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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Iridium-Catalyzed C−H Borylation of Cyclopropanes

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Supporting Information

ABSTRACT: The borylation of cyclopropanes catalyzed by the combination of (η^6-mes)IrBpin$_3$ or [Ir(COD)-OMe]$_2$ and a phenanthroline derivative is reported. The borylation occurs selectively at the methylene C−H bonds of the cyclopropane ring over methine or methyl C−H bonds. High diasteroselectivities were observed from reactions catalyzed by the combination of iridium and 2,9-Me$_2$phenanthroline. The cyclopropylboronate esters that are generated are versatile synthetic intermediates that can be converted to trifluoroborate salts, boronic acids, cyclopropylarenes, cyclopropylamines, and cyclopropanols.

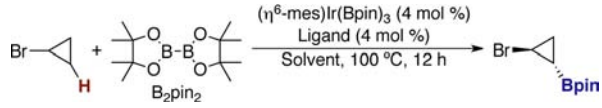
Cyclopropanes are common structural motifs that are parts of natural products and many biologically active molecules.[1−5] Cyclopropanes have unique steric and electronic properties and reactivities that originate from the rigid and highly strained structure. A classic method to synthesize cyclopropanes is the Simmons−Smith cyclopropanation of an olefin and a carbene.[6−8] Many stereoselective variants of this reaction have been reported.[9,10] Recently, other methods to introduce the cyclopropyl group have emerged that rely on metal-catalyzed cross-coupling of an organometallic cyclopropyl precursor and an aryl halide.[10−13] In addition, oxidative coupling reactions of cyclopropylboronic acids and amines to form cyclopropylamines have been reported.[14,15]

An attractive alternative to the synthesis of cyclopropanes from olefins is the C−H functionalization of substituted and readily available cyclopropanes. Yu and co-workers reported the stereoselective C−H functionalization of cyclopropylamides.[16] In this case, the reaction occurred with substrates that contain a basic group that coordinates to the catalyst to facilitate C−H functionalization. Based on this directing effect, the products of these reactions are *cis*-substituted cyclopropanes. In addition, Cramer and co-workers reported an asymmetric, intramolecular C−H functionalization of cyclopropanes, but intermolecular reactions were not reported.[17] Here, we describe the borylation of cyclopropane C−H bonds in the presence of an iridium-phenanthroline catalyst to yield predominantly the *trans*-substituted cyclopropylboronate esters without a directing group.

Previously, our laboratory reported the borylation of primary aliphatic C−H bonds with a diboron reagent in the presence of rhodium or ruthenium catalysts.[18−20] However, these catalysts were unreactive toward the functionalization of secondary C−H bonds. Studies on the stoichiometric reactivity of aromatic C−H bonds with iridium-trisboryl complexes, which are intermediates in the borylation of arenes, showed that more electron-rich iridium-trisboryl complexes react faster with aromatic C−H bonds than do less electron-rich complexes, and iridium-trisboryl complexes containing bulky phosphine ligands react more slowly with aromatic C−H bonds than do complexes containing bipyridine ligands.[21−25] Based on these observations, we developed the borylation of primary and secondary C−H bonds of cyclic ethers with an iridium-catalyst ligated by 3,4,7,8-tetramethylphenanthroline (Me$_4$phen).[26]

To expand the synthetic utility of the borylation of aliphatic C−H bonds, we sought to identify an iridium catalyst for the C−H borylation of cyclopropanes. The effect of various reaction parameters on the yields of the borylation of a representative cyclopropane is shown in Table 1. The reaction

Table 1. Borylation of Bromocyclopropane



entry	ligand	solvent	yield (%)[a]	d.r.
1	4,4′-dtbpy	Cy-H	42	59:41
2	3,4,7,8-Me$_4$phen	Cy-H	68	60:40
3	2,9-Me$_2$phen	Cy-H	65	97:3
4	2,9-Me$_2$phen	THF	73[b]	97:3
5	2,9-Me$_2$phen	Bu$_2$O	53	97:3
6	2,9-Me$_2$phen	THF	38[c]	97:3
7	2,9-Me$_2$phen	THF	81[d]	97:3

[a]Yield of boronate ester based on bromocyclopropane (0.25 mmol) determined by gas chromatographic analysis with isododecane as an internal standard. [b]10% diborylation product. [c]Pinacolborane as the boron reagent. [d]1.3 equiv of bromocyclopropane and 1.0 equiv of B$_2$pin$_2$.

catalyzed by (η^6-mes)IrBpin$_3$ (mes = mesitylene) and 4,4′-di-*tert*-butylbipyridine (dtbpy) proceeded in a modest 42% yield (Table 1, entry 1). Dtbpy is the ligand that generated the most reactive iridium catalyst for the borylation of arene C−H bonds.[20,27] The reaction of bromocyclopropane with bis-(pinacolato)diboron (B$_2$pin$_2$) at 100 °C in the presence of 4 mol % of (η^6-mes)IrBpin$_3$ and Me$_4$phen, which is the same combination of iridium and ligand that catalyzed the borylation of cyclic ethers, generated 68% yield of the cyclopropylboronate ester product (entry 2). However, this reaction occurred with low diastereoselectivity (60:40).

Received: January 5, 2013
Published: February 19, 2013

   dx.doi.org/10.1021/ja400103p | J. Am. Chem. Soc. 2013, 135, 3375−3378

High yield and diastereoselectivity were achieved by conducting the reaction with a more sterically hindered, chelating nitrogen ligand. The reaction catalyzed by (η^6-mes)IrBpin$_3$ and 2,9-dimethylphenanthroline (Me_2phen) occurred with 97:3 diastereoselectivity (entry 3). Presumably, this increase in diastereoselectivity is due to the greater steric demand of the 2,9-dimethyl ligand near the metal center.

The borylation of bromocyclopropane occurred faster and in higher yield when conducted in THF solvent than when conducted in cyclohexane or Bu_2O (entries 3–5); however, a small amount of product from diborylation of the cyclopropane (ca. 10%) was observed. Reactions conducted with pinacolborane as the boron reagent occurred in lower yield than those with B_2pin_2. By employing a slight excess of the cyclopropane, relative to B_2pin_2, the diborylation of bromocyclopropane was reduced, and the reaction occurred in 81% yield with 97:3 diastereoselectivity.

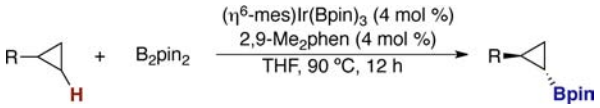
The scope of the borylation of cyclopropanes with B_2pin_2 as reagent in the presence of (η^6-mes)IrBpin$_3$ and Me_2phen as catalyst is shown in Table 2. Cyclopropanes containing halide, ester, carbonyl, protected carbonyl, and nitrile functionalities were converted to the corresponding boronate esters in good yields (entries 1–5).

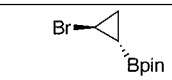
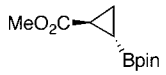
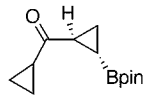
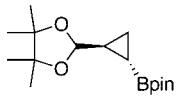
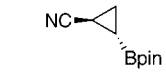
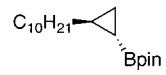
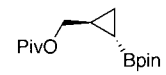
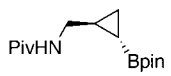
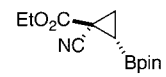
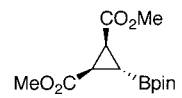
The diastereoselectivity correlates with the size of the substituent on the cyclopropane, and the yield depended on the electronic properties of the cyclopropane. For example, a much lower diastereoselectivity was observed for cyanocyclopropane (64:36) than for bromocyclopropane (97:3) (entries 1 and 5). Cyclopropanes containing alkyl substituents were less reactive toward C–H borylation than cyclopropanes containing electron-withdrawing groups. Reactions of these cyclopropanes in THF solvent gave products from borylation of the cyclopropane and the THF solvent (ca. 3:1). However, these less reactive cyclopropanes were converted to the corresponding cyclopropyl boronate esters in acceptable yield in cyclohexane as solvent and with an excess (3 equiv) of the cyclopropane to the diboron reagent (entries 6–8). The excess of the cyclopropane increased the rate of the reaction and eliminated the formation of diborylation products.

Under these conditions, alkylcyclopropanes containing various substituents formed the borylation product. The reaction of cyclopropanes containing protected alcohols and amines were converted to the corresponding boronate esters (entries 7 and 8). 1,1-Disubstituted cyclopropanes were much less reactive under these borylation conditions than were monosubstituted cyclopropanes, but a moderate yield of the borylcyclopropane was achieved from reactions of 1,1-disubstituted cyclopropanes in which one of the two substituents is relatively small (entry 9). Finally, *cis*-1,2-disubstituted cyclopropanes underwent the borylation to give the product containing the boryl group trans to the other two substituents. A minor diastereomer resulted from epimerization of the product containing the two ester groups trans to each other. The origin of this epimerization is not known at this time.

Reactions conducted with (η^6-mes)IrBpin$_3$ as a catalyst precursor are faster and occur with higher turnover numbers than those conducted with common iridium(I) catalyst precursors. However, to allow a more widespread use of this chemistry, we also evaluated the borylation of cyclopropanes with a commercially available iridium catalyst precursor. The borylation of cyclopropanes occurred with commercial [Ir(COD)OMe]$_2$ (COD = cyclooctadiene) to give moderate

Table 2. Scope of the Borylation of Cyclopropanes



entry	product	yield (%)[a]	d.r.
1		81	97:3
2		76	83:17
3		96	96:4
4		50	99:1
5		76	64:36
6		57[c,d]	90:10
7		59[c]	90:10
8		65[c]	91:9
9		52	85:15
10		67[e]	76:24

[a]Yield of boronate ester based on B_2pin_2 (0.50 mmol) determined by gas chromatographic analysis with isododecane as an internal standard. [b]Reaction conducted with 3 equiv of cyclopropane. [c]Reaction conducted with 3 equiv of cyclopropane in Cy-H at 100 °C with 6 mol % Ir catalyst. [d]Reaction conducted with Me_4phen as ligand. [e]Reaction was conducted with 1.0 equiv of cyclopropane and 1.5 equiv of B_2pin_2.

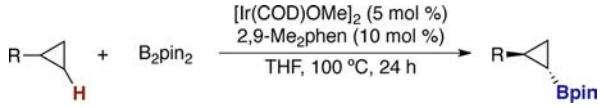
yields of the products when the reactions were conducted with catalyst loadings of 10 mol % and a temperature of 100 °C.[28] These loadings and temperatures are higher than those of reactions initiated with (η^6-mes)IrBpin$_3$ (4 mol %, 90 °C; Table 3, entries 1–4), but the reactions do occur in acceptable yield.

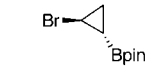
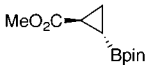
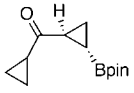
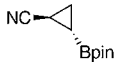
The cyclopropylboronate esters that are formed in these reactions are versatile synthetic intermediates that can be converted to a number of other products (Scheme 1). The cyclopropylboronate ester was converted to the trifluoroborate salt under standard conditions in the presence of KHF_2(aq) in MeOH in good yield. In addition, the same boronate ester was converted into the boronic acid in the presence of $NaIO_4$ and HCl(aq). Cyclopropylboronic acids and trifluoroborate salts are known to undergo Suzuki–Miyaura cross-coupling reactions in good yields.[10,11,13] Cyclopropylboronic acids also react in Cu-mediated oxidative coupling reactions with amines.[14,15]

Like their pinacol-substituted arylboronate ester counterparts, these pinacol-substituted cyclopropylboronic esters are less reactive than the corresponding boronic acids and boronic

dx.doi.org/10.1021/ja400103p | J. Am. Chem. Soc. 2013, 135, 3375–3378

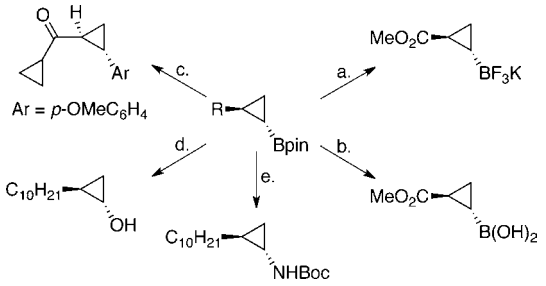
Table 3. Borylation of Cyclopropanes with $[Ir(COD)OMe]_2$



entry	product	GC yield (%)[a]	isolated yield (%)[b]
1		72	48
2		54	44
3		60	54
4		58	40

[a]Yield of boronate ester based on B_2pin_2 (1.0 mmol) determined by gas chromatographic analysis with isododecane as an internal standard. [b]Isolated yield following purification by silica gel chromatography.

Scheme 1. Functionalization of Cyclopropylboronate Esters[a]



[a]Conditions: (a) KHF_2(aq) (4.5 M, 5 equiv), MeOH, 22 °C, 3 h, 82% yield; (b) $NaIO_4$ (1.5 equiv), HCl(aq) (1 M, 1 equiv), 22 °C, 12 h, 74% yield; (c) 4-bromoanisole (1.5 equiv), $Pd(dba)_2$ (5 mol %), PCy_3 (10 mol %), KO*t*-Bu (3 equiv), THF, 100 °C, 12 h, 50% yield; (d) NaOH(aq) (1 M), H_2O_2 (30%, 2 equiv), THF, 0 °C, 30 min, 83%; (e) *n*Bu-Li (5 equiv), $MeONH_2$ (5 equiv), THF, −78 °C to 60 °C, 12 h; Boc_2O (5 equiv), 22 °C, 1 h, 40% yield.

esters of less hindered diols. Thus, the conversion of the pinacol-substituted cyclopropylboronate esters from the C−H activation process into other functionalized cyclopropanes was more challenging. Nevertheless, conditions were developed for cross-coupling, oxidation, and amination of the cyclopropylboronate esters.

The cyclopropylboronate ester containing a carbonyl group was found to undergo Suzuki−Miyaura cross-coupling. The reaction of this cyclopropylboronate ester with 4-bromoanisole occurred in the presence of $Pd(dba)_2$ and PCy_3 as catalyst and KO*t*-Bu as base to give the aryl cyclopropane in 50% yield. The identity of the base was important for this reaction to occur in high conversion. Reactions conducted with inorganic bases, such as hydroxide, fluoride, or carbonate, occurred with lower overall conversion (<20%) of the cyclopropylboronate ester.

In addition, the cyclopropylboronate ester was converted to the cyclopropanol in the presence of NaOH(aq) and hydrogen peroxide in THF at 0 °C in good yield. It was necessary to conduct the reaction at low temperature and short reaction times to eliminate overoxidation and fragmentation of the cyclopropane, but the cyclopropanol derived from decylcyclopropane formed in 83% yield under these carefully controlled conditions.

Finally, the borylcyclopropane was converted to the corresponding cyclopropylamine. So far, Cu-mediated oxidative coupling reactions of cyclopropylboronate pinacolate esters with amines (Chan−Lam coupling reactions) have not generated cyclopropylamine products. However, the *trans*-1,2-decylcyclopropylboronate ester formed by C−H borylation was converted to the corresponding protected amine by a procedure recently reported by Morken and co-workers.[29] The boronate ester was treated with deprotonated $MeONH_2$, followed by treatment with excess Boc_2O to generate the protected aminocyclopropane in modest yield.

In conclusion, we have identified a catalyst and conditions for the intermolecular borylation of cyclopropane C−H bonds. These reactions occur in good yields with good diastereoselectivity favoring the trans isomer with the new iridium catalyst ligated by 2,9-Me_2phen. The products of these reactions are versatile synthetic intermediates that undergo a series of transformations to substituted cyclopropanes.

■ 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.

■ ACKNOWLEDGMENTS

We thank the NSF (CHE-1213409) for support of this work, Johnson Mathey for $[Ir(COD)OMe]_2$ and $[Ir(COD)Cl]_2$, and AllyChem for B_2pin_2. C.W.L. thanks Abbott Laboratories and the NSF graduate research fellowship program for predoctoral fellowships.

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(28) We previously showed that the trisboryl complex ligated by dtbpy can be formed in situ with pinacolborane, but use of this method to generate the active catalyst did not increase the rate or yield of the C−H borylation product.
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