**The Story of a Mechanism-Based Solution to an Irreproducible Synthesis
Resulting in an Unexpected Closed-System Requirement for the
LiBEt₃H-Based Reduction: the Case of the Novel Subnanometer Cluster,
[Ir(1,5-COD)(μ-H)]₄, and the Resulting Improved, Independently
Repeatable, Reliable Synthesis**

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Keywords: synthesis; tetra-iridium subnanometer cluster; reproducible syntheses; mechanism and radical-cage chemistry; super hydride reductions; hydrogen formation from super hydride.

Abstract

Reproducibility is the hallmark of reliable science. Reproducible synthetic procedures are of central importance in the chemical sciences, yet $\geq 12\%$ of syntheses submitted for publication to publications that explicitly check procedures before their publication, such as *Inorganic Syntheses* and *Organic Syntheses*, are reported as having to be rejected since the submitted synthesis could not be repeated. In the present contribution paper we re-examine our own 2012 synthesis of $[\text{Ir}(\text{1,5-COD})(\mu\text{-H})]_4$ which, frustratingly, we were unable to reproduce once the first author of the original publication completed his stint in our labs. We detail the approach we took to uncover the problems in the synthesis, a key step in which was constructing a “paper mechanism” that led to the key hypothesis of what was going wrong in our attempts to repeat the published synthesis. The results have led to an improved synthesis, one shown to be reproducible by a second researcher working only from the detailed written procedure. Also detailed are the 4 conceptual Steps that were used to find the main problems in the synthesis, as well as the 7 specific alternative hypotheses that were involved and 20 experimental trials which discovered the missing detail in the original synthesis—the previously unknown need to employ a *closed reaction system*—and which led to the present, further improved, synthesis which we demonstrate can be reproduced by an independent researcher with no prior Schlenk-technique experience working from only the written procedure. The hard-won insight of the need for a closed system is likely of broader significance and applicability to analogous syntheses involving metal-reductions by LiBEt_3H and probably other anionic hydrides. A summary and conclusion section is included, one striving towards assisting the design and reporting of more reproducible syntheses in the chemical sciences.

Introduction

Tetranuclear, M_4 (M = transition-metal) subnanometer clusters are of both increasing interest and occurrence because they provide precisely defined molecular subnanometer clusters able to serve as synthons or as novel precatalysts [1]. A good example is our 2012 report of the then unknown organometallic complex, $[\text{Ir}(1,5\text{-COD})(\mu\text{-H})_4]$ [1]. This black, crystalline, and well-characterized compound is coordinatively unsaturated (with 56 total electrons, 17 at each iridium), has labile 1,5-COD ligands, and as a result is quite reactive. The published synthesis reports a 78% initial, 55% recrystallized yield as shown in Scheme 1.

Scheme 1. The balanced reaction stoichiometry and reaction conditions of the published 2012 synthesis [1] of $[\text{Ir}(1,5\text{-COD})(\mu\text{-H})_4]$. The reagents are air / moisture sensitive and the product air sensitive; hence, the synthesis below is performed as reported [1] under argon using Schlenk-line and drybox methods.

The resultant $[\text{Ir}(1,5\text{-COD})(\mu\text{-H})_4]$ product was unequivocally characterized by single-crystal XRD, XAFS, ESI MS, UV-visible, IR and NMR [1]. Five reasons why the previously unknown, tetranuclear, coordinatively unsaturated $[\text{Ir}(1,5\text{-COD})(\mu\text{-H})_4]$ cluster is of interest for future research were also listed in that publication [1].

It was therefore exceedingly disappointing and frustrating when two of us (SÖ, WL) attempted to repeat the synthesis—that is, our own, seemingly straight-forward synthesis, Scheme 1—yet 3 attempts to do so failed [1]. Since we have considerable experience with challenging inorganic syntheses (i.e., notably in the area of polyoxometalate syntheses [2,3,4]), and since we have worked on ways to record and report a high level of detail needed for others to be able to repeat syntheses working from only the written procedure, we were again frustrated if not humiliated by being unable to repeat our own synthesis. We also recognized that problems with irreproducible syntheses—and therefore the need for fully

documented, truly reproducible syntheses by one “skilled in the art”—are much broader, arguably omnipresent current issues in synthesis across all areas of the chemical sciences [5,6]. Producing reproducible syntheses in self-assembly inorganic and complex-materials syntheses, where many of the intermediates or key reaction variables are often unknown and where it can be hard to follow the reaction’s progress directly, can be especially challenging [2,4,5].

Hence, we decided to dig into our reported synthesis, stick with it until we found the problem(s), and then provide an honest, detailed reporting of how we proceeded, including missteps that we took along the way. The goals of this report are (i) first and foremost to improve our written synthetic procedure for the $[\text{Ir}(1,5\text{-COD})(\mu\text{-H})_4]$ product to make it reproducible in independent hands, but also (ii) to assist others in uncovering the problems in literature or their own irreproducible syntheses.

Results and Initial Discussion

What follows is a largely historical account of the steps we took en route to developing a synthesis that proved reproducible in the hands of an independent investigator working only from the written procedure.

Step #1: *Repeat the Original Synthesis Exactly As Written ≥ 3 Times, While Also Making Sure That One Is Following All Reactions Directly Wherever Possible*

Our first experience-based-rule [4] when encountering apparently irreproducible syntheses is to repeat the procedure *exactly* as written (i.e., to the extent that is possible) at least 3 times and with ≥ 2 researchers—as the first needed control to try to ensure it is not one researcher’s “hands” that are the issue. Three attempts (trials 1-3) by 2 of us (SÖ, WL) to repeat the synthesis “as described” failed.

Our thoughts then turned to another, well-known rule of synthesis that we try to strictly adhere to, namely that one should “follow all reactions directly” whenever possible. Fortunately, a successful synthesis of $[\text{Ir}(1,5\text{-COD})(\mu\text{-H})_4]$ is readily identified by a) the development of its green

color, as well as b) a black powder solid final product *that dissolves in benzene* to form a dark green but clear solution with no precipitate, plus c) the diagnostic ^1H NMR hydride signal at -2.9 ppm characteristic of the desired $[\text{Ir}(\text{1,5-COD})(\mu\text{-H})_4]_4$ product. Hence, while we could have gone to the trouble of monitoring the reaction directly by NMR (or possibly by in-situ IR), we reasoned that the problems presented by the low temperature dropwise addition of the LiBHEt_3 made such monitoring both non-trivial and unnecessary. Instead, the green color of the desired product provides a simple, visual method for diagnosing failed vs successful syntheses. In addition, “failed” reactions produce a (different) black powder when worked up that is *insoluble in benzene*¹ and lacks the -2.9 ppm NMR hydride signal diagnostic of the desired $[\text{Ir}(\text{1,5-COD})(\mu\text{-H})_4]_4$ product. In short, we reasoned that we were adhering to the important rule of “follow all reactions directly”.

Step #2: *Construction of a List of All Conceivable, "Reasonable" Alternative Hypotheses for Why the Synthesis Failed—Including a Look Back at the Relevant Literature*

Next, we employed that key step of the scientific method [7,8] in which one constructs a list of all reasonable alternative hypotheses to explain the observations at hand—in the present case, all plausible explanations for the failure of the reported synthesis. We developed 3 initial hypotheses that could explain the synthetic problems and conducted 8 experiments (summarized in Table 1) to test them. In constructing our hypotheses, we also employed that principle of efficient science of “go to the literature” by going back and carefully relooking at the literature of the rhodium congener, $[\text{Rh}(\text{1,5-COD})(\mu\text{-H})_4]_4$. Interestingly, one finds 3 different syntheses [9,10,11] for the Rh_4 -based subnanometer cluster, syntheses which differ in the starting $[\text{Rh}(\text{1,5-COD})\text{Cl}]_2$ precursor concentration (30 mM or 60 mM in THF) and in the use of LiBEt_3H vs NaBEt_3H at -78 °C, 0 °C, or room temperature [9,10,11]. This reanalysis of the literature suggests that especially the -78 °C component of our

synthesis [1] may not be optimum or even necessary, a hypothesis we will return to in testing hypotheses #3 and #6 in what follows.

Hypothesis #1: That Scale is the Key Issue: Experimental Trials # 4, 5, Table 1

In discussions with the pioneer and co-author of our reported synthesis, Professor K-H.Yin, we discovered a few important details that were incorrectly recorded during the writing of the paper’s experimental section [1]. Specifically, we discovered that the scale of the reaction as 2 mmol of starting $[(\text{1,5-COD})\text{IrCl}]_2$ reactant (i.e., 4 mmol Ir) is a misreport; the actual experiments were in fact run at half that, a 1 mmol scale. *Photographs* of the reaction at various stages that were available (but not previously published, but which are now given as Figure S2) proved useful in eventually confirming (*vide infra*) what had been done in the original synthesis.

This information produced the first logical hypothesis for the failed reactions, namely that the scale and/or the initial concentrations are somehow critical variables. Hence, this first hypothesis was tested using 1 mmol scale (trial 4) and 0.5 mmol using 35 mL of THF (trial 5) experiments, Table 1. However, both scales produced failed reactions. In short, changing the scale of the reaction or the concentration of precursors did not improve the reaction; hence, hypothesis #1 is disproven.

Hypothesis #2: That Impure Reactants Are the Culprit: Trials # 6, 7, Table 1

Our reactions to this point used LiBEt_3H which had been stored in our lab refrigerator for ca. 1 year, but we had obtained its ^1H NMR spectrum and confirmed that it matched the literature. Nevertheless, fresh LiBEt_3H was ordered and used in the trials that follow. In addition, we dried a fresh sample of THF in a fresh sodium/benzophenone still, and used a portion of that dark-blue benzophenone ketyl to prepare a sample of 35 mL THF with 2 mmol ketyl as a visual indicator that neither oxygen nor water contamination were a problem at the 2 mmol/35 ml = 0.057 M level, that is, at the level of iridium used in the synthesis. In addition, a control was done in which the 0.057 M dark blue benzophenone ketyl was put though the entire Schlenk-tube and line-based experimental procedure and shown to remain dark-blue even after argon purified on the Schlenk-line was bubbled through the

¹ While we have not investigated the insoluble black precipitate, a reasonable hypothesis is that it could be a 1,5-COD deficient *oligomer*, something like “ $[(\text{Ir}_4\text{H}_4(\text{1,5-COD})_4)_x]_n$ ”. If so, then this in turn would suggest a role for the added, excess 1,5-COD previously found empirically¹ to give higher yields of the desired $(\text{Ir}_4\text{H}_4(\text{1,5-COD})_4)$ product.

solution for ~30 minutes. This control shows that adventitious oxygen or water, at the level of the iridium precursor concentration used, is *not* the cause of the failed syntheses. However, despite the above successful controls and despite the use of freshly purchased LiBEt_3H , trial 6 still failed—brown solutions that never turned green were produced, Table 1.

However, during the above investigations we recalled a paper hanging on the walls in our lab because of its general usefulness [12], a paper which demonstrates that THF dried by the common procedure of sodium/benzophenone can still retain ~44 ppm water, which for our synthesis would be 7.6 mol% water per iridium at a reaction scale of 1 mmol of iridium chloride dimer. Hence in Trial 7 (and hereafter), we employed that paper's [12] prescription for more complete drying of THF by storing the distilled THF over 20% m/v 3 Å molecular sieves for >72 hours, thereby reducing the water content by another factor of 10. Trial 7 briefly exhibited a greenish hue while warming from -78 °C, and a ca. 24% yield of isolated black powder which, when dissolved in C_6D_6 , formed a dark opaque solution with a hint of green plus black precipitate in the bottom of the NMR tube. The partially successful synthesis in Trial 7 shows ^1H NMR peaks indicative of the $[\text{Ir}(\text{1,5-COD})(\mu\text{-H})_4]$ product, including the distinctive hydride peak at -2.9 ppm (see Figure S1 in the Supporting Information for a representative spectrum), but also numerous other impurities—so Trial 7 was therefore deemed a largely failed reaction. Nevertheless, the useful result from the testing of hypothesis 2 is that even <0.1 equivalent (10%) of water can affect the synthesis, so that *the THF should be stored over molecular sieves to achieve additional drying*.

Hypothesis #3: That the Time and/or Temperature of the 1,5-COD Addition Are Key Variables: Trials # 8, 9, 10, 11, Table 1

Next we tested the hypothesis that the 1,5-COD might need to be added at a lower temperature than the room temperature employed in the published synthesis [1]. Hence, in trial 8 the 1,5-COD was added while the solution was warming up from -78 °C, and before it reached room temperature, while in trial 9, the solution was allowed to warm up more slowly over ca. 1 h before the 1,5-COD was finally added at room temperature, and in trial 10, the 1,5-COD was at -78 °C before warming. Trials 8 and 9

produced brown solutions, but trial 10 produced a slight greenish-brown color and an NMR spectra indicating impurities with lots of black, benzene insoluble precipitate in the NMR tube.

Given the minor success of trials 7 and 10, trial 11 investigated adding the 1,5-COD at -78 °C (along distilled THF subsequently stored over molecular sieves for >72 hours. A distinctly green-brown solution post warming to room temperature resulted, and significantly less precipitate than preceding samples was seen. However, the reaction still showed the same, numerous impurity peaks in the ^1H NMR spectra (see Figure S1 in the Supporting Information) and black precipitate in the NMR tube. In short, the testing of hypothesis 3 suggested that *the 1,5-COD is probably best added below room temperature, for example, at 0 °C*.

Overall, about 13 person-days had been invested at this point to try to solve irreproducible synthesis problem. We had shown via the mock control reactions with blue benzophenone ketyl that our air and moisture avoidance Schlenk technique was adequate for the synthesis. We had gained the insight THF purified more rigorously than directed by the original synthesis [1] was a good idea, but not the primary problem, and we had shown that adding 1,5-COD at low temperatures gives some improvements, especially when combined with use of the drier THF, resulting in the marginal success of a 24% yield of impure product. However and despite our 13 person-days and three hypotheses tested via 11 experimental trials, no understanding had been achieved as to why the synthesis was generally failing or, at best, producing low yields of impure product.

Table 1. Reaction parameters tested and the results of the syntheses including testing if sodium/benzophenone distilled THF should also be stored over molecular sieves for >72 hours, what temperature the 1,5-COD is best added at, what color the reaction solution turned, whether there was precipitate (abbreviated as PPT in Table 1) in C₆D₆ in the NMR tube and, and whether the product was detectable by the -2.9 ppm ¹H NMR signal of the desired product. Except where noted, each experiment was run at a 1 mmol scale in 35 mL THF.

#	Temp for 1,5-COD add	Solution color	PPT in NMR tube?	¹ H NMR result	Additional Comments
4	RT	Brown	N/A	N/A	
5	RT	Brown	N/A	N/A	70 mL THF, 0.5 mmol scale
6	RT	Brown	N/A	N/A	new reactants used
7	RT	slight green	lots	impure product	THF stored over molecular sieves
8	~0 °C	Brown	N/A	N/A	1,5-COD added while warming
9	RT	Brown	N/A	N/A	warmed slowly
10	-78 °C	slight green	lots	impure product	
11	-78 °C	green & brown	some	impure product	THF stored over molecular sieves

Step #3: A Detailed Mechanistic Analysis

At this point, we reasoned that *it was time to stop and rethink the problem completely and thoroughly*. Doing so provided the needed breakthrough. Specifically, a breakthrough came when we realized that because this reaction is relatively simple (e.g., at least in its stoichiometry), there are presumably a limited number of *possible mechanisms* one could write. Indeed, we reasoned that we know the possible mechanisms of this type of organometallic reaction at this stage of the science [13,14]. Hence, construction of the possible mechanisms should at least be attempted and might prove illustrative. Indeed, we realized that despite the apparent simple nature of at least the balanced reaction in Scheme 1 and the apparent ready success of our first synthesis, an earlier misstep is that we should have taken time from *day one (vide infra)* to scratch out plausible mechanisms as part of our prior, synthetic publication.

The possible mechanistic scheme, as it was written down in step 3 of this investigation, is reproduced in Scheme 2. The initial cleavage of the [(1,5-COD)IrCl]₂ dimer by THF has some precedent [15], after which the plausible mechanisms considered deviate according to “concerted” or “electron transfer”-based transition states en route to the final

product. Solvent-cage chemistry is an important part of these “paper mechanisms”—that is, mechanisms that “may or may not prove to be worth the paper they are written on”.

One possibility, shown on the left of Scheme 2, is a putative multi-centered, “concerted” reaction, with an inner-sphere electron-transfer process in-the-solvent-cage which would make, in that case, a key “Ir(1,5-COD)H(solvent)” fragment. That “Ir(1,5-COD)H(solvent)” monomer would then diffuse out of the cage and aggregate to the observed, tetrameric [Ir(1,5-COD)(μ-H)]₄ product.

Alternatively and more likely we reasoned, *outer-sphere electron-transfer in the solvent cage* could occur, as shown in the right half of Scheme 2. It was then realized that cage escape would then be the fastest process [16]. That is, even with the expected lowering [17] of its otherwise ≥70 kcal/mol Ir-Cl bond energy [18] to about 1/3 its value to, say, ~25 kcal/mol in the putative key, [Ir---Cl]^{•-} intermediate (shown above in the right-hand part of Scheme 2), then the cleavage of even that greatly weakened bond will *still be orders of magnitude slower than cage escape* (whose rate constant is expected to be in the range of ~10⁹⁻¹⁰ s⁻¹ [16]). *This in turn means that the key intermediates would then diffuse apart, and side reactions such as 2 BHEt₃[•] → H₂ + 2 BEt₃ become possible.*

Scheme 2. Plausible “paper mechanism” that was written at the time for the formation of $\text{Ir}(\text{1,5-COD})(\mu\text{-H})_4$ from the LiBEt_3H and $[\text{Ir}(\text{1,5-COD})\text{Cl}]_2$ precursors.

The above, crude mechanistic analysis then led to the fourth and crucial hypothesis, namely: (i) that a key intermediate consists of either $\text{BEt}_3\text{H}^\bullet$ and/or H_2 , (ii) that the procedure as written did not elaborate that the reaction *should be a closed system*; and therefore (iii) that using the “normal” Schlenk practice of hooking the system up to a bubbler, so as to keep the flask pressure at 1 atm while going from -78°C to room temperature as part of the synthesis, *was likely sweeping out much of a volatile but critical $\text{BEt}_3\text{H}^\bullet$ or, more likely, H_2 intermediate provided by the required, precisely 1.0 equivalent of LiBEt_3H reducing reagent*. Such an intermediate could produce up to 25-49 mL of gas at room temperature (for, respectively, 1 mmol gaseous H_2 gas or 2 mmol of putatively gaseous $\text{BEt}_3\text{H}^\bullet$ at STP), reductant-derived gas which in turn could largely

escape in an unsealed, open reaction flask hooked up to a bubbler. Noteworthy here is that most researchers experienced in Schlenk methods would hook the side-arm-containing, round-bottomed Schlenk reaction flask in this synthesis to a bubbler *unless explicitly told not to do so*. A search of the literature of LiBEt_3H reductions reveals that, while representative procedures typically state that the “reductions were done under a N_2 atmosphere” [19], *they do not specifically state if open or closed flask were employed—or should be employed*, or might be able to employ excess LiBEt_3H in their particular synthesis, which would tend to avoid problems with loss of volatile intermediates.

Additional mechanism-based predictions were also immediately clear from Scheme 2, notably (iv) that a very low, -78°C temperature for the LiBEt_3H addition may not be needed (nor optimum; 0°C being one logical alternative). The mechanistic thinking summarized in Scheme 2 led, then, to (the winning, *vide infra*) hypothesis #4 examined experimentally next.

Hypothesis #4: The Reaction Should Be Run In a Closed System to Prevent Escape of Any Volatile Intermediates. Trials # 12-18

The hypothesis of “a closed system is key” was tested next by running a synthesis in a sealed Schlenk flask using THF stored over molecular sieves. The very next trial, #12 in Table 2, resulted *in an improved, distinctly green solution*, albeit one that still turned green and brown upon warming to room temperature. Importantly, the spectra for the crude product matched the spectra from the crude material produced in the published synthesis [1], including several known and unknown impurities (see the Supporting Information Figure S3-A,B). As a separate, additional test of the hypothesis that “a closed system is key”, the conditions of experiment #12 were replicated in trial #13, Table 2, except that argon *was deliberately bubbled through the solution*. In that control, deliberate bubbling purified inert gas through the reaction solution resulted in a brown, *totally failed* reaction.

Trials #12 and #13 in Table 2 are, therefore, strong evidence in support of the sealed flask hypothesis: working with a closed system gives a significant, *reproducible improvement* in the synthesis, every reaction in a sealed flask (including subsequent ones, *vide infra*) produced the expected ^1H NMR spectrum

with green solutions at some point of the reaction. Clearly, the mechanistic analysis, however crude or however far off from the actual mechanism, served its purpose and proved to be key in producing the final, independently reproducible (*vide infra*) synthesis!

However, we were still not finished in that even after trial 12, the best yield was 40%, below our previously reported 78% yield [1]. In addition, a small amount of black solid settled to the bottom of the NMR tube. Hence, an additional series of 4 hypotheses and 7 experiments (trials 14-20, Table 2) were conducted to further test and optimize the synthesis.

Hypothesis #5: An Improved Reaction is Possible at 0 °C. Trial #14. The details of the tests of hypothesis #5 are provided in the SI for the interested reader. The key finding is that a $\geq 10\%$ improved yield from 40% to 50% if the reaction was run with the addition of LiBEt_3H at 0 °C, Table 2.

Table 2. A summary of experiments performed in order to test the mechanism and optimize the reaction for yield and purity. Except for the bubbling control in #13, all reactions were performed in a sealed Schlenk flask.

#	LiBEt_3H add. (°C)	COD add. (°C)	Time before 1,5-COD (min)	Time After 1,5-COD (min)	Solution color	Yield	NMR Acid Peak	PPT in NMR Tube?	Additional Comments
12	-78	RT	10	30	green & brown	40%	Yes	some	Literature procedure
13	-78	RT	10	30	very green to very brown	N/A	N/A	N/A	Open Flask
14	0	RT	10	30	green & brown	50%	—	some	
15	0	RT	10	10	green & brown	60%	—	some	
16	0	0	10	None	green to brown	67%	—	none	
17	0	0	20	None	green to brown	53%*	Yes	some	Extra washing
18	0	0	5	None	green to brown	62%	—	none	
19	0	0	5	None	green to brown	80%	—	none	2 mmol scale
20	0	0	5	None	green to brown	54%	—	none	2 mmol scale, new researcher

* Note that this experiment involved an additional washing procedure using twice the standard volume of acetone, in an attempt to remove the “acid peak”[1] in the NMR spectra, which is likely a reason for the somewhat lower yield in the indicated trial.

Hypothesis #6: Warming the Solution and Waiting to Add 1,5-COD Results in Product Degradation, So that the 1,5-COD Should Be Added at 0 °C,

Approximately 5 Minutes After the LiBEt_3H . Trials # 15, 16, 17, 18

The results of these experiments is that the yield was improved to 60%, trial #15, Table 2, and that minimizing the time both before and after the addition of 1,5-COD produces both a higher yield (up to 67%) and a higher product purity, trials #16 and #17, Table 2.

Hypothesis #7: An Even Higher Yield Can Be Obtained Using a Larger Scale Reaction. Trial # 19

Next, we decided to revisit the scale of the synthesis using the now critical details of employing a closed system, using THF stored over molecular sieves, using a constant temperature of 0 °C for the entire reaction to achieve a more consistent procedure, and minimizing the time before adding 1,5-COD while also minimizing the heating afterwards.

Running the otherwise identical procedure at 2.0 mmol scale improved the yield of the previous best synthesis from 67% to a final best yield of 80%, intriguingly nearly identical to the 78% yield reported by Professor Yih [1]. Note that this higher scale experiment was still performed in the same style 100 mL rounded bottom flask as the previous experiments, with ca. 60% more THF, so the additional improvement in yield may reflect factors such as a reduction of headspace within the flask, an increase in the concentration of products within the solution, or some other factor associated with the larger reaction scale. In summary, the result of testing hypothesis 7 is that *a 2 mmol scale synthesis with all the other improvements described to this provides an 80% yield.*

Step #4: *Have the synthesis checked by an independent researcher working only from the written procedure and any other materials that an outside researcher will have available. Trial # 20*

Reproducibility is the hallmark of reliable science; it is certainly a critical aspect of reliable and thus useful synthetic chemistry. Hence, one of us (SF; who is on a completely distinct project in our group) repeated the synthesis *while working from only the written procedure and without having any prior Schlenk-tube nor Schlenk-line experience.* As reported as part of the procedure in the Experimental section, the mock control with the 0.057 M dark blue

benzophenone ketyl was done first to show that he had sufficient air-free technique to do the synthesis.

The synthesis check proved successful in its first trial, resulting in product with the expected ^1H NMR spectra, albeit a somewhat lower, 54%. However, during this checking it a typo about the filter frit used in the final step was discovered, and may be responsible for some of the lower yield as could be the fact that this was the researcher's first synthesis using Schlenk technique. Overall, the result of checking the synthesis was deemed a success since *the synthesis was repeatable the first time using only the written instructions by a researcher performing his first Schlenk-line based synthesis.*

Evidence for the Production of Gaseous H_2 . Finally, we decided to see if we could not provide independent evidence for the postulated mechanism in Scheme 2 by seeing if we could demonstrate the production of gaseous H_2 , as Scheme 2 predicts. A simple apparatus was designed in which a solution for cyclohexene hydrogenation catalysis was placed into a small, 2 dram vial that was, in turn, carefully lowered (and thereby coaxially placed) into a 50 mL round-bottomed flask. A normal $\text{Ir}_4\text{H}_4(\text{COD})_4$ synthesis was then done in the 50 mL round bottomed flask (but outside of the 2 dram vial), so that the $\text{Ir}_4\text{H}_4(\text{COD})_4$ synthesis and cyclohexene hydrogenation solutions were physically separate, but in gaseous contact—and both in the *closed system* of the septa capped 50 mL round-bottomed flask. The conversion of cyclohexene by captured, gaseous H_2 formed in the $\text{Ir}_4\text{H}_4(\text{COD})_4$ synthesis, as Scheme 2 predicts, was then quantitated by the amount of cyclohexane produced (as detected by GLC of an aliquot of the 2 dram vial and its hydrogenation catalysis solution). The Experimental section can be consulted for a more detailed description of the apparatus and the other details of this experiment.

The result of this simple, but telling, experiment to detect gaseous H_2 produced is that a 23% yield over 24 h of the possible total amount of H_2 , that could have been produced from the 2.0 mmole of added LiBEt_3H , was captured in cyclohexane. Note that one does not expect to be able to capture much more than this level of H_2 , since the two systems—the formation of $\text{Ir}_4\text{H}_4(1,5\text{-COD})_4$ and the hydrogenation of cyclohexene to cyclohexane—are in competition for the available H_2 formed in the closed system.

Most importantly, the results provide incontrovertible evidence for gaseous H_2 production, and therefore support for Scheme 2 which predicted the production of gaseous H_2 from the cage escape of $\text{BEt}_3\text{H}\cdot$ radicals.

Summary and Conclusions

In conclusion, the following are the key findings of this work:

- The irreproducibility in the original synthesis of the useful $[\text{Ir}(1,5\text{-COD})(\mu\text{-H})]_4$ sub-nanometer cluster derives, according to all the available evidence, from the previously unknown and thus previously unreported, but key, experimental detail that the synthesis must be done in a sealed Schlenk flask that serves as a closed system (i.e., and not an open system connected to a bubbler as would otherwise be standard Schlenk practice for this particular synthesis by researchers “skilled in the art”).
- A search of the literature of LiBEt_3H reductions reveals that the insight of needing to employ a closed flask, especially when the reaction requires using precisely stoichiometric amounts of LiBEt_3H (i.e., where excess LiBEt_3H cannot be used), has not been previously reported, at least that we could find.
- Additional improvements in the synthesis of $[\text{Ir}(1,5\text{-COD})(\mu\text{-H})]_4$ also resulted from the 20 experiments performed and are part of the present contribution, specifically: (i) the THF used should be distilled over sodium/benzophenone, and then stored over 3A molecular sieves for >72 hours, so as to dry the THF more thoroughly; (ii) the preferred synthesis is carried out in a preferred manor by running the reaction at 0 °C and adding the LiBEt_3H and 1,5-COD before removing excess THF and prior to warming to room temperature, and (iii) the highest yield observed is produced at a higher, 2mmol scale—with implied possible yields even higher than 80% at even larger scales, although this was not specifically tested experimentally.
- The improvements in the present synthesis so noted, the basic features of the synthesis provided by Prof. K.-H.Yih's original work *still stand*—a well-deserved tribute to his synthetic skills and chemical intuition which allowed him to discover the main features of the original synthesis when all prior

researchers had failed to attain yields better than 1%. Noteworthy is that those preferred features include working in a closed Schlenk system, either superb intuition or a bit of luck at the time!

- The 4 conceptual steps that were used successfully to find and disentangle the contributing problems in the prior synthesis are: (i) to try to repeat the synthesis with multiple researchers ≥ 3 times, (ii) to use a sound scientific method by listing all reasonable multiple alternative hypotheses as to the possible causes for the irreproducibility; (iii) to examine the “paper mechanism(s)” of the reaction in order to highlight any additional hypotheses that could affect the reaction, and finally and importantly, (iv) to check the final experimental procedure via an independent researcher working from only the written procedure as outside researchers would (only) have. One can argue that an even better approach would be to: (i) start with (as listed above) step (iii), then step (ii), then steps (i) and, then once the problems were found and overcome, to perform step (iv).

- The mechanistic analysis which yielded the key, previously non-obvious hypothesis of “a close system is needed” leads to an important corollary: that mechanistic analysis should have been performed long ago, before *any* experiments were attempted in, even, the original synthesis. All other syntheses where any reasonable background of mechanistic knowledge is available, researchers should try to write a detailed mechanism upfront, a point well known to organic chemists for example, and their predilection to “arrow push” all their reactions. The value of up-front mechanistic analyses so noted, the current, proposed / working electron-transfer mechanism in the right half of Scheme 2 remains just a working hypothesis consistent with the available evidence, including the independent detection of the predicted gaseous H_2 . Additional experimental scrutiny and disproof of all reasonable alternative mechanisms remains to be accomplished to put the proposed mechanism in Scheme 2 on firmer ground.²

² A H/D (i.e., LiBEt_3H vs LiBEt_3D) kinetic isotope effect is, for instance, one experiment that could help distinguish the two mechanisms shown back in Scheme 2. However, that potentially powerful mechanistic experiment will require development of a method to follow the kinetics of the reaction.

- A more detailed, 100% accurate reporting of what was actually done in the original synthesis¹ may well have avoided the irreproducibility problem, but would not have yielded the refined, improved synthesis reported herein. That said, it is unlikely that all but the most experienced, skilled, and insightful researchers would have recognized the need to specifically draw attention to the closed Schlenk reaction flask. It is for this reason that experimental details should be provided in as much detail as possible, even when techniques are standard and well known. If it had simply been reported that the original synthesis was performed in a closed system, then the synthesis would likely have worked in others’ hands, at least for those that strictly followed the written synthesis. That said, having the present, hard-won *insight of the need for a closed system is likely of much broader significance to analogous, metal-reduction syntheses involving LiBEt_3H and probably at least some other anionic hydrides.*

- In addition, the significance of taking time and expending the money and effort *to check any new synthesis independently prior to publication cannot be overemphasized.* If we had done so with our original synthesis (our seemingly simple, seemingly straightforward, seemingly-did-not-need-checking synthesis), then we would have at least taken advantage of our best chance to catch some of the missing, key experimental details in that original, written procedure. A corollary here is that adding additional information that can enhance the written procedure, such as photographs or videos placed in the Supporting Information, is another useful tool en route to reproducible syntheses.³ Indeed, it was a photograph of a reaction flask taken by Prof. Yih (Figure S2 of the Supporting Information) which, when carefully re-examined in light of the mechanism written in Scheme 2 and the experimental data showing the need for a closed system, which confirmed that the original synthesis had in fact been performed in a sealed flask without a bubbler.

³ A referee added that, from an engineering and catalysis perspective, one should think about the fact that “syntheses take place in reactors; it is not just about the reaction, it is also about the reactor. Consult people who understand reactor analysis and engineering--think about mixing, mass transfer, and heat transfer. If there is a catalyst involved, think about the possible catalyst deactivation.”

Finally, this experience has been humbling, but educational. We have taken time to share the story of that education with the synthetic community, since fully reproducible syntheses continue to be a significant issue in apparently *at least* $\geq 12\%$ (and probably more like ≥ 15 if not 20%)⁴ [5,6] of all the new syntheses being reported across all of the chemical sciences if one reflects upon the available data⁴ [5,6,20,21]. In this regard, the recent *Nature Chemistry* article titled “Reproducibility”, and which addresses “the perennial problem of reproducibility” in reactions and synthesis, is recommended reading—note the “10 commandments” given therein [20]. Finally, the series of Editorials and Comments or Perspectives in the journal *Nature*, regarding the issue of irreproducibility in studies of complex biological systems, is related, recommended reading [22].

Experimental

We have placed the full experimental details of each individual synthesis performed in this work in the Supporting Information. Additionally, to avoid any miscommunications or accidental omissions or additions, the previously published experimental details are provided there *word for word*, except where we have determined that changes are necessary based on the experiments herein, or additional relevant details have been added. Those changes or additions are, as we have done before [4], underlined in the Supporting Information in order to easily distinguish them from what was published previously in our original synthesis [1].

Materials

All compounds were ACS reagent grade and were used as received except where noted. LiBEt₃H solution (1.0 M in THF Aldrich, 99.8%) and (1,5-

COD) (Aldrich) were used as received and stored in a 5 °C refrigerator. [Ir(1,5-COD)Cl]₂ (99%, Strem) was stored double bottled in a nitrogen-filled Vacuum Atmospheres drybox. Argon (99.9% Airgas) was passed over an activated O₂ scavenging copper catalyst and new 3 A molecular sieves (that were activated by heating under vacuum before use as detailed below). THF (99.9%, HPLC grade, anhydrous) was refluxed in a nitrogen atmosphere over sodium metal and benzophenone for >72 hours until it had turned dark blue or purple. The THF was then distilled and ~150 mL were transferred under nitrogen to a 200 mL Schlenk flask sealed with a rubber stopper and for noted reactions, containing ~30 g of 3A molecular sieves activated by heating in a vacuum oven at 200 °C under a vacuum of 635 torr for 2 days followed by cooling under an inert gas (N₂ or Ar). Before use of THF, it was connected to a Schlenk line and a needle was used to bubble argon through the solution for 5-10 minutes to fully remove any O₂ which had diffused through the stopper. THF was re-purified at least weekly to limit contamination or degradation. Acetone (Burdick & Jackson <0.4% H₂O) was degassed by bubbling with argon in a sealed round-bottomed flask for 20 minutes before use. Distilled water (18 MΩ from a nanopure filtration system) was degassed by bubbling with argon in a sealed round-bottomed flask for 30 minutes before use.

Instrumentation and Glassware

All manipulations were performed either under N₂ in a Vacuum Atmospheres drybox (≤ 2 ppm O₂ as monitored by a Vacuum Atmospheres O₂-level monitor) or, where noted, using a Schlenk line. All glassware was dried overnight in an oven at 160 °C, cooled under vacuum of the drybox ante chamber as they were transferred into the drybox. Air-free procedures were performed with Schlenk line techniques on an argon flushed line with, again, glassware stored overnight in a 160 °C oven and cooled under dried argon or nitrogen. A Vacuum Atmospheres drybox was used to prepare [Ir(1,5-COD)Cl]₂ samples in the Schlenk flask, and to prepare product samples for NMR characterization. Nuclear magnetic resonance spectra were obtained in 5.0-mm-o.d. NMR tubes using C₆D₆, prepared in the drybox and capped with rubber airtight stoppers. ¹H and ¹³C NMR spectra were recorded on Varian Inova 400 MHz spectrometer at 21 °C under N₂ with the NMR tubes sealed by a rubber septum. Gas-liquid

⁴ A November 2014 SciFinder search of “irreproducible syntheses” yielded only 53 hits, a number that has to be orders of magnitude less than 12% times the number of new syntheses reported in the SciFinder data bank. While this single, simple search likely finds only a fraction of the papers that deal in some way with an irreproducible synthesis, it is still very likely true in our opinion that the following are receiving much less attention and effort than they fundamentally deserve: (i) the (under) reporting of irreproducible syntheses; (ii) efforts to ensure reproducible syntheses (such as independent checking of one’s synthesis prior to submitting it for publication); and (iii) efforts to clean up, improve and render reproducible

chromatography (GLC) for the determination of cyclohexane and cyclohexene was performed using a HewlettPackard 5890 Series II chromatograph, equipped with a flame ionization detector and a Supelco SPB-1 (Aldrich, 30 m $\times$ 0.25 mm $\times$ 0.25 μ m) fused silica column. The GLC parameters were as follows: initial oven temperature, 50 $^{\circ}$ C; initial time, 3.0 min; rate, 10 $^{\circ}$ C/min; final temperature, 160 $^{\circ}$ C; injector temperature, 180 $^{\circ}$ C; detector temperature, 200 $^{\circ}$ C; injection volume, 2 μ L.

Trial #19: The Preferred and Checked Synthesis of [Ir(1,5-COD)(μ -H)]₄ at 2 mmol Scale in A Closed Flask at 0 $^{\circ}$ C

In the drybox, the orange powdered [Ir(1,5-COD)(μ -Cl)]₂ (1.3434 g, 4.0 mmol in Ir) was weighed out in a 2 dram vial and then transferred into a 100 mL round-bottomed Schlenk flask equipped with a side arm and a $\frac{5}{8} \times \frac{5}{16}$ in. Teflon-coated magnetic stirbar. The flask was sealed with a rubber sleeve type septum stopper, removed from the drybox, and placed on a Schlenk line under Ar via its side arm. Next, 30 mL of room temperature THF which had been distilled and then stored over molecular sieves for >72 hours was added to the flask using a cannula, forming an orange solution with some undissolved orange powder and stirred for ca. 10 minutes while the solid dissolved. The flask containing the orange solution of [Ir(1,5-COD)(μ -Cl)]₂ was then sealed under Ar atmosphere; *again, no bubbler was used*. The flask was then placed in an ice bath at 0 $^{\circ}$ C and stirred for 15 min. A 5 mL gastight syringe was purged three times with Ar using the Schlenk line and then used to measure out 4.0 mL (4.0 mmol) of LiBEt₃H. LiBEt₃H was then added dropwise to the orange [Ir(1,5-COD)(μ -Cl)]₂ solution at a rate of 1 drop per second under Ar atmosphere with vigorous stirring. The original orange color of the solution changed to nearly black and then green upon the dropwise addition of LiBEt₃H. The resulting solution was stirred at 0 $^{\circ}$ C for an additional 5 min. Then, without warming, 1,5-COD (12.3 mL, 25 equiv per Ir) was measured out with a 10 mL gastight syringe purged with Ar and then added to the solution at a rate of 2-3 drops per second. After the addition of 1,5-COD over ca. 8-9 minutes, the solution was opened to vacuum to remove THF while still in the ice bath. After 10 minutes, the flask was removed from the ice bath to facilitate solvent removal. The solution was concentrated to ~10 mL under vacuum at room

temperature using the Schlenk line, while the solution turned black, and produced a visually apparent black powder. After addition of 30 mL acetone to the solution, the black powder was separated from the remaining brown solution under Ar using a Schlenk-ware fine-porosity glass frit of ca. 8 μ m pore size. The open end of the Schlenk glass frit was sealed by a rubber septum. The black powder collected on top of the glass frit was washed with degassed H₂O (10 mL $\times$ 2) and then degassed acetone (10 mL $\times$ 3) using a gastight syringe that was previously purged with Ar. The black powder was then dried overnight under vacuum at room temperature, resulting in a black powder (0.959 g, 80% yield) which was transported to the drybox for preparation for ¹H NMR analysis. That ¹H NMR showed a spectrum similar to the material produced in 2012 by the original synthesis, see Figure S3 C which shows the NMR spectra from this trial. The color of the solution dissolved in C₆D₆ was green and clear, with no apparent precipitate in the bottom of the NMR tube after sitting for 2 days.

Trial 20: Testing the Reproducibility of the Synthesis Using Only the Written Procedure.

One of us (SF) with no prior Schlenk synthesis experience repeated the synthesis using only the written procedure. First, the necessary Schlenk technique for the reaction procedure was practiced in a “mock” reaction involving all the steps of the synthesis using a fresh sample of 35 mL THF plus 2 mmol benzophenone ketyl solution prepared as described in trial #6 in the Supporting Information. The deep-blue color of the benzophenone ketyl solution was maintained throughout this mock trial.

The reaction as written in Trial 19 was then repeated exactly, with the one exception that a medium porosity frit was used to separate the black powder from the solution during the workup as a result of a typo in the draft of the experimental procedure at the time—a good example of how checking the procedure by an independent researcher using only the written procedure is able to catch such errors. The synthesis was successfully reproduced, albeit in this first attempt with a yield of 54%, possibly lower than our best 80% yield due to the use of the medium porosity frit, and / or possibly since this was the researcher’s first Schlenk-ware based syntheses. However, 2 mg of the product dissolved in C₆D₆ resulted in the expected ¹H NMR spectra, and no visible precipitate settled to the

bottom of the NMR tube over 2 days, demonstrating the purity of product.

Independent Evidence for the Production of Gaseous H₂. In the drybox, orange powdered [Ir(1,5-COD)(μ-Cl)]₂ (0.672 g, 2.0 mmol in Ir) was weighed out into a 50 mL round-bottomed flask into which was also placed a 1 × ⁵/₁₆ in. Teflon-coated magnetic stirbar. A ⁵/₈ × ⁵/₁₆ in. Teflon-coated magnetic stirbar was placed into a 2 dram vial along with 2.5 mL of propylene carbonate solvent, 2 mmol of cyclohexene and 7.2 μmol of Ir(0) nanoparticles prepared according to a literature procedure [23], those particular Ir(0) nanoparticles being picked because they are a convenient preparation of an active hydrogenation catalyst. The 2 dram vial was then carefully lowered into a 50 mL round-bottomed flask. This simple apparatus, consisting of a 2-dram vial (containing the hydrogenation catalysis solution) coaxially placed inside the 50 mL round-bottomed reaction flask, was then sealed with a rubber-septum stopper that fit into the 50 mL round-bottomed flask. That stoppered 50 mL flask was removed from the drybox, and placed on a magnetic stirrer.

Next, 20 mL THF was added to the 50 mL round-bottomed flask using a cannula (so that 30 mL of gaseous headspace resulted); that is, the THF was added very careful to ensure that all the THF wound up *outside* of the 2-dram vial, and (instead) into the 50 mL round-bottomed flask. An orange solution formed while stirring for ca. 10 minutes at room temperature. A 5 mL gastight syringe was purged three times with Ar using the Schlenk line and then used to measure out 2.0 mL (2.0 mmol) of LiBEt₃H. Post cooling to at 0 °C in an ice bath, the LiBEt₃H was then added dropwise to the orange [Ir(1,5-COD)(μ-Cl)]₂ solution (i.e., and while avoiding adding any of that solution to the 2 dram vial) at a rate of 1 drop per second under Ar the atmosphere with good stirring, all still at 0 °C *and in the closed system* where the two separate reaction chambers were in gaseous contact with each other. The system was then warmed up to room temperature. Both solutions were stirred for 24 h at room temperature. An aliquot was taken from the catalyst solution for GC analysis using a 100 μL gas tight syringe. The ratio of the areas of the cyclohexane peak at 1.59 min to the cyclohexene peak at 1.69 min indicated a conversion of 11.5% of the 2 mmol of cyclohexene to cyclohexane. Hence, 0.23 mmole (23%) of the possible total of 1.0 mmol H₂ had been captured in

the cyclohexene hydrogenation reaction to form 11.5% of cyclohexene.

Acknowledgements

We thank Prof. K-H. Yih for his assistance via multiple e-mail discussions that proved helpful in uncovering the improved synthesis reported herein. This work was supported by the Chemical Sciences, Geosciences, and Biosciences Division, Office of Basic Energy Sciences, Office of Science, U.S. Department of Energy (Grant DE-FG02-03ER15453).

Electronic Supporting Information available: representative NMR spectra, detailed experimental procedures, and a picture of the original syntheses in process, as well as a synthetic diagram provided by Prof. K-H. Yih during his original synthesis.

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