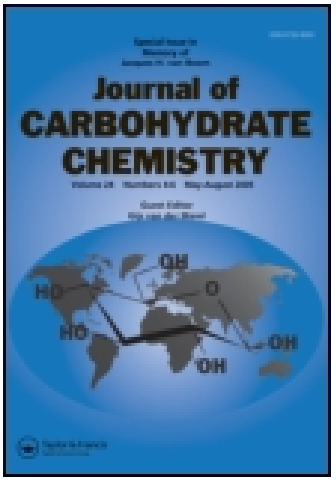

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Matched/Mismatched Interactions in Chiral Brønsted Acid-Catalyzed Glycosylation Reactions with 2-Deoxy-Sugar Trichloroacetimidate Donors

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The stereochemical outcome of glycosylation reactions of 2-deoxy-sugar trichloroacetimidates promoted by chiral Brønsted acids is shown to be dependent on both the chirality of the catalyst and the configuration of the leaving group. High levels of selectivity (1:16 α:β) can be obtained with (S)-catalysts and an α-trichloroacetimidate donor. Conversely, (R)-catalysts require longer reaction times and provide the product in much lower selectivity (6.6:1 α:β). These observations demonstrate that stereochemical "match" and "mismatch" between donor and acceptor are important factors in chiral Brønsted acid-promoted glycosylations.

Keywords Glycosylation; Diastereoselectivity; Brønsted acid; Deoxy-sugars

The routine construction of stereodefined glycosidic linkages remains a major challenge in organic chemistry. While a number of elegant approaches have been developed to control the stereochemical outcome of glycosylation reactions,[1] a general promoter system that provides high levels of selectivity with a broad range of substrates remains to be developed. This is especially true of glycosylation reactions utilizing 2-deoxy-sugar donors, which, owing to the lack of stabilizing and/or directing groups at C-2, frequently provide products as mixtures of anomers.[2–4] Particularly challenging is the case of β-linked 2-deoxy-sugars, for which only a handful of methods for direct synthesis

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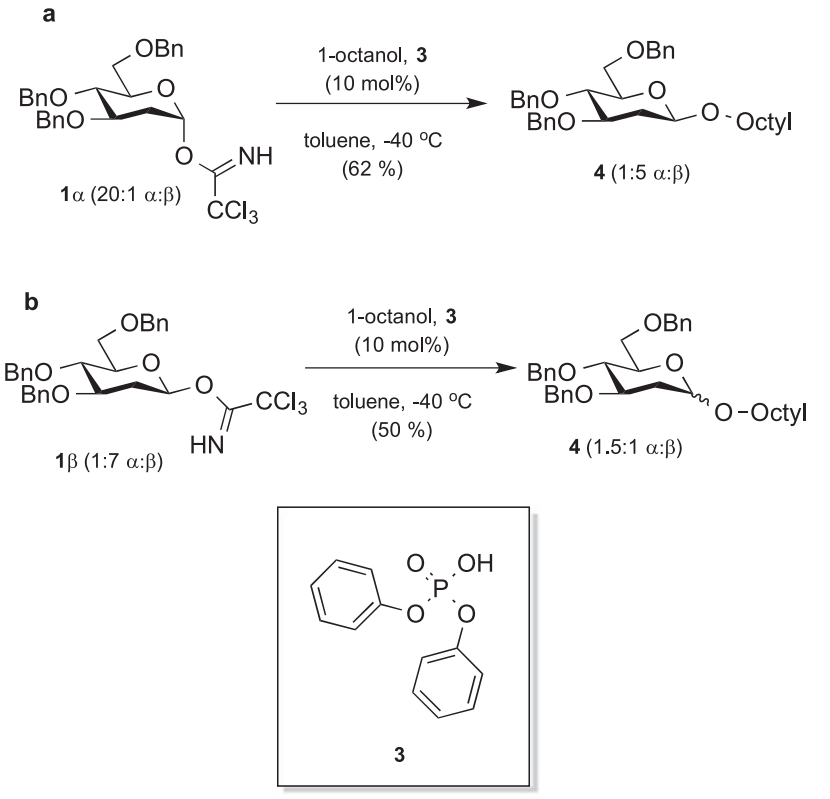
have been reported.[5–9] Consequently, many routes to 2-deoxy sugars rely on the use of temporary directing groups or de novo synthesis,[2,4] which necessarily requires the addition of several transformations to the synthetic route. Our group has an interest in addressing this issue through the development of promoters designed to place the stereoselectivity of glycosylation reactions with 2-deoxy-sugar donors entirely under the control of the glycosylation promoter.[10–13] In our continued effort in this area, we chose to examine chiral promoters that could be used in a catalytic fashion to control the selectivity of glycosylations.

The use of chiral catalysts to control the selectivity of additions to oxonium cations has gained significant interest in recent years.[14] Reports describing the application of this technology to glycosylation reactions are much less common. In 2010, Fairbanks and coworkers demonstrated that chiral BINOL-derived phosphoric acids could promote stereoselective glycosylation reactions between galactose-derived trichloroacetimidates and various acceptors.[15] While selectivity in the reaction was sensitive to the nature of the protecting groups on the donor, the reaction provided an elegant example of how diastereoselectivity in glycosylation reactions can be placed entirely under the control of the promoter. More recently, both the Toshima and Nagorny groups reported the use of similar catalysts for resolution of racemic acceptors during glycosylation and regioselective protection of carbohydrate diols, respectively.[16,17] In their study, the Toshima group noted that activation of α-trichloroacetimido-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside with (*S*)-BINOL provided useful levels of selectivity in glycosylations when simple acceptors were employed in the reaction. Intrigued by these results, we chose to examine whether a similar relationship between catalyst chirality and leaving group configuration existed with 2-deoxy-sugar donors. Here we report the results of model studies to determine these relationships.

For this study, we chose to examine the reaction between deoxy-sugar **1** and 1-octanol (**2**) as an achiral acceptor in order to eliminate any matching or mismatching between chiral reactants.[18] The diastereomerically enriched known imidates[19] **1**α and **1**β were prepared by treating the corresponding hemiacetal with trichloroacetonitrile in the presence of either NaH or K_2CO_3, according to the method of Schmidt.[20,21] It should be noted that these compounds were extremely reactive and had to be purified using aminopropyl silica gel and used immediately after purification. Owing to the instability of these molecules, we opted to conduct the study at low temperature (–40°C) to minimize substrate decomposition in the presence of the acid catalyst. We first examined the reaction between **1** and **2** promoted by achiral phosphoric acid **3** in order to determine the intrinsic diastereofacial preference of each substrate (Sch. 1). Under these conditions, the α-linked imidate **1**α reacted in a modestly selective fashion, providing the product **4** as a 1:5 mixture of α:β isomers (Sch.

1a). In contrast, the reaction using donor **1**β proceeded in lower yield and was much less selective (1.5:1 α:β, Sch. 1b).

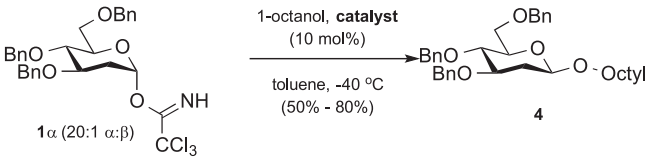


Scheme 1: Relationship between imidate configuration and product stereochemistry.

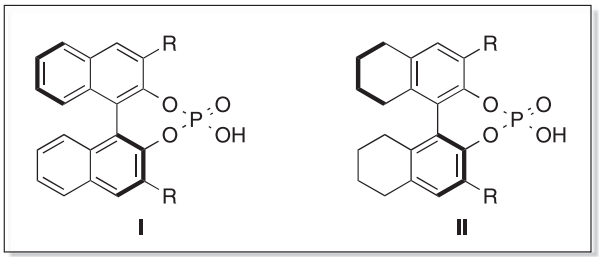
Since **1**α afforded higher levels of selectivity with achiral catalysts, we chose to use this substrate for catalyst optimization. To this end, we synthesized and screened a small library of catalysts in the reaction. We initially chose to examine (*S*)-catalysts, as both the Fairbanks and Toshima groups reported that they provide higher levels of induction than the corresponding (*R*)-catalysts in glycosylations.[15,16] Similar to control reactions, we used 1-octanol as a model acceptor and conducted the glycosylation at –40°C. The crude products from the reactions were analyzed using ^{1}H NMR to determine the diastereoselectivity of the reaction (Table 1). Through these studies we identified two catalysts, (*S*)-**5** and (*S*)-**11**, both of which increased the β-selectivity of the reaction from 5:1 to 16:1.

Having established which catalysts to use for optimal selectivity, we examined the effect of catalyst chirality on the course of the reaction. Upon scale-up, both (*S*)-**5** and (*S*)-**11** provided the desired glycosylation product in good yield

Table 1: Chiral Brønsted acid screen



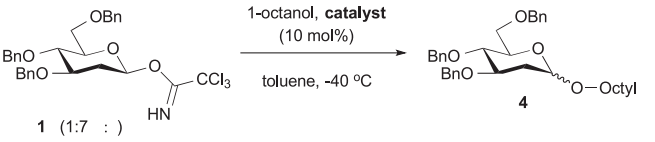
entry	catalyst	catalyst backbone	R	α:β
1	**5**	**I**	**2,4,6-*i*-Pr$_3$Ph**	**1:16**
2	**6**	**I**	4-adamantyl-2,6-*i*-Pr$_2$Ph	1:10
3	**7**	**I**	3,5-*t*-Bu$_2$Ph	NR
4	**8**	**I**	CHPh$_2$	1:8
5	**9**	**II**	Adamantyl	1:6
6	**10**	**II**	CH$_2$Ph	1:12
7	**11**	**II**	**4-adamantyl-2,6-*i*-Pr$_2$Ph**	**1:16**
8	**12**	**II**	CH(4-*t*-BuPh)$_2$	1:10
9	**13**	**II**	CH(3,5-*t*-Bu$_2$Ph)$_2$	1:10



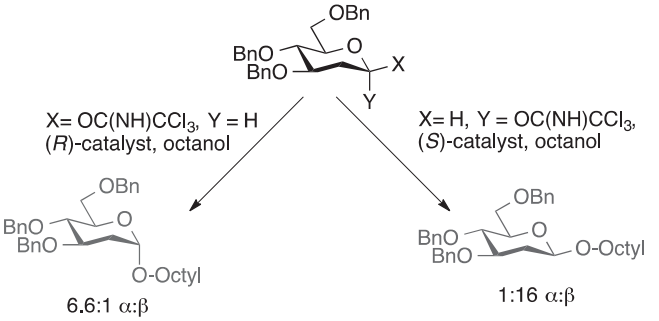
(80% and 75%, respectively) without a loss in selectivity (Table 2, entries 1 and 2). In an attempt to reverse the selectivity of the reaction, we examined the ability of catalysts (*R*)-**5** and (*R*)-**11** to promote the reaction. The use of these catalysts resulted in a decrease in the selectivity of the reaction compared to both (*S*)-catalysts and achiral **4** (Table 2, entries 3 and 4). These results indicate that the chirality of the catalyst is mismatched to the α-imidate donor. The lower selectivity observed with the larger (*R*)-**11** is presumably due to the bulky adamantyl group further reinforcing substrate/catalyst mismatch.

We reasoned that these results were due to the (*S*)-catalysts being "matched" with the α-imidate, while the (*R*)-catalysts were "mismatched" with this donor.[22] To establish that this was due to the configuration of the leaving group, we next examined the use of donor **1**β in the reaction (Table 3). We reasoned that since the (*S*)-catalysts gave high levels of selectivity with α-imidates, the corresponding (*R*)-catalysts would be able to reverse the selectivity of the reaction when the β-imidate was used as a donor. Once again we examined both enantiomers of **5** and **11** in the reaction. These studies showed

Table 2: Selectivities of catalyst with α-imidates



entry	catalyst	t(h)	yield(%)	α:β
1	(*S*)-**5**	60	80	1:16
2	(*S*)-**11**	44	75	1:16
3	(*R*)-**5**	168	73	1:4
4	(*R*)-**11**	168	33	1:2.5

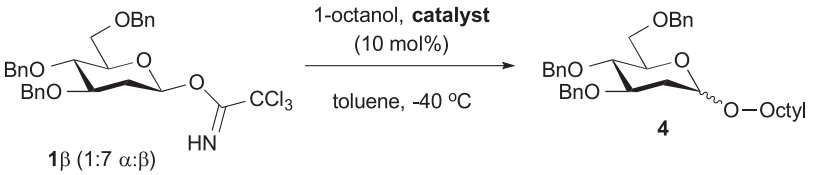


that changing the chirality of the catalyst affected the selectivity of the reaction; however, only catalyst (*R*)-**11** provided a significant enrichment of one anomer of the product over the other, albeit in low yield and with long reaction times (entry 4).

The fact that we were unable to obtain the high levels of β-selectivity using the β-imidate and the (*S*)-catalysts further underlines the importance of the leaving group configuration. We believe that different reaction manifolds are at play here, with both the configuration of the imidate and the catalyst dictating what pathway the reaction will take. In the case of the highly β-selective reaction between the α-imidate and the (*S*)-catalyst, the reaction most likely proceeds through hydrogen bond activation, leading to an S_N2-like manifold, similar to what has been proposed by the Toshima group.[16] The much lower selectivity observed with this catalyst and the β-imidate is more consistent with substrate ionization and subsequent S_N1 reaction with the resulting oxocarbenium cation. In addition, the longer reaction times point to stereochemical mismatch between the D-pyranose backbone and the (*R*)-catalyst.

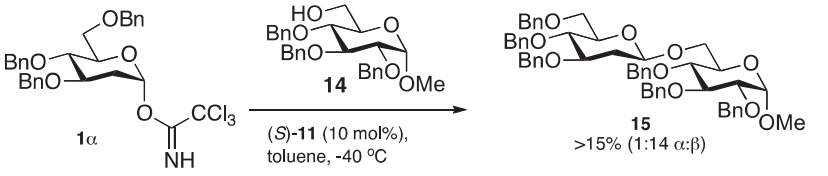
Having established the optimal combination of donor reactivity and catalyst chirality, we turned our attention to the ability of the catalyst to promote the formation of disaccharides. To this end, we examined the ability of the (*S*)-**11** to promote the reaction between **1**α and **14** (Sch. 2). While the reaction again

Table 3: Selectivities of catalyst with β-imidate



entry	catalyst	t(h)	yield(%)	α:β
1	(*S*)-**5**	42	83	1:2
2	(*S*)-**11**	77	78	1:1.6
3	(*R*)-**5**	77	79	1.4:1
4	(*R*)-**11**	168	39	6.6:1

appeared to be selective for one anomer, the product **15**[13] was obtained in very low yield (>15%) and was accompanied by significant amounts of glucal formation. The results indicate that these catalysts are not effective promoters for the reaction between 2-deoxy-sugar imidates and complex alcohol acceptors.



Scheme 2: Attempts to extend methodology to more hindered acceptors.

From these observations, we conclude that the ability of the chiral phosphoric acids to control diastereoselective glycosylations is highly sensitive to the configuration of the leaving group. Accordingly, we feel it unlikely that a single enantiomeric pair of catalysts will be able to serve as universally selective glycosylation promoters. Rather, for this approach to be successful, it will be necessary to construct a toolbox of chiral promoters, based on different scaffolds, for different classes of monosaccharides.

In conclusion, we have demonstrated that for chiral Brønsted acids to be effective promoters for glycosylations with trichloroacetimidate donors, they must be carefully matched to the configuration of the leaving group. These results indicate that this particular class of catalysts may at best have utility as promoters for a small subset of diastereoselective glycosylation reactions. More importantly, they illustrate that great care must be taken when attempting to use chiral Brønsted acid catalysts to control diastereoselectivity in glycosylation reactions, even in cases such as 2-deoxy-sugars where chirality is distal from the reaction center.

EXPERIMENTAL

General Experimental

All reactions were carried out in oven- or flame-dried glassware under an argon atmosphere unless otherwise noted. Reactions were monitored by analytical thin layer chromatography (TLC) using Merck precoated silica gel plates or Wako precoated NH_2 silica gel (both 0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm) and phosphomolybdic acid stain. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted. Reagents and solvents were purchased at the highest commercial quality and used as received unless otherwise noted. Toluene, dichloromethane, and THF were dried using a PURE SOLV solvent purification system from Innovative Technology. 1-Octanol (99+%) purchased from Aldrich was dried over sodium, distilled under reduced pressure, and stored over 4Å molecular sieves. Potassium carbonate was heated to 100°C under high vacuum overnight prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500-HMZ spectrometer. Mass spectra were obtained with a Thermo-Finnigan LTQ ESI mass spectrometer. Optical rotations were measured using an AUTOPOL IV digital polarimeter (Rudolph Research Analytical, NJ).

Synthesis of Glycosyl Donors

The compounds 3,4,6-tri-*O*-benzyl-2-deoxy-α/β-D-glucopyranosyl trichloroacetimidate[19] were prepared according to the procedures introduced by Schmidt et al.[20,21]

*3,4,6-Tri-*O*-benzyl-2-deoxy-α-D-glucopyranosyl trichloroacetimidate (1α).* NaH (neat 27 mg, pretreated with anhydrous pentane) was added to a solution of 3,4,6-Tri-*O*-benzyl-2-deoxyglucopyranose[23] (270 mg, 0.62 mmol, 1.0 eq) and trichloroacetonitrile (0.30 mL, 5.0 eq) in dichloromethane (3 mL) at rt. After stirring for 1 h, hexanes (6 mL) were added and the reaction mixture was filtered through a plug of aminopropyl silica gel, washed with hexanes/dichloromethane (2:1), and concentrated in vacuo to afford **1**α (348 mg, 97% yield, $\alpha:\beta = 25:1$) possessing spectroscopic data identical with literature values.

*3,4,6-Tri-*O*-benzyl-2-deoxy-β-D-glucopyranosyl trichloroacetimidate (1β).* Freshly dried potassium carbonate (260 mg) was added to a solution of 3,4,6-tri-*O*-benzyl-2-deoxyglucopyranose (226 mg, 0.52 mmol, 1.0 eq) in dichloromethane (2.6 mL) under ice cooling (3°C). Then trichloroacetonitrile (0.13 mL, 2.5 eq) was added to the mixture. After 4 h of stirring at this temperature, hexane (5.2 mL) was added and the mixture was filtered through a short pad of aminopropyl silica gel, washed with *n*-hexane/dichloromethane

(2:1), and concentrated in vacuo to afford **1**β (239 mg, 82% yield, β:α = 7:1) as a colorless syrup with spectroscopic data identical to literature values.

Typical Glycosylation Procedure

Glycosyl donors and phosphate catalysts were individually dried by co-evaporation with toluene in vacuo (3×). A solution of the catalyst (10 mol%) in toluene (0.3 mL) was added dropwise to a solution of glycosyl donor (100 mg, 0.17 mmol) and *n*-octanol (54 μL, 0.34 mmol) in toluene (1.4 mL) at −40°C. The reaction mixture was stirred for the time indicated in the tables, then quenched with triethylamine (0.2 mL), warmed to rt, and concentrated. The residue was purified by flash chromatography on silica gel using hexanes/ethyl acetate (8:1) as eluent. The spectroscopic data of the above isolated product *n*n–octyl 3,4,6-tri-*O*-benzyl-2-deoxy-α/β-D-*arabino*-hexopyranoside were identical with literature values.[24]

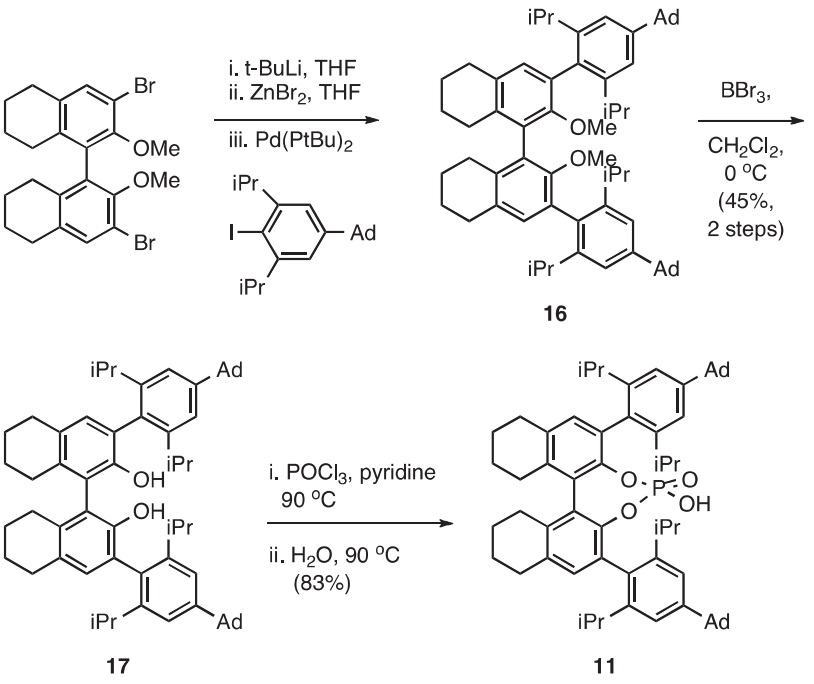
n-*Octyl 3,4,6-tri*-O-*benzyl-2-deoxy-β-D*-arabino-*hexopyranoside*[24] *(4β).* ^{1}H NMR (500 MHz, d_6-DMSO): δ = 7.24−7.36 (m, 13 H), 7.18−7.22 (m, 2 H), 4.79 (d, J = 11 Hz, 1 H), 4.65 (d, J = 12 Hz, 1 H), 4.46−4.57 (m, 5 H), 3.69−3.75 (m, 1 H), 3.59−3.69 (m, 3 H), 3.37−3.44 (m, 2 H), 3.30−3.35 (m, 1 H), 2.32 (m, 1 H), 1.50 (m, 2 H), 1.17−1.37 (m, 11 H), 0.85 (t, J = 6.9 Hz, 3 H).

n-*Octyl 3,4,6-tri*-O-*benzyl-2-deoxy-α-D*-arabino-*hexopyranoside*[24] *(4α).* ^{1}H NMR (500 MHz, d_6-DMSO): δ = 7.24−7.36 (m, 13H), 7.18−7.22 (m, 2H), 4.88 (d, J = 2.4 Hz, 1H), 4.79 (d, J = 11.1 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H), 4.44−4.56 (m, 4H), 3.75−3.83 (m, 1H), 3.58−3.69 (m, 3H), 3.49−3.56 (m, 1H), 3.35−3.43 (m, 1H), 3.28−3.35 (m, 1H), 2.23 (dd, J = 12.2, 5.1 Hz, 1H), 1.44−1.55 (m, 3H), 1.16−1.31 (m, 10H), 0.83 (t, J = 6.9 Hz, 3H).

*Synthesis of Catalyst (*S*)- and (*R*)-11*

The synthesis of catalyst **11** was carried out according to the route shown in Scheme 3.

*(*S *or* R*)-3,3′-Bis[4-(1-adamantyl)-2,6-diisopropylphenyl]-5,5′,6,6′,7,7′,8,8′-octahydro-2,2′-dimethoxy-1,1′-binaphthyl (16). tert*-Butyl lithium (1.7 M in pentane, 0.51 mL, 4.2 eq) was slowly added to a solution of (*S*)-3,3'-Dibromo-5,5',6,6',7,7',8,8'-octahydro-2,2'-dimethoxy-1,1'-binaphthyl[25,26] (0.10 g, 0.21 mmol, 1.0 eq) in tetrahydrofuran (1 mL) at −78°C. After 1 h of stirring, a solution of $ZnBr_2$ (0.13 g, 2.8 eq) in tetrahydrofuran (0.5 mL) was added. The reaction was stirred at –78°C for 20 min, then warmed to rt. After stirring for an additional hour, the reaction was treated with 4-(1-adamantyl)-2,6-diisopropylphenyl iodide[27] (0.20 g, 2.3 eq) and $Pd(P^tBu_3)_2$ and heated to 70°C for 40 h. The reaction was then cooled to rt, treated with 3 N HCl (10 mL), and extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. Flash chromatography (silica gel, 100% hexanes → 40:1 hexanes/ethyl acetate) afforded a pale yellow solid mixture (0.12 g) of the title product and



Scheme 3: Synthesis of catalysts **11**.

mono-coupling side product, which could be used for the next step without further purification. Analytically pure (*S*)-product was isolated by flash chromatography on silica gel using hexanes/dichloromethane (8:1), while the (*R*)-enantiomer was not further purified and characterized. mp >297°C (dec.); $[\alpha]_D^{27.5^\circ C} = +28$ (*S*, c 1.25, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.16$ (d, $J = 1.8$ Hz, 2H), 7.15 (d, $J = 1.8$ Hz, 2H), 6.79 (s, 2H), 3.08 (s, 6H), 2.72–2.87 (m, 8H), 2.38–2.47 (m, 2H), 2.18–2.27 (m, 2H), 2.1 (m, 6H), 1.97 (m, 12H), 1.68–1.85 (m, 20H), 1.19 (d, $J = 6.8$ Hz, 6H), 1.14 (d, $J = 6.6$ Hz, 6H), 1.13 (d, $J = 6.7$ Hz, 6H), 1.12 (d, $J = 6.7$ Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.9, 150.0, 146.4, 146.2, 135.4, 133.7, 131.4, 131.3, 130.7, 129.8, 118.9, 118.8, 59.1, 43.3, 37.0, 36.4, 30.8, 30.6, 29.4, 29.2, 27.3, 25.6, 25.4, 23.6, 23.4, 23.3, 23.2. MS (ESI) m/z: calcd for $C_{66}H_{86}O_2Na$ $[M+Na]^+$ 933.6, found: 933.4. HRMS (ESI) m/z: calcd for $C_{66}H_{86}O_2Na$ $[M+Na]^+$ 933.6520, found 933.6513.

*(*S *or* R*)-3,3′-Bis[4-(1-adamantyl)-2,6-diisopropylphenyl]-5,5′,6,6′,7,7′,8,8′-octahydro-2,2′-dihydroxy-1,1′-binaphthyl (17).* The above pale yellow crude solid (0.11 g) was dissolved in dichloromethane (3 mL), cooled at 0°C, and treated with boron tribromide (1 M in dichloromethane, 0.85 mL). After 30 min the reaction mixture was warmed up to rt and stirred for 21 h. The reaction was then cooled to 0°C, quenched with water (10 mL), and warmed to

rt. The mixture was extracted with dichloromethane (2 × 20 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash chromatography (silica gel, 40:1 hexanes/ethyl acetate → 20:1 hexanes/ethyl acetate) afforded the title product (76 mg, 45% yield over two steps). mp >292°C (dec.); $[\alpha]_D^{26.5^\circ C} = +35$ (*S*, c 0.75, $CHCl_3$); $[\alpha]_D^{27.7^\circ C} = -33$ (*R*, c 1.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, J = 1.8 Hz, 2H), 7.19 (d, J = 1.8 Hz, 2H), 6.83 (s, 2H), 4.40 (s, 2H), 2.72–2.85 (m, 6H), 2.66 (septet, J = 6.8 Hz, 2H), 2.30–2.47 (m, 4H), 2.11 (m, 6H), 1.97 (m_c, 12H), 1.70–1.85 (m, 20H), 1.15 (d, J = 6.9 Hz, 6H), 1.11 (d, J = 6.9 Hz, 6H), 1.06 (d, J = 6.9 Hz, 6H), 1.00 (d, J = 6.9 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.8, 148.5, 147.3, 147.1, 135.8, 131.1, 130.9, 129.0, 124.1, 120.5, 119.3, 119.2, 43.2, 36.9, 36.4, 30.8, 30.7, 29.2, 29.1, 27.0, 24.3, 24.1, 23.9, 23.2, 23.1. MS (ESI) m/z: calcd for $C_{64}H_{82}O_2Na$ $[M+Na]^+$ 905.6, found: 905.5. HRMS (ESI) m/z: calcd for $C_{64}H_{82}O_2Na$ $[M+Na]^+$ 905.6207, found 905.6228

*(*S *or* R*)-3,3′-Bis[4-(1-adamantyl)-2,6-diisopropylphenyl]-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl phosphate (11).* Phosphorous oxychloride (0.14 mL, 4.2 eq) was slowly added to a solution of (*S*)-3,3′-bis[4-(1-adamantyl)-2,6-diisopropylphenyl′-5,5′,6,6′,7,7′,8,8′-octahydro-2,2′-dihydroxy-1,1′-binaphthyl (0.32 g, 0.37 mmol, 1.0 eq) in pyridine (3.6 mL) at rt. The reaction mixture was then heated to 90°C for 17 h, then cooled to rt. The reaction was then treated with water (3.6 mL) and heated to 90°C for 6 h. After cooling to rt, the solvent was removed in vacuo, and the residue was partitioned between dichloromethane (30 mL) and 6 N HCl (10 mL). The aqueous layer was extracted with dichloromethane (30 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 100% dichloromethane → 50:1 dichloromethane/methanol → 20:1 dichloromethane/methanol). The product was partitioned between dichloromethane (50 mL) and 4 N HCl (10 mL), and the organic layer was dried over sodium sulfate, filtered, and concentrated to provide **10** (289 mg, 83% yield) as a pale yellow solid. Analytically pure compound could be obtained by further flash chromatography on silica gel using hexanes/ethyl acetate (1:1) and acidifying with 4 N HCl. mp >270°C (dec.); $[\alpha]_D^{27.2^\circ C} = +89$ (*S*, c 0.49, $CHCl_3$); −85 (*R*, c 0.40, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.04 (d, J = 1.6 Hz, 2H), 7.02 (d, J = 1.6 Hz, 2H), 6.94 (s, 2H), 2.74–2.89 (m, 6H), 2.59 (septet, J = 6.8 Hz, 2H), 2.45–2.57 (m, 2H), 2.27–2.38 (m, 2H), 2.06 (m, 6H), 1.68–1.95 (m, 32H), 1.07 (d, J = 6.7 Hz, 6H), 0.98 (m, 6H), 0.89 (d, J = 6.8 Hz, 6H), 0.79 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.0, 147.2, 146.6, 144.2 (J = 9.0 Hz), 136.5, 133.8, 132.6, 131.5, 129.6, 126.9, 119.2, 118.3, 43.2, 37.0, 36.3, 30.8, 30.7, 29.3, 29.1, 27.9, 26.7, 25.1, 23.5, 23.0, 22.9. MS (ESI) m/z: calcd for $C_{64}H_{80}O_4P$ $[M-H]^-$

943.6, found: 943.7. HRMS (ESI) m/z: calcd for $C_{64}H_{80}O_4P$ $[M\text{-}H]^-$ 943.5800, found 943.5778.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

REFERENCES

1. Zhu, X.; Schmidt, R.R. New principles for glycoside-bond formation. *Angew. Chem. Int. Ed.* **2009**, *48*, 1900.

2. Hou, D.; Lowary, T.L. Recent advances in the synthesis of 2-deoxy-glycosides. *Carbohydr. Res.* **2009**, *344*, 1911.

3. Crich, D. Methodology development and physical organic chemistry: a powerful combination for the advancement of glycochemistry. *J. Org. Chem.* **2011**, *76*, 9193.

4. Borovika, A.; Nagorny, P. Recent advances in the synthesis of natural 2-deoxy-β-glycosides. *J. Carbohydr. Chem.* **2013**, *31*, 255–283.

5. Hashimoto, S.-i.; Sano, A.; Sakamoto, H.; Nakajima, M.; Yanagiya, Y.; Ikegami, S. An attempt at the direct construction of 2-deoxy-β-glycosidic linkages capitalizing on 2-deoxyglycopyranosyl diethyl phosphites as glycosyl donors. *Synlett* **1995**, 1271–1273.

6. Lam, S.N.; Gervay-Hague, J. Efficient route to 2-deoxy β-*O*-aryl-D-glycosides via direct displacement of glycosyl iodides. *Org. Lett.* **2003**, *5*, 4219–4222.

7. Tanaka, H.; Yoshizawa, A.; Takahashi, T. Direct and stereoselective synthesis of β-linked 2,6-deoxyoligosaccharides. *Angew. Chem. Int. Ed.* **2007**, *46*, 2505–2507.

8. Baryal, K.N.; Adhikari, S.; Zhu, J. Catalytic stereoselective synthesis of β-digitoxosides: direct synthesis of digitoxin and C1'-epi-digitoxin. *J. Org. Chem.* **2013**, *78*, 12469–12476.

9. Zhu, D.; Baryal, K.N.; Adhikari, S.; Zhu, J. Direct synthesis of 2-deoxy-β-glycosides via anomeric *O*-alkylation with secondary electrophiles. *J. Am. Chem. Soc.* **2014**, *136*, 3172–3175.

10. Nogueira, J.M.; Nguyen, S.N.; Bennett, C.S. Cyclopropenium cation promoted dehydrative glycosylations using 2-deoxy- and 2,6-dideoxy-sugars. *Org. Lett.* **2011**, *13*, 2814.

11. Nogueira, J.M.; Issa, J.P.; Chu, A.-H.; Sisel, J.A.; Schum, R.S.; Bennett, C.S. Halide effects on cyclopropenium cation promoted glycosylation with deoxy sugars: highly α-selective glycosylations using a 3,3-dibromo-1,2-diphenylcyclpropene promoter. *Eur. J. Org. Chem.* **2012**, 4927–4930.

12. Issa, J.P.; Lloyd, D.; Steliotes, E.; Bennett, C.S. Reagent controlled β-specific dehydrative glycosylation reactions with 2-deoxy-sugars. *Org. Lett.* **2013**, *15*, 4170–4173.

13. Issa, J.P.; Bennett, C.S. A reagent-controlled S_N2-glycosylation for the direct synthesis of β-linked 2-deoxy-sugars. *J. Am. Chem. Soc.* **2014**, *136*, 5740–5744.

14. Brak, K.; Jacobsen, E.N. Asymmetric ion-pairing catalysis *Angew. Chem. Int. Ed.* **2013**, *52*, 534–561.

15. Cox, D.J.; Smith, M.D.; Fairbanks, A.J. Glycosylation catalyzed by a chiral Brønsted acid. *Org. Lett.* **2010**, *12*, 1452.

16. Kimura, T.; Sekine, M.; Takahashi, D.; Toshima, K. Chiral Brønsted acid mediated glycosylation with recognition of alcohol chirality. *Angew. Chem. Int. Ed.* **2013**, *52*, 12131–12134.

17. Mensah, E.; Camasso, N.; Kaplan, W.; Nagorny, P. Chiral phosphoric acid directed regioselective acetalization of carbohydrate-derived 1,2-diols. *Angew. Chem. Int. Ed.* **2013**, *52*, 12932–12936.

18. Spijker, N.M.; van Boeckel, C.A.A. Double stereodifferentiation in carbohydrate coupling reactions: the mismatched interaction of donor and acceptor as an unprecedented factor governing the α/β ratio of glycoside formation. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 180.

19. Schene, H.; Waldman, H. Synthesis of deoxy glycosides under neutral conditions in $LiClO_4$/solvent mixtures. *Synthesis* **1999**, 1411.

20. Schmidt, R.R.; Michel, J.; Roos, M. Glycosylimidate, 12 direkte synthese von *O*-α- und *O*-β-glycosylimidaten. *Liebigs Ann. Chem.* **1984**, 1343.

21. Schmidt, R.R.; Stumpp, M. Glycosylimidate, 8. Synthese von 1-thioglycosiden. *Liebigs Ann. Chem.* **1983**, 1249.

22. Masamune, S.; Choy, W.; Peterson, J.S.; Sita, L.R. Double asymmetric synthesis and a new strategy for stereochemical control in organic synthesis. *Angew. Chem. Int. Ed.* **1985**, *24*, 1.

23. Barnes, N.J.; Probert, M.A.; Wightman, R.H. Synthesis of 2-deoxy-α- and –β-*arabino*-hexopyranosyl phosphonic acids and related compounds. *J. Chem. Soc., Perkin Trans. 1* **1996**, 431.

24. Rauter, A.P.; Almeida, T.; Vicente, A.I.; Ribeiro, V.; Bordado, J.C.; Marques, J.P.; Ribeiro, F.R.; Ferreira, M.J.; Oliveira, C.; Guisnet, M. Reactions of N-, *S*-, and *O*-nucleophiles with 3,4,6-tri-*O*-benzyl-D-glucal mediated by triphenylphosphane hydrobromide versus those with HY zeolite. *Eur. J. Org. Chem.* **2006**, 2429.

25. McDougal, N.T.; Trevellini, W.L.; Rodgen, S.A.; Kliman, L.T.; Schaus, S.E. The development of the asymmetric Morita-Baylis-Hillman reaction catalyzed by chiral Brønsted acids. *Adv. Synth. Catal.* **2004**, *346*, 1231.

26. Schrock, R.R.; Jamieson, J.Y.; Dolman, S.J.; Miller, S.A.; Bonitatebus Jr., P.J.; Hoveyda, A.H. New chiral molybdenum catalysts for asymmetric olefin metathesis that contain 3,3'-disubstituted octahydrobinaphtholare or 2,6- dichlorophenylimido ligands. *Organometallics* **2002**, *21*, 409.

27. Jiao, P.; Nakashima, D.; Yamamoto, H. Enantioselective 1,3-dipolar cycloaddition of nitrones with ethyl vinyl ether: the difference between Brønsted and Lewis acids. *Angew. Chem. Int. Ed.* **2008**, *47*, 2411.