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The Quest for Palladium-Catalysed Alkyl–Nitrogen Bond Formation

Kilian Muñiz,*[a,b] Claudio Martínez,[a] and Álvaro Iglesias[a]

ABSTRACT: Our interest in the development of transition-metal catalysis for the realisation of vicinal diamination reactions of alkenes started about a decade ago. A number of successful transformations in this area have been developed using palladium catalysis. As a challenging aspect of major importance, the palladium-catalysed coupling of alkyl–nitrogen bonds constitutes the second step in diaminations of alkenes. We here discuss the details that led us to consider high-oxidation-state palladium catalysis as a key feature in such C–N bond-forming reactions. This work discusses both our own contributions and the ones from colleagues and combines the discussion of catalytic reactions and stoichiometric control experiments. It demonstrates that reductive alkyl–nitrogen bond formation from palladium(IV) proceeds with a low activation barrier and through a linear transition state of nucleophilic displacement.

Keywords: alkenes, amination, oxidation, reductive elimination, palladium

1. Introduction

Palladium catalysis has enabled the realisation of a variety of different carbon–heteroatom and carbon–carbon bond-forming reactions and represents one of the major success stories in modern organometallic chemistry.[1]

In the area of carbon–nitrogen bond formation, the seminal results by Buchwald and Hartwig[2] and Barluenga[3] on carbon–nitrogen bond formation within the Csp²-hybridised domains have been a major centre of attention (Scheme 1). These reactions provide access to aniline derivatives in the case of aryl couplings,[2] while they generate enamines for the coupling with vinyl derivatives.[3] A large number of synthetically important protocols have been developed, which include variation of the ligands to palladium, base and reaction conditions in general. The common mechanistic feature of these reactions consists of the formation of intermediary monomeric σ-aryl palladium amido complexes and their involvement in a direct three-centre-four-electron (3c-4e) reductive elimination[4] to

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regenerate the low-oxidation-state palladium catalyst and establish the final carbon–nitrogen bond. We were intrigued to develop comparable conditions in order to realise the corresponding alkyl–nitrogen bond formations.

Theoretical reports predicted the general feasibility of such sp³-carbon–nitrogen coupling processes. In 2003, Macgregor reported density functional calculations that predicted the possibility of reductive C–N bond formation from monomeric palladium(II) complexes.[5] For the model complex cis-(PH$_3$)$_2$Pd(Me)NH$_2$, an activation barrier of 30.5 kcal/mol was found. This energy barrier was significantly lower when the dissociation of one phosphine ligand was considered. For the corresponding tricoordinate complex (PH$_3$)Pd(Me)NH$_2$, the 3c-4e reductive elimination required an activation energy of 20.3 kcal/mol. Despite these encouraging predictions, the corresponding experimental proof has not yet been delivered.

Attempts in this area by Cloke have led to the synthesis of monomeric σ-neopentyl palladium complexes bearing N-heterocyclic carbenes (Figure 1).[6] Coordination of primary and secondary amines to the palladium centre generated stable palladium complexes **1** and **2**, respectively. These were considered suitable model complexes for a putative catalytic cycle of palladium-mediated alkyl–nitrogen coupling. However, attempts towards their base-mediated conversion to the corresponding amide palladium complexes or towards direct C–N coupling all failed. This outcome was rationalised by the assumption that the required amine deprotonation was hampered due to the high electron density at the palladium centre, which precludes the required acidification of the N–H bond.
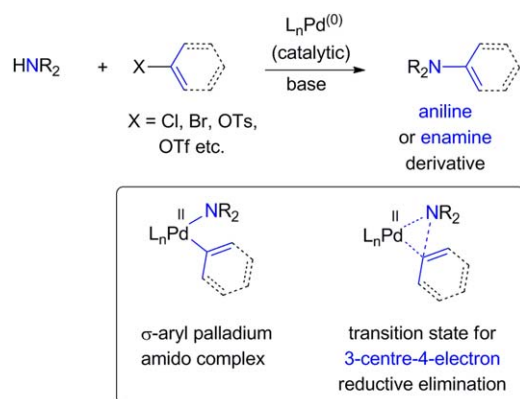
The common understanding that alkyl–nitrogen bond formation within the palladium(II) coordination sphere is not an anticipated pathway is nicely underlined by a series of isolated palladacycles from the Overman laboratory's studies on the installation of quaternary stereocentres through enantioselective Heck reactions.[7] Isolated palladacycles **3α** and **4β** are representative for a range of different complexes and were characterised by X-ray analysis. While conditions towards the

Scheme 1. Conventional palladium-catalysed C_{sp^2}–N bond formation.

Fig. 1. Isolated palladium complexes that do not promote direct reductive C–N formation.

corresponding hydride elimination pathways were studied in detail, the potentially competing C–N bond formation reactions were obviously not anticipated and therefore not even discussed as a possible alternative.

Reactions of C_{sp^3}–N bond formation may be possible under special conditions. Stahl discovered an interesting palladium and copper co-catalysed aerobic amination reaction (Scheme 2).[8] This transformation couples two norbornene molecules **5** and tosylamide to afford the product **6**. The reaction was suggested to start from an aminopalladation on norbornene to intermediate **7** followed by insertion of another alkene into the σ-alkyl–palladium bond. The resulting σ-alkyl–palladium intermediate **8** undergoes

reductive C–N bond formation to product **6**. The exact mechanistic details of this coupling have remained elusive so far.

The discussed transformations give an accurate picture of the status of palladium catalysis in alkyl–nitrogen bond formation in the early 2000s.[9] A noteworthy exception is represented by the palladium-catalysed C–N bond formation at allylic positions. This particular C–N bond formation is readily available due to the greatly enhanced reactivity within the established allylic palladium chemistry (aza-Tsuji–Trost).[10] Recent important examples to this end include the palladium-

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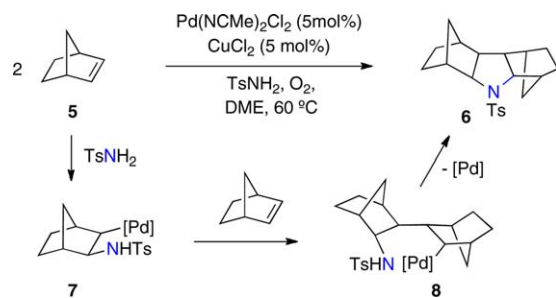
Scheme 2. C–N bond formation in the palladium-catalysed aerobic amination reaction of norbornene.

catalysed direct allylic amination[11] and its involvement in the diamination of 1,3-butadienes.[12]
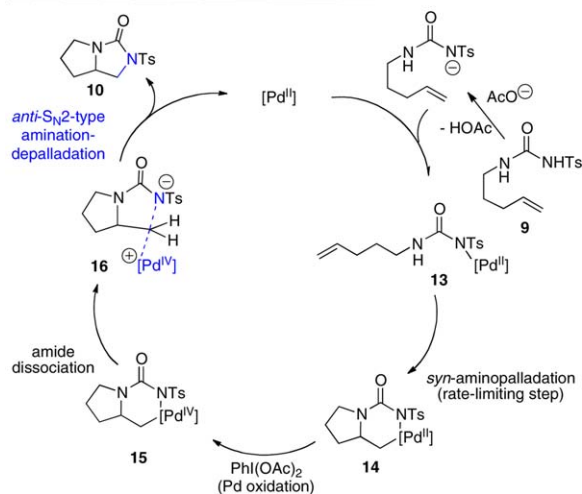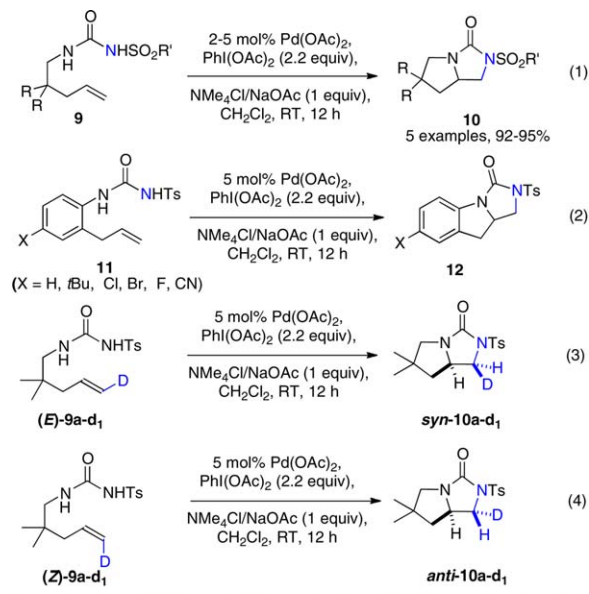
2. Intramolecular Diamination of Alkenes

High-Oxidation-State Palladium(IV) Catalysis

As mentioned, our interest in palladium-catalysed alkyl–nitrogen bond-forming reactions originates from our occupation with the development of catalytic reactions that would enable the direct vicinal diamination of alkenes.[13] Realising that alkyl–nitrogen bond formation is obviously not trivial within the conventional palladium(0/II) catalysis manifold, a different approach was pursued.[14] In fact, suitable reaction conditions based on stoichiometric palladium chemistry had been devised as early as in the 1970s. Pioneering research by Bäckvall revealed that palladium(II) complexes can promote the diamination of alkenes using an excess of *tert*-butylamine as the nitrogen source, provided that the transformation was conducted in the presence of a strong oxidant.[15] The postulation of a monomeric palladium(IV) key intermediate for C–N bond formation was clearly ahead of its time.

We built upon this insight and subsequently arrived at the first successful catalytic vicinal diamination of alkenes (Scheme 3).

The reaction is based on nitrogen-tethered ω-alkenes. The *N*-sulfonylated ureas **9** and **11** were identified as the best substrates, and a catalytic amount of a palladium(II) salt such as palladium diacetate together with an acetate base is employed.[16,17] Polyvalent iodine(III) reagents such as PhI(OAc)$_2$ function as the terminal oxidant.[18] As depicted in Scheme 3, successful substrates lead to products **10** and **12** with aliphatic and aromatic backbones (Eq. 1 and 2).

The reaction proceeds within the palladium(II/IV) manifold.[19] It occurs with complete stereospecificity regarding the double-bond geometry, as demonstrated for selectively deuterated substrates (**E**)- and (**Z**)-**9a-d₁** (Eq. 3 and 4). Based on additional NMR titration experiments and Hammett correlation studies, the underlying catalytic cycle was determined.[17]

Scheme 3. General reaction, control experiments and catalytic cycle for the pioneering urea-based intramolecular diamination of alkenes under Pd(II/IV) catalysis.

The catalytic diamination originates from pre-coordination of the palladium(II) catalyst to the deprotonated urea **9** (intermediate **13**). For geometric reasons, the subsequent intramolecular aminopalladation[20] must then proceed with *syn* stereochemistry to give the intermediary palladacycle **14**. This step could be monitored by NMR and represents the rate-limiting step of the cycle. In agreement with this result, a Hammett correlation study on the diamination of the aniline derivatives **11** demonstrated a significant electronic influence for the initial amination. The second C–N bond-formation event is then accomplished through a palladium(IV) catalyst state, which arises from oxidation of **14** to **15**. In accord with the diastereoselective outcome from labelling studies on (**E**)-
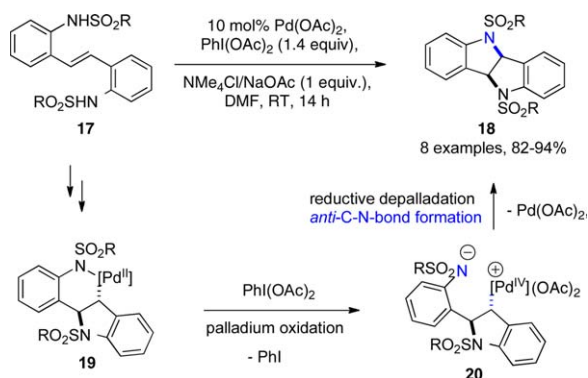
Scheme 4. Palladium(II/IV)-catalysed intramolecular diamination of stilbenes.

Scheme 5. Intramolecular vicinal diamination under Pd(II)/Cu(II) catalysis.

and (Z)-9a-d$_1$, the final step of C–N bond formation must proceed with inversion of configuration in order to account for the overall stereochemistry of the cyclic urea products 10a-d$_1$. An S$_N$2 transition state 16, reminiscent of the one from the platinum(IV)-catalysed methane oxidation in the related Shilov reaction,[21,22] was suggested for this step. The required nucleophilicity of the nitrogen anion and its capacity for previous dissociation from the palladium centre confirms the design of the N-tosylated urea.
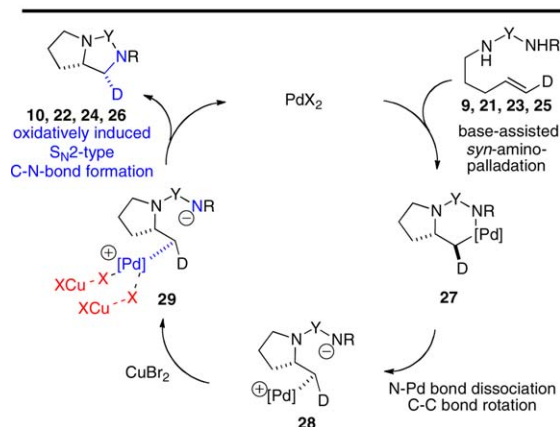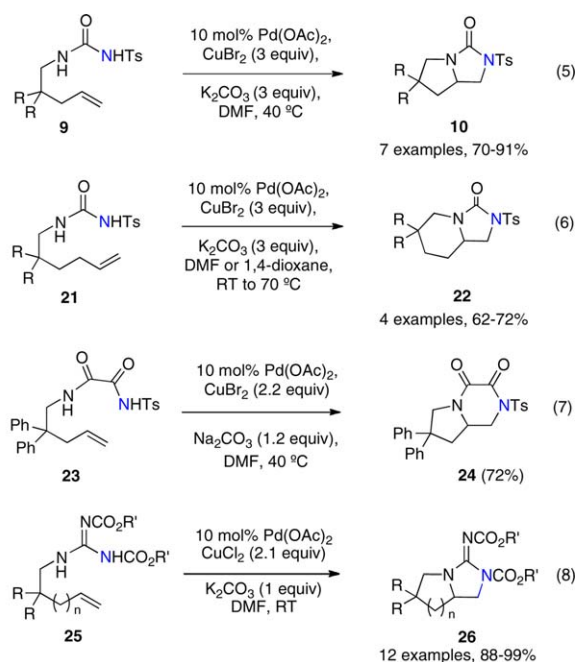
It is noteworthy that a theoretical investigation on this process proposed the alternative anti-aminopalladation/syn-C–N bond formation to be operative. These data suggested the required 3c-4e reductive elimination to proceed with an unrealistically low barrier of only 17.2 kcal/mol.[23]

The identical stereochemical pathway for the second C–N bond formation may be involved in the palladium(II/IV)-catalysed diamination of stilbenes 17 as internal alkenes (Scheme 4).[24] Here, geometric constraints should favour an initial endo-selective anti-aminopalladation to intermediate 19. Palladium oxidation followed by sulfonamide dissociation provides the cationic palladium(IV) intermediate 20 for anti-C–N bond formation toward 18.

Copper-Mediated Transient Oxidation

The concept of transient palladium oxidation for the reductive generation of C–X bonds was defined by Henry in the context of Wacker-type oxidations.[25] In fact, the beneficial combination of palladium and copper is still best underlined by the seminal success of the Wacker process.[26]
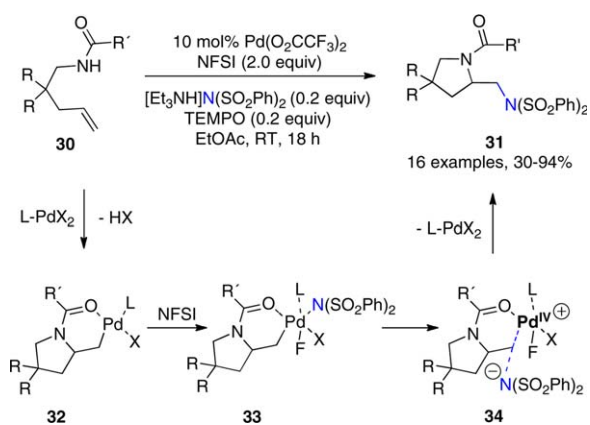
For the particular case of vicinal diamination of alkenes, several different transformations have been developed (Scheme 5), in which the combination of palladium and copper was explored as an alternative to the earlier Pd(II)/iodine(III) system. First, the standard urea-based substrates 9 from Pd(II/IV) catalysis could be employed with similar success when a catalytic amount of palladium diacetate is complemented by the use of three equivalents

of copper bromide (Eq. 5).[27] In addition, six-membered ring annellation toward 22 is significantly accelerated when compared to the earlier system (Eq. 6). The scope could further be extended to include the oxalimide 23, which is not reactive under the previous conditions using polyvalent iodine (Eq. 7).[14] Finally, for the case of guanidines 25, the combination of palladium diacetate and copper chloride generated mild conditions for the corresponding cycloguanidation reaction to proceed with complete selectivity, for both the concomitant five- and six-membered ring annelations (products 26, Eq. 8).[28] This is a noteworthy accomplishment, since the alternative Pd(OAc)$_2$/PhI(OAc)$_2$ catalysis provides aminoacetoxylation species as the only products.

This successful outcome invokes a decisive effect of copper on the palladium catalyst state in the final C–N bond formation, and the mechanistic rationale for the new type of
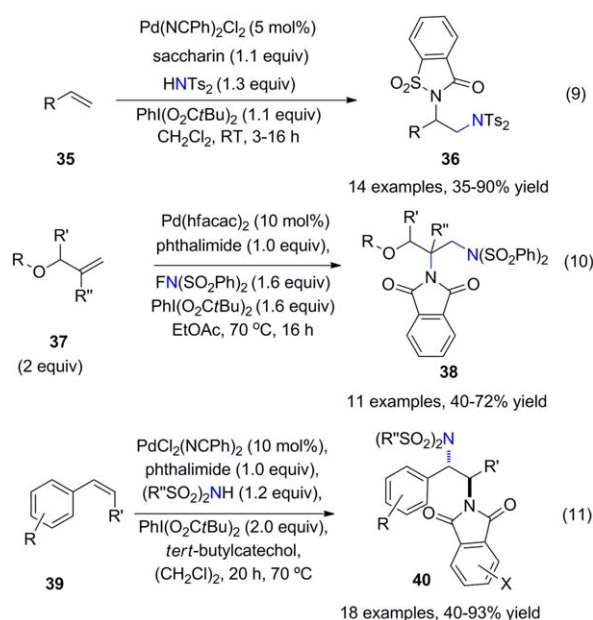
Scheme 6. Diamination upon intermolecular C–N bond formation (X = F, O₂CCF₃).

Scheme 7. Palladium(II/IV)-catalysed diamination of terminal and internal alkenes under intermolecular reaction control.

palladium catalysis using copper oxidants has indeed been based on the *transient oxidation* concept.[25] The general catalytic cycle for palladium(II)/copper(II) diamination is depicted in Scheme 5. The reaction starts with a base-induced *syn*-aminopalladation to **27** followed by dissociation of the Pd–N bond to afford **28** prior to or during the oxidation step. Obviously, due to a lower oxidation potential, copper(II) salts are not expected to generate palladium(IV) intermediates. Instead, an oxidation based on anion coordinative interaction between copper(II) and palladium(II) is assumed. Upon electron transfer from palladium to copper, the σ-alkyl–palladium bond is rendered more electrophilic and engages in a subsequent S_N2-reaction with the neighbouring nitrogen nucleophile. This transient oxidation state **29** enables direct regeneration of the palladium(II) catalyst upon product formation. The reduced copper compound should in principle be prone to aerobic re-oxidation;[25,29] however, the basic conditions of the overall reaction have rendered such reaction conditions problematic.[30] A transient oxidation may also be involved in the above-mentioned C–N bond formation from Scheme 2.[31]

Intermolecular C$_{sp^3}$–N Bond Formation in Diamination Reactions

A particularly versatile development was made by Michael, who introduced *N*-fluoro-bis(phenylsulfonyl)imide (NFSI) for diamination reactions, involving an intra-/intermolecular sequence (Scheme 6).[32] This versatile reagent[33] allowed for the development of a palladium-catalysed diamination reaction, in which the initial aminopalladation proceeds in an intramolecular fashion from **30**. The resulting aminopalladated intermediate **32** is selectively oxidised by NFSI to generate the corresponding hexacoordinated palladium(IV) intermediate **33**.[34] Upon dissociation of the bissulfonimide anion from the Pd coordination sphere, a cationic pentacoordinated palladium complex **34** is reached as the key intermedi-

ate. The latter undergoes nucleophilic substitution by the bissulfonimide to form the second C–N bond in products **31** in a manner analogous to the intramolecular pathway from Scheme 3. The same reaction could be carried out in an enantioselective manner, when a chiral quinoline oxazoline ligand was employed.[32b]

3. Intermolecular Diamination of Alkenes

High-Oxidation-State Palladium(IV) Catalysis

The development of palladium-catalysed vicinal diamination of alkenes under complete intermolecular reaction control was realised by our group starting in 2010 (Scheme 7). The first two protocols involved the use of terminal alkenes. In the initial study, terminal alkenes **35** were cleanly converted into the corresponding diamines **36** (Eq. 9).[35]

This reaction calls for the use of saccharin as nitrogen source for the aminopalladation and, after oxidation to Pd(IV) with the polyvalent iodine(III) reagent, establishes the second C–N bond with bissulfonimides such as Ts₂NH. The second variant employs allylic ethers **37**, palladium(II) hexafluoroacetylacetonate as catalyst source and phthalimide as nitrogen source for the initial aminopalladation (Eq. 10).[36,37] A combination of polyvalent iodine(III) and NFSI provides the required palladium(IV) intermediate for the second amination towards **38**, which is reminiscent of the final step from Scheme 6.
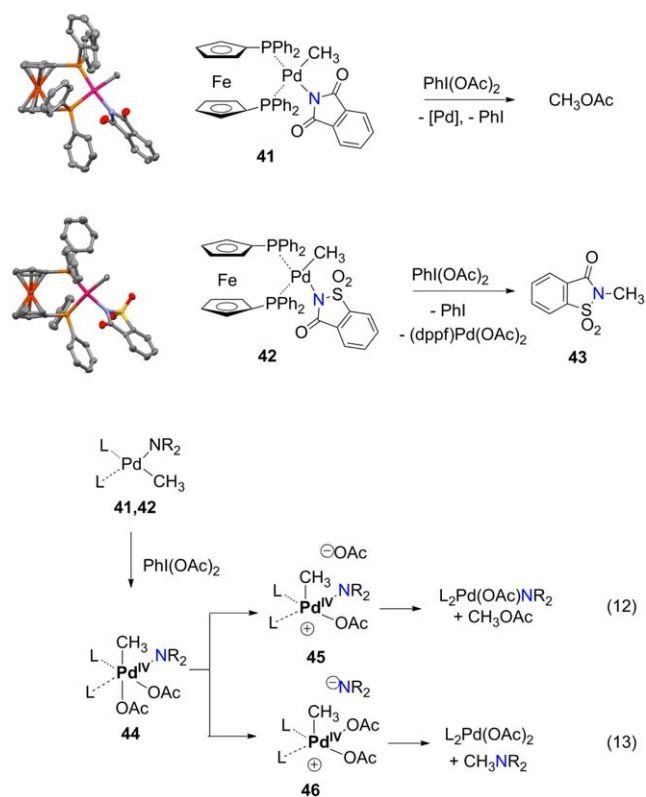
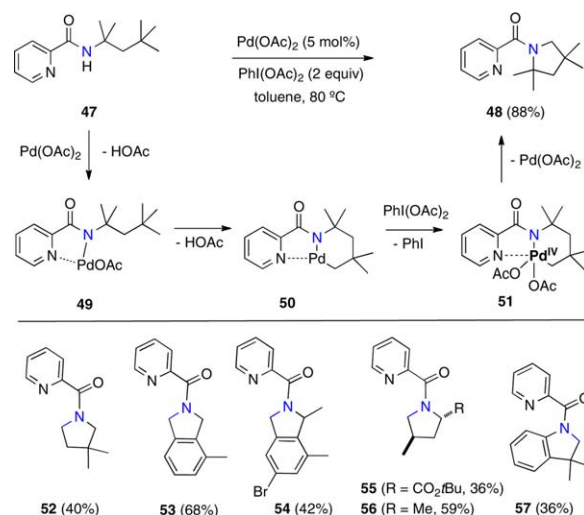**Scheme 8.** Palladium model complexes for C–N bond formation.

Scheme 9. Intramolecular palladium(II/IV)-catalysed C–H amination.

Based on these precedents, an important vicinal diamination was then developed for internal alkenes **39** (Eq. 11).[38] It employs bis(benzonitrile)palladium(II) dichloride as catalyst source and phthalimide in the aminopalladation.[39,40] As for **35**, the reagent combination of polyvalent iodine reagent di(pivaloxy)iodobenzene and bissulfonimides[41] enables the second carbon–nitrogen bond formation, which proceeds at the benzylic position and with complete stereoselectivity to chemoselectively access products **40** as single diastereoisomers.

While the exact mechanistic details of these reactions are still under investigation, the concept of catalytic C–N amination using palladium(IV) high-oxidation-state chemistry has indeed proven successful for the second amination step, which tolerates both terminal and internal carbon centres.
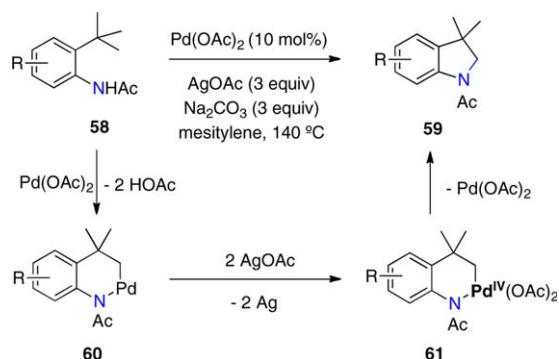
4. Palladium-Catalysed Alkyl–Nitrogen Coupling

Palladium Model Complexes, Mechanistic Evaluation and Catalysis

The role of high-oxidation-state palladium intermediates in carbon–nitrogen bond formation was investigated in more detail using isolated palladium(II) complexes. To this end, a series of monomeric palladium(II) complexes incorporating both a methyl substituent as representative σ-alkyl group and different amide groups such as phthalimide (**41**) and saccharide (**42**) were synthesised.[42,43] In a first set of experiments, dppf-ligated complexes **41** and **42** were submitted to oxidation with the polyvalent iodine reagent PhI(OAc)$_2$ (Scheme 8). Although the two compounds share almost identical structural features and the inability to undergo thermally induced C–N bond formation, their reaction outcome upon oxidation with polyvalent iodine(III) reagents is significantly different. Upon oxidation with PhI(OAc)$_2$, compound **41** undergoes reductive elimination to methyl acetate, without any of the desired N-methylphthalimide being detected. In contrast, complex **42** delivers N-methylsaccharin **43** upon oxidation with PhI(OAc)$_2$. This significant difference was rationalised through the different leaving group capacity of the nitrogen anions that are involved. In the case of phthalimide, with its high pK_a value of 8.3, the oxidation of **41** results in an octahedral palladium(IV) state **44**, from which acetate dissociation is preferred over phthalimide dissociation. As a result, the nucleophilic attack at the σ-methyl palladium bond in **45** is carried out by the acetate, which ultimately leads to the undesired oxygenation reaction (Eq. 12). In contrast, the more acidic saccharin (pK_a = 1.6) provides a stabilised anion with a superior leaving group ability than acetate and therefore by dissociation from **44** generates the reactive cationic Pd(IV) complex **46**, which enables the desired C–N bond-forming reaction (Eq. 13). These model complexes **41** and **42** provided the first insight into the influence of different anions on reductive carbon–heteroatom bond formation from palladium(IV) complexes. The conclusion that the major prerequisite to guarantee selective C–N bond formation rests with the leaving group ability of the nitrogen source matches related observations from catalytic reactions within the palladium(II/IV) manifold.[17,28]
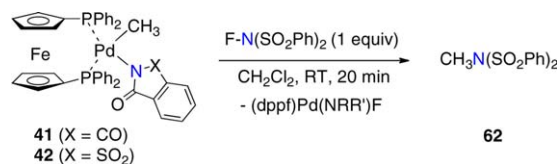
Scheme 10. Intramolecular palladium-catalysed C–H amination.

Scheme 11. Model complexes for reductive C–N bond formation with NFSI.

Scheme 12. Palladium(II/IV)-catalysed intermolecular C–H amination (bc = bathocuproine).

The suitability of such polyvalent-iodine-promoted pathways for application in palladium-catalysed alkyl–nitrogen bond formation via consecutive N–H/C–H bond activation was demonstrated by Nadres and Daugulis (Scheme 9).[44] The reaction is based on a picolinamide as both a chelating group and a nitrogen source. As discussed for compound **47** as a representative example, coordination of palladium upon chelation provides the intermediate **49**, which undergoes position-selective C–H palladation[45] to the six-membered palladaazacycle **50**. Oxidation of this σ-alkylpalladium(II) complex **50** with diacetoxyiodobenzene provides the corresponding palladium(IV) intermediate **51**, which generates the C–N coupling product **48** and regenerates the palladium(II) diacetate catalyst. No details are available on the exact course of the reductive C–N bond formation. Apart from **47**, several additional alkyl–nitrogen bond-forming reactions at methyl positions were reported for compounds **52–56** (36–68% yield). As in the case of **47**, C–H amination at another neopentylic position was accomplished for **57**, although in a reduced 36% yield.

A related palladium-catalysed process to form C–N bonds at neopentylic positions was developed by Glorius (Scheme 10).[46] This reaction starts from coordination of palladium to the acetamide unit in **58** followed by intramolecular C–H palladation to provide the palladaazacycle **60** as an intermediate. A plausible subsequent pathway would consist of a silver-mediated oxidation at the palladium centre to arrive at a palladium(IV) intermediate **61**, which would promote reductive C–N bond formation to product **59**.

An alternative pathway would consist of a direct thermally induced C–N bond formation from **60** resulting in a Pd(0/II) catalytic cycle. Although such a scenario appears less probable based on the discussed reluctance of palladium(II) species to undergo C–N bond formation, it cannot be excluded in view of the elevated reaction temperatures. Alongside the successful formation of **59**, the authors presented a total of 16 examples with different 4-substitution patterns at the arene (60–83% yield) and five examples for 5- and 6-substitution (46–81% yield).
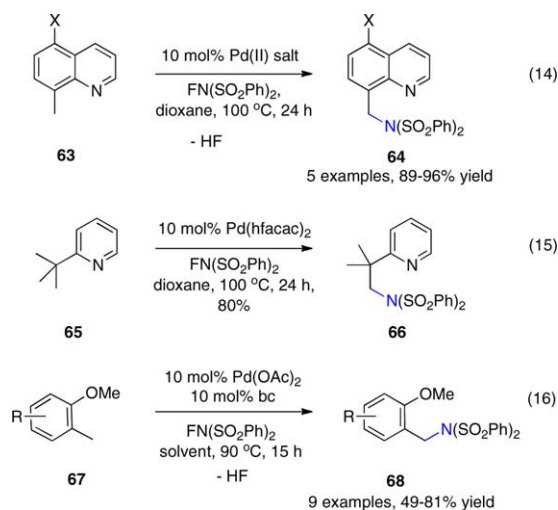
Following the recognition that the leaving group capacity of the nitrogen source was of key importance, Muñiz and Iglesias performed another set of experiments with preformed complexes such as **41** and **42**, which revealed that NFSI as oxidant provided selective C–N bond formation in favour of *N*-methyl bis(phenyl-sulfonyl)imide **62** as the only observable product (Scheme 11).[42] Related complexes bearing different ligands and nitrogen anions led to the same outcome, confirming that the C–N bond formation is general. Furthermore, it represents a rapid process, as deduced from a kinetic control experiment between the two complexes **41** and **41-d₃**, which reacted at comparable rates and without an observable kinetic isotope effect.

These results appeared instructive for the development of a catalytic C–H bond amination using NFSI as oxidant and nitrogen source. This particular compound had been explored in diamination reactions as discussed above. It was subsequently chosen as the reagent in a novel palladium-catalysed amination of methyl groups (Scheme 12).[47]

The reaction was initially developed for 8-methyl quinolines **63**, which underwent the well-established cyclopalladation upon C–H bond metallation.[48] In the presence of NFSI, clean oxidative benzylic amination is observed and products **64** are formed in high yields (Eq. 14). A related reaction for 2-*tert*-butylpyridine **65** results in selective monoamination at the neopentylic terminal carbon to give **66** (Eq. 15). Finally, a
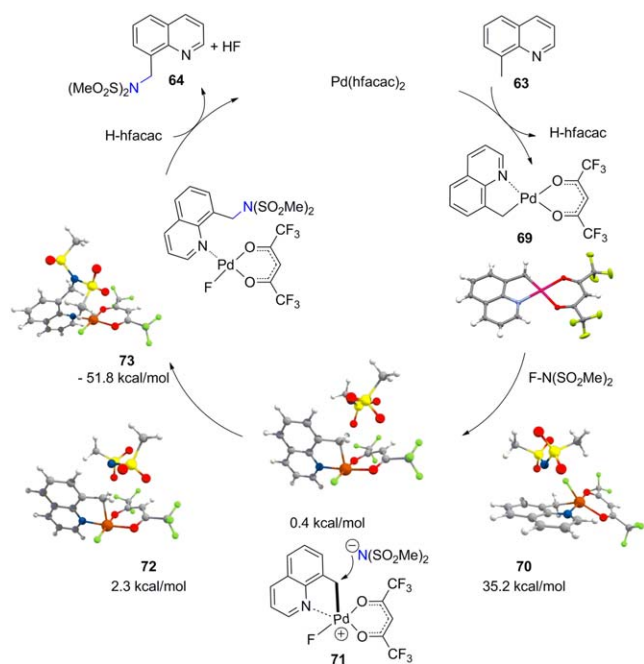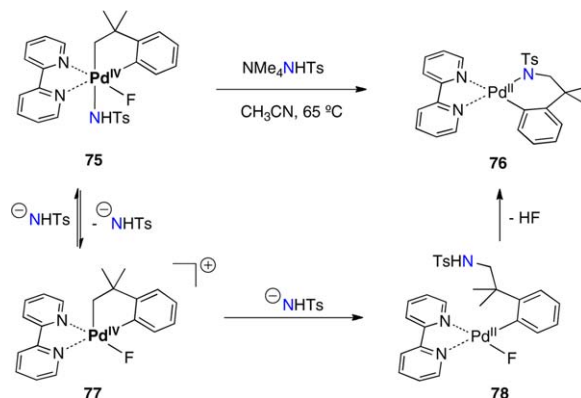
Fig. 2. Mechanism of the palladium(II/IV)-catalysed intermolecular C–H amination.

Scheme 13. Stoichiometric C–N bond formation with NFSI.

Scheme 14. Stoichiometric C–N bond formation from palladium(IV).

number of 2-methylanisole derivatives **67** could be aminated under palladium catalysis (Eq. 16), in which the methoxy group acts as a labile coordinating group.[49] While the reaction occurs with complete selectivity, the reduced coordination ability of anisoles to palladium renders the cyclopalladation less straightforward than in the case of the quinuclidines.

The catalytic cycle contains a directed C–H palladation to intermediate **69**, which undergoes oxidation via transition state **70** to the monomeric palladium(IV) intermediate **71** (Figure 2).[47] By theoretical analysis with bismesylimide as nitrogen source, this Pd compound was found to be a penta-coordinated, square-planar pyramidal cationic complex[50] with the bissulfonimide as counterion. Upon approximation, this nitrogen anion does not act as a possible ligand for palladium, which renders the assumed neutral hexacoordinate Pd(IV) intermediates that were discussed for diamination[32] highly improbable. Instead, direct attack at the methylene group leads to C–N bond formation. The reductive elimination proceeds with an activation barrier of 2 kcal/mol and through the expected transition state **72** with an almost linear Pd–C–N angle of 176°. This pathway thus resembles the nucleophilic substitution as widely established in synthetic organic chemistry mechanisms based on more common leaving groups. In the present case, palladium(IV) acts as a high-quality leaving group due to the high-oxidation-state nature of the metal centre. The more stable palladium(II) oxidation state **73** is reached upon reduction, which is believed to represent the overall driving force of this process.

This outcome clarifies the powerful concept of high-oxidation-state palladium(IV) catalysis as currently the best approach to palladium-catalysed alkyl–nitrogen bond formation.

Altogether, these observations on stoichiometric or catalytic palladium-mediated alkyl–nitrogen bond formations from Schemes 8 and 11 and Figure 2 were illustrative for the development of alkene diamination reactions under truly intermolecular reaction control as discussed in Scheme 7.

NFSI could further be employed for selective amination within a related set of reactions on a preformed dimeric palladium complex **74** (Scheme 13). Upon treatment with NFSI, reductive C–N bond formation to **64** was induced.[51] This observation is of importance to the second step of benzylic amination in the palladium-catalysed aminofluorination of styrenes.[33c]

The widely noted preference for C–N over C–F bond formation was investigated in detail by Sanford.[52] In this study, model complex **75** (Scheme 14) was synthesised as the major component of a 6:1 mixture of two geometrical isomers and characterised by X-ray analysis. Thermal exposure of compound **75** led to preferential alkyl–fluorine bond formation as the major product. However, the alternative alkyl–nitrogen bond formation toward **76** was the major pathway when additional tosylamide was added in form of its tetramethylammonium salt (85% yield). Addition of two equivalents of bipy further increased the yield to 98%. Experiments with tetramethylammonium mesylamide demonstrated the lability of the
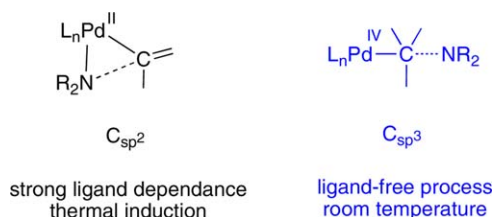
Fig. 3. Different mechanistic scenarios for palladium-mediated C—N coupling reactions.

sulfonamide ligand and led to the conclusion that formation of **76** proceeds through a preequilibrium of tosylamide dissociation. The resulting cationic palladium intermediate **77** is attacked by free tosylamide at the σ-alkyl–palladium bond to furnish the desired reductive C–N bond formation. Due to the reaction with non-coordinated amide, no competing aryl–nitrogen bond formation takes place. The formed palladium(II) complex **78** loses hydrogen fluoride to form stable product complex **76**.

A potentially competing direct S_N2 reaction between neutral **74** and tosylamide is ruled out on the basis of the observed first-order dependence on [**74**] and zero-order dependence on [NMe$_4$NHTs]. Although the reaction proceeds formally via nucleophilic substitution at a neopentylic position, the overall stabilisation of the palladium centre should be sufficient to drive the reaction.

5. Conclusions

To conclude, intermediate high-oxidation-state palladium catalysts have emerged as a powerful non-canonical tool for the formation of alkyl–nitrogen bonds under defined conditions. These protocols preferentially employ strong oxidants and discrete palladium(IV) intermediates. They may also proceed with lower palladium oxidation states such as bimetallic interactions, as in the transient oxidation scenario. A linear transition state reminiscent of nucleophilic substitution is preferred, which outperforms the established classical 3c-4e reductive elimination from related C_{sp^2}–N bond-forming reactions (Figure 3). The common mechanistic scenario is characterised by the absence of any ligand dependence and mild reaction conditions.

In contrast to these now-established pathways using palladium in a high oxidation state, possible C–N bond formation within conventional palladium(0/II) cycles notably still remains unexplored. It therefore constitutes a worthwhile target for future investigations in the area.

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