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Mechanistically informed selection rules for competing β-hydride and β-heteroatom eliminations

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Abstract:

Alkylpalladium complexes are important intermediates in several industrially relevant catalytic reactions such as the Mizoroki–Heck, alkyl C–H activation and ethylene polymerisation. β-elimination - of either a hydride (β-H) or a heteroatom (β-X) - is the most common decomposition pathway for these intermediates; this can either lead to 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. Here, 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 β-eliminations in the design of chemoselective catalytic reactions for a wide range of applications.

Main Text:

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 β-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 β-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 β-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 added 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 β-eliminations in the design of chemoselective catalytic transformations.

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).

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). This represents a rare example of β-H being preferred over β-F and is line with early computational studies which suggested this could be the case. [38–40]

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.[41,42] Next, we focused on the most common combination of Pd and phosphine in the literature, namely Pd/PPh_3.[43] 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.

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 steric and electronic properties, we decided to first interrogate the effect of varying the electronic properties, as this is easily achieved without

affecting steric parameters 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, [44,45] 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–C_6H_4)$_3$ and P^tBu_3 lead to opposite outcomes, suggesting an overriding influence of steric effects (Fig. 3b). It is known that Pd(P^tBu_3)$_2$ forms monophosphine T-shaped Pd-aryl complexes after oxidative addition, as a result of the large steric demand of the P^tBu_3 ligand.[46–49] 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.[50] 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^tBu_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^tBu_3 during the course of the reaction, providing additional evidence supporting the monophosphine intermediate hypothesis (see SI section S5.6).

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).[51–53] 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 = *p*–NO_2–C_6H_4), 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.[54]

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 others.[20,55]

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. This acceleration of the β-H elimination has been suggested before as a reason for the inherent challenge of using large ligands (which promote reductive elimination) in alkyl-alkyl cross-couplings.[56] This is further supported by the fact that in order to suppress β-H elimination, multidentate ligands are often employed and that tetracoordinate complexes are found to require dissociation of one ligand prior to β-H.[57,58] 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 some selection 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.

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 electronic effects is much smaller than that of steric effects. 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.

Methods:

Intramolecular Competition Reactions. The appropriate Pd(0) complex (1.0 eq.) and HMDSO (internal standard, varying amount) was dissolved in THF-d_8 (0.4 mL) on a Schlenk-line using an NMR tube adapter. The appropriate benzyl bromide (1.0 eq.), which was previously dried on the Schlenk-line using vacuum/N2 cycles, was then also dissolved in THF-d_8 (0.3 mL) and transferred to the NMR tube using a syringe and metal needle. For reactions using $Pd(P^tBu_3)_2$, an ^1H NMR spectrum of the sample was then measured within 10 minutes (time elapsed from addition of the electrophile solution to end of acquisition of the spectrum) from the start of the reaction. The reaction was then periodically monitored by ^1H NMR over time to collect kinetic information about the reaction.

Selectivity Expression and Regression Function. For our analyses, we decided to employ the following function to express the obtained ratios of β-hydride (β-H) and β-heteroatom (β-X) products as a single value:

$$f\left(\frac{[\beta H]}{[\beta X]}\right) = 1 - \frac{[\beta H]}{[\beta X]} \quad for \quad \frac{[\beta X]}{[\beta H]} \geq 1 \quad \boldsymbol{or} \quad f\left(\frac{[\beta H]}{[\beta X]}\right) = \frac{[\beta X]}{[\beta H]} - 1 \quad for \quad \frac{[\beta X]}{[\beta H]}$$

This expression ensures a continuous function without asymptotes (*e.g.* expressing the selectivity as a ratio leads to infinity when one of the two products is not detected) which also provides intuitive bounds. A value of 1 represents complete β-X selectivity, -1 represents complete β-H selectivity and 0 represents a 1:1 mixture of β-H and β-X products.

For building the model which allows for prediction of new values, we employed a Gompertz equation of the form:

$$f(pK_{aH}) = A\, e^{(-e^{(B - C\, pK_{aH})})} + D$$

The following references are relevant to the methods employed in this paper and have been discussed in the supplementary information. [59–86]

Data Availability:

The experimental data as well as the characterization data for all the compounds prepared during these studies are provided in the Supplementary Information. Crystallographic data are available from the Cambridge Crystallographic Data Centre with the following codes: CCDC 2150620 and CCDC 2150621. Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

Code Availability:

All code and raw data files are available on Zenodo at 10.5281/zenodo.6617212.

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Author contributions:

MKB conceived the project. All authors contributed to the design of experiments. MKB, OS, AB and MGL performed all experiments. BM supervised the research. All authors contributed to the writing and editing of the manuscript and supplementary information. MKB wrote the code used for data analysis and data visualisation.

Competing interests:

Authors declare that they have no competing interests.

Figure Legends/Captions:

Fig. 1. Background and description of current work. (**a**) The importance of both β-H and β-X in enabling transition-metal catalysed reactions, illustrated by the synthesis of the natural product cethromycin and the functionalisation of carbohydrate derivatives. (**b**) Some challenges posed by β-eliminations in cross-coupling of alkyl electrophiles and in the copolymerisation of vinyl halides with ethylene, where they lead to off-cycle species and polymerisation-inactive complexes respectively. (**c**) Relevant previous work involving catalytic Pd-assisted β-X elimination (Tran *et. al*) and their competition with β-H elimination in stoichiometric reactions (Zhang *et al.*). (**d**) The work described here, assessing the relative preference for β-X or β-H elimination reactions in Pd-alkyl monodentate phosphine complexes, which leads to the derivation of selection rules for achieving chemoselectivity for either elimination.

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, with X groups used outlined. (**b**) Selectivity *vs.* the aqueous pK_a of the conjugate acid of the X group (pK_{aH}) for reactions which utilise $Pd(P^tBu_3)_2$. Selectivity ranges from 1 (exclusive β-X) to -1 (exclusive β-H) and 0 represents no selectivity *i.e.* a ratio of 1:1 β-X and β-H organic products. The colour of the datapoints indicates whether β-H (green) or β-X (purple) is preferred. This graph depicts kinetic selectivities. The line represents a fitted parametric Gompertz equation. The darker grey shading represents the 1σ confidence interval of fit and the lighter grey the 1σ prediction interval; they are depicted with the shown bounds as beyond these the model predicts exclusive selectivity for either β-H (-1) or β-X (1). The data labels specify which X group the data point corresponds to. (**c**) Predicted and experimental values for the selectivity in the reaction with the fluorine bearing substrate and $Pd(P^tBu_3)_2$, using the model depicted in the graph in (b). (**d**) Selectivity against pK_{aH} of the X group for $Pd(PPh_3)_3$; details for the graph are the same as (b).

Fig. 3. Effect of phosphine ligand choice on reaction outcome. (**a**) Examination of the role of ligand electronic effects on the β-X and β-H competition, using the acetate bearing substrate as a model. The graph depicts the selectivity (defined as in Fig. 2b) plotted against the Tolman electronic parameter (TEP) of the tested phosphines. (**b**) Divergent reactivity of two phosphines with similar TEP values. The monophosphine-Pd 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. Some examples are provided showing that aryl phosphines form diphopshine-benzyl-Pd complexes and PCy_3 forms diphosphine-Pd complexes and has TEP similar to P^tBu_3. (**c**) Experiments comparing the reaction of different substrates with Pd complexes with $Pd(P^tBu_3)_2$ and $Pd(PCy_3)_2$, which form T-shaped monophosphine-Pd and square planar diphosphine-Pd intermediates respectively, while having similar electronic profiles. (**d**) Short summary of the derived selection rules from our investigations. Phosphine ligands which are very sterically demanding enforce the formation of a T-shaped monophosphine-Pd intermediate and so promote β-H, as do electron-poor ligands. Conversely, electron-rich ligands can more effectively donate into the C-X σ* orbital and so promote β-X. Smaller ligands which form square planar diphosphine-Pd intermediate also promote β-X relative to β-H due to the lack of a vacant coordination site which is required for β-H.

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Fig 1

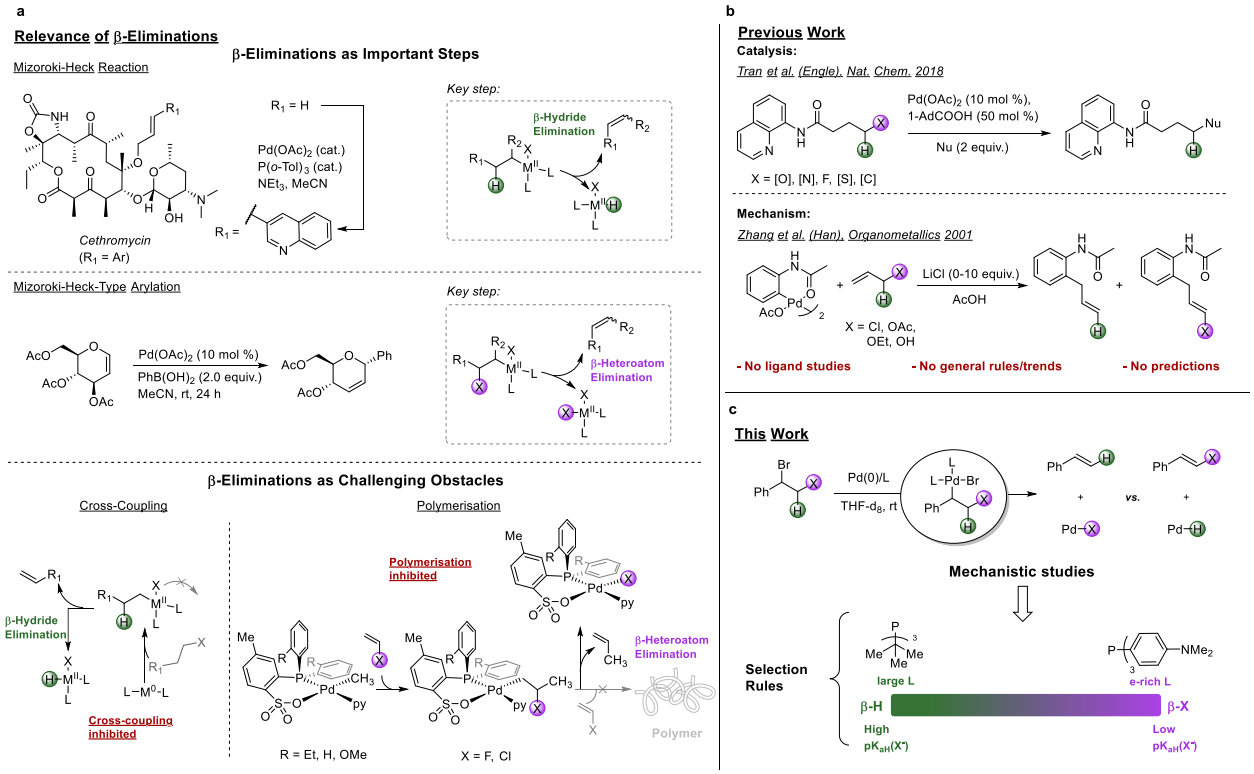

a
Relevance of β-Eliminations
β-Eliminations as Important Steps
Mizoroki-Heck Reaction
Cethromycin
(R1 = Ar)
R1 = H
Pd(OAc)2 (cat.)
P(o-Tol)3 (cat.)
NEt3, MeCN
R1 =
Key step:
β-Hydride Elimination
Mizoroki-Heck-Type Arylation
Pd(OAc)2 (10 mol %)
PhB(OH)2 (2.0 equiv.)
MeCN, rt, 24 h
Key step:
β-Heteroatom Elimination
β-Eliminations as Challenging Obstacles
Cross-Coupling
Polymerisation
β-Hydride Elimination
Cross-coupling inhibited
Polymerisation inhibited
β-Heteroatom Elimination
Polymer
R = Et, H, OMe
X = F, Cl
b
Previous Work
Catalysis:
Tran et al. (Engle). Nat. Chem. 2018
Pd(OAc)2 (10 mol %),
1-AdCOOH (50 mol %)
Nu (2 equiv.)
X = [O], [N], F, [S], [C]
Mechanism:
Zhang et al. (Han). Organometallics 2001
LiCl (0-10 equiv.)
AcOH
X = Cl, OAc,
OEt, OH
- No ligand studies
- No general rules/trends
- No predictions
c
This Work
Pd(0)/L
THF-d8, rt
vs.
Mechanistic studies
Selection Rules
large L
e-rich L
β-H
β-X
High
pKaH(X•)
Low
pKaH(X•)

Fig 2

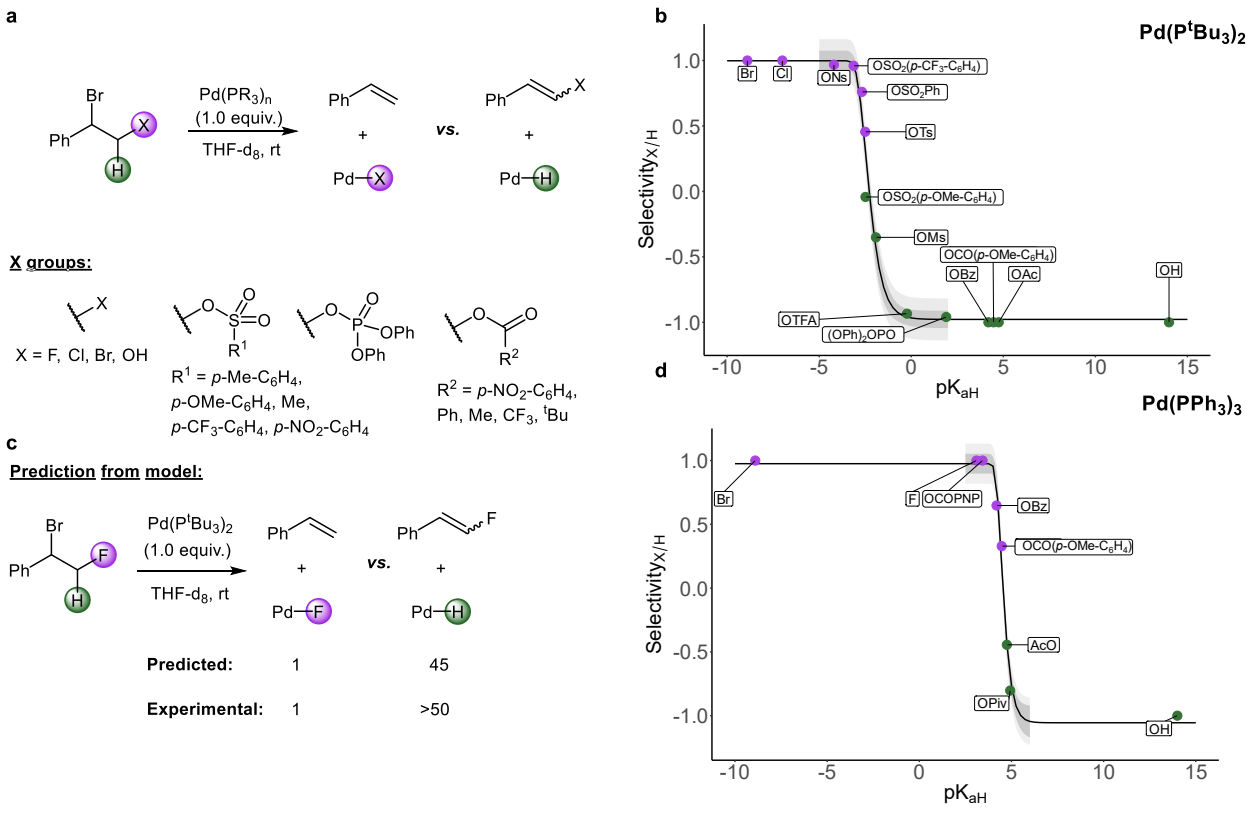
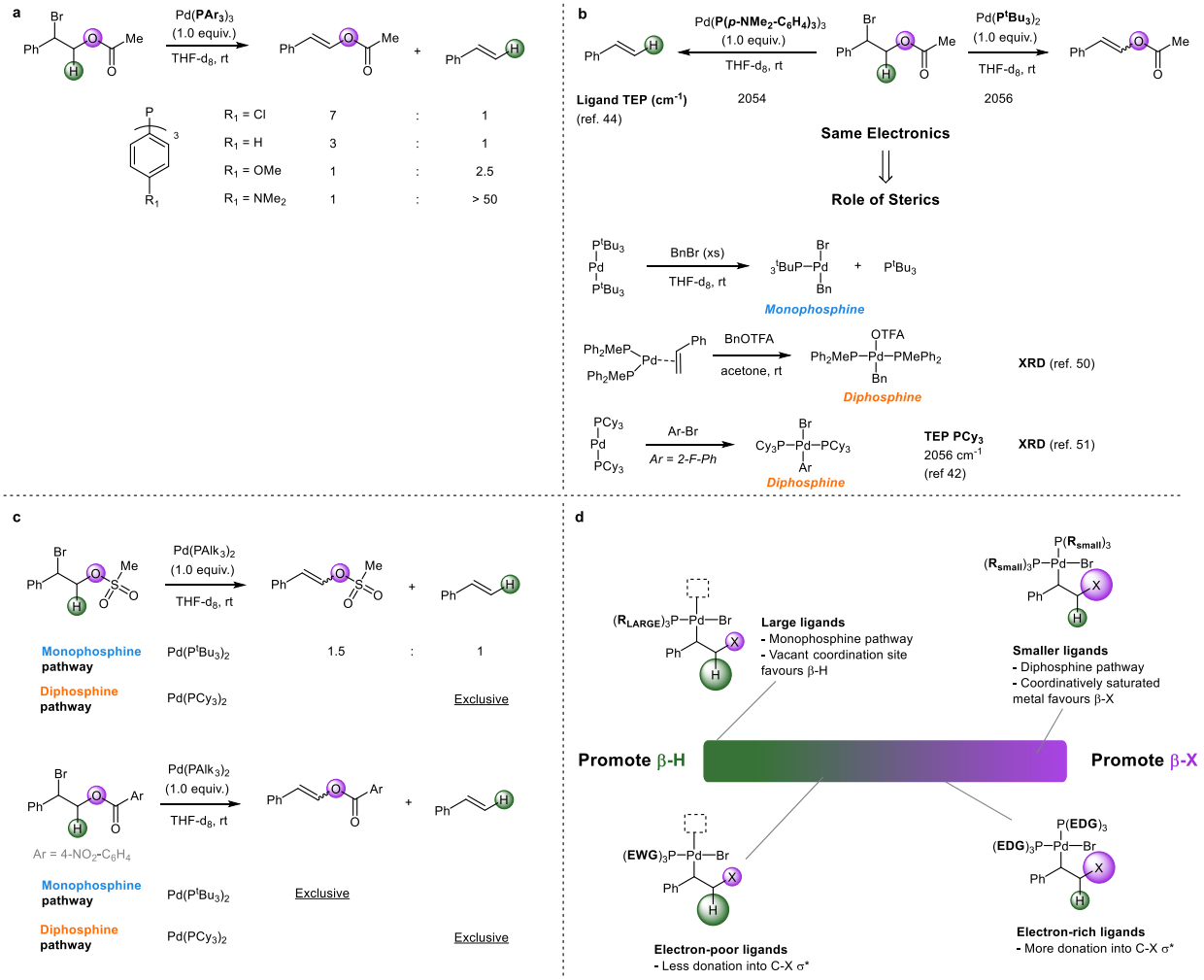

a
Pd(PR3)n
(1.0 equiv.)
THF-d8, rt
vs.
X groups:
X = F, Cl, Br, OH
R1 = p-Me-C6H4,
p-OMe-C6H4, Me,
p-CF3-C6H4, p-NO2-C6H4
R2 = p-NO2-C6H4,
Ph, Me, CF3, tBu
c
Prediction from model:
Pd(PtBu3)2
(1.0 equiv.)
THF-d8, rt
vs.
Predicted: 1 45
Experimental: 1 >50
b
Pd(PtBu3)2
Br
Cl
ONs
OSO2(p-CF3-C6H4)
OSO2Ph
OTs
OSO2(p-OMe-C6H4)
OMs
OCO(p-OMe-C6H4)
OBz
OAc
OH
OTFA
(OPh)2OPO
Selectivity X/H
pKaH
d
Pd(PPh3)3
Br
F
OCOPNP
OBz
OCO(p-OMe-C6H4)
AcO
OPiv
OH
Selectivity X/H
pKaH

Fig 3


a
Pd(PAr3)3
(1.0 equiv.)
THF-d8, rt
R1 = Cl 7 : 1
R1 = H 3 : 1
R1 = OMe 1 : 2.5
R1 = NMe2 1 : > 50
b
Pd(P(p-NMe2-C6H4)3)3
(1.0 equiv.)
THF-d8, rt
Pd(PtBu3)2
(1.0 equiv.)
THF-d8, rt
Ligand TEP (cm-1)
(ref. 44)
2054
2056
Same Electronics
Role of Sterics
BnBr (xs)
THF-d8, rt
Monophosphine
BnOTFA
acetone, rt
Diphosphine
XRD (ref. 50)
Ar-Br
Ar = 2-F-Ph
Diphosphine
TEP PCy3
2056 cm-1
(ref 42)
XRD (ref. 51)
c
Pd(PAlk3)2
(1.0 equiv.)
THF-d8, rt
Monophosphine pathway
Pd(PtBu3)2
1.5 : 1
Diphosphine pathway
Pd(PCy3)2
Exclusive
Ar = 4-NO2-C6H4
Monophosphine pathway
Pd(PtBu3)2
Exclusive
Diphosphine pathway
Pd(PCy3)2
Exclusive
d
Large ligands
- Monophosphine pathway
- Vacant coordination site favours β-H
Smaller ligands
- Diphosphine pathway
- Coordinatively saturated metal favours β-X
Promote β-H
Promote β-X
Electron-poor ligands
- Less donation into C-X σ*
Electron-rich ligands
- More donation into C-X σ*