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Regioselective Borylation of the C–H Bonds in Alkylamines and Alkyl Ethers. Observation and Origin of High Reactivity of Primary C–H Bonds Beta to Nitrogen and Oxygen

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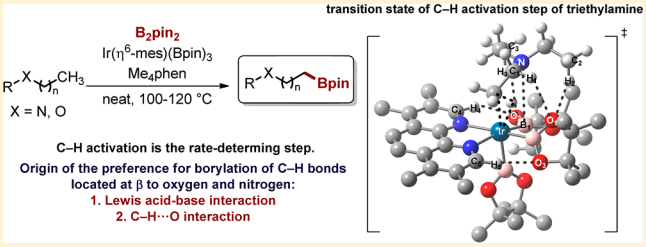
Supporting Information

ABSTRACT: Borylation of aliphatic C–H bonds in alkylamines and alkyl ethers to form primary aminoalkyl and alkoxyalkyl boronate esters and studies on the origin of the regioselectivity of these reactions are reported. The products of these reactions can be used directly in Suzuki–Miyaura cross-coupling reactions or isolated as air-stable potassium trifluoroborate salts. Selective borylation of the terminal C–H bond at the positions β to oxygen and nitrogen occurs in preference to borylation of the other terminal C–H bonds. Experimental studies and computational results show that C–H bond cleavage is the rate-determining step of the current borylation reactions. The observed higher reactivity of C–H bonds at the terminal position of ethylamines and ethers results from a combination of attractive Lewis acid–base and hydrogen-bonding interactions, as well as typical repulsive steric interactions, in the transition state. In this transition state, the heteroatom lies directly above the boron atom of one boryl ligand, creating a stabilizing interaction between the weak Lewis acid and Lewis base, and a series of C–H bonds of the substrate lie near the oxygen atoms of the boryl ligands, participating in a set of weak C–H···O interactions that lead to significant stabilization of the transition state forming the major product.

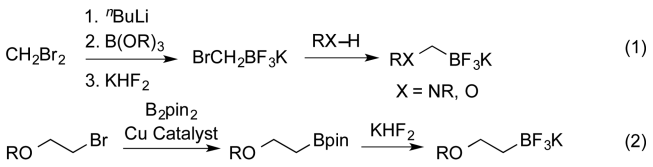


INTRODUCTION

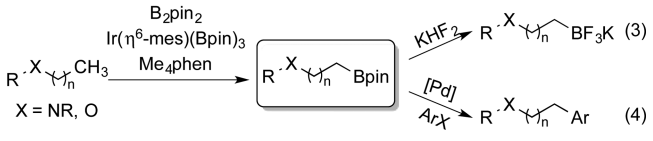
Alkylboron reagents are versatile synthetic intermediates that undergo a variety of transformations.[1] These transformations include recently developed cross-coupling and amination reactions of aliphatic organoboron compounds,[2] as well as classic oxidations of alkylboron reagents to alcohols. Traditional methods to form these aliphatic organoboron reagents include the addition of a reactive organometallic species, such as an alkyl lithium or alkyl Grignard reagent, to an electrophilic boron compound and the hydroboration of olefins.[3] Both of these methods require a functionalized precursor, such as an alkyl halide or an olefin. Furthermore, the hydroboration of enol ethers or simple acyclic enamines derived from aldehydes to form alkoxyboranes and aminoboranes often results in elimination products.[4−6]

Aminoalkyl and alkoxyalkyl trifluoroborate salts have been shown recently by Molander and co-workers to undergo Suzuki–Miyaura cross-coupling.[7−15] These reagents were synthesized from potassium bromomethyltrifluoroborates by nucleophilic displacement reactions (eq 1)[16] or by conversion of the bromoethyl ethers into the corresponding organoboron species through a Cu-catalyzed borylation reaction (eq 2).[11] Although these reactions occur in good yields, prefunctionalized alkyl halide starting materials are required. A synthesis of alkyl boronates directly from alkylamines or ethers would avoid the need for halogenated reagents.[17]

Previous work



This work



During the past decade, our laboratory reported the functionalization of aliphatic C–H bonds with metal-boryl catalysts, and high selectivity was observed for functionalization of terminal C–H bonds over internal C–H bonds. Rhodium and ruthenium catalysts that contain pentamethylcyclopentyldienyl ligands (Cp*) catalyzed the formation of 1-alkyl boronate esters from alkanes and diboron or borane reagents. The selectivity of these aliphatic C–H borylation processes is controlled by the steric properties of the substrate. We recently

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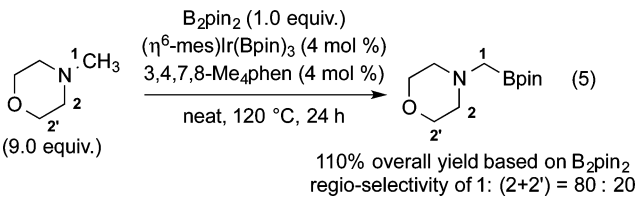
delineated the origin of this steric control, which results from a more favorable equilibrium for activation of primary over secondary C−H bonds and a lower barrier for formation of the B−C bond by reductive elimination from a primary alkyl complex than from a secondary alkyl complex.[18]

In this article, we report the synthesis of aminoalkyl- and alkoxyalkylboron reagents by Ir-catalyzed C−H borylation reactions. The products of these C−H bond functionalization reactions can be converted to stable trifluoroborate salts (eq 3) or used directly in Suzuki−Miyaura cross-couplings (eq 4). These C−H borylation reactions occur with an unusual but pronounced preference for the formation of product from the C−H bond located at the β positions to oxygen and nitrogen over the other C−H bonds in ethers and amines and over the C−H bonds in alkanes. These reactions also occur in good yield at the methyl C−H bonds of *N*-methyl cyclic amines. Experimental mechanistic and computational studies are consistent with irreversible and rate-determining C−H bond cleavage through a transition state containing a weak, stabilizing Lewis acid−base interaction and a series of weak C−H···O interactions between the C−H bonds of the substrate and the oxygen atoms of the boryl ligand. These attractive interactions contribute significantly to the observed selectivity.

EXPERIMENTAL RESULTS

Previously, we reported the borylation of primary aliphatic C−H bonds catalyzed by Cp*Rh and Cp*Ru complexes. However, the small scale and high temperatures (150 °C) of these reactions limited their synthetic utility.[19−21] Recently, we reported a more active iridium catalyst containing 3,4,7,8-tetramethylphenanthroline (Me_4phen) as ligand for C−H bond functionalization with main group reagents;[22] this system catalyzes the borylation of secondary C−H bonds in cyclic ethers[23] and cyclopropanes[24] and the primary C−H bonds in methylsilanes[25a] to form the corresponding boronate ester products. To determine the potential of this new iridium system to catalyze the borylation of primary C−H bonds of common organic compounds in a more practical fashion, we investigated the borylations of alkyl ethers and alkylamines on a preparative scale. The high reactivity of different ethers and amines toward this iridium catalyst led us to study the origins of selectivity in the borylation of these reagents and to compare the factors controlling selectivity in this system to those controlling selectivity in reactions catalyzed by Cp*Rh complexes.

Development of the Borylation of Methylamine C−H Bonds. We began our investigation of the borylation of ethers and amines by studying the C−H borylation of *N*-methyl cyclic amines. These amines contain just one type of primary C−H bond and could, therefore, be selective for the formation of a single product. The reaction of bis-pinacolatodiboron (B_2pin_2) as limiting reagent with neat *N*-methylmorpholine in the presence of (η^6-mes)Ir$Bpin_3$ (mes = mesitylene) and Me_4phen as ligand generated the aminomethyl boronate ester product in 88% yield based on B_2pin_2 (eq 5). Reactions catalyzed by



complexes containing a series of dative nitrogen ligands related to Me_4phen were also conducted, but these reactions occurred in lower yields than those with the catalyst containing Me_4phen. (For details, see the Supporting Information.) Although competitive borylation of the secondary C−H bonds occurred, borylation of the primary C−H bond occurred in high yield.[25] The same reaction catalyzed by $[Cp^*RhCl_2]_2$ gave the product from borylation of the methyl group in a low (<30%) yield.[20]

We attempted to isolate the product from borylation of *N*-methylmorpholine by several methods, including standard distillation and chromatography, as well as conversion to the potassium trifluoroborate salt, but the isolated material was contaminated with impurities. However, the crude product of this borylation reaction was suitable for cross-coupling with aryl halides. The reaction of 4-bromoanisole with the product from borylation of *N*-methylmorpholine, prepared by C−H borylation under the above conditions followed by evaporation of the volatile components, proceeded in good yield (83% isolated yield based on ArX) in the presence of $Pd(dba)_2$ (5 mol %), Q-Phos (5 mol %), and CsF. Only the aminomethyl boron compound reacted; no product from coupling of the secondary boronate ester side product was observed.

The scope of the one-pot borylation and arylation of methylamines under the developed conditions is summarized in Table 1. This reaction sequence occurred with a number of cyclic methylamines, including *N*-methyl-substituted morpholine, piperidine, piperazine, and pyrrolidine (entries 1−5). Both electron-rich (entries 6 and 7) and electron-deficient aryl bromides (entries 8−11) underwent the coupling reaction with the aminomethyl boronate esters in good yields. Reactions of these boronate esters with aryl chlorides also occurred, although the yields were slightly lower than those of reactions conducted with aryl bromides (entries 7−10). Heteroaryl bromides also underwent the cross-coupling reaction with the borylation product (entries 12 and 13). The C−H borylation occurred with commercially available $[Ir(COD)OMe]_2$ in place of the trisboryl catalyst precursor, but higher loadings of the catalyst components were required (entry 2).

Borylation of Cyclic and Acyclic Ethyl- and Propylamines. Most classes of C−H bond functionalization reactions occur at the C−H bonds α to a nitrogen atom, due to electronic effects.[26] To assess the relationship between the relative reactivity of different C−H bonds of amines and ethers and the selectivity of prior systems, we evaluated the reactions of longer-chain *N*-alkyl cyclic amines and acyclic amines. Borylation of these substrates occurred with the same catalyst as we used for the borylation of *N*-methylamines to form the corresponding 1-aminoalkyl boronate esters in good yields (Table 2). The examples in Table 2 show that borylation of the ethyl groups in amines occurs preferentially over borylation of methyl, propyl, and butyl groups in amines.

To facilitate isolation of the aliphatic boronate esters, the crude products were converted to the corresponding air-stable potassium trifluoroborate salts. In some cases, the yields exceeded 100%, based on the quantity of diboron reagent. These values indicate that the HBpin byproduct also reacts with the amines to form some of the functionalized product (Table 2, entries 1−4).

The C−H borylation of diethylamines, as well as triethylamine, occurred in good yield (entries 1−4) to form aminoethyl boronate esters. The C−H borylation of Et_2NMe occurred exclusively at the primary C−H bonds of the ethyl

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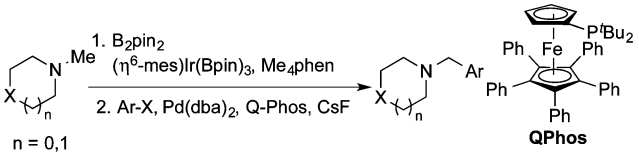
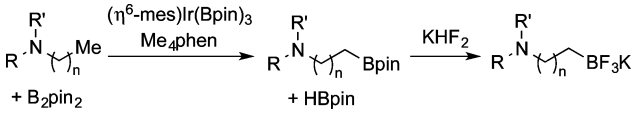
Table 1. One-Pot Borylation and Arylation of Methylamines

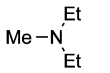
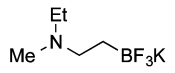
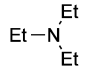
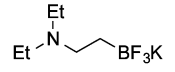
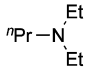
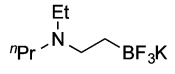
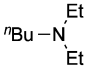
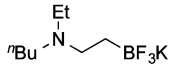
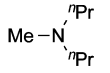
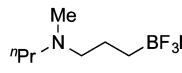
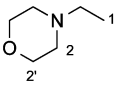
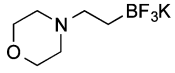
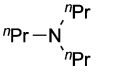
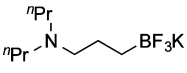


entry	product [a]	entry	product [a]
1	X = Br, 83%	8	X = Br, 75% X = Cl, 75%
2	(55%) [b,c]		
3	X = Br, 72% [c]	9	X = Br, 70% X = Cl, 68%
4	X = Br, 70%	10	X = Br, 64% X = Cl, 45%
5	X = Br, 55% [c]	11	X = Br, 85%
6	X = Br, 78%	12	X = Br, 66%
7	X = Br, 82% X = Cl, 59%	13	X = Br, 69%

[a]Reaction conditions: 1. ArX (1.0 equiv), B_2pin_2 (1.3 equiv), amine (12.0 equiv based on ArX, 9.0 equiv based on B_2pin_2), (η^6-mes)IrBpin$_3$ (4 mol % to B_2pin_2), 3,4,7,8-Me_4phen (4 mol %), neat, 120 °C, 24 h; 2. Ar-X (1.0 equiv), Pd(dba)$_2$ (5 mol % to B_2pin_2), Q-phos (5 mol %), CsF (3 equiv), dioxane:H_2O (5:1), 100 °C, 24 h. The reported yield in this table is the isolated yield based on ArX. Secondary C−H borylation products cannot be avoided in each reaction, but they can be easily separated with the primary C−H borylation product by following Suzuki cross-coupling. [b]Reaction conducted with B_2pin_2 (1.5 equiv), [Ir(COD)OMe]$_2$ (5 mol %), and 3,4,7,8-Me_4phen (10 mol %). [c]Reaction conducted for 48 h.

Table 2. Ir-Catalyzed C−H Borylation of Alkylamines



entry	substrate	product	GC yield of RBpin[a]	isolated yield[b]
1			84%	54%
2			103%	68%
3			108% Et:^{n}Pr = 83:17	79%
4			129% Et:^{n}Bu = 86:14	92%
5			69%[c] ^{n}Pr:Me = 96:4	52%[d]
6			98%[c] 1:(2+2′) = 94:6	74%[d]
7			95%[c]	78%

[a]Reaction conditions: B_2pin_2 (1.0 equiv), amine (9.0 equiv), (η^6-mes)IrBpin$_3$ (2 mol %), 3,4,7,8-Me_4phen (2 mol %), neat, 120 °C, 24 h. Yield determined by gas chromatographic analysis with isododecane as internal standard. The yield is based on the moles of product per mole of B_2pin_2; a yield above 100% reflects the conversion of the HBpin byproduct to the alkylBpin. [b]Isolated as trifluoroborate salt. Conditions: KHF_2 (4.5 M, aq, 4.0 equiv), MeOH, 22 °C, 3 h. Some isolated products contain small quantities (about 8−15%) of KBF_4 impurity. The yields reported are corrected for the amount of this impurity, based on ^{11}B NMR spectroscopy. For details, see the Supporting Information. [c]4 mol % catalyst. [d]Contained 10% of an inseparable impurity by ^{1}H NMR spectroscopy; see Supporting Information for details.

group over the more acidic and weaker C−H bonds of the *N*-methyl position (entry 1). Borylation of Et_2N^nPr and Et_2N^nBu occurred preferentially at the ethyl groups over the longer-chain alkyl groups to give the two types of isomeric products in 83:17 and 86:14 ratios, respectively (entries 3 and 4). The reaction of MeN^nPr_2 occurred selectively at the propyl group, showing that the methyl C−H bonds of *N*-methylamines are the least reactive of the primary C−H bonds in alkylamines (entry 5).

Similarly, borylation of *N*-ethylmorpholine occurred to give one major product resulting from the borylation of the primary C−H bond in the ethyl group (**1**:(**2**+**2′**) = 94:6, entry 6). This selectivity for the primary C−H bond is higher than that for borylation of the methyl group of *N*-methylmorpholine (**1**:(**2**+**2′**) = 80:20). Although borylation at an ethyl group was shown to occur in preference to that at a propyl group, $^nPr_3N$ did undergo borylation in good yield with 4 mol % catalyst loading (entry 7). The origin of this selectivity for reaction at an ethyl group will be discussed later in this paper.

Borylation of Ethers. An Ir-catalyzed borylation of ethers that is analogous to the Ir-catalyzed borylation of amines would be useful because alkoxyalkyl boron compounds are valuable synthetic intermediates. Thus, we evaluated the site selectivity for borylation of the C−H bonds in alkyl ethers.

Borylation of the primary C−H bonds of alkyl ethers occurred in good yields with the same catalyst that led to the functionalization of the primary C−H bonds in alkylamines (Table 3). The catalyst loadings required for borylation of alkyl ethers were lower than those required for borylation of methyl- and ethylamines, and the reactions occurred with high selectivity for the primary C−H bonds of ethyl groups. Alkyl ethyl ethers underwent the borylation reaction with just 1 mol % of the catalyst in good yields. Again, the yields exceeded 100% in some cases based on the quantity of diboron reagent, indicating that the HBpin byproduct reacts with the ethers to form some of the functionalized product (entries 1−4). Borylation of dibutyl ether occurred in good yield, but a higher catalyst loading was required for this reaction than was required for reactions of ethyl ethers (entry 5).[27] Pivalate-protected alcohols also underwent C−H borylation at the ethyl group of

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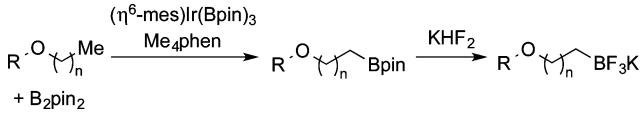
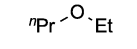
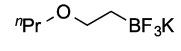
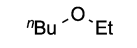
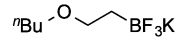
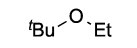
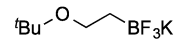
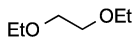
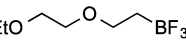
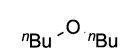
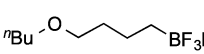
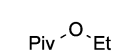
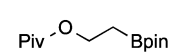
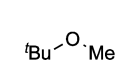
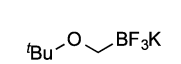
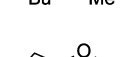
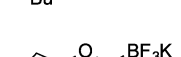
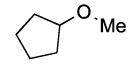
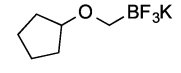
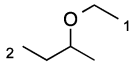
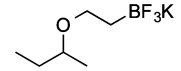
Table 3. Ir-Catalyzed C−H Borylation of Alkyl Ethers



entry	substrate	product	GC yield of RBpin[a]	isolated yield[b]
1			146% Et:^{n}Pr = 85:15	104%
2			130% Et:^{n}Bu = 87:13	101%
3			112%[c]	79%
4			142%	112%
5			118%[d]	99%
6			67%[d,e,f]	60%[g]
7			77%[d,e,h]	56%
8			65%[d,e,h]	52%
9			111% 1:2 = 86:14	86%
10			70%[d]	56%[g]

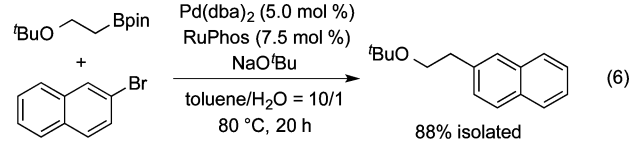
[a]Reaction conditions: B_2pin_2 (1.0 equiv), ether (9.0 equiv), (η^6-mes)IrBpin$_3$ (1 mol %), 3,4,7,8-Me$_4$phen (1 mol %), neat, 120 °C, 24 h. Yield determined by gas chromatographic analysis with isododecane as internal standard. The yield is based on the moles of product per mole of B_2pin_2; a yield above 100% reflects the conversion of the HBpin byproduct to the alkylBpin. [b]Isolated as trifluoroborate salt. Conditions: KHF_2 (4.5 M, aq, 4.0 equiv), MeOH, 22 °C, 3 h. Some isolated products contain small quantities (about 8−15%) of KBF_4 impurity. The yields reported are corrected for the amount of this impurity, based on ^{11}B NMR spectroscopy. For details, see the Supporting Information. [c]36 h. [d]4 mol % catalyst. [e]100 °C. [f]3 h. [g]Isolated as boronate ester. [h]10 h.

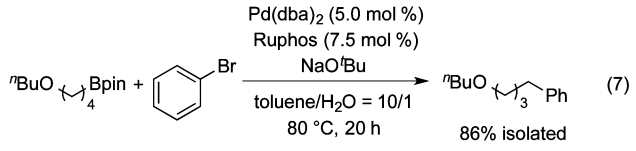
the ether chain, illustrating the potential of the borylation reaction to form α,ω-functionalized products (entry 6).

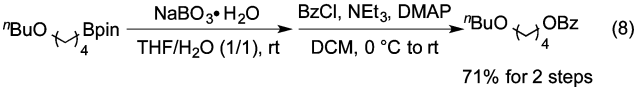
Methyl ethers also underwent C−H borylation. These reactions were selective for borylation at the methyl group (entries 7 and 8) over a *tert*-butyl group or a cycloalkyl group. The products of the borylation of methyl ethers were somewhat unstable to the reaction conditions, leading to a lower yield of the products than was obtained from the borylation of ethers containing longer alkyl chains. This instability was corroborated by the product distribution from the borylation of two methyl positions of *n*-BuOMe over time. During the first 6 h at 100 °C, the selectivity for borylation of *n*-BuOMe was 85:15 in favor of the product from borylation of the methyl group over the primary C−H bond of the butyl group. This selectivity is similar to that for the reaction of *n*-BuOEt, indicating that the rates of borylation of methoxy and ethoxy groups are similar to each other. However, after 10 h, the ratio of the two products was a lower 62:38, and after 16 h the absolute amount of alkoxymethyl boronate was less than that at 10 h, suggesting that decomposition of the product from borylation at the methyl group occurs.

Like the borylation of ethylamines, the borylation of ethyl ethers occurred preferentially at the ethyl group over longer-chain alkyl groups. The reaction of ethyl *n*-propyl and ethyl *n*-butyl ether occurred with 85:15 and 87:13 selectivity for reaction at the ethyl group over the longer-chain alkyl groups, respectively. In addition, the borylation occurred with selectivity for functionalization at the ethyl group of ethers that contain three different types of primary C−H bonds. For example, borylation of ethyl *sec*-butyl ether occurred with 86:14 selectivity for a primary C−H bond of the ethyl group over the less hindered of the two types of primary C−H bonds in the *sec*-butyl group (entry 9). Finally, borylation of ethyl menthyl ether occurred exclusively on the ethyl group (entry 10).

Transformations of the Borylation Products. The boronate esters generated from borylation of C−H bonds in ethyl and butyl ethers can be converted into further functionalized products resulting from cross-coupling and oxidation. The pinacolate esters of ethoxy- and butoxyboronic acids underwent Suzuki−Miyaura cross-coupling with aryl bromides under conditions reported recently by Steel, Marder, and Liu (eqs 6 and 7).[28] In addition, oxidation of the product from borylation of dibutyl ether occurred under standard conditions in good yield (eq 8).







Competition Experiments. To gain a clearer view of the relative rate of borylation of a primary C−H bond in an ether versus an alkane, we conducted the reaction of a mixture of *n*-BuOEt and octane (Et_2O is too volatile to ensure the correct concentrations under these conditions). The C−H borylation occurred preferentially with the C−H bonds of the ether over the C−H bonds of octane to give an 84:12:4 ratio of the functionalized products, reflecting a 96:4 ratio of products from functionalization of the ether over those from functionalization of the alkane (eq 9). Thus, the primary C−H bonds in both alkoxy groups of the ether are substantially more reactive toward this borylation process than is the primary C−H bond of an alkyl group.

We also evaluated the relative rate of borylation of a methyl C−H bond in an ether versus that in an amine by conducting the reaction of a mixture of *n*-PrOEt and *n*-PrNEt$_2$. The rate of borylation of the C−H bonds in the ether was similar of that in the amine. A 44:56 ratio of the products was formed from functionalization of the ether and amine (eq 10; the ratios

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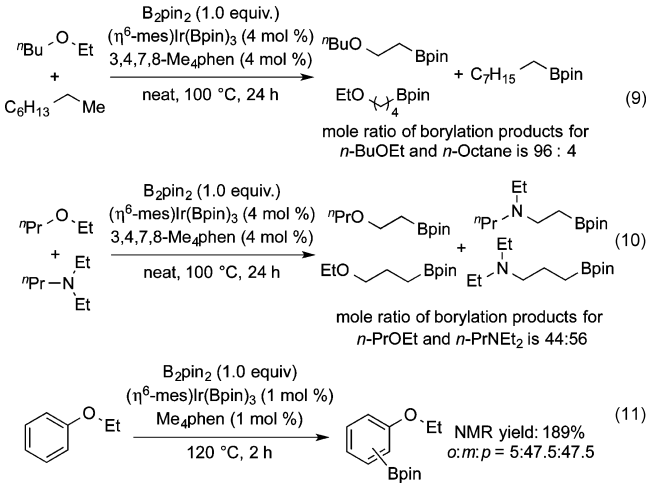
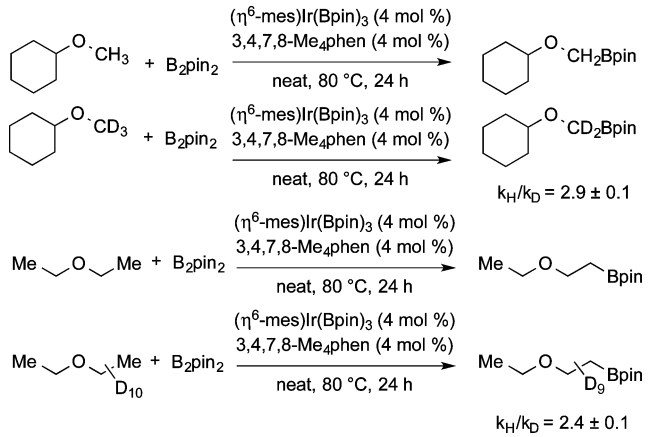


within the ether and amine were ethyl ether:*n*-propyl ether = 37:7; ethylamine:*n*-propylamine = 47:9)

Because the terminal C−H bonds in ethyl ethers and ethylamines are more reactive than other C−H bonds in ethers and amines, we determined whether these aliphatic C−H bonds were even more reactive than aromatic C−H bonds. To do so, we studied the borylation of ethyl phenyl ether. This reaction formed the product from borylation of the aromatic C−H bonds, with an *o*:*m*:*p* ratio of 5:47.5:47.5 (eq 11). This result shows that the reactivity of a methyl C−H bond β to oxygen in an ether lies between that of an unactivated alkyl C−H bond and that of an unactivated aryl C−H bond.

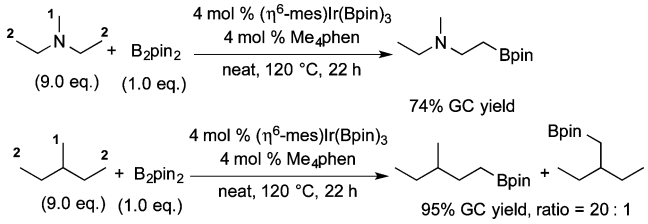
Kinetic Isotope Effects (KIEs). To gain insight into the origin of the site selectivity, we sought to determine if the C−H bond-cleavage step was irreversible and controlling the site selectivity or if the C−H bond-cleavage step was reversible, and a step after C−H bond cleavage was controlling the selectivity. To do so, we measured the KIE for borylation of methyl and ethyl ethers. A primary KIE of 2.9 at 100 °C was observed for the C−H borylation of cyclohexyl methyl ether and cyclohexyl methyl ether-d_3 conducted in separate vessels. A similar primary KIE of 2.4 was observed for the C−H borylation of diethyl ether and diethyl ether-d_{10} in separate vessels (Scheme 1). This primary KIE implies that the C−H bond-cleavage step is irreversible and the step during which site selectivity is determined.

Scheme 1. Kinetic Isotope Effects for Borylation of Methyl and Ethyl Ethers



Regioselectivity of the Borylation of Diethyl Methylamine. To gain further information on the origin of the regioselectivity of this iridium-catalyzed borylation, we conducted the borylation of 3-methylpentane, which has a structure that is similar to that of diethyl methylamine. The major product resulted from borylation of the terminal C−H bond in the ethyl group over borylation of the methyl group to give two constitutional isomers in a ratio of 20:1 (Et:Me, Scheme 2). This result suggests that steric hindrance is one

Scheme 2. Borylation of 3-Methylpentane



factor that causes the methyl group to be less reactive than the ethyl group in diethyl methylamine toward the present iridium-catalyzed borylation. Other factors that influence the regioselectivity will be discussed in detail in the section describing computational studies.

COMPUTATIONAL RESULTS

To understand the origins of the selectivity for borylation of C−H bonds located α and β to the oxygen and nitrogen atoms of ethers and amines, we evaluated the steps that cleave the C−H bonds and form the C−B bonds by DFT calculations. We sought to reveal the origin of the differences in rates for C−H bond cleavage and C−B bond formation at the α and β positions.

To do so, we first computed the overall potential energy surface for the C−H borylation of triethylamine. These calculations were conducted with the Me_4phen-ligated iridium-trisboryl complex (Figure 1) as the active catalyst. This complex is the Me_4phen analogue of the trisboryl intermediate in the C−H borylation of arenes catalyzed by $[Ir(OMe)(COD)]_2$ and di-*tert*-butylbipyridine.[29,30] We propose that the reaction occurs by a similar boron-assisted

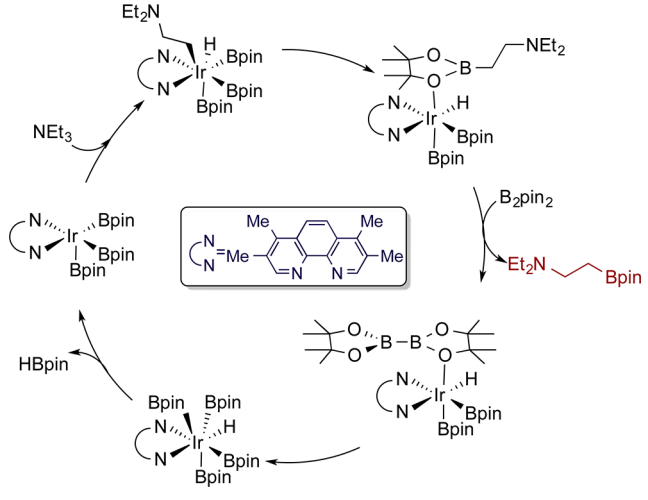


Figure 1. Proposed mechanism of the borylation of triethylamine.

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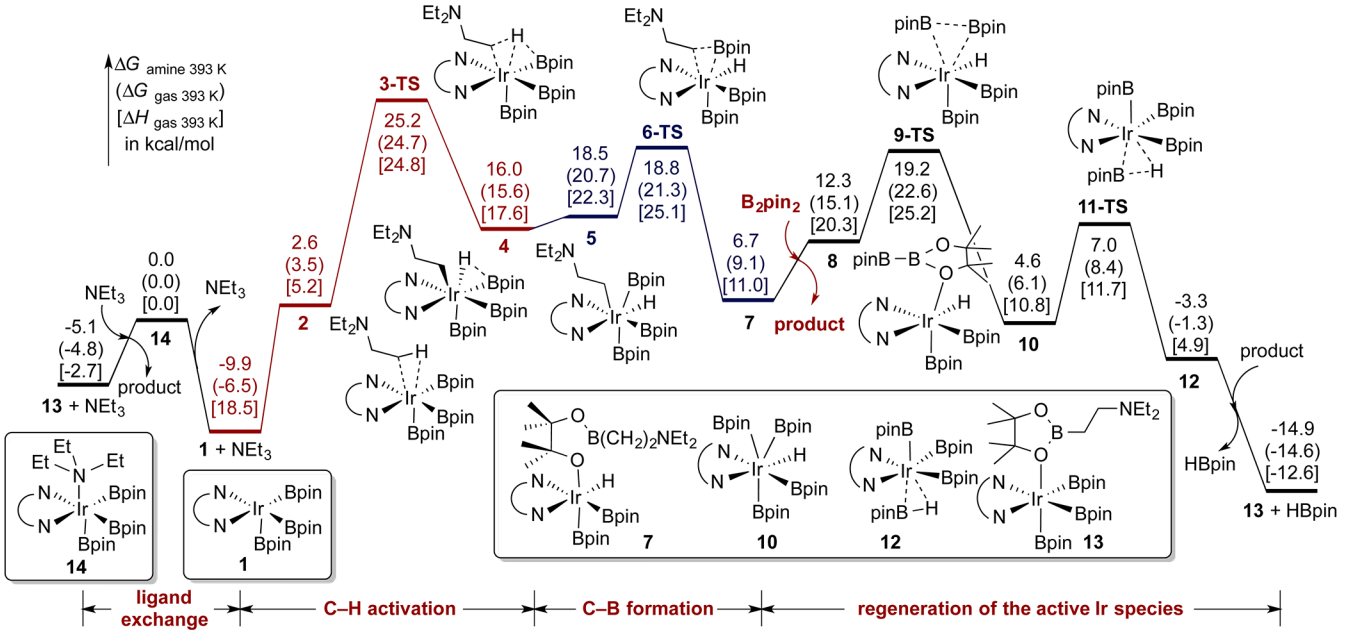

Figure 2. Potential energy surface for the borylation of triethylamine.

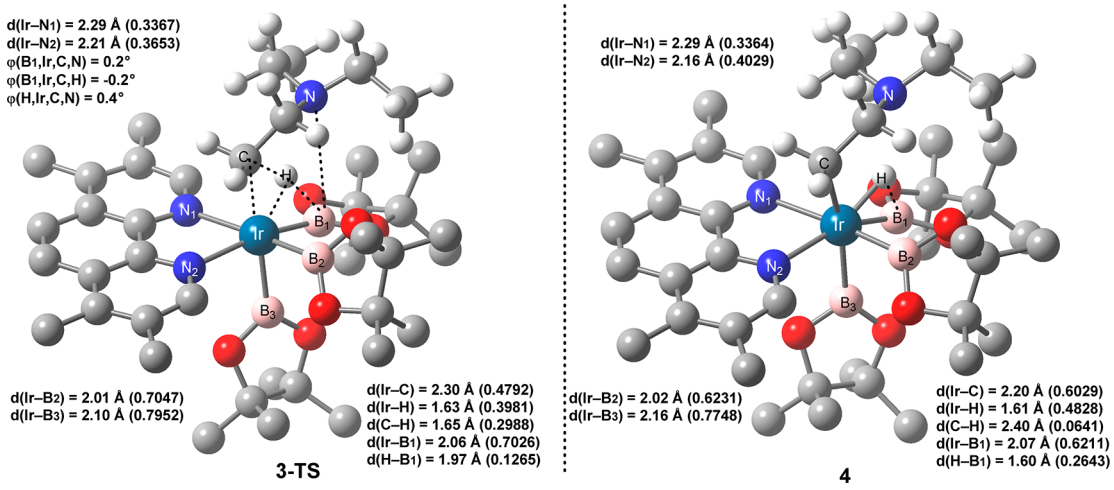

Figure 3. Structures of the transition state for C–H bond cleavage **3-TS** and of the Ir–H intermediate **4**. The hydrogen atoms in 3,4,7,8-Me_4phen and Bpin ligands are deleted for clarity. The data in parentheses are the bond order for the corresponding bond.

oxidative addition of the C–H bond and reductive elimination of the C–B bond that has been computed to occur for the borylation of arenes.[31,32] A combination of product displacement by B_2pin_2, oxidative addition of the diboron compound, and reductive elimination of HBpin would regenerate the catalyst.

Potential Energy Surface for the Borylation of Triethylamine. We computed the potential energy surface for the borylation of triethylamine by the mechanism shown in Figure 1, and this surface is represented in Figure 2. The key steps in this borylation process are ligand exchange, C–H bond cleavage, C–B bond formation, and regeneration of the iridium–trisboryl complex.

A single turnover begins with ligand exchange between the substrate and the iridium complex **13** containing bound product (generated by the previous catalytic cycle) to yield the iridium complex **14** containing bound substrate. To release the reactive iridium complex **1**, the substrate must dissociate from the iridium center in complex **14** to generate complex **1** and the free substrate. This ligand exchange step is endergonic by 4.8 kcal/mol.

The key bond-cleaving and bond-forming steps occur after this initial generation of 16-electron complex **1**. In contrast to the rate-determining step of the rhodium-catalyzed borylation of alkanes,[18] the rate-determining step of the iridium-catalyzed C–H borylation of the amine is the C–H bond-cleavage step, not the C–B bond-forming step. The overall activation free energies of the C–H bond-cleavage (via **3-TS**) and C–B bond-forming (via **6-TS**) steps are 35.1 and 28.7 kcal/mol, respectively.[33] The C–H bond-cleavage step is assisted by the adjacent B1 atom (Figure 3) to generate an Ir(V) species **4**, in which the activated hydrogen atom is partially coordinated to the same boron atom B1 as in **3-TS**. The C–B bond-forming step generates complex **7** containing bound alkyboronate ester.

To regenerate the active iridium–trisboryl complex, a ligand exchange between complex **7** and B_2pin_2 occurs. This step is endergonic by 5.6 kcal. After this ligand exchange, the oxidative addition of B_2pin_2 and the reductive elimination of HBpin

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occur. These steps are facile and have free-energy barriers of just 6.9 and 2.4 kcal/mol from intermediates **8** and **10**, respectively. After the release of HBpin, a more stable complex **13** forms between the iridium center and the product.

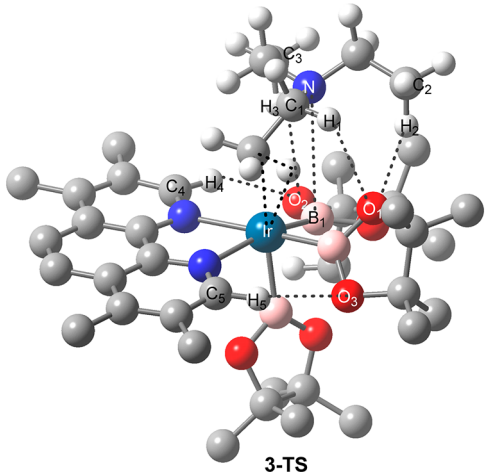
In our prior paper on the borylation of the secondary C−H bonds in cyclic ethers catalyzed by the same iridium catalyst, we speculated that the high selectivity for borylation of the secondary C−H bond β to the oxygen atoms of cyclic ethers results from the coordination of the Lewis basic oxygen atom of the cyclic ether to the Lewis acidic boryl ligand to form a five-membered ring in the transition state.[23] However, we had not obtained any experimental data or conducted computations to evaluate this hypothesis.

Our current computations reveal a more complex set of interactions between the substrate and the catalyst that controls selectivity. As shown in Figure 3, the transition state of the C−H bond-cleavage step, **3-TS**, adopts a structure in which the iridium center, the C−H bond undergoing cleavage, the Lewis acidic boron atom B1, and the Lewis basic nitrogen atom in the substrate lie in nearly the same plane. This coplanarity is revealed by the dihedral angles of φ(B1,Ir,C,N), φ(B1,Ir,C,H), and φ(H,Ir,C,N), which are 0.2°, −0.2°, and 0.4°, respectively. This unique structure alignment allows the Lewis acidic boron atom B1 to play two important roles in the C−H activation step.

First, the boron atom B1 interacts with the hydrogen atom of the activated C−H bond. The distance of the hydrogen atom of the activated C−H bond and the B1 atom in the boryl ligand is 1.97 Å. According to the natural bond orbital (NBO) analysis, the bond order between the hydrogen atom and the boron atom is 0.1265, indicating that the C−H activation step is assisted by this boryl ligand.[34]

Second, the Lewis acidic B1 atom in the boryl ligand interacts with the Lewis basic nitrogen atom of the triethylamine substrate in the transition state **3-TS**. The orientation of the B1 and N atoms in **3-TS** suggests that a similar coordination occurs between the Lewis basic nitrogen atom of the amine and the Lewis acidic boryl ligand because the nitrogen atom in triethylamine lies directly above the plane of the B1 atom in the boryl ligand. The dihedral angle of φ(B1,Ir,C,N) is only 0.2°. However, this stabilizing effect in the transition state for C−H bond cleavage is low because the distance between the B1 and N atoms is long (3.55 Å, with a bond order of only 0.0079 between N and B). Indeed, NBO second-order perturbation analysis indicates that the stabilizing effect from coordination of the amine to the B1 center in the transition state **3-TS** is small (0.6 kcal/mol).

This alignment of atoms in **3-TS** creates a structure with a series of C−H···O interactions[35] between the substrate and the oxygen atoms in the boryl ligand. The distances between the hydrogen and the oxygen atoms listed in Figure 4 are all shorter than the sum of their van der Waals radii (2.72 Å).[36] Using NBO second-order perturbation analysis, we computed the stabilizing energy provided by these C−H···O interactions between the triethylamine substrate and the boryl ligands. These values are 0.7 (C1−H1···O1), 1.0 (C2−H2···O1), and 1.2 kcal/mol (C3−H3···O2). The sum of the energies of these C−H···O interactions is larger than the energy of the weak Lewis acid−base interaction mentioned above. In addition to the C−H···O interactions between the substrates and the boryl ligands, we identified significant C−H···O interactions between the Me_4phen ligand and the boryl ligands (2.8 kcal/mol for C4−H4···O2, and 0.7 kcal/mol for C5−H5···O3). Differences



3-TS

C−H···O interaction	E_{NBO}(C-H activation TS) (in kcal/mol)	d(C−O) (in Å)	d(O−H) (in Å)	∠(C−H−O)
C1−H1···O1	0.7	3.25	2.49	125.0°
C2−H2···O1	1.0	3.31	2.51	128.9°
C3−H3···O2	1.2	3.57	2.50	163.9°
C4−H4···O2	2.8	3.18	2.26	140.0°
C5−H5···O3	0.7	3.39	2.46	142.1°

Figure 4. C−H···O interactions in the transition state for C−H bond cleavage, **3-TS**.

between the strengths of the C−H···O interactions between the C−H of the Me_4phen ligand and the boryl oxygen atoms in the different transition states appear to affect the selectivity of the C−H bond-cleavage steps (vide infra).

Regioselectivity of the Borylation of Diethyl Methylamine. Because borylation at the terminal C−H bond of the ethyl group in diethyl methylamine occurred *exclusively* over borylation of the methyl group, whereas borylation of the ethyl group in 3-methylpentane was only 20 times more reactive than that of the methyl group, we considered that attractive interactions like those in the transition state computed for the borylation of triethylamine might account for the particularly high selectivity for reaction at the ethyl group in mixed *N*-alkyl ethylamines. Because the C−H bond-cleavage step is irreversible, we analyzed the differences in energies and structures of the transition states for C−H bond cleavage of the different primary C−H bonds in diethyl methylamine to understand the regioselectivity of the borylation of mixed alkylamines.

We located four transition states for C−H bond cleavage at the primary C−H bonds of the methyl and ethyl groups of diethyl methylamine. The two transition states for activation of the primary C−H bonds of the methyl group (**15-TS-Me-a**) and the primary C−H bonds of the ethyl group (**15-TS-Et-a**) with the amine oriented proximal to one of the boryl ligands are shown at the top of Figure 5. The barrier for C−H bond cleavage at the ethyl group via **15-TS-Et-a** was computed to be 7.3 kcal/mol lower than that for C−H bond cleavage at the methyl group via **15-TS-Me-a**. Significant differences were identified between the structures of these two transition states. A weak Lewis acid−base interaction and several C−H···O interactions between the substrate and the boryl ligands were observed in transition state **15-TS-Et-a**, but neither class of interaction was found in the computed transition state **15-TS-Me-a**. Moreover, in **15-TS-Me-a**, the C−H···O interactions

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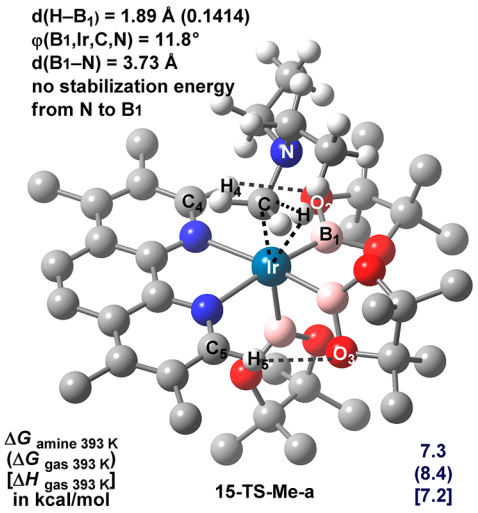
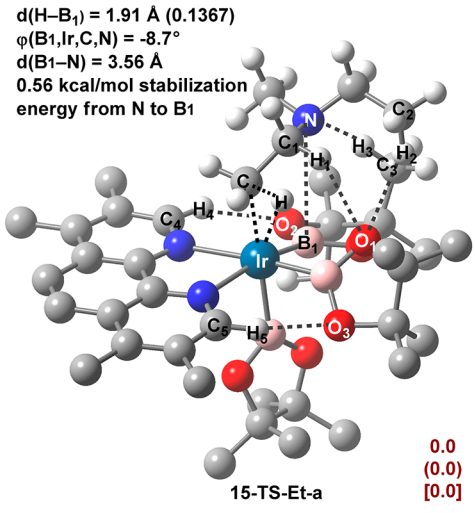
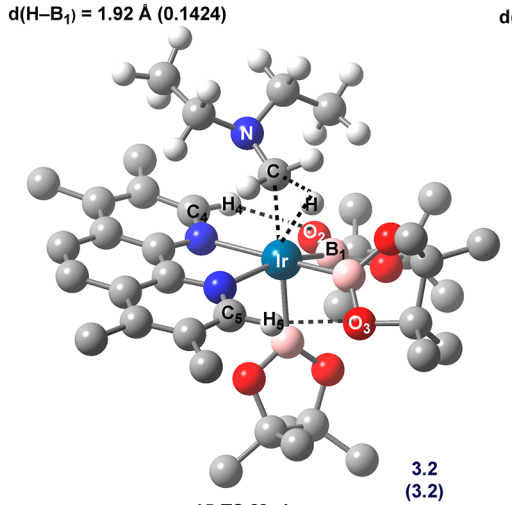


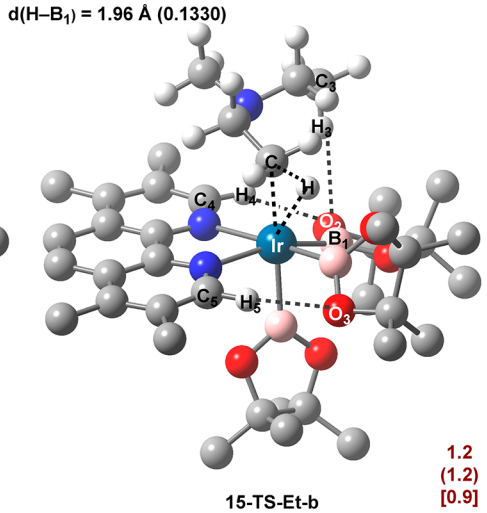
C–H···O interaction	E_{NBO}(C-H activation TS) (in kcal/mol)	d(C–O) (in Å)	d(O–H) (in Å)	∠(C–H–O)
C4–H4···O2	2.4	3.25	2.32	141.8°
C5–H5···O3	0.9	3.35	2.43	142.1°



C–H···O interaction	E_{NBO}(C-H activation TS) (in kcal/mol)	d(C–O(N)) (in Å)	d(O(N)–H) (in Å)	∠(C–H–O(N))
C1–H1···O1	0.7	3.25	2.47	127.1°
C6–H2···O1	0.7	3.36	2.59	126.3°
C3–H3···N	0.7	3.65	2.68	147.8°
C4–H4···O2	2.7	3.19	2.28	139.6°
C5–H5···O3	1.6	3.32	2.39	141.3°



C–H···O interaction	E_{NBO}(C-H activation TS) (in kcal/mol)	d(C–O) (in Å)	d(O–H) (in Å)	∠(C–H–O)
C4–H4···O2	2.5	3.19	2.29	138.7°
C5–H5···O3	1.7	3.33	2.39	143.3°



C–H···O interaction	E_{NBO}(C-H activation TS) (in kcal/mol)	d(C–O) (in Å)	d(O–H) (in Å)	∠(C–H–O)
C3–H3···O2	1.0	3.61	2.55	163.4°
C4–H4···O2	2.1	3.21	2.32	137.2°
C5–H5···O3	1.3	3.35	2.43	140.7°

Figure 5. Transition states for C−H bond cleavage at the terminal C−H bond in methyl and ethyl groups of diethyl methylamine.

between the Me_4phen ligand and the two boryl ligands in the same plane are weaker than those in **15-TS-Et-a**.

We also located two transition states for cleavage of the methyl and ethyl C−H bonds of the diethyl methylamine in which the amine lies in a position that avoids steric hindrance between the substrate and the boryl ligand. These two transition states are shown at the bottom of Figure 5 and are labeled as **15-TS-Me-b** and **15-TS-Et-b**. The computed barrier for the C−H bond cleavage at the methyl group via **15-TS-Me-b** is 4.1 kcal/mol lower than that via **15-TS-Me-a**. The lower activation energy for C−H bond cleavage via **15-TS-Me-b** results from less steric hindrance between the methylamino moiety of the substrate and the boryl ligands, as well as stronger C−H···O interactions between the Me_4phen and the boryl ligands (4.2 kcal/mol in **15-TS-Me-b** vs 3.3 kcal/mol in **15-TS-Me-a**). In contrast to the relative energies of the transition states for cleavage of the methyl C−H bonds, the computed barrier for cleavage of the primary C−H bond of the ethylamino moiety via **15-TS-Et-b** is 1.2 kcal/mol higher in free energy than that via **15-TS-Et-a**. Because **15-TS-Et-a** has greater steric interactions, this result further implies that the weak Lewis acid−base interaction between the nitrogen atom in the ethylamine moiety and boron atom B1 in the boryl ligand and the set of C−H···O interactions stabilizes the transition state for cleavage of the primary C−H bond in the aminoethyl moiety.

To assess further the origins of the selectivity for reactions occurring at different primary C−H bonds of mixed alkyl-

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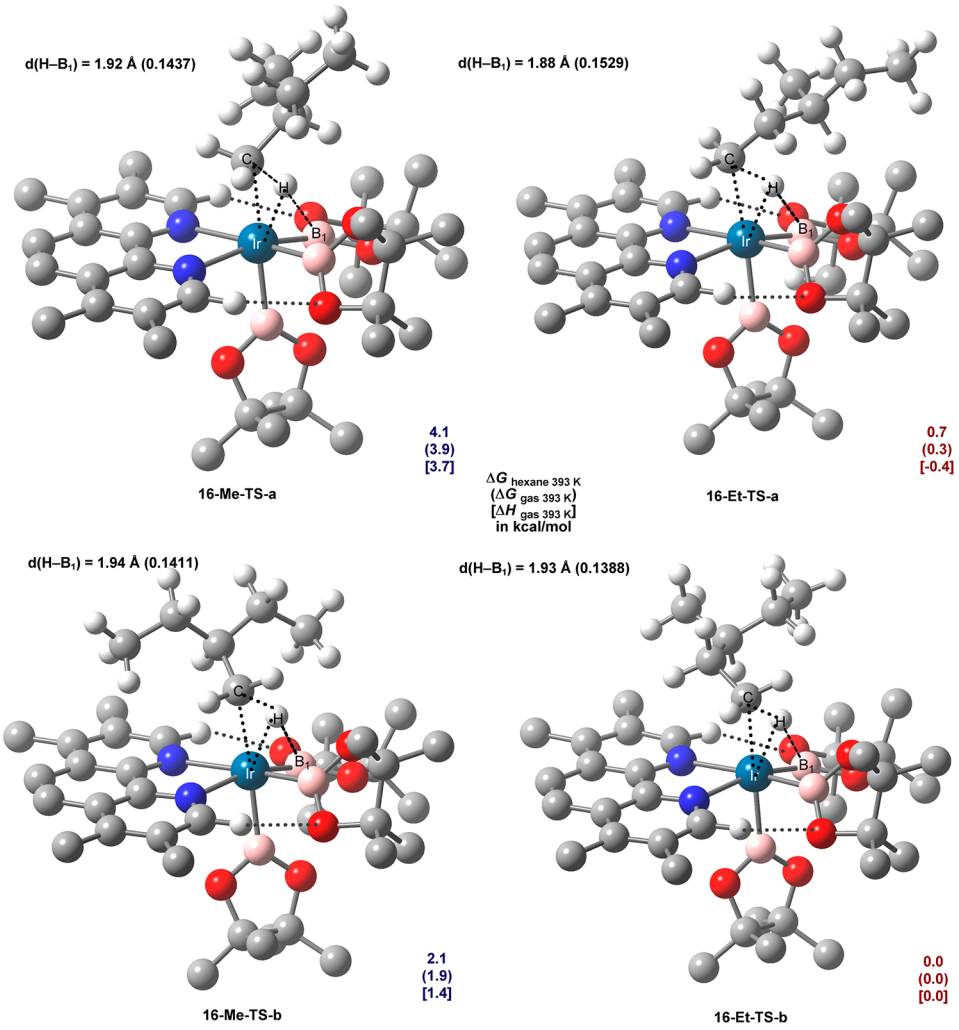

Figure 6. Transition states for cleavage of the terminal C–H bonds in 3-methylpentane.

amines, we calculated the transition states for cleavage of the primary C–H bonds in 3-methylpentane. The transition state for cleavage of the C–H bond of 3-methylpentane at the ethyl group via **16-TS-Et-b** (Figure 6, bottom right), which contains the substrate lying between the Me_4phen ligand and the boryl ligand, is lower in energy than the transition state **16-TS-Et-a** (Figure 6, top right), in which the substrate is positioned above the plane of the boron in the boryl ligand. These relative energies are the opposite of the relative energies of the analogous transition states for cleavage of the primary ethyl C–H bonds in the amine. Because there is no Lewis acid–base interaction involving the alkane, these relative energies are consistent with an influence of the Lewis acid–base interaction on the energy of the transition state for cleavage of the ethyl C–H bond of the amine.

Like the relative energies for transition states **16-TS-Et-a** and **16-TS-Et-b**, the transition state for C–H bond cleavage at the more hindered methyl group of this alkane via **16-TS-Me-b** (Figure 6, bottom left), in which the substrate lies between the Me_4phen ligand and the boryl ligand, is lower in energy than the transition state **16-TS-Me-a** (Figure 6, top left), in which the substrate is positioned above the plane of the boron in the boryl ligand. As a result of the absence of the effect of attractive Lewis acid–base and C–H···O interactions, the calculated activation free energy for cleavage of the ethyl C–H bond (position 2 in Scheme 2, via **16-TS-Et-b**) is lower than that for cleavage of the methyl C–H bond (position 1 in Scheme 2, via **16-TS-Me-b**) by only 2.1 kcal/mol. This difference in activation free energies is consistent with the observation of two constitutional isomers in a 20:1 ratio (Et:Me) (Scheme 2).

Thus, our computational results analyzing the origin of the higher reactivity of the terminal C–H bonds at the β position of the nitrogen atom than that at the α position toward iridium-catalyzed borylation indicate that both repulsive and attractive interactions affect the rates and selectivities of the C–H bond functionalization. In each transition state, there is a steric repulsion between the boryl ligand and the alkyl groups of the amine or alkane. However, a detailed comparison of the origins of selectivity for reaction of an alkane and an alkylamine suggests that attractive interactions contribute to the difference in free energy barriers to formation of isomeric products.

In each transition state, there is an attractive C–H···O interaction between the 2- and 9- hydrogens of the phenanthroline ligand and the oxygen atom of a boryl group, and the strength of this interaction varies with the structural changes in the transition state of the C–H bond-cleavage step. In the most favorable transition states for C–H bond cleavage of the ethylamines, a series of attractive C–H···O interactions between the C–H bonds in the substrate and the oxygen atoms of the boryl ligands were found by computation. The

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stabilization energies of these C−H···O interactions sum to 2.9 and 2.1 kcal/mol in the transition state for cleavage of the primary ethyl C−H bonds of triethylamine and diethylmethylamine, respectively. These computed transition states also contain weak Lewis acid−base interactions between the boron atom of a boryl group and the nitrogen atom of the amine.

In contrast, these stabilizing C−H···O interactions and weak Lewis acid−base interactions are not observed in the computed transition state for cleavage of the methyl C−H bond of diethyl methylamine. The absence of these interactions contributes to making the transition state for cleavage of this primary C−H bond higher in energy than that for cleavage of the primary C−H bond of the ethyl group. A similar combination of interactions is likely affecting the rates and selectivities of the reactions of ethers.

CONCLUSION

We reported the C−H borylation of alkylamines and ethers to produce aliphatic boron compounds that can be difficult to produce through traditional methods. These studies show that the high reactivity observed for borylation of the β-position of cyclic ethers extends to borylation of acyclic ethers and amines. The aminomethyl boronate ester product from borylation of *N*-methyl groups directly undergoes Suzuki−Miyaura cross-coupling reactions, while the products from borylation of the acyclic alkylamines and alkyl ethers were readily converted to the stable trifluoroborate salts.

Experimental data and computational studies indicate that C−H bond cleavage is the rate-determining step of this Ir-catalyzed borylation reaction of alkyl C−H bonds. Computational studies indicate that the higher reactivity of C−H bonds at the terminal position of ethylamines and ethers observed experimentally results from a transition state structure for cleavage of the primary ethyl C−H bond in which the heteroatom lies directly above the boron atom in the boryl ligand. The weak attractive Lewis acid−base interaction in this structure, along with attractive C−H···O interactions between the substrate and the boryl ligand, are likely leading to the faster rates for borylation of amines and ethers than for borylation of alkanes. We assert that such attractive interactions will likely be found to affect the regioselectivity and stereoselectivity of a range of reactions of substrates containing functional groups as methods to compute such interactions become used more widely.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectra for all new compounds, and coordinates for the computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[§]Q.L. and C.W.L. contributed equally.

Notes

The authors declare no competing financial interest.

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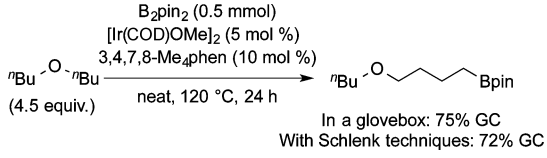

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(33) The overall free energy of activation for C−H bond-cleavage (via **3-TS**) of triethylamine is calculated to be 35.1 kcal/mol at 393 K. This value is somewhat higher than the measured experimental activation bairrier of 31.0 kcal/mol. To assess the effect of the basis sets on this difference, we computed the activation energy using the lanl2tz-f basis set for iridium and 6-311++g** basis set for other atoms. Because our reactants consist of 120 atoms, it was not feasible to optmize all structures with these higher basis sets. However, with these basis sets, we computed the single-point energies for C−H activation of triethylamine and for C−B reductive elimination of the functionalized product from the structures that had been optimized with lanl2dz for iridium and 6-31g** for other atoms. The overall activation free energies of the C−H bond-cleavage (via **3-TS**) and C−B bond-forming (via **6-TS**) steps were computed to be 31.8 and 25.7 kcal/mol, respectively. The computed free energy of activation at these levels is remarkably close to the estimated experimental value. Moreover, the free energy of activation for the C−H bond cleavage is higher than that of the C−B bond-forming steps from the calculation at the higher level. However, the computed difference in free energy (3.2 kcal/mol) from the single-point calculation with the higher basis sets agreed less with the 20:1 experimental ratio than did the calculation with the lower basis set, although the difference was small (1.1 kcal/mol). For consistency, and because of the small differences, we have reported the values for the ground state and activation energies of structures with energies and geometries optimized using the lanl2dz basis set for iridium and 6-31g** basis set for the other atoms.
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