ChemComm

Halide redistribution in Pd-catalysed 1,6-diene cycloisomerisation†

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Received (in Cambridge, UK) 21st November 2000, Accepted 12th December 2000
First published as an Advance Article on the web 8th January 2001

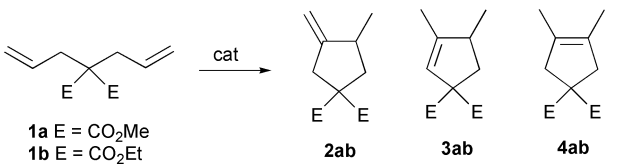
$[(MeCN)_3PdCl]^+$, generated *in situ*, reversibly disproportionates to give $[(MeCN)_2PdCl_2]$ and $[(MeCN)_4Pd]^{2+}$. The neutral species is a reactive and highly regioselective catalyst for 1,6-diene cycloisomerisation.

Early examples of transition metal-catalysed cycloisomerisation reactions[1] employed hepta-1,6-dienes (*e.g.* **1**) as substrates.[2–4] Since dialkyl diallylmalonates **1** may form cyclopentane **2** and cyclopentenes **3** and **4**, much of the focus in their cycloisomerisation has been the efficient control of regioselectivity (Scheme 1). A pioneer in this area was Grigg,[4] who reported regioselective $[(PPh_3)_3RhCl]$-catalysed isomerization of **1b** to **2b** ($CHCl_3$, reflux 8 h)‡ or **4b** (EtOH, reflux, 12 h).‡ Under palladium catalysis [5 mol% $Pd(OAc)_2$ or $PdCl_2$] isomeric **3b** and **4b** were obtained in good yields (80–88%) and with good regioselectivity (92−94%) for **3b** ($CHCl_3$, reflux 6–8 h).‡ Much more recently, a number of other catalyst systems have been developed for selective isomerisation of **1** to **2** or **4**,[5] although catalysts for selective conversion of **1** to **3** still remain rare.[4,6] Our attention was drawn to the recent report by Heumann and Moukhliss[7] on the use of $[(MeCN)_{(4-m)}Pd(Cl)_m]^{(2-m)+}$ {generated *in situ* from the neutral complex $[(MeCN)_2PdCl_2]$} for cycloisomerisation. By use of 1 or 2 equivalents of $AgBF_4$ (per Pd), **1b** was isomerised to **3b** (79%, 18 h, reflux, 5 mol% Pd, $CHCl_3$) or to **2b** (39%, 8 h, reflux, $CHCl_3$), respectively. This led the authors to conclude that it is the catalyst charge that controls the regioselectivity.[7]

We have recently been studying the mechanism by which $[(MeCN)_2Pd(allyl)]^+$ (5 mol%) in $CHCl_3$ cycloisomerises **1a**.[8] The primary and predominant product is **2a**, however, on co-addition of 1 mol% $[Cl_2Pd_2(allyl)_2]$, which is not itself an active catalyst, both **2a** and **3a** are generated at approximately equal rates. This suggested to us that it could be the presence of chloride, rather than the charge, that determines the regioselectivity in the Heumann system.[7] Consequently, we attempted to isolate $[(MeCN)_3PdCl]^+$ from a freshly prepared solution {AgOTf, MeCN, $CHCl_3$, $[(MeCN)_2PdCl_2]$, filter}. However, chloride redistribution through monomer/μ-halide dimer equilibrium resulted in crystallisation of the neutral dichloride $[(MeCN)_2PdCl_2]$,§ leaving the more soluble complex $[(MeCN)_4Pd][OTf]_2$¶ in solution. Since nearly all Pd-catalysed 1,6-diene cycloisomerisations employ cationic pro-catalysts[5b,c,6,7] there seems to be a general assumption that halide abstraction to generate a mono- or di-cation is a pre-requisite for activity. In fact, pure neutral $[(MeCN)_2PdCl_2]$ turned out to be a far more active catalyst than the analogous mono- or di-cationic complexes. For example, in the presence of 5 mol% $[(MeCN)_2PdCl_2]$, a $CHCl_3$ solution of **1a** was quantitatively cycloisomerised in just a few minutes at 60 °C. The catalyst was also active at lower temperatures, *e.g.* at 40 °C, 100% conversion was achieved in under 2 h with 97% regioselectivity for **3a** and no trace of **2a** evident by GC.‖

Neutrality and the presence of chloride appear to be important features in the activity of $[(MeCN)_2PdCl_2]$: simple salts** $[PdI_2, Pd(OAc)_2, Pd(O_2CCF_3)_2]$ failed to isomerise **1a** at 60 °C in the presence or absence of added MeCN (10 mol%) over a period of many hours. As indicated above, the cations are much less reactive and addition of 5 mol% NBu_4X (X = Cl, Br or I) to $[(MeCN)_2PdCl_2]$, to generate an anionic palladate-type species, completely inhibited catalysis. A stoichiometric reaction between **1a** and $[(MeCN)_2PdCl_2]$ in $CDCl_3$ was followed by ^1H NMR (500 MHz) at 25 °C. There were no observable complexation processes,†† just the slow consumption of **1a** and appearance of **3a**. To gain more information, the kinetics of the catalytic reaction (5 mol% Pd) were measured (HRGC) in $CHCl_3$, CH_2Cl_2 and 1,2-dichloroethane (DCE) at 23, 40 and 60 °C. In nearly all cases, an induction period was followed by a pseudo-zero-order rate profile over three to four half-lives (*ca.* 90% conversion).

The induction period indicates that $[(MeCN)_2PdCl_2]$ must be a pro-catalyst, however, there is no direct reaction between the complex and **1a** observable by NMR, *vide supra*, and although the induction period is followed by pseudo-zero order kinetics (*i.e.* steady-state catalyst concentration) no trace of any co-product from pro-catalyst reaction is evident by GC analysis.‡‡ We also prepared and evaluated $[(PhCN)_2PdCl_2]$, $[(Bu^tCN)_2PdCl_2]$, $[(DMSO)_2PdCl_2]$ and $[(PhCN)_2PdI_2]$ as cata-



Scheme 1 Transition metal-catalysed cycloisomerisation of 1,6-diene **1**.

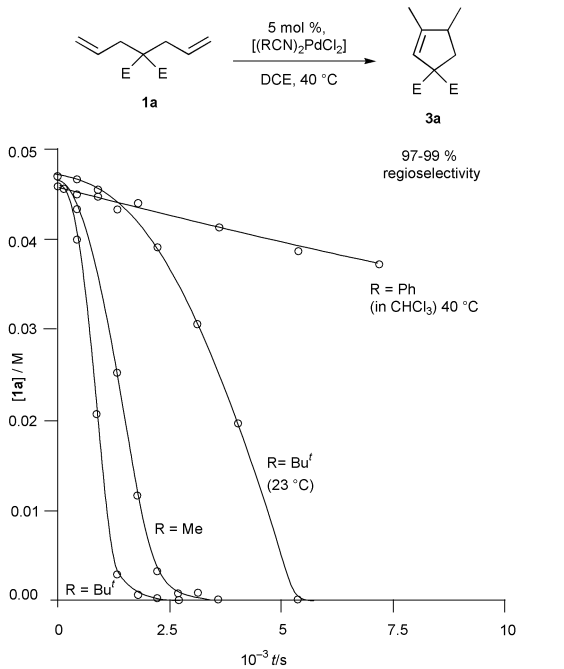


Fig. 1 Plot of variation of the concentration of 1,6-diene **1a** (M, *y*-axis) with time (*s*, *x*-axis) during cycloisomerisation by 5 mol% $[(RCN)_2PdCl_2]$ in 1,2-dichloroethane (DCE) or $CHCl_3$ at 23 or 40 °C. Concentration determined by GC analysis. For full details see ESI†.

† Electronic supplementary information (ESI) available: general experimental procedure, typical GC analyses and table of regioselectivities obtained with the various catalysts. See http://www.rsc.org/suppdata/cc/b0/b009356o/

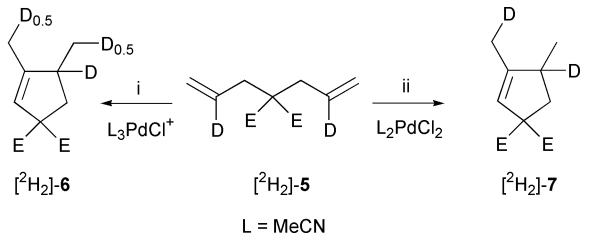
DOI: 10.1039/b009356o

lysts. Only the chloro-complexes were active for cycloisomerisation of **1a**. The rate of reaction of **1a** using the pro-catalysts of type $[(RCN)PdCl_2]$ were similar, with DCE proving the best solvent. The Bu^{t}CN-bearing complex generally showed the highest activity. With the more coordinating ligand, DMSO, the catalyst was substantially less active (*ca.* 70% conversion in 42 h at 40 °C in DCE). However, it was highly selective, giving a 110 : 1 ratio of **3a** over isomeric **2a** and **4a**. By preparing the μ-halide dimer, $[(DMSO)_2Pd_2(\mu\text{-}Cl_2)Cl_2]$ we obtained a more reactive catalyst (90% conversion, 22 h, 40 °C, DCE) which still displayed excellent regioselectivity for **3a** (99%).

The regioselectivity of the isomerisation of **1a** to **3a** mirrors, but far exceeds, that observed by Grigg using $PdCl_2$, *vide supra*. However, $PdCl_2$, being a relatively insoluble polymeric species, requires use of more vigorous conditions (8 h, reflux in $CHCl_3$).‡ In contrast, monomeric complexes $[L_2PdCl_2]$ (L = RCN or DMSO)[9] allow reaction at lower temperatures, under neutral conditions and extremely high regioselectivity is attained. For example, using $[(Bu^tCN)_2PdCl_2]$ as catalyst, > 99% conversion of **1a** occurred in 90 min at 40 °C in $CHCl_3$ and **3a** was isolated in 96% yield and high purity (97.5%) after chromatography. In summary, compared to the analogous cations $[(RCN)_3PdCl]^+$ and $[(RCN)_4Pd]^{2+}$, complexes of the type $[(RCN)_2PdCl_2]$, are far more active pro-catalysts for 1,6-diene cycloisomerisation.[10] Furthermore, most catalysts[4,6,7] generate isomeric **2** and **4** from **1**, whereas with the neutral catalysts the regioisomer **3** is obtained with very high selectivity. Ironically, $[(MeCN)_2PdCl_2]$ has been used as a precursor for $[(MeCN)_3PdCl]^+$ generation *in situ*, however, due to chloride redistribution, it remains present in the reaction mixture. Nonetheless, preliminary labelling experiments employing $[^2H_2]$-**5**,[11] demonstrate that catalysis by $[(MeCN)_2PdCl_2]$ is not the exclusive process when '$[(MeCN)_3PdCl]^+$' is employed (Scheme 2).

Of note is the finding that, unlike labelling studies of cationic Pd-catalysts that generate the regioisomer **2a**,[5c,8] no scrambling of ^2H is observed with the neutral chloride catalysts (*cf.* $[^2H_2]$-**7**, Scheme 2). This bodes well for elucidation of the complete pathway between **1** and **3** and detailed NMR, kinetic and isotopic labelling studies,[8] to distinguish hydropalladation, cyclometallation and C–H insertion pathways,[1–5] will be reported in full in due course. Additionally, novel chiral ligands allowing the generation of analogous neutral complexes are being tested for asymmetric induction.

We thank the University of Bristol and the EPSRC (GR/N05208) for support. We also thank Professor Ross A. Widenhoefer (Duke University, USA) for sharing results prior to publication.



Scheme 2 Conditions: *i*, 5 mol% $[(MeCN)_3PdCl][OTf]$ (prepared from $[(MeCN)_2PdCl_2]$ by halide abstraction in MeCN with 1 equivalent AgOTf, then removal of AgCl by filtration, evaporation and redissolution in $CHCl_3$), 40 °C, $CHCl_3$; *ii*, 5 mol% $[(MeCN)_2PdCl_2]$, 40 °C, $CHCl_3$.

Notes and references

‡ To effect catalyst activation, the solvent was pre-saturated with HCl gas before addition of the substrate and heating to reflux.

§ $[(MeCN)_2PdCl_2]$ was isolated in 66% yield (based on Cl) and its identity confirmed by comparison (FT-IR and mp) with an authentic sample.

¶ Such disproportionation to generate the achiral pro-catalyst $[(MeCN)_2PdCl_2]$ may well explain why cycloisomerisation of **1b** with 5 mol% '$[(MeCN)_3PdCl]^+$/sparteine' in $CHCl_3$, generates **3b** in essentially racemic form, but with '$[(MeCN)_4Pd]^{2+}$/sparteine', **2b** and **3b** are obtained in 60 and 37% ee respectively, see ref. 7.

‖ When pure **2a** was exposed to 5 mol% $[(MeCN)_2PdCl_2]$, no isomerisation could be detected (^1H NMR) over a period of 22 h at 40 °C. However, in some reactions small quantities of the isomer **2a** were generated. Most often, these disappeared in the later stages of reaction and the maximum level of **2a** reached during reaction was < 0.5% of the total mixture of alkenes.

** In contrast to $Pd(OAc)_2$ and $Pd(CF_3CO_2)_2$, it may be noted that PdI_2 is essentially insoluble in $CHCl_3$. However, the soluble complex $[(PhCN)_2PdI_2]$ was also found to be ineffective. Furthermore, the insoluble polymer $PdCl_2$ (or a combination of $Pd(OAc)_2$/HCl) generates a moderately active catalyst, see ref. 4(*c*).

†† However, in the last *ca.* 20% reaction a slight broadening of the signals of **1a** became apparent suggesting reversible and unfavourable complexation at the NMR timescale.

‡‡ This suggests the possibility of substrate-induced establishment of a pre-equilibrium (dissociation of nitrile or chloro-bridged dimers) or solvent–catalyst reaction to generate the active species. Ongoing studies will address this issue through full analysis of the kinetics.

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