C-H BOND ACTIVATION

Catalyst-controlled selectivity in the C-H borylation of methane and ethane

Amanda K. Cook, Sydonie D. Schimler, Adam J. Matzger, Melanie S. Sanford*

The C–H bonds of methane are generally more kinetically inert than those of other hydrocarbons, reaction solvents, and methane functionalization products. Thus, developing strategies to achieve selective functionalization of CH₄ remains a major challenge. Here, we report transition metal–catalyzed C–H borylation of methane with bis-pinacolborane (B₂pin₂) in cyclohexane solvent at 150 °C under 2800 to 3500 kilopascals of methane pressure. Iridium, rhodium, and ruthenium complexes all catalyze the reaction. Formation of mono- versus diborylated methane is tunable as a function of catalyst, with the ruthenium complex providing the highest ratio of CH₃Bpin to CH₂(Bpin)₂. Despite the high relative concentration of cyclohexane, minimal quantities of borylated cyclohexane products are observed. Furthermore, all three metal complexes catalyze borylation of methane with >3.5:1 selectivity over ethane.

ver the past 50 years, numerous homogeneous transition-metal catalysts have been developed for the C-H functionalization of liquid alkanes [for example, via dehydrogenation (1), oxygenation (2), carbonylation (3), borylation (4–7), and C-, N-, and O-atom insertion (8, 9)]. However, relatively few of these catalysts have been translated to analogous reactions of methane (10–14). This is largely due to the particular challenges associated with methane C-H functionalization. First, the C-H bonds

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, MI 48109, USA. *Corresponding author. E-mail: mssanfor@umich.edu of methane are stronger than those of most liquid alkanes [the C-H bond dissociation energies (BDEs) of methane, *n*-hexane (1°C-H), and cyclohexane are 105, 101, and 99.5 kcal/mol, respectively (*15*, *16*)]. As such, methane C-H bond cleavage is prohibitively slow with many catalysts. Second, homogeneous alkane functionalization reactions are typically conducted by using neat alkane as the solvent (*4*, *5*, *14*), so the use of methane gas as a substrate poses challenges with respect to identifying a compatible reaction solvent (*12*, *17*). Last, the reaction solvent and the CH₃X products of methane functionalization typically contain more reactive C-H bonds than those of CH₄. As such, developing strategies to achieve selective functionalization of CH₄ in the presence of solvent and CH₃X remains a challenging problem (10–14).

We sought to identify a methane C-H functionalization process in which selectivity (both for CH4 versus CH3X functionalization and for CH4 versus solvent C-H functionalization) could be tuned through modification of the homogeneous transition-metal catalyst. To accomplish this goal, we focused on the catalytic C-H borylation of methane with B₂pin₂ (Fig. 1A). Over the past 15 years, there has been tremendous progress in the development of transition-metal catalysts for the C-H borylation of liquid alkane substrates. Catalysts based on iridium (Ir) (18, 19), rhodium (Rh) (20-22), rhenium (Re) (23), and ruthenium (Ru) (24) have been reported for liquid alkane C-H borylation, typically by using the alkane substrate as the solvent and $B_2 pin_2$ as the borylating reagent (19, 21, 23-25). With the vast majority of liquid alkane substrates, the selectivity of C-H borylation is dominated by steric factors, with terminal (primary) C(sp³)-H bonds undergoing selective functionalization over secondary or tertiary C-H sites (25, 26). This selectivity has been reported to be largely independent of the nature of the transition-metal catalyst. For example, the C-H borylation of *n*-alkanes $(n-C_nH_{2n+2})$ with B₂pin₂ affords 1-Bpin-C_nH_{2n+1} as the sole detectable product with Ir-, Rh-, Re-, and Ru-based catalysts (18, 20, 23, 24).

In certain contexts, the introduction of a Bpin substituent has been shown to electronically activate adjacent C-H bonds toward further C-H borylation by rendering them more acidic (27, 28). This electronic activation has been best studied in the context of benzylic substrates, in which the C-H borylation of 1°-benzylic C-H bonds is often slower than that of the 2° α -boryl benzylic C-H bonds of the products (29, 30). However, the interplay between these steric and electronic effects has not been extensively explored in the C-H borylation literature, especially as a function of catalyst metal identity. As discussed below, these

A Proposed selective mono-C–H borylation of methane:



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Fig. 1. Reactivity and selectivity challenges in the C–H borylation of methane. (A) Proposed methane C–H borylation reaction. (B) Challenges with selectivity in methane C–H borylation.

issues are expected to be particularly salient in the context of methane C-H borylation (Fig. 1B).

In 2005, Hall and co-workers reported density functional theory (DFT) calculations that suggest that Cp*Rh complexes (Cp*, pentamethylcyclopentadienyl) should be capable of catalyzing the C-H borylation of CH₄ (22). Despite these encouraging computational results, there have been no subsequent experimental studies establishing the feasibility and/or exploring the selectivity of methane C-H borylation with these or any other catalysts. In a methane C-H borylation reaction, three major C-H bond-containing molecules will be present in solution: methane, CH3Bpin, and solvent (cyclohexane) (Fig. 1B). Among these three molecules, methane has the most sterically accessible C-H bonds, CH₃Bpin has the most electronically activated (acidic) C-H bonds, and the reaction solvent, cyclohexane, is statistically favored because of its high concentration. Our studies sought to (i) experimentally establish the feasibility of metalcatalyzed methane C-H borylation; (ii) determine which factor (or factors) dominate selectivity in this transformation (sterics, electronics, or statistics); and (iii) probe whether different catalysts can be used to tune the selectivity of the reaction.

We selected Rh complex 1 for our initial investigations of methane C-H borylation on the basis of Hall and co-workers' DFT calculations, which predicted a relatively low barrier for CH₄ activation with this complex (22). The initial reactions were conducted in a Parr high-pressure batch reactor (45 mL volume) at 150 °C, using 1.5 mole percent (mol %) of 1, 3500 kPa of methane, and 0.89 mmol of B_2pin_2 as the limiting reagent (31). As discussed above, the choice of solvent is particularly critical because any C-H bonds in the solvent must be less reactive with 1 than those of CH₄. Thus, we first examined solvents without C-H bonds [perfluoromethylcyclohexane (PFMCH) and perfluorohexane (PFH)]. However, modest yields of methane C-H borvlation products were obtained (Table 1, entries 1 and 2), likely because of the low solubility of the Rh catalyst in these media. We next examined cyclopentane (c-C₅H₁₀) and cyclohexane $(c-C_6H_{12})$ as solvents (Table 1, entries 3 and 4). These cycloalkanes are both known to be poor substrates for Rh-catalyzed C-H borylation (6, 20, 21) because the 2°C-H bonds are relatively sterically congested and weakly acidic (32). Cyclohexane proved to be optimal, affording CH₃Bpin in 74% yield with only traces (~2%) of the solvent C-H borylation product c-C₆H₁₁Bpin (Table 1, entry 4). Under these conditions, high selectivity was also observed for the mono-borylation of methane [ratio of CH3Bpin to bis-borylated CH₂(Bpin)₂ was 10:1]. Increasing the loading of catalyst 1 to 3 mol % resulted in 99% yield of CH3Bpin, while maintaining excellent selectivity for CH₃Bpin over c-C₆H₁₁Bpin and CH₂(Bpin)₂ (entry 6). Lowering the catalyst loading to 0.75 mol % resulted in decreased yield of CH3Bpin (51%) but increased turnover number (68 turnovers) (entry 5) relative to the standard conditions.

We next examined Ir and Ru complexes **2/3** and **4** as potential catalysts for methane C-H borylation. These complexes were selected on the basis of their



1	1.5	PFMCH	<1%	<1	na†	na†
2	1.5	PFH	26%	17	na†	8:1
3	1.5	c-C ₅ H ₁₀	69%	46	8:1	10:1
4	1.5	c-C ₆ H ₁₂	74%	49	48:1	10:1
5	0.75	c-C ₆ H ₁₂	51%	68	46:1	18:1
6	3	c-C ₆ H ₁₂	99%	33	59:1	9:1

*Yields and ratios of all products were determined by means of gas chromatography–flame ionization detector (GC-FID) and are based on B_2pin_2 as the limiting reagent. †na, not applicable.



H ₃ C H + B ₂ pin ₂	catalyst	CH ₃ Bpin + HBpin +		
3500 kPa	150 °C, 14 h	$CH_2(Bpin)_2 + c-C_6H_{11}Bpin$	Bpin N N	ĊI (4)

Entry	Catalyst	Time (hours)	Yield*	TON	CH ₃ Bpin:CyBpin*	CH ₃ Bpin:CH ₂ (Bpin) ₂ *
1	2/3	14	45%	15	3:1	4:1
2	4	14	67%	22	83:1	21:1
3	4†	6	50%	17	82:1	31:1

*Yields and ratios of all products were determined by means of GC-FID and are based on B₂pin₂ as the limiting reagent. †Reactions stopped before completion in order to compare selectivity at similar yields.

18

54%

Fig. 2. Time studies showing formation of CH₃Bpin using 2800 kPa of CH₄. Rh complex 1 is indicated with red squares, Ir complex 2/3 with blue circles, and Ru complex 4 with green triangles.

1†

1

4



36:1

known catalytic activity for the C-H borylation of liquid alkanes (*18*, *19*, *24*, *33*, *34*). Under the optimal conditions for catalyst **1**, the combination of Ir complex **2** and ligand **3** (*18*) afforded moderate yield (45%) of CH₃Bpin, whereas Ru complex **4** provided 67% yield (Table 2, entries 1 and 2). To more quantitatively compare these three catalysts, reaction progress was monitored as a function of time, and the results are shown in Fig. 2. These studies show that all of the reactions achieve a maximum yield within 10 hours. However, the initial reaction rate with Rh catalyst **1** is approximately four times faster than that with **2/3**. Furthermore, **4** displays a lengthy induction period (~ 2 hours), suggesting that it serves as a precatalyst for this transformation (*24, 35*).

20:1

Fig. 3. Evaluation



Fig. 4. Comparison of catalysts for ethane borylation. (A) Batch ethane borylation results for catalysts 2/3, 1, and 4. (B) Methane and ethane one-pot competition. Selectivity factor is the preference for methane over ethane borylation corrected for statistics and solubility.

In the Table 2 data, the choice of catalyst has a major impact on the selectivity of C-H borylation, both for methane versus cyclohexane and for methane versus CH3Bpin. In particular, Rh and Ru catalysts 1 and 4 exhibit much higher selectivity for CH_4 than does the Ir catalyst system 2/3. This effect is observed even when the reactions are stopped at similar yield of CH_3Bpin (~50% yield; Table 2, entries 1, 3, and 4 for comparison). The ratio of CH₃Bpin to c-C₆H₁₁Bpin ranged from 82:1 (with catalyst 4) to 3:1 (with catalyst 2/3). Similarly, the CH3Bpin to CH2(Bpin)2 ratio ranged from 31:1 (with catalyst 4) to 4:1 (with catalyst 2/3). These results indicate that tuning of the catalyst structure can be used to control this undesired overfunctionalization reaction.

To more quantitatively evaluate selectivity as a function of catalyst, we conducted competition experiments between CH_4 (3500 kPa, 1.1 M) (36) and CH₃Bpin (0.13 M, 1 equivalent relative to B_2pin_2) with each of the catalysts **1**, **2/3**, and **4**. The time course of each reaction is shown in Fig. 3. The yield of CH₃Bpin (Fig. 3, blue circles, right *y* axes) represents the additional CH₃Bpin formed from the C-H borylation of CH₄ (measured in excess of 100%, given the CH₃Bpin equivalent added at the outset), whereas the yield of CH₂ (Bpin)₂ (Fig. 3, red squares, left *y* axes) represents the product of C-H borylation of CH₃Bpin.

With Ir catalyst 2/3 (Fig. 3A), the quantity of diborylated product present exceeds that of CH₃Bpin at all time points. In contrast, the concentration of CH₃Bpin is much greater than that of CH₂(Bpin)₂ throughout the reactions catalyzed by Rh complex **1** and Ru complex **4** (Fig. 3, B and C, respectively). Using the ratio of CH₃Bpin:CH₂ (Bpin)₂ obtained at early time points and the concentrations of CH₄ and CH₃Bpin added at the

of the selectivity in CH₄/CH₃Bpin borylation. (A to C) Reaction time profiles (top) for (A) Ir catalyst 2/3, (B) Rh catalyst 1, and (C) Ru catalyst 4. Red squares (left y axes) represent formation of CH₂(Bpin)₂, and blue circles (right y axes) represent formation of CH₃Bpin. CH₃Bpin: CH₂(Bpin)₂ ratios at early time points, relative rates, and $\Delta\Delta G^{\ddagger}$ values for the three catalyst systems are given below their respective time profile graphs.

onset, we can estimate $k_{\rm CH4}/k_{\rm CH3Bpin}$ (and thus approximate $\Delta\Delta G^{\ddagger}$) for the C–H borylation of CH₄ versus CH₃Bpin for each catalyst (complete details of these calculations are provided in the supplementary materials). As shown in the bottom of Fig. 3, positive $\Delta\Delta G^{\ddagger}$ values are observed for catalysts **1** and **2/3**, reflecting faster C–H borylation of CH₃Bpin versus CH₄. The values of $\Delta\Delta G^{\ddagger}$ are estimated as 0.53 and 2.48 kcal/mol for **1** and **2/3**, respectively. In contrast, Ru catalyst **4** shows a reversal in selectivity, exhibiting a preference for CH₄ over CH₃Bpin, with an estimated $\Delta\Delta G^{\ddagger}$ of -0.5 kcal/mol.

The relative reactivity of methane and ethane is another important issue (given that ethane is the secondmost abundant component of natural gas) but is rarely addressed in alkane C-H functionalization reactions. In the few reported systems in which this has been studied, ethane is usually found to be much more reactive (*17*, 37–39). As shown in Fig. 4A, catalysts **1**, **2**/**3**, and **4** all catalyze the C-H borylation of ethane at 150 °C in cyclohexane. Again, ethane borylation occurs in preference to cyclohexane borylation and shows a similar dependence on metal catalyst as with methane, with selectivities ranging from 5:1 (with **2**/**3**) to >100:1 (with **4**).

To probe catalyst selectivity for methane versus ethane, known molar quantities of each gas were added to the high-pressure reactor. The reactions were run to complete conversion of B₂pin₂, and the ratio of CH₃Bpin to CH₃CH₂Bpin was determined with each catalyst. These ratios were then corrected for the number of C-H bonds in each substrate as well as the relative solubilities of the two gases (36). As shown in Fig. 4B, all three catalysts exhibit a >3.5:1 preference for the C-H borvlation of methane relative to ethane, which is consistent with sterically controlled selectivity. Additionally, the level of selectivity varies with the catalyst. The Ir catalyst 2/3 and Ru catalyst 4 both react approximately fourfold faster with methane C-H bonds, whereas 1 is more selective for methane (approximately sixfold faster). These

results further highlight the impact of catalyst on both reactivity and selectivity in the C-H borylation of light alkanes.

Overall, we have demonstrated that catalyst structure has a major impact on reaction rates and selectivities in the C-H borylation of methane. Over-functionalization of the initial product, CH₃Bpin, can be limited through the appropriate selection of catalyst. These results open up exciting possibilities for catalyst design (to further modulate reactivity and selectivity in methane C-H borylation) as well as the application of the concepts delineated here for other light alkane C-H functionalization reactions.

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ACKNOWLEDGMENTS

The work conducted by A.K.C. (primarily involving evaluation of catalysts 1 and 2/3) was supported by NSF under the Centers for Chemical Innovation (CCI) Center for Enabling New Technologies through Catalysis (CENTC) Phase II Renewal, CHE-1205189. The work conducted by S.D.S. (primarily involving evaluation of catalyst 4 and gas solubility measurements) was supported by the U.S. Department of Energy Office of Basic Energy Sciences (contract DE-FG02-08ER 15997). The Parr reactors used in this work were

purchased with funds from the NSF, under the CCI CENTC Phase II Renewal, CHE-1205189. We gratefully acknowledge D. Samblanet for assistance with the gas solubility measurements. The University of Michigan has filed for a provisional patent on this work.

SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/351/6280/1421/suppl/DC1 Materials and Methods Supplementary Text Figs. S1 to S19 Tables S1 to S14 References (40-57)

24 November 2015; accepted 18 February 2016 10.1126/science.aad9289

C-H BOND ACTIVATION

Catalytic borylation of methane

Kyle T. Smith,¹ Simon Berritt,¹ Mariano González-Moreiras,¹ Seihwan Ahn,^{2,3} Milton R. Smith III,⁴* Mu-Hyun Baik,^{2,3}* Daniel J. Mindiola¹*

Despite steady progress in catalytic methods for the borylation of hydrocarbons, methane has not yet been subject to this transformation. Here we report the iridium-catalyzed borylation of methane using bis(pinacolborane) in cyclohexane solvent. Initially, trace amounts of borylated products were detected with phenanthroline-coordinated Ir complexes. A combination of experimental high-pressure and high-throughput screening, and computational mechanism discovery techniques helped to rationalize the foundation of the catalysis and identify improved phosphine-coordinated catalytic complexes. Optimized conditions of 150°C and 3500kilopascal pressure led to yields as high as ~52%, turnover numbers of 100, and improved chemoselectivity for monoborylated versus diborylated methane.

ctivation of methane is challenging because it is nonpolar, has strong sp³ C-H bonds, is sparingly soluble in both polar and nonpolar solvents, and has very high ionization energies and very low triple, boiling, and flashing points (1-8). Homogeneous catalysts that convert methane to products that could be used as liquid fuels are known, but these systems often require strong electrophiles and, in some cases, superacids and/or powerful oxidants (1, 2, 9-17). Chemoselectivity is another limitation in methane activation and functionalization. For instance, H_3C -R (R = functional group) products resulting from methane activation and functionalization have more reactive C-H bonds than methane itself, hence often resulting in poor selectivity, overfunctionalization, and overoxidation.

The pioneering work by Hartwig, Marder, and Smith on C-H bond borylation inspired our investigation into the catalytic functionalization of methane using a similar approach (18). Whereas stoichiometric and catalytic borylations of alkanes show marked selectivity for monoborylation of terminal methyl groups (18), analogous reac-

¹Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, PA 19104, USA. ²Institute for Basic Science-Center for Catalytic Hydrocarbon Functionalizations, Daejeon, Korea. ³Department of Chemistry, Korea Advanced Institute of Science and Technology, Daejeon, Korea. ⁴Department of Chemistry, Michigan State University, 578 South Shaw Lane, East Lansing, MI 48824, USA. *Corresponding author. E-mail: smithmil@msu.edu (M.R.S.); mbaik2805@kaist.ac.kr (M.-H.B.); mindiola@sas.upenn.edu (D.J.M.) tions with methane have not been thoroughly explored, despite this reaction being known for more than a decade. Fundamentally important is that the methyl-derived product is arguably a form of a mildly nucleophilic methyl transfer reagent, which complements the chemistry observed in electrophilic activation reactions in Shilov-type chemistry (9). Theory predicts that borylation of hydrocarbons with a borane (Eq. 1) is thermoneutral, whereas the weaker B-B bond in diboron reagents provides an enthalpic driving force of at least 12 kcal/mol, as shown in Eq. 2 (18). These considerations led us to pursue the catalytic borylation of methane using diboron reagents such as B_2pin_2 (pin = pinacolate).

$$\begin{split} \mathrm{H_3C\text{-}H} \ + \ \mathrm{H\text{-}B(OR)_2} \rightarrow \mathrm{H_3C\text{-}B(OR)_2} + \\ \mathrm{H\text{-}H} \ \Delta H_{\mathrm{o}} = -1 \ \mathrm{to} \ +1 \ \mathrm{kcal/mol} \qquad (1) \end{split}$$

$$\begin{split} \mathrm{H_3C\text{-}H} \ + \ (\mathrm{RO})_2\mathrm{B\text{-}B}(\mathrm{OR})_2 &\rightarrow \mathrm{H_3C\text{-}B}(\mathrm{OR})_2 + \\ \mathrm{H\text{-}B}(\mathrm{OR})_2 \ \Delta H_\circ \ = \ -13 \ \mathrm{kcal/mol} \ \ (2) \end{split}$$

Iridium systems are particularly promising for C-H activation of methane (1, 2), and some of the most active borylation catalysts use this transition metal (18). Therefore, we focused our attention on the commercially available iridium reagents [Ir(COD)(µ-Cl)]₂, [Ir(COD)(µ-OMe)]₂ (COD = 1,5cyclooctadiene), and (MesH)Ir(Bpin)₃ (MesH = mesitylene) (19), modifying them with a range of





Catalyst-controlled selectivity in the C–H borylation of methane and ethane Amanda K. Cook *et al. Science* **351**, 1421 (2016); DOI: 10.1126/science.aad9289

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