

# Air- and Water-Stable Catalysts for Hydroamination/Cyclization. Synthesis and Application of CCC–NHC Pincer Complexes of Rh and Ir

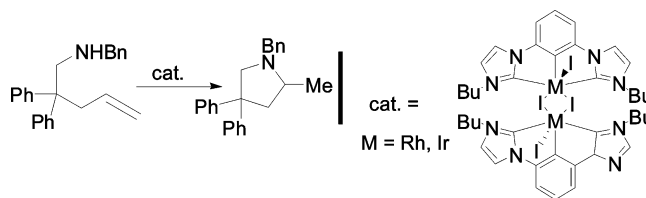
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## ABSTRACT



The scope of CCC–NHC pincer complex synthetic methodology by metalation/transmetalation has been extended to Ir. Structural characterization revealed that it is isomorphous with the Rh complex. Both Rh and Ir complexes are efficient catalysts for the hydroamination/cyclization of secondary amines in the presence of air and/or water.

The ability to functionalize alkenes with nitrogen is still in its infancy, despite examples of efficient and asymmetric C–N bond formation.<sup>1</sup> Recently, the Overman group has developed highly efficient catalysts for the allylic imide rearrangement to afford C–N bonds<sup>2</sup> and has found ever-

broadening applicability of their chiral variants.<sup>3</sup> C–N bond formation through asymmetric aminohydroxylation has seen advances.<sup>4</sup> Aryl amination is another area of C–N bond formation that has seen breakthroughs recently.<sup>5</sup> A most atom-economical method of C–N bond formation is the direct addition of N–H to unactivated C–C double bonds, hydroamination/ cyclization. Mark's seminal report of lanthanide catalysts for hydroamination has sparked a flurry of activity in the field.<sup>6–8</sup> Recent reports include hydroamination/cyclization employing a Pt catalyst that was not sensitive

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(1) Li, G. G.; Chang, H. T.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 451–454. Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780–10781. DuBois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *Acc. Chem. Res.* **1997**, *30*, 364–372. Evans, D.; Faul, M.; Bilodeau, M.; Anderson, B.; Barnes, D. *J. Am. Chem. Soc.* **1993**, *115*, 5328–5329. Li, Z.; Conser, K.; Jacobsen, E. *J. Am. Chem. Soc.* **1993**, *115*, 5326–5327.

(2) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449–1456. Hollis, T. K.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8837–8840.

(3) For a recent report see: Anderson, C. E.; Donde, Y.; Douglas, C. J.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 648–657. Kirsch, S. F.; Overman, L. E.; Watson, M. P. *J. Org. Chem.* **2004**, *69*, 8101–8104.

(4) Li, G. G.; Chang, H. T.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1996**, *35*, 451–454.

(5) For a recent review see: Hartwig, J. F. in *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; Wiley: New York, 2002; Vol. 1, pp 1051–1096.

(6) a) Gagne, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108–4109. b) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673–686.

to the addition of water,<sup>9</sup> Rh,<sup>10</sup> and numerous other examples.<sup>6b,11,12</sup> Several groups have recently reported asymmetric variants.<sup>13</sup>

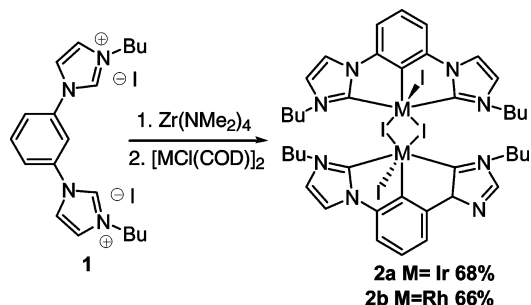
We report the extension of the metalation/transmetalation methodology for the synthesis of CCC–NHC pincer complexes to Ir<sup>14</sup> and the first examples of Rh and Ir NHC pincer complexes for the catalysis of intramolecular hydroamination/cyclization of unactivated alkenes. These systems are highly active catalysts giving near quantitative yields with low catalyst loadings for secondary amine substrates. They function in the presence of air and with water as solvent. The new CCC–NHC pincer catalysts have been prepared in high yield by a general synthetic methodology and have been structurally characterized.

Synthesis of NHC pincer complexes has been an area of intense research activity lately.<sup>15</sup> Numerous groups have contributed to the development of pyridyl bridged,<sup>16</sup> xylyl bridged,<sup>17</sup> and 2,6-lutidinyl bridged systems.<sup>17a,18</sup> We have been focused on developing phenylene bridged systems<sup>19</sup> and have developed a methodology for the synthesis of the ligand

precursor and an efficient metalation strategy.<sup>14,20</sup> Pincer complexes, in general, have shown a great variety of chemistries.<sup>21</sup> A notable recent example is in the area of N–H bond activation.<sup>22</sup>

We recently reported a general methodology for the synthesis of CCC–NHC pincer complexes that exploited the basicity and electrophilicity of Zr(NMe<sub>2</sub>)<sub>4</sub> to activate three C–H bonds simultaneously coupled with transmetalation from Zr to prepare late transition metal CCC–NHC complexes of Rh (Scheme 1, **2b**).<sup>14,20</sup> We have extended that methodology to include Ir **2a**.

**Scheme 1.** Synthesis of Pincer Complexes **2a** and **2b**



While evaluating several routes to late transition metal CCC–NHC pincer complexes, it was found that metalation with Zr followed by transmetalation to Rh or Ir was a high-yielding process providing Ir **2a** in 68% and Rh **2b** in 66% (see Supporting Information). The bis imidazolium salt **1** was treated in situ with 2.5 equiv of Zr(NMe<sub>2</sub>)<sub>4</sub>. It was then stirred with [IrCl(COD)]<sub>2</sub> for 8 h. The resulting iodo-bridged dimer was isolated in 68% yield. An X-ray quality crystal was grown by slow evaporation of a CH<sub>2</sub>Cl<sub>2</sub> solution.

A single-crystal X-ray analysis of **2a** revealed a structure that is isomorphous with the Rh analogue (Figure 1). The iodo-bridges between the Ir centers complete the octahedral environment. The molecular structure contains a center of symmetry that relates the two halves of the molecular structure. Unlike the Rh analogue, no Ir ammine adduct was noted spectroscopically, but it is anticipated that in solution this dimer is readily split by coordination to the amine functional group of the substrate. Select metric data are included in Figure 1. Other than the geometric constraints of the tridentate ligand, the geometry of the complex is within the normal ranges. Due to the chelating rings the C6–Ir–C2 angle is only 78°, a significant deviation from the idealized 90°. Likewise the C2–Ir1–C2' angle is 156°, compared to the idealized angle of 180°.

Our initial evaluation of these complexes as catalysts for the intramolecular hydroamination/cyclization focused on

(7) For recent examples see: Takaya, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5756–5757. Hoover, J. M.; Petersen, J. R.; Pikul, J. H.; Johnson, A. R. *Organometallics* **2004**, *23*, 4614–4620.

(8) For asymmetric examples see: Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857–10858. Hultsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367–391. Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737–1739.

(9) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070–1071.

(10) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042–6043.

(11) For leading references see: Molander, G. A.; Hasegawa, H. *Heterocycles* **2004**, *64*, 467–474. Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P. *Organometallics* **2005**, *24*, 4241–4250. Lai, R. Y.; Surekha, K.; Hayashi, A.; Ozawa, F.; Liu, Y. H.; Peng, S. M.; Liu, S. T. *Organometallics* **2007**, *26*, 1062–1068. Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P.; Fails, T. *Organometallics* **2007**, *26*, 2058–2069. Burling, S.; Field, L. D.; Messerle, B. A.; Rumble, S. L. *Organometallics* **2007**, *26*, 4335–4343.

(12) For reviews see: Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, 935–946. Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673–686. Molander, G. A.; Romero, J. A. C. *Chem. Rev.* **2002**, *102*, 2161–2185. Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–703.

(13) Martinez, P. H.; Hultsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221–2223. Horrillo-Martinez, P.; Hultsch, K. C.; Gil, A.; Branchadell, V. *Eur. J. Org. Chem.* **2007**, 3311–3325. Gribkov, D. V.; Hultsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748–3759. Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731–4733. Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354–358. Kim, H.; Kim, Y. K.; Shim, J. H.; Kim, M.; Han, M. J.; Livinghouse, T.; Lee, P. H. *Adv. Synth. Catal.* **2006**, *348*, 2609–2618.

(14) Rubio, R. J.; Andavan, G. T. S.; Bauer, E. B.; Hollis, T. K.; Cho, J.; Tham, F. S.; Donnadieu, B. *J. Organomet. Chem.* **2005**, *690*, 5353–5364.

(15) For a recent review see: Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239–2246.

(16) For a leading reference see: Wright, J. A.; Danopoulos, A. A.; Motherwell, W. B.; Carroll, R. J.; Ellwood, S.; Sassmannshausen, J. *Eur. J. Inorg. Chem.* **2006**, 4857–4865.

(17) (a) Grundemann, S.; Albrecht, M.; Loch, J. A.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2001**, *20*, 5485–5488. (b) Nielsen, D. J.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Inorg. Chim. Acta* **2002**, *327*, 116–125. (c) Danopoulos, A. A.; Tulloch, A. A. D.; Winston, S.; Eastham, G.; Hursthouse, M. B. *Dalton Trans.* **2003**, 1009–1015. (d) Magill, A. M.; McGuinness, D. S.; Cavell, K. J.; Britovsek, G. J. P.; Gibson, V. C.; White, A. J. P.; Williams, D. J.; White, A. H.; Skelton, B. W. *J. Organomet. Chem.* **2001**, *617*, 546–560.

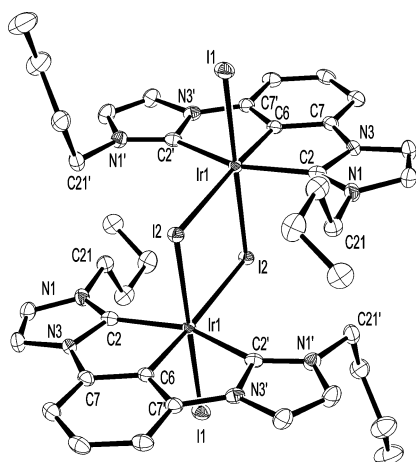
(18) Tulloch, A. A. D.; Danopoulos, A. A.; Tizzard, G. J.; Coles, S. J.; Hursthouse, M. B.; Hay-Motherwell, R. S.; Motherwell, W. B. *Chem. Commun.* **2001**, 1270–1271.

(19) Vargas, V. C.; Rubio, R. J.; Hollis, T. K.; Salcido, M. E. *Org. Lett.* **2003**, *5*, 4847–4849.

(20) Andavan, G. T. S.; Bauer, E. B.; Letko, C. S.; Hollis, T. K.; Tham, F. S. *J. Organomet. Chem.* **2005**, *690*, 5938–5947.

(21) For recent reviews see: *The Chemistry of Pincer Compounds*; Morales-Morales, D.; Jensen, C., Eds.; Elsevier: New York, 2007.

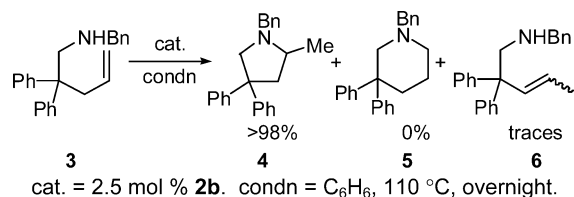
(22) Kanzelberger, M.; Zhang, X.; Emge, T. J.; Goldman, A. S.; Zhao, J.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13644–13645 and references therein.



**Figure 1.** ORTEP representation of the molecular structure of CCC-NHC Ir pincer complex **2a**. Selected geometric data: Ir1–C6, 1.965(3) Å; Ir1–C2, 2.059(4) Å; Ir1–I1, 2.6720(3) Å; Ir1–I2, 2.6803(3) Å; Ir1–I2', 2.8175(3) Å; C6–Ir1–C2, 78.36(14)°; C2–Ir1–C2', 156.47(13)°; C6–Ir1–I1, 92.38(10)°; C2–Ir1–I1, 89.07(10)°; I1–Ir1–I2, 177.705(9)°; C6–Ir1–I2', 174.89(10)°.



alkenylamine **3**. The crude product from the preparation of **3** was employed in the evaluations without further purification. No purification of solvents or attempt to exclude air was performed in the assay of the catalysts. Initial results indicated the formation of pyrrolidine **4** with no evidence for the formation of piperidine **5**. In some experiments new resonances appeared in the olefin region of the  $^1\text{H}$  NMR spectrum consistent with trace formation of internal alkene isomers **6**. The use of environmentally friendly solvents such

**Scheme 2.** Initial Hydroamination Results with **2a** and **2b**



as water for the synthesis of organic compounds serves as a cornerstone of green chemistry.<sup>23</sup> Since no special purification or exclusion of water was required in the initial experiments, the catalysts were evaluated with water as the solvent. The results are presented in Table 1. Evaluation of pincer complexes **2a** and **2b** in water showed no appreciable loss of catalytic activity. In all cases there was no detectable formation of isomerization products. The only cyclized product observed by  $^1\text{H}$  NMR was pyrrolidine **4**. Similar

**Table 1.** Comparison of Benzene and Water as Solvent for Hydroamination/Cyclization of Unactivated Alkenes with 2.5 mol % **2b**

amine	heterocycle	solvent	cycl / isom <sup>a</sup>	
			catalyst	
			<b>2a</b>	<b>2b</b>
		benzene	>98 / <2	>95 / <5
		water	>98 / <2	>95 / <5

<sup>a</sup> % alkene isomerization.

<sup>a</sup> Percent alkene isomerization.

results were obtained when THF, benzene, or toluene was employed as solvent.

Control experiments were performed without adding catalyst by heating the substrate neat, in benzene, or in water. In each of these cases no reaction occurred, and only starting

**Table 2.** Intramolecular Hydroamination/Cyclization of Unactivated Alkenes Yielding Pyrrolidines and Piperidines Catalyzed by 2.5 mol % **2a** or **2b**<sup>a</sup>

entry	amine	heterocycle
	<b>R</b>	<b>2a(Ir)</b> <b>2b(Rh)</b>
1	Bn	>98 <sup>d</sup> /c >90/c
2	n-Pr	95/<5 75/<5
3	Ph	>98 <sup>e</sup> /<2 -
4	H	0/50 0/75
5	$\text{CH}_2\text{P-C}_6\text{H}_4\text{Br}$	>98 <sup>f</sup> /b -
	<b>R</b>	<b>2a(Ir)</b>
6	Bn	90/<5
7	n-Pr	80/10
8	i-Pr	90/5
9	Ph	>80 <sup>f</sup> /15
	<b>R</b>	<b>2a(Ir)</b>
10	Ph	90/c
11	H	0/100
	<b>n</b>	<b>2b(Rh)</b>
12	1	>98/c
13	2	79 <sup>g</sup> /c

<sup>a</sup> Reaction conditions:  $\text{C}_6\text{D}_6$ , 110 °C, 16 h. Conversion determined by  $^1\text{H}$  NMR. <sup>b</sup> (% conversion to heterocycle/% alkene isomerization). <sup>c</sup> Isomerization not detected. <sup>d</sup> Isolated yield: 77%. <sup>e</sup> Isolated yield: 80%. <sup>f</sup> Isolated yield: 80%. <sup>g</sup> 22 h.

(23) Anastas, P. T.; Williamson, T. C. *Green Chemistry: Designing Chemistry for the Environment*; American Chemical Society: Washington, DC, 1996. Nelson, W. M. *Green Solvents for Chemistry: perspectives and practice*; Oxford University Press: Oxford, New York, 2003.

material was recovered. A control experiment that excluded air and used purified solvent showed no loss of activity. Additional control experiments were run adding catalytic quantities of I<sub>2</sub> in place of **2a** and **2b** to check for iodine- or acid-catalyzed hydroamination as reported by Bergman.<sup>24</sup> Under these conditions the product formed was a cyclized iodine addition product based on <sup>1</sup>H NMR and MS data.

An examination of the scope of these catalysts is presented in Table 2. Secondary aminoalkene substrates gave good yields of the desired hydroamination/ cyclization products. Excellent isolated yields were obtained for selected examples (entries 1, 3, 9; see footnotes), and *exo-trig* cyclization products were obtained exclusively (entries 1, 10). Lack of substitution on the  $\beta$ -position (R = H) led to a dramatic decrease in the rate of cyclization and an increase in the isomerization product as the only product (entry 11). Primary amines did not yield cyclization products (entry 4). Aryl amines were cyclized successfully also (entries 3, 9). The presence of an aryl bromide was tolerated by the catalysts (entry 5). The Ir catalyst **2a** was found to give superior results for the diphenyl derivatives and was employed in the evaluation of the dimethyl derivatives in entries 6–9. Pincer complexes **2a** or **2b** typically had produced near 90% conversion at 6 h in examples that were checked. Attempts at intermolecular cyclization did not yield hydroamination products, and 6-*exo-trig* cyclization was found exclusively in the formation of the piperidinyl derivative (entry 10). Finally, spirocyclic compounds could be formed in excellent yields efficiently (entries 12 and 13). Analysis of these data suggest that the chelate effect along with the Thorpe–Ingold effect are required of the substrate to achieve efficient cyclization.

The lack of hydroamination with primary amines is not consistent with the formation of imido complexes as part of the catalytic mechanism, which is seen in early transition

metal complexes.<sup>25–27</sup> It is consistent with M–N bond formation, olefin coordination, and migratory insertion followed by reductive elimination, or  $\pi$ -coordination with amine attack.<sup>9,10,28</sup>

In summary, we have reported the efficient synthesis of a CCC–NHC Ir pincer complex with applications of the Rh and Ir pincer complexes as air and water-stable hydroamination/cyclization catalysts for the formation of five- and six-membered nitrogen-containing rings. Further work on the scope, limitations, functional-group tolerance and mechanism of this reaction and applications of these catalysts are ongoing. Extension of the synthetic methodology is also underway.

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**Supporting Information Available:** Experimental details for the preparation and molecular structure determination of **2a**, characterization data for the amines and heterocyclic products, and a typical catalysis procedure. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(25) Straub, B. F.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4632–4635.

(26) Ryu, J.; Marks, T. J.; McDonald, F. E. *J. Org. Chem.* **2004**, *69*, 1038–1052.

(27) Anderson, L. L.; Schmidt, A. R.; Arnold, J.; Bergman, R. G. *Organometallics* **2006**, *25*, 3394–3406.

(28) Hartwig, J. F. *Pure. Appl. Chem.* **2004**, *76*, 507–516.

(24) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542–14543.