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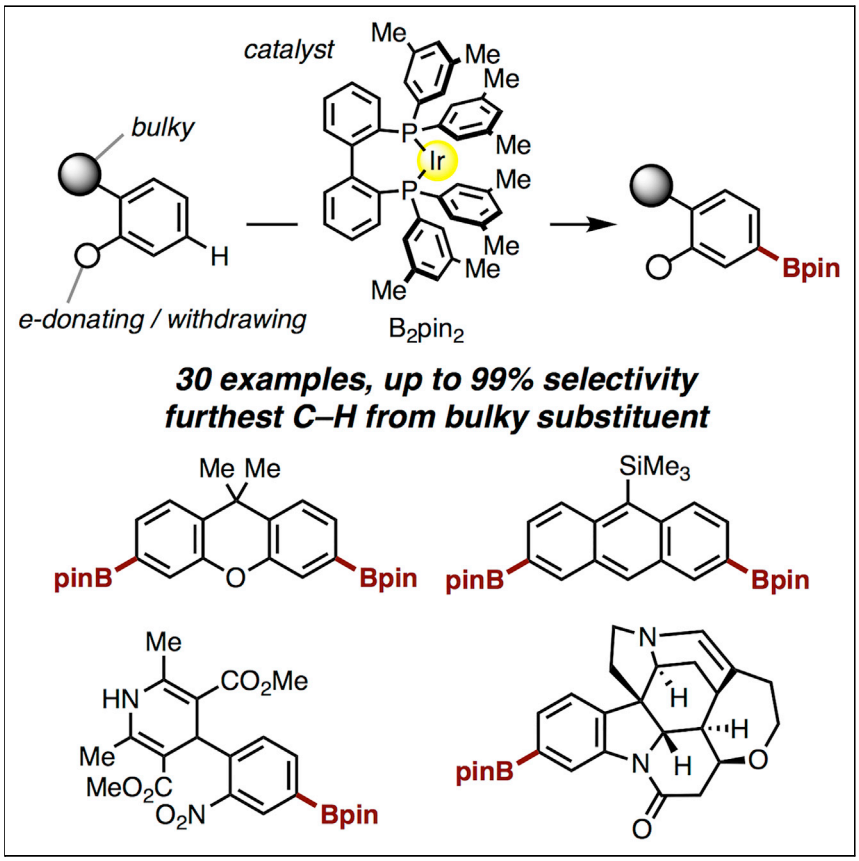
Selective Transformation of Strychnine and 1,2-Disubstituted Benzenes by C–H Borylation



Saito et al. present the highly C3-selective C–H borylation of strychnine along with olefin isomerization, catalyzed by an iridium complex with a diphosphine ligand. This method enabled the rapid production of 15 strychnine derivatives. This catalyst system was also generally effective for the C–H functionalization of unsymmetric 1,2-disubstituted benzene derivatives, including fused π-systems and pharmaceuticals, in which the C–H positions furthest away from the bulky groups were borylated with high selectivity.

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HIGHLIGHTS

The C–H borylation of strychnine along with olefin isomerization

Rapid preparation of 15 strychnine derivatives

C–H borylation of fused π-systems and pharmaceuticals with high site selectivity

Predictable site selectivity at the furthest position of bulky substituents

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Selective Transformation of Strychnine and 1,2-Disubstituted Benzenes by C–H Borylation

Yutaro Saito,[1,4] Kotono Yamanoue,[2,3] Yasutomo Segawa,[1,2,*] and Kenichiro Itami[1,2,3,5,*]

SUMMARY

C–H functionalizations of complex molecules such as natural products, pharmaceuticals, and π-conjugated systems are at the heart of constructing and modifying organic molecules, whereby the selectivity and predictability are of the utmost importance. Herein, we report the highly C3-selective C–H borylation of strychnine along with olefin isomerization, catalyzed by an iridium complex with a diphosphine ligand. This method enabled us to rapidly produce 15 strychnine derivatives by using the corresponding C3-borylated and isomerized analog as the common synthetic intermediate. The present catalyst system was also generally effective for the C–H functionalization of unsymmetric 1,2-disubstituted benzene derivatives, including fused π-systems (xanthenes, fluorenes, naphthalenes, and anthracenes) and pharmaceuticals (Nifedipine), in which the C–H positions furthest away from the bulky groups were borylated with high selectivity.

INTRODUCTION

Methods for the functionalization of complex natural organic compounds have received much attention in recent years, especially in the context of drug discovery.[1–5] Even though many complex organic molecules are readily available from natural sources, their artificial synthesis remains challenging. Accordingly, the derivatization of complex natural compounds offers an effective strategy for the rapid construction of libraries of drug candidates with high structural complexity and diverse functionality. Meanwhile, the methods for the selective introduction of functional groups into complex structures are still relatively limited, and therefore, simple and predictable functionalization methods are urgently required.[6–12]

Strychnine, the indole alkaloid isolated from the seeds of *Strychnos nux-vomica*,[13,14] represents one of the most famous natural products, given its very complex structure and long history in natural-product synthesis and medicinal science.[15–18] Strychnine ($C_{21}H_{22}N_2O_2$) contains tertiary amine, amide, alkene, ether, and indoline moieties with six asymmetric carbon atoms, including a quaternary carbon center. Strychnine is severely neurotoxic, as it inhibits the chloride channel of the glycine receptor.[19] Even though various health benefits have been reported,[20] strychnine has been used predominantly as a poison in e.g., rodenticides. Considering the lower toxicity of brucine, which is a natural analog of strychnine with dimethoxy groups at the aromatic C–H positions (C2 and C3),[21] and the X-ray crystal structure analysis of the human glycine receptor bound to strychnine,[22] it seems feasible to expect a significantly reduced toxicity from strychnine derivatives that contain substituents at C2 and/or C3.

The Bigger Picture

The derivatization of complex natural organic compounds has recently received much attention, especially in the field of drug discovery. Even though many complex organic molecules are readily available from natural sources, their controlled synthesis is difficult. Yet, the derivatization of complex natural compounds enables the rapid construction of libraries of drug candidates with structural complexity and diverse functionality. Herein, we report a site-selective C–H borylation reaction of an arene moiety in a variety of 1,2-disubstituted benzenes. We demonstrated that a variety of strychnine derivatives (15 examples) were readily prepared by using a common synthetic intermediate. This result indicates that such mild and site-selective C–H functionalizations could find applications in medicinal chemistry and materials science.

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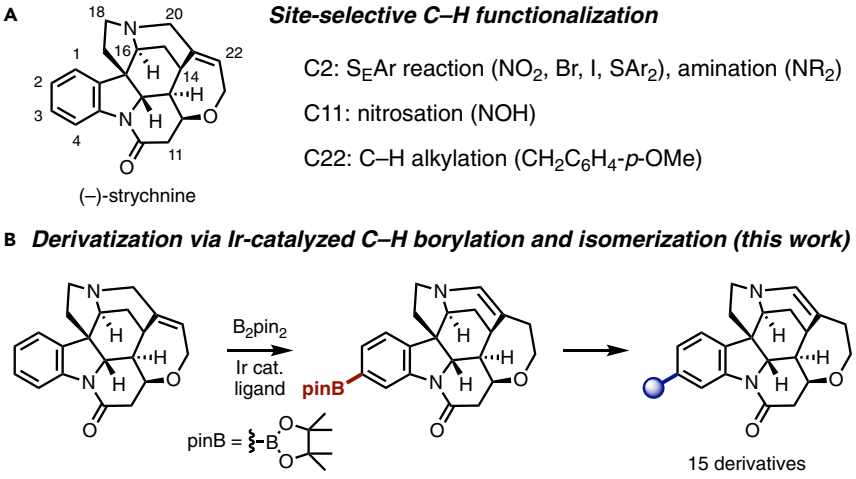

Figure 1. Site-Selective C–H Functionalization of Strychnine along with Olefin Isomerization

(A) Structure of strychnine and its site-selective C–H functionalization.

(B) Derivatization of strychnine via an Ir-catalyzed C–H borylation along with olefin isomerization.

However, despite their potential importance, methods for the selective C–H functionalization at C2 and C3 of strychnine remain scarce.[23–34] As shown in Figure 1A, there are only three reported methods for the site-selective C–H functionalization of strychnine.[23–28] The nitrosation of the C11 position, the α-position relative to the carbonyl group, has been used for the conversion into other natural products.[23] The selective alkylation of an alkenyl C–H (C22) was achieved using a Ru-based catalyst.[24] Among the aromatic C–H positions of strychnine (C1–C4), only C2 can be functionalized selectively and directly by S_EAr-type reactions such as nitration,[25] halogenation,[26,27] amination,[28] and thianthrenation.[29] The photoinduced amination using aminium radicals occurs at the most nucleophilic position (C2),[30] which means that the synthesis of C3-functionalized strychnine requires multistep transformations.[27,31] Unselective C–H functionalizations of strychnine are represented by the radical C–H activation and conjugate addition to a dehydroalanine derivative at C16, C18, and C20;[32] the sulfonylation at C14, C20, and C22;[33] as well as the acid-mediated C–H oxygenation at C2 and C4.[34] Given the structural complexity and potential utility of strychnine and related complex alkaloids, methods for their site-selective C–H functionalization remain as challenging as they can be expected to be rewarding.[35]

Herein, we report the highly C3-selective C–H borylation of strychnine, catalyzed by an iridium complex with a diphosphine ligand along with an olefin isomerization (Figure 1B). This method enabled us to rapidly produce 15 strychnine derivatives from the common synthetic intermediate. Surprisingly, this catalyst system was generally effective for the C–H functionalization of unsymmetric 1,2-disubstituted benzene derivatives, including fused π-systems and pharmaceuticals, in which the furthest C–H positions of bulky groups (e.g., quaternary carbons) are borylated with high selectivity.

RESULTS AND DISCUSSION

Initially, we carried out ligand screening for the C–H borylation of strychnine (**1a**) catalyzed by iridium complexes. The conventional catalyst system $[Ir(cod)OMe]_2$/dtbpy (cod = 1,8-cyclooctadiene and dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridyl)[36] afforded a complex mixture of borylated products including mono-, di-, and

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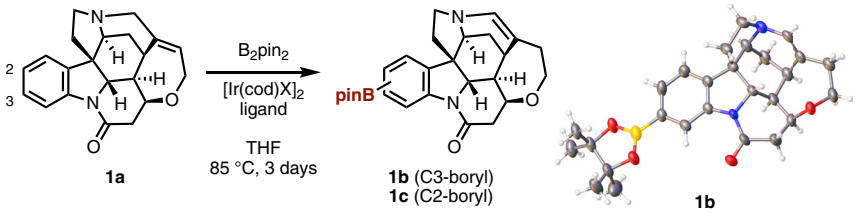

ligand	X	result
dtbpy	OMe	complex mixture of mono-, di-, and triborylated products
MeO-Xyl-BIPHEP	OH	29% (C3/C2 = 29:71)
L1	OH	65% (C3/C2 = 73:27)

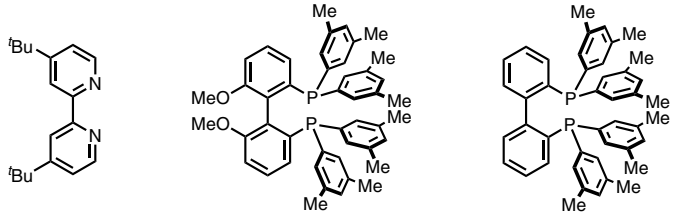

Figure 2. Site-Selective C–H Borylation along with Olefin Isomerization of Strychnine
ORTEP of **1b** was shown with thermal ellipsoids at 50% probability; solvent molecules are omitted for clarity.

tri-borylated strychnines, probably due to the low selectivity of the C–H activation that occurred not only at the aromatic positions (C1–C4) but also at the alkenyl (C22) and possibly aminoalkyl (C16, C18, and C20) positions. When our previously reported catalyst ([Ir(cod)OH]$_2$/MeO-Xyl-BIPHEP)[37] (Figure 1) was used under the originally reported conditions (in hexane), the borylation did not proceed because of the low solubility of **1a** in hexane. In tetrahydrofuran (THF), the borylation occurred in low yield (29%). After extensive ligand screening, we found that [Ir(-cod)OH]$_2$/**L1** (THF, 85°C, 3 days) successfully borylates **1a** in 65% yield with high C3-selectivity (C3/C2 = 73:27). The C3- (**1b**) and C2-borylation products (**1c**) were isolated and their structures were determined by single-crystal X-ray diffraction analysis (Figure 2). The X-ray crystallography revealed that the four chiral centers, the carbonyl group, and the highly nucleophilic amine moiety of strychnine remained unchanged under the applied borylation conditions, whereas the C21–C22 double bond was isomerized to the C20–C21, where isomerization of strychnine was known to occur by the treatment of transition metal catalysts.[38,39] Thus, these catalysts enable the one-pot two-step transformation of strychnine.

Subsequently, we used the thus-obtained strychnine derivative, **1b**, in a further transformation reaction. Using previously reported protocols, **1b** was easily converted into a variety of derivatives (**1d–1r**) (Figure 3).[40–46] Each derivative was obtained from **1b** in a single step in e.g., oxidation, Cu-catalyzed iodination, Cu-mediated trifluoromethylation, Cu-catalyzed azidation, Cu-catalyzed amination, and Pd-catalyzed Suzuki-Miyaura cross-coupling reactions. Given that the synthesis of **1d–1r** requires numerous steps when using conventional total synthesis routes, the present regioselective C–H borylation is of outstanding synthetic utility. Subsequently, we examined the binding ability of **1d–1r** toward the glycine receptor, as this determines the toxicity of the strychnine derivatives (see Supplemental

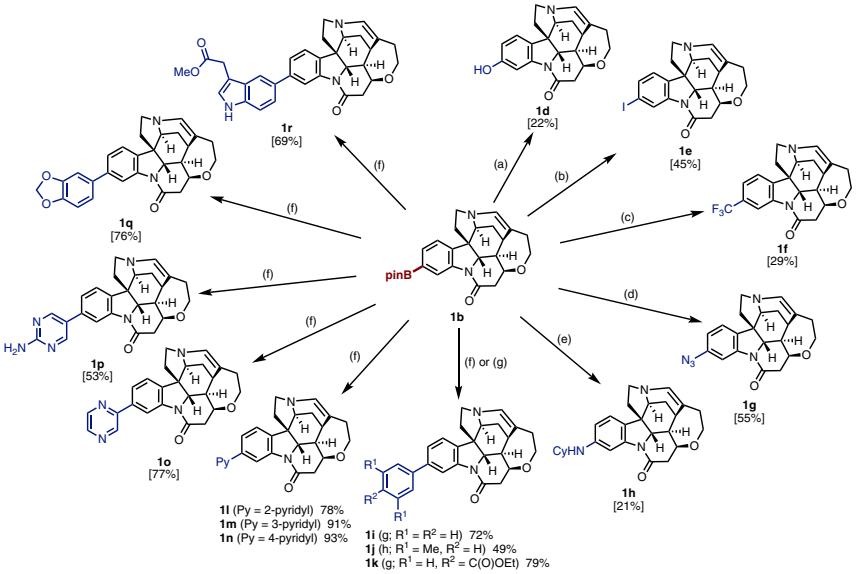

Figure 3. Rapid Derivatization from 1b

Reaction conditions: (A) 1 M NaOH (1.0 equiv), 35% H_2O_2 (2.3 equiv), THF, rt, 5.5 h; (B) CuI (10 mol %), phen (20 mol %), KI (1.5 equiv), MeOH/H_2O, 80°C, 4 h; (C) Cu(phen)CF_3 (1.2 equiv), KF (1.0 equiv), DMF, 50°C, 3 h; (D) NaN_3 (1.8 equiv), $Cu(OAc)_2$ (9.3 mol %), MeOH, 55°C, 1.5 h; (E) $CyNH_2$ (1.9 equiv), $Cu(OAc)_2 \cdot H_2O$ (23 mol %), KF (3.9 equiv), MeCN, MS 4A, O_2, 80°C, 12.5 h; (F) ArBr or ArI (1.5–5.3 equiv), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (4.9–11 mol %), K_2CO_3 (20–22 equiv), toluene/H_2O, 80°C, 12–22 h; and (G) 1-bromo-3,5-dimethylbenzene (1.2 equiv), $Pd(PPh_3)_4$ (1.8 mol %), K_2CO_3 (2.3 equiv), toluene/H_2O, 80°C, 12 h. phen, 1,10-phenanthroline; Cy, cyclohexyl.

Information for detail). All derivatives with substituents at the C3 position showed a clearly decreased binding affinity to the glycine receptor.[39]

With these C–H borylation conditions in hand, we investigated the substrate scope (Figure 4). The borylation proceeds selectively at the least hindered position (C5, i.e., the *para*-position relative to the *tert*-butyl group) of **2a** and **3a**, even in the presence of coordinative directing groups, such as methoxy and methoxymethyl (MOM) groups.[47] The hydroxy group of **4a** is well tolerated under these reaction conditions. The reaction also proceeds smoothly in the presence of a *para*-substituted benzene ring (**5a**). Not only quaternary carbon atoms but also the trimethylsilyl group of **6a** can be used as a bulky substituent. The small increase in steric bulk by employing a *tert*-amyl group in **7a** does not affect the reactivity and regioselectivity of this borylation. Fortunately, the selectivity is preserved even when using slightly smaller substituents. Substrates with tertiary carbon atoms, i.e., **8a** (cyclohexyl group) and **9a** (isopropyl group), are borylated with high regioselectivity. Excellent selectivity (97:3) is also obtained for benzene rings with sterically demanding substituents, albeit the yield is low (**10a**). Ketal moieties, obtained from the protection of carbonyl groups, can also be used as bulky substituents. The effect of the presence of other groups was investigated through the borylation of **11a–20a**. The methoxy group in **11a** can be replaced with a methyl (**12a**) or a trifluoromethyl group (**13a**). Given that both electron-donating (OMe) and -withdrawing (CF_3) groups afford the same regioselectivity (87:13), the selectivity of the current reaction should be virtually independent of the electronic effects of the relatively small substituents. Carbon-halogen bonds, such as C–Br, C–Cl, and C–F, remain intact under the borylation conditions applied in this study and furnish the corresponding borylated products (**14b–16b**). Arenes fused with saturated rings (**17a–19a**), which are frequently encountered in

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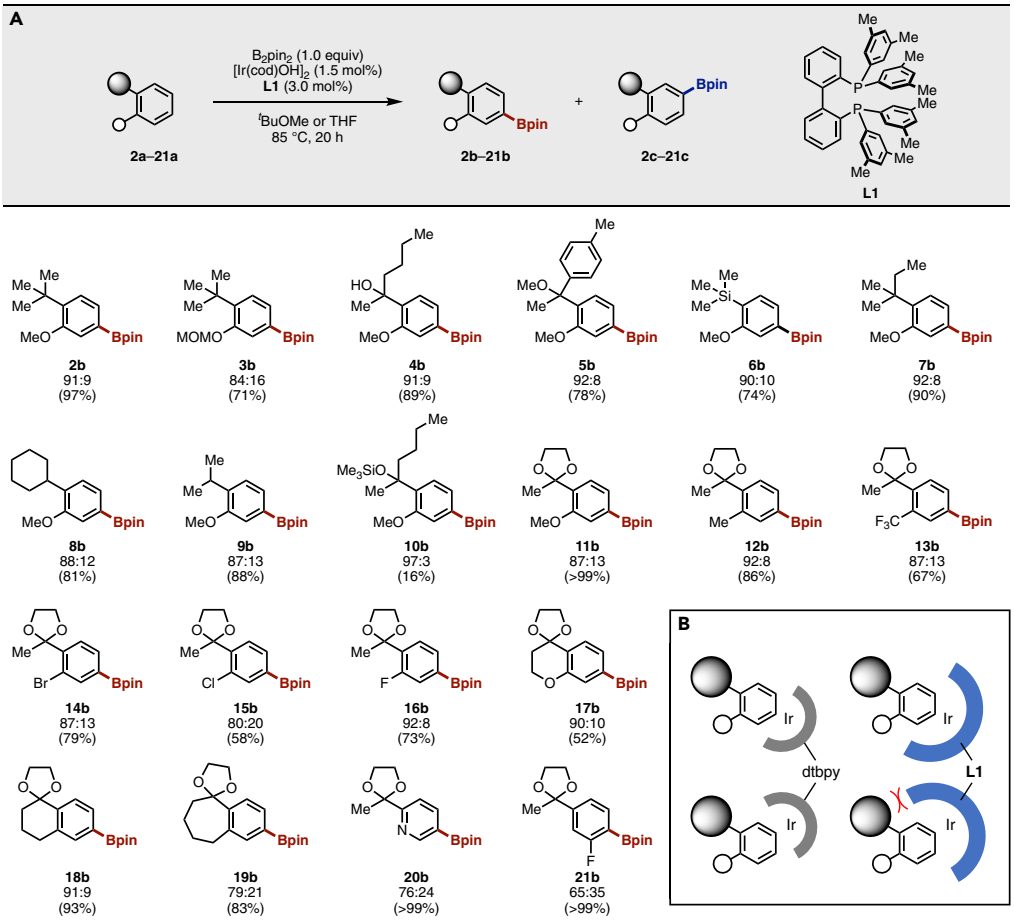

Figure 4. The Regioselective C–H Borylation of Unsymmetrically 1,2- and 1,3-Disubstituted Benzenes

(A) Yields refer to the combined yields of the borylated products (**b** + **c**), structures of the major products (**2b**–**21b**) are shown, the **b**/**c** ratio was determined by ^{1}H NMR spectroscopy, and the combined isolated yields of the borylation products are shown in parentheses.

(B) Hypothetical schematic illustrations of the mechanism of the C–H borylation with the conventional ligand dtbpy (left) or **L1** (right).

synthetic intermediates of bioactive compounds, are borylated in good yield with high selectivity. Furthermore, pyridine derivative **20a** can also be borylated with moderate selectivity. The hypothetical schematic illustrations of the mechanism of C–H borylation are shown in Figure 4B. The Ir/dtbpy moiety can be considered as an iridium center surrounded by a small ligand (gray), which repulses only *ortho*-substituents. On the other hand, as we have previously revealed using theoretical calculations, the Ir/MeO-Xyl-BIPHEP catalyst contains a relatively large reaction pocket[48] and Ir/**L1** has similar steric factor (see Supplemental Information for the DFT calculation of Ir/MeO-Xyl-BIPHEP and Ir/**L1**). Thus, the steric repulsion between the ligand and the bulky substituent contributes to the selectivity in addition to the effect of the adjacent groups.

Subsequently, we discovered a distinct regioselectivity difference between conventional iridium catalysts and the present $[Ir(cod)_2OH]_2$/**L1** catalyst system in the C–H borylation of 1,3-disubstituted benzene **21a**. Using the $[Ir(cod)_2OMe]_2$/dtbpy catalyst, **21a** is borylated predominantly at the C5 position (**21b**/**21c** = 39:61), which is not entirely surprising, given that the borylation of the *ortho*-position of the fluoro group is not completely suppressed on account of the relatively small size of the fluoro group (see Table S2). In contrast, when using the

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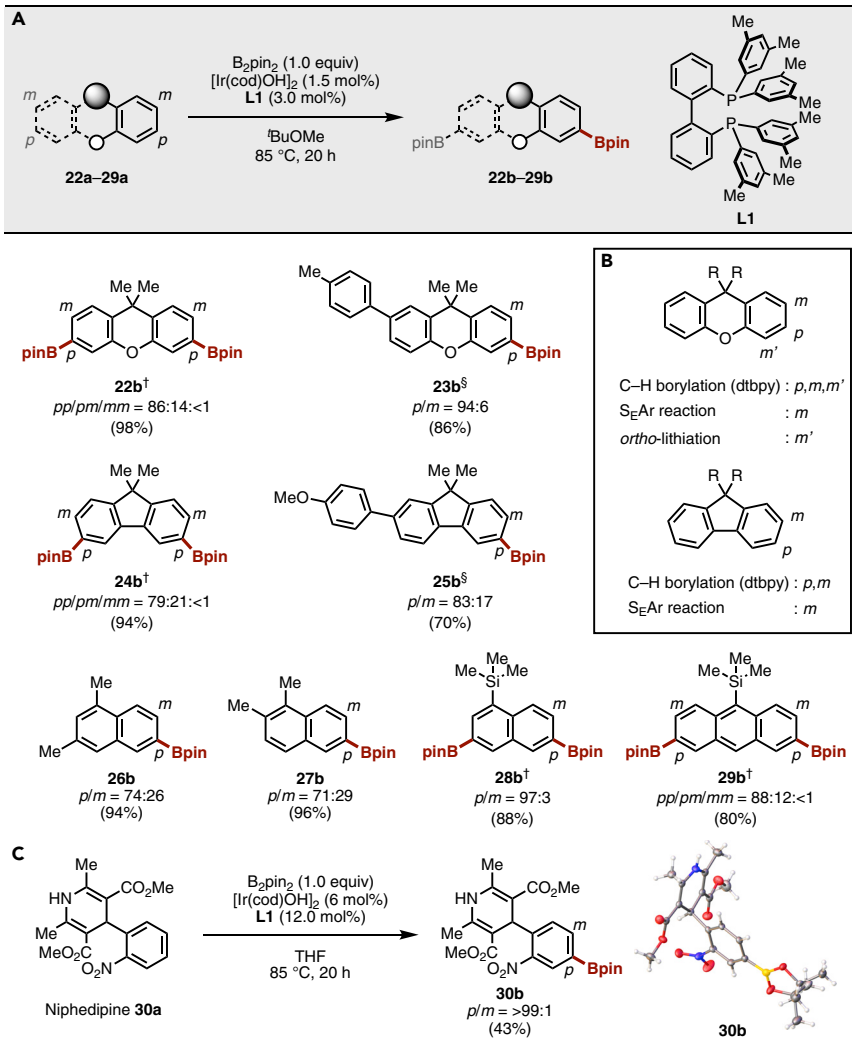

Figure 5. The Regioselective C–H Borylation of Fused π-systems (22a–29a) and a Pharmaceutical Compound (30a)

(A) Yields refer to the combined yields of the borylated products, the structures of the major products (**22b**–**29b**) are shown, the product ratio was determined by ^{1}H NMR spectroscopy, and the combined isolated yields of the borylation products are shown in parentheses. † B_2pin2 (2.0 equiv), $[Ir(cod)OH]_2$ (3.0 mol %), and **L1** (6.0 mol %) were used. § THF was used instead of ^{t}BuOMe.

(B) The positions of the C–H functionalization in xanthene and fluorene (for dtbpy, see Supplemental Information).

(C) Selective C–H borylation of Niphedipine. ORTEP of **30b** is drawn with thermal ellipsoids at 50% probability.

$[Ir(cod)_2OH]_2$/**L1** catalyst, the C6-borylated product **21b** is the major product (**21b**/**21c** = 65:35). This difference was attributed to the different three-dimensional shape of the catalysts.

The current C–H borylation catalyst also allows the regioselective functionalization of a range of aromatic C–H bonds that are otherwise difficult to cleave selectively (Figures 5A–5C). Xanthene and fluorene moieties are fundamentally important structural motifs in organic materials.[49,50] Although the C2- and C3-positions of xanthenes are functionalized selectively by S_EAr reactions and *ortho*-metalations,[51]

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efficient methods to selectively functionalize only the C3-position remain elusive. In addition, conventional C–H borylations randomly occur at the 2-, 3-, and 4-positions to afford complex mixtures (Figure 5B). Similar problems are encountered for fluorenes,[52] which has been attributed to a lack of C–H functionalization controlled by remote steric effects (Figure 5B). As shown in Figure 5A, 9,9-dimethyl-9H-xanthene (**22a**) is selectively borylated under the current reaction conditions at the C3 and C6 positions, i.e., at the positions farthest from its quaternary sp^3 carbon, to yield **22b**. The *p*-anisyl derivative of xanthene **23a** is also borylated with excellent regioselectivity, and surplus borylation at the *p*-anisyl group does not occur. Diborylated fluorene derivative **24b** is obtained from the regioselective borylation of **24a**, which again underlines the synthetic utility of the present reaction, given that multiple steps are necessary to synthesize **24b** using a previously reported method.[53] The borylation of *p*-tolylfluorene **25a** also proceeds with high regioselectivity. This transformation is also applicable to naphthalene and anthracene derivatives. The borylation occurs at the positions farthest from the methyl groups when dimethylnaphthalenes **26a** and **27a** are subjected to the optimal conditions. 1-(Trimethylsilyl)naphthalene **28a** is borylated with high selectivity at the C3 and C6 positions to yield diborylated **28b**. 9-Silylanthracene **29a** is also converted selectively into 3,7-diborylated **29b**. Nifedipine (**30a**), a widely used calcium channel antagonists,[54] could also be borylated at the *para*-position of the bulky substituent with excellent selectivity (>99:1, Figure 5C), while a complex mixture was afforded when dtbpy was used instead (see the Supplemental Information). Overall, the developed regioselective C–H borylation can be used to functionalize aromatic C–H bonds with a site selectivity that is difficult to attain using conventional methods.

Conclusions

In summary, we have developed a regioselective C–H borylation method for strychnine and unsymmetrically 1,2-disubstituted benzenes catalyzed by an Ir-based complex with a diphosphine ligand that exerts a remote steric effect, in addition to adjacent sterics. The protocol was applied to the rapid derivatization of a strychnine analog, which delivered 15 derivatives in only one step from a common borylated intermediate. The developed protocol offers complementary regioselectivity to conventional methods for the functionalization of arenes that can otherwise not be accomplished without difficulty. Moreover, a variety of π-systems that represent important structural motifs in functional materials and a pharmaceutical compound, Nifedipine, were borylated regioselectively. The remote steric effect, which affects the regioselectivity in this system, should open new research avenues in the area of C–H functionalization chemistry.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

DATA AND CODE AVAILABILITY

Crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC) under reference numbers CCDC: 1853061, 1853063, 1853064, and 1971283. These data can be obtained free of charge from CCDC at http://www.ccdc.cam.ac.uk/data_request/cif.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.chempr.2020.02.004.

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AUTHOR CONTRIBUTIONS

Y. Segawa and K.I. conceived and directed the project. Y. Saito performed the experiments. K.Y. discovered the borylation of Niphedipine. Y. Segawa analyzed the X-ray crystal structures. Y. Saito, Y. Segawa, and K.I. wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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REFERENCES

1. Carlson, E.E. (2010). Natural products as chemical probes. ACS Chem. Biol. *5*, 639–653.
2. Bunnage, M.E. (2011). Getting pharmaceutical R&D back on target. Nat. Chem. Biol. *7*, 335–339.
3. Kesavan, S., and Marcaurelle, L.A. (2013). Translational synthetic chemistry. Nat. Chem. Biol. *9*, 210–213.
4. Robles, O., and Romo, D. (2014). Chemo- and site-selective derivatizations of natural products enabling biological studies. Nat. Prod. Rep. *31*, 318–334.
5. Bauer, A., and Brönstrup, M. (2014). Industrial natural product chemistry for drug discovery and development. Nat. Prod. Rep. *31*, 35–60.
6. Godula, K., and Sames, D. (2006). C–H bond functionalization in complex organic synthesis. Science *312*, 67–72.
7. McMurray, L., O'Hara, F., and Gaunt, M.J. (2011). Recent developments in natural product synthesis using metal-catalysed C–H bond functionalisation. Chem. Soc. Rev. *40*, 1885–1898.
8. Yamaguchi, J., Yamaguchi, A.D., and Itami, K. (2012). C–H bond functionalization: emerging synthetic tools for natural products and pharmaceuticals. Angew. Chem. Int. Ed. Engl. *51*, 8960–9009.
9. Wencel-Delord, J., and Glorius, F. (2013). C–H bond activation enables the rapid construction and late-stage diversification of functional molecules. Nat. Chem. *5*, 369–375.
10. Hartwig, J.F., and Larsen, M.A. (2016). Undirected, homogeneous C–H bond functionalization: challenges and opportunities. ACS Cent. Sci. *2*, 281–292.
11. Cernak, T., Dykstra, K.D., Tyagarajan, S., Vachal, P., and Krska, S.W. (2016). The medicinal chemist's toolbox for late stage functionalization of drug-like molecules. Chem. Soc. Rev. *45*, 546–576.
12. Shugrue, C.R., and Miller, S.J. (2017). Applications of nonenzymatic catalysts to the alteration of natural products. Chem. Rev. *117*, 11894–11951.
13. Pelletier, P.J., and Caventou, J.B. (1818). Note sur un nouvel alcali. Ann. Chim. Phys. *8*, 323.
14. Pelletier, P.J., and Caventou, J.B. (1819). Mémoire sur un nouvel alcali végétal (la strychnine) trouvé dans la fève de Saint-Ignace la noix vomique etc. Ann. Chim. Phys. *10*, 142.
15. Bonjoch, J., and Solé, D. (2000). Synthesis of strychnine. Chem. Rev. *100*, 3455–3482.
16. Cannon, J.S., and Overman, L.E. (2012). Is there no end to the total syntheses of strychnine? Lessons learned in strategy and tactics in total synthesis. Angew. Chem. Int. Ed. Engl. *51*, 4288–4311.
17. Martin, D.B.C., and Vanderwal, C.D. (2011). A synthesis of strychnine by a longest linear sequence of six steps. Chem. Sci. *2*, 649–651.
18. Jones, S.B., Simmons, B., Mastracchio, A., and MacMillan, D.W.C. (2011). Collective synthesis of natural products by means of organocascade catalysis. Nature *475*, 183–188.
19. Betz, H., and Laube, B. (2006). Glycine receptors: recent insights into their structural organization and functional diversity. J. Neurochem. *97*, 1600–1610.
20. Barron, S.E., and Guth, P.S. (1987). Uses and limitations of strychnine as a probe in neurotransmission. Trends Pharmacol. Sci. *8*, 204–206.
21. Guo, J., Meng, H., Li, H.H., and Wang, Q.F. (2016). Determination of strychnine, brucine, strychnine N-oxide, and brucine N-oxide in plasma samples after the oral administration of processed semen strychni extract by high-performance liquid chromatography with ultrasound-assisted mixed cloud point extraction. J. Sep. Sci. *39*, 2553–2561.
22. Huang, X., Chen, H., Michelsen, K., Schneider, S., and Shaffer, P.L. (2015). Crystal structure of human glycine receptor-α3 bound to antagonist strychnine. Nature *526*, 277–280.

23. Zlotos, D.P., Buller, S., Stiefl, N., Baumann, K., and Mohr, K. (2004). Probing the pharmacophore for allosteric ligands of muscarinic M2 receptors: SAR and QSAR studies in a series of bisquaternary salts of caracurine V and related ring systems. J. Med. Chem. *47*, 3561–3571.

24. Lee, D.H., Kwon, K.H., and Yi, C.S. (2011). Selective catalytic C–H alkylation of alkenes with alcohols. Science *333*, 1613–1616.

25. Rosenmund, P. (1961). Über 2-diazo-strychnin. Chem. Ber. *94*, 3342–3345.

26. Petzold, D., and König, B. (2018). Photocatalytic oxidative bromination of electron-rich arenes and heteroarenes by anthraquinone. Adv. Synth. Catal. *360*, 626–630.

27. Wang, J., Li, R., Dong, Z., Liu, P., and Dong, G. (2018). Complementary site-selectivity in arene functionalization enabled by overcoming the ortho constraint in palladium/norbornene catalysis. Nat. Chem. *10*, 866–872.

28. Ruffoni, A., Juliá, F., Svejstrup, T.D., McMillan, A.J., Douglas, J.J., and Leonori, D. (2019). Practical and regioselective amination of arenes using alkyl amines. Nat. Chem. *11*, 426–433.

29. Berger, F., Plutschack, M.B., Riegger, J., Yu, W., Speicher, S., Ho, M., Frank, N., and Ritter, T. (2019). Site-selective and versatile aromatic C–H functionalization by thianthrenation. Nature *567*, 223–228.

30. Svejstrup, T.D., Ruffoni, A., Juliá, F., Aubert, V.M., and Leonori, D. (2017). Synthesis of arylamines via aminium radicals. Angew. Chem. Int. Ed. Engl. *56*, 14948–14952.

31. Tedeschi, E., Dukler, S., Pfeffer, P., and Lavie, D. (1968). Studies on strychnine derivatives and conversion into brucine. Tetrahedron *24*, 4573–4580.

32. Aycock, R.A., Pratt, C.J., and Jui, N.T. (2018). Aminoalkyl radicals as powerful intermediates for the synthesis of unnatural amino acids and peptides. ACS Catal. *8*, 9115–9119.

33. Edward, J.T., Farrell, P.G., Samad, S.A., Wojtowski, R., and Wong, S.C. (1980). Sulfonation of strychnine and some related compounds by sulfur dioxide – manganese dioxide (the Leuchs reaction). Can. J. Chem. *58*, 2380–2385.

34. Börgel, J., Tanwar, L., Berger, F., and Ritter, T. (2018). Late-stage aromatic C–H oxygenation. J. Am. Chem. Soc. *140*, 16026–16031.

35. He, J., Hamann, L.G., Davies, H.M.L., and Beckwith, R.E.J. (2015). Late-stage C–H functionalization of complex alkaloids and drug molecules via intermolecular rhodium-carbenoid insertion. Nat. Commun. *6*, 5943.

36. Ishiyama, T., Takagi, J., Ishida, K., Miyaura, N., Anastasi, N.R., and Hartwig, J.F. (2002). Mild iridium-catalyzed borylation of arenes. High turnover numbers, room temperature reactions, and isolation of a potential intermediate. J. Am. Chem. Soc. *124*, 390–391.

37. Saito, Y., Segawa, Y., and Itami, K. (2015). *para*-C-H borylation of benzene derivatives by a bulky iridium catalyst. J. Am. Chem. Soc. *137*, 5193–5198.

38. Chakravarti, R.N., and Robinson, R. (1947). Strychnine and brucine; the preparation of neostrychnine and neobrucine. J. Chem. Soc. 78–80.

39. Mohsen, A.M.Y., Heller, E., Holzgrabe, U., Jensen, A.A., and Zlotos, D.P. (2014). Structure–activity relationships of strychnine analogs at glycine receptors. Chem. Biodivers. *11*, 1256–1262.

40. Miyaura, N., and Suzuki, A. (1995). Palladium-catalyzed cross-coupling reactions of organoboron compounds. Chem. Rev. *95*, 2457–2483.

41. Liskey, C.W., and Hartwig, J.F. (2013). Iridium-catalyzed C–H borylation of cyclopropanes. J. Am. Chem. Soc. *135*, 3375–3378.

42. Partridge, B.M., and Hartwig, J.F. (2013). Sterically controlled iodination of arenes via iridium-catalyzed C–H borylation. Org. Lett. *15*, 140–143.

43. Litvinas, N.D., Fier, P.S., and Hartwig, J.F. (2012). A general strategy for the perfluoroalkylation of arenes and arylbromides by using arylboronate esters and [(phen)CuRF]. Angew. Chem. Int. Ed. *51*, 536–539.

44. Grimes, K.D., Gupte, A., and Aldrich, C.C. (2010). Copper(II)-catalyzed conversion of aryl/heteroaryl boronic acids, boronates, and trifluoroborates into the corresponding azides: substrate scope and limitations. Synthesis *2010*, 1441–1448.

45. Tzschucke, C.C., Murphy, J.M., and Hartwig, J.F. (2007). Arenes to anilines and aryl ethers by sequential iridium-catalyzed borylation and copper-catalyzed coupling. Org. Lett. *9*, 761–764.

46. Nifant'ev, I.E., Ivchenko, P.V., Bagrov, V.V., Nagy, S.M., Mihan, S., Winslow, L.N., and Churakov, A.V. (2013). Reaction of 2,8-bis(o-hydroxyaryl)quinolines with group 4 metal alkyls resulting in three distinct coordination modes of the tridentate ligand. X-ray structure of complexes and performance as precursors in ethylene polymerization catalysis. Organometallics *32*, 2685–2692.

47. Snieckus, V. (1990). Directed Ortho metalation. Tertiary amide and o-carbamate directors in synthetic strategies for polysubstituted aromatics. Chem. Rev. *90*, 879–933.

48. Haines, B.E., Saito, Y., Segawa, Y., Itami, K., and Musaev, D.G. (2016). Flexible reaction pocket on bulky diphosphine–Ir complex controls regioselectivity in *para*-selective C–H borylation of arenes. ACS Catal. *6*, 7536–7546.

49. Chen, X., Pradhan, T., Wang, F., Kim, J.S., and Yoon, J. (2012). Fluorescent chemosensors based on spiroring-opening of xanthenes and related derivatives. Chem. Rev. *112*, 1910–1956.

50. Grimsdale, A.C., Chan, K.L., Martin, R.E., Jokisz, P.G., and Holmes, A.B. (2009). Synthesis of light-emitting conjugated polymers for applications in electroluminescent devices. Chem. Rev. *109*, 897–1091.

51. Adams, D.J., Cole-Hamilton, D.J., Harding, D.A.J., Hope, E.G., Pogorzelec, P., and Stuart, A.M. (2004). Towards the synthesis of perfluoroalkylated derivatives of xantphos. Tetrahedron *60*, 4079–4085.

52. Shaya, J., Deschamps, M.A., Michel, B.Y., and Burger, A. (2016). Air-stable Pd catalytic systems for sequential one-pot synthesis of challenging unsymmetrical aminoaromatics. J. Org. Chem. *81*, 7566–7573.

53. Kobin, B., Grubert, L., Blumstengel, S., Henneberger, F., and Hecht, S. (2012). Vacuum-processable ladder-type oligophenylenes for organic–inorganic hybrid structures: synthesis, optical and electrochemical properties upon increasing planarization as well as thin film growth. J. Mater. Chem. *22*, 4383–4390.

54. Vater, W., Kroneberg, G., Hoffmeister, F., Saller, H., Meng, K., Oberdorf, A., Puls, W., Schlossmann, K., and Stoepel, K. (1972). [pharmacology of 4-(2'-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid dimethyl ester (nifedipine, bay a 1040)]. Arzneimittelforschung *22*, 1–14.