Title

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Journal

Journal of the American Chemical Society, 146(11)

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Publication Date

2024-03-20

DOI

10.1021/jacs.3c12981

Peer reviewed

HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2024 December 05.

Published in final edited form as:

J Am Chem Soc. 2024 March 20; 146(11): 7124–7129. doi:10.1021/jacs.3c12981.

2-Aminophenanthroline Ligands Enable Mild, Undirected, Iridium-Catalyzed Borylation of Alkyl C–H Bonds

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Abstract

The catalytic, undirected borylation of alkyl C–H bonds typically occurs at high reaction temperatures or with excess substrate, or both, because of the low reactivity of alkyl C–H bonds. Here we report a new iridium system comprising 2-anilino-1,10-phenanthroline as the ligand that catalyzes the borylation of alkyl C–H bonds with little to no induction period and with high reaction rates. This superior activation and reactivity profile of 2-aminophenanthroline-ligated catalysts leads to broader reaction scope, including reactions of sensitive substrates, such as epoxides and glycosidic acetals, enhanced diastereoselectivity, and higher yields of borylated products. These catalysts also enable the borylation of alkanes, amines, and ethers at room temperature for the first time. Mechanistic studies imply that facile *N*-borylation occurs under the reaction conditions and that iridium complexes containing *N*-boryl aminophenanthrolines are competent precatalysts for the reaction.

The functionalization of C–H bonds creates the potential to modify hydrocarbon chemical feedstocks and conduct late-stage diversification of complex molecules.[1–3] The borylation

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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c12981.
Experimental procedures, characterization of new compounds, and spectroscopic data (PDF)

Accession Codes

CCDC 2302728–2302729 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

of C–H bonds is particularly valuable because the boronic ester products are precursors to a wide range of functional groups.[4] Such borylations of aryl C–H bonds catalyzed by iridium complexes with nitrogen-based ligands have been studied intensively because of the mild reaction conditions and the high tolerance for auxiliary functional groups. Thus, borylations of C–H bonds have been used for applications from medicine to materials.[5]

In contrast, the borylation of unactivated alkyl C–H bonds with iridium catalysts is under development. Such reactions have required higher temperatures and superstoichiometric quantities of substrate,[6–12] except for reactions of activated alkyl C–H bonds in cyclopropanes,[13] in methylarenes,[14] or nearby a directing group.[15–29] The photochemical and electrochemical borylations of alkyl C–H bonds occur at mild temperatures but have required high loadings of the substrate or metal.[30–33] These limitations have prevented the widespread adoption of alkyl C–H borylation by synthetic chemists.

Recent developments have begun to transform the catalytic undirected borylation of alkyl C–H bonds into an increasingly practical method to access alkyl boronic esters (Figure 1). Schley and Kuninobu reported ligands that form complexes that catalyze the borylation of alkyl C–H bonds with higher turnover numbers than were observed previously,[34,35] but these reactions still occur at relatively high temperatures (≥100 °C) and require superstoichiometric amounts of substrate.

In parallel, our group discovered that iridium complexes formed from 2-methylphenanthroline (2-mphen) catalyze the borylation of alkyl C–H bonds at rates higher than those observed with phenanthrolines, such as 3,4,7,8-tetramethylphenanthroline (tmphen), used previously for these reactions. The use of 2-mphen enabled the borylations of alkyl C–H bonds to occur with the substrate as the limiting reagent, albeit at 100 °C.[36,37] A substantial induction period in these reactions was observed and necessitated higher reaction temperatures than are needed for the catalytic cycle and limiting the total amount of active catalyst. Mechanistic experiments implied that slow modification of the 2-methyl substituent, presumably by borylation of one or more C–H bonds, leads to the active catalytic species. We report that the combination of 2-aminophenanthrolines with iridium leads to facile activation of the catalyst at reduced temperature, thus enabling the borylation of alkyl C–H bonds to occur at temperatures below those of any previous catalyst and to occur even at room temperature.

To identify ligands that generate the active catalyst for the borylation of alkyl C–H bonds without an extensive induction period, we studied phenanthrolines containing an amino group in place of a 2-methyl group. This change would enhance modification of the substituent at the 2-position because catalyzed or uncatalyzed borylations of N–H bonds are more rapid than those of C–H bonds.[38] In addition, 2-aminophenanthrolines are more readily prepared by a modular synthesis than 2-alkylphenanthrolines (Figure 2).

Thus, we prepared a variety of 2-aminophenanthrolines and tested them for the borylation of neat tetrahydrofuran at 100 °C. In contrast to the borylation of THF catalyzed by Ir complexes of 2-methylphenantholine, the borylations catalyzed by Ir complexes of 2-aminophenanthrolines occurred with little to no induction period (Figure 3). The yields

of the alkylboronic ester product even exceeded 100%, indicating a partial reaction of the HBpin byproduct with THF to form the same 3-boryl-THF.

With the facile generation of the active catalyst, reactions catalyzed by Ir and 2-aminophenanthrolines occurred at lower temperatures. Reactions with limiting quantities of *tert*-butyloctyl ether **1b** as a model substrate in the presence of a series of ligands and metal precatalysts at 65 °C are shown in Table 1.

These studies showed that the iridium system formed from 2-anilinyl-1,10-phenanthroline (**L3**) and $[Ir(cod)OMe]_2$ catalyzed the borylation of **1b** to form **1a** in good yield with the substrate as the limiting reagent. Varying the metal precursor, boron reagent, or substituent on the amino group did not lead to significant increases in yield (see Figure S1–S4 for details on the reaction development). In contrast, the reaction with 2-mphen as the ligand gave no product after 18 h at 65 °C. Low yields of the boronic ester were observed from reactions with the parent 2-aminophenanthroline **L1** as the ligand. Higher yields, but still lower than those with **L3** as the ligand, were observed with **L2** as the ligand, and no yield was obtained from reactions with the dialkylaminophenanthroline **L4**. Control experiments showed that both **L3** and the iridium precursor were necessary to form the product. Yields for reactions conducted with $(MesH)Ir(Bpin)_3$ as the iridium source were similar to those conducted with commercially available $[Ir(cod)OMe]_2$.

Under the conditions for the borylation of model substrate **1b**, we explored the scope of the undirected borylation of alkyl C–H bonds (Table 2). The borylations of a variety of substrates occurred smoothly; most occurred with 5 mol % loading of the catalyst with **L3** and 1.5 equiv of the diboron reagent. Common protecting groups or those with minor modifications to prevent borylation of an aryl C–H bond in the protecting group were tolerated. Alkyl ether **1b** and *N*-methyl amine **2b** underwent borylation at their primary C–H bonds. Cyclopropane **3b** and cyclobutane **4b** underwent borylation at secondary C–H bonds within the strained carbocycle, and epoxide **5b** and azetidine **6b** underwent borylation at the most accessible secondary C–H bond on the strained heterocyclic ring. Spirocyclic cyclobutanes, such as **7b** and **8b**, also underwent borylation cleanly, albeit requiring higher catalyst loading and affording lower yields of the product than monosubstituted cyclobutanes, presumably because of steric hindrance. Less strained saturated hetero-cycles also underwent borylation at the position *β*- to the heteroatom (**9b–12b**). Highly strained bicyclopentane **13b** underwent selective borylation of the bridgehead, tertiary C–H bond.

The mild reaction conditions were conducive to the borylation of complex substrates containing many C–H bonds and functional groups. The fenchol derivative **14b** underwent borylation of the cyclobutane moiety. The cholesterol derivative **15b** underwent borylation of the bicyclopentane moiety. Primary C–H bonds in 6-deoxysugars, such as L-fucose (**16b**, **17b**), underwent borylation cleanly and were applied to the synthesis of the corresponding rare L-galactose **17c**.[39,40]

The yields of reactions conducted with **L3** at 65 °C were generally higher than those with 2-mphen at 100 °C in closed vials, which are most easily run on mmol scale. Broadly speaking, these higher yields can be attributed to either improved functional group

tolerance due to the mild conditions or improved catalyst activity. (See Section 4.1 of the SI for discussions on mass balance of the 2-mphen reactions.) For example, we see less decomposition of the boryl epoxide product in the case of **5a**, and we see only the desired product with **L3** in the cases of **7a** and **8a**. In the case of amide **11a**, we see reduction of the amide to the corresponding amine by the HBpin byproduct when the reaction was run with 2-mphen at 100 °C.

The high activity and rapid activation of the iridium catalyst containing **L3** was further exemplified by observing the borylation of neat substrates at room temperature (Table 3). To avoid an induction period observed for the borylation of THF at room temperature with $[Ir(cod)(OMe)]_2$ as precursor (Figure S8), $(MesH)Ir(Bpin)_3$ was used as the Ir source. With this modification, a variety of acyclic and cyclic ethers, amines, and alkanes underwent borylation at room temperature. While long reaction times did maximize conversion to product **9a**, a majority of the product formed within 48 h (62% of the 74% formed after 7 days, see Figure S8).

All of these substrates previously required temperatures of 100 °C or higher with Ir catalysts under similar conditions. Other iridium catalysts reported for undirected borylation of alkyl C–H bonds, including those with 3,4,7,8-tetramethyl, 2-silylmethyl, and 2-methyl-substituted phenanthroline ligands, as well as 2,2′-dipyridylarylmethane ligands,[9,34–36] gave 0–1% yields of tetrahydrofuryl product **9a** at room temperature (Figure S5).

Preliminary mechanistic insight was gained from a kinetic isotope effect (KIE). The lack of an induction period with **L3** as the ligand allowed an accurate KIE value to be obtained from the initial rates of separate reactions with THF or THF-d_8. A primary KIE of 3.2 ± 0.2 was observed (Figure 4a, S9), and this value is consistent with the irreversible, rate-limiting cleavage of the C–H bond by the active catalyst.

Initial information about the origin of the high activity of the catalyst generated from **L3** has been obtained. The requirement for an unsubstituted N–H bond in the ligand for reactivity at 65 °C implies that functionalization of the N–H bond occurs under the reaction conditions. The combination of **L3** and $(MesH)Ir(Bpin)_3$ in the presence of B_2pin_2 generated a complicated mixture, and clean formation of iridium complexes was hampered by low solubility of **L3** and borylation of the ligand at aryl C–H bonds of the phenanthroline unit, in addition to the N–H bond (Figure S11). However, reactions with the more soluble **L1** generated an iridium complex that we assigned as (**L5**)$Ir(Bpin)_3$ (see below, Figure S12), resulting from borylation of the amino group. At 65 °C, the temperature at which the catalytic reaction occurs within hours, this single species evolved into additional complexes, likely resulting from multiple non-selective borylation events on the ligand, that we have not identified (Figure S13).

The borylation of **L1** with HBpin at room temperature occurred at the N–H moiety in the presence of 1 mol % of $(MesH)Ir(Bpin)_3$ to form the borylamino ligand **L5** (Figure 4b), whereas the analogous reactions with 2-mphen formed products predominantly from borylation at the 8-position (Figure S10).

The combination of **L5** and (MesH)Ir(Bpin)$_3$ in the presence of B_2pin_2 formed a clean iridium species that we assigned as (**L5**)Ir(Bpin)$_3$ on the basis of the ^{1}H NMR spectrum (Figure 4c, S14). The addition of triphenyl phosphite to this complex formed (**L5**)Ir(Bpin)$_3$(P(OPh)$_3$), which was characterized by X-ray diffraction. Complex (**L5**)Ir(Bpin)$_3$ generated *in situ* is competent as a precatalyst for the borylation of neat THF, but with a short induction period (Figure 4d, S15). Furthermore, the stoichiometric reaction of this complex with THF did not form 3-boryl THF. Thus, more detailed studies are needed to determine how (**L5**)Ir(Bpin)$_3$ converts to the active catalyst, but we suggest that a second borylation occurs to make a ligand more similar in structure to that resulting from the borylation of **L3**. We hypothesize that the phenanthroline ligand in the active catalyst formed from **L3** bears a trisubstituted nitrogen atom with at least one Bpin group, and that this boryl substituent accelerates the oxidative addition of the C–H bond of the substrate, which is the rate-limiting step according to parallel KIE experiments with both ligands that contain and lack a 2-substituent.[9] Detailed studies of the role of this boryl substituent in the oxidative addition step are underway that combine DFT calculations in conjunction with designed ligands that form discrete active catalysts, and our findings will be reported in due course.

In summary, the iridium catalyst containing 2-anilinophenanthroline **L3** enables the borylation of alkyl C–H bonds under mild conditions with little induction period and with the substrate as the limiting reagent, thereby enhancing the scope and stereoselectivity of the borylation of diverse substrates. Modification of the 2-amino substituent initiates catalytic activity, and many 2-aminophenanthrolines led to Ir catalysts for the borylation of alkyl C–H bonds. This class of tunable ligands puts practical borylation of alkyl C–H bonds within reach. Ongoing efforts seek to understand the identity of the active catalyst and to apply this 2-aminophenanthroline motif to the site-selective borylation of alkyl C–H bonds in synthetic applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported by the NIGMS of the NIH under R35GM130387. I.F.Y. gratefully acknowledges the National Science Foundation Graduate Research Fellowship Program for support under DGE 1752814 and DGE 2146752. K.A.D. is supported by an NIH Kirschstein NRSA postdoctoral fellowship (F32-GM146425). A.D.H.M. is appreciative to the Berkeley Amgen Scholars Program for supporting a summer research internship. We thank Hasan Celik and Raynald Giovine and UC Berkeley's NMR facility in the College of Chemistry (CoC-NMR) for spectroscopic assistance. Instruments in the CoC-NMR are supported in part by NIH S10OD024998. We thank the QB3/Chemistry Mass Spectrometry Facility and the Catalysis Center at UC Berkeley for assistance with mass spectrometry. We thank Nick Settineri for advice on X-ray data collection and solution. We wish to thank Caleb Karmel, Jake Wilson, Jenna Manske, and Connor Delaney for helpful discussions.

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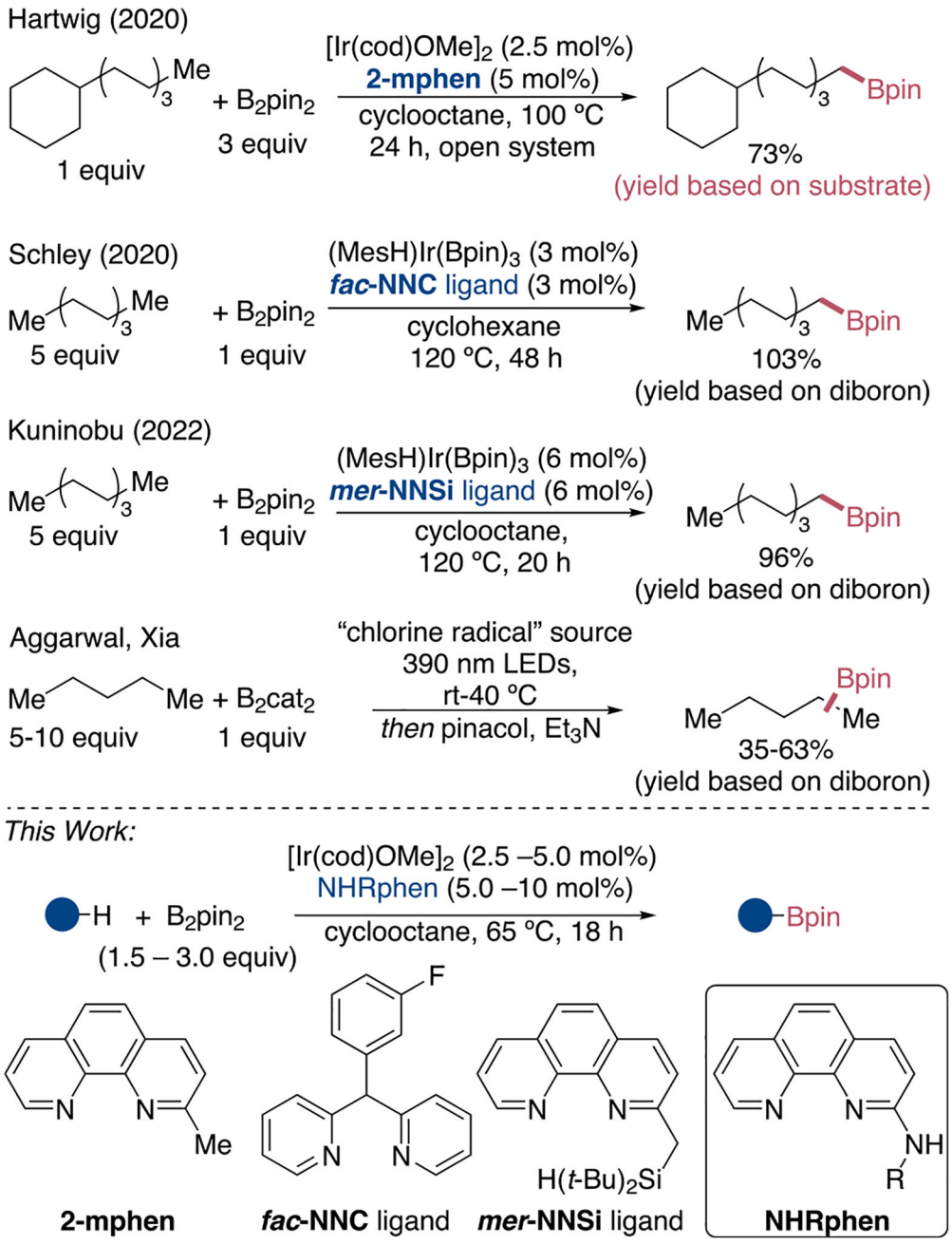


Figure 1.

Prior reports of undirected borylation of alkyl C–H bonds with limiting or near-limiting quantities of substrate and this work on milder reactions and facile activation with aminophenanthroline ligands.

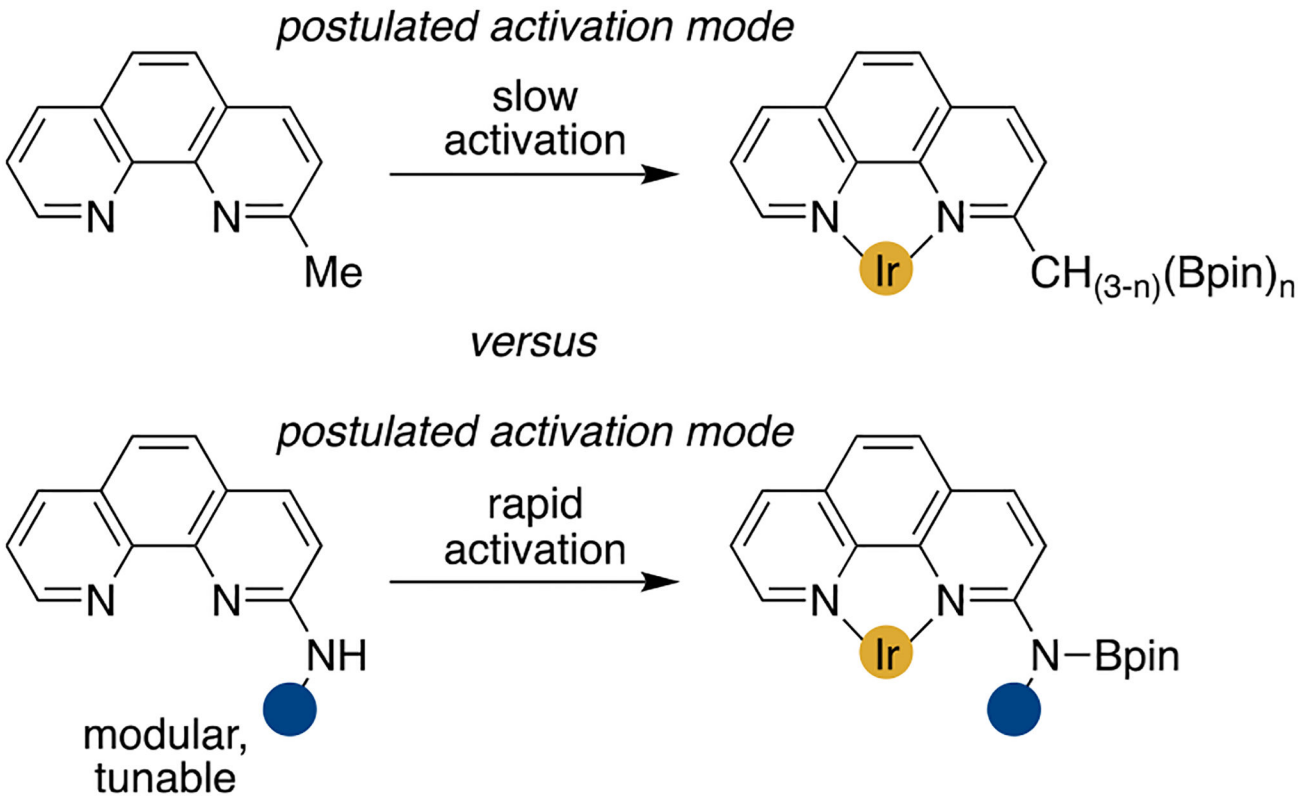


Figure 2.
Illustration of a possible mode for activation of catalysts containing 2-mphen and design of modular and tunable ligands for more rapid activation.

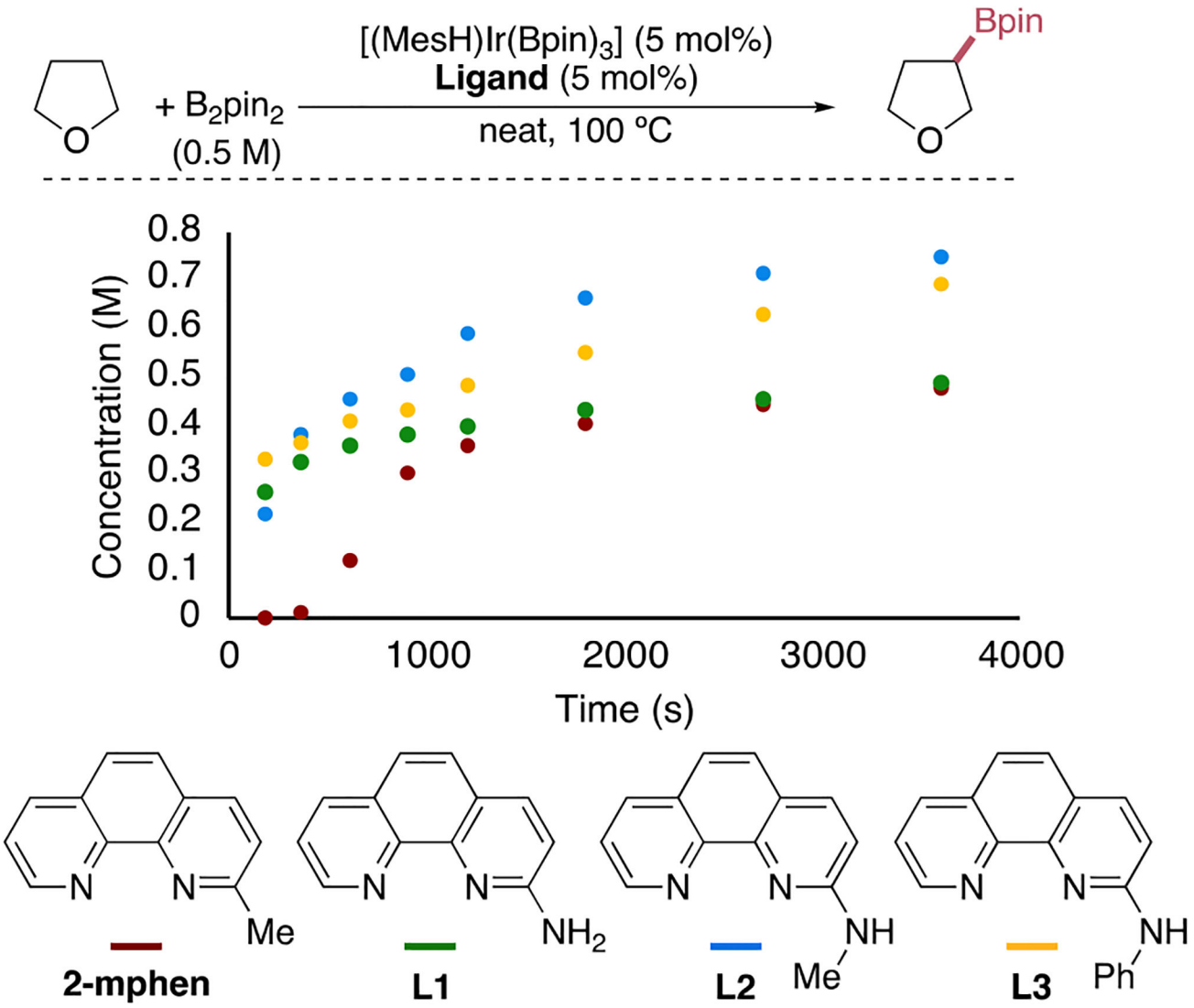


Figure 3.

Evaluation of the reactivity of 2-aminophenthrolines. Time courses of the borylation of tetrahydrofuran with either 2-mphen or a variety of 2-aminophenanthrolines at 100 °C.

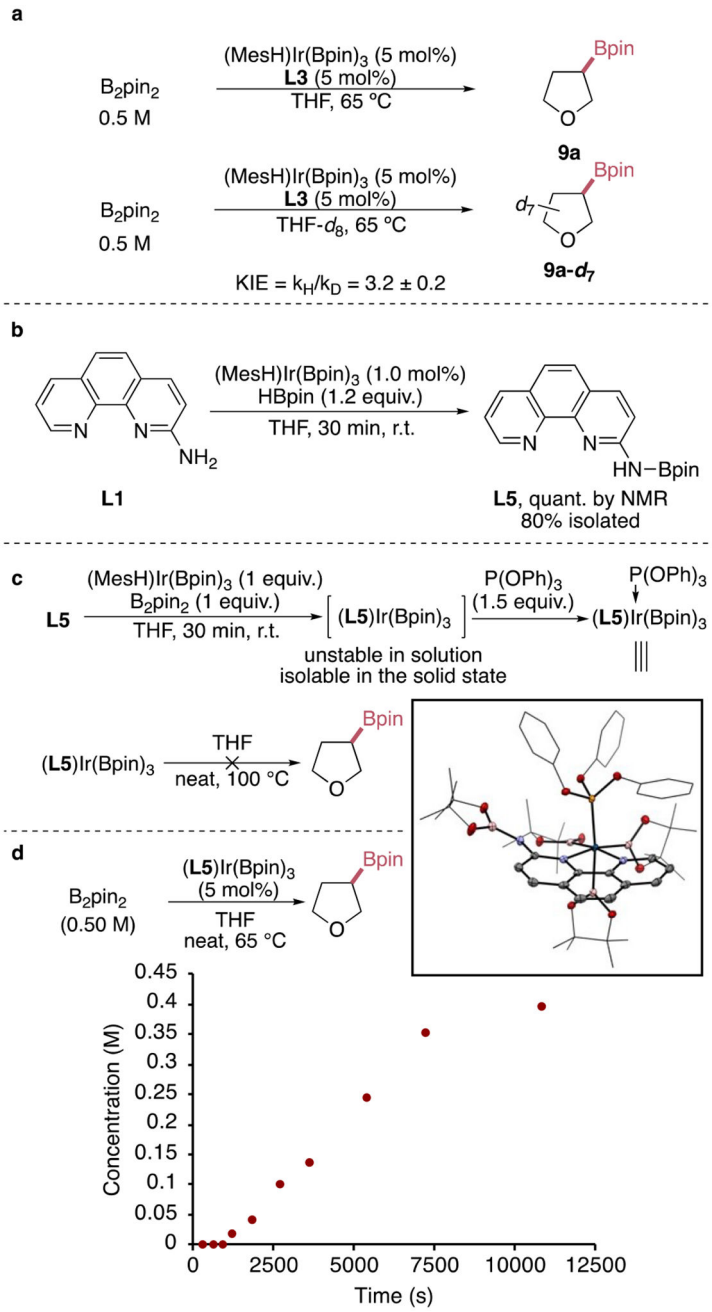
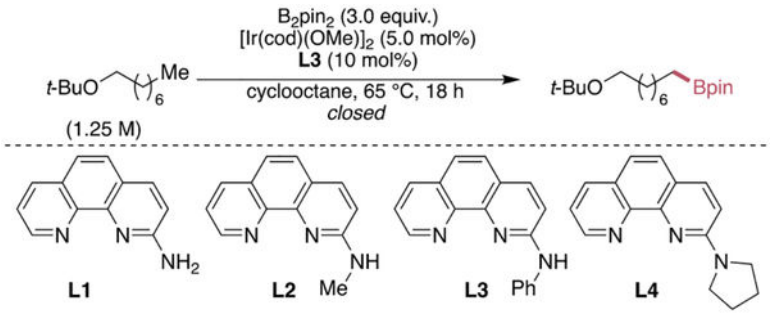


Figure 4.

Mechanistic experiments. (a) KIE for the borylation of THF. (b) Synthesis of *N*-borylated 2-aminophenanthroline **L5**. (c) Synthesis of an iridium trisboryl complex containing **L5**. (d) Catalytic reactivity of **(L5)**Ir(Bpin)$_3$.

Table 1.

Reaction Development for the Catalytic Borylation of Alkyl C–H Bonds under Limiting Substrate Conditions



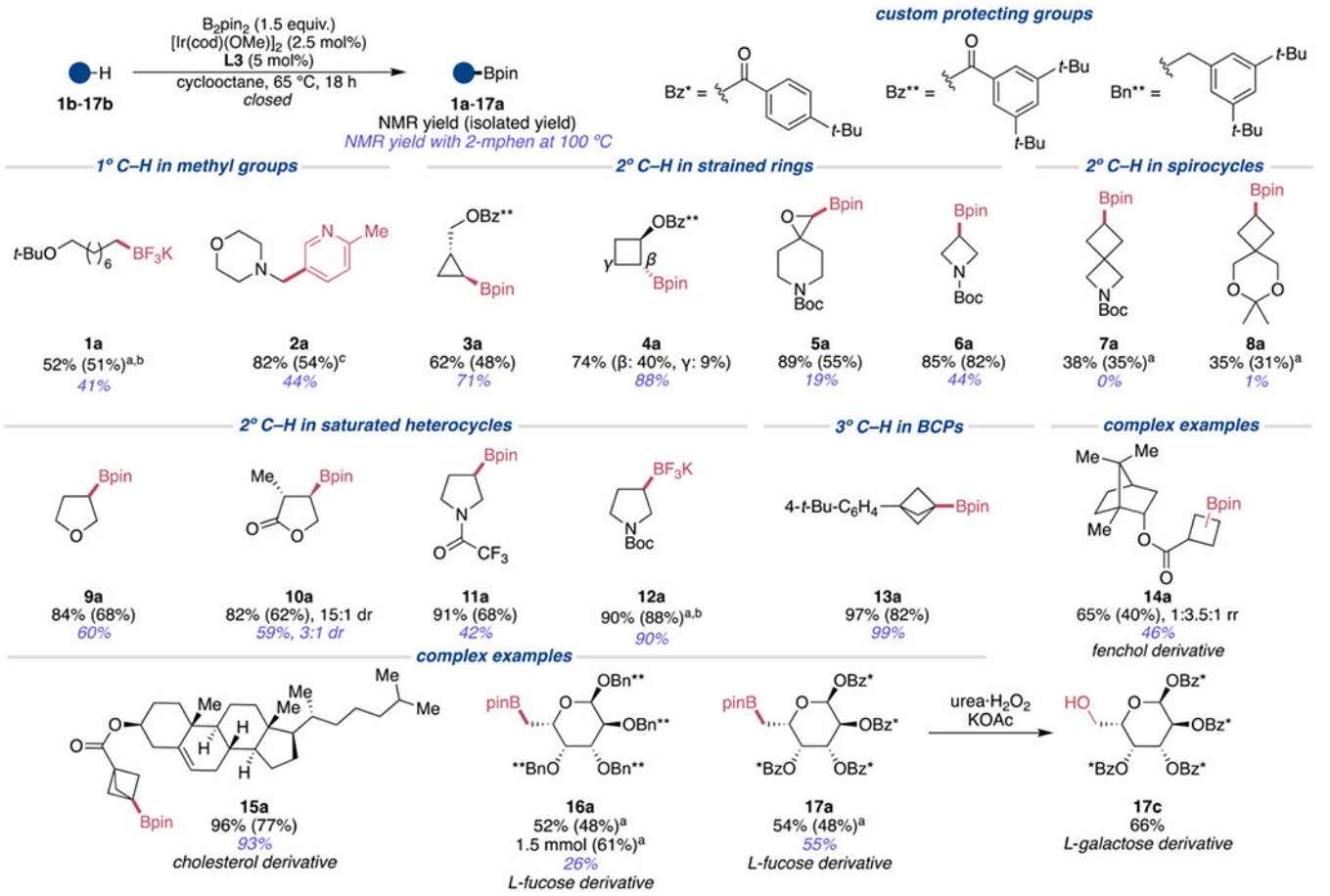
entry	precatalyst (mol %)	variation	yield[a] (%)
1	$[Ir(cod)OMe]_2$ (5)	none	52
2	$[Ir(cod)OMe]_2$ (2.5)	5 mol % of **L3**, 1.5 equiv of B_2pin_2	24
3	$[Ir(cod)OMe]_2$ (5)	100 °C	39
4	$[Ir(cod)OMe]_2$ (5)	2-mphen instead of **L3**	0
5	$[Ir(cod)OMe]_2$ (5)	**L1** instead of **L3**	6
6	$[Ir(cod)OMe]_2$ (5)	**L2** instead of **L3**	10
7	$[Ir(cod)OMe]_2$ (5)	**L4** instead of **L3**	0
8	none	none	0
9	$[Ir(cod)OMe]_2$ (5)	no ligand added	0
10	$(MesH)Ir(Bpin)_3$ (10)	none	53
11	$[Ir(cod)Cl]_2$ (5)	none	35
12	$[Rh(cod)Cl]_2$ (5)	none	0
13	$[Ir(cod)OMe]_2$ (5)	HBpin instead of B_2pin_2	0
14	$[Ir(cod)OMe]_2$ (5)	$Et_3SiBpin$ instead of B_2pin_2	0

[a]Determined by ^1H NMR spectroscopy with dibromomethane as the internal standard. MesH = 1,3,5-trimethylbenzene.

J Am Chem Soc. Author manuscript; available in PMC 2024 December 05.

Table 2.

Scope of the Borylation of Alkyl C–H Bonds with Limiting Substrate



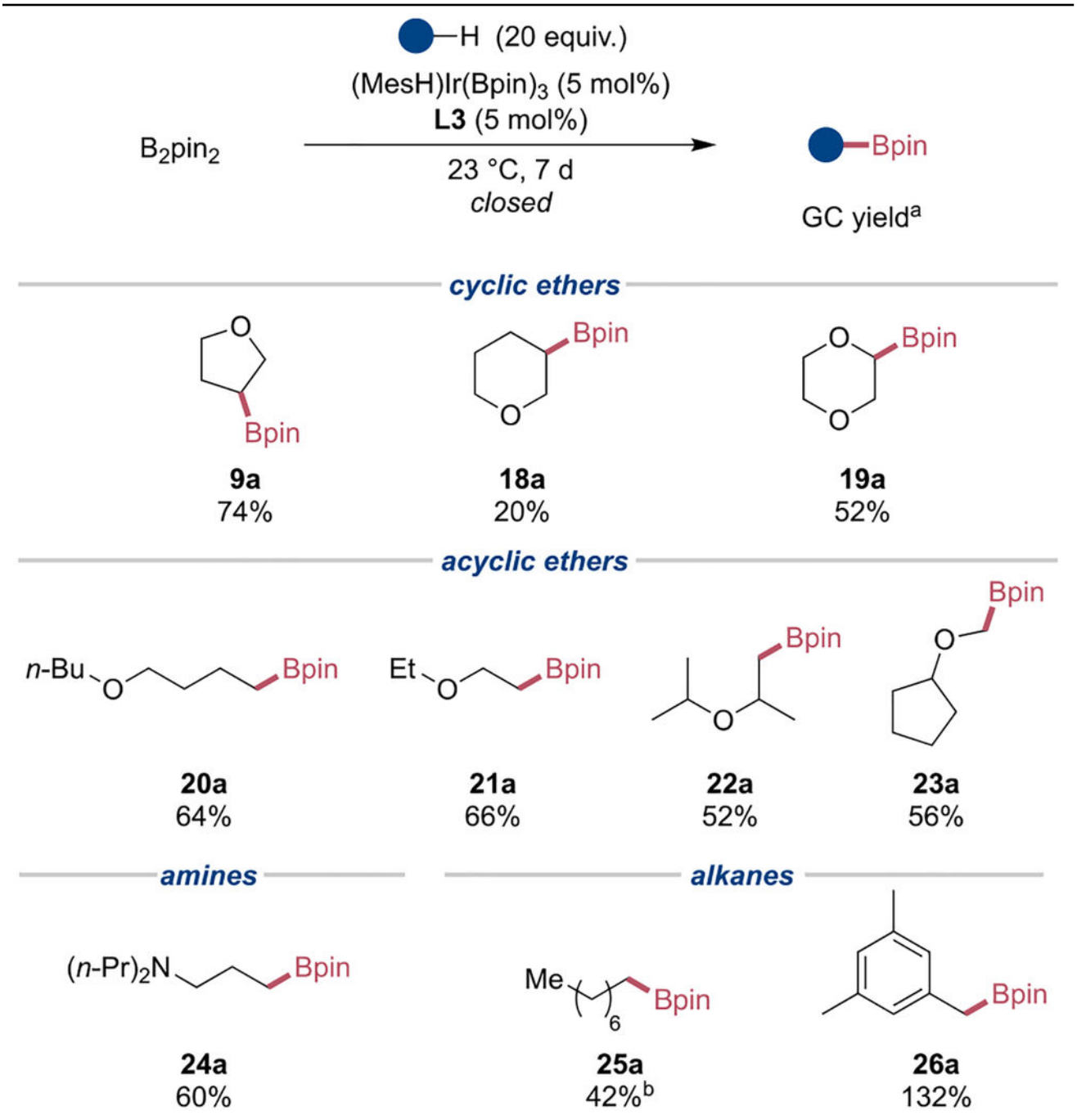
[a] 10 mol % catalyst, 3.0 equiv B_2pin_2.

[b] Treatment with KF and tartaric acid.

[c] One-pot cross-coupling with ArBr in the presence of $Pd_2(dba)_3$, QPhos, and CsF.

Table 3.

Borylation of Alkyl C–H Bonds at Room Temperature



[a] Determined by GC-FID with adamantane as the internal standard.

[b] 10 mol % catalyst.