



## Carbene Based Palladium-catalyzed Mizoroki-Heck Reaction

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(Received: September 01, 2012; Accepted: October 06, 2012)

### ABSTRACT

Different perhydrobenzimidazolium chloride salts were used as a ligand for Pd-catalyzed Mizoroki-Heck reaction. The *in situ* generation of carbene is the attractive feature of this catalytic system. The corresponding Mizoroki-Heck products were obtained in good yield.

**Key words:** Carbene, Mizoroki-Heck reaction, Palladium.

### INTRODUCTION

C-C bond formation is one of the most fundamental and important reactions in the area of organic synthesis and Pd catalysis is the backbone of this bond formation<sup>1</sup>. Palladium complex with phosphine-assisted approach<sup>2</sup> has become a classical and well-established method to give excellent results in most cases. Yet significant drawbacks remain for this approach like phosphine ligands are expensive, toxic, and unrecoverable while handling. In large-scale industrial production, the phosphines might be a more serious economical burden than even palladium itself. Another reason is the poor reactivity often associated with fully ligated complexes of palladium<sup>3</sup>. Further 2 limitations are found in that amine or carbonate bases and often other additives, usually silver or thallium salts, must be screened in order to optimize the yield<sup>4</sup>.

Recently, *N*-heterocyclic carbenes (NHCs) came to light as efficient ancillary ligands than phosphine. Increased stability of the active catalyst, lower operational catalyst loadings, tolerance of increased reaction temperatures etc<sup>5-7</sup> are the main advantages of carbene based Pd catalysis. Although the nature of the NHC ligand on complexes has a tremendous influence on the rate of catalyzed reactions, the use of perhydrobenzimidazolium ligand in Heck and Suzuki reactions have been already reported. Perhydrobenzimidazolium chlorides (3 a, b, c), containing a saturated benzimidazole ring offers *in situ* palladium-carbene based catalytic system for Heck and Suzuki cross-coupling with improved yields.

Other important Pd-catalyzed C-C coupling reactions are the Mizoroki-Heck [8] and Sonogashira<sup>9-12</sup>. In order to extend the use of this

catalytic system we have used this system for Mizoroki-Heck arylation of alkenes.

### EXPERIMENTAL

All the chemicals were purchased from Sigma Aldrich, Acros or Fluka and all the experiments were carried out under nitrogen unless noted. NMR spectra were recorded on standard Bruker 300WB spectrometer with an Avance console at 300 and 75 MHz for  $^1\text{H}$  and  $^{13}\text{C}$  NMR respectively. The residue was purified by flash chromatography with hexane/ethyl acetate.

A high pressure tube was charged with the aryl halide (1 mmol), styrene (1.5 mmol), salt (3a-c, 2% molar ratio), base (2 mmol), Pd (OAc) $_2$  (see Table) and DMF/water (3:3 mL). The mixture was stirred at 120 °C and the reaction progress was monitored by GLC. The reaction mixture was cooled to room temperature and an aqueous solution of 1M HCl (10 mL) was added. The mixture was poured into ethyl acetate (10 mL) and washed with 2M HCl (2 x 10 mL) and H $_2$ O (2 x 30 mL). The organic layer was dried over MgSO $_4$ , and the solvents were removed under vacuum. The residue was purified by flash chromatography with hexane/ethyl acetate.

### RESULTS AND DISCUSSION

The catalytic activity of the palladium-carbene based catalytic system was optimized for the Mizoroki-Heck cross-coupling reaction of 4-

bromoacetophenone 1a with *tert*-butyl acrylate 1b (Figure 1 and Table 1). The reaction was carried out in dimethylformamide/water solvent system using different bases (e.g. NEt $_3$ , *i*Pr $_2$ NH, NaOAc and K $_2$ CO $_3$ ).

According to table 1, Pd/carbene system worked well in the DMF/H $_2$ O solvent system with K $_2$ CO $_3$  for Mizoroki-Heck cross-coupling reaction between 4-bromoacetophenone 1a with *tert*-butyl acrylate 1b and offer the respected product in high yield in case of 3a. We took 3a as an ideal salt for further study of Mizoroki-Heck cross-coupling reaction where we took different aromatic halides and styrenes. In most of the cases the corresponding Mizoroki-Heck cross-coupling products were obtained in good to high yield.

Hydroxylated stilbenoids, specially resveratrol [3,4',5-trihydroxy-(*E*)-stilbene], are a very important class of natural products with important biological activity<sup>13</sup>. The stilbenoid unit is used in molecular photonics and optoelectronics<sup>14</sup>. In addition, methoxylated stilbenoids have shown activity against several human cancer cell lines<sup>15</sup> and are potent CYP1B1 inhibitors valuable for the development for chemopreventive and therapeutic agents for cancer<sup>16</sup>. We have also synthesized 3,4',5-trihydroxy-(*E*)-stilbene<sup>17</sup> (Table 1, Entry 9) using Pd/carbene catalytic system by arylation of 4-methoxystyrene with 3,5-dimethoxyiodobenzene in high yield.

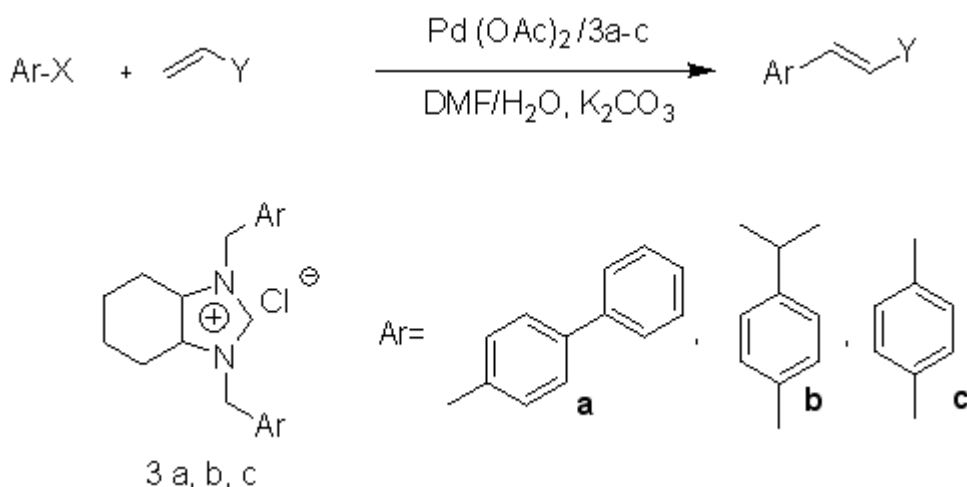

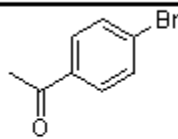
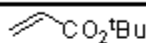
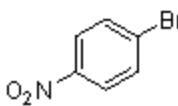

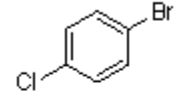
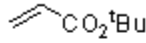
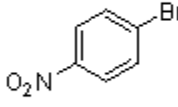

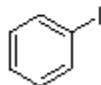

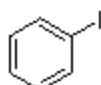

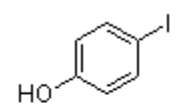

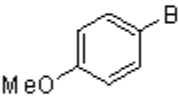
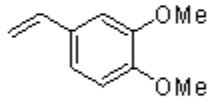
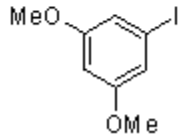
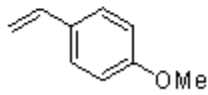


Fig. 1: Mizoroki-Heck cross-coupling reaction

Table 1: Mizoroki-Heck reactions with different aryl halides and styrenes

Entry	Aryl halide (Ar-X)	Styrene 	Salt (3 a, b, c)	Yield (%) <sup>a, b</sup>
1.			3a	100
			3b	82
			3c	74
	<b>1a</b>	<b>1b</b>		
2.			3a	92
3.			3a	98
4.			3a	87
5.			3a	100
6.			3a	79
7.			3a	78
8.			3a	95
9.			3a	98

Reaction conditions: aryl halide (1.0 mmol), styrene (1.5 mmol), base 2mmol, Pd(OAc)<sub>2</sub> 1% (molar ratio), 3a-c 2% (molar ratio), water /DMF (1:1), 130°C, 2 h. a) isolated yields are based on aryl bromide. b) the compound purity was checked by NMR.15

### CONCLUSION

We have extended the use of palladium-carbene based catalytic using perhydrobenzimidazolium chlorides (Table 1,

Entry 3 a-c) as ligand for Mizoroki-Heck cross-coupling reaction with high yield. Synthesis of biologically active compound 3, 4', and 5-trihydroxy-(E) stilbene is a major outcome of our work.

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