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Pseudo-enantiomeric carbohydrate-based N-heterocyclic carbenes as promising chiral ligands for enantiotopic discrimination†

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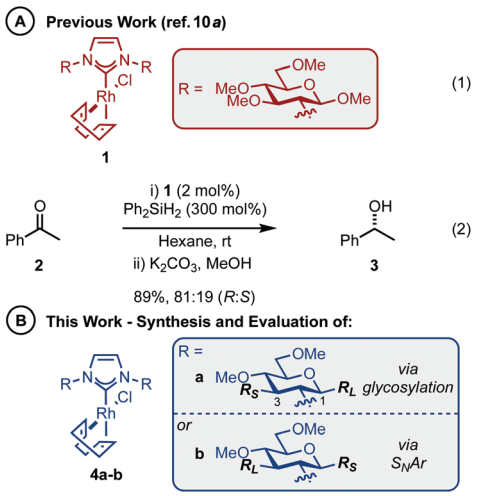
The practical synthesis of carbohydrate-based NHC–Rh complexes bearing C1 or C3 sterically differentiated positions, accessed by glycosylation or S_NAr strategies, is reported. These catalysts exhibit pseudo-enantiomeric behaviour in the hydrosilylation of acetophenone. We show that steric bulk at C1 gives preference for (*S*)-phenyl-1-ethanol, while bulk at C3 leads to the (*R*)-enantiomer. These results represent the first example of pseudo-enantiomeric carbohydrate-based NHC ligands leading to enantiotopic discrimination.

The search for stable and effective N-heterocyclic carbene (NHC) transition metal (TM) complexes is of great interest for catalytic applications.[1] NHCs with tailored electronic and steric properties have become indispensable in many applications of transition metal and main group chemistry.[2] For instance, the success of NHC ligands in non-stereoselective reactions, such as cross-coupling and olefin metathesis,[3] has prompted the incorporation of homochiral units into NHC scaffolds and this offers exciting new opportunities in reaction development.[4] Typical strategies to monodentate NHC ligands suitable for asymmetric TM-catalysis have employed commercially available enantioenriched amines,[5] featured the resolution of racemic material[6] and involved chiral pool substrates, such as amino acid and natural product derivatives.[7] Enantiopure NHCs encompassing a diverse array of ligand architectures have been evaluated in a plethora of asymmetric reactions and, although highly effective examples exist, the search for increasingly more efficient systems is paramount.[4–7] However, a limiting factor and general problem in the synthesis and assessment of novel NHC ligands is the ability to obtain readily modifiable building blocks, such as enantioenriched amines.[8]

The abundance of inherently chiral, biologically derived saccharide material provides useful starting compounds with a range of stereochemistries for ligand syntheses. Indeed, the application of carbohydrates as the enantioinduction component in stereoselective catalysis is frequently encountered within the literature and a multitude of efficient ligands have been reported.[9] Towards this end, our laboratory and others have described the use of carbohydrate-based NHCs for asymmetric catalysis in an effort to solve the issues highlighted above.[10] Our initial report disclosed the expedient assembly of C_2-symmetric NHC ligands from per-alkylated β-glucosamines.[10a] Upon successful ligation to $[Rh(cod)Cl]_2$, the carbohydrate-based NHC complexes (*e.g.* **1**, Scheme 1A, eqn (1)) were evaluated in the asymmetric hydrosilylation of ketones (*e.g.* **2**, Scheme 1A, eqn (2)).[2,11] Ultimately, catalyst **1**, featuring permethylated β-glucoside residues attached to the NHC moiety, was most efficient and provided phenyl-1-ethanol (**3**) in modest er (81 : 19 *R* : *S*).[10a]



Scheme 1 Carbohydrate-based NHC complexes. R_L = large group; R_S = small group.

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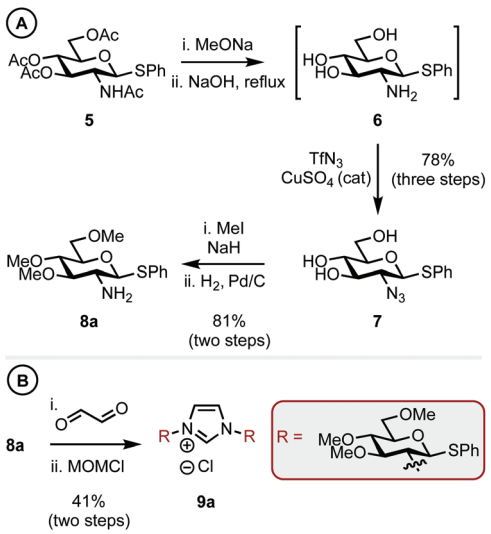
One of the advantages of carbohydrate chiral synthons is the ability to chemoselectively incorporate functional groups at each of the different OH groups. We thus sought to achieve greater asymmetric induction from **1** by sterically differentiating the C1 and C3 positions which flank the connecting position (C2) between the carbohydrate and the imidazolylidene scaffold (**4a–b**, Scheme 1B). Practically, this can be realised in two different ways: (1) by employing a carbohydrate unit with a large group (R_L) at C1 and a small group (R_S) at C3, as depicted in **4a**, or (2) *vice versa* as in **4b**. We surmised that an aryl group would serve as an effective R_L candidate as this motif is readily available. From a synthetic viewpoint, installation of an aryl residue (*e.g.* phenol or thiophenol) at C1 by stereoselective glycosylation is well known.[12] Accessing a related C3–OH arylated carbohydrate derivative is conceptually more challenging, however, this could be achieved using S_NAr-based methdology recently developed in our laboratory.[13] Therefore, our aims were to synthesize sterically differentiated carbohydrate amines, access the corresponding C2-symmetric imidazolium salts, ligate to a Rh source and subsequently evaluate the complexes in the hydrosilylation of acetophenone (**2**).

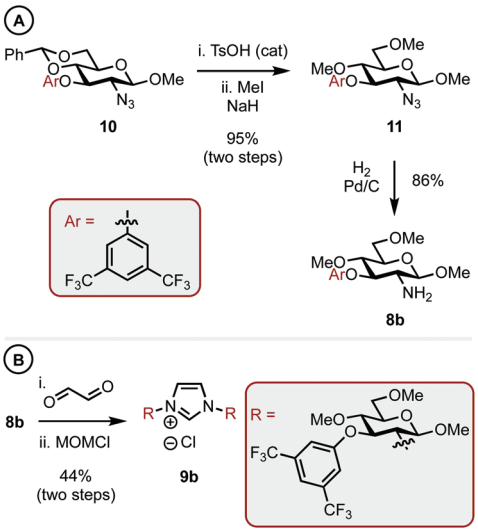
Thioglycoside **5**,[14] synthesized in two steps from D-glucosamine HCl in 70% yield (see ESI† for details), was chosen as it was a commonly used building block in carbohydrate synthesis and thus easily accessible. **5** was globally deprotected by stirring with NaOMe in methanol to remove the ester groups, this was followed by addition of aq. NaOH at reflux to give amine intermediate **6**[15] (Scheme 2A). Cu-catalyzed azide formation from **6** with TfN_3 gave triol **7** in 78% yield over the three steps. Methylation of the remaining hydroxyl positions using MeI and NaH and subsequent azide hydrogenation (H_2, Pd/C) gave C1 sterically differentiated amine **8a** in an 81% yield. It is pertinent to note that a methyl ether (OMe) was selected as the R_S group based on our previous observations.[10a] Elaboration of **8a** into imidazolium salt **9a** was achieved in 41% yield by condensation with aq. glyoxal and then cyclization with MOMCl (Scheme 2B).



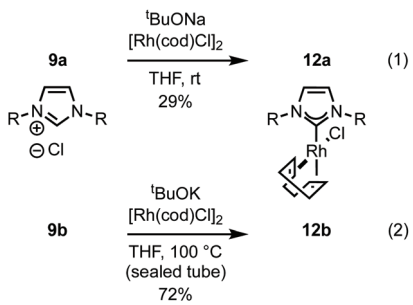
Scheme 2 Synthesis of a carbohydrate-based imidazolium salt with steric bulk at C1.

With a C1 sterically differentiated carbohydrate-based NHC·HCl salt in hand, our attention turned to the C3 analogue (Scheme 3A and B).[16] The synthesis of carbohydrate-aryl ether **10** was accomplished by an S_NAr reaction between the appropriate fluoro-arene and the corresponding OH-bearing carbohydrate.[13] Next, under sonication, TsOH acid catalyzed deprotection of the benzylidene acetal revealed the O4 and O6 hydroxyls, which were methylated as before to give **11** in 95% overall yield. Heterogeneous hydrogenation gave amine **8b** and the corresponding imidazolium salt (**9b**) was accessed in 44% yield utilizing the same procedure outlined before.

Imidazolium salt **9a** was deprotonated by ^{t}BuONa at rt and ligated to $[Rh(cod)Cl]_2$ which afforded complex **12a** in usable yield (Scheme 4, (1)). NHC·HCl **9b** required the action of ^{t}BuOK at 100 °C to effect ligation and this allowed isolation of **12b** in 72% yield (Scheme 4, (2)). Unfortunately, neither complex was crystalline but HRMS confirmed product formation (see the Experimental section) and the carbenic ^{13}C



Scheme 3 Synthesis of a carbohydrate-based imidazolium salt with steric bulk at C3.

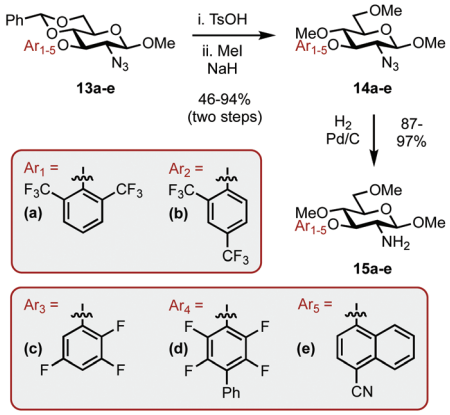


Scheme 4 Ligation of **9a–b** to $[Rh(cod)Cl]_2$.

NMR resonance was visible for **12b** (δ_C: 189.2 ppm). The ^{1}H NMR data of **12a–b** is similar to other β-glucoside-based NHC–Rh compounds and the spectra also featured significant peak broadening, which further supports metal ligation.[10a] In **12b** the backbone imidazolylidene protons were not obscured and appeared at δ_H: 6.95 and 6.80 ppm respectively, indicating that the complex does not possess C_2-symmetry and, therefore, it is likely the pyranoside rings are each in unique environments. From this information we infer that our NHC ligands are dynamic in solution. Indeed, Grubbs and co-workers have observed rotation around $C_{Carbohydrate}$–$N_{Imidazolylidene}$ bonds in metathesis catalysts featuring carbohydrate-based NHC ligands.[10c]

Next, complexes **12a–b** were evaluated in the hydrosilylation of acetophenone as model system and both were found to be catalytically competent (Table 1). Interestingly, although the enantiomer ratios (er) of the product were modest, **12a** resulted in the isolation of **3** with a distinguishable preference for the *S*-enantiomer (30 : 70 *R* : *S*, entry 1), whereas **12b** gave preference for the *R*-enantiomer (75 : 25 *R* : *S*, entry 2). Carbohydrates largely exist in nature in the D-configuration and this causes complications when employing them as ligands because sufficient quantities of the antipode are not normally available. Therefore, an asymmetric process must often rely on pseudo-enantiomeric ligands to give access to each enantiomer of the product.[17] While pseudo-enantiomerism has been documented in carbohydrate-based ligands, such as phosphinites[18] and phosphites,[19] and carbohydrate-based organocatalysts,[20] to the best of our knowledge this is the first example concerning a carbohydrate-based NHC ligand.

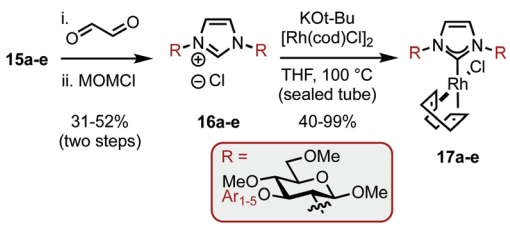
Encouraged by the results, we envisaged optimizing the asymmetric induction potential of the carbohydrate-based NHC ligands by altering the size and substitution pattern of the C3 aryl group.[21] Commercially available fluoro-aryls bearing a range of structural motifs (*ortho*-, *meta*- and *para*-substitution patterns; biaryls and bicyclics) were introduced using S_NAr, expediently delivering a small library of carbohydrate-aryl ethers (**13a–e**) as previously described.[13] The ethers were then transformed into the required amines (**15a–e**) by benzylidene acetal cleavage, methylation of the OHs (**14a–e**) and reduction of the azide functionality as before (Scheme 5).



Scheme 5 Synthesis of S_NAr modified amines **15a–e**.

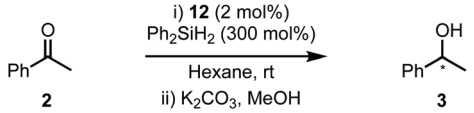
The S_NAr modified amines were swiftly elaborated into the corresponding imidazolium salts (**16a–e**) by treatment with aq. glyoxal and then MOMCl (Scheme 6). Deprotonation with ^{t}BuOK and ligation to Rh was performed in THF at reflux to give complexes **17a–e** in 40–99% yields. While the yields for both of these steps were predominantly good, the example featuring Ar_1 (bearing *ortho–ortho* aryl substitution, *e.g.* **13a–17a**) was consistently low yielding despite our best efforts and this was attributed to the level of steric bulk present in the system.

Complexes **17a–e** were then evaluated in the hydrosilylation of **2** and the results are displayed in Table 2. Catalysts **17a–b**, featuring an *ortho*-CF_3 substituted aryl group (Ar_{1-2}), gave negligible stereoinduction in **3** (entries 1 and 2). However, **17c** (entry 3) resulted in the isolation of **3** in high yield and with



Scheme 6 Synthesis of complexes **17a–e**.

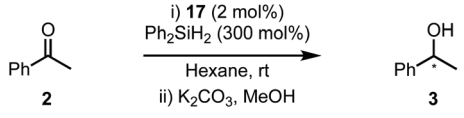
Table 1 Evaluation of **12a–b** in the hydrosilylation of acetophenone



Entry	12	Yield[a] (%)	Er[b] (*R* : *S*)
1	**a**	75	30 : 70
2	**b**	95	75 : 25

[a] Isolated yield. [b] Determined by chiral HPLC.

Table 2 Evaluation of **17a–e** in the hydrosilylation of acetophenone



Entry	17	Yield[a] (%)	Er[b] (*R* : *S*)
1	**a**	72	51 : 49
2	**b**	15	50 : 50
3	**c**	89	86 : 14
4	**d**	70	61 : 39
5	**e**	73	78 : 22

[a] Isolated yield. [b] Determined by chiral HPLC.

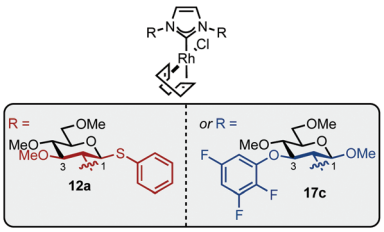


Fig. 1 Pseudo-stereochemical ligands **12a** and **17c**.

the greatest er to date (86 : 14). Both **17d** and **17e** (entries 4 and 5) afforded **3** with detectable er's but were ultimately less efficient systems.

Conclusions

In summary, a series of pseudo-enantiomeric carbohydrate-based NHC-ligands featuring sterically differentiated groups at positions C1 or C3 of the carbohydrate were synthesized by simple glycosylation or S_NAr strategies and evaluated in the Rh-catalyzed hydrosilylation of acetophenone. We show that ligands bearing a bulky group at C1 lead to a preference for (*S*)-phenyl-1-ethanol, while the presence of large groups at C3 afforded preferentially the (*R*)-enantiomer. Our results suggest this effect is achieved by the steric differentiation of the carbohydrate's C1 and C3 positions which flank the attachment to the imidazolylidene scaffold. This "pseudoenantiomeric" design feature is shown in Fig. 1.[22]

While our efforts to achieve a high level of asymmetric induction in the benchmark hydrosilylation reaction[11,12] have been less successful, we have surpassed our previous result[9] and shown, to the best of our knowledge for the first time, that the judicial functionalization of carbohydrate synthons can lead to pseudo-enantiomeric NHC-ligands for asymmetric catalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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