Synthesis of Constrained-Geometry Chiral Di-N-Heterocyclic Carbene Ligands and Their Silver(I) and Palladium(II) Complexes

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Summary: Silver(I) and palladium(II) complexes of constrained-geometry chiral di-N-heterocyclic carbenes have been prepared from trans-1,2-diaminocyclohexane via the base-induced 1,3-cycloaddition of tosylmethyl isocyanide to diimines.

Since the discovery of stable N-heterocyclic carbenes (NHC), increasing attention has been focused on using these compounds as ancillary ligands for a number of late-transition-metal-mediated catalytic reactions.[1] In general, it appears that catalytic reactions which employ transition-metal complexes of tertiary phosphines may also be catalyzed using complexes of NHC, and many of the precatalysts studied to date exhibit excellent thermal stability and the need for excess NHC ligand is not required.[1−5] In addition, further interest lies in the unusual structural motif rendered at the metal atom by NHC ligands, and in this respect a concurrent development has been the investigation of chiral NHC derivatives to induce enantioselective reactivity.[6−21] In comparison to tertiary phosphine chemistry, reported examples where chiral NHC complexes give good enatioselectivity are rare, in most cases primarily due to the flexibility of the ligand systems investigated. However, the recent reports by Burgess et al. of >99% ee for the iridium-catalyzed asymmetric hydrogenation of aryl alkenes, using a constrained-geometry NHC-oxazoline ligand, exemplify the potential of chiral NHC ligands.[22,23] Excellent levels of enantioselectivity have been observed for symmetry-breaking metathesis reactions using NHC ligands that exhibit a well-defined geometry.[24,25] also demonstrating that further investigation into chiral NHC ligands is justified.

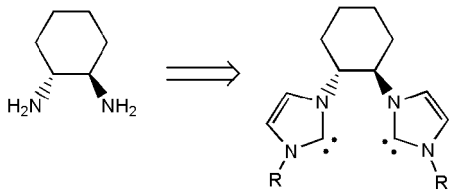

Figure 1. Target NHC.

By far the most common method for the synthesis of chelating NHC ligands and their hybrids is from reaction between an imidazole and a suitable precursor. In part, the application of NHC ligands to asymmetric catalysis has been limited by the paucity of synthetic routes to their preparation.

Here we wish to report the synthesis of constrained-geometry chiral di-NHC ligands derived from *trans*-1,2-diaminocyclohexane. The synthesis of silver(I) and palladium(II) complexes and an X-ray crystal structure of a palladium(II) complex are also presented.

Our aim was to prepare chiral chelating NHC ligand precursors derived from chiral diamines, including the readily accessible enantiomers of *trans*-1,2-diaminocyclohexane, which we envisaged would exhibit a well-defined geometry, as shown in Figure 1. We were motivated in part by the availability of structurally diverse chiral diamines and in particular by the success of ligand sets based on chiral diamines in several metal-mediated enantioselective catalytic reactions.[26−28] In

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addition the only other two di-NHC compounds reported that contain a chiral linking motif both exhibit a trans configuration in square-planar palladium(II) complexes, which appears to be detrimental to asymmetric catalysis.[11,17]

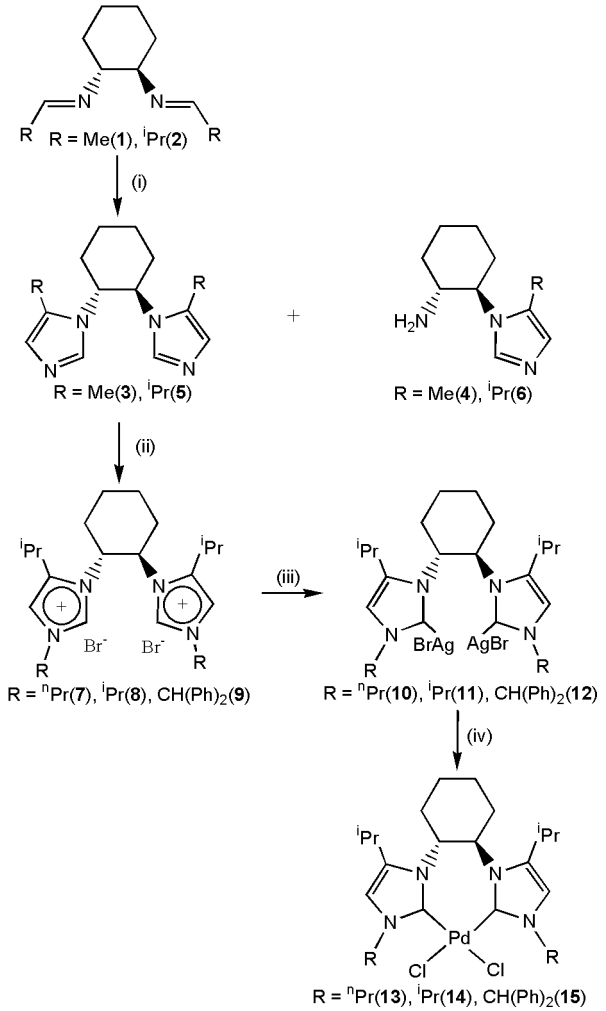
The most common method for the preparation of an imidazole ring is cocondensation of an amine, ammonia, paraformaldehyde, and a dione.[29] Perhaps unsurprisingly, initial attempts to prepare diimidazoles from (1*R*,2*R*)-1,2-diaminocyclohexane using cocondensation routes lead to the formation of oligomeric mixtures, and therefore an alternative strategy was sought. Of the many reactions used to prepare imidizoles, the base-induced 1,3-cycloaddition of tosylmethyl isocyanide (TosMIC) to imines[30,31] appeared the most suitable for the preparation of diimidazoles; therefore, we investigated the reaction between TosMIC and diimine derivatives **1** and **2**, as shown in Scheme 1. Several initial reactions between **1** and 2 equiv of TosMIC did give the target diimidazole **3**; however, ^{1}H NMR spectroscopy indicated that a large mole fraction of the imidazole−amine **4** had also formed. Variation in reaction parameters gave **3** in a maximum isolated yield of ca. 45% that we could not completely purify free from **4**. We presumed that formation of compound **4** was due to either thermal degradation, which was also observed for the parent diimine **1**, or competitive hydrolysis. Therefore, reaction between 2 equiv of TosMIC and the more thermally and hydrolytically stable diimine **2** was investigated, giving the diimidazole **5** and imidazole−amine **6** in a 4:1 ratio, as judged by ^{1}H NMR spectroscopy. Compound **5** could be readily purified by recrystallization from hot diethyl ether and isolated in ca. 50% yield.

The ^{1}H and ^{13}C{^{1}H} NMR spectra of **3** and **5** are indicative of a C_2-symmetric diimidazole. For example, compound **3** exhibits a signal at δ 3.93 ppm that is attributable to the two equivalent protons of the cyclohexyl group adjacent to the nitrogen atoms ($^{c-hex}CH$), and ^{13}C{^{1}H} NMR shows only three signals attributable to the cyclohexyl carbons. Due to the higher yield and ease of isolation all subsequent efforts were concentrated on the chemistry of compound **5**.

Imidazolium salt derivatives of **5** that serve as NHC ligand precursors (vide infra) were prepared from reaction between **5** and the hydrocarbyl bromides RBr, where R = ^{n}Pr, ^{i}Pr, $CHPh_2$, giving the corresponding N-substituted imidazolium salts (**7**−**9**) as shown in Scheme 1 in ≥85% yield.

^{1}H and ^{13}C{^{1}H} NMR spectroscopy of compounds **7**−**9** is also consistent with C_2 symmetry, and the ^{1}H NMR spectrum displays a signal between δ 11.67 and 12.39 ppm that is characteristic for the NC(*H*)N proton of an imidazolium cation. Compounds **7**−**9** are air-stable, hygroscopic white solids that are soluble in water, alcohols, chlorinated solvents, and THF but are insoluble in diethyl ether and hydrocarbons.

Scheme 1. Synthesis of 1−15[a]



[a] Conditions: (i) TosMIC, K_2CO_3, MeCN, 25−50 °C; (ii) RBr, MeCN, 100 °C; (iii) Ag_2O, CH_2Cl_2, 25−50 °C; (iv) $PdCl_2(MeCN)_2$, MeCN, 90 °C.

Wang and Lin first demonstrated that silver(I) halide complexes of NHC are useful ligand transfer agents to palladium(II),[32] and therefore, we investigated the synthesis of silver(I) complexes derived from **7**−**9**. Reaction between **7**−**9** and Ag_2O in CH_2Cl_2 gave the corresponding silver(I) bromide complexes **10**−**12**, as shown in Scheme 1, in ≥72% yield. ^{1}H NMR spectra of complexes **10**−**12** are similar to those of the parent imidazolium salts, except for the expected absence of signals attributed to the NC(*H*)N proton. Compounds **10**−**12** are air-stable solids that are soluble in most common organic solvents, except for diethyl ether and nonaromatic hydrocarbons, and in the presence of light solutions decompose within hours.

To determine the coordination and structural features of these di-NHC ligands, the synthesis of palladium(II) complexes was investigated by reaction between compounds **10**−**12** and [$PdCl_2(MeCN)_2$].[33] Complexes **13**−**15** were isolated in ≥79% yield as white or pale yellow air-stable solids. ^{1}H and ^{13}C{^{1}H} NMR spectroscopy is consistent with the proposed formulations and C_1 symmetry, indicating that the ligand in complexes **13**−**15** is chelating. Particular NMR indicators of bidentate

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coordination are the signals attributable to the $^{c-hex}CH$ protons. Representative of the palladium(II) complexes is the ^{1}H NMR spectrum of **15**, which shows two signals at δ 4.16 and 7.64 ppm for the $^{c-hex}CH$ protons, and the ^{13}C NMR spectrum, which shows two carbene signals at δ 157.7 and 164.1 ppm, respectively.

The molecular structure of **15** was determined from a single-crystal X-ray diffraction study, confirming bidentate coordination of the di-NHC ligand in this molecule.[33] Complex **15** crystallizes with two molecules in the asymmetric unit, and one molecule is shown in Figure 2. The two molecules differ significantly only in the relative orientation of the two phenyl groups, which in Figure 2 contain C(64) and C(83). In both molecules the two remaining phenyl groups appear to be disposed in a π-stacking arrangement with the distance between the phenyl centroids being 3.72 and 3.82 Å, respectively. A distorted cis square-planar geometry is exhibited at the palladium atom, and the Pd−C and Pd−Cl bond lengths are within the range observed for other Pd-NHC complexes. The seven-atom palladacycle adopts a pseudo-boat-like conformation, and the di-NHC C−Pd−C bite angles are 83.0(2) and 84.2(2)°, respectively, for each molecule in the asymmetric unit, similar to palladium-(II) complexes of chelating bis-phosphines that contain a two-carbon-atom linker.[34]

To gain some insight into whether palladium(II) complexes incorporating these di-NHC ligands are stable to water and likely to be conformationally robust, ^{1}H NMR spectroscopy of **15** was performed at 90 °C in d_6-DMSO containing approximately 5 equiv of water. The sample was also heated for 7 days at 90 °C and the spectrum subsequently recorded at room temperature. In comparison to NMR spectra recorded at room temperature, no significant changes were observed for **15** at 90 °C, and no decomposition was observed after heating **15** at 90 °C for 1 week.

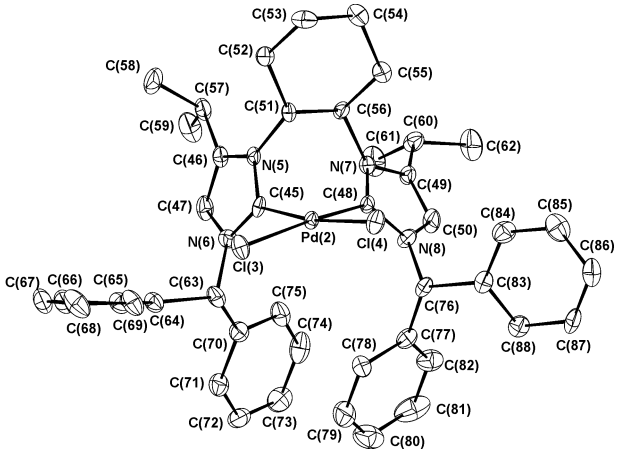

Figure 2. Molecular structure of **15**. Hydrogen atoms have been removed for clarity. Thermal ellipsoids are set at the 30% probability level. Selected bond lengths (Å) and angles (deg): Pd(2)−C(45) = 1.987(5), Pd(2)−C(48) = 2.003(5), Pd(2)−Cl(3) = 2.3488(14), Pd(2)−Cl(4) = 2.3654(14); C(45)−Pd(2)−C(48) = 84.2(2), C(45)−Pd(2)−Cl(3) = 90.76(16), C(48)−Pd(2)−Cl(3) = 172.16(16), C(45)−Pd(2)−Cl(4) = 171.49(17), C(48)−Pd(2)−Cl(4) = 93.58(15), Cl(3)−Pd(2)−Cl(4) = 92.30(5). $C(70)_{Ph-centroid}$−$C(77)_{Ph-centroid}$ = 3.82 Å.

In conclusion, we have shown that the base-induced 1,3-cycloaddition of TosMIC to diimines can be used for the synthesis of chiral diimidazoles which serve as an entry into chiral chelating di-NHC ligands and that palladium(II) complexes of these ligands chelate in exclusively cis coordination. The synthetic route to the diimidazoles described should also provide a basis for the synthesis of a wide range of chiral NHC ligands derived from chiral diamines. We are now investigating the potential of this new class of chiral ligand for application to transition-metal-mediated asymmetric catalysis.[35]

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Supporting Information Available: Text and figures giving experimental procedures and characterization data for compounds **1**−**15** and tables of crystal data, fractional atomic coordinates, bond distances, bond angles, and anisotropic thermal parameters for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(33) Synthesis of **15**: in an ampule sealed with a Teflon stopcock, an acetonitrile solution (15 mL) of $[Pd(MeCN)_2Cl_2]$ (25 mg, 0.10 mmol) was added to an acetonitrile solution (15 mL) of **12** (100 mg, 0.10 mmol) under argon. The solution was stirred at 90 °C for 48 h, giving a white precipitate (AgBr) and a yellow supernantant. The mixture was filtered through Celite and dried under reduced pressure to give **15** as a yellow solid. Yield: 71 mg, 82%. Anal. Found (calcd): C, 64.95 (65.23); H, 5.61 (5.97); N, 6.83 (6.92). MS (FAB+): *m/z* 771 (100%) $[M - Cl]^+$. MS (HRFAB+): calcd for $C_{44}H_{48}N_4ClPd$, 771.2608; found, 771.2607. ^{1}H NMR ($CDCl_3$, 270 MHz): δ 0.97 (d, $^3J_{H-H}$ = 6.7 Hz, 3H, CH_3), 1.07 (vt, $^3J_{H-H}$ = 6.7 Hz, 6H, CH_3), 1.14 (d, $^3J_{H-H}$ = 6.7 Hz, 3H, CH_3), 1.51−2.69 (m, 8H, CH_2), 2.78 (vsep, $^3J_{H-H}$ = 6.7 Hz, 1H, CH(CH$_3$)$_2$), 3.03 (vsep, $^3J_{H-H}$ = 6.7 Hz, 1H, CH(CH$_3$)$_2$), 4.16 (m, 1H, $^{c-hex}CH$), 5.82 (s, 1H, CHC(*i*Pr)), 5.85 (s, 1H, CHC(*i*Pr)), 6.24 (s, 2H, CH(C$_6$H$_5$)$_2$), 6.77−7.34 (m, 20H, C$_6H_5$), 7.64 (m, 1H, $^{c-hex}CH$), 8.37 (s, 1H, CH(C$_6$H$_5$)$_2$). ^{13}C{^{1}H} NMR ($CDCl_3$, 67.5 MHz): δ 20.5 (*C*H$_3$), 23.0 (*C*H$_3$), 23.2 (*C*H$_3$), 23.5 (*C*H$_3$), 24.5 (*C*H(CH$_3$)$_2$), 24.8 (*C*H$_2$), 25.3 (*C*H(CH$_3$)$_2$), 25.7 (*C*H$_2$), 30.3 (*C*H$_2$), 37.2 (*C*H$_2$), 61.2 (*C*H(C$_6$H$_5$)$_2$), 63.6 (*C*H(C$_6$H$_5$)$_2$), 66.4 ($^{c-hex}CH$), 67.2 ($^{c-hex}CH$), 116.7 (*C*HC(*i*Pr)), 117.6 (*C*HC(*i*Pr)), 127.5 (2 × *C*$_6$H$_5$), 127.8 (*C*$_6$H$_5$), 128.1 (2 × *C*$_6$H$_5$), 128.2 (*C*$_6$H$_5$), 128.3 (*C*$_6$H$_5$), 128.4 (3 × *C*$_6$H$_5$), 128.6 (*C*$_6$H$_5$), 129.6 (*C*$_6$H$_5$), 137.8 (*ipso*-*C*$_6$H$_5$), 137.8 (*ipso*-*C*$_6$H$_5$), 139.5 (*ipso*-*C*$_6$H$_5$), 139.8 (*ipso*-*C*$_6$H$_5$), 140.9 (*C*(*i*Pr)), 141.7 (*C*(*i*Pr)), 157.7 (*C*Pd), 164.1 (*C*Pd). Crystal data for **15**·1.5CH_2Cl_2 ($C_{45.5}H_{49}N_4Cl_5Pd$): triclinic, *P*1, a = 11.4458(9) Å, b = 12.5768(10) Å, c = 16.2774(13) Å, α = 99.443(2)°, β = 90.387(2)°, γ = 94.486(2)°, V = 2303.9(3) Å^3, Z = 2, ρ = 1.349 g cm^{-3}, T = 115 K, θ range for data collection 1.27−25.30°, limiting indices $-13 \le h \le 13$, $-14 \le k \le 14$, $-18 \le l \le 18$, 26 323/13 187 collected/unique reflections (R(int) = 0.0263), absolute structure parameter 0.00(2), goodness of fit on F^2 1.079, final R indices ($I > 2\sigma(I)$) R1 = 0.0444, wR2 = 0.1144. The structure was solved using SHELXS-97 and refined using SHELXL-97. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *467*−*473*, A46. Sheldrick, G. M. SHELXL-97, a computer program for crystal structure refinement; University of Göttingen, Göttingen, Germany, 1997.

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(35) The asymmetric intramolecular cyclization of *N*-(2-bromophenyl)-*N*-methyl-2-(1-naphthyl)propanamide using 5 mol % **15** and 1.5 equiv of NaO^{t}Bu in 1,4-dioxane at 80 °C for 72 h gave (+)-1,3-dimethyl-3-(1-naphthyl)oxindole in 90% yield and 11% ee. This result does not compare favorably with a previous study of this reaction, where ee's up to 70% were obtained. See: Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402.