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para-C–H Borylation of Benzene Derivatives by a Bulky Iridium Catalyst

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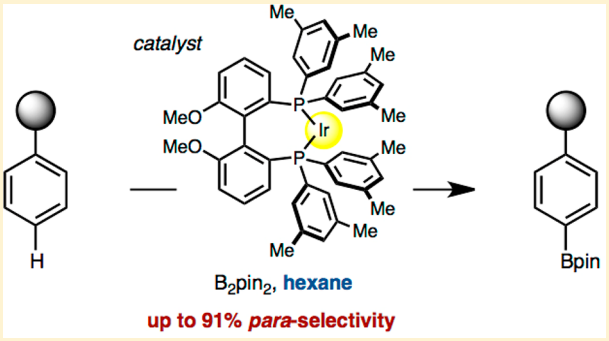
Supporting Information

ABSTRACT: A highly *para*-selective aromatic C–H borylation has been accomplished. By a new iridium catalyst bearing a bulky diphosphine ligand, Xyl-MeO-BIPHEP, the C–H borylation of monosubstituted benzenes can be affected with *para*-selectivity up to 91%. This catalytic system is quite different from the usual iridium catalysts that cannot distinguish *meta*- and *para*-C–H bonds of monosubstituted benzene derivatives, resulting in the preferred formation of *meta*-products. The *para*-selectivity increases with increasing bulkiness of the substituent on the arene, indicating that the regioselectivity of the present reaction is primarily controlled by steric repulsion between substrate and catalyst. Caramiphen, an anticholinergic drug used in the treatment of Parkinson's disease, was converted into five derivatives via our *para*-selective borylation. The present $[Ir(cod)OH]_2$/Xyl-MeO-BIPHEP catalyst represents a unique, sterically controlled, *para*-selective, aromatic C–H borylation system that should find use in streamlined, predictable chemical synthesis and in the rapid discovery and optimization of pharmaceuticals and materials.



INTRODUCTION

The benzene ring is one of the most important and frequently used building blocks in chemistry. Because the benzene ring not only is stable and easy to install into organic frameworks but also offers unique dimensionality and rigidity, it is frequently found in biologically active compounds including amino acids, proteins, natural products, pharmaceuticals, and agrochemicals.[1] In addition, benzene's unique π-electron system and aromaticity introduce a range of important properties to functional materials such as electrical conductance, the ability to absorb and emit light, and unique magnetic properties that are extensively utilized in optoelectronic materials, liquid crystals, and many other organic materials.[2] In the process of optimizing the properties of benzene-containing lead compounds, one common approach chemists have taken in both biology- and materials-related fields is to alter the *para*-substituents (Figure 1). The properties of *para*-substituents on benzene rings are very important from both electronic and steric points of view. For example, since the in vivo aromatic hydroxylation catalyzed by various cytochrome P450 enzymes takes place at the *para*-positions of benzene rings in many cases,[3] blocking these sites in bioactive compounds has enormous impact on improving the metabolic stability, activity, and selectivity. Improving metabolic stability is crucial in pharmaceuticals for achieving overall improvements in oral pharmacokinetics and dose size.[4] In the field of materials science, fine-tuning of optoelectronic properties is usually conducted at the *para*-positions because these positions significantly affect the electronic nature of

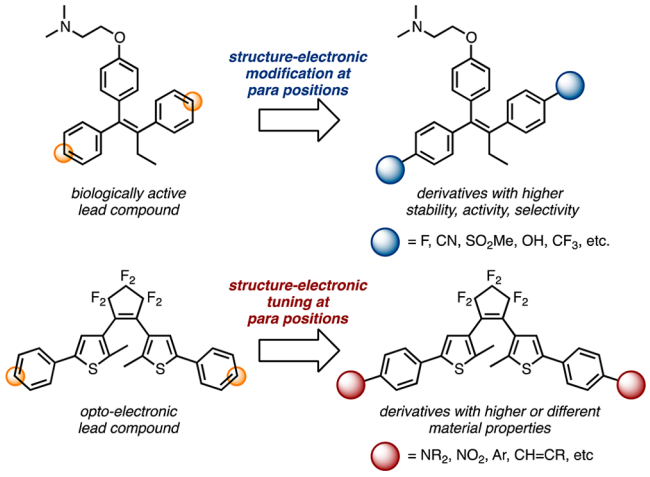


Figure 1. Structure–electronic modification and tuning of biologically active and/or optoelectronic lead compounds by *para*-functionalization.

benzene-based materials due to effective π-conjugation between *para*-substituents.[2] The *para*-substituents not only change the absorption fluorescence profiles of parent molecules but also add donor–acceptor properties and stimuli-responsible characteristics. However, in most cases, these "*para*" modifications

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can only be effected via lengthy synthetic sequences that lack modularity and often require separate starting materials and/or reagents for each proposed derivative.

Although a general *para*-selective C−H functionalization reaction would greatly accelerate the development of new functional molecules through a late-stage diversification of core structures,[5] unfortunately, there is no general method to accomplish this using the current repertoire of organic reactions (Figure 2a).[6] The electrophilic aromatic substitution (S_EAr) reaction can be *para*-selective, but this is only possible when strongly electron-donating groups (EDG) such as a dimethylamino group are attached onto the benzene rings.[7] In addition, such EDG-induced S_EAr reactions often produce the corresponding *ortho*-products in concert with the desired *para*-derivatives.

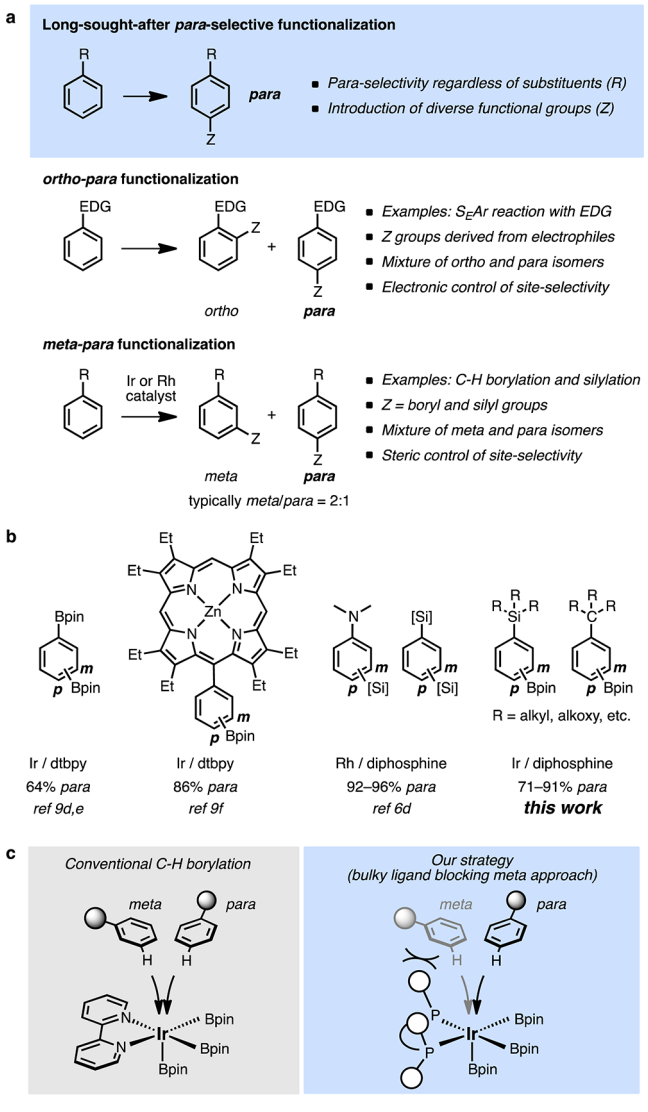

Figure 2. (a) Existing and expected *para*-functionalization reactions. EDG = electron-donating group. (b) Previously reported highly *para*-selective C−H borylation and silylation reactions and this work (Bpin = pinacolatoboryl, dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridyl, [Si] = $SiMe(OSiMe_3)_2$). (c) Conventional iridium-catalyzed C−H borylation leading to *meta*-rich products and our strategy to achieve *para*-selective C−H borylation.

In recent years, metal-catalyzed aromatic C−H borylation and silylation reactions[8] have received significant attention in the synthetic chemistry community in the context of C−H functionalization[5,6,9] as well as due to their unique site-selectivity, which is primarily determined by the steric interactions between the substituents on benzene rings and the catalyst.[8b] For example, when monosubstituted benzene derivatives are used as substrates, *ortho*-products are usually not observed and a mixture of *meta*- and *para*-products are statistically formed in a ca. 2:1 ratio favoring *meta*-isomers (Figure 2a).[8,10a−c] There have been several exceptions not following the 2:1 rule (Figure 2b). Smith found that a pinacolatoboryl group (Bpin) has a *para*-directing effect under room temperature to obtain 64% *para*-selectivity,[10d] which was re-examined by Marder and Steel to reveal that *para*-selectivity can be increased up to 68% by using a bis(2,4,6-trimethylphenyl)boryl group.[10e] Shinokubo and Osuka found that C−H borylation of octaethylporphyrinylbenzene took place in 86% *para*-selectively owing to the bulkiness of the huge porphyrinyl group.[10f] Quite recently, Hartwig reported rhodium-catalyzed aromatic C−H silylations in which monosubstituted benzene derivatives with electron-donating groups are preferentially silylated at the *para*-positions (Figure 2b).[6d,e] Recently, Ingleson reported *para*-selective electrophilic borylation of halobenzenes.[10g] However, in all cases, *para*-selectivity was derived from the electronic feature of the substituents except in the porphyrin's case. Moreover, it is very hard to suppress the formation of *meta,meta*-diborylated products under usual conditions.

We envisioned that a catalyst-controlled, *para*-selective C−H borylation could be achieved by applying iridium catalysts with sterically hindered ligands. In the proposed mechanism of C−H borylation,[8c−e] arenes approach from the top side of square pyramidal iridium triboryl complex (Figure 2c, left). The bulky substituents on diphosphine ligands restrict the upper hemisphere around the iridium center so that the *para*-C−H bond reacts preferentially over those in *meta*-positions (Figure 2c, right). Because the boryl group can be easily converted into various functional groups,[11] *para*-selective C−H borylation would be an extremely powerful method in organic synthesis. Herein we describe the first highly *para*-selective C−H borylation of monosubstituted benzene rings. Dramatic ligand effects are uncovered, and applications to pharmaceutically relevant molecules are also described.

RESULTS AND DISCUSSION

Ligand Screening for *para*-Selective C−H Borylation.

We initiated this study by identifying suitable ligand structures and catalytic conditions for the *para*-selective aromatic C−H borylation using trimethylphenylsilane (**1a**) as a model substrate (Table 1). In early experiments, we found that $[Ir(cod)OH]_2$ (cod = 1,5-cyclooctadiene) is superior to the standard $[Ir(cod)OMe]_2$ as a catalyst precursor. Thus, the borylation of **1a** (1.0 equiv) with B_2pin_2 (1.0 equiv) was conducted in the presence of $[Ir(cod)OH]_2$ (1.5 mol %) and various ligands (3.0 mol %) in tetrahydrofuran (THF) at 85 °C (Table 1, left column). In addition to the standard bipyridyl-type ligands, somewhat unusual diphosphine ligands were also investigated. Table 1 summarizes the total yield of borylation products **1b**−**1d** and the ratio of *para*-product **1b** and *meta*-products **1c** and **1d**. As already well-documented, the use of 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbpy), the standard ligand for C−H borylation introduced by Ishiyama, Miyaura, and

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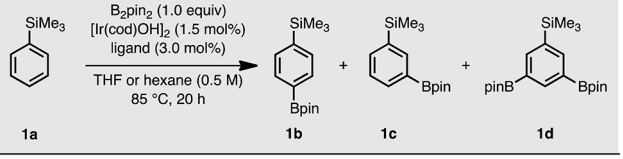
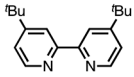
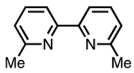
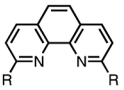
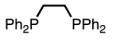
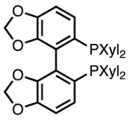
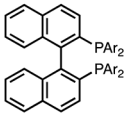
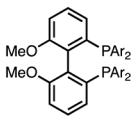
Table 1. Effects of Ligand and Solvent in the Regioselectivity of Iridium-Catalyzed C−H Borylation of Trimethylphenylsilane (1a)[a]



1a 1b 1c 1d

ligand		solvent = THF		solvent = hexane	
		yield	1b/(1c+1d)	yield	1b/(1c+1d)
	**dtbpy**	95%	29:71	88%	26:74
	**N1**	28%	27:73	<1%	–
	**N2** (R = Me)	93%	48:52	>99%	44:56
	N3 (R = ^{n}Bu)	>99%	46:54	>99%	42:58
	**dppe**	17%	35:65†	8%	28:72†
	**P1** Xyl = 3,5-$Me_2C_6H_3$	53%	86:14†	5%	56:44†
	**P2** (Ar = Ph)	9%	71:29†	2%	47:53†
	P3 (Ar = Xyl)	45%	80:20†	3%	48:52†
	**P4** (Ar = Ph)	<1%	–	5%	47:53†
	P5 (Ar = Xyl)	50%	77:23†	94%§	88:12†
	P6 (Ar = 3,4,5-$(MeO)_3C_6H_2$)	6%	38:62†	3%	40:60†

[a]Reaction conditions: **1a** (1.0 equiv), B_2pin_2 (1.0 equiv), $[Ir(cod)OH]_2$ (1.5 mol %), ligand (3.0 mol %), THF or *n*-hexane (0.5 M), 85 °C, 20 h. Yields are determined by GC analysis with *n*-dodecane as an internal standard, and the ratio of the regioisomer was determined by ^{1}H NMR analysis. †**1d** was not observed. §Isolated yield.

Hartwig,[8a−c] produced mainly the *meta*-products **1c** and **1d**, thus resulting in 29% selectivity for the *para*-isomer (**1b**/**1c**/**1d** = 29:44:27). As it is well-documented, a significant amount of *meta*,*meta*-diborylated product **1d** (27%) was observed. We next introduced substituents such as methyl and *n*-butyl groups at the 3,3′-positions of bipyridine (**N1**) and 2,9-positions of phenanthroline (**N2** and **N3**),[12] and as expected, the *para*-selectivity was increased to 48% when 2,9-dimethyl-1,10-phenanthroline (**N2**) was used as the ligand. We further screened 15 different bipyridyl- and phenanthroline-type ligands with various substitution patterns, but a ligand displaying higher *para*-selectivity was not identified (see the Supporting Information for details).

We then turned our attention to diphosphine ligands, but as already known,[8e,13] the use of 1,2-(diphenylphosphino)ethane showed much lower catalytic activity (17% yield) and site-selectivity (35% *para*). Surprisingly, however, we observed high *para*-selectivity when bulky diphosphines **P1**−**P5** were employed as ligands. Moreover, in line with our sterically controlled borylation scenario, the formation of *meta*,*meta*-diborylated product **1d** was completely suppressed with these diphosphine ligands. For example, the use of a SEGPHOS-type ligand having 3,5-xylyl groups on phosphorus (**P1**) furnished the borylation products with 86% *para*-selectivity. The beneficial effect of the 3,5-xylyl group was also observed in the BINAP series (**P3**: 80% *para*-selectivity, 45% yield). The bulky BIPHEP ligand Xyl-MeO-BIPHEP (**P5**) showed 77% *para*-selectivity, albeit with moderate catalytic activity (50% yield). Given the recent report by Hartwig that similar BIPHEP-type ligand **P6** performs well in the rhodium-catalyzed aromatic C−H silylation,[6d,e] we also tested **P6** in the iridium-catalyzed C−H borylation. Very interestingly, the use of **P6** gave the borylation products in much lower *para*-selectivity (38% *para*) and yield (6%). As clearly observed in the BIPHEP series (**P4**−**P6**), subtle differences of substituents on phosphorus atoms significantly affect both the site-selectivity and catalytic activity (highlighted in blue in Table 1).[14]

After further optimization of the reaction conditions, we found that the effect of solvent is also dramatic. In particular, when the $[Ir(cod)OH]_2$/Xyl-MeO-BIPHEP-catalyzed C−H borylation of **1a** was conducted in *n*-hexane, both the yield and *para*-selectivity were dramatically increased (94% isolated yield, 88% *para*-selectivity; highlighted in yellow). Very interestingly, the solvent effect of hexane was found to be specific only for Xyl-MeO-BIPHEP (**P5**) (Table 1, right column). Taken together, we have established a highly *para*-selective aromatic C−H borylation by $[Ir(cod)OH]_2$/Xyl-MeO-BIPHEP catalyst in *n*-hexane, which overturns the prevailing orthodoxy that iridium catalysts cannot distinguish *meta*- and *para*-C−H bonds of monosubstituted benzene derivatives.

C−H Borylation of Arenes by Ir/Xyl-OMe-BIPHEP. We next attempted borylation of monosubstituted benzene derivatives under the established $[Ir(cod)OH]_2$/Xyl-MeO-BIPHEP catalysis in *n*-hexane. As shown in Figure 3, extremely high *para*-selectivity (83−90%) was obtained for the C−H borylations of triethylphenylsilane (**2**), *tert*-butylbenzene (**3**), and *tert*-amylbenzene (**4**). Decreasing the steric bulk of the substituent to isopropyl (**5**) or ethyl (**6**) reduced the *para*-selectivity (58 and 31%, respectively), which indicates that the steric repulsion between the substituent on the benzene ring and the ligand (iridium catalyst) is the major factor in inducing *para*-selectivity.[15] We tested a number of other monosubstituted benzene derivatives having a quaternary carbon center (R_3C, **7**−**9**; $R_2(RO)C$, **10**−**12**; $R(RO)_2C$, **13**, where R is carbyl or silyl) on the benzene rings, and they were all transformed to the corresponding C−H borylation products with high *para*-selectivity (71−91%). Not only aliphatic substituents but also functional groups such as aromatic groups, ester groups, silyl ethers, and ketals were tolerated well under the present conditions. Alcohols **9** and **10** were also applicable with slightly lower yields. When yields were moderate to low, reasonable amounts of starting materials remained. It is worth noting that the highly *para*-selective C−H borylation of a bisphenol AP derivative **7** can be applied to postsynthesis functionalization of polymeric materials.

To understand the effect of the peculiar ligand Xyl-MeO-BIPHEP (**P5**), disubstituted benzene derivatives were also subjected to the established C−H borylation conditions. Figure 4 shows that *ortho*-disubstituted benzene derivatives **14**−**16** were borylated in high yields (84−87%), almost independent of their electronic characteristics. In contrast, borylation yields of *meta*-disubstituted benzene derivatives **17**−**19** decreased as the substituents become bulkier (OMe < Me < CF_3). The C−H borylation of unsymmetrical *ortho*-disubstituted benzenes

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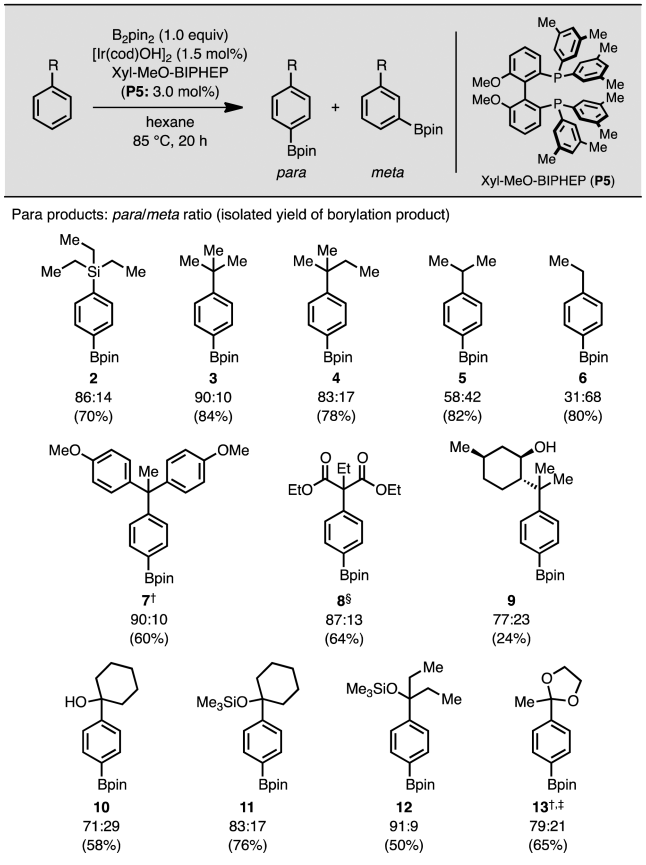

Figure 3. Scope of C−H borylation of monosubstituted benzene derivatives by $[Ir(cod)OH]_2$/Xyl-MeO-BIPHEP catalyst. †3 mol % of Ir and 6 mol % of **P5**. ‡40 h. §3 days.

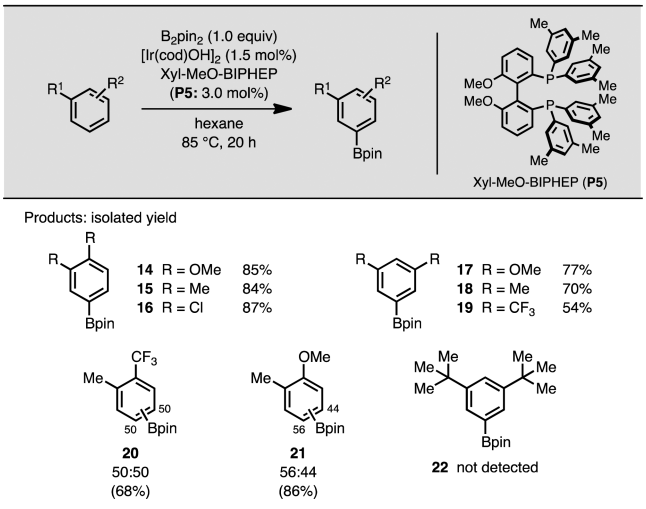

Figure 4. Scope of C−H borylation of disubstituted benzene derivatives by $[Ir(cod)OH]_2$/Xyl-MeO-BIPHEP catalyst.

having substituents that are similar in size but electronically different (**20** and **21**) yielded almost equal amounts of the two regioisomers. Manifestation of small electronic effects in terms of regioselectivity is in sharp contrast to Hartwig's rhodium-catalyzed C−H silylation.[6d,e] The very bulky substrate 1,3-di-*tert*-butylbenzene (**22**) did not react under the present conditions. Overall, the present $[Ir(cod)OH]_2$/Xyl-MeO-BIPHEP catalyst represents a unique, steric-controlled, *para*-selective, aromatic C−H borylation that should find use in streamlined and predictable chemical synthesis.

Application to Pharmaceutical Molecules. Finally, we demonstrated the utility of the newly developed C−H borylation in the late-stage functionalization of pharmaceutical molecules. As listed in Figure 5a, there are a number of

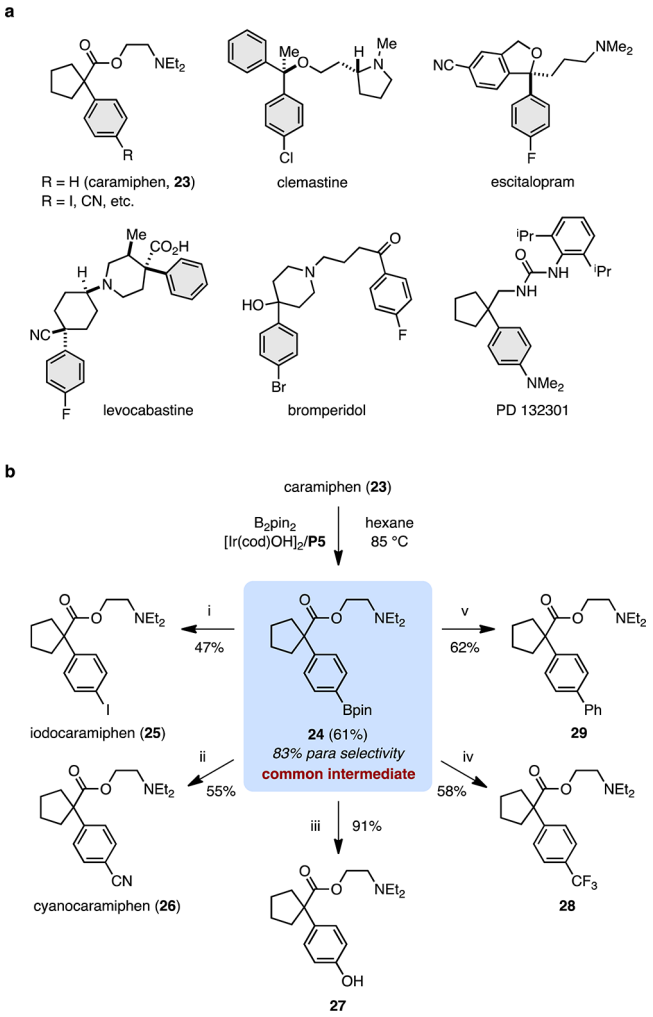

Figure 5. *para*-Selective functionalization of pharmaceutically relevant molecules. (a) Representative pharmaceutical molecules having benzene moieties substituted by a quaternary carbon. (b) Rapid synthesis of caramiphen derivatives by C−H borylation and subsequent C−B functionalization. Reaction conditions: (i) CuI, 1,10-phenanthroline·H_2O, KI, MeOH/H_2O, 80 °C, 12 h; (ii) $Cu(NO_3)_2 \cdot 3H_2O$, $Zn(CN)_2$, CsF, MeOH/H_2O, 100 °C, 6 h; (iii) aq NaOH, aq H_2O_2, THF, 25 °C, 3 h; (iv) Cu(1,10-phenanthroline)-CF_3, KF, 50 °C, 2 h; (v) PhI, $Pd(PPh_3)_4$, K_2CO_3, toluene/H_2O, 80 °C, 36 h.

pharmaceutically relevant molecules having benzene moieties substituted by quaternary carbon substituents, which are suitable for rapid derivatization via our *para*-selective C−H borylation reaction.[16] For example, caramiphen (**23**) is an anticholinergic drug used in the treatment of Parkinson's disease.[17] It is known that the activity and selectivity of caramiphen can be improved by functionalization at the *para*-position of the benzene ring.[18] By using our method, caramiphen was borylated directly with high *para*-selectivity (83%) even in the presence of ester and amino groups (Figure 5b). The *para*-borylated caramiphen **24**, isolated in 61% yield,

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was then easily converted into known caramiphen derivatives, iodocaramiphen (**25**) and cyanocaramiphen (**26**), as well as new derivatives **27**−**29** by the reported C−B functionalization procedures (Figure 5b).[19] Considering that caramiphen derivatives **25** and **26** were synthesized through five steps from a simple molecule in previous report,[18b] the highly step-economical structure diversification shown here bodes well for the potential of *para*-selective C−H borylation in medicinal chemistry.

CONCLUSION

The development of predictable and truly general site-selective C−H functionalization is at the heart of future chemical synthesis. Although both steric and electronic effects influence the regiochemical outcome of chemical reactions, in most cases, devising a C−H functionalization method that relies solely on steric factors not only represents a fundamental challenge but also has significant impacts in numerous applications, particularly in the rapid discovery and optimization of pharmaceuticals and materials. The developed $[Ir(cod)OH]_2$/Xyl-MeO-BIPHEP catalyst is a new-generation catalyst toward this end, affecting one of the most important reactions (*para*-selective aromatic C−H functionalization) controlled by sterics. The simple, yet powerful, concept of using a bulky catalyst to allow exclusive chemical reactions at *para*-C−H bonds over *ortho*- and *meta*-C−H bonds will likely be applicable to a range of aromatic C−H functionalization reactions.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all 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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