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'ClickCarb': modular sugar based ligands via click chemistry

Noureddine Khiar [a,*], Raquel Navas [a], Inmaculada Fernández [b,*]

[a] Instituto de Investigaciones Químicas, C.S.I.C-Universidad de Sevilla, c/Américo Vespucio, 49, Isla de la Cartuja, 41092 Sevilla, Spain
[b] Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad de Sevilla, c/Profesor García González, 2, 41012 Sevilla, Spain

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ABSTRACT

Reported is a modular approach for the synthesis of a number of structurally diverse ligands derived from carbohydrates. The use of the highly functional hydroxy amino azide **1** derived from glucosamine allows the synthesis of a number of useful ligands for organic and organometallic catalyses. The key step of the approach is the Huisgen cycloaddition of the anomeric sugar azide and diverse alkynes.

As a consequence of the importance of chiral compounds in agriculture, fragrance, medicine, and material science, the asymmetric synthesis of enantiopure entities, is currently one of the most dynamic and creative fields in organic synthesis.[1] Within the different ways developed so far for the synthesis of enantiopure entities, asymmetric catalysis is the method of choice, as it combines efficiency, versatility, atom economy, and is well-suited for the "green chemistry" initiative.[2] Enantioselective catalysis is usually achieved by using chiral organic ligand, responsible for the enantiodiscrimination, either alone,[3] or bound to a transition metal. Consequently, a considerable effort in this area has been devoted to the development of new ligands, which combine efficiency and ease of access. Among the different candidates which can be used in this task carbohydrates hold a prominent role.[4] Indeed, carbohydrates account for 93% of the renewable biomass on earth, are the cheapest enantiopure compounds in the market, possess various hydroxyl groups in different orientations, and compared to other biomolecules, their chiral coding information capacity is by far the most significant.[5] Based on these premises, and within our interest in the synthesis and application of chiral sulfur compounds in asymmetric synthesis,[6] we have recently found that S/S and mixed S/P ligands derived from D-sugars are excellent catalyst precursors in Pd-catalyzed allylic substitution and in Rh(I)-catalyzed enamide hydrogenation.[7,8] In our continuous search for new ligands derived from carbohydrates, in the present Letter we report our preliminary results on the assessment of compound **1**, Figure 1, derived from glucosamine as a central scaffold for the synthesis of a number of ligands of interest. One of the key steps for enhancing the molecular diversity of the thought ligands is the unrivaled copper-catalyzed azide–alkyne cycloaddition (CuAAC), the paradigmatic example of 'click chemistry'.[9] The great advantages of the Huisgen cycloaddition, namely smooth, fast, and predictable coupling conditions are at the basis of its successes in many synthetic areas.[10] In the carbohydrate field, sugar azides have been widely used as privileged partners in the synthesis of glycoclusters based triazol.[11] Additionally, click chemistry has also been used for the synthesis and optimization of a number of P/P,[12] P/N,[13] and P/S ligands.[14]

For the synthesis of 4,6-benzylidene-2-deoxy-2-amino-β-glucopyranosyl azide **1**, two basic problems must be solved. The first one

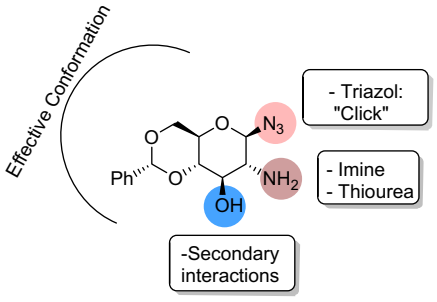

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Figure 1. Structure of compound **1** with three orthogonal functional groups.

* Corresponding authors.
E-mail address: khiar@iiq.csic.es (N. Khiar).

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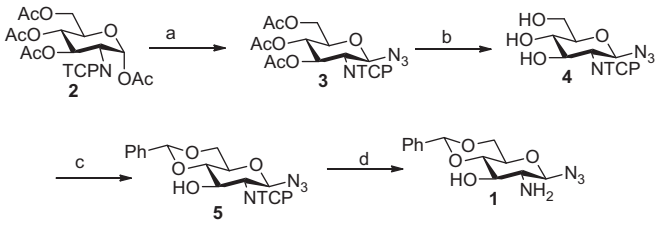
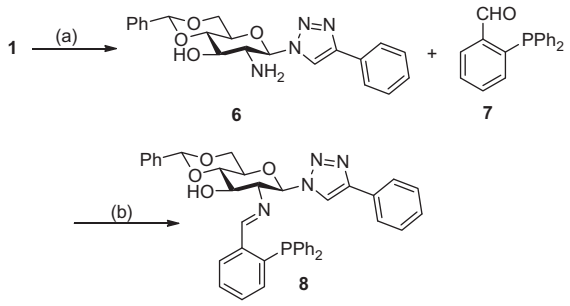
is a stereoselective approach for the introduction of the azide function in a stereoselective manner, and the second one is the use of an amine protective group which can be easily removed once needed. The widely used method for the synthesis of azido sugar is either the Lewis-acid-catalyzed substitution of the anomeric acetate,[15] or the nucleophilic substitution of anomeric halide with azide anions.[16] Additionally, in order to accede to the desired 1,2-*trans* amino azide in a diastereoselective manner the starting glycosyl donor must have a participating group at the 2 position. Taking into account all the above, we used as starting material the known tetrachlorophthalimide (TCP) protected glucosamine derivative **2**.[17] Condensation of trimethylsilyl azide on the rather inert axial acetate **2**,[18] using tin tetrachloride as the catalyst in methylene chloride afforded the desired azide in an 85% yield. Azide **3** was obtained as a single diastereoisomer as a result of the known efficient anchimeric assistance of the TCP-group. Owing to the sensitivity of the TCP group to basic conditions, the acetate group could not be removed by Zemplen deacetylation, and therefore acid conditions were used to obtain the trialcohol **4** in quantitative yield. Benzylidene acetal formation in acetonitrile leads to compound **5** in 80% yields. Treatment of the protected compound **5** with ethylenediamine, at 60 °C as described by Fraser–Reid leads to the free amine **1** in a moderate yield (Scheme 1).[17a] We have found that the use of microwave activation, enhances substantially the yield of the deprotection step, allowing the synthesis of the free amine with an 80% yield.[19]

Compound **1** possesses three orthogonal functional groups which can be separately and adequately manipulated for the synthesis of the desired ligands. Such manipulation may consist either in appending a coordinating atom, in the creation of a well-defined chiral environment or simply in masking a functional group whose reactivity is not required. For the synthesis of the first derivative which was designed to act as a P,N coordinating ligand, the anomeric azide was transformed into a triazol group, and the coordinating P atom was appended at the 2 position.

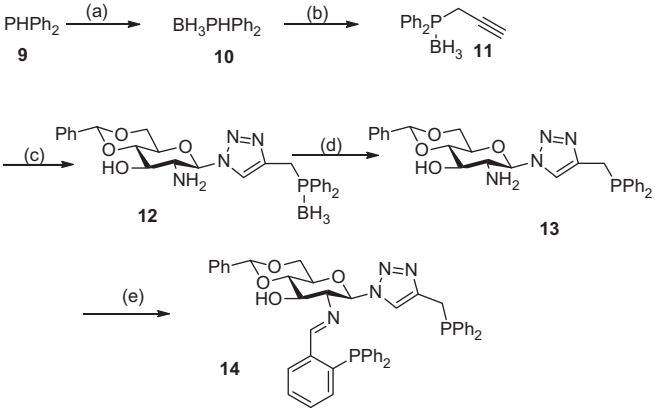
'Click' reaction between sugar azide **1** and phenyl acetylene using $CuSO_4$ sodium ascorbate as Cu(I) source, afforded the 1, 4-disubstituted 1,2,3-triazol **6** in excellent yield (Scheme 2). Condensation of **6** with 2-diphenylphosphine benzaldehyde **7** in methylene chloride using copper sulfate as the dehydrating agent leads to the P,N ligand **8** in excellent yield.[20] For the synthesis of the second family of ligands, we decided to synthesize a polydentate ligands through the introduction of two electronically different coordinating P atoms, the first one at anomeric position and the second at the 2-position. Propynyl phosphine **11**[13a] (Scheme 3), obtained in two steps from diphenylphosphine **9** has been used as the alkyne partner for the synthesis of sugar based diastereomerically pure 'clickcarb'. Huisgen cycloaddition between sugar azide **1** and alkyne **11** using $CuSO_4$–sodium ascorbate as Cu(I) source afforded the 1,4-disubstituted 1,2,3-triazol **12** in excellent yield (Scheme 3).



Scheme 1. Synthesis of 4,6-benzylidene-2-deoxy-2-amino-β-glucopyranosyl azide **1**. Reagents and conditions: (a) $TMSN_3$, $SnCl_3$, CH_2Cl_2, 85%; (b) HCl, acetone/H_2O, 70 °C, quant.; (c) $PhCH(OMe)_2$, CSA, CH_3CN, 80%; (d) ethylenediamine, MW)), 80%.



Scheme 2. Synthesis of the P,N ligand **8** by click chemistry. Reagents and conditions: (a) PhCCH, $CuSO_4$, Na–ascorbate, THF/H_2O (2:1), 70%; (b) $CuSO_4$, CH_2Cl_2, quant.



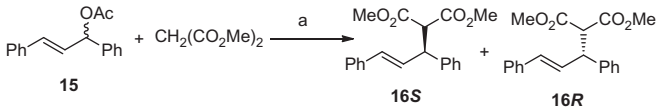
Scheme 3. Synthesis of the polydentate ligand **14**. Reagents and conditions: (a) BH_3, THF, quant.; (b) *n*-BuLi, $CHCCH_2Br$, −78 °C, THF, 94%; (c) **1**, $CuSO_4$, sodium ascorbate, THF/H_2O (2:1), 70%; (d) DABCO, toluene, 55%; (e) *p*-$MeOC_6H_4CHO$, $CuSO_4$, CH_2Cl_2, 70%.

The unprotected hydroxyamino click phosphine ligand **13** has been obtained in quantitative yield after phosphine deprotection. Compound **13** still possesses two other sites for heteroatom ligation namely the amino group at position 2, and the hydroxyl function at position 3. Along this way the condensation of **13** with 2-diphenylphosphine benzaldehyde in methylene chloride using copper sulfate as the dehydrating agent leads to the polydentate ligand **14** in excellent yield.

Once demonstrated the ability of compound **1** to create molecular diversity, we studied the ability of the prepared ligands **8**, **13**, and **14** to act as catalyst precursors in the palladium catalyzed allylic alkylation of 1,3-diphenylpropenylacetate **15** with dimethyl malonate, and the results are collected in Table 1.

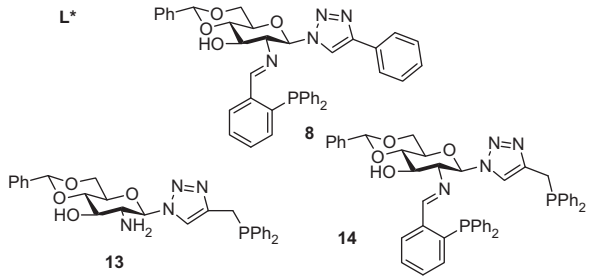
As can be seen from Table 1, all the ligands tested are active catalyst precursors as the allylated product **16** was obtained in all the assays in quantitative yield (Table 1, entries 1–3). In terms of enantioselectivity, the best ligand is the P,N-ligand **8** which gives the desired product **16** in moderate to acceptable enantioselectivity (Table 1, entries 1, 4–10), while ligands **13** and **14** afforded the allylated product in racemic form (vide infra). With the best ligand **8** we conducted studies in order to assess the solvent and temperature effects on course of the allylation reaction. Significantly, while the reaction did not proceed in THF (Table 1, entry 4), the product was obtained in good yield in toluene, methylene chloride and acetonitrile. Nevertheless, the best solvents seem to be acetonitrile, and toluene, where the product **16***S* was obtained in quantitative yield and a good 76% enantiomeric excess (Table 1, entries 5 and 6). Lowering the catalyst loading to 1 mol% has a negative effect both on the chemical yield and on the enantioselectivity (Table 1, entry 7). Yet,

Table 1
Pd-catalyzed allylic alkylation of 1,3-diphenylpropenyl acetate **15** with dimethyl malonate using ligands **8**, **13** and **14**[a]



15 16*S* 16*R*

(a) **L*** (4mol%), $[PdCl(C_3H_5)]_2$(1.5%), BSA, KOAc, Solv.



Entry 1[a]	Ligand	Solvent	Temp (°C)	Yield (%)[b]	Enantiomeric ratio (**16***S*/**16***R*)[c,d]
1	**8**	CH_2Cl_2	25	100	80/20
2	**13**	CH_2Cl_2	25	100	50/50
3	**14**	CH_2Cl_2	25	100	50/50
4	**8**	THF	25	0	—
5	**8**	Toluene	25	100	88/12
6	**8**	CH_3CN	25	100	88/12
7	**8**	CH_2Cl_2	25	14	77/23[e]
8	**8**	CH_2Cl_2	0	100	80/20
9	**8**	Toluene	0	80	90/10
10	**8**	CH_3CN	0	100	90/10

[a] All reactions were conducted in CH_2Cl_2 using 4 mol % of the ligand and 1.5 mol % of $[PdCl(C_3H_3)]_2$.
[b] Isolated yield.
[c] Determined by HPLC using chiral column Chiralpack-AD.
[d] *R* or *S* configurations based on specific rotation.
[e] The reaction was conducted using 1 mol % of the ligand.

lowering the temperature has a beneficial effect on the enantioselectivity allowing the preparation of the **16***S* isomer in quantitative yield and an excellent 80% ee at 0 °C (Table 1, entries 9 and 10).

Surprising for us was that the polydentate ligand **14**, afforded the allylated product **16** in a racemic form. However P,N and P,P ligands have been successfully used in the palladium catalyzed asymmetric allylation in particular and in enantioselective catalysis in general.

Although further coordination studies are needed, a possible explanation for the result obtained is summarized in Figure 2. Owing to the polydentate nature of ligand **14**, and without taking into account secondary interactions exerted by the 3-OH,[20] three different plausible scenarios may be invoked in the coordination of the ligand to the metal. The ligand can putatively act as P,P ligand, if the metal is coordinated by the two phosphorus atoms (pathway A). On the other hand, ligand **14** can act as P,N ligand in two different manners, either through the triazol nitrogen and the diaryl alkyl phosphine (pathway B), or through the imine nitrogen and the triaryl phosphine (pathway C). For the process to be selective, the palladium coordination should be close to the sugar skeleton such as the P,P and P,N coordination in the pathways A and C. Taking into account that the allylated product **16** was obtained in a racemic form, we can assume that chelate B is more favoured than chelate A and C.[21] Indeed, when the sugar 'clickphine' **13** was applied as the catalyst in the allylic alkylation, the allylated compound **16** was obtained in quantitative yield and in racemic form (Table 1, entry 2). A further proof of this assumption is that ligand **8**, afforded the allylated product with good enantioselectivity. To address this issue, the Pd(II)-complex of the ligand **8**, was synthesized in an 80% yield by treatment of the free ligand with 1 mol equiv of $[PdCl_2(CH_3CN)_2]$ in methylene chloride, Scheme 4.

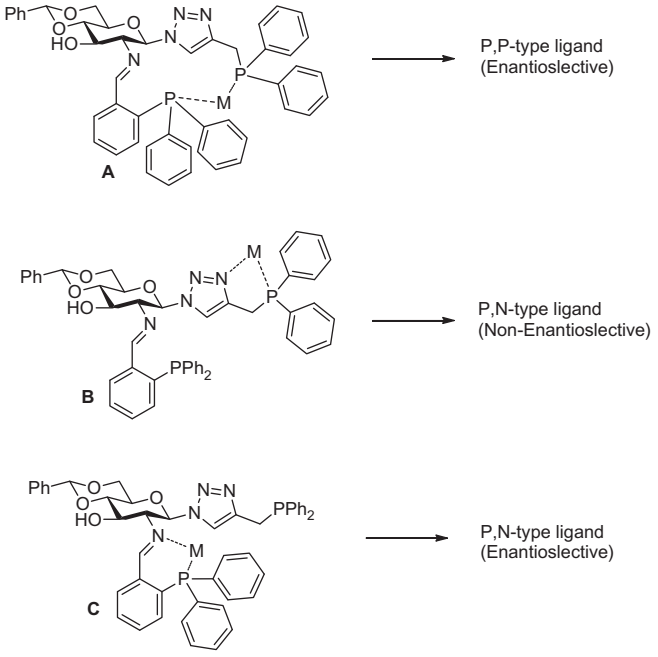
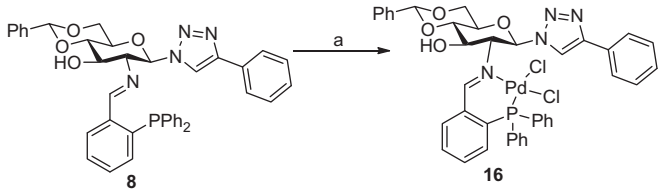


Figure 2. Possible coordination sites of polydentate ligand **14**.



Scheme 4. Synthesis of Pd(II) complex **16**. Reagents and conditions: (a) $[PdCl_2(CH_3CN)_2]$, CH_2Cl_2, 80%.

The structure of the complex **16** was determined by NMR analysis, as we could not get adequate crystal for X-ray analysis. The most significant characteristics of the Pd(II) complex are the downfield chemical shifts of the anomeric proton (from 5.7 ppm to 6.9 ppm), and the H-2 proton (from 3.8 ppm to 5.5 ppm). Beside the downfield chemical shift (from 8.6 pp to 9.2 ppm), the imine proton appears as a singlet in the complex instead of a doublet as in the free ligand. These data are indicative of a Pd-coordination through the nitrogen atom of the imine. On the other hand the ^{31}PNMR analysis of the complex shows that the phosphorus atom registers a 46 ppm downfield chemical shift, and appears at 35 ppm instead of −11 ppm as in the free ligands (see Supplementary data). All these data indicate that ligand **8** acts as a mixed P,N ligand and coordinates the palladium through an enantioselective chelate (similar to pathway C).

In conclusion, 4,6-benzylidene-2-deoxy-2-amino-β-glucopyranosyl azide **1**, with three orthogonal functional groups is an interesting scaffold for the synthesis of chiral structurally diverse ligands. Using click chemistry as key step of the approach, allows the synthesis of triazol based ligands which are potential catalyst precursors both in metal promoted and organic catalyses. The preliminary results reported in this Letter illustrate the potential of the approximation as a new P/N ligand for Pd(0) allylic alkylation has been discovered. Other ligands, such as bifunctional organocatalyst with a phosphine and a thiourea moieties are easily obtained from the developed method. These ligands are of interest as organocatalysts for processes such as the Morita–Baylis–Hillmann reaction, Aza Baylis–Hillmann reaction, and intramolecular Ruhut–Currier reaction. Work along these lines is actually under active investigation in our group.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.043.

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19. Data of compound **1**: white solid. mp: 158–161 °C. $[\alpha]_D^{20}$ −40.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.50 (m, 2H), 7.45–7.35 (m, 3H), 5.56 (s, 1H), 4.52 (d, 1H, *J* = 8.8 Hz), 4.37 (dd, 1H, *J* = 10.5, 4.4 Hz), 3.79 (t, 1H, *J* = 10.0 Hz), 3.61–3.47 (m, 3H), 2.70 (t, 1H, *J* = 9.0 Hz), 2.25 (br, 2H, NH_2). ^{13}CNMR (125 MHz): δ = 136.9, 129.4, 128.4, 126.2, 110.3, 102.0, 92.1, 81.0, 73.1, 68.5, 68.4, 57.5. Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.42; H, 5.52; N, 19.05.
20. Data of compound **8**: colorless oil. $[\alpha]_D^{20}$ −32.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, 1H, *J* = 3.8 Hz), 7.82–7.81 (m, 2H), 7.63–7.17 (m, 22H), 6.87–6.84 (m, 1H), 5.64 (s, 1H), 5.60 (d, 1H, *J* = 8.5 Hz), 4.38 (m, 1H), 4.13–4.04 (m, 2H), 3.89–3.85 (m, 2H), 3.80–3.74 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.9, 164.8, 147.3, 138.7, 138.5, 138.4, 138.3, 137.7, 137.6, 136.9, 134.2 134.1, 133.7, 133.5, 130.6, 130.2, 129.3, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 126.3, 125.8, 119.7, 102.1, 87.2, 79.8, 72.4, 69.8, 68.3. ^{31}P NMR (121.4 MHz, $CDCl_3$): δ = 10.69. HMRS: calcd for $C_{40}H_{36}N_4O_4P$: 667.24770, found: 667.24770.
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