Communication

Amide-Ligand-Controlled Highly *para*-Selective Arylation of Monosubstituted Simple Arenes with Arylboronic Acids

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S *Supporting Information*

ABSTRACT: Pd-catalyzed highly *para*-selective arylations of monosubstituted simple arenes with arylboronic acids to widely existed biaryls have been developed. Inspired by requisite amide-directing groups in reported selective oxidative couplings, amide ligands, especially DMF, are designed and found to be critical for the selectivity control in current arylations.

The direct arylations of C–H bonds of (hetero)arenes to construct ubiquitous and important structural motifs, bi(hetero)aryls,[1] have attracted considerable attention during the past decades, owing to more environmentally friendly and economic characters of these arylations than that of traditional couplings between two prefunctionalized (hetero)aryls.[2] Among a wide range of substrates, heteroarenes and chelate-assisted arenes are two of the most widely explored classes of substrates,[2,3] in which the presences of hetero atoms and chelate-assisted groups lead to relatively easier reactivity improvement and selectivity control (Scheme 1a). However, nonchelate-assisted simple arenes with various C–H bonds displaying very subtle discrepancy in reactivity have been less explored.[4] Monosubstituted arenes, one of the most challenging classes of substrates for selective functionalization,[3,5] have been short of general and efficient methods for arylation with good

selectivity (regioisomer ratios >5:1). Despite great advances have been reported recently on selective arylation of monosubstituted arenes with various arylating reagents, such as diaryliodonium salts (Sanford and Gaunt),[6] arylsilanes (Russell),[7] and electron-poor arenes (Laali and Larrosa),[8] the scope of monosubstituted arenes with good selectivities was still very limited (Scheme 1b, path (i)). Selectivity control often depended on steric and electronic factors of substrates, and high selectivity was observed mainly for electron-rich arenes, like anisole. Until a major breakthrough was achieved independently almost at the same time by Yu and Cheng,[9] who developed Pd^{IV}-catalyzed *para*-selective oxidative couplings of mononsubstited arenes with chelate-assisted arenes, high selectivity control was then generalized to a broader range of monosubstituted arenes, like alkylbenzenes, halobenzenes and alkoxybenzenes (Scheme 1b, path (ii)).[10,11] In these reactions, different directing groups embedded in arylating reagents proved essential for high selectivity control, though this requirement not only restricted the scope of accessible biaryls but also needed additional synthetic steps for directing group manipulations. And thus, the development of efficient strategy for highly selective arylations of monosubstituted arenes with more general arylating reagents without special directing groups, such as readily available arylboronic acids[12] and aryl halides,[13] is still very challenging and in demand. Herein, we report the first highly *para*-selective arylation of monosubstituted arenes with arylboronic acids, in which the use of amide ligand proved to be crucial for selectivity control (Scheme 1b, path (iii)).

Inspired by recent highly selective oxidative arylations of monosubstituted arenes with directing-group-containing arenes, wherein the selectivity control was supposedly attributed to the use of Pd^{IV} species and amide directing groups in arylating reagents,[9–11] we envisioned that a separate amide ligand instead of amide directing group in the coupling partner could play a comparable role in controlling selectivity of Pd^{IV}-catalyzed arylation of monosubstituted arenes with more general arylating reagents, for example, commonly used arylboronic acids, aryl halides, and so on.

Following this hypothesis, we commenced our studies by using phenylboronic acid as the arylating reagent, and toluene as the model substrate under reported Pd^{IV}-catalyzed conditions.[9–11] Initial extensive screening revealed that various

Scheme 1. C–H Arylation of (Hetero)Arenes
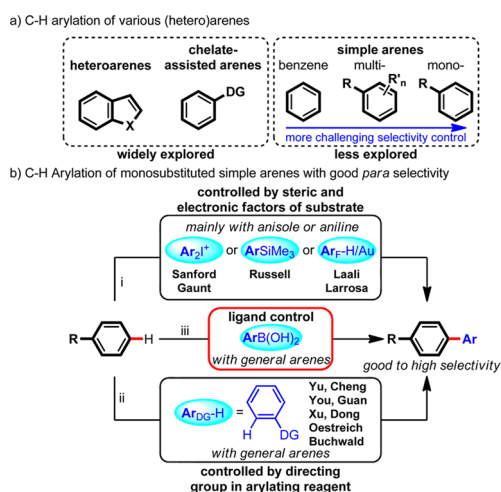
amide ligands indeed greatly affected both the reactivity and selectivity of toluene arylation under conditions of Pd(OAc)$_2$ as the catalyst and *N*-fluorobenzenesulfonamide (NFSI) as the oxidant.[9] *N,N*-dimethylformamide (DMF, **L7**) was finally found to be the optimal ligand with 12% total yield of biaryls and 7.9/4.4/87.7 isomer ratio (Table 1). The formyl group of N in the

Table 1. Amide Effect and Conditions Optimization

entry	[Pd] (10 mol %)	NFSI (eq)	T (°C)	additive (μL)	yield (o/m/p)^b
1	Pd(OAc)$_2$	1.5	100		12% (7.9/4.4/87.7)
2	Pd(TFA)$_2$	1.5	100		14% (15.0/12.5/72.5)
3	PdCl$_2$/AgOTf (1:2)	1.5	100		22% (9.1/9.1/81.8)
4	PdCl$_2$/AgSbF$_6$ (1:2)	1.5	100		41% (3.4/5.7/90.9)
5	PdCl$_2$/AgSbF$_6$ (1:3)	1.5	100		44% (2.5/4.2/93.2)
6	PdCl$_2$/AgSbF$_6$ (1:3)	3.0	100		51% (2.0/4.1/93.9)
7	PdCl$_2$/AgSbF$_6$ (1:3)	3.0	100	^{i}PrOH (46)	54% (0.6/3.2/96.2)
8	PdCl$_2$/AgSbF$_6$ (1:3)	3.0	80	^{i}PrOH (46)	59% (0.3/3.2/96.5)
9	PdCl$_2$/AgSbF$_6$ (1:3)	3.0	80	^{i}PrOH/H$_2$O (46)^c	63% (0.6/3.2/96.2)
10	PdCl$_2$/AgSbF$_6$ (1:3)	3.0	80	HFIP/H$_2$O (520)^d	58% (0.7/1.0/98.2)
11^e	PdCl$_2$/AgSbF$_6$ (1:3)	3.0	80	HFIP/H$_2$O (520)^d	73% (0.8/1.6/97.7)
12^e	PdCl$_2$/AgSbF$_6$ (1:3)	3.0	60	HFIP/H$_2$O (520)^d	**82% (0.5/0.9/98.6)**

^{a}Reaction conditions: toluene (2.0 mL), PhB(OH)$_2$ (0.2 mmol), Pd(OAc)$_2$ (10 mol %), NFSI (1.5 equiv), **L** (2.0 equiv), 100 °C under air for 24 h; combined yield of isomers and regioselectivity (*ortho/meta/para*, shown in parentheses) were determined by GC. ^{b}DMF (2.0 equiv) under N$_2$. ^{c}v/v = 10/1. ^{d}v/v = 25/1. ^{e}DMF (0.3 mL, 20 equiv).

amide could not be replaced by alkyls (**L1**-**L3**), *tert*-butoxy (**L4**), and alkylaminos (**L5** and **L6**), otherwise the reactivity and selectivity would drop dramatically. However, the other substituted groups of N in the amide could vary in a wider range without significant effect on the selectivity and reactivity (**L8**, and **L10**−**L12**), except for phenyl group (**L9**) with a very low yield. Notably, the use of two equivalents of DMF at this stage proved to be the best choice, more or fewer loadings resulted into lower yields.

Encouraged by this ligand screening result, we then examined a wide range of reaction parameters employing DMF (2.0 equiv) as the ligand (entries 1−5, Table 1, and see the Supporting Information) to optimize further the reaction, and delightedly found that the use of cationic palladium catalyst, Pd(SbF$_6$)$_2$ formed in situ,[14] greatly promoted the yield to 44% (entry 5). With the increasing loadings of NFSI to 3 equiv, the yield was further improved to 51% (entry 6). Considering that the transmetalation of phenyl from phenylboronic acid to palladium could be critical to this coupling reaction, we next investigated numerous additives to promote this step (entries 7−12). The results showed that the combination of ^{i}PrOH and water enhanced the yield to 63% (entries 7−9), and the replacement of ^{i}PrOH by more acidic hexafluoroisopropanol (HFIP) led to a slightly lower yield (58%, entry 10). But importantly, the presence of HFIP facilitated accomplishment of the optimal

result by increasing the loading of DMF at lower temperature (entries 11 and 12). The use of stoichiometric amount of DMF was presumably ascribed to its weak coordination to metal, and hence much effort to design various bidentate and tridentate amide ligands with potentially stronger coordination was made, but only lower yields and poorer site-selectivities were obtained (see the Supporting Information, Table S13). Under the optimal conditions, various amide ligands were reexamined and the results showed DMF was still the best one (see Table S14).

With the above optimized reaction conditions in hand, we first explored an array of arylboronic acids to test the generality of the reaction (Table 2). Various arylboronic acids bearing either

Table 2. Scope of ArB(OH)$_2$

^{a}Reaction conditions: toluene (2.0 mL), ArB(OH)$_2$ (0.2 mmol), PdCl$_2$ (10 mol %), AgSbF$_6$ (30 mol %), NFSI (3.0 equiv), DMF (0.3 mL), HFIP (0.5 mL), H$_2$O (20 μL), 60 °C under N$_2$ for 24 h. ^{b}Isolated combined yield and regioselectivity (*ortho/meta/para*, shown in parentheses) was determined by GC.

electron-donating (**3b**−**3i**) or electron-withdrawing substituents (**3j**−**3t**) were well tolerated, providing biaryls with extremely high *para*-selectivities (up to 0.5/0.9/98.6 for *ortho/meta/para*) in most cases. Notably, arylboronic acids bearing electron-donating groups at the *para* position generally led to relatively lower yields but still high *para*-selectivities (see the Supporting Information, Table S16), with an exception of methoxy group (**3i**) that provided a low *para*-selectivity. Arylboronic acids bearing with halogens, including F (**3j**), Cl (**3k**), and Br (**3l**), were also compatible with this catalytic system, which suggested that the catalytic species could be Pd^{II} and Pd^{IV},[15] without involving Pd^0. Additionally, excellent *para*-selectivity was not affected by coordinating groups, such as CO$_2$Me (**3n**), COMe (**3o**), NO$_2$ (**3p**), CN (**3q** and **3r**), and CHO (**3s** and **3t**) on arylboronic acids, indicating that the DMF ligand still has strong enough coordination to avoid the interference of stoichiometric amount of coordinating groups. Surprisingly, *ortho*-substitutents on arylboronic acids were found to significantly affect the reactivity and selectivity. *ortho*-Methyl (**3u**) almost inhibited this arylation reaction, whereas smaller *ortho*-F (**3v**), coordinating *ortho*-CHO (**3w**), and sterically hindered 1-naphthylboronic

acid (**3x**) did not cause obvious deterioration of reactivity and selectivity. Overall, the considerable influence on reactivity and selectivity exerted by various substituents at different positions of arylboronic acid suggested that the transmetalation of aryl from arylboronic acid to Pd could take place prior to the selective C−H activation of toluene, and then the aryl might act as an additional ligand in the reaction.

Next, the compatibility of a variety of monosubstituted arenes with this arylation reaction was examined. As shown in Table 3,

Table 3. Scope of Simple Arenes

^{a}Reaction conditions: arene (2.0 mL), $PhB(OH)_2$ (0.2 mmol), $PdCl_2$ (10 mol %), $AgSbF_6$ (30 mol %), NFSI (3.0 equiv), DMF (0.3 mL), HFIP (0.5 mL), H_2O (20 μL), 60 °C under N_2 for 24 h. ^{b}Isolated combined yield and regioselectivity (*ortho/meta/para*, shown in parentheses) was determined by GC. ^{c}DMF (0.7 mL) was used. ^{d}DMF (0.7 mL) and HFIP (0.1 mL) was used. $Ar_E = (p$-$MeO_2C)C_6H_4$.

various monosubstituted arenes proved to be good substrates in coupling reactions with phenylboronic acid (**4a−g**), providing moderate to high yields and high *para*-selectivities in most cases. Unexpectedly, lower *para*-selectivities were observed with alkoxybenzenes (**4c** and **4d**), which are totally different from most reported procedures,[5−11] wherein anisole generally gave the best *para*-selectivity. We reasoned that the presence of excess alkoxybenzene around Pd could interfere with ligand coordination, leading to the selectivity decline. On the basis of this hypothesis, we attempted to increase DMF loadings to compete with substrates in these two cases, and pleasingly found that *para*-selectivities were greatly improved for both anisole (**4c**) and ethoxybenzene (**4d**). The current method is also applicable to disubstituted arenes (**4h−k**), and even sterically hindered mesitylene (**4l**) with good yields and excellent regio-selectivities. It is worth noting that *m*-xylene mainly provided a *para*-selective product other than usual less-hindered *meta*-arylated product.[4] More surprisingly, there is no reaction observed for *p*-xylene under the optimal conditions. These results suggested that the current catalytic system could be different from common substrate-controlled selective arylation of multisubstituted arenes.

To understand the mechanism of this arylation and high *para*-selectivity, we conducted some additional experiments. Neither one-pot competitive arylation (eq 1, Scheme 2a) nor parallel arylation reaction (see the Supporting Information, Figure S2) between toluene and d_8-toluene gave significant kinetic isotope effect, which demonstrates that C−H bond cleavage is not turnover limiting and is consistent with an S_EAr pathway for C−H bond cleavage. Replacement of NFSI by other oxidants, such

Scheme 2. Mechanistic Discussion
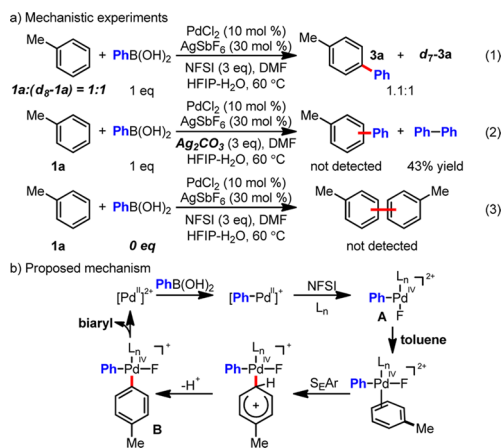
as $PhI(OAc)_2$, $Na_2S_2O_8$ and Ag_2CO_3, almost inhibited the arylation reaction. In the case of Ag_2CO_3 as the oxidant, only homocoupling product of phenylboronic acid was formed in 43% yield (eq 2). These results implied that Pd^{II} could participate easily in the transmetalation of phenylboronic acid, whereas Pd^{II} itself could not promote the C−H arylation of toluene. The real reactive catalytic species in the reaction could be $[F−Pd^{IV}]$ species,[9] despite the fact that other fluorinated oxidants such as SelectFluoro or *N*-fluoropyridinium triflate were not effective for this reaction (see Table S4 in the Supporting Information). We reasoned that byproducts from these oxidants, like tertiary amine and pyridine, could inhibit the reactivity of Pd center in the absence of strong ligand or directing group. When phenylboronic acid was removed from the reaction, there was no oxidative coupling product detected, suggesting that the formation of Pd^{IV} species could require the transmetalation of phenylboronic acid first (eq 3). On the basis of these experiments, we proposed a catalytic cycle as follows (Scheme 2b): an initial transmetalation of Pd^{II} with phenyl-boronic acid was followed by the oxidation of NFSI to produce the reactive catalytic species $[F−Pd^{IV}]$ (**A**), which then reacted with toluene to selectively form Ar−Pd intermediate (**B**) through an S_EAr mechanism. Final reductive elimination provided the biaryl product along with the regeneration of Pd^{II} species. In the structure of $[F−Pd^{IV}]$ (**A**), phenyl from phenylboronic acid could also play a ligand-like role, and its electronic and steric factors would have substantial effect on the reactivity and selectivity of arylation. Either one or multiple amides coordinating to Pd^{IV}, would impose direct effect on the reactivity and selectivity, like what amide directing group did in the oxidative coupling. In view of the lability of weak coordination of monodentate amide, a design of more powerful amide ligand to explore further other selective C−H functionalization reactions of monosubstituted arenes at lower loadings of amide ligand would be feasible.

In summary, we have developed the first example of highly *para*-selective arylation of monosubstituted simple arene with arylboronic acid. The use of amide ligands, especially DMF, is critical for the high selectivity in the presence of cationic palladium catalyst and NFSI oxidant. The current ligand control strategy provides a new choice for the development of selective C−H functionalizations of nonchelate-assisted simple arenes, which could be potentially applicable to other types of coupling reactions. A main limitation for current method is the requirement for a large excess of arene substrate and amide

ligand, which means further efforts to search more powerful catalyst system need to be made in the future.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12907.

Experimental procedures, characterization data, and spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

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