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A NOVEL PALLADIUM(0) CATALYSED TANDEM 1,3-ALLYL SHIFT AND HECK ARYLATION

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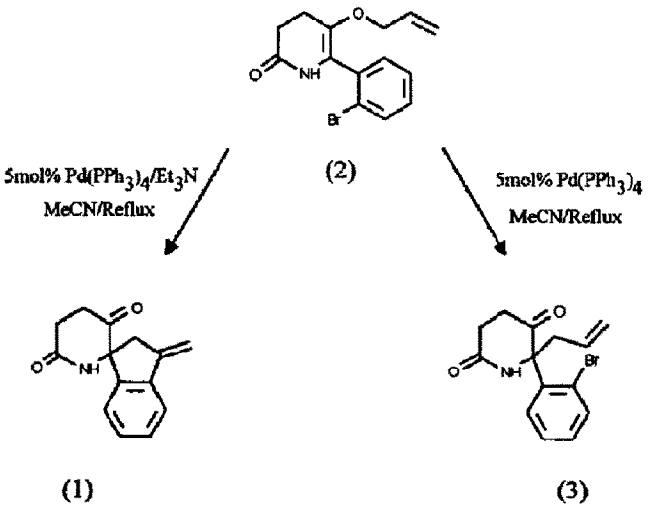
Abstract: On treatment with $Pd(PPh_3)_4$ allyl vinyl ether (1) undergoes a Pd(0) catalysed 1,3 oxygen to carbon allyl shift to afford α-allyl ketone (2). In the presence of both $Pd(PPh_3)_4$ and base the allyl vinyl ether undergoes a Pd(0) catalysed tandem 1,3 allyl shift and intramolecular Heck arylation to give the spiro indane (3). Mechanistic investigations suggest that the 1,3-allyl shift proceeds via a π-allyl palladium intermediate.

As part of an ongoing substance P antagonist programme we identified the spiro indane (1) as a key synthetic intermediate[1]. In the course of the work leading to the preparation of this intermediate we encountered some interesting palladium chemistry. We found that allyl vinyl ether (2) undergoes a palladium(0) catalysed 1,3 oxygen to carbon allyl shift to afford α-allyl ketone (3) and that furthermore, in the presence of base, the allyl enol ether (2) undergoes a novel palladium(0) catalysed tandem 1,3-allyl shift and Heck arylation to afford the spiro-indane (1)



(1) (3)

Palladium(II) catalysis of [3,3]sigmatropic reaarangements (eqn. 1) is well documented[2], whereas to our knowledge palladium (0) catalysed [3,3] sigmatropic rearrangements are unknown. Palladium(0) will however catalyse 1,3 allyl shifts[3] but these rearrangements are non-concerted and do not show the regiospecificity associated with genuine [3,3] sigmatropic rearrangements although their products are

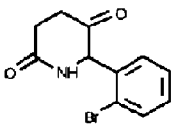
sometimes indistinguishable. Examples of palladium (0) catalysed 1,3 allyl shifts from oxygen to carbon (eqn. 1, X=O) seem to be particularly unusual as only isolated reports exist[4].

Equation 1

Herein we report the palladium (0) catalysed allylic 1,3 oxygen to carbon shift of enol ether (2) to afford the α-allyl ketone (3). Furthermore we report that when the reaction is performed in the presence of base the ketone (3), undergoes subsequent Heck arylation to afford the spiro-indane (1).

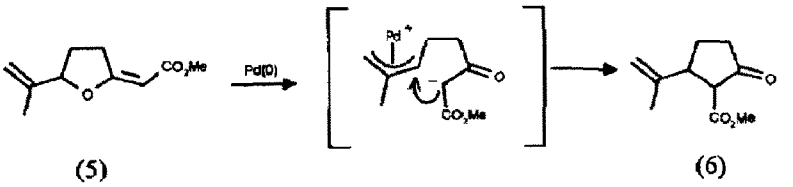
We had originally envisaged that the spiro-indane (1) could be assembled via an intramolecular Heck arylation[5] of the α-allyl ketone (3), which could in turn be prepared by alkylation of the corresponding ketone (4). However, presumably due to steric effects arising from the presence of the o-bromine atom[6], treatment of the ketone (4) with allyl bromide and sodium hydride in dimethylformamide afforded predominantly the O-allylated product, enol ether (2). However as outlined above we found that the allyl enol ether (2) is readily transformed into the spiro-indane (1).

On heating at reflux in acetonitrile in the presence of 5mol% tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) the allyl vinyl ether (2) readily undergoes rearrangement to afford the α-allyl ketone (3) in 66% yield[7,8]. If the allyl vinyl ether is heated at reflux in the presence of 5mol% $Pd(PPh_3)_4$ and triethylamine the reaction does not halt after the rearrangement but the α-allyl ketone (3) undergoes subsequent Heck arylation to afford the spiro-indane (1) in one pot in 53% overall yield[9,10]. This tandem process proceeds smoothly and efficiently. The conversion of (2) through (3) to (1) is easily followed by thin layer chromatography and indeed all three species can be simultaneously observed for a significant period.



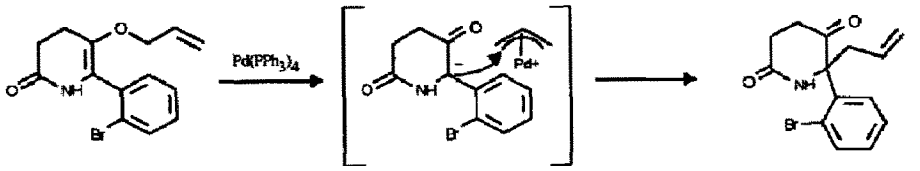
(4)

Whilst the rearrangement of the allyl ether (2) to afford the α-allyl ketone (3) satisfied our immediate synthetic needs[1] we were keen to examine its mechanism. Whilst the transformation of (2) into (3) formally represents a Claisen rearrangement we thought it unlikely the reaction was a genuine [3,3] sigmatroic rearrangement as palladium(0) catalysis of [3,3] sigmatropic rearrangements is unprecedented It is well established[11] that palladium(0) treatment of allylic systems which bear a leaving group at the allylic carbon generates π-allyl palladium(II) species which are in turn trapped by nucleophiles. Indeed Trost et al[4] had demonstrated that the palladium(0) catalysed 1,3 allylic shift of (5) to afford (6) proceeds via the formation of a π-allyl palladium intermediate which is trapped by the α-carbon atom of the liberated enolate (eqn. 2). We thus anticipated that palladium(0) catalysed rearrangement of (2) could proceed via an analogous mechanism in which a π-allyl palladium species is trapped by the α-carbon of the enolate of ketone (4) (eqn. 3).



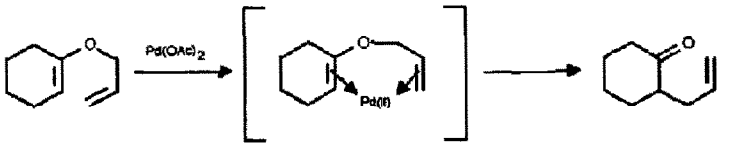
(5) (6)

Equation 2



Equation 3

However, whilst palladium(0) catalysed Claisen rearrangements are unknown, palladium(II) catalysed Claisen rearrangments have been reported[12,13] (e.g. eqn. 4[12]). Palladium(II) is thought to co-ordinate simulaneously to both the double bonds of the substrate to give a stabilized cationic cyclic transition state (eqn. 4). As under the conditions of the rearrangement of (2) palladium(II) could in principal be generated by oxidative addition of palladium(0) into the aryl-bromine bond, the possibility of the rearrangement of (2) to (3) representing a palladium(II) catalysed Claisen rearrangement could not be discounted.



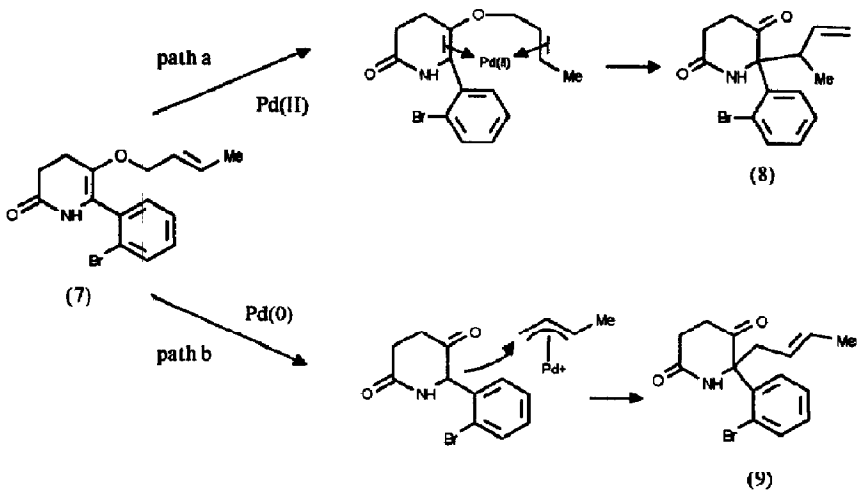
Equation 4

We endeavoured to distinguish between these two possible mechanisms of rearrangement via the crotyl ether (7). If the palladium(II) mechanism were to operate (Scheme; path a) rearrangement of crotyl ether (7) would afford the Claisen product (8) in which the terminal methyl group is transferred to the allylic carbon. In contrast, if the rearrangement were to occur via the palladium(0) catalysed dissociative mechanism (scheme; path b), one would anticipate that the intermediate π-allyl species would be trapped preferentially from its least hindered end to afford predominantly (9) in which the methyl group remains at the olefin terminus.

Alkylation of ketone (4) with crotyl bromide afforded the crotyl ether (7). Treatment of this compound with $Pd(PPh_3)_4$ under the conditions described for the rearrangement of (2) afforded the ketone (9) exclusively (as observed by ^1H NMR spectroscopy). Transfer of the methyl group from olefin terminus to olefin terminus strongly suggests that the rearrangements of both (1) and (7) proceed via a π-allyl palladium intermediate.

In summary, it has been found that allyl enol ether (2) undergoes a novel palladium(0) catalysed tandem 1,3 allyl shift and intramolecular Heck arylation reaction, and that it is highly probable that the 1,3 allyl shift occurs via a π-allyl palladium intermediate. The tandem reaction is an interesting addition to the burgeoning field of palladium catalysed tandem and cascade processes[14]. Further investigations of both the rearrangement and tandem reaction are in progress.

Scheme



References and Notes

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3. See for example; Schenk, T.G. and Bosnich, B.; *J. Amer. Chem. Soc.*, 1985,107,2058.
4. Trost, B.M.; Runge, T.A. and Jungheim, L.M.; *J. Amer. Chem. Soc.*, 1980,102,2840.
5. Tour, J.M. and Negishi, E.; *J. Amer. Chem. Soc.*, 1985,107,8289.
6. Under identical conditions des-bromo (4) is allylated exclusively at the α-carbon
7. There was no evidence for the rearrangement occuring when (2) was identically treated in the absence of $Pd(PPh_3)_4$
8. **α-Allyl Ketone (4)** $Pd(PPh_3)_4$ (56mg,5mol%) was added to a solution of the ether (2) (300mg,0.92mmol) in acetonitrile (25ml) and the mixture heated at reflux under nitrogen for 18h. The mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (ether/dichloromethane (1:1) as eluent) to afford the α-allyl ketone (2) as an off-white solid (200mg,66%). ^1H NMR ($CDCl_3$,250MHz)δ 2.7-3.0(6H,m,$H_{4\alpha}$,$H_{4\beta}$,$H_{5\alpha}$,$H_{5\beta}$ & $CH_2CH=CH_2$) 5.2-5.3(2H,m,$CH=CH_2$) 5.57(1H,m,$CH=CH_2$) 6.33 (1h,brs,NH), 7.2-7 70(4H,m,aromatics). Found C,54.60; H,4.49; N,4.32; $C_{14}H_{14}BrNO_2$ requires, C,54.56; H,4.58; N,4.55%
9. **Spiro-Indane (1)** $Pd(PPh_3)_4$ (50mg,5mol%) was added to a solution of the ether (2) (280mg,0.92mmol) and triethylamine (0.70ml,1.8mmol) in acetonitrile (8ml) and the mixture heated at reflux under nitrogen for 6h. 8% w/v Aqueous sodium hydrogen carbonate (100ml) was added and the mixture extracted with dichloromethane (3x50ml). The combined extracts were washed with satd. brine (50ml) and concentrated *in vacuo* to afford a brown solid. Purification by flash column chromatography on silica gel (dichloromethane/ethyl acetate (2:1) as eluent) followed by trituration with ether afforded the spiro-indane (1) as a white powder (110mg,53%). ^1H NMR ($CDCl_3$,250MHz)δ 2.7-3.0(5H,m,$H_{4\alpha}$,$H_{4\beta}$,$H_{5\alpha}$,$H_{5\beta}$ & $CH_aH_bCH=CH_2$) 3.42(1h,dt,$CH_aH_bC=CH_2$) 5.17 & 5.59(2H,t + t,$CH=CH_2$) 6.17 (1H,brs,NH), 7.2-7.60(4H,m,aromatics). Found C,73.66; H,5.75; N,6.02; $C_{14}H_{13}NO_2$ requires, C,73.99; H,5.77; N,6.16%
10. Formation of spiro-indane (1) is accompanied by formation of ca. 10% of the isomeric spiro-methylindene. Migration of exocyclic double bonds is an acknowledged problem when forming rings by Heck arylation; for example see ref. 5.
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14. see for example Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P. and Worakun, T.; *Tetrahedron*,1992,48,7297 and Ableman, M.M. and Overman, L.E. *J. Amer. Chem. Soc.*, 1988,110,2328.

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