Meta Selective C–H Borylation Directed by Secondary Silicon Oxygen Interaction

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Meta Selective C–H Borylation Directed by Secondary Silicon Oxygen Interaction

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Summary Paragraph: Remote meta selective C–H functionalization¹,²,³ of aromatic compounds remains a challenging problem in chemical synthesis. Here, we report an iridium catalyst bearing a bidentate pyridine-pyridone (PY-PYRI) ligand framework that efficiently catalyzes this meta selective borylation reaction. We demonstrate that the developed concept can be employed to introduce a boron functionality at the remote meta position of phenols, phenol containing bioactive and drug molecules, which was an extraordinary challenge. Moreover, we have demonstrated that the method can also be applied for the remote C6 borylation of indole derivatives including tryptophan that was the key synthetic precursor for the total synthesis of Verruculogen and Fumitremorgin A alkaloids. The origin of the remote meta selectivity was described as a secondary silicon oxygen interaction⁴ that was never used in C–H functionalization chemistry.
Transition metal-catalyzed C–H bond activation and functionalization \(^5,6,7,8,9,10,11\) of aromatic compounds has been branded as one of the most significant chemical transformations. This has a profound impact in modern synthetic organic chemistry, ranging from laboratory methods to industrial deployment. \(^12,13\) However, the key underlying principles for the success of the metal catalysis lies on the two important factors, such as: (i) design and synthesis of new generation ligand framework that can produce highly reactive catalyst system \(^14,15\) and (ii) substrates’ structure modifications \(^16\) by which site selectivity could be controlled by the steric crowding \(^17,18,19,20,21\) or various weak interactions \(^22,23,24,25\) of the aromatic compounds among several similar type of C–H bonds via the ligand–substrate pre-organization \(^26,27\). In recent times, many elegant approaches \(^28\) have been developed for the functionalization of proximal \(^15,29,30,31\) and remote C–H bonds \(^1,3,32,33,34,35,36,37,38\) of arenes by the design of either new ligand frameworks with an extended architectures featuring a weak coordinating functional groups \(^39\) or templates \(^40\) as well as transient mediators \(^41\) or transient directing groups \(^42\) attached with the substrates. While ligand having an extended architecture or template approaches are extremely important to functionalize the remotely located C–H bonds of arenes, but requirement of multi-step preparation of the linkers of the ligands and templates of the aromatic substrates significantly limit the wide application of the methods. \(^43\)

Among numerous aromatic substrates, phenols are the most widespread aromatic compounds that acquired household products including several bioactive to important drug molecules. \(^44\) Moreover, it is well-documented that 10% of the top 200 selling pharmaceuticals contain a phenol and several others employ phenols as synthetic intermediates. \(^45\) Furthermore, phenols are also key components of the biopolymers melanin, lignin, resins and polyphenylene oxides. \(^44,45,46\) In industry, phenol is routinely used as a raw material to make numerous important components by means of its diversification via the synthetic manipulation. \(^44,45\) Thus, direct functionalization of phenols would be a significant development for the rapid access of numerous important products. \(^46\) In this context, traditional electrophilic substitution is an alternative methods that affords variously substituted phenols (Fig. 1A, a). \(^47\) Employing this method, one can easily access ortho and para substituted phenol derivatives, although often remain a chance to have mixture of isomers. However, functionalization of the remote meta C–H bonds of phenols is extremely difficult because of the extreme inertness of the meta C–H bonds. Several pioneering approaches have been developed by Yu and others either using template method \(^48,49,50\) or transient directing group by Larrosa \(^2\) (Fig 1A, b, c). But, achieving the meta functionalized products using these methods, it is essential to have specialized substrates that limits the application of the methods.

Having tremendous importance of catalytic C–H borylation \(^51,52,53,54,55,56\) in organic synthesis, we report here a concept for the meta selective C–H borylation of phenols via an unprecedented Si–O interaction that has never been utilized in C–H functionalization chemistry. Literature reports revealed\(^4\) that the most common structural motif for this O–Si interaction can be found in the amide skeleton, where a filled p-orbital of oxygen atom can interact with the vacant d-orbital of the tetracoordinated silicon atom consisting of at least one electronegative atom. The role of this electronegative atom is to make silicon atom more electropositive by developing a partial positive charge on the silicon atom (Fig. 1B, a). Notably, while various reports of O–Si weak interactions have been shown in a number of intermediates (Fig 1B, b–e), \(^4,57,58\) there was no report of utilization of these interactions in the catalysis research. Inspired from this background reports, \(^4,57,58\) we have proposed a hypothesis where phenol is protected with an easily removable electropositive silane group and silane protected phenol meet all the necessary criteria (having electropositive silane with attached electronegative oxygen atom) for the O–Si weak interaction with 2-pyridone moiety having amide skeleton (4). (Fig. 1C). The reaction design (ligand and catalyst design) is shown in Fig. 1D, a, b. The designed ligand (PY-PYRI) consists of two parts, one part is the simple pyridine unit (PY) and another part is a 2-pyridone (PYRI) unit \(^59\) which was redesigned by the skeletal modification of bipyrindone core structure. The origin of the remote meta selectivity is presented in Fig. 1D, b. We hypothesized that the designed ligand (PY-PYRI) would control the remote meta selectivity owing to the following two considerations. Firstly, in presence of [Ir(cod)(OMe)]\(_2\), the ligand (PY-PYRI) will generate a complex (Int-A) without tautomerization of the 2-pyridone unit. Secondly, the p-orbital of the oxygen atom of the 2-pyridone unit will interact with the vacant d-orbital of the tetracoordinated electropositive silicon atom of the substrate (Fig. 1D, b).
The designed ligand (PY-PYRI) was prepared by the known synthetic methods (SI, for details), which was employed for the reaction optimization of steering silane group attached with phenol (Fig. 2A). We started our initial studies with the substrate (1a-I) featuring SiMe₃ as the steering group under iridium-catalyzed conditions using the designed ligand (L₁: PY-PYRI) at 40 °C temperature, which afforded good meta/para selectivity (m/p = 87/13) with 68% conversion. Evaluating other silane based steering groups under the same reaction conditions, we observed that Si(iPr)₃ produced best meta selectivity (entry 2a: m/p = 94/6) with excellent conversion (95%). With this optimized Si(iPr)₃ as steering group, different other ligands have also been tested to observe the effect on the selectivity (Fig. 2B). It was found that replacing the tert-butyl group with methyl group, ligand (L₂) gave 91% meta selectivity with less conversions (68%). Similar selectivity was obtained when the reaction was performed with the ligand (L₃) without any substituents on the pyridine unit of the ligand. Notably, the meta selectivity and conversion was found to be less using the bipyridine ligand (L₄) compared to the ligands (L₁-L₃), which indicated the important role of the

**Fig. 1. Conceptual outline and proposed concept for the meta borylation of phenol.**

A. Meta functionalization of phenol: meta functionalization not well explored and ortho & para functionalization Highly accessible and well explored.

B. Conceptual background:

- **Dative O-Si interaction in amide skeleton:**
  - Common structural motif for O–Si interaction: X = halogen atom
  - Electronegative atom: tetracoordinate silicon atom
  - Si have vacant d-orbital
  - Pyridone O have filled p-orbital

C. Hypothesis:

- **Electronegativity difference:**
  - Si–O bond: 1.7
  - polarised O-Si bond generates partial opposite charges on O and Si atom

D. Reaction design:

- **Proposed working model:**
  - Weak interaction mediated meta borylation
  - Easily removable silane group

**Proposed approach for meta borylation:**

- **Int-A**
  - Partial (+) charge at O atom of pyridine

**Structural modification of bpy based ligand:**

- **2-pyridone unit PY-PYRI**
  - Catalyst design

**Known Literature reports**

- **Organometallics, 2011**
- **J. Mol. Struct, 2021**
- **Organometallics, 2013**

**Novelty**

- Pre-installation of template
- Deprotection of the template
- Multi-step method

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2-pyridone unit of the designed (PY-PYRI) ligand. Employment of other ligands (L5-L8) resulted in no reaction except the ligands (L9 & L10), which gave moderate meta selectivity.

At the outset, we proposed the tentative hypothesis that an O–Si secondary interaction between the oxygen atom of the 2-pyridone unit of the ligand and the silicon atom of the substrate’s steering group would interact each other via the filled p-orbital and empty d-orbital (Fig. 2C). Moreover, due to the high electronegativity difference between oxygen and silicon, the O–Si bond will be highly polarized, thereby may interact via a weak O–Si interaction. To prove this hypothesis for the origin of the meta selectivity, we performed a reaction with substrates featuring C–Si bond (-CH₂Si(Me)₃: 1a-VIII and -CH₃Si(Me)₃: 1a-VII, Fig. 2D), in which lacking of electronegative atom attached with silicon atom causes non-polarised bond, resulted in very low meta selective borylation due to loss of interaction between 2-pyridone of catalyst and substrates silicon atom. This experiment indicated an “O–Si” secondary interaction between the ligand and substrate that guides the selectivity of the borylation.

Using L1 (PY-PYRI) as ligand and Si(Pr)₃ as steering group, we next performed the iridium-catalyzed meta borylation of a variety of phenols that afforded excellent meta selectivity and yields of the isolated borylated products (Fig. 3). For example, we first tested 2-chlorophenol for the borylation reaction, while our designed ligand (L1) gave high meta selectivity (m/p = 92/8), traditional dtbpy ligand provided poor meta selectivity (m/p = 63/37), which clearly demonstrated the utility of the designed (L1: PY-PYRI) ligand. Other 2-substituted phenols, such as 2-bromo (1c) and 2-iodo (1d) afforded high meta selectivity that have great synthetic values owing to the two different types of handles on the phenols. Likewise, phenols bearing various alkyl chain ranging from methyl to pentyl (1e-1g) at the...
2-positions along with trifluoromethyl (1h), isopropyl (1i) and trifluoromethoxy (1j) smoothly underwent meta borylation irrespective of the nature of the substituent. Amino phenol (1k), substrate of momentous importance for the chemical and pharmaceutical industries, is borylated with high meta selectivity (m/p = 97/3) without borylation next to the amino group, which is known to give ortho borylation under iridium-catalyzed borylation conditions via in situ generation of NHBPin group. Thioether (1l) that usually directs borylation at the ortho position also underwent borylation with good meta selectivity. We observed that phenols containing functional groups such as cyano (1m), Bpin (1n), cyclic amine (1o), cyclohexyl (1p), ketomethyl (1q) and homologous ester (1r) afforded high level of meta selectivity and tolerated well under the employed reaction conditions.

![Fig. 3. Substrates scope for substituted arenes. Reactions are in 0.5 mmol scale. *Conversion was reported. a1.5 equiv. Bpinn was used. 22.0 equiv. Bpinn was used. See SI for details.](image)

Amide functionalities (1s & 1t) that are known to undergo numerous synthetic transformations exhibited excellent meta selective borylation. Borylation of phenols having CF₃ (1h) and CN (1m) substituents at the ortho position afforded exclusively meta borylation, the same substituents at the meta position of phenols (1u & 1v) also gave meta selective borylation, which indicated the generality of the developed method. Moreover, fluoro-substituted...
arene, which typically gives borylation next to the fluorine atom under standard iridium-catalyzed conditions, in this case, 3-fluorophenol (1w) gave meta borylation as the major product. Several disubstituted phenols (1x-1ag) were also examined under the developed conditions that reacted smoothly to afford variously substituted meta borylated products in high yields. 2,2'-Biphenol, compound of paramount importance in medicinal chemistry as well as in chemical industry, can selectively be mono- and diborylation (2ah & 2ai) by tuning the amount of boron reagent. A bulky substituent at the ortho positions (1aj) did not hamper the reaction that gave 96% meta borylated product with 90% isolated yield.

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**Fig. 4. Substrates scope for the 4-substituted arenes and C6 borylation of indoles.** Reactions are in 0.5 mmol scale. *Conversions were reported. **2.0 equiv. B2pin2. See SI for details.

Next, we focused on the meta borylation of those phenols bearing a substituent at the para position (Fig. 4). Because, borylation at the remote meta position in presence of a para substituent remains an extraordinary challenge due to the steric reason. Moreover, we selected those substituents at the para position that already provided exclusive meta borylation of phenols when they were located at either ortho or meta positions. The reason for this selection is mainly to observe the overall effects of the borylation by the same substituents. For the
testification, we begun with the 4-methyl phenol (3a) that afforded 91% meta selective borylation. Increasing the chain length from small methyl group to the relatively bulkier alkyl groups such as, ethyl (3b), pentyl (3c), hexyl (3d) and isopropyl (3e), the borylation underwent smoothly with further enhancement of the meta selectivity from 91% to 100%. Para-substituted ethers and thiethers bearing electronically different substituents (3f-3j) reacted with 100% meta selectivity, which revealed that the scope of the meta borylation is very general regardless of the nature of the substituents. While 2-CN, 3-CN as well as 2-CF$_3$ and 3-CF$_3$ bearing phenols resulted in excellent meta borylation, the same substituents at the para position reacted to yield 100% meta borylation. Likewise, we also observed that chloro (3m) and bromo (3n) containing phenols reacted to give the meta borylation products solely irrespective of their position in the phenol. Moreover, it has been found that the phenols featuring bulky substituents at the para position (3o-3r) also gave exclusively meta borylation, although conversion was moderate in case of the cyclohexyl group.

In 2015, Baran et al. reported the first total synthesis of Verruculogen and Fumitremorgin A enabled by ligand-controlled C–H borylation as the key step of TIPS protected tryptophan. We were curious if our designed ligand system could provide the remote C6 borylation of TIPS protected indoles and TIPS protected tryptophan. For that reason we performed borylation of TIPS-protected tryptophan (3s) (synthetic key precursor of bioactive alkaloids Verruculogen and Fumitremorgin A) which provided C6 borylation with 91% selectivity with excellent conversions. We also found that TIPS-protected other indole derivatives (3t & 3u) and TIPS-protected carbazole (3v) smoothly underwent remote borylation affording excellent selectivity and conversion. This developed method provided a simple way to borylate the 3-substituted indoles derivatives that might be beneficial for the total synthesis or the late-stage functionalization of several bioactive molecules.

Late-stage functionalization of complex bioactive and medicinally important molecules by the site selective C–H activation is a powerful method for the development of new drug candidates. In this context, introducing a boron functionality into the bioactive and medicinally important molecules would further enhance the identification of new lead molecules not only for the enormous importance of the boron-bearing small molecules but also for the uniqueness of the boron group towards the diverse derivatization towards numerous other functional groups. Thus, we tested our developed method for several commercially available bioactive and drug molecules (Fig. 5A). For example, cannabinoid core (5a: used as a psychoactive drug), methyl salicylate derivatives (5b: an anti-inflammatory and analgesic agent), tyrosol derivatives (5c: an antioxidant), eugenol derivatives (5d: a flavouring agent), sesamol derivatives (5e: an antioxidant), naproxen derivatives (5f: a nonsteroidal anti-inflammatory drug, NSAID), deoxyarbutin derivatives (5g: used for treatment of hyperpigmentation disorders) and homosalate (5h: used as a sunscreen) were meta borylated under very mild reaction conditions at room temperature (ethylene glycol, KF, 1h) that afforded the meta borylated phenols in high yields (Fig. 5B). Notably, the meta borylated phenols can further be transformed to a number of substituted phenols/resorcinols that are difficult to prepare by otherwise.

Next, we aimed to prepare the active catalyst (10) that was proposed to form in situ between the reaction of the designed ligand (L1: PY-PYRI) and [Ir(cod)(OMe)$_2$] during the meta selective borylation conditions. Accordingly, we performed the reaction and isolated the catalyst [10: Ir(cod)(PY-PYRI)] in 90% yield (Fig. 5C). The catalyst structure was confirmed by X-ray crystallography and other spectroscopic data. The catalytic efficiency of this catalyst [10: Ir(cod)(PY-PYRI)] was further tested in the meta borylation reactions, which exhibited same level of meta selectivity with better product conversion (compared to the in situ generation) (Fig. 5D). Moreover, we checked the stability of the catalyst [10: Ir(cod)(PY-PYRI)] and found highly stable that can even be stored in open air. Furthermore, to verify the broad utility of this air stable catalyst [10: Ir(cod)(PY-PYRI)], we performed several test experiments using this catalyst [10: Ir(cod)(PY-PYRI)] that was stored in open air and found no loss of catalytic activity even after 30 days (Fig. 5D, SI for details).
In conclusion, we report a new class of ligand and catalyst that has demonstrated remarkable efficiency for the remote meta selective borylation of phenols featuring all types of substitutions at the arene ring. In addition, we have seen that our developed ligand system is beneficial for the remote C6-borylation of indoles derivatives including tryptophan which is a synthetic precursor of bioactive alkaloids (Verruculogen and Fumitremorgin A). Several late-stage meta borylations have been showcased with bioactive and drug molecules that might be useful for repurposing medicines and identification of new lead drug candidates. For the first time, an “O–Si” secondary interaction has been employed to tune the remote selectivity. We anticipate that the designed ligand and catalyst will also find wide application in the context of other C–H functionalization reactions.

References and notes

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Author contributions: BC conceived the concept. SG developed the ligand. SG, MMMH and SD performed the experiments. BC supervised the project. All authors contributed to writing and proofreading of manuscript and SI.

Competing interests: We have filled an Indian Patent (Patent Application No: 202211036590) based on this work (including the ligand and catalyst).

Data and materials availability: X-ray dataset for catalyst 10 is freely available at the Cambridge Crystallographic Data Centre under deposition number 2180880.
Supplementary Files

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- SupportingInformation.pdf