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Diastereoselective Synthesis of Adjacent P,C-Stereogenic β-*N*-Glycosidic Linked α-Aminophosphinates

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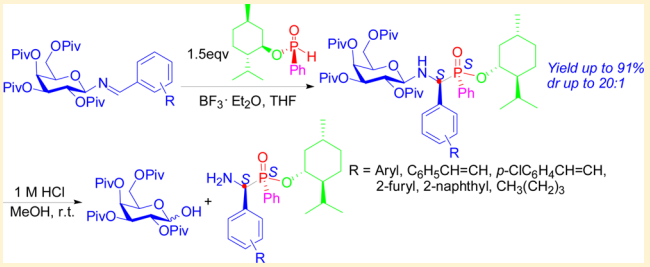
Supporting Information

ABSTRACT: The diastereoselective formation of adjacent P,C-stereogenic β-*N*-glycosidic linked α-aminophosphinates is developed in high yields via a phospha-Mannich reaction. The reaction was performed by employing (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate and *O*-pivaloylated *N*-galactosylimine for double stereodifferentiation and $BF_3{\cdot}Et_2O$ as a promoter in THF. *O*-Pivaloylated *N*-galactosylphenyl imine **2** and (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** were converted to *N*-galactosyl α-aminoalkylphosphinate **3** with ratios of diastereomers up to 20:1. The synthetic method of the conversion provides a rapid access to adjacent P,C-stereogenic chiral α-aminophosphinates.



INTRODUCTION

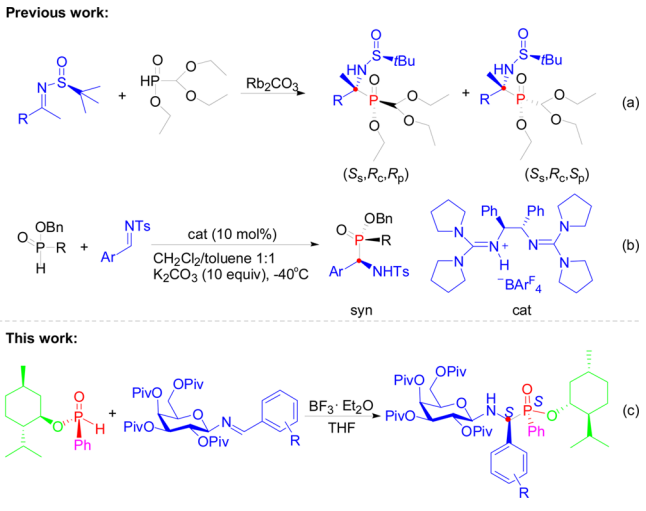
P-Stereogenic organophosphorus compounds have attracted great interest due to their potential applications in the fields of pharmaceutical chemistry[1] and material science[2] and as ligands for asymmetric catalysis[3] and chiral reagents and organocatalysts.[4] The applications of P-chirogenic derivatives in agrochemistry, biology, and drugs significantly increased in the recent past.[5]

Considering the growing interest for P-chirogenic phosphorus compounds in modern chemistry, the preparation of enantiomerically enriched phosphorus compounds with P-stereogenic centers has received considerable attention. The stereoselective functionalized chiral phosphine oxides and phosphines possessing chiral centers at phosphorus and/or carbon atoms are typically prepared using enantiopure starting materials, chiral auxiliaries, organocatalytic asymmetric P−C bond formation, or recrystallization resolution of racemic phosphines.[6] These strategies corresponded to a variety of efficient ways to obtain versatile chiral phosphorus compounds.

The addition of achiral P−H species ($[R_2PH]$,[7] $[R_2P(O)H]$,[8] and $[(RO)_2P(O)H]$[9]) to imines is a widely utilized method for the newly created P−C bond and the preparation of chiral α-aminophosphonic acids.[10] α-Aminophosphorus compounds are structurally analogous to natural α-amino acids and therefore have biological and biochemical properties in their role as enzyme inhibitors, agrochemicals, or pharmaceuticals.[11] Successful enantioselective approaches for the preparation of α-aminophosphinates employed catalysts such as metal complexes,[12] guanidinium salt,[13] thiourea,[14] and chiral phosphoric acid.[15] However, in those systems, efficient preparation of α-aminophosphinates with P-stereogenic centers still remains challenging. In particular, controlling the stereochemistry of chiral α-aminophosphorus compounds with an adjacent P,C-stereogenic center has been scarcely reported.[13]

In 2008, Yuan and Zhang reported the nucleophilic addition of ethyl diethoxymethylphosphinate to *N*-(*S*)-(*tert*-butanesulfinyl)methylphenylketimine by using Rb_2CO_3 as base. This procedure leads to the enantiomerically enriched α-aminophosphinates with two stereogenic atoms but with different configurations on the phosphorus atom (Scheme 1a).[13a] In 2009, Tan and co-workers reported the enantioselective phospha-Mannich reaction catalyzed by chiral guanidi-

Scheme 1. Previous and Proposed Work



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nium salt involving secondary phosphine oxides and *H*-phosphinates as the P-nucleophile. A series of optically pure α-amino phosphine oxides, α-aminophosphinates, and *H*-phosphinates containing a P-chiral center were prepared (Scheme 1b).[13b]

In 2008, we demonstrated the asymmetric synthesis of β-*N*-glycosidically linked α-aminophosphonic acids derivatives by glycosylation-induced and Lewis acid catalyzed methods.[16] As a natural extension, we developed the enantioselective synthesis of α-amino(phenyl)methyl(phenyl)phosphinic acids by Mannich-type reactions between *O*-pivaloylated D-galactosylamines and ethyl phenylphosphinate.[17] Continuing with our interest in the chemistry of aminophosphorus derivatives, here we report the Lewis acid catalyzed double-stereodifferentiation[18] asymmetric phospha-Mannich reaction between (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** and *O*-pivaloylated *N*-galactosylimine **2** (Scheme 1c). This methodology provides chiral α-aminophosphinates with rich stereochemistry at both phosphorus and α-carbon centers in high yields with high diastereoselectivities.

RESULTS AND DISCUSSION

We initially investigated the reaction of (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1**[19] with *O*-pivaloylated *N*-galactosylphenyl imine **2a**[16,20] in THF without the aid of Lewis acid. Surprisingly, no desired product **3a** was observed even when the reaction time was extended to 24 h (Table 1, entry 1). Since the nucleophilicity of chiral P−H species is low and the electrophilicity of imines is only moderate, a Lewis acid was required to active these compounds and drive the reaction to completion. In this sense, various Lewis acids were screened in the reaction of the *N*-galactosylphenylimine **2a** with (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** in THF, and the results are shown in Table 1. The results revealed that CuCl, CuBr, CuI, and $ZnCl_2$·Et_2O only caused anomerization of the Schiff base **2a** (Table 1, entries 2−5). Other Lewis acids tested (e.g., $SnCl_4$, $AlCl_3$, and BF_3·Et_2O) were able to promote the desired reaction to afford moderate yields and stereoselectivities (Table 1, entries 6−8).

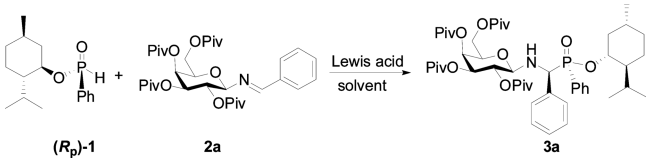
Compared with $SnCl_4$ and $AlCl_3$, BF_3·Et_2O gave the best result in THF at 0 °C to room temperature. The desired product **3a** was obtained in 60% yield with good diastereoselectivity (dr = 14:1) (Table 1, entry 8). When the reactions performed in THF with equimolar or higher than equimolar amounts of BF_3·Et_2O, within 12 h the reactions were finished in good yields and moderate to excellent diastereoselectivities (Table 1, entries 8−10). The ratio of diastereomers **3a** was detected by ^{31}P NMR in THF. From a the stereochemical point of view, four diastereoisomers could be formed in this reaction because of the anomeric carbon, and one stereogenic center was created at the α-position of chiral phosphinate. The four anomeric diastereomers have the $\beta S_c R_p$, $\beta R_c R_p$, $\alpha S_c R_p$, and $\alpha R_c R_p$ configurations. From the stereochemical outcome of the reaction, it could be shown that the corresponding α-anomer was not detected in this reaction. It was found that the configuration of phosphorus was stable and maintained (R_p/S_p > 99:1) in all of the tested reactions.

Solvent effect investigation indicated that the reaction could not work if CH_2Cl_2 or Et_2O was used as solvent (Table 1, entries 11 and 12). Toluene delivered the desired product with a high conversion rate but with a decrease in the diastereomeric ratio (Table 1, entry 13). The screening of solvents identified THF as the optimal solvent for this reaction (Table 1, entry 10).

To further increase the reaction diastereoselectivity, a suitable amount of chiral P−H species (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** was investigated by performing the reaction in the presence of 2 equiv of BF_3·Et_2O in THF at 0 °C for 1 h followed by warming to room temperature. The reaction of imine **2a** with equimolar (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** gave the desired product **3a** in 59% yield with 7:1 diastereoselectivity (Table 1, entry 14). When 1.5 equiv of (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** was used, superior results were obtained in terms of yield and diastereoselectivity of **3a** (85% yield, > 20:1 dr, Table 1, entry 10). A further increase in the amount of (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** had no positive change in either yield or stereoselectivity (Table 1, entry 15). Thus, the optimal reaction conditions for this transformation were determined to be 0.5 mmol of **2a**, 1.5 equiv of (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1**, and 2 equiv of BF_3·Et_2O in THF as solvent at 0 °C to rt.

Under the optimum conditions, the phospha-Mannich reaction was investigated with different imines (Table 2). It was found that the desired products **3a−p** can be successfully obtained in good to high yields and diastereoselectivities, irrespective the electronic properties and position of the aryl substituents on *O*-pivaloylated *N*-galactosylimine **2**. As for the aldimine in which R was a phenyl group, good yield and stereoselectivity were realized under identical conditions (Table 1, entry 1). Similar conclusions were drawn from the hydrophosphinylation of *O*-pivaloylated *N*-galactosylimine **2b−h** in which the yields of the process were only slightly

Table 1. Optimization of the Reaction Conditions[a]



(R_p)-**1** **2a** **3a**

entry	Lewis acid (equiv)	solvent	reaction time (h)	yields[b] (%)	dr[c]
1		THF	48	nr[d]	
2	CuCl (1)	THF	48	nr	
3	CuBr (1)	THF	48	nr	
4	CuI (1)	THF	48	nr	
5	$ZnCl_2$ (1)	THF	48	nr	
6	$SnCl_4$ (1)	THF	16	48	8:1
7	$AlCl_3$ (1)	THF	24	14	7:1
8	BF_3·Et_2O (1)	THF	12	60	14:1
9	BF_3·Et_2O (1.5)	THF	12	70	15:1
10	BF_3·Et_2O (2)	THF	12	85	>20:1
11	BF_3·Et_2O (2)	CH_2Cl_2	48	nr	
12	BF_3·Et_2O (2)	Et_2O	48	nr	
13	BF_3·Et_2O (2)	$PhCH_3$	24	60	6:1
14[e]	BF_3·Et_2O (2)	THF	12	59	7:1
15[f]	BF_3·Et_2O (2)	THF	12	82	>20:1

[a]Unless otherwise specified, all reactions were carried out using (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** (0.3 mmol, 1.5 equiv) and *O*-pivaloylated *N*-galactosylphenylimine **2a** (0.2 mmol, 1 equiv) in 2 mL of solvent at 0 °C to room temperature. [b]Yields of pure products after purification by chromatography. [c]Diastereomeric ratio (dr) determined by ^{31}P NMR spectroscopic assay of unpurified products. [d]No reaction. [e]1 equiv of (R_p)-**1** was used. [f]2 equiv of (R_p)-**1** was used.

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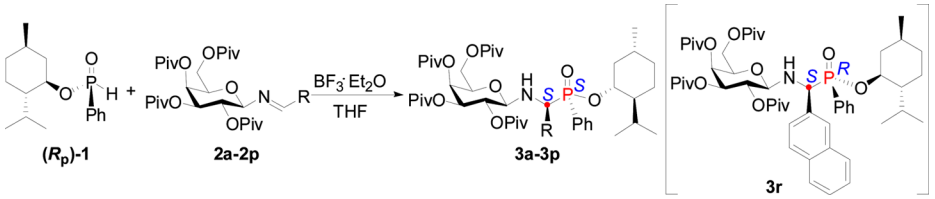
Table 2. Phospha-Mannich Reaction of *N*-(2,3,4,6-Tetra-*O*-pivaloylated-D-galactosyl)aldimines 2a−q



entry	product	R	time (h)	yield[a] (%)	dr[b]
1	**3a**	C_6H_5 (**2a**)	12	85	>20:1
2	**3b**	*p*-$CH_3C_6H_4$ (**2b**)	12	73	>20:1
3	**3c**	*p*-FC_6H_4 (**2c**)	6	85	>20:1
4	**3d**	*p*-ClC_6H_4 (**2d**)	6	85	>20:1
5	**3e**	*p*-BrC_6H_4 (**2e**)	6	88	>20:1
6	**3f**	*p*-$NO_2C_6H_4$ (**2f**)	6	81	>20:1
7	**3g**	*p*-CNC_6H_4 (**2g**)	6	84	>20:1
8	**3h**	*m*-$CH_3C_6H_4$ (**2h**)	12	75	>16:1
9	**3i**	*p*-$OCH_3C_6H_4$ (**2i**)	12	77	7:1
10	**3j**	*o*-FC_6H_4 (**2j**)	12	63	7:1
11	**3k**	*o*-ClC_6H_4 (**2k**)	12	46	7:1
12	**3l**	*o*-BrC_6H_4 (**2l**)	12	45	9:1
13	**3m**	$C_6H_5CH{=}CH$ (**2m**)	12	80	>20:1
14	**3n**	*p*-$ClC_6H_4CH{=}CH$ (**2n**)	12	79	>20:1
15	**3o**	2-furyl (**2o**)	12	51	1:1
16	**3p**	2-naphthyl (**2p**)	12	91	>20:1
17	**3q**	$CH_3(CH_2)_3$ (**2q**)	24	trace	
18[c]	**3r**	2-naphthyl (**2p**)	24	67	>20:1

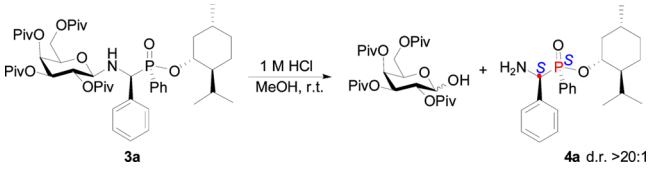
[a]Yields of pure products after purification by chromatography. [b]Diastereomeric ratio (dr) determined by ^{31}P NMR spectroscopic assay of unpurified products. [c](S_p)-*O*-(+)-menthyl-*H*-phosphinate **1′** was used.

influenced by the substituents present in the aromatic ring (Table 2, entries 2−8). A *p*-methoxyl substituent on the benzene ring of imine **2i** displayed good compatibility with the standard reaction conditions, providing the desired product **3i** in good yield with relatively low diastereoselectivity (Table 2, entry 9).

The steric properties have a remarkable effect on the yields and stereoselectivities. Yields, however, were much lower for the imines derived from 2-fluorobenzaldehyde, 2-chlorobenzaldehyde, and 2-bromobenzaldehyde, respectively, and afforded **3j**, **3k**, and **3l** in lower yields and poor stereoselectivities (Table 2, entries 10−12). In particular, this process was efficient for cinnamaldehydes and afforded the desired products **3m** and **3n** in good yields with excellent diastereoselctivities (Table 2, entries 13 and 14). Notably, heteroaromatic *O*-pivaloylated *N*-galactosylimine **2o** was reacted under optimized reaction conditions with (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1**, and the desired *α*-aminophosphinate **3o** was obtained in 51% yield with poor stereoselectivity (Table 2, entry 15). The bulky 2-naphthylimine **2p** could also afford the corresponding product **3p** in high yield with good selectivity (Table 2, entry 16). Furthermore, the reaction of aliphatic aldehyde derived Schiff base **2** with (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** led to the product in very low yield, and only anomerization and decomposition occurred (Table 2, entry 17).

The absolute configuration at the phosphorus atom of the product **3d** from *O*-pivaloylated *N*-galactosyl-4-chlorophenyl imine **2d** with (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** was determined unambiguously by X-ray analysis (see the details in Supporting Information),[21] showing that this phospha-Mannich reaction takes place with retention of the configuration at phosphorus. The structure shows that the relative configuration of *β*-*N*-glycoside-*α*-aminophosphinate main product can be assigned as Gala$_\beta S_c S_p$Men$_L$. This illustrates that in this novel reaction high diastereoselectivity of both *α*-C and P were realized simultaneously, supporting the stereogenic nature of phosphorus atom of *α*-aminophosphinates. To confirm the efficient removal of the auxiliary, compound **3a** was treated with a solution of hydrochloric acid in methanol to give **4a** in 86% yield, which maintains excellent diastereoselectivity (Scheme 2).

Scheme 2. Removal of the Chiral Auxiliary of 3a



To explore the mechanism, some control experiments were carried out. Under the identified conditions, (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** added to *N*-benzylbenzylimine **5** to generate two diastereoisomers with a diastereomeric ratio (dr) of 1:1 in 75% yield (Scheme 3a). When the enantiomerically enriched (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** was resubjected to the reaction conditions in the absence of imine **5** for 24 h, no racemization was observed. The treatment of the diastereoisomeric mixture [(R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1**: (S_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** = 2.27:1] with 2-naphthyl imine **2p** under the standard reaction conditions provided two stereoisomers **3p** and **3p′**. In the ^{31}P NMR spectra, the corresponding peaks were observed at 35.23 and 37.39 ppm, representing Gala$_\beta S_c S_p$Men$_L$

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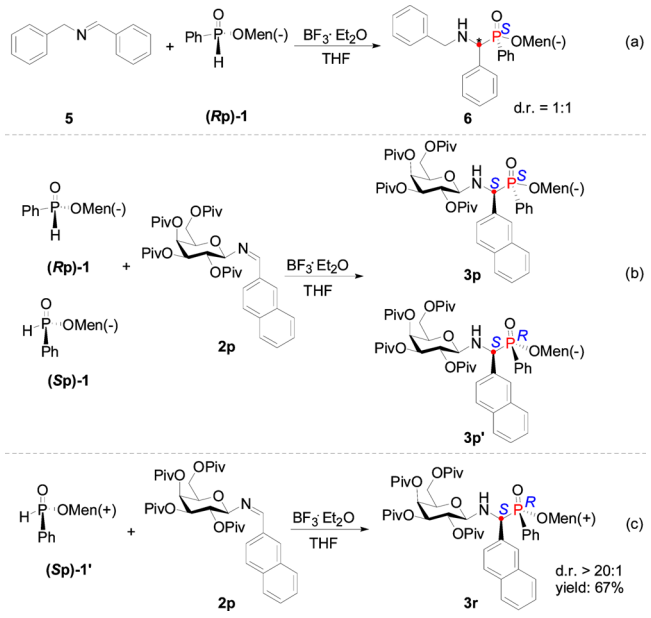
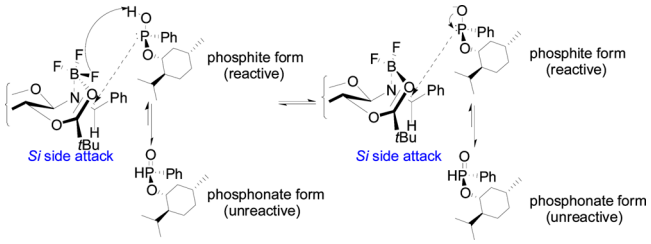
Scheme 3. Investigation of the Mechanism of the Phospha-Mannich Reaction



and Gala$_\beta S_c R_p$Men$_L$ in a ratio of 1.48:1, respectively (Scheme 3, b). In a separate experiment, (S_p)-*O*-(+)-menthyl *H*-phenylphosphinate **1′** reacted with 2-naphthyl imine **2p** and gave the desired product **3r** in 67% yield with excellent diastereoselectivity (Scheme 3c and Table 2, entry 18). These results indicated that high diastereoselectivity was determined by the combination of (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** and *O*-pivaloylated *N*-galactosylimine **2**. The chiral imine **2** is the major controlling element in the phospha-Mannich reaction, and the stereoselectivity could be modulated by double-asymmetric induction.

According to these observations, we can propose the following models as an explanation for the diastereoselectivity of the P−C bond formation as shown in Scheme 4. The

Scheme 4. Proposed Reaction Mechanism



diastereoselectivity of the Gala$_\beta S_c S_p$Men$_L$-configured diastereomer of **3** at α-C position of phosphinate is the result of the preferential formation of the transition state corresponding to an attack of (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** from the *Si* side of (*E*)-*N*-galactosylaldimines **2**. In the transition state, the boron atom has tetra coordination to the front side coordinating the imine nitrogen and the carbonyl oxygen (C-2) of the pivaloyloxy group, and one of the three fluorines may be removed when (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** is introduced. It appears that the imine·BF_3 complex maintains the *H*-eclipsed conformation where the chelation by the auxiliary's pivaloyl group inhibits rotation along the N−C* bond. The presence of the bulky pivaloyl group forces the S_N2'-type attack of (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** from the back side of the imine to be initiated.

It is suggested that the OH moiety of (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** is important in determining the high diastereoselectivity since the required tautomeric equilibrium liberates the P(III) phosphonous form from the P(V) phosphinic form. From these results, this hypothesis would explain the course of the main isomer synthesis. The mechanism indicates that the Piv4Gala group has a significant role in controlling the regio- and stereoselectivity of (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** to *N*-galactosylimines **2**.

CONCLUSION

In conclusion, we have described a convenient and efficient synthesis protocol for preparation of adjacent P,C-stereogenic β-*N*-glycosidic linked α-aminophosphinates in high yields with high diastereoselectivities, employing $BF_3{\cdot}Et_2O$ as the promoter and both (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** and *O*-pivaloylated *N*-galactosylimine **2** for double stereodifferentiation by means of phospha-Mannich reactions. *O*-Pivaloylated *N*-galactosylimine **2** is an effective stereodifferentiating tool in this reaction, and boron trifluoride presumably forms a tetracoordination intermediate that induces the *S* configuration at the Cα center by attack at the sterically less hindered the *Si* side of the imine. Further efforts on the application of the P-stereogenic phosphinate as a catalyst in asymmetric reactions are current underway in our laboratory and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an inert atmosphere of nitrogen and in oven-dried glassware with magnetic stirring. Anhydrous THF was distilled from sodium. Flash chromatography was performed with silica gel (particle size 10−40 μm). ^{1}H, ^{13}C, and ^{31}P NMR spectra were obtained in $CDCl_3$ using 300 MHz (300 MHz for ^{1}H, 75 MHz for ^{13}C, 100 MHz for ^{31}P) and 400 MHz (400 MHz for ^{1}H, 162 MHz for ^{13}C, 121 MHz for ^{31}P) spectrometers. Chemical shifts are reported in ppm downfield from internal $Si(CH_3)_4$ and external 85% H_3PO_4, respectively. NMR data are reported as follows: chemical shift, peak information (br = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Data collections for crystal structure were determined on an X-ray diffractometer. High-resolution mass spectra (HRMS) were obtained using an (ESI) mass spectrometer (TOF). Melting points were determined on a melting apparatus without correction.

General Procedure for the Preparation of Optically Pure (R_p)-(−)-Menthyl *H*-Phenylphosphinate 1 and (S_p)-(+)-Menthyl *H*-Phenylphosphinate 1′.[19] The mixture of (−)-menthol (20 g, 128 mmol) and pyridine (10.3 mL, 128 mmol) in Et_2O (40 mL) was added dropwise with stirring to a $PhPCl_2$ (17.4 mL, 128 mmol) solution in Et_2O (20 mL) at 0 °C and then stirred at room temperature overnight. Water (3 mL, 167 mmol) was added, and the reaction mixture was washed with water and extracted with hexane. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Recrystallization of the mixture in hexane (twice) at −30 °C gave pure (R_p)-(−)-menthyl hydrogenophenylphosphinate **1** as a white crystal (4.18 g, 23% yield, R_P/S_P > 99/1). (S_p)-(+)-Menthyl hydrogenophenylphosphinate **1′** was prepared similarly from $PhPCl_2$ and (+)-menthol.

(R_p)-(−)-Menthyl H-phenylphosphinate 1: $[\alpha]_D^{25}$ = −35.6 (*c* = 2.0, CH_2Cl_2); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.74; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (dd, *J* = 13.7, 6.7 Hz, 6H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.99−1.10 (m, 2H), 1.24 (dd, *J* = 23.3, 12.0 Hz, 1H), 1.43−1.49 (m, 2H), 1.66−1.72 (m, 2H), 2.17−2.24 (m, 2H), 4.29 (qd, *J* = 10.5, 4.5

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Hz, 1H), 7.51 (td, J = 7.4, 3.5 Hz, 2H), 7.58−7.61 (m, 1H), 7.66 (d, J = 553.0 Hz, 1H), 7.76−7.81 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.8, 21.1, 21.9, 23.0, 25.8, 31.7, 34.0, 43.6, 48.7 (d, J = 6.1 Hz), 79.0 (d, J = 7.3 Hz), 128.7 (d, J = 14.0 Hz), 130.7 (d, J = 11.8 Hz), 133.0 (d, J = 2.4 Hz).

(S_p)-(+)-Menthyl H-phenylphosphinate 1′: $[\alpha]_D^{25}$ = +35.3 (c = 2.0, CH_2Cl_2); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.71; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.99−1.10 (m, 2H), 1.20−1.29 (m, 1H), 1.43−1.49 (m, 2H), 1.66−1.72 (m, 2H), 2.17−2.24 (m, 2H), 4.29 (qd, J = 10.4, 4.3 Hz, 1H), 7.66 (d, J = 553.0 Hz, 1H), 7.50−7.61 (m, 3H), 7.78 (dd, J = 13.8, 7.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.8, 21.0, 21.9, 22.9, 25.8, 31.6, 33.9, 43.5, 48.7 (d, J = 6.2 Hz), 78.9 (d, J = 7.3 Hz), 128.7 (d, J = 14.0 Hz), 130.6 (d, J = 11.7 Hz), 132.9 (d, J = 2.7 Hz).

General Procedure for the Preparation of *O*-Pivaloylated *N*-Galactosylimine 2. To a stirred solution of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine[20] (0.515 g, 1 mmol) and aldehyde (1.3 mmol) in 2-propanol (2.5 mL) were added 2−3 drops of acetic acid, and the mixture was stirred at room temperature for about 0.5 h. The appearance of a precipitate from the solution indicated the formation of **2**. The mixture was filtered off, and the precipitate was washed with ice-cold 2-propanol and dried under reduced pressure. *N*-Galactosylaldimine **2** was isolated as a colorless solid.

General Procedure for the Preparation of *N*-Galactosyl α-Aminoalkylphosphinates 3. To a stirred solution of *N*-galactosylaldimine **2** (0.2 mmol) in THF (2 mL) were added (R_p)-(−)-menthyl hydrogenophenylphosphinate **1** (0.084 g, 0.3 mmol) and $BF_3{\cdot}Et_2O$ (0.057 g, 0.4 mmol) at 0 °C, and the mixture was stirred at room temperature for 12 h. After completion of the reaction, the mixture was diluted with an aqueous saturated solution of sodium bicarbonate (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to yield the crude products **3**. The residue was purified by column chromatography on silica gel [petroleum ether/ethyl acetate, 5:1 (v/v)] to provided pure compounds **3**.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](phenyl)-phosphinate (**3a**):* white solid (149.6 mg, 85% yield); mp 115−117 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.38; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 1.09 (s, 9H), 1.11 (s, 9H), 1.18 (s, 11H), 1.27 (s, 11H), 1.46 (dd, J = 19.4, 7.9 Hz, 1H), 1.57−1.73 (m, 2H), 1.79 (d, J = 11.8 Hz, 1H), 2.10−2.18 (m, 1H), 2.69 (dd, J = 12.5, 6.5 Hz, 1H), 3.66 (t, J = 6.5 Hz, 1H), 3.82 (dd, J = 12.5, 8.4 Hz, 1H), 3.95 (dd, J = 11.1, 6.5 Hz, 1H), 4.02 (dd, J = 11.1, 7.0 Hz, 1H), 4.42 (m, 1H), 4.69 (d, J = 19.7 Hz, 1H), 5.00 (dd, J = 10.2, 3.1 Hz, 1H), 5.02−5.09 (m, 1H), 5.32 (d, J = 2.5 Hz, 1H), 7.07−7.19 (m, 4H), 7.19−7.25 (m, 1H), 7.28−7.34 (m, 2H), 7.43−7.54 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.9, 21.3, 21.9, 23.0, 25.9, 27.1, 27.3, 31.5, 34.1, 38.7, 38.8, 39.1, 43.1, 48.8 (d, J = 5.4 Hz), 59.3 (d, J = 105.5 Hz), 61.7, 67.4, 68.8, 71.4, 71.7, 77.8 (d, J = 7.8 Hz), 85.4 (d, J = 14.6 Hz), 127.7, 127.8, 127.9, 129.3 (d, J = 5.2 Hz), 130.4, 132.1, 132.8 (d, J = 9.0 Hz,), 133.6 (d, J = 5.7 Hz), 176.9, 177.1, 177.4, 177.9; HRMS (ESI) m/z calcd for $C_{49}H_{75}NO_{11}P$ $[M + H]^+$ 884.5072, found 884.5069.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](4-methylphenyl)phosphinate (**3b**):* white solid (130.2 mg, 73% yield); mp 181−183 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.50; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, J = 6.5 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 1.10 (m, 18H), 1.18 (s, 11H), 1.26 (s, 11H, 1.43−1.48 (m, 1H), 1.60−1.69 (m, 2H), 1.78 (d, J = 11.9 Hz, 1H), 2.09−2.13 (m, 1H), 2.30 (d, J = 1.9 Hz, 3H), 2.65 (dd, J = 12.5, 6.2 Hz, 1H), 3.65 (t, J = 6.7 Hz, 1H), 3.81 (dd, J = 12.5, 8.4 Hz, 1H), 3.95 (dd, J = 11.1, 6.4 Hz, 1H), 4.01 (dd, J = 11.1, 7.1 Hz, 1H), 4.39−4.42 (m, 1H), 4.65 (d, J = 19.4 Hz, 1H), 4.99 (dd, J = 10.2, 3.2 Hz, 1H), 5.00−5.06 (m, 1H), 5.31 (d, J = 2.3 Hz, 1H), 6.97−7.01 (m, 4H), 7.29−7.35 (m, 2H), 7.44−7.53 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.9, 21.2 (d, J = 11.5 Hz), 21.9, 23.0, 25.9, 27.1, 27.1, 27.2, 29.7, 31.5, 34.1, 38.7, 38.8, 39.1, 43.1, 48.7 (d, J = 5.3 Hz), 59.1 (d, J = 106.8 Hz), 61.8, 67.3, 68.8, 71.3, 71.7, 77.7 (d, J = 7.5 Hz), 85.3 (d, J = 14.8 Hz), 127.7 (d, J = 12.7 Hz), 128.6, 129.2 (d, J = 5.4 Hz), 130.3 (d, J = 6.1 Hz), 132.0, 132.8 (d, J = 9.0 Hz), 137.6, 176.9, 177.1, 177.4, 177.9; HRMS (ESI) m/z calcd for $C_{50}H_{77}NO_{11}P$ $[M + H]^+$ 898.5229, found 898.5227.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](4-fluorophenyl)phosphinate (**3c**):* white solid (152.5 mg, 85% yield); mp 176−178 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.16 (d, J = 4.7 Hz); ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 1.10 (d, J = 6.7 Hz, 18H), 1.18 (s, 9H), 1.26−1.31 (m, 11H), 1.42−1.48 (m, 1H), 1.61−1.65 (m, 2H), 1.71−1.78 (m, 3H), 2.06−2.09 (m, 1H), 2.68 (dd, J = 12.5, 6.6 Hz, 1H), 3.66 (t, J = 6.6 Hz, 1H), 3.78 (dd, J = 12.4, 7.8 Hz, 1H), 3.94 (dd, J = 11.4, 6.9 Hz, 1H), 4.02 (dd, J = 11.1, 7.1 Hz, 1H), 4.39−4.42 (m, 1H), 4.66 (d, J = 19.3 Hz, 1H), 5.02−5.06 (m, 2H), 5.32 (s, 1H), 6.86 (t, J = 8.4 Hz, 2H), 7.08−7.09 (m, 2H), 7.27−7.34 (m, 2H), 7.46−7.51 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 16.0, 21.4, 22.0, 23.2, 26.0, 27.2, 27.4, 31.6, 34.1, 38.85, 38.89, 39.2, 43.2, 48.9, 58.6 (d, J = 106.7 Hz), 61.8, 67.4, 68.9, 71.4, 71.9, 78.1 (d, J = 6.7 Hz), 85.6 (d, J = 9.3 Hz), 115.1, 128.0 (d, J = 12.7 Hz), 130.8, 130.9, 131.0, 132.4, 132.9 (d, J = 9.0 Hz), 176.9, 177.2, 177.5, 178.0; HRMS (ESI): m/z calcd for $C_{49}H_{74}NO_{11}PF$ $[M + H]^+$ 902.4978, found 902.4980.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](4-chlorophenyl)phosphinate (**3d**):* white solid (156.5 mg, 85% yield); mp 233−235 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.83; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 5.7 Hz, 18H), 1.18 (s, 11H), 1.26 (s, 11H), 1.43−1.45 (m, 1H), 1.61−1.78 (m, 3H), 2.03−2.08 (m, 1H), 2.69 (dd, J = 12.5, 6.7 Hz, 1H), 3.66 (t, J = 6.7 Hz, 1H), 3.77 (dd, J = 12.5, 7.8 Hz, 1H), 3.94 (dd, J = 11.1, 6.5 Hz, 1H), 4.01 (dd, J = 11.1, 7.0 Hz, 1H), 4.41 (dd, J = 6.8, 4.2 Hz, 1H), 4.65 (d, J = 19.7 Hz, 1H), 4.98−5.06 (m, 2H), 5.32 (d, J = 1.9 Hz, 1H), 7.03−7.04 (m, 2H), 7.05−7.06 (m, 2H), 7.14−7.16 (m, 2H), 7.47−7.51 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.9, 21.2, 21.9, 23.0, 25.9, 27.1, 27.2, 31.5, 34.0, 38.7, 38.8, 39.1, 43.1, 48.7 (d, J = 5.8 Hz, CH), 58.7 (d, J = 105.4 Hz), 61.6, 67.2, 68.8, 71.3, 71.7, 78.0 (d, J = 7.6 Hz), 85.4 (d, J = 14.8 Hz), 127.8, 128.0, 128.1 (d, J = 2.5 Hz), 130.5 (d, J = 5.0 Hz), 132.3 (d, J = 6.0 Hz), 132.7 (d, J = 9.6 Hz), 133.8 (d, J = 4.0 Hz), 176.8, 177.1, 177.4, 177.9; HRMS (ESI) m/z calcd for $C_{49}H_{74}ClNO_{11}P$ $[M + H]^+$ 918.4683, found 918.4687.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](4-bromophenyl)phosphinate (**3e**):* white solid (169.3 mg, 88% yield); mp 193−195 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.63; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 1.10 (d, J = 7.6 Hz, 20H), 1.18 (s, 11H), 1.26 (s, 9H), 1.42 (s, 1H), 1.61−1.66 (m, 2H), 1.77 (d, J = 11.7 Hz, 1H), 2.04−2.07 (m, 1H), 2.69 (dd, J = 12.5, 6.8 Hz, 1H), 3.67 (t, J = 6.5 Hz, 1H), 3.78 (dd, J = 12.1, 7.4 Hz, 1H), 3.94 (dd, J = 11.1, 6.4 Hz, 1H), 4.01 (dd, J = 11.1, 7.0 Hz, 1H), 4.41 (dd, J = 6.5, 4.3 Hz, 1H), 4.64 (d, J = 19.7 Hz, 1H), 5.02−5.06 (m, 2H), 5.33 (s, 1H), 6.99−7.01 (m, 2H), 7.29−7.35 (m, 4H), 7.48−7.52 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.9, 21.2, 21.9, 23.0, 25.9, 27.1, 27.2, 27.2, 31.5, 34.0, 38.7, 38.8, 39.0, 43.1, 48.7 (d, J = 5.4 Hz), 58.7 (d, J = 105.0 Hz), 61.6, 67.2, 68.8, 71.3, 71.8, 78.0 (d, J = 7.7 Hz), 85.4 (d, J = 14.3 Hz), 121.9 (d, J = 4.2 Hz), 127.9 (d, J = 12.7 Hz), 128.7, 130.0, 130.8 (d, J = 5.0 Hz), 131.1, 132.3, 132.7 (d, J = 9.0 Hz), 176.7, 177.0, 177.3, 177.8; HRMS (ESI) m/z calcd for $C_{49}H_{74}BrNO_{11}P$ $[M + H]^+$ 962.4177, found 962.4175.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](4-nitrophenyl)phosphinate (**3f**):* white solid (151.1 mg, 81% yield); mp 245−247 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.98; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 13.3 Hz, 18H), 1.17 (s, 9H), 1.27 (s, 11H), 1.43−1.47 (m, 2H), 1.61−1.66 (m, 3H), 1.70−1.76 (m, 1H), 2.04 (s, 1H), 2.81 (dd, J = 12.5, 7.6 Hz, 1H), 3.66 (t, J = 6.6 Hz, 1H), 3.75 (dd, J = 12.5, 8.3 Hz, 1H), 3.93 (dd, J = 11.1, 6.5 Hz, 1H), 4.02 (dd, J = 11.1, 6.9 Hz, 1H), 4.42−4.45 (m, 1H), 4.81 (d, J = 21.2 Hz,

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1H), 5.01 (dd, J = 10.2, 3.0 Hz, 1H), 5.03−5.06 (m, 1H), 5.33 (d, J = 3.0 Hz, 1H), 7.30−7.36 (m, 4H), 7.44−7.53 (m, 3H), 8.03−8.05 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.9, 21.2, 21.9, 23.1, 26.0, 27.2, 27.3, 27.3, 31.6, 34.0, 38.8, 38.9, 39.1, 43.1, 48.7 (d, J = 5.3 Hz), 59.2 (d, J = 101.7 Hz), 61.6, 67.1, 68.9, 71.1, 71.9, 78.6 (d, J = 7.3 Hz), 85.7 (d, J = 13.6 Hz), 123.1 (d, J = 2.1 Hz), 128.1 (d, J = 12.8 Hz), 129.8 (d, J = 4.5 Hz), 132.7 (d, J = 8.7 Hz), 142.1 (d, J = 5.4 Hz), 147.6 (d, J = 4.1 Hz), 176.8, 177.1, 177.4, 177.9; HRMS (ESI) m/z calcd for $C_{49}H_{74}N_2O_{13}P$ $[M + H]^+$ 929.4923, found 929.4933.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](4-cyanophenyl)phosphinate (**3g**):* white solid (152.4 mg, 84% yield); mp 231−233 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.12; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 8.6 Hz, 18H), 1.17 (s, 11H), 1.26 (s, 9H), 1.43−1.45 (m, 2H), 1.61−1.68 (m, 3H), 1.76 (d, J = 11.9 Hz, 1H), 2.00−2.05 (m, 1H), 2.76 (dd, J = 12.5, 7.6 Hz, 1H), 3.66 (t, J = 6.8 Hz, 1H), 3.74 (dd, J = 12.5, 7.9 Hz, 1H), 3.92 (dd, J = 11.1, 6.6 Hz, 1H), 4.01 (dd, J = 11.1, 6.9 Hz, 1H), 4.42 (dd, J = 6.8, 4.1 Hz, 1H), 4.74 (d, J = 20.8 Hz, 1H), 4.99−5.07 (m, 2H), 5.33 (d, J = 1.9 Hz, 1H, 7.23−7.25 (m, 2H), 7.32−7.37 (m, 2H), 7.46−7.53 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.9, 21.2, 21.9, 23.0, 26.0, 27.1, 27.2, 31.5, 33.9, 38.7, 38.8, 39.1, 43.1, 48.7 (d, J = 5.5 Hz), 59.2 (d, J = 102.3 Hz), 61.5, 67.1, 68.8, 71.2, 71.8, 78.5 (d, J = 7.6 Hz), 85.6 (d, J = 13.6 Hz), 111.7, 118.7, 128.0 (d, J = 12.8 Hz), 129.7 (d, J = 5.0 Hz), 131.6, 132.6 (d, J = 9.1 Hz), 140.0, 176.8, 177.1, 177.4, 177.9; HRMS (ESI) m/z calcd for $C_{50}H_{74}N_2O_{11}P$ $[M + H]^+$ 909.5025, found 909.5022.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](3-methylphenyl)phosphinate (**3h**):* yellow oil (135.1 mg, 75% yield); ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.59 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 1.10 (d, J = 8.3 Hz, 18H), 1.18 (s, 9H), 1.23−1.31 (m, 11H), 1.31−1.43 (m, 2H), 1.59−1.66 (m, 3H), 1.69−1.70 (m, 1H), 2.11−2.14 (m, 1H), 2.18 (s, 3H), 2.67 (dd, J = 12.5, 6.4 Hz, 1H), 3.66 (t, J = 6.6 Hz, 1H), 3.82 (dd, J = 12.5, 8.3 Hz, 1H), 3.95 (dd, J = 11.1, 6.4 Hz, 1H), 4.01 (dd, J = 11.1, 7.1 Hz, 1H), 4.40−4.43 (m, 1H), 4.65 (d, J = 19.6 Hz, 1H), 4.98−5.07 (m, 2H), 5.32 (d, J = 2.3 Hz, 1H), 6.88−6.93 (m, 2H), 7.03−7.05 (m, 2H), 7.32−7.33 (m, 2H), 7.45−7.50 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.9, 21.3, 21.9, 23.0, 25.9, 27.1, 27.2, 29.7, 31.5, 34.1, 38.7, 38.8, 39.1, 43.1, 48.8 (d, J = 5.4 Hz), 59.3 (d, J = 104.4 Hz), 61.8, 67.4, 68.8, 71.4, 71.7, 77.7 (d, J = 8.4 Hz), 85.4 (d, J = 14.7 Hz), 126.5, 127.7 (d, J = 12.0 Hz), 128.7, 129.2, 129.9 (d, J = 6.0 Hz), 132.0, 132.8 (d, J = 9.3 Hz), 133.4 (d, J = 5.6 Hz), 137.4, 176.8, 177.1, 177.4, 177.9; HRMS (ESI) m/z calcd for $C_{50}H_{77}NO_{11}P$ $[M + H]^+$ 898.5229, found 898.5224.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](4-methoxyphenyl)phosphinate (**3i**):* yellow oil (141.5 mg, 77% yield); ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.50; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (d, J = 6.5 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 1.11 (t, J = 7.1 Hz, 18H), 1.21 (d, J = 8.6 Hz, 11H), 1.28 (d, J = 2.7 Hz, 11H), 1.47 (dd, J = 18.2, 7.2 Hz, 1H), 1.62−1.71 (m, 2H), 1.80 (d, J = 7.3 Hz, 1H), 2.11−2.14 (m, 1H), 2.66 (dd, J = 12.5, 5.9 Hz, 1H), 3.67 (t, J = 6.6 Hz, 1H), 3.80 (s, 3H), 3.83 (dd, J = 8.5, 4.2 Hz, 1H), 3.97 (dd, J = 11.1, 6.4 Hz, 1H), 4.04 (dd, J = 11.1, 7.0 Hz, 1H), 4.41−4.42 (m, 1H), 4.64 (d, J = 18.9 Hz, 1H), 5.01 (dd, J = 10.2, 3.1 Hz, 1H), 5.03−5.08 (m, 1H), 5.34 (d, J = 2.2 Hz, 1H), 6.73 (t, J = 8.1 Hz, 2H), 7.01−7.03 (m, 2H), 7.35 (td, J = 7.8, 3.5 Hz, 2H), 7.48−7.54 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.9, 21.3, 21.9, 23.0, 25.9, 27.10, 27.13, 27.2, 27.3, 31.5, 34.1, 38.7, 39.1, 43.1, 48.7 (d, J = 5.6 Hz), 55.2, 58.6 (d, J = 107.7 Hz), 61.7, 67.3, 68.8, 71.4, 71.8, 77.7 (d, J = 8.0 Hz), 85.3 (d, J = 14.9 Hz), 113.4, 125.2 (d, J = 6.2 Hz), 127.8 (d, J = 12.6 Hz), 129.2, 130.4 (d, J = 5.3 Hz), 132.0 (d, J = 2.7 Hz), 132.8 (d, J = 9.0 Hz), 176.9, 177.1, 177.4, 177.9; HRMS (ESI) m/z calcd for $C_{50}H_{77}NO_{12}P$ $[M + H]^+$ 914.5178, found 914.5174.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl-α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](2-fluorophenyl)phosphinate (**3j**):* white solid (113.8 mg, 63% yield); mp 86−88 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.70 (d, J = 4.7 Hz); ^1H NMR (400 MHz, $CDCl_3$) δ 0.68 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.5 Hz, 3H), 0.81 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 2.3 Hz, 18H), 1.20 (s, 9H), 1.25−1.27 (m, 11H), 1.27−1.29 (m, 2H), 1.60−1.63 (m, 2H), 1.70−1.73 (m, 3H), 2.64−2.69 (m, 1H), 3.67 (t, J = 6.7 Hz, 1H), 3.76−3.87 (m, 3H), 4.30 (dd, J = 6.8, 4.2 Hz, 1H), 4.96−5.07 (m, 3H), 5.30 (d, J = 1.9 Hz, 1H), 7.02 (dt, J = 15.2, 8.6 Hz, 2H), 7.04−7.07 (m, 2H), 7.22−7.25 (m, 2H), 7.44−7.46 (m, 1H), 7.69−7.74 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.4, 21.2, 21.8, 22.7, 25.2, 27.1, 27.1, 27.2, 31.4, 33.9, 38.7, 39.0, 43.0, 48.7 (d, J = 5.5 Hz), 50.4 (d, J = 107.7 Hz), 61.5, 67.1, 68.6, 71.4, 71.5, 77.6 (d, J = 7.6 Hz), 86.3 (d, J = 12.3 Hz), 115.0 (d, J = 22.4 Hz), 123.6, 128.0 (d, J = 12.7 Hz), 129.2, 130.7, 132.3, 132.7 (d, J = 9.3 Hz), 176.7, 177.1, 177.2, 178.0; HRMS (ESI) m/z calcd for $C_{49}H_{74}FNO_{11}P$ $[M + H]^+$ 902.4978, found 902.4981.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](2-chlorophenyl)phosphinate (**3k**):* yellow oil (29.0 mg, 16% yield); ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.88; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (d, J = 6.9 Hz, 3H), 0.69−0.73 (m, 6H), 1.06 (s, 9H), 1.17 (s, 9H), 1.21 (s, 9H), 1.26 (s, 11H), 1.42 (d, J = 7.8 Hz, 2H), 1.55 (d, J = 11.0 Hz, 2H), 1.62 (d, J = 12.3 Hz, 1H), 1.78−1.86 (m, 2H), 2.73 (t, J = 9.3 Hz, 1H), 3.64 (t, J = 6.7 Hz, 1H), 3.67−3.71 (m, 1H), 3.72−3.76 (m, 1H), 3.93−4.03 (m, 1H), 4.15−4.25 (m, 1H), 4.44 (dd, J = 32.7, 6.0 Hz, 1H), 4.86−4.99 (m, 2H), 5.26 (d, J = 2.7 Hz, 1H), 7.10−7.23 (m, 2H), 7.33−7.40 (m, 2H), 7.42−7.48 (m, 2H), 7.53−7.61 (m, 1H), 7.73−7.81 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.3, 21.2, 21.8, 22.6, 24.9, 27.06, 27.10, 27.12, 27.2, 31.4, 33.9, 38.7, 38.7, 38.7, 39.0, 42.9, 48.7 (d, J = 5.6 Hz), 54.0 (d, J = 106.6 Hz), 61.2, 67.0, 68.6, 71.3, 71.4, 77.5 (d, J = 7.8 Hz), 86.7 (d, J = 11.6 Hz), 126.4, 128.1 (d, J = 12.8 Hz), 128.8, 129.1, 130.2, 131.4, 132.4, 132.7 (d, J = 9.4 Hz), 133.8 (d, J = 4.8 Hz), 135.0 (d, J = 7.0 Hz), 176.7, 177.1, 177.2, 177.9; HRMS (ESI) m/z calcd for $C_{49}H_{74}ClNO_{11}P$ $[M + H]^+$ 918.4683, found 918.4682.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](2-bromophenyl)phosphinate (**3l**):* white solid (48.3 mg, 25% yield); mp 76−78 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.88; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (d, J = 6.9 Hz, 3H), 0.71−0.74 (m, 6H), 1.07−1.08 (m, 18H), 1.18−1.22 (m, 11H), 1.22 (s, 9H), 1.27−1.30 (m, 2H), 1.42−1.44 (m, 1H), 1.55−1.65 (m, 3H), 1.89−1.92 (m, 1H), 2.72−2.78 (m, 1H), 3.65−3.68 (m, 1H), 3.70−3.73 (m, 1H), 3.75−3.81 (m, 1H), 3.98−4.08 (m, 1H), 4.21−4.24 (m, 1H), 4.88−4.99 (m, 2H), 5.15−5.23 (m, 1H), 5.28 (d, J = 3.0 Hz, 1H), 7.12−7.22 (m, 2H), 7.40−7.42 (m, 1H), 7.45−7.50 (m, 2H), 7.54−7.61 (m, 2H), 7.79−7.83 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.3, 21.2, 21.8, 22.5, 24.9, 27.1, 27.1, 27.2, 31.4, 33.9, 38.7, 38.7, 39.0, 42.9, 48.7 (d, J = 5.4 Hz), 56.7 (d, J = 107.4 Hz), 61.0, 66.9, 68.6, 71.2, 71.4, 77.4 (d, J = 8.1 Hz), 86.6 (d, J = 11.6 Hz), 125.7 (d, J = 7.5 Hz), 127.0, 128.1 (d, J = 12.7 Hz), 129.1, 130.2, 131.6 (d, J = 3.7 Hz), 132.4, 132.7 (d, J = 9.7 Hz), 135.5, 176.7, 177.1, 177.2, 177.9; HRMS (ESI) m/z calcd for $C_{49}H_{74}BrNO_{11}P$ $[M + H]^+$ 962.4177, found 962.4174.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](3-phenylallyl)phosphinate (**3m**):* white solid (145.6 mg, 80% yield); mp 118−120 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.77; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, J = 6.3 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 1.09 (s, 9H), 1.15 (s, 9H), 1.25 (s, 9H), 1.32−1.35 (m, 11H), 1.48−1.54 (m, 2H), 1.67−1.76 (m, 3H), 1.86−1.89 (m, 1H), 2.30−2.33 (m, 1H), 2.48−2.53 (m, 1H), 3.87 (t, J = 6.6 Hz, 1H), 4.04 (dd, J = 10.8, 7.0 Hz, 1H), 4.11−4.15 (m, 2H), 4.32 (dd, J = 20.0, 8.0 Hz, 1H), 4.49−4.52 (m, 1H), 5.04−5.16 (m, 2H), 5.43 (d, J = 1.6 Hz, 1H), 5.72−5.79 (m, 1H), 6.61 (dd, J = 15.9, 4.9 Hz, 1H), 7.26−7.37 (m, 5H), 7.48−7.49 (m, 2H), 7.57−7.59 (m, 1H), 7.80−7.82 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.9, 21.2, 21.9, 22.7, 23.0, 26.0, 27.0, 27.07, 27.12, 27.2, 29.7, 31.5, 34.0, 38.7, 38.7, 39.1, 43.2, 48.7 (d, J = 5.5 Hz), 57.8 (d, J = 107.2 Hz), 61.5, 67.2, 68.6, 71.3, 71.7, 77.9 (d, J = 8.1 Hz), 85.7 (d, J = 14.9 Hz), 122.6 (d, J = 8.6 Hz), 126.4, 128.0 (d, J = 7.7 Hz), 128.1, 128.6, 129.7, 131.0, 132.2 (d, J = 2.0 Hz), 132.6 (d, J = 9.0 Hz), 135.3 (d, J = 12.4 Hz),

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136.4, 176.8, 177.0, 177.2, 177.9; HRMS (ESI) m/z calcd for $C_{51}H_{77}NO_{11}P$ $[M + H]^+$ 910.5229, found 910.5226.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](4-chlorophenylallyl)phosphinate (**3n**):* white solid (148.3 mg, 79% yield); mp 125−127 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.53; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 1.03 (s, 9H), 1.09 (s, 9H), 1.19 (s, 9H), 1.26 (s, 9H), 1.42−1.47 (m, 4H), 1.67−1.72 (m, 4H), 2.23−2.25 (m, 1H), 2.44 (dd, J = 12.4, 7.1 Hz, 1H), 3.97 (dd, J = 10.4, 7.4 Hz, 2H), 4.07−4.09 (m, 2H), 4.30 (dd, J = 14.2, 7.4 Hz, 1H), 4.44 (dd, J = 6.7, 4.1 Hz, 1H), 5.04 (dt, J = 19.0, 8.6 Hz, 2H), 5.37 (d, J = 2.7 Hz, 1H), 5.69 (ddd, J = 15.8, 8.0, 5.5 Hz, 1H), 6.50 (dd, J = 16.0, 5.5 Hz, 1H), 7.12−7.14 (m, 2H), 7.42 (dt, J = 7.3, 3.7 Hz, 2H), 7.52−7.53 (m, 2H), 7.70−7.74 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.9, 19.2, 21.2, 21.8, 23.0, 25.6, 27.1, 27.2, 31.5, 34.0, 38.6, 38.7, 39.0, 43.2, 48.7 (d, J = 5.5 Hz), 64.3 (d, J = 129.0 Hz), 67.96, 68.02, 68.6, 71.3, 71.7, 78.0 (d, J = 5.3 Hz), 85.8 (d, J = 14.0 Hz), 123.5 (d, J = 6.5 Hz), 127.5, 128.0, 128.5 (d, J = 64.4 Hz), 129.7, 130.9, 132.3, 132.6 (d, J = 9.2 Hz), 133.6, 133.9 (d, J = 12.4 Hz), 134.9 (d, J = 3.7 Hz), 176.8, 177.0, 177.2, 177.9; HRMS (ESI) m/z calcd for $C_{51}H_{76}ClNO_{11}P$ $[M + H]^+$ 944.4839, found 944.4836.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](furyl)-phosphinate (**3o**):* yellow oil (88.8 mg, 51% yield); ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.01, 33.94; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, J = 6.5 Hz, 3H), 0.90−0.95 (m, 6H), 1.09−1.13 (m, 18H), 1.25 (d, J = 5.5 Hz, 11H), 1.30 (s, 11H), 1.46−1.53 (m, 1H), 1.64−1.73 (m, 2H), 1.85 (d, J = 11.5 Hz, 1H), 2.23−2.25 (m, 1H), 2.72−2.76 (m, 1H), 3.54 (t, J = 6.9 Hz, 1H), 3.74−3.78 (m, 1H), 3.83−3.88 (m, 1H), 4.00−4.14 (m, 1H), 4.18−4.22 (m, 1H), 4.40−4.43 (m, 1H), 4.72 (dd, J = 85.5, 11.7 Hz, 1H), 5.04−5.08 (m, 1H), 5.23−5.32 (m, 1H), 5.38−5.44 (m, 1H), 6.04−6.28 (m, 1H), 6.32 (s, 1H), 7.43−7.52 (m, 1H), 7.53−7.56 (m, 2H), 7.58−7.70 (m, 1H), 7.80−7.95 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.2,15.9, 21.3, 21.9, 22.5, 25.8, 27.01, 27.07, 27.12, 27.2, 31.5, 34.0, 38.6, 38.7, 38.8, 39.0, 43.2, 48.8 (d, J = 18.5 Hz), 52.5 (d, J = 117.4 Hz), 61.4, 65.8, 67.7, 68.1, 71.2, 77.6 (d, J = 7.6 Hz), 81.0 (d, J = 13.0 Hz), 109.8 (d, J = 6.3 Hz), 110.5 (d, J = 2.2 Hz), 110.6 (d, J = 7.0 Hz), 110.8, 127.8, 128.0 (d, J = 13.1 Hz), 132.6 (d, J = 9.1 Hz), 142.5 (d, J = 10.3 Hz), 147.1, 176.6, 176.8, 177.3, 177.6; HRMS (ESI) m/z calcd for $C_{47}H_{73}NO_{12}P$ $[M + H]^+$ 874.4865, found 874.4867.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](2-naphthyl)phosphinate (**3p**):* white solid (169.5 mg, 91% yield); mp 93−95 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.30; ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J = 6.9 Hz, 3H), 0.76 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 7.0 Hz, 3H), 1.08 (s, 9H), 1.16 (s, 9H), 1.18 (s, 9H), 1.27−1.30 (m, 10H), 1.43−1.46 (m, 2H), 1.60−1.68 (m, 4H), 1.79 (d, J = 11.8 Hz, 1H), 2.05−2.09 (m, 1H), 2.77 (dd, J = 12.6, 6.5 Hz, 1H), 3.61 (t, J = 6.7 Hz, 1H), 3.85 (dd, J = 12.3, 9.0 Hz, 1H), 3.94 (dd, J = 11.2, 6.4 Hz, 1H, 4.02 (dd, J = 11.2, 7.0 Hz, 1H), 4.42−4.46 (m, 1H), 4.85 (d, J = 19.4 Hz, 1H), 4.96 (dd, J = 10.3, 3.4 Hz, 1H), 5.07 (dd, J = 10.1, 9.0 Hz, 1H), 5.30 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.30 (td, J = 7.7, 3.6 Hz, 2H), 7.43−7.46 (m, 3H), 7.48−7.51 (m, 2H), 7.58−7.65 (m, 3H), 7.78−7.80 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.8, 21.2, 21.8, 23.0, 25.9, 27.09, 27.14, 27.2, 27.3, 31.5, 34.0, 38.7, 38.8, 39.1, 43.1, 48.7 (d, J = 5.7 Hz), 59.5 (d, J = 105.6 Hz), 61.8, 67.4, 68.8, 71.3, 71.8, 77.9 (d, J = 7.7 Hz), 85.4 (d, J = 14.3 Hz), 126.0, 126.9 (d, J = 3.7 Hz), 127.4, 127.6, 127.7 (d, J = 5.5 Hz), 127.9, 128.6 (d, J = 6.5 Hz), 130.4, 131.3 (d, J = 5.7 Hz), 132.1, 132.8 (d, J = 9.3 Hz), 176.8, 177.0, 177.4, 177.9; HRMS (ESI) m/z calcd for $C_{53}H_{77}NO_{11}P$ $[M + H]^+$ 934.5229, found 934.5226.

*(((1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-[(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl)amino](2-naphthyl)phosphinate (**3r**):* white solid (126 mg, 67% yield); mp 119−121 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 37.32; ^1H NMR (400 MHz, $CDCl_3$) δ 0.67 (d, J = 6.5 Hz, 3H, 0.91 (d, J = 6.9 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 1.07 (s, 9H), 1.12 (s, 9H), 1.18 (s, 9H), 1.30 (s, 10H), 1.30−1.43 (m, 3H), 1.56−1.59 (m, 1H), 1.64−1.70 (m, 3H), 2.35−2.39 (m, 1H), 2.96−2.98 (m, 1H), 3.54 (t, J = 6.7 Hz, 1H), 3.84 (t, J = 10.1 Hz, 1H), 3.95 (dd, J = 11.2, 6.2 Hz, 1H), 4.06 (dd, J = 11.2, 7.1 Hz, 1H), 4.38 (dd, J = 6.3, 4.4 Hz, 1H), 4.48−4.93 (m, 2H), 5.10−5.15 (m, 1H), 5.28 (d, J = 2.6 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H), 7.20−7.25 (m, 2H), 7.31−7.35 (m, 2H), 7.43−7.48 (m, 4H), 7.55−7.58 (m, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.80−7.82 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.6, 21.2, 21.8, 22.7, 25.8, 27.09, 27.13, 27.2, 27.3, 31.4, 33.9, 38.68, 38.72, 39.1, 43.2, 48.8 (d, J = 5.8 Hz), 59.5 (d, J = 109.2 Hz), 61.9, 67.4, 68.6, 71.5, 71.8, 77.8 (d, J = 7.6 Hz), 85.0 (d, J = 16.4 Hz), 126.1 (d, J = 3.0 Hz), 127.1 (d, J = 3.6 Hz), 127.3, 127.55 (d, J = 5.2 Hz), 127.64, 128.7 (d, J = 6.8 Hz), 130.0, 130.6, 131.4 (d, J = 7.4 Hz), 132.1, 133.0 (d, J = 20.3 Hz), 133.2 (d, J = 9.1 Hz), 176.9, 177.0, 177.1, 177.8; HRMS (ESI) m/z calcd for $C_{53}H_{77}NO_{11}P$ $[M + H]^+$ 934.5229, found 934.5231.

General Procedure for the Preparation of (((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-Amino(phenyl)-phosphinate 4a. A solution of compound **3a** (0.40 mmol) in dry methanol (5 mL) was treated with a freshly prepared (1.0 M) solution of HCl (0.62 mL). The solution was stirred for 2 days (TLC control). Then the mixture was filtered to give **4a** as a white solid in 86% yield.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenyl α-amino(phenyl)phosphinate (**4a**):* white solid (132.3 mg, 86% yield); mp 231−233 °C; ^{31}P NMR (162 MHz, DMSO) δ 30.92; ^1H NMR (400 MHz, DMSO) δ 0.34 (d, J = 6.6 Hz, 3H), 0.53 (d, J = 6.8 Hz, 3H), 0.62 (d, J = 6.4 Hz, 3H), 0.66−0.83 (m, 3H), 1.03 (s, 2H), 1.11−1.19 (m, 1H), 1.31 (d, J = 12.1 Hz, 1H), 1.44 (t, J = 11.3 Hz, 2H), 3.94 (d, J = 10.8 Hz, 1H), 5.12 (s, 1H), 7.44−7.45 (m, 2H), 7.61−7.62 (m, 3H), 7.73 (t, J = 7.2 Hz, 1H), 7.90−7.94 (m, 2H), 8.84 (s, 2H); HRMS (ESI) m/z calcd for $C_{23}H_{33}NO_2P$ $[M + H]^+$ 386.2243, found 386.2241.

General Procedure for the Preparation of (((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)phenylbenzyl α-Amino-(phenyl)phosphinate (6). A solution of *N*-benzylidene-1-phenyl-methanamine **5** (0.119 g, 0.2 mmol) in THF (2 mL) was cooled to 0 °C, and (R_p)-*O*-(−)-menthyl *H*-phenylphosphinate **1** (0.084 g, 0.3 mmol) was added. The mixture was stirred for 12 h at room temperature. Then an aqueous saturated solution of sodium bicarbonate (25 mL) was added, and the mixture was stirred at room temperature for 5 min. Then the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), and the organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo to yield the crude products **6**, which were purified by column chromatography on silica gel [petroleum ether/ethyl acetate, 6:1 (V/V)] to provide pure compounds **6**.

*(((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)oxy)phenylbenzyl α-amino(phenyl)phosphinate (**6**):* white solid (70.9 mg, 75% yield); mp 101−103 °C; ^{31}P NMR (162 MHz, $CDCl_3$) δ 35.65, 37.23; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (d, J = 6.5 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 7.1 Hz, 3H), 1.02−1.04 (m, 2H), 1.28−1.33 (m, 2H), 1.44−1.46 (m, 1H), 1.61−1.70 (m, 2H), 1.83 (d, J = 11.9 Hz, 1H), 2.36−2.40 (m, 2H), 3.54 (d, J = 13.2 Hz, 1H), 3.79 (d, J = 13.2 Hz, 1H), 4.13 (d, J = 17.4 Hz, 1H), 4.41−4.44 (m, 1H), 7.14−7.15 (m, 2H), 7.20−7.25 (m, 5H), 7.27−7.31 (m, 5H), 7.43−7.51 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 15.5, 21.2, 21.9, 22.7, 25.5, 31.5, 34.1, 43.2, 49.0 (d, J = 5.3 Hz), 51.4 (d, J = 15.1 Hz), 63.4 (d, J = 108.0 Hz), 77.5, 127.0, 127.4 (d, J = 3.4 Hz), 127.6, 127.7, 128.0 (d, J = 2.2 Hz), 128.3 (d, J = 4.7 Hz), 128.8 (d, J = 5.3 Hz), 130.0, 131.3, 131.9, 132.6 (d, J = 8.9 Hz), 135.5, 139.6; HRMS (ESI) m/z calcd for $C_{30}H_{39}NO_2P$ $[M + H]^+$ 476.2713, found 476.2719.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02877.

^{31}P NMR, ^1H and ^{13}C NMR spectra for all products (PDF)

X-ray data for compound **3d** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected reviews, see: (a) Montchamp, J. L. *Acc. Chem. Res.* **2014**, *47*, 77. (b) Dubrovina, N. V.; Börner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5883. (c) *Organophosphorus Reagents in Asymmetric Reactions*; Tang, C. C., Zhou, Z. H., Eds.; Nankai University Press: Tianjin, 2012. (d) *New Aspects in Phosphorus Chemistry*; Majoral, J. P., Ed.; Springer: Berlin, 2003; Vols. *1*−*5*. (e) *Organophosphorus Reagents*; Murphy, P. J., Ed.; Oxford University Press: Oxford, 2004. (f) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley Interscience: New York, 2000.

(2) For selected reviews, see: (a) Queffélec, C.; Petit, M.; Janvier, P.; Knight, D. A.; Bujoli, B. *Chem. Rev.* **2012**, *112*, 3777. (b) Baumgartner, T.; Réau, R. *Chem. Rev.* **2006**, *106*, 4681. (c) Dutartre, M.; Bayardon, J.; Jugé, S. *Chem. Soc. Rev.* **2016**, *45*, 5771.

(3) For selected examples, see: (a) *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*; Kamer, P. C. J., Leeuwen, P. W. N. M., Eds.; Wiley: 2012. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(4) For selected recent reviews, see: (a) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (b) Zhao, Q. Y.; Lian, Z.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 1724. (c) Wang, S. X.; Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Synlett* **2011**, *2011*, 2766. (d) Xie, P. Z.; Huang, Y. *Eur. J. Org. Chem.* **2013**, *2013*, 6213. (e) Gomez, C.; Betzer, J. F.; Voituriez, A.; Marinetti, A. *ChemCatChem* **2013**, *5*, 1055. (f) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927. (g) Rémond, E.; Jugé, S. *Chem. Today* **2014**, *32*, 49.

(5) (a) Spangler, L. A.; Mikolajczyk, M.; Burdge, E. L.; Kielbasinski, P.; Smith, H. C.; Lyzwa, P.; Fisher, J. D.; Omelańczuk, J. *J. Agric. Food Chem.* **1999**, *47*, 318. (b) Sato, T.; Ueda, H.; Nakagawa, K.; Bodor, N. *J. Org. Chem.* **1983**, *48*, 98. (c) Meyer, A.; Pourceau, G.; Vasseur, J. J.; Morvan, F. *J. Org. Chem.* **2010**, *75*, 6689.

(6) For recent examples, see: (a) Geer, A. M.; Serrano, A. L.; de Bruin, B.; Ciriano, M. A.; Tejel, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 472. (b) Lu, J.; Ye, J.; Duan, W. L. *Chem. Commun.* **2014**, *50*, 698. (c) Zhao, D.; Wang, R. *Chem. Soc. Rev.* **2012**, *41*, 2095. (d) Xu, Q.; Han, L. B. *J. Organomet. Chem.* **2011**, *696*, 130. (e) Zhang, H.; Sun, Y. M.; Zhao, Y.; Zhou, Z. Y.; Wang, J. P.; Xin, N.; Nie, S. Z.; Zhao, C. Q.; Han, L. B. *Org. Lett.* **2015**, *17*, 142. (f) Zhang, H.; Sun, Y. M.; Yao, L.; Ji, S. Y.; Zhao, C. Q.; Han, L. B. *Chem. - Asian J.* **2014**, *9*, 1329. (g) Sun, Y. M.; Xin, N.; Xu, Z. Y.; Liu, L. J.; Meng, F. J.; Zhang, H.; Fu, B. C.; Liang, Q. J.; Zheng, H. X.; Sun, L. J.; Zhao, C. Q.; Han, L. B. *Org. Biomol. Chem.* **2014**, *12*, 9457. (h) Xie, P. Z.; Guo, L.; Xu, L. L.; Loh, T. P. *Chem. - Asian J.* **2016**, *11*, 1353.

(7) (a) Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4504. (b) Ibrahem, I.; Rios, R.; Vesely, J.; Hammar, P.; Eriksson, L.; Himo, F.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4507.

(8) (a) Fu, X.; Jiang, Z.; Tan, C. H. *Chem. Commun.* **2007**, 5058. (b) Wen, S.; Li, P.; Wu, H.; Yu, F.; Liang, X.; Ye, J. *Chem. Commun.* **2010**, *46*, 4806. (c) Hong, L.; Sun, W.; Liu, C.; Zhao, D.; Wang, R. *Chem. Commun.* **2010**, *46*, 2856. (d) Sun, W.; Hong, L.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 3914. (e) Geng, Z. C.; Zhang, J. X.; Li, N.; Chen, J.; Huang, X. F.; Zhang, S. Y.; Li, H. Y.; Tao, J. C.; Wang, X. W. *Tetrahedron* **2014**, *70*, 417.

(9) (a) Tibhe, G. D.; Lagunas-Rivera, S.; Vargas-Díaz, E.; García-Barradas, O.; Ordoñez, M. *Eur. J. Org. Chem.* **2010**, *2010*, 6573. (b) Deng, H. P.; Shi, M. *Eur. J. Org. Chem.* **2012**, *2012*, 183.

(10) (a) Merino, P.; Marqués-López, E.; Herrera, R. P. *Adv. Synth. Catal.* **2008**, *350*, 1195. (b) Gröger, H.; Hammer, B. *Chem. - Eur. J.* **2000**, *6*, 943.

(11) (a) Hiratake, J.; Oda, J. *Biosci., Biotechnol., Biochem.* **1997**, *61*, 211. (b) Parsons, W. H.; Patchett, A. A.; Bull, H. G.; Schoen, W. R.; Taub, D.; Davidson, J.; Combs, P. L.; Springer, J. P.; Gadebusch, H.; Weissberger, B.; Valiant, M. E.; Mellin, T. N.; Busch, R. D. *J. Med. Chem.* **1988**, *31*, 1772.

(12) (a) Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 10521. (b) Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 6656. (c) Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4600. (d) Saito, B.; Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2007**, *129*, 1978. (e) Gröger, H.; Saida, Y.; Arai, S.; Martens, J.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 9291. (f) Gröger, H.; Saida, Y.; Sasai, H.; Yamaguchi, K.; Martens, J.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 3089. (g) Schlemminger, I.; Saida, Y.; Gröger, H.; Maison, W.; Durot, N.; Sasai, H.; Shibasaki, M.; Martens, J. *J. Org. Chem.* **2000**, *65*, 4818.

(13) (a) Zhang, D. H.; Yuan, C. Y. *Chem. - Eur. J.* **2008**, *14*, 6049. (b) Fu, X.; Loh, W. T.; Zhang, Y.; Chen, T.; Ma, T.; Liu, H. J.; Wang, J. M.; Tan, C. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 7387. (c) Yang, M.; Xu, H.; Zhou, Z. Y.; Zhang, H.; Liu, L. J.; Sun, Y. M.; Nie, S. Z. *Tetrahedron: Asymmetry* **2016**, *27*, 815.

(14) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102.

(15) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583.

(16) Wang, Y. D.; Wang, F.; Wang, Y. Y.; Miao, Z. W.; Chen, R. Y. *Adv. Synth. Catal.* **2008**, *350*, 2339.

(17) Wang, Y. D.; Wang, Y. Y.; Yu, J. P.; Miao, Z. W.; Chen, R. Y. *Chem. - Eur. J.* **2009**, *15*, 9290.

(18) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(19) (a) Xu, Q.; Zhao, C. Q.; Han, L. B. *J. Am. Chem. Soc.* **2008**, *130*, 12648. (b) Moraleda, D.; Gatineau, D.; Martin, D.; Giordano, L.; Buono, G. *Chem. Commun.* **2008**, 3031. (c) Ma, Y. N.; Yang, S. D. *Chem. - Eur. J.* **2015**, *21*, 6673.

(20) Kunz, H.; Sager, W.; Schanzenbach, D.; Decker, M. *Liebigs Ann. Chem.* **1991**, *1991*, 649.

(21) Crystallographic data for the structural analysis of compound **3d** have been deposited at the Cambridge Crystallographic Data Centre (no. CCDC 1472583). These data can be obtained free of charge by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk.

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