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Asymmetric aza-Friedel–Crafts reaction of indoles induced by *O*-pivaloylated D-galactosylamine as the chiral auxiliary

Haohao Yang [a], Bing Cui [a], Guiping Wu [a], Zhiwei Miao [a,b,*], Ruyu Chen [a,*]

[a] State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, PR China
[b] Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Tsinghua University, Beijing 100084, PR China

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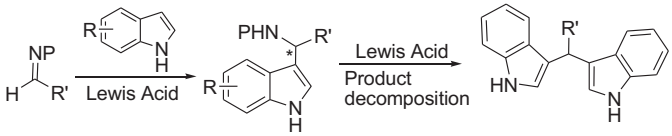
ABSTRACT

The diastereoselective formation of β-*N*-glycosidically linked 3-indolyl methanamine derivatives **5** has been achieved with high yield via an aza-Friedel–Crafts reaction. The reaction was performed by using *O*-pivaloylated galactosylamine **1** as a chiral template and $SnCl_4$ combining TBAI as catalyst in DCM at −50 °C.

1. Introduction

The development of diastereo- and enantioselective synthetic methods for the preparation of indole derivatives remains an important goal in modern organic synthesis because of their biological activities.[1] Various indole derivatives such as 3-substituted indoles, are common components of drugs and are generally found to be of pharmaceutical interest in a variety of therapeutic area.[2] Accordingly, considerable efforts have been devoted to the development of stereoselective approaches for indole derivatives synthesis.[3] The asymmetric Friedel–Crafts reaction of indoles with imines represents the most direct and convenient approach in terms of reagent availability.[4] The products of this reaction provide easy access to the synthesis of enantiopure 3-indolyl methanamine derivatives.[5] In view of the significance of controlling the stereochemistry in an absolute sense, the strategies of asymmetric catalysis,[6] enzymatic resolution[7] and chiral auxiliary-mediated induction[8] have been employed for the preparation of 3-substituted indoles. However, the issues of unprotected indole substrate usage, reaction stereoselectivity control and amine *N*-substituent removal remain to be addressed and are the subject of intense investigation. Especially, during the reaction of direct asymmetric aza-Friedel–Crafts reaction of indoles with aldimines for the synthesis of 3-indolyl methanamine derivatives, bisindole alkylation events are very difficult to be avoided (Scheme 1).[9]



Scheme 1. Enantioselective aza-Friedel–Crafts reaction towards 3-indolyl methanamines.

Carbohydrates are valuable as enantiomerically pure starting materials in chiral pool syntheses of many chiral natural products and drugs.[10] Carbohydrate derivatives are efficient auxiliaries for stereo-differentiation in many stereoselective chiral syntheses.[11,12] Lewis acid induced nucleophilic addition to Schiff bases of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl amine **1** was firstly reported by Kunz in 1987.[13] This chiral auxiliary has already been used in diastereoselective Strecker,[13] Ugi,[14] Mannich[15] and tandem Mannich–Michael reactions.[16] Recently, we reported a convenient and efficient synthetic protocol for preparation of α-aminophosphinic acid derivatives in high yields and high

* Corresponding authors. Tel.: +86 22 2350 4783; fax: +86 22 2350 2351; e-mail address: miaozhiwe@nankai.edu.cn (Z. Miao).

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enantiostereoselectivities, utilizing $SnCl_4$ as the promoter and *O*-pivaloylated D-galactosylamine as chiral auxiliary by means of Mannich-type reactions.[17] Herein we report an efficient asymmetric synthesis of 3-indolyl methanamine derivatives in which glycosylamine **1** was used as the stereodifferentiating auxiliary.

2. Results and discussion

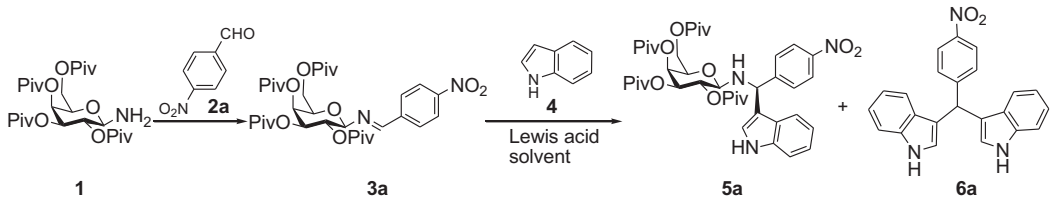
The synthesis of β-*N*-glycosidically linked (3-indolyl)methanamine derivatives **5** started with the condensation of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl amine **1** and arylaldehyde **2**. In order to prepare *N*-(2,3,4,6-tetra-*O*-pivaloyl-D-galacopyranosyl) aldimines **3**, *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-galacopyranosyl) amine **1** was reacted with aldehydes in the presence of acetic acid in 2-propanol. The reactions proceeded smoothly within a short period of time at room temperature under dehydrating conditions.[18] We initially investigated the reaction of *O*-pivaloylated *N*-galactosylimine **3a** (R=*p*-$NO_2C_6H_4$) with indole **4** in dichloromethane (DCM) without the aid of Lewis acid, no product **5a** was detected (Table 1, entry 1). Since the nucleophilicity of indole is low and the electrophilicity of imines **3** is only moderate, the reaction between these compounds requires activation by a Lewis acid to proceed. In this sense, various Lewis acids were tested in the reaction of the *O*-pivaloylated *N*-galactosylimine **3a** with indole **4** in DCM at room temperature.

The results revealed that $Mg(ClO_4)_2$, $Cu(OTf)_2$, $FeCl_3$ and $SnCl_4$ only gave the double-alkylation product **6a** when used in a stoichiometric amount, and no desired product of **5a** was observed (Table 1, entries 2–5). Other Lewis acids were tested (e.g., $AlCl_3$, CuI, CuBr, $MgCl_2$, $Cu(OAc)_2$ and $NiCl_2$) were able to promote the addition and gave moderate yields and diastereoselectivities (Table 1, entries 6–11). Particularly, when lowering the reaction temperature to −50 °C and decreasing the loading amount of catalyst, $SnCl_4$ (20 mol %) was able to catalyze the addition and obtained the product in 83% yield with the ratio of diastereoselectivity 10:1 (Table 1, entries 12 and 14). Higher diastereoselectivity may be maintained at catalyst loadings as low as 10 mol % (13:1 dr, 73% yield, Table 1, entry 15). Compared with $SnCl_4$, both $BF_3\cdot Et_2O$ and $ZnCl_2\cdot Et_2O$ applied in DCM at −50 °C can catalyze this reaction with lower yields and diastereoselectivities (Table 1, entries 16 and 17). The molar equivalents of indole **4** relative to that of **3a** is 2:1 (Table 1, entries 1–22).

Following this evaluation of Lewis acids, a solvent screen was undertaken. The reaction proceeded in Et_2O, THF, and $CHCl_3$ to afford the desired product in good to high yields and with moderate diastereoselectivities (Table 1, entries 18–20). Toluene gave a high conversion rate but with a slight decrease in the diastereomeric excess (Table 1, entry 21). Among the solvents tested, DCM was found to be the best with respect to catalytic activity and asymmetric induction. When decreasing the amount of catalyst, a drop-off in both the reaction rate and dr value of the product was observed (Table 1, entry 22).

To determine the optimal conditions, the suitable amount of indole was examined by running the reaction at −50 °C. In the presence of 10 mol % of $SnCl_4$ in DCM, reaction of imine **3a** with equimolar indole **4** gave the desired product **5a** in 59% yield with

Table 1
Survey of the conditions for the formation of **5a**[a]



Entry	Lewis acid (equiv)	*T* (°C)	Solvent	Reaction time (h)	Indole (equiv)	Yield[b] (**5a**/**6a**) [%]	dr[d] [%]
1	—	rt	DCM	20	2	n.r.[c]	—
2	$Mg(ClO_4)_2$ (1)	rt	DCM	20	2	0:85	—
3	$Cu(OTf)_2$ (1)	rt	DCM	20	2	0:82	—
4	$FeCl_3$ (1)	rt	DCM	20	2	0:78	—
5	$SnCl_4$ (1)	rt	DCM	20	2	0:80	—
6	$AlCl_3$ (1)	rt	DCM	20	2	83:7	8:1
7	CuI (1)	rt	DCM	11	2	31:55	6:1
8	CuBr (1)	rt	DCM	10	2	68:11	6:1
9	$MgCl_2$ (1)	rt	DCM	10	2	53:15	4:1
10	$Cu(OAc)_2$ (1)	rt	DCM	23	2	17:55	5:1
11	$NiCl_2$ (1)	rt	DCM	12	2	57:11	4:1
12	$SnCl_4$ (1)	−50	DCM	1	2	0:77	—
13	$SnCl_4$ (0.5)	−50	DCM	1	2	0:73	—
14	$SnCl_4$ (0.2)	−50	DCM	8	2	83:Trace	10:1
15	$SnCl_4$ (0.1)	−50	DCM	8	2	73:Trace	13:1
16	$BF_3\cdot Et_2O$ (0.1)	−50	DCM	4	2	70:Trace	10:1
17	$ZnCl_2\cdot Et_2O$ (0.1)	−50	DCM	32	2	80:Trace	9:1
18	$SnCl_4$ (0.1)	−50	Et_2O	18	2	50:22	6:1
19	$SnCl_4$ (0.1)	−50	THF	19	2	91:Trace	7:1
20	$SnCl_4$ (0.1)	−50	$CHCl_3$	2	2	77:Trace	9:1
21	$SnCl_4$ (0.1)	−50	Toluene	18	2	97:Trace	6:1
22	$SnCl_4$ (0.05)	−50	DCM	8	2	74:Trace	9:1
23	$SnCl_4$ (0.1)	−50	DCM	8	1	59:Trace	7:1
24	$SnCl_4$ (0.1)	−50	DCM	8	3	85:Trace	14:1
25	$SnCl_4$ (0.1)	−50	DCM	8	5	81:Trace	13:1

[a] All reactions were carried out under the optimal conditions reported in the text, unless otherwise indicated.
[b] Isolated yield.
[c] No reaction.
[d] Determined from the crude product by ^1H NMR.

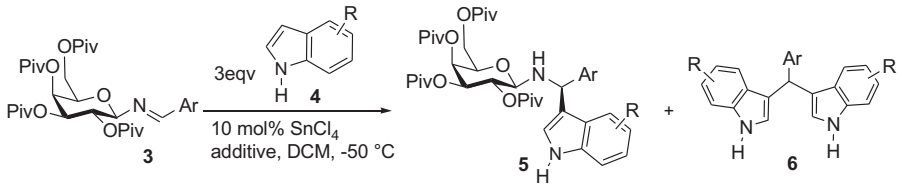
7:1 diastereoselectivity (Table 1, entry 23). When we increased the amount of indole, the reaction proceeded faster and led to the product with a slightly higher selectivity. When 3 equiv of indole was used, an optimal result was obtained in terms of both the yield and diastereoselectivity of **5a** (85% yield, 14:1 dr, Table 1, entry 24). A further increase of the amount of indole had no significant effect on the yield or the selectivity (Table 1, entry 25). Thus, the optimal reaction conditions for this transformation were determined to be 0.5 mmol of **3**, 3 equiv of indole **4**, 10 mol % of $SnCl_4$ in DCM as solvent at −50 °C.

Under these optimum conditions, we next examined the generality of this reaction with various aldimines **3** and indoles **4**. Surprisingly, except imines **3a** and **3k**, other aldimines **3** only led to bis-alkylation products **6** quantitatively (Table 2, entries 1–11). In general, the aza-Friedel–Crafts reaction of less activated substrates, such as imines of aromatic aldehydes, was limited mainly due to the lower reactivity and the formation of double-alkylation product **6**.[19] In order to overcome this drawback, the influence of additives on the reaction was examined. The reaction of *O*-pivaloylated *N*-galactosylimine **3b** (R=*p*-ClC_6H_4) with indole **4** in the presence of 10 mol % $SnCl_4$ in dichloromethane (DCM) at −50 °C was chosen as an initial example. It was found that the addition of Ph_3P or Et_3N made almost no difference on the outcome of the reaction (Table 2, entries 12–13). When 2 equiv of acetone was added, the reaction proceeded smoothly to provide corresponding Friedel–Crafts adducts in good yield and high dr value (76% yield, >19:1 dr, entry 14). However, the reaction time was taken 96 h. Interestingly, good result was obtained (83% yield, >19:1 dr) when 20 mol % of tetrabutylammonium iodide (TBAI) was employed in this reaction (Table 2, entry 15). Thus, the optimal reaction conditions for this transformation were determined to be 0.5 mmol *O*-pivaloylated *N*-galactosylimine **3**, 3 equiv of indole **4**, 10 mol % of $SnCl_4$ combined with 20 mol % of TBAI in DCM as solvent at −50 °C.

With these optimized conditions in hand, the general scope of aldimines **3** and indole derivatives was examined in this asymmetric Friedel–Crafts reaction. As expected, *O*-pivaloylated *N*-galactosylimine **3** bearing both electron-rich and electron-poor aromatic groups gave the corresponding asymmetric aza-Friedel–Crafts products **5a**–**j** in good to high yields and diastereoselectivities (Table 2, entries 16–24), which contrast the results of a chiral copper complex that showed a strong electronic effect for this reaction.[5b] Furthermore, several substituted indoles have been tested in the reaction with imine **3b**, respectively. For the substrates with electron-donating group (**4b**) and electron-withdrawing group (**4c**), the reactions underwent smoothly, affording the products with high yields and diastereoselectivities (Table 2, entries 25 and 26).[20]

The diastereomeric ratio of **5** was determined by ^1H NMR of the crude reaction mixture. Consistent with our experimental results, there exists only β-anomer in the chiral auxiliary that is controlled by both electronic and steric effects. Therefore, with the newly formed stereocenter in the reaction, only two diastereoisomers β*S*- and β*R*-**5** were generated. The absolute configuration of the major product **5** was defined as β*S* by X-ray analysis of compound **5a**

Table 2
The aza-Friedel–Crafts reaction of *N*-(2,3,4,6-tetra-*O*-pivaloylated-D-galactosyl)aldimines **5a**–**k**



Entry	Ar	R	Additive (equiv)	Time [h]	Yield[a] (**5**/**6**) [%]	dr[b]
1	*p*-$NO_2C_6H_4$ (**3a**)	H (**4a**)	—	8	85:trace	14:1
2	*p*-ClC_6H_4 (**3b**)	H (**4a**)	—	0.5	0:93	—
3	*o*-ClC_6H_4 (**3c**)	H (**4a**)	—	0.5	0:92	—
4	*m*-ClC_6H_4 (**3d**)	H (**4a**)	—	0.5	0:90	—
5	*p*-BrC_6H_4 (**3e**)	H (**4a**)	—	0.5	0:97	—
6	*o*-BrC_6H_4 (**3f**)	H (**4a**)	—	0.5	0:97	—
7	*o*-FC_6H_4 (**3g**)	H (**4a**)	—	0.5	0:91	—
8	*p*-FC_6H_4 (**3h**)	H (**4a**)	—	0.5	0:98	—
9	*m*-$CH_3C_6H_4$ (**3i**)	H (**4a**)	—	0.5	0:96	—
10	*p*-$CH_3C_6H_4$ (**3j**)	H (**4a**)	—	0.5	0:90	—
11	2-NO_2–3-$OCH_3C_6H_3$ (**3k**)	H (**4a**)	—	12	85:Trace	>19:1
12	*p*-ClC_6H_4 (**3b**)	H (**4a**)	Ph_3P (0.2)	48	0:79	—
13	*p*-ClC_6H_4 (**3b**)	H (**4a**)	TEA (0.2)	48	0:89	—
14	*p*-ClC_6H_4 (**3b**)	H (**4a**)	Acetone (2)	96	76:Trace	>19:1
15	*p*-ClC_6H_4 (**3b**)	H (**4a**)	TBAI (0.2)	8	83:Trace	>19:1
16	*p*-$NO_2C_6H_4$ (**3a**)	H (**4a**)	TBAI (0.2)	8	89:Trace	14:1
17	*o*-ClC_6H_4 (**3c**)	H (**4a**)	TBAI (0.2)	8	92:Trace	13:1
18	*m*-ClC_6H_4 (**3d**)	H (**4a**)	TBAI (0.2)	8	77:Trace	>19:1
19	*p*-BrC_6H_4 (**3e**)	H (**4a**)	TBAI (0.2)	8	96:Trace	>19:1
20	*o*-BrC_6H_4 (**3f**)	H (**4a**)	TBAI (0.2)	8	75:Trace	12:1
21	*o*-FC_6H_4 (**3g**)	H (**4a**)	TBAI (0.2)	8	93:Trace	>19:1
22	*p*-FC_6H_4 (**3h**)	H (**4a**)	TBAI (0.2)	8	71:Trace	>19:1
23	*m*-$CH_3C_6H_4$ (**3i**)	H (**4a**)	TBAI (0.2)	8	72:Trace	>19:1
24	*p*-$CH_3C_6H_4$ (**3j**)	H (**4a**)	TBAI (0.2)	8	70:Trace	>19:1
25	*p*-ClC_6H_4 (**3b**)	5-OCH_3 (**4b**)	TBAI (0.2)	8	86:Trace	>19:1
26	*p*-ClC_6H_4 (**3b**)	5-Br (**4c**)	TBAI (0.2)	8	83:Trace	>19:1
27	*p*-BrC_6H_4 (**3e**)	H (**4a**)	TBACl (0.2)	4	0:80	—

[a] After purification by chromatography.
[b] Diastereomeric ratio determined from the crude product by HPLC.

(Fig. 1).[21] To demonstrate the efficient removal of the auxiliary, compound **5h** was treated with a solution of sodium methoxide in methanol to give **8h** in quantitative yield, which was reacted with benzyloxycarbonyl chloride (CbzCl) to provide less polar compound **9h** in order to facilitate the determination of its enantiomeric excess by chiral HPLC (Scheme 2).

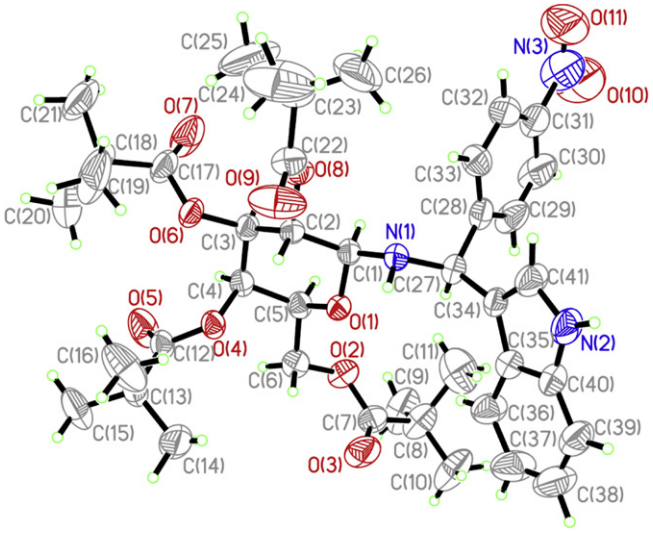
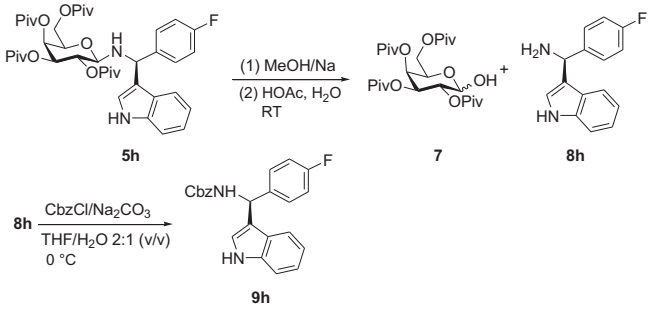


Fig. 1. The ORTEP drawing of **5a**.



Scheme 2. Synthesis of (*S*)-(4-fluorophenyl)(1*H*-indol-3-yl)methanamine **8h**.

Based on Kunz's findings[22] and our experimental results, a plausible mechanism was proposed in Fig. 2. The preferred formation of the *S*-configured diastereomer of **5** can be rationalized by an attack of indole from *Re* side of (*E*)-imines **3**. In the transition state, the tin should have octahedral coordination. Two coordination sites of the tin(IV) chloride are occupied by the imine nitrogen and the carbonyl oxygen atoms of the (C-2) pivaloyloxy group (TS I). The imine·$SnCl_4$ complex maintains the H-eclipsed conformation, because chelation by the auxiliary's pivaloyl group inhibits rotation along the N–C* bond. According to this rationalization, the SN2′-type attack of indole **4** from the front side of the imine is initiated and form TS II. The mechanism indicates that the pivaloyl group in the aldimines **3** plays a significant role in controlling the diastereoselective addition of indoles **4** to *N*-galactosylaldimines **3**. We envisaged that the coordination of the Sn^{IV} catalyst to the *N*-glycoside nitrogen of the initial Friedel–Crafts reaction product (TS III) resulting from *N*-galactosylaldimine **3** would enhance the ability of the *N*-glycoside moiety as a leaving group, facilitating the formation of the highly stabilized carbocation intermediate (TS IV), required for the final Friedel–Crafts alkylation.

In contrast, in the presence of TBAI, it is reasonable to assume a preferential coordination of the Sn^{IV} atom to the iodine atom of TBAI, instead of the *N*-glycoside nitrogen, resulting in a lower leaving group capacity of the *N*-glycoside moiety, which would make more difficult the cleavage of the C–N bond and formation of the carbocation intermediate (TS III). To support this hypothesis, and to have an insight of the coordination mode around the tin atom, tetrabutylammonium chloride (TBACl) was employed in this reaction. Compared with TBAI, there was only double-alkylation product **6** obtained in quantitative yield when TBACl combining $SnCl_4$ as catalyst in the reaction (Table 2, entry 27).

3. Conclusion

In conclusion, we have developed the asymmetric aza-Friedel–Crafts reaction of indole in high yields and high diastereoselectivities, utilizing $SnCl_4$ combining TBAI as catalyst and *O*-pivaloylated D-galactosylamine **3** as chiral auxiliary. The *O*-pivaloylated galactosylamine **3** is an effective chiral template in the synthesis of chiral *N*-galactosyl 3-indolyl methanamine **5**.

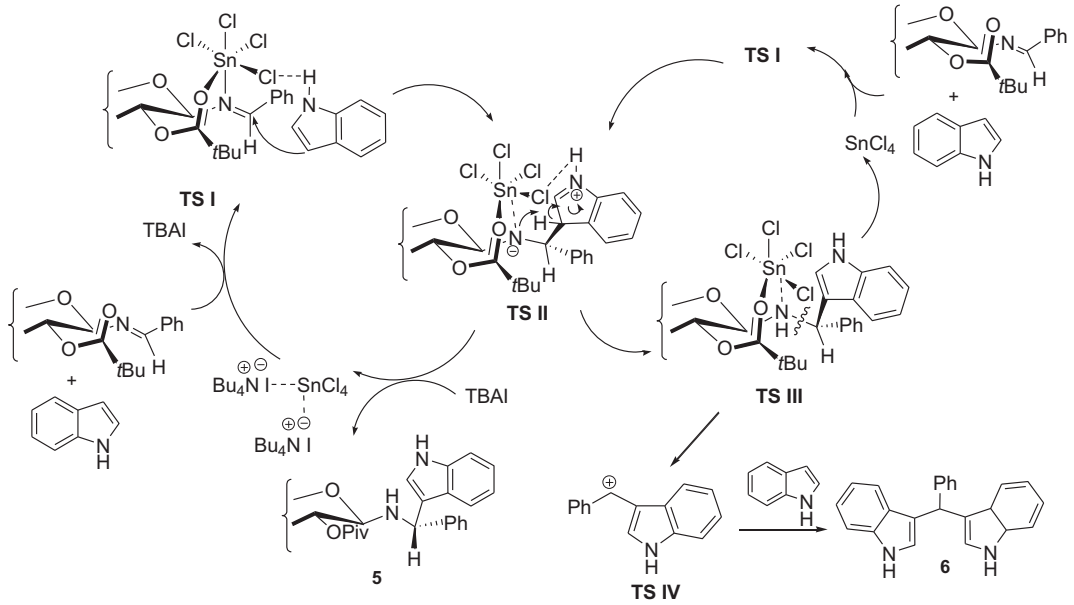


Fig. 2. Plausible reaction mechanism.

(*S*)-3-Indolyl (phenyl) methanamine **8** can be detached easily from the carbohydrate template, which can be recycled. Further studies are being conducted with regard to scope of this reaction and related Friedel–Crafts-type additions induced by carbohydrate as chiral auxiliary.

4. Experimental section

4.1. General experimental section

All reactions were carried out under an inert atmosphere and in heat-dried glassware. Anhydrous DCM was obtained by distillation from calcium hydride. Flash column chromatography was performed on silica gel (particle size 10–40 μm, Ocean Chemical Factory of Qingdao, China). Nitrogen gas (99.999%) was purchased from Boc Gas Inc. ^{1}H, and ^{13}C spectra were recorded on Brucker-400 (400 MHz for ^{1}H, 101 MHz for ^{13}C) spectrometers. Chemical shifts were reported in parts per million downfield from internal $Si(CH_3)_4$. The crystal structure was determined on a Bruker SMART 1000 CCD diffractometer. Mass spectra were recorded on a LCQ advantage spectrometer with ESI resource. HRMS were recorded on APEXII and ZAB-HS spectrometer. Melting points were determined on a T-4 melting point apparatus (uncorrected).

4.2. General procedure for the preparation of *O*-pivaloylated *N*-galactosylimines 3

To a solution of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl amine **1** (0.515 g, 1 mmol) and aldehyde **2** (1.3 mmol) in 2-propanol (2.5 mL), 2–3 drops of acetic acid were added 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 **3**, after the precipitate was filtered off, then washed with ice cold 2-propanol and dried in vacuum, *N*-galactosylaldimines **3** were isolated as a white solid.

4.3. General procedure for the synthesis of β-*N*-glycosidic linkages (3-indolyl)methanamine derivatives 5

A solution of *N*-galactosylaldimines **3** (0.156 mmol), TBAI (1.2 mg, 0.003 mmol) and indole (0.468 mmol) in DCM (3 mL) was cooled to −50 °C, and $SnCl_4$ (0.0018 mL, 0.0156 mmol) was added. The mixture was stirred for 8 h at this temperature. The mixture was hydrolyzed with aqueous saturated solution of $NaHCO_3$ (5 mL) and the mixture was stirred at room temperature for 5 min. The aqueous phase was extracted with CH_2Cl_2 (3×5 mL), and the organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to yield the crude products **5**, which were purified by flash column chromatography on silica gel [petroleum ether/ethyl acetate, 6:1(v/v)] to provide pure products **5**.

*4.3.1. N-[Indol-3-yl-(4-nitrophenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5a**).* White solid, mp 197–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 9H, C(CH_3)$_3$), 1.23 (s, 9H, C(CH_3)$_3$), 1.26 (s, 9H, C(CH_3)$_3$), 1.27 (s, 9H, C(CH_3)$_3$), 2.65 (d, $^3J_{1,NH}$=13.2 Hz, 1H, N–H), 3.85 (t, $^3J_{5,6}$=6.8 Hz, 1H, 5-H), 3.94–4.01 (m, 1H, 1-H), 4.05 (dd, $^2J_{6a,6b}$=11.1 Hz, $^3J_{5,6a}$=6.8 Hz, 1H, 6a-H), 4.25 (dd, $^2J_{6a,6b}$=11.1 Hz, $^3J_{5,6b}$=6.8 Hz, 1H, 6b-H), 5.07–5.17 (m, 2H, 2-H, 3-H), 5.41 (d, $^3J_{3,4}$=2.5 Hz, 1H, 4-H), 5.80 (s, 1H, C–H), 6.92 (d, $^3J_{2',\ indole-NH}$=2.3 Hz, 1H, 2′-H), 7.09 (t, *J*=7.5 Hz, 1H, Ph), 7.20 (t, *J*=7.6 Hz, 1H, Ph), 7.35 (d, *J*=8.2 Hz, 1H, Ph), 7.66 (t, *J*=8.9 Hz, 3H, Ph), 8.13 (s, 1H, indole N–H), 8.17 (d, *J*=8.6 Hz, 2H, Ph). ^{13}C NMR (101 MHz, $CDCl_3$): δ=26.08, 26.14, 26.17, 26.37, 37.78, 37.92, 38.08, 52.53, 60.73, 66.28, 68.03, 70.45, 70.78, 85.43, 110.41, 117.30, 117.86, 118.90, 120.83, 121.65, 122.65, 124.38, 127.68, 135.42, 146.17, 149.18, 175.94, 176.23, 176.55, 177.01; MS (ESI): *m*/*z*: 788.4 [M+Na$^+$]; HRMS (ESI): *m*/*z* calcd for $C_{41}H_{55}N_3O_{11}$+Na$^+$: 788.3734 [M+Na$^+$]; found: 788.3736.

*4.3.2. N-[Indol-3-yl-(4-chlorophenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5b**).* White solid, mp 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 9H, C(CH_3)$_3$), 1.24 (s, 9H, C(CH_3)$_3$), 1.24 (s, 9H, C(CH_3)$_3$), 1.26 (s, 9H, C(CH_3)$_3$), 2.57 (d, $^3J_{1,NH}$=13.0 Hz, 1H, N–H), 3.83 (t, $^3J_{5,6}$=6.8 Hz, 1H, 6a-H), 3.97 (dd, $^3J_{1,NH}$=13.0, $^3J_{1,2}$=8.1 Hz, 1H, 1-H), 4.04 (dd, $^2J_{6a,6b}$=11.1 Hz, $^3J_{5,6a}$=6.8 Hz, 1H), 4.23 (dd, $^2J_{6a,6b}$=11.1 Hz, $^3J_{5,6b}$=6.8 Hz, 1H, 6b-H), 5.06–5.15 (m, 2H, 2-H, 3-H), 5.40 (d, $^3J_{3,4}$=2.0 Hz, 1H, 4-H), 5.67 (s, 1H, C–H), 6.95 (d, $^3J_{2',indole-NH}$=2.2 Hz, 1H, 2′-H), 7.07 (t, *J*=7.4 Hz, 1H, Ph), 7.18 (t, *J*=7.3 Hz, 1H, Ph), 7.26 (s, 1H, Ph), 7.28 (s, 1H, Ph), 7.33 (d, *J*=8.2 Hz, 1H, Ph), 7.41 (d, *J*=8.4 Hz, 2H, Ph), 7.62 (d, *J*=7.9 Hz, 1H, Ph), 8.01 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=27.11, 27.19, 27.21, 27.37, 38.73, 38.78, 38.89, 39.08, 53.41, 61.87, 67.41, 69.01, 71.48, 71.67, 86.28, 111.21, 119.10, 119.55, 119.55, 121.42, 122.46, 125.64, 128.47, 129.48, 132.90, 136.41, 140.70, 176.94, 177.17, 177.56, 177.99; MS (ESI): *m*/*z*: 777.3 [M+Na$^+$]; HRMS (ESI): *m*/*z* calcd for $C_{41}H_{55}ClN_2O_9$+Na$^+$: 777.3488 [M+Na$^+$]; found: 777.3491.

*4.3.3. N-[Indol-3-yl-(2-chlorophenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5c**).* White solid, mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 9H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$), 1.24 (s, 9H, C(CH_3)$_3$), 1.26 (s, 9H, C(CH_3)$_3$), 2.54 (d, $^3J_{1,NH}$=12.9 Hz, 1H, 1-H), 3.91 (t, $^3J_{5,6}$=6.8 Hz, 1H, 5-H), 3.97–4.03 (m, 1H, 1-H), 4.06 (dd, $^2J_{6a,6b}$=11.1 Hz, $^3J_{5,6a}$=6.8 Hz, 1H, 6a-H), 4.26 (dd, $^2J_{6a,6b}$=11.1 Hz, $^3J_{5,6b}$=6.8 Hz, 1H, 6b-H), 5.03–5.15 (m, 2H, 2-H, 3-H), 5.41 (s, 1H, 4-H), 6.19 (s, 1H, C–H), 6.86 (d, $^3J_{2',indole-NH}$=2.1 Hz, 1H, 2′-H), 7.08 (t, *J*=7.3 Hz, 1H, Ph), 7.16–7.21(m, 3H, Ph), 7.29–7.35 (m, 2H, Ph), 7.75–7.83 (m, 2H, Ph), 8.06 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=27.14, 27.18, 27.23, 27.41, 38.77, 38.91, 39.11, 50.07, 61.77, 67.46, 69.12, 71.70, 71.72, 86.78, 111.16, 118.45, 119.58, 119.69, 122.17, 122.36, 125.92, 126.63, 128.26, 129.49, 129.76, 134.04, 136.40, 139.87, 176.98, 177.28, 177.48, 178.12; MS (ESI): *m*/*z*: 777.4 [M+Na$^+$]; HRMS (ESI): *m*/*z* calcd for $C_{41}H_{55}ClN_2O_9$+Na$^+$: 777.3488 [M+Na$^+$]; found: 777.3481.

*4.3.4. N-[Indol-3-yl-(3-chlorophenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5d**).* White solid, mp 87–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 9H, C(CH_3)$_3$), 1.24 (s, 9H, C(CH_3)$_3$), 1.26 (s, 18H, 2C(CH_3)$_3$), 2.53 (br., 1H, N–H), 3.85 (t, $^3J_{5,6}$=6.6 Hz, 1H, 5-H), 3.94–4.02 (m, 1H, 1-H), 4.05 (dd, $^2J_{6a,6b}$=11.2 Hz, $^3J_{5,6a}$=6.6 Hz, 1H, 6a-H), 4.23 (dd, $^2J_{6a,6b}$=11.2 Hz, $^3J_{5,6b}$=6.6 Hz, 1H, 6b-H), 5.06–5.19 (m, 2H, 2-H, 3-H), 5.40 (d, $^3J_{3,4}$=1.4 Hz, 1H, 4-H), 5.67 (s, 1H, C–H), 6.95 (s, 1H, 2′-H), 7.08 (t, *J*=7.1 Hz, 1H, Ph), 7.17 (d, *J*=7.7 Hz, 1H, Ph), 7.22 (d, *J*=4.9 Hz, 2H, Ph), 7.34 (d, *J*=7.8 Hz, 2H, Ph), 7.50 (s, 1H, Ph), 7.66 (d, *J*=7.9 Hz, 1H, Ph), 8.02 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=27.11, 27.19, 27.41, 38.74, 38.78, 38.91, 39.08, 53.53, 61.89, 67.44, 68.96, 71.53, 71.72, 86.33, 111.23, 119.08, 119.33, 119.75, 121.61, 122.46, 125.64, 126.38, 127.49, 127.93, 129.51, 134.37, 136.38, 144.52, 176.96, 177.21, 177.65, 178.01; MS (ESI): *m*/*z*: 777.3 [M+Na$^+$]; HRMS (ESI): *m*/*z* calcd for $C_{41}H_{55}ClN_2O_9$+Na$^+$: 777.3488 [M+Na$^+$]; found: 777.3486.

*4.3.5. N-[Indol-3-yl-(4-bromophenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5e**).* White solid, mp 187–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 9H, C(CH_3)$_3$), 1.23 (s, 9H, C(CH_3)$_3$), 1.24 (s, 9H, C(CH_3)$_3$), 1.26 (s, 9H, C(CH_3)$_3$), 2.56 (br, 1H, N–H), 3.83 (t, $^3J_{5,6}$=6.6 Hz, 1H, 5-H), 3.93–4.00 (br, 1H, 1-H), 4.04 (dd, $^2J_{6a,6b}$=11.2 Hz, $^3J_{5,6a}$=6.6 Hz, 1H, 6a-H), 4.23 (dd, $^2J_{6a,6b}$=11.2 Hz, $^3J_{5,6b}$=6.6 Hz, 1H, 6b-H), 5.03–5.17 (m, 2H, 2-H, 3-H), 5.40 (d, $^3J_{3,4}$=1.9 Hz, 1H, 4-H), 5.65 (s, 1H, C–H), 6.94 (d, $^3J_{2,indole-NH}$=2.1 Hz, 1H, 2′-H), 7.06 (t, *J*=7.5 Hz, 1H, Ph), 7.17 (t, *J*=7.6 Hz, 1H, Ph), 7.32 (s, 1H, Ph), 7.34 (d, *J*=2.1 Hz, 1H, Ph), 7.37 (s,

1H, Ph), 7.42 (d, J=8.3 Hz, 2H, Ph), 7.62 (d, J=7.8 Hz, 1H, Ph), 8.01(s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=27.13, 27.20, 27.22, 27.39, 38.75, 38.80, 38.91, 39.10, 53.50, 61.89, 67.45, 69.06, 71.53, 71.70, 86.32, 111.25, 119.09, 119.40, 119.71, 121.03, 121.50, 122.45, 125.64, 129.88, 131.43, 136.46, 141.31, 176.97, 177.20, 177.59, 178.01; MS (ESI): m/z: 821.2 [M+Na^+]; HRMS (ESI): m/z calcd for $C_{41}H_{55}BrN_2O_9$+Na^+ 821.2983 [M+Na^+]; found: 821.2990.

*4.3.6. N-[Indol-3-yl-(2-bromophenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5f**).* White solid, mp 126–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 9H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$), 1.23 (s, 9H, C(CH_3)$_3$), 1.26 (s, 9H, C(CH_3)$_3$), 2.56 (d, $^3J_{1,NH}$=12.4 Hz, 1H, N–H), 3.94 (t, $^3J_{5,6}$=6.8 Hz, 1H, 5-H), 3.97–4.03 (m, 1H, 1-H), 4.07 (dd, $^2J_{6a,6b}$=10.9 Hz, $^3J_{5,6b}$=6.8 Hz, 1H, 6b-H), 4.28 (dd, $^2J_{6a,6b}$=10.9 Hz, $^3J_{5,6a}$=6.8 Hz, 1H, 6a-H), 5.00–5.18 (m, 2H, 2-H, 3-H), 5.42 (s, 1H, 4-H), 6.14 (s, 1H, C–H), 6.87 (d, $^3J_{2,indole-NH}$=1.9 Hz, 1H, 2′-H), 7.09 (dd, J=14.2 Hz, 6.8 Hz, 2H, Ph), 7.17 (t, J=7.5 Hz, 1H, Ph), 7.23 (d, J=7.5 Hz, 1H), 7.32 (d, J=8.1 Hz, 1H, Ph), 7.53 (d, J=7.8 Hz, 1H, Ph), 7.75 (d, J=6.6 Hz, 1H, Ph), 7.83 (d, J=7.9 Hz, 1H, Ph), 8.07 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=26.11, 26.17, 26.19, 26.37, 37.74, 37.86, 38.07, 51.82, 60.59, 66.36, 68.08, 70.63, 70.65, 85.72, 110.09, 117.65, 118.68, 118.72, 121.11, 121.37, 123.45, 124.93, 126.23, 127.62, 129.12, 131.75, 135.37, 140.45, 175.89, 176.21, 176.43, 177.04; MS (ESI): m/z: 821.3 [M+Na^+]; HRMS (ESI): m/z calcd for $C_{41}H_{55}BrN_2O_9$+Na^+: 821.2983 [M+Na^+]; found: 821.2986.

*4.3.7. N-[Indol-3-yl-(2-fluorophenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5g**).* White solid, mp 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.14 (s, 9H, C(CH_3)$_3$), 1.24 (s, 9H, C(CH_3)$_3$), 1.27 (s, 9H, C(CH_3)$_3$), 1.29 (s, 9H, C(CH_3)$_3$), 2.55 (d, $^3J_{1,NH}$=12.8 Hz, 1H, N–H), 3.91 (t, $^3J_{5,6}$=6.6 Hz, 1H, 5-H), 4.01–4.15 (m, 2H, 1-H, 6a-H), 4.25 (dd, $^2J_{6a,6b}$=11.1 Hz, $^3J_{5,6b}$=6.6 Hz, 1H, 6b-H), 4.99–5.09 (m, 2H, 2-H, 3-H), 5.43 (s, 1H, 4-H), 6.11 (s, 1H, C–H), 7.01 (s, 1H, 2′-H), 7.04 (d, J=9.7 Hz, 1H, Ph), 7.10 (t, J=7.4 Hz, 2H, Ph), 7.16–7.27 (m, 2H, Ph), 7.35 (d, J=8.1 Hz, 1H, Ph), 7.69 (t, J=6.9 Hz, 1H, Ph), 7.77 (d, J=7.9 Hz, 1H, Ph), 8.06 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=26.08, 26.18, 26.34, 28.67, 37.72, 37.87, 38.06, 45.40, 60.86, 66.49, 68.05, 70.62, 70.77, 85.62, 110.09, 114.33 (d, $^2J_{C,F}$=22.0 Hz), 117.62, 118.62, 120.81, 121.30, 122.86 (d, $^4J_{C,F}$=3.1 Hz), 124.74, 127.52 (d, $^3J_{C,F}$=8.0 Hz), 128.35,128.22, 128.39, 135.33, 160.07 (d, $^1J_{C,F}$=247.2 Hz), 175.97, 176.22, 176.49, 177.10; MS (ESI): m/z: 761.4 [M+Na^+]; HRMS (ESI): m/z calcd for $C_{41}H_{55}FN_2O_9$+Na^+: 761.3784 [M+Na^+]; found: 761.3778.

*4.3.8. N-[Indol-3-yl-(4-fluorophenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5h**).* White solid, mp 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.10 (s, 9H, C(CH_3)$_3$), 1.24 (s, 18H, 2×C(CH_3)$_3$), 1.26 (s, 9H, C(CH_3)$_3$), 2.58 (d, $^3J_{1,NH}$=13.1 Hz, 1H, N–H), 3.83 (t, $^3J_{5,6}$=6.8 Hz, 1H, 5-H), 3.93–4.00 (m, 1H, 1-H), 4.04 (dd, $^2J_{6a,6b}$=11.2 Hz, $^3J_{5,6a}$=6.8 Hz, 1H, 6a-H), 4.23 (dd, $^2J_{6a,6b}$=11.2 Hz, $^3J_{5,6b}$=6.8 Hz, 1H, 6b-H), 5.01–5.13 (m, 2H, 2-H, 3-H), 5.40 (d, $^3J_{3,4}$=2.1 Hz, 1H, 4-H), 5.67 (s, 1H, C–H), 6.96 (s, 1H, 2′-H), 6.99 (d, J=8.6 Hz, 2H, Ph), 7.06 (t, J=7.5 Hz, 1H, Ph), 7.17 (t, J=7.2 Hz, 1H, Ph), 7.34 (d, J=8.2 Hz, 1H, Ph), 7.42 (d, J=5.5 Hz, 1H, Ph), 7.44 (d, J=5.5 Hz, 1H, Ph), 7.61 (d, J=7.9 Hz, 1H, Ph), 8.00 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=27.13, 27.20, 27.22, 27.37, 38.75, 38.80, 38.89, 39.10, 53.39, 61.90, 67.45, 69.03, 71.53, 71.67, 86.28, 111.21, 115.12 (d, $^2J_{C,F}$=21.4 Hz), 119.14, 119.67, 119.83, 121.37, 122.41, 125.70, 129.66 (d, $^3J_{C,F}$=8.0 Hz), 136.46, 137.81 (d, $^4J_{C,F}$=2.9 Hz), 162.04 (d, $^1J_{C,F}$=245.4 Hz), 176.96, 177.20, 177.59, 178.01; MS (ESI): m/z: 761.3 [M+Na^+]; HRMS (ESI): m/z calcd for $C_{41}H_{55}FN_2O_9$+Na^+: 761.3784 [M+Na^+]; found: 761.3790.

*4.3.9. N-[Indol-3-yl-(3-methylphenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5i**).* White solid, mp 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.03 (s, 9H, C(CH_3)$_3$), 1.16 (s, 9H, C(CH_3)$_3$), 1.18 (s, 18H, 2×C(CH_3)$_3$), 2.21 (s, 3H, CH_3), 2.45 (d, $^3J_{1,NH}$=12.7 Hz, 1H, N–H), 3.75 (t, $^3J_{5,6}$=6.5 Hz, 1H, 5-H), 3.90–4.01 (m, 2H, 1-H, 6a-H), 4.16 (dd, $^2J_{6a,6b}$=10.9 Hz, $^3J_{5,6b}$=6.5 Hz, 1H, 6b-H), 4.97–5.09 (m, 2H, 2-H, 3-H), 5.31 (s, 1H, 4-H), 5.58 (s, 1H, C–H), 6.86 (s, 1H, 2′-H), 6.97 (t, J=7.2 Hz, 2H, Ph), 7.05 (d, J=7.6 Hz, 1H, Ph), 7.10 (t, J=7.7 Hz, 1H, Ph), 7.17–7.25 (m, 3H, Ph), 7.59 (d, J=7.8 Hz, 1H, Ph), 8.06 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=20.41, 26.03, 26.09, 26.17, 26.36, 37.71, 37.75, 37.86, 38.06, 52.99, 60.96, 66.54, 68.04, 70.58, 85.34, 110.12, 118.20, 118.44, 118.93, 120.44, 121.13, 124.33, 124.81, 127.02, 127.67, 135.39, 136.74, 141.10, 175.99, 176.21, 176.59, 177.01; MS (ESI): m/z: 757.4 [M+Na^+]; HRMS (ESI): m/z calcd for $C_{42}H_{58}N_2O_9$+Na^+: 757.4035 [M+Na^+]; found: 757.4028.

*4.3.10. N-[Indol-3-yl-(4-methylphenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5j**).* White solid, mp 115–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.14 (s, 9H, C(CH_3)$_3$), 1.28 (s, 9H, C(CH_3)$_3$), 1.29 (2s, 18H, 2×C(CH_3)$_3$), 2.36 (s, 3H, CH_3), 2.57 (d, $^3J_{1,NH}$=12.9 Hz, 1H, N–H), 3.85 (t, $^3J_{5,6}$=6.7 Hz, 1H, 5-H), 3.98–4.05 (m, 1H, 1-H), 4.08 (dd, $^2J_{6a,6b}$=11.2 Hz, $^3J_{5,6a}$=6.7 Hz, 1H, 6a-H), 4.26 (dd, $^2J_{6a,6b}$=11.2 Hz, $^3J_{5,6b}$=6.7 Hz, 1H, 6b-H), 5.08–5.20 (m, 2H, 2-H, 3-H), 5.42 (d, $^3J_{3,4}$=2.3 Hz, 1H, 4-H), 5.69 (s, 1H, C–H), 7.00 (s, 1H, 2′-H), 7.07 (t, J=7.5 Hz, 1H, Ph), 7.13 (d, J=7.8 Hz, 2H, Ph), 7.17 (t, J=7.4 Hz, 1H, Ph), 7.33 (d, J=8.1 Hz, 1H, Ph), 7.39 (d, J=7.8 Hz, 2H, Ph), 7.67 (d, J=7.9 Hz, 1H, Ph), 8.11 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=21.15, 27.14, 27.23, 27.41, 38.76, 38.81, 38.92, 39.11, 53.81, 62.01, 67.57, 69.06, 71.59, 86.33, 111.13, 119.26, 119.50, 120.14, 121.31, 122.20, 125.85, 128.14, 128.98, 136.45, 136.83, 139.05, 177.04, 177.25, 177.68, 178.07; MS (ESI): m/z: 757.4 [M+Na^+]; HRMS (ESI): m/z calcd for $C_{42}H_{58}N_2O_9$+Na^+: 757.4035 [M+Na^+]; found: 757.4028.

*4.3.11. N-[Indol-3-yl-(2-methoxy-3-nitrophenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5k**).* White solid, mp 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.10 (s, 9H, C(CH_3)$_3$), 1.20 (s, 9H, C(CH_3)$_3$), 1.22 (s, 9H, C(CH_3)$_3$), 1.24 (s, 9H, C(CH_3)$_3$), 2.64 (d, $^3J_{1,NH}$=13.0 Hz, 1H, N–H), 3.89 (s, 3H, OCH_3), 3.98 (dd, $^3J_{1,NH}$=13.0 Hz, $^3J_{1,2}$=8.6 Hz, 1H, 1-H), 4.01–4.08 (m, 2H, 5-H, 6a-H), 4.25 (dd, $^2J_{6a,6b}$=14.2 Hz, $^3J_{5,6b}$=9.6 Hz, 1H, 6b-H), 5.04–5.16 (m, 2H, 2-H, 3-H), 5.42 (d, $^3J_{3,4}$=2.9 Hz, 1H, 4-H), 5.69 (s, 1H, C–H), 6.86–6.92 (m, 1H, 2′-H), 7.08 (t, J=7.4 Hz, 2H, Ph), 7.17 (t, J=7.5 Hz, 1H, Ph), 7.28–7.34 (m, 3H, Ph), 7.77 (d, J=8.0 Hz, 1H, Ph), 8.15 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=27.14, 27.20, 27.38, 38.74, 38.86, 39.06, 48.97, 56.36, 61.05, 67.15, 68.97, 71.49, 71.53, 86.26, 110.90, 111.13, 117.53, 119.94, 121.34, 121.86, 122.54, 125.42, 130.42, 135.49, 136.36, 142.15, 150.00, 176.86, 177.19, 177.52, 177.95; MS (ESI): m/z: 818.4 [M+Na^+]; HRMS (ESI): calcd for $C_{42}H_{57}N_3O_{12}$+Na^+: 818.3834 [M+Na^+]; found: 818.3839.

*4.3.12. N-[5-Methoxy-indol-3-yl-(4-chlorophenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5l**).* White solid, mp 123–124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.03 (s, 9H, C(CH_3)$_3$), 1.16 (s, 18H, 2×C(CH_3)$_3$), 1.18 (s, 9H, C(CH_3)$_3$), 2.47 (d, $^3J_{1,NH}$=13.0 Hz, 1H, N–H), 3.74 (s, 3H, OCH_3), 3.79 (t, $^3J_{5,6}$=6.7 Hz, 1H, 5-H), 3.91 (dd, $^3J_{1,NH}$=13.0 Hz, $^3J_{1,2}$=7.6 Hz, 1H, 1-H), 3.98 (dd, $^2J_{6a,6b}$=11.0 Hz, $^3J_{5,6a}$=6.7 Hz, 1H, 6a-H), 4.16 (dd, $^2J_{6a,6b}$=11.0 Hz, $^3J_{5,6b}$=6.7 Hz, 1H, 6b-H), 4.98–5.08 (m, 2H, 2-H, 3-H), 5.33 (s, 1H, 4-H), 5.54 (s, 1H, C–H), 6.52–6.78 (m, 2H, Ph, 2′-H), 7.00 (d, J=1.8 Hz, 1H, Ph), 7.14 (d, J=8.8 Hz, 1H, Ph), 7.16–7.24 (m, 2H, Ph), 7.34 (d, J=8.3 Hz, 2H, Ph), 7.91 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=26.10, 26.17, 26.35, 37.72, 37.76, 37.86, 38.05, 52.31, 54.74, 60.84, 66.42, 67.94, 70.54, 70.72, 85.56, 99.67, 110.95, 111.66, 118.11, 121.44, 125.11, 127.43, 128.47, 130.51, 131.91, 139.69, 153.13, 175.90, 176.15, 176.51, 176.94; MS (ESI): m/z: 807.4 [M+Na^+]; HRMS (ESI): calcd for $C_{42}H_{57}ClN_2O_{10}$+Na^+: 807.3594 [M+Na^+]; found: 807.3587.

*4.3.13. N-[5-Bromo-indol-3-yl-(4-chlorophenyl)methyl]-(2,3,4,6-tetra-O-pivaloyl-β-D-galactosyl)amine (**5m**).* White solid, mp 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 9H, C(CH_3)$_3$), 1.24 (s, 18H, 2×C(CH_3)$_3$), 1.27 (s, 9H, C(CH_3)$_3$), 2.50 (d, $^3J_{1,NH}$=13.0 Hz, 1H, N–H), 3.86 (t, $^3J_{5,6}$=6.7 Hz, 1H, 5-H), 3.94–4.03 (m, 1H, 1-H), 4.10 (dd, $^2J_{6a,6b}$=11.1 Hz, $^3J_{5,6a}$=6.7 Hz, 1H, 6a-H), 4.25 (dd, $^2J_{6a,6b}$=11.1 Hz, $^3J_{5,6b}$=6.7 Hz, 1H, 6b-H), 5.00–5.18 (m, 2H, 2-H, 3-H), 5.41 (s, 1H, 4-H), 5.59 (s, 1H, C–H), 6.88 (s, 1H, 2′-H), 7.21 (t, J=7.8 Hz, 1H, Ph), 7.24–7.29 (m, 3H, Ph), 7.40 (d, J=8.3 Hz, 2H, Ph), 7.83 (s, 1H, Ph), 8.13 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$): δ=27.12, 27.20, 27.26, 27.39, 38.75, 38.80, 38.91, 39.11, 53.29, 61.88, 67.37, 69.01, 71.50, 71.78, 86.44, 112.66, 113.09, 119.13, 121.85, 122.90, 125.39, 127.41, 128.57, 129.36, 133.09, 135.08, 140.41, 176.98, 177.17, 177.60, 177.97; MS (ESI): m/z: 855.3 [M+Na^+]; HRMS (ESI): calcd for $C_{41}H_{54}BrClN_2O_9$+Na^+: 855.2593 [M+Na^+]; found: 855.2591.

4.4. General procedure for the synthesis of (*S*)-(4-fluorophenyl)(1*H*-indol-3-yl)methanamine 8h

A solution of compound **5h** (295 mg, 0.4 mmol) in dry methanol (2 mL) was treated with freshly prepared (0.5 M) solution of sodium methoxide (2 mL). The reaction mixture was stirred for 4 h (TLC control). Then a few drops of water were added to the mixture, and the mixture was neutralized with acetic acid. The mixture was stirred at room temperature for another 4 h. The mixture was extracted with EtOAc (3×5 mL) and the organic phase was washed with saturated aqueous $NaHCO_3$ (3×5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to yield the crude product **8h**. The residue was purified by column chromatography on silica gel [CH_2Cl_2/MeOH=30:1, with 0.1% Et_3N], yielding the corresponding compound **8h** (93 mg, 97% yield) as a white solid.

*4.4.1. Compound **8h**.* White solid, yield 97%; mp 108–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.92 (s, 1H, C–H), 6.94 (m, 3H, Ph), 6.99–7.05 (m, 1H, Ph), 7.13 (t, J=7.1 Hz, 1H, Ph), 7.27 (d, J=7.8 Hz, 1H, Ph), 7.31–7.46 (m, 3H, Ph), 8.45 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=53.15, 111.18, 119.48, 119.59, 121.66, 122.15, 126.06, 126.97, 128.45, 136.69, 145.68. HRMS (ESI): calcd for $C_{15}H_{13}FN_2$–H^+: 239.0990 [M–H]; found: 239.0995.

4.5. General procedure for the synthesis of (*S*)-benzyl(4-fluorophenyl)(1*H*-indol-3-yl)methylcarbamate 9h for % ee determination by chiral HPLC

Compound **8h** (30 mg, 0.125 mmol) was dissolved in THF (3 mL), after which water (1.5 mL) was added. The resulting mixture was vigorously stirred at 0 °C to which was added Na_2CO_3 (52 mg, 0.5 mmol, 4.0 equiv). The resulting mixture was stirred at 0 °C for 5 min, then benzyl chloroformate (42 mg, 0.25 mmol, 2.0 equiv) was introduced to this mixture via a syringe. The reaction mixture was stirred at room temperature for an additional 10 min, and then diluted with EtOAc (10 mL). The organic layer was collected, washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to flash chromatography on silica gel [petroleum ether/ethyl acetate, 5:1 to 3:1 (v/v)] to give compound **9h** (46 mg, 99% yield) as a pale pink oil.

*4.5.1. Compound **9h**.* Pink oil, yield 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.03 (d, $^2J_{H,H}$=12.3 Hz, 2H, CH_2), 5.41 (d, $^3J_{NH,H}$=6.9 Hz, 1H, C–H), 6.17 (d, $^3J_{NH,H}$=6.9 Hz, 1H, N–H), 6.56 (s, 1H, indole-2-H), 6.96 (t, J=7.4 Hz, 1H, Ph), 7.08 (t, J=7.5 Hz, 1H, Ph), 7. 15–7.31 (m, 10H, Ph), 7.36 (d, J=7.9 Hz, 1H, Ph), 8.11 (s, 1H, indole N–H); ^{13}C NMR (101 MHz, $CDCl_3$) δ=52.42, 66.91, 111.43, 117.32, 119.39, 119.91, 122.50, 123.41, 125.87, 126.93, 127.34, 128.10, 128.50, 136.55, 136.76, 141.69, 155.81.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.03.115.

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20. When 1-methyl-1*H*-indole was employed, a drop in the yield (75%) and diastereoselectivity (10:1) was observed. *N*-[1-Methyl-indol-3-yl-(4-chlorophenyl)methyl]-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosyl)amine (**5n**). White solid, mp 172–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.03 (s, 9H, C(CH_3)$_3$), 1.16 (s, 9H, C(CH_3)$_3$), 1.18 (s, 9H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$), 2.46 (d, $^{3}J_{1,NH}$=12.6 Hz, 1H, N–H), 3.62 (s, 3H, *N*–CH_3), 3.77 (t, $^{3}J_{5,6}$=6.7 Hz, 1H, 5-H), 3.92 (dd, $^{3}J_{1,NH}$=12.6 Hz, $^{3}J_{12}$=7.9 Hz, 1H, 1-H), 3.97 (dd, $^{2}J_{6a,6b}$=11.1 Hz, $^{3}J_{5,6a}$=6.7 Hz, 1H, 6a-H), 4.16 (dd, $^{2}J_{6a,6b}$=11.1 Hz, $^{3}J_{5,6b}$=6.7 Hz, 1H, 6b-H), 4.94–5.10 (m, 2H, 2-H, 3-H), 5.32 (s, 1H, 4-H), 5.59 (s, 1H, C–H), 6.66 (s, 1H, 2′-H), 6.99 (t, *J*=7.3 Hz, 1H, Ph), 7.13 (t, *J*=7.4 Hz, 1H, Ph), 7.19 (dd, *J*=8.1, 3.8 Hz, 3H, Ph), 7.35 (d, *J*=8.2 Hz, 2H, Ph), 7.57 (d, *J*=7.9 Hz, 1H, Ph); ^{13}C NMR (101 MHz, $CDCl_3$): δ=26.09, 26.16, 26.35, 31.73, 37.71, 37.75, 37.86, 38.06, 52.27, 60.85, 66.40, 68.01, 70.54, 70.64, 85.33, 108.33, 116.85, 118.15, 118.18, 120.95, 125.04, 125.34, 127.41, 128.37, 136.13, 131.76, 140.00, 175.90, 176.14, 176.45, 176.94; MS (ESI): *m*/*z*: 791.5 [M+Na^+]; HRMS (ESI): calcd for $C_{42}H_{57}ClN_2O_9$+Na^+: 791.3645 [M+Na^+]; found: 791.3631
21. Crystallographic data for the structural analysis of compound **5a** has been deposited at the Cambridge Crystallographic Data Centre as No. CCDC 787519. 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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