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Pd-catalysed carbonylations: versatile technology for discovery and process chemists

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1. Introduction

1.1. Palladium-catalysed three-component reactions

Traditionally, the organic chemist has increased complexity in a molecule by the stepwise formation of individual bonds. It would be more efficient if several bonds could be synthesised in one operation, from simple starting materials, without the need to isolate the intermediates or engage in stepwise protection/deprotection steps. Reactions of this type employing three or more components are known collectively as cascade processes. One such example is palladium-catalysed carbonylation reactions. These play an important role in both drug discovery and manufacturing processes.

These reactions work through a discrete sequence of chemical transformations, in which each preceding reaction generates the functionality required to trigger the next reaction, and so on, until the desired product is formed. Strictly speaking,[1] the reaction conditions are kept constant throughout, but it is not unusual for reagents to be added as the reaction progresses to extend the cascade further. This process is known as reaction telescoping.

Cascade reactions have generated considerable interest over the years and numerous reviews have been published.[2–4] Benefits include high atom economy and rapid progress to structurally complex materials from simple starting materials. They also present savings in time and labour costs and reduced wastage.

These reactions often involve transition metal catalysts: palladium-catalysed reactions are particularly valuable in this respect. Using these methodologies, it is possible to incorporate, for example, carbon monoxide as reported by Heck almost 30 years ago.[5] Chemists can therefore generate a range of carbonyl compounds[6,7] including aldehydes with H_2[7] or a hydride source,[8] ketones and carboxylic acid derivatives,[6] usually under mild conditions, with palladium providing wide functional-group tolerance in the cascade process. A number of reviews[6,9,10] on carbonylation chemistries have been published in recent years: the aim of the present review is to summarise the variety of palladium-catalysed applications associated with CO gas, focussing mainly on advances from 2005–2008.

2. Effects of CO and phosphines on Pd reactions

2.1. π-Back-bonding

The Dewar–Chatt–Duncanson model of ligand-metal binding involves the donation of a ligand lone pair into an empty metal orbital forming a σ-bond (Fig. 1) and donation from filled d-orbitals on the metal into the π* orbitals of the ligand (Fig. 2 N.B. there is another π*–d-orbital interaction at right angles to that shown). Overall, the M–C bond becomes stronger with the C–O bond becoming longer and weaker.[11,12] Carbon monoxide is an excellent example of a π-acceptor, since its π*-orbitals are able to interact with filled metal d-orbitals where electron density flows from the metal to the ligand, a process known as back-bonding.[11] In this instance, the CO is acting as a π-Lewis acid (back-bonding) and a σ-Lewis base (σ-donation). In square-planar complexes of palladium the d_{Z^2}, d_{yz} and d_{xz} orbitals are involved.[11] The ability of the metal to back-donate and the strength of the M–C bond also depend on the nature of the phosphine ligand.

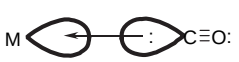


Figure 1. σ-Bond formation. Empty metal orbital, lone pair in σ-orbital.

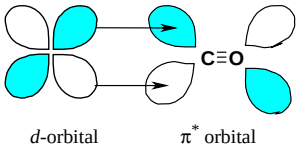


Figure 2. π-Back-bonding.[11]

2.1.1. Phosphine (PR_3) complexes. Phosphines are common ligands in palladium chemistry. They are used to both solubilise the metal in an organic solvent and to 'tune' the metal's reactivity in a systematic way, achieved by altering the phosphine's steric and electronic properties. Phosphorus, unlike nitrogen (and therefore amines), has low-lying empty d-orbitals able to accept electron density and thus stabilise low oxidation states of transition metals; an alternative view is that the back-bonding occurs from the filled metal d-orbitals into the P–R σ* bond.[13]

As the electronegativity of the R group increases, the π-acceptor character of P increases: other π-acceptors (e.g., CO) are not required to accept as much electron density[13] resulting in M–P bond shortening and M–CO bond lengthening. However, steric effects must also be considered.

Phosphines are in equilibrium with the metal (Fig. 3) and the position of this equilibrium depends on the bulk of the R groups. The extent of dissociation decreases in the order: PPh^tBu_2> $P(Cy)_3$>P^iPr_3=PEt_3>$PMePh_2$>PMe_2Ph>PMe_3.[13] This equilibrium is important, as it will determine the availability of metal co-ordination sites. Whilst bulky ligands can dissociate easily, they will not all dissociate from a metal. The remaining ligands have a steric effect on substrate binding. The concept of 'cone angle' (θ) enables the size of the phosphine ligand to be calculated (Fig. 4). The M–P distance is set at 2.28 Å (close to the actual situation): bulky phosphines (e.g., $^tBu_3P$) have large cone angles.

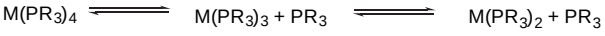


Figure 3. Phosphine/metal equilbria.[13]

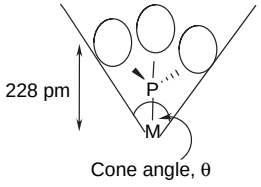


Figure 4. Definition of the cone angle. Spheres denote arbitrary groups.[13]

Another factor that must be taken into account is the natural 'bite' angle (βn) in bidentate phosphines.[14] This is defined as the selective chelation angle (P–M–P bond angle) dictated by the diphosphine ligand backbone (Fig. 5).

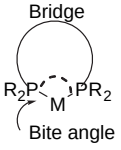


Figure 5. Definition of bite angle, βn.

Two further effects are recognised: steric bite angle and electronic bite angle. The steric bite angle effect involves the steric interactions between ligands or between a ligand and a substrate[14] and can influence the reaction regiochemistry: e.g., in hydroformylation.[15] The electronic bite angle effect relates to the electronic changes that occur when the bite angle is modified[14] and can govern the rate of reaction: e.g., rate of reductive elimination.[15]

In a reaction involving bidentate ligands, the ligand will adopt a binding geometry to minimise steric repulsions with the substrate. In carbonylation chemistry, this has the effect of forcing the CO closer to the aryl/vinyl group, aiding the formation of the ArC(=O)Pd species (vide infra). The larger the bite angle, the faster the rate of acylpalladium formation, with maximum rates seen in the range of 95–105°.[14] Larger bite angles than this can led to the formation of different intermediates (trigonal bipyramidal complexes), due to the extra stabilisation afforded.[14] Bidentate ligands can also dissociate to give monodentate ligands, freeing up a co-ordination site and aiding transmetallation, which again is influenced by the cone angle.[14] The most stable complexes are those involving five-membered chelates, which allow the natural angle of 90° in square-planar complexes.

2.1.2. Conclusions. The result of all these effects (back-bonding, cone and bite angles) is that:

1. Electron-rich phosphines increase the rate of oxidative addition, as they make the metal more nucleophilic.
2. Electron-rich metals will back-bond to CO to a greater extent, thus slowing the rate of ArC(=O)Pd formation.
3. Electron-poor phosphines slow the rate of oxidative addition, but reduce the amount of back-bonding to CO.
4. Bulky ligands retard the oxidative addition, but promote both ArC(=O)Pd formation and reductive elimination.
5. Bidentate ligands slow the oxidative addition, but promote both ArC(=O)Pd formation and reductive elimination, depending on the bite angle.

These factors will need to be taken into consideration when designing a catalytic system, as well as the Ar–X bond strength and steric effects within Ar–X.

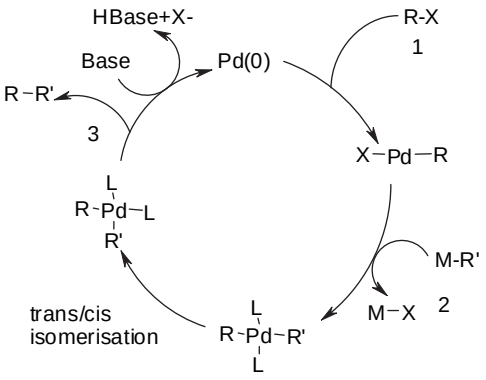
2.1.3. Carbenes as Pd ligands. In palladium-*N*-heterocyclic carbene (Pd/NHC) complexes, the NHCs act as powerful, neutral two-electron donors to form a single bond to the metal atom.[16–19] As such, they increase the electron density on the metal, thus facilitating oxidative addition. Carbenes are generally thought to be σ-donors, with little or no metal-to-ligand π-back-bonding. Recent studies[20] have shown that some back-bonding to the metal d-orbitals may occur via the carbon σ* orbital.

Compared with phosphines, NHC complexes form considerably stronger bonds to the metal atom.[21,22] Employing NHCs as 'phosphine mimics' has proved to be extremely fruitful in catalyst refinement.[17,18] NHCs are stronger σ-electron donors than even the most electron-rich phosphines, as evidenced by the change in CO stretching frequencies in the IR spectra of complexes of the type $[LNi(CO)_2]$ or $[LNi(CO)_3]$[23] and $[LIr(CO)_2Cl]$ or $[LRh(CO)_2Cl]$[24] (where L=NHC or PR_3). Both phosphines and NHCs display similar electronic structures, but the topology of co-ordination to the metal centre is vastly different. The three substituents on the phosphine project backwards, away from the metal, thereby forming a cone. The substituents on the NHC nitrogen atoms project forward to form a pocket around the metal centre, allowing them to have a much stronger impact. Varying these substituents allows the 'tuning' of the reactivity, in an analogous fashion to phosphine ligands. An excellent review[25] on the use of carbenes in non-carbonylative Pd cross-coupling reactions from a synthetic chemists' standpoint has recently been published.

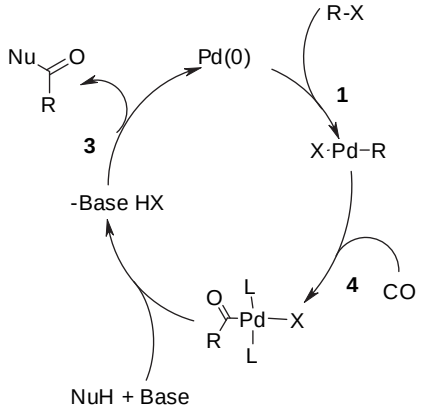
3. Carbonylation reactions

3.1. Introduction

Palladium-catalysed processes involving an organic halide (or pseudohalide) follow a common pathway (Scheme 1) in which (**1**) undergoes oxidative addition with palladium(0), resulting in a palladium(II) complex. This is then followed by transmetallation (**2**) by another organometallic species (e.g., stannanes, boronic acids, alkylzincs etc.), followed by a reductive elimination (**3**) and treatment with base to yield the coupled product and regeneration of the palladium catalyst. Non-oxidative palladium-catalysed carbonylations, reported by Heck almost 30 years ago, generally proceed via the same common catalytic cycle (Scheme 2),[9] but with carbon monoxide co-ordination and subsequent migratory insertion (**4**) to form an acylpalladium species, that is, susceptible to attack by nucleophiles, e.g., forming esters with alcohols or benzoic acids with water (*alkoxycarbonylation*) and amides from amines (*aminocarbonylation*). In forming disubstituted ketones, CO insertion (i.e., **4**) must occur before transmetallation, otherwise the biaryl/alkyl product will form preferentially.

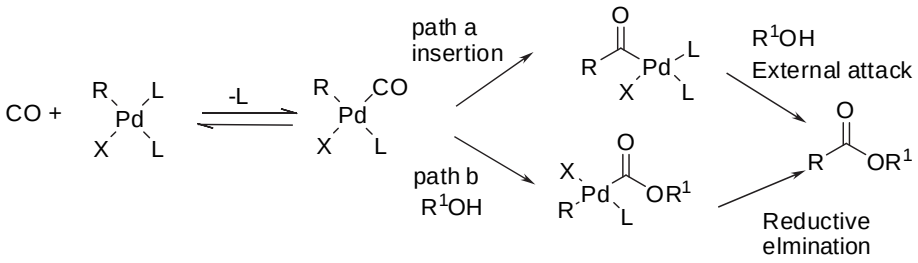


Scheme 1.



Scheme 2.

There are two potential mechanisms for the synthetically useful alkoxycarbonylation process (Scheme 3). Invariably, the process proceeds via external attack of the alcohol on the Pd/acyl complex (path a),[5] rather than path b. However, kinetic studies by Yanamoto with $PdI(Ph)(PPh_3)$ suggest that route b is in operation.[26] These pathways also apply to amide formation (vide infra).



Scheme 3. Possible pathways to ester formation.

In the rare cases of double carbonylation, the mechanism proceeds via CO insertion into the Pd–R bond before reductive elimination occurs.[27] This is usually a consequence of high CO pressure (vide infra).

3.2. Alkoxycarbonylations

3.2.1. Alkoxycarbonylation of aryl chlorides and bromides. Aryl chlorides are attractive starting materials for 3-component cascades, due to their lower cost and wider availability than the corresponding bromides and iodides. However, they are more reluctant than the other halogens to undergo oxidative addition. This could in part be attributed to 'soft/soft' interactions: Pd(0) is a soft species, and the 'softness' of the halogens decreases in the order I>Br>Cl. If the transition state of the oxidative addition is assumed to be three-coordinate (Fig. 6), then the large dissociation energy associated with C(sp2)–Cl will also disfavour oxidative addition.

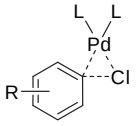
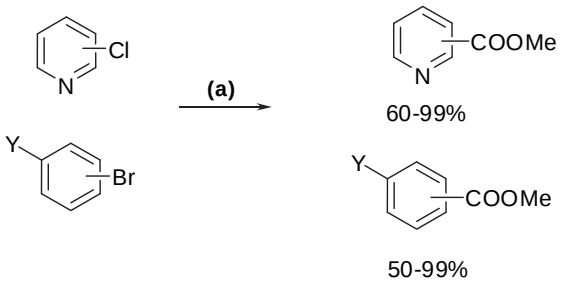


Figure 6. Three-centre co-ordination transition state for Pd(0) insertion into C(sp^2)–Cl bond.

This problem is compounded by the co-ordination of CO to the metal centre, which reduces the nucleophilicity of Pd(0); Pd clusters can also form readily in the presence of CO,[28] further retarding the catalyst activity. The reactions traditionally required high temperatures (130–160 °C) and high CO pressures (15–110 bar).

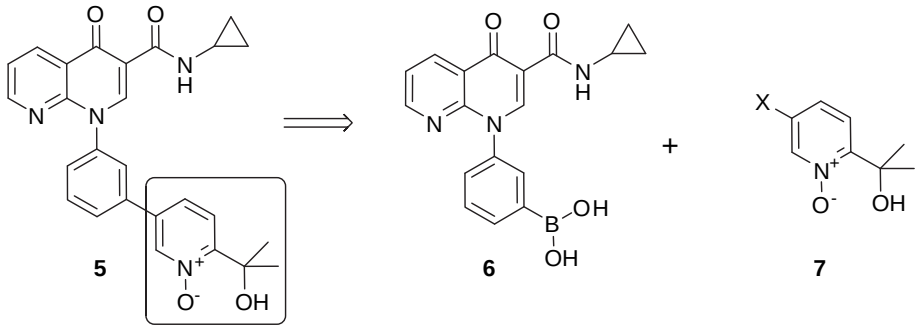
However, in the past decade, notable advances have been made. Beller et al.[29] have successfully utilised $PdCl_2(PhCN)_2$/Josiphos and a $PdCl_2(PhCN)_2/PCy_3$/modified Josiphos system to bring about the required transformation with modest CO pressure (3 bar) and up to 99% conversion, although a high temperature (140 °C) and a [Pd]/ligand ratio of 1:8 are required. Before this work, the best example utilised bis(diisopropylphosphino)propane (dippp), a difficult-to-synthesise, pyrophoric ligand with high sensitivity to air and moisture.[30]

Noting the requirement that successful C–Cl carbonylations utilised bidentate ligands, Albaneze-Walker et al.[31] showed that (*rac*-BINAP)$PdCl_2$ could provide a route to carbonylated heterocycles, with bromoanilines and anisoles also performing well under these conditions (Scheme 4). The bidentate ligand bite angle was found to be critical, with around 90° being optimal.

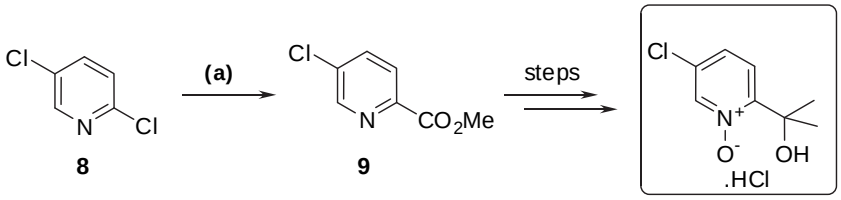


Scheme 4. Reagents and conditions: (a) halide (3.0 mmol), (BINAP)$PdCl_2$ (1 mol %), Et_3N (1.3 equiv), CO (50 psig), MeOH (15 ml), 100 °C, 5–48 h.

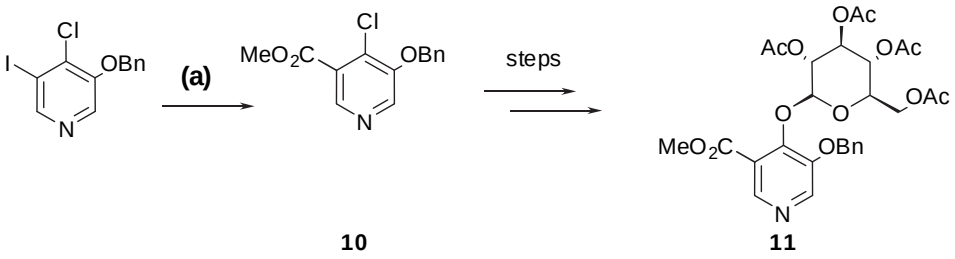
Bidentate ligands were utilised[32] in the kilo-scale synthesis of a potent PDE IV inhibitor **5**, (Scheme 5) requiring the boronic acid **6** and the halopyridine-*N*-oxide **7**. A key step was the synthesis of **9** from the dichloropyridine **8** (Scheme 6). Utilising dppf as the ligand



Scheme 5. Potential PDE IV inhibitor **5** and key intermediates (**6** and **7**).



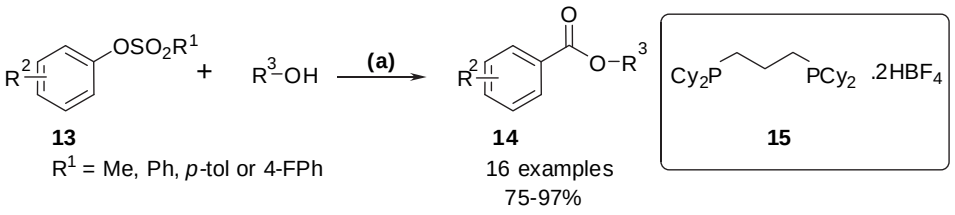
Scheme 6. Reagents and conditions: (a) **8** (13.51 mol), $Pd(OAc)_2$ (0.2 mol %), dppf (0.4 mol %), Et_3N (1.90 l, 1.01 equiv), CO (50 psig), MeOH (8.0 l), 100 °C, 11 h, 99%.



Scheme 7. Reagents and conditions: (a) Iodopyridine (1.50 g, 4.34 mmol), (*rac*-BINAP)$PdCl_2$ (86.9 μmol), Et_3N (8.69 mmol) CO (0.4 MPa), MeOH (40 ml), 85 °C, 5 h.

and reducing the amount of triethylamine to 1.01 equiv gave optimum conversion with only a trace of the diester. The corresponding dibromopyridine suffered from ~30% diester formation (Scheme 6).

Koert et al.[33] utilised Albaneze-Walker's original conditions to furnish pyridine **11** in their synthesis of potential glycosidase inhibitors **12** (Scheme 7).

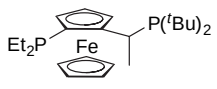


Scheme 8. Reagents and conditions: (a) **13** (1.0 mmol), alcohol (3.0 mmol), $Pd(OAc)_2$ (2 mol %), **15** (2.2 mol %), CO (1 atm), K_2CO_3 (2 equiv), 4 Å mol sieves, PhMe (1.0 ml), 80–110 °C, 15 h.

Beller et al.[34] have shown that their cata*X*Cium A® ligand/[Pd] system (vide infra) is efficient in the alkoxycarbonylation of aryl bromides, with low catalyst loadings (0.5 mol % Pd) and 5 bar CO, achieving 52–99% yield. Electron-rich/poor aromatics/heteroaromatics performed equally well in the reaction and a variety of nucleophiles were employed, yielding esters, amides and arylcarboxylic acids, in 63–89% yield. Ledbeater and Kormos[35] have shown that stoichiometric amounts of CO gas can be employed efficiently in the microwave synthesis of esters from aryl iodides.

3.2.2. Alkoxycarbonylation of pseudohalides. Aryl tosylates, readily accessible from phenols, are air-stable crystalline solids that are convenient to handle. They offer more synthetic scope than aryl halides, as the phenolic OH can be used to introduce further substituents into the aromatic ring. Mesylates would offer an atom-economy advantage over tosylates, but the relative acidity of the methyl group renders them incompatible with strong bases. Carbonylation of triflates occurs at lower temperatures than aromatic chlorides (60–120 °C), but they are expensive and less stable.[36]

There have been limited reports in the literature of the use of tosylates in carbonylation chemistry. In 2006, Cai et al.[36] published the first general procedure for the carbonylation of arylsulfonates to form esters. A modified Josiphos ligand **12** was crucial for the reaction, and elevated pressures and temperatures were required to allow oxidative addition to the relatively inert C–O bond. The use of *p*-fluorobenzenesulfonates gave the best yields (70–96%), with both electron-rich and poor aryl arenesulfonates.



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In 2008, Buchwald et al.[37] published ground-breaking research in this area. They demonstrated that aryl tosylates and mesylates **13** (which had not been reported to take part in carbonylations until this time) could be carbonylated with a variety of alcohols to afford the esters **14**. They utilised CO (1 atm) and temperatures from 80–110 °C (Scheme 8), employing a commercially available bidentate ligand **15**. Crucial to the reaction was the use of 4 Å molecular sieves, without which the reaction failed to go to completion, presumably with some of the tosylate being hydrolysed.[37]

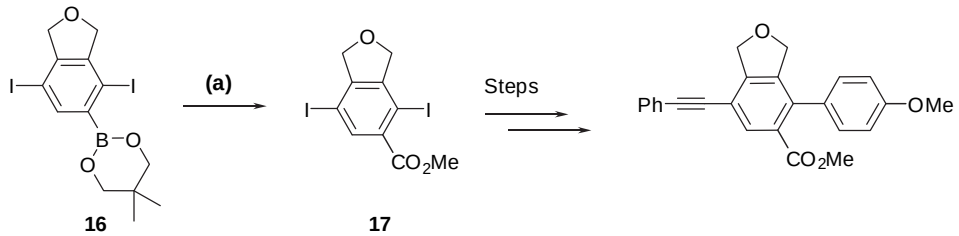
Initially, NaOPh[38] was utilised as a base, but this led to mixtures of carbonylated products, due to a Williamson reaction between the aryl sulfonate and sodium phenoxide. Switching to K_2CO_3 completely eliminated this problem. Electron-rich and electron-poor aryl and heteroaryl tosylates and mesylates gave good yields of the ester products. Aryl tosylates and mesylates bearing aldehyde, ketone, ester and cyano groups all gave high yields of the desired ester. Esters with *ortho* substituents could also be obtained in good yield. Sulfonates with an unactivated aryl ring benefited from using the 4-F–C_6H_4 sulfonate as the pseudohalogen coupling partner.

Aryl triflates derived from enantiopure phenylglycine have been utilised by Grimm et al.[39] in carbonylations. Racemisation at the α-position was suppressed by the use of hindered bases such as $^{i}Pr_2NEt$. The use of such bases led to high retention of stereochemistry (88 to>99% ee), whilst forming the benzoic acid in 97% yield. Methyl esters could also be generated in high yields and ees by switching from DMF/H_2O to DMF/MeOH under the same conditions.

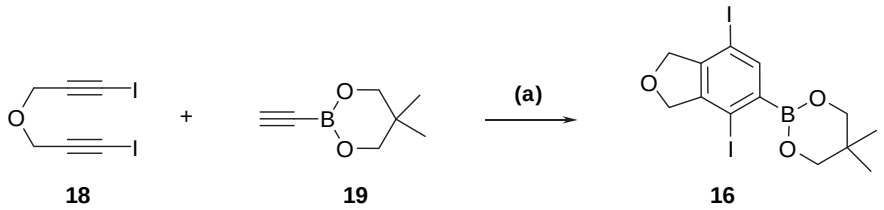
Boronic esters have also been utilised in a pseudohalogen role.[40] Methyl esters are formed regioselectively in the presence of iodides on the same aromatic ring **16**, to give highly functionalised 1,3-dihydro-2-benzofuran derivatives **17** (Scheme 9). This intriguing demonstration of the relative rates of C–B versus C–I insertion will clearly find many more applications.

These diiodoboronates were accessed by [Cp*RuCl(cod)]-catalysed cycloaddition of tethered diiododiynes **18** with three equivalents of ethynylboronate **19** (Scheme 10). Moreover, the boronate group sterically blockades one iodide, allowing their selective differentiation.

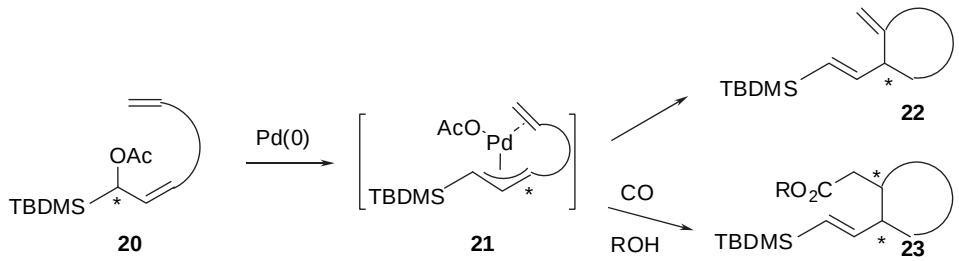
3.2.3. Alkoxycarbonylation in carbocycle and natural product synthesis. Alkoxycarbonylations can be utilised to construct optically active carbocycles. Optically active α-alkenyl-α-acyloxysilanes (**20**) can transfer their chirality by generating a π-allyl species (**21**)[41] (Scheme 11): this species can then be trapped by external or



Scheme 9. Reagents and conditions: (a) **16** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), *p*-benzoquinone (1.0 mmol), CO (1 atm), MeOH, 1 h, 71%.



Scheme 10. Reagents and conditions: (a) **18** (1.0 equiv), **19** (3.0 equiv), [Cp*RuCl(cod)] (10 mol %), 1,2-dichloroethane (3.5 ml), argon, 12 h, rt.

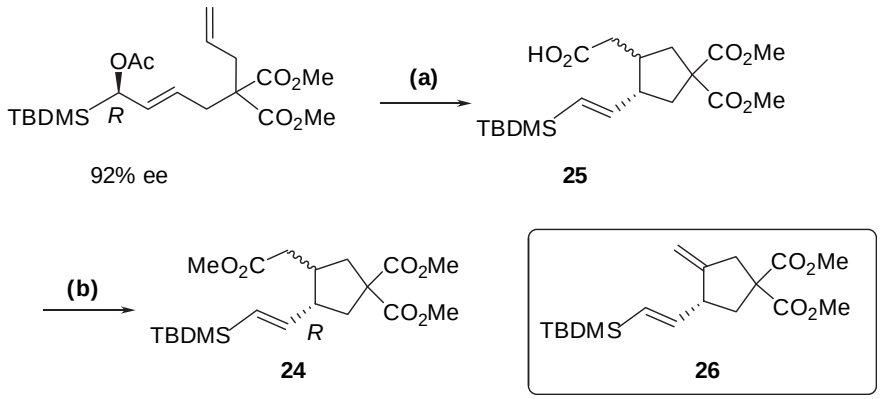


Scheme 11.

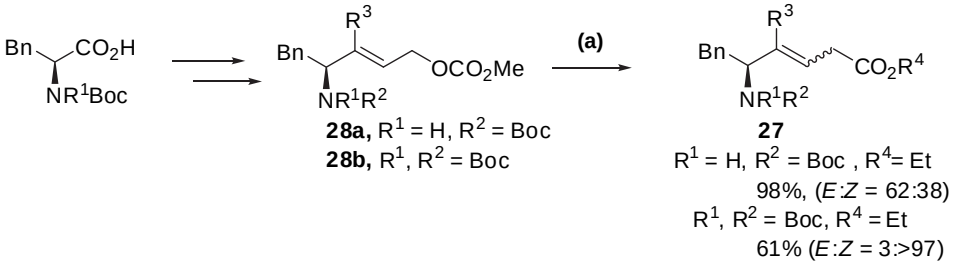
internal nucleophiles to give cyclic γ-vinylsilanes (**22**). The α-silyl group plays a crucial role in the regio- and stereoselectivity of the reaction.[42,43] If CO is incorporated into the reaction, then carbonylated products (**23**) are produced.[44,45]

Ohfune et al.[46] have utilised this methodology to synthesise several optically active carbocycles (Scheme 12), employing CO (5 atm) followed by esterification afforded the triester **24** as a 1:2.3 *E*/*Z* mixture in 88% yield. It was hoped that the reaction would proceed to the [3.3.0] fused carbocycle, but the steric bulk of the TBDMS group prevented olefin insertion in the acylpalladium species. Decreasing the CO pressure to 1 atm gave a 3:1 mixture of the acid **25** and *exo*-methylene species **26**. This result demonstrates that a higher CO pressure results in carbonylation occurring before β-hydride elimination.

Allylic carbonates can be utilised to directly capture CO, giving esters, rather than undergoing a Heck reaction. This has been used in a stereoselective approach to (*Z*)-trifluoromethylalkene dipeptide isosteres (CF_3-ADIs)[47] of the type **27** (R^3=CF_3). Such compounds are valued as they are less susceptible to enzymatic degradation. The (*Z*)-alkene-CF_3 compounds have a dipole moment (2.3 D) close to that of the amide carbonyl (3.4 D), and the fluorinated sp^3 carbon should create more favourable peptide isosteres.[48] However, the stereoselective synthesis of CF_3-ADIs of the type Xaa–Gly via the reported methodologies[49,50] would be difficult, as construction of a stereogenic centre at the δ-position relies upon the chirality of the α-carbon. The initial synthesis focused on the mono-*N*-Boc CF_3 allylic carbonates **28a** as the ester precursors (Scheme 13), which are derived in nine steps from *N*-Boc-L-phenylalanine.



Scheme 12. Reagents and conditions: (a) $Pd(PPh_3)_4$ (0.1 equiv), PPh_3 (0.1 equiv), CO (5 atm), 95 °C, 3 h then H_2O, 45 °C, 1 h; (b) CH_2N_2, 88% over two steps.



Scheme 13. Reagents and conditions: (a) **28** (0.124 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mol %), PPh_3 (40 mol %), CO (3.0 MPa), EtOH (5 ml), 50 °C, 12 h.

However, the CF_3 moiety could only be introduced in the presence of the highly carcinogenic HMPA. Other R^3 groups were introduced via Gilman or Suzuki methodologies when R^3=I.

Unfortunately, these processes delivered low *E*/*Z* selectivities, despite variation of the percentage catalyst, ligand type, solvent or reaction time. Carbonylations of this type favour the *trans*-isomers, due to the preference for *syn*-π-allylpalladium species. Thus the sterically demanding CF_3 prefers conformer **30**, thus reducing 1,3-interactions (Fig. 7).

The indole moiety is ubiquitous in nature[57,58] and 2-carboxyindole alkaloids are known inhibitors of HIV-integrase,[59] tubulin polymerisation[60] and Factor Xa.[61] Whilst there are many routes to carboxyindoles in the literature,[62] Alper et al.[62] have recently disclosed a novel route, involving 2-(2,2-dibromovinyl)phenylamines **31**, which undergo tandem N/C coupling followed by methoxycarbonylation of the remaining bromine to give **32** (Scheme 14).

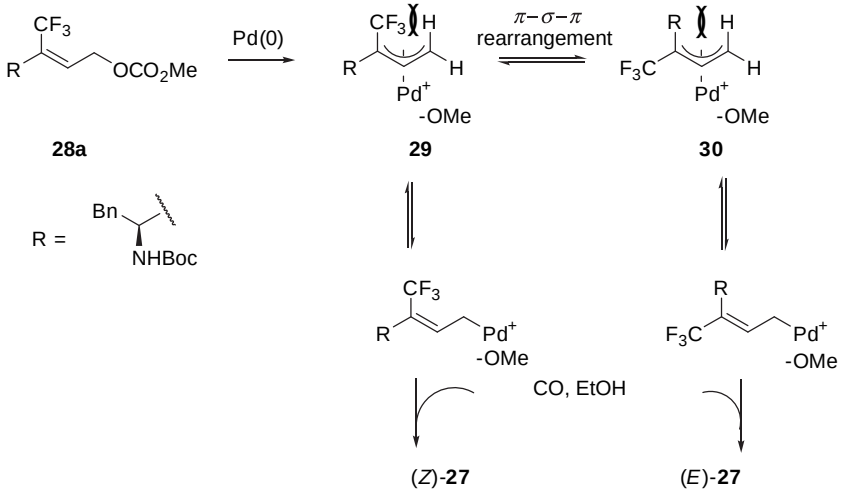
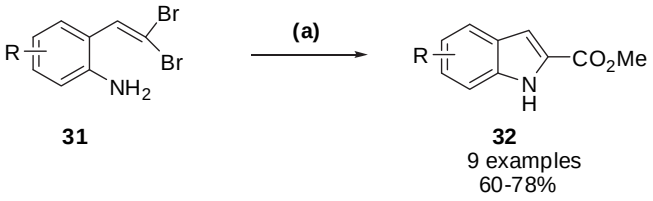


Figure 7. Possible configurations to account for the observed stereochemical outcome with **28a**.

Switching to the *N*,*N*-diBoc compounds (**28b**) and carbonylating under the best conditions, led, via conformer **29**, to the desired (*Z*)-β,γ-enolates as single isomers in moderate yields. However, replacing the CF_3 group with ^{n}Bu, ^{i}Pr, Me or Ph gave the mono-*N*-Boc-(*Z*)-β,γ-enolates as single isomers.

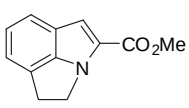
These results suggest the CF_3 group in the mono-*N*-Boc compound has some interesting effects on the formation of (*E*)-**27** that are not simply related to steric effects; substitution reactions involving sodium malonate in the absence of CO with the CF_3 carbonate **28a** are known to proceed with retention.[51,52]

The alkoxycarbonylation of styrene could potentially give both the α-branched and linear products. The regioselectivity of the process is crucial, as 2-arylpropionic acids and their derivatives are known intermediates in non-steroidal *anti*-inflammatory products.[53] It has been shown that monodentate phosphine ligands favour the branched products, whilst bidentate ligands favour the linear, but it has been recently reported[53] that *P*,*S*-ferrocene and *P*,*P*-bisphosphole ligands favour the branched systems, adding to the three other known exceptions.[54–56] However, these systems give lower yields and require higher CO pressures than the simple monodenate ligands.



Scheme 14. Reagents and conditions: (a) **31** (1.0 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), PPh_3 (10 ml%); DIPEA (2.0 mol equiv), CO (10 atm), THF/MeOH (1:1 v/v, 8 ml), 110 °C, 20 h.

The cascade tolerates chlorine and fluorine groups on the aniline ring, as well as other electron-withdrawing and -donating groups with no obvious yield bias for either type. Substitution was also tolerated on the aniline nitrogen, with four examples of *N*-alkylated indoles formed in 50–72% yield. Using *N*-tosyl aniline gave the lowest yield whilst the tricyclic system **33** was synthesised in good yield.



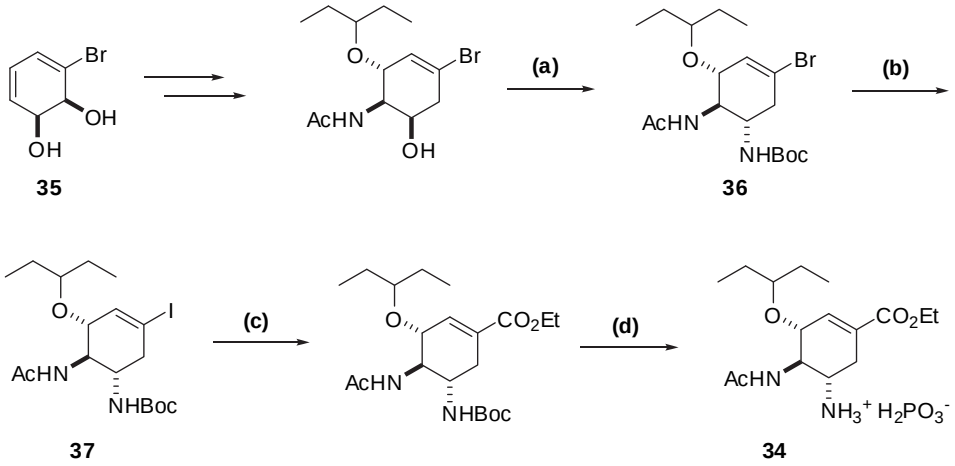
33, 69%

Reaction screening had shown that $Pd(PPh_3)_4$ was an inferior catalyst system to $PdCl_2(PPh_3)_2$, and so the additional PPh_3 may be acting to reduce the Pd(II) complex to the catalytically active Pd(0). Utilising THF or MeOH alone as the solvent gave lower yields than the co-solvent system, and switching to EtOH/THF gave the ethoxy esters. Overall, this route is advantageous due to the synthetic accessibility of 2-(2,2-dibromovinyl)phenylamines and it eliminates the traditional use of azides.[63]

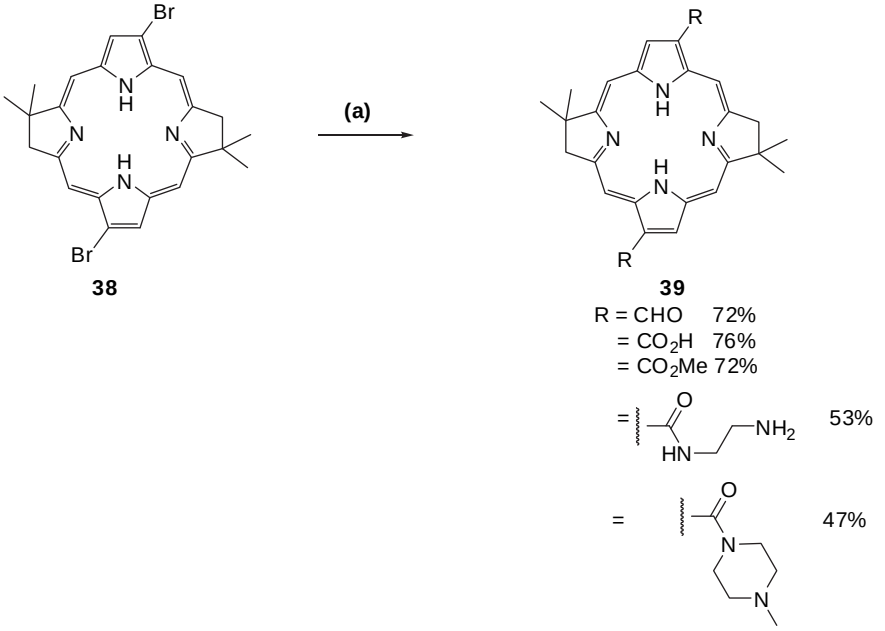
Tamiflu® (oseltamivir phosphate, **34**) is a known treatment for influenza[64–66] and its mode of action involves hepatic ester hydrolysis before acting on the neuraminidase enzyme of the influenza virus. However, the current large-scale synthesis requires the use of pure naturally occurring shikimic acid,[64] which is often difficult to obtain in sufficient purity, as well as the need for an azide intermediate. Fang et al.[67] have recently disclosed a concise, 11-step synthesis (Scheme 15) in 21% overall yield on a gram scale, starting from bromobenzene, which is oxidised enzymatically on a large scale to the bromoarene *cis*-1,2-dihydrodiol **35**.

This route avoids the requirement to use an explosive azide and the toxic $[Ni(CO)_2(PPh_3)_2]$, which is used to introduce the ester moiety, as well as eliminating the need for shikimic acid. Catalytic alkoxycarbonylation at room temperature was used to introduce the ester moiety, but this required the more active vinyl iodide **36** to proceed. Tetrabutylammonium cyanate and ^{t}BuOH were utilised to introduce the carbamate group in **37**.

Bacteriochlorins are attractive candidates for photodynamic therapy for diverse medical indications, owing to their strong absorption in the near-infrared (NIR) region, but their use has been stymied by the lack of access to stable, synthetically malleable molecules with a nearly full complement of substituents around the perimeter of the porphyrin-type macrocycles[68] and their susceptibility to adventitious dehydrogenation (yielding the chlorine or porphyrin, which lack the NIR absorption).[69–71] To overcome these limitations, 3,13-dibromobacteriochlorin[72] (**BC**–**Br**^{3}**Br**^{13}, **38**), possessing geminal dimethyl group in each pyrroline ring to prevent adventitious dehydrogenation, has been exploited as a building block in the synthesis of diverse bacteriochlorins via Pd-mediated coupling reactions, including peripheral carbonylations with a variety of nucleophiles (Scheme 16).



Scheme 15. Reagents and conditions: (a) DDQ, PPh_3, ^{n}Bu$_4$NOCN, MeCN, rt, 18 h then: ^{t}BuOH, reflux 24 h, 78%; (b) CuI, KI, DMEDA, ^{n}BuOH, 120 °C, 24 h; (c) [Pd(OAc)], NaOAc, CO, EtOH, rt, 24 h (82% from **35**); (d) H_3PO_4, EtOH, 50 °C, 6 h, 81%.



Scheme 16. Reagents and conditions: (a) **38** (1.0 equiv), $Pd(PPh_3)_4$ (2.0 equiv), NuH (2.0 equiv to excess), CO (bubbling, 2 h), DMF/PhMe (1:1 v/v), 70 °C, 2.5 h.

Attempted carbonylation with a catalytic amount of $Pd(PPh_3)_4$ gave multiple products, but predominantly the unreacted **38**, due to Pd chelation by the macrocycle. By contrast, the use of super-stoichiometric amounts of $Pd(PPh_3)_4$ with the desired nucleophile gave compounds of the type **39** in good yield. Acids, esters and amides were formed by the addition of the appropriate sodium salt to the CO-saturated reaction mixture. Whilst the synthesis of the above amides was straightforward, the yields were low and a large amount of the ketoamide by-product was obtained, which co-eluted with the desired product. Therefore, a large-scale synthesis of the diacid was undertaken and this was subsequently converted into the acid chloride and quenched with the desired amine.

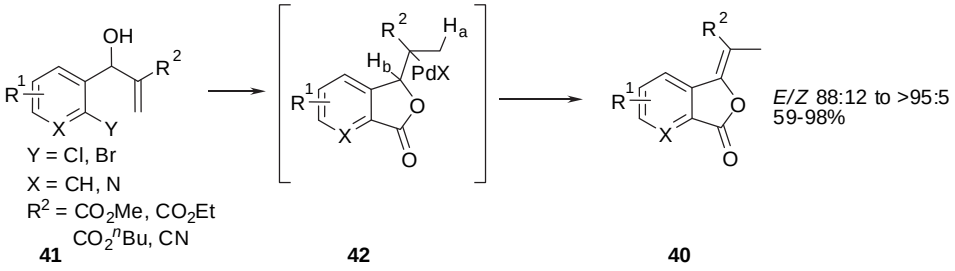
3.2.4. Alkoxycarbonylations in heterocycle synthesis. Various heterocycles can be accessed via palladium-catalysed cyclocarbonylation reactions. For example, Coelho et al.[73] reported the stereoselective synthesis of 3-alkenylphthalides (**40**), a moiety found in several natural products.[74–76] Phthalides are also utilised in the synthesis of functionalised naphthalenes and anthracenes, which in turn are used in the synthesis of linear aromatic natural products.[77]

The synthesis of the phthalide core utilised a palladium-catalysed carbonylative cyclisation of the Baylis–Hillman adducts **41**, synthesised from the corresponding aldehyde (Scheme 17). The reaction probably proceeds via the intermediate **42**, giving the terminal alkene first (loss of H_a). This is then isomerised by [H/Pd/X] to the more stable alkene. This mechanism accounts for the isolation of the terminal alkene species in some instances. The stereochemical outcome (*E*/*Z*) of the reaction bears no relation to the size of the R^2 group on the acrylate. However, when the aryl halide was a quinoline, the *E*/*Z* ratio was reversed.

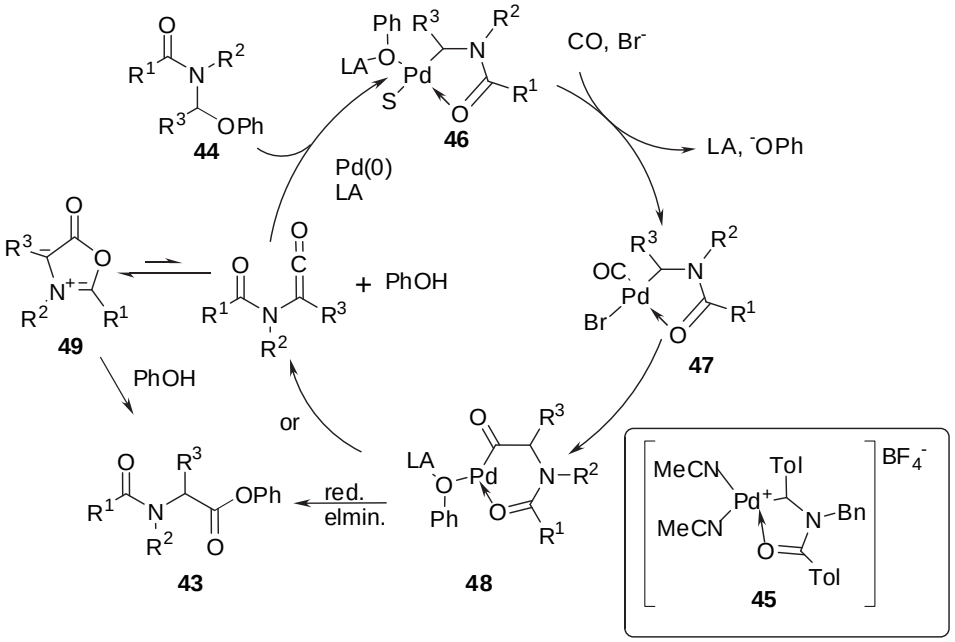
Arndsten and Lu[78] reported the synthesis of unnatural *R*-α-amino esters **43** from amide ethers **44** under mild conditions employing Lewis acids (LAs) to activate the ether oxygen (Scheme 18). Ethers are usually stable enough to be used as protecting groups in palladium-catalysed reactions. Notable was that the reaction proceeded with bulky or electron-withdrawing aminol ethers as well when R^3=H, since none of these substituents were tolerated in the previously reported carbonylations of imines and acid chlorides (vide infra).[79–81]

The use of AlF_3 proved to be most beneficial to the reaction, allowing it to proceed smoothly without palladacycle degradation. Pd(0) was supplied from the palladacycle **45**. The mechanism shows the requirement for a LA, which activates the phenol leaving group (**46**) and CO displacement of the phenol (**47**), followed by migration, forms **48**. The product (**43**) forms via reductive elimination, or by trapping the münchone **49** with PhOH.

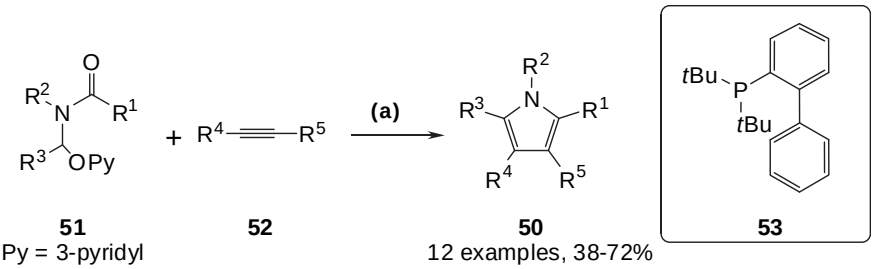
The münchnone **49** generated during this cascade can also be utilised in the formation of pyrroles **50**,[82] via the use of α-aminoethers **51** and alkynes **52** (Scheme 19) and loss of CO_2. The use of –OPy (Py=3-pyridyl) removes the need for a strong Lewis acid. This change allows a β-hydride elimination step to occur (forming the münchnone) and the greater activation of the C–O bond, facilitating oxidative addition. The absence of strong Lewis acids allows the incorporation of small enolisable R groups (e.g., R^1=Me) and other



Scheme 17. Reagents and conditions: **41** (1.12 mmol), Pd_2dba_3 (1–2 mol %), $P(^tBu)_3$ (4–8 mol %), Cy_2NMe (1.1 equiv), CO (2 atm), anhyd 1,4-dioxane (3 ml), 70–90 °C, 5–78 h.



Scheme 18. Reagents and conditions: (a) **44** (0.20 mmol), **45** (10 mol %), Bn_4NBr (0.10 mmol), AlF_3 (0.4 mmol), CO (4 atm), MeCN (2 ml), 65 °C, 14 h. Tol=*p*-Tolyl, S=solvent.



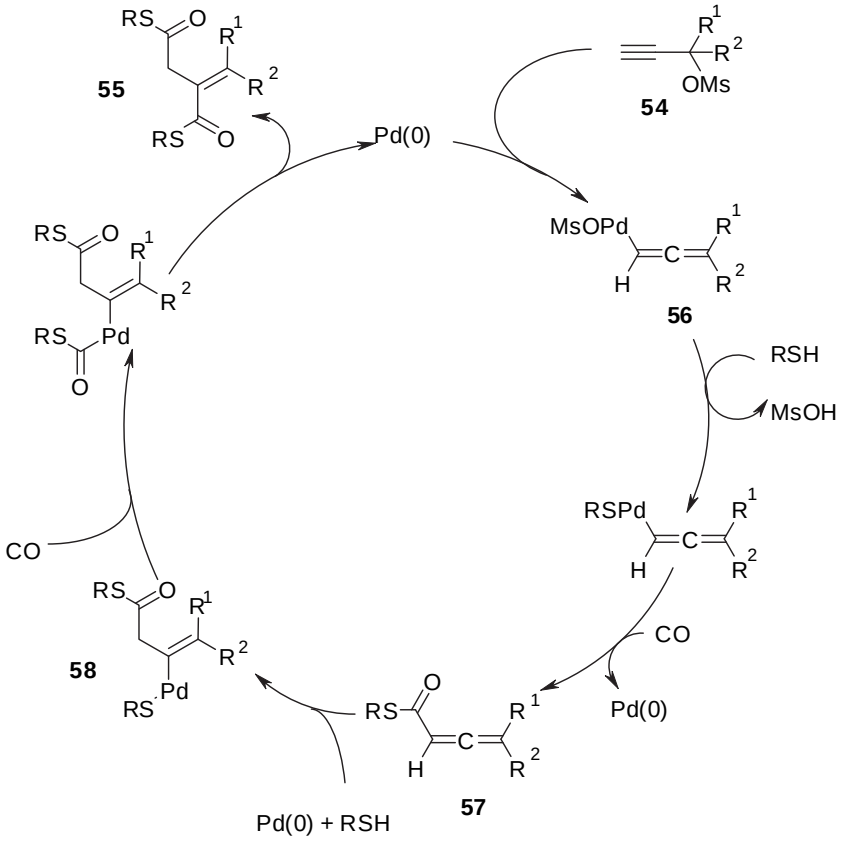
Scheme 19. Reagents and conditions: (a) **51** (0.20 mmol), **52** (0.30 mmol), **45** (10 mol %), **53** (15 mol %), CO (60 psi), Bu_4NBr (0.10 mmol), MeCN (2 ml), 65 °C, 24 h.

acid-sensitive functionalities (furyl, indole). In addition, R^2 and R^3 can be aryl- or alkyl-forming products not accessible by other procedures.

The cycloaddition reaction tolerates base-sensitive R^1 groups, and bulky or aromatic R^2 groups, as well as base-sensitive alkynes. In addition, electron-poor alkenes have been utilised, forming trisubstituted pyrroles. Sterically bulky and basic ligand **53** was found to be the most effective. This route eliminates the need to first generate imines and the use of acid chlorides (vide infra).

a pseudohalogen in the Liebeskind–Srogl modified Suzuki reaction without detrimental effects.[86]

Alper and Xiao[87] have continued to work in this area and, in 2005, reported the first example of the dithiocarbonylation of thiols with propargylic mesylates **54**. The reaction showed a high degree of stereoselectivity for the (*E*)-dithioesters **55**, with a range of these compounds formed in 57–88% yield (Scheme 20).



Scheme 20. Reagents and conditions: (a) **54** (1.0 equiv), thiol (2.0 equiv), $Pd(PPh_3)_4$ (3 mol %), CO (400 psi), THF, 90 °C, 48 h.

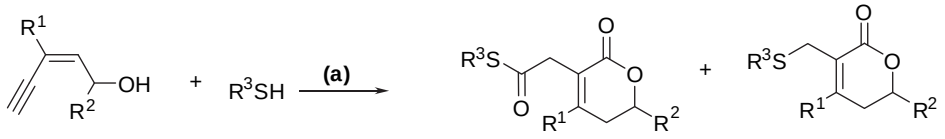
3.3. Thiocarbonylations

The strong thiophilicity of transition metals[83] had been thought to play a detrimental role in transition metal-catalysed reactions. However, in recent years, this idea has been challenged. For instance, the use of $Co_2(CO)_8$ in the carbonylation of sulfur compounds showed that cobalt and sulfur are compatible,[84] as is ruthenium, which was utilised in 'thioformylation' reactions.[85] Palladium is also compatible with sulfur:sulfur is even utilised as

Mechanistically, the reaction follows traditional Pd chemistry. Oxidative addition to **54** gives the allene **55**, which undergoes thiocarbonylation and reductive elimination to give **57**. Michael-type addition to the species carbon of **57** from the least-hindered face ($R^1 > R^2$) gives **58** (and therefore (*E*)-selectivity), which undergoes another thiocarbonylation and reductive elimination sequence to yield the dithioester **55**.

In 2006, Alper et al.[88] extended this work to the first reported high-pressure (500 psi) double carbonylation of ynols (**59**) and

thiols to form the thioester-substituted α,β-unsaturated six-membered lactones **60**. These lactones are useful subunits in natural product synthesis[88] as well as chiral building blocks, for example, in the synthesis of the Prelog-Djerassi lactone.[88] The reaction was found to produce two products: the thioester **60** and the thioether **61**; with modification of the reaction conditions, the desired product **60** could be produced in 23–81% yield (Scheme 21).

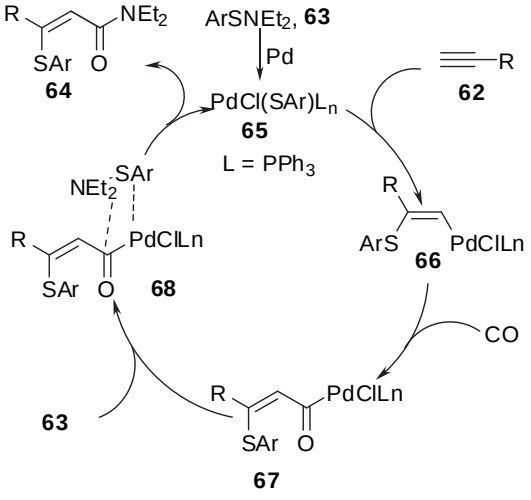


59 **60** **61**

Scheme 21. Reagents and conditions (a): **59** (3.0 mmol), thiol (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol), THF (15 ml), CO (500 psi), 110 °C, 36 h.

It was found that THF and high pressures of CO gave increased yields of the di-carbonylated products (cf. propargylic mesylates) and thiophenol gave the highest yields, although substituted thiophenols and aliphatic thiols were tolerated. Ynols with an internal alkyne were unreactive under these conditions.

Kuniyasu et al.[89] achieved the high-pressure thiocarbamoylation of terminal alkynes **62** with aryl-substituted sulphonamides **63** to generate **64**. Substitution on the aryl ring of the sulphenamides was crucial for the reaction to (i) incorporate the alkyne into the product (or a thiocarbamate would be formed) and (ii) achieve good *E*/*Z* selectivity, with 2,4,6-trichlorophenylsulphenamide giving the best result (Scheme 22).

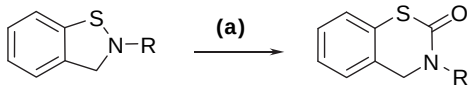


Scheme 22. Reagents and conditions: **63** (1.2 mmol), **62** (1.0 mmol), $[Pd(PPh_3)_2Cl_2]$ (0.02 mmol), PPh_3 (0.04 mmol), $^nBu_4NCl$ (0.08 mmol), CO (20 $kgcm^{-2}$), MeCN (0.5 ml), 120 °C, 3 h.

The reaction tolerated a wide variety of substituted alkynes, giving **64** in 62–86% yield with *E*/*Z* ratios of 17:83 to 0:100.

The reaction mechanism proposed is unusual, in that the active catalyst **65** is formed from $Pd(PPh_3)_2Cl_2$ and **63**. It was further proposed that the reason for the high rate of **64** formation is due to the reluctance of **65** to undergo disproportionation, unlike other Pd/sulphenamide complexes.[89] The vinyl/Pd complex **66** also disfavours C–Cl bond formation on thermodynamic grounds;[89] CO insertion into this complex generated the acylpalladium species **67**, which then undergoes σ-bond metathesis between the Pd–C bond and the N–S bond of the sulphenamide (**68**), generating the product and the active catalyst. At this time, the roles of the additional PPh_3 and Bu_4NCl are unclear.

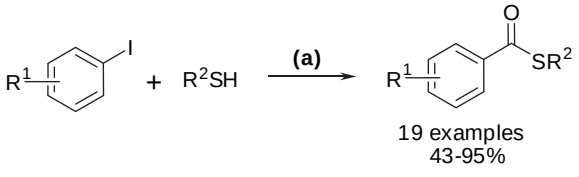
This idea that the N–S bond undergoes metathesis with Pd catalysts with CO insertion has been utilised by Alper and Rescourio[90] in their synthesis of 3,4-dihydro-2*H*-1,3-benzothiazin-2-ones **69**. Until this report, only one method for their synthesis was known,[91] which utilised phosgene gas in refluxing benzene, giving the corresponding 3,4-dihydro-2*H*-1,3-benzothiazin-2-ones in 33–62% yield. The 3,4-dihydro-2*H*-1,3-benzothiazin-2-ones were synthesised in 56–92% yield with complete regioselectivity (Scheme 23). It should be noted that only *N*-substituted precursors were utilised in this study and the starting materials **70** are not commercially available.



70 **69**

Scheme 23. Reagents and conditions (a): **70** (0.5 mmol), $Pd(PPh_3)_4$ (0.025 mmol), pyridine (1 ml), CO (300 psi), 80 °C, 24 h.

The use of ionic liquids both as a reaction medium and as a means of recycling the palladium catalyst has recently been reported in the high-pressure synthesis of thioesters (**71**) (Scheme 24).[92]



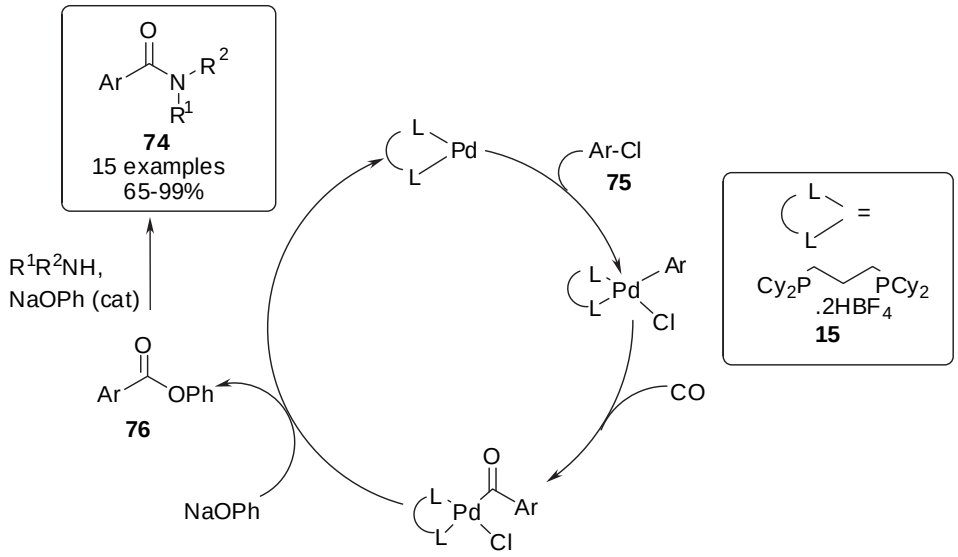
72 **73** **71**

Scheme 24. Reagents and conditions: (a) **72** (1.2 mmol), **73** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (20 mol %), CO (200 psi), Et_3N (2.0 mmol), PSIL (1.5 g), 100 °C, 18 h. PSIL=$(C_6H_{13})_3P^+(CH_2)_{13}CH_3 \cdot PF_6^-$.

The reaction tolerated electron-rich and -poor aryl iodides **72**, with thiophenols and alkylthiols **73** with electron-withdrawing groups giving the best yields; *ortho*-substitution was also tolerated. It was shown that the ionic liquid allowed easy compound recovery (addition of hexane and decanting) and that the catalyst remained active, demonstrated by the sequential carbonylation reactions with the same batch of catalyst without loss of activity.

3.4. Aminocarbonylations

3.4.1. Aminocarbonylation of halides and pseudohalides. Palladium-catalysed aminocarbonylation of aryl halides or triflates is a powerful tool for the synthesis of aromatic secondary and tertiary amides. The Buchwald group has recently[38] disclosed the synthesis of aromatic amides (**74**) from the corresponding aryl chlorides (**75**), aided by the dual role of sodium phenoxide, using CO (1 atm) (Scheme 25). Electron-deficient, -neutral, and -rich aryl and heteroaryl chlorides were all successfully transformed, as were the

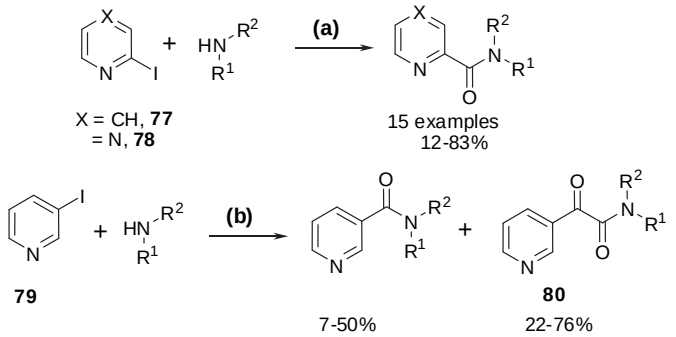


Scheme 25. Reagents and conditions: **75** (1.0 mmol), amine (3.0–4.0 mmol), NaOPh (2.0 mmol), CO (1 atm), $Pd(OAc)_2$ (2 mol %), **15** (4–5 mol %), 4 Å mol sieves (150 mg), DMSO (1 ml), 100–120 °C, 15 h.

co-reactants: primary, α-branched primary, cyclic secondary, acyclic secondary and aryl amines.

The critical innovation in this process was the use of sodium phenoxide in two distinct roles in the reaction: (i) to trap the acylpalladium species to generate **76** (possibly a lower energy intermediate), as observed by in situ IR measurements of the reaction showing a distinct ester absorption band, followed by the amide absorption after a few minutes; and (ii) to act as a Brønsted base in the conversion of ester into amide. This was evidenced by running the carbonylation reaction in the absence of NaOPh with the preformed **76** showing very slow conversion into the amide ($t^1/_2 \approx 10$ h). Addition of NaOPh (1 equiv) showed the rapid formation of **74** ($t^1/_2 \approx 12$ min). The optimal ligand type proved to be the electron-rich bulky bisphosphine **15**, which aids both oxidative addition and acyl migration.

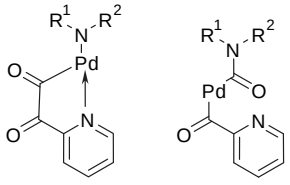
Palladium-catalysed aminocarbonylation has also proved to be an efficient method for the functionalisation of *N*-containing iodoheteroaromatics.[93] The position of the iodo-substituent relative to the nitrogen determines the chemoselectivity towards mono- and di-carbonylated products, with 2-iodopyridine (**77**) and -iodopyrazine (**78**) giving amides, while 3-iodopyridine (**79**) gave mixtures of carboxamides and the double carbonylated 2-keto-carboxamides **80** (Scheme 26).



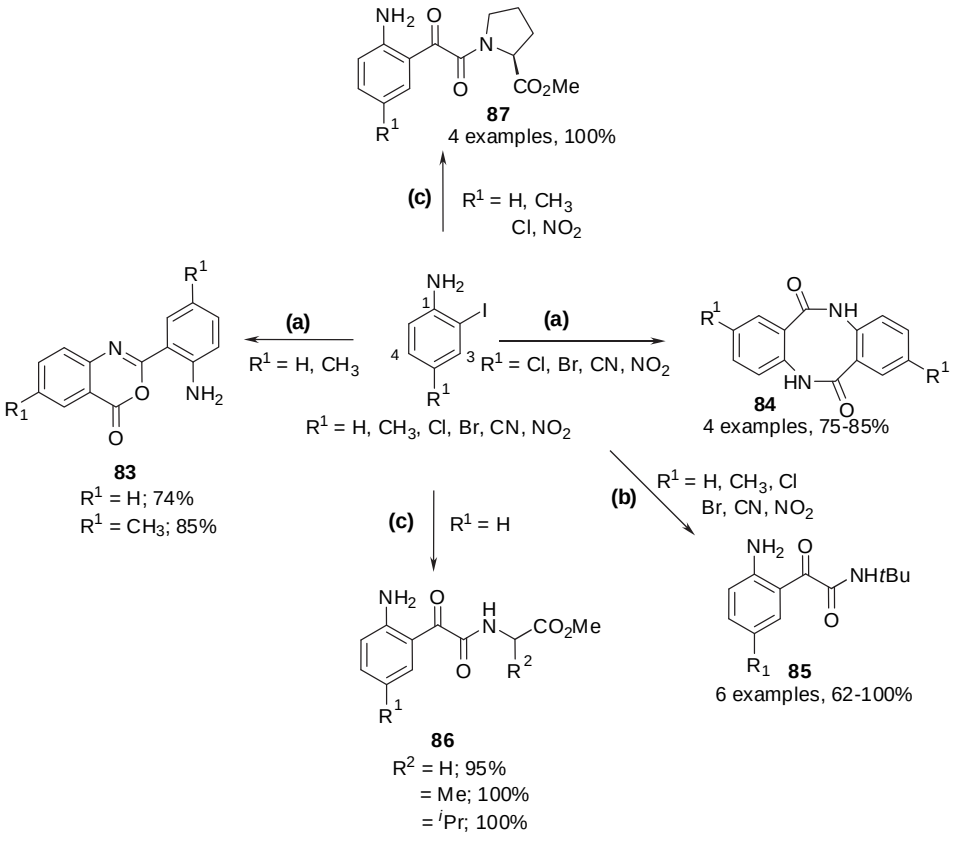
Scheme 26. Reagents and conditions: (a) **77** or **78** (1.0 mmol), amine (3.0 mmol) or amino acid methyl ester HCl (1.1 mmol), $Pd(OAc)_2$ (2.5 mol %), PPh_3 (5 mol %), CO (1 atm), Et_3N (0.5 ml), DMF (10 ml) (if **78** and amino acid, then P_{CO} (40 atm)), 50 °C, 6–137 h; (b) as for (a), but utilising **79** and CO (40 atm), 50 °C, 24–70 h.

With **77**, only amides were observed, while incomplete conversion and poor yields were obtained when aniline and amino acids were employed as the nucleophiles. Only amides were observed with **78**, but employing higher pressures of CO (40 atm) gave 74–82% yield of the *N*-substituted amino acids. Conversely, **79** gave the opposite selectivity, with significant amounts of ketoamide **80** formed at 1 atm; increasing the pressure to 40 atm gave mainly **80**, except with aniline and proline methyl ester.

The authors suggested that the exclusive formation of amides with **77** and **78** could be explained by the formation of a glyoxolate intermediate **81**, which is prevented from undergoing reductive elimination by chelation of the pyridine nitrogen. However, mechanistic studies suggest that double carbonylation does not go through such an intermediate, preferring instead to proceed via **82**.[27,94]



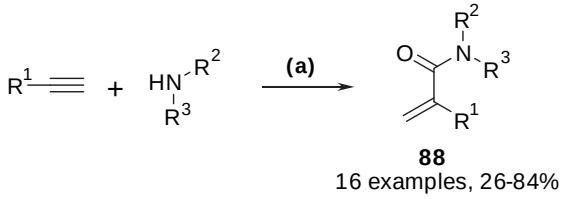
2-Oxoamides are reported to be potent inhibitors of digestive lipases[95] and Group VIA phospholipase A2.[96,97] Ács et al.[98] utilised 2-iodoaniline derivatives as bifunctional substrates in carbonylation reactions, generating ketocarboxamides as the major products in each case (Scheme 27). Depending on the C-4 substituent, two types of compounds were obtained: with methyl or hydrogen in the 4-position 2-aryl-benzo[*d*][1,3]oxazin-4-one derivatives **83** were produced, whilst chloro, bromo, cyano or nitro groups in the same position resulted in the formation of dibenzo[*b*,*f*][1,5]-diazocine-6,12-dione derivatives **84**. A high-pressure (100 bar CO) was required in each case, due to the poor nucleophilicity of the anilines. Various primary (**85** and **86**) and secondary (**87**) ketoamides were formed (Scheme 27) with external nucleophiles, whilst the aniline moiety remained unchanged. A similar prevalence of 2-oxo-carboxamides over carboxamides in the aminocarbonylation of iodoaromatics has been reported,[99] probably due to the high pressures of CO (>30 bar) employed.



Scheme 27. Reagents and conditions: (a) iodoaniline (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.05 mmol), CO (100 bar), Et_3N (0.5 ml), DMF (10 ml), 140 h, 50 °C; (b) iodoaniline (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.05 mmol), $NH_2{}^tBu$ (5.0 mmol) CO (40 bar), Et_3N (0.5 ml), DMF (10 ml), 20 h, 50 °C; (c) iodoaniline (1.0 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.05 mmol), amino acid hydrochloride (1.25 mmol), CO (40 bar), Et_3N (0.5 ml), DMF (10 ml), 6–70 h, 50 °C.

Vinyl iodides can also be utilised as the halide partner.[100] α-Iodostyrene and α,α′-diiodo-1,4-divinylbenzene, which are potential asymmetric building blocks (via asymmetric reduction of the double bond), gave *N*-substituted phenylacrylamides, formed chemoselectively in up to 83% yield. This was achieved both with unfunctionalised simple amines and amino acid methyl esters under mild conditions.

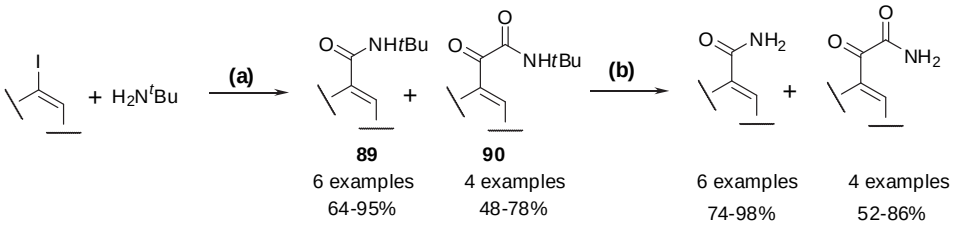
An alternative route to acrylamides utilises the regiospecific aminocarbonylation of alkynes in ionic liquids (Scheme 28).[101] The reaction is >99:1 selective for the *exo*-methylene product, with an ionic liquid ([bmim][Tf_2N]) acting as the reaction medium and promoter. The enamides **88** were obtained in 56–84% yield and importantly, the catalyst could be recycled fivefold without loss of activity. No carbonylation was observed when using DMF, THF or [bmim]BF_4.



Scheme 28. Reagents and conditions: (a) alkyne (1.0 mmol), amine (5.0 mmol), $Pd(OAc)_2$ (3 mol %), dppp (6 mol %), CO (200 psi), [bmim][Tf_2N] (2 g), 110 °C, 22 h.

Application to primary amides is restricted, due to the low nucleophilicity of ammonia and the difficulties in handling this toxic reactant. However, various ammonia synthons can be used in most reactions.[102–104]

Primary amides can be synthesised from the corresponding aryl/alkenyl *N*-*tert*-butyl amides **89** and aryl *N*-*tert*-butyl ketoamides **90** with unprecedented selective cleavage of the ^tBu group by TBDMSOTf.[105] Chemoselectivity (**89** vs **90**) was achieved by temperature control: 60 °C for aromatic ketoamides and 100 °C for aromatic amides (Scheme 29), probably due to a lower CO solubility at higher temperature. With vinyl iodides, under the same conditions, amides are obtained in high yield (92–95%), even at 60 °C, with both electron-rich and -poor aromatics.



Scheme 29. Reagents and conditions: (a) alkenyl/aryl iodide (1.0 mmol), $^tBuNH_2$ (5.0 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), CO (1 atm), Et_3N (3.5 mmol), toluene (10 ml), 60–100 °C, 8–10 h; (b) amide/ketoamide (0.5 mmol), TBDMSOTf (0.5 mmol), toluene (5 ml), N_2 (g), 60–100 °C, 8 h.

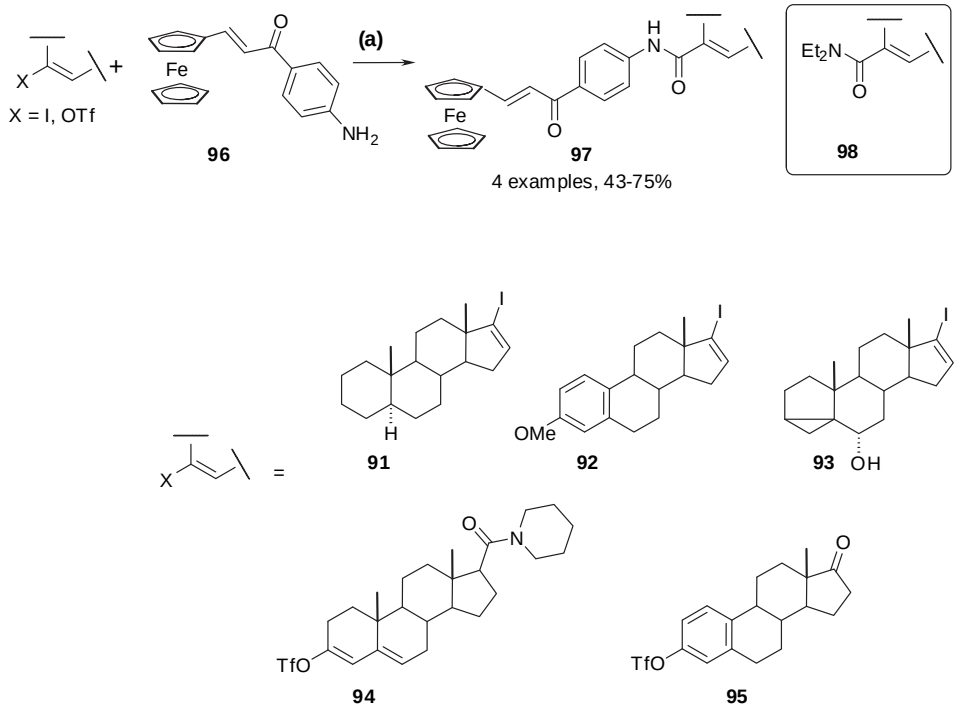
This protocol also furnishes primary amides/ketoamides in good yield but the deprotection conditions are incompatible with steroidal skeletons bearing an OH or NH moiety. Ammonium carbonate could be utilised as the ammonia synthon, overcoming this incompatibility and leading directly to the primary amide under 1 atm of CO in 1,4-dioxane.[106] Ammonium carbonate proved to be superior to both ammonium hydroxide and formamide under the reaction conditions.[106]

(*N*-Ferrocenylmethyl) amines derived from vicinal steroidal amino alcohols and amines exhibit outstanding antimicrobial activity against mycobacteria and multi-resistant staphylococci.[107] Balogh et al.[108] disclosed a new route to such ferrocenyl steroids via aminocarbonylation of the alkenyl iodides/enol triflates **91**–**95** utilising (*E*)-1-(4′-aminophenyl)-3-ferrocenyl-prop-2-en-1-one **96** as the nucleophile. The products (**97**) were obtained in 43–75% yield (Scheme 30).

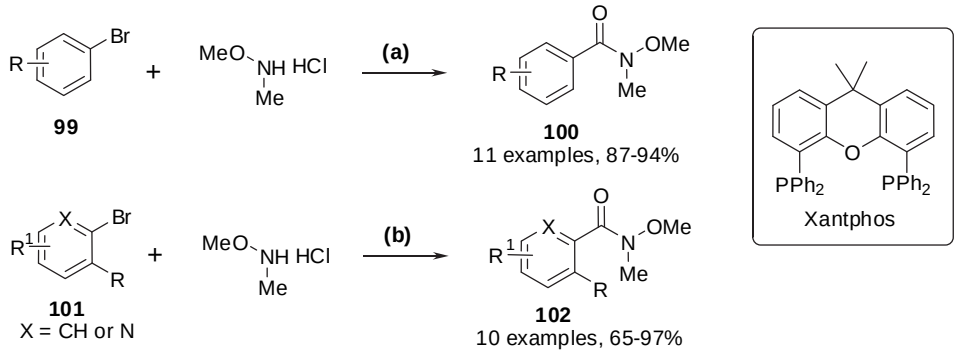
Weinreb amides are well-established acylating agents and their ability to undergo selective addition of one equivalent of a variety of organometallic reagents is key to their utility. In 2006, Buchwald et al.[110] reported the conversion of aryl bromides **99** into the corresponding Weinreb amides **100** via Pd-catalysed aminocarbonylation at atmospheric pressure (Scheme 31).

Electron-deficient, -neutral, and -rich aryl bromides were all efficiently transformed into the products and the reaction tolerated a wide variety of functional groups. However, *ortho*-substituted aryl bromides or pyridines **101** were not satisfactorily converted into **102** under the standard conditions, but utilising K_3PO_4 as a base and a 2:1 ratio of Xantphos/Pd overcame this problem.[111]

This work has been applied[112] to the direct transformation of lactam-, lactone-, and thiolactone-derived enol-triflates **103** into Weinreb amides **104** (Scheme 32). *N*-Methoxy-*N*-methyl amine hydrochloride could be successfully replaced with the more readily



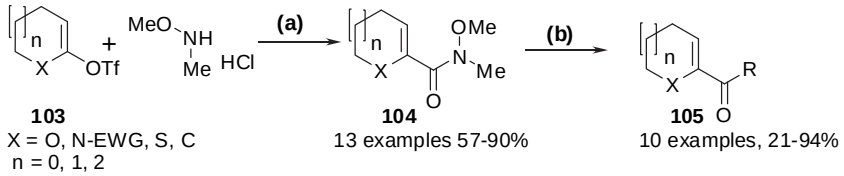
Scheme 30. Reagents and conditions: (a) steroidal substrate (0.24 mmol), **96** (0.2 mmol), $Pd(OAc)_2$, (10 mol %), PPh_3 (20 mol %), CO (1 atm), Et_3N (100 μL) dioxane (2 ml), 100 °C, 16 h.



Scheme 31. Reagents and conditions: (a) **99** (1.0 mmol), $Pd(OAc)_2$ (2 mol %), Xantphos (2 mol %), amine (1.5 mmol), CO (1 atm), Na_2CO_3 or Et_3N (3.0 mmol), toluene (2 ml), 5–22 h, 80 °C; (b) **101** (1.0 mmol), $Pd(OAc)_2$ (2.5 mol %), Xantphos (5 mol %), amine (1.5 mmol), CO (1 atm), K_3PO_4 (3.0 mmol), toluene (2 ml), 20 h, 100 °C. If X=N or R=Cy, F then $Pd(OAc)_2$ (3 mol %), *m*-xylene (2 ml), 20 h 110–120 °C is required.

Small amounts (<10%) of the byproduct (**98**) were encountered. This arises from [Pd] dehydrogenation of the triethylamine, whilst **95** gave no product, even when dppp was employed as the ligand.[109]

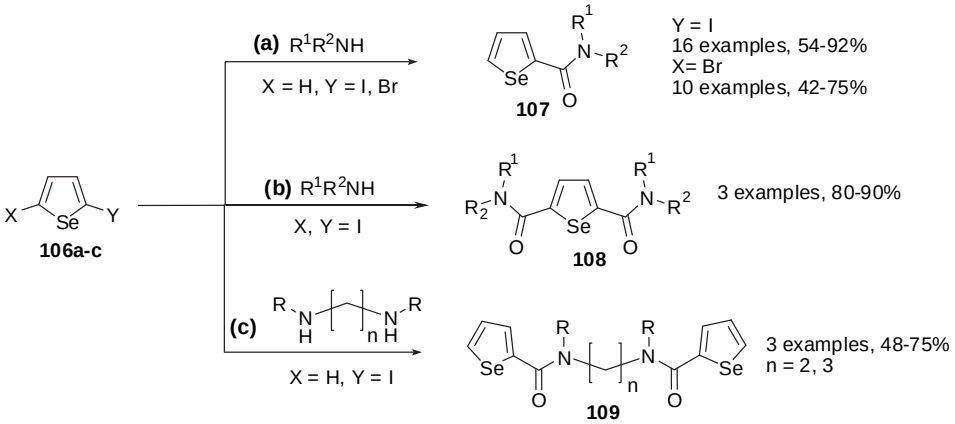
available morpholine to afford the corresponding morpholino enamides, which can successfully replace the 'classical' Weinreb amide.[112] Reactions with nucleophiles afforded acylated aza-, oxa- and thio-heterocycles **105**. This route is complementary to the



Scheme 32. Reagents and conditions: (a) **103** (1 mmol), $Pd(OAc)_2$ (2 mol %), Xantphos (2 mol %), amine (1 mmol), CO (1 atm), Na_2CO_3 (3 mmol), THF (13 ml), rt, overnight; (b) **104**, Grignard reagent (2.0 mmol), THF (5 ml) −78 °C to rt.

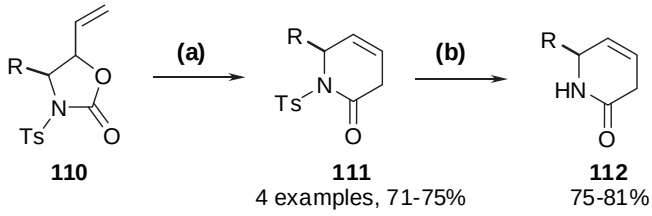
carbonylative-Suzuki reaction on similar substrates (vide infra) and the products are useful substrates for Nazarov cyclisation.

Halo-selenophenes **106** undergo selective carbonylation[113] giving selenophene-2-carboxamides **107**, selenophene-2,5-dicarboxamides **108** and 2,2′-*N*,*N*′-bridged selenophene-2-carboxamides **109** in good yield (Scheme 33). The reaction proceeds with both primary and secondary amines, under mild conditions, in the absence of a high pressure of carbon monoxide. This reaction is analogous to the carbonylative-Suzuki reaction of selenophenes (vide infra).



Scheme 33. Reagents and conditions: (a) **106a** (0.5 mmol), amine (0.8 mmol), $Pd(PPh_3)_4$ (10 mol %), CO (1 atm), aqueous Na_2CO_3 (2.2 mmol, 2 M), toluene (3 ml), reflux, 2–12 h; (b) **106b** (0.5 mmol), amine (1.6 mmol), CO (1 atm), Na_2CO_3 (2.2 mmol, 2 M), $Pd(PPh_3)_4$ (20 mol %), toluene (5 ml), reflux, 12 h; (c) **106c** (1.0 mmol), diamine (0.8 mmol), $Pd(PPh_3)_4$ (10 mol %), CO (1 atm), aqueous Na_2CO_3 (2.2 mmol, 2 M), toluene (3 ml), reflux, 12 h.

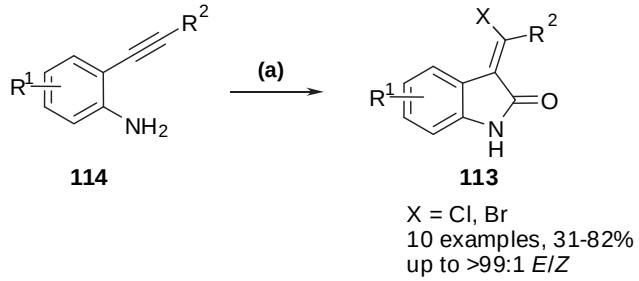
3.4.2. Heterocycle synthesis. 5-Vinyloxazolidin-2-ones undergo a stereospecific, high-pressure (60 atm) palladium-catalysed decarboxylative carbonylation to afford 3,6-dihydro-1*H*-pyridin-2-ones.[114] Location of an electron-withdrawing group on the oxazolidinone nitrogen activates the molecule towards decarboxylation and the subsequent carbonylation reaction, allowing the decarboxylative carbonylation of **110**, **111** to occur at atmospheric pressure (Scheme 34).[115] The reaction proceeds in high yield with no loss of enantiopurity. Mild detosylation conditions (sodium naphthalenide) give the products **112** in good yields.



Scheme 34. Reagents and conditions: (a) **110** (0.625 mmol), $Pd_2(dba)_3$ (5 mol %) PPh_3 (10 mol %), CO (1 atm), benzene (6 ml), 4 h, 60 °C; (b) **111** (0.12 mmol), naphthalene (3.07 mmol), Na (3.44 mmol), DME (11 ml), −65 °C to rt, 1 h.

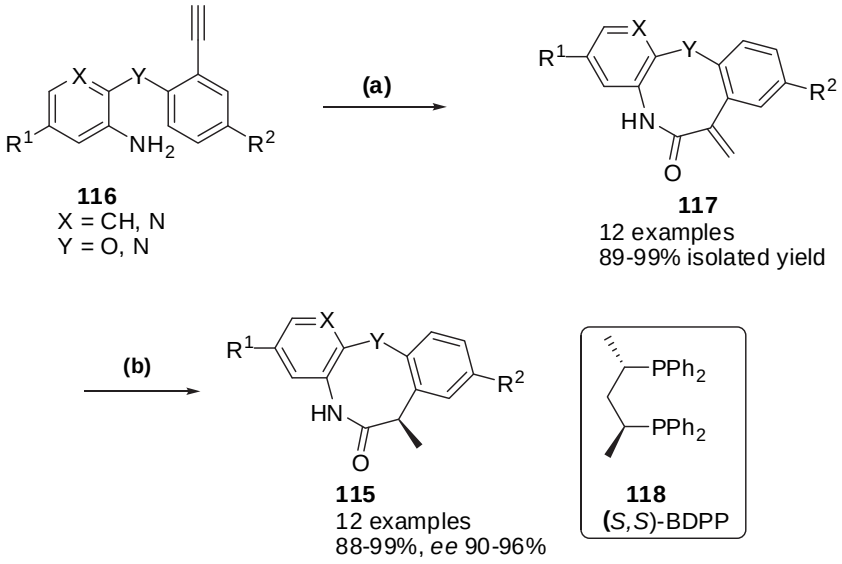
The indolin-2-one system is presented in many naturally occurring and biologically active compounds.[116–118] A novel and selective palladium-catalysed carbonylative annulation process for the synthesis of 3-(halomethylene)indolin-2-ones **113** was recently reported.[119] A primary aniline amine and substitution on the terminus of the alkyne **114** (i.e., $R^2 \neq H$) are essential for success, whereas electron-withdrawing groups on the aniline ring have no effect on the reaction outcome (Scheme 35).

E/*Z* ratios of up to >99:1 were achieved with the double bond geometry probably originating from PdX_2 co-ordination to amine and alkyne. The *E*/*Z* ratio drops dramatically when R^2 is a *para*-substituted benzene. In some cases, where the aniline was substituted protected (NHAc) or R^1=2,4-dichloro, the 1*H*-indole was formed exclusively. The vinyl halide moiety in the products provides an attractive route to introduce a new functionality.



Scheme 35. Reagents and conditions: (a) **114** (0.5 mmol), PdX_2 (5 mol %), CuX_2 (3 equiv), CO (1 atm, bubbling), benzene/THF (10:1, 5.0 ml), rt, 4–24 h.

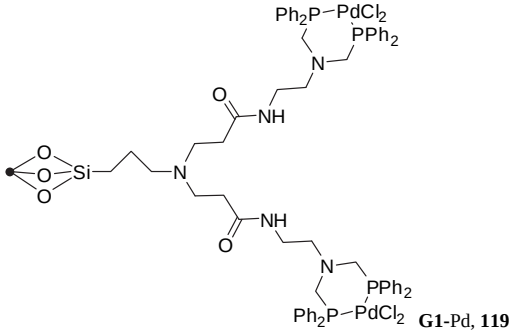
Adapting this methodology to synthesise medium-size lactams, especially dibenzoxazocinones **115**, has been reported by Alper and Lu.[120] These systems are found in many pharmaceutically active compounds, such as HIV-1 reverse transcriptase inhibitors, and pyschotropic and hypotensive agents. A variety of dibenzoxazocinones, starting from a selection of substituted 2-(2-ethynylphenoxy)anilines (**116**), were reported. Electron-withdrawing or -donating groups had little effect on the reaction time or yield (Scheme 36). The reactions were completely regioselective for **117**, with no *endo*-isomers observed. The reaction also tolerated an amine linker. The *exo*-methylene could be reduced asymmetrically to **115** by $Rh(COD)_2BF_4$ and (*S*,*S*)-BDPP (**118**). This is the first example of an α,β-unsaturated lactam being reduced in high ee, even with the



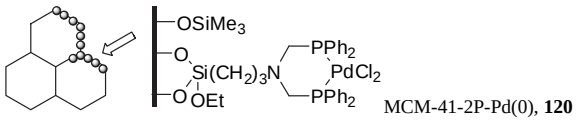
Scheme 36. Reagents and conditions: (a) **115** (1 mmol), **119** (15 mg), *p*-TsOH (0.03 mmol), CO, (100 psi), DCM (10 ml), 80 °C, 22 h; (b): **117** (1.0 mmol), $Rh(COD)_2BF_4$ (0.01 mmol), **118** (0.01 mmol), H_2 (20 psi), MeOH (5 ml), 0 °C, 48 h.

inability of the alkene to rotate towards the carbonyl and thus chelate to the metal complex. The reaction required low temperatures, low pressures of H_2 and prolonged reaction times to achieve both high yields and ees. Nine- and ten-membered lactams were also synthesised, although the ees diminished with increasing ring size.

The dendrimer-supported palladium catalyst **G1**-Pd (**119**) was utilised to synthesise the *exo*-methylene compounds. Dendrimer catalysts are attractive from a sustainability perspective, as they allow the easy recovery of the catalyst and **119** can be filtered in air and re-used up to 10-fold with minimal loss in activity.



Hao et al. have also reported a series of silica-supported palladium catalysts[121–123] and have recently disclosed[124] an easy to synthesise catalyst MCM-41-2P-Pd(0) **120**, based on the mesoporous material MCM-41, which has a regular pore size of 5 nm and a surface area of $>700\ m^2\ g^{-1}$.[125] The large pore size facilitates the penetration of organic molecules.

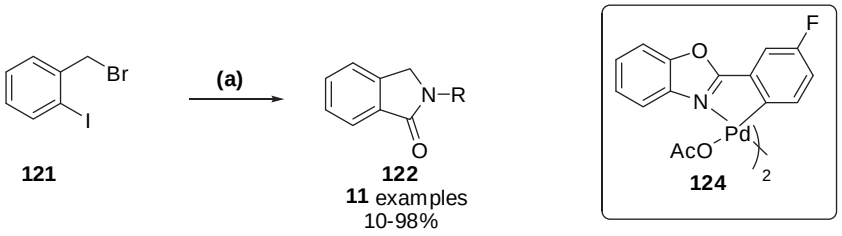


The bidentate catalyst proved to be efficient in both amino- and alkoxycarbonylation with iodides (84–96% yield). Aryl bromides require higher temperatures (130 vs 100 °C), with electron-poor aryl bromides being the most active. Alkoxycarbonylation of electron-poor bromides only occurred in the presence of a catalytic amount of PPh_3. Aryl chlorides were unreactive with this protocol. The catalyst could be recovered by filtration and re-used without loss of activity after five consecutive runs. No leaching of the Pd from the support was noted.

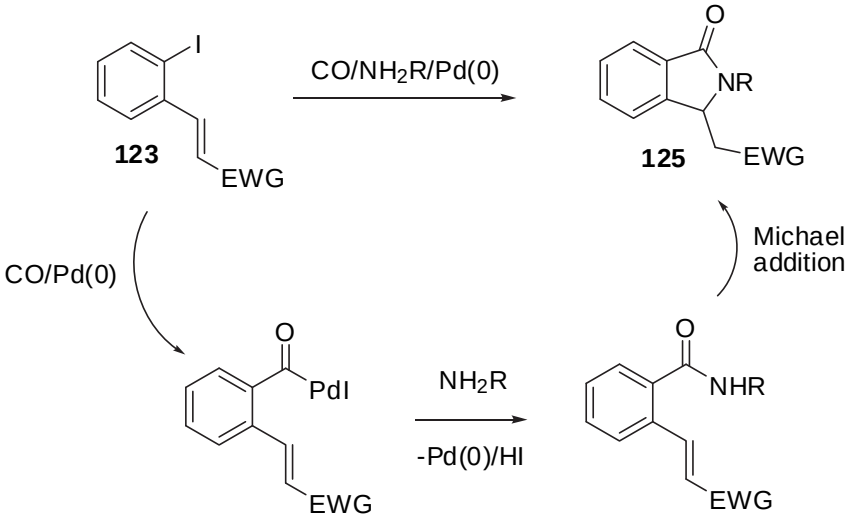
Isoindolones and their derivatives are found in many pharmaceutically active and natural products and, as such, have been the subject of recent interest.[126–131] The Grigg group has described two novel palladium-catalysed cascade processes for the synthesis of *N*-substituted isoindolones and from easily accessible starting materials, such as **121** (Scheme 37), where R (in **122**) is an aliphatic or aromatic primary amine and **123** (Scheme 38). Reactions were run in the absence of phosphine ligands, with palladacycle **124** utilised as a source of Pd nanoparticles.

Substituted isoindolones of general structure **125** were synthesized from **123** using a palladium-catalysed, three-component carbonylation/amination/Michael addition cascade sequence in 43–99% yield (Scheme 38).

The basic cascade was subsequently extended by the use of mono- and di-substituted hydrazines,[127] which can give two potential products: either the *N*-aminoisoindolones **126** or the



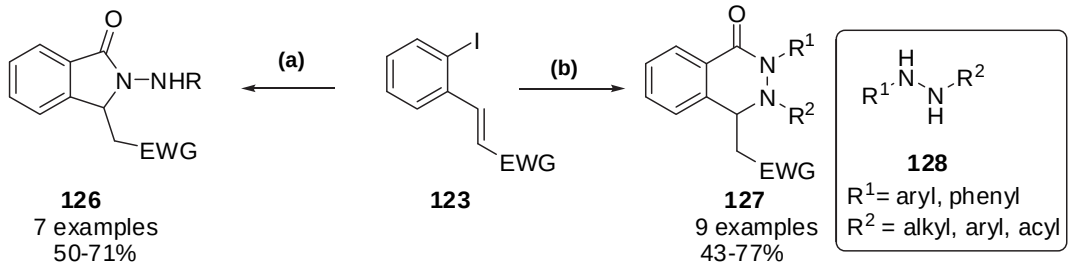
Scheme 37. Reagents and conditions: (a) **121** (1 mol equiv), aromatic or aliphatic primary amine (1–1.2 mol equiv), **124** (1 mol %) and K_2CO_3 (2 mol equiv), CO (1 atm), dry DMF, rt or 80 °C, 12–48 h.



Scheme 38. Proposed sequence of carbonylation/amination/Michael addition cascade. EWG=electron-withdrawing group e.g., ester, CN or COR.

phthalazones **127**, via 5-*exo*-*trig* or 6-*exo*-*trig* ring closure, respectively. Mono-substituted hydrazines, containing aryl or electronegative substituents, afforded the *N*-aminoisoindolones **126** (Scheme 39).

All processes were highly stereoselective, and gave the *Z*-isomer as the main product (up to 95:5 *Z*/*E* was observed). When X=Cl, the reaction stopped at the first step and afforded only the Sonogashira coupling product. No carbonylative Sonogashira products were



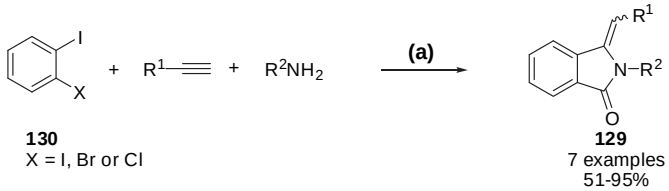
Scheme 39. Reagents and conditions: (a) aryl iodide (1.0 mmol), monosubstituted hydrazine (1.2 mmol), $Pd(OAc)_2$ (0.03–0.05 mmol), PPh_3 (0.06–0.10 mmol), CO (1 atm), Cs_2CO_3 (2.0 mmol), PhMe (20 ml), 90 °C, 3–18 h; (b) aryl iodide (0.5 mmol), **128** (0.7 mmol), palladacycle **124** (0.025 mmol), CO (1 atm), Cs_2CO_3 (1.0 mmol), DMF (5 ml).

Switching to a more sterically hindered hydrazine (R=isobutyl), gave a 1:1 mixture of the *N*-aminoisoindolone **126** and phthalazone **127** (R^1=isobutyl; R^2=H).

Using 1,2-disubstituted hydrazines (of general structure **128**) in the cascade allowed access to the phthalazones **127** (Scheme 39). The regioselectivity of the process was established by X-ray crystallography and rationalised by an initial attack of the deprotonated aniline subunit on the acylpalladium species.

Employing a 1,2-disubstituted hydrazine ($PhNHNHCOCF_3$) containing a trifluroacetamide moiety allowed the regioselective synthesis of a mono-*N*-substituted phthalazone (R^1=Ph, R^2=H, Scheme 39), as this moiety undergoes in situ hydrolysis.

Alper et al.[126] have recently reported a novel route to 3-methyleneisoindolin-1-ones (**129**) via a one-pot 4-component Sonogashira-carbonylation–hydroamination of 1-bromo-2-iodobenzene **130** (X=Br) in ionic liquids (Scheme 40).



Scheme 40. Reagents and conditions: (a) aryl dihalide (1.0 mmol), alkyne (1.2 mmol), amine (3.0 mmol), $PdCl_2(PPh_3)_2$/CuI (0.05 mmol), DBU (2 mmol), CO (1 atm), PSIL (2.0 g), 36 h, 110 °C.

observed. The results also reveal that bromide anion-containing media are the most effective. Ionic liquids containing [NTf_2^-] and [PF_6^-] gave no product.[126]

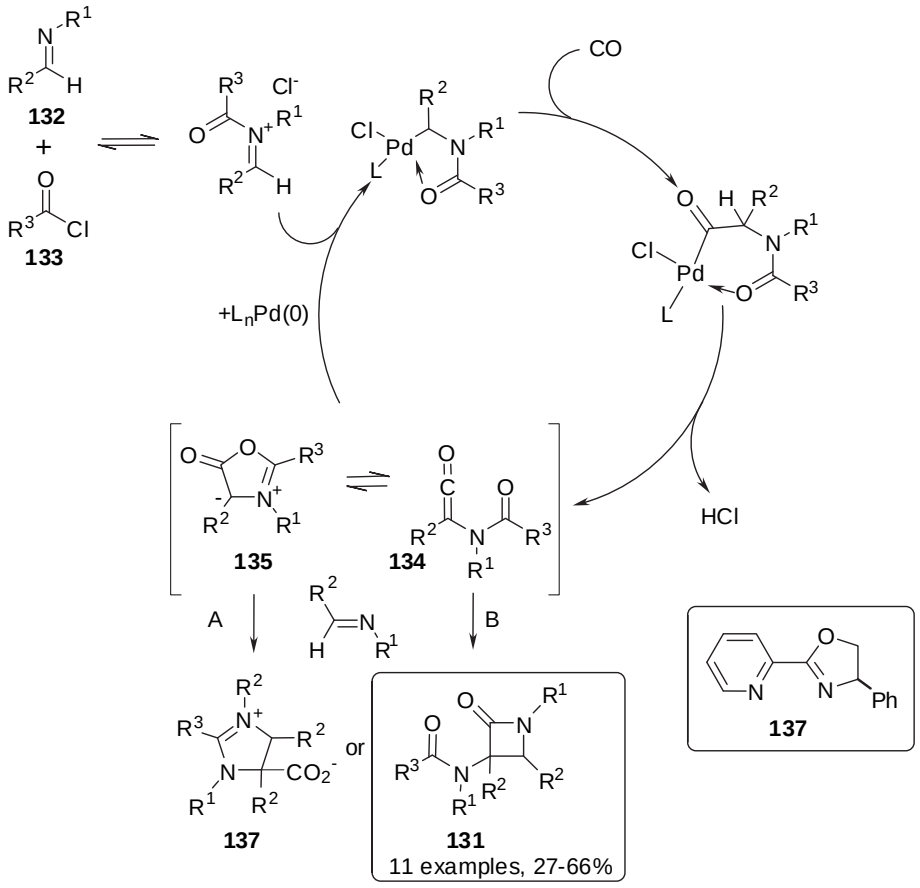
In 2006, Arndsten et al.[81] have reported a one-pot synthesis of β-lactams **131** from imines **132**, acyl chlorides **133** and CO (1 atm) under mild conditions (Scheme 41). Importantly, aromatic ether, thioether and heteroaromatic functionalities do not inhibit the reaction. Both aryl and alkyl acyl chlorides can be employed, but the yields are generally modest.

The reaction proceeds via the ketene **134**, with which the münchnone **135** is known to be in equilibrium.[132] If the HCl produced in the reaction is not eliminated, imidazoline **137** is generated via a 1,3-dipolar cycloaddition (path A).

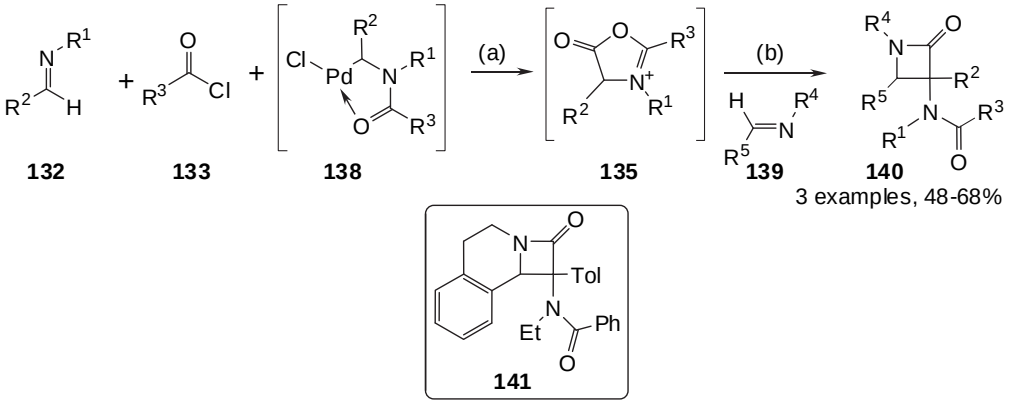
The use of a suitable base allows the reaction to proceed to the desired β-lactam (path B) via a formal [2+2] cycloaddition. Low yields were obtained in the absence of the ligand **137**. The lower the Pd concentration, the higher the yield, as Pd degrades the münchnone.

The generation of β-lactams incorporating two different imines has been accomplished. The münchnone **135** was generated from **138**, **132** catalyst **133** and CO (4 atm) in the absence of an imine trap (Scheme 42)[79] reacts with a second of imine **139** to give the β-lactam product **140**. The tricyclic product **141** was similarly synthesised in 48% yield.

The drawback with this reaction is that the appropriately functionalised catalyst (e.g., R^1 on the imine must be the same as R^1 in the catalyst) needs to be prepared each time; otherwise, the desired product will be contaminated with small amounts of other β-lactams.



Scheme 41. Reagents and conditions: **132** (1.2 mmol), **133** (0.54 mmol), $Pd_2(dba)_3.CHCl_3$ (1.4 mol %), **146** (2.7 mol %), CO (1 atm), EtN^iPr_2 (0.54 mmol), 1:1 v/v MeCN/THF, 96 h, 55 °C.

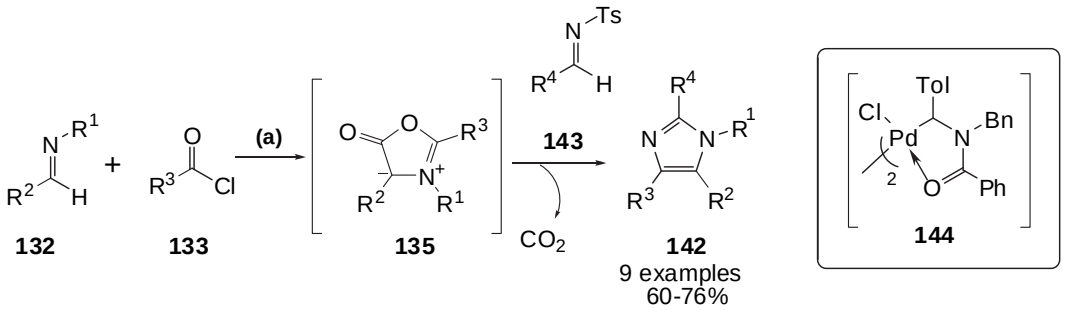


Scheme 42. Reagents and conditions: (a) **132** (0.54 mmol), **133** (0.76 mmol), Bu_4NBr (0.54 mmol), **138** (5 mol %), CO (4 atm), NEt^iPr_2 (0.84 mmol), 55 °C, 24–30 h; (b) **139** (0.54 mmol), 55 °C, 24 h.

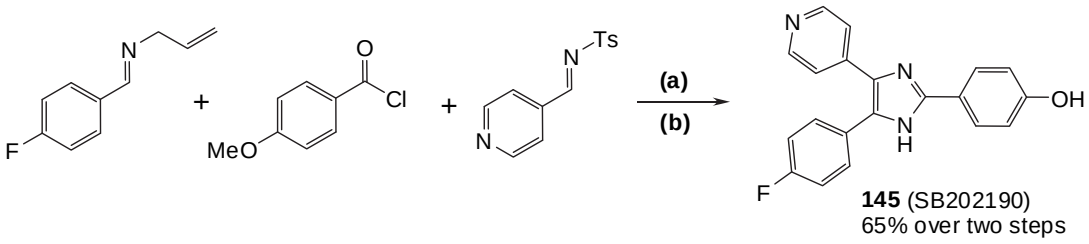
Imidazoles **142** can be generated by a one-pot, 1,3-dipolar cycloaddition[80] via the münchone **135** (path A, Scheme 41), formed from the imine **132** and acyl chloride **133**. The known equilibrium of ketene and münchone allows the selection of the *N*-tosyl imine **143** for cycloaddition[133] with münchones to furnish the desired imidazoles in 60–76% yield with concomitant loss of CO_2. The lower nucleophilicity of **143** retards its ability to react with the acyl chloride **133**, thus preventing mixtures of imidazoles from being formed (Scheme 43) and LiCl prevents the iminium chloride from undergoing degradation. Addition of an electron-rich phosphine ($P(o\text{-Tol})_3$) increased the yield and rate of catalysis. An alternative Pd source to **144** is Pd_2dba_3.

The reaction tolerates both *N*-alkyl and *N*-aryl imines, as well as non-enolizable alkyl imines, whilst aryl, heteroaryl and alkyl acid chlorides can be employed. *N*-Tosyl imines tolerated an even greater diversity, including aryl, alkyl, heterocyclic and α,β-unsaturated substituents, whilst enolizable imines can replace *N*-tosyl imine.

This approach has led to the synthesis of **145** (Scheme 44), a potent p38 MAP kinase inhibitor and a lead in the design of new *anti*-inflammatory agents.[134] The original route is a multi-step synthesis: the one-pot route offers the opportunity for much greater substrate variety, thus aiding molecular diversity.

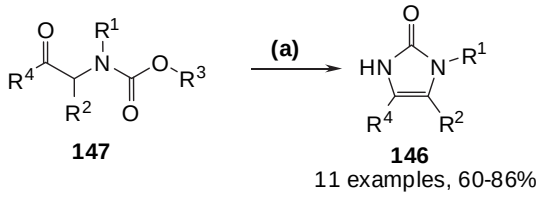


Scheme 43. Reagents and conditions: (a) **133** (0.95 mmol), **132** (0.68 mmol), **143** (0.82 mmol), **144** (5 mol %), P(*o*-Tol)$_3$ (15 mol %), CO (4 atm), NEt^{i}Pr$_2$ (3 equiv), LiCl (3 equiv), 45 °C, 18 h.



Scheme 44. Reagents and conditions: (a) as for Scheme 43; (b) PhSiH$_3$, [Pd(PPh$_3$)$_4$] (5 mol %), HBr.

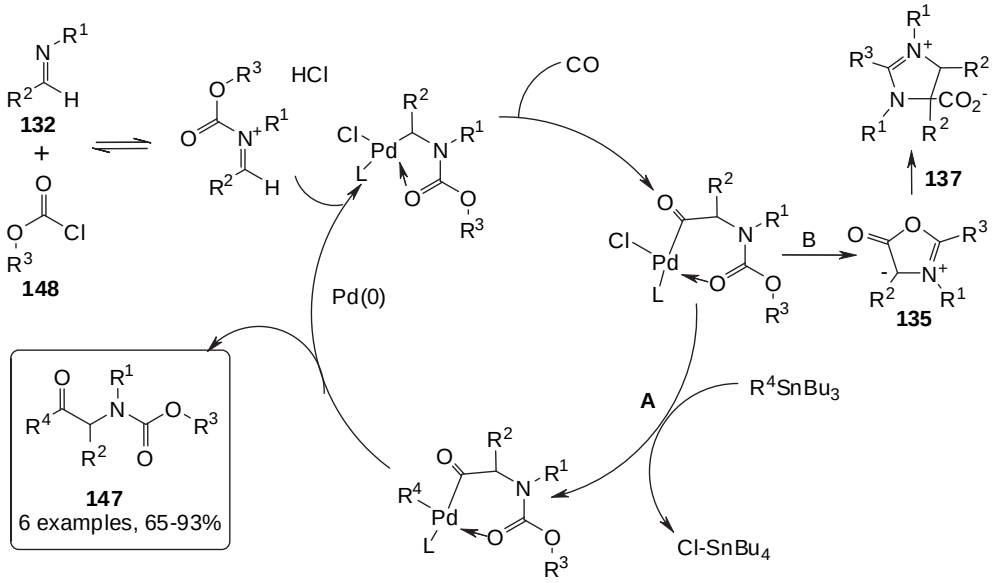
By switching to the use of chloroformates[135] in these one-pot reactions, it is possible to form imidazolones **146**, via the ketocarbamates **147**, in good yield (Scheme 45). Imidazolones are found in a range of biologically active compounds, including *anti*-inflammatory,[136] anticancer,[137] and cardioactive agents.[138]



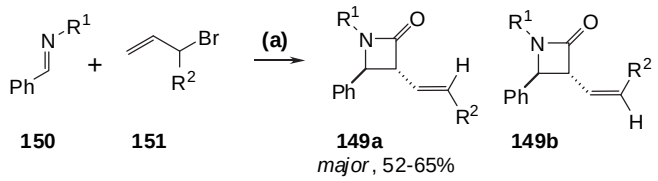
Scheme 45. Reagents and conditions: (a) **147**, acetic acid (50 ml/mmol), NH$_4$OAc (15 equiv), reflux, 16 h.

The proposed mechanism for ketocarbamate formation is shown in Scheme 46 and is similar to that shown in Scheme 41 (vide supra), the crucial difference being that the münchnone **135** is prevented from forming and thus undergoing cycloaddition to form **137** by employing chloroformates. The switch to the chloroformate **148** lowers the electrophilicity of the carbonyl coordinated to Pd, allowing the transmetallation step to proceed (path A).

The formal [2+2] ketene-imine cycloaddition has also been exploited in the synthesis of alkenyl-β-lactams **149a**,**b**.[139,140] The reaction employed simple imines **150**, allyl bromides **151** and CO (400 psi). The alkenyl-β-lactams were formed with trans diastereoselectivity in both the β-lactam ring and the vinylic moiety (Scheme 47).



Scheme 46. Reagents and conditions: **132** (0.48 mmol), **148** (1.90 mmol), organotin reagent (0.52 mmol), Pd$_2$dba$_3$.CHCl$_3$ (5 mol %), CO (1 atm), Bu$_4$NBr (0.57 mmol), MeCN/CH$_2$Cl$_2$ (2:1v/v; 15 ml), rt, 24–48 h.



Scheme 47. Reagents and conditions: (a) **150** (1 equiv), **151** (1.5 equiv), $Pd(OAc)_2$ (2 mol %), PPh_3 (8 mol %), CO (400 psi), Et_3N (2 equiv), THF, 100 °C, 18 h.

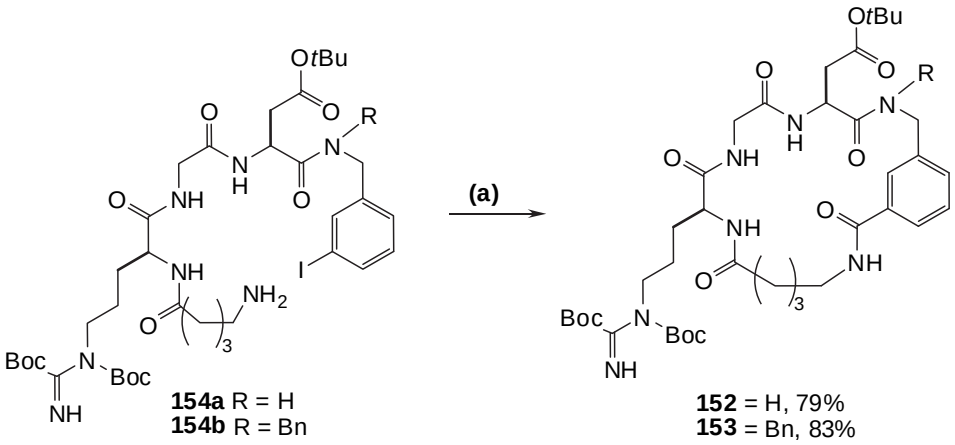
Aminocarbonylation reactions have also been utilised in the formation of macrocyclic RGD peptides **152** and **153** (Scheme 48).[141] Cyclic RGD models have been studied as selective integrin receptor antagonists,[142,143] starting from acyclic precursors **154a**,**b**. Peptidomimetics, especially macrocyclic derivatives, are important in drug discovery allowing access to potent drug candidates by precise tuning of their conformation.[144]

The use of molecular sieves prevents loss of the Boc groups, whilst the $P(^tBu)_3$ ligand electronically and sterically accelerates both the oxidative addition and the final reductive elimination step and delivers the best yield. The *N*-benzyl group (**154b**) can be effectively utilised as a solid-phase linker, permitting the synthesis of various cyclic RGD combinatorial libraries.

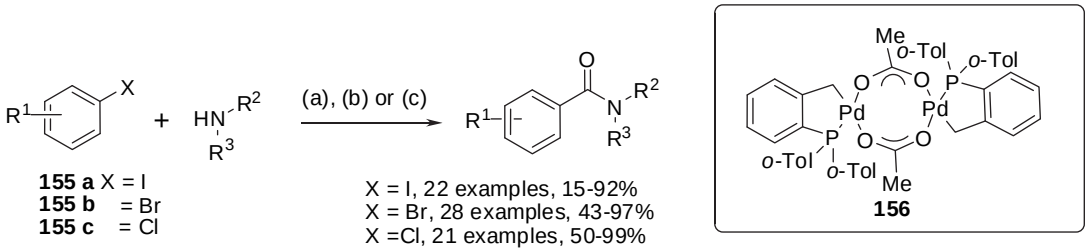
3.4.3. Alternative CO sources. The main disadvantage of traditional carbonylation chemistry is the handling of the toxic and flammable CO gas, which also limits parallel synthesis applications.

Larhed et al.[145] utilised $Mo(CO)_6$ as an alternative CO source to furnish aromatic amides from primary and secondary amines under microwave irradiation (mwi) in water from aryl iodides **155a**, bromides **155b** and chlorides **155c** in air (Scheme 49). With **155b** and **155c**, Pd-nanoparticle precursor **156** was employed. In addition, $^tBu_3P$ was required with **155c** to overcome the inherent reaction sluggishness. The process tolerates electronically and sterically diverse coupling partners. Only trace amounts of the corresponding carboxylic acids were detected.

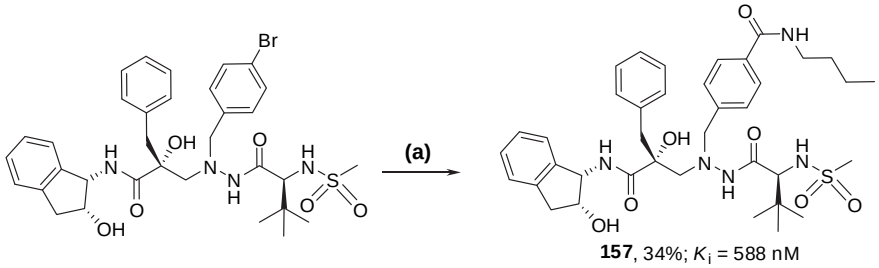
This aqueous carbonylation procedure was utilised in the preparation of a novel HIV-1 protease inhibitor **157** (Scheme 50).



Scheme 48. Reagents and conditions: (a) **154** (1.0 mmol), $[PdP(^tBu_3)_2]$ (10 mol %), 4 Å mol sieves, CO (10 atm) THF (300 ml/mmol), 50 °C, 12 h.



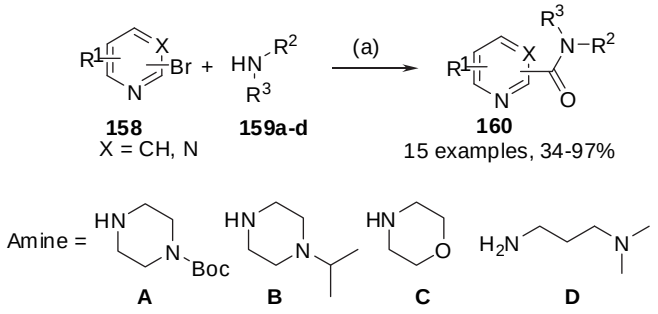
Scheme 49. Reagents and conditions: (a), **155a** (1.0–2.0 mmol), amine (1.0–5.0 equiv), $Mo(CO)_6$ (0.50 equiv), Na_2CO_3 (3.0 equiv), $Pd(OAc)_2$ (5 mol %), H_2O (2.0 ml), mwi, 110 °C, 10 min; (b) **155b** (0.8–1.0 mmol), amine (3.0–5.0 equiv), **156** (5 mol %), $Mo(CO)_6$ (0.50–0.75 equiv), Na_2CO_3 (3.0 equiv), H_2O (2.0 ml), mwi, 170–180 °C, 10–15 min; (c) **155c** (1.0–5.0 mmol), amine (1.0–5.0 equiv), **156** (5 mol %), $[(^tBu)_3PH]BF_4$ (10 mol %), $Mo(CO)_6$ (0.50 equiv), Na_2CO_3 (3.0 equiv), H_2O (2.0 ml), mwi, 170 °C, 10–30 min.



Scheme 50. Synthesis of HIV-1 protease inhibitor. Reagents and conditions: (a) Aryl bromide (0.131 mmol), ^{n}butylamine (1.31 mmol), $Mo(CO)_6$ (0.328 mmol), **156** (5 mol %), $[(^tBu)_3PH]BF_4$ (10 mol %), Na_2CO_3 (0.786 mmol), water (2.0 ml), mwi, 140 °C, 20 min.

THF can be utilised as a solvent in the microwave carbonylation of aryl chlorides.[146]

The utility of the $Mo(CO)_6$/palladacycle/$[(^tBu)_3PH]BF_4$ system has been extended to include the microwave carbonylation of five- and six-membered heterocycles **158** with a variety of amines (**159a–d**) to give 34–97% yield of the desired amides **160** (Scheme 51).[147] Amine and methoxy substitution on the heterocycle are tolerated. 2-Bromothiazole and 5-bromo-1-methyl-1*H*-imidazole gave 52 and 61% yield, respectively, of the desired amide (from amines **159b** and **159c**, respectively), whilst 4-bromoindole furnished the amide in 34% yield. However, with 2-bromopyrimidine, only the Buchwald-type product was observed.



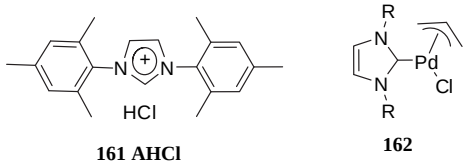
Scheme 51. Reagents and conditions: (a) **158** (2.01 mmol), **159** (2.80 mmol), **156** (1.2 mol %), $[(^tBu)_4PH]BF_4$ (2.9 mol %), $Mo(CO)_6$ (0.96 mmol), DBU (1.34 mmol), THF (4 ml), 125 °C (mwi), 6 min.

3.5. Carbonylative cross-coupling reactions

3.5.1. Carbonylative Suzuki reactions. Boronic acids and their esters are generally non-toxic and air- and moisture-stable. Consequently, the palladium-catalysed Suzuki cross-coupling reaction has emerged as a powerful synthetic tool in the past 20 years.

In 1993, Suzuki et al.[148] introduced the carbonylation cascade version of the Suzuki reaction, allowing the one-pot formation of biaryl ketones from aryl iodides, arylboronic acids and carbon monoxide. Electron-withdrawing groups on the aryl halide accelerate the rate and selectivity for the biaryl ketone versus the biaryl. However, this ketone selectivity dropped further when using bromides.[148] This was overcome, to some extent, by employing dppf as the phosphine ligand and up to three equivalents of NaI or KI,[149] suggesting that a Finkelstein-type process was operating.

3.5.1.1. Carbene ligands in carbonylative Suzuki reactions. Pyridine and its derivatives form an important component of many pharmaceutically active compounds and the nitrogen atom activates halogen in the 2-, 4- and 6-positions, allowing chlorides to be used. Castanet et al.[150] investigated the carbonylative Suzuki cross coupling of a variety of mono-iodopyridines and -bromopyridines with $PhB(OH)_2$ and CO (5–50 bar) using various palladium-phosphine systems. The best system ($[Pd(Cl)_2(PCy_3)_2]$; 3 mol %) gave ketones in high yield (80–95%). The scope and selectivity were later extended[151] by employing the *N*-heterocyclic carbene ligand **AHCl**, (**161**; 0.12 mol %) and $Pd(OAc)_2$ (0.06 mol %).

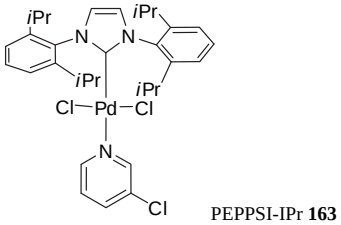


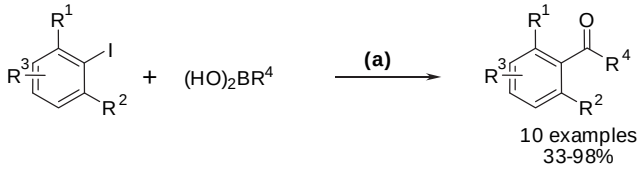
R = (2,6-diisopropyl)phenyl

However, the same catalytic system utilised with the economically more attractive but less reactive, chloropyridines and chloroquinolines, suffered from incomplete conversion, required a high temperature (140 °C) and was accompanied by ligand degradation at this temperature, resulting in the formation of trimethylaniline in the reaction mixture.

Switching to the pre-formed Pd complex **162**[151] allowed the successful use of mono- and di-chloropyridines in the cascade at a lower reaction temperature (120 vs 140 °C), slower catalyst degradation and complete conversion of the starting material, representing by far the best system to date. Carbonylative Suzuki coupling of chloropyridines appears to be much more difficult than simple cross coupling without CO.

ortho-Disubstituted aryl ketones are common scaffolds in many natural products and biologically active small molecules. The employment of the 3-component carbonylative-Suzuki reaction could overcome the inherent limitations encountered with the more traditional methodologies, such as Friedel–Craft reactions and Fries rearrangements, in the construction of these ketones. Until recently, only one carbonylative synthesis of an *ortho*-disubstituted ketone had been reported[149] and the conditions were found to be non-general.[152] O'Keefe et al. have recently[152] disclosed a general process for *ortho*-disubstituted aryl ketones employing a commercially available PEPPSI–IPr catalyst **163**, under a balloon pressure (1 atm) of CO (Scheme 52).

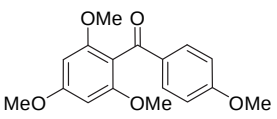


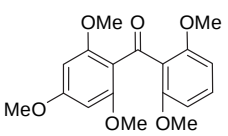


Scheme 52. Reagents and conditions: (a) aryl iodide (1.0 mmol), boronic acid (3.0 mmol), **163** (3 mol %), Cs_2CO_3 (3.0 mmol), CO (1 atm), chlorobenzene (5 ml), 80 °C, 24 h.

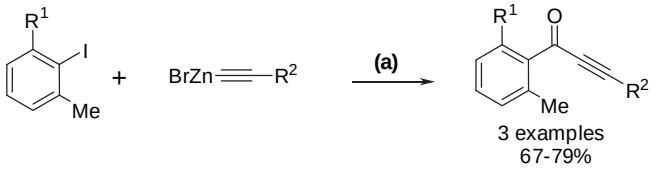
It was found that mono- and bidentate phosphine ligands led to either mixtures of biaryl and biaryl ketone products, or the exclusive formation of the biaryl product, even at elevated CO pressure (60 bar). In contrast, biaryl ketone formation was favoured when NHC ligands were employed. The best yields were obtained with PEPPSI–IPr at atmospheric CO pressure, lower temperatures (80 vs 140 °C) and surprisingly, employing chlorobenzene as the solvent, even though PEPPSI–IPr has been shown to catalyse the Suzuki coupling of aryl chlorides.[153]

The reaction tolerates both electron-rich and electron-poor boronic acids (the latter requiring dioxane as solvent to give high ketone yields), heterocyclic boronic acids and electron-rich/poor aryl iodides. Base-sensitive aryl iodides[154] benefited from employing K_2CO_3 as the base. It was also possible to synthesise the hindered ketones **164** and **165** in modest yields, despite the fact that electron-rich aryl halides disfavour oxidative addition.





The synthetic utility of the PEPPSI–IPr system was further extended to include the Negishi carbonylative cross coupling of alkynylzincs and aryl iodides (Scheme 53). Normally, the more reactive organozinc reagents (cf. organoboron derivatives) predominantly form the directly coupled product.[155]



Scheme 53. Reagents and conditions: (a) aryl iodide (1.0 mmol), alkynylzinc (2.0 mmol), LiBr (3.0 mmol) (if R^1=OMe, PPh_3 (3 mol %) also employed), PEPPSI–IPr (3 mol %), CO (1 atm), THF/NMP (5 ml), 60–170 °C, 24 h.

When R^1=Me (Scheme 53), the reaction tolerated electron-rich and -neutral alkynylzincs; the more electron-rich 2-iodo-3-methylanisole (R^1=OMe) required the addition of PPh_3,[156] as well as an elevated temperature (170 °C), although no catalyst degradation was observed.

3.5.1.2. Phosphine ligands in carbonylative Suzuki reactions. In 2008,[157] Beller et al. reported that their air-stable $Pd(OAc)_2$/di-1-adamantyl-*n*-butylphosphine (cata*CX*ium A®; **166**) system is highly active in the Suzuki-carbonylation cascade and represents the most general catalyst system reported to date. It is noteworthy that this catalyst system is selective for Br versus Cl, leaving C–Cl bonds intact during the reaction. A broad range of aryl/heteroaryl bromides and arylboronic acids were converted into the corresponding diaryl ketones at a low (0.5 mol %) catalyst loading (Scheme 54).

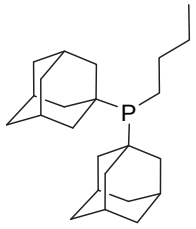
Thiophenes, both as the boronic acids and the bromides, have been successfully used, along with 3-bromobenzo[*b*]thiophene. The reaction offers efficient access to various biologically active compounds as shown by the two-step preparation of Suprofen **167** (Scheme 55),[158] which could, on paper, suffer from competing Heck, carbonylative-Heck and Suzuki reactions.

Remarkable features of this catalyst are the high selectivity and improved yields.

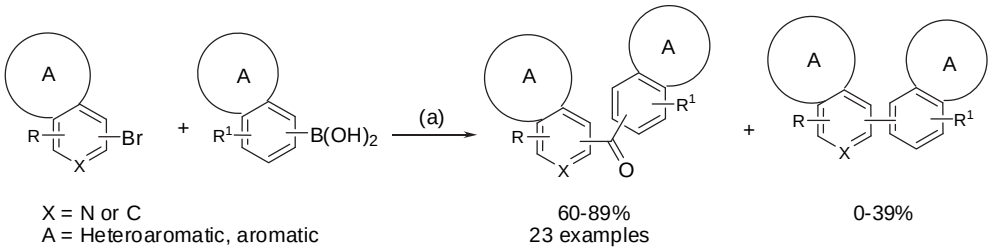
Recently, Bartali et al.[159] have reported a thorough study of the carbonylative Suzuki reaction of enol-triflates **168** for the synthesis of unsymmetrical dienones **169**. Coupling of structurally different enol triflates derived from lactams, lactones and thiolactones with various alkenylboronic acids at room temperature was achieved, utilising 1 atm of CO with 1–5 mol % palladium catalyst, to afford the carbonylated products **169** in 31–77% yield (Scheme 56).

With seven-membered lactams, with all lactones and with thiolactams, dppf (6.25 mol %) were used as the phosphine ligand to suppress direct alkylated product formation **170**. This methodology allows the rapid preparation of substrates useful in conjugate additions and in Nazarov reactions.

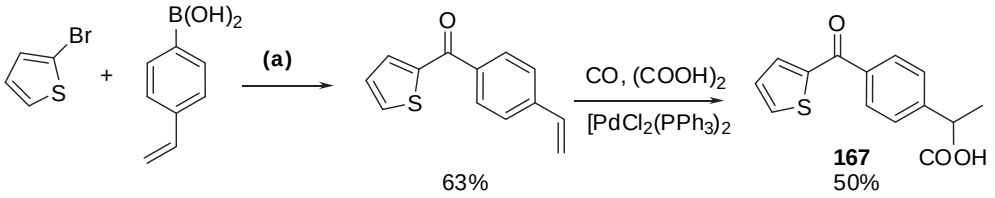
The ring heteroatom influenced the electron density (*) at C-2 (Scheme 56), which, in turn, affected the ketone yield. The highest ratio of A/B (A/B=7:1) was obtained with five- and six-membered *N*-heterocyclic vinyl triflates. The smaller ratios for X=O (A/B=1.6:1) and X=S (A/B=1.3:1) could be explained by the heteroatom effect on the reaction cycle. In the case of X=O, a low C-2



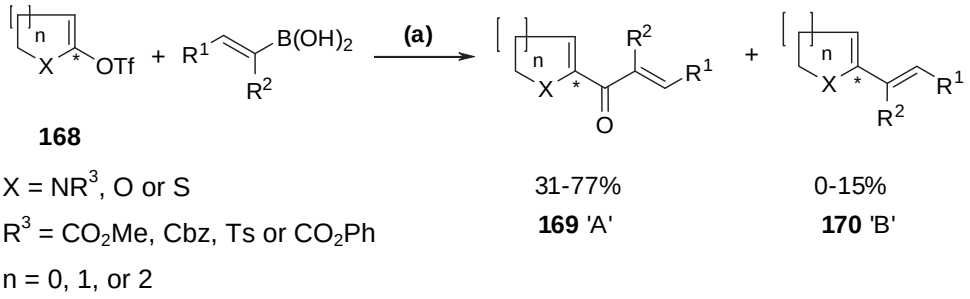
166 cata*CX*ium A®



Scheme 54. Reagents and conditions: (a) aryl bromide (2.0 mmol), arylboronic acid (3.0 mmol), $Pd(OAc)_2$ (0.5 mol %), **166** (1.5 mol %), TMEDA (1.0 equiv), CO (2.5–5.0 bar), toluene (2 ml), 80–120 °C, 24 h; A=five- or six-membered ring.



Scheme 55. Reagents and conditions: (a) 2-bromothiophene (2.0 mmol), 4-vinylphenylboronic acid (3.0 mmol), $Pd(OAc)_2$ (0.5 mol %), **166** (1.5 mol %), TMEDA (1 equiv), CO (2.5 bar), 80 °C.

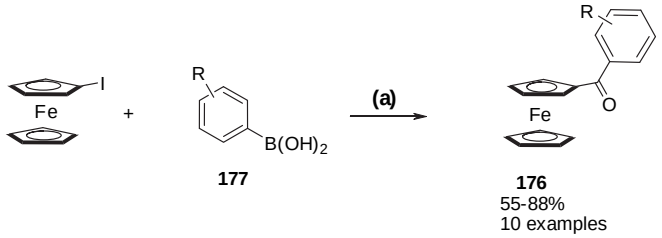


Scheme 56. Reagents and conditions: (a) triflate (0.5–1.5 mmol), boronic acid (2.0 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), CsF (3.0 mmol), THF, rt, 3–4 h.

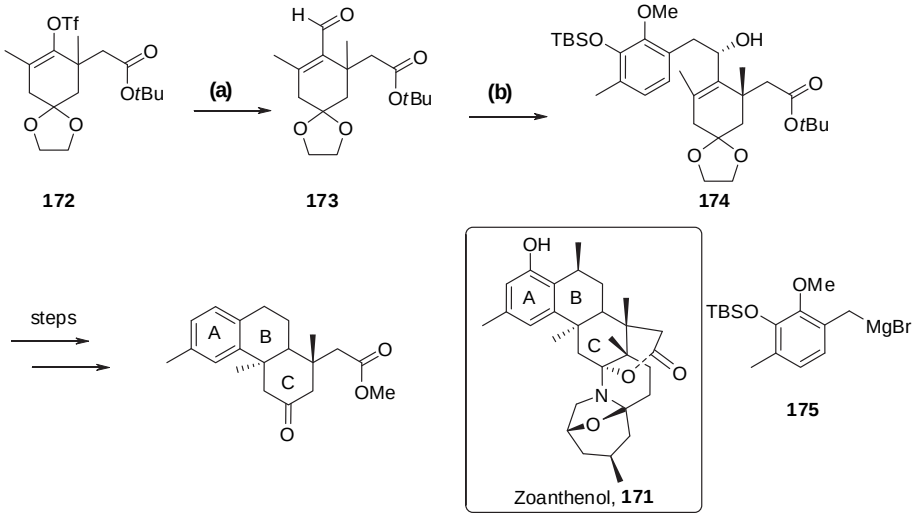
electron density could retard the co-ordination and/or migration of CO to form the acylpalladium complex, while with X=S, a high C-2 electron density could instead slow down the coordination-insertion of CO.

The formation of carbonyl compounds from vinyl triflates has been used in the synthesis of the natural product Zoanthenol **171**, a member of the Zoanthus family of alkaloids.[8] Stoltz et al. utilised the reductive carbonylation of vinyl triflate **172** at 1 bar CO pressure and 1.76 equivalents of triethylsilane (TES/H) at 35 °C to furnish **173**, this being the first reported carbonylative reduction of a hindered vinyl triflate to the enal oxidation state. This could then be taken on to form **174** via a chemoselective Grignard reaction with **175** at the aldehyde with good stereoselectivity (dr>15:1) via chelation control (Scheme 57). This is a key intermediate in the synthesis of the A/B/C-ring system of Zoanthenol.

Carbonylative-Suzuki cascades have been utilised to prepare a range of mono-substituted ferrocenes **176**, in an efficient and convenient protocol developed by Yang et al.[161] The reaction tolerates a variety of substituents on the aryl ring **177**, with-electron-withdrawing and sterically hindered boronic acids giving

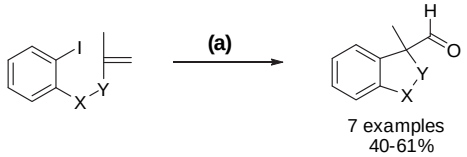


Scheme 59. Reagents and conditions: (a) iodoferrocene (0.5 mmol), **177** (0.75 mmol), $Pd(PPh_3)_4$ (3 mol %), Cs_2CO_3 (1 ml of 2 M soln), CO (1 atm), toluene (3 ml), 110 °C, 5–6 h.



Scheme 57. Reagents and conditions: (a) **172** (5.27 mmol), LiCl (14.2 mmol), $Pd(OAc)_2$ (0.70 mmol), 1,4-bis(dicylcohexylposphino)butane (0.70 mmol), TES/H (9.86 mmol, over 10 h), Et_3N (18.6 mmol), CO (1 atm), DMA (24.5 ml), 35 °C, then $KF{\cdot}H_2O$ (2.00 g), 76%; (b) **173** (10.7 mmol), **175** (17.1 mmol), Et_2O/CH_2Cl_2 (2.7:1 v/v), 0 °C, 1 h.

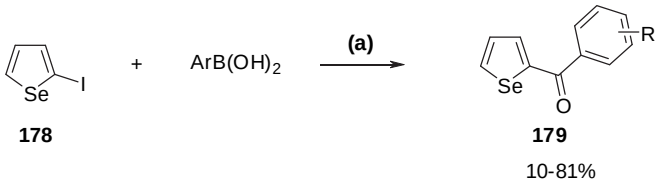
An earlier related 'reductive' cycloformylation cascade carbonylation sequence (Scheme 58) appears to be capable of significant further applications.[160]



Scheme 58. Reagents and conditions: (a) aryl iodide (1.0 equiv), $Ph_2Si(Me)H$ (2.0 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Et_4NCl (1.0 equiv), CO (1 atm), toluene, 90 °C, 7 h.

moderate-to-high yields (Scheme 59). Ferrocene derivatives are used in a variety of chemistries[162,163] and applications,[164] but their synthesis normally relies on Friedel–Crafts acylation, often leading to the formation of diacylated derivatives.[165,166]

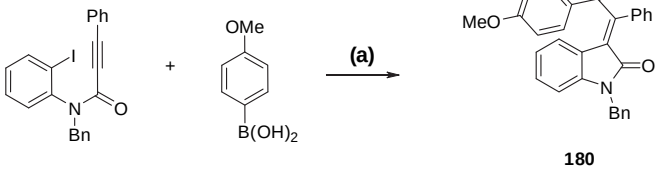
Selenium-containing compounds have attracted recent interest, due to their regio- chemo- and stereoselective reactions,[167] as well as their useful biological activity.[168] Prediger et al.[169] reported the first successful carbonylation of 2-iodoseleophene **178** with a variety of functionalised arylboronic acids, including mesitylboronic acid under mild conditions to afford **179** (Scheme 60). Strongly electron-withdrawing groups on the boronic acid gave a poor, or zero yield of the desired ketone, with only the directly coupled



Scheme 60. Reagents and conditions (a): **178** (0.5 mmol), boronic acid (0.75 mmol), $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 (2.2 mmol), CO (1 atm), H_2O (1.2 ml), toluene (3 ml), 110 °C, 12 h.

product observed, indicating that these groups retard the complexation and/or insertion of CO.

A recent application of Suzuki carbonylation involving the in situ formation of an alkenyl Pd species has been used[170] to synthesise a known biologically active oxindole. A one-pot Heck–carbonylation–Suzuki cascade under mild conditions led to the CDK inhibitor **180** in 70% yield (Scheme 61).



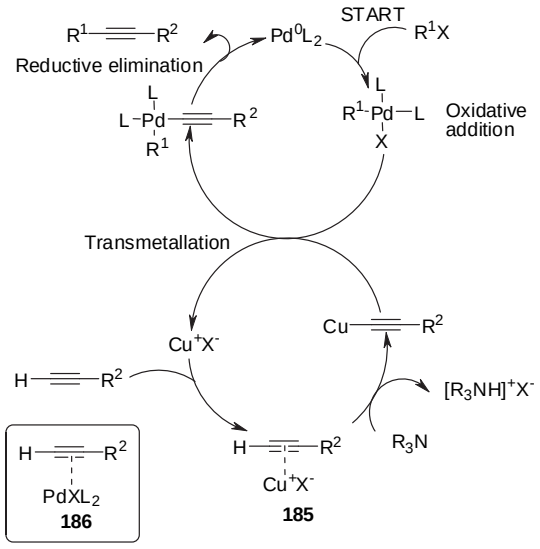
180

Scheme 61. Reagents and conditions: (a) iodoalkyne (0.10 mmol), 4-MeO–$PhB(OH)_2$ (0.11 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), CO (1 atm), CsF (3.0 mmol), THF, 60 °C, 3 h.

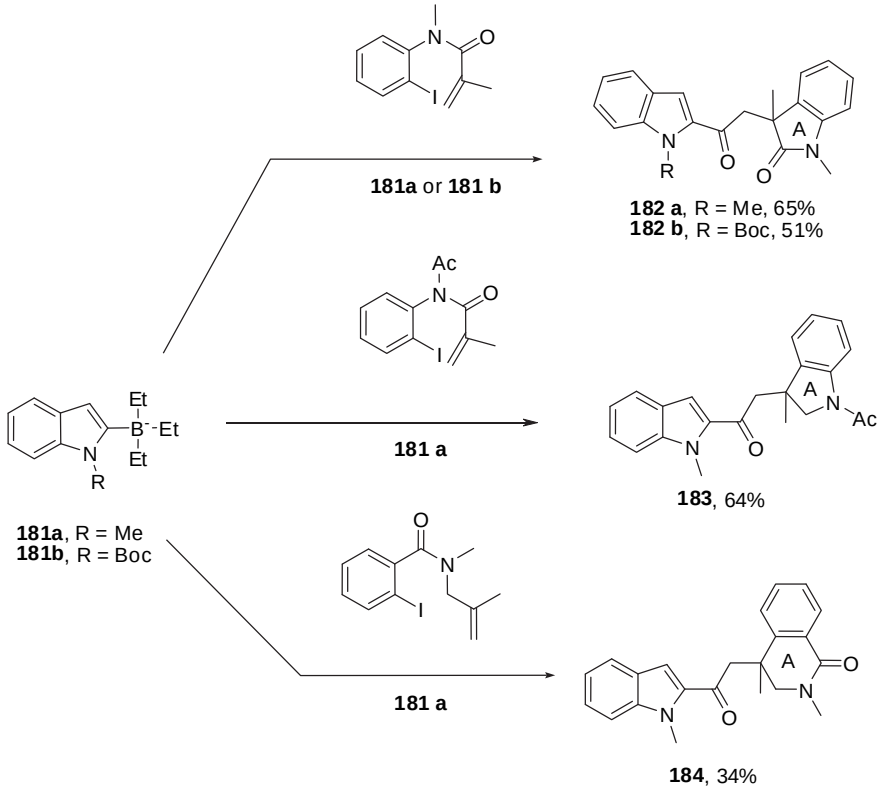
It is not necessary to use a boronic acid. Ishikura et al.[171] investigated the use of a directly formed 'ate' complex, indolyltriethylborates **181a**,**b** as an indole-transfer reagent in both Suzuki and carbonylative Suzuki reactions, the latter forming indolyl ketones (Scheme 62). These are examples of the cyclisation-anion capture methodology developed by the Grigg group at Leeds, with CO acting as a relay switch.[172–174]

$[PdCl_2(PPh_3)_2]$, without the use of base, was employed as the catalyst, but all the cascades suffered from competition with the direct Heck–Suzuki pathway, although, for **182a**,**b** and **183**, this was a minor component. Increasing ring A to six carbons (i.e., **184**) had a detrimental effect on the yield and resulted in increased by-product formation. However, these examples show that **181a** or **181b** is an efficient transfer reagent in such reactions and should provide an expedient route to various substituted indolyl ketones.

3.5.2. Carbonylative Sonogashira reactions. The non-carbonylative Sonogashira cross coupling involves the palladium-catalysed coupling of terminal alkynes with aryl and vinyl halides to furnish enynes. Utilising a copper(I) halide (halide=I or Br) co-catalyst allows the reaction to be performed at, or slightly above, room temperature. The mechanism (Scheme 63) and role of the copper(I)



Scheme 63. Mechanism of Sonogashira reaction.



Scheme 62. Reagents and conditions: **181a**/**181b** (2.0 mmol), aryl iodide (1.0 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), CO (10 atm), THF, 60 °C, overnight.

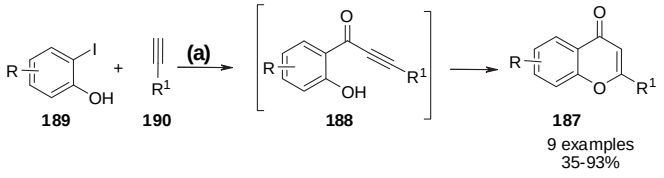
salt are still a matter of some debate[175] and, therefore, the classic 'textbook' mechanism is shown and follows the Suzuki mechanism, with Cu replacing $B(OR)_2$.

Amine bases (such as Et_2NH) are not basic enough to deprotonate the alkyne and so a π-alkyne/Cu complex **185** is proposed.[176] This complex reduces the pK_a of the alkyne proton, allowing facile deprotonation. Copper-free versions of the cross couplings are known, with a proposed η^2-($R^2C{\equiv}CH$)$PdXL_2$ complex **186**[177] taking the role of **185**. In carbonylative Sonogashira reactions, CO insertion occurs after oxidative addition and before transmetallation.

Until recently, only a few mild carbonylative methods for the formation of alkynyl ketones had been reported.[178,179] Trzeciak et al.[180] used a $PdCl_2(P(O)Ph_3)_2$ pre-catalyst and arylacetylenes, under mild conditions (1 atm CO, 80 °C) in the absence of a copper co-catalyst, to give 24–76% of the desired ketones. The reaction was also performed in ionic liquids, facilitating the recovery of the catalyst, although the results with the recovered catalyst were not reported.

Xia et al.[181] have recently shown that 5% Pd/C and triethylamine is an efficient, recyclable catalyst system for many carbonylation cascades, although high pressures of CO (0.5–2.0 MPa) are required for the reaction. Worthy of note, however, is that the catalyst is reusable up to 10-fold without loss of activity and only 5 mg of 5% Pd/C is required on a 2.5 mmol scale.

In 2005, Yang et al.[179] published the synthesis of a range of flavones **187** via the transient alkynyl ketones **188** (Scheme 64). These reactions were copper free and run in water at room temperature. It was reasoned that, in the absence of copper(I) halides, the less-reactive alkyne (compared with a more-reactive copper–alkyne 'ate' complex) would react with the electron-deficient acylpalladium(II) complex, rather than the Ar/Pd/I complex, thus allowing carbonyl insertion to occur. Substitution on both the alkyne and the *o*-iodophenol was tolerated, with the exception of electron-withdrawing groups (e.g., esters) on the aryl system **189**, which gave poor yields (35%).



Scheme 64. Reagents and conditions: (a) **189** (2.0 mmol), **190** (2.4 mmol), $PdCl_2$ (5 mol %), PPh_3 (10 mol %), Et_3N (6.0 mmol), CO (1 atm), H_2O, rt, 24 h.

Additionally reported were non-cyclative carbonylative-Sonogashira reactions carried out at room temperature in water with substitution on both **189** and **190**. The yields dropped from 95% in water to 12% in THF. Phosphine ligands were also essential to achieve a high yield, otherwise palladium black precipitation occurred rapidly.

This idea of carbonylative-Sonogashira cyclisation has been utilised by Haddad et al.[182] in their convergent synthesis of the quinolone **191** in 70% yield. This quinolone is a key subunit of the hepatitis C inhibitor, BILN 2061 (Scheme 65).

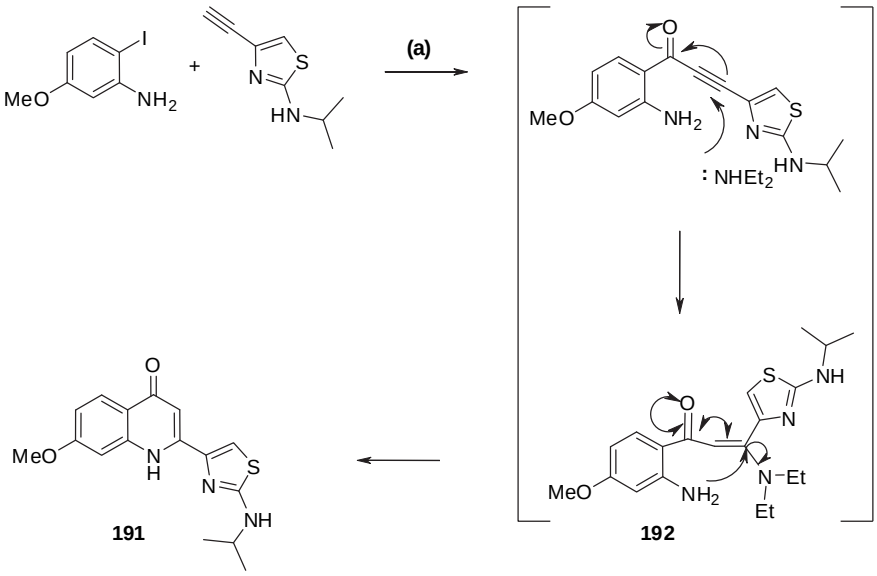
By routing the reaction through the intermediate **192**, Haddad achieved complete regiocontrol via 6-*endo*-cyclisation, with no 5-*exo* product observed. Reducing the CO pressure to 50 psi increased the reaction time to 24 h and decreased the yield to 60%.

Nicolaou's group utilised the carbonylative Sonogashira reaction in their total synthesis of Biyouyanagin A **193**,[183] a natural product found in the leaves of various Japanese plants. A key step was the conversion of the propargylic alcohol **194** into the spirolactone **195** as a 3:1 mixture of diastereoisomers in 77% yield (Scheme 66).

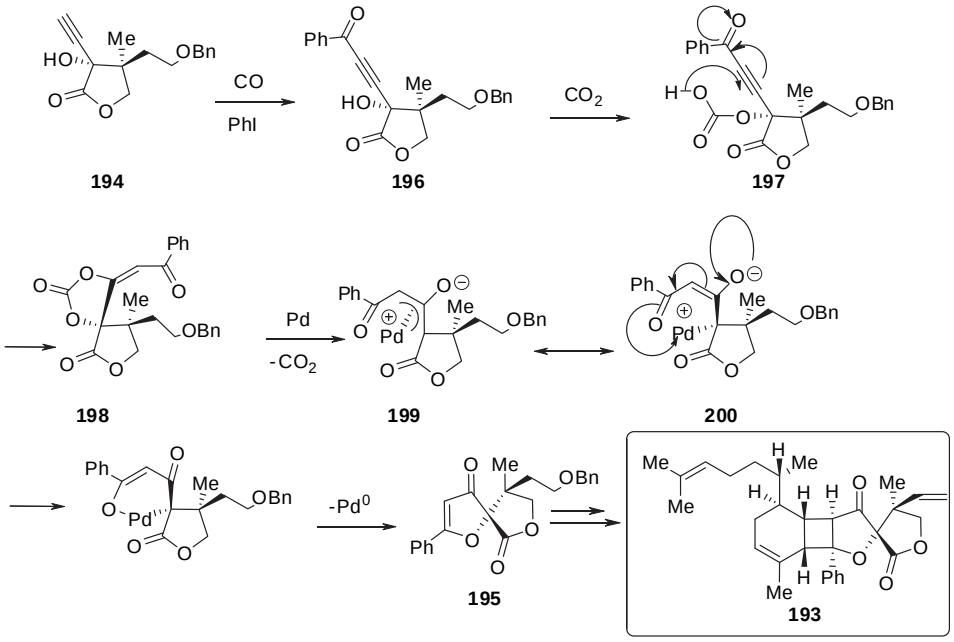
The initial carbonylative Sonogashira product **196** forms the carbonate **197**, on reaction with CO_2, which then undergoes a Michael addition to form the spirocarbonate **198**. This system now contains an allylic carbonate and Pd(0) then co-ordinates trans to the carbonate, effecting its elimination under stereoelectronic control. Loss of CO_2 gives the π-allyl species **199**, which can convert into the σ-complex **200**. This species contains an oxonium ion, which then cyclises onto the palladium. Reductive elimination affords the desired spirolactone **195**.

In 2005, Mori et al.[184] reported the synthesis of pyrazoles **201** and isoxazoles via a four-component, one-pot cascade under mild conditions (Scheme 67).

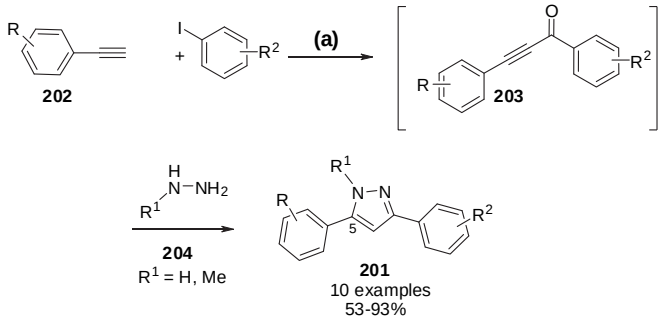
The reactions are regiospecific, with the aryl substituent in the 5-position derived from the alkyne **202**, presumably via the ynone intermediate **203**.[184] The mechanism of the reaction, however, remains unclear, as no α,β-alkynyl ketone was observed in the reaction mixture (TLC), and so, if the α,β-alkynyl ketone is formed, it must be reacting immediately with the hydrazine. α,β-Alkynyl ketones are known to react with hydrazines, but, in the absence or presence of palladium in THF/H_2O with pre-formed α,β-alkynyl ketones this reaction did not occur. The use of phenylhydrazine failed to produce any pyrazole product, presumably due to the reduced nucleophilicity of the terminal NH_2 in **204** (R^1=aryl).



Scheme 65. Reagents and conditions: (a) Iodoaniline (0.9 mmol), alkyne (1.2 mmol), $PdCl_2$(dppf) (0.014 mmol), Et_2NH (3.0 ml), CO (250 psi), 120 °C, 6 h.



Scheme 66. Reagents and conditions: (a) [$Pd(PPh_3)_4$] (5 mol %), PhI, CO (200 psi), CO_2 (200 psi), Et_3N, 100 °C, 5 h, 77%.

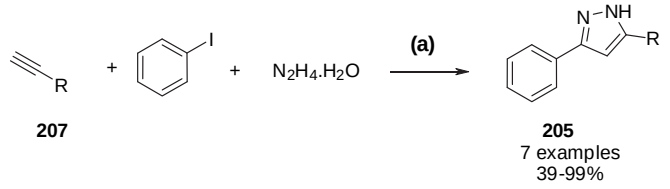


Scheme 67. Reagents and conditions: (a) **202** (0.6 mmol), aryl iodide (1.5 mmol), **204** (0.5 mmol), CO (1 atm), $PdCl_2(PPh_3)_2$ (1 mol %), 1:1 v/v THF/H_2O (6 ml) rt, 24–36 h.

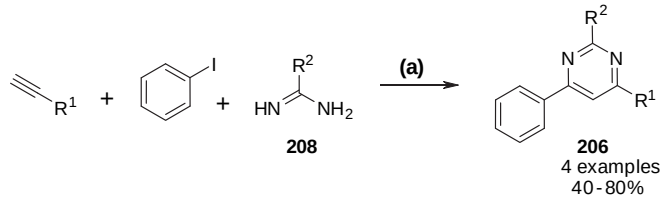
Isoxazoles were synthesised via an analogous route using hydroxylamines as nucleophiles. The solvent was switched to H_2O/DMF, as H_2O/THF gave no product. Aqueous ammonia was employed to liberate the hydroxylamines in situ from their HCl salts.

In 2007, Kondo and Iizuka[185] utilised $Pd(^tBu_3P)_2$ to furnish alkynyl ketones using $Mo(CO)_6$ or CO (1 atm) at room temperature with 100% conversion of the aryl iodide. The use of this electron-rich phosphine complex completely eliminates the formation of the direct Sonogashira product. The reaction tolerated a wide variety of substitution on the aryl iodide (NO_2, COOEt, Ac or OMe). The choice of base was crucial: Et_3N was required with $Mo(CO)_6$, but, with CO(g), this gave a sluggish conversion. However DABCO yielded excellent conversion. The combination of $Pd_2dba_3/P(^tBu)_3$ gave an equally good conversion to the product. The reaction scope was further extended to include the synthesis of *N*-methyl pyrazoles from methylhydrazine, aryl iodides, acetylenes and $Mo(CO)_6$ in a four-component, one-pot synthesis at room temperature in 58–94% yield.

Stonehouse et al.[186] recently reported using the carbonylative-Sonogashira reaction in the one-pot synthesis of pyrazoles **205** (Scheme 68) and pyrimidines **206** (Scheme 69) utilising $Mo(CO)_6$ as the CO source. The proposed carbonylated intermediate in each case was similar to **203**. Indeed, in the absence of hydrazine, the ynone was formed in 60% yield.



Scheme 68. Reagents and conditions: (a) **207** (1.5 mmol), iodobenzene (1.0 mmol), hydrazine hydrate (2.0 mmol), $Mo(CO)_6$ (1.5 mmol), $Pd(OAc)_2$ (0.05 mmol), CuI (0.02 mmol), $^tBu_3P$ (0.1 mmol) and Cs_2CO_3 (2.5 mmol), 1:1 v/v toluene/MeCN (5 ml), 80 °C, 18 h.



Scheme 69. Reagents and conditions: (a) alkyne (1.5 mmol), iodobenzene (1.0 mmol), **208** (2.0 mmol), $Mo(CO)_6$ (1.5 mmol), $Pd(OAc)_2$ (0.05 mmol), CuI (0.02 mmol), $^tBu_3P$ (0.1 mmol) and Cs_2CO_3 (2.5 mmol), 1:1 v/v toluene/MeCN (5 ml), 80 °C, 18 h.

The synthesis of *N*-unsubstituted pyrazoles **205** occurred with wide functional-group tolerance on the alkyne **207**, with the exception of R=EtO_2C, which gave no product. Heterocycles (thiophene and pyridyl) were well tolerated, with THP-protected prop-2-ynol fairing the worst (39%).

3-Pyridyl- and phenyl-hydrazines afforded the *N*-substituted pyrazoles. Methyl- and phenylhydrazine gave exclusively one isomer, whereas, with 3-pyridylhydrazine, a mixture of the regioisomers was obtained.

Amidines **208** afforded trisubstituted pyrimidines **206** in good yield, as did *N*,*N*-disubstituted guanidines (Scheme 69).

Unfortunately, the use of urea gave none of the desired product and changing the nucleophile to the parent unsubstituted guanidine provided only trace amounts of product.

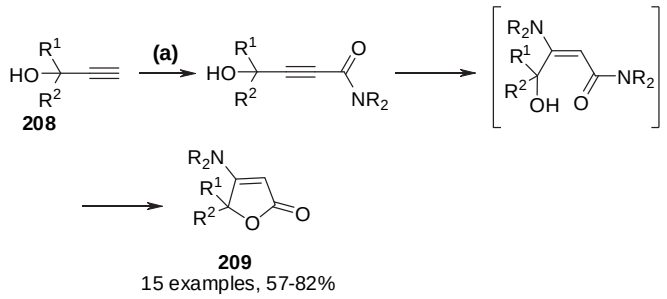
3.6. Oxidative carbonylations

The discovery of oxidative carbonylation of olefins dates back to the 1960s when Tsuji et al. first noted that the palladium-mediated chlorocarbonylation of ethene occurred with simultaneous reduction of Pd(II) to Pd(0) (Scheme 70).[187]

Scheme 70. Pd-catalysed oxidative carbonylation of ethene.

This and other early reactions used stoichiometric amounts of Pd and were later made catalytic by the introduction of a suitable oxidant, such as benzoquinone, copper (II) chloride, oxygen (or air).

3.6.1. Oxygen-containing heterocycles. 2-Ynamides can be synthesised from the corresponding terminal alkyne via aminocarbonylation in good yield. The reaction utilises iodine (generated from the oxidation of HI by O_2) as the palladium oxidant.[188] This methodology has been applied to the synthesis of 4-dialkylamino-5*H*-furan-2-ones **209**, starting from the simple α-unsubstitued 2-yn-1-ols **210**, CO, dialkylamines and O_2 (Scheme 71).[189] PdI_2 was used, with KI in a 10-fold excess with respect to PdI_2.



Scheme 71. Reagents and conditions: (a) **208** (1 equiv), alkylamine (1 equiv), PdI_2 (1 mol %), KI (10 mol %), CO/air (4:1, 20 atm), DME, 100 °C, 15–24 h.

The PdI_2/KI catalyst system has been utilised in the synthesis of various other oxygen heterocycles, such as benzofurans **211**[190] and benzo[*c*]pyrans **212**.[191] Both products utilised similar starting materials, but 6-*endo*-dig cyclisation was favoured when ketones were employed as the starting material **213** (Scheme 72).

This was later extended to include amides,[193] whereby amines were utilised in the presence of MeOH or MeCN (as solvents) to give the corresponding 2-benzofuran-2-ylacetamides in 60–87% yield. In this case, the PdI_2/KI ratio needed to be either 1:100 or 1:200 to ensure good conversion.[193]

In related work, Gabriele et al. converted the readily available 2-(1-hydroxyprop-2-ynyl)phenols **217** into coumarins **218**, based on an unprecedented palladium-catalysed dicarbonylation process.[194] The coumarins were obtained in good-to-high isolated yields (Scheme 74), again utilising the PdI_2/KI system. It was proposed that the alkyne inserted into a Pd–C bond of an alkoxycarbonylpalladium species, giving the intermediate **219**. Loss of OH followed the process described in Scheme 74 (vide supra).

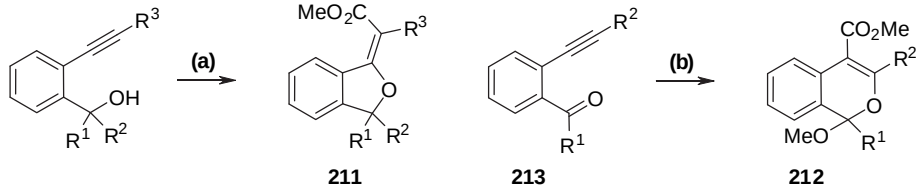
Selectivity for the coumarin versus benzofuran turned out to be highly dependent on both the carbon monoxide pressure and reaction temperature. Very good selectivity for coumarins was obtained at room temperature under 90 atm of CO.

The use of Pd(II) to activate alkynes in carbonylative processes was utilised by Kato et al.[195] in their asymmetric synthesis of optically active bicyclo[4.3.0]nonanes **220** from 2-alkyl-2-propargylcyclohexane-1,3-diones **221** (Scheme 75), the bicyclo[4.3.0]-nonane ring being found in many natural products.[195] Chiral induction was achieved via the use of chiral iosoxazoline 'box' ligands, with **222** and Me_2SnCl_2 giving the best yield (78%) and 76% ee.

Substitution at the propyne/cyclohexanone ring junction was also tolerated, with ees ranging from 76–82%, as was increasing the size of the A-ring from six to seven atoms.

The mechanism is based on two observations: (1) the bulkiness of the alcohol employed affected the ee and yield, suggesting that it was incorporated early in the reaction as the hemiacetal before cyclisation[195] and (2) earlier work[196] suggested that a cis relationship between the alcohol and the [Pd(II)]-activated propargyl group **223** (i.e., chelation) is more reactive in the cyclisation than the corresponding *trans*-hemiacetal **224**.[195] On cyclisation, the vinylpalladium species **225** is formed, which undergoes alkoxycarbonylation with the alcohol solvent to form the product **220** and generate Pd(0), which is subsequently re-oxidised by the *p*-benzoquinone. The Me_2SnCl_2 is employed as a Lewis acid to promote hemiacetal formation, affording an 8% increase in yield.

Palladium(II) can also activate alkenes towards cyclisation and carbonylation to form fused carbocycles. This approach was

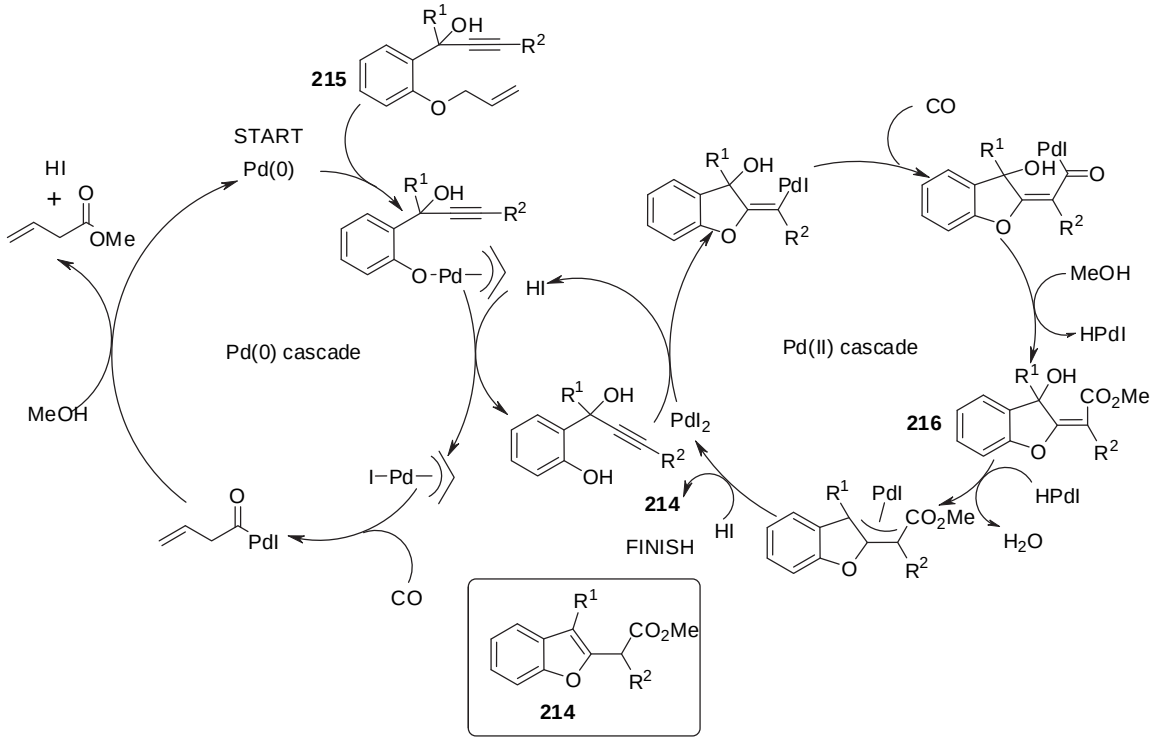


Scheme 72. Reagents and conditions: (a) PdI_2 (0.1 mol %), KI (1 mol %), CO/air (4:1, 3.2 MPa), MeOH, 60–70 °C, 7 h; (b) PdI_2 (3 mol %), KI (30 mol %), CO/air (3:1, 3.2 MPa), MeOH, 70–105 °C, 24–48 h.

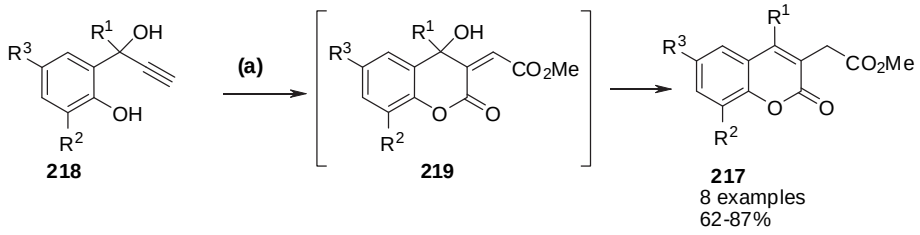
Benzofurans, especially the 2-acetic esters **214**, have important biological activity and Gabriele et al.[192] have utilised a novel 'sequential homobimetallic catalysis' system, in which the oxidative couple of Pd(0) and Pd(II) is utilised in the same pot via two sequential catalytic cycles. The use of PPh_3 and H_2O with CO allowed the in situ formation of Pd(0) via the water-gas shift reaction, allowing PdI_2 to act as precursor for both the Pd(0) and Pd(II) catalytic cycles (Scheme 73). Allyl-protected starting material (**215**) is required, with H/Pd/I promoting the reduction of the allylic alcohol species **216** via a π-allyl species.

utilised by Szolcsányi et al.[197] in their four-step racemic synthesis of calvine **226** and epicalvine **227** in 29% overall yield (Scheme 76).

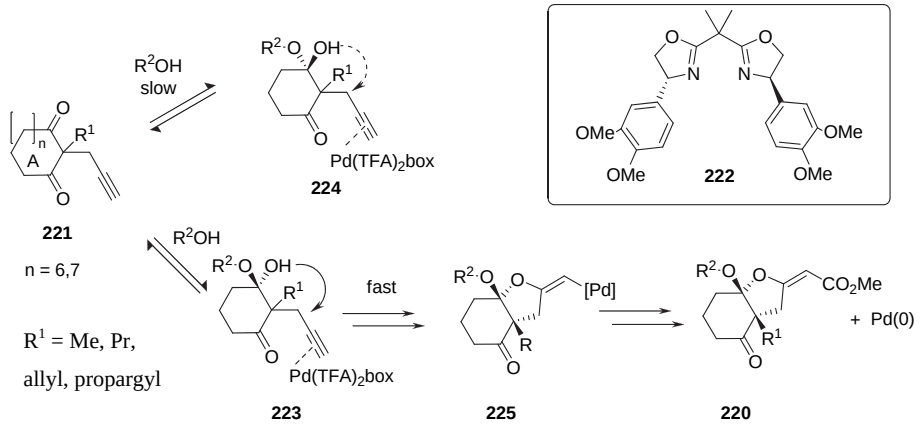
Calvine and epicalvine were subsequently isolated in 55% yield for the carbonylation step, in a 2.2:1 ratio in favour of calvine. Formation of the by-product **228** arises when the alcohol moiety of **229** first forms an O–Pd bond, followed by CO insertion to form the 'ester'. This is then trapped by the amine, rather than by sequential addition of the amine to the double bond, followed by cyclisation.



Scheme 73. Reagents and conditions: (a) **215** (2.0 mmol), PdI_2 (1 mol %), KI (1 equiv), PPh_3 (4 mol %), H_2O (2 equiv), CO (30 atm), MeOH (1.0 ml per 0.22 mol **215**), 100 °C, 15–24 h; 26 examples, 55–88%.



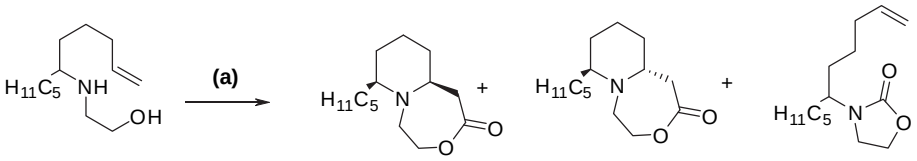
Scheme 74. Reagents and conditions: (a) if R^1=H: alkyne (5.0 mmol), PdI_2 (2.5 mol %), KI (2.5 mmol), CO (90 atm), MeOH (10 ml), rt, 8–15 h, 70–83% yield; if $R^3 \neq$ H: alkyne (5.0 mmol), PdI_2 (5 mol %), KI (2.5 mmol), CO (90 atm), MeOH (10 ml), rt, 24 h.



Scheme 75. Reagents and conditions: **221** (0.3 mmol), $Pd(TFA)_2$ (5 mol %), ligand **222** (10 mol %), Me_2SnCl_2 (5 mol %), *p*-benzoquinone (0.33 mmol), CO (1 atm), R^2OH (6 ml), −40 to 0 °C, 2–6 days.

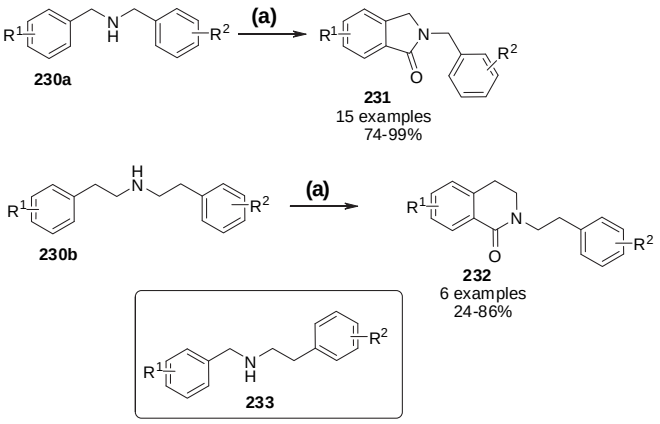
3.6.2. Nitrogen-containing heterocycles via C–H activation. The synthesis of benzolactams has been known since the 1970s but until recently there was no direct C–H activation route to these compounds. This has recently been achieved,[198] starting from phenylalkylamines **230a**,**b**. A variety of 5-(**231**) and 6-(**232**) membered benzolactams have been formed in 28–99% yield (Scheme 77), utilising a catalytic system of $Pd(OAc)_2/Cu(OAc)_2$ under a CO/air atmosphere.

Electron-donating (EDG) and -withdrawing (EWG) groups are both equally tolerated, those rings with EDG groups tending to form isoindolones **231**. In six-membered ring formation **232**, the



229 226 227 228

Scheme 76. Reagents and conditions: (a) **229** (0.469 mmol), $PdCl_2$ (10 mol %), $CuCl_2$ (0.937 mmol), AcONa (0.937 mmol), anhydrous dioxane (9 ml), CO (1 atm), 40 °C, 7 h, **226** (38%), **227** (17%), **228** (4%).

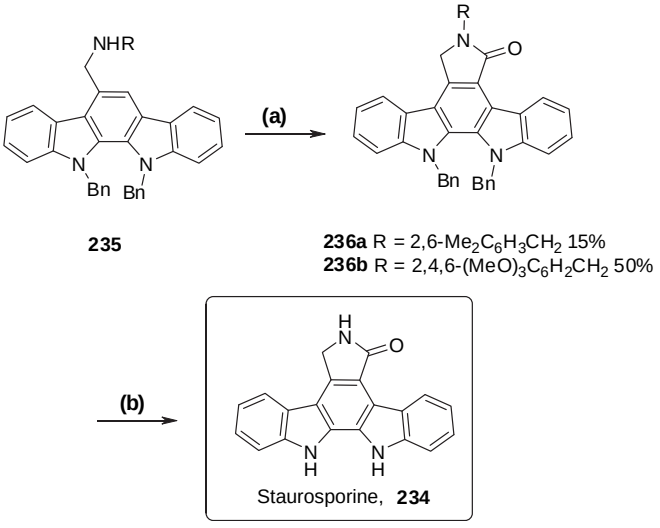


Scheme 77. Reagents and conditions: (a) **248** (0.1 M in toluene), HNR^2R^2 (0.12–0.2 equiv), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (50 mol %), CO (1 atm), air, (1 atm), reflux, 2 h.

presence of a *meta*-methylenedioxy substituent accelerated ring formation by 10-fold, due to its ability to chelate to Pd(II) and small steric repulsion.[199] With **233**, the five-membered ring product predominated forming around 11-fold faster than the six-membered ring. It is suggested that the Pd(0) is re-oxidised in a manner similar to that of the Wacker process.[200]

This idea of direct aromatic metallation and lactam formation has been utilised[201] in studies towards the total synthesis of Staurosporinone **234**, an indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloid. These alkaloids display remarkable biological activities[201] and have been the focus of several groups.[201]

The carbazole **235** was subjected to $Pd(OAc)_2$-catalysed direct aromatic carbonylation to give the *N*-protected Staurosporinones **236a** and **236b**. Treatment with $AlCl_3$ in anisole removed the *N*-benzyl groups, affording **234** quantitatively (Scheme 78).

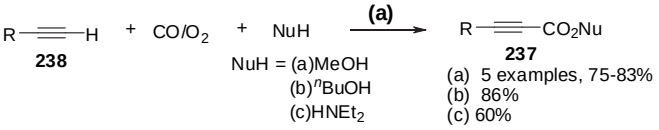


Scheme 78. Reagents and conditions: (a) **235** (0.1 mmol), $Pd(OAc)_2$ (5 mol %), $Cu(OAc)_2$ (50 mol %), CO (1 atm), air (0.5 mol equiv O_2), toluene (2 ml), reflux 12 h; (b) $AlCl_3$ (0.3 mmol), **236b** (0.05 mmol) anisole (1 ml), 0 °C. Then 110 °C, 1 h, 100%.

The low yields initially encountered with **236a** prompted a switch from toluene to DMSO (110 °C), which improved the yield of **236b** from 35 to 50%.

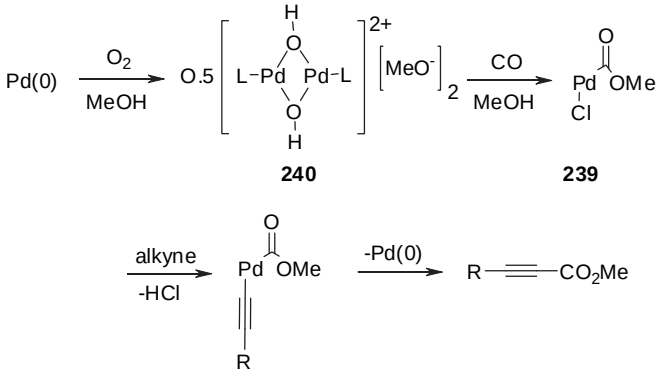
3.6.3. Use of single oxidising agent. The use of additional additives (in addition to O_2) to re-oxidise palladium(0) to Pd(II) can cause problems in the purification and so their elimination would be desirable.[202]

In this respect, Izawa et al.[202] have utilised air as the sole oxidant in their synthesis of 2-alkynoates **237**. These constitute an important class of biologically active substances and are versatile intermediates in the synthesis of butenolides,[203] macrolides[204] and carbapenem intermediates.[205] It was shown that terminal alkynes **238** undergo carbonylation-nucleophile capture at atmospheric pressure of CO/air with a variety of nucleophiles in good yield (Scheme 79).



Scheme 79. Reagents and conditions: (a) **238** (1.0 mol), NuH (50.0 mol), $PdCl_2$ (10 mol %), PPh_3 (20 mol %), CO/O_2 (1:1, 1 atm), NaOAc (30 mol %), DMF, rt, 48 h.

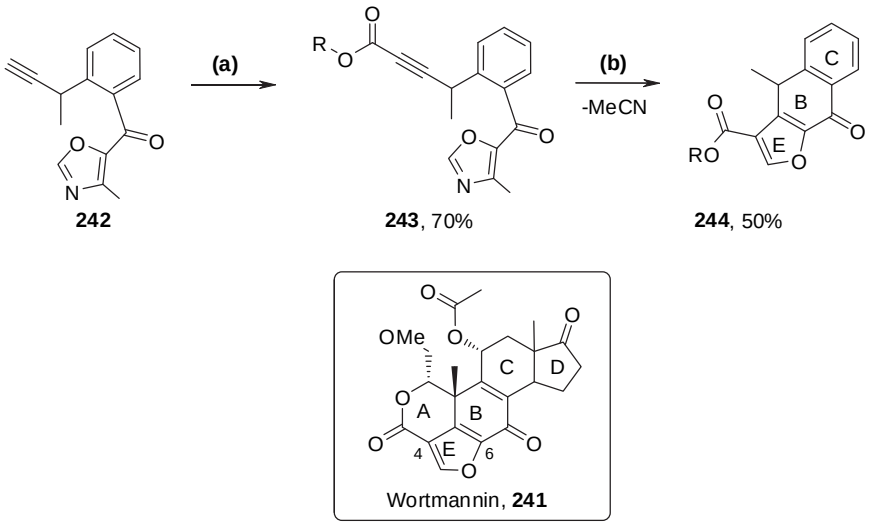
The mechanism (Scheme 80), in the case of MeOH as nucleophile, was shown to proceed via the methoxycarbonyl intermediate **239** before alkyne co-ordination, followed by reductive elimination. Re-oxidation occurred via the intermediate **240**. $[Pd(PPh_3)_4]$ could be added as the Pd source, but required the addition of LiCl to undergo the oxidation.



Scheme 80. Mechanism of alkyne oxidative methoxycarbonylation.

The furanosteroids are a class of novel pentacyclic fungal metabolites, characterised in part by a furan ring bridging positions 4 and 6 of the steroid skeleton. Wortmannin **241** has been shown to be a potent inhibitor of the mammalian Polo-like kinase 1 (PLK1), an enzyme vital to cellular growth cycles that offers a new target in cancer therapy.[206]

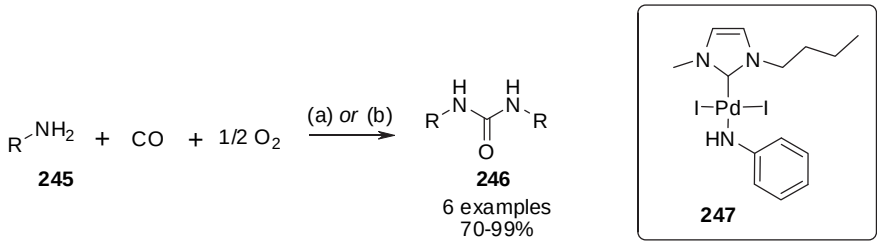
Sessions et al.[207] have utilised the oxidative alkoxycarbonylation of the alkynyl oxazole **242**, to access **243**, an advanced wortmannin intermediate, which, after thermolysis, affords the B/C/E-ring system **244** (Scheme 81). Subsequent elaboration of **244** with



Scheme 81. Reagents and conditions: (a) **242** (0.092 mmol), EtOH (50.0 equiv), $Pd(OAc)_2(PPh_3)_2$ (10 mol %), CO/O_2 (1:1, 1 atm), dry DMF (2.5 ml), rt, 25 h; (b) **243** (0.161 mmol), dry *o*-xylene (3.2 ml), argon, rt, 10 min, then reflux, 3 h.

sequential Mukiayama–aldol reaction (ring B), saponification and lactonisation to furnish ring A proved problematic, when R=Et. Switching to the benzyl ester (R=benzyl), however, afforded the A/B/C/E ring system in 11% yield over five steps.

A highly efficient oxidative carbonylation of primary amines **245** to ureas **246** employing the NHC/palladium complex **247** and utilising O_2 as the sole oxidant has been acheived.[208] Both aliphatic amines and aromatic amines were transformed in 70–99% yield (Scheme 82).



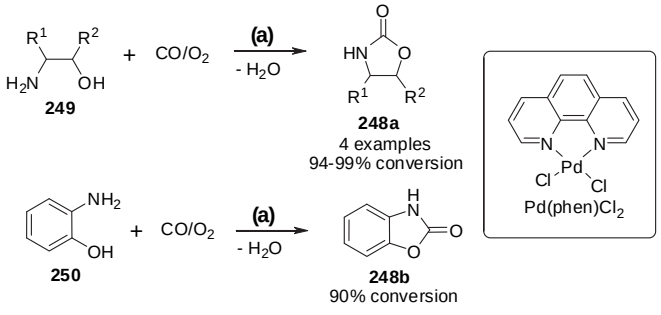
Scheme 82. Reagents and conditions: (a) **245** (22 mmol), **247** (0.02 mol %), $P_{(CO,O_2)}$=3.2; 0.8 MPa, DMF (6 ml), 150 °C, 1 h; (b) if amine is aliphatic: $MeOCH_2CH_2OMe$ (6 ml), 100 °C, 10 h.

Aromatic amines bearing *para* electron-withdrawing groups gave the lowest yields, but sterically crowded precursors afforded the ureas in good yield. Aliphatic amines required the use of $MeOCH_2CH_2OMe$ as the solvent to afford the desired product with minimal side-product formation. Only symmetrical ureas were formed in each case, although this limitation can be overcome to some extent by employing up to 2 equiv of a different amine in the same reaction.[198] This requires the presence of $Cu(OAc)_2$ as the oxidant in order to achieve catalysis.[198]

2-Oxazolidinones **248** are very important intermediates in the manufacture of pharmaceuticals, cosmetics, pesticides and other fine chemicals.[209] They are mainly synthesised by the addition of phosgene gas to the corresponding 1,2-amino alcohols **249** or 2-aminophenol **250**.[209]

To eliminate the use of phosgene, Li and Xia[209] utilised a biphasic oxidative cyclocarbonylation of **249** and **250** to furnish the corresponding 2-oxazolidinones **248a** and **248b**, with an ionic liquid-stabilised $Pd(phen)Cl_2$ complex (Scheme 83). The results showed that 1-butyl-3-methyl-imidazolium iodide (BMImI) can act simultaneously as a specific stabiliser for [Pd], enhancing the catalytic performance, and as a solvent. It could also be utilised to recycle the catalyst with unprecedented TOF values, as it is immiscible with DME, allowing a simple decanting to recover the catalyst.[209]

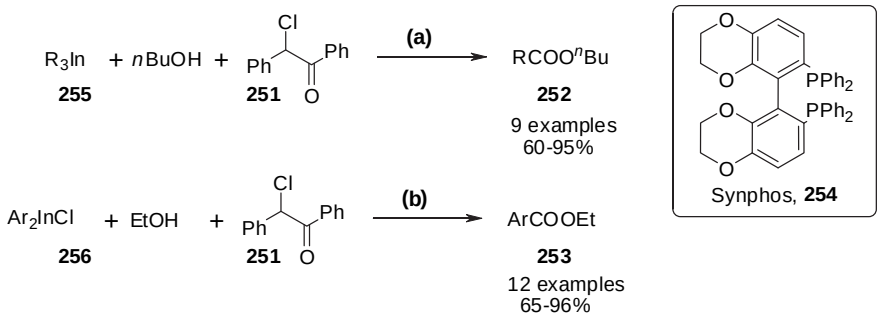
The reaction mechanism is not well understood at this stage, with experiments utilising $Pd(phen)Cl_2$ complex alone giving poor



Scheme 83. Reagents and conditions: (a) aminoalcohol (10 mmol), $Pd(Phen)Cl_2$ (1 mg), CO (5.0 MPa), O_2 (0.2 MPa), BMImI (BMIm=1-butyl-3-methylimidazolium, 1 ml), DME (6 ml), 120 °C, 1 h.

results, as does the addition of conventional inorganic iodides or ammonium iodide.

Desyl chloride (2-chloro-1,2-diphenylethanone, **251**) can also act as an oxidant and has recently been utilised in the oxidative synthesis



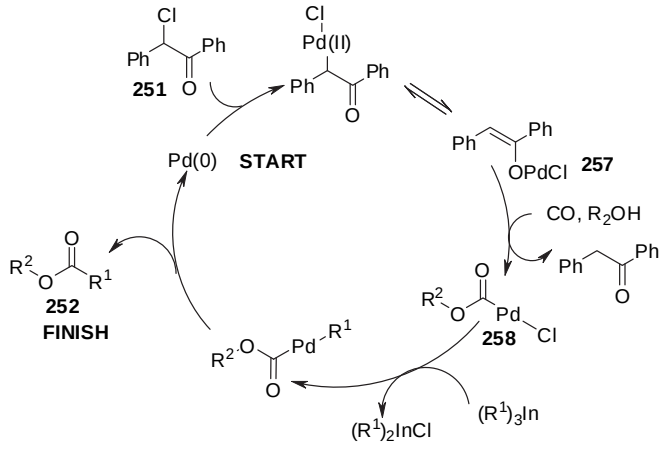
Scheme 84. Reagents and conditions: (a) **255** (0.6 mmol), **251** (0.5 mmol), $PdCl_2(MeCN)_2$ (3 mol %), **254** (4 mol %), CO (50 psi), ^{n}BuOH, 60 °C, 24 h; (b) **256** (0.6 mmol), **251** (0.5 mmol), $PdCl_2$(dppf) (5 mol %), CO (1 atm), Et_3N (1.0 mmol), EtOH, 60 °C, 24 h.

of various alkyl **252** and aromatic esters **253**, employing organoindium reagents as the metal partner (Scheme 84) under mild conditions.[210] Primary and secondary alkylindium reagents with β-hydrogens are suitable partners. Synphos **254** was essential to the reaction success, with trialkylindium reagents **255**; with other bidentate or monodenate phosphines, conversions were <76%.

R groups bearing β-hydrogens showed no β-hydride elimination and the desired products were formed in 60–95% yield. Homocoupled by-product and dialkyl ketone were formed in trace amounts.

Unlike trialkylindium reagents, diarylindium chlorides **256**, bearing electron-withdrawing or electron-donating substituents, could undergo oxidative carbonylation with $PdCl_2$(dppf), with only bromo groups showing a reduction in yield. However, the presence of an *ortho*-substituent gave lower yields, probably due to steric hindrance.

Preliminary mechanistic studies (Scheme 85) suggest that oxidative addition to the activated C–Cl bond of **251** occurs first. This tautomerises to give a palladium enolate species **257**, which then undergoes displacement of the enolate group by R^2OH, followed by CO insertion, to give the alkoxycarbonylpalladium complex **258**. Transmetallation with $R^1{}_3In$ followed by reductive elimination affords the product **252** and Pd(0). The same mechanism is believed to apply to the use of **256** as the transmetallating reagent.



Scheme 85. Mechanism of Pd(II)-catalysed In(III) cross-coupling reaction.

4. Conclusions

Palladium-catalysed carbonylation processes offer the organic chemist an invaluable set of tools to access a wide variety of carbonyl compounds usually via one-pot methods under mild conditions. Palladium carbonylations have also opened up new routes to various substituted heterocycles, often with high atom economy, from relatively small building blocks. Work to increase the scope and potential of palladium-catalysed carbonylations seems likely to retain a high profile.

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Biographical sketch

Simon Mutton was born in Truro, UK. He graduated from the University of Leeds in 2004 before moving to AstraZeneca Ltd as a graduate chemist researching novel kinase inhibitors. He then returned to Leeds as the Mary and Alice Smith Memorial Scholar in 2005 to carry out his PhD studies under the supervision of Professor R. Grigg. His research focussed on the application of 3-component cascades utilising either carbonylation or allene gas for the synthesis of novel inhibitors of motor neurone disease. In 2009, he joined the AstraZeneca Global Catalysis Screening Group at Avlon as a post-doctoral researcher, working on palladium-catalysed methodologies.

Ron Grigg gained his Chemistry degree at evening classes whilst working for GlaxoSmithKline and then moved on to a Ph.D. at Nottingham University. His Ph.D. research was on porphyrins, corrins and their metal complexes and was followed by postdoctoral research at Cambridge on vitamin B12. He was appointed Professor of Organic Chemistry at Queens University, Belfast, in 1974 where he founded the Questor Centre for pre-competitive multidisciplinary research. In 1989 he moved to Leeds University where he founded the Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre. He is currently Professor of Medicinal Chemistry and Director of the MIDAS Centre. He is a fellow of the Royal Society and has received the Tilden Lectureship, the Pedler Lectureship, the Heterocyclic Chemistry Medal and the Organic Synthesis Medal of the Royal Society of Chemistry. His research interests include the design of catalytic cascade reactions, asymmetric synthesis, metalloenzyme inhibitors, combinatorial chemistry and novel 1,3 - dipolar cycloaddition reactions, and their application to medicinal and biochemical problems. He is the inventor of a widely used forensic reagent for the detection of latent fingerprints and has published over 450 papers.