Published in final edited form as:

J Am Chem Soc. 2011 September 7; 133(35): 13864–13867. doi:10.1021/ja206572w.

Pd(II)-Catalyzed *para*-Selective C–H Arylation of *mono*-Substituted Arenes

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Abstract

Pd-catalyzed *para*-selective C–H arylation of mono-substituted arenes including toluene is developed for the first time using F^+ as a bystander oxidant. This finding provides a new retrosynthetic disconnection for biaryl synthesis.

The electrophilic palladation of arenes observed in the 1960s mainly involves either highly reactive electron-rich arenes or excess benzene to promote palladation through high molarity.¹ Extensive efforts to exploit directed *ortho*-palladation to develop synthetically useful reactions has witnessed encouraging progress during the past decade.² Recently, the use of a mono-protected amino acid ligand has demonstrated the potential to enhance reactivity³ as well as control regioselectivity^{3a} and stereoselectivity.⁴ From the viewpoint of synthetic applications, the next fundamental challenge in this field is to seek a new approach to achieve *meta*- and *para*-selectivity with mono-substituted and generally representative arene substrates.^{5,6} Herein, we report the first *para*-selective arylation of representative *mono*-substituted arenes via a two-fold C–H activation process to provide a unique route for accessing biaryls (Eq 1). The combination of an acidic amide directing group for the first C–H activation and the bystander oxidant F^+ for the second C–H activation is crucial for high *para*-selectivity. Taken together with several recent literature reports on two-fold C–H coupling reactions lacking regioselectivity in the second C–H activation step,⁷ the high *para*-selectivity observed in this work suggests that this reaction proceed through a *para*-selective C–H cleavage by Pd(IV) species which are known to be formed in the presence of F^+ .⁸

(1)

Direct coupling of two aryl C–H bonds⁹ has regained interest recently owing to the prospect of achieving predominant hetero-coupling by increasing the reactivity of one of the two arenes. This has been achieved by using either an electron-rich arene¹⁰ or installing a directing group⁷ to one of the arene substrates to suppress undesired homo-C–H coupling. Among numerous seminal contributions, the use of amide directing groups by the Dong group has exhibited the most encouraging substrate scope to include broadly useful benzoic

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Supporting Information Available: Experimental procedure and characterization of all new compounds (PDF). This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

acid and phenyl acetic acid skeletons, albeit limited to electron-neutral and -rich arenes.^{7f} A common problem in these reactions is the typical formation of a mixture of regio-isomers when a mono-substituted arene is used as the other coupling partner, rendering them synthetically impractical.

We have recently employed F^+ as a bystanding oxidant to promote selective reductive elimination from Pd(IV) in a number of C–H activation/C–N and C–O bond forming reactions.¹¹ Michael and co-workers have observed that a Pd-alkyl intermediate generated from the carboamination of olefins reacted with toluene in the presence of *N*-fluorobenzenesulfonimide to give mainly the *para*-alkylated toluene as the isolated products in 45–90% yields.¹² In our previous fluorination of benzyltriflamide with F^+ ,¹³ a small amount of *ortho*-arylation product (<10%) was also formed when toluene was used as the solvent. In this case, toluene was activated with moderate selectivity (*para/meta/ortho* = 12/4/1) (eq 2).

(2)

Guided by these observations, we began to search for a suitable arylating reagent and reaction conditions that would allow highly *para*-selective arylation of toluene. Since the acidic amide derived from 4-trifluoromethyl-2,3,5,6-tetrafluoroaniline ($ArNH_2$) has demonstrated superior reactivity for C–H activation,¹⁴ we focused on amide **1** and screened oxidants and additives known to promote C–H activation (Table 1). We found that the use of F^+ as an oxidant and 2 equiv DMF as additive promoted the arylation of toluene to give the desired product in 70% yield with a *para/meta* ratio of 13/1 (entry 14). No *ortho*-arylation was observed. Intriguingly, the use of previously used oxidant $K_2S_2O_8$ ^{7f} instead of F^+ gave the arylated products with poor selectivity (*para/meta*, 1.7/1) (entry 13). Considering the result shown in Eq 2, these experimental observations suggest that both our directing group and the use of F^+ are crucial for obtaining high *para*-selectivity.

With the insight that the use of an F^+ oxidant is crucial for *para* regioselectivity, we next tested various F^+ sources. In all cases, uniformly high *para*-selectivity was observed and NFSI gave the highest yield (Table 2).

Under these optimized conditions, an array of synthetically useful benzamides was reacted with toluene (Table 3). Benzamides containing no substituent and those substituted with electron-donating groups were arylated smoothly to give the biaryl products with excellent *para*-selectivity with respect to toluene (**2b–e**). A number of halogenated benzamides also reacted with toluene in similar regioselectivity to give the biaryls in good yields (**2f–i**). The chloro and bromo substituent are useful handles for synthetic elaborations. Of special importance, benzamides containing electron-withdrawing groups including trifluoromethyl, ketone and cyano groups are also compatible with this catalytic system (**2j–m**). Notably, previously reported twofold C–H activation reactions were typically not compatible with these electron-deficient arylating reagents,⁷ which illustrates the efficiency of this acidic amide directing group and the reactivity of the Pd(IV) species in C–H activation.

The *para*-selectivity was also consistently observed with other substituted arenes containing alkyl, methoxy and halide groups (Table 4). The compatibility of halide groups with the reaction conditions allows for synthetic elaboration through the powerful cross-coupling and Buchwald-Hartwig amination reactions.

The exceedingly high *para*-selectivity observed for such two-fold C–H activation reactions could have significant mechanistic implications. Since the first C–H activation involving the directing group is relatively well understood,¹⁴ we focused on the second C–H activation step. The absence of a significant kinetic isotope effect (Figure 1) indicates that the second C–H activation step is not a rate-limiting event. Since rapid oxidation of ArPd(II) to ArPd(IV) species by F⁺ is well established,^{8,11} it is reasonable to propose that ArPd(IV) is the active species for the second C–H activation event. Low selectivity observed with other oxidant such as Na₂S₂O₈ seems to suggest that involvement of Pd(IV) species is advantageous for obtaining regioselectivity. The significantly lower *para*-selectivity observed with the triflamide directing group (Eq 2) also indicates that directing group has great impact on the regioselectivity as discussed in previous reports.^{7f}

In summary, we have developed a two-fold C–H activation protocol to achieve *para*-selective arylation of *mono*-substituted arenes including toluene. Electron-withdrawing groups such as ketone and cyano on one of the coupling partners are tolerated. Further development of these types of reactions could potentially lead to new tools for biaryl synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge The Scripps Research Institute, the National Institutes of Health (NIGMS, 1 R01 GM084019-02), Amgen, Eli Lilly and Novartis for financial support. We thank A*STAR for a postdoctoral fellowship (D. L.).

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Figure 1.
Kinetic isotope effect

Table 1

Pd(II)-Catalyzed Oxidative Cross Coupling: Survey of Oxidants^{a,b}

entry	oxidant (equiv.)	yield (%)	entry	oxidant (equiv.)	yield (%)
1	AgOAc (3.0)	0	8	(PhCOO) ₂	0
2	Cu(OAc) ₂ (1.5)	0	9	NCS (1.5)	0
3	AgOAc/CuCl ₂ (1.5/1.5)	0	10	PhI(OAc) ₂ (1.5)	0
4	PhCO ₃ But ^t (1.5)	0	11	PhI(TFA) ₂ (1.5)	0
5	Oxone (3.0)	0	12	PhI(OPiv) ₂ (1.5)	0
6	Ce(SO ₄) ₂ (2.0)	0	13 ^c	K ₂ S ₂ O ₈ (3.0)	75 (1.7/1) ^d
7	(<i>n</i> -BuO) ₂ (1.5)	0	14	NFTMPT (1.5)	70 (13/1) ^d

^a Unless otherwise noted, the reaction conditions were as follows: Ar = 4-trifluoromethyl-2,3,5,6-tetrafluorophenyl; **1a** (0.2 mmol), Pd(OAc)₂ (10 mol%), oxidant (1.5 equiv.), DMF (2.0 equiv.), toluene (2 mL), 100 °C, 24 h.

^b Isolated yield.

^c CF₃COOH (TFA, 5 equiv.) was added.

^d Regioselectivity determined by GC analysis (*para/meta*) was shown in parentheses.

Table 2

Survey of F⁺ oxidants^{a,b,c}

 3 18% (8/1)	 4 14% (13/1)	 5 5% (17/1)	 6 11% (10/1)
 7 14% (13/1)	 8 49% (12/1)	 NFTMPT, 9 70% (13/1)	 NFSI, 10 81% (13/1)

^aUnless otherwise noted, the reaction conditions were as follows: **1a** (0.2 mmol), Pd(OAc)₂ (10 mol%), oxidant (1.5 equiv.), DMF (2.0 equiv.), toluene (2 mL), 100 °C, 24 h.

^bIsolated yield.

^cRegioselectivity determined by GC analysis (*para/meta*) was shown in parentheses.

Table 3

Scope of benzamides^{a,b,c}

^aUnless otherwise noted, the reaction conditions were as follows: **1** (0.2 mmol), Pd(OAc)₂ (10 mol%), oxidant (1.5 equiv.), DMF (2.0 equiv.), toluene (2 mL), 70 °C, 48 h.

^bIsolated yield.

^cRegioselectivity determined by GC analysis (*para/meta*, no *ortho*-product was observed) was shown in parentheses.

^d90 °C, 24 h.

^e80 °C, 36 h.

^fPd(OAc)₂ (15 mol%) was used.

ξ_{100}^g °C, 24 h.

Table 4

Scope of mono-substituted arenes^{a,b,c} structure wrong, 2O

^aUnless otherwise noted, the reaction conditions were as follows: **1** (0.2 mmol), Pd(OAc)₂ (10 mol%), NFSI (1.5 equiv.), DMF (2.0 equiv.), arene (2 mL), 70 °C, 48 h.

^bIsolated yield.

^cRegioselectivity determined by GC analysis (*para/meta*, no *ortho*-product was observed) was shown in parentheses.

^d100 °C, 24 h.