N-Heterocyclic Carbenes

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Chiral Palladium(II) Complexes Possessing a Tridentate N-Heterocyclic Carbene Amidate Alkoxide Ligand: Access to Oxygen-Bridging Dimer Structures**

*Satoshi Sakaguchi, Kyung Soo Yoo, Justin O'Neill, Joo Ho Lee, Timothy Stewart, and Kyung Woon Jung**

N-Heterocyclic carbenes (NHCs) and their palladium complexes have been developed to facilitate the formation of carbon–carbon and carbon–heteroatom bonds.[1] NHC complexes exhibit unique chemical properties such as strong Pd–NHC σ bonding, which enhances the stabilities of active organometallic compounds relative to conventional phosphane complexes.[2] Moreover, chiral NHC ligands have been synthesized to promote asymmetric catalysis.[3]

Most of the chiral NHC ligands that have been utilized for asymmetric Pd^{II} catalysis are monodentate, as Lee and Hartwig demonstrated moderate enantioselectivities (71–76% *ee*) in α-arylation.[4] However, monodentate ligands caused practical difficulties including concomitant formation of inactive palladium–ligand complexes, such as those with a *trans* conformation. Bidentate NHC ligands exhibited better stabilities and selectivities: Douthwaite reported better enantioselectivities (up to 92% *ee*) for asymmetric allylic alkylation[5a,b] than reactions employing the corresponding monodentate ligand.[5c]

We envisioned tridentate NHCs would enhance the stabilities of Pd^{II} complexes and enantioselectivities of various asymmetric reactions. As depicted in Figure 1, we sought a "chiral $\{Pd(OAc)_2\}$ complex" and designed and synthesized novel chiral tridentate NHC–Pd^{II} complexes (**II**). Notably, ligand systems with NHCs, amidates, and oxygen functionalities (a C,N,O triad) could exert high electron densities and strong coordination on the Pd^{II} complexes to increase stabilities even in nucleophilic solvents such as water and alcohols. Therefore, labile ligands such as water, alcohols, and acetonitrile are likely to be removed easily and thus enhance the reactivities and efficiencies of NHC–Pd catalysts.

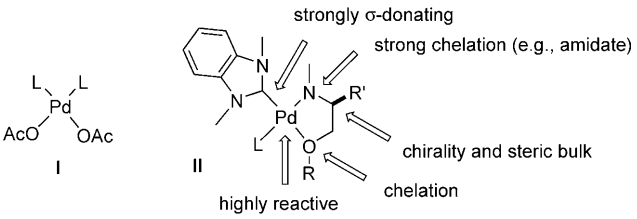
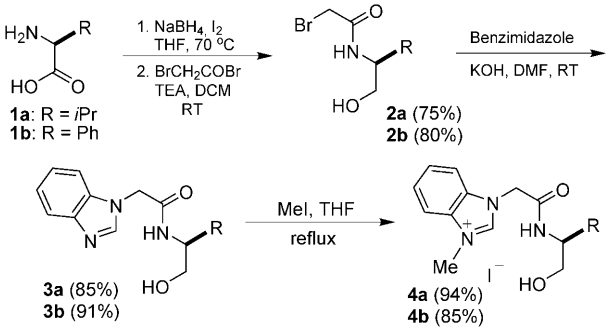


Figure 1. Design of a chiral $\{Pd(OAc)_2\}$ complex (**II**) for asymmetric catalysis.

We report herein the synthesis of chiral tridentate NHC–Pd^{II} complexes and their applications in an asymmetric oxidative Heck-type reaction as a proof of concept.

The preparation of chiral ligands **4** is shown in Scheme 1. Hydroxyamide compounds **2** were prepared by reduction of amino acids **1** and subsequent N-alkylation with bromoacetyl bromide. Treatment of **2** with benzimidazole in the presence



Scheme 1. Synthesis of chiral NHC ligands **4a** and **4b**. TEA = triethylamine; DCM = dichloromethane.

of KOH in DMF provided compounds **3**, which were subjected to methylation to yield the amido alcohol substituted benzimidazolium salts **4**. The structure was confirmed by ^1H NMR spectroscopic analysis; new peaks assigned to the NCH_3 appeared at $\delta = 4.18$ (**4a**) and 4.15 ppm (**4b**). Also, the imidazole H resonances shifted significantly as expected for iodine salts, appearing at $\delta = 9.55$ (**4a**) and 9.50 ppm (**4b**).

Because direct coordination of ligands **4** to palladium was not efficient under numerous conditions, the ligands were transferred to palladium via silver NHC complexes.[6] As described in Scheme 2, compounds **4a** and **4b** were treated with Ag_2O in CH_2Cl_2 to give silver NHC complexes.

[*] Dr. K. S. Yoo, J. O'Neill, Dr. J. H. Lee, T. Stewart, Prof. K. W. Jung
Loker Hydrocarbon Research Institute and
Department of Chemistry
University of Southern California, Los Angeles, CA 90089 (USA)
Fax: (+1) 213-821-4096
E-mail: kwjung@usc.edu
Dr. S. Sakaguchi
Department of Applied Chemistry, Kansai University
Suita, Osaka 564-8680 (Japan)

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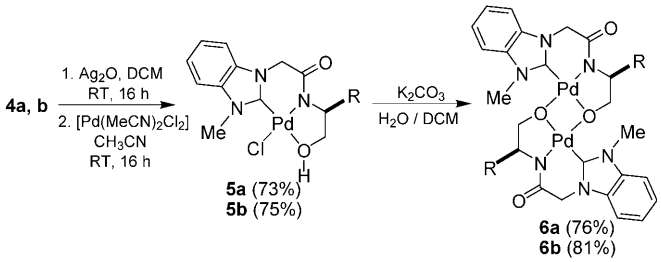


Scheme 2. Synthesis of NHC-coordinated Pd^{II} complexes.

Subsequent treatment of the silver compounds with $[PdCl_2(CH_3CN)_2]$ in CH_3CN at room temperature provided the palladium(II)/NHC ligand complexes **5a** and **5b** in 73 and 75% yields, respectively, for the two steps. Their structures were confirmed with ^1H and ^{13}C NMR spectroscopy by the complete disappearance of the imidazole protons and by the observation of the expected change in chemical shifts for the NCH_2CO peaks [$\delta = 5.43/5.35$ to 5.82/5.49 ppm for **5a**, $\delta =$ 5.42 (singlet) to 5.74/5.65 ppm for **5b**] relative to those of ligands **4a** and **4b**; HRMS analysis further confirmed the assignment by showing molecular ion peaks at m/z 416.0356 ([M+H]; calcd for **5a**: 416.0357) and m/z 405.0279 ([M+H]; calcd for **5b**: 405.0201), respectively.

Dehydrohalogenation of **5a** and **5b** in the presence of K_2CO_3 produced NHC–Pd^{II} complexes **6a** and **6b** in high yields. Only one isomer of each of the dimeric compounds was detected in solution by ^1H NMR spectroscopic analysis; their spectra exhibited an upfield shift [$\delta = 5.82/5.49$ to 4.99/4.91 ppm for **6a** and $\delta = 5.74/5.65$ to 5.05/4.92 ppm for **6b**] of the NCH_2CO signals, implying moderate structural distortion of the square-planar Pd^{II} complexes relative to **5**. HRMS spectra (molecular peaks at m/z 759.1105 ([M+H]) for **6a** and m/z 828.0789 ([M+H]) for **6b**) supported the assigned dimeric molecular-based structures. We sought optimal reaction conditions by screening various carbonate and hydroxide bases. The use of carbonate bases such as Na_2CO_3, $KHCO_3$, and $NaHCO_3$ provided the dimeric palladium complex in decent yields (70–52%). However, in the presence of NaOH, dehydrohalogenation of **5** afforded dimeric complex **6** in a decreased conversion of 48%.

After further purification, complexes **5a** and **6a** were crystallized from CH_2Cl_2/Et_2O. The molecular structures of **5a** and **6a** were established by single-crystal X-ray diffraction studies (Figures 2 and 3). The solid-state structures of **5a** and **6a** show that the NHC rings are aligned roughly perpendicular to the square-planar Pd coordination plane. Notably, the Pd–N bond lengths of both structures are shortened (1.980(2) Å for **5a** and 1.978(3) Å for **6a**) relative to other Pd–N bonds, such as with protonic amines, azides, and imines.[7] This peculiar structural feature indicates that the Pd–N bonding is anionic coordination. For example, the geometry about N2 in **6a** is approximately trigonal planar as shown by the torsion angle (10.8°) for C3···C12···Pd1···N2 and the sum of the bond angles (355.80°). Therefore, these torsional parameters highlight the utility of anionic coordination between nitrogen and palladium, which is distinguished from a lone-pair coordination, such as for Pd–NH.

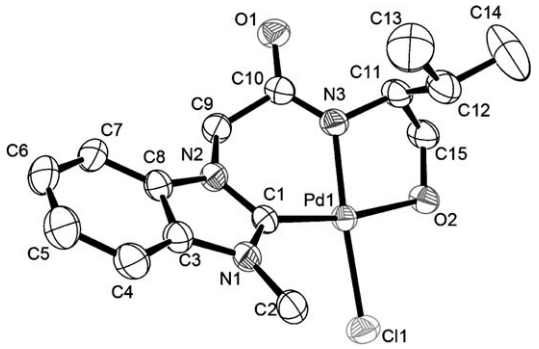


Figure 2. Solid-state molecular structure of **5a**. Hydrogen atoms and solvent molecules are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd1–C1 1.937(2), Pd1–N3 1.980(2), Pd1–O2 2.1102(18), Pd1–Cl1 2.3031(7), C1-Pd1-N3 88.60(9), C1-Pd1-O2 170.05(9), N3-Pd1-O2 81.67(8), C1-Pd1-Cl1 97.89(7), N3-Pd1-Cl1 172.90(6), O2-Pd1-Cl1 91.94(5).

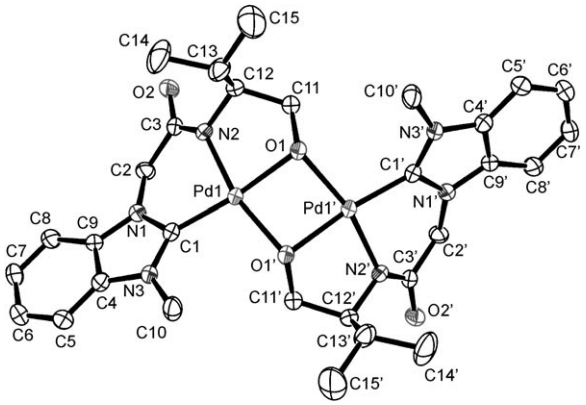


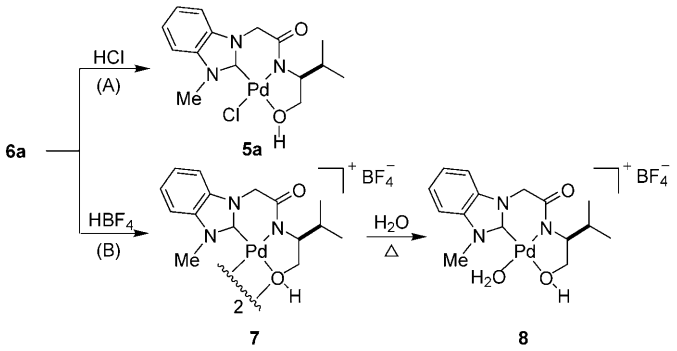
Figure 3. Solid-state molecular structure of **6a**. Hydrogen atoms and solvent molecules are omitted for clarity. Selected bond lengths [Å] and angles [°]: Pd1–C1 1.947(3), Pd1–N2 1.978(3), Pd1–O1 2.052(2), Pd1–O1′ 2.072(2), Pd1···Pd1′ 2.9731(5), C1-Pd1-N2 90.04(12), C1-Pd1-O1′ 104.01(11), N2-Pd1-O1′ 165.12(11), Pd1-O1-Pd1′ 92.26(10), O1-Pd1-O1′ 81.94(11).

Regarding oxygen and neighboring atoms, the Pd–O bond length in a Pd–OH bond (anionic bonding) is shorter (0.05–0.15 Å) than the Pd–O bond length (dative bonding) observed for known aqua complexes.[8] In addition, the Pd–O bond in **6a** is slightly shorter than the Pd–O bond in **5a**, which is informative evidence that the O1 atom in **6a** contributes to the Pd_2O_2 bridging through delocalization of the electrons from the oxygen donors. The dimeric palladium complex **6a** crystallized in the chiral space group *C*2 with bridging of the oxygen atom to the palladium atom. The Pd_2O_2 core is not planar, but inclined at a dihedral angle of 145.5° about the Pd···Pd axis. The substituents of the alkoxide oxygen atoms adopt an *endo* arrangement, which makes the structure of the dimeric palladium complex unique among dimeric palladacycles. Conclusively, **5a** and **6a** are unprecedented Pd^{II} complexes consisting of a carbene, amidate, and alkoxide.

More importantly, the dimeric structure **6a** was completely stable in air and water environments. Both dimeric

and monomeric catalysts survived harsh conditions, including water and protic solvents, unlike other known Pd catalysts. Thus, these kinds of catalysts can provide opportunities to effect difficult reactions, including C–H activation, which we will report in due course.

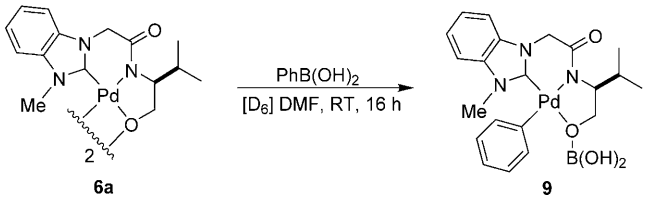
The isolated dimeric structure itself did not show active catalytic properties, presumably by reaching a stable resting stage. However, this structure was easily converted into various active monomeric Pd–ligand structures. Dimer–monomer catalyst equilibrium has been reported for a number of palladium-catalyzed reactions, and prior investigations support the concept that the dimer can act as a reservoir for the active monomer.[9] As shown in Scheme 3, Pd^{II}–NHC complex



Scheme 3. Conversion of **6a** into monomeric Pd^{II} complexes by HCl (with a coordinating anion; A) and HBF_4 (with a noncoordinating anion; B).

6a was converted into monomeric Pd complex **5a** (as confirmed by ^{1}H NMR spectroscopy) by cleavage of the Pd_2O_2 core in the presence of HCl (coordinating anion). In contrast, the protonated dimeric complex **7** was afforded by aqueous HBF_4 (noncoordinating anion) solution and then conveniently transformed into cationic Pd^{II} complex **8** by heating.

Using this concept, we monitored the conversion of dimer **6a** into monomer in the presence of phenylboronic acid as a coordinated anion substrate. The transformation reaction was carried out using dimeric Pd^{II} complex **6a** (16 μmol) and phenylboronic acid (32 μmol), in [D_6]DMF at room temperature for 16 h (Scheme 4). Arylmetalation of phenylboronic acid was observed to give phenylpalladium(II) complex **9** in 82% conversion (^{1}H NMR spectroscopy), although the reaction was very slow in DMF. On the basis of this result, the observed intermediate structure can provide evidence of a

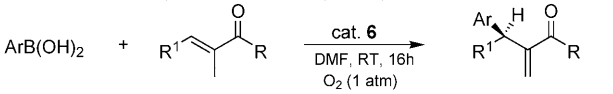


Scheme 4. Conversion of **6a** into monomeric Pd^{II} complex **9** by phenylboronic acid.

transmetallation step between palladium and an aryl boronic acid (or aryl halide) which can be encountered in palladium-catalyzed reactions such as Suzuki and boron Heck-type reactions.

In this context, asymmetric catalytic properties of air- and water-stable complexes **6** were examined by subjecting these novel catalysts to oxidative boron Heck couplings between aryl boronic acids and acyclic olefins.[10] First, we screened representative oxidants for asymmetric coupling reaction with methyl tiglate and phenylboronic acid in the presence of **6a**. Under an O_2 atmosphere (1 atm), the desired product **10** was obtained in 49% yield. In contrast, the reaction under an air atmosphere resulted in low yield of **10** (11%), and no reaction occurred by employing $CuCl_2$ as an oxidant. Therefore, the coupling reactions were carried out in DMF at room temperature under O_2 atmosphere (Table 1). The desired

Table 1: Selected results for catalytic oxidative Heck-type reaction of aryl boronic acids with acyclic alkenes catalyzed by **6a** and **6b**.[a]



Entry	Ar	R^1, R	Cat.	Product (yield, *ee*)[b,c]	Conf.[d]
1	Ph	Me, OMe	**6a**	**10** (49%, 91% *ee*)	*R*
2	2-naphthyl	Me, OMe	**6a**	**11** (61%, 92% *ee*)	–
3	Ph	Me, H	**6a**	**12** (31%, 98% *ee*)	*R*
4	*p*-$MeOC_6H_4$	Me, H	**6b**	**13** (32%, 90% *ee*)	*R*

[a] All reactions were carried out with 1.1 equiv aryl boronic acids and 5 mol% **6**. [b] Yields of isolated products. [c] Determined by chiral HPLC analysis (Daicel Chiracel OD; mobile phase: *i*PrOH:hexane = 5:95 v/v%, rate: 1 mL min^{-1}) and NMR analysis with a chiral Eu reagent. [d] Absolute configuration.

rearrangement products were obtained in modest yields, but still far higher than the corresponding Heck reactions (less than 5% yields). However, both dimers **6a** and **6b** provided excellent enantioselectivities (greater than 90% *ee*), and the absolute configurations of **10**, **12**, and **13** were confirmed as *R*-enriched by transforming the products into the corresponding phenyl propionic esters and comparing them with authentic samples.[11] To our knowledge, these examples are the first cases to demonstrate high enantioselectivities (greater than 90% *ee*) in intermolecular Heck-type reactions. Above all, the distinguished degree of asymmetric induction should stem from tight binding of tridentate ligands to Pd metal during the entire catalytic processes.

Another interesting feature of Heck-type reactions carried out using dimeric catalysts was the observation of a nonlinear dependence of reaction rate on the concentration of Pd. For example, van Leeuwen and co-workers recently found a half-order dependence on catalyst concentration and attributed this result to the formation of a dimeric [{PdLArX}$_2$] species.[9d] Hence, the oxygen-bridging dimeric complex behaves chemically as a catalyst precursor.

In summary, we have designed novel Pd^{II} catalysts and developed an efficient synthesis of chiral tridentate amidate/

alkoxy/carbene Pd^{II} complex **6**. These catalytic complexes facilitated an asymmetric oxidative Heck-type reaction between aryl boronic acids and acyclic alkenes, which offered high enantioselectivities unprecedented in intermolecular Heck-type couplings. This ligand architecture can be readily altered by using different chiral substrates and can then be expanded for use with various palladium catalyzed coupling reactions. Currently in progress are further studies focusing on the preparation of conformationally stable and enantiomerically pure Pd^{II} analogues and their applications toward asymmetric cross-coupling reactions using various substrates, as well as investigations to gain mechanistic insights.

Experimental Section

5a: A suspension of benzimidazolium salt **4a** (500 mg, 1.23 mmol) and silver(I) oxide (150 mg, 0.65 mmol) in CH_2Cl_2 (52 mL) was stirred for 2 h in the dark at room temperature. The reaction mixture was concentrated under reduced pressure to give a dark-red solid. $[PdCl_2(CH_3CN)_2]$ (260 mg, 1 mmol) was added to a suspension of the silver complex in CH_3CN (50 mL) in the dark at room temperature. Then, the resulting suspension was stirred for 2 h and filtered through a plug of glass fiber filter paper. The filtrate was evaporated to dryness in vacuo to afford product **5a** (378 mg, 73% yield) as an orange solid; ^{1}H NMR (CD_3OD): $\delta = 7.61$ (d, $J = 16.0$ Hz, 1H), 7.54 (d, $J = 16.4$ Hz, 1H) 7.37 (m, 2H), 5.82 (d, $J = 16.4$ Hz, 1H), 5.49 (d, $J = 16.4$ Hz, 1H), 4.35 (s, 1H), 3.75 (q, 1H), 3.61–3.51 (ABX, $J =$ 16.4 Hz, 2H), 1.82 (m, 1H), 0.84 (d, $J = 6.7$ Hz, 3H), 0.77 ppm (d, $J =$ 6.7 Hz, 3H); ^{13}C NMR (CD_3OD): $\delta = 168.9$, 136.1, 135.9, 135.8, 135.6, 124.9, 124.7, 111.9, 62.9, 58.5, 52.4, 35.1, 29.8, 20.0, 19.0, 18.6, 18.5 ppm; HRMS-ESI (m/z) $[M+H^+]$ calcd for $C_{15}H_{21}ClN_3O_2Pd$: 416.0357, found: 416.0356.

6a: K_2CO_3 (207 mg, 1.5 mmol) was added to a solution of **5a** (208 mg, 0.5 mmol) in water (15 mL, HPLC grade). The suspension was stirred for 8 h at room temperature. Then, CH_2Cl_2 (75 mL) was added, and the mixture was stirred for 1 h. The aqueous layer was washed with CH_2Cl_2 (2×50 mL), and the organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated to give a yellow solid **6a** (154 mg, 81%). Crystals for X-ray diffraction were obtained by layering solutions of **6a** in dichloromethane with Et_2O and allowing slow diffusion at room temperature. ^{1}H NMR (CD_3OD): $\delta = 7.64$–7.69 (m, 2H), 7.44–7.46 (m, 2H), 4.99 (d, $J = 16.4$ Hz, 1H), 4.91 (d, $J = 16.4$ Hz, 1H), 4.17 (s, 3H), 3.62 (m, 1H), 3.45 (m, 2H), 2.18 (m, 1H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.75 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (CD_3OD): $\delta = 166.8$, 164.7, 135.4, 134.6, 125.4, 125.2, 112.2, 111.7, 74.4, 70.7, 54.7, 52.4, 33.8, 30.5, 20.4, 19.8 ppm; HRMS-ESI (m/z) $[M+H^+]$ calcd for $C_{30}H_{39}N_6O_4Pd_2$: 759.1102, found: 759.1105.

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