Title
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Journal
Angewandte Chemie International Edition, 56(25)

ISSN
1433-7851

Authors
Su, Bo
Zhou, Tai-Gang
Xu, Pei-Lin
et al.

Publication Date
2017-06-12

DOI
10.1002/anie.201702628

Peer reviewed

HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2018 June 12.

Published in final edited form as:

Angew Chem Int Ed Engl. 2017 June 12; 56(25): 7205–7208. doi:10.1002/anie.201702628.

Enantioselective Borylation of Aromatic C-H Bonds with Chiral Dinitrogen Ligands

Dr. Bo Su,
Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education College of Chemistry and Molecular Engineering, Peking University, Beijing, China. Department of Chemistry, University of California Berkeley, CA 94720 (USA)

Dr. Tai-Gang Zhou,
Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education College of Chemistry and Molecular Engineering, Peking University, Beijing, China

Pei-Lin Xu,
Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education College of Chemistry and Molecular Engineering, Peking University, Beijing, China

Prof. Dr. Zhang-Jie Shi, and
Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education College of Chemistry and Molecular Engineering, Peking University, Beijing, China

Prof. Dr. John F. Hartwig
Department of Chemistry, University of California Berkeley, CA 94720 (USA)

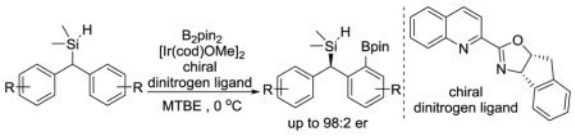
Abstract

The borylation of C-H bonds catalyzed by transition metals has been investigated extensively in the past two decades, but no iridium-catalyzed enantioselective borylation of C-H bonds has been reported. We report a set of transition metal-catalyzed enantioselective borylations of aromatic C-H bonds. This reaction relies on a set of newly developed iridium catalysts ligated by chiral quinolinyl oxazoline ligands. This process proceeds under mild conditions with good to excellent enantioselectivity, and the borylated products can be converted to enantioenriched derivatives containing new C-O, C-C, C-Cl, or C-Br bonds.

Enantioselective C-H Borylation

The first Ir-catalyzed enantioselective borylation of aromatic C-H bonds was developed with up to 98:2 er. The success of this reaction relies on a newly developed catalyst that derives from an iridium precursor and a chiral quinolinyl oxazoline ligand.

Correspondence to: Zhang-Jie Shi; John F. Hartwig.



Keywords

asymmetric catalysis; C-H activation; chiral dinitrogen ligand; iridium; borylation

Arylboron compounds are important and versatile synthetic intermediates in organic synthesis that are widely used in drug discovery and material science.[1] Among various reactions that form C-B bonds, the direct borylation of aromatic C-H bonds catalyzed by transition metals is particularly valuable.[2], [3] The borylation occurs under mild conditions with high functional group compatibility. The reactions of arenes occur at the least sterically hindered aromatic C-H bond (Scheme 1a).[2d]

To achieve selectivity that complements that of undirected borylation reactions, the borylations of C-H bonds have been conducted with arenes containing directing groups that coordinate to the transition metal catalyst (Scheme 1b).[2e, 4] However, most directing groups are difficult to remove after the introduction of the boryl group. To address this issue, our group developed silyl-directed borylations of C-H bonds (Scheme 1c).[5] The silyl directing group can be easily installed and removed or it can be used to create additional functionality at the position of the silyl substituent.

Although these undirected and directed borylations of C-H bonds are now commonly used, no iridium-catalyzed enantioselective borylation of C-H bonds has been reported.[6] The absence of such an enantioselective process can be traced to the type of catalyst typically used for the borylation of C-H bonds. The borylation of C-H bonds occurs under the mildest conditions with iridium catalysts containing planar bipyridine and phenanthroline ligands, which are achiral. The lack of steric demand and strong electron donation of these ligands are two properties that have been proposed to be crucial to the activity of these catalysts,[2d] so a chiral analog of such ligands should fit these requirements to achieve both reactivity and selectivity Rhodium complexes containing chiral bisphosphines catalyze the silylation of aryl C-H bonds and could be an alternative platform on which to develop enantioselective borylation,[7] but rhodium complexes with such bisphosphines have not been reported to catalyze the borylation of C-H bonds.

Recently, we described the preparation of a series of chiral pyridyl and quinolinyl oxazoline ligands.[8] Specific ligands in this class and an iridium precursor were shown to form complexes that catalyze the enantioselective silylation of C-H bonds.[9] Here, we show that a complex generated from an iridium precursor and a specific chiral quinolinyl oxazoline ligand catalyzes the enantioselective borylation of aromatic C-H bonds (Scheme 1d)[10] at or below room temperature with good to excellent enantioselectivity. The process occurs with the highest yield and enantioselectivity with a ligand related to, but distinct from, that for the enantioselective silylation, underscoring the importance of creating a modular library of ligands for this class of enantioselective reaction.

To identify a chiral catalyst for the enantioselective borylation of aromatic C-H bonds, the reaction of diarylmethylsilane **1a** was studied. The silyl group in this substrate should direct the borylation to an ortho C-H bond on the arene, and the borylated product would contain a C-B bond and a C-Si bond that can be converted individually to distinct functionalities under the appropriate conditions. For this reaction, we first examined the combination of $[Ir(cod)OMe]_2$ and a series of commercially available, C2-symmetric ligands, including bisphosphine ligand **L1**, tridentate nitrogen PyBOX ligand **L2**, bipyridine ligand **L3** and BOX ligands **L4** and **L5.** Complexes generated from these ligands were inactive as catalysts for the borylation reaction.

In contrast, when C1-symmetric ligands containing two nitrogen donors were used in the reaction, the reactivity was higher, and the enantioselectivity was measurable. For example, reactions conducted with the pyridinyl oxazoline ligand **L6** formed the functionalized product in 37% yield, albeit with a low 54:46 er. The same reaction catalyzed by a combination of quinolinyl oxazoline **L7** and $[Ir(cod)OMe]_2$ formed the borylated product **2a** in 64% yield with a higher 72:28 er.

Reactions conducted with ligands **L8**–**L14** revealed the effect of the steric properties of the oxazoline ligand on enantioselectivity. Reactions conducted with **L8** and **L11** containing *tert*-butyl and cyclohexyl groups in the position of an isopropyl group in **L7** afforded **2a** with slightly higher enantioselectivity than those conducted with **L7.** However**,** the reactions catalyzed by complexes of the other ligands (**L9**, **L10**, and **L12**) containing smaller benzyl, phenyl, and even larger diphenylmethyl groups and with **L13** containing geminal dimethyl substituents buttressing the isopropyl group occurred with lower enantioselectivity. The steric effect at the C8 position of the quinoline was also investigated. **L14** containing a methyl group at the C8 position formed a catalyst that was less reactive and selective than **L7**. Thus, an increase in steric hindrance at the oxazoline ring and the 8-position of the quinoline ring without further changes to the structure did not significantly increase the enantioselectivity.

Reactions catalyzed by complexes of **L15** containing an electron-donating OMe group and of **L16** containing an electron-withdrawing trifluoromethyl group revealed the effect of the electronic properties of the quinoline ring. Complexes of these ligands catalyzed the borylation in yields that were comparable and enantioselectivity that was slightly lower than those of reactions catalyzed by complexes of **L7**. Thus, varying the electronic properties of the ligand also was not a path to higher enantioselectivity.

In contrast to varying the steric and electronic properties of the nitrogen heterocycles, fusion of an indane skeleton to the oxazoline ring (**L17**) led to catalysts that formed product **2a** with a higher er of 85:15 and a yield of 62%. Although ligand **L18** generated a more reactive and stereoselective catalyst than **L17** during our recent study on iridium-catalyzed enantioselective silylation of aromatic C-H bonds, the yield and enantioselectivity of the borylation catalyzed by the Ir-**L18** system were lower than those catalyzed by the Ir-**L17** system. This result pointed to the importance of the quinoline ring in this class of ligand and illustrates the value of a library of ligands for which a small change in structure can lead to significant changes in reactivity and stereoselectivity.

After identifying a chiral ligand that generates an active and enantioselective catalyst, additional reaction parameters, including temperature, solvent, ratio of substrate **1a** to B_2pin_2, and catalyst loading, were examined (see supporting information, Table S1). The enantioselectivity was higher (87:13 er) when the reaction was conducted at 0 °C than when conducted at room temperature (85:15 er) (Table S1, entry 1). The enantioselectivity was even higher (93:7 to 96:4 er) when the reaction was run in alkane or less polar ether solvents, but the yields were lower (35 to 62%) in these solvents than they were in THF (66%) (Table S1, entry 1–6). Thus, the reactions were run with a small excess of B_2Pin_2 (1.2 vs 1.0 equiv) and a slightly higher catalyst loading (3 mol % vs 2 mol %, Table 2, entries 7 and 8). With this stoichiometry in methyl *tert*-butyl ether (MTBE) solvent, the product **2a** was obtained in 81% isolated yield with 96:4 er and less than 10% diborylated product.

Because rhodium complexes containing phosphines also catalyze the borylation of aromatic C-H bonds,[3c, 4d] we tested various combinations of rhodium precursors and chiral phosphines as catalyst for the enantioselective borylation (for details, see Supporting Information). However, no conversion was observed for reactions conducted with any of the rhodium catalysts generated from $[Rh(cod)Cl]_2$ and chiral bisphosphine ligands.

The scope of the borylation of diarylmethylsilane **1a** under the conditions described above is shown in Table 2. The reaction occurred with high enantioselectivity with alkyl, aryl and alkoxy substituents on the aryl ring. For example, the reactions of unsubstituted **1a** and the *meta*-substituted **1b**–**1f** formed the corresponding products **2a**-**2f** with excellent enantioselectivity (95:5 to 98:2 er). The reaction of *meta*-chloro **1g** led to the corresponding product **2g** in slightly lower enantioselectivity (85:15 er). For reasons we do not understand, the reaction of *para*-fluoro **1h** formed product **2h** with significantly low er (61:39 er). The reactions of substrates (**1i**–**1l**) containing alkyl, aryl, and silyl groups at the para position proceeded with moderate to good enantioselectivity. The presence of an *ortho*-substituent had a significant negative influence on the yield and enantioselectivity, suggesting that this substituent causes the substrate to adopt an unfavorable conformation. The enantioselectivity of the reaction of *ortho*-methyl-substituted **1n** was lower than that of *ortho*-fluoro substituted **1m**. Disubstituted substrates (**1o**–**1q**) also underwent borylation with high enantioselectivity. However, the reaction of naphthyl-substituted **1r** formed product **2r** with moderate enantioselectivity.

The enantioselective borylation occurs on larger scale as well as on small scale. The reaction of **1a** on a 5 mmol scale (eq 1) formed **2a** in 71% yield and 95:5 er with just 0.75% mol % catalyst instead of the 3 mol % of reactions on an 0.25 mmol scale.

To illustrate the utility of the reaction, we investigated transformations of the silyl and the boryl groups in compound **2a** (Scheme 2). Silane **2a** was transformed to silyl ether **3** in 75% yield in the presence of an iridium catalyst. Treatment of compound **3** with H_2O_2 and $KHCO_3$, converted the silyl and boryl groups to hydroxyl groups. Other processes led to reaction exclusively at the C-B bond. Under Suzuki coupling conditions, the reaction of **3** formed product **5** from coupling at the C-B bond in 65% yield. Reaction of compound **3** with $CuCl_2$ or $CuBr_2$ led to conversion of the C-B bond to a C-Cl or C-Br bond, respectively. Under these conditions, the silyl ether hydrolyzed to the corresponding silanol,

forming products **6** and **7** in 75% and 89% yields, respectively. Silanols have been studied in medicinal chemistry because the hydrogen-bonding abilities and acidity of silanols are higher than those of their carbon analogues.[11] No significant erosion of the enantiopurity of the products was observed during any of the transformations.

In summary, we have developed the first Ir-catalyzed enantioselective borylation of aromatic C-H bonds through a silyl-directed desymmetrization. The success of the reaction relies on the development of a catalyst derived from an iridium precursor and a chiral quinolinyl oxazoline ligand. The borylated products can be converted to a series of final products containing a series of different functional groups at the position of the aryl-boron bond. Further studies to elucidate the mechanism of the reaction and to expand the scope of the enantioselective borylation of C-H bonds are ongoing in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

B.S. thanks the MSD Scholarship. B.S. and Z.J.S thank the MOST (2015CB856600 and 2013CB228102) and NSFC (Nos. 21332001 and 21431008) for support of work at Peking University. B.S. and J.F.H. thank the NIH (GM-11581201) for support of work at Berkeley.

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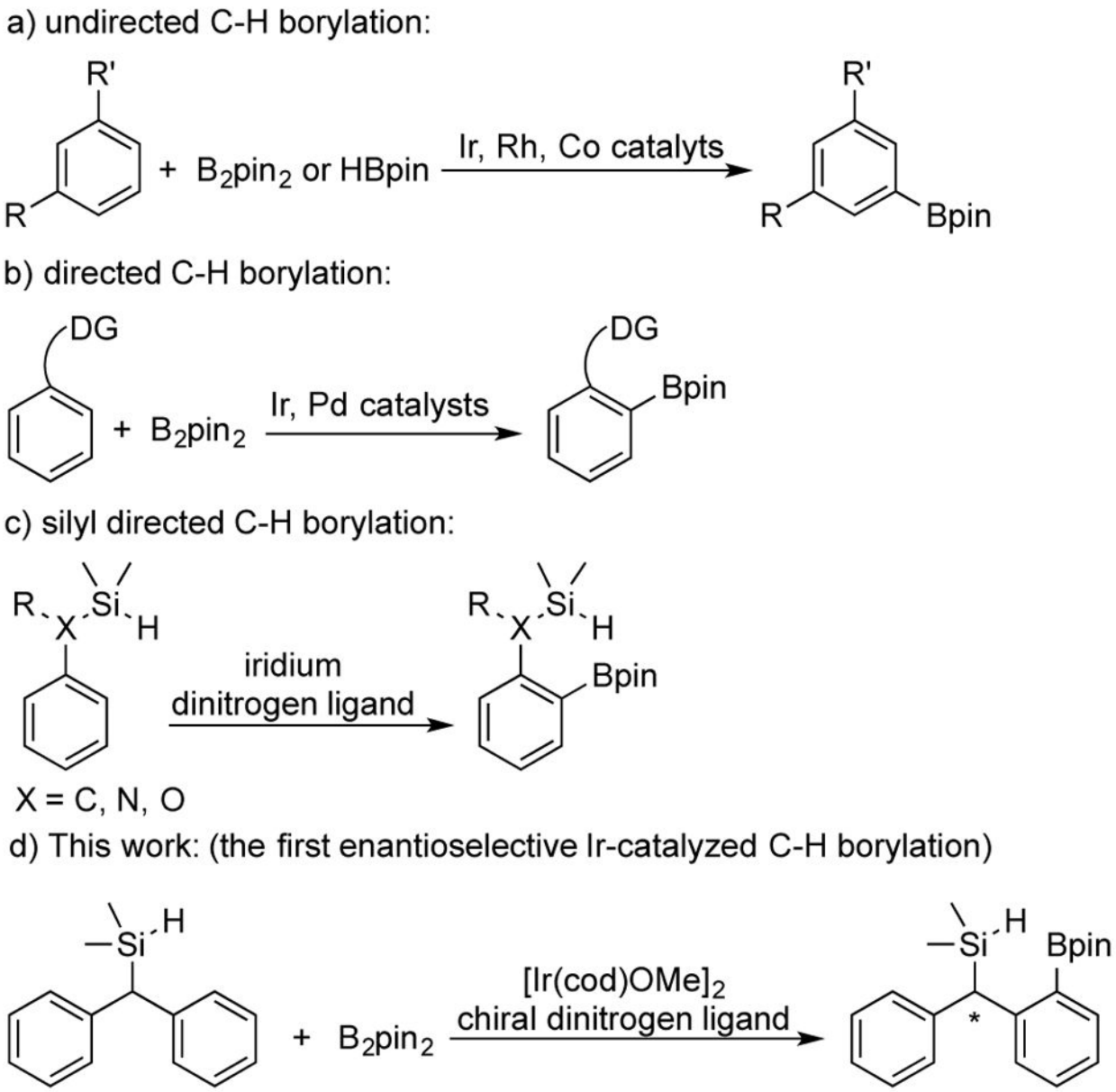
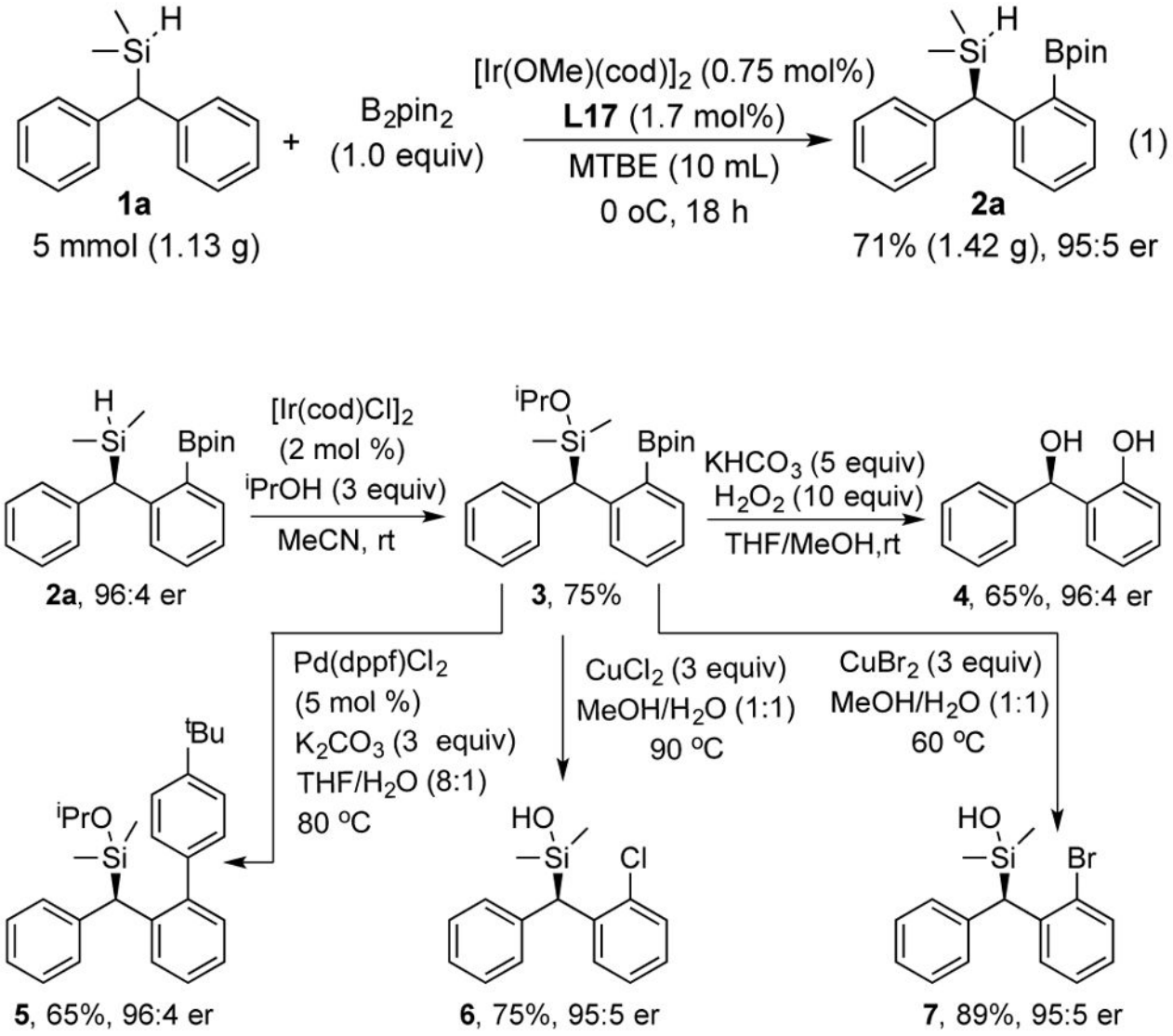


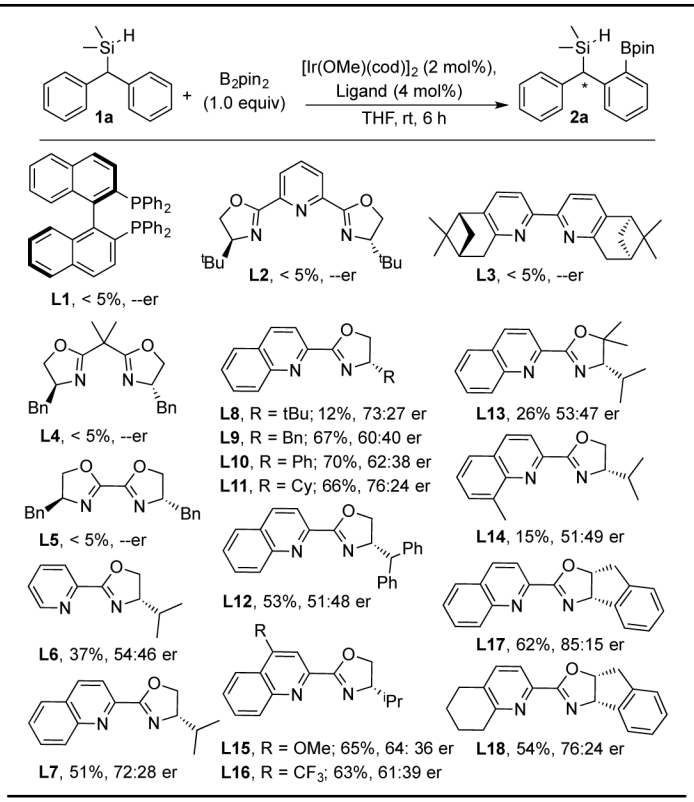
Scheme 1.
Transition metal-catalyzed borylation of aromatic C-H bonds.



Scheme 2.
Versatile transformations of the borylated products

Table 1

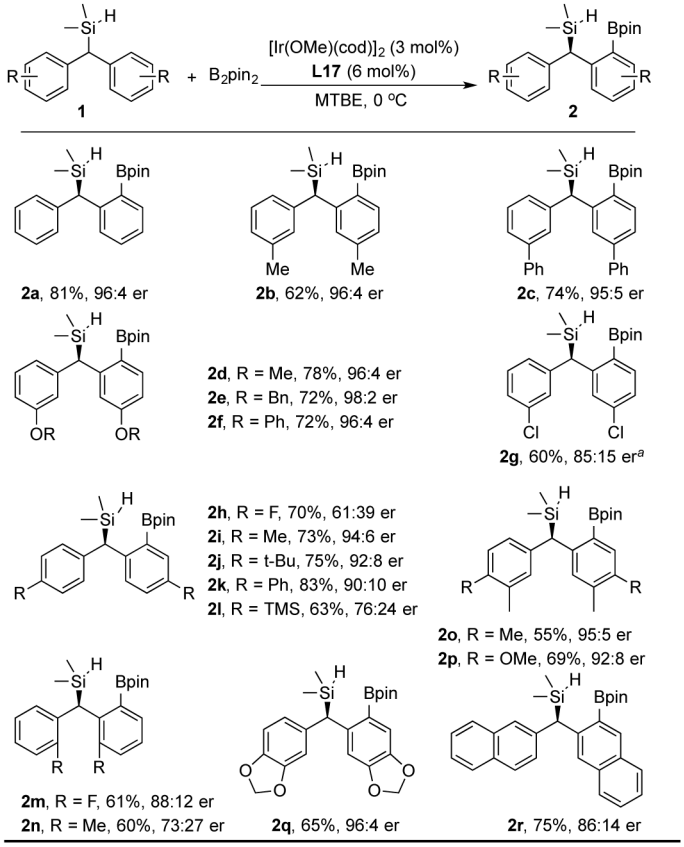
Evaluation of chiral ligands for the enantioselective borylation of a diarylmethylsilane.[a]



[a]The yields refer to values obtained by ^{1}H NMR spectroscopy with CH_2Br_2 as internal standard, and the er values were determined by chiral HPLC.

Table 2

Scope of the enantioselective borylation of aromatic C-H bonds.[a]



[a]Yields of isolated products for reactions conducted on a 0.25 mmol or 0.10 mmol scale. The er values were determined by chiral HPLC. The absolute configuration was assigned by analogy (details see Supporting Information).