

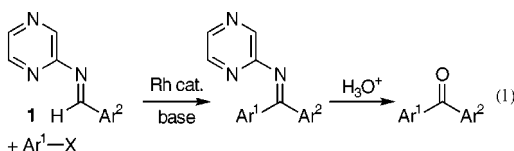
## A Heck-Type Reaction Involving Carbon–Heteroatom Double Bonds. Rhodium(I)-Catalyzed Coupling of Aryl Halides with *N*-Pyrazolyl Aldimines

Tatsuo Ishiyama\*<sup>‡</sup> and John Hartwig\*

Department of Chemistry, Yale University  
P.O. Box 208107, New Haven, Connecticut 06520-8107

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The transition metal-catalyzed reaction of organic halides or triflates with alkenes to generate substituted olefins, generally referred to as the Heck reaction, is one of the most important catalytic carbon–carbon bond-forming processes.<sup>1–6</sup> Recent advances with this reaction have included the olefination of chloroarenes using highly active catalysts,<sup>7,8</sup> the formation of polycyclic systems by cascade events,<sup>9,10</sup> and enantioselective variants using optically active ligands.<sup>11–14</sup> In contrast to this now common reaction, the analogous process using aldehydes or aldimines, instead of alkenes, has not been developed. We disclose a set of rhodium-catalyzed intermolecular Heck-type reactions between aryl iodides and *N*-heterocyclic aldimines to form the corresponding ketimines, which form ketones upon hydrolysis (eq 1).



We initially evaluated complexes generated from Pd(dba)<sub>2</sub>, Ni(COD)<sub>2</sub>, and [RhCl(COD)]<sub>2</sub> to uncover a Heck-type coupling of iodobenzene with aldehydes and aldimines under various reaction conditions. Several research groups have recently shown that complexes of these metals catalyze the formation of alcohols and amines by the addition of organic halides<sup>15–17</sup> or main group organometallic reagents to aldehydes and imines.<sup>18–21</sup> In contrast reactions of aryl halides with typical aldehydes and imines, such as benzaldehyde, *N*-benzylideneaniline (PhN=CHPh) and *N*-

benzylidene-*p*-toluenesulfonamide (TosN=CHPh), did not produce any of the desired ketone or ketimine product when using selected phosphines in combination with these catalyst precursors. We presumed that the insertion of aldehyde or imine into a transition metal–aryl linkage, which would be formed from oxidative addition of the aryl halide, was slow.

To overcome this problem, we used aldimines bearing an ancillary donor atom that would coordinate to the metal, deliver the imine to the metal center, and facilitate insertion. This strategy followed the lead of Jun and Hong, who showed that *N*-pyridylimines undergo C–H additions to olefins more rapidly than do aldehydes or simple imines.<sup>22</sup> After evaluating several *N*-heterocyclic imines as substrates, we found that *N*-pyrazolyl imines<sup>23</sup> reacted with phenyl iodide in the presence of rhodium(I) catalysts to form the corresponding ketimine.

We found that a 1,4-relationship between the nitrogen donor atom and the imine carbon atom was most favorable. The *N*-2-pyridyl derivatives (2-Pyr)N=CHPh participated in the coupling process, indicating that the nitrogen at the 4-position of the pyrazolyl ring provides an electronic effect and does not trigger a binuclear mechanism. However, *N*-heterocyclic aldimines derived from benzaldehyde bearing longer tethers, such as the *N*-(2-pyridylmethyl) or *N*-[2-(2-pyridyl)ethyl] derivatives [2-Pyr(CH<sub>2</sub>)<sub>*n*</sub>]N=CHPh (*n* = 1, 2) were not suitable substrates. Benzaldehyde-*N,N*-pentamethylene hydrazone ((CH<sub>2</sub>)<sub>5</sub>N–N=CHPh), which contains a 1,3-relationship between the nitrogen donor and the imine carbon, also did not produce any ketimine product.

Rhodium(I) complexes generated in situ from [RhCl(COD)]<sub>2</sub> and 1 equiv per rhodium of the sterically unhindered trialkylphosphines P(*n*-Pr)<sub>3</sub> provided the most active catalysts. Complexes generated from PPh<sub>3</sub> produced coupled products in yields that were generally 20% lower than those with the unhindered trialkylphosphine, but catalysts containing P(*o*-Tol)<sub>3</sub>, dppf, and P(*t*-Bu)<sub>3</sub> were ineffective. Complexes formed from Pd(dba)<sub>2</sub> or Ni(COD)<sub>2</sub> and these phosphine ligands were ineffective, despite their catalytic activity in the common Heck processes involving olefins.

We also evaluated several bases and solvents for this process. Among the combinations tested, NaOBu<sup>*t*</sup> and *m*-xylene (method A) and K<sub>2</sub>CO<sub>3</sub> and diglyme (method B) were most effective. The combination of strong base and polar solvent led to decomposition of the aldimine before any coupling occurred.

Representative Heck-type couplings between aryl halides and *N*-pyrazolyl aldimines in the presence of the most active catalyst, comprised of 2.5 mol % of [RhCl(COD)]<sub>2</sub> and 5 mol % of P(*n*-Pr)<sub>3</sub>, are summarized in Table 1. To allow for convenient analysis of isolated products, the initially formed ketimine was converted to the corresponding ketone by acid hydrolysis. The reaction occurred smoothly when using aryl iodides as substrate. Aryl bromides reacted much more slowly (entry 2), and no coupling was observed with aryl chlorides. However, electron-rich, electron-poor, and ortho-substituted aryl iodides all reacted with the aldimines to give good yields when using one of the base and solvent combinations. To achieve acceptable yields from the coupling of electron-poor aryl iodides with electron-poor aldimines (entry 10) and from the coupling of aryl iodides bearing an ortho substituent (entries 12 and 13), 10–20 mol % of catalyst was required.

Arylrhodium halide and iminoacylrhodium hydride complexes were prepared to determine their kinetic and chemical competence to be reaction intermediates. These two types of complexes would be formed by oxidative addition of aryl iodide or aldimine to a phosphine-ligated Rh(I) halide complex. Although it is well accepted that Heck reactions are initiated by aryl halide oxidative

<sup>‡</sup> Permanent Address: Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan.

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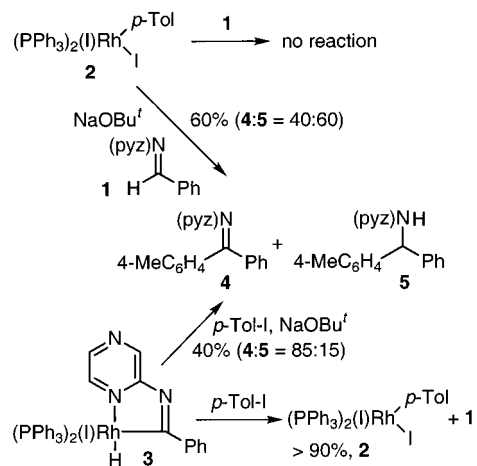
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**Table 1.** Rh-Catalyzed Coupling of Aryl Halides with Aldimines **1** (eq 1)<sup>a</sup>

entry	aryl halide	<b>1</b> , Ar <sup>2</sup> =	yield/% <sup>b</sup> (time/h)	
			method A	method B
1	PhI	Ph	83 (26)	86 (26)
2	PhBr	Ph	32 (168)	47 (168)
3	PhI	4-MeOC <sub>6</sub> H <sub>4</sub>	71 (50)	82 (74)
4	PhI	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	64 (26)	77 (146)
5	4-MeOC <sub>6</sub> H <sub>4</sub> I	4-MeOC <sub>6</sub> H <sub>4</sub>	77 (26)	99 (50)
6	4-MeOC <sub>6</sub> H <sub>4</sub> I	Ph	79 (26)	84 (50)
7	4-MeOC <sub>6</sub> H <sub>4</sub> I	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	82 (26)	83 (98)
8	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> I	4-MeOC <sub>6</sub> H <sub>4</sub>	50 (98)	73 (50)
9	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> I	Ph	55 (50)	80 (50)
10	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> I	4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	68 <sup>c</sup> (5)	66 <sup>c</sup> (50)
11	PhI	2-MeC <sub>6</sub> H <sub>4</sub>	19 (50)	95 (26)
12	2-MeC <sub>6</sub> H <sub>4</sub> I	Ph	45 <sup>d</sup> (5)	67 <sup>d</sup> (50)
13	2-MeC <sub>6</sub> H <sub>4</sub> I	2-MeC <sub>6</sub> H <sub>4</sub>	26 <sup>d</sup> (5)	74 <sup>d</sup> (74)

<sup>a</sup> All reactions were conducted using aryl halide (1.0 equiv), **1** (1.0 equiv), **1** (1.5 equiv), RhCl(COD)/P(*n*-Pr)<sub>3</sub> (5 mol %), and base (1.5 equiv). Method A: NaOBu<sup>t</sup>/*m*-xylene/135 °C. Method B: K<sub>2</sub>CO<sub>3</sub>/diglyme/160 °C. <sup>b</sup> GLC yields of biaryl ketones after hydrolysis of ketimines with 6 N HCl at room temperature for 16 h. <sup>c</sup> 10 mol % of catalyst was used. <sup>d</sup> 20 mol % of catalyst was employed.

**Scheme 1**<sup>a</sup>

<sup>a</sup> All reactions were conducted in *m*-xylene at 135 °C for 30 min in the presence of PPh<sub>3</sub>.

addition,<sup>1–3</sup> oxidative addition of an aldimine C–H bond is a reasonable initial step for the process reported here. Indeed, both iodotoluene and *N*-benzylideneaminopyrazine (**1**) reacted with Rh(I)(PPh<sub>3</sub>)<sub>2</sub><sup>24</sup> to form the oxidative addition products (4-MeC<sub>6</sub>H<sub>4</sub>)Rh(I)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (**2**) and [(C<sub>4</sub>H<sub>3</sub>N<sub>2</sub>)N=}(Ph)C]Rh(I)(I)(PPh<sub>3</sub>)<sub>2</sub> (**3**) shown in Scheme 1.<sup>25,26</sup>

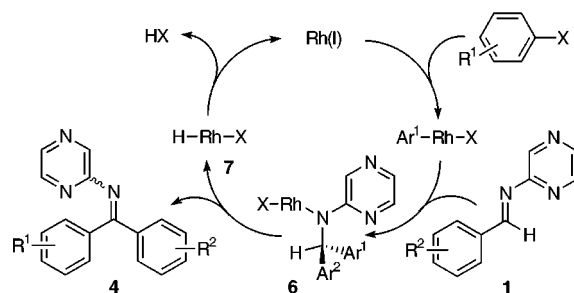
Reactions of these two complexes with their complementary reagents are summarized in Scheme 1.<sup>27</sup> Arylrhodium complex **2** reacted with excess of aldimine **1** at 135 °C, the temperature of the catalytic process, in the presence of NaOBu<sup>t</sup> and PPh<sub>3</sub> in *m*-xylene to form two coupling products: ketimine **4** and amine **5** (40:60) in a combined yield of 60% (Scheme 1). This combined yield is comparable to that obtained from the catalytic reactions employing PPh<sub>3</sub> as ligand. No reaction between arylrhodium **2** and aldimine **1** occurred in the absence of base. Iminoacyl complex **3** reacted with an excess of 4-iodotoluene in the presence of NaOBu<sup>t</sup> to form ketimine and amine (4:5 = 85:15), but the combined yield was only 40%. Importantly, reaction of iminoacyl complex **3** with tolyl iodide in the absence of base produced

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**Scheme 2**

arylrhodium **2** and free aldimine **1** in nearly quantitative yields. Presumably, these products are formed by the reductive elimination of aldimine followed by oxidative addition of iodotoluene. Moreover, the generation of **2** and free imine from **3** in the absence of base occurred more rapidly than did the generation of coupled product from heating **3**, tolyl iodide, and base. Thus, the products resulting from heating of **3** with iodotoluene and base probably form from reaction of free aldimine with **2**.

A possible mechanism for the coupling process involving an arylrhodium halide complex that reacts with imine is shown in Scheme 2. This mechanism includes (a) oxidative addition of aryl halide to rhodium(I) to form an arylrhodium(III) complex, (b) insertion of aldimine **1** into the rhodium–carbon bond to give a rhodium(III) amide complex **6**, perhaps after the prior coordination of the aldimine nitrogen, (c)  $\beta$ -hydride elimination from **6** to give ketimine **4** and hydridorhodium(III) complex **7**,<sup>28,29</sup> and (d) reductive elimination of HX from **7** to regenerate the starting rhodium(I) complex.

Additional studies will be required to define the exact structures of the intermediates because several observations are not explained by this mechanism. For example, no reaction occurred between arylrhodium **2** and aldimine **1** in the absence of base, suggesting that the base modifies the arylrhodium complex prior to insertion. In addition, the ratio of ketimine and amine products formed from reaction of **2** with aldimine was different from the ratio observed in the catalytic process. Thus, reaction of imine with an arylrhodium(III) complex is a reasonable step in the catalytic process, but the precise ligand set on the arylrhodium complex that reacts with aldimine is probably different from that in **2**.<sup>27</sup>

Insertions of olefins into late metal–carbon bonds are common, but such insertions of imines and aldehydes are rare, perhaps because they form a reactive late metal–amide or –alkoxide from a more stable metal–alkyl or –aryl. Imine and aldehyde insertion has been postulated as a step in the metal-catalyzed additions of organic halides<sup>15–17</sup> and main group organometallic reagents<sup>18–21</sup> to aldehydes, ketones, and imines. However, direct evidence for this step from studies of discrete intermediates has not been obtained. Our studies on the reaction of aldimine **1** with arylrhodium complex **2** provide evidence that this elementary step is part of a stoichiometric reaction involving a well-known aryl halide complex.

An understanding of imine and aldehyde insertions should point toward a set of new catalytic processes based on analogies to those that involve olefin insertion. Further mechanistic work and further development of such catalytic processes will be the subject of future studies.

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**Supporting Information Available:** Experimental procedures for Table 1 and Scheme 1, including preparation of **2** and **3**, and spectral analyses of all reaction products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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