

pubs.acs.org/OPRD

Hydrogen Evolution from Telescoped Miyaura Borylation and Suzuki Couplings Utilizing Diboron Reagents: Process Safety and Hazard Considerations

Jeremy M. Merritt,* Indrakant Borkar, Jonas Y. Buser, Alison Campbell Brewer, Odilon Campos, Jeffrey Fleming, Caoimhe Hansen, Ashley Humenik, Stephen Jeffery, Prashant B. Kokitkar, Stanley P. Kolis, Mindy B. Forst, Gordon R. Lambertus, Joseph R. Martinelli, Ciaran McCartan, Hossam Moursy, Donal Murphy, Michael M. Murray, Kevin O'Donnell, Rita O'Sullivan, Gary A. Richardson, and Han Xia



ABSTRACT: The hazard assessment of a telescoped Miyaura borylation and Suzuki coupling reaction employing bis(pinacolato)diboron (BisPin), used in the developmental synthesis of an intermediate for abemaciclib, led to the observation of hydrogen being generated. Quantitative headspace GC and solution ¹¹B NMR were used to show that the rapid decomposition of the excess BisPin from the borylation under the aqueous basic conditions of the Suzuki reaction was responsible for H₂ generation. The moles of H₂ observed were found equal to the BisPin excess, which is rationalized by mass balance and a stoichiometric reaction. The possible generation of the stoichiometric levels of H₂ should be considered in hazard assessments of this class of reaction. Kinetic and process modeling was used to minimize the risk upon scale-up, and results for commercial manufacturing batches are presented, which showed good agreement with the lab scale data. Furthermore, the hydrogen evolution potentials of other common borylating agents including bisboronic acid (BBA) and pinacol borane were demonstrated.

KEYWORDS: safety, hydrogen, abemaciclib, borylation, Miyaura, Suzuki, risk assessment

INTRODUCTION

Diboron coupling agents, bis(pinacolato)diboron (BisPin) and tetrahydroxy-diboron (bisboric acid or BBA) for example, have found wide utility as reagents in Miyaura borylation and Suzuki cross-coupling reactions, which are powerful reactions for the formation of carbon–carbon bonds.^{1,2} Telescoping the two reactions together has been widely demonstrated,³⁻⁶ often resulting in a streamlined process, the removal of additional unit operations associated with the isolation of the boronic ester, and a higher overall yield. The diboron reagent is often used in excess in borylation reactions to favor the desired reaction over the possibly competing Suzuki homocoupling of the aryl halide starting material and the formed boronate ester or to reduce reaction completion time in the case of a first order dependence on BisPin concentration. When telescoping, there is no purge of the excess diboron reagent prior to the initiation of the Suzuki coupling. If common aqueous basic conditions are used for the Suzuki reaction, the hydrolysis of the remaining diboron reagent is expected. Here, we report that this hydrolysis may be accompanied by hydrogen evolution, which could result in explosive and flammable headspace concentrations of hydrogen, a possibility that should be included in hazard assessments for lab scale reactions and commercial manufacturing. The reaction of BBA with alcohol solvents (methanol) was previously highlighted in the development of a Miyaura borylation process, however the

safety considerations or hydrogen generation rate were not discussed. 7

The proposed hydrolysis and hydrogen evolution mechanism is given in Scheme 1. The boron hydride species (III, VI) were not directly observed in this work but are proposed as reactive intermediates. It has been noted previously that BBA in the presence of water can liberate traces of hydrogen.⁸ The rate of hydrogen increased somewhat by the addition of acid, however the reaction was rapid upon the addition of NaOH. Hence, the mechanism below is drawn assuming base catalyzed conditions, which is the case during the Suzuki reaction described here. Furthermore, the presence of a borane intermediate (III or VI) has also been proposed previously to explain the mechanistic studies of hydrogenation reactions. The hydrolysis of BisPin (I) to BBA (II) is not a required first step, and boron pinacol ester analogues of the downstream products may exist (pinacol borane (VI), boronic acid pinacol esters (V)). According to the proposed mechanism, one

Special Issue: Excellence in Industrial Organic Synthesis 2021

Received: May 28, 2021



Scheme 1. Proposed Hydrolysis Mechanism of Diboron Reagents Resulting in Hydrogen Formation



Scheme 2. Telescoped Borylation Suzuki Coupling



Figure 1. Calibrated H₂ concentration (vol %) and raw nitrogen counts recorded by headspace GC during the Suzuki reaction.

equivalent of H_2 evolution is possible with respect to any diboron reagent equivalent under aqueous conditions. The equilibrium of any comparable species with and without pinacol may also be possible and is illustrated in the reaction scheme just for boronic acid (IV) and pinacol boronic acid (V) for illustrative purposes.

A telescoped Miyaura borylation and Suzuki coupling was being developed for the synthesis of an intermediate in the route to abemaciclib, 10,11 a CDK 4/6 inhibitor that was at the time under investigation as an oncolytic agent (Scheme 2) and

later commercialized as Verzenio.¹² The borylation reaction rate was dependent on BisPin concentration, and 1.2 equiv of BisPin was used to reduce the reaction completion time and improve the cycle-time for manufacturing. After the completion of the borylation, Ar^2Cl and aqueous K_2CO_3 solution were added to initiate the Suzuki reaction. As the K_2CO_3 reacts during the Suzuki reaction, gaseous CO_2 is evolved, which hindered the initial observation of hydrogen. The hypothesis for possible hydrogen generation was prompted by hazard assessments of the process and

Article



Figure 2. Expanded view of H₂ evolution with experimental annotations.



Figure 3. Waterfall plot of ¹¹B NMR spectra recorded during a BisPin hydrolysis tube experiment.

mechanistic modeling efforts to understand the possible sources of base consumption. These hazard assessments require fully balanced chemical reactions, and such chemical equations were not available at the time, which accounted for BisPin decomposition. Therefore, experiments were undertaken to more fully understand the BisPin hydrolysis mechanism and possibility of H_2 generation.

RESULTS AND DISCUSSION

A baseline reaction was performed with gas phase headspace sampling using a gas chromatograph (GC) and 1.2 equiv BisPin. Details of the lab model (lab model 1) and reactor setup are given in the Experimental Section. Hydrogen was not observed during the borylation. The time trends for H_2 and N_2 during the Suzuki reaction are given in Figure 1. A rapid burst of hydrogen was observed after the addition of the aqueous carbonate solution to the completed borylation reaction mixture. The headspace concentration reached a peak of ~27 vol % H₂, which is above the flammability limit¹³ and the lower explosive limit (LEL). As the reaction proceeded, the raw N₂ GC signal decreased and then returned to baseline. The first drop in N₂ counts can largely be attributed to the H₂ off-gassing. As the hydrogen release completes, the N₂ signal recovers; however, a second slower decrease and then recovery is observed, which is due to CO₂ evolution from the carbonate base. CO₂ could not be directly quantified using the current GC method conditions. However, CO₂ off-gassing was previously identified for this reaction using mass spectrometry.

An expanded view of the H₂ trend with procedural annotations is given in Figure 2. The aqueous carbonate solution was added approximately linearly over the times indicated, and the pyrimidine Ar²Cl solution was charged rapidly (bolus) at the time indicated. Interestingly, H₂ was not observed until the carbonate solution was completely added. This time delay is hypothesized to be due to a combination of possible effects: (1) a base concentration effect during the linear base addition as the hydrolysis is expected to be catalytic in hydroxide, (2) a slow initial hydrolysis of BisPin and finite lifetime of the intermediates on their way to forming H_{2} (3) the solvent system transitions from homogeneous to two liquid phases at intermediate THF/H2O ratio, which depends on temperature and salt content, and the hydrolysis may react preferentially in the created water rich phase, (4) a gas-liquid mass transfer effect of supersaturating the liquors with hydrogen, and (5) a headspace turnover time of approximately 10 min (for lab scale). Note that the effect of headspace turnover can be readily modeled with the assumption of perfect mixing in the headspace. However, this assumption can often be poor for large scale reactors unless turbulent gas flows are used or intentional gas phase mixing.

The GC H₂ trend was numerically integrated to quantify the total amount of H₂ evolved during the reaction (eq 1). The total volume of H₂ was determined by multiplying the N₂ flow rate set point (F_{N_2}) by the H₂ vol % determined by GC and normalizing by the raw N₂ counts to account for the change in output flow due to H₂ and CO₂ evolution. This volume of H₂ was then converted to moles using the ideal gas law and assuming 1 atm and 298 K, which apply at the outlet of the condenser (eq 1: numerical integration formula used to determine the total volume of hydrogen.).

$$V_{\rm H_2} \,(\rm mL) = \sum F_{\rm N_2} \left(\frac{\rm mL}{\rm min}\right) \Delta t \,(\rm min) \, H_2 \,(\%) \, \frac{N_2(t=0)}{N_2(t)}$$
(1)

The analysis showed 0.18 equiv of H_2 , in excellent agreement with the theoretical excess of BisPin used (0.2 equiv), illustrating essentially complete conversion. The peak hydrogen concentration, and therefore the magnitude of the process hazard, would be dependent on the purging gas flow rate, headspace volume, amount of diboron reagent remaining after the borylation, aqueous K_2CO_3 charging rate, and hydrogen generation rate.

¹¹B NMR Characterization. The hydrolysis reaction of BisPin (0.072 mol/L) and K_2CO_3 (0.036 mol/L) in 50/50 THF/H₂O was setup in an NMR tube and monitored by ¹¹B NMR at room temperature. In contrast to the biphasic Suzuki reaction (with approximately 9 wt % water in the organic layer), these conditions were homogeneous, facilitating the

measurements. A waterfall plot of the resulting NMR spectra is shown in Figure 3, where spectra were recorded every 5 min. A large range of chemical shifts is displayed in the figure due to the relatively large shifts and breadth of possible ¹¹B resonances and to emphasize that no additional peaks were observed outside the region 0–40 ppm. The very broad peak near 0 ppm is a background resonance due to the NMR tube itself.

Relative area percent for the observed peaks versus time are given in Figure 4. The peak at 30 ppm is assigned to BisPin on



Figure 4. Relative concentration profiles from ¹¹B NMR experiment.

the basis of spiking studies and the literature¹⁴ but also overlaps with BBA (also confirmed by spiking and the literature¹⁵). The BisPin (or BBA) peak area in Figure 4 was corrected for its NMR response due to the two identical boron nuclei by dividing by 2. No correction was performed for any other peaks. The peak at 30 ppm is observed to be consumed during the hydrolysis, resulting in the production of two major product peaks at ~17 and 7 ppm. During the first 30 min, the downfield product peak shows a shift from ~10 to 17 ppm. This broader resonance is attributed to $B(OH)_3$, $B(OH)_4^-$, and possibly $B_3O_3(OH)_4^-$, which are known to rapidly interconvert and exhibit a single chemical shift dependent on pH.^{16–18} The peak at 7 ppm is tentatively assigned as a higher order polyborate species such as $[[B(OH)_3]_q(OH)_p]^{-p}$ with p,q > 1 due to literature precedence¹⁹ and observed concentration dependence (vide infra, Figure 5).

A higher concentration benchtop experiment was performed with NaOH instead of K₂CO₃ to rule out gas generation due to CO_2 to help identify the polyborate species ¹¹B NMR assignment, and determine a qualitative rate of reaction. The addition of NaOH (0.3 M) to BisPin (0.3 M) in 50/50 THF/ H₂O at room temperature led to the immediate vigorous generation of gas, which persisted for approximately 10 min before subsiding and ultimately stopping after approximately 30 min. A small amount of a white precipitate was observed at the end of the reaction, which is attributed to sodium salts of the resulting boric acid. A sample at the end of the reaction was taken for ¹¹B NMR and compared to the NMR tube experiment with K_2CO_3 (Figure 5). Both samples were found to contain the same species but with an altered intensity ratio. The higher intensity ratio of the peak attributed to polyborate species is rationalized by the \sim 4 times higher concentration used in the NaOH experiment. On the basis of the observed



Figure 5. Individual ¹¹B NMR spectra recorded at the end of the BisPin hydrolysis.

hydrogen evolution, the reaction rate is relatively rapid, however the conversion implied by the NMR tube data could be misleading due to sample preparation and analysis time as no quench was used. A more quantitative measurement of the kinetics under these conditions was obtained in a calorimetry experiment described below.

Heat of Reaction. The enthalpy of reaction for the BisPin hydrolysis (BisPin and NaOH (0.3 mol/L) in 50/50 THF/ H_2O at 25 °C) was measured to further understand the thermal hazard. Calorimetry data was collected using a Thermal Hazard Technology Micro Reaction calorimeter run under isothermal conditions. A baseline run without BisPin was used to subtract the inherent heat of mixing due to the experimental addition protocol of adding aqueous NaOH

solution to initiate the reaction. The differential and integrated heat flow with baseline subtracted is shown in Figure 6.

The overall enthalpy of reaction was determined to be approximately 450 J/g (114 kJ/mol). Note that this is an overall reaction enthalpy and is not corrected for contributions due to hydrogen gas liberation and precipitation of a small amount of boric acid salts. From this measurement, it is apparent the reaction kinetics are quite fast, which were in good agreement with the qualitative benchtop experimental observations (e.g., complete hydrolysis of BisPin and hydrogen evolution in <30 min at 25 °C). To further classify the process hazard, the adiabatic temperature rise was calculated according to eq 2. A heat capacity (C_p) of 2.95 J/g K was used for the 1:1 volumetric ratio of THF/H₂O at room temperature.²⁰ This analysis results in a ΔT_{ad} of 13 °C, indicating low risk due to the temperature rise alone.

$$\Delta T_{\rm ad} = \frac{\Delta H_{\rm r}}{mC_{\rm p}} \tag{2}$$

Calorimetry and hydrogen off-gassing experiments were followed up with larger scale experiments using a 1 L MP10 reactor with a Mettler Toledo RC-1mx reaction calorimeter. A micro-GC was used to monitor the headspace. Furthermore, experiments were also performed using bisboronic acid and pinacol borane as reagents. The experiments were performed by replicating the molar concentrations in the described lab model (see lab model 2) but only charging the boron reagent, THF, K₂CO₃, and water. The reactions were performed at 55 °C instead of 65 °C to allow for the collection of calorimetry without the complication of refluxing. The calorimeter software accounts for the heat required to raise the temperature of the RT dosed solution in the calorimetric analysis. For BisPin and BBA, the observation of hydrogen was initiated by the addition of the aqueous K_2CO_3 solution. In the case of pinacol borane, however, a small amount of hydrogen was observed immediately upon addition to the THF solution



Figure 6. Differential and integrated heat flow from a calorimetry experiment examining the BisPin hydrolysis.

Та	ble	1.	Evolved	Hyc	lrogen	Quantit	уC	Comparison
----	-----	----	---------	-----	--------	---------	----	------------

starting material (SM)	amount (g)	SM potency (%)	potency adjusted SM (mmol)	H ₂ evolution (mmol)	equiv H_2 (mole of H_2 per mole of reactant)
BisPin	4.6829	99.3	18.31	10.63	0.58
pinacol borane w/o K ₂ CO ₃	2.43	91.7	17.41	11.00	0.63
pinacol borane	2.43	91.7	17.41	9.78	0.56
bisboronic acid	1.74	100.0	19.41	11.29	0.58

even at RT. With this observation, the hydrogen evolution was allowed to complete at 55 °C before moving on. At the end of hydrogen evolution, which persisted for approximately 45 h (Figure 8), the aqueous K_2CO_3 solution was charged, which resulted in no additional hydrogen generation, indicating that the reaction had likely fully consumed the boron reagent. A separate experiment was performed for pinacol borane where the aqueous K₂CO₃ solution was charged immediately after charging the starting material to THF and immediate heating to 55 °C to compare the hydrogen evolution with the other boron reagents. A quantitative summary of the total hydrogen evolved in the four trials is shown in Table 1. The potency of the starting materials was estimated using GC and NMR. In this case, only ~60% of the starting material was converted into hydrogen in contrast with the near stoichiometric reaction described above. Note that the same reaction for BisPin using different reagent lots described below for modeling work did give $\sim 100\%$ conversion to H₂ in previous attempts. It is hypothesized that there could be other side reactions or polymerization reactions, inaccurate potency determination of the starting materials or possibly equipment setup, or GC calibration, which could account for the lower than the quantitative yield. Importantly, all these boron reagents exhibit the hydrogen evolution risk, and a stoichiometric reaction could be considered worst case.

The calorimetry results indicated an overall reaction that was slightly endothermic or near zero enthalpy difference in all cases. The smaller heat of reaction compared to the microcalorimetry experiment described above is attributed to efficient hydrogen evolution in the purged experiments. This process is endothermic, which was hindered in the sealed vials of the microcal. This endothermic evaporation likely balances the slightly exothermic chemical reaction.

Hydrogen Evolution Comparison of BisPin with BBA and Pinacol Borane. An overlay of the hydrogen off gassing rate for the reactions of BisPin, BBA, and pinacol borane is given in Figure 7. Time zero for the pinacol borane, BBA, and BisPin trends in the figure is the start of the K_2CO_3 addition



Figure 7. Hydrogen evolution comparison of BisPin, BBA, and pinacol borane.

(30 min). For the pinacol borane experiment where no K_2CO_3/H_2O was added, time zero was defined as the time when the reagents were charged to THF at RT.

One can see that the slight delay from the base feed and onset of hydrogen is reproduced for BisPin; however, in the case of BBA and pinacol borane, the hydrogen is observed immediately. These results support the hypothesis that the hydrolysis of the pinacol moiety may be the first step in this reaction cascade or that they are slightly less reactive than the boronic acid or borane species. Because hydrogen evolution was observed for pinacol borane before even adding the K₂CO₃ solution, a separate experiment was performed just monitoring the hydrogen evolution from the solution in THF, which is shown in Figure 8. In this case, the pinacol borane appears to be more reactive than BisPin or BBA as no hydrogen evolution was detected prior to K₂CO₃/H₂O addition in those cases. Given the absence of water or base (absence of relevant amounts water in the THF was confirmed via Karl Fischer titration), other side reactions or selfcondensation must be at play in the case of pinacol borane. At this time, more detailed studies of this decomposition were not completed, however it should be emphasized that, due to the slow rate of hydrogen generation without the addition of a base, this scenario is of lower risk.

Kinetic and Process Modeling. A fit-for-purpose kinetic model of the BisPin process was developed in Dynochem²¹ to understand the hydrogen generation and to aid in understanding the risk at scale. Since the hydrogen evolution profile was found to be similar between running the full chemistry (lab model 1; Figure 2) and a simplified procedure using only BisPin, K₂CO₃, and solvents (lab model 2; Figure 7); the latter was used for the bulk of the modeling effort. Reactions were performed at 30, 55, and 65 °C (reflux) to allow for the extraction of the key rate constants and activation energies. The mechanism was approximated by the reactions given in Table 2. The fitted rate constants (k), activation energies (E_a) , and associated confidence intervals (CI) are also given in the table. Note that the reaction is modeled as homogeneous, however in reality it is biphasic. Also, the role and amount of base is neglected in the model. This approximation was deemed acceptable as these process parameters would not be varied in future campaigns. In attempts to vary the pH, an experiment with no K₂CO₃ was run. Hydrogen was observed, however the headspace concentration much lower than the data shown here, confirming that the rate is sensitive to pH. This reaction without K₂CO₃ was single phase as opposed to the others that were biphasic, and so it was not attempted to have the model bridge these conditions.

The mass transfer of hydrogen from the liquid to gas phase was modeled using the standard approach with the driving force governed by the hydrogen solubility, which was modeled according to Henry's law. The Henry's law coefficient was taken as a linear combination of the values in water and THF depending on the process solvent mass fraction, which varies



Figure 8. Hydrogen evolution from pinacol borane in THF only.

Table 2. Fit for Purpose Kinetic Model of BisPinDegradation to Form Hydrogen

reaction	k (L/mol·s)	CI (%)	E_{a} (kJ/mol)	CI (%)
BisPin + $H_2O \rightarrow pinacol$ borane + pinacol boronic acid	1.55×10^{-5}	1.9	18.64	9.8
pinacol borane + $H_2O \rightarrow$ pinacol boronic acid + H_2	1.42×10^{-4}	1.7	37.48	12.5

along the water/ K_2CO_3 addition. The Henry's law coefficients for THF and water were taken from the Dynochem Hydrogen solubility property tool (25 500 and 131 200 Pa·m³/mol values were used, respectively). Comparatively, the predicted temperature dependence of the solubility was small and thus neglected. A mass transfer coefficient of 0.1 s⁻¹ was used in the simulations, which was fast enough to make the predictions insensitive to this value, as the data did not show characteristics of mass transfer limitation. The reactor headspace composition calculation takes into account the reactor geometry, changing liquid level, and associated N₂ sweep rate. The headspace pressure was maintained at 1 atm by modeling a pressure controller with proportional and integral (PI) control. The quality of the fits to lab data is shown in Figure 9. The BisPin used for the temperature studies was found to be only 66% potent. The model takes into account the potency, thus improving the agreement of the hydrogen amounts. A sample of BisPin from manufacturing was obtained (found to be $\sim 100\%$ potent) and also used in the fit of the model (see Figure 9). For this lot, a much higher concentration of H₂ was observed, as explained by the much higher potency of the starting material. One can see that the model fits the data quite reasonably, supporting the model parametrization. It should be noted that the decay of H₂ at longer times is mostly control by the headspace turnover. At 65 °C, the reaction is just starting to reflux. This boil-up rate could also influence the effective gas purge rate, which may explain the slightly narrower experimental profiles at 65 °C compared to the other temperatures.

With a kinetic model in hand, the effects of various process and kinetic parameters including temperature, addition rates, reactor fill level, and nitrogen purge rate were simulated to



Figure 9. Model fit to lab scale hydrogen data.



Figure 10. Solvents exiting the condenser at temperatures below reflux temperature. The percent headspace was varied from 20 to 40%, the temperature from 15 to 60 $^{\circ}$ C, and N₂ flow from 60 to 1020 SCFH.



Figure 11. Solvents exiting the condenser at reflux temperature.

understand their impact on the headspace and outlet hydrogen concentrations. The goal was to design the nitrogen purge rates at scale to control the headspace of the reactor to \sim 30% as observed in the lab and to be below 25% of the LEL in the downstream ductwork at the point where oxygen could be present.

Condenser Modeling. As a significant nitrogen sweep was identified as a good control for the hydrogen level in the tank, condenser modeling was also performed to predict solvent loss. In order to evaluate the condenser performance for condensing

solvent vapors in the presence of significant amounts of noncondensable gases consisting of nitrogen, CO₂, and hydrogen, a model was developed using Aspen Plus.²² Model simulations were performed to test condenser performance under different conditions of tank levels, temperature, and nitrogen purge rates representative of manufacturing scale. Figure 10 shows the solvent loss from the condenser for all combinations of tank levels and nitrogen flow rates at all temperatures below the reflux temperature, and Figure 11 shows the equivalent graph at the reflux temperature. On the



Figure 12. Model predictions and experimental data for one of the manufacturing batches.

basis of these results, it was determined that the solvent loss associated with the nitrogen sweep over the range of proposed conditions was acceptable.

Scale-Up. Once the hydrogen risk was identified, precautions were made for future scale-up campaigns. The process was transferred to a IIC ATEX rated tank, which increased the acceptable limit of hydrogen in the headspace of the reactor to essentially 100%. Previously an IIB ATEX rated tank with a limit of 30 vol % hydrogen was used, which was near the observed maximum hydrogen concentration. Despite the ability to run with a high hydrogen content in the headspace of the reactor, the process needed to be designed such that exhaust gases were below 25% of the LEL in the downstream ductwork at the point where oxygen could be present. Therefore, a secondary nitrogen stream was used after the condenser to dilute the hydrogen levels appropriately. The model was used to help determine the appropriate set points for the nitrogen flows. Additionally, the model showed that, by elongating the K₂CO₃ addition, additional control could be afforded. This addition was intentionally done hot to prevent the accumulation of hydrogen due to a reduced reaction rate at a lower temperature. After the bulk of the hydrogen is evolved, the solution is then cooled and the second charge for the Suzuki reaction takes place. Due to constraints set forth by the process, other changes were not possible. For example, lowering the BisPin excess was not possible due to a very sharp increase in borylation reaction time and risk of incomplete conversion and impurities. Online GC monitoring was also installed at manufacturing scale to verify the observations made at lab scale. An example of the hydrogen evolution during a scale-up campaign using 2000 gallon equipment (240 kg basis) and the accompanying model simulation is given in Figure 12. The K₂CO₃ and pyrimidine charges can be visualized by the liquid volume trend in the figure. One can see that the model captures the hydrogen levels quite reasonably. Here, a 200 SCFH N2 flow rate was introduced into the headspace. On the basis of the experimental results at scale, the lag time before hydrogen is observed is reproduced from the lab run but is somewhat longer. As pointed out above, this lag time could arise from

many factors that are not fully understood at this time. The model does not capture this detail accurately, however additional safety factors were put in place on top of the model predictions and so this degree of agreement was deemed acceptable.

SUMMARY

Hydrogen gas was generated in the described telescoped borylation and Suzuki reaction, which is attributed to the hydrolysis of the excess BisPin reagent during the Suzuki reaction. Good mass balance was observed on the hydrogen moles relative to the BisPin excess. This phenomenon was also demonstrated for BBA and pinacol borane reagents, hence the hydrogen risk is expected to be general to any diboron or reactive monoboron coupling reagent used in a telescoped borylation-Suzuki reaction sequence, and therefore, the possibility of hydrogen evolution should be considered in process safety assessments for this class of reactions. The experimental conditions for the lab scale experiment resulted in hydrogen concentrations above the flammability limit. The peak hydrogen concentration is dependent on both chemical and physical phenomenons. Physical factors include the following: the purge gas flow rate and the headspace volume/batch size. The chemical factors include the hydrogen generation rate, which may be influenced by temperature, the aqueous K2CO3 charging rate, and equivalents, the identity of the boron coupling agent used, and the amount of diboron reagent remaining after the borylation. A fit for purpose kinetic model was built for the case of BisPin in the telescoped reaction to assess these factors for scale-up. The model was used to design nitrogen flows such that hydrogen concentrations in the headspace would be similar to that observed at lab scale and the outlet gas would be below the LEL. Using GC at manufacturing scale, it was found that hydrogen was indeed being generated to \sim 30 vol % in the reactor headspace for full scale manufacturing batches in good agreement with the model and lab-scale predictions. This work has illustrated a very under-recognized safety hazard of a reaction that is now quite common. The insight to such a risk was developed first by applying simple principles of understanding mass balance and

I

Organic Process Research & Development

fate of all reagents, not only during a reaction but also what can happen during workup. It is important for researchers and industrial practitioners to be aware of these potential hazards, and hence, the value of process safety evaluations and detailed process understanding cannot be overemphasized. With this understanding, a suitable control strategy was able to be designed into the described process to mitigate the associated safety hazards to an acceptable level.

EXPERIMENTAL SECTION

Lab Model 1. $Ar^{1}Br$ is the basis for all charges. Fifteen grams of $Ar^{1}Br$ (limiting reagent), potassium acetate (KOAc, 3.0 equiv), BisPin (1.2 equiv), PPh₃ (0.03 equiv), PdCl₂(PPh₃)₂ (0.03 equiv), and THF (6 L/kg, N₂-sparged) were charged to a 500 mL reactor. The reaction mixture is heated to reflux (65–72 °C) for 6–10 h or until reaction completion. Potassium carbonate (K₂CO₃, 3.0 equiv) and H₂O (10 L/kg) were charged to a separate reactor and degassed. $Ar^{2}Cl$ (1.5 equiv), PdCl₂(PPh₃)₂ (0.02 equiv), and THF (6.0 L/kg, N₂-sparged) were charged to a separate reactor. The carbonate solution and the $Ar^{2}Cl/catalyst$ mixture were charged to the completed borylation reaction mixture. The liquid/liquid biphasic reaction mixture was heated to reflux (65–72 °C) with adequate mixing to disperse the phases until the Suzuki reaction was complete.

Lab Model 2. Ar¹Br (15 g) is the basis for all charges but was not added. BisPin (0.2 equiv) and THF (12 L/kg, N₂-sparged) were charged to a 1 L reactor and heated to 55 °C. A 15 mL/min N₂ flow was used. Potassium carbonate (K₂CO₃, 3.0 equiv) and H₂O (10 L/kg) were charged to a separate reactor and degassed. The carbonate solution was charged to the reactor containing the boron reagent over 30 min. The liquid/liquid biphasic reaction mixture was maintained at 55 °C with adequate mixing to disperse the phases until the reaction was complete.

For lab model 1, a 500 mL reactor was setup with a subsurface N₂ inlet, stirrer, thermocouple, and glycol cooled condenser. During the reaction, the purge gas was flowed continuously at a rate of 15.6 mL/min and, upon exiting the condenser, was tied into a GC for monitoring. The purge flow rate was set above the gas draw required for the GC to prevent back mixing or pulling air into the system. The headspace volume was ~150 mL after K₂CO₃/H₂O addition so the gas turnover time was \sim 8 min. The flow of gas from the subsurface sparge to the outlet was designed to minimize short circuiting of the gas flow in the headspace by promoting good gas phase mixing. The Suzuki reaction is biphasic with an organic layer of ~15 volumes. The phase partitioning of the various BisPin hydrolysis products was not determined. Assuming the BisPin excess stays in the organic layer, a concentration of ~0.05 M is expected.

 $\rm H_2$ concentrations were monitored in the gas phase by gas chromatography. A set of external standards with known % $\rm H_2$ were used to calibrate the raw data. An Inficon (East Syracuse, New York) 3000 Micro Gas Chromatograph (GC) equipped with a thermal conductivity detector (TCD) was used to monitor $\rm H_2$ concentrations. The separation was performed using argon as the carrier gas (25 psi) and a molecular sieve column (GC-MOD-30, diameter 0.32 mm, length 10 M with 3 m long PLOT-U precolumn)). The inlet and injector temperatures were maintained at 90 °C while the column temperature was set at 140 °C. The GC was fluidically connected to the gas vent of the reactor (downstream of the condenser) via a 4 ft length of 1/16" Teflon tubing. The ~15 mL/min gas flow rate used in the small-scale experiments results in a high linear velocity that minimizes any delay of the sample reaching the GC. Reactor sampling was done using an internal pump pulling at 10 mL/min for 40 s, allowing for thorough flushing of the sampling system prior to acquisition. Injection was done using a fixed volume of 1.0 μ L sample loop with a 50 ms inject time and 8 s back flush on the PLOT-U precolumn. Data was collected for 80 s using the standard detector sensitivity setting and a rate of 50 Hz.

A schematic of the experimental setup to quantitate hydrogen evolution is given in Figure 13. Note that it was



Figure 13. Experimental setup used to quantitate hydrogen evolution.

important to have the N_2 sweep rate higher than the flow rate the GC pulls during sampling to prevent air from entering the system or altering the headspace pressure.

¹¹B{H} NMR spectra were obtained with a 500 MHz Bruker Avance III equipped with a 5 mm BBO probe. Samples were run unlocked, and the literature chemical shifts of BisPin were used as a reference.

AUTHOR INFORMATION

Corresponding Author

Jeremy M. Merritt – Synthetic Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States; orcid.org/0000-0003-3331-1545; Phone: 317-651-2818; Email: merrittje@lilly.com

Authors

- Indrakant Borkar Synthetic Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States
- Jonas Y. Buser Synthetic Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States
- Alison Campbell Brewer Synthetic Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States; orcid.org/0000-0002-6487-5717

Organic Process Research & Development

pubs.acs.org/OPRD

Odilon Campos – Synthetic Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States

Jeffrey Fleming – Engineering Technology Center, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States

Caoimhe Hansen – Eli Lilly Kinsale, Dunderrow, Kinsale, Co. Cork P17 NY71, Ireland

Ashley Humenik – Eli Lilly Kinsale, Dunderrow, Kinsale, Co. Cork P17 NY71, Ireland

Stephen Jeffery – Eli Lilly Kinsale, Dunderrow, Kinsale, Co. Cork P17 NY71, Ireland

Prashant B. Kokitkar – Engineering Technology Center, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States

Stanley P. Kolis – Synthetic Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States; orcid.org/0000-0001-6268-9470

Mindy B. Forst – Synthetic Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States

Gordon R. Lambertus – Synthetic Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States; orcid.org/0000-0001-7413-929X

Joseph R. Martinelli – Synthetic Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States

Ciaran McCartan – Eli Lilly Kinsale, Dunderrow, Kinsale, Co. Cork P17 NY71, Ireland

Hossam Moursy – Eli Lilly Kinsale, Dunderrow, Kinsale, Co. Cork P17 NY71, Ireland

Donal Murphy – Eli Lilly Kinsale, Dunderrow, Kinsale, Co. Cork P17 NY71, Ireland

Michael M. Murray – Eli Lilly Kinsale, Dunderrow, Kinsale, Co. Cork P17 NY71, Ireland

Kevin O'Donnell – Eli Lilly Kinsale, Dunderrow, Kinsale, Co. Cork P17 NY71, Ireland

Rita O'Sullivan – Eli Lilly Kinsale, Dunderrow, Kinsale, Co. Cork P17 NY71, Ireland

Gary A. Richardson – Synthetic Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States

Han Xia – Synthetic Molecule Design and Development, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46221, United States; Orcid.org/0000-0002-8738-3010

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.1c00198

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors would like to acknowledge the help of Matt Embry for NMR support.

REFERENCES

(1) Liu, X. Bis (pinacolato) diboron. Synlett 2003, No. 15, 2442–2443.

(2) Hall, D. G. Structure, Properties, and Preparation of Boronic Acid Derivatives. Overview of Their Reactions and Applications.

Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine; Wiley-VCH Verlag GmbH & Co., 2006; pp 1–99.

(3) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. Synthesis of arylboronates via the palladium(0)-catalyzed cross-coupling reaction of tetra(alkoxo)diborons with aryl triflates. *Tetrahedron Lett.* **1997**, *38* (19), 3447–3450.

(4) Molander, G. A.; Trice, S. L. J.; Kennedy, S. M. Scope of the Two-Step, One-Pot Palladium-Catalyzed Borylation/Suzuki Cross-Coupling Reaction Utilizing Bis-Boronic Acid. J. Org. Chem. 2012, 77 (19), 8678–8688.

(5) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. Palladium-Catalyzed Borylation of Aryl Chlorides: Scope, Applications, and Computational Studies. *Angew. Chem., Int. Ed.* **2007**, *46* (28), 5359–5363.

(6) Wang, L.; Cui, X.; Li, J.; Wu, Y.; Zhu, Z.; Wu, Y. Synthesis of Biaryls through a One-Pot Tandem Borylation/Suzuki-Miyaura Cross-Coupling Reaction Catalyzed by a Palladacycle. *Eur. J. Org. Chem.* **2012**, No. 3, 595–603.

(7) Gurung, S. R.; Mitchell, C.; Huang, J.; Jonas, M.; Strawser, J. D.; Daia, E.; Hardy, A.; O'Brien, E.; Hicks, F.; Papageorgiou, C. D. Development and Scale-up of an Efficient Miyaura Borylation Process Using Tetrahydroxydiboron. *Org. Process Res. Dev.* **2017**, *21* (1), 65– 74.

(8) Wartik, T.; Apple, E. F. The Reactions of Diboron Tetrachloride with Some Hydrogen Compounds of Non-metallic Elements and with Dimethyl Sulfide1. J. Am. Chem. Soc. **1958**, 80 (23), 6155–6158.

(9) Cummings, S. P.; Le, T.-N.; Fernandez, G. E.; Quiambao, L. G.; Stokes, B. J. Tetrahydroxydiboron-Mediated Palladium-Catalyzed Transfer Hydrogenation and Deuteriation of Alkenes and Alkynes Using Water as the Stoichiometric H or D Atom Donor. *J. Am. Chem. Soc.* **2016**, *138* (19), 6107–6110.

(10) Frederick, M. O.; Kjell, D. P. A synthesis of abemaciclib utilizing a Leuckart Wallach reaction. *Tetrahedron Lett.* **2015**, *56*, 949–951.

(11) Merritt, J. M.; Andiappan, M.; Pietz, M. A.; Richey, R. N.; Sullivan, K. A.; Kjell, D. P. Mitigating the Risk of Coprecipitation of Pinacol during Isolation from Telescoped Miyaura Borylation and Suzuki Couplings Utilizing Boron Pinacol Esters: Use of Modeling for Process Design. *Org. Process Res. Dev.* **2016**, *20* (2), 178–188.

(12) Asghar, U.; Witkiewicz, A. K.; Turner, N. C.; Knudsen, E. S. The history and future of targeting cyclin-dependent kinases in cancer therapy. *Nat. Rev. Drug Discovery* **2015**, *14* (2), 130–146.

(13) ISO 10156 defines the international standard for determining the flammability of gases or gas mixtures. Gas mixtures that contain > 5.5 mol% hydrogen in nitrogen were classified as flammable.

(14) Ishiyama, T.; Chen, H.; Morken, J. P.; Mlynarski, S. N.; Ferris, G. E.; Xu, S.; Wang, J. 4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi-1,3,2-dioxaborolane. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd.: Chichester, UK, 2013; pp 1–18.

(15) Trice, S. L. J. Figure 3.2. Palladium-Catalyzed Borylation And Cross Coupling Of Aryl And Heteroaryl Halides Utilizing Dibora Derivatives. Publicly Accessible Penn Dissertations, University of Pennsylvania, **2012**; p 712.

(16) Dewar, M. J. S.; Jones, R. New heteroaromatic compounds. XXV. Studies of salt formation in boron oxyacids by boron-11 nuclear magnetic resonance. *J. Am. Chem. Soc.* **1967**, *89* (10), 2408–2410.

(17) Ishihara, K.; Nagasawa, A.; Umemoto, K.; Ito, H.; Saito, K. Kinetic Study of Boric Acid-Borate Interchange in Aqueous Solution by 11B NMR Spectroscopy. *Inorg. Chem.* **1994**, 33 (17), 3811–3816.

(18) Trice, S. L. J. Figure 3.1. Palladium-Catalyzed Borylation And Cross Coupling Of Aryl And Heteroaryl Halides Utilizing Dibora Derivatives. Publicly Accessible Penn Dissertations, University of Pennsylvania, 2012; p 712.

(19) Momii, R. K.; Nachtrieb, N. H. Nuclear magnetic resonance study of borate-polyborate equilibria in aqueous solution. *Inorg. Chem.* **1967**, No. 6, 1189–1192.

(20) Kiyohara, O.; D'Arcy, P. J.; Benson, G. C. Ultrasonic velocities, compressibilities, and heat capacities of water+ tetrahydrofuran mixtures at 298.15 K. *Can. J. Chem.* **1979**, *57* (9), 1006–1010.

(21) Dynochem, version 4.0.0; Scale-up Systems Inc.: Dublin, Ireland, 2011.

(22) Aspen Plus, version 8.4; Aspen Technology, Inc.: Bedford, MA, 2013.