S. Nadri et al.

## Letter

# 1,1'-Methylene-3,3'-bis[(*N*-(*tert*-butyl)imidazol-2-ylidene] and Its Effect in Palladium-Catalyzed C–C Coupling

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Received: 10.10.2014 Accepted after revision: 27.11.2014 Published online: 14.01.2015 DOI: 10.1055/s-0034-1379954; Art ID: st-2014-d0853-I

**Abstract** A catalytic system utilizing a chelate carbene ligand containing bulk *tert*-butyl groups is described for palladium-catalyzed Heck and Suzuki coupling reactions. The Heck reaction focused on the coupling of different aryl bromides with mono- and 1,1-disubstituted ole-fins while the Suzuki reaction involved the coupling of aryl bromides and phenylboronic acid to afford the corresponding biphenyls. The catalyst system performs well with low  $Pd(OAc)_2$  levels (0.025 mol% Pd). In all cases with monosubstituted olefins, the *trans*-configured products were obtained, while the results of Heck reaction of 1,1-disubstituted olefins exhibited a high selectivity favoring the terminal product.

**Key words** palladium, carbene Ligand, C–C coupling, Heck reaction, Suzuki reaction

Whilst the benefits of phosphine ligands are obvious in a variety of transition-metal-catalyzed reactions, there is growing interest in the search for the design of new organometallic catalysts with carbene ligands, particularly with Nheterocyclic carbene (NHC) ligands.<sup>1-3</sup> The interest is due to a combination of factors, including strong  $\sigma$ -donor property concomitant with a negligible  $\pi$ -accepting ability, and high stability toward heat, air, and moisture. Thus, carbene ligands are useful as a mimic of phosphines in catalysis. Imidazole–carbene ligands display different coordination modes. They have been found to act as monodentate ligands where the imidazolium ring is coordinated to the metal center at the C(2) position on the ring,<sup>4,5</sup> but mainly act as bidentatechelating<sup>6,7</sup> or pincer-type ligands<sup>8</sup> (Figure 1).

The N-substituent group and nature of the linker that connects the pair of NHC rings are two important factors which influence the coordination mode and activity of che-



Figure 1 Examples of monodentate, chelating, and pincer-type carbene ligands

lating bis-NHC ligands. Applications of both aliphatic and aromatic linkers have been reported in the literature.<sup>6,8</sup> Additionally, the effect of the nature of the N-substituent groups R in the NHC backbone on structure and catalytic activity has been investigated by several research groups. For example, studies from Organ's group have shown that NHC-based ligands bearing isopentylphenyl N-substituents are more reactive in amination reactions than the isopropylphenyl one and reported that this difference in activity can be rationalized in terms of the difference in amine coordination and/or deprotonation.<sup>9,10</sup> The catalytic activity for a family of complexes of general formula (NHC)-Pd(allyl)Cl in aryl amination has been investigated by Nolan's group, and this relative reactivity trend is attributed to the steric nature of the N-substituent groups.<sup>11,12</sup>

We previously reported the synthesis and structural characterization of bis-NHC platinum complex **2**, [PtMe<sub>2</sub>(bis-NHC)], in which bis-NHC, 1,1'-methylene-3,3'-bis[(*N*-(*tert*-butyl)imidazol-2-ylidene] (**1**) acts as a chelating ligand (Scheme 1).<sup>13</sup> The chelating complex **2** demonstrated the ability to fix aerial CO<sub>2</sub>.

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620

S. Nadri et al.

Svn lett



Because of its similarity to platinum, we envisaged that palladium may also be able to behave in a similar fashion, and 1,1'-methylene-3,3'-bis[(*N*-(*tert*-butyl)imidazol-2-ylidene] (1), could be an effective ligand in palladium-cata-lyzed coupling reactions, owing to its chelating coordination mode as well as its electronically rich and sterically hindered *tert*-butyl groups. In this direction, to understand the utility of NHC ligand 1 in palladium-catalyzed coupling reactions and based on our experience in cross-coupling reactions, <sup>14–20</sup> we have chosen the Heck and Suzuki reactions as test cases. In this paper we present our results in detail.

Our initial experiments focused on Heck coupling between bromobenzene and butyl acrylate as the vinylic substrate.<sup>21</sup> Using NHC ligand **1**, a preliminary experiment in *N*,*N*-dimethylformamide (DMF) at 135 °C with potassium carbonate ( $K_2CO_3$ ) as the base and 0.025 mol% of Pd(OAc)<sub>2</sub> was successful, and about 97% yield of coupling product was achieved after one hour without the need for any tetraalkylammonium salt as additive (Table 1, entry 1). Since the yield of the coupling product was satisfactory, further optimization of reaction conditions was not carried out. We then checked the generality and scope of the catalyst with a wide range of substrates with different electronic and steric effects. As shown in Table 1,Pd(OAc)<sub>2</sub>/NHC ligand 1 was found to be tolerant towards different functional groups on the aryl bromides. The reaction of 4bromotoluene proceeded well to give the desired product in 93% yield (Table 1, entry 2). When the substitution position of the methyl group on the aryl bromide changed from para to meta (Table 1, entry 3), the activity remained unchanged, which seems to suggest that the steric hindrance of meta substituent on the arvl ring does not affect the vield and reaction time. For the electron-rich aryl bromide, 4bromoanisole, the catalyst was efficient and conversion approached nearly 80% within three hours (Table 1, entry 4). In the cases of 1-bromo-4-nitrobenzene and 4-bromobenzaldehyde the maximum yield of Heck products were 79% and 62%, respectively (Table 1, entries 5 and 6), because such substrates are prone to suffer a competing dehalogenation process, which is more likely to take place with aryl halides bearing electron-withdrawing groups.<sup>22</sup> Furthermore, as reported by Svennebring et al. the competing reductive amination is another side reaction that can occur on formyl-functionalized compounds, albeit at very high temperature conditions.<sup>23</sup>

Table 1	Table 1         Heck Reaction of Various Aryl Bromides with Monosubstituted Olefins <sup>a</sup>					
	$R^{1}$ $Br + R^{2} = CO_{2}n$ -Bu or	$(OAc)_2, NHC-ligand 1 \qquad R^1_{4}$ $\xrightarrow{P}_{2}CO_3, DMF, 135 °C \qquad trans$	$R^2 + R^1$	+ $R^1 \frac{1}{U}$ gem	7 <sup>2</sup>	
Entry	Aryl bromide	Olefin	Time (h)	trans (%)	TON <sup>b</sup>	
1	Br	n-butyl acrylate	1	97	3880	
2	Me	n-butyl acrylate	1	94	3760	
3	Me Br	n-butyl acrylate	1	95	3800	
4	MeO-Br	n-butyl acrylate	2	80	3200	
5°	O <sub>2</sub> N-Br	n-butyl acrylate	4	79	3160	

## Syn<mark>lett</mark>

## S. Nadri et al.

Table 1	(continued)
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Entry	Aryl bromide	Olefin	lime (h)	trans (%)	ION
6	OHC-Br	n-butyl acrylate	5	62	2480
7 <sup>c</sup>	NC-Br	<i>n</i> -butyl acrylate	2	90	3600
8	Br	<i>n</i> -butyl acrylate	2	81	3240
9	Br Br	n-butyl acrylate	7	20	800
10	∏Br	n-butyl acrylate	2	84	3360
11	Br	styrene	2	92	3680
12	Br	styrene	2	88	3520
13	Br	styrene	2	90	3600
14	MeO	styrene	2	51	2040
15	Br	styrene	4	73	2920
16	Br	styrene	3	83	3320

621

<sup>a</sup> Reaction conditions: aryl bromide (4 mmol), olefin (4 mmol),  $K_2CO_3$  (4 mmol), Pd(OAc)<sub>2</sub> (0.025 mol%), ligand 1 (0.05 mol%), DMF (3 mL).

<sup>b</sup> TON = turnover number (mol product/mol catalyst).

<sup>c</sup> N-(Butyl)<sub>3</sub> was used as the base.

4-Bromobenzonitrile led to an excellent yield (Table 1, entry 7). This observation was of interest since, in our previous work,<sup>20</sup> this substrate was completely unreactive when 2,6-bis(diphenylphosphino)pyridine was employed as the ligand; probably due to steric effects exerted by competitive coordination of the cynao group to the palladium center, as reported by Hong's group.<sup>24</sup> Here it seems that the chelating coordination mode of NHC ligand **1** effectively prevents the cyano group from the coordinating to the palladium center. While fused aromatic bromides such as 1bromonaphthalene reacted cleanly to give the corresponding Heck product (Table 1, entry 8), 4-bromobiphenyl was unreactive and only gave the coupled product in 20% yield after seven hours (Table 1, entry 9). The reason for this incomplete conversion is not clear for us at this time. Apart from the above substrates, we found that the  $Pd(OAc)_2/NHC$  ligand **1** combination could also catalyze the Heck reaction of heterocyclic substrates such as 3-bromothiophene (Table 1, entry 10). The reaction of aryl bromides with styrene was also tested under our conditions (Table 1, entries 11–16). A similar catalytic activity of the  $Pd(OAc)_2/NHC$  ligand **1** system has been observed in the Heck reaction with styrene; though, the yield of products were slightly lower than for the reaction of butyl acrylate.

It has already been reported that addition of silver(I) oxide (Ag<sub>2</sub>O) facilitates formation of the Pd–NHC complex by transmetalation of the NHC ligand from the corresponding Ag–NHC compound to the palladium center.<sup>25–27</sup> Recently,

## S. Nadri et al.

we had successfully demonstrated this strategy,<sup>13</sup> where treatment of the silver carbene complex,  $[Ag_2(bis-NHC-1)Br_2]$ , generated in situ from the corresponding bis(imidazolium) dibromide salt and Ag<sub>2</sub>O with  $[Pt_2Me_4(\mu-SMe_2)_2]$ , allowed the isolation of bis(carbene)platinum complex  $[Pt(Me)_2(bis-NHC-1)]$  (2). We should mention here that, in contrast to earlier works, we found that the addition of Ag<sub>2</sub>O is not necessary to achieve successful Heck coupling catalyzed by Pd(OAc)<sub>2</sub>/NHC ligand **1**. This observation means that the complexation of NHC ligand **1** to the palladium center proved to be accessible by the standard synthetic routes such as in situ deprotonation and reaction with Pd(OAc)<sub>2</sub> or direct metalation by reaction with palladium species.

The efficiency of  $Pd(OAc)_2/NHC$  ligand **1** system may be partly due to chelating coordination mode of NHC ligand **1** that affects the binding properties of the substrates around the metal center, and partly due to appreciate the role of bulky substituents such as *tert*-butyl in the ligand backbone in regard to basicity and steric hindrance, which would affect the efficiency of some of the steps in a catalytic cycle. In other words, chelation of NHC ligand **1** and the existence of *tert*-butyl groups led to a synergistic effect which gave rise to the activity and stability of the derived palladium catalyst. It should be noted that the catalytic system was nonsensitive to oxygen, and the coupling reactions could be performed under air effectively. Other thing to be considered is that all reactions were found to be completely regio- and stereoselective, giving only *trans*-configured products on the less substituted carbon with lower electron density of the olefin double bond, regardless of the stereoelectronic properties of the aryl bromides.

Given our success with the Pd(OAc)<sub>2</sub>/NHC ligand 1 combination for the coupling of monosubstituted olefins, we felt that it might also be quite effective for the coupling of 1,1-disubstituted olefins which are known to be hard substrates because of steric reasons. As illustrated in Scheme 2 from the intermediate **A** that is formed after olefin migratory insertion step, there are two possible pathways for palladium  $\beta$ -hydride elimination to occur. Intermediate **A** can



622

Table 2         Heck Coupling Reaction of 1,1-Disubstituted Ole	fins
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	ArHBr +	R Pd(OAc) <sub>2</sub> , NH K <sub>2</sub> CO <sub>3</sub> , DMF	C ligand <b>1</b> → , 135 °C	Ar +	Ar R + Ar	R Ar	
	$R=CO_2I$	ז-Bu or Ph		internal	terminal doub	ble arylated	
Entry	Aryl bromide	Olefin	Time (h)	Internal (%)	Terminal (%)	Double arylated (%)	TON <sup>b</sup>
1	Br-Br	<i>n</i> -butyl methacrylate	3	16	81	0	3240
2	Me Br	n-butyl methacrylate	3	0	72	0	2880
3	Br	α-methylstyrene	5	15	85	0	3400
4	Me Br	α-methylstyrene	3	10	79	0	3160

<sup>a</sup> Reaction conditions: aryl bromide (4 mmol), olefin (4 mmol), K<sub>2</sub>CO<sub>3</sub> (4 mmol), Pd(OAc)<sub>2</sub> (0.025 mol%), ligand 1 (0.05 mol%), DMF (3 mL).

<sup>b</sup> TON = turnover number (mol product/mol catalyst).

# Syn lett

#### S. Nadri et al.

Table 3 Suzuki Reaction of Aryl Bromides with Phenylboronic Acida

	R	Pd(OAc) <sub>2</sub> , NHC ligand <b>1</b> K <sub>2</sub> CO <sub>3</sub> , DMF, H <sub>2</sub> O, 135 °C	→ R-	$\langle \rangle$
Entry	Aryl bromide	Time (h)	Yield (%)	TON <sup>b</sup>
1	Br	1	96	3840
2	Me	1	94	4760
3	OHC Br	5	73	2920
4	Br	3	82	3280

623

<sup>a</sup> Reaction conditions: aryl bromide (4 mmol), phenylboronic acid (4 mmol), K<sub>2</sub>CO<sub>3</sub> (4 mmol), Pd(OAc)<sub>2</sub> (0.025 mol%), ligand 1 (0.05 mol%), DMF (3 mL), H<sub>2</sub>O (1 mL). <sup>b</sup> TON= turnover number (mol product/mol catalyst).

eliminate H<sub>B</sub> on the methyl group and eventually generates the Heck product 3 with an internal double bond, the stereochemistry of which can be E or Z. The other pathway involves elimination of H<sub>B</sub> from the benzylic methylene group which would afford compound 4 bearing a disubstituted double bond, which is susceptible to further arylation to give 5.

Beller has reported that regioselectivity and product distribution is base-dependent, as inorganic bases such as sodium acetate gave a mixture of the two regioisomers with the terminal olefin as the major product; whereas the internal olefin was favored by organic bases such Bu<sub>3</sub>N or diisopropylethylamine (DIPEA) and proposed that a direct proton abstraction by the amine takes place toward the most acidic benzylic protons.<sup>28</sup> In contrast, Morales obtained the internal olefin as the major product, irrespective of the nature of the base.<sup>29</sup>

As shown in Table 1<sup>21</sup> the reactivity of 1,1-disubstituted olefins is reduced compared to monosubstituted ones. The results indicate that, under our reaction conditions, the elimination of methyl hydrogen is much faster than that of benzylic hydrogen and both *n*-butyl methacrylate and  $\alpha$ methylstyrene gave terminal olefins as the major coupling products, and only a small amount of internal olefins were formed (Table 2). This may be because the methyl group has three hydrogens increasing the chances of elimination.

Biaryls are an important class of 'building blocks' that are widely employed in organic synthesis and pharmaceutical or agrochemical areas making the Suzuki coupling reaction one of the most important modern synthetic methods. Thus, it remained to be seen whether the combination of Pd(OAc)<sub>2</sub>/NHC ligand 1 could be also effective in Suzuki reactions (Table 3).

Preliminary testing for Suzuki reaction was carried out by treating bromobenzene with phenylboronic acid in DMF and K<sub>2</sub>CO<sub>3</sub>.<sup>30</sup> A minimal amount of water was added to the reaction to help dissolve the phenylboronic acid. The reaction proceeded well to afford biphenyl in 94% yield after one hour (Table 3, entry 1). We next examined the coupling of several other representative aryl bromides with phenylboronic acid with the results listed in Table 3. With respect to the electron-rich, electron-neutral, and electron-poor arvl bromides as well as sterically hindered substrates, all reacted with phenylboronic acid smoothly to provide the corresponding biaryl products in good to high yields.

In conclusion, the catalytic system generated in situ from Pd(OAc)<sub>2</sub> and NHC ligand **1** can be useful for both Heck and Suzuki coupling reactions with a number of substrates under an air atmosphere. It is worth noting that addition of Ag<sub>2</sub>O, which is sometimes required for fast coordination of carbene ligands to metal centers, was not necessary.

# Acknowledgment

The authors thank Razi University Research Council for support of this work.

## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379954.

624

## S. Nadri et al.

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- (21) Typical Experimental Procedure for the Heck Arylation
- A reaction tube was charged with aryl bromide (4 mmol), olefin (4 mmol), and  $K_2CO_3(4 \text{ mmol})$  under air. A solution of Pd(OAc)<sub>2</sub> (0.025 mol% in 1 mL of DMF) followed by a solution of NHC ligand **1** (0.05 mol% in 2 mL of DMF) was added through a rubber septum, and the resulting mixture was heated at 135 °C for the appropriate time. Upon completion of the reaction, the reaction mixture was cooled to r.t. and quenched with H<sub>2</sub>O. After extraction with CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered, the solvent was evaporated, and the crude residue was purified by silica gel chromatography, using *n*-hexane–EtOAc as eluent to provide the desired product. The products were characterized by NMR spectroscopy.
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## (30) General Procedure for the Suzuki Coupling

A reaction tube was charged with PhB(OH)<sub>2</sub> (4 mmol), aryl bromide (4 mmol), and K<sub>2</sub>CO<sub>3</sub>(4 mmol) under an air atmosphere. A solution of Pd(OAc)<sub>2</sub> (0.025 mol% in 1 mL of DMF) along with a solution of NHC ligand **1** (0.05 mol% in 2 mL of DMF) was added through a rubber septum. After addition of H<sub>2</sub>O (1 mL), the resulting mixture was heated at 135 °C for the appropriate time. After extraction with Et<sub>2</sub>O, the organic phase was dried over MgSO<sub>4</sub>, filtered, the solvent evaporated, and the crude product was characterized by NMR spectroscopy.

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