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Introduction

The Mizoroki–Heck reaction (Scheme 1) is nowadays the most important palladium-catalyzed C–C bond forming process for the arylation of olefins and, thus, the method of choice for the preparation of vinylbenzenes.^{1,2} Even though recent developments have considerably increased the activity of Heck catalysts,² a typical reaction protocol with aryl bromides as substrates still requires catalyst loadings between 1 and 5 mol%, a reaction temperature of 140 °C (lower reaction

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Mizoroki–Heck reactions catalyzed by palladium dichloro-bis(aminophosphine) complexes under mild reaction conditions. The importance of ligand composition on the catalytic activity†

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Dichloro-bis(aminophosphine) complexes of palladium with the general formula $[(P\{(NC_5H_{10})_3)$ $_{n}(C_{6}H_{11})_{n})_{2}Pd(Cl)_{2}$ (where n = 0-2) are easily accessible, cheap and air stable, highly active and universally applicable C-C cross-coupling catalysts, which exhibit an excellent functional group tolerance. The ligand composition of amine-substituted phosphines (controlled by the number of P–N bonds) was found to effectively determine their catalytic activity in the Heck reaction, for which nanoparticles were demonstrated to be their catalytically active form. While dichloro{bis[1,1',1''-(phosphinetriyl)tripiperidine]}palladium (1), the least stable complex (towards protons) within the series of $[(P\{(NC_5H_{10})_{3-n})^2 + (P(NC_5H_{10})_{3-n})^2 + (P(NC_5$ $(C_6H_{11})_0)_2Pd(Cl)_2$ (where n = 0-3), is a highly active Heck catalyst at 100 °C and, hence, a rare example of an effective and versatile Heck catalyst that efficiently operates under mild reaction conditions (100 °C or below), a significant successive drop in activity was noticed for dichloro-bis(1,1'-(cyclohexylphosphinediyl)dipiperidine)palladium (2, with n = 1), dichloro-bis(1-(dicyclohexylphosphinyl)piperidine)palladium (3, with n = 2) and dichloro-bis(tricyclohexylphosphine)palladium (4, with n = 3), of which the latter is essentially inactive (at least under the reaction conditions applied). This trend was explained by the successively increasing complex stability and its ensuing retarding effect on the (water-induced) generation of palladium nanoparticles thereof. This interpretation was experimentally confirmed (initial reductions of **1–4** into palladium(0) complexes of the type $[Pd(P\{(NC_5H_{10})_{3-n}(C_6H_{11})_n\})_2]$ (where n = 0-3) were excluded to be the reason for the activity difference observed as well as molecular (Pd⁰/Pd^{II}) mechanisms were excluded to be operative) and thus demonstrates that the catalytic activity of dichloro-bis(aminophosphine) complexes of palladium can – in reactions where nanoparticles are involved – effectively be controlled by the number of P–N bonds in the ligand system.



Scheme 1 General scheme of a Heck cross-coupling reaction between an aryl bromide and an olefin.

temperatures typically lead to a dramatic drop of activity) and reaction times of up to 24 hours for high conversions.

Moreover, in most reports only few reactions with rather simple substrates and coupling partners are tested. In addition, modified reaction conditions (*e.g.* reaction temperatures, catalyst loadings, bases, solvents, and additives) are often reported for different substrates, which strongly limit their general application in laboratory syntheses and industrial processes. Furthermore, many catalysts exhibit low thermal stability and suffer from inefficiency, low functional group tolerance and/or sensitivity towards both, air and moisture. In

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addition, their (multi-step) syntheses are often time-consuming or difficult, require inert-atmosphere techniques and typically are made with expensive and toxic starting materials of poor stability, which clearly refers to the need for new and improved, cheap and easily accessible, stable but reactive and generally applicable but green versions of Heck catalysts with a high functional group tolerance, which efficiently and reliably operate at low catalyst loadings with general applicable reaction protocols – preferably under mild reaction conditions.

Dichloro-bis(aminophosphine) complexes of palladium (1-3, Fig. 1) are easily accessible, cheap and air stable, highly active and universally applicable C-C cross-coupling catalysts as well as exhibit an excellent functional group tolerance.⁷ The reason for their excellent catalytic activity and general applicability is due to the unique properties of aminophosphines: the steric bulk as well as the σ -donor strength of aminophosphines is essentially the same when compared to their phosphinebased analogues.^{7e} Thus, complexes of type $[(P\{(NC_5H_{10})_{3-n})^2]$ $(C_6H_{11})_n$ }₂Pd(Cl)₂] (where n = 0-3; Fig. 1) show - independently from the number of n – comparable levels of activity in cross-coupling reactions where molecular mechanisms are operative. On the other hand, the labile character of P-N bonds in aminophosphine-based ligands (sensitivity towards protons; in the form of water for example) also offers the possibility to efficiently promote the formation of nanoparticles in the respective complexes. Consequently, 1-3 (Fig. 1) and the phosphine based analogue (4) were found to exhibit similar catalytic activities in the Negishi reaction and the hydrothiolation of alkynes, where molecular (Pd⁰/Pd^{II}) mechanisms were shown to be operative.^{7b,f} This, however, is in striking contrast to the Heck, Suzuki and cyanation reactions for example, where palladium nanoparticles were demonstrated to be their catalytically active form: while the aminophosphine-based cross-coupling catalysts 1-3 generally show excellent levels of activity in these reactions, dramatically reduced conversion





Fig. 1 The effect of the ligand composition of dichloro{bis[1,1',1''-(phosphine-triyl)tripiperidine]}palladium (1), dichloro-bis(1,1'-(cyclohexylphosphinediyl)di-piperidine)palladium (2, with n = 1) and dichloro-bis(1-(dicyclohexylphosphinyl) piperidine)palladium (3, with n = 2) as well as their phosphine-based analogue (4, with n = 3) on the complex stability and, hence, on the ease of (water-induced) nanoparticle formation.

rates and yields were found for the phosphine-based catalyst **4**. $^{7a,c-e}$

Furthermore, the catalytic performance of dichloro-bis(aminophosphine) complexes can (in reactions where nanoparticles are involved) effectively be controlled by simple ligand modifications: an increasing number of P-N bonds in the ligand system successively eases their water-induced degradation and consequently the formation of nanoparticles from the respective complexes. Accordingly, substitution of 1,1',1"-(phosphinetrivl)tripiperidine from 1 by 1,1'-(cyclohexylphosphinediyl)dipiperidine), 1-(dicyclohexylphosphinyl)piperidine) or tricyclohexylphosphine successively increases the complex stability and, hence, retards the (water-induced) formation of nanoparticles thereof. As a result, while dichloro-bis(1-(dicyclohexylphosphinyl)piperidine)palladium (3), the most stable aminophosphine complex (with one P-N bond in the aminesubstituted phosphine), was found to be the catalyst of choice in the Heck reaction performed at 140 °C (only a very poor catalytic activity was observed for the phosphine based complex 4), 7d,e the highest catalytic activity was expected to be obtained dichloro{bis[1,1',1"-(phosphinetriyl)tripiperidine]}pallafor dium $[(P(NC_5H_{10})_3)_2Pd(Cl)_2]$ (1), the least stable (and greenest) complex within the series of $[(P\{(NC_5H_{10})_{3-n}(C_6H_{11})_n\})_2Pd(Cl)_2]$ (where n = 0-3; Fig. 1), when the reaction temperature was lowered - if too fast palladium nanoparticle formation does not inhibit catalysis. Therefore, we were intrigued by the possibility to efficiently and reliably promote the Heck reaction with aryl bromides - the substrates of choice for industrial applications - in the presence of 1 at 100 °C (or even below) and, hence, under much milder reaction conditions than typical in the Heck reaction applied.

We report herein the catalytic performance of air-stable 1 in the vinylation of a wide variety of different, electronically activated, non-activated, deactivated, sterically hindered, and functionalized aryl bromides as well as sulfur and nitrogen containing heterocyclic aryl bromides with different olefins at 100 °C in NMP (N,N-dimethylpyrrolidone) or DMF (N,N-dimethylformamide) and K2CO3 as solvents and base in the presence of 0.05 mol% of a catalyst and ~10 mol% of tetrabutylammonium bromide, which was (in contrast to the Heck reactions performed at 140 °C) found to be essential as an additive for the reliable conversion of the substrates into the cross-coupling products with 1 at 100 °C.^{8,9} 1 was quantitatively prepared by treatment of toluene suspensions of [Pd- $(Cl)_2(cod)$ (cod = cycloocta-1,5-diene) with two equivalents of readily prepared 1,1',1"-(phosphinetriyl)tripiperidine (1,1',1"-(phosphinetriyl)tripiperidine is almost quantitatively prepared in one step by the dropwise addition of 6 equiv. of piperidine to cooled diethyl ether solutions of PCl₃ and subsequent filtration) in air at 25 °C within only a few minutes (Scheme 2)

[Pd(Cl) ₂	2(C0	od)]	t	2 olu	P	(N ne,	C ₅ 10	H ₁ mi	o) in,	3 , r.1	•		[(P	{(N	10	; ₅	I ₁	o)	3}	·)2	P	d(C	l);	2]	(*	(1)		
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Scheme 2 Synthesis of dichloro{bis[1,1',1''-(phosphinetriyl)tripiperidine]}palladium (1).

and, hence, is one of the cheapest (the ligand costs for the preparation of **1** with 1 g of palladium precursor is less than 1 Euro), the most convenient and the most efficient and, hence, greenest cross-coupling catalysts available.

We show that dichloro{bis[1,1',1"-(phosphinetriyl)tripiperidine]}palladium $[(P(NC_5H_{10})_3)_2Pd(Cl)_2]$ (1) is - in contrast to dichloro-bis(1,1'-(cyclohexylphosphinediyl)dipiperidine)palladium $[(P\{(NC_5H_{10})_2(C_6H_{11})\})_2Pd(Cl)_2]$ (2) and dichloro-bis(1-(dicyclohexylphosphinyl)piperidine)palladium $[(P{(NC_5H_{10})(C_6H_{11})_2})_2$ $Pd(Cl)_2$ (3) as well as their phosphine-based analogue $[(P(C_6H_{11})_3)_2Pd(Cl)_2]$ (4), for which a successive and dramatic drop in activity was noticed - a highly efficient, reliable, and extremely versatile Heck catalyst, which offers the possibility to efficiently convert also thermally less stable substrates into the respective Heck products in high yields within reasonable reaction times. Moreover, the reaction protocols are uniformly applicable and, thus, can directly be adapted to other substrates without the necessity to be changed and, thus, demonstrate the general applicability of 1 in this process. Accordingly, 1 is commercially available as well as was successfully applied in industry. Mechanistic investigations indicate that palladium nanoparticles are the catalytically active form of 1, which provides a simple explanation for the successive (dramatic) drop in activity with decreasing *n* and hence from **1** to 4.

Results and discussion

Catalysis

Complex 1 is a highly active, reliable, and versatile Heck catalyst with excellent functional group tolerance. The coupling products are typically obtained in excellent yields within only few hours at 100 °C, of which the E-isomer of the arylated olefins is often exclusively and cleanly formed (side-products were not detectable). Exemplary reactions were successfully performed with styrene (a), 1-ethenyl-3-nitrobenzene (b), 1-chloro-3-ethenylbenzene (c), 1-ethenyl-4-methoxybenzene (d) and 4-ethenylpyridine (e) (Table 1) as well as N,N-dimethylacrylamide (f), 4-acryloylmorpholine (g), and butyl acrylate (h) (Table 2), which demonstrate its general applicability. For example, when electronically activated, non-ortho-substituted aryl bromides, such as 1-bromo-4-nitrobenzene, 1-bromo-4fluorobenzene, 4-bromobenzophenone, and 3-bromobenzaldehyde, were coupled with styrene and derivatives of it, smooth C-C bond formation and exclusive, quantitative product formation were achieved in almost all the reactions examined within 8 hours. Exclusive Caryl-Br bond activation was noticed when bromochlorobenzenes were used and, thus, quantitative formation of 1-chloro-3-[(E)-2-phenylethenyl]benzene (a7) was observed when 1-bromo-3-chlorobenzene was applied. Essentially the same conversion rates and yields were achieved when electronically non-activated aryl bromides, such as 1-bromo-4tert-butylbenzene or 1-bromonaphthalene as well as aromatic bromides with increased electron density on the aryl unit (e.g. 1-bromo-4-phenoxybenzene, 1-(benzyloxy)-4-bromobenzene or

1-bromo-3,5-dimethoxybenzene), were applied: 1-bromo-4-phenoxybenzene and 1-(benzyloxy)-4-bromobenzene, for example, were almost fully converted into 1-(phenoxy)-4-[(E)-2-phenylethenvl]benzene (a9) and $1-\{(E)-2-[4-(benzyloxy)phenyl]$ ethenyl}-3-nitrobenzene (b2) within 1 and 8 hours, respectively. Even 1-bromo-3,5-dimethoxybenzene was fully converted into 1,3-dimethoxy-5-[(E)-2-phenylethenyl]benzene (a11) when prolonged reaction times (24 hours) were applied. Moreover, the Heck reactions also performed well with protic substrates as well as any bromides with methylsulfanyl groups. Exemplary reactions with 4-bromophenol, 3-bromoaniline, N-(4-bromo-2methylphenyl)acetamide and 1-bromo-4-(methylsulfanyl)benzene smoothly yielded 4-[(E)-2-phenylethenyl]phenol (a13, 97% within 6 h), 3-[(E)-2-(4-methoxyphenyl)ethenyl]aniline (d3, 84% within 24 h), N-{4-[(E)-2-(3-chlorophenyl)ethenyl]-2methylphenyl}acetamide (c3, 99% within 9 h), and 1-(methylsulfanyl)-4-[(E)-2-phenylethenyl]benzene (a18, 91% within 24 h), respectively. A reduced level of activity was generally obtained when sterically hindered aryl bromides were used as substrates: whereas only a slight decrease in activity was noticed when 1-bromo-2-methylbenzene was coupled with styrene, a significant drop in activity was found for 2-bromo-1,3,5-trimethylbenzene. Even though prolonged reaction times were required 3-bromopyridine or 3-bromoquinoline were fully converted into 3-[(E)-2-phenylethenyl]pyridine (a16) and <math>3-[(E)-2-phenylethenyl]pyridine (a16) and <math>3-[(E)-2-phenylethenylethenylethenyl]pyridine (a16) and <math>3-[(E)-2-phenylethenyl2-phenylethenyl]quinoline (a17), respectively. Similarly, prolonged reaction times were required to achieve high conversions with 4-ethenylpyridine (e) as a coupling partner (e1-e3). Similar yields but higher conversion rates were generally found when the Heck reactions were performed with electronically activated olefins, such as N,N-dimethylacrylamide (f), 4-acryloylmorpholine (g) and butyl acrylate (h). Moreover, the E-isomers of the respective coupling products were in all the reactions examined exclusively formed. Impressively, also heterocyclic aromatic bromides were successfully coupled with alkenes at 100 °C: for example, when ethyl 1-(6-bromopyridin-2-yl)piperidine-3-carboxylate – a 6-bromopyridine-2-amine – was coupled with butyl acrylate (**h**), ethyl $1-\{6-[(E)-2-(4-methoxy$ phenyl)ethenyl]pyridin-2-yl}piperidine-3-carboxylate (h5) was quantitatively formed within 12 hours. An excellent performance was also noticed when sulfur-containing aryl bromides were used as substrates: for example, when 2-bromothiophene, 2-bromo-5-methylthiophene, and 2,5-dibromothiophene were coupled with N,N-dimethylacrylamide (f) or butyl acrylate (h), (2E)-N,N-dimethyl-3-(5-methylthiophen-2-yl)prop-2-enamide (f4), (2E,2'E)-3,3'-thiene-2,5-diylbis(N,N-dimethylprop-2-enamide) (f5), and butyl (2E)-3-thiophen-2-ylprop-2-enoate (h6) were exclusively and quantitatively formed within 24 hours. Impressively, when 5,5'-dibromo-2,2'-bithiophene was coupled with 4-acryloylmorpholine (g) at 100 °C, 4,4'-{2,2'-bithiene-5,5'-diylbis-[(1E)-3-0x0prop-1-ene-1,3-diyl]dimorpholine (g4) was quantitatively formed within 24 hours.¹⁰

Catalytic performance and other advantages of 1

Overall, dichloro{bis[1,1',1"-(phosphinetriyl)tripiperidine]}palladium (1) is a highly active, efficient and one of the most



^{*a*} Reaction conditions: 1.0 mmol aryl bromide, 1.5 mmol olefin (relative to bromide), 2.0 mmol K_2CO_3 , 2.5 ml NMP, tetrabutylammonium bromide (10 mol%), a catalyst (0.05 mol%) added in a solution (THF), reaction performed at 100 °C in an N_2 atmosphere. The conversions and product ratios (*trans/gem/cis*) are determined by GC/MS and are based on aryl bromide. Isolated yields are given in brackets. ^{*b*} DMF was used as a solvent.

versatile and convenient Heck catalysts, which allows a wide variety of aryl bromides, which may contain nitro, chloro, fluoro or trifluoromethane groups, ketones, aldehydes, ethers, esters, amides, amines, anilines, phenols, as well as heterocyclic aryl bromides, such as pyridines and derivates, or thiophenes and aryl bromides with methylsulfanyl groups, to be selectively coupled with various olefins in very high conversion rates and yields at 100 °C. Thus, 1 is a rare example of a Heck catalyst that allows this transformation to be efficiently catalyzed under mild reaction conditions. However, two other systems, $[Pd(OAc)_2]/Et_4NCl/Cy_2NMe$ and $[Pd_2(dba)_3]/P(tBu)_3/P(tBu)_$ Cy_2NMe (dba = dibenzylideneacetone),^{11,12} may be mentioned, which catalyze the Heck reaction at temperatures of ~100 °C (or below). Even if the former system allows the cross-coupling of aryl bromides with disubstituted derivates of alkyl acrylates (unsubstituted derivatives have not been tested) at reaction temperatures between 85 and 110 °C, high catalyst loadings (2-4 mol%) and prolonged reaction times (16-60 hours) were

required to achieve conversions between 51 and 84%. The latter catalyst, on the other hand, is the only system that allows the Heck reaction to be performed at room temperature for which product yields from 64 up to 97% were achieved in reaction times between 1 and 3 days in the presence of 1 mol% (rel. to palladium) of $[Pd_2(dba)_3]$ and 1–3 mol% of the ligand.

Moreover, dichloro{bis[1,1',1''-(phosphinetriyl)tripiperidine]}palladium (1) also compares favorably with $[Pd(OAc)_2]$,¹³ $[(PC^{NHC}P)Pd(Cl)][Cl]$,¹⁴ $[(C_6H_3-2,6-(CH_2PiPr_2)_2Pd(TFA)]$ (TFA = trifluoroacetate),¹⁵ $[(C_6H_4-2-(CH_2P(tBu)_2)Pd(OAc)]_2$,¹⁶ and $[(C_6H_2-3,5-(tBu)_2-2-{OP(OAr)_2}Pd(Cl)]_2$,¹⁷ even if the Heck reactions were carried out at considerably higher temperatures (140 °C) than applied for 1. On the other hand, $[(C_5H_3N-2,6-(NHC^{Me})Pd(Br)]^{+18}$ and the very recently reported systems $[(C^{NHC}N)Pd(fppz)]$ (fppzH = 2-[3-(trifluoromethyl)-1H-pyrazol-5-yl]pyridine) and *trans*-di(µ-aceto)bis[2-diphenylphospino-2'-methylbiphenyl]dipalladium,^{19,20} show a higher level of

Table 2 Heck cross-coupling reactions between any bromides and N,N-dimethylacrylamide (f), 4-acryloylmorpholine (g), and butyl acrylate (h), catalyzed by 1^a



^{*a*} Reaction conditions: 1.0 mmol aryl bromide, 1.5 mmol olefin (relative to bromide), 2.0 mmol K_2CO_3 , 2.5 ml NMP, tetrabutylammonium bromide (10 mol%), a catalyst (0.05 mol%) added in a solution (THF), reaction performed at 100 °C in an N₂ atmosphere. The conversions and product ratios (*trans/gem/cis*) are determined by GC/MS and are based on aryl bromide. Isolated yields are given in brackets. ^{*b*} DMF was used as a solvent. ^{*c*} The product ratio refers to (*trans-trans/trans-gem/trans-cis*).

activity at 140 °C, but were inferior when the reaction temperature was increased to 140 °C for 1 as well.

Despite the high catalytic activity, efficiency and functional group tolerance of dichloro{bis[1,1',1"-(phosphinetriyl)tripiperidine]}palladium (1), a great advantage of 1 when compared to Heck catalysts ligated by water-insoluble ligand systems includes the well-known fate of the catalyst after catalysis: treatment of 1 with aqueous hydrochloric acid in air and, thus, under work-up conditions leads to a rapid and complete catalyst degradation, accompanied by the formation of phosphonates, piperidinium salts and insoluble palladium-containing decomposition products, which are easily separated from the coupling products. This is an often ignored, but very important issue to be considered (from ecologic and economic points of view) and is of particular importance for the preparation of pharmaceutically relevant compounds.

The effect of ligand composition on the catalytic performance of 1–4

The effect of the ligand composition in nanoparticle formation (see below) of amine-substituted phosphines and, hence, on the catalytic activity of dichloro-bis(aminophosphine)palladium complexes of palladium (1–3) and their phosphine based analogue **4** in the Heck reaction at 100 °C – was found to be huge. While **1**, the least stable compound (towards protons) within the series of $[(P\{(NC_5H_{10})_{3-n}(C_6H_{11})_n\})_2Pd(Cl)_2]$ (where n = 0-3) where the formation of nanoparticles is most efficient, exhibit the highest catalytic activity in the Heck reaction at 100 °C, a dramatic successive drop in activity was noticed in all the reactions examined when 1,1',1''-(phosphinetriyl)tripiperidine was substituted by 1,1'-(cyclohexylphosphinediyl)-dipiperidine), 1-(dicyclohexylphosphinyl)piperidine) and tricyclohexylphosphine. Thus, $[(P(C_6H_{11})_3)_2Pd(Cl)_2]$ **4**, the most

stable compound, shows (by far) the lowest level of activity and is in most reactions applied even inactive. For example, whereas the cross-coupling of 1-bromonaphthalene with styrene quantitatively yielded the coupling product with 1 after 14 hours, a dramatically reduced level of activity and, hence, a conversion of only 32% was achieved when dichloro-bis(1,1'-(cyclohexylphosphinediyl)dipiperidine)palladium (2, with n = 1) was used as a catalyst. A further drop in activity was found for dichloro-bis(1-(dicyclohexylphosphinyl)piperidine)palladium (3, with n = 2), for which a conversion of 21% was found after 14 hours. No product formation at all was detectable when their phosphine-based analogue (4) was applied. The same observation was made by using sterically hindered 1-bromo-2-methylbenzene as a substrate. Even though complete product formation was also found in single cases for 4 - typically with electronically activated substrates, such as ethyl 4-bromobenzoate (Fig. 2) - the



Fig. 2 Catalytic activities of **1–4** in the Heck reaction of electronically activated ethyl 4-bromobenzoate and styrene at 100 °C in NMP in the presence of ~10 mol% of tetrabutylammonium bromide and 0.05 mol% of a catalyst.

trend observed is obvious: the higher the number of P–N bonds in aminophosphines the more active the respective dichloro-bis(aminophosphine)palladium complexes (under the reaction conditions applied) are, which is opposed to the trend found at 140 °C for 1-3.^{7e,21}

Consequently, 1 is the catalyst of choice for Heck reactions performed at 100 °C and 3 for reactions at 140 °C. Complex 4, on the other hand, is, in none of the reactions examined and the conditions applied, even competitive. This demonstrates that the nanoparticle formation and, hence, the catalytic activity of dichloro-bis(aminophosphine) complexes of palladium can (in reactions where nanoparticles are involved) effectively be controlled by the number of P-N bonds in the ligand system and, thus, allows the catalyst activity to be adapted to the reaction conditions applied. This unique structure-reactivity relationship of aminophosphines, their cheap and easy accessibility is the reason for the high catalytic activity and versatility of the respective dichloro-bis(aminophosphine) complexes of palladium, which make them some of the most attractive cross-coupling catalysts for organic syntheses as well as industrial processes.

The effect of ligand composition on the catalytic activity of dichloro-bis(aminophosphine) complexes of palladium

The successive drop in activity of dichloro{bis[1,1',1"-(phosphinetrivl)tripiperidine]}palladium (1, with n = 0), dichloro-bis-(1,1'-(cyclohexylphosphinediyl)dipiperidine)palladium (2, with n = 1), dichloro-bis(1-(dicyclohexylphosphinyl)piperidine)palladium (3, with n = 2) and dichloro-bis(tricyclohexylphosphine) palladium (4, with n = 3) in the Heck reaction performed at 100 °C was explained by the successively increasing complex stability and its ensuing retarding effect on the (waterinduced) generation of palladium nanoparticles thereof. This interpretation gained strong experimental support by: (1) the electrochemical reduction of 1-4 in THF,²² showing for all complexes an identical (irreversible) reduction wave (Fig. 3), which for the aminophosphine based systems (1-3) are located at -1.35 V, -1.34 V and -1.31 V and for the phosphine-based system $[Pd(P(C_6H_{11})_3)_2(Cl)_2]$ (4) at -1.21 V and, hence, would suggest - if from these electrochemically determined reduction potentials an activity trend in the Heck reaction is deducible at all and if a molecular mechanism were operative - an opposite trend in activity than it was experimentally observed and (2) the catalytic activity of bis(aminophosphine)palladium(0) complexes of the type [Pd- $(P\{(NC_5H_{10})_{3-n}(C_6H_{11})_n\})_2$ (where n = 0-3) in the Heck reaction at 100 °C, which show the same trend in activity as it was found to be the case for 1-4.

For example, whereas full conversion of 1-bromonaphthalene and styrene into 1-[(*E*)-2-phenylethenyl]naphthalene (**a15**) was achieved with both, 1 and bis[1,1',1"-(phosphinetriyl)tripiperidine]palladium(0) [Pd(P(NC₅H₁₀)₃)₂], within 14 hours, no product formation at all was found for their phosphine-based analogues 4 and [Pd(P(C₆H₁₁)₃)₂], respectively, demonstrating that the initial reduction of dichloro-bis(aminophosphine)palladium(π) (1–3) and their phosphine-based analogue 4 into



Fig. 3 Reduction of **1** (top left), **2** (top right), **3** (bottom left) and **4** (bottom right) (0.5 mM) into palladium(0) complexes of the type $[Pd(P\{(NC_5H_{10})_{3-n^{-1}}(C_6H_{11})_n\})_2]$ (where n = 0-3),²² in THF (containing n-Bu₄NBF₄, 0.1 M): cyclic voltammetry with gold as the working and Pt as auxiliary electrodes and Ag/AgCl as a reference electrode with a scan rate $\nu = 0.1 \text{ V s}^{-1}$, at 22 °C. All potentials are given *versus* Ag/AgCl (Fc/Fcl at +500 mV).

palladium(0) complexes of the type $[Pd(P_{10})_{3-n}]$ $(C_6H_{11})_n$ }] (where n = 0-3) – their catalytically active species in molecular (Pd⁰/Pd^{II}) mechanisms - cannot be the reason for the activity difference observed. Indeed, catalytic cycles involving complexes with Pd(0) centers were ruled out to be operative in the Heck reaction catalyzed by 1-4, as indicated by the results obtained from the (recently developed) dibenzyl-test:²³ dibenzyl formation was - in contrast to Heck reactions catalyzed by palladium(0) complexes of the type $\left[Pd(P_{10}^{(NC_5H_{10})})_{3-n} \right]$ $(C_6H_{11})_n$ (where n = 0-3) – not detectable by GC/MS when reaction mixtures of aryl bromide, olefin, benzyl chloride (~10 mol% rel. to aryl bromide), a catalyst and a base were thermally treated (100 °C). Moreover, dibenzyl was neither formed in the presence of [Pd(OAc)₂] as a catalyst - another piece of evidence that nanoparticles are their catalytically active form in the Heck reaction - at least under the reaction conditions applied.

Mechanistic investigations

The following experimental observations strongly indicate the involvement of palladium nanoparticles in the catalytic cycle of the Heck reaction catalyzed by dichloro-bis(aminophosphine) complexes of palladium (1-3) as well as $[(P(C_6H_{11})_3)_2-Pd(Cl)_2]$ (4) and, hence, fully confirms the above results as well as their interpretation and provides a simple and the only possible explanation for the activity difference observed in the Heck reaction catalyzed by 1-4:²⁴ (1) the steric bulk of 1,1',1''-(phosphinetriyl)tripiperidine, 1,1'-(cyclohexylphosphinediyl)-

dipiperidine, 1-(dicyclohexylphosphinyl)piperidine and tricyclohexylphosphine are almost identical as well as their σdonor strength (as shown by the CO stretching frequency of complexes of the type $cis-[(PR_3)(NC_5H_{10})Mo(CO)_4])$.^{7e,25} Thus, whereas very similar catalytic activities will be obtained for dichloro-bis(aminophosphine)palladium complexes 1-3 and $[(P(C_6H_{11})_3)_2Pd(Cl)_2]$ (4) in reactions where molecular mechanisms are operative (as it was found to be the case in the Negishi cross-coupling reaction and in the hydrothiolation of alkynes),^{7b,f} a significant difference in activity will be observed in reactions where palladium nanoparticles are involved, as it was recently found to be the case in the Suzuki, cyanation and Heck reactions (carried out at 140 °C).^{7a,c-e} (2) The coupling reactions follow for all the complexes a sigmoidal-shaped kinetics (Fig. 2), which is characteristic of metal-particle formation and autocatalytic surface growth, which can lead to soluble monodisperse nanoclusters or insoluble bulk metal formation.²⁶ (3) The addition of a large excess of metallic mercury to reaction mixtures of aryl bromide, olefin and catalyst efficiently stopped catalysis at any time of its addition and no product formation at all was observed when few drops of metallic mercury were added at the beginning of the reaction. The same observations were made when poly(4-vinylpyridine) (PVPy) (2% cross-linked with divinylbenzene) was added instead.²⁷ (4) No product formation at all was obtained when 0.1 equiv. (rel. to the catalyst) of CS_2 was added to the reaction mixtures. (5) Whereas only very low conversions were observed in the absence of tetrabutylammonium bromide (due to fast (visibly observable) deposition of inactive palladium black),⁹ excellent and highly reproducible conversion rates and product yields were found in its presence (~10 mol% rel. to the substrate) at 100 °C. Finally, (6) the formation of palladium nanoparticles could be verified by analysis of the reaction mixtures of exemplary Heck cross-coupling reactions for all dichloro-bis(aminophosphine) complexes of palladium by a



Fig. 4 TEM image showing aggregated palladium nanoparticles (as identified by EDX analysis) from the cross-coupling reaction of 1-bromo-4-methoxybenzene with styrene, catalyzed by 0.05 mol% of dichloro{bis[1,1',1''-(phosphine-triyl)tripiperidine]}palladium (1) at 100 °C in DMF in the presence of ~10 mol% of tetrabutylammonium bromide.

transmission electron microscope (TEM) equipped with an energy dispersive X-ray (EDX) analyzer (Fig. 4).

Conclusions

In conclusion, dichloro{bis[1,1',1"-(phosphinetriyl)tripiperidine]}palladium (1) is - in contrast to dichloro-bis(1,1'-(cyclohexylphosphinediyl)dipiperidine)palladium (2), dichloro-bis(1-(dicyclohexylphosphinyl)piperidine)palladium (3) and the phosphine-based analogue dichloro-bis(tricyclohexylphosphine)palladium (4) - a highly efficient Heck catalyst with an excellent functional group tolerance, which reliably couples a wide variety of aryl bromides, which may contain nitro, chloro, fluoro or trifluoromethane groups, nitriles, ketones, aldehydes, ethers, esters, amides, anilines, phenols, and heterocyclic aryl bromides, such as pyridines and derivates, as well as thiophenes and aryl bromides containing methylsulfanyl groups with various different alkenes at 100 °C in DMF or NMP and K₂CO₃ as solvents and base in the presence of ~10 mol% tetrabutylammonium bromide and only 0.05 mol% of the catalyst. Thus, 1 is a rare example of an effective and versatile Heck catalyst that efficiently operates under mild reaction conditions (100 °C or below) and, hence, offers the possibility to efficiently convert also thermally less stable substrates into the respective coupling products within reasonable reaction times. The dramatic successive drop in activity observed for complexes of the type $[(P\{(NC_5H_{10})_{3-n}(C_6H_{11})_n\})_2Pd(Cl)_2]$ (where n =0-3) when 1,1',1"-(phosphinetriyl)tripiperidine was substituted by 1,1'-(cyclohexylphosphinediyl)dipiperidine), 1-(dicyclohexylphosphinyl)piperidine) and tricyclohexylphosphine was explained by the successively increasing complex stability (from 1 to 4) and its ensuing retarding effect on the (waterinduced) generation of palladium nanoparticles thereof. This interpretation was experimentally confirmed: initial reduction of 1-4 into palladium(0) complexes of the type $\left[Pd(P_{10}^{(NC_5H_{10})})_{3-n} \right]$ $(C_6H_{11})_n$ (where n = 0-3) was (e.g. electrochemically) excluded to be the reason for the activity difference observed and also molecular (Pd⁰/Pd^{II}) mechanisms were ruled out to be operative (by the dibenzyl-test). On the other hand, mechanistic investigations strongly indicated the involvement of nanoparticles as the catalytically active form of 1-4 and demonstrate that the catalytic activity of dichloro-bis(aminophosphine) complexes of palladium can - in reactions where palladium nanoparticles are their catalytically active form effectively be controlled by the number of P-N bonds in the ligand system. As a consequence, the catalyst activity can be adapted to the reaction conditions (e.g. reaction temperature) applied, resulting that 1 is the catalyst of choice for Heck reactions performed at 100 °C and 3 for reactions at 140 °C. Complex 4, on the other hand, was in none of the reactions examined and reaction conditions applied even competitive and demonstrates the unique properties of aminophosphines. Finally, aminophosphines are cheap and easily accessible and modular. Thus, dichloro-bis(aminophosphine) complexes of palladium belong to some of the most attractive cross-coupling catalysts, having great potential of finding applications in organic syntheses as well as in industrial processes.

Experimental section

General procedure for Heck reactions

A Young Schlenk (10 mL) was charged in a N₂ atmosphere with the appropriate amounts of olefin (1.5 mmol), aryl halide (1.0 mmol), K₂CO₃ (2.0 mmol), tetrabutylammonium bromide (~10 mol% relative to the aryl bromide), and DMF or NMP (2.5 ml). The mixture was vigorously stirred and heated to 100 °C. Then the correct amount of a catalyst was added by a syringe as a solution in THF (0.05 mol%, 0.1 mL of a 5×10^{-3} M solution). Samples were periodically taken from the reaction mixture, quenched with 1 M HCl (or 1 M Na₂CO₃, if basic functional groups were present in the substrates), extracted with ethyl acetate, and analyzed by GC/MS. At the end of catalysis, the reaction mixtures were allowed to cool to room temperature, quenched with 1 M HCl (or 1 M NaOH respectively), and extracted with ethyl acetate $(3 \times 25 \text{ mL})$. The combined extracts were dried (MgSO₄) and evaporated to dryness. The crude material was purified by flash chromatography on silica gel or basic aluminium oxide, as necessary.

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