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Stereodivergent Alkyne Reduction Using Water as the Hydrogen Source

Santhosh Rao and Kandikere Ramaiah Prabhu*[a]

Dedication ((optional))

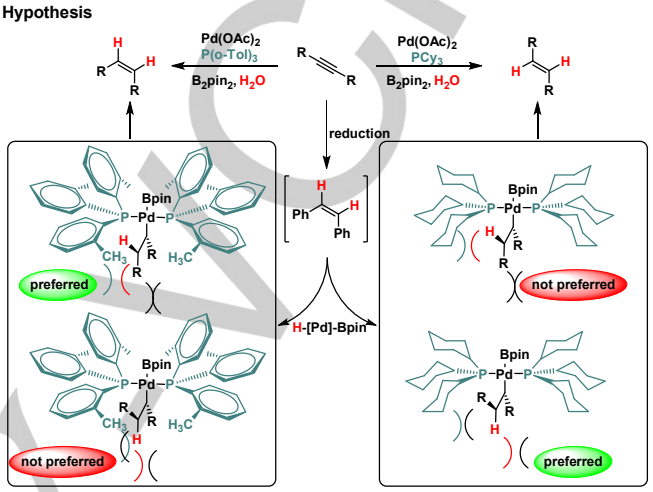
Abstract: A homogeneous Pd-catalyzed stereodivergent reduction of alkynes to *Z*- and *E*-alkenes using H_2O as the H_2 source is presented. Mediated by a diboron reagent, the transfer hydrogenation has been accomplished to yield the desired geometrical isomer by rational ligand selection. The switchable stereoselectivity achieved using simple phosphine ligands is generally excellent. D_2O has also been used as a D_2 source for synthesizing corresponding deuterated olefins. Supported by a gram scale synthesis, the reaction can easily be scaled up making it an efficient way to prepare alkenes commercially as well. Mechanistic studies suggest formation of H-PdL_2-OAc as the crucial step leading to the presence of two pathways involving H-Pd-B$(OR)_2$ and molecular H_2 as active intermediates.

Introduction

Alkene functionality is an integral part of many natural products as well as biologically interesting molecules,[1] and a key intermediate in many chemical transformations. One of the common approaches for preparing alkenes is by selective reduction of corresponding readily available alkynes. The reduction strategies of an internal alkyne are known to furnish two possible geometrical stereoisomers. Undesired over-reduction is also frequently encountered. Methods for synthesizing *Z*-alkenes mainly involve Lindlar's catalyst,[2] whereas utility of heterogeneous catalysts[3] for a selective reduction of alkynes for obtaining *E*-alkenes is relatively scarce.[3a-d] The reason for this may be due to the intrinsic feature of most of the transition metals, wherein metals tend to facilitate *syn* hydrogenation.[3]

On the other hand, relatively very few homogeneous methods have been developed in this direction, which can be attributed to the inherent difficulty associated with controlling the stereoselectivity.[3] Additionally, there are a few notable semireduction methods, which offer switchable selectivity to obtain either the *E*- or *Z*-alkene under similar conditions.[4]

Majority of the above methods involve the direct use of gaseous H_2 which adds additional difficulty of handling gaseous H_2, due to the safety reasons, particularly in large-scale commercial applications. Other methods also have been explored to circumvent the use of H_2 gas by using transfer hydrogenating reagents such as boranes,[5] silanes,[6] formic acid,[4a,7] NH_3-BH_3,[4b,8] ammonium formate,[9] etc. Hydroboration[10]/hydrosilylation[11] followed by protonolysis (acidification/methanolysis) is also noteworthy. Yet, practical applications of these methods are limited. Using omnipresent and environmentally benign H_2O as a source of H_2 can lead to a significant advancement in developing practical and controlled reduction strategies.



Scheme 1. Ligand guided stereoselective synthesis of *E*- and *Z*-olefins.

Recently, Stokes observed H_2O as a H_2 donor under $B_2(OH)_4$ mediated Pd-catalyzed heterogeneous conditions.[12] In an independent contemporary study using B_2pin_2 as the mediator and as part of our extensive work related to Pd-catalyzed boron mediated reactions,[13] our group also has reported a homogeneous Pd-catalyzed reduction of alkenes using H_2O as the H_2 source.[13a] Since then, a reasonable progress has been made using diboron reagent as a mediator for transfer reduction of various alkenes and heterocycles.[14]

A general, safe and operationally convenient method leading to a selective reduction of alkynes to *Z*- and *E*-alkenes is a challenge, till date.[15] In this direction, we have addressed these aspects, wherein both *E*- and *Z*-alkenes have been prepared in a stereoselective fashion using H_2O as the H_2 source (Scheme 1). Notably, the reaction has been achieved by the judicial selection of ligands with suitable electronic and steric parameters.

Results and Discussion

We initiated the optimization study using $Pd(OAc)_2$ as the catalyst. Diphenylacetylene, an internal alkyne (**1a**), was chosen as the standard substrate and B_2pin_2 was used as the transfer hydrogenation mediator from H_2O. To optimize the reaction conditions, we have considered both steric and electronic parameters of the reaction.

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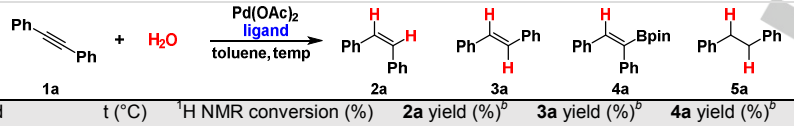
Table 1. Reaction Optimization.[a]



entry	ligand	t (°C)	^{1}H NMR conversion (%)	**2a** yield (%)[b]	**3a** yield (%)[b]	**4a** yield (%)[b]	**5a** yield (%)[b]
1	**PCy_3**	**rt**	**>95**	**nd**	**>95 (98)**	**nd**	**<2**
2	none	rt	0	nr	nr	nr	nr
3	P(*t*But)$_3$	rt	9	7	nd	nd	nd
4	$P(OEt)_3$	rt	7	5	nd	nd	nd
5	**PPh_3**	**rt**	**>95**	**nd**	**nd**	**>95 (63)**	**nd**
6	P(*p*-F-phenyl)$_3$	rt	>95	nd	nd	95	5
7	P(*p*-anisyl)$_3$	rt	>95	nd	nd	>95	<1
8	P(*p*-Tol)$_3$	rt	>95	nd	nd	>95	<1
9[c]	rac BINAP	rt	<5	nr	nr	nr	nr
10[c]	DPPF	rt	85	5	nd	78	nd
11	P(2-furyl)$_3$	rt	<5	nr	nr	nr	nr
12	P(*o*-Tol)$_3$	rt	>95	12	nd	88	nd
13	$P(Mes)_3$	rt	<1	nr	nr	nr	nr
14	XPhos	rt	54	3	7	44	nd
15	P(*o*-Tol)$_3$	80	>95	52	nd	31	nd
16[d]	P(*o*-Tol)$_3$	80	>95	21	19	51	5
17[e]	P(*o*-Tol)$_3$	80	56	41	nd	nd	nd
18[f]	**P(*o*-Tol)$_3$**	**80**	**>95**	**75 (72)**	**trace**	**nd**	**nd**

[a] Reaction conditions: **1a** (0.5 mmol), B_2pin_2 (0.6 mmol), H_2O (2.5 mmol), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), toluene (1.5 mL), entries 1-14 = rt, entries 15-18 = 80 °C; [b] Measured by ^{1}H NMR with terephthalaldehyde as the internal standard, nr = no reaction, nd = not detected. The numbers in parentheses are isolated yields; [c] bidentate ligand (5 mol %); [d] B_2pin_2 (1 mmol); [e] B_2pin_2 (0.3 mmol); [f] B_2pin_2 (0.5 mmol).

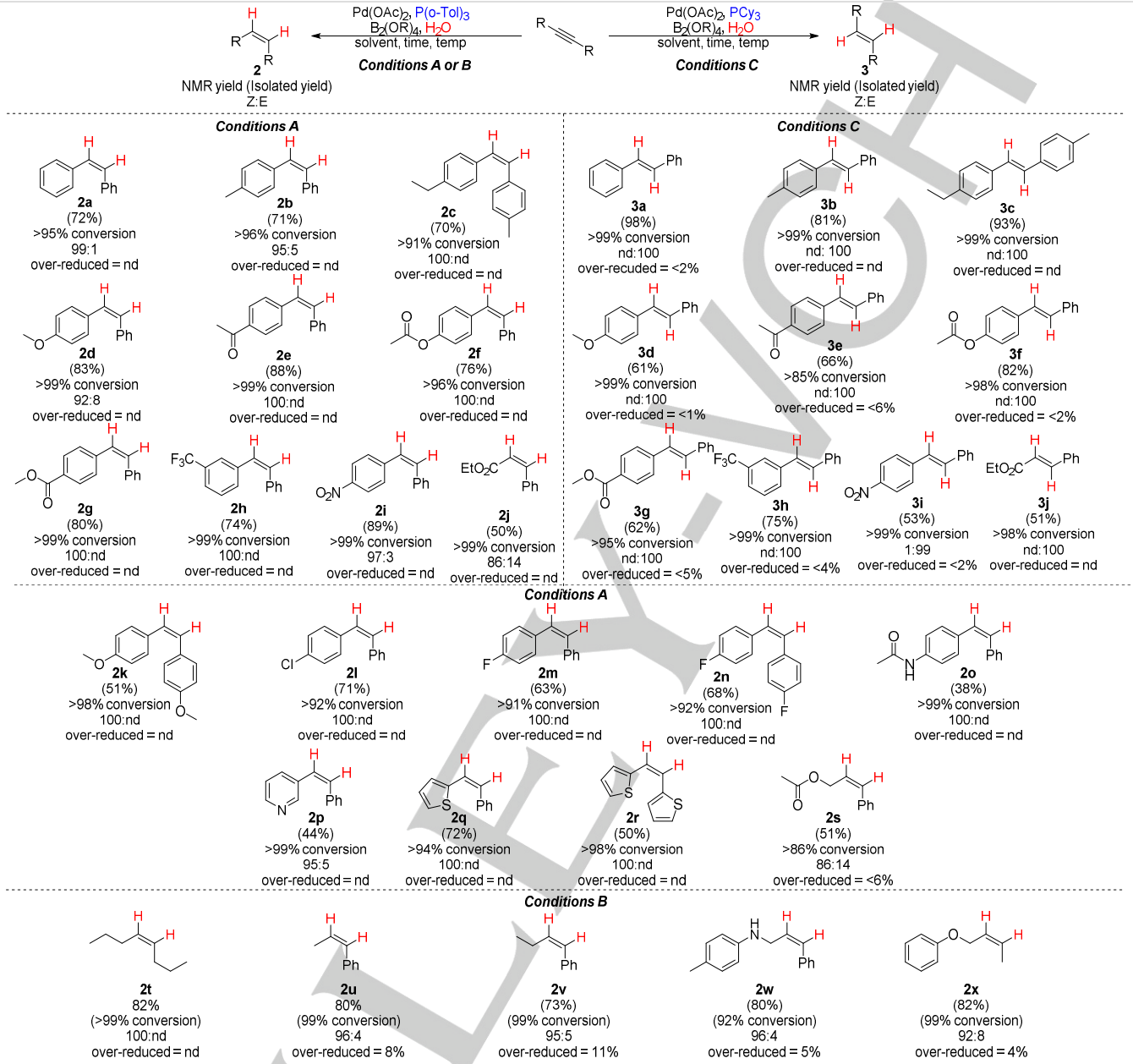
We envisioned that the key parameter that would determine the reaction outcome, particularly the stereoselectivity, was the ligand. Hence, phosphine was chosen as the ligand, considering its extensive electronic and steric tunability (Table 1). After a few initial set of controls, we were able to achieve the exclusive *E*-alkene using PCy_3 as the ligand at room temperature (entry 1, Table 1). As expected, excluding the ligand resulted in no reaction (entry 2).

Interestingly, P(t-But)$_3$, a bulkier trialkyl ligand but with similar electronic character to as that of PCy_3, gave a trace amount of the expected *Z*-alkene **2a** instead of **3a** exclusively (entry 3). This reaction indicated that the bulkier ligand can assist the formation of *Z*-alkene. A sterically less hindered, but a poor σ-donor ligand $P(OEt)_3$ gave a trace amount of the expected product **2a** exclusively as well (entry 4). This suggested a probable role of relatively weaker σ-donor capability of the ligand, along with the sterical hindrance, in favoring the product (**2a**) formation.

Replacing PCy_3 with PPh_3, which is a relatively poor σ-donor and a better π-acceptor, resulted in exclusive formation of the hydroborylated product **4a** in >95%; the likely reaction intermediate (entry 5). However, only 63% of **4a** could be isolated due to the over-adsorption on silica.[10c] In this reaction it was observed that the starting material **1a** underwent complete conversion. Inspired by this promising result, and our comprehension from the previous controls, we tried different triaryl phosphines. All, electronically similar, electron-withdrawing (*p*-fluoro) and electron-donating (*p*-OMe) substituents on the triaryl phosphines gave exclusive hydroborylated product **4a** (entries 6–8). Even the *cis*-enforcing bidentate phosphine ligands, either failed or gave trace amounts of the expected product **2a** (entries 9–10). Therefore, we decided to vary the steric bulk on the aromatic system of the phosphines. A relatively less bulky P(2-furyl)$_3$, compared to PPh_3, was incapable of inducing the desired reactivity (entry 11). However, increasing the steric hindrance by using P(o-Tol)$_3$ resulted in complete conversion of the starting material, and a promising 12% yield of the *cis*-product **2a** was observed (entry 12). Increasing the steric bulk further by using $P(Mes)_3$ and XPhos ligands failed to give a better result (entry 13–14).

To increase the protodeborylation of the intermediate, we increased the temperature to 80 °C with P(*o*-Tol)$_3$ as a ligand to obtain a better yield of **2a** (52%) along with 31% of hydroborylated product (entry 15). Rising the reaction temperature further did not result in a better outcome (See SI for further details). Increasing B_2pin_2 equivalents (2 equiv) resulted in 5% of over reduced saturated alkane (**5a**) as side product as well (entry16). Reducing the diboron equivalents to 0.6 equiv, astonishingly, resulted in exclusive formation of the expected product **2a** in 41% yield (entry 17). This result revealed the probable role of excess diboron reagent in deterring the reaction from completion. Hence, using B_2pin_2 in 1 equiv gave the desired product **2a** exclusively in 75% yield (72% isolated yield). The optimization studies further corroborated our hypothesis of the stereoselectivity induced by the ligand.

Table 2. Substrate scope



Conditions A: **1** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), P(*o*-Tol)$_3$ (10 mol %), B_2pin_2 (0.5 mmol), H_2O (2.5 mmol), toluene (1.5 mL), 12h, 80 °C. **Conditions B**: **1** (0.5 mmol), $Pd(OAc)_2$ (1 mol %), P(*o*-Tol)$_3$ (2 mol %), $B_2(OH)_4$ (0.6 mmol), H_2O (2.5 mmol), NEt_3 (1 mmol) CH_2Cl_2 (1.5 mL), 3h, rt. **Conditions C**: **1** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), B_2pin_2 (0.6 mmol), H_2O (10 mmol), toluene (1.5 mL), 24h, rt. ^{1}H NMR yield was measured with terephthalaldehyde as the internal standard. nd = not detected in ^{1}H NMR. The numbers in parentheses are isolated yields. Conversion and *Z*:*E* ratio have been determined using ^{1}H NMR.

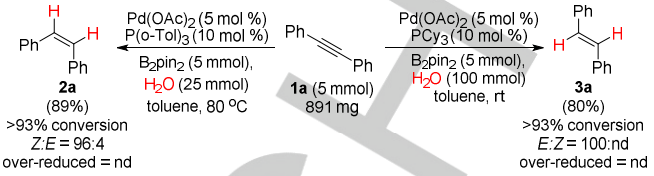
Following the optimization of the reaction, substrate scope was studied with different internal alkynes (Table 2). Initially, various aromatic substituted diarylalkynes were tested. As expected alkyl substitution had no effect on the reaction yield giving excellent yields of both *Z*- and *E*-alkenes (**2b**, **2c**, and **3b**, **3c** respectively). Electronic donating –OMe group increased the *Z*-alkene yield (**2d**, 83%) with respect to the standard substrate but *E*-alkene yield was slightly reduced (**3d**, 61%). Alkynes with carbonyl groups as well provided excellent yield for both the olefin isomers in excellent selectivity (**2e**-**g** and **3e**-**g** respectively). Interestingly, carbonyl groups were found intact under the given reducing conditions showcasing excellent chemoselectivity of the present method. Electron withdrawing groups such as $–CF_3$ and $–NO_2$ also reacted well to give *Z*- and *E*-olefins (**2h**-**2i** and **3h**-**3i** respectively) in good to excellent yields and excellent stereoselectivity. It can be noted here that a non-reduction of $–NO_2$ group to corresponding $–NH_2$ was an indication of absence of a heterogeneous catalytic system.[17b]

Alternatively, ethyl phenylpropiolate gave corresponding olefins in only moderate yields (**2j** and **3j**). Further, in case of *Z*- alkene product (**2j**), the selectivity was found to be reduced slightly due to the lack of steric bulk and to some extent the presence of electron withdrawing ester group attached directly to the multiple bond.

Proceeding further, some of the alkynes failed to furnish the *E*-olefin, but provided only the *Z*-olefins in excellent stereoselectivity (**2k**, **2l**, **2m**, **2n**, and **2o**, in 51, 71, 63, 68 and 38% yields, respectively). Intriguingly, even heterocyclic compounds viz. pyridyl and thiophene containing molecules, reacted well to give the corresponding *Z*-alkene (**2p**, **2q**, and **2r** in 44, 72, and 50% yields, respectively) in excellent stereoselectivity. The reaction of propargylic ester such as 3-phenylprop-2-yn-1-yl acetate was facile furnishing the corresponding alkene (**2s**) in 51% yield and good stereoselectivity. Although a direct rationale could not be arrived at with respect to the failed reactivity of substrates to form *E*-alkenes, the reason could be attributed to the relatively poor stability of the hydroborylated products under the given conditions. While there was no direct reactivity trend observed with regard to the electronic nature of the groups on the substrates, we presume the substrate steric bulk played a crucial role in the stereoselectivity observed in the reaction.

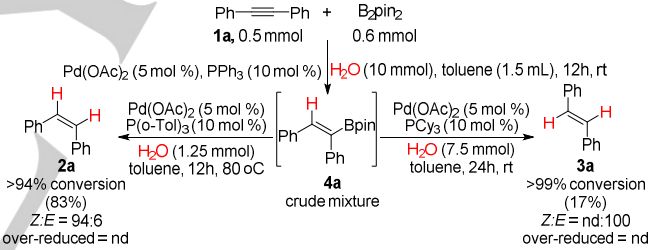
A few dialkyl and aryl-alkyl alkynes (**1**-**x**), under the optimized conditions, failed to furnish the desired alkenes, which can be attributed to the relatively less activated than the corresponding diaryl alkyenes. To circumvent this problem, a more reactive diboron reagent, i.e., tetrahydroxydiboron was used to achieve the reduction. In addition, NEt_3 was used as a base, which was necessary to achieve complete conversion of the starting alkyne.[16a] In this modified conditions, both dialkyl and aryl-alkyl substituted alkynes reacted well to give the corresponding *Z*-alkenes **2t**, **2u**, and **2v** in 82, 80 and 81% yields, respectively. Interestingly, even propargylamine and propargyl ether derivative reacted well to provide corresponding allylamine (**2w**), and allyl ether (**2x**) in 80, and 82% yields, respectively. However, trace/small amounts of over-reduced products were observed. Attempts to obtain corresponding *E*-alkenes with PCy_3 as a ligand did not give the desired alkene, instead furnished *Z*-alkene. The yield and the *Z*:*E* ratio also were comparable to that obtained with P(*o*-Tol)$_3$, presumably due to a faster rate of reduction and lack of steric hindrance required for the isomerization.[16b]

The reaction scale was increased 10 fold (5 mmol scale) to verify its applicability in preparative scale synthesis (Scheme 2). In the case of *E*-selective reaction, the amount of B_2pin_2 used was reduced to 1 equiv to overcome the formation of over-reduced alkene in relatively significant amount (>7%), which was observed while employing 1.2 equiv of B_2pin_2. Gratifyingly, the reaction proceeded well with excellent yield and stereoselectivity. Here, the yield of *E*-stilbene decreased to 80% from 98% presumably because of using relatively a lower amount of B_2pin_2 (1 equiv) in the reaction. On the contrary, the yield of the *Z*-olefin improved to 89% compared to its 0.5 mmol counterpart (72%). It is noteworthy that the reaction is not only stereoselective but also provided the desired products without any significant side products, which require cumbersome isolation processes.



Scheme 2. Gram Scale (5 mmol) Reaction.

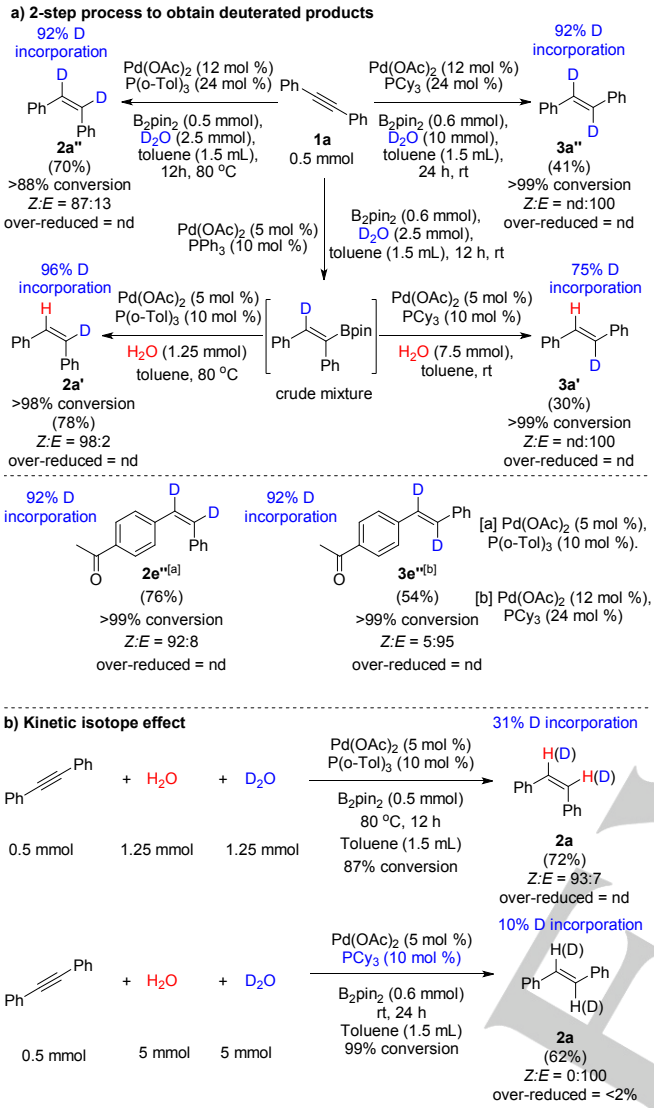
A two-step process was carried out to determine if the hydroborylated product (**4a**) was indeed the intermediate for the present reaction (Scheme 3). Therefore, **4a** (as crude mixture obtained by filtration of the reaction mixture through a short column with silica) was subjected to further protodeborylation step under the standard conditions hoping to obtain the corresponding *Z*- and *E*- olefins. Interestingly, the *Z*-stilbene was obtained exclusively in 83%. However, under *E*-olefin formation conditions, poor yield of the corresponding *E*-alkene was observed (17%). This observation clearly substantiates our understanding that **4a** as the active intermediate for the formation of *Z*-alkene. In contrast, *E*-olefin formation was not on par with the standard *E*-selective reaction suggesting a probable additional alternate route leading to *E*-selective reduction.



Scheme 3. Determining the Reaction Intermediate.

Further, the reaction of diphenylacetylene (**1a**) under optimal conditions using D_2O instead of H_2O, as expected, deuterated *E*/*Z* alkenes (**2a"/3a"**) were obtained in excellent selectivity (Scheme 4a). However, the reaction required higher loading of catalyst. Intrigued by this, an equimolar mixture of H_2O and D_2O was employed to investigate the presence of kinetic isotope effect (Scheme 4b). Both, the *Z*- and *E*-selective reactions revealed a primary kinetic isotopic effect of 2.2 and 6.7 respectively. This observation was crucial indicating water molecule was involved in the rate determining step

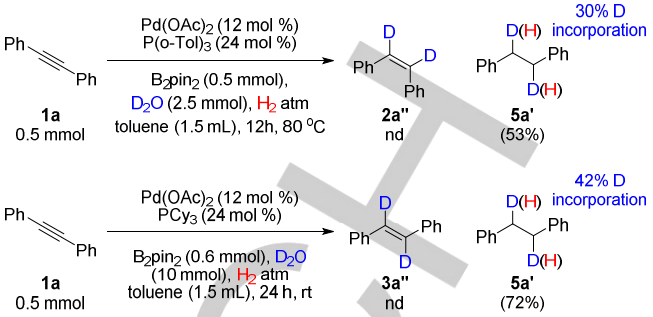
Following a similar strategy, as discussed in Scheme 3, a two-step process was carried out to obtain monodeuterated *Z*- and *E*-alkenes using D_2O to obtain the corresponding deuteroborylated product (Scheme 4a). This crude reaction mixture (obtained by filtration of the reaction mixture through a short column with silica), without purification, was directly subjected to corresponding protodeborylation conditions to obtain the corresponding monodeuterated *Z*- and *E*-alkenes **2a'** (78% yield) and **3a'** (30% yield), respectively. The additional



Schheme 4. D_2O as deuterium source

substrate with acetyl functionality such as 1-(4-(phenylethynyl)phenyl)ethan-1-one resulted in the stereoselective formation of desired dideuterated *Z*- and *E*-olefins (**2e"** and **3e"**) in 76 and 54%, respectively.

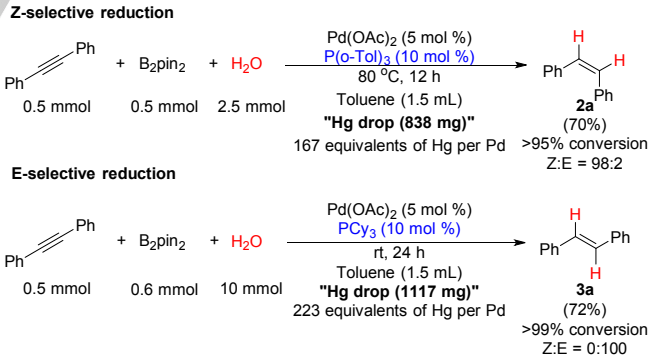
To gain a further mechanistic insight, a control reaction was carried out (Scheme 5) under H_2 atmosphere. As can be construed from the reaction outcome, the H incorporation from an external source was observed for both *Z*- and *E*- selective conditions (70% and 58% H incorporation respectively) indicating the catalyst's ability to utilize gaseous hydrogen gas. This observation further corroborates our understanding that the present catalytic system is an efficient way of generating H_2 gas,[13a] which has been efficiently applied to reduce alkynes stereoselectively.



Scheme 5. Reaction under gaseous H_2 atmosphere.

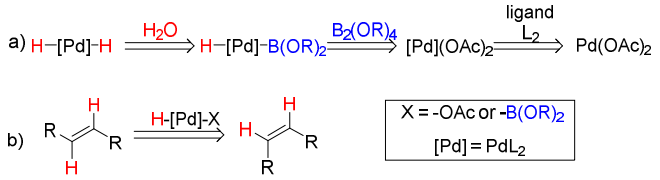
These observations (Schemes 3-5) indicate the presence of more than one probable reduction pathways involving both hydroborylation followed by protodemetallation as well as direct hydrogenation using the generated H_2 gas generated during the course of the reaction. Further, considering the quantitative details of the outcome, the *Z*-selective reduction appears to proceed majorly by hydroboration/protodemetallation pathway, whereas, the *E*-selective reductions follows mainly the reduction with gaseous H_2 generated during the course of the reaction. Nonetheless, we believe both the pathways are operative at any given time.

"Mercury drop" test was carried out to probe the homogeneity of the reaction and to address the role of palladium nanoparticles, if any, which may be formed in the present reductive conditions (Scheme 6).[17] Here, the reactions either remained unaffected (in case of *Z*-selective reduction) or the yield reduced marginally (in case of *E*-selective reduction). In both the cases, the reaction did not show any reduction of yield by several orders.[12,17] The lowering of the yield in the case of the *E*-selective reaction may be attributed to partial inhibition of catalyst-activation step by the added Hg(0) from the outset.[17b]



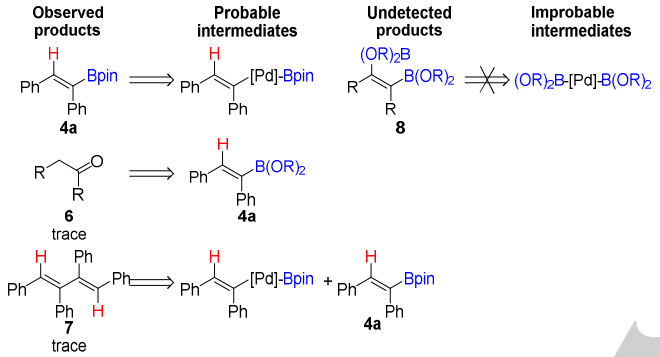
Scheme 6. Probing the homogeneity.

Hence, a retro-mechanistic analysis can be envisioned to understand the reaction pathway by identifying the two essential factors: reactive intermediates, and sequence of their formation. Based on our initial set of experimental observations, the present reaction involves the following confirmed intermediates at different stages of the reaction (Scheme 7).



Scheme 7. Retro-mechanistic analysis.

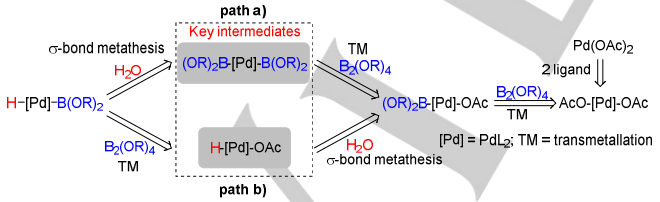
Therefore, we set out to determine the remaining unknown intermediates leading to the formation of the already identified ones. A straightforward way of determining the unknown species is by identifying their corresponding products in the reaction mixture (Scheme 8).



Scheme 8. Retrospective prediction of catalytic species.

All the above observed products can be traced back to corresponding H-[Pd]-B(OR)$_2$ species. However, oxidative insertion of Pd into the B-B bond can be ruled out since no corresponding alkyne diborylated product was observed. Controls in the following section further support this conclusion.

Hence, recognizing the species originating from the pre-catalyst Pd(OAc)$_2$ and leading to H-[Pd]-B(OR)$_2$ can resolve the mechanistic conundrum of the formation of the active catalytic species. Thus, we are now left with two possible pathways for the generation of active catalytic species that can lead to H-Pd-B(OR)$_2$ (Scheme 9).

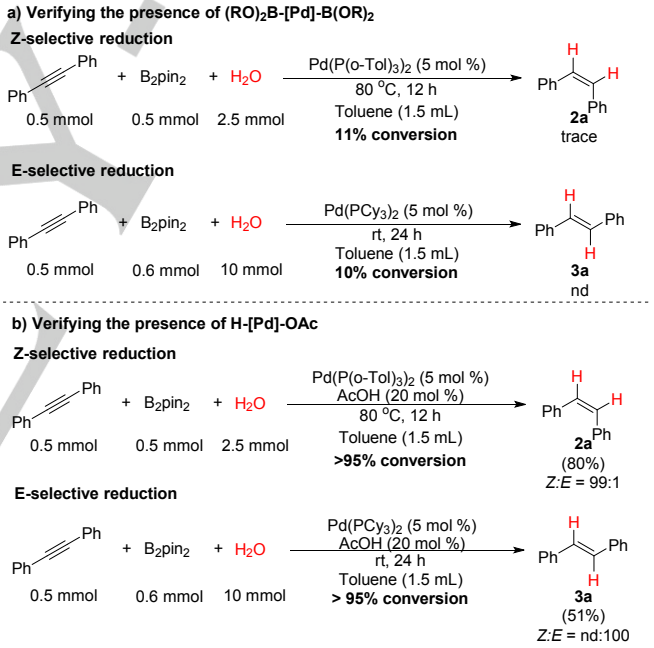


Scheme 9. Retrospective prediction of catalytic species.

The two paths (**a** and **b**) are differentiated by the sequence in which diboron reagent reacts with AcO-[Pd]-OAc. Both the pathways involve (RO)$_2$B-[Pd]-OAc as the crucial intermediate; however, are essentially differentiated by the occurrence of either H-[Pd]-OAc or (RO)$_2$B-[Pd]-B(OR)$_2$.

In order to determine the sequence of formation of H-[Pd]-B(OR)$_2$ from (RO)$_2$B-[Pd]-OAc (see Scheme 9), we had to ascertain the presence of either H-[Pd]-OAc or (RO)$_2$B-[Pd]-B(OR)$_2$. Hence, the reaction path can be verified by performing a reaction with PdL$_2$ (L = P(*o*-tol)$_3$ & PCy$_3$), instead of Pd(OAc)$_2$ and externally added phosphine ligands. A positive control would suggest path **a)**, i.e. H-[Pd]-B(OR)$_2$ is formed directly from PdL$_2$ and B$_2$(OR)$_4$ and hence the reaction does not require -OAc counter ion. As can be noted here, (RO)$_2$B-[Pd]-B(OR)$_2$ can be formed via either direct oxidative addition of Pd between B-B bonds or two consecutive transmetallations between [Pd](OAc)$_2$ and B$_2$(OR)$_4$ (Scheme 10a). However, both *Z* and *E*-selective reactions did not furnish the desired products.

PdL$_2$ and H-OAc can generate H-Pd-OAc species by oxidative addition of Pd^0. Hence in the second control, we envisaged including catalytic amount of H-OAc along with the pre-synthesized PdL$_2$ (L = P(*o*-Tol)$_3$ & PCy$_3$), instead of Pd(OAc)$_2$ and 2 phosphine ligands. A positive control would suggest path **b)** i.e. formation of H-[Pd]-OAc is essential in the formation of H-[Pd]-B(OR)$_2$ (Scheme 10b).

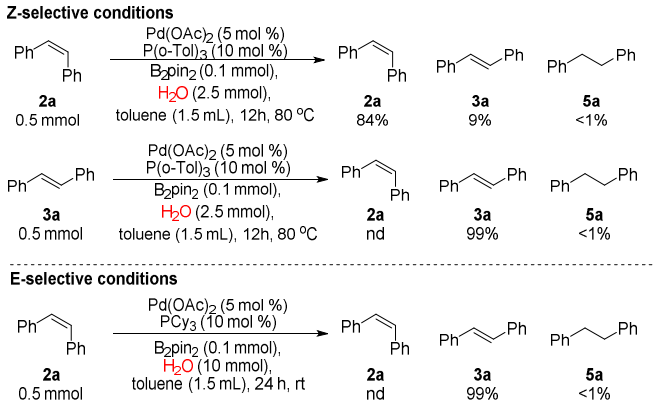


Scheme 10. Determining the catalyst generation sequence.

As can be seen from the above controls, presence of catalytic amount of AcOH was crucial in the formation of the corresponding product supporting the catalytic generation pathway **b)** (see Scheme 9).

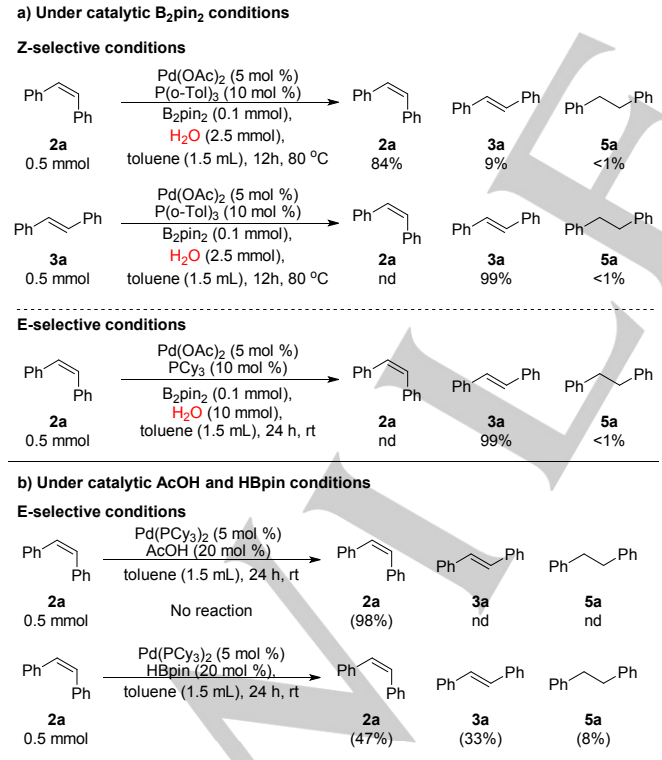
An additional control was carried out using a catalytic amount of the diboron reagent (B$_2$pin$_2$) to determine possible isomerizations during the course of the reaction (Scheme 11). When *Z*- and *E*-alkenes were subjected to *Z*-selective conditions, insignificant or no trace of isomerization was observed. However, under *E*-selective conditions, the corresponding *Z*-alkene completely isomerized to the *E*-isomer. This control suggested a reversible hydride addition to alkenes leading to isomerization to

the more stable *E*-alkene. Interestingly, only a trace amount of reduced products was observed with both the controls.



Scheme 11. Isomerization of alkenes.

Final set of controls were carried out to identify the exact catalytic species responsible for isomerizing the *Z*-alkene to *E*-alkene under the given *E*-selective reaction conditions (Scheme 12). Hence, the possible catalytic species can be narrowed down to either H-[Pd]-OAc or H-[Pd]-B(OR)$_2$. Thus, a set of separate controls comprising catalytic amount of H-OAc and H-Bpin under the *E*-selective conditions were carried out to confirm the exact catalytic species responsible for the isomerization.



Scheme 12. Isomerization of alkenes.

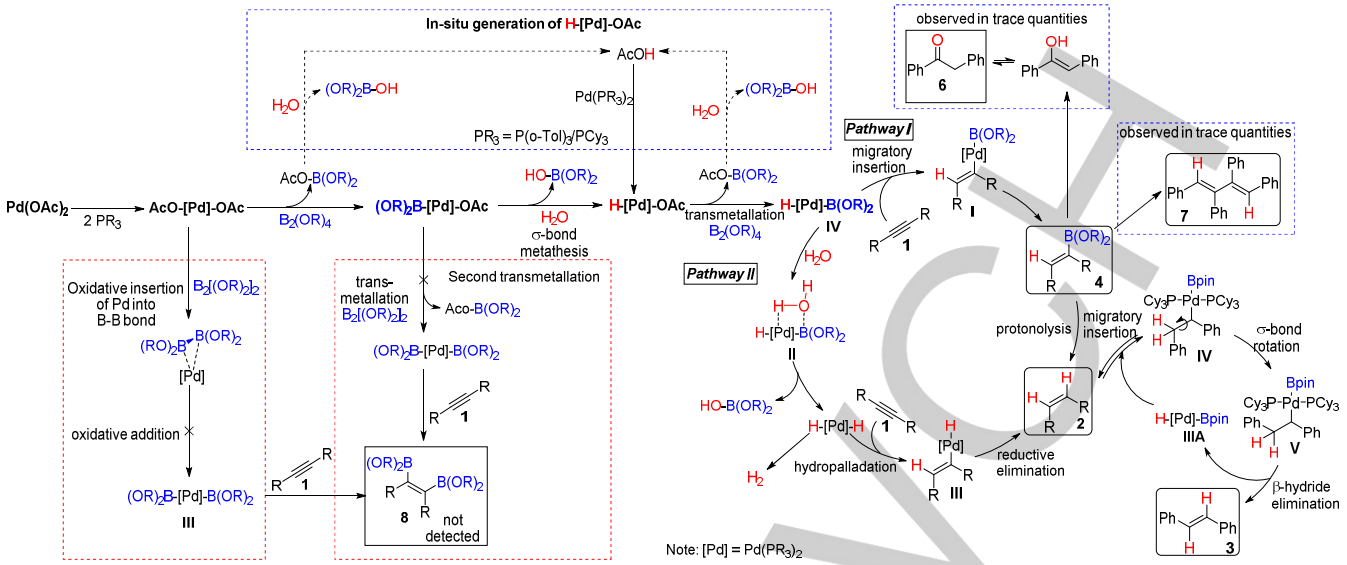
As can be understood from the controls described in the scheme 11, H-[Pd]-Bpin is capable of isomerizing the *Z*-alkene to corresponding *E*-alkene and H-[Pd]-OAc was ineffective in inducing any isomerization.

Extensive experimental and theoretical studies have been carried out related to palladium and diboron systems vis-à-vis platinum based catalysts.[18] Based on the literature precedence and experimental observations, we have arrived at a putative mechanism (Scheme 13). It is well documented that direct insertion of Pd into the B-B bond is difficult.[18b-f] Consequently, no diborylated product **8** was detected in the present reaction system as well. The first step is coordination of phosphine ligands to the palladium center to get Pd(PR$_3$)$_2$ (here afterwards represented as [Pd]). A subsequent facile transmetallation step with B$_2$(OR)$_4$ provides (RO)$_2$B-[Pd]-OAc, and (RO)$_2$B-OAc as the side product. Although, under reductive conditions, pre-catalyst Pd(OAc)$_2$ is known to give zerovalent active catalytic species Pd(PR$_3$)$_2$ in presence of B$_2$(OR)$_4$ and two equiv of PR$_3$ generating 2 equiv of AcOBpin as side product,[18a] the transmetallation step appears to be favored.

The next step is σ-bond metathesis of (RO)$_2$B-[Pd]-OAc with water to generate H-[Pd]-OAc along with HO-B-(OR)$_2$ as a side product.[18c] This step appears to be the rate determining step as evident from deuterium labelling studies. The existence of H-[Pd]-OAc and its role as a pertinent reaction intermediate has been confirmed by using pre-synthesized Pd(PR$_3$)$_2$ [PR$_3$ = P(*o*-Tol)$_3$ or PCy$_3$] and AcOH as the catalytic system to achieve the present transformation.[18j] H-[Pd]-OAc can now undergo a second transmetallation step with the second equivalent of B$_2$(OR)$_4$ to generate H-[Pd]-B(OR)$_2$, and an additional equivalent of (RO)$_2$B-OAc.

(OR)$_2$B-OAc can undergo hydrolysis to generate AcOH and (OR)$_2$B-OH, and hence the catalytic cycle is repeated with the [Pd]^0 generated in the final step of the cycle.

The complex H-[Pd]-B(OR)$_2$ can now react in two ways. In pathway 1, it can add on to the alkyne substrate **1** generating the hydropalladated complex **I** via migratory insertion. A reductive elimination of the complex **I** generates the corresponding hydroborylated product **4**. As can be understood from Schemes 3 and 4, hydroborylated product **4** in the presence of the palladium catalyst conditions, undergoes protonolysis to the corresponding *Z*-alkene **2** by protodepalladation. Products **6**[18g] and **7**[18c] were detected using ^{1}H NMR in trace amounts in 0.5 mmol scale *E*-selective reaction of **1a**. **7** was successfully isolated in the 5 mmol scale reaction as the side product and confirmed by single crystal XRD. Formation of **7** can be understood by transmetallation of complex **I** with the already formed hydroborylated product **4.** Hence presence of the oxidized product **6**, and **7** further suggests the occurrence of complex H-[Pd]-B(OR)$_2$.



Scheme 13. Plausible mechanism.

In an alternate pathway 2, a second σ-bond metathesis step can be visualized with between H_2O and H-[Pd]-$B(OR)_2$. First step involving OH group of water and H-[Pd]-$B(OR)_2$ leading to *in situ* generation of the H-[Pd]-H species which further can disintegrate to H_2 gas and $[Pd]^0$. This observation is consistent with our previous report wherein H_2 liberation was studied and quantified in the Pd-B_2pin_2-H_2O system.[13a] As observed in Scheme 5, palladium catalyst present in the system can efficiently utilize the H_2 gas as well to reduce the alkyne **1** to the corresponding *Z*-alkene **2** *via* complex **III**.

Unlike in P(o-Tol)$_3$ system, in the presence of PCy_3 ligand the migratory insertion step becomes a reversible process leading to the formation of complex **IV** and can further lead to the isomerization of *Z*-alkene (**2**) to the thermodynamically more favored *E*-alkene (**3**) as the sole product. This observation is also supported by our previous report.[13b] Overall, the reaction furnishes the desired olefins **2** or **3** along with $(RO)_2B$-OH (and $(RO)_2B$-O-$B(OR)_2$, if water is not in excess) as the side product.[13a-b]

Conclusions

In summary, we have developed a stereodivergent synthesis of *Z/E*- olefins using H_2O as the H_2 source and diboron compound as the mediator under homogeneous Pd-catalytic conditions. The high stereoselectivity has been achieved by employing P(*o*-Tol)$_3$ and PCy_3 ligands to obtain *Z*- and *E*-alkenes respectively. D_2O has been used to obtain deuterium incorporated *Z*/*E*-olefins. The practicality of this method is supported by gram scale synthesis of *Z*- and *E*-stilbene. We have also identified the pertinent catalytic intermediates responsible for the hydride transfer from water under diboron conditions.

Experimental Section

Full experimental details are given in the Supporting Information, together with copies of NMR spectra.

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Keywords: palladium • stereodivergent • reduction • diboron • water

[1] a) G. R. Pettit, S. B. Singh, M. R. Boyd, E. Hamel, R. K. Pettit, J. M. Schmidt, F. J. Hogan, *Med. Chem.* **1995**, *38*, 1666; b) S. A. Joyce, A. O. Brachmann, I. Glazer, L. Lango, G. Schwär, D. J. Clarke, H. B. Bode, *Angew. Chem. Int. Ed.* **2008**, *47*, 1942; *Angew. Chem.* **2008**, *120*,1968; c) M. Jang, L. Cai, G. O. Udeani, K. V. Slowing, C. F. Thomas, C. W. W. Beecher, H. H. S. Fong, N. R. Farnsworth, A. D. King-horn, R. G. Mehta, R. C. Moon, J. M. Pezzuto, Science **1997**, *275*, 218; For selected reviews, see: d) C. Oger, L. Balas, T. Durand, J-M. Galano, *Chem. Rev.* **2013**, *113*, 1313.

[2] a) H. Lindlar, *Helvetica Chim. Acta* **1952**, *35*, 446–450; b) H. Lindlar, R. Dubuis, *Org. Synth.* **1966**, *46*, 89.

[3] For selected heterogeneous semireduction of alkynes, see: a) S. Liang, G. B. Hammond, B. Xu, *Chem. Commun.* **2016**, *52*, 6013; b) E. D. Slack, C. M. Gabriel, B. H. Lipshutz, *Angew. Chem. Int. Ed.* **2014**, *53*, 14051; *Angew. Chem.* **2014**, 126, 14275; For selected *E*-selective reductions, see: c) K.; Tokmic, A. R. Fout, *J. Am. Chem. Soc.* **2016**, *138*, 13700; d) Z. Chen, M. Luo, Y. Wen, G. Luo, L. Liu, *Org. Lett.* **2014**, *16*, 3020; For homogeneous semireduction of alkynes, see: e) M. W. van Laren, C. J. Elsevier, *Angew. Chem. Int. Ed.* **1999**, *38*, 3715; *Angew. Chem.* **1999**, *111*, 3926; f) R. R. Schrock, J. A. Osborn, *J. Am. Chem. Soc.* **1976**, *98*, 2143; g) Y. Blum, D. Czarkie, Y. Rahamim, Y. Shvo, *Organometallics* **1985**, *4*, 1459; h) E. Shirakawa, H. Otsuka, T. Hayashi, *Chem. Commun.* **2005**, 5885; i) H. S. La Pierre, J. Arnold, F.

D. Toste, *Angew. Chem., Int. Ed.* **2011**, *50*, 3900; *Angew. Chem.* **2011**, *123*, 3986; For transition-metal free frustrated-Lewis-pair catalyzed approach, see: j) K. Chernichenko, Á. Madarász, I. Pápai, M. Nieger, M. Leskelä, T. Repo, *Nat. Chem.* **2013**, *5*, 718.

[4] For selected alkyne semi reduction under switchable selectivity, see: a) E. Richmond, J. Moran, *J. Org. Chem.* **2015**, *80*, 6922; b) S. Fu, N.-Y. Chen, X. Liu, Z. Shao, S.-P. Luo, Q. Liu, *J. Am. Chem. Soc.* **2016**, *138*, 8588; c) F. Luo, C. Pan, W. Wang, Z. Ye, J. Cheng, *Tetrahedron* **2010**, *66*, 1399; d) R. Kusy, K. Grela, *Org. Lett.* **2016**, *18*, 6196; e) R. Barrios-Francisco, J. J. Garcia, *Inorg. Chem.* **2009**, *48*, 386; f) J. Li, R. Hua, *Chem. -Eur. J.* **2011**, *17*, 8462; g) T. Schabel, C. Belger, B. Plietker, *Org. Lett.* **2013**, *15*, 2858; h) Y. Liu, L. Hu, H. Chen, H. Du, *Chem. -Eur. J.* **2015**, *21*, 3495.

[5] For semihydrogenation with boranes, see: a) H. C. Brown, G. Zweifel, *J. Am. Chem. Soc.* **1959**, *81*, 1512; b) H. C. Brown, G. Zweifel, *J. Am. Chem. Soc.* **1961**, *83*, 3834; c) H. Yatagai, Y. Yamamoto, K. Maruyama, A. Sonoda , S. Murahashi, *J. Chem. Soc., Chem. Commun.*, **1977**, 852; d) H. Yatagai, Y. Yamamoto, K. Maruyama, *J. Chem. Soc., Chem. Commun.*, **1978**, 702.

[6] For semihydrogenation with silanes, see: a) B. M. Trost, R. Braslau, *Tetrahedron Lett.* **1989**, *30*, 4657; b) S. Enthaler, M. Haberberger, E. Irran, *Chem. Asian J.* **2011**, *6*, 1613; c) K. Semba, T. Fujihara, T. Xu, J. Terao, Y. Tsuji, *Adv. Synth. Catal.* **2012**, *354*, 1542; d) A. M. Whittaker, G. Lalic, *Org. Lett.* **2013**, *15*, 1112; e) G.-H. Wang, H.-Y. Bin, M. Sun, S.-W. Chen, J.-H. Liu, C.-M. Zhong, *Tetrahedron* **2014**, *70*, 2175.

[7] For HCO_2H mediated reductions, see: a) K. Tani, N. Ono, S. Okamoto, F. Sato, *J. Chem. Soc., Chem. Commun.* **1993**, 386; b) P. Hauwert, G. Maestri, J. W. Sprengers, M. Catellani, C. J. Elsevier, *Angew. Chem., Int. Ed.* **2008**, *47*, 3223; *Angew. Chem.* **2008**, *120*, 3267; c) C. Belger, N. M. Neisius, B. Plietker, *Chem. Eur. J.* **2010**, *16*, 12214; d) J. Li, R. Hua, T. Liu, *J. Org. Chem.* **2010**, *75*, 2966; e) R. Shen, T. Chen, Y. Zhao, R. Qiu, Y. Zhou, S. Yin, X. Wang, M. Goto, L.-B. Han, *J. Am. Chem. Soc.* **2011**, 133, 17037; f) J. Broggi, V. Jurcik, O. Songis, A. Poater, L. Cavallo, A. M. Z. Slawin, C. S. J. Cazin, *J. Am. Chem. Soc.* **2013**, *135*, 4588; g) R. M. Drost, T. Bouwens, N. P. van Leest, B. de Bruin, C. J. Elsevier, *ACS Catal.* **2014**, *4*, 1349.

[8] For NH_3-BH_3 mediated reductions, see: a) R. Barrios-Francisco, J. García, *J. Appl. Catal., A* **2010**, *385*, 108; b) E. Vasilikogiannaki, I. Titilas, G. Vassilikogiannakis, M. Stratakis, *Chem. Commun.*, **2015**, *51*, 2384; c) C. E. Hartmann, V. Jurcík, O. Songis, C. S. J. Cazin, *Chem. Commun.* **2013**, 49, 1005.

[9] For Ammonium formate mediated reductions, see: a) S. Ram, R. E. Ehrenkaufer, *Synthesis* **1988**, *1988,* 91; b) S. Iyer, A. K. Sattar, *Synth. Commun.* **1998**, *28*, 1721.

[10] For hydroboration followed by protonolysis, see: a) C.-C. Tai, M.-S. Yu, Y.-L. Chen, W.-H. Chuang, T.-H. Lin, G. P. A. Yap, T.-G. Ong, *Chem. Commun.* **2014**, *50*, 4344; b) G. A. Molander, N. M. *J.* Ellis, *Org. Chem.* **2008**, *73*, 6841; For study related to over-adsorption of pinacolboronic esters, see: c) S. Hitosugi, D. Tanimoto, W. Nakanishi, H. Isobe, *Chem. Lett.* **2012**, *41*, 972.

[11] For silylation followed by protonolysis, see: a) C. Belger, B. Plietker, *Chem. Commun.* **2012**, *48*, 5419; b) L. Yong, K. Kirleis, H. Butenschoen, *Adv. Synth. Catal.* **2006**, *348*, 833.

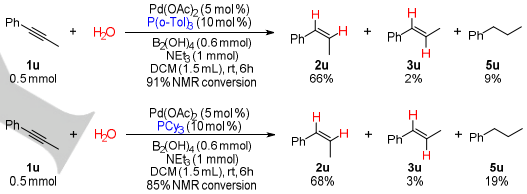
[12] S. P. Cummings, T.-N. Le, G. E. Fernandez, L. G. Quiambao, B. J. Stokes, *J. Am. Chem. Soc.* **2016**, *138*, 6107.

[13] a) D. P. Ojha, K. Gadde, K. R. Prabhu, *Org. Lett.*, **2016**, *18*, 5062; b) D. P. Ojha, K. Gadde, K. R. Prabhu, *J. Org. Chem.,* **2017**, *82*, 4859; c) D. P. Ojha, K. R. Prabhu, *Org. Lett.,* **2016**, *18,* 432.

[14] For diboron mediated transfer hydrogenation with H_2O, see: a) S.-S. Li, X. Liu, Y.-M. Liu, H.-Y. He, K.-N. Fan, Y. Cao, *Chem. Commun.* **2014**, *50*, 5626; b) Q. Xuan, Q. Song, *Org. Lett.* **2016**, *18*, 4250; c) W. Kong, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 3987; *Angew. Chem.* **2017**, *129*, 4045; d) Y.-T. Xia, X.-T. Sun, L. Zhang, K. Luo, L. Wu, *Chem. – Eur. J.* **2016**, *22*, 17151; e) Q. Xuan, C. Zhao, Q. Song, *Org. Biomol. Chem.* **2017**, *15*, 5140; f) Y. Zhou, H. Zhou, S. Liu, D. Pi, G. Shen, *Tetrahedron* **2017**, *73*, 3898; g) M. Flinker, H. Yin, R. W. Juhl, E. Z. Eikeland, J. Overgaard, D. U. Nielsen, T. Skrydstrup, *Angew. Chem. Int. Ed.* **2017**, *56*, 15910; *Angew. Chem.*, **2017**, *129*, 16126.

[15] E. C. Neeve, S. J. Geier, I. A. I. Mkhalid, S. A. Westcott, T. B. Marder, *Chem. Rev.* **2016**, *116*, 9091.

[16] a) A. N. Trzeciak, Z. Ciunik, J. Ziółkowski, J. *Organometallics*, **2002**, *21*, 132; b) The use of both *Z*- and *E*- selective ligands viz. P(*o*-Tol)$_3$ and PCy_3 respectively, resulted in similar reaction outcome under tetrahydroxydiboron conditions.



[17] a) D. R. Anton, R. H. Crabtree, *Organometallics* **1983**, *2*, 855; b) R. H. Crabtree, *Chem. Rev.* **2012**, *112*, 1536.

[18] For literature related to mechanistic considerations, see: a) C. S. Wei, G. H. M. Davies, O. Soltani, J. Albrecht, Q. Gao, C. Pathirana, Y. Hsiao, S. Tummala, M. D. Eastgate, *Angew. Chem., Int. Ed.* **2013**, *52*, 5822; *Angew. Chem.*, **2013**, *125*, 5934 b) H. E. Burks, S. Liu, J. P. Morken, *J. Am. Chem. Soc.* **2007**, *129*, 8766; c) E. Shirakawa, G. Takahashi, T. Tsuchimoto, Y. Kawakami, *Chem. Commun.* **2001**, 2688; d) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; e) I. Beletskaya, C. Moberg, *Chem. Rev.* **1999**, *99*, 3435; f) N. Selander, K. J. Szabó, *Chem. Rev.* **2011**, *111*, 2048; g) X. Xu, W. Du, Y. Zeng, B. Dai, H. Guo, *Org. Lett.* **2014**, *16*, 948; h) Q. Cui, D. G. Musaev, K. Morokuma, *Organometallics* **1998**, *17*, 742; i) S. Sakaki, T. Kikuno, *Inorg. Chem.* **1997**, *36*, 226; j) B. M. Trost, D. L. Romero, F. Rise, *J. Am. Chem. Soc.* **1994**, *116*, 4268.

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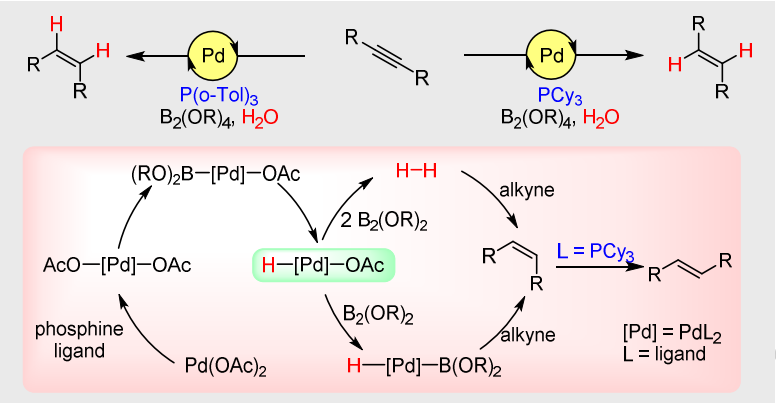

*S. Rao and K. R. Prabhu)**

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Stereodivergent Alkyne Reduction Using Water as the Hydrogen Source

Ligand guides the reduction of alkynes in stereodivergent fashion. For this reduction, the hydrogen is generated from H_2O using a diboron reagent. Homogeneous reduction has been accomplished using palladium catalyst to obtain *E*- or *Z*-alkenes selectively.