β-X vs. β-H Elimination. Selection Rules for Chemoselectivity Enabled by Mechanistic Studies

Authors: Michael K. Bogdos,[1] Olivera Stepanović,[1] Alessandro Bismuto,[1] Mauro G. Luraschi,[1] Bill Morandi*[1]

[1]Laboratory of Organic Chemistry, Department of Chemistry and Applied Biosciences, ETH Zürich, Zürich, Switzerland
*Corresponding author. Email: bill.morandi@org.chem.ethz.ch

Abstract:

Alkylpalladium complexes are important intermediates in several industrially relevant catalytic reactions such as the Mizoroki–Heck, alkyl C–H activation and ethylene polymerisation. Beta-elimination - of either a hydride (β-H) or a heteroatom (β-X) - is the most common decomposition pathway for these intermediates; this can either promote the desired reaction as in the Mizoroki–Heck reaction, or it can hinder reaction progress as in ethylene/vinyl halide co-polymerisations. Despite the importance of these elimination processes, little mechanistic understanding exists with respect to the factors that control them. We present a systematic investigation of the factors governing the competition between β-H and β-X in catalytically relevant alkylpalladium complexes. These results enabled us to derive selection rules which dictate ligand choice to control selectivity for either elimination. This knowledge may allow chemists to manipulate beta-eliminations in the design of chemoselective catalytic reactions for a wide range of applications.

Introduction:

The discovery and study of organometallic species have spurred the development of synthetic methods that have had a transformative impact on society, from the preparation of essential medicines to modern materials.[1,2] A broad family of essential catalytic reactions, including Ziegler–Natta polymerisation, Mizoroki–Heck cross coupling, and alkyl C–H activation rely on transition metal-alkyl intermediates.[3] These complexes are notably unstable, as they are prone to decompose through rapid beta-elimination reactions of either a hydride (β-H) or a heteroatom (β-X), generating an alkene and a M–H or M–X bond, respectively.[3] Depending on the desired synthetic outcome, these eliminations need to be either prevented or promoted, which makes understanding and predicting this behavior essential to the design of catalytic reactions, since they lead to chemically distinct products.

Beta-hydride elimination (β-H) is the main decomposition pathway for transition metal-alkyl complexes, often hindering their use in cross-coupling reactions (Fig. 1a). [1,3,4] It is also an integral part of catalytic cycles for many important reactions, including the Mizoroki–Heck reaction, which has been used in the synthesis of highly complex and clinically important molecules such as cethromycin (Fig. 1a).[5–8] As such, it has been studied extensively, with many metals and organic substrates being examined.[3,9] Beta-heteroatom elimination (β-X) is related to β-H, is similarly ubiquitous, but generally less studied and understood. It is also a transition metal-alkyl decomposition pathway, with important implications in polymer chemistry, where it inhibits the co-polymerisation of ethylene and vinyl halides or vinyl ethers and their derivatives (Fig. 1a).[10–12] Many examples of stoichiometric β-X eliminations have been reported, involving metals such as Ni, Pd, Co, Rh and others.[13–19] This fundamental step has also been exploited in catalysis. Examples include Mizoroki–Heck-type reactions (Fig. 1a) and asymmetric catalysis by Paioti *et al.*, as well as the work of Tran *et al.* which shows a wide variety of X groups being eliminated in a synthetically relevant context (Fig. 1b).[7,20–23]

As both beta-elimination reactions proceed through metal-alkyl complexes, they will often be in direct competition, leading to chemically distinct alkene products; such competitions have thus far been optimised empirically and have been comprehensively reviewed by Le Bras and Muzart.[24] Despite this inherent competition in most systems, the ubiquity of both beta-elimination reactions, and the potential for controlling reactivity to produce chemodivergent outcomes, there is a paucity of systematic studies examining the

factors controlling their competition. Such studies would ideally reveal general mechanistic trends, offer in-depth understanding and predictive power for reaction design. To the best of our knowledge, only two examples studying such competitions exist, by Zhu and Zhang *et al.* respectively (Fig. 1b).[25,26] These studies are limited to a narrow set of parameters (few X groups, no ligands) and offer no general guidelines for reaction control. A thorough investigation of the β-H/β-X competition would provide fundamental understanding and insight into how to control it, thereby increasing chemists' ability to design chemoselective catalytic reactions. Such findings would have wide impact, since transition metal-alkyl intermediates are of increasing importance, as saturated species are critical in the development of both materials science and medicinal chemistry.[27–29]

We report mechanistic investigations into the β-X/β-H competition in phosphine-ligated palladium-alkyl complexes. We were able to understand the origin of the observed selectivity and to derive selection rules for diverting the intermediates selectively down either pathway. Such information may aid chemists in manipulating beta-eliminations in the design of chemoselective catalytic transformations.

Results and Discussion:

For our investigation we selected Pd as the metal of interest and monophosphines as the ligands, given that this combination represents one of the most used classes of catalyst in synthetically important reactions such as the Suzuki–Miyaura, Mizoroki–Heck, Negishi, Tsuji–Trost and Kumada–Corriu.[30] As transition metal-alkyl complexes are quite unstable, we generated them *in situ* through oxidative addition of benzyl bromides, which bear the X group of interest at the homobenzylic position (Fig. 1c).

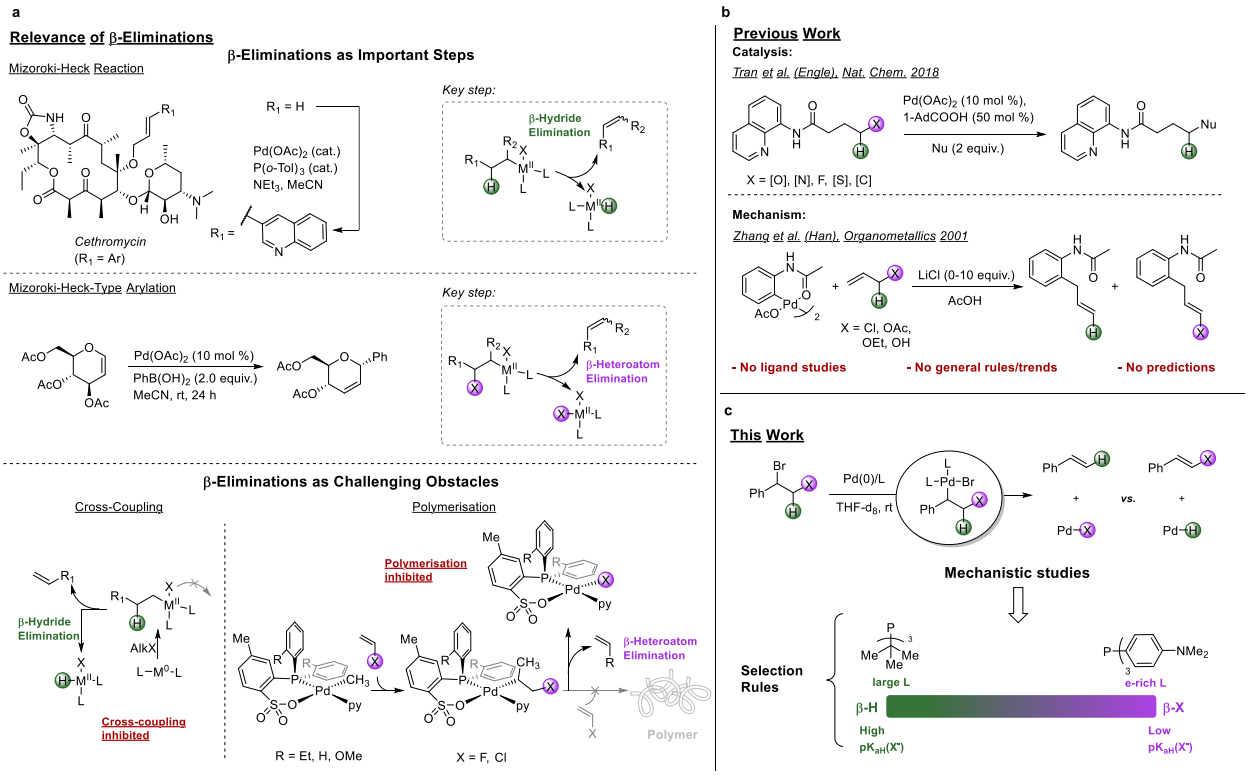

Fig. 1. Background and description of current work. (**a**) Importance of both β-H and β-X in the context of transition-metal catalysed reactions and some challenges which beta-eliminations pose in cross-coupling of alkyl electrophiles and in the copolymerisation of vinyl halides with ethylene. (**b**) Previous work involving catalytic Pd-assisted β-X and their competition with β-H in stoichiometric reactions (Zhang). (**c**) The work described in this report, assessing the relative preference for β-X or β-H elimination reactions in Pd-alkyl monodentate phosphine complexes.

We prepared several substrates bearing various synthetically relevant X groups; these include halides, phosphate, sulfonate and carboxylate esters (Fig. 2a). To gain insight on the kinetics of the competition, we monitored reaction progress over time using ^{1}H NMR. The organic products of the reactions serve as convenient reporters for the reaction selectivity. We initiated our studies using Pd(P^tBu_3)$_2$ as the model Pd source, as it is a well-defined, highly reactive, and commercially available complex, which has been used

as a catalyst in numerous transformations.[31] Upon reaction with our substrates it gave rise to fast oxidative addition, followed by β-H and/or β-X elimination, all at room temperature.

The experimentally obtained selectivity was plotted against the aqueous pK_a of the conjugate acid (pK_{aH}) of the X group being examined, in analogy to classic physical organic chemistry analyses (Fig. 2b).[32] The y axis is a scale which represents the selectivity of the reaction; 1 represents complete β-X selectivity, -1 complete β-H selectivity, and 0 a 1:1 mixture of the two products (see SI section S3.1). The obtained graph shows a sigmoidal relationship between the two variables, with the function crossing the x axis at a pK_{aH} of approximately -2 (Fig. 2b). The data was fit with a logistical regression function and the confidence intervals for both fit (dark grey) and prediction (light grey) are shown (see SI section S3.3). Based on the observed relationship between pK_{aH} and selectivity, we conclude that Pd-assisted β-X eliminations are promoted by better leaving groups (see SI section S3.2 and S4.3). Next, we examined the case of fluoride (pK_{aH} ~ 3) elimination, as it is a synthetically important example,[33–35] since β-F elimination is common in methods involving β-X[21,23,36,37] and is difficult to circumvent.[38] Our model predicts a ratio of 45:1 favouring β-H; indeed, an experimental ratio of >50:1 in favour of β-H was obtained, illustrating the predictive capability of the selectivity/pK_{aH} relationship (Fig. 2c).

Having validated our approach and observed a clear trend for a commonly used phosphine-Pd system, we next sought to probe whether the nature of the ligand could influence the overall selectivity of the process, as is the case for many other reactions involving Pd.[39,40] Next, we focused on the most common combination of Pd and phosphine in the literature, namely Pd/PPh_3.[41] As with $Pd(P^tBu_3)_2$, the relationship between selectivity and pK_{aH} of X displayed a sigmoidal relationship, with the same equation describing the function of best fit (Fig. 2d), further validating our previous findings. The data show that the choice of phosphine strongly affects the preference of Pd-assisted β-X eliminations, with a difference of nearly 7 units in the pK_{aH} of X that results in 1:1 competition. Interestingly, despite the preference of PPh_3 to favour β-X, the overall trend remains similar and a clear correlation with the pK_{aH} of the leaving X group is still observed.

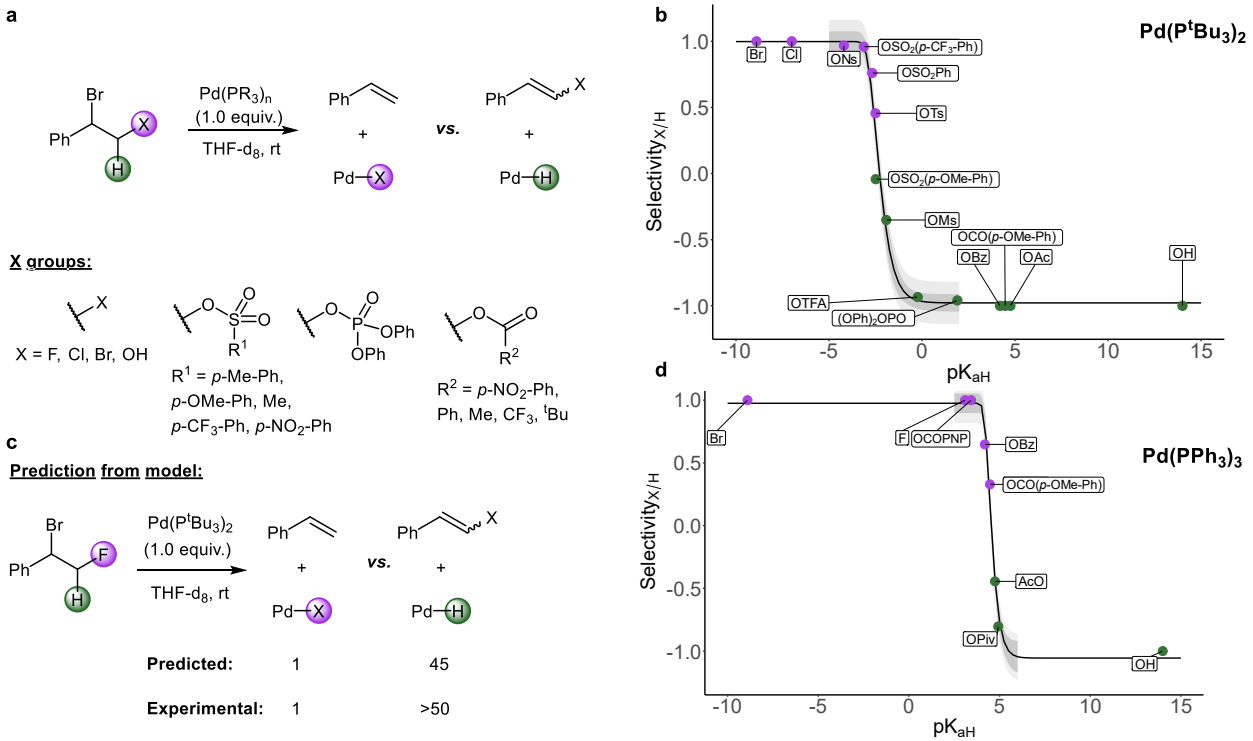

Fig. 2. Investigation of the influence of X group. (**a**) Reactions carried out to assess the effect of X group identity in the β-X vs. β-H competition experiments. (**b**) Graph of selectivity against the pK_{aH} of the X group for $Pd(P^tBu_3)_2$; the y axis ranges from 1 (exclusive β-X) to -1 (exclusive β-H). The darker grey shading represents the 1σ confidence interval of fit and the lighter grey the 1σ prediction interval. (**c**) Predicted and experimental values for the fluorine bearing substrate. (**d**) Graph of selectivity against the pK_{aH} of the X group for $Pd(PPh_3)_3$; confidence intervals depicted as in (b).

To understand the origin of the strong ligand effect, we decided to systematically probe the role of the phosphine ligand on the reaction. Since PPh_3 and P^tBu_3 differ in both sterics and electronics, we decided to first interrogate the effect of varying the electronics, as this is easily achieved without affecting sterics by

using various *para*-substituted triarylphosphines. We selected the substrate with X = OAc as the model substrate for these studies, since it displayed competition near 1:1 in our studies with PPh_3.

We reacted the chosen substrate with isolated homoleptic Pd(0) complexes ligated with *para*-substituted triarylphosphines bearing electron-withdrawing (Cl) and electron-donating (OMe, NMe_2) groups (Fig. 3a). By plotting the obtained selectivity against the Tolman electronic parameter (TEP) for each ligand, [42,43] we observe that β-X is promoted by more electron rich ligands.

Despite having very similar electronic character (TEP 2054 cm^{-1} and 2056 cm^{-1} respectively), P(*p*–NMe_2–Ph)$_3$ and P^{t}Bu$_3$ lead to opposite outcomes, suggesting an overriding influence of sterics (Fig. 3b). It is known that Pd(P^{t}Bu$_3$)$_2$ forms monophosphine T-shaped Pd-aryl complexes after oxidative addition, as a result of the large steric demand of the P^{t}Bu$_3$ ligand.[44–47] In contrast, the less sterically demanding aryl phosphine Pd(0) complexes are known to generally form diphosphine square planar Pd(II) complexes after oxidative addition of aryl or benzyl electrophiles.[48] We hypothesised that this sterically controlled change in ligation state of the reactive intermediate could be the reason for the observed discrepancy. To experimentally confirm that the speciation change also occurs with benzyl electrophiles, we reacted Pd(P^{t}Bu$_3$)$_2$ with excess BnBr and characterised the product of the reaction by $^{31}P\{^1H\}$ NMR and single crystal X-ray diffraction, confirming the presence of only one phosphine (Fig. 3b; see SI sections S2.2 and S6). We also performed *in situ* variable temperature NMR experiments, which showed the continued presence of P^{t}Bu$_3$ during the course of the reaction, providing additional evidence supporting the monophosphine intermediate hypothesis (see SI section S5.6).

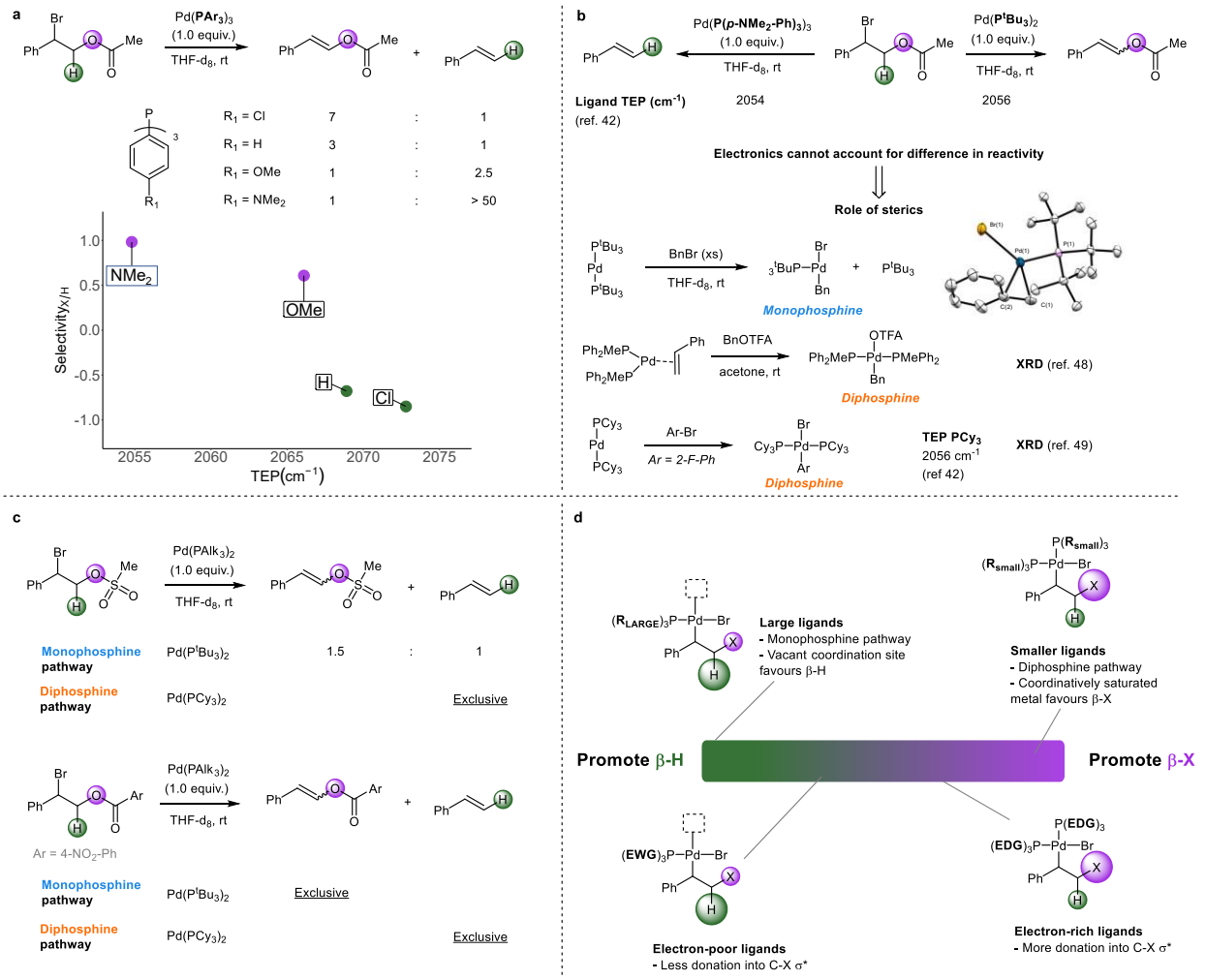

Fig. 3. Effect of phosphine ligand choice on reaction outcome. (**a**) Examination of the effect of electronics on the competition. The graph depicts the selectivity plotted against the TEP of the tested phosphines. (**b**) Divergent reactivity of two phosphines with similar TEP values. The product of oxidative

addition of BnBr with $Pd(P^tBu_3)_2$ was characterized by XRD and is shown; thermal ellipsoids are shown at 50% probability and hydrogen atoms are omitted for clarity. (**c**) Experiments comparing different substrates reacted with alkyl phosphine Pd complexes with similar electronics but different sterics. (**d**) Short summary of the derived selection rules from our investigations.

To further examine our hypothesis about the effect of the intermediate's ligation state on β-X/β-H selectivity, we selected another trialkyl phosphine with a similar TEP to P^tBu_3 in order to evaluate its reactivity. In contrast to P^tBu_3, PCy_3 has been shown to form diphosphine ligated complexes and has the appropriate electronic profile (TEP 2056 cm^{-1}, Fig. 3b).[49–51] If the hypothesis holds, reaction of a substrate that displays β-X/β-H competition with P^tBu_3 should give exclusive β-X with PCy_3. Reacting the appropriate substrate (X = OMs) with both $Pd(P^tBu_3)_2$ and $Pd(PCy_3)_2$, we obtained β-X/β-H competition and exclusive β-X products respectively, in line with the ligation state hypothesis (Fig. 3c). This is further corroborated by reaction with the substrate with X = OCOAr (Ar = 4–NO_2–Ph), where $Pd(P^tBu_3)_2$ gives rise to exclusive β-H and $Pd(PCy_3)_2$ to exclusive β-X. It should be noted that the ligation state of transition metal-phosphine species has been recently shown to have a strong influence on reactivity by Newman-Stonebreaker *et al*, further supporting our hypothesis.[52]

To rationalise the striking difference in elimination preference, we undertook experiments using stereochemical probes to investigate the stereochemical requirements of β-X (see SI section S5.5). By using the two diastereomers of 1,2-dibromopropylbenzene, we were able to deduce that both *syn*- and *anti*-eliminations are permissible pathways for β-X, the latter being preferred; these findings agree with the results reported by Sugita *et al*.[53]

Based on the above evidence, we propose that sterically demanding ligands promote the formation of three-coordinate T-shaped intermediates, which accelerate the stereospecific *syn*-β-H elimination by virtue of their vacant coordination site. The relative preference for β-X is not altered by the vacant coordination site, due to both *syn*- and *anti*-eliminations being accessible. This leads to a relative increase in β-H, allowing selective β-H in the presence of X groups that are eliminated in reactions where diphosphine intermediates are at play (*e.g.* X = F).

Overall, these investigations have led us to derive someselection rules for the β-X/β-H competition (Fig 3d). Electron-rich ligands promote β-X, possibly due to an increased electron density which can be donated into the C–X σ*. Ligands that are small enough to permit the formation of diphosphine-Pd(II) intermediates also promote β-X relative to β-H. Conversely, electron-poor ligands promote β-H relative to β-X, as do large ligands which promote the formation of monophosphine-Pd(II) intermediates.

Conclusion:

In summary, by studying the stoichiometric reactivity of Pd complexes bearing monodentate phosphine ligands, we have uncovered the factors governing the competition between β-X and β-H. The first observation we made was that the ability to perform β-X is contingent on the leaving group ability of the X group; lower pK_{aH} of X enables β-X. More electron-rich ligands promote β-X, while β-H is promoted by more electron-poor ligands, though the influence of electronics is much smaller than that of sterics. The size of the ligand influences the reaction by controlling the ligation state of the intermediate. A monophosphine and a diphosphine pathway operate; the former is promoted by large ligands and strongly favours β-H due to the presence of a free coordination site on Pd. This allows selective β-H elimination in the presence of X groups with a $pK_{aH} > 0$ at room temperature. The diphosphine pathway is favoured by smaller ligands and appears to preferentially eliminate X groups with an approximate $pK_{aH} < 6$ at room temperature.

We believe that this work will serve as a roadmap for further study of this competition and for guiding catalyst selection for the development of new methods incorporating β-X and β-H elementary steps. Further investigations into the role of Lewis acids, salt additives, bases, the choice of metal, the denticity and class of ligand and other factors are still necessary to fully appreciate the opportunities available for control over the selectivity.

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