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# A new catalytic hetero-Heck type reaction

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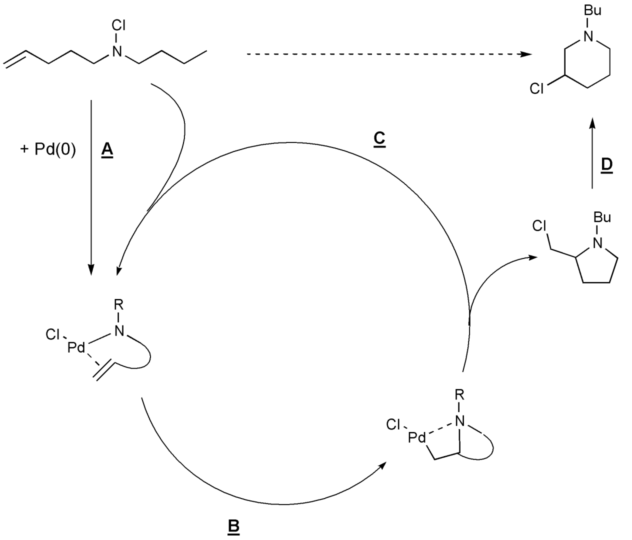
**Unsaturated *N*-chloroamines have been found to cyclise under palladium-catalysis in good yield, the proposed mechanism includes an oxidative addition of the chloroamine to Pd(0), thus opening a new entry to the amides of the late transition metals.**

In the last two decades the use of transition metals as catalysts for organic transformations has increased drastically and to date numerous highly valuable catalytic reactions have been developed.[1] Amongst the transition metals palladium plays a key role. It can be used for catalytic carbon–carbon bond formations *e.g.* allylic substitutions,[2] the Stille-,[3] Suzuki-[4] and Negishi-coupling[5] or the Heck-reaction.[6] In these reactions carbon–heteroatom bonds are employed which react with palladium(0) under oxidative addition, forming intermediates with palladium–carbon bonds that undergo further transformations. It is surprising that, in spite of the synthetic value of transition metal amides,[7] extensive research is only performed in the field of oxidative addition of nitrogen–hydrogen bonds to transition metals, whilst the more reactive (and thus more promising) nitrogen–heteroatom bonds[8] remain mainly unnoticed. To the best of our knowledge only Narasaka *et al.* have recently reported the use of the nitrogen–oxygen bond of oxime derivatives to perform a hetero-Heck reaction.[9]

In the course of our studies towards the intramolecular catalytic addition of nitrogen–heteroatom bonds to double bonds to form heterocycles[10] we envisioned that an intramolecular Heck-type reaction could be possible using *N*-chloroamines as substrates. Oxidative addition of these amine derivatives to palladium(0) complexes should lead to transition metal amides, which would be a totally new way to synthesise these compounds (Scheme 1, **A**).[7]

These could in turn react with a double bond under aminopalladation, leading to β-amino-organopalladium species (**B**). Due to the coordination of the nitrogen lone pair to the metal, these intermediates are less prone to undergo β-hydride elimination,[11] the next step in the Heck reaction. We envisioned that these species could be long lived enough to be instead oxidised by another molecule of chloroamine (**C**),[12] leading to 2-chloromethylpyrrolidines and regenerating the palladium amide, thus closing the catalytic cycle. Under neutral conditions 2-chloromethylpyrrolidines are not stable but rearrange *via* two subsequent $S_N2$-reactions and an aziridinium ion as the intermediate to the thermodynamically more stable 3-chloropiperidines (**D**).[13]



**Scheme 1** Proposed catalytic cycle for the intramolecular hetero-Heck type reaction.

We tried to perform this reaction using palladium tetrakis(triphenylphosphine) as the catalyst and the chloroamine **1a**. To our great pleasure the reaction proceeded well at room temperature (Scheme 2), giving the desired piperidine **2a** in good yield.

Surprisingly, upon reducing the amount of catalyst to 5% or 1% led to an increased yield of the cyclisation product. This is probably due to oxidation of the phosphine ligands by chloroamine, a known reaction.[14] As the phosphine ligands of 1% catalyst consume 4% of the starting material, the reduction of the catalyst amount left more chloroamine for the cyclisation reaction.

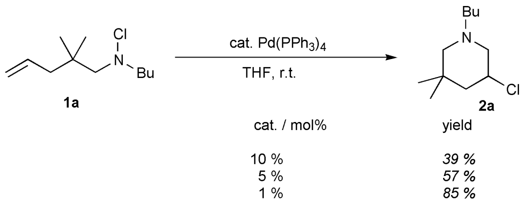
This new reaction is however not limited to palladium complexes, but a variety of transition metal complexes prone to oxidative addition (like Ni(0)-, Rh(I)- or Ir(I)-complexes) can be used as efficient catalysts.

Even though the cyclisation works well, to date we are not able to isolate any intermediates of this reaction. The transition metal amides can undergo β-hydride elimination and all attempts to crystallise them failed, giving only transition metal chloride complexes as products. There is however evidence from the studies of Narasaka[9] and others[15] that the postulated oxidative addition can occur.

To check the generality of this new reaction we synthesised a variety of *N*-chloropentenylamines and reacted them with catalytic amounts of palladium(0) tetrakis(triphenylphosphine) (Table 1).

All compounds with a *gem* dialkyl group in the pentenyl chain gave good yields of piperidines. However upon employing chloroamines without this *gem* dialkyl group (**1g** and **1h**) the yield dropped.

This is most likely due to a competing β-hydride elimination of the transition metal amides, leading to imines and, upon work-up, to volatile aldehydes. Obviously the *gem* dialkyl effect[16] accelerates the cyclisation enough to make the β-hydride elimination a minor reaction pathway. However,



**Scheme 2** The yield of piperidine increases upon using less catalyst.

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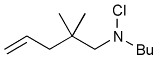
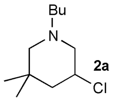
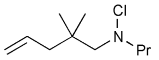
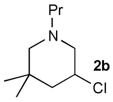
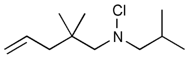
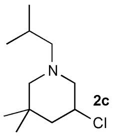
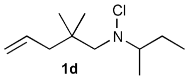
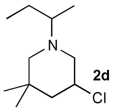
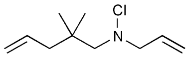
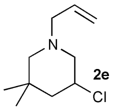
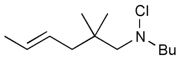
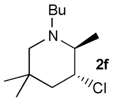
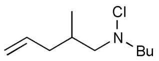
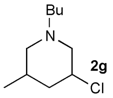
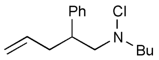
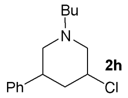
**Table 1** Cyclisation of different unsaturated chloroamines using 1% $Pd(PPh_3)_4$ in THF at rt. Yields given are for the isolated products after chromatography

| Chloroamine | Piperidine | Yield |
|---|---|---|
|  **1a** |  **2a** | 85% |
|  **1b** |  **2b** | 86% |
|  **1c** |  **2c** | 73% |
|  **1d** |  **2d** | 55% |
|  **1e** |  **2e** | 51% |
|  **1f** |  **2f** | 48% |
|  **1g** |  **2g** | 43% |
|  **1h** |  **2h** | 47 |

without this effect β-hydride elimination competes with the cyclisation.

It might be argued that this reaction proceeds *via* radicals, as known for the copper(I)- or iron(II)-catalysed cyclisation of chloroamines.[17] Unlike as expected for aminyl-radical cyclisations[18] we observed almost no influence of added acid or base on the reaction and obtained **2a** in good yield from **1a** even when 3 equiv. of TMEDA were added. Furthermore, if the addition proceeds *via* radicals, one would expect a cascade cyclisation[19] in the case of chloroamine **1e** which was not observed. Another argument against a radical mechanism is the highly stereoconvergent cyclisation of **1f**. In the case of a radical mechanism one would expect an almost 1:1 mixture of diastereomers.[20] Therefore this reaction does not proceed *via* radicals.[21]

We are currently further investigating the mechanism and are trying to find catalysts that are less prone to β-hydride elimination, thereby broadening the scope of the reaction.

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