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Nickel-Catalyzed Reductive 2-Pyridination of Aryl Iodides with Difluoromethyl 2-Pyridyl Sulfone

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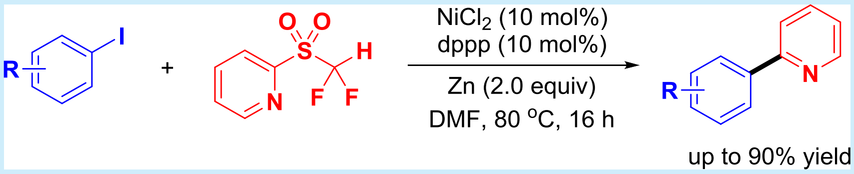

ABSTRACT: A novel nickel-catalyzed reductive cross-coupling between aryl iodides and difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$) enables $C(sp^2)-C(sp^2)$ bond formation through selective $C(sp^2)-S$ bond cleavage, which demonstrates the new reactivity of 2-$PySO_2CF_2H$ reagent. This method employs readily available nickel catalyst and sulfones as cross-electrophile coupling partners, providing facile access to biaryls under mild reaction conditions without pregeneration of arylmetal reagents.

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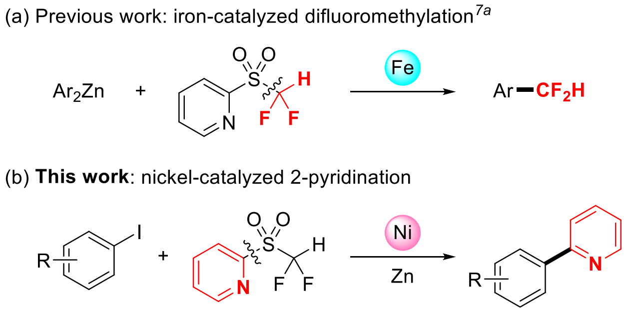
Transition-metal-catalyzed C−C and C−heteroatom bond-forming reactions are among the most widely used transformations in modern synthetic organic chemistry.[1] Transition-metal-catalyzed cross-coupling reactions of organic electrophiles and organometallic reagents have emerged as powerful synthetic tools, and a variety of such reactions have been developed, including the Suzuki, Negishi, Hiyama, Kumada, and Stille coupling reactions. Aside from traditional cross-coupling between a nucleophile and an electrophile, reductive cross-coupling of two different electrophiles represents an alternative reaction type, which typically occurs in the presence of a transition-metal catalyst (Ni, Co, Pd, or Fe) and a suitable metallic reductant (Zn, Mn, or Mg).[2] The advantage of this strategy lies in avoiding the use of preformed organometallic reagents, which are unstable and require special care to exclude water and dioxygen, whereas most electrophilic coupling partners can be easily stored and handled. In addition, reductive cross-coupling reactions possess excellent functional group compatibility because no stoichiometric amount of strong base or nucleophile is needed. Despite the fact that extensive studies have been done on the reductive cross-coupling of aryl halides with alkyl electrophiles,[3] the reductive cross-coupling between aryl halides and (hetero)aryl electrophiles remains underdeveloped.[4]

On the other hand, sulfones have served as the electrophilic coupling partners in transition-metal-catalyzed cross-coupling reactions. However, the majority of the research on such transformations has focused on the nickel- or iron-catalyzed cross-coupling of sulfones with Grignard reagents for C−C bond formation.[5,6] In 2018, we reported the first iron-catalyzed difluoromethylation of arylzincs with difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$) via selective $C(sp^3)-S$ bond cleavage (Scheme 1a).[7,8] The Baran group developed a nickel-catalyzed cross-coupling between aryl zinc reagents and alkyl heteroaryl sulfones to form $C(sp^3)-C(sp^2)$ bonds.[9] To the best of our knowledge, however, the transition-metal-catalyzed cross-coupling of sulfones with aryl halides has been much less investigated under reductive reaction conditions.[10] Herein we report our recent success in a nickel-catalyzed reductive cross-coupling of aryl iodides with 2-$PySO_2CF_2H$ to forge $C(sp^2)-C(sp^2)$ bonds via selective $C(sp^2)-S$ bond cleavage, which was different from our previous work (Scheme 1b).

Scheme 1. Transition-Metal-Catalyzed Cross-Coupling of 2-$PySO_2CF_2H$ via Regioselective C−S Bond Cleavage



Our study commenced with the nickel-catalyzed reductive cross-coupling of 4-iodotoluene (**1a**) with 2-$PySO_2CF_2H$ (**2a**). Initially, when we employed 10 mol % of $NiCl_2$, 10 mol % of 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbbpy), 2.0 equiv of zinc

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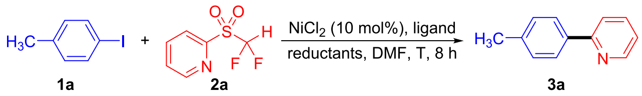
powder, DMF as the reaction solvent, and stirring for 8 h at 80 °C, a full consumption of **2a** led to the formation of the desired biaryl **3a** (detected by GC-MS) in 18% NMR yield, with the formation of the difluoromethanesulfinate as the only detectable fluorinated side product (Table 1, entry 1). A further improvement in yield was observed when using other bidentate nitrogen ligands (Table 1, entries 2 and 3). Then, phosphorus ligands were evaluated to improve the reaction efficiency (Table 1, entries 4−16). It was found that the monodentate phosphine ligand triphenylphosphane (PPh_3) provided a 41% yield of the desired product **3a** (Table 1, entry 4), whereas the bidentate phosphine ligand 1,3-bis(diphenylphosphino)propane (dppp) delivered **3a** in 56% NMR yield (51% isolated yield) (Table 1, entry 5). In these two cases, there still remain substantial amounts of **1a** and **2a**. We found that the reductive cross-coupling reaction with dppp as the ligand proceeded smoothly to give biaryl **3a** in 82% isolated yield when the reaction time was extended to 16 h (Table 1, entry 6). However, when the reaction proceeded at room temperature or 50 °C for 16 h, no desired biaryl **3a** was detected (Table 1, entries 7 and 8). Increasing the temperature to 110 °C led to a lower yield (Table 1, entry 9). Manganese powder could also be used as reductant, giving a moderate yield, as did zinc powder (Table 1, entry 10). Iron, magnesium and copper metals, in contrast, were found to be ineffective (Table 1, entries 11−13). Additionally, we noted that the variation of the amounts of zinc powder proved to have an influence on the reaction efficiency. (See the SI.) In the absence of a ligand, only a trace amount of product **3a** was detected (entry 14). Control experiments showed that a nickel catalyst, ligand, and reductant were essential for this transformation (entries 14−16). After a brief screening of the choices of nickel catalyst, ligand, reductant, solvent, and temperature, the optimal isolated yield of **3a** (82%) was obtained when the combination of 10 mol % of $NiCl_2$, 10 mol % of dppp, and 2.0 equiv of zinc in DMF at 80 °C was used (Table 1, entry 6). It is worth noting that no $C(sp^3)-C(sp^2)$ coupling product, namely, $Ar-CF_2H$ was detected, which is in sharp contrast with our previous report on the iron-catalyzed cross-coupling reaction between arylzincs and 2-Py-SO_2CF_2H.[7a]

Table 1. Optimization of the Reaction Conditions[a]

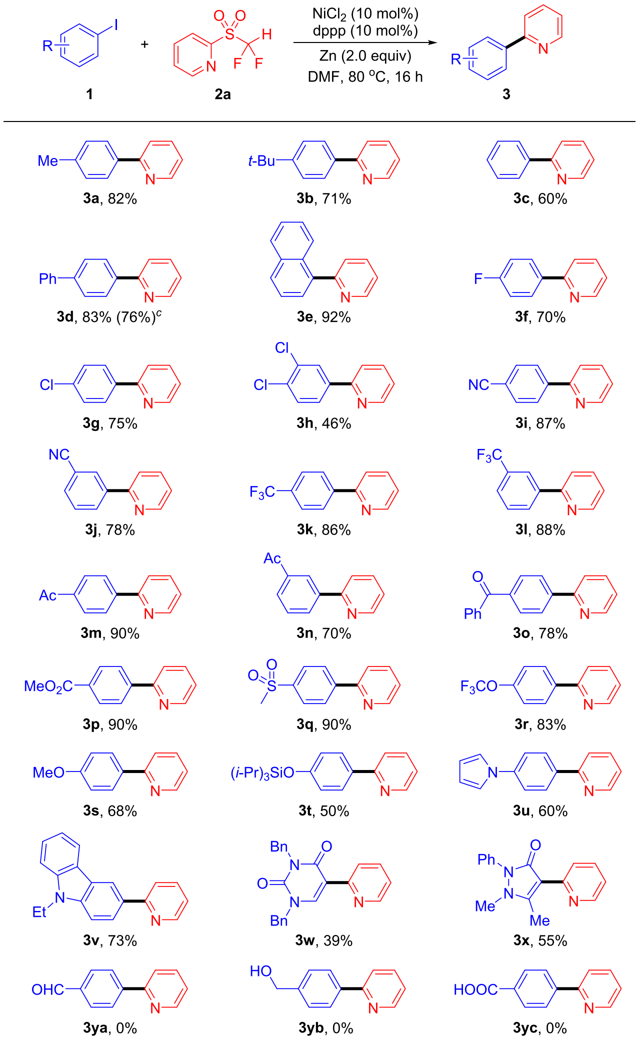


entry	ligand	reductant (equiv)	T (°C)	**3a**, yield (%)[b]
1	dtbbbpy	Zn (2.0)	80	18
2	2,2′-bipy	Zn (2.0)	80	40
3	1,10-Phen	Zn (2.0)	80	51
4	PPh_3	Zn (2.0)	80	41
5	dppp	Zn (2.0)	80	56 (51[c])
6[d]	dppp	Zn (2.0)	80	87 (82[c])
7[d]	dppp	Zn (2.0)	rt	0
8[d]	dppp	Zn (2.0)	50	0
9[d]	dppp	Zn (2.0)	110	72
10[d]	dppp	Mn (2.0)	80	50
11[d]	dppp	Fe (2.0)	80	trace
12[d]	dppp	Mg (2.0)	80	trace
13[d]	dppp	Cu (2.0)	80	6
14[d]		Zn (2.0)	80	trace
15[d,e]	dppp	Zn (2.0)	80	0
16[d]	dppp		80	0

[a] Reaction condition: **1a** (0.5 mmol, 1.0 equiv), **2a** (0.75 mmol, 1.5 equiv), $NiCl_2$ (10 mol %), ligand (10 mol %), reductant (1.0 mmol, 2.0 equiv), solvent (3.0 mL), 80 °C, 8 h. [b] Yields were determined by ^1H NMR using 4-iodoanisole as the internal standard. [c] Isolated yield. [d] 16 h. [e] $NiCl_2$ (0 mol %).

Having established the standard conditions for the reductive cross-coupling reaction (Table 1, entry 6), we next assessed the scope of the nickel-catalyzed reductive cross-coupling of aryl iodides with 2-$PySO_2CF_2H$ (Scheme 2). It turned out that the reaction was compatible not only with electron-poor (**3f**−**r**) and electron-rich (**3s** and **3t**) aryl iodides but also with aryl iodides bearing a variety of functional groups (**3u**−**x**). As shown in Scheme 2, in general, a variety of aryl iodides with electron-withdrawing substituents (such as fluorine (**3f**), chlorine (**3g**, **3h**), cyano (**3i** and **3j**), trifluoromethyl (**3k** and **3l**), ketone (**3m**−**o**), ester (**3p**), sulfone (**3q**), and trifluoromethoxy (**3r**) groups) reacted with 2-$PySO_2CF_2H$

Scheme 2. Scope of Ni-Catalyzed Reductive Cross-Coupling of Aryl Iodides with 2-$PySO_2CF_2H$[a,b]

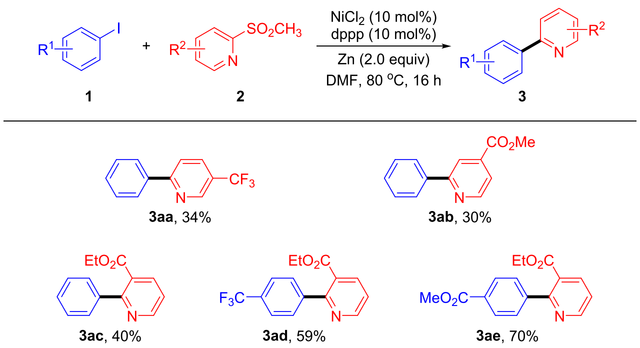


[a] Reaction conditions: **1** (0.8 mmol, 1.0 equiv), **2a** (1.2 mmol, 1.5 equiv), $NiCl_2$ (10 mol %), dppp (10 mol %), Zn (1.6 mmol, 2.0 equiv), DMF (5.0 mL), 80 °C, 16 h. [b] Isolated yield. [c] Isolated yield of the reaction performed on a 1.2 mmol scale is given in parentheses.

smoothly to afford the desired biaryl products in good to excellent yields (46−90%), whereas the substrates bearing electron-donating groups (**3s** and **3t**) gave inferior yields (68 and 50%, respectively). The cross-coupling reaction proceeded smoothly with substrates bearing a range of heterocyclic motifs, such as pyrrole (**3u**, 60%), carbazole (**3v**, 73%), pyrimidine (**3w**, 39%), and pyrazole (**3x**, 55%). Vinyl iodides (**3w** and **3x**) were also able to couple to 2-$PySO_2CF_2H$. However, substrates with an acidic proton (such as free alcohol and acid) were not viable in the current nickel-catalyzed reductive 2-pyridination (**3ya**, **3yb**, and **3yc**).

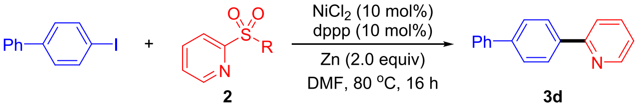
In addition to 2-$PySO_2CF_2H$, 2-(methylsulfonyl)pyridine (2-$PySO_2CH_3$) and its derivatives were also employed to examine their reactivity in nickel-catalyzed reductive cross-coupling with aryl iodides. As shown in Scheme 3, these electron-withdrawing group-substituted methyl sulfones underwent reductive cross-coupling reactions, giving the corresponding products **3aa−ae** in moderate yields. Moreover, we also found that electron-deficient aryl iodides showed better reactivity in this reaction. Finally, we investigated the reactivity of different fluoroalkylated 2-pyridyl sulfones under the standard reaction conditions (Scheme 4) and found that the reductive cross-coupling of 2-$PySO_2CF_2H$ (**2a**) and fluoromethyl 2-pyridyl sulfone (**2b**, 2-$PySO_2CFH_2$) with 4-iodobiphenyl proceeded smoothly to deliver the desired biaryl **3d** in 83 and 62% yield, respectively. However, the reactions with trifluoromethyl 2-pyridyl sulfone (**2c**, 2-$PySO_2CF_3$) and methyl 2-pyridyl sulfone (**2d**, 2-$PySO_2CH_3$) provided only a trace amount of **3d** under the standard reaction conditions.

Scheme 3. Substrate Scope of 2-$PySO_2CH_3$ Derivatives[a,b]



[a]Reaction conditions: **1** (0.8 mmol, 1.0 equiv), **2** (1.2 mmol, 1.5 equiv), $NiCl_2$ (10 mol %), dppp (10 mol %), Zn (1.6 mmol, 2.0 equiv), DMF (5.0 mL), 80 °C, 16 h. [b]Isolated yield.

Scheme 4. Cross-Coupling with Different Fluoroalkyl 2-Pyridyl Sulfones[a,b]

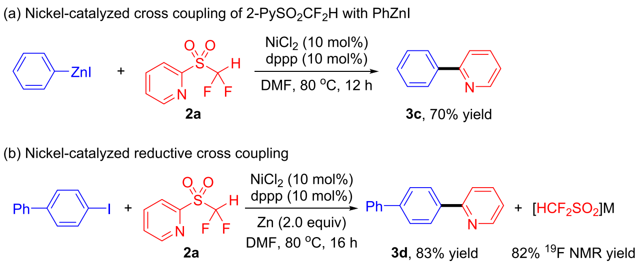


2	**3d**, yield
2a, R = CF_2H	83%
2b, R = CFH_2	62%
2c, R = CF_3	trace
2d, R = CH_3	trace

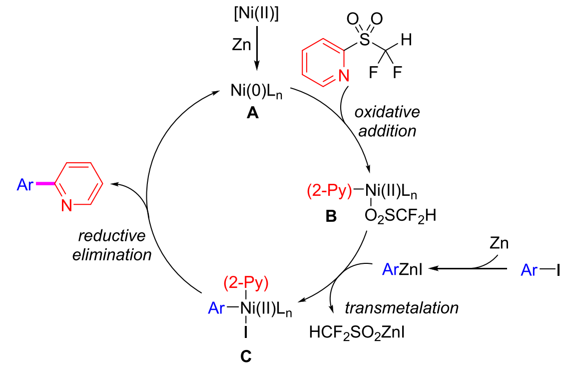
[a]Reaction conditions: 4-iodobiphenyl (0.8 mmol, 1.0 equiv), **2** (1.2 mmol, 1.5 equiv), $NiCl_2$ (10 mol %), dppp (10 mol %), Zn (1.6 mmol, 2.0 equiv), DMF (5.0 mL), 80 °C, 16 h. [b]Isolated yield.

To gain mechanistic insights into this nickel-catalyzed reductive cross-coupling reaction with zinc, we conducted several preliminary mechanistic experiments (Scheme 5). First, we performed nickel-catalyzed cross-coupling of 2-$PySO_2CF_2H$ with preformed phenylzinc iodide, which gave the product **3c** in 70% yield, suggesting that an arylzinc reagent might be engaged in this nickel-catalyzed cross-electrophile coupling process. Furthermore, difluoromethanesulfinate salt was observed as a byproduct via ^{19}F NMR in 82% yield under the standard reaction conditions, which suggests that the generation of a difluoromethyl radical from 2-$PySO_2CF_2H$ (as a major pathway) is unlikely during the reaction. Furthermore, the detection of 1,1′-biphenyl in this reaction (via GC-MS) also supports the involvement of arylzinc. Although the exact mechanism remains unclear, on the basis of these experiments and the previous investigation, we propose a plausible mechanism for the present nickel-catalyzed cross-electrophile coupling reaction (Scheme 6). The catalytic cycle may be initiated by the reduction of $NiCl_2(dppp)_n$ to Ni(0) species **A** by Zn(0). The oxidative addition of 2-$PySO_2CF_2H$ to Ni(0) species **A** affords an arylnickel(II) species **B**.[11] The subsequent transmetalation of the arylnickel(II) species **B** with the arylzinc reagent, which is in situ generated from aryl iodides and Zn(0),[12] furnishes Ni(II) species **C**. Finally, the reductive elimination from **C** delivers the desired product **D** and regenerates the catalytically active Ni(0) species **A**.[13]

Scheme 5. Mechanistic Investigation



Scheme 6. Proposed Mechanism



In summary, we have developed a novel nickel-catalyzed reductive cross-coupling reaction of 2-$PySO_2CF_2H$ with aryl iodides to forge $C(sp^2)-C(sp^2)$ bonds via selective $C(sp^2)-S$ bond cleavage. This synthetic protocol employs readily available starting materials and reagents, proceeds under mild conditions, and tolerates a range of functional groups and heterocycles. Moreover, this method avoids the need for the pregeneration of arylmetal reagents, which is a notable advantage for synthetic applications. Unlike our previous work on iron-catalyzed reactions (Scheme 1a),[7a] the present work not only provides a new strategy for the formation of biaryls but also gives new insights into the new reactivity of fluoroalkyl sulfones. Compared with results previously reported by us[7a] and others,[9,10] we conclude that the selectivity of the cross-coupling reaction of heteroaryl sulfones is influenced by both the transition-metal catalyst and the type of the heteroaryl substituent of the sulfone. Further studies on the transition-metal-catalyzed coupling reactions using sulfones are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03939.

Experimental procedures and characterization data for products (PDF)

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Notes

The authors declare no competing financial interest.

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