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Carbon Monoxide as a One Carbon Component in Palladium Catalysed Cycloaddition Reactions

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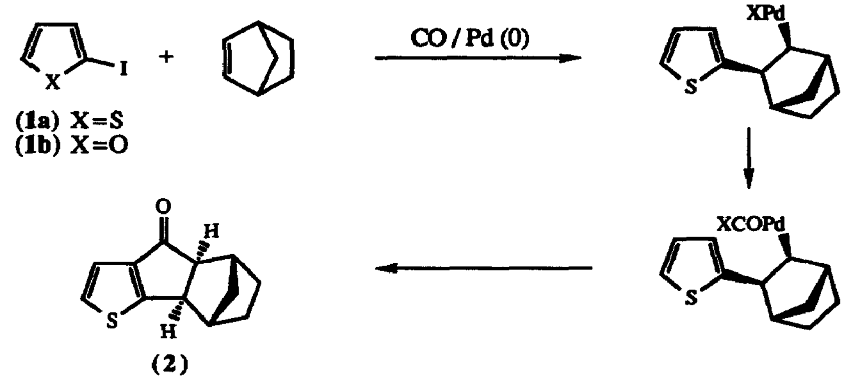
Abstract: Pd(0), generated *in-situ*, in combination with TlOAc promotes a range of catalytic bi- and tri-molecular cycloadditions of aryl / heteroaryl iodides in which carbon monoxide (1 atm) functions as a one carbon component furnishing 5 - 7 membered rings in good yield.

The utilisation of carbon monoxide as a one carbon component in cycloaddition reactions is an attractive goal since it results in ring formation with concomitant introduction of the synthetically useful carbonyl group. Incorporation of carbon monoxide into cycloaddition reactions forming 5-membered rings has been achieved with stoichiometric amounts of $Co_2(CO)_8$ (the Pauson-Khand reaction)[1] and various iron carbonyl complexes including the iron carbonyl mediated equivalent of the Pauson-Khand reaction.[2] Several other metal carbonyls including $Ni(CO)_4$ and $Mo(CO)_6$ give analogous reactions,[3] and a recent publication disclosed a titanium catalysed formation of bicyclic cyclopentenones from enynes utilising an isocyanide as the carbonyl "source". However, a general catalytic protocol with greater substrate and ring size flexibility has been lacking.

We recently reported a general palladium catalysed cycloaddition strategy[5] and provided examples of [3+2]-, [2+2+1]-, [4+2]- and [2+2+2]- processes.[5,6] One of the potential problems in attempting to incorporate carbon monoxide as a one carbon component in the general protocol is that carbonylation reactions of vinyl or aryl / heteroaryl bromides and iodides frequently require high temperatures and pressures.[7] However, we have recently shown that vinyl (unpublished) or aryl / heteroaryl bromides and iodides can be carbonylated at atmospheric pressure and moderate temperatures in the presence of TlOAc.[8,9] We now report the successful applications of this latter methodology to the incorporation of carbon monoxide as a one carbon component in our general palladium catalysed cycloaddition methodology thereby furnishing 5-7 membered rings by a variety of approaches. An additional general, and synthetically valuable, feature of using carbon monoxide as a one carbon component is that nucleophilic attack (O, N, S, carbanions) on the palladium acyl intermediate by suitably located nucleophiles can be used to terminate the cycloaddition. Examples of such processes are provided below.

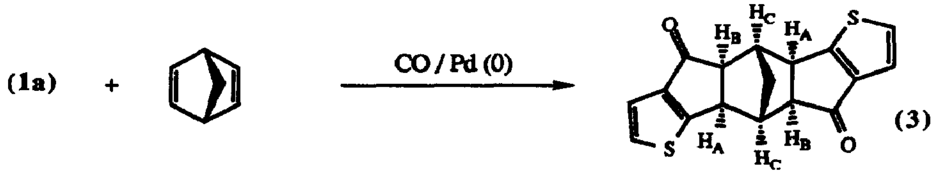
[2+2+1] - Processes. 2-Iodothiophene (**1a**) reacts (MeCN, 80 °C, 16 h) with norbornene and carbon monoxide (1 atm) in the presence of TlOAc (1.2 mol) and 10 mol% of Pd (0)[10] to afford (**2**) (75%) *(Scheme 1)*. The analogous reaction with norbornadiene gave (**3**) (56%). Stereo- and regio-chemistry was determined from ^1H n.m.r. spectral data. In particular H_A and H_B give rise to an AB splitting pattern at δ 3.44 and 3.11 whilst H_C appears as a singlet at δ 2.76. Heterocycles (**1a,b**) react in an analogous manner with dicyclopentadiene to furnish **(4a,b)** as a mixture of double bond isomers in 70 and 65% yield respectively. Examination of **(4a)** by h.p.l.c. (Hypercarb column, 85% MeOH - H_2O) and ^1H n.m.r. spectroscopy showed it to comprise a 2.5:1 mixture of double bond isomers.



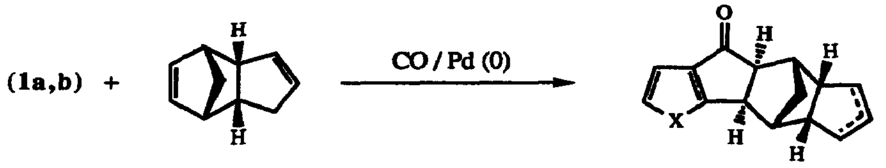
(1a) X=S
(1b) X=O

(2)

Scheme 1

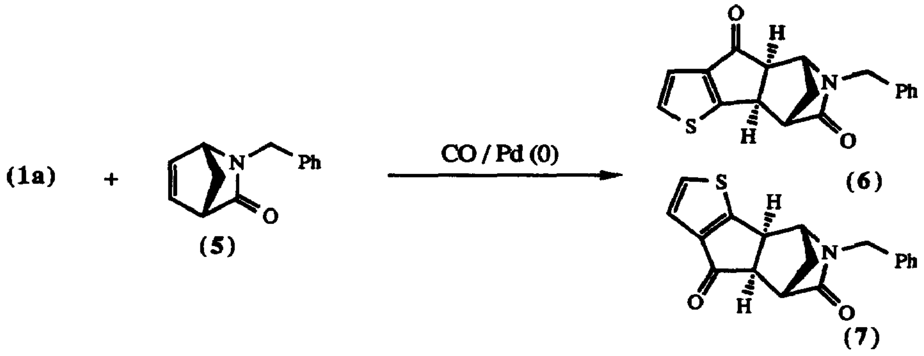


(3)



(4a) X=S
(4b) X=O

2-Iodothiophene **(1a)** also reacts in an analogous fashion with homochiral N-benzyl-2-azabicyclo[2.2.1] hept-5-en-3-one **(5)** to give a (1:1) mixture of the regioisomers **(6)** and **(7)** in 62% yield. Cleavage of the amide linkage will lead to functionalised (5,5)-carbocycles with four contiguous stereogenic centres.

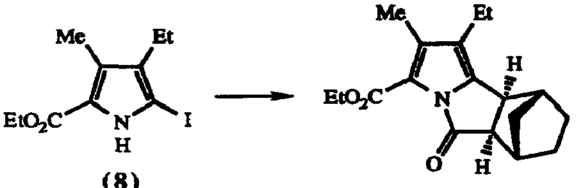


(5)

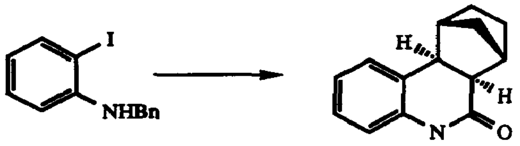
(6)

(7)

The 2-iodopyrrole **(8)** functions as a two atom (C-N) component and reacts under analogous conditions to give **(9)** (60%).

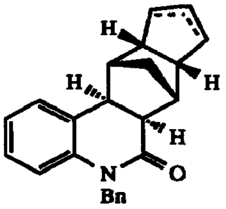


(8) **(9)**

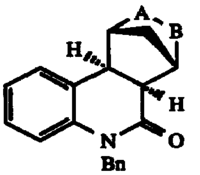


(10) **(11)**

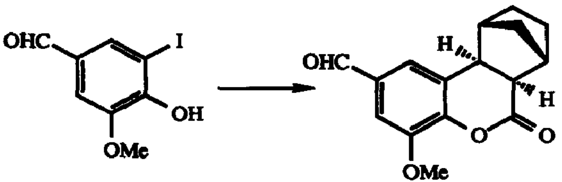
*[3+2+1] - **Processes.*** The iodoaniline **(10)** functions as a 3-atom component and reacts with norbornene and carbon monoxide to give **(11)** (70%). Similar reactions of **(10)** with dicyclopentadiene and norbornenone furnish **(12)** and **(13a,b)** as regioisomeric mixtures in 52% and 64% yield respectively. The ratio of **(13a)**:**(13b)** was determined by n.O.e to be 4:1. The iodophenol **(14)** undergoes analogous reactions e.g. with norbornene and carbon monoxide it furnishes **(15)** (65%).



(12)

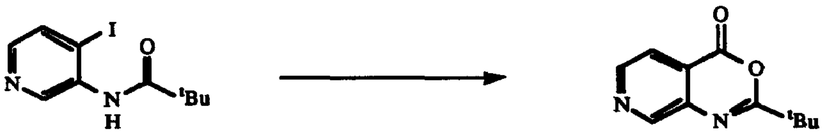


(13a) A=CH_2, B=CO
(13b) A=CO, B=CH_2



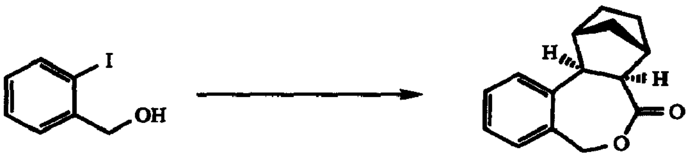
(14) **(15)**

*[5+1] - **Processes.*** The iodopyridine **(16)** reacts with carbon monoxide in the presence of a palladium catalyst to give **(17)** in 56% yield, even in the presence of norbornene.

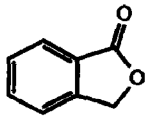


(16) **(17)**

*[4+2+1] - **Processes.*** Only one example of this combination has been studied so far. 2-Iodobenzyl alcohol **(18)** reacts (MeCN, 50 °C, 16 h) with norbornene and carbon monoxide using our standard catalyst system[10] and thallium (I) acetate (1.2 mol) to give **(19)** (65%). The reaction was run at higher concentration than usual [0.26M in **(18)**]. At lower concentration and higher temperature yields are much lower due to formation of the 5-membered lactone **(20)**.



(18) (19)



(20)

Further work on the scope of these cycloadditions is underway.

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References and Notes.

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7. In contrast carbonylation of vinyl or aryl triflates can usually be achieved at atmospheric pressure e.g. (a) Brown, A.; Grigg, R.; Ravishanker, T.; *Tetrahedron Lett.*, in press. (b) Meyers, A. I.; Robichaud, A. J.; McKennon, M. J.; *Tetrahedron*, 1992, **48**, 1181-1184. (c) Freskos, J. N.; Laneman, S. A.; Reilly, M. L.; Ripin, D. H.; *Tetrahedron Lett.*, 1994, **35**, 835-838.

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10. The catalyst used for all the cycloadditions in this paper was generated *in situ* from 10 mol% $Pd(OAc)_2$ and 20 mol% PPh_3. No attempts at catalyst optimisation were made.

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