Effect of *N1*-substituted pyrazolic hybrid ligands on palladium catalysts for the Heck reaction

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ABSTRACT

In this paper we have explored the influence of several linkers present on the [PdCl$_2$(L)] complexes, where **L** is 3,5-dimethylpyrazolic hybrid ligand *N1*-substituted by polyether chains and/or phenyl groups. These complexes have been used as pre-catalysts in the Heck reaction between phenyl halides and *tert*-butyl acrylate. The corresponding complexes efficiently catalyze the Heck olefination and provide good yields under phosphine-free conditions, even for aryl chlorides. Different reaction conditions were investigated and it was found that the nature of the ligand has an important influence on the effectiveness of the catalytic system. Ligand 1,8-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-3,6-dioxaoctane (**L1**), which has previously shown to be the most flexible and versatile, achieved high turnover numbers within very short reaction times and low catalyst loadings.

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1. Introduction

The great importance of palladium-catalyzed carbon–carbon bond-forming reactions has encouraged the chemical community to search for very active, and at the same time stable, palladium-based catalysts, which should also be versatile and efficient systems [1–4]. This pertains particularly to the vinylation of aryl halides called the Heck reaction which is a "classical" process in organic synthesis and material science [5–10]. This construction of C–C single bond has attracted increasing attention due to their synthetic versatility; the recent development of many efficient procedures involving Pd-catalyst precursors is quite impressive [11–19].

The Heck reaction is normally carried out in the presence of phosphine ligands and a base under an inert atmosphere to minimize the deleterious effect of oxygen in the air. Therefore, the development of catalysts under phosphine-free conditions would be an important achievement and many research groups have been seriously involved in the development of easy-handling catalysts. To date, a number of reports on phosphine-free catalyst systems for the Heck reaction have been made [20–23]. However, far less attention has been devoted to phosphine-free nitrogen-based catalysts such as imines, imidazoles, pyrazoles, or 1,2,3-triazoles, even though nitrogen-based catalysts have also proved to be efficient catalysts for C–C and C–N bond-forming reactions [24–29].

The use of pyrazole (*pz*) ligands is interesting due to their straightforward preparative chemistry that includes modification of the substituents as well as the linkers that hold the pyrazolyl moieties together. The nature of substituents affects the nucleophilicity of the nitrogen atoms and hence the strength of bonding to the coordinated metal. Thus, the overall electrophilic nature of the metal complex can be fine tuned by the suitable choice of *pz*'s substituents, linkers, or both [30–34].

Recently, we have successfully developed Pd-catalysts for the Heck reaction containing pyridylpyrazole ligands; the most efficient catalyst were the ones in which the pyrazole ring has a hydroxyethyl substituent in the *N1*-position ([PdCl$_2$(L)]) (*L* = 2-(5-phenyl-3-pyridin-2-yl-pyrazol-1-yl)ethanol) [35]. In this case, the presence of an OH group in the ligand favours the Pd–X dissociation, due to the further stabilization of the resulting cationic complex.

As an extension of our work, we have recently reported the synthesis and characterization of several 3,5-dimethylpyrazolic hybrid ligands the reactivity of them with Pd^{II} and other M^{II} transition metals has also been studied [36,37]. The aim of our research work is to develop an efficient catalyst system for the cross-coupling of aryl halides with both activated (electron-deficient) and deactivated (electron-rich) alkenes, and study the effect provoked by the different ligands in the catalytic activity.

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In this paper we describe the study of the catalytic activity of several Pd^{II} complexes in the Heck reaction with the main objective of checking the influence of the linkers between the pyrazole rings.

2. Experimental

All experiments were carried out under an inert atmosphere using standard Schlenk-type techniques. The quantification of the catalytic reaction was carried out using a Hewlett Packard HP5890 gas chromatograph equipped with a flame ionization detector (FID), and a Hewlett Packard HP-5 column (30 m long, 0.32 mm internal diameter and 0.25 mm film thickness). The stationary phase consists of 5% diphenyl/95% dimethyl polysiloxane. Complexes 1 [37], 2, 3, and 4 [36] were prepared according to the literature methods. NMR spectra were recorded on a Bruker DPX-300 spectrometer. Chemical shifts are referenced to an internal Me$_4$Si standard for ^{1}H and ^{13}C NMR.

### 2.1. General procedure for the Heck-type coupling reactions

Prescribed amount of base (1.4 equiv), alkene (1.5 equiv), aryl halide (1.0 equiv) and decane (GC internal standard) were placed in a round bottom flask under a dry nitrogen atmosphere with a magnetic stirring bar. A solution of the palladium complex (2 mL) was added through a rubber septum and the resulting mixture was heated to the prescribed temperature until reaction completion. The reaction mixture was then cooled to room temperature. After extraction with CH$_2$Cl$_2$ (3 × 20 mL), the combined organic phases were dried over MgSO$_4$. The solvent was evaporated and a crude product analyzed by GC. The cross-coupling products were characterized by their ^{1}H NMR or GC analysis.

3. Results and discussion

We have previously reported the synthesis and characterization of the ligands 1,8-bis(3,5-dimethyl-1H-pyrazol-1-yl)-3,6-dioxaoctane (L1) [37], 1,2-bis[4-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxabutyl]benzene (L2), 1,3-bis[4-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxabutyl]benzene (L3), and 1,4-bis[4-(3,5-dimethyl-1H-pyrazol-1-yl)-2-oxabutyl]benzene (L4) [36] (Scheme 1a). These ligands and their corresponding complexes [PdCl$_2$(L)] (L = L1 (1), L2 (2), L3 (3) and L4 (4)) were prepared in good yields using the method previously described in the literature by our research group (Scheme 1b) [36,37].

Complexes 1–4 have been used as pre-catalysts in the Heck reaction between phenyl halides and tert-butyl acrylate. A characteristic of these complexes is the thermal stability, which makes it possible to perform the reactions even at temperatures above 140 °C. In some cases, the reaction has also been studied using styrene as the olefin. The reaction progress was analyzed by gas chromatography (GC). The use of complexes 1–4 for the Heck olefination of aryl halides gives rise exclusively to the formation of trans-acrylic acid esters (^{1}H NMR). These complexes were not sensitive to oxygen or moisture; no change in their efficiencies was observed even if the Heck coupling reactions were carried out under aerobic conditions. During the reaction, a black solid precipitated from the reaction mixture. This solid was identified as Pd^0 through the mercury poisoning test [38]. The results of the catalytic Heck olefination of aryl iodides, bromides and chlorides using complexes 1–4 are summarized in Table 1.

Preliminary catalytic studies of complexes 1 and 2 in the Heck reaction between iodobenzene and tert-butyl acrylate at 140 °C (bath temperature) and with triethylamine (Et$_3$N) as base in dimethylformamide (DMF) showed that they have similar efficiencies (entries 1–4). We have found that complexes 1 and 2 are more effective catalysts than classical Pd^{II} salts (even PdCl$_2$ is an
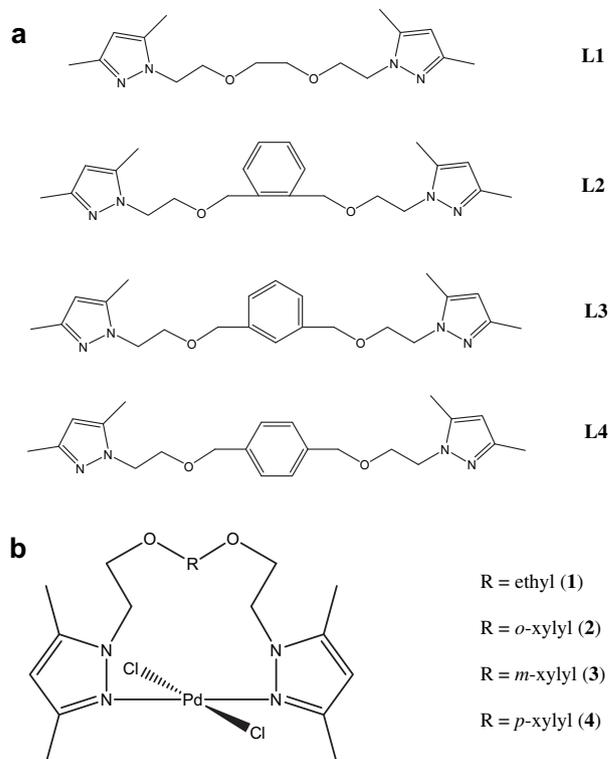
Scheme 1.

active catalyst for the Heck reactions when aryl iodides are used). It is worthy to note that the normally inactive styrene can also proceed the cross-coupling reaction smoothly under the same reaction conditions to afford the cross-coupled products in quantitative yields (entries 5–6). However, the reaction time has to be prolonged to get a complete conversion. Otherwise, the use of bromobenzene as reagent yields slightly lower results (entry 7–8), especially for complex 2 (entry 9–10). However, it is remarkable that complex 1 has a better catalytic activity than complex 2. This behaviour may be explained by the higher flexibility exhibited by L1 (its square planar Pd^{II} complex is less distorted) [37].

For several years, aryl bromides and iodides have been preferably used as substrates in such reactions; aryl chlorides are transformed very sluggishly by standard palladium catalysts due to the strength of the C–Cl bond. There has been a growing interest in finding catalytic systems that can successfully catalyze cross-coupling reactions with aryl chlorides [39,40]. Therefore, in order to check the activity of complexes 1–4 and try to optimize the conditions of the reaction, we have chosen the reaction of chlorobenzene with tert-butyl acrylate as olefinic counterpart. Interestingly, we have found that complex 1 shows the bests catalytic results (entries 11–12) and no marked differences in the reactivity between complexes 2, 3, and 4 have been observed (entries 13–18). All these observations are in agreement with those published by our group for L1. This ligand has a major flexibility and versatility than their analogous because L1 is able to accommodate a wide range of metal coordination geometries (tetrahedral, cis/trans-square planar, or octahedral) [37]. In consequence, the presence of the phenyl group (linker) in the alkyl chain of the complex provokes an important decreasing effect in the catalytic activity. Moreover, there is no significant difference between the relative positions of the substituents in the phenyl ring (ortho, meta and para). In spite of that, complex 1 exhibits good catalytic results in the Heck reaction even for less reactive olefin such as styrene (entries 19–20) and these results are better than those obtained for complex 2 (entries 21–22).

Table 1
Heck coupling reaction[a] of Aryl Halides using Pre-Catalysts **1**–**4**.
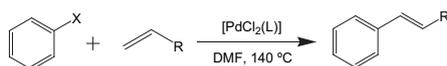
Entry	Ar-X	Catalyst[b]	mol %	R[c]	Base	t (h)	Yield[d] (%)	TON	TOF (h^{-1})
1	I	**1**	0.1	t-BA	Et$_3$N	0.05	100	1011	20226
2	I	**1**	0.01	t-BA	Et$_3$N	1.75	100	9708	5548
3	I	**2**	0.1	t-BA	Et$_3$N	0.25	100	1139	4677
4	I	**2**	0.01	t-BA	Et$_3$N	3	100	11234	3745
5	I	**1**	0.1	sty	Et$_3$N	0.35	100	991	2831
6	I	**1**	0.01	sty	Et$_3$N	9	100	9611	1068
7	Br	**1**	0.1	t-BA	Et$_3$N	2	93	942	496
8	Br	**1**	0.01	t-BA	Et$_3$N	12	75	7294	608
9	Br	**2**	0.1	t-BA	Et$_3$N	3.5	75	854	244
10	Br	**2**	0.01	t-BA	Et$_3$N	18	56	6252	347
11	Cl	**1**	0.1	t-BA	Et$_3$N	53	89	895	17
12	Cl	**1**	0.01	t-BA	Et$_3$N	60	71	6850	115
13	Cl	**2**	0.1	t-BA	Et$_3$N	29	34	395	14
14	Cl	**2**	0.01	t-BA	Et$_3$N	30	28	3126	104
15	Cl	**3**	0.1	t-BA	Et$_3$N	30	32	372	12
16	Cl	**3**	0.01	t-BA	Et$_3$N	35	26	2902	83
17	Cl	**4**	0.1	t-BA	Et$_3$N	29	31	353	12
18	Cl	**4**	0.01	t-BA	Et$_3$N	31	24	2680	86
19	Cl	**1**	0.1	sty	Et$_3$N	72	49	502	7
20	Cl	**1**	0.01	sty	Et$_3$N	25	32	3084	124
21	Cl	**2**	0.1	sty	Et$_3$N	33	28	326	10
22	Cl	**2**	0.01	sty	Et$_3$N	50	22	2456	49
23	Cl	**1** + 10 L1	0.1	t-BA	Et$_3$N	37	28	276	8
24	Cl	**1** + 10 L1	0.01	t-BA	Et$_3$N	51	31	2991	59
25[e]	Cl	**1′**	0.1	t-BA	Et$_3$N	23	25	255	11
26[e]	Cl	**1′**	0.01	t-BA	Et$_3$N	24	20	1930	80
27	Cl	**1**	0.1	t-BA	K$_2$CO$_3$	26	36	362	14
28	Cl	**1**	0.01	t-BA	K$_2$CO$_3$	22	28	2701	123

[a] Reaction conditions: 1.0 equiv of phenyl halide, 1.5 equiv of alkene, 1.4 equiv of base, 0.5 equiv of NBu$_4$Br, 5 mL solvent (DMF).
[b] See Scheme 1.
[c] Alkene: tert-butyl acrylate (t-BA) or styrene (sty).
[d] determined by GC, based on the phenyl halide using decane as internal standard.
[e] 1′ Catalytic complex generated "in situ". X = I, Br or Cl. L = L1–L4.

For this reason, we have carried out several reactions with complex **1** to examine the scope of the present catalyst system. Firstly, in order to check the influence of the excess of the ligand, we have added ten equivalents of the ligand to the catalytic system and the result was an important decreasing of the catalytic activity (entries 23–24); this effect could be due to the saturation of the metallic centre and, therefore, the lack of coordination vacancies. Another additional experiments consisted in generating "in situ" the catalytic complex adding at the same time the metallic precursor [PdCl$_2$(CH$_3$CN)$_2$] [41] and the **L1** ligand. Unfortunately, it also had a negative effect in the catalytic results (entries 25–26). In this case, it could be due to the low stability of the metallic salt in these extreme conditions (140 °C in DMF). Finally, we have studied the effect of the replacement of triethylamine by K$_2$CO$_3$. Once again, the effect of this change was not successful (entries 27–28).

4. Conclusions

In summary, we have demonstrated that the previously described air- and heat-stable Pd^{II} complexes **1**–**4** derived from N1-substituted 3,5-dimethylpyrazolic hybrid ligands could be effective catalysts under phosphine-free conditions for the Heck reaction. Moreover, we have checked the influence of the different linkers in each mixed ligand (**L1**–**L4**) and we have observed that the more flexible is the ligand, the better catalytic results are obtained. The most efficient catalyst is the one in which the linker between the two ether moieties is an ethyl chain (complex **1**). The advantages of this practical and efficient catalyst system include its generality and high catalytic activity even for aryl chlorides under mild and convenient conditions. Further studies aimed at the improvement of the catalytic activity of our nitrogen catalysts in the Heck reaction with wide substrate scope are currently in progress.

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