

Intramolecular Hydroamination of Unactivated Alkenes with Secondary Alkyl- and Arylamines Employing $[\text{Ir}(\text{COD})\text{Cl}]_2$ as a Catalyst Precursor

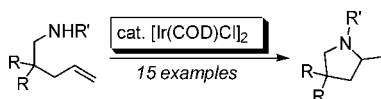
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ABSTRACT



Commercially available $[\text{Ir}(\text{COD})\text{Cl}]_2$ is an effective precatalyst for the intramolecular hydroamination of a range of unactivated alkenes with pendant secondary alkyl- or arylamines, at relatively low loadings (typically 0.25–5.0 mol % Ir) and without the need for added ligands or other cocatalysts.

Current interest in the identification of catalysts for the intramolecular hydroamination of unactivated alkenes arises from the utility of this C–N bond-forming reaction as an atom economical route to synthetically useful nitrogen heterocycles.¹ Notwithstanding the progress that has been made by use of lanthanide and early metal catalysts,^{1,2} their air-sensitivity and lack of functional group tolerance has prompted the development of late metal catalysts for such challenging transformations. While significant advances have been made in the use of late metal catalysts for the intramolecular addition of amides and carbamates to unactivated alkenes,³ related transformations involving simple alkyl- or arylamines are extremely rare.^{4–6} The first catalyst of this type was disclosed by Widenhoefer and co-workers,⁴ who employed $[\text{PtCl}_2(\text{H}_2\text{C}=\text{CH}_2)]_2/\text{PPh}_3$ and later $\text{PtCl}_2/$

biarylphosphine (5–10 mol % Pt) for the cyclization of secondary alkylamines. More recently, Hollis and co-workers⁵ reported the use of Rh and Ir complexes supported by pincer-type *N*-heterocyclic carbene ligands (5 mol % M) for the hydroamination of terminal alkenes by tethered secondary alkyl- and phenylamines, while Liu and Hartwig⁶ disclosed the use of $[\text{Rh}(\text{COD})_2]\text{BF}_4/\text{Cy-DavePhos}$ (COD = η^4 -cyclooctadiene; Cy-DavePhos = 2-dicyclohexylphosphino-2'-*N,N*-dimethylamino-biphenyl; 2.5–7.5 mol % Rh) for the cyclization of aminoalkenes that contain primary or secondary alkylamines and terminal or internal alkenes. In the quest to expand the synthetic repertoire of late metal-mediated hydroamination, and encouraged by breakthroughs in Ir-mediated intermolecular hydroamination of activated olefins,^{7,8} we sought to identify commercially available single-component Ir precatalysts that complement established late metal catalysts and which exhibit broad substrate scope in the intramolecular hydroamination of unactivated alkenes.⁹

(1) For a comprehensive review, see: Müller, T. E.; Hultsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

(2) Selected recent examples: (a) Stubbert, B. C.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 6149. (b) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354.

(3) Representative examples: (a) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 2786. (b) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (c) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938. (d) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747.

(4) (a) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070. (b) Bender, C. F.; Hudson, W. B.; Widenhoefer, R. A. *Organometallics* **2008**, *27*, 2356.

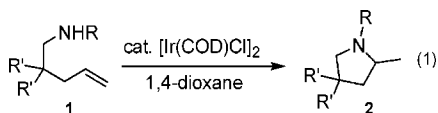
(5) Bauer, E. B.; Andavan, G. T. S.; Hollis, T. K.; Rubio, R. J.; Cho, J.; Kuchenbeiser, G. R.; Helgert, T. R.; Letko, C. S.; Tham, F. S. *Org. Lett.* **2008**, *10*, 1175.

(6) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570.

(7) (a) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738. (b) Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857.

(8) Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.

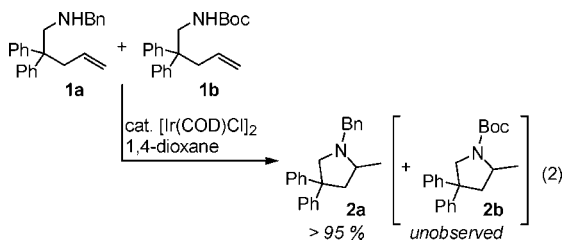
In this vein, we report herein that $[\text{Ir}(\text{COD})\text{Cl}]_2$ is an effective precatalyst for the hydroamination of unactivated alkenes with pendant secondary alkyl- or arylamines, at relatively low loadings (typically 0.25–5 mol % Ir) and without the need for added ligands or cocatalysts.



The cyclization of **1a** ($\text{R} = \text{Bn}$, $\text{R}' = \text{Ph}$) to **2a** in 1,4-dioxane (eq 1) was selected as a test reaction for canvassing the catalytic abilities of group 9 complexes for the intramolecular hydroamination of unactivated alkenes at relatively low catalyst loadings (1.0 mol % Rh or Ir). Gratifyingly, $[\text{Ir}(\text{COD})\text{Cl}]_2$ proved to be a highly effective precatalyst under these conditions, affording **2a** cleanly (>95%, ^1H NMR) after only 1 h at 110 °C.^{10a} Other commercially available group 9 precatalysts including $[\text{Ir}(\eta^2\text{-cyclooctene})_2\text{-Cl}]_2$, $[\text{Ir}(\text{COD})\text{OMe}]_2$, $[(\eta^5\text{-C}_5\text{Me}_5)\text{IrCl}_2]_2$, $[(\text{COD})\text{Ir}(\text{PCy}_3)(\text{pyridine})]^+\text{PF}_6^-$ (Crabtree's catalyst), and $[\text{Rh}(\text{COD})\text{Cl}]_2$ were significantly less effective under these conditions, as was $[\text{Ir}(\text{MeCN})_2(\text{COD})]\text{BF}_4$ (Table S1, Supporting Information^{10b}). However, the observation that the performance of $[\text{Ir}(\text{COD})\text{Cl}]_2/2 \text{ AgBF}_4$ mirrors that of $[\text{Ir}(\text{COD})\text{Cl}]_2$ suggests that the formation of $[\text{Ir}(1,4\text{-dioxane})_2(\text{COD})]\text{Cl}$ may figure importantly in hydroamination reactions employing $[\text{Ir}(\text{COD})\text{Cl}]_2$ in 1,4-dioxane.

Catalyst optimization studies revealed that the clean conversion of **1a** into **2a** in 1,4-dioxane can also be achieved by use of only 0.125 mol % $[\text{Ir}(\text{COD})\text{Cl}]_2$ (3 h, 110 °C; Table 1, entry 1–1), or by employing higher Ir loadings at lower temperatures (2.5 mol % Ir; 7 h, 80 °C¹¹).

Despite the utility of late metal complexes in promoting the intramolecular hydroamination of carbamates,³ the N-Boc aminoalkene **1b** proved unreactive (^1H NMR) in the presence of $[\text{Ir}(\text{COD})\text{Cl}]_2$ (1.0 mol % Ir; 3 h, 110 °C, 1,4-dioxane). However, the observation that the cyclization of **1a** (entry 1–1) proceeds unhampered (^1H NMR) when using a 1:1 mixture of **1a,b** (eq 2) suggests that **1b** does not poison the active catalyst derived from $[\text{Ir}(\text{COD})\text{Cl}]_2$; rather, $[\text{Ir}(\text{COD})\text{Cl}]_2$ may offer chemoselectivity in the hydroamination of more complex olefinic substrates that contain both carbamate- and benzyl-protected amines.



The use of $[\text{Ir}(\text{COD})\text{Cl}]_2$ as a precatalyst proved effective for the hydroamination of a range of unactivated alkenes tethered to secondary alkylamines, including those featuring polar groups (Table 1). In exploring the influence of *para*-

Table 1. Intramolecular Hydroamination of Unactivated Alkenes by Secondary Alkylamines Employing $[\text{Ir}(\text{COD})\text{Cl}]_2$ as a Pre-Catalyst^a

| entry | aminoalkene | product | mol % Ir (time, h) | yield (%) ^b |
|-------|-------------|---------|--------------------|--------------------------------------|
| 1-1 | | | 0.25 (3) | 88 |
| 1-2 | | | 1.0 (3) | 85 |
| 1-3 | | | 1.0 (3) | 87 |
| 1-4 | | | 2.5 (3) | 89 |
| 1-5 | | | 1.0 (7) | 88 |
| 1-6 | | | 2.5 (7) | 86 |
| 1-7 | | | 5.0 (24) | 84 |
| 1-8 | | | 5.0 (24) | 81 ^c (1.5:1) ^d |
| 1-9 | | | 5.0 (24) | 72 ^e |
| 1-10 | | | 2.5 (16) | 88 |
| 1-11 | | | 10 (48) | 52 ^f |

^a Conditions: 0.25 mmol aminoalkene in 0.5 mL 1,4-dioxane at 110 °C; conversion to product >95% (^1H NMR) unless stated. ^b Isolated yield unless stated (average of two runs). ^c ^1H NMR yield, with the balance corresponding to an alkene isomerization product (ca. 10%) and unreacted aminoalkene (ca. 5%). ^d Diastereomeric ratio (dr, ^1H NMR). ^e Reaction run at 80 °C; conversion to the piperidine was 75% (^1H NMR) with the balance corresponding to an alkene isomerization product. ^f ^1H NMR yield, with the balance corresponding to unreacted aminoalkene.

substitution on the benzyl fragment in derivatives of **1a**, the presence of halide (entry 1–2), ester (entry 1–3), or alkoxy (entry 1–4) substituents did not significantly influence the reaction; also tolerated was the bulky N-methylcyclohexyl derivative (entry 1–5). Notably, the catalytic performance of $[\text{Ir}(\text{COD})\text{Cl}]_2$ in the aforementioned hydroamination reactions is on par with, and in some cases is superior to (in terms of catalyst loading), that of all reported^{4–6} late metal catalysts with comparable substrates.

Alternative *gem*-disubstituted relatives of **1** also proved to be suitable hydroamination substrates (entries 1–6 and

(9) For some recent reports of Ir-mediated intramolecular hydroamination of alkynes, see: (a) Ebrahimi, D.; Kennedy, D. F.; Messerle, B. A.; Hibbert, D. B. *Analyst* **2008**, 817. (b) Burling, S.; Field, L. D.; Messerle, B. A.; Rumble, S. L. *Organometallics* **2007**, 26, 4335. (c) Lai, R.-Y.; Surekha, K.; Hayashi, A.; Ozawa, F.; Liu, Y.-H.; Peng, S.-M.; Liu, S.-T. *Organometallics* **2007**, 26, 1062. (d) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, 7, 5437.

(10) (a) The intramolecular hydroamination of 2-(phenylethynyl)-aniline proceeded cleanly in the presence of $[\text{Ir}(\text{COD})\text{Cl}]_2$ (2.5 mol % Ir; 3 h, 110 °C, 1,4-dioxane; 96% isolated yield), in keeping with a recent combinatorial survey.^{9a} (b) Tables S1 and S2 are provided in the Supporting Information.

(11) 1,2-Dichloroethane, 1,2-dimethoxyethane, and toluene each proved to be less a effective solvent under these conditions (45–76%; see Table S2 in the Supporting Information).

1–7), as did the monosubstituted isopropyl variant featured in entry 1–8 (cf. 62% yield and 1.2:1 dr obtained using $[\text{PtCl}_2(\text{H}_2\text{C}=\text{CH}_2)]_2/\text{PPh}_3$, 5 mol % Pt^{4a}). The *gem*-disubstituted N-benzylhex-5-en-1-amine featured in entry 1–9 was also cyclized in the presence of $[\text{Ir}(\text{COD})\text{Cl}]_2$. However, in contrast to the established ability of $\text{PtCl}_2/\text{biarylphosphine}^{4b}$ and $[\text{Rh}(\text{COD})_2]\text{BF}_4/\text{biarylphosphine}^6$ to mediate the hydroamination of unactivated 4-pentenyl^{4b} and 5-hexenyl^{4b,6} alkylamines that lack substituents on the linker chain which bias the substrate toward cyclization, $[\text{Ir}(\text{COD})\text{Cl}]_2$ proved incapable of inducing the hydroamination of these substrates, as well as primary amine substrates, under our typical reaction conditions (Table 1).

Given the particular challenge presented by the intramolecular hydroamination of unactivated disubstituted alkenes, we turned our attention to such transformations; notably, $[\text{Ir}(\text{COD})\text{Cl}]_2$ proved capable of mediating the cyclization of a *gem*-disubstituted olefin (entry 1–10), as well as an unstrained internal alkene (entry 1–11¹²).

The metal-mediated intramolecular hydroamination of unactivated alkenes by secondary arylamines remains essentially unexplored, and is limited to a single report by Hollis and co-workers featuring two simple N-Ph substrates.⁵ In a preliminary study, $[\text{Ir}(\text{COD})\text{Cl}]_2$ proved capable of promoting the cyclization of secondary arylamines (Table 2), including the parent substrate **1c** (R, R' = Ph; eq 1), as

known for the intramolecular hydroamination of unactivated alkenes revealed that the cyclization of such arylamines can be problematic. Whereas the catalytic performance of $\text{PtCl}_2/\text{'Bu-DavePhos}^{4b}$ in the hydroamination of **1c** proved to be competitive with $[\text{Ir}(\text{COD})\text{Cl}]_2$ (entry 2–5), both $[\text{Rh}(\text{COD})_2]\text{BF}_4/\text{Cy-DavePhos}^6$ (entry 2–6) and $\text{Au}(o\text{'Bu}_2\text{P-biphenyl})\text{Cl}/\text{AgOTf}^{3d}$ (entry 2–7) proved to be ineffective in mediating this transformation under similar conditions.

Our observation that the intramolecular hydroamination of arylamines (Table 2) is enhanced by para-methyl or -methoxy substitution on the N-aryl fragment is divergent from trends documented by Zhou and Hartwig.⁸ These workers reported that both electron-rich and -poor anilines were less reactive than electron-neutral anilines in the (bisphosphine)Ir-mediated intermolecular hydroamination of activated bicyclic alkenes, which was shown to proceed by way of N–H oxidative addition/alkene insertion reaction cycle.⁸

While a comprehensive mechanistic evaluation of hydroamination catalysis mediated by $[\text{Ir}(\text{COD})\text{Cl}]_2$ is ongoing in our laboratory, preliminary observations documented herein may point to a reaction pathway in 1,4-dioxane involving attack by a tethered nitrogen nucleophile on an olefin that is coordinated to a cationic IrL_n fragment (in keeping with well-documented Pd ,^{3a} Pt ,⁴ and Au ^{3d} hydroamination catalyst systems), rather than N–H oxidative addition/alkene insertion reaction sequences that have been documented for (bisphosphine)Ir systems.^{7a,8} This mechanistic proposal is consistent with our observations that the performance of $[\text{Ir}(\text{COD})\text{Cl}]_2/2 \text{ AgBF}_4$ mirrors that of $[\text{Ir}(\text{COD})\text{Cl}]_2$ (*vide supra*), and that hydroamination is promoted by increasing the nucleophilicity of the arylamine nitrogen (Table 2). Furthermore, the conversion of **1a** to **2a** was completely inhibited when employing 0.5 mol % $[\text{Ir}(\text{COD})\text{Cl}]_2$ at 110 °C in 1,4-dioxane in the presence of an equivalent of K_2CO_3 (relative to **1a**) or 1.0 mol % DBU, possibly underscoring the involvement of a key Ir–C protonolysis step en route to **2a**. While definitive NMR spectroscopic characterization data that would enable the identification of intermediates in hydroamination catalysis mediated by $[\text{Ir}(\text{COD})\text{Cl}]_2$ have thus far remained elusive, no Ir–H resonances were observed (¹H NMR) when examining the reaction of **1a** with $[\text{Ir}(\text{COD})\text{Cl}]_2$ in dioxane-*d*₈ over a range of temperatures. Encouraged by the possibility that such catalysis may involve reactive $[\text{L}_n\text{Ir}(\text{COD})]^+$ species, we are currently targeting enantioselective variants of these transformations by using Ir precatalysts supported by chiral diene ligands.

In summary, we have identified $[\text{Ir}(\text{COD})\text{Cl}]_2$ as an effective precatalyst for the intramolecular hydroamination of a range of unactivated alkenes with pendant secondary alkyl- or arylamines. This represents the first commercially available late metal catalyst system to function at relatively low catalyst loading without the need for added ligands or cocatalysts, and serves to complement the few other late metal catalysts^{4–6} that mediate such challenging transformations. The quest to develop mechanistic insights into hydroamination catalysis employing $[\text{Ir}(\text{COD})\text{Cl}]_2$, as well as

Table 2. Late Metal-Mediated Intramolecular Hydroamination of Unactivated Alkenes by Secondary Arylamines^a

| entry | aminoalkene | product | mol % M | yield (%) ^b |
|------------------|---|---------|---------|------------------------|
| | | | | |
| 2-1 | R = Ph (1c) | | 2.5 | 95 |
| 2-2 | R = 4-C ₆ H ₄ F | | 2.5 | 95 |
| 2-3 | R = 4-C ₆ H ₄ Me | | 1.0 | 96 |
| 2-4 | R = 4-C ₆ H ₄ OMe | | 0.5 | 94 |
| 2-5 ^d | R = Ph (1c) | | 2.5 | > 95 ^c |
| 2-6 ^e | R = Ph (1c) | | 2.5 | < 5 ^c |
| 2-7 ^f | R = Ph (1c) | | 5 | < 5 ^c |

^a Conditions: 0.25 mmol aminoalkene in 0.5 mL 1,4-dioxane at 110 °C for 7 h, using 0.25–1.25 mol % $[\text{Ir}(\text{COD})\text{Cl}]_2$, unless stated. ^b Isolated yields (average of two runs), unless stated. ^c ¹H NMR yield. ^d Using $\text{PtCl}_2/\text{'Bu-DavePhos}$ (2.5 mol % Pt and 2.5 mol % ligand) in place of $[\text{Ir}(\text{COD})\text{Cl}]_2$. ^e Using $[\text{Rh}(\text{COD})_2]\text{BF}_4/\text{Cy-DavePhos}$ (2.5 mol % Rh and 3 mol % ligand) at 70 or 110 °C in place of $[\text{Ir}(\text{COD})\text{Cl}]_2$. ^f Using $\text{Au}(o\text{'Bu}_2\text{P-biphenyl})\text{Cl}/\text{AgOTf}$ (5 mol % Au and 5 mol % Ag) in place of $[\text{Ir}(\text{COD})\text{Cl}]_2$.

well as for the first time arylamine substrates featuring electron-withdrawing (entry 2–2) and electron-donating (entries 2–3 and 2–4) substituents. At first glance, the lower basicity of the nitrogen center in arylamines such as **1c**, relative to related alkylamines (e.g., **1a**), could be envisioned to render arylamine substrates more susceptible to metal-mediated hydroamination; however, a comparative survey involving some of the most effective late metal catalysts

(12) The performance of $[\text{Ir}(\text{COD})\text{Cl}]_2/2 \text{ AgBF}_4$ mirrored that of $[\text{Ir}(\text{COD})\text{Cl}]_2$ in entry 1–11.

to establish chemoselective and asymmetric variants of these Ir-mediated intramolecular hydroaminations, is ongoing.

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Supporting Information Available: Full experimental details, characterization data, and tabulated catalysis results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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