Reaction Mechanism

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Cryptocatalytic 1,2-Alkene Migration in a σ-Alkyl Palladium Diene Complex**

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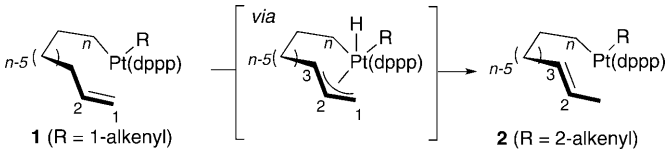
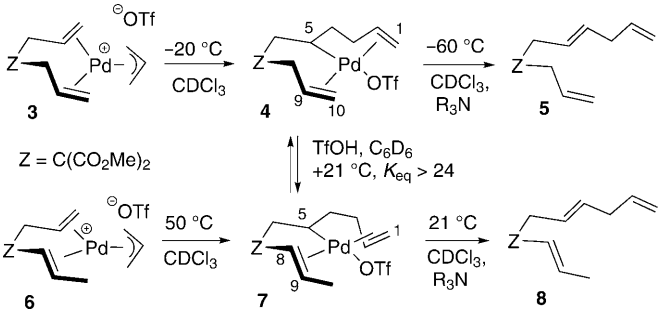
Alkene migration is frequently encountered in transition-metal-catalyzed reactions as part of the productive cycle[1] or as a competing process.[2] The observation of alkene migration in isolated *n*-metallo-1-alkene complexes[3] is rare,[3a,4] and provides a valuable opportunity for mechanistic study, which has the potential to yield information for the control of selectivity in related catalytic reactions.



Scheme 1. Thermal isomerization of **1** to **2** (toluene, 110 °C), with a proposed (κ^1-dppp)$Pt^{IV}H(\eta^3$-allyl) intermediate.[4a] dppp = propane-l,3-diylbis(diphenylphosphane).

A recent example involves alkene migration in *cis*-Pt(κ^2-dppp)(alkenyl)$_2$ complexes (**1**→**2**; Scheme 1),[4a] for which a unimolecular mechanism involving a Pt^{IV}(H) complex was proposed on the basis of 1) reactions being faster in dilute solution,[5] 2) there being no inhibition by Hg metal, and 3) a rate retardation upon addition of excess dppp.[4a] Herein, we report our investigation of an analogous migration in a palladium complex (**4**→**7**; Scheme 2) by using NMR spectroscopy, mass spectrometry, and isotopic labeling (^{2}H, ^{13}C, ^{108}Pd). The outcome eliminates the appealingly simple intramolecular allylic C–H insertion process analogous to Scheme 1, and reinforces the caveat that what appears on first inspection to be a relatively simple intramolecular process, rarely is.

The palladium complexes **4** and **7** were readily prepared. Cationic diallyl malonate complex **3** (Scheme 2) undergoes intramolecular allyl palladation at −20 °C to give the neutral η^5-alkyldiene complex **4**.[6] σ-Alkyl palladium complexes bearing β-hydrogen atoms are usually susceptible to elimination, and **4** is no exception, thus generating triene **5** in the presence of a proton sponge (1,8-bis(dimethylamino)naphthalene) at −60 °C.[6a] The isomeric η^5-alkyldiene complex **7** can be generated analogously from the 1,5-diene complex **6**[7] at 50 °C[8] and undergoes elimination of a β hydrogen to give triene **8** at 21 °C.



Scheme 2. Generation and β-hydride elimination of complexes **4** and **7**, and their equilibration mediated by TfOH. Empirical first-order rate constants (s^{-1}) for **3**→**4**: $(1.0\pm0.4)\times10^{-2}$; **4**→**5**: $(3.4\pm0.4)\times10^{-3}$; **6**→**7**: $(1.5\pm0.1)\times10^{-5}$; **7**→**8**: $(6.0\pm0.2)\times10^{-6}$. Tf = trifluoromethanesulfonyl.

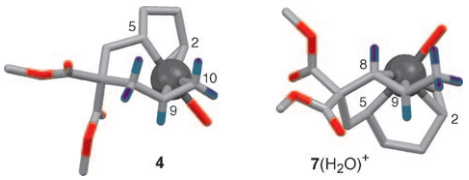


Figure 1. X-ray structures of **4** and **7**·H_2O.[9] All protons apart from those on C8–C10 (highlighted in purple) are omitted for clarity. Complex **7** crystallized with a water molecule bound to Pd in place of the triflate counterion (not shown), which has a weak intermolecular contact (Pd–O = 248 pm). In **4**, only the palladium-bound oxygen atom of the triflate is shown.

In the absence of base, **4** and **7** are remarkably stable, thus allowing detailed structural analysis (Figure 1).[9] However, over a period of months in $CDCl_3$ solution, **4** underwent 1,2-alkene migration at C9 and C10 as well as diastereofacial inversion at C1 and C2 to generate the thermodynamically more stable complex **7**.

Acid-catalyzed alkene migration in iridium complexes has been reported by Shaw and co-workers.[4b] Accordingly, the addition of one equivalent of TfOH to **4** in $CDCl_3$ (28.6 mM) resulted in reversible and diastereoselective protonation of the malonate carbonyl group and induced clean 1,2-alkene migration to generate **7**.[10] Although protonation of the

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carbonyl group was immediate, the migration occurred after a variable and sometimes extreme induction period (up to 8 h) during which the time-average ^{1}H NMR signal of $(TfOH)_n$ migrated from $\delta = (12.75 \pm 0.15)$ to (13.5 ± 0.6) ppm. Upon switching to C_6D_6 as the solvent, so that dimeric acid $(TfOH)_2$ more rapidly monomerizes,[11] the kinetics of alkene migration (**4**→**7**) became more reproducible but remained sigmoidal in character (Figure 2a). The analysis of the maximal rate $(d[\mathbf{7}]/dt)_{max}$ as a function of TfOH concentration indicates an approximately first-order dependency (see filled circles in Figure 2b).

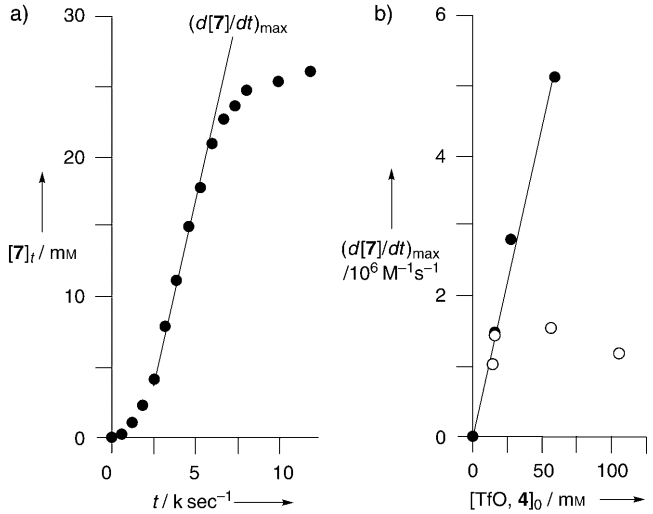


Figure 2. a) Temporal evolution of **7** during isomerization of **4** (29 mM) with TfOH (1 equiv) in C_6D_6, see the Supporting Information for full details. b) Relationship between maximal rate (*y* axis) and initial concentration (*x* axis) of TfOH (filled circles) and **4** (open circles).

We considered a number of mechanisms (Scheme 3) to explain the alkene migration at C9 and C10 (**4**→**7**), including acid-mediated[4b,12] (**A**) and allylic C–H insertion[4a,c,d,f] (**D**) mechanisms. Other possibilities include mechanisms involving the generation of a hydride[4g,h] through β-hydride elimination[6a]/re-addition sequences emanating from C4 (**B**) or C6 (**C**), as well as a palladium-assisted 1,3-suprafacial shift of a hydrogen atom (**E**).[13]

By using a library of ^{2}H, ^{13}C, and ^{108}Pd labeled[14] forms of **4**, we conducted reactions with TfOH(D) in C_6D_6. We employed a combination of $^{13}C\{^1H\}$ NMR spectroscopy ($^1J_{CD}$ and $\Delta\delta C_{H,D}$) and ESI-MS to quantify and locate ^{2}H-populations. The key experiments are summarized in Experiments (1)–(5) in Scheme 4.

Experiment 1 ruled out any direct involvement of the acid, (e.g. **A**) as migration induced by TfOD resulted in no deuterium incorporation in either **4** or **7**, even when eight equivalents of TfOD was used.

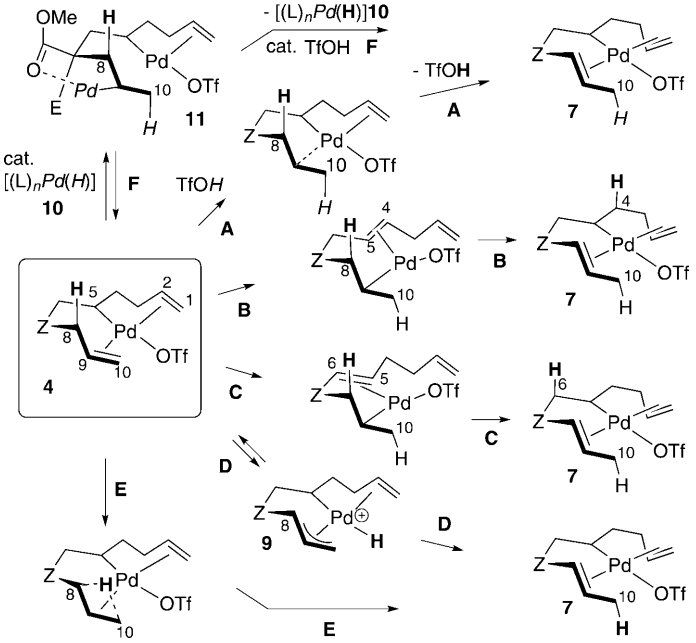
Experiment 2 ruled out mechanism **B** (and any involvement of alkene C1=C2), as the reaction of **4a** gave $[^2H_n,^{13}C_1]$-**7** without any detectable incorporation of ^{2}H at C1 or C4.

Experiment 3 ruled out mechanism **C**, as the reaction of **4b**/**4b′** gave $[^2H_n,^{13}C_1]$-**7** in which no ^{2}H was detected at ^{13}C-labeled C6. This outcome also rules out mechanism **E**, as a 1,3-suprafacial shift in **4b** can only involve ^{1}H. Meanwhile, the ^{13}C-labeled C10 in **7** was partially deuterated, suggestive of intermolecularity between **4b** and **4b′** in the alkene migration step.

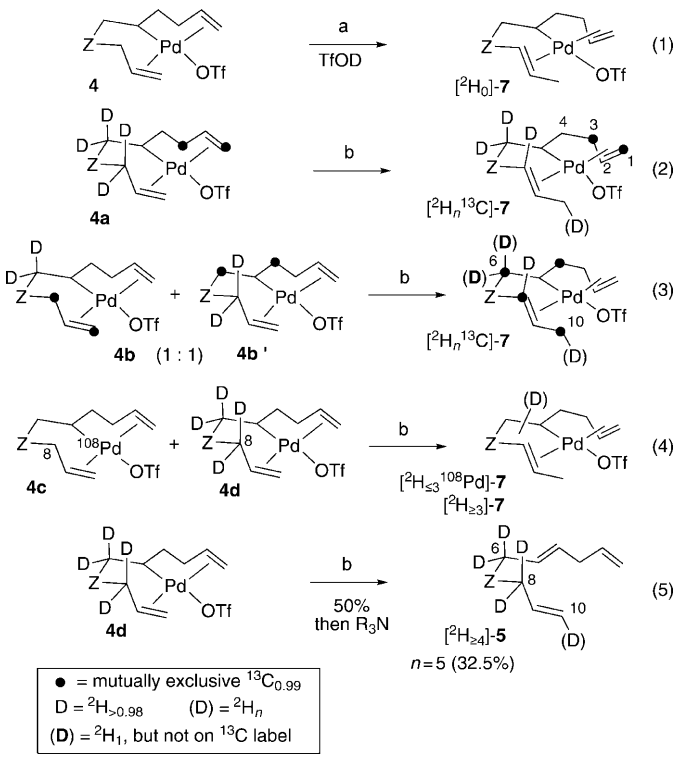
Experiment 4 confirmed that there is intermolecular transfer of a hydrogen atom, but not palladium, as the coreaction of **4c** (≥95% ^{108}Pd) with **4d** gave two distinct isotope clusters $[^2H_{\leq 3},^{108}Pd]$-**7** and $[^2H_{\geq 3}]$-**7** upon ESI-MS analysis. Simulation of the spectrum indicated that multiple ^{1}H/^{2}H transfers had occurred, for example, for $[^2H_n,^{108}Pd]$-**7**, $n=1$ (10%), $n=2$ (5%), and $n=3$ (2.5%). Mechanism **D** would allow hydride exchange by dimerization of the Pd(H) intermediate **9**. However, for this process to facilitate multiple transfers, generation of **9** would need to be reversible and ^{1}H/^{2}H exchange would only occur at C8.

Experiment 5 confirmed ^{1}H/^{2}H exchange in the substrate, but ruled out mechanism **D** because after 50% conversion into **7** the remaining **4d** had become partially deuterated at C10 but had not lost any deuterium atoms at C8 or C6. The two complexes are isobaric by ESI-MS, and key to the analysis of **4** without interference by **7** was their difference in reactivity towards the proton sponge (Scheme 2), thus allowing the generation of triene $[^2H_n]$-**5**, as a proxy for **4d**, without the generation of **8**.

Experiments 1 to 5 excluded all reasonable mechanisms for hydrogen migration which directly involved the palladium centre in **4** or the proton from the TfOH (mechanisms **A** to **E**).[15] In further experiments, it was found that analogues of **4** that lacked the conformationally unrestricted malonate ester moieties did not undergo migration at C9 and C10[16] (even



Scheme 3. Six mechanisms (**A** to **F**) for alkene migration **4**→**7**, with the key hydrogen-migration source and destinations indicated (as **H** and *H*), see text for full details. Dissociative[6a] diastereofacial inversion at C1 and C2 can occur before, during, or after alkene migration at C9 and C10. E = CO_2Me.



Scheme 4. ^2H, ^{13}C, and ^{108}Pd labeling to probe the mechanism of **4**→**7**. Conditions and reagents: a) TfOD (1–8 equiv), C_6D_6; b) TfOH (1 equiv), C_6D_6.

when coreacted with **4**) and thus the carbonyl group is essential for reactivity.

In earlier studies we showed that the "elimination" of triene **5** from σ-alkyl palladium complex **4** (Scheme 2) proceeded indirectly: a Pd(H) species was generated in very low equilibrium concentration with **4** by reversible dissociation at C1 and C2 as well as *syn*-β-hydride elimination at C4, and it is this Pd(H) complex that is deprotonated.[6a] In the absence of base, trace quantities of any Pd(H) species irreversibly liberated from this equilibrium will be capable of catalyzing 1,2-alkene migration in the bulk complex.[17] Mechanism **F** (Scheme 3) in which reaction of the [$(L)_nPd(H)$] complex **10** (L = alkene[6a,17e]) with **4** to generate **11** accounts for all of the isotopic labeling results: reversible hydropalladation at C9 and C10 of **4** allows intermolecular $^1H/^2H$ exchange at C10 and 1,2-alkene migration, without any cross-over of ^{108}Pd in 5,9-dipalladium complex **11**.[18] The malonate carbonyl serves to precoordinate the [$(L)_nPd(H)$] catalyst **10**, thus delivering it to C9 and C10 and stabilizing the resulting σ-alkyl/palladium intermediate; similar oxo-chelate derivatives have been identified in cycloisomerization.[17g]

In the absence of added TfOH, complex **4** undergoes slow alkene migration, and thus the acid[10] acts to accelerate the process rather than facilitate it.[19] The approximately first-order dependency on TfOH concentration suggests that it assists in product liberation from the resting state (**11**) of the catalytic cycle. Complex **11** cannot undergo *syn*-β-hydride elimination at C8 without ring opening of the oxo-chelate species.[20] Protonation of the carbonyl group in **11** by TfOH[10] would assist this process.

In summary, the simplicity of mechanisms **A** to **E** make them appealing as explanations for alkene migration in *n*-metallo-1-alkene complexes.[4] However, for the case of **4**→**7**, isotopic labeling experiments rule out all of these processes. In analogous migrations, the possibility of a "cryptocatalytic" intermolecular mechanism (**F**, Scheme 3) should thus be considered, whether it be a stoichiometric process[4] or an integral part of a catalytic cycle.[1]

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[1] See for example: a) F. Ozawa, A. Kubo, T. Hayashi, *J. Am. Chem. Soc.* **1991**, *113*, 1417–1419; b) O. Loiseleur, P. Meier, A. Pfaltz, *Angew. Chem.* **1996**, *108*, 218–220; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 200–202; c) T. G. Kilroy, A. J. Hennessy, D. J. Connolly, Y. M. Malone, A. Farrell, P. J. Guiry, *J. Mol. Catal. A* **2003**, *196*, 65–81; for elegant labeling studies of this system, see: d) B. M. M. Wheatley, B. A. Keay, *J. Org. Chem.* **2007**, *72*, 7253–7259.

[2] See for example: a) S. J. Miller, H. E. Blackwell, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 9606–9614; b) A. Fürstner, O. R. Thiel, L. Akermann, J.-J. Schanz, S. P. Nolan, *J. Org. Chem.* **2000**, *65*, 2204–2207; c) B. Schmidt, *Eur. J. Org. Chem.* **2004**, 1865–1880.

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[5] The temporal fractional conversion should in fact be concentration independent. There is also an induction period evident with **1** (R = butenyl), see Figure 4 in reference [4a].

[6] a) G. C. Lloyd-Jones, P. A. Slatford, *J. Am. Chem. Soc.* **2004**, *126*, 2690–2691; b) The OTf group is uniquely effective for the generation of **4**, analogous reactions using BF_4, PF_6, SbF_6, OTs, or OAc failed. Ts = 4-toluenesulfonyl.

[7] L. A. Evans, N. Fey, J. N. Harvey, D. Hose, G. C. Lloyd-Jones, P. Murray, A. G. Orpen, R. Osborne, G. J. Owen-Smith, M. Purdie, *J. Am. Chem. Soc.* **2008**, *130*, 14471–14473.

[8] Complex **6** acts as an efficient reagent for the generation of **3** from the corresponding the 1,6-diene. DFT calculations on

model complexes suggest the difference in insertion rates (21.5 versus 30.1 kcal mol^{-1}) arises from interactions between the terminal methyl group and the approaching allyl group in **6**, see the Supporting Information.

[9] CCDC 720419 (**7**.H_2O) and 720420 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[10] HBF_4·Et_2O, and CF_3CO_2H were also effective, however, AcOH, TsOH, and HCl were not. Reactions induced by HBF_4·Et_2O were the most efficient but varied substantially from batch to batch, even though the addition of NaF or TBAF to reactions conducted in the presence of TfOH had no effect. TBAF = tetra-*n*-butylammonium fluoride.

[11] E. S. Stoyanov, K.-C. Kim, C. A. Reed, *J. Phys. Chem. A* **2004**, *108*, 9310 – 9315.

[12] M. P. Muñoz, G. C. Lloyd-Jones, *Eur. J. Org. Chem.* **2009**, 516 – 524.

[13] Preliminary DFT studies of intramolecular mechanisms identified feasible intermediates for **B** and **C** (12 and 13 kcal mol^{-1} above **4**), but the calculated barriers in excess of 40 kcal mol^{-1} for **C**, **D**, and **E** would not be energetically accessible under the general reaction conditions (21 °C), and no suitable transition state was located for pathway **B**. See the Supporting Information for a discussion.

[14] a) P. Drozdzewski, M. Musiala, M. Kubiak, *Aust. J. Chem.* **2006**, *59*, 329 – 335; b) P. Drozdzewski, A. Brozyna, M. Kubiak, T. Lis, *Vib. Spectrosc.* **2006**, *40*, 118 – 126, for preparation of simple ^{104}Pd/^{110}Pd mixed-label coordination complexes.

[15] See the Supporting Information for additional reactions of **4**, and analogues, that reinforce this conclusion.

[16] Complexes tested: Z = diethyl, ethyl methyl, and di(*tert*-butyl) malonate, *N*-tosylamide, 4′,4′-dimethyl-3′,5′-dioxan-2′,6′-dionyl, and 3′,5′-dioxan-4-onyl. See the Supporting Information.

[17] The intermolecular ^{1}H/^{2}H transfers are reminiscent of a palladium-catalyzed diene cycloisomerization mediated by a Pd(H) species that has been generated in situ. Such reactions commonly display induction periods and pseudo zero-order substrate dependency: a) K. L. Bray, I. J. S. Fairlamb, J. P. H. Charmant, G. C. Lloyd-Jones, *Chem. Eur. J.* **2001**, *7*, 4205 – 4215; b) K. L. Bray, I. J. S. Fairlamb, J.-P. Kaiser, G. C. Lloyd-Jones, P. A. Slatford, *Top. Catal.* **2002**, *19*, 49 – 59; c) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215 – 236; d) K. L. Bray, G. C. Lloyd-Jones, M. P. Muñoz, P. A. Slatford, E. H. P. Tan, A. R. Tyler-Mahon, P. A. Worthington, *Chem. Eur. J.* **2006**, *12*, 8650 – 8663; e) R. S. Widenhoefer, *Acc. Chem. Res.* **2002**, *35*, 905 – 913; f) L. A. Goj, G. A. Cisneros, W. Yang, R. A. Widenhoefer, *J. Organomet. Chem.* **2003**, *687*, 498 – 507.

[18] Addition of a stoichiometric quantity of [$(PCy_3)_2$Pd(H)Cl] (Cy = cyclohexyl; prepared according to I. D. Hills, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 13178 – 13179) to **4** in $CDCl_3$ led to very slow decomposition to give a mixture of products, including **5** (ca. 50% over 12 h), but with no trace of **7** evident by ^{1}H NMR analysis. Addition of 10 mol% [$PdCl_2(MeCN)_2$] to **4** in $CDCl_3$ (2 h) and subsequent addition of 10 mol% Ph_3SiH resulted in no significant change over 12 h.

[19] TfOH may also generate the active catalyst **10** from **4**, for example by demethylative lactonization (see reference [12]) then β-hydride elimination at C6. Despite careful GCMS/NMR analysis, we were unable to identify any coproducts from this process.

[20] A five-ring oxo-chelate with palladium σ-bonded to C8 is also feasible, provided that the requisite Pd,H dyotropy (see reference [1d]) is stereospecific and reversible, so that there is no ^{2}H/^{1}H scrambling between C8 and C9.

