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Iridium-Catalyzed Borylation of Secondary C−H Bonds in Cyclic Ethers

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Supporting Information

ABSTRACT: The borylation of secondary C−H bonds, specifically secondary C−H bonds of cyclic ethers, with a catalyst generated from tetramethylphenanthroline and an iridium precursor is reported. This borylation occurs with unique selectivity for the C−H bonds located β to the oxygen atoms over the weaker C−H bonds located α to oxygen atoms. Mechanistic studies imply that the C−H bond cleavage occurs directly at the β position rather than at the α position followed by isomerization of a reaction intermediate.

The selective cleavage and functionalization of C−H bonds by transition-metal complexes offers new strategies for the formation of fine chemicals and complex molecules from relatively simple starting materials. One of the greatest challenges associated with C−H functionalization reactions is to achieve high selectivity for a single C−H bond among many related types of C−H bonds. Thus, new catalytic reactions that functionalize C−H bonds with novel selectivities are being actively sought.

Many of the current methods to functionalize aliphatic C−H bonds selectively occur with a group that chelates to a metal center and directs the C−H functionalization[1,2] or with C−H bonds that are inherently more reactive based on electronic effects.[3,4] For instance, insertion reactions with carbenes typically occur at the most electron-rich C−H bond. Although these strategies for C−H functionalization lead to selective transformations, the scope of such transformations is limited to substrates that contain a chelating group in close proximity to the C−H bond that becomes functionalized or a C−H bond that is inherently more reactive based on the electronic properties of the substrate.

Our laboratory previously reported the functionalization of aliphatic C−H bonds with metal-boryl catalysts and discrete complexes in which high selectivity for terminal C−H bonds was observed.[5] Rhodium and ruthenium catalysts that contain pentamethylcyclopentyldienyl ligands (Cp*) catalyzed the formation of 1-alkylboronate esters from alkanes and diboron or borane reagents.[6−8] The selectivity of these aliphatic C−H borylation processes is controlled by the steric properties of the substrate, and we recently delineated the origin of this steric control.[9] Although the borylation of aliphatic C−H bonds with Cp*Rh catalysts occurs in high yields, the exquisite selectivity of this catalyst for reactions of primary C−H bonds has precluded the borylation of secondary C−H bonds with this system, and no subsequent catalyst has been reported that functionalizes secondary C−H bonds with boron reagents.

Here, we describe the development of an iridium−phenanthroline catalyst that functionalizes secondary C−H bonds for the first time in good yield. In particular, cyclic ethers undergo borylation with a unique selectivity. Prior C−H activation[10,11] and functionalization[4] of cyclic ethers has occurred at the weaker C−H bond α to oxygen. This C−H borylation occurs at the C−H bond β to oxygen.

Initially, we sought to identify conditions for the iridium-catalyzed borylation of alkyl C−H bonds by evaluating the reactivity of several catalysts for the reaction of *n*-octane with bis(pinacolato)diboron (B_2pin_2). Recent studies on the reactivity of Ir-trisboryl complexes toward aromatic C−H bonds[12,13] showed that more electron-rich iridium-trisboryl complexes react faster with aromatic C−H bonds than do less electron-rich complexes, while Ir-trisboryl complexes containing bulky phosphine ligands react much more slowly with aromatic C−H bonds than do complexes containing bipyridine ligands. On the basis of these observations with arene substrates, we proposed that Ir complexes containing planar, strongly electron-donating bidentate ligands could catalyze the borylation of aliphatic C−H bonds.

Although the combination of $[Ir(COD)OMe]_2$ (COD = cyclooctadiene) and 4,4′-di-*tert*-butylbipyridine (dtbpy) catalyzes the borylation of arenes at low temperatures with high turnover numbers, no alkylborane products were observed from the reaction of *n*-octane with B_2pin_2 in the presence 5 mol % $[Ir(COD)OMe]_2$ and 10 mol % dtbpy. A series of reactions of *n*-octane with B_2pin_2 in the presence of $[Ir(COD)OMe]_2$ and various ligands containing imine, pyridine, and *N*-heterocyclic carbene moieties[14] showed that the combination of $[Ir(COD)OMe]_2$ and phenanthroline ligands gave the product of alkane borylation. The borylation of *n*-octane in the presence of 10 mol % of a combination of $[Ir(COD)OMe]_2$ and 1,10-phenanthroline (phen) gave the 1-octylboronate ester product in 45% yield. However, the borylation of octane with a catalyst ligated by the more strongly electron-donating ligand 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4phen) at 120 °C gave a high 88% yield of the 1-octylboronate ester product (eq 1), consistent with the hypothesis that more electron-rich boryl complexes catalyze C−H bond functionalization more readily than less electron-rich boryl complexes.[15,16] The reaction of *n*-octane under these conditions occurs with the same high

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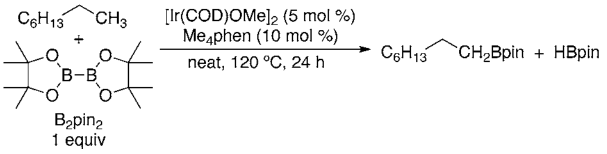
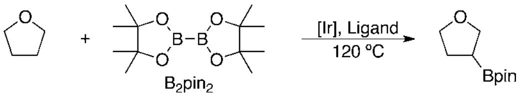


(1)

selectivity for the borylation of primary C−H bond that is observed with rhodium and ruthenium catalysts.

Most striking, reactions of octane in tetrahydrofuran (THF) catalyzed by Me$_4$phen and [Ir(COD)OMe]$_2$ showed that this system also catalyzes the borylation of secondary C−H bonds. The reaction of THF with B$_2$pin$_2$ in the presence of 10 mol % of this catalyst combination at 120 °C formed 3-boryl tetrahydrofuran in 70% yield (Table 1, entry 1). Again, the borylated product was formed in lower yield from reactions with phen as the ligand (entry 2) than from those with Me$_4$phen as the ligand. A significantly higher yield was observed from reactions conducted with (η^6-mes)IrBpin$_3$ (mes = mesitylene) as the source of iridium, presumably due to the formation of the active catalyst in a higher yield with a preformed trisboryl complex than with a species that must convert to a boryl complex before catalysis occurs (entry 3). The reaction also occurred with 5 equiv of THF in the presence of an inert solvent, but a lower yield of the boronate ester was observed (entry 4).

Table 1. Borylation of Tetrahydrofuran

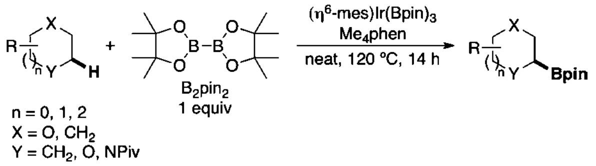


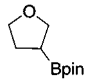
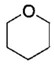
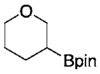
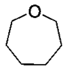
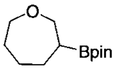
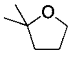
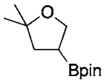
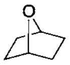
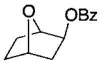
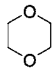
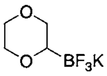
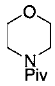
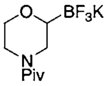
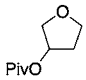
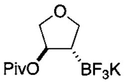
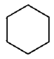
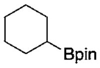
entry	source of Ir	ligand	catalyst	yield (%)[a]
1	[Ir(COD)OMe]$_2$	Me$_4$phen	10 mol %	70
2	[Ir(COD)OMe]$_2$	phen	10 mol %	48
3	(η^6-mes)IrBpin$_3$	Me$_4$phen	4 mol %	104
4	(η^6-mes)IrBpin$_3$	Me$_4$phen	4 mol %	72[b]

[a]Yield of boronate ester based on B$_2$pin$_2$ as determined by gas chromatographic analysis. [b]Reaction was conducted in isododecane as solvent with 5 equiv of THF.

The scope of this C−H borylation of secondary C−H bonds in cyclic ethers catalyzed by Me$_4$phen and (η^6-mes)IrBpin$_3$ is shown in Table 2. The borylation of five-, six-, and seven-membered cyclic ethers all proceeded in good yield (entries 1−3). In all cases, the C−H functionalization occurred with high selectivity at the position β to oxygen. The functionalization of tetrahydropyran at the β-position implies that the selectivity for β-borylation arises from an enhanced reactivity of the catalyst for this type of C−H bond, rather than a decreased reactivity of the catalyst toward the α C−H bonds. Even reaction of the seven-membered ether hexamethylene oxide occurred with almost exclusive selectivity at a C−H bond β to oxygen, further demonstrating the enhanced reactivity of this position for the iridium catalyst. Further work is needed to achieve the borylation of smaller-ring oxygen heterocycles. The borylation of oxetanes occurred, but the products were unstable to the reaction conditions leading to low yields; the borylation of epoxides did not occur under the conditions for the borylation of the substrates in Table 2.

Table 2. Borylation of Secondary C−H Bonds



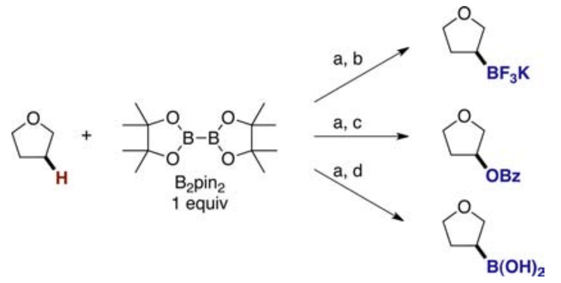
Entry	Reactant	Product	Catalyst (mol %)	Yield (%)[a]
1			4	83
2			4	90
3			6	72[b]
4			4	61
5			6	63[c,d]
6			4	64[e]
7			8	41[e,f]
8			6	40[e]
9			10	39[g]

[a]Yield of isolated secondary boronate ester product following purification by silica-gel chromatography. [b]10:1 ratio of products was observed by GC. [c]Isolated as the protected alcohol. [d]10:1 ratio of products by GC. [e]Isolated as the trifluoroborate salt. [f]Reaction conducted with 5 equiv of substrate in Cy-H. [g]Reaction conducted at 140 °C; yield determined by gas chromatography.

The C−H borylation also occurred with substituted cyclic ethers. C−H borylation occurred with both 2,2- and 2,5-disubstituted cyclic ethers in good yield (entries 4−5). The reaction occurred diasteroselectively to form predominantly the endo product of the oxabicyclonorbornane. Cyclic ethers containing a heteroatom at the 4-position also underwent the C−H borylation reaction (entries 6−7). The reaction of 1,4-dioxane occurred in high yield, indicating that the reaction can occur α to oxygen when the substrate lacks C−H bonds β to oxygen. (In this case, it was necessary to convert the pinacol boronate ester resulting from this process to the corresponding trifluoroborate salt, *vide infra*, to facilitate isolation under the conditions described above.) The borylation of *N*-pivaloyl morpholine also occurred α to the oxygen atom. Because *N*-pivaloylpiperidine, which lacks the oxygen of the morpholine derivative, reacted in low yield (ca. 15%) and gave multiple products, we presume that the selectivity of the reaction of the *N*-pivaloyl morpholine is due to the steric bulk of the pivalate substituent on the nitrogen atom, suppressing reaction at the position β to oxygen. The examples in Table 2 also show that the borylation reaction is compatible with cyclic ethers containing protected alcohol and amino functionalities (entries 7−8). Finally, the borylation of cyclohexane also occurred for the first time, but this reaction required higher temperatures and catalyst loadings and occurred in lower yield (entry 9).

A one-pot conversion of secondary C−H bonds to further derivatives can be important for the isolation of stable products and utility of the alkylboronate ester products. Thus, we developed conditions for the conversion of the tetrahydrofuranylboronate ester to the corresponding trifluoroborate, boronic acid, and alcohol (Scheme 1). The reaction of THF and B_2pin_2 in the presence of (η^6-mes)$IrBpin_3$ (4 mol %) and Me_4phen (4 mol %) to generate the 3-boryltetrahydrofuran product, followed by addition of an aqueous solution of KHF_2 in methanol solvent to the crude boronate ester, led to the trifluoborate salt in 63% yield. The 3-tetrahydrofuryl boronic ester product was also converted *in situ* to the corresponding boronic acid. 3-Tetrahydrofuranylboronic acid was isolated in 76% yield over two steps by treating the boronate ester with $NaIO_4$ and HCl (aq).

Scheme 1. Functionalizations of 3-Boryltetrahydrofuran[a]

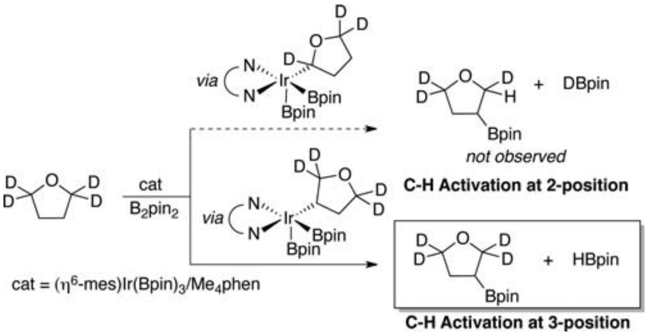


[a]Conditions: (a) B_2pin_2 (0.50 mmol), (η^6-mes)$IrBpin_3$/Me_4phen (4 mol %), neat, 120 °C, 14 h; (b) KHF_2 (aq, 4.5 M, 4.5 equiv), MeOH, 63% yield; (c) $NaBO_3\cdot 4H_2O$, THF/H_2O; BzCl, Et_3N, DMAP, DCM, 74% yield; (d) $NaIO_4$ (1.5 equiv), HCl (aq, 1 M, 1 equiv) 76% yield.

These products were also converted to alcohols under standard conditions. 3-Hydroxytetrahydrofuran was generated in a straightforward fashion by treating the crude boronate ester with aqueous $NaBO_3$. Because the corresponding 3-hydroxytetrahydrofuran is volatile, the alcohol was isolated as the benzoate ester in 73% overall yield. Efforts to identify catalysts for the coupling of these secondary boronate derivatives are ongoing.

The high β-selectivity observed in the iridium-catalyzed borylation of cyclic ethers could result from two general pathways (Scheme 2). One pathway involves direct functionalization of the β C−H bond through a 3-tetrahydrofuranyliridium boryl complex, and one, the more common activation of the α C−H bond, followed by isomerization of the 2-tetrahydrofuranyl complex to the same 3-tetrahydrofuranyl complex. The direct functionalization pathway is shown at the bottom of Scheme 2, and the indirect pathway is shown at the top of Scheme 2. Both pathways form the B−C bond by reductive elimination from a 3-tetrahydrofuranyliridium species.

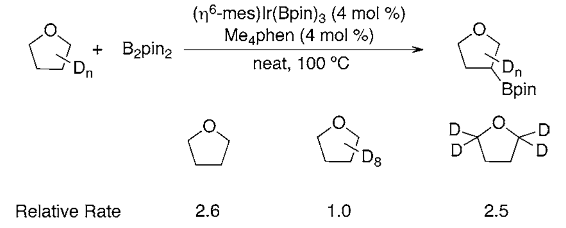
Scheme 2. Potential Pathways for C−H Functionalization



To distinguish between these two pathways, a deuterium labeling experiment was performed. The borylation of 2,2,5,5-tetradeuterotetrahydrofuran (THF-d_4) was conducted in the presence of (η^6-mes)$IrBpin_3$ and Me_4phen (Scheme 2). No loss of deuterium in the borylated product was detected by mass spectrometry, and no incorporation of a proton into the 2-position was detected by ^1H NMR spectroscopy. Moreover, HBpin, not DBpin, was observed as the side product by ^{11}B NMR spectroscopy. These observations are consistent with a direct C−H activation at the 3-position, not by initial C−H activation at the 2-position followed by isomerization to a 3-tetrahydrofuranyliridium species.

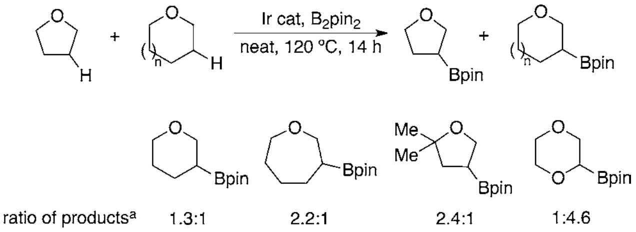
The rate constants for the Ir-catalyzed C−H borylation of THF were measured independently, and a primary kinetic isotope effect of 2.6 was observed for the reaction of THF-d_8 vs THF (Scheme 3). However, a kinetic isotope effect was not observed for the borylation of 2,2,5,5-THF-d_4 vs THF. These data are further inconsistent with an initial C−H cleavage at the 2-position followed by isomerization.

Scheme 3. Measurement of the Kinetic Isotope Effect



To determine the relative rates for borylation of cyclic ethers with varying structures, we conducted competition experiments. The relative ratios of products from the borylation of tetrahydrofuran versus cyclic ethers containing different ring sizes and substitution patterns are shown in Scheme 4. The borylation of the five-membered cyclic ether occurs preferentially over the borylation of six- or seven-membered cyclic ethers. This trend correlates with the slightly higher Lewis basicity of the oxygen atom of the five-membered cyclic ether, compared to that of the oxygen in the six- and seven-membered cyclic ethers.[17,18] Also, the borylation of THF occurred faster than the borylation of 2,2-dimethyltetrahydrofuran, but by only a 2.4:1 ratio. This ratio is again consistent with the greater

Scheme 4. Competition Experiments for the Borylation of Cyclic Ethers



[a]The ratio of product yields for the borylation of THF compared to other cyclic ethers was determined by GC analysis.

Lewis basicity of the oxygen atom in THF compared to that in 2,2-dimethyltetrahydrofuran. Finally, the borylation occurs preferentially with dioxane over THF by a factor of 4.6:1. Although dioxane is less Lewis basic than THF, the C−H bonds in dioxane are weaker than the β C−H bonds in THF. Based on these data for the labeling and competition experiments, we tentatively propose the high β-selectivity of the secondary C−H borylation arises from the coordination of the Lewis basic oxygen atom of the cyclic ether to the Lewis acidic boryl ligand to form a six-membered transition state (Figure 1).

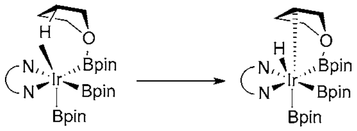


Figure 1. Proposed origin of selectivity in secondary C−H borylation.

In summary, we have identified an Ir complex that catalyzes the borylation of secondary C−H bonds for the first time in good yield. Moreover, this C−H borylation reaction occurs with unique selectivity for the 3-position of cyclic ethers. A series of isotopic labeling experiments are consistent with high selectivity for direct C−H cleavage at the 3-position, rather than initial cleavage of the weaker C2 C−H bond, followed by isomerization. Computational studies are currently underway to help elucidate the details of the mechanism and origin of selectivity of this reaction.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(14) See Supporting Information for details of the ligands examined.

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