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Synthesis of Chiral Imidazolinium Carbene from a Carbohydrate and Its Rhodium(I) Complex[‡]

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A chiral imidazolinium salt with two bulky carbohydrate subunits, *N*,*N*′-1,3-bis(methyl 4,6-*O*-benzylidene-3-deoxy-α-D-altropyrano-3-yl)imidazolinium chloride (**4**), was synthesized in high yield. Deprotonation of **4** with sodium *tert*-butoxide in the presence of $[RhCl(COD)]_2$ produced NHC-coordinated rhodium complex **5** along with water adduct **6** to a lesser extent depending on the moisture content of the reaction mixture. These compounds were fully characterized by IR, MS, and ^1H and $^{13}C\{^1H\}$ NMR spectroscopy.

1. Introduction

Since the isolation and characterization of stable N-heterocyclic carbenes (NHCs) by Arduengo in 1991,[1] these compounds have generated considerable interest in catalysis reactions, both as a transition metal ligand[2] and directly as a nucleophilic catalyst.[3] The strong σ-donating character of NHCs combined with their poor π-accepting properties generate metal centers that are electron-rich relative to the corresponding phosphane-coordinated complexes.[4] Consequently, these carbene ligands do not appear to dissociate from the metal centers, and their complexes tend to be highly active in oxidative addition steps.[5] These properties of NHCs have led to significant improvements in some reactions that originally used phosphane-coordinated catalysts, such as Ru-catalyzed olefin metathesis[6] and Pt-catalyzed olefin hydrosilylation.[7]

Chiral phosphanes have been widely used in asymmetric catalysis, and the advances achieved have had a significant impact on both academic and industrial research. It was therefore a logical extension to similarly modify NHCs with a chiral moiety.[8] An advantage of chiral NHCs is that an excess of the ligand is not necessary as a result of its low propensity to dissociate from the metal center. Recently, high levels of enantiomeric excess were reported in several catalysis reactions using chiral NHCs. These reactions include the iridium-catalyzed asymmetric hydrogenation of aryl alkenes,[9] Ru-catalyzed symmetry-breaking olefin metathesis,[10] Rh-catalyzed hydrogenation of α,β-unsaturated esters,[11] and the hydrosilylation of methyl ketones.[12] In addition to these examples of bidentate NHC ligands, a monodentate NHC ligand with two bulky chiral [2,2]-paracyclophane groups was reported to give excellent enantiomeric excess in the rhodium-catalyzed enone addition.[13] These examples highlight the potential and promise of chiral NHC ligands in asymmetric catalysis. However, when compared to chiral phosphanes, the field of asymmetric catalysis with chiral NHCs remains in its infancy and further work in the area, primarily the synthesis of new chiral NHCs, is well justified.

Carbohydrates are a diverse and widely available source of chirality. Chiral phosphanes derived from carbohydrates have been used in the commercial synthesis of optically pure products; however, there have been no reports of chiral NHCs prepared from carbohydrates so far. Previously, we have selectively incorporated diphenylphosphanyl groups into the C-2 and C-3 positions of a pyrano rings in high yields through an epoxide ring-opening reaction.[14] The resulting chiral phosphanes were found to be versatile ligands in the coordination of late transition metals[15] and were successfully applied in nickel-catalyzed asymmetric hydrovinylation reactions.[16] Herein we wish to report the synthesis of a chiral imidazolinium salt with two bulky subunits derived from D-glucose, as well as the synthesis of a rhodium complex from the corresponding chiral N-heterocyclic carbene ligand.

2. Results and Discussion

Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) can be easily prepared from D-glucose on a large

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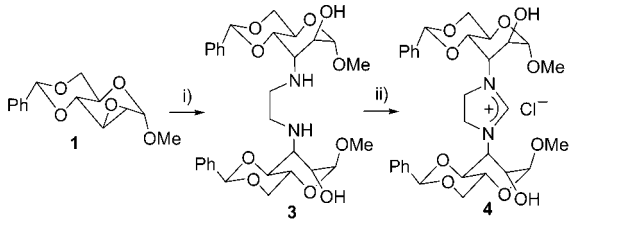
scale, and it is also commercially available (Scheme 1).[17] Our initial synthetic approach to the imidazolium salt by the co-condensation of methyl 3-deoxy-3-amino-4,6-benzylidene-α-D-altropyranoside (**2**), made from ammonolysis of epoxide **1**,[18] with glyoxal and formaldehyde was unsuccessful.[19] The failure of this approach seemed to result from the hydrolysis of the protecting groups in **1** and with difficulties in the isolation of the desired product. Therefore, an alternative route was pursued that used ethane-1,2-diamine instead of ammonia.

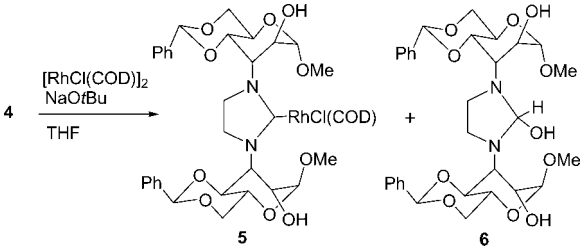


[a] Conditions: i) ethane-1,2-diamine, MeOH, 140 °C; ii) NH_4Cl, $CH(OEt)_3$, 110 °C.

Scheme 1. Synthesis of an imidazolinium chloride.[a]

By raising the reaction temperature to 140 °C, an 86% yield of diamine **3** was readily obtained. The higher reaction temperature that was necessary for this reaction was attributed to the steric hindrance in the reaction of the second epoxide with the diamine. By heating **3** at 110 °C for 3 h in neat triethylorthoformate in the presence of NH_4Cl, imidazolinium salt **4** was produced in 92% yield as a precipitate upon cooling the reaction mixture. Crude **4** was pure enough to be used directly in the next step. It is worth noting that when the reaction was conducted with NH_4BF_4 instead of NH_4Cl, which is more frequently used for the ring-closure of imidazolinium salts,[20] several side products resulted, which made isolation of the desired imidazolium salt tedious. At the present time, the reason for this is uncertain, but we speculate that NH_4BF_4 may be unstable at high temperature and that it may generate trace amounts of acid that hydrolyze the protecting groups in **1**. Compounds **3** and **4** were fully characterized by IR, MS, and ^1H and $^{13}C\{^1H\}$ NMR spectroscopy (see Supporting Information). The ^1H and $^{13}C\{^1H\}$ NMR spectra of chiral products **3** and **4** are indicative of a C_2-symmetric product, and the presence of only one set of signals also suggests that no racemization occurred in the synthesis of **4**. The signal at δ = 8.83 ppm in the ^1H NMR spectrum of **4** is characteristic of the NCHN proton in the imidazolinium salt.[21]

We next examined the coordination properties of the chiral N-heterocyclic carbene generated from **4**. Deprotonation of **4** with sodium *tert*-butoxide in a THF solution of $[RhCl(COD)]_2$ at 45 °C for 48 h afforded NHC-coordinated Rh complex **5** in 76% yield. The extent of dryness of imidazolinium salt **4** was found to be crucial to the yield of **5**; if **4** was not carefully dried with P_2O_5 under vacuum, the yield of **5** dropped significantly to 20–50%, and the water adduct of the carbene, compound **6**, could be seen at approximately 20% yield (Scheme 2). The fact that nearly no reaction occurred at room temperature suggests that steric hindrance around the carbene hampered its coordination to rhodium. This would further suggest that the carbene reaction with water to yield **6** is faster than its complexation to yield **5**, as our observations would indicate. Evidence for a highly steric environment around rhodium can be seen in the ^1H and $^{13}C\{^1H\}$ NMR spectrum. The C_2-symmetry seen in **4** disappeared in **5**, and in **6** as well. The loss of C_2-symmetry in **6**, with its relatively small hydroxy group in the imidazolidine ring, is indicative of a carbene center surrounded by two bulky chiral substituents. It would be interesting to evaluate the chiral induction ability of the NHC-coordinated rhodium complex with its two large carbohydrate subunits. The assignments of **5** and **6** are based on MS and NMR spectroscopic data. The HRMS measurement of 809.2529 $[M - Cl]^+$ for NHC-coordinated Rh complex **5** is consistent with the calculated value of 809.2520. A peak at 617 $[M + 1]^+$ in the MS of **6** suggests that it is an H_2O adduct of the carbene derived from **4**.



Scheme 2. Synthesis of NHC-coordinated Rh^I complex.

In conclusion, we have synthesized the first example of a chiral imidazolinium salt with two bulky carbohydrate subunits and its corresponding rhodium complex. The reaction conditions for the rhodium complex and the NMR signals suggest that the carbene center is highly encumbered by the two bulky chiral subunits. Future studies will focus on (1) the use of rhodium complex **5** in asymmetric catalysis, (2) the deprotection of **5** to form a polyhydroxy complex as a potential water-soluble asymmetric catalyst, and (3) the synthesis of more chiral N-heterocyclic carbenes from carbohydrates and their corresponding transition-metal complexes.

3. Experimental Section

General Procedures. All reactions and manipulations involving air- and/or moisture-sensitive compounds were carried out by using standard Schlenk techniques under an atmosphere of nitrogen. NMR spectra were recorded with a BRUKER DRX 400 MHz or Varian INOVA 400 MHz spectrometer. Chemical shifts are reported in δ relative to $CDCl_3$. High-resolution mass spectra (HRMS, ESI) were obtained with a Micromass Q-Tof Micro (Micromass Inc., Manchester, England). THF was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen. NaO*t*Bu was used as received. $[RhCl(COD)]_2$ and methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**)[17] were prepared according to the literature methods, respectively.

***N*,*N*′-Bis(methyl 4,6-*O*-benzylidene-3-deoxy-α-D-altropyrano-3-yl)-1,2-diaminoethane (3):** A mixture of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**; 4.1 g, 15.5 mmol) and ethane-1,2-diamine (0.4 g, 6.67 mmol) in methanol (60 mL) was stirred in an autoclave at 140 °C for 12 h. After cooling the reaction mixture, the solvent was evaporated, and the residue was purified by chromatography (3–10% methanol in dichloromethane) to afford the product. Yield: 3.4 g (86%). M.p. 91–93 °C. $[\alpha]_D^{21}$ = +112.2 (*c* = 1.0, ethanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.30 (m, 10 H), 5.47 (s, 2 H), 4.52 (s, 2 H), 4.30–4.25 (m, 2 H), 4.10–4.00 (m, 2 H), 3.95–3.90 (m, 2 H), 3.91 (br., 2 H), 3.80–3.70 (m, 2 H), 3.34 (s, 6 H), 3.22 (br., 2 H), 3.10–3.05 (m, 2 H), 2.90–2.85 (m, 2 H), 2.65–2.55 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.64 129.06 128.38 (2 C), 126.21 (2 C), 102.05 (2 C), 77.86, 70.80, 69.50, 58.69, 57.10, 55.47, 47.08, 46.11 ppm. IR (KBr): $\tilde{\nu}$ = 3440, 2907, 1637, 1457, 1380, 1105, 1067, 1044, 974, 755, 670 cm^{-1}. MS (ES): *m*/*z* (%) = 589 (100) $[M + 1]^+$.

***N*,*N*′-1,3-Bis(methyl 4,6-*O*-benzylidene-3-deoxy-α-D-altropyrano-3-yl)imidazolinium chloride (4):** A mixture of diaminoethane **3** (2.0 g, 3.4 mmol) and NH_4Cl (0.3 g, 5.6 mmol) in triethylorthoformate (40 mL) was stirred at 110 °C for 3 h. Upon cooling of the reaction mixture to room temperature, ashen solids appeared and were collected by filtration and washed with hexane. The solid was dissolved in dichloromethane and purified through a short column to remove excess NH_4Cl. Yield: 2.0 g (92%). M.p. 153–154 °C. $[\alpha]_D^{20}$ = +127.9 (*c* = 1.0, ethanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (s, 1 H), 7.40–7.15 (m, 10 H), 5.88 (br., 2 H), 5.50 (s, 2 H), 4.57 (s, 2 H), 4.30–4.05 (m, 8 H), 3.90 (br., 2 H), 3.75–3.60 (m, 4 H), 3.10 (s, 6 H), 3.06 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.29, 136.96, 129.44, 128.45 (2 C), 126.12 (2 C), 102.55, 100.70, 74.51, 69.30, 66.86, 58.66, 58.22, 55.43, 50.09 ppm. IR (KBr): $\tilde{\nu}$ = 3440, 3257, 2930, 1642, 1459, 1409, 1262, 1138, 1104, 995, 964, 772, 707 cm^{-1}. MS (ESI): *m*/*z* (%) = 599 (100) $[M - Cl]^+$.

NHC-Coordinated Rh complex 5: A mixture of dried imidazolinium salt **4** (1.35 g, 2.15 mmol), $[RhCl(COD)]_2$ (0.40 g, 0.82 mmol), and NaO*t*Bu (0.31 g, 3.2 mmol) was stirred in THF (20 mL) at 45 °C for 48 h. The reaction mixture was filtered through celite, evaporated, and the residue was then purified by silica gel chromatography (2% methanol in dichloromethane). Yield: 1.06 g (77%). M.p. 157–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.20 (m, 11 H), 6.60–6.62 (m, 1 H), 5.80 (br., 1 H), 5.71 (s, 1 H), 5.64 (s, 1 H), 5.05–4.90 (m, 2 H), 4.69 (d, *J* = 3.2 Hz, 1 H), 4.66 (s, 1 H), 4.42 (br., 1 H), 4.35–4.25 (m, 3 H), 4.11 (br., 2 H), 4.05–3.98 (m, 1 H), 3.92–3.81 (m, 2 H), 3.80–3.65 (m, 5 H), 3.64–3.55 (m, 2 H), 3.46 (s, 3 H), 3.39 (br., 1 H), 3.27 (s, 3 H), 2.55–2.42 (m, 2 H), 2.35–2.22 (m, 2 H), 2.10–1.98 (m, 2 H), 1.82–1.67 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137 ppm. 65, 137.42, 129.00, 128.56, 128.40, 128.04, 126.30, 126.01, 102.31, 101.40, 101.21, 74.70, 73.80, 71.67, 70.22, 69.94, 69.04, 68.90, 62.41, 61.72, 59.38, 58.52, 55.48, 55.09, 49.23, 47.41, 34.18, 31.68, 29.96, 27.96. IR (KBr): $\tilde{\nu}$ = 3421, 2933, 2875, 1486, 1452, 1378, 1266, 1133, 1112, 1087, 972, 819, 754, 689 cm^{-1}. MS (ESI): *m*/*z* (%) = positive 809 (100) $[M - Cl^-]$; negative 879 (100) $[M + Cl^-]$. HRMS: calcd. for $C_{39}H_{50}N_2O_{10}Rh$ $[M - Cl]^+$ 809.2520; found 809.2529.

***N*,*N*′-1,3-Bis(methyl 4,6-*O*-benzylidene-3-deoxy-α-D-altropyrano-3-yl)-2-hydroxyimidazolidine (6):** The compound was isolated as a side product in the preparation of **5**; its yield is around 5–20% depending on the dryness of imidazolinium salt **4** used. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 7.50–7.30 (m, 10 H), 5.55 (s, 1 H), 5.44 (s, 1 H), 4.65–4.60 (m, 2 H), 4.35–4.25 (m, 2 H), 4.15–4.10 (m, 2 H), 4.07–4.00 (m, 2 H), 3.95–3.91 (m, 2 H), 3.90–3.77 (m, 4 H), 3.68–3.60 (m, 2 H), 3.51–3.40 (m, 8 H), 3.38–3.10 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.28, 137.38, 137.07, 129.17, 128.36, 128.29, 126.46, 126.31, 126.08, 102.51, 102.33, 102.03, 101.88, 77.40, 75.80, 69.88, 69.68, 69.49, 69.08, 61.74, 59.55, 58.92, 58.66, 55.60, 55.54, 47.16, 45.51 ppm. IR (KBr): $\tilde{\nu}$ = 3409, 3257, 2934, 1654, 1455, 1380, 1136, 1107, 1049, 974, 756, 700 cm^{-1}. MS (ESI): *m*/*z* (%) = 617 (20) $[M + 1]^+$.

Supporting Information (see footnote on the first page of this article): Full characterization of compounds **3**–**6**.

Acknowledgments

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