Letter

F+ Reagent-Promoted Pd-Catalyzed C7-H Arylation of 1-Naphthamides

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.9b04352 • Publication Date (Web): 21 Nov 2019

F+ Reagent-Promoted Pd-Catalyzed C7–H Arylation of 1-Naphthamides

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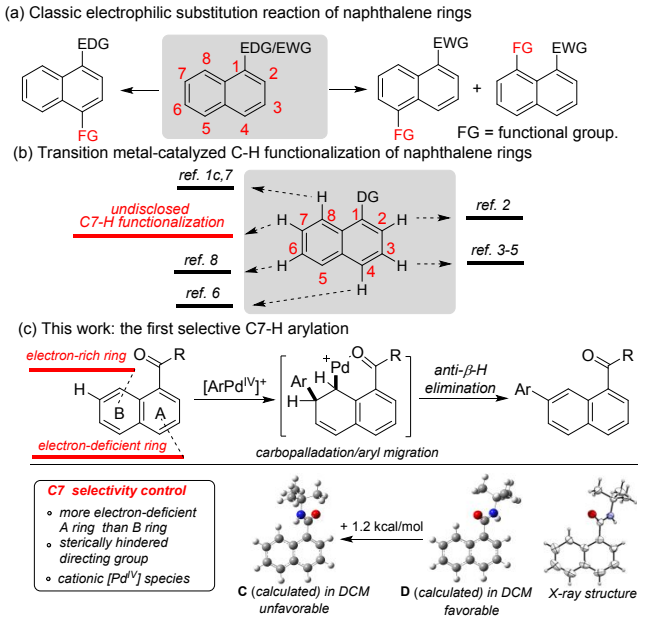
ABSTRACT: *The development of a strategy for remote C7–H functionalizations of the naphthalene rings is greatly challenging. Disclosed herein is an example of direct and regioselective arylation of the naphthalene rings at the C7 position promoted by F+ reagents. This protocol features good tolerance of reactive functional groups, mild reaction conditions and simple reaction system. By control experiments, kinetic isotope effect (KIE) experiment, and NMR experiments, the mechanistic pathway involving a carbopalladation/aryl migration has been illustrated clearly. Beyond the simple directing function, the sterically hindered N-(t-butyl)amide plays an important role in the regioselectivity control via a carbopalladation/aryl migration.*

KEYWORDS: *palladium catalysis, C7-arylation, naphthalene, F+ reagent, regioselectivity*

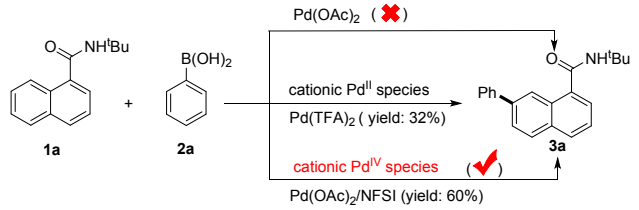
Naphthalenes are very important bicyclic aromatic compounds frequently found in natural products, drugs, agrochemicals and organic functional materials. Thus, the highly regioselective functionalization of the naphthalene rings has been an extremely attractive research topic for a long time. However, controlling site-selectivity on the substituted naphthalenes is challenging due to seven subtly different C–H bonds that may all be functionalized. Electrophilic aromatic substitutions of mono-substituted naphthalenes are classic approaches to synthesize disubstituted naphthalenes, but usually deliver lower yields because of the regioselectivity problem (Scheme 1a).[1] The naphthalenes bearing an electron-donating group (EDG) at C1 typically undergo C4 functionalization, while those with an electron-withdrawing group (EWG) give the C5 and/or C8-subsitutued products. With the development of C–H functionalization of simple aromatics, transition metal-catalyzed site-selective C–H functionalizations of naphthalenes have gradually been illustrated along with the generality of aromatic substrates (Scheme 1b). Various directing groups (DGs) have been demonstrated to control *ortho*-selectivity in diverse functionaliztions of naphthalenes.[2] Several strategies for *meta*-C–H functionalzation of simple aromatics have been applied to C3 functionalization of naphthalenes, including directed remote C–H functionalization[3,4] and use of norbornene as a transient mediator.[5] Electron-rich 1-naphthylamines have special reactivity at remote C4 position via single electron transfer (SET).[6] Transition metal-catalyzed directed *peri*-C–H functionalization of 1-substituted naphthalenes has been developed for the synthesis of 1,8-disubstituted naphthalenes.[1c,7] Recently, in the investigation of *para*-selective alkylation of benzamides, the alkylations of *N,N*-diethyl-1-naphthamide have been found to exhibit C6-selectivity.[8] However, there are not any examples on the selective remote C7–H functionalizations, clearly illustrating the challenge of achieving C7 selectivity of naphthalenes.



Scheme 1. C–H functionalizations of naphthalene rings

Transition metal-catalyzed C–H arylation via the carbopalladation/aryl migration has been documented to enable *meta*-C–H arylation of (hetero)aromatic ring.[9] Inspired by these works, we envisioned that the C7–H arylation of naphthalenes could occur via such a palladation/aryl migration pathway with the assistance of a directing group at C1-position (Scheme 1c). The key yet challenging problem encountered in this proposed path is selectivity control, ie, how to reach high selectivity at C7. The *N*-(*t*-butyl)amide as a sterically hindered directing group has been extensively used in the directed C–H functionalizations. Beyond the simple directing function, we herein attempt to use such a strategy to address the regioselectivity issue. Firstly, the installation of the *N*-(*t*-butyl)amide at C1 may promote palladation at C2 or C8. X-ray

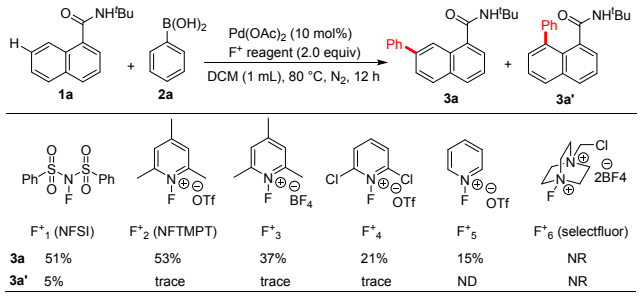
single crystal structure shows that the carbonyl *O*-atom is located to allow the cyclometallation at C8 rather than C2.[10] The DFT calculation further indicates that the **C** conformation is slightly higher in energy than **D** in solution state. Secondly, the *N*-(*t*-butyl)amide at C1 makes the **A** ring more electron-deficient than the **B** ring. Thus, the electrophilic catalytic system enables the preferential cyclometallation at C8 (**B** ring). Thirdly, the complexation of the palladium center with a DG is kinetically favourable for the carbopalladation[11] and is beneficial to restrain the deprotonation and re-aromatization at C8.



[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol) and [Pd] (1.0 equiv) in 1 mL of dichloromethane (DCM) at 80 °C for 12 h under N_2.

Scheme 2. Evaluation of stoichiometric reaction systems[a]

Following the above proposal,[9b,9c] we began our investigation by the reaction of 1-naphthamide (**1a**) and $PhB(OH)_2$ (**2a**) in the presence of stoichiometric palladium species (Scheme 2). Unfortunately, $Pd(OAc)_2$ did not deliver the arylated naphthalene **3a**. However, the replacement of $Pd(OAc)_2$ with the cationic $Pd(TFA)_2$ afforded **3a** in 32% yield. We envisioned a more electrophilic high-valent cationic Pd^{IV} species might further promote the C7–H arylation. As well-known, a cationic Pd^{IV} species can be formed with electrophilic fluorination reagents[12] and *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (NFSI) can react with Pd^{II} and arylation reagents to form Ar–Pd^{IV} species.[13] Thus, the reaction of **1a** with **2a** was performed in the presence of $Pd(OAc)_2$ and NFSI, affording **3a** in 60% yield (Scheme 2). This reaction could also be extended to a catalytic version, delivering **3a** in 51% yield along with 5% yield of the C8–arylated byproduct **3a'** (Scheme 3). Other electrophilic fluorination reagents showed less efficiencies partly owing to the unfavourable coordination of the tertiary amine or pyridyl moiety to the palladium center.[13] The yields were improved with the increase of the steric hindrance around pyridyl moiety, which might inhibit the coordination (F^+_2, F^+_3, F^+_4 and F^+_5). Considering the high price of NFTMPT, NFSI was selected as the oxidant for the following investigation.

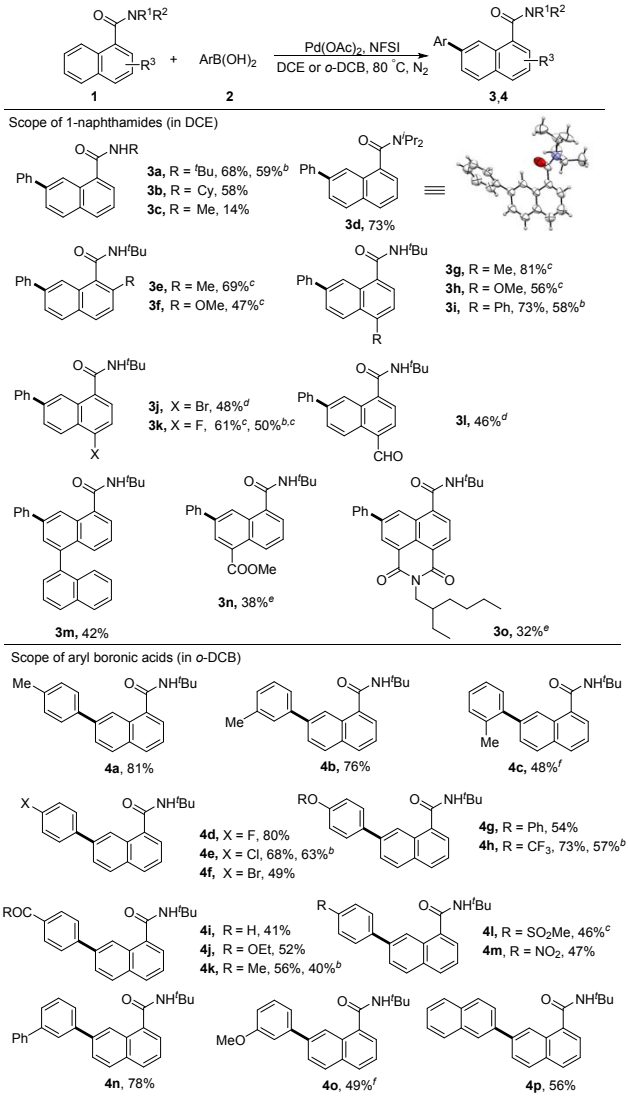


[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (10 mol%) and F+ reagent (2.0 equiv) in 1 mL of DCM.

Scheme 3. Survey of F+ reagents[a]

The reaction condition was further optimized (Tables S3-7). Either higher or lower temperatures than 80 °C led to inferior yields (Table S3, entries 1-5). Screening of solvents indicated that DCE (1,2-dichloroethane), HFIP (hexafluoroisopropanol) and *o*-DCB (1,2-dichlorobenzene) were superior to DCM, providing approximately 60% yield (Table S4). When the reaction was operated in the presence of 1.25 equiv of NFSI and **2a**, the desired product **3a** was obtained in 68% yield along with the C8–arylated byproduct **3a'** in 4% yield (**3a**/**3a'**= 17:1) and 1,1'-biphenyl in 13% yield (Table S6, entry 5). In addition, 2.0 equiv of other oxidants (e.g., Ag_2O, $Cu(OAc)_2$, DTBP (di-*t*-butyl peroxide), *m*CPBA (*m*-chlorobenzoperoxoic acid), $K_2S_2O_8$, $PhI(OAc)_2$, and DDQ (2,3-dicyano-5,6-dichlorobenzoquinone)) instead of NFSI did not afford **3a** or only gave a trace amount of **3a**, indicating the unique effect of F+ reagents (Table S7, entries 1-8). The replacement of $PhB(OH)_2$ with iodobenzene (PhI) did not afford any desired product (Table S7, entry 10). Furthermore, no arylation was detected in the reaction of **1a**, phenyl bromide and PivOK in *N*,*N*-dimethylacetamide in the absence of NFSI (Table S7, entry 11).

Table 1: **Scope of 1-naphthamides and aryl boronic acids**[a]

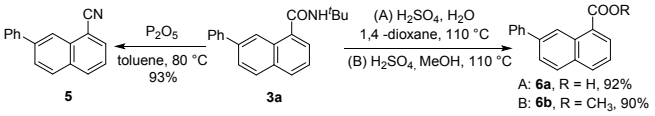


[a]Reaction conditions: **1** (0.10 mmol), **2** (0.125 mmol), $Pd(OAc)_2$ (10 mol%), and NFSI (0.125 mmol) in 1 mL of DCE or *o*-DCB at 80 °C for 12 h under N_2. [b]3 mol% of $Pd(CF_3COO)_2$ instead of 10 mol% of $Pd(OAc)_2$, 36 h. [c]at 100 °C. [d]NFTMPT instead of NFSI. [e]HFIP instead of DCE. [f]HFIP instead of *o*-DCB.

With the optimized conditions in hand, the scope of naphthalenes was first explored. As shown in Table 1, various

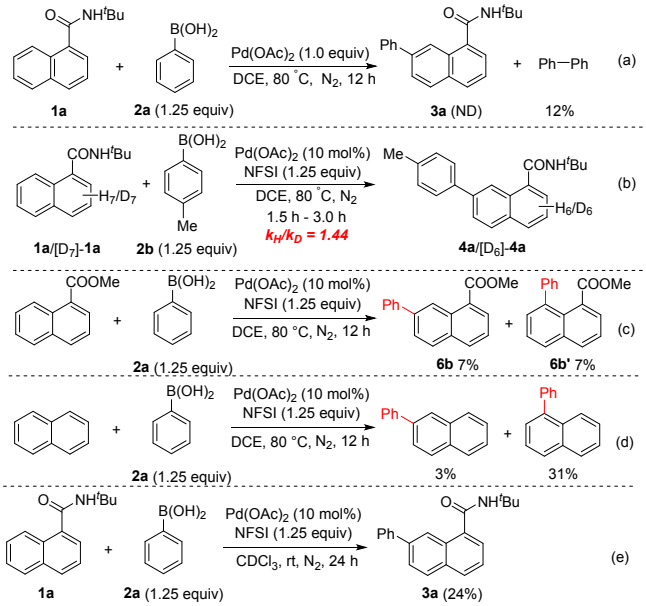
1-naphthamides successfully underwent the C7-arylation with $PhB(OH)_2$. As we proposed, the steric effect of the amide group seemed to have significant influence on the cross-coupling reaction. Depending on the steric effect, the C7-arylated products were obtained in the range of 14~73% yields (**3a-3d**).[10] No C2-arytlated product was detected. 1-Naphthamides with both the electron-donating (e.g., methyl, and methoxy) and electron-withdrawing (e.g., formyl, fluoro group and ester) substituents smoothly underwent the arylation (**3e-i**, **3k-l** and **3n**). No or only trace amounts of the C8-arylated products were detected. The very reactive bromo group could be retained and no Suzuki-Miyaura coupling product was detected (**3j**). Binaphthylamide was also a suitable substrate (**3m**). Naphthalimide, an important organic photoelectric functional skeleton, could deliver the π-extended product **3o** under the slightly modified reaction condition. Notably, even 3 mol% of [Pd] species could efficiently promote the C7-arylation (**3a**, **3i** and **3k**). No obvious decomposition of substrate **1** was detected and the remaining substrates could be recovered, as exemplified by **1f**, **1j**, **1n** and **1o** (see the supporting information). In addition, the attempts of *N*-(*t*-butyl)-8-phenyl-1-naphthamide **3a'** and *N*-(*t*-butyl)-7-phenyl-1-naphthamide **3a** under the standard conditions led to a complex inseparable mixture and no reaction, respectively.

Next, we tested the scope of arylboronic acids. Arylboronic acids with various functional groups, such as methyl, fluoro, chloro, bromo, aryl, trifluoromethoxy, formyl, ether, acyl, methylsulfonyl, nitro and methoxy, at either *para*, *meta*, or *ortho* position of the phenyl ring could react with 1-naphthamide to afford the C7-arylated products in moderate to high yields (**4a-4p**). In contrast to the *para* and *meta*-substituent groups, the *ortho*-substituents led to diminishing yields (**4a-4c**), suggesting that the increased steric congestion could influence the reactivity.



Scheme 4. Transformations of 3a

To further illuminate the synthetic utility of this method, we investigated the transformations of C7-arylated naphthalenes (Scheme 4). For example, **3a** was treated with P_2O_5 to afford 7-phenyl-1-naphthonitrile **5** in 93% yield. Treatment of **3a** with dilute sulfuric acid in 1,4-dioxane and conc. H_2SO_4 in MeOH gave 7-phenyl-1-naphthoic acid **6a** and methyl 7-phenyl-1-naphthoate **6b** in 92% and 90% yields, respectively.



Scheme 5. Control experiments for the reaction mechanism

To get some insights into the reaction mechanism, a series of control experiments were conducted. First, the reaction of **1a** and **2a** in the presence of stoichiometric $Pd(OAc)_2$ could deliver biphenyl in 12% yield along with the 95% recovery of **1a**, indicating that Pd^{II} could participate in the transmetalation of phenylboronic acid (Scheme 5a).[9b,13b] Next, the parallel competition reactions between *p*-tolylboronic acid **2b** and *N*-(*tert*-butyl)naphthamide **1a** or [D_7]-**1a** were carried out. A KIE value of 1.44 suggests that a typical S_EAr pathway for the C–H bond activation is less likely in the C7-arylation because the k_H/k_D value of a typical electrophilic palladation mechanism is approximately 1.0.[13a,14] This result also demonstrates that the cleavage of the C7–H bond could not be included in rate-determining step (Scheme 5b). Finally, methyl 1-naphthoate and naphthalene instead of **1a** were examined under the standard conditions. The arylation of methyl 1-naphthoate generated a mixture of C7-/C8-arylated product with a ratio of 1:1, and the reaction of naphthalene delivered 1-phenylnaphthalene in 31% yield and 2-phenylnaphthalene in 3% yield,[15] demonstrating the key role of the amide directing group in the carbopalladation/aryl migration process (Scheme 5c and 5d).

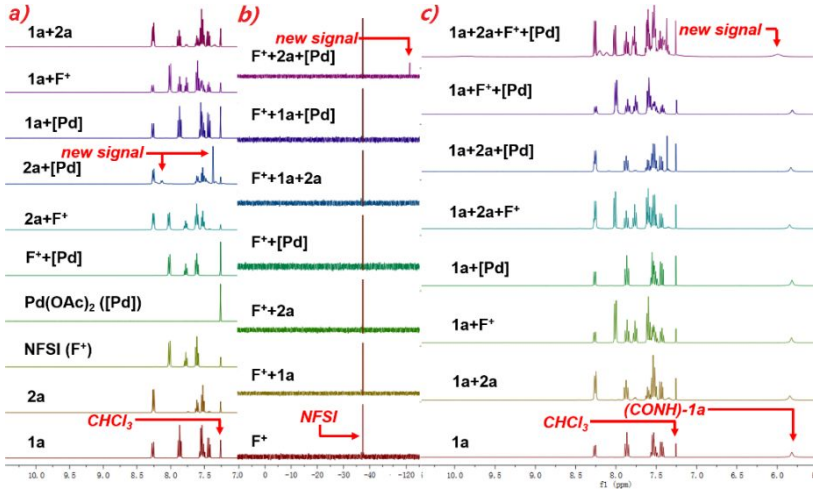
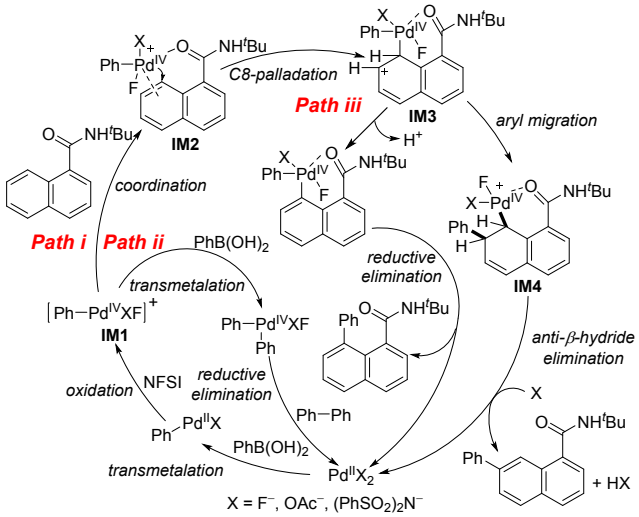


Figure 1. a) ^{1}H NMR spectra of **1a**, **2a**, [Pd] and NFSI in $CDCl_3$. b) ^{19}F NMR spectra of NFSI in $CDCl_3$. c) ^{1}H NMR spectra of the amide proton of **1a** in $CDCl_3$

Considering that the C7-arylation could occur in $CDCl_3$ at RT (Scheme 5e), a series of ^{1}H NMR spectra of the mixed reactants (**1a**, **2a**, $Pd(OAc)_2$ and NFSI) in $CDCl_3$ at RT in 8 hour period were investigated. As shown in Figure 1a, only a combination of **2a** and $Pd(OAc)_2$ leads to new proton signals, further suggesting that the first step could be a transmetalation of phenylboronic acid to form Ph–Pd^{II}.[9b,13b] A mixture of $Pd(OAc)_2$ and NFSI did not gave rise to new peaks in the ^{19}F NMR spectrum, revealing that NFSI could not directly oxidize $Pd(OAc)_2$ to Pd^{IV} species (Figure 1b). Upon addition of **2a**, a mixture of **2a**, $Pd(OAc)_2$ and NFSI leads to a fresh ^{19}F signal, suggesting that NFSI takes part in the catalytic cycle after the transmetalation of **2a** and oxidizes Ph–Pd^{II} to produce [F–Pd^{IV}–Ph] species.[13b] As illustrated in Figure 1c, the signal of the amide proton of **1a** shifts downfield from 5.85 to 5.99 ppm only in the presence of all four reactants, indicating the coordination of palladium center to the amide group in this case. This result further implies that the oxygen atom of the amide group coordinates to palladium center rather than the nitrogen atom.



Scheme 6. Plausible mechanistic pathway.

Based on the above mechanistic studies and previous literature,[9,16] a plausible pathway is proposed (Scheme 6). Firstly, the transmetalation of Pd(II) species with $PhB(OH)_2$ (**2a**) generates a Ph–Pd^{II} species, which is subsequently oxidized by NFSI to produce a reactive cationic [Ph–Pd^{IV}–F] species **IM1**.[12,13] Next, **IM1** may undergo transmetalation to afford the $Ph_2Pd^{IV}FX$ species and subsequent reductive elimination to deliver 1,1'-biphenyl (path ii). Alternatively, **IM1** coordinates with *N*-(*tert*-butyl)-1-naphthamide (**1a**) to provide intermediate **IM2** (path i). **IM2** then goes through the C8-palladation to form the cationic intermediate **IM3**.[9] **IM3** may experience a typical S_EAr pathway to bring the C8-arylated byproduct (path iii)[13] or undergo the aryl migration from Pd center to C7 to form intermediate **IM4**. The six-membered ring structure enhanced the stability of cyclic palladium complex **IM3** and rendered the carbopalladation event (aryl migration) kinetically favorable to give **IM4**.[11] **IM4** then undergoes an anti-*β*-hydride elimination to deliver the C7-arylated naphthalene and regenerate Pd(II) species. Additionally, a typical Heck-type mechanism seems less favored because the deprotonation process requires *syn β*-hydride elimination, in which the C–C bond rotation of cyclometallic intermediate **IM4** is prerequisite but difficult.[16] The arylation may occur at both the C7 and C8 positions (Scheme 3 and Scheme 5d), further indicating the pathway involving an aryl migration.

In conclusion, we have accomplished the C7-selective arylation of 1-naphthamides with aryl boronic acids through the carbopalladation/aryl migration. This protocol avoids the use of extra ligands and additives, and exhibits high catalytic activity and good tolerance of reactive functional groups. The electrophilic fluorination reagents are demonstrated as a unique oxidant to enhance the reaction efficiencies of C7–H arylation of naphthalenes. We believe that this work will give inspiration for other types of C7-regioselective functionalizations of naphthalene rings.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

This work was supported by grants from the National NSF of China (Nos 21432005, 21672154 and 21502123).

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures, characterization of related compounds, crystallographic data, and X-ray crystal structures (CIF) of **1a** (CCDC-1912345) and **3d** (CCDC-1911106) are available in the Supplementary Information. The Supporting Information is available free of charge on the ACS Publications website.

ACKNOWLEDGMENT

The authors acknowledge the support from the Comprehensive Training Platform of Specialized Laboratory, College of Chemistry, Sichuan University.

ABBREVIATIONS

KIE, kinetic isotope effect; EDG, electron-donating group; EWG, electron-withdrawing group; DGs, directing groups; NFSI, *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide; NFTMPT, *N*-fluoro-2,4,6-trimethylpyridinium triflate; DCE, 1,2-dichloroethane; HFIP, hexafluoroisopropanol; *o*-DCB, 1,2-dichlorobenzene; DTBP, di-*t*-butyl peroxide; *m*CPBA, *m*-chlorobenzoperoxoic acid; DDQ, 2,3-dicyano-5,6-dichlorobenzoquinone; S_EAr, electrophilic aromatic substitution.

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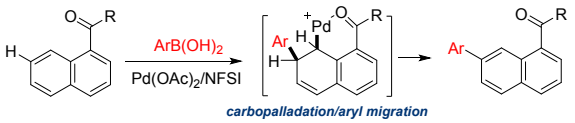
O
R
H
ArB(OH)2
Pd(OAc)2/NFSI
+Pd
Ar
H
carbopalladation/aryl migration