

Hydroamination of methyl methacrylate catalyzed by cationic palladium diphosphinoazine complexes

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Abstract

Hydroaminations of methyl methacrylate with pyrrolidine and piperidine were found to proceed without a catalyst under mild conditions. Hydroamination with morpholine catalyzed by cationic palladium diphosphinoazine complexes was studied at temperatures 20–80 °C with catalyst loadings 0.1–1.05 mol%. Yields up to 91% were achieved and the promotion of the catalysis by triflic acid or its silver salt established. The influence of the phosphorus substitution in the diphosphinoazine on the catalytic activity was also observed.

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1. Introduction

Intermolecular addition of N–H bonds across carbon–carbon multiple bonds known as hydroamination received great deal of attention recently because being a 100% atom-economy reaction it allows direct access to amines which are important end-products or intermediates in organic chemistry. Several excellent reviews were published [1–4], reflecting the difference between hydroamination of alkenes and alkynes [5] and also the difference between hydroamination and related oxidative amination reaction. The differences between intra- and intermolecular variants of the hydroamination were not usually clearly cut though it is apparent on the basis of entropic arguments that the former reaction is more facile. A personal account of one group's research has also appeared [6].

While not attempting to repeat the information from those reviews here, important recent developments will be summarized to show the focus of this paper.

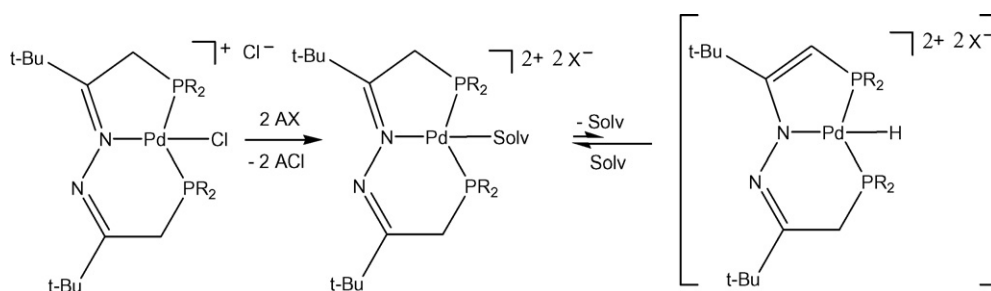
Hydroamination is known to be catalyzed by early transition metal complexes, lanthanide complexes and late transition metal complexes, especially of Groups 9 and 10. Owing to the known tolerance of functional groups, characteristic of the catalysts based on late transition metals, many newly devel-

oped catalysts [7–9] concentrate on them. The breakthrough in hydroamination of alkenes came in 2000 when Hartwig et al. [10] published intermolecular reaction of vinylarenes with arylamines using palladium phosphine complexes either with a noncoordinating triflate counterion or in the presence of triflic or trifluoroacetic acids as cocatalysts. Alkylamines could also react under Hartwig's conditions [11] although at higher catalyst loadings (5% versus 2% with arylamines). Dppf (1,1'-bis(diphenylphosphino)ferrocene) was the ligand of choice in both cases. The addition took place in anti-Markovnikov fashion and strong evidence both computational [12] and experimental [13] (through isolation and reactions of intermediates) was brought forward to support the intermediacy of a η^3 -phenethyl palladium complex. The mechanism started with the formation of a Pd(II) hydride which afterwards coordinated an alkene. Then insertion of the alkene led to an η^3 -phenethyl complex followed by the external nucleophilic attack of an amine. The liberation of the product simultaneously regenerated the hydride.

Palladium complexes with sterically hindered PCP and PNP ligands were found to catalyze the hydroamination of primary and secondary alkylamines with more activated alkenes—the acrylic Michael type acceptors [14]. In this case, carrying out the reaction at room temperature for 8–18 h was sufficient except in reactions of aniline with acrylic nitriles, which required 100 °C.

Dicationic (diphosphine)palladium complexes were also found to catalyze the hydroamination of secondary alkyl and cycloalkyl as well as benzylic and aromatic amines to acrylic-

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Scheme 1.

type alkenes [15]. More forcing conditions were necessary for the reactions of vinylarenes with substituted anilines but isolated yields were in most cases very good; the best phosphine was again dppf. The same catalytic reaction in an enantioselective variant [16] (BINAP ligand) gave with certain anilines e.e.'s as high as 93%.

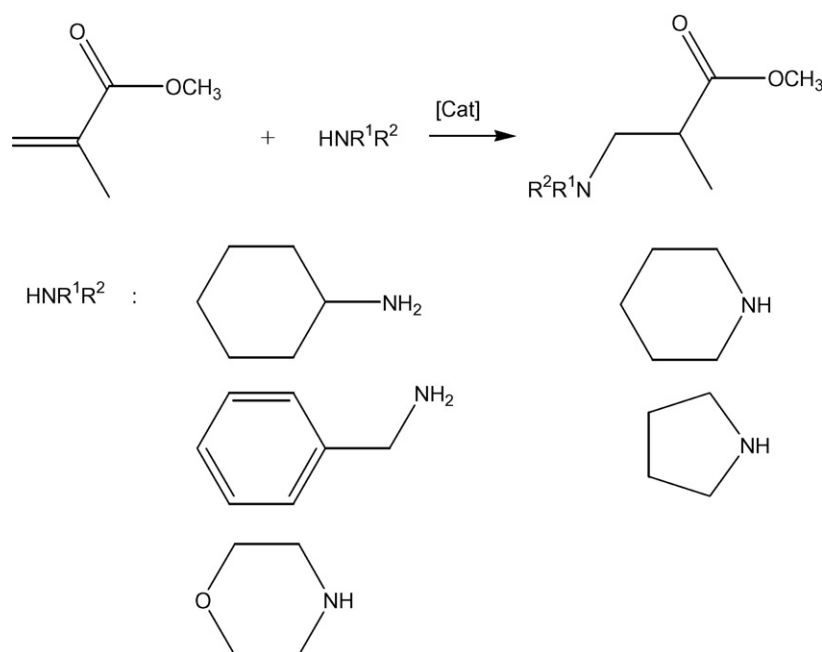
We recently published [17] synthesis of cationic palladium complexes with PNP-coordinated diphosphinoazines as precursors for the synthesis of Pd(II) amido complexes. However, the cationic complexes themselves may be considered as source of the hydride coming from the ligand backbone [18], if both halogen atoms can be removed from the coordination sphere of palladium (Scheme 1, X = noncoordinating anion). The formulation of the hydride transient species in a Pd(IV) oxidation state is still speculative. However, recent study of XANES spectra of several series of palladium complexes with didentate phosphines of varied bite angles [19] has shown the effective oxidation state of palladium to be strongly dependent on the bite angle, the bite angles of *trans*-phosphines in our complexes reaching values around 165°. Recently, the first stable Pd(IV) complex was reported, containing two orthometallated 2-arylpyridine ligands [20]. Since a palladium hydride is supposed to be the species

starting the hydroamination catalytic cycle (see above) we reasoned that the cationic diphosphinoazine palladium complexes may catalyze the reaction.

2. Results and discussion

2.1. Hydroaminations without a palladium catalyst

Although simple nonactivated alkenes undergo hydroamination [7,21], carrying out the reaction under reasonably mild conditions (<120 °C, ambient pressure) requires alkenes activated by electron-withdrawing substituents. Both vinylarenes and acrylic type substrates contain activated double bonds, the latter are considerably more reactive, however. Since there are some indications in the literature [15] that such alkenes do react in hydroamination without a catalyst we decided first to verify the fact in more detail. Methyl methacrylate was chosen as a typical acrylic substrate and reacted under stirring with several secondary and primary amines (Scheme 2, no [Cat] used). The results (Table 1) showed considerable reactivity of some of the amines with methyl methacrylate without a catalyst. Quantitative yields of the anti-Markovnikov pyrrolidine adduct



Scheme 2.

Table 1
Uncatalyzed methyl methacrylate hydroamination

Substrate	Temperature (°C)	Reaction time (h)	Yield (%)
Cyclohexylamine	20	70	4
Benzylamine	20	70	6
Morpholine	20	69	2.3
Pyrrolidine	20	70	100
Piperidine	60	20	71
Pyrrolidine	60	19.3	99.5
Morpholine	80	20.5	1.5

were achieved, piperidine was somewhat less reactive. Cyclohexylamine and benzylamine are much less reactive whereas morpholine could be considered practically unreactive. The differences in the amine reactivity were previously ascribed to the great sensitivity of the hydroamination reaction to the differences in the amine basicity [21,22]. Comparison of our results with the data on the amine basicity in dilute aqueous solutions [23] showed strongly nonlinear correlation of the reactivity; the basicity of pyrrolidine (pK_a of the conjugate acid 11.27) is slightly higher than that of piperidine (11.12) whereas the morpholine basicity is appreciably lower (8.23). Benzylamine (9.33) and especially cyclohexylamine (10.66) are more basic than morpholine and their reactivities were in between those of piperidine and morpholine.

The blank experiments had shown morpholine to be the substrate of choice owing to its low activity in the uncatalyzed

reaction of the acrylic substrates, therefore most of our catalytic hydroamination experiments used this amine.

2.2. Catalyzed hydroaminations

Four cationic diphosphinoazine complexes (**1–4**) were employed as methyl methacrylate hydroamination catalysts.

2.2.1. Structures

The reactions (Table 2) gave exclusively the same anti-Markovnikov product as was provided by other palladium catalyzed hydroaminations [15] and by the uncatalyzed reaction as well. Comparison of the catalyzed and uncatalyzed runs with morpholine as a substrate showed pronounced increase of reaction yields of the former runs at all reaction temperatures, documenting thus the true catalytic effect of palladium complexes. In the literature, especially that dealing with comparably less reactive vinylarene substrates, catalyst loadings as high as 10 mol% can be found [10] which, with some catalysts having molecular weights 5–7 times higher than those of substrates, means more than 50 wt.% of palladium catalyst used. On the other hand, with acrylic substrates like methyl methacrylate catalyst loadings cannot decrease too much in attempt of testing the catalyst robustness and obtaining the highest possible TON because product yields are not negligible without a catalyst after long reaction times. For example, even if the uncatalyzed methyl methacrylate hydroaminations by pyrrolidine

Table 2
Hydroamination of methyl methacrylate with morpholine

Entry	Catalyst	Amine/catalyst	Cocatalyst/catalyst	Temperature (°C)	Reaction time (h)	Yield (%)
1	1	100	–	20	21	2
2	1	200	–	60	20	14
3	1	952	–	80	22.5	40
4	1	105	2.68 ^a	20	21	23
5	1	488	1.95 ^a	80	17.5	55
6	1	105	1.05 ^b	20	21	11
7	1	200	1.0 ^b	80	20	32
8	2	200	–	20	22.5	1
9	2	217	–	60	20	8
10	2	100	–	80	20.5	17
11	2	182	2.18 ^a	20	22.5	13
12	2	105	2.34 ^a	80	4.5	18
13	2	105	2.34 ^a	80	20.5	57
14	2	95	0.81 ^b	80	20.5	78
15	3	1000	–	20	17	4
16	3	769	–	60	21.5	16
17	3	1000	–	80	18.5	25
18	3	190	2.57 ^a	80	20	91
19	3	1000	1.35 ^b	80	18.5	51
20	4	100	–	20	69	5
21	4	182	–	60	20	16
22	4	182	–	80	18	46
23	4	105	2.74 ^a	20	69	47
24	4	200	2.6 ^a	80	20	82
25	4	95	0.95 ^b	20	69	19
26	4	200	1.0 ^b	80	18	68

^a Silver trifluoromethanesulfonate.

^b Trifluoromethanesulfonic acid.

Table 3
Hydroamination of methyl methacrylate with benzylamine and cyclohexylamine

Entry	Catalyst	Amine/catalyst	Cocatalyst/catalyst	Temperature (°C)	Reaction time (h)	Yield (%)
27	3 ^a	1053	–	60	21.5	11
28	2 ^a	1000	–	80	18.5	19
29	2 ^a	1111	1.5 ^b	80	18.5	25
30	2 ^c	1176	–	20	68	7
31	2 ^c	1000	3.95 ^d	20	68	10

^a Benzylamine.

^b Trifluoromethanesulfonic acid.

^c Cyclohexylamine.

^d Silver trifluoromethanesulfonate.

dine and piperidine are slow, the conditions of the most practical protocol for the reactions would likely be 60 °C, 20 h without a catalyst. For the study of the influence of various parameters on the course of the reaction we have chosen moderate catalyst loadings 0.1–1.05 mol% and comparably mild temperatures 20–80 °C.

As expected, the yields increased with temperature in the above mentioned range (e.g. entries 20–22) and also invariably with reaction time; the data obtained do not allow detailed time-yield curves to be drawn, however.

Strong positive effect of cocatalysts, silver trifluoromethanesulfonate or trifluoromethanesulfonic acid, on the yield of hydroamination products was observed, in accord with the results of Hartwig et al. [10,14]. At 20 °C the silver salt seemed to be a better cocatalyst but the acid gave better yields at 80 °C. We believe that the primary effect of the cocatalyst is the exchange of the chloride for the noncoordinating triflate ion thus freeing the coordination position at the metal.

The catalytic activity of diphosphinoazine complexes varied, the trends being kept at different temperatures. The least active was complex **2** with tertiary butyl substituents on phosphorus atoms, although with about equimolar amount of triflic acid it catalyzed the hydroamination with 78% yield. The cyclohexyl complex **1** was more active but the best yields were achieved with isopropyl, **3**, and phenyl, **4**, complexes. Thus, 91% yield of morpholine addition product was obtained in the reaction catalyzed by 0.5 mol% of **3** with 2.6 molar excess (over palladium) of silver triflate (entry 18). Similarly, complex **4** with the same amount of the cocatalyst gave 82% yield under the same conditions (entry 24). While the conclusions regarding the different reactivity of the complexes as catalysts are only preliminary, it seems that their activity depends on steric factors. The less hindered is the palladium atom in the complexes the higher is the activity. This is in keeping with the effect of cocatalysts helping to free the access to the metal centre, too.

Hydroamination runs with cyclohexylamine and benzylamine are summarized in Table 3. Under conditions of low catalyst loading (<0.1 mol%) the increase of the yield of catalyzed versus uncatalyzed reaction in spite of a prolonged reaction time is low, the yields still not reaching preparative values. The positive effect of cocatalyst was also less pronounced than in the morpholine hydroamination.

2.3. Conclusions

With activated Michael-type alkenes high yields of some amine adducts, viz. pyrrolidine and piperidine, were observed in hydroamination of methyl methacrylate under mild conditions (20–80 °C). Positive but strongly nonlinear correlation of the reactivity of an amine with its basicity was found.

Cationic diphosphinoazine palladium complexes catalyzed the hydroamination with morpholine and considerable increase of the yield of hydroamination products was achieved using silver triflate or triflic acid as cocatalysts. Catalytic activity of diphosphinoazine complexes decreased with increasing steric bulk of the substituents on phosphorus. Both catalyzed and uncatalyzed hydroaminations proceeded with anti-Markovnikov regioselectivity.

It should be mentioned in conclusion that care has to be taken when planning catalytic hydroamination experiments with activated alkenes since some amines are reactive enough that no catalyst is needed. It is the activity (i.e. TOF) that has to be improved with future catalysts not their durability (i.e. TON), in order to really justify the use of a catalyst.

3. Experimental

3.1. General

All the manipulations were carried out in an inert atmosphere of nitrogen or argon using standard Schlenk techniques unless stated otherwise. Starting methyl methacrylate (Aldrich), benzylamine (Aldrich, 99.5%), cyclohexylamine (Schuchardt, 99.5%), piperidine (Aldrich, 99%), pyrrolidine (Fluka, 99%), and morpholine (Fluka, 99%) were distilled and stored under inert atmosphere, methyl methacrylate at the temperature 7 °C. Toluene (Chemapol, UV quality), trifluoromethanesulfonic acid (Aldrich, 98%), and silver trifluoromethanesulfonate (Aldrich, 99%) were commercial products used without further purification. Diphosphinoazine complexes (**1–4**) were prepared according to literature [17,24].

3.2. Hydroaminations

Palladium complex (0.002–0.02 mmol) was dissolved in toluene, amine (2 mmol) and methyl methacrylate (3 mmol) added with syringe. Reaction mixtures were kept at desired

temperature in a thermostated glass reactor with magnetic stirring. Cocatalysts (if used) were added to the dissolved catalyst, AgOTf as a solid, TFOH in the form of an emulsion in toluene homogenized by the use of ultrasound.

3.3. Analyses of the reaction mixtures

Samples of the reaction mixtures (200 μ l) were decomposed in 1 ml of K_2CO_3 solution (15%) and organics extracted in air into toluene (1 ml). Organic layer was separated and samples for GC–MS analysis prepared by dilution and addition of 1,2,4,6-tetrachlorobenzene as an internal standard.

GC–MS analysis was run on a Varian 3500 gas chromatograph equipped with a capillary column coated with poly(dimethylsiloxane-co-5% methylphenylsiloxane) phase (temperature program 50–250 $^{\circ}C$) connected to a Finnigan Mat mass ITD detector working at 70 eV. The acquisition range was 45–350 amu.

Hydroamination products except cyclohexylamine adduct were isolated from combined reaction runs. After distillation, 1H and ^{13}C NMR spectra showed them to be identical with reported compounds [15,25]. During the analysis of the reaction runs the products were characterized by their mass spectra (m/u): 91, 106, 208 (benzylamine adduct); 112, 124, 156, 200 (cyclohexylamine adduct); 100, 188 (morpholine adduct); 98, 186 (piperidine adduct); 84, 172 (pyrrolidine adduct). The yields are related to the particular amine.

The amount of palladium in the alkaline water layer after catalyst decomposition was checked by AAS to be over 90% of the original. Methyl methacrylate and hydroamination products remained in the organic layer, some of the amines were extracted into the aqueous layer, however. In those cases amine conversions were calculated using mass balance of methyl methacrylate and the hydroamination product in reaction mixtures both before and after the reaction.

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References

- [1] M. Beller, C. Breindl, M. Eichberger, C.G. Hartung, J. Seayad, O.R. Thiel, A. Tillack, H. Trauthwein, *Synlett* (2002) 1579.
- [2] M. Nobis, B. Driessen-Hoelscher, *Angew. Chem. Int. Ed.* 40 (2001) 3983.
- [3] T.E. Mueller, M. Beller, *Chem. Rev.* 98 (1998) 675.
- [4] D.M. Roundhill, *Catal. Today* 37 (1997) 155.
- [5] F. Alonso, I.P. Beletskaya, M. Yus, *Chem. Rev.* 104 (2004) 3079.
- [6] J.F. Hartwig, *Pure Appl. Chem.* 76 (2004) 507.
- [7] J.-J. Brunet, M. Cadena, N.C. Chu, O. Diallo, K. Jacob, E. Mothes, *Organometallics* 23 (2004) 1264.
- [8] R. Pryadun, D. Sukumaran, R. Bogadi, J.D. Atwood, *J. Am. Chem. Soc.* 126 (2004) 12414.
- [9] L. Fadini, A. Togni, *Chimia* 58 (2004) 208.
- [10] M. Kawatsura, J.F. Hartwig, *J. Am. Chem. Soc.* 122 (2000) 9546.
- [11] M. Utsunomiya, J.F. Hartwig, *J. Am. Chem. Soc.* 125 (2003) 14286.
- [12] L.K. Vo, D.A. Singleton, *Org. Lett.* 6 (2004) 2469.
- [13] U. Nettekoven, J.F. Hartwig, *J. Am. Chem. Soc.* 124 (2002) 1166.
- [14] M. Kawatsura, J.F. Hartwig, *Organometallics* 20 (2001) 1960.
- [15] K. Li, P.N. Horton, M.B. Hursthouse, K.K. Hii, *J. Organometall. Chem.* 665 (2003) 250.
- [16] K. Li, K.K. Hii, *Chem. Commun.* (2003) 1132.
- [17] J. Storch, J. Čermák, P. Vojtíšek, I. Cisařová, *Inorg. Chim. Acta* 357 (2004) 4165.
- [18] S.D. Perera, B.L. Shaw, M. Thornton-Pett, *J. Chem. Soc., Dalton Trans.* (1996) 3111.
- [19] M. Tromp, J.A. van Bokhoven, G.P.F. van Strijdonck, P.W.N.M. van Leeuwen, D.C. Konigsberger, D.E. Ramaker, *J. Am. Chem. Soc.* 127 (2005) 777.
- [20] A.R. Dick, J.W. Kampf, M.S. Sanford, *J. Am. Chem. Soc.* 127 (2005) 12790.
- [21] D.R. Coulson, *Tetrahedron Lett.* (1971) 429.
- [22] R.D. Closson, J.P. Napolitano, G.G. Ecker, A.J. Kolka, *J. Org. Chem.* 22 (1957) 646.
- [23] D.R. Lide (Ed.), *CRC Handbook of Chemistry and Physics*, 76th ed., CRC Press, 1995.
- [24] S.D. Perera, B.L. Shaw, M. Thornton-Pett, *J. Chem. Soc., Dalton Trans.* (1993) 3653.
- [25] S. Das, J.S.D. Kumar, K. Shivaramayya, M.V. George, *J. Chem. Soc., Perkin Trans. 1* (1995) 1797.