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Synthesis of heterocycles by carbonylation of acetylenic compounds

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1. Introduction

The carbonylation of unsaturated hydrocarbons, alcohols, organic halides and other substrates catalysed by transition metals, salts of transition metals and organometallic complexes is a widely used method for the synthesis of new carbonyl-, carboxyl- and alkoxycarbonyl- containing compounds including the creation or modification of heterocycles.[1–9] The information on the synthesis of heterocycles by carbonylation of acetylenic compounds in previous references is, however, practically absent and many of these have appeared more than 25 years ago. In the present review, we present the latest data on the preparation of various heterocyclic compounds.

2. Synthesis of alkoxycarbonyl derivatives of dimethylenepyrrolidines

It was found by Chiusoli et al.[10,11] that α,α-tetraalkyl-substituted dipropargylamines react with carbon monoxide and alcohols or water in the presence of a $PdCl_2$-thiourea complex, forming the alkoxycarbonyl derivatives of dimethylenepyrrolidines (**1**,**2**) (Scheme 1).

When $PdCl_2$ was used as a catalyst in the presence of carbon monoxide (CO/O_2=90:10) in methanol, dimethoxycarbonyl dimethylenepyrrolidines (**3** and **4**) were mainly formed. The monomethoxycarbonyl derivatives **1** and **2** were produced as byproducts. A similar pattern occurred if the reaction was catalysed by Pd^0/C in the presence of KI and oxygen (CO/O_2=94:6). On the other hand, the stereoisomeric, dimethoxycarbonyl dimethylene-pyrrolidine (**5**), was also obtained in low yield[12] (Scheme 2).

Upon oxidative alkoxycarbonylation of dipropargylamines and amides using a mixture of CO/air at **4** bar pressure in an alcohol in the presence of a Pd^0/C catalyst and KI, the 3,4-bis(alkoxycarbonylmethylene)pyrrolidines **6** were obtained. The isomerisation of **6** under various conditions leads to the formation of pyrroles **7** and free pyrrole-3,4-diacetic acid **8**[13] (Scheme 3).

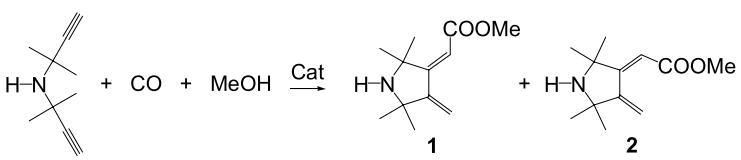
3. Synthesis of alkoxycarbonyl derivatives of tetrahydropyridine

In addition to the $PdCl_2$-catalysed oxidative methoxycarbonylation reactions of *N*,*N*-dipropargyl-arylamines by carbon monoxide in methanol, $PdCl_2$ in the presence of $CuCl_2$ and NaOAc as co-catalysts can be used to produce the cyclic compounds, the dimethyl-1-aryl-5-methoxycarbonylmethylene-1,2,5,6-tetrahydro-pyridine-3,4-dicarboxylates **10**. In some cases, **10** were produced together with the byproducts, the alicyclic diesters of aminodicarboxylic acids **9** (Scheme 4).[14,15]

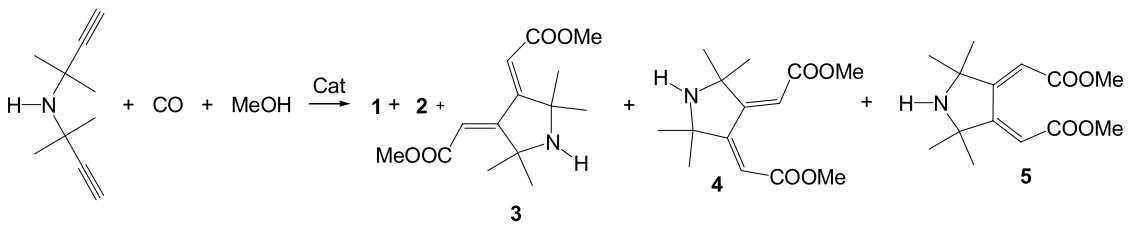
The formation of the cyclic aminotriesters **10** takes place by additive methoxycarbonylation of one of the triple bonds of the arylaminodiesters **9**, followed by cyclisation. The formation of the cyclic compounds **10** and the arylaminodiesters **9** is dependent on the nature and position of the substituent X in the aryl ring (when X=*p*-Me, *p*-OMe and *p*-Br no traces of the cyclic compound **10** were observed) and, apparently, the stability of the intermediate complexes of the arylaminodiesters **9** with the catalyst $PdCl_2$ determines the reaction course.[15]

4. Synthesis of tetrahydrofuran and pyrrolidine derivatives

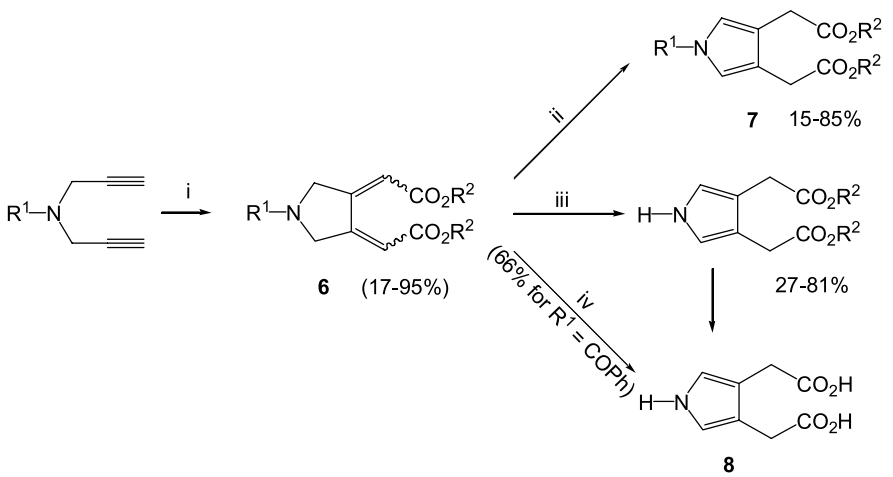
The intramolecular silylcarbocyclisation (SiCaC) of 1,6-enynes **11** catalysed by Rh or Rh–CO complexes leads to the tetrahydrofuran and pyrrolidine derivatives **12** in high yields[16,17] (Scheme 5). Under a high pressure of CO



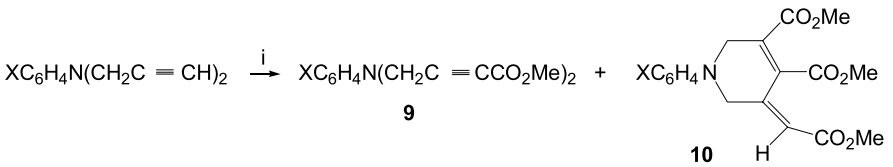
Scheme 1.



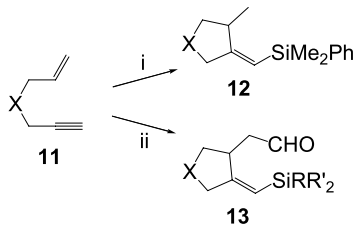
Scheme 2.



Scheme 3. R^1=alkyl, aryl, alkoxycarbonyl, tosyl; R^2=alkyl. (i) CO/air, R^2OH, Pd/C, KI; (ii) DMSO or MeCN/Et_3N, 25–70 °C, 3–70 h, (iii) R^2OH, Et_3N, 25–80 °C, 5–70 h; (iv) (1) $Ba(OH)_2/H_2O$, 100 °C, 15 h, (2) H_2SO_4/H_2O; (v) (1) NaOH/H_2O, 100 °C, 30–40 min, (2) H_2SO_4/H_2O, 0 °C.



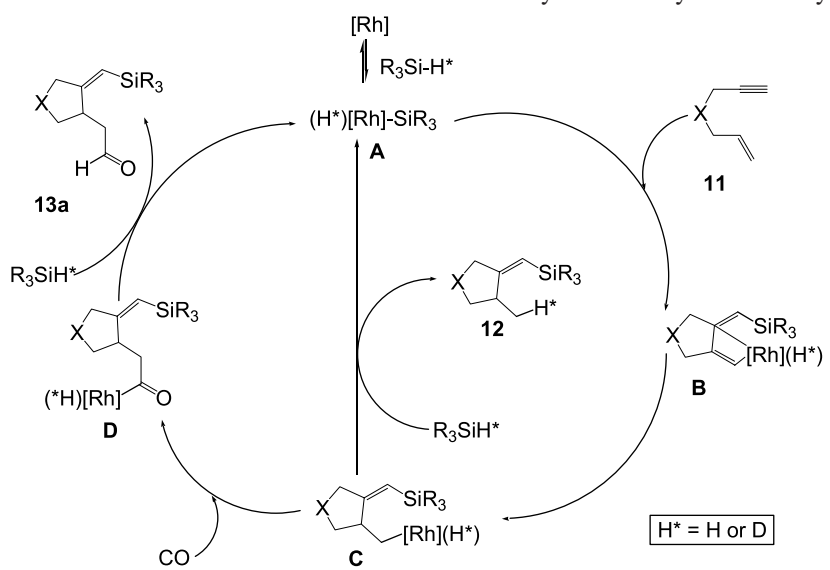
Scheme 4. (i) CO, MeOH, $PdCl_2$ (10 mol%), $CuCl_2$ (4 equiv.), NaOAc (1 equiv.). Compound **10**: X=H (11%), *p*-Cl (36%), *m*-Cl (40%), *m*-Br (47%), *o*-Cl (24%), *o*-Br (45%).



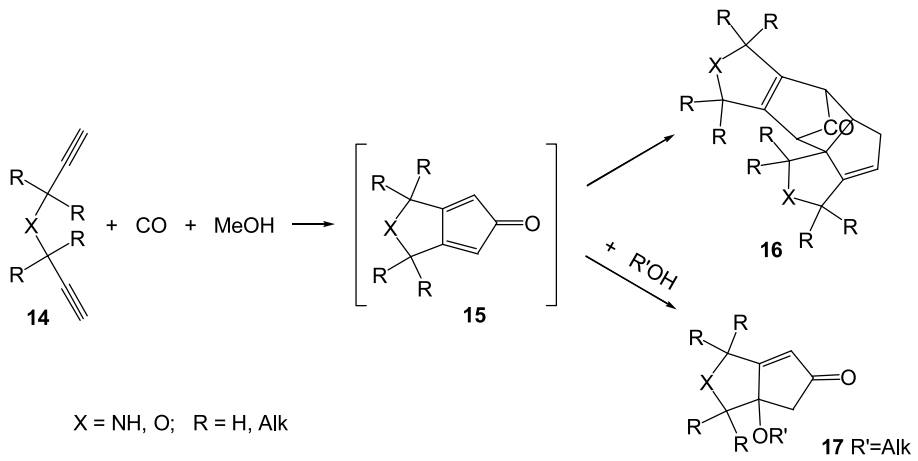
Scheme 5. (i) [Rh] cat. (0.5 mol%), $PhMe_2SiH$ (1–1.5 equiv.); CO (1 atm), toluene or hexane, 22 or 70 °C; (ii) [Rh] cat (0.5 mol%), $P(OEt)_3$ (10 mol%), RR′SiH (1–1.05 equiv.); CO (10–20 atm), toluene or dioxane, 65–105 °C. Compound **12**: cat.—$Rh(acac)(CO)_2$; X=O (82%); cat.—$Rh_4(CO)_{12}$, X=NCH_2CH=CH_2 (74%); X=NCHMePh (89%); X=NBr (83%); X=NTs (86%). Compound **13**: cat.—$Rh(acac)(CO)_2$; R=R′=Et, X=O (15–20%); cat.—$Rh_4(CO)_{12}$, R=Ph, R′=Me, X=NTs (86%); X=NMs (56%).

(10–20 atm), the SiCaC reaction of allylpropargyl ether or allylpropargylamines with Et_3SiH or Me_2PhSiH catalysed by $Rh(acac)(CO)_2$ or $Rh_4(CO)_{12}$ with the addition of 10 mol% $P(OEt)_3$ took place to give the corresponding exo-silylmethylene tetrahydrofuran and pyrrolidine derivatives **13** bearing a formylmethyl moiety at the C-2 position in high yields (Scheme 5).[16,17]

The most plausible mechanism for the silylcarbocyclisation of the enynes **11**, which can accommodate the formation of both SiCaC products **12** and CO–SiCaC products **13a**, is proposed in Scheme 6. The silylcarbocyclisation of enynes should begin with the formation of the active catalyst species, the silyl-[Rh] complex **A**, followed by insertion of the acetylene moiety of the enyne **11** to generate the



Scheme 6.



Scheme 7.

β-silylvinyl-[Rh] complex **B**. Coordination of the olefin moiety, followed by intramolecular carbometallation, leads to the formation of the *exo*-methylenecyclopentylmethyl-[Rh] complex **C**. In the absence of CO or at a very low concentration of CO, hydrosilane-promoted reductive elimination takes place, to give the SiCaC product **12** and regeneration of the silyl-[Rh] complex **A**. At higher CO concentrations, migratory insertion of CO into the alkyl-[Rh] bond of **C** occurs, leading to the formation of the acyl-[Rh] complex **D**. Subsequent hydrosilane-promoted reductive elimination affords the CO–SiCaC product **13a** and regenerates the active catalyst species **A**. A CO atmosphere is not essential for the SiCaC process. The use of a CO atmosphere however, appears to stabilise the active [Rh] catalyst species, especially when the Rh carbonyl clusters are used for a prolonged period of time.

5. Polycyclic heterocycle formation

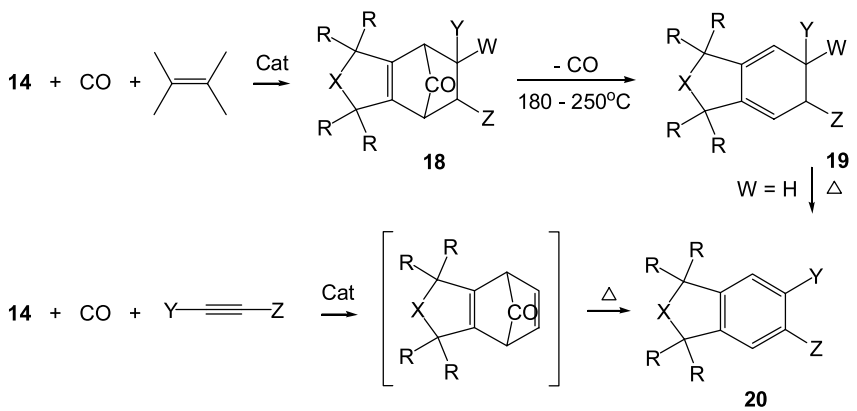
Chiusoli and co-workers have found, that the polycyclic products **16** were formed by carbonylation of the 1,6-diynes **14** in the presence of Pd^0 on charcoal[18] (Scheme 7).

The reaction proceeded at room temperature and at atmospheric pressure of carbon monoxide and the polycyclic compounds **16** were formed by dimerisation of the cyclopentadienone **15**. When the reaction is carried out in a base/alcohol medium (X=NH, NMe; R=alkyl), the cyclopentadienone **15** is attached by an alkoxyl group with the formation of the corresponding alkoxycyclopentenones **17**. Utilising various alkenes and alkynes as dienophiles allowed a further extension to the new types of heteropolycyclic compounds **18**-**20** (Scheme 8).[19]

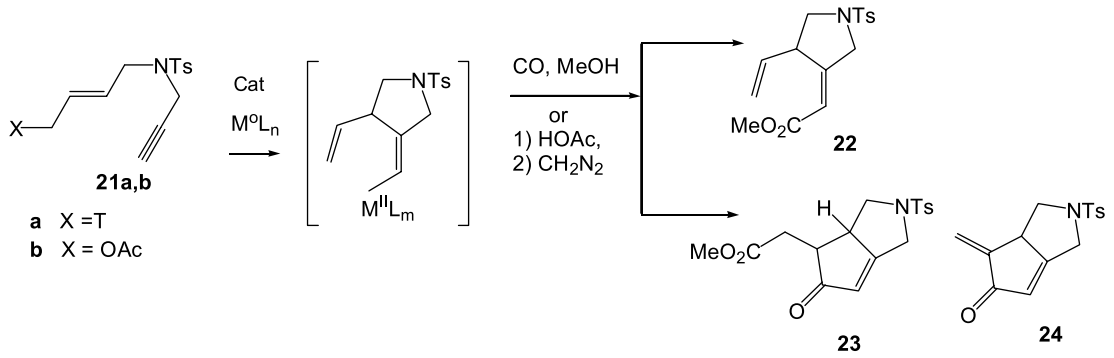
Palladium on charcoal (10%), and other Pd^0 complexes such as $Pd_2(dba)_3$ (dba=dibenzylideneacetone) or palladium salts and metallic Pd are used as catalysts. Heating the alkynes as dienophiles spontaneously furnished the aromatic products. The best yields were obtained for the polycyclic compounds **18** and **20** (up to 98%) using alkynes and alkenes with terminal double and triple bonds. In the absence of CO, under the same conditions, the reactions did not proceed, but using Ni and Co complexes as catalysts, the cycloaromatisation reaction of the dialkynes **14** proceeded smoothly.[20]

6. Highly stereoselective cyclisation/carbonylation of alkynylallylamines

Oppolzer et al. have shown that catalysts comprising nickel or palladium complexes promote a highly stereoselective cyclisation/carbonylation reaction of the propargylallylamines



Scheme 8. X=NH, NCO_2Me, NCOPh, O; Y=Ph, CO_2Me, H, CN, $CH=CH_2$; Z=H, Me, CO_2Me; W=H, Me, CO_2Me.

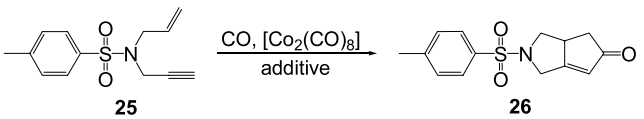


Scheme 9.

Table 1. Nickel(°)/and palladium(°) catalysed cyclisation/carbonylation of amines **21a**,**b**

N	21	Catalyst	Reaction conditions (time, h)	Products (yields, %)		
				22	23	24
1	**A**	$Ni(CO)_3PPh_3$	A (20)	69	—	—
2	**A**	$Ni(cod)_2$/dppb	A (12)	23	57	—
3	**B**	$Pd(dba)_2/PPh_3$	B (2)	13	50	16

A: 25 mol%Ni(0), THF/MeOH 4:1, CO (1 atm), rt. B: 10 mol% Pd(0), HOAc, CO (1 atm), 45 °C.

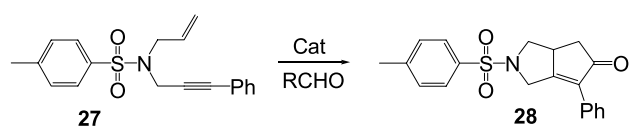


Scheme 10.

Using an intramolecular catalytic Pauson–Khand reaction (CPKR) of the propargylallylamide of *p*-toluenesulphonic acid **25** with octacarbonyldicobalt(°) catalyst the bicyclic derivative of pyrrolidine **26** has been prepared[23–27] (Scheme 10, and entries 1–3 in Table 2). 1,2-Dimethoxyethane (DME) was found to be the best promoter, giving the cycloaddition products in very good yields (Table 2, entry 3).[25] A catalytic conversion of the enyne **25** into **26** employing phosphites as coligands was reported by Jeong and coworkers (Table 2, entry 4).[26] Remarkably, under 1 atm of CO, the use of phosphites as coligands did not show any positive effect on the CPKR conversions. A disadvantage of this procedure is that it takes place only at apparent pressures of 3 atm. Kraft et al. used cyclohexylamine ($CyNH_2$) as an additive for the thermal CPKR (Table 2, entry 5). They developed a set of conditions that avoided the need for rigorous purification of the $[Co_2(CO)_8]$.[24] Hashimoto and coworkers have proved that the addition of phosphine sulphides to the CPKR improved the reaction

Table 2. Influence of different additives on the cobalt-catalysed Pauson–Khand reaction

Entry	$Co_2(CO)_8$ (mol%)	Additive (mol%)	T (°C)	p CO (atm)	Solvent	Reaction time (h)	Yield of **26** (%)	Ref.
1	7.5	None	60	1	DME	12	86	23
2	10	None	70	1	DME	10.5	63	24
3	3	DME (12)	120	7	Toluene	10	84	25
4	5	$P(Oph)_3$ (20)	120	3	DME	24	94	26
5	10	$CyNH_2$ (20)	70	1	DME	14	89	24
6	5	Bu_3PS (30)	70	1	Benzene	4	87	27



Scheme 11.

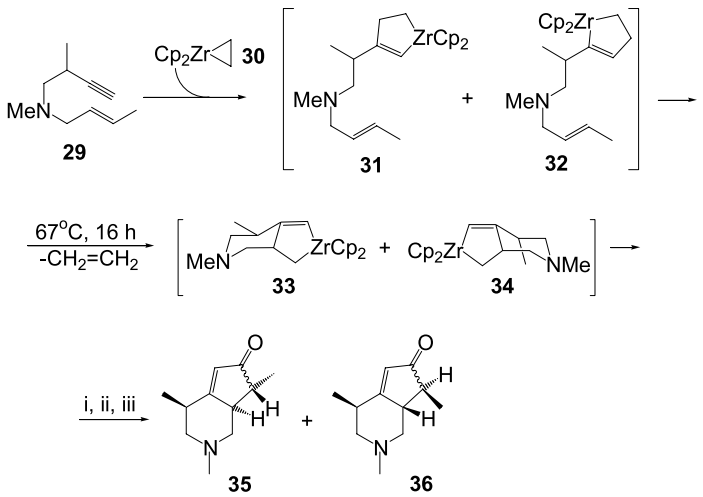
21a,**b**, which furnished the mono- **22** and bicyclic **23**,**24** derivatives of pyrrolidines (Scheme 9), depending on the catalyst used and the reaction conditions[21,22] (Table 1).

yield, and a faster conversion under 1 atm of CO was attained (Table 2, entry 6).[27]

More recently, two independent research groups have reported the use of aldehydes as a CO source for the Pauson–Khand reaction of the alkynylallylamide **27** to produce **28** (Scheme 11, and Table 3).[28,29] In a search for CO-transfer catalysts, Morimoto et al. tested different aromatic aldehydes with Rh, Ir and Ru species. They found that the most active system was a combination of the complex $[\{RhCl(cod)\}_2]$ (0.05 equiv.) with C_6F_5CHO

Table 3. CPKR using aldehydes as CO source

Entry	Catalyst (mol%)	Additive (mol%)	RCHO	Solvent, atmosphere	T, (°C)	Reaction time (h)	Yield of **28** [mol %]
1	$[Rh(cod)]_2$ (5)	dppp (11)	C_6F_5CHO (2 equiv.)	Xylene, N_2	130	4	95
2	$Rh(dppp)_2Cl$ (5)	—	cinnam-aldehyde (20 equiv.)	—, Ar	120	2	98



Scheme 12. (i) CO, −78 °C, 2 h; (ii) I_2 (2 equiv.), −78 °C to rt; (iii) MeOH/$NaHCO_3$ aq.

(2 equiv.), and several enynes could be cyclised under a nitrogen atmosphere (Table 3, entry 1).[28]

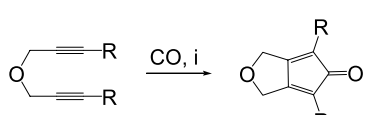
Shibata et. al. tested different aldehydes in a solvent-free system, employing the rhodium species $[Rh(dppp)_2Cl]$ (dppp=1,3-bis(diphenylphosphinyl)propane as a catalyst.[29] In this case, cinnamaldehyde was the most efficient aldehyde among those tested. The reactions were carried out employing 0.05 equiv. of the catalyst under 1 atm of argon (Table 3, entry 2).

Reaction of the enyne **29** catalysed by the in situ-generated zirconocene ethylene **30** at room temperature afforded the monocyclic products **31** and **32** (3:1). Heating at reflux in THF for 3 h gave complete conversion to the zirconabicycles **33** and **34**. Carbonylation (1 atm CO, rt 16 h) furnished an easily separable 4:1 mixture of (±)-tecomanine **35** and (±)-4-*epi*-tecomanine **36** in a non-satisfactory 21% overall yield based on **29** (Scheme 12). The yield was slightly increased to 31% by carrying out the carbonylation at −78 °C for 2 h and then working up with iodine (2 equiv.).[30]

7. Synthesis of bicyclic derivatives of tetrahydrofuran

The iridium complex-catalysed carbonylative alkyne–alkyne coupling provides bicyclopenta-dienones **37** in high isolated yields. Among the examined iridium complexes and phosphine ligands, IrCl(cod)(dppp) and $IrCl(CO)(PPh_3)_2$ (Vaska's complex) gave the best results (Scheme 13).[31,32]

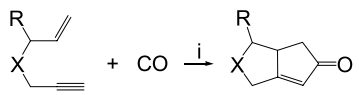
An intramolecular catalytic cycloaddition reaction of alkynylalkenylic ethers or amines and carbon monoxide



37 a R = $SiPh_3$ (78%)
b R = Ph (65%)

Scheme 13. (i) Ir complex (10 mol%), CO (1 atm), xylene, reflux.

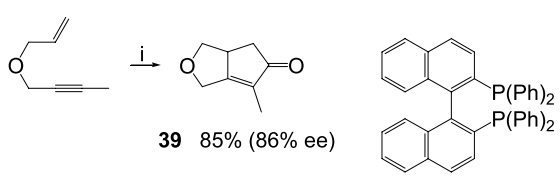
employing catalytic amount of $Co(acac)_2$ and $NaBH_4$ was developed for the synthesis of heterocyclic derivatives of cyclopentenone **38a-c**[33] (Scheme 14).



38a-c
a X = NTs; R = H (85%)
b X = O; R = $CH_2OTBDPS$ (82%)
c X = O; R = H (59%)

Scheme 14. (i) Co(acac) (0.05–0.1 mol), $NaBH_4$ (0.1–0.2 mol%), CO (30–40 atm), CH_2Cl_2, 100 °C, 48 h.

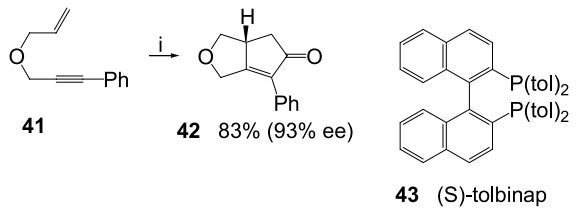
Jeong and co-workers recently reported an asymmetric rhodium-based catalytic system for the synthesis of bicyclic derivatives of tetrahydrofuran **39**.[34] The conditions were optimised with respect to the partial pressure of carbon monoxide, reaction temperature, and time. Good to very good *ee* values were found for a small range of intramolecular substrates when treated with $[RhCl(CO)_2]_2$ (0.03 equiv.), (*S*)-binap **40** (0.09 equiv.) and AgOTf (0.12 equiv.), as shown in Scheme 15.



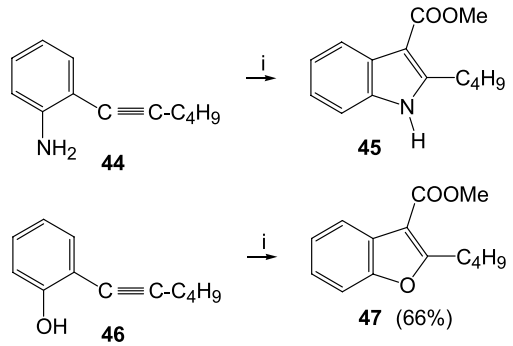
39 85% (86% ee)
40 (S)-binap

Scheme 15. (i) (*S*)-Binap **40** (0.09 equiv.), $[RhCl(CO)_2]$ (0.03 equiv.), AgOTf (0.12 equiv.), THF, 130 °C, 20 h, CO (2 atm).

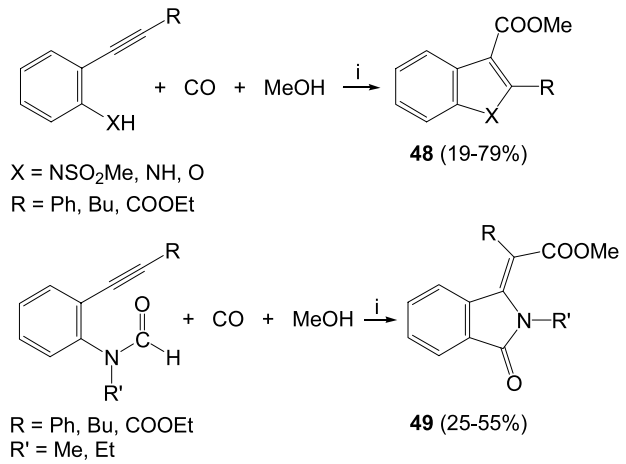
Shibata and Tagaki have studied the catalytic effect of $[Ir(cod)Cl]_2$ for the cyclisation of the allylalkynyl ether **41**.[35] They observed that the addition of phosphanes as coligands improved the yields of the reaction, and decided to use (*S*)-tolbinap **43** as an additive ligand. Excellent yields



Scheme 16. (i) (*S*)-Tolbinap **43** (0.2 equiv.), $[Ir(cod)Cl]_2$ (0.1 equiv.), toluene (0.12 equiv.), reflux, 18 h, CO (1 atm).



Scheme 17. (i) CO, MeOH, NaOH, $PdCl_2$, $CuCl_2$.



Scheme 18. (i) $PdCl_2$, $CuCl_2$, NaOAc (or K_2CO_3), 3 h, 20 °C.

and enantiomeric excesses of the bicyclic derivative of tetrahydrofuran **42** were obtained (Scheme 16).

8. Synthesis of indoles and benzofurans

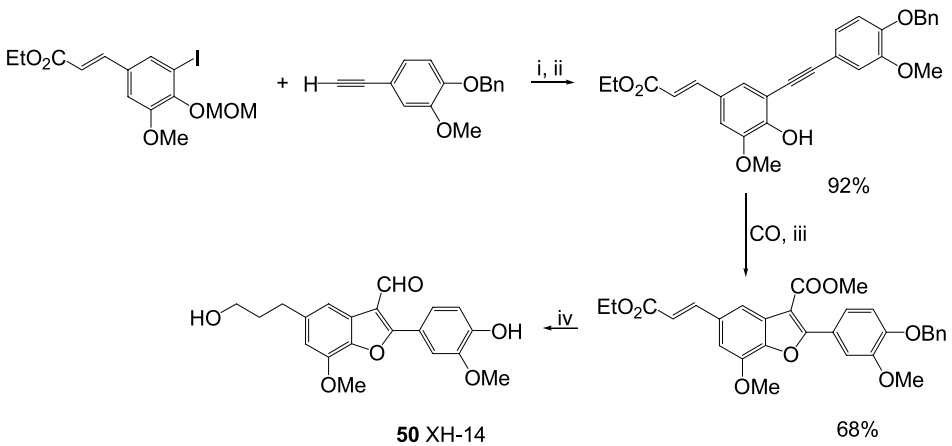
Palladium chloride-catalysed carbonylation of the *o*-hexynylaniline **44** and -phenol **46** produced the methyl 2-butylindole-3-carboxylate **45** and methyl 2-butylbenzofuran3-carboxylate **47**, respectively[36] (Scheme 17).

The reaction mechanism includes the formation of an intermediate bicyclic Pd complex, followed by carbonylating with CO into an acylpalladium complex. Treatment with methanol furnished the final product and a Pd^0 species. The catalyst regeneration as Pd^0 occurred by Pd^{2+} oxidation with participation of $CuCl_2$.[36]

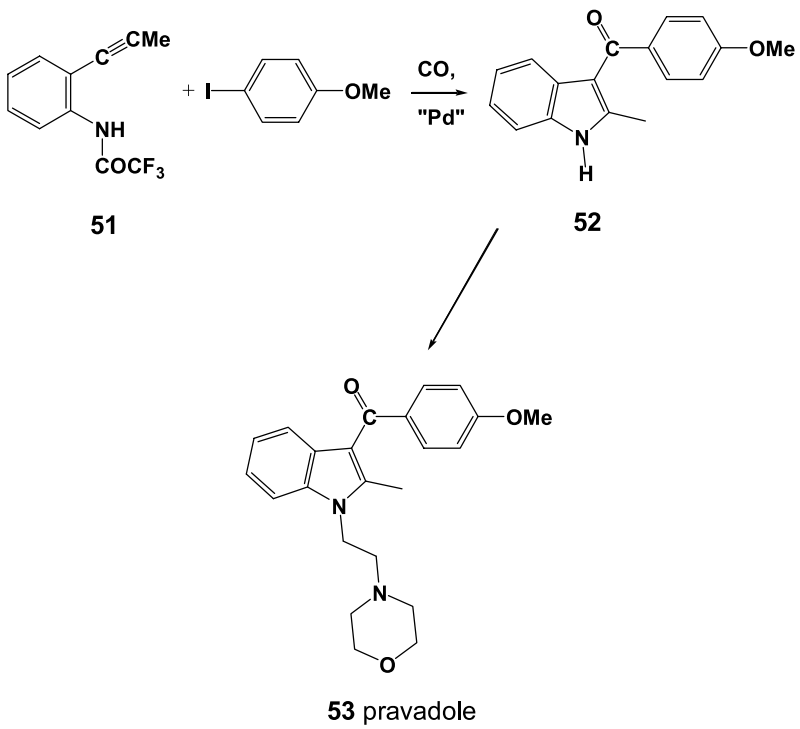
More recently, the reaction cycle has been extended, and a series of 2-substituted 3-methoxy-carbonylindoles and benzofurans **48** has been obtained. Only the lactams **49** have been formed from the 2-alkynylformanilides under these conditions[37] (Scheme 18).

A related synthetic strategy has been used to prepare the natural product XH-14 **50**, which possesses a benzo[*b*]furan skeleton. The synthesis involved the use of palladium-catalyzed cyclisation, with concomitant carbonylation via insertion of carbon monoxide, to introduce regioselectively a formyl group in the 3-position[38] (Scheme 19).

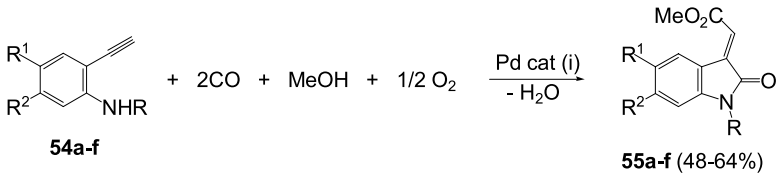
The palladium-catalysed reaction of the readily accessible 2-alkynyltrifluoroacetanilides with aryl halides and vinyl triflates under a carbon monoxide atmosphere (1 or 7 atm) in the presence of potassium carbonate produced the 2-substituted-3-acylindoles in fair to good yield. The acidity of the nitrogen–hydrogen bond proved to be of primary importance for the success of the reaction. This methodology has been applied to the synthesis of pravadole **53**, a drug that shows analgesic activity against postoperative pain. Pravadole **53** was prepared from the acylindole **52**, which was obtained by palladium-catalysed carbonylative cyclisaton of the alkynyltrifluoracetanilide **51** with *p*-iodanisole[39] (Scheme 20).



Scheme 19. (i) $PdCl_2(PPh_3)_2$ (1 mol%); CuI (2 mol%), NEt_3, MeCN; (ii) HO_2CCO_2H, MeOH, H_2O; (iii) $PdCl_2$, MeOH, $CuCl_2$, NaOAc, MeCN; (iv) (1) H_2, Pd–C, THF/HOAc (81% yield); (2) DIBAL, CH_2Cl_2 (61% yield); (3) MnO_2, EtOAc (87% yield).



Scheme 20.



Scheme 21. a R=R^1=R^2=H; **b** R=Bn, R^1=R^2=H; **c** R=Bu, R^1=R^2=H; **d** R=H, R^1=Me, R^2=H; **e** R=H, R^1=Cl, R^2=H; **f** R=R^1=H, R^2=Cl. (i) PdI_2 (2×10^{-3}–5×10^{-3} equiv.), KI (0.2–0.5 equiv.).

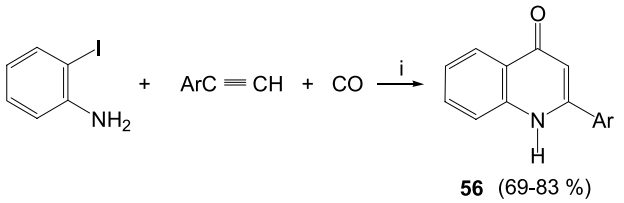
9. Synthesis of (*E*)-3-(methoxycarbonyl)methylene-1,3-dihydroindol-2-ones

Gabriele, et al. have reported a direct synthesis of (*E*)-3-(methoxycarbonyl)-methylene-1,3-dihydroindol-2-ones **55a-f** in good yields by the palladium-catalysed oxidative carbonylation of 2-ethynylanilines **54a-f**.[40] The reactions were carried out in MeOH as the solvent at 50–70 °C in the presence of catalytic amounts of PdI_2 in conjunction with KI under a 4:1 CO/air mixture (20 atm total pressure at 25 °C) (Scheme 21). The (*E*)-configuration around the double bond of **55a** was confirmed by a single crystal X-ray analysis.

The authors proposed that the formation of **55** could be interpreted by the formation of a carbamoylpalladium species, which then inserts into the triple bond. Another probable mechanism is the formation of an I–Pd–CO_2Me species by the reaction between PdI, CO and MeOH, followed by triple-bond insertion. In any event, however, the triple bond insertion is expected to be *syn*, to give vinylpalladium intermediates with (*Z*)-stereochemistry. Isomerisation of a (*Z*)-vinylpalladium intermediate into the corresponding (*E*)-isomer, followed by methoxycarbonylation, therefore appears to be the likely explanation for the stereoselective formation of the (*E*)-products **55**.

10. Synthesis of 2-aryl-4-quinolones

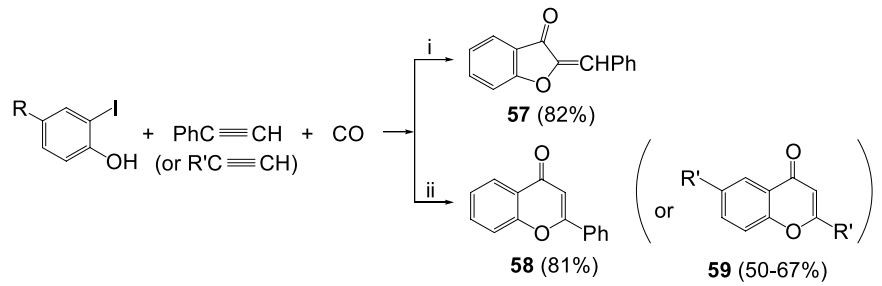
Kalinin et al. have shown that the carbonylation of *o*-iodoaniline and terminal arylacetylenes in the presence of palladium complexes leads to the 2-aryl-4-quinolones **56**.[41] The optimised reaction conditions with respect to pressure, amines, solvents and catalysts are listed in Scheme 22, the best catalyst being the $PdCl_2$(dppf) complex (dppf=1,1′-bis(diphenylphosphinoferrocene).

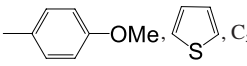


Scheme 22. (i) Et_2NH, 'Pd' cat, 120 °C, 20 atm, 1 h, Ar=Ph, C_6H_4OMe.

11. Synthesis of aurones and chromones

Carbonylation of *o*-iodophenol in the presence of phenylacetylene, potassium acetate and $Pd(PPh_3)_4$ in anisole at 1 atm CO leads to aurone **57** formation (Scheme 23).[42] When the reaction was carried out in the secondary amine

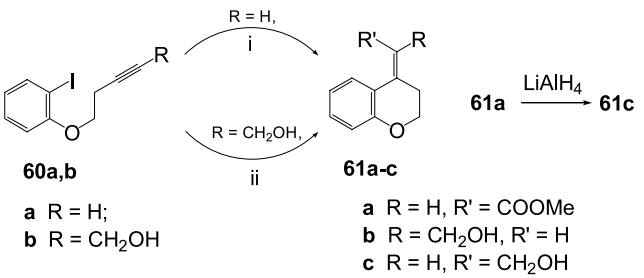


Scheme 23. (i) KOAc, $Pd(PPh_3)_4$, CO (1 atm), anisole; (ii) $PdCl_2$(dppf) (2 mol%), CO (20 atm), Et_2NH, 120°, 2 h R=H, R′=  , C_5H_{11}; R=Me, R′=Ph.

(the best was Et_2NH) at 20 atm CO and with catalysis by 2 mol% $PdCl_2$(dppf), the flavone **58** was formed (Scheme 23).[43] Selective formation of the aurone or flavone by carbonylation of *o*-iodophenol and phenylacetylene was achieved by manipulation of the reaction conditions (temperature, CO pressure) and the bases used. The influence of the nature of the solvent, amine, catalyst, CO pressure, and temperature on the yield of the flavone was studied.[43,44] The palladium-catalysed coupling of *o*-iodophenols proceeded either with aryl or heteroaryl halides and alkylacetylenes, giving the corresponding 2-substituted chromones **59** in good yield.[44]

12. Synthesis of (*E*)- and (*Z*)-substituted methylene-3,4-dihydro-2*H*-1-benzopyrans

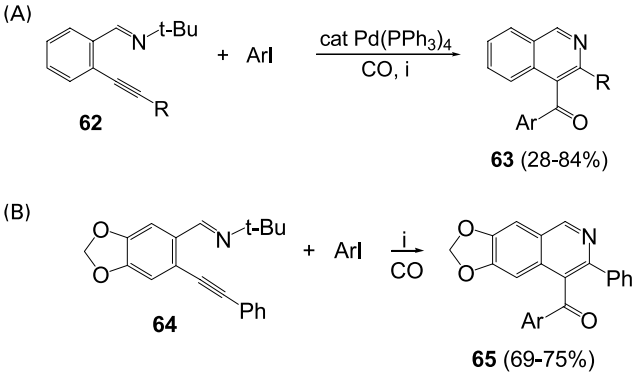
A stereoselective controlled synthetic approach to (*E*)- and (*Z*)-substituted methylene-3,4-dihydro-2*H*-1-benzopyrans **61a-c** was developed starting from the *o*-iodoalkynes **60a**,**b** through palladium-catalysed intramolecular cyclic carbopalladation of iodoalkynes **60**, followed by carbonylation or a hydride ion capture process (Scheme 24).[45] The influence of various solvents, catalysts and additives on the yields of the benzopyrans **61** was studied. The maximum yields obtained were 79% for benzopyran **61a** and 79% for benzopyran **61b**.



Scheme 24. (i) $Pd(PPh_3)_4$ (10 mol%), CO (1 atm), Et_3N (4 equiv.), AgOAc (3 equiv.) in MeOH–DMF–H_2O (1:1:0.2) at 100 °C; (ii) HCOONa (2 equiv.), Bu_4NCl (2 equiv.), $Pd(OAc)_2$ (10%), PPh_3 (20%) in DMF at 80 °C.

13. Synthesis of 3-substituted 4-aroylisoquinolines

Dai and Larock have shown that the *o*-(1-alkynyl)benzaldimines **62** and **64** react with aryl iodides at 1 atm of CO in the presence of tri-*n*-butylamine and $Pd(PPh_3)_4$ catalyst to afford in good yields the 3-substituted 4-aroylisoquinolines **63** or **65** by acylpalladation of the carbon–carbon triple bond and cyclisation (Scheme 25).[46,47]

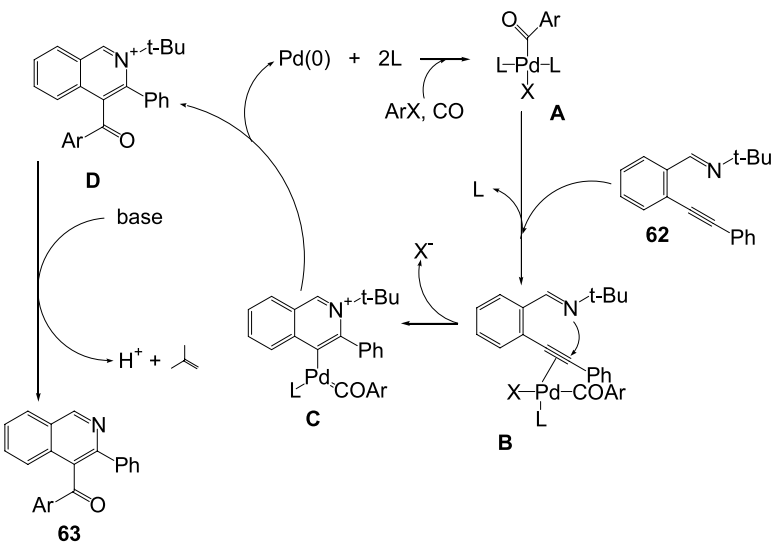


Scheme 25. (A): R=Ph, 1-cyclohexenyl, *n*-Bu, 3-cyanopropyl, *p*-$OMeC_6H_4$ Ar=*p*-(*m*- or *o*-)$MeOC_6H_4$,*p*-(*m*- or *o*-)MeC_6H_4, Ph, 1-naphthyl, 2-(3-)thienyl, *p*-BrC_6H_4, *m*-(*o*-)$EtO_2CC_6H_4$, *m*-(*p*-)$F_3CC_6H_4$, *p*-(*m*- or *o*-)$O_2NC_6H_4$. (B): Ar=*p*-$MeOC_6H_4$, *m*-$F_3CC_6H_4$ (i) DMF, $Pd(PPh_3)_4$ (4 mol%), Bu_3N (5 equiv.), 100 °C.

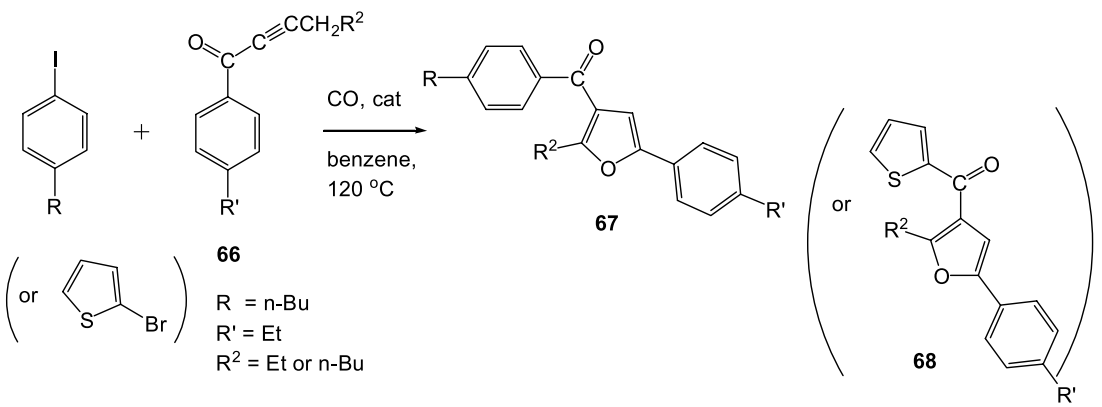
The authors proposed,[46,47] that the mechanism of this process (Scheme 26) includes the following key steps: (1) oxidative addition of the aryl halide to the Pd^0 catalyst, followed by CO insertion; (2) coordination of the resulting acylpalladium intermediate **A** to the alkyne triple bond of **62** to form the complex **B**, which activates the triple bond towards nucleophilic attack; (3) intramolecular nucleophilic attack of the nitrogen atom of the imine on the activated carbon–carbon triple bond to afford the intermediate **C**; (4) reductive elimination to form a carbon–carbon bond between the carbonyl group and the isoquinoline ring in **D** and simultaneous regeneration of the Pd^0 catalyst; and (5) cleavage of the *tert*-butyl group from the nitrogen to release the strain between the *tert*-butyl group and the 3-phenyl group with simultaneous generation of the 3-substituted 4-aroylisoquinoline **63**.

14. Synthesis of substituted furans

2-Substituted-3-(4-substituted-benzoyl)-5-(4-substituted-phenyl)furans **67** were synthesised by palladium-catalysed cross-carbonylation of aryl iodides and 1-aryl-2-alkynyl-1-ones **66** with CO in benzene in the presence of $PdCl_2(PPh_3)_2$ at 120 °C (Scheme 27). In a similar manner, 2-substituted-3-thienoyl-4-substituted-phenyl)furans **68** were obtained from 2-bromothiophene and the arylalkynylketones **66**.[48]



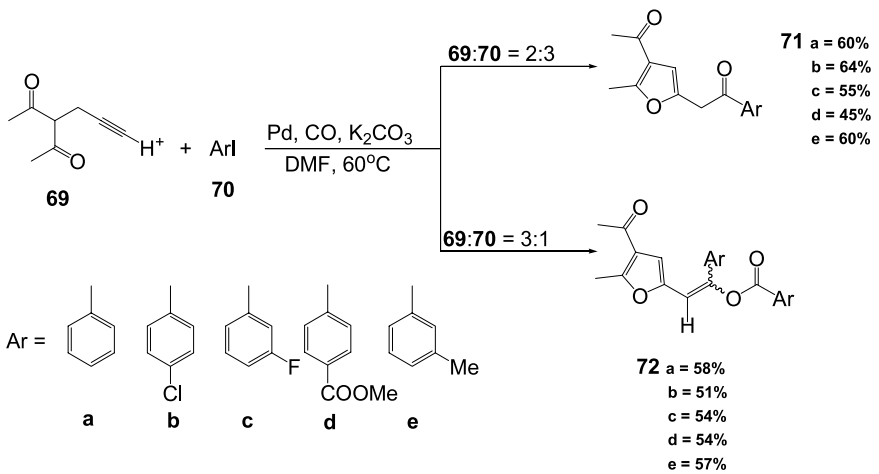
Scheme 26.



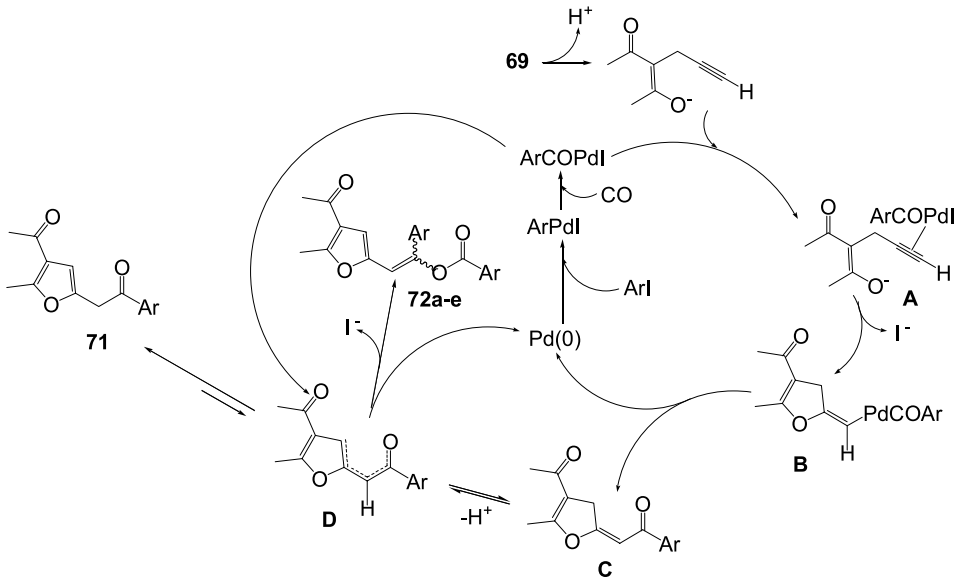
Scheme 27.

The palladium-catalysed reaction of 3-acetyl-5-hexyn-2-one with aryl iodides **70** under a CO atm produced different 2,3,5-trisubstituted furans **71**, and **72** depending on the alkyne/aryl iodide ratio (Scheme 28).[49]

An investigation of the influence of the catalysts, temperature and the **69**:**70** ratio on the reaction outcome has shown that palladium complexes with weakly coordinated ligands gave satisfactory results. The use of $Pd(OAc)_2/P(o\text{-tol})_3$, as a catalytic system, in acetonitrile, under a CO atmosphere at 60 °C and a **69**:**70** ratio of 2:3 enabled a chemoselective synthesis of **71**. Both $Pd(OAc)_2$ and $(PhCN)_2PdCl_2$, in the absence of phosphine ligands, were also effective catalysts.



Scheme 28.



Scheme 29.

The authors proposed that the cyclisation of **69** can be rationalised according to the following sequence: (a) formation of the oxidative addition complex ArPdI between ArI and a Pd^0 species generated in situ; (b) carbonylation of ArPdI to give the σ-acylpalladium intermediate ArCOPdI; (c) generation of the π-alkynyl-palladium complex **A**; (d) generation of the σ-vinyl-palladium complex **B** via the regioselective *trans* addition of oxygen and palladium across the carbon–carbon triple bond (*exo*-dig process); and (e) reductive elimination of **C** to give Pd^0, followed by isomerisation of **C** to **71** (Scheme 29). Upon changing the **69**:**70** ratio from 2:3 to 3:1, further acylation of **D** was achieved by the capture of acylpalladium intermediates ArCOPdI furnishing the enol esters **72** as the sole product.[49]

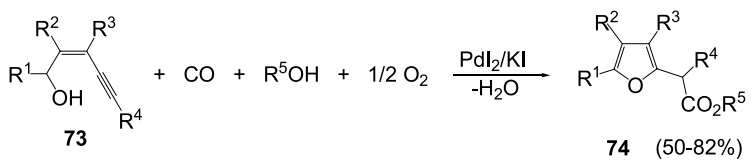
Gabriele et al. have shown that carbonylation of (*Z*)-2-en-4-yn-1-ols **73** under oxidative conditions gave the substituted furan-2-acetic acid esters **74** in good yields (Scheme 30). The cyclisation–alkoxycarbonylation process occurs in alcoholic media at 50–70 °C and under 100 atm pressure of a 9:1 mixture of CO and air in the presence of catalytic amounts of PdI_2 in conjunction with KI.[50]

The proposed reaction pathway involves the in situ isomerisation of the initially formed (*E*)-2-[(alkoxy-carbonyl)methylene]-2,5-dihydrofuran species **75** and **75a**, which in some cases have been isolated and proved to be the intermediates (Scheme 31).

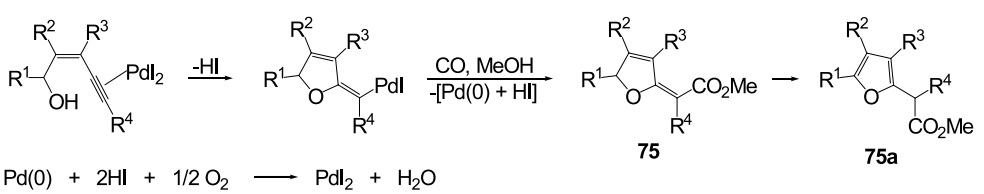
15. Synthesis of substituted pyrroles

Gabriele et al. have found recently that carbon dioxide effectively promotes the Pd-catalysed oxidative cyclisation–alkoxycarbonylation of (*Z*)-(2-en-4-ynyl)amines **76**, leading to the pyrrol-2-acetic acid esters **77** (Scheme 32).[51] In the absence of carbon dioxide, the yields of the pyrroles **77a**,**b** were lower (45 and 36% respectively) in addition to a mixture of the competitive cycloisomerisation products being formed.

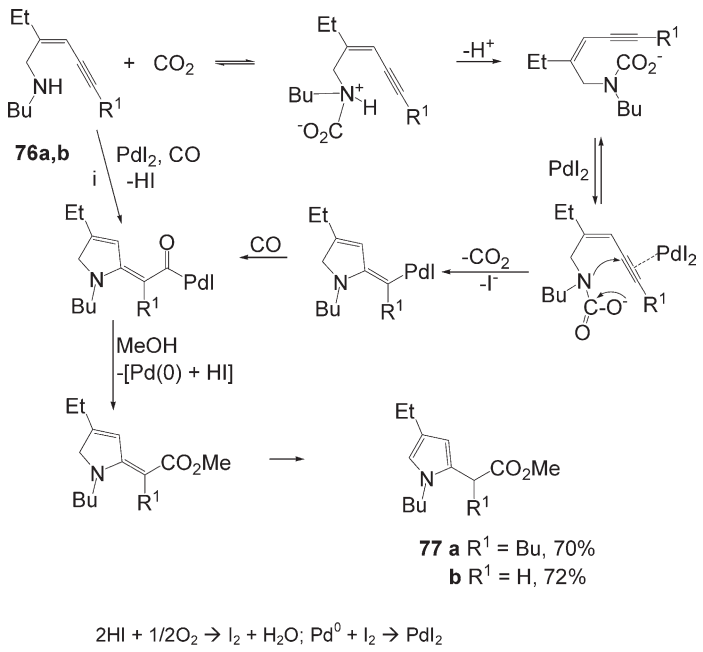
A convenient and general method for the formation of substituted pyrroles from an alkyne, an imine and carbon monoxide has been developed by Gao et al.,[52] who reported that the titanium–acetylene complexes **78**, which were generated in situ from the acetylenes, $Ti(OiPr)_4$ and *i*PrMgX



Scheme 30. R^1=H, Pr, Et, Ph; R^2=H, Et, Ph; R^3=H, Me, Et, Ph; R^4=H, Bu, Ph, TMS; R^5=Me, Bu.



Scheme 31.



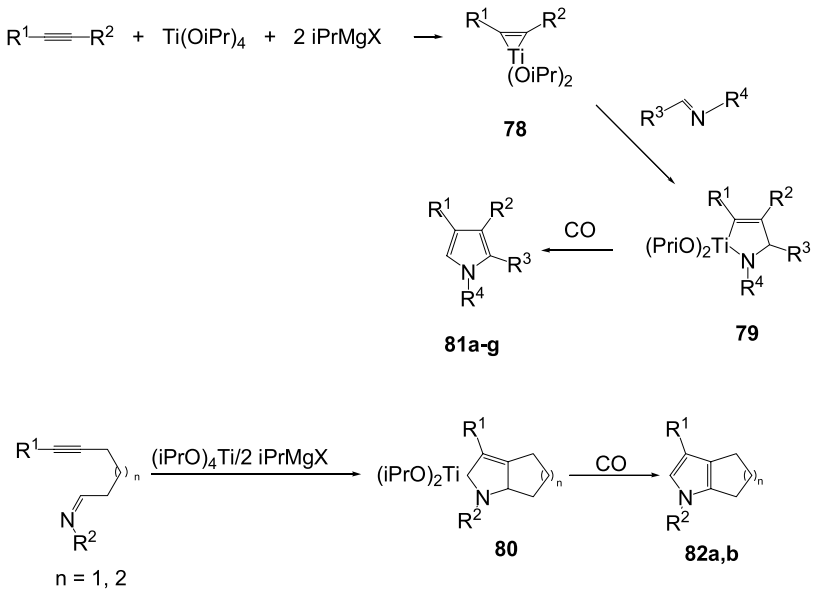
Scheme 32. (i) PdI_2:KI:**76** mol ratio=1:200:100, CO (30 atm), air (10 atm), CO_2 (50 atm), conc. −0.05 mmol/ml, MeOH, 70 °C, h.

(X=Cl or Br), react with imines to afford the azatitanacyclopentenes **79**. Similarly, bicyclic azatitanacyclopentenes **80** are formed from unsaturated imines, $Ti(OiPr)_4$ and *i*PrMgX (Scheme 33). Treatment of **79** and **80** with CO afforded the products **81** and **82**, respectively.

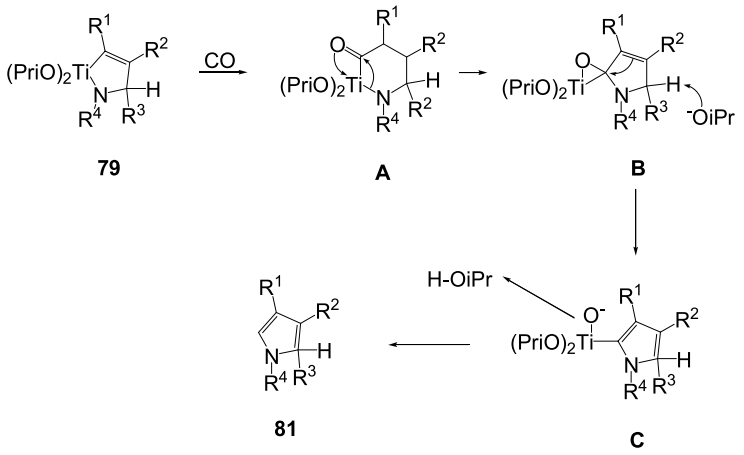
The authors proposed that insertion of CO into the Ti–C bond of **79** would produce the metallacyle **A**. Migration of the nitrogen atom from titanium to the acyl carbon would produce the titanium complex **B**. The intermediate **B** may undergo prototropic rearrangement induced by the *i*PrO anion (generated by the reaction of $Ti(OiPr)_4$ with *i*PrMgCl) to give **C** which affords the pyrrole **81** by alcoholysis with *i*PrOH produced in situ (Scheme 34).

16. Synthesis of 2*E*-[(methoxycarbonyl)methylene]tetrahydrofurans

4-Yn-1-ols **83a-d** bearing a terminal carbon–carbon triple bond undergo oxidative cycliation alkoxycarbonylation in methanol at 70 °C and 100 atm of a 9:1 mixture of CO/air in the presence of catalytic amounts of $[PdI_4]^{2-}$ in conjunction with an excess of KI to give the 2*E*-[(methoxycarbonyl) methylene]tetrahydrofurans **84a-d** in good yields, together



Scheme 33. 81: **a** R^1=R^2=R^4=Pr, R^3=Ph, (61%); **b** R^1=$SiMe_3$, R^2=C_6H_{13}, R^3=Ph, R^4=Pr, (71%); **c** R^1=$SiMe_3$, R^2=C_6H_{13}, R^3=Et, R^4=CH_2Ph, (74%); **d** R^1=$SiMe_3$, R^2=$(CH_2)_3OTBS$, R^3=Ph, R^4=Pr, (64%); **e** R^1=$SiMe_3$, R^2=$(CH_2)_3Br$, R^3=Ph, R^4=Pr, (63%); **f** R^1=$SiMe_3$, R^2=C_6H_{13}, R^3=$(CH_2)_3CH$, R^4=iPr, (67%); **g** R^1=$SiMe_3$, R^2=iPr, R^3=Ph, R^4=Pr, (76%). **82**: **a** R^1=$SiMe_3$, R^2=iPr, n=1 (84%); **b** R^1=$SiMe_3$, R^2=iPr, n=2 (82%).



Scheme 34.

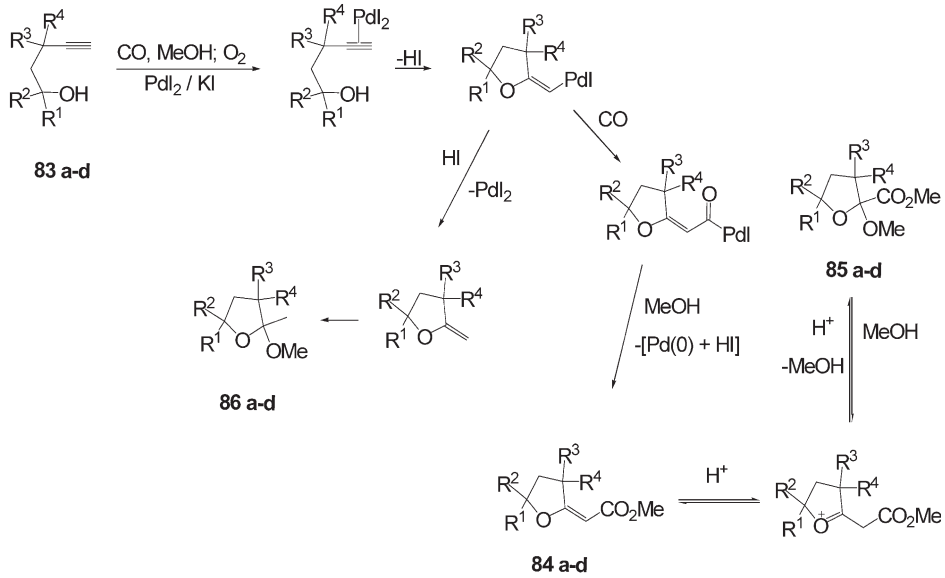
with the products **85**, which can be derived from methanol addition to the vinyl ethereal bond of **84**. A competing reaction, cyclic isomerisation and hydromethoxylation, leads to the 2-methoxy-2-methyltetrahydrofurans **86**, and this can be easily curtailed by increasing the KI excess. Alternatively, the latter products can be prepared from 4-yn-1-ols and MeOH in high yields using the same catalytic system and without a KI excess in the absence of CO (Scheme 35).[53]

Kato et al. presented the first example of asymmetric cyclisation–carbonylation of cyclic-2-methyl-2-propargyl-1,3-diols **87** catalysed by palladium(II) with chiral bisoxazolines. The reaction of **87** in the presence of palladium(II)-chiral ligands/*p*-benzoquinone in methanol at 0 to −40 °C under a carbon monoxide atmosphere (balloon) afforded the (*E*)-bicyclic-β-alkoxyacrylates **88** (Scheme 36) in excellent yields with moderate enantioselectivities.[54]

The oxidative cyclisation carbonylation of 4-yn-1-ones **89** in the presence of $(MeCN)_2PdCl_2$/*p*-benzoquinone in methanol under a CO atmosphere (balloon) afforded the 5-methoxy-2*E*-[(methoxycarbonyl)methylene]tetrahydrofurans **90** (Scheme 37).[55] The products **90** can be easily converted into the 2-cyclopentenone carboxylates **91**.

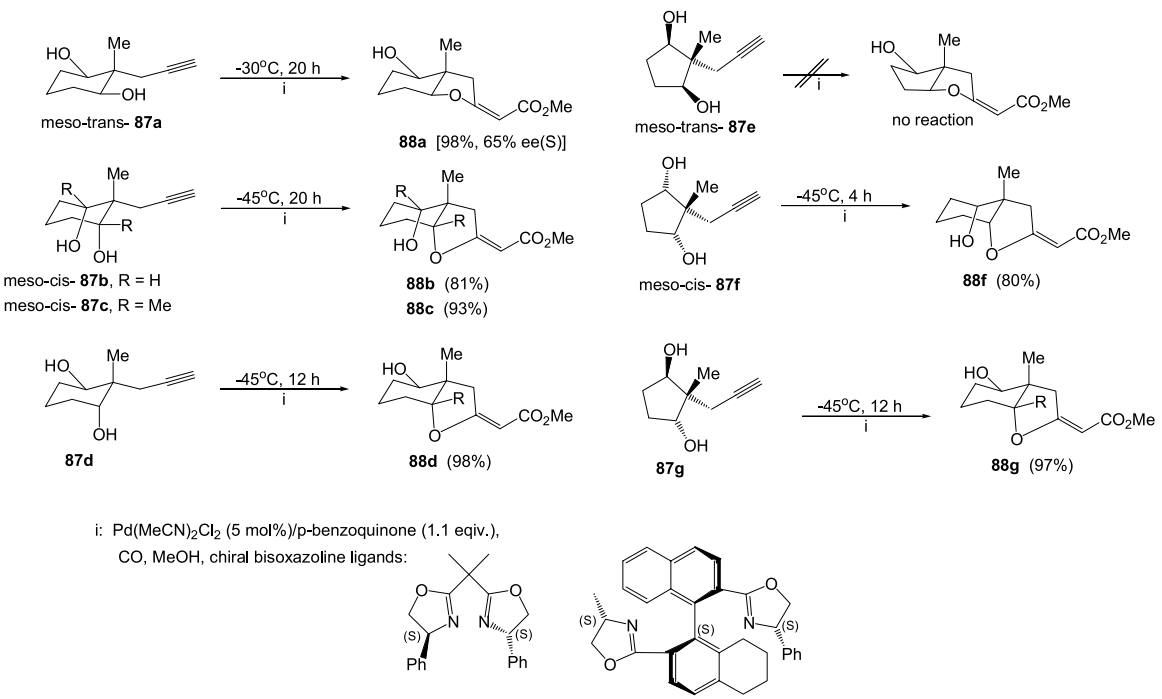
A conceivable mechanism of the reaction may be proposed as shown in Scheme 38 on the basis of the experimental results.

Recently, Kato et al. reported the first example of asymmetric cyclisation–carbonylation of the 2-propargyl-1,3-diones **92** and **94** into the substituted 2*E*-[alkoxycarbonyl)methylene]tetrahydrofurans **93** or **95**, the reaction

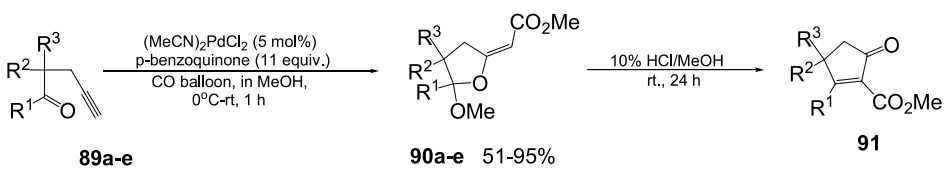


$$Pd(0) + 2HI + 1/2\ O_2 \rightarrow PdI_2 + H_2O$$

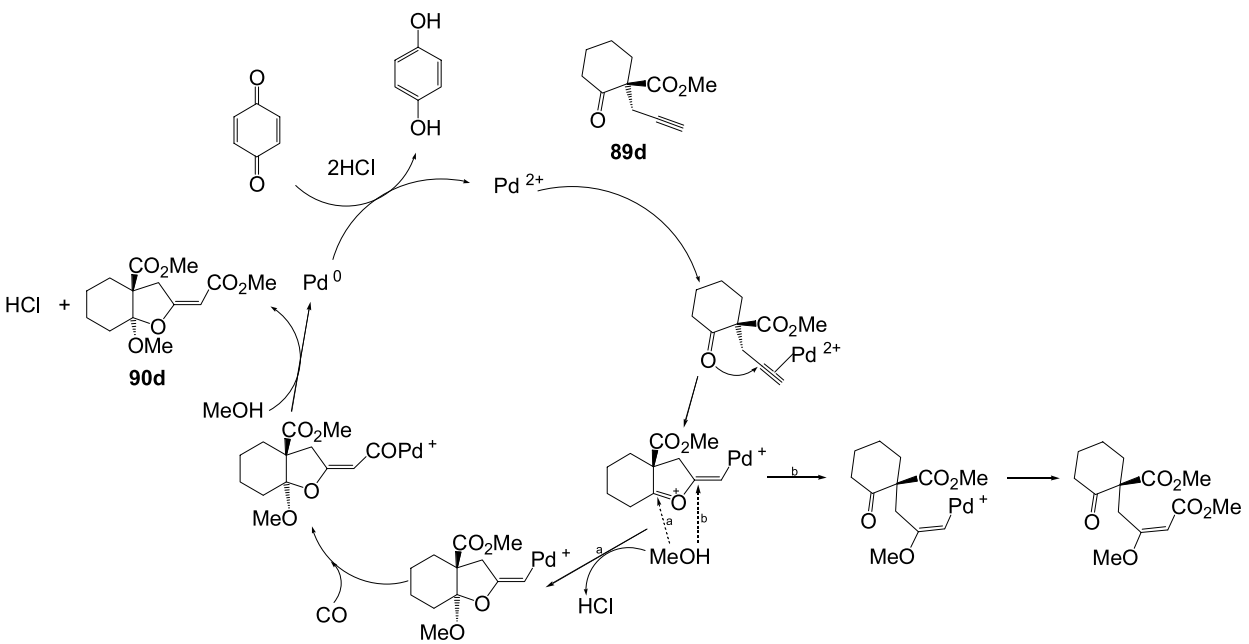
Scheme 35. a $R^1{=}R^2{=}R^3{=}R^4{=}H$, **84** 24%, **85** 40%, **86** 15%. **b** $R^1{=}Me$, $R^2{=}R^3{=}R^4{=}H$, **84** 32%, **85** 45%, **86** 16%. **c** $R^1{=}R^2{=}Me$, $R^3{=}R^4{=}H$, **84** 41%, **85** 37%, **86** 13%. **d** $R^1{=}R^2{=}H$, $R^3{=}R^4{=}Me$, **84** 29%, **85** 19%, **86** 20%.



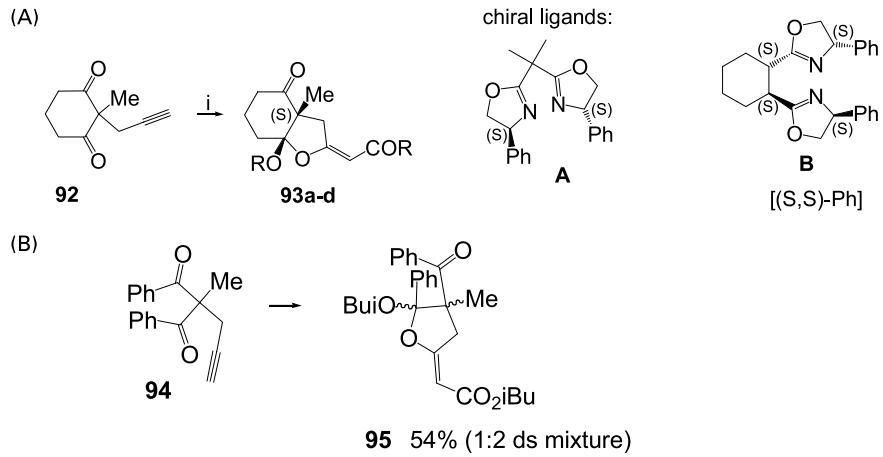
Scheme 36.



Scheme 37. 88: **a** R^1=R^3=Me, R^2=CO_{23}Me, (82%); **b** R^1=Me, R^2=CO_2Me, R^3=H (51%); **c** R^1=$(CH_2)_3CO_2$Me, R^2=Me, R^3=H, (95%); **d** R^1 R^2=$(CH_2)_4$, R^3=CO_2Me (64%); **e** R^1 R^2=$(CH_2)_4$, R^3=CO_2Et (70%).



Scheme 38.



Scheme 39. (A) (i) $Pd(CF_3CO_2)_2$ (5 mol%), chiral ligand (5 mol%); *p*-benzoquinone (1.1 equiv.), CO, ROH (solvent). **93**: **a** R=Me, yield 90%, ee 8% (*R*) with ligand A; **b** R=*i*Pr, yield 54%, ee 33% (*S*) with ligand A; **c** R=Bu, yield 62%, ee 27% (*S*) with ligand A; **d** R=*i*Bu, yield 48%, ee 43% (*S*) with ligand A; yield 54%, ee 59% (*R*) with ligand B. (B) (i) $Pd(CO_2CF_3)_2$ (5 mol%), ligand A (5 mol%), CO, *i*BuOH, 0 °C, 48 h.

being catalysed by palladium(II) with chiral bisoxazolines. The use of the chiral bisoxazolines **A** and **B** has given the best enantioselectivity among all of the investigated chiral ligands[56] (Scheme 39).

17. Unusual formation of cyclic orthoesters

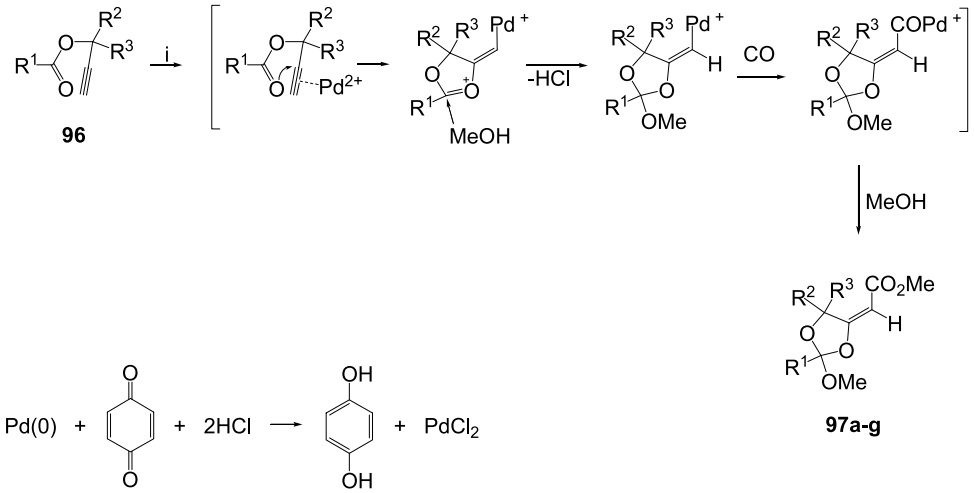
Kato et al. reported the oxidative cyclisation methoxycarbonylation of the propargylic acetates **96** in the presence of $(MeCN)_2PdCl_2$/*p*-benzoquinone in methanol under CO atmosphere which afforded the (*E*)-cyclic-orthoesters **97** in moderate yields (Scheme 40).[57]

18. Facile stereoselective synthesis of oxathiolanes

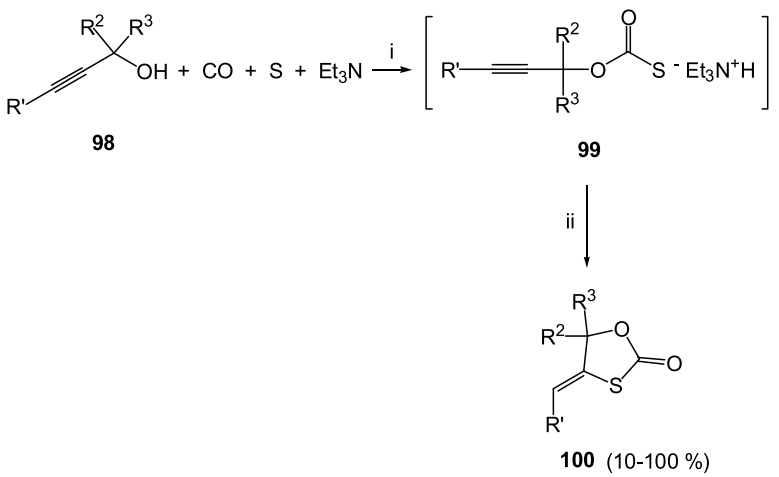
The stereoselective interaction of alkynols **98** with elemental sulphur, carbon monoxide and triethylamine offers the salts **99**. The latter salt can be cyclised into 4-alkylidene-2-oxo-1,3-oxathiolanes **100** under catalytic conditions (Scheme 41). CuI was shown to have the best activity among the various studied catalysts (CuCl, $CuCl_2$, CuBr, $CuBr_2$, CuI, $CuSO_4$, $FeCl_2.4H_2O$, $FeCl_3$, $CoCl_2$, $CoBr_2$, CoI_2, $NiCl_2$, $ZnCl_2$, $ZnBr_2$, ZnI_2 and $PdCl_2$).[58]

19. Stereoselective synthesis of selenium-containing heterocycles

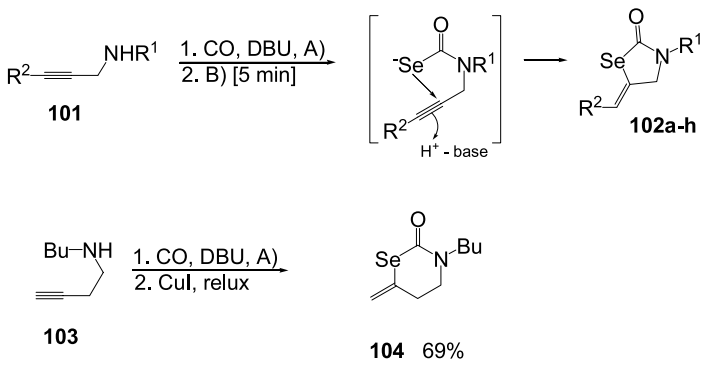
Carbonylation of the aminoalkynes **101** and **103** with carbon monoxide in the presence of selenium provides access towards carbamoselenoate intermediates, which subsequently undergo intramolecular cycloaddition to furnish the corresponding alkylideneselenazolinones **102** and **104**. The reaction of the internal aminoalkynes **101g**, and **101h** afforded the products **102g**, and **102h** as the *Z*-isomers exclusively (Scheme 42).[59]



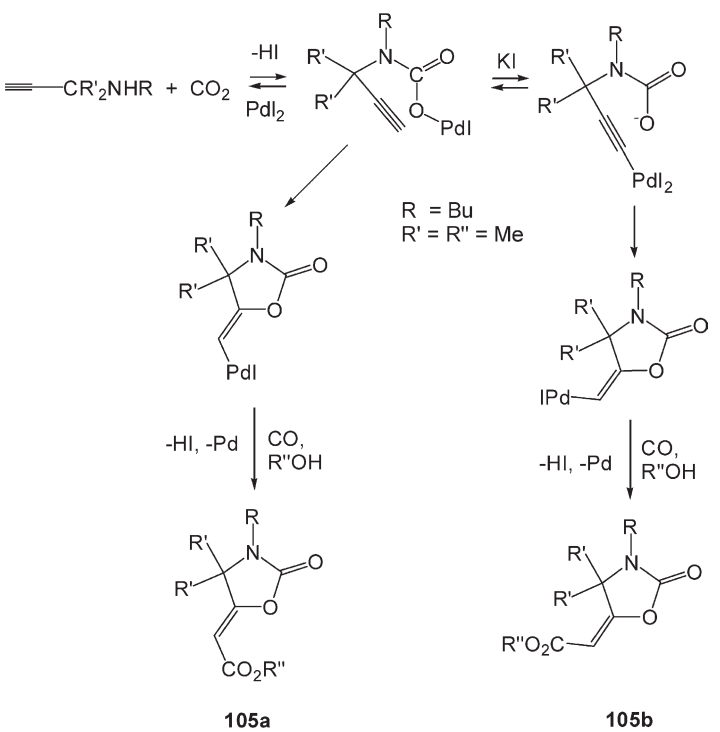
Scheme 40. (i) $(MeCN)_2PdCl_2$(5 mol%), p-benzoquinone (1.1 equiv.), CO (balloon), MeOH, 0 °C or rt. 0.5–7.0 h. **97**: **a** R^1=Me, R^2 R^3=$(CH_2)_5$, yields 65%; **b** R^1=Me, R^2 R^3=$(CH_2)_6$, yield 65%; **c** R^1=Me, R^2=Me, R^3=CH_2Bn, yield 61% (as a 2:1 diastereomeric mixture); **d** R^1=Me, R^2 R^3=$(CH_2)_2$-N(BOC)-$(CH_2)_2$, yield 71%; **e** R^1=Ph, R^2 R^3=$(CH_2)_5$, yield 80%; **f** R^1=*p*-NO_2Ph, R^2 R^3=$(CH_2)_5$, yield 21%; **g** R^1=*p*-MeOPh, R^2 R^3=$(CH_2)_5$, yield 83%.



Scheme 41. (i) THF, 30 atm, 80 °C, 4 h; (ii) CuI, rt, 18 h R′, R^2, R^3=H, Me, Et, CH_2OH, Ph.

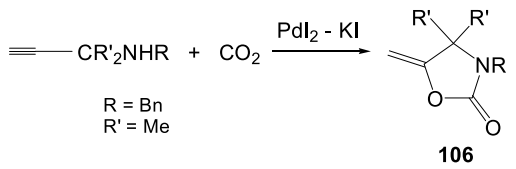


Scheme 42. 102: R^2=H; **a** R^1=Bu, 95%; **b** R^1=i-Pr, 56%; **c** R^1=Cy, 76%; **d** R^1=t-Bu, 10%; **e** R^1=Ph, 0%; **f** R^1=H, 0%; **g** R^1=Bu, R^2=Et, 68%; **h** R^1=Bu, R^2=$SiMe_3$, 22%. (A) 0.8 equiv. Se, THF, 25 °C, 1 atm [1.5 h]; (B) conc. aq. NH_4Cl, 25 °C.



$$2HI + {}^1/_2O_2 \rightarrow H_2O + I_2; \quad Pd + I_2 \rightarrow PdI_2$$

Scheme 43.



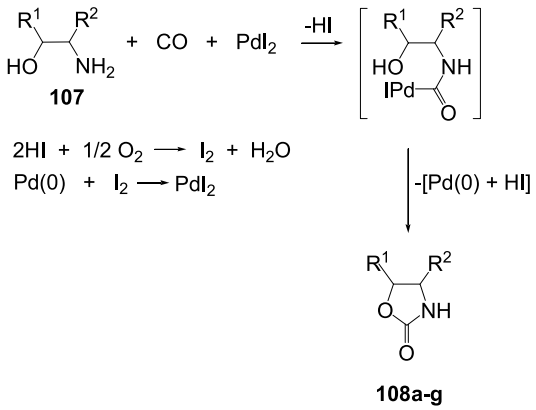
Scheme 44.

20. Oxazolidin-2-ones synthesis

Chiusoli et al. have shown for the first time that upon simultaneous interaction of the propargyl-alkylamines with carbon monoxide and a carbon dioxide catalysed by PdI_2 or Pd^0/C in the presence of KI, sequential carboxylation and alkoxycarbonylation reactions proceed, leading to the (*Z*)- and (*E*)-[(alkoxycarbonyl)methylene]oxazolidin-2-ones **105a** and **105b**[60,61] (Scheme 43).

In the absence of carbon monoxide, only the oxazolidinone **106** was formed (Scheme 44).

Recently, the same authors have shown that the 2-oxazolidinones **108** are obtained in excellent yields (up to 100%) with unprecedented catalytic efficiencies (up to 2000 mol product/mol of used catalyst) by the direct PdI_2/KI-catalysed oxidative carbonylation of the readily available 2-amino-1-alkanols **107** (Scheme 45). The reactions are carried out in MeOH as the solvent at 100 °C using a 1:6:5 $CO:O_2$:air mixture (60 atm total pressure at 25 °C).[62] The authors believe that a large excess of iodide anion and oxygen are primarily required to ensure a fast re-oxidation of Pd^0, according to Scheme 45.



Scheme 45. 108: **a** R^1=R^2=H, 90%; **b** R^1=Me, R^2=H, 100%; **c** R^1=Ph, R^2=H, 87%; **d** R^1=H, R^2=Me, 93%; **e** R^1=H, R^2=Ph, 98%; **f** R^1=H, R^2=Me_2CH, 100%; **g** R^1=H, R^2=$PhCH_2$, 86%.

21. Formation of substituted lactams

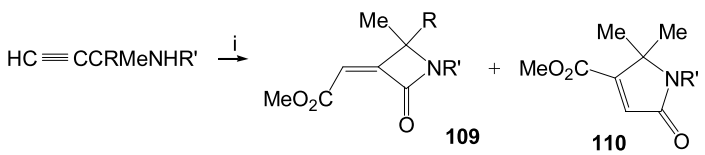
α-Methylene-β-lactams **109** are formed by carbonylation of α,α-disubstituted propargyl-alkylamines and γ-lactams **110** are formed from unsubstituted or acylated amines[63] (Scheme 46).

Mori and Ochifuji have developed a protocol for synthesizing the lactams **112-115** using the alkynes **111a-f** having an amide function in the molecules.[64] The reaction proceeds via a vinylketene complex **A**, generated from the alkyne and the Fisher chromium carbene complex, and the lactam ring was formed from carbon monoxide, alkyne, and the tosylamide nitrogen atom. The four-, five-, six-, and seven-membered lactams **112a-d** having a substituent at the α-position were obtained in good yields (Scheme 47).

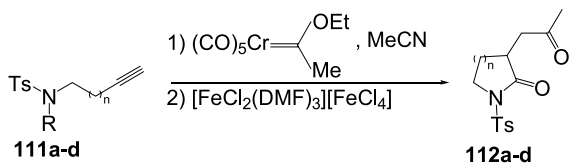
The cyclocarbonylation of the 1,6- and 1,7-yne-imines **116a-e** to the bicyclic α,β-unsaturated lactams **117a-e** can be achieved in the presence of a catalytic amount of $Ru_3(CO)_{12}$ (Scheme 48). The reaction, a [2+2+1] cycloaddition, incorporates the acetylene π-bond, and the carbon atom of CO. The presence of substituents, such as alkyl, aryl, and silyl on the acetylenic terminal carbon is essential for the yne-imines to undergo cyclocarbonylation to give the bicyclic α,β-unsaturated lactams. The absence of substituents on the acetylenic terminal carbon does not offer the corresponding lactam, but rather a dihydropyridine derivative without the incorporation of CO.[65]

Alper and Van den Hoven have shown[66] that the tandem cyclohydrocarbonylation/CO insertion of the α-iminoalkynes **118a-o** requires CO, H_2 and catalytic quantities of the zwitterionic rhodium complex (η^6-$C_6H_5BPh_3$)Rh^+(1,5-cod) with triphenyl phosphite in order to gain the aldehyde-substituted pyrrolinones **119a-e** or **120f-o** in 67–82% yields. This transformation is readily applied to iminoalkynes containing alkyl, alkoxyl, vinyl, and aryl substituents (Scheme 49) and gives an attractive route to prepare highly functionalised pyrrolinones, which are important and versatile pharmaceutical. The authors discussed the postulated mechanism of **119** formation, which includes the generation of the active rhodium complex $HRhL_x$ binding to the acetylenic imine **118** via the triple bond and the imine, followed by intramolecular hydrorhodiation, and subsequent carbonylation cyclisation with a second CO insertion ended by hydration.

Alcaide et al. have found that the [2+2+1] carbonylative cyclisation of 2-azetidinone tethered allenynes **121** lead to the fused tricyclic β-lactams **123** bearing a central seven-membered ring as a single isomer. The cycloadducts **123** presumably arise from the isomerisation of the initially formed adducts **122** (Scheme 50). Conjugation of the

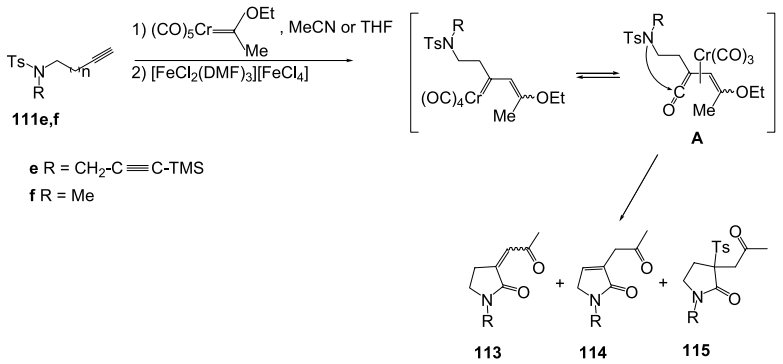


Scheme 46. R=Me, Et; R′=CH_2Ph, Alk, H, CH_2Alk. (i) CO/air, Pd^0/C, KI, MeOH.



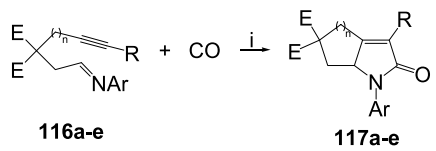
a R = H, $SiMe_3$, n = 0
b R = H, $SiMe_3$, n = 1
c R = H, n = 2
d R = H, n = 3

a n = 0, R = H (16%), R = $SiMe_3$ (50%)
b n = 1, R = H or $SiMe_3$ (85%)
c n = 2, R = H (82%)
d n = 3, R = H (84%)



R = CHC≡CTMS	22%	21%	0
R = Me	17%	0	13%

Scheme 47.



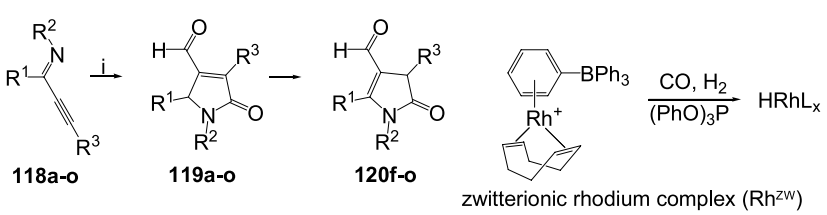
Scheme 48. 116, **117**: E=COOEt; Ar=*p*-$MeOC_6H_4$. **117 a** R=$SiMe_3$, n=1 (66%); **b** R=Ph, n=1 (45%); **c** R=Et, n=1 (43%); **d** R=$(CH_2)_2OBn$, n=1 (43%); **e** R=$SiMe_3$, n=2 (51%). (i) $Ru_3(CO)_{12}$ (5 mol%), toluene, CO (5 atm), 160 °C, 20 h.

dienone moiety with the lone pair of the nitrogen atom is believed to promote the formation of the compound **123**.[67]

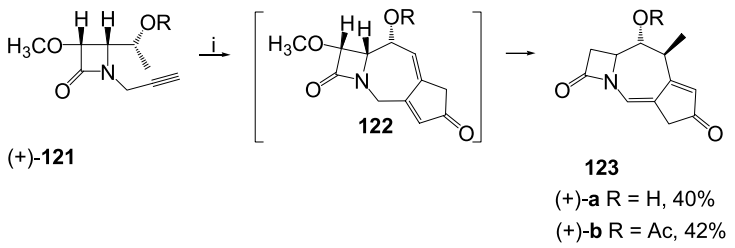
22. Synthesis of 2-(*Z*)-6-(*E*)-4*H*-[1,4]-thiazepin-5-ones

Van den Hoven and Alper have reported the cyclohydrocarbonylative ring expansion of the acetylenic thiazoles **124** in the presence of CO, H_2, catalytic quantites of the zwitterionic rhodium complex (η^6-$C_6H_5BPh_3$)Rh^+(1,5-cod) and triphenyl phosphite to furnish the 2-(*Z*)-6-(*E*)-4*H*-[1,4]-thiazepin-5-ones **125** in 61–90% yields.[68] Thiazepinones are pharmacologically important compounds for the treatment of cancer, heart and inflammatory diseases. This novel transformation of a five- to a seven-membered heterocycle is readily applied to acetylenic thiazoles containing hydro, alkyl, alkyl halide, vinyl, and benzo substituents in positions 4 and 5 of the thiazole ring, in addition to alkyl-, ether-, ester-, vinyl- and aryl-substituted alkynes at position 2 (Scheme 51).

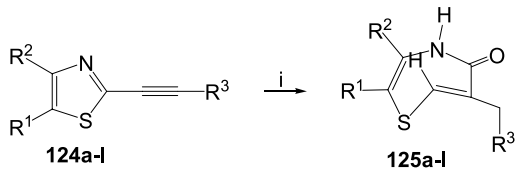
The authors propose a possible mechanism for the conversion of the acetylenic thiazoles **124** to the thiazepin-5-ones **125** (Scheme 52). The active rhodium complex $HPhL_x$, formed from the (η^6-$C_6H_5BPh_3$)Rh^+(1.5-cod)



Scheme 49. (i) Rh^{ZW} (2 mol%), $(PhO)_3P$ (8 mol%), CH_2Cl_2, CO/H_2 (21–42 atm), 75–100 °C, 18–36 h. **119a-e** R^1=Me, R^3=Et; **a** R^2=*n*-Bu (82%); **b** R^2=*i*Pr, (79%); **c** R^2=Cy (80%); **d** R^2=$CH_2[CHO(CH_2)_3]$ (73%); **e** R^2=$(CH_2)_2Ph$, (75%). **119**, **120f-j** R^1=Ph, R^2=*n*-Bu; **f** R^3=*n*-Bu, (78%); **g** R^3=Me, (72%); **h** R^3=[=$C(CH_3)_2$] (67%); **i** R^3=*i*-Pr; **j** R^3=CH_2–Cy (79%). **119**, **120k-o** R^2=*i*Pr; R^3=*n*-Bu; **k** R^1=Ph (80%); **e** R^1=*p*-MeC_6H_4 (81%); **m** R^1=*p*-MeC_6H_4 (78%); **n** R^1=*p*-ClC_6H_4 (72%); **o** R^1=β-napth (75%).

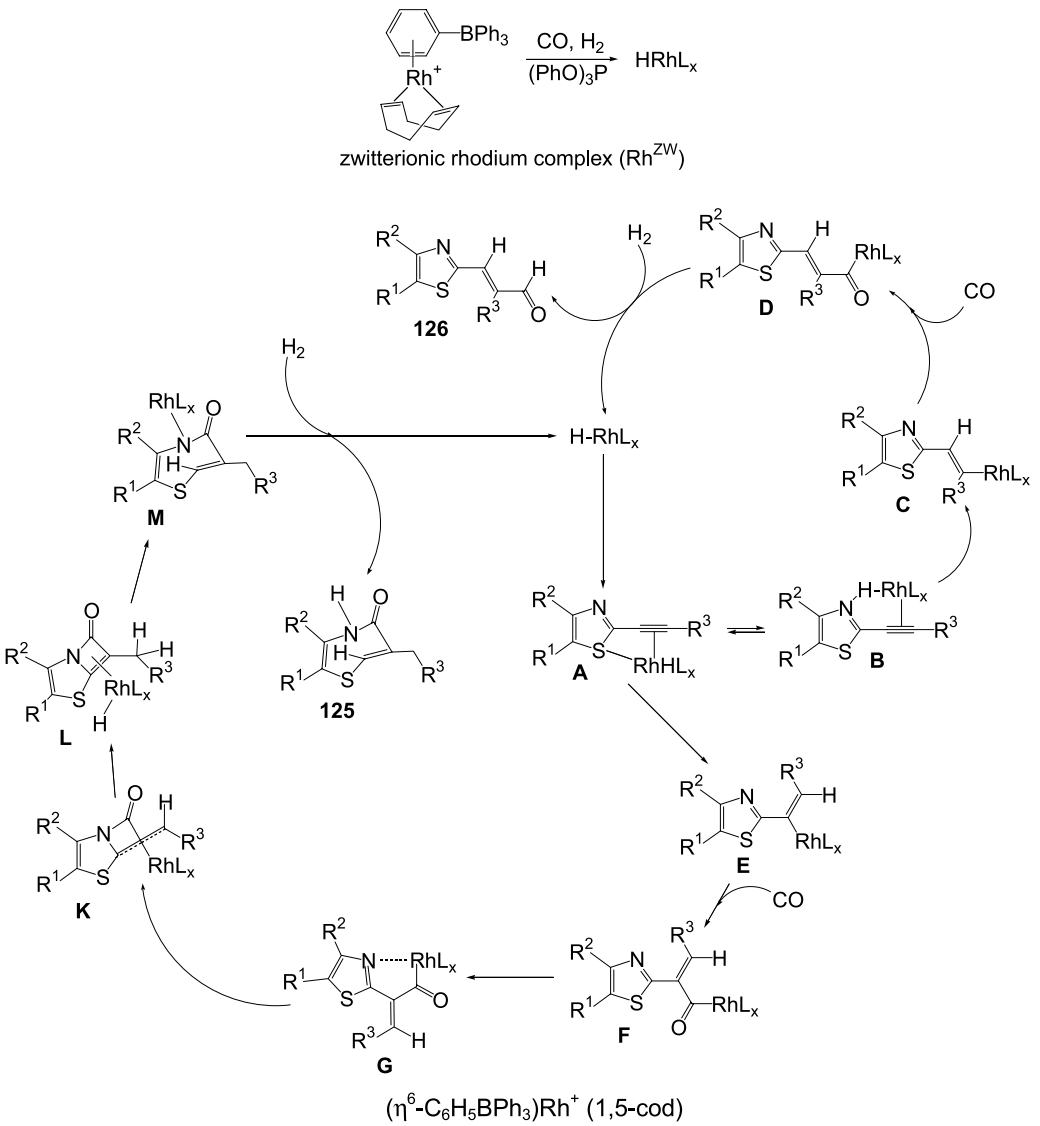


Scheme 50. (i) CO, $Co_2(CO)_8$ (1.1 equiv.), Me_3NO (2 equiv.), CH_2Cl_2, rt.

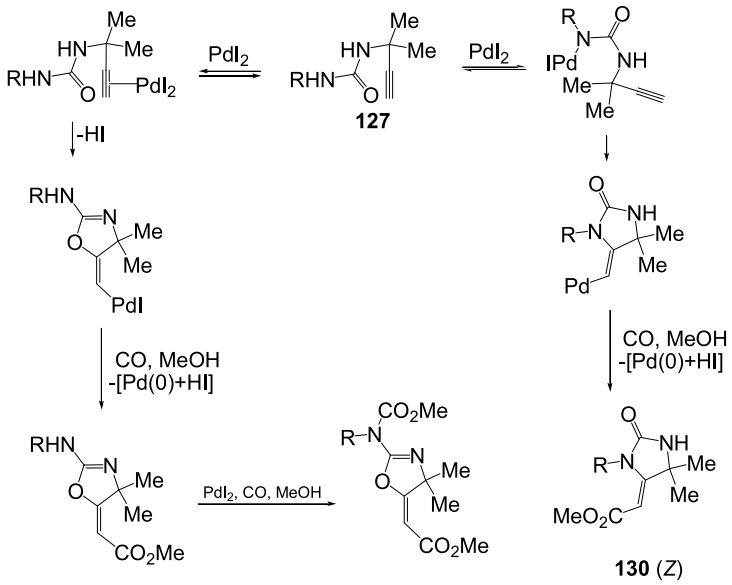


Scheme 51. (i) Rh^{ZW} (2 mol%), $(PhO)_3P$ (8 mol%), 21 CO/H_2 (1:1, 21 atm), CH_2Cl_2, 110 °C, 18–36 h. **125a-g** R^1=R^2=H; **a** R^3=*n*-Bu (86%); **b** R^3=*t*-Bu (89%); **c** R^3=Ph (90%); **d** R^3=*n*-MeC_6H_4 (87%); **e** R^3=*i*-Pr (72%); **f** R^3=CH_2OMe (74%); **g** R^3=$CH_2OC(O)Me$ (61%). **125h-l** R^3=*n*-Bu; **h** R^1=H, R^2=Me (83%); **i** R^1=R^2=Me (78%); **j** R^1=$(CH_2)_2Cl$, R^2=Me (78%); **k** R^1=CH(Me)C(O)H, R^2=Me, (81%); **l** R^1R^2=$(CH)_4$, (76%).

complex, binds to the thiazolyne **124** via the triple bond and a heteroatom (**A**) or possibly by H-bonding to the thiazole ring (**B**). Depending on the equilibrium between **A** and **B** two products may result. If **B** is favoured, subsequentent intramolecular insertion of the H–Rh bond into the alkyne would generate **C**. Carbonylation of the latter and subsequent addition of hydrogen to **D** would give the hydroformylation product **126**. On the other hand, if **A** is favoured, the intramolecular hydroformylation would proceed in the opposite manner to form **E**, carbonylation of which would give **F** and coordination with the heterocyclic nitrogen could then afford **G**. The intermediate



Scheme 52.



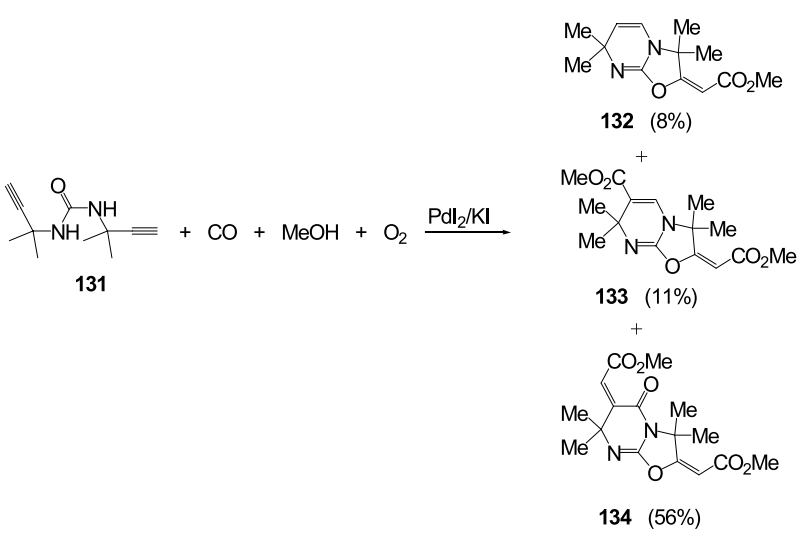
127		128 (%)	129 (%)	130 (%)
a	R = Pr	**a** 70	3	23
b	R = CH_2Ph	**b** 33	-	53
c	R = Ph	**c** 34	33	7
d	R = p-MeC_6H_4	**d** 47	-	35
e	R = H	**e** -	28	46

Scheme 53.

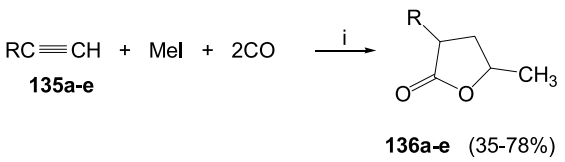
G can undergo intramolecular cyclisation, resulting in the formation of a β-lactam with allyl-type bonding to Rh (**K**). Hydrogen addition to **K** may afford a strained azetidinone-Rh hydride **L**. Hydrogen transfer with ring opening would form **M** as the *E*-isomer, with nitrogen coordinated to the rhodium. Addition of hydrogen completes the thiazepinone ring **125** and regenerates the rhodium complex $HRhL_x$.

23. Heterocycles from acetylenic ureas

Chiusoli et al. have shown that acetylenic ureas **127** readily undergo oxidative cyclisation–alkoxycarbonylation reactions in the presence of PdI_2- (or Pd/C)–KI as a catalyst in methanol under mild conditions (65 °C and 24 bar of a 3:1 mixture of CO and air).[69] Cyclisation occurs by *trans*-attack of oxygen or *cis*-attack of nitrogen functions on the triple



Scheme 54.



Scheme 55. a R=Ph, **b** R=$(CH_2)_2$Ph, **c** R=Bu, **d** R=Hex, **e** R=p-MeC_6H_4. (i) $Mn(CO)_5Br$ (1 equiv.), 5 N NaOH, CH_2Cl_2, $[PhCH_2NEt_3]^+Cl^-$-, 35 °C, CO (1 atm).

bond, followed by stereospecific carbonylation, resulting in (*E*)-**128**, (*E*)-**129** or (*Z*)-**130**, respectively (Scheme 53).

In the case of cyclisation–alkoxycarbonylation of the diacetylenic ureas **131**, condensed ring **132**-**134** formation occurs (Scheme 54). The structure of the main product **134** was determined by X-ray diffraction. It contains an (*E*)- and a (*Z*)-(methoxycarbonyl)methylene chain which were bonded to the condensed oxazoline and pyrimidinone rings, respectively.[69]

24. Synthesis of lactones

The alkynes **135a-e** react with methyl iodide, bromopentacarbonylmanganese (or dimanganese decacarbonyl), and carbon monoxide under phase-transfer catalysis conditions to give the 2,4-disubstituted γ-butyrolactones **136a-e**. The reaction conditions are mild (35 °C, 1 atm), and the process is regiospecific (Scheme 55).[70]

The α-substituted lactones **139** can be formed in a one-pot reaction of the alkynes **137** bearing a hydroxyl or silyloxyl group with the Fischer chromium carbene complex **138**. The reaction proceeds in a highly stereoselective manner (Scheme 56), and the desired monocyclic and bicyclic lactones **139** were obtained in good yields (Table 4).[71]

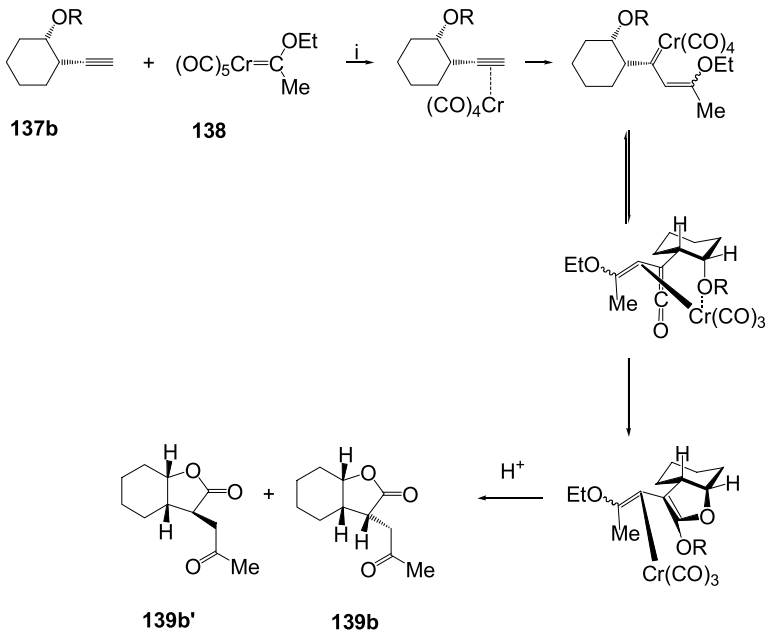
When the carbonylation of 5-hydroxy-1-pentyne was carried out in the presence of benzenethiol and $Pt(PPh_3)_4$ (3 mol%) under 3 atm of CO at 120 °C for 4 h, the cyclocarbonylation took place successfully to attain α[(phenylthio)methyl]-δ-lactone **140** selectively in a high yield (Scheme 57).[72]

25. α-Methylene-γ- and -δ-lactone synthesis

Novel synthetic methods for α-methylene-γ-butyrolactones are of interest owing to the high biological activity of these compounds and the wide spectrum of physiological action of natural products containing an α-methylenelactonic unit, for example, elephantopin, euparotin acetate and vernolepin, which show antitumor activity,[73] and the natural sesquiterpene lactone, phantomolin, which shows cytotoxic activity.[74] The method for catalytic cyclocarbonylation of acetylene alcohols is not compatible with the other methods and is not of great interest, owing to the low yields of α-methylene-γ-butyrolactones such as **141**, which was attained by reacting 3-butyn-1-ol with stoichiometric amount of nickel tetracarbonyl[75] (Scheme 58).

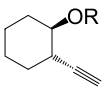
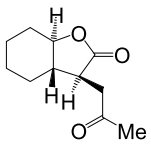
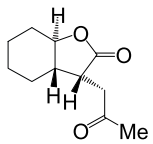
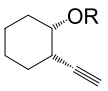
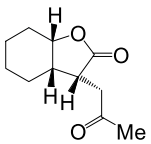
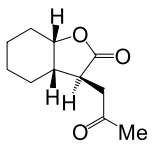
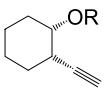
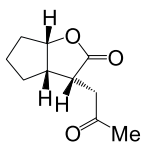
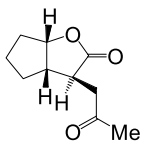
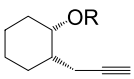
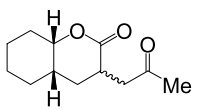
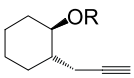
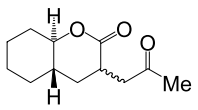
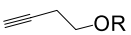
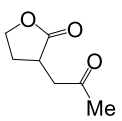
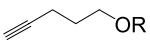
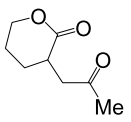
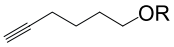
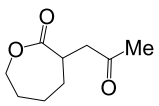
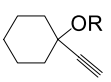
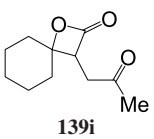
Later, Norton et al. developed a general method of α-methylenelactone **142** synthesis in mild conditions, which was based on cyclocarbonylation of ethynyl alcohols on organopalladium complexes as catalysts[76,77] (Scheme 59).

A comparative study of the ability of the various catalytic systems to cyclocarbonylate acyclic and cyclic alcohols showed that system comprising $PdCl_2$, anhydrous $SnCl_2$ and 2 equiv. of a tertiary phosphine in acetonitrile is the most favoured. In this system, not only α-methylene-γ-lactones, but also -δ-lactones, of various structure in *cis*- and *trans*-fused rings can be synthesised in rather high yields, if the substrate concentration is kept sufficiently low (0.1–1.0 M), to direct the reaction into an intramolecular cyclisation. A study of the cyclocarbonylation mechanism showed that a carboalkoxy intermediate species is initially formed from



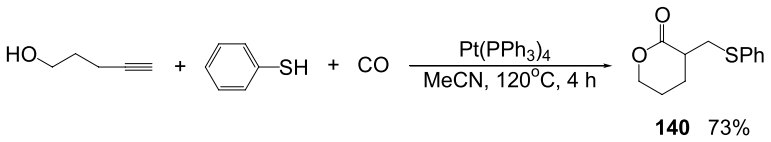
Scheme 56. (i) (1) **138** (1.2 equiv), MeCN, 70 °C, 0.5 h. (2) $[FeCl_2(DMF)_3][FeCl_4]$ (3 equiv.).

Table 4. Construction of lactones **139** from various alcohols and silyl ethers

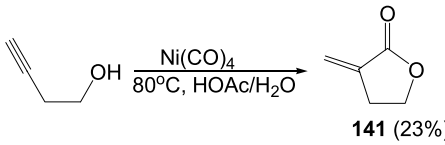
	Substrate **137**	Products **139**, **139′**	Yield (%)	Ratio (139:139′)
a		 **139a**  **139′**	R=H 85	92:8
b		 **139b**  **139b′**	R=H 94 R=TBS 76	94:6 48:52
c		 **139c**  **139c′**	R=H 94 R=TBS 96	93:7 98:2
d		 **139d**	R=H 78 R=TBS 100	70:30 85:15
e		 **139d**	R=H 89 R=TBS 57	59:41 66:34
f		 **139f**	R=H 86 R=TBS 43	
g		 **139g**	R=H 62 R=TBS 53	
h		 **139h**	R=H 63	
i		 **139i**	R=H 30	

Pd(II), CO and the acetylene alcohol, followed by intramolecular *cis* addition to the triple bond[77,78] (Scheme 60).

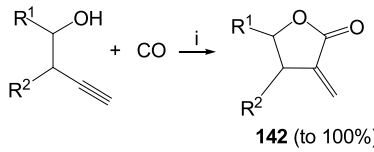
Competitive intermolecular insertion of the triple bond in another substrate can occur, leading to dimeric and polymeric products. Cleavage of the vinyl-palladium bond was achieved by the initially generated proton and the product was then obtained in addition to the regeneration of the initial Pd(II) complex. In the course of their mechanistic



Scheme 57.



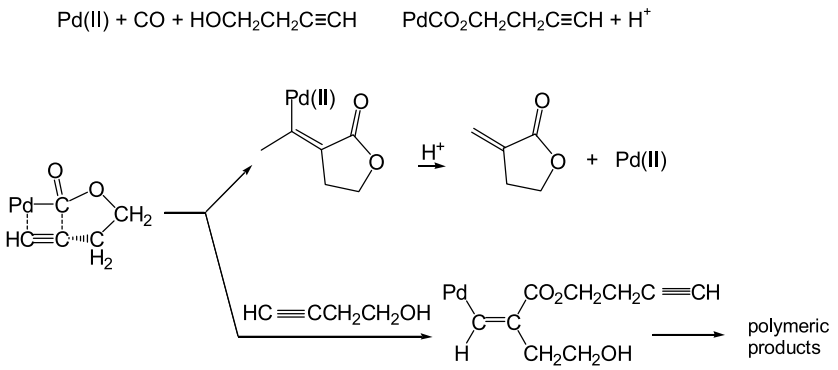
Scheme 58.



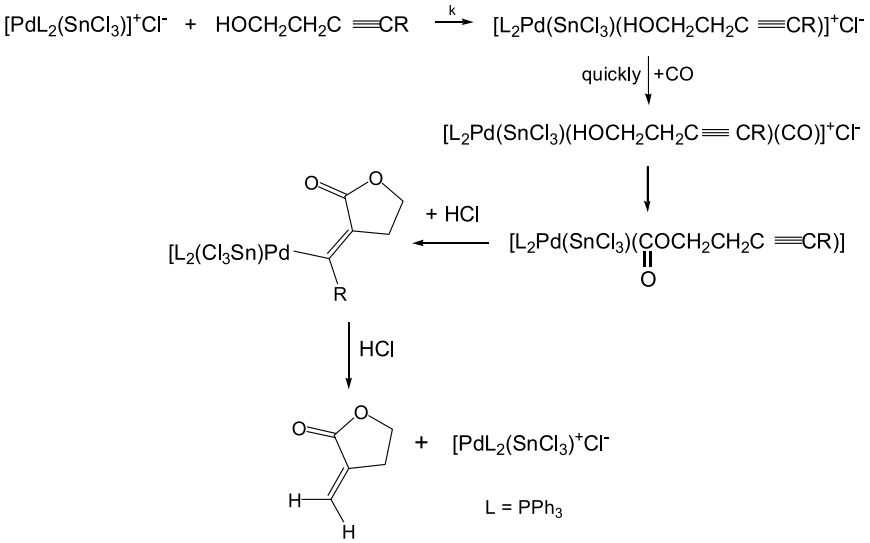
Scheme 59. R^1, R^2=H, $(CH_2)_2Br$, $(CH_2)_2CH=CH_2$, $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$. I: $PdCl_2$ (0.07 equiv.), $SnCl_2$ (0.07 equiv.), PPh_3 (or PBu_3) (0.14 equiv.), CO (to 7.8 atm), MeCN, 65–75 °C.

studies, the authors proposed a much more efficient Pd(II) catalyst system with $SnCl_2$ as a cocatalyst which has a role in labilising the palladium coordination sphere. As in PdI_2/Bu_3P/MeCN catalyst system, the rate-determining step is evidently the uptake of CO by Pd. Similarly, in the second catalyst system ($PdCl_2/2Ph_3P/SnCl_2$/MeCN), the rate-determining step is coordination of the substrate, followed by rapid uptake of CO and completion of the cyclocarbonylation reaction[78] (Scheme 61).

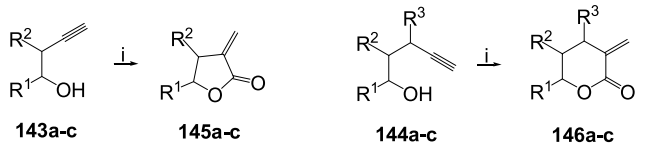
Dupont et al. have shown that the carbonylation of terminal 3-alkyn-1-ols **143a-c** and 4-alkyn-1-ols **144a-c** by $Pd(OAc)_2$ associated with 2-(diphenylphosphino)pyridine (2-$PyPPh_2$) dissolved in organic solvents, or in 1-butyl-3-methyl imidazolium ionic liquids, afforded quantitatively and selectively the *exo*-α-methylene-γ- and -δ-lactones **145a-c**, and **146a-c**, respectively (Scheme 62). When the reactions were performed in ionic liquids (biphasic conditions), the lactones **145a-c**, and **146a-c** were isolated



Scheme 60.



Scheme 61.



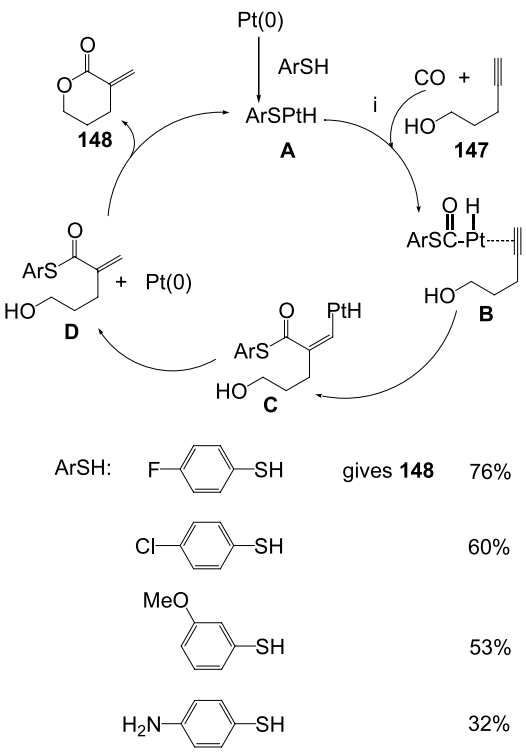
Scheme 62. 145 a R^1=R^2=H (97% yield); **b** r^1=Me, R^2=H (99%); **c** R^1 R^2=$(CH_2)_4$ (99%). **146 a** R^1=R^2=R^3=H (98%); **b** R^1 R^2=$(CH_2)_4$, R^3=H (50%); **c** R^1=H, R^2 R^3=$(CH_2)_4$ (93%). (i) $Pd(OAc)_2$/2-$PyPPh_3$/$MePhSO_3$-H/alkynol=1/10 /10 /1000, toluene, CO (25 atm), 60 °C, 2 h.

by simple distillation, which enabled the re-use of the ionic catalyst solution.[79]

The carbonylative lactonisation of 5-hydroxy-1-pentyne **147** to produce α-methylene-δ-lactone **148** has been found to proceed efficiently by using catalytic $Pt(PPh_3)_4$ in the presence of small amounts of aromatic thiols. A possible reaction pathway for this carbonylative lactonisation is depicted in Scheme 63 and comprises: (1) oxidative addition of ArSH to low-valent platinum generating the ArS–[Pt]–H species (**A**), which undergoes coordination of the hydroxyacetylene **147** and insertion of CO to form species **B**; (2) regioselective acylplatination leading to species **C**, followed by reductive elimination to produce the α,β-unsaturated thioester **D** and Pt(0); and (3) intramolecular cyclisation of **D** to provide α-methylene-δ-lactone **148** and ArSH, the latter adding oxidatively to Pt^0 and regenerating the catalyst **A**.[72]

26. Stereoselective synthesis of (*Z*)-α-(alkoxycarbonyl)methylene-β- and -γ-lactones

(*Z*)-α-(Alkoxycarbonyl)methylene-β- **150** and -γ-lactones **152** can be obtained in fair to excellent yields using the catalytic system (PdI_2/KI) to efficiently catalyse the oxidative dialkoxycarbonylation of propynyl alcohols (α,α-dialkyl-substituted or α-monoalkyl-substituted) with a sufficiently bulky alkyl group **149** and but-3-yn-1-ols **151**, respectively. The reactions are carried out in alcoholic media under mild conditions (70–80 °C and 20 atm of a 3:1 mixture of CO and air) (Scheme 64).[80,81] Possible reaction pathways are discussed.[80,81]



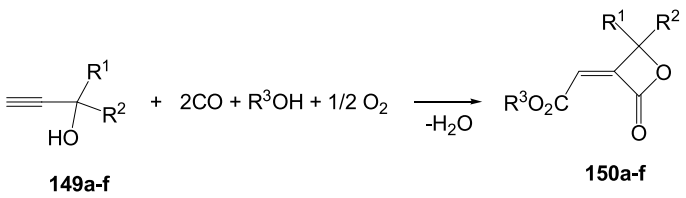
Scheme 63. (i) $Pt(PPh_3)_4$ (3 mol%), ArSH (10 mol%), MeCN, 120 °C, CO (30 atm), 4 h.

The presence of alkyl substituents α to the triple bond is essential in order to achieve a high selectivity for the β-lactones **150**. The yields of the β-lactones derived from α-monoalkyl-substituted propynyl alcohols are very low if the alkyl group is not sufficiently hindered. But-3-yn-2-ol **149f** produced only 2% of the corresponding β-lactone **150f** at 80% conversion. The maleic diester **153** (50%), its cyclic tautomer **154** (9%), the fumaric derivative **155** (12%) and the γ-lactone **156** (6%) accounted for the converted substrate (Scheme 65). In contrast to the propynyl alcohols, α substitution of the triple bond in but-3-yn-1-ols **151** is not necessary in order to direct the carbonylation process towards ring closure to give the γ-lactones selectively, and but-3-yn-1-ol **151a**, pent-4-yn-2-ol **151b** and *cis*-2-ethynylcyclopentan-1-ol **151d** were, in fact, converted into their corresponding γ-lactones **152a**, **152b** and **152d** in excellent yields. When the dialkyl substitution α to the triple bond was as in **151c**, the reaction was slower and the product yield of the γ-lactone **152** was lower. If the cyclisation is not favoured by molecular geometry, as in the case of *trans*-2-ethynylcyclopentan-1-ol **151e**, the product distribution changes, favouring the maleate, and the γ-lactone **152e** is the byproduct.[80]

Palladium (II)-catalysed dicarbonylation of the 4-(trimethylsilyl)-3-butyn-1-ols **157a** and **157b** in the presence of propylene oxide and ethyl orthoacetate in methanol–dichloromethane under a carbon monoxide atmospheric pressure afforded the *cis*-dicarbonylated α-methylene-γ-butyrolactones **158a**, and **158b**, respectively. On the other hand, the 4-alkyl- and 4-aryl-3-butyn-1-ols **157c-g**, undergo *trans*-alkoxycarbonylation across the triple bond and selectively furnish the (*E*)-tetrasubstituted α-methylene-γ-butyrolactones **159c-g** (Scheme 66).[82]

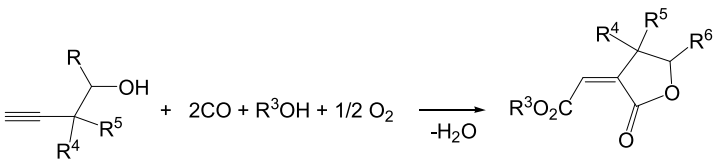
27. Formation of α-(triorganosilyl)methylene-β-, -γ- and -δ-lactones

Cyclocarbonylation of the acetylenic alcohols **160**, **163** and **164** with the assistance of an appropriate base and $Rh_4(CO)_{12}$ gave the α-(triorganosilyl)-methylene-β- **161**, -γ- **165**, and -δ- **166** lactones together with the byproducts **167** and **168**. Lactone formation depends on both steric and electronic factors and the ratio of the β-lactone **161** to the 3-silylpropenal **162** was markedly affected by the silane and the base employed in the carbonylation of the acetylenic alcohols **160**. An improvement in the β-lactone selectivity was attained using either a more bulky silane, such as *t*-$BuMe_2SiH$, or a stronger base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[83] (Scheme 67). Carbonylation of **160** without a base, however, resulted in the formation of **162** selectively.



149a-f **150a-f**

a $R^1 = R^2 = Me$	**a** $R^1 = R^2 = R^3 = Me$ (80%)
b $R^1 = Et$, $R^2 = Me$	**b** $R^1 = Et$, $R^2 = R^3 = Me$ (76%)
c R^1 ñ $R^2 = (CH_2)_5$	**c** R^1 ñ $R^2 = (CH_2)_5$, $R^3 = Me$ (57%)
d $R^1 = H$, $R^2 = CHEt_2$	**d** $R^1 = H$, $R^2 = CHEt_2$, $R^3 = Me$ (52%)
f $R^1 = H$, $R^2 = Me$	**e** $R^1 = R^2 = Me$, $R^2 = R^3 = Me$ (22%)
	f $R^1 = H$, $R^2 = R^3 = Me$ (2%)



151a-e **152a-e**

a $R^4 = R^5 = R^6 = H$	**a** $R^4 = R^5 = R^6 = H$, $R^3 = Me$ (86%)
b $R^4 = R^5 = H$, $R^6 = Me$	**b** $R^4 = R^5 = H$, $R^3 = R^6 = Me$ (94%)
c $R^4 = R^5 = Me$, $R^6 = H$	**c** $R^3 = R^4 = R^5 = Me$, $R^6 = H$ (73%)
d $R^4 = H$, $R^5 R^6 = (CH_2)_3$(*cis*)	**d** $R^4 = H$, $R^5 R^6 = (CH_2)_3$ (*cis*), $R^3 = Me$ (93%)
e $R^4 = H$, $R^5 R^6 = (CH_2)_3$(*trans*)	**e** $R^4 = H$, $R^5 R^6 = (CH_2)_3$ (*trans*), $R^3 = Me$ (28%)

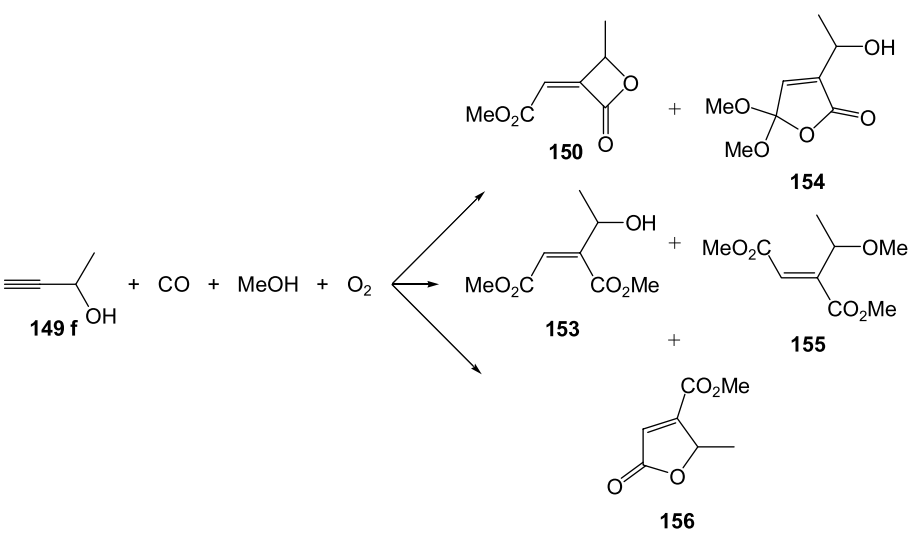
Scheme 64.

The γ-lactone **165** is derived from the homopropargyl-type alcohols **163** with the employment of Me_2PhSiH and Et_3N. Although the combined use of *t*-$BuMe_2SiH$ and Et_3N is required for the formation of the six-membered ring α-silylmethylene, this method is applicable for the selective synthesis of the δ-lactone **166**. The intermediate **A** is proposed to be the common intermediate to give the lactone and propenal derivatives.

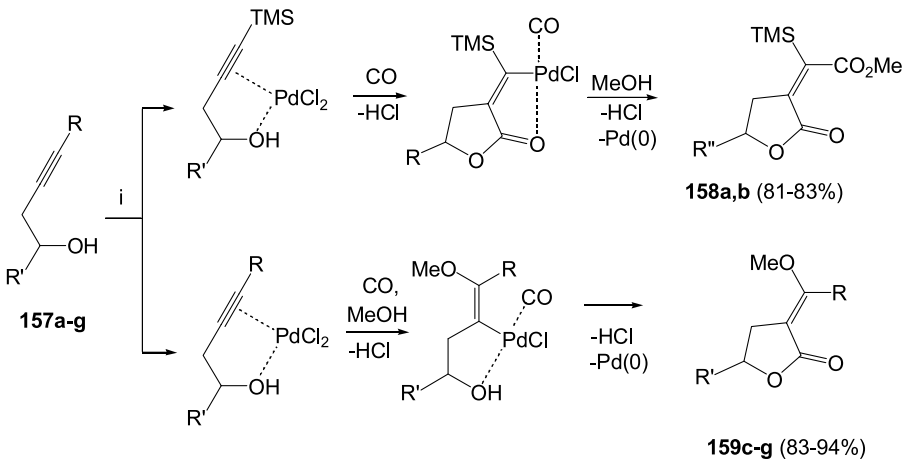
28. Selective synthesis of furan-2(5*H*)-ones

Carbonylation of 2-methylbut-3-yn-2-ol catalysed by $Co_2(CO)_8$ in benzene proceeds with low yield, but 100% selectively, giving 5,5-dimethylfuran-2(5*H*)-one **169** (Scheme 68).[84]

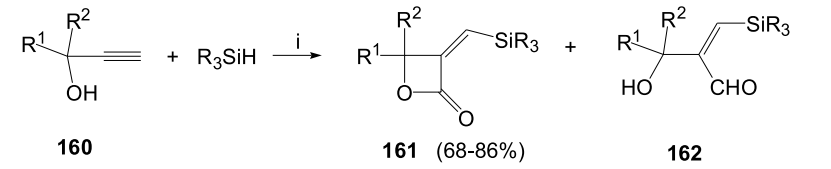
The unsaturated lactone **171** is formed when the alkynol **170**

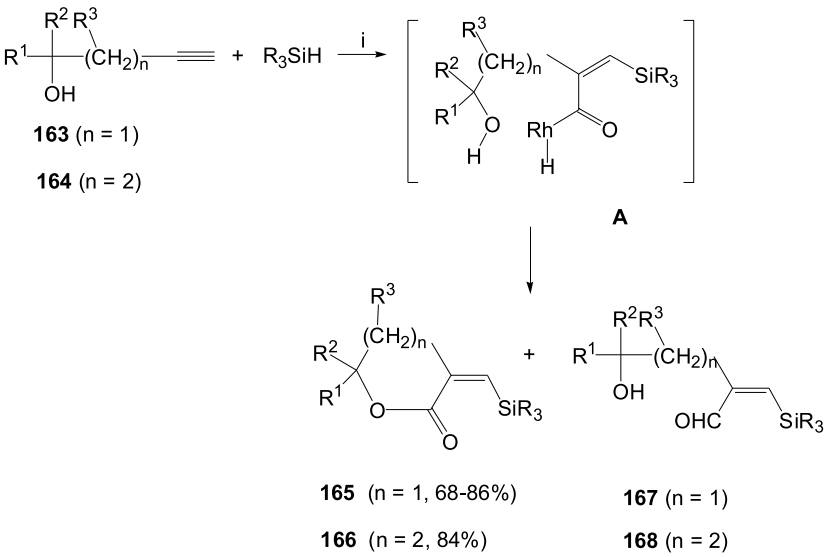


Scheme 65.

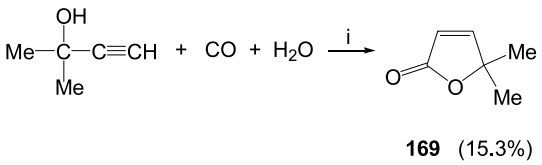


Scheme 66. **a** R=TMS (trimethylsilyl), R=H; **b** R=TMS, R=Me; **c** R=Me, R′=H; **d** R=Et, R=H; **e** R=Et, R=Me; **f** R=t-Bu, R=Me; **g** R=Ph, R=Me. (i) CO (1 atm), $PdCl_2$ (0.01–0.1 equiv.), $CuCl_2$ (3 equiv.), propylene oxide (5 equiv.), $MeC(OEt)_3$ (0.4 equiv.), MeOH, rt.

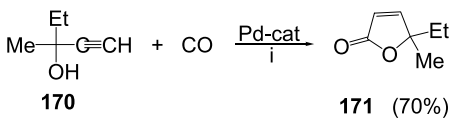




Scheme 67. R^1, R^2=H, Me, $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_6$; R=Me, Ph, tBu, Et, iPr. (i) CO (15–40 kg/cm^2), base (1 equiv. Et_3N, 0.1 equiv. DBU or DABCO—1,4-diazabicyclo[2.2.2]octane), $Rh_4(CO)_{12}$ (0.001 equiv.), 100 °C, benzene.



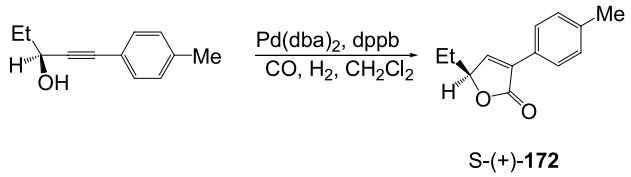
Scheme 68. (i) 150°, 100 atm, $Co_2(CO)_8$ (5 mol%) benzene.



Scheme 69. (i) $Pd(dba)_2$, dppb, DME, CO (20 atm), 150 °C, 48 h.

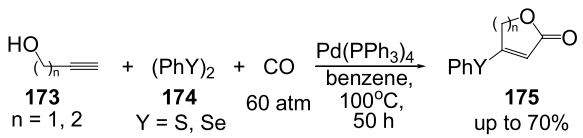
is carbonylated with the palladium(0) catalyst, bis(dibenzylidenacetone)palladium (dba), and 1,4-bis(diphenyl-phosphino)butane (dppb) in 1,2-dimethoxyethane (DME) (Scheme 69).[85]

This method was used for the synthesis of unnatural (*S*)-incrustoporin **172**, the enantiomer of the antifungal antobiotic isolated from the basidiomycete *Incrustoporia carneola* (Scheme 70).[86,87] Ethynyl alcohols also produce 2(5*H*)furanones upon carbonylation using $Pd(MeCN)_2$-$(PPh_3)_2(BF_4)_2$ as catalyst.[88]



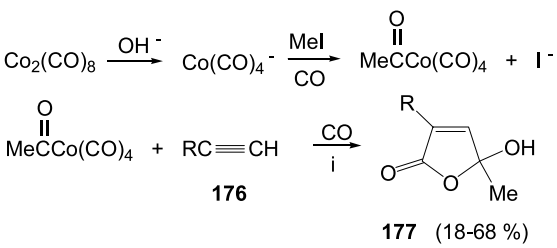
Scheme 70.

A one-pot lactonisation of the alkynols **173** in the presence of the thio–thio or seleno–seleno organic compounds **174** and carbon monoxide occurred to furnish the substituted unsaturated lactones **175** in up to 70% yield (Scheme 71).[89]



Scheme 71.

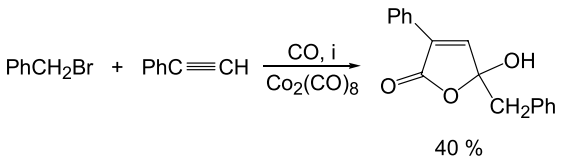
The alkynes **176** react smoothly with CO and MeI in a liquid–liquid two-phase system to yield regioselectivly the corresponding but-2-enolides **177** (Scheme 72), most probably via the intermediate formation of an acylcobalt complex.[90,91]



Scheme 72. R=Ph, Cy, 17-testosteronyl. (i) 5 N NaOH/benzene, CTAB (cetyltrimethylammonium bromide), rt, CO (1 atm).

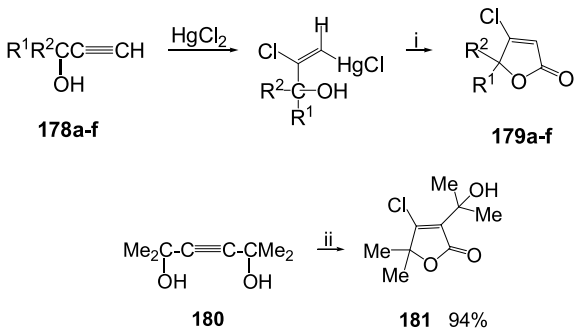
When benzyl bromide was used, no but-2-enolide was formed, due to the fast hydrolysis of the acylcobalt intermediate prior to the alkyne complexation, and phenylacetic acid was the only product obtained. This inconvenience was circumvented by performing the reaction in the absence of water in a solid–liquid system using a new kind of chelating agent, $N[(CH_2)_2O(CH_2)_2OMe]_3$ (TDA), which has the same properties as a crown ether but without the toxicity and the work-up difficulties encountered with the macrocyclic catalysts[92] (Scheme 73).

The mercuration and subsequent carbonylation of the



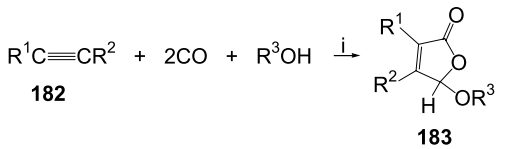
Scheme 73. (i) $Co_2(CO)_8$ (30 mol%), NaOH, TDA (6 mol%), toluene, 60 °C, 12 h, CO (1 atm).

propargylic alcohols **178** or the diol **180** has provided another route to the butenolide (4-chloro-furan-2(5*H*)-one) ring system **179** and **181** in quantitative yields (Scheme 74). Carbonylation can be effected using stoichiometric amounts of palladium chloride and 1 atm of carbon monoxide, or only catalytic amounts of palladium chloride if cupric chloride is used as a re-oxidant and benzene as the solvent.[93,94]



Scheme 74. (i) $PdCl_2$ (1 equiv.), LiCl (2 equiv.), THF, 5 °C, 24 h, MgO (1 equiv.) or none. **179a** R^1=R^2=H, (96%); **b** R^1=R^2=Me (99%); **c** R^1=Me, R^2=Et, (98%); **d** R^1 R^2=$(CH_2)_4$, (96%); **e** R^1 R^2=$(CH_2)_5$ (95%); **f** R^1 R^2=$(CH_2)_6$ (81%). (ii) $HgCl_2$, CO, $LiCl_3$ (2 equiv.), $PdCl_3$, THF, reflux, 5 h, MgO.

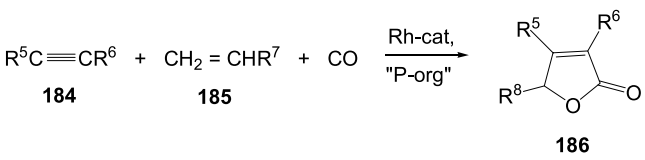
The rhodium carbonyl-catalysed carbonylation of acetylenes in alcohols **182**, giving the 5-alkoxyfuran-2-(5*H*)-ones **183** in satisfactory yields, has been reported (Scheme 75).[95–97] Combinations of rhodium catalysts with various bases were examined and the $Rh_4(CO)_{12}$/NaOAc system was found to be the most suitable catalytic system.[97]



Scheme 75. (i) CO (50 atm), 125 °C, 6 h, $Rh_4(CO)_{12}$ (0.1–0.2 mol%)/-NaOAc (5–10 mol%). **183** R^1=R^2=Ph, R^3=Me (86%); R^3=Et (87%); R^3=*n*-Pr (65%); R^3=*i*Pr (60%); R^3=C_8H_{17} (31%); R^1=R^2=Me, R^3=Et (67%); R^1=R^2=Et, R^3=Et (60%); R^1=Ph, R^2=Me, R^3=Me (54%); R^3=Et (78%); R^1=Me, R^2=Ph, R^3=Me (21%); R^3=Et (15%).

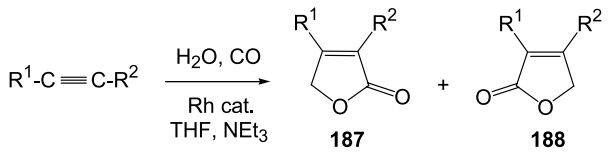
The reaction of the acetylene analogue **184** and the alkenes **185** with CO in the presence of rhodium catalysts and organophosphoric compounds [$PR^1R^2R^3$, $P(OR^1)(OR^2)OR^3$ or $R^1R^2P(CH_2)PR^3R^4$, R^1–R^4=H, alkyl, n=1–4] gives the unsaturated lactones **186** in high yields (Scheme 76).[98]

Doyama, et al. have proposed a general method for the selective synthesis of furan-2(5*H*)-ones **187** and **188** from acetylenes that have been elaborated by water vapour and carbon monoxide (100 atm) in THF containing triethylamine at 100 °C in the presence of a rhodium carbonyl



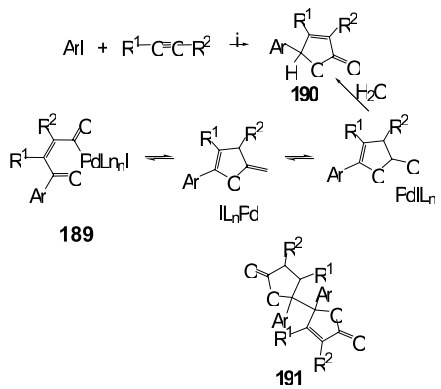
Scheme 76. R^5, R^6=H, Alkyl, Aryl, Silyl, Alkoxycarbonyl, Acyl; R^7=H, Hal, Alkyl, Alkoxycarbonyl, CN, Acyl; R^6=$CH_2CH_2R^7$ or $CHMeR^7$.

cluster catalyst[99,100] (Scheme 77). The isomer ratio of the formed furanones **187** and **188** is dependent on the electronic and steric nature of the substituents, such as the rhodium carbonyl clusters [$Rh_4(CO)_{12}$ and $Rh_6(CO)_{16}$], which were the most efficient among the other tested transition metal complexes tested. Ruthenium carbonyls showed a very low activity and cobalt and iron carbonyls were almost inactive for the present reaction. The presence of amines such as diethylamine or triethylamine is essential for the selective synthesis of furanones. The absence of amines resulted in a marked decrease in both the catalytic activity and product selectivity.

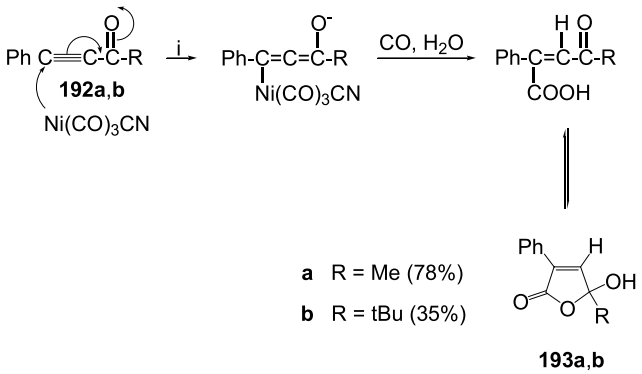


Scheme 77.

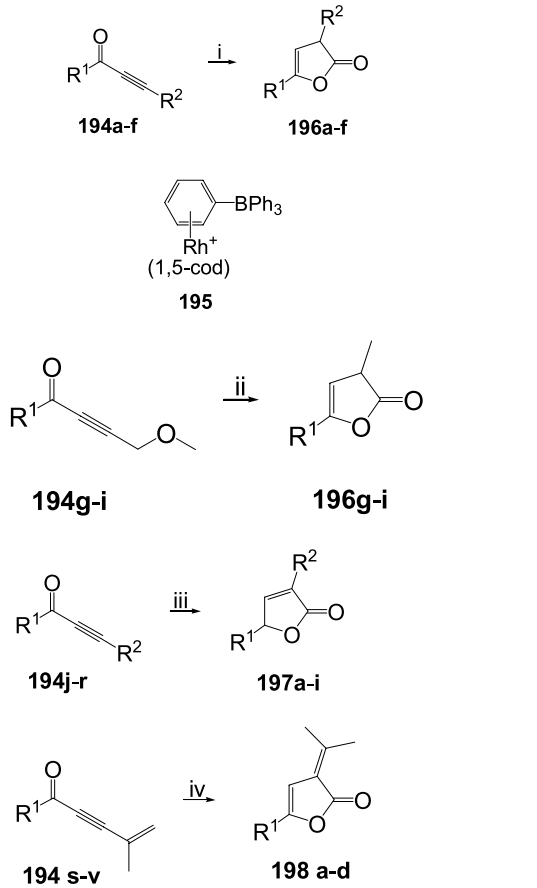
Negishi et al. have reported[101] that the reaction of an internal alkyne—organic halide mixture with CO in the presence of a Pd–phosphine catalyst, for example, Cl_2-$Pd(PPh_3)_2$, can give rise to an acylpalladium derivative that can be represented by **189** as an intermediate which is converted into the corresponding 2-butenolides **190** in the presence of water (H donor). Either in the absence of water (or any other suitable H source) or in the presence of some factors disfavouring the butenolide formation, the same reaction afforded the corresponding dimeric product **191** (Scheme 78).



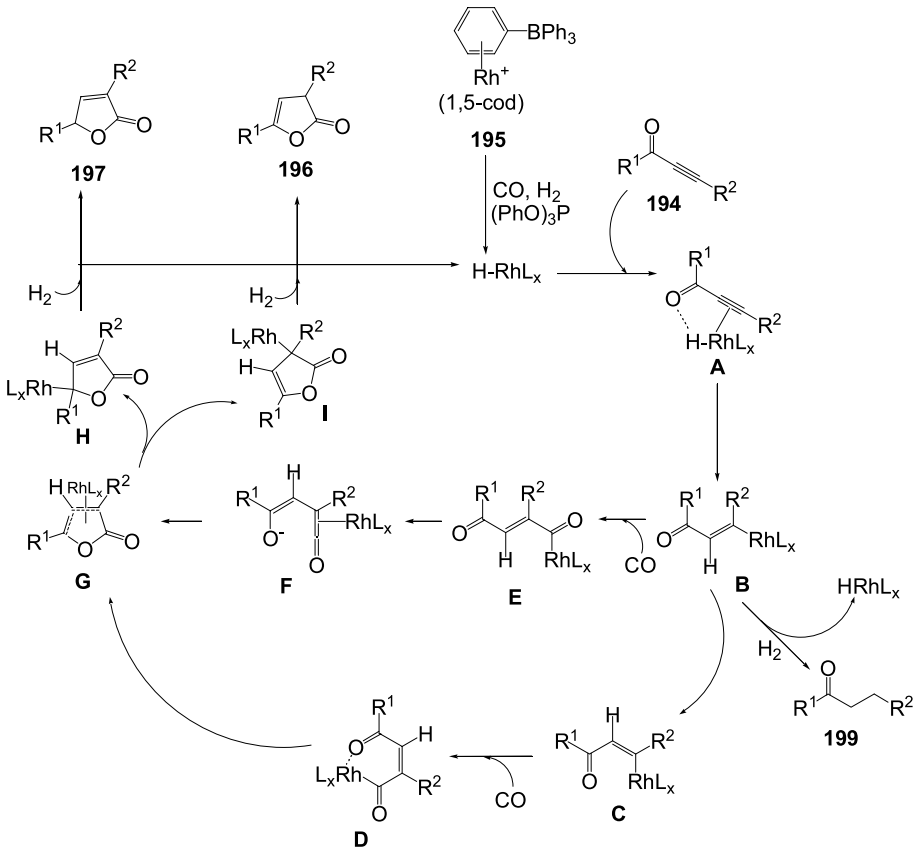
Scheme 78. (i) CO (20 atm), $Cl_2Pd(PPh_3)_2$ (5 mol%), H_2O (1 equiv.), NEt_3 (8 equiv.) or $NaHCO_3$ (4 equiv.), benzene, 130 °C, 20 h. **190**, **191a-c** R^1=R^2=*n*-Pr; **a** Ar=*p*-An (combined yield 66%); **b** Ar=*m*-Tol (comb. yield 50%); **c** Ar=*p*-ClC_6H_4 (comb. yield 40%); **d** R^1=R^2=Bn, Ar=*m*-Tol (comb. yield 42%); **e** R^1=Bu, R^2=*p*-An, Ar=Ph, (comb. yield 65%, **190**:**191**=89:11); **f** R^1=Bu, R^2=R^3=*p*-An, (comb. yield 65%, **190**:**191**=91:9); **g** R^1=Bu, R^2=*p*-An, R^3=*p*-$MeO_2C_6H_4$, (comb. yield 35%, **187**:**188**=91:9); **h** R^1=$SiMe_3$, R^2=Pr, R^3=Ph, (comb. yield 39%, **190**:**191**=94:6); **i** R^1=$SiMe_3$, R^2=Pr, R^3=*p*-An, (comb. yield 37%, **190**:**191**=94:6).



Scheme 79. (i) $Ni(CN)_2{\cdot}4H_2O$ (10 mol%), CO (1 atm), PhMe/5 N NaOH (1:1), TBAB (3 mol%).



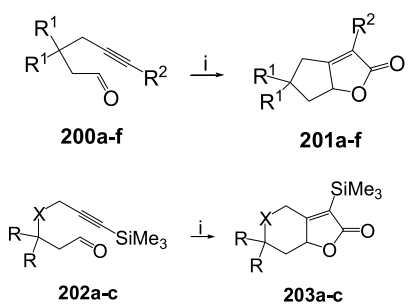
Scheme 80. 194, **196 a** R^1=Me, R^2=Et, (91%); **b** R^1=iPr, R^2=Bu (88%); **c** R^1=CH-Et-Bu, R^2=Bu, (83%); **d** R^1=Cy, R^2=n-Bu (63%); **e** R^1=tBu, R^2=Bu, (64%); **f** R^1=Ph, R^2=Bu (63%). (i) **194** (1.5 mmol), **195** (0.03 mmol) (2 mol%), $(PhO)_3P$, 0.18 mmol (32 mol%), CH_2Cl_2 910 ml), CO (38.5 atm), H_2 (3.5 atm), 90 °C, 21 h. **194**, **196 g** R^1=iPr (92%); **h** R^1=CH-Et-Bu, (91%); **i** R^1=tBu (89%). (ii) **194** 1.5 mmol, **195**, 2 mol%; $(PhO)_3P$, 8 mol%; Cu_2Cl_2 10 ml; CO (17.5 atm), H_2 (3.5 atm), 70 °C, 24–36 h. **197 a** R^1=Me, R^2=Ph (83%); **b** R^1=iPr, R^2=Ph (88%); **c** R^1=CH-Et-Bu, R^2=Ph (87%); **d** R^1=Cy, R^2=Ph (84%); **e** R^1=tBu, R^2=Ph (85%); **f** R^1=R^2=Ph (61%); **g** R^1=2-Fur, R^2=Ph, (67%); **h** R^1=Ph, R^2=Bu (61%); **i** R^1=2-Fur, R^2=Bu (68%). (iii) **194** 1.5 mmol, **195**, 2 mol%; $(PhO)_3P$, 32 mol%; Cu_2Cl_2, 10 ml; CO (38.5 atm), H_2 (3.5 atm), 120 °C, 24–48 h. **198 a** R^1=iPr (71%); **b** R^1=CH-Et-Bu, (76%); **c** R^1=tBu (69%); **d** R^1=Ph (75%). (iv) **194** 1.5 mmol, **195**, 2 mol%; $(PhO)_3P$, 8 mol%; CH_2Cl_2 10 ml; CO (17.5 atm), H_2 (3.5 atm), 70 °C, 24 h.



Scheme 81.

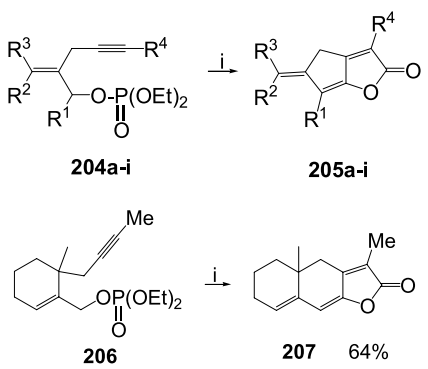
The α-keto alkynes **192a**,**b** without an α-H atom on the α-carbon atom to the alkynyl group are carbonylated in the presence of $Ni(CN)_2$ under phase-transfer conditions [toluene, 5 N NaOH, tetrabutyl-ammonium bromide (TBAB)] to give the unsaturated hydroxybutyrolactones **193a**,**b** (Scheme 79).[102]

The cyclohydrocarbonylaton of the α-keto alkynes **194a**-**r** was readily accomplished by the zwitterionic rhodium complex **195** and triphenyl phosphite in the presence of CO and H_2. The temperature and pressure required were sometimes milder than those previously reported for other reactions. Good chemo- and regioselectivity were observed for a variety of multifunctionalised alkynes to produce the 2(3*H*)-furanones **196a**-**i**, 2(5*H*)furanones **197a**-**i** and 2-furanones **195a**-**d** as the sole products (Scheme 80).[103]



Scheme 82. 200, **201 a** R^1=COOEt, R^2=$SiMe_3$ (82%); **b** R^1=COOEt, R^2=Ph (62%); **c** R^1=COOEt, R^2=$(CH_2)_2OCH_2Ph$ (80%); **d** R^1=COOEt, R^2=$(CH_2)_2C{\equiv}CSiMe_3$ (91%); **e** R^1=COOEt, R^2=CH=CHPh (83%); **f** R^1=H, R^2=$SiMe_3$ (92%). **202**, **203 a** R=COOEt, X=CH_2, (93%); **b** R=Me, X=O (89%); **c** R=H, X=NTs (74%). (i) CO (10 atm), $Ru_3(CO)_{12}$ (2 mol%), toluene, 160 °C, 20 h.

The authors[103] have indicated that a number of factors influenced the preparation of the unsaturated γ-lactones **196**-**198** from the α-keto alkynes **194**. Only a five-membered ring was formed, indicating that the acyl-rhodium intermediate always originates at the triple bond carbon close to R^2. The nature of R^1 and R^2 substantially influences both the formation of the unsaturated lactone and hydrogenation. The authors proposed a mechanism (Scheme 81) for the preparation of furanones from α-keto alkynes **194** which involves the following steps: (1) the rhodium hydride complex $HRhL_x$ binds to the triple bond of the alkynone with a possible weak H-bonding interaction to the ketone functionality **A**; (2) intramolecular addition of the rhodium hydride to the triple bond of the α-keto alkyne afford the E-isomer **B**; (3) depending upon the extent of the interaction between R^1 and R^2, one of two possible pathway may occur in the next stage of the process; appreciable steric interaction between R^1 and R^2 would destabilise **B** resulting in further hydrogenation of the alkenyl intermediate to the ketone **199** and regeneration of $HRhL_x$. Whilst if **B** is stable, carbonylation **E** and rearrangement to the zwitterionic ketene **F**, or isomerisation **C** and carbonylation **D**, would generate **G** via intramolecular cyclisation and (4) either the rhodium–furanone complex **H** or **I** will form. The reaction of either rhodium complex with H_2 affords the 2(3*H*)-furanone **196** or the 2(5*H*)-furanone **197** and regeneration of the rhodium hydride.



Scheme 83. 204, **205 a** R^1=R^2=R^3=H, R^4=Bu (73%); **b** R^1=R^2=R^3=H, R^4=Cy (94%); **c** R^1=R^2=R^3=H, R^4=tBu (87%); **d** R^1=R^2=R^3=H, R^4=Me (52%); **e** R^1=R^2=H, R^3=Bu, R^4=Me (80%, *Z*/*E*=2:1); **f** R^1=Bu, R^2=R^3=H, R^4=Me (88%, *Z*/*E*=2:1); **g** R^1=H, R^2=H, R^3=Ph, R^4=Me (50%, *Z*/*E*=1:1); **h** R^1=H, R^2=R^3=R^4=Me (73%); **i** R^1+R^2=CH_2CMe_2-CH_2, R^3=H, R^4=Me (72%). (i) CO (1 atm), [{(η^3-C_3H_5)PdCl}$_2$], CyNMe (2 equiv.), THF, 80 °C, 12 h.

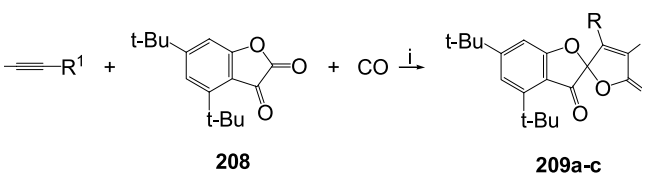
29. Synthesis of bi- and polycyclic α,β-unsaturated γ- and δ-lactones

Chatani et al. have demonstrated the first example of a Ru-catalysed cyclocarbonylation of yne-aldehydes **200a**-**f**, **202a**-**c** with CO to bicyclic γ-butenolides **201a**-**f**, and **203a**-**c** in high yields (Scheme 82).[104]

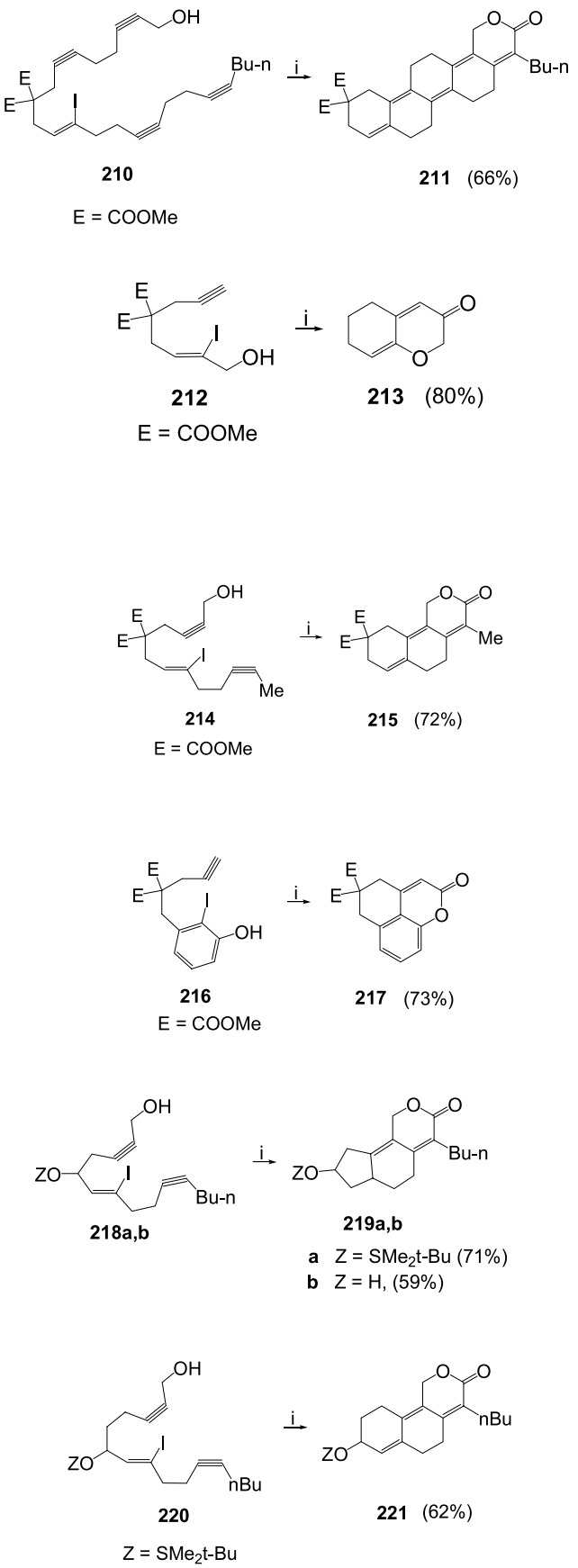
Recently, Kamitani and coworkers have developed a new method for the construction of the highly unsaturated bicyclic lactones **205a**-**i**, and **207** by the Pd-catalyzed carbonylation of 2-propargylallyl phosphates **204a**-**i**, **206** (Scheme 83). The reaction proceeds smoothly, even under mild conditions.[105]

The ruthenium-catalysed reaction of the benzofuran-2,3-dione derivative **208** with CO and alkynes results in a carbonylative [2+2+1] cycloaddition in which the ester-carbonyl group is incorporated into a two-atom assembling unit to give the spirolactone derivatives **209a**-**c** (Scheme 84).[106]

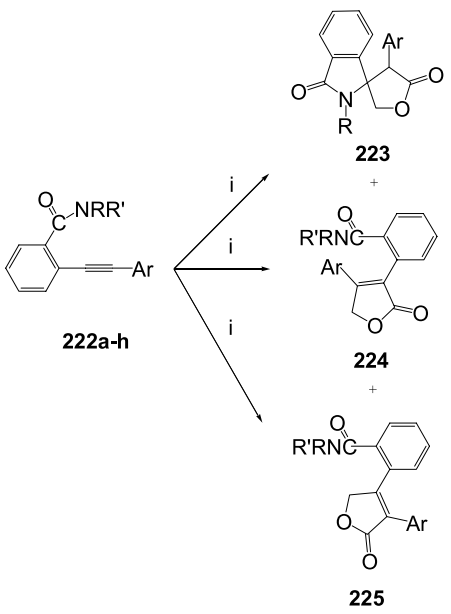
Sugihara et al. have reported[107] that the catalytic cyclic carbopalladation of alkynes can proceed under the conditions for carbonylation of the organopalladium without premature incorporation of CO and the in situ regeneration of a Pd–phosphine catalyst can be accomplished by termination of the carbopalladation cascade via deferred carbonylative esterification, such as the conversion of **210** to **211** (Scheme 85) and the related conversion of **212**, **214**, **216**, **218a**,**b** and **220** to **213**, **215**, **217**, **219a**,**b** and **221**, respectively.



Scheme 84. 209 a R=R^1=Ph (83%); **b** R=Me, R^1=$SiMe_3$ (95%); **c** R=Ph, R^1=$SiMe_3$ (95%). (i) CO (5 atm, rt), $Ru_3(CO)_{12}$ (2.5 mol%); P(4-$CF_3C_6H_4$)$_3$ (7.5 mol%), toluene, 160 °C, 20 h.



Scheme 85. (i) CO (1.1 atm), $Cl_2Pd(PPh_3)_2$ (5 mol%), NEt_3 (2 equiv.), MeOH, 75 °C, 1 h.



Alkyne	R	Rí	Ar	Yield (%)		
222				**223**	**224**	**225**
a	H	H	Ph	34	45	-
b	Me	H	Ph	37	58	-
c	Ph	H	Ph	25	65	-
d	Me	Me	Ph	-	47	47
e	H	H	p-OMePh	33	55	-
f	H	H	p-CNPh	27	40	-
h	H	H	α-Naphth	21	40	16

Scheme 86. (i) $Rh_6(CO)_{16}$ (0.32 mol%), NEt_3 (1.4 equiv.), H_2O (5.5 equiv.), 1,4-dioxane, CO (100 atm), 80 °C, 3 days.

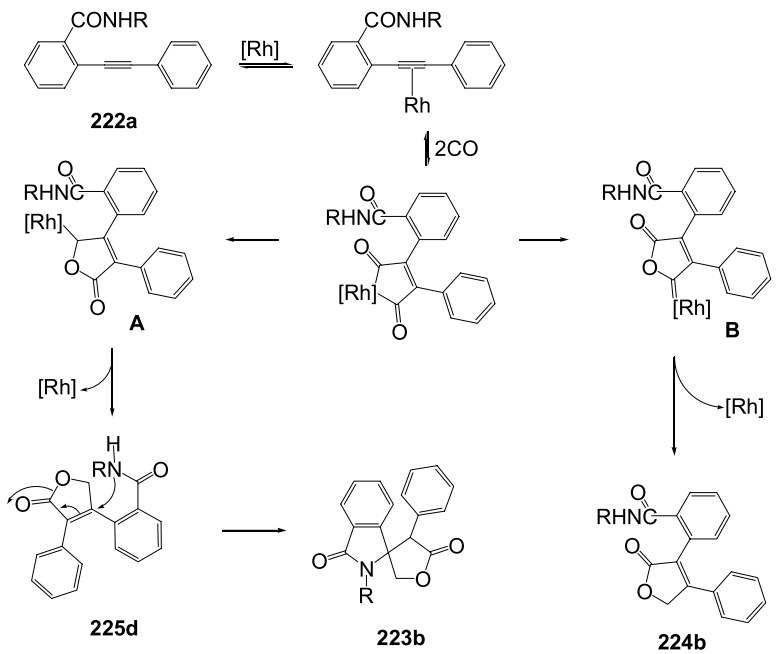
The authors have also shown[107] that the relative rates of various competing processes in a decreasing rate order are: CO insertion (and five- or six-membered lactonisation) ~5-*exo*- or 6-*exo*-alkyne carbopalladation>5-*exo*-alkyne acylpalladation>acylpalladium trapping with MeOH> intermolecular carbopalladation or acylpalladation.

Under water–gas shift reaction conditions, rhodium carbonyl-catalysed carbonylation of the 2-arylethynylbenzamides **222a-h** gave two kinds of products, the novel spiro compounds **223** and two 2(5*H*)-furanones **224** and **225** (Scheme 86), which were produced by cyclic carbonylation of a carbon–carbon triple bond. The spiro derivatives were formed by participation of the amide group adjacent to the carbon–carbon triple bond in the cyclisation process (Scheme 87).[108]

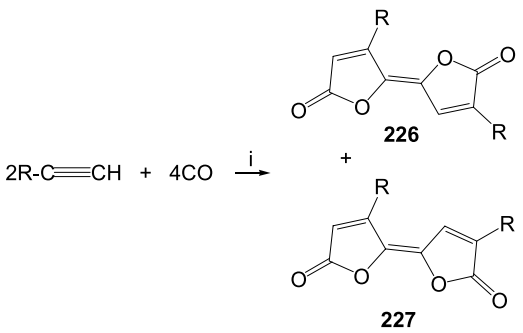
30. (*E*)- and (*Z*)-2,2′-Bifurylidene-5,5′-diones

Two groups have independently published the results of a catalytic reaction between CO and certain simple alkynes,[108–112] acetylene,[109,110,112] propyne,[109,111] hex-1-yne and some arylacetylenes[109]) that produces (*E*)- and (*Z*)-2,2′-bifurylidene-5,5′-diones **226** and **227** or bifurandiones,[109] octatrienediolides,[110–112] 5-(oxofuran-2(5*H*)-ylidene)furan-2(5*H*)-ones according to a previous and systematic nomenclature (Scheme 88).

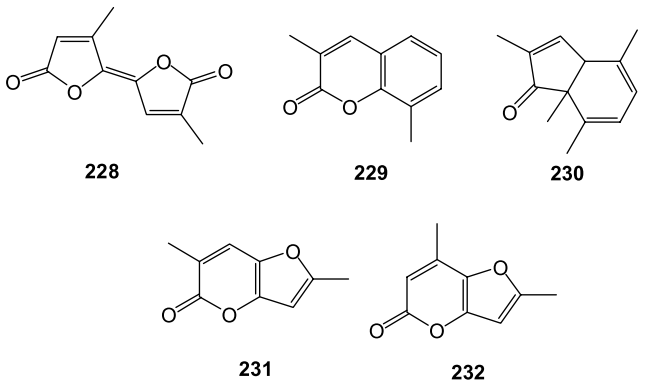
The reaction was performed at an approximate temperature of 100 °C and CO pressures of 100–300 and up to 1000 bar using $[Co_2(CO)_8]$ as a catalyst. Polar aprotic solvents, such as MeCN, $MeNO_2$, acetone, *N*,*N*,*N*′,*N*′-tetramethylurea, esters and ethers, appear to be most suitable. When acetone was used as a solvent, the yields have been improved by adding phosphines or phosphates.[113] It was also shown that Co complexes are intermediates in the catalytic reactions that lead to the bifurylidenediones.[114,115] In the course of the



Scheme 87.



Scheme 88. R=H, Me, Bu, Ph, *p*-ClPh, *o*-MeOPh. (i) $Co_2(CO)_8$, 90–120 °C, 100–300 bar.



Scheme 89.

re-investigation of this [$Co_2(CO)_8$]-catalysed reaction between propyne and CO in acetone at 110° and 170 bar, five major products were produced: (*E*)-3,4′-dimethyl-2,2-bifurylidene-5,5-dione **228**, 3,5,8-trimethylcoumarin **229**, 3a,7a-dihydro-2,4,7,7a-tetramethyl-1*H*-inden-1-one **230**, 2,6-dimethyl-5*H*-furo[3,2-*b*]pyran-5-one **231** and 2,7-dimethyl-5*H*-furo[3,2-*b*]pyran-5-one **232**[116] (Scheme 89). In addition, the products distribution is strongly affected by the CO pressure and propyne concentration. The structures of **230**, **231** and **232** were established by X-ray diffraction.[116]

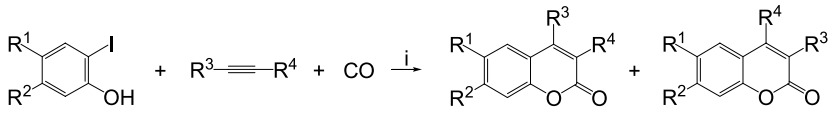
31. Synthesis of coumarins

Kadnikov and Larock have reported[117] that the palladium-catalysed coupling of *o*-iodophenols, internal alkynes, and carbon monoxide allowed the efficient synthesis of 3,4-disubstituted coumarins **233** and **234** bearing a variety of functional groups (Scheme 90).

Heterocyclic analogues of *o*-iodophenol are also effective in the carbonylative annulations of internal alkynes, 3-iodo-2-pyridone **235** affording the azacoumarin **236** in good yield (Scheme 91) in the same conditions.[117]

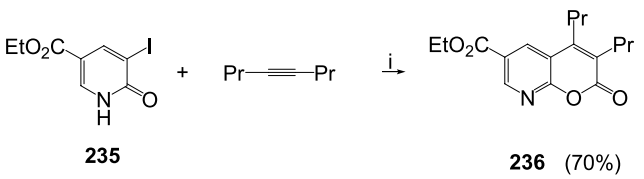
32. Synthesis of pyranopyrandiones

Kondo, et al. have shown[118] that unsymmetrical substituted pyranopyrandiones **237** were generally obtained in good to



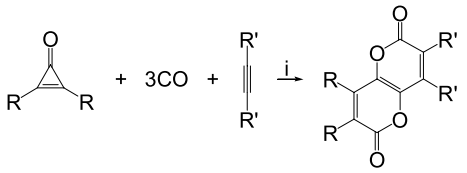
R^1	R^2	R^3	R^4	Time, (h)	**233**	**234**	combined % isolated yield (ratio **233**:**234**)
H	H	Pr	Pr	24	**a**	-	63
H	H	Ph	Ph	48	**b**	-	59
H	H	Me	Ph	24	**c**	**c**	72 (79:21)
H	H	Et	Ph	24	**d**	**d**	78 (72:28)
H	H	Me	tBu	24	**e**	-	9
H	H	CH_2OBn	Ph	24	**f**	**f**	65 (75:25)
H	H	Me	$SiMe_3$	24	**g**	-	43
H	H	Et	CH_3CO	24	**h**	**h**	61 (90:10)
CO_2Et	H	Pr	Pr	24	**i**	-	59
OMe	H	Pr	Pr	12	**j**	-	66
H	CO_2Me	Pr	Pr	6	**k**	-	62

Scheme 90. (i) Iodophenol (0.5 mmol), alkyne (2.5 mmol), pyridine (1.0 mmol), Bu_4NCl (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol, 5 mol%) in DMF (5 ml), 120 °C.



235 **236** (70%)

Scheme 91.

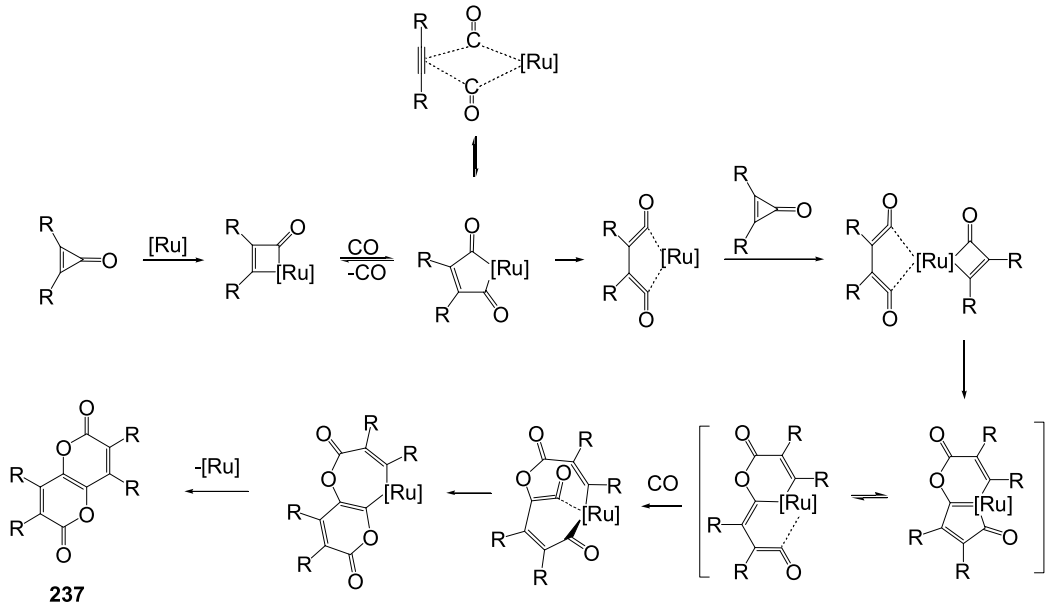


237a-d

Scheme 92. (i) CO (20 atm), $Ru_3(CO)_{12}$ (3.3 mol%), Et_3N (10 mol%), toluene, 150 °C, 20 h. **237**: **a** R=Et, R′=Pr (54%); **b** R=Pr, R′=Bu, (63%); **c** R=Pr, R′=Pen (71%); **d** R=Bu, R′=Pen (82%).

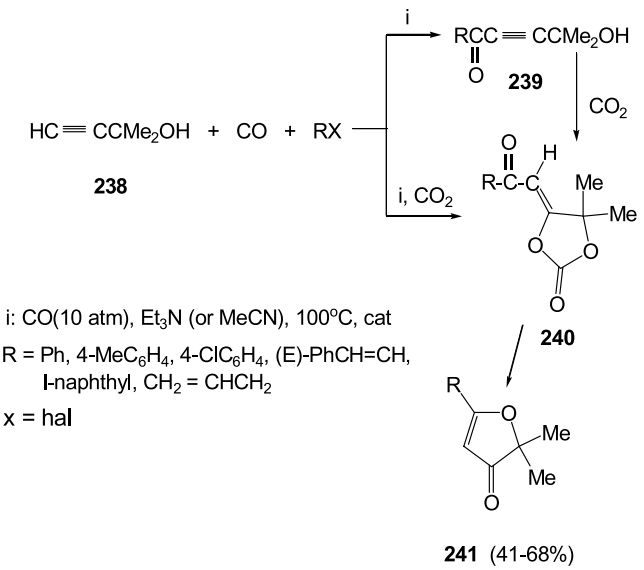
high yields by a novel ruthenium-catalysed cross-carbonylation of cyclopropenones with internal alkynes (Scheme 92).

The use of ^{13}CO gave the corresponding ^{13}C-labelled pyanopyrandiones **237a-d**. The authors believe that the initial step in the present reaction might be consistent with the oxidative addition of the C–C bond between a carbonyl and the α-carbon in cyclopropenone to an active ruthenium centre to give a ruthenacyclobutenone intermediate. Carbonylation of ruthenacyclobutenone (or carbonylative cyclisation of alkynes on the ruthenium) would initially give a malceylruthenium intermediate. Subsequent isomerisation of the maleoylruthenium intermediate produces an active (η^4-bisketene)ruthenium intermediate, which reacts with another molecule of cyclopropenone by oxidative addition and insertion reactions to give a (ketene)ruthenium intermediate. Rapid tautomerisation would give a ruthenium carbene intermediate, and insertion of carbon monoxide into



237

Scheme 93.



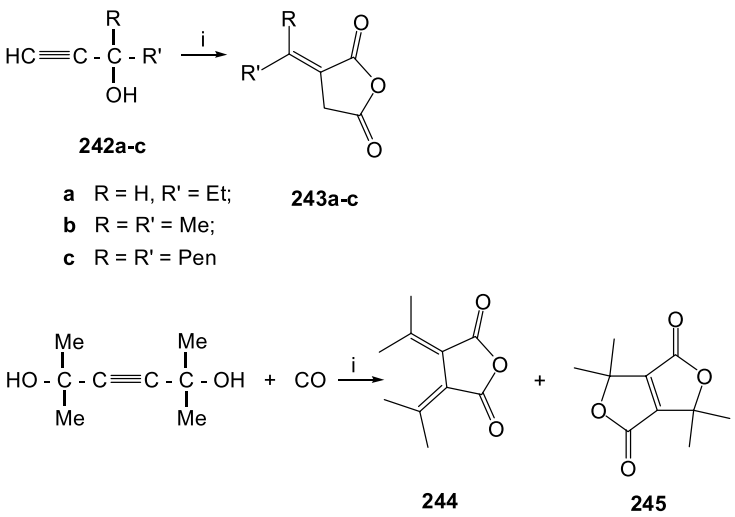
241 (41-68%)

Scheme 94.

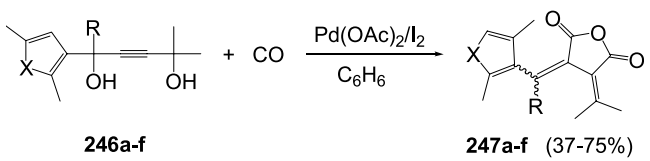
the carbene–ruthenium bond would give a new ketene intermediate. Finally, insertion of a carbonyl group of a ketene moiety into an acyl-ruthenium bond and reductive elimination would give the desired pyranopyrandione **237** (Scheme 93).

33. Synthesis of 3(2*H*)-furanones

When the transition metal triphenylphosphine complexes of Fe, Co, Ni, Ru, Rh, Pt and Pd [the best being $PdCl_2(PPh_3)_2$] were used as catalysts, 3(2H)furanones **241** were formed from 1,1-dimethylprop-2-ynol **238**, CO and RX in a carbon dioxide atmosphere. The reaction mechanism includes the intermediate production of the acetylenic ketones **239**, followed by the formation of the cyclic carbonates **240** from the ketones and CO_2. The compounds **240** can easily decarboxylate quantitatively into the furanones **241**[119] (Scheme 94). The cyclisation of 1-methylprop-2-ynol or prop-2-ynol in a similar manner was unsuccessful.



Scheme 95. (i) $PdCl_2$ (10–20%), benzene, CO (100 atm), 100 °C.



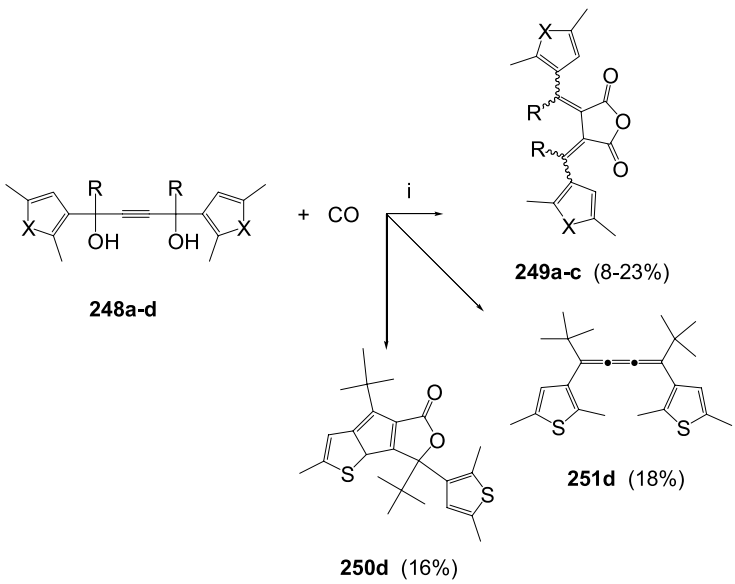
Scheme 96. **a** X=S, R=Me; **b** X=O, R=Me; **c** X=S, R=i-Pr; **d** X=S, R=tBu; **e** X=O, R=iPr; **f** X=O, R=tBu.

34. Cyclic anhydride and imide synthesis

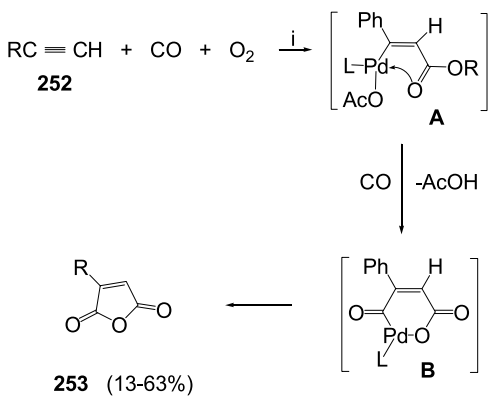
Carbonylation of propargyl alcohol in benzene produced only resinous substances. Substituted propargyl alcohols such as 1-pentyn-3-ol **242a**, 2-methyl-3-butyn-2-ol **242b** and 1-ethynylcyclohexanol **242c** afforded the anhydrides of propylidenesuccinic acid **243a** (19%), teraconic acid **243b** (42%) and cyclohexylidenesuccinic acid **243c** (45%), respectively. The carbonylation of 2,5-dimethyl-3-hexyn-2,5-diol in benzene proceeds smoothly to give the anhydride of diisopropylidenesuccinic acid **244** (49%), as the major product, accompanied by bis(1-hydroxy-1-methylethyl)-furanic acid dilactone **245** (14%) (Scheme 95).[120]

Photochromic anhydrides (fulgides) such as **247** have attracted attention as functional molecules which can be applied to photochemical memory devices.[121] Kiji et al. have proposed a convenient synthetic route to the sterically congested fulgides **247a-f** by the palladium-catalysed carbonylation of heterocycle-substituted 2-butyne-1,4-diol derivatives **246** (Scheme 96).[122,123]

The same authors have applied this method to the synthesis of bisfuryl- or bisthienylfulgides **249a-c** (Scheme 97).[124,125] The diols **248a-c** bearing a methyl or isopropyl group as the alkyl substituent furnished the photochromic fulgides **249a-c**. On the other hand, the carbonylation of the diol bearing a bulky *t*-butyl group **248d** did not afford the corresponding fulgide, but the lactone **250d**, together with butatriene **251d** (Scheme 97).



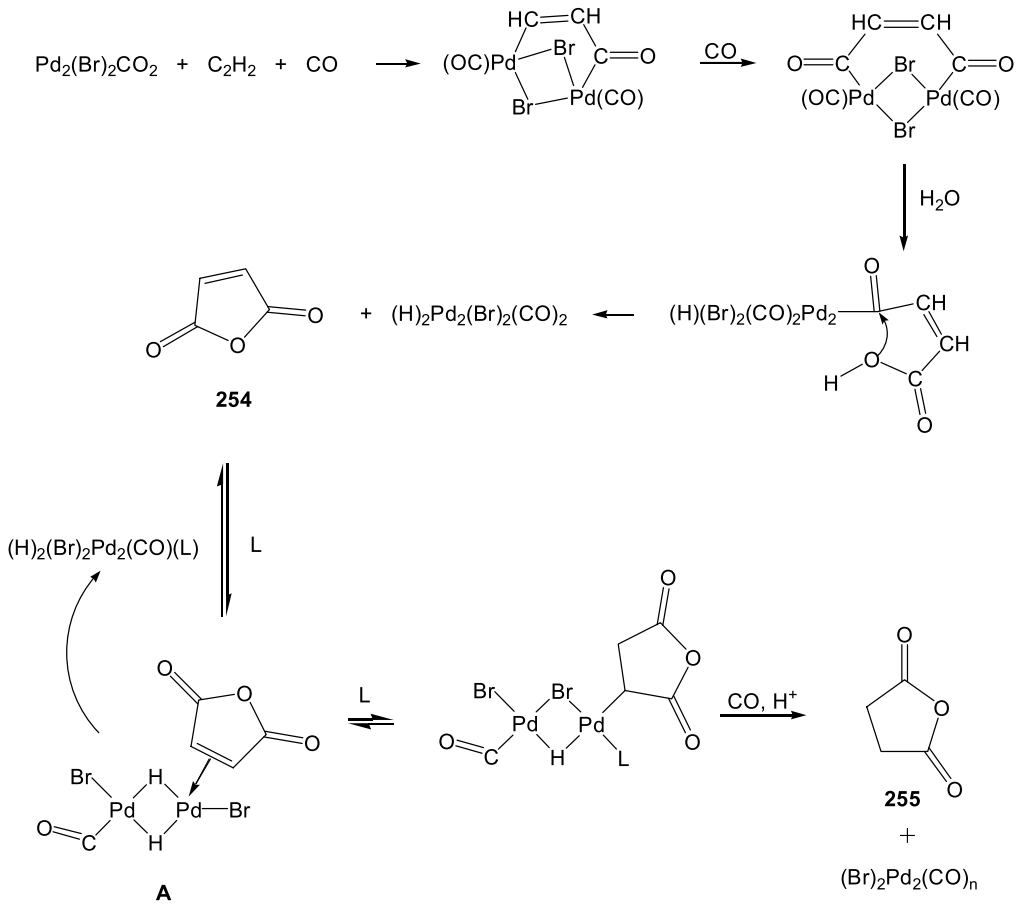
Scheme 97. (i): $Pd(OAc)_2$ (10 mol%), I_2 (5 mol%), benzene, CO (95 atm), 90 °C, 15 h **a** X=S, R=Me; **b** X=O, R=Me; **c** X=S, R=Pr; **d** X=S, R=*t*Bu.



Scheme 98. R=Ph; 4-MeC_6H_4; 4-ClC_6H_4; tBu, Hex, $C_5H_4CH(OH)$. (i) $Pd(OAc)_2$/HQCl/NPMoV, $MeSO_3H$, dioxane, 25 °C, 15 h.

give the corresponding anhydride **253a**. Yamamoto et al. have reported that the carbonylation of 3-butenoic acid with CO by a Pd-complex proceeds through a Pd-containing cyclic intermediate to give the anhydride (Scheme 98).[129]

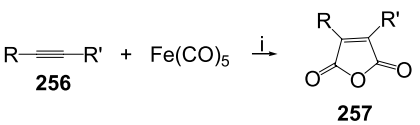
Bruck et al. have shown that the carbonylation of acetylene using the catalytic system $PdBr_2$–LiBr–MeCN produces maleic **254** and succinic **255** anhydrides.[130] A study of the in situ formation of the organic intermediates, the kinetic isotope effect, the isotope exchange, and the oxygen effect on the process direction, revealed that maleic anhydride **254** is most likely a key intermediate in the succinic anhydride **255** formation. Maleic anhydride undergoes transformations through the mediation of a palladium hydride complex **A** (Scheme 99). This complex was detected in the catalytic solution at −40 °C using ^1H NMR techniques.[130]



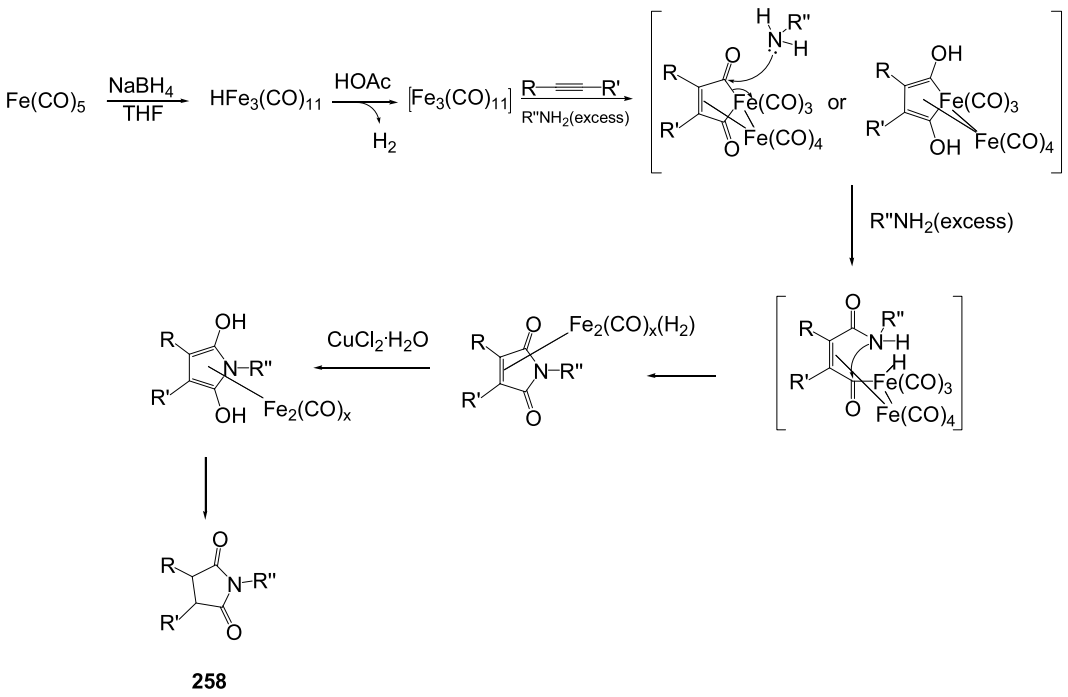
Scheme 99.

The reaction of the alkynes **252** with CO/O_2 in dioxane catalysed by a new triple catalytic system, $PdCl_2$/chlorohydroquinone(HQCI)/NPMoV produced the maleic anhydrides **253** (Scheme 98).[126] The authors[126] consider that the reaction proceeds via a similar mechanism to that shown by Heck[127] for carboalkoxylation and by Alper[128] for dicarbonylation of terminal alkynes. A vinylcarboxylpalladium complex **A** is thought to be a key intermediate in the present carbonylation. When the reaction was performed in dioxane, the insertion of CO into the vinyl complex **A** (R=H) and the elimination of AcOH successively took place to form a palladium complex **B**, which subsequently undergoes reductive elimination to

Periasamy et al.[131] have shown that the reaction of the alkynes **256** with $Fe(CO)_5$ in the presence of pyridine N-oxide (1:1) at 70 °C furnished the corresponding anhydrides **257**, after $CuCl_2.2H_2O$ oxidation (Scheme 100).



Scheme 100. a R=H, R′=Pen (64%), **b** R=H, R′=Ph (58%). (i) (1) Pyridine N-oxide (5 equiv.), $Fe(CO)_5$ (5 equiv.), THF, 67 °C, 12 h; (2) $CuCl_2{\cdot}2H_2O$ (10 equiv.), acetone.



Scheme 101. 258 a R=C_5H_{11}, R′=H, R″=Bu (57%); **b** R=Ph, R′=H, R″=Bu (55%); **c** R=Hex, R′=H, R″=Bu (62%); **d** R=R′=Ph, R″=Bu (55%); **e** R=C(Me)(Ph)OH, r′=Pen, R″=Bu (64%); **f** R=C(OH)Et_2, R′=Pen, R″=Bu, (61%); **g** R=R′=Ph, R″=Oct (53%); **h** R=Pen, R′=H, R″=CH_2Ph (51%).

In addition, the authors have reported[131] that alkyne–iron carbonyl complexes, prepared from $Fe(CO)_5$, $NaBH_4$, HOAC, amine, and alkyne or from $Fe_3(CO)_{12}$, amine and alkyne reagent systems, react with an excess of amine at 25 °C to give the imides **258** in moderate to good yields, after $CuCl_2{\cdot}2H_2O$ oxidation (Scheme 101).

35. Conclusions

This review has discussed new strategies for the synthesis of unsaturated heterocycles, containing nitrogen and oxygen atoms, and carbonyl or alkoxycarbonyl groups in the rings or in the substituents, using catalytic cyclocarbonylation of acetylenic compounds. Heterocycles represent the core of many biologically or pharmaceutically interesting compounds. Acetylene is a multithousand tonne chemical feedstock, which is now mainly produced by the pyrolysis of hydrocarbons. In view of the rapid depletion of hydrocarbon resources, acetylene and its derivatives, which can alternatively be manufactured from coal and other carbon-containing materials, including wastes, are expected to acquire an increasingly more important role as universal chemical intermediates and building blocks. The high and flexible reactivity of these compounds makes the syntheses with their participation easier and less energy consuming than those with alkenes. Nucleophilic attack at the acetylenic moiety leads to diverse vinyl compounds, acetylenic alcohols, allenes, 1,3-dienes and many different heterocycles. The most recent syntheses of functionalised pyrroles, dihydropyridines, quinolines and other fundamental heterocycles by the reaction of carbon monoxide and propargyl derivatives are reviewed. In addition, the recent advances in the modernisation of the classic reactions of acetylene and its derivatives with nucleophiles (superbase-catalysed vinylation of alcohols, polyols or thiols, ethynylation of carbonyl compounds and prototropic rearrangements) are analysed from an up-to-date standpoint. Metal-, mainly palladium-, catalysed reactions serve as versatile tools in synthetic organic chemistry. By using these methodologies, carbon monoxide can be introduced directly into a number of different sites in an organic molecule, leading to the synthesis of carbonyl compounds and carboxylic acid derivatives. The substrate is reacted with a nucleophile such as an alcohol (alkoxycarbonylation), a primary or secondary amine (aminocarbonylation) or water (hydroxycarbonylation) or an organometallic reagent (formylation, cross-coupling reactions) in the presence of carbon monoxide and a palladium complex. Cyclocarbonylation, leading to a variety of heterocyclic compounds, can be regarded as a special type of the former reactions. Double carbonylation usually takes place at elevated CO pressures and produces α-keto-amides or -esters. Cascade reactions may be defined as multireaction, ‘one-pot’ sequences, in which the first reaction creates the functionality to trigger the second. The use of two-phase processes has made catalyst recovery and recirculation, one of the greatest drawbacks of homogeneous catalytic processes, attainable. As palladium-catalysed carbonylations usually tolerate a great variety of functional groups, they are attractive methods for the selective synthesis of intermediates of natural and/or biologically active products.

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