Alkyne hydroarylation with palladium(II) complexes bearing chelating N-heterocyclic ligands: effect of non-coordinated nitrogens on catalyst efficiency

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Palladium(II) complexes with chelating N-heterocyclic ligands bearing uncoordinated nitrogen atoms are efficient catalysts in the hydroarylation of alkynes, giving selectively *trans*-hydroarylation of the triple bond. The catalytic efficiency of these systems is markedly dependent on the strength of the acid added as reaction promoter, thus suggesting the formation, *via* ligand protonation, of highly electrophilic metal intermediates, which are responsible for the observed selectivity.

Introduction

The coupling reaction of aromatic rings with alkynes currently stands out as one of the most promising C–H bond activation–functionalisation reactions from a technological point of view.[1,2] Products of formal *trans*-hydroarylation of the triple bond are, in fact, obtained, starting from cheap, unfunctionalised and commercially available reagents. This reaction is usually catalysed by simple palladium salts, like palladium(II) acetate, in a strong acidic medium, and gives selectively the thermodynamically less favoured *cis*-arylalkene.[3] Other noble metal centres, such as platinum(II),[4] gold(I) and gold(III),[5] as well as non-noble metal salts and complexes[6] have been successfully employed as alternative catalysts, but their applicability appears to be more limited than that of palladium(II).

Recently, we have found that N-heterocyclic dicarbene palladium(II) complexes exhibit a very high activity and selectivity in this reaction under very mild conditions.[7] The catalytic cycle presumably involves an electrophilic activation of the substrates upon interaction with an electron-poor palladium centre.[8]

With this basic point in mind we have tried to tune the charge density on the metal by using coordination sets bearing chelating N–N or C–C ligands containing non-coordinated nitrogen atoms.

Complexes of this kind, particularly those containing the bipyrimidine ligand, have already proven useful as electrophilic catalysts in strongly acidic environments; for example the platinum(II) complex analogous to **1** in Fig. 1 is able to catalyse the oxidation of methane to methanol in oleum.[9,10]

It has been proposed that the high catalytic efficiency of these catalysts under acidic conditions might be related to the protonation of the ligand nitrogen atoms, not involved in the coordination to the metal centre; this hypothesis has been mainly investigated by DFT calculations,[11] although studies on the Pt(II) bipyrimidine complex in strong acidic media (like HF–SbF_5)[12] or on Ru(II) complexes seem to confirm it.[13] The nitrogen protonation should decrease the electron-donating ability of the coordinated ligands and indeed create highly electrophilic metal species.

In this contribution we report the results obtained in the hydroarylation of ethyl propiolate using the palladium(II) catalysts **1–3** and we compare their catalytic efficiency and selectivity with that of our reference complex **4**.

Results and discussion

The bipyrimidine complex **1** catalyses the reaction between pentamethylbenzene and ethyl propiolate (Scheme 1) with an efficiency which strongly depends on the employed acid. Under our standard optimised conditions[7] ([reagents] *ca.* 2.1 M, 0.1 mol% Pd complex, 0.2 mol% AgX salt, [HX] 2.1 M, 1,2-dichloroethane, room temperature) the hydroarylation reaction does not occur in trifluoroacetic acid. An increase in the acid/arene molar ratio from 1/1 to 4/1 has no effect and only at 80 °C does the complex show a moderate catalytic activity (62% conversion after 48 h), inferior to that displayed by the dicarbene complex **4** at room temperature under otherwise identical reaction conditions. In addition, the selectivity towards the *trans*-hydroarylation product **a** exhibited by complex **1** is lower compared with complex **4** (65% *versus* 96% after 48 h), because of the concurrent formation of the double insertion product **c** and especially of the isomeric *E* olefin **b**.

Complex **1** is instead active at room temperature using stronger acids, like triflic or tetrafluoroboric acid (Fig. 2). The initial activity of the catalytic system in triflic acid (Fig. 2, open squares) is markedly higher than the one in tetrafluoroboric acid (Fig. 2, filled squares), although the conversions with both acids tend to reach similar values for long reaction times, and are even slightly higher than that shown by dicarbene complex **4** with the same acid (Fig. 2, open circles). The efficiency of the bipyrimidine complex **1** in different HX acids appears directly correlated with their strength: HTFA

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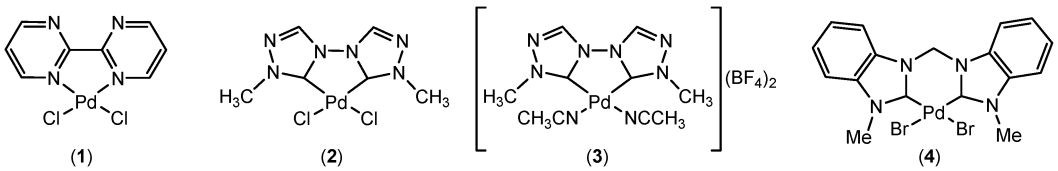
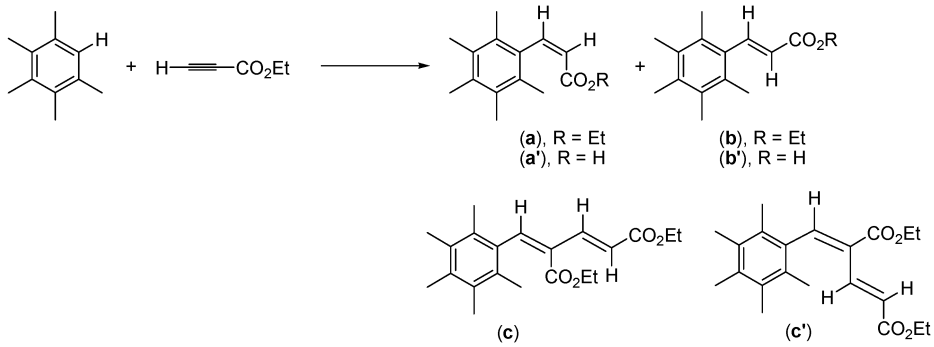


Fig. 1 Complexes **1–4**.



Scheme 1 Hydroarylation reaction between pentamethylbenzene and ethyl propiolate.

($pK_a = -0.25$) < HBF_4 ($pK_a = -4.9$) < HOTf ($pK_a = -14$). A reasonable explanation for the observed behaviour takes into account the different abilities of the investigated acids to protonate one of the two non-coordinated nitrogen atoms of the bipyrimidine ligand. The protonation of the bipyrimidine ligand, together with the substitution of the two halide ligands with weakly coordinating anions, such as OTf^- and BF_4^-, generates an almost "tricationic" Pd(II) complex, highly electrophilic and therefore more active in the hydroarylation reaction.[8] An indirect proof that this mechanism is operational is provided by the observation that the dependence of the catalytic activity on the strength of the employed acid is much more pronounced with complex **1** than with complex **4**, which exhibits a good catalytic activity already with trifluoroacetic acid but only small differences of reactivity between tetrafluoroboric and triflic acid.

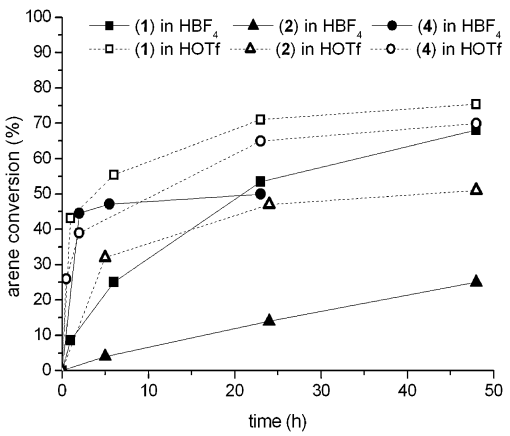


Fig. 2 Conversion (%) *vs.* time curves for the hydroarylation of pentamethylbenzene and ethyl propiolate catalysed by complexes **1**, **2** and **4**[7a] with the addition of AgX, in different HX acids. Reaction conditions: arene (13.2 mmol), palladium(II) complex (0.013 mmol), AgX (0.026 mmol), HX acid (13.2 mmol), alkyne (13.2 mmol) and 1,2-dichloroethane, 25 °C.

The selectivity of the hydroarylation process is also an important issue in the development of novel catalytic systems for this reaction. Indeed, we[7a] and others[14] have very recently shown that the hydroarylation reaction can be controlled to produce mainly the single or the double insertion product (products **a** or **c** in Scheme 1, respectively) by choosing an appropriate chelating ligand[14] and/or by changing the reaction conditions. In particular, we have shown that with HBF_4 as the acid the dicarbene complex catalyst **4** yields almost exclusively the double alkyne insertion product;[7a] consequently, the reaction stops at about 50% arene conversion when using equimolar quantities of arene and alkyne (Fig. 2, filled circles).

In this respect, the behaviour of the bipyrimidine catalyst **1** is completely different; while complex **4** forms preferentially the double insertion product **c** (85% selectivity after 48 h), the bipyrimidine complex **1** is selective towards the *Z* olefin (**a** + **a**′) (97% selectivity after 48 h) (Fig. 3). Even after decreasing the arene/alkyne molar ratio from 1/1 to 1/2 in the case of complex **1** we did not observe any change in selectivity but only a slight increase in the initial reaction rate.

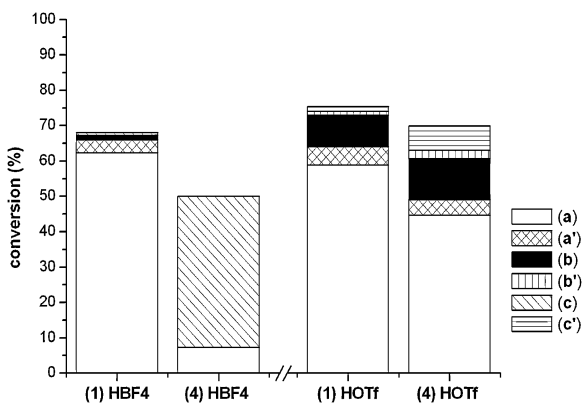
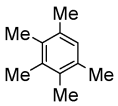
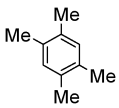
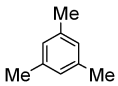


Fig. 3 Yields (%) of the reaction products after 48 h in the hydroarylation reaction between pentamethylbenzene and ethyl propiolate catalysed by complexes **1** and **4** in the presence of 2 equiv. AgX in HX.

Table 1 Arene screening in the hydroarylation reaction of ethyl propiolate catalysed by complex **1** with added $AgBF_4$ in HBF_4

Entry	Arene	Time/h	Conversion[a]	Yield[b] **a**	Yield[b] **c**
1		6	25	25	0
		23	53	50	1
		48	68	62	1
2		5	7	7	0
		24	18	18	0
		48	20	20	0
3		5	24	24	0
		24	34	25	9
		48	50	42	5

[a] Conversion based on the arene. [b] % yield determined by GC-MS and/or ^{1}H-NMR. Reaction conditions: arene (13.2 mmol), alkyne (13.2 mmol), complex **1** (0.013 mmol), $AgBF_4$ (0.026 mmol), HBF_4 (13.2 mmol), 1,2-dichloroethane, 25 °C.

The selectivity exhibited by complex **1** in HBF_4 towards product **a** has been evaluated with respect to the arene (Table 1). Complex **1** (0.1 mol%) in the presence of $AgBF_4$ (0.2 mol%) was used under standard reaction conditions.

The *trans*-hydroarylation product **a** was the almost exclusive product with all employed substrates. The prevalent by-products of the reaction were the hydrolysed product of the ester function **a′** and the double insertion product **c**.

The selectivity exhibited by complexes **1** and **4** in HOTf is instead similar, in that they both give mainly the *trans*-hydroarylation product (**a** + **a′**) during the first hours of the reaction (94% for **1** *vs.* 87% for **4**). For prolonged reaction times (48 h) in both cases the selectivity decreases (85% for **1** *vs.* 70% for **4**) because of acid induced isomerisation of the double bond (Fig. 3).

We then moved to investigate the reactivity of the dicarbene complexes **2** and **3**, which differ only by the replacement of the chloride ligands by two neutral acetonitrile molecules.[15] It is expected that complex **2** in the presence of 2 equivalents of AgX salt undergoes halide removal, thereby exhibiting a catalytic efficiency rather similar to that of complex **3** without silver additives. This is confirmed by the conversion data in Table 2. Both complexes are active at room temperature using an arene/acid molar ratio of 1/1 and, once more, their efficiency depends on the acidity of the employed acid. The best performance, both at short and long reaction times, is indeed registered in triflic acid, which is the strongest acid compared with tetrafluoroboric and trifluoroacetic acid. However, in general the efficiencies of these complexes are lower than that displayed by complexes **1** or **4** under the same experimental conditions (for comparison see Fig. 2, filled and open triangles).

Regarding the selectivity at 48 h, complexes **2** and **3** are always selective towards the *trans*-hydroarylation product (90–95% selectivity in HTFA, respectively, 100–75% in HBF_4 and 70–69% in HOTf); the low figure recorded in triflic acid is due to the strong acidic environment, which promotes *cis–trans* olefin isomerisation.

Table 2 Conversion (%) for the hydroarylation of pentamethylbenzene and ethyl propiolate catalysed by complexes **2** and **3** with the addition of AgX, in different HX acids.

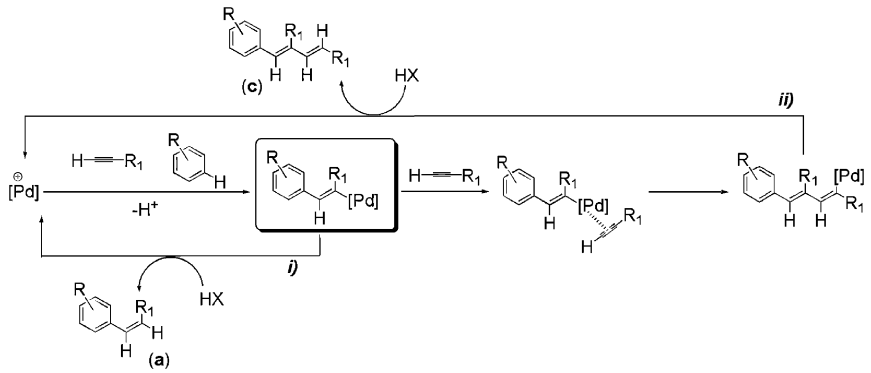
Catalyst	Time/h	Conversion[a] HTFA	Conversion[a] HBF_4	Conversion[a] HOTf
2	4	1	4	32
	24	12	14	47
	48	21	25	51
3	5	2	4	24
	24	13	11	36
	48	24	24	43

[a] Conversion based on the arene; % yield determined by GC-MS and/or ^{1}H-NMR. Reaction conditions: arene (13.2 mmol), palladium(II) complex (0.013 mmol), AgX (0.026 mmol, no silver salt was added in the catalytic tests with complex **3**), HX acid (13.2 mmol), alkyne (13.2 mmol), 1,2-dichloroethane, 25 °C.

Remarkably, the selectivity observed with complexes **1–3** in tetrafluoroboric acid is completely inverted with respect to the one obtained with complex **4** under the same experimental conditions.

The whole of these results gives important information on the factors influencing the catalytic efficiency and selectivity of this complex reaction, and can be discussed in the light of the simplified reaction mechanism outlined in Scheme 2. Complexes **1**, **2** (and **4**) in the presence of AgX salt and the related HX acid give the real metal catalysts with composition $[Pd(L–L)X_{2-n}(Solv)_n]^{n+}$, where the number of solvent molecules and resulting charge of the complex depends on the coordinating ability of X. This is simplified in Scheme 2 by indicating a +1 charge just to show the necessity of an electrophilic metal centre. At the same time the negligible activity exhibited by complex **1** at room temperature in trifluoroacetic acid indicates that the neutral bipyrimidine ligand is a much worse ligand compared with the dicarbene ones. The situation is reversed in stronger acids like HBF_4 and HOTf, where most likely protonation of the bipyrimidine ligand occurs leading to more electrophilic metal intermediates. A reasonable explanation for the different selectivity exhibited by the "protonable" complexes **1–3** and by **4** is at the moment rather speculative.

The course of the reaction is determined by the fate of the palladium(II)–vinyl intermediate, whose evolution is responsible for the formation of the two different products **a** (Scheme 2, path i) and **c** (Scheme 2, path ii). Path ii requires coordination of an alkyne moiety, which can be influenced by steric and electronic factors. Regarding the former, both bipyrimidine and 1,1′-dimethyl-4,4′-bi-1,2,4-triazol-5,5′-diylidene ligands lie on the plane defined by the palladium centre and the other two coordination sites. On the other hand, the two carbene units in dicarbene complexes similar to **4** form an angle α of 45–49° with the same plane (α for complex **3** is 1.5°).[16] It results that from the steric point of view, path ii should be more favored in complexes **1–3** if coordination of the incoming alkyne occurs along the *z*-axis. This assumption is very reasonable, in fact it is well known, for example, that substitution reactions in square-planar complexes of Pd(II) and Pt(II) imply the formation of a pentacoordinate intermediate



Scheme 2 Formation and possible evolution of Pd–vinyl intermediate.

via interaction of the incoming ligand with the p_z metal orbital. However, since complexes **1–3** do not react along path ii, electronic rather than steric effects are likely to be responsible for the observed chemoselectivity. In particular, the interaction along the *z*-axis is expected to be stronger with more electron-rich, softer metal centres and this may explain the prevalence of path ii with the complex bearing the more basic ligand 1,1′-dimethyl-3,3′-methylene-dibenzimidazolin-2,2′-diylidene.[15,17] The prevalence of electronic factors explains also why the simple palladium(II) acetate, which should be the least hindered and electron-rich catalyst, gives selectively only the *trans*-hydroarylation product **a**.[7a]

Experimental

General comments

All manipulations were carried out using standard Schlenk techniques under an atmosphere of argon or dinitrogen. The reagents were purchased by Aldrich as high-purity products and generally used as received. Complexes **1**,[18] **3**[15] and **4**[7c] were prepared according to literature procedures. All solvents were used as received as technical grade solvents. NMR spectra were recorded on a Bruker Avance 300 MHz (300.1 MHz for ^{1}H and 75.5 for ^{13}C).

Synthesis of complex 2

NaCl (31 mg, 0.53 mmol) was added to a solution of complex **3** (140 mg, 0.26 mmol) in acetonitrile (10 mL). The mixture was stirred at room temperature for 24 h, giving a bright yellow solid, which was filtered, washed several times with acetonitrile and finally dried under vacuum (73% yield). The solid was practically insoluble in most common organic solvents, thus preventing a NMR characterisation. Anal. calc. for $C_6H_8Cl_2N_6Pd$ (M = 341.49): C, 21.10; H, 2.36; N, 24.61%. Found: C, 20.55; H, 2.16; N, 23.92%.

General procedure for the catalytic tests

The arene (13.2 mmol, if solid), the palladium(II) complex (0.013 mmol) and the proper silver salt AgX (0.026 mmol, no silver salt was added for the catalytic tests with complex **3**) were placed in a 100 mL round bottomed flask, previously evacuated and filled with argon. The HX acid (13.2 mmol), 1,2-dichloroethane (the quantity necessary to reach a total volume of 6.3 mL) and the arene (if liquid) were then added and the resulting solution was stirred at 25 °C for 5 min. Finally the alkyne (13.2 mmol) was added and the reaction mixture was further stirred at 25 °C for the time indicated in the tables. Portions of the solution (0.2 mL) were drawn off from the reaction mixture and analysed by ^{1}H-NMR or GC-MS.

Conclusions

Palladium(II) complexes with chelating ligands bearing uncoordinated nitrogen atoms are good catalysts in model hydroarylation reactions. The catalytic efficiency of these systems increases with the strength of the acid additive; this effect has been previously observed with chelating dicarbene palladium(II) catalysts and attributed to an acceleration of the proton attack on the palladium(II)–vinyl intermediate to release the arylation product. In the complexes under study, though, a much more marked dependence of the catalytic activity on the strength of the acid additive is recorded, which appears most likely related to the protonation in strongly acidic media of the uncoordinated nitrogens to afford more electrophilic metal complexes. Most importantly, the new set of bidentate ligands allows the selectivity of the catalytic system to be modified, so that complexes **1–3** display in HBF_4 a high selectivity towards the *Z* olefin **a**, in stark contrast with the results observed with our reference dicarbene catalyst **4** and related N-heterocyclic dicarbene palladium(II) complexes bearing different substituents at the nitrogen atoms and a variety of bridging groups between the carbene units.[19] We are currently exploring this behaviour through DFT calculations, investigating the role played by the electronic and steric properties of the chelating ligand in determining these different selectivities.

Acknowledgements

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