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Evaluation of disaccharide-based ligands for Pd(0)-catalyzed asymmetric allylations

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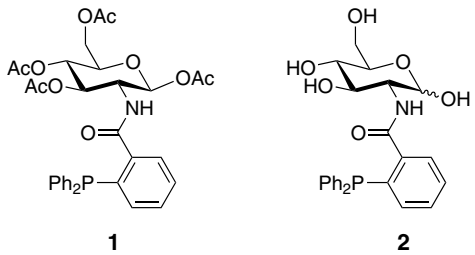
Abstract—A series of phosphines based on disaccharides containing a D-glucosamine framework were prepared and tested for their abilities as ligands for the palladium(0)-catalyzed asymmetric allylic allylation of racemic 1,3-diphenyl-2-propenyl acetate with various nucleophiles. In contrast to previous results exploiting monosaccharides, the iminophosphines generally afforded higher enantiomeric excesses, up to 99%.

Asymmetric allylic alkylation catalyzed by palladium(0) complexes represents a synthetically valuable protocol for the construction of asymmetric carbon–carbon and carbon-heteroatom bonds.[1] Although many asymmetric catalytic systems have been described, Trost's P–P ligand[2] and Pfaltz's P–N ligand[3] are amongst the best ligands for these reactions providing enantioselectivities as high as 95%. Nevertheless, for the achievement of high catalytic activity as well as high enantioselectivity, typically several experimental parameters require optimization of which one is the ligand structure.

Within the last few years, there has been an increasing interest in the application of chiral ligands prepared from carbohydrates in asymmetric catalysis.[4] The configurational and conformational diversity among these highly functionalized compounds provide excellent basis for the preparation of new chiral ligands. The design and fine-tuning of carbohydrate-based ligands is facilitated by the multiple functional groups within this class of compounds. Several sugar ligands have already been reported in the literature for asymmetric allylic alkylation including P–N, P–P, S–S, and S–X (X = P or N) type ligands derived from ferrocenylglucose,[5] bis-thioglycosides[6] and oxazoline-thioglucose.[7] However, the most successful so far includes a phosphinoaryloxazoline,[8] as well as a phosphinite-oxazoline ligand, both derived from D-glucosamine.[9]

An alternative and structurally simpler carbohydrate-based P–O ligand was introduced by Denis Sinou's group in 2003 represented by phosphine-amide **1** in Figure 1.[10] This ligand is easily prepared from readily available 1,3,4,6-tetra-*O*-acetylglucosamine and provides enantioselectivities up to 97% in the Pd(0)-catalyzed allylic alkylation of 1,3-diphenyl-2-propenyl acetate with a variety of nucleophiles. The acetyl groups on the ligand were necessary for obtaining high ees in these reactions, since similar experiments carried out with the nonacetylated derivative **2** led to the formation of an inactive catalyst.[10]



1 **2**

Figure 1.

Keywords: Disaccharide; D-Glucosamine; Iminophosphine; Asymmetric allylation; Palladium.
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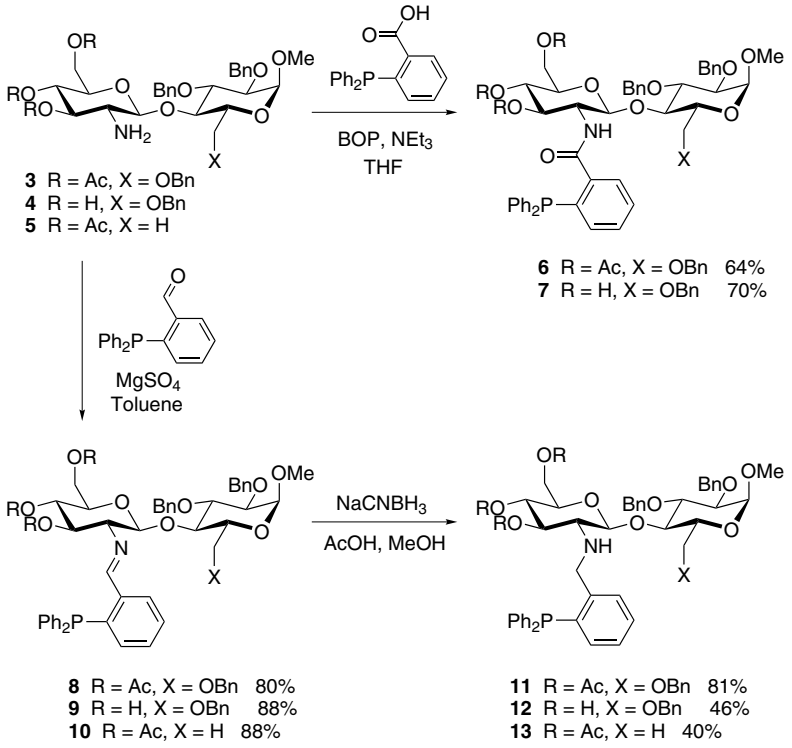
In this Letter, we report the influence of an additional sugar ring at the anomeric position of these carbohydrate ligands in this palladium catalyzed allylic alkylation. In contrast to observations made with the monosaccharide ligands,[11] the disaccharide phosphine-imines proved superior to the corresponding phosphine-amides, providing higher enantiomeric excesses. In addition, the acetylation of the glucosamine unit was not required for the obtention of high enantioselectivities.

In a previous paper, we described the synthesis of three disaccharides **3**, **4** and **5** all containing a free primary amine (Scheme 1).[12] Functionalization of these amines with different phosphine derivatives gives access to a variety of monophosphine ligands. Phosphine-amide ligands **6** and **7** were obtained in yields of 64% and 70% respectively, from the coupling of *o*-(diphenylphosphino)benzoic acid with the primary amine of the disaccharide, using BOP[13] as the coupling reagent in the presence of triethylamine. Compared to phosphine-amide ligand **1** generated from D-glucosamine, the two corresponding ligands **6** and **7** derived from **3** and **4**, respectively, possess a bulky sugar unit in the anomeric position of the D-glucosamine unit instead of an acetate group. With the presence of the *O*-benzyl groups on the D-glucose sugar, it was expected that only a slight difference in the solubility properties between the disaccharides would exist, thereby allowing a comparison of the influence of such ligands on the reactivity and enantioselectivity of the catalyst with or without the acetyl groups on the D-glucosamine unit.

The analogous imino- and aminophosphine ligands **8**–**10** and **11**–**13** were also synthesized in order to compare their reactivity with **6** and **7**, although previous work with the monosaccharide revealed these P–P or P–N types of ligands to be inferior to phosphine-amide **1**.[11] Iminophosphines **8** and **9** were prepared in good yields by the condensation of *o*-(diphenylphosphino)benzylaldehyde with the corresponding D-glucosamine derivatives **3** and **4** in toluene using $MgSO_4$ as a drying agent under inert atmosphere. The imino functionality was then reduced with $NaBH_3CN$ to provide amines **11** and **12** with yields in the range of 40–81%. All ligands derived from disaccharides were purified using silica gel chromatography under inert atmosphere. Finally, an amino- and iminophosphine ligands **10** and **13** were synthesized from C6-deoxy disaccharide **5**. Removal of the benzyloxy group allows a preliminary assessment of the role of this C6-substituent on the catalyst activity, to determine whether the overall sterical bulk of the D-glucose sugar is necessary, or whether there is a possible participation of a benzyl group in the shielding of one of the two faces of the allyl palladium(II) cation intermediate.

The results of the palladium-catalyzed allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate with dimethyl malonate reaction applying the chiral disaccharide-based ligands are summarized in Table 1. The reactions were performed in THF (0.125 M) using 2 mol % of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 4–8 mol % ligand with variations in both the reaction temperature and base.[10] Several interesting trends were noted from this study. Of the three phosphine ligands **6**, **8** and **11** bearing a



3 R = Ac, X = OBn
4 R = H, X = OBn
5 R = Ac, X = H

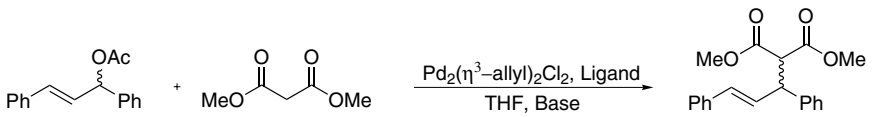
6 R = Ac, X = OBn 64%
7 R = H, X = OBn 70%

8 R = Ac, X = OBn 80%
9 R = H, X = OBn 88%
10 R = Ac, X = H 88%

11 R = Ac, X = OBn 81%
12 R = H, X = OBn 46%
13 R = Ac, X = H 40%

Scheme 1.

Table 1. Pd(0)-catalyzed allylic alkylation studies using disaccharide-based phosphine ligands[a]



Entry	Ligand	Pd/L	Time (h)	Temp. (°C)	Base	Conv.[b] (%)	Yield[c] (%)	ee[d] (%) (config.)[e]
1	**6**	1/1	24	60	BSA-KOAc	73	65	56 (*S*)
2	**6**	1/2	48	60	BSA-KOAc	15	—	44 (*R*)
3	**8**	1/1	24	25	BSA-KOAc	100	98	68 (*S*)
4	**8**	1/2	24	25	BSA-KOAc	82	77	86 (*S*)
5	**11**	1/1	24	25	BSA-KOAc	100	98	39 (*S*)
6	**11**	1/2	24	25	BSA-KOAc	78	68	31 (*S*)
7	**10**	1/1	24	25	BSA-KOAc	100	98	81 (*S*)
8	**10**	1/2	24	25	BSA-KOAc	60	55	81 (*S*)
9	**13**	1/1	24	25	BSA-KOAc	60	54	47 (*S*)
10	**13**	1/2	24	25	BSA-KOAc	45	38	49 (*S*)
11	**9**	1/1	96	25	K_2CO_3	21	—	85 (*S*)
12	**9**		24	60	K_2CO_3	32	—	68 (*S*)
13	**9**	1/2	24	25	K_2CO_3	96	93	88 (*S*)
14	**7**	1/1	24	25	K_2CO_3	0	—	—
15	**7**		72	60	K_2CO_3	15	—	12 (*S*)
16	**7**	1/2	72	25	K_2CO_3	<5	—	—
17	**7**		24	60	K_2CO_3	53	48	76 (*S*)
18	**12**	1/1	48	25	BSA-KOAc	37	–	31 (*S*)
19	**12**		48	25	K_2CO_3	70	68	32 (*S*)
20	**12**		24	60	K_2CO_3	95	91	30 (*S*)
21	**12**	1/2	24	25	K_2CO_3	44	–	31 (*S*)
22	**12**		24	60	K_2CO_3	91	88	32 (*S*)

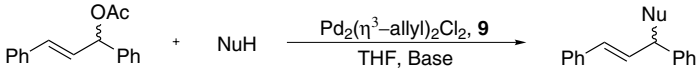
[a] [1,3-Diphenyl-2-propenyl acetate]/[dimethyl malonate]/[Base]/[Pd] = 1/3/3/0.02; solvent [0.125 M].
[b] Conversion determined by GC analysis.
[c] Isolated pure product.
[d] Determined by HPLC analysis (column Chiralpak AD 0.46 × 25 cm).
[e] Determined by comparison with an authentic sample.

3,4,6-triacetylated D-glucosamine unit (Table 1, entries 1–6), the iminophosphine derivative **8** provided the highest enantioselecitivity (86% ee), exceeding that of the monosaccharide phosphine-amide **1** (83% ee).[10a] Best results were obtained with a ligand/Pd ratio of 2:1 (Table 1, entry 4), suggesting that the imino ligand binds to the palladium metal centre in a monodentate fashion, in contrast to the bidentate nature of the phosphine-amide ligands. Interestingly, the configuration of the obtained product is opposite to that observed for the reactions exploiting ligand **1**.[10] Phosphine-amide **6** afforded lower ees compared to monosaccharide ligand **1**, suggesting that the addition of a bulky unit at C1 has a detrimental affect on the asymmetric induction of these ligands. Whereas good conversions were observed for aminophosphine **11** with a ligand/Pd ratio of 1:1 (Table 1, entry 5), disaccharide amide ligand proved less reactive (Table 1, entry 1). In any case, the higher enantiomeric excesses observed for both phosphines with a ligand/Pd ratio of 1:1 supports a bidentate role for these types of ligands. Allylation reactions performed with the disaccharide ligand **10** lacking a C6-benzyloxy group, afforded good ees suggesting that this substituent is not important for either reactivity or enantioselectivity (Table 1, entries 7 and 8). The higher reactivity of the catalyst composed of a ligand/Pd ratio of 1:1 is nevertheless puzzling. On the other hand, a decrease in reactivity of the aminophosphine was observed with ligand **13** compared to **11**, whereas a small increase in the ees followed (Table 1, entries 9 and 10).

To our surprise, iminophosphine ligand **9**,[14] displaying free hydroxyl groups on the D-glucosamine framework resulted in an exceptionally high reactivity and enantioselectivity (93% yield, 88% ee) after a reaction time of 24 h at 20 °C (Table 1, entry 13). A ligand/Pd ratio of 2:1 was again the preferred combination for the generation of an active catalyst. As in the previous experiments, the corresponding phosphine-amide or aminophosphine **7** and **12**, respectively, proved to be less optimal, providing either lower conversions or lower ees (Table 1, entries 14–21). The excellent results obtained with ligand **9** were unexpected, considering the inactivity observed for the deacetylated phosphino-amide **2**, thereby providing support that an effective and potentially water soluble D-glucosamine ligand may eventually be possible.

Finally, a series of Pd-catalyzed asymmetric allylation reactions were performed with 1,3-diphenyl-2-propenyl acetate and a variety of nucleophiles, in order to examine the scope of the iminophosphine ligand **9**, the results of which are illustrated in Table 2. In contrast to observations made with phosphine-amide **1**, experiments performed with nucleophiles such as α-methyl or α-acetamido malonate led to both poor conversions and enantioselectivities (Table 2, entries 1–3). Undoubtedly,

Table 2. Pd(0)-catalyzed allylic alkylation studies using iminophosphine ligand **9**[a]



Entry	NuH	Pd/L	Time (h)	Temp. (°C)	Conv.[b] (%)	Yield[c] (%)	ee[d] (%) (config.)[e]
1	$MeCH(CO_2Me)_2$	1/2	24	25	32	—	46 (*R*)
2	$AcNHCH(CO_2Me)_2$	1/2	72	25	0	—	—
3	$AcNHCH(CO_2Me)_2$	1/2	48	60	51	45	19 (*R*)
4	$C_6H_5CH_2NH_2$	1/1	24	25	20	—	60 (*R*)
5	$C_6H_5CH_2NH_2$	1/2	24	25	12	—	85 (*R*)
6	$C_6H_5CH_2NH_2$	1/2	24	25	21[f]	—	76[f] (*R*)
7	Morpholine	1/1	48	25	100	96	85 (*R*)
8	Morpholine	1/2	48	25	100	96	99[g] (*R*)

[a] [1,3-Diphenyl-2-propenyl acetate]/[dimethyl malonate]/[Base]/[Pd] = 1/3/3/0.02; solvent [0.125 M].
[b] Conversion determined by GC analysis.
[c] Isolated pure product.
[d] Determined by HPLC analysis (column Chiralpak AD 0.46 × 25 cm).
[e] Determined by comparison with an authentic sample.
[f] Reaction performed in CH_3CN/H_2O (1/1) with K_2CO_3 as base.
[g] $[\alpha]_D^{20}$ −4.5 (*c* 0.5, $CHCl_3$).

it appears that the metal complexes prepared with ligand **9** are sensitive to the sterical bulk of the nucleophile. Gratifyingly, the amine nucleophiles such as benzyl amine and morpholine provided high ees (85% and 99%, respectively) with a ligand/Pd ratio of 2:1 (Table 2, entries 5 and 9). Again, the monodentate nature of this ligand was confirmed by the lower ees obtained with a ligand/metal ratio of 1:1. Additionally, with morpholine as the nucleophile the reaction furnished the allylic amine in an excellent yield of 96% after a reaction time of 48 h at 25 °C.[15] On the other hand, with benzylamine only low conversions were observed either in solvents such as THF or acetonitrile/water mixtures. Possibly, either complexation of the primary amine to the metal centre may result in deactivation of the catalyst, or the amine may be interfering with the Pd-bound imine functionality of the ligand. In any case, it is interesting to note the high selectivity displayed by this disaccharide ligand **9** for the various substrates tested.

In conclusion, a series of disaccharide phosphine ligands composed of a D-glucosamine unit have been prepared and examined in asymmetric allylic alkylation. Surprisingly, a Pd-complex with an imino phosphine derivative of this disaccharide possessing free hydroxyl groups on the glucosamine sugar proved to be the most active catalyst with respect to conversion and enantioselectivity with a preference for unsubstituted malonate and a secondary amine such as morpholine. Further work is now underway to investigate the importance of the reducing sugar end of this ligand and whether it can be substituted with a simple bulky alkyl group. Additionally, work is in the process to systematically understand how these carbohydrate ligands exert their chiral effect. This work will be reported in due course.

Acknowledgements

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13. Benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium-hexafluorophosphate.
14. *Data for iminophosphine* **9**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) δ 8.70 (d, 1H, $J = 3.9$ Hz), 7.81 (dd, 1H, $J = 3.7$, 7.4 Hz), 7.41–7.18 (m, 27H), 6.91 (dd, 1H, $J = 4.3$, 7.4 Hz), 4.88 (d, 1H, $J = 11.2$ Hz), 4.81 (d, 1H, $J = 11.2$ Hz), 4.79 (d, 1H, $J = 12.3$ Hz), 4.64 (d, 1H, $J = 12.3$ Hz), 4.60 (d, 1H, $J = 7.8$ Hz), 4.55 (d, 1H, $J = 3.5$ Hz), 4.49 (d, 1H, $J = 12.1$ Hz), 4.43 (d, 1H, $J = 11.9$ Hz), 3.83–3.73 (m, 2H), 3.72–3.63 (m, 2H), 3.54–3.36 (m, 5H), 3.33 (s, 3H), 3.20–3.11 (m, 2H), 2.94 (t, 1H, $J = 8.0$ Hz), 2.5 (br s, 1H), 1.87 (br s, 1H), 1.71 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 163.7 (d, $J = -16.1$ Hz), 139.5, 139.3 (d, $J = -16.8$ Hz), 138.6, 138.4, 138.2 (d, $J = -20.6$ Hz), 137.5 (d, $J = -8.4$ Hz), 137.0 (d, $J = -9.9$ Hz), 134.6, 134.4, 134.2 (2C), 134.0, 133.8, 130.8, 129.3, 129.1, 129.0, 128.9 (2C), 128.7, 128.6, 128.4, 128.1, 127.9 (2C), 127.7, 101.3, 98.5, 80.5, 79.3, 77.2, 76.7, 75.6 (2C), 73.8, 73.4, 70.3, 70.2, 68.5, 62.5, 55.6. ^{31}P NMR ($CDCl_3$, 162 MHz) δ (ppm) δ −9.9. ES-HRMS $C_{53}H_{56}NNaO_{10}P$ [$M+Na^+$]; calcd: 920.3540; found, 920.3539.
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