

## Unusually Large Primary $^2\text{H}/^1\text{H}$ Kinetic Isotope Effects Accompanying a *syn*- $\beta$ -H Elimination Reaction in a $\sigma$ -Alkyl–Palladium Complex

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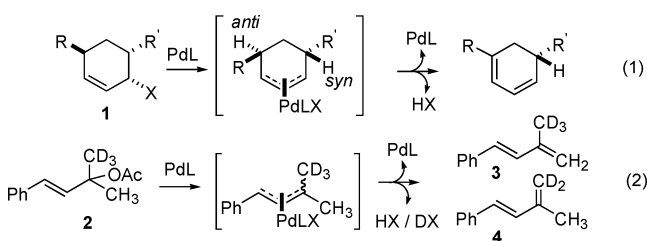
*syn*- $\beta$ -Hydride elimination of  $\sigma$ -bound alkyl, alkoxy, or alkylamine ligands is a fundamental process in organometallic catalysis,<sup>1</sup> and the stereochemistry of such processes can have important mechanistic consequences. Indeed, the restrictions placed on C–C rotation by use of a cyclic substrate and the *syn* nature of the  $\beta$ -hydride elimination that develops from an agostic interaction<sup>2</sup> are essential components of the asymmetric Heck reaction.<sup>3</sup> The ubiquitous nature of *syn*- $\beta$ -H elimination from Pd– $\sigma$ -alkyl complexes, has resulted in the rather rare cases of *anti*- $\beta$ -H elimination attracting significant attention.<sup>4</sup> For example, general base-mediated *anti*- $\beta$ -H eliminations in the Pd-catalyzed generation of dienes from allylic esters of type **1** have been independently demonstrated by Andersson<sup>4a</sup> and by Takacs,<sup>4b</sup> Scheme 1, eq 1.

In the absence of additional stereochemical information, e.g. in acyclic substrates, the primary kinetic isotope effect (*prim*-KIE) for  $\beta$ -H elimination from {H/D–C–C–Pd} has been employed to distinguish between *syn*- ( $k_{\text{H}}/k_{\text{D}}$  ca. 2–3)<sup>4b</sup> and *anti*- ( $k_{\text{H}}/k_{\text{D}}$  ca. 5–7) mechanisms.<sup>5</sup> For example, large  $k_{\text{H}}/k_{\text{D}}$  values (5.4–6.9) were found by Takacs for the Pd-catalyzed elimination of **2** to give **3/4** (Scheme 1, eq 2).<sup>4b</sup> Herein we demonstrate that large  $k_{\text{H}}/k_{\text{D}}$  values (6–7) can also accompany a *syn*- $\beta$ -H elimination process in a  $\sigma$ -alkyl Pd complex and the magnitude of  $k_{\text{H}}/k_{\text{D}}$  should thus be interpreted with caution.

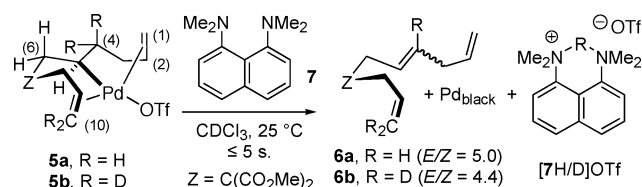
The fully characterized Pd– $\sigma$ -alkyl complex **5a**<sup>6</sup> (Scheme 2), is remarkably stable<sup>7</sup> in  $\text{CDCl}_3$  solution ( $\leq 20\%$  decomposition after 5 d at 25 °C).<sup>6c</sup> Single-crystal X-ray diffraction of **5a**<sup>6b</sup> shows that a non-*syn*-relationship between the Pd and the four  $\beta$ -hydrogens (C(4) and C(6)) is enforced by coordination of the C(1)=C(2) and C(9)=C(10) alkene units to Pd. In  $\text{CDCl}_3$  solution, NMR analysis confirms that **5a** is the sole observable species and that the conformation and diastereoface coordination of both alkenes are analogous to the solid state.<sup>6b</sup> However, on addition of stoichiometric water and catalytic halide (NaI), smooth  $\beta$ -H elimination occurs at C(4) over a period of ca. 60 min at 25 °C to yield triene **6a**.<sup>6a</sup> Since both halide and water alone are not effective, we considered the possibility that aqueous halide acts as a general base catalyst in an *anti*- $\beta$ -H elimination. Consistent with the expectation that a stronger base would effect more efficient elimination,  $\text{Et}_3\text{N}$ , pyridine, Hünig's base, and Proton Sponge (**7**, Scheme 2) were all found to effect rapid generation of **6a**.

The reaction of **5a** with **7** in  $\text{CD}_2\text{Cl}_2$  and in  $\text{CDCl}_3$  solution was studied in detail by  $^1\text{H}$  NMR. At 25 °C, reaction was essentially instantaneous, and titration with 0.1 equiv aliquots of **7** demonstrated a strict 1/1 stoichiometry to give **6a**/[7H]OTf as the only NMR-observable products, together with a Pd black deposit. An analogous NMR-titration of a 50/50 mixture of **5a** and the D-labeled complex **5b** in which  $\beta$ -D elimination must occur, yielded a net  $k_{\text{H}}/k_{\text{D}}$  value of  $6 \pm 1$ .<sup>8</sup> In contrast to *syn*- $\beta$ -H elimination which would generate a Pd<sup>II</sup>(H)(alkene) complex, *anti*- $\beta$ -H elimination would lead directly to a Pd<sup>0</sup>(alkene) complex. Conducting the reaction of **5a** and **7** at low temperature ( $-60$  °C,  $\geq 90\%$ , 1.5 h)

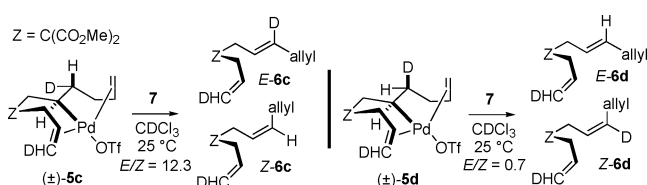
### Scheme 1



### Scheme 2



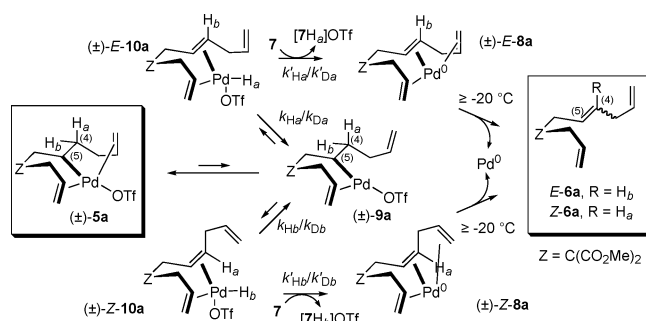
### Scheme 3



gave a colorless solution containing a highly fluxional complex (**8a**) together with [7H]OTf but no trace of **6a** ( $^1\text{H}$  NMR). On warming the solution slowly, **6a** and Pd<sub>black</sub> were irreversibly generated from **8a** at ca.  $-20$  °C.<sup>9</sup> However, addition of TFOH to **8a** ( $-60$ – $25$  °C) cleanly regenerated **5a** ( $>95\%$ ). The primary and rather unstable product (**8a**) from reaction of **5a** with **7** is thus assigned as a Pd<sup>0</sup> complex of **6a**, most likely  $\eta^6$  in nature.<sup>10</sup> All of the above are suggestive of a general base-catalyzed *anti*- $\beta$ -H elimination. However, inconsistent with this conclusion, the rates of reaction of *separate* samples of **5a** and **5b** with **7** at  $-60$  °C in  $\text{CD}_2\text{Cl}_2$  were found to be pseudo-first-order and indistinguishable ( $k_{\text{obs}} = 3.5 \pm 0.4 \times 10^{-4} \text{ s}^{-1}$ ).<sup>11</sup> Thus, in contrast to the competition experiment at 25 °C, the *prim*-KIE on the absolute rate of reaction at  $-60$  °C is negligible.

The base-mediated reaction of **5a** generates *E* and *Z* isomers of triene **6a**. With **7** at room temperature, the *E/Z* ratio of **6a** is found to be  $5.0 \pm 0.1$ .<sup>12</sup> By preparation of stereospecifically  $^2\text{H}$ -labeled complexes, **5c** and **5d**, Scheme 3,<sup>13</sup> in which the  $\beta$ -carbon (C(4)) bears one D and one H, we were able to study both the stereochemistry of the  $\beta$ -H elimination process and also perturb the *E/Z* partitioning through KIEs. The reactions of **5c** and **5d** demonstrate that the  $\beta$ -H elimination proceeds via a *syn* mechanism and is thus not a base-mediated *anti* elimination.<sup>14</sup> However, analysis of the *E/Z* ratios in **6c/6d** yields net  $k_{\text{H}}/k_{\text{D}}$  values of up to 7.1  $\pm$

Scheme 4



0.3,<sup>15</sup> more than *double* the maximum *prim*-KIE expected for *syn*- $\beta$ -H elimination.<sup>5</sup>

Using the  $k_H/k_D$  values from **5c/5d**, and assuming *sec*-KIEs are small, an *E/Z* ratio of 1.8 is predicted for **5b**→**6b** (see Supporting Information). However, the experimental *E/Z* ratio of  $4.4 \pm 0.2$  is closer to that of **5a**→**6a** and this suggests that the *E/Z* partitioning is controlled by more than a single step.<sup>12</sup> The complex features of the generation of **6** from **5** mediated by **7** can be accommodated by the mechanism outlined in Scheme 4. Reversible and unfavorable dissociation of the alkene unit (C(1)=C(2)) in **5** generates **9** in which *syn*- $\beta$ -H elimination, presumably with a “normal”  $k_H/k_D$  value, is now possible due to free C(4)–C(5) rotation. The primary products would be diene–Pd–H complexes *E*-/*Z*-**10**, which, in the absence of base, undergo rapid intramolecular hydropalladation to regenerate **9**. The stereospecific nature of both the *syn*- $\beta$ -H elimination and addition results in the diastereoisotopic stability of **5c** and **5d**.

In the presence of base, the *syn*- $\beta$ -H elimination product *E*-/*Z*-**10** undergoes deprotonation at Pd ( $k'_H/k'_D$ ) to yield complex *E*-/*Z*-**8** which can be observed by NMR below  $-20$  °C. At high [7] and low temperature ( $-60$  °C), the absolute rate of reaction of **5** is controlled by alkene dissociation and thus pseudo-first-order kinetics, with net  $k_H/k_D$  close to unity is found for **5b**.<sup>11</sup> In NMR titration experiments at room temperature, with low and limiting [7],<sup>8</sup> the relative rates of generation, hydropalladation, and deprotonation of **10a/10b** result in a large net  $k_H/k_D$  value (up to ca. 6). Moreover, the equilibrium distributions, equilibration rates, and the efficiency of the base in partitioning *E*-**10** and *Z*-**10** all contribute to the net *E/Z* ratios in **6a**–**d** and thus the large  $k_H/k_D$  values (up to ca. 7).<sup>8</sup>

In summary, diastereospecific labeling (**5cd**) shows the generation of triene **6** from Pd- $\sigma$ -alkyl complex **5** to proceed with *syn* stereochemistry. NMR/kinetic studies suggest that the base serves to deprotonate isomeric Pd–H diene complexes *E*-/*Z*-**10**. The complex interplay of three *prim*-KIEs ( $\beta$ -H elimination, hydropalladation and Pd–H deprotonation) gives rise to *net* kinetic/equilibrium  $k_H/k_D$  values which are much larger than those usually associated with *syn*- $\beta$ -H elimination. It is of note that the conventional mechanism for the Heck reaction<sup>3</sup> involves dissociation of [Pd–H] from the alkene *before* its reduction to Pd<sup>0</sup>. In the asymmetric Pd–BINAP catalyzed arylation of dihydrofuran, the strong hindered base **7** is found to upgrade the initial selectivity through diastereoselective liberation of the minor enantiomer of primary alkene product, prior to Pd/H dyotropy.<sup>16</sup> Weak ion-pairing

in [7H]OAc has been suggested as the origin of this effect.<sup>16a</sup> Diastereoselective deprotonation of the primary (alkene)Pd(X)–H species by **7**<sup>16b</sup> or by acetate would provide an alternative explanation.

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**Supporting Information Available:** Procedures for preparation/reaction of complexes and selected  $k_H/k_D$  values for  $\beta$ -H elimination in H–C–C–M. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (5) The transition state for *syn*- $\beta$ -H elimination has nonsymmetric vibrational modes involving H and thus an associated  $\Delta$ ZPE. This limits predicted max  $k_H/k_D$  to ca. 1.7–2.3 at 25 °C. See More O’Ferrall, R. A. *J. Chem. Soc. (B)* **1970**, 785. For a recent example of *syn*- $\beta$ -H elimination in simple alkyl Pd complex for which a  $k_H/k_D$  value of 3 is found see Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910. See Supporting Information for additional examples. In the transition state for *anti*- $\beta$ -H elimination where H in Pd–C $_{\alpha}$ –C $_{\beta}$ –H is transferred to general base “B”, the reaction coordinate involves what approximates as symmetric stretching, and  $k_H/k_D$  is predicted to be limited to ca. 6.8 at 25 °C. For elegant kinetic and computational studies applying the More O’Ferrall analysis to Pd “insertion” into allylic C–H ( $k_H/k_D$  values of  $5.4 \pm 1$ ), see Chrisope, D. R.; Beak, P.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 230.
- (6) (a) Bray, K. L.; Charmant, J. P. H.; Fairlamb, I. J. S.; Lloyd-Jones, G. C. *Chem. Eur. J.* **2001**, *7*, 4205. (b) Charmant, J. P. H.; Fairlamb, I. J. S.; Lloyd-Jones, G. C.; Slatford, P. S. Manuscript in preparation. (c) **5a** undergoes slow C(9)=C(10) to C(8)=C(9) double bond isomerisation.
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- (8) Preliminary kinetic simulation suggests that stepwise addition results in cycles of pseudo-first-order/second-order kinetics with large  $k_H/k_D$  occurring in the latter. Ongoing work aims to probe the individual steps. The possibility of tunneling has not yet been probed by study of the relationship of  $k_H/k_D$  with *T*.
- (9) When this was repeated in the presence of 1.5 equiv dibenzylidene acetone (dba), the colorless solution became deep red at ca.  $-20$  °C to yield Pd<sub>2</sub>(dba)<sub>3</sub>, **6a**, and [7H]OTf as the only products.
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- (11) The kinetics for **5c/5d** were also found to display  $k_H/k_D$  close to unity.
- (12) The *E/Z* ratio is the kinetic ratio and is independent of [5] and [7]. In the conventional mechanism for the Heck reaction, the *kinetic E/Z* ratio is determined by competing *syn*- $\beta$ -H elimination/Pd–H dissociation steps and not the base. With H<sub>2</sub>O/NaI, Et<sub>3</sub>N, pyridine, and Hünig’s base, *E/Z* ratios ranging from 4.9 to 6.2 were obtained (see Supporting Information).
- (13) See Supporting Information. Complexes **5c** and **5d** are diastereoisotopically stable at both D-labeled carbons in CDCl<sub>3</sub> over long periods.
- (14) The efficacy of **7**, suggests the classic four-centred *syn*- $\beta$ -H elimination (cyclo-H–C–C–Pd) and not specific base catalysis via amine coordination.
- (15) Similar, but not identical, values were obtained with other bases (see Supporting Information), but in all cases these values are of significant magnitude for contributions by secondary isotope effects to be minor.
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