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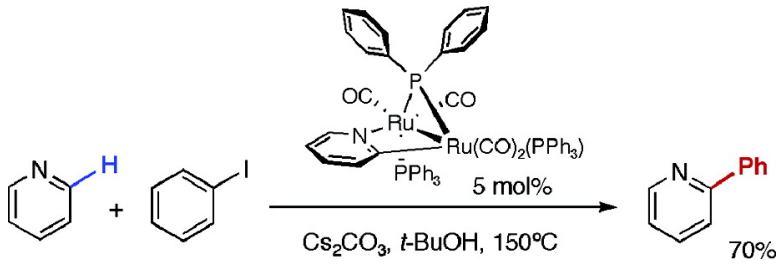

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Site-Specific Phenylation of Pyridine Catalyzed by Phosphido-Bridged Ruthenium Dimer Complexes: A Prototype for C−H Arylation of Electron-Deficient Heteroarenes

Kamil Godula, Bengü Sezen, and Dalibor Sames*

Department of Chemistry, Columbia University, 3000 Broadway, New York, New York 10027

Received December 13, 2004; E-mail: sames@chem.columbia.edu

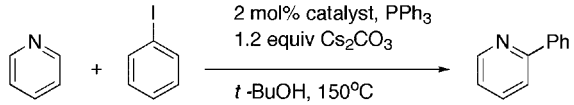
Functionalized azines (e.g., pyridine, pyrimidine, pyrazine) are indispensable architectural units in the design of biologically active compounds, pharmaceuticals, and other functional synthetics. Although significant progress has been achieved in the development of catalytic alkylation, alkenylation, and acylation reactions at the pyridine nucleus,[1] direct and selective C−H arylation of π-deficient heteroarenes represents an unsolved challenge.[2] Currently, the preparation of aryl azines relies heavily on traditional cross-coupling processes, such as the Suzuki[3] and Stille[4] couplings, which require the establishment of proper functionalities on both coupling partners. Herein we report a novel cross-coupling of iodobenzene and pyridine, catalyzed by a phosphido-bridged binuclear ruthenium complex.

In the course of a systematic study, $Ru_3(CO)_{12}$ was identified as a catalyst for the coupling of iodobenzene and pyridine, affording 2-phenylpyridine as the sole product in 36% yield (Table 1, entry 1). The choice of solvent and base as well as the presence of phosphine ligand was essential for the success of this transformation.

$Ru_3(CO)_{12}$ has long been known to undergo the oxidative addition of C−H bonds at the α-position of various azines[5] to form hydride clusters such as **1** (Figure 1). Recently, Moore and Murai successfully utilized this phenomenon to achieve catalytic acylation of pyridine[1b] and other aza-heterocycles.[1c] However, no experimental data were generated to gain better mechanistic understanding beyond the intermediacy of **1**. In contrast, we noted that in the present arylation system neither $Ru_3(CO)_{12}$ nor complex **1** was the catalytically active species. Consequently, we initiated a detective effort to identify the active catalyst via both the isolation work and independent synthesis.

Fast consumption of $Ru_3(CO)_{12}$ and formation of a set of new ruthenium complexes were observed at temperatures ranging between 80 and 110 °C, before the catalytic system reached the reaction temperature of 150 °C. The stoichiometric experiments with $Ru_3(CO)_{12}$ in the absence of iodobenzene revealed a series of transformations, leading to the formation of bisruthenium species **4** and byproduct **5** (Figure 1). Initially, $Ru_3(CO)_{12}$ was converted to hydride **2** in the presence of an excess of pyridine and 1 equiv of PPh_3 at 100 °C. This occurs through oxidative addition of the pyridine C−H bond and the carbonyl−phosphine exchange, presumably in either order. One sequence was illustrated by an independent synthesis of complex **2** from **1** (Figure 1, conditions b). Complex **2** was subsequently converted to a bisphosphine complex **3** by the action of another equivalent of PPh_3 with concomitant release of CO. The latter complex underwent an intriguing fragmentation in the presence of Cs_2CO_3 at 110 °C to furnish phosphido-bridged bisruthenium complex **4**, presumably via P−C bond cleavage of one of the phosphine ligands, followed by the loss of 1 equiv of benzene and double Ru−Ru bond cleavage.[5b,6] The byproduct was identified as an inseparable mixture of bishydride triruthenium cluster **5a** and its C2 symmetrical isomer **5b**, in which the nitrogen atoms of both pyridine rings are coordinated to the same ruthenium center.

Table 1. Catalytic 2-Phenylation of Pyridine[a]



entry	catalyst	PPh_3/mol %	time/h	yield/%
1	$Ru_3(CO)_{12}$	4	18	36
2	**1**	4	18	36
3	**2**	2	18	41
4	**3**	0	18	39
5	**4**	0	18	32[b]
6	**5a**,**b**	0	18	0
7	**6a**,**b**	0	18	55
8	**6a**,**b**	0	66	70[c]

[a] Conditions: Pyridine (1 equiv), iodobenzene (1 equiv), Cs_2CO_3 (1.2 equiv), catalyst (2 mol %), PPh_3, *t*-BuOH, $c = 0.52$ M, 100 °C 0.5 h, 110 °C 0.5 h, 150 °C 17 h. [b] 30% of catalyst recovered. [c] 5 mol % of catalyst employed. Yields are an average of at least two trials with an error within ±3%.

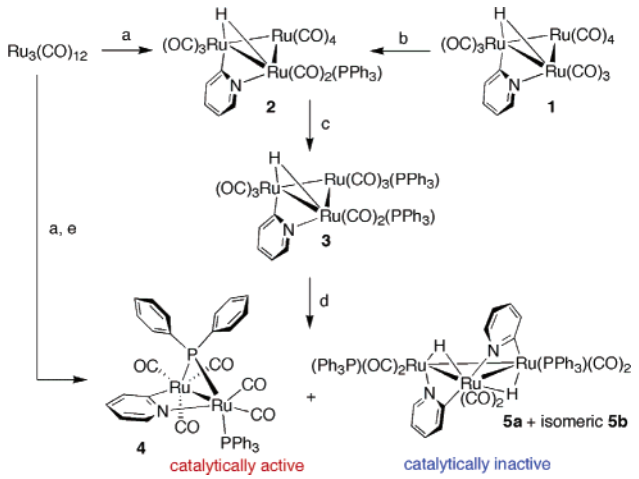


Figure 1. Generation of ruthenium dimer **4**. All complexes were fully characterized by NMR, IR, and MS spectroscopy and by elemental analysis. X-ray crystallographic data were obtained for complexes **2**, **4**, and **5**. Conditions: (a) PPh_3 (1 equiv), pyridine (8 equiv), *t*-BuOH, 100 °C, 95%. (b) PPh_3 (1 equiv), *t*-BuOH, 100 °C, 98%. (c) PPh_3 (1 equiv), *t*-BuOH, 100 °C, 52%. (d) Cs_2CO_3 (1.5 equiv), *t*-BuOH, 110 °C, 36% of **4**, and 10% of **5a**,**b**. (e) PPh_3 (1 equiv), Cs_2CO_3 (1.5 equiv), *t*-BuOH, 100 °C (1 h) then 110 °C, 33% of **4** after two steps.

Indeed, complexes **4**, **5a**, and **5b** were detected under the catalytic conditions and, hence, were tested separately for the catalytic activity. While **4** catalyzed the cross-coupling of pyridine with iodobenzene (Table 1, entry 5), the mixture of **5a** and **5b** was inactive (entry 6). As complexes **1**, **2**, and **3** were also active, a likely pathway toward **4**, taking place in situ, may be constructed

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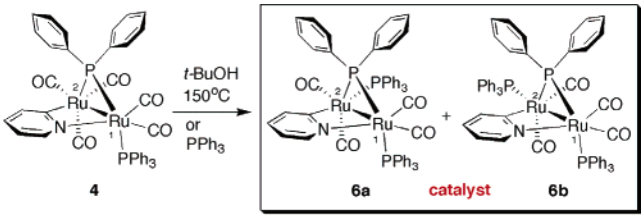

Figure 2. Thermal disproportionation of complex **4**.

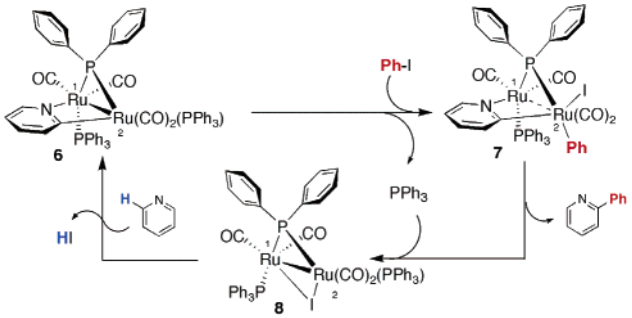

Figure 3. Proposed catalytic cycle.

(Figure 1). Further analysis of this complex system revealed the formation of yet another complex which led us to suspect that complex **4** was not the actual catalytic species but instead underwent further transformation under the reaction conditions.

Heating complex **4** under the reaction conditions resulted in slow conversion to a mixture of inseparable isomers, which were identified as bisphosphine ruthenium dimers **6a** and **6b** (Figure 2). The unsaturated ruthenium species resulting from this phosphine disproportionation was not detected and presumably underwent decomposition. The identical mixture of **6a** and **6b** may also be prepared by treatment of **4** with 1 equiv of PPh_3 at 150 °C.[7] These complexes provided a superior yield in comparison to other catalytically active compounds (entries 7 and 8, Table 1); up to 70% of 2-phenylpyridine can be obtained in one step. Furthermore, **6a** and **6b** were detected as the principle ruthenium species in the reaction mixture after 18 h. These observations strongly suggest that the mixture of **6a** and **6b** represents the resting state of the catalyst in this new process.

On the basis of these results, we propose the following model of a catalytic cycle. A phosphine ligand is dissociated from complex **6**, creating a coordinately unsaturated site at Ru(2), which undergoes the oxidative addition with iodobenzene (Figure 3).[8] The C−C bond is formed by the subsequent reductive elimination, and the resulting empty coordination site is filled by the free phosphine to afford the putative complex **8**. Coordination of pyridine (or replacement of the product by pyridine), followed by C−H activation, and elimination of hydrogen iodide would then complete the cycle. The oxidative addition of iodobenzene may also occur at Ru(1), wherein no direct pathway for the product formation is available and thus a mechanism for the phenyl group transfer between the ruthenium nuclei would have to be available.[9] Labeling studies showed that PPh_3 is not the source of the phenyl group;[7] it is more likely that the oxidative addition is reversible, and thus the corresponding product at Ru(1) lies outside the productive cycle. The choice of base was also important, and presumably it is directly involved in the dehydroiodination step (not shown). This simple model will serve as the starting point for the future mechanistic and optimization studies.

In conclusion, a novel protocol for site-specific phenylation of pyridine was discovered, thus setting the precedent for the development of new methodologies for direct arylation of π-deficient heteroarenes. Formation of catalysts **6a** and **6b** involving a sequence of C−H and C−P bond cleavage, cluster fragmentation, and disproportionation has been uncovered. These crystalline, air, and moisture stable complexes can be prepared in three steps in 30% overall yield. This work also demonstrates the potential of bi- and polynuclear metallic species in catalysis.[10] The possibility of facilitating processes requiring two consecutive oxidative addition steps, through synergistic actions of multiple metal centers and the incorporation of ligands such as phosphines to enable the transient generation of a coordinately unsaturated polymetallic species, is especially noteworthy. Rational design of such multifunctional catalysts may lead to the development of new, thus far unforeseen, chemical transformations.

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Supporting Information Available: Experimental procedures, spectral data, elemental analyses, and tables and figures pertaining to X-ray crystallographic studies of **2**, **4**, and **5** (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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