outstanding antivirus and anticancer activities, making modification of the ribose moiety become an advanced research hotspot.[1] Representative examples are shown in Figure 1. **Sofosbuvir**, bearing a chiral quaternary stereocenter in the sugar ring, has been approved by the FDA for the treatment of HCV (hepatitis C virus) infection.[2] In particular, three-membered nucleosides containing a cyclopropane moiety, which generates constrained conformation, have received increasing research interest.[3] **Besifovir**, a cyclopropyl carbocyclic nucleoside bearing a quaternary carbon, has been approved as an anti-HBV (hepatitis B virus) drug in 2017.[4] In addition, cyclopropyl cytosine nucleoside **I** with an all-carbon quaternary center shows moderate anti-HCMV (human cytomegalovirus) activity.[5] Meanwhile, cyclopropyl cytosine nucleoside **II**, also bearing an all-carbon quaternary center, exhibits potential anti-cancer activity.[6] Furthermore, the absolute configuration of the chiral center in cyclopropyl nucleosides usually plays a crucial role in their relevant biological activities. In the case of **A5021**, the (1′*S*,2′*R*)-A5021 is nearly 100 times more active than its (1′*R*,2′*S*)-enantiomer against HSV-1

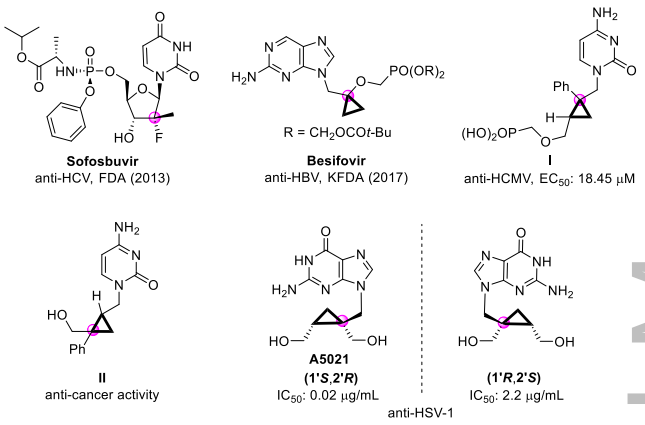

Figure 1. Selected nucleosides containing a quaternary carbon with biological activities.

(herpes simplex virus-1).[7] Therefore, developing an efficient method to synthesize chiral cyclopropyl carbocyclic nucleoside analogues containing all-carbon quaternary stereocenters is highly desirable.

The asymmetric intermolecular cyclopropanation reaction between olefins and diazo compounds is one of the most powerful strategies to synthesize optically active cyclopropanes.[8-10] In 2016, we reported a direct route for the synthesis of chiral carbocyclic pyrimidine nucleosides *via* the Ru(II)-Pheox catalyzed enantioselective cyclopropanation of N1-vinylpyrimidines with α-diazoesters.[11] With respect to α-diazoester reactants, when methyl 2-diazoacetate (R^1 = H) was used, the corresponding carbocyclic pyrimidine nucleoside products could be generated in good yields (71-96% yields), high diastereoselectivities (10:1->20:1 dr), and excellent enantioselectivities (96-99% *ee*) (Scheme 1a, **i**). In contrast, in the case of α-phenyl diazoacetate (R^1 = Ph), the cyclopropanation reaction did not occur (Scheme 1a, **ii**). In order to solve this problem, herein,

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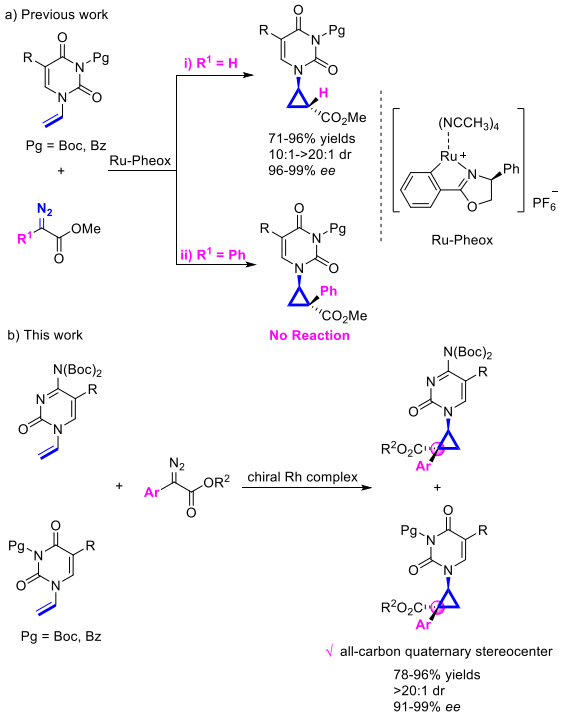
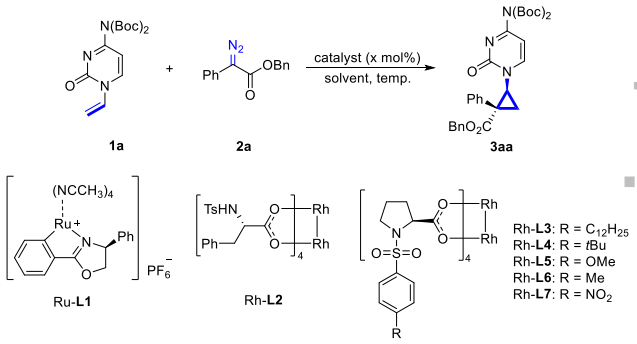
we report the asymmetric intermolecular cyclopropanation reaction between α-aryl diazoesters and N1-vinylpyrimidines, affording the chiral carbocyclic pyrimidine nucleoside analogues[12] containing all-carbon quaternary stereocenters in good yields (up to 96% yield), high diastereoselectivities (>20:1 dr), and excellent enantioselectivities (up to 99% *ee*) (Scheme 1b).



Scheme 1. Synthesis of chiral cyclopropyl carbocyclic nucleoside analogues.

Initially, Boc protected N1-vinylcytosine **1a** and α-phenyl diazoacetate **2a** were selected as the model substrates (Table 1). When Ru(II)-Pheox **L1** was employed as the catalyst in toluene at room temperature for 24 h, the cyclopropanation reaction did not occur (entry 1). To our delight, with dirhodium (II) carboxylate Rh-**L2** as the catalyst, the cyclopropanation proceeded well, generating the desired chiral carbocyclic cytosine nucleoside analogue **3aa** with an all-carbon quaternary stereocenter in 93% yield, >20:1 dr, albeit with 24% *ee* (entry 2). Then, several chiral dirhodium (II) carboxylates were evaluated (entries 3-7), and Rh-**L7** could provide better results (entry 7, 93% yield and 64% *ee*). Lowering the reaction temperature from room temperature to -20 °C, the *ee* value of **3aa** increased from 64 to 82% *ee* (entries 7-8). After that, the reaction temperature was further investigated and -50 °C was selected as the better reaction temperature, giving **3aa** in 90% yield and 97% *ee* (entries 9-11). Subsequently, various solvents were tested in the presence of Rh-**L7** at -50 °C, but the results were generally inferior to that in toluene (entries 10, 12-16). When the catalyst loading was decreased from 4 to 2 mol%, excellent results (90% yield and 96% *ee*) could still be obtained (entries 10 and 17). Even 1 mol% of the catalyst could give **3aa** in 97% *ee*, albeit with lower yield after prolonging the reaction time to 48 h (entry 18). Further evaluation of the concentration showed that 1.0 mL of toluene was a suitable volume to dissolve α-phenyl diazoacetate **2a** (0.4 mmol), delivering **3aa** in 92% yield, >20:1 dr, and 98% *ee* (entries 17, 19-20). Thus, the optimal reaction conditions were as follows: 2 mol% Rh-**L7** in toluene at -50 °C for 6 h, with α-phenyl diazoacetate **2a** (0.4 mmol) dissolved in 1.0 mL of toluene (entry 19).

Table 1. Optimization of the intermolecular cyclopropanation of α-phenyl diazoester.[a]



Entry	Catalyst.	x	Temp [°C]	Solvent	t [h]	Yield[b] [%]	*ee*[c] [%]
1	Ru-**L1**	4	rt	toluene	24	N.R.	
2	Rh-**L2**	4	rt	toluene	4	93	24
3	Rh-**L3**	4	rt	toluene	4	86	56
4	Rh-**L4**	4	rt	toluene	4	92	34
5	Rh-**L5**	4	rt	toluene	4	94	46
6	Rh-**L6**	4	rt	toluene	4	73	60
7	Rh-**L7**	4	rt	toluene	4	93	64
8	Rh-**L7**	4	-20	toluene	4	93	82
9	Rh-**L7**	4	-40	toluene	4	92	90
10	Rh-**L7**	4	-50	toluene	6	90	97
11	Rh-**L7**	4	-60	toluene	13	90	96
12	Rh-**L7**	4	-50	n-hexane	6	N.R.	
13	Rh-**L7**	4	-50	CH_2Cl_2	6	30	84
14	Rh-**L7**	4	-50	THF	6	N.R.	
15	Rh-**L7**	4	-50	PhCl	6	80	94
16	Rh-**L7**	4	-50	mesitylene	6	40	96
17	Rh-**L7**	2	-50	toluene	14	90	96
18	Rh-**L7**	1	-50	toluene	48	60	97
19[d]	Ru-**L7**	2	-50	toluene	6	92	98
20[e]	Ru-**L7**	2	-50	toluene	6	92	95

[a] Unless otherwise noted, the reaction conditions are as follows: **1a** (0.05 mmol) and catalyst (x mol%) were dissolved in solvent (1.0 mL), then **2a** (0.4 mmol, 8.0 equiv) in solvent (2.0 mL) was added dropwise to the reaction mixture *via* syringe pump for 4 hours. For all the cases, the dr values were >20:1, which were determined by ^{1}H NMR of the crude products. N.R. = No Reaction.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] **2a** (0.4 mmol, 8.0 equiv) was dissolved in toluene (1.0 mL) and added *via* syringe pump for 2 hours.

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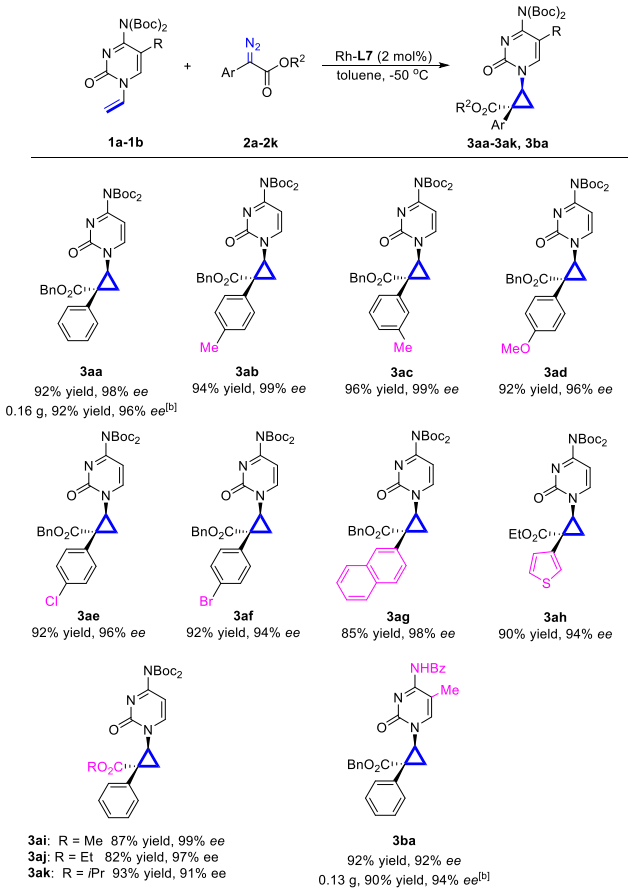
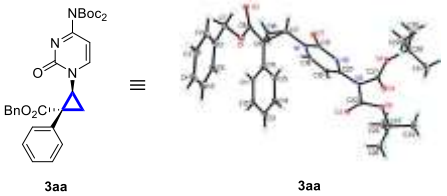
[e] **2a** (0.4 mmol, 8.0 equiv) was dissolved in toluene (0.5 mL) and added *via* syringe pump for 1 hours.

Scheme 2. Substrate scope of α-aryl diazoacetates and N1-vinylcytosines.[a]



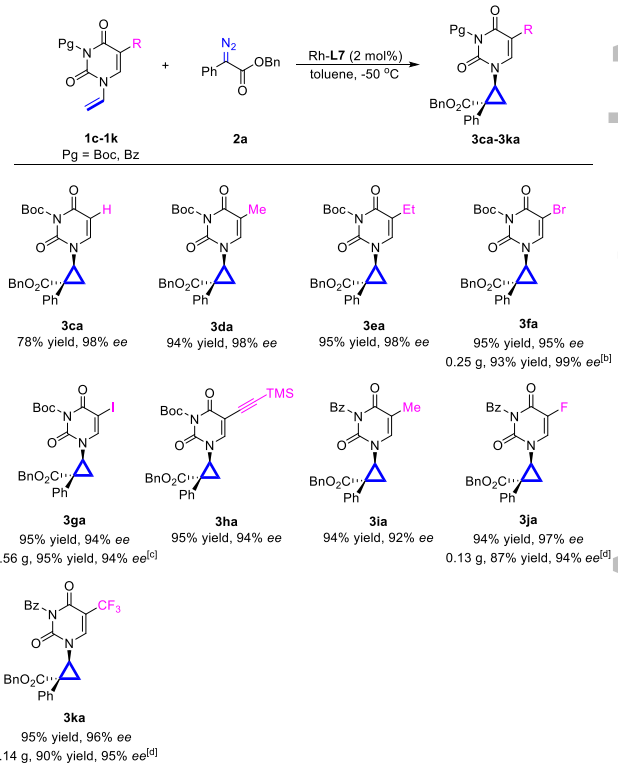
[a] Reaction conditions: **1** (0.05 mmol) and Rh-**L7** (2 mol%) were dissolved in toluene (1.0 mL), then **2** (0.4 mmol, 8.0 equiv) in toluene (1.0 mL) was added dropwise to the reaction mixture *via* syringe pump for 2 hours, and the reaction was stirred for overnight. For all the cases, the dr values were >20:1, which were determined by ^{1}H NMR of the crude products. The yield referred to the isolated yield and the *ee* values were determined by HPLC analysis. [b] The reaction was performed on a 0.3 mmol scale.



Scheme 3. X-ray structure of **3aa**.

Under optimized reaction conditions, the substrate scope with respect to α-aryl diazoacetates was explored for asymmetric cyclopropanation with N1-vinylcytosine **1a** (Scheme 2). In the cases of electron-donating groups (Me, OMe) substituted α-aryl diazoacetates **2b-2d**, excellent results (92-96% yields and 96-99% *ee*) could be obtained for **3ab-3ad**. When electron-withdrawing groups (Cl, Br) substituted α-aryl diazoacetates **2e-2f** were used, excellent results (92% yield and 94-96% *ee*) could still be obtained for **3ae-3af**. In addition, 2-naphthyl substituted diazoacetate **2g** served as a good reactant to form the adduct **3ag** with excellent enantioselectivity (98% *ee*). Meanwhile, the thiophenyl derived diazoacetate **2h** was also a suitable substrate to afford the desired adduct **3ah** in excellent results (90% yield and 94% *ee*). Then, several α-aryl diazoacetates **2i-2k** with different ester groups were investigated, and the corresponding adducts **3ai-3ak** were obtained in good yields (82-93% yields) and excellent enantioselectivities (91-99% *ee*). As for Bz-protected 5-methylcytosine derived alkene **1b**, the cyclopropanation reaction proceeded well, delivering the cycloadduct **3ba** in 92% yield and 92% *ee*. In the case of N1-vinylcytosines **1a** and **1b**, when the asymmetric cyclopropanations with α-phenyl diazoacetate **2a** were carried out on a 0.3 mmol scale, the desired adducts **3aa** and **3ba** were generated in 0.16 g and 0.13 g, respectively, with similar yield and enantioselectivities. It should be noted that for all the chiral cyclopropyl carbocyclic nucleoside analogues, excellent diastereoselectivities were obtained (>20: dr). The absolute configuration of the chiral carbocyclic cytosine nucleoside analogue **3aa** was determined to be (1*R*,2*S*) by the single-crystal X-ray diffraction analysis (Scheme 3).[13]

Scheme 4. Substrate scope of N1-vinyluracils.[a]



[a] Reaction conditions: **1** (0.05 mmol) and Rh-**L7** (2 mol%) were dissolved in toluene (1.0 mL), then **2a** (0.4 mmol, 8.0 equiv) in toluene (1.0 mL) was added dropwise to the reaction mixture *via* syringe pump for 2 hours, and the reaction was stirred for overnight. For all the cases, the dr

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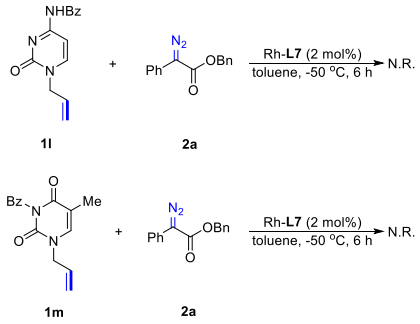
values were >20:1, which were determined by ^{1}H NMR of the crude products. The yield referred to the isolated yield and the *ee* values were determined by HPLC analysis. [b] The reaction was performed on a 0.5 mmol scale. [c] The reaction was performed on a 1.0 mmol scale. [d] The reaction was performed on a 0.3 mmol scale.

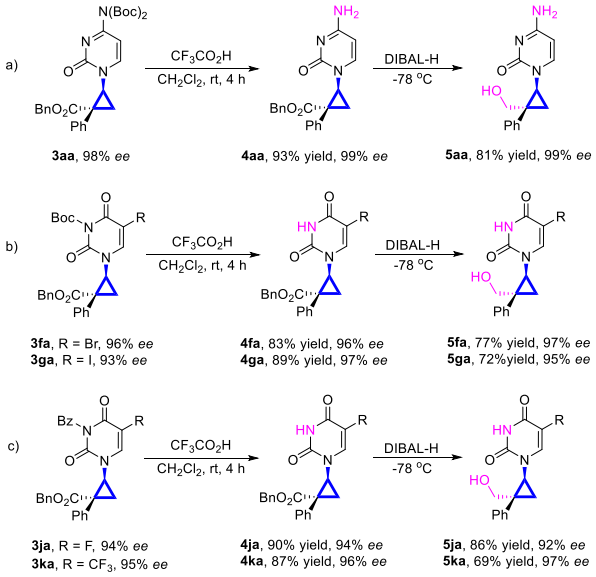
Subsequently, a series of N1-vinyluracils **1c-1k** with different substituents at the C5 position were investigated in the asymmetric cyclopropanation reaction with α-phenyl diazoacetate **2a** (Scheme 4). When Boc-protected N1-vinyluracil **1c** was used, the desired carbocyclic uracil nucleoside analogue **3ca** was obtained in good yield (78% yield) and excellent enantioselectivity (98% *ee*). In the case of 5-methyl- or 5-ethyl-substituted N1-vinyluracil (**1d** or **1e**), the corresponding cyclopropanation adducts **3da-3ea** were obtained in 94-95% yields and 98% *ee*. 5-Halo-substituted uracils derived alkenes **1f-1g** were also suitable reactants, affording the desired carbocyclic uracil nucleoside analogue **3fa-3ga** in excellent yields and 94-95% *ee*. When the asymmetric cyclopropanation of 5-Br-substituted uracil derived alkene **1f** with α-phenyl diazoacetate **2a** was carried out on a 0.5 mmol scale, the corresponding adduct **3fa** was given in 0.25 g without any loss of the enantioselective. Furthermore, the cyclopropanation of 5-I-substituted uracil derived alkene **1g** was performed on a 1.0 mmol scale, and the desired nucleoside analogue **3ga** was obtained in 0.56 g with the maintain of the yield and enantioselectivity. Meanwhile, alkynyl substituted uracil derived alkene **1h** participated well in the cyclopropanation reaction, generating the corresponding adduct **3ha** in 95% yield and 94% *ee*. After that, several Bz-protected uracil derived alkenes **1i-1k** were evaluated. 5-Methyl, 5-fluoro-, and 5-CF_3-substituted N1-vinyluracils **1i-1k** were also suitable substrates for the cyclopropanation, delivering the targeted nucleoside analogues **3ia-3ka** in high yields (94-95% yields) and excellent enantioselectivities (92-97% *ee*).



Scheme 5. The cyclopropanations of N1-allylpyrimidines with α-phenyl diazoacetate.

Subsequently, the asymmetric cyclopropanations of N1-allylpyrimidines with α-phenyl diazoacetate were investigated to generate nucleosides, in which a methylene moiety was involved as the association between pyrimidine ring and cyclopropane ring. As shown in Scheme 5, with N1-allylcytosine **1l** or N1-allyluracil **1m** as the reactant, the asymmetric cyclopropanations of α-phenyl diazoacetate **2a** did not occur, and the α-phenyl diazoacetate **2a** completely decomposed along with the recovery of N1-allylpyrimidine.

After that, derivatization of the chiral carbocyclic pyrimidine nucleoside analogues were performed (Scheme 6). The Boc protecting groups in cytosine nucleoside analogue **3aa** could be easily removed by treatment of trifluoroacetic acid, giving carbocyclic cytosine nucleoside analogue **4aa** in 93% yield and 99% *ee*. With cytosine nucleoside analogue **4aa** as the starting material, the reduction reaction under DIBAL-H proceeded well, affording chiral carbocyclic cytosine nucleoside **5aa** containing a hydroxymethyl group in 81% yield and 99% *ee* (Scheme 6a). Under similar procedures, the Boc protecting group in uracil nucleoside analogues (**3fa** and **3ga**) and Bz protecting group in uracil nucleoside analogues (**3ja** and **3ka**) could also be removed under trifluoroacetic acid, giving the corresponding uracil nucleoside analogues (**4fa**, **4ga**, **4ja**, and **4ka**) in 83-90% yields. With uracil nucleoside analogues (**4fa**, **4ga**, **4ja**, and **4ka**) as the starting materials, in the presence of DIBAL-H, the corresponding uracil nucleosides (**5fa**, **5ga**, **5ja**, and **5ka**) bearing a hydroxymethyl group were generated in 69-86% yields with the keep of the enantioselectivities (Schemes 6b and 6c).



Scheme 6. Derivatization of chiral carbocyclic pyrimidine nucleoside analogues.

In summary, we have reported an efficient route to synthesize chiral carbocyclic pyrimidine nucleoside analogues containing all-carbon quaternary stereocenters *via* asymmetric intermolecular cyclopropanation of N1-vinylpyrimidines with α-aryl diazoesters. In the presence of 2 mol% chiral dirhodium (II) carboxylate Rh-**L7**, a variety of chiral carbocyclic cytosine or uracil nucleoside analogues

could be generated in good yields (up to 96% yield), high diastereoselectivities (>20:1 dr), and excellent enantioselectivities (up to 99% *ee*). Furthermore, the chiral carbocyclic uracil nucleoside could be easily generated from deprotection and reduction.

Experimental Section

In a test tube, **1a** (0.05 mmol) and Rh-**L7** (1.4 mg, 2 mol%) were dissolved in toluene (1.0 mL) and the reaction was cooled to -50 °C. After that, **2a** (8.0 equiv) in toluene (1.0 mL) was added dropwise to the reaction mixture *via* syringe pump for 2 hours, and the reaction was stirred for another 4 hours. The mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 2/1) to afford adduct **3aa**. Yellow solid, m.p. = 177.8-179.9 ºC, 92% yield, 25.8 mg, 98% *ee*. $[\alpha]_D^{20}$ = 176.0 (*c* = 0.7, CH_2Cl_2). HPLC CHIRALCEL IA, *n*-hexane/2-propanol = 80/20, flow rate = 0.6 mL/min, temperature = 25 ºC, λ = 250 nm, retention time: 18.900 min, 24.207 min. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32–7.29 (m, 5H), 7.23–7.20 (m, 5H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.2 Hz, 1H), 5.20 (d, *J* = 12.6 Hz, 1H), 5.11 (d, *J* = 12.6 Hz, 1H), 4.43 (t, *J* = 7.2 Hz, 1H), 2.22 (t, *J* = 7.8 Hz, 1H), 2.05 (t, *J* = 6.6 Hz, 1H), 1.52 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 160.1, 149.9, 147.4, 140.5, 135.6, 131.7, 130.9, 128.7, 128.6, 128.2, 127.6, 101.3, 86.9, 67.4, 53.6, 43.7, 35.5, 27.6, 17.2. **HRMS** (ESI): m/z calcd. For $C_{31}H_{35}N_3NaO_7$ $[M+Na]^+$ 584.2367, found m/z 584.2362.

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[13] CCDC 1814407 (**3aa)** 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

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UPDATE

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