

# Intramolecular Alkyne Hydroalkoxylation and Hydroamination Catalyzed by Iridium Hydrides

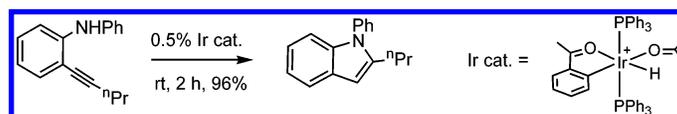
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Received September 11, 2005

## ABSTRACT



Iridium(III) hydrides prove to be air-stable active catalysts for intramolecular hydroalkoxylation and hydroamination of internal alkynes with proximate nucleophiles. The cyclization follows highly selective 6-*endo-dig* regiochemistry when regioselectivity is an issue.

When bound to transition metals, alkynes can be activated for attack by a variety of nucleophiles, including amines,<sup>1</sup> alcohols,<sup>2</sup> water,<sup>3</sup> halides,<sup>4</sup> nitro groups,<sup>5,6</sup> imines,<sup>7</sup> carboxylic acids,<sup>8</sup> phenols,<sup>9</sup> carbonyl groups,<sup>10</sup> keto esters,<sup>11</sup> enol ethers,<sup>12</sup> and hemiacetals generated in situ.<sup>13</sup> Binding to Lewis acids or electrophiles can give similar chemistry.<sup>13a,14</sup> Catalytic applications with various metals have been reported;

(1) (a) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527. (b) Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*, 89.

(2) (a) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251. (b) Kadota, I.; Lutete, L. M.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6207. (c) Nakamura, H.; Ohtaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 7631.

(3) Ogo, S.; Uehara, K.; Abura, T.; Watanabe, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **2004**, *126*, 16520.

(4) Wang, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 5213.

(5) Asao, N.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 5675.

(6) Li, X.; Incarvito, C. D.; Vogel, T.; Crabtree, R. H. *Organometallics* **2005**, *24*, 3066.

(7) (a) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (b) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86.

(8) (a) Hua, R.; Tian, X. *J. Org. Chem.* **2004**, *69*, 5782. (b) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145.

(9) (a) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297. (b) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387.

(10) (a) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (b) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (c) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814. (d) Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267. (e) Kusama, H.; Funami, H.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2004**, *6*, 605.

(11) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526.

intramolecular examples are particularly useful in giving heterocycles. Metal-catalyzed hydroamination of alkynes has wide synthetic applications.<sup>15</sup>

Iridium-mediated activation of alkynes toward nucleophilic attack is uncommon,<sup>16</sup> especially for weak nucleophiles such as esters or nitro compounds.<sup>3,17</sup> We recently reported a stoichiometric intramolecular nitro oxygen transfer to the C≡C bond of *o*-RC≡CC<sub>6</sub>H<sub>4</sub>NO<sub>2</sub> upon coordination to cationic iridium hydrides and proposed electrophilic activation of the alkynes on binding to Ir(III).<sup>6</sup> Strong product binding inhibited catalysis in this case. Moving to nucleophiles stronger than the nitro group, we now report *catalytic* intramolecular hydroamination and hydroalkoxylation of

(12) (a) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978. (b) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928.

(13) (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764. (b) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139.

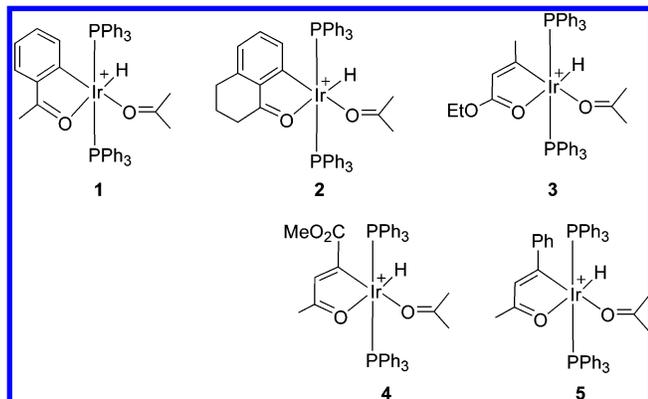
(14) (a) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vols. 1 and 2. (b) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (c) Yue, D.; Cà, N. D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581. (d) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437. (e) Barluenga, J.; Vázquez-villa, H.; Ballesteros, A.; González, J. M. *Org. Lett.* **2003**, *5*, 4121. (f) Barluenga, J.; Vázquez-villa, H.; Ballesteros, A.; González, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028.

(15) (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (b) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.

(16) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4949.

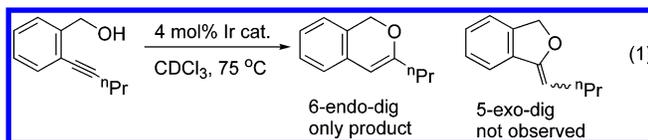
internal alkynes using closely related hydrido-iridium catalysts. The reactions even proceeded in undistilled solvents, without exclusion of air and water. The catalytic process is limited to internal alkynes, as terminal alkynes rearrange to vinylidenes, which are rapidly trapped by pendant nucleophiles to afford highly stable Fischer carbene complexes stoichiometrically.<sup>18</sup>

The iridium hydride catalysts (**1**–**5**, Figure 1) are obtained by a previously described cycloiridation reaction.<sup>19</sup> The



**Figure 1.** Hydrido-iridium complexes screened for cyclization of **6**.

complexes are stable to air and moisture in both the solid form and in solution. These complexes were initially studied for the cyclization of **6** (eq 1). Each complex is an active catalyst for selective conversion of the starting alcohol to the isochromene **7** by 6-*endo-dig* cyclization, and screening revealed a reactivity order: **1** > **2** > **3** ≥ **4** > **5**. [IrH<sub>2</sub>(acetone)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>]SbF<sub>6</sub> also catalyzes the same cyclization, but the reaction is not as clean (80 °C, full conversion, 80% NMR yield). We therefore chose **1** as a catalyst for further studies.



Various 2-alkynylbenzyl alcohols *o*-RC≡C(C<sub>6</sub>H<sub>4</sub>)CH<sub>2</sub>OH undergo regioselective cyclization with 4 mol % loading of **1** (Table 1). For **6** (R = <sup>n</sup>Pr), the starting material was fully converted to the corresponding isochromene **7** in high yield (94% NMR; 77% isolated), slightly better than that reported with PdI<sub>2</sub>–KI as catalyst.<sup>2a</sup> For **8** (R = Ph), the starting material was also fully converted, but the corresponding

(17) (a) Field, L. D.; Messerle, B. A.; Wren, S. L. *Organometallics* **2003**, *22*, 4393. (b) Burling, S.; Field, L. D.; Messerle, B. A.; Turner, P. *Organometallics* **2004**, *23*, 1714.

(18) Li, X.; Vogel, T.; Incarvito, T.; Crabtree, R. H. *Organometallics* **2005**, *24*, 62.

(19) Li, X.; Chen, P.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2005**, *24*, 4810.

**Table 1.** Cyclization of Ortho-Substituted Internal Alkynes<sup>a</sup>

entry	substrate	product	loading (%)	conditions	yield (%) <sup>e</sup>
1	<b>6</b>	<b>7</b>	4	80 °C, 2 h <sup>b</sup>	77
2	<b>8</b>	<b>9</b>	3	85 °C, 2 h <sup>b</sup>	70
3	<b>10</b>	<b>11</b>	4	60 °C, 5 h <sup>b</sup>	85
		<b>12</b>			
4	<b>13</b>	<b>14</b>	4	75 °C, 3 h <sup>b</sup>	69
5	<b>15</b>	<b>16</b>	3	rt, 14 h <sup>c</sup>	87
6	<b>17</b>	<b>18</b>	3	110 °C, 2 h <sup>d</sup>	72
7	<b>19</b>	<b>20</b>	3	75 °C, 1 h <sup>b</sup>	89
8	<b>21</b>	<b>22</b>	3	75 °C, 1 h <sup>b</sup>	91
9	<b>23</b>	<b>24</b>	1	35 °C, 1 h <sup>c</sup>	92
10	<b>25</b>	<b>26</b>	1	35 °C, 1 h <sup>c</sup>	93
11	<b>27</b>	<b>28</b>	0.5	25 °C, 2 h <sup>c</sup>	96
12	<b>29</b>	—	8	85 °C, 12 h <sup>b</sup>	0
13	<b>30</b>	—	5	85 °C, 12 h <sup>b</sup>	0

<sup>a</sup> **1** as the catalyst. <sup>b</sup> CHCl<sub>3</sub>. <sup>c</sup> CH<sub>2</sub>Cl<sub>2</sub>. <sup>d</sup> PhMe. <sup>e</sup> Isolated yields.

isochromene **9** was observed in only 70% NMR yield, together with unidentified decomposition products. Cyclization of **8** has been reported under basic conditions using NaOH,<sup>20</sup> KH,<sup>20</sup> and TBAF<sup>21</sup> or a Pd catalyst,<sup>2a</sup> but with only 5-*exo-dig*<sup>20,21</sup> or poor regioselectivity.<sup>2a</sup> In the present work,

(20) Weingarten, M. D.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 4717.

(21) Hiroya, K.; Jouka, R.; Kameda, M.; Yasuhara, A.; Sakamoto, T. *Tetrahedron* **2001**, *57*, 9697.

we consistently obtain 6-*endo* regiochemistry for both R = alkyl and aryl groups. Cyclization of **10**, having two OH groups, gives the two regioisomeric spiroacetals **11** and **12** in a ratio of 11:1, presumably by nucleophilic addition of the pendant  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$  group to an isochromene or benzofuran intermediate. Analogously, **12** cyclizes to spiroacetal **13** much more efficiently than in a previous route.<sup>22</sup> Alcohol **30** failed to cyclize ( $\text{CDCl}_3$ , 85 °C, 12 h), however.

Similarly, 2-alkynylphenols [ $\text{RC}\equiv\text{C}(\text{C}_6\text{H}_4)\text{OH}$ ] undergo cyclization to give benzofurans, where no regiochemical complication applies. Compound **15** cyclizes cleanly (91% NMR yield) at room temperature with 3% loading of **1**. The cyclization of **17** is more difficult, but catalyst **1** efficiently gives the benzofuran **18** in 72% yield in refluxing toluene. Previously reported methods for the cyclization of 2-alkynylphenols include strong bases,<sup>23a,b</sup> Lewis acids,<sup>23c</sup> or palladium catalysis.<sup>9</sup>

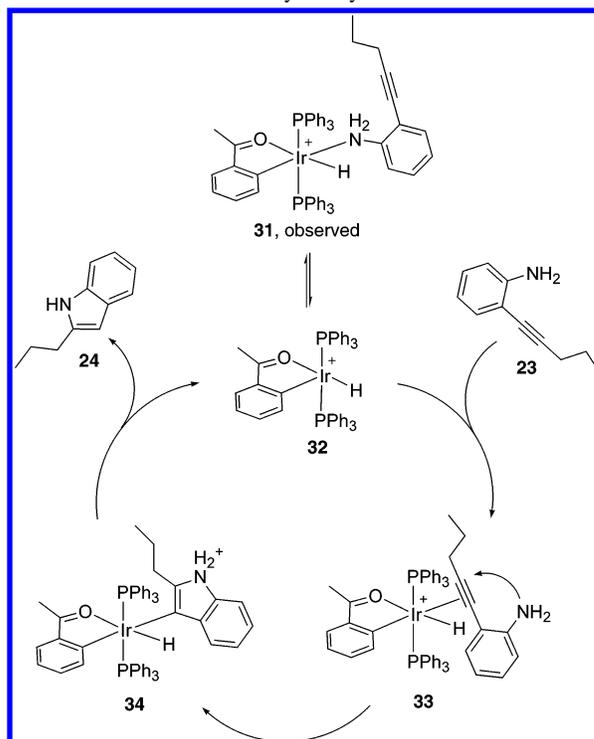
Although the cyclization of 2-alkynylbenzoic acids  $o\text{-RC}\equiv\text{C}(\text{C}_6\text{H}_4)\text{COOH}$  can be catalyzed by strong acids, palladium, or silver compounds, the previously obtained products are often mixtures from both 6-*endo-dig* and 5-*exo-dig* pathways.<sup>8b,24</sup> Here, for both R = <sup>n</sup>Pr (**19**) and Ph (**21**), we observed only the isocoumarins **20** and **22**, respectively, from selective 6-*endo-dig* cyclization, in high isolated yields.

The cyclization (intramolecular hydroamination) of *o*-alkynylanilines often involves palladium catalysts.<sup>1,25</sup> A base-promoted cyclization using <sup>t</sup>BuOK or KH has also been reported.<sup>23a,b</sup> Hydride **1** is a highly active catalyst to convert these substrates nearly quantitatively to indoles under mild conditions (rt or 35 °C). The aniline substrates **23** and **25** both give nearly quantitative yield of the corresponding indoles, and cyclization of the diarylamine **27** to the indole **28** was achieved with even lower catalyst loading (0.5 mol %). Surprisingly, the cyclization of **29** failed, even with 8% loading of **1** at 85 °C.

The rarity both of iridium complexes and of metal hydrides as hydroamination catalysts led us to make some preliminary mechanistic observations.<sup>16</sup> A mechanism involving aminoiridation of the alkyne seems unlikely, as only 4-*exo* cyclization is feasible, and the observed 5-*endo* regioselectivity would require subsequent rearrangements. To determine if the Ir-H was directly involved, we prepared **1-d<sub>8</sub>**, containing Ir-D, by reaction (acetone, 65 °C, 5 h) of acetophenone-*d<sub>8</sub>* with  $[\text{IrH}_2(\text{acetone})_2(\text{PPh}_3)_2]\text{SbF}_6$  and an excess (20 equiv) of *tert*-butylethylene as a hydrogen acceptor. By <sup>1</sup>H NMR spectroscopy the deuterium content

of Ir-D was 94%. The cyclization of **23** catalyzed by 10 mol % **1-d<sub>8</sub>** (with 94% Ir-D) in  $\text{CD}_2\text{Cl}_2$  was monitored by <sup>1</sup>H NMR spectroscopy at  $-10$  °C. All resonances for **24** maintain the same ( $\pm 4\%$ ) integration throughout, indicating essentially no deuterium incorporation.<sup>26</sup> Meanwhile, at no point was there any change ( $\pm 4\%$ ) in integration observed for the residual Ir-H signal and for the proton residue of the acetophenone backbone. Even assuming an error of 10% given the weak signal for residual Ir-H, the maximum hydrogen incorporation into the iridium center can therefore be reliably estimated to be  $<1\%$  (10% error  $\times$  6% Ir-H) with respect to total catalyst (Ir-D + Ir-H) and  $<0.1\%$  with respect to substrate. If a mechanism involving initial insertion of the alkyne into Ir-H were operative, significant deuterium incorporation at the 3-position of **24** would be expected at low conversion, coupled with replacement of Ir-D by Ir-H, which would be the highest at full conversion. As this was not observed, a mechanism involving initial insertion can be ruled out. Similar results were observed for substrate **27** ( $-35$  °C). Given this result, the most straightforward mechanism involves electrophilic activation of the alkyne toward nucleophilic attack by binding to the Ir(III) center, followed by direct selective protonolysis of the Ir-C (indole) bond (Scheme 1).

**Scheme 1.** Proposed Mechanism for the Cyclization of **23** Catalyzed by **1**



The cyclization reactions of **23** and **27**, observed at low temperature with 10% catalyst loading, showed surprisingly

(26) At early reaction times, big  $[\text{Ir-D}]/[\text{24}]$  ratios makes deuterium incorporation into **24** easily seen by <sup>1</sup>H NMR spectroscopy given appropriate precautions. See: Burk, M. J.; Crabtree, R. H. *J. Am. Chem. Soc.* **1987**, *109*, 8025.

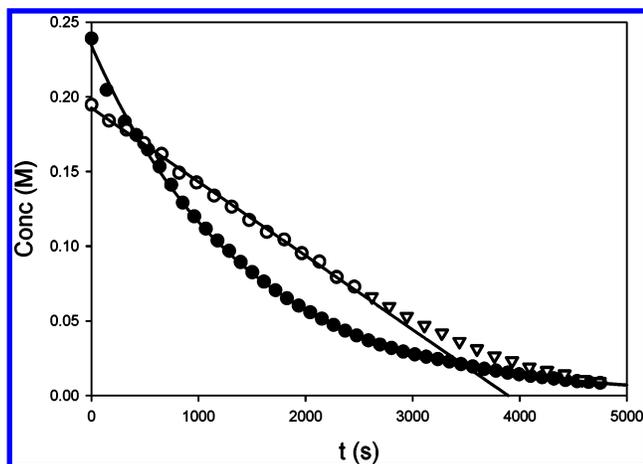
(22) Fugami, K.; Hagiwara, N.; Okeda, T.; Masanori, K. *Chem. Lett.* **1998**, 81.

(23) (a) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571. (b) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488. (c) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432.

(24) (a) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533. (b) Mukhopadhyay, R.; Kundu, N. G. *Tetrahedron* **2001**, *57*, 9475.

(25) (a) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *Tetrahedron Lett.* **2005**, *46*, 2101. (b) Müller, T. E.; Berger, M.; Grosche, M.; Herdtweck, E.; Schmidtchen, F. P. *Organometallics* **2001**, *20*, 4384. (c) Iritani, K.; Matsubara, S.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799. (d) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856. (e) Yu, M. S.; de Leon, L. L.; McGuire, M. A.; Botha, G. *Tetrahedron Lett.* **1998**, *39*, 9347.

different behavior. For **23**, the catalyst resting state is assigned by  $^1\text{H}$  and  $^{13}\text{C}$  NMR as the N-bound substrate complex **31** (Scheme 1). In a kinetic experiment, *zero-order* consumption of substrate was observed for the majority of the reaction (Figure 2). This is consistent<sup>27</sup> with reversible

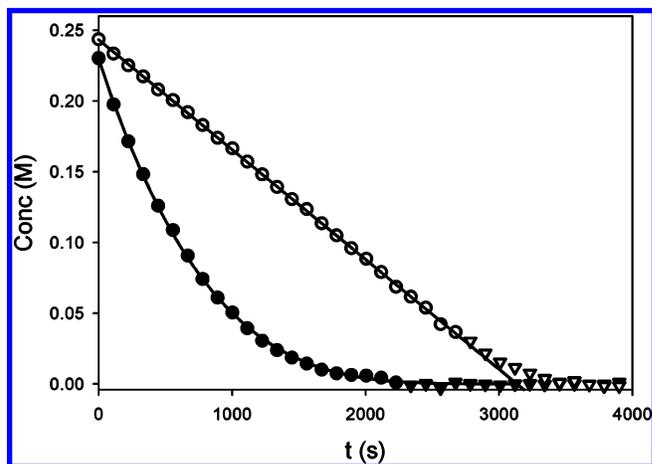


**Figure 2.** Kinetic data for the cyclization of **23** (open symbols) and **27** (closed symbols), catalyzed by 10 mol % **1**. For **23**, the linear portion of the graph (open circles) was used for linear regression analysis.

dissociation of **23** from **31** to generate the reactive five-coordinate intermediate **32**. Catalysis may then proceed by re-coordination of **23** to **32** through the  $\text{C}\equiv\text{C}$  bond to give **33**, nucleophilic attack on the alkyne moiety to generate **34**, and direct protonolysis of the  $\text{Ir}-\text{C}$  bond to complete the cycle (Scheme 1). Coordination of **23** through nitrogen thus leads to unproductive substrate binding<sup>25b,28</sup> inhibiting catalytic turnover. Although this kinetic result is also consistent with saturation behavior, we consider a direct reaction of the amine complex to be unlikely (see above).

For the cyclization of **27**, the observed catalyst resting state is now the acetone complex **1**, and the kinetics is first order with respect to the substrate (Figure 2). We propose a mechanism analogous to that for **23**, except that here the secondary amine **27** is a weaker N-donor and it does not inhibit the catalytic reaction by binding to iridium. The first-order kinetic behavior is consistent<sup>27</sup> with rate-determining reaction of **27** with a steady-state concentration of the reactive iridium complex **32**, generated by reversible dissociation of acetone from the resting complex **1**.

To provide support for the hypothesis of unproductive substrate binding in the cyclization of **23**, a competition experiment was performed with **23** and **27** both present. The kinetic plots are shown in Figure 3. As expected, the cyclization of **23** was unaffected by the presence of **27**. The cyclization of **27**, however, behaved consistently<sup>27</sup> with a model of *decreasing inhibition* as substrate **23** is consumed,



**Figure 3.** Kinetic data for the *competitive* cyclization of **23** (open symbols) and **27** (closed symbols), catalyzed by 10 mol % **1**. For **23**, the linear portion of the graph (open circles) was used for linear regression analysis. For **27**, the non-zero portion of the graph (closed circles) was used for curve-fitting.

which strongly supports fast reversible dissociation of **23** from **31** on the time scale of the cyclization reaction. The consumption of **27** fits a curve defined by eq 2, where  $A$  is derived from the linear fit of the consumption of **23**.<sup>27</sup> Interestingly, the exponent in eq 2,  $k_{23}/k_{27}$ , corresponds to the ratio of intrinsic turnover frequencies for the consumption of **23** vs **27**, factoring out the unproductive binding by **23**.<sup>27</sup> The observed value of ca. 4.0 for  $k_{23}/k_{27}$  indicates that **27** is consumed four times faster than **23**. This is inconsistent with a simple rate-limiting nucleophilic attack of  $\text{NHR}$  on  $\text{C}\equiv\text{C}$ , as **27** is less nucleophilic, but may be explained by the increased  $\text{NH}$  acidity of **27** (as in a concerted nucleophilic attack/proton-transfer pathway).

$$[\mathbf{27}] = [\mathbf{27}]_{\text{init}}(1 - At)^{k_{27}/k_{23}} \quad (2)$$

In summary, we report a novel class of hydrido-iridium(III) catalysts for the intramolecular hydroalkoxylation and hydroamination of ortho-substituted aryl alkynes, using a variety of tethered nucleophiles. When regioselectivity is an issue, highly selective 6-*endo-dig* cyclization is observed. Mechanistic experiments indicate that the reaction likely proceeds via electrophilic activation of the alkyne toward nucleophilic attack, followed by direct protonolysis of the resulting  $\text{Ir}-\text{C}$  bond. Moderately basic amines are shown to bind to iridium through nitrogen, providing a well-characterized example of unproductive substrate binding in organometallic catalysis.

**Acknowledgment.** We thank the U.S. DOE and the Johnson Matthey Co. for support and Leah Appelhans for assistance.

**Supporting Information Available:** Syntheses, derivation of eq 2, NMR spectra, and kinetics data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(27) See the Supporting Information.

(28) Pirrung, M. C.; Liu, H.; Morehead, A. T. *J. Am. Chem. Soc.* **2002**, *124*, 1014.