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Short Communication

Intermolecular phosphine-free Heck reactions: Amino alcohols as effective ligands

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1. Introduction

Over the past twenty years, we have studied the unichiral amino alcohol-mediated asymmetric protonation of enolic species produced under Pd-catalysis [1,2]. This led us to examine the interactions of palladium with amino alcohols, especially (-)-ephedrine (1) [3,4], and Heck reactions of allylic alcohols [4–6]. Here, we firstly rebut the proposal concerning the active catalytic species of Heck reactions carried out with *trans*-PdCl₂[NH(CH₂CH₂OH)₂]₂ (2) [7,8], and secondly, we disclose intermolecular phosphine-free Heck reactions occurring in the presence of catalytic amounts of both palladium acetate and amino alcohols.

2. Discussion and Results

In 2009, Petrović et al. reported the efficient Heck reaction, at 110 °C, between PhX (X = I, Br) and styrene or acrylate esters using **2** as the catalyst and HN(CH₂CH₂OH)₂ as a base and solvent [7]. The structure of **2** (Scheme 1) was demonstrated by X-ray crystallography [8]. On the basis of DFT studies, Petrović et al. assumed that the active species of their Heck reactions is the anionic complex [ClPdNH (CH₂CH₂OH)₂]⁻ (**3**, Scheme 1) [7,9,10]. According to the authors, the base-promoted elimination of one of the two *N*-ligands of **2** affords HOCH₂CH₂NHCH₂CHO and [HPdCl₂NH(CH₂CH₂OH)₂]⁻, reductive elimination from this complex leading to HCl and **3** [7,9,10]. The

ABSTRACT

Intermolecular phosphine-free Heck reactions occur in high yields, under basic conditions, using a catalytic mixture of $Pd(OAc)_2$ and a β -amino alcohol. It is assumed that the active catalytic species are *N*-liganded Pd^0 species. The recent mechanistic proposal, from Petrović et al., concerning Heck reactions catalyzed with $PdCl_2$ [NH(CH₂CH₂OH)₂]₂ is commented.

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team has also carried out theoretical studies on the interaction of **3** with phenyl iodide [11].

Even if calculations agree with the possible *in-situ* formation of **3** [7,9,10], we are not confident in the Petrović proposal of **3** as the active catalyst. Moreover, the authors wrote "the precatalyst *trans*-[PdCl₂ (DEA)₂] was recycled two times without significant loss in activity" [11]. DEA being the abbreviation used for diethanolamine, the back reaction $\mathbf{3} \rightarrow \mathbf{2}$ would, according to the authors, occur under their conditions. Experimental results from us and other teams, which are summarized below, are not in agreement with the formation of species such **3**.

We have prepared neutral palladium complexes **4**, **5** and **6** which have (–)-ephedrine or/and (–)-ephedrinate as ligand (Scheme 2) [3,4]. The formulas of **4** and **6** have been determined from their spectroscopic data and elemental analysis [3], *trans*-structure of **6** being assumed from calculations [4]. As for **5**, its structure has been determined from X-ray crystallography [3]. The van Koten team has identified various neutral bis-(*N*,*O*-ligated) Pd^{II} complexes **7** from the reaction of Pd(OAc)₂ and K₂CO₃ with amino alcohols (Scheme 3) [12]. Warad and co-workers have isolated, in quantitative yield, the chelate complex **8** from the reaction of PdCl₂ with 1,3-diaminopropan-2-ol (Scheme 4) [13]. Very recently, complexes **9** and **10** (Scheme 5), obtained from the reaction of L-prolinol with PdCl₂, have been characterized by X-Ray analysis [14].

The results depicted in Schemes 2 to 5 exemplify the reluctance towards oxidation of the hydroxyl group of amino alcohols in the presence of stoichiometric amounts of Pd^{II} species. In fact, the problematic Pd-mediated oxidation of β -amino alcohols is known [15]; this is likely due to the impossibility, from a (*N*,O)-ligated Pd^{II} complex, to reach the H-C-O-Pd *syn*-coplanarity required for a β -H elimination.

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Scheme 1. Active catalyst formed from PdCl₂[NH(CH₂CH₂OH)₂]₂ according to Petrović and coworkers.



Scheme 2. Neutral palladium complexes from PdX_2 (X = Cl, OAc) and (-)-ephedrine.

Given the experimental results shown in Schemes 2 (path *b*), 3 and 5, the reaction of **2** under basic conditions should afford the corresponding bis-(*N*,*O*-ligated) Pd^{II} complex rather than **3**. Furthermore, we suspect that the *N*-ligand of **3** will be also eliminated if the **2** \rightarrow **3** reaction would occur. In fact, the claimed formation of HOCH₂CH₂NHCH₂CHO from **2** has not been demonstrated [7,9].

We have used a 1:2 mixture of $Pd(OAc)_2$ and cinchonine as the catalytic system and NaHCO₃ as the base to synthesize 2-substituted-1-indanones via the 5-*endo-trig* cyclisation of 1-(*o*-bromoaryl)-2-substitued-prop-2-en-1-ols [4]. The Petrović experimental conditions are rather similar to ours, a β -amino alcohol (either diethanolamine or (–)-ephedrine and cinchonine) being used by both teams. This urged us to compare the efficiency of both procedures (Scheme 6 and Table 1). The Pd(OAc)₂/cinchonine/NaHCO₃ association led to higher yields than the **2**/HN(CH₂CH₂OH)₂ system for the coupling of phenyl iodide with either styrene or ethyl acrylate (Entries 1 and 2). The use of (–)-ephedrine instead of cinchonine afforded similar results (Entries 3 and 4). In contrast, the reaction of phenyl bromide with styrene was more effective under Petrović's conditions (Entry 5).

This study was completed by the analysis, using a LC/MS apparatus, of the crude reaction mixture obtained from the reaction of styrene with phenyl iodide (1 equiv.) in the presence of $Pd(OAc)_2$ (0.05 equiv.), (–)-ephedrine (0.1 equiv.) and NaHCO₃ (1.1 equiv.) in DMF at 120 °C for 20 h. It appeared that (–)-ephedrine survived to these conditions. Moreover, no degradation compound of this amino alcohol was detected. Consequently, we suspect that HOCH₂CH₂-NHCH₂CHO is not formed from **2** under Petrović's experimental conditions.

It has been proposed that Pd^{IV} intermediates could be involved in Heck-type reactions [16], but it is admitted that they usually occur



Scheme 3. Neutral bis-(N,O-ligated) Pd^{II} complexes from Pd(OAc)₂ and amino diols.

through only Pd⁰ and Pd^{II} intermediates, even when the starting catalyst is a Pd^{II} salt or complex [17,18]. The literature contains reports on the Pd^{II} \rightarrow Pd⁰ reduction in the presence of amines [19,20] or C = C bonds [21], and on *N*-ligated Pd⁰ complexes [22]. Moreover, the stabilization of Pd nanoparticles by a diamine gel-type polymer containing a secondary hydroxy unit [23], and of active Pd⁰ species by the *N*,*O*-bidentate ligand formed in situ via hydrogen bonding between DMF and EtOH [24] has been recently disclosed. This leads us to presume that the Heck reactions carried out with **2**, **6** or Pd (OAc)₂/**1** are catalyzed by *in-situ* produced *N*-ligated Pd⁰ complexes.

In conclusion, the Pd^{II}/ β -amino alcohol systems are effective catalysts for phosphine-free Heck reactions [25]. We assume that their efficiency is due to the stabilization or/and activation of Pd⁰ species by *N*-ligands. This agrees with Petrović's proposal, but the active catalyst would not be, under their conditions, an anionic species such as **3** [26].

3. Experimental

To a mixture of $Pd(OAc)_2$ (11 mg, 0.05 equiv.), (+)-cinchonine (30 mg, 0.1 equiv.) or (-)-ephedrine (18.2 mg, 0.1 equiv.) and NaHCO₃ (92 mg, 1.1 equiv) under an argon atmosphere was added a solution of **9** (1 mmol) and **10** (1 to 1.05 mmol) in DMF (2 mL). The mixture was heated at 120 °C with an oil-bath for 16 h. After cooling to room temperature and addition of diethyl ether, the mixture was filtered over a small pad of Celite. The filtrate was successively washed with water and brine, then dried over MgSO₄. After elimination of the solvent, **11** was isolated by flash-chromatography (hexane/ethyl acetate = 9:1). The adducts have been identified from their NMR spectra.



Scheme 4. Chelate complex from PdCl₂ and 1,3-diaminopropan-2-ol.



Scheme 5. Neutral palladium complexes from PdCl₂ and L-prolinol.



Scheme 6. Palladium-catalyzed intermolecular phosphine-free Heck reactions.

Table 1 Heck reactions.^a

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	Entry	9	10	Amino alcohol	Product	Yield % ^{a,b}	Yield % ^{b,c}
	1	9a	10a	(+)-cinchonine	11a	89	75
	2	9a	10b	(+)-cinchonine	11b	98	80
	3	9a	10a	(-)-ephedrine	11a	83	75
	4	9a	10b	(-)-ephedrine	11b	98	80
	5	9b	10a	(+)-cinchonine	11a	43	82

^a Isolated yield under conditions depicted in Scheme 6.

^b Only the *trans* product was detected from ¹H NMR analysis.

^c Isolated yield at 110 °C using **2** as the catalyst and HN(CH₂CH₂OH)₂ as the base [7].

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