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COMMUNICATION

Unprecedented diastereoselective generation of chiral-at-metal, half sandwich Ir(III) and Rh(III) complexes *via* anomeric isomerism on "sugar-coated" N-heterocyclic carbene ligands†‡

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The first example of the diastereoselective synthesis induced by anomeric isomerism of sugar units in ligands of metal complexes was demonstrated. *S* and *R* configurations of chiral-at-metal Ir(III) and Rh(III) complexes were selectively obtained by using chelate-type NHC ligands with α- and β-glucopyranosyl units, respectively.

Controlling the chirality around a metal center in chiral-at-metal complexes[1] is important for preparing effective asymmetric catalysts. Using chiral organic functional groups is the most useful method for synthesizing chiral catalysts.[2]

Although phosphine ligands have mostly been used in this area, chiral N-heterocyclic carbene (NHC) ligands have started to be used in recent years.[3] From our approach using metal complexes with anomeric isomers of sugar units, we have observed kinetic and thermodynamical discrimination of the chiral-at-metal center, which demonstrates the important role of anomeric isomerism of sugars in controlling the chirality of metal complexes.

In the case of Ru and Mn cyclopentadienyl complexes with phosphine ligands,[4] 16-electron intermediates, generated by dissociation of one of the ligands, have pyramidal structures whose chirality is inverted through a trigonal planar structure with higher energy. Although in the case of chiral-at-metal NHC complexes, the mechanisms for generation and inversion of the chirality are probably similar to those for phosphine complexes, the differences in the nature of NHCs and phosphines, such as σ-donating and π-accepting abilities, should affect the mechanisms. Use of sterically demanding chiral substituents on NHC ligands will be useful for investigating the mechanisms.

Sugars, especially D-glucose, are excellent candidates for use as chiral sources because they are the most abundant bioresource in nature.[5] We previously synthesized the first example of sugar-coated NHC complexes.[6] When an anomeric carbon is directly attached to an imidazolylidene nitrogen, α- or β-glucosides can be isolated. Use of the steric effects attributed to the anomers of D-glucopyranosyl units would be an excellent approach to controlling the absolute conformation of metal complexes. The combination of the chirality and the anomeric isomerism of glucose should produce sufficient environments in metal complexes for such a purpose. We report here incorporation of α- and β-AcGlc groups into chelate-type NHC ligand precursors, which were used for diastereoselective syntheses of chiral-at-metal half-sandwich Ir(III) and Rh(III) complexes. In other words, to the best of our knowledge, this is the first report of controlling chirality using anomeric isomerism of sugars.

Ir(III) and Rh(III) complexes were produced *via* a carbene transfer reaction[7] using silver NHC complexes **3α** or **3β**, which were obtained quantitatively by reacting Ag_2O with **2α** and **2β**, respectively (Scheme 1). From ^{1}H NMR spectroscopy, **3α** and **3β** were consumed completely within 5 min, and the Ir(III) and Rh(III) complexes formed almost quantitatively. In the ^{1}H NMR spectra of the final products, only two sets of the signals for the Cp* and sugar-coated NHC ligands with ratios of 95 : 5 for **Ir4α**, 85 : 15 for **Ir4β**, 90 : 10 for **Rh4α**, and 85 : 15 for **Rh4β** were observed. These results suggest that the produced Ir and Rh complexes have two diastereomers due to the pseudo-tetrahedral structure around the metal center. The major diastereomers of **Ir4β** and **Rh4β**, isolated by fractional crystallization of the corresponding PF_6^- salt (**Ir4β-PF$_6$** and **Rh4β-PF$_6$**, respectively), adopted *R* absolute configurations from X-ray analysis, and those of **Ir4α** and **Rh4α**

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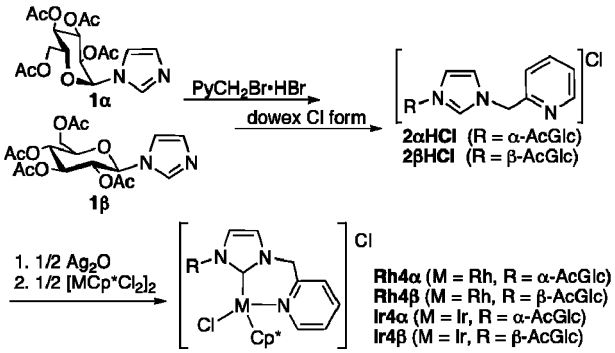
† Electronic supplementary information (ESI) available: Full experimental procedures and data for **1α**, **1β**, **2αHCl**, **2βHCl**, **3α**, **3β**, **Ir4α**, **Ir4β**, **Rh4α**, and **Rh4β**. CCDC reference numbers 796414 and 796415 for Ir and Rh complexes, respectively. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0dt01634a

‡ Crystal data for ***R*-Ir4β-PF$_6$·2CH$_3$OH·H$_2$O**: $C_{35}H_{52}ClF_6IrN_3O_{12}P$, M_r = 1079.44, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 12.6224(13) Å, b = 15.2989(18) Å, c = 22.254(3) Å, V = 4297.4(9) Å^3, Z = 4, T = 193(1) K, D_{calcd} = 1.668 g cm^{-3}, reflections collected 42 049, independent reflections 9707, R_{int} = 0.069, R_1 = 0.0455 ($I > 2\sigma(I)$), wR_2 = 0.0968 (all data), GOF = 1.002, Flack parameter = 0.051(7). Crystal data for ***R*-Rh4β-PF$_6$·CH$_2$Cl$_2$**: $C_{34}H_{44}Cl_3F_6N_3O_9PRh$, M_r = 992.96, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 12.5638(7) Å, b = 15.2175(9) Å, c = 22.2295(14) Å, V = 4250.0(4) Å^3, Z = 4, T = 193(1) K, D_{calcd} = 1.552 g cm^{-3}, reflections collected 41 443, independent reflections 9654, R_{int} = 0.043, R_1 = 0.0454 ($I > 2\sigma(I)$), wR_2 = 0.1062 (all data), GOF = 1.021, Flack parameter = 0.00(2).



Scheme 1 Syntheses of sugar-coated NHC ligand precursors and their Ir and Rh complexes.

adopted *S* configurations, which were deduced by using circular dichroism (CD) spectroscopy, as mentioned below. Crystals of the diastereomers of **Ir4α** and **Rh4α** suitable for X-ray analysis have not yet been obtained.

The X-ray structure of ***R*-Ir4β-PF$_6$** is shown in Fig. 1. The structures of the major diastereomers of the Ir and Rh complexes are similar to each other, and the absolute configuration around the metal ions was determined to be *R* by using the structure of the chiral D-glucopyranosyl unit as an internal reference and the Flack parameter.[8] ^{1}H NMR spectra of both the Ir or Rh complexes showed one set of signals for the ligands, indicating that the structure observed in the solid state was maintained in organic solvents.

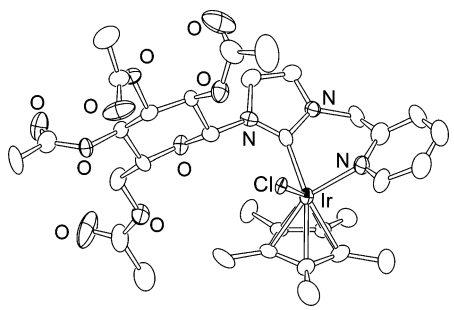


Fig. 1 Structure of the major diastereomer of **Ir4β-PF$_6$** with 50% probability of thermal ellipsoids. Hydrogen atoms, counter ions, and solvent molecules were omitted for clarity.

In order to deduce the absolute configuration around the metal center for the α-complexes, CD spectroscopy was performed. The diastereomers of **Ir4α** and **Rh4α** have yet to be separated. Thus, we compared the CD spectra of crude mixtures of the diastereomers of the α- and β-complexes, which contained the major and minor diastereomers in about a 9 : 1 ratio. Interestingly, the CD spectra of the α-complexes and the corresponding β-complexes were mirror images of each other (Fig. 2).

The CD spectra indicate that each major diastereomer of the α-complexes has the opposite absolute configuration to that of the *R*-β-complexes. Thus, the major diastereomers of the α-complexes, **Ir4α** and **Rh4α**, have an *S* configuration. It should be noted that the D-glucopyranoside chromophore should not contribute to the CD around 220–500 nm, since no absorption occurs in this region. Similar relationships between the CD spectra have been reported for other chiral-at-metal complexes.[4] These results, together with

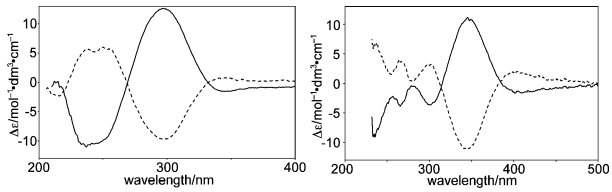


Fig. 2 CD Spectra of complexes. Left: **Ir4α** (dashed line) and **Ir4β** (solid line) in H_2O. Right: **Rh4α** (dashed line) and **Rh4β** (solid line) in CH_2Cl_2. Each sample was a crude diastereomeric mixture with the 9 : 1 ratio of the major and minor diastereomers.

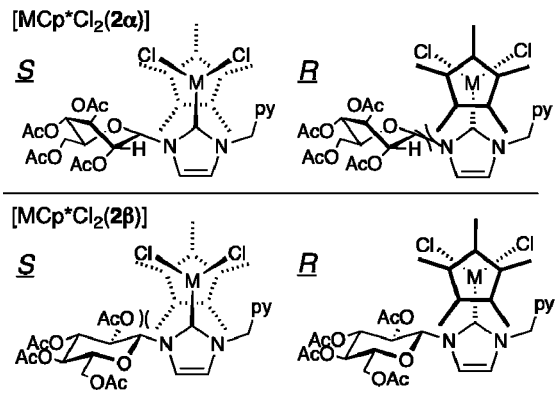
the NMR measurements, show that diastereoselective synthesis is possible because of the steric repulsion between the uncoordinated glucopyranosyl units during the carbene transfer reaction. α- and β-Anomeric isomerism of the glucopyranosyl units incorporated into the NHC ligand in concert with the chirality at the anomeric carbon atom in the glucopyranosyl units control the diastereoselectivity of the formation of the chiral-at-metal complexes.

In order to determine the steric factors governing the selective formation of the *S* and *R* isomers of the α- and β-complexes, respectively, the conformations of the glucopyranosyl units in the complexes were examined by using ^{1}H NMR spectroscopy. In the ^{1}H NMR spectra of the α-ligand precursor **2αHCl**, the $^3J_{H-H}$ coupling constants of 4 Hz between the 1- and 2-positions of the glucopyranosyl unit and ~7 Hz between the other positions are rather small in comparison to that for the typical C1 chair ($^3J_{H-H}$ = 9 Hz) due to distortion in the C1 chair conformation, whereas in the spectra of the β-ligand precursor **2βHCl**, coupling constants ($^3J_{H-H}$ = 9 Hz) consistent with the C1 chair conformation were observed. The coupling constants for all of the β-complexes corresponding to the C1 chair conformation of the glucopyranosyl units followed a similar trend. On the other hand, the $^3J_{H-H}$ coupling constants corresponding to the major diastereomers of the α-complexes **Ir4α** and **Rh4α** were 10 Hz between the 4- and 5-positions of the glucopyranosyl unit and ~5 Hz between the other methyne protons. These coupling constants are consistent with a skewed form of the glucopyranosyl unit.

When the α-ligand coordinates to the metal ion, the imidazolylidene group occupies the axial position causing considerable steric hindrance between the peracetylated glucopyranosyl group and the H atom at the 5-position of the imidazolylidene or the other coordinated ligands around the metal center. The optimized structure of ***S*-chair-[Ir4α]** obtained by DFT calculation (B3LYP/LanL2DZ (for Ir) and 6-31G(d) (for the others)) shows that the shortest distance between the methyne proton of the glucopyranosyl group and the imidazolylidene backbone proton is about 2.1 Å, which is shorter than the sum of the van der Waals radii (2.4 Å) (Table. S2, Fig. S6, ESI†). In order to avoid such steric repulsion, the α-glucopyranoside group adopts the skewed conformation in the *S*-α-complexes (Fig. S1, ESI†).

Usually, substitution reactions, including carbene transfer, involving piano-stool type complexes proceed through 16e intermediates produced by the dissociation of one of the ligands. The intermediate in the initial carbene-transfer process of the formation reaction, which does not affect the chirality of the final product, affords a pseudo-tetrahedral monodentate NHC complex, [MCp*LCl$_2$] (M = Ir, Rh; L = **2α**, **2β**), similar to those of

the [IrCp*(NHC)Cl_2] complexes. The second step involves chelate formation of the pyridyl group to the intermediate to produce *R* or *S* chirality at the metal center. The major products were the *S*-isomers for the α-complexes and the thermodynamically unstable *R*-isomers for the β-complexes. These results show that generation of the complexes is a kinetically-controlled process. Prochiral pseudo-tetrahedral or 16-electron pseudo-planar intermediates should be involved in the isomerization reaction, and the fact that the reaction of **3β** with [MCp*Cl_2]$_2$ finished within 5 min, as mentioned above, means that the high-energy pseudo-planar transition state is not involved. In this process, the configuration of the pseudo-tetrahedral intermediate determines the chirality at the metal center of the final product. There are steric repulsions between the Cp* ligand and the H atom or the acetyl group located at the 2-position of the glucopyranosyl unit in the pseudo-tetrahedral intermediate, as shown in Scheme 2. The configurations of the α-*S* and β-*R* intermediates afford the ***S*-M4α** and ***R*-M4β** (M = Ir or Rh) complexes, respectively, *via* the dissociation of the chloro ligand and coordination of the pyridyl group.



Scheme 2 Possible intermediates for diastereoselective formation.

There is another possible reaction pathway in which coordination of pyridine occurs first and subsequent carbene transfer reaction afforded half sandwich complexes. However, in this route, the chiral sugar moiety is too far from the metal center to lead to diastereoselective formation of the complexes.

The α-complexes did not isomerize in solution, such as $CHCl_3$, CH_2Cl_2, CH_3CN, DMSO, and H_2O confirmed by ^1H NMR and CD spectroscopies. On the other hand, the CD spectra of the Ir and Rh *R*-β-complexes in H_2O changed gradually. In other words, isomerization to the opposite diastereomer occurred *via* isosbestic points (Fig. S2, ESI†), indicating that the isomerization reaction involves only two species. In addition, the isomerization was observed *via* ^1H NMR spectroscopy in D_2O, $CDCl_3$, DMSO-d_6, and CD_3CN. A pseudo-planar intermediate must be involved in the isomerization process, and the slow isomerization reaction is consistent with a high-energy barrier to form the pseudo-planar intermediate. The isomerization speed of [β-M]PF_6 was slower than [β-M]Cl and the isomerization proceeded most quickly in water. [β-M]$^+$ forms an ion pair with PF_6^- due to the less solvated nature of PF_6^- than Cl^- possibly leading to the slower reaction. Dication intermediates favored the highly polar solution of water and it probably helps to reduce the energy barrier for formation of the intermediate.

In order to gain further information about the isomerization of ***R*-Ir4β** and ***R*-Rh4β**, DFT calculations at the B3LYP/LanL2DZ (for Ir)/6-31G(d) (for others) level were performed on ***R*-[Ir4β]$^+$**, which was crystallographically characterized, and its diastereomer ***S*-[Ir4β]$^+$** and on the diastereomers of the Ir α-complexes ***R*-[Ir4α]$^+$** and ***S*-[Ir4α]$^+$** with chair and skewed conformations (Table S2, ESI†). The skewed conformation of the glucopyranosyl unit with an *S* configuration at the metal center was determined to be the most stable for the α-complex, whereas the chair conformation with an *S* configuration was the most stable for the β-complex. The results of the calculations are consistent with the experimental results that the *S*-α-complex does not isomerize and that the *R*-β-complex isomerizes to the *S* diastereomer. In addition, it was found that the *R*-β-complex was the kinetically favored product.

Chiral-at-metal Ir(III) and Rh(III) complexes were diastereoselectively synthesized using chelate-type NHC ligands with α- or β-glucopyranosyl units. To the best of our knowledge, this is the first example of the diastereoselective syntheses induced by anomers of sugar units incorporated into the ligands of metal complexes. The configuration of the metal center was affected by the conformation of the α-glucopyranosyl group, which adopts a skewed form in the complexes, though it adopts a chair form in the ligand precursor.

Glucopyranosyl imidazoles can be utilized to synthesize a variety of precursors of N-heterocyclic carbene ligands having a glucopyranosyl unit by reaction with primary alkyl halides. Since steric repulsion between acetyl protecting groups is one of the factors governing the configuration of the complexes, the use of other protecting groups will affect the configuration of the metal complexes. Utilization of the anomeric isomers of sugar groups to control stereochemistry of metal complexes will be important for preparing new asymmetric catalysts.

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