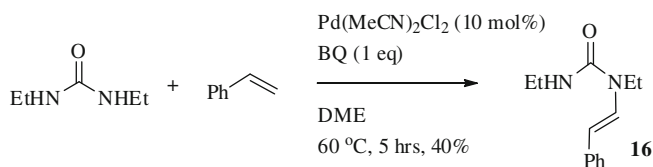


## Chapter 2

# Pd(II) Catalysed Aminocarbonylation of Alkenes

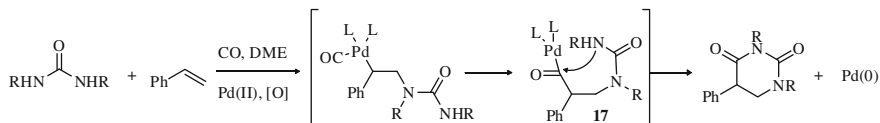
### 2.1 Background

Following on from the work of Bar on the diamination of conjugated dienes [18], a study of the diamination of simple alkenes revealed modest yields of enamide **16** (Scheme 2.1).



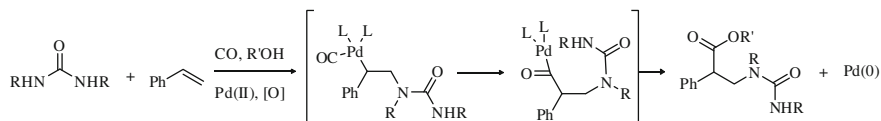
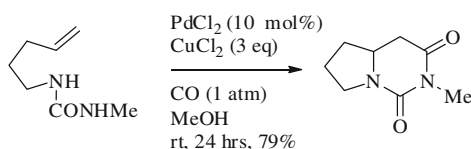
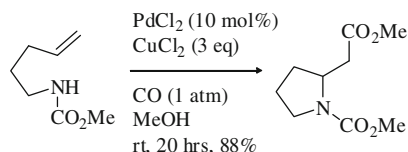
**Scheme 2.1** Palladium (II) catalysed diamination of styrene

It was thought possible to affect a novel heterocycle synthesis of pyrimidiones through a similar process in the presence of carbon monoxide. The interception of palladate **17** via the terminal urea nitrogen would lead to cyclisation (Scheme 2.2). If successful, such a sequence could have wide synthetic applications and potential for functionality via different alkenes and ureas.



**Scheme 2.2** Palladium (II) catalysed, three component pyrimidione formation

When performing this reaction in alcoholic solvents it may also be possible to synthesise  $\beta$ -amino acid derivatives (Scheme 2.3).

**Scheme 2.3** Carbonylation— $\beta$ -amino acid synthesis**Scheme 2.4** Pd(II) catalysed intramolecular aminocarbonylation of exo-ureas**Scheme 2.5** Pd(II) catalysed intramolecular aminocarbonylation of exo-carbamates

In 1988 Tamaru et al. published an intramolecular cyclisation utilising mild conditions of 1 atm CO pressure and  $\text{CuCl}_2$  as the re-oxidant (Scheme 2.4) [1]. Furthermore in 1997 this work was expanded by the same group to include carbamates (Scheme 2.5) [2].

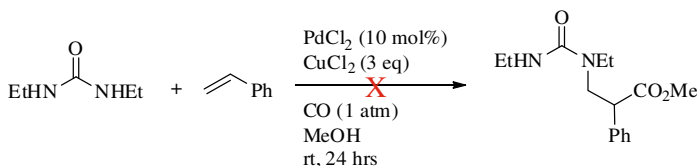
As of yet there is no general method for the intermolecular version of this reaction.

## 2.2 Results and Discussion

### 2.2.1 Attempted $\beta$ -Amino Acid Synthesis

Initial reactions between 1,3-diethyl urea and styrene in methanol failed to yield any traces of product.  $\text{CuCl}_2$  was employed as the re-oxidant and the optimal conditions of Tamaru [1] were followed, introducing an atmosphere of CO via a balloon (Scheme 2.6).

Tamaru reported large solvent effects between protic and non-protic media.  $\text{CH}_2\text{Cl}_2$  and THF were slow and less efficient but a mixture of acetic acid and sodium acetate (3 eq) improved yields (up to 95 % from 79 % in methanol) and reduced the reaction times dramatically (from 3 days to <1 day). It was hoped a similar effect could be observed in the pursuit of  $\beta$ -amino acids. Increased solvation of the chloride ion from  $\text{PdCl}_2$  through hydrogen bonding could expose the Pd(II) centre leading to better coordination to the alkene. Protonation of the urea

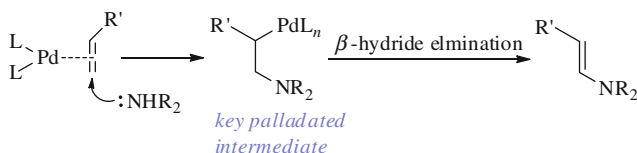


**Scheme 2.6** Initial reaction screening

nitrogen should also lead to a weaker complexation to the palladium centre which has been known to shut down catalytic reactivity [3].

Unfortunately a comprehensive solvent screen (with or without the use of sodium acetate as an additive) did not furnish the expected product. Trace amounts of a Wacker oxidation product was observed by  $^1\text{H}$  NMR but in an insignificant yield (approximately 3 %).

AA change in approach to conditions more familiar within the Booker-Milburn group was next adopted. The combination of  $\text{Pd}(\text{MeCN})_2\text{Cl}_2$  with BQ as an oxidant has been successfully employed by Bar [4], and Elliott [5] in similar but non-carbonylative systems (Scheme 2.7).

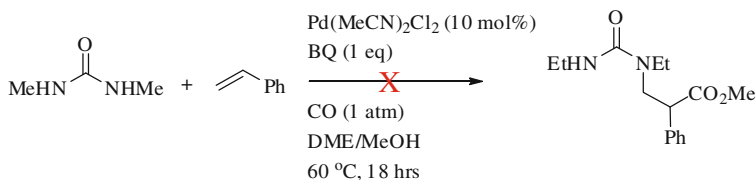
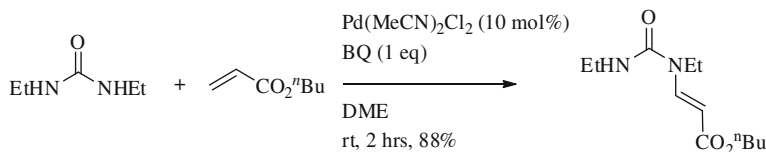
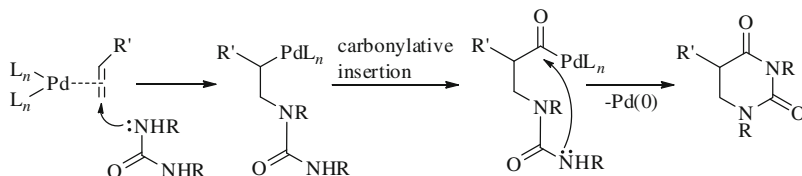


**Scheme 2.7** Pd(II) mediated enamide formation

The palladated intermediate prior to  $\beta$ -hydride elimination is the key species which must undergo carbonylative insertion in order to form  $\beta$ -amino acids. With the knowledge that this intermediate forms under  $\text{Pd}(\text{MeCN})_2\text{Cl}_2/\text{BQ}$  conditions, various attempts to intercept the  $\beta$ -hydride elimination pathway with CO were undertaken (Scheme 2.8).

With styrene as the alkene coupling partner, numerous experiments varying temperature, concentration, stoichiometries and solvents were trialled but to no avail.

Bar reported a 45 % yield of enamide formation between the reaction of styrene and 1,3-diethylurea in the absence of CO [1]. [9], However in the author's hands, a maximum of 30 % was obtained. Despite this discrepancy, it is obvious that the intermediate described in Scheme 2.7 is not formed efficiently and the reaction is therefore impeded before the CO is even involved. It was therefore decided to investigate alternative alkenes. Elliott and Wigglesworth have demonstrated a range of acrylate derivatives undergoing 2,2 di-functionalisation via an aza-Wacker reaction [5], using *N*-tosylethanolamine derivatives as the nucleophile. During this study, urea nucleophiles were demonstrated to form enamides under facile conditions in excellent yields (Scheme 2.9).

**Scheme 2.8** Pd(MeCN)<sub>2</sub>Cl<sub>2</sub>/BQ aminocarbonylation conditions**Scheme 2.9** Facile enamide formation with *n*butyl acrylate**Scheme 2.10** Pathway for the formation of pyrimidiones

Once again, this reaction proceeds via the key palladated intermediate prior to  $\beta$ -hydride elimination (Scheme 2.7). With the knowledge that this intermediate is formed efficiently, the reaction was repeated under an atmosphere of carbon monoxide. Only enamide was formed however, with CO seemingly having no effect (either detrimental or beneficial) to the efficiency or overall yield.  $\beta$ -Hydride elimination seems too facile in this particular case for the carbonylation to proceed. Alternative acrylate species were examined and discussed later (Sect. 2.2.2).

With no sign of CO incorporation in the initial screens, a simple lack of CO in solution may have been responsible. Performing the reactions at increased pressures therefore should negate this issue. Increased pressures may also aid in overcoming  $\beta$ -hydride elimination by forcing the CO ligand to migrate into the carbon-palladium bond.

Despite attempts at a variety of pressures (2, 5, 20 and 50 bar) and under different temperatures (rt, 50 °C and 70 °C) no products were detected with inactive palladium black appearing to form quickly.

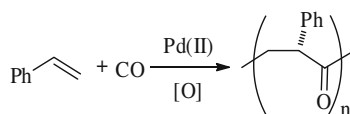
With little evidence of  $\beta$ -amino acid formation, it was hoped intramolecular attack from the second urea nitrogen on the desired acyl palladate would be more efficient. Pyrimidione formation was therefore investigated (Scheme 2.10).

### 2.2.2 Pyrimidione Formation

Initial screens were carried out using styrene and 1,3-diethylurea using the conditions described above. Both  $\text{PdCl}_2/\text{CuCl}_2$  and  $\text{Pd}(\text{MeCN})_2\text{Cl}_2/\text{BQ}$  systems were examined in the absence of methanol to effect the ring closure. A comprehensive solvent screen was also undertaken looking at a range of different properties. In particular, increased solubility of CO has been shown with fluorinated solvents [6] and within this series there is evidence trifluoroethanol [7] (TFE) can enhance the reactivity of many transition metal-based catalysis reactions. Due to these properties, dry and degassed TFE was used in the attempted cyclisation, once again this was to no avail. Alternative Pd(II) salts also proved ineffective as was a switch to 1,3-diethylurea.

All the main constituents are present for the much studied and industrially important copolymerisation of styrene (Scheme 2.11) [8]. Despite the apparent lack of polymer formation, the reaction was performed without the urea to ensure this was not a detrimental pathway.

**Scheme 2.11** CO/vinyl polyketone synthesis



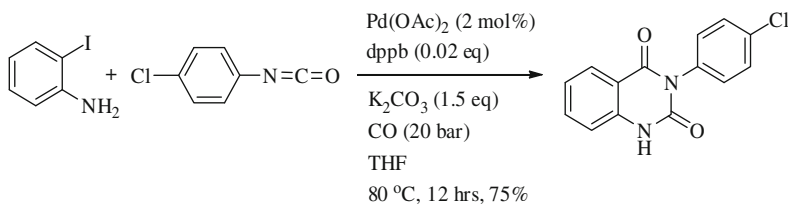
Only starting materials were isolated with an intact mass balance, so this potentially harmful pathway can be eliminated.

The fundamental problem of achieving carbonylative insertion still seemed to be impeding synthetic progress. Whether this was from lack of CO in solution or rapid  $\beta$ -hydride elimination was still unclear at this stage.

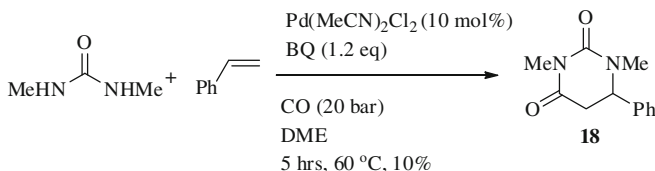
In efforts to resolve this situation, a reaction screen was performed under 20 bar of CO pressures. As mentioned previously, carbonylation occurs during a ligand migration process promoted by external ligands filling the vacant site left on the metal. With the added pressure there would be no uncertainty as to the CO being in solution and the insertion process itself would be given the best possible chance. If enamide **16** was still produced, the  $\beta$ -hydride elimination pathway would seem too efficient for the designed reaction to proceed. Precedent for this reaction with 20 bar of CO pressures came from the work by Alper [9], in which an in situ urea is produced from an *o*-iodoaniline and an isocyanate. Oxidative addition into the iodide bond followed by cyclocarbonylation completes the sequence (Scheme 2.12).

Operating under 20 bar of CO it was pleasing to observe (under standard conditions as described by Bar [18],) enamide formation no longer occurring and the desired pyrimidione was formed (Scheme 2.13).

Following on from this positive result it seemed the previous reactions at 1 atm suffered from a lack of CO in solution or decarbonylation rather than rapid  $\beta$ -hydride elimination. A further change in technique was adopted to determine whether the reaction could be facilitated at lower pressures. After charging the



**Scheme 2.12** Palladium catalysed cyclocarbonylation of *o*-iodoanilines with heterocumulenes



**Scheme 2.13** Successful pyrimidione formation

reaction with CO, the Schlenk tube was sealed but this time with the balloon (via a needle) inside the vessel, left fully open. It was hoped that this would provide enough positive pressure to enable the reaction to occur. Again the result was an encouraging one and with DME as the solvent, a 7 % yield of **18** was obtained.

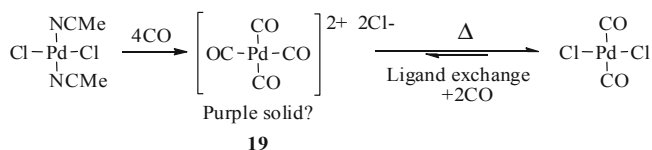
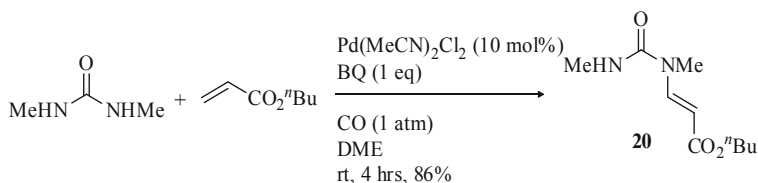
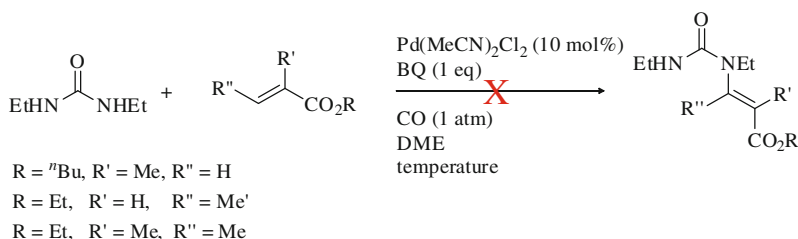
Having facilitated the reaction under milder conditions (using a balloon rather than 20 bar pressure) due to the technical advantages, experimental ease and wider possible applications, all subsequent attempts to increase the yield were performed using this method.

Reports by Stahl [47], have shown in similar Pd(II) catalysed systems, a first order dependence on the concentration of the alkene. Due to this, several experiments were carried out in order to ascertain if the yield could be improved. 0.6 M concentrations of styrene have been used up until this point; this was increased to 1.6 M and 3.3 M but with little effect.

A screen of catalysts was also performed in the hope that a change of electron density on the metal centre would increase the efficiency of the reaction. However  $\text{Pd}(\text{MeCN})_2\text{Br}_2$ ,  $\text{Pd}(\text{MeCN})_2\text{I}_2$ ,  $\text{Pd}(\text{OAc})_2$  and  $\text{Pd}(\text{TFA})_2$  were all ineffective.

During the process of charging the reaction mixture by bubbling CO into the solution, a purple precipitate was observed. Isolation and characterisation of this solid proved difficult, however it can be speculated to be a palladium complex, perhaps  $[\text{Pd}(\text{CO})_4]^+ 2\text{Cl}^-$  (**19**). This species is reportedly extremely unstable unless at low temperatures [11] matching the observation that the purple solid re-dissolved after gentle warming or continuous stirring. With rapid ligand exchange between the associate  $\text{Cl}^-$  counter ions it is easy to see how this process can occur (Scheme 2.14).

With the reaction appearing to be stoichiometric in palladium, investigations into the alkene source were undertaken. As mentioned in Sect. 2.2.2, styrene may not be the ideal reagent due to the modest reactivity shown in the formation of

**Scheme 2.14** Formation of a pre-catalyst?**Scheme 2.15** Enamide formation under a CO atmosphere**Scheme 2.16** Unsuccessful acrylate substrates

enamides via an aza-Wacker type reaction (Scheme 2.7). *n*Butyl acrylate was investigated in an effort to observe catalytic activity. Initial experiments with 1 atm of CO exclusively produced the enamide in an excellent yield (Scheme 2.15).

Surprised by the efficiency and rate of  $\beta$ -hydride elimination, the reaction was repeated at increased pressures of CO to try and overcome this. Disappointingly, enamide formation was still the predominant pathway up to pressures of 50 bar. Increased reaction temperatures and times, with or without the combination of pressure also failed to impede  $\beta$ -hydride elimination.

A switch to substituted acrylate species may retard enamide formation, changing conformations of intermediates and allowing time for carbonylative insertion. Of course substitution at the beta position would remove the hydrogens for the elimination step to occur. Combinations of acrylate derivatives were therefore screened (Scheme 2.16).

All substrates failed to yield either pyrimidione or even enamide under the conditions described. Removal of carbon monoxide from the system also produced the same result indicating change in substrate is responsible for the shutdown in reactivity. This is perhaps unsurprising as a lack of tolerance to substitution is a

well known limitation of many Pd(II) catalysed functionalisation of activated alkenes [1, 12]. Not only does the stability of an alkene-palladium complex decrease as alkene substitution increases but the approach of a nucleophile to the sterically crowded electrophilic centre can also be inhibited. Once again, increased temperatures and pressures of CO did not yield the title pyrimidione.

With extensive investigations proving unsuccessful, a change in direction towards the *ortho*-carbonylation of aryl ureas was initiated.

## References

1. Tamaru Y, Hojo M, Higashimura H, Yoshida ZJ (1988) Am Chem Soc 110:3994–4002
2. Harayama H, Abe A, Sakado T, Kimura M, Fugami K, Tanaka S, Tamaru YJ (1997) Org Chem 62:2113–2122
3. Elliott L (2010) Unpublished Results
4. Bar GLJ, Lloyd-Jones GC, Booker-Milburn KI (2005) Am Chem Soc 127:7308–7309
5. Elliott LD, Wrigglesworth JW, Cox B, Lloyd-Jones GC, Booker-Milburn KI (2010) Org Lett 13:728–731
6. Deschamps J, Menz DH, Padia AAH, Costa-Gomes MFJ (2007) Chem Thermodyn 39: 847–854
7. Scarel A, Durand J, Franchi D, Zangrando E, Mestroni G, Milani B, Gladiali S, Carfagna C, Binotti B, Bronco S, Gragnoli TJ (2005) Organomet Chem 690:2106–2120
8. Coates GW, Hustad PD, Reinartz S (2002) Angew Chem Int Ed 41:2236–2257
9. Larksarp C, Alper HJ (2000) Org Chem 65:2773–2777
10. Kotov V, Scarborough CC, Stahl SS (2007) Inorg Chem 46:1910–1923
11. Shriver DF, Atkins PW, Langford CH (1992) Inorganic chemistry. Oxford Press, Langford
12. Hartley FR (1973) The chemistry of platinum and palladium. Wiley, New York





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