Reaction Mechanisms

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$[(RCN)_2PdCl_2]$-Catalyzed *E*/*Z* Isomerization of Alkenes: A Non-Hydride Binuclear Addition–Elimination Pathway**

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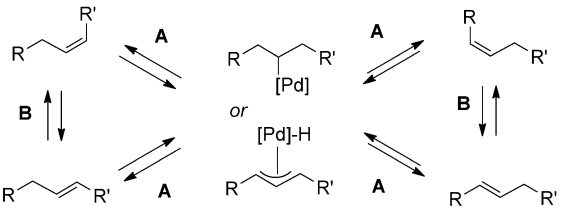
It has been known since the 1960s that $[(RCN)_2PdCl_2]$ complexes efficiently catalyze double-bond migration and geometric *E*/*Z* interconversion in alkenes.[1] Herein we propose a new addition–elimination mechanism with a binuclear Pd species that selectively effects *E*/*Z* interconversion;[2] before describing this, we consider the mechanisms previously proposed for this process.[1,3,4] A key aspect of the discussion herein, is that although there has been considerable debate as to whether isomerization involves, inter alia,[1f,g,3h,4] [Pd-H] species and η^1-alkyl intermediates,[1a,i] or η^3-Pd(H) intermediates,[1b,d,e,g,h,2a] when concurrent with alkene migration,[1a–e,g–i] the process of *E*/*Z* interconversion is assumed to arise through the same mechanism (pathway **A**, Scheme 1).



Scheme 1. Alkene isomerization catalyzed by $[(RCN)_2PdCl_2]$. Pathway **A** effects both migration and *E*/*Z* interconversion through addition–elimination of in situ generated [Pd-H] species, or allylic C—H insertion. Pathway **B** effects *E*/*Z* interconversion without migration.

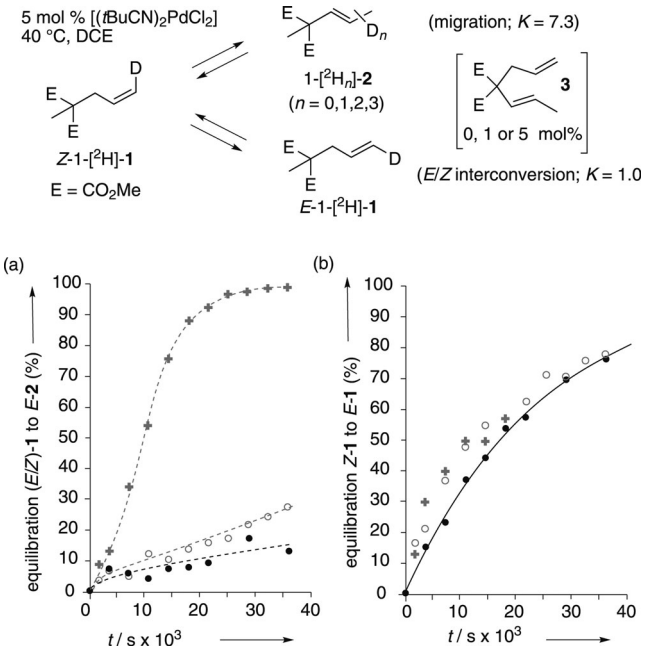


Figure 1. Isomerization of 1-(*Z*)-[^{2}H]-[**1**] (0.15 M) to a) [^{2}H]-[**2**] and b) 1-(*E*)-[^{2}H]-[**1**] catalyzed by $[(tBuCN)_2PdCl_2]$ and diene **3** (0 mol% (crosses), 1 mol% (open circles), 5 mol% (filled circles)). a) Dashed lines are solely a guide to the eye. b) $k_{obs}/[Pd] = 2.7\times10^{-3}\,M^{-1}\,s^{-1}$; $\Delta G^{\ddagger} = 22$ kcal mol^{-1}.[12]

Unpublished observations[5] made during mechanistic studies[6] of Pd-catalyzed 1,6-diene cycloisomerization[7] led us to suspect that there is a mechanistic dichotomy in $[(RCN)_2PdCl_2]$-catalyzed alkene isomerization,[1] and thus to investigate selective decoupling of migration from *E*/*Z* isomerization using [Pd-H] traps.[6e,f,8] We began with the isomerization of deuterium labeled methyl allyl malonate (*Z*)-1-[^{2}H]-**1** (Figure 1). Alkene migration displayed sigmoidal kinetic profiles, whereas, *E*/*Z* interconversion proceeded directly, that is, without an induction period. However, detailed analysis of the kinetics was precluded by extensive H/D exchange.[9] Repeating the isomerization in the presence of 1 to 5 mol% 1,5-diene **3**,[6e,f] an efficient [Pd-H] trap, induced substantial suppression of both the alkene migration and the isotopic scrambling. Simple pseudo first-order equilibrium kinetics were then observed for *E*/*Z* interconversion, see solid line in Figure 1b.[10]

The sigmoidal kinetic profile for migration and its inhibition by substoichiometric [Pd-H] trap **3**, adds to the body of evidence[1a,i] for $[(RCN)_2PdCl_2]$-catalyzed alkene migration involving low concentrations of in situ generated [Pd-H] species. The selectivity of the inhibition[11] is the first experimental demonstration that concurrent *E*/*Z* interconversion can follow a pathway (**B**) that is mechanistically independent from the pathway for migration (**A**).

The isomerization of *Z*-1-phenyl-buten-2-ene (*Z*-**4**) was studied under analogous conditions (Scheme 2).[12] For this alkene, migration is thermodynamically more favorable[13] than *E*/*Z* interconversion, resulting ultimately in >95% *E*-**5**. Nonetheless, both isomerization processes displayed approximate pseudo first-order equilibrium kinetics, allowing

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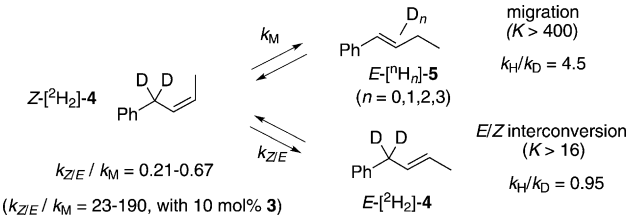
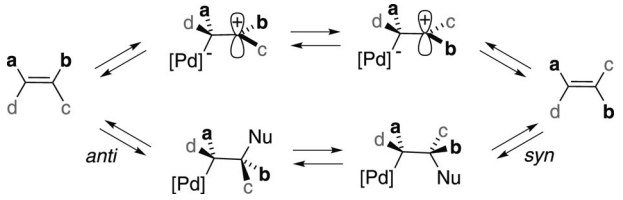


Scheme 2. Isomerization of *Z*-**4** and *Z*-[$^2H_2$]-**4** (0.5 M) catalyzed by 10 mol% [$(MeCN)_2PdCl_2$][15] at 21 °C in solvent polarities ranging from $\varepsilon = 0.9$ to 21.0.[12] Linear correlations of empirical rate constants for pseudo first-order equilibration: k_M (s^{-1}) $= 2.7\times10^{-6}\,\varepsilon$, $r^2 = 0.94$; $k_{Z/E}$ (s^{-1}) $= 0.8\times10^{-6}\,\varepsilon$, $r^2 = 0.67$.

direct analysis of the relative rates ($k_{Z/E}/k_M$) under a variety of conditions.[12] Isomerization was favored by polar solvents, with a linear correlation of k_{obs} versus solvent dielectric (ε) for both processes.[12] However, the effect was relatively small;[14] ruling out substantial charge generation in the catalytic intermediates in either process. With *Z*-1,1-[$^2H_2$]-**4**, migration was attenuated by a primary kinetic isotope effect ($k_H/k_D = 4.5$)[12] and accompanied by extensive intermolecular deuterium migration, just as would be expected for a [Pd-H]-based mechanism for pathway **A**. Addition of [Pd-H] traps such as diene **3** or TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl),[8] led to substantial (up to 600-fold) increases in $k_{Z/E}/k_M$,[12] through selective inhibition of migration (k_M).

The kinetics of *E*/*Z* interconversion of *Z*-β-methyl styrene **6** (Figure 2a),[2a,b] for which alkene migration is endergonic,[13] were not suppressed by a [Pd-H] trap, and corresponded to a simple pseudo first-order conversion of *Z*-**6** to *E*-**6** ($K = 32$), through pathway **B**. Alternative mechanisms to the η^1-alkyl[1a,i] and η^3-Pd(H)[1b,d–h,2a] pathways (**A**) have been previously suggested[1f,16] for Pd^{II}-catalyzed *E*/*Z* isomerization.[17] Rericha et al. have proposed that Pd^{II}–alkene coordination results in 31% "softening" of the double bond character.[16] However, examination of models shows that torsion of the C=C bond alone is not enough to effect *E*/*Z* isomerization, and we were unable to find an isomerization transition state of this type in DFT calculations.[18] From an experimental study of [$(PhCN)_2PdCl_2$]-catalyzed *E*/*Z* isomerization in 1,2-[$^2H_2$]-ethylene, which cannot proceed through allylic C–H insertion, and does not involve intermolecular H/D migration, Wells et al.[1f] proposed that alkene coordination to Pd^{II} results in an incipient β-carbocation,[4,19] facilitating C–C rotation, see upper pathway in Scheme 3.



Scheme 3. Generic mechanisms for geometric interconversion of an alkene through incipient β-carbocation and nucleophilic addition routes.

Indeed, we found the more electrophilic complexes [$(MeCN)_4Pd][OTf]_2$ and [$(MeCN)_2Pd(OTs)_2$] induced >100-fold faster isomerization of *Z*-**4** than [$(RCN)_2PdCl_2$].[12] However, on addition of the [Pd-H] trap **3**, there was substantial suppression (up to 3000-fold) in both isomerization processes ($k_{Z/E}/k_M \le 1$), indicative of predominant catalysis by [Pd-H] species (pathway **A**) with these sulfonate catalysts.

The low sensitivity of pathway **B** to solvent polarity,[12] as well as a negligible secondary KIE ($k_H/k_D = 0.95$) obtained with (*Z*)-1,1-[$^2H_2$]-**4**[12] weigh against the incipient β-carbocation mechanism.[1f,4,19] This conclusion was firmly reinforced by DFT studies[18] that indicated a high $\Delta G^{\ddagger}$ (53.3 kcal mol^{-1}) for C–C rotation in [$(ethene)_2PdCl_2$], through a β-carbocation, inconsistent with the values observed for alkenes **1**, **4** and **6** (20–24 kcal mol^{-1}). Varying the computational method or the ancillary ligands (e.g. [(ethene)-$(CH_3CN)PdCl_2$]) did not materially change the calculated barrier; adding an alkene substituent ([(propene)-(ethene)$PdCl_2$]) lowers the barrier, but only to 46.6 kcal mol^{-1}.

An addition–elimination process, see lower pathway in Scheme 3, could bypass the generation of a β-carbocation, provided that it can proceed through a *syn*-then-*anti*, or an *anti*-then-*syn*, sequence.[20] Alkene chloropalladation with [$Li_2Pd_2Cl_6$] in AcOH has been shown by Henry to be non-stereospecific.[21] An analogous mechanism with [$(RCN)_2PdCl_2$] (Scheme 3; Nu = Cl) would effect *E*/*Z* interconversion. However, this would necessitate addition–elimination of chloride ion,[21] inconsistent with the low sensitivity of the reaction to solvent polarity.[12] Nonetheless, the concept of a reversible chloropalladation process was further considered when a more detailed analysis of the kinetics of *E*/*Z* interconversion of *Z*-**6** (Figure 2b) revealed alkene inhibition, and a palladium dependency that was greater than first-

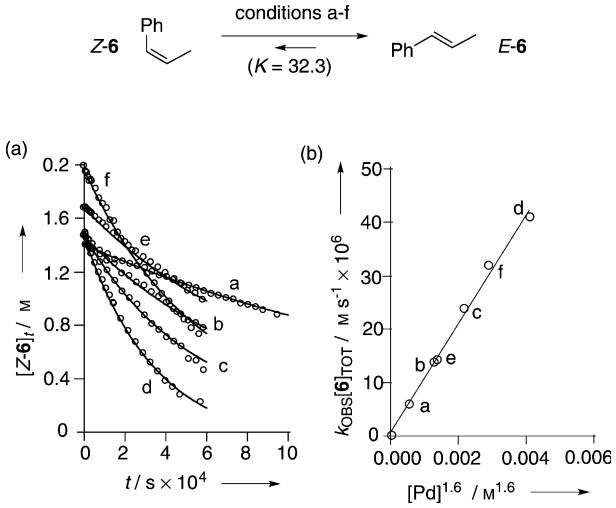
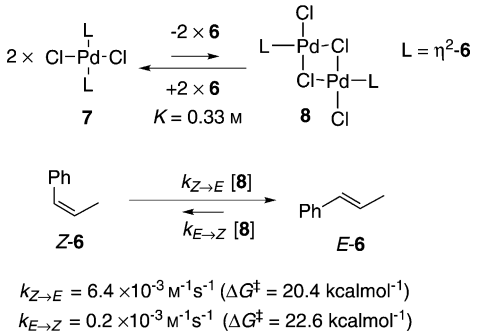


Figure 2. a) Isomerization of *Z*-**6** to *E*-**6** catalyzed by [($tBuCN)_2PdCl_2$] in CD_2Cl_2 at 25 °C with $[\mathbf{6}]_{TOT} = 0.144$–0.205 M and [Pd] = 8.2–30.6 mM. Conditions a–f (mol% Pd): a, 6.0; b, 9.8; c, 13.7; d, 17.0; e, 9.6; f, 10.8.[12] Lines through data are kinetic simulations employing the model in Scheme 4. b) Empirical pseudo first-order rate constant: $k_{obs} = 1.3\times10^{-3}\,[Pd]^{1.6}[\mathbf{6}]_{TOT}^{-1}$.

order.[12] A simple model in which there is an alkene-dependent equilibrium between mononuclear (**7**) and binuclear (**8**) alkene complexes,[22] with *E*/*Z* interconversion catalyzed only by the binuclear complex **8** (Scheme 4) satisfactorily simulated all of the kinetic data (see solid lines through data in Figure 2) using a single set of equilibrium and rate constants (K, $k_{Z\rightarrow E}$ and $k_{E\rightarrow Z}$).[12]

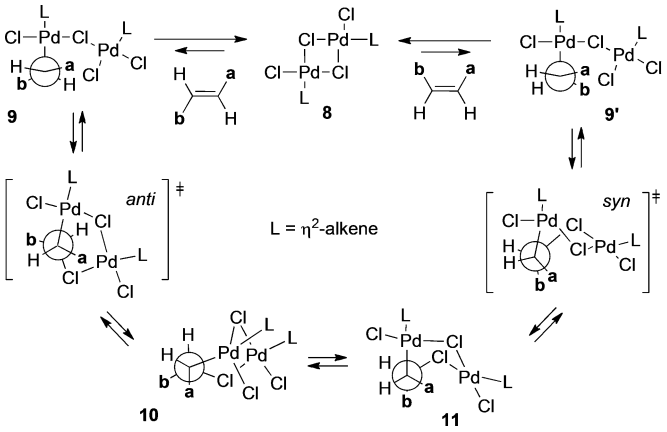


Scheme 4. Model used for simulation of the kinetics of *E*/*Z* interconversion of β-methyl styrene (**6**), starting from *Z*-**6** (Figure 2).[12]

Using model complexes where L = η²-ethene, DFT predicts $\Delta G = +3.9$ kcal mol^{-1} for **7** + **7** → **8** + 2L,[18] consistent within computational error with the dimerization equilibrium employed in the kinetic model ($\Delta G = +0.7$ kcal mol^{-1}), where L = η²-β-methyl styrene **6** (Scheme 4). The same binuclear species **8** [{(alkene)PdCl$_2$}$_2$] was suggested by Sparke et al.[1c] in 1965 to be the active catalyst for alkene isomerization (migration and *E*/*Z* interconversion) by [(PhCN)$_2$PdCl$_2$], albeit without kinetic evidence or a specific mechanistic proposal. The involvement of binuclear complexes was also noted by Henry for *anti*-chloropalladation of alkenes by [Li$_2$Pd$_2$Cl$_6$].[20] However, the reaction was proposed to proceed in a pseudo mononuclear manner, with the second Pd center simply serving to reduce the electrostatic repulsion of an external chloride nucleophile. Since these anionic interactions do not apply in the current system, we sought to find a mechanism that specifically requires the involvement of both Pd centers. In other words, a binuclear non-ionic chloropalladation process, that is able to proceed in both a *syn* and an *anti* manner, thereby generating a pathway for *E*/*Z* isomerization.

DFT calculations[18] show that an alkene (ethene or propene) can add to bis-chloro bridged complex **8** (L = η²-ethene) to form various metastable species lying just a few kcal mol^{-1} higher in free energy than **8** + alkene, including a monobridged species **9** (L = η²-ethene, Scheme 5).[3g] The long Pd–Cl bonds (2.38–2.45 Å) and acute Cl-Pd-Cl bond angles (90°) in the key monobridged species **9** facilitate a reversible binuclear 1,2-chloropalladation of the alkene, involving the coordinated Pd unit and a chloride on the "other" Pd center.

There are two modes of binuclear 1,2-chloropalladation: an *anti*-addition and a *syn*-addition, generating six-membered ring adducts **10** and **11**, respectively, with boatlike geometries. These adducts can undergo facile interconversion through processes akin to conformational isomerization in a cyclohexane ring. The net process of bridge-cleavage (→**9**), binuclear 1,2-chloropalladation (→**10**/**11**), binuclear elimination (→**9**), and bridge-closure (→**8**) effects catalysis of *E*/*Z* isomerization in the bulk alkene (Scheme 5). The turnover-limiting step for pathway **B** with propene (Figure 3) is predicted to be the *anti* addition (or *anti* elimination in the reverse direction), with a calculated $\Delta G^{\ddagger}$ of 22.9 kcal mol^{-1} above propene + **8** (26.8 kcal mol^{-1} in the case of ethene), consistent with the measured rates of *E*/*Z* isomerization for alkenes 1-[^{2}H]-**1**, **4** and **6** ($\Delta G^{\ddagger} = 20$–24 kcal mol^{-1}).



Scheme 5. *E*/*Z* interconversion of a generic 1,2-disubstituted (**a**,**b**) alkene (in Newman projection when Pd coordinated) through *syn* and *anti* binuclear 1,2-chloropalladation. See Figure 3 for structures and energies, according to DFT calculations, where the alkene is propene.

In summary, based on prior observations in diene cycloisomerization,[6] we have reinvestigated the isomerization of alkenes catalyzed by [(RCN)$_2$PdCl$_2$].[1,2] Using [Pd-H] traps[6e,f,8] to inhibit migration, we reveal a background

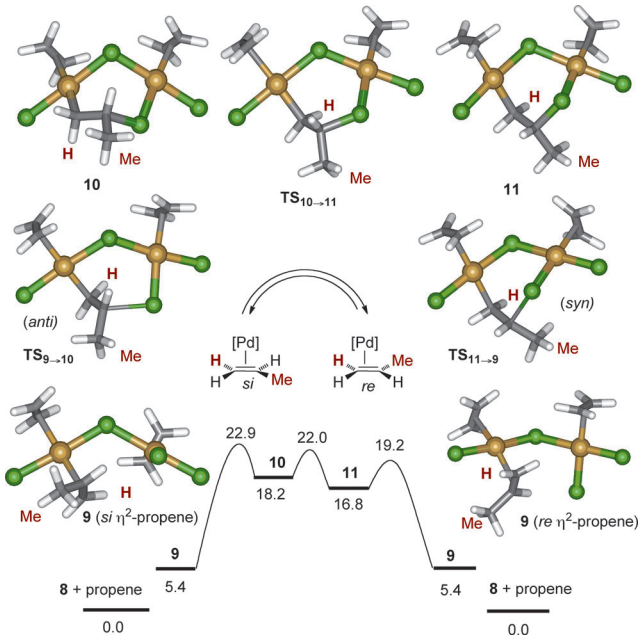


Figure 3. ΔG°(298 K) profile (kcal mol^{-1}; DFT[18]) for degenerate geometric isomerization (permutation) of propene catalyzed by the binuclear complex **8**, where L = η²-ethene.

interconversion of *E*/*Z* isomers that does not involve [Pd-H] species,[1a,i] or allylic C–H insertion,[1b,d–h,2a] or incipient β-carbocations.[1f,4,19] Kinetic simulations, isotopic labeling and DFT studies support *E*/*Z* interconversion proceeding through reversible *syn* and *anti* binuclear chloropalladation of the alkene (Scheme 5 and Figure 3).

This binuclear addition–elimination mechanism may also explain why double-bond[23] and H-migration[1f] is not observed in other Pd-catalyzed *E*/*Z* isomerization processes. The geometries of the proposed intermediates should also facilitate the design of selective isomerization catalysts based on variation of the spectator alkenes (L) in complexes **8**–**11**. The selective inhibition of Pd-catalyzed alkene migration, using [Pd-H] traps such as 1,5-diene **3**[6e,f] or TEMPO,[8] may also find application in other catalytic processes, for example in Mizoroki–Heck reactions.[24] It is also evident from Figure 3, that **9**→**10**→**11**→**9** can effect intramolecular enantiofacial interconversion of a coordinated prochiral alkene, that is without dissociation from the metal or involvement of an external ligand; a feature that may be of importance in asymmetric catalysis.

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[5] Cycloisomerization proceeded with sigmoidal kinetics[6d,e] whereas *E*/*Z* interconversion, detected by ^{1}H NMR spectroscopy in D-labeled substrate, proceeded with pseudo first-order equilibrium kinetics and no induction period. See the Supporting Information for full details.

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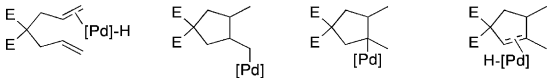
[7] The Pd-H based mechanism below has been proposed for cycloisomerization of dimethyl diallyl malonate.[6b–e]



[8] DPPH and TEMPO are efficient [Pd-H] traps, through Pd^{II} to Pd^{I} reduction, see: A. C. Albéniz, P. Espinet, R. López-Fernández, A. Sen, *J. Am. Chem. Soc.* **2002**, *124*, 11278–11279.

[9] GCMS/NMR analysis showed deuterium transfer to and from C(1) in **1** to C(2)/C(3) in **1** and **2**. Intermolecular transfer was faster than migration, consistent with nonproductive hydropalladation/β-hydride elimination at C(1)=C(2), in both orientations.

[10] Linear regression of $0.5 \times \ln(x_Z - 0.5) = -k_{obs}t$; x_Z = mol fraction *Z*-**1**.

[11] Other [Pd-H] traps were also tested, including norbornadiene, DPPH,[8] TEMPO,[8] C(1)-Ph **3**, N(*i*Pr)$_2$Et), Proton Sponge, and CCl_4.[12]

[12] See the Supporting Information for full details.

[13] Equilibrium mol fractions for **4**/**5** at 40 °C in THF were estimated as *Z*-**4** (0.002), *E*-**4** (0.032), *Z*-**5** (0.011), and *E*-**5** (0.955) by isomerization of **5** (*E*/*Z* 50/50; Wittig olefination) for 4 days. Equilibrium mol fractions at 21 °C in CH_2Cl_2 for **6** were estimated analogously, as *Z*-**6** (0.03), *E*-**6** (0.97), and 1-phenylprop-2-ene (< 0.001).

[14] For example, there is only a 12-fold increase in k_M and a 7-fold increase in $k_{Z/E}$, on changing from CH_2Cl_2 ($\varepsilon = 0.9$) to acetone ($\varepsilon = 21$); see the Supporting Information for full details.

[15] $[(t\text{BuCN})_2PdCl_2]$, $[(MeCN)_2PdCl_2]$, and $[(PhCN)_2PdCl_2]$ all catalyzed isomerization at similar rates.[12] No isomerization was detected over a period of 15 days using 10 mol % $[Pd(CN)_2]$,

$[(PPh_3)_2PdCl_2]$, $[(MeCN)_2Pd(O_2CCF_3)_2]$, $[Pd(O_2CCF_3)_2]$, or $[(DMSO)_2PdCl_2]$.
[16] R. Ponec, R. Rericha, *J. Organomet. Chem.* **1988**, *341*, 549 – 557.
[17] The mechanism of Pd^0-catalyzed interconversion of *E/Z* alkenes has been studied in detail: L. Canovese, C. Santo, F. Visentin, *Organometallics* **2008**, *27*, 3577 – 3581; there is no evidence for reduction of Pd^{II} to Pd^0 in the systems reported herein.
[18] Calculations were performed using the B3LYP functional, a relativistic effective core potential (ECP) on Pd with an associated triple-zeta valence basis, and the 6-31G(d) basis on other atoms. The −D3 dispersion correction to energies was included. See the Supporting Information for full details.
[19] P. M. Henry, *J. Am. Chem. Soc.* **1972**, *94*, 7316 – 7322.
[20] Addition of neutral nucleophiles, for example, RCN or H_2O, to Pd-catalyzed *E*/*Z* interconversion of *Z*-**6** caused no significant rate enhancement.[12]
[21] P. M. Henry, *J. Org. Chem.* **1972**, *37*, 2443 – 2447.
[22] For early examples of crystal structures of binuclear μ-chloroalkene Pd complexes analogous to **8**, see: a) J. N. Dempsey, N. C. Baenziger, *J. Am. Chem. Soc.* **1955**, *77*, 4984 – 4987; b) J. R. Holden, N. C. Baenziger, *J. Am. Chem. Soc.* **1955**, *77*, 4987 – 4990; c) M. Zettlitzer, H. tom Dieck, L. Stamp, *Z. Naturforsch. B* **1986**, *41*, 1230 – 1238; for a recent review of binuclear Pd complexes and their reactions, see: d) V. K. Jain, L. Jain, *Coord. Chem. Rev.* **2005**, *249*, 3075 – 3197.
[23] See for example: I. S. Kim, G. R. Dong, Y. H. Jung, *J. Org. Chem.* **2007**, *72*, 5424 – 5426; and specifically entries 5, 6 and 8 in Table 2.
[24] See for example: a) F. Ozawa, A. Kubo, Y. Matsumoto, T. Hayashi, E. Nishioka, K. Yanagi, K. Moriguchi, *Organometallics* **1993**, *12*, 4188 – 4196; b) G. C. Lloyd-Jones, P. A. Slatford, *J. Am. Chem. Soc.* **2004**, *126*, 2690 – 2691; c) B. M. M. Wheatley, B. A. Keay, *J. Org. Chem.* **2007**, *72*, 7253 – 7259.

