Communication

Non-covalent Interactions in Ir-Catalyzed C–H Activation: L-Shaped Ligand for Para-Selective Borylation of Aromatic Esters

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Non-covalent Interactions in Ir-Catalyzed C–H Activation: L-Shaped Ligand for Para-Selective Borylation of Aromatic Esters

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Supporting Information Placeholder

ABSTRACT: An efficient strategy for the para-selective borylation of aromatic esters is described. For achieving high para selectivity, a new catalytic system has been developed modifying the core structure of the bipyridine. It has been proposed that the L-shaped ligand is essential to recognize the functionality of the oxygen atom of the ester carbonyl group via non-covalent interaction, which provides an unprecedented controlling factor for para selective C–H activation/borylation.

Controlling the chemical reactivity of similar types of C–H bonds within the substrate, use of non-covalent interactions is an area of great potential. The C–H bond functionalizations using this interaction have been identified in many areas of catalysis,[1] for instance, hydrophobic interactions in C–H hydroxylations,[2] host-guest encapsulated C–H activations[3] and hydrogen bonding directed C–H functionalizations.[4] The utility of this interaction is not restricted to biological systems and organo-catalysis, but also found in transition metal catalysis.[1] This growing interest of non-covalent interactions in transition metal catalysis has opened up new avenues for the C–H bond activation chemistry.

Chart 1. Non-Covalent Interactions for the Remote C–H Bond Activation and Borylation of Arenes
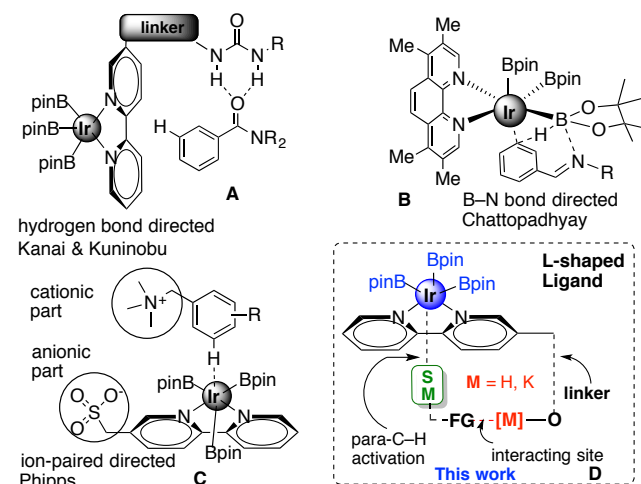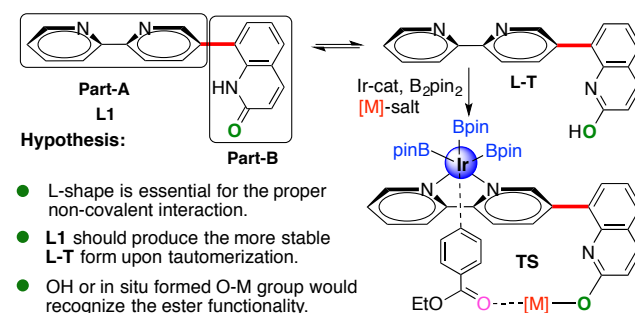

Whereas numerous C-H bond functionalization[5] are currently available, the C–H bond borylation has demonstrated potential owing to the synthetic usefulness[6] of the B–C bonds and to their sterically[7] controlled unique site-selectivity. Although, many methods have been developed for the ortho borylation[8] of arenes, but, remote C–H bond (meta & para) borylation still difficult to realize, nevertheless practically valuable.[9] Literature reports show that only one type of meta C−H borylation is

available,[10] from 1,3-disubstituted arenes and the regiochemistry results essentially from sterics.[11] Recently, three new paradigms of meta-selective borylation have been developed using the concept of non-covalent interaction[12] between the substrate and ligand (Chart 1, A-C).[13]

In sharp contrast, there is no general method[14] for the para-selective borylation except Itami and Segawa's para borylation by a bulky diphosphine ligand.[15] Notably, after submission of this Communication, a paper appeared by Nakao[16] et al describing a novel concept of para borylation of benzamides and pyridines via a cooperative Ir/Al catalysis. The para selectivity was controlled by a bulky aluminum-based Lewis acid catalyst. Herein, we report Ir-catalyzed para C–H borylation of aromatic esters controlled by a non-covalent interaction between the substrate and a L-shaped ligand (Chart 1, D).

We designed a L-shaped ligand (**L1**) modifying the core moiety of the bipyridine (Chart 2). The designed ligand (**L1**) consists two parts (Part-A and Part-B). Part-A is the simple bipyridine core unit and the part-B is a quinolone moiety. We hypothesized that the L-shaped ligand (**L1**) would be suitable for the para C–H activation due to the following three considerations. First, the Part-B of the ligand (**L1**) may undergo tautomerization to generate the more stable form **L-T** due to the aromatic resonance stabilization. Second, in presence of [Ir(cod)(OMe)]₂ and B₂pin₂, it would form the standard tris(boryl)iridium complex, which would facilitate the C–H borylation. Third, either OH group or the in-situ generated O–M (M = Li, Na, K) group of the ligand (**L1**) would recognize the functionality of the carbonyl oxygen[17] atom of the aromatic ester through the non-covalent interaction as shown in the proposed **TS**.

Chart 2. Ligand Development for the Para C–H Borylation of Aromatic Ester via Non-Covalent Interactions

- L-shape is essential for the proper non-covalent interaction.
- **L1** should produce the more stable **L-T** form upon tautomerization.
- OH or in situ formed O-M group would recognize the ester functionality.

The designed ligand (**L1**) was synthesized using two-step process by the Miyaura borylation and Suzuki coupling. Next, we sought to test the para borylation of ethyl benzoate (**1a**). Considering a novel concept[18] by Marder and Steel that π-electron

acceptors and donors favor para and meta borylation respectively, under classic Ir/dtbpy system at 25 °C, we tested borylation using that conditions (Table 1, entry 1), which gave 1.2/1 para/meta selectivity. When the same reaction was conducted at 80 °C, it resulted a 1:1 mixture of para/meta borylated products (entry 2). Next, the designed ligand (**L1**) was employed for the borylation at the 25 °C to validate the proposed hypothesis. Pleasingly, a high level of para/meta (6.1/1.0) selectivity was observed, which validates the proposed hypothesis for the secondary hydrogen-bonding concept (entry 3). Notably, we did not notice any ortho borylation[19] of ethylbenzoate under the reaction conditions.

Table 1. Optimization for the Para Selective Borylation[a]

#	ligand	T °C	MO^{t}Bu	conv. (%)	m,m-di(%)[b]	para/meta
1	dtbpy	25	-	89	40	1.2/1.0
2	dtbpy	80	-	93	31	1.1/1.0
3	L1	25	-	97	12	6.1/1.0
4	L1	50	-	98	13	5.7/1.0
5	L1	80	-	98	17	3.0/1.0
6	L1	50	LiO^{t}Bu	0	-	-
7	L1	50	NaO^{t}Bu	75	-	3.8/1.0
8	L1	50	KO^{t}Bu	95 (92)	-	32.3/1.0
9	L1	80	KO^{t}Bu	99	-	24/1.0
10	dtbpy	50	KO^{t}Bu	95	20	1.4/1.0

[a]Reaction scale 0.2 mmol. GC ratios; conversions are based on dodecane as internal standard. In parentheses, isolated yields.

However, increasing the reaction temperature from 25 to 50 °C to 80 °C, selectivity was dropped gradually from 6.1/1.0 to 5.7/1.0 to 3.0/1.0 (entries 3-5), which is indicating that the effective hydrogen bonding at relatively high temperature is lost to some extent. As per proposed hypothesis (Chart 2, TS), next we examined alkali metal salts for the borylation. However, no borylation occurred using catalytic amount of LiO^{t}Bu (entry 6). We reasoned that LiO^{t}Bu is acting as a poison for the borylation, which is confirmed by the control experiment (SI, for details). Use of NaO^{t}Bu resulted moderate para/meta selectivity (3.8/1.0, entry 7). Remarkably, replacing the alkali metal salt from NaO^{t}Bu to KO^{t}Bu,[20] the selectivity was shifted enormously from 3.8/1.0 to the 32.3/1.0 (entry 8). For this extreme alteration of the regioselectivity from Li$^+$→Na$^+$→K$^+$ ion, we reasoned that K$^+$ ion interacts well with the carbonyl oxygen atom of the ester group, which predominantly control the high degree of para selectivity. Notably, somewhat para selectivity was diminished (entry 9) when the same reaction (entry 8) was performed at 80 °C. In sharp contrast, borylation with dtbpy in presence of KO^{t}Bu[21] (entry 10) resulted in very low selectivity.

With these encouraging results, borylations for a series of aromatic esters were performed (Table 2). Irrespective of the substituents present in the aromatic ring such as halogens, alkyl, aryl, alkoxy, amine, and ester were well tolerated under the borylation conditions affording excellent para selectivity. For example, in all cases of ortho-mono-substituted substrates (**2b-2j**), high level of para selectivity was observed. Substrate bearing a highly electron-donating group (**2h**) produced moderate yield of the product. In case of ortho-di-substituted (**2k-**

2n) and meta-substituted substrates (**2o-2q**), para selectivity was found to be remarkably high. Substituents at meta[22] and various other positions (**2r-2v**) also appeared to be general offering good to excellent selectivity. Importantly, para borylation of substrates containing arene substitution at ortho position, the arene C−H bonds are unperturbed, producing exclusively the para borylated product (**2w-2y**). Moreover, substrates having the bromo and chloro group at different position, offered a unique opportunity for the subsequent Pd-catalyzed coupling chemistry.

Table 2. Scope of Aromatic Esters for Para Borylation[a]

[a]Reaction scale 0.2 mmol, Isolated yields. [b]Without KO^{t}Bu; due to unstability, **2o** was isolated via arylation. [c]Without KO^{t}Bu.

To this end, borylation of homophthalic ester (**3**) was conducted, which gave exclusively the para product **4** (Chart 3). For the high para selectivity, we reasoned that ester group directly attached to the benzene ring might be generating the stable TS via non-covalent interaction. On the contrary, for the other ester group, we assumed that due to the intervening methylene group between the ester and phenyl ring, it fails to generate the stable TS.

Chart 3. Competition Between Two Ester Functionalities
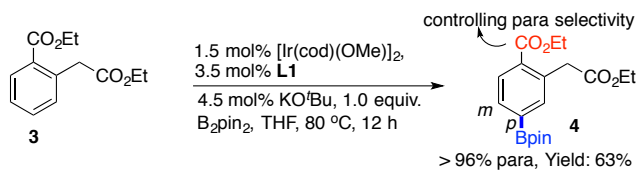
Next, we focused on the para-selective borylation of heterocyclic esters (Table 3). While entry **6a** gave 8/1 para/other selectivity, introduction of a methyl substituent next to ester group afforded complete para borylation (entry **6b**). However, entry **6c** having two ester groups, showed slightly lower para selectivity. Borylation of indole esters (entries **6d-6g**) are interesting. While dtbpy is known[23] to give exclusively C2 borylation of indole (**6d**), our ligand system (**L1** and KO*t*Bu) failed to undergo borylation, which might be due to the preferential chelation between the NH group and the catalyst.[24]

Table 3. Remote C–H Borylation of Heterocycles & Other Types of Substrates[a]
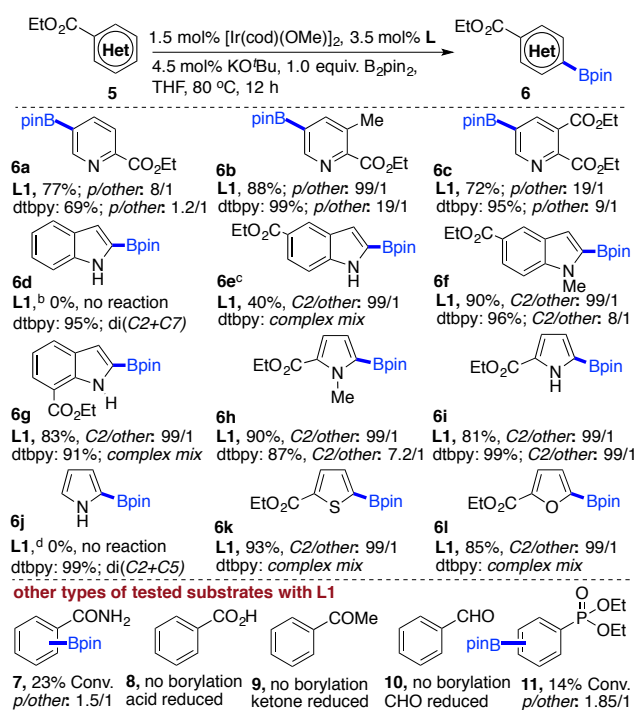

[a]Reaction scale 0.2 mmol; with dtbpy conditions, SI for details. Yields are isolated. [b]no borylation; but, without KO*t*Bu, 25% GC conv. (C2 only). [c]GC conv., in absence of KO*t*Bu. [d]no borylation; but without KO*t*Bu, 45% GC conv. (C2 and C2+C5 mixture).

Interestingly, borylation of ester bearing indole, resulted the remote C2 borylation (**6e**), which is consistent with the notion that free NH group is chelating with the catalyst and thus inhibiting the borylation. We envisioned that protecting the free NH group would enhance the borylation and indeed borylation of N-Me indole gave excellent yield of the product (**6f**). Moreover, entry **6g** solely resulted C2 borylation. Likewise, same trend was observed for pyrrole borylation with the **L1** ligand (**6h-6j**).[24] As expected, borylation of **5k** and **5l** with **L1**, afforded remote C5 isomer (**6k-6l**). Notably, to see the comparison between the **Ir/L1** system and the classic **Ir/dtbpy** system for heterocycles, control experiments were performed, which shown poor selectivity (Table 3, **6a-6l**) with the classic **Ir/dtbpy** system (except **6i**). We next studied applicability to

substrates containing other functional groups (Table 3, **7-11**). While amide (**7**) and phosphonate ester (**11**) afforded para isomer as the major product, benzoic acid (**8**), acetophenone (**9**) and benzaldehyde (**10**) failed to undergo borylation and produced alcohols after reduction.

The standard reaction mechanism of the borylation has been reported earlier[25] and the current para borylation of aromatic esters probably proceeds via the same route. However, to get a better understanding of the non-covalent (C=O····K–O) interactions between the substrates and the ligand **L1**, we executed the following control experiments using **L2** and **L3** (Chart 4).

Chart 4. Mechanistic Support by Control Experiments
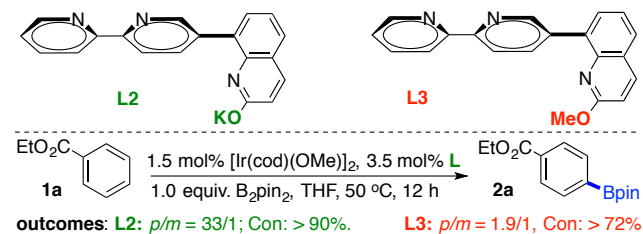
We hypothesized that the C=O····K–O interaction would be more favored with the ligand **L2** giving high para selectivity and for ligand **L3**, this interaction should be disfavored affording poor para selectivity. Following this hypothesis, borylations were performed with the ligands **L2** and **L3**. While **L2** afforded 33/1 para/meta selectivity, ligand **L3** resulted only 1.9/1, which is evidencing the proof-of-concept for the (C=O····K–O) interaction between the potassium ion and the carbonyl oxygen.

To gain further insight into the (C=O····K–O) interaction, we performed control experiments with crown ether (Chart 5). According to the literature reports, crown ether is one of the most proven host molecules,[26] which shows strong binding selectivity for alkali metal cations in solution phase. Thus, we envisioned that 18-Crown-6 might play significant role in borylation using **L1** ligand in combination of KO*t*Bu. We first conducted borylation in presence of 20 mol% 18-Crown-6 and observed that without KO*t*Bu there is no effect and the selectivity remained same. Then we hypothesized that if the K^{+} ion plays an important role for the non-covalent interaction, use of 18-Crown-6 would alter the para-selectivity.

Chart 5. Control Experiments for the Mechanism
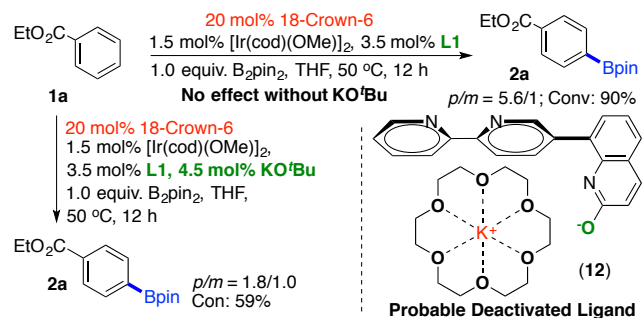
To verify this, borylation was carried out in presence of 20 mol% 18-Crown-6 and found that the ratio of para/meta selectivity dramatically decreased from 33/1 to 1.8/1.0. We presumed that due to the strong binding selectivity of the K^{+} ion with the 18-Crown-6, it forms the deactivated complex **12** producing poor selectivity, which is again supporting the concept of (C=O····K–O) interaction.

In conclusion, we have developed an efficient method for the para-selective borylation of esters using a designed iridium catalyst having a L-shaped ligand with a pendant non-covalent interacting site. The essential feature of this borylation is the non-covalent interaction between the substrate and the catalyst, which primarily controls the selectivity. The developed method shows very broad substrate scope and functional group tolerance. More efforts are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information Available: Full characterization, copies of all spectral data, experimental procedures. 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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4

TOC

via

TS

non-covalent interaction

42 examples
para selectivity: >99%

CO₂Et

Ir-cat., B₂pin₂, L1
————————————
KOᵗBu