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tack of the aromatic C–H bond by cationic Pd(II) species to form **IMa** followed by coordination of alkyne to give **IMb**. A trans insertion of C–C triple bonds to the σ-aryl-Pd bond (*23–25*) results in **IMc**, and 1/1 arene/alkyne adduct would be released from Pd(II) (*24*) upon protonation of **IMc**. The possible involvement of Pd(II)-vinylidine and Pd(II)-allenyl complexes could be excluded (*26, 27*). In the addition of alkoxyarenes to activated alkenes, the involvement of the carbocations from alkenes may be possible.

Many of the products offered by this reaction [such as coumarins, 2(1*H*)-quinolinones, and *cis*-aryl-α,β–unsaturated carbonyl compounds] are biologically relevant compounds and cannot otherwise be easily accessed by known reactions. This process offers a general, simple, and efficient method for converting simple arenes directly to potentially useful compounds in one step under mild conditions. This method should have many applications in organic and medical chemistry and possibly be applied by chemical and pharmaceutical industries.

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21. Two control reactions also support the formation of **IMc** in the reaction: (i) The D-containing adduct of reaction 1 in Fig. 4 cannot be formed from H/D exchange of the corresponding 1/1 arene/alkyne adduct in TFA-d_1, and (ii) the 1/2 arene/alkyne adduct as $\mathbf{ArA_2}$ (in Fig. 2) cannot result from the reaction in TFA-d_1 or from the reaction of 1/1 arene/alkyne adduct with another alkyne. $\mathbf{ArA_2}$ would be formed by cis addition of the vinyl-Pd complex **IMc** to the alkyne, followed by protonation.
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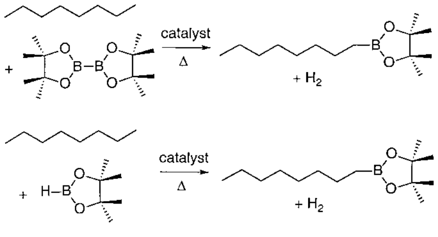
Thermal, Catalytic, Regiospecific Functionalization of Alkanes

Huiyuan Chen,[1] Sabine Schlecht,[1] Thomas C. Semple,[2] John F. Hartwig[1]*

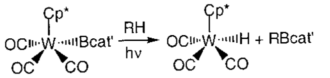
The formation of a single product from terminal functionalization of linear alkanes from a transition metal–catalyzed reaction is reported. The rhodium complex $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ (Cp^*, C_5Me_5; Me, methyl) catalyzes the high-yield formation of linear alkylboranes from commercially available borane reagents under thermal conditions. These reactions now allow catalytic, regiospecific functionalization of alkanes under thermal conditions. The organoborane products are among the most versatile synthetic intermediates in chemistry and serve as convenient precursors to alcohols, amines, and other common classes of functionalized molecules.

Alkanes are among the most abundant but least reactive molecules. This low reactivity, particularly at the terminal position of the alkane, has prevented their direct conversion into industrially important chemicals such as linear alcohols, linear amines, and α-olefins. Instead of selectively producing these desired products, which contain a single functional group at the end of an alkyl chain, reactions of alkanes typically form mixtures. When good selectivity is observed, internal positions or both internal and terminal positions of the alkane react to produce, for example, *tert*-butylhydroperoxide from isobutane or maleic anhydride from *n*-butane (*1*). Certain transition metals do react cleanly at the end of the alkane to produce *n*-alkyl complexes (*2, 3*), but these transformations involve stoichiometric amounts of expensive metal reagents; catalytic reactions that selectively functionalize the terminal positions of alkanes are rare. Transition metal–catalyzed dehydrogenation gives alkene regioisomers (*4–6*), and photocatalytic carbonylation produces secondary photoproducts (*7*). Both processes also suffer from unfavorable thermodynamics. Enzymes that oxidize higher alkanes than methane and ethane give regioisomeric mixtures. Here, we report a regiospecific catalytic functionalization of linear alkanes under thermal conditions: the coupling of alkanes with borane reagents to form linear alkylboranes (Scheme 1). These borane products are common, well-developed synthetic intermediates in organic chemistry. They are easily converted to amines, alcohols, alkenes, and other classes of functionalized molecules in a single step (*8, 9*).



Scheme 1.

We previously reported the stoichiometric reaction of transition metal–boryl complexes ($L_nM\text{-}BR_2$, where L is a ligand, M is a metal, and R is an organic substituent) with alkanes to produce linear alkylboranes:

 (1)

$$Cp^*W(CO)_3Bcat' \xrightarrow[h\nu]{RH} Cp^*W(CO)_3H + RBcat' \quad (1)$$

(*10, 11*). We then pursued a selective catalytic reaction of alkanes that incorporates a similar stoichiometric step into a catalytic cycle. We disclosed the reaction of diboron reagents (R_2BBR_2; R_2 = pinacolate) with alkanes catalyzed by $Cp^*Re(CO)_3$ (Cp^*, C_5Me_5; Me, methyl) to produce linear alkylboranes under photochemical conditions (*12*). This photochemistry led to the selective, catalytic reactions under the thermal conditions described below (*13*).

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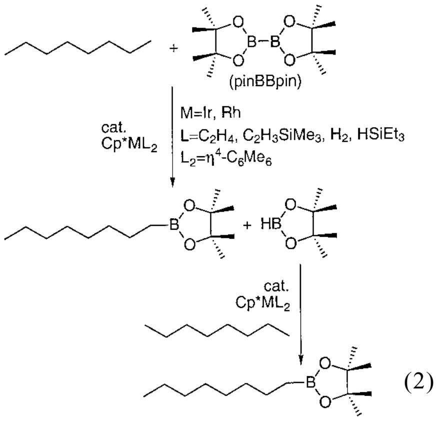
For thermal alkane functionalization, we focused on transition metal complexes that contained a Cp* ligand to provide structural similarity to our photocatalyst and to systems that add alkanes stoichiometrically (*2, 3, 14–17*). We also sought systems that would generate boryl complexes from R_2BBR_2 or HBR_2 by oxidative addition (*18*) and would form unsaturated boryl complexes by thermal dative-ligand dissociation. Metal polyhydrides extrude H_2 under thermal conditions (*19, 20*), and alkene complexes dissociate alkene thermally. Thus, we initially tested Cp^*IrH_4 (**1**) (*21*) and $Cp^*Ir(C_2H_4)_2$ (**2**) (*22*) as catalysts for the reaction of 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane (pinBBpin) (*23*) with octane:



(2)

Reactions catalyzed by 10 mol% **1** gave some functionalized product, but yields were low and never exceeded 20%. In contrast, reactions catalyzed by 10 mol% **2** gave 58% yield for the two-step process that produces two equivalents of 2-(1-octyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (*n*-octylBpin) for each diboron reagent (*24*). However, these reactions were slow; complete conversion of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBpin) generated from pinBBpin and octane required 10 days at 200°C.

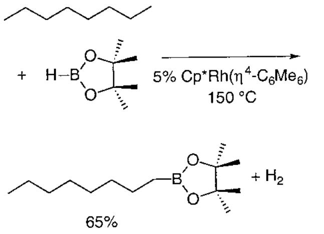
To accelerate this reaction, we used the second-row analog of **2**, $Cp^*Rh(C_2H_4)_2$ (**3**) (*22*). Indeed, complex **3** catalyzed the reaction of octane with pinBBpin at 150°C to give complete conversion of pinBBpin to HBpin after 1 hour. The yield of *n*-octylBpin was actually higher than the amount of converted diboron reagent, which suggested that HBpin was also reacting with octane on this time scale. Heating for an additional 4 hours led to complete consumption of HBpin and to the formation of *n*-octylBpin in 84% overall yield.

Analysis of the borane products by gas chromatography–mass spectrometry (GC-MS) showed that *n*-octylBpin was the only isomer formed. No products from functionalization at the internal positions were observed. The 2-octyl isomer was prepared independently from 2-chlorooctane and was shown to be absent from the catalytic reaction mixtures by GC-MS techniques. However, a number of minor organoborane products formed from the ethylene ligands. EthylBpin, $C_2H_4(Bpin)_2$, $C_2H_3(Bpin)_3$, and $C_2H_2(Bpin)_4$ were all detected by GC-MS. These products were not prepared independently and therefore are known only by their elemental composition. It was clear that improved yields relied on limiting reactivity of the alkene ligands or reducing catalyst loads.

Surprisingly, reactions catalyzed by the more labile vinylsilane complex $Cp^*Rh(C_2H_3SiMe_3)_2$ (**4**) (*25*) or the alkene-free complex $Cp^*Rh(H)_2(SiEt_3)_2$ (**5**) (*26*) occurred in lower yields than those catalyzed by **3**. Thus, we tested the rarely studied hexamethylbenzene complex $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ (**6**) (*27*) that would extrude unreactive hexamethylbenzene. Reactions of pinBBpin with octane catalyzed by 5 mol% **6** at 150°C showed no ligand borylation products, and the rates were faster than those for reactions catalyzed by **4** or **5**. Analysis of the crude reactions by GC again showed that the terminal product was the only octylborane formed. After 25 hours, complete conversion of the borane had occurred, and the yield for the overall process in Eq. 2 was 88%. Reactions catalyzed by hexamethylbenzene complex **6** were initially slower than those catalyzed by bis(ethylene) complex **3**, but **6** showed greater long-term activity. Reactions catalyzed by 1 mol% **6** gave complete conversion and 72% yield for the overall reaction in Eq. 2 after 80 hours. The reaction catalyzed by 1 mol% **3** under identical conditions gave 64% yield after 110 hours.

Table 1 shows the yields for reactions of several alkanes, di-*n*-butyl ether, and benzene with pinBBpin to form functionalized product and H_2. Reactions of 2-methylheptane provided only products from primary C-H bond functionalization in a 5:1 mixture of regioisomers favoring functionalization of the less hindered methyl group. Reactions of methylcyclohexane were slow, perhaps because of the lower concentration and greater steric hindrance of the methyl groups. Reaction of di-*n*-butyl ether with the diboron reagent was rapid, but the subsequent reaction of pinacolborane was slow. Thus, higher catalyst loadings were required, and lower yields were observed after 80 hours than were observed for reactions of alkanes. Benzene was particularly reactive, and 82% yield of arylboronate ester was observed when using 0.5 mol% catalyst (328 turnovers).

The clean reaction between octane and the HBpin formed in situ suggested that a dehydrogenative coupling of pinacolborane with octane could be observed without initiating the reactions with diboron reagents. Indeed, reaction of pinacolborane with octane in the presence of 5 mol% **6** formed *n*-octylBpin in 14 hours, in 65% yield:



(3)

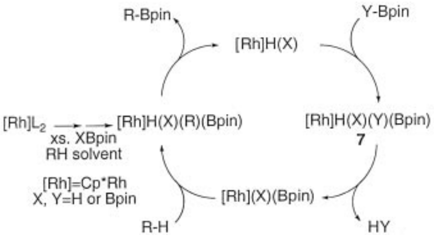
Again, the reactions were regiospecific for the terminal position of the alkane.

The exclusive selectivity for borylation at alkane methyl groups results from kinetic factors. The reaction of pinBBpin with octane was conducted in the presence of 2-(2-butanyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in a sealed tube, and no isomerization of the 2-butyl boronate ester to the 1-butyl isomer occurred. Thus, the terminal product is not formed by isomerization of an internal alkylboronate ester formed initially. The high selectivity for the termini of alkanes is similar to that for the stoichiometric reaction of certain transition metal complexes with linear alkanes (*2, 3*) and, in simple terms, results from a steric preference for formation of a linear metal-alkyl complex.

Table 1. Regiospecific, catalytic functionalization of alkanes, alkyl ethers, and benzene. A solution of catalyst and diboron compound was heated at 150°C. A known amount of dodecahydrotriphenylene (internal standard) was added to the reaction after complete consumption of both pinBBpin and HBpin. Yields were determined by GC for the overall reaction pinBBpin + R-H → RBpin + H_2.

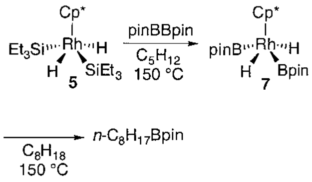
Entry	Substrate	Catalyst	Time (hours)	Yield of RBpin (%)
1	*n*-Octane	**3**, 5.0 mol%	5	84
2	*n*-Octane	**3**, 1.0 mol%	110	64
3	*n*-Octane	**6**, 5.0 mol%	25	88
4	*n*-Octane	**6**, 1.0 mol%	80	72
5	2-Methylheptane	**3**, 2.5 mol%	30	73
6	2-Methylheptane	**6**, 1.0 mol%	60	61
7	Methylcyclohexane	**6**, 6.0 mol%	80	49
8	*n*-Butyl ether	**6**, 4.0 mol%	80	64
9	Benzene	**6**, 5.0 mol%	2.5	92
10	Benzene	**6**, 0.5 mol%	45	82

A detailed mechanism for the overall catalytic process cannot yet be deduced, but an outline of a potential mechanism is provided in Scheme 2. Oxidative addition of borane or diboron compound, depending on the boron reagent present, could form a hydridorhodium boryl complex or a rhodium bis(boryl) complex. After elimination of H_2 or borane to create an open coordination site, such complexes could then react with alkane to produce an alkylrhodium boryl complex. Rapid B-C bond formation would then lead to product. To probe for the presence of metal-boryl intermediates, we obtained ^{11}B nuclear magnetic resonance (NMR) spectra of reactions of the diboron compound with octane at high catalyst loads. We observed a resonance at δ40 during the reaction, and this chemical shift, which is located downfield of the organoboronate esters and pinacolborane, is characteristic of a metal-boryl species.



Scheme 2.

To determine the identity of this observed complex, we conducted a variety of reactions of pinBBpin and HBpin with nearly stoichiometric amounts of rhodium complex in alkane solvent. Of these reactions, we found that the combination of silyl complex **5** and pinBBpin at 150°C in pentane solvent in a sealed tube most cleanly formed a metal-boron complex that displayed the same ^{11}B NMR signal at δ40 as was observed in the catalytic reaction:



(4)

Despite efforts using various reaction conditions, a maximum conversion to this complex of 60% was achieved. However, we were able to separate the two metal complexes from the free boron products. We could tentatively assign a structure for the metal-boron species as **7** from ^1H NMR data of a mixture of the metal-boron complex and **5**. A single pinacol methyl resonance was observed, which suggests the trans geometry of **7**. A broad doublet signal was observed for the two hydrides at −12.78 ppm (coupling constant $J_{H\text{-}Rh}$ = 48 Hz), which integrated 2:15 versus the Cp* resonance. This signal did not show direct scalar B-H coupling, but line widths increased with temperature. These data are consistent with slower time constants T_1 and small scalar couplings to the quadrupolar boron at higher temperatures (*28*). Reaction of isolated **7** with octane at 150°C was rapid and generated two equivalents of *n*-octylBpin per Cp*Rh fragment in 90% yield, confirming the presence of two boryl ligands on **7**. Again, no internal alkylborane products were formed. These data indicate that **7** is kinetically and chemically competent to be an intermediate in the catalytic reactions.

If compound **7** or a species generated from **7** is an intermediate, then reactions catalyzed by alkene and arene complexes **3** and **6** would show the same selectivity. Indeed, reaction of pinBBpin with an equimolar mixture of octane and octane-d_{18} showed a rate constant ratio k_H/k_D (150°C) of 1.9 ± 0.1 for reactions catalyzed by **3** and 2.0 ± 0.1 for those catalyzed by **6** (*29*). In addition, the product ratio from reaction of pinBBpin at the two termini of 2-methylheptane was the same for reactions catalyzed by **3** (4.8 ± 0.4) and **6** (5.3 ± 0.4). The same selectivity (5.0 ± 0.5) was observed with isolated **7**, which suggests that it is involved in the catalytic process. Complicated H/D exchange of the alkanes prevented accurate isotope effect measurements for the stoichiometric reaction of **7** with octane.

Unusual thermodynamic properties of borane reagents provide the driving force for the overall process. The B-B, B-C, and B-H bond energies of closely related boron compounds have been determined computationally (*30, 31*). From these data, the B-C (112 kcal/mol) and B-H (111 kcal/mol) bonds formed in the initial stage of the reaction are, taken together, 21 kcal/mol stronger than the B-B (104 kcal/mol) and C-H (98 kcal/mol) (*32*) bonds broken, whereas the B-C and H_2 (104 kcal/mol) bonds formed in the second stage are 7 kcal/mol stronger than the B-H and C-H bonds broken.

The organoboranes produced by the borylation process are among the most versatile synthetic intermediates in chemistry. Reactions of organoboranes with hydrogen peroxide, hydroxylamine, and CO yield alcohols, amines, and ketones, respectively. Simple thermolysis under vacuum can produce α-olefins (*8, 33, 34*). With the proper substituents at boron, this final process could extrude the same borane reagent that was used in the alkane functionalization step to allow recycling of the main group reagent for large-scale synthesis. In addition, this type of alkane functionalization could deliver a functional group to the end of an alkyl chain during the synthesis of more complex structures than those in linear alcohols, amines, or alkenes.

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