

Rational Design of a Catalyst for the Selective Monoborylation of Methane

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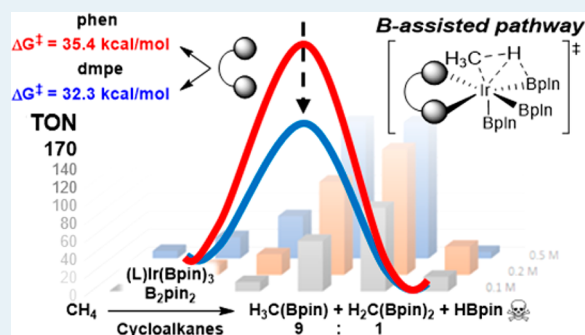
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Supporting Information

ABSTRACT: Combined computational and experimental studies elucidate the mechanism and suggest rational design and optimization strategies of a bis(phosphine)-supported iridium-catalyst for methane monoborylation. The activation of the C–H bond in methane via oxidative addition using tris(boryl) iridium(III) complexes bearing bis-chelating supporting ligands is modeled computationally. This model shows that the use of the soft Lewis base ligand such as 1,2-bis(dimethylphosphino)ethane (dmpe) lowers the activation barrier of the rate-determining step as it facilitates polarization of the metal-center, lowering the barrier of the oxidative addition to afford a seven-coordinate iridium(V) intermediate. The experimental optimization of this reaction using high-throughput methods shows that up to 170 turnovers can be achieved at 150 °C (500 psi) within 16 h using bis(pinacolato)diboron, a well-defined homogeneous and monomeric catalyst (dmpe)Ir(COD)Cl that is readily available from commercial precursors, with selectivity for the monoborylation product. High-boiling cyclic aliphatic solvents decalin and cyclooctane also prove suitable for this reaction, while being inert toward borylation. In accordance with the lower calculated activation barrier, catalytic turnover is also observed at 120 °C with up to 50 turnovers over the course of 4 days in cyclohexane solvent. It was found that the borylation of methane is only achieved via one catalytic cycle, and buildup of pinacolborane, a side-product from methane borylation with bis(pinacolato)diboron, inhibits catalytic activity.

KEYWORDS: homogeneous catalysis, borylation, methane activation, mechanism, oxidative addition, computational molecular modeling



INTRODUCTION

Methane is the simplest of all hydrocarbons, and it accounts for nearly 70–90% of the natural gas feedstocks worldwide. The sustainable catalytic functionalization of methane at a large scale with high selectivity (e.g., without overoxidation or burning) is considered one of the greatest challenges in chemical research. Many C–H functionalization methods for hydrocarbons have been developed in the past,^{1–7} with transition-metal catalyzed reactions being most useful.^{8–16} Methane continues to be a challenge, due to its kinetic inertness but also the thermodynamic stability of its C–H bonds.^{17–23} With the C–H bond dissociation energy being nearly 103 kcal/mol,^{24,25} harsh conditions such as strong oxidants, superacidic media, or high temperatures are required to activate methane. We turned our attention to the transition-metal mediated borylation of hydrocarbons,^{26–29} which has seen remarkable progress recently. A large body of work including pioneering contributions by Hartwig,^{30–37} Marder,^{38–41} and Smith^{42–47} established the borylation of C–H bonds as a robust and useful tool in organic chemistry. While

the borylation of methane with diborane reagents is generally close to thermoneutral and hence should be suitable for catalytic processes, efficient catalysts for this reaction remained scarce.

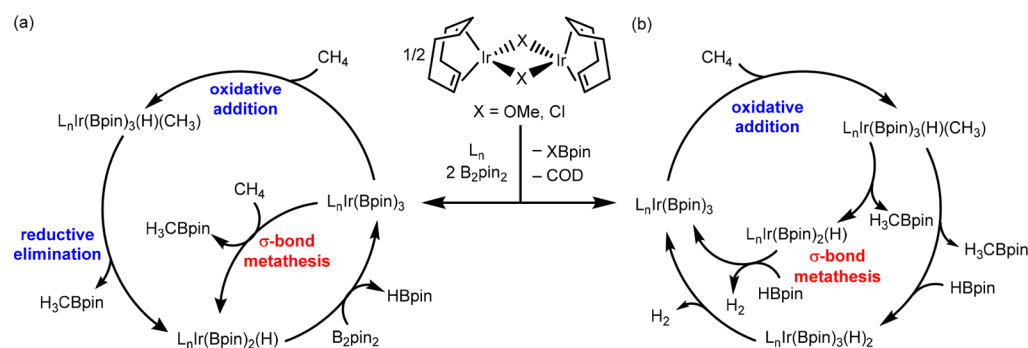
Motivated by the efficiency of Ir-complexes for activating alkylic (aliphatic) C–H bonds, we questioned if an Ir-based methane borylation catalyst could be designed rationally by combining insights from theoretical and experimental studies following the general mechanism outlined in Scheme 1a. Indeed, we were able to show recently that methane borylation could be performed with a yield as high as 52% and the turnover number (TON) being a respectable ~100.⁴⁸ Notably, we showed that the use of the 1,2-bis(dimethylphosphino)ethane (dmpe) ligand led to a significant increase in catalytic efficiency compared to various diimine-supported catalysts, which are commonly used in C–H borylation. In this study,

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Scheme 1. Proposed Pathways^a to the Monoborylation of Methane via the Use of an Iridium Precatalyst, dmpe (L_n), and with (a) B_2pin_2 and (b) HBpin



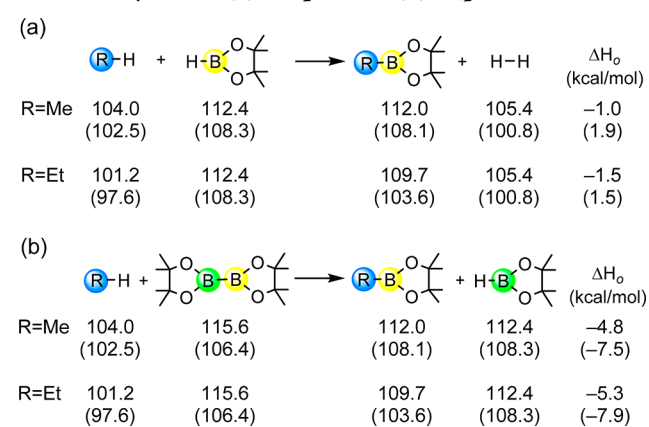
^aOther possible permutations such as the oxidative addition of HBpin to the iridium precatalyst are not shown for the purpose of clarity.

we disclose the mechanistic rationale for the design of a chelating phosphine-based catalyst. We elaborate on the role of the diboron reagent (bis(pinacolato)diboron, B_2pin_2), which not only is a coupling partner, but also serves as a cocatalyst assisting the C–H bond cleavage. In addition, experimental optimization using a well-defined mononuclear catalyst precursor shows that TONs of up to 170 can be achieved with catalyst loading as low as 0.1 mol %, and with monoborylation being at least 9 times preferred over diborylation. Catalytic turnover observed at 120 °C further supports the lower activation barrier enabled by the bis-(phosphine) ligand, as predicted by the calculations. High-throughput techniques employing solvents with high boiling points namely decalin and cyclooctane further add to the observation previously made for cyclohexane in that cyclic alkanes remain inert toward borylation. Finally, we found that the side-product pinacolborane (HBpin) can poison the catalyst and does not participate in a separate borylation cycle, as shown in Scheme 1b, that generally is proposed to occur in tandem with the bis(pinacolato)diboron cycle shown in Scheme 1a.

RESULTS AND DISCUSSION

An important choice to make when designing a catalytic borylation reaction is which borylation reagent to employ. We considered several possibilities and evaluated the reaction enthalpies of potential candidates computationally. Of particular interest were pinacolborane (HBpin) and bis-(pinacolato)diboron (B_2pin_2) and their putative reactions with ethane and methane, which were modeled at the G-3 level of theory.^{49–51} Whereas density-functional-theory-based (DFT-based) methods are most efficient computationally and are used for the mechanistic portion of this study, they are not reliable for evaluating bond energies of small molecules at high levels of accuracy. G-3 calculations offer much more trustworthy energies, albeit at orders of magnitude higher computational cost, but are considered state of the art for bond dissociation energies and driving forces of chemical reactions.^{52–56} The details of these high-level calculations are given in the Supporting Information, and the most salient results are summarized in Scheme 2. Unsurprisingly, the C–H bond dissociation energies (BDEs) of methane and ethane are calculated to be 104.0 and 101.2 kcal/mol, respectively, in good agreement with widely accepted values.⁵⁷ The BDE of the B–H bond of pinacolborane is estimated to be 112.4 kcal/mol, whereas the Me–B bond is computed to be 112.0 kcal/

Scheme 2. Bond Dissociation Enthalpy^a of Methane and Ethane Borylation: (a) HBpin and (b) B_2pin_2



^aThe values in parentheses were obtained using M06/B2//M06/B1.

mol, leading to an enthalpic driving force of -1.0 kcal/mol for the borylation of methane. The DFT-based energies are given in parentheses. In general, the bond strengths are underestimated by 1–4 kcal/mol, and error cancellation leads to a predicted driving force of $+1.9$ kcal/mol. Similar trends are seen for the putative reaction with ethane, where the G-3 theory predicts a driving force of -1.5 kcal/mol compared to a DFT-calculated value of $+1.5$ kcal/mol. Thus, we may conclude that pinacolborane is a potentially useful reaction partner, when designing a catalytic cycle, since it renders the desired reaction nearly thermoneutral, which is advantageous for catalyst recovery and cyclability of a reaction. A potential disadvantage is that the reaction affords hydrogen gas, which may pose some kinetic challenges and also may be an inconvenient side-product for the implementation of the reaction into a catalytic system since it could result in formation of polyhydrides.

The diboron reagent B_2pin_2 is a promising reagent. As summarized in Scheme 2b, the borylations of methane and ethane become enthalpically more favorable, -4.8 and -5.3 kcal/mol, respectively. The calculated BDEs show that although the B–B bond is worth 115.6 kcal/mol and is quite comparable in strength with the B–H bond in pinacolborane (112.4 kcal/mol), the thermodynamic driving force of the borylation reaction can be increased by ~ 4 kcal/mol by utilizing the hydrogen atom from the C–H activation to form an equivalent of pinacolborane instead of hydrogen gas, which

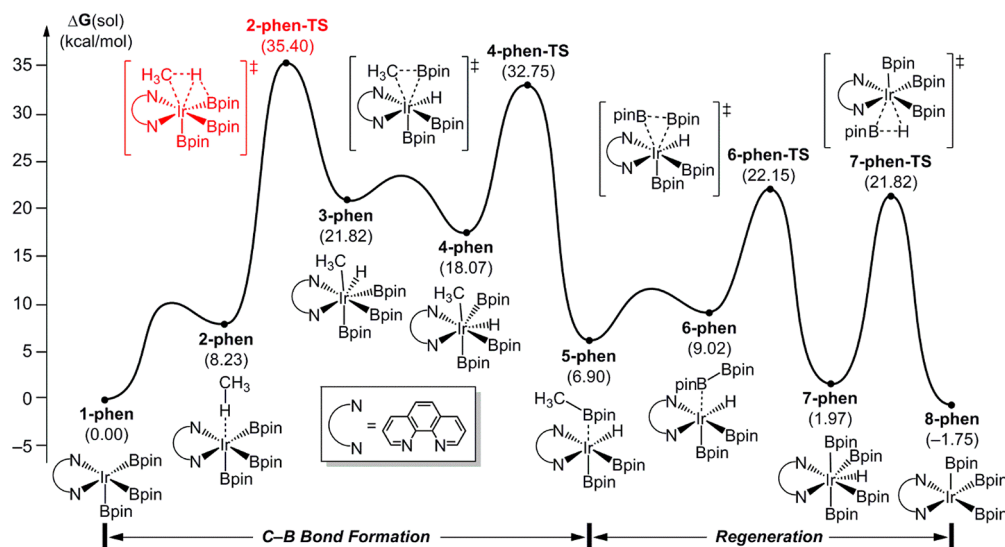


Figure 1. Reaction profile (M06/B2//M06/B1) of methane activation catalyzed by **1-phen** which is simplified with the N-based chelate caricature.

has a BDE of only 105.4 kcal/mol. DFT calculations again underestimate the bond strengths notably, and the B–B bond of diborane is computed to have an energy of 106.4 kcal/mol, which is ~ 9 kcal/mol lower than what is obtained by G-3 calculations. As seen before, error cancellation gives driving forces of -7.5 and -7.9 kcal/mol that compare very well to the -4.8 and -5.3 kcal/mol obtained by the G-3 calculations. These calculated energies highlight the widely acknowledged fact that DFT calculations are very useful, but should not be thought of being truly accurate methods. Whereas the somewhat large deviation from the much more trustworthy G-3 calculations may seem discouraging, it must be emphasized that the computational cost of the DFT calculations is extremely low compared to that of the G-3 calculations,⁵⁸ and it is technically impossible to construct the full reaction energy profile discussed below with G-3 methods. Whereas the absolute energies obtained with DFT calculations show significant errors when compared to the G-3 values, the chemically meaningful trends are consistently reproduced.

Methane Activation by 1-phen. With the computed energies for the overall reaction in hand, the next step is to identify a catalyst that can lower the barriers of the methane activation reaction enough to make the process feasible under realistic conditions. A widely used catalyst that has received much attention^{34–37,44,45} is the Ir-complex (phen)Ir(Bpin)₃ (**1-phen**) bearing polypyridyl groups such as 1,10-phenanthroline (phen) and three pinacolboranyl ligands, as shown in Figure 1. This catalyst is highly efficient for the catalytic borylation of alkylic and aryl (aromatic) C–H bonds,^{34–37,44,45} but has not been known to borylate methane until very recently by us⁴⁸ and Sanford.⁵⁹ Given that aryl C–H bonds are generally much stronger than alkylic C–H bonds, including those in methane, it is fundamentally not clear why **1-phen** cannot engage in methane borylation. To better understand how methane may interact with **1-phen**, we constructed the reaction energy profile of a putative catalytic borylation of methane employing **1-phen**, as shown in Figure 1.

As depicted in Figure 1, the overall catalytic cycle can be divided into two parts. The earlier phase of the cycle consists of C–H activation followed by methylborane formation (H₃CBpin). The second phase of the cycle regenerates the iridium-catalyst through a sequence of reactions that consumes

an equivalent of diborane and releases pinacolborane HBpin. The catalytic cycle starts with methane approaching the active state of the catalyst, **1-phen**, which consists of an Ir(III)-*d*⁶-center offering an open coordination site to the substrate. In the reactant complex (phen)Ir(Bpin)₃(H–CH₃) (**2-phen**), the Ir–H–CH₃ fragment adopts a linear arrangement. Next, the methane substrate rearranges into a side-on geometry to traverse the transition state **2-phen-TS**, in which the C–H bond is then broken. We located this transition state for oxidative addition at 35.4 kcal/mol. Therefore, the immediate product of this key step is the intermediate (phen)Ir(Bpin)₃(H)(CH₃) (**3-phen**) at 21.8 kcal/mol, formally an Ir(V)-methyl hydride-complex. Remarkably, this intermediate is a rare example of a seven-coordinate Ir-complex.^{60–65} To release the H₃CBpin product, the carbon–boron bond must be formed likely in a reductive elimination step, which requires the migration of one Bpin ligand. The migratory mobility of the boryl group may be increased by a structural rearrangement leading to an isomeric form of **3-phen**, **4-phen**. Here, one of the three boryl ligands and the hydride share one coordination site *trans* to the pyridyl-moiety. As a result, reductive elimination from this intermediate is much easier and is associated with a barrier of only 14.7 kcal/mol via **4-phen-TS**.⁶⁶

The second phase of the catalytic cycle begins with (phen)Ir(Bpin)₂(H)(H₃CBpin) (**5-phen**) as a result of C–B bond formation. Addition of an equivalent of diborane B₂pin₂ yields (phen)Ir(Bpin)₂(H)(B₂pin₂) (**6-phen**) along with H₃CBpin, and is followed by oxidative addition involving the B–B bond to form intermediate (phen)Ir(Bpin)₄(H) (**7-phen**), which then undergoes reductive elimination of HBpin involving one of the boryl ligands and the hydride originally derived from methane. Release of the hydroborane byproduct HBpin regenerates the active state of the Ir-catalyst and completes the catalytic cycle. The oxidative addition of B₂pin₂ is associated with a step barrier of 13.1 kcal/mol, whereas the reductive elimination requires 19.9 kcal/mol. Thus, these barriers are lower than that of the C–H cleavage step, which is proposed to be rate-limiting. This conclusion is in good agreement with previous work on alkyl-borylation reactions.^{67–72}

Whereas this mechanism is reasonable, there are plausible alternatives to consider, such as σ -bond metathesis of the hydrocarbon. Our calculations indicate that the σ -bond metathesis pathway is associated with much higher barriers of ~ 58 kcal/mol and is therefore unlikely to be operative. Variations on the structural features of the transition state of the oxidative addition process may be important. In particular, it is not clear whether or not the assistance of the equatorial boryl ligand that leads to the four-membered ring structure in the transition state **2-phen-TS** is required. After some exploration, we concluded that the aforementioned mechanism is the lowest-energy pathway to product. Some of the alternative mechanisms that we considered are described in the [Supporting Information](#).

Experimental Confirmation. The high activation barrier of 35.4 kcal/mol indicates that the reaction should be slow and inefficient even under harsh conditions, but may give products in small amounts under forcing conditions. This insight is helpful, as it answers an important design question, namely, whether or not methane is special in the sense that it requires an entirely different catalyst design or it is simply a substrate presenting a C–H bond that is particularly strong. Our calculations suggest that **1-phen** should be able to break the C–H bond in methane, although it may not be very efficient doing so. Thus, methane is not a special substrate in this context. Interestingly, our experiments demonstrated that these predictions are correct, and we were able to detect trace amounts of monoborylated methane H_3CBpin product in the low single-digit percentage yields.⁴⁸

In conclusion, our calculations suggest that the Ir-catalyst carrying the 1,10-phenanthroline ligand should be able to borylate methane, but the high barrier of 35.4 kcal/mol indicates that the reaction should be inefficient and low-yielding even at elevated temperatures, which is in good agreement with the experimental observations.

Catalyst Design. The high barrier for the oxidative addition step (**2-phen-TS**, 35.4 kcal/mol) that is identified as the bottleneck of the reaction can be analyzed with the aim of identifying potential functionalization strategies that lower the barrier and enable a more efficient catalysis. After some trial-and-error attempts, we concluded that the most plausible and useful way of analyzing the transition-state energy is dividing it into several component energies, as the reactant complex changes structure to reach the transition state: (i) First, the C–H bond of methane is broken to a significant extent, indicated by its elongation from 1.10 to 1.65 Å in the transition state, as illustrated in [Figure 2](#). This process is energetically uphill and is of course mainly responsible for the barrier. (ii) Two new bonds, Ir–CH₃ and Ir–H, are partially formed at bond lengths of 2.26 and 1.61 Å, respectively, which recover some energy and lower the transition-state energy. (iii) Our calculations suggest that the C–H bond is broken heterolytically where formally a methyl-cation and a hydride-anion are formed. The hydride can form an Ir–H bond by acting as a Lewis base interacting with the Lewis-acidic Ir-center. However, the Ir–CH₃ bond formation requires that two electrons that were initially localized on a metal d-orbital must be moved to the ligand formally, constituting the oxidative component of the oxidative addition reaction. As this process can be viewed as partial oxidation of the Ir(III) toward an Ir(V)-center, it will increase the transition-state energy. (iv) The hydride is transiently stabilized by the boryl ligand, which acts as a prototypical Lewis acid and helps to lower the barrier.

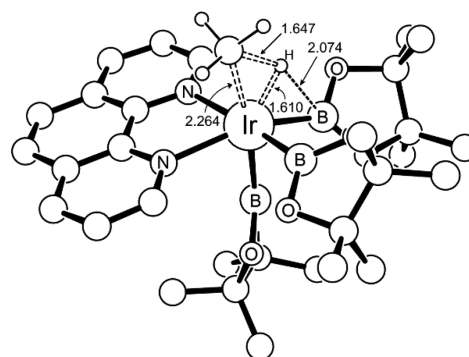


Figure 2. Computed structure of the transition state **2-phen-TS**. Nonessential hydrogen atoms are not shown. All distances are given in Å.

This conceptual analysis is helpful, as it allows for deriving strategies for modulating these component energies, for example, by changing the molecular composition of the catalyst. Among the many possibilities, we hypothesized that the partial oxidation required for forming the Ir–CH₃ bond is a feature that can be exploited. If the partial oxidation could be made easier, that is, the Ir-center turned into a softer Lewis base that offers a more polarizable metal-center, then the transition-state energy may be lowered. In short, to make the oxidative addition step more effective, the Ir-center should be made more polarizable. The relatively hard Lewis-basic character of the Ir-center is of course a direct outcome of the relatively hard N-donor ligands. Therefore, a plausible hypothesis is to replace the phenanthroline ligand by a more polarizable donor ligand, such as a phosphine. To investigate this proposal, we considered 1,2-bis(dimethylphosphino)ethane (dmpe), a chelating ligand providing a much softer Lewis-basic phosphorus instead of pyridyl-nitrogens, to afford the hypothetical catalyst (dmpe)Ir(Bpin)₃ (**1-dmpe**).

Methane Activation by 1-dmpe. The calculated energy profile of the methane activation catalyzed by **1-dmpe** is shown in [Figure 3](#). Overall, the catalytic cycle compares well to that found for the catalyst **1-phen** and commences with methane approaching the catalyst **1-dmpe** to give the adduct (dmpe)Ir(Bpin)₃(H–CH₃) (**2-dmpe**). The oxidative addition is attained through transition state **2-dmpe-TS**. Interestingly, this transition state is associated with a barrier of 32.3 kcal/mol, which is notably lower by 3.1 kcal/mol than what was found with the phenanthroline ligand (*vide supra*). The remainder of the catalytic cycle proceeds via the same trajectory as found for **1-phen** with slightly different energies. In summary, these calculations clearly suggested that replacing the N-donor ligands with P-donor ligands is a viable strategy for obtaining a more effective catalyst. If the computed energy difference of $\Delta\Delta G^\ddagger \sim 3$ kcal/mol is taken by face value, the phosphine-carrying Ir-catalyst should display a catalytic performance that is ~ 4 orders of magnitude faster and more efficient. Although reaction barriers computed in density functional calculations should be evaluated with some care, this decisive and chemically sensible difference was encouraging, and we decided to prepare and study the phosphine analogues of the iridium-catalyst. Additionally, we examined the isoelectronic system for Os, Ir, and Pt. Catalyst **1-dmpe** was the most promising among these metal systems, as summarized in [Figure S5](#).

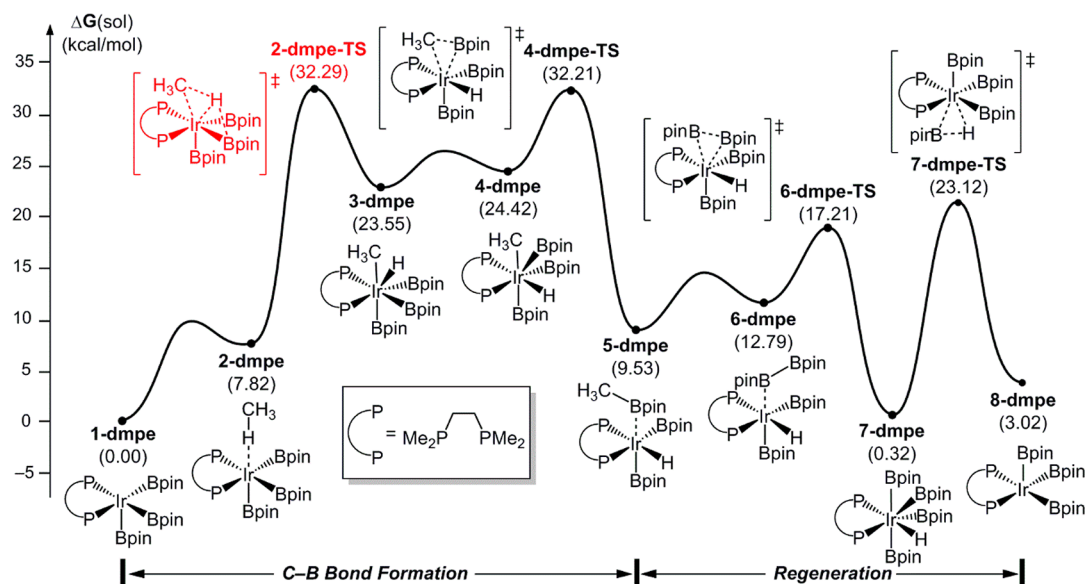


Figure 3. Calculated energy profile (M06/B2//M06/B1) catalyzed by 1-dmpe.

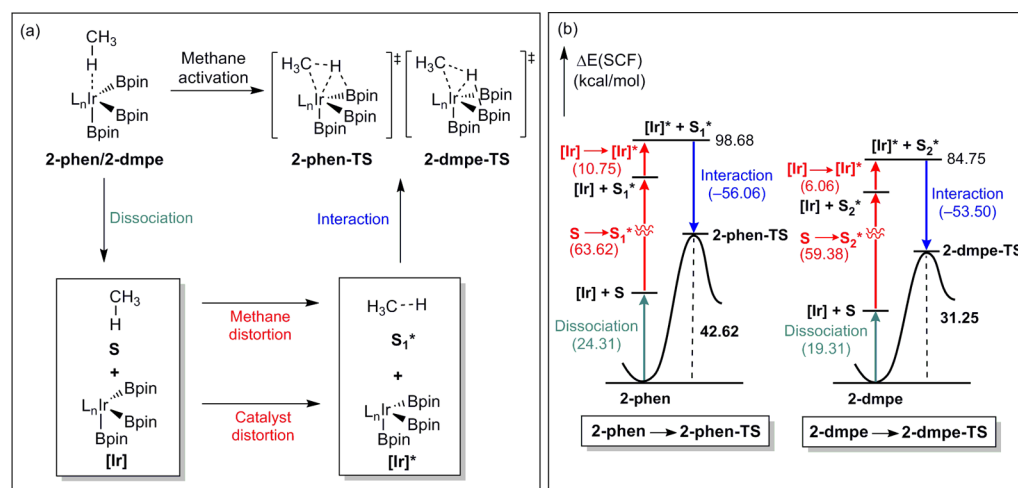


Figure 4. (a) Conceptual steps to form the transition state of oxidative addition of methane. (b) Electronic energy difference (M06/B2//M06/B1) for the interaction, and distortion steps.

To obtain a better understanding of the origin of the computed barrier difference at the C–H cleavage step and ensure that the computed barrier difference is chemically reasonable and not the result of a numerical artifact of the DFT calculation, we carried out an energy decomposition analysis⁷³ by dividing the transition states into methane and the catalyst fragments, as depicted in Figure 4. The electronic energy of the oxidative addition transition state **2-phen-TS** is 42.6 kcal/mol higher than that of **2-phen**, whereas 31.3 kcal/mol is found for **2-dmpe-TS** compared to **2-dmpe**. To understand this energy difference, we constructed a theoretical thermodynamic cycle, as illustrated in Figure 4a, where we formally dissociate the methane substrate from the reactant complex $(L_n)\text{Ir}(\text{Bpin})_3(\text{H}-\text{CH}_3)$, distort the structures of methane and the catalyst to what is found in the transition state, and assemble the transition state by letting the fragments interact with each other. This formal scheme allows for quantifying the energy components mentioned above, and the results are summarized in Figure 4b.

The methane dissociation energy was found to be 24.3 and 19.3 kcal/mol for **2-phen** and **2-dmpe**, respectively. To reach the structure that methane adopts in the transition state, an energy of 63.6 and 59.4 kcal/mol, respectively, must be invested. This energy is marked as $S \rightarrow S^*$ in Figure 4b. Of course, the distortion is mainly a C–H bond elongation. The structure of the catalyst remains nearly identical with the main change being slight distortions in the $L_n\text{--Ir--Bpin}$ ($L_n = \text{phen}$ or **dmpe**) angle associated with energies of 10.8 and 6.1 kcal/mol uphill, respectively, marked as $[\text{Ir}] \rightarrow [\text{Ir}]^*$ in Figure 4b. The sum of these three components is 98.7 and 84.8 kcal/mol, respectively, and indicates that **2-phen-TS** may be characterized as being a late transition state compared to **2-dmpe-TS** regarding the C–H bond breaking. The rationale is simple: As the Ir-center in **2-dmpe** is more polarizable, the carbocationic character at the methyl-moiety does not need to develop to the same extent as for the less polarizable **2-phen**-catalyst. This later transition state also forces a slightly higher degree of distortion on the catalyst side, requiring a greater amount of structural distortion energy. Overall, the energy that must be

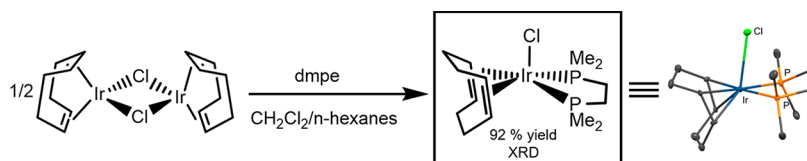


Figure 5. Left: Reaction to form the precatalyst (dmpe)Ir(COD)Cl. Right: Schematic representation and solid-state structure of (dmpe)Ir(COD)Cl with thermal ellipsoids at 50% probability, and hydrogen atoms omitted for clarity.

invested to formally dissociate the substrate and distort the fragments to what is found in the transition state amounts to 98.7 kcal/mol when the phen ligand is used. With the dmpe ligand, on the other hand, only 84.8 kcal/mol is required, as the transition state is earlier with respect to the C–H bond cleavage. Finally, the distorted fragments interact with each other, and 56.1 kcal/mol is recovered in when phen is employed as the ligand. When Ir carries the dmpe ligand, the fragment interaction energy is 53.5 kcal/mol. Thus, although the fragment interaction energy is ~ 2.5 kcal/mol more favorable in **2-phen-TS** than in **2-dmpe-TS**, it is not enough to compensate for the 13.9 kcal/mol excess energy that must be invested to transform **2-phen** to **2-phen-TS**. These electronic energies are very plausible and offer an easy to understand concept. The solvation energy reduces this energy difference to finally afford the solution phase free energy difference of ~ 3 kcal/mol.

Optimizations of the Catalytic Process. As reported previously, the experimentally determined performance of the dmpe-supported iridium-catalyst for methane borylation exceeds that of the phenanthroline-supported systems significantly in good agreement with our calculations.⁴⁸ In that study, we reported a borylation yield of 52% and turnover number of 104.⁴⁸ In a parallel study, Sanford et al.⁵⁹ reported turnover numbers of up to 68, and yields of up to 99% using various concentrations of a rhodium(I) precursor, as well as a TON of 22, corresponding to a 67% yield using a ruthenium(III) precursor. Notably, they also employed a phenanthroline/tris(boryl)-catalyst akin to the systems described in our study, reaching a TON of 15 and corresponding yield of 45%. In order to test the limitations of our system, high-throughput and high-pressure screening techniques were employed, as described in detail in the [Supporting Information](#). The experimental optimization aimed at three main issues: (i) identification of a well-defined precatalyst for clean production of the active tris(pinacolborate)(dmpe)iridium(III) catalyst, (ii) exploring alternative solvents with higher boiling points to allow high-temperature conditions, and (iii) screening of how substrate, side-products, and catalyst concentrations impact the catalytic activity.

Refining our previously reported procedure for catalyst preparation, we found that the reaction of dmpe in hexanes with a dichloromethane solution of the iridium(I) dimer $[(\text{COD})\text{Ir}(\mu\text{-Cl})]_2$ (COD = 1,5-cyclooctadiene) yields the monomer (dmpe)Ir(COD)Cl in nearly quantitative yield based on NMR spectroscopy. Slow vapor diffusion of hexane or pentane into a concentrated dichloromethane solution of the monomer yielded yellow single crystals of (dmpe)Ir(COD)Cl. Although a solid-state structural motif for this complex has been previously reported, details regarding the structure, and preparation of this complex, are lackluster.^{74,75} This complex has previously been reported for C–H activation of acetonitrile and H_2 , but its documentation is otherwise unexplored.^{74,75} Thus, we characterized (dmpe)Ir(COD)Cl by

single-crystal X-ray diffraction studies, which revealed a distorted square-pyramidal coordination geometry with the COD and dmpe ligands bound to the basal positions and the chloride ligand occupying the axial position, as illustrated in [Figure 5](#). Despite a mirror plane seemingly cutting the structure in two symmetric halves (space group $P2_1/m$), disorder reveals that the complex in fact adopts two alternate C_1 symmetric conformations where the COD and dmpe ligands are twisted relative to each other, accompanied by a tilt of the chloride ligand to two positions close to the pseudomirror plane. The iridium-center is located within the plane defined by the phosphorus and two carbon donor atoms, and the bite angles of the two chelating ligands are 83.1° for dmpe, and 85.9° for COD, respectively. P–Ir (2.293–2.321 Å), C–Ir (2.133–2.205 Å), and Ir–Cl (2.565 Å) are within the usual range for bis(phosphine)-complexes of iridium(I) having both COD and chloride-complexes.^{76,77}

The room temperature NMR spectrum of (dmpe)Ir(COD)Cl is consistent with a C_{2v} symmetric system in contrast to the C_s symmetry observed in the solid state, which is indicative of rapid interconversion of the ligands via a Berry-type pseudorotation.⁷⁸ The $^{31}\text{P}\{^1\text{H}\}$ -NMR spectrum shows a sharp singlet with a chemical shift of 14.6 ppm. Regarding the proposed resting state (dmpe)Ir(Bpin)₃, Smith et al.⁷⁹ reported previously that a variety of tris(boryl)-complexes with chelating bis(phosphine) ligands can be prepared from the η^6 -mesitylene iridium(III) tris(pinacolborate) with the notable exception being the dmpe analogue due to the formation of (Bpin)₃(dmpe)Ir(μ -dmpe-1- κ -P1,2- κ -P2)Ir(Bpin)₃(dmpe). This coordinatively saturated dinuclear complex subsequently showed no catalytic activity. Accordingly, we have found that using (Mes)Ir(Bpin)₃ as an iridium(III) precursor with one equivalent of dmpe ligand does not result in catalytic turnover in our experimental setup. Hence, we hypothesized that the use of (dmpe)Ir(COD)Cl represents a suitable alternative strategy for the *in situ* formation of the catalytically active bis(phosphino)-tris(boryl)-iridium(III) species through elimination of ClBpin and oxidative addition of B_2pin_2 . We probed the reactivity of (dmpe)Ir(COD)Cl with a small excess (5 equiv) of B_2pin_2 in cyclohexane and in the absence of methane. Unfortunately, the dinuclear iridium(I) chloride precursor is not soluble in this solvent at room temperature, but dissolves in the presence of excess B_2pin_2 upon heating of the mixture to 150 °C. After 1 h, the room temperature $^{31}\text{P}\{^1\text{H}\}$ -NMR spectrum of this mixture reveals one major product peak at 6.69 ppm, as well as several other species in the 22.31–50.94 ppm range. Unfortunately, the $^{11}\text{B}\{^1\text{H}\}$ -NMR spectrum of the mixture is inconclusive, showing two sharp resonances at 28.04 and 27.7 ppm, the former of which we attribute to HBpin being formed from some cyclooctadiene borylation. However, the $^{11}\text{B}\{^1\text{H}\}$ -NMR spectrum does reveal a broad resonance at 37 ppm, generally characteristic of a bis(phosphino)-tris(borato)-iridium(III) species based on previous studies by Smith and co-workers.⁷⁹ Nonetheless, mass spectrometry

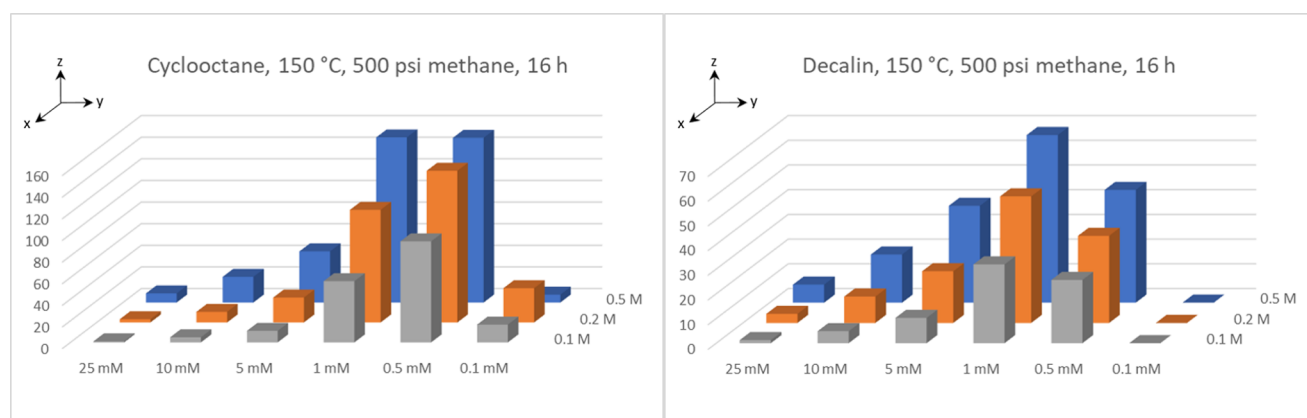


Figure 6. Turnover numbers (TONs, *z*-axis) for monoborylated methane being produced in a high-throughput and high-pressure setup with different concentrations of catalyst (dmpe)Ir(COD)Cl (*x*-axis) and diboron substrate (*y*-axis).

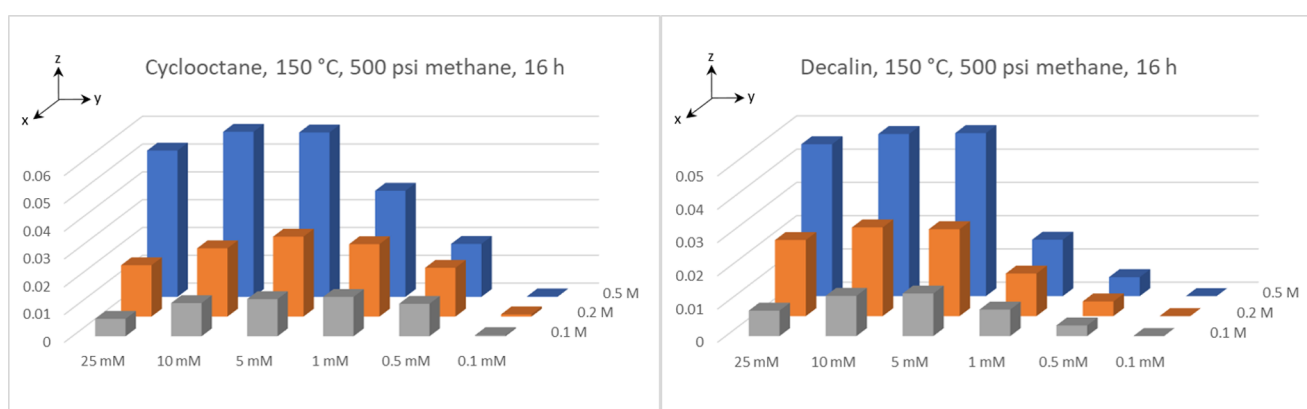


Figure 7. Total yields in mmol (*z*-axis) for monoborylated methane in a high-throughput setup with different concentrations of catalyst (dmpe)Ir(COD)Cl (*x*-axis) and B₂pin₂ substrate (*y*-axis).

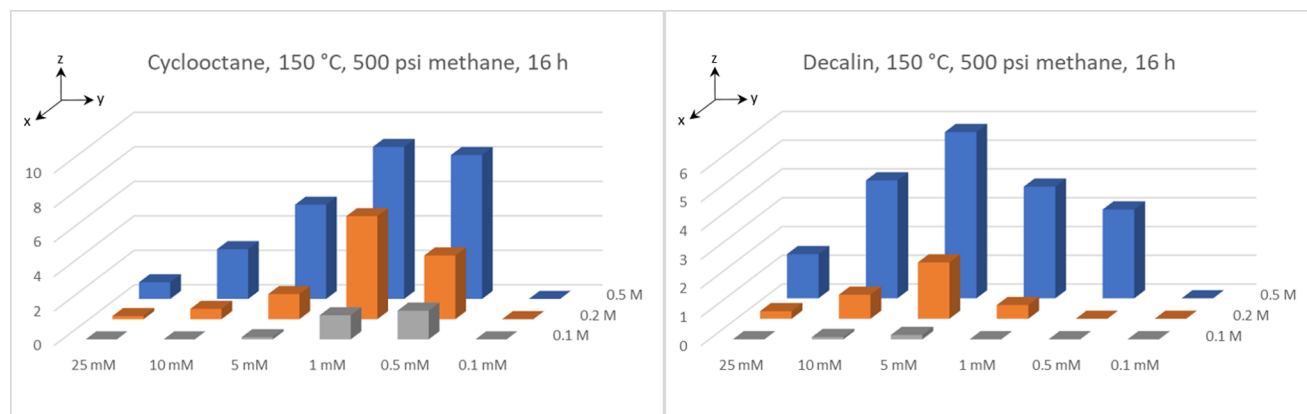


Figure 8. Turnover numbers (TONs, *z*-axis) for diborylated methane product, H₂C[Bpin]₂, in a high-throughput and high-pressure setup with different concentrations of catalyst (dmpe)Ir(COD)Cl (*x*-axis) and B₂pin₂ substrate (*y*-axis).

analysis of the mixture confirms the formation (dmpe)Ir(Bpin)₃ (**1-dmpe**) from (dmpe)Ir(COD)Cl in cyclohexane in the presence of excess B₂pin₂ as characterized by the corresponding isotopic pattern centered around an *m/z* = 723.7, as well as the acetonitrile adduct at *m/z* = 764.3.

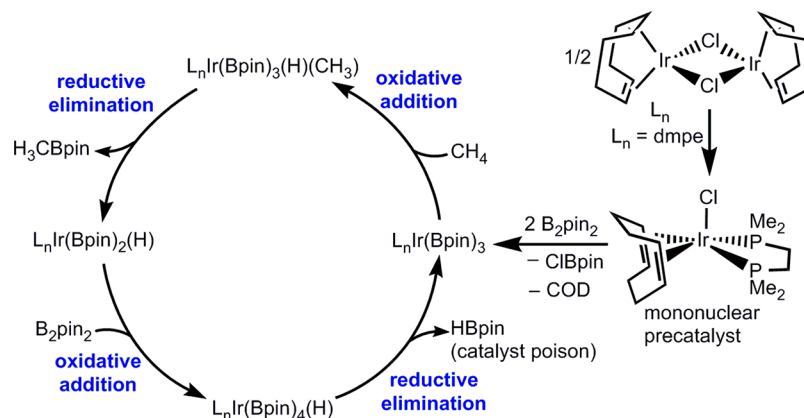
As previously reported, cyclohexane was found to be an optimal solvent for the catalytic activity, as it appeared to be inert toward borylation and provided sufficient solubility for methane.⁸⁰ However, since considerable catalytic activity had thus far only been observed at 150 °C, the use of higher-

boiling solvents was explored as a more practical solution in particular when using high-throughput methods, in which individual reactions are open to the reactor environment, and solvent loss has been observed with low-boiling solvents, as detailed in the experimental section in the [Supporting Information](#). Based on the observation that cyclohexane remained inert toward borylation, we hypothesized that other cyclic alkanes might behave similarly. Hence, cyclooctane (bp 150–152 °C) and decalin (racemic mixture of *cis*- and *trans*-isomers, bp 189–191 °C) were indeed found to be suitable

Table 1. Turnover Numbers, Conversions, and Yields Determined by High-Throughput Optimization

catalyst	B ₂ pin ₂	cyclooctane			decalin		
		0.5 M	0.2 M	0.1 M	0.5 M	0.2 M	0.1 M
1 mM	TON ^a	170	116	59	76	52	33
	conversion ^{b,c}	38.2	26.0	14.2	17.0	12.8	8.0
	yield ^b	31%	52%	57%	14%	26%	32%
0.5 mM	TON ^a	169	148	97	52	35	26
	conversion ^b	19.0	17.5	11.7	5.7	4.4	3.2
	yield ^b	15%	35%	47%	5%	9%	13%

^aCombined for H₃CBpin and H₂C[Bpin]₂. ^bFor H₃CBpin. ^c[mmol].

Scheme 3. Our Proposed Mechanism for the Iridium-Catalyzed Borylation of Methane

alternative solvents for this reaction, with essentially no detectable traces of borylation product.

The substrate and catalyst concentration dependence in methane borylation was probed by previously reported high-throughput and high-pressure methods, with decalin and cyclooctane as solvents to find conditions for optimal turnover and selectivity. The concentrations considered for B₂pin₂ were 0.5, 0.2, and 0.1 M, whereas the precatalyst (dmpe)Ir(COD)Cl was utilized in concentrations of 25, 10, 5, 1, 0.5, and 0.1 mM. Consistent with the proposed mechanism, where the oxidative addition of methane is rate-limiting, we found that an increase of the catalyst concentration leads to an increase in yield until complete consumption of B₂pin₂ is observed above 5 mM of (dmpe)Ir(COD)Cl. It was found that higher concentrations of catalyst, i.e., 5, 10, or 25 mM, not only reduce the turnover number, but also lead to an increase in the formation of diborylated methane (H₂C[Bpin]₂) and, consequently, result in a decrease in selectivity.

Turnover numbers (TONs) were determined in order to identify the best conditions for catalyst efficiency. The results depicted in Figure 6 show that the maximum TONs are achieved at a catalyst concentration of 0.5–1.0 mM, B₂pin₂ concentration of 0.5 M, which corresponds to a 0.1–0.2 mol % catalyst loading. The catalytic activity drops at catalyst concentrations both at 0.1 mM⁸¹ and above 1 mM. The latter is predominantly due to a plateau of the total conversion; hence an increase in catalyst concentration leads to the inverse for TON. The total conversion in terms of molar yield is depicted in Figure 7. The observed increase in conversion with increased catalyst loading before reaching such a plateau further supports the premise that this borylation process involves a molecular catalytic mechanism.

As previously reported, formation of H₂C[Bpin]₂ was observed as a side reaction.⁵⁹ Notably, as shown in Figure 8,

it was found that at low substrate concentration (0.1 M B₂pin₂) formation of H₂C[Bpin]₂ is essentially negligible. Based on these studies, a maximum turnover number (for mono- and diborylated product combined) of 170 with a selectivity of 9:1 for monoborylated H₃CBpin over diborylated H₂C[Bpin]₂ methane was established, while using cyclooctane as the solvent media (cf. Table 1), which is in good agreement with our previous findings. The dmpe-based catalyst hence outperforms the phenanthroline-based catalyst also in terms of selectivity over diborylation. In contrast, Sanford et al. only found a 4:1 selectivity for their phenanthroline/iridium-catalyst, as compared to 31:1 using ruthenium, and 10:1 using rhodium. C–H activation of cyclohexane was also reported with corresponding selectivities of 37:1 for rhodium, 82:1 for ruthenium, and only 3:1 for iridium.⁵⁹ In contrast, we could find no evidence for the borylation of these cyclic aliphatic solvents when using catalyst (dmpe)Ir(COD)Cl.

Motivated by the DFT-calculated lower activation barrier, we further probed for catalytic activity at lower temperature, namely, at 120 °C. Indeed, it was found that TONs of up to 9 at optimized conditions were obtained after 16 h (see the SI for details). In order to probe for maximum catalytic activity under these conditions, a longer reaction time of 96 h was probed at optimized conditions (i.e., 0.5 M B₂pin₂, 1 mM catalyst, cyclohexane) in a single batch reactor, yielding a maximum TON of 51 at 120 °C.

Intriguingly, it appears that, under all the conditions probed within this study, catalytic efficiency eventually shuts off before reaching 100% conversion, even when using high catalyst loadings. Sanford et al. also reported that, in contrast to their rhodium-based catalyst, catalytic activity using their optimized iridium-catalyst likewise reached a plateau at ~45%.⁵⁹ Considering how clean our reaction is based on the conversion to products when assayed by GCMS analysis, a plausible

hypothesis is that pinacolborane (HBpin) has an inhibitory effect and poisons the catalyst. Accordingly, we found that addition of more than 10% of HBpin relative to the diboron substrate B_2pin_2 shuts down catalytic activity completely. Under these conditions, no H_3CBpin was formed, supporting the notion that HBpin can act as a catalyst poison possibly via the formation of iridium hydrides or polyhydrides.^{82,83} Additional work aimed at examining the role of HBpin in the catalytic process and finding ways around this inhibition is underway in our laboratories. As a result, our combination of theory and experiment suggests a catalytic cycle which is shown in Scheme 3. Upon addition of 2 equiv of dmpe to the dinuclear $[(COD)Ir(\mu-Cl)]_2$ precursor, a mononuclear catalyst $(dmpe)Ir(COD)Cl$ is formed, at which point reaction with B_2pin_2 at higher temperatures results in a combination of steps such as COD demetalation, oxidative addition, and transmetalation to form the active state of the catalyst, **1-dmpe**. Based on computational work, we favor the oxidative addition of CH_4 followed by a reductive elimination to engender B–C bond formation, thus extruding H_3CBpin . Oxidative addition of B_2pin_2 to the Ir(III)-center in $(dmpe)Ir(Bpin)_2(H)$ followed by a second reductive elimination step closes the cycle along with the formation of HBpin. We show how the latter side-product does not engage in a second catalytic cycle (Scheme 1b, *vide supra*), but instead inhibits the reaction once it reaches ~50% conversion. Scheme 3 summarizes the refined mechanistic cycle we propose based on a combination of theory and experiments (cf. Scheme 1a, *vide supra*).

CONCLUSION

The catalytic activation of methane remains a challenge that continues to inspire much work. Recently, some significant advances were made in designing catalytic systems that can activate methane under relatively mild conditions with encouraging selectivities. The notable advances that organometallic and organic chemists made in the recent decades in understanding and designing C–H activation processes are helpful for targeting the most challenging of the hydrocarbons. Employing a fully integrated discourse between computer models and experimental work, we were able to design a catalytic reaction with unprecedentedly high efficacy for the catalytic borylation of methane. A clear and intuitively understandable concept based on principles of hard and soft acids/bases was derived, which predicted that a chelating phosphine ligand should render the iridium-center a much more capable catalyst for the oxidative addition step involving methane, which was identified as the most difficult step of the catalysis. Subsequent experimental optimization of the catalytic process using high-throughput and high-pressure techniques show that with the current system TONs as high as 170 can be achieved with high selectivity for monoborylation of methane. In accordance with the lower activation barrier of 32.3 kcal/mol determined by calculations, it was found that catalytic turnover can be achieved with temperatures as low as 120 °C and TON as high as 51 after 96 h. We found that pinacolborane, HBpin, a major side-product from methane borylation is responsible for the shutdown of the catalytic activity and that a mononuclear catalyst, $(dmpe)Ir(COD)Cl$, can be readily obtained from commercial sources such as $[(COD)Ir(\mu-Cl)]_2$ and dmpe.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b02771.

Crystallographic information file and checkCIF report (ZIP)

Additional computational details; DFT-optimized geometries; general experimental procedures; high-throughput setup; GCMS data; and crystal structure parameters (PDF)

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Notes

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