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Ligand-Controlled *Para*-Selective C−H Arylation of Monosubstituted Arenes

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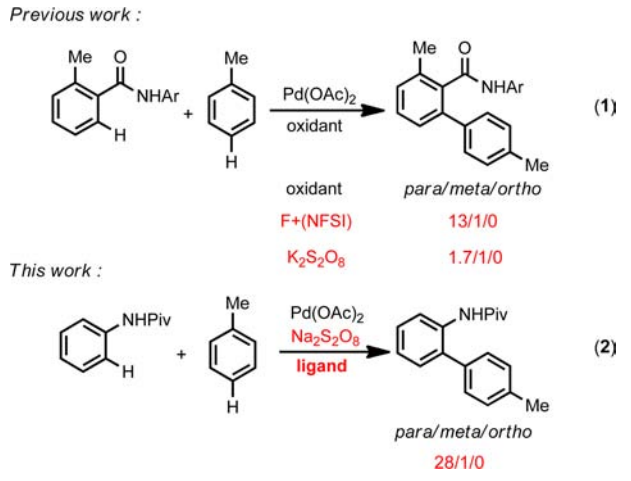
Supporting Information

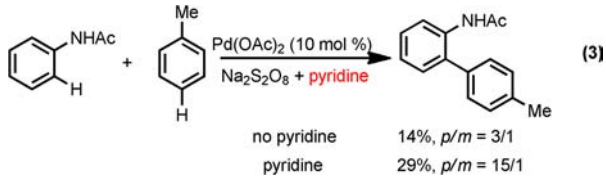
ABSTRACT: In a Pd-catalyzed double C−H activation reaction, a pyridine-type ligand is identified, for the first time, to enable a highly *para*-selective C−H arylation of monosubstituted arenes. Excellent *para*-selectivity is achieved with a variety of arenes containing alkyl, methoxyl, and halo substituents.

Biaryls are an important structural motif in natural products, biologically active compounds, drug molecules, and organic materials.[1] Formation of biaryls via C−H/C−H coupling is potentially an attractive method as the prefunctionalization step is omitted.[2] However, achieving regioselectivity on both arene-coupling partners is challenging.[3] Moderate success has been achieved by combining *ortho*-directed C−H activation with nondirected C−H activation.[4−6] While the *ortho*-selectivity of one of the two arenes is secured by the directing group, regioselectivity on the monosubstituted arenes containing no directing group remains to be substantially improved.[5] For example, *para*-selective C−H arylation of monosubstituted electron-rich anisole has been reported with encouraging *para*-regioselectivity.[5b,d,g] Recently, we reported a Pd-catalyzed *para*-selective C−H arylation of monosubstituted arene using F^+ as the bystanding oxidant (eq 1).[7] The observed



para-selectivity is crucially dependent on the use of a stoichiometric F^+ reagent. Based on an earlier related study,[8,9] we attributed this selectivity to a *para*-selective C−H cleavage by [ArPd(IV)F] species. However, achieving *para*-selectivity using oxidants other than a stoichiometric F^+ source has not been successful. Herein, we report the use of a catalytic amount of ligand that significantly enhances the *para*-selectivity in a double C−H activation reaction without involving [ArPd(IV)-F] species, thus demonstrating the feasibility of developing a ligand for achieving *para*-selectivity (eq 2).

We have recently systematically established that Pd(II)-catalyzed C−H activation can be drastically influenced by pyridine- and quinoline-based ligands.[10] The observed ligand effects encouraged us to test if we could replace the fluoride at the Pd(IV) center by a suitable ligand and still afford *para*-selectivity in the C−H cleavage step. To test this hypothesis, we began to investigate the regioselectivity of the well-established C−H coupling of acetanide with toluene.[5b,c,g] In one of the studies, a *ortho*/*meta*/*para* selectivity of 1/16/16 was obtained.[5b] Preliminary screening of our pyridine ligands afforded a significantly improved *para* to *meta* selectivity (15/1) when pyridine ($\mathbf{L_3}$) was used as a ligand, albeit in low yield (eq 3). The use of pivaloyl-protected aniline substrate PhNHCO-*t*-Bu (**1a**) gave improved yield and selectivity, while other directing groups were inferior (Scheme 1).



Using PhNHCO-*t*-Bu as the substrate, we further examined a variety of ligands (Scheme 2). In the absence of ligand, treatment of PhNHCO-*t*-Bu (**1a**) and toluene afforded arylated products (mono and di) in 53% yield with a *para*/*meta* ratio of

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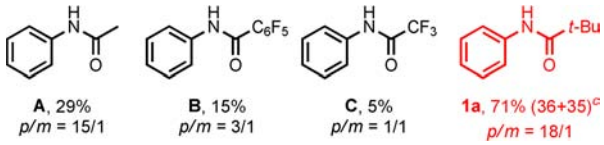
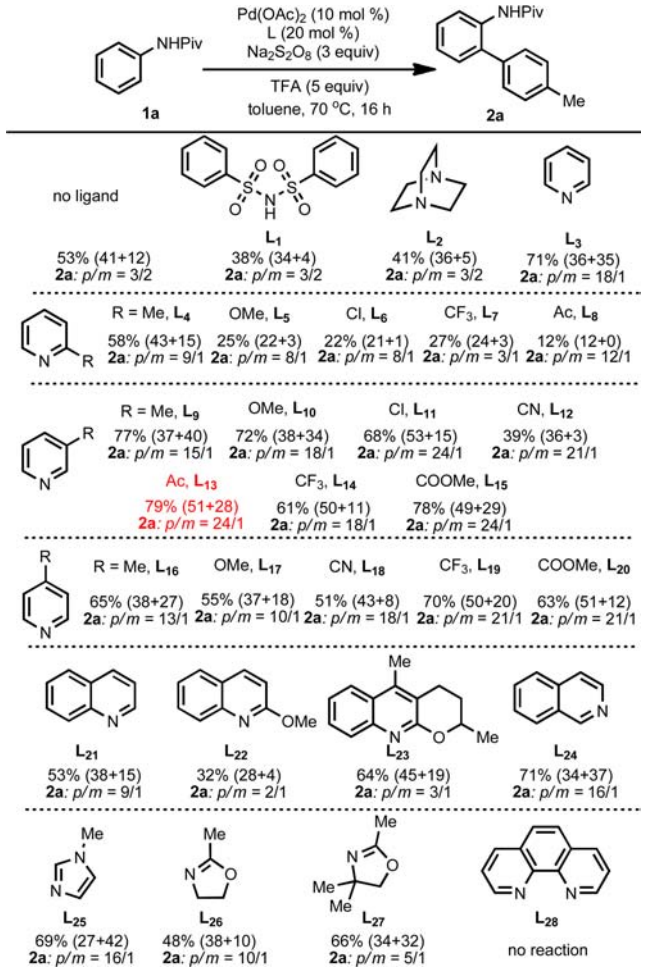
Scheme 1. Screening of Directing Group[a–d]



[a]Reaction conditions: **1a**, **A**–**C** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), pyridine (20 mol %), TFA (1.0 mmol), $Na_2S_2O_8$ (0.6 mmol), toluene (2 mL), 70 °C, 16 h. [b]Yield is determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. [c]Mono- and diarylation (mono + di) is shown in parentheses. [d]Regioselectivity of **2a** is determined by GC analysis.

Scheme 2. Screening of Ligands[a–c]

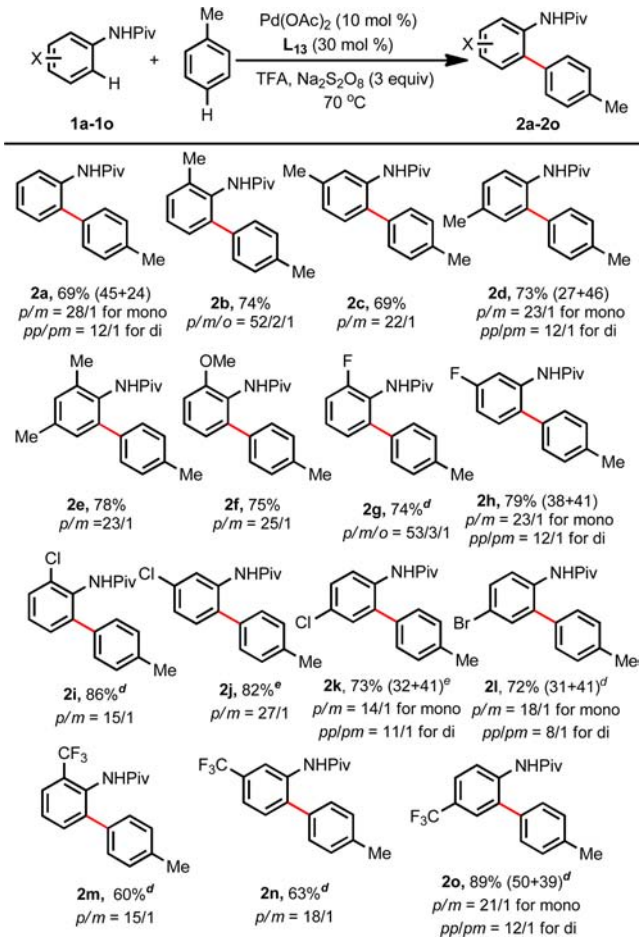


[a]Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), L (20 mol %), TFA (1.0 mmol), $Na_2S_2O_8$ (0.6 mmol), toluene (2 mL), 70 °C, 16 h. [b]Yield determined by ^1H NMR analysis of crude reaction mixture using CH_2Br_2 as an internal standard. Mono- and diarylation (mono + di) is shown in parentheses. [c]Regioselectivity of **2a** is determined by GC analysis.

3/2 for monoproduct **2a**. Since the F^+ reagents used to achieve the *para*-selectivity in our previous study contain amines and amides $\mathbf{L_1}$–$\mathbf{L_2}$, we also tested these ligands and obtained poor regioselectivity ($\mathbf{L_1}$–$\mathbf{L_2}$). Among the various tested pyridine- and quinoline-based ligands, we found that 3-acetylpyridine ($\mathbf{L_{13}}$) and methyl nicotinate ($\mathbf{L_{15}}$) gave the best result in terms of both *para*-selectivity and yields. The regioselectivity of the nondirected C–H activation sensitively depends on the structure of the ligands. Compared with *para*- and *meta*-substituted pyridine, *ortho*-substituted pyridine only gave lower regioselectivity. Meanwhile, the electron-withdrawing group at the *para*- and *meta*-positions of pyridine showed a higher *para*/*meta* ratio than the electron-donating group. Some other nitrogen-containing heterocycles were also tested ($\mathbf{L_{21}}$–$\mathbf{L_{27}}$). When bidentate ligand $\mathbf{L_{28}}$ was employed, no desired product was formed. We further investigated the loading of ligand $\mathbf{L_{13}}$ and found that 30 mol % of ligand gave better result with a *para*/*meta* ratio of 28/1 for **2a** (see the Supporting Information).

With these optimized conditions in hand, we began with a survey of variously substituted anilide substrates. As shown in Scheme 3, anilides containing electron-donating methyl and

Scheme 3. Scope of Anilides[a–c]



[a]Reaction conditions: **1a**–**o** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), $\mathbf{L_{13}}$ (30 mol %), TFA (1.0 mmol), $Na_2S_2O_8$ (0.6 mmol), toluene (2 mL). [b]Isolated yields are given. Mono- and diarylation (mono + di) is shown in parentheses. [c]Regioselectivity is determined by GC analysis. [d]$\mathbf{L_3}$ (30 mol %), TFA (2.0 mmol). [e]TFA (2.0 mmol).

methoxy groups were arylated with toluene to give the corresponding biaryl product with an excellect *para*/*meta* ratio (≥22/1) with respect to toluene. By increasing the amount of TFA and/or using $\mathbf{L_3}$ as ligand, anilides containing electron-withdrawing fluoro, chloro, bromo, and trifluoromethyl groups also reacted with toluene to give the biaryl products in good yields but slightly lower regioselectivity. The chloro

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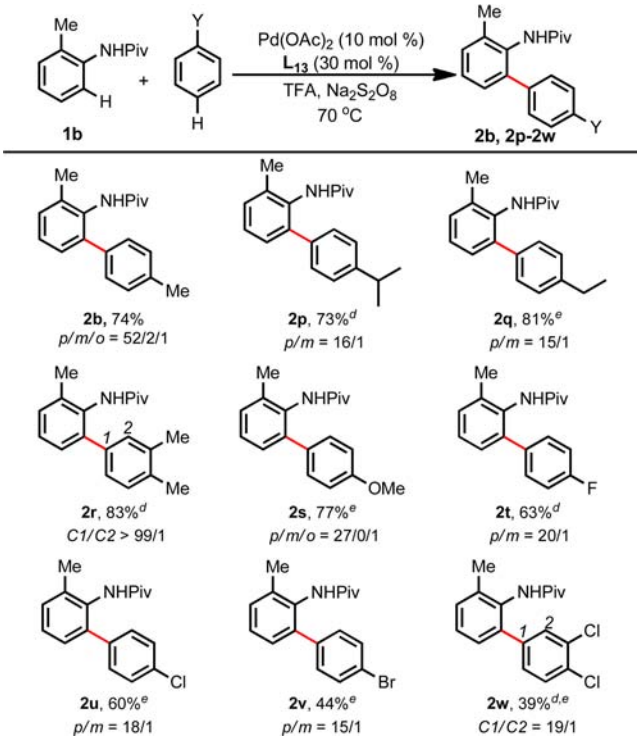
and bromo groups in products **2i–l** are useful handles for further structural elaborations.

This protocol is also applied to the other substituted arenes containing alkyl, methoxyl, and halo groups, and high levels of *para*-selectivity and moderate to good yields are obtained (Scheme 4). In sharp contrast to the *meta*-selectivity observed

Scheme 4. Scope of Substituted Arenes[a–c]



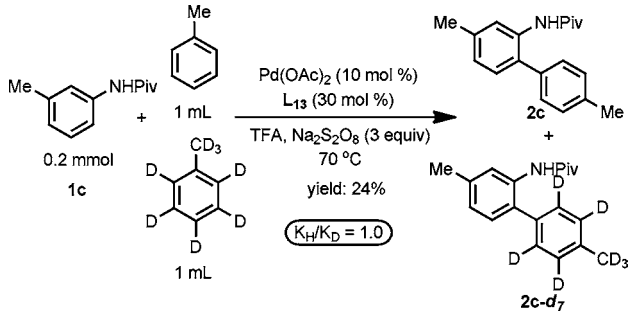
[a]Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), L_{13} (30 mol %), TFA (1.0 mmol), $Na_2S_2O_8$ (0.6 mmol), ArH (2 mL). [b]Isolated yields are given. [c]Regioselectivity is determined by GC analysis. [d]TFA (2.0 mmol). [e]L_3 (30 mol %).

in the [$Rh^{III}Cp^*$]-catalyzed *ortho*-coupling of benzamides with monohalogenated benzene (*meta*/*para* ratio 2.6/1–4.7/1),[5f] our reaction gives highly *para*-selective product with a *para*/*meta* ratio of 15/1–20/1.

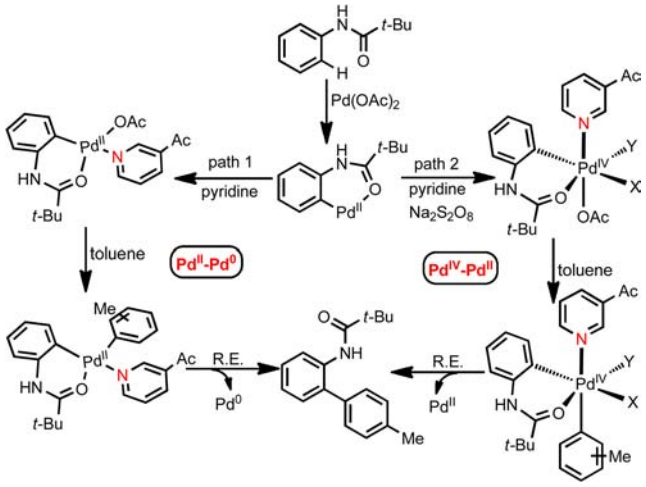
Since the cyclopalladated complex of the first C–H activation step involving anilide directing group is well-known,[5d,11] we focused on the second C–H activation step. A lack of kinetic isotope effect determined by intermolecular competition experiments between toluene and toluene-d_8 infers that the second C–H activation step most likely involves an electrophilic palladation by the ligand-supported Pd(II)[3d,4a,d,e] or Pd(IV)[5d,7–9] species (Scheme 5 and 6). It is known that the π-acceptor character of pyridine ligands could increase the electrophilicity of Pd centers.[12] Presumably, the ligand-bearing Pd center is sterically hindered and prefers to react at the *para*-position via an electrophilic palladation pathway.

In conclusion, we have developed a ligand that can drastically improve the *para*-selectivity of Pd-catalyzed *ortho*-arylation of monosubstituted arenes without using stoichiometric F^+ reagent. This finding paves the way for further development of ligand-controlled regioselective arylation of monosubstituted arene with or without directing groups.

Scheme 5. Kinetic Isotope Effect



Scheme 6. Proposed Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01802.

Experimental procedure and characterization of all new compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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