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# Nickel-Catalyzed α-Arylation of Zinc Enolates with Polyfluoroarenes via C−F Bond Activation under Neutral Conditions

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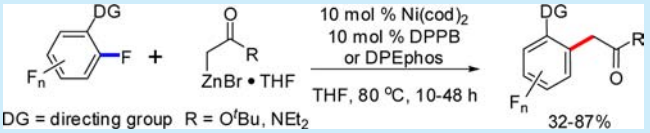
Supporting Information

**ABSTRACT:** The first nickel-catalyzed α-arylation of 2-(polyfluorophenyl) pyridine with zinc enolates of esters or amides via C−F bond activation under neutral conditions is described. A variety of functional groups such as ester, amide, ether, and amine were tolerated. This method provides a simple and useful tool to synthesize fluorinated α-aryl carboxylic acids and α-aryl amides that are important intermediates for drug discovery.




α-Aryl carboxylic acids and amides are among the most important structural motifs presented in a wide range of medicinally relevant molecules,[1] such as Plavix, Sector, Ibuprofen, Naproxen, and Piperacillin sodium, as illustrated in Figure 1. In addition, the α-aryl carbonyl compounds could be readily converted into other useful synthetic intermediates with alcohol, amine, imine, nitrile, or olefin functional groups.[2] Thus, development of efficient methods for the formation of α-aryl carboxylic acids and amides is of current interest. One general strategy for the preparation of α-aryl carboxylic acids and amides is the transition-metal-catalyzed direct α-arylation of carbonyl compounds.[3] Since the initial discoveries by Buchwald, Hartwig, and Miura independently in 1997,[4] enormous progress has been achieved for the Pd- or Ni-catalyzed α-arylation reactions. While a variety of electrophilic aryl halides[3] (X = I, Br, Cl), aryl triflates,[5] and tosylates[6] have been described for this transformation, to the best of our knowledge, the α-arylation of aryl fluorides remains elusive.

Development of transition-metal-catalyzed α-arylation of aryl fluorides via C−F bond activation of polyfluorinated arenes is challenging. One problem associated with this transformation is the difficulty in controlling the selective activation of C−F bonds in polyfluorinated arenes, mainly because the C−F bond is one of the strongest single bonds and the difference of the kinetic barriers for the activation of the C−F bonds in polyfluoroarene is small.[7] To address this problem, several groups including the Love,[8] Chatani,[9] Kakiuchi,[10] Li,[11] Cao,[12] Zhang,[13] and Shen and Lu[14] groups recently developed a new strategy by employing a directing group which facilitated the selective activation of the *ortho* C−F bond of polyfluoroarenes. Several Pd- or Ni-catalyzed cross-coupling reactions of polyfluoroarenes with different directing groups have thus been reported under mild conditions. Despite these promising developments, transition-metal-catalyzed α-arylation of aryl fluorides via C−F bond activation of polyfluorinated arenes was not reported.

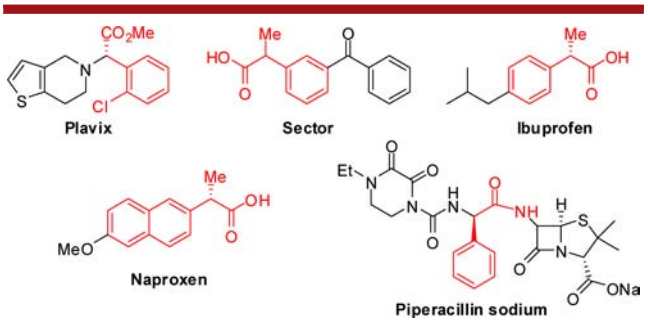



**Figure 1.** Pharmaceuticals with α-aryl carboxylic acid and amide structural unit.

A secondary problem for the transition-metal-catalyzed α-arylation of aryl fluorides via C−F bond activation of polyfluorinated arenes arises from the base used for classic α-arylation reactions. Typically, a strong base such as NaO$^t$Bu, LiHMDS, and $LiNCy_2$ is required to deprotonate the α-proton of the carbonyl compounds.[15] However, these strong bases may react with polyfluoroarenes via a nucleophilic aromatic substitution reaction ($S_NAr$) to give *para*-substituted polyfluoroarenes. To prevent the undesired side reaction, we considered the use of zinc enolates (Reformatsky reagents)[16,17] as the coupling partners since it is well-known that reactions with Reformatsky reagents generally proceed under neutral conditions,[18] thus circumventing the use of strong bases. Herein, we report the first nickel-catalyzed α-arylation of Reformatsky reagents with polyfluorinated arenes via directed selective C−F bond activation. The reactions occurred under mild conditions and were compatible with a variety of functional groups.

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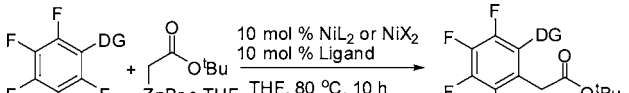
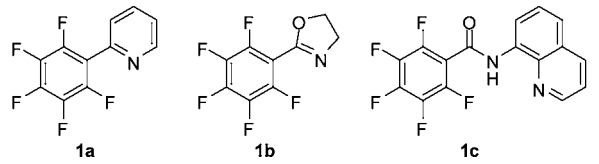
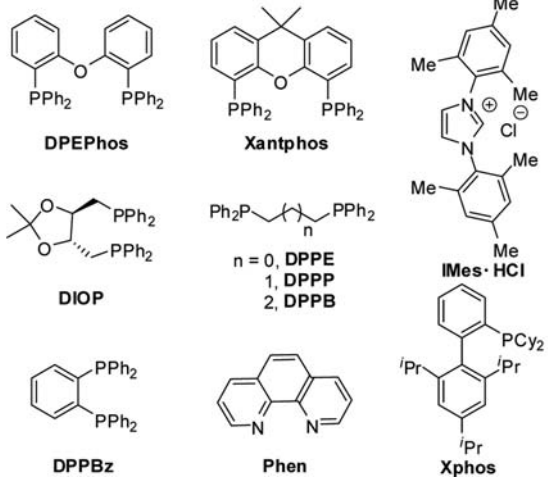
**Table 1. Optimization Studies for Nickel-Catalyzed α-Arylation of Polyfluoroarenes**[a]



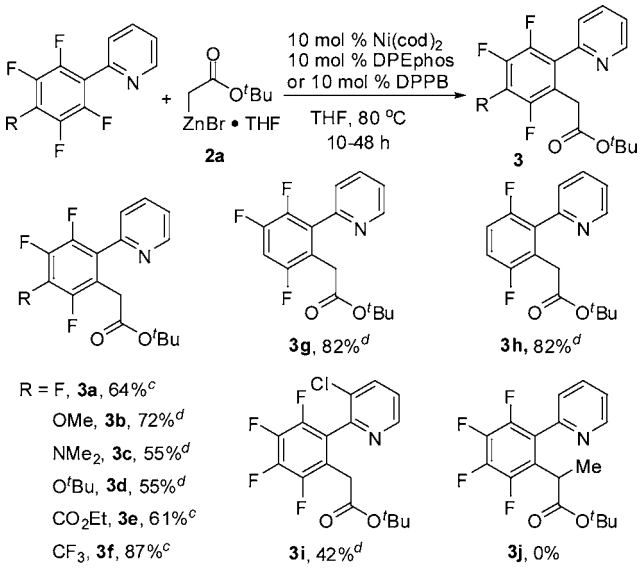

| entry | substrate | catalyst | ligand | yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** | $NiCl_2$ | DPPE | - |
| 2 | **1a** | $Ni(acac)_2$ | DPPE | - |
| 3 | **1a** | $Ni(OAc)_2$ | DPPE | - |
| 4 | **1a** | $Ni(cod)_2$ | DPPE | 50 |
| 5 | **1a** | $Ni(cod)_2$ | DPPP | 68 |
| 6 | **1a** | $Ni(cod)_2$ | DPPB | 74 |
| 7 | **1a** | $Ni(cod)_2$ | DPEphos | 67 |
| 8 | **1a** | $Ni(cod)_2$ | Xantphos | <5 |
| 9 | **1a** | $Ni(cod)_2$ | DPPBz | <5 |
| 10 | **1a** | $Ni(cod)_2$ | DPPF | 16 |
| 11 | **1a** | $Ni(cod)_2$ | BINAP | <5 |
| 12 | **1a** | $Ni(cod)_2$ | $^tBu_3P$ | 10 |
| 13 | **1a** | $Ni(cod)_2$ | $Cy_3P$ | <5 |
| 14 | **1a** | $Ni(cod)_2$ | Xphos | <5 |
| 15 | **1a** | $Ni(cod)_2$ | IMes·HCl | 8 |
| 16 | **1a** | $Ni(cod)_2$ | Phen | <5 |
| 17 | **1b** | $Ni(cod)_2$ | DPPB | <5 |
| 18 | **1c** | $Ni(cod)_2$ | DPPB | <5 |




[a]Reaction conditions: polyfluoroarene **1a**–**c** (0.10 mmol), Reformatsky reagent **2a** (0.15 mmol), $Ni(COD)_2$ or $NiX_2$ (10 mol %), and ligand (10 mol %) in THF (1.0 mL) were stirred at 80 °C for 10 h. [b]Yields were determined by $^{19}F$ NMR analysis of the crude product using 1-fluoronaphthalene as an internal standard.

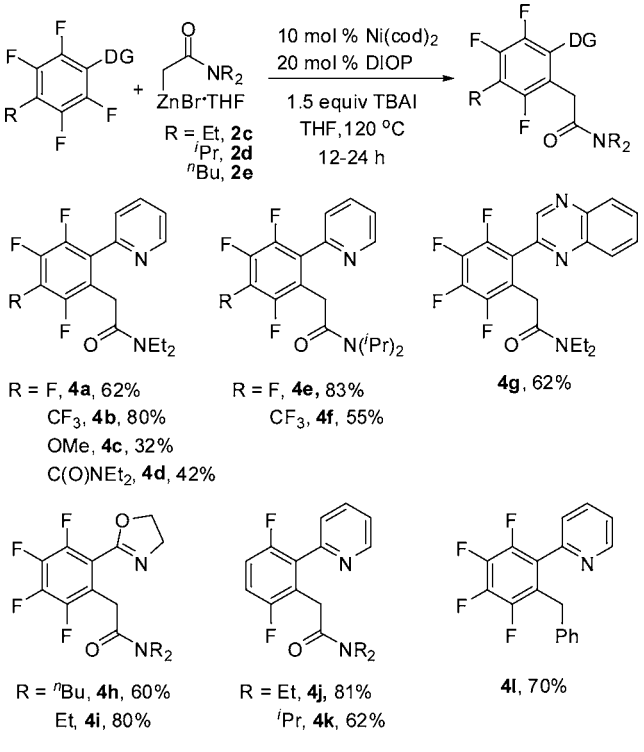
With these considerations in mind, we initially studied the reaction of 2-(pentafluorophenyl) pyridine **1a** and Reformatsky reagent **2a** in the presence of 10 mol % of different nickel salts and 10 mol % of DPPE in THF. To our delight, the expected product **3a** was obtained in 50% yield after 10 h at 80 °C in the presence of $Ni(COD)_2$, while no desired products were formed when $NiCl_2$, $Ni(acac)_2$, or $Ni(OAc)_2$ was used as the catalyst precursor (Table 1, entries 1–4). Since no side products were observed by $^{19}F$ NMR spectroscopy in this reaction, we sought to use other phosphine ligands to accelerate the reaction. It was found that reactions using bidentate ligands such as DPPP, DPPB, and DPEphos occurred faster to afford the desired product **3a** in 67–74% yields (Table 1, entries 5–7). In

**Scheme 1. Nickel-Catalyzed α-Arylation of Zinc Enolate of Esters with Polyfluoroarenes via C–F Activation**[a,b]




[a]Reaction conditions: polyfluoroarene **1a** (1.0 mmol), Reformatsky reagent **2a** (1.5 mmol), $Ni(cod)_2$ (0.10 mmol), and ligand (0.10 mmol) in THF (10 mL) were stirred at 80 °C for 10–48 h. [b] Isolated yields. [c] DPPB as ligand. [d] DPEphos as ligand.

**Scheme 2. Nickel-Catalyzed α-Arylation of Zinc Enolates of Amides with Polyfluoroarenes**[a,b]




[a]Reaction conditions: polyfluoroarene **1a** (0.5 mmol), Reformatsky reagent **2c** (0.75 mmol), $Ni(cod)_2$ (10 mol %), DIOP (20 mol %), and 1.5 equiv of tetrabutylammonia iodide (TBAI) in THF (5.0 mL) were stirred at 120 °C for 12–24 h. [b] Isolated yield.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contrast, reactions in the presence of bidentate ligands such as BINAP, Xantphos, DPPF, or DPPBz occurred much more slowly in less than 16% yields (Table 1, entries 8−11). Interestingly, electron-rich monodentate phosphines such as $^{t}Bu_3P$, $PCy_3$, Xphos, or *N*-heterocyclic ligand IMes were not effective for this reaction (Table 1, entries 12−15). Likewise, another bidentate ligand, 1,10-phenanthroline (Phen), gave the coupling product in less than 5% yield (Table 1, entry 16). The directing group is very important for the reaction. When oxazoline or 8-aminoquinoline was used as the directing group, the reaction occurred in less than 5% yields (Table 1, entries 17−18). The yields of the reaction could not be further improved by switching to other solvents such as toluene or dioxane, increasing the reaction temperature or reaction time (see Table S1 in the Supporting Information for details) .

With the optimal conditions in hand, we examined the scope of Ni-catalyzed $\alpha$-arylation with a Reformatsky reagent, as illustrated in Scheme 1. In general, reactions of 4-substituted-tetrafluorophenyl-2-pyridines with an electron-rich or -withdrawing group occurred smoothly to give the desired products in good yields (Scheme 1, **3a**−**f**). It was found that DPPB was the most effective ligand for the coupling of 2-(*para*-substituted-2,3,5,6-tetrafluorophenyl)pyridine with electron-withdrawing groups, and DPEphos was the optimal ligand for those with electron-donating groups.[19] Reactions of less fluorinated arenes are much less reactive.[20] For example, reactions of tetrafluorophenyl-2-pyridine and trifluorophenyl-2-pyridine with Reformatsky reagent **2a** generated the corresponding products in good yields (Scheme 1, **3g**−**h**). Reaction of 2-(2,3,6-trifluorophenyl)pyridine occurred preferentially at the 2-position due to the electron-withdrawing effect of the adjacent fluorine atom (Scheme 1, **3h**). Notably, unlike Love's case,[8g] the reaction of 2-(2,3,4,5-tetrafluorophenyl)pyridine with a C−H bond and a C−F bond at the *ortho* position failed to give the desired product under standard reaction conditions. When 3-chloropyridine was used as the directing group, the reaction was very slow and required 72 h to give the desired product **3i** in 42% yield. It is likely due to the steric hindrance of the directing group that makes it more difficult to form the cyclometalated intermediate (Scheme 1, **3i**). It should be noted that no desired product was observed when the Reformatsky reagent of *tert*-butyl propionate **2b** was used as the coupling partner (Scheme 1, **3j**). Likewise, the reaction of the Reformatsky reagent of methyl or ethyl propionate did not form the desired products. Instead, we found that there is a background aldol-type reaction when the Reformatsky reagent of methyl or ethyl propionate was used under the standard reaction conditions.

Encouraged by these findings, we next explored the Ni-catalyzed $\alpha$-arylation of polyfluoroarenes with Reformatsky reagents that were derived from amides. Initial attempts using the zinc enolate of amide **2c** as the coupling partner in the presence of $Ni(cod)_2$/DPPB as the catalyst led to a less than 5% yield even after 10 h at 80 °C. After careful investigation, it was found that reactions using DIOP as the ligand occurred much faster than those using DPPB. In addition, using tetrabutylammonium iodide (TBAI) as an additive could further accelerate the $\alpha$-arylation of the zinc enolate of amides (see Tables S2−S3 in the Supporting Information for details). A number of zinc enolates of amides and polyfluorinated arenes were then investigated, and the results are summarized in Scheme 2. Reactions of polyfluorinated arenes with electron-donating groups occurred much more slowly and in lower yields than those with electron-withdrawing groups (Scheme 2, **4a**−**d**). Zinc enolates of *N*,*N*-di-isopropylacetamide reacted with polyfluoroarenes to afford the corresponding products in good yields (Scheme 2, **4e**−**f**). Under these conditions, polyfluoroarenes with other directing groups such as quinoxaline or oxazoline could couple with the zinc enolate of amides to give the corresponding products in 60−80% yields (Scheme 2, **4g**−**i**). Similar to the case of Reformatsky reagent **2a**, reaction of 2-(2,3,6-trifluorophenyl)pyridine with Reformatsky reagent **2c** derived from amides occurred preferentially at the 2-position (Scheme 2, **4j**−**k**). Interestingly, when benzylzinc was used, both the mono- and diarylated products were observed by $^{19}F$ NMR spectroscopy in 70% and 16% yields, respectively (Scheme 2, **4l**).

In summary, we have developed the first nickel-catalyzed $\alpha$-arylation of polyfluoroarenes via C−F bond activation. The reaction occurred under neutral conditions and was compatible with various functional groups. Further studies to study the mechanism of $\alpha$-arylation of aryl fluorides are ongoing currently in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

All experimental procedures and spectroscopic data of compounds **3a**−**i** and **4a**−**l**. 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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(19) We examined the reaction of 2,3,5,6-tetrafluoro-4-(pyridin-2-yl)benzonitrile with the zinc enolate of the ester under standard reaction conditions. No expected product was obtained, and the starting material was recovered.

(20) A reviewer pointed out that less fluorinated arenes are more relevant to pharmaceutical targets. In general, the arenes with fewer fluorines are much less reactive. We have tried many di-, tri-, and tetrafluorinated arenes under the standard reaction conditions, but no desired products were observed. We are currently studying the $\alpha$-arylation of zinc enolates with these less reactive polyfluoroarenes using other transition metal catalysts.