Intramolecular aminopalladation of alkenes as a key step to pyrrolidines and related heterocycles

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Palladium catalysis for the intramolecular amination of alkenes is a powerful approach in heterocycle synthesis. The initial common step in this approach consists of an aminopalladation reaction. This *tutorial review* describes the synthesis of 2-amino alkyl–palladium compounds and renders special attention on the subsequent manipulation of the alkyl-palladium group. By carefully choosing the appropriate conditions, a wide variety of different heterocyclic structures are accessible which arise from reactions such as hydroamination, aza-Heck coupling, aminocarbonylation or oxidative processes such as aza-Wacker reaction and 1,2-difunctionalisation.

Introduction

Synthesis of nitrogen heterocycles through C–N bond formation represents a useful and widely applied synthetic tool. The application of transition metal complexes as catalysts for this process has been considered an attractive approach, and palladium salts have emerged as particularly exciting catalysts over the course of the past two decades.[1] This overview deals with the intramolecular functionalisation of alkenes within two consecutive steps of palladium catalysis. These start upon an intramolecular nitrogen transfer to form an N–C bond and by this aminopalladation reaction readily provide heterocycles. The subsequent second step relies on the particular reaction conditions and is responsible for the creation of the additional functional group embedded within the heterocyclic product.

In principle, both a nitrogen atom from an amine or amide group and an alkene represent electron rich functional character. As a consequence, their direct reaction is characterised by a high activation energy and is usually not straightforward. However, coordination to a transition metal centre such as palladium(II) induces an *umpolung* of the original alkene reactivity and renders the alkene susceptible to nucleophilic attack. The coordination of alkenes to palladium can be understood following the general principles of the classical Chatt–Dewar–Dunkanson model.[1] All aminopalladation reactions described within this article make use of amides,

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Ana Minatti

Ana Minatti was born in Bonn, Germany in 1977. She studied chemistry at the University of Bonn and graduated in 2001 with highest honours. That year she commenced her PhD studies in the research group of Karl-Heinz Dötz and worked on Fischer-carbene-complexes as a tool for ligand and natural product synthesis. She obtained her PhD in Organic and Organometallic Chemistry in 2006. She further worked for three months on iodonium-induced cyclization reactions in the research group of José Barluenga at the University of Oviedo, Spain. In 2006, she joined the research group of Stephen L. Buchwald at the Massachusetts Institute of Technology. She received a Theodor-Laymann-fellowship from the University of Bonn, a PhD fellowship from the Fonds der Chemischen Industrie, a DAAD exchange fellowship and a postdoctoral fellowship from the Alexander-von-Humboldt foundation. In 2006, she was awarded the Edmund-ter-Meer-prize from the University of Bonn.

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Kilian Muñiz was born in 1970. From 1990 to 1996 he studied Chemistry at Hannover University, Germany, at the Imperial College London, UK and at University of Oviedo, Spain. In 1996 he joined the group of Carsten Bolm at the RWTH Aachen, Germany to obtain his doctorate in 1998. In 1999/2000 he worked as a post-doctoral associate with Ryoji Noyori at Nagoya University, Japan. He began his independent research in December 2000 at the Kekulé-Department in Bonn, Germany to finish his Habilitation in 2005. In the autumn of 2005 he joined the Institut de Chimie at ULP Strasbourg as an Associate Professor and was promoted to Full Professor in 2006. His research has been recognised by several awards and honours, among them the German–Israeli Young Investor Award and the German ADUC Prize for Habilitands. In 2006 he was awarded a Chaire d'Excellence from the French National Research Agency.

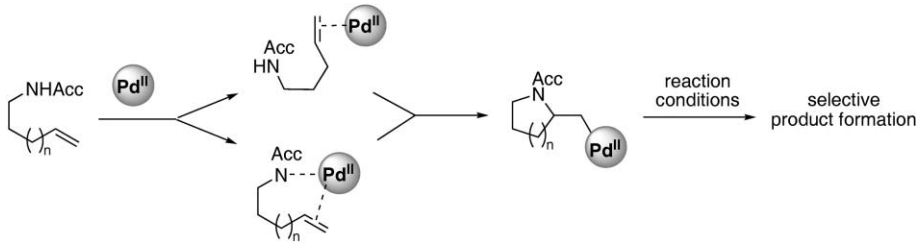


Fig. 1 Mechanistic background of aminopalladation for heterocycle synthesis.

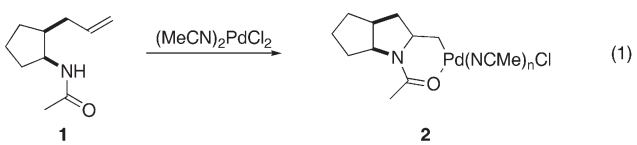
carbamates and sulfonamides as nitrogen sources. This is due to the mostly irreversible coordination of free amines to palladium complexes which have widely suppressed the development of catalytic aminopalladation reactivity of this type.[2]

Aminopalladation: common first step

For most reactions that are discussed within this review, the exact pathways remain unknown. In principle, the reaction may be initiated by palladium–amide interaction followed by simultaneous transfer to the alkene, which may also be considered as alkene insertion into the amide–palladium bond (Fig. 1). Alternatively, it may start from direct alkene coordination to palladium and subsequent nitrogen attack to the complexed C–C double bond. While the former process should lead to *syn*-aminopalladation, the latter results in *anti*-configured 2-aminoalkyl palladium compound.

No definite answer to this stereochemical problem has been established yet and generally, no 2-aminoalkyl palladium compounds have been isolated and characterised. As a noteworthy exception, Hegedus in his pioneering research described the isolation of a stable product from treatment of **1** with stoichiometric amounts of bis(acetonitrile)palladium dichloride.[3] The supposed product **2** proved stable under a variety of conditions, but no further data on it has become available (Scheme 1, eqn (1)).

In the following, we will discuss the reaction conditions for intramolecular aminopalladation and subsequent selective transformations of the resulting alkyl–palladium bond in order to generate functionalised nitrogen heterocycles. These reactions will be presented in a subjective order where it is intended to show structural similarities arising from different reaction conditions. These may involve catalysts with differentiating metal oxidation states, namely, reactions without Pd(II) oxidation state change, those by classical Pd(0)/Pd(II) catalysis and those which presumably follow a Pd(II)/Pd(IV) oxidation state cycle.



Scheme 1 Isolated 2-aminopalladium complex from stoichiometric intramolecular aminopalladation.

Hydroamination reaction

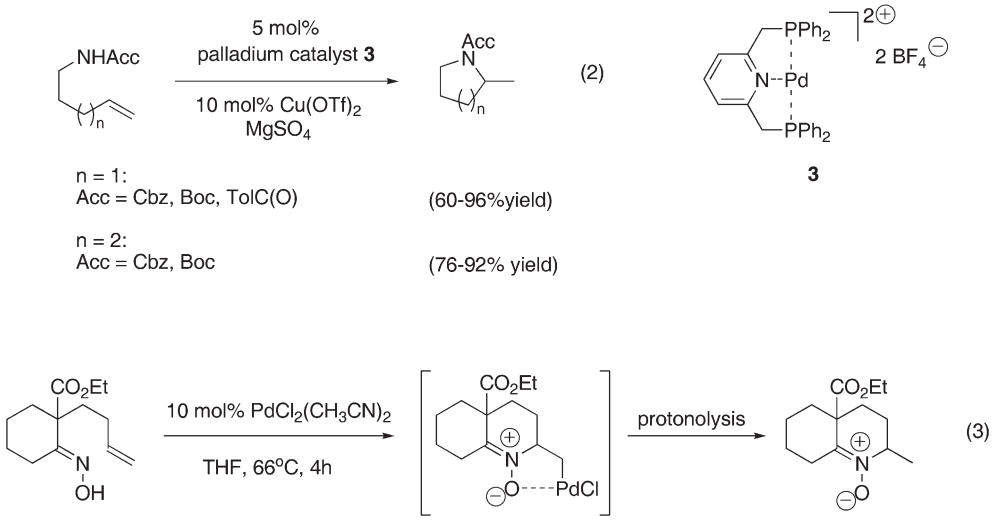
In principle, 2-aminoalkyl palladium compounds should serve as suitable intermediates for hydroamination processes of unactivated alkenes. By this, simple pyrrolidines, piperidines and related heterocyclic cores should be accessible from protonolysis of the carbon-palladium bond. Such a process had posed a significant long-term problem since organometallic palladium intermediates usually undergo β-hydride elimination (*vide infra*) at a higher rate. It was only recently solved by Michael who employed a preformed palladium complex **3** bearing 2,6-bis(diphenylphosphinomethyl)pyridine as a ligand.[4] This complex had been introduced in stoichiometric aminopalladation reactions earlier, and the application of the pincer ligand is believed to prevent formation of any open coordination sides at palladium, thereby suppressing undesired reactions such as β-hydride elimination to take place.[5] Indeed, several ω-amino alkenes undergo clean hydroamination at room temperature in the presence of 5 mol% of palladium catalyst **3** (Scheme 2, eqn (2)). The hydroamination pathway was proven by a deuteration experiment in which *N*-deuterated substrate gave clean deuterium incorporation at the newly formed methyl group of the product.

The reaction requires a substoichiometric amount of copper triflate for stabilisation. At present, it is still rather limited in scope: it requires carbamate amide substitution pattern at nitrogen, tolerates only terminal alkenes, and coordinating solvents completely inhibit the reaction. In particular, it is only successful in the presence of the tridentate PNP ligand. Still, the reaction closed a methodological gap and confirmed that simple protonolysis of an intermediary C–Pd bond can indeed be a feasible process.

Earlier, Grigg and co-workers had demonstrated that free oximes can undergo intramolecular palladium-catalysed nitrogen transfer to alkenes. The resulting alkyl–palladium bond is protonated by the acid liberated in the initial step. The resulting nitrone, which for the shown example is formed as a 1 : 1 mixture of isomers, could be submitted to subsequent intra- or intermolecular [3 + 2]-cycloaddition reactions with alkenes yielding higher elaborated isoxazolidine heterocycles.[6]

Aza-Wacker reactions

For the elaboration of more diversified structures, simple hydroamination represents a less desirable process. β-Hydride eliminating processes represent standard demetallation reactions in organometallic chemistry. As such, it has also found wide application in palladium-catalysed intramolecular

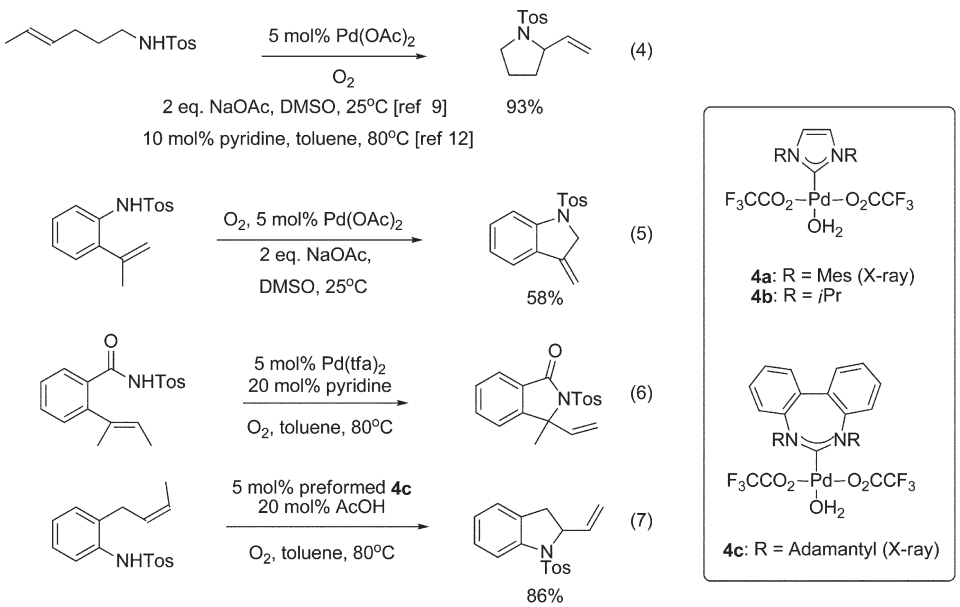


Scheme 2 Intramolecular hydroamination of alkenes: role of catalyst **3** and synthesis of nitrones.

amination reactions and, in principle, constitutes the most productive pathway once the initial aminopalladation has taken place. Depending on the substitution pattern, β-hydride elimination of 2-aminoalkyl palladium can furnish enamides or allylic amides, respectively, the latter representing the more common product. This particular process has received multiple investigation and the early work was reviewed several times before.[7,8] Among recent examples is the observation by Michael that palladium catalysis in the absence of ligand **3** gives rise to the expected enamide and amido-ketone product after hydrolysis.[4]

Recent development in this area focussed on the use of aerobic conditions for environmentally benign oxidation. To this end, Larock disclosed a convenient catalysts system consisting of 5 mol% of palladium acetate as catalyst precursor, sodium acetate as base and DMSO as solvent.[9] Under atmospheric oxygen pressure, a variety of different tosylamides underwent intramolecular aza-Wacker cyclisation to yield the corresponding allylic amides in yields of 40–93%. Eqn (4) in Scheme 3 gives a representative example for a room-temperature reaction. An interesting example of *endo*-amino-palladation was reported for the reaction in eqn (5) yielding the indene derivative with an exocyclic double bond.

Stahl and co-workers reported a further improvement by using a combination of 5 mol% palladium acetate in toluene with 10 mol% of pyridine.[10] Again, the reaction is characterised by high selectivity and by carrying out the oxidations at 80 °C, reaction times could be significantly lowered to about 2 h. Under such conditions, 87% yield was obtained for the cyclisation of eqn (4). A related protocol from Stoltz and co-workers showed that carbamides as substrates can also be employed.[11] With palladium trifluoroacetate as catalyst



Scheme 3 Intramolecular aza-Wacker cyclisation.

precursor, clean cyclisation reactions were obtained, and a representative example is depicted in eqn (6) in Scheme 3. All these reactions under aerobic conditions are believed to proceed *via* direct reoxidation of palladium, presumably through a pallada–peroxo intermediate.

A recent protocol by Stahl and co-workers described the use of N-heterocyclic carbene ligands for this transformation.[12] Therein, palladium complexes **4a–c** allowed for a clean reaction which proceeded under air in the presence of strong acid instead of oxygen pressure. Typical examples included the aza-Wacker cyclisation of eqn (4) and (7) in Scheme 3. With the successful application of catalyst precursors such as **4c**, the development of efficient chiral catalysts appears within reach.

Enantioselective aminopalladation of functionalised alkenes

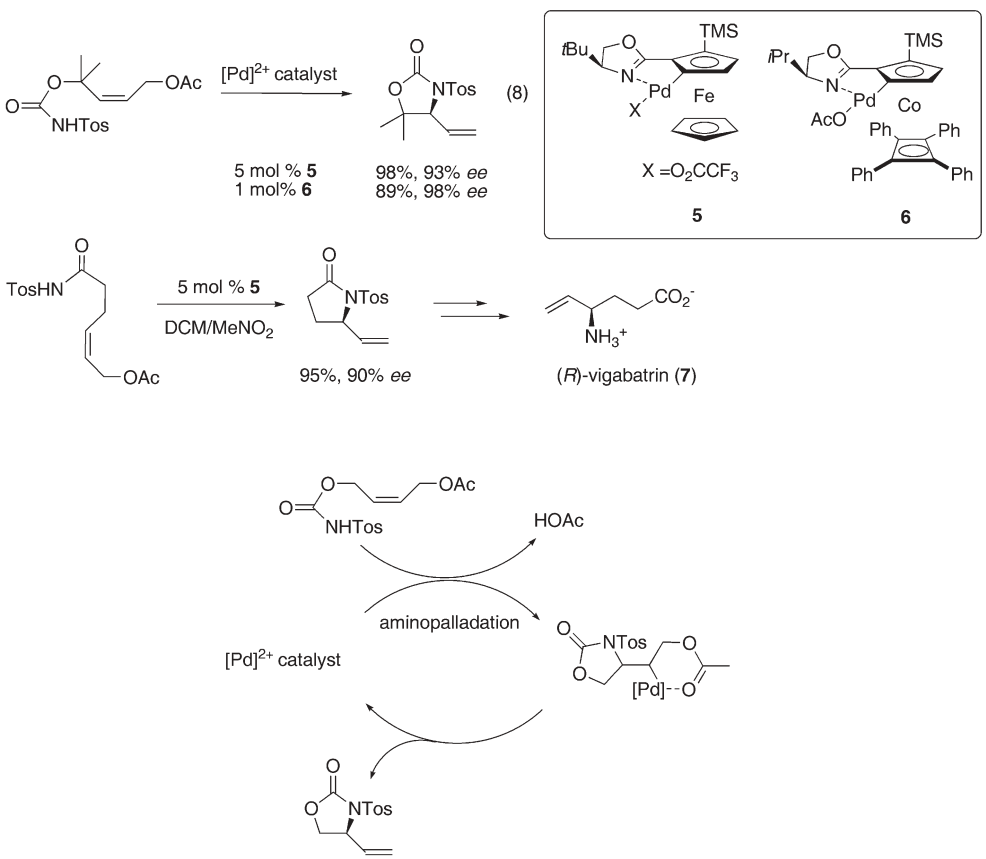
In principle, β-positioned leaving groups other than hydride should also be applicable for palladium removal. A sequence of enantioselective aminopalladation followed by deoxygenative depalladation was developed by Overman and Remarchuk.[13,14] This sequence employs planar-chiral palladacycles such as **5** or **6** as catalyst precursors. Initially, ferrocene based structure **5** allowed for efficient catalytic cyclisations with catalyst loadings in the range of 0.5–5 mol%.[13] As a disadvantage, these catalysts are generated from the inactive palladium iodide precursor upon silver salt activation and are not shelf-stable. With the cobalt sandwich **6**, a more robust catalyst precursor was developed which routinely performed well on the basis of a 1 mol% catalyst loading.[15] With these catalysts, various carbamates can be employed for intramolecular amidopalladation yielding the corresponding oxazolidin-2-ones.

Formation of pyrrolidinones is also feasible. An example is given for the conversion of a carbamate precursor which gives the corresponding enantiomerically enriched vinyl oxazolidin-2-one (Scheme 4, eqn (8)), which in turn can be transferred to (*R*)-vigabatrin **7**, the unnatural enantiomer of a powerful anti-epileptic drug.

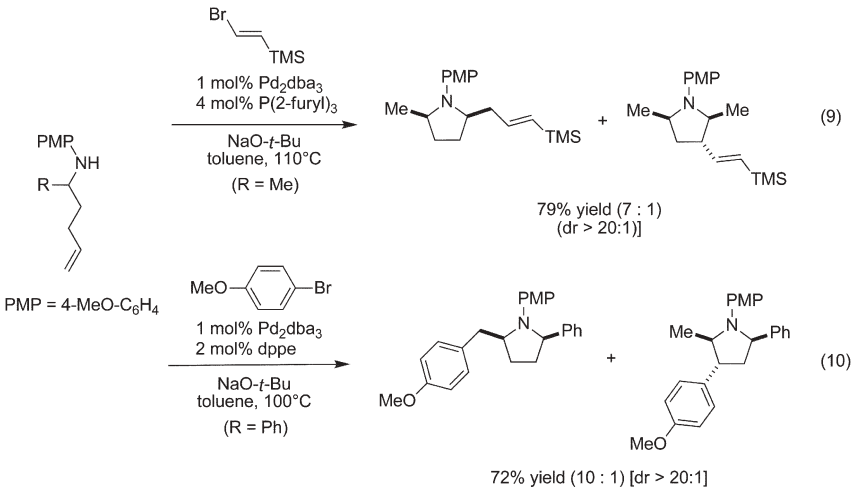
The reaction is initiated by aminopalladation of the alkene releasing a molecule of acetic acid from the catalyst (Scheme 4). Both *syn*- and *anti*-aminopalladation was discussed by the authors and the exact mechanistic course of this step remains undetermined. Once the intermediary alkyl–palladium species is formed, the product is released through a concerted depalladation which regenerates the initial catalyst state of palladium acetate. It is worthy of note that the catalyst oxidation state remains Pd(II) throughout the whole cycle.

Amino-Heck-type reactions

A stereoselective synthesis of *N*-aryl pyrrolidines has been developed by Wolfe from γ-(*N*-arylamino)alkenes and aryl bromides or vinyl bromides, using 1 mol% $Pd_2(dba)_3$, the appropriate phosphine ligand and NaO*t*Bu.[16,17] This carboamination reaction is believed to rely on the intramolecular



Scheme 4 Enantioselective aminopalladation chemistry and catalytic cycle.



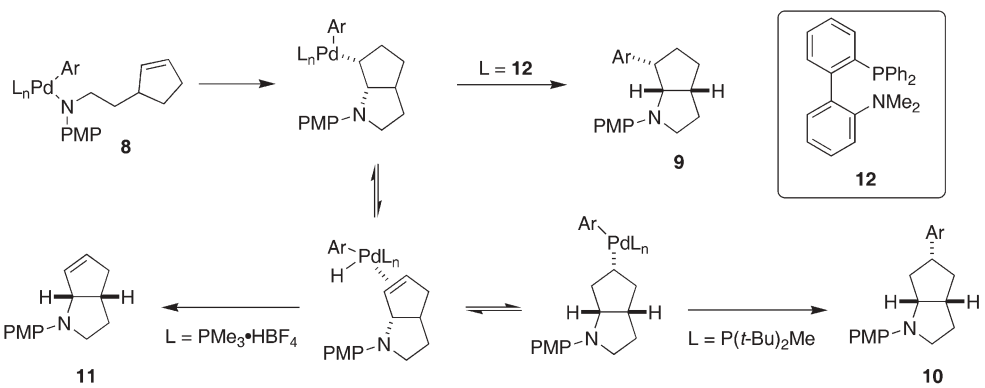
Scheme 5 Stereoselective synthesis of pyrrolidines.

insertion of the alkene into the previously formed Pd–N bond of the aryl- or vinylpalladium amido intermediate as outlined in Fig. 1, followed by a carbon–carbon bond forming reductive elimination to yield *N*-aryl-2-benzyl- (Scheme 5, eqn (10)) or *N*-aryl-2-allyl-pyrrolidines (Scheme 5, eqn (9)), respectively. The use of 1- or 3-substituted γ-(*N*-arylamino)alkenes allows for the synthesis of *cis*-2,5- and *trans*-2,3-disubstituted pyrrolidines with very good diastereomeric ratios of up to 20 : 1 (Scheme 5, eqn (10)).

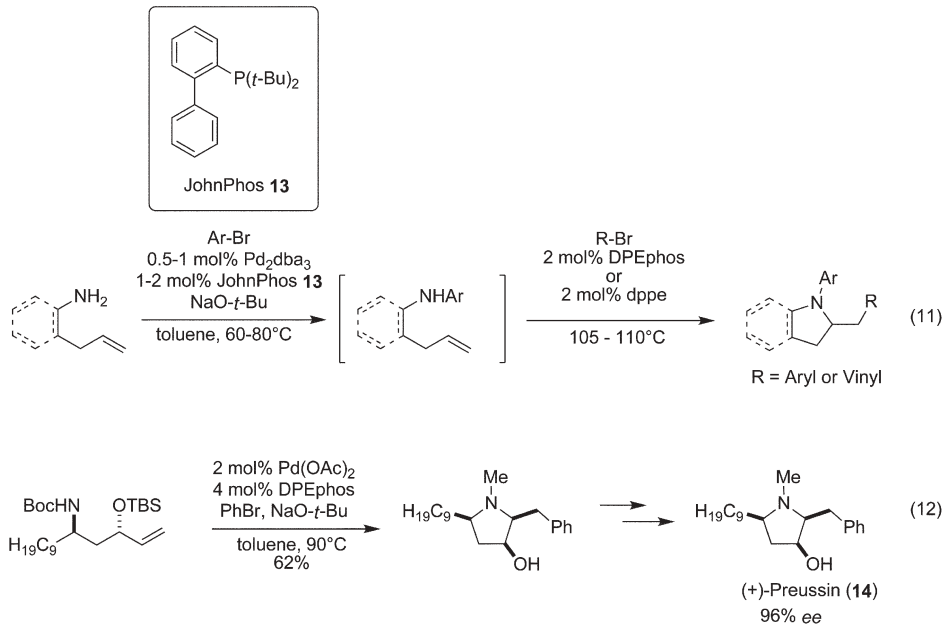
In both cases the formation of a minor regioisomer was observed, which originates from β-hydride elimination and subsequent reinsertion processes prior to the final carbon–carbon bond-forming reductive elimination. The same authors have studied the possibility of controlling relative rates of C–N and C–C bond forming reductive elimination, β-hydride elimination, alkene insertion and alkene displacement by changing the nature of the palladium–phosphine catalyst in order to convert the *in-situ* formed palladium(aryl)amido complex **8** selectively into 6-aryl octahydrocyclopenta[*b*]-pyrroles **9**, 5-aryl octahydrocyclopenta[*b*]-pyrroles **10** or amino-Heck-products **11** (Scheme 6).[18]

Furthermore, Wolfe and co-workers developed an efficient sequential one-pot catalytic transformation, which combines the synthesis of the *N*-arylated amines and the carboamination reaction.[17,19,20] Although the palladium-catalysed *N*-arylation of primary amines requires the bulky and electron-rich Buchwald ligand JohnPhos **13** as the phosphine ligand, which is not effective for the carboamination reaction, the two reactions can be conducted subsequently in one-pot *via* an *in-situ* ligand exchange protocol that allows modification of the catalyst structure after the first reaction step. This principle has been applied to the synthesis of *N*-aryl-2-benzylpyrrolidines,[20] *N*-aryl-2-allylpyrrolidines,[17] *N*-aryl-2-benzylindolines[19] and *N*-aryl-2-allylindolines[17] starting from γ-aminoalkenes or 2-allylanilines, respectively, by simply displacing JohnPhos **13** with a chelating bisphosphine ligand such as DPEphos or dppe (Scheme 7, eqn (11)).

Despite the utility of the transformations presented for the synthesis of *N*-arylpyrrolidines, these products cannot be easily converted into other *N*-substituted or unsubstituted pyrrolidines, as cleavage of the C–N bond is not readily accomplished. This limitation has been overcome by extending the established reaction protocol to *N*-acyl and *N*-Boc protected γ-aminoalkenes.[21] This strategy permitted the stereoselective total synthesis of the antifungal and antitumor agent (+)-preussin **14** and analogues thereof with an overall yield of 12% in nine steps starting from commercially available decanal (Scheme 7, eqn (12)).[22]



Scheme 6 Pathways to annulated pyrrolidines.



Scheme 7 Intermolecular coupling following aminopalladation.

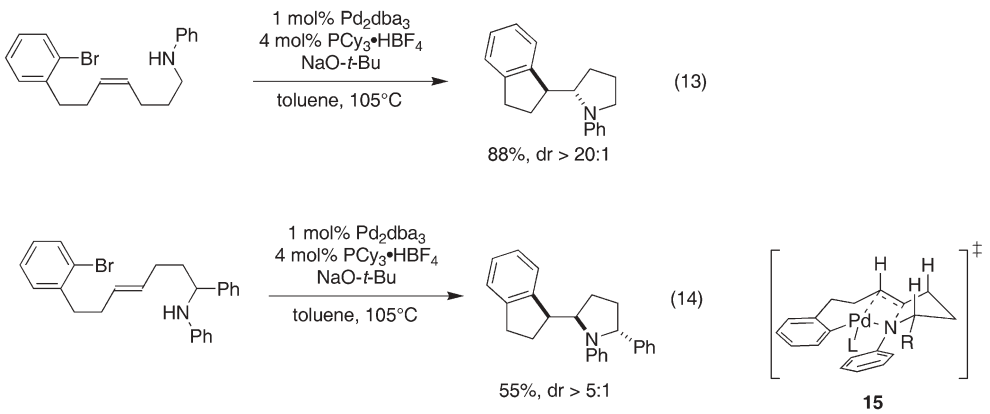
Most recently, this methodology has been employed for the stereoselective construction of heterocycles bearing attached carbocyclic rings by appending the aryl halide moiety to the unsaturated amine.[23] The stereospecificity (dr > 20 : 1) of the reaction can be rationalised by assuming a *syn*-insertion of the macrocyclic pallada-intermediate into the (*E*)- or (*Z*)-configured alkene, in analogy to the intermolecular reaction. Substrates bearing tethered anilines with α-stereocentres proceeded with complete *syn*-selectivity, affording the *trans*-pyrrolidine in case of the (*E*)-alkene as the major diastereoisomer. The authors assume that the pseudo-equatorial orientation of group R in the transition state **15** avoids energetically unfavorable transannular interactions in case of a pseudo-axial orientation (Scheme 8).

Aminopalladation in aza-Heck-type reactions

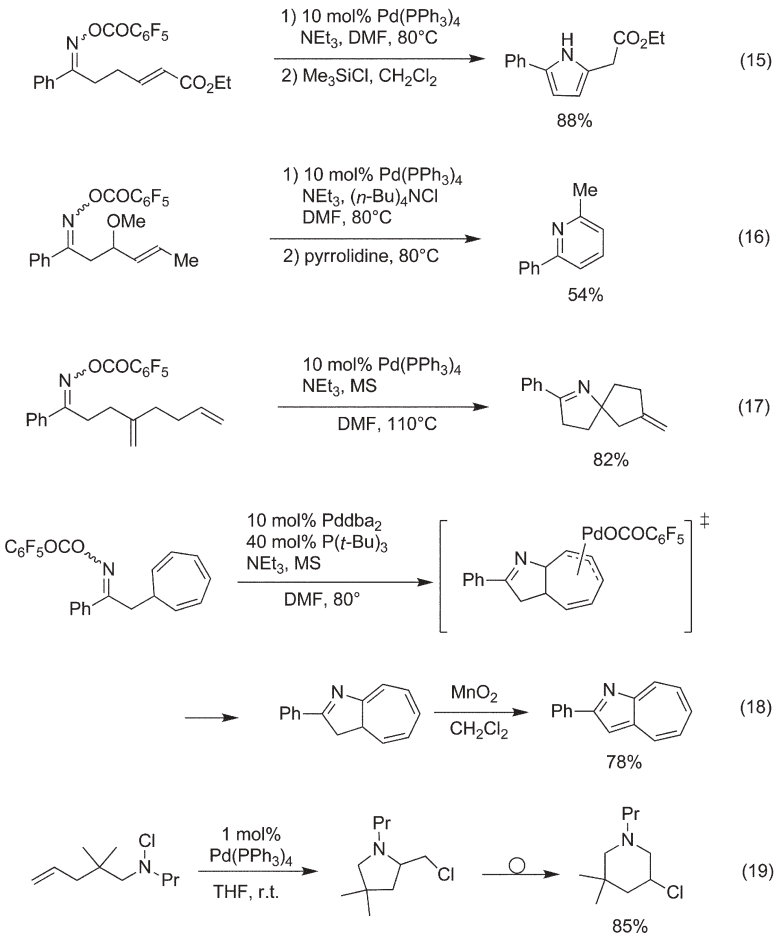
Unsaturated oxime derivatives have been employed by Narasaka and Kitamura in intramolecular amino-Heck-type reactions for the synthesis of a variety of aza-heterocycles.[24,25] In particular, the *O*-pentafluorobenzoyloxime moiety proved to be reactive towards oxidative addition with a palladium(0) complex yielding highly reactive alkylidene amino–palladium species, which showed insertion of the tethered alkene into the C–N bond. It was further observed, that the amino-Heck chemistry was independent of the stereochemistry of the oxime.

The synthesis of pyrroles was accomplished in moderate to good yields in the presence of 10 mol% $Pd(PPh_3)_4$ and NEt_3 from the corresponding γ,δ-unsaturated oxime derivative. The initial dihydropyrrole formed from a 5-*exo*-*trig*-cyclization isomerised either spontaneously under the cyclisation conditions or proceeded upon addition of TMSCl (Scheme 9, eqn (15)).

The introduction of a methoxy group in β-position of the γ,δ-unsaturated oxime allowed for the synthesis of pyridines in moderate yields adding $(n\text{-Bu})_4NCl$ to the original cyclisation protocol. The intramolecular coordination of the methoxy



Scheme 8 Intramolecular aminopalladation cross-coupling processes.



Scheme 9 Intramolecular aza-Heck-type reactions

group to the palladium(II) centre is assumed to direct the cyclisation to a 6-*endo* mode or accelerate elimination of methanol (Scheme 9, eqn (16)). Some rare examples of formation of isoquinolines have been reported using δ,ε-unsaturated oxime derivatives. A cascade amino-Heck reaction was performed by trapping the alkyl palladium intermediate with an additional olefin resulting in the synthesis of spiro-imines (Scheme 9, eqn (17)).[26] Addition of molecular sieves was effective to accelerate the reaction and increase the yield of the desired product.

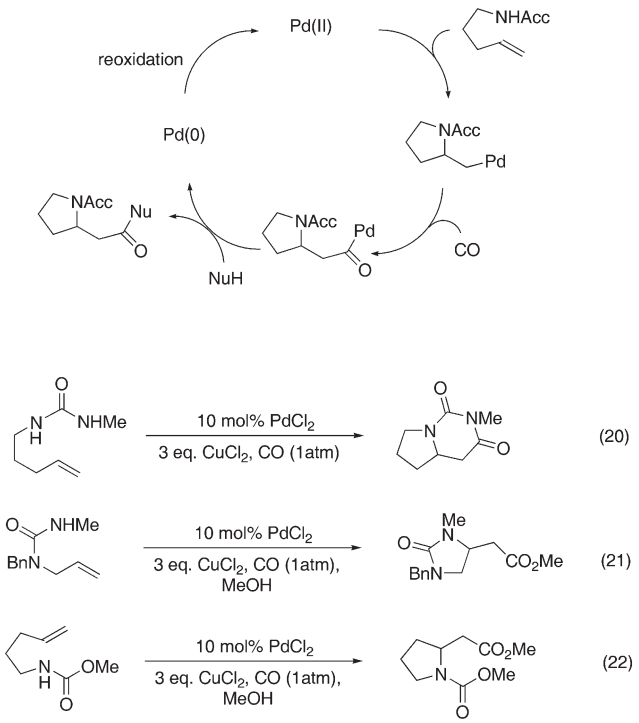
Finally, an unprecedented synthetic approach to a variety of 1-azaazulenes was developed by incorporating the γ,δ-unsaturated moiety in the form of a cycloheptatrienyl group.[27] Good yields for the amino-Heck cyclisation were obtained by using 10 mol% $Pd(dba)_2$ and 40 mol% P(*t*-Bu)$_3$ in the presence of molecular sieves. Successive oxidation of the crude product mixture with MnO_2 yielded the desired product (Scheme 9, eqn (18)).

In a different approach, *N*-chloroamines were employed for oxidative insertion of palladium in the N–Cl bond.[28] The β-amino-organopalladium species generated in the presence of 1 mol% $Pd(PPh_3)_4$ at room temperature proved to be stable enough towards β-hydride-elimination to be oxidised by another chloroamine molecule, leading to 2-chloromethylpyrrolidine. Under neutral conditions 2-chloromethylpyrrolidines are usually not stable and rearrange to 3-chloropiperidines (Scheme 9, eqn (19)). Overall, the substrate scope was rather limited due to the necessity of a geminal dialkyl group in the pentenyl chain in order to avoid competing β-hydride-elimination.

Aminocarbonylation reactions

The insertion of carbon monoxide into the alkyl–palladium bond constitutes a particularly beneficial way of activating 2-aminoalkylpalladium intermediates. Indeed, this reaction represents a viable pathway for the otherwise stable amino-palladation product from Scheme 1.[3] Tamaru described further catalytic reactions which initiate with the usual amidopalladation and proceed with CO insertion to yield the corresponding acyl–palladium intermediates (Scheme 10).[29–31] Such compounds can directly react in an intramolecular fashion for those cases where a suitable nucleophilic group is present. A representative example is given in eqn (20) in Scheme 10, where a nitrogen atom from the urea moiety displaces palladium from the acyl–palladium intermediate.[29] Alternatively, alcohols, which can function as solvent, may act as external nucleophile for palladium displacement (Scheme 10, eqn (21) and (22)).[30,31]

For all cases, this final step is reductive in nature and releases a palladium(0) catalyst state. For catalyst regeneration,

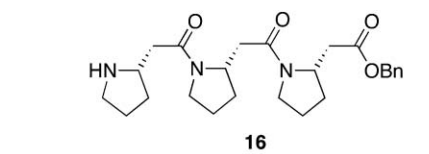


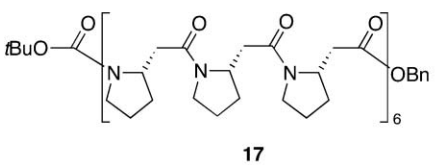
Scheme 10 Catalytic cycle for aminopalladation followed by CO insertion and representative reactions.

re-oxidation to palladium(II) is required and is usually accomplished with the aid of copper salts. Hence, these reactions are capable to construct higher functionalised products by sequentially transforming alkyl–palladium bonds into more reactive acyl–palladium groups which are then transformed into esters, amides or related functional groups (Scheme 10). Hence, the products from the mentioned reactions display interesting structural motifs. While pyrimidyldione derivatives from *endo*-cyclisation (Scheme 10, eqn (20)) have gained interest as leading structures in pharmaceutical research, the related products from exo-cyclisation (Scheme 10, eqn (21)) are protected derivatives of the as yet relatively unexplored β,γ-diamino carboxylic acids. Finally, the cyclisation and carbonylation of the carbamate from eqn (22) represents a particularly interesting approach to β-homoproline. In his seminal work on β-amino peptide secondary structures, Seebach investigated β-homoproline as an important example for the construction of β-peptide chains that are devoid of amide protons.[32] The chemistry of these compounds is of high interest, especially since the pyrrolidine core of the amino acid enforces the absence of N–H bonds. Still, the circular dichroism spectra support the presence of an ordered secondary structure. Fig. 2 depicts a trimeric derivative **16**, the X-ray structure its tris-tfa adduct and a *N*-terminally protected hexamer **17**.

Aminocarbonation reactions

Based on earlier stoichiometric work by Hegedus, a Heck-type termination for a catalytic sequential amidocarbonation reaction was reported recently.[33] Here, *N*-acroyl substituted aniline derivatives were submitted to oxidative cyclisations forming consecutively a nitrogen–carbon and carbon–carbon bond before displacing the palladium through β-hydride elimination yielding the unsaturated products (Scheme 11, eqn (23)). The palladium(II) catalyst is finally regenerated under aerobic conditions. Eleven examples were presented for achiral cyclisations employing 10 mol% of palladium acetate, 40 mol% pyridine, and toluene as solvent at 50 °C. A particularly interesting feature of the palladium-catalysed C–C bond formation relies in the complete regioselectivity of





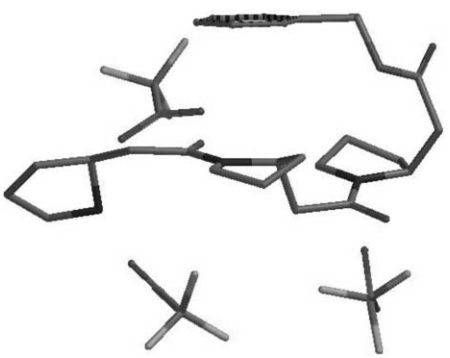
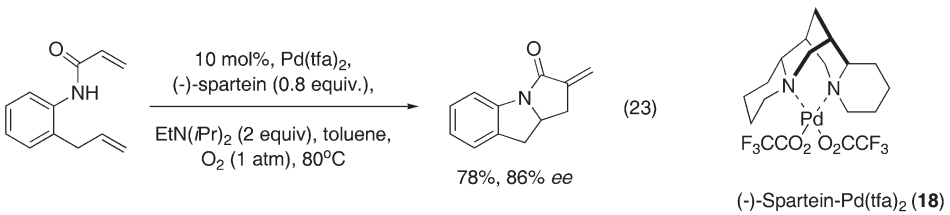


Fig. 2 β-Homoproline trimer **16** and oligomer **17**.



Scheme 11 Tricyclic heterocycle formation from sequential catalytic aminocarbonation.

5-*exo*-*trig* ring formation overriding completely the Michael acceptor nature of the alkene. Finally, the initial amidopalladation could be carried out in an enantioselective fashion by use of a sparteine/palladium catalyst. In the present study, the catalyst was generated *in-situ*, however, isolated [(−)-sparteine]palladium(II) complexes such as **18** are known from seminal investigation on enantioselective aerobic alcohol oxidation reactions.[34] Under these conditions, enantiomerically enriched tricyclic compounds could be obtained in the presence of Hunig base employing aerobic reoxidation. For other substrates, enantiomeric excesses in the range of 75 to 91% were obtained.

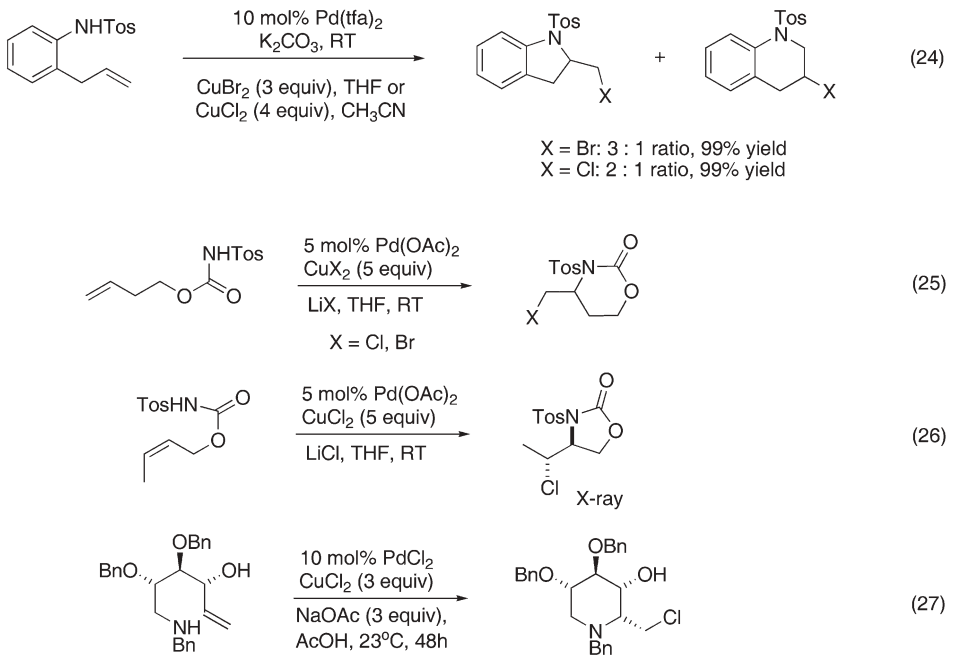
Aminohalogenation reactions

Interactions between palladium and copper are well established processes, the most prominent example being the use of copper chloride as re-oxidant in Wacker chemistry. Two recent reports have further broadened the application of copper salts in palladium catalysis and have shown that 2-aminoalkyl palladium intermediates are susceptible toward direct construction of carbon–halogen bonds. Such a reaction outcome had already been observed as an undesired side-reaction in the earlier aminocarbonylation reaction (Scheme 10, eqn (22)) where copper salts were employed as re-oxidants.[31] Recently, Chemler and co-workers showed that various aminohalogenation reactions proceed in THF or acetonitrile in the presence of potassium carbonate as base.[35] The reactions allow for moderate to excellent yields in the presence of an excess of the copper oxidant (3 to 4 equivalents). However, they usually suffer from rather low selectivity in the initial aminopalladation giving rise to mixtures of pyrrolidines and piperazines (Scheme 12, eqn (24)). Alternatively to palladium trifluoroacetate, palladium dibromide was equally effective. A stoichiometric reaction with net palladium bromide gave only Wacker cyclisation product and alkene isomerisation suggesting that the presence of copper(II) salts at the stage after the aminopalladation is crucial for the overall process. The exact role of the copper(II) has not been clarified so far and both palladium(II) and palladium(IV) intermediates may be involved in the final stage of carbon–halogen bond formation.

Related cyclisation processes were investigated by Lu and co-workers for carbamate and urea derivatives.[36] In these reactions, additional halogen sources in the form of lithium salts were employed and the reactions were carried out with a catalyst from palladium acetate and in THF at room temperature (Scheme 12, eqn (25)). The reaction was found to proceed with complete stereospecificity. Submitting a (*Z*)-configured compound to aminochlorination gave diastereomerically pure product in 50% yield (Scheme 12, eqn (26)). X-Ray analysis confirmed the expected relative configuration and the authors favoured a sequence of *trans*-aminopalladation followed by oxidative cleavage of the carbon–palladium bond with retention of configuration. Finally, palladium-catalysed aminochlorination was employed for the synthesis of aminoalkenitols (Scheme 12, eqn (27)).[37] Polar solvents such as glacial acetic acid were usually required in order to achieve high yield and selectivity. Hence, under the depicted conditions 70% yield were obtained for a product formation, which favoured the shown L-*ido* derivative over the D-*gluco* epimer in a 19 : 1 ratio (90% de).

Aminoacetoxylation reactions

An oxidation protocol (Scheme 13, eqn (28)) for the direct aminoacetoxylation of alkenes was developed by Sorensen and co-workers.[38] It provides a convenient approach to various pyrrolidines, piperazines, lactams, oxazolidin-2-ones and oxazinan-2-ones with vicinal acetoxy group. The reaction requires tosyl amides or *N*-tosyl carbamates as the nitrogen



Scheme 12 Aminohalogenation reactions employing copper salts as halogen source.

component and proceeds through initial aminopalladation. The intermediary 2-aminopalladium complex is supposedly oxidised to a palladium(IV) species by iodosobenzene diacetate. The latter can also serve as acetate source, however, depending on the respective reaction protocol, addition of tetrabutylammonium acetate or conducting the reaction in acetic acid–acetic anhydride may be preferential. In all cases, the product will arise from reductive acetoxylation of the palladium(IV) intermediate.

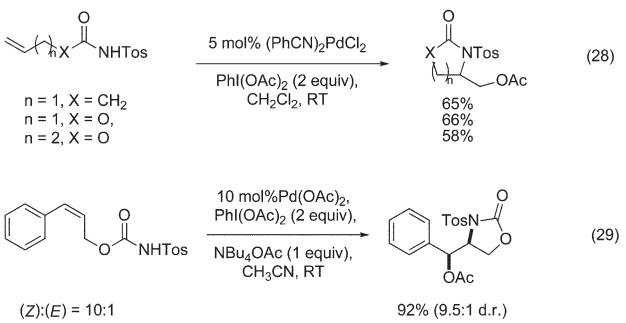
It is important to note that the reaction is not restricted to terminal alkene precursors. For example, a (*Z*)-configured cinnamyl derivative underwent clean aminoacetoxylation with complete preservation of stereoinformation (Scheme 13, eqn (29)), while the corresponding pure (*E*)-isomer gave the corresponding diastereomeric product in 65% yield.

Diamination reactions

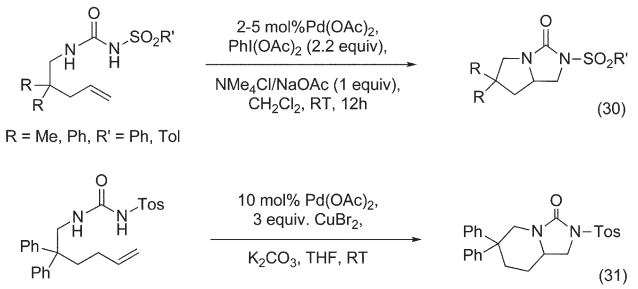
The consecutive transfer of two nitrogen atoms to an alkene results in the synthesis of a vicinal diamine group. A reaction of this type was realised with the aid of urea groups as a tethered source for the two nitrogen atoms.[39] Hence, when terminal alkenes were submitted to intramolecular diamination, exclusive nitrogen transfer took place giving the corresponding diamines in high yields (Scheme 14, eqn (30)). These are embedded within the urea core and from the viewpoint of heterocycle formation, the reaction constitutes a new approach toward annulated urea derivatives. Deprotection of the urea core yields vicinal diamines with different substitution pattern at the respective nitrogen atoms.

Position-selective deuteration was employed in order to get a first insight into the stereochemical course of the reaction. Thus, when a *trans*-configured monodeuterated alkene was submitted to oxidation, diastereoselective diamination was obtained.

The same outcome was observed within the development of a recent alternative process which makes use of copper(II) bromide as reoxidant (Scheme 14, eqn (31)).[40] Under these conditions, internal alkenes could be converted into the corresponding urea products and again, the (*E*)-geometry of the double bond from the starting material was cleanly transferred into the products relative stereochemistry. In addition, formation of six-membered annulated products could be accomplished with a significantly lower catalyst loading of 10 mol%.



Scheme 13 Aminoacetoxylation reactions employing iodosobenzene diacetate as oxidant and acetoxy source.



Scheme 14 Cyclic ureas from intramolecular diamination of alkenes.

Several initial steps during this catalytic process appear to be reversible which explains the complete selectivity both in the initial heterocycle formation by aminopalladation as well as the exclusive diamination without any detectable amount of oxo-incorporation from the urea or, alternatively, aminoacetoxylation being observed. The selective transfer of double bond geometry into the product stereochemistry is in agreement with the observation in the related aminochlorination reaction (Scheme 12). In principle, sequences of *trans*-aminopalladation followed by C–N-bond formation with retention at the carbon centre or, alternatively, *syn*-aminopalladation with subsequent S_N2-type depalladation are both possible. Detailed mechanistic investigation will be required also for the present oxidation reaction in order to settle this question.

Summary and outlook

Palladium catalysis for the intramolecular amination of alkenes is a mature synthetic process.

The high structural diversity that can be obtained from alkene amination processes as key step proves the synthetic versatility of palladium catalysts. While the initial aminopalladation necessarily requires palladium(II) as the catalyst oxidation state, the exact course of the subsequent catalysis steps to a large extent depend on the chosen reaction conditions, among which the electronic situation at the palladium centre is a key issue. If the conditions are chosen carefully, several pyrrolidine, piperazine, oxazolidin-2-one, pyridine, pyrimidyldione, urea and amino acid forming reactions can be accomplished together with concommitant elaboration of additional functional groups which open further synthetic opportunities for broad structural diversification.

At present, several open issues remain to be solved. These include the development of a broader scope regarding internal alkenes and the development of efficient ligands for palladium. The latter aspect is of particular importance since it may be crucial in order to trigger the reactivity as in the case of hydroamination (Scheme 2). In addition, the development of suitable chiral ligands for asymmetric protocols is obviously a necessary task to ensure access to enantiomerically enriched heterocycles. This is of particular importance for a variety of processes as for example the synthesis of more elaborate biomolecules such as homoprolines (Fig. 2), but especially desirable for the oxidative processes of aminohalogenation, aminoacetoxylation and diamination.

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